Bioorganic & Medicinal Chemistry Letters 20 (2010) 2801–2805

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Identification and structure–activity relationship of 8-hydroxy-quinoline-7-carboxylic acid derivatives as inhibitors of Pim-1 kinase

Faten Sliman [a], Mélina Blairvacq [b], Emilie Durieu [b], Laurent Meijer [b], Jordi Rodrigo [a], Didier Desmaële [a,*]

[a] UMR 89076 BIOCIS, Faculté de Pharmacie, Université Paris Sud, 5 rue J.-B. Clément, 92296 Châtenay-Malabry, France
[b] USR3151, Protein Phosphorylation & Human Disease Group, Station Biologique, B.P. 74, 29682 Roscoff, France

ARTICLE INFO

Article history:
Received 5 February 2010
Revised 11 March 2010
Accepted 12 March 2010
Available online 15 March 2010

Keywords:
Pim-1 kinase
Inhibitors
Styrylquinolines
Quinoline-2-carboxamides
Molecular docking

ABSTRACT

Pim-1 kinase is a cytoplasmic serine/threonine kinase that controls programmed cell death by phosphorylating substrates that regulate both apotosis and cellular metabolism. A series of 2-styrylquinolines and quinoline-2-carboxamides has been identified as potent inhibitors of the Pim-1 kinase. The 8-hydroxy-quinoline 7-carboxylic acid moiety appeared to be a crucial pharmacophore for activity. Molecular modeling indicated that interaction of this scaffold with Asp186 and Lys67 residues within the ATP-binding pocket might be responsible for the kinase inhibitory potency.

Pim-1 is an oncogene-encoded cytoplasmic serine/threonine kinase primarily expressed in hematopoietic and germ cell lines which is involved in the control of cell growth, differentiation, proliferation and apoptosis.[1] Expression of Pim-1 is induced by a variety of growth factors, cytokines, mitogens and hormones suggesting that Pim-1 may be involved in signal transduction initiated from these factors.[2] Pim overexpression has been reported in diffuse B cell lymphoma, chronic lymphocytic leukemia, prostate cancer and FLT3-mediated acute myelogenous leukemia.[3–6] Pim-2 and Pim-3, the two other members of the Pim kinase family, have 53% and 65% sequence homology respectively with Pim-1. The kinase Pim-2 is ubiquitously expressed with highest levels in brain and lymphoid cells. Elevated levels of Pim-2 were mostly found in hematological malignancies and prostate cancer.[7] Pim-3 is expressed with highest levels in kidney, breast and brain. Increased Pim-3 expression was observed in different solid tumors like hepatocellular carcinoma, pancreatic and colon cancer.[8]

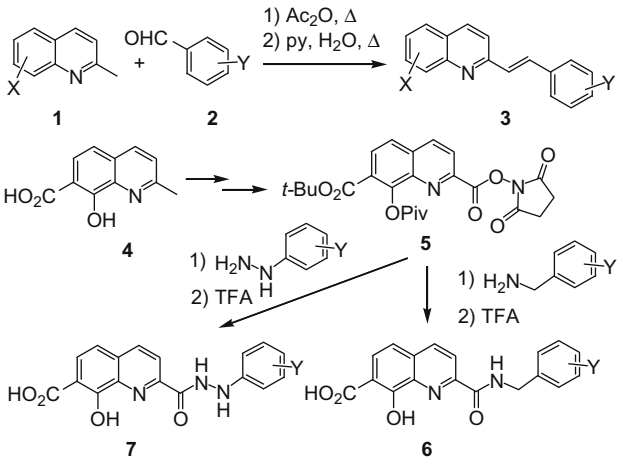
In light of its oncogenic potential, the Pim-1 kinase is emerging as an important new target for drug discovery. The fact that Pim-1 knockout mice showed no obvious phenotype suggests that side effects for such a drug should be minimal.[9] Given this promising target profile, many academic institutions and pharmaceutical companies have been involved in the development of Pim-1 inhibitors. Recent crystallographic studies including co-crystal structures of complexes with ATP analogue and inhibitors have provided characteristic structural features for Pim-1 to help inhibitor design.[10–19] Although the Pim-1 kinase displays a high degree similarity to other serine/threonine kinases, it possesses a unique proline residue (Pro123) in the hinge region where other hydrophobic amino acids are more typically found. Thus, in the absence of the main chain amide nitrogen available to participate in a hydrogen bond, novel interactions will be required to design selective and potent ligands. Hence, we can expect that new scaffolds which have not been previously reported as kinase inhibitors proved to be efficient inhibitors for Pim-1. We here report the identification of a novel series of Pim-1 inhibitors based on the 2-substituted 7-carboxy-8-hydroxy-quinoline scaffold and outline the potential binding mode of these molecules in the hinge pocket region using docking studies.

In 2005 Knapp and co-workers[20] identified several scaffolds for Pim-1 kinase inhibition including staurosporine, bisindoyl-maleimides, flavonoids, chromene[3,4]diones, imidazo[1,2-*b*]pyridazines[21,22] and pyrazolo[1,5-*a*]pyrimidines. Since this impressive report, many other classes of inhibitors were discovered such as, morpholino substituted chromones,[11] 3-arylimino-1,3-dihydro-indol-2-ones and 3,4-dihydroxyquinolin-2-ones,[13] substituted 2-cyanopyridones,[15] ruthenium and osmium complexes of pyridocarbazole ligands,[16,23,24] 4-aryl-pyrimidin-2-amines and 2,3-diphenyl-indole-7-carboxylic acid,[25] indolyl-pyrrolones,[26] isoxazolo[3,4-*b*]quinolin-3,4-diones,[27] triazolo[4,3-*b*]pyridazines,[28] 5-(benzylidene) thiazolidin-2,4-diones,[29] 3-(3-pyrazin-2-yl-phenyl)-acrylic acids,[17] pyrrolo[2,3-*a*]carbazoles,[18] 3*H*-benzo[4,5]thieno[3,2-*d*]pyrimidin-4-ones.[19]

Recent reports concerning the potency of flavonoids against Pim-1 kinase[20,30,31] prompted us to evaluate polyhydroxylated styrylquinolines on this target. The styrylquinoline class, which

* Corresponding author. Tel.: +33 01 46 83 57 53; fax: +33 01 46 83 57 52.
E-mail address: didier.desmaele@u-psud.fr (D. Desmaële).

0960-894X/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2010.03.061

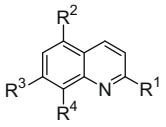


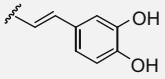
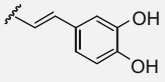
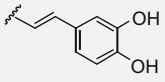
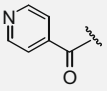
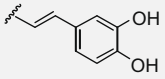
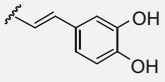
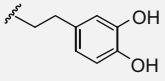
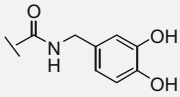
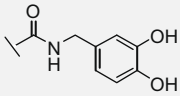
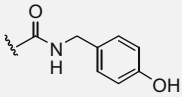
Scheme 1. General synthetic scheme for styryquinolines **3**, quinoline-2-carboxamides **6** and hydrazides **7**.

was initially described as HIV-1 integrase inhibitors[32–36] was recently found to display antiproliferative activity on tumor cell lines.[37] On the other hand, quercetagetin is a known HIV-1 integrase inhibitor with IC_{50} of 0.8 μM.[38] These findings clearly show that both classes of molecules not only share common structural features but also some biological targets.

Hence, as an initial approach to the identification of Pim-1 inhibitors a small set of quinoline derivatives was screened. The synthesis of most compounds has been previously reported.[32–36,39,40] Briefly, the styrylquinoline derivatives **3** were prepared from the corresponding quinaldine **1** by Perkin-type condensation in refluxing acetic anhydride, followed by hydrolysis in a pyridine water mixture. Styrylquinolines **12**, **27**, **34**, **36** were obtained according to this general procedure from 2-methyl-8-hydroxy-5-quinoline carboxylic acid[41] and 2-methyl-8-hydroxy-7-quinoline carboxylic acid,[32] respectively. The others derivatives were obtained from the pivotal *N*-hydroxysuccinimidyl ester **5** available in five steps from the 8-hydroxy-2-methylquinoline-7-carboxylic acid **4**. Condensation of **5** with the requisite amines followed by TFA-deprotection provided quinoline-2-carboxamides **6** in 15–90% overall yield. Similarly con-

Table 1
Pim-1 inhibition assay results for compounds **4**, **8**–**19**



Compd	R_1	R_2	R_3	R_4	IC_{50}[a] (μM)
4	CH_3	H	CO_2H	OH	>10
8	CH_3	H	H	CO_2H	>10
9	CH_3	Ph	CO_2H	OH	>10
10	CH_3	H	H	$NHSO_2Me$	>10
11		H	H	OH	>10
12		CO_2H	H	OH	>10
13		H		OH	>10
14		H	H	CO_2H	>10
15		H	CO_2H	OH	1.7
16		H	CO_2H	OH	5
17		Cl	Cl	OH	>10
18		H	CO_2H	OH	2.1
19		H	H	CO_2H	>10

[a] IC_{50} values are shown as the average of three experiments. Variations between determinations are less than 5%.

densation of **5** with arylhydrazines afforded the corresponding hydrazides **7** (Scheme 1). Compounds **17** and **19** were prepared as described above for **6**, from 2-methyl-quinoline-8-carboxylic acid[34] and 5,7-dichloro-2-methyl-quinolin-8-ol,[42] respectively.

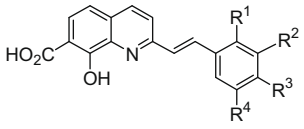
The compounds were submitted to a preliminary biological assay to evaluate the percent inhibition of Pim-1 activity at 10 μM. IC_{50} values were determined only for compounds able to reduce significantly Pim-1 activity (>50%).[43] Results of the biological evaluation are listed in Table 1.

Simple quinolines bearing hydroxyl and/or carboxyl groups in various positions were found to be inactive. On the other hand, compounds which displayed an ancillary aromatic ring bound to the C-2 position of the 8-hydroxy-quinoline-7-carboxylic acid scaffold through various spacers exhibited micromolar Pim-1 inhibitory potency (compounds **15**, **16**, **18**). The fact that a simple vinyl spacer as well as a saturated two-carbon linker or an amide groups provided almost equally potent compounds indicated that the coplanar conformation of the two aromatic rings seemed to be not a stringent structural requisite. Replacement of the 7-carboxyl-8-hydroxy substitution pattern by other groups while maintaining the free catechol moiety (**12**, **13**, **17**) led to inactive compounds.

Following these initial results, we screened additional 8-hydroxy-styrylquinoline-7-carboxylic acid derivatives bearing various substituents on the ancillary ring (Table 2). Within this series most compounds were found active whatever the substitution of the ancillary aromatic ring. While a simple phenyl ring was sufficient to insure micromolar activity, the 2,4-dihydroxyl, 3,5-dihydroxyl and 3-hydroxyl-4-methoxy patterns (compounds **25**, **26**, **30**) were found to provide submicromolar Pim-1 inhibitors which seems to indicate the importance of hydrogen bonding of the ancillary part to substantially stabilize the inhibitor-enzyme complex but also illustrating the fragile nature of the H-bonding network in this area.

In an attempt to get deeper insight into the molecular bases of the inhibitory potency of the styrylquinoline class we performed

Table 2
Pim-1 inhibition assay results for styrylquinolines **15**, **20**–**38**



Compd	R_1	R_2	R_3	R_4	IC_{50}[a] (μM)
15	H	OH	OH	H	1.7
20	H	H	H	H	3.2
21	H	H	CH_2OH	H	5.0
22	H	H	OH	H	0.7
23	H	H	NO_2	H	3.4
24	H	H	NH_2	H	4.0
25	OH	H	OH	H	0.5
26	H	OH	H	OH	0.4
27	OH	OH	H	H	7.0
28	H	CO_2H	OH	H	3.1
29	H	OMe	OH	H	2.0
30	H	OH	OMe	H	0.5
31	H	OH	OH	OH	5.5
32	H	OMe	OH	OH	3.1
33	H	OMe	OH	OMe	2.5
34	H	OMe	OH	Cl	4.5
35	H	Br	OH	Br	2.1
36	H	NO_2	OH	OMe	2.8
37	H	F	F	H	4.5
38	H	OCH_2O		H	3.0

[a] IC_{50} values are shown as the average of three experiments. Variations between determinations are less than 5%.

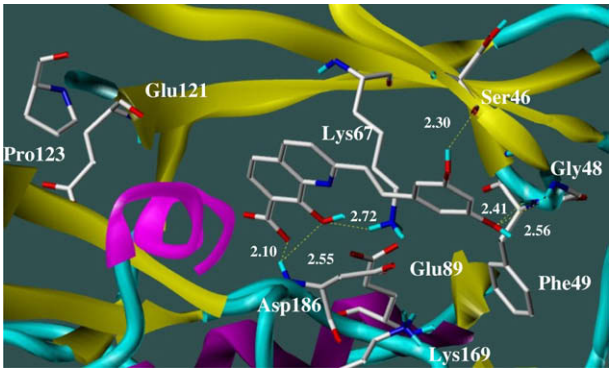


Figure 1. Computational docking of styrylquinoline **26** to the Pim-1 kinase showing interaction with the amino acid residues of the ATP-binding pocket. Close contacts are indicated by dotted lines and distances are provided in Angstroms.

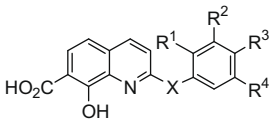
docking studies using the GOLD 4.0 software.[44] The starting point to establish the most suitable settings for docking experiments was the crystallographic structure of the co-crystal of Pim-1 with substituted 2-cyanopyridones (PDB ID: 2OBJ).[15] Docking studies showed that the styrylquinoline **26** fit into the active site deep inside the pocket, with both its C-7 carboxylate group and the oxygen atom of the C-8 phenol group participating in hydrogen bonds with the backbone NH group of Asp186. Additional interaction involved in the anchoring of the quinoline ring is a hydrogen bond between the C-8 phenol group and the charged amino group of Lys67. The ancillary ring is projected toward the Gly-rich loop of the active site and is in close proximity to the main chain of Phe49. Such conformation allows formation of hydrogen bonds between the C-3′ hydroxyl group and Ser46 while the C-5′ forms other H-bonds with the backbone NH groups of Phe49 and Gly48 (Fig. 1).

The SAR around the substitution pattern on the phenyl ring is difficult to rationalize. Clearly, a suitable hydroxyl substitution pattern seems to be necessary to insure sufficient hydrogen bonding within the ATP-binding site. However, the fairly good activity of non-substituted styrylquinoline **20** can be explained by stronger hydrophobic interactions between its aromatic ring and the phenyl ring of Phe49. 2,4-Dihydroxy substitution (compound **25**) led to high inhibitory activity, while the close styrylquinoline **27** which displays the 2,3-dihydroxy pattern was more than ten-fold less potent. Docking studies with these derivatives (see Supplementary data) indicated a strong hydrogen bond interaction between the C-2′ hydroxyl group and Asp186. The additional interaction with Phe49 that strongly favored the binding of **25** is not possible with the ortho-hydroxyl group in **27**.

In search for more potent inhibitors we screened 7-carboxyl-8-hydroquinoline derivatives possessing a functionalized linker such as amide, hydrazide or urea, assuming that additional interactions from these groups might improve the overall binding. The results are depicted in Table 3. All the compounds tested were found to be active including urea **45** whose ancillary ring was tethered with a long four-atom linker. Among them, the quinoline-2-carboxamide **40** which displayed the 2,4-dihydroxy pattern exhibited an IC_{50} of 200 nM.

Docking studies with this compound indicated that the binding pose of the quinoline core is roughly identical with that of the styrylquinoline **26**. However, because of the greater length of the linker the whole molecule must be substantially bent to accommodate the crucial hydrogen bonds with Lys67, Asp186 and Phe49 and Gly48. In this conformation, which belongs to the cluster of lowest energy conformations initially selected, the hydroxyl group in C-2′ is perfectly positioned to make a strong hydro-

Table 3
Pim-1 inhibition assay results for compounds **18**, **39**–**48**



Compd	X	R_1	R_2	R_3	R_4	IC_{50}[a] (μM)
18	$CONHCH_2$	H	H	OH	OH	2.1
39	$CONHCH_2$	OH	OH	H	H	2.8
40	$CONHCH_2$	OH	H	OH	H	0.2
41	$CONHCH_2$	H	OH	H	OH	0.6
42	$CONHCH_2$	H	OH	OH	OMe	3.3
43	CONH	H	OH	OH	OMe	1.0
44	HNCONH	H	H	OH	OH	1.0
45	$HNCONHCH_2$	H	H	OH	OH	0.5
46	$HNCONHCH_2$	H	H	OMe	H	2.0
47	CONHNH	H	H	H	H	5.1
48	CONHNH	NO_2	H	NO_2	H	3.0

[a] IC_{50} values are shown as the average of three experiments. Variations between determinations are less than 5%.

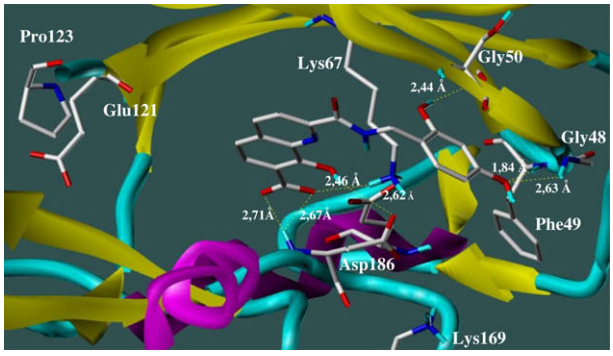


Figure 2. Computational docking of amidoquinoline **40** to the Pim-1 kinase showing interaction with the amino acid residues of the ATP-binding pocket. Close contacts are indicated by dotted lines and distances are provided in Angstroms.

gen bond with the backbone carbonyl group of Gly50 (Fig. 2). It is somewhat surprising that the substantially longer molecule **45** still maintained a similar potency. However docking studies (see Supplementary data) clearly showed that the overall pose is similar though the overall backbone is slightly more curved than is the case of **40**. Thanks to the conformational liberty around the urea linker, the salicylic moiety of **45** donates hydrogen bonds with Asp186, and Lys67, whereas the ancillary ring hydroxyl groups form H-bonds with the backbone carbonyl of Phe49 in the G-loop and with the side chain carboxyl group of Asp186.

Finally, compounds **30** and **40** were evaluated against some other kinases. As shown in Table 4, both compounds displayed good selectivity towards Pim-1 compared to CDK-1 and GSK-3.[45] By contrast these compounds were almost equally potent to inhibit DYRK 1A a serine/threonine kinase known to play a critical role in neurodevelopment.[46] The ability of DYRK 1A to accommodate Pim-1 ligands such as pyrazolidine-3,5-diones derivatives have been previously observed.[47]

Table 4
Kinase selectivity profile of compounds **30** and **40**

Kinase	IC_{50} (μM)	
	Compd **30**	Compd **40**
Pim-1	0.50 ± 0.04	0.40 ± 0.03
GSK-3α/β	>10	>10
CDK1/cyclin B	>10	>10
CDK1/cyclin A	>10	>10
CDK5/p25	>10	>10
CK1	>10	>10
Dyrk 1A	1.30 ± 0.09	4.5 ± 0.5
DYRK2	1.10 ± 0.09	6.3 ± 0.5
CLK1	8.30 ± 0.66	>10

In conclusion, we have identified a novel class of Pim-1 kinase inhibitors in which several candidates endowed with a significant activity emerged. The active compounds displayed the 8-hydroxyquinoline-7-carboxylic acid core. Docking experiments seem to indicate that the heterocyclic core was critically positioned within Pim-1 binding site and that the ancillary ring reinforced the binding through hydrogen bonds. Following these promising results, further studies including synthesis of new analogues and evaluation of the antiproliferative effect in cell-based assays are under investigation.

Acknowledgments

This work was made possible by an initial screening of the BIOCIS compound library. Fellowship (FS) from Tishreen University, Lattakia, (Syria) is gratefully acknowledged. This work was also supported by grants from the 'Cancéropole Grand-Ouest', the 'Association France-Alzheimer Finistère', the 'Association pour la Recherche sur le Cancer' (ARC-1092) and the 'Ligue Nationale contre le Cancer (Comité Grand-Ouest)' (L.M.).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2010.03.061.

References and notes

1. Wang, Z.; Bhattacharya, N.; Weaver, M.; Petersen, K.; Meyer, M.; Gapter, L.; Magnuson, N. S. *J. Vet. Sci.* **2001**, *2*, 167.
2. Bachmann, M.; Möröy, T. *Int. J. Biochem. Cell. Biol.* **2005**, *37*, 726.
3. Amson, R.; Sigaux, F.; Przedborski, S.; Flandrin, G.; Givol, D.; Telerman, A. *Proc. Natl. Acad. Sci. U.S.A.* **1989**, *86*, 8857.
4. Valdman, A.; Fang, X.; Pang, S.-T.; Ekman, P.; Egevad, L. *Prostate* **2004**, *60*, 367.
5. Dhanasekaran, S. M.; Barrette, T. R.; Ghosh, D.; Shah, R.; Varambally, S.; Kurachi, K.; Pienta, K. J.; Rubin, M. A.; Chinnaiyan, A. M. *Nature* **2001**, *412*, 822.
6. Kim, T.-K.; Baird, K.; Ahn, J.-Y.; Meltzer, P.; Lilly, M.; Levis, M.; Small, D. *Blood* **2005**, *105*, 1759.
7. Allen, J. D.; Verhoeven, E.; Domen, J.; van der Valk, M.; Berns, A. *Oncogene* **1997**, *15*, 1133.
8. Popivanova, B. K.; Li, Y.-Y.; Zheng, H.; Omura, K.; Fujii, C.; Tsuneyama, K.; Mukaida, N. *Cancer Sci.* **2007**, *98*, 321.
9. Larid, P. W.; Van der Lugt, N. M. T.; Clarke, A.; Domen, J.; Linders, K.; McWhir, J.; Berns, A.; Hooper, M. *Nucleic Acids Res.* **1993**, *21*, 4750.
10. Qian, K. C.; Studts, J.; Wang, L.; Barringer, K.; Kronkaitis, A.; Peng, C.; Baptiste, A.; LaFrance, R.; Mische, S.; Farmer, B. *Acta Crystallogr., Sect. F* **2005**, *61*, 96.
11. Jacobs, M. D.; Black, J.; Futer, O.; Swenson, L.; Hare, B.; Fleming, M.; Saxena, K. *J. Biol. Chem.* **2005**, *280*, 13728.
12. Qian, K. C.; Wang, L.; Hickey, E. R.; Studts, J.; Barringer, K.; Peng, C.; Kronkaitis, A.; Li, J.; White, A.; Mische, S.; Farmer, B. *J. Biol. Chem.* **2005**, *280*, 6130.
13. Kumar, A.; Mandiyan, V.; Suzuki, Y.; Zhang, C.; Rice, J.; Tsai, J.; Artis, D. R.; Ibrahim, P.; Bremer, R. *J. Mol. Biol.* **2005**, *348*, 183.
14. Bullock, A. N.; Debreczeni, J.; Amos, A. L.; Knapp, S.; Turk, B. E. *J. Biol. Chem.* **2005**, *280*, 41675.
15. Cheney, I. W.; Yan, S.; Appleby, T.; Walker, H.; Vo, T.; Yao, N.; Hamatake, R.; Hong, Z.; Wu, J. Z. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1679.
16. Maksimoska, J.; Williams, D. S.; Atilla-Gokcumen, G. E.; Smalley, K. S. M.; Caroll, P. J.; Webster, R. D.; Filippakopoulos, P.; Knapp, S.; Herlyn, M.; Meggers, E. *Chem. Eur. J.* **2008**, *14*, 4816.
17. Qian, K.; Wang, L.; Cywin, C. L.; Farmer, B. T., II; Hickey, E.; Homon, C.; Jakes, S.; Kashem, M. A.; Lee, G.; Leonard, S.; Li, J.; Magboo, R.; Mao, W.; Pack, E.; Peng, C., ; Prokopowicz, A., III; Welzel, M.; Wolak, J.; Morwick, T. *J. Med. Chem.* **2009**, *52*, 1814.
18. Akué-Gédu, R.; Rossignol, E.; Azzaro, S.; Knapp, S.; Filippakopoulos, P.; Bullock, A. N.; Bain, J.; Cohen, P.; Prudhomme, M.; Anizon, F.; Moreau, P. *J. Med. Chem.* **2009**, *52*, 6369.
19. Tao, Z.-F.; Hasvold, L. A.; Leverson, J. D.; Han, E. K.; Guan, R.; Johnson, E. F.; Stoll, V. S.; Stewart, K. D.; Stamper, G.; Soni, N.; Bouska, J. J.; Luo, Y.; Sowin, T. J.; Lin, N.-H.; Giranda, V. S.; Rosenberg, S. H.; Penning, T. D. *J. Med. Chem.* **2009**, *52*, 6621.

20. Bullock, A. N.; Debreczeni, J. E.; Fedorov, O. Y.; Nelson, A.; Marsden, B. D.; Knapp, S. *J. Med. Chem.* **2005**, *48*, 7604.
21. Chen, L. S.; Redkar, S.; Bearss, D.; Wierda, W. G.; Gandhi, V. *Blood* **2009**, *114*, 4150.
22. Mumenthaler, S. M.; Ng, P. Y. B.; Hodge, A.; Bearss, D.; Berk, G.; Kanekal, S.; Redkar, S.; Taverna, P.; Agus, D. B.; Jain, A. *Mol. Cancer Ther.* **2009**, *8*, 2882.
23. Debreczeni, J. E.; Bullock, A. N.; Atilla, G. E.; Williams, D. S.; Bregman, H.; Knapp, S.; Meggers, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 1580.
24. Anand, R.; Maksimoska, J.; Pagano, N.; Wong, E. Y.; Gimotty, P. A.; Diamond, S. L.; Meggers, E.; Marmorstein, R. *J. Med. Chem.* **2009**, *52*, 1602.
25. Pierce, A. C.; Jacobs, M.; Stuver-Moody, C. *J. Med. Chem.* **2008**, *51*, 1972.
26. Olla, S.; Manetti, F.; Crespan, E.; Maga, G.; Angelucci, A.; Schenone, S.; Bologna, M.; Botta, M. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1512.
27. Tong, Y.; Stewart, K. D.; Thomas, S.; Przytulinska, M.; Johnson, E. F.; Klinghofer, V.; Leverson, J.; McCall, O.; Soni, N. B.; Luo, Y.; Lin, N.-h.; Sowin, T. J.; Giranda, V. L.; Penning, T. D. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5206.
28. Grey, R.; Pierce, A. C.; Bemis, G. W.; Jacobs, M. D.; Stuver-Moody, C.; Jajoo, R.; Mohal, N.; Green, J. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3019.
29. Xia, Z.; Knaak, C.; Ma, J.; Beharry, Z. M.; McInnes, C.; Wang, W.; Kraft, A. S.; Smith, C. D. *J. Med. Chem.* **2009**, *52*, 74.
30. Holder, S.; Lilly, M.; Brown, M. L. *Bioorg. Med. Chem.* **2007**, *15*, 6463.
31. Holder, S.; Zemskova, M.; Zhang, C.; Tabrizizad, M.; Bremer, R.; Neidigh, J. W.; Lilly, M. B. *Mol. Cancer Ther.* **2007**, *6*, 163.
32. Mekouar, K.; Mouscadet, J.-F.; Desmaële, D.; Subra, F.; Leh, H.; Savouré, D.; Auclair, C.; d'Angelo, J. *J. Med. Chem.* **1998**, *41*, 2846.
33. Zouhiri, F.; Mouscadet, J.-F.; Mekouar, K.; Desmaële, D.; Savouré, D.; Leh, H.; Subra, F.; Le Bret, M.; Auclair, C.; d'Angelo, J. *J. Med. Chem.* **2000**, *43*, 1533.
34. Polanski, J.; Zouhiri, F.; Jeanson, L.; Desmaële, D.; d'Angelo, J.; Mouscadet, J.-F.; Gieleciak, R.; Gasteiger, J.; Le Bret, M. *J. Med. Chem.* **2002**, *45*, 4647.
35. Bénard, C.; Zouhiri, F.; Normand-Bayle, M.; Danet, M.; Desmaële, D.; Leh, H.; Mouscadet, J.-F.; Mbemba, G.; Thomas, C.-M.; Bonnenfant, S.; Le Bret, M.; d'Angelo, J. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2473.
36. Normand-Bayle, M.; Bénard, C.; Zouhiri, F.; Mouscadet, J.-F.; Leh, H.; Thomas, C.-M.; Mbemba, G.; Desmaële, D.; d'Angelo, J. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4019.
37. Podeszwa, B.; Niedbala, H.; Polanski, J.; Musiol, R.; Tabak, D.; Finster, J.; Serafin, K.; Milczarek, M.; Wietrzyk, J.; Boryczka, S.; Mol, W.; Jampilek, J.; Dohnal, J.; Kalinowski, D. S.; Richardson, D. R. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6138.
38. Nicklaus, M. C.; Neamati, N.; Hong, H.; Mazumder, A.; Sunder, S.; Chen, J.; Milne, G. W. A.; Pommier, Y. *J. Med. Chem.* **1997**, *40*, 920.
39. Nakamura, H.; Yoshida, T.; Todoko, M.; Ueno, K.; Takagi, M. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2839.
40. Sliman, F.; Desmaële, D. *Synthesis* **2010**, 619.
41. Zouhiri, F.; Danet, M.; Bénard, C.; Normand-Bayle, M.; Mouscadet, J.-F.; Leh, H.; Thomas, C.-M.; Mbemba, G.; d'Angelo, J.; Desmaële, D. *Tetrahedron Lett.* **2005**, *46*, 2201.
42. Chang, P.-T.; Kung, F.-L.; Talekar, R. S.; Chen, C.-S.; Lai, S.-Y.; Lee, H.-Y.; Chern, J.-W. *Anal. Chem.* **2009**, *81*, 6944.
43. Pim kinase assays were conducted according to: Bettayeb, K.; Oumata, N.; Echalier, A.; Ferandin, Y.; Endicott, J. A.; Galons, H.; Meijer, L. *Oncogene* **2008**, *27*, 5797.
44. Jones, G.; Willett, P.; Glen, R. C.; Leach, A. R.; Taylor, R. *J. Mol. Biol.* **1997**, *267*, 727.
45. Ali, A.; Hoeflich, K. P.; Woodgett, J. R. *Chem. Rev.* **2001**, *101*, 2527.
46. Kimura, R.; Kamino, K.; Yamamoto, M.; Nuripa, A.; Kida, T.; Kazui, H.; Hashimoto, R.; Tanaka, T.; Kudo, T.; Yamagata, H.; Tabara, Y.; Miki, T.; Akatsu, H.; Kosaka, K.; Funakoshi, E.; Nishitomi, K.; Sakaguchi, G.; Kato, A.; Hattori, H.; Uema, T.; Takeda, M. *Hum. Mol. Genet.* **2007**, *16*, 15.
47. Koo, K. A.; Kim, N. D.; Chon, Y. S.; Jung, M.-S.; Lee, B.-J.; Kim, J. H.; Song, W.-J. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2324.