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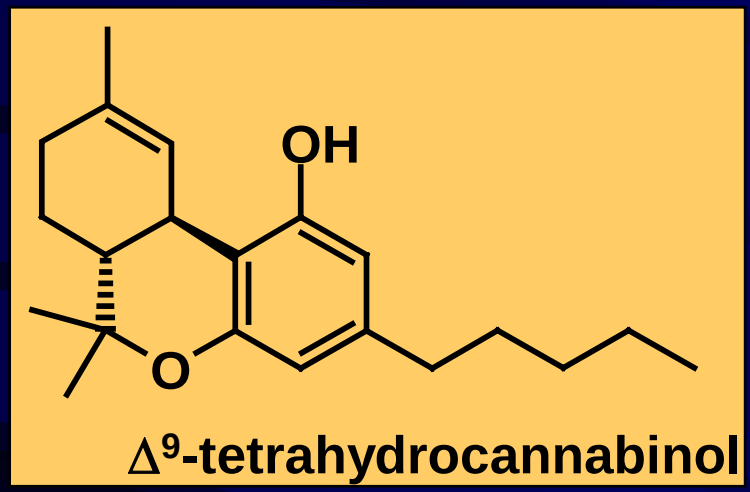
Arylpropionic and arylacetic acid derivatives as analogs of endogenous cannabinoids

Cannabinoids

- structure elucidation of Δ^9-THC in 1964



- first evidence for the existence of specific binding sites for canabinoids in 1988

Endogenous cannabinoid system

- two subtypes, CB_1 and CB_2
- CB_1 receptors are located in the CNS, predominantly on interneurons in regions for motor function, pain and learning
- CB_2 receptors are located in the peripheral nervous and immune system, e.g. on mast cells, B- and T-lymphocytes
- endogenous ligands are anandamide, 2- arachidonylglycerol and noladinether

Cannabinoid receptors

- CB_1 receptors:

  Central nervous system, areas responsible for cognition, short-term memory, motor function, pain

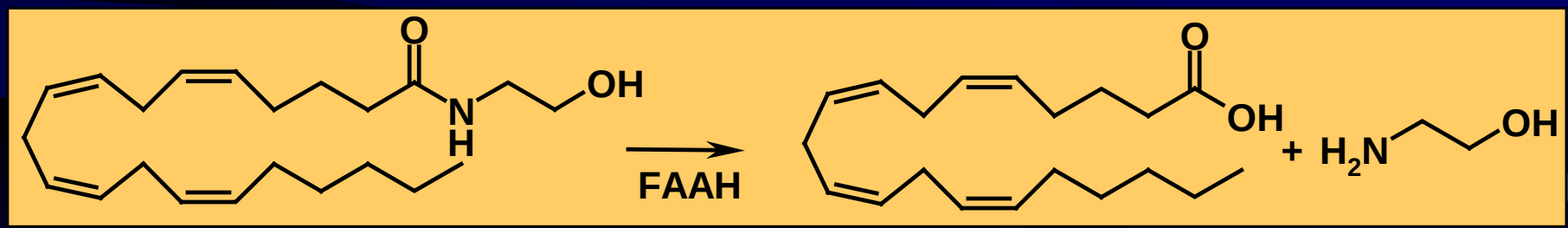
- CB_2 receptors:

  immune system, mast cells and B- and T-lymphocytes

Both receptors are coupled through $G_{i/o}$ proteins

Inactivation system

- uptake of anandamide
- intracellular degradation, catalysed by FAAH



Endogenous cannabinoid system

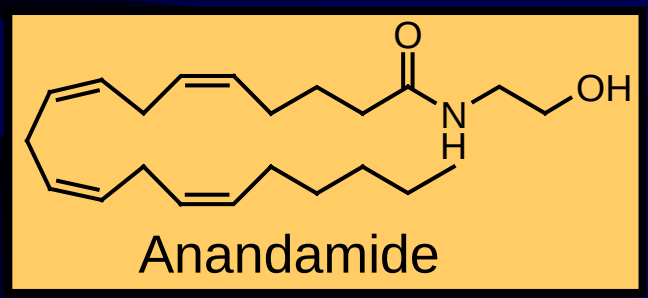
takes part in:

antinociception, brain development, control of motor function, immune regulation, cell proliferation

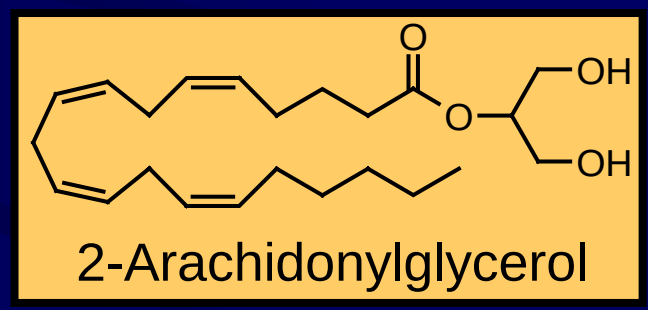
compounds influencing the ECS are potential therapeutics for treatment of pain or neurodegenerative diseases like multiple sklerosis

K_i [nM] of endogenous ligands

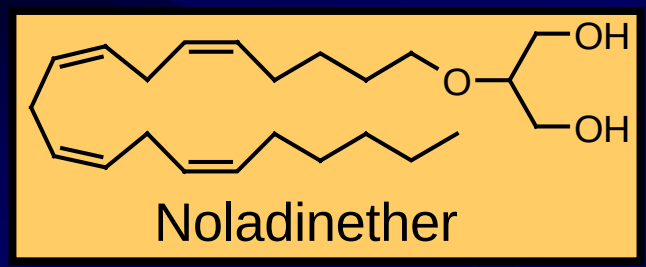
	Anandamide	Noladinether	2-Arachidonylglycerol
CB_1	89	21.2	58.3
CB_2	371	>3000	145



Anandamide

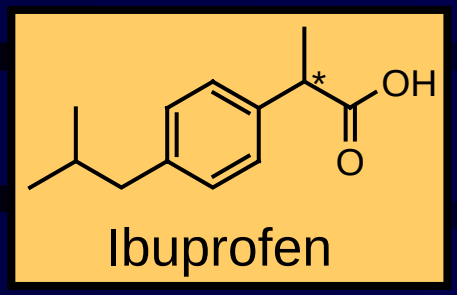


2-Arachidonylglycerol

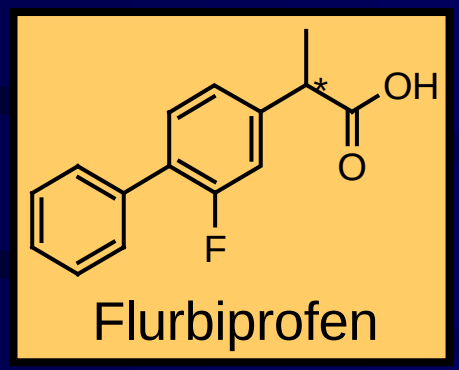


Noladinether

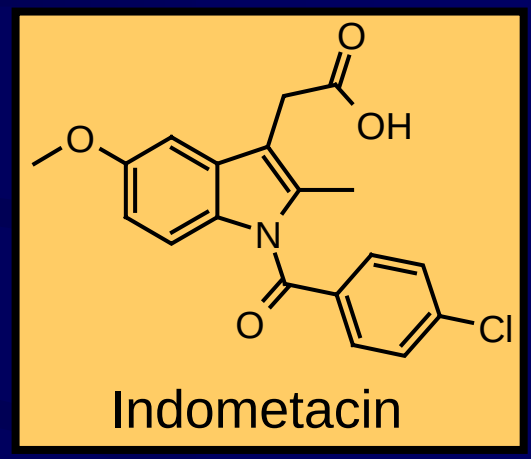
COX inhibitors



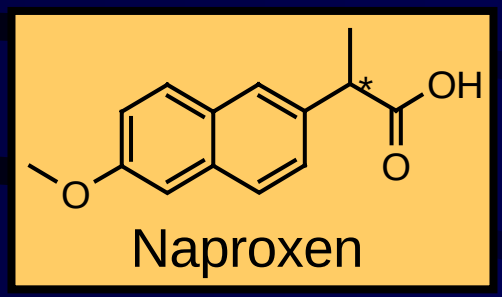
Ibuprofen



Flurbiprofen



Indometacin



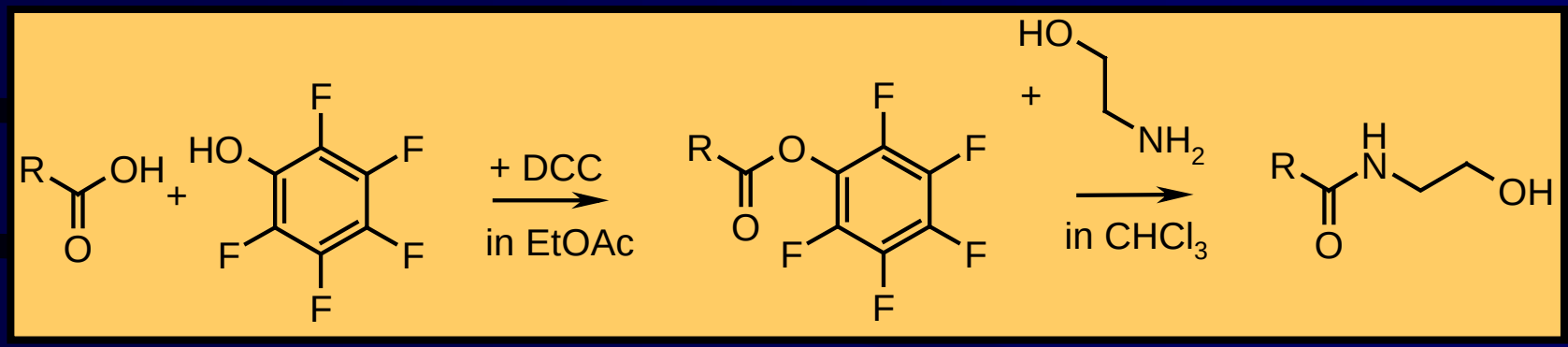
Naproxen

- only S-enantiomers inhibit COX
- R-enantiomers also have analgetic potency
- mimic arachidonic acid

Arylpropionic acids interact with the endogenous cannabinoid system

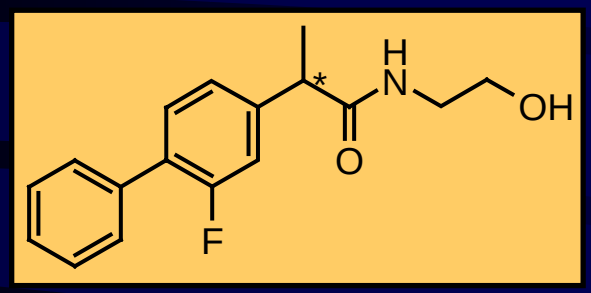
- Ibuprofen and flurbiprofen inhibit the hydrolysis of anandamide at pharmacologically relevant concentrations
- R-(-)-Ibuprofen is about 2-3 times more potent than the S-(+)-enantiomer
- co-injection of PGE_2 hardly affects analgesia, but AM-251 (selective CB_1 inhibitor) suppresses it

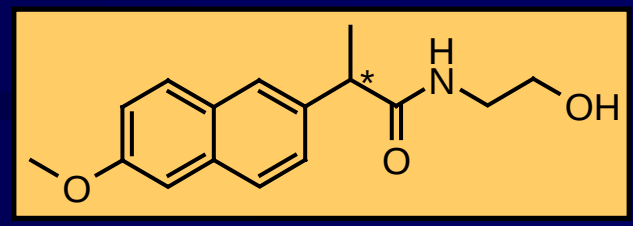
Synthesis of ethanolamides

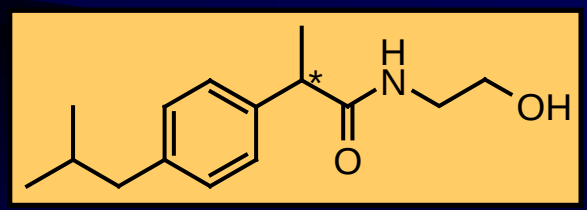


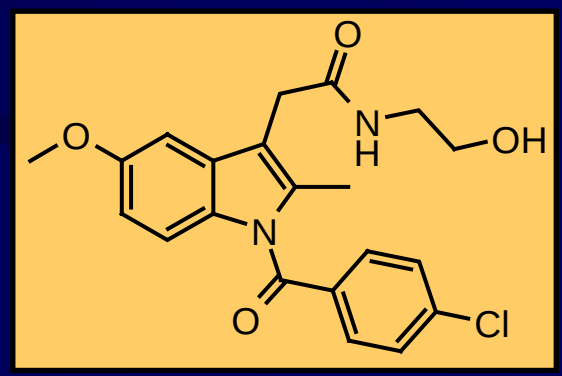
- reactivity of pentafluorophenyl esters towards N- nucleophiles comparable to acid chlorides, but much more stable towards O-nucleophiles
- purification via flash chromatography

Synthesised arylacetic and arylpropionic acid derivatives



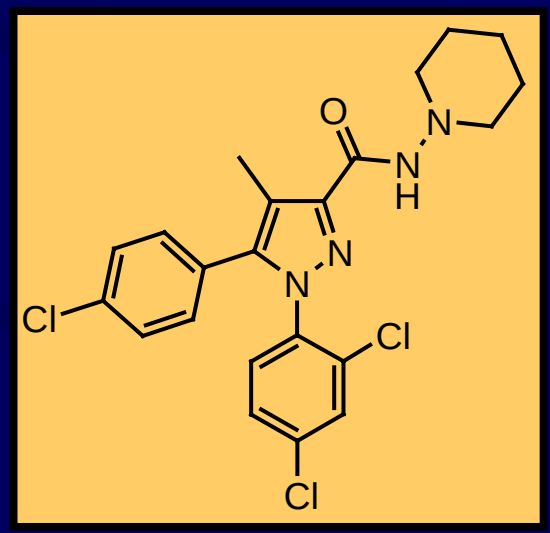




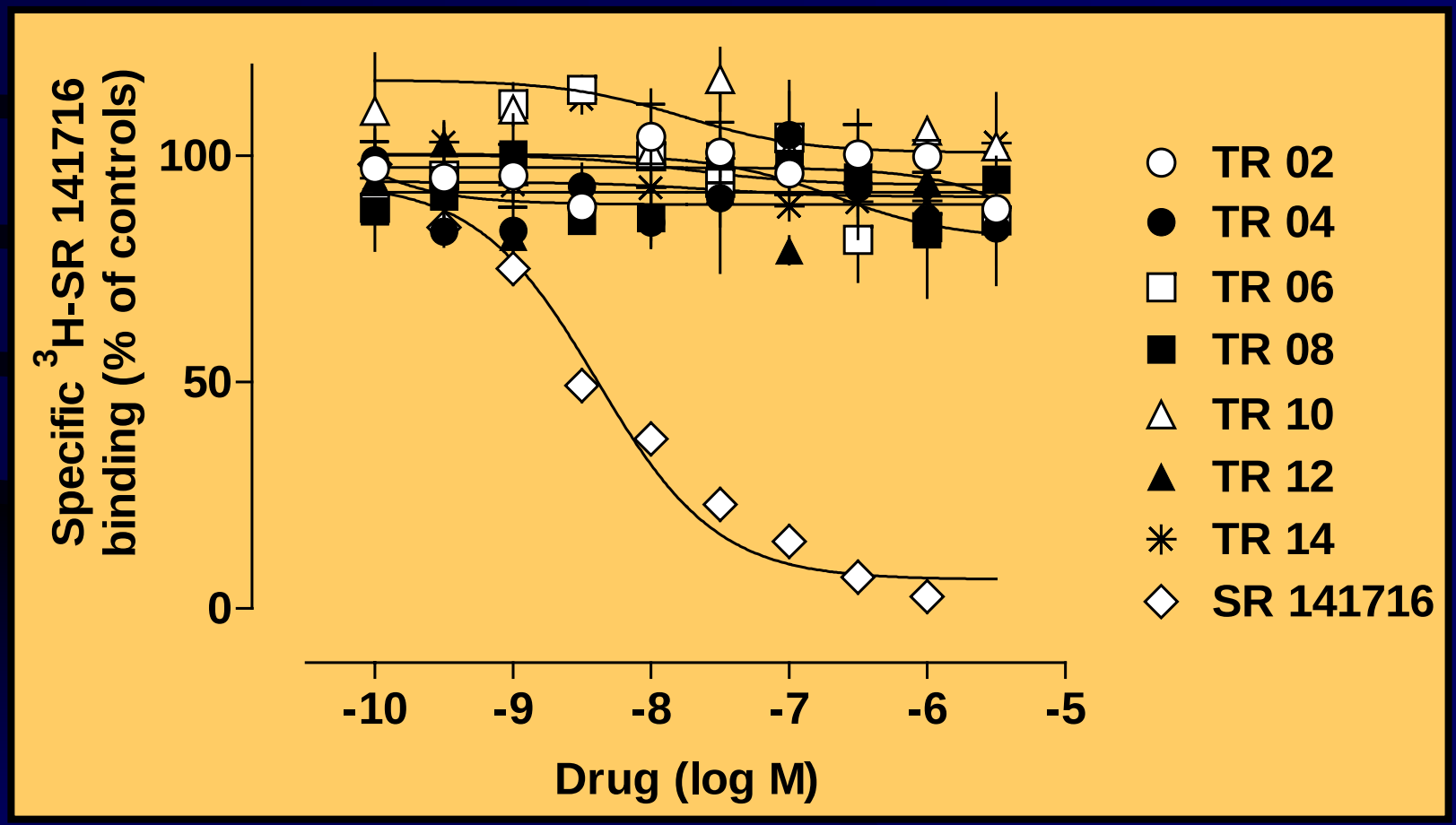


Affinity of ethanolamides towards CB_1 receptors

- CB_1 receptors were extracted from the cerebral cortex of male rats
- incubation with [^{3}H]-SR 141716
- determination of residual radioactivity



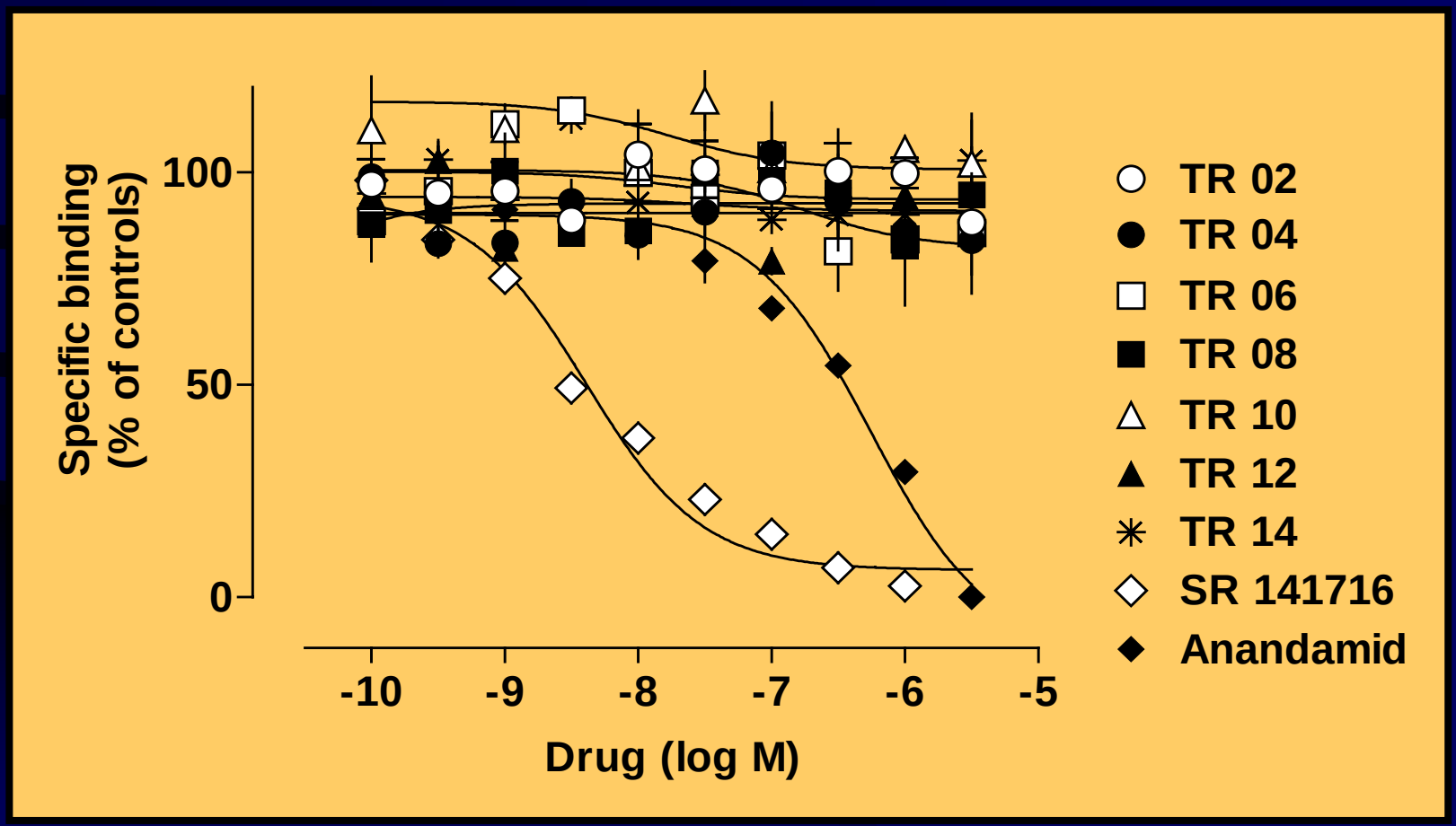
Affinity of ethanolamides towards CB_1 receptors



Affinity of ethanolamides towards CB_1 receptors

- recent studies suggest that there are two binding regions for cannabinoids at CB_1
  (McAllister et al. *J.Med.Chem* **2003**, 46, 5139)
- one for aminoalkylindols and diaryl pyrazoles like SR 141716
- one for endogenous ligands like anandamide and nonclassical agonists

Affinity of ethanolamides towards CB_1 receptors



Summary

- mechanism of analgetic potency of R-enantiomers unknown yet
- possible interaction with cannabinoid system
- no affinity towards CB_1 receptors of synthesised ethanolamides

Outlook

possible affinity towards following targets - to be tested:

- CB_2 receptors (less demanding concerning substrate geometry)
- FAAH (fatty acid amidohydrolase)
- VR_1 receptors (vanilloid receptors)

synthesis of other metabolites e.g. symmetric glycerol esters