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INTRINSIC ACTIVITY

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MEETING ABSTRACT

A2.5

Search for HCA2, FFAR2 and FFAR3 receptor ligands in pyranopyrimidine and hexahydroquinoline ranges

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Background: Hydroxycarboxylic acid receptor HCA2 (GPR109A, niacin receptor) and short-chain free fatty acid receptors FFAR2 (GPR43) and FFAR3 (GPR41) are G protein-coupled receptors expressed in human adipocytes, immune cells, such as macrophages, monocytes, neutrophils, and colon epithelial cells. The receptors are of interest as potential targets for treatment of various conditions and disorders related to dyslipidemia, diet-induced obesity and chronic inflammatory diseases such as arthritis, asthma, colitis and atherosclerosis [1, 2].

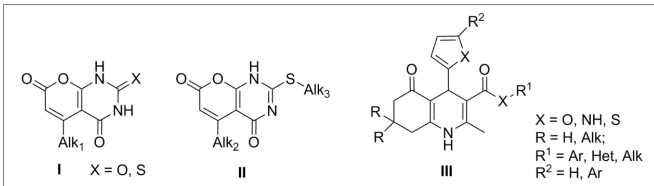
Objectives: Until now, pyranopyrimidine derivatives **I** have been studied only as niacin receptor ligands, but their *S*-alkyl derivatives **II** have been studied very little and occasionally. In turn, hexahydroquinoline derivatives have been studied only as ligands for FFAR2 and FFAR3 receptors—both agonists and antagonists.

Methods: Functional activity of synthesized compounds was assessed by modulation of forskolin-stimulated cAMP production in human Flp-In-293 cell lines that express recombinant HCA2, FFAR2 and FFAR3 receptors.

Results: In the present study we have synthesized novel representatives of compounds **I**–**III** (Fig. 1). Pyranopyrimidines of groups **I** and **II** were confirmed to be dual receptor (HCA2 and FFAR2, or HCA2 and FFAR3, respectively) ligands.

Hexahydroquinolines **III** showed specific affinity toward FFAR2 or FFAR3 receptors, but they were inactive toward the HCA2 receptor.

Data on some dual receptor ligands (Fig. 2) inhibiting forskolin-stimulated cAMP production are presented in Table 1.



I X = O, S **II** **III**

Figure 1: Derivatives of pyranopyrimidine (**I** and **II**) and hexahydroquinoline (**III**).

Compound A: **I** X = O $Alk_1 = CH_2CH_2CH_2CH_2Cl$
Compound B: **I** X = S $Alk_1 = CH_2CH_2CH_2CH_3$
Compound C: **II** $Alk_2 = CH_3$ $Alk_3 = CH_2CH{=}CHC_6H_5$
Compound D: **III** X = O R = H $R_1 = C_6H_4CH_3$-*o* $R_2 = H$

Figure 2: Dual receptor ligands.

Table 1: Inhibition of forskolin-stimulated cAMP production by some dual receptor ligands (EC_{50} or % units).

Receptors	A	B	C	D
HCA2	5.40×10^{-8} M	$3.5\cdot\times10^{-7}$ M	49%	NA
FFAR2	$3.8\ \times10^{-7}$ M	$7.4\ \times10^{-7}$ M	54%	NA
FFAR3	2.15×10^{-7} M	1.90×10^{-7} M	1.3×10^{-6} M	2.7×10^{-7} M

Conclusions: This study shows that several selective and potent FFAR2 and FFAR3 receptors agonists could be identified from a series of hexahydroquinoline derivatives.

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Keywords: HCA2 receptors – FFAR2 receptors – FFAR3 receptors – ligands

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