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Synthesis and SAR of 4-(pyrazol-3-yl)-pyridines as novel c-jun N-terminal kinase inhibitors

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ABSTRACT

The design and synthesis of a novel series of c-jun N-terminal kinase (JNK) inhibitors is described. The development of the 4-(pyrazol-3-yl)-pyridine series was discovered from an earlier pyrimidine series of JNK inhibitors. Through the optimization of the scaffold **2**, several potent compounds with good in vivo profiles were discovered.

Protein kinases catalyze the phosphorylation of tyrosine and serine/threonine residues in proteins involved in the regulation of diverse cellular functions. Aberrant kinase activity is implicated in many diseases, which makes the inhibition of kinases an attractive target for the pharmaceutical industry.[1] As a member of the mitogen-activated protein kinase (MAPK) family, the c-jun N-terminal kinases (JNKs) regulate the serine/threonine phosphorylation of several transcription factors when they are activated in response of a variety of stress-based stimuli such as cytokines, ultraviolet irradiation, heat shock, fatty acids and osmotic shock.[2,3] Three distinct genes (jnk1, jnk2 and jnk3) encoding the ten splice variants of JNK (JNK1α1, JNK1β1, JNK1α2, JNK1β2; JNK2α1, JNK2β1, JNK2α2, JNK2β2; JNK3α1, JNK3α2) have been identified.[4] These isoforms differ in their tissue distribution profile and functions, with JNK1 and JNK2 being ubiquitously expressed, whereas JNK3 is expressed predominantly in the brain and at lower levels in the heart and testis.[5,6]

In recent studies, JNK-1, often in concert with JNK-2, has been suggested to play a central role in the development of obesity-induced insulin resistance which implies therapeutic inhibition of JNK1 may provide a potential solution in type-2 diabetes mellitus.[7,8] JNK2 has been described in the pathology of autoimmune disorders such as rheumatoid arthritis and asthma, and it also has been implicated to play a role in cancer, as well as in a broad range of diseases with an inflammatory component.[9–13] JNK3 has been shown to play important roles in the brain to mediate neurodegeneration, such as beta amyloid processing, Tau phosphorylation and neuronal apoptosis in Alzheimer's disease, as well as the mediation of neurotoxicity in a rodent model of Parkinson's disease.[14–16] JNK3 is almost exclusively found in the brain. Identifying potent inhibitors of JNK3, with selectivity within the wider MAPK family (one of which is p38), may contribute towards neuroprotection therapies with reduced side effect profiles.

Therefore, developing JNK inhibitors as therapeutics has gained considerable interest over the past few years.[17–32] As part of our medicinal chemistry research program, we initiated a JNK3 project with a key objective of identifying brain penetrant compounds with good JNK3 potency and selectivity over p38. We previously reported on the synthesis and SAR of 4-phenyl substituted pyrimidines.[31] Compounds in this class had good in vitro potency, but only modest in vivo profiles (rodent pk and brain penetration). In the continuous development and optimization of JNK3 inhibitors, we found 4-pyrazole substituted pyrimidines were also potent inhibitors.[33] The first synthesized 4-(pyrazol-3-yl)-pyrimidine, compound **1**, inhibited JNK3 with an IC_{50} = 0.63 μM with no detectable inhibition of p38 (>20 μM). Encouraged by the JNK3 potency and selectivity against p38, we initiated a structure–activity relationships (SAR) study.[34] Our strategy was based on scaffold **2** and more precisely on the maintenance of the core structure of **1** wherein we could vary either X, Y, R^1, R^2 and R^3 groups by modification or introduction of substituents (Fig. 1).

The analogs **7–9** were synthesized from compound **3** or **5** as described in Scheme 1 and data is shown in Table 1.[35] The 2- and 4-positions of pyrimidine **3** were subsequently replaced with a substituted aniline and a chlorine atom to afford intermediate **4**. The pyrazole ring was introduced via a Suzuki coupling to give compounds **7** with R^1 = H. N-alkylation with alkyl halides gave

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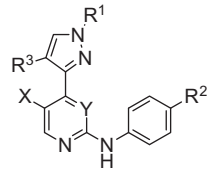

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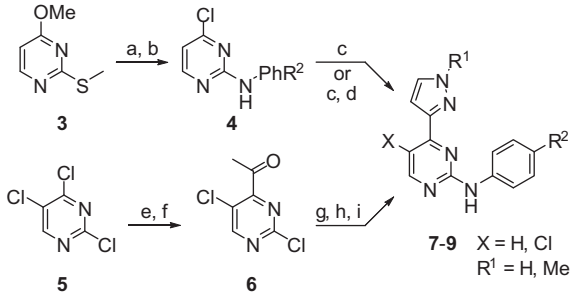
Figure 1. Pyrazole pyrimidine JNK inhibitors.



Scheme 1. Reagents and conditions: (a) R^2PhNH_2, $EtO(CH_2)_2OH$, 75 °C, 16 h; (b) concd HCl, 90 °C, overnight; $POCl_3$, 100 °C; (c) 3-pyrazoleboronic acid, $Pd(PPh_3)_4$, K_2CO_3, DME/H_2O, 140 °C, 1 h, microwave; (d) MeI, K_2CO_3, DMF, 50 °C, overnight; (e) tributyl(1-ethoxyvinyl)tin, $Pd(PPh_3)_4$, toluene, 125 °C, 1.5 h, microwave; (f) concd HCl, THF, 2 h, rt; (g) R^2PhNH_2, $EtO(CH_2)_2OH/H_2O$, 120 °C, 15 h; (h) *N*,*N*-dimethylformamide dimethylacetal, 110 °C, overnight; (i) $MeNHNH_2$, EtOH, rt, 55 h.

Table 1
JNK3 inhibition by analogs of **7–9**

Compds	X	R^1	R^2	JNK3 IC_{50}[a] (μM)	p38 IC_{50}[a] (μM)
1	H	H	A	0.63	>20
7	H	Me	A	1.45	nt
8	Cl	Me	A	0.86	nt
9	Cl	Me	B	0.73	nt

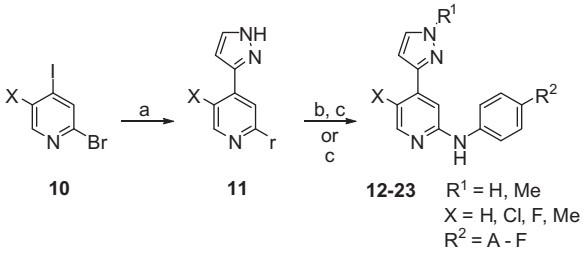
[a] Values are means of three experiments, nt = not tested, all standard deviation ⩽ 20%.

7 with R^1 = alkyl. The analogs **8** were synthesized from compound **5** in five-steps. Stille coupling of trichloropyrimidine **5** followed by hydrolysis afforded ketone **6**. Introduction of the aniline followed by pyrazole ring formation via a two-step procedure gave compounds **8–9**.

Unfortunately, compounds containing pyrrazoles bearing free NH's had poor brain penetration. To decrease the polarity of our lead compounds, and hopefully improve brain penetration, the nitrogen atom of the pyrazole ring was alkylated with a methyl group. This led to a decrease in JNK3 inhibition to 1.45 μM for **7** (Table 1). The introduction of a 5-chloro group on the pyrimidine ring recovered some of the potency (**8**) lost by N-alkylation. We also found that modification of the R^2 substituent did little in the way of improving inhibition (i.e., **9**), but did play a role in modulating in vivo parameters.

In the literature, kinase inhibitors with a central pyrimidine core are ubiquitous whereas those containing pyridine cores are far less common.[33,36–41] With intermediates in hand, we decided to investigate if 4-pyrazole substituted pyridines had any activity against JNK3. Additionally, removing one heteroatom from the pyrimidine core would further reduce polarity. Pyridine analogs were synthesized as described in Scheme 2.

The halogenated pyridine **10** was coupled with pyrazole boronic acid to give **11**. Anilines were introduced into the 2-position via Buchwald–Hartwig conditions to afford compounds **12–13** with a



Scheme 2. Reagents and conditions: (a) 3-pyrazoleboronic acid, $Pd(PPh_3)_4$, K_2CO_3, DMF, 100 °C, 3 h; (b) MeI, K_2CO_3, DMF, 50 °C, overnight; or Ar^1X, CuI, K_2CO_3, *trans*-*N*,*N*′-dimethylcyclohexane-1,2-diamine, dioxane, 120 °C, overnight; (c) R^2PhNH_2, $Pd(OAc)_2$, xantphos, Cs_2CO_3, dioxane, 130 °C, 1 h, microwave.

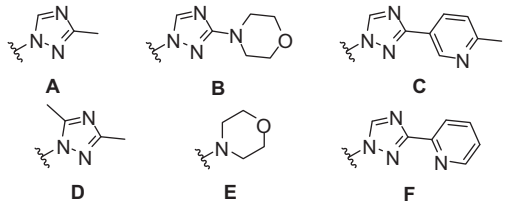


Figure 2. R^2 substituents.

hydrogen atom as the R^1 substituent.[42] Compounds **14–23** were synthesized by N-alkylation (R^1 = alkyl) or by a variation of the Ullmann reaction (R^1 = aryl), followed by a Buchwald–Hartwig reaction. The rapid synthesis of these compounds allowed us to evaluate a series of analogs with a variety of substituents (not all data shown). Of all R^2 substituents examined, only a few (A–F) are presented here (Fig. 2).

Surprisingly, pyridine containing compounds were more potent than their corresponding pyrimidine analogs (Table 2). Compound **12** with no substitution at the 1-position on the pyrazole ring or at the 5-position on the pyridine ring had an IC_{50} value 160 nM for the inhibition of JNK3 with no detectable activity against p38. The introduction of a chlorine atom at C-5 (X substituent in **13**) provided a two-fold boost in activity. Unfortunately, the N-alkylation of the pyrazole nitrogen (**14**) led to a slight decrease in potency which is a trade-off as it also serves to reduce compound polarity. Once again, modification of the aniline substituent provided no advantage with regards to in vitro potency. A 5-fluoro substituent (**18**) was equipotent to the 5-chloro (**14**) substituted compound. Substitution at C-5 with a methyl group (**23**) led to a four-fold drop in potency (**23** vs **16** and **22**). Fortunately, all analogs tested showed no inhibition against p38.

Surprisingly, the phenyl ring in the aniline did not tolerate substitution, as both fluoro-substituted analogs were inactive against

Table 2
Inhibition of JNK3 by compounds **12–23**

Compds	X	R^1	R^2	JNK3 IC_{50}[a] (μM)	p38 IC_{50}[a] (μM)
12	H	H	E	0.16	>20
13	Cl	H	E	0.07	>20
14	Cl	Me	E	0.13	>20
15	Cl	Me	D	0.16	>20
16	Cl	Me	B	0.20	>20
17	Cl	Me	C	0.60	>20
18	F	Me	E	0.16	>20
19	F	Me	D	0.34	>20
20	F	Me	C	0.20	>20
21	F	Me	F	0.48	>20
22	F	Me	B	0.16	>20
23	Me	Me	B	0.75	>20

[a] Values are means of three experiments, all standard deviation ⩽ 20%.

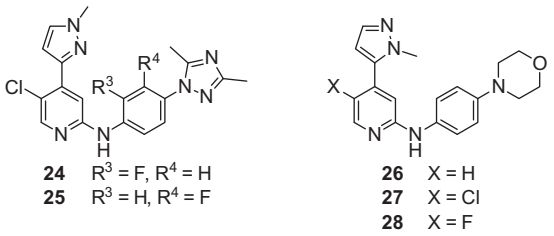
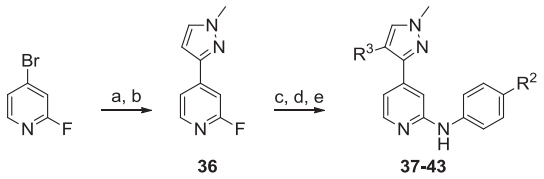
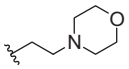


Figure 3. Additional pyrazole JNK inhibitors.



Scheme 3. Reagents and conditions: (a) 3-pyrazoleboronic acid, $Pd(PPh_3)_4$, K_2CO_3, DMF, 100 °C, 3 h; (b) MeI, K_2CO_3, DMF, 50 °C, overnight; (c) NBS, DMF, 50 °C, 4 h; (d) $R^3B(OH)_2$, $Pd(PPh_3)_4$, K_2CO_3, DME/H_2O, 100 °C, 1 h, microwave; (e) R^2PhNH_2, HCl(1 M)/H_2O/dioxane (ratio 2:4:1).

Table 3
Inhibition of JNK3 by compounds **29**–**35**

Compds	X	R^1	R^2	JNK3 IC_{50}[a] (μM)	p38 IC_{50}[a] (μM)
29	F	Bn	E	0.10	>20
30	F	$(CH_2)_2Ph$	E	0.17	>20
31	F		E	0.32	>20
32	H	3-MeOPh	D	0.65	>20
33	H	3-CNPh	D	0.24	>20
34	H	4-MeSPh	D	1.33	>20
35	H	2-Py	D	0.34	>20

[a] Values are means of three experiments, all standard deviation ⩽ 20%.

JNK3 (>20 μM) (Fig. 3, compounds **24** and **25**). Additionally, 1-methyl-5-pyrazole isomers **26–28** (JNK3 IC_{50} 1.6 μM, 6.0 μM and 6.2 μM, respectively) were considerably less potent JNK inhibitors than their corresponding 1-methyl 3-pyrazole isomers (**14** and **18**).

We then looked to optimize pyrazole substitution (R^1) as a means to improve JNK3 inhibition (Table 3). Compound **29** with an *N*-benzyl group was slightly more potent than **18** (R^1 = Me). Phenethyl substitution (**30**) led to a slight decrease in potency. The morpholino-ethyl group was also less active (compound **31**). The introduction of substituted aromatic rings (**32–35**) also led to a drop in JNK potency depending on substitution.

We next investigated substitution at the 4-position on the pyrazole ring (Table 4, R^3). To facilitate SAR of the R^3 substituent, we chose to use an *N*-methyl as the R^1 substituent, and dimethyltriazole or morpholine (respectively noted D and E) as the R^2 substituent.

The synthesis of analogs (**37–43**) is outlined in Scheme 3. Compound **36** was obtained in two-steps via a Suzuki coupling followed by N-alkylation. The regioselective bromination of the pyrazole ring at the 4-position, followed by another Suzuki coupling allowed for the introduction of R^3-substituents.[43] The last step was the introduction of the substituted aniline under acidic conditions which provided the desired compounds.

Table 4
4-Substituted pyrazole SAR

Compds	R^2	R^3	JNK3 IC_{50}[a] (μM)	p38 IC_{50}[a] (μM)
37	D	4-FPh	0.007	0.02
38	D	3-Py	0.11	1.14
39	E		0.15	0.19
40	E		0.39	>20
41	E		0.39	>20
42	D	*n*-Pr	1.40	>20
43	D	Me	0.40	>20

[a] Values are means of three experiments, all standard deviation ⩽ 20%.

Table 5
Key brain penetration and pharmacokinetic parameters

Compds	Drug concentration[a] (μM) plasma/brain	Clp[b] (mL/min/kg)	$t_{½}$[b]	Oral AUC[b] (μM h)	%F[b]
15	10.4/5.3	9.0	1.3	7.1	73
16	6.6/3.5	0.9	6.5	45	75
20	9.0/10.3	4.2	2.3	10	69
21	3.3/0.74	4.0	3.4	14.9	73
37	9.0/1.4	6.4	1.5	6	51

[a] Mouse; 10 mg/kg IP, 2 h.
[b] Rat; 1 mg/kg IV; 2 mg/kg PO.

Interestingly, 4-fluorophenyl substitution (**37**) resulted in a big boost in JNK3 potency concomitant with the loss of the selectivity between JNK3 and p38. This was true for several other phenyl substituted analogs (not shown). Heterocyclic rings did not afford the magnitude of potency enhancement that came with phenyl or substituted phenyl rings (**38–41**). However, it was interesting that pyrazole substitution, and smaller alkyl groups did not pick up p38 activity, although JNK activity also decreased.

Several compounds from this series were analyzed in vivo (Table 5).[44] The compounds with morpholine as a R^2 substituent (E) suffer from poor pharmacokinetics (high clearance, short half-life and low bioavailability). For the other R^2 substituents, the compounds had a much improved in vivo profile (low clearance, good half-life and very good bioavailability). For most compounds tested in this series, the blood brain barrier penetration was also quite good (30–100%).

In summary, a novel series of pyrazole substituted pyrazoles has been developed. Optimization of this scaffold by modification of five substituents (X, Y R^1, R^2 and R^3) afforded a series of potent JNK3 inhibitors free of p38 inhibition. Several compounds from this class have good pharmacokinetics and brain penetration. Evaluation of compounds of this type in vivo in CNS models of human disease (Parkinson's and Alzheimer's disease, stroke) is ongoing and will be reported in due course.

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44. *Rat pharmacokinetics and mouse brain penetration*: pharmacokinetics of test compounds was assessed in Sprague–Dawley rats ($n = 3$). Compounds were dosed intravenously at 1 mg/kg and orally by gavage at 2 mg/kg. Blood was taken at eight time points (5, 15, 30 min, 1, 2, 4, 6, 8 h) and collected into EDTA containing tubes and plasma was generated using standard centrifugation techniques. Plasma proteins were precipitated with acetonitrile and drug concentrations were determined by LC–MS/MS. Data was fit by WinNonLin using a noncompartmental model and basic pharmacokinetic parameters including peak plasma concentration (C_{max}), oral bioavailability, exposure (AUC), half-life ($t_{1/2}$), clearance (CL), and volume of distribution (Vd) were calculated. CNS exposure was evaluated in C57Bl6 mice ($n = 3$). Compounds were dosed at 10 mg/kg intraperitoneally and after 2 h blood and brain were collected. Plasma was generated and the samples were frozen at −80 °C. The plasma and brain were mixed with acetonitrile (1:5 v/v or 1:5 w/v, respectively). The brain sample was sonicated with a probe tip sonicator to break up the tissue, and samples were analyzed for drug levels by LC–MS/MS. Plasma drug levels were determined against standards made in plasma and brain levels against standards made in blank brain matrix. All procedures were approved by the Scripps Florida IACUC.