International Journal of Pharma Research and Health Sciences, 2022; 10(5): 3483-86.
DOI:10.21276/ijprhs.2022.05.03
Kaur T *et al.*

CODEN (USA)-IJPRUR, e-ISSN: 2348-6465

**Short Communication**

# Physico-Chemical Optimization of Drugs for GPCR A Family

Tranum Kaur[*], Pardeep Singh Sidhu[*], Maulikkumar Bholabhai Katrodiya[#], Nafisa Sayeed[#], Utsav Bhardwaj[#], Richa Chandrakant Bhatt[#], Abhishek Gadhvi[#], Jareen Tasnim Orpa[#], Tamima Binta Islam[#], Md Abidur Rahman Emran[#], Sandra Daboh Nyantakyi[#], Hajra Iqbal[#], Hasib Al Hasan[#]

* Faculty, Department of Chemistry and Biochemistry, University of Windsor, Ontario N9B3P4, Canada.
[#]Graduate students, MMB Program, Department of Chemistry & Bio-chemistry,University of Windsor, Windsor, Canada.

**ARTICLE INFO:**
Received: 02 June 2022
Accepted: 23 Aug 2022
Published: 30 Oct 2022

**Corresponding author ***
Dr Tranum Kaur,
Coordinator, Faculty, Department of Chemistry and Biochemistry, University of Windsor, Ontario N9B3P4, Canada.
E-mail: tranum@uwindsor.ca

**ABSTRACT:**
This article reviews current knowledge for the largest GPCR family regulating an incredible range of physiological functions and diseases ranging from endocrinology to cardiovascular to sensory disorders. In this study, preferred physicochemical parameters such as molecular weight, lipophilicity, number of rotatable bonds, and water solubility were evaluated as drug design optimizing parameters for druggable GPCR-A targeting compounds. The SWISS ADME bioinformatics tool was utilized in this investigation to determine the relative relationship between drug-likeness and physicochemical characteristics.

**Keywords:** GPCR-A drugs, physicochemical properties, molecular weight, lipophilicity, rotatable bond, water solubility, bioavailability, SWISS ADME.

## 1. INTRODUCTION

GPCRs (G protein coupled receptors) represent the largest variety of extracellular signalling protein that responds to a wide number of chemicals consisting of neurotransmitters, ions, odorants and other stimuli [1]. The majority of medical therapeutic targets belong to one of the five protein families namely G protein-coupled receptors (GPCRs), ion channels, kinases, nuclear hormone receptors, and proteases [2]. G protein-coupled receptors (GPCRs) are imperative for various biological functions, including vision, smell, and aging. They're engaged in various human pathophysiological conditions (diabetes, obesity, and Alzheimer disease and some of CNS disorders) and are among the foremost critical targets of therapeutic drugs [2]. As seen in Figure 1, GPCRs are majorly divided into different families based on their structural composition and similarities [3]. GPCR class A (Rhodopsin-like) remains one of the largest groups among them. In fact, GPCRs class A nearly targets one third of all prescribed medical drugs since most of them share common activation mechanisms [4]. A very popular approach to finding hits and leads for targets where structural information is available is called Fragment-based drug discovery (FBDD) used to screen drug fragments[5]. Many physicochemical parameters such as molecular weight, water solubility, number of rotatable bonds and lipophilicity values are being considered and optimized during the fragment based drug discovery process while designing innovative medications for the GPCR A family [6]. Rules such as Lipinski rule and Egan's rule are used as standards to optimize the drug, which helps in optimizing drug's bioavailability and better ADME safety profile [6]. FBDD uses the applications of biophysical and biochemical methods to detect very small molecules or so-called "fragments" in binding to a specific target [5]. Typically, FBDD starts with a screening of a small library of various molecular weight compounds for binding to a particular target. These fragments are very small molecules, usually should obey the 'Lipinski rule' whereby molecular weight must be less than 500 Da[5]. The molecular weight range can vary for particular GPCR A family selected in order to focus the benchmarking set on compounds with similar properties to those present in chemical libraries used in virtual screening [6]. For example, chemosensory receptors which are classified as class A GPCR, show drug-likeness that have molecular weight between 200 and 500 Daltons, representing molecules that are most effective within this molecular weight range[7]. Additionally, the commonly applied molecular weight cut-off that is 500 does not itself significantly separate compounds with poor oral bioavailability from those with acceptable values in this extensive data set. Despite Lipinski's rule restriction, 18% of

the drug molecules possess a molecular weight in excess of 500[6]. Clearly, better understanding of physicochemical properties for drug likeness are needed for predicting therapeutic ligands that aid in the development of new promiscuous GPCR-A drugs.

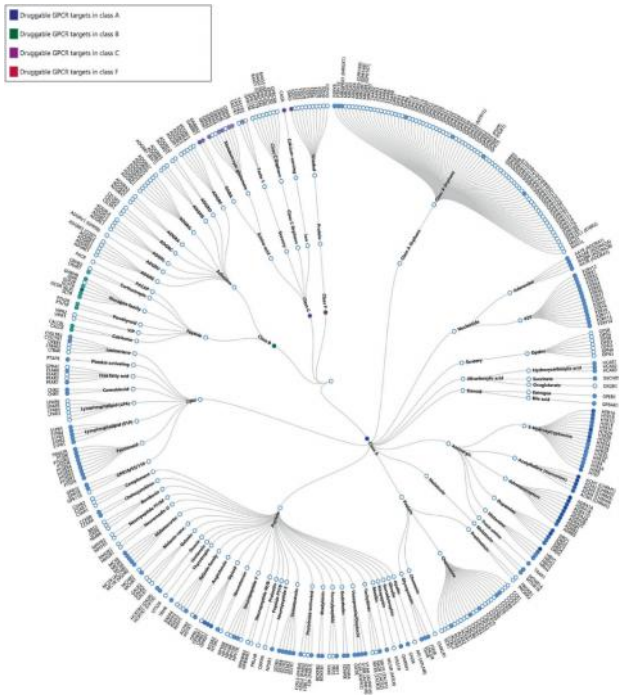

**Fig 1: Evolutionary relationships of GPCRs as drug targets [20].**

## 2. MATERIALS AND METHODS

**PubChem (https://pubchem.ncbi.nlm.nih.gov/)**

PubChem, an open chemistry database at the National Institutes of Health (NIH), was utilized for accessing simplified molecular-input line-entry system (SMILES) for each of the selected GPCR-A drugs. The SMILES were then inputted into the SWISS ADME, a publicly available freeweb server.

**Swiss ADME (www.swissadme.ch)**

Swiss ADME software is developed and maintained by the Molecular Modelling Group of the SIB | Swiss Institute of Bioinformatics. Ten selected GPCR-A selected drugs SMILES were inputted directly on the submission page of SWISS ADME web browser to compute physicochemical descriptors and support drug discovery process.

## 3. RESULTS AND DISCUSSION

In this article, physiochemical properties such as molecular weight, water solubility, number of rotatable bonds and lipophilicity values of selected GPCR-A targeted drugs were reviewed from literature and evaluated to gain better insights as drug design optimizing parameters for druggable GPCR-A targeting compounds. The ten selected GPCR drugs fall under range of the molecular weight between 200 to 500 Da belonging to the group of small molecules [6, 8]. They are also pharmaceutically competent as it seems logical to restrict the development of new innovative compounds to a MW of under 500 Dalton, when topical dermatological therapy or percutaneous systemic therapy or vaccination is the objective [8].

Lipophilicity is a direct indicator of a compound's ability to pass biological membranes after molecular weight. Drug molecules must be soluble enough to get through membranes but not too soluble to become trapped in them [9]. It has been proved that lipid solubility is a significant physicochemical property that greatly influences drug absorption, distribution, metabolism, excretion, and plays a critical role in assisting researchers limit the liabilities of new drug candidates and achieve desired in *vivo* pharmacokinetics. To aid in drug selection and analogue optimization, drug candidates are frequently tested using log P, among other factors. Controlling lipophilicity within a predefined optimum range has been shown to increase compound quality and reduce the likelihood of therapeutic failure [10]. According to 'Lipinski's Rule of 5' the log P of a compound intended for oral administration should be <5. A drug targeting the CNS should ideally have a log P value around 2, for oral and intestinal absorption the ideal value is 1.35–1.8, while a drug intended for sublingual absorption should have a log P value >5 [11]. According to a GPCR case study, Xlog P not greater than 3.5, improved scoring function of the drug likeness of a GPCR target new drug molecule [12]. The values of log P for GPCR-A target drugs selected for our study ranges from 0.85 to 3.86 (Table 1) and are in agreement with Lipinski's rule and drug likeliness for a promising new drug. For an instance, Clopidogrel has good lipophilicity with a consensus value of Log Po/w - 3.50, is insoluble in water, and evenly penetrates the lipid bilayer of the cellular membranes with good absorption property among our ten selected medications [13].

Rotatable bond is another important consideration for molecular flexibility determination and development of bioactive molecules as therapeutic agents [14]. The development of a sufficient understanding of rotatable bonds, as pioneered by Lipinski rule, is a crucial goal for drug research in order to enable the design of feasible novel therapeutic candidates [14]. The observational study done by Veber *et al*. suggests that oral compounds which meet the criteria of 10 or fewer rotatable bonds will have a high probability of better drug efficacy which also follow the Lipinski rule [14]. In their study, over the low molecular weight (MW) 220-770 data set, the quartile averages confirm that higher oral bioavailability is associated with lower rotatable bond counts. In the MW < 400 set, their study showed 90% of the compounds have 10 or fewer rotatable bonds, and 70% have seven or fewer[14]. According to another study, 79% of compounds in the human metabolite dataset have 1-10 rotatable bonds, with the average number of rotatable bonds per molecule in pharmaceuticals being 6 [9]. Morgan et al. found that using a dataset with a maximum number of rotatable bonds of 8, docking scores of GPCR drugs improve, resulting in

enhanced physicochemical diversity [12]. Literature supports our results of GPCR A family drugs which fall within this range of 1-10 rotatable bonds. For example, Prazosin has 5 rotatable bonds (as per Swiss ADME) that influence the binding potency and bioavailability of the drug as well as makes the drug flexible which aids in gaining a better understanding of drug efficacy and will also be useful in the prediction or optimization of small compounds as therapeutic ligands [9, 14].

**Table 1: Physiochemical properties of GPCR-A targeted drugs [21]**

| Name of Drug | Mol. wt. (g/mol) | Lipo-philicity (Log p) | No. of rotatable bond | Water solubility | Bio availability score | Therapeutic system |
|---|---|---|---|---|---|---|
| Levodopa | 197.19 | 0.85 | 3 | Highly soluble to Soluble | 0.55 | Nervous |
| Salbutamol | 239.31 | 1.22 | 5 | Very highly soluble to soluble | 0.44 | Respiratory |
| Morphine | 285.34 | 1.41 | 0 | Soluble | 0.55 | Nervous |
| Clopidogrel | 321..82 | 2.5-3.5 | 4 | Soluble | 0.55 | Circulatory |
| Naloxone | 327.34 | 2.09 | 2 | Soluble | 0.55 | Nervous |
| Indomethacin | 357.79 | 3.63 | 5 | Moderately soluble | 0.85 | Cardiovascular & Musculo-Skeletal |
| Prazosin | 383.4 | 1.42 | 5 | Soluble | 0.55 | Cardiovascular |
| Buspirone | 385.5 | 2.22 | 6 | Soluble | 0.55 | Nervous |
| Losartan | 422.9 | 3.86 | 8 | Freely soluble | 0.56 | Cardiovascular |
| Candesartan | 440.45 | 3.51 | 7 | Poor soluble | 0.56 | Cardiovascular |

For a successfully marketed drug, satisfactory drug absorption depends on a set of three factors, namely, dose, solubility, and permeability [15, 16]. For an instance, a successfully marketed antibiotic, azithromycin with excellent oral activity counterbalances a very low absorption rate in the intestinal loop with very high-water solubility [15]. From our findings, the water solubility of the studied ten GPCR A drug from computational Swiss ADME ranges from poorly soluble to highly soluble (Table 1). One of the core issues being confronted for some GPCR receptor-acting drugs for their clinical use is water solubility. Strategies are needed to overcome this issue as there is limited information or a clear framework in the literature for water solubility approaches and druggability. For example, structural activity relationship (SAR) analysis of Lemborexant resulted in hydroxyl group added to cycloheptane ring with improved water solubility of this drug (Figure2) [17].Another strategy to improve water solubility for future GPCR-A drug discoveries, which could be explored include, disrupting the molecular planarity and symmetry [18]. The disruption of the molecular planarity and symmetry helps to reduce the crystal packing influencing crystallinity of solute and water interaction [19]. Furthermore water solubility can be increased by decreasing the melting point which is related to the disruption of molecular planarity and symmetry [18]. Hence, for the GPCR-A related drug discoveries, decreasing the melting point and reduction in crystal packing will also be a promising strategy in improving water solubility.

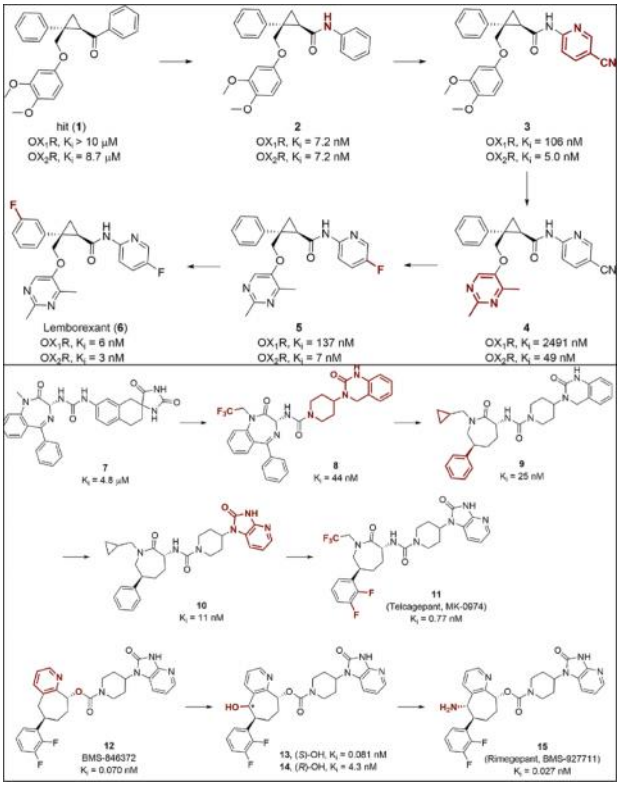


**Fig 2: SAR investigations led to the development of Lemborexant, a dual orexin receptor antagonist and CGRP antagonists [20].**

## 4. CONCLUSION

The present study provides an overview of the physicochemical properties of ten common GPCR A drugs used in the treatment of various pathophysiological conditions. Four physicochemical properties of the drugs, namely the molecular weight, water solubility, number of rotatable bonds and lipophilicity, were investigated using Swiss ADME. The study revealed significant variation in the properties of the ten drugs with the molecular weight ranging from 150-450 g/mol, number of rotatable bonds ranging from 1-10, and lipophilicity ranging from 0.85-3.86. These ranges are consistent with Lipinski's rule of 5 and Egan's rule used to determine a drug binding ability. In terms of solubility, the drugs were found to have a wide range of solubility from poorly soluble to highly soluble. The study provides insights for GPCR-A drugs with low molecular weight compounds and rotatable bonds of 1-10 as good candidates for predicting therapeutic ligands. This article aids in the discovery and development of new therapeutic and promiscuous GPCR-A drugs and deepens our understanding for physicochemical properties of the drugs that can be favourably modified using strategies such as reducing molecular flexibility and disrupting the molecular planarity and symmetry.

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**ACKNOWLEDGEMENT:** None

**CONFLICT OF INTEREST:** The authors declare no conflict of interest, financial or otherwise.

**SOURCE OF FUNDING:** None.

**AVAILABILITY OF DATA AND MATERIALS:** Not applicable.

**CONSENT FOR PUBLICATION**: Not applicable.

**ETHICS APPROVAL AND CONSENT TO PARTICIPATE:** Not applicable.

**Abbreviations:** GPCR: G protein Coupled Receptors, CNS: Central Nervous System, ADME: Absorption Distribution Metabolism Excretion, FBDD: Fragment Based Drug Discovery, Da: Dalton