ACS Medicinal Chemistry Letters

In This Issue

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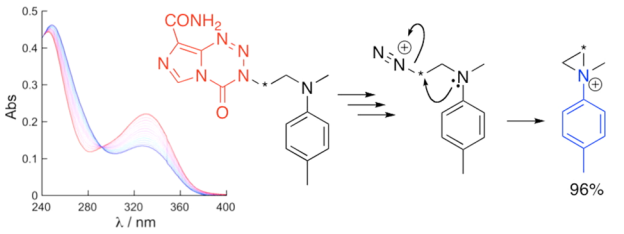
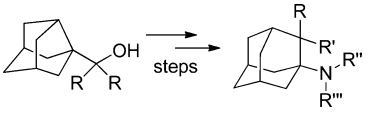
IMIDAZOTETRAZINE PRODRUGS



The imidazotetrazine ring possesses valuable pharmaceutical properties such as acid stability, oral availability, CNS penetration, and even tumor localization. However, despite achieving blockbuster status, the anticancer prodrug Temozolomide remains the only drug in the imidazotetrazine class of compounds. This could be attributed to the constraints on Temozolomide activity imposed by its dependence on DNA mismatch repair for activity and ready inactivation by O6-alkylguanine-DNA alkyltransferase-mediated repair. Both of these factors limit the range of tumors able to respond to Temozolomide treatment.

In this issue, Garelnabi et al. (DOI: 10.1021/ml300132t) report the design, synthesis, and preliminary evaluation of new generation of imidazotetrazines engineered to tame the latent, reactive intermediates released by hydrolysis of the tetrazine ring, which could yield greater therapeutic benefit. Compounds tested in an ovarian carcinoma cell line model showed activity with greatly reduced mismatch repair dependence and independence of O6-alkylguanine-DNA alkyltransferase. These compounds present promising leads for new drugs to treat Temozolomide-resistant tumors.

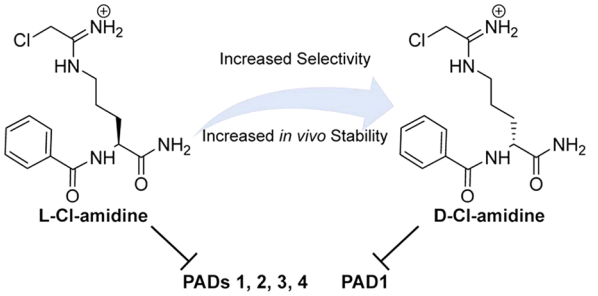
NEW AMANTADINE ANALOGUES AGAINST FLU



The M2 channel protein on the virus membrane of influenza A is the main target of adamantane-based drugs, the most successful of which are M2 ion channel blockers amantadine and rimantadine. However, most of the circulating strains are resistant or rapidly acquire resistance by mutating the M2 protein. Accordingly, novel anti-influenza virus drugs are urgently needed.

Here, Torres et al. (DOI: 10.1021/ml300279b) report the synthesis of new amantadine analogues using a novel synthetic approach. Several of the new compounds display low micromolar activity against the influenza A/H1N1 virus subtype while not being cytotoxic. The results suggest that these compounds are not targeting the M2 protein of the virus, as amantadine does, but acting through a different mechanism of action. This new approach to 2,2-dialkyl-1-aminoadamantanes could find a broad application in synthetic and medicinal chemistry.

A NEW CLASS OF PAD INHIBITORS



The protein arginine deiminases (PADs) play crucial roles in the onset and progression of multiple inflammatory diseases, including rheumatoid arthritis, inflammatory bowel disease, and cancer. However, it is not known how each of the five PAD isozymes contributes to disease pathogenesis. Thus, the development of potent, selective, and bioavailable PAD inhibitors that can be used to elucidate the specific roles of each isozyme is imperative.

In this issue, Bicker et al. (DOI: 10.1021/ml300288d) describe the design, synthesis, and evaluation of a series of PAD inhibitors based on D-amino acid isomers of previously reported L-amino acid-based PAD inhibitors, given that D-amino acids often possess enhanced in cellulo stability. They demonstrate that D-Cl-amidine and D-o-F-amidine are potent and highly selective inhibitors of PAD1, further showing that changes to scaffold orientation could impart selectivity against one of the PAD enzymes and stability to the compounds in vivo. These inhibitors represent an important step in the development of stable, bioavailable, and highly selective inhibitors for all of the PAD isozymes.

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