Isonimesulide and Its Carborane Analogues as Isoform-Selective COX Inhibitors and Antitumor Agents

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Abstract

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most widely used therapeutics against pain, fever, and inflammation; additionally, antitumor properties are reported. NSAIDs reduce the synthesis of prostaglandins by inhibiting the cyclooxygenase (COX) isoforms COX-1 and COX-2. As nonselective inhibition is associated with off-target effects, strategies to achieve selectivity for the clinically preferred isoform COX-2 are of high interest. The modification of NSAIDs using carborane clusters as phenyl mimetics is reported to alter the selectivity profile through size exclusion. Inspired by these findings, isonimesulide and its carborane derivatives are prepared. The biological screening shows that the carborane containing compounds exhibit a stronger antitumor potential compared to nimesulide and isonimesulide. Furthermore, the replacement of the phenyl ring of isonimesulide with a carborane moiety resulted in a shift of the COX activity from nonactive to COX-active compounds.