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Original article

Novel 9-oxo-thiazolo[5,4-*f*]quinazoline-2-carbonitrile derivatives as dual cyclin-dependent kinase 1 (CDK1)/glycogen synthase kinase-3 (GSK-3) inhibitors: Synthesis, biological evaluation and molecular modeling studies

Cédric Logé [a,*], Alexandra Testard [b], Valérie Thiéry [b], Olivier Lozach [c], Mélina Blairvacq [c], Jean-Michel Robert [a], Laurent Meijer [c], Thierry Besson [b,**]

[a] *Université de Nantes, Nantes Atlantique Universités, Biomolécules et Cibles Thérapeutiques, Département de Pharmacochimie, BioCiT, UPRES EA 1155, UFR Sciences Pharmaceutiques, 1 rue Gaston Veil, F-44035 Nantes Cedex 1, France*
[b] *Laboratoire de Biotechnologies et de Chimie Bio-organique, FRE CNRS 2766, UFR Sciences Fondamentales et Sciences pour l'Ingénieur, Université de La Rochelle, Bâtiment Marie Curie, 17042 La Rochelle, France*
[c] *Cell Cycle Group, UMR7150 & UPS2682, Station Biologique, B. P. 74, 29682 Roscoff Cedex, Bretagne, France*

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Abstract

Continuous efforts in microwave-assisted synthesis and the structure–activity relationships' (SARs) studies of novel modified 9-oxo-thiazolo[5,4-*f*]quinazoline-2-carbonitriles, allowed identification of new amidine and imidate derivatives as potent and dual CDK1/GSK-3 inhibitors. Combination of lead optimization and molecular modeling studies allowed identification of a dual CDK1/GSK-3 inhibitor (compound **13d**) with submicromolar values.

Keywords: CDK1 inhibitor; GSK-3 inhibitor; Molecular modeling; Microwave-assisted chemistry; Quinazolinones

1. Introduction

Protein kinases have a fundamental role in signal transduction pathways, and aberrant kinase activity has been observed in many diseases. In recent years, kinase inhibition has become a major area for therapeutic intervention and a variety of kinase inhibitor pharmacophores has been described. Most kinase inhibitor molecules currently developed are targeted at the ATP-binding site, an ubiquitous domain in nature, and mimic mainly the H-bonding motif of the ATP aminopyrimidine ring. Among the 518 human kinases [1], two classes have been particularly explored: the cyclin-dependent kinases (CDKs) which are involved in regulating the cell division cycle, apoptosis, neuronal cell physiology, pain signaling, transcription, RNA splicing and insulin release, among other activities [2,3] and the glycogen synthase kinase-3 (GSK-3) which is a family of kinases involved in cell cycle control, insulin action, apoptosis, neuronal cell death and developmental regulation, among other processes [4,5]. Both families of kinases are implicated in various human diseases such as cancers, Alzheimer's disease, diabetes and therefore both have

Abbreviations: CDK, cyclin-dependent kinase; GSK-3, glycogen synthase kinase-3; ATP, adenosine triphosphate; MEPs, molecular electrostatic potentials; MW, microwave; AMP-PNP, 5′-adenylyl-imidodiphosphate; pdb code, RCSB Protein Data Bank.

* Corresponding author. Tel.: +33 (0) 240411108; fax: +33 (0) 240412876.
** Corresponding author. Present address: UMR CNRS 6014, Laboratoire de Chimie Pharmaceutique, UFR Médecine-Pharmacie, Université de Rouen, 22 Boulevard Gambetta, 76183 Rouen Cedex 1, France. Tel.: +33 (0) 235148399; fax: +33 (0) 235148423.
E-mail addresses: cedric.loge@univ-nantes.fr (C. Logé), thierry.besson@univ-rouen.fr (T. Besson).

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been extensively used as targets to identify small molecular weight pharmacological inhibitors of potential therapeutic interest. A recent mini-review also shows that CDK/GSK-3 inhibitors may emerge as effective therapeutic agents for proliferative renal diseases, furthering the prospect that these inhibitors may emerge as effective therapeutic agents in the near future [6]. Over the past decades, several groups have identified and characterized a fair number of potent CDK inhibitors (olomoucine, roscovitine, purvalanols, indirubins, aloisines, hymenialdisine, etc.). Many of these molecules are derived from marine organisms. The most advanced compound, the purine analogue (*R*)-roscovitine (CYC-202), a CDK2 selective inhibitor, is currently in phase 2 clinical trials against non-small cell lung cancer, breast cancer and various B-cell malignancies, in phase 1 against various kidney inflammations (glomerulonephritis), in pre-clinical, animal testing against Alzheimer's disease and stroke. Interestingly, many inhibitors are in fact dual inhibitors of CDKs and GSK-3, due mainly to the high degree of homology (~86%) between the ATP-binding site of the two kinases.

In an attempt to identify a potent and selective GSK-3 inhibitor focused on 2,8-substituted 9-oxo-thiazoloquinazoline-2-carbonitriles, we unexpectedly discovered a compound, bearing an *N*-isopropyl side chain on the N-8 nitrogen and an amidine function with a bulky *N*,*N*-dimethylethylenediamine group at the C-2 position of the thiazole moiety. This compound showed submicromolar IC_{50} against GSK-3 but also a moderate activity against CDKs (Table 1, entry **15c**) [7]. This article describes our continued efforts in the structure–activity relationships' (SARs) studies and toward the identification of new amidine and imidate derivatives as potent and dual CDK1/GSK-3 inhibitors.

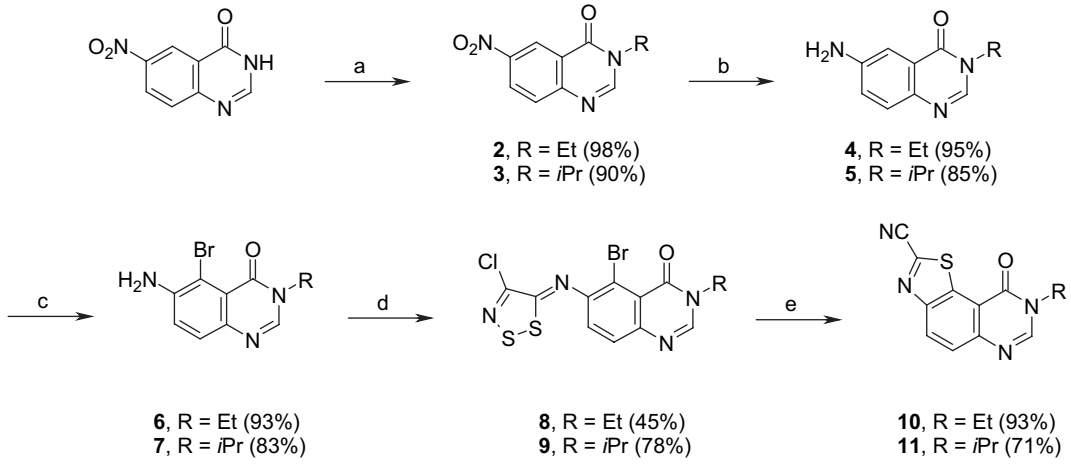
Table 1
Kinase inhibition values (IC_{50} in μM) for compounds **12**–**15** (NT = not tested)

Compounds	CDK1/cyclin B	CDK5/p25	GSK-3α/β
12a	50	NT	2.1
12b	4.3	NT	0.64
12c	1.4	NT	0.15
12d	1.3	>100	0.17
12e	1.4	4	0.3
13a	13	43	0.15
13b	5.2	NT	0.26
13c	2.4	NT	0.28
13d	0.15	>100	0.13
14a	>100	NT	7.2
14b	>10	>10	2.4
14c	17	NT	1.3
15a	>100	NT	9.4
15b	9	>10	0.52
15c	10	4	0.56
(*R*)-Roscovitine	0.45	0.16	130

2. Chemistry

2.1. Synthesis of the thiazoloquinazolinone core

The expected 9-oxo-thiazolo[4,5-*f*]quinazoline-2-carbonitrile derivatives (**10** and **11**) (Scheme 1) were obtained in six steps from commercially available 5-nitroanthranilic acid. The multistep synthesis was mainly performed under microwaves taking in account of our experience in this domain [8–10]. The experimental conditions and the yields of the different steps are described in Scheme 1. The 6-nitro-3*H*-quinazolin-4-one **1** was synthesized as we previously described by microwave heating, at atmospheric pressure, of 5-nitroanthranilic acid with 5 equiv of formamide (150 °C) [11]. Selective *N*-alkylation in position 3 of the quinazolin-4-one ring was performed at atmospheric pressure by treatment of **1** with sodium hydride and ethyl or isopropyl iodide as alkylating agents. Reduction of the 3-substituted-6-nitroquinazolin-4-ones **2** and **3** led to the 6-amino derivatives **4** and **5** by using ammonium formate for catalytic transfer hydrogenation in ethanol. Compounds **4** and **5** were brominated in the presence of bromine in acetic acid, to give the *ortho* brominated imines **6** and **7**. The latest were condensed, under microwaves, with 4,5-dichloro-1,2,3-dithiazolium chloride (Appel's salt) [12] in dichloromethane and in a sealed tube. Addition of pyridine led to the desired imino-1,2,3-dithiazoloquinazolinones **8** and **9**. Products **10** and **11** were obtained by microwave-assisted thermolysis consisting of a rapid



Scheme 1. Reaction conditions: (a) alkyl iodide, NaH, DMF, (MW) 140 °C, 5 min; (b) HCO_2NH_4, Pd/C, EtOH, (MW) 80 °C; 15 min; (c) Br_2, AcOH, rt, 2 h; (d) 4,5-dichloro-1,2,3-dithiazolium chloride, pyridine, CH_2Cl_2, (MW) 80 °C, 4 min; (e) CuI, pyridine, (MW) 160 °C, 1 min.