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Design and synthesis of disubstituted thiophene and thiazole based inhibitors of JNK

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ABSTRACT

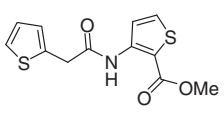
From high throughput screening, we discovered compound **1**, the prototype for a series of disubstituted thiophene inhibitors of JNK which is selective towards closely related MAP kinases p38 and Erk2. Herein we describe the evolution of these compounds to a novel class of thiophene and thiazole JNK inhibitors that retain favorable solubility, permeability, and P-gp properties for development as CNS agents for treatment of neurodegeneration. Compound **61** demonstrated JNK3 IC_{50} = 77 nM and retained the excellent broad kinase selectivity observed for the series.

The c-Jun N-terminal kinases (JNKs) are serine/threonine protein kinases within the mitogen-activated protein (MAP) kinase family which are upregulated in response to external and internal stressors.[1] There are 10 splice variants of human JNK which are encoded by three genes: *Jnk1*, *Jnk2*, and *Jnk3*. The isoforms JNK1 and JNK2 are widely expressed in the body, but JNK3 is expressed primarily in the brain.[2]

JNK3 has been further implicated as a key player in neurodegenerative disorders, including Alzheimer's[3] and Parkinson's[4] disease. To avoid potential toxic effects from broad kinase inhibition, it was critical to generate selective inhibitors toward the JNKs. In particular, we required selectivity between the JNKs and the most closely related MAP kinases p38 and Erk2.[5,6] With this in mind, our goal was the development of brain penetrant JNK inhibitors which were selective over these other kinases. As yet, it is unclear whether systemic inhibition of any or all of the isoforms JNK1, JNK2, or JNK3 results in clinically observed adverse effects.[7] Thus, we did not focus on isoform selective inhibitors.

We opted to pursue JNK inhibitors from a high throughput screening campaign of the Elan small molecule compound library. Compound **1** emerged as a promising hit, exhibiting JNK3 IC_{50} = 2.2 μM with good solubility, excellent passive permeability, and a lack of recognition by permeability glycoprotein (P-gp) in vitro, which are all critical characteristics for a series of compounds to be developed for a CNS target (Fig. 1). This series was potent mainly on the isoforms JNK1 and JNK3, with 10-fold selectivity over JNK2. Compound **1** exhibited remarkable selectivity over closely related kinases p38α and Erk2.

The crystal structure of JNK3 in complex with compound **1** in the presence of a peptidic portion of JNK-interacting protein (JIP1) was determined to 2.2 Å resolution as shown in Figure 2. This was performed in analogy to work reported with JNK1.[9] Compound **1** was found to be a Type I ATP-competitive kinase inhibitor where



Compound 1
JNK3 IC_{50} = 2.2 μM
JNK2 IC_{50} = 23 μM
JNK1 IC_{50} = 1.6 μM
p38α IC_{50} > 50 μM
Erk2 IC_{50} > 50 μM
HBSS solubility = 72 μM
MDR MDCK A>B = 144 nm/sec
P-gp efflux = 0.93

Figure 1. In vitro characteristics of screening hit compound **1**.[8,9]

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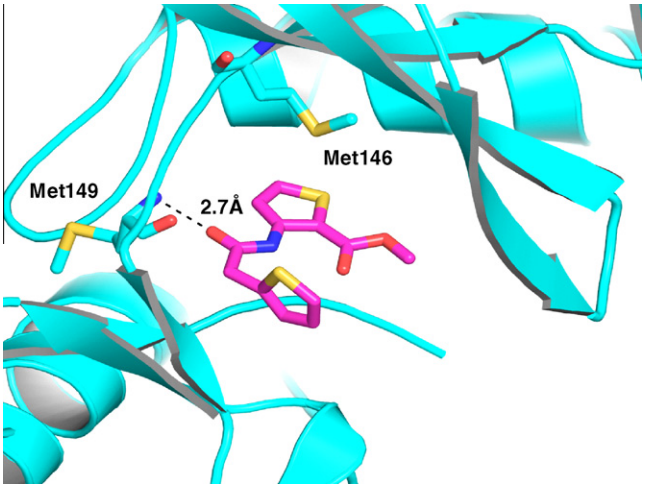


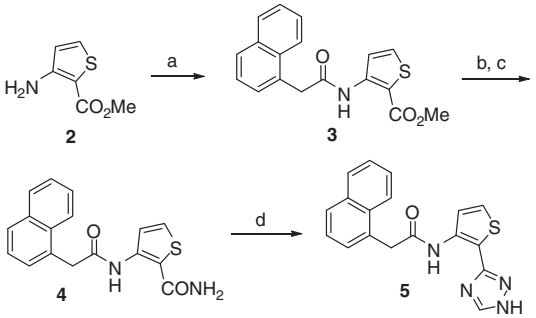
Figure 2. Binding mode of the thiophenes: X-ray co-crystal structure of compound **1** with JNK3 in the presence of JIP1 peptide at 2.2 Å resolution.[9] The pdb code is 3OXI.

the critical hydrogen bond formed between the inhibitor carbonyl and the NH of Met-149. The thiophene ring of the inhibitor was found to be within hydrophobic contact of the gatekeeper Met-146 side chain. In addition, the inhibitor ester substituent formed an internal hydrogen bond with the amide NH, thus creating planarity on the right half of the molecule. The left side 2-thienylacetyl portion formed a 90° turn within the inhibitor, pointing the arylacetyl group toward solvent.

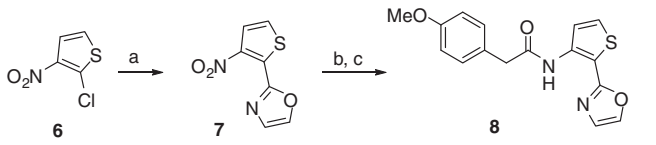
Analogs of compound **1** were synthesized according to Scheme 1. The ester inhibitor **3** was readily synthesized from amide coupling[10] of the commercial amino ester **2**. The methyl ester was saponified under basic conditions, and then converted to the primary amide **4**. The triazole analog **5** was in turn provided from treatment of **4** with dimethylformamide dimethyl acetal (DMFDMA) to give the desired triazole inhibitor.[11,12]

Alternatively, JNK inhibitors were synthesized from the commercial 2-chloro-3-nitrothiophene (**6**), as exemplified with compound **8** (Scheme 2). Displacement or metal-mediated coupling at the site of the activated halogen, followed by nitro reduction, and then amide coupling under $POCl_3$ conditions provided a number of the analogs.

The initial SAR was generated on variations of the *N*-arylacetyl portion of the molecule (Table 1).[13] Not surprisingly, phenyl (**9**) was a viable isosteric replacement of the 2-thienyl group,[14] but the more polar 4-pyridyl analog (**10**) lost eightfold in potency. Pendant *para* substituted hydrophilic phenylacetyl groups (**11–13**),

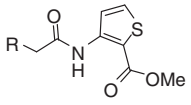


Scheme 1. Reagents and conditions: (a) 1-naphthylacetic acid, $POCl_3$, pyridine, 0 °C; (b) NaOH, 1:1 THF/H_2O, 50 °C, 20 h, 75%; (c) $SOCl_2$, 60 °C, 30 min, then concd NH_4OH, CH_3CN, 54%; (d) $(OMe)_2CHNMe_2$, 110 °C, 30 min, then H_2NNH_2–H_2O, AcOH, 90 °C.



Scheme 2. Reagents and conditions: (a) 10 mol % $Pd(PPh_3)_4$, 2-tributylstannyloxazole, DMF, 100 °C; (b) 10% Pd/C, 40 psi H_2, EtOAc, 50 °C; (c) 4-methoxyphenylacetic acid, $POCl_3$, pyridine, 0 °C.

Table 1
JNK1, JNK2, and JNK3 biochemical IC_{50} for thiophene ester analogs[13]



Compds	R	JNK3 IC_{50}[a] (μM)	JNK2 IC_{50}[a] (μM)	JNK1 IC_{50}[a] (μM)
1	2-Thienyl	2.2	21.4	1.8
9	Ph	2.7	22.8	0.7
10	4-Pyridyl	17.2	>50	6.6
11	4-OMePh	1.0	14.1	0.8
12	4-(4-Pyridyl)–Ph	0.69	>50	0.46
13	4-(Imidazolyl)-Ph	1.6	>50	1.0
14	4-CF_3–Ph	6.9	>50	2.0
15	2-Naphthyl	3.9	>50	0.6
3	1-Naphthyl	1.5	14.6	0.40
16	2-(1,2,3-Triazol-4-yl)-phenyl	12.6	35.0	7.0
17	5-Isoquinolyl	0.61	3.1	0.27
18	5-Quinolyl	0.61	3.0	0.30

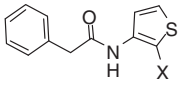
[a] See Ref. 9.

but not a bulkier hydrophobic group (**14**), were tolerated or gave slightly improved activity in JNK1 and JNK3. Larger bicyclic naphthylacetyls (**3 and 15**) were also tolerated. Attempts to gain another hydrogen bond interaction with the hinge through 2-substituted phenacetyls (e.g., **16**) were not successful. The polar N-termini 5-isoquinolylacetyl (**17**) and 5-quinolylacetyl (**18**) gave a moderate fourfold increase in JNK3 activity and sevenfold increase in JNK1 activity compared with compound **1**. The only modest improvements in activity were consistent with the X-ray co-crystal structure, which indicated that this portion of the molecule pointed toward solvent, and likely did not form significant interactions with the enzyme.

Since the ester function did not form any hydrogen bonds with the enzyme, we postulated that it could be replaced (Table 2). We quickly discovered that any functionality of similar size to the methyl ester, but without the ability to hydrogen bond with the amide NH, such as the methyl alcohol **20** and the isopropenyl **22**, led to compounds which were not active, indicating that the planarity was necessary for JNK inhibition in this series. Regardless, even simple replacements which preserved the hydrogen bond acceptor present in the ester, such as the ketone (**19**) or oxime (**21**), also lost 6-fold and 11-fold activity versus JNK3, respectively. Simple primary and secondary amides (**25–27**) were tolerated, but these were also slightly less active than the ester. The tertiary amide led to complete loss in activity. Larger esters, such as the ethyl (**23**) and isopropyl (**24**) esters, led to slight increases in JNK3 inhibition. With the exception of the esters and amides, we were unable to replace the methyl ester with other acyclic hydrogen bond accepting groups, and the rationale for that remained unclear.

Concurrent with the study performed in Table 1, we also examined whether the central thiophene could be replaced in these inhibitors. As compound **3** was discovered early, we began with

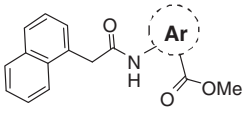
Table 2
JNK1, JNK2, and JNK3 biochemical IC_{50} for thiophenes containing acyclic ester variations



Compds	X	JNK3 IC_{50}[a] (μM)	JNK2 IC_{50}[a] (μM)	JNK1 IC_{50}[a] (μM)
9	CO_2Me	2.7	22.8	0.7
19	COMe	17	>50	6.3
20	CH_2OH	>50	na	na
21	C(=N–OH)Me	29	na	na
22	$C(=CH_2)Me$	>50	na	na
23	CO_2Et	0.7	46.6	0.3
24	CO_2i-Pr	1.4	47.7	0.5
25	$CONH_2$	4.4	>50	2.6
26	$CONH(CH_2)_2OMe$	3.8	>50	2.3
27	$CONMe(CH_2)_2OMe$	>50	>50	na

na = data not available.
[a] See Ref. 9.

Table 3
Effect of the central ring variation on JNK1, JNK2, and JNK3 biochemical IC_{50}



Compds	Ar	JNK3 IC_{50}[a] (μM)	JNK2 IC_{50}[a] (μM)	JNK1 IC_{50}[a] (μM)
3		1.5	14.6	0.4
28		>50	>50	>50
29		>50	>50	>50
30[b]		>50	>50	>50
31		>50	>50	>50
32		>50	>50	>50
33		>50	>50	>50
34		>50	>50	na
35		1.7	13.1	2.1
36[c]		0.90	9.9	0.89
37		5.4	26.7	2.1
38		6.5	23.6	6.4

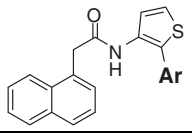
na = data not available.
[a] See Ref. 9.
[b] Ethyl ester.
[c] Phenylacetamide N-terminus.

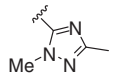
variations on that analog. However, a number of heterocyclic replacements failed to give compounds with any measureable inhibition toward JNK3 (Table 3). This is likely due to the detrimental energetics between the heterocyclic rings which presented a hydrogen bond acceptor toward the C=O function of Glu-147, including the five-membered ring analogs isothiazole, oxadiazole, thiadiazole, and thiazole (**28**–**31**) as well as the six-membered ring pyridyl and pyrazine analogs (**32**–**34**).

Nevertheless, we discovered a few rings other than thiophene which were tolerated by JNK3 (Table 3). Phenyl (**35**) was an acceptable isostere, and yielded a comparable JNK3 inhibitor to the thiophene. Other compounds which yielded somewhat weaker JNK3 inhibitors included NH pyrazole and 3,4-disubstituted pyridyl analogs (**37** and **38**). The 3,4-disubstituted thiophene (**36**) indicated that location of the sulfur on the ring was unimportant for maintenance of the hydrophobic interaction with the enzyme.

Due to the perceived metabolic liability of the methyl ester, we were eager to discover replacements which would be more stable and perhaps more potent against JNK3. Despite our initial disappointment with acyclic replacements in Table 2, we were able to replace the ester function with heteroaryl groups that could form the internal hydrogen bond with the secondary amide of the inhibitor. We discovered that the C-linked triazole (**5**) and methyltriazole

Table 4
Biochemical IC_{50} and in vitro oxidative stability for thiophene inhibitors



Compds	Ar	JNK3 IC_{50}[a] (μM)	JNK2 IC_{50}[a] (μM)	JNK1 IC_{50}[a] (μM)	Stability[b,c] (m, h)
39		5.3	27.1	3.2	1, 7
40		9.0	>50	26.9	0, 17
41		3.6	>50	3.2	0, 5
5		0.92	3.0	0.53	1, 11
42		2.1	16.3	1.8	0, 4
43		42.5	>50	24.1	0, 0
44		0.55	2.4	0.25	1, 1
45		31.5	>50	30.3	1, 1
46		9.4	1.5	3.4	1, 2

[a] See Ref. 9.
[b] In vitro metabolic stability measured as the percent remaining after 30 min incubation with mouse or human microsomes.
[c] See Ref. 8 for protocols.

(**44**) analogs were the most active (Table 4). Many other heteroaryl groups, including oxadiazoles (**39 and 42**) and pyrazoles (**41** and **46**), afforded inhibitors which were comparable or resulting in only slightly attenuated activity compared with the methyl ester **3**. The imidazole (**40**), and *N*-Me triazole (**45**) or pyrazole (**43**) analogs led to significant losses of activity. Despite removal of the ester, all of these compounds exhibited poor metabolic stability, perhaps due to the oxidation of the naphthyl function.

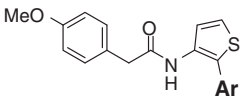
It became clear that, while a 2-substituted heteroatom capable of acting as hydrogen bond acceptor, such as N or O, was necessary for JNK inhibition in this series, it was not sufficient for activity in a number of analogs (Table 5). Interestingly, the N-linked 1,2,4-triazole (**47**) lost activity, while the symmetrical 1,2,3-triazole (**48**) retained JNK3 inhibition. The basic imidazoles (**52** and **53**) and non-aryl carbamate (**49**) lost significant activity, while triazoles **50** and **51**, oxazole **8**, and simple pyrazine **54** retained potency against JNK1 and JNK3.

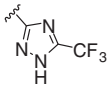
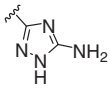
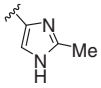
Overall, the metabolic stability remained poor, with the exception of aminotriazole **51** and weakly active carbamate **49**. However, the passive permeability of these compounds remained at a level compatible with CNS penetration.

Combination of the favorable heterocyclic replacements and N-termini in the thiophene series also led to more potent analogs which retained favorable permeability properties (Fig. 3). The *N*-quinolylacetamide triazole **55** showed submicromolar potency against JNK1 and JNK3, retained excellent solubility and selectivity against Erk2, and moderate to good oxidative stability, but began to exhibit P-gp efflux in vitro. The *N*-isoquinolylacetamide thiazole **56** showed similarly good potency and selectivity, as well as solubility, but lower in vitro metabolic stability with enhanced P-gp properties compared with **55**.

We also examined the 4,5-disubstituted thiazoles, which also were suitable replacements for the 2,3-disubstituted thiophenes (Table 6). The NH triazoles (**58** and **59**), pyrazine (**60**), and bisthiazole (**61**) analogs provided greater inhibition versus JNK3 compared with the ester (**57**). None of the derivatives **57**–**60** showed acceptable stability in murine microsomes. Significantly, the bisthiazole analog **61** afforded the most potent JNK3 inhibitor thus far with IC_{50} <100 nM and with good in vitro stability in the

Table 5
Biochemical IC_{50}, in vitro oxidative stability, and passive permeability data for thiophene inhibitors[13]



Compds	Ar	JNK3 IC_{50}[a] (μM)	JNK2 IC_{50}[a] (μM)	JNK1 IC_{50}[a] (μM)	Stability[b,c] (m, h)	Perm[c] (nm/s)
47		45.6	>50	43.6	na	na
48		1.5	5.0	0.83	1, 0	150
49		37.0	>50	>50	26, 83	260
50		5.9	15.0	3.4	8, 71	na
51		1.6	8.7	0.79	44, 87	243
52		31.0	>50	23.9	1, 49	70
8		0.80	11.9	0.22	9, 14	na
53		27.0	>50	23.4	0, 17	338
54		1.5	5.7	1.1	0, 0	222

na = data not available.
[a] See Ref. 9.
[b] In vitro metabolic stability measured as the percent remaining after 30 min incubation with mouse or human microsomes.
[c] See Ref. 8 for protocols.

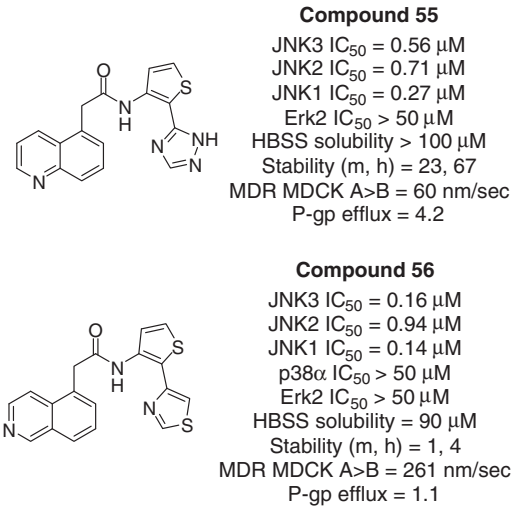
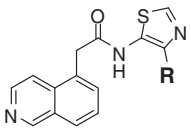


Figure 3. In vitro data for thiophenes **55** and **56**.

Table 6
JNK biochemical IC_{50}, oxidative stability, and passive permeability of thiazole analogs[13]



Compds	R	JNK3 IC_{50}[a] (μM)	JNK2 IC_{50}[a] (μM)	JNK1 IC_{50}[a] (μM)	Stability[b,c] (m, h)	P-gp efflux[c]
57	CO_2Me	1.6	5.3	1.7	11, 41	0.8
58		0.82	2.6	0.71	15, 14	5.0
59		1.6	7.6	1.4	0, 100	1.1
60		0.47	2.0	0.41	3, 2	0.73
61		0.077	0.47	0.048	50, 79	1.9

[a] See Ref. 9.
[b] In vitro metabolic stability measured as the percent remaining after 30 min incubation with mouse or human microsomes.
[c] See Ref. 8 for protocols.

presence of murine and human liver microsomes. Furthermore, it maintained the remarkable selectivity against a panel of 36 non-JNK kinases,[13,15] including both p38α and Erk2 (IC_{50} >50 μM), and showed only a low degree of P-gp efflux in MDR-MDCK cells.

In conclusion, we discovered a series of JNK1/3 selective thiophene inhibitors through high throughput screening. The ATP-competitive thiophene and thiazole inhibitors were improved by replacement of the ester with heterocyclic rings, which retained the inhibitor's internal hydrogen bonding to maintain the planarity of much of the molecule. The best bis-thiazole inhibitor **61** showed IC_{50} <100 nM for both JNK1 and JNK3, with good in vitro stability against liver microsomes. Further investigation of these inhibitors will be reported in due course.

Acknowledgments

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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.2010.10.066.

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