New Product Highlights

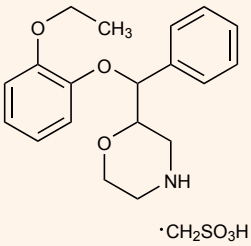
Reboxetine mesylate: A selective norepinephrine reuptake inhibitor (SNRI)

Several therapeutic approaches are available for the treatment of depression. Historically, tricyclic antidepressants (TCAs), such as **desipramine** (Prod. No. D 3900), **nortryptiline** (Prod. No. N 7261) and **imipramine** (Prod. No. I 7379), and monoamine oxidase inhibitors (MAOIs) have been most successful. However, although effective, these drugs are not ideal because while they enhance noradrenergic or serotonergic neurotransmission, they interact with other receptor sites that result in undesirable side effects. Current development of antidepressants focuses on increasing the specificity of action in an effort to improve the safety and tolerance of treatment. Notably, the selective serotonin reuptake inhibitors **fluoxetine** (Prod. No. F-132), **fluvoxamine** (Prod. No. F 2802) and **citalopram** (Prod. No. C 7861) have proven more effective. **Tomoxetine** (LY-139603, Atomoxetine, Prod. No. T 7947), a selective norepinephrine reuptake inhibitor (SNRI), has proven effective in the treatment of attention-deficit hyperactivity disorder (ADHD).

Sigma-RBI has recently introduced **reboxetine mesylate** (Prod. No. R 6527), an SNRI [1,2]. Reboxetine possesses nanomolar potency at the norepinephrine transporter (NET) and unprecedented selectivity over both serotonin (SERT) and dopamine (DAT) transporters displaying IC_{50} values of 8.5 nM and 6.9 µM in rat hippocampal synaptosomes versus [^{3}H]-norepinephrine and [^{3}H]-serotonin, respectively and 89 µM in rat striatal synaptosomes versus [^{3}H]-dopamine [3]. Thus, reboxetine represents the first selective SNRI.

Agents that are effective in facilitating cessation of cigarette smoking act through their interactions with the nicotinic acetylcholine receptor (nAChR). Recently, reboxetine was shown to inhibit nAChR function and, thus, may have potential for use as a smoking cessation agent [4].

Regardless of its clinical potential, reboxetine represents an interesting and useful pharmacological tool with which to study NET and mechanisms of depression and to evaluate next-generation antidepressants.



Reboxetine
(Prod. No. R 6527)

References
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3. Millan, M.J., et al., *J. Pharmacol. Exp. Ther.*, **298**, 565-580 (2001).
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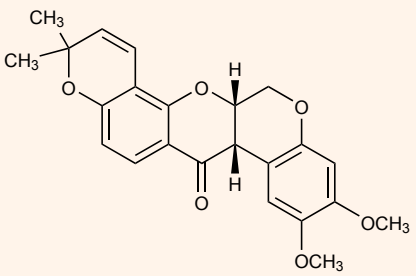
Deguelin: An inhibitor of activated Akt with chemopreventive properties

Deguelin (Prod. No. D 0817), a naturally occurring rotenoid plant insecticide, has recently been synthesized by Sigma-RBI. Deguelin specifically inhibits protein kinase B/Akt, a downstream component of the phosphatidylinositol 3-kinase (PI3K) pathway. The renewed interest in rotenoids, and specifically in deguelin, is based on the discovery of the involvement of the PI3K signaling pathway in the early stages of lung carcinogenesis. The pharmacological mechanism by which deguelin decreases the cancer-related increase in Akt activity is therefore of considerable interest [1,2].

Chun et al. [3] derived several premalignant and malignant cell lines from simian virus 40-immortalized human bronchial epithelial (HBE) cells. The growth of premalignant and malignant HBE cells was inhibited by deguelin (IC_{50} 10 nM) in a dose- and time-dependent manner. Of all the cell lines examined, premalignant 1799 cells, which represent the earliest stage in the lung cancer model, were the most sensitive to deguelin displaying a 67% decrease in cell growth following exposure to 100 nM deguelin for 1 day. In 1799 cells, deguelin had no discernible effect on ERK1/2 and JNK activity, but decreased PI3K activity by approximately 55%. This reduction was not accompanied by decreased expression of PI3K. These findings indicate that deguelin appears to preferentially affect the PI3K/Akt signaling pathway in 1799 cells, although it may also inhibit Akt activity through PI3K-independent pathways.

In conclusion, deguelin has been identified as a novel agent for preventing premalignant and malignant HBE cell growth and will prove useful in studying the PI3K/Akt pathway and its implications in lung cancer research.



Deguelin
(Prod. No. D 0817)

References
1. Crowell, J.A. and Steele, V.E., *J. Natl. Cancer Inst.*, **95**, 292-302 (2003).
2. Vivanco, I. and Sawyers, C.L., *Nat. Rev. Cancer*, **2**, 489-501 (2002).
3. Chun, K.H., et al., *J. Natl. Cancer Inst.*, **95**, 291-302 (2003).