Synthesis and In Vitro Biological Evaluation of p-Carborane-Based Di-tert-butylphenol Analogs

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Abstract

Targeting inflammatory mediators and related signaling pathways may offer a rational strategy for the treatment of cancer. The incorporation of metabolically stable, sterically demanding, and hydrophobic carboranes in dual cycloxygenase-2 (COX-2)/5-lipoxygenase (5-LO) inhibitors that are key enzymes in the biosynthesis of eicosanoids is a promising approach. The di-tert-butylphenol derivatives R-830, S-2474, KME-4, and E-5110 represent potent dual COX-2/5-LO inhibitors. The incorporation of p-carborane and further substitution of the p-position resulted in four carborane-based di-tert-butylphenol analogs that showed no or weak COX inhibition but high 5-LO inhibitory activities in vitro. Cell viability studies on five human cancer cell lines revealed that the p-carborane analogs R-830-Cb, S-2474-Cb, KME-4-Cb, and E-5110-Cb exhibited lower anticancer activity compared to the related di-tert-butylphenols. Interestingly, R-830-Cb did not affect the viability of primary cells and suppressed HCT116 cell proliferation more potently than its carbon-based R-830 counterpart. Considering all the advantages of boron cluster incorporation for enhancement of drug biostability, selectivity, and availability of drugs, R-830-Cb can be tested in further mechanistic and in vivo studies.