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Design and synthesis of brain penetrant selective JNK inhibitors with improved pharmacokinetic properties for the prevention of neurodegeneration

Simeon Bowers [a,*], Anh P. Truong [a,*], R. Jeffrey Neitz [a], Roy K. Hom [a], Jennifer M. Sealy [a], Gary D. Probst [a], David Quincy [a], Brian Peterson [a], Wayman Chan [a], Robert A. Galemmo Jr. [a], Andrei W. Konradi [a], Hing L. Sham [a], Gergely Tóth [b], Hu Pan [b], May Lin [b], Nanhua Yao [b], Dean R. Artis [b], Heather Zhang [c], Linda Chen [c], Mark Dryer [c], Bhushan Samant [c], Wes Zmolek [c], Karina Wong [c], Colin Lorentzen [c], Erich Goldbach [c], George Tonn [c], Kevin P. Quinn [c], John-Michael Sauer [c], Sarah Wright [d], Kyle Powell [d], Lany Ruslim [d], Zhao Ren [d], Frédérique Bard [d], Ted A. Yednock [a,b,c,d], Irene Griswold-Prenner [d]

[a] Department of Chemical Sciences, Elan Pharmaceuticals, 180 Oyster Point Boulevard, South San Francisco, CA 94080, United States
[b] Department of Molecular Design, Elan Pharmaceuticals, 180 Oyster Point Boulevard, South San Francisco, CA 94080, United States
[c] Department of Lead Finding, Drug Disposition, and Safety Evaluation, Elan Pharmaceuticals, 800 Gateway Boulevard, South San Francisco, CA 94080, United States
[d] Department of Biology, Elan Pharmaceuticals, 1000 Gateway Boulevard, South San Francisco, CA 94080, United States

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ABSTRACT

The SAR of a series of brain penetrant, trisubstituted thiophene based JNK inhibitors with improved pharmacokinetic properties is described. These compounds were designed based on information derived from metabolite identification studies which led to compounds such as **42** with lower clearance, greater brain exposure and longer half life compared to earlier analogs.

The *c*-Jun N-terminal kinases (JNKs) are members of the mitogen-activated protein kinase (MAPK) family and activate transcription factors such as *c*-jun by phosphorylation of serine/threonine residues.[1] The JNKs regulate signal transduction in response to stress stimuli such as UV light, reactive oxygen species, cytokines, hypoxia and protein misfolding.[1,2] Three isoforms of JNK have been identified: JNK1, JNK2 and JNK3.[1] JNK1 and JNK2 are ubiquitously expressed while JNK3 is localized primarily in the brain. The up regulation of the JNKs is implicated in numerous disease states such as obesity, cancer, Type 2 diabetes and more specifically, JNK3 has been implicated in playing important roles in neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Huntington's disease, and cerebral ischemia.[3] JNK3 knockout mice are viable and are resistant to induced neurodegeneration compared to wild type animals[4] suggesting that inhibition of JNK may be tolerated and neuroprotective.[3]

For a JNK inhibitor to be neuroprotective, it must be brain penetrant and have a high degree of kinase selectivity to avoid potential toxicity. In the case of JNK this is particularly challenging due to the closely related MAP kinases p38α and ERK2. In our two previous papers,[5] we reported the development of a series of di- and trisubstituted thiophenes which started from micromolar hits and resulted in low nanomolar JNK inhibitors. Compounds **1** and **2** (Fig. 1) are typical examples from this series. They are essentially equipotent on the JNK isoforms but possess excellent selectivity for JNK over p38α and ERK2. Additionally, compound **1** has a clean profile when screened against a panel of 38 kinases.[5b] Furthermore, compound **1** demonstrated robust in vivo oral JNK activity as measured by phospho-*c*-jun reduction in our kainic acid mouse model, a crucial step towards the development of neuroprotective agents.[5b] Reported in this Letter are our efforts to improve the pharmacokinetic properties of this scaffold while retaining the excellent kinase selectivity of this class of compounds.

Compound **1** displayed only modest stability when incubated with liver microsomes and moderate P-gp efflux in MDR–MDCK cells which resulted in sub-optimal brain levels when dosed orally.

* Corresponding authors.
E-mail addresses: simeon.bowers@elan.com (S. Bowers), anh.truong@elan.com (A.P. Truong).

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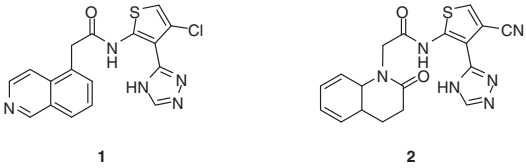


1

JNK3 IC_{50} = 11 nM
JNK2 IC_{50} = 43 nM
JNK1 IC_{50} = 14 nM
p38α IC_{50} > 50 μM
ERK2 IC_{50} > 50 μM
HBSS solubility = 25 μM
OxMet% m, r, h = 29, 9, 50
MDR MDCK A>B = 270 nm/sec
P-gp efflux ratio = 1.6

2

JNK3 IC_{50} = 7 nM
JNK2 IC_{50} = 8 nM
JNK1 IC_{50} = 9 nM
p38α IC_{50} > 50 μM
ERK2 IC_{50} > 50 μM
HBSS solubility = 95 μM
OxMet% m, r, h = 37, 0, 39
MDR MDCK A>B = 179 nm/sec
P-gp efflux ratio = 4.6

Figure 1. In vitro characteristics of trisubstituted thiophene based JNK inhibitors.[6]

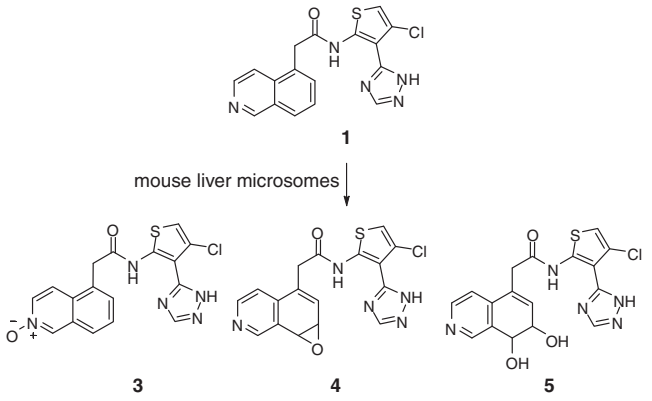


Figure 2. Metabolites of compound **1** identified by LC–MS/MS analysis of compound (10 μmol) incubated with mouse liver microsomes.

In order to locate the major sites of metabolism, compound **1** was incubated with mouse liver microsomes for 2 h and the resulting metabolites were analyzed by LC–MS/MS. Based on this analysis the putative structures of the major metabolites **3**, 4 and **5**, were derived (Fig. 2). Interestingly, no evidence of oxidation on the thiophene portion of the molecule was observed but the isoquinoline region of the inhibitor was extensively oxidized and revealed itself to be the metabolic soft spot in this scaffold.

It was envisioned that the incorporation of heteroatoms and/or electron withdrawing substituents on to the biaryl ring would reduce metabolism on the aryl acetamide portion of the molecule. To determine the sites of the inhibitor where modification of the structure could take place without affecting the JNK3 potency, the co-crystal structure of trisubstituted thiophene **2** in complex with JNK3 in the presence of the JIP1 peptide was examined (Fig. 3).

Compound **2** forms a hydrogen bond between the NH of Met149 and the carbonyl of the inhibitor (Fig. 3). The nitrile at the 4-position of the thiophene lies within proximity to the gatekeeper residue (Met146) and previous SAR studies showed that chloro-, bromo- and methyl- substituents were also tolerated in this position.[5b] The fused bicyclic ring points toward solvent with the carbonyl of the quinolinone engaging in a hydrogen bond with Asn152. It is clear from this crystal structure that substituents may be tolerated on the solvent exposed edge of the bicyclic ring system with minimal risk of reduction in potency.

The first series of analogs that were targeted intended to improve the metabolic stability of the quinoline and isoquinoline series of aryl acetamides by the incorporation of fluoro and trifluoromethyl substituents. The aryl acetamides were prepared using either one of two general methods outlined in Scheme 1.[7]

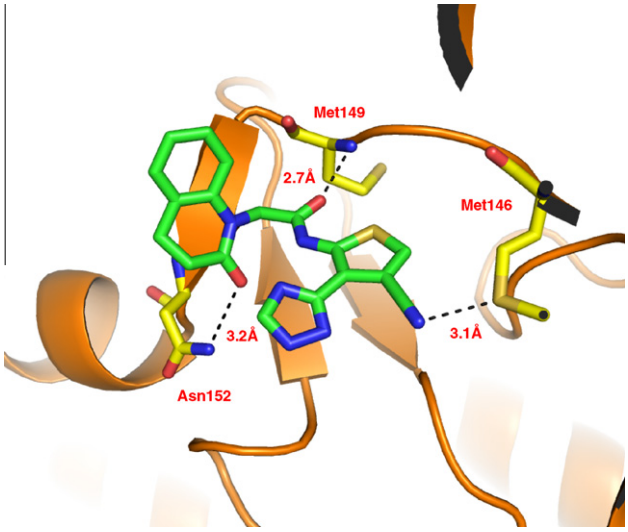
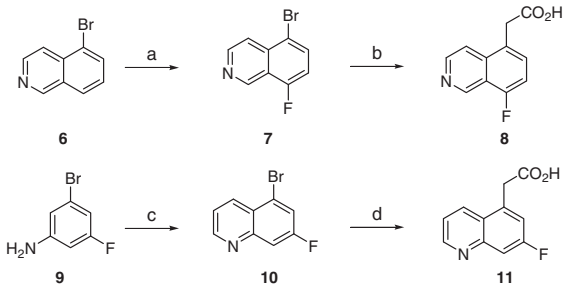


Figure 3. Crystal structure of compound **2** in green bound to JNK3 (2.4 Å resolution) The PBD deposition code is 3RTP. For experimental conditions see Ref. 6.

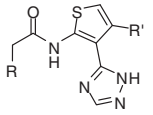


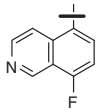
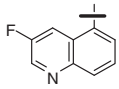
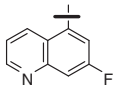
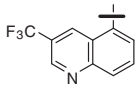
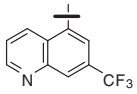
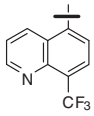
Scheme 1. Reagents and conditions: (a) (i) KNO_3, H_2SO_4 (aq), 0 °C, 20 min; (ii) Fe, NH_4Cl, MeOH, 100 °C, 3 h; (iii) $NaNO_2$, HBF_4, H_2O, 0 °C, 1 h then 150 °C, 18 h; (b) DIPA, *n*BuLi, Pd_2dba_3, 2′-(dicyclohexylphosphino)-*N*,*N*-dimethylbiphenyl-2-amine, *t*-butylacetate, toluene, rt; (ii) HCO_2H, CH_2Cl_2, 50 °C, 16 h; (c) glycerol, nitrobenzene, H_2SO_4, $FeSO_4{\cdot}7H_2O$, 80 °C, 18 h; (d) (i) $Pd_2(dba)_3$, Q-Phos, (2-*tert*-butoxy-2-oxoethyl)zinc(II) bromide, THF, rt–50 °C; (ii) HOAc, HCl, 60 °C, 18 h.

In the first method, fluorine substituents were incorporated into the bicyclic ring via a Schiemann[8] reaction with an appropriate bicyclic amine followed by introduction of the acetic acid via alpha-arylation of the bromoheterocycle **7** in the presence $Pd_2(dba)_3$.[9] Alternatively, quinoline analogs could be accessed using the Skraup quinoline synthesis[10] starting with an appropriately substituted aniline (**9**) followed by elaboration to the aryl acetamide using the conditions mentioned above. This method was used for analogs **21**, 23 and **24**, (Table 1).

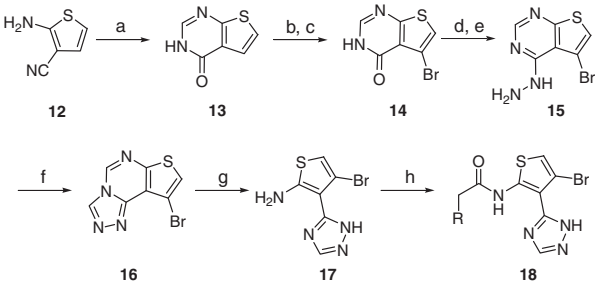
With the aryl acetic acids in hand it remained to couple them to an aminothiophene. Our previous synthesis of trisubstituted thiophenes[5b] involved the conversion of an ester into a triazole in a three-step procedure at the end of the synthesis. While this method allowed access to many compounds it suffered from low yielding reactions over multiple steps and therefore we sought an alternative route whereby the triazole would be formed prior to coupling with the aryl acetic acids. This was accomplished as shown in Scheme 2. Aminothiophene **12** was converted into thieno[2,3-*d*]pyrimidin-4(3*H*)-one 13 followed by dibromination and selective debromination at the 2-position of the thiophene to give compound **14**. Treatment with $POCl_3$ followed by hydrazine gave compound **15** which was subsequently converted into tricyclic intermediate **16** upon reaction with triethyl orthoformate. Reaction of compound **16** with *N*-methylethane-1,2-diamine gave the key synthetic intermediate, aminothiophene **17**. Compound **17**

Table 1
JNK inhibition and in vitro metabolic stability for compounds **1** and **19–24**



Compds	R	R′	JNK3 IC_{50}[a] (nM)	JNK1 IC_{50}a (nM)	JNK2 IC_{50}[a] (nM)	OxMet% (m, r, h)[b]
1		Cl	11	14	43	29, 9, 50
19		Br	24	16	68	34, 5, 44
20		Br	30	17	92	2, 17, 39
21		Br	41	14	140	5, 18, 42
22		Br	52	21	164	3, 20, 37
23		Br	280	178	337	3, 16, 31
24		Cl	183	81	24	3, 1, 32

[a] See Ref. 6 Values are means of at least three experiments at 10 μM ATP concentration.
[b] See Ref. 6 Percent remaining after 30 min incubation with liver microsomes (m = mouse, r = rat and h = human).

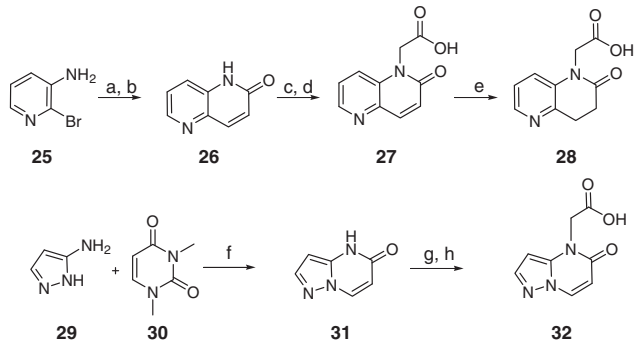


Scheme 2. Reagents and conditions: (a) HCO_2H, concd H_2SO_4, microwave, 100 °C, 15 min.; (b) Br_2, AcONa, AcOH, reflux; (c) Zn, AcOH, H_2O; (d) $POCl_3$, 100 °C, microwave, 0.5 h; (e) hydrazine, EtOH, 75 °C; (f) $HC(OEt)_3$, EtOH, 100 °C; (g) N^1-methylethane-1,2-diamine, MeOH, 60 °C; (h) RCH_2CO_2H, $POCl_3$, pyridine, 0 °C, 0.5 h.

was then coupled with the aryl acetic acids generated as shown in Scheme 1 to give the analogs shown in Table 1.

The introduction of a single fluorine substituent (**19**, **20** and **21**) resulted in a slight decrease in the JNK3 activity of the inhibitors compared to compound **1** and did not improve the compounds' metabolic stabilities. Similarly, the introduction of trifluoromethyl substituents into the 3, 7 and 8-positions on the quinoline (**22**, **23**, and **24**, **respectively),** resulted in compounds with reduced potency and less metabolic stability compared to the parent compound **1**. Interestingly, analogs with trifluoromethyl substituents at the 7- or 8-position of the quinoline (**23** and **24**) were four to fivefold less potent than the analog with the trifluoromethyl csubstituent at the 3-position of the quinoline (compound **22**) and substitution at the 7 and 8-positions was avoided in future analogs.

We next turned our attention to the quinolinone series of inhibitors. As reported in our earlier Letter,[5b] the quinolinone analogs were often more potent against JNK3 compared to the quinolines and isoquinolines and we endeavored to take advantage of this potency increase in our search for more metabolically stable analogs. A series of naphthyridinones was prepared and it was expected that the additional heteroatom in the bicyclic ring would lower the log *P* of the compounds and therefore improve their metabolic stability. These compounds were prepared as outlined in Scheme 3.



Scheme 3. Reagents and Conditions: (a) ethyl acrylate, $Pd(OAc)_2$, P(o-tol)$_3$, Et_3N, DMF, 120 °C, 24 h; (b) NaOEt, EtOH, reflux, 2 h; (c) methyl 2-bromoacetate, LiHMDS, DMF, rt, 0.5 h; (d) NaOH, H_2O, THF, 70 °C, 0.5 h; (e) Pd-C, H_2 (40 psi), MeOH, 18 h; (f) NaOEt, EtOH, 60 °C, 2 h; (g) methyl 2-bromoacetate, NaH, DMF, rt, 1 h; (h) Me_3SnOH, 1,2-dichloroethane, reflux, 2 h.

Heck coupling of 3-amino-2-bromopyridine (**25**) with ethyl acrylate followed by cyclization gave 1,5-naphthyridin-2(1*H*)-one (**26**).[11] Alkylation of **26** with methyl 2-bromoacetate followed by ester hydrolysis gave the desired aryl acetic acid **27** which could be hydrogenated to give **28**. This route was used to prepare all the naphthyridinones shown in Table 2. Pyrazolopyrimidines were prepared by reaction of 3-aminopyrazole (**29**) with 1,3-dimethyluracil to give intermediate **31**[12] which was alkylated as described above and converted to the desired carboxylic acid **32** upon reaction with trimethyltin hydroxide.[13] These aryl acetic acids were coupled with aminothiophene **17** as shown in Scheme 2 to give the analogs displayed in Table 2.

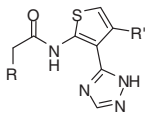
In this series of analogs, the naphthyridinones were slightly more potent than quinolinone **33** but more importantly, they were significantly more stable when incubated with liver microsomes. For example, compound **34** had 83% compound remaining after a 30 min incubation with human liver microsomes whereas compound **33** only had 24% compound remaining. Cyanothiophene **35** was approximately twofold more potent than the corresponding bromothiophene **34** and also possessed greater metabolic stability in lower species. As observed with the quinoline and isoquinoline analogs (Table 1), the addition of trifluoromethyl substituents (**37** and **38**) did not provide a further increase in metabolic stability. Alternative bicyclic ring systems were also explored with pyrazolopyrimidines **39** and **40** which had similar potency to the naphthyridinones but did not offer any advantages in terms of metabolic stability.

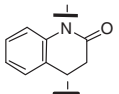
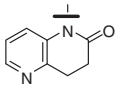
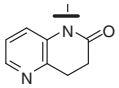
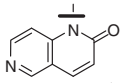
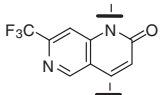
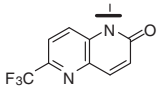
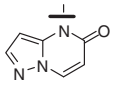
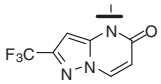
The SAR of the quinolinones was expanded by the addition of electron withdrawing substituents such as trifluoromethyl, fluoro and cyano (Table 3). These analogs were accessed using the same route outlined in Scheme 3 using anilines in place of aminopyridines. Difluoroquinolinone **41** provided a modest increase in stability compared to **33** (Table 2) but the addition of trifluoromethyl substituents was more effective with substitution at the 6-position (**42**) providing the greatest increase in stability. The addition of cyano substituents into the quinoline ring afforded extremely potent compounds with compound **47** (JNK3 IC_{50} = 2 nM) being 14-fold more potent than its parent **33** (JNK3 IC_{50} = 28 nM).

Finally, we turned our attention to the triazole region of the inhibitor in an effort to optimize the potency and metabolic stability of the compounds. Our earlier report[8a] identified both oxazoles and thiazoles as viable triazole replacements and these thiophene substituents were combined with the favored quinolinone and naphthyridinone aryl acetamides. These analogs were prepared by Stille coupling of bromothiophene **49**[14] with the appropriate heterocyclic stannane followed by reduction of the nitro group and $POCl_3$ mediated amide formation (Scheme 4).

With the dihydronaphthyridione aryl acetamide (A) (Table 4) both oxazol-2-yl (**52**) and thiazol-2-yl (**53**) were less stable than their triazole counterpart (**34**), although, they maintained the excellent potency against JNK3. *N*-Methyltriazole (**54**) was fourfold more potent than NH-triazole (**34**) but suffered a loss in metabolic stability presumably due to *N*-dealkylation. Our earlier Letter[5b] demonstrated that 4-cyanothiophenes are generally more stable that the 4-bromothiophenes and therefore this substituent was combined with the triazole replacements. With the naphthyridinone aryl acetamide, cyanothiophene (**55**) was not significantly more stable than (**53**) suggesting that the thiazole ring was causing

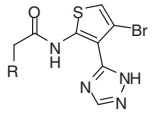
Table 2
JNK inhibition and in vitro metabolic stability for compounds **33–40**

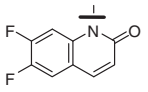
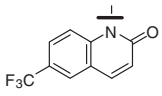
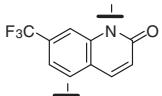
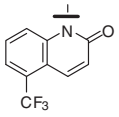
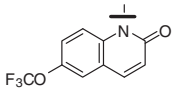
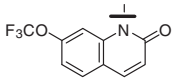
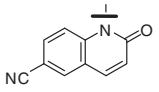
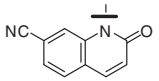


Compds	R	R′	JNK3 IC_{50}[a] (nM)	JNK1 IC_{50}[a] (nM)	JNK2 IC_{50}[a] (nM)	OxMet% (m, r, h)[b]
33		Br	28	25	42	0, 0, 24
34		Br	14	9	32	55, 50, 83
35		CN	6	5	18	84, 81, 80
36		Br	7	4	8	51, 60, 85
37		Br	6	4	21	43, 43, 77
38		Br	14	8	38	35, 2, 64
39		Br	8	8	74	50, 71, 72
40		Br	14	3	36	3, 42, 48

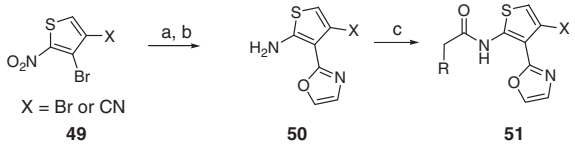
[a] See Ref. 6 Values are means of at least three experiments at 10 μM ATP concentration.
[b] See Ref. 6 Percent remaining after 30 min incubation with liver microsomes (m = mouse, r = rat and h = human).

Table 3
JNK inhibition and in vitro metabolic stability data for compounds **41**–**48**



Compds	R	JNK3 IC_{50}[a] (nM)	JNK1 IC_{50}[a] (nM)	JNK2 IC_{50}[a] (nM)	OxMet%[c] (m, r, h)[b]
41		5	3	15	14, 9, 38
42		9	2	5	58, 35, 67
43		9	6	21	29, 25, 44
44		71	31	193	27, 1, 49
45		6	2	12	16, 39, 64
46		19	11	68	10, 26, 29
47		2	1	10	60, 46, 69
48		2	1	10	44, 62, 59

[a] See Ref. 6 Values are means of at least three experiments at 10 μM ATP concentration.
[b] See Ref. 6 Percent remaining after 30 min incubation with liver microsomes (m = mouse, r = rat and h = human).



Scheme 4. Reagents and Conditions: (a) 2-(tributylstannyl)oxazole, $Pd(PPh_3)_4$, DMF, 90 °C, 18 h; (b) Fe, AcOH, 50 °C, 1 h; (c) RCH_2CO_2H, $POCl_3$, pyridine, 0 °C, 0.5 h.

the degradation in stability. With the quinolinone aryl acetamide (B) the stability of the triazole replacements improved. Within this series, oxazole (**56**) and thiazol-4-yl (**58**) were considerably less stable than thiazol-2-yl (**57**), which had stability similar to the parent triazole **42**.

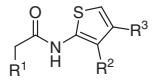
In order for these inhibitors to be effective neuroprotective agents, they must be able to pass through the blood–brain barrier to reach the target and therefore, must have a high rate of permeability and a low P-gp efflux. Illustrated in Table 5 are the in vitro derived permeability and P-gp efflux ratios of the more metabolically stable analogs. Naphthyridinones generally had higher P-gp efflux in MDR–MDCK cells compared to isoquinoline **1**. Both difluoroquinolinone **41** and 6-trifluoromethyl quinolinone **42** had low P-gp efflux ratios but with lower permeability compared to the naphthyridinone **34**. Replacement of the trifluoromethyl substituent of **42** with a nitrile (**47**) resulted in a dramatic increase in the P-gp efflux of the inhibitor. Consistent with previous compounds in this series, none of these new compounds had any measurable IC_{50} against ERK2 or p38α at the concentrations tested. In order to determine the broader kinase selectivity of our latest generation of thiophene based inhibitors, compound **42** was subjected to a screen of 36 kinases. This screen revealed an exceptionally clean profile with only JNK3 being inhibited at 10 μM compound concentration.[6]

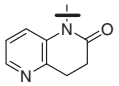
On the basis of their improved in vitro stability, select compounds were evaluated in in vivo pharmacokinetic studies and the results are shown in Table 6. The brain exposures of these analogs track well with the in vitro derived P-gp efflux ratios. For example, compounds with P-gp ratios greater than 1.6 showed brain/plasma ratios less than 0.5 and low exposure in the brain (**1**, and **34**) when dosed at 1 mg/kg in mice. Both compounds **41** and **42** had low P-gp efflux ratios and displayed brain/plasma ratios close to 1. Compounds with good in vitro stability (**42** and **34**) generally had low clearance and longer half lives compared to less stable analogs such as **41**.

Compound **42** displayed the most favorable combination of high brain exposure, good brain/plasma ratio and low clearance and the neuroprotective properties of this inhibitor were evaluated in a human cortical neuronal amyloid-β neurotoxicity assay.[6,15] In this assay, compound **42** has an EC50 of 2.9 μM suggesting that this series JNK inhibitors maybe viable neuroprotective agents.

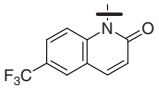
In conclusion, we have prepared trisubstituted thiophene based JNK inhibitors with improved pharmacokinetic properties compared to earlier analogs. This was accomplished by identifying the metabolites generated upon treatment of our earlier

Table 4
JNK inhibition and in vitro metabolic stability data for compounds **52**–**58**. SAR of the heterocycle





A

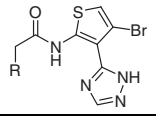


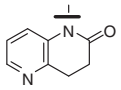
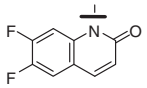
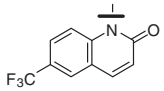
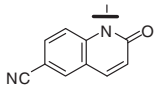
B

Compds	R^1	R^2	R^3	JNK3 IC_{50}[a] (nM)	JNK1 IC_{50}[a] (nM)	JNK2 IC_{50}[a] (nM)	OxMet% (m, r, h)[b]
52	A		Br	6	7	66	0, 0, 11
53	A		Br	15	13	145	0, 0, 3
54	A		Br	3	1	13	33, 37, 46
55	A		CN	11	10	62	7, 1, 16
56	B		CN	8	4	29	4, 2, 24
57	B		CN	9	7	53	52, 76, 75
58	B		CN	8	2	17	17, 8, 32

[a] See Ref. 6 Values are means of at least three experiments at 10 μM ATP concentration.
[b] See Ref. 6 Percent remaining after 30 min incubation with liver microsomes (m = mouse, r = rat and h = human).

Table 5
P-gp, permeability and kinase selectivity data for select analogs



Compds	R	JNK3 IC_{50}[a] (nM)	P38α IC_{50}[a] (μM)	ERK2 IC_{50}[a] (μM)	OxMet% (m, r, h)[b]	P_{app}[b] (nm/s)	P-gp Efflux[b]
1[c]		11	>50	>50	29, 9, 50	270	1.6
34		14	>50	>0.5	55, 50, 84	368	1.8
41		5	>50	>50	14, 19, 38	83.1	0.68
42		5	>50	>50	42, 39, 62	36.2	0.61
47		2	>50	>50	60, 46, 69	34.3	4.18

[a] See Ref. 6 Values are means of at least three experiments at 10 μM ATP concentration.
[b] Percent remaining after 30 minute incubation with liver microsomes (m = mouse, r = rat and h = human).
[c] 4-Chlorothiophene instead of 4-bromothiophene.

generation of inhibitors with liver microsomes and using this information to design more metabolically stable analogs. This led to compound **42**, a brain penetrant selective JNK inhibitor which had vastly improved brain exposure and low clearance

Table 6
In vivo pharmacokinetic data for select analogs

Cmpds	Mouse (1 mg/kg IV)		Rat			
	AUC brain (ng h/mL)	Brain/plasma	IV (1 mg/kg)		PO(2 mg/kg)	
			$t_{1/2}$ (min)	Clearance (mL/h/kg)	AUC (nmol h/mL)	F%
1	88	0.4	na	na	na	na
34	35	0.24	2.5	660	2720	91
41	160	1.4	2.3	1351	571	40
42	235	0.7	4.6	554	1314	34

compared to earlier analogs and had demonstrated in vitro neuroprotection in human cortical neurons. Future efforts to develop these compounds as neuroprotective agents will be reported in due course.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2011.06.100.

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