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IN THIS ISSUE

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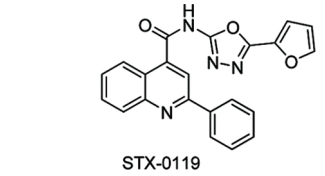
STAT3 Inhibition, Orally

Activation of the oncogenic transcription factor STAT3 is a hallmark of many human malignancies. STAT3 activation involves dimerization though the intermolecular pTyr-SH2 interaction. Thus, antagonizing this interaction to inhibit STAT3 activation is a feasible approach in treating for cancer therapy. Now, Matsuno et al. (DOI: 10.1021/ml1000273) describe the synthesis and activity of a novel small molecule inhibitor of STAT3 dimerization. The small molecule abrogated the biological effects of STAT3 dimerization. This is likely the first demonstration of in vivo efficacy of a STAT3 dimerization inhibitor by oral administration.



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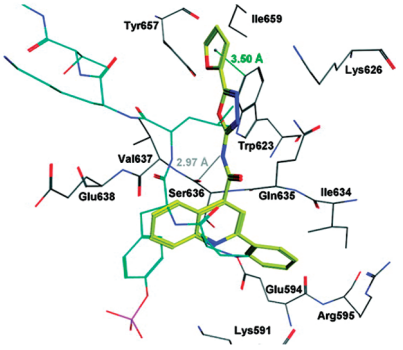
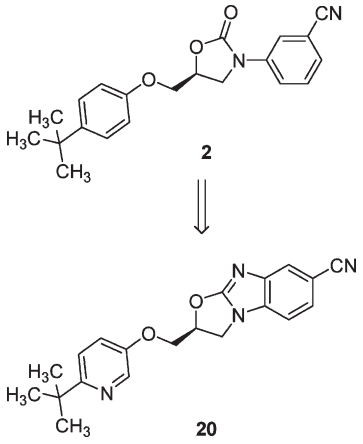


Schizophrenia and the Metabotropic Glutamate Receptor

L-Glutamate is the major excitatory neurotransmitter in the mammalian central nervous system. It is thought that elevated glutamate transmission in the brain is linked to symptoms of schizophrenia. Therefore, a treatment that diminishes synaptic glutamate levels might be beneficial for treating this neurodegenerative disease. Normalization of excessive glutamate neurotransmission through activation of the metabotropic glutamate receptor 2 (mGluR2) represents a novel approach for the treatment of schizophrenia. Clinical validation of this approach was achieved in a phase II study in schizophrenic patients with an orthosteric mGluR2/3 agonist. Alternatively, positive allosteric modulators (potentiators) of mGluR2 may offer advantages over orthosteric mGluR2/3 agonists as a result of their unique mode of action and selectivity.

In this current study, Garbaccio et al. (DOI: 10.1021/ml100115a) describe the lead optimization of an oxazolidinones class of mGluR2 potentiators into oxazolobenzimidazoles and report preclinical results, which suggest that these compounds might be useful as starting points for potential therapeutic treatments for schizophrenia.



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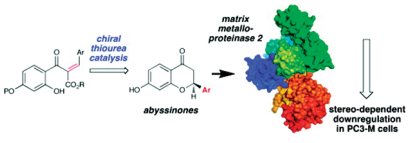
Abyssinones as Anticancer Agents

The abyssinones are a family of bioactive flavanone natural products. Previously, a racemic mixture of abyssinones I and II was evaluated as potential anticancer agent. Now, Farmer et al. (DOI: 10.1021/ml100110x) describe the first enantioselective total synthesis of all four members of the abyssinone family and their unnatural enantiomers and biologically evaluate these compounds against a metastatic prostate cancer cell line. The authors demonstrate that the enantiomers of abyssinones III and IV 4′-OMe inhibit cancer cell growth and expression of matrix metalloproteinase 2, an enzyme implicated in metastasis, in a stereodependent manner. For the first time, it has been shown that these enantio-enriched small molecules act as differential inhibitors of prostate cancer growth and metastasis.



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