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Syntheses and structure–activity relationships for some triazolyl p38α MAPK inhibitors

Jean-Paul G. Seerden [a,*], Gabriela Leusink-Ionescu [a], Robin Leguijt [a], Catherine Saccavini [a], Edith Gelens [a], Bas Dros [a], Titia Woudenberg-Vrenken [b], Grietje Molema [b], Jan A. A. M. Kamps [b], Richard M. Kellogg [a]

[a] Syncom B.V., Kadijk 3, Groningen 9747AT, The Netherlands
[b] Laboratory for Endothelial Biomedicine & Vascular Drug Targeting Research, University Medical Center Groningen, University of Groningen, Hanzeplein 1, Groningen 9713 GZ, The Netherlands

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ABSTRACT

The design, synthesis and biological evaluation of novel triazolyl p38α MAPK inhibitors with improved water solubility for formulation in cationic liposomes (SAINT-O-Somes) targeted at diseased endothelial cells is described. Water-solubilizing groups were introduced via a 'click' reaction of functional azides with 2-alkynyl imidazoles and isosteric oxazoles to generate two small libraries of 1,4-disubstituted 1,2,3-triazolyl p38α MAPK inhibitors. Triazoles with low IC_{50} values and desired physicochemical properties were screened for in vitro downregulation of proinflammatory gene expression and were formulated in SAINT-O-Somes. Triazolyl p38α MAPK inhibitor **88** (IC_{50} = 0.096 μM) displayed the most promising in vitro activity.

The design and synthesis together with pharmacological and clinical evaluation of p38α MAPK (mitogen-activated protein kinase) inhibitors have formed an intense area of research in both the pharmaceutical industry and academia. The subject has been thoroughly reviewed.[1] The p38α MAP kinase signaling pathway is responsible for the expression of pro-inflammatory cytokines, including tumor necrosis factor alpha (TNF-α), interleukine 1-beta (IL-1β), IL-6 and COX-2. These cytokines are elevated or dysregulated in many inflammatory and autoimmune diseases such as rheumatoid arthritis, osteoarthritis, septic shock, asthma, chronic obstructive pulmonary disease, inflammatory bowel disease, Crohn's disease, psoriasis, acute coronary syndrome, multiple sclerosis, diabetes mellitus and cancer. The discovery of p38α MAP kinase as the target of the widely studied pyridinyl imidazoles, with SB203580[2] as lead compound, has led to a continuing search for increased specificity and potency as exemplified by structurally related ATP competitive inhibitors, such as RWJ67657,[3] ML 3403,[4] JNJ7583979,[5] L-790070[6] and RPR203494[7] (Fig. 1). Despite the potential benefits none of the pyridinyl imidazoles has reached the clinic yet because of toxicity problems, often related with off-target selectivity and their highly lipophilic character.[8] Synthetic approaches to this class of compounds have been described starting from cyclocondensation of ketoamides with amines, reaction 1,2-dicarbonyl compounds with ammonia and aldehydes, Suzuki cross-coupling arylations of 2,4,5-tribromoimidazole and cycloaddition of tosylmethylisocyanide with aldimines.[9]

We desired a cost-effective and rapid synthetic method to construct a library of novel pyridinyl imidazoles with improved physicochemical properties that would allow incorporation into cationic liposomes (SAINT-O-Somes) targeted at diseased endothelial cells.[10] The preferred position to modify physicochemical properties is the imidazole C-2 position.[1] As alternative to the previously described methods powerful cross coupling reactions[11] methods may provide the flexibility necessary for construction of such libraries with complete regioselectivity using a versatile pyridinyl imidazole building block obtained from simple 1-methyl-*1H*-imidazole. Our aim was to replace the 4-methylsulfanylphenyl group in lead compound SB203580 at imidazole C-2 by functionalized 1,4-disubstituted 1,2,3-triazoles obtained by means of the well-established 1,4-regioselective Cu(I)-catalyzed 1,3-dipolar cycloaddition ('click' reaction)[12] of azides and alkynes (CuAAC). As described below this strategy enabled the synthesis of a library of novel pyridinyl imidazoles with the possibility to improve physicochemical properties by varying the azide substituents. The general synthetic approach started with the highly efficient straightforward multigram synthesis of the novel C-2 unsubstituted imidazole **6** and the known isosteric oxazole 11[13] scaffolds (Scheme 1).

Regioselective Pd-catalyzed direct C-5 arylation[14] of 1-methyl-1*H*-imidazole **2** with 4-bromopyridine HCl **1** afforded the 4-(1-methyl-1*H*-imidazol-5-yl)pyridine **3** in 70% yield. Regioselective

* Corresponding author. Tel.: +31 050 5757386; fax: +31 050 5757399.
E-mail address: j.p.g.seerden@syncom.nl (J.-P. G. Seerden).

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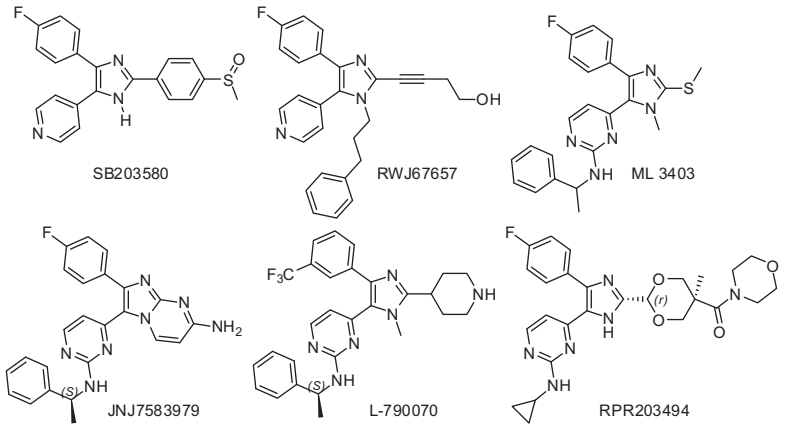
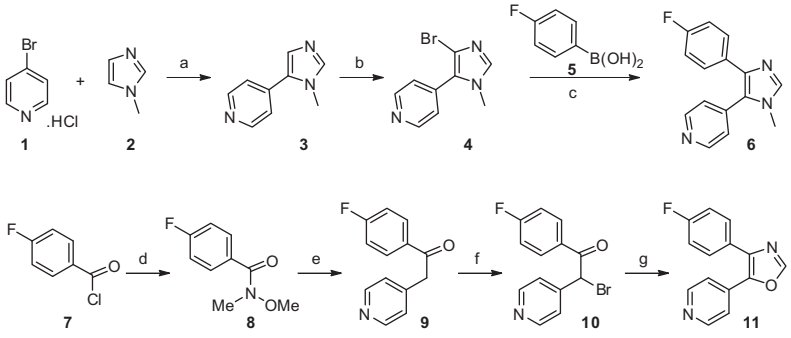


Figure 1. Pyridinyl imidazole type p38α MAP kinase inhibitors.



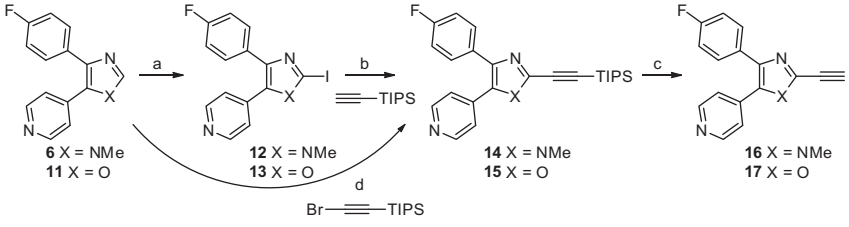
Scheme 1. Regioselective synthesis of **6** and **11**. Reagents and conditions: (a) $Pd(OAc)_2$, PPh_3, K_2CO_3, DMF, 110 °C, 67 h, 70%; (b) NBS, CH_3CN, 93%; (c) $Pd(dppf)Cl_2$, CsF, $BnEt_3NCl$, toluene, H_2O, reflux, 24 h, 90%; (d) *N*,*O*-dimethylhydroxylamine HCl, Et_3N, CH_2Cl_2, 100%; (e) LDA, −78 °C, 4-picoline, 1 h, then rt, 18 h, 98%; (f) Br_2, AcOH, quant.; (g) formamide, H_2SO_4, 15 min 150 °C, microwave, 15%.

imidazole C-4 bromination with NBS gave 4-(4-bromo-1-methyl-1*H*-imidazol-5-yl)pyridine **4** in 93% yield. The subsequent $Pd(dppf)Cl_2$ catalyzed Suzuki reaction of **4** with 4-fluorophenylboronic acid **5** under phase transfer conditions gave 4-(4-(4-fluorophenyl)-1-methyl-1*H*-imidazol-5-yl)pyridine **6** in 90% yield. The synthesis of isosteric oxazole **11** was performed in 15% overall yield from 4-fluorobenzoyl chloride **7** over four steps according to literature procedures.[14] Subsequent C-2 lithiation of **6** or **11** followed by iodination gave 2-iodoimidazole derivative **12** or 2-iodooxazole derivative **13** (Scheme 2).

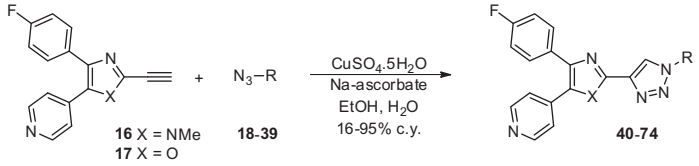
Pd-catalyzed Sonogashira alkynylation of **12** and **13** with 1-triisopropylsilylacetylene afforded the TIPS protected ethynyl imidazole **14** and oxazole **15**, initially in 16–17% yield on use of lutidine as solvent and base. The yield of **15** could be increased to 81% by using Et_3N as base in THF solution. Alternatively, a $Ni(cod)_2$/dppbz (1,2-bis(diphenylphosphino)benzene) catalyzed direct C-2 alkynylation of **6** or **11** with 2-bromo-1-triisopropylsilyl-acetylene[11b] afforded the protected alkynes **14** and **15**, respectively, in one step. TBAF deprotection of the TIPS group afforded the key alkyne building blocks **16** and **17** in 79% and 60% yield. A structurally diverse set of aromatic and aliphatic azides was purchased (**19**, **21**, **25**, **28**–**37**) or prepared (**23**, **24**, **26**, **27**, **38**, **39**)[15] prior for use in the subsequent CuAAC reaction with **16** and **17** to provide novel triazolyl p38α MAPK inhibitors **40**–**74** (Scheme 3).

The aryl azides **18**, **20**, **22** were prepared in situ from the corresponding arylboronic acids using a Cu(II)-catalyzed Chan–Lam type reaction[16] and were used without isolation in a two-step one-pot fashion by addition of Na-ascorbate to promote the subsequent Cu(I)-catalyzed cycloaddition with alkynes **16** and **17** (Scheme 4).

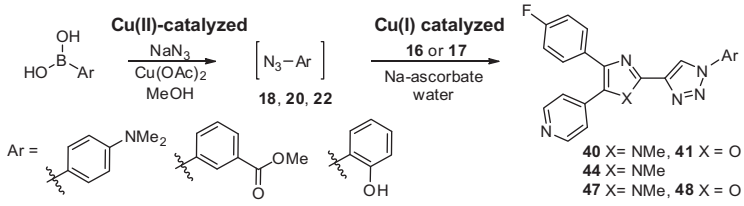
In general, the conversion of the alkyne and azide in the Cu-catalyzed regioselective 1,3-dipolar cycloaddition was high and was accelerated by microwave heating (20 min, 100 °C). For example, triazole **52** was prepared in 65% yield after 20 min heating at 100 °C compared to 20% yield after 6 days at room temperature. The isolated yields of the triazole cycloadducts **40**–**74** were moderate to good. Imidazole based triazoles were obtained in higher yields than the isosteric oxazole based triazoles. Many different functional groups such as alcohols, amines, and carboxylic acids



Scheme 2. Alkynes **16** and **17** via direct C-2 alkynylation. Reagents and conditions: (a) LDA, I_2, 93% (**12**); (b) TIPS-acetylene, $Pd(PPh_3)_4$, CuI, lutidine, 17% (**14**), 16% (**15**; Et_3N, THF: 81%); (c) TBAF, THF, 79% (**16**) and 60% (**17**); (d) Br-acetylene-TIPS, $Ni(cod)_2$, CuI, dppbz, 55% (**14**), 47% (**15**).



Scheme 3. Synthesis of triazolyl p38α MAPK inhibitors **40**–**74**.

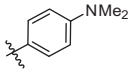
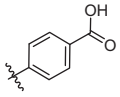
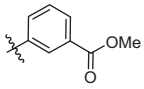
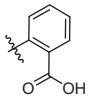
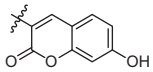
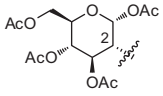
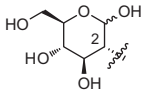
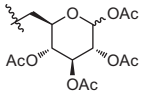


Scheme 4. Two-step one-pot copper(II)- and copper(I)-catalyzed synthesis of 1,2,3-triazoles from arylboronic acids.

could be used in this reaction without the need for protective groups.

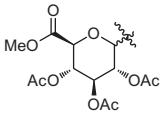
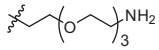
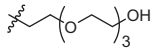
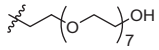
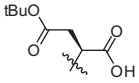
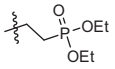
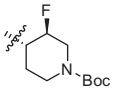
The inhibition of p38α MAP kinase by the first set of triazolyl pyridinyl imidazoles **40**–**74** was determined by a radiometric IC_{50} profiling assay. The IC_{50} data, the calculated LLE[17] (Ligand Lipophilicity Efficiency) and LogS (water-solubility) values are given in Table 1. The results show that the imidazole based triazolyl compounds displayed stronger p38α MAPK inhibition than their isosteric isoxazoles but were less active than the lipophilic reference compounds SB203580 or JNJ7583979.[18] No significant p38α MAPK inhibition was observed with lipophilic substituents such as *N*,*N*-dimethylanilines **40** and **41**, tetra-*O*-acetyl-protected 2-glucose **50** and **51**, ethyleneglycol ethers **58**–**62**, benzyl **65**, ethyl ester **67** and diethyl phosphonate **73**. The influence of the position of the water solubility enhancing substituents R on IC_{50}, LLE and Log*S* was further investigated by simple functional group transforma-

Table 1
Yield, IC_{50}, LLE and Log*S* of novel triazoles

Azide	R	Triazole	c.y.[a] (%)	IC_{50}[f] (μM)	LLE[g]	Log*S*[h]
18		**40** X = NMe **41** X = O	20 16	1.4 19.5	1.6 0.8	−6.05 −5.62
19		**42** X = NMe **43** X = O	94 91[c]	0.14 0.19	2.9 3.1	−5.81 −5.38
20		**44** X = NMe	46	0.99	2.1	−5.87
21		**45** X = NMe **46** X = O	51[c,d] 44[c,d]	1.53 6.51	2.2 2.0	−5.51 −5.08
22		**47** X = NMe **48** X = O	26[d] 22[d]	1.59 2.17	2.2 2.4	−4.71 −4.28
23		**49** X = O	24	n.d.	n.d.	n.d.
24		**50** X = NMe **51** X = O	92 58	>100 >100	n.d. n.d.	−5.96 −5.53
25		**52** X = NMe **53** X = O	65[c] 30	0.71 1.19	6.2 6.4	−3.95 −3.52
26		**54** X = NMe **55** X = O	93[c] 46[c]	n.d. n.d.	n.d. n.d.	n.d. n.d.

(*continued on next page*)

Table 1 (*continued*)

Azide	R	Triazole	c.y.[a] (%)	IC_{50}[f] (μM)	LLE[g]	Log*S*[h]
27		**56** X = NMe **57** X = O	66[c] 79[c]	n.d. n.d.	n.d. n.d.	n.d. n.d.
28		**58** X = NMe	40	5.18	4.2	−2.72
29		**59** X = NMe **60** X = O	82 83	11.2 12.5	3.9 4.2	−3.74 −3.31
30		**61** X = NMe **62** X = O	58 95	11.6 23.5	5.0 5.0	−5.40 −4.97
31	TMS (H)[b]	**63** X = NMe **64** X = O	66[e] 33[e]	0.14 0.38	4.0 4.0	−4.02 −3.58
32		**65** X = O	64	158	−1.1	−5.68
33		**66** X = NMe	30	0.50	4.4	−3.48
34		**67** X = NMe **68** X = O	75 46	1.87 n.d.	2.8 n.d.	−4.65 n.d.
35		**69** X = NMe **70** X = O	74 43	1.44 11.4	4.6 4.1	−2.96 −2.26
36		**71** X = NMe	33	1.49	1.7	−3.18
37		**72** X = NMe	83	n.d.	n.d.	n.d.
38		**73** X = NMe	42	>100	n.d.	n.d.
39		**74** X = NMe	74	n.d.	n.d.	n.d.

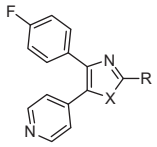
[a] Isolated yields with >98% purity.
[b] Both azide **31** (R = TMS) and NaN_3 gave **63** and **64** (R = H).
[c] Microwave, 20 min, 100 °C.
[d] HCl salt.
[e] Microwave, 20 min, 140 °C, dioxane, NMP.
[f] Radiometric p38α MAPK IC_{50} assay, ProQinase GmbH, Germany.
[g] LLE (Ligand Lipophilicity Efficiency) = pIC_{50}—*c*Log*P*.
[h] Log*S*: calculated water solubility (moles/L) using EPIWEB 4.0 WSKOWWIN v1.41; n.d.: not determined.

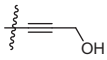
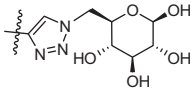
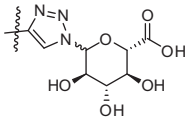
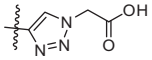
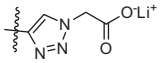
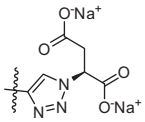
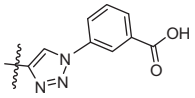
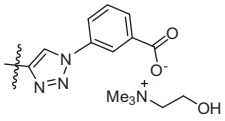
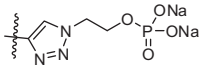
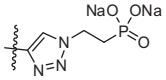
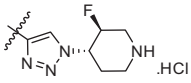
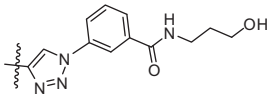
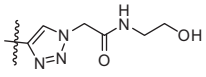
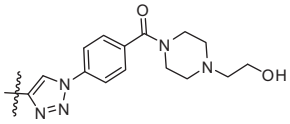
tions of some of the triazolyl cycloadducts **40**–**74**. For example, carboxylic, phosphate or phosphonate ester saponification (with LiOH, I_2 or TMSBr, respectively) afforded the corresponding carboxylate, phosphate or phosphonate derivatives **76**–**87** with lowered IC_{50} and improved aqueous solubility (Table 2). The 2-hydroxyethyl group in **66** displayed activity similar to that of acetic acid derivative **80** or phosphate derivative **86** indicating a favorable hydrogen bond donor/acceptor interaction in the ATP-binding pocket. Conformational restriction by substituents α to the carboxylic acid in **69**, **70**, **71**, **72** and **83** lowered the potency. From a medicinal chemistry point of view the aryl series displayed some interesting differences. The *para*- and *meta*-benzoic acids **42**, **43** and **84** were ten times more potent than the *ortho*-benzoic acids **45** and **46** indicating again a favorable H-bonding interaction in the kinase ATP pocket. The *ortho*-phenols **47** and **48** showed similar poorer IC_{50} values than the *ortho*-benzoic acid **46**. The pK_a of the triazolyl substituent was further varied by introduction of amino alcohols and basic amines via HATU-mediated reaction with carboxylic acids **80** and **84** to provide amides **89**, **90**, **91**, **92** with increased hydrophilic properties. The 3-hydroxypropylamino- or 2-hydroxyethylamino amides **89** and **90** displayed p38α MAPK inhibition similar to the parent carboxylic acids.

Introduction of the *N*-2-hydroxyethyl-piperazine amide as in **91** and **92** increased the IC_{50} values. Boc-deprotection of **74** afforded the potent fluoropiperidine HCl salt **88** with IC_{50} = 96 nM. Introduction of a 3-fluoropiperidine improved the physicochemical properties and oral bioavailability of selective B-raf kinase inhibitors and $5HT_{2B}$ antagonists.[19] The regioselectivity of the CuAAC 1,3-dipolar cycloaddition of **16** and ethyl 2-azidoacetate **34** was reversed by using 15 mol % $Cp^*Ru(PPh_3)_2Cl$ as catalyst in refluxing toluene to afford the corresponding 1,5-disubstituted 1,2,3-triazole[20] **93**, the formal 1,5-regioisomer of **65**, in 56% yield. Ester hydrolysis of **93** with 4 N HCl in dioxane at room temperature for 4 days followed by conversion to the choline salt and lyophilization gave **94** in 46% c.y. The 1,5-disubstituted 1,2,3-triazoles **93** and **94** did not exhibit relevant p38α MAPK inhibition.

The IC_{50} data and the calculated LLE and Log*S* values were among the drug-like selection criteria[21] for in vitro screening of seventeen compounds for inhibition of inflammatory gene expression of TNF-α-activated HUVECs (human umbilical vein endothelial cells) and for lipid based formulation. SB203580, imidazole **6** and fluoropiperidine **88** displayed equipotent in vitro inhibition of COX-2 and IL-6 gene expression (10 μM). Glucose derivative **52** showed low in vitro activity. Liposomal formulation of

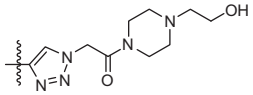
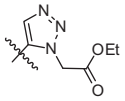
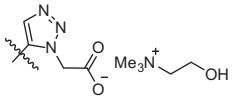
Table 2
IC_{50}, LLE and Log*S* of novel p38α MAPK inhibitors



Compound	X	R	IC_{50} (μM)	LLE	Log*S*
JNJ7583979			0.006	4.4	−5.55
SB203580	NH	PhS(O)Me	0.040	4.6	−4.34
6	NMe	H	0.43	3.7	−3.73
11	O		0.60	3.5	−3.31
16	NMe		0.73	2.7	−4.14
17	O		1.79	2.7	−3.71
75	NMe		0.46	3.8	−3.57
76	NMe		0.40	6.8	−3.65
77	O		5.73	6.1	−3.22
78	NMe		0.59	6.2	−3.77
79	O		1.17	6.3	−3.34
80	NMe		0.74	6.1	−2.90
81	NMe		0.43	8.1	−1.88
82	O		3.2	7.6	−1.45
83	NMe		2.3	5.8	−3.2[a]
84	NMe		0.185	2.8	−5.81
85	NMe		0.091	n.d.	n.d.
86	NMe		0.25	5.5	−4.0[a]
87	NMe		0.35	9.7	−1.23
88	NMe		0.096	7.1	−3.85
89	NMe		0.29	4.0	−5.24
90	NMe		0.89	5.1	−3.12
91	O		2.4	4.6	−4.03

(*continued on next page*)

Table 2 (*continued*)

Compound	X	R	IC_{50} (μM)	LLE	Log*S*
92	NMe		3.8	4.6	−3.45
93	NMe		56	1.3	−4.65
94	NMe		4.2	n.d.	n.d.

[a] Water solubility calculated for corresponding carboxylic acid.

SB203580 or JNJ7583979 into SAINT-O-Somes[10] failed due to their high lipophilicity. Formulation of **52** proceeded with 84% retention after 7 days but after anti-E-selectin antibody coupling no in vitro activity was observed. Formulation of carboxylic acids **80** (16% retention) and **84** into SAINT-O-Somes was not effective, whereas the isosteric water-soluble oxazole **82** gave 67% retention. The disodium phosphate **86** degraded to alcohol **66** during formulation. Remote loading of **6** and **88** into SAINT-O-Somes resulted after 7 days in 95% and 92% retention, respectively. Anti-E-selectin antibody coupling to these formulated liposomes resulted however in complete release of **6** whereas **88** partially remained inside the SAINT-O-Somes.

In summary, we have applied a reaction sequence of regioselective direct C–H arylation and cross coupling alkynylation of imidazoles and oxazole, followed by azide 'click' reactions with complete regioselective control, to provide access to novel triazolyl p38α MAPK inhibitors with improved water solubility for further biological evaluation and drug delivery studies.[22] We believe that the chosen synthetic strategy can find wider application for the library synthesis of other triazolyl trisubstituted azoles with improved water solubility.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2014.01.034. These data include MOL files and InChiKeys of the most important compounds described in this article.

References and notes

1. (a) Laufer, S.; Margutti, S. Medicinal Chemistry Approaches for the Inhibition of the p38 MAPK Pathway. In: *Protein Kinases as Drug Targets*, Klebl, B., Müller, G., Hamacher, M., Eds.; Methods and Principles in Medicinal chemistry, Wiley-VCH, **2011**; Vol. 49, Chapter 9, pp 271–304.; (b) Scior, T.; Domeyer, D. M.; Cuanalo-Contreras, K.; Laufer, S. A. *Curr. Med. Chem.* **2011**, *18*, 1526; (c) Müller, S.; Knapp, S. *Expert Opin. Drug Discovery* **2010**, *5*, 867; (d) Coulthard, L. R.; White, D. E.; Jones, D. L.; McDermott, M. F.; Burchill, S. A. *Trends Mol. Med.* **2009**, *15*, 369; (e) Karcher, S. C.; Laufer, S. A. *Curr. Top. Med. Chem.* **2009**, *9*, 655; Sarma, R.; Sinha, S.; Ravikumar, M.; Kumar, M. K.; Mahmood, S. K. *Eur. J. Med. Chem.* **2008**, *43*, 2870.
2. (a) Cuenda, A.; Rouse, J.; Doza, Y. N.; Meier, R.; Cohen, P.; Gallagher, T. F.; Young, P. R.; Lee, J. C. *FEBS Lett.* **1995**, *364*, 229; (b) Chakravarty, S.; Dugar, S. *Annu. Rep. Med. Chem.* **2002**, *37*, 177.
3. Zhong, H.; Dubberke, S.; Müller, S.; Rossler, A.; Schultz, T.W.; Korey, D.J.; Otten, T.; Walker, D.G.; Abdel-Magid, A. US2003/0045723.
4. (a) Laufer, S.A.; Wagner, G.K.; Kotschenreuther, D.A.; Albrecht, W. J. Med. Chem. **2003**, *46*, 3230; (b) Laufer, S.; Striegel, H.G.; Albrecht, W.; Tollmann, K. WO03/09673A1.
5. Brown, L.J.; Geesin, J.C.; Fang, C.H.; Siekierka, J.J. US2009/0162351 and US2009/0162376.
6. Liverton, N. J.; Butcher, J. W.; Claiborne, C. F.; Claremon, D. A.; Libby, B. E.; Nguyen, K. T.; Pitzenberger, S. M.; Selnick, H. G.; Smith, G. R.; Tebben, A. *J. Med. Chem.* **1999**, *42*, 2180.
7. Collis, A. J.; Foster, M. L.; Halley, F.; Maslen, C.; McLay, I. M.; Page, K. N.; Redford, E. J.; Souness, J. E.; Wilsher, N. E. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 693.
8. (a) Koeberle, S. C.; Romir, J.; Fischer, S.; Koeberle, A.; Schattel, V.; Albrecht, W.; Grütter, C.; Werz, O.; Rauh, D.; Stehle, T.; Laufer, S. A. *Nat. Chem. Biol.* **2012**, *8*, 141; (b) Davis, M. I.; Hunt, J. P.; Herrgard, S.; Ciceri, P.; Wodicka, L. M.; Pallares, G.; Hocker, M.; Treiber, D. K.; Zarrinkar, P. P. *Nat. Biotechnol.* **2011**, *29*, 1046; (c) Anastassiadis, T.; Deacon, S. W.; Devarajan, K.; Ma, H.; Peterson, J. R. *Nat. Biotechnol.* **2011**, *29*, 1039; pyridinyl imidazoles as BRAF and CK1 inhibitors: (d) Niculescu-Duvaz, D.; Niculescu-Duvaz, I.; Suijkerbuijk, B. M. J. M.; Ménard, D.; Zambon, A.; Davies, L.; Pons, J.-F.; Whittaker, S.; Marais, R.; Springer, C. J. *Bioorg. Med. Chem.* **2013**, *21*, 1284; adenosine A3 antagonists: Ohkawa, S.; Kanzaki, N.; Miwatashi, S.; PCT Int. Appl., WO 2000064894.; glucagon receptor antagonists: Chang, L. L.; Sidler, K. L.; Cascieri, M. A.; de Laszlo, S.; Koch, G.; Li, B.; MacCoss, M.; Mantlo, N.; O'Keefe, S.; Pang, M.; Rolando, A.; Hagmann, W. K. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2549.
9. (a) Deng, X.; Mani, N. S. *Org. Lett.* **2006**, *8*, 269; (b) Bellina, F.; Cauteruccio, S.; Rossi, R. *Tetrahedron* **2007**, *63*, 4571.
10. (a) Adrian, J. E.; Morselt, H. W.; Süss, R.; Barnert, S.; Kok, J. W.; Asgeirsdóttir, S. A.; Ruiters, M. H.; Molema, G.; Kamps, J. A. A. M. *J. Controlled Release* **2010**, *144*, 341; (b) Kowalski, P. S.; Lintermans, L. L.; Morselt, H. W. M.; Leus, N. G. J.; Ruiters, M. H. J.; Molema, G.; Kamps, J. A. A. M. *Mol. Pharmaceutics* **2013**, *10*, 3033.
11. (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174; (b) Matsuyama, N.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2009**, *11*, 4156; (c) Dudnik, A. S.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2010**, *49*, 2096.
12. (a) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2004**, *2001*, 40; (b) Kolb, H. C.; Sharpless, K. B. *Drug Discovery Today* **2003**, *8*, 1128; (c) Lewis, W. G.; Green, L. G.; Grynszpan, F.; Radic, Z.; Carlier, P. R.; Taylor, P.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 1053.
13. (a) Revesz, L.; Di Padova, F. E.; Buhl, Th.; Feifel, R.; Gram, H.; Hiestand, P.; Manning, U.; Zimmerlin, A. G. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1261; (b) Collis, A.J.; Halley, F.; McLay, I.M., WO00/35911.
14. (a) Bellina, F.; Cauteruccio, S.; Di Fiore, A.; Rossi, R. *Eur. J. Org. Chem.* **2008**, 5436; (b) Roger, J.; Doucet, H. *Tetrahedron* **2009**, *65*, 9772.
15. **24**: Sivakumar, K.; Xie, F.; Cash, B. M.; Long, S.; Barnhill, H. N.; Wang, Q. *Org. Lett.* **2004**, *6*, 4603. **26**: prepared from D-glucose; **27** from acetobromo-α-D-glucuronic acid methyl ester; **38** from diethyl 2-bromoethylphosphonate; **39** from racemic (3:1) *cis*-/*trans*-1-Boc-3-fluoro-4-hydroxypiperidine.
16. Rimes, K. D.; Gupte, A.; Aldrich, C. C. *Synthesis* **2010**, 1441.
17. (a) Edwards, M. P.; Price, D. A. *Annu. Rep. Med. Chem.* **2010**, *45*, 380; (b) Leeson, P. D.; Empfield, J. R. *Annu. Rep. Med. Chem.* **2010**, *45*, 393.
18. JNJ7583979 was prepared analog to Rupert, K. C.; Henry, J. R.; Dodd, J. H.; Wadsworth, S. A.; Cavender, D. E.; Olini, G. C.; Fahmy, B.; Siekierka, J. J. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 347.
19. (a) Newhouse, B. J.; Hansen, J. D.; Grina, J.; Welch, M.; Topalov, G.; Littman, N.; Callejo, M.; Martinson, M.; Galbraith, S.; Laird, E. R.; Brandhuber, B. J.; Vigers, G.; Morales, T.; Woessner, R.; Randolph, N.; Lyssikatos, J.; Olivero, A. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 3488; (b) Thuring, J.W.J.F.; Verdonck, L.A.L. WO2012028614.
20. Zhang, L.; Chen, X.; Xue, P.; Sun, H. H. J.; Williams, I. D.; Sharpless, K. D.; Fokin, V. V.; Jia, G. *J. Am. Chem. Soc.* **2005**, *127*, 15998.
21. Selection criteria: IC_{50} <1 μM, LLE > 5, Log*S* >−4, rule of 3/75: *c*Log*P* <3, TPSA > 75 Å^2, Mol Wt <500.
22. Kuldo, J. M.; Westra, J.; Asgeirsdóttir, S. A.; Kok, R. J.; Oosterhuis, K.; Rots, M. G.; Schouten, J. P.; Limburg, P. C.; Molema, G. *Am. J. Physiol. Cell Physiol.* **2005**, *289*, C1229; Kuldo, J. M.; Ogawara, K. I.; Werner, N.; Asgeirsdóttir, S. A.; Kamps, J. A.; Kok, R. J.; Molema, G. *Curr. Vasc. Pharmacol.* **2005**, *3*, 11.