



2011-2012 POCC Lecture Series

February 23, 2012, 8:00 PM

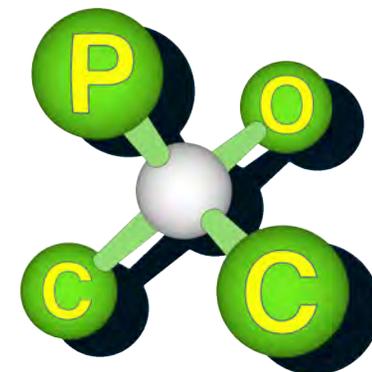
Dr. Daniel V. Paone

Merck

Discovery of Telcagepant (MK-0974): The First Orally Bioavailable Calcitonin Gene-Related Peptide (CGRP) Receptor Antagonist for Migraine Treatment

Carolyn Hoff Lynch Lecture Hall
Chemistry Building, University of Pennsylvania

The Philadelphia Organic Chemist's Club

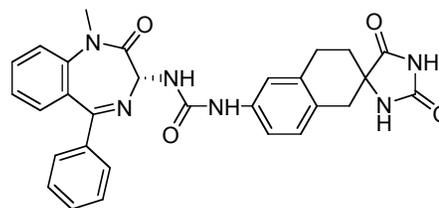


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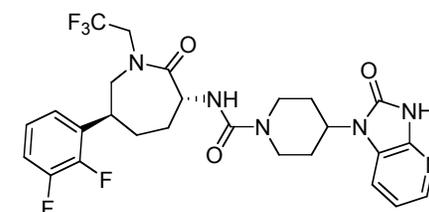
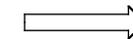
Dan received his B.S. in Chemistry at the University of Delaware where he performed undergraduate research for Professor Cynthia McClure. He then attended the University of Pennsylvania to pursue graduate studies while working in the laboratories of Professor Amos B. Smith, III towards the total synthesis of (-)-cylindrocyclophane A. After receiving his Ph.D. in 1998, Dan accepted a post-doctoral position with Professor Larry Overman at the University of California, Irvine where he completed total syntheses of polypyrroloindoline alkaloids including (-)-chimonanthine and ditryptophenaline. He began his medicinal chemistry career at Merck and Co., Inc. (West Point) in 2001 where he currently is a program team lead chemist. His past projects have included those in the pain and neuroscience therapeutic areas.

Abstract: Calcitonin gene-related peptide (CGRP) is a 37 amino acid neuropeptide that has been implicated in the pathogenesis of migraine. Since CGRP receptor antagonists promote normalization of dilated blood vessels through a non-vasoconstrictive mechanism, this class of compounds would prove effective in the relief of migraine without the adverse cardiovascular effects that are sometimes associated with existing therapies. Our research program targeted non-peptide, small molecule CGRP receptor antagonists with favorable pharmacokinetic profiles that would result in the first oral drug in this class. Core truncation of a high-throughput screening lead followed by extensive SAR studies provided potent derivatives with improved oral bio-

availabilities. Further refinement resulted in Telcagepant (MK-0974), ultimately providing the optimal blend of potency and pharmacokinetic profiles. This compound showed efficacy in a capsaicin-induced dermal vasodilation pharmacodynamic assay in rhesus and advanced to Phase III clinical trials for the treatment of acute migraine. Clinical efficacy will be summarized and the synthetic chemistry developed to access these compounds will also be described.



HTS lead
 $K_i = 4800 \text{ nM}$



Telcagepant
 $K_i = 0.8 \text{ nM}$