Bioorganic & Medicinal Chemistry Letters 24 (2014) 5666–5670

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Synthesis and biological evaluation of 4-oxoquinoline-3-carboxamides derivatives as potent anti-fibrosis agents

Jun Zhu [a,†], Lin He [a,†], Liang Ma [a,†], Zhe Wei [a], Jiqiang He [a], Zhuang Yang [b], Yuzhi Pu [a], Dong Cao [a], Yuzhe Wu [b], Mingli Xiang [a], Aihua Peng [a], Yuquan Wei [a], Lijuan Chen [a,*]

[a] State Key Laboratory of Biotherapy and Cancer Center/Collaborative Innovation Center for Biotherapy, West China Hospital, West China Medical School, Sichuan University, Chengdu, Sichuan 610041, PR China
[b] College of Chemistry, Sichuan University, Chengdu, Sichuan 610064, PR China

ARTICLE INFO

Article history:
Received 3 September 2014
Revised 9 October 2014
Accepted 22 October 2014
Available online 29 October 2014

Keywords:
4-Oxoquinoline-3-carboxamides
Pulmonary fibrosis
TGF-β1
Collagen accumulation
TNF-α
Anti-inflammatory

ABSTRACT

Thirty-one 4-oxoquinoline-3-carboxamides derivatives were synthesized and evaluated for their anti-fibrotic activities by the inhibition of TGF-β1-induced total collagen accumulation and anti-inflammatory activities by the inhibition of LPS-stimulated TNF-α production. Among them, three compounds (**10a**, **10l** and **11g**) exhibited potent inhibitory effects on both TGF-β1-induced total collagen accumulation and LPS-stimulated TNF-α production. Furthermore, oral administrations of **10l** at a dose of 20 mg/kg/day for 4 weeks effectively alleviated lung inflammation and injury, and decreased lung collagen accumulation in bleomycin-induced pulmonary fibrosis model. Histopathological evaluation of lung tissue confirmed **10l** as a potential, orally active agent for the treatment of pulmonary fibrosis.

Pulmonary fibrosis (PF), characterized by the disruption of normal lung tissue architecture and loss of pulmonary function, is one of the major clinical problems of cystic fibrosis and chronic obstructive pulmonary disease.[1–4] Its incidence most recently has been estimated to be between 14 and 42.7 per 100,000 and has been increasing,[5–7] the expected survival time of patients suffered from PF is estimated to be 2.5–3.5 years.[8] However, the pathogenesis of PF is still unknown, the excessive deposition of extracellular matrix (ECM) in lung tissues caused by inflammation has been recognized as a crucial reason leading to the destruction of the lung architecture.[9,10]

A number of studies have documented that cytokines such as TGF-β1, TNF-α play key roles during the pathogenesis of the PF.[11] TGF-β1 is a fibrogenic cytokine involved in pathological fibrosis of PF by regulating extracellular matrix (ECM) deposition in the response to lung tissues injury.[12–14] TNF-α, an important pro-inflammatory cytokine released by macrophages and lymphocytes, involved in regulating the inflammation respond to lung tissue injury.[15]

Ivacaftor (Fig. 1), a 4-oxoquinoline-3-carboxamide compound, has been approved as a small-molecule drug to treat cystic fibrosis,[16] which is studied for chronic obstructive pulmonary disease in clinic.[17] Treatment with *Ivacaftor* had significant and sustained improvement in their lung function in cystic fibrosis.[18,19] In our preliminary studies, *Ivacaftor* was also observed to reveal in vitro anti-fibrotic activities by the inhibition of TGF-β1-induced total collagen accumulation in rat fibroblast cells (NRK-49F), which has been recognized an effect of good and convenient origin for anti-fibrotic agent in vitro screening model.[20] Therefore, these pharmacological properties of *Ivacaftor* provided us the impetus to develop novel and potent anti-fibrotic agents containing 4-oxoquinoline-3-carboxamide moiety by using *Ivacaftor* as a lead.

Ivacaftor derivatives (**9a**–**9f**) were synthesized according to previous reported procedures (Scheme 1).[21–23] The 2,4-di-*tert*-butylphenol **1** was treated with methyl chloroformate to give **2**. Nitration of **2** with cooled mixture of HNO_3 and H_2SO_4 (v:v 1:1) obtained **3**. Treatment of **3** with 10% Pd/C, $HCOONH_4$ yielded **4**. The pivotal 4-quinolones intermediates **5a**–**5f** were obtained by the condensation of appropriate anilines with diethyl ethoxymethylenemalonate, followed by the cyclization of the intermediate to give **6a**–**6f**. Compound **6a**–**6f** were hydrolyzed to the corresponding acid **7a**–**7f**, the intermediates **7a**–**7f** were reacted with **4** to afford **8a**–**8f**, further deprotected to give **9a**–**9f**. *Ivacaftor* analogues **10a**–**10o** and **11a**–**11j** were outlined in Scheme 2. The intermediate **7e** was treated with anilines to afford the desired products

* Corresponding author. Tel.: +86 28 85164063; fax: +86 28 85164060.
E-mail address: chenlijuan125@163.com (L. Chen).
† These authors contributed equally.

http://dx.doi.org/10.1016/j.bmcl.2014.10.071
0960-894X/

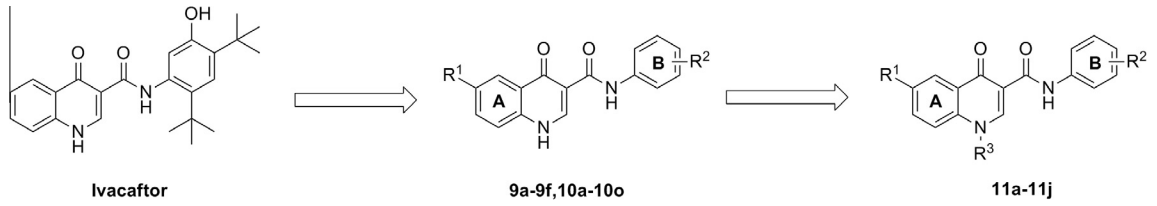
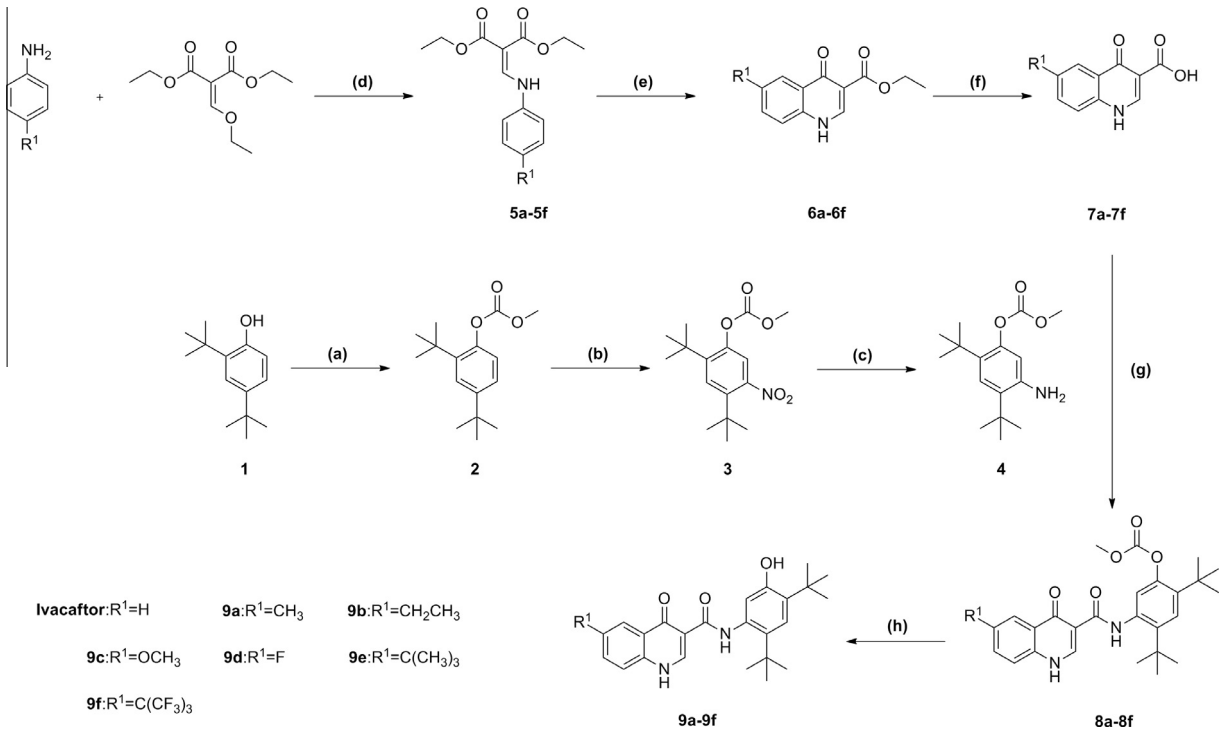
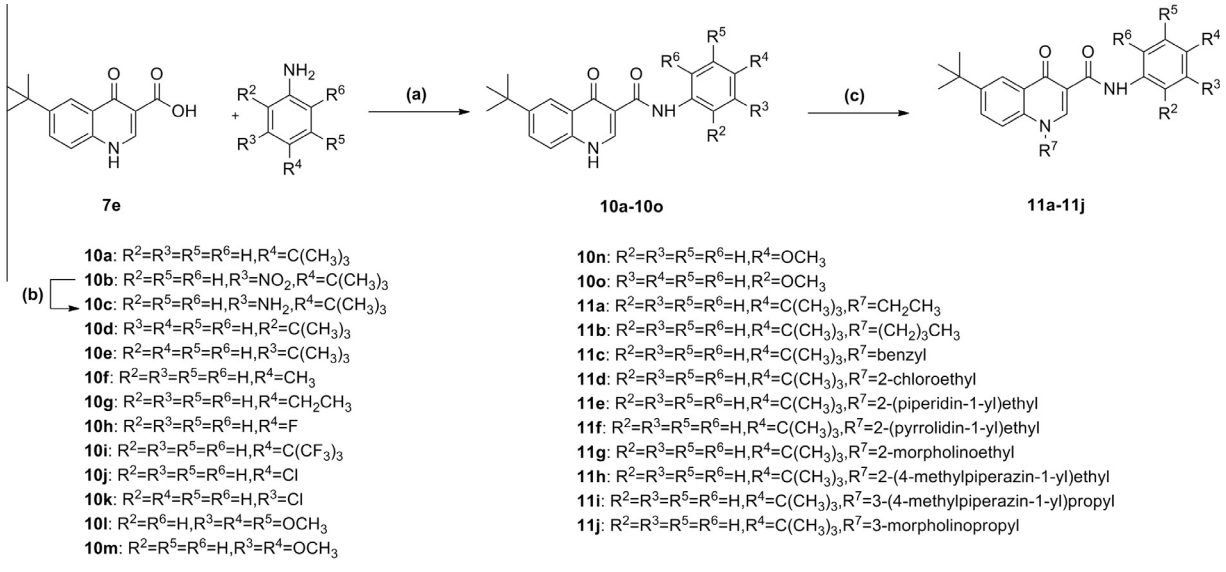


Figure 1. *Ivacaftor* and 4-oxoquinoline-3-carboxamides derivatives.



Scheme 1. General synthesis of *Ivacaftor* derivatives. Reagents and conditions: (a) methyl chloroformate, DMAP, Et_3N, DCM, rt, overnight; (b) HNO_3/H_2SO_4 (1:1), 0 °C, rt, 2 h. (c) 10% Pd/C, $HCOONH_4$, EtOH, reflux, 2 h; (d) EtOH, reflux, 4 h; (e) diphenyl ether, reflux, 1 h; (f) (i) 10% KOH, 100 °C, 3 h; (ii) 1 N HCl, pH = 4–5; (g) HATU, Et_3N, DMF, rt, overnight; (h) KOH, CH_3OH, rt, 2 h.



Scheme 2. General synthesis of *Ivacaftor* analogues. Reagents and conditions: (a) HATU, Et_3N, DMF, rt, overnight; (b) Fe powder, NH_4Cl, EtOH/H_2O (3:1), reflux, 4 h; (c) RX, Cs_2CO_3, CH_3CN, reflux, overnight.