

# **Epidermal Growth Factor Receptor (EGFR) inhibitors for tumor anti-angiogenesis activity.**

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**Abstract:**

The EGFR family plays an essential role in normal organ development by mediating morphogenesis and differentiation through effects on cell proliferation, differentiation, apoptosis, invasion, and angiogenesis. Unlike normal cells that have tight regulatory mechanisms controlling EGFR pathways, tumor cells often have dysregulated EGFR signaling, allowing them to proliferate under adverse conditions, invade surrounding tissues, and increase angiogenesis. Epidermal growth factor receptor (EGFR) is a trans-membrane receptor tyrosine kinase that belongs to the Human epidermal receptor (HER) family of receptors. Receptor protein tyrosine kinases play a key role in signal transduction pathways that regulate cell division and differentiation. Among the growth factor receptor kinases that have been identified as being important in cancer is epidermal growth factor receptor (EGFR) kinase (also known as erb-B1 or HER-1) and the related human epidermal growth factor receptor HER-2 (also known as erbB-2). The quinazoline and other heterocyclic skeletons are of great importance to chemists as well as biologists as it is available in a large variety of naturally occurring compounds. In this article we are emphasizing on various heterocycles such as Quinazoline, pyrrolotriazines etc. as promising anticancer agents. These heterocycles showed the anticancer activity through the inhibition of EGFR enzyme. Attempt will be taken to provide details information on the said topic in the benefit of medicinal chemist.

**Keywords:** Anticancer agents, EGFR inhibitors, Heterocycles

## 1. Introduction

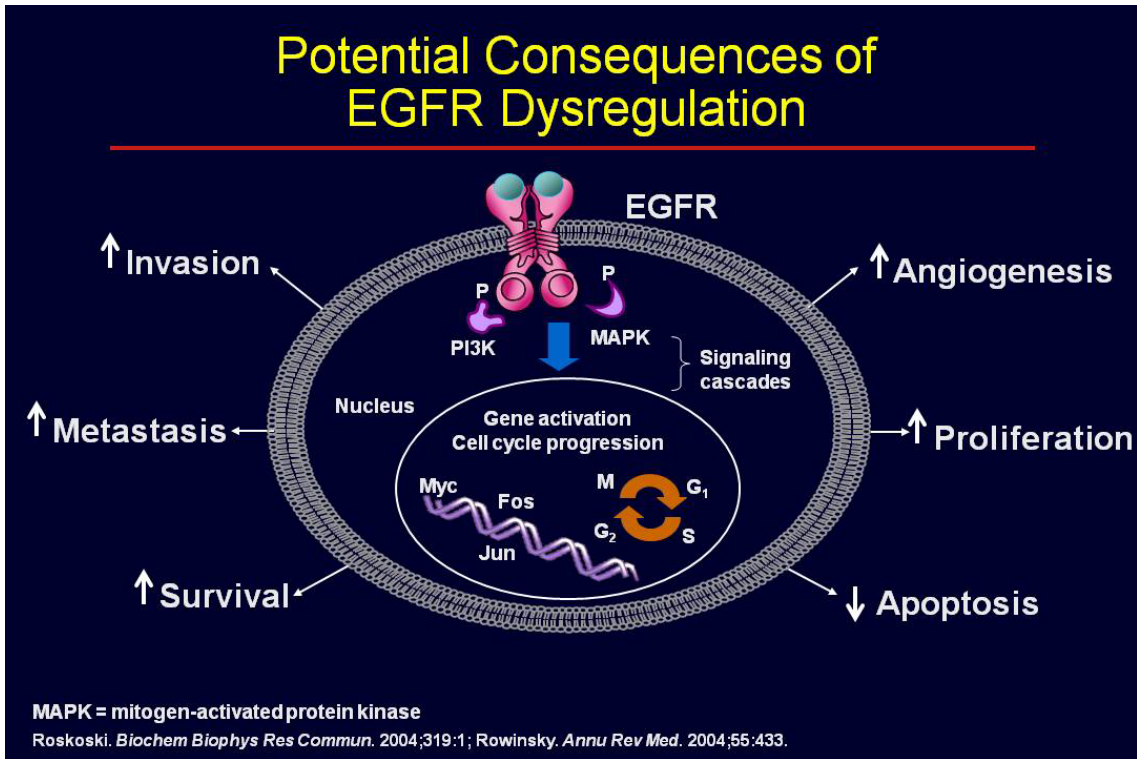
The quinazoline<sup>1</sup> and other heterocyclic skeletons are of great importance to chemists as well as biologists as it is available in a large variety of naturally occurring compounds. It is also found in clinically useful molecules having diverse biological activities<sup>2</sup> such as antiviral<sup>3</sup>, antimalarial<sup>4</sup>, Anticonvulsant<sup>5,6</sup>, Antimicrobial<sup>7,8</sup>, Antitoxoplasmosis<sup>9</sup>, Antihyperglycemic<sup>10</sup>, Antiplatelet<sup>11</sup>, Anxiolytic<sup>12</sup>, Antifungal<sup>13</sup>, Antihypertensive<sup>14</sup>.

Cancer chemotherapy has entered a new era of molecularly targeted therapeutics, which is highly selective and not associated with the serious toxicities of conventional cytotoxic drugs<sup>15</sup>.

The EGFR family plays an essential role in normal organ development by mediating morphogenesis and differentiation through effects on cell proliferation, differentiation, apoptosis, invasion, and angiogenesis<sup>16, 17</sup>. Unlike normal cells that have tight regulatory mechanisms controlling EGFR pathways (Figure1), tumor cells often have dysregulated EGFR signaling, allowing them to proliferate under adverse conditions, invade surrounding tissues, and increase angiogenesis. Normally EGFR must be activated by a ligand to initiate downstream signaling, but tumor cells can circumvent this requirement through a number of mechanisms<sup>18</sup>. Epidermal growth factor receptor (EGFR) is a trans-membrane receptor tyrosine kinase that belongs to the Human epidermal receptor (HER) family of receptors<sup>19</sup>.

The first group of these novel anticancer drugs is those targeting mutant or aberrantly expressed oncogenic growth factor receptor and non-receptor tyrosine kinases involved in mitogenic or proliferative signal transduction pathways in cancer cells.<sup>20</sup> Receptor protein tyrosine kinases play a key role in signal transduction pathways that regulate cell division

and differentiation. Among the growth factor receptor kinases that have been identified as being important in cancer is epidermal growth factor receptor (EGFR) kinase (also known as erb-B1 or HER-1) and the related human epidermal growth factor receptor HER-2 (also known as erbB-2). Deregulation of growth-factor signaling due to hyperactivation of the ErbB receptors (primarily EGFR and HER-2) is seen in several cancer types.<sup>21,22</sup> Activation of EGFR may be because of overexpression, mutations resulting in constitutive activation, or autocrine expression of ligand. In contrast, activation of HER-2 occurs mainly by overexpression, which leads to spontaneous homodimerization and activation of downstream signaling events in a ligand-independent manner.<sup>23, 24</sup>

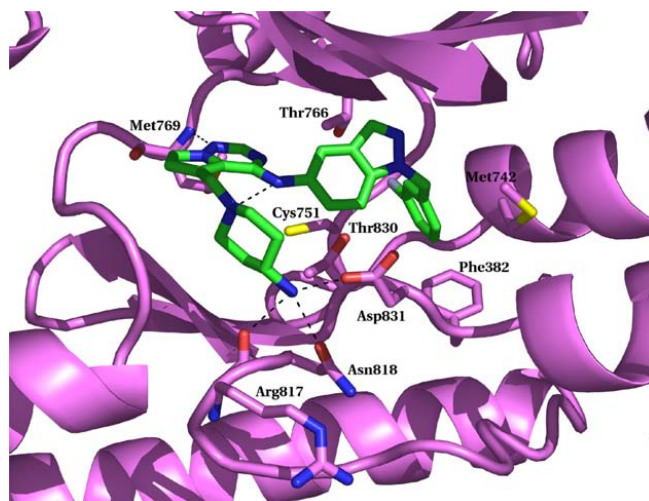


**Figure1:** EGFR pathway

This review is originated from the literature survey on the quinazoline and other important heterocyclic moiety<sup>25-41</sup> which shows the good EGFR/VEGFR inhibitory activity.

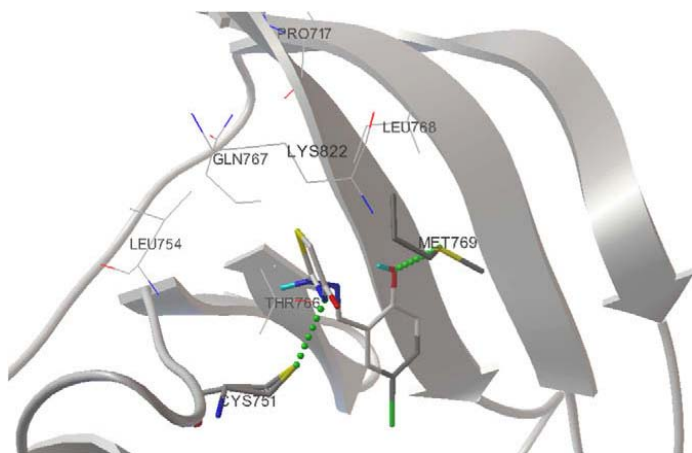
Quinazoline is the chemical entity that shows a very good promising anticancer activity through the EGFR inhibition, some moieties which are developed for good EGFR inhibitor activity are as follows.

Harold Mastalerz *et al* designed **14** compounds of Pyrrolotriazine dual EGFR/HER2 kinase inhibitors in that a 5-((4-aminopiperidin-1-yl) methyl) solubilizing group were found to be superior to analogs with previously reported C-5 solubilizing groups having IC<sub>50</sub> value 0.035.<sup>25</sup>



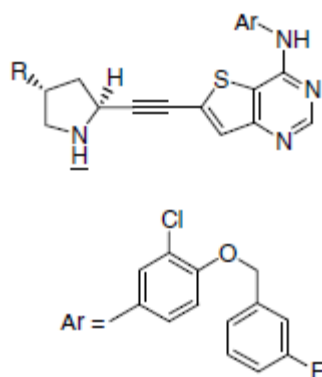
**Figure 2** Predicted binding mode of compound **1** modeled in the X-ray structure of the lapatinib/EGFR kinase complex, The C-5 side chain extends into the ribose-phosphate binding region where the protonated amino group off the piperidine ring may form hydrogen bonds with Asp831, Asn818, and/or Arg817.

Peng-Cheng Lv *et al* synthesize compound 2-(2-(5-bromo-2-hydroxybenzylidene)hydrazinyl) thiazol-4(5H)-one (**2**) displayed the most potent inhibitory activity ( $IC_{50} = 0.09$   $\mu M$  for EGFR and  $IC_{50} = 0.42$   $\mu M$  for HER-2), comparable to the positive control erlotinib.<sup>26</sup>



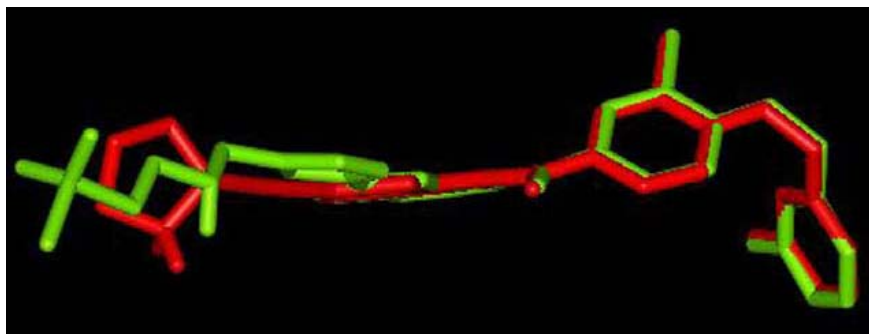
**Figure 3** Molecular modeling of compound **2** with EGFR kinase: the hydroxyl group of compound **2** forms hydrogen bond with mercapto group of Met 769, and the nitrogen atom of thiazolidinone ring of compound **2** also forms hydrogen bond with the side chain mercapto group of Cys 751.

A novel class of substituted pyrrolidinyl-acetylenic thieno[3,2-d]pyrimidines(**15** compounds) has been synthesized by Robert D. Hubbard *et al* and compound **3** shows potent and selective inhibitors of both EGFR/ErbB-2 receptor tyrosine kinases with  $IC_{50}$  nM valve 14(ND),115(21%).<sup>27</sup>



R=OH

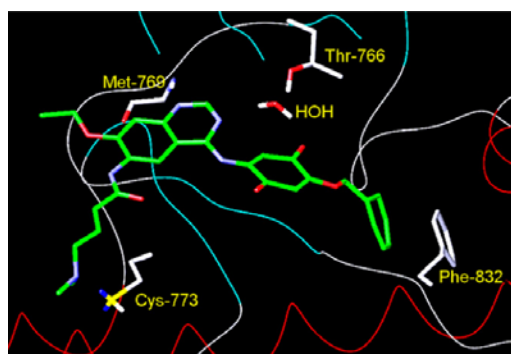
**3**



**Figure 4** Superimposition of a possible binding conformation of lapatinib (green) and 3(red) docked into ErbB-2.

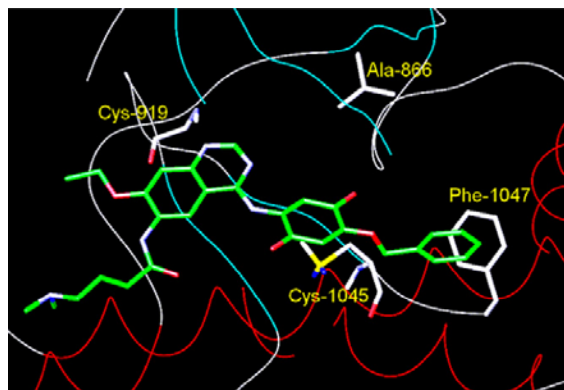
Allan Wissner *et al* discovered **20** derivatives of phthalazine (**4**) and the quinazoline (**5**) and are reported to be ATP competitive inhibitors of VEGFR-2 and they confirmed their activities against this target. The compound **6** ( $IC_{50}$  (nM)  $1\mu\text{M ATP}=18.7$ ) showed modest EGFR kinase inhibitory activity.<sup>28</sup>





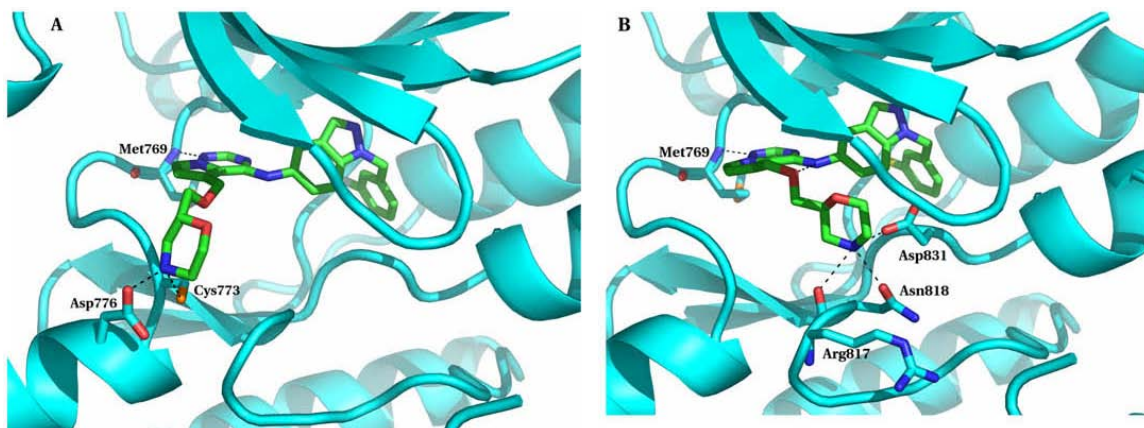
**Figure 5** Proposed binding model for **6** bound to the kinase domain of EGFR.

The ligand was removed from this crystal structure and, with the exception of the water molecule that bridges the N3 atom of the quinazoline and Thr-766, the water molecules were removed. The inhibitor was docked and the resulting model shows the inhibitor oriented in a manner consistent with the way other quinazoline derivatives have been shown to bind to different kinases.



**Figure 6** Binding model for **6** bound to the kinase domain of VEGFR-2.

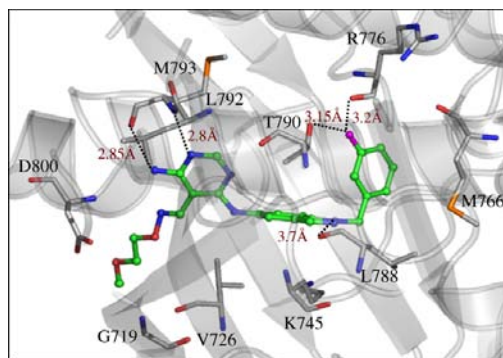
Harold Mastalerz *et al* developed novel C-5 substituted pyrrolotriazines **7** are optimized for dual EGFR and HER2 protein tyrosine kinase inhibition ( $IC_{50}$  ( $\mu M$ ) = 0.061). The lead compound exhibited promising oral efficacy in both EGFR and HER2 driven human tumor xenograft models. It is hypothesized that its C-5 morpholine side chain binds in the ribose phosphate portion of the ATP binding pocket.<sup>29</sup>



**Figure 6** Predicted binding modes of compound **7** modeled in the X-ray structure of the lapatinib/EGFR kinase complex. In part A of the figure the C-5 side chain extends out toward the solvent where the protonated morpholine NH hydrogen bonds with Cys773 and Asp776. In part B of the figure the C-5 side chain extends into the ribose phosphate binding region where the protonated morpholine NH hydrogen bonds with the Asp831, Asn818, and Arg817.

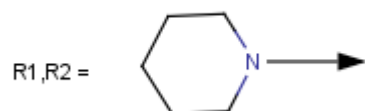
Celia Fernandes *et al* *in vitro* assays indicate that the halogenated quinazolines (**9**) and (**10**) inhibit intact A431 cell growth and also inhibit completely autophosphorylation of the receptor in intact A431 cells at the concentration of 0.1  $\mu$ M. These results demonstrate that the introduction of a  $\beta$ -halopropionamide chain at the 6 position of the quinazoline moiety has improved the capability of inhibition of A431 cell growth and autophosphorylation of EGFR when compared to the parent quinazoline (**5**)<sup>30</sup>. At the lowest concentration tested (0.1  $\mu$ M) the halogenated derivatives (**9** and **10**) showed almost complete inhibition of phosphorylation, suggesting that the IC<sub>50</sub> values are in the low nM range.

Guozhang Xu *et al* synthesized 4-aminopyrimidine-5-carboxaldehyde oxime derivatives are capable of affording potent EGFR/ErbB-2 inhibition. They selected the 1-(3-fluorobenzyl)indazol-5-amino group as the C-6 side chain since it has been shown in both pyrrolotriazine and quinazoline scaffolds to provide optimal dual EGFR and ErbB-2 kinase inhibitions. They were delighted to find that compound (**11**) displayed potent inhibition against both EGFR and ErbB-2 with  $IC_{50}$  nM = 8 and 12, respectively, However, methyl substitution of the C-4 amino group abrogated both EGFR and ErbB-2 activities. Such a pronounced drop in activity against the enzyme suggested that C-4  $NH_2$  is necessary for binding, or that the methyl group prevents the molecule from attaining a proper conformation for binding to the enzyme.<sup>31</sup>



**Figure 8** Interactions between EGFR and compound **11**. Compound **11** is shown in green, protein residues are colored gray and atoms are colored by element for both molecules with nitrogen blue, oxygen red and fluorine light green.

Guozhang Xu, Marta C. Abad *et al* synthesized novel class of 4-amino-6-arylamino-pyrimidine-5-carbaldehyde hydrazones (**13**) were identified as potent dual ErbB-2/EGFR kinase inhibitors ( $IC_{50}\mu M = 0.030$ ) using concept-guided design approach. These compounds inhibited the growth of ErbB-2 over-expressing human tumor cell lines (BT474, N87, and SKBR-3) *in vitro*.<sup>32</sup>



Caterina Carmi *et al* synthesized series of 1,5-disubstituted hydantoins (**14**) some 1-phenethyl and a 5-(E)-benzylidene substituent, inhibits EGFR autophosphorylation and polyGAT phosphorylation, and also inhibits the growth and proliferation of human A431 cells, which overexpress EGFR. These compounds can therefore be regarded as examples of a new scaffold for tyrosine kinase inhibitors.<sup>33</sup>

Anilinoalkynyl pyrimidines were prepared and evaluated by Alex G. Waterson *et al* as dual EGFR/ErbB2 kinase inhibitors. A preference was found for substituted phenyl and heteroaromatic rings attached to the alkyne (**15**). In addition, the presence of a potential hydrogen bond donor appended to this ring was favored.<sup>34</sup>

Two series of new 6-alkoxy-4-substituted-aminoquinazolines (**16–17**) and their bioisoteric quinoline congeners were designed and synthesized by Khaled Abouzid *et al*. Most of the tested compounds exploited potent antitumor activity with IC<sub>50</sub> values in the nanomolar range.<sup>35</sup>

The benzamides **18** and the benzamidines (**19–20**) were synthesized by Toru Asano *et al* as the mimics of 4-anilinoquinazolines, which possess inhibition of epidermal growth factor receptor (EGFR) tyrosine kinase (IC<sub>50</sub> values are 0.09–0.32mM.) and tested for cytotoxicity toward A431 and inhibitory activity toward autophosphorylation by the enzyme assay.<sup>36</sup>

A series of 4-anilinoquinazolines **21** with C–C multiple bond substitutions at the 6-position were synthesized and investigated for their potential to inhibit epidermal growth factor receptor (EGFR) tyrosine kinase activity by Hyun Seung Ban *et al*. These compounds inhibited EGF-mediated phosphorylation of EGFR in A431 cells, resulting in cell-cycle arrest and apoptosis induction. The C–C multiple bonds substituted at the C-6 position of the anilinoquinazoline



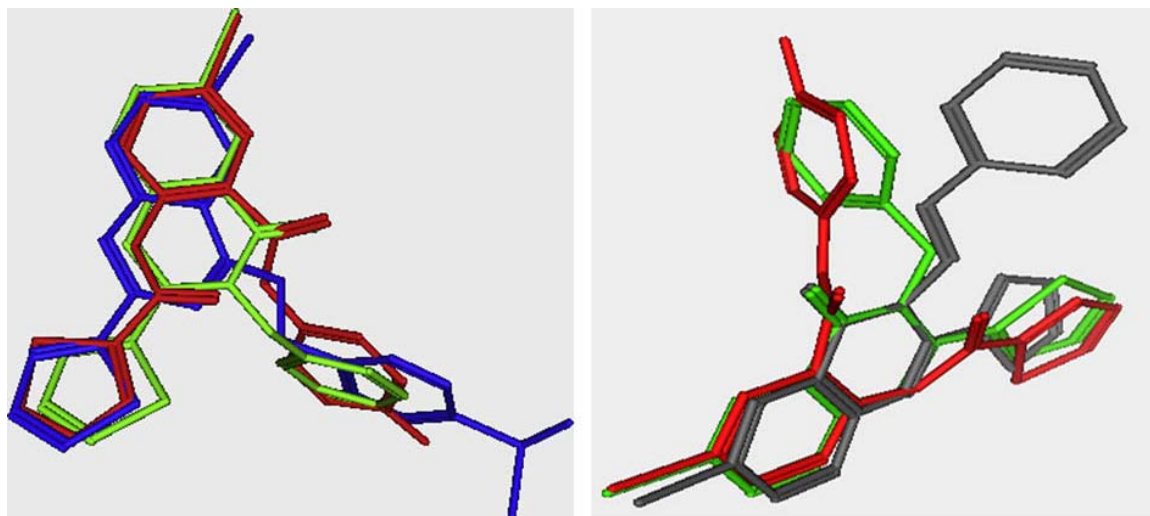
framework were essential for the significant inhibitory activity. Compounds with long carbon chains (n = 3–6) shows prolonged inhibitory activity.<sup>37</sup>

Robert D. Hubbard *et al.* developed 2-OMe substituted pyrazolopyrimidines **22** multitargeted inhibitors of both the insulin-like growth factor receptor (IGF-IR) and members of the epidermal growth factor family of receptor tyrosine kinases.

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Abdulrahman M *et al* synthesized compounds 2-(2-thienylcarbonylamino)-5-iodo-N-(4-hydroxyphenyl)-benzamide (**23**), 2-(2-thieno)-6-iodo-3-phenylamino-3,4-dihydro-quina-zolin-4-one (**24**), and 2-(2-thieno)-4-[4-

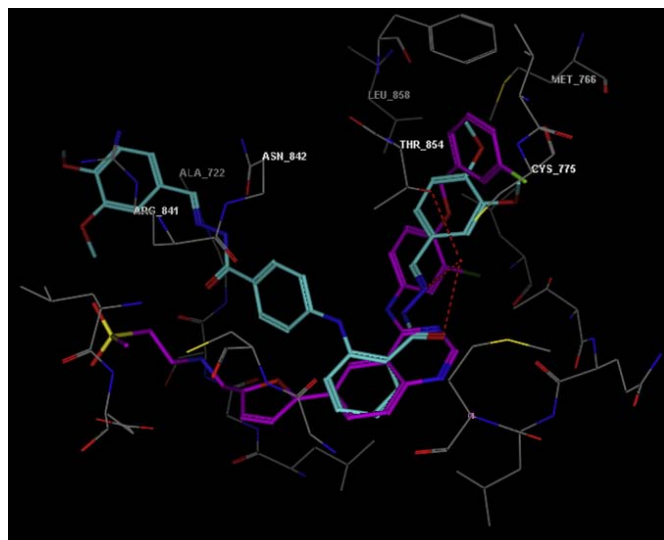
sulfonamidobenzylamino]-6-iodo-quinazoline (**25**), with  $GI_{50}$  values of 12.7, 10.3, 16.9 mM, respectively, proved to be the most active members in this study, as compared to the known drug 5-Fluorouracil.<sup>39</sup>



**Figure 9** Flexible alignments of the most active compounds (left panel): 23 (in red), 24 (in green) and 25 (in blue). Right panel showed the flexible alignments of the inactive compound 26 (in gray) and the active compounds 23 (in red), 24 (in green).

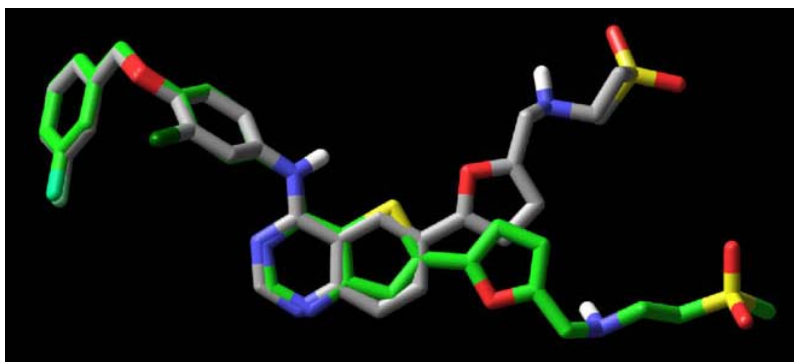
Sahar Mahmoud Abou-Seri discovered 2,4-bis substituted diphenylamines as anticancer agents and potential epidermal growth factor receptor tyrosine kinase inhibitors.<sup>40</sup>





**Figure 10** The superposition of lapatinib (purple) and compound **28** (blue) docked in the ATP binding site of EGFR PTK, showing perfect overlay of the quinazoline ring in lapatinib and 2-benzoyl moiety in **28**.

4-anilinoquinazoline core (**29**, **30**) and several analogs containing the thieno [3,2-d]pyrimidine core showed anti-proliferative activity with  $IC_{50}$  values less than 1  $\mu$ M against human tumor cells *in vitro*.<sup>41</sup>



**Figure 11** Overlay of **30** (green, Core A) model with crystal structure of **3** (gray) in EGFR.

The role of EGFR-related signal transduction pathways in cancer development explains the great effort made in the last 20 years to design therapeutic agents. A variety of inhibitors can be used to target EGFR, including MAbs (Monoclonal antibodies) that bind the extra-cellular domain of the receptor and compete with endogenous ligands; small-molecules TKIs (tyrosine kinase inhibitors) that act by binding the intracellular portion of the receptor. In all the data above mentioned concludes that for the potential inhibition of the EGFR we need the heterocyclic rings e.g. quinazoline, pyrimidines are the most effectively used.

## References

1. Brown, D. J.; Quinazolines, Supplement I; The Chemistry of Heterocyclic Compounds, Vol.55; John Wiley & Sons: Chichester, **1996**.
2. (a) Ravina, A. J. Organic Preparations and Procedures Int. **1973**, 5, 174.  
(b) Stevens, G. Diuretics; Academic Press Inc.: New York, **1963**; p12.  
(c) Hess, H. J.; Cronin, T. H.; Sciabine, A.; Antihypertensive 2-amino-4(3H)-Quinazolinones. *J. Med. Chem.* **1968**, 11, 130.  
(d) Leszkuszy, C.; Erdely, I.; Tardos, L. The Pharmacology of quinazolinone derivatives. *Acta. Physiol. Acad. Sci. Hung.* **1965**, 27, 81.  
(e) Gupta, C. M.; Hussain, S. T.; Bhaduri, A. P.; Khana, N. M.; Mukherjee, S. K. New potent blood sugar lowering compound. *Nature* 1969, **223**, 524.
3. Krishnan Suresh Kumar.; Swastika Ganguly.; Ravichandran Veerasamy.; Erik De Clercq.; Synthesis, antiviral activity and cytotoxicity evaluation of Schiff bases of some 2-phenyl quinazolin-4(3H)-ones. *European Journal of Medicinal Chemistry*, 45, **2010**, 5474-5479.
4. Shuren Zhu.; Joe Wang.; Gudise Chandrashekar.; Erika Smith.; Xianjun Liu.; Yongshen Zhang.; Synthesis and evaluation of 4-quinazolinone compounds as potential antimalarial agents. *European Journal of Medicinal Chemistry*, 45, **2010**, 3864-3869.
5. Said A. Said.; Abd El-Galil E. Amr.; Nermien M. Sabry.; Mohamed M. Abdalla.; Analgesic, anticonvulsant and anti-inflammatory activities of some synthesized benzodiazepine, triazolopyrimidine and bis-imide derivatives. *European Journal of Medicinal Chemistry*, 44, **2009**, 4787-4792.
6. Helen C.; Jackson.; Holger C.; Hansen, Anticonvulsant profile of the imidazoquinazolines NNC 14-0185 and NNC 14-0189 in rats and mice. *European Journal of Pharmacology*, 308, **1996**, 21-30.
7. Rondla Rohini.; P. Muralidhar Reddy.; Kanne Shanker.; Anren Huc.; Vadde Ravinder.; *European Journal of Medicinal Chemistry*, 45, **2010**, 1200-1205.
8. Soad M.; Abdel-Gawad.; Mohamed S.A.; El-Gaby.; Moustafa M. Ghorab.; Synthesis and antifungal activity of novel '3,4,5-triazolo[2,3-b]quinazolines, 'pyrazolo[2,3-b]quinazolines and pyrazolo[2',3':4,5]thiazolo[2,3-b]quinazolines *Il Farmaco*, 55, **2000**, 287-292.
9. Alaa A. El-Tombary.; Khadiga A. Ismail.; Novel triazolo[4,3-a]quinazolinone and bis-triazolo[4,3-a:4,3'-c]quinazolines: synthesis and antitoxoplasmosis effect. *Il Farmaco* 54, **1999**, 486-495.
10. Vishnu Ji Ram.; Farhanullah.; Brajendra K. Tripathi.; Arvind K. Srivastava.; Synthesis and antihyperglycemic activity of suitably functionalized 3H-quinazolin-4-ones. *Bioorganic & Medicinal Chemistry*, 11, **2003**, 2439-2444.
11. Yu-An Ding.; Tz-Chong Chou.; Antiplatelet actions of 2-[4-[1-(2-chlorophenyl)piperazinyl]] methyl-2,3-dihydroimidazo[1,2-c]quinazolin-5(6H)-one, *Thrombosis Research*, Vol. 77, No. 3, **1995**, 291-303,

12. R. K. Goel,; Vipin Kumar,; M. P. Mahajan,; Quinazolines revisited: search for novel anxiolytic and GABAergic agents. *Bioorganic & Medicinal Chemistry Letters*, 15, **2005**, 2145–2148.
13. Soad M.; Abdel-Gawad,; Mohamed S.A.; El-Gaby,; Moustafa M. Ghorab,;. Synthesis and antifungal activity of novel pyrazolo[4,5-*b*]thiazolo[2,3-*b*]quinazolines, pyrazolo[4,5-*b*]thiazolo[2,3-*b*]quinazolines and pyrazolo[2',3':4,5]thiazolo[2,3-*b*]quinazolines. *Il Farmaco*, 55, **2000**, 287–292.
14. Veerachamy Alagarsamy,; and Urvishbhai S. Pathak,; Synthesis and antihypertensive activity of novel 3-benzyl-2-substituted-3*H*-[1,2,4]triazolo[5,1-*b*]quinazolin-9-ones. *Bioorganic & Medicinal Chemistry*, 15, **2007**, 3457–3462.
15. Seymore, L.; Novel anti-cancer agents in development: exciting prospects and new challenges. *Cancer Treat. Rev.* 25, **1999**, 301.
16. A. Partanen,; Epidermal growth factor and transforming growth factor- $\alpha$  in the development of Epithelialmesenchymal organs of the mouse. *Curr. Top. Dev. Biol.*, 24 **1990**, 31–55.
17. E. Adamson,; Developmental activities of the epidermal growth factor receptor. *Curr. Top. Dev. Biol.* **1990**, 1–29.
18. N. Normanno,; A. De Luca,; C. Bianco,; L. Strizzi, M. Mancino,; M.R. Maiello,; et al., Epidermal growth factor receptor (EGFR) signaling in cancer, *Gene*, 366, **2006**, 2–16.
19. Y. Yarden,; The EGFR family and its ligands in human cancer. Signalling mechanisms and therapeutic opportunities. *Eur. J. Cancer*, 37, (Suppl. 4), **2001**, S3–S8.
20. Adjei, A. A. J. *Natl. Cancer Inst.* **2001**, 93, 1062.
21. Yarden, Y.; Sliwkowski, M. X. Untangling the ErbB signalling network *Mol. Cell. Biol.* **2001**, 2, 127.
22. Hynes, N. E.; Stern, D. F. *Biochim. Biophys. Acta* **1994**, 1198, 165.
23. Slamon, D. J.; Clark, G. M.; Wong, S. G.; Levin, W. J.; Ullrich, A.; McGuire, W. L.; Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science*, **1987**, 235, 177.
24. Slamon, D. J.; Godolphin, W.; Jones, L. A. Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. *Science*, **1989**, 244, 707.
25. Harold Mastalerz, Ming Chang,; Ping Chen,; Brian E. Fink,; 5-((4-Aminopiperidin-1-yl)methyl)pyrrolotriazine dual inhibitors of EGFR and HER2 protein tyrosine kinases. *Bioorganic & Medicinal Chemistry Letters* 17, **2007**, 4947–4954.
26. Peng-Cheng Lv, Chang-Fang Zhou, Jin Chen, Peng-Gang Liu, Kai-Rui Wang, Wen-Jun Mao, Huan-Qiu Li, Ying Yang, Jing Xiong, Hai-Liang Zhu, Design, synthesis and biological evaluation of thiazolidinone derivatives as potential EGFR and HER-2 kinase inhibitors. *Bioorganic & Medicinal Chemistry*, 18, **2010**, 314–319.
27. Robert D. Hubbard,; Scott H. Dickerson,; Holly K. Emerson,; Robert J. Griffin,; Michael J. Reno,; Keith R. Hornberger,; David W. Rusnak,; Edgar R. Wood,; David E. Uehling,; Alex G. Waterson,; Dual EGFR/ErbB-2 inhibitors from novel



- pyrrolidinyl-acetylenicthieno[3,2-d]pyrimidines. *Bioorganic & Medicinal Chemistry Letters* 18, **2008**, 5738–5740.
28. Allan Wissner,; Heidi L. Fraser,; Charles L. Ingalls,; Russell G. Dushin,; M. Brawner Floyd,; Kinwang Cheung,; Thomas Nittoli,; Malini R. Ravi,; Xingzhi Tan and Frank Loganzo,; Dual irreversible kinase inhibitors: Quinazoline-based inhibitors incorporating two independent reactive centers with each targeting different cysteine residues in the kinase domains of EGFR and VEGFR-2. *Bioorganic & Medicinal Chemistry*, 15, **2007**, 3635–3648.
  29. Harold Mastalerz,; Ming Chang,; Ping Chen,; 5-((4-Aminopiperidin-1-yl)methyl)pyrrolotriazine dual inhibitors of EGFR and HER2 protein tyrosine kinases. *Bioorganic & Medicinal Chemistry Letters*, 17, **2007**, 2036–2042.
  30. Celia Fernandes,; Cristina Oliveira,; Lurdes Gano,; Athanasia Bourkoula,; Ioannis Pirmettis,; and Isabel Santos,; Radioiodination of new EGFR inhibitors as potential SPECT agents for molecular imaging of breast cancer, *Bioorganic & Medicinal Chemistry*, 15, **2007**, 3974–3980.
  31. Guozhang Xu,; Lily Lee Searle,; Terry V. Hughes,; Amanda K. Beck,; Peter J. Connolly,; Discovery of novel 4-amino-6-arylaminopyrimidine-5-carbaldehyde oximes as dual inhibitors of EGFR and ErbB-2 protein tyrosine kinases. *Bioorganic & Medicinal Chemistry Letters*, 18, **2008**, 3495–3499.
  32. Guozhang Xu,; Marta C. Abad,; Peter J. Connolly,; Michael P. Neeper,; 4-Amino-6-aryl-amino-pyrimidine-5-carbaldehyde hydrazones as potent ErbB-2/EGFR dual kinase inhibitors, *Bioorganic & Medicinal Chemistry Letters*, 18, **2008**, 4615–4619.
  33. Caterina Carmi,; Andrea Cavazzoni,; Valentina Zuliani,; 5-Benzylidene-hydantoins as new EGFR inhibitors with antiproliferative activity. *Bioorganic & Medicinal Chemistry Letters*, 16, **2006**, 4021–4025.
  34. Alex G. Waterson,; Kirk L. Stevens,; Michael J. Reno,; Alkynyl pyrimidines as dual EGFR/ErbB2 kinase inhibitors. *Bioorganic & Medicinal Chemistry Letters*, 16, **2006**, 2419–2422.
  35. Khaled Abouzid,; Samia Shouman,; Design, synthesis and in vitro antitumor activity of 4-aminoquinoline and 4-aminoquinazoline derivatives targeting EGFR tyrosine kinase. *Bioorganic & Medicinal Chemistry*, 16, **2008**, 7543–7551.
  36. Toru Asano,; Tomohiro Yoshikawa,; Hiroyuki Nakamura,; Yoshimasa Ueharac and Yoshinori Yamamoto,; Synthesis and biological evaluation of benzamides and benzamidines: structural requirement of a pyrimidine ring for inhibition of EGFR tyrosine kinase. *Bioorganic & Medicinal Chemistry Letters*, 14, **2004**, 2299–2302.
  37. Hyun Seung Ban,; Yuko Tanaka,; Wataru Nabeyama,; Masako Hatori,; Hiroyuki Nakamura,; Enhancement of EGFR tyrosine kinase inhibition by C–C multiple bonds-containing anilinoquinazolines. *Bioorganic & Medicinal Chemistry*, 18, **2010**, 870–879.
  38. Robert D. Hubbard, Nwe Y. Bamaung, Steve D. Fidanze, Scott A. Erickson, Fabio Palazzo,; Julie L. Wilsbacher,; Qian Zhang,; Lora A. Tucker,; Xiaoming Hu, Peter Kovar, Development of multitargeted inhibitors of both the insulin-like growth factor receptor (IGF-IR) and members of the epidermal growth factor

- family of receptor tyrosine kinases. *Bioorganic & Medicinal Chemistry Letters*, 19, **2009**, 1718–1721.
39. Abdulrahman M. Al-Obaid,; Sami G. Abdel-Hamide,; Hassan A. El-Kashef,; Alaa A.-M. Abdel-Aziz,; Adel S. El-Azab,; Hamad A. Al-Khamees,; Hussein I. El-Subbagh,; Substituted quinazolines, part 3. Synthesis, in vitro antitumor activity and molecular modeling study of certain 2-thieno-4(3H)-quinazolinone analogs. *European Journal of Medicinal Chemistry*, 44, **2009**, 2379–2391.
  40. Sahar Mahmoud Abou-Seri,; Synthesis and biological evaluation of novel 2,4-bis substituted diphenylamines as anticancer agents and potential epidermal growth factor receptor tyrosine kinase inhibitors. *European Journal of Medicinal Chemistry*, 45, **2010**, 4113-4121.
  41. Tara R. Rheault,; Thomas R. Caferro,; Thienopyrimidine-based dual EGFR/ErbB-2 inhibitors. *Bioorganic & Medicinal Chemistry Letters*, 19, **2009**, 817–820.