

New Product Highlights

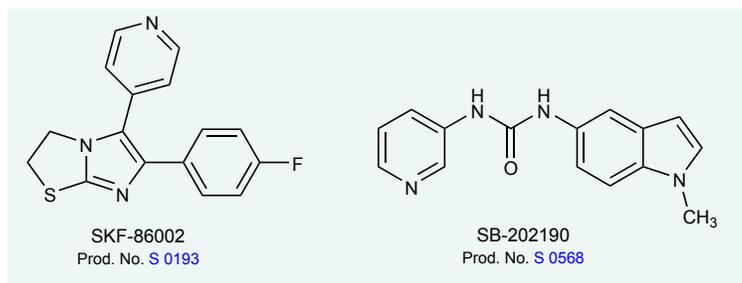
SKF-86002 and SB-202190: Potent and selective p38 MAP kinase inhibitors

The p38 mitogen activated protein kinases (MAPK) are stress-activated members of the MAPK superfamily of serine/threonine kinases. The four isoforms of p38 MAPK are referred to as α , β , δ , γ , of which **p38 α** (Prod. No. [M 8057](#)) is the best studied. The isoforms differ in tissue distribution, mode of activation, and in phosphorylation of downstream substrates [1]. p38 activation occurs through dual phosphorylation on a TGY motif within the kinase activation loop by upstream kinases. Upstream activation of MAPK kinase 3 (MEK3) or **MEK6** (Prod. No. [M 5814](#)) by cellular stressors such as lipopolysaccharide (LPS) leads to p38 phosphorylation, resulting in subsequent phosphorylation of transcription factors including ELK1, **c-jun** (Prod. No. [C 5859](#)), ATF2 and **MSK1** (Prod. No. [M 2064](#)), as well as other protein kinases. p38 MAPK has been shown to be involved in a variety of cellular processes, including apoptosis, cytokine production, transcriptional regulation, and cytoskeletal reorganization [2]. Inhibitors of p38 MAPK have therefore proved useful in studying several diseases including inflammation and arthritis [1].

Sigma-RBI is pleased to offer two new potent and specific p38 MAP kinase inhibitors, **SKF-86002** (Prod. No. [S 0193](#)) and **SB-202190** (Prod. No. [S 0568](#)). The two compounds potently inhibit p38 MAP kinase without inhibition of related JAK/STAT, ERK or other serine/threonine kinases. SKF-86002 has been shown to inhibit LPS-stimulated **interleukin 1 β** (IL-1 β ; Prod. Nos. [I 5271](#), [I 9401](#)) and **tumor necrosis factor α** (TNF- α ; Prod. Nos. [T 7539](#), [T 5944](#), [T 0157](#), [T 6674](#)) production, displaying IC₅₀ values of 1 μ M in monocytes [3] and 5 μ M in macrophages [4]. SB-202190,

of the pyridinyl imidazoline structural class, was previously found to inhibit cytokine synthesis in monocytes with an IC₅₀ value of 50 nM [5]. More recently, it was reported to inhibit LPS-induced gene expression in monocytes with IC₅₀ values between 41-123 nM [6]. SB-202190 promotes neuronal survival *in vitro* [7] through p38 α inhibition, but was found to promote apoptosis in Jurkat cells by inhibition of p38 β [8].

Specific p38 MAP kinase inhibitors have been utilized to clarify the role of p38 kinase function in the immune and central nervous systems. Such investigations may ultimately offer therapeutic benefits to patients with sepsis, ischemic heart disease, arthritis and Alzheimer's disease [2].



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References:

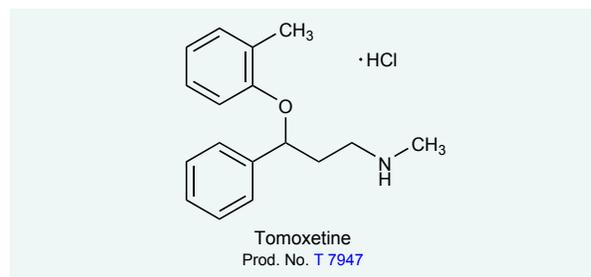
1. Lee, J.C., et al., *Immunopharmacology*, **47**, 185-201 (2000).
2. Obata, T., et al., *Crit. Care Med.*, **28**, N67-77 (2000).
3. Prabhakar, U., et al., *Int. J. Immunopharmacol.*, **15**, 205-209 (1993).
4. Olivera, D.L., et al., *Agents Actions*, **39**, C55-57 (1993).
5. Lee, J.C., et al., *Nature*, **372**, 739-746 (1994).
6. Manthey, C.L., et al., *J. Leukoc. Biol.*, **64**, 409-417 (1998).
7. Horstmann, S., et al., *J. Neurosci. Res.*, **52**, 483-490 (1998).
8. Nemoto, S., et al., *J. Biol. Chem.*, **273**, 16415-16420 (1998).

Tomoxetine: Selective norepinephrine reuptake inhibitor effective against ADHD

First available from Sigma-RBI!

The norepinephrine transporter (NET) was characterized by its sensitivity to the tricyclic antidepressants **desipramine** (Prod. No. [D 3900](#)), **nortryptiline** (Prod. No. [N 7261](#)) and **imipramine** (Prod. No. [I 7379](#)). **Tomoxetine** (LY 139603; Atomoxetine, Prod. No. [T 7947](#)), a non-tricyclic antidepressant, was subsequently developed as a selective norepinephrine reuptake inhibitor (SNRI). It has now been shown to be effective in the treatment of Attention Deficit/Hyperactivity Disorder (ADHD) in both children and adults. Unlike other drugs approved for use in treating ADHD such as **methylphenidate** (Prod. Nos. [M 2892](#), [M 6810](#), [M 6935](#)) and desipramine, tomoxetine exhibits no stimulant properties and is not a controlled substance. Thus, tomoxetine represents a new class of drugs in the treatment of

ADHD and will continue to prove useful in the study of biogenic amine reuptake.



References

1. Bymaster, F.P., et al., *Neuropsychopharmacology*, **27**, 699-711 (2002).
2. Hwang, B.H., et al., *Neurosci. Lett.*, **265**, 151-154 (1999).