ACS Medicinal Chemistry Letters

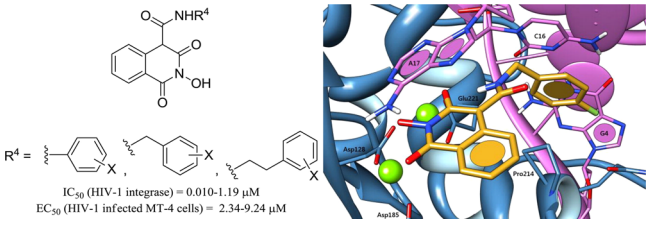
In This Issue

pubs.acs.org/acsmedchemlett

NOVEL CLASS OF HIV-1 INTEGRASE INHIBITORS

HIV-1 integrase plays a critical role in HIV infection and has been expansively studied as a target in the field of AIDS antiretroviral therapy. Numerous HIV-1 integrase inhibitors that target the catalytic center have been investigated to overcome the virus' resistance to the classical therapy. To date, there are only two integrase stand transfer inhibitors that are approved by the US Food and Drug Administration, but cross-resistances to these inhibitors have already appeared. Thus, the search for novel next-generation catalytic site inhibitors continues.

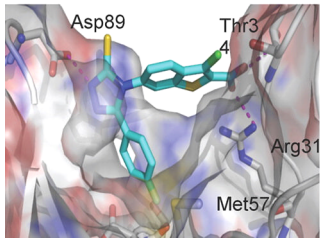
Here, Billamboz et al. (DOI: 10.1021/ml400009t) report the substitution and evalution of a previously investigated *N*-hydroxyimide scaffold by carboxamido chains. The resulting carboxamide series were evaluated for anti-integrase and antiviral properties and were found to show strong HIV-1 integrase inhibitions in the nanomolar range, similar to FDA-approved inhibitor, raltegravir. Careful examination shows that one compound displayed a novel inhibition mechanism, which could give new insights into the integrase inhibition cellular mechanism.

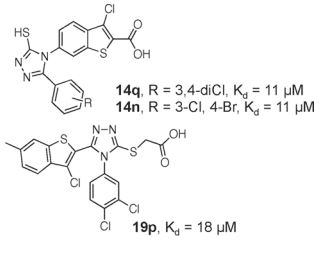


FRAGMENT SCREEN YIELDS POTENT RPA INHIBITORS

Replication Protein A (RPA) is a DNA binding protein that is needed in DNA replication and repair. RPA is responsible for the initiation of DNA damage response pathways via protein−protein interactions involving the N-terminal domain of the 70 kDa subunit (RPA70N) with partner proteins. Inhibition of these interactions increases cellular sensitivity toward DNA damage and increases replication stress. Therefore, the inhibition of RPA function may be a potential strategy for cancer drug discovery.

In this study, Patrone et al. (DOI: 10.1021/ml400032y) report the identification of chemical inhibitors of the RPA N-terminal domain, disrupting the protein−protein interactions it mediates. Two lead series of compounds, derived from hits obtained from a fragment-based screen, were shown to bind to RPA70N with good affinity. Optimization of these lead compounds for binding affinity resulted to the most potent inhibitors of the RPA−ATRIP interaction to date, exhibiting low micromolar affinity. These compounds may offer a promising starting point for the discovery of clinically useful RPA inhibitors.

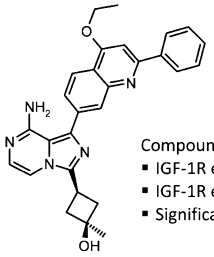




NEW IGF-1R INHIBITORS WITH UNIQUE TIME-DEPENDENT BINDING KINETICS AND SLOW OFF-RATES

Insulin-like growth factor-I receptor (IGF-1R) is expressed in most transformed cells. Its signaling has been implicated as a key driver in certain forms of solid tumors and hematologic malignancies. Specifically, IGF-1R has been shown to be involved in progression of multiple types of cancer including hepatocellular carninoma, nonsmall cell lung carcinoma, and in gynecologic cancers. As such, IGF-1R is considered a good target for cancer treatment.

Here, Jin et al. (DOI: 10.1021/ml400160a) describe their discovery and development of a series of small molecule IGF-1R inhibitors with unique time-dependent binding kinetics, which lead to slow dissociation rates from the receptors. One compound was identified as a highly potent, selective, and orally bioavailable IGF-1R slow off-rate inhibitor, exhibiting significant tumor growth inhibition at a remarkably low, intermittent dose. This study highlights the significance of incorporating characterization of binding kinetics into the drug discovery process.



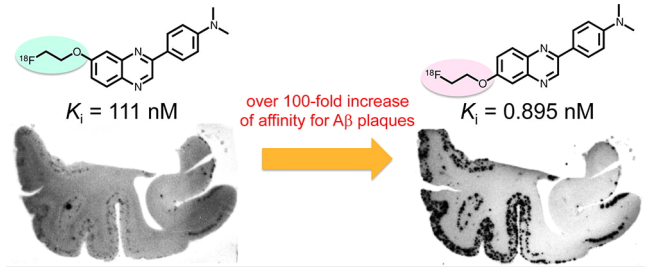
Compound **2**:

- IGF-1R enzyme IC_{50} = 0.6 nM, cellular IC_{50} (pIGF-1R) = 4 nM
- IGF-1R enzyme dissociative half life ($t_{1/2}$) = 133 h
- Significant tumor growth inhibition at low and intermittent dose

NEW PROBE FOR IMAGING OF β-AMYLOID PLAQUES

Alzheimer's disease is a leading cause of dementia. Alzheimer's disease patients lose their memory and their cognitive abilities due to the death of nerve cells that are responsible for the storage and processing of information. However, no diagnostic or therapeutic methods have been established for this disease. The amyloid cascade hypothesis points to senile plaques as the major player in the disease progression. Thus, in vivo imaging of the plaques could be useful for the presymptomatic diagnosis of the disease.

In the present study, Yoshimura et al. (DOI: 10.1021/ml4000707) report the design and synthesis of new fluorinated phenylquinoxaline derivatives as potential tracers for positron



Published: July 11, 2013

dx.doi.org/10.1021/ml400225u | *ACS Med. Chem. Lett.* 2013, 4, 570−571

emission tomography targeting β-amyloid plaques in the brains of patients with Alzheimer's disease. This new probe labeled Aβ plaques in Alzheimer's disease brain sections so much more clearly. The findings in their study suggest that the novel radiotracers reported could be a new candidate for PET imaging of Aβ plaques.

dx.doi.org/10.1021/ml400225u | *ACS Med. Chem. Lett.* 2013, 4, 570−571