Carborane-Based Tebufelone Analogs and Their Biological Evaluation In Vitro

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Abstract

The presence of inflammatory mediators in the tumor microenvironment, such as cytokines, growth factors or eicosanoids, indicate cancer-related inflammatory processes. Targeting these inflammatory mediators and related signal pathways may offer a rational strategy for the treatment of cancer. This study focuses on the incorporation of metabolically stable, sterically demanding, and hydrophobic dicarba-closo-dodecaboranes (carboranes) into dual cyclooxygenase-2 (COX-2)/5-lipoxygenase (5-LO) inhibitors that are key enzymes in the biosynthesis of eicosanoids. The di-tert-butylphenol derivative tebufelone represents a selective dual COX-2/5-LO inhibitor. The incorporation of meta- or para-carborane into the tebufelone scaffold resulted in eight carborane-based tebufelone analogs that show no COX inhibition but 5-LO inhibitory activity in vitro. Cell viability studies on HT29 colon adenocarcinoma cells revealed that the observed antiproliferative effect of the para-carborane analogs of tebufelone is enhanced by structural modifications that include chain elongation in combination with introduction of a methylene spacer resulting in higher anticancer activity compared to tebufelone. Hence, this strategy proved to be a promising approach to design potent 5-LO inhibitors with potential application as cytostatic agents.