Naturalistic Painkillers: Design, Synthesis, and Biological Evaluation of Novel Fatty Acid Binding Protein Inhibitors

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Pain is one of the most pervasive aspects of daily life, afflicting more Americans than cancer and heart disease combined. Recent 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 (AEA), which has proven therapeutic effects on pain, inflammation, stress, and drug withdrawal. Previous investigations have demonstrated that an α-truxillic acid 1-naphthyl mono-ester (SB-FI-26) is a potent inhibitor of FABP5, but has a reduced anti-nociceptive effect on FABP7. Thus, the current study aims to optimize this lead compound, SB-FI-26, to develop a more effective FABP inhibitor. To this end, a comprehensive three-step approach was employed involving: computational modeling, chemical synthesis of analogs, and biological testing. A library of small-molecule drug compounds was first rationally designed by attaching hydroxyl and methoxl groups to the lead in varying permutations. Molecular DOCKing of these ligands with multiple FABPs, to determine both the efficacy and specificity of the designed compounds, revealed that the para-hydroxy analog, SB-FI-71 (4-hydroxy-truxillic acid mono-1-naphthyl ester), obtained the highest overall energy scores. The subsequent synthesis of SB-FI-71 and in vitro protein assays strongly supported the hypothesized analgesic effects of SB-FI-71 in competitive binding, especially for FABP7. Taken together, the combined potency of SB-FI-26 for FABP5 and SB-FI-71 for FABP7 points to the highly favorable prospect of using these two drugs in tandem as a two-pronged approach to targeting pain receptors, a novel approach to pain relief and management.

Awards Won:

Third Award of $1,000