Amer Tarawneh et al., Med chem (Los Angeles) 2018, Volume 8
DOI: 10.4172/2161-0444-C1-039

Discovery and structure - activity relation study of small-molecule as CB2 selective ligand

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The CB1 receptor was originally called the cannabinoid receptor before the CB2 receptor was discovered, but CB1 did not explain the immunomodulatory effects of cannabis, which were already well-documented at this time. In 1993, this effect was accounted by the finding of the CB2 receptor in a human promyelocytic leukemia cell line. Both CB1 and CB2 are G-protein coupled receptors, which share a 48% sequence identity. There have been numerous studies on the pharmacology of CB2, giving it the name receptor with an identity crisis. Because CB2 (unlike CB1) is largely not expressed in the central nervous system, but rather in the spleen and immune cells, it is known as the peripheral cannabinoid receptor soon after its discovery. When CB2 expression was found in the neurons and in the microglial cells of the brain, this terminology was determined to be inaccurate, and CB2 expression has since been shown to be correlated with neuroinflammation. A 2005 study showed a 200-fold up regulation of the CB2 receptors in the microglial cells in an *in vitro* model of autoimmune encephalomyelitis many of these studies are now considered questionable because further research has shown that the anti-CB2 antibodies used in these Immunohistochemical methods have non-specific binding with other proteins. However, the immunomodulatory effects of CB2 remain unchallenged. In addition, CB2 expression has more recently been associated with neurodegenerative diseases such as Huntington and Alzheimer. CB2-selective Positron Emission Tomography (PET) tracers in Alzheimer's mice have demonstrated increased expression of CB2, concomitant with the formation of amyloid-beta plaques. This suggests that CB2 PET tracers may have potential as a diagnostic tool for neuro-inflammation. In order to counteract these effects, studies are underway to develop selective CB2 ligand. This research began with testing of a series of isoxazole and triazole derivatives, which lead to discovery of a novel ligand highly selective for cannabinoid receptor 2. Compound ATJ-31 produced a concentration-dependent inhibition of specific [3H] - CP55, 940 (CB2) binding with a Ki value of 105 nM, while no binding affinity toward CB1 receptor was observed. The current study aims to design, synthesize and biologically evaluate potential CB2 receptor ligand.

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