ACS Medicinal Chemistry Letters

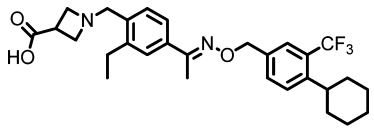
In This Issue

pubs.acs.org/acsmedchemlett

TAKING AIM AT MULTIPLE SCLEROSIS

FTY720 is a recently approved drug for treating multiple sclerosis. This drug elicits its therapeutic effects by binding as an agonist to four Sphingosine-1-phosphate (S1P) receptors: $S1P_1$, $S1P_3$, $S1P_4$, and $S1P_5$. However, clinical studies have shown that FTY720 causes bradycardia due to $S1P_3$ agonism. In this issue, Pan et al. (DOI: 10.1021/ml300396r) report the development of FTY720 derivatives which are $S1P_3$-sparing $S1P_1$ agonists which circumvent this deleterious side effect.

Following wide-ranging structure activity relationship studies on FTY720 derivatives, the authors discovered BAF312 (Siponimod), which showed superior potency, selectivity, and other drug-like properties. Importantly, BAF312 causes a dose-dependent reduction of peripheral lymphocyte counts, a pharmacodynamics biomarker for efficacy in autoimmune disease. This compound is now being tested in advanced clinical trials in patients with multiple sclerosis.

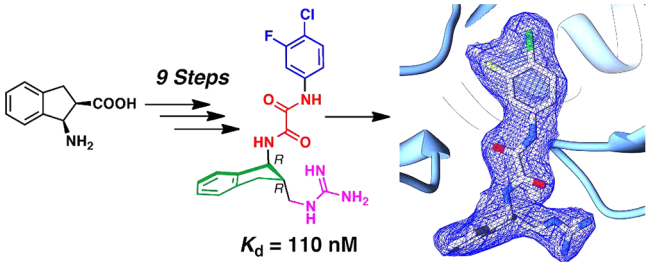


BAF312 (Siponimod)

DESIGNING AN HIV-1 ENTRY INHIBITOR

Significant research efforts are directed at developing inhibitors which target different stages of the HIV-1 viral life cycle. One such stage is viral attachment of the viral envelope protein, gp120, to the human host cell receptor, CD4. LaLonde et al. (DOI: 10.1021/ml300407y) report the development of an inhibitor that targets the CD4−gp120 complex and inhibits viral entry.

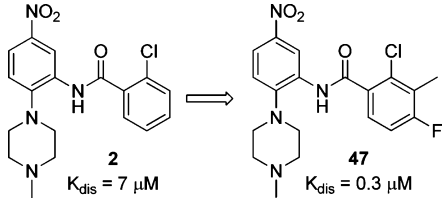
The authors used cocrystal structures of gp120 bound to guanidinium containing *trans*-1,2-indanes, a previously reported HIV-1 entry inhibitor, to design and optimize a more potent small molecule antagonist. Multiple assays showed that the newly designed inhibitor exhibits submicromolar binding affinity and inhibits viral entry. Thus, this study demonstrates the utility of developing potent inhibitors targeting the CD4−gp120 interface to fight HIV-1 infection.



NEW LEAD COMPOUND FOR MLL-REARRANGED LEUKEMIAS

Mixed-Lineage Leukemia (MLL) function is critical to embryonic development and other biological processes, but rearrangements of the MLL gene have also been implicated in several cancers. The MLL gene encodes a histone methyltransferase responsible for methylation of histone 3 at lysine 4 on chromatin. For optimal methylation activity, MLLs require complex formation with other components, such as WDR5, RbBP5, ASH2L, and DPY-30. In the current issue, Bolshan et al. (DOI: 10.1021/ml300467n) describe WDR5−MLL interaction inhibitors that may be crucial in developing treatments for MLL-rearranged leukemias.

MLLs show nominal to no activity in the absence of WDR5. Therefore, identifying WDR5−MLL interaction antagonists is an attractive alternative to using direct active-site inhibitors of MLL. Toward this goal, the authors undertook a SAR-optimization scheme whose design was based on the X-ray crystal structure of WDR5 in complex with a previously reported antagonist, WDR5-0102. The SAR-optimization unveiled a new antagonist with a more than 25 times greater potency.



Published: March 14, 2013

dx.doi.org/10.1021/ml4000723 | *ACS Med. Chem. Lett.* 2013, 4, 312−312