Title - Design and Synthesis of Endocannabinoid Enzyme Inhibitors for Peripheral Selectivity
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Abstract: Peripherally selective compounds that contribute to the enhanced activity of the endocannabinoid receptors have been shown to offer advantages in some indication such as eye wound healing and modulation of gastrointestinal pain. Cannabinoid receptor 1 (CB1), an endocannabinoid receptor located ubiquitously in the human body, is activated by the endocannabinoids anandamide (AEA) and 2-arachyidonoylglycerol (2-AG). However, both of these ligands are rapidly hydrolyzed by the enzymes fatty acyl amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL). Therefore, to enhance CB1 activation, FAAH and MAGL were targeted for therapeutic inhibition. Peripherally selective inhibitors were designed and synthesized as sulfonamide derivatives, which would have higher topological polar surface area (TPSA). This modification was done so that the compounds with high TPSA would not cross the blood-brain barrier and thus potentially would avoid any adverse effect on the central nervous system. The compounds were purified through the use of radial preparative layer chromatography, and their identity as the desired products were confirmed through nuclear magnetic resonance (NMR). Cayman's FAAH inhibitor MAGL inhibitor screening assay kits were used to assess the percent inhibition that the desired compounds exert on FAAH and MAGL respectively. The control inhibitor was selected as JZL, a well-studied inhibitor of endocannabinoid receptors.