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Small Molecule JNK (c-Jun N-Terminal Kinase) Inhibitors

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Introduction

JNKs[a] (c-jun NH2-terminal kinases) are members of the MAP kinase family[1] that are primarily activated by cytokines and exposure to environmental stress.[2,3] JNKs are serine/threonine kinases that are able to phosphorylate the N-terminal transactivation domain of c-Jun, resulting in enhancement of c-Jun dependent transcriptional events. Human JNKs are encoded by three genes, *Jnk1*, *Jnk2*, and *Jnk3*,[2,4−6] and they are derived from 10 splice variants.[7] JNK1 and JNK2 are ubiquitously expressed, whereas JNK3 has much more limited expression, primarily confined to the nervous system with low level of expression in the heart and testes.[6] JNK1, JNK2, and JNK3 knockout mice develop normally; however, dual JNK1 and JNK2 mice die prematurely and exhibit abnormalities attributed to apoptosis.[8,9]

The signaling network of JNKs is not well understood and continuously evolving.[10] JNKs are activated by MKK4 and MKK7, and activation of MKKs is performed by a large number of kinases including ASK1, TAK1, MLKs, and MAPKKKs such as Tpl2. JNKs are deactivated by MAP kinase phosphatases including MKP1 and MKP5. Scaffolding proteins that assemble the molecules of the JNK pathway, termed JIP (Jnk interacting proteins), are involved in mediating the stimulus and compartment specific signals. Nuclear translocation of JNK leads to the phosphorylation of a number of transcription factors, most notably the c-Jun component of AP-1. JNKs act at several points in the apoptosis cascade interacting with antiapoptotic proteins Bcl-2, Bcl-xL, and Mcl-1 and proapopototic proteins Bim, Bmf, and Bad, thus triggering the mitochondrial cell death machinery (Figure 1). An emerging role of JNK in endoplasmic reticulum (ER) stress via IRE-1 involving TNF-receptor-associated factor 2 links JNK signaling with metabolic syndrome.[11,12] The central role of JNK in many physiological processes makes it an interesting target, thus providing multiple opportunities for the design of small molecule inhibitors that might modulate specific components of JNK signaling. The growing list of diseases where interfering with JNK mediated signaling may play an important role is summarized in the following sections.

CNS Disorders

Neurodegeneration, an area of intense research characterized by Alzheimer's disease, multiple sclerosis, Parkinson's disease, to mention a few, is of great unmet medical need. Restricted expression of JNK3 in brain makes it an interesting drug target. It has been shown that mice lacking JNK3 were resistant to kianic acid induced seizures with significant decrease in excitotoxicity, suggesting a potential role of JNK3 in seizure control.[13] JNK3 and JNK2 and dual JNK3/JNK2 knockout mice were resistant to MPTP (1-methyl-4-phenyl-1,2,3,4-tetrahydropyridine) induced neurodegeneration of motor deficit and displayed significantly improved motor function as compared to wild type MPTP lesioned mice, indicating the potential for JNK inhibition in Parkinson's disease.[14] In mice and rat models of middle cerebral artery occlusion (MCAO) a cell penetrant peptide significantly decreased the volume of lesion, thus suggesting the utility of JNK inhibitors as promising neuroprotective agents for stroke.[15]

Post-mortem brain sections of Alzheimer's disease patients revealed altered distribution and activation of JNKs in different subcellular structures specific to the Alzheimer's disease.[16,17] It has been shown that β-amyloid induced cell death is attenuated in cortical neurons from JNK3 null mice, and JNK3 mediates the cell death through activation of c-Jun and enhanced expression of Fas ligand.[18] JNK has been shown to directly regulate APP through phosphorylation at Thr668[19] and also phosphorylates Tau in vitro.[20] A recent study has shown that TNF-α mediated regulation of γ-secretase is mediated via JNK.[21] Additionally, the Toll → NFkB pathway mediates neuropathalogical effect of human Alzheimer's Aβ42 via JNK mediated apoptosis.[22] These data implicate JNK in Alzheimer's disease.

AMPA-type glutamate receptors mediate the majority of fast excitatory neurotransmission in the brain. Regulation of AMPA receptors plays critical roles in forms of synaptic plasticity such as long-term potentiation. In a recent study it was shown that AMPA subunits GluR4 and GluR2L are endogenous substrates of JNKs in neurons, demonstrating the role of JNK in the regulation of AMPA-receptor trafficking.[23]

JNK pathway plays an important role in primary sensory neurons after tissue or nerve injury, which is required for the

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[a] Abbreviations: JNK, c-Jun N-terminal kinase; MAP, Mitogen-activated protein; MKK4, mitogen-activated protein kinase kinase 4; MKK7, mitogen-activated protein kinase kinase 7; MAPKKKs, mitogen-activated protein kinase kinase kinases; ASK1, apoptosis signal-regulating kinase 1; Tpl2, tumor progression loci-2; MKP1, mitogen-activated protein kinase phosphatase 1; MKP5, mitogen-activated protein kinase phosphatase 5; JIP, JNK activating protein; AP-1, activator protein 1; ATF2, activating transcription factor 2; Bcl-2, B-cell leukemia/lymphoma-2; Bcl-xL, B-cell leukemia/lymphoma-extra large; Mcl-1, myeloid cell leukemia-1; TNF, tumor necrosis factor; hERG, human ether-a-go-go related gene.

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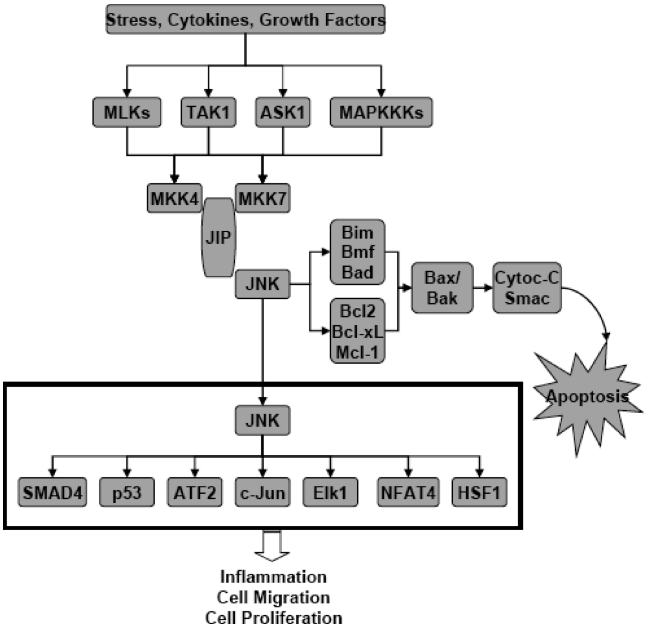


Figure 1. JNK signaling cascade.

development of hyperalgesia and allodynia. In particular, JNK is persistently activated in astrocytes of the spinal cord after nerve injury, and this activation can maintain central sensitization and mechanical allodynia.[24]

Growing evidence linking JNK to various pathologies including neurodegeneration and pain suggests JNK as a potential target, provided highly selective inhibitors devoid of overt toxicity can be designed.

Cardiovascular and Metabolic Disorders

JNK1 knockout mice have been shown to exhibit decreased adiposity and significantly increased insulin sensitivity.[25] An emerging role of JNK linking inflammation with metabolic syndrome via modulation of IRS and ER stress provides a potential opportunity to design small molecule inhibitors for metabolic disorders.[26] Recently it has been shown that a small molecule pan-JNK inhibitor, dosed orally and compared to rimonabant and rosiglitazone, significantly impacted parameters such as adiposity, glucose levels, and insulin sensitization without any effect on liver enzymes, thus establishing the role of JNK as a useful target for metabolic syndrome linked to prediabetic state.[27] A JNK1 specific antisense oligonucleotide was studied in ob/ob and diet-induced obese mice models. Profound improvement in insulin sensitivity, glucose levels, plasma cholesterol level, and adiposity without negative impact on liver function was observed. Decreased body weight and lowered adiposity were attributed to increased fuel combustion/metabolic rate and decreased lipogenesis.[28]

In a recent study, JNK2 knockout mice fed with a high cholesterol diet were protected from hypercholesterolemia-induced endothelial dysfunction and oxidative stress, thus suggesting the role of JNK2 in vascular disease and atherosclerosis.[29]

Inflammatory Disorders

An overactivated immune system is believed to be associated with several immunological diseases such as inflammatory bowel disease (IBD), psoriasis, and rheumatoid arthritis (RA). Multiple cytokines are involved in these diseases including TNF-α that is regulated by the JNK pathway via modulation of AP-1 and ATF2.[30] It has been reported that adjuvant induced arthritic rats treated with a JNK inhibitor show significant reduction of joint destruction with modest effects on paw swelling.[31] Activation of JNK has been shown to play an important role in the intestinal inflammation in patients with IBD. However, the mechanism by which JNK activation leads to intestinal inflammation is not well understood.[32]

Inflammation is the primary initiating pathology in many lung diseases. Since AP-1 is a central regulator of cytokine and inflammatory gene expression, it is highly likely that JNK is important in the regulation of many proinflammatory mediators. Additionally, corticosteroids and JNK inhibitors both inhibit many common proinflammatory genes including TNF-α, IL-4, and IL-13, suggesting a common mechanism that may provide therapeutic opportunities that are complementary to existing treatments of respiratory diseases.[33]

Other Disorders

In addition to the role in the above-mentioned diseases, targeting JNK mediated apoptosis may also provide therapeutic uses.[34] JNK has been implicated in oncogenic transformation, and high levels of JNK activity has been found in several cancer cell lines.[35] Genetic deletion of c-Jun and/or JNK mutations at phosphorylation sites necessary for JNK activation results in reduced tumor size and prolonged lifespan in mice.[36] It has been suggested that pharmacological inhibition of the JNK pathway during pancreatic islet isolation and transplantation may improve successful engraftment.[37] One of the causes of hearing loss and deafness is related to necrosis and apoptosis of hair cells of cochlea. It has been shown that JNK inhibitors provide an otoprotective effect in organ culture of neonatal mouse cochlea and adult guinea pigs.[38]

X-ray Crystal Structures

X-ray crystal structures of all three JNK isoforms have been reported.[39−42] The overall architecture of JNKs is highly similar to that of other MAP kinases ERK2 and p38, consisting of an N-terminal domain with mostly β strands, a predominantly α helical C-terminal domain, and a deep cleft between N and C domains that comprises the ATP-binding site. The amino acid sequence identity of the JNK kinases is greater than 90% with >98% homology within the ATP-binding site. High homology of the ATP-binding site among JNKs makes it challenging to design isoform specific ATP-site directed inhibitors; however, inhibitor imposed conformational changes may provide adequate differentiation to design isoform selective inhibitors.[43−45] MAP kinases, including JNKs, utilize other regulatory sites that may be amenable to small molecule inhibitors.[46] The crystal structure of the pepJIP1−JNK1[41] complex provides insight into the role of the docking site where JIP1 binds to JNK away from ATP site. Binding of JIP1 derived peptide, pepJIP1, to the docking site affects conformational changes resulting in distortion of the ATP site of kinase domain. The docking site is large and hydrophobic with a potential to accommodate small molecule inhibitors. The pepJIP1−JNK1 structure highlights the role of multiple binding sites in modulating JNK mediated signals.

A survey of literature in published research articles and patents reveals several novel classes of JNK inhibitors. Most of the JNK inhibitors can be broadly classified into two

categories, ATP-site kinase domain inhibitors and non-ATP site allosteric inhibitors. Most of the inhibitors reported to date fall into the former category. Given the high homology of the ATP binding pocket of the three JNK isoforms, it is not surprising that the majority of the reported inhibitors are pan-JNK inhibitors. However, there are a few reports where attempts to design JNK isoform selective inhibitors that occupy the ATP binding site have been described.

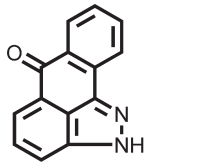
Pan-JNK Inhibitors

One of the early small molecule JNK inhibitors, SP600125, **1**, was reported by the Signal Research Division of Celgene (Figure 2).[47] The compound possesses modest pan-JNK activity and reported selectivity in a small number of kinases that is competitive with ATP. Compound **1** inhibits c-Jun phosphorylation and modulates expression of inflammatory cytokines such as IL-2, IFN-γ, and TNF-α. Mice induced with lipopolysaccharide (LPS), when treated with **1**, showed reduced TNF-α levels in a dose-dependent manner. Compound **1** has been the subject of numerous studies suggesting the role of JNKs in multiple ailments such as Parkinson's, diabetes, inflammation, and other diseases.[48]

Serono reported two classes of JNK inhibitors.[49,50] The first generation thiophene sulfonamide **2** was identified after extensive iterative SAR of a hit derived from high-throughput screening (Figure 3). Compound **2** was selective against a panel of 80 kinases and afforded neurons protection from cell death with IC_{50} = 1.7 μM. The poor pharmacokinetic profile and low solubility of compound **2** led to a search for an improved JNK inhibitor. A structurally distinct series of benzothiazole inhibitors was identified, which upon further optimization resulted in inhibitor **3** that was more potent in enzyme assays and had 38% oral bioavailability in rats. Compound **3** exhibited a dose dependent reduction in TNF-α levels in lipopolysaccharide (LPS) induced mice with ED_{50} = 3 mg/kg. Moreover, compound **3** also elicited significant reduction in paw swelling and a reduced clinical score at 60 mg/kg in a collagen induced adjuvant (CIA) rheumatoid arthritis mouse model. It has also been demonstrated that compound **3** was effective in ischemia reperfusion injury and myocardial infarction models.[51,52]

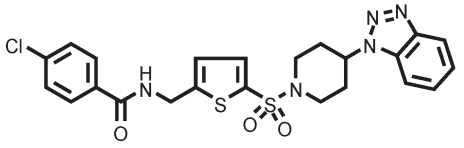
Scientists at Abbott have reported a series of aminopyridine amide-based inhibitors (Figure 4).[53−55] High-throughput screening identified pyridine acetamide **4** with JNK1 IC_{50} = 750 nM that was ATP competitive and displayed selectivity against a panel of 74 kinases. An X-ray crystal structure of one of the aryl derivatives of **4** in the JNK1 ATP pocket revealed that the amide carbonyl and 4-amino group make weak out-of-plane hydrogen bonds with the hinge region, whereas the cyano group forms a weak hydrogen bond with the side chain of lysine. The pyridine scaffold lies in a hydrophobic pocket and the ethoxy group points to a more polar ribose binding region. SAR guided by the X-ray crystal structure resulted in compound **5** that showed improved potency in enzyme and p-cJun assays with an oral bioavailability of 31% in rats. Reverse amides provided inhibitors with improved metabolic stability, resulting in the identification of **6** with enhanced potency in enzyme and cell-based p-cJun assays. Compound **6** had a clean profile in multiple counterscreen assays including hERG, together with an improved oral bioavailability in rats of 54.7%.

Scientists at Eisai reported the design and synthesis of JNK3 inhibitors (Figure 5).[56] Initial design started with compound **7**, an iodo derivative with IC_{50} = 46 nM for p38α. In order to rigidify the structure, they decided to constrain the molecule into a general structure **8** with the hope that introduction of a chiral center would enable further control of selectivity, particularly against p38α, as this kinase contributes to synaptic plasticity within the CNS.

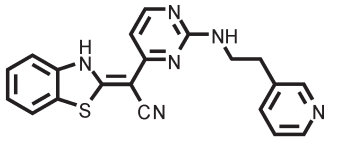


1
IC_{50} (JNK1) = 40 nM
IC_{50} (JNK2) = 40 nM
IC_{50} (JNK3) = 90 nM

Figure 2. Pyrazoloanthrone pan-JNK inhibitor SP600125.

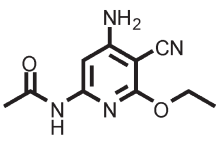


2
IC_{50} (JNK2) = 650 nM
IC_{50} (JNK3) = 150 nM

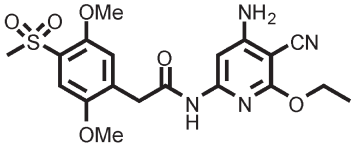


3
IC_{50} (JNK1) = 150 nM
IC_{50} (JNK2) = 220 nM
IC_{50} (JNK3) = 70 nM

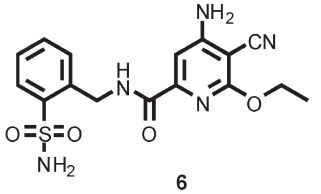
Figure 3. Thiophene and benzothiazole pan-JNK inhibitors.



4
IC_{50} (JNK1) = 750 nM
IC_{50} (JNK2) = 1100 nM
EC_{50} (p-cJun) = 6800 nM



5
IC_{50} (JNK1) = 38 nM
IC_{50} (JNK2) = 150 nM
EC_{50} (p-cJun) = 1300 nM



6
IC_{50} (JNK1) = 12 nM
IC_{50} (JNK2) = 53 nM
EC_{50} (p-cJun) = 110 nM

Figure 4. Aminopyridineamide pan-JNK inhibitors.

Optimization based on general structure **8** resulted in modestly selective compounds **9** and **10**. Both compounds were tested for their effect on neuroprotection in cerebellar granule neurons for c-Jun phosphorylation and apoptosis. Compound **10** showed a clear effect at 1 μM, whereas compound **9** and its enantiomer completely suppressed c-Jun phophorylation. These results were further corroborated by survival of cerebellar granule neurons.

Investigators at Takeda evaluated a potential role for JNK in the progression of heart failure.[57,58] From the high-throughput screening, an isoquinolone lead **11** was obtained that showed modest JNK1 activity and selectivity over related MAP kinases, p38α and ERK1 (Figure 6). Docking of **11** in the ATP-binding site of JNK1 suggested a series of interactions with the protein surface including hydrogen bonding of the carbonyl oxygen of isoquinolone with Met^{111} in the hinge region, and these observations guided SAR that resulted in identification of compound **12** with improved potency, selectivity against panel of kinases, and 14% oral bioavailability in rats. Compound **12** was evaluated for suppressive effects on development of cardiac hypertrophy in a rat pressure-overload model. Following once a day dosing for 7 days, compound **12** exhibited significant suppression of cardiac hypertrophy without an effect on systolic blood pressure, even at an elevated dose of 30 mg/kg. Compound **13** was much improved in biochemical and cellular assays and showed relatively good absorption and 15% oral bioavailability. It was effective in suppression of cardiac hypertrophy at a much lower dose of 1 mg/kg.

Investigators at Pfizer have reported a pyrimidinylpyrazole class of inhibitors (Figure 7).[27,59] General structure **14** has been claimed among 571 compounds with a range of JNK activity. Several inhibitors claimed to have JNK activity less than 10 nM are exemplified by compound **15**. Compound **16** was claimed to have effects on inflammatory markers, adiposity, and insulin and glucose levels. Compound **16** was dosed orally at 30 mg/kg in diet-induced obese mice for 24 days and compared with CB1 antagonist rimonabant (dose: 3 mg/kg) for change in body weight. Compound **16** reduced the body weight by 13% vs 4.1% for rimonabant. The weight loss of rimonabant treated mice showed a plateau within the first week of dosing, whereas compound **16** treated mice continued to lose weight throughout the 24 days. Cessation of dosing of compound **16** resulted in weight gain back to the original levels within the 18 days. Moreover, termination of dosing did not increase the consumption of food and there was 30.1% reduction in fat mass compared to vehicle. Postrecovery period body composition of all mice treated with compound **16** was not different from vehicle treated mice, and there was no alteration in liver enzymes, suggesting that weight loss is not a result of toxicity. Compound **16** was also evaluated for insulin sensitivity in diet-induced obese mice. Obese mice were dosed twice a day for 21 days with 30 mg/kg compound **16** and 1.5 mg/kg rosiglitazone. Both compound **16** and rosiglitazone showed significant reduction in triglycerides levels. However, only compound **16** showed significant reduction in fed glucose levels. It was also demonstrated that compound **16** normalizes body weight in high-fat diet fed mice and produces improvements in insulin sensitivity, compared with vehicle treated mice.

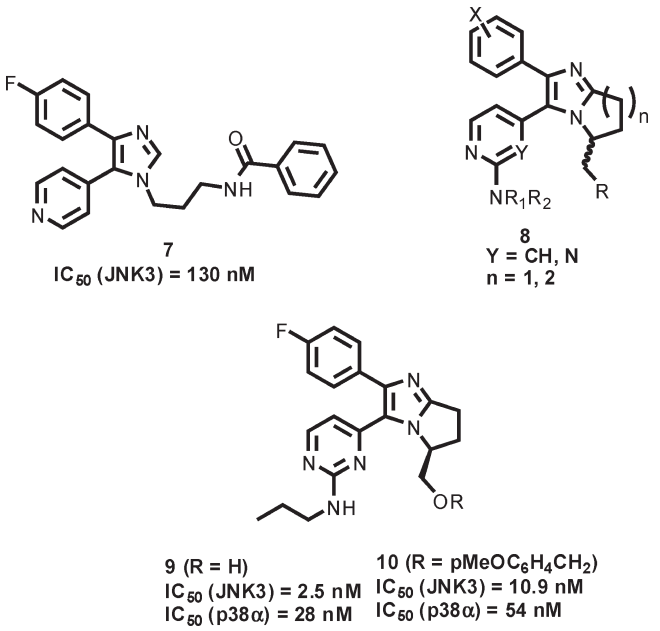


Figure 5. Imidazopyrrolidine pan-JNK inhibitors.

Isoform Selective JNK Inhibitors

Investigators at AstraZeneca reported indazole and aminopyridine classes of inhibitors that are JNK3 selective (Figure 8).[43,44] The X-ray crystal structure of a modestly potent JNK3 selective lead **17** revealed inhibitor induced conformational changes. The anilino group of the lead **17** fits into an induced pocket resulting from the movement of the

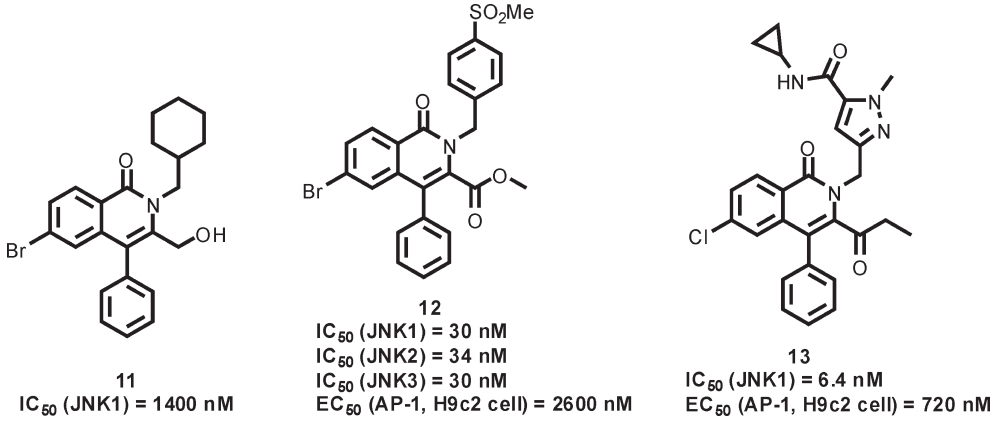


Figure 6. Isoquinolone pan-JNK inhibitors.

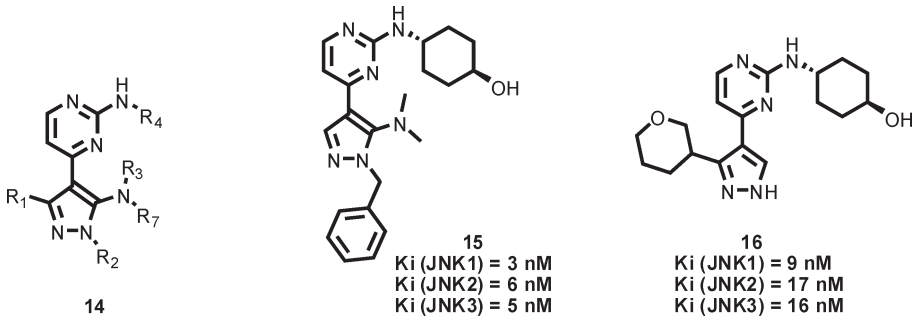


Figure 7. Pyrimidinylpyrazole pan-JNK inhibitors.

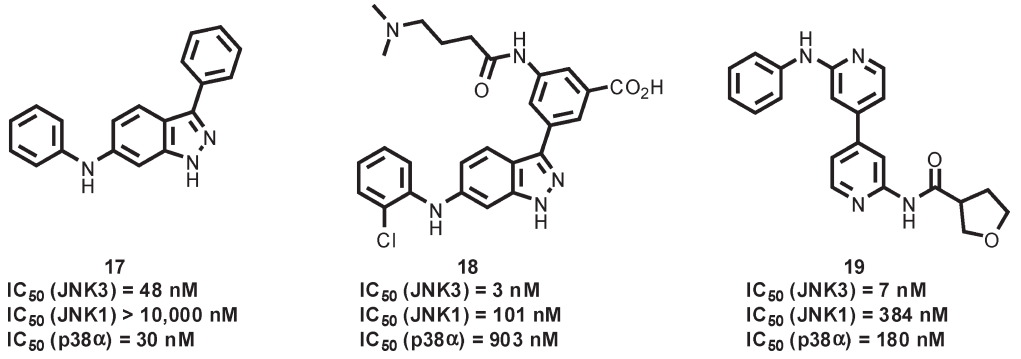


Figure 8. Indazole and pyridine based JNK3 selective inhibitors.

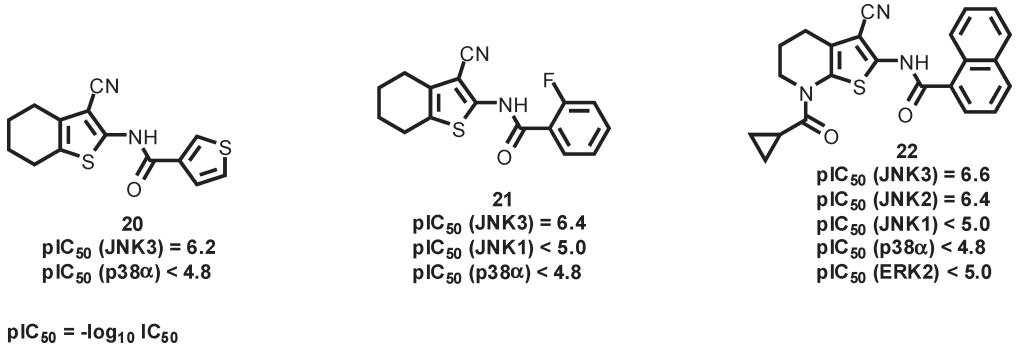


Figure 9. Tetrahydrobenzothiopheneamide based JNK3 selective inhibitors.

side chain of the gatekeeper residue Met[146]. X-ray crystal structure-guided optimization led to identification of improved compound **18**, which was selective against both JNK1 and p38α. A second series of aminopyridine based hits derived from screening revealed similar movement of the Met[146] side chain in the JNK3 crystal structure enabling an "induced fit" of the anilino group. Structure-guided SAR studies led to the design of inhibitor **19** which had selectivity against JNK1 and p38α. Compound **19** was relatively stable in rat liver microsomes and showed good Caco2 permeability with 16% oral bioavailability in rats.

Scientists at GSK reported several novel classes of JNK3 inhibitors (Figure 9).[60] Identification of compound **20** from high-throughput screening and further optimization afforded compound **21**. An X-ray crystal structure of the compound bound to JNK3 revealed that the cyano group acted as a hydrogen bond acceptor from Met[149] in the hinge region, whereas the sulfur atom of the Met[146] side chain made a rare hydrogen bond with the amide N−H of the inhibitor. The ortho substituted phenyl group occupied an "induced-fit" hydrophobic pocket as a result of the rearrangement of the "gatekeeper" residue Met[146]. Guided by X-ray structure, it was hypothesized that the 6 and 7 positions of the tetrahydrothiophene scaffold might provide opportunity to introduce additional interactions, as the groups should project into the solvent front region of the protein. Thus, compound **22** was designed and found to be a potent JNK3 inhibitor. Compound **22** was an equally potent JNK2 inhibitor as expected due to the difference of only one amino acid (JNK3 Met[115] to JNK2 Leu[77]); however, it was determined to be selective against JNK1 and a panel of 30 kinases including p38α and ERK2.

Non-ATP-Site Allosteric Inhibitors

Owing to the high homology of the ATP binding site among the three JNK family members, it has been challenging to design selective inhibitors. The lack of adequate selectivity may manifest undesirable effects, especially in situations where chronic drug administration is required. Therefore, non-ATP-site allosteric inhibitors may provide an alternative approach to selective JNK inhibitors.

Figure 10. Non-ATP-site allosteric inhibitors.

It is well documented that scaffolding proteins contribute to physiological regulation of MAP kinases.[61] The JIP group of scaffolding proteins, encoded by four genes termed JIP1, JIP2, JIP3, and JIP4, is involved in regulating JNK activities. JIP1 is reported to interact with kinesin light chain, amyloid precursor protein and LDL receptors. It has been shown that overexpression of the JIP1 potently inhibits JNK signaling as a result of JIP1 blocking the nuclear translocation of JNK.[62] The minimum region of the JIP1 peptide inhibits JNK activity in vitro toward recombinant c-Jun, ELK, and ATF2 and shows no inhibition of related Erk and p38 MAP kinases.[63]

An X-ray crystal structure of JNK1 in complex with an 11-residue peptide, pepJIP1, **23**, has been reported (Figure 10).[41] The binding affinity of pepJIP1 to JNK1 was determined to be 420 nM, implying specific interactions with the protein. An X-ray crystal structure revealed that pepJIP1 binds to the docking groove of JNK1, a surface of the C-terminal domain which is distant from the ATP pocket. The total binding surface area where pepJIP1 binds to JNK1 is 1034 Å which consists mostly of hydrophobic amino acids including Met^{121}, Val^{118}, Leu^{115}, Ala^{113}, Leu^{123}, Val^{59}, and Cys^{163}, indicating a potential binding surface amenable to small molecule inhibitors. In an assay designed to screen small molecule libraries to disrupt the interaction of pepJIP1 with JNK1, hydroxytriazole inhibitors were identified (Figure 10).[64] BI-78D3, **24**, bound to substrate binding site of JNK1 in a dose dependent manner with IC_{50} = 500 nM with selectivity against p38α, mTOR, and PI3α and with EC_{50} = 12.4 μM in TNF-α stimulated phosphorylation of c-Jun assay. Additionally, BI-78D3 abrogated ConA-induced liver damage and restored insulin sensitivity compared to vehicle control in mouse models.

Perspective

The complexity of the JNK signaling pathway provides multiple opportunities for modulation using small molecule inhibitors. The requirement for JNK activity in experimental disease models illuminates the possibility of developing small molecules that can be evaluated in humans. Early reports linking JNK mediated events to inflammatory pathways in disease models such as rheumatoid arthritis have highlighted the importance of JNK inhibitors. An emerging role of JNK in the metabolic syndrome provides an exciting opportunity to evaluate small molecule JNK inhibitors in diabetes models.[26,27] Significant progress in developing selective pan-JNK inhibitors has been made, and many of them have shown useful pharmacological effects in a variety of disease models ranging from inflammatory to CNS disorders.[48] However, selective inhibitors of JNK isoforms would provide highly desirable pharmacological agents, as substantial evidence indicates that specific inhibitors of JNK1 may be useful agents against metabolic syndrome,[25,26] whereas isoform selective JNK3 inhibitors may provide therapeutic benefits against various neurodegenerative diseases including Parkinson's disease.[14,15] However, high homology of ATP site of JNK isoforms has impeded the development of potent isoform selective JNK inhibitors. The recent discovery of small molecule JNK inhibitors targeting the JIP1 docking site has provided an additional avenue to develop "non-kinase-like" inhibitors.[64] As the JIP binding site is different from the ATP binding site, it may be facile to identify kinase selective inhibitors. However, more structural information is needed to assess the feasibility of identifying isoform selective inhibitors directed to JIP binding site. Multiple approaches to identify JNK inhibitors may provide further understanding of the pathways leading to effective agents with improved safety profile.[65]

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Biographies

M. Arshad Siddiqui received his Ph.D. in Organic Chemistry from University of Waterloo, Waterloo, Ontario, Canada, with Professor Victor A. Snieckus. He was an Associate Director, Antiviral Chemistry at BioChem Pharma in Montreal, Canada, where he was involved in development of antiviral agents for HIV, HCMV, and HCV. He was a co-recipient of Prix-Galien Canada (Research) in 1996 for the discovery of 3TC (Epivir). He moved to NeoGenesis Pharmaceutical as a Senior Director, Medicinal Chemistry. In his current position as Director, Chemical Research at Merck Research Laboratories, Cambridge, MA, he is involved in drug discovery research in the area of inflammation and oncology.

Panduranga A. Reddy earned his Ph.D. in Organic Chemistry from Osmania University, India, and worked as an Assistant Professor at the same university. He pursued postdoctoral studies at City University of New York and Thomas Jefferson University in the area of design, synthesis, and conformational studies of peptides and peptidomimetics. He moved to pharmaceutical discovery in the Serono Research Institute, Rockland, MA, where he worked in the women's health therapeutic area. In his current position as Senior Principal Scientist, Chemical Research at Merck Research Laboratories, Cambridge, MA, he is involved in drug discovery research in the area of oncology.

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