REVERSED AMIDE DERIVATIVES OF ARACHIDONOYL ETHANOL AMIDE -SYNTHESIS, CB1-RECEPTOR ACTIVITY AND ENZYMATIC STABILITY

Teija Parkkari,[a] Juha R. Savinainen,[b] Tapio Nevalainen,[a] Laura Mäkipaja,[a] Tuomas Sirviö,[a] Susanna M. Saario,[a] Jarmo T. Laitinen,[b] Riku Niemi,[a] and Tomi Järvinen[a]

[a]Department of Pharmaceutical Chemistry and [b]Department of Physiology, University of Kuopio, P.O.Box 1627, FIN-70211 Kuopio, Finland

The growing understanding of the endogenous cannabinoid system (ECS) as a new neuronal signaling system has offered fascinating opportunities for the drug discovery. Drugs effecting through the ECS have been suggested for the treatment of several disorders; pain, anxiety, glaucoma, nausea, obesity, head injuries and Parkinson's disease as a few examples. The ECS consists of cannabinoid receptors (CB1 and CB2) and their ligands (endocannabinoids), membrane bound carrier proteins and metabolizing enzymes (FAAH, MGL). The cannabinoid receptor ligands and enzyme inhibitors are believed to provide new therapeutical insights for the future. Two major endocannabinoids, *N*-arachidonoyl ethanol amide (AEA) and 2-arachidonoyl glycerol (2-AG), are excellent ligands for the cannabinoid receptors, and they have been shown to act as therapeutic agents in several *in vitro* and *in vivo* models. However they degrade enzymatically very fast *in vivo*. In order to provide good probes for the cannabinoid drug research and design based on endogenous cannabinoids, their structures must be modified. In the present study, seven reversed amide derivatives **(**Fig. 1.; **1a-d, 2a-c**) of AEA were synthesized and evaluated for their CB1 receptor activation by a [^{35}S]GTP$_\gamma$S binding assay using rat cerebellar membranes. The primary goal of the study was to develop CB1 receptor agonists having improved enzymatic stability compared to endogenous AEA. Furthermore, by reversing the amide bond of AEA, the formation of arachidonic acid would be prevented. Finally, an effect of the carbonyl carbon position of the CB1 receptor activity was explored by synthesizing analogues having different chain lengths (**1a-d**, C_{20}; **2a-c**, C_{19}). All the synthesized compounds, except **1d**, showed dose-dependent CB1 activity. For example, the potency values for the compounds **1b** and **2b** were E_{max} = 305 ± 10 % basal, pEC$_{50}$ = 5.7 ± 0.1 and E_{max} = 222 ± 9 % basal, pEC$_{50}$ = 5.4 ± 0.2, respectively, and for the reference compound AEA E_{max} = 415 ± 3 % basal, pEC$_{50}$ = 5.3 ± 0.1. In rat brain homogenate, the reversed amides possessed significantly higher stability against FAAH induced degradation than AEA. Therefore, the reversed amide analogues of AEA may serve as enzymatically stable structural basis for the drug design based on the endogenous cannabinoids.

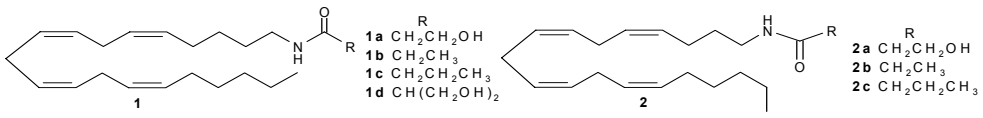

Figure 1. Chemical structures of reversed amides **1a-d, 2a-c**.