NOVEL DIHYDROPYRIMIDINOISOQUINOLINONES AND PHARMACEUTICAL COMPOSITIONS THEREOF FOR THE TREATMENT OF INFLAMMATORY DISORDERS (GPR84 ANTAGONISTS)

FIELD OF THE INVENTION

[0001] The present invention relates to novel compounds that antagonize GPR84, a G-protein-coupled receptor that is involved in inflammatory conditions.

[0002] The present invention also provides methods for the production of these novel compounds, pharmaceutical compositions comprising these compounds, and methods for the prevention and/or treatment of inflammatory conditions (e.g. inflammatory bowel diseases (IBD), rheumatoid arthritis, vasculitis), lung diseases (e.g. chronic obstructive pulmonary disease (COPD) and lung interstitial diseases (e.g. idiopathic pulmonary fibrosis (IPF))), neuroinflammatory conditions, infectious diseases, autoimmune diseases, endocrine and/or metabolic diseases, and/or diseases involving impairment of immune cell functions by administering a compound of the invention.

BACKGROUND OF THE INVENTION

[0003] GPR84 was recently isolated and characterized from human B cells (Wittenberger et al., 2001, J Mol Biol, 307, 799-813) as the result of an expressed sequence tag data mining strategy, and also using a degenerate primer reverse transcriptase-polymerase chain reaction (RT-PCR) approach aimed to identify novel chemokine receptors expressed in neutrophils (Yousefi S et al. 2001 J Leukoc Biol;69, 1045–52).

[0004] GPR84 (also known as EX33) remained an orphan GPCR until the identification of medium-chain FFAs with carbon chain lengths of 9-14 as ligands for this receptor (Wang et al. (2006) J. Biol. Chem. 281:3457-64). GPR84 was described to be activated by capric acid (C10:0), undecanoic acid (C11:0) and lauric acid (C12:0) with potencies of 5 μM, 9 μM and 11 μM, respectively. Three small molecules were also described to have some GPR84 agonist activity: 3,3'-diindolylmethane (DIM) (Wang et al. (2006) J. Biol. Chem. 281:3457-64), embelin (WO 2007/027661) and 6-*n*-octylaminouracil (6-OAU) (Suzuki et al. (2013) J. Biol Chem. 288:10684-91).

[0005] GPR84 has been shown to be expressed in immune cells at least but not limited to polymorphonuclear leukocytes (PMN), neutrophils, monocytes, T cells and B cells. (Wang et al. (2006) J. Biol. Chem. 281:3457-64, Yousefi S et al. 2001 J Leukoc Biol;69, 1045–52, Venkataraman and Kuo, 2005, Immunology Letters, 101, 144-153, WO2007/027661). Higher levels of GPR84 were measured in neutrophils and eosinophils than in T-cells and B-cells. GPR84 expression was demonstrated in tissues that may play a role in the propagation of the inflammatory response such as lung, spleen, bone marrow.