Bioorganic & Medicinal Chemistry Letters 27 (2017) 4309–4313

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Quinazoline-1-deoxynojirimycin hybrids as high active dual inhibitors of EGFR and α-glucosidase

Yaling Zhang, Hongliang Gao, Renjie Liu, Juan Liu, Li Chen, Xiabing Li *, Lijun Zhao, Wei Wang, Baolin Li *

Key Laboratory of the Ministry of Education for Medicinal Resources and Natural Pharmaceutical Chemistry, National Engineering Laboratory for Resource Development of Endangered Crude Drugs in Northwest of China, School of Chemistry & Chemical Engineering, Shaanxi Normal University, Xi'an 710062, PR China

ARTICLE INFO

Article history:
Received 18 June 2017
Revised 15 August 2017
Accepted 16 August 2017
Available online 18 August 2017

Keywords:
Quinazoline
1-Deoxynojirimycin
Hybrids
Epidermal growth factor receptor (EGFR)
α-Glucosidase
Enzyme inhibitors

ABSTRACT

A series of novel quinazoline-1-deoxynojirimycin hybrids were designed, synthesized and evaluated for their inhibitory activities against two drug target enzymes, epidermal growth factor receptor (EGFR) tyrosine kinase and α-glucosidase. Some synthesized compounds exhibited significantly inhibitory activities against the tested enzymes. Comparing with reference compounds gefitinib and lapatinib, compounds **7d**, **8d**, **9b** and **9d** showed higher inhibitory activities against EGFR (IC_{50}: 1.79–10.71 nM). Meanwhile the inhibitory activities of **7d**, **8d** and **9c** against α-glucosidase (IC_{50} = 0.14, 0.09 and 0.25 μM, respectively) were obvious higher than that of miglitol (IC_{50} = 2.43 μM), a clinical using α-glucosidase inhibitor. Interestingly, compound **9d** as a dual inhibitor showed high inhibitory activity to $EGFR^{wt}$ tyrosine kinase (IC_{50} = 1.79 nM), also to α-glucosidase (IC_{50} = 0.39 μM). The work could be very useful starting point for developing a new series of enzyme inhibitors targeting EGFR and/or α-glucosidase.

Cancer and diabetes are common diseases with tremendous impact on human health. People with diabetes are at significantly higher risk for many forms of cancer.[1,2] Diabetes is typically divided into two major subtypes, type 1 and type 2 diabetes.[1,3,4] Type 2 diabetes, previously referred to as "noninsulin-dependent diabetes" or "adult-onset diabetes", accounts for 90–95% of all diabetes,[4] and there is no specific treatment algorithm that is appropriate for all patients.[5] Pharmacological agents, such as metformin,[6] orlistat,[7] acarbose, voglibose and miglitol (α-glucosidase inhibitors),[8,9] pioglitazone, rosiglitazone and troglitazone (thiazolidinediones),[10] have each been shown to decrease incident diabetes to various degrees.[11] Likewise, cancer is typically classified by its anatomic origin, of which there are over 50 types, e.g., lymphoma, leukemia, lung and breast cancer etc.[1] Lung cancers are malignant tumors with poor prognoses and ranked as the top cause of cancer-related deaths in the world.[12,13] In 2014, approximately 1.5 million new lung cancer cases were diagnosed globally, and 80% of the patients were non-small cell lung cancer (NSCLC),[14,15] which was a major cause of death from cancer.[15,16] Despite the availability of the conventional treatments, including surgery, radiotherapy, and chemotherapy, there was still tremendous mortality, which can be due to two reasons: first, a high proportion of lung cancer patients are only diagnosed at an advanced stage, and second, a large population of patients manifests drug resistant, and local or distant metastasis.[17] Along with the wide recognition of genomic alterations such as epidermal growth factor receptor (EGFR) mutations, EGFR tyrosine kinase inhibitors (TKI) known as adjuvant therapy were widely used in cancer patients with an activating EGFR mutation, and its high efficacy could potentially improve the cure rate.[15] EGFR, also known as ErbB1/HER1, a member of the ERBB family of receptor tyrosine kinases (TK),[18–20] has been found to be amplified in NSCLC,[21] also, it showed a significantly higher expression level in squamous cell carcinoma with diabetics versus without diabetics.[22]

Cancer and diabetes are diagnosed within the same individual more frequently than would be expected by chance.[1] Only in the year of 2005, 321 incident lung cancer were diagnosed in 114,915 diabetes patients in the Taiwanese general population.[23] In 2002–2009, there were 30 diabetes patients in 159 patients with clinical stage III NSCLC in Japan.[24] From the Veterans Integrated Services Network 16 (VISN 16) data warehouse, there were 87,678 male patients diagnosed to have diabetes, and of them, 1371 had lung cancer.[25] Hence, great interest is currently focused on the development of new series of compounds that can not only promote the regression rate of type 2 diabetes, but also improve the cure rate of cancer. Regression of type 2 diabetes has been confirmed during treatment of chronic myeloid leukemia with imatinib, a known inhibitor of the c-kit and platelet-derived growth-factor receptor (PDGFR) tyrosine kinases.[26,27] Especially,

* Corresponding authors.
E-mail addresses: xiabingli@snnu.edu.cn (X. Li), baolinli@snnu.edu.cn (B. Li).

http://dx.doi.org/10.1016/j.bmcl.2017.08.035
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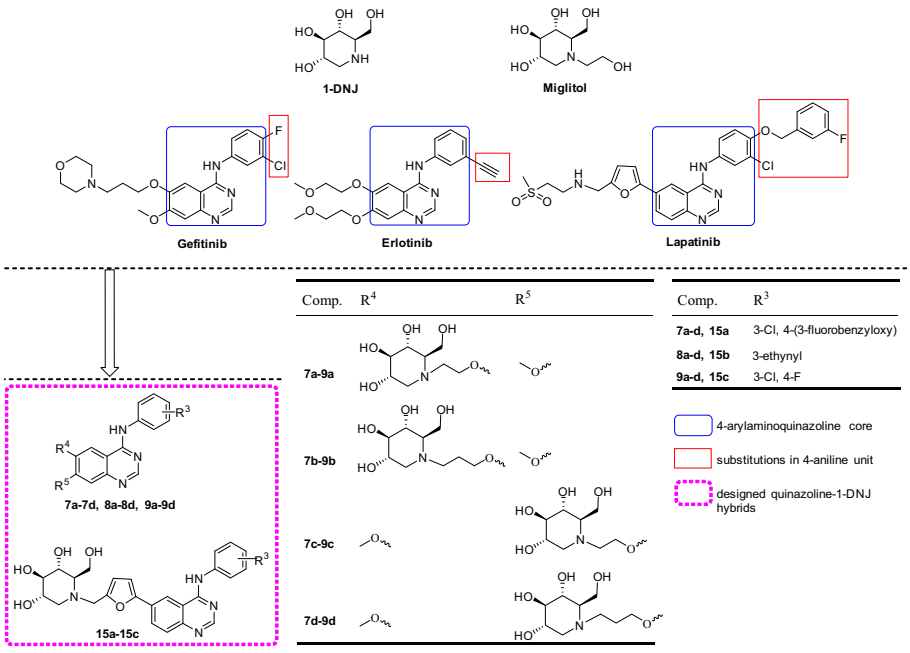
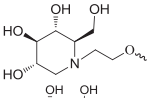
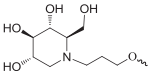
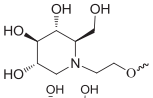
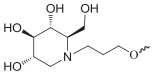
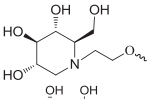
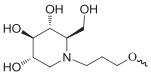
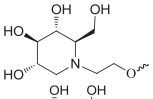
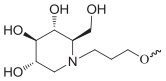
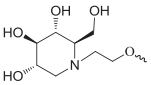
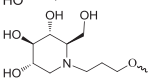
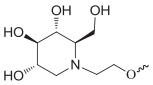


Fig. 1. Structures of enzyme inhibitors and design of novel quinazoline-1-DNJ hybrids.

Table 1
Inhibitory activities of synthesized quinazoline-1-DNJ hybrids against $EGFR^{wt}$ and α-glucosidase enzyme *in vitro*.[a]

Comp.	R_3	R_4	R_5	Inhibition Rate (%)[b] (against $EGFR^{wt}$, comp. in 50 nM)	IC_{50} (nM)	IC_{50} (μM)
					$EGFR^{wt}$	α-Glucosidase
Gefitinib				82.48 ± 2.90	3.22 ± 1.45	>100
Lapatinib				73.32 ± 4.68	27.06 ± 3.77	N.D.
7a	3-Cl, 4-(3-fluorobenzyloxy)			66.55 ± 0.50	N.D.	64.09 ± 6.56
7b	3-Cl, 4-(3-fluorobenzyloxy)			74.87 ± 3.02	N.D.	21.23 ± 4.54
7c	3-Cl, 4-(3-fluorobenzyloxy)			N.D.	N.D.	N.D.
7d	3-Cl, 4-(3-fluorobenzyloxy)			78.24 ± 5.20	4.53 ± 0.10	0.14 ± 0.03
8a	3-ethynyl			56.42 ± 5.31	N.D.	7.18 ± 0.54
8b	3-ethynyl			79.64 ± 0.40	N.D.	6.19 ± 0.56
8c	3-ethynyl			53.45 ± 5.91	N.D.	6.25 ± 1.04
8d	3-ethynyl			83.18 ± 2.62	4.87 ± 2.80	0.09 ± 0.01
9a	3-Cl, 4-F			65.20 ± 0.32	N.D.	8.40 ± 0.57
9b	3-Cl, 4-F			83.55 ± 2.16	10.71 ± 1.32	4.34 ± 0.53
9c	3-Cl, 4-F			53.70 ± 7.52	N.D.	0.25 ± 0.07