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In This Issue

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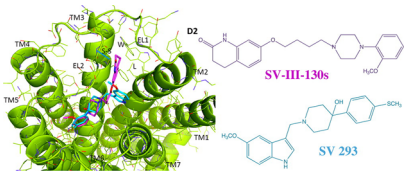
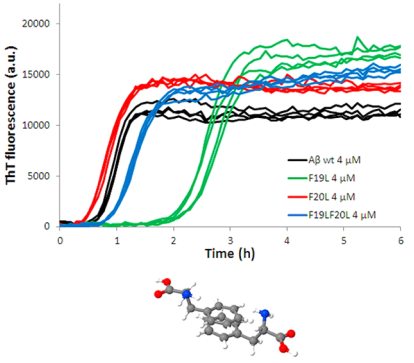
SELECTIVE COMPOUNDS TARGET D2 DOPAMINE RECEPTOR SUBTYPE



The dopaminergic pathways have been implicated in the pathogenesis of neurological, neuropsychiatric, and hormonal disorders. Dopamine receptors are a class of G protein-coupled receptors which are subdivided into two types, that is, D1-like (D1 and D5 subtypes) and D2-like (D2, D3, and D4 subtypes). In this issue, Luedtke et al. (DOI: 10.1021/cn300142q) studied the molecular basis for the binding specificity of two D2 dopamine selective compounds.

The authors evaluated the functional properties of the two compounds (SV 293 and SV-III-130s) using three assays: adenylyl cyclase inhibition, phosphorylation of ERK, and ligand-dependent G protein-coupled inward-rectifying potassium channel activation. While the SV293 was found to be an antagonist in each of these assays, SV-III-130s was found to be a partial agonist for adenylyl cyclase inhibition and an antagonist in the other two functional assays. Therefore, the D2 receptor selective SV293 appears to be functionally selective.

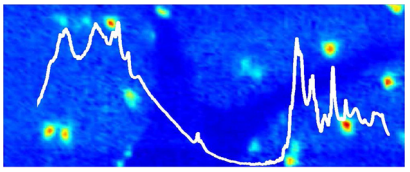
ASSESSING AROMATIC INTERACTIONS FOR AMYLOID β-PROTEIN AGGREGATION



The aggregation of the amyloid β-protein (Aβ) has been widely linked to Alzheimer's disease progression. Thus far, there is no cure for this devastating disease. Previous work has implicated a central aromatic region spanning residues 17−21 in Aβ aggregation. Cukalevski et al. (DOI: 10.1021/cn300073s) provide a much-needed kinetic assessment of the role of these aromatic residues in aggregation.

The authors used Thioflavin T, a dye commonly used to assay Aβ aggregation, to conduct kinetic studies comparing Aβ aromatic residues of the hydrophobic region with corresponding leucine mutants. Residue F19 was shown to stimulate fibril formation, whereas F20 hinders aggregation. These findings could stimulate the search for compounds that bind these residues and modulate Aβ aggregation.

SCREENING CREATINE DEPOSITS IN BRAIN TISSUE



Phosphocreatine is a major source of high-energy phosphates under ATP-depleted conditions. A drop in phosphocreatine levels with a corresponding increase in dephosphorylated creatine is observed in several neurodegenerative disorders associated with ischemic conditions. In the current issue, Hackett et al. (DOI: 10.1021/cn300093g) utilize FTIR spectroscopic imaging to show that creatine deposits are a general marker of brain ischemia and are not a specific biomarker for any neurodegenerative disorder.

The authors used FTIR spectroscopic imaging to observe ex vivo development of creatine microdeposits in situ in the cerebellum of mice suffering from cerebral malaria. They showed that creatine deposits were generated from creatine crystallization upon tissue dehydration post tissue-cutting and cannot be used as a specific marker of brain pathogenesis.

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