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In This Issue

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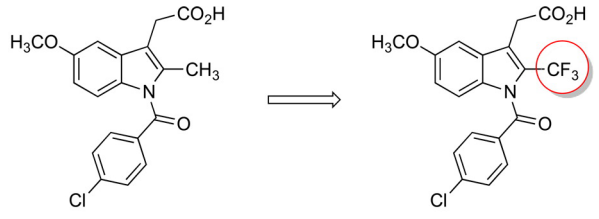
ELIMINATING SIDE-EFFECTS OF AN ANTI-INFLAMMATORY DRUG

Indomethacin is a potent nonsteroidal anti-inflammatory and analgesic drug. These properties are primarily due to the inhibition of the cyclooxygenase enzyme, COX-2. However, this drug also targets another isoform, COX-1, which leads to severe side-effects such as gastrointestinal toxicity and increased bleeding times. In the current issue, Blobaum et al. (DOI: 10.1021/ml400066a) present an Indomethacin derivative specific for COX-2 inhibition.

By simply exchanging a methyl group for a trifluoromethyl group in the indomethacin structure, the authors produced CF3-indomethacin that specifically inhibits COX-2, while retaining the potency of the parent compound. The selectivity of this enzyme is a result of the interaction with a small hydrophobic pocket not present on the COX-1 isoform. Furthermore, CF3-indomethacin showed specificity to COX-2 in human head-neck cancer cells and in the rat footpad model of inflammation.

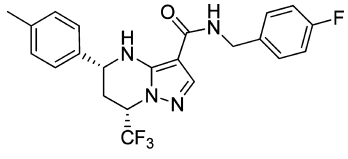


Inhibits COX-1 > COX-2 COX-2-Selective

A MORE POTENT ANTI-TB DRUG

Strains of *Mycobacterium tuberculosis* (Mtb) that are resistant to classic anti-TB drugs, such as isoniazid and rifampicin, have led to a rise in multidrug-resistant tuberculosis. Thus, there is an urgent need for new anti-TB drugs, especially those that can be included in combination therapy against AIDS. Now, Yokokawa et al. (DOI: 10.1021/ml400071a) have identified a promising new compound for treatment of tuberculosis.

Using a combination of high-throughput screening and structure−activity relationship studies, the authors produced a compound (called "Compound 9") with superior potency toward Mtb. Compound 9, a derivative of a previously reported anti-TB tetrahydropyrazolopyrimidine scaffold, showed potent oral efficacy in an acute TB mouse model.



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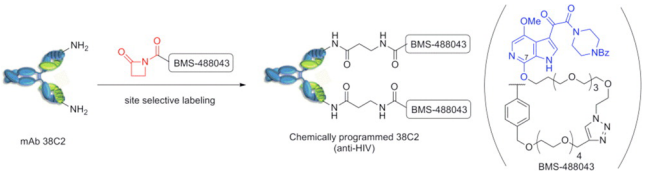
A NEW CONCEPT IN HIV THERAPY

Currently available therapies against the AIDS-causing retrovirus, HIV-1, have side-effect complications and other problems, such as viral escape. Given that the number of infected individuals is expected to increase by 2.5 million per year worldwide, new therapies are greatly needed. The viral envelope protein, gp120, which plays a role in host cell entry, is an appealing target. In the current issue, Sato et al. (DOI: 10.1021/ml400097z) present the design, synthesis, and initial biological evaluation of a new class of anti-HIV agents that target gp120.

Bristol-Myers Squibb Pharmaceutical Research Institute previously reported the gp120 inhibitors, BMS-378806 and BMS-488043. These compounds, however, displayed short pharmacokinetic profiles that limited their utility in the clinic. To improve the efficacy of the gp120 inhibitors, the authors conjugated compound BMS-488043 to a monoclonal antibody, 38C2. The conjugate retained good biological activity in neutralizing HIV-1. Importantly, this study identified an appropriate linkage position for the molecule to be bound to the antibody without losing biological activity. This study opens the door for a potentially new way to tackle the AIDS epidemic.



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