Carborane Conjugates with Ibuprofen, Fenoprofen and Flurbiprofen: Synthesis, Characterization, COX Inhibition Potential and In Vitro Activity

Info

PUBLIZIERT AM
2024-11-08

JOURNAL
ChemMedChem

LINK
https://doi.org/10.1002/cmdc.202400018

Autoren

Sonam Sonam Sanja Jelača Markus Laube Jonas Schädlich **Jens Pietzsch** Danijela Maksimović-Ivanić Sanja Mijatović Goran N. Kaluđerović Evamarie Hey-Hawkins

Abstract

The most effective anticancer drugs currently entail substantial and formidable side effects, and resistance of tumors to chemotherapeutic agents is a further challenge. Thus, the search for new anticancer drugs as well as novel therapeutic methods is still extremely important. Non-steroidal anti-inflammatory drugs (NSAIDs) can inhibit COX (cyclooxygenase), overexpressed in some tumors. Carboranes are emerging as promising pharmacophores. We have therefore combined both moieties in a single molecule to design drugs with a dual mode of action and enhanced effectiveness. The NSAIDs ibuprofen, flurbiprofen, and fenoprofen were connected with 1,2-dicarba-closo-dodecaborane(12) via methylene, ethylene or propylene spacers. Three sets of carborane-NSAID conjugates were synthesized and analyzed through multinuclear (1H, 11B, and 13C) NMR spectroscopy. Conjugates with methylene spacers exhibited the most potent COX inhibition potential, particularly conjugates with flurbiprofen and fenoprofen, displaying higher selectivity towards COX-1. Furthermore, conjugates with methylene and ethylene spacers were more efficient in suppressing the growth of human cancer cell lines than their propylene counterparts. The carborane-flurbiprofen conjugate with an ethylene spacer was the most efficient and selective toward the COX-2-negative cell line HCT116. Its mode of action was basically cytostatic with minor contribution of apoptotic cell death and dominance of cells trapped in the division process.