Bioorganic Chemistry 115 (2021) 105234

Contents lists available at ScienceDirect

Bioorganic Chemistry

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

Novel, selective acrylamide linked quinazolines for the treatment of double mutant EGFR-L858R/T790M Non-Small-Cell lung cancer (NSCLC)

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ARTICLE INFO

Keyword:
Non Small-Cell Lung Cancer (NSCLC)
EGFR L858R/T790M
Acrylamide linked Quinazolines
MD simulation

ABSTRACT

T790M mutation is the most common mechanism of acquired resistance to first-generation epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs). To overcome this resistance, 4-anilinoquinazoline-based irreversible inhibitors afatinib, dacomitinib has been developed. However, the clinical application of these irreversible inhibitors is limited due to its narrow selectivity against L858R/T790M mutant EGFR. In an attempt to develop potent and selective EGFR T790M inhibitors, we have designed and synthesized two series of novel acrylamide linked quinazolines. Among them, compounds **2i** (IC_{50} 0.171 μM) and **11h** (IC_{50} 0.159 μM) were identified as potent compounds, which displayed selective and potent anti-proliferative activity on gefitinib-resistant cell line NCI-H1975 as compared to the gefitinib and WZ4002 in cellular assay. Furthermore, a molecular dynamic simulation of **11h** was carried out to assess the stability to form a complex with the L858R/T790M EGFR Kinase domain, which demonstrated that complex was stable for the 100 ns and form strong crucial covalent binding contacts with the thiol group of Cys797 residue. Finally, satisfactory *in silico* pharmacokinetics properties of **2i, 11h** and **11i** compounds were predicted. The synthesized compounds were also evaluated for *in vitro* cytotoxic activity/hepatotoxicity against HepG2 cell line through MTT assay. The results revealed that compounds exhibited lower cytotoxicity to HepG2 cells.

1. Introduction

Non-small-cell lung cancer (NSCLC) accounts for about 80–85% of lung cancer with a 5-year survival rate of less than 20%, which is the most frequent reason for cancer-related deaths worldwide [1-4]. Epidermal growth factor receptor (EGFR) plays a crucial role in cell proliferation, survival, migration, adhesion, and differentiation and is overexpression in various solid tumors. Therefore, EGFR is one of the most valuable clinically validated drug targets for anti-cancer therapies, especially for NSCLC treatment [5-7].

In NSCLC, EGFR mutations generally manifest EGFR overexpression or 'Classic Mutation' in the frame of exon 19 deletions (delE746-A750), and predominant single point mutation in exon 21, L858R, accounts for 90% of the activating mutations [8,9]. USFDA approved first-generation EGFR tyrosine kinase inhibitors (TKIs), namely gefitinib and erlotinib, for EGFR-activating mutations. However, acquired drug resistance mostly occurs after about 12 months of gefitinib or erlotinib treatment [10-12]. A secondary Thr790 to Met790 mutation (T790M) in the gatekeeper position of the EGFR catalytic domain often occurred, which is approximately 50% of the clinically acquired drug resistance in NSCLC. Mutated bulky methionine moiety sterically blocks the binding of these reversible inhibitors and disrupt the formation of a water-mediated hydrogen bond among the inhibitors and the T790M of EGFR (Fig. 1) [13].

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https://doi.org/10.1016/j.bioorg.2021.105234
Received 1 June 2021; Received in revised form 21 June 2021; Accepted 29 July 2021
Available online 8 August 2021

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BIOORGANIC CHEMISTRY

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ISSN / eISSN: 0045-2068 / 1090-2120

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