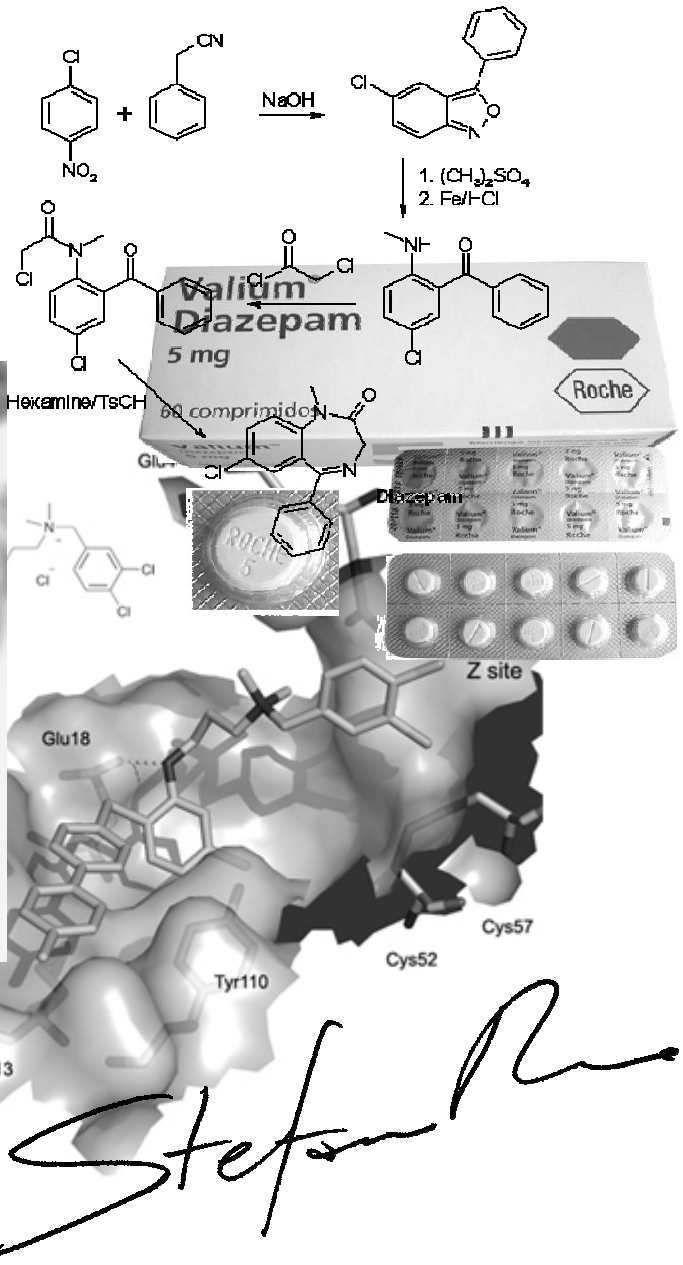
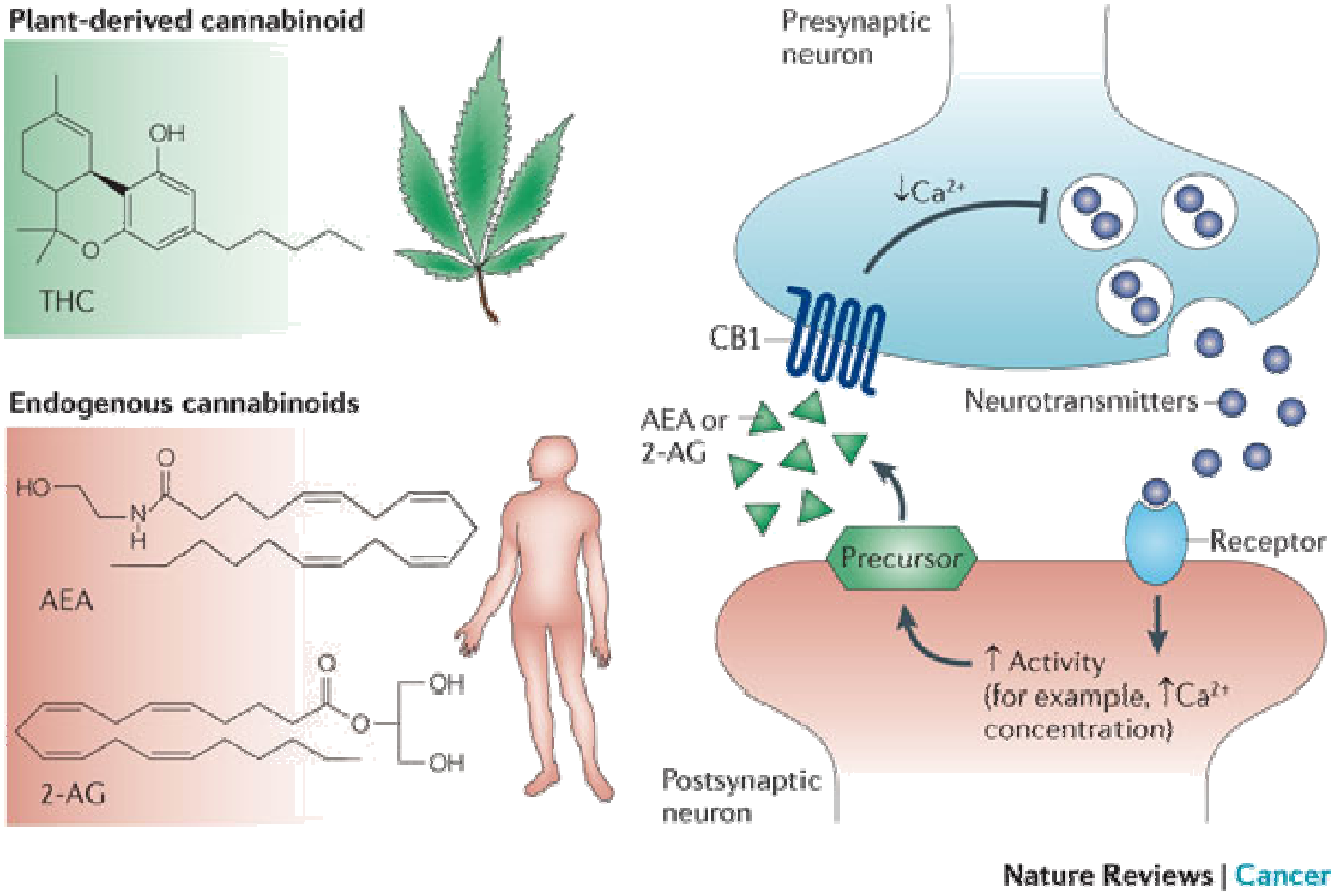
Chimica Farmaceutica e Tossicologica – Parte II



Endocannabinoid system

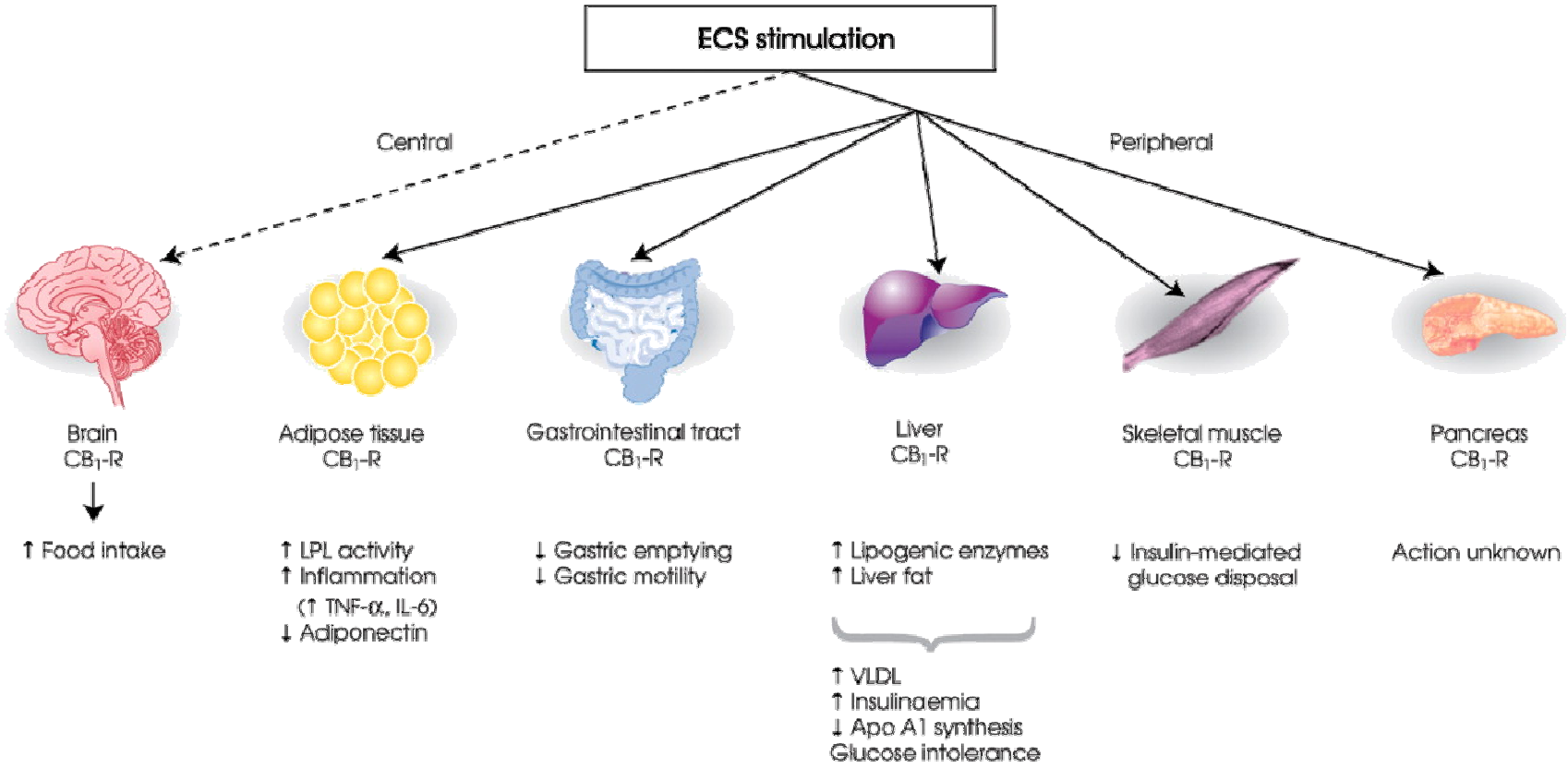
Parte I

1. Endocannabinoid system



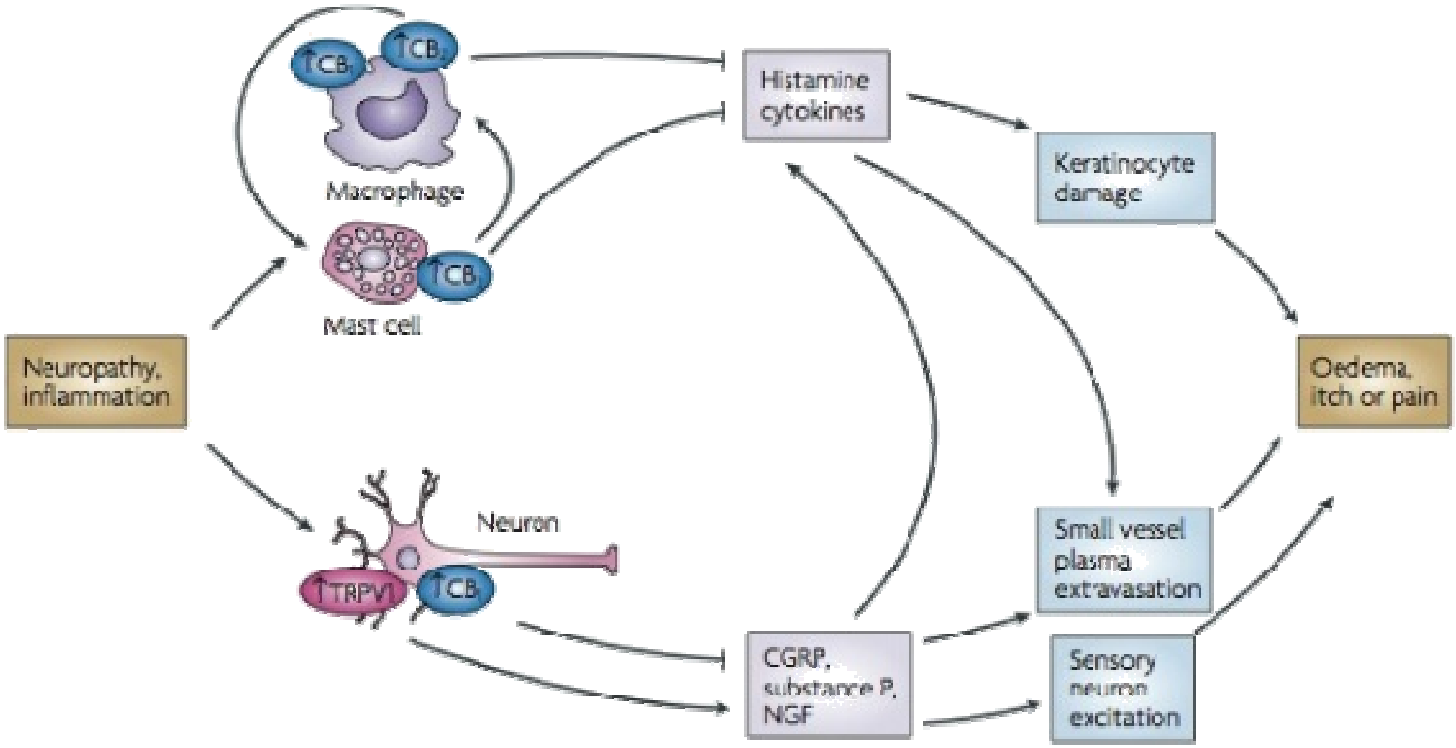
1. Endocannabinoid system

1.1 Endocannabinoid system stimulation



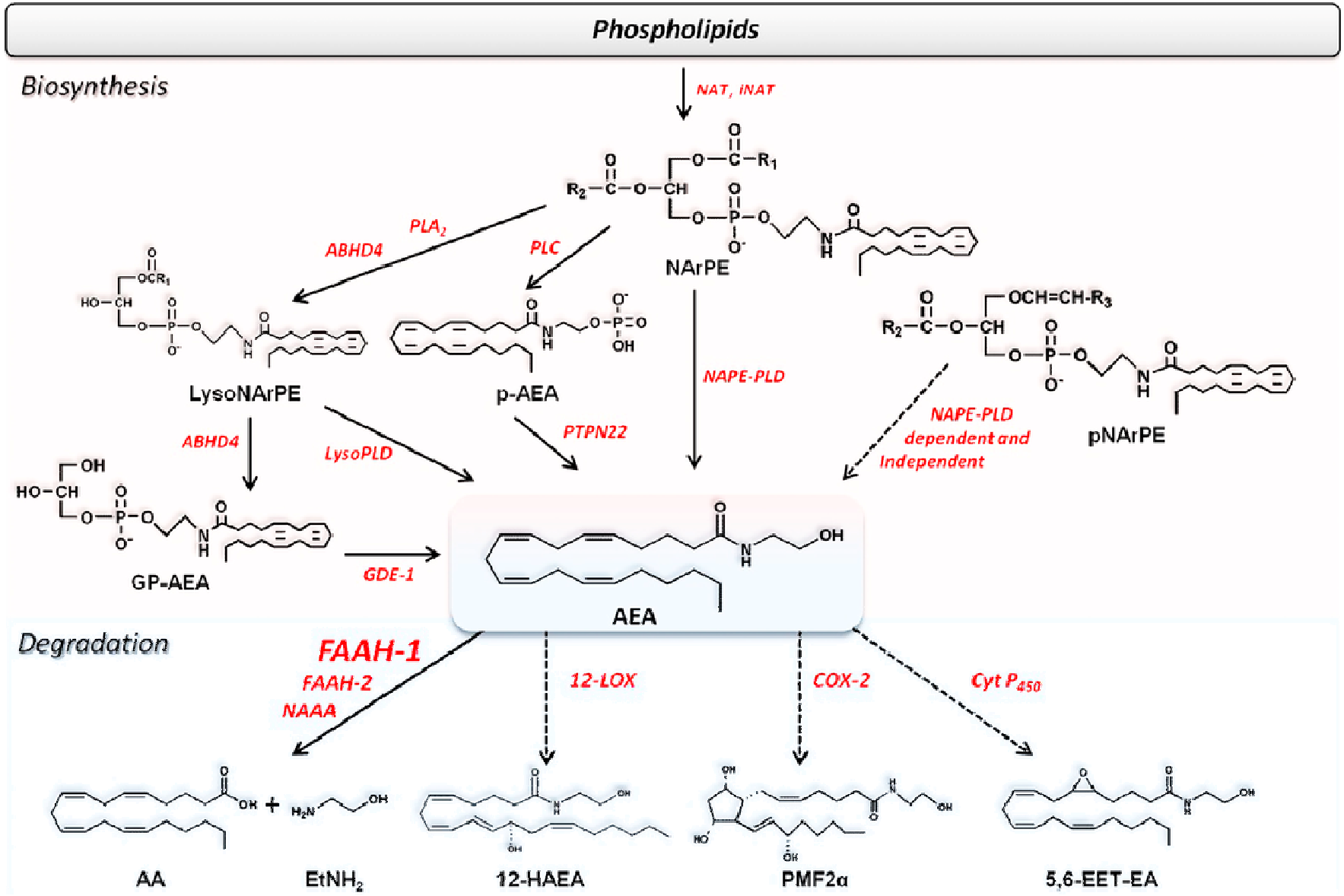
1. Endocannabinoid system

1.2 Endocannabinoid as immune modulators



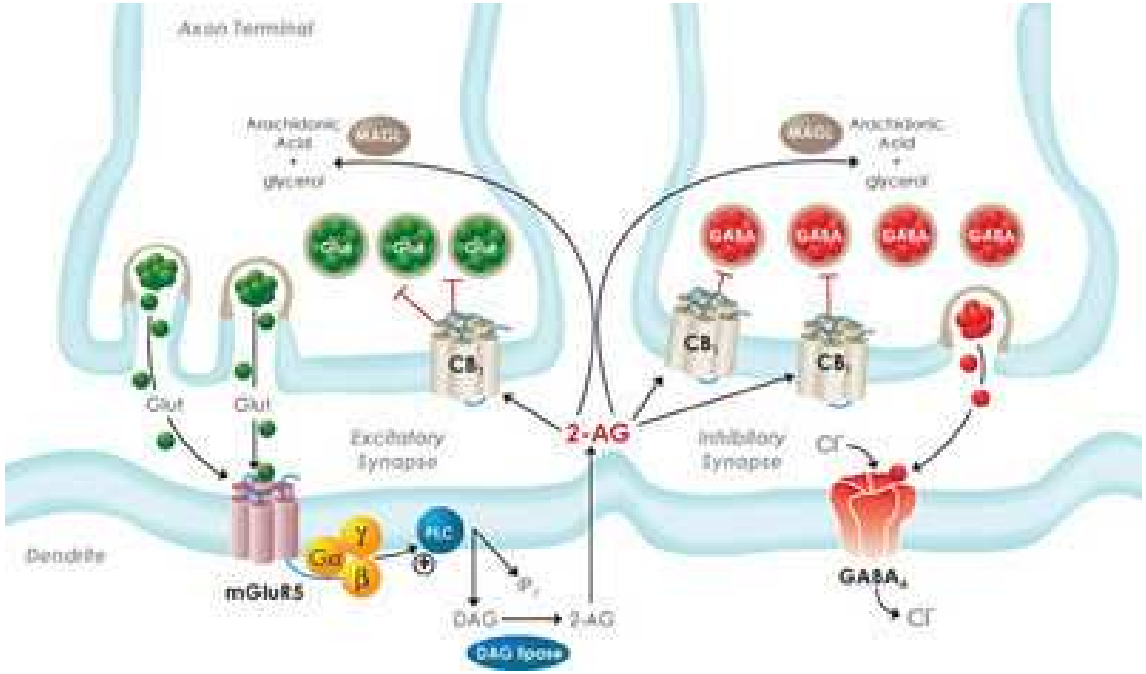
Nature Rev Drug Disc 2008;7:438-455

1. Endocannabinoid system



1. Endocannabinoid system

1.3 Endocannabinoid receptors



Synthesis and retrograde action of endoCBs. Produced in stimulated neurons, endoCBs are secreted and activate specific receptors on presynaptic axons. The effects of endoCBs, like 2-AG, are suppressive, including the inhibition of neurotransmitter release

1. Endocannabinoid system

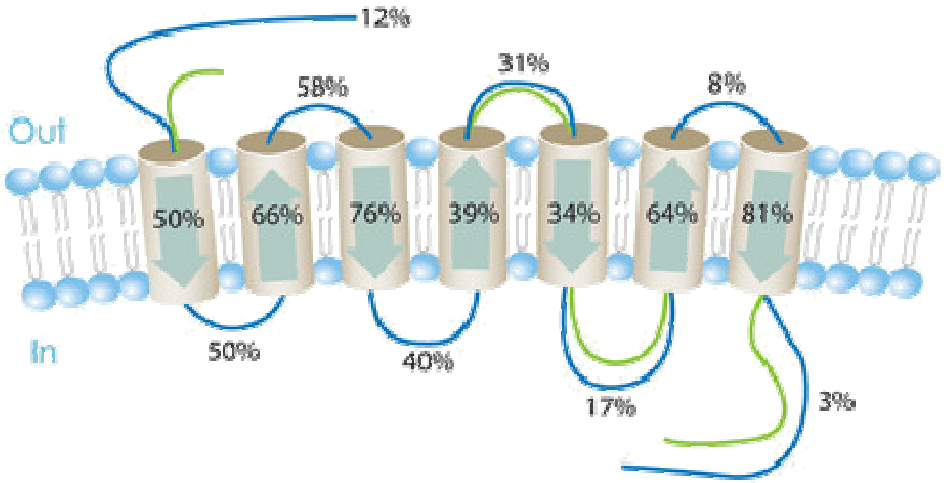
1.3 Endocannabinoid receptors

The CB1 and CB2 receptors are activated by several natural agonists, or endocannabinoids (endoCB), including 2-arachidonoyl glycerol (2-AG) and anandamide (arachidonoyl ethanolamide, AEA). 2-AG and AEA are small, lipophilic molecules secreted by cells in the brain and immune system. These intercellular messengers are not stored in vesicles but are rapidly synthesized *via* regulated enzymatic pathways. For example, the synthesis of 2-AG is initiated by the activation of a Gαq-coupled receptor, such as the glutamate receptor mGluR5. Signaling through Gα leads to PLC-mediated release of diacylglycerol (DAG) from arachidonate-containing membrane phospholipids. A specific DAG lipase converts DAG to 2-AG, which is secreted from the source cell to activate CB1 or CB2 on nearby target cells. CB1 or CB2 are Gαi-coupled receptors that commonly inhibit many processes: for example, at the presynaptic terminal, activation of CB1 inhibits release of neurotransmitters like glutamate and GABA. In this case, signaling is termed 'retrograde' since the mediator, 2-AG, feeds back from the post-synaptic dendrite to regulate the action of axon terminals. In general, lipid mediators commonly have actions that are paracrine (acting on nearby target cells) or autocrine (modulating the source cell itself).

1. Endocannabinoid system

1.3 Endocannabinoid receptors

While other receptors may respond to endoCBs, the focus here will be on CB1 and CB2. CB1 is restricted primarily to neuronal cells and located at various sites within the brain. CB2 is more diffusely distributed, being present on leukocytes (including glia), splenocytes, peripheral and enteric neurons, and possibly other cell types. Both CB1 and CB2 are 7-transmembrane G-coupled receptors in which the binding domain for the lipophilic ligands involves membrane-spanning residues that form a pocket within the hydrophobic layer of the membrane. Perhaps for this reason, the greatest homology between CB1 and CB2 lies in certain membrane-spanning helices, rather than in the loops or tails.



Nmbers indicate percent homology between CB1 (blue) and CB2 (green) for the indicated segment

1. Endocannabinoid system

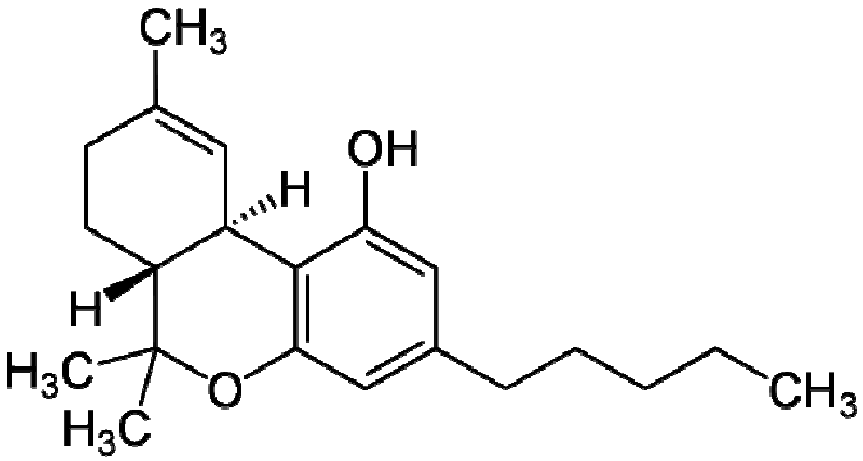
1.3 Endocannabinoid receptors

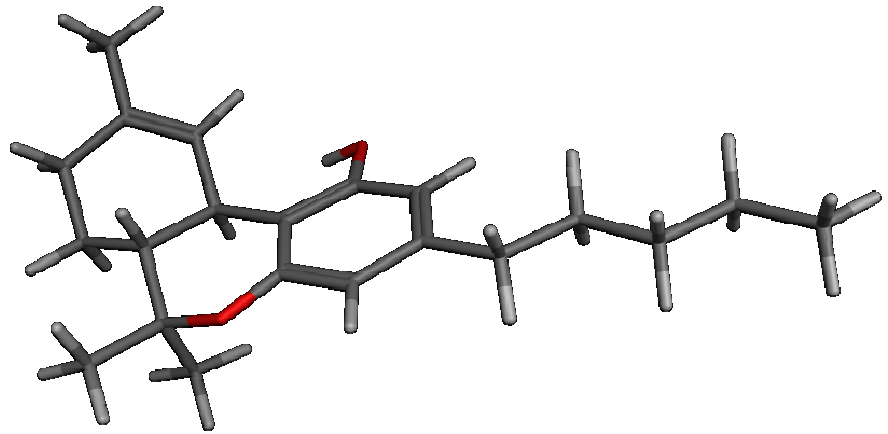
CB1 has been targeted therapeutically with an antagonist (*rimonabant*) and, more recently, an inverse agonist (*taranabant*). Rimonabant is marketed worldwide under the name AcompliaTM as an anti-obesity drug, but use in the U.S. has been blocked by the FDA because of side effects Working in the other direction, the activation of CB1 can reduce neuropathic pain, nausea and AIDs-related anorexia. Cayman offers both endoCB analogues (methanandamide , 2-Arachidonyl Glycerol ether) and non-cannabinoid ((+)-WIN 55,212-2 (mesylate)) CB1 agonists.

Activation of **CB2** can reduce bone loss in ovariectomized mice, suggesting that CB2 agonists could reduce osteoporosis in post-menopausal women. Selective CB2 agonists also reduce inflammatory and neuropathic pain, alter leukocyte adhesion and migration4 and reduce intestinal inflammation.

1. Endocannabinoid system

1.4 Tetrahydrocannabinol (THC)



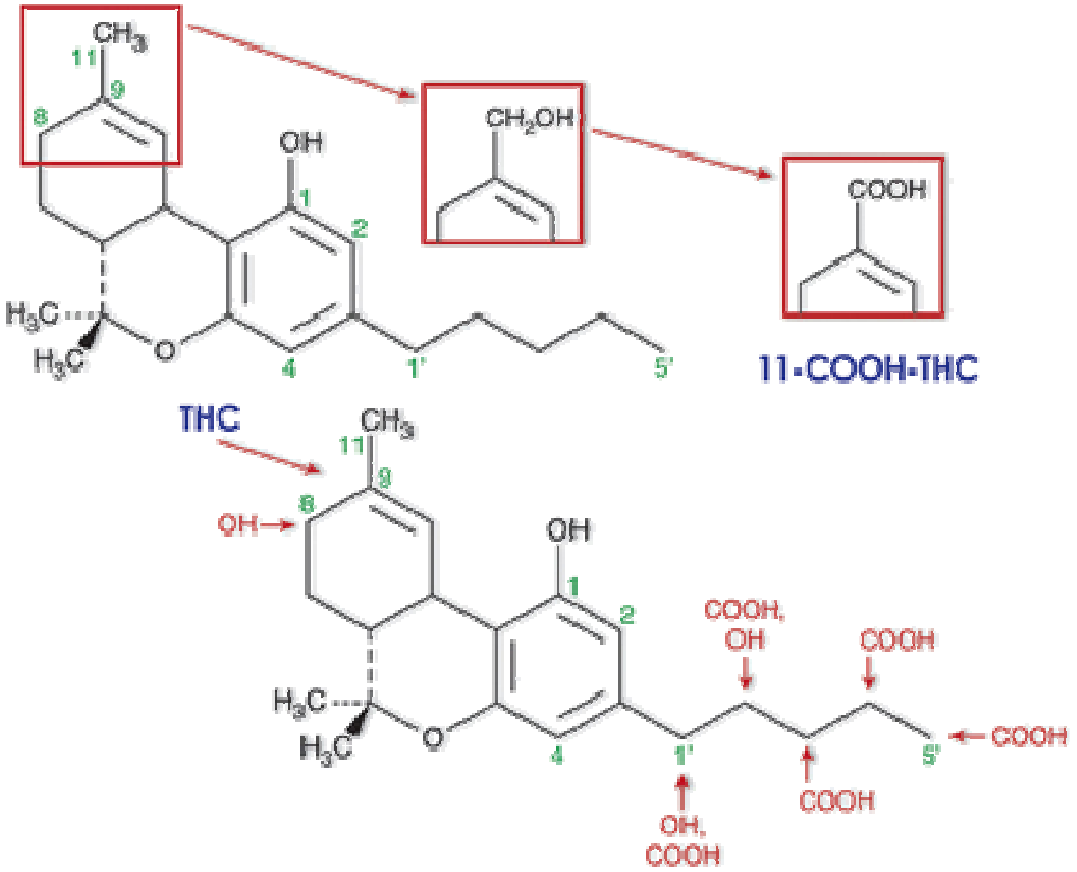


log P = 5.6

Tetrahydrocannabinol (THC), or more precisely its main isomer (−)-*trans*-Δ9-tetrahydrocannabinol **(**(6aR,10aR)-delta-9-tetrahydrocannabinol), is the principal psychoactive constituent (or cannabinoid) of cannabis. First isolated in 1964 by Israeli scientists Prof. Raphael Mechoulam and Dr. Yechiel Gaoni at the Weizmann Institute of Science.

1. Endocannabinoid system

1.4 Tetrahydrocannabinol (THC): metabolism

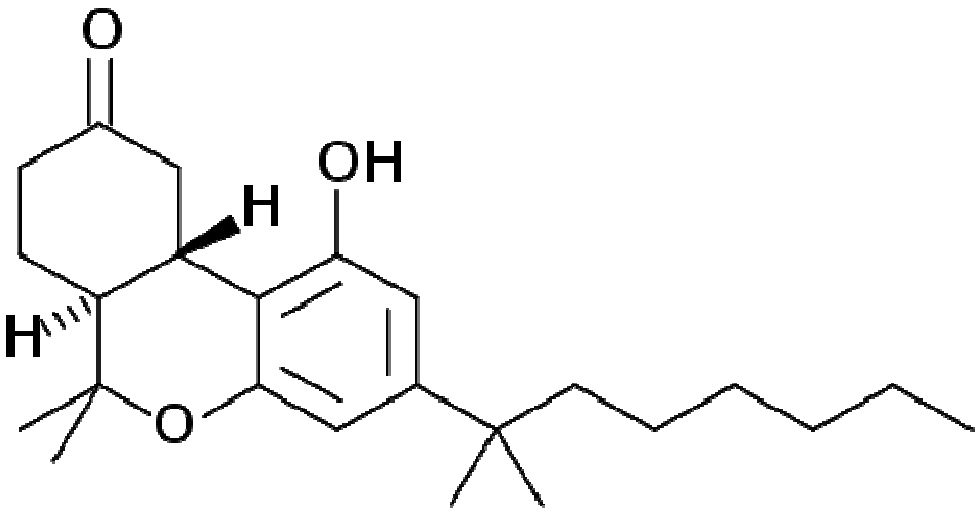


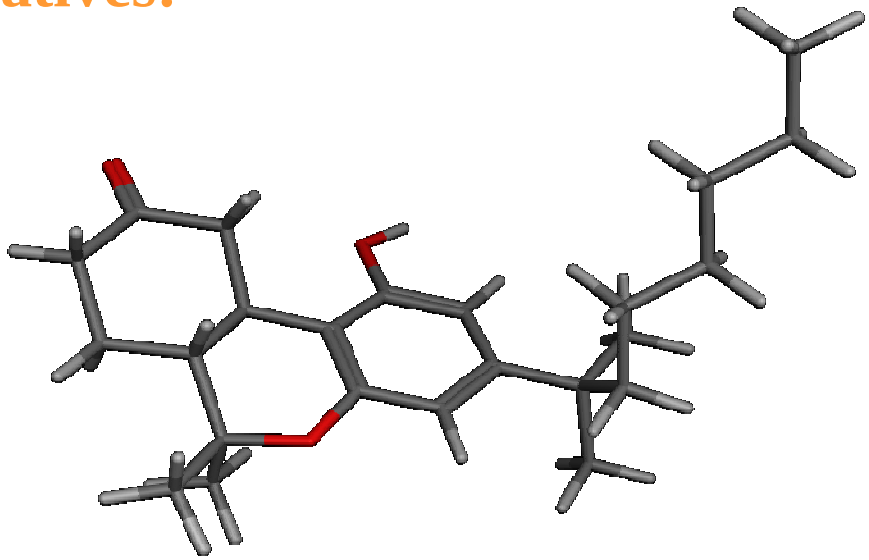
1. Endocannabinoid system

1.4 Tetrahydrocannabinol (THC): formulations

1. Endocannabinoid system

1.5 Tetrahydrocannabinol derivatives:



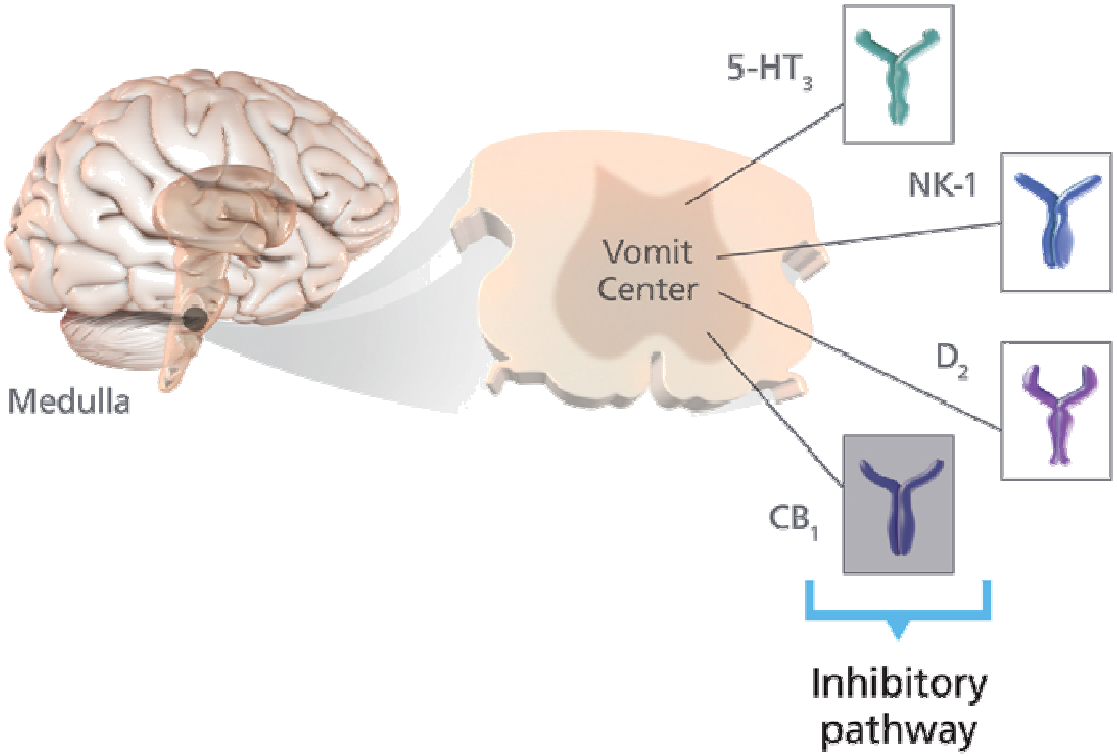


log P = 6.8

Nabilone is a synthetic cannabinoid with therapeutic use as an antiemetic and as an adjunct analgesic for neuropathic pain. It mimics tetrahydrocannabinol (THC), Nabilone is a racemic mixture consisting of the *(S,S)* and the *(R,R)* isomers (*"trans"*)_(*"trans"*)._Used for the control of nausea and vomiting, caused by chemotherapeutic agents used in the treatment of cancer, in patients who have failed to respond adequately to conventional antiemetic treatments.

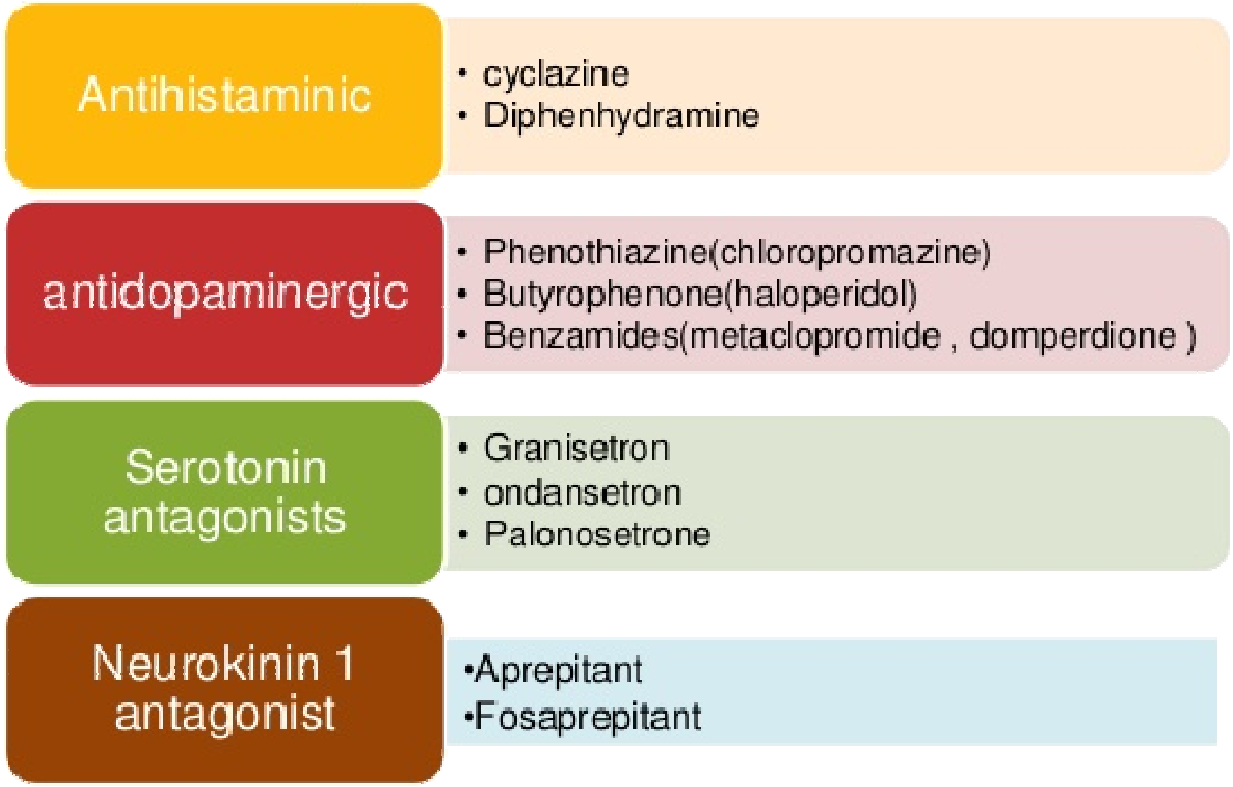
1. Endocannabinoid system

1.5 Tetrahydrocannabinol derivatives:



1. Endocannabinoid system

1.6 Other anti-emetic classes:




TITLE
"CHIMICA FARMACEUTICA E TOSSICOLOGICA II"
DIRECTOR
Stefano Moro
CAMERA
Chimica e Tecnologia Farmaceutiche
DATE
SCENE
TAKE