Bioorganic & Medicinal Chemistry Letters 23 (2013) 3935–3941

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Design, synthesis and biological evaluation of 2-mercapto-3-phenethylquinazoline bearing anilide fragments as potential antitumor agents: Molecular docking study

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ARTICLE INFO

Article history:
Received 9 February 2013
Revised 17 April 2013
Accepted 22 April 2013
Available online 29 April 2013

Keywords:
Synthesis
Quinazoline
In-vitro antitumor evaluation
NCI
Molecular docking

ABSTRACT

A novel series of 2-(3-phenethyl-4(3*H*)quinazolin-2-ylthio)-N-substituted anilide and substituted phenyl 2-(3-phenethyl-4(3*H*) quinazolin-2-ylthio)acetate were designed, synthesized and evaluated for their in-vitro antitumor activity. Compound **15** possessed remarkable broad-spectrum antitumor activity which almost sevenfold more active than the known drug 5-FU with GI_{50} values of 3.16 and 22.60 μM, respectively. Compound **15** exhibited remarkable growth inhibitory activity pattern against renal cancer (GI_{50} = 1.77 μM), colon cancer (GI_{50} = 2.02 μM), non-small cell lung cancer (GI_{50} = 2.04 μM), breast cancer (GI_{50} = 2.77 μM), ovarian cancer (GI_{50} = 2.55 μM) and melanoma cancer (GI_{50} = 3.30 μM). Docking study was performed for compound **15** into ATP binding site of EGFR-TK which showed similar binding mode to erlotinib.

Cancer is continuing to be a major health problem in developed as well as undeveloped countries.[1–5] The great cancer incidence worldwide increases the search for new, safer and efficient anticancer agents, aiming the prevention or the cure of this illness. Although many classes of drugs are being used for the treatment of cancer, the need for more potent selective antitumor agents is still not precluded. Quinazolines are frequently used in medicine because of their wide spectrum of biological activities.[6–23] It is well known that quinazoline derivatives are potent inhibitors of epidermal growth factor receptor (EGFR).[24–36] The epidermal growth factor receptor (EGFR) is cellular trans-membrane tyrosine kinases that are over-expressed in a significant number of human tumors (e.g., breast, ovarian, colon, renal, and prostate).[37–40] Overexpression of EGFR family receptors have always been observed in these tumors, approximately in 60% of all tumors. A number of small molecule EGFR kinase inhibitors have been evaluated in cancer clinical trials.[24–40] For example, anilinoquinazoline-containing compounds erlotinib (**A**) (TarcevaTM),[31] gefitinib (**B**) (IressaTM),[28–40] lapatinib (**C**) (TykerbTM, also known as GW-572016) and Vandetanib (ZactimaTM) were recently approved for the treatment of breast cancer and non-small-cell lung cancer.[32–36] Moreover a series of salicylanilides (**D**) were synthesized and determined their inhibitory activity against tyrosine kinases (Fig. 1), some of them indeed proved to be potent and selective EGFR tyrosine kinase inhibitors (Fig. 1).[41] We have recently studied a series of 4-substituted quinazoline derivatives which were evaluated for their antitumor activities (**E**) (Fig. 1).[20,21] Owing to our continues studies on quinazoline derivatives as an attractive candidates as antitumor agents, we have designed a number of new quinazoline derivatives containing anilide fragments[41] (**F**) and biologically evaluated there in-vitro antitumor activities (Fig. 1). In the present study, the substitution pattern at the 2-substituted quinazoline pharmacophores was selected based on different electronic environment which would affect the lipophilicity, and hence the activity of the target molecules. The objective of forming these hybrids is an attempt to attain an active antitumor agent with potentiated activity and selectivity toward cancerous cells. Molecular docking methodology was used to identify the structural features required for the antitumor properties of these new series. These models are necessary to obtain a consistent and more precise picture of the biological active molecules at the atomic level and furthermore, provide new insights that can be used to design novel therapeutic agents.[21,42–49] Moreover, the results of this molecular docking could support the postulation

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http://dx.doi.org/10.1016/j.bmcl.2013.04.056

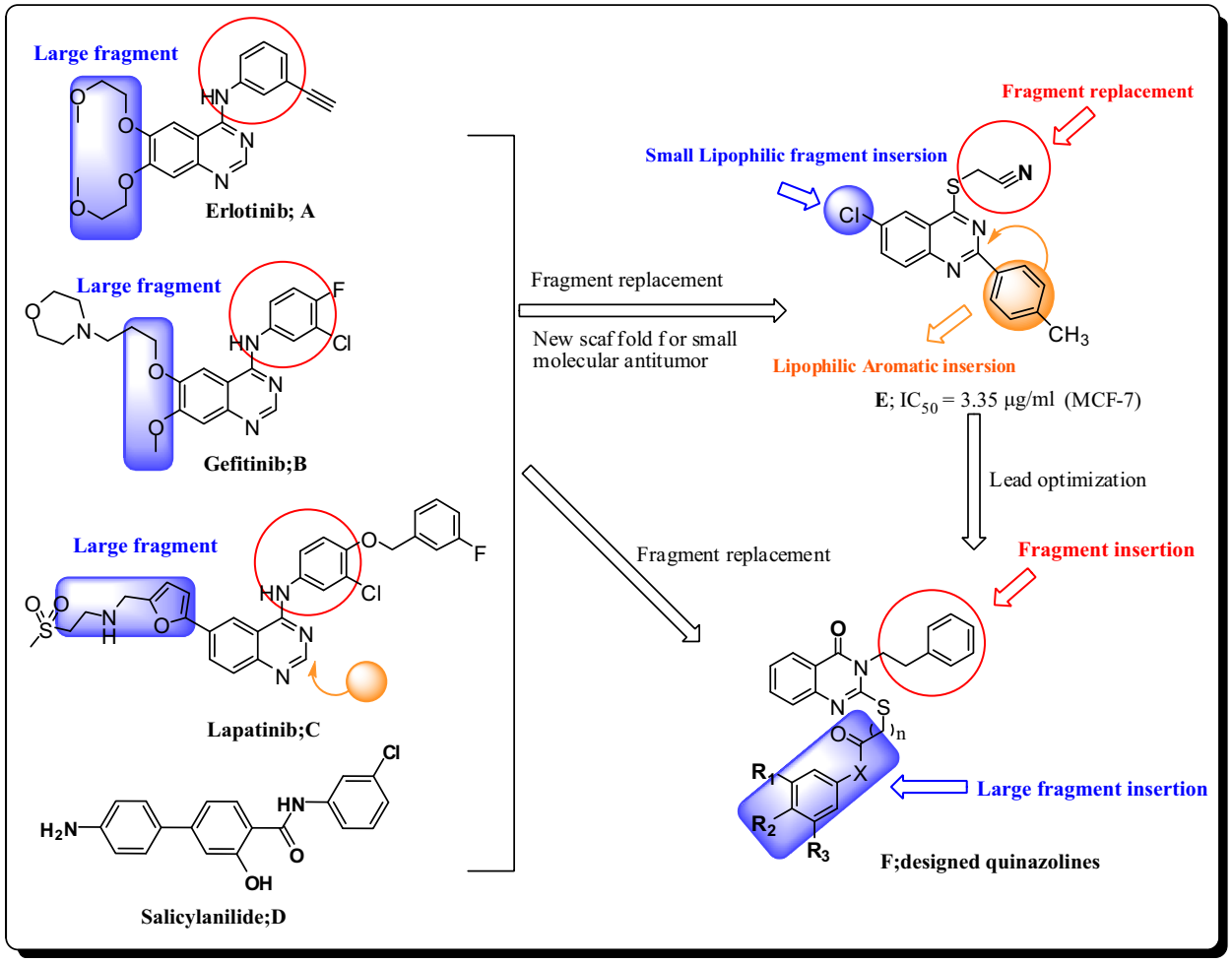

Figure 1. Reported and proposed quinazoline derivatives as antitumor.

that our active compounds may act on the same enzyme target where EGFR inhibitor acts confirming the molecular design of the reported class of antitumor agents.

Synthesis of 2-mercapto-3-phenethylquinazolin-4(3*H*)-one (**1**) as a key intermediate was achieved by the reaction of anthranilic acid with 2-phenylethyl isothiocyanate in absolute ethanol in 78% yield. The reaction of compound **1** with various 2-chloro-N-substituted phenylacetamide and/or substituted phenyl-2-chloroacetate in anhydrous acetone in the presence of potassium carbonate gave 2-(quinazolin-2-ylthio)-N-substituted anilide and/or 2-(quinazolin-2-ylthio) substituted acetate derivatives **2**–**22** in 84–95% yield (Scheme 1).

The synthesized compounds **1**–**22** were subjected to the National Cancer Institute (NCI) in-vitro disease-oriented human cells screening panel assay for in-vitro antitumor activity. A single dose (10 µM) of the test compounds were used in the full NCI 60 cell lines panel assay which includes nine tumor subpanels namely; Leukemia, Non-small cell lung, Colon, CNS, Melanoma, Ovarian, Renal, Prostate, and Breast cancer cells.[50–52] The data reported as mean-graph of the percent growth of the treated cells, and presented as percentage growth inhibition (GI %) caused by the test compounds (Table 1).

Concerning broad spectrum antitumor activity; the results of this study demonstrated that compounds **15**, **16** and **19** are the most remarkable broad spectrum antitumor agents. Close examination of the data presented in Table 1, revealed that compound **15** are the most active member of this study showing effectiveness toward numerous cell lines belong to different tumor subpanels. Consequently, compound **15** was carried over and tested against a panel of 60 different tumor cell lines at a 5-log dose range.[50–52] Three response parameters, GI_{50}, TGI, and LC_{50} were calculated for each cell line, using the known drug 5-Fluorouracil (5-FU) as a positive control. Compound **15** exhibited remarkable growth inhibitory activity pattern against renal cancer (GI_{50} = 1.77 µM), colon cancer (GI_{50} = 2.02 µM), non-small cell lung cancer (GI_{50} = 2.04 µM), breast cancer (GI_{50} = 2.77 µM), ovarian cancer (GI_{50} = 2.55 µM) and melanoma cancer (GI_{50} = 3.30 µM). Compound **15** is almost sevenfold more active than the known drug 5-FU with GI_{50} values of 3.16 and 22.60 µM, respectively (Table 2).

Regarding the activity toward individual cell lines; Non-small cell lung; compounds **8**, **15** and **16** proved to be susceptible to the HOP-62 cancer cell line with GI values of 52%, 91% and 49% respectively. NCI-H522 cell line proved to be selectively sensitive to compounds **10**, **15**, **16** and **19** with GI values of 51, lethal, 85% and 52%, respectively. In addition, compound **15** showed strong activity against A549/ATCC, NCI-H226, NCI-H23, NCI-H322M and NCI-H460 cancer cell lines in 76%, lethal, 74%, 73% and lethal respectively. Respecting colon cancer; compound **15** verified strong selectively sensitive to colon HCT-116, HCC-2998, COLO 205, HT29, KM12 and SW-620 cancer cell lines in lethal, 71%, 66%, 85%, 93% and 52%, respectively. Concerning CNS cancer; Compounds **5**, **8**, **15** and **16** showed GI values of 63%, 72%, lethal and 74% to SNB-75 cancer cell line respectively, while compounds **15** and **19** illustrated potent activity against SF-539 cancer cell line