Difluoromethylene Transfer Reagents

Technology #2018-375

Benzylc methylene linkages are commonly found in many compounds of therapeutic interest but are quickly oxidized by cytochrome P450 enzymes and thus have undesirably short biological half-lives. An attractive approach for improving their metabolic stability is to replace the benzylc methylene linkage with a benzylc difluoromethylene functionality (Ar-CF2-R). These fluorinated linkages have shown significant potential as metabolically-resistant replacements for benzylc linkages and can be used as bioisosteres in place of ketone, cyclopropyl, and dimethylmethylene groups in medicinal chemistry.

Despite their promise, there are relatively few synthetic approaches for accessing Ar-CF2-R linkages and the few options available generally require the use of harsh reagents that are toxic, generate explosive byproducts, or otherwise demonstrate poor functional group tolerance and reaction selectivity. University of Michigan researchers have developed a new approach that is highly general and will allow for the expanded inclusion of this attractive functionality in libraries of compounds of therapeutic interest with enhanced pharmacodynamic properties.

A source of aryl difluoromethanide nucleophiles compatible with an array of electrophiles

The available technology is a synthetic methodology for the production of a variety of (hetero)aryl difluoromethanide nucleophiles that react efficiently with a number of electrophiles. This approach will allow for the convergent synthesis of large numbers of diverse compounds with aryl difluoromethylene linkages and could be effectively leveraged to develop next-generation compound libraries for drug-discovery applications. Alternatively, the technology could be used to improve current synthetic schemes for the production of difluoromethylene containing compounds or in the generation of analogs of approved drugs with enhanced pharmacodynamic properties. Broadly, this approach is accomplished through the deprotonation of aryl difluoromethyl containing compounds and the subsequent stabilization of the anionic species using a Lewis acid. The resulting complex serves as an effective transfer reagent that promotes the reaction of the difluoromethanide nucleophile with a range of electrophiles including aldehydes, aryl halides, esters, chalcones, aryl isocyanates, imines, and disulfides.

Applications

* Improving current synthetic schemes for accessing compounds containing aryl difluoromethylene linkages (Ar-CF2-R)

* Robust tool for the production of next-generation compound libraries containing molecules with improved metabolic stability for drug discovery applications

* Facile synthesis of stabilized analogs of current molecules of therapeutic interest that contain aryl methylene linkages.
Advantages

* Highly general in both electrophile and (hetero)aryl difluoromethanide nucleophile

* Enables new and highly robust retросynthetic disconnection at the C-C bond of aryl difluoromethylene linkages between organic fragments

* Uses relatively benign reagents that mitigate many of the safety concerns associated with currently available fluorination reagents and protocols

* Aryl difluoromethylene (Ar-CF2-R) bioisostere improves metabolic resistance and biological half-life of compounds

Inventors

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