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3,5-Disubstituted quinolines as novel c-Jun N-terminal kinase inhibitors

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Abstract—The structure-based design and synthesis of a novel series of c-Jun N-terminal kinase (JNK) inhibitors with selectivity against p38 is reported. The unique structure of 3,5-disubstituted quinolines (**2**) was developed from the previously reported 4-(2,7-phenanthrolin-9-yl)phenol (**1**). The X-ray crystal structure of **16a** in JNK3 reveals an unexpected binding mode for this new scaffold with protein.

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 via upstream kinase signaling cascade in response to environmental stress. Three distinct genes encoding JNKs have been identified (jnk1, jnk2, and jnk3).[1] JNK1 and JNK2 are ubiquitously expressed, while JNK3 is primarily localized in neuronal tissues and to a lesser extent in the heart and testis.[2,3]

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.[4,5] 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.[6–10] JNK3 has been shown to mediate neuronal apoptosis and make inhibiting this isoform a promising therapeutic target for neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, and other CNS disorders.[11–13]

Therefore, developing JNK inhibitors as therapeutics has gained considerable interest over the past few years.[14–20] Evaluation of the primary and patent literature reveals limited structural diversity amongst JNK inhibitors, though this is not unusual for kinase targets given that most are ATP-competitive inhibitors.[21] Previously, 4-(2,7-phenanthrolin-9-yl)phenol (**1**, Fig. 1), discovered by screening the Merck compound collection, was reported as a 590-nM JNK3 inhibitor with no detectable activity against p38.[22] We were particularly interested in this compound not only because its unique structure is strikingly different from most of the kinase inhibitors published in literature, but also because its relatively small size provides plenty of opportunities to improve potency and selectivity by rational structure-based design. Herein, we report a novel series of JNK inhibitors based on the 3,5-disubstituted quinoline scaffold (**2**, Fig. 1) which was derived from phenanthroline (**1**).

The initial SAR strategy was to maintain the core structure of **1** (the a, b, c ring system), since 2-key hydrogen

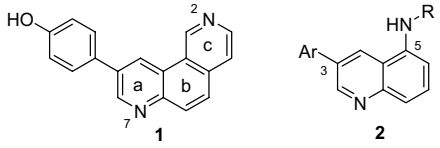

Figure 1. Novel JNK scaffolds.

Keywords: c-Jun N-terminal kinase; 3,5-disubstituted quinolines.
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bonding interactions were identified between the two nitrogen atoms of **1** and the main chain of the JNK3 ATP binding site as illustrated in the co-crystal structure of **1** and JNK3.[22,23] Thus, our first attempt was to modify the phenol group at the C-9 position of the phenanthroline. Compound **1** and analogs **1a**–**i** were synthesized in four steps as described in Scheme 1. Pomeranz–Fritsch isoquinoline synthesis of 3-bromobenzaldehyde and 2,2-dimethoxyethylamine provided two separable isomers, 7- and 8-bromoisoquinoline. Amination of 7-bromoisoquinoline followed by Combes quinoline synthesis and deprotection furnished **1**.

Nine analogs of compound **1** have been tested for JNK3 inhibitory activities which are shown in Table 1. Substituents such as hydrogen, phenyl, pyrazole, and mopholino failed to improve potency against JNK3 (**1a**–**d**), but small polar hydrogen bond donor groups such as NH_2, NHAc, and NHMs (**1e**, **1g**, **1h**) had comparable activities to the parent compound **1**. The sulfonamide **1i**, was nearly 3× as potent, but exhibited poor solubility as did other analogs. Other modifications including *ortho*- and *meta*-substituted phenyl derivatives (not shown) as well as substitutions on the b-ring failed to improve JNK3 inhibitory activity. This series of inhibitors also suffered from poor rodent pharmacokinetics (high Cl_p, short $t_{1/2}$, low %*F*).

To improve the overall physicochemical properties of the molecules as well as to facilitate chemical SAR, the b-ring of **1** was eliminated, resulting in compounds of type **3** (Fig. 2). These compounds (data not shown) were considerably more soluble; however, despite synthesizing numerous analogs, we were unable to improve JNK3 inhibition below 10 μM even though the nitrogen atoms from the two pyridyl rings are still present as hydrogen bond acceptors. Presumably, some degree of planarity in **1** is required for potency that is lost in structure **3**. To slightly increase conformational rigidity, we decided to keep the a- and b-rings of **1**, and this time, break down the c-ring (**4**, Fig. 2). Introduction of substituents at the 5-position of the quinoline would hopefully pick up the purported hydrogen bonding interaction of the phenanthroline N-2, with the quinoline nitrogen atom maintaining the conserved hydrogen bond with Met 149 in the hinge region.[22] In order to explore the SAR of the R^5 position efficiently,

Table 1. Inhibition of JNK3 by phenanthroline derivatives **1**

Compound	R	JNK3 IC_{50}[a,24] (μM)	p38 IC_{50}[a,24] (μM)
1	OH	0.59 ± 0.04	>20
1a	H	1.0 ± 0.17	>20
1b	Phenyl	>20	nt
1c	5-Pyrazolyl	3.6 ± 0.68	nt
1d	Morpholino	1.3 ± 0.22	nt
1e	NH_2	0.51 ± 0.03	>20
1f	NAc_2	1.6 ± 0.27	nt
1g	NHAc	0.53 ± 0.08	>20
1h	NHMs	0.93 ± 0.10	>20
1i	NMs_2	0.21 ± 0.02	>20

[a] Values are means of three experiments; nt, not tested.

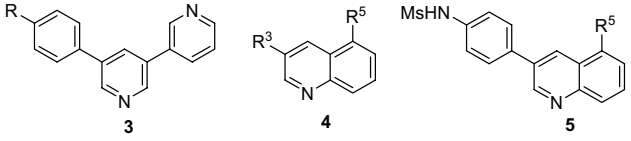
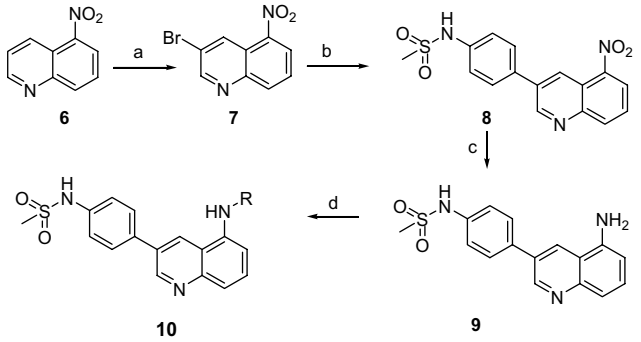


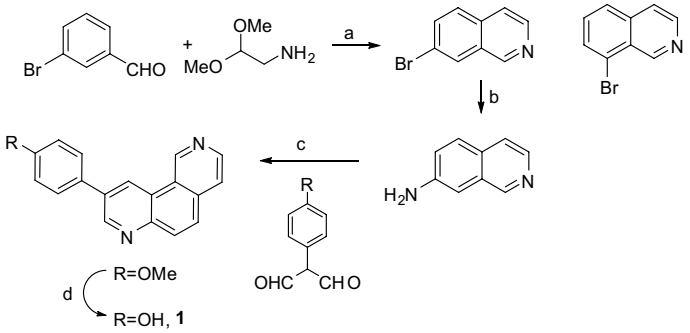
Figure 2. Modifications to phenanthroline scaffold.

para-phenylmethanesulfonamide was chosen as a standard R^3 (**5**, Fig. 2).

The initial round of compounds was N-linked through C-5 of the quinoline ring, and the synthesis is outlined in Scheme 2. Regioselective bromination of commer-



Scheme 2. Reagents: (a) Br_2, pyridine; (b) 4-(methylsulfonamido)phenylboronic acid, $Pd(PPh_3)_4$, K_2CO_3, DME; (c) Pd/C, MeOH; (d) Pd_2dba_3, Cs_2CO_3, Xantphos, DME.



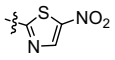
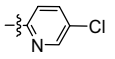
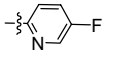
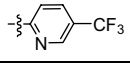
Scheme 1. Reagents and conditions: (a) i—Toluene, 120 °C; ii—concd H_2SO_4, P_2O_5; (b) i—Pd_2dba_3, BINAP, NaOtBu, $Ph_2C{=}NH$, toluene; ii—1 N HCl, THF; (c) HOAc, 120 °C; ii—concd H_2SO_4, 100 °C; (d) BBr_3, Et_2O, 0 °C.

cially available 5-nitro-quinoline (**6**) with bromine in pyridine at elevated temperature provided 3-bromo-5-nitro-quinoline (**7**) which was subsequently treated with 4-(methylsulfonamido)phenylboronic acid under Suzuki conditions to afford compound **8**. Reduction of **8** followed by acylation or Buchwald amination furnished compound **10**. The rapid synthesis of the core quinoline allowed us to evaluate a series of analogs with a variety of R^5-substituents.

The SAR for this class of compounds revealed that a 2-pyridyl-amino group at C-5 (**10a,** Table 2) slightly improved potency compared to **1**. This was a significant breakthrough as this was the first time we were able to get away from the phenanthroline ring system and maintain inhibitory activity against JNK3. Introduction of an extra nitrogen atom in the ring (**10b**) is tolerable, but the 2-pyridinylamide (**10c**) is not. Five-membered ring heterocycles are also allowed (**10d**). The largest improvements in potency came with small *meta*-substituted 2-pyridylamine groups (**10g** and **10h**), whereas large substituents or substitution at other positions diminished activity (**10e**, **10f**, and **10i**). Fortunately, conversion of the phenanthroline to a quinoline scaffold did not pick up p38 activity, as all analogs tested were essentially inactive.

Attempts were then made to eliminate the C-5 amino group and to attach the pyridyl ring directly to the quinoline core (Table 3). Analogs **13** were synthesized in two steps from 5-amino-quinoline **11** by Sandmeyer reaction followed by Suzuki coupling with 2-pyridine boronic acid (Scheme 3). The 2-pyridyl analog, **13a**, could then place its nitrogen atom in the same position in space as phenanthroline **1** as observed in a 2-dimensional overlap. It was surprising that the **13a** was completely inactive versus JNK3, whereas the 3- and 4-pyridyl analogs (**13b** and **13c**), though slightly better, were still considerably less active than the N-linked analogs **10a**–**i**. At this time, it was unclear what role the NH-group played in conferring potency to analogs described in Table 2.

Table 2. Inhibition of JNK3 by phenanthroline derivatives **10**

Compound	R	JNK3 IC_{50}[a] (μM)	p38 IC_{50}[a] (μM)
10a		0.44 ± 0.09	>20
10b		0.48 ± 0.06	>20
10c		3.6 ± 0.32	nt
10d		0.76 ± 0.15	nt
10e		15 ± 0.17	nt
10f		6.5 ± 0.53	nt
10g		0.12 ± 0.02	>20
10h		0.14 ± 0.02	nt
10i		0.49 ± 0.06	nt

[a] Values are means of three experiments; nt, not tested.

Table 3. Inhibition of JNK3 by pyridyl derivatives **13**

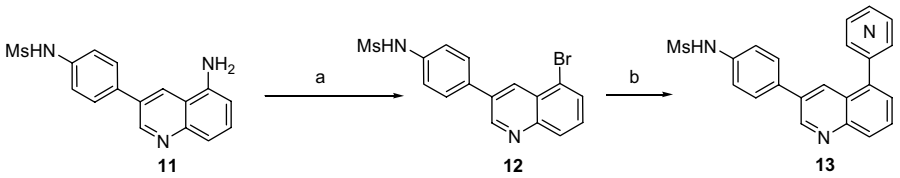
Compound	R	JNK3 IC_{50}[a] (μM)	p38 IC_{50}[a] (μM)
13a		>20	nt
13b		5.2 ± 0.39	>20
13c		5.0 ± 0.37	>20

[a] Values are means of three experiments; nt, not tested.

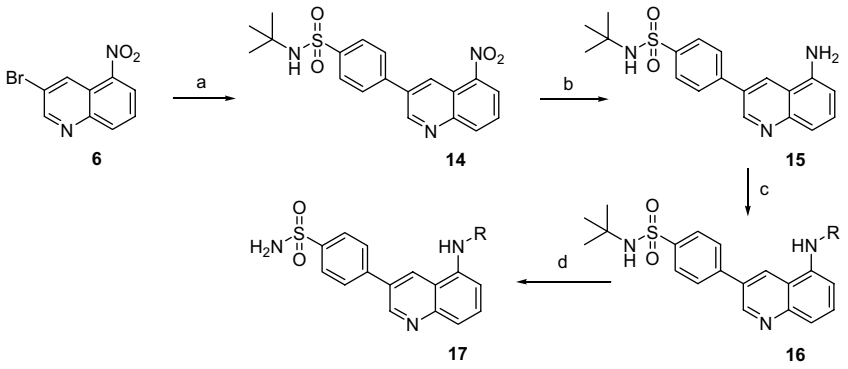
Having somewhat optimized the C-5 substituent, we continued to probe the 4-substituted phenyl group at the C-3 position. Following the procedure described in Scheme 4, the inverse sulfonamide **16** was synthesized from 3-bromo-5-nitro-quinoline (**6**) in three steps. Elimination of the *t*-butyl group with 90% trifluoroacetic acid in dichloromethane generated primary sulfonamide **17**. The inverse sulfonamide *t*-butyl analog **16a** was 3× more potent than **10a**, and 4× more potent than **1** (Table 4). Unfortunately, installation of the potency enhancing *m*-chloro substituent in **16b** did not result in any boost in potency as seen for **10a** → **10g**.

A crystal structure of **16a** was pursued in an attempt to help explain its binding mode and further aid in structure-based drug design. Surprisingly, compound **16a** bound in a completely unexpected manner, and quite differently from phenanthroline **1** (Fig. 3). Apparently the newly introduced 2-aminopyridine group binds to the hinge region in JNK3, much like many other kinase inhibitors. This forces the rest of the molecule to wrap around the hinge region and extend out into solvent exposed space. The sulfonamide group picks up additional hydrogen bonding interactions outside the active site. We anticipate using this crystal structure to design and synthesize new, more potent analogs which might take advantage of the rest of the currently unoccupied ATP binding site.

In summary, a series of 3,5-disubstituted quinolines as a new structural type of JNK3 inhibitors has been developed from structure-based drug design originating from a published compound **1**. Optimization by introduction of an aminopyridinyl group at the 5-position of the quinoline led to the discovery of compounds **10a** and **16a** as more potent JNK3 inhibitors. These compounds have a completely different binding mode from **1** and most other kinase inhibitors by not taking advantage of most of the ATP binding site, which, perhaps will lead to unanticipated selectivities against other closely related kinases. Synthesis and characterization of more

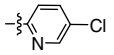
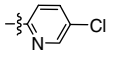


Scheme 3. Reagents: (a) i—$NaNO_2$, HBr; ii—CuBr; (b) $Pd(PPh_3)_4$, DME, Na_2CO_3, $ArB(OH)_2$.



Scheme 4. Reagents and condition: (a) *N-t*-butyl-4-(4,5-dimethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide, $Pd(PPh_3)_4$, K_2CO_3, DME, microwave; (b) Pd/C, MeOH; (c) RX, Pd_2dba_3, Cs_2CO_3, Xantphos, DME, microwave; (d) 90% TFA in CH_2Cl_2.

Table 4. Inhibition of JNK3 by inverse sulfonamides **16** and **17**

Compound	R	JNK3 IC_{50}[a] (μM)	p38 IC_{50}[a] (μM)
16a		0.15 ± 0.02	>20
16b		0.25 ± 0.03	>20
17a		0.20 ± 0.02	nt
17b		0.24 ± 0.01	nt

[a] Values are means of three experiments; nt, not tested.

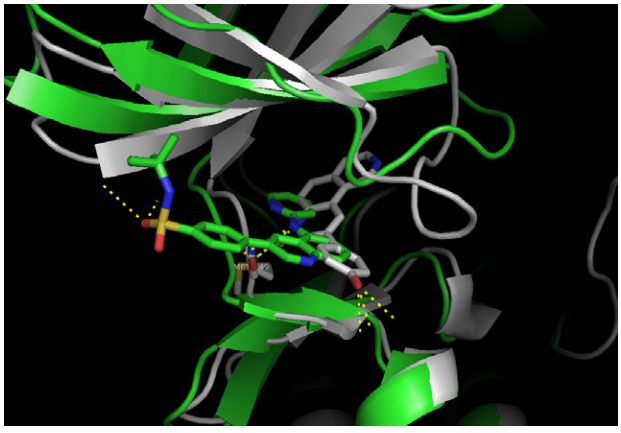


Figure 3. Overlay X-ray crystal structure of **16a** (green structure) (2R9S) and 4-(2,7-phenanthrolin-9-yl)phenol **1** (gray structure) (1PMU) in JNK3.

potent analogs will continue and will be reported in due course.

Acknowledgments

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23. Removal of N-2 on the C-ring of phenanthroline (**1**) completely abolishes the inhibitory activity against JNK3.
24. Biochemical IC_{50}s for JNK3 and p38 were determined using HTRF. Briefly, final assay concentrations of JNK3, biotinylated-ATF2 and ATP were 0.3 nM, 0.4 nM, and 1 μM, respectively. Final assay concentrations of p38, biotinylated-ATF2, and ATP were 1 nM, 0.4 nM, and 11.5 μM, respectively. In both assays, the phosphor-Thr71-ATF-2 product was detected by a Europium-cryptate-labeled anti-phospho-Thr71-ATF-2 antibody. Streptavidin–allophycocyanin–XL was used as the acceptor. A 10-point dose–response curve for each compound was generated in duplicate and data were fit to a four-parameter logistic.