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Virtual Screening for Potential New Chemotherapeutic Agents for the GPR119 Receptor, a Target for Type II Diabetes

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VIRTUAL SCREENING FOR POTENTIAL NEW CHEMOTHERAPEUTIC AGENTS FOR THE GPR119 RECEPTOR, A TARGET FOR TYPE II DIABETES

A Thesis

by

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ABSTRACT

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Three frames from a molecular dynamics simulation run of a GPR119 receptor homology model were used for this study. The homology model was validated by virtually screening 76 known GPR119 receptor. 85% of these agonists bound to the receptor. Following the validation, 21,000 molecules were selected for the virtual screening study. 862 ligands came from the GPCR Selleckchem/Prestwick library, 42 compounds from the Prestwick Phytochemical library, 20,000 compounds from the ZINC library, plus four molecules from the literature. All ligands were built, geometry-optimized, and docked in the GPR119 models using a protocol combining High Throughput Virtual Screening, Standard Precision, and Extra Precision Glide docking. 2,100 compounds fit inside the GPR119 model binding pocket. The agonists AR231453, AR437735, and oleoyl serinol as well as compound SRT1720 were tested for activation of GPR119 using an ELISA cAMP assay. The results agreed with values in the literature and with the computational results.

DEDICATION

I dedicate this work to the man I love, my always supportive and loving husband, Dennis K. Kim, this journey would not have been possible without your encouragement and unconditional love, thank you for always believing in me even when I doubted myself.

I also want to dedicate this thesis to my parents and my sisters who cheered for me since day one, thank you guys for being my pillars and my balance. Finally, I want to thank God for not leaving my side even in my darkest hours, for all honor and glory to him.

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I want to give special thanks to my friend and lab peer Matthew D. Rosales, you have been an incredible mentor and friend, thank you for all the help in the computational aspects of the project and in the wet lab techniques. Without you, I would not have completed my project in time, thank you for always being willing to come and help no matter the time of the day; you are awesome.

Lastly, I would like to thank the rest of the lab members, Naila Bravo (my sister) thank you for being there for me and making sure my mental and physical health was always in check, I love you dearly. Thank you, Ashley, Solomon, and Jesus for putting up with me, even when I was super annoying or cranky due to the lack of caffeine.

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CHAPTER I

INTRODUCTION

G-protein coupled receptors (GPCRs) are a subtype of proteins that are found in great numbers in the cell membrane of eukaryotic cells[1]. Conformational changes in the GPCR receptor caused by ligands binding, induce activation or deactivation of the receptor, which in turn allows and/or restricts the transduction of information to the inside of the cell for it to respond accordingly to the messages (secretion of hormones, regulation signals, etc). Their role is an essential part for the sustaining of life especially for humans; therefore, the study of the function of these types of receptors is key to discover how human physiology works, and how to treat targeted-receptor diseases that afflict people[2].

GPCRs are transmembrane receptors with one end exposed to the extracellular matrix and the other to the cytosol of the cell[3-4]. The transmembrane helices are connected by loops that are flexible and move to aid the binding of a molecule into the receptor pocket or to obstruct the entrance of the binding pocket making the ligand stay inside the receptor for added stability[4]. **Figure 1** shows a simple representation of the receptor; the nitrogen terminal on the extracellular part of the cell is followed by seven transmembrane α-helices (TMHs 1-7) that loop in and out of the cell membrane (extracellular loops ECL 1, ECL 2, ECL 3 and intracellular loops ICL 1, ICL 2 and ICL 3) ending by the carboxyl terminus in the inside of the cell[5].

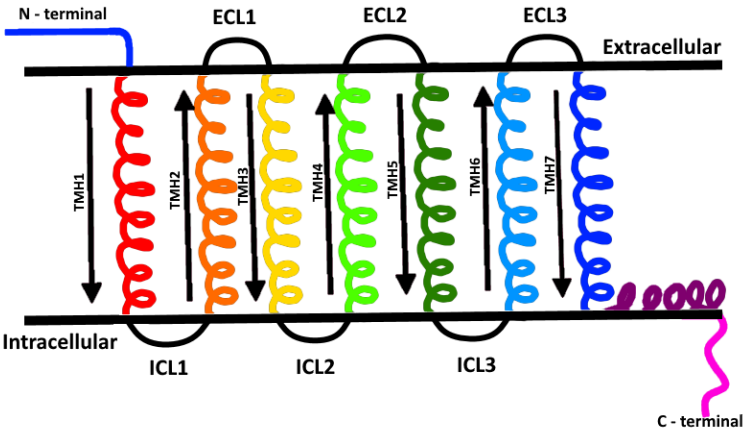

Figure 1. General structure of a G protein-coupled receptor.

Literature reports that more than a thousand GPCRs have been identified in the vertebrate genome, which tend to be highly specific towards their possible activators[6-7]; this specificity allows for ligands to activate a targeted receptor without affecting the rest. The process of activation by a ligand occurs when the molecule in the bloodstream interacts with the extracellular part of the receptor and then enters the hydrophobic binding pocket. Once inside, the ligand causes a series of rearrangements of the binding pocket that lead to changes in the intracellular end of the receptor where the heterotrimeric G protein binds and gets activated. Upon activation the G protein decouples from the receptor and the Gα subunit dissociates from the Gβ and Gγ subunits and it exchanges the GDP molecule with a GTP[6, 8]. Once the Gα subunit is done with the communication process, GTPase activity converts GTP back into a GDP, and it rejoins the receptor and reforms the G-protein by binding with a Gβ and a Gγ subunit.[3-4]

GPCRs ligands can be separated into three types depending on their effect on the receptor. If a ligand is able to activate the receptor and increase its activity, it is considered an agonist. Within the spectrum of agonists there are full agonists and partial agonists. A molecule is called a full agonist if it increases the receptor activity close to 100%, otherwise the molecule

is categorized as a partial agonist. An antagonist is a molecule that binds to the receptor and it prevents an agonist from binding and activating it. A ligand considered as an antagonist does not alter the receptor activity; therefore, it does not affect the basal activity of the receptor. Basal activity, also referred as constitutive activity, is the signaling of a receptor in the absence of an agonist. The last class, the inverse agonists, not only prevent increased activity by blocking agonists, but also decrease basal activity levels[4, 9-10]. All these examples can be seen in a graphical representation in **Figure 2**.

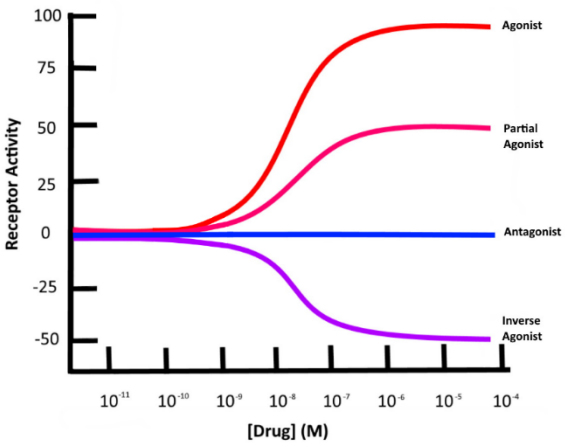

Figure 2. GPCR receptor activity based on drug interaction.

1.1 G Protein-Coupled Receptor GPR119

The GPR119 receptor, a type A GPCR, is also known as glucose-dependent insulinotropic receptor[11-13]. The GPR119 receptor is one of the most common transmembrane receptors found in the gastrointestinal L-cells and K-cells as well as in the pancreatic β-cells of mammalian organisms[10]. Upon activation, the levels of cyclic adenosine monophosphate (cAMP) in the cell rise, which can cause L-cells and K-cells to secrete hormones like

glucagonlike peptide 1 (GLP1), glucose dependent insulinotropic peptide (GIP) and peptide YY (PYY). Similarly, activation of the GPR119 receptor in the pancreatic β-cells promotes the release of insulin into the bloodstream[14]. The ability of the GPR119 receptor to influence the secretion of insulin makes it an attractive target for the treatment of diabetes mellitus type 2 since people with this condition struggle to keep glucose homeostasis in their body.

In-vivo experiments and *in-vitro* experiments such as ELISA cAMP colorimetric analysis, immunofluorescence northern hybridization blot, liquid chromatography-mass spectrometry (LC-MS) among others[11-12, 15] can provide information about the activation of the GPR119 receptor. However, these studies do not provide insight into conformational response of the receptor based on the ligand used, nor information of the chemical interactions happening inside the binding pocket [16-17]. The advances in computational methods have opened the door to visualization of molecules and modeling of their behavior under controlled environments.

There is not yet an x-ray crystal structure for the GPR119 receptor[10, 18]. Research groups and pharmaceutical companies therefore have had to construct their own 3-dimensional homology models to study how molecules bind and interact with the binding pocket of the GPR119 receptor. Depending on how the homology model was developed (template used, conformation of helices, etc), there could be differences in how a ligand can fit in the binding pocket. Therefore, the homology model needs to be validated. If the *in vitro* results cannot be explained by using the homology model, then that model would have to be reworded until similar results are obtained. **Figure 3** shows a cartoon representation of the in-house GPR119 receptor model used for this study.

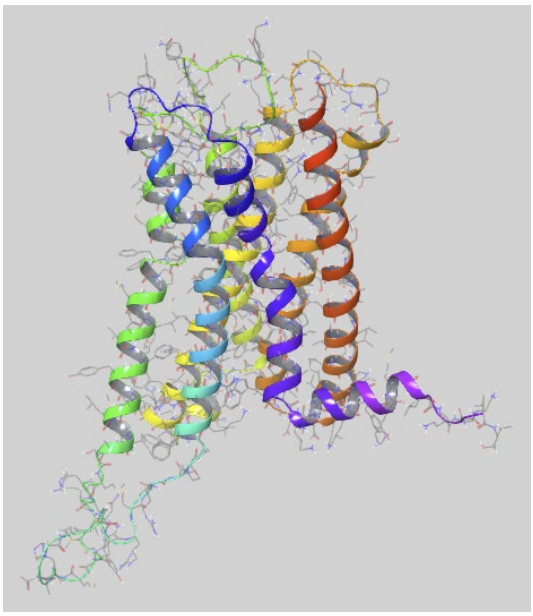

Figure 3. 3D in-house homology model of the GPR119 receptor.

1.2 G Protein-Coupled Receptor Ligands and Libraries

A compound library is a collection of chemical substances. These chemical substances are either theoretical molecules or molecules that have been synthesized, which can be used in diverse types of research[19]. These databases provide from thousands to billions of molecules which could be pre-screened for different purposes such as in the medical field to analyze how ligands fit a targeted receptor, in industry to give information about light activated chemicals, or in pharmaceutical industry to discover natural organic compounds for plant-based drug applications[19-20].

Chemical libraries are usually subsets of larger databases of compounds that have been selected based on properties such as similar molecular structures or comparable chemical properties. The information provided about the molecules by a chemical library varies, basic libraries include information such as compound name (UPAC or other names by which the

molecules are also known), chemical structure, and sometimes chirality. Advanced libraries like those provided by chemical companies often also include information about solubility, receptor targets and a small summary about their properties.

The GPCR chemical libraries contain a great number of molecules that bind to the orthosteric site of different known G coupled receptors; however, not all ligands fit the same receptors. The ligands for the GPR119 receptor, the receptor of interest for this study, seem to have some general characteristics which were used as criteria in the selection of ligands that may fit in the binding pocket and possibly activate the receptor. These agonists are typically long with slender profile and are composed of rings (aromatic and unsaturated rings) and often have a polar group in one end [5, 9, 21-22]. However, even if the criteria for the selection of ligands are met, there is no guarantee that a ligand that fits into the binding pocket would be able to activate the receptor. Ultimately, the ligands identified from the chemical libraries will need to be tested experimentally to confirm if they bind and activate the receptor.

1.3 High Throughput Virtual Screening, Standard Precision and Extra Precision Screening

In order to ensure the fit of ligands into GPCRs, a molecular mechanics (MM) docking technique called high throughput virtual screening is done to eliminate those molecules that do not fulfil the criteria of the specific receptor to be studied[23]. High throughput virtual screening (HTVS) eliminates molecules that are too polar, bulky, wrongly oriented or chiral in some cases. High throughput analysis is a compatibility assay for data processing that screens thousands of molecules in parallel and scores them to minimize the number of intermediate confirmations[24]. This type of screening to be the first step in finding compounds that will eventually produce lead compounds for further studies[16-17, 19, 25].

Standard precision screening (SP) uses the same docking algorithm as the HTVS method but does a more thorough torsional refinement and sampling eliminating more compounds that do not fit the binding pocket.

Extra precision screening (XP) is much more thorough method of screening compared to HTVS and SP analysis. Extra precision performs more extensive sampling that only allow a small number of ligands to pass to the last steps of the analysis. XP screening docks ligands flexibly and uses an anchor-and-grow procedure that considers the position of the molecules as well as how they fit into the receptor's binding pocket[26-28]. The XP screening method penalizes and disregards double positives caused by the different ways a ligand fit in the binding pocket [28].

1.4 Drug Design and Ligands

Drug design requires an enormous amount of work and resources: select and test vast numbers of compounds, identify lead compounds, then design derivatives of those compounds, synthesize them, purify them, verify their structure of using spectroscopic methods such as nuclear magnetic resonance (NMR), test them *in vitro* and *in vivo* experiments to confirm or disprove the suitability of that compound to be moved further in the drug development process. In short, for pharmaceutical companies and independent research groups, drug design is an intense and expensive process. Molecular modeling and calculations such as Glide HTVS, SP and XP screening can expedite the drug discovery process and save companies and research groups' invaluable time and money.

1.5 *In Vitro* Studies and the Role of cAMP in Assessing GPR119 Receptor Activity

In vitro experiments employ cultured cells to study the effect of external stimuli such as chemical compounds, on cell signaling pathways. The ligand-induced cAMP production assay, a

secondary messenger assay, was selected for the study of the GPR119 receptor activation since it has been reported that upon activation of the receptor, cAMP accumulates inside the cell, making it a perfect quantitative analysis assay to understand the effect of varying drug concentrations in the cells[4, 12, 29].

The effect of compounds on a receptor cannot be precisely determined using only computational methods. *In vitro* experiments can be employed to confirm or disprove the proposed mechanism of action of these compounds. Certain compounds that might serve as an agonist for a target receptor might behave as an antagonist for others[30-31]. In vitro experiments can help elucidate the mechanism of action of different compounds and the signaling pathways activated by binding to different receptors in the cells to avoid undesired effects by compounds that are drug candidates.

CHAPTER II

LITERATURE REVIEW

2.1 Background of GPR119 Receptor

The GPR119 receptor was discovered in the early 2000s and was identified as a rhodopsin-like, class A GPCR [13]. Since then, the activation of this receptor has been studied through *in vivo* and *in vitro* experiments as well as thought computational methods. In 2009, Brubaker *et al.* monitored GLP-1 secretion after GPR119 activation with the endogenous ligand oleoylethanolamide (OEA) in mGLUtag cells and *in vivo* studies treating euglycemic rats. OEA is the endogenous ligand that naturally activates the GPR119 receptor in the body. The *in vitro* results showed a GLP-1 increase of 2.1 ± 0.2–fold from basal levels at 10 μmol/L, while the intraluminal *in vivo* results yielded 1.5 ± 0.2 increased fold at 20 nmol/rat that lasted for the duration of the experiment (60 minutes) [32].

In 2014, Engelstoft *et al*. applied computational modeling to complement *in vitro* experiments in order to explain the mechanics behind the activation of the receptor. OEA and the synthetic compound AR231453 were used as agonists for his studies. The *in vitro* experiments were performed on COS7 cells (monkey kidney cells) using wild type and mutated (FLAG tagged) cells. The computational studies were performed using their in-house homology model of the GPR119 receptor that was created using a hybrid method. They combined the method proposed by Mobarec *et al.* 2009 that used multiple structures of other type A GPCRs as templates for homology model development[33]; and Worth *et al*., 2011 that

used a fragment-based approach to create homology models of GPCRs from readily available type A GPCR crystal structures[34].

The computational results of Engelstoft *et al*., indicated that TMHs III,V, VI and VII (TMSs 3, 5, 6 and 7), as well as ECL 2 are of great importance for ligand interaction and signaling since these transmembrane helices encompass the binding pocket and give an insight to the interaction of the agonist with the amino acids of the toggle switch ($W^{6.48}$ and $F^{3.36}$) located in the center of the transmembrane region of the receptor. The mutations made in the ECL 2 also provided information for its role in keeping ligands inside the binding pocket. The *in vitro* analysis showed that the EC_{50} of OEA was 250 nM and that of AR231453 was 1.9 nM, proving that both compounds are strong agonists. Even though the wet lab experiments were in agreement with the results of the computations (OEA and AR231453 fit in the binding pocket and interact with the amino acids that shown to be important in the *in vitro* experiments), there was still uncertainty regarding the mode of binding of the agonists in the receptor pocket (43 possible different confirmations were found after performing docking calculations 1000 times). It was concluded that more computational studies applying MD simulations are necessary to fully understand the conformational interactions of the receptor with the ligands [4].

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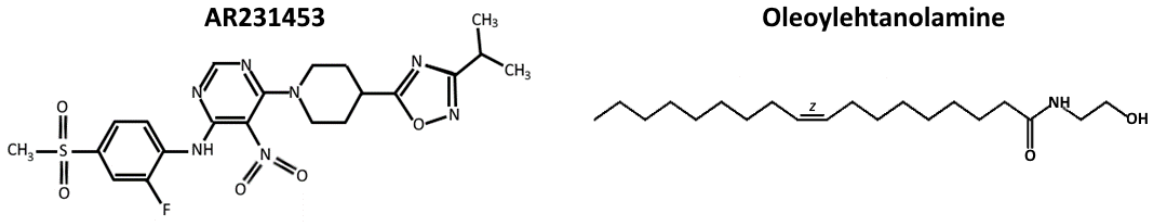

Figure 4. Chemical structures of the agonists AR231453 and OEA.

2.2 Ligand Interactions with the GPR119 Receptor

Ligands approach receptors extracellularly, bind to the receptor binding pocket causing it to activate signaling pathways thus transmitting information to the cell. The GPR119 receptor increases the production of cAMP upon activation if a full agonist or partial agonist interacts with the binding pocket. In 2015, Ritter *et al.* provided a list of full agonists from leading pharmaceutical companies such as Arena, AztraZeneca, Pfizer, Prosidion, Merck and Astellas. The EC_{50}s of leading agonist varied from Arena's AR231453 at 1.355 nM to Astellas's AS1269574 at 2.6 μM. The higher the concentration of a compound the receptor needs to have the desired biological effect, the least likely it is that the company will pursue if for drug development[21].

An inverse agonist shuts down the constitutive activity of the receptor by stabilizing its inactive confirmation. Engelstoft *et al.* in 2014 reported that compound TM43718 is an inverse agonist of the GPR119 receptor in a dose-dependent manner where its IC_{50} was determined to be1.5 μM[4]. Similarly, Norn *et al.* in 2015, claimed that AR437948, a third generation ligand derived from of AR231453, presented inverse agonistic behavior. The IC_{50} of that inverse agonist was not provided[10]. Antagonists on the other hand, are molecules that block agonist-induced activity without affecting the basal activity of the receptor. Syed *et al.* in 2012, performed cAMP colorimetric analysis and western blot experiments where he concluded that oleoyl serotonin (0.7 μM), SB-366791 (10 μM) and arvanil (50 μM) antagonized the AR231453-induced cAMP activity of the GPR119 receptor via competitive inhibition[30].

2.3 Database Screening

In the past, pharmaceutical companies would search for new drugs by performing high throughput screening of thousands of compounds using biological assays and other quantitative and qualitative methods of analysis. Once computational methods were developed, companies would first perform high throughput virtual screening of libraries of compounds to remove compounds that may not fit in the binding pocket and thus reduce the number of compounds to be tested physically and make the drug discovery process faster and more cost effective. In 2004, Shoichet discussed the advantages and disadvantages of using virtual analysis of molecules for their interactions with cellular receptors. He mentioned that the use of molecular modeling has proven beneficial for the screening of large databases since it relies on ligand receptor interactions that are governed by thermodynamic and quantum mechanical forces that permit the calculation of the energies of the ligand-receptor complexes. The downside of this type of analysis however was the introduction of compounds that are false negatives and false positives and would not be able to be identified until the compounds were tested experimentally[35].

Frienser *et al*. reported that before the introduction of Glide docking (grid-based ligand docking with energetics), the most commonly used virtual screening platforms in the 2000s were GOLD, FlexX and DOCK. While docking software prior to Glide treated the ligands as rigid when binding them into the PBD receptor, Glide considered the orientational, positional and conformational space of the ligands and their interaction with the binding pocket which doubled the docking accuracy from the former models[17]. Glide also allowed the refinement of compound analysis by introducing algorithms such as standard precision (SP), high throughput virtual screening (HTVS) and extra precision virtual screening (XP).

In 2006, Halgren *et al.* used Glide employing the SP algorithm to test 15,000 ligands from 15 different libraries. The ligands were energy-minimized and geometry-optimized using the Merc Molecular force field 94 (MMFF94) and were subsequently docked to nine different receptor types. From this analysis it was concluded that 70% of the enriched molecules pre-selected to bind to the receptors actually matched the experimental data and even though the results were promising, more work and understanding about ligand flexibility was required for a conclusive analysis[27].

High throughput virtual screening has a similar scoring algorithm as SP; however, its use has been reported to give more detailed information about conformational analysis by providing extra details about docking orientations and reducing the toughness of the final torsional refinement and sampling. In a paper published in 2010 by Sciabola *et al.* it was mentioned that the use of GRID-MIFs (molecular interaction fields) and the FLAP (fingerprints for ligands and proteins) method in HTVS studies facilitated the ability to find unique ligands for target-receptor validation and for hit/lead identification (ligand-protein relationships) by using ligands that were structurally similar to drugs which have been previously reported to work in *in silico* or *in vitro* experiments.

The use of XP docking was first reported in 2006 by Friesner *et al.* as a novel addition to Glide 4.0 which incorporated new quantification terms like desolvation energy, hydrophobic enclosures, neutral- neutral and charged-charged interaction between hydrogen bonds , and also very importantly it excluded false positives [26]. Triphati *et al.* (2013) used Glide XP docking to study the effect of 27 small 3,5-diaminoindazoles, imidazo(1,2-b)pyridazines, and triazolo(1,5-a)pyridazine derivatives for the inhibition of cyclin-dependent kinases (CDK2). The calculation results provided three possible CDK2 inhibitors from the initial 27 kinds and selected several

main binding postures based on their high-scoring binding affinity. The results were further corroborated by the use of MM/GBSA rescoring numbers that were consistent with literature[28].

CHAPTER III

EXPERIMENTAL METHODS

3.1 In-House GPR119 Receptor Homology Model Validation

The in-house GPR119 receptor homology model was validated through the docking of 76 GPR119 agonist ligands reported by Ritter *et al.* (2015). The ligands were constructed using Schrödinger Maestro simulation software considering the chirality and charge (if any) reported in the paper [21]. The minimization was performed using force field OPLS3e and restraining bonds to metals around the input geometry. The calculation was carried on in no solvent using a distant dependent dielectric of 2(hydrophobic environment) and using charges from the force field. Extended cutoffs were used (8 Å van der Waals cutoff, 20 Å electrostatic cutoff and 4 Å hydrogen bond cutoff) and no constrains were applied on the ligand. The Polac-Ribier Conjugate Gradient (PRCG) minimization method was used. The maximum number of iterations was set to 5000, and the calculation convergence method was set gradient with a threshold of 0.05. The library of 76 agonists were further subjected to a LigPrep analysis that creates all the different chemical and structural possibilities a ligand can sample, before performing the virtual screening.

The GPR119 receptor homology model was extracted from four frames (frames 150, 200, 250, 300 and 350) of a 7-ns NAMD molecular dynamics (MD) simulation. These frames correspond to different conformations of the receptor, frame 150 where the transmembrane region is more compact to frame 350 where the receptor transmembrane region is more relaxed and the binding pocket is hydrate. The docking/virtual screening calculation was performed for

each one of the receptor conformations corresponding to the four frames. The virtual screening parameters were the following: pH was set to 7.4 ± 0.02 using Epik (to simulate the pH in the human body) and the high energy ionization/tautomer states were removed retaining up to four unspecified stereocenters and generate only one low energy conformer per ligand. The docking grid encompassing the receptor binding pocket was generated by Glide using the center of mass of the amino acids Phe157 (ECL2), Trp6.48^{238}, Arg7.36^{262}, Trp7.39^{265}, Cys155 (ECL2) and Arg3.28^{81} that line the pocket. A combination of HTVS, SP, and XP docking algorithms was used keeping compounds with a Glide score of -3 kcal/mol and above.

3.2 Library Preparations and Computational Screening

Four databases were selected for the purpose of this study. These databases were Prestwick Phytochemicals, SelleckChem GPCRs, Prestwick GPCR library and Zinc Naturals (ZINC15) library. The Prestwick Phytochemicals library contained 320 compounds from which 41 were manually selected for the docking experiments. Charged compounds and compounds with a MW<200 g/mol were excluded. The SelleckChem GPCRs (738 compounds) and Prestwick GPCR library (265 compounds) totaling 1003 compounds were used as well. However, upon inspection it was concluded that 141 compounds repeated between these libraries and were excluded which reduced the number of testing ligands to 862. The Zinc Naturals library contains 120 million compounds, but only the first 20,000 were selected for docking[36].

The approximately 21,000 compounds were visually examined for missing hydrogens which were added; they were desalted and then they were energy minimized using the parameters covered in section 3.1. Once the ligands were prepared, they were used as input for docking on the GPR119 receptor homology model conformers from frames 150, 200, and 250.

The docking parameters used were those mentioned in section 3.1. The docking calculations were done in two way: a) the automated sequential virtual screening protocol that takes the results of HTVS step and uses them as input for the SP step, and the SP results are used as input for the XP step and b) docking all the ligands using each one of the three docking methods separately (HTVS, SP and XP).

In addition to the libraries virtual screening calculations, four more molecules were built and docked in the GPR119 receptor because we had a certain amount of each in the lab and we can test them using a cAMP colorimetric assay. Of the four molecules, oleoyl serinol (OS), SRT1720, and AR231453 were purchased from Sigma-Aldrich and AR437735 was synthesized by a collaborator. AR231453, AR437735 and oleoyl serinol are known GPR119 receptor agonists whereas SRT1720 has not been tested for activity against the GPR119 receptor.

3.3 Maintaining of Eukaryotic HEK293 Cells

Human embryonic kidney cells (HEK293) were used to measure activation of the GPR119 receptor. The HEK293 cells were allowed to grow in 10 cm plates containing Dulbecco's Modified Eagle Medium (DMEM) and 10% fetal bovine serum (FBS), and 1% penicillin/streptomycin and 1% antibiotic-antimitotic additives were added in order to prevent bacterial and fungal contamination. Subsequently, the cells were placed in an incubator (5% CO_2, humidified at 37°C) and left to grow for 3-4 days or until they reached a 90% confidence. Once this point was reached they were ready to be passaged to a new plate.

The passaging consisted of carefully aspirating the medium from the plate while avoiding disruption of the cells attached to the plate. Then 5 mL of trypsin solution (0.05% trypsin, 0.5m MEDTA) to lift the cells from the plate. Using a 5 mL pipette the trypsin was pipetted up and

down about 12 times until the cell agglomerations were broken up and well dispersed in the solution. From this mixture 1-1.2 mL was added to a new plate that contained 10 mL of DMEM with the respective additives 10% FBS, 1% pen/strep, 1% anti-anti. The plate was then rocked front and back as well as side to side to assure a good dispersion of the cells in the new medium.

3.4 Preparing HEK293 Cells for Transfection

The medium was aspirated from the plate and 5 mL of trypsin was added to homogeneously suspend the cells. The mixture of trypsin and cells was then transferred to a 50 mL centrifuge tube. To prevent the further digestion of the HEK293 cells by the trypsin, 7.5 mL of DMEM containing 10% FBS was added to the tube. The 50 mL tube was centrifuged at 1000 RPM at 25 °C for 5 minutes to form a cell pellet at the bottom of the tube. After centrifugation the medium was aspirated from the tube and the cells were resuspended in 10 ml of DMEM (10% FBS).

A 20 µL micropipette was used to acquire 15 µL of the resuspended cells and dispense it to a hemacytometer. The hemacytometer was used to estimate the concentration of the cells in the centrifuge tube. The cells were counted from 4 base quadrants each containing 4 smaller ones within. The cells directly on top of the divisor lines between the major 4 quadrants were not considered. Once the total cells were accounted they were averaged to get the number of cells in 100 nL per quadrant. The averaged number was then multiplied by 10,000 to convert the the nanoliters to cells per milliliter. The resulting number was then multiplied by the total milliliters in the 50 mL centrifuge tube and divided by 250,000 (amount of cells desired per mL). This

provided the amount of DMEM required to deliver the desired amount of cells per mL of medium (dilution formula $M_1V_1=M_2V_2$).

Once the new volume of DMEM was added to the 50 mL test tube, often to an approximate volume of ~42 mL, 2 mL of the homogeneously mixed cells were pipetted into each well of three 6-well plates for a final concentration of 500,000 cells/well. The completed 6-well plates were rocked gently to evenly disperse the cells around the wells and then they were placed in the incubator (5% CO_2, humidified at 37°C) and allowed them to grow for 2 days.

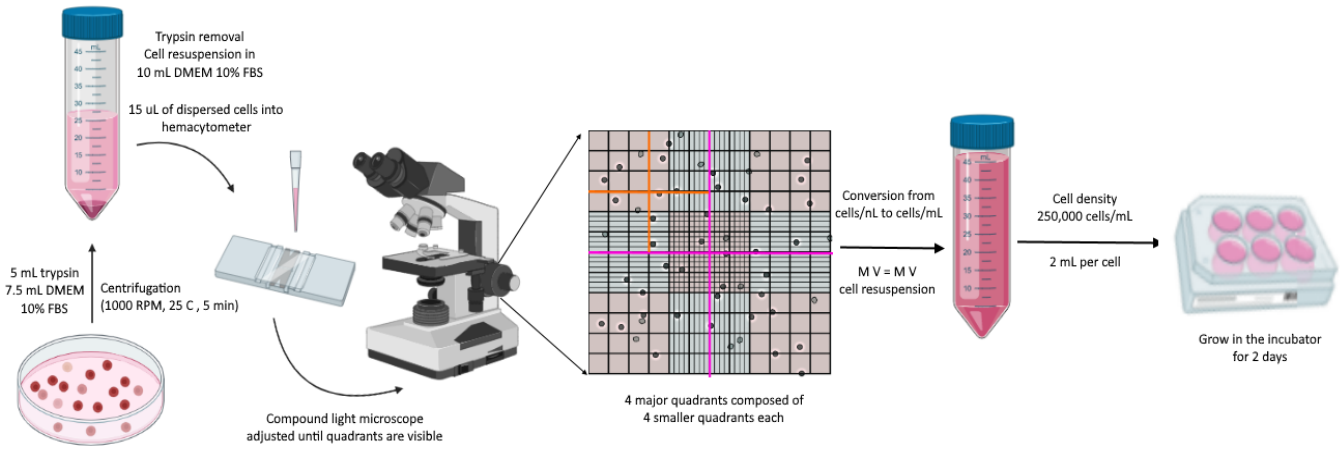

Figure 5. Pre-transfection procedure of HEK293 cells.

3.5 Transfection of HEK293 Cells with Wild Type GPR119 DNA

This procedure was based on the protocol provided by the Invitrogen Lipofectamine™ transfection kit. Eight tubes were labeled A and four were labeled B. Tubes A contained 125 µL of lipofectamine™ and 3.75 µL lipofectamine 3000 reagent (mixed on the vortex) and tubes B contained 250 µL of lipofectamine™, 5 µL of p3000 reagent and 2.5 ng of DNA of the wild type

GPR119 receptor. Tubes B were mixed gently and no more than 5 times due to the fragility of the DNA. DNA from tubes B (125 µL) was then added to each tube A and mixed by gentle pipetting. Subsequently, the lipofectamine-DNA complex was left to form for 30 minutes.

The 6-well plates were removed from the incubator and 16 wells were transfected with the wild type GPR119 receptor DNA while two wells were left as controls; the plates were then placed in the incubator for four hours. The medium was aspirated from the plates and 2 mL of DMEM (10% charcoal-stripped fetal bovine serum) was added to each well. The switch to charcoal-stripped FBS at this point is important to remove undesired activating molecules from the cell medium. Charcoal-stripped FBS is made by passing the serum through a bed of charcoal, which absorbs hydrophobic compounds. This removes compounds such as steroids and lipids which can act as activating ligands for GPCRs or nuclear receptors.

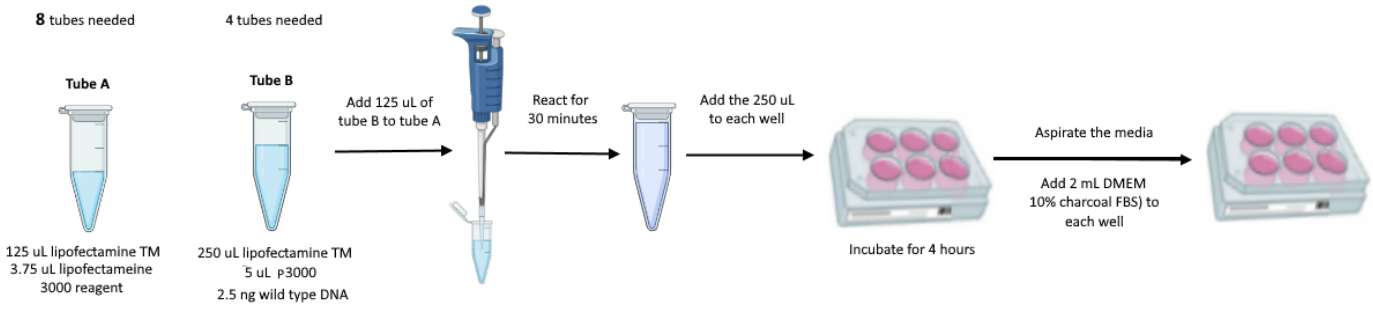

Figure 6. Transfection of HEK293 cells with wild type GPR119 DNA.

3.6 Drug Treatment of GPR119 Transfected HEK293 Cells

The compounds AR231453, AR437735, SRT1720 and oleoyl serinol were each dissolved in dimethyl sulfoxide (DMSO) to a final concentration of 10 mM. Since it is known that

AR231453 is a potent and recognized agonist for the GPR119 receptor, it was selected as a positive control and the performance of the other ligands were compared to the AR231453 activity in the cAMP production assay. The stock solutions for AR231453 and the compounds of interest were made by mixing 1 mL DMEM, 65.2 µl of charcoal-stripped FBS and 10 µL of specific ligand in a 50 mL centrifuge tube. The non-stock solution on the other hand was made combining 14 mL of DMEM, 350 µl of charcoal-stripped FBS and 250 µL of DMSO in a 50 mL tube. The 'stock' and 'non-stock' vials are shown in **Figure 7**.

An aliquot from the stock of AR231453 was serially diluted to form the following concentrations: 10000 nM, 1000 nM, 100 nM, 10 nM, 1.0 nM, 0.1 nM, and 0.01 nM. After the serial dilutions, the 6-well plates were removed from the incubator and the medium was removed by aspiration. The cells were then washed with 1.0 mL of Hank's balanced salt solution (HBSS) followed by the careful addition 1.0 mL of DMEM to each well. Finally, 1 mL of the desired ligand concentration was pipetted into the wells and the plates were placed in the incubator for 30 minutes.

Once the incubation time passed, the cells were scraped from the plates and deposited in accordingly labeled 15 mL tubes. The tubes were then centrifuged at a temperature of 21 °C for 5 minutes at 1000 RPM. Upon completion of the cycle, the medium from the tubes was aspirated and the formed cell pellet was resuspended in 2.0 mL of a phosphate buffer solution (PBS). The cells were then centrifuged again under the same conditions used previously. The PBS was aspirated from all the 15 mL tubes and 286 µL of cold lysis buffer (thimerosal 0.01%, Triton X-100 2.0%) was added to the cells in a way that the pellet was not disturbed. The sample tubes were kept on an ice to prevent degradation of cAMP by cellular enzymes.

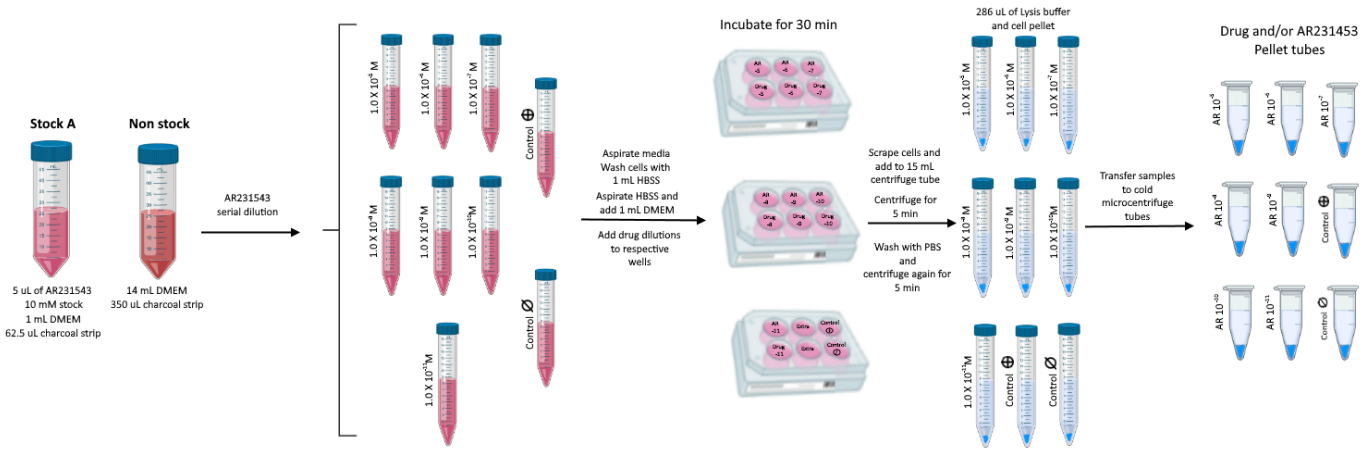

Figure 7. Drug treatment of transfected HEK293 cells.

3.7 cAMP ELISA Colorimetric Assay

The contents of the 15 mL centrifuge tubes (286 µL lysis buffer + samples) were transferred to smaller scale 1.5-mL microfuge tubes for easier handling. The samples were then thoroughly mixed using a vortex and they were subjected to two cycles of freeze (dry ice/ethanol) and thaw (37°C water bath) that lasted 3 minutes each. The cells were then centrifuged at 13,000 RPM at 4°C for 10 minutes. Subsequently, 200 µL of the supernatant was transferred to a new microfuge tube that was placed in an ice bath to minimize degradation of cAMP. The 200 µl of cell lysate sample was meticulously mixed 6 times and 100 µL was transferred to a third and final 1.5-mL microfuge tube.

A dilution (1:100) of peroxidase cAMP tracer conjugate was made by using 12 µl of tracer solution and 1188 µl of assay diluent (Thimerosal 0.01%) and 50 µL of this dilution was added to each of the sample tubes. A set of cAMP standards were prepared based on the

manufacturer's protocols and they were added in duplicate directly to the goat anti-rabbit antibody-coated plate (columns 1 & 2 in **Figure 8**) followed by the addition of 25 uL of the diluted peroxidase cAMP tracer conjugate to each cell.

The samples were then added in duplicates to the goat anti-rabbit antibody-coated plate. Columns 3 and 4 were reserved for the AR231453 treated cell extracts and columns 5 and 6 were for the cell extracts treated with the comparator ligand (refer to **Figure 8** for identification). A (1:500) dilution of rabbit anti-cAMP polyclonal antibody was made using 4.8 µl of rabbit anti-cAMP polyclonal antibody stock and 2395.2 µL of assay diluent. 50 µL of this rabbit antibody dilution was then transferred to each of the testing wells.

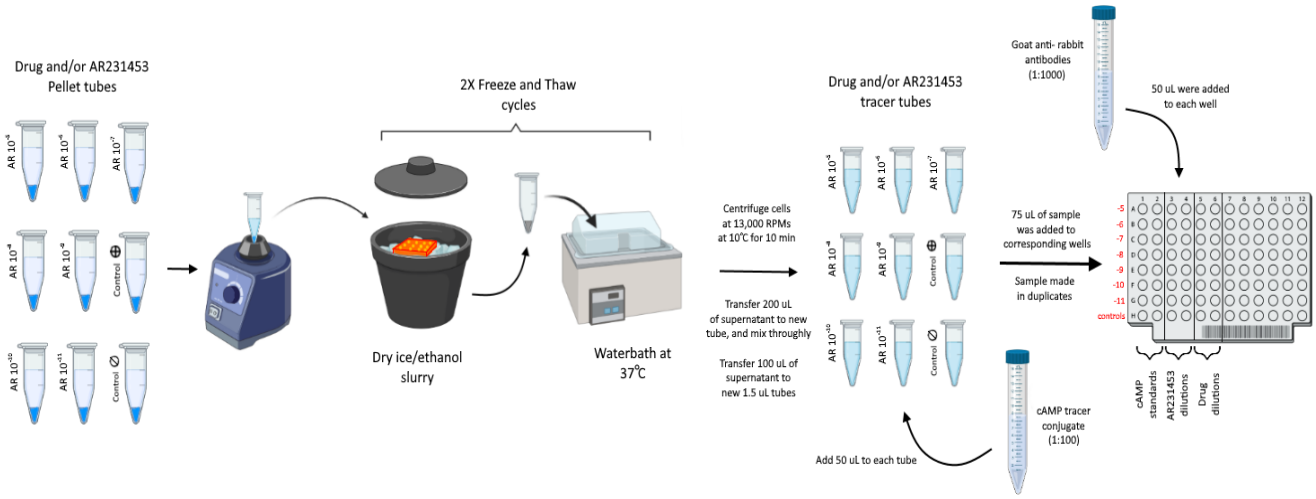

Figure 8. Procedure before tracer/rabbit cAMP assay reaction.

The goat anti-rabbit antibody-coated plate was then placed on an orbital shaker for 2 hours. After the reaction, the contents of the wells were decanted and the wells were washed a total of six times with 200 µL of wash buffer (Thimerosal 0.02%). Subsequently, 100 µL of the

substrate solution was added to each well. If the experiment went correctly, the contents of the cells containing low concentrations of cAMP would turn blue. The plate was returned to the orbital shaker to mix for an additional 15 minutes. The reaction was stopped by adding 100 µL of the stop solution (0.5 N sulfuric acid) to each of the wells which would turn the contents yellow. The plate was then spectroscopically analyzed using a BioRad 480 micro-plate reader at a primary wavelength of 450 nm.

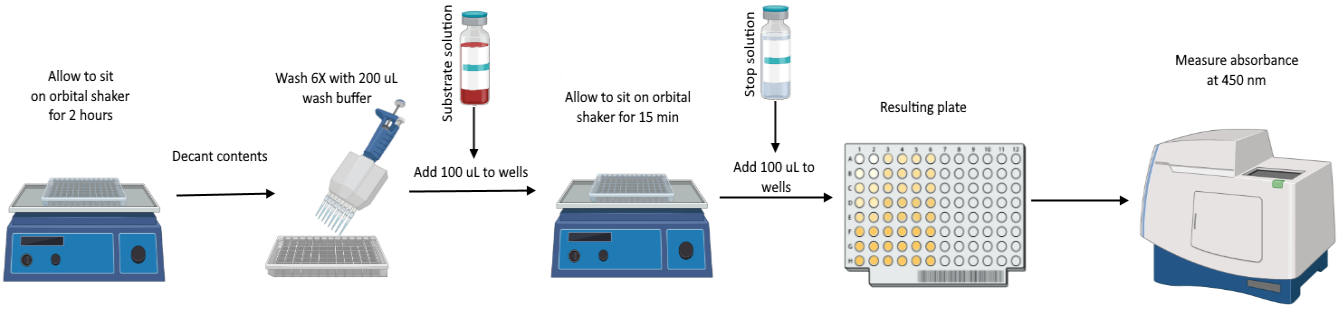

Figure 9. cAMP assay after tracer/rabbit reaction

3.8 Data Analysis of cAMP ELISA

Microsoft excel was used to create an absorbance vs concentration plot obtained from the cAMP standards. Beer's law was then employed to use the absorbance of the wells in order to determine the approximate concentration of cAMP produced in each lysate sample. SigmaPlot 11 (Systat Software Inc., San Jose, CA) was the graphical software employed to create a sigmoidal dose-response curve considering the production of cAMP in nM vs. the log concentration of the test compounds. The cAMP levels produced by the controls were used to normalize the values of cAMP produced by GPR119 activation. The cAMP values of the

samples were also scaled and normalized to the plateau of cAMP achieved by the ligand (100%). The sigmoidal dose-response curve was set to produce a hillslope of 2.0 and the values of log EC50 and EC50 produced by SigmaPlot 11 were converted to concentration in nM.

CHAPTER IV

RESULTS AND DISCUSSION

4.1 Homology Model Validation

Due to the lack of a crystallographic structure for the GPR119 receptor, an in-house homology model was built using Schrödinger software by taking fragments of several type A GPCR receptors such as the cannabinoid 1, the adenosine A_{2A} and β2 adrenergic receptors that have similar sequence and motifs, as well as structurally verifying the model with those provided by the literature [4, 8]. In general, homology models tend to vary in some degree based on the templates used for modeling of the structures, sequence alignment, model building and model refinement[37]. Therefore, it was imperative to validate the in-house built homology model through the use docking results before applying it to more extensive experiments.

The 76 molecules obtained from Ritter *et al.* paper were all found in the published literature from pharmaceutical companies like Arena, Pfizer, Roche, Bristol Meyer Squibb (BMS), Merck and AstraZeneca. The molecules varied in size and composition and among them there were agonists, inverse agonists and antagonists[21]. From a 7-ns MD simulation of the GPR119 receptor homology model embedded in a hydrated lipid bilayer patch, 5 frames were obtained and designated Frame 150, 200, 250, 300 and 350. The receptor structure was extracted from each frame and used for the docking calculations. **Table 1** shows the docking results obtained for each of the frames. For the majority of the compounds, the proper name of the

structure was not supplied by the paper. Instead, an identity number was provided, which was used to locate their common and/or UPAC name which was used for easier identification and comparison.

Frame 150 had the tightest transmembrane region (or least relaxed) of the five GPR119 homology model structures. This is reflected by allowing the least number of ligands to fit the receptor, In contrast, the GPR119 homology model structure from frame 350 was the most relaxed and open. The percentage of ligands that fit in the receptors were 78%, 87%, 92%, and 97% for frames 150, 200, 250, and 350 respectively. It was evident that as the receptor relaxed and opened to a greater extent, it allowed more complex ligands to fit. However, frame 300 was an exception since only 64 out of 76 ligands fit (84%). A possible explanation of this discrepancy might be that, although the receptor structure from frame 300 appears to have relaxed and have a large binding pocket, the amino acids lining the binding pocket (such as the large Trp7.39^{265}) have enough room to swing into the binding pocket partially obstructing it.

From the docking results, it was verified that the GPR119 homology model met the criteria for a relatively effective model, since it allowed a high percentage of known agonists to fit into the binding pocket. It is important to mention that the receptor was able to fit ligands that were long, slender and aromatic, just like the most commonly used high-potency agonist on the market, AR231453. However, the binding pocket was also able to accommodate large and bulky molecules, which affords the possibility that a wider number of molecules may be tested and new scaffolds may be discovered. Since it is understood that the GPR119 receptor is not a static structure it was necessary to take the results of a combination of less open/relaxed and more open/relaxed frames to make the most robust study. Frames 150, 200 and 250 were selected to be used for the library analysis.

Table 1-Frame comparison results of the Ritter *et al.* manuscript molecules				
Frame 150	**Frame 200**	**Frame 250**	**Frame 300**	**Frame 350**
AS1669058	(2*S*)-3-[[2-(4-Chloro-2,5-difluorophenyl)-6-ethyl-4-pyrimidinyl]amino]-1,2-propanediol	Methyl (8*S*)-8-[(3-fluorophenyl)methyl]-7,8-dihydro-2-(hydroxymethyl)-3-[4-(trifluoromethyl)phenyl]-6*H*-pyrazolo[1,5-*a*]pyrrolo[3,4-*e*]pyrimidine-8-carboxylate	Ethyl (α*R*)-α-methyl-α-(phenylmethyl)-3-[4-(trifluoromethyl)phenyl]pyrazolo[1,5-*a*]pyrimidine-7-acetate	[2,5-Difluoro-4-({[8-(3-phenyl-1,2,4-oxadiazol-5-yl)-1-oxa-2,8-diazaspiro[4.5]dec-2-en-3-yl]carbonyl}amino)phenyl](methyl)sulfoniumolate
Methyl (8*S*)-8-[(3-fluorophenyl)methyl]-7,8-dihydro-2-(hydroxymethyl)-3-[4-(trifluoromethyl)phenyl]-6*H*-pyrazolo[1,5-*a*]pyrrolo[3,4-*e*]pyrimidine-8-carboxylate	Ethyl (α*R*)-α-methyl-α-(phenylmethyl)-3-[4-(trifluoromethyl)phenyl]pyrazolo[1,5-*a*]pyrimidine-7-acetate	Spiro[2*H*-1-benzopyran-2,4'-piperidine]-1'-carboxylic acid, 3,4-dihydro-6-[4-[[(2-pyridinylmethyl)sulfonyl]methyl]phenyl]-, (1*R*)-2,2,2-trifluoro-1-methylethyl ester	5-Propyl-2-(4-{5-[1-(propylsulfonyl)-1,2,3,6-tetrahydro-4-pyridinyl]-2,3-dihydro-1-benzofuran-2-yl}-1-piperidinyl)pyrimidine	3-{[4-{4,7-Difluoro-2-[1-(5-propyl-2-pyrimidinyl)-4-piperidinyl]-2,3-dihydro-1-benzofuran-5-yl}-3,6-dihydro-1(2H)-pyridinyl]sulfonyl}-1-propanol
Ethyl α-[(2-chloro-6-fluorophenyl)methyl]-3-(4-chlorophenyl)pyrazolo[1,5-*a*]pyrimidine-7-acetate	7-[[6-Chloro-4-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-2-pyridinyl]oxy]-1-[(4-chlorophenyl)sulfonyl]-1,2,3,4-tetrahydroquinoline	Ethyl (α*R*)-α-methyl-α-(phenylmethyl)-3-[4-(trifluoromethyl)phenyl]pyrazolo[1,5-*a*]pyrimidine-7-acetate	N-(4-Cyano-2,5-difluorophenyl)-8-(3-phenyl-1,2,4-oxadiazol-5-yl)-1-oxa-2,8-diazaspiro[4.5]dec-2-ene-3-carboxamide	Spiro[2*H*-1-benzopyran-2,4'-piperidine]-1'-carboxylic acid, 3,4-dihydro-6-[4-[[(2-pyridinylmethyl)sulfonyl]methyl]phenyl]-, (1*R*)-2,2,2-trifluoro-1-methylethyl ester
(2*S*)-3-[[2-(4-Chloro-2,5-difluorophenyl)-6-ethyl-4-pyrimidinyl]amino]-1,2-propanediol	[2,5-Difluoro-4-({[8-(3-phenyl-1,2,4-oxadiazol-5-yl)-1-oxa-2,8-diazaspiro[4.5]dec-2-en-3-yl]carbonyl}amino)phenyl](methyl)sulfoniumolate	(2*S*)-3-[[2-(4-Chloro-2,5-difluorophenyl)-6-ethyl-4-pyrimidinyl]amino]-1,2-propanediol	[2,5-Difluoro-4-({[8-(3-phenyl-1,2,4-oxadiazol-5-yl)-1-oxa-2,8-diazaspiro[4.5]dec-2-en-3-yl]carbonyl}amino)phenyl](methyl)sulfoniumolate	2-(4-{4,7-Difluoro-5-[1-(propylsulfonyl)-1,2,3,6-tetrahydro-4-pyridinyl]-2,3-dihydro-1-benzofuran-2-yl}-1-piperidinyl)-5-propylpyrimidine
1-Methylcyclopropyl 4-[(1*S*)-1-fluoro-2-[[2-(2,3,6-trifluorophenyl)acetyl]amino]ethyl]-1-piperidinecarboxylate	Ethyl α-[(2-chloro-6-fluorophenyl)methyl]-3-(4-chlorophenyl)pyrazolo[1,5-*a*]pyrimidine-7-acetate	2-(4-{4,7-Difluoro-5-[1-(propylsulfonyl)-1,2,3,6-tetrahydro-4-pyridinyl]-2,3-dihydro-1-benzofuran-2-yl}-1-piperidinyl)-5-propylpyrimidine	1-[2-(4-Chloro-2,5-difluorophenyl)-5,7-dihydro-6,6-dioxidothieno[3,4-*d*]pyrimidin-4-yl]-4-piperidineacetamide	AS1669058
Ethyl (α*R*)-α-methyl-α-(phenylmethyl)-3-[4-(trifluoromethyl)phenyl]pyrazolo[1,5-*a*]pyrimidine-7-acetate	5-Propyl-2-(4-{5-[1-(propylsulfonyl)-1,2,3,6-tetrahydro-4-pyridinyl]-2,3-dihydro-1-benzofuran-2-yl}-1-piperidinyl)pyrimidine	Ethyl α-[(2-chloro-6-fluorophenyl)methyl]-3-(4-chlorophenyl)pyrazolo[1,5-*a*]pyrimidine-7-acetate	Ethyl α-[(2-chloro-6-fluorophenyl)methyl]-3-(4-chlorophenyl)pyrazolo[1,5-*a*]pyrimidine-7-acetate	4-Chloro-*N*-[3-[[2,3-dihydro-6-methyl-2-(1-methylethyl)-1,3-dioxo-1*H*-pyrrolo[3,4-*c*]pyridin-4-yl]oxy]-4-fluorophenyl]benzenesulfonamide

1,1-Dimethylethyl 4-[1-methyl-2-[[2-(2,3,6-trifluorophenyl)acetyl]amino]ethyl]-1-piperidinecarboxylate	1,1-Dimethylethyl 4-[1-methyl-2-[[2-(2,3,6-trifluorophenyl)acetyl]amino]ethyl]-1-piperidinecarboxylate	5-Propyl-2-(4-{5-[1-(propylsulfonyl)-1,2,3,6-tetrahydro-4-pyridinyl]-2,3-dihydro-1-benzofuran-2-yl}-1-piperidinyl)pyrimidine	2-[4-[(1*R*,2*R*)-2-[[[2-Fluoro-4-(methylsulfonyl)phenyl]methoxy]methyl]cyclopropyl]-1-piperidinyl]-5-(methoxymethyl)pyrimidine	7-[[6-Chloro-4-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-2-pyridinyl]oxy]-1-[(4-chlorophenyl)sulfonyl]-1,2,3,4-tetrahydroquinoline
[2,5-Difluoro-4-({[8-(3-phenyl-1,2,4-oxadiazol-5-yl)-1-oxa-2,8-diazaspiro[4.5]dec-2-en-3-yl]carbonyl}amino)phenyl](methyl)sulfoniumolate	Ethyl (8*R*)-7,8-dihydro-8-(phenylmethyl)-3-[4-(trifluoromethyl)phenyl]-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-8-carboxylate	3-{[4-{4,7-Difluoro-2-[1-(5-propyl-2-pyrimidinyl)-4-piperidinyl]-2,3-dihydro-1-benzofuran-5-yl}-3,6-dihydro-1(2H)-pyridinyl]sulfonyl}-1-propanol	Ethyl (8*R*)-7,8-dihydro-8-(phenylmethyl)-3-[4-(trifluoromethyl)phenyl]-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-8-carboxylate	N-(4-Cyano-2,5-difluorophenyl)-8-(3-phenyl-1,2,4-oxadiazol-5-yl)-1-oxa-2,8-diazaspiro[4.5]dec-2-ene-3-carboxamide
6-({2-Fluoro-3-[1-(3-isopropyl-1,2,4-oxadiazol-5-yl)-4-piperidinyl]propyl}amino)-1-indanone	1-Methylcyclopropyl 4-[(1*R*)-1-fluoro-2-[[2-(2,3,6-trifluorophenyl)acetyl]amino]ethyl]-1-piperidinecarboxylate	1-Methylcyclopropyl 4-[(1*S*)-1-fluoro-2-[[2-(2,3,6-trifluorophenyl)acetyl]amino]ethyl]-1-piperidinecarboxylate	1-Methylcyclopropyl 4-[(1*S*)-1-fluoro-2-[[2-(2,3,6-trifluorophenyl)acetyl]amino]ethyl]-1-piperidinecarboxylate	2-[4-[(1*R*,2*R*)-2-[[[2-Fluoro-4-(methylsulfonyl)phenyl]methoxy]methyl]cyclopropyl]-1-piperidinyl]-5-(methoxymethyl)pyrimidine
1-Methylcyclopropyl 4-[(1*R*)-1-fluoro-2-[[2-(2,3,6-trifluorophenyl)acetyl]amino]ethyl]-1-piperidinecarboxylate	Methyl (8*S*)-8-[(3-fluorophenyl)methyl]-7,8-dihydro-2-(hydroxymethyl)-3-[4-(trifluoromethyl)phenyl]-6*H*-pyrazolo[1,5-*a*]pyrrolo[3,4-*e*]pyrimidine-8-carboxylate	1,1-Dimethylethyl 4-[1-methyl-2-[[2-(2,3,6-trifluorophenyl)acetyl]amino]ethyl]-1-piperidinecarboxylate	1-Methylcyclopropyl 4-[(1*R*)-1-fluoro-2-[[2-(2,3,6-trifluorophenyl)acetyl]amino]ethyl]-1-piperidinecarboxylate	Ethyl α-[(2-chloro-6-fluorophenyl)methyl]-3-(4-chlorophenyl)pyrazolo[1,5-*a*]pyrimidine-7-acetate
Compound 3j [PMID: 21444206]	2-Methyl-2-propanyl 3-[(4-cyano-2,5-difluorophenyl)carbamoyl]-1-oxa-2,8-diazaspiro[4.5]dec-2-ene-8-carboxylate	[2,5-Difluoro-4-({[8-(3-phenyl-1,2,4-oxadiazol-5-yl)-1-oxa-2,8-diazaspiro[4.5]dec-2-en-3-yl]carbonyl}amino)phenyl](methyl)sulfoniumolate	7-[[6-Chloro-4-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-2-pyridinyl]oxy]-1-[(4-chlorophenyl)sulfonyl]-1,2,3,4-tetrahydroquinoline	Ethyl (α*R*)-α-methyl-α-(phenylmethyl)-3-[4-(trifluoromethyl)phenyl]pyrazolo[1,5-*a*]pyrimidine-7-acetate
1,1-Dimethylethyl (3*R*)-4-[5-[(3-cyano-4-pyridinyl)methoxy]-2-pyrimidinyl]-3-methyl-1-piperazinecarboxylate	6-({2-Fluoro-3-[1-(3-isopropyl-1,2,4-oxadiazol-5-yl)-4-piperidinyl]propyl}amino)-1-indanone	1-Methylcyclopropyl 4-[(1*R*)-1-fluoro-2-[[2-(2,3,6-trifluorophenyl)acetyl]amino]ethyl]-1-piperidinecarboxylate	6-({2-Fluoro-3-[1-(3-isopropyl-1,2,4-oxadiazol-5-yl)-4-piperidinyl]propyl}amino)-1-indanone	(2*S*)-3-[[2-(4-Chloro-2,5-difluorophenyl)-6-ethyl-4-pyrimidinyl]amino]-1,2-propanediol
AS1269574	N-(4-Cyano-2,5-difluorophenyl)-8-(3-phenyl-1,2,4-oxadiazol-5-yl)-1-oxa-2,8-diazaspiro[4.5]dec-2-ene-3-carboxamide	GSK1292263	Methyl (8*S*)-8-[(3-fluorophenyl)methyl]-7,8-dihydro-2-(hydroxymethyl)-3-[4-(trifluoromethyl)phenyl]-6*H*-pyrazolo[1,5-*a*]pyrrolo[3,4-*e*]pyrimidine-8-carboxylate	Methyl (8*S*)-8-[(3-fluorophenyl)methyl]-7,8-dihydro-2-(hydroxymethyl)-3-[4-(trifluoromethyl)phenyl]-6*H*-pyrazolo[1,5-*a*]pyrrolo[3,4-*e*]pyrimidine-8-carboxylate
5-Chloro-2-[4-[(1*R*,2*S*)-2-[2-[[5-(methylsulfonyl)-2-pyridinyl]oxy]ethyl]cyclopropyl]-1-piperidinyl]pyrimidine	4-Pyrimidinecarbonitrile, 6-methyl-2-[2-[(1*R*,2*S*)-2-[1-(5-methyl-2-pyrimidinyl)-4-piperidinyl]cyclopropyl]ethoxy]-, *rel*-	4-Chloro-*N*-[3-[[6-chloro-4-[3-(1-methylethyl)-1,2,4-oxadiazol-5-yl]-2-pyridinyl]oxy]phenyl]benzenesulfonamide	5-Chloro-2-[4-[(1*R*,2*S*)-2-[2-[[5-(methylsulfonyl)-2-pyridinyl]oxy]ethyl]cyclopropyl]-1-piperidinyl]pyrimidine	5-Propyl-2-(4-{5-[1-(propylsulfonyl)-1,2,3,6-tetrahydro-4-pyridinyl]-2,3-dihydro-1-benzofuran-2-yl}-1-piperidinyl)pyrimidine

[4,4'-Bipiperidine]-1-carboxylic acid, 1'-(3-pyridinyl)-, 1,1-dimethylethyl ester	1-Piperidinecarboxylic acid, 4-[[*trans*-4-[[5-(methylsulfonyl)-2-pyrazinyl]oxy]cyclohexyl]oxy]-, (1*R*)-2,2,2-trifluoro-1-methylethyl ester	2-[4-[(1*R*,2*R*)-2-[[[2-Fluoro-4-(methylsulfonyl)phenyl]methoxy]methyl]cyclopropyl]-1-piperidinyl]-5-(methoxymethyl)pyrimidine	(2*S*)-3-[[2-(4-Chloro-2,5-difluorophenyl)-6-ethyl-4-pyrimidinyl]amino]-1,2-propanediol	1-[2-Fluoro-4-(methylsulfonyl)phenyl]-4-{[1-(5-propyl-2-pyrimidinyl)-4-piperidinyl]oxy}-2(1H)-pyridinone
6-({3-[1-(5-Ethyl-2-pyrimidinyl)-4-piperidinyl]propyl}amino)-1-indanone	5-Chloro-2-[4-[(1*R*,2*S*)-2-[2-[[5-(methylsulfonyl)-2-pyridinyl]oxy]ethyl]cyclopropyl]-1-piperidinyl]pyrimidine	PSN119-1M	AS1669058	BMS-WO2010009207
2-[4-[(1*R*,2*R*)-2-[[[2-Fluoro-4-(methylsulfonyl)phenyl]methoxy]methyl]cyclopropyl]-1-piperidinyl]-5-(methoxymethyl)pyrimidine	Isopropyl 9-({5-methyl-6-[(2-methyl-3-pyridinyl)oxy]-4-pyrimidinyl}oxy)-3-oxa-7-azabicyclo[3.3.1]nonane-7-carboxylate –agonistic isomer	4-Pyrimidinecarbonitrile, 6-methyl-2-[2-[(1*R*,2*S*)-2-[1-(5-methyl-2-pyrimidinyl)-4-piperidinyl]cyclopropyl]ethoxy]-, *rel*-	Thieno[3,4-*d*]pyrimidine, 2-(4-chloro-2,5-difluorophenyl)-5,7-dihydro-4-(4-morpholinyl)-, 6,6-dioxide	*N*-[3-[(3-Cyano-4,6-dimethyl-2-pyridinyl)oxy]phenyl]-4-methylbenzenesulfonamide
MBX-2982	3-(Trifluoromethyl)-3-oxetanyl (3*R*)-4-[5-[(3-cyano-4-pyridinyl)methoxy]-2-pyrimidinyl]-3-methyl-1-piperazinecarboxylate	AS1669058	4-Chloro-*N*-[3-[[6-chloro-4-[3-(1-methylethyl)-1,2,4-oxadiazol-5-yl]-2-pyridinyl]oxy]phenyl]benzenesulfonamide	MXB-2982
APD597	2-Methyl-2-propanyl 4-{4-[(1,1-dioxido-2,3-dihydro-1-benzothiophen-5-yl)amino]-4-oxobutyl}-1-piperidinecarboxylate	Ethyl (8*R*)-7,8-dihydro-8-(phenylmethyl)-3-[4-(trifluoromethyl)phenyl]-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-8-carboxylate	6-({3-[1-(5-Ethyl-2-pyrimidinyl)-4-piperidinyl]propyl}amino)-1-indanone	5-[[2-Fluoro-4-ylsulfonyl)phenyl]methoxy]-2-[(2*R*)-2-ethyl-4-[3-(trifluoromethyl)-1,2,4-diazol-5-yl]-1-piperazinyl]pyrimidine
AR231453	AS1669058	1-Piperidinecarboxylic acid, 4-[[[1,2-dihydro-1-[4-(methylsulfonyl)phenyl]-2-oxo-4-pyridinyl]oxy]methyl]-, 1,1-dimethylethyl ester	4-Pyrimidinecarbonitrile, 6-methyl-2-[2-[(1*R*,2*S*)-2-[1-(5-methyl-2-pyrimidinyl)-4-piperidinyl]cyclopropyl]ethoxy]-, *rel*-	5-[[2-Fluoro-4-[(methylsulfonyl)methyl]phenyl]methoxy]-2-[(2*R*)-2-methyl-4-[3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl]-1-piperazinyl]pyrimidine
Isopropyl 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate	1-Methylcyclopropyl 4-[(1*S*)-1-fluoro-2-[[2-(2,3,6-trifluorophenyl)acetyl]amino]ethyl]-1-piperidinecarboxylate	7-[[6-Chloro-4-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-2-pyridinyl]oxy]-1-[(4-chlorophenyl)sulfonyl]-1,2,3,4-tetrahydroquinoline	3-(Trifluoromethyl)-3-oxetanyl (3*R*)-4-[5-[(3-cyano-4-pyridinyl)methoxy]-2-pyrimidinyl]-3-methyl-1-piperazinecarboxylate	2-Methyl-2-propanyl 3-[(4-cyano-2,5-difluorophenyl)carbamoyl]-1-oxa-2,8-diazaspiro[4.5]dec-2-ene-8-carboxylate
2-Methyl-2-propanyl 3-[(4-cyano-2,5-difluorophenyl)carbamoyl]-1-oxa-2,8-diazaspiro[4.5]dec-2-ene-8-carboxylate	Isopropyl 4-({5-methyl-6-[(2-methyl-3-pyridinyl)oxy]-4-pyrimidinyl}oxy)-1-piperidinecarboxylate	6-({2-Fluoro-3-[1-(3-isopropyl-1,2,4-oxadiazol-5-yl)-4-piperidinyl]propyl}amino)-1-indanone	Compound 3j [PMID: 21444206]	4-Chloro-*N*-[3-[[6-chloro-4-[3-(1-methylethyl)-1,2,4-oxadiazol-5-yl]-2-pyridinyl]oxy]phenyl]benzenesulfonamide

2-Methyl-2-propanyl 4-(5-{[4-(methylsulfonyl)benzyl]oxy}-2-pyrimidinyl)-1-piperazinecarboxylate	Thieno[3,4-*d*]pyrimidine, 2-(4-chloro-2,5-difluorophenyl)-5,7-dihydro-4-(4-morpholinyl)-, 6,6-dioxide	2-Methyl-2-propanyl 4-{4-[(1,1-dioxido-2,3-dihydro-1-benzothiophen-5-yl)amino]-4-oxobutyl}-1-piperidinecarboxylate	5-[[2-Fluoro-4-ethylsulfonyl)phenyl]methoxy]-2-*R*)-2-methyl-4-[3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl]-1-piperazinyl]pyrimidine	PSN119-2
1-Piperidinecarboxylic acid, 4-[[*trans*-4-[[5-(methylsulfonyl)-2-pyrazinyl]oxy]cyclohexyl]oxy]-, (1*R*)-2,2,2-trifluoro-1-methylethyl ester	2-[4-[(1*R*,2*R*)-2-[[[2-Fluoro-4-(methylsulfonyl)phenyl]methoxy]methyl]cyclopropyl]-1-piperidinyl]-5-(methoxymethyl)pyrimidine	4-Methyl-6-[1'-(5-methyl-2-pyrazinyl)[4,4'-bipiperidin]-1-yl]-2-pyrimidinecarbonitrile	5-[[2-Fluoro-4-[(methylsulfonyl)methyl]phenyl]methoxy]-2-[(2*R*)-2-methyl-4-[3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl]-1-piperazinyl]pyrimidine	Compound 3j [PMID: 21444206]
BMS-903452	1-[2-(4-Chloro-2,5-difluorophenyl)-5,7-dihydro-6,6-dioxidothieno[3,4-*d*]pyrimidin-4-yl]-4-piperidineacetamide	Compound 3j [PMID: 21444206]	1,1-Dimethylethyl 4-[1-methyl-2-[[2-(2,3,6-trifluorophenyl)acetyl]amino]ethyl]-1-piperidinecarboxylate	6-({2-Fluoro-3-[1-(3-isopropyl-1,2,4-oxadiazol-5-yl)-4-piperidinyl]propyl}amino)-1-indanone
Isopropyl 4-{4-[4-(methylsulfonyl)phenoxy]-1H-pyrazolo[3,4-d]pyrimidin-1-yl}-1-piperidinecarboxylate	4-Chloro-*N*-[3-[[6-chloro-4-[3-(1-methylethyl)-1,2,4-oxadiazol-5-yl]-2-pyridinyl]oxy]phenyl]benzenesulfonamide	5-[[2-Fluoro-4-ethylsulfonyl)phenyl]methoxy]-2-*R*)-2-methyl-4-[3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl]-1-piperazinyl]pyrimidine	AR231453	4-Methyl-6-[1'-(5-methyl-2-pyrazinyl)[4,4'-bipiperidin]-1-yl]-2-pyrimidinecarbonitrile
4-Pyrimidinecarbonitrile, 6-methyl-2-[2-[(1*R*,2*S*)-2-[1-(5-methyl-2-pyrimidinyl)-4-piperidinyl]cyclopropyl]ethoxy]-, *rel*-	5-[[2-Fluoro-4-ethylsulfonyl)phenyl]methoxy]-2-*R*)-2-methyl-4-[3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl]-1-piperazinyl]pyrimidine	5-[[2-Fluoro-4-[(methylsulfonyl)methyl]phenyl]methoxy]-2-[(2*R*)-2-methyl-4-[3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl]-1-piperazinyl]pyrimidine	APD668	Ethyl (8*R*)-7,8-dihydro-8-(phenylmethyl)-3-[4-(trifluoromethyl)phenyl]-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-8-carboxylate
4-Methyl-6-[1'-(5-methyl-2-pyrazinyl)[4,4'-bipiperidin]-1-yl]-2-pyrimidinecarbonitrile	5-[[2-Fluoro-4-[(methylsulfonyl)methyl]phenyl]methoxy]-2-[(2*R*)-2-methyl-4-[3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl]-1-piperazinyl]pyrimidine	1-Methylcyclopropyl 6-{5-methyl-6-[(2-methyl-3-pyridinyl)oxy]-4-pyrimidinyl}-2,6-diazatricyclo[3.3.1.1^{3,7}]decane-2-carboxylate	Isopropyl 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate	Benzonitrile, 4-[1'-(1-methylethyl)o[benzofuran-2(3*H*),4'-piperidin]-5-yl]-
1-Methylcyclopropyl 6-{5-methyl-6-[(2-methyl-3-pyridinyl)oxy]-4-pyrimidinyl}-2,6-diazatricyclo[3.3.1.1^{3,7}]decane-2-carboxylate	1-Methylcyclopropyl 6-{5-methyl-6-[(2-methyl-3-pyridinyl)oxy]-4-pyrimidinyl}-2,6-diazatricyclo[3.3.1.1^{3,7}]decane-2-carboxylate	PSN119-2	[4,4'-Bipiperidine]-1-carboxylic acid, 1'-(3-pyridinyl)-, 1,1-dimethylethyl ester	1-Methylcyclopropyl 4-[(1*S*)-1-fluoro-2-[[2-(2,3,6-trifluorophenyl)acetyl]amino]ethyl]-1-piperidinecarboxylate
PSN119-2	AR231453	Isopropyl 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate	enzonitrile, 4-[1'-(1-methylethyl)o[benzofuran-2(3*H*),4'-piperidin]-5-yl]-	6-({3-[1-(5-Ethyl-2-pyrimidinyl)-4-piperidinyl]propyl}amino)-1-indanone

1-Piperidinecarboxylic acid, 4-[[*trans*-4-[[5-(methylsulfonyl)-2-pyrazinyl]oxy]cyclohexyl]oxy]-, 1,1-dimethylethyl ester	*N*-[3-[(3-Cyano-4,6-dimethyl-2-pyridinyl)oxy]phenyl]-4-methylbenzenesulfonamide	BMS-WO2010009207	BMS-WO2010009207	1-Piperidinecarboxylic acid, 4-[2-[2-fluoro-4-(methylsulfonyl)phenyl]-2,6-dihydropyrrolo[3,4-*c*]pyrazol-5(4*H*)-yl]-, 1-methylethyl ester
PSN119-1M	BMS-903452	BMS-903452	PSN119-2	5-Chloro-2-[4-[(1*R*,2*S*)-2-[2-[[5-(methylsulfonyl)-2-pyridinyl]oxy]ethyl]cyclopropyl]-1-piperidinyl]pyrimidine
Isopropyl 4-({5-methyl-6-[(2-methyl-3-pyridinyl)oxy]-4-pyrimidinyl}oxy)-1-piperidinecarboxylate	PSN119-2	4-Chloro-*N*-[3-[[2,3-dihydro-6-methyl-2-(1-methylethyl)-1,3-dioxo-1*H*-pyrrolo[3,4-*c*]pyridin-4-yl]oxy]-4-fluorophenyl]benzenesulfonamide	1,1-Dimethylethyl (3*R*)-4-[5-[(3-cyano-4-pyridinyl)methoxy]-2-pyrimidinyl]-3-methyl-1-piperazinecarboxylate	Isopropyl 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate
2-Methyl-2-propanyl 4-({1-[4-(methylsulfonyl)phenyl]-2-oxo-1,2-dihydro-4-pyridinyl}oxy)-1-piperidinecarboxylate	PSN119-1M	2-Methyl-2-propanyl 3-[(4-cyano-2,5-difluorophenyl)carbamoyl]-1-oxa-2,8-diazaspiro[4.5]dec-2-ene-8-carboxylate	*N*-[3-[(3-Cyano-4,6-dimethyl-2-pyridinyl)oxy]phenyl]-4-methylbenzenesulfonamide	1-Piperidinecarboxylic acid, 4-[[2-[2,3-dihydro-5-(methylsulfonyl)-1*H*-indol-1-yl]-4-pyrimidinyl]oxy]-, 1-methylethyl ester
3-(Trifluoromethyl)-3-oxetanyl (3*R*)-4-[5-[(3-cyano-4-pyridinyl)methoxy]-2-pyrimidinyl]-3-methyl-1-piperazinecarboxylate	APD597	3-(Trifluoromethyl)-3-oxetanyl (3*R*)-4-[5-[(3-cyano-4-pyridinyl)methoxy]-2-pyrimidinyl]-3-methyl-1-piperazinecarboxylate	Isopropyl 9-({5-methyl-6-[(2-methyl-3-pyridinyl)oxy]-4-pyrimidinyl}oxy)-3-oxa-7-azabicyclo[3.3.1]nonane-7-carboxylate – agonistic isomer	Isopropyl 4-({6-[5-(methylsulfonyl)-2,3-dihydro-1H-indol-1-yl]-4-pyrimidinyl}oxy)-1-piperidinecarboxylate
5-[[2-Fluoro-4-(methylsulfonyl)phenyl]methoxy]-2-[(2*R*)-2-methyl-4-[3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl]-1-piperazinyl]pyrimidine	Compound 3j [PMID: 21444206]	APD597	Isopropyl 9-({5-methyl-6-[(2-methyl-3-pyridinyl)oxy]-4-pyrimidinyl}oxy)-3-oxa-7-azabicyclo[3.3.1]nonane-7-carboxylate – antagonistic isomer	2,6-Diazatricyclo[3.3.1.13,7]decane-2-carboxylic acid, 6-[6-[2-fluoro-4-(1*H*-tetrazol-1-yl)phenoxy]-5-methyl-4-pyrimidinyl]-, 1-methylcyclopropyl ester
5-[[2-Fluoro-4-[(methylsulfonyl)methyl]phenyl]methoxy]-2-[(2*R*)-2-methyl-4-[3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl]-1-piperazinyl]pyrimidine	BMS-WO2010009207	N-(4-Cyano-2,5-difluorophenyl)-8-(3-phenyl-1,2,4-oxadiazol-5-yl)-1-oxa-2,8-diazaspiro[4.5]dec-2-ene-3-carboxamide	6-({3-[1-(5-Ethyl-2-pyrimidinyl)-4-piperidinyl]butyl}amino)furo[3,2-c]pyridin-3(2H)-one	BMS-903452
Ethyl (8*R*)-7,8-dihydro-8-(phenylmethyl)-3-[4-(trifluoromethyl)phenyl]-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine-8-carboxylate	4-Chloro-*N*-[3-[[2,3-dihydro-6-methyl-2-(1-methylethyl)-1,3-dioxo-1*H*-pyrrolo[3,4-*c*]pyridin-4-yl]oxy]-4-fluorophenyl]benzenesulfonamide	*N*-[3-[(3-Cyano-4,6-dimethyl-2-pyridinyl)oxy]phenyl]-4-methylbenzenesulfonamide	1-Methylcyclopropyl 6-{5-methyl-6-[(2-methyl-3-pyridinyl)oxy]-4-pyrimidinyl}-2,6-diazatricyclo[3.3.1.1^{3,7}]decane-2-carboxylate	Isopropyl 4-{4-[4-(methylsulfonyl)phenoxy]-1H-pyrazolo[3,4-d]pyrimidin-1-yl}-1-piperidinecarboxylate

6-({3-[1-(5-Ethyl-2-pyrimidinyl)-4-piperidinyl]butyl}amino)furo[3,2-c]pyridin-3(2H)-one	[4,4'-Bipiperidine]-1-carboxylic acid, 1'-(3-pyridinyl)-, 1,1-dimethylethyl ester	Isopropyl 9-({5-methyl-6-[(2-methyl-3-pyridinyl)oxy]-4-pyrimidinyl}oxy)-3-oxa-7-azabicyclo[3.3.1]nonane-7-carboxylate – agonistic isomer	1-Piperidinecarboxylic acid, 4-[4-[[[2-fluoro-4-(methylsulfonyl)phenyl]amino]methyl]-1*H*-pyrazol-1-yl]-, 1-methylethyl ester	6-({3-[1-(5-Ethyl-2-pyrimidinyl)-4-piperidinyl]butyl}amino)furo[3,2-c]pyridin-3(2H)-one
Isopropyl 9-({5-methyl-6-[(2-methyl-3-pyridinyl)oxy]-4-pyrimidinyl}oxy)-3-oxa-7-azabicyclo[3.3.1]nonane-7-carboxylate – antagonistic isomer	1-Methylcyclopropyl 4-[(5-fluoro-6-{[2-methyl-6-(methylsulfonyl)-3-pyridinyl]oxy}-4-pyrimidinyl)oxy]-1-piperidinecarboxylate	[4,4'-Bipiperidine]-1-carboxylic acid, 1'-(3-pyridinyl)-, 1,1-dimethylethyl ester	APD597	APD668
4-Chloro-*N*-[3-[[2,3-dihydro-6-methyl-2-(1-methylethyl)-1,3-dioxo-1*H*-pyrrolo[3,4-*c*]pyridin-4-yl]oxy]-4-fluorophenyl]benzenesulfonamide	6-({3-[1-(5-Ethyl-2-pyrimidinyl)-4-piperidinyl]butyl}amino)furo[3,2-c]pyridin-3(2H)-one	6-({3-[1-(5-Ethyl-2-pyrimidinyl)-4-piperidinyl]propyl}amino)-1-indanone	PSN119-1M	1-Methylcyclopropyl 4-[(1*R*)-1-fluoro-2-[[2-(2,3,6-trifluorophenyl)acetyl]amino]ethyl]-1-piperidinecarboxylate
1-Piperidinecarboxylic acid, 4-[5-[2-fluoro-4-(methylsulfonyl)phenyl]-5,6-dihydropyrrolo[3,4-*c*]pyrazol-2(4*H*)-yl]-, 1-methylethyl ester	GSK1292263	AR231453	4-Methyl-6-[1'-(5-methyl-2-pyrazinyl)[4,4'-bipiperidin]-1-yl]-2-pyrimidinecarbonitrile	Thieno[3,4-*d*]pyrimidine, 2-(4-chloro-2,5-difluorophenyl)-5,7-dihydro-4-(4-morpholinyl)-, 6,6-dioxide
enzonitrile, 4-[1'-(1-methylethyl)o[benzofuran-2(3*H*),4'-piperidin]-5-yl]-	AS1269574	1,1-Dimethylethyl (3*R*)-4-[5-[(3-cyano-4-pyridinyl)methoxy]-2-pyrimidinyl]-3-methyl-1-piperazinecarboxylate	2-Methyl-2-propanyl 3-[(4-cyano-2,5-difluorophenyl)carbamoyl]-1-oxa-2,8-diazaspiro[4.5]dec-2-ene-8-carboxylate	2-Methyl-2-propanyl 4-{4-[(1,1-dioxido-2,3-dihydro-1-benzothiophen-5-yl)amino]-4-oxobutyl}-1-piperidinecarboxylate
Isopropyl 4-({6-[5-(methylsulfonyl)-2,3-dihydro-1H-indol-1-yl]-4-pyrimidinyl}oxy)-1-piperidinecarboxylate	1-Piperidinecarboxylic acid, 4-[4-[[[2-fluoro-4-(methylsulfonyl)phenyl]amino]methyl]-1*H*-pyrazol-1-yl]-, 1-methylethyl ester	5-Chloro-2-[4-[(1*R*,2*S*)-2-[2-[[5-(methylsulfonyl)-2-pyridinyl]oxy]ethyl]cyclopropyl]-1-piperidinyl]pyrimidine	4-[[[2-[(2*R*)-2-Methyl-4-[5-(1-methylethyl)-1,2,4-oxadiazol-3-yl]-1-piperazinyl]-5-pyrimidinyl]oxy]methyl]-3-pyridinecarbonitrile	1,1-Dimethylethyl (3*R*)-4-[5-[(3-cyano-4-pyridinyl)methoxy]-2-pyrimidinyl]-3-methyl-1-piperazinecarboxylate
4-Chloro-*N*-[3-[[6-chloro-4-[3-(1-methylethyl)-1,2,4-oxadiazol-5-yl]-2-pyridinyl]oxy]phenyl]benzenesulfonamide	Isopropyl 4-({7-[2-fluoro-4-(methylsulfonyl)phenyl]-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl}oxy)-1-piperidinecarboxylate	4-[[[2-[(2*R*)-2-Methyl-4-[5-(1-methylethyl)-1,2,4-oxadiazol-3-yl]-1-piperazinyl]-5-pyrimidinyl]oxy]methyl]-3-pyridinecarbonitrile	1-Piperidinecarboxylic acid, 4-[[*trans*-4-[[5-(methylsulfonyl)-2-pyrazinyl]oxy]cyclohexyl]oxy]-, (1*R*)-2,2,2-trifluoro-1-methylethyl ester	2-Methyl-2-propanyl 4-(5-{[4-(methylsulfonyl)benzyl]oxy}-2-pyrimidinyl)-1-piperazinecarboxylate
N-(4-Cyano-2,5-difluorophenyl)-8-(3-phenyl-1,2,4-oxadiazol-5-yl)-1-oxa-2,8-diazaspiro[4.5]dec-2-ene-3-carboxamide	2-Methyl-2-propanyl 4-(5-{[4-(methylsulfonyl)benzyl]oxy}-2-pyrimidinyl)-1-piperazinecarboxylate	1-Methylcyclopropyl 4-[(5-fluoro-6-{[2-methyl-6-(methylsulfonyl)-3-pyridinyl]oxy}-4-pyrimidinyl)oxy]-1-piperidinecarboxylate	1-Piperidinecarboxylic acid, 4-[[*trans*-4-[[5-(methylsulfonyl)-2-pyrazinyl]oxy]cyclohexyl]oxy]-, 1,1-dimethylethyl ester	4-Pyrimidinecarbonitrile, 6-methyl-2-[2-[(1*R*,2*S*)-2-[1-(5-methyl-2-pyrimidinyl)-4-piperidinyl]cyclopropyl]ethoxy]-, *rel*-

1-Piperidinecarboxylic acid, 4-[4-[[[2-fluoro-4-(methylsulfonyl)phenyl]amino]methyl]-1*H*-pyrazol-1-yl]-, 1-methylethyl ester	2,6-Diazatricyclo[3.3.1.13,7]decane-2-carboxylic acid, 6-[6-[2-fluoro-4-(1*H*-tetrazol-1-yl)phenoxy]-5-methyl-4-pyrimidinyl]-, 1-methylcyclopropyl ester	1-Piperidinecarboxylic acid, 4-[[*trans*-4-[[5-(methylsulfonyl)-2-pyrazinyl]oxy]cyclohexyl]oxy]-, (1*R*)-2,2,2-trifluoro-1-methylethyl ester	GSK1292263	GSK1292263
1-[2-(4-Chloro-2,5-difluorophenyl)-5,7-dihydro-6,6-dioxidothieno[3,4-*d*]pyrimidin-4-yl]-4-piperidineacetamide	Isopropyl 4-({6-[5-(methylsulfonyl)-2,3-dihydro-1H-indol-1-yl]-4-pyrimidinyl}oxy)-1-piperidinecarboxylate	6-({3-[1-(5-Ethyl-2-pyrimidinyl)-4-piperidinyl]butyl}amino)furo[3,2-c]pyridin-3(2H)-one	2-Methyl-2-propanyl 4-({1-[4-(methylsulfonyl)phenyl]-2-oxo-1,2-dihydro-4-pyridinyl}oxy)-1-piperidinecarboxylate	Isopropyl 4-[(5-fluoro-6-{[2-methyl-6-(methylsulfonyl)-3-pyridinyl]amino}-4-pyrimidinyl)oxy]-1-piperidinecarboxylate
N-[3-[(3-Cyano-4,6-dimethyl-2-pyridinyl)oxy]phenyl]-4-methylbenzenesulfonamide	Isopropyl 4-{4-[4-(methylsulfonyl)phenoxy]-1H-pyrazolo[3,4-d]pyrimidin-1-yl}-1-piperidinecarboxylate	1-Piperidinecarboxylic acid, 4-[[*trans*-4-[[5-(methylsulfonyl)-2-pyrazinyl]oxy]cyclohexyl]oxy]-, 1,1-dimethylethyl ester	2-Methyl-2-propanyl 4-(5-{[4-(methylsulfonyl)benzyl]oxy}-2-pyrimidinyl)-1-piperazinecarboxylate	1-Piperidinecarboxylic acid, 4-[[*trans*-4-[[5-(methylsulfonyl)-2-pyrazinyl]oxy]cyclohexyl]oxy]-, (1*R*)-2,2,2-trifluoro-1-methylethyl ester
1-Methylcyclopropyl 4-[(5-fluoro-6-{[2-methyl-6-(methylsulfonyl)-3-pyridinyl]oxy}-4-pyrimidinyl)oxy]-1-piperidinecarboxylate	4-[[[2-[(2*R*)-2-Methyl-4-[5-(1-methylethyl)-1,2,4-oxadiazol-3-yl]-1-piperazinyl]-5-pyrimidinyl]oxy]methyl]-3-pyridinecarbonitrile	Thieno[3,4-*d*]pyrimidine, 2-(4-chloro-2,5-difluorophenyl)-5,7-dihydro-4-(4-morpholinyl)-, 6,6-dioxide	1-Piperidinecarboxylic acid, 4-[5-[2-fluoro-4-(methylsulfonyl)phenyl]-5,6-dihydropyrrolo[3,4-*c*]pyrazol-2(4*H*)-yl]-, 1-methylethyl ester	AR231453
APD668	Isopropyl 9-({5-methyl-6-[(2-methyl-3-pyridinyl)oxy]-4-pyrimidinyl}oxy)-3-oxa-7-azabicyclo[3.3.1]nonane-7-carboxylate – antagonistic isomer	1-[2-(4-Chloro-2,5-difluorophenyl)-5,7-dihydro-6,6-dioxidothieno[3,4-*d*]pyrimidin-4-yl]-4-piperidineacetamide	2-Methyl-2-propanyl 4-{4-[(1,1-dioxido-2,3-dihydro-1-benzothiophen-5-yl)amino]-4-oxobutyl}-1-piperidinecarboxylate	4-[[[2-[(2*R*)-2-Methyl-4-[5-(1-methylethyl)-1,2,4-oxadiazol-3-yl]-1-piperazinyl]-5-pyrimidinyl]oxy]methyl]-3-pyridinecarbonitrile
BMS-WO2010009207	4-Methyl-6-[1'-(5-methyl-2-pyrazinyl)[4,4'-bipiperidin]-1-yl]-2-pyrimidinecarbonitrile	AS1269574	MBX-2982	Isopropyl 9-({5-methyl-6-[(2-methyl-3-pyridinyl)oxy]-4-pyrimidinyl}oxy)-3-oxa-7-azabicyclo[3.3.1]nonane-7-carboxylate – antagonistic isomer
GSK1292263	2-Methyl-2-propanyl 4-({1-[4-(methylsulfonyl)phenyl]-2-oxo-1,2-dihydro-4-pyridinyl}oxy)-1-piperidinecarboxylate	Isopropyl 4-{4-[4-(methylsulfonyl)phenoxy]-1H-pyrazolo[3,4-d]pyrimidin-1-yl}-1-piperidinecarboxylate	Isopropyl 4-[(5-fluoro-6-{[2-methyl-6-(methylsulfonyl)-3-pyridinyl]amino}-4-pyrimidinyl)oxy]-1-piperidinecarboxylate	1-[2-(4-Chloro-2,5-difluorophenyl)-5,7-dihydro-6,6-dioxidothieno[3,4-*d*]pyrimidin-4-yl]-4-piperidineacetamide
1-Piperidinecarboxylic acid, 4-[2-[2-fluoro-4-(methylsulfonyl)phenyl]-2,6-dihydropyrrolo[3,4-*c*]pyrazol-5(4*H*)-yl]-, 1-methylethyl ester	6-({3-[1-(5-Ethyl-2-pyrimidinyl)-4-piperidinyl]propyl}amino)-1-indanone	enzonitrile, 4-[1'-(1-methylethyl)o[benzofuran-2(3*H*),4'-piperidin]-5-yl]-	AS1269574	1-(6-{[1-(3-Isopropyl-1,2,4-oxadiazol-5-yl)-4-piperidinyl]oxy}-4-pyrimidinyl)-5-(methylsulfonyl)indoline

PSN-632408	MBX-2982	1-Piperidinecarboxylic acid, 4-[4-[[[2-fluoro-4-(methylsulfonyl)phenyl]amino]methyl]-1*H*-pyrazol-1-yl]-, 1-methylethyl ester	Isopropyl 4-{4-[4-(methylsulfonyl)phenoxy]-1H-pyrazolo[3,4-d]pyrimidin-1-yl}-1-piperidinecarboxylate	1-Methylcyclopropyl 6-{5-methyl-6-[(2-methyl-3-pyridinyl)oxy]-4-pyrimidinyl}-2,6-diazatricyclo[3.3.1.1^{3,7}]decane-2-carboxylate
Isopropyl 4-[(5-fluoro-6-{[2-methyl-6-(methylsulfonyl)-3-pyridinyl]amino}-4-pyrimidinyl)oxy]-1-piperidinecarboxylate	1,1-Dimethylethyl (3*R*)-4-[5-[(3-cyano-4-pyridinyl)methoxy]-2-pyrimidinyl]-3-methyl-1-piperazinecarboxylate	Pyrrolo[3,4-*c*]pyrazole, 5-[1-(5-ethyl-2-pyrimidinyl)-4-piperidinyl]-2-[2-fluoro-4-(methylsulfonyl)phenyl]-2,4,5,6-tetrahydro-	1-(6-{[1-(3-Isopropyl-1,2,4-oxadiazol-5-yl)-4-piperidinyl]oxy}-4-pyrimidinyl)-5-(methylsulfonyl)indoline	APD597
2,6-Diazatricyclo[3.3.1.13,7]decane-2-carboxylic acid, 6-[6-[2-fluoro-4-(1*H*-tetrazol-1-yl)phenoxy]-5-methyl-4-pyrimidinyl]-, 1-methylcyclopropyl ester	1-Piperidinecarboxylic acid, 4-[[*trans*-4-[[5-(methylsulfonyl)-2-pyrazinyl]oxy]cyclohexyl]oxy]-, 1,1-dimethylethyl ester	Isopropyl 4-[(5-fluoro-6-{[2-methyl-6-(methylsulfonyl)-3-pyridinyl]amino}-4-pyrimidinyl)oxy]-1-piperidinecarboxylate	1-Methylcyclopropyl 4-[(5-fluoro-6-{[2-methyl-6-(methylsulfonyl)-3-pyridinyl]oxy}-4-pyrimidinyl)oxy]-1-piperidinecarboxylate	1-Piperidinecarboxylic acid, 4-[4-[[[2-fluoro-4-(methylsulfonyl)phenyl]amino]methyl]-1*H*-pyrazol-1-yl]-, 1-methylethyl ester
2-Methyl-2-propanyl 4-{4-[(1,1-dioxido-2,3-dihydro-1-benzothiophen-5-yl)amino]-4-oxobutyl}-1-piperidinecarboxylate	Isopropyl 4-[(5-fluoro-6-{[2-methyl-6-(methylsulfonyl)-3-pyridinyl]amino}-4-pyrimidinyl)oxy]-1-piperidinecarboxylate	2,6-Diazatricyclo[3.3.1.13,7]decane-2-carboxylic acid, 6-[6-[2-fluoro-4-(1*H*-tetrazol-1-yl)phenoxy]-5-methyl-4-pyrimidinyl]-, 1-methylcyclopropyl ester	4-Chloro-*N*-[3-[[2,3-dihydro-6-methyl-2-(1-methylethyl)-1,3-dioxo-1*H*-pyrrolo[3,4-*c*]pyridin-4-yl]oxy]-4-fluorophenyl]benzenesulfonamide	1-Methylcyclopropyl 4-[(5-fluoro-6-{[2-methyl-6-(methylsulfonyl)-3-pyridinyl]oxy}-4-pyrimidinyl)oxy]-1-piperidinecarboxylate
4-[[[2-[(2*R*)-2-Methyl-4-[5-(1-methylethyl)-1,2,4-oxadiazol-3-yl]-1-piperazinyl]-5-pyrimidinyl]oxy]methyl]-3-pyridinecarbonitrile	1-Piperidinecarboxylic acid, 4-[5-[2-fluoro-4-(methylsulfonyl)phenyl]-5,6-dihydropyrrolo[3,4-*c*]pyrazol-2(4*H*)-yl]-, 1-methylethyl ester	MBX-2982	Isopropyl 4-({6-[5-(methylsulfonyl)-2,3-dihydro-1H-indol-1-yl]-4-pyrimidinyl}oxy)-1-piperidinecarboxylate	PSN-632408
	APD668	APD668	Isopropyl 4-({5-methyl-6-[(2-methyl-3-pyridinyl)oxy]-4-pyrimidinyl}oxy)-1-piperidinecarboxylate	AS1269574
	1-Piperidinecarboxylic acid, 4-[2-[2-fluoro-4-(methylsulfonyl)phenyl]-2,6-dihydropyrrolo[3,4-*c*]pyrazol-5(4*H*)-yl]-, 1-methylethyl ester	Isopropyl 4-({6-[5-(methylsulfonyl)-2,3-dihydro-1H-indol-1-yl]-4-pyrimidinyl}oxy)-1-piperidinecarboxylate	BMS-903452	[4,4'-Bipiperidine]-1-carboxylic acid, 1'-(3-pyridinyl)-, 1,1-dimethylethyl ester
	enzonitrile, 4-[1'-(1-methylethyl)o[benzofuran-2(3*H*),4'-piperidin]-5-yl]-	1-(6-{[1-(3-Isopropyl-1,2,4-oxadiazol-5-yl)-4-piperidinyl]oxy}-4-pyrimidinyl)-5-(methylsulfonyl)indoline	1-Piperidinecarboxylic acid, 4-[2-[2-fluoro-4-(methylsulfonyl)phenyl]-2,6-dihydropyrrolo[3,4-*c*]pyrazol-5(4*H*)-yl]-, 1-methylethyl ester	1-Piperidinecarboxylic acid, 4-[[*trans*-4-[[5-(methylsulfonyl)-2-pyrazinyl]oxy]cyclohexyl]oxy]-, 1,1-dimethylethyl ester

	Spiro[2*H*-1-benzopyran-2,4'-piperidine]-1'-carboxylic acid, 3,4-dihydro-6-[4-[[(2-pyridinylmethyl)sulfonyl]methyl]phenyl]-, (1*R*)-2,2,2-trifluoro-1-methylethyl ester	2-Methyl-2-propanyl 4-(5-{[4-(methylsulfonyl)benzyl]oxy}-2-pyrimidinyl)-1-piperazinecarboxylate	PSN-632408	3-(Trifluoromethyl)-3-oxetanyl (3*R*)-4-[5-[(3-cyano-4-pyridinyl)methoxy]-2-pyrimidinyl]-3-methyl-1-piperazinecarboxylate
	Pyrrolo[3,4-*c*]pyrazole, 5-[1-(5-ethyl-2-pyrimidinyl)-4-piperidinyl]-2-[2-fluoro-4-(methylsulfonyl)phenyl]-2,4,5,6-tetrahydro-	Isopropyl 9-({5-methyl-6-[(2-methyl-3-pyridinyl)oxy]-4-pyrimidinyl}oxy)-3-oxa-7-azabicyclo[3.3.1]nonane-7-carboxylate – antagonistic isomer		PSN119-1M
	PSN-632408	1-Piperidinecarboxylic acid, 4-[5-[2-fluoro-4-(methylsulfonyl)phenyl]-5,6-dihydropyrrolo[3,4-*c*]pyrazol-2(4*H*)-yl]-, 1-methylethyl ester		1,1-Dimethylethyl 4-[1-methyl-2-[[2-(2,3,6-trifluorophenyl)acetyl]amino]ethyl]-1-piperidinecarboxylate
		PSN-632408		1-Piperidinecarboxylic acid, 4-[5-[2-fluoro-4-(methylsulfonyl)phenyl]-5,6-dihydropyrrolo[3,4-*c*]pyrazol-2(4*H*)-yl]-, 1-methylethyl ester
		Isopropyl 4-({5-methyl-6-[(2-methyl-3-pyridinyl)oxy]-4-pyrimidinyl}oxy)-1-piperidinecarboxylate		2-Methyl-2-propanyl 4-({1-[4-(methylsulfonyl)phenyl]-2-oxo-1,2-dihydro-4-pyridinyl}oxy)-1-piperidinecarboxylate
		2-Methyl-2-propanyl 4-({1-[4-(methylsulfonyl)phenyl]-2-oxo-1,2-dihydro-4-pyridinyl}oxy)-1-piperidinecarboxylate		Isopropyl 4-({5-methyl-6-[(2-methyl-3-pyridinyl)oxy]-4-pyrimidinyl}oxy)-1-piperidinecarboxylate
		1-Piperidinecarboxylic acid, 4-[2-[2-fluoro-4-(methylsulfonyl)phenyl]-2,6-dihydropyrrolo[3,4-*c*]pyrazol-5(4*H*)-yl]-, 1-methylethyl ester		Isopropyl 9-({5-methyl-6-[(2-methyl-3-pyridinyl)oxy]-4-pyrimidinyl}oxy)-3-oxa-7-azabicyclo[3.3.1]nonane-7-carboxylate – agonistic isomer
				Pyrrolo[3,4-*c*]pyrazole, 5-[1-(5-ethyl-2-pyrimidinyl)-4-piperidinyl]-2-[2-fluoro-4-(methylsulfonyl)phenyl]-2,4,5,6-tetrahydro-
				3-Pyridinecarbonitrile, 4-[[[2-[8-[5-(1-methylethyl)-1,2,4-oxadiazol-3-yl]-3,8-diazabicyclo[3.2.1]oct-3-yl]-5-pyrimidinyl]oxy]methyl]-

				3,8-Diazabicyclo[3.2.1]octane-8-carboxylic acid, 3-[5-[(3-cyano-4-pyridinyl)methoxy]-2-pyrimidinyl]-, 2,2,2-trifluoroethyl ester
				Benzonitrile, 3-chloro-4-[[6-[[(3-*exo*)-8-(cyclopropylsulfonyl)-8-azabicyclo[3.2.1]oct-3-yl]oxy]-5-methyl-4-pyrimidinyl]amino]-

Table 1. Extra precision results for the GPR119 receptor model from the molecular dynamics simulations frames 150, 200, 250 and 350. The 76 tested ligands can be accessed through DOI:10.1021/acs.jmedchem.5b01198

4.2 Computational Analysis

Prestwick phytochemicals offered 320 total molecules, from which 42 were handpicked for the docking experiments. The criteria for the selection was based on size and polarity. If a ligand had a molecular weight less than 200 g/mol, the assumption was that it would not be big or long enough to interact with the conserved Trp6.48 residue found in TMH 6, which acts as a toggle switch for the activation of the GPR119 receptor[9]. The second point was charge; if a molecule was charged, the likelihood of the ligand entering the binding pocket was low, due to the overall non-polar environment created by the seven transmembrane helices. Therefore, these 42 molecules had the optimal size and charge and were docked to each of the GPR119 receptor frames.

For clarity in the display of the results, the top ten best Glide scoring molecules were selected for each frame analyzed; the rest of the molecules are shown in the Appendix. Out of the approximately 21,000 molecules analyzed through the sequential virtual screening protocol (automated) using HTVS, SP and XP, 1,632 compounds docked in the frame 150 GPR119 receptor structure (7.8%); 1,735 compounds docked in the frame 200 GPR119 receptor structure (8.3%) and 1,701 compounds docked in the frame 250 GPR119 receptor structure (8.1%).

A second computational study was done in parallel to the automated sequential virtual screening study where the ligands were docked using HTVS by itself, the results obtained from that algorithm were used as input for a SP docking calculation, and subsequently, the results from the SP docking where used as input for XP docking.

This stepwise (manual) set of calculations were done to see if the resulting molecules were the same for both analyses and to compare the time it took to perform the automated and the stepwise calculations. The results of the stepwise analysis for frames 150, 200 and 250 were

1,135 (5.4%), 1,217 (5.8%), and 1,179 (5.6%) molecules, respectively. The difference in the results between the two computational methods might be due to the variation in parameters in the algorithms compared to when they ran using the sequential virtual screening protocol. The variation is most probably due to the number of conformations retained for each ligand. When the docking algorithms are run through the automatic protocols, some of the options are preset compared to when using just one of the docking methods. Also, since HTVS and SP use the same algorithm, but different docking criteria, it is safe to say that the results would not vary much between these steps. However, when run together with more specific restrictions, like those imposed by XP, the calculation might not have been able to eliminate double positives or penalize unfavorable interactions[20, 34, 38].

For the time analysis comparison, the stepwise experiment took longer than the automated sequential virtual screening protocol. For example, for the 20,000 compounds of the Zinc library, the stepwise experiment the HTVS calculation took approximately 4 hours, the SP calculation took 6 hours and the XP calculation took 32 hours for a total of 42 hours. In the automated sequential virtual screening analysis, the complete calculation took approximately 34 hours. This time difference was not as noticeable with the Prestwick phytochemical library, which only contained 42 compounds, since both the stepwise and the automated docking protocols took around 5 hours. Even though the automated sequential virtual screening calculation might take less time than the stepwise calculations, it is important to understand that false positives or different docking poses of the same structure might be present.

The analysis of the results of the Prestwick phytochemicals for each of the GPR119 receptor structures from the chosen frames are represented in **Tables 2, 5** and **8**. Molecules that tended to repeat between frames makes them attractive candidates for in vitro analysis, because

they fit into the GPR119 receptor (Glide scores -12.434 to -7.940 kcal/mol), regardless of how closed or open it was. The molecules that repeated between the three frames were verbenalin (average Glide score -10.03 kcal/mol), 4,4'-(2,3-dimethyltetramethylene)dipyrocatechol (average Glide score -10.31 kcal/mol) and chlorogenic acid (average glide score -9.763 kcal/mol).

For the SelleckChem and Prestwick GPCR libraries, it can be seen in **Tables 3, 6** and **9** that the compounds that got the highest (more negative) Glide scores varied from frame to frame. However, just like for the Prestwick phytochemicals library, a trend was observed, where the top compounds tended to repeat more often between frame 150 and frame 200, and at a reduced frequency in frame 250. It may be that this trend is associated with the state of the receptor, since for frames 150 and 200 the receptor is in a more closed conformation, before the binding pocket becomes more hydrated as in frame 250. Therefore, similar intermolecular forces should be found among them. The highest Glide score achieved in the GPCR libraries was obtained for D-Glucitol, 1,5-anhydro-1-*C*-[3-[[5-(4-fluorophenyl)-2-thienyl]methyl]-4-methylphenyl]-, (1*S*)- (-12.87 kcal/mol) and the lowest was by dobutamine (-8.477 kcal/mol), both from frame 250.

Tables 4, 7 and **10** show the results for the Zinc Naturals library. Most of the names for this library were found by searching databases and literature; nevertheless, some of them were not able to be identified. For the compounds for which names were not found the Zinc ID was provided. As shown in **Tables 4, 7** and **10,** the compounds varied in molecular weight from the mid 200 Da to the high 500 Da, which highlights the versatility of the GPR119 receptor for interacting with both simple and more complex molecules. The Glide scores were among the highest (-11.68 kcal/mol to -13.57 kcal/mol) for each of the frames, which signifies that the ligands from Zinc Naturals library are more likely to fit better in the binding pocket of the GPR119 receptor compared to the other libraries.

The molecular structure of the ligands for each library is presented right after the corresponding tables. In frame 150, the molecules selected tended to be long and slender, similar to AR231453 and its derivates. As expected, as the receptor relaxed and opened up, as in frame 250, the ligands selected showed increased structural complexity. Accordingly, in the more open frames, the sizes of the ligands covered a wider range of molecular weight, with the smallest molecule being chrysin (MW 254 g/mol) and the largest one being naringin (MW 580 g/mol). The molecules selected were also increasingly aromatic and some structures even presented extended ring structures containing 7,8 or even 9 atoms.

Frame 150

Table 2- Frame 150. Top 10 compounds using the automated sequential virtual screening protocol (HTVS, SP, XP) for Prestwick phytochemicals				
Chem spider ID	**Chemical name**	**Molecular formula**	**Monoisotopic mass (Da)**	**Glide score (kcal/mol)**
66163	Verbenalin	$C_{17}H_{24}O_{10}$	388.1	-10.04
64490	4,4'-(2,3-dimethyltetramethylene)dipyrocatechol	$C_{18}H_{22}O_4$	302.1	-9.854
58507	Baicalin	$C_{21}H_{18}O_{11}$	446.1	-9.484
9734	Glycocholic Acid	$C_{26}H_{43}NO_6$	465.3	-9.311
1405788	Chlorogenic acid	$C_{16}H_{18}O_9$	354.1	-9.279
2442	(+) s-Camptothecine	$C_{20}H_{16}N_2O_4$	348.1	-8.616
32815523	Menaquinone	$C_{36}H_{48}O_2$	512.4	-8.049
91814	(-) α-Lobeline	$C_{22}H_{27}NO_2$	337.2	-8.015
9710	Glycyrrhetinic acid	$C_{30}H_{46}O_4$	470.3	-7.944
1265957	Capsaicin	$C_{18}H_{27}NO_3$	305.2	-7.940

Table 2. 10 best Glide scoring compounds for Prestwick phytochemicals in Frame 150

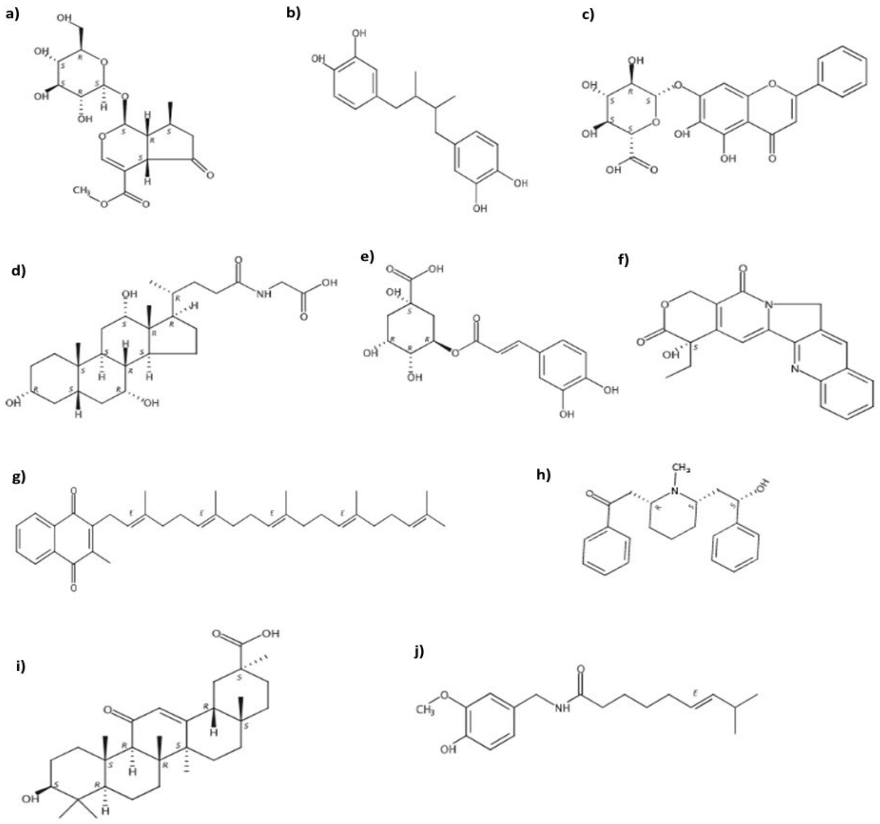

Figure 10. Best glide scoring Pretwick phytochemicals molecules for Frame 150. a) verbaline, b) 4,4'-(2,3-dimethyltetramethylene)dipyrocatechol), c) baicalin, d) glycocholic acid, e) chlorogenic acid, f) (+) s-camptothecine, g) menaquinone, h) (-) α-lobeline, i) glycyrrhetinic acid and j) capsaicin

Table 3- Frame 150. Top 10 compounds using the automated sequential virtual screening protocol (HTVS, SP, XP) for Selleckchem and Prestwick GPCRs				
Chem spider ID	**Chemical name**	**Molecular formula**	**Monoisotopic mass (Da)**	**Glide score (kcal/mol)**
10123957	Empagliflozin	$C_{23}H_{27}ClO_7$	450.1	-11.23
8063384	Dapagliflozin	$C_{21}H_{25}ClO_6$	408.1	-10.88
16498836	Phlorizin	$C_{21}H_{24}O_{10}$	436.1	-10.86
10122984	Shanzhiside	$C_{16}H_{24}O_{11}$	392.1	-10.26
5293454	Flibanserin	$C_{20}H_{21}F_3N_4O$	390.2	-10.11
4953629	Netupitant	$C_{30}H_{32}F_6N_4O$	578.2	-10.10

3292	Formoterol	$C_{19}H_{24}N_2O_4$	344.2	-9.171
3690	Ketanserin	$C_{22}H_{22}FN_3O_3$	395.2	-9.006
3056	Droperidol	$C_{22}H_{22}FN_3O_2$	379.2	-9.016
5208	Terazosin	$C_{19}H_{25}N_5O_4$	387.2	-8.875

Table 3. 10 best Glide scoring compounds for the GPCRs libraries in Frame 150

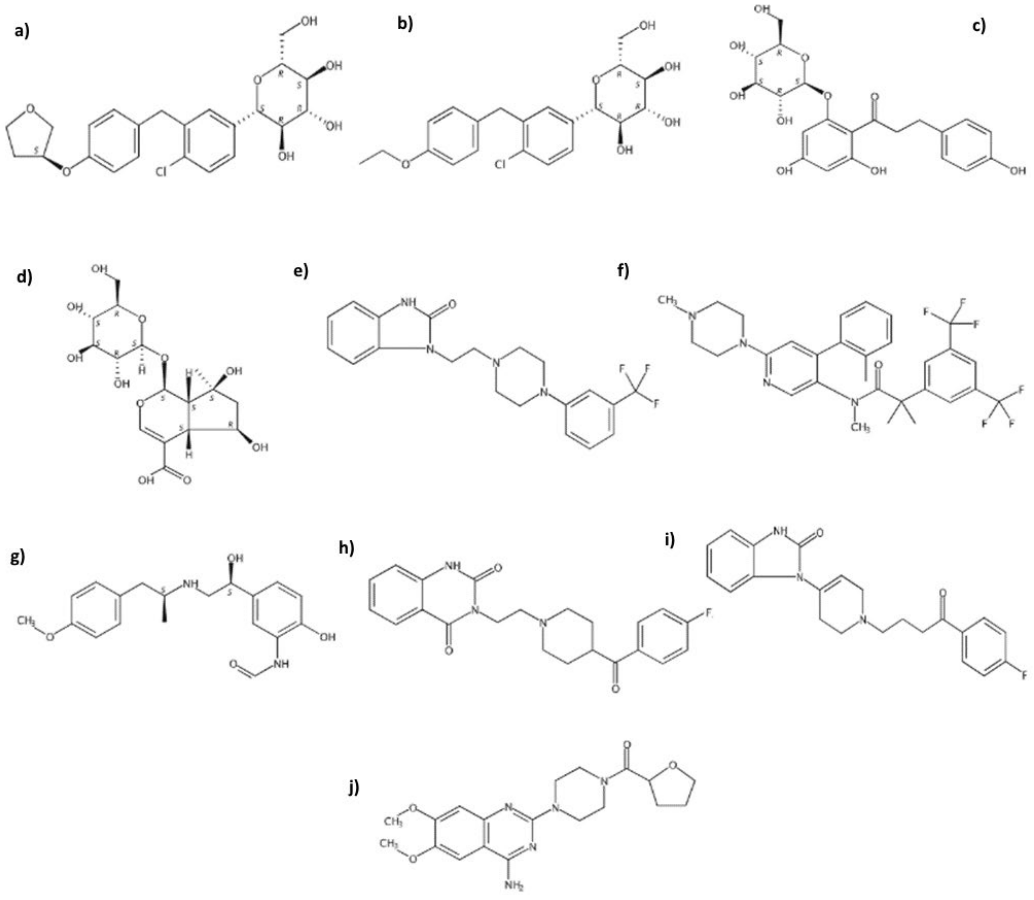

Figure 11. Best glide scoring for GPCR molecules for Frame 150. a) empagliflozin, b) dapagliflozin, c) phlorizin, d) shanzhiside, e) flibanserin, f) netupitant, g) formoterol, h) ketanserin, i) droperidol and j) terazosin

Table 4- Frame 150. Top 10 compounds using the automated sequential virtual screening protocol (HTVS, SP, XP) for Zinc Naturals library				
Zinc Naturals ID	**Chemical name**	**Molecular formula**	**Monoisotopic mass (Da)**	**Glide score (kcal/mol)**
ZINC31155896	β-D-Glucopyranoside, 2-(1,3-benzodioxol-5-yl)-3-hydroxypropyl	$C_{16}H_{22}O_9$	358.1	-12.63
ZINC35457506	ZINC35457506	$C_{21}H_{40}O_9$	436.3	-12.54
ZINC36728548	ZINC36728548	$C_{19}H_{20}O_9$	358.1	-11.78
ZINC03842067	1-[(3S,3AR,6R,6aS)-6-phenylmethoxy-2,3,3a,5,6,6a-hexahydrofuro[3,2-*b*]furan-3-yl]-3-(3-cyanophenyl)thiourea	$C_{21}H_{21}N_3O_3S$	395.1	-11.74
ZINC05414350	4-Piperidineacetamide, *N*-cyclohexyl-1-(cyclopropylcarbonyl)-3-ethyl-, (3*R*,4*S*)-	$C_{19}H_{32}N_2O_2$	320.2	-11.68
ZINC31155429	2-Cyclohexen-1-one, 4-[(1*E*)-3-(β-D-glucopyranosyloxy)-1-buten-1-yl]-3,5,5-trimethyl-	$C_{19}H_{30}O_7$	370.2	-11.66
ZINC35442872	1*H*-Benzimidazole, 2-[(3*S*)-1-[(4-methylphenyl)sulfonyl]-3-pyrrolidinyl]-	$C_{18}H_{19}N_3O_2S$	341.1	-11.52
ZINC35442868	Methanone, [(3*S*)-3-(1*H*-benzimidazol-2-yl)-1-pyrrolidinyl](4-fluorophenyl)-	$C_{18}H_{16}FN_3O$	309.1	-11.51
ZINC01667455	2(3*H*)-Furanone, dihydro-3-hydroxy-3,4-bis[(4-hydroxy-3-methoxyphenyl)methyl]-, (3*S*,4*S*)-	$C_{20}H_{22}O_7$	374.1	-11.50
ZINC35457485	ZINC35457485	$C_{20}H_{22}O_{11}$	438.1	-11.68

Table 4. 10 best Glide scoring compounds for the Zinc Naturals library in Frame 150

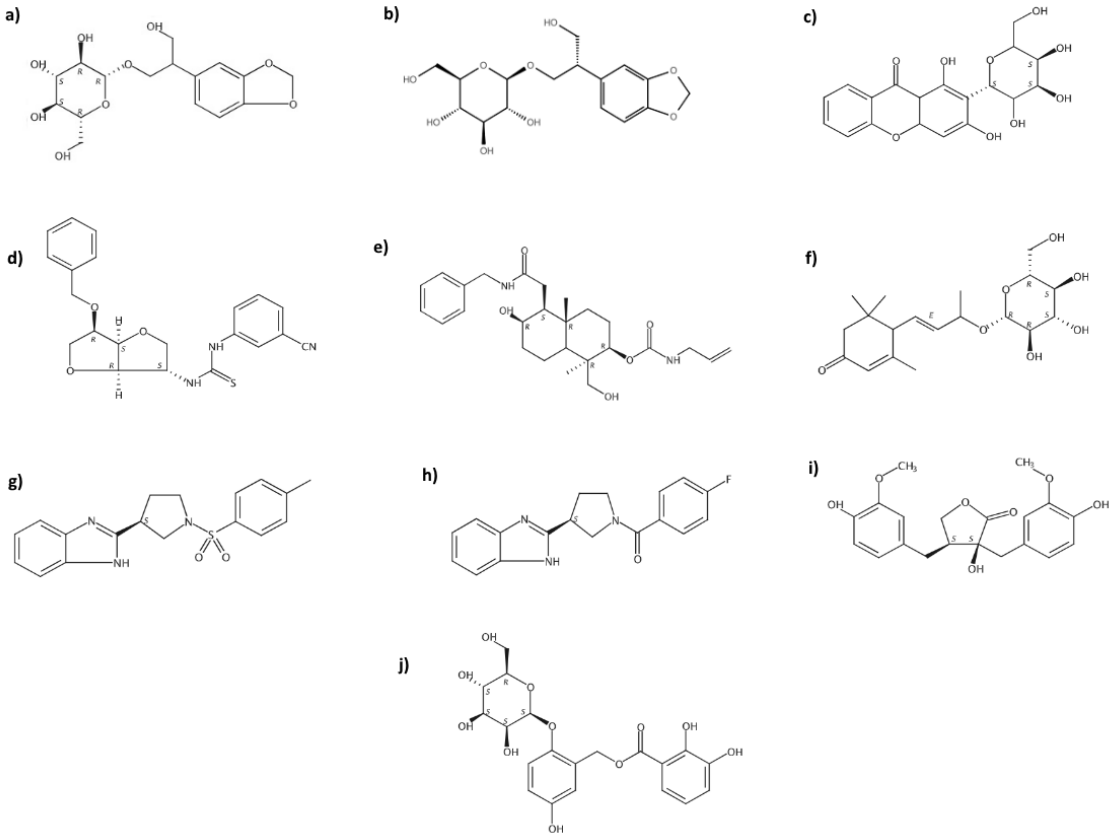

Figure 12. Best glide scoring for zinc library molecules for Frame 150. a) ZINC31155896, b) ZINC35457506, c) ZINC36728548, d) ZINC03842067, e) ZINC05414350, f) ZINC31155429, g) ZINC35442872, h) ZINC35442868, i) ZINC01667455, and j) ZINC35457485

Frame 200

Table 5- Frame 200. Top 10 compounds using the automated sequential virtual screening protocol (HTVS, SP, XP) for Prestwick Phytochemicals				
Chem spider ID	**Chemical name**	**Molecular formula**	**Monoisotopic mass (Da)**	**Glide score (kcal/mol)**
390868	Naringin	$C_{27}H_{32}O_{14}$	580.1791	-12.434
9734	Glycocholic Acid	$C_{26}H_{43}NO_6$	465.3090	-10.789

839564	Curcumin	$C_{21}H_{20}O_6$	368.1259	-10.155
58507	Baicalin	$C_{21}H_{18}O_{11}$	446.0849	-9.793
2442	(+) s-Camptothecine	$C_{20}H_{16}N_2O_4$	348.1109	-9.663
64490	4,4'-(2,3-dimethyltetramethylene)dipyrocatechol	$C_{18}H_{22}O_4$	302.1517	-9.610
4444351	Calciferol	$C_{28}H_{44}O$	396.3392	-9.286
66163	Verbenalin	$C_{17}H_{24}O_{10}$	388.1369	-8.907
1405788	Chlorogenic acid	$C_{16}H_{18}O_9$	354.0950	-8.807
91930	(-)-Cinchonidine	$C_{19}H_{22}N_2O$	294.1732	-8.489

Table 5. 10 best Glide scoring compounds for Prestwick phytochemicals in Frame 200

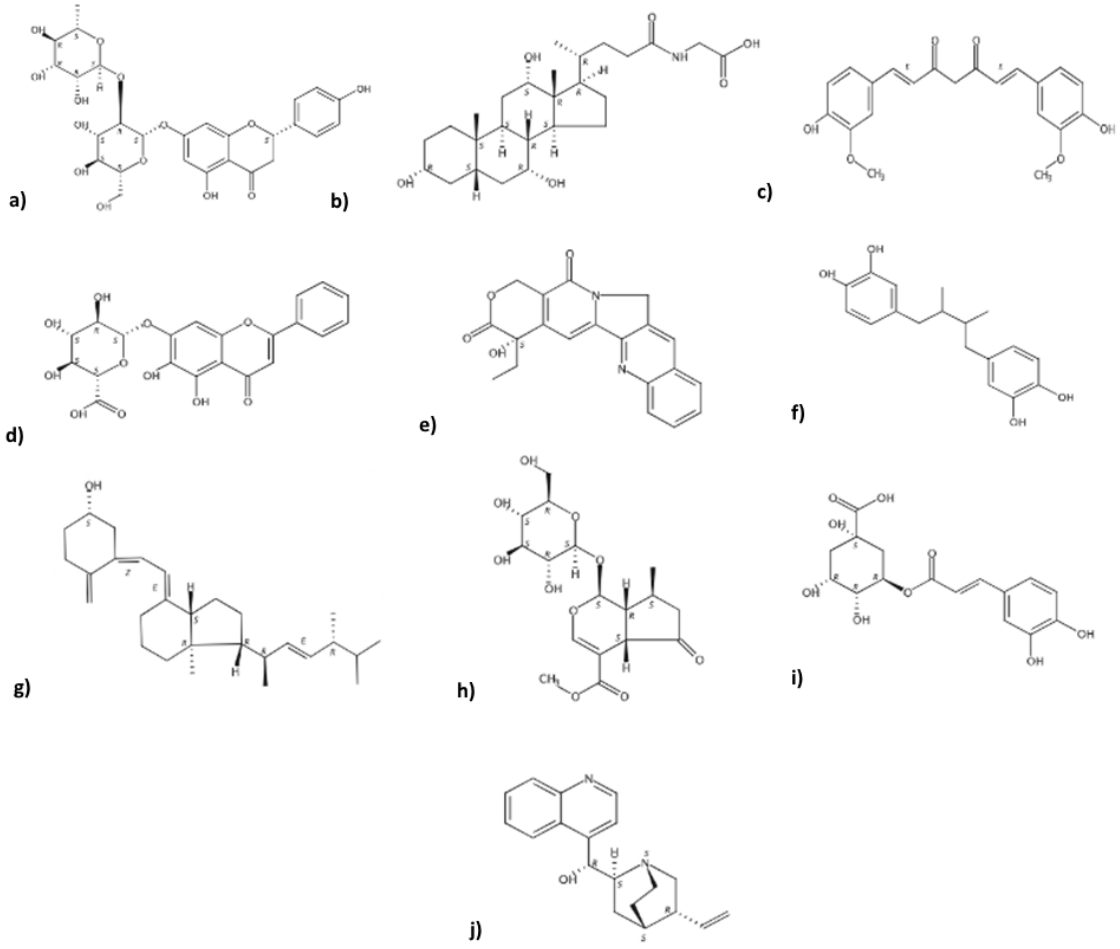

Figure 13. Best glide scoring Pretwick phytochemicals molecules for Frame 200. a) naringin, b) glycocholic acid, c) curcumin, d) baicalin, e) (+) s-camptothecine, f) 4,4'-(2,3-dimethyltetramethylene)dipyrocatechol, g) calciferol, h) verbenalin, i) chlorogenic acid and j) (-)-cinchonidine

Table 6- Frame 200. Top 10 compounds using the automated sequential virtual screening protocol (HTVS, SP, XP)for Selleckchem and Prestwick GPCR libraries				
Chem spider ID	**Chemical name**	**Molecular formula**	**Monoisotopic mass (Da)**	**Glide score (kcal/mol)**
9413866	Azilsartan medoxomil	$C_{30}H_{24}N_4O_8$	568.2	-11.36
8629286	Ipragliflozin	$C_{21}H_{21}FO_5S$	404.1	-11.33
16498836	Phlorizin	$C_{21}H_{24}O_{10}$	436.1	-11.30
31017	Penfluridol	$C_{28}H_{27}ClF_5NO$	523.2	-11.26
16736476	Tropisetron	$C_{17}H_{20}N_2O_2$	284.1	-11.13
4682	Pirenzepine	$C_{19}H_{21}N_5O_2$	351.2	-10.74
3292	Formoterol	$C_{19}H_{24}N_2O_4$	344.2	-10.21
4895	Risperidone	$C_{23}H_{27}FN_4O_2$	410.2	-10.20
17942	1-Azoniabicyclo[2.2.2]octane, 4-[(2-hydroxy-2,2-diphenylacetyl)oxy]	$C_{22}H_{26}BrNO_3$	431.1	-10.13
3255	Fluphenazine	$C_{22}H_{26}F_3N_3OS$	437.2	-10.07

Table 6. 10 best Glide scoring compounds for the GPCRs libraries in Frame 200.

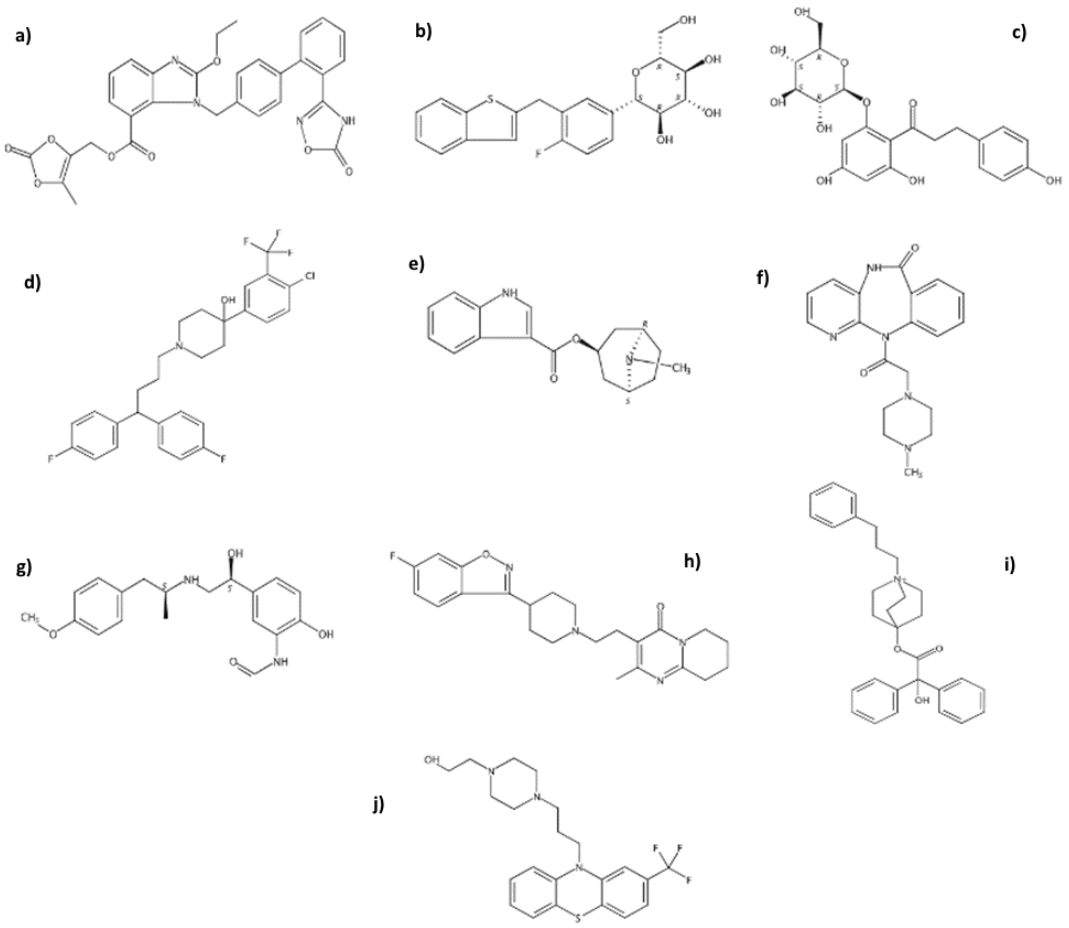

Figure 14. Best glide scoring for GPCR molecules for Frame 200. a) azilsartan medoxomil, b) ipragliflozin, c) phlorizin, d) penfluridol, e) tropisetron, f) pirenzepine, g) formoterol, h) risperidone, i) 1-azoniabicyclo[2.2.2]octane, 4-[(2-hydroxy-2,2-diphenylacetyl)oxy]l and j) Fluphenazine.

Table 7- Frame 200. Top 10 compounds using the automated sequential virtual screening protocol (HTVS, SP, XP) for Zinc Naturals library				
Zinc Naturals ID	**Chemical name**	**Molecular formula**	**Monoisotopic mass (Da)**	**Glide score (kcal/mol)**
ZINC33838191	Pinoresinol-4-*O*-β-D-glucopyranoside	$C_{26}H_{32}O_{11}$	520.2	-12.74
ZINC31163744	ZINC31163744	$C_{20}H_{24}O_{10}$	424.1	-12.30
ZINC04235989	Pyrazino[2,1-*c*][1,4]benzodiazepine-6,12(2*H*,11*H*)-dione, 1,3,4,12a-tetrahydro-2-[(2*S*)-2-hydroxy-2-phenylacetyl]-8-[3-(trifluoromethyl)phenyl]-, (12a*R*)-	$C_{27}H_{22}F_3N_3O_4$	509.2	-11.98

ZINC20463632	(1R,2R,3S,4S,5S)-4-(Bis(cyclopropylmethyl)amino)-2-[4-(2-methoxyphenyl)piperazin-1-yl]-7,8-dioxabicyclo[3.2.1]octan-3-ol	$C_{25}H_{37}N_3O_4$	443.3	-11.56
ZINC35457506	ZINC35457506	$C_{21}H_{40}O_9$	436.3	-11.43
ZINC06041521	(1S)-1,5-Anhydro-1-[5,7-dihydroxy-2-(4-hydroxyphenyl)-4-oxo-4H-chromen-8-yl]-D-glucitol	$C_{21}H_{20}O_{10}$	432.1	-11.44
ZINC08662732	4*H*-1-Benzopyran-4-one, 3-[4-(β-D-glucopyranosyloxy)phenyl]-5-hydroxy-7-methoxy	$C_{22}H_{22}O_{10}$	446.1	-11.25
ZINC35415777	1-Azabicyclo[2.2.2]octane-2-methanamine, 5-(1-methyl-3-phenyl-1*H*-pyrazol-5-yl)-*N*-(phenylmethyl)-, (2*R*,4*S*,5*R*)-	$C_{25}H_{30}N_4$	386.2	-11.21
ZINC31155532	4*H*-1-Benzopyran-4-one, 2-[4-(β-D-glucopyranosyloxy)-1-hydroxy-2,5-cyclohexadien-1-yl]-5-hydroxy-7-methoxy-	$C_{22}H_{24}O_{11}$	464.1	-11.21
ZINC08662730	4*H*-1-Benzopyran-4-one, 3-[4-(α-D-glucopyranosyloxy)phenyl]-5-hydroxy-7-methoxy	$C_{22}H_{22}O_{10}$	446.1	-11.20

Table 7. 10 best Glide scoring compounds for the Zinc Naturals library in Frame 200.

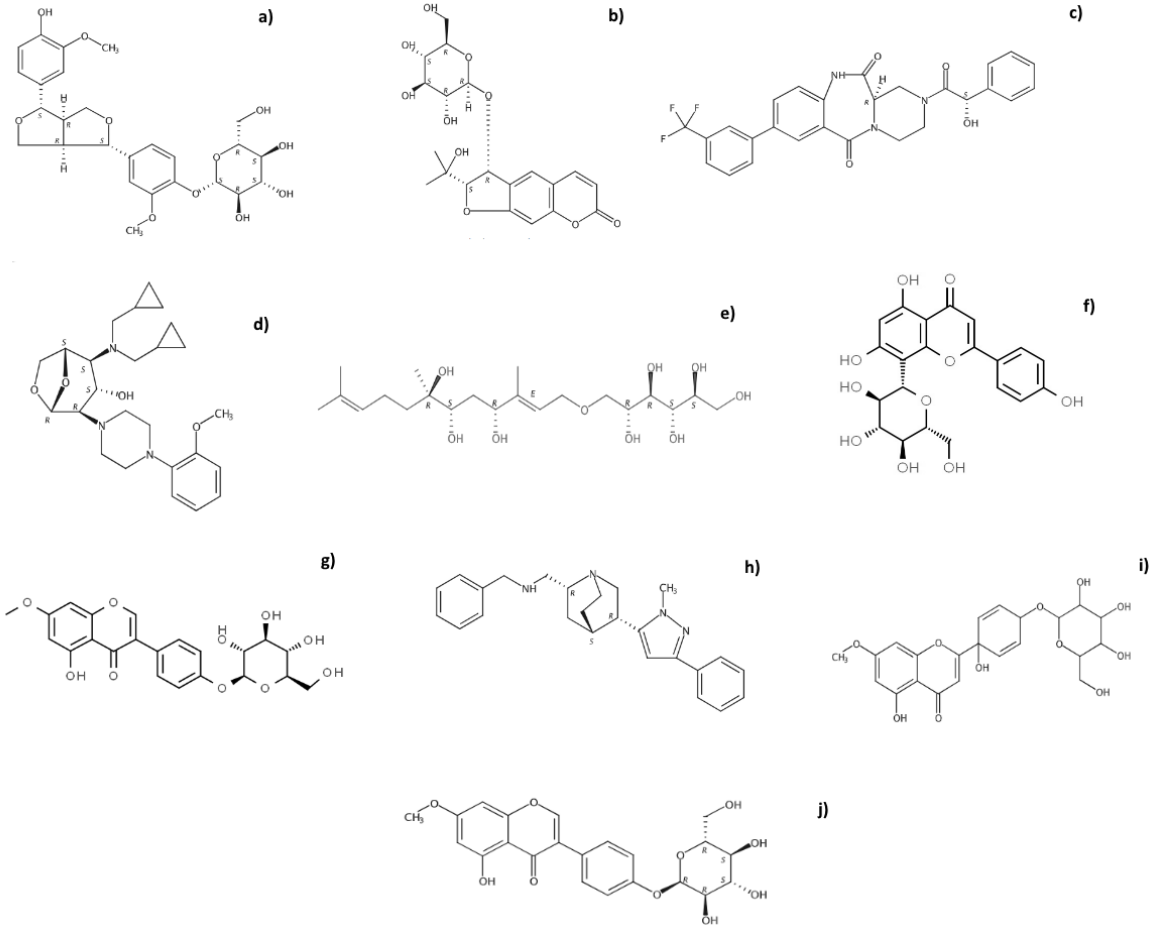

Figure 15. Best glide scoring for zinc molecules for Frame 200. a) ZINC33838191, b) ZINC31163744, c) ZINC04235989, d) ZINC20463632, e) ZINC35457506, f) ZINC06041521, g) ZINC08662732, h) ZINC35415777, i) ZINC31155532, and j) ZINC08662730.

Frame 250

Table 8- Frame 250. Top 10 compounds using the automated sequential virtual screening protocol (HTVS, SP, XP) for Prestwick Phytochemicals library				
Chem spider ID	**Chemical name**	**Molecular formula**	**Monoisotopic mass (Da)**	**Glide score (kcal/mol)**
64490	4,4'-(2,3-dimethyltetramethylene)dipyrocatechol	$C_{18}H_{22}O_4$	302.2	-11.48
1405788	Chlorogenic acid	$C_{16}H_{18}O_9$	354.1	-11.21

57895	Verbenalin	$C_{17}H_{24}O_{10}$	388.1	-10.81
1265957	Capsaicin	$C_{18}H_{27}NO_3$	305.2	-10.20
10127	Abietic acid	$C_{20}H_{30}O_2$	302.2	-10.20
10595	Berlambine	$C_{20}H_{17}NO_5$	351.1	-9.756
4444926	Chrysin	$C_{15}H_{10}O_4$	254.1	-9.538
390541	Ajmalicine	$C_{21}H_{24}N_2O_3$	352.2	-9.388
388383	Naringenine	$C_{15}H_{12}O_5$	272.1	-9.250
4444757	Olivacine	$C_{17}H_{14}N_2$	246.1	-9.003

Table 8. 10 best Glide scoring compounds for Prestwick phytochemicals in Frame 250.

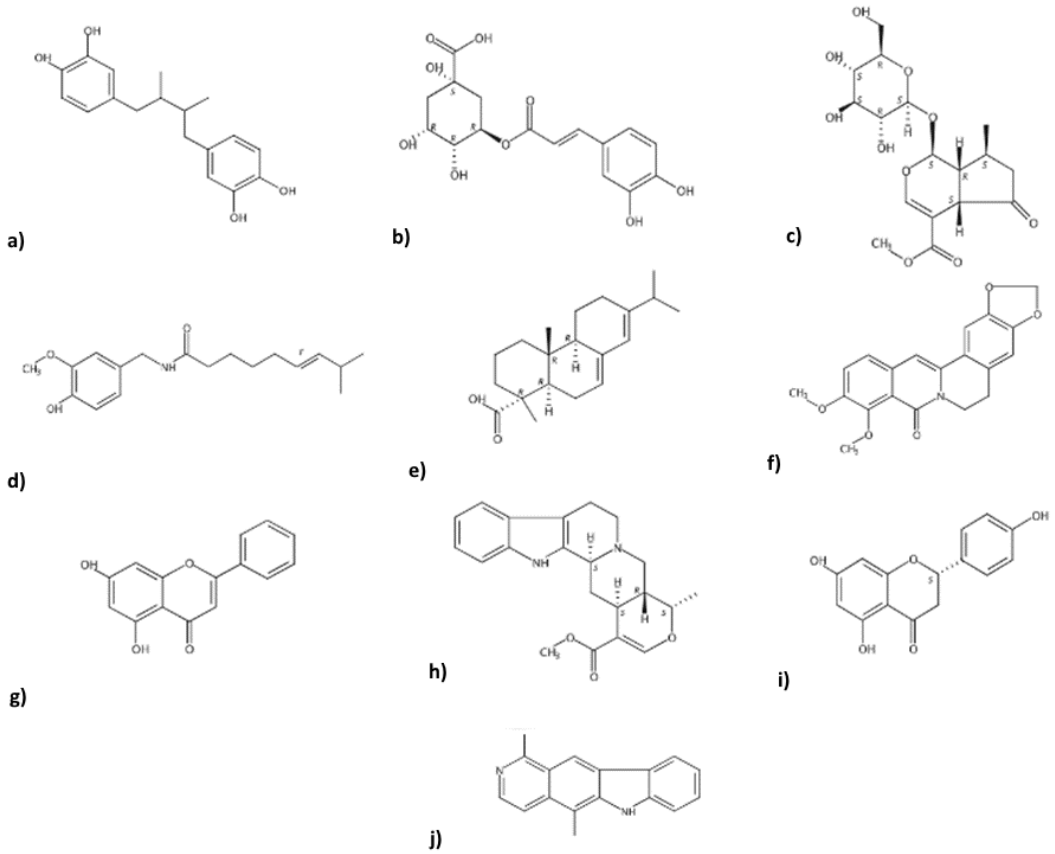

Figure 16. Best glide scoring Prestwick phytochemicals molecules for Frame 250. a) 4,4'-(2,3-dimethyltetramethylene) dipyrocatechol, b) chlorogenic acid, c) verbenalin, d) capsaicin, e) abietic acid, f) berlambine, g) chrysin, h) ajmalicine, i) naringenine and j) olivacine.

Table 9- Frame 250. Top 10 compounds using the automated sequential virtual screening protocol (HTVS, SP, XP)for Selleckchem and Prestwick GPCR libraries				
Chem spider ID	**Chemical name**	**Molecular formula**	**Monoisotopic mass (Da)**	**Glide score (kcal/mol)**
30922970	D-Glucitol, 1,5-anhydro-1-*C*-[3-[[5-(4-fluorophenyl)-2-thienyl]methyl]-4-methylphenyl]-, (1*S*)-	$C_{24}H_{25}FO_5S$	444.1	-12.87
21927676	5-Heptenoic acid, 7-[(1*R*,2*R*,3*R*,5*S*)-3,5-dihydroxy-2-[(3*R*)-3-hydroxy-5-phenylpentyl]cyclopentyl]-, 1-methylethyl ester, (5*Z*)-	$C_{26}H_{40}O_5$	432.3	-9.114
17942	1-Azoniabicyclo[2.2.2]octane, 4-[(2-hydroxy-2,2-diphenylacetyl)oxy]	$C_{22}H_{26}BrNO_3$	431.1	-9.036
3255	Fluphenazine	$C_{22}H_{26}F_3N_3OS$	437.2	-9.003
2703	Cloperastine	$C_{20}H_{24}ClNO$	329.2	-8.930
3690	Ketanserin	$C_{22}H_{22}FN_3O_3$	395.2	-8.898
65040	2-{1-[2-(2,3-Dihydro-1-benzofuran-5-yl)ethyl]-3-pyrrolidinyl}-2,2-diphenylacetamide	$C_{28}H_{30}N_2O_2$	426.2	-8.876
2487	Carvedilol	$C_{24}H_{26}N_2O_4$	406.2	-8.950
599958	Piperidinium, 3-[(2-hydroxy-2,2-diphenylacetyl)oxy]-1,1-dimethyl-, (3*R*)-	$C_{21}H_{26}NO_3$	340.2	-8.509
33786	Dobutamine	$C_{18}H_{23}NO_3$	301.2	-8.477

Table 9. 10 best Glide scoring compounds for the GPCRs libraries in Frame 250.

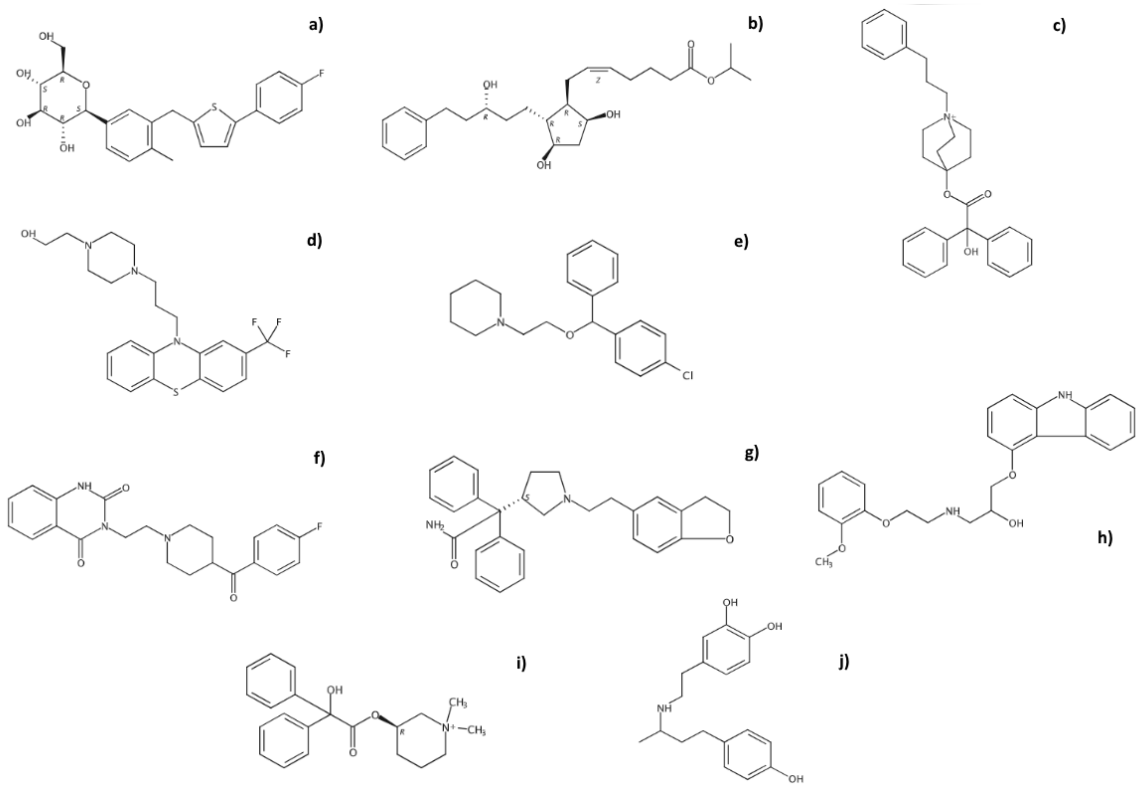

Figure 17. Best glide scoring for GPCR molecules for Frame 250. a) d-Glucitol, 1,5-anhydro-1-*C*-[3-[[5-(4-fluorophenyl)-2-thienyl]methyl]-4-methylphenyl]-, (1*S*)-, b) 5-Heptenoic acid, 7-[(1*R*,2*R*,3*R*,5*S*)-3,5-dihydroxy-2-[(3*R*)-3-hydroxy-5-phenylpentyl]cyclopentyl]-, 1-methylethyl ester, (5*Z*)-, c) 1-Azoniabicyclo[2.2.2]octane, 4-[(2-hydroxy-2,2-diphenylacetyl)oxy], d) fluphenazine, e) cloperastine, f) ketanserin, g) darifenacin, h) carvedilol, i) Piperidinium, 3-[(2-hydroxy-2,2-diphenylacetyl)oxy]-1,1-dimethyl-, (3*R*)-, j) dobutamine.

Table 10- Frame 250. Top 10 compounds using the automated sequential virtual screening protocol (HTVS, SP, XP)for Zinc Naturals library				
Zinc Naturals ID	**Chemical name**	**Molecular formula**	**Monoisotopic mass (Da)**	**Glide score (kcal/mol)**
ZINC36728548	ZINC36728548	$C_{19}H_{20}O_9$	358.1	-13.67
ZINC31155902	β-D-Glucopyranoside, 2-(1,3-benzodioxol-5-yl)-3-hydroxypropyl	$C_{16}H_{22}O_9$	358.1	-13.09

ZINC04236655	Carbamic acid, *N*-(4-methoxyphenyl)-, 5-[2-[(2-furanylmethyl)amino]-2-oxoethyl]decahydro-6-hydroxy-1-(hydroxymethyl)-1,4a-dimethyl-2-naphthalenyl ester	$C_{28}H_{38}N_2O_7$	514.3	-12.73
ZINC35457506	ZINC35457506	$C_{21}H_{40}O_9$	436.3	-12.70
ZINC31155664	2-Cyclohexen-1-one, 4-[(3*R*)-3-(β-D-glucopyranosyloxy)butyl]-3,5,5-trimethyl-, (4*R*)-	$C_{19}H_{32}O_7$	372.2	-12.65
ZINC04236552	Carbamic acid, *N*-ethyl-, (1*R*,2*R*,4a*R*,5*S*,6*R*)-decahydro-6-hydroxy-1-(hydroxymethyl)-5-[2-[[(4-methoxyphenyl)methyl]amino]-2-oxoethyl]-1,4a-dimethyl-2-naphthalenyl ester	$C_{26}H_{40}N_2O_6$	476.3	-12.64
ZINC35457671	β-D-Glucopyranoside, 5-[2-(3-hydroxy-4-methoxyphenyl)ethyl]-2-hydroxy-6-methoxyphenyl	$C_{22}H_{28}O_{10}$	452.2	-12.64
ZINC08681833	4*H*-1-Benzopyran-4-one, 2-[4-(β-D-glucopyranosyloxy)phenyl]-2,3-dihydro-7-hydroxy-, (2*S*)-	$C_{21}H_{22}O_9$	418.1	-12.46
ZINC04236634	Carbamic acid, *N*-(1-methylethyl)-, (1*R*,2*R*,4a*R*,5*S*,6*R*)-decahydro-6-hydroxy-1-(hydroxymethyl)-5-[2-[(2*S*)-2-(hydroxymethyl)-1-pyrrolidinyl]-2-oxoethyl]-1,4a-dimethyl-2-naphthalenyl ester	$C_{24}H_{42}N_2O_6$	454.3	-12.40
ZINC04236575	Carbamic acid, *N*-2-propen-1-yl-, (1*R*,2*R*,4a*R*,5*S*,6*R*)-decahydro-6-hydroxy-1-(hydroxymethyl)-1,4a-dimethyl-5-[2-oxo-2-[(phenylmethyl)amino]ethyl]-2-naphthalenyl ester	$C_{26}H_{38}N_2O_5$	458.3	-12.37

Table 10. 10 best Glide scoring compounds for the Zinc Naturals library in Frame 250.

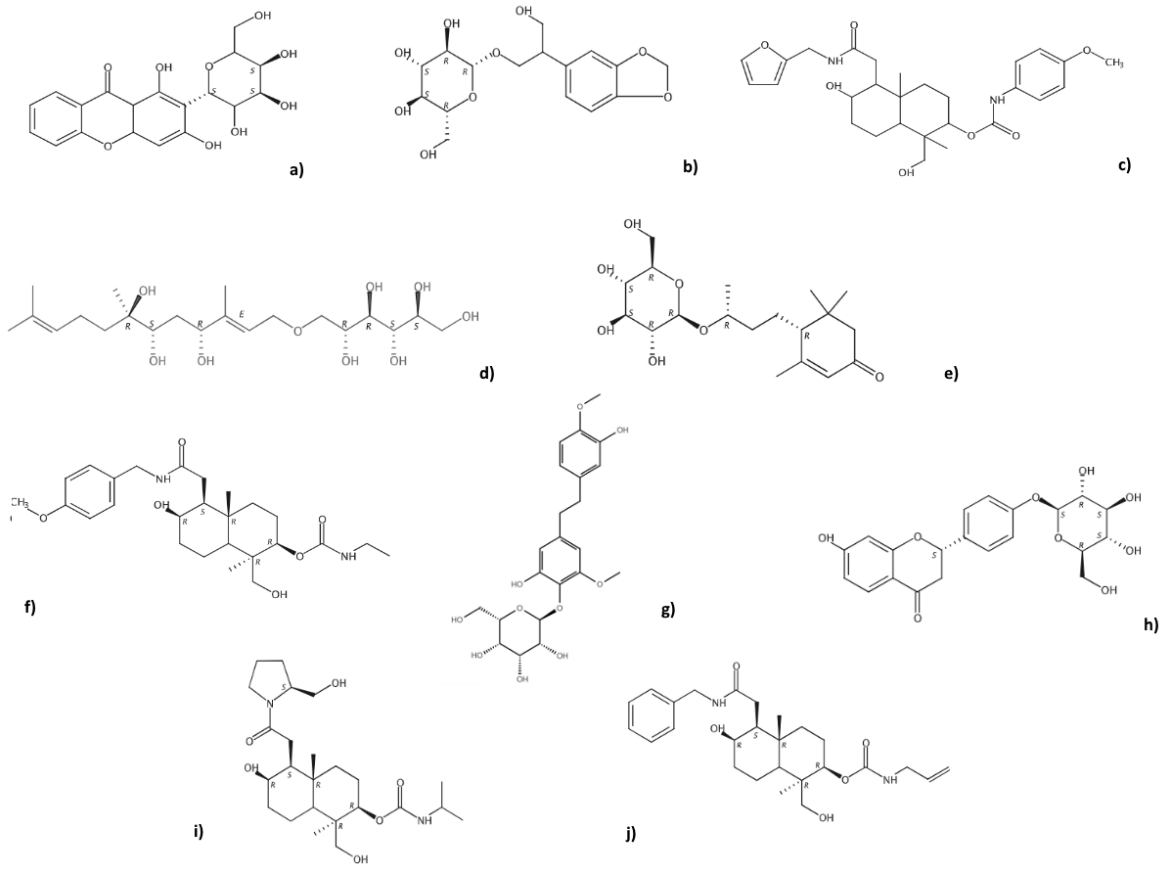

Figure 18. Best glide scoring for zinc molecules for Frame 250. a) ZINC36728548, b) ZINC31155902, c) ZINC04236655, d) ZINC35457506, e) ZINC31155664, f) ZINC04236552, g) ZINC35457671, h) ZINC08681833, i) ZINC04236634, j) ZINC04236575.

4.3 Wet Lab Ligand Selection and Computational Results

After the computational analysis performed on the chemical libraries, the procedure was implemented on 4 molecules that were already in wet lab. Three of these molecules AR231453, AR437735, and oleoyl serinol shown in **Figure 19** have been reported in the literature to be agonists for the GPR119 receptor[4, 18, 21, 39]. AR437735 was made by a collaborator's organic

synthesis group, and this molecule is a variation of the consolidated agonist AR231453, both previously patented by Arena pharmaceuticals. Oleoyl serinol was chosen for the experiment due to its close resemblance to the natural body activator of GPR119, oleoylethanolamide (OEA), and lastly SRT1720 was a novel molecule chosen for the experiment even though it has never been studied for the interaction with this specific receptor. It has been reported that SRT1720, shown in **Figure 19,** is a selective activator of the SIRT1 receptor belonging to sirtuin family of proteins which are associated with diseases like aging, metabolism impairment and periapical peridionitis. Therefore, it would be interesting to see if this compound could be repurposed for a new receptor [40-41].

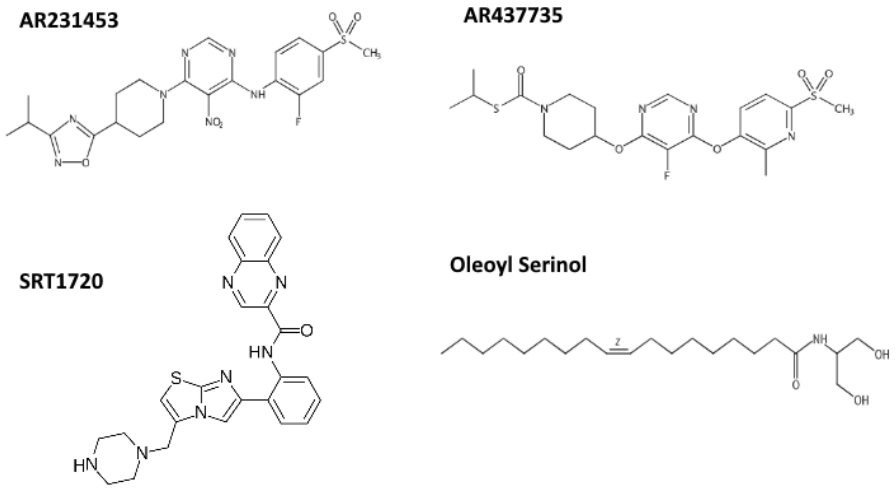

Figure 19. Molecular structures for the molecules used in the wet lab experiments

Table 11 presents the computational results of the automated sequential virtual screening protocol analysis based on the GPR119 homology model structure from frames 150, 200, 250 and 300. In Frame 150, the only molecules that fit were oleoyl serinol and SRT1720; oleoyol serinol is a lipid-like molecule that can fit in the receptor with no problem since the GPR119

tends to accept molecules with this type of structure. However, SRT1720, as seen in **Figure 12,** is bulky and elongated. Typical observations of the almost closed receptor at Frame 150 would suggest that SRT1720 would not be able to fit in the pocket but perhaps the intermolecular interactions with the α helical bundle are favorable for the structure in this stage of the homology model. Frame 200 allowed all molecules with exception of AR437735, and frames 250 and 300, which were more open and the binding pocket more hydrated, were able to fit the four molecules. To create some consistency between the results of the library and give a realistic image of the receptor in the body, frame 250 was selected for the automated sequential virtual screening protocol analysis.

Table 11-Frame comparison of HTVS, SP and XP results for the experimentally tested molecules			
Frame 150	**Frame 200**	**Frame 250**	**Frame 300**
Oleoyl Serinol	Oleoyl Serinol	Oleoyl Serinol	Oleoyl Serinol
SRT1720	AR231453	SRT1720	AR437735
	SRT1720	AR231543	AR231543
		AR437735	SRT1720

Table 11. The automated sequential virtual screening protocol results for oleoyl serinol, AR231453, AR437735 and SRT1720.

The results of the computational analysis done in Frame 250 can be seen in **Table 12**. The highest glide score (-7.961 kcal/mol) was found to be for oleoyl serinol, which was not surprising since as previously mentioned, it has a very similar chemical structure to OEA, predicting its favorable fitting into the binding pocket of GPR119. AR231453 and AR437735 had very similar Glide scores, which could be attributed to AR147735 having a chemical core

based on AR231453, as shown in **Figure 12**. SRT1720, on the other hand, had one of the lowest glide scores of the overall computational analysis (~21,000 compounds) at -3.758 kcal/mol, which indicates that the molecule can fit in the receptor binding pocked, but that the fit would be more strained than for the other compounds analyzed.

Table 12- Drugs used for the cAMP determination experiment (frame 250)					
Chem spider ID	**Chemical name**	**Molecular formula**	**Monoisotopic mass (Da)**	**Glide score (kcal/mol)**	**EC_{50} (nM)**
21377588	Oleoyl Serinol	$C_{21}H_{41}NO_3$	355.3	-7.961	96.64
23330691	AR231453	$C_{21}H_{24}FN_7O_5S$	505.2	-7.286	10.89
CAS No. 1628699-93-3	AR437735	$C_{21}H_{24}FN_7O_5S$	505.2	-7.186	10.06
20581461	SRT1720	$C_{25}H_{23}N_7OS$	469.2	-3.758	N/A

Table 12. Drugs used for the ELISA cAMP colorimetric assay.

4.4 *In Vitro* Studies

Once the results from the computational analysis indicated that three of the four molecules in **Figure 19** (oleoyl serinol, AR231453, and AR437735) would more than likely fit into the receptor, cAMP ELISA colorimetric assays were performed for each compound. **Figure 20** shows the results of the oleoyl serinol vs the AR231453. As can be seen from the graph, both

ligands present agonistic activity, varying only in the EC_{50} values (half maximal response achieved by concentration of drug). In the cAMP analysis for oleoyl serinol the calculated EC_{50} was 96 nM which correlates with the good Glide score, -7.96 kcal/mol, from the computational analysis. Also, the experimental EC_{50} of oleoyl serinol was comparable, though better, to 1.6 µM, the EC_{50} value reported for Cohen *et al.* for a cAMP assay using ACTOne HEK293 cells transfected with GPR119 receptor. The difference in values of the EC_{50}s for oleoyl serinol for the cAMP assay might be due to differences in the procedures. For example the Cohen *et al.* paper does not mention that they used charcoal-stripped FBS to prevent early activation of the receptor[42].

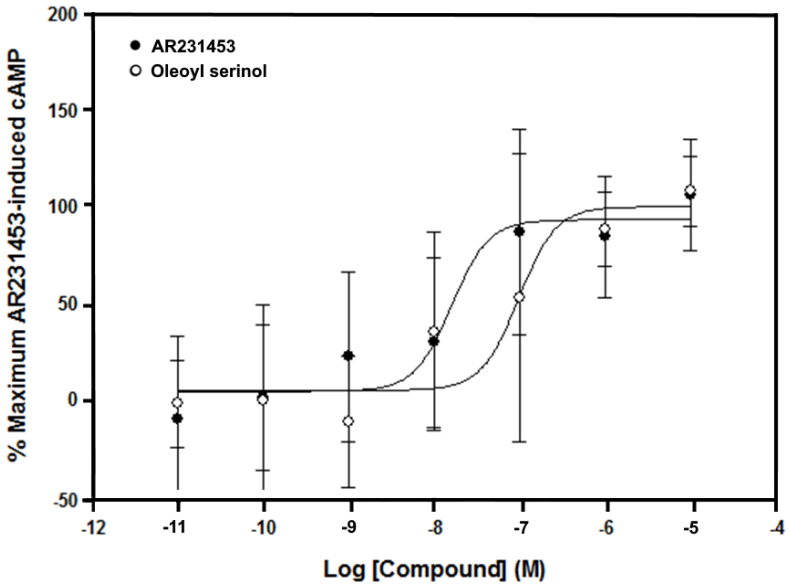

Figure 20. Dose-response curve of wild type HEK293 cells treated with AR231453 and oleoyl serinol and ligand effects on cAMP production.

Figure 21 demonstrates the agonistic activity of AR437735 and from the image it can be seen that there are slight variations between the sigmoidal plots of both tested ligands, with

AR437735 tending to have greater standard deviations and some stray points like the one found at a concentration of $1.0X10^{-5}$ M. Nonetheless, both compounds show a similar activation of the receptor; this is confirmed by comparing the Glide scores which were -7.286 kcal/mol for AR231453 and -7.186 kcal/mol for AR437735. Literature EC_{50}s were also in accordance with the results, providing a value of 10.5 nM for AR231453 and 0.1-1 nM for AR437735. More than likely, the difference in the results could be attributed to differences in the experimental methods.

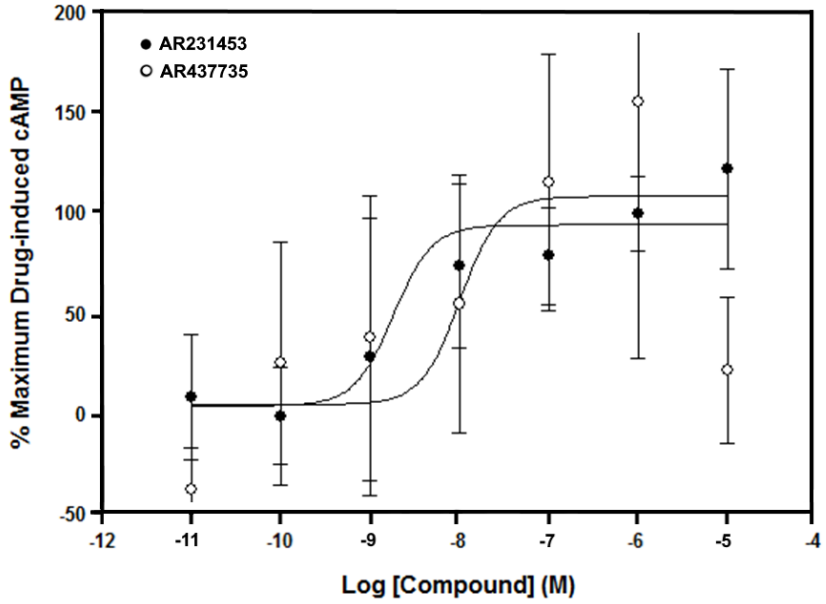

Figure 21. Dose-response curve of wild type HEK293 cells treated with AR231453 and AR437735 and ligand effects on cAMP production.

The SRT1720 vs AR231453 results are shown in **Figure 22**. The SRT1720 ligand had never been tested with the GPR119 receptor even though it has been reported that its target receptor, SRIT1, could be involved in the activity of other GPCR receptors, like GPR30, which regulates the GPER pathway (breast cancer influencer)[43]. From **Figure 22**, it can be seen that SRT1720 did not promote any receptor-dependent cAMP production, since its activity is in the

zero range. This statement is also shown in **Table 12** where no EC_{50} was able to be calculated from the results of the ligand. The computational analysis for SRT1720 suggested that the ligand may fit into the receptor's binding pocket since a Glide score was reported. However, the Glide score is move positive, -3.758 kcal/mol, compared to the agonists suggesting that SRT1720 may not fit well in the binding pocket and so it was not able to activate the GPR119 receptor.

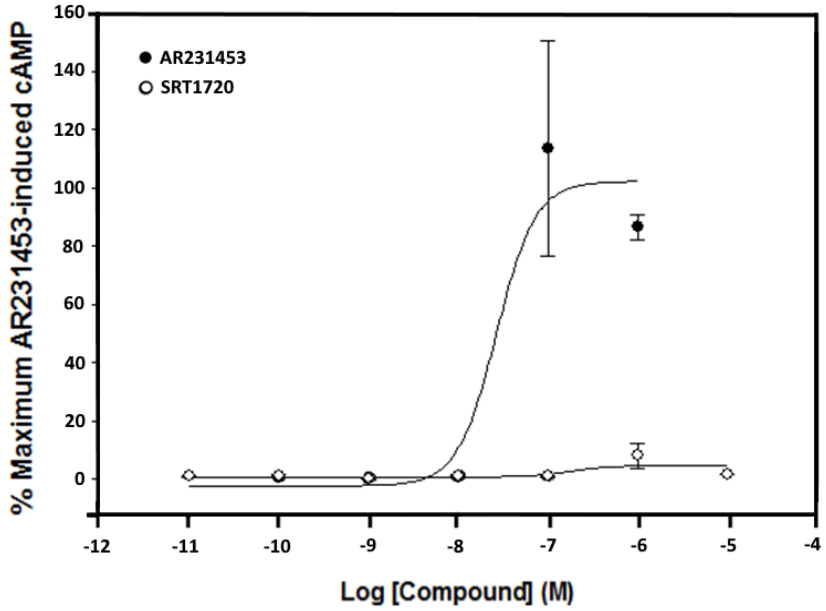

Figure 22. Dose-response curve of wild type HEK293 cells treated with AR231453 and SRT1720 and ligand effects on cAMP production.

CHAPTER V

CONCLUSION

GPR119 is a transmembrane receptor that belongs to the type A GPCR family and is involved in the regulation of insulin levels and other hormones. Due to its influence on insulin secretion, research has focused on finding possible drugs to regulate its activity. Pharmaceutical companies have the ability to computationally screen millions of drugs using homology models to find agonists like AR231453, which activate the receptor without major secondary effects. However, their search tends to be solely based on HTVS, a "quick-and-dirty" algorithm.

This study proposed the possibility of using three computational screening algorithms (high throughput virtual screening, standard precision and extra precision virtual screening) in sequentially, based on an in-house homology model of the GPR119 receptor for the efficient and cost-effective analysis of 21,000 chemical compounds from 4 chemical libraries. From the automated sequential virtual screening protocol results, approximately ~2,100 compounds fit the GPR119 receptor with promising Glide scores (likelihood of fitting in a binding pocket) varying from -3.20 kcal/mol to -13.80 kcal/mol.

The compounds AR231453, AR437735, oleoyl serinol and SRT1720 available in the lab, were tested both computationally (virtual screening using Glide docking) and experimentally using a cAMP ELISA colorimetric assay to test the correlation between virtual screening/Glide docking results of the ligands and their ability to induce GPR119 mediated cAMP production. The results showed that AR231453, AR437735 and oleoyl serinol, which had a more negative Glide score compared to SRT1720, promoted agonistic activity in the receptor and their EC_{50}

values were in close accordance with the literature. SRT1720 on the other hand, which had a more positive Glide score, did not promote any cAMP build up. This result might suggest either that SRT1720 does not fit well in the receptor binding pocket resulting in no activation, or that it could be an antagonist for the receptor. However, competitive inhibition experiments would need to be made to prove this characterization of SRT1720.

REFERENCES

1. Zhou, Q., et al., Common Activation Mechanism of Class a Gpcrs. *eLife* **2019**, *8*, e50279.

2. Latorraca, N. R.; Venkatakrishnan, A. J.; Dror, R. O., Gpcr Dynamics: Structures in Motion. *Chem Rev* **2017**, *117*, 139-155.

3. Lameh, J.; Cone, R. I.; Maeda, S.; Philip, M.; Corbani, M.; Nádasdi, L.; Ramachandran, J.; Smith, G. M.; Sadée, W., Structure and Function of G Protein Coupled Receptors. *Pharmaceutical Research* **1990**, *7*, 1213-1221.

4. Engelstoft, M. S.; Norn, C.; Hauge, M.; Holliday, N. D.; Elster, L.; Lehmann, J.; Jones, R. M.; Frimurer, T. M.; Schwartz, T. W., Structural Basis for Constitutive Activity and Agonist-Induced Activation of the Enteroendocrine Fat Sensor Gpr119. *British Journal of Pharmacology* **2014**, *171*, 5774-5789.

5. Tyurenkov, I. N.; Ozerov, A. A.; Kurkin, D. V.; Logvinova, E. O.; Bakulin, D. A.; Volotova, E. V.; Borodin, D. D., Structure and Biological Activity of Endogenous and Synthetic Agonists of Gpr119. *Russian Chemical Reviews* **2018**, *87*, 151-166.

6. Keshelava, A.; Solis, G. P.; Hersch, M.; Koval, A.; Kryuchkov, M.; Bergmann, S.; Katanaev, V. L., High Capacity in G Protein-Coupled Receptor Signaling. *Nature Communications* **2018**, *9*, 876.

7. Dunham, J. H.; Hall, R. A., Enhancement of the Surface Expression of G Protein-Coupled Receptors. *Trends in biotechnology* **2009**, *27*, 541-5.

8. Latorraca, N. R.; Venkatakrishnan, A. J.; Dror, R. O., Gpcr Dynamics: Structures in Motion. *Chemical Reviews* **2017**, *117*, 139-155.

9. Holst, B.; Nygaard, R.; Valentin-Hansen, L.; Bach, A.; Engelstoft, M. S.; Petersen, P. S.; Frimurer, T. M.; Schwartz, T. W., A Conserved Aromatic Lock for the Tryptophan Rotameric Switch in Tm-Vi of Seven-Transmembrane Receptors. *J Biol Chem* **2010**, *285*, 3973-3985.

10. Norn, C.; Hauge, M.; Engelstoft, M. S.; Kim, S. H.; Lehmann, J.; Jones, R. M.; Schwartz, T. W.; Frimurer, T. M., Mutation-Guided Unbiased Modeling of the Fat Sensor Gpr119 for High-Yield Agonist Screening. *Structure* **2015**, *23*, 2377-2386.

11. Chu, Z.-L., et al., N-Oleoyldopamine Enhances Glucose Homeostasis through the Activation of Gpr119. *Molecular Endocrinology* **2010**, *24*, 161-170.

12. Flock, G.; Holland, D.; Seino, Y.; Drucker, D. J., Gpr119 Regulates Murine Glucose Homeostasis through Incretin Receptor-Dependent and Independent Mechanisms. *Endocrinology* **2011**, *152*, 374-383.

13. Pamir, N., et al., Glucose-Dependent Insulinotropic Polypeptide Receptor Null Mice Exhibit Compensatory Changes in the Enteroinsular Axis. *American journal of physiology. Endocrinology and metabolism* **2003**, *284*, E931-9.

14. Odori, S., et al., Gpr119 Expression in Normal Human Tissues and Islet Cell Tumors: Evidence for Its Islet-Gastrointestinal Distribution, Expression in Pancreatic Beta and Alpha Cells, and Involvement in Islet Function. *Metabolism* **2013**, *62*, 70-78.

15. Tough, I. R.; Forbes, S.; Herzog, H.; Jones, R. M.; Schwartz, T. W.; Cox, H. M., Bidirectional Gpr119 Agonism Requires Peptide Yy and Glucose for Activity in Mouse and Human Colon Mucosa. *Endocrinology* **2018**, *159*, 1704-1717.

16. Zhang, M., et al., High-Throughput Screening for Gpr119 Modulators Identifies a Novel Compound with Anti-Diabetic Efficacy in Db/Db Mice. *PLOS ONE* **2013**, *8*, e63861

17. Friesner, R. A., et al., Glide: A New Approach for Rapid, Accurate Docking and Scoring. 1. Method and Assessment of Docking Accuracy. *Journal of Medicinal Chemistry* **2004**, *47*, 1739-1749.

18. Shiri, F.; Teymoori, M., In Silico Approaches to Explore Structure of New Gpr 119 Agonists for Treatment of Type 2 Diabetes Mellitus. *Medicinal Chemistry Research* **2017**, *26*, 947-961.

19. Walters, W. P., Virtual Chemical Libraries. *Journal of Medicinal Chemistry* **2019**, *62*, 1116-1124.

20. Zhang, X.; Betzi, S.; Morelli, X.; Roche, P., Focused Chemical Libraries--Design and Enrichment: An Example of Protein-Protein Interaction Chemical Space. *Future medicinal chemistry* **2014**, *6*, 1291-307.

21. Ritter, K.; Buning, C.; Halland, N.; Pöverlein, C.; Schwink, L., G Protein-Coupled Receptor 119 (Gpr119) Agonists for the Treatment of Diabetes: Recent Progress and Prevailing Challenges. *Journal of Medicinal Chemistry* **2016**, *59*, 3579-3592.

22. Valentin-Hansen, L.; Holst, B.; Frimurer, T. M.; Schwartz, T. W., Phevi:09 (Phe6.44) as a Sliding Microswitch in Seven-Transmembrane (7tm) G Protein-Coupled Receptor Activation *. *Journal of Biological Chemistry* **2012**, *287*, 43516-43526.

23. Ghosh, S.; Nie, A.; An, J.; Huang, Z., Structure-Based Virtual Screening of Chemical Libraries for Drug Discovery. *Current Opinion in Chemical Biology* **2006**, *10*, 194-202.

24. Dragojlovic, V., Conformational Analysis of Cycloalkanes. *ChemTexts* **2015**, *1*, 14.

25. Mayr, L. M.; Bojanic, D., Novel Trends in High-Throughput Screening. *Current opinion in pharmacology* **2009**, *9*, 580-8.

26. Friesner, R. A.; Murphy, R. B.; Repasky, M. P.; Frye, L. L.; Greenwood, J. R.; Halgren, T. A.; Sanschagrin, P. C.; Mainz, D. T., Extra Precision Glide: Docking and Scoring Incorporating a Model of Hydrophobic Enclosure for Protein−Ligand Complexes. *Journal of Medicinal Chemistry* **2006**, *49*, 6177-6196.

27. Halgren, T. A.; Murphy, R. B.; Friesner, R. A.; Beard, H. S.; Frye, L. L.; Pollard, W. T.; Banks, J. L., Glide: A New Approach for Rapid, Accurate Docking and Scoring. 2. Enrichment Factors in Database Screening. *Journal of Medicinal Chemistry* **2004**, *47*, 1750-1759.

28. Tripathi, S. K.; Muttineni, R.; Singh, S. K., Extra Precision Docking, Free Energy Calculation and Molecular Dynamics Simulation Studies of Cdk2 Inhibitors. *Journal of theoretical biology* **2013**, *334*, 87-100.

29. Kotsikorou, E.; Lynch, D. L.; Abood, M. E.; Reggio, P. H., Lipid Bilayer Molecular Dynamics Study of Lipid-Derived Agonists of the Putative Cannabinoid Receptor, Gpr55. *Chemistry and physics of lipids* **2011**, *164*, 131-43.

30. Syed, S. K.; Bui, H. H.; Beavers, L. S.; Farb, T. B.; Ficorilli, J.; Chesterfield, A. K.; Kuo, M.-S.; Bokvist, K.; Barrett, D. G.; Efanov, A. M., Regulation of Gpr119 Receptor Activity with Endocannabinoid-Like Lipids. *American Journal of Physiology-Endocrinology and Metabolism* **2012**, *303*, E1469-E1478.

31. Zhang, S.-y.; Li, J.; Xie, X., Discovery and Characterization of Novel Smallmolecule Agonists of G Protein-Coupled Receptor 119. *Acta Pharmacologica Sinica* **2014**, *35*, 540-548.

32. Lauffer, L. M.; Iakoubov, R.; Brubaker, P. L., Gpr119 Is Essential for Oleoylethanolamide-Induced Glucagon-Like Peptide-1 Secretion from the Intestinal Enteroendocrine L-Cell. *Diabetes* **2009**, *58*, 1058-66.

33. Mobarec, J. C.; Sanchez, R.; Filizola, M., Modern Homology Modeling of G-Protein Coupled Receptors: Which Structural Template to Use? *Journal of Medicinal Chemistry* **2009**, *52*, 5207-5216.

34. Worth, C. L.; Kreuchwig, A.; Kleinau, G.; Krause, G., Gpcr-Ssfe: A Comprehensive Database of G-Protein-Coupled Receptor Template Predictions and Homology Models. *BMC Bioinformatics* **2011**, *12*, 185.

35. Shoichet, B. K., Virtual Screening of Chemical Libraries. *Nature* **2004**, *432*, 862-5.

36. Sterling, T.; Irwin, J. J., Zinc 15 – Ligand Discovery for Everyone. *Journal of Chemical Information and Modeling* **2015**, *55*, 2324-2337.

37. Meier, A.; Söding, J., Automatic Prediction of Protein 3d Structures by Probabilistic Multi-Template Homology Modeling. *PLoS computational biology* **2015**, *11*, e1004343.

38. Wellenzohn, B.; Lessel, U.; Beller, A.; Isambert, T.; Hoenke, C.; Nosse, B., Identification of New Potent Gpr119 Agonists by Combining Virtual Screening and Combinatorial Chemistry. *Journal of Medicinal Chemistry* **2012**, *55*, 11031-11041.

39. Li, N. X., et al., Gpr119 Agonism Increases Glucagon Secretion During Insulin-Induced Hypoglycemia. *Diabetes* **2018**, *67*, 1401.

40. Mitchell, S. J., et al., The Sirt1 Activator Srt1720 Extends Lifespan and Improves Health of Mice Fed a Standard Diet. *Cell Rep* **2014**, *6*, 836-843.

41. Pacholec, M., et al., Srt1720, Srt2183, Srt1460, and Resveratrol Are Not Direct Activators of Sirt1. *The Journal of biological chemistry* **2010**, *285*, 8340-8351.

42. Cohen, L. J., et al., Commensal Bacteria Make Gpcr Ligands That Mimic Human Signalling Molecules. *Nature* **2017**, *549*, 48-53.

43. Liarte, S.; Alonso-Romero, J. L.; Nicolás, F. J., Sirt1 and Estrogen Signaling Cooperation for Breast Cancer Onset and Progression. *Front Endocrinol (Lausanne)* **2018**, *9*, 552-552.

APPENDIX

APPENDIX

Complete Tables for Frame 150

Table 13-Frame 150: Sequential virtual screening protocol of Prestwick phytochemicals			
Verbenaline	Curcumin	Berberine	Kawain
4,4'-(2,3-dimethyltetramethylene)dipyrocatechol	Cardamonin	Isoliquiritigenin	Conessine
Glycocholic Acid	Naringenine	Biotin	Rauwolscine
Baicalin	Berlambine	Velpinic acid	Corynanthine
Chlorogenic acid	Sanguinarine_min_out	Olivacine	Harmine
Camptothecine (s,+)	1-8-dihydroxy-3-methylanthraquinone	Lysergol	Artane
Menaquinone	Abietic acid	Coralyne	
Lobeline alpha negative	Ajmalicine	Lapachol	
Glycyrrhetinic acid_min_out	Chrysin	Halpopine	
Capsaicin	(-)-Cinchonidine	Reserpinic acid	

Table 13. 36 ligands out of the 41 Prestwick phytochemical compound library bound to the GPR119 receptor

Table 14-Frame 150: Sequential virtual screening protocol of GPCR libraries						
Molindone	Methyldopate	Octopamine	Phenol, 4-[3-(dimethylamino)-1-(2-pyridinyl)propyl]-	Moxisylyte	Baicalin	ENDOMETRIN_progesterone
Formoterol	Benperidol	Raclopride	(-)-Hyoscine	Methoxamine	AM251	S5480_Clidinium_Bromide
Tropicamide	(8,8-dimethyl-8lambda5-azabicyclo[3.2.1]octan-3-yl) 3-hydroxy-2-phenyl-propanoate	4H-Pyrido[1,2-a]pyrimidin-4-one, 3-[2-[4-(4-fluorobenzoyl)-1-piperidinyl]ethyl]-2-methyl	Betazole	Bethanechol	S3735_Umeclidinium_bromide	MRS_2578
Ketanserin	1-(tert-Butylamino)-3-((5,6,7,8-tetrahydro-cis-6,7-dihydroxy-1-naphthyl)oxy)-2-propanol	Guanabenz	Cyclopentolate	Xylazine	Estradiol_benzoate	Sotagliflozin_LX4211
Droperidol	1,1-Ethenediamine, N'-[2-[[[2-[(dimethylamino)methyl]-4-thiazolyl]methyl]thio]ethyl]-N-methyl-2-nitro-	Salbutamol	Orciprenaline	Tolazoline	S4624_Methylbenactyzine_Bromide	Hesperetin
Terazosin	Tiapride	Acefylline	Alfuzosin	Mephentermine	Rimonabant	Phloretin

Tegaserod	Isoxuprine	Cathine	Dexpramipexole	Betahistine	BML_190	Unamed
3a_tropylmandelat	Meptazinol	Betaxolol	Naphazoline	Carbachol	S5472_Nafronyl_oxalate_salt	S5087_Tianeptine
Melatonine	Trimebutine	Isoetarine	Oxprenolol	Dimaprit	S4709_Latanoprost	CCG_1423
Famotidine	Baclofen	Bisoprolol	Adrenaline	Empagliflozin_BI10773	S5469_Bavachin	Org_27569
Ziprasidone	Theobromine	Benzyl [(1,6-dimethylergolin-8-yl)methyl]carbamate	Isometheptene	Ipragliflozin_ASP1941	Unamed	Estradiol_Valerate
Labetalol	2-(4-Hydroxyphenethylamino)-1-(4-hydroxyphenyl)propanol	Isoprenaline	Emedastine	S5566_Dapagliflozin_propanediol_monohydrate	ZM241385	Disopyramide_Phosphate
Pronetalol	Fenfluramine	Esmolol	Pindolol	Canagliflozin	17_Hydroxyprogesterone	ARN_509
Phenoxybenzamine	3,4-DIMETHYLPHENETHYLAMINE	Mepyramine	Apomorphine	Unamed	Benzethonium_chloride	ATROVENT_HFA_ipratropium_bromide
Sulpiride	Risperidone	Clonidine	Doxylamine	Unamed	S3701_Benactyzine_hydrochloride	4_Hydroxytamoxifen_4_HT_Afimoxifene
(1,1-dimethyl-3,4,5,6-tetrahydro-2H-pyridin-3-yl) 2-hydroxy-2,2-diphenyl-acetate	Carteolol	Piribedil	Lofexidine	Phlorizin	Oxybutynin chloride	MIFEPREX_mifepristone
9-Methyl-9-oxido-3-oxa-9-azatricyclo[3.3.1.02,4]non-7-yl tropate	Thioperamide	DL-Atenolol	Perphenazine	S9307_Shanzhiside_methyl_ester	Unamed	S4660_Glycopyrrolate
Prazosin	Amisulpride	Ticlopidine	Phentolamine	S3716_Flibanserin	Clomifene_citrate	SB408124
8-Methyl-8-azabicyclo[3.2.1]oct-3-yl tropate	Practolol	Azaperone	Etilefrine	S4654_Netupitant	Unamed	Drospirenone
ZOLMITRIPTAN, (R)-	Guanfacine	Acebutolol	Brimonidine	S3927_Swertiamarin	Tolvaptan	PHTPP
Ifenprodil	LEVOBUNOLOL	Clenbuterol	Oxymetazoline	Ponesimod_ACT_128800	GW_9508	Unamed
Fenoterol	Xamoterol	Sotalol	Histamine	S5049_Thiocolchicoside	ABC294640	Equol
Trimethobenzamide	Meta-hydroxynorephedrine	8-[(Methylsulfanyl)methyl]-6-propylergoline	(1Z)-1-Hydrazono-1,8a-dihydrophthalazine	Puerarin	Ehop_016	Bithionol
Sumatriptan	Propranolol	Aceclidine	Xylometazoline	S5413_Ertugliflozin	S3635_Medroxyprogesterone	AM1241
1H-Indol-5-ol, 3-(2-aminoethyl)-	Fenspiride	Terbutaline	Tetrahydrozoline	Penfluridol	Ticagrelor	FLI_06
Tripelennamine	Ethanol, 2-[2-(4-dibenzo[b,f][1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]	Caffeine	(z)-ranitidine	CID16020046_CID_16020046	Escitalopram_oxalate	Hexestrol
Rizatriptan	Eticlopride	Metoclopramide	Nordefrin	Trospium_chloride	Racecadotril	Ospemifene

1H_benzotriazole_5_carboxamide_6_methoxy_N_[[2_propen_1_yl)_2_pyrrolidinyl]methyl]_	Cimetidine	Metoprolol	Methacholine	K_Ras_G12C_inhibitor	MK_4101	Estriol
Carvedilol	Midodrine	Timolol	Methapyrilene	Dihydromyricetin	Ginkgolide_A	Yohimbine_hydrochloride
Dobutamine	Celiprolol	Alprenolol	3-Bromo-N-[(1-ethyl-2-pyrrolidinyl)methyl]-2,6-dimethoxybenzamide	Dapagliflozin	Meclizine_dihydrochloride	Trihexyphenidyl_hydrochloride
Domperidone	Phentermine	Propafenone	Synephrine	Ivabradine_hydrocloride	Unamed	Forskolin
Buphenine	Itopride	1-(2-Chlorophenyl)-2-[(2-methyl-2-propanyl)amino]ethanol	2,4(1H,3H)-Pyrimidinedione, 6-[[3-[4-(2-methoxyphenyl)-1-piperazinyl]propyl]amino]-1,3-dimethyl-	CCG_203971	DIETHYLSTILBESTROL_diethylstilbestrol	S3972_Lobeline_hydrochloride
Unamed	Gestodene	BQU57	QUETIAPINE_FUMARATE_quetiapine_fumarate	S3816_Dehydroevodiamine	S4639_Brexpiprazole	Sertraline_hydrochloride
Tropisetron_hydrochloride	S4883_Lynestrenol	XENAZINE_tetrabenazine	Salirasib	ALESSE_ethinyl_estradiol	Naftopidil	Amitriptyline_hydrochloride
PAMINE_methscopolamine_bromide	S4839_Mosapride	S4673_Etonogestrel	Unknown	Atropine_sulfate_monohydrate	Prasugrel	Ramelteon
Diphenidol_hydrochloride	Unamed	CPI_444	JTE_013	S5358_Regadenoson	Clemastine_fumarate	Unamed
S4629_Chlorotrianisene	Norethindrone	Trazodone_hydrochloride	ML141	Naloxone_HCL	S5326_Dolasetron	CTEP
Maprotiline_hydrochloride	S4834_Propanthelin e_bromide	Reparixin_Repertaxin	Mestranol	5_Iodotubercidin	SB_334867	GW842166x
Pregnenolone	Unamed	S5239_Paroxetine_mesylate	S5288_Estropipate	SB_269970_hcl	Cyclobenzaprine_hcl	Benztropine_mesylate
Dienogest	S3820_Dehydroevodiamine_hydrochloride	INVEGA_paliperidone	S5464_Psoralidin	Catharanthine	HALDOL_haloperidol	S5664_Orphenadrine_Hydrochloride
S5538_Tropisetron	EQUIPIN_homatropine_methylbromide	S4637_Prasugrel_Hydrochloride	Estradiol	S5385_Imidafenacin	Unamed	S9326_Scopolamine
Mosapride_citrate	Azelastine_hydrochloride	Iloperidone	S4749_Citalopram_hbr	Reversine	Unamed	S3671_Quinestrol
Unamed	ADX47273	S3758_Sinomenine_hydrochloride	Unamed	Untitled	PF-5274857	S5437_4_4_DDE
Altrenogest	Mesoridazine_besylate	S5034_Melitracen_hydrochloride	S3884_Jatrorrhizine	WAY_100635_meleate	Homatropine_bromide	ESI_09
PNU200577	MK571	Ambrisentan	S9069_Jatrorrhizine_chloride	S3657_Promestriene	K_Ras_G12C_inhibitor	Scopolamine_hydrobromide
S5479_Cloperastine_hydrochloride	Naratriptan Hydrochloride	S3634_6_Hydroxyflavone	Hyoscyamine_L	S3819_Decursinol_angelate	Pizotifen_malate	Ethynodiol_diacetate
Levonorgestrel	Loratadine_Alavert_Claritin	Ketotifen_fumarate	Unamed	Azatadine_dimaleate	S3723_Ramosetron_Hydrochloride	BMY7378
S4638_Desogestrel	Adiphenine_hydrochloride	Unamed	ESTROGENIC_SUBSTANCE_estrone	Darifenacin_hydrobromide	Levosulpiride	Doxazosin_mesylate
Promethazine_hydrochloride	Unamed	S4732_MPTP_hydrochloride	Unamed	Unamed	PD128907	Granisetron_Hydrochloride

NEOTHYLLINE_dyphylline	S5559_Tetrahydropalmatine	Unamed	S5447_Triprolidine_hydrochloride_monohydrate	Choline_Chloride	Indacaterol_Maleate	Unamed
JNJ7777120	S4892_Phenibut	Unamed	Amantadine_hcl	Pramipexole	S5654_Indacaterol	Solifenacin_succinate
Prochlorperazine_dimaleate_salt	Unamed	Nizatidine	Rupatadine_fumarate	D_glutamine	Unamed	8_OH_DPAT_8_Hydroxy_DPAT
Unamed	Unamed	Unamed	Unamed	AMD3465	Lamotrigine	Lu_AA21004_vortioxetine
Flumazenil	Epinephrine_hcl	Unamed	S5499_Amantadine	S4575_Pralidoxime_chloride	Unamed	AZD1981
Unamed	Unamed	SQ22536	Cytisine	Phenylephrine_hydrochloride	Epinastine_hcl	Unamed
Unamed	S5337_Rauwolscine_hydrochloride	Neostigmine_bromide	Rotundine	IEM_1754_dihydrobromide	S9239_Isocoryneoxeine	Alverine_citrate
Diphenhydramine_hydrochloride	Chlorpheniramine_Maleate	CP_945598_hydrochloride	Hexamethon_iumbromide	Unamed	S5655_Venlafaxine	Unamed
S5238_Solifenacin	Bambuterol_hcl	CETIRIZINE_DI_HCL	Pircetam	Unamed	Ozanimod	Almotriptan_malate
S3120_Doxepin_hydrochloride	Dopamine_hydrochloride	S3627_Tryptamine	Clomipramine_hydrochloride	S4700_4_Aminobutyric_acid	S5676_Zearalenone	ABILIFY_aripiprazole
S3706_Sarpogrelate_hydrochloride	Tolterodine_tartrate	Unamed	S9258_Isocorynoline	S5131_Homotaurine	Clozapine	S4281_Tasimelteon
VU_0364439	S5075_Acotiamide	Unamed	S3854_Tetrahydropalmatine_hydrochloride	S4718_Acetylcholine_iodide	Agomelatine	PRX_08066_maleate
Clopidogrel_bisulfate	Tianeptine_sodium_salt	VUF_10166	S5071_Duloxetine	Unamed	S4617_Dextromethorphan_hydrobromide_hydrate	S5052_Granisetron
Matrine	Bepotastine_besilate	Fluoxetine_hydrochloride	S4747_Jervine	S3953_L_Lysine_hydrochloride	Procaine_hydrochloride	Adrenalone_hydrochloride
Etomidate	PNU_120596	Tamsulosin	Duloxetine_hydrochloride	Reboxetine_mesylate	Melatonin	Palmatine_hydrochloride
Amfebutamone_hcl	Unamed	Rotigotine	Paroxetine_hydrochloride	S5281_Dapiprazole_Hydrochloride	BRL54443	Loxapine_succinate
Urapidil_hydrochloride	Fluvoxamine_maleate	S5042_Bevantolol_hydrochloride	Tizanidine_hydrochloride	Conivaptan_hydrochloride	Palonosetron_hcl	Kobe0065
RILUZOLE_riluzole	Mirabegron	Unamed	Bicuculline	Unamed	S3769_Palmatine	Desvenlafaxine
Hydroxyzine_dihydrochloride	Unamed	Gabapentin_hcl	Decamethonium_bromide	Unamed	S5364_DY131	Unamed
Unamed	Clorprenaline_hcl	S4661_Tiagabine_hydrochloride	S3988_Theophylline_7_acetic_acid	Unamed	SB225002	SB_271046
Bemegride	S4694_Alosetron_Hydrochloride	S4675_Tiagabine	Serotonin_hydrochloride	Unamed	S5018_Mebhydrolin_napadisylate	Irsogladine
Cyclizine_2hcl	S4649_Atipamezole_hydrochloride	S4849_Levocetirizine_Dihydrochloride	Acesulfame_potassium	S3662_Pirenzepine_dihydrochloride	S5506_Vortioxetine	LY2119620
S5153_Tetrahydroberberine	Varenicline_tartrate	Unamed	Succinylcholine_Chloride_Dihydrate	S4748_Ondansetron_hcl	Unamed	S4588_Docusate_Sodium
WZ_811	JTC801	Unamed	S4574_Piperazine	S_38093	Galanthamine_hydrobromide	S3866_Galanthamine
BRL15572	Aniracetam	SB_742457	Unamed	Alizapride_hydrochloride	ZK756326	Prucalopride_succinat

S5400_3_chloro_5_hydroxybenzoic_Acid	Oxiracetam	S3661_2_Methoxy_1_4_naphthoquinone	Flopropione	Donepezil_hcl	Unamed	Prucalopride
Istradefylline	Buflomedil_hydrochloride	Latrepirdine	NSC23766	Diphemanil_methylsulfate	TARACTAN_chlorprothixene	Mianserin_hydrochloride
Olanzapine	Medetomidine_hcl	VU_0361737	Unamed	Unamed	VU_0357121	K_Ras_G12C_inhibitor
Unamed	GF_109203X_G_6850	Unamed	S5537_Tizanidine	Pemirolast_potassium	Pergolide_mesylate_salt	Roxatidine_acetate_hydrochloride
S4776_Harmaline	Fty720	S3625_Tyramine	Levodropropizine	MIRTAZAPINE_mirtazapine	S5399_Chlorprothixene_hydrochloride	Nefiracetam
Cinacalcet Hydrochloride	Unamed	Unamed	NEURONTIN_gabapentin	SKF38393	Asenapine_maleate	Unamed
VU_0364770	Naltrexone_hydrochloride	Azasetron_hydrochloride	SANT_1	S4696_arbinoxamine_Maleate	S5267_Nylidrin_Hydrochloride	Unamed
PF_04418948	S5137_O_Phospho_L_serine	Ritodrine_hydrochloride	S4992_Nanofin	HJC0350	S5427_Alloxazine	OC000459
AMINOPHYLLINE_aminophylline	S4932_Proxyphylline	ARS_853	Carbamyl-beta_methylcholine_chloride	S4625_Alcaftadine	Rivastigmine	S4587_Dithranol
Daphnetin	Unamed	S4618_Fenoldopan_mesylate	S5428_Promazine_Hydrochloride	Unamed	Unamed	Unamed
ALPHACAINE_lidocaine	S9249_Securinine	Pilocarpine_hcl	Ly404039	S3800_Lycorine_hydrochloride	MI_136	Unamed
S4667_Lidocaine_hydrochloride	Unamed	Dexmedetomidine	Unamed	Venlafaxine_hydrochloride	Detomidine_hydrochloride	Unamed
S5119_Olivetol	IRBESARTAN_irbesartan	S5066_Pramipexole_dihydrochloride	Scopine	Brompheniramine_maleate	Eprosartan_mesylate	Unamed
Epinephrine_bitartrate	S4650_Atipamezole	S9413_Yangonin	Chlorpromazine_hcl	S5073_Donepezil	S4117	Noradrenaline_bitartrate
Pheniramine_maleate	S4714_Menthol	Unamed	Atomoxetine_hydrochloride	Ondansetron hydrochloride	S3761_Eucalyptol	S5341_Metroprolol_succinate
S4751_Cisapride	S3639_Tacrine_hydrochloride_hydrate	IMURAN_azathioprine	MESTINON_pyridostigmine bromide	S3903_Lycorine	S5701_Alvimopan_dihydrate	
SCH58261	Dapoxetine_hydrochloride	Rivastigmine_tartrate	S3748_Acamprosate_Calcium	S5280_Dimemorfan_phosphate	Unamed	
S5324_Oxidopamine_hydrobromide	Flavoxate_HCL	Ciproxifan	S4774_Xanthurenic_Acid	Unamed	Vilazodone_Hydrochloride	
S9176_Pimpinellin	Unamed	Unamed	MPEP	Endoxifen_hcl	Phenothiazine	

Table 14. 646 ligands out of the 862 Prestwick and Selleckchm GPCR compound libraries bound to the GPR119 receptor

Table 15-Frame 150: Sequential virtual screening protocol of Zinc Naturals library						
ZINC31155896	ZINC13660070	ZINC03838697	ZINC13459733	ZINC04260652	ZINC00388156	ZINC03838821
ZINC35457506	ZINC05414249	ZINC04235815	ZINC12530083	ZINC02512484	ZINC03881368	ZINC20463802
ZINC36728548	ZINC35442830	ZINC04235875	ZINC04235903	ZINC03838687	ZINC12529820	ZINC20463917
ZINC03842067	ZINC03838994	ZINC03841746	ZINC04260804	ZINC14692058	ZINC02504624	ZINC02242928
ZINC05414350	ZINC03872493	ZINC04259694	ZINC04235756	ZINC00388555	ZINC02382136	ZINC04235946
ZINC31155429	ZINC06131137	ZINC04235766	ZINC05762051	ZINC04236098	ZINC03841669	ZINC04096827
ZINC35442872	ZINC04235904	ZINC03838803	ZINC04236110	ZINC13459830	ZINC00895230	ZINC04260672
ZINC35442868	ZINC35442839	ZINC04260687	ZINC03873955	ZINC35457384	ZINC00518229	ZINC02386443
ZINC01667455	ZINC03838766	ZINC04235922	ZINC05396119	ZINC03841200	ZINC12529941	ZINC03838817
ZINC35457485	ZINC03838799	ZINC03839770	ZINC14620030	ZINC04235974	ZINC18153302	ZINC03838841
ZINC35442861	ZINC35442899	ZINC35465795	ZINC06131133	ZINC12604305	ZINC03838668	ZINC13660164
ZINC04096936	ZINC05414366	ZINC35442864	ZINC03838761	ZINC04259418	ZINC04334576	ZINC35415881
ZINC03838734	ZINC03838862	ZINC14504521	ZINC14505032	ZINC12529855	ZINC02530676	ZINC31163452
ZINC03838744	ZINC03841696	ZINC03838867	ZINC13536861	ZINC04236093	ZINC03839119	ZINC00388241
ZINC31163768	ZINC14720477	ZINC35442876	ZINC04236336	ZINC00057969	ZINC04259109	ZINC20463929
ZINC03838854	ZINC35442873	ZINC02567802	ZINC31163356	ZINC00154077	ZINC02565724	ZINC05396437
ZINC31155673	ZINC05414260	ZINC03838759	ZINC04260751	ZINC13433654	ZINC30730664	ZINC01684095
ZINC13507844	ZINC04236130	ZINC03838885	ZINC35442841	ZINC00517887	ZINC03157602	ZINC35415786
ZINC36728545	ZINC04235908	ZINC03838984	ZINC00389617	ZINC05396463	ZINC05396688	ZINC04235943
ZINC01667453	ZINC35457316	ZINC04236107	ZINC03838975	ZINC12530041	ZINC04632115	ZINC04260676
ZINC13507846	ZINC05414247	ZINC03838945	ZINC04259434	ZINC14684865	ZINC00388037	ZINC04334587
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ZINC04235900	ZINC03871576	ZINC06131135	ZINC04235744	ZINC04236016	ZINC02525206	ZINC12529905
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ZINC31163589	ZINC04235936	ZINC00168294	ZINC03649942	ZINC00435898	ZINC12529858	ZINC03838650
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ZINC04236118	ZINC14770271	ZINC35457377	ZINC04096829	ZINC35442888	ZINC18275062	ZINC04236092
ZINC03838732	ZINC14728050	ZINC03841195	ZINC01718636	ZINC12529987	ZINC02169262	ZINC03838640
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ZINC04235763	ZINC35457454	ZINC03839018	ZINC04260657	ZINC03873958	ZINC04236104	ZINC01671299
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ZINC04235887	ZINC03838863	ZINC12604320	ZINC04259571	ZINC00269224	ZINC12530030	ZINC05396246
ZINC00519621	ZINC13334942	ZINC03861548	ZINC00057958	ZINC12529940	ZINC35415850	ZINC04259146
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ZINC03841748	ZINC13815053	ZINC05413174	ZINC35442836	ZINC30730667	ZINC20463670	ZINC12529994
ZINC04260726	ZINC35442859	ZINC35442896	ZINC31170318	ZINC04259701	ZINC04329264	ZINC04260806
ZINC03838770	ZINC05414227	ZINC04259580	ZINC02569506	ZINC04241432	ZINC05839889	ZINC12529808
ZINC03838797	ZINC04556627	ZINC03839012	ZINC02047002	ZINC12530040	ZINC12530033	ZINC04260115
ZINC35457184	ZINC05762066	ZINC06131130	ZINC35442902	ZINC12529867	ZINC12530047	ZINC31163715
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ZINC35457009	ZINC02567806	ZINC06131127	ZINC35442907	ZINC04236170	ZINC12529846	ZINC35442831
ZINC35442869	ZINC40413191	ZINC04260631	ZINC12604297	ZINC02516803	ZINC20463852	ZINC03838750
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ZINC35442834	ZINC00517336	ZINC12529983	ZINC12530011	ZINC04236050	ZINC02168652	ZINC20463798
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ZINC03869685	ZINC13838494	ZINC12529784	ZINC04236334	ZINC01575524	ZINC02530677	ZINC02576919
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ZINC03838944	ZINC03838895	ZINC05414424	ZINC13433660	ZINC03881969	ZINC03838831	ZINC12530077
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ZINC04235902	ZINC35457346	ZINC35442835	ZINC01658651	ZINC02012003	ZINC00163157	ZINC04260637
ZINC35442849	ZINC12604317	ZINC04235858	ZINC12529959	ZINC12529803	ZINC03838832	ZINC35442891
ZINC14504553	ZINC03841698	ZINC06131128	ZINC31163441	ZINC00388262	ZINC04260635	

ZINC03841699	ZINC03838988	ZINC01561231	ZINC04235949	ZINC01850617	ZINC04236090	
ZINC03838737	ZINC03841706	ZINC04235739	ZINC35442871	ZINC31163592	ZINC03927198	

Table 15. 949 ligands out of the 20,000 Zinc Naturals library compounds bound to the GPR119 receptor

Complete tables for Frame 200

Table 16-Frame 200: Sequential virtual screening protocol of Prestwick phytochemicals			
Naringin	Naringenine	1-8-dihydroxy-3-methylanthraquinone	Rauwolscine_min_out
Glycocholic Acid	cardamonin_min_out	Corynanthine_min_out	Coralyne
Curcumin_min_out	Tocophenol (R,S)	Ajmalicine	Conessine
Baicalin	Olivacine	Berlambine	Harmine
Camptothecine (s,+)	capsaicin_min	Kawain	Acridine
4,4'-(2,3-dimethyltetramethylene)dipyrocatechol	Chrysin	Berberine	Lobeline alpha negative
Calciferol_min_out	Velpinic acid	Piperine	Isoliquiritigenin
Verbenaline	Biotin	Lapachol	Halpopine_min_out
Chlorogenic acid	Abietic acid	Reserpinic acid_min_out	
(-)-Cinchonidine	Lysergol	Sanguinarine_min_out	

Table 16. 38 ligands out of the 41 Prestwick phytochemical compound library bound to the GPR119 receptor

Table 17-Frame 200: Sequential virtual screening protocol of GPCR libraries						
Pirenzepine	melatonine	Betazole	CCG_203971	S9326_Scopolamine	unamed	Ozanimod
Formoterol	2-Chloro-9-[3-(dimethylamino)propylidene]thioxanthene	Acebutolol	Rotigotine	S3716_Flibanserin	JTE_013	unamed
Risperidone	practolol	clenbuterol	Diphenidol_hydrochloride	S3820_Dehydroevodiamine_hydrochloride	S9258_Isocorynoline	Varenicline_tartrate

Naloxone	clozapine	Baclofen	S3671_Quinestrol	norethindrone	5_Iodotubercidin	ARS_853
1-Azoniabicyclo[2.2.2]octane, 4-[(2-hydroxy-2,2-diphenylacetyl)oxy]	Promazine	LEVOBUNOLOL	Estradiol_benzoate	S4776_Harmaline	unamed	Pizotifen_malate
Fluphenazine	Tegaserod	Betahistine	Org_27569	Pregnenolone	Etomidate	S5052_Granisetron
Sulpiride	Doxylamine	Levomepromazine	S4629_Chlorotrianisene	Neostigmine_bromide	Nebivolol_HCl	S4747_Jervine
Loratadine	Ropinirole	tripelennamine	S3721_Bilastine	Promethazine_hydrochloride	6H05	Mirabegron
2-[diisopropyl(methyl)-lambda5-azanyl]ethyl 9H-xanthene-9-carboxylate	Trimethobenzamide	Olanzapine	Adiphenine_hydrochloride	unamed	Disopyramide_Phosphate	Desvenlafaxine
mebeverine	(2-Chlorophenyl)(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)acetic acid	Itopride	Candesartan	unamed	unamed	unamed
11,15-Dihydroxy-9-oxoprostan-1-oic acid	pimozide	Terbutaline	Forskolin	procaine_hydrochloride	PNU200577	Ciproxifan
17_(Cyclopropylmethyl)_3_14_dihydroxy_4_5_epoxymorphinan_6_one	Chlorphenamine	isometheptene	Benztropine_mesylate	S5464_Psoralidin	PF-5274857	S5239_Paroxetine_mesylate
Methyl (13E)-11,16-dihydroxy-16-methyl-9-oxoprost-13-en-1-oate	domperidone	Acefylline	ENDOMETRIN_progesterone	Reboxetine_mesylate	Tianeptine_sodium_salt	S3903_Lycorine
8-[(Methylsulfanyl)methyl]-6-propylergoline	Eticlopride	Caffeine	unamed	WAY_100635_meleate	Epinastine_HCl	Epinephrine_bitartrate
ifenprodil	ipsapirone	bambuterol	unamed	S4673_Etonogestrel	S4774_Xanthurenic_Acid	S9413_Yangonin
Prosta_5_13_dien_1_oic acid, 9,11,15_trihydroxy_(5Z,9a,11a,13E,15s)_	Chlorpromazine	alfuzosin	ZCL_278	Phloretin	unamed	Bemegride
oxybutynin	Phentolamine	celiprolol	Gestodene	S5358_Regadenoson	SB_269970_HCl	S4932_Proxyphylline
2-(Diethylamino)ethyl 3-(1-naphthyl)-2-(tetrahydro-2-furanylmethyl)propanoate	Oxymetazoline	2,4(1H,3H)-Pyrimidinedione, 6-[[3-[4-(2-methoxyphenyl)-1-piperazinyl]propyl]amino]-1,3-dimethyl-	S4617_Dextromethorphan_hydrobromide_hydrate	Clorprenaline_HCl	S5511_Ethyl_triphenylphosphoranylidene_acetate	Carbamyl-beta_methylcholine_chloride
1-Ethyl-3-piperidinyl diphenylacetate	Antazoline	Methapyrilene	Alizapride_hydrochloride	Eletriptan_hydrobromide	Rupatadine_fumarate	Amantadine_HCl
Labetalol	2-[3-(Diisopropylamino)-1-phenylpropyl]-4-methylphenol	Piribedil	S5701_Alvimopan_dihydrate	RS_127445	S5676_Zearalenone	RAPAFLO_silodosin
mizolastine	timolol	Histamine	unamed	S3816_Dehydroevodiamine	Baicalin	Rivastigmine
(1,1-dimethyl-3,4,5,6-tetrahydro-2H-pyridin-3-yl) 2-hydroxy-2,2-diphenyl-acetate	metoclopramide	Cimetidine	ARN_509	Homatropine_bromide	Naltrexone_hydrochloride	SB225002

8-Methyl-8-azabicyclo[3.2.1]oct-3-yl tropate	Silodosin	Dimaprit	Pergolide_mesylate_salt	Nefiracetam	S5087_Tianeptine	Bicuculline
Methantheline	Famotidine	Azilsartan	S4838_Acotiamide_hydrochloride	S5432_N_2_Chloroethyl_dibenzylamine_Hydrochloride	unamed	S3800_Lycorine_hydrochloride
(8,8-dimethyl-8lambda5-azabicyclo[3.2.1]octan-3-yl) 3-hydroxy-2-phenyl-propanoate	mepyramine	Ipragliflozin_ASP1941	DESLORATADINE_desloratadine	ADL5859	MPEP	Pircetam
buphenine	Terazosin	unamed	17_Hydroxyprogesterone	Melatonin	unamed	Nolvadex_Tamoxifen_Citrate
Biperiden	Perphenazine	Phlorizin	Alverine_citrate	Dexmedetomidine	Granisetron_Hydrochloride	SB_742457
Sertindole	(10-Methoxy-1,6-dimethylergolin-8-yl)methyl 5-bromonicotinate	penfluridol	SKF38393	estradiol	Almotriptan_malate	S3625_Tyramine
Fenoterol	Loxapine	S5538_Tropisetron	S5469_Bavachin	unamed	NEOTHYLLINE_dyphylline	Venlafaxine_hydrochloride
Ethanol, 2-[2-(4-dibenzo[b,f][1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]	Prazosin	Canagliflozin	Catharanthine	Galanthamine_hydrobromide	Nitenpyram	sertraline_hydrochloride
Cyproheptadine		unamed	mesoridazine_besylate	Ginkgolide_B	unknown	ZK756326
Amisulpride	Pindolol	4_Hydroxytamoxifen_4_HT_Afimoxifene	Hesperetin	VU_0357121	unamed	S5400_3_chloro_5_hydroxybenzoic_Acid
clemastine	Nordefrin	Empagliflozin_BI10773	DIETHYLSTILBESTROL_diethylstilbestrol	S4975_Fimasartan	Doxazosin_mesylate	S4992_Nanofin
9-Methyl-9-oxido-3-oxa-9-azatricyclo[3.3.1.02,4]non-7-yl tropate	Hydroxyzine	ki16425	MK_4101	Chlorpheniramine_Maleate	Succinylcholine_Chloride_Dihydrate	PD128907
Ticlopidine	Emedastine	CID16020046_CID_16020046	S5385_Imidafenacin	unamed	unamed	SQ22536
mesoridazine	Dibenz[b,e]oxepin-2-acetic acid, 11-[3-(dimethylamino)propylidene]-6,11-dihydro-, (11Z)	Ponesimod_ACT_128800	PRX_08066_maleate	S4883_Lynestrenol	S4714_Menthol	MI_136
Racemethorphan	Methyldopate	Fosaprepitant_dimeglumine	CPI_444	ESTROGENIC_SUBSTANCE_estrone	unamed	S5324_Oxidopamine_hydrobromide
Apomorphine	ZOLMITRIPTAN, (R)-	Dapagliflozin	unamed	S3657_Promestriene	S5034_Melitracen_hydrochloride	Dopamine_hydrochloride
Tropicamide	adrenaline	PAMINE_methscopolamine_bromide	Pimavanserin_ACP_103	Brompheniramine_maleate	SB408124	Gabapentin_hcl

3-(Diphenylmethoxy)-8-methyl-8-azabicyclo[3.2.1]octane	4H-Pyrido[1,2-a]pyrimidin-4-one, 3-[2-[4-(4-fluorobenzoyl)-1-piperidinyl]ethyl]-2-methyl	SB_271046	ADX47273	Medroxyprogesterone_acetate	Amfebutamone_HCl	S3627_Tryptamine
Isoxuprine	Tetrahydrozoline	S3927_Swertiamarin	Estradiol_Valerate	Hyoscyamine_L	Adrenalone_hydrochloride	unamed
homochlorcyclizine	Levocabastine	CGS_21680_hydrochloride	unamed	S4638_Desogestrel	unamed	MESTINON_pyridostigmine bromide
telenzepine	meta-hydroxynorephedrine	S5566_Dapagliflozin_propanediol_monohydrate	S3723_Ramosetron_Hydrochloride	S3634_6_Hydroxyflavone	Flumazenil	NEURONTIN_gabapentin
5H-Benzo[5,6]cyclohepta[1,2-b]pyridine, 8-chloro-6,11-dihydro-11-(4-piperidinylidene)-	Cinnarizine	S5413_Ertugliflozin	matrine	Scopolamine_hydrobromide	Epinephrine_HCl	Nizatidine
Cloperastine	Meclizine	S4709_Latanoprost	S4639_Brexpiprazole	Equol	Cinacalcet Hydrochloride	unamed
Naftopidil	dobutamine	S3664_Flupenthixol_dihydrochloride	S3819_Decursinol_angelate	S3866_Galanthamine	unamed	S5018_Mebhydrolin_napadisylate
Ketanserin	17-(Cyclopropylmethyl)-6-methylene-4,5-epoxymorphinan-3,14-diol	Tropisetron_hydrochloride	QUETIAPINE_FUMARATE_quetiapine_fumarate	Duloxetine_hydrochloride	S5153_Tetrahydroberberine	S5428_Promazine_Hydrochloride
Molindone	Moxisylyte	Puerarin	Reparixin_Repertaxin	Levonorgestrel	unamed	unamed
ketotifen	Carvedilol	Vilazodone_Hydrochloride	Diphemanil_methylsulfate	unamed	S4588_Docusate_Sodium	Palonosetron_HCl
1H_benzotriazole_5_carboxamide_6_methoxy_N_[[2_propen_1_yl)_2_pyrrolidinyl]methyl]_	Rizatriptan	unamed	unamed	S5399_Chlorprothixene_hydrochloride	Istradefylline	Latrepirdine
isoetarine	centirizine	bimatoprost	unamed	S3769_Palmatine	Eprosartan_mesylate	unamed
clemizole	spiperone	unamed	S5655_Venlafaxine	WZ_811	Lamotrigine	S4575_Pralidoxime_chloride
camylofin	(+)-yohimbine	S3735_Umeclidinium_bromide	ZM241385	untitled	S4675_Tiagabine	S5499_Amantadine
pimethixene	Naphazoline	unamed	S4618_Fenoldopan_mesylate	Trospium_chloride	unamed	untitled
Triflupromazine	cathine	S9307_Shanzhiside_methyl_ester	S3635_Medroxyprogesterone	Kobe0065	S5281_Dapiprazole_Hydrochloride	Choline_Chloride
Diphenylpyraline	bisoprolol	S5480_Clidinium_Bromide	Azatadine_dimaleate	Phenothiazine	Smoothened_agonist_SAG_HCl	Ritodrine_hydrochloride
4_(Diphenylmethylene0_1_1_dimethylpiperidinium	etilefrine	ML141	Atropine_sulfate_monohydrate	S5364_DY131	Levodropropizine	Fluvoxamine_maleate
5H-Benzo[5,6]cyclohepta[1,2-	Dexpramipexole	PHTPP	unamed	HJC0350	S4650_Atipamezole	untitled

b]pyridine, 6,11-dihydro-11-(1-methyl-4-piperidinylidene)						
1H-3-Benzazepine-7,8-diol, 6-chloro-2,3,4,5-tetrahydro-1-(4-hydroxyphenyl)-	propafenone	S4624_Methylbenactyzine_Bromide	VU_0364439	Bithionol	CETIRIZINE_DI_HCL	Yohimbine_hydrochloride
pridinol	Raclopride	S3726_Selexipag	S4839_Mosapride	S4281_Tasimelteon	Iloperidone	Oxiracetam
pronetalol	Zotepine	Fluoxetine_hydrochloride	PF_04418948	unamed	PNU_120596	SANT_1
Ziprasidone	lofexidine	Clomifene_citrate	OC000459	unamed	Dapoxetine_hydrochloride	Prucalopride
Esmolol	3,4-DIMETHYLPHENETHYLAMINE	S4834_Propantheline_bromide	Ethynodiol_diacetate	Pemirolast_potassium	unamed	Tamsulosin
Asenapine	procyclidine	S4749_Citalopram_HBr	unamed	ALPHACAINE_lidocaine	S5119_Olivetol	unamed
Isoprenaline	Metoprolol	S3701_Benactyzine_hydrochloride	unamed	S4667_Lidocaine_hydrochloride	VUF_10166	unamed
N-(1-Hydroxy-2-butanyl)-6-methyl-9,10-didehydroergoline-8-carboxamide	Metitepine	Donepezil_HCl	S4625_Alcaftadine	AM1241	S4849_Levocetirizine_Dihydrochloride	unamed
droperidol	Midodrine	Naratriptan Hydrochloride	Rotundine	BRL15572	RILUZOLE_riluzole	8_OH_DPAT_8_Hydroxy_DPAT
Thioridazine	(z)-ranitidine	Tofogliflozin_CSG_452	S3120_Doxepin_hydrochloride	S4674_Hydroxyprogesterone_caproate	Pramipexole	Flopropione
Azaperone	Thioperamide	Estradiol_cypionate	S5506_Vortioxetine	Clopidogrel_bisulfate	unamed	S9249_Securinine
Sumatriptan	Bethanechol	S_38093	SCH58261	Daphnetin	S5137_O_Phospho_L_serine	Acesulfame_potassium
Azacyclonol	Xamoterol	S5073_Donepezil	Estriol	unamed	S4649_Atipamezole_hydrochloride	S4694_Alosetron_Hydrochloride
DL-atenolol	mephentermine	Dihydromyricetin	XENAZINE_tetrabenazine	unamed	S3972_Lobeline_hydrochloride	JTC801
Meptazinol	(1Z)-1-Hydrazono-1,8a-dihydrophthalazine	Escitalopram_oxalate	S5067_Losartan	unamed	unamed	S4587_Dithranol
Acepromazine	methoxamine	S5472_Nafronyl_oxalate_salt	Drospirenone	S9176_Pimpinellin	unamed	Tizanidine_hydrochloride
fenfluramine	1-(tert-Butylamino)-3-((5,6,7,8-tetrahydro-cis-6,7-dihydroxy-1-naphthyl)oxy)-2-propanol	S5559_Tetrahydropalmatine	unamed	unamed	Amitriptyline_hydrochloride	S3748_Acamprosate_Calcium
tiapride	Alimemazine	unamed	CCG_1423	Reversine	Mozavaptan	AZD1981
Chlorcyclizine	Alprenolol	S5280_Dimemorfan_phosphate	S5326_Dolasetron	Azelastine_hydrochloride	AMINOPHYLLINE_aminophylline	S5537_Tizanidine
Mirtazapine	guanfacine	Sotagliflozin_LX4211	Ramelteon	JNJ7777120	Irsogladine	Ondansetron hydrochloride

Sotalol	Phentermine	Solifenacin_succinate	unamed	K_Ras_G12C_inhibitor	Pilocarpine_HCl	S4751_Cisapride
N-Pentanoyl-N-{[2'-(1H-tetrazol-5-yl)-4-biphenylyl]methyl}valine	Triprolidine	ATROVENT_HFA_ipratropium_bromide	K_Ras_G12C_inhibitor	unamed	HALDOL_haloperidol	S5253_Cisapride
Orphenadrine	xylometazoline	S3854_Tetrahydropalmatine_hydrochloride	Agomelatine	ALESSE_ethinyl_estradiol	S4732_MPTP_hydrochloride	unamed
Bromopride	Carbachol	ABC294640	unamed	S5071_Duloxetine	unamed	Sodium_valproate
Zuclopenthixol	Xylazine	unamed	Mosapride_citrate	ESI_09	MK571	unamed
3-Bromo-N-[(1-ethyl-2-pyrrolidinyl)methyl]-2,6-dimethoxybenzamide	Theobromine	Roxatidine_acetate_hydrochloride	S5042_Bevantolol_hydrochloride	Go_6983	IMURAN_azathioprine	Prucalopride_succinat
2-{1-[2-(2,3-Dihydro-1-benzofuran-5-yl)ethyl]-3-pyrrolidinyl}-2,2-diphenylacetamide	Salbutamol	Racecadotril	Aclidinium_bromide	Trazodone_hydrochloride	VU_0364770	unamed
Phenol, 4-[3-(dimethylamino)-1-(2-pyridinyl)propyl]-	Clsapride	GW_9508	FLI_06	mestranol	Cyclobenzaprine_HCl	S5714_lurasidone
Fenspiride	octopamine	S4660_Glycopyrrolate	BQU57	GF_109203X_G_6850	Clomipramine_hydrochloride	ly404039
1-(2-Chlorophenyl)-2-[(2-methyl-2-propanyl)amino]ethanol	Benzyl [(1,6-dimethylergolin-8-yl)methyl]carbamate	GDC_0810	GW842166x	S5654_Indacaterol	unamed	LY2119620
Cyclopentolate	(+_-)-Promethazine	INVEGA_paliperidone	BMY7378	S5238_Solifenacin	TARACTAN_chlorprothixene	Urapidil_hydrochloride
(-)-Hyoscine	Carteolol	S4637_Prasugrel_Hydrochloride	Altrenogest	Lu_AA21004_vortioxetine	S4117	unamed
orciprenaline	propranolol	EQUIPIN_homatropine_methylbromide	S5337_Rauwolscine_hydrochloride	CTEP	Phenylephrine_hydrochloride	Buflomedil_hydrochloride
1,2-Ethanediamine,N2,N2-dimethyl, N1-(4-chlorophenyl), N1-pyridinyl	1,1-Ethenediamine, N'-[2-[[[2-[(dimethylamino)methyl]-4-thiazolyl]methyl]thio]ethyl]-N-methyl-2-nitro-	Toremifene_Citrate	Dienogest	Detomidine_hydrochloride	S9239_Isocorynoxeine	S4574_Piperazine
Mianserin	Synephrine	EHT_1864	S3884_Jatrorrhizine	unamed	unamed	D_glutamine
benperidol	Brimonidine	S5267_Nylidrin_Hydrochloride	pheniramine_maleate	NPS_2143	unamed	S3988_Theophylline_7_acetic_acid
phenoxybenzamine	Guanabenz	Levosulpiride	Ticagrelor	S5288_Estropipate	S3661_2_Methoxy_1_4_naphthoquinone	Serotonin_hydrochloride
Trimebutine	methacholine	prasugrel	S5427_Alloxazine	unamed	Aniracetam	unamed
cyclizine	l-Penbutolol	Salirasib	SB_334867	Lafutidine	CP_945598_hydrochloride	Scopine
3a_tropylmandelat	Clonidine	Cyproheptadine_hydrochloride	S3758_Sinomenine_hydrochloride	Palmatine_hydrochloride	S4892_Phenibut	unamed

trihexyphenidyl	Aceclidine	AM251	S5437_4_4_DDE	Bepotastine_besilate	Cytisine	IEM_1754_dihydrobroMide
carbinoxamine	Diphenhydramine	K_Ras_G12C_inhibitor	unamed	S3706_Sarpogrelate_hydrochloride	fty720	S4718_Acetylcholine_iodide
Astemizole	Betaxolol	unamed	Maprotiline_hydrochloride	Atomoxetine_hydrochloride	VU_0361737	unamed
1H-Pyrido[4,3-b]indole, 2,3,4,5-tetrahydro-2-methyl-5-(phenylmethyl)	Oxprenolol	S4635_Cyproheptadine_hydrochloride	S4696_ArbinoxaMine_Maleate	Azasetron_hydrochloride	unamed	S3639_Tacrine_hydrochloride_hydrate
1H-Indol-5-ol, 3-(2-aminoethyl)-	Tolazoline	Hexestrol	ABILIFY_aripiprazole	Endoxifen_HCl	S3761_Eucalyptol	Arecoline_hydrobromide
Pheniramine	2-(4-Hydroxyphenethylamino)-1-(4-hydroxyphenyl)propanol	S3953_L_Lysine_hydrochloride	Medetomidine_hcl	Hexamethon_ium bromide	unamed	unamed
3469_LCZ696	S5341_Metroprolol_succinate	S4700_4_Aminobutyric_acid	unamed	S5131_Homotaurine	unamed	AMD3465
NSC23766	S5066_Pramipexole_dihydrochloride	unamed				

Table 18. 741 ligands out of the 862 Prestwick and Selleckchm GPCR compound libraries bound to the GPR119 receptor

Table 18-Frame 200: Sequential virtual screening protocol of Zinc Naturals library						
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ZINC04096762	ZINC04556626	ZINC13459712	ZINC05414621	ZINC03158986	ZINC03839011	ZINC02504624
ZINC04235881	ZINC03841728	ZINC35457353	ZINC00518620	ZINC35442831	ZINC02530669	ZINC02242928
ZINC04096936	ZINC04260780	ZINC04259454	ZINC00518554	ZINC23549974	ZINC20463674	ZINC14686696
ZINC05396521	ZINC04236020	ZINC00968436	ZINC06131127	ZINC13433660	ZINC04236304	ZINC05839889

ZINC04235916	ZINC04236023	ZINC31163592	ZINC35415841	ZINC04044989	ZINC13412698	ZINC20463798
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ZINC35465799	ZINC03838975	ZINC05414570	ZINC12529988	ZINC31163684	ZINC04235741	ZINC00389532
ZINC04236118	ZINC05396959	ZINC04235888	ZINC03838816	ZINC12530032	ZINC02379366	ZINC04236055
ZINC03977840	ZINC05438686	ZINC06018481	ZINC05414209	ZINC12529805	ZINC12530036	ZINC12480664
ZINC05414276	ZINC04236244	ZINC02567802	ZINC12529983	ZINC35457392	ZINC03838680	ZINC02525209
ZINC05414542	ZINC35457471	ZINC04260115	ZINC04259745	ZINC14684865	ZINC20463737	ZINC20463689
ZINC14455079	ZINC03838972	ZINC04236157	ZINC15841736	ZINC35442838	ZINC13412691	ZINC03838655
ZINC00526624	ZINC05414292	ZINC35457219	ZINC05396385	ZINC20463677	ZINC20463804	ZINC03838653
ZINC04260665	ZINC03839131	ZINC31163402	ZINC20218724	ZINC04235929	ZINC04334576	ZINC00388237
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ZINC04933690	ZINC04259810	ZINC35442834	ZINC06131125	ZINC12529864	ZINC02506844	ZINC20463787
ZINC12530281	ZINC20463667	ZINC04235804	ZINC14728051	ZINC04236233	ZINC04096937	ZINC01748627
ZINC03875158	ZINC35457454	ZINC12529761	ZINC03838697	ZINC04235974	ZINC05414376	ZINC02041110
ZINC03838865	ZINC20463699	ZINC05414267	ZINC04235752	ZINC12529994	ZINC04259410	ZINC14687784
ZINC04236047	ZINC03871633	ZINC12530240	ZINC04260783	ZINC12530063	ZINC31163376	ZINC03839116
ZINC08215728	ZINC05438633	ZINC04259725	ZINC31163661	ZINC12529870	ZINC01718636	ZINC20268617
ZINC03838742	ZINC20463691	ZINC05396378	ZINC04235845	ZINC12604183	ZINC04236227	ZINC00388241
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ZINC14720477	ZINC04236075	ZINC04236136	ZINC14504544	ZINC04236339	ZINC12530030	ZINC03838668
ZINC03839018	ZINC03872488	ZINC04235824	ZINC06131139	ZINC00057951	ZINC03841696	ZINC03838845
ZINC04260720	ZINC06483435	ZINC35442849	ZINC31155764	ZINC12529872	ZINC00526257	ZINC03008621
ZINC04260648	ZINC35442864	ZINC04235867	ZINC05396527	ZINC27642636	ZINC03841449	ZINC15117859
ZINC04260676	ZINC03838843	ZINC03838849	ZINC14504547	ZINC00334890	ZINC02243378	ZINC12530303
ZINC12529758	ZINC04259758	ZINC20463670	ZINC34965022	ZINC04081837	ZINC05396259	ZINC00163154
ZINC03841682	ZINC04259418	ZINC04235890	ZINC12529914	ZINC03838933	ZINC05396237	ZINC04329286
ZINC04260801	ZINC04096827	ZINC03839088	ZINC03838883	ZINC12480498	ZINC04235869	ZINC02386443

ZINC03869685	ZINC04260479	ZINC03838717	ZINC12530268	ZINC14494726	ZINC04236221	ZINC04235946
ZINC03839020	ZINC04235871	ZINC04235965	ZINC12529811	ZINC03839000	ZINC14620030	ZINC03838651
ZINC04260807	ZINC35442841	ZINC04260670	ZINC35457852	ZINC04091013	ZINC04259143	ZINC16030234
ZINC35442862	ZINC03838718	ZINC13451932	ZINC35442886	ZINC12529804	ZINC04236222	ZINC03839126
ZINC31155673	ZINC35415789	ZINC05414279	ZINC05414273	ZINC03838881	ZINC06131130	ZINC03838646
ZINC03881558	ZINC04235970	ZINC02525206	ZINC04235983	ZINC04236091	ZINC05396244	ZINC20463868
ZINC04235874	ZINC04235979	ZINC04259879	ZINC35457849	ZINC03838846	ZINC02579120	ZINC00163151
ZINC04236069	ZINC04235860	ZINC35415858	ZINC04259698	ZINC12530057	ZINC02168652	ZINC03838647
ZINC04235966	ZINC03838748	ZINC04235763	ZINC35457216	ZINC12530073	ZINC01788405	ZINC04235954
ZINC27330476	ZINC20463919	ZINC04096828	ZINC35457346	ZINC35466020	ZINC00089763	ZINC03838666
ZINC03841714	ZINC04235897	ZINC05415389	ZINC05396569	ZINC00518644	ZINC01847470	ZINC01684095
ZINC35442887	ZINC31155975	ZINC06131138	ZINC03814360	ZINC12529916	ZINC03841444	ZINC00488403
ZINC03838768	ZINC04236026	ZINC04236154	ZINC03838939	ZINC20464000	ZINC00389717	ZINC01575525
ZINC03840428	ZINC06069724	ZINC04235937	ZINC35442855	ZINC02567808	ZINC04259582	
ZINC05414282	ZINC04025169	ZINC35442867	ZINC12529748	ZINC12530278	ZINC13412695	
ZINC05767050	ZINC00689654	ZINC19364225	ZINC01671299	ZINC01631261	ZINC04236090	

Table 18. 956 ligands out of the 20,000 Zinc Naturals library compounds bound to the GPR119 receptor

Complete tables for Frame 250

Table 19-Frame 250: Sequential virtual screening protocol of Prestwick phytochemicals			
4,4'-(2,3-dimethyltetramethylene)dipyrocatechol	Isoliquiritigenin	Camptothecine (s,+)	Piperine
Chlorogenic acid	Conessine	Baicalin	Biotin
Verbenaline	Corynanthine_min_out	Lysergol	
capsaicin_min	cardamonin_min_out	1-8-dihydroxy-3-methylanthraquinone	
Abietic acid	Lapachol	(-)-Cinchonidine	

Berlambine	Rauwolscine_min_out	Velpinic acid	
Chrysin	Halpopine_min_out	Lobeline alpha negative	
Ajmalicine	Reserpinic acid_min_out	Kawain	
Naringenine	Harmine	Berberine	
Olivacine	Sanguinarine_min_out	Acridine	

Table 19. 32 ligands out of the 41 Prestwick phytochemical compound library bound to the GPR119 receptor

Table 20-Frame 250: Sequential virtual screening protocol of GPCR libraries						
Baclofen	Hydroxyzine	Moxisylyte	S4638_Desogestrel	unamed	Diphenidol_hydrochloride	Lu_AA21004_vortioxetine
pimozide	2,4(1H,3H)-Pyrimidinedione, 6-[[3-[4-(2-methoxyphenyl)-1-piperazinyl]propyl]amino]-1,3-dimethyl-	Methapyrilene	17_Hydroxyprogesterone	Ciproxifan	S5337_Rauwolscine_hydrochloride	PF-5274857
2-(Diethylamino) ethyl 3-(1-naphthyl)-2-(tetrahydro-2-furanylmethyl) propanoate	Tetrahydrozoline	Oxprenolol	Atropine_sulfate_monohydrate	S3735_Umeclidinium_bromide	Serotonin_hydrochloride	Acesulfame_potassium
Zuclopenthixol	Azaperone	Ticlopidine	Pregnenolone	S5432_N_2_Chloroethyl_dibenzylamine_Hydrochloride	mesoridazine_besylate	S4694_Alosetron_Hydrochloride
Isopropyl (5Z)-7-[3,5-dihydroxy-2-(3-hydroxy-5-phenylpentyl)cyclopentyl]-5-heptenoate	Sumatriptan	Carbachol	OC000459	DIETHYLSTILBESTROL_diethylstilbestrol	AMINOPHYLLINE_aminophylline	unamed
1-Azoniabicyclo[2.2.2]octane, 4-[(2-hydroxy-2,2-diphenylacetyl)oxy]	Carteolol	Cimetidine	unamed	S4625_Alcaftadine	unamed	S4732_MPTP_hydrochloride
Fluphenazine	benperidol	methacholine	GW842166x	S5358_Regadenoson	unamed	Alverine_citrate
Cloperastine	tripelennamine	(z)-ranitidine	S5399_Chlorprothixene_hydrochloride	AZD1981	SQ22536	Tamsulosin
Ketanserin	clozapine	metoclopramide	untitled	Irsogladine	Melatonin	unamed
2-{1-[2-(2,3-Dihydro-1-benzofuran-5-yl)ethyl]-3-pyrrolidinyl}-2,2-diphenylacetamide	Benzyl [(1,6-dimethylergolin-8-yl)methyl]carbamate	mephentermine	unamed	unamed	unamed	unamed

Carvedilol	1H-Indol-5-ol, 3-(2-aminoethyl)-	Canagliflozin	SKF38393	S3816_Dehydroevodiamine	Varenicline_tartrate	unamed
(1,1-dimethyl-3,4,5,6-tetrahydro-2H-pyridin-3-yl) 2-hydroxy-2,2-diphenyl-acetate	DL-Atenolol	unamed	PAMINE_methscopolamine_bromide	S4776_Harmaline	Adrenalone_hydrochloride	S5655_Venlafaxine
dobutamine	melatonine	Fosaprepitant_dimeglumine	RS_127445	unamed	S4892_Phenibut	Ondansetron hydrochloride
Biperiden	tiapride	Empagliflozin_BI10773	S5088_Labetalone_hydrochloride	S5506_Vortioxetine	Aniracetam	Carbamyl-beta_methylcholine_chloride
Loratadine	Perphenazine	S3738_Travoprost	S4637_Prasugrel_Hydrochloride	IMURAN_azathioprine	Paroxetine_hydrochloride	Venlafaxine_hydrochloride
3-(Diphenylmethoxy)-8-methyl-8-azabicyclo[3.2.1]octane	Tegaserod	Ponesimod_ACT_128800	S4883_Lynestrenol	IRBESARTAN_irbesartan	S5239_Paroxetine_mesylate	unamed
Nordefrin	1H_benzotriazole_5_carboxamide_6_methoxy_N_[[2_propen_1_yl)_2_pyrrolidinyl]methyl]_	S5566_Dapagliflozin_propanediol_monohydrate	Adiphenine_hydrochloride	unamed	Donepezil_HCl	unamed
ifenprodil	timolol	unamed	TARACTAN_chlorprothixene	unamed	S4661_Tiagabine_hydrochloride	S3748_Acamprosate_Calcium
homochlorcyclizine	4H-Pyrido[1,2-a]pyrimidin-4-one, 3-[2-[4-(4-fluorobenzoyl)-1-piperidinyl]ethyl]-2-methyl	Ipragliflozin_ASP1941	unamed	BRL15572	S4675_Tiagabine	unamed
(8,8-dimethyl-8lambda5-azabicyclo[3.2.1]octan-3-yl) 3-hydroxy-2-phenyl-propanoate	Triflupromazine	S5413_Ertugliflozin	ABILIFY_aripiprazole	HJC0350	ZK756326	ZOMIG_zolmitriptan
camylofin	octopamine	Tofogliflozin_CSG_452	S3120_Doxepin_hydrochloride	Agomelatine	NPS_2143	unamed
clemastine	Emedastine	Puerarin	Estradiol_Valerate	S5238_Solifenacin	Dexmedetomidine	Ritodrine_hydrochloride
Ziprasidone	(2-Chlorophenyl)(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)acetic acid	S3664_Flupenthixol_dihydrochloride	PRX_08066_maleate	unamed	Dexmedetomidine_hydrochloride	Arecoline_hydrobromide
Methyl (13E)-11,16-dihydroxy-16-methyl-9-oxoprost-13-en-1-oate	Meclizine	bimatoprost	Levonorgestrel	S9326_Scopolamine	WZ_811	unamed
Ethanol, 2-[2-(4-dibenzo[b,f][1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]	propafenone	CCG_1423	S3716_Flibanserin	unamed	Iloperidone	S4992_Nanofin

Molindone	Ropinirole	unamed	S4673_Etonogestrel	S4774_Xanthurenic_Acid	Prochlorperazine_dimaleate_salt	unamed
domperidone	Sotalol	S3927_Swertiamarin	S5437_4_4_DDE	S5137_O_Phospho_L_serine	unamed	unamed
Apomorphine	1-Ethyl-3-piperidinyl diphenylacetate	S9307_Shanzhiside_methyl_ester	Lafutidine	Levodropropizine	unamed	Sodium_valproate
9-Methyl-9-oxido-3-oxa-9-azatricyclo[3.3.1.02,4]non-7-yl tropate	Oxymetazoline	ki16425	PNU_120596	unamed	unamed	Buflomedil_hydrochloride
Triprolidine	3-Bromo-N-[(1-ethyl-2-pyrrolidinyl)methyl]-2,6-dimethoxybenzamide	Sotagliflozin_LX4211	K_Ras_G12C_inhibitor	S3634_6_Hydroxyflavone	Detomidine_hydrochloride	Epinephrine_HCl
3a_tropylmandelat	fenfluramine	Clomifene_citrate	Darifenacin_hydrobromide	Daphnetin	Naltrexone_hydrochloride	IEM_1754_dihydrobroMide
l-Penbutolol	Alprenolol	Estradiol_benzoate	Gestodene	unamed	Yohimbine_hydrochloride	Succinylcholine_Chloride_Dihydrate
Formoterol	etilefrine	Ethynodiol_diacetate	S5364_DY131	Phenothiazine	S3661_2_Methoxy_1_4_naphthoquinone	Clorprenaline_HCl
Tropicamide	celiprolol	MK_4101	estradiol	Istradefylline	Neostigmine_bromide	S4649_Atipamezole_hydrochloride
11,15-Dihydroxy-9-oxoprostan-1-oic acid	Isoprenaline	4_Hydroxytamoxifen_4_HT_Afimoxifene	S4617_Dextromethorphan_hydrobromide_hydrate	S9258_Isocorynoline	S3761_Eucalyptol	S4587_Dithranol
5H-Benzo[5,6]cycloheptа[1,2-b]pyridine, 6,11-dihydro-11-(1-methyl-4-piperidinylidene)	pronetalol	ATROVENT_HFA_ipratropium_bromide	S5464_Psoralidin	SB408124	S5385_Imidafenacin	unamed
pimethixene	1,1-Ethenediamine, N'-[2-[[[2-[(dimethylamino)methyl]-4-thiazolyl]methyl]thio]ethyl]-N-methyl-2-nitro-	S5326_Dolasetron	levobetaxolol_hydrochloride	Solifenacin_succinate	SB_271046	unamed
Sulpiride	spiperone	Tropisetron_hydrochloride	BRL54443	S5281_Dapiprazole_Hydrochloride	S4932_Proxyphylline	MESTINON_pyridostigmine bromide
trihexyphenidyl	Acepromazine	Dihydromyricetin	Promethazine_hydrochloride	untitled	Maprotiline_hydrochloride	S5341_Metoprolol_succinate
droperidol	lofexidine	QUETIAPINE_FUMARATE_quetiapine_fumarate	BQU57	unamed	S4714_Menthol	Hexamethon_iumbromide
Azacyclonol	Acebutolol	CID16020046_CID_16020046	S5288_Estropipate	Desvenlafaxine	Cytisine	unamed

Prosta_5_13_dien_1_oic acid, 9,11,15_trihydroxy_(5Z,9a,11a,13E,15s)_	1-(tert-Butylamino)-3-((5,6,7,8-tetrahydro-cis-6,7-dihydroxy-1-naphthyl)oxy)-2-propanol	ML141	VU_0364439	unknown	S5400_3_chloro_5_hydroxybenzoic_Acid	S4700_4_Aminobutyric_acid
2-Chloro-9-[3-(dimethylamino)propylidene]thioxanthene	Bromopride	S5398_Nefazodone_hydrochloride	CTEP	unamed	Noradrenaline_bitartrate	S4575_Pralidoxime_chloride
mizolastine	clenbuterol	S5472_Nafronyl_oxalate_salt	S9069_Jatrorrhizine_chloride	Equol	AM1241	D_glutamine
N-(1-Hydroxy-2-butanyl)-6-methyl-9,10-didehydroergoline-8-carboxamide	Zotepine	Forskolin	S3721_Bilastine	unamed	S4117	Scopine
5H-Benzo[5,6]cyclohepta[1,2-b]pyridine, 8-chloro-6,11-dihydro-11-(4-piperidinylidene)-	adrenaline	S3671_Quinestrol	S3758_Sinomenine_hydrochloride	INVEGA_paliperidone	Clomipramine_hydrochloride	S4574_Piperazine
oxybutynin	practolol	S5480_Clidinium_Bromide	unamed	Urapidil_hydrochloride	ADL5859	S5662_Ranitidine
pridinol	Betazole	S5469_Bavachin	Reparixin_Repertaxin	Azasetron_hydrochloride	ALPHACAINE_lidocaine	Pramipexole
ketotifen	isoetarine	Bithionol	S5676_Zearalenone	ZM241385	S4667_Lidocaine_hydrochloride	S5131_Homotaurine
2-[diisopropyl(methyl)-lambda5-azanyl]ethyl 9H-xanthene-9-carboxylate	mebeverine	unamed	unamed	BMY7378	unamed	S4650_Atipamezole
Doxazosin	Asenapine	Macitentan_ACT_064992	Roxatidine_acetate_hydrochloride	S3972_Lobeline_hydrochloride	SB_742457	S4718_Acetylcholine_iodide
Fenoterol	Esmolol	Estriol		unamed	unamed	Choline_Chloride
Phenol, 4-[3-(dimethylamino)-1-(2-pyridinyl)propyl]-	1H-Pyrido[4,3-b]indole, 2,3,4,5-tetrahydro-2-methyl-5-(phenylmethyl)		ESTROGENIC_SUBSTANCE_estrone	unamed	S_38093	S4703_Choline_bitartrate
Naftopidil	Guanabenz	Rupatadine_fumarate	SB_334867	RAPAFLO_silodosin	unamed	S3953_L_Lysine_hydrochloride
carbinoxamine	2-[3-(Diisopropylamino)-1-phenylpropyl]-4-methylphenol	S5067_Losartan	unamed	Ramelteon	Cyproheptadine_hydrochloride	unamed
Racemethorphan	Pindolol	prasugrel	S4281_Tasimelteon	Cinacalcet Hydrochloride	sertraline_hydrochloride	unamed
procyclidine	Metoprolol	GW_9508	Diphemanil_methylsulfate	Vilazodone_Hydrochloride	S5018_Mebhydrolin_napadisylate	Rivastigmine_tartrate
buphenine	(1Z)-1-Hydrazono-1,8a-dihydrophthalazine	Tolvaptan	MI_136	unamed	unamed	Rivastigmine

Chlorphenamine	centirizine	CCG_203971	S3820_Dehydroevodiamine_hydrochloride	S5087_Tianeptine	Fluoxetine_hydrochloride	Phenylephrine_hydrochloride
Diphenylpyraline	Theobromine	S5538_Tropisetron	Galanthamine_hydrobromide	Scopolamine_hydrobromide	VUF_10166	procaine_hydrochloride
8-Methyl-8-azabicyclo[3.2.1]oct-3-yl tropate	meta-hydroxynorephedrine	SCH58261	S5267_Nylidrin_Hydrochloride	Go_6983	S3627_Tryptamine	RANITIDINE_ranitidine
Chlorpromazine	Synephrine	BAF312_Siponimod	CETIRIZINE_DI_HCL	Nebivolol_HCl	unamed	unamed
Orphenadrine	17_(Cyclopropylmethyl)_3_14_dihydroxy_4_5_epoxymorphinan_6_one	S4629_Chlorotrianisene	K_Ras_G12C_inhibitor	Bepotastine_besilate	unamed	ly404039
guanfacine	Clonidine	JNJ7777120	S3866_Galanthamine	S5324_Oxidopamine_hydrobromide	Prucalopride_succinat	ZOLMITRIPTAN, (R)-
Alimemazine	Itopride	unamed	CPI_444	Eletriptan_hydrobromide	unamed	Midodrine
Meptazinol	Dimaprit	Estradiol_cypionate	S5427_Alloxazine	Kobe0065	Nitenpyram	Labetalol
Chlorcyclizine	Candesartan	Pimavanserin_ACP_103	unamed	Pemirolast_potassium	S5499_Amantadine	Doxylamine
4_(Diphenylmethylene0_1_1_dimethylpiperidinium	8-[(Methylsulfanyl)methyl]-6-propylergoline	S4660_Glycopyrrolate	S4839_Mosapride	S3723_Ramosetron_Hydrochloride	8_OH_DPAT_8_Hydroxy_DPAT	Mirtazapine
(+_-)-Promethazine	Histamine	AM251	S4639_Brexpiprazole	Amfebutamone_HCl	Azatadine_dimaleate	Trimebutine
Mianserin	telenzepine	unamed	WAY_100635_meleate	unamed	Amantadine_HCl	Pheniramine
phenoxybenzamine	Brimonidine	SB225002	Palmatine_hydrochloride	S3639_Tacrine_hydrochloride_hydrate	Dopamine_hydrochloride	Pirenzepine
Terazosin	Promazine	Bazedoxifene_acetate	Amitriptyline_hydrochloride	Disopyramide_Phosphate	Prucalopride	cathine
3,4-DIMETHYLPHENETHYLAMINE	Terbutaline	S3657_Promestriene	fty720	Flumazenil	S9239_Isocorynoxeine	Cyclopentolate
17-(Cyclopropylmethyl)-6-methylene-4,5-epoxymorphinan-3,14-diol	Loxapine	Racecadotril	unamed	Etomidate	unamed	Racloprid e
5-{[2-{1-[3,5-Bis(trifluoromethyl)phenyl]ethoxy}-3-(4-fluorophenyl)-4-morpholinyl]methyl}-1,2-dihydro-3H-1,2,4-triazol-3-one	Isoxuprine	S5393_Cyclofenil	Hexestrol	S5119_Olivetol	S4747_Jervine	Betahistine
ipsapirone	Aceclidine	FLI_06	K_Ras_G12C_inhibitor	NEOTHYLLINE_dyphylline	Pilocarpine_HCl	isomethep tene

Trimethobenzamide	orciprenaline	ABC294640	Levosulpiride	PD128907	S3854_Tetrahydropalmatine_hydrochloride	Olanzapine
Salbutamol	1-(2-Chlorophenyl)-2-[(2-methyl-2-propanyl)amino]ethanol	ARN_509	S4696_ArbinoxaMine_Maleate	PF_04418948	Pizotifen_malate	propranolol
Rizatriptan	Dexpramipexole	EQUIPIN_homatropine_methylbromide	Bicuculline	S9249_Securinine	unamed	xylometazoline
methoxamine	(+)-yohimbine	JTC801	unamed	Reversine	Bemegride	bambuterol
Methyldopate	Metitepine	ADX47273	Tianeptine_sodium_salt	VU_0361737	S5559_Tetrahydropalmatine	Bethanechol
Naloxone	LEVOBUNOLOL	ENDOMETRIN_progesterone	VU_0357121	Lamotrigine	Flopropione	Piribedil
Betaxolol	Phentermine	Phlorizin	Medetomidine_hcl	S5052_Granisetron	Epinephrine_bitartrate	Acefylline
Thioperamide	Xylazine	S4749_Citalopram_HBr	5_Iodotubercidin	Alizapride_hydrochloride	Pircetam	ALESSE_ethinyl_estradiol
mepyramine	Clsapride	unamed	SANT_1	Phloretin	S4635_Cyproheptadine_hydrochloride	S3706_Sarpogrelate_hydrochloride
Phentolamine	1H-3-Benzazepine-7,8-diol, 6-chloro-2,3,4,5-tetrahydro-1-(4-hydroxyphenyl)-	Dienogest	Epinastine_HCl	unamed	S3625_Tyramine	Benztropine_mesylate
(-)-Hyoscine	2-(4-Hydroxyphenethylamino)-1-(4-hydroxyphenyl)propanol	S5034_Melitracen_hydrochloride	Mosapride_citrate	unamed	Pergolide_mesylate_salt	Homatropine_bromide
1,2-Ethanediamine,N2,N2-dimethyl, N1-(4-chlorophenyl), N1-pyridinyl	Haloperidol	unamed	Trazodone_hydrochloride	Granisetron_Hydrochloride	RILUZOLE_riluzole	S3701_Benactyzine_hydrochloride
Prazosin	Tolazoline	BML_190	Brompheniramine_maleate	unamed	unamed	S5280_Dimemorfan_phosphate
Sertindole	Fenspiride	ESI_09	Indacaterol_Maleate	unamed	S5537_Tizanidine	Altrenogest
Diphenhydramine	cyclizine	Salirasib	S5654_Indacaterol	unamed	S3903_Lycorine	Org_27569
Amisulpride	Xamoterol	Escitalopram_oxalate	S3769_Palmatine	S9413_Yangonin	Duloxetine_hydrochloride	Naratriptan Hydrochloride
Risperidone	Eticlopride	Dapoxetine_hydrochloride	Chlorpheniramine_Maleate	Eprosartan_mesylate	S3800_Lycorine_hydrochloride	mestranol
Levomepromazine	Famotidine	norethindrone	matrine	unamed	Oxiracetam	Clopidogrel_bisulfate
bisoprolol	alfuzosin	S3635_Medroxyprogesterone	Hyoscyamine_L	S5153_Tetrahydroberberine	Fluvoxamine_maleate	Hesperetin
Naphazoline	Caffeine	Cyclobenzaprine_HCl	S9176_Pimpinellin	Nefiracetam	Palonosetron_HCl	unamed

Rotigotine	MPEP	NEURONTIN_gabapentin	Tizanidine_hydrochloride	S5701_Alvimopan_dihydrate	Gabapentin_hcl	SB_269970_HCl
unamed	S5073_Donepezil	S4618_Fenoldopan_mesylate	XENAZINE_tetrabenazine	unamed	Ticagrelor	VU_0364770
S4751_Cisapride	Nizatidine	Atomoxetine_hydrochloride	S5071_Duloxetine	S3819_Decursinol_angelate	S4849_Levocetirizine_Dihydrochloride	S5042_Bevantolol_hydrochloride
Latrepirdine	unamed	Rotundine	S3988_Theophylline_7_acetic_acid	S4838_Acotiamide_hydrochloride	unamed	

Table 20. 698 out of the 862 Prestwick and Selleckchem GPCR compound libraries bound to the GPR119 receptor

Table 21-Frame 200: Sequential virtual screening protocol of Zinc Naturals library						
ZINC36728548	ZINC04095762	ZINC04259418	ZINC04235983	ZINC04236091	ZINC02579120	ZINC00519489
ZINC31155902	ZINC03838798	ZINC03838763	ZINC05414242	ZINC04259265	ZINC28542039	ZINC35457212
ZINC04236655	ZINC00526624	ZINC04259143	ZINC05414218	ZINC03838711	ZINC35457849	ZINC01575525
ZINC35457506	ZINC04556629	ZINC03839252	ZINC04236337	ZINC31155764	ZINC00391177	ZINC04236100
ZINC31155664	ZINC35457586	ZINC35442867	ZINC35457229	ZINC04235869	ZINC05396463	ZINC04236512
ZINC04236552	ZINC13372048	ZINC31170321	ZINC12529831	ZINC12530114	ZINC00518044	ZINC12530038
ZINC35457671	ZINC35442887	ZINC14504521	ZINC04235915	ZINC04260807	ZINC18043251	ZINC02572861
ZINC08681833	ZINC35442873	ZINC05397153	ZINC04259752	ZINC04100760	ZINC02567808	ZINC03839001
ZINC04236634	ZINC05554081	ZINC03838770	ZINC20464148	ZINC05414495	ZINC20464047	ZINC12530057
ZINC04236575	ZINC35465795	ZINC04235763	ZINC03838992	ZINC12529875	ZINC02379366	ZINC04236049
ZINC31155668	ZINC31155532	ZINC04235974	ZINC02567800	ZINC12529803	ZINC12530079	ZINC20464040
ZINC36728547	ZINC03874879	ZINC04236252	ZINC35442878	ZINC05415389	ZINC04236215	ZINC12495027
ZINC35457540	ZINC35457686	ZINC04236213	ZINC03874215	ZINC12341708	ZINC12530019	ZINC12530011
ZINC59736941	ZINC05396964	ZINC06131125	ZINC35442845	ZINC12529785	ZINC20464009	ZINC12530542
ZINC03839443	ZINC03841400	ZINC04236528	ZINC04236118	ZINC12529805	ZINC12530027	ZINC04236249
ZINC31155673	ZINC04260810	ZINC05397012	ZINC12529911	ZINC05414376	ZINC04260743	ZINC20463821

ZINC04236564	ZINC28956634	ZINC03839491	ZINC04098166	ZINC00057951	ZINC03838687	ZINC03838647
ZINC31155433	ZINC14589862	ZINC04235867	ZINC01561231	ZINC20463913	ZINC35442905	ZINC31163380
ZINC04236548	ZINC05684973	ZINC12604320	ZINC12529880	ZINC05996912	ZINC00689654	ZINC03839348
ZINC35457636	ZINC04236270	ZINC03814360	ZINC03841652	ZINC13459735	ZINC20463737	ZINC03842036
ZINC04236630	ZINC04236247	ZINC04235887	ZINC03874216	ZINC12530501	ZINC12530036	ZINC35457450
ZINC31155443	ZINC03947435	ZINC04259917	ZINC04081837	ZINC03839412	ZINC06069724	ZINC14692054
ZINC35457498	ZINC04259294	ZINC04260804	ZINC12529959	ZINC03839359	ZINC00391162	ZINC00388037
ZINC04236620	ZINC03838973	ZINC35457009	ZINC12480615	ZINC31155759	ZINC03838961	ZINC08215728
ZINC20463746	ZINC03841673	ZINC04259727	ZINC12529820	ZINC04429989	ZINC31163791	ZINC12529758
ZINC05414276	ZINC00004749	ZINC04261000	ZINC03839416	ZINC08681862	ZINC02574996	ZINC13660055
ZINC36728545	ZINC04235979	ZINC04260439	ZINC14728117	ZINC01280222	ZINC04252553	ZINC12604305
ZINC40817993	ZINC31163472	ZINC03838742	ZINC04236012	ZINC04976790	ZINC04260474	ZINC03838642
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ZINC35457544	ZINC14455080	ZINC14589859	ZINC04236004	ZINC04096827	ZINC19594534	ZINC04933692
ZINC06137698	ZINC03838885	ZINC04260950	ZINC35457715	ZINC31163677	ZINC12602397	ZINC12480698
ZINC04236585	ZINC35415837	ZINC03841711	ZINC13373847	ZINC12529842	ZINC03898896	ZINC04236436
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ZINC31163661	ZINC04235965	ZINC00491073	ZINC03838946	ZINC12530467	ZINC12480790	ZINC19796104
ZINC03841685	ZINC03839398	ZINC03841758	ZINC05396959	ZINC31156264	ZINC20464050	ZINC12529988
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ZINC35457590	ZINC04260736	ZINC14504547	ZINC03838981	ZINC04260726	ZINC00435898	ZINC12530528
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ZINC31163744	ZINC12530281	ZINC03838975	ZINC04236095	ZINC03881558	ZINC00088576	ZINC00518488

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ZINC03872494	ZINC03838853	ZINC06500184	ZINC12530507	ZINC03873955	ZINC04261011	ZINC02565724
ZINC05414282	ZINC04236244	ZINC06131122	ZINC04259547	ZINC03838825	ZINC18006959	ZINC04097103
ZINC31163592	ZINC04235871	ZINC13459714	ZINC04235936	ZINC13433656	ZINC00167329	ZINC02530672
ZINC31163764	ZINC35465797	ZINC13826681	ZINC03847505	ZINC12530478	ZINC14494723	ZINC02525203
ZINC03872488	ZINC05998696	ZINC00518644	ZINC06131127	ZINC12530287	ZINC20464098	ZINC03839401
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ZINC31163596	ZINC04235814	ZINC00189959	ZINC04235883	ZINC04236227	ZINC35442896	ZINC00968436
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ZINC04236173	ZINC04235760	ZINC04260801	ZINC02525207	ZINC05414813	ZINC01847470	ZINC00170377
ZINC35457628	ZINC03815424	ZINC05396378	ZINC03839411	ZINC20463726	ZINC04334576	ZINC03838846
ZINC13372046	ZINC14728051	ZINC00518797	ZINC03838790	ZINC20464027	ZINC00389717	ZINC20463804
ZINC31155438	ZINC00001283	ZINC00156620	ZINC03839322	ZINC12530121	ZINC35415779	ZINC20463798
ZINC05414840	ZINC12530167	ZINC12530040	ZINC12530003	ZINC03839352	ZINC20463924	ZINC12530021
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ZINC03842067	ZINC03839472	ZINC12530437	ZINC04236383	ZINC12529940	ZINC02015685	ZINC03838841
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ZINC31156113	ZINC04081985	ZINC04235768	ZINC12529824	ZINC14686696	ZINC04236222	ZINC01686925
ZINC13333976	ZINC04236214	ZINC01639355	ZINC02525206	ZINC02525209	ZINC12530032	ZINC04259816

ZINC34345738	ZINC35465792	ZINC03995861	ZINC35415789	ZINC20464164	ZINC12530042	ZINC20463809
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ZINC05414292	ZINC04235990	ZINC20464179	ZINC05414800	ZINC00389747	ZINC03874615	ZINC12530523
ZINC04235907	ZINC03839467	ZINC20464173	ZINC14641306	ZINC14684865	ZINC04236253	ZINC03860469
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ZINC04236556	ZINC35442872	ZINC35442870	ZINC04235879	ZINC00518554	ZINC15841736	ZINC03874738
ZINC13372050	ZINC03839981	ZINC03838789	ZINC35442876	ZINC04259336	ZINC01850617	ZINC03874658
ZINC04259745	ZINC04236313	ZINC05684949	ZINC05414809	ZINC03838994	ZINC15118046	ZINC02504624
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ZINC35457373	ZINC35457576	ZINC12529776	ZINC12529821	ZINC00057969	ZINC31163688	ZINC14445203
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ZINC04236262	ZINC14720477	ZINC03838986	ZINC04260670	ZINC02506844	ZINC12529839	ZINC12480690
ZINC35457485	ZINC04259698	ZINC40413191	ZINC12529870	ZINC03838988	ZINC14692058	ZINC02242928
ZINC00519621	ZINC13366960	ZINC05398450	ZINC00387872	ZINC04236233	ZINC01847568	ZINC02019242
ZINC04259790	ZINC03838750	ZINC12530085	ZINC04236107	ZINC31163376	ZINC04236482	ZINC02019243
ZINC03871633	ZINC12530462	ZINC35457226	ZINC04235756	ZINC12480725	ZINC00089558	ZINC03838843
ZINC05413174	ZINC05762066	ZINC12530001	ZINC00518620	ZINC04235744	ZINC02530669	ZINC12480659
ZINC03874736	ZINC05397426	ZINC12529996	ZINC12480901	ZINC04252699	ZINC04236223	ZINC12604183
ZINC04236005	ZINC03132353	ZINC04260780	ZINC20218724	ZINC12530556	ZINC00389519	ZINC04235946
ZINC13372044	ZINC35442861	ZINC05414231	ZINC03861768	ZINC35442841	ZINC12530387	ZINC00388241

ZINC31163600	ZINC35442862	ZINC03839437	ZINC00518486	ZINC20463991	ZINC03839057	ZINC02386443
ZINC12529770	ZINC12529768	ZINC04236381	ZINC06131130	ZINC04260478	ZINC15676218	ZINC03839107
ZINC12529916	ZINC14589889	ZINC03838748	ZINC04236358	ZINC04236483	ZINC00526257	ZINC31163684
ZINC31163888	ZINC05554072	ZINC03838939	ZINC04260660	ZINC03894725	ZINC20463787	ZINC35457852
ZINC03838960	ZINC03839414	ZINC15262723	ZINC01718636	ZINC03838845	ZINC00089763	ZINC12530073
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ZINC05414209	ZINC13376806	ZINC03841766	ZINC35457404	ZINC03838760	ZINC12530266	ZINC00164623
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ZINC06095504	ZINC04236019	ZINC39741069	ZINC12529834	ZINC20464030	ZINC03839013	ZINC20463677
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ZINC04260984	ZINC06068882	ZINC06932857	ZINC02243331	ZINC20463715	ZINC02576919	ZINC00895230
ZINC03841679	ZINC06137699	ZINC35457724	ZINC13433660	ZINC05396237	ZINC12604297	ZINC20268617
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ZINC01532042	ZINC13459712	ZINC35442859	ZINC31155826	ZINC12530498	ZINC04236090	ZINC00163154
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ZINC04236052	ZINC06483435	ZINC12529836	ZINC03838895	ZINC04259309	ZINC03838651	ZINC12405084
ZINC04556626	ZINC12530483	ZINC35457346	ZINC04100761	ZINC12529902	ZINC35457662	ZINC00488403
ZINC20464207	ZINC01723552	ZINC04235804	ZINC00057958	ZINC03841195	ZINC00083317	ZINC35466020
ZINC04235975	ZINC04236340	ZINC05415343	ZINC12529828	ZINC03838881	ZINC12360704	ZINC01788405
ZINC31155896	ZINC12529932	ZINC04236075	ZINC05767050	ZINC03839002	ZINC03873977	ZINC00488402
ZINC04236549	ZINC35415846	ZINC35466030	ZINC05998739	ZINC19376338	ZINC12529804	ZINC01684095
ZINC04235874	ZINC03838886	ZINC04260652	ZINC35457730	ZINC31163985	ZINC02574998	ZINC12530294
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ZINC03839470	ZINC03838816	ZINC03839131	ZINC31163344	ZINC00586482	ZINC03157602	
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ZINC14646634	ZINC26574948	ZINC35457219	ZINC20463723	ZINC12529983	ZINC00039702	
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ZINC01631261	ZINC03871094	ZINC19364219	ZINC12530305	ZINC04934608	ZINC35466022	

Table 21. 968 ligands out of the 20,000 Zinc Naturals library compounds bound to the GPR119 receptor

BIOGRAPHICAL SKETCH

Jennifer Lizeth Bravo was born on February 12, 1991 in the city of Linares, Nuevo Leon Mexico. She started her early studies in Mexico and upon moving to the United States in 2006 she continued to pursue a career in science. For her undergraduate she attended The University of Texas Pan American and graduated as a magna cum laude with a BS in chemistry in 2015. In 2019, she joined Dr. Evangelia Kotsikorou's computational chemistry laboratory where she studied computational algorithms for the analysis of big chemical libraries with the purpose of finding possible ligands to fit the GPR119 receptor. Mid 2020, Jennifer started to be co-advised by biochemist Dr. Frank Dean, and she started performing ELISA cAMP analysis on some molecules of the library that produced good receptor fitting scores. She earned her MS in Chemistry degree in May 2021 from the University of Texas Rio Grande Valley. Her email is jennybrav2@gmail.com.