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In This Issue

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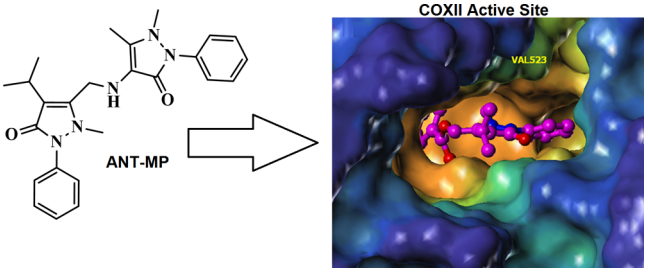
STRATEGIES FOR DEVELOPMENT OF SELECTIVE CYCLOOXYGENASE-2 PRODRUGS

NSAIDs are widely prescribed for pain management and for the treatment of various inflammatory disorders. The use of NSAIDs has several limitations, including gastroduodenal, renal, and cardiovascular toxicities. These drugs act by inhibiting the biosynthesis of prostaglandins through inhibition of the cyclooxygenase isoforms cyclooxygenase-1 (COXI) and cyclooxygenase-2 (COXII). COXII is considered to be an inducible isoenzyme that plays an important role in acute pain and inflammatory processes.

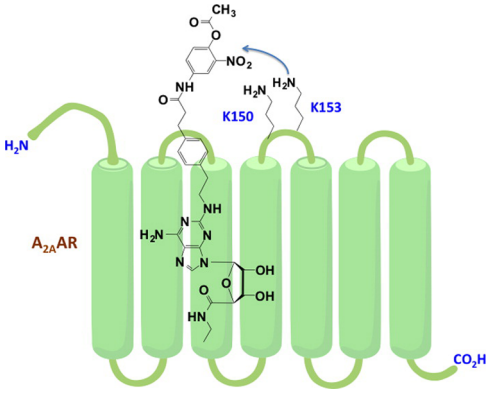
Herein, Radwan et al. (DOI: 10.1021/ml500156v) describe the generation of esterase hydrolyzable prodrugs that combine propyphenazone with known NSAIDs and block a carboxylic acid moiety associated with toxicity. Three mutual prodrugs have been evaluated both in vitro and in vivo. One compound showed unique selectivity toward the COXII enzyme through investigation using molecular modeling techniques. One COXII selective lead merits further investigation of its analgesic and anti-inflammatory properties.



STRUCTURE-BASED DESIGN OF A2A ADENOSINE RECEPTOR COVALENT MODIFIER

Covalent modification of proteins is a useful technique that benefits from a wide range of possible chemical attachments and has therapeutic utility. Affinity labeling reagents for receptors were previously designed empirically but have now evolved to include rational design.

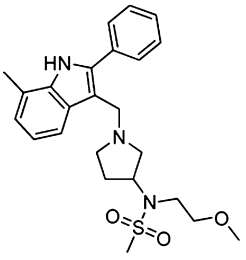
Guided by X-ray crystallographic structural data and computational docking, Moss et al. (DOI: 10.1021/ml5002486) designed agonist ligands to bind covalently to the A2A adenosine receptor. Unlike most receptor affinity labels, the acylating nucleosides reported in this Letter were intended to deliver a chemically functionalized handle to a nucleophilic amino group on the receptor. The nucleoside portion is designed as a leaving group, and the portion covalently bound to the receptor acts as a reporter group for its characterization. Thus, this technique has implications for receptor characterization, imaging, and drug design.



NEW ANTI-TB SCAFFOLDS

While a large number of antibiotics are available against tuberculosis, there is a critical need to develop new treatment with novel mechanisms with the emergence of multi- and extreme-drug resistant (MDR and XDR) *Mycobacterium tuberculosis* (Mtb) strain.

In this study, Naik et al. (DOI: 10.1021/ml5001933) report the identification and optimization of two chemical series that have potent antimycobacterial activity both in vitro and in macrophage infection models. The molecular scaffolds show promising structure–activity relationships, and the compounds exhibit submicromolar cellular potency. Importantly, the compounds did not inhibit known primary antitubercular targets or mechanisms, suggesting a possible new mode of action. This study provides new scaffolds for lead development, which could also serve as tool compounds in uncovering novel mechanisms for tuberculosis drug discovery.



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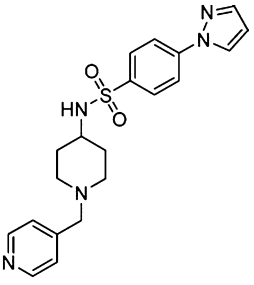

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