EXPLORING THE ORPHAN GPCR GPR18 THROUGH NOVEL SYNTHETIC CANNABIDIOL DERIVATIVES

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INTRODUCTION

GPR18 is an orphan GPCR highly expressed in lymphoid tissues and the central nervous system that regulates cellular migration, proliferation, nociociception, and immunomodulation. The endocannabinoid derivative N-Arachidonoylglycine (NAGly) has been proposed as the putative endogenous ligand. Several other cannabinoids also interact with GPR18, such as Abn-CBD and Δ^9-THC. However, very few potent synthetic GPR18 ligands have been described so far.

A new family of compounds based on the cannabidiol scaffold were designed to target GPR18. Calcium mobilization imaging studies[1] and docking studies in a *in silico* model[2] were used to evaluate the activity of compounds and their mechanism of action, respectively. Here, two of the best compounds are exemplified: **S5**, a GPR18 agonist, and **S4**, a GPR18 antagonist.

METHODS

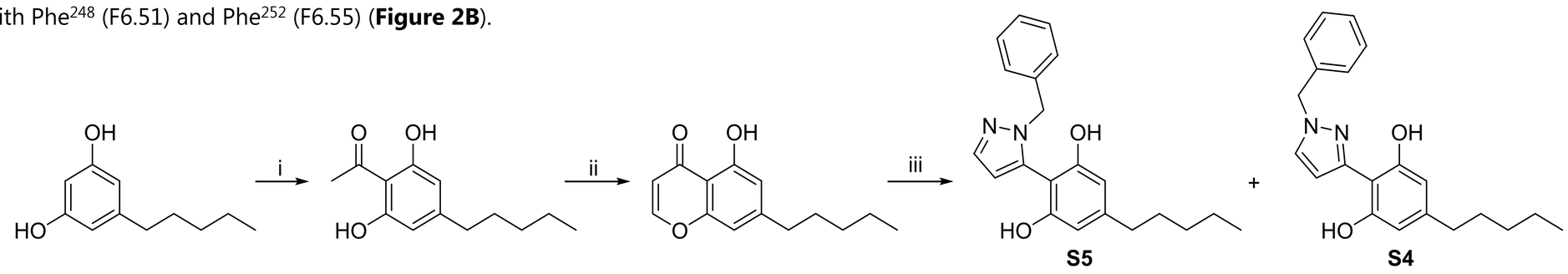
Synthesis. A new family of GPR18 ligands were synthesized following procedure exemplified in **Scheme 1**.

Calcium imaging. Intracellular calcium measurements were performed in hGPR18-CHO-K1 cells, following a procedure previously described by us [1].

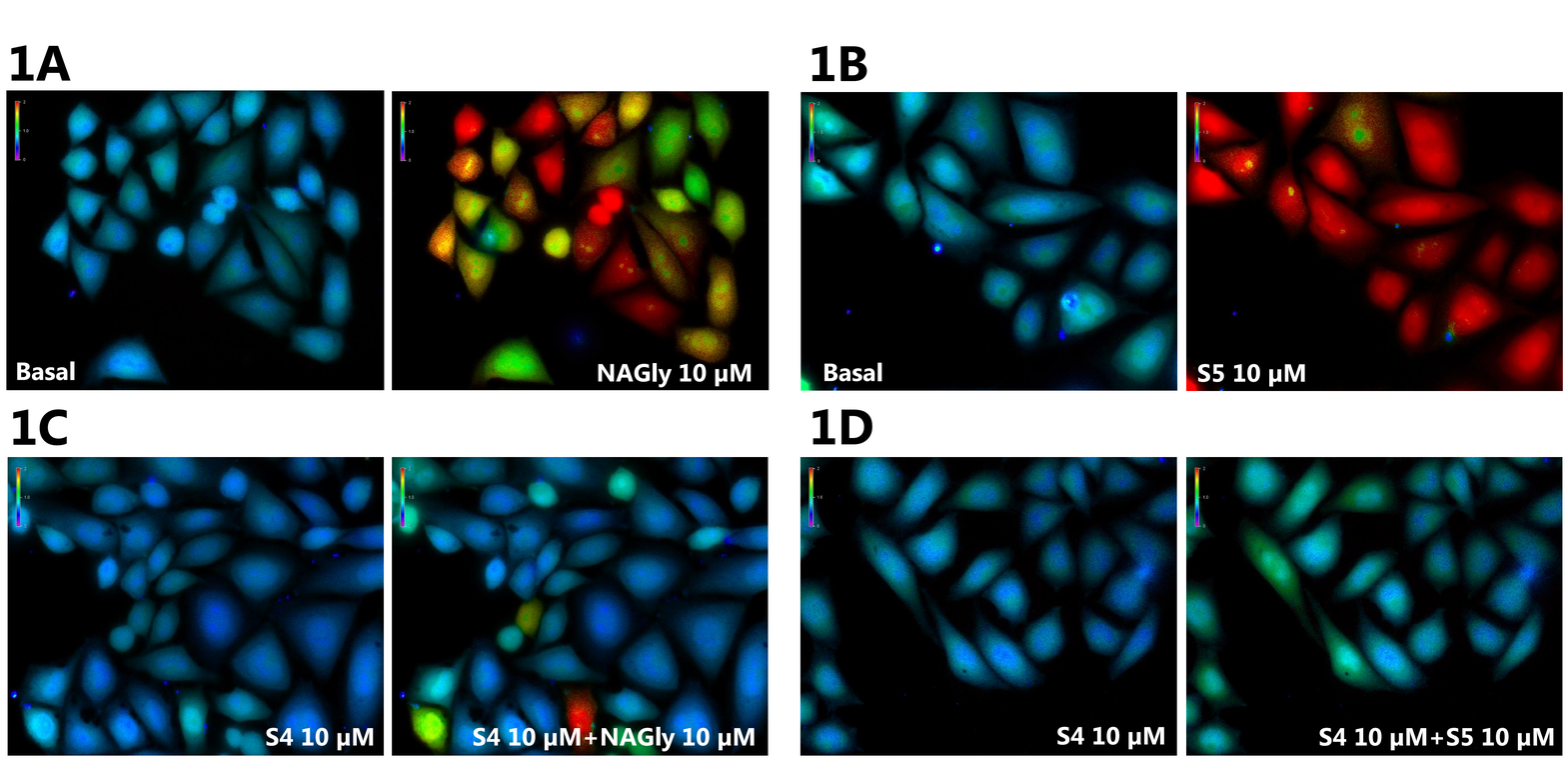
Docking. Global minimum energy conformers of each ligand were carried out with *ab initio* Hartree-Fock 6-31G* calculations with Spartan (Wave Function, Inc., Irvine CA) and manually docked into the receptor model previously published[2].

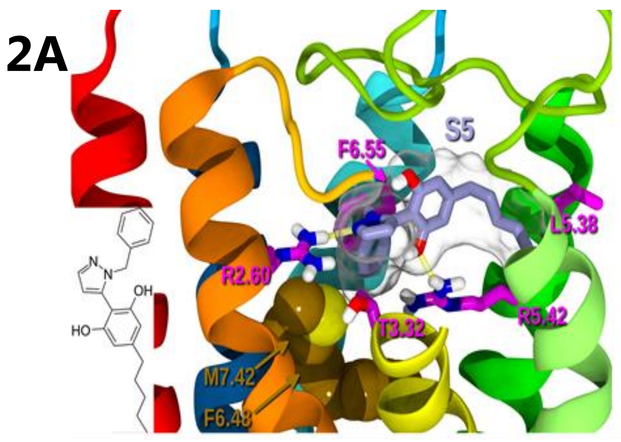
RESULTS

Among the novel structures, **S4** and **S5** showed the best results in the pharmacological evaluation (**Figure 1A-D**). Docking studies revealed that the complex of **S5** and the active state of the GPR18 is stabilized through H-bonds with Arg^{191} (R5.42) and Arg^{78} (R2.60), an aromatic H-bond with Y^{180} and aromatic stacking with Phe^{252} (F6.55) (**Figure 2A**). Meanwhile, the complex of **S4** with the inactive state of GPR18 is stabilized by H-bond with Arg^{191} (R5.42), cation-π interactions with Arg^{191} (R5.42) and Arg^{78} (R2.60) and aromatic stacking with Phe^{248} (F6.51) and Phe^{252} (F6.55) (**Figure 2B**).



Scheme 1. i) $BF_3 \cdot Et_2O$, AcOH, 80 ºC, O/N (75 %); ii) $BF_3 \cdot Et_2O$, CH_3SO_2Cl, 90 ºC, 4 h (86 %); iii) $BzNHNH_2 \cdot 2$ HCl, EtOH, reflux, 3 h, (**S5**: 85 %; **S4:** 14 %).





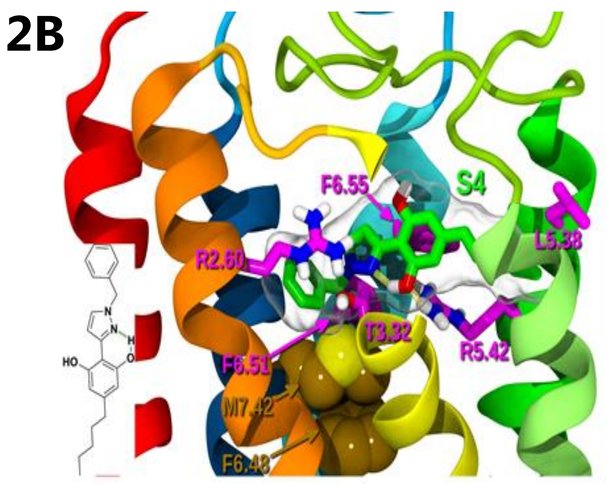


Figure 1. A,B: Representative micrograph of intracellular calcium mobilization in CHO-K1/GPR18 cells before and after exposure to NAGly 10 µM **(A),** and S5 10 µM **(B)**. **C,D:** GPR18 antagonism of S4 10 µM of NAGly 10 µM **(C),** and S5 10 µM **(D)**.

Figure 2. Docking of S5 **(in violet)** complexed with GPR18* (active state) **(A),** and S4 **(in green)** complexed with GPR18 (inactive state) **(B)**. Relevant residues are higlighted in **magenta** in each bundle.

CONCLUSIONS

GPR18 is a very promising pharmacological target. However, the lack of potent and selective ligands for this orphan GPCR has limited its potential. As shown in the present work, we have generated a new set of synthetic compounds with a cannabidiol-like scaffold and a robust activity over GPR18. Two of most relevant compounds from this family, **S4** and **S5** are here represented. Docking studies in either the active or inactive states of GPR18 revealed the main sites of interaction of the ligands. Further in vitro and in vivo studies are needed to fully determine their signaling mechanisms and their potential as novel anti-inflammatory agents.

1. Console-Bram, L.; Brailoiu, E.; Brailoiu, G. C.; Sharir, H.; Abood, M. E. *Br. J. Pharmacol.* **2014**, *171* (16), 3908–3917.
2. Sotudeh, N.; Morales, P.; Hurst, D. P.; Lynch, D. L.; Reggio, P. H. *Int. J. Mol. Sci.* **2019**, *20* (9).

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