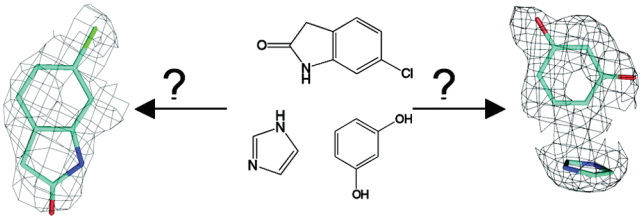
ACS Medicinal Chemistry Letters

In This Issue

pubs.acs.org/acsmedchemlett

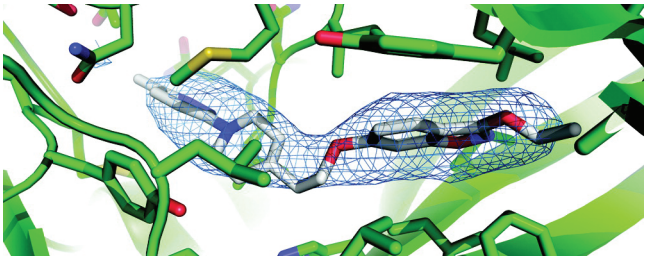
FRAGMENT-BASED DRUG DESIGN'S TIME TO SHINE



Scientific advances have given the drug research community important tools such as combinatorial chemistry, high-throughput screening, and sequencing. Another emerging method in the past decade has been fragment-based drug design (FBDD). FBDD is increasingly used in rational drug design.

In this issue, Nair et al. (DOI: 10.1021/ml300015u) illustrate how theoretical approaches based on molecular dynamics simulations and free energy calculations can be used to overcome the potential limitations of the X-ray crystallography-based protocols currently used in FBDD. Using phenylethanolamine *N*-methyltransferase as an example, the authors show that crystallography protocols can fail to detect cooperative binding of fragments as weak binding is often disregarded as noise. Futhermore, they show how theoretical approaches such as FBDD can be used to validate potential hits and pursue leads that are otherwise regarded as false positives.

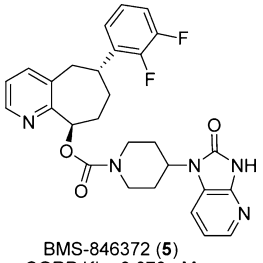
NEW HUMAN RHINOVIRUS INHIBITOR GOES TO TRIAL



Respiratory infections, largely caused by viruses, have been described as the most common illness experienced in otherwise healthy people and are responsible for an enormous burden in cost and inconvenience. When these infections occur in people with underlying health issues, they can have very serious consequences. Human rhinovirus, the principle agent of the common cold, has been associated with exacerbations of underlying clinical conditions such as asthma and is frequently isolated from patients who require hospitalization for this condition. Despite this clear medical need and numerous attempts, the technical challenges of discovering and developing an antiviral drug for human rhinovirus have proven insurmountable to date, as only a few compounds have progressed into clinical trials and even fewer have shown signs of being safe and effective.

Here, Feil et al. (DOI: 10.1021/ml2002955) describe the discovery of a potent, broad-spectrum inhibitor that is shown to specifically target human rhinoviruses and other related viruses. It is shown to be effective in an experimental human infection study and is currently under phase IIb clinical studies to assess its effect on natural human rhinovirus infection of asthma sufferers.

ANTAGONIZING MIGRAINE

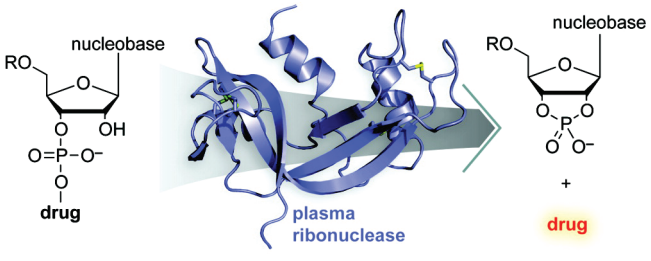


BMS-846372 (**5**)
CGRP Ki = 0.070 nM

Roughly 46% of the adult population worldwide suffers from headache disorder, with migraine, also called episodic headache, affecting 10% of the population. Elevated levels of calcitonin gene-related peptide (CGRP) have been shown to be an early critical part of migraine pathophysiology. While there has been a decade long effort to discover orally available CGRP receptor antagonists, only a number of antagonists have been effective in clinical trials, and none has so far advanced to the market.

In this work, Luo et al. (DOI: 10.1021/ml300021s) describe the synthesis and evaluation of a potent, orally active CGRP receptor antagonist. The compound displays good oral bioavailability, strong exposure-dependent in vivo efficacy, and acceptable off-target liabilities. It is active in vivo and represents an opportunity for human dosing.

INTRODUCING RIBONUCLEASE PRODRUG



Cancer treatment using antiproliferative agents generally suffers from narrow therapeutic indices. To enhance efficient delivery to malignant cells and to reduce toxicity to normal cells, selective therapies have emerged, including prodrugs. With a timed-release prodrug strategy, a steady plasma concentration of a therapeutic can be better achieved.

Here, Ellis et al. (DOI: 10.1021/ml2002554) report on a new strategy for time-released drug administration. This strategy avails the ability of a serum enzyme, pancreatic type ribonuclease, to catalyze the cleavage of a prodrug. The authors demonstrate the efficacy of the strategy by synthesizing a prodrug that releases hydroxytamoxifen upon addition of human pancreatic ribonuclease. In addition, they show that the ribonuclease increases the toxicity of the prodrug for human breast cancer cells. The success of this strategy could provide means of generating active drugs at unusual sites.

Published: April 12, 2012

dx.doi.org/10.1021/ml300066w | *ACS Med. Chem. Lett.* 2012, 3, 264–264