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Inhibitors of fatty acid amide hydrolase (FAAH): SAR and results in pre-clinical pain models

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Pharmacologically active preparations of *Cannabis sativa* have been recognized since ancient times as having potentially useful therapeutic effects, including analgesia. With the discovery and cloning of the cannabinoid receptors CB1 and CB2, and the subsequent discovery of anandamide, the first endogenous substance with agonist activity at both receptors, a rationale for the analgesic effects of cannabis was developed. Anandamide has a short half-life, due to rapid hydrolysis by the enzyme fatty acid amide hydrolase (FAAH) resulting in low resting concentrations in the CNS. FAAH knockout mice have been described and have elevated resting brain concentrations of anandamide, and manifest a phenotypic analgesia in several commonly used models of pain. Furthermore, known inhibitors of FAAH show amelioration of pain behaviors in rats. The present account describes the discovery of a novel classes of FAAH inhibitors and describes our work to characterize the SAR and pharmacology of these FAAH inhibitors.

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