Bioorganic & Medicinal Chemistry Letters 23 (2013) 2007–2013

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Design, synthesis, and molecular modelling of pyridazinone and phthalazinone derivatives as protein kinases inhibitors

Mohamed Elagawany [a,b,c,*,†], Mohamed A. Ibrahim [a,b,d,†], Hany Emary Ali Ahmed [c,e], A. Sh. El-Etrawy [b], Adel Ghiaty [c], Zakaria K. Abdel-Samii [d], Said A. El-Feky [d], Jürgen Bajorath [f]

[a] Laboratoire d'innovation thérapeutique, UMR 7200, Faculté de Pharmacie, Université de Strasbourg, 74-route du Rhin, BP 60024, 67401 ILLKIRCH Cedex, France
[b] Organic Chemistry Department, College of Pharmacy, Misr University for Science and Technology, Al-Motamayez District, 6th of the October, PO Box 77, Egypt
[c] Organic Chemistry Department, Faculty of Pharmacy, Al-Azhar University, Cairo 11884, Egypt
[d] Department of Pharmaceutical Organic Chemistry, Faculty of Pharmacy, Zagazig University, Zagazig-44519, Egypt
[e] Pharmacognosy and Pharmaceutical Chemistry Department, Pharmacy College, Taibah University, Al-Madinaha Al-Munawaraha, Saudi Arabia
[f] Department of Life Science Informatics, B-IT, LIMES Program Unit Chemical Biology and Medicinal Chemistry, Rheinische Friedrich-Wilhelms-Universität Bonn, Dahlmannstr. 2, D-53113 Bonn, Germany

ARTICLE INFO

Article history:
Received 21 December 2012
Revised 24 January 2013
Accepted 2 February 2013
Available online 13 February 2013

Keywords:
Pyridazinone
Phthalazinone
Kinases
Docking
GSK3

ABSTRACT

The design and synthesis of pyridazinone and phthalazinone derivatives are described. Newly synthesized compounds were tested on a panel of four kinases in order to evaluate their activity and potential selectivity. In addition, the promising compounds were tested on four cancer cell lines to examine cytotoxic effects. The compounds inhibited DYRK1A and GSK3 with different activity. SAR analysis and docking calculations were carried out to aid in the interpretation of the results. Taken together, our findings suggest that pyridazinone and phthalazinone scaffolds are interesting starting points for design of potent GSK3 and DYRK1A inhibitors.

Large numbers of protein kinases are involved in controlling the phosphorylation of protein in cells. This process plays an important role in the regulation of various cellular processes.[1–3] Alterations of this kinase signalling are found in numerous human pathologies.[4] Accordingly, kinase inhibitors continue to be of high interest for therapeutic intervention. Currently, large numbers of small molecule kinase inhibitors are undergoing clinical trials for the treatment of cancer and other diseases, showing that kinases constitute important therapeutic targets.

The role of cyclin-dependent kinases (CDKs) to regulate the cell cycle and apoptosis have been well explored.[5–8] They are involved in several diseases, including cancer, Alzheimer's disease, Parkinson's disease, stroke, diabetes, polycystic kidney disease, glomerulonephritis, inflammation, and AIDS.[5,9] Glycogen synthase kinase-3 (GSK-3) plays an important role in a large number of cellular processes, apoptosis control, neurodegenerative disorders (Alzheimer's disease) and cardiovascular diseases.[9] Furthermore, casein kinase 1 (CK1) plays an important role in controlling cell differentiation, proliferation, apoptosis, circadian rhythms and has been implicated in neurodegenerative diseases.[10,11] Dual specificity, tyrosine phosphorylation regulated kinase 1A (DYRK1A) plays a key role in Alzheimer's disease and Down syndrome.[12]

Several structurally diverse ligands were previously reported to inhibit GSK-3. Examples include thiadiazolidindiones (TDZD), hydantoins, triazoles, thiazoles, maleimides, dithiazolidindiones, and pyrazolepyridines.[13–19] Many current efforts toward the development of novel kinase inhibitors concentrate on structure-based ligand design. A large number of X-ray structures of kinase-inhibitor complexes are deposited in the Protein Data Bank with resolutions in the range of 1.95–2.8 Å that provide a basis for compound design and optimization. We have explored pyridazinone and phthalazinone scaffolds as potentially novel kinase inhibitors. Herein, we report the design, synthesis and evaluation of novel pyridazinone and phthalazinone derivatives.

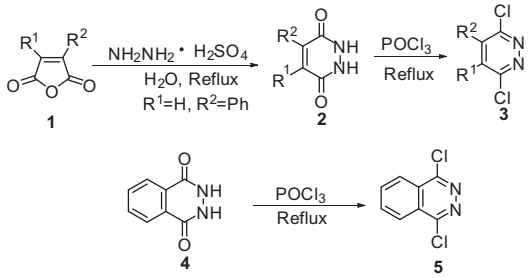
The synthesized compounds were tested for kinase inhibitory activity against four protein kinases including DYRK1A, CK1, CDK5, and GSK3 types and, in addition, for cytotoxic activity against four different human cancer cell lines. Structure–activity relationships and the potential contribution of kinase inhibition to anti-tumor properties are discussed.

* Corresponding author. Tel.: +20 1001231305.
E-mail addresses: alfath_tours@yahoo.com, drmmonem@yahoo.com (M. Elagawany).
† These authors equally contributed to this work.

0960-894X/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.bmcl.2013.02.027

A detailed literature survey revealed that the majority of currently available kinase inhibitor scaffolds consist of planar heterocycles that carry both hydrogen bond donors and acceptor moieties.[20–22] The analysis of cyclin-dependent kinase inhibitors and comparison with pyridazinone and phthalazinone cores suggested that derivatives of these scaffolds should merit consideration as potential kinase inhibitors (Fig. 1). Hence, we synthesized pyridazinone and phthalazinone derivatives and evaluated their kinase inhibitor property.

Heating 3-phenylmaleic anhydride **1** under reflux with hydrazine sulfate in water yielded intermediate **2**.[23,24] Further treatment of **2** with $POCl_3$ gave the dichloro derivatives **3**.[24] Similarly, 1,4-dichlorophthalazine **5**[25] was synthesized from the commercially available 2,3-dihydrophthalazine-1,4-dione **4** by treating with $POCl_3$ (Scheme 1).



Scheme 1. Synthesis of the dichloro derivatives **3** and **5**.

Amination of intermediates **3** and **5** was carried out with various amines (Scheme 2a and b). The use of excess amine with intermediate **3** leads to the formation of two isomers **6a–h**. The two isomers can be separated easily using flash chromatography to give each isomer in pure form except in the cases of **6g** and **6h** where close rf resulted in poor separation and yielded only a small amount of pure **6g**. The use of the microwave was found to accelerate the reaction rate and reduce the reaction time dramatically from 3 h to 30 min.[26] Compounds **7a–g** were obtained by heating **6a–g** with acetic acid in presence of sodium acetate under reflux overnight using conventional heating.[27] The same result was achieved by heating the same reaction mixture in microwave at 120 °C for 5 min.

The use of excess amine in the case of intermediate **5** gives the diamine **8e**. Mono-substitution of intermediate **5** was achieved using an equimolar quantity of the appropriate amine in presence of base to afford **8a–d** as single isomers. Hydrolysis of **8a–d** was achieved using the above mentioned method to afford **9a–d.**

Simple amino substituted compounds **10a**, **10b** and **16** were synthesised by the direct amination of chloro aromatics **3** and **5** with NH_4OH either under reflux overnight or microwave irradiation for 30 min (see Scheme 3a and b).

Hydrolysis of compound **10a** with acetic acid in the presence of sodium acetate for 3 h, gave two products **11a** and **11b**, which

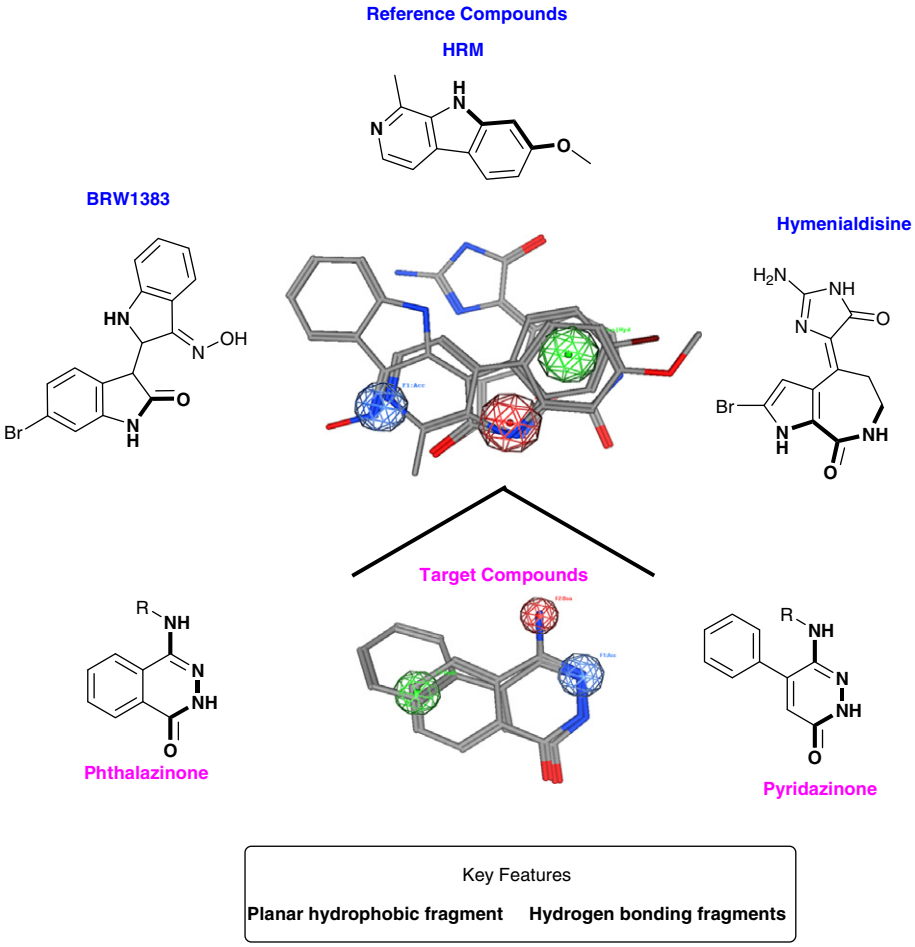


Figure 1. Structural similarity of cyclin-dependent kinase inhibitors and pyridazinone and phthalazinone scaffolds. HRM, a selective DYRK1A inhibitor, hymenialdisine, an inhibitor of different kinases, and BRW1383, a selective GSK3 inhibitor, are compared to pyridazinone and phthalazinone. These compounds display pharmacophoric resemblance. Key structural features are highlighted in red or bold lines.