Carborane-Based Analogs of Celecoxib and Flurbiprofen, their COX Inhibition Potential, and COX Selectivity Index

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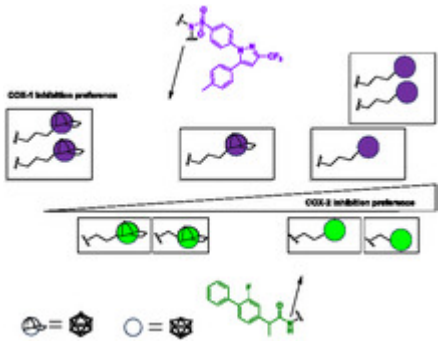
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Graphical Abstract

Eight nido- and ortho-carborane compounds based on celecoxib and flurbiprofen were synthesized and their COX inhibition was determined. The deboronation of the di-substituted celecoxib derivative results in a switch from COX-1 inhibitory preference to COX-2 inhibition. The nido-carborane-flurbiprofen derivative with a methylene spacer outperformed the derivative with ethylene spacer and literature-known flurbiprofen-carborane conjugates. All nido-carborane analogs exceed the parent ortho-carborane derivatives.

Abstract

The cylcooxygenase isoforms COX-1 and COX-2 are involved in the production of prostaglandins in physiological and pathological processes. The overexpression of COX-2 under inflammatory conditions, its role in cancer and neurodegenerative diseases necessitates the need to develop and improve nonsteroidal anti-inflammatory drugs. These mainly unselective COX inhibitors, e.g. aspirin, are used to reduce the symptoms of inflammation. To reduce unwanted side effects connected with unselective inhibition, the development of novel COX-2 selective inhibitors is a major goal. Herein, the synthesis, characterization and in vitro biological evaluation of eight flurbiprofen- and celecoxib-based carborane analogs are described. Carboranes as hydrophobic surrogates are suitable substituents that can contribute to a selectivity increase toward COX-2 due to size exclusion. The inhibitory efficacy for COX-1 and COX-2 of the four ortho- and four nido-carborane derivatives has been tested. The nido compounds are much more potent than their closo-carborane analogs. The celecoxib-based nido-carborane compound 10 shows an IC50(COX-2) value in the sub-μM range and slight selectivity for COX-2. This is in contrast to its ortho-carborane counterpart 9, which

shows an inhibition preference for COX-1. While none of these carborane derivatives outperforms their organic analogs, the flurbiprofen-based nido-carborane derivatives 14a and 14b surpass the known carborane-based flurbiprofen analogs.