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Synthesis and structure-activity relationships of 4-fluorophenyl-imidazole p38α MAPK, CK1δ and JAK2 kinase inhibitors

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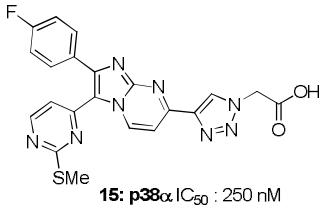
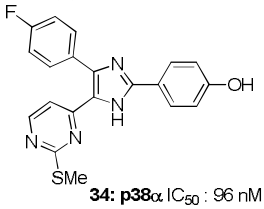
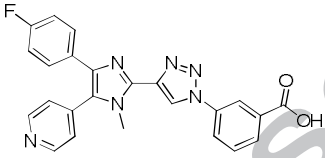


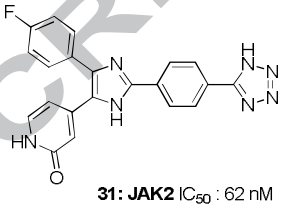
15: p38α IC_{50} : 250 nM



34: p38α IC_{50} : 96 nM



3: CK1δ IC_{50} : 89 nM



31: JAK2 IC_{50} : 62 nM

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Synthesis and structure-activity relationships of 4-fluorophenyl-imidazole p38α MAPK, CK1δ and JAK2 kinase inhibitors

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ABSTRACT

The synthesis and structure-activity relationships of novel 4-(4'-fluorophenyl)imidazoles as selective p38α MAPK, CK1δ and JAK2 inhibitors with improved water solubility are described. Microwave-assisted multicomponent reactions afforded 4-fluorophenyl-2,5-disubstituted imidazoles. Carboxylate and phosphonate groups were introduced via 'click' reactions. The kinase selectivity was influenced by the heteroaryl group at imidazole C-5 and the position of a carboxylic acid or tetrazole at imidazole C-2. For example, pyrimidines **15** and **34** inhibited p38α MAPK with IC_{50} = 250 nM and 96 nM, respectively. Pyridine **3** gave CK1δ inhibition with IC_{50} = 89 nM and pyridin-2-one **31** gave JAK2 inhibition with IC_{50} = 62 nM.

The discovery and development of small-molecule kinase inhibitors to treat inflammatory and immune-related diseases and cancer with minimal undesirable side effects are subjects of major attention in the pharmaceutical industry. Resistance, gene point mutations, multi-kinase inhibition and the need for selectivity are major issues in the design of therapeutically relevant kinase inhibitors[1]. Despite recent FDA approval and successful marketing of small-molecule tyrosine kinase inhibitors that target vascular endothelial growth factor (VEGF), epidermal growth factor receptor (EGFR), Bcl-Abl, and Janus kinase (JAK1, JAK2 and JAK3) for the treatment of chronic myeloid leukemia (CML), non-small cell lung cancer, kidney and breast cancer, myelofibrosis (MF), and rheumatoid arthritis, many specific kinase inhibitors have not been further developed owing to toxicity or poor ADME[2]. The poor developability for oral administration is correlated to the increased lipophilicity of kinase inhibitors and resembles a classical medicinal chemistry problem. The highly lipophilic character of many potent kinase inhibitors is a consequence of the highly lipophilic binding pocket next to the small polar hinge recognition site. Improving the water solubility of these highly lipophilic kinase inhibitors without lowering the potency and/or proper formulation into targeted liposomes might solve the problem and make potent kinase inhibitors become orally or intravenously available for the benefit of patients[3]. Previously we have described regioselective direct C-H arylation and cross coupling alkynylation of 4-fluorophenyl-imidazoles, followed by regioselective azide 'click' reactions, to provide access to novel triazolyl p38α MAPK inhibitors with improved water solubility for further biological evaluation and drug delivery studies[4]. The 4-fluorophenyl-imidazole chemical scaffold is not only present in p38α MAPK inhibitors, such as SB203580, SB202190 or the highly potent JNJ 7583979[5], but also in caseine kinase I delta (CK1δ) inhibitors PF-670462[6], CKP138[7] and others[8], as well as in some JAK inhibitors, such as conformationally rigid pan-JAK inhibitor Pyridone 6[9] and related pyridones[10] (Figure 1).

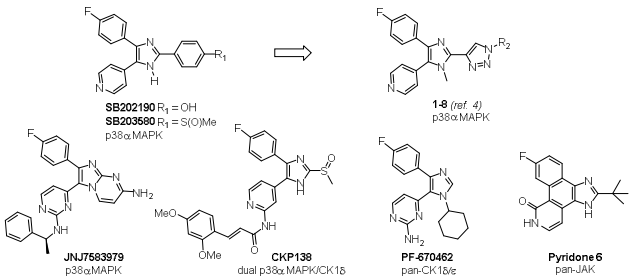

Figure 1. 4-(4-Fluorophenyl)-5-aryl imidazole kinase inhibitors

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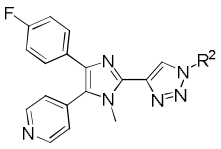
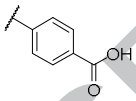
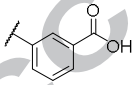
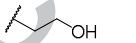
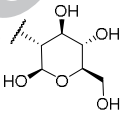
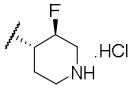
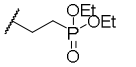
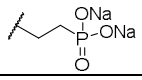
In addition, several p38α MAPK inhibitors such as SB203580 and SB202190 have been shown to be moderate CKδ1 inhibitors[11] and cross reactivity between p38α and CK1δ in Wnt β-catenine signaling[12] has been reported. No p38α MAPK or CK1δ kinase inhibitors have been approved yet. The discovery of activating mutations in JAK2 and myeloproliferative leukemia virus oncogene (MPL) in patients with myeloproliferative neoplasms (MPN) has led to the rapid clinical development of several JAK kinase inhibitors and recent approval of JAK1/2 inhibitor ruxolitinib for the treatment of MF. Many JAK2 inhibitors are being examined for oncological applications.

The previously developed 'click' strategy for the synthesis of other triazolyl trisubstituted azoles with improved water solubility was further explored, using the 4-fluorophenyl-imidazoles in Figure 1 as model compounds[4]. The various chemotypes of 4,5-diarylimidazoles[13] were prepared from α-bromo ketones and 2-aminopyrimidines or from 1,2-dicarbonyl compounds in a highly efficient 3-component reaction with ammonia and aldehydes. The replacement of the 4-pyridyl group, essential for p38α selectivity, with a pyrimidine or 2-oxo-1,2-dihydropyridin-4-yl group and scaffold hopping from triazolyl-aryl to aryl triazolyl moieties were investigated in order to have impact on the selectivity and potency for p38α MAPK, CK1δ, JAK1, JAK2 and JAK3 kinase inhibition. A selection of our previously prepared small library of triazolyl 4-fluorophenyl-imidazole p38α MAPK inhibitors[4] was assayed for p38α, CK1δ, JAK1, JAK2 and JAK3 inhibition. The results are depicted in Table 1.

Table 1. Triazolyl 4-fluorophenyl-imidazoles as dual p38α MAPK/CK1δ inhibitors (IC_{50} in μM)



1-8 *(ref. 4)*

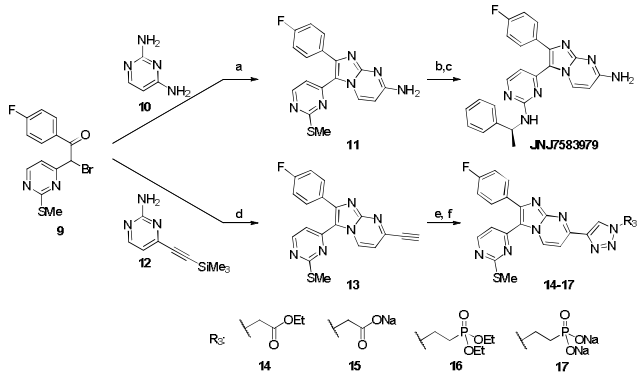
Compound	R^2	p38α MAPK IC_{50} (μM)[a]	CK1δ IC_{50} (μM)[a]	Log *S*[c]
SB202190	-	0.009	0.188	-4.35
1	H	0.21 (0.14)[b]	0.202	-4.02
2		0.166 (0.14)[b]	1.60	-5.81
3		0.185	0.089	-5.81
4		0.783 (0.50)[b]	0.24	-3.48
5		1.02	0.439	-3.95
6		0.096	0.437	-3.85
7		2.48 (>100)[b]	3.10	-5.24
8		0.345	0.225	-4.0[d]

[a] IC_{50} determined by radiometric assay, ProQinase GmbH, Germany; JAK1, JAK2, JAK3 IC_{50} >100 μM; [b] reported IC_{50} values from ref 4 in brackets; [c] calculated solubility (moles/L) using EPIWEB 4.1 WSKOWWIN v1.42; the actual aqueous solubility has not been determined; [d] water solubility calculated for corresponding phosphonic acid.

None of the 4-(4'-fluorophenyl)-pyridinylimidazoles **1-8** significantly inhibited any of the JAK1, JAK2 or JAK3 enzymes (IC_{50} >100 μM) and therefore these results have been omitted in Table 1. SB202190 was used as reference p38α MAPK inhibitor (IC_{50} = 0.009 μM). It also showed CK1δ inhibition (IC_{50} = 0.188 μM) in agreement with the literature[9]. All triazolyl p38α MAPK inhibitors **1-8** were able to inhibit CK1δ kinase with various IC_{50} values. The unsubstituted triazole **1** behaved as a dual p38α MAPK/CK1δ inhibitor (IC_{50} ~ 0.2 μM). The water-soluble racemic *trans*-3-fluoropiperidine HCl salt **6** showed the best p38α MAPK inhibition (IC_{50} = 0.096 μM) and also some CK1δ inhibition (IC_{50} = 0.437 μM). Interestingly, from a medicinal chemical point of view, the difference in selectivity and potency for p38α MAPK or CK1δ inhibition was most pronounced between the *para*- and *meta*-benzoic acid derivatives **2** and **3**, respectively. Whereas **2** and **3** gave almost equal p38α inhibition (IC_{50} = 0.166 μM and 0.185 μM respectively), the *para*-benzoic acid **2** was 10-fold more selective for p38α than CK1δ, its *meta*-benzoic acid analog **3** gave 18-fold stronger CK1δ inhibition (IC_{50} = 0.089 μM) than **2** (IC_{50} = 1.6 μM). Despite its poor water-solubility and low retention efficiency upon formulation into SAINT-O-Somes[4] the *meta*-benzoic acid **3** could serve as further starting point for the design of more selective CK1δ inhibitors by varying substituent R^2. Caseine kinase 1 (CK1), a family of conserved serine/threonine kinases (e.g. CK1δ), modulates Wnt signaling pathways and has been implicated in the regulation of vesicular trafficking, DNA damage repair, cell cycle progression, cytokinesis and circadian rhythms[14].

The highly potent p38α MAPK inhibitor JNJ 7583979[15] was prepared from α-bromo ketone **9** by condensation with 2,5-diaminopyrimidine **10** to provide imidazo[1,2-a]pyrimidine **11** (42% yield.), followed by S-oxidation and substitution with (*S*)-1-phenylethylamine in low yield (*Scheme 1*). For applying the 'click' approach to enhance aqueous solubility the required alkyne group was introduced via a condensation reaction of α-bromo ketone **9** with 4-((trimethylsilyl)ethynyl)pyrimidin-2-amine **12**[16] in refluxing EtOH for 16 hours. Subsequent deprotection with 1M TBAF in THF afforded the key 7-ethynyl-imidazo[1,2-a]pyrimidine **13** in 13% yield over two steps[17]. The subsequent Cu-catalyzed 'click' reaction of **13** with azido ethyl acetate gave the 7-(1,2,3-triazol-4-yl)imidazo[1,2-a]pyrimidine **14** in 50% yield. Saponification of **14** gave the corresponding sodium carboxylate **15**. In a similar way the Cu-catalyzed 'click' reaction of **13** with freshly prepared diethyl (2-azidoethyl)phosphonate[18] afforded the diethylphosphonate **16**. Deprotection of the phosphonate with TMSBr, purification by preparative LC and subsequent treatment with stoichiometric NaOH and lyophilization afforded water soluble disodium phosphonate **17**. The lipophilic esters **14** and **16** were synthetic intermediates for the preparation of the water-soluble compounds **15** and **17** and were not screened for their potency on kinase inhibition.

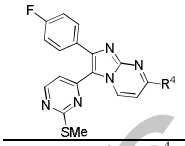
Scheme 1. Synthesis of 7-(1,2,3-triazol-4-yl)imidazo[1,2-a]pyrimidines **14**-**17**

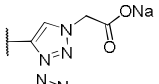
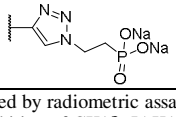


Reagents and conditions: a) EtOH, reflux, 13 h, 42% c.y.; b) oxone (3 eq.), H_2O, MeOH, 20 h, room temp., 78% c.y.; c) (*S*)-phenylethylamine, 24% c.y.; d) EtOH, reflux, 16 h; 1M TBAF in THF, 13% c.y.; e) $CuSO_4$, Na-ascorbate, H_2O, room temp. **14**: azido ethyl acetate (50% c.y.) or **16**: diethyl (2-azidoethyl)phosphonate (48% c.y.); f) **15**: aq. NaOH, MeOH reflux, 88% c.y.; **17**: TMSBr, DMF; aq. NaOH; lyophilization, 27% c.y.

The inhibition of p38α MAPK by imidazo[1,2-a]pyrimidines **11**, **13**, **15** and **17**, the calculated Ligand Lipophilicity Efficiency (LLE[19]) and aqueous solubility (Log *S*) are presented in Table 2. The reference compound JNJ7583979 was a potent and selective p38α MAPK inhibitor with IC_{50} = 8.5 nM.[5] No significant CK1δ, JAK1, JAK2, or JAK3 inhibition was found (IC_{50} > 100 μM). The presence of the lipophilic (*S*)-1-phenylethylamino group in JNJ7583979 is crucial[20] for its high potency as compared to 14-fold less potent thiomethyl imidazo[1,2-a]pyrimidine analog **11** (IC_{50} = 120 nM; R_4 = NH_2). The replacement of the amino group in **11** by the triazolyl acetate group in **15** (IC_{50} = 250 nM) resulted in an 11-fold increase in aqueous solubility with concomitant 2-fold decrease in p38α inhibition. This demonstrates that introduction of a triazolyl acetate group is an effective way of improving the physicochemical property without a dramatic decrease in potency. The integrated physicochemical properties of **15** (LLE = 7.9, Log *S* = -2.95) have met our initially hypothesized requirements for further evaluation in formulation studies[21]. Note, however, that on further increase of the aqueous solubility by introduction of the 1,2,3-triazolyl-1-ethyl disodium phosphonate group in **17** no p38α MAPK inhibition was achieved.

Table 2. Imidazo[1,2-a]pyrimidine p38α MAPK inhibition, LLE and Log *S*

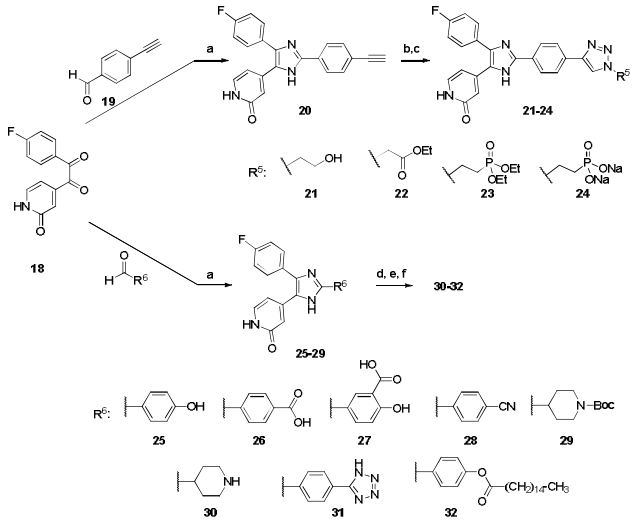


compound	R^4	p38α IC_{50} (μM)[a]	LLE[b]	Log *S*[c]
JNJ 7583979		0.0085	3.3	-5.55
11	NH_2	0.12	4.3	-4.02
13		2.51	1.8	-5.10
15		0.25	7.9	-2.95
17		>100	n.d.	-2.19

[a] IC_{50} determined by radiometric assay, ProQinase GmbH, Germany; no significant inhibition of CK1δ, JAK1, JAK2, JAK3 was found (IC_{50} >100 μM); [b] LLE = pIC50 – cLogP; [c] calculated water solubility (moles/L) using EPIWEB 4.1 WSKOWWIN v1.42.

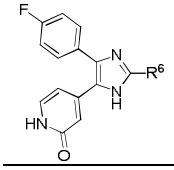
The 'click' strategy for enhancing solubility was also applied to the 4-fluorophenylimidazoles with a pyridine group at C-5 by introducing the solubilizing group at the imidazole C-2 position. The 1,2,3-triazole-substituted "click" products **1**-**8** were less effective p38 MAPK inhibitors than SB203580[4] or SB202190 (Table 1), an effect that might originate from less efficient π-stacking with the Tyr35 residue in the ATP-binding pocket of p38 MAP kinase. The influence of the 1,2,3-triazole group was now studied by scaffold hopping, interchanging the triazole and benzoic acid group in triazolylbenzoic acid p38α MAPK inhibitors **2** and **3**. Improved p38 MAPK inhibition by successful replacement of the essential 4-pyridine, which gives a strong hydrogen bond between the p38 amide NH of Met109 and the pyridine nitrogen, by a pyrimidine has been demonstrated in many 4-fluorophenylimidazoles also to minimize cytochrome P450 inhibition. The pyridone ring of 'Pyridone 6' (*Figure 1*) binds in the ATP-binding site of JAK and the amide segment forms key dual H-bonds to the hinge region of the protein[1]. A double hydrogen bond of the 4-pyridone group with Met_{109}-Gly_{110} in the p38α MAP kinase ATP-pocket might give stronger interactions and lower p38α IC_{50} values. An efficient microwave-assisted multicomponent Debus-Radziszewski[22] reaction of diketone **18**[23] and 4-ethynyl-benzaldehyde **19** using 10 eq. ammonium acetate in acetic acid for 10 minutes at 180 °C in a closed vessel afforded the new building block 4-(2-(4-ethynylphenyl)-1*H*-imidazol-5-yl)pyridin-2(1*H*)-one **20** on multigram scale (*Scheme 2*). Subsequent regioselective Cu-catalyzed 'click' reactions with azido ethanol, azido ethyl acetate and diethyl (2-azidoethyl)phosphonate afforded the corresponding 1*H*-1,2,3-triazol-4-yl)phenyl)-1H-imidazol-5-yl)pyridin-2(1*H*)-ones **21-23**, respectively. Saponification of the diethylphosphonate ester **23** with TMSBr in DMF gave the water-soluble disodium phosphonate **24**. The analogous 4-(4-(4-fluorophenyl)-1*H*-imidazol-5-yl)pyridin-2(1*H*)-ones **25**-**29** were efficiently prepared in a similar way from diketone **18** via a microwave-assisted Debus-Radziszewski reaction with ammonium acetate and 4-hydroxybenzaldehyde, 4-carboxybenzaldehyde, 3-hydroxy-4-carboxybenzaldehyde, 4-cyanobenzaldehyde and Boc-4-N-piperidine carboxaldehyde, respectively. The corresponding water-soluble sodium salts **26.Na** and **27.Na** of the poorly water-soluble carboxylic acids **26** and **27** were obtained after lyophilization. Deprotection of **29** under acidic conditions afforded piperidine **30** as a water-soluble HCl salt in 29% yield over 2 steps. The tetrazole **31** was prepared in 16% yield from poorly soluble nitrile **28** via a 1,3-dipolar cycloaddition with aqueous sodium azide in the presence of $ZnBr_2$[24] using 2-propanol as cosolvent, followed by purification by preparative LC. The corresponding tetrazolyl potassium salt of **31** was highly water-soluble. The tetrazole group is considered to be a bioisostere of the carboxylic acid group in **26**. The palmitoyl ester prodrug **32** was prepared from phenol **25** and palmitoyl chloride (Et_3N, DCM, DMF; isolated after preparative LC). The inhibition of p38α MAPK, CK1δ, JAK1, JAK2 and JAK3 kinase was determined by a radiometric IC_{50} profiling assay. The results in Table 3 only summarize the p38α and JAK2 IC_{50} data because no significant inhibition of the other kinases was observed with IC_{50} > 10 μM.

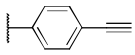
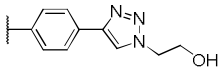
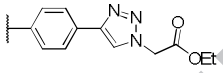
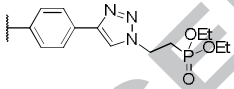
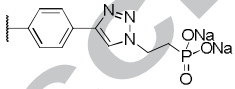
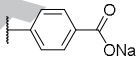
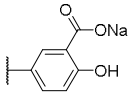
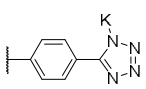
Scheme 2. Synthesis of 4-fluorophenylimidazole-pyridin-2(1H)-ones **20**-**31**



Reagents and conditions: a) NH_4OAc (10 eq.), AcOH, 10 min. 180 °C microwave heating; **20**: 86% c.y.; **25**-**29**: 78-96% c.y.; b) $CuSO_4$, Na-ascorbate, H_2O, **21**: azido ethanol, 68% c.y.; **22**: azido ethyl acetate, 79% c.y.; **23**: diethyl (2-azidoethyl)phosphonate, 34% c.y.; c) **24**: TMSBr, DMF, prep. LC, d) **29**, aq. HCl: **30** (29% c.y. over 2 steps from **18**); e) **28**, $ZnBr_2$, NaN_3: **31** (16%); f) **25**, palmitoyl chloride, Et_3N, DCM, DMF: **32** (54% c.y.).

Table 3. Selective JAK2 inhibition[a] (IC_{50} µM) by pyridones **20**-**31**, LLE and Log *S*



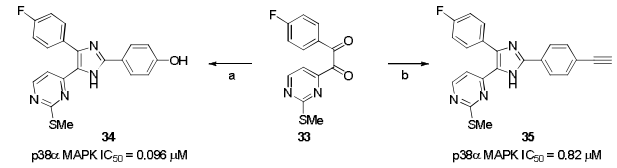
	R^6	p38α IC_{50} (µM)	JAK2 IC_{50} (µM)	LLE	Log *S*
20		9.39	14.3	1.27	-4.84
21		18.6	0.50	4.24	-4.18
22		32.9	0.352	3.38	-5.35
23		>100	4.20	2.29	-5.94
24		>100	45.5	5.72	-1.93
25		4.96	0.911	3.22	-3.56
26.Na		2.94	0.274	7.52	-2.59
27.Na		6.81	3.71	5.62	-2.79
30		1.14	6.62	2.81	-3.69
31.K		2.53	0.061	6.72	-2.81

[a] IC_{50} determined by radiometric assay (ProQinase GmbH, Germany); no significant inhibition of CK1δ (IC_{50} >10 µM; except **30**: IC_{50} = 1.20 µM), JAK1 (IC_{50} >10 µM; except **31**: IC_{50} = 1.68 µM), or JAK3 (IC_{50} >10 µM except **31**: IC_{50} = 0.783 µM) was found; [b] Log *S*: calculated water solubility (moles/L) using EPIWEB 4.1 WSKOWWIN v1.42.

No significant inhibition of p38α MAPK, CK1δ, JAK1 or JAK3 was found (IC_{50} >1 µM) for any of the pyridones **20-31** including the highly water-soluble disodium phosphonate **24**. However, the JAK2-selective benzoate **26** (JAK2: IC_{50} = 0.274 µM; JAK1: IC_{50} = 14.1 µM; JAK3: IC_{50} = 3.90 µM) displayed a 10- to 100-fold stronger inhibition of JAK2 against p38α (IC_{50} = 2.94 µM) and CK1δ (IC_{50} = 24.8 µM), respectively. The bioisosteric tetrazole potassium salt **31** was the most potent JAK2 inhibitor (IC_{50} = 0.061 µM) with comparable JAK2 selectivity against p38α (IC_{50} = 2.53 µM), CK1δ (IC_{50} = 12.1 µM), JAK1 (IC_{50} = 1.68 µM) and JAK3 (IC_{50} = 0.783 µM) as benzoate **26**. In addition to their JAK2 kinase inhibition the pyridones **26.Na** and **31.K** show improved water solubility with desired physicochemical properties (LLE and Log *S*).

The synthetic approach shown in Scheme 3, as an obvious modification of Scheme 2, allows investigation of the influence of the 5-heteroaryl substituent in the 4-fluorophenylimidazoles on the kinase selectivity and potency (IC_{50}). This is further exemplified by pyridinyl-imidazole SB202190, pyridonyl-imidazole **26** and pyrimidinyl-imidazole **34**. The p38α MAPK inhibitors **34** and **35** were both prepared from a common diketone intermediate **33** via a clean multicomponent Debus-Radziszewski reaction using microwave heating similar to the synthesis of **20** and **25-29** respectively (*Scheme 3*). The pyrimidine **34** is a p38α MAPK inhibitor with IC_{50} = 0.096 µM and is a 10-fold less potent analogue of SB202190. Replacement of the 4-OH substituent with a 4-ethynyl group in **35** caused a 8-fold drop in potency (IC_{50} = 0.82 µM). No significant inhibition of CK1δd, JAK1, JAK2, JAK3 was found (IC_{50} >100 µM). Note that the alkyne **35** could serve as building block for the library synthesis of triazole analogues with improved physicochemical properties.

Scheme 3. Synthesis of 4-fluorophenylimidazolyl-pyrimidines **34** and **35**



a) 4-hydroxybenzaldehyde (1 eq.), NH_4OAc (10 eq.), AcOH, 10 min. 180 °C microwave heating, 93% ; b) aldehyde **19** (1 eq.), NH_4OAc (10 eq.), AcOH, 10 min. 180 °C microwave heating, 87%.

Preliminary results show that in TNFα activated HUVEC cells the (4-fluorophenyl)imidazolyl pyridones **25**, **26.Na**, **27.Na** and **30** (at 10 µM concentration) did not downregulate IL-6, or COX-2 or VCAM-1 gene expression (1 h TNFα stimulation; incubation for 4 h, then harvesting cells for mRNA and analysis by real-time RT-PCR) in contrast to SB203580 or the potent p38α MAPK inhibitor **6**[4]. Poor membrane permeability and low potency might be major reasons. Liposomal formulation of some of the prepared kinase inhibitors might improve the cellular activity. The highly potent p38α inhibitor JNJ583979 was too lipophilic for efficient encapsulation into cationic liposomes (SAINT-O-Somes[25]) by remote loading. Formulation of the disodium phosphonates **8**, **17** and **24** into SAINT-O-Somes was not successful despite their good water solubility. HPLC-MS analyses of eight different formulations of the piperidines **6** and **30** showed that 92% of **6** remained in 10% SAINT-O-Somes, (DSPC : SAINT : cholesterol : DSE-PEG = 45 : 10 : 40 : 5), but **30** was not retained at all, although both have similar aqueous solubility. The difference in pKa between pyridine **6** and pyridone **30** might be responsible for

this effect. In addition, the β-fluoro substituent in **6** not only decreases the pKa of the piperidine nitrogen but also is expected to improve the bioavailability[26]. As an alternative approach the palmitoyl ester prodrug **32** was formulated (ca. 1%) into the lipid bilayer of 18% SAINT-O-Somes (DSPC : SAINT : cholesterol : DSE-PEG = 37 : 18 : 40 : 5) by remote loading. After E-Selectine antibody conjugation all **32** was converted to the phenol **25** which was detected by HPLC-MS. Further studies of this prodrug approach will reveal its applicability for liposomal formulation of poorly soluble drugs.

In summary, we have demonstrated that the introduction of a (1*H*-1,2,3-triazol-1-yl)acetate or phosphonate via a 'click' reaction lowered the lipophilicity and improved water solubility of kinase inhibitors that share a common 4-fluorophenyl-imidazole scaffold. The multicomponent Debus-Radziszewski reaction using microwave heating is a generally applicable synthetic method for ready access to various 2,4,5-triarylimidazoles. For p38α binding and selectivity a basic pyridine or pyrimidinyl group is essential but a pyridone precludes p38α or CK1δ inhibition. Dual p38α/CK1δ inhibition was observed for some triazole-derived 4-fluorophenylimidazoles. The pyridone series displayed good JAK2 selectivity and culminated in tetrazole **31** as potent JAK2 inhibitor. We believe that the chosen synthetic strategy can find wider application for the library synthesis of other triazolyl trisubstituted azoles with improved physicochemical properties and for the development of "clickable" photoaffinity probes in molecular biology for finding new biological targets.[27]

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References and notes

Supplementary Material

Supplementary data associated with this article can be found in the online version. These data include typical synthetic and *in vitro* procedures, NMR and IC_{50} data, MOL files and InChiKeys of the most important compounds described in this article.

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