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In This Issue

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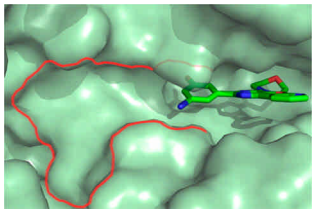
NEW DIRECTION FOR INHIBITORS OF PI3Kα

Hyperactivation of phosphatidylinositol 3-kinase alpha (PI3Kα) is inextricably linked to cancer survival and resistance to existing therapy in a large proportion of human cancers. As one of the first synthesized PI3Kα inhibitors, PI103 has been a promising chemical template for the discovery of PI3Kα inhibitors.

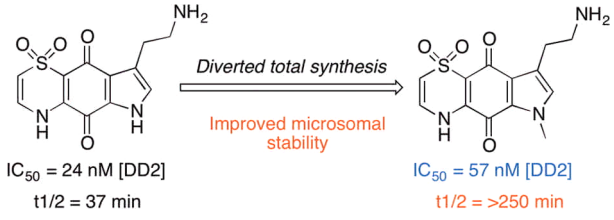
Here, Zhao et al. (DOI: 10.1021/ml400378e) determined the kinase-inhibitor crystal complex and demonstrated that the substitution of appropriate groups at the phenol portion of PI103 near a key amino acid in the catalytic site results in derivatives with better binding affinities. This study can provide a potential new direction to designing more potent and selective inhibitors against PI3Kα.



TOTAL SYNTHESIS OF AN ANTIMALARIAL NATURAL PRODUCT

Approximately 3.3 billion people are at risk of developing malaria, with children under the age of five being most at risk. The World Health Organization (WHO) recommends interventions that include treatment with antimalarial drugs. The current drug therapy uses artemisinin in combination with other compounds. However, parasite resistance to artemisinin-based combination therapy (ACT) is of a growing concern. Thus, new antimalarial drugs with unique mechanisms of action are urgently needed.

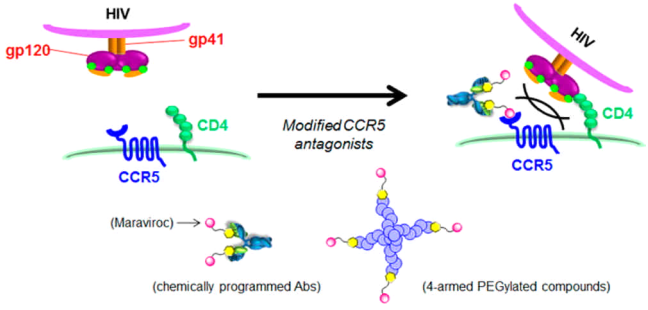
Thiaplakortone A is an antimalarial natural product. Pouwer et al. (DOI: 10.1021/ml400447v) reports their successful synthesis of Thiaplakortone A as a first step toward developing a new antimalarial compound. The natural product itself was found to be rapidly metabolized and would not be a useful drug for human use. The group also reports the synthesis of related compounds with improved half-life. These promising results lay the foundation for the development of this structurally unprecedented natural product.



CONJUGATED MARAVIROC

The retrovirus HIV-1, which causes acquired immune deficiency syndrome (AIDS), has infected 34 million people worldwide, and this number is expected to increase by 2.5 million each year into the near future. Although the combination reverse transcriptase inhibitor/protease inhibitor treatment, known as HAART, has proven successful, side effects and viral escape are significant issues, and new treatments are needed.

CCR5, a cell-surface receptor used by HIV to enter and infect cells, is an attractive target for small molecule treatment of HIV infection. Drugs that inhibit this interaction, such as the FDA-approved compound Maraviroc, are known as entry inhibitors. In this issue, Asano et al. (DOI: 10.1021/ml400370w) expand on the potential of Maraviroc by studying derivatives that enable functional linkage of this small molecule to long-lived carriers. The resulting compounds effectively inhibit infection of a variety of HIV isolates and show dramatically extended circulating serum half-life in comparison to Maraviroc. Derivation of a successful conjugation strategy for Maraviroc could facilitate the development of new therapeutic approaches to combat the HIV-1 epidemic.



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