ACS Medicinal Chemistry Letters

In This Issue

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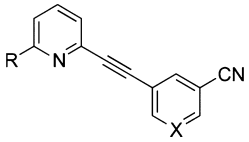
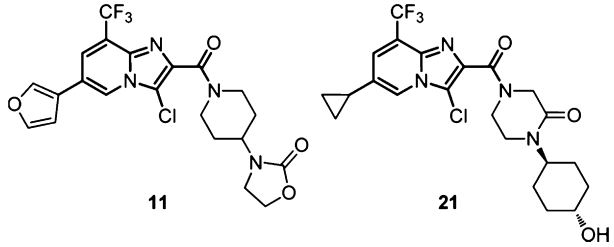
NEW TOOLS FOR MGLUR5 TARGET STUDIES



The metabotropic glutamate receptor subtype 5 (mGluR5) is a G protein-coupled receptor highly expressed in specific regions of the brain. In recent years, these receptors have emerged as key targets for the design of neuropsychiatric disorders as attenuation of mGluR5 signaling shows promising results in preclinical models for conditions as diverse as Parkinson's disease, anxiety, fragile X syndrome, and drug abuse.

In this issue, Keck et al. (DOI: 10.1021/ml3000726) describe the design, synthesis, and in vitro evaluation of a novel series of mGluR5-selective negative allosteric modulators and identify the structure–activity relationship for the improvement of mGluR5 affinity and inverse agonist potency over the parent molecule. Several of these compounds demonstrated potent activity of 10–300 times more in mouse models of anxiety than the parent molecules, supporting their value as in vivo tools for studying the mGluR5 as a target for therapeutic development.

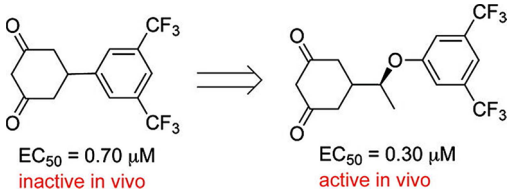
TARGETING HEPATITIS C NS4B



The prospect of generating potent inhibitors of hepatitis C replication without relying on DNA polymerase, protease, or NS5A represents a significant step in the HCV field. Cross-resistance represents a significant hurdle for combination therapies, especially for a community working toward a cure for hepatitis C, wherein it is currently unknown how many antiviral agents would consist of an effective cure.

Here, Shotwell et al. (DOI: 10.1021/ml300090x) report the first disclosure of highly optimized HCV replication inhibitors with a novel mode of action by direct interaction with NS4B. Their discovery includes a series of imidazopyridines that (i) bind directly to the viral protein as evidenced by direct binding studies and resistance passaging, (ii) have been optimized to afford single-digit nanomolar potencies for the inhibition of HCV replicons, and (iii) have been optimized to possess in vivo properties consistent with progression to preclinical repeat-dosing toxicology studies.

A NEW POTENT ALS DRUG



Amyotrophic lateral sclerosis (ALS) is a progressive fatal disorder devastating the human spinal cord and brain. Currently, riluzole remains the only disease-modifying therapy available to ALS patients as other putative neuroprotective therapies failed to demonstrate positive treatment outcomes.

In this issue, Zhang et al. (DOI: 10.1021/ml3000963) describe the development of a novel therapeutic class for the treatment of ALS. Their in vitro preliminary results identified cyclohexane 1,3-diones as a class of molecules active against mutant Cu/Zn superoxide dismutase-induced toxicity. However, their most potent analogue was found to be inactive in the mouse model and did not penetrate into neurons. Additional analogues were synthesized, and the authors found two racemic derivatives to be active in cortical neurons. The most potent compound exhibited greater life extension to the ALS mouse than the FDA-approved ALS drug riluzole. This study demonstrates the importance of studying cortical neuron activity before mouse trials.

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