ACS Medicinal Chemistry Letters

IN THIS ISSUE

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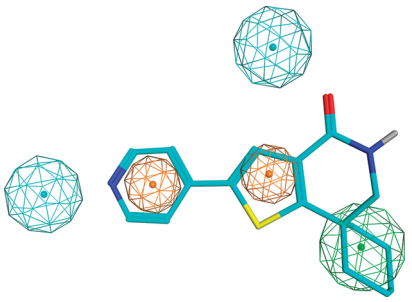
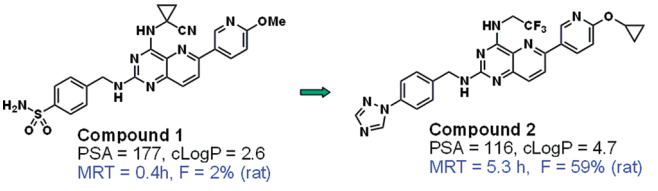
Three-Dimensional Pharmacophore Modeling Approach



Recently, there has been a wide range of interest on serine/threonine kinase CDC7 as an emerging target for cancer therapy. CDC7, a serine/threonine kinase, is a key player in the initiation of DNA replication in eukaryotic cells. However, in the absence of protein crystal structure, the discovery of CDC7 inhibitors has been a challenge.

In this issue, Lindvall et al. (DOI: 10.1021/ml200029w) used structures and SAR data of known CDC7 inhibitors in a ligand-based 3D pharmacophore model to generate new inhibitors from advanced, commercially available intermediate that partially match the pharmacophore. The 3D pharmacophore model led to the discovery of a series of novel thienopyridone inhibitors. This approach could potentially yield lead compounds that are overlooked by molecular docking to homology models and complement receptor-based approaches.

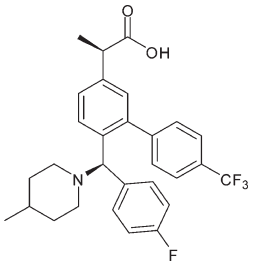
Lipophilicity and Polarity as Predictors of Bioavailability



More than 130 million people worldwide are infected with chronic hepatitis C virus (HCV). Current treatments for HCV provide poor rates of cure and are heavily associated with side effects. Pursuit of antiviral compounds with high potency and high oral bioavailability remains a priority.

In this issue, Lazerwith et al. (DOI: 10.1021/ml200163b) describe the identification of HCV replication inhibitors with improved pharmacokinetics. Important associations between physicochemical properties and pharmacokinetics were established and used to guide the design of compounds, which led to the discovery of several inhibitors with favorable oral bioavailability in rat. In addition, their study highlights the value of tracking the compounds' physicochemical properties as a predictor of bioavailability.

Building Better γ-Secretase Modulators

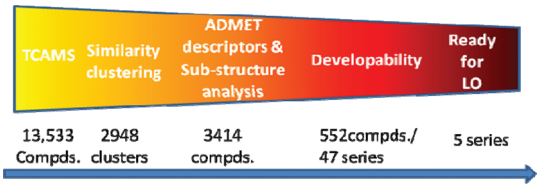


BIIB042 (**10a**)
Aβ42 EC_{50} = 70-170 nM
40% brain Aβ42 reduction
in mice at 10 mg/kg p.o.

Alzheimer's disease is a devastating neurodegenerative disease for which there is currently no cure. It is characterized by amyloid β peptide accumulation in the brain, which perturbs synaptic function and elicits inflammation. γ-Secretase is a pivotal enzyme in the amyloid cascade and has been pursued extensively as an attractive therapeutic target for Alzheimer's disease. While γ-secretase inhibitors have been shown to have toxic effects, γ-secretase modulators are emerging as promising new compounds because they act by modulating amyloid β production without impairing γ-secretase function.

Here, Peng et al. (DOI: 10.1021/ml200175q) describe the synthesis and structure−activity relationships of a series of more potent carboxylic acid-derived γ-secretase modulators with better brain penetration than current ones. One compound showed excellent pharmacokinetic parameters across species and is selected for preclinical safety evaluation.

On the Trail of Antimalarial Drug



In spite of global eradication efforts, malaria remains as one of the most prevalent infectious diseases today. There is a pressing need for new antimalarial drugs due in part to the adverse effects of existing therapies and the increase of drug-resistant strains. A major challenge in discovering new drugs is identifying the most promising molecular candidates to pursue for lead optimization out of thousands of chemical starting points.

Now, Calderon et al. (DOI: 10.1021/ml200135p) describe a prioritization process and significant criteria in discovering new antimalarial therapeutic candidates. After clustering by structural similarity and using filters such as antimalarial activity, druglike properties, and reduced risk for resistance, the 13 533 compounds were whittled down to 47 clusters of compounds. Ultimately, five series of compounds were selected for further studies. The authors also extend an invitation for collaboration to other scientists in following up on the 47 starting points for lead optimization.

   dx.doi.org/10.1021/ml200214r | *ACS Med. Chem. Lett.* 2011, 2, 714–714