Available online at www.sciencedirect.com
ScienceDirect
Bioorganic & Medicinal Chemistry Letters
Bioorganic & Medicinal Chemistry Letters 17 (2007) 5978–5982

Synthesis and structure–activity relationship of 4-(2-aryl-cyclopropylamino)-quinoline-3-carbonitriles as EGFR tyrosine kinase inhibitors

Madhavi Pannala,[a] Sunil Kher,[a] Norma Wilson,[a] John Gaudette,[a] Ila Sircar,[a] Shao-Hui Zhang,[b] Alexei Bakhirev,[b] Guang Yang,[b] Phoebe Yuen,[b] Frank Gorcsan,[b] Naoki Sakurai,[b] Miguel Barbosa[b] and Jie-Fei Cheng[a,*]

[a]*Department of Chemistry, Tanabe Research Laboratories USA, Inc., 4540 Towne Centre Court, San Diego, CA 92121, USA*
[b]*Department of Biology, Tanabe Research Laboratories USA, Inc., 4540 Towne Centre Court, San Diego, CA 92121, USA*

Received 22 June 2007; revised 17 July 2007; accepted 18 July 2007
Available online 21 August 2007

Abstract—Synthesis and structure–activity relationship of a series of 4-(2-aryl-cyclopropylamino)-quinoline-3-carbonitrile derivatives as EGFR inhibitors is described. Compounds **29** and **30** showed potent in vitro inhibitory activity in the enzymatic assay as well as in the functional cellular assay. They are moderately selective against other types of tyrosine kinases.

The epidermal growth factor receptor (EGFR) is a transmembrane glycoprotein that belongs to the erbB family of closely related cell membrane receptors that includes EGFR (erbB-1 or HER1), erbB-2 (HER2), erbB-3 (HER3), and erbB-4 (HER4). It is a 170 kDa protein composed of three major functional domains: an extracellular ligand-binding domain, a hydrophobic transmembrane domain, and a cytoplasmic tyrosine kinase domain. Binding of ligands to EGFR leads to autophosphorylation of the receptor tyrosine kinase and subsequent activation of signal transduction pathways. EGFR plays an important role in initiating the signaling that directs the behavior of epithelial cells and tumors of epithelial cell origin.[1] EGFR is highly expressed in many human cancers (e.g., bladder, cervical, head and neck, and ovarian) and has been found to be associated with poor prognosis and correlated with decreased survival. EGFR is overexpressed in 40%–80% of non-small-cell lung cancers (NSCLC), depending on histology.[2a] Its pivotal role in governing cellular proliferation, survival, and metastasis makes EGFR an attractive molecular target, especially for the treatment of solid tumors.[3]

Small molecule EGFR inhibitors have been shown to be effective antitumor agents. Iressa (**1**) and Tarceva (**2**), two closely related quinazoline-based EGFR inhibitors, have efficacy against several types of cancers in human clinical trials and were approved for the treatment of NSCLC and colon cancers. Irreversible EGFR inhibitors such as EKB569 (**3**) and a number of small molecule EGFR inhibitors are also undergoing clinical trials.[2b] In addition, several antibodies (e.g., cetuximab, panitumumab, matuzumab, and nimotuzumab that bind to the extracellular domain of the EGFR and antisense oligonucleotides against EGFR receptors are either approved or undergoing clinical trials for the treatment of cancers. Most EGFR inhibitors such as **1**–**3** possess an anilinyl group at the C-4 position of the quinazoline or quinoline-3-carbonitrile core structures. Herein, we describe the synthesis and structure–activity relationship of a new series of quinoline-3-carbonitrile derivatives (**4**) as potent EGFR inhibitors. These compounds possess an arylcyclopropylamino group at the C-4 position of the quinoline-3-carbonitrile core structure. Some of the compounds showed excellent EGFR inhibitory activity both in enzymatic and cell-based assays (Fig. 1).

6,7-Dialkoxyquinoline-3-carbonitrile derivatives **7** were prepared as shown in Scheme 1. Thus, 4-chloro-7-hydroxy-6-methoxy-quinoline-3-carbonitrile (**5**)[4] underwent Mitsunobu reaction with a series of substituted

Keywords: EGFR inhibitor; Quinoline-3-carbonitrile.
* Corresponding author. Tel.: +1 858 622 7029; fax: +1 858 558 9383; e-mail: jcheng@trlusa.com

0960-894X/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2007.07.071

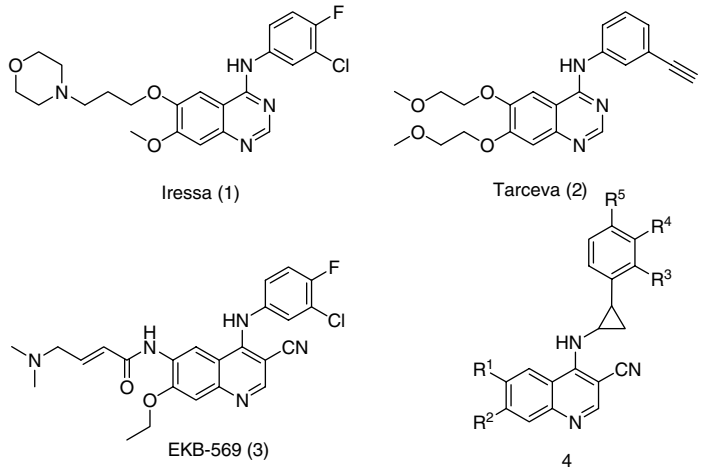
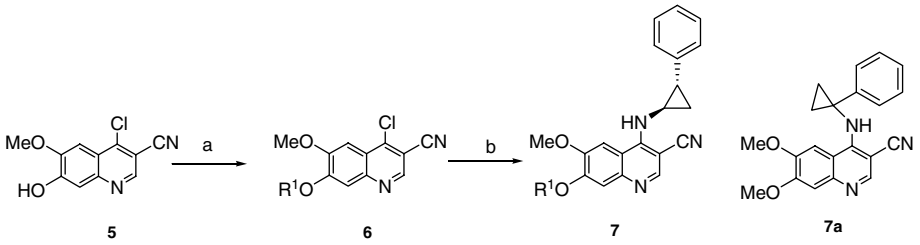
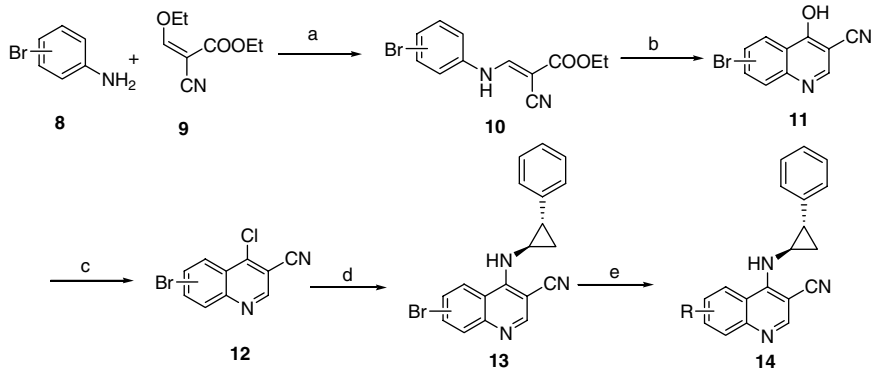


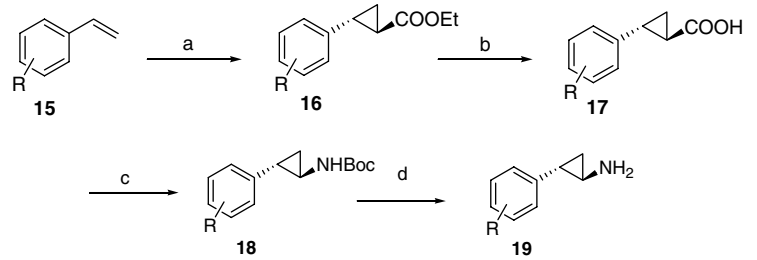
Figure 1. EGFR inhibitors.



Scheme 1. Reagents and conditions: (a) R^1OH, PPh_3P, DIAD DCM, 0 °C, rt; (b) (±)-2-*trans*-phenylcyclopropyl amine, 2-ethoxyethanol, pyridine hydrochloride, reflux, 3 h.



Scheme 2. Reagents and conditions: (a) Toluene, reflux, 2 h; (b) Dowtherm A, reflux, 10 h; (c) Oxalyl chloride, DCM, rt, 48 h; (d) (±)-2-*trans*-phenylcyclopropylamine, 2-ethoxyethanol, pyridine hydrochloride, reflux, 4 h; (d) $RB(OH)_2$, $Pd(PPh_3)_4$, aq K_2CO_3; DME, reflux 12 h.



Scheme 3. Reagents and conditions: (a) Ethyl diazoacetate, Cuacac, 40 °C, 12 h; (b) 5 N NaOH, dioxane, reflux, 1 h; (c) DPPA, Et_3N, cyclohexane, *t*-BuOH, 70 °C, 18 h, $(Boc)_2O$, 3 h; (d) 1 N HCl in ether, 6 h.