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Aminopyridine carboxamides as c-Jun N-terminal kinase inhibitors: Targeting the gatekeeper residue and beyond

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Abstract—The structure–activity relationships of 5,6-positions of aminopyridine carboxamide-based c-Jun N-terminal Kinase (JNK) inhibitors were explored to expand interaction with the kinase specificity and ribose-binding pockets. The syntheses of analogues and the impact of structural modification on in vitro potency and cellular activity are described.

Dysregulation of the insulin receptor (IR) and reduced tyrosine phosphorylation of the insulin receptor substrate (IRS) proteins contribute significantly to peripheral insulin resistance and β-cell failure.[1] Increased serine phosphorylation of IRS-1 is a common finding during insulin resistance and type 2 diabetes.[2] c-Jun N-terminal kinase-1 (JNK-1), a member of the MAP kinase family, associates with IRS-1 and phosphorylates Ser307.[3] This phosphorylation blocks the interaction between IRS-1 and IR, inhibits insulin action.[4] Phosphorylated ser307 also targets IRS-1 for degradation by the proteasome and affects the subcellular distribution of IRS-1. Targeted disruption of the JNK-1 gene in mice protects the animals from diet-induced obesity, and results in decreased adiposity and enhanced secretion of adiponectin.[5] The JNK-1 KO mice maintain lower fasting plasma glucose and insulin levels compared to wild-type littermates and demonstrate greater insulin sensitivity in both oral glucose and intraperitoneal insulin tolerance tests.[5] Small molecule JNK inhibitors can potentially offer therapeutic utility for the treatment of diabetes and insulin resistance.[6] A number of JNK inhibitors have recently appeared in the patent and primary literatures.[7]

Recently we disclosed a novel series of aminopyridine carboxamides as potent, selective, ATP-competitive pan-JNK inhibitors, as represented by compounds **1** and **2** (Fig. 1).[8,9] The binding modes of this series of JNK inhibitors have been determined by X-ray crystallography. As shown in Figure 2, the 4-aminopyridine amide of **2** displayed hydrogen bonds (as highlighted by the dashed lines in magenta color) to the backbones of amino acid Glu109 and Met111 as the 'classical' hinge interactions.

Closer examination of the structural complex also revealed that the 5-cyano group of the pyridine pointed to the gatekeeper residue Met108 (Fig. 2). It is well known that this single residue in the ATP-binding pocket can act as a gatekeeper and control kinase selectivity to a wide range of structurally unrelated compounds.[10] Thus, modification of the 5-cyano group would provide the possibility of expanding into the hydrophobic

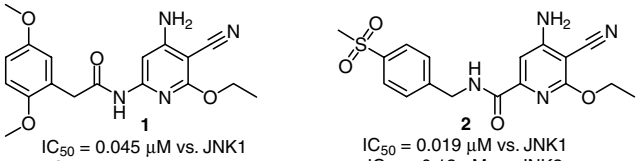

Figure 1. Selected 4-aminopyridine carboxamide JNK inhibitors from our laboratories.

Keywords: JNK inhibitors; Gatekeeper residue; Specificity pocket; Ribose pocket.
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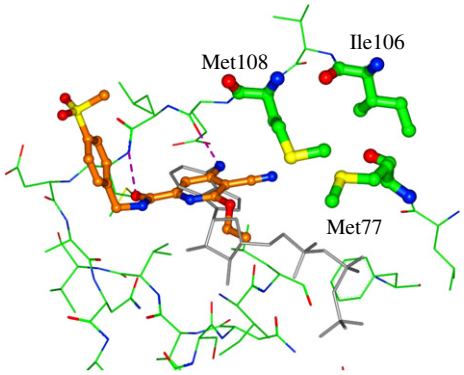


Figure 2. X-ray crystal structure of **2** (in brown color) in the JNK1 active site overlaid with ATP (in gray color).

specificity pocket beyond the gatekeeper residue. The amino acid sequences in the specificity pocket are somewhat different among the three JNK isoforms, for example, Ile106 and Met77 in JNK1 are mutated to *Leu* and *Leu* in JNK2, respectively. 4-(4-Pyrimidinyl)-5-phenylimidazole derivative **3a** was reported as a potent pan-JNK inhibitor with interaction to the specificity pocket (Fig. 3).[11] The recently disclosed 6-anilinoimdazole-based JNK3 inhibitor **3b**[12] and aniniliobipyrine-based JNK3 inhibitor **3c**[13] were shown to occupy the specificity pocket of JNK3 via the hydrophobic aniline groups, while achieving some degree of selectivity for JNK3 over JNK1 (Fig. 3).

Additionally, further extension of the 6-ethoxy group of **2** could increase the interaction with the ribose triphosphate-binding sites of the ATP pocket. The extensive structural modification of the 5,6-positions of the pyridine core of **2** to locate and optimize these potential interactions is described in this communication. These interactions, if realized, were expected to further improve the potency and general kinase selectivity of the resulting inhibitors.

Modification of the 5-cyano group of **2** was achieved starting from commercially available dichloropyridine **4** (Scheme 1). One of the chlorine was displaced with an ethoxy group, while the other one was subsequently subject to a palladium-mediated carbonylation to give methyl ester **5**. Selective iodination of the 5-position of the pyridine, saponification of the ester, followed by condensation between the resulting acid and amine created 5-iodopyridine **6**. This key intermediate **6** could then undergo Sonogashira-type coupling with terminal acetylenes to provide 5-alkynyl analogues **7a**–**f**,[14] while Suzuki coupling of **6** using vinyl boronic acids generated 5-alkenyl derivatives **8a**–**d**. Interestingly, Sonogashira coupling of **6** with trimethylsilylacetylene yielded TMS-enyne **9**, which was desilylated to give enyne **8e**. A second carbonylation of **6** yielded the ester **10**. Subsequent hydrolysis and coupling afforded the amides **11a**–**b**.

The 6-chloropyridine intermediate was prepared according to the procedure shown in Scheme 2. The readily available 2-hydroxy-6-chloropyridine **12**[15] was activated as a triflate. Selective palladium-catalyzed carboxylation under 60 psi of carbon monoxide at room temperature yielded a methyl ester, which was saponified to give acid **13**. Condensation of **13** with *p*-methylsulfonylbenzylamine provided the versatile intermediate **14**. Suzuki-type coupling of 6-chloropyridine **14** with aryl/alkenyl boronic acids yielded most of the 6-carbon analogues **15a**–**p**.

The aromatic nucleophilic substitution for forming the 6-ether analogues did not work with alkoxides even under forced conditions in a microwave reactor. We found that a copper-catalyzed ether formation protocol[16] worked relatively well to provide several analogues (**16a**–**e**) for SAR evaluation (Scheme 2). 6-Amino-substituted pyridine modifications (**17a**–**r**) could be readily generated with various amines under microwave-assisted SNAr conditions using DMA as a solvent. The 6-chloropyridine could also be further carboxylated at elevated temperature to provide 6-carboxylate, which was converted to amide **18**.

A 6-bromopyridine was needed for the desired Heck-type coupling. The previously disclosed 6-ethoxyester **19**[9] was converted to 6-bromopyridine **20** in low yield as shown in Scheme 3. Hydrolysis and coupling with amine provided 6-bromopyridine amide **21**. Heck coupling of **21** with acrylate was successful to give a *tert*-butyl ester, which was deprotected to yield acid **15q**. Hydrogenation of the olefin led to the propoinic acid **15r**.

The inhibitory activity of JNK inhibitors discussed in this communication was evaluated in JNK1 and JNK2 kinase assays measuring inhibition of phosphorylation of a synthetic peptide substrate at K_m ATP concentration for each enzyme as described previously.[8] Most of the active analogues were also assayed for their capacity to inhibit c-Jun phosphorylation in HepG2 cells.[8]

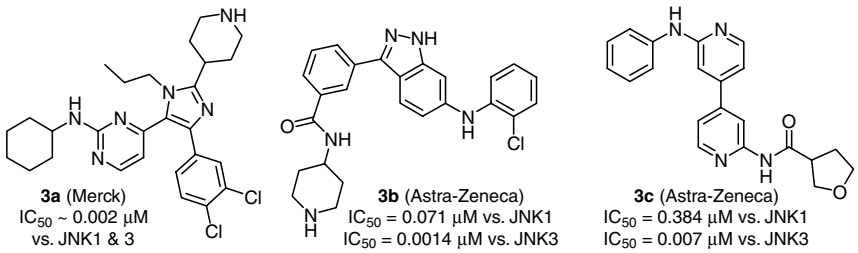
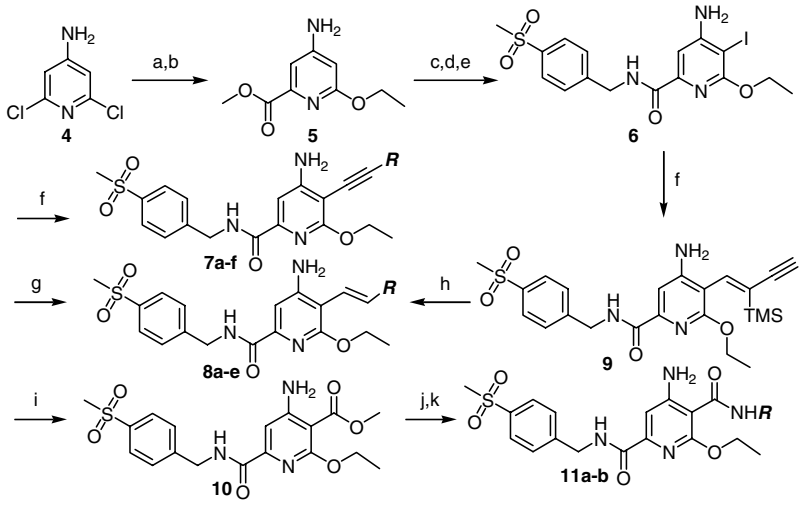
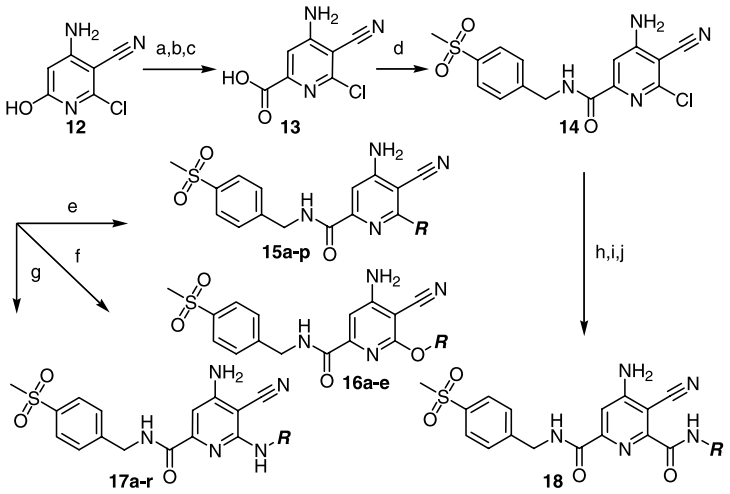


Figure 3. Selected JNK inhibitors from the literature.



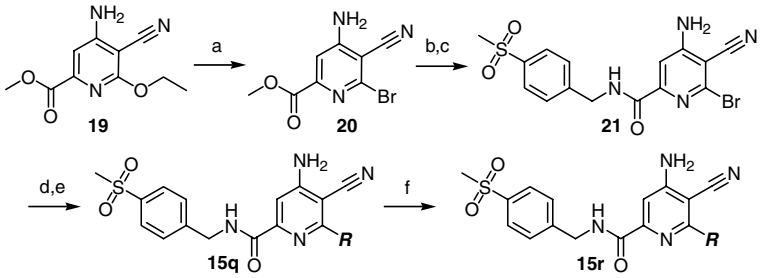
Scheme 1. Reagents and conditions: (a) EtONa, EtOH, 150 °C, 2 h; (b) CO, $PdCl_2$(dppf), MeOH, 100 °C, 4 h, 63% over two steps; (c) chloramine-T, NaI, AcOH, rt, 30 min; (d) LiOH, MeOH/THF, rt; (e) *p*-methylsulfonylbenzyl amine, TBTU, Et_3N, DMF, rt, 81% over three steps; (f) alkynes, $PdCl_2(PPh_3)_2$, CuI, Et_3N, DMF, 120 °C, 20 min, ~30%; (g) alkenyl boronic acids, $Pd(PPh_3)_4$, Na_2CO_3, DMF/THF/H_2O, 120 °C, 20 min, ~50%; (h) TBAF, THF, rt, 80%; (i) CO, $PdCl_2$(dppf), MeOH, 60 °C, 16 h, 80%; (j) LiOH, MeOH/THF, rt; (k) H_2NR, TBTU, Et_3N, DMF, rt, ~65% over two steps.



Scheme 2. Reagents and conditions: (a) Tf_2O, pyridine, CH_2Cl_2, rt, 6 h, 69%; (b) 60 psi CO, Et_3N, MeOH, $PdCl_2$(dppf), rt, 16 h; (c) LiOH, MeOH/THF, rt, 82% over two steps; (d) *p*-methanesulfonylbenzylamine, TBTU, Et_3N, DMF, rt, 88%; (e) $RB(OH)_2$, $PdCl_2(PPh_3)_2$, Na_2CO_3, DME/EtOH/H_2O (7:2:3), 160 °C, 10 min, 70–80%; (f) ROH, CuI, 1,10-phenanthroline, Cs_2CO_3, 110 °C, 24 h, 60–70%; (g) RNH_2, DMA, 160 °C, 20 min, 35–80%; (h) 60 psi CO, Et_3N, MeOH, $PdCl_2$(dppf), 100 °C, 16 h; (i) 3N aq NaOH, MeOH, rt, 45% over two steps; (j) *i*-$PrNH_2$, TBTU, Et_3N, DMF, rt, 85%.

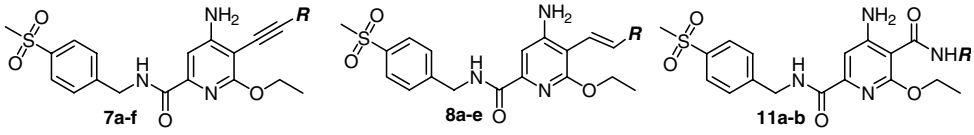
Using the readily available 5-iodopyridine **6**, we tried to replace the 5-cyano group of **2** with alkynes, hoping that further extension of the alkyne would reach into the kinase specificity pocket. The results, as shown in Table 1, were generally disappointing. Only the terminal alkyne **7a** possessed a meaningful potency, any other substituents (non-polar or polar, aliphatic or aromatic) off the alkyne led to essentially inactive compounds (**7b**–**f**). We also examined some 5-alkene-substituted pyridines as shown in Table 1. 5-Vinyl pyridine **8a** is about 3-fold less active than the 5-ethynyl analogue **7a**. Further decoration of the olefin with either aromatic (**8b**) or aliphatic group (**8c**) seemed to have little impact on the potency of resulting compounds. Interestingly, we found that acrylonitrile (**8d**) and but-1-en-3-ynyl (**8e**) substituted pyridines possessing progressively improved JNK inhibitory potency with encouraging cellular potency for **8d** as well. Replacing the 5-cyano group with a primary amide (**11a**) yielded a somewhat active analogue, however, with much reduced cellular activity, while a propyl amide replacement led to a virtually inactive analogue **11b**.

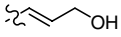
For the modification of the 6-position of the pyridine, we started with 3-substituted phenyl groups as a way to extend into the sugar pocket. As shown in Table 2, a hydrophobic 3-chloro phenyl (**15a**) led to a 100-fold decrease of potency from **2**, while 3-hydroxyphenyl (**15b**) and 3-methoxyphenyl (**15c**) derivatives exhibited sub-micromolar potency. A 3-methanesulfonylphenyl analogue **15d** is only 2-fold less active than **3**. However, its cellular potency was much worse.



Scheme 3. Reagents and conditions: (a) $POBr_3$, pyridinium hydrobromide, H_3PO_4, 125 °C, 25 min, 27%; (b) LiOH, MeOH/THF, rt; (c) *p*-methanesulfonylbenzylamine, TBTU, Et_3N, DMF, rt, 90% over two steps; (d) *tert*-butyl acrylate, $Pd(OAc)_2$, P(*o*-tolyl)$_3$, Et_3N, 100 °C, over night, 22%; (e) TFA/CH_2Cl_2, rt, 57%; (f) 10% Pd/C, H_2, MeOH, rt, 100%.

Table 1. SAR of 5-pyridine carboxamide modifications

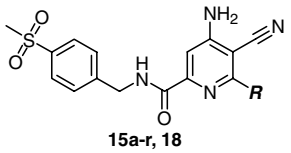


Compound	R	JNK1 IC_{50}[a] (μM)	JNK2 IC_{50}[a] (μM)	Pc-Jun IC_{50} (μM)
7a	H	0.35 (±0.17)	0.30 (±0.03)	1.89
7b		>10	NT	NT
7c		3.43 (±0.73)	>10	NT
7d		1.09 (±0.15)	NT	5.7
7e		2.24 (±1.04)	4.61 (±0.51)	7.36
7f		1.55 (±0.35)	4.32 (±0.22)	5.24
8a	H	1.18 (±0.08)	1.46 (±0.58)	4.63
8b		2.43 (±0.53)	4.13 (±0.43)	6.92
8c		2.93 (±0.53)	4.16 (±2.56)	>10
8d		0.41 (±0.12)	1.79 (±0.39)	0.807
8e		0.079 (±0.001)	0.30	1.4
11a	H	0.318 (±0.088)	0.969	7.54
11b		5.25	NT	NT

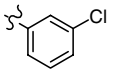
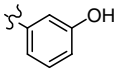
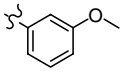
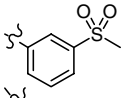
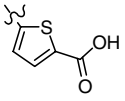
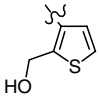
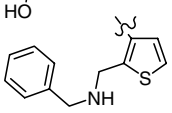
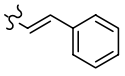
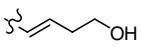
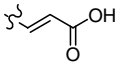
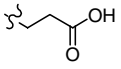
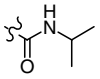
[a] Values are geometric means of at least two experiments, standard error is given in parentheses. NT, not tested.

Heteroaryls were also evaluated for accessing the ribose pocket off the 6-position. 3-Thiophene yielded fairly potent analogue **15e**, and 3-furanyl analogue **15f** is only 4-fold less potent than **2**. 2-Hydroxymethyl-substituted (**15h**) and 2-benzylaminomethyl-substituted thiophene (**15i**) are progressively less potent than the unsubstituted **15e**. It is interesting to note that 3-carboxy-2-thiophene derived **15g** is fairly potent in vitro, however, its cellular potency suffered due to the charge present in the molecule. The six-membered heterocycles such as pyridines (**15j–k**) and pyrimidine (**15l**) were roughly equipotent as 2-furanyl analogue **15f** with much reduced cellular potency.

Table 2. SAR of 6-pyridine modification with carbon-linked side chains

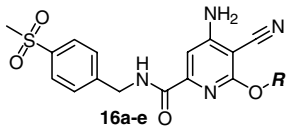


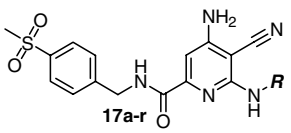
15a-r, 18

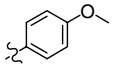
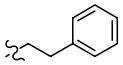
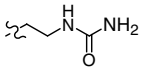
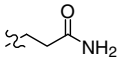
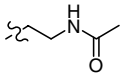
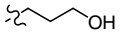
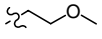
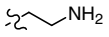
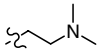
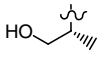
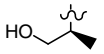
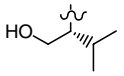
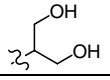
Compound	R	JNK1 IC_{50}[a] (μM)	JNK2 IC_{50}[a] (μM)	Pc-Jun IC_{50} (μM)
15a		1.18 (± 0.35)	0.84	1.2
15b		0.20 (±0.08)	0.24 (±0.15)	9.4
15c		0.43 (±0.20)	0.60 (±0.38)	1.8
15d		0.043 (±0.004)	0.097 (±0.039)	10.5
15e		0.081 (±0.005)	0.39 (±0.12)	0.61
15f		0.27 (±0.07)	0.53 (±0.11)	4.3
15g		0.25 (±0.05)	0.16 (±0.10)	>10
15h		0.57 (±0.20)	0.68 (±0.27)	10.8
15i		1.99 (±0.49)	NT	8.01
15j		0.32 (±0.06)	0.34 (±0.01)	7.3
15k		0.53 (±0.12)	0.66 (±0.06)	NT
15l		0.62 (±0.06)	0.86 (±0.02)	>10.0
15m		0.048 (±0.010)	0.23 (±0.07)	0.89
15n		0.15 (±0.04)	0.26 (±0.05)	5.5
15o		1.45 (±0.35)	1.29 (±0.19)	0.35
15p		0.17 (±0.08)	0.24 (±0.08)	5.3
15q		0.30 (±0.03)	0.43 (±0.03)	>2.5
15r		1.64 (±0.86)	6.92 (± 2.70)	NT
18		0.43 (±0.19)	0.12 (±0.02)	2.9

[a] Values are geometric means of at least two experiments, standard error is given in parentheses. NT, not tested.

Table 3. SAR of 6-pyridine modification with amine/ether linked side chains





Compound	R	JNK1 IC_{50}[a] (μM)	JNK2 IC_{50}[a] (μM)	Pc-Jun IC_{50} (μM)
16a		0.015 (±0.003)	0.038 (±0.06)	0.25
16b		0.023 (±0.006)	0.047 (±0.013)	0.56
16c		0.088 (±0.044)	0.37 (±0.05)	0.70
16d		0.39 (±0.03)	0.61 (±0.04)	0.49
16e		0.42 (±0.06)	0.45 (±0.08)	NT
17a		0.067 (±0.024)	0.084 (±0.006)	0.49
17b		0.032 (±0.009)	0.069 (±0.009)	1.2
17c		0.085 (±0.029)	0.16 (±0.01)	0.62
17d		0.096 (±0.006)	0.29 (±0.12)	0.48
17e		0.82	4.7	NT
17f		0.26	1.0	2.7
17g		0.093 (±0.036)	NT	>10
17h		0.066 (±0.001)	0.087 (±0.026)	>10
17i		0.059 (±0.001)	0.081 (±0.015)	>10
17j		0.054 (±0.002)	0.18 (±0.03)	8.3
17k		0.093 (±0.021)	0.15 (±0.02)	>10
17l		0.12 (±0.04)	0.21 (±0.06)	5.9
17n		1.6 (±0.5)	NT	NT
17o		7.3	9.2	NT
17p		0.022 (±0.005)	0.030 (±0.015)	2.6
17q		0.18 (±0.05)	0.32 (±0.14)	>10
17r		1.5 (±0.3)	1.4	NT
17m		0.076 (±0.002)	0.10 (±0.02)	>10

[a] Values are geometric means of at least two experiments, standard error is given in parentheses. NT, not tested.

Olefinic substitutions off the 6-position pyridine offered some interesting analogues. *trans*-Propene derivative **15m** is only 2-fold less potent than lead compound **1** in both enzymatic and cellular assays. In comparison, the *cis*-isomer **15n** is 3- to 8-fold less potent in vitro and in cells, respectively. Styrene substitution **15o** showed a 20-fold decrease in potency. Interestingly, **15o** was shown to be more potent in HepG2 cells than in the enzymatic assay. The possibility of cellular toxicity could not be ruled out although the cells appeared healthy during the cellular assay. Polar groups appended to the *trans*-double bond, such as hydroxyethyl **15p** or carboxylic acid **15q**, provided fairly potent analogues. Saturation of the propenic acid (**15r**) reduced the inhibitory potency by about 5-fold. Among the several 6-carboxamide derivatives, only the isopropyl amide **18** possessed sub-micromolar IC_{50} versus JNK1&2.

More productive SAR came from the 6-amino or 6-ether analogues (Table 3). Isopropoxy compound **16a** is equipotent to the lead compound **2** in vitro, and 2-fold more active in c-Jun phosphorylation assay than **2**. Some other smaller alkoxides seemed to work well too, such as cyclopropylmethoxy **16b** and isopropylmethoxy **16c**. In comparison, larger alkoxide **16d** and phenoxide **16e** led to slightly weaker analogues.

Due to the relative ease of synthesis of 6-amino analogues, more functional groups were explored with this set of modification. Similar to the ether analogues, small hydrophobic amines were favored to give inhibitors (**17a–d**) with double-digit nanomolar IC_{50} values. The benzylamine and phenethyl amine derivatives (**17e–f**) showed reduced potency against JNK1&2. Neutral polar extensions (**17g–l**) off the ethylamine were generally well tolerated, such as urea, amides, alcohol, and ether. Basic groups, such as primary amine (**17n**) or tertiary amine (**17o**) off the ethylamine, led to analogues with substantially reduced inhibitory potency. Alpha-substituents off the 6-amino group were introduced to provide a means for accessing the sugar pocket in the presence of hydrophilic terminal groups. (*S*)-alaninol derivative **17p** is among the most potent analogues within the series, while the (*R*)-enantiomer (**17q**) is 6-fold less potent. Further extension with (*S*)-leucinol (**17r**) led to 50-fold drop of potency, presumably due to unfavorable steric interaction. A symmetrical diol branch led to a fairly potent analogue **17m**. For 6-aminopyridine analogues, there seemed to be a larger discrepancy between in vitro IC_{50}s and their cellular activity except the more lipophilic **17a**, **17c–d**. Increased hydrophilicity could potentially hinder the effective diffusion of the inhibitors into HepG2 cells.

There are two possible reasons behind the challenges associated with targeting the gatekeeper residue of JNK kinases. As mentioned earlier, the gatekeeper residue in the ATP-binding pocket has been shown to control kinase selectivity to a wide range of structurally unrelated compounds. This residue is conserved as a threonine or larger amino acids in the human kinome, and structural analysis has shown that the size of this gatekeeper residue restricts access to a pre-existing cavity within the ATP-binding pocket.[17] Kinases with a threonine at this position are readily targeted by a diverse classes of small molecule inhibitors that can access this natural pocket, including the kinase inhibitors currently in clinical use (Gleevec, Iressa, Tarceva). Having a larger methionine as the gatekeeper residue in JNK made it intrinsically more difficult to reach the 'specificity pocket'.

The second reason may have something to do with the 4-aminopyridine carboxamide template we were using to access the 'specificity pocket'. The particular vector provided by extension off the 5-position of pyridine **1** may not be as favorable as X-ray structure and molecular modeling had suggested. The 6-anilinoimdazole-based JNK3 inhibitor **3b** (Fig. 3) binds to JNK3 in an induced-fit manner, with the gatekeeper residue Met146 (JNK3 numbering) moved out of way to accommodate the aniline portion of the molecule in the 'specificity pocket'. Such precedent suggests that with appropriate molecular template, it is possible to target the 'specificity' pocket with methionine as the gatekeeper residue.

In summary, we have investigated structural modifications to reach both the kinase specificity and ribose pockets of JNK1 using our proprietary 4-aminopyridine carboxamide template. Although several modifications were identified as equivalent in terms of in vitro and cellular potency to lead compound **2**, we have yet to find the extensions that optimize interaction with either the kinase specificity pocket or the ribose pocket. The insights gained from this work will facilitate future optimization efforts in other domains of the lead compounds.

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