ACS Medicinal Chemistry Letters

In This Issue

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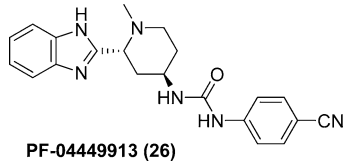
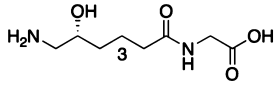


PF-04449913 (26)

The Hedgehog signaling pathway has been implicated to be a participant in cancer development and metastasis. In recent years, a slew of Hedgehog pathway inhibitors have been developed for cancer treatments, including inhibitors of the key signaling transducer, the Smoothened component of the pathway. One class of inhibitors, benzimidazoles, has chemically attractive motifs but suffers from metabolic stability.

Now, Munchhof et al. (DOI: 10.1021/ml2002423) report the discovery and characterization of a potent and orally bioavailable inhibitor of this pathway. This Smoothened inhibitor showed potency and an ideal pharmacokinetic profile. On the basis of its promising preclinical profile, this new compound has been advanced to human clinical trials.

A DIFFERENT STRATEGY FOR DUCHENNE MUSCULAR DYSTROPHY



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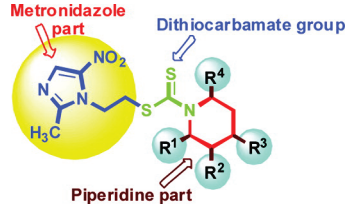
Duchenne muscular dystrophy, the most common form of dystrophy, affects 1 in 3500 men. This disorder is caused by a mutation found in the genetic coding for the protein dystrophin in the X chromosome. Current treatments include corticosteroids for skeletal muscle weakness, afterload reduction for cardiomyopathy, and noninvasive ventilation for respiratory failure. However, these treatments are temporary and inadequate and sometimes plagued with significant side effects. Emergence of "readthrough drugs" could provide a new therapeutic strategy for gene-related diseases such as Duchenne muscular dystrophy.

Here, Taguchi et al. (DOI: 10.1021/ml200245t) identified a new potent readthrough agent, which can skip a premature termination codon in the nonsense-mutated dystrophin gene in vivo. This agent, derived from natural product negamycin, exhibited increased functionality and lower toxicity than the parent compound and might be useful for the long-term treatment of Duchenne muscular dystrophy.

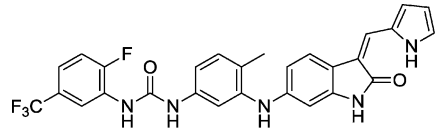
NEW ANTI-TRICHOMONIASIS COMPOUNDS WITH SPERMICIDAL ACTIVITIES

Trichomoniasis is the most common, yet most poorly investigated, sexually transmitted infection. This disease is caused by the flagellated protozoan parasite *Trichomonas vaginalis*. Currently, metronidazole is the most prescribed, out of all of the approved, effective drugs for treating trichomoniasis. Unfortunately, development of drug resistance to metronidazole, the mechanism of which remains unknown, is fairly common.



In this issue, Kumar et al. (DOI: 10.1021/ml200161t) designed and evaluated 13 compounds for spermicidal activity and drug resistance to provide drugs with dual targeted actions: trichomoniasis treatment and contraception. QSAR analysis yielded five new compounds with highly improved appreciable antitrichomonas activity, with 3−10-fold activity increase as compared to metronidazole and complementary spermicidal activity.

A TOOL FOR UNDERSTANDING TROPOMYOSIN-RELATED KINASE ROLE IN CANCER BIOLOGY



GNF-5837

Tropomyosin-related kinases are a family of receptor tyrosine kinases activated by neutrophins. They have been shown to play important roles in tumor cell growth and survival signaling as well as in pain sensation. As a consequence, inhibitors of tropomyosin receptor kinases have the potential to provide treatments for cancer and pain.

In this issue, Albaugh et al. (DOI: 10.1021/ml200261d) describe a potent and very selective tropomyosin-related kinase inhibitor with demonstrated efficacy in vivo. Because of its selectivity and pharmacokinetic properties, this inhibitor could be used as a tool to further elucidate the kinase's biology in cancer and in other nononcology indications. In addition, the authors show the first cocrystal structure of the enzyme with a selective inhibitor. This may aid in the design of other classes of selective inhibitors for tropomyosin-related kinases.

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