Next Generation Fatty Acid Binding Protein Inhibitors: Computer-Aided Drug Design and Synthesis of Novel Truxillic Acid Diesters for Chronic Pain Inhibition

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Demand for non-addictive, tissue-specific pain relief has been growing ever since the IOM confirmed that pain afflicts more Americans than cancer, heart disease, and diabetes combined. In years past, public health officials have prescribed the use of over-the-counter and opioid painkillers for treating ailments, both of which can induce side effects such as gastroduodenal erosion, tolerance build-up, and death when taken in excess. Such undesirable aftereffects of current painkillers justify the search for developing new anti-inflammatory agents with greater selectivity for areas of nociception. To this end, recent pharmaceutical research has focused on producing localized pain relievers that target FABP5 and FABP7, two fatty acid binding proteins (FABPs) responsible for the intracellular transport of the endocannabinoid anandamide, which has proven therapeutic effects on pain, inflammation, stress, and drug withdrawal. SB-FI-26 (an α-truxillic acid 1-naphthyl mono-ester) has demonstrated to be a potent inhibitor of FABP5, but a poor binder to FABP7. This study aims to optimize SB-FI-26 to selectively inhibit both FABP5 and FABP7 in order to amplify endocannabinoid-mediated agonistic effects. To do so, a four-part methodology was employed: (a) rational designing and library optimization of SB-FI-26 analogs, (b) DOCKing studies, (c) chemical syntheses of the analogs, and (d) biological testing. Taken together, it was revealed that diesters with the octahydro-1H-inden2-yl ester moiety increases the intermolecular interactions with the FABP5 active site and that the charged carboxylate present in SB-FI-26 may not be completely necessary for potent FABP inhibition, which offers the prospect of using these drug candidates as a novel approach for managing chronic pain.

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