

# In Vitro and In Silico Characterization of G-protein Coupled Receptor (GPCR) Targets of Phlorofucofuroeckol-A and Dieckol

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**Table S1.** Hydrogen bonding interaction residues between ligand-GPCRs (hA<sub>2A</sub>R, hα<sub>2C</sub>AR, and hDOP).

Compounds	Target GPCRs (PDB ID)				
	hA <sub>2A</sub> R (3eml)	Binding score (kcal/mol)	hα <sub>2C</sub> AR (6kuw)	Binding score (kcal/mol)	hδ-OPR (4ej4)
Standard agonist <sup>a</sup>	Ser277, Glu169, Asn253	−5.56	Asp131 (Salt bridge, H-bond), Ser218, Val132, Thr136, Ser214	−6.63	Asp128 (Salt bridge), Ile277, His278, Lys214
Standard antagonist <sup>b</sup>	Asn253, Glu169	−8.93	Asp131 (Salt bridge), Ser218	−11.68	Asp128 (Salt bridge, H-bond)
Dieckol	Ile80, Asp170,	−9.18	Asn111, Ser108, Cys202, Asp206, Gly203	−7.13	Asp128, Met132, Cys198
Phlorofucofuroeckol-A	His278, Ala59, Ala81, Ser67	−9.03	Val414, Asp131, Ser401, Gln413	−9.11	Leu200, Lys214, Ile304, Asp128

<sup>a</sup> 5'-N-ethylcarboxamidoadenosine (NECA) for hA<sub>2A</sub>R, epinephrine for hα<sub>2C</sub>AR, and DPI-287 for hDOP.

<sup>b</sup> ZM241385 for hA<sub>2A</sub>R, RS-79948 for hα<sub>2C</sub>AR, and naltrindole for hDOP.

**Table S2.** Hydrophobic and electrostatic interaction residues between ligand-GPCRs (hA<sub>2A</sub>R, hα<sub>2C</sub>AR, and hDOP).

Compounds	Target GPCRs (PDB ID)		
	hA <sub>2A</sub> R (3eml)	hα <sub>2C</sub> AR (6kuw)	hδ-OPR (4ej4)
Standard agonist <sup>a</sup>	Pi-Pi: Phe168 Pi-Sigma: His250 Pi-Alkyl: Leu249, Met270	Pi-Pi: Phe399 (T-shaped) Pi-Sigma: Val132 Pi-Alkyl: Cys135	Pi-Pi: Tyr308 Pi-Sigma: Val281, Tyr129 Pi-Sulfur: Met132 Pi-Alkyl: Val281, Ile277, Ile304, Val217 Alkyl: Met132, Met199, Leu125
Standard antagonist <sup>b</sup>	Pi-Pi: Phe168 Pi-Anion: Glu169 Pi-Sigma: Leu249 Pi-Sulfur: Met270 Pi-Alkyl: Met177	Pi-Sigma: Phe423, Tyr402 Pi-Sulfur: Phe398, Phe419 Pi-Alkyl: Phe423	Pi-Pi: His278 (T-shaped), Trp284 (T-shaped) Pi-Sigma: Val281 / Pi-Sulfur: Met132 Pi-Alkyl: Val281, Trp284, Trp274, Tyr308, Ile277
Dieckol	Pi-Pi: Phe168 Pi-Sigma: Leu249, Ile274 Pi-Sulfur: Met270 / Pi-Anion: Asp170 Amide-Pi stacked: Phe62 Pi-Alkyl: Leu167, Leu267, Val84, Ala63, Ile66, Val84, Met270	Pi-Pi: Phe419, Phe423, Tyr405 Pi-Alkyl: Leu204	Pi-Sigma: Ile304, Val281 Pi-Sulfur: Cys198 Pi-Anion: Asp128 / Pi-Cation: Lys108 Pi-Alkyl: Ile277, Val197, Lys108, Met132 Sulfur-O: Met132
Phlorofucofuroeckol-A	Pi-Pi: Phe168 Pi-Sigma: Val84, Leu249, Ile274 Pi-Alkyl: Ile274, Ile66, Ala63, Leu167	Pi-Pi: Phe419, Tyr405 (T-shaped) Pi-Sigma: Gly203 Pi-Anion: Asp131 Pi-Alkyl: Leu204 Pi-Lone pair: Tyr405	Pi-Pi: Tyr308 Pi-Anion: Asp128, Asp210 Pi-Lone Pair: Tyr129 Pi-Alkyl: Leu200

<sup>a</sup> 5'-N-ethylcarboxamidoadenosine (NECA) for hA<sub>2A</sub>R, epinephrine for hα<sub>2C</sub>AR, and DPI-287 for hDOP.<sup>b</sup> ZM241385 for hA<sub>2A</sub>R, RS-79948 for hα<sub>2C</sub>AR, and naltrindole for hDOP.

**Table S3.** Hydrogen, halogen, or electrostatic bonding interaction residues between ligand-GPCRs (hCB<sub>1</sub>R and hGLP-1).

Compounds	Target GPCRs			
	hCB <sub>1</sub> R	Binding score (kcal/mol)	hGLP-1	Binding score (kcal/mol)
Standard agonist <sup>a</sup>	Ser173, Ser383, Ile267	-10.50	Gln37, Lys197, Arg380 (Attractive charge)	-14.10
Standard antagonist <sup>b</sup>	Ser173, Ser383, Ser173 (F), Phe189 (F), Lys192 (F)	-9.34	Thr355, Ser352, Asn406	-10.06
Dieckol	ND	ND	Ser352, Ile328, Leu354	-5.46
Phlorofucofuroeckol-A	Ser173, His178, Met363	-6.40	Ile328, Thr355, Val405, Ser352	-6.73

<sup>a</sup> CP 55940 (ligand for 6kqi) for hCB<sub>1</sub>R and PF-06882961 (ligand for 6x1a) for hGLP-1.

<sup>b</sup> Taranabant (ligand for 5u09) for hCB<sub>1</sub>R, and NNC0640 (ligand for 5vex) for hGLP-1.

ND Not determined.

**Table S4.** Hydrophobic interaction residues between ligand-GPCRs (hCB<sub>1</sub>R and hGLP-1).

Compounds	Target GPCRs	
	hCB <sub>1</sub> R	hGLP-1
Standard agonist <sup>a</sup>	Pi-Pi: Phe170 (T-shaped), Phe268 (T-shaped) Pi-Alkyl: Phe170, Phe174, Phe177, Tyr275, Trp279, Trp356 Alkyl: Leu276, Val196, Leu359	Pi-Pi: Trp33, Phe230 (T-shaped) Pi-Sigma/Alkyl: Leu217, Trp203, Phe230, Phe381, Lys197, Leu32, Val36 Alkyl: Cys296
Standard antagonist <sup>b</sup>	Pi-Pi: Phe170, Phe268, Trp279 (T-shaped) Pi-Sigma/Sulfur/Alkyl: Thr197, Cys386, Trp279, Phe174, His178, Phe189, Phe268, Phe379, Val196, Leu193, Met363 Alkyl: Ile267, Lys192, Leu193, Leu276, Met363	Pi-Sigma/Alkyl: Arg348, Thr355, Leu354, Lys351, Val405
Dieckol	ND	Pi-Cation: Lys351 Pi-Sigma: Ile328 Pi-Alkyl: Ile328, Lys351, Val405, Arg348, Leu354, Val331,
Phlorofucofuroeckol-A	Pi-Pi: Phe177, Trp279 (T-shaped), Phe268 (T-shaped) Pi-Alkyl: Val196, Leu193, Met363	Pi-Cation: Lys351 Pi-Sigma: Leu354 Pi-Alkyl: Leu354, Lys351, Ile328, Val331, Ala350, Lys351, Val405

<sup>a</sup> CP 55940 (ligand for 6kqi) for hCB<sub>1</sub>R and PF-06882961 (ligand for 6x1a) for hGLP-1.

<sup>b</sup> Taranabant (ligand for 5u09) for hCB<sub>1</sub>R, and NNC0640 (ligand for 5vex) for hGLP-1.

ND Not determined.

**Table S5.** Hydrogen bonding interaction residues between ligand-GPCRs (hV<sub>1A</sub>R and h5-HT<sub>1A</sub>R).

Compounds	Target GPCRs			
	hV <sub>1A</sub> R	Binding score (kcal/mol)	h5-HT <sub>1A</sub> R	Binding score (kcal/mol)
Standard agonist <sup>a</sup>	Asp202 (Salt-bridge), Glu54, Asp112, Ile330	−9.14	Asp116 (Salt bridge), Thr200, Thr121	−6.77
Standard antagonist <sup>b</sup>	Gln131, Gln108, Lys128	−8.98	Asp116 (Salt bridge), Asn386	−10.31
Dieckol	Gln131, Ala334, Asp112	−8.33	Asp116, Thr200, Ser190, Asn386, Tyr96	−10.38
Phlorofucofuroeckol-A	Ser338, Cys203, Met135, Glu54, Ala101	−9.34	Thr188, Glu372, Tyr96, Asn386	−7.45

<sup>a</sup> AVP for hV<sub>1A</sub>R and serotonin for h5-HT<sub>1A</sub>R.<sup>b</sup> SR49059 for hV<sub>1A</sub>R and WAY 100635 for h5-HT<sub>1A</sub>R.

**Table S6.** Hydrophobic and electrostatic interaction residues between ligand-GPCRs (hV<sub>1A</sub>R and h5-HT<sub>1A</sub>R).

Compounds	Target GPCRs	
	hV <sub>1A</sub> R	h5-HT <sub>1A</sub> R
Standard agonist <sup>a</sup>	Pi-Cation: Trp204 Pi-Alkyl: Ala101, Ala334, Val132, Met135 Alkyl: Ile330	Pi-Pi: Phe362 (T-shaped) Pi-Cation: Phe361 Pi-Sulfur: Cys120 Pi-Alkyl: Val117, Ala203
Standard antagonist <sup>b</sup>	Pi-Pi: Trp204 (T-shaped), Phe307 (T-shaped) Pi-Sigma: Phe307 Pi-Alkyl: Trp204, Ala334, Ala205 Alkyl: Val132, Met135	Pi-Pi: Phe362 (T-shaped) Pi-Sulfur: Cys120 Pi-Lone Pair: Asn386 Pi-Alkyl: Phe112, Ala203 Alkyl: Ile113
Dieckol	Pi-Pi: Trp204 Pi-Cation: Lys128 Pi-Sulfur: Met135 Pi-Alkyl: Ala101, Ala334, Lys128, Val132	Pi-Sigma: Thr188, Ile19, Thr196 Pi-Alkyl: Ile189, Val117
Phlorofucofuroeckol-A	Pi-Pi: Phe189 (T-shaped), Phe307 (T-shaped) Pi-cation: Lys128 Pi-Sulfur: Met220 Pi-Alkyl: Val132, Val100, Ala101, Met135, Ala334, Ala205, Val105	Pi-Pi: Phe361 Pi-Sigma: Thr188 Pi-Alkyl: Lys191 Pi-Anion: Asp116 Pi-Cation: Lys191

<sup>a</sup> AVP for hV<sub>1A</sub>R and serotonin for h5-HT<sub>1A</sub>R.<sup>b</sup> SR49059 for hV<sub>1A</sub>R and WAY 100635 for h5-HT<sub>1A</sub>R.