European Journal of Medicinal Chemistry 46 (2011) 3690–3695

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

# Single step synthesis of new fused pyrimidine derivatives and their evaluation as potent Aurora-A kinase inhibitors

Mohamed R. Shaaban [a,b,*], Tamer S. Saleh [c,d], Abdelrahman S. Mayhoub [e], Ahmad M. Farag [b]

[a] Department of Chemistry, Faculty of Applied Science, Umm Al-Qura University, Makkah 21955, Saudi Arabia
[b] Department of Chemistry, Faculty of Science, Cairo University, Giza 12613, Egypt
[c] Department of Green Chemistry, National Research Center, Dokki, Giza 12622, Egypt
[d] Department of Chemistry, Faculty of Science, King AbdulAziz Univeristy, Jeddah 21589, Saudi Arabia
[e] Department of Organic Chemistry, Faculty of Pharmacy, Al-Azhar University, Cairo 11884, Egypt

ARTICLE INFO

*Article history:*
Received 2 December 2010
Received in revised form
11 May 2011
Accepted 13 May 2011
Available online 20 May 2011

*Keywords:*
Aurora-A
Kinase inhibitors
Colon tumor
Pyrazolo[1,5-*a*]pyrimidine
Triazolo[1,5-*a*]pyrimidine
Pyrimido[1,2-*a*]benzimidazole
Structure–activity relationship (SAR)
Molecular modeling

ABSTRACT

A simple, facile, efficient and one pot three-component procedure for the synthesis of pyrazolo[1,5-*a*] pyrimidines, triazolo[1,5-*a*]pyrimidines and pyrimido[1,2-*a*]benzimidazoles ring systems incorporating phenylsulfonyl moiety was developed *via* the reaction of 1-aryl-2-(phenylsulfonyl)ethanone derivatives **1a**–**d** with the appropriate heterocyclic amine and triethyl orthoformate and evaluated as Aurora-A kinase inhibitors. The cytotoxic activity of the newly synthesized compounds against HST116 colon tumor cell line was investigated. 2,7-Diphenyl-6-(phenylsulfonyl)pyrazolo[1,5-*a*]pyrimidine (**4b**) and its *p*-methoxy analogue **4c** were found to be equipotent to Doxorubicin as a reference drug. Molecular modeling study was carried out in order to rationalize the *in vitro* anti-tumor results.



## 1. Introduction

Colon cancer is one of the most common tumors that occurs in the western world and usually ranks high in incidence and mortality among new malignant cases [1]; there is a strong correlation between aurora kinase expressions and colon carcinoma. The expression of aurora kinase protein was found to be related to grade of tumor, p16 expression, and telomerase activity. These findings are important to select patients for clinical trials of Aurora kinase inhibitors [2–5].

Aurora-A is a member of a family of mitotic serine/threonine kinases which includes also types B and C. It is implicated with important processes during mitosis and meiosis whose proper function is integral for healthy cell proliferation. Its activity peaks have been observed during the G2 phase to M phase transition in the cell cycle [6]. Aurora-A kinase plays an important role in mitosis. It is associated with centrosome maturation and separation and thereby regulates spindle assembly and stability [7]. Over-expression or deregulation of Aurora-A has been associated with a high occurrence of cancer [8]. Deregulation of Aurora-A may lead to cancer because it is required for the completion of cytokinesis.

If the cell begins mitosis, duplicates its DNA, but is then unable to divide into two separate cells, it becomes an aneuploid (i.e. it contains more chromosomes than normal). Aneuploidy is a trait of many cancerous tumors [9]. Among compounds that can be used as Aurora kinase inhibitors, pyrazolo[1,5-*a*]pyrimidine occupy an important position [10].

In continuation of our recent work aiming at the synthesis of a variety of heterocyclic systems with remarkable biological importance [11–26], we report here on the utility of β-keto-sulfones as molecular scaffold for the synthesis of pyrazolo[1,5-*a*] pyrimidine, 1,2,4-triazolo[1,5-*a*]pyrimidine and pyrimido[1,2-*a*] benzimidazole derivatives. The synthesized compounds were evaluated as Aurora-A kinase inhibitors and as anti-colon tumor agents in order to explore new class of compounds that could be optimized for potent anticancer agents. In addition, docking study has been carried out to rationalize the biological activity.

* Corresponding author. Department of Chemistry, Faculty of Applied Science, Umm Al-Qura University, Makkah 21955, Saudi Arabia. Tel.: +966 545917568; fax: +966 255635580.
*E-mail address:* rabiemohamed@hotmail.com (M.R. Shaaban).

0223-5234/$ – see front matter © 2011 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.ejmech.2011.05.033