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New agonists of the CB_2 cannabinoid receptor: Discovery of a new class of analgesic compounds

Pier Giovanni Baraldi, Giulia Saponaro, Romeo Romagnoli, Delia Preti, Stefania Baraldi, Katia Varani, Pier Andrea Borea and **Mojgan Aghazadeh Tabrizi**
Università di Ferrara, Italy

Interest in the potential medicinal use of cannabinoids grew recently with the discovery of 2 cannabinoid receptors, CB_1 and CB_2. The CB_1 receptor is abundantly expressed in the central nervous system (CNS) and is responsible for the psychotropic side effects. The CB_2 receptor is mainly found in cells of the immune system, though it may be upregulated in the CNS under pathological conditions. The main signal transduction pathway triggered is through G_i proteins, resulting in an inhibition of adenylate cylase activity and a decrease in cyclic AMP levels. Recent developments indicate that CB_2 receptor ligands have the potential to become therapeutically important. To explore this potential, it is necessary to develop compounds with high affinity for the CB_2 receptor. Within a research program to identify novel CB_2 agonists, our group designed a hybrid chemical structure that incorporated the structural features of known cannabinoid ligands. The new series of oxazinoquinolone derivatives exhibiting high affinity and selectivity for the CB_2 receptor (hCB_2 K_i=8.12 nM, hCB1 Ki>10000, selectivity index (SI)>1231). The potency of the new oxazinoquinoline-6-carboxamides was measured in functional assays, revealing that the novel series behaved as CB_2 receptor full agonists. The effect of a novel CB_2 agonist (MT178) was evaluated in different animal models of pain. In this context, very recently, we have also reported the medicinal chemistry of a series of heteroaryl-4-oxopyridine/7-oxo-pyrimidine derivative which displayed high affinity at the CB2 receptor (hCB2 K_i=11.4 nM, hCB_1 Ki=4568, SI=401). In this study, additional CB_2 ligands were synthesized by replacing the pyrazolo ring with different heterocycles that were found to be potent CB_2 receptor ligands. Moreover, it was shown that the functionality of these ligands is controlled by the nature of the heteroaryl function condensed with the pyridine ring. In 3, 5-cyclic adenosine monophosphate (cAMP) assays, they showed a dose-dependent effect in the modulation of forskolin-induced cAMP production, revealing different behaviors as full agonists, partial agonists and inverse agonists. Finally, we synthesized the structural isomers of our previously reported pyrazolo[3, 4-b]pyridines that allowed us to conduct a pharmacophore exploration and optimization effort around the heteroaryl central scaffold. The newly synthesized 7-oxo-pyrazolo[1, 5-a]pyrimidine-6-carboxamides were tested in competition binding assays toward both rat CB_1 and CB_2 receptors expressed in native tissues (rat brain or spleen) and human CB_1 and CB_2 receptors expressed in CHO cells. Affinity data (K_i, nM) were used to calculate the selectivity of newly synthesized compounds for the CB_2 receptors. All of the new compounds showed high affinity and selectivity for the CB_2 receptor in the nanomolar range. In 3, 5-cyclic adenosine monophosphate (cAMP) assays, the novel series shows stimulatory effects on forskolin-induced cAMP production acting as inverse agonists.

Biography

Pier Giovanni Baraldi received his degree in Chemistry in 1974 from the University of Ferrara, where he held a position of Lecturer in the Faculty of Pharmacy (1977-1980) and Associate Professor of Medicinal Chemistry (1980-1987). In 1987, he became full professor of Medicinal Chemistry at the University of Bologna. In 1992, he returned to the University of Ferrara as full professor of Medicinal Chemistry. His expertise in Medicinal Chemistry is recognized by the important scientific production consisting in more than 410 publications including 60 patents.

brlpgv@unife.it