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

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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

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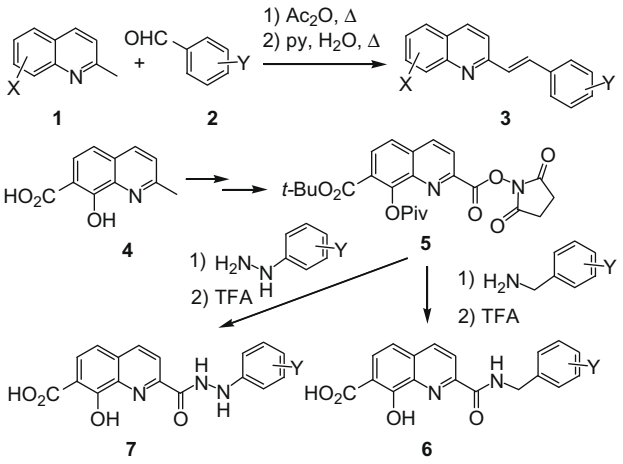
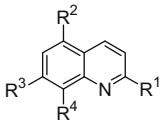


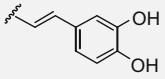
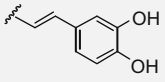
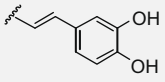
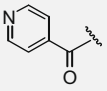
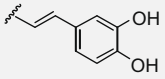
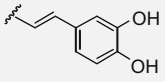
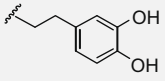
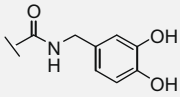
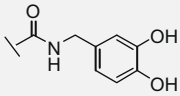
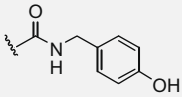
Scheme 1. General synthetic scheme for styryquinolines **3**, quinoline-2-carboxamides **6** and hydrazides **7**.

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%.