

REVIEW ARTICLE

In Silico Studies Targeting G-protein Coupled Receptors for Drug Research Against Parkinson's Disease

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Abstract: Parkinson's Disease (PD) is a long-term neurodegenerative brain disorder that mainly affects the motor system. The causes are still unknown, and even though currently there is no cure, several therapeutic options are available to manage its symptoms. The development of novel anti-parkinsonian agents and an understanding of their proper and optimal use are, indeed, highly demanding. For the last decades, L-3,4-DihydroxyPhenylAlanine or levodopa (L-DOPA) has been the gold-standard therapy for the symptomatic treatment of motor dysfunctions associated to PD. However, the development of dyskinesias and motor fluctuations (*wearing-off* and *on-off* phenomena) associated with long-term L-DOPA replacement therapy have limited its antiparkinsonian efficacy. The investigation for non-dopaminergic therapies has been largely explored as an attempt to counteract the motor side effects associated with dopamine replacement therapy. Being one of the largest cell membrane protein families, G-Protein-Coupled Receptors (GPCRs) have become a relevant target for drug discovery focused on a wide range of therapeutic areas, including Central Nervous System (CNS) diseases. The modulation of specific GPCRs potentially implicated in PD, excluding dopamine receptors, may provide promising non-dopaminergic therapeutic alternatives for symptomatic treatment of PD. In this review, we focused on the impact of specific GPCR subclasses, including dopamine receptors, adenosine receptors, muscarinic acetylcholine receptors, metabotropic glutamate receptors, and 5-hydroxytryptamine receptors, on the pathophysiology of PD and the importance of structure- and ligand-based *in silico* approaches for the development of small molecules to target these receptors.

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1. INTRODUCTION

Parkinson's Disease (PD) was originally described by James Parkinson, in 1817, as a neurological disturbance consisting of resting tremor and a distinctive form of the progressive motor disorder, designated as *shaking palsy* or *paralysis agitans* in his monograph entitled *An Essay On the Shaking Palsy* [1]. Currently, it is considered the second

most common neurodegenerative disorder after Alzheimer's Disease (AD), affecting approximately 1% of the population worldwide over 55 years old. PD has been defined as a progressive, irreversible, and chronic neurological disorder characterized by increasingly disabling motor symptoms that are associated to impaired coordinated movements including bradykinesia (slowness of initiation of voluntary movements), resting tremor, cogwheel rigidity, postural instability, and gait disorders [2-4]. In addition, the majority of PD patients do not suffer from motor disabilities alone and numerous non-motor symptoms may lead to a decrease in the quality of life in patients: cognitive impairment, hallucinations, psychosis, anxiety, and depression [5, 6]. Another frequent anomalies related to autonomic (gastrointestinal and cardiovascular), sensory and Rapid Eye Movement (REM)

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and sleep behaviour dysfunctions are also clinically manifested in PD patients. Despite decades of comprehensive study and knowledge concerning the etiology and pathogenesis of PD, much has yet to be discovered in order to understand the pathophysiological mechanisms that contribute to the neuronal cell death (neurodegeneration) in PD. Although normal aging represents the most important risk factor, a combination of environmental (e.g. exposure to pesticides and herbicides, toxins, and organic solvents) and genetic factors may contribute to the onset of PD [7]. Two distinctive pathological manifestations have been associated to the clinical diagnosis of PD in *post-mortem* patients, including the selective and progressive degeneration of dopaminergic neuromelanin-containing neurons from the Substantia Nigra pars compacta (SNc) of the midbrain and striatum of the brain and the presence of Lewy bodies, intraneuronal inclusions of presynaptic protein α -synuclein in brain neurons [2-6].

The reduction of dopamine levels and the loss of SNc dopaminergic neurons have shown to influence directly the appearance of motor dysfunctions associated to PD in 6-HydroxyDopamine (6-OHDA)- and 1-Methyl-4-Phenyl-1,2,3,6-TetrahydroPyridine (MPTP)-treated animals. Since the degree of SNc dopaminergic neurodegeneration correlates positively with the severity of PD, dopamine replacement therapies have become the most effective therapeutic alternative to ameliorate daily function, quality of life, and survival in PD patients. However, the therapeutic strategy of direct administration of dopamine itself is not feasible, due to their inability to cross the Blood-Brain Barrier (BBB) [8]. An alternative BBB-permeable dopamine precursor, L-3,4-DihydroxyPhenylAlanine or levodopa (L-DOPA), was conceived to effectively enhance dopamine concentration in the Central Nervous System (CNS). The antiparkinsonian effects of L-DOPA were first described by Carlsson and co-workers in reserpine-treated animals [9] and, later, in human PD patients after intravenous [10] and oral administration of low doses of L-DOPA [11]. Currently, L-DOPA is considered the most effective medication for correcting dopamine deficiency in PD, significantly attenuating the motor symptoms in human patients. Upon administration to systemic circulation, L-DOPA is converted into dopamine through a decarboxylation catalyzed by the naturally occurring enzyme Aromatic L-Amino acid DeCarboxylase (AADCs; EC 4.1.1.28) in both the CNS and Peripheral Nervous System (PNS). An excessive production of dopamine in the periphery can contribute to severe side effects that impair dopamine replacement therapy for PD patients. The administration of L-DOPA with AADC inhibitors as well as inhibitors of dopamine-metabolizing enzymes, including MonoAmine Oxidase-B (MAO-B; EC 1.4.3.4) and peripheral Catechol-O-MethylTransferase (COMT; EC 2.1.1.6) constitutes an alternative therapeutic approach to selectively increase dopamine levels in the CNS [12-14].

Despite the effectiveness of dopamine replacement therapies in symptomatic PD treatment, their clinical efficacy often decreases, particularly after chronic administration of L-DOPA, leading to the *wearing-off* [15, 16] and *on-off* phenomena [17, 18] due to oscillations of L-DOPA/drug levels, and to the development of long-term motor complica-

tions, such as the troublesome dyskinesias (involuntary muscle movements) [18, 19]. In addition, dopaminergic therapies focused on targeting dopamine receptors (DRs) with agonists have displayed favorable outcomes in early stages of PD, exhibiting antiparkinsonian effects with the lower risk of occurrence of problematic dyskinesias. DR agonists have also been used in combination with L-DOPA to delay the development of motor complications in late stages of the disease. Nevertheless, the use of DR agonists may result in non-motor complications (psychiatric disorders, nausea, vomiting, orthostatic hypotension, increased somnolence and sleep attacks, fatigue, and ankle edema) more severe than L-DOPA. Therefore, the occurrence of motor and non-motor complications associated to all types of dopamine replacement therapy suggested that the symptomatic treatment of PD focused on the re-establishment of dopaminergic neurotransmission may possess restricted therapeutic benefits for patients. Apart from dopaminergic therapies, the modulation of non-dopaminergic neurotransmission systems, including noradrenergic, cholinergic, adenosinergic, glutamatergic, and serotonergic, has been explored as alternative therapeutic approaches for symptomatic monotherapy and in combination with dopaminergic therapies. Interestingly, numerous studies have emphasized the relevance of pharmacological modulation of specific G-protein coupled receptors (GPCRs) for PD symptomatic therapy in preclinical PD animal models and clinical studies with PD patients. The present review highlights the impact of specific GPCR subclasses in the pathophysiology of PD, the structure-, and the ligand-based *in silico* approaches widely used in the identification of small-molecule modulators of these particular receptors.

2. G-PROTEIN-COUPLED RECEPTORS AS THERAPEUTIC TARGETS FOR PARKINSON'S DISEASE

With the increasing number of new cases per year of PD, there has been a considerable increase in the search for new therapeutic alternatives. While the research and development of promising drugs are demanding for all emerging therapeutic areas, the discovery of new therapeutic agents acting on PD and other CNS diseases has been particularly demanding and is associated to a very high attrition rate [20]. GPCRs-targeted agents represent approximately ~30-40% of currently marketed drugs for human therapeutics and these receptors have been subjected to a substantial number of computational studies [21] including as PD targets. GPCRs, also called seven TransMembrane (TM)-spanning receptors, represent the largest family of cell surface receptors of human genome and are characterized by a single polypeptide chain with a variable length that crosses the phospholipid bilayer seven times adopting the typical structure of seven TM α -helices connected by three ExtraCellular (ECL) and three IntraCellular Loops (ICL) [22]. To date, over 800 human GPCRs have been identified and placed into five major families according to their amino acid sequence homology and phylogenetic analysis: *glutamate* (Class C, 22 members), *rhodopsin* (Class A, 672 members), *adhesion* (33 members), *frizzled/taste2* (Class F, 36 members), and *secretin* (Class B, 15 members) [22]. Their members share >20% sequence identity in their TM domains and they mediate several downstream signaling pathways of physiological significance by responding to a plethora of structurally diverse

ligands, particularly endogenous (biogenic amines, nucleotides, peptides, hormones, neurotransmitters, lipids, glycoproteins, and ions) and exogenous ligands (therapeutic agents, photons, tastants, and odorants) [23, 24]. The complexity of GPCR-mediated responses is determined by the association between the activated receptors and specific heterotrimeric Guanine nucleotide-binding-proteins (G-proteins). Heterotrimeric G-proteins are composed of two functional units, a Guanine-binding α -subunit (G_α) and a dimer consisting of the β - and γ - subunits ($G_{\beta\gamma}$). In the absence of a GPCR agonist, G_α is bound to Guanosine DiPhosphate (GDP) and associated with $G_{\beta\gamma}$. Agonist-mediated GPCR activation promotes conformational changes in GPCRs, contributing to the stabilization of active conformation of the receptor, and to the coupling and activation of heterotrimeric G-proteins. The coupling of GPCRs with G-proteins leads to GDP release and Guanosine TriPhosphate (GTP) binding to the G_α subunit. Subsequently, the GTP binding induces conformational alterations on G_α subunit, promoting the release of G-proteins from GPCR and the dissociation of heterotrimeric G-proteins into G_α and $G_{\beta\gamma}$ subunits [25]. The G_α (G_{as} , $G_{ai/o}$, G_{aq} , $G_{\alpha12/13}$) and $G_{\beta\gamma}$ subunits amplify and propagate their cell transduction signals through the modulation of various downstream effectors [26], including Adenylyl Cyclase (AC; EC 4.6.1.1) and PhosphoLipase C (PLC; EC 3.1.4.3), that, in turn, regulate the production of second messengers, such as Ca^{2+} , cyclic Adenosine MonoPhosphate (cAMP), cyclic Guanosine MonoPhosphate (cGMP), DiAcylGlycerol (DAG), and Inositol-1,4,5-triPhosphate (IP_3), the modulation of ion channels, and the activation of kinases cascades, triggering a wide array of cellular responses of physiological importance [27, 28] (Fig.

1). Nevertheless, not all GPCR signaling events are dependent on the activation of G-proteins. In fact, upon prolonged or repeated stimulation of GPCRs by agonists, a process of receptor desensitization induces a progressive attenuation of receptor responsiveness. Second-messenger-dependent protein kinases, Protein Kinase A (PKA; EC 2.7.11.11) and Protein Kinase C (PKC; EC 2.7.11.13), and G-protein coupled Receptor Kinases (GRKs; EC 2.7.11.14, EC 2.7.11.15, and EC 2.7.11.16) are the two families of regulatory proteins that participate in the receptor signaling desensitization, a mechanism independent of the activation of G-proteins. While second-messenger-dependent protein kinases promote phosphorylation of multiple GPCRs, suppressing agonist responsiveness to these receptors even in the absence of agonist occupation (heterologous desensitization), the recruitment of GRKs for receptor phosphorylation preferentially requires an agonist-bound conformation of GPCRs (homologous desensitization), leading to an attenuation of receptor signaling [29, 30]. GRK-dependent phosphorylation promotes GPCRs binding to a class of intracellular scaffolding proteins, β -arrestins, that sterically prevent further interactions between G-proteins and the activated receptors, causing desensitization [31] and ultimately internalization of GPCRs *via* clathrin-mediated endocytosis [32]. Additionally, β -arrestins are by themselves also able to stimulate different pathways, in particular, ligand-bias signaling [33]. Receptor proteolysis mediated by lysosomes [34] and GTP hydrolysis by Regulators of G-protein Signaling (RGS) proteins [35, 36] provide alternative mechanisms of GPCR downregulation. These regulatory mechanisms are critical not only for receptor desensitization but also for receptor resensitization for the next round of GPCR activation and signaling [37].

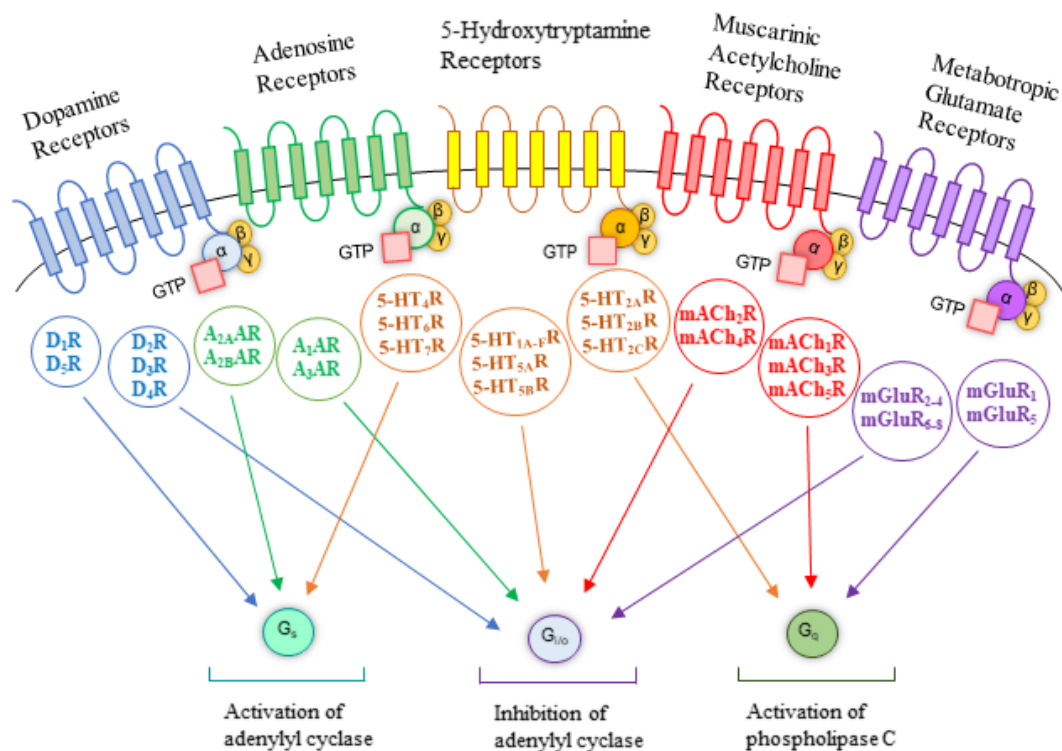


Fig. (1). Signaling cascade of the distinct subtypes of GPCRs potentially involved in PD.

Drug discovery efforts targeting GPCRs have been made on the development of conventional agonists/antagonists that interact with the orthosteric binding site to modulate the activity of neurotransmitter receptors. However, the high conservation of orthosteric binding sites among subtypes of specific GPCR subfamilies has proven to be challenging for the design of therapeutic agents with high receptor subtype selectivity [38, 39]. Additionally, the ligands that interact with orthosteric sites for some GPCRs, in particular, peptide or protein receptors, possess physicochemical and pharmacokinetic properties that are unsuitable for drug discovery of small-molecule ligands [38, 39]. Recently, the identification of novel therapeutic agents acting as allosteric modulators of GPCRs has provided an alternative approach for the development of subtype-selective small molecules potentially useful for the treatment of CNS disorders, such as PD. Allosteric modulators interact to topographically distinct binding sites (allosteric sites) from the orthosteric sites of the endogenous ligands, to either increase (positive allosteric modulators, PAMs) or reduce (negative allosteric modulators, NAMs) receptor responsiveness to ligands. The presence of less highly conserved regions often present in allosteric sites of GPCRs enables the molecular optimization of modulators in order to achieve higher subtype selectivity [38, 39]. Overall, the exploration of allosteric sites of GPCRs for drug design is of utmost importance in medicinal chemistry, possessing several advantages including the possibility to target selective GPCR-signaling pathways without modulating others that may lead to adverse effects and to search for considerable diversity of chemical scaffolds to optimize the pharmacological profile of drug candidates (*e.g.* brain exposure) [38, 39].

Molecular Dynamics (MD) simulation studies have been widely employed as a useful complement to experimental methods in the determination of the atomic-level mechanisms for allostery, since these techniques can capture the motion of proteins in full atomic detail and predict the position of each atom in biomolecular systems as function of time using Newton's second law [40]. The identification of atomic-level mechanisms for allostery is relevant not only for understanding protein function but also for the application of structure-based drug design approaches [41]. MD simulations were employed already in order to understand how allostery is responsible for modulation of the behavior of different receptors. Experimental studies comparing the action of both agonists and antagonists have shed light on conformational changes on β_2 AR upon binding to an irreversible agonist [42]. Another study used MD to compare the solved X-ray structure of an agonist-bound A_{2A} AR [43] with the previously determined X-ray structure of an antagonist-bound structure of the same receptor [44]. By doing so, the researchers were able to determine how the structure was affected by both classes of orthosteric ligands and concluded that TM3, TM5, TM6, and TM7 were the most affected domains. ECL2 and ECL3 also showed considerable displacement, explained by their proximity to the binding site. Interestingly, ICL3, critical for several GPCR functions such as activation and recycling [45-47], was also shown to be considerably altered when comparing agonist- and antagonist-bound structures. This can highlight the ligand-bias mecha-

nism and how it affects GPCR function. Only a few computational studies have addressed this problem. For example, a computational study by Dror *et al.* [48] using the M2 muscarinic receptor revealed that using cationic orthosteric ligands and cationic negative allosteric modulators hinders the binding of both, depending on the total charge and charge location of both ligand and modulator. This was found to be due to charge repulsion and, mostly, conformational rearrangements in orthosteric and allosteric binding sites upon allosteric modulator and orthosteric ligand binding, respectively. Additionally, the interaction between positive allosteric modulators and orthosteric ligands seem to increase binding affinity due to conformational changes as well, particularly binding site wider openings. Other computational studies addressed allostery only, such as the different conformational changes in 5-HT_{1A} upon agonist, partial agonist and antagonist [49] – which pointed towards TM5 and TM6 as the most altered domains when comparing agonist- and antagonist-bound structures – or how buspirone, a 5-HT_{1A} partial agonist, differently changes the 5-HT_{1A} and 5-HT_{2A} conformation upon binding [50]. To date, a substantial number of allosteric modulators of GPCRs have exhibited pharmacotherapeutic potential for the treatment of PD and other CNS diseases. Specifically, for PD, the development of allosteric modulators of muscarinic Acetylcholine Receptors (mAChRs) and metabotropic Glutamate Receptors (mGluRs) have demonstrated potential therapeutic applications in pre-clinical PD models.

2.1. Dopamine Receptors

Dopamine is an endogenous chemical belonging to catecholamine and phenethylamine families that functions as a catecholaminergic neurotransmitter and neurohormone, modulating various physiological actions on CNS such as voluntary movements, feeding, affect, reward, sleep, attention, working memory, and learning. In addition, hormonal regulation, cardiovascular functions, immune system, and renal functions are also influenced by dopamine [51, 52]. These physiological functions of dopamine are mainly mediated through activation of five subtypes of DRs, which are placed into two major classes, according to their ligand specificity, G-protein coupling, anatomical distribution, and physiological effects. The D₁-like receptors, including D₁R and D₅R, promotes the activation of AC with concomitant stimulation of cAMP production *via* G_{s/olf} proteins, whereas the D₂-like receptors, including D₂R, D₃R, and D₄R, are preferentially coupled with G_{i/o} proteins to inhibit AC activity and, consequently, the production of cAMP [51, 52].

The evidence of selective loss of dopaminergic neurons in SNc as the most relevant pathological hallmark of PD has suggested that the use of dopamine replacement therapies as a therapeutic strategy to regulate dopamine levels in the brain may provide some symptomatic relief for PD patients. Despite the motor fluctuations and the occurrence of dyskinesias associated to a long-term administration of L-DOPA, alternative therapeutic opportunities have emerged as plausible approaches to counteract the prevalence of L-DOPA-induced motor complications. Apart from the combination of L-DOPA with AADC (EC 4.1.1.28), MAO-B (EC 1.4.3.4), and peripheral COMT (EC 2.1.1.6) inhibitors, the develop-

ment of drug delivery systems and the use of long-acting drug candidates capable of stimulating presynaptic and postsynaptic DRs, such as the DR agonists may contribute to a more effective attenuation of motor fluctuations and reduction of induced dyskinesias. In MPTP-parkinsonian non-human primates, the administration of long-acting selective D₂-like receptor agonists induced a significantly lower tendency to produce dyskinesia comparing to those treated with L-DOPA [53, 54]. In addition, DR agonists act directly on their receptors without the necessity of metabolic conversion. DR agonists may also provide a wider therapeutic window with reduced risk of dyskinesias, presumably due to their longer plasma half-lives and better pharmacokinetic profiles than L-DOPA, thereby producing more prolonged receptor stimulation. Moreover, DR agonists possess the ability to target certain receptor subtypes, resulting in more specific therapeutic effects and avoiding the occurrence of side effects derived from non-specific activation of receptors induced by L-DOPA. Unlike L-DOPA, their metabolism does not produce hazardous reactive oxygen species (ROS) on dopaminergic neurons. Several studies have suggested that DR agonists might present neuroprotective properties *via* direct scavenging of free radicals or enhancing the activity of enzymes that scavenge these radicals, increasing neurotrophic activity. Therefore, the involvement of DRs in the modulation of PD has led medicinal chemists to invest in the research of DR agonists with higher subtype selectivity. Until recently, several classes of small molecules targeting D₂Rs and D₃Rs have been discovered [55-67]. According to their chemical scaffolds, these DR agonists have been classified into two major classes (see Fig. 2): ergoline derivatives, including bromocriptine (1), cabergoline (2), lisuride (3), pergolide (4), and α -dihydroergocryptine (5), and non-

ergoline derivatives, including ropinirole (6), pramipexole (7), rotigotine (8), apomorphine (9), and pibedilil (10). Both classes exhibit comparable antiparkinsonian efficacy. However, ergoline-derived DR agonists have been associated with the occurrence of adverse effects such as cardiovascular, retroperitoneal, and pleuro-pulmonary fibrosis and, therefore, their use for clinical therapy has been significantly diminished. Alternatively, the development of non-ergoline derivatives may offer the same therapeutic benefits of ergoline derivatives without the mentioned side effects.

2.2. Adenosine Receptors

Adenosine is an endogenous neuromodulator involved in various pathophysiological functions through the interaction with four major subtypes of AR, A₁ (A₁AR), A_{2A} (A_{2A}AR), A_{2B} (A_{2B}AR), and A₃ (A₃AR) [68, 69]. While A₁ARs and A₃ARs are negatively coupled with AC *via* G_{i/o} proteins, exerting an inhibitory effect on the production of cAMP [69], the activation of A_{2A}ARs and A_{2B}ARs enhances AC activity *via* G_s proteins, causing an increase on cAMP levels [70]. In opposition to the ubiquitous distribution of A₁ARs and A_{2B}ARs in the brain, A_{2A}ARs are densely expressed in restricted regions within the CNS and exist primarily in striatum, nucleus accumbens, and olfactory tubercles [71, 72], where they are coexpressed and physically interact with D₂Rs, forming A_{2A}AR-D₂R heterodimers [73, 74]. A_{2A}ARs and D₂Rs possess antagonistic effects on AC activity and experimental data have suggested the involvement of A_{2A}ARs-mediated adenosinergic neurotransmission on the negative regulation of D₂Rs-dependent dopaminergic signaling [75, 76]. Preclinical studies have demonstrated that the pharmacological inhibition with selective A_{2A}AR antagonists induce significant beneficial effects in animal models of PD,

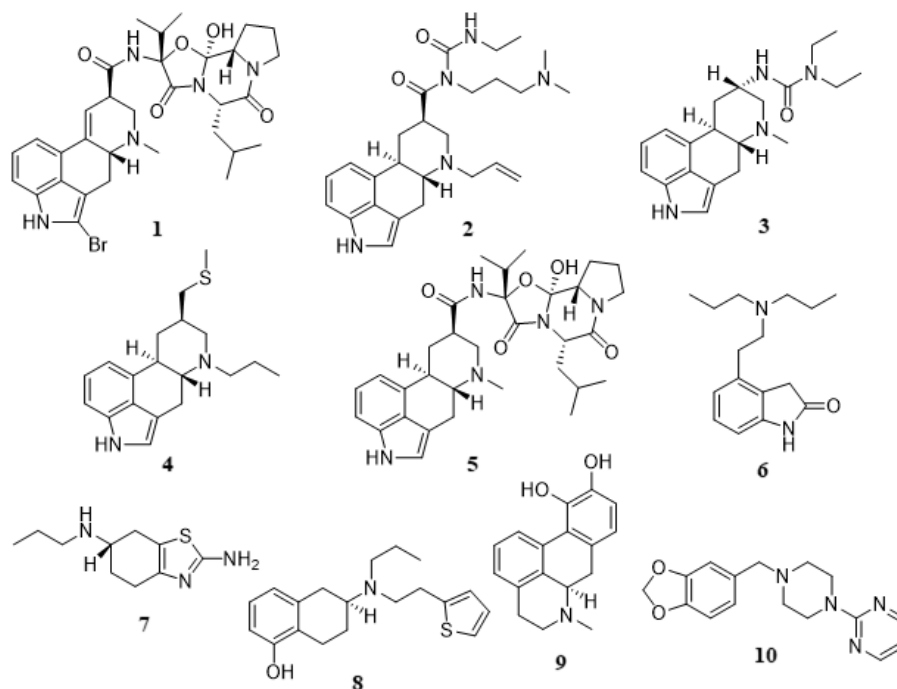


Fig. (2). Chemical structures of ergoline (1-5) and non-ergoline derivatives (6-10): bromocriptine (1), cabergoline (2), lisuride (3), pergolide (4), α -dihydroergocryptine (5), ropinirole (6), pramipexole (7), rotigotine (8), apomorphine (9), and pibedilil (10).

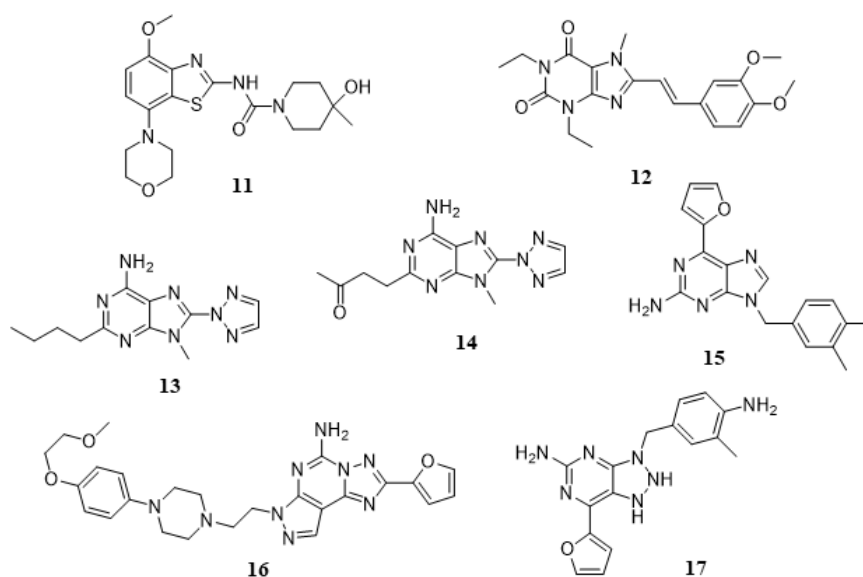


Fig. (3). Chemical structures of A_{2A}AR antagonists in clinical trials for PD treatment: SYN-115 or Tozadenant (**11**), KW-6002 or Istradefylline (**12**), ST1535 (**13**), ST4206 (**14**), BIIB014/V2006 (**15**), SCH-420814/MK-3814 or Preladenant (**16**), and V-81444 (**17**). The chemical structure of PBF-509 was not disclosed.

reversing catalepsy induced by haloperidol (D₂R antagonist) in rodents [77] and cynomolgus monkeys [78], improving motor functions in 6-OHDA-lesioned rats [79], and attenuating PD-like lesions caused by administration of neurotoxin MPTP in mice [80] and cynomolgus monkeys [81]. Interestingly, coadministration of A_{2A}AR antagonists with L-DOPA not only enhance the therapeutic effects of L-DOPA on the improvement of motor symptoms and on prevention of disease progression but also can minimize the incidence of L-DOPA-induced *wearing-off* and L-DOPA-related dyskinesias after long-term treatment [82]. Moreover, antiparkinsonian activity in preclinical animal models has been reported when A_{2A}AR antagonists are administered in combination with selective D₂R agonists. These evidences have led researchers to explore the inhibition of A_{2A}AR with selective antagonists as potential enhancers of dopaminergic neurotransmission for symptomatic treatment of PD. Also, the selective and restricted localization of A_{2A}AR in the basal ganglia provides a therapeutic opportunity for A_{2A}AR antagonists to regulate motor functions without inducing non-specific effects in other brain regions. Therefore, A_{2A}AR has been considered a promising therapeutic target for negative modulation by small-molecule drug candidates to be used either as monotherapy or in combination with dopaminergic drugs for PD therapeutics. A diverse plethora of chemical families of A_{2A}AR antagonists have been identified [83-99] and among these small-molecule drug candidates, eight A_{2A}AR antagonists have progressed to clinical studies (Fig. 3) to date by distinct pharmaceutical companies, including SYN-115 (**11**, Tozadenant) from Biotie Therapies and UCB Pharma S.A., KW-6002 (**12**, Istradefylline or NOURIAST®) from Kyowa Hakko Kirin Co. Ltd, ST1535 (**13**) and ST4206 (**14**) from Sigma-Tau, SCH-420814/MK-3814 (**15**, Preladenant) from Merck & Co. Inc., BIIB014/V2006 (**16**, Vipadenant) from Vernalis Plc-Biogen Idec Inc., V81444 (**17**) from Vernalis Plc, and PBF-509 (chemical structure not disclosed)

from PaloBiofarma S.L., and [100]. Apart from their encouraging pharmacokinetic properties, safety and tolerability profile, the reported clinical studies have demonstrated that A_{2A}AR antagonists significantly reduced L-DOPA-induced *wearing-off* effect, decreased the time spent by PD patients in a state of immobility (off-time) without impairing troublesome dyskinesia, and increased the time spent by PD patients in a state of mobility (on-time) with a moderate increase of non-troublesome dyskinesia, in L-DOPA-administered patients at an advanced stage of PD [100]. In 2013, KW6002 was approved for manufacturing and marketing in Japan as a novel therapeutic option for improvement of *wearing-off* effect in patients with PD when KW6002 is concomitantly administered with L-DOPA-containing products [101].

2.3. Muscarinic Receptors

Five distinct subtypes of muscarinic Acetylcholine Receptors (mAChR₁-mAChR₅ or M₁-M₅) [102] mediate the metabotropic actions of acetylcholine through regulation of distinct signaling pathways: mAChR₁, mAChR₃, and mAChR₅ activate PLC *via* G_q proteins whereas mAChR₂ and mAChR₄ inhibit AC *via* G_{i/o} proteins [103]. The modulation of cholinergic system dependent on mAChRs plays a critical role in a wide plethora of central nervous system (CNS) functions, including the modulation of neuronal excitability and synaptic plasticity, sensorimotor gating, locomotor activity, memory and learning mechanisms, among other functions [104,105]. Due to their role in a number of CNS processes, mAChRs have been recognized as an attractive therapeutic target for discovery of drug candidates targeting CNS pathologies, namely PD, AD, Attention Deficit Hyperactivity Disorder (ADHD), and schizophrenia. Specifically, for PD, the characteristic dysfunction of dopaminergic neurotransmission in the striatum may contribute to a dysregulation of the dynamic equilibrium between cholinergic and do-

paminergic systems. In fact, the loss of dopaminergic neurons triggers an excessive release of Acetylcholine (ACh) through activation of mACh autoreceptors and an overactivation of cholinergic system that results in the occurrence of serious motor and cognitive disturbances associated to PD [106]. Therefore, inhibition of mAChRs has been suggested as a promising strategy to overcome the increased cholinergic activity and to re-establish the cholinergic/dopaminergic balance. Among the five subtypes of mAChRs, mAChR₁ and mAChR₄ subtypes have been suggested to participate in modulation of PD pathophysiology. Pharmacological blockade of mAChR₁ have shown therapeutic benefits in preclinical models of PD through blockade of carbachol-induced excitation of striatal medium spiny neurons, reversal of reserpine-induced akinesia and of haloperidol-induced catalepsy [107]. Additionally, selective mAChR₁ and mAChR₄ antagonists relieved unilateral 6-OHDA lesion-elicited motor deficits in mice [108] and mAChR₄ antagonism suppressed pilocarpine- and pimozide-induced tremulous jaw movements [109,110]. The mAChR₄ knockout enhanced dopaminergic neurotransmission [111], increased locomotor activity in D₁R agonist-treated mice [112], and attenuated haloperidol- and risperidone-induced catalepsy in scopolamine-treated mice [113]. These results have suggested the inactivation of mAChR₁ and mAChR₄ with small-molecule antagonists as an encouraging approach for PD therapeutics.

The high sequence conservation within the orthosteric binding site of the five mAChRs has demonstrated to be unfavorable for the discovery and development of antagonists which specifically target the blockade of one mAChR subtype. A highly subtype-selective mAChR antagonist provides a more direct pharmacological effect, contributing to the elimination of potential side effects. Also, a mAChR antagonist could be used as a pharmacological tool and aid in the development of selective mAChR antagonists, which in turn, may be useful for treatment of PD. Numerous small-molecule antagonists acting on mAChR₁ [114-126] and on mAChR₄ [127-133] have been identified.

2.4. Metabotropic Glutamate Receptors

The amino acid glutamate is considered the major excitatory neurotransmitter in the brain. Glutamate elicits and modulates synaptic responses in CNS by activating two classes of glutamate receptors: ionotropic (iGluRs) and metabotropic glutamate receptors (mGluRs). iGluRs constitute a class of ligand-based ion channels subdivided into three families, including *N*-Methyl-D-Aspartate (NMDA), α -Amino-3-hydroxy-5-Methyl-4-isoxazole Propionic Acid (AMPA), and Kainate (KA) receptors. Belonging to *glutamate*-like or class C GPCRs, mGluRs are composed of eight subtypes which are classified into three groups according to the receptor structure, their pharmacological profile, and ligand binding specificity: Group I (mGluR₁ and mGluR₅), Group II (mGluR₂ and mGluR₃), and Group III (mGluR₄, mGluR₆, mGluR₇, and mGluR₈). The activation of group I mGluRs enhances the production of IP₃ and DAG through stimulation of PLC *via* G_q proteins, whereas group II and group III mGluRs inhibit AC activity-dependent on G_i/G_o proteins [134].

Several studies performed in preclinical animal PD models have suggested that the pharmacological blockade of group I mGluRs as well as the activation of group II and group III mGluRs may provide plausible therapeutic strategies for treatment of PD. Regarding the group I mGluRs, the administration of mGluR₅ NAMs reversed parkinsonian symptoms, ranging from alleviation of akinesia in 6-OHDA-lesioned rats [135] to inhibition of muscle rigidity electromyographic activity, hypolocomotion, and catalepsy induced by haloperidol [136-138]. Interestingly, the coadministration of mGluR₅ antagonists with A_{2A}AR antagonists produces a synergistic effect on stimulation of locomotor activity in both untreated and reserpine-treated mice [139] and promoted a complete recovery of akinesia in 6-OHDA-lesioned rats in reaction time tasks [140]. Similarly, the combination of mGluR₅ antagonists with NMDA receptor antagonists, at suboptimal doses, induced significant improvements on PD symptomatology, producing an anti-akinetic effect after 6-OHDA infusion in rats [141]. In rats with partial bilateral 6-OHDA lesions, the long-term administration of mGluR₅ antagonists significantly reversed the overactive glutamatergic neurotransmission of striatum and subthalamic nucleus (STN) and SNr, thereby resulting in the alleviation of motor symptoms [135, 142, 143]. In addition, acute and chronic administration of mGluR₅ NAMs significantly attenuate the development of L-DOPA induced dyskinesias in 6-OHDA-lesioned rats and in MPTP-treated monkeys chronically administered with L-DOPA [138, 144, 145]. In combination with L-DOPA, the mGluR₅ NAMs induced antidyskinetic effects and prolonged the motor stimulant effects of L-DOPA in both rat and monkey PD models [145]. These evidences suggest that mGluR₅ NAMs alone and/or coadministered with L-DOPA, A_{2A}AR and NMDA receptor antagonists may provide a viable approach for symptomatic treatment of PD.

Interestingly, the mGluRs have shown to be implicated in processes of neurodegeneration/neuroprotection and to modulate excitatory synaptic neurotransmission, providing alternative therapeutic opportunities for neuroprotective drug candidates. More specifically, the mGluR₅ knock-out in mice protected against MPTP-induced nigrostriatal damage, which suggested that blockade of mGluR₅ may confer neuroprotective effects in animal models [146]. Additionally, in rodents, the administration of mGluR₅ NAMs reduced the extent of nigrostriatal toxicity in rodents in response to MPTP [146, 147], 6-OHDA [148, 149], and methamphetamine [150], supporting the use of these drug candidates to exert neuroprotective activity and to slow the progression of neurodegeneration in PD. The relevance of pharmacological blockade of these receptors has inspired the researchers to discover antagonists and NAMs [151-164] targeting mGluR₅.

The therapeutic benefits of activators of group II mGluRs have been demonstrated in several animal models. In fact, the intranigral or intracerebroventricular administration of mGluR₂/mGluR₃ agonists attenuated reserpine-induced akinesia and systemic administration of mGluR₂/mGluR₃ agonists impaired haloperidol-elicited catalepsy and muscle rigidity in rats [165, 166]. Interestingly, the activation of group II mGluRs may exert neuroprotective effects in rat

SNC neurons. Consistent with this hypothesis, administration of mGluR₂/mGluR₃ agonists decreased the extent of rat SNC neurodegeneration caused by 6-OHDA- [148] and MPTP-induced neurotoxicity [167, 168], underlying their role as disease-modifying agents in PD. Likewise, several evidences have suggested that the activation of group III mGluRs may alleviate PD symptoms by reducing glutamate and γ -aminobutyric acid (GABA) neurotransmission at both the striatopallidal and STN-SNr synapses of the indirect pathway in the basal ganglia circuit [169-171]. Supporting this hypothesis, intracerebroventricular administration of group III mGluRs agonists has shown to reverse both acute (haloperidol-elicited catalepsy and reserpine-induced akinesia) and chronic (forelimb asymmetry caused by unilateral 6-OHDA-lesion) rat models of parkinsonism [170, 172]. Intrapallidal administration of group III mGluRs agonists alleviate both cataleptic and akinetic effects in rodents [172, 173], evidencing the importance of modulating synaptic neurotransmission as therapeutic strategy for symptomatic treatment of PD. In addition, the activation of group III mGluRs in the basal ganglia has displayed neuroprotective effects, reducing excitatory neurotransmission in the SNC by STN overactivity [174] and protecting against NMDA-elicited toxicity. The symptomatic and neuroprotective properties of group III mGluRs agonists are prevented in mGluR₄ knockout mice, which suggest that the modulation of mGluR₄ has the potential to exert antiparkinsonian activity in animal models. Overall, the pharmacological activation with mGluR₂/mGluR₃ [175-180] and mGluR₄ [181-186] with agonists and PAMs may offer an alternative approach for PD therapeutics.

2.5. 5-Hydroxytryptamine Receptors

Being one of the most commonly studied neurotransmitters, 5-Hydroxytryptamine (5-HT) or serotonin regulates a wide array of physiological functions in the brain, particularly in emotion, modulation of sleep-wake cycles, cognition, memory, and motor behaviour. These functions are mediated through the interaction with 5-Hydroxytryptamine (5-HTRs) or serotonin Receptors, which are subdivided into thirteen subclasses: (i) 5-HT_{1A}R, 5-HT_{1B}R, 5-HT_{1D}R, 5-HT_{1E}R, 5-HT_{1F}R, 5-HT_{5A}R, and 5-HT_{5B}R promote the down-regulation of AC activity *via* G_i/G_o proteins; (ii) 5-HT₄R, 5-HT₆R, and 5-HT₇R stimulate the production of cAMP through activation of AC *via* G_s proteins; (iii) 5-HT_{2A}R, 5-HT_{2B}R, and 5-HT_{2C}R induce the activation of PLC [187]. Several studies have suggested that the serotonergic activity is markedly impaired in PD. In fact, in PD patients, serotonin has shown to be reduced in the cortex, caudate nucleus, and hippocampus [188], the raphe nucleus and in the substance P-containing preganglionic neurons in the dorsal motor vagal nucleus [189], while serotonin markers are decreased in the caudate nucleus and putamen [190]. Interestingly, the pharmacological activation/blockade of specific 5-HTR subtypes with small molecules has displayed beneficial outcomes in preclinical PD models and clinical studies. Regarding the 5-HT_{1A}Rs, the administration of 5-HT_{1A}R agonists has shown to attenuate/reverse 6-OHDA- [191] and haloperidol-induced catalepsy [192, 193], and to increase the motor activity in reserpine-administered rats [194]. In 6-OHDA-lesioned rats,

5-HT_{1A}R agonists improve the performance in the forepaw adjusting steps test, an indicator of antiparkinsonian activity [195]. Pharmacological modulation of 5-HT_{1A}R with agonists has shown to induce contraversive rotations in 6-OHDA-treated rats, to alleviate the parkinsonian symptoms in MPTP-lesioned common marmosets [196], and to attenuate L-DOPA induced motor complications [197-199]. Similarly to 5-HT_{1A}Rs, the activation of 5-HT_{1B}Rs mitigates the occurrence of dyskinesia and abnormal involuntary movements induced by L-DOPA [200-202]. Curiously, a synergistic effect on the decrease of abnormal involuntary movements was observed when 5-HT_{1B}R agonists were co-administered with 5-HT_{1A}R agonists [202]. Overall, targeting 5-HT_{1A}Rs [203-207] and 5-HT_{1B}Rs [208-211] with agonists may provide potential benefits on the reversal of PD symptoms.

On the other hand, the inactivation of 5-HT_{2A}R and 5-HT_{2C}R has demonstrated potential antiparkinsonian effects in human patients and animal models. In fact, trazodone, a dual 5-HT_{2A}R/5-HT_{2C}R antagonist, is effective on the treatment of PD-associated depression and on improvement of motor functions in human subjects [212]. Other dual 5-HT_{2A}R/5-HT_{2C}R antagonist, ritanserin, has shown to reduce bradykinesia and ameliorate gait disorder in human patients [213]. In MPTP-treated mice, peripheral administration of 5-HT_{2A}R antagonists alone and in combination with dual 5-HT_{2A}R/5-HT_{2C}R antagonists enhanced motor performance on the beam walking apparatus [214, 215]. Regarding the 5-HT_{2C}Rs, the intracerebral administration of 5-HT_{2C}R antagonists into the SNR elicited contraversive rotations to the injection side and enhanced antiparkinsonian action of D₁R and D₂R agonists in 6-OHDA-treated rats [216, 217]. To date, diverse chemical families of antagonists of 5-HT_{2A}R [218-225] and 5-HT_{2C}R [223-227] have been reported.

2.6. GPCR-based Drug Discovery for PD: An Overview of *in silico* Methodologies

Over the last years, the development of Computer-Assisted Drug Design (CADD) methodologies has been of extreme relevance for the identification of GPCR modulators targeting PD, contributing to increase the cost-efficiency and to speed up the drug discovery process. *In silico* drug design of GPCR modulators can be achieved by applying structure-based and ligand-based drug design methodologies.

2.6.1. Application of Structure-based Design Techniques for GPCR-based Drug Discovery

The field of structure-based drug design [228, 229] has been a rapidly growing area in which many advances in the drug discovery process have occurred in recent years. The explosive development of the structural biology focused on determination of high resolution three-dimensional (3D) structures of GPCRs has furnished a myriad of therapeutic opportunities for drug design of GPCR modulators inspired by structure-based drug design methodologies such as molecular docking simulations, structure-based, and fragment-based virtual screening techniques. Since GPCRs are membrane-bound protein receptors, experimental elucidation of their 3D structure, by X-ray crystallography and Nuclear

Table 1. Three-dimensional structures of GPCRs retrieved from the Research Collaboratory for Structural Bioinformatics Protein Data Bank (RCSB PDB) until February 2018.

<i>Rhodopsin-like or Class A GPCRs</i>					
PDBid	GPCR	Main Ligand(s) / Binding Partner(s)	Resolution / [Å]	Release Date	Refs.
4IAQ	5-HT _{1B} R	Dihydroergotamine (agonist)	2.80	2013	[232]
4IAR	5-HT _{1B} R	Ergotamine (agonist)	2.70	2013	[232]
5V54	5-HT _{1B} R	Methiothepin (inverse agonist)	3.90	2018	[233]
4IB4	5-HT _{2B} R	Ergotamine (agonist)	2.70	2013	[234]
4NC3	5-HT _{2B} R	Ergotamine (agonist)	2.80	2013	[235]
5TUD	5-HT _{2B} R	Ergotamine (agonist) and anti-5-HT _{2B} (antibody)	3.00	2017	[236]
5TVN	5-HT _{2B} R	Lysergic acid diethylamide (agonist)	2.90	2017	[237]
6BQG	5-HT _{2C} R	Ergotamine (agonist)	3.00	2018	[238]
6BQH	5-HT _{2C} R	Ritanserin (inverse agonist)	2.70	2018	[238]
5UEN	A ₁ AR	DU172 (antagonist)	3.20	2017	[239]
2YDO	A _{2A} AR	Adenosine (agonist)	3.00	2011	[240]
2YDV	A _{2A} AR	5'-(<i>N</i> -Ethylcarboxamido)adenosine (agonist)	2.60	2011	[240]
3EML	A _{2A} AR	ZM241385 (antagonist)	2.60	2008	[44]
3PWH	A _{2A} AR	ZM241385 (antagonist)	3.30	2011	[241]
3QAK	A _{2A} AR	UK-432097 (agonist)	2.71	2011	[43]
3REY	A _{2A} AR	Xanthine amine congener (antagonist)	3.31	2011	[241]
3RFM	A _{2A} AR	Caffeine (antagonist)	3.60	2011	[241]
3VG9	A _{2A} AR	ZM241385 (antagonist) and Fab2838 (inverse agonist)	2.70	2012	[242]
3VGA	A _{2A} AR	ZM241385 (antagonist) and Fab2838 (inverse agonist)	3.10	2012	[242]
3UZA	A _{2A} AR	6-(2,6-Dimethylpyridin-4-yl)-5-phenyl-1,2,4-triazin-3-amine (antagonist)	3.27	2012	[243]
3UZC	A _{2A} AR	4-(3-Amino-5-phenyl-1,2,4-triazin-6-yl)-2-chlorophenol (antagonist)	3.34	2012	[243]
4E1Y	A _{2A} AR	ZM241385 (antagonist)	1.80	2012	[244]
4UG2	A _{2A} AR	CGS21680 (agonist)	2.60	2015	[245]
4UHR	A _{2A} AR	CGS21680 (agonist)	2.60	2015	[245]
5G53	A _{2A} AR	5'-(<i>N</i> -Ethylcarboxamido)adenosine (agonist) and G _s proteins	3.40	2016	[246]
5IU4	A _{2A} AR	ZM241385 (antagonist)	1.72	2016	[247]
5IU7	A _{2A} AR	2-(Furan-2-yl)- <i>N</i> ⁵ -(2-(4-phenylpiperidin-1-yl)ethyl)-1,2-dihydro-[1,2,4]triazolo[1,5- <i>a</i>][1,3,5]triazine-5,7-diamine (antagonist)	1.90	2016	[247]
5IU8	A _{2A} AR	2-(Furan-2-yl)- <i>N</i> ⁵ -(2-(4-methylpiperazin-1-yl)ethyl)-1,2-dihydro-[1,2,4]triazolo[1,5- <i>a</i>][1,3,5]triazine-5,7-diamine (antagonist)	2.00	2016	[247]
5IUA	A _{2A} AR	2-(Furan-2-yl)- <i>N</i> ⁵ -(3-(4-phenylpiperazin-1-yl)propyl)-1,2-dihydro-[1,2,4]triazolo[1,5- <i>a</i>][1,3,5]triazine-5,7-diamine (antagonist)	2.20	2016	[247]
5IUB	A _{2A} AR	<i>N</i> ⁵ -(2-(4-(2,4-Difluorophenyl)piperazin-1-yl)ethyl)-2-(furan-2-yl)-1,2-dihydro-[1,2,4]triazolo[1,5- <i>a</i>][1,3,5]triazine-5,7-diamine (antagonist)	2.10	2016	[247]
5JTB	A _{2A} AR	ZM241385 (antagonist)	2.80	2017	[248]
5K2A	A _{2A} AR	ZM241385 (antagonist)	2.50	2016	[249]

(Table 1) contd....

<i>Rhodopsin-like or Class A GPCRs</i>					
PDBid	GPCR	Main Ligand(s) / Binding Partner(s)	Resolution / [Å]	Release Date	Refs.
5K2B	A _{2A} AR	ZM241385 (antagonist)	2.50	2016	[249]
5K2C	A _{2A} AR	ZM241385 (antagonist)	1.90	2016	[249]
5K2D	A _{2A} AR	ZM241385 (antagonist)	1.90	2016	[249]
5NLX	A _{2A} AR	ZM241385 (antagonist)	2.14	2017	[250]
5NM2	A _{2A} AR	ZM241385 (antagonist)	1.95	2017	[250]
5OLG	A _{2A} AR	ZM241385 (antagonist)	1.87	2018	[251]
5OLH	A _{2A} AR	Vipadenant (antagonist)	2.60	2018	[251]
5OLO	A _{2A} AR	Tozadenant (antagonist)	3.10	2018	[251]
5OLV	A _{2A} AR	LUA447070 (antagonist)	2.00	2018	[251]
5OLZ	A _{2A} AR	4-(3-Amino-5-phenyl-1,2,4-triazin-6-yl)-2-chlorophenol (antagonist)	1.90	2018	[251]
5OM1	A _{2A} AR	4-(3-Amino-5-phenyl-1,2,4-triazin-6-yl)-2-chlorophenol (antagonist)	2.10	2018	[251]
5OM4	A _{2A} AR	4-(3-Amino-5-phenyl-1,2,4-triazin-6-yl)-2-chlorophenol (antagonist)	2.00	2018	[251]
5UIG	A _{2A} AR	5-Amino- <i>N</i> -[(2-methoxyphenyl)methyl]-2-(3-methylphenyl)-2 <i>H</i> -1,2,3-triazole-4-carboximidamide (antagonist)	3.50	2017	[252]
5UVI	A _{2A} AR	ZM241385 (antagonist)	3.20	2017	[253]
5VRA	A _{2A} AR	ZM241385 (antagonist)	2.35	2017	[254]
5WF5	A _{2A} AR	UK432097 (antagonist)	2.60	2018	[255]
5WF6	A _{2A} AR	UK432097 (antagonist)	2.90	2018	[255]
6AQF	A _{2A} AR	ZM241385 (antagonist)	2.51	2018	[256]
5VBL	APJR	AMG3054 (agonist)	2.60	2017	[257]
4YAY	AT ₁ R	ZD7155 (antagonist)	2.90	2015	[258]
4ZUD	AT ₂ R	Olmesartan (inverse agonist)	2.80	2015	[259]
5UNF	AT ₂ R	L-161,638 (antagonist)	2.80	2017	[260]
5UNG	AT ₂ R	L-161,638 (antagonist)	2.80	2017	[260]
5UNH	AT ₂ R	(<i>N</i> -[(Furan-2-yl)methyl]- <i>N</i> -(4-oxo-2-propyl-3-{{2'-(2 <i>H</i> -tetrazol-5-yl)[1,1'-biphenyl]-4-yl)methyl}-3,4-dihydroquinazolin-6-yl)benzamide) (antagonist)	2.90	2017	[260]
6F3Y	B ₁ R	Des-Arg10-kallidin (agonist)	NMR	2018	[261]
6F3V	B ₂ R	Bradykinin (agonist)	NMR	2018	[261]
2VT4	β ₁ AR	Cyanopindolol (antagonist)	2.70	2008	[262]
2Y00	β ₁ AR	Dobutamine (partial agonist)	2.50	2011	[263]
2Y01	β ₁ AR	Dobutamine (partial agonist)	2.60	2011	[263]
2Y02	β ₁ AR	Carmoterol (agonist)	2.60	2011	[263]
2Y03	β ₁ AR	Isoprenaline (agonist)	2.85	2011	[263]
2Y04	β ₁ AR	Salbutamol (partial agonist)	3.05	2011	[263]
2YCY	β ₁ AR	Cyanopindolol (antagonist)	3.15	2011	[264]
2YCW	β ₁ AR	Carazolol (antagonist)	3.10	2011	[264]
2YCX	β ₁ AR	Cyanopindolol (antagonist)	3.25	2011	[264]
2YCZ	β ₁ AR	Iodocyanopindolol (antagonist)	3.65	2011	[264]
3ZPQ	β ₁ AR	4-(Piperazin-1-yl)-1 <i>H</i> -indole (antagonist)	2.80	2013	[265]

(Table 1) contd....

<i>Rhodopsin-like or Class A GPCRs</i>					
PDBid	GPCR	Main Ligand(s) / Binding Partner(s)	Resolution / [Å]	Release Date	Refs.
3ZPR	β_1 AR	4-Methyl-2-(piperazin-1-yl)quinoline (antagonist)	2.70	2013	[265]
4AMI	β_1 AR	Bucindolol (agonist)	3.20	2012	[266]
4AMJ	β_1 AR	Carvedilol (agonist)	2.30	2012	[266]
4BVN	β_1 AR	Cyanopindolol (antagonist)	2.10	2014	[267]
4GPO	β_1 AR	-	3.50	2013	[268]
5A8E	β_1 AR	7-Methylcyanopindolol (inverse agonist)	2.40	2015	[269]
5F8U	β_1 AR	Cyanopindolol (antagonist)	3.35	2015	[270]
2R4R	β_2 AR	Fab5 (antibody) and carazolol (inverse agonist)	3.40	2007	[271]
2R4S	β_2 AR	Fab5 (antibody) and carazolol (inverse agonist)	3.40	2007	[271]
2RH1	β_2 AR	Carazolol (inverse agonist)	2.40	2007	[272]
3D4S	β_2 AR	Timololol (partial inverse agonist)	2.80	2008	[273]
3KJ6	β_2 AR	Fab5 (antibody)	3.40	2010	[274]
3NY8	β_2 AR	ICI-118,551 (inverse agonist)	2.84	2010	[275]
3NY9	β_2 AR	Ethyl 4-((2 <i>S</i>)-2-hydroxy-3-[(1-methylethyl)amino]propyl)oxy)-3-methyl-1-benzofuran-2-carboxylate (inverse agonist)	2.84	2010	[275]
3NYA	β_2 AR	Alprenolol (antagonist)	3.16	2010	[275]
3P0G	β_2 AR	Nb80 (nanobody) and BI-167107 (agonist)	3.50	2011	[276]
3PDS	β_2 AR	FAUC50 (agonist)	3.50	2011	[42]
3SN6	β_2 AR	G _s proteins	3.20	2011	[277]
4GBR	β_2 AR	Carazolol (inverse agonist)	3.99	2012	[278]
5D5A	β_2 AR	Carazolol (inverse agonist)	2.48	2016	[279]
5D5B	β_2 AR	Carazolol (inverse agonist)	3.80	2016	[279]
5JQH	β_2 AR	Nb60 (nanobody) and carazolol (inverse agonist)	3.20	2016	[280]
5X7D	β_2 AR	Carazolol (inverse agonist) and 4-carbamoyl- <i>N</i> -[(2 <i>R</i>)-2-cyclohexyl-2-phenylacetyl]- <i>L</i> -phenylalanyl-3-bromo- <i>N</i> -methyl- <i>L</i> -phenylalaninamide (NAM)	2.70	2017	[281]
5O9H	C5aR ₁	NDT9513727 (inverse agonist)	2.70	2018	[282]
5U09	CB ₁ R	Taranabant (inverse agonist)	2.60	2016	[283]
5TGZ	CB ₁ R	AM6538 (antagonist)	2.80	2016	[284]
5T1A	CCR ₂	BMS-681 (orthosteric antagonist) and CCR-RA-[<i>R</i>] (NAM)	2.81	2016	[285]
2RRS	CCR ₅	-	NMR	2012	[286]
4MBS	CCR ₅	Maraviroc (antagonist)	2.71	2013	[287]
5LWE	CCR ₉	Vercirmon (NAM)	2.60	2016	[288]
2LNL	CXCR ₁	-	NMR	2012	[289]
3ODU	CXCR ₄	IT1t (antagonist)	2.50	2010	[290]
3OE0	CXCR ₄	CVX15 (antagonist)	2.90	2010	[290]
3OE6	CXCR ₄	IT1t (antagonist)	3.20	2010	[290]
3OE8	CXCR ₄	IT1t (antagonist)	3.10	2010	[290]
3OE9	CXCR ₄	IT1t (antagonist)	3.10	2010	[290]
4RWS	CXCR ₄	vMIP-II complex (antagonist)	3.10	2015	[291]
2N55	CXCR ₅	CXCL12 (agonist)	NMR	2016	[292]

(Table 1) contd....

<i>Rhodopsin-like or Class A GPCRs</i>					
PDBid	GPCR	Main Ligand(s) / Binding Partner(s)	Resolution / [Å]	Release Date	Refs.
6CM4	D ₂ R	Risperidone (inverse agonist)	2.87	2018	[293]
3PBL	D ₃ R	Eticlopride (antagonist)	2.89	2010	[294]
5WIU	D ₄ R	Nemonapride (antagonist)	1.96	2017	[295]
5WIV	D ₄ R	Nemonapride (antagonist)	2.14	2017	[295]
4N6H	DOR	Naltrindole (antagonist)	1.80	2013	[296]
4RWA	DOR	DIPP-NH ₂ (antagonist)	3.28	2015	[297]
4RWD	DOR	DIPP-NH ₂ (antagonist)	2.70	2015	[297]
5GLH	ET _B R	Endothelin-1 (agonist)	2.80	2016	[298]
5GLI	ET _B R	-	2.50	2016	[298]
4PHU	FFAR ₁	TAK-875 (PAM)	2.33	2014	[299]
5TZR	FFAR ₁	MK-8666 (partial agonist)	2.20	2017	[300]
5TZY	FFAR ₁	AP8 (ago-PAM) and MK-8666 (partial agonist)	3.22	2017	[300]
4AY9	FSHR	FSH (agonist)	2.50	2012	[301]
4MQW	FSHR	FSH (agonist)	2.90	2014	[302]
3RZE	H ₁ R	Doxepin (antagonist)	3.10	2011	[303]
4DJH	KOR	JDTic (antagonist)	2.90	2012	[304]
6B73	KOR	Nb39 (nanobody) and MP1104 (agonist)	3.10	2018	[305]
4Z34	LPAR ₁	ONO9780307 (antagonist)	3.00	2015	[306]
4Z35	LPAR ₁	ONO9910539 (antagonist)	2.90	2015	[306]
4Z36	LPAR ₁	ONO3080573 (antagonist)	2.90	2015	[306]
5CXV	mAChR ₁	Tiotropium (inverse agonist)	2.70	2016	[307]
3UON	mAChR ₂	<i>R</i> -(-)-Quinuclidinyl benzilate (inverse agonist)	3.00	2012	[308]
4MQS	mAChR ₂	Iperoxo (agonist)	3.50	2013	[309]
4MQT	mAChR ₂	Iperoxo (agonist) and LY2119620 (PAM)	3.70	2013	[309]
4DAJ	mAChR ₃	Tiotropium (inverse agonist)	3.40	2012	[310]
4U14	mAChR ₃	Tiotropium (inverse agonist)	3.57	2014	[311]
4U15	mAChR ₃	Tiotropium (inverse agonist)	2.80	2014	[311]
4U16	mAChR ₃	<i>N</i> -Methylscopolamine (antagonist)	3.70	2014	[311]
5DSG	mAChR ₃	Tiotropium (inverse agonist)	2.60	2016	[307]
4DKL	MOR	β -Funaltrexamine (antagonist)	2.80	2012	[312]
5C1M	MOR	BU72 (agonist)	2.10	2015	[313]
4EJ4	N/OFQR	Naltrindole (antagonist)	3.40	2012	[314]
4GRV	N/OFQR	Neurotensin ₈₋₁₃ (agonist)	2.80	2012	[315]
5DHG	N/OFQR	C35 (antagonist)	3.00	2015	[316]
5DHH	N/OFQR	SB612111 (antagonist)	3.00	2015	[316]
3ZEV	NTSR ₁	TM86V- Δ IC3A	3.00	2014	[317]
4BUO	NTSR ₁	TM86V- Δ IC3B	2.75	2014	[317]
4BV0	NTSR ₁	OGG7V- Δ IC3A	3.10	2014	[317]
4BWB	NTSR ₁	HTGH4- Δ IC3	3.57	2014	[317]
4XEE	NTSR ₁	Neurotensin/Neuromedin N (agonist)	2.90	2015	[318]
4XES	NTSR ₁	Neurotensin/Neuromedin N (agonist)	2.60	2015	[318]

(Table 1) contd....

<i>Rhodopsin-like or Class A GPCRs</i>					
PDBid	GPCR	Main Ligand(s) / Binding Partner(s)	Resolution / [Å]	Release Date	Refs.
5T04	NTSR ₁	Neurotensin ₈₋₁₃ (Arg-Arg-Pro-Tyr-Ile-Leu; agonist)	3.30	2016	[319]
4ZJ8	OX ₁ R	Suvorexant (antagonist)	2.75	2016	[320]
4ZJC	OX ₁ R	SB-674042 (antagonist)	2.83	2016	[320]
4S0V	OX ₂ R	Suvorexant (antagonist)	2.50	2015	[321]
4XNV	P2Y ₁ R	BPTU (antagonist)	2.20	2015	[322]
4XNW	P2Y ₁ R	MRS2500 (antagonist)	2.70	2015	[322]
4NTJ	P2Y ₁₂ R	AZD1283 (agonist)	2.62	2014	[323]
4PXZ	P2Y ₁₂ R	2MeSADP (agonist)	2.50	2014	[324]
4PY0	P2Y ₁₂ R	2MeSATP (partial agonist)	3.10	2014	[324]
3VW7	PAR ₁	Vorapaxar (antagonist)	2.20	2012	[325]
5NDD	PAR ₂	AZ8838 (antagonist)	2.80	2017	[326]
5NDZ	PAR ₂	AZ3451 (antagonist)	3.60	2017	[326]
5NJ6	PAR ₂	Fab3949 (antibody) and AZ7188 (antagonist)	4.00	2017	[326]
1F88	RHO	11- <i>cis</i> -Retinal (agonist)	2.80	2000	[231]
1GZM	RHO	11- <i>cis</i> -Retinal (agonist)	2.65	2003	[327]
1HZX	RHO	11- <i>cis</i> -Retinal (agonist)	2.80	2001	[328]
1JFP	RHO	11- <i>cis</i> -Retinal (agonist)	NMR	2001	[329]
1L9H	RHO	11- <i>cis</i> -Retinal (agonist)	2.60	2002	[330]
1LN6	RHO	11- <i>cis</i> -Retinal (agonist)	NMR	2002	[331]
1U19	RHO	11- <i>cis</i> -Retinal (agonist)	2.20	2004	[332]
2G87	RHO	11- <i>cis</i> -Retinal (agonist)	2.60	2006	[333]
2HPY	RHO	11- <i>cis</i> -Retinal (agonist)	2.80	2006	[334]
2I35	RHO	11- <i>cis</i> -Retinal (agonist)	3.80	2006	[335]
2I36	RHO	-	4.10	2006	[335]
2I37	RHO	-	4.15	2006	[335]
2J4Y	RHO	11- <i>cis</i> -Retinal (agonist)	3.40	2007	[336]
2PED	RHO	11- <i>cis</i> -Retinal (agonist)	2.95	2007	[337]
2X72	RHO	G _{α1} and 11- <i>cis</i> -retinal (agonist)	3.00	2011	[338]
2Z73	RHO	11- <i>cis</i> -Retinal (agonist)	2.50	2008	[339]
2Z1Y	RHO	11- <i>cis</i> -Retinal (agonist)	3.70	2008	[340]
3AYM	RHO	11- <i>cis</i> -Retinal (agonist)	2.80	2011	[341]
3AYN	RHO	11- <i>cis</i> -Retinal (agonist)	2.70	2011	[341]
3C9L	RHO	11- <i>cis</i> -Retinal (agonist)	2.65	2008	[342]
3C9M	RHO	11- <i>cis</i> -Retinal (agonist)	3.40	2008	[342]
3CAP	RHO	-	2.90	2008	[343]
3DQB	RHO	G _{α1}	3.20	2008	[344]
3PQR	RHO	G _{α1} and 11- <i>cis</i> -retinal (agonist)	2.85	2011	[345]
3PXO	RHO	11- <i>cis</i> -Retinal (agonist)	3.00	2011	[345]
3OAX	RHO	β-Ionone and 11- <i>cis</i> -retinal (agonist)	2.60	2011	[346]
4A4M	RHO	G _{α3} and 11- <i>cis</i> -retinal (agonist)	3.30	2012	[347]
4BEY	RHO	G _{α2}	2.90	2013	[348]

(Table 1) contd....

Rhodopsin-like or Class B GPCRs					
PDBid	GPCR	Ligand(s) / Binding Partner(s)	Resolution / [Å]	Release Date	Refs.
4BEZ	RHO	-	3.30	2013	[348]
4J4Q	RHO	G _{α1}	2.65	2013	[349]
4PXF	RHO	Arrestin-1	2.75	2014	[350]
4X1H	RHO	G _{α1}	2.29	2015	[351]
4ZWJ	RHO	-	3.30	2015	[352]
5DGY	RHO	Visual arrestin-1	7.70	2016	[353]
5DYS	RHO	11- <i>cis</i> -Retinal (agonist)	2.30	2016	[354]
5EN0	RHO	G _{α3} and 11- <i>cis</i> -retinal (agonist)	2.81	2016	[354]
5TE3	RHO	-	2.70	2017	[355]
5TE5	RHO	(2E)-{(4E)-4-[(3E)-4-(2,6,6-Trimethylcyclohex-1-en-1-yl)but-3-en-2-ylidene]cyclohex-2-en-1-ylidene}acetaldehyde	4.01	2017	[355]
5W0P	RHO	Visual arrestin-1	3.01	2017	[356]
5WKT	RHO	Transducin G _α peptide (G _α CT2)	3.20	2017	[254]
3V2W	S1PR ₁	ML056 (antagonist)	3.35	2012	[357]
3V2Y	S1PR ₁	CYM-5442 (agonist)	2.80	2012	[357]
2XWT	TSHR	K1-70 (antagonist)	1.90	2011	[358]
3G04	TSHR	Thyroid-stimulating human monoclonal autoantibody (M22)	2.55	2009	[359]
4XT1	US28	CX3CL1 (agonist)	2.89	2015	[360]
4XT3	US28	CX3CL1 (agonist)	3.80	2015	[360]
4JQI	V ₂ R	Arrestin-2	2.60	2013	[361]
Secretin-like or Class B GPCRs					
PDBid	GPCR	Ligand(s) / Binding Partner(s)	Resolution / [Å]	Release Date	Refs.
3EHS	CRFR ₁	-	2.76	2008	[362]
3EHT	CRFR ₁	CRF (agonist)	3.40	2008	[362]
3EHU	CRFR ₁	CRF (agonist)	1.96	2008	[362]
4K5Y	CRFR ₁	CP-376395 (antagonist)	2.98	2013	[363]
4Z9G	CRFR ₁	CP-376395 (antagonist)	3.18	2016	[364]
3AQF	CRLR	RAMP2	2.60	2011	[365]
3N7P	CRLR	RAMP1	2.80	2010	[366]
3N7R	CRLR	RAMP1 and telcagepant (antagonist)	2.90	2010	[366]
3N7S	CRLR	RAMP1 and olcegepant (antagonist)	2.10	2010	[366]
5UZ7	CRLR	G _s proteins	4.10	2017	[367]
5V6Y	CRLR	RAMP1 and adrenomedullin variant (antagonist)	2.80	2018	[368]
4ERS	GLP ₁ R	mAb1 (antagonist)	2.64	2012	[369]
4L6R	GLP ₁ R	Glucagon (agonist)	3.30	2013	[370]
5EE7	GLP ₁ R	MK-0893 (antagonist)	2.50	2016	[371]
5NX2	GLP ₁ R	Peptide 5 (agonist)	3.70	2017	[372]
5VAI	GLP ₁ R	G _s proteins	4.10	2017	[373]
5VEW	GLP ₁ R	PF-06372222 (NAM)	2.70	2017	[374]
5VEX	GLP ₁ R	NNC0640 (NAM)	3.00	2017	[374]
3H3G	PTH ₁ R	PTHrP	1.94	2009	[375]

(Table 1) contd....

<i>Glutamate-like or Class C GPCRs</i>					
PDBid	GPCR	Ligand(s) / Binding Partner(s)	Resolution / [Å]	Release Date	Refs.
4MQE	GABABR	-	2.35	2013	[376]
4MQF	GABABR	2-Hydroxysaclofen (antagonist)	2.22	2013	[376]
4MR7	GABABR	CGP54626 (antagonist)	2.15	2013	[376]
4MR8	GABABR	CGP35348 (antagonist)	2.15	2013	[376]
4MR9	GABABR	SCH50911 (antagonist)	2.35	2013	[376]
4MRM	GABABR	Phaclofen (antagonist)	2.86	2013	[376]
4MS1	GABABR	CGP46381 (antagonist)	2.25	2013	[376]
4MS3	GABABR	γ -Aminobutyric acid (agonist)	2.50	2013	[376]
4MS4	GABABR	Baclofen (agonist)	1.90	2013	[376]
4OR2	mGluR ₁	FITM (NAM)	2.80	2014	[377]
1EWK	mGluR ₁	Glutamate (agonist)	2.20	2000	[378]
1EWT	mGluR ₁	-	3.70	2000	[378]
1EWV	mGluR ₁	-	4.00	2000	[378]
5CNI	mGluR ₂	Glutamate (agonist)	2.69	2015	[379]
5CNJ	mGluR ₂	LY2812223 (agonist)	2.65	2015	[379]
2E4U	mGluR ₃	Glutamate (agonist)	2.35	2007	[380]
2E4V	mGluR ₃	DCG-IV (agonist)	2.40	2007	[380]
2E4W	mGluR ₃	1 <i>S</i> ,3 <i>S</i> -ACPD (agonist)	2.40	2007	[380]
2E4X	mGluR ₃	1 <i>S</i> ,3 <i>R</i> -ACPD (agonist)	2.75	2007	[380]
2E4Y	mGluR ₃	2 <i>R</i> ,4 <i>R</i> -APDC (agonist)	3.40	2007	[380]
5CNK	mGluR ₃	Glutamate (agonist)	3.15	2015	[379]
5CNM	mGluR ₃	LY2812223 (agonist)	2.84	2015	[379]
4009	mGluR ₅	Mavoglurant (NAM)	2.60	2014	[381]
5CGC	mGluR ₅	3-Chloro-4-fluoro-5-[6-(1 <i>H</i> -pyrazol-1-yl)pyrimidin-4-yl]benzotrile (NAM)	3.10	2015	[382]
5CGD	mGluR ₅	HTL14242 (NAM)	2.60	2015	[382]
6FFH	mGluR ₅	Fenobam (NAM)	2.65	2018	[383]
6FFI	mGluR ₅	MMPEP (NAM)	2.20	2018	[383]
2E4Z	mGluR ₇	-	3.30	2007	[380]
<i>Frizzled/taste2-like or Class F GPCRs</i>					
PDBid	GPCR	Ligand(s) / Binding Partner(s)	Resolution / [Å]	Release Date	Reference
4JKV	Smo	LY2940680 (antagonist)	2.45	2013	[384]
4N4W	Smo	SANT-1 (antagonist)	2.80	2014	[385]
4O9R	Smo	Cyclopamine (antagonist)	3.20	2014	[386]
4QIM	Smo	Anta XV (antagonist)	2.61	2014	[385]
4QIN	Smo	SAG1.5 (agonist)	2.60	2014	[385]
5KZV	Smo	20(<i>S</i>)-Hydroxycholesterol (agonist)	1.62	2016	[387]
5KZY	Smo	Cyclopamine (antagonist)	2.48	2016	[387]
5KZZ	Smo	-	1.33	2016	[387]
5L7D	Smo	Cholesterol (agonist)	3.20	2016	[388]
5L7I	Smo	Vismodegib (antagonist)	3.30	2016	[388]

(Table 1) contd....

Frizzled/taste2-like or Class F GPCRs					
PDBid	GPCR	Ligand(s) / Binding Partner(s)	Resolution / [Å]	Release Date	Reference
5V56	Smo	TC114 (antagonist)	2.90	2017	[389]
5V57	Smo	TC114 (antagonist)	3.00	2017	[389]
Adhesion GPCRs					
PDBid	GPCR	Ligand(s) / Binding Partner(s)	Resolution / [Å]	Release date	Reference
5KVM	ADGRG ₁	FN3 monobody	2.45	2016	[390]
4RMK	ADGRL ₃	-	1.61	2015	[391]
4RML	ADGRL ₃	-	1.60	2015	[391]
5FTT	ADGRL ₃	Unc5D and FLRT2	3.40	2016	[392]
5FTU	ADGRL ₃	Unc5D and FLRT2	6.01	2016	[392]

Abbreviations: (5-HTR - 5-HydroxyTryptamine receptor; ADGRG1 - Adhesion G-protein coupled Receptor G1; ADGRL3 - Adhesion G-protein coupled Receptor L3; AR - Adenosine Receptor; APJR - Apelin Receptor; ATR - Angiotensin II Receptor; BR - Bradykinin Receptor; β AR - β -Adrenergic Receptor; C5aR - C5a anaphylatoxin chemotactic Receptor; CBR - Cannabinoid Receptor; CCR - CC Chemokine Receptor; CRF - Corticotropin Releasing Factor; CRFR - Corticotropin Releasing Factor Receptor; CRLR - Calcitonin Receptor-Like Receptor; CXCR - CXC Chemokine Receptor; DOR - δ -Opioid Receptor; DR - Dopamine Receptor; ETR - Endothelin Receptor; FFAR - Free Fatty Acid Receptor; FLRT2 - Fibronectin Leucin-Rich Transmembrane protein 2; FN3 - FibroNectin type III domain; FSH - Follicle-Stimulating Hormone; FSHR - Follicle-Stimulating Hormone Receptor; GABAR - γ -AminoButyric Acid Receptor; GLPR - Glucagon-Like Peptide Receptor; HR - Histamine Receptor; KOR - κ -Opioid Receptor; LPAR - LysoPhosphatidic Acid Receptor; mAChR - muscarinic AcetylCholine Receptor; mGluR - metabotropic Glutamate Receptor; MOR - μ -Opioid Receptor; N/OFQR - Nociceptin/Orphanin FQ Receptor; NTSR - Neurotensin Receptor; OXR - Orexin Receptor; P2YR - Purinergic P2Y Receptor; PAR - Protease-Activated Receptor; PTHR - ParaThyroid Hormone-related peptide Receptor; PTHrP - ParaThyroid Hormone-related Peptide; RAMP - Receptor-Activity Modifying Protein; RHO - Rhodopsin; S1PR - Sphingosine-1-Phosphate Receptor; Smo - Smoothened Receptor; TSHR - Thyroid-Stimulating Hormone Receptor; Unc5D - Unc5D guidance receptor; US28 - Cytomegalovirus-encoded chemokine Receptor; VIPR - Vasoactive Intestinal Peptide Receptor; VR - Vasopressin Receptor).

Magnetic Resonance (NMR) studies, has been a tremendously challenging task comparing to globular proteins due to problems associated to receptor purification, receptor instability, among others (reviewed in [230]). Until the elucidation of the X-ray diffraction structure at 2.8 Å resolution of bovine rhodopsin in 2000 (PDBid 1F88) [231], no X-ray structures of any GPCR were available. The 3D structural determination of bovine rhodopsin allowed a deeper understanding of GPCR functioning at the molecular level and, for many years, provided the only template for structure-based drug design approaches in homologous GPCRs for the study of drug-GPCR interactions. With the development of receptor crystallization strategies, a number of technical issues related to the low expression of GPCRs and their structural instability have been surmounted, thereby resulting in an accelerated increase of solved GPCR structures [230]. More than 200 3D structures of apo-GPCRs, protein-, natural ligand-, agonist-, and antagonist-bound GPCRs have been solved so far (Table 1), in which the *rhodopsin*-like or class A GPCRs have been the most reported class [42-44, 231-361]. Additionally, the 3D structures of four subfamilies of *secretin*-like or class B GPCRs (Corticotropin-Releasing Factor Receptors, CRFRs; Calcitonin Receptor-Like Receptors, CRLRs; Glucagon-Like Peptide Receptors, GLPRs; ParaThyroid Hormone-related peptide Receptors, PTHRs) [362-375], two subfamilies of *glutamate*-like or class C GPCRs (metabotropic Glutamate Receptors, mGluRs; γ -AminoButyric Acid Receptors, GABARs) [376-383], one subfamily of *frizzled/taste2*-like or class F GPCR (Smoothened receptors, Smo) [384-389], and two subfamilies of *adhesion* GPCRs (Adhesion G-protein coupled Receptor G1, ADGRG1; Adhesion G-protein coupled Receptor L3, ADGRL3) [390-392] have been disclosed on PDB (reported until February 2018).

Molecular docking is one of the most frequently used methods in structure-based drug design due to its ability to predict the conformation of ligands within an appropriate binding site with a considerable degree of accuracy [393-398]. Each ligand is docked onto the X-ray or NMR structure of the target protein or, if the 3D structure is not available, onto a model of the target (retrieved by homology modeling), applying molecular docking algorithms that explore the different binding poses of the ligands inside the binding site of the target. The identification of the most likely binding conformations involves the exploration of a large conformational space representing the various potential binding poses of the ligands and the prediction of the interaction energy associated to each of the predicted binding poses. Regarding the conformational search step, the structural parameters of ligands (translational, torsional, and rotational degrees of freedom) are increasingly modified, and several conformational search algorithms execute this stage by employing stochastic and systematic search methods [393-398]. Independently of the specificities of each search method, any conformational search algorithm should explore a broader range of energy landscape within an affordable computational time. Subsequently, the strength of the binding affinity of the predicted ligand-protein complexes is estimated by the use of scoring functions, which are given in most cases by the Gibbs free energy (ΔG) and the dissociation constant (K_d). Scoring functions are estimated mathematical functions that evaluate the most relevant physicochemical parameters involved in the ligand-protein interaction, in particular, the intermolecular interactions, desolvation, and entropic effects. The use of a high number of physicochemical parameters seems to increase the accuracy of the scoring function [393-398]. The molecular docking programs are executed through a cyclic and iterative process, in which the different ligand

binding conformations are evaluated by the scoring functions until converging to a minimum energy conformation [393-398]. However, as the computational cost also increases proportionally with the number of included parameters, there should be a perfect combination between the accuracy and the speed of the calculation, which is crucial for databases containing a considerable number of chemical compounds. Nowadays, new scoring functions based on Machine-Learning (ML) algorithms are emerging [399, 400].

The determination of the scoring functions can be extremely useful in drug discovery for the virtual screening of commercially available compounds and *in-house* ligands that have been already synthesized and tested *in vitro*, or even pre-assembled databases of virtual drug candidates in order to identify the ligand structures that are most likely to interact to a protein target of interest, according to their docking scores. Apart from their applicability to virtual screening, the scoring functions can also be employed for *de novo* drug design of novel chemical structures targeting a specific protein and for *hit-to-lead* optimization of pharmacodynamic parameters of drug candidates [393-398]. Table 2 describes the most relevant docking studies performed for distinct chemical classes of modulators of GPCRs potentially involved in PD, using X-ray structures of GPCRs available on PDB and receptor models constructed from GPCR templates.

2.6.2. Application of Ligand-based and Pharmacophore-based Design Techniques for GPCR-based Drug Discovery

The availability of structural data information for multiple GPCRs still remains scarce and, for that reason, computational drug design strategies have relied on theoretical models, in which the 3D model of a receptor structure is constructed by applying homology modeling techniques [489] and on ligand-based approaches [490]. The identification of an increasing number of small-molecule modulators with diverse chemical scaffolds together with experimental biological/pharmacological data (*e.g.* binding affinity values) has helped to the increased development of ligand-based drug design approaches. Among these ligand-based approaches, numerous CADD methodologies can be employed to large databases of compounds with drug-like properties ranging from pharmacophore modeling to quantitative structure-activity relationships (QSAR) and 3D-QSAR techniques such as Comparative Molecular Field Analysis (CoMFA) and Comparative Molecular Similarity Index Analysis (CoMSIA) [490].

The generation of pharmacophore models involves the identification of steric and electronic determining features that assure an optimal interaction towards a particular therapeutic target, triggering its pharmacological activity [491]. Thus, pharmacophore modeling is a computational tool that searches for common pharmacophoric patterns or chemical features (hydrogen bond acceptors and donors, hydrophobic groups, aromatic rings, *etc.*) shared by a set of active ligands with similar pharmacological activity and which may interact to the same binding sites. A pharmacophore model can be generated either in the absence of structural data information (ligand-based pharmacophore modeling) or based on the

3D structure of a therapeutic target (structure-based pharmacophore modeling) [491]. The development of structure-based pharmacophore models involves the examination of the pharmacophoric patterns in the binding site of the target and their spatial relationships. On the other hand, the ligand-based pharmacophore modeling implies the generation of a conformational space for each ligand of the training set to represent their conformational flexibility. A myriad of software tools and algorithms used for construction of a conformational space possess the ability to determine the different conformational geometries of the bioactive conformation and other similar geometries. An appropriate computational software for conformational search needs to generate all conformational geometries that the ligands can adopt when they are interacting with the therapeutic target. Subsequently, the multiple ligands of the training set are superimposed and the common 3D structural features crucial for biological/pharmacological activity are uncovered [491]. Once a pharmacophore model is constructed, it can be used for *in silico* screening of large databases of virtual and *in-house* drug candidates, in which a pharmacophore hypothesis is considered as a template for the discovery of hit ligands with similar pharmacophoric characteristics. In addition, the pharmacophore modeling can be applied to the generation of new chemical scaffolds and/or structures (*de novo* drug design), including the chemical features of a given pharmacophore hypothesis [492].

On the other hand, the investigation of QSAR has been a remarkably useful technique in early stages of the drug discovery process. The fundamental basis of this ligand-based methodology is that variations in the biological/pharmacological activity for congeneric and non-congeneric series of chemical compounds (training set) that target a common mechanism of action are correlated with variations in their physicochemical and structural properties [493-495]. Since structural features of chemical ligands can be efficiently uncovered by experimental or computational approaches, a statistically validated QSAR model is able to predict the biological/pharmacological activity of new chemical ligands, avoiding the time- and money-consuming chemical synthesis and biological evaluation of potentially uninteresting ligands. The generation of a QSAR model involves the collection of a statistical population of ligands and the determination of descriptor variables that can suitably explain the correlation of structural properties of ligands and their biological activity data (*e.g.* topological descriptors, electronic descriptors, geometrical descriptors, constitutional descriptors, *etc.*). Subsequently, various statistical methods within supervised ML techniques, including Partial Least Square (PLS) [496], Multiple (or multivariate) Linear Regression (MLR) [497], and Linear Discriminant Analysis (LDA) [498], and non-linear modeling, including Artificial Neural Networks (ANN) [499] and Support Vector Machines (SVM) [500] are applied to derive a robust mathematical correlation that explains the dependence of particular descriptor variables (independent variables) to the biological/pharmacological activity of a set of ligands (dependent variables). The resulting QSAR model is subjected to several validation tests to corroborate the reliability of the correlation models, in particular to internal validation or cross-validation and to external validation.

Table 2. Structure-based drug design methodologies reported for ligands targeting GPCRs potentially involved in PD.

Dopamine D ₂ Receptor (D ₂ R) Agonists			
Entry	Method(s)	Ligand(s)	Relevant Ligand-receptor Interactions
1	Docking onto D ₂ R model using AutoDock 3.0.5 software package [401] (Template: X-ray structure of human β_2 AR; PDBid 2RH1 [272])	Dopamine, 2-(aminomethyl)chromans	Dopamine: salt bridge interactions involving Asp114; hydrogen bond interactions with Ser193 and Ser197; π - π interactions involving Trp245, Phe248, and Phe249. 2-(Aminomethyl)chromans: salt bridge interactions involving Asp114; π - π interactions with Phe248; hydrogen bond interactions involving Ser193, Ser194, and/or Ser197 residues [402].
2	Docking onto D ₂ R model using MOE software package [403] (Template: X-ray structure of human β_2 AR; PDBid 2RH1 [272])	(R)-(-)-2-OH-NPA	R-(-)-2-OH-NPA: salt bridge interactions involving Asp114; hydrogen bond interactions with Asn186, Ser193, and Ser393; hydrophobic interactions involving Thr412 and π - π interactions with Phe390 [404].
3	Docking onto D ₂ R model using GLIDE module from Schrödinger Suite [405-407] (Template: X-ray structure of D ₃ R; PDBid 3PBL [294])	Substituted piperidines, (2-methoxyphenyl) piperazines	Substituted piperidines: salt bridge interactions involving Asp114; π - π interactions with Phe393, His397, and the hydrophobic pocket composed by Phe386, Trp390, and Tyr420; hydrogen bond interactions with Ser193. (2-Methoxyphenyl) piperazines: salt bridge interactions involving Asp114; π - π interactions with Phe394 and the hydrophobic pocket composed by Phe386, Trp390, and Tyr420 [408].
4	Docking onto D ₂ R model using GLIDE module of Schrödinger Suite [405-407] (Template: X-ray structure of D ₃ R; PDBid 3PBL [294])	1-(2-Methoxyphenyl)-4-(1-phenethylpiperidin-4-yl)piperazines, 1-(2-methoxyphenyl)-4-[(1-phenethylpiperidin-4-yl)methyl]-piperazines	1-(2-Methoxyphenyl)-4-(1-phenethylpiperidin-4-yl)piperazines: hydrophobic interactions with the hydrophobic pocket formed by Phe386, Trp390, and Tyr42 residues; salt bridge interactions involving Asp114; hydrogen bond interactions involving Asp114, Ser194, and Ser197 residues. Two possible binding conformations for 1-(2-Methoxyphenyl)-4-[(1-phenethylpiperidin-4-yl)methyl]-piperazines: (i) arylpiperazine moiety interacts with hydrophobic pocket of orthosteric binding site and the head part makes hydrogen bond interactions with Ser194 and Ser197; (ii) the head part interacts with hydrophobic pocket and arylpiperazine group makes hydrogen bond interactions with Ser194 and Ser197 [409].
5	Docking onto D ₂ R model using AutoDock Vina [410] and AutoDock 4.2 [411] softwares (Template: X-ray structure of D ₃ R; PDBid 3PBL [294])	(R)-7-OH-DPAT, (R)-7-OH-PIPAT, pramipexole, ropinirole, rotigotine, quinpirole, dopamine, PD128907 and cis-8-OH-PBZI	Hydrogen bond interactions involving Asp114, Val190, Ser193, and Ser194 residues; hydrophobic interactions involving Phe110, Val111, Val115, Ile184, Trp386, Phe389, Phe390, His393, Gly415, and Tyr416 residues [412].
6	Docking onto D ₂ R model using AutoDock 3.0 software [401] (Template: X-ray structure of bovine RHO; PDBid 1F88 [231])	Raclopride, L-741,626	Raclopride: hydrogen bond interactions involving Asp114, Cys118, and Thr119; hydrophobic interactions with a hydrophobic region mainly composed by Tyr408 and Phe410 residues. L-741,626: Salt bridge interactions involving Asp114; hydrogen bond interactions with Ser221 and Thr412; π - π interactions involving Phe389 and Phe411 residues [413].
7	Docking onto D ₂ R model using Docking module of INSIGHT II software (Accelrys Inc., Cambridge, UK) [414] (Template: X-ray structure of bovine RHO; PDBid 1F88 [231])	5-{2-[4-(2-Methoxyphenyl)piperazin-1-yl]ethoxy}-1,3-dihydro-2H-benzimidazole-2-thione	5-{2-[4-(2-Methoxyphenyl)piperazin-1-yl]ethoxy}-1,3-dihydro-2H-benzimidazole-2-thione: salt bridge interactions involving Asp 86; hydrogen bond interactions with Trp115, Ser122, Ser141, Phe185, and His 189; π - π interactions involving Phe 178, Trp182, and Tyr216 residues [415].
8	Docking onto D ₂ R using LIBDOCK module from Discovery Studio software [416] (Template: X-ray structure of bovine RHO; PDBid 1F88 [231])	Arylpiperazines	Arylpiperazines: hydrophobic interactions involving Leu125, Leu126, Phe144, Val146, and Ile190 residues; hydrogen bond interactions involving Asn135 and Asn141; π - π interactions with Phe144 and His189 residues [417].
Dopamine D ₃ Receptor (D ₃ R) Agonists			
Entry	Method(s)	Ligand(s)	Results/Conclusions
9	Docking onto D ₃ R model performed by CERIUS ² software (version 4.6) [418] (Template: X-ray structure of bovine RHO; PDBid 1F88 [231])	(R)-(+)-7-OH-DPAT	R-(+)-7-OH-DPAT: salt bridge interactions involving Asp110; hydrogen bond interactions with Ser192; hydrophobic interactions with Phe106, Val107, Val111, Cys114, Phe345, Phe346, and Tyr373 residues [419].

(Table 2) contd....

Dopamine D ₃ Receptor (D ₃ R) Agonists			
Entry	Method(s)	Ligand(s)	Results/Conclusions
10	Docking onto X-ray structure of D ₃ R (PDBid 3PBL [294]) using AutoDock Vina [410] and AutoDock 4.0 softwares [420, 421]	Glycyrrhetic acid, E.resveratrol, curcumin, hirsutanonol, glabridin, alloin, diacerein, bromocriptine, apomorphine, ropinirole	Hydrogen bond interactions with Asp110, Ser192, His349, Thr369, and Tyr373 residues; hydrophobic interactions involving the binding pocket Asp110, Ile183, Ser192, Phe346, His349, Thr369, and Tyr373 [422].
11	Docking onto X-ray structure of D ₃ R (PDB id 3PBL [294]) using SurFlex Dock software method of SYBYL-X 1.3 package [423]	(<i>E</i>)- <i>N</i> -((1 <i>S</i> ,4 <i>r</i>)-4-(2-(((<i>S</i>)-2-Amino-4,5,6,7-tetrahydrobenzo[<i>d</i>]thiazol-6-yl)(propyl)amino)ethyl)cyclohexyl)-3-(4-chlorophenyl)acrylamide, <i>N</i> -((1 <i>S</i> ,4 <i>r</i>)-4-(2-(((<i>S</i>)-2-amino-4,5,6,7-tetrahydrobenzo[<i>d</i>]thiazol-6-yl)(propyl)amino)ethyl)cyclohexyl)-3-(5-methyl-1,2,4-oxadiazol-3-yl)benzamide, <i>N</i> -((1 <i>S</i> ,4 <i>r</i>)-4-(2-(((<i>S</i>)-2-amino-4,5,6,7-tetrahydrobenzo[<i>d</i>]thiazol-6-yl)(propyl)amino)ethyl)cyclohexyl)-2-chloropyridine-3-sulfonamide	(<i>E</i>)- <i>N</i> -((1 <i>S</i> ,4 <i>r</i>)-4-(2-(((<i>S</i>)-2-Amino-4,5,6,7-tetrahydrobenzo[<i>d</i>]thiazol-6-yl)(propyl)amino)ethyl) cyclohexyl)-3-(4-chlorophenyl)acrylamide: hydrogen bond interactions with Asp110 and Ile183; van der Waals interactions with Phe106, Phe345, Tyr365, and Tyr373 residues; hydrophobic interactions involving Ser182, Phe345, and Ser366 residues. <i>N</i> -((1 <i>S</i> ,4 <i>r</i>)-4-(2-(((<i>S</i>)-2-Amino-4,5,6,7-tetrahydrobenzo[<i>d</i>]thiazol-6-yl)(propyl)amino)ethyl) cyclohexyl)-3-(5-methyl-1,2,4-oxadiazol-3-yl)benzamide: hydrogen bond interactions with Asp110 and Ile183; hydrophobic interactions involving Val111, Ser182, Ile183, Val189, Ser192, Phe345, Phe346 residues. <i>N</i> -((1 <i>S</i> ,4 <i>r</i>)-4-(2-(((<i>S</i>)-2-Amino-4,5,6,7-tetrahydrobenzo[<i>d</i>]thiazol-6-yl)(propyl)amino)ethyl) cyclohexyl)-2-chloropyridine-3-sulfonamide: hydrogen bond interactions with Glu90 and Ser192; hydrophobic interactions with Asp110, Ser182, Ile 183, Phe345, Phe346, and Tyr373 residues [424].
12	Docking onto X-ray structure of D ₃ R (PDB id 3PBL [294]) using AutoDock Vina [410] and AutoDock 4.2 [411] softwares	<i>R</i> -7-OH-DPAT, <i>R</i> -7-OH-PIPAT, pramipexole, ropinirole, rotigotine, quinpirole, dopamine, PD128907 and <i>cis</i> -8-OH-PBZI	Hydrogen bond interactions involving Asp110, Val111, Thr115, Ser192, and Ser196 residues; hydrophobic interactions with Phe106, Val107, Val111, Ile183, Phe188, Trp342, Phe345, Phe346, His349, Thr369, and Tyr373 residues [412].
13	Docking onto X-ray structure of D ₃ R (PDB id 3PBL [294]) using InducedFit docking software [425-427]	[4-(4-Carboxamidobutyl)-1-aryl]piperazines	<i>N</i> -(4-(4-(2-(<i>tert</i> -Butyl)-6-(trifluoromethyl)pyrimidin-4-yl)-piperazin-1-yl)butyl)imidazo[1,2- <i>a</i>]pyridine-2-carboxamide: hydrogen bond interactions involving Thr115 and Ser196; hydrophobic interactions with Ile183, Val189, and Val350 residues. The arylamide moiety of this ligand and other analogues may adopt three different conformations: (i) the arylamide group is docked onto Glu90; (ii) the arylamide moiety is placed in proximity to Val180 and Ser182 residues; (iii) the arylamide moiety is involved in π - π interactions with Tyr365 and in hydrogen bond interactions with Thr369 [66].
Adenosine A _{2A} receptor (A _{2A} AR) antagonists			
Entry	Method(s)	Ligand(s)	Results/Conclusions
14	Docking onto A _{2A} AR model using MOE software [428] (Template: X-ray structure of A _{2A} AR; PDBid 3EML [44])	8-Substituted 9-ethyladenine derivatives	Two different ligand binding orientations towards A _{2A} AR, interacting with key residues Phe163, Glu164, and Asn248 of A _{2A} AR model (corresponding to Phe168, Glu169, and Asp253 of human A _{2A} AR). Ligand binding orientation 1: π - π interactions involving Phe163; hydrogen bond interactions with Glu164 and Asn248. Ligand binding orientation 2: π - π interactions involving Phe163; hydrogen bond interactions with Asn248 [96].
15	Docking onto X-ray structure of A _{2A} AR (PDBid 4E1Y [244]) using AutoDock 4.2 software [411]	3-[4-Amino-6-(2-chlorobenzyl)thieno[2,3- <i>d</i>]pyrimidin-2-yl]benzonitrile	3-[4-Amino-6-(2-chlorobenzyl)thieno[2,3- <i>d</i>]pyrimidin-2-yl]benzonitrile: hydrophobic interactions involving Leu190, Leu194, Tyr197, Phe201, Ala236, Val239, and Ala243 residues [429].
16	Docking onto X-ray structure of A _{2A} AR (PDBid 3EML [44]) using GLIDE module from Schrödinger suite [405-407]	10 ligands with the best docking scores selected from a library of 46 A _{2A} AR antagonists	Hydrogen bond interactions involving Asn253 for all ligands and Ile180, Ala81, and Tyr271 residues for some ligands; π - π interactions with Phe168 [430].
17	Docking onto X-ray structure of A _{2A} AR (PDBid 3EML [44]) using DOCK 5.4 software [431]	7-Substituted 5-amino-2-(2-furyl)pyrazolo[4,3- <i>e</i>]-1,2,4-triazolo[1,5- <i>c</i>]pyrimidines, piperazine derivatives of triazolotriazine and triazolopyrimidines	7-Substituted 5-amino-2-(2-furyl)pyrazolo[4,3- <i>e</i>]-1,2,4-triazolo[1,5- <i>c</i>]pyrimidines: hydrogen bond interactions involving Thr88; π - π interactions involving Phe182 and Phe257 residues; hydrophobic interactions with Ile66, Ile92, Ile244, and Trp276 residues. Piperazine derivatives of triazolotriazine and triazolopyrimidines: hydrogen bond interactions involving Thr27; π - π stacking interactions with Phe182; hydrophobic interactions involving Ile92, Phe93, and Val186 residues [432].

(Table 2) contd....

Dopamine D ₃ Receptor (D ₃ R) Agonists			
Entry	Method(s)	Ligand(s)	Results/Conclusions
18	Docking onto X-ray structure of A _{2A} AR (PDBid 4E1Y [244]) using GLIDE module from Schrödinger suite [405-407]	5'-Substituted amiloride derivatives	5'-Substituted amiloride derivatives: hydrogen bond and salt bridge interactions with Asn52 and Thr88; π - π interactions with Trp246; hydrophobic interactions with Phe168, Met177, Leu249, and Ile274 residues [433].
19	Docking onto A _{2A} AR model using GLIDE module from Schrödinger suite [405-407] (Template: X-ray structure of β_1 AR; PDBid 2VT4 [262])	4-(3-Aminoamino-5-phenyl-1,2,4-triazin-6-yl)-2-chlorophenol, 6-(2,6-dimethylpyridin-4-yl)-5-phenyl-1,2,4-triazin-3-amine	4-(3-Amino-5-phenyl-1,2,4-triazin-6-yl)-2-chlorophenol: hydrogen bond interactions involving Asn253 and His278; π - π interactions with Phe168, and hydrophobic interactions involving Met270. 6-(2,6-Dimethylpyridin-4-yl)-5-phenyl-1,2,4-triazin-3-amine: hydrogen bond interactions involving Asn253; π - π interactions with Phe168; and hydrophobic interactions with Met270, with a pocket comprised by Leu84, Leu85, Met177, Asn181, Trp246, Leu249, and His250 and a pocket formed by Ala63, Ile66, Ser277, and His278 residues [243].
20	Docking onto A _{2A} AR model using FlexiDock utility in the Biopolymer module of SYBYL 6.7.1 (Tripos, St Louis, MO) [434] (Template: X-ray structure of RHO; PDBid 1BRD [435])	CGS15943	CGS15943: hydrophobic interactions between quinazoline ring and Leu85, Ile135, Leu167, Phe168, Phe182, Val186, Trp246, and Leu249, and between furan ring and Ile80, Val84, and Ile274; hydrogen bond interactions involving Asn181 and Asn253 residues [436].
21	Docking onto X-ray structure of A _{2A} AR (PDBid 3EML [44]) using GLIDE module from Schrödinger suite software [405-407], Induced-Fit docking software [425-427], and ICM molecular modeling software (Molsoft, LLC) [437]	ZM241385	ZM241385: hydrogen bond interactions involving Glu169 and Asn253 residues; hydrophobic interactions with Phe168, His264, Ile267, Met270, and Ile274 residues [438-440].
22	Docking onto A _{2A} AR model using GLIDE module from Schrödinger suite software [405-407] and InducedFit docking software [425-427] (Template: X-ray structure of β_2 AR; PDBid 2RH1 [272])	ZM241385	ZM241385: hydrogen bond interactions involving Asn253; hydrophobic interactions with Leu85, Thr88, Trp246, and Leu249 residues; π - π interactions with Phe168 [438].
23	Docking onto X-ray structure of A _{2A} AR (PDBid 3EML [44]) using AutoDock Vina program [411].	Caffeine	Five binding poses of caffeine to A _{2A} AR were analysed and the most relevant residues involved in caffeine-A _{2A} AR interaction are: Ala63, Val84, Leu85, Thr88, Phe168, Glu169, Met177, Trp246, Leu249, His250, Asn253, Ile274, and His278 [441].
24	Docking onto A _{2A} AR model using CAChe 6.1 [442] and CAChe 7.5 softwares [442] (Template: X-ray structures of bovine RHO and β_2 AR; PDBid 1U19 [332] and 2RH1 [272])	XAC, KW6002, ZM241385	In bovine rhodopsin, the purine ring of XAC and the phenyl rings of KW6002 and ZM241385 are accommodated in a pocket formed by Leu85, Thr88, Gln89, Ile135, Leu167, Phe168, Val178, Asn181, and Phe182. The purine ring of KW6002 and ZM241385 and the aminoethylphenoxyacetamid group of XAC occupies a pocket comprised by Glu13, Val55, Ile60, Ala63, Phe80, Ile274, Ile275, and His278. The furan moiety of ZM-241385 interacts with a lipophilic pocket formed by Phe62, Ile66, and Val164. In β_2 AR, the purine ring of ligands is accommodated in a pocket formed by Leu48, Ala51, Asp52, Leu87, Thr88, Ser91, Leu95, Ile238, Phe242, Trp246, His250, Ser277, His278, Asn280, Ser281, and Asn285. The aromatic rings are placed in a pocket comprised by Val55, Ala59, Val60, Phe62, Ala63, Val84, Gln89, Glu169, Trp246, Ile274, and His278. XAC makes hydrogen bond interactions with Glu169, Ser277, His278, and Ser281 residues [443].
25	Docking onto a theoretical model of A _{2A} AR (PDBid 1MMH) using DOCK 5.4 software [431]	Xanthine derivatives (KW6002, KF17837, BS-DMPX) Non-xanthine derivatives (7-substituted 5-amino-2-(2-furyl)pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidines and piperazine derivatives of [1,2,4]triazolo[1,5-a]triazine)	Xanthine derivatives: hydrogen bond interactions involving Ser277; π - π interactions involving Tyr179, His250, and Phe257 residues; hydrophobic interactions with hydrophobic domains located at the entrance and at the bottom of binding pocket formed by Ser91, Ile92, Trp246, Leu249, Ala273, and His278 residues. Non-xanthine derivatives: hydrogen bond interactions involving Thr88 and Thr271 residues; π - π interactions involving Phe82 and Phe257 residues. The furan ring accommodates in a hydrophobic pocket comprised by Ile66, Ile92, Ile244, and Trp276 in 7-substituted 5-amino-2-(2-furyl)pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidines and in a hydrophobic pocket comprised by Ile92, Phe93, and Val186 in piperazine derivatives of [1,2,4]triazolo[1,5-a]triazine) [444].

(Table 2) contd....

Dopamine D ₃ Receptor (D ₃ R) Agonists			
Entry	Method(s)	Ligand(s)	Results/Conclusions
26	Docking onto TM2, TM3, TM5, TM6, and TM7 domains of A _{2A} AR (PDBid 3PWH [241]) performed by Autodock using Lamarckian Genetic Algorithm [401]	Pyrimidine and triazine derivatives, pyrazolo[3,4- <i>d</i>]pyrimidines, pyrrolo[2,3- <i>d</i>]pyrimidines, triazolo[4,5- <i>d</i>]pyrimidines, 6-arylurines, thieno[3,2- <i>d</i>]pyrimidines	Hydrogen bond interactions involving Glu169 and Asn253 residues; hydrophobic interactions with Val84, Leu249, Met270 and Ile274; π - π interactions with Phe168 of A _{2A} AR [445].
27	Docking onto X-ray structure of A _{2A} AR (PDBid 3PWH [241]) using GLIDE module from Schrödinger suite [405-407]	2-(Furan-2-yl)-[1,2,4]triazolo[1,5- <i>f</i>]pyrimidin-5-amines, 2-(furan-2-yl)-[1,2,4]triazolo[1,5- <i>a</i>]pyrazin-8-amines, 2-(furan-2-yl)-[1,2,4]triazolo[1,5- <i>a</i>][1,3,5]triazin-7-amines	Hydrogen bond interactions involving Glu169 and Asn253 residues; π - π interactions with Phe168 and His250. Weak interactions with Ser67 (hydrogen bond interactions) and Tyr271 (π - π interactions) for some derivatives [446].
M ₁ muscarinic acetylcholine receptor (mAChR ₁) antagonists / negative allosteric modulators (NAMs)			
Entry	Method(s)	Ligand(s)	Results/Conclusions
28	Docking onto X-ray structure of mAChR ₁ (PDBid 5CXV [307]) using GLIDE module from Schrödinger suite [405-407]	Tiotropium	Tiotropium: hydrogen bond interactions involving Asp residue [307].
29	Docking onto mAChR ₁ model using DOCK 4.01 [447], FlexX 1.8 [448], and GOLD 1.1 softwares [449] (Template: X-ray structure of bovine RHO; PDBid 1F88 [231])	Pirenzepine	Pirenzepine: salt bridge interactions between the basic nitrogen atom and Asp residue at TM3, the lactam ring interacts with Asn residue at TM6 and its aromatic nitrogen atom with Thr residue at TM5 [450].
30	Docking onto mAChR ₁ model using GOLD software [449] (Template: X-ray structure of bovine RHO; PDBid 1F88 [231])	<i>N</i> -Methyl-4-piperidyl benzylates	<i>N</i> -Methyl-4-piperidyl benzylates: salt bridge interactions involving Asp105; hydrophobic interactions involving Tyr404; hydrogen bond interactions with Tyr179 [116].
Metabotropic Glutamate Receptor 2 (mGluR ₂) agonists / positive allosteric modulators (PAMs)			
Entry	Method(s)	Ligand(s)	Results/Conclusions
31	Docking onto mGluR ₂ model using GLIDE module from Schrödinger suite [405-407] (Template: X-ray structures of mGluR ₁ , mGluR ₃ , and β_2 AR (PDBid 4OR2 [377], 4OO9 [381], and 3SN6 [277])	JNJ-42153605	JNJ-42153605: hydrophobic interactions involving Leu639, Phe643, Leu732, Trp773, and Phe776 residues; hydrogen bond interactions involving Ser731 and Asn735; π - π interactions with His723 [451].
32	Docking onto X-ray structure of mGluR ₂ (PDBid 5CNJ [379]) using MOE v. 2013.08 [452]	LY2812223	LY2812223: salt bridge interactions involving Arg61, Asp295, and Lys377 residues; hydrogen bond interaction involving Ser165, Ala166, Thr168, and Glu273 residues; water-mediated hydrogen bond interactions with Asp301; π -H interactions with the Ser272 [379].
Metabotropic Glutamate Receptor 3 (mGluR ₃) agonists / positive allosteric modulators (PAMs)			
Entry	Method(s)	Ligand(s)	Results/Conclusions
33	Docking onto X-ray structure of mGluR ₃ (PDBid 2E4U [380]) using Induced Fit algorithm [425-427]	Glutamate	Glutamate: hydrogen bond interactions with Ser151, Ala172, Ser173, and Thr174 residues; salt bridge interactions involving Arg64, Arg68, Asp301, and Lys389 residues [453].
34	Docking onto X-ray structures of mGluR ₃ (PDBid 2E4V [380], 2E4W [380], 2E4X [380], and 2E4Y [380])	DCG-IV, <i>1S,3S</i> -ACPD, <i>1S,3R</i> -ACPD, <i>2R,4R</i> -APDC	DCG-IV: hydrogen bond interactions involving Arg68, Ser151, Ala172, Thr174, Tyr222, Ser278, Asp301, and Lys389; water-mediated hydrogen bond interactions with Arg64; van der Waals interactions involving Tyr150. <i>1S,3S</i> -ACPD: hydrogen bond interactions involving Arg68, Ser151, Ala172, Thr174, Asp301, and Lys389; water-mediated interactions with Arg64 and Ser278; van der Waals interactions involving Tyr222 and Gly302. <i>1S,3R</i> -ACPD: hydrogen bond interactions involving Arg68, Ser151, Ala172, Thr174, Asp301, and Lys389; van der Waals interactions with Tyr222 and Gly302. <i>2R,4R</i> -APDC: hydrogen bond interactions involving Arg68, Ser151, Ala172, Thr174, Asp301, and Lys389; van der Waals interactions with Tyr222 [380].

(Table 2) contd....

Metabotropic Glutamate Receptor 4 (mGluR ₄) agonists / positive allosteric modulators (PAMs)			
Entry	Method(s)	Ligand(s)	Results/Conclusions
35	Docking onto mGluR ₄ model using AutoDock 3.0 software [401] (Template: X-ray structure of mGluR ₄ ; PDBid 1EWK [378])	L-Glutamate, L-AP4, S-PPG	L-Glutamate, L-AP4, and S-PPG interact with the agonist binding site of mGluR ₄ composed by Arg78, Ser159, and Thr182 [454].
36	Docking onto VFT domain of mGluR ₄ using Discovery Studio 2.5.5 software (Accelrys Inc., Cambridge, UK) [455]	LSP4-2022	The hydroxybenzyl moiety of LSP4-2022 interacts with Lys74 and Lys317 and the glutamate-like moiety interacts with Arg78, Ser159, Ala180, Thr182, Tyr230, Asp312, and Lys405. The phenoxyacetic acid group of LSP4-2022 is involved in hydrogen bond interactions with Thr108, Ser157, and Gly158 [456].
37	Docking onto mGluR ₄ model using Discover 3.0 and WHATIF softwares [413] (Template: X-ray structures of LIVBP, LBP, and AmiC; PDBid 2LIV [457], 2LBP [458], and 1PEA [459])	ACTP-1	Docking to the open form of mGluR ₄ model, built from LIVBP and LBP templates, has shown that ACTP-1 interacts with Lys74, Arg78, Ser159, and Thr182. Docking to the closed form of mGluR ₄ model, built from AmiC template, has shown that ACTP-1 interacts with Tyr230, Asp312, Ser313, and Lys317 [460].
Metabotropic Glutamate Receptor 5 (mGluR ₅) antagonists / negative allosteric modulators (NAMs)			
Entry	Method(s)	Ligand(s)	Results/Conclusions
38	Docking onto X-ray structure of mGluR ₅ (PDBid 4OO9 [381]) using Maestro v.9.3 (Schrodinger) software [461]	Mavoglurant	Mavoglurant: hydrogen bond interactions involving Ser805, Ser809, and Asn747 residues; hydrophobic interactions involving two pockets (one hydrophobic pocket formed by Gly624, Ile625, Gly628, Ser654, Pro655, Ser658, Tyr659, Val806, Ser809, Ala810, and Ala813 residues, and other hydrophobic pocket consisted of Ile651, Val740, Pro743, and Leu744 residues) [381].
39	Docking onto X-ray structure of mGluR ₅ (PDBid 5CGC [382], 5CGD [382]) using PyMOL (Schrodinger) [462]	3-Chloro-4-fluoro-5-[6-(1 <i>H</i> -pyrazol-1-yl)pyrimidin-4-yl]benzotrile, HTL14242	3-Chloro-4-fluoro-5-[6-(1 <i>H</i> -pyrazol-1-yl)pyrimidin-4-yl]benzotrile: hydrogen bond interactions involving Ser809; water-mediated hydrogen bond interaction with Val 740; π - π interactions with Trp785 and Phe788 residues. HTL14242: hydrogen bond interactions involving Ser809; water-mediated hydrogen bond interaction with Val 740; π - π interactions with Tyr659, Trp785, and Phe788 residues. The pyrazole and pyridyl rings of 3-chloro-4-fluoro-5-[6-(1 <i>H</i> -pyrazol-1-yl)pyrimidin-4-yl]benzotrile and HTL14242, respectively, are docked onto a pocket defined by Ile625, Gly628, Ser654, Pro655, Ser658, Tyr659 and Ser809. The pyrimidine linker of both ligands is located in a pocket formed between Pro655, Tyr659, Val806, and Ser809 residues [382].
40	Docking onto X-ray structure of mGluR ₅ (PDBid 4OO9 [381]) using CDocker [463] in Discovery Studio 3.1 (Accelrys Inc., Cambridge, UK)	4-Bromo- <i>N</i> -(3-bromophenyl)thiazole-2-carboxamide, 4-bromo- <i>N</i> -(6-methylpyridin-2-yl)thiazole-2-carboxamide	4-Bromo- <i>N</i> -(3-bromophenyl)thiazole-2-carboxamide: hydrogen bond interactions involving Tyr659; hydrophobic interactions involving two pockets (one hydrophobic pocket formed by Gly624, Ile625, Gly628, Ser654, Pro655, Ser658, Tyr659, Val806, Ser809, Ala810, and Ala813 residues, and other hydrophobic pocket defined by Pro655, Tyr659, Val806, and Ser809 residues). 4-Bromo- <i>N</i> -(6-methylpyridin-2-yl)thiazole-2-carboxamide: hydrogen bond interactions involving Tyr659; hydrophobic interactions with Ile625, Pro655, Ala810, and Ala813 residues [446] [464].
41	Docking onto X-ray structure of mGluR ₅ (PDBid 4OO9 [381]) using CDocker software [463]	Aglaiduline, 5- <i>O</i> -ethyl-hirsutanonol, yakuchinone A	Aglaiduline: hydrophobic interactions involving two pockets (one hydrophobic pocket formed by Arg648, Ile651, Val740, and Pro743 residues, and other hydrophobic pocket defined by Ser654, Pro655, and Ala810 residues); hydrogen bond interactions involving Asn747. Yakuchinone A: hydrophobic interactions involving two pockets (one hydrophobic pocket formed by Arg648, Ile651, Val740, and Pro743 residues, and other hydrophobic pocket defined by Ser654, Pro655, and Ala810); hydrogen bond interactions involving Ser805. 5- <i>O</i> -Ethyl-hirsutanonol: hydrogen bond interactions involving Ser805 and Ser809 [465].
42	Docking onto mGluR ₅ model using AutoDock 3.0.5 software [401] (Template: X-ray structures of mGluR ₁ , PDBid 1EWK [378], 1EWV [378], 1EWT [378])	S4-CPG, MCPG	Hydrogen bond interactions involving Tyr43, Ser152, and Thr154 residues [466].
43	Docking onto mGluR ₅ model using ROSETTA v3.4 software [467] (Template: X-ray structures of β_2 AR, S1PR ₁ , and D ₃ R; PDBid 2RH1 [272], 3V2Y [357], and 3PBL [294])	CHPyEPC, 1,4-BisPEB, MPEP, 1,3-BisPEB	All NAM ligands make interactions with Leu630, Ile651, Gly652, Pro655, Trp785, Phe788, Tyr792, Val806, and Ser809 residues. CHPyEPC, 1,4-BisPEB, and 1,3-BisPEB interact with Val740, Pro743, Leu744, and Asn747 residues [468].

(Table 2) contd....

5-Hydroxytryptamine Receptor 1A (5-HT _{1A} R) Agonists			
Entry	Method(s)	Ligand(s)	Results/Conclusions
44	Docking onto 5-HT _{1A} R model using Affinity module from INSIGHT II software [414] (Template: X-ray structures of RHO; PDBid 1F88 [231], 1HZX [328], and 1L9H [330])	N ¹ -Substituted N-arylpiperazines	N ¹ -Substituted N-arylpiperazines: salt bridge interactions involving Asp116; π - π interactions involving Phe361 and Tyr390 residues; hydrogen bond interactions with Thr188. Some ligands are involved in π - π interactions with hydrophobic pocket formed by Phe204, Leu 359, and Phe362 [469].
45	Docking onto 5-HT _{1A} R model using Affinity module from INSIGHT II software [414] (Template: X-ray structures of RHO; PDBid 1F88 [231], 1HZX [328], and 1L9H [330])	1-Cinnamyl-4-(2-methoxyphenyl) piperazines	1-Cinnamyl-4-(2-methoxyphenyl)piperazines: salt bridge interactions involving Asp116; π - π interactions involving Phe361 and Tyr390 residues; hydrogen bond interactions with Thr188 [470].
46	Docking onto 5-HT _{1A} R model using Affinity from INSIGHT II software [414] (Template: X-ray structures of RHO; PDBid 1F88 [231], 1HZX [328], and 1L9H [330])	4-Halo-6-[2-(4-arylpiperazin-1-yl)ethyl]-1H-benzimidazoles	4-Halo-6-[2-(4-arylpiperazin-1-yl)ethyl]-1H-benzimidazoles: salt bridge interactions involving Asp116; hydrogen bond interactions involving Ser199 and Trp358; π - π interactions involving Phe361 and Tyr390 residues [471].
47	Docking onto 5-HT _{1A} R model using FlexX-Pharm from SYBYL 7.0 software [472] (Template: X-ray structure of bovine RHO; PDBid 1F88 [231])	Arylpiperazines	Arylpiperazines: salt bridge interactions involving the Asp residue; π - π interactions with the Phe residue; hydrogen bond interactions with Asn, Cys, Ser, Thr, and Tyr residues [473].
48	Docking onto 5-HT _{1A} R model using AutoDock 3.0.5 software [401] (Template: X-ray structure of RHO; PDBid 2R4R [271])	1-(Benzo[b]thiophen-2-yl)-3-(4-arylpiperazin-1-yl)-propan-1-one derivatives	1-(Benzo[b]thiophen-2-yl)-3-(4-pyridin-2-yl)-piperazin-1-yl)-propan-1-one: salt bridge and hydrogen bond interactions involving Asp116; ion-dipole interactions with Asn385; π - π interactions involving Phe361 [474].
49	Docking onto 5-HT _{1A} R model using GOLD 4.0 software [449] (Template: X-ray structure of β_1 AR; PDBid 2Y03 [263])	Carboxamide and sulfonamide alkyl piperazine analogues	Carboxamide and sulfonamide alkyl piperazine analogues: salt bridge interactions involving Asp116; hydrogen bond interactions with Ser199 and Thr200; π - π interactions involving Tyr96, Phe361, Phe362, Trp387, and Tyr390 residues [475].
50	Docking onto 5-HT _{1A} R model using AutoDock 4.0 software [411] (Template: X-ray structure of β_2 AR; PDBid 3P0G [276])	3-[3-(4-Aryl-1-piperazinyl)-propyl]-1H-indole derivatives	3-[3-(4-Aryl-1-piperazinyl)-propyl]-1H-indole derivatives: salt bridge interactions involving Asp116; π - π interactions with Phe and Tyr residues; hydrogen bond interactions with the Ser residue [476].
5-Hydroxytryptamine receptor 2A (5-HT _{2A} R) antagonists			
Entry	Method(s)	Ligand(s)	Results/Conclusions
51	Docking onto 5-HT _{2A} R model using QXP software [477] (Template: X-ray structure of bovine RHO; PDBid 1F88 [231])	(Aminoalkyl)benzo and heterocycloalkanones	(Aminoalkyl)benzo and heterocycloalkanones: hydrogen bond interactions involving Cys148, Asp155, and Ser159; hydrophobic interactions with residues located in TM2 and TM7 [478].
52	Docking onto X-ray structure of 5-HT _{2A} R (PDBid 2VT4 [262]) using GLIDE module from Schrödinger suite [405-407]	4-Aryl-2,7,7-trimethyl-5-oxo-N-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxamides	4-Aryl-2,7,7-trimethyl-5-oxo-N-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxamides: interaction with Cys199, Asn310, and Asn329 residues [479].
53	Docking onto 5-HT _{2A} R model using GOLD 4.12 software [449] (Template: X-ray structure of β_2 AR; PDBid 2RH1 [272])	Ketanserin, 05245768	Ketanserin: salt bridge interactions involving the Asp residue; hydrogen bond interactions involving the Ser residue; hydrophobic interactions with Phe and Tyr residues. 05245768: salt bridge interactions involving the Asp residue; hydrogen bond interactions involving the Ser residue; hydrophobic interactions with Ile, Phe, and Tyr residues [480].
54	Docking onto 5-HT _{2A} R model using FlexiDock from SYBYL-X 1.2 software (Tripos, St Louis, MO) [434] (Template: X-ray structure of β_2 AR; PDBid 2RH1 [272])	(2R,4S)-PAT, (2S,4R)-PAT, (2R,4S)-4'-Cl-PAT, (2S,4R)-4'-Cl-PAT	(2S,4R)-PAT: salt bridge interactions involving the Asp residue; π - π interactions involving the Phe residue. (2R,4S)-PAT and (2S,4R)-4'-Cl-PAT: salt bridge interactions involving the Asp residue (2R,4S)-4'-Cl-PAT salt bridge interactions involving the Asp residue; hydrogen bond interactions with the Ser residue [481].

(Table 2) contd....

5-Hydroxytryptamine Receptor 1A (5-HT _{1A} R) Agonists			
Entry	Method(s)	Ligand(s)	Results/Conclusions
55	Docking onto 5-HT _{2A} R model using GLIDE module from Schrödinger suite [405-407] (Template: X-ray structure of β_2 AR; PDBid 2RH1 [272])	Nefazodone, aripiprazole, haloperidol, cyproheptadine, trazodone, clozapine, ketanserin, spiperone, risperidone	Interaction with a binding pocket comprised by Ile152, Asp155, Val156, Ser207, Met208, Pro211, Leu229, Asp231, Val235, Leu236, Ser239, Phe339, Asn343, and Asn363 residues [482].
56	Docking onto 5-HT _{2A} R model using AutoDock Vina 1.1.1 [410] (Template: X-ray structure of β_2 AR; PDBid 3D4S [273])	Arylpiperazines	Arylpiperazines: salt bridge interactions involving Asp155; hydrogen bond interactions with Asn343; hydrophobic interactions involving two hydrophobic pockets (one hydrophobic pocket comprised by Leu123, Ser159, Trp336, Phe339, Val366, and Tyr370 residues, and the other pocket formed by Trp151, Ile152, Leu229, Ala230, Phe234, and Val235 residues) [483].
57	Docking onto 5-HT _{2A} R model using ICM Pro docking algorithm [437], GLIDE from Schrödinger suite [405-407], and GOLD programs [449] (Template: X-ray structures of bovine RHO and β_2 AR; PDBid 1U19 [332] and 2RH1 [272])	Nantenine analogues	Nantenine analogues: salt bridge interactions involving Asp155; hydrogen bond interactions involving Asn343. The majority of nantenine analogues interact with Asp155, Val156, Ser159, Ile210, Leu228, Phe234, Gly238, Ser242, and Ile341 residues. Other ligands interact with Ile152, Thr160, Ile163, Ile206, Ser239, Phe243, Ser244, Pro338, Phe339, Phe340, Thr342, Asn343, Met345, Val366, and Gly369 residues [484].
58	Docking onto 5-HT _{2A} R model using GLIDE module from Schrödinger suite [405-407] (Template: X-ray structure of human A _{2A} AR; PDBid 2YDV [240])	Ketanserin, risperidone, ziprasidone	Ketanserin: salt bridge and hydrogen bond interactions involving Asp155; hydrogen bond interactions with Trp151; hydrophobic interactions with Phe125 and Val130; van der Waals interactions involving Leu126, Pro129, Leu154, Phe158, Val204, and Met208 residues. Risperidone: salt bridge and hydrogen bond interactions involving Asp155; hydrogen bond interactions with Trp151; van der Waals interactions involving Leu126, Val130, Ile152, Leu154, Phe158, and Met208 residues. Ziprasidone: hydrogen bond interactions involving Trp151; π - π interactions involving Phe158; hydrophobic interactions involving Leu122, Leu126, and Phe158 residues; van der Waals interactions involving Ile118, Phe193, Ile196, Ile197, and Trp200 residues [485].
59	Docking onto 5-HT _{2A} R model using GLIDE module from Schrödinger suite [387-389] (Template: X-ray structure of human A _{2A} AR; PDBid 2YDV [240])	<i>N</i> -[3-(4-(1 <i>H</i> -indol-2-yl)phenoxy)propyl]-4-chlorophenylamine	<i>N</i> -[3-(4-(1 <i>H</i> -Indol-2-yl)phenoxy)propyl]-4-chlorophenylamine: hydrogen bond interactions involving Leu362 and Asn363 residues; π - π interactions involving Phe339; hydrophobic interactions with Thr342 and Asn343; van der Waals interactions with Leu136, Ala230, Phe339, Asn343, Ala346, Val347, Glu355 and Val366 residues [485].
60	Docking onto 5-HT _{2A} R model using AutoDock 4.2 software [411] (Template: X-ray structure of β_2 AR; PDBid 2RH1 [272])	(<i>R</i>)-Roemerine	(<i>R</i>)-Roemerine: salt bridge and hydrogen bond interactions involving Asp155; dipole-dipole interactions involving Ser159 and Tyr370, van der Waals interactions involving Ser239, Ala242, Trp336, Phe339, Phe340, Val366, and Tyr370 residues [486].
5-Hydroxytryptamine Receptor 2C (5-HT _{2C} R) Antagonists			
Entry	Method(s)	Ligand(s)	Results/Conclusions
61	Docking onto 5-HT _{2C} R model using QXP software [477] (Template: X-ray structure of bovine RHO; PDBid 1F88 [231])	(Aminoalkyl)benzo and heterocycloalkanones	(Aminoalkyl)benzo and heterocycloalkanones: hydrogen bond interactions involving Cys148, Asp155, and Ser159; hydrophobic interactions with residues located in TM2 and TM7 [478].
62	Docking onto 5-HT _{2C} R model using FlexX software [448] (Template: X-ray structure of β_2 AR; PDBid 2RH1 [272])	<i>N</i> -(3-(4-Methylimidazolidin-1-yl)phenyl)-5,6-dihydrobenzo[<i>h</i>]quinazolin-4-amine, <i>N</i> -(4-methoxy-3-(4-methylpiperazin-1-yl)phenyl)-1,2-dihydro-3 <i>H</i> -benzo[<i>e</i>]indole-3-carboxamide, 1-(3,5-difluorophenyl)-3-(4-methoxy-3-(2-(piperidin-1-yl)ethoxy)phenyl)imidazolidin-2-one, <i>N</i> -(3-(2-((3-(piperazin-1-yl)pyrazin-2-yl)oxy)ethoxy)benzyl)propan-2-amine	Hydrophobic interactions involving Val106, Val135, Phe137, Phe214, Val215, Val221, Ala222, Phe223, Trp324, Phe327, Phe328, Leu350, and Leu354 residues. <i>N</i> -(3-(4-Methylimidazolidin-1-yl)phenyl)-5,6-dihydrobenzo[<i>h</i>]quinazolin-4-amine: hydrogen bond interactions with Asp134 and Arg195 residues. <i>N</i> -(4-Methoxy-3-(4-methylpiperazin-1-yl)phenyl)-1,2-dihydro-3 <i>H</i> -benzo[<i>e</i>]indole-3-carboxamide: hydrogen bond interactions involving Asp134 and Tyr358 residues. 1-(3,5-Difluorophenyl)-3-(4-methoxy-3-(2-(piperidin-1-yl)ethoxy)phenyl)imidazolidin-2-one: hydrogen bond interactions involving Arg195 and Tyr358 residues. <i>N</i> -(3-(2-((3-(Piperazin-1-yl)pyrazin-2-yl)oxy)ethoxy)benzyl)propan-2-amine: hydrogen bond interactions involving Arg195, Val208, Asn351, and Tyr358 residues [487].

(Table 2) contd....

5-Hydroxytryptamine Receptor 2C (5-HT _{2C} R) Antagonists			
Entry	Method(s)	Ligand(s)	Results/Conclusions
63	Docking onto 5-HT _{2C} R model using FlexiDock from SYBYL-X 1.2 software (Tripos, St Louis, MO) [434] (Template: X-ray structure of β_2 AR; PDBid 2RH1 [272])	(2 <i>R</i> ,4 <i>S</i>)-PAT, (2 <i>S</i> ,4 <i>R</i>)-PAT, (2 <i>R</i> ,4 <i>S</i>)-4'-Cl-PAT, (2 <i>S</i> ,4 <i>R</i>)-4'-Cl-PAT	(2 <i>S</i> ,4 <i>R</i>)-PAT: salt bridge interactions involving the Asp residue; π - π interactions involving the Phe residue. (2 <i>R</i> ,4 <i>S</i>)-PAT and (2 <i>S</i> ,4 <i>R</i>)-4'-Cl-PAT: salt bridge interactions involving the Asp residue (2 <i>R</i> ,4 <i>S</i>)-4'-Cl-PAT salt bridge interactions involving the Asp residue; hydrogen bond interactions with the Ser residue [481].
64	Docking onto 5-HT _{2C} R model using GLIDE module from Schrödinger suite [387-389] [405-407] (Template: X-ray structure of β_2 AR; PDBid 2RH1 [272])	(<i>E</i>)-3-(2-chlorophenyl)-1-(5-methoxy-6-(2-(piperidin-1-yl)ethoxy)indolin-1-yl)prop-2-en-1-one	(<i>E</i>)-3-(2-chlorophenyl)-1-(5-methoxy-6-(2-(piperidin-1-yl)ethoxy)indolin-1-yl)prop-2-en-1-one: salt bridge interactions involving Asn331, Ser334 and Val354 residues; hydrogen bond interactions involving Asn331; hydrophobic interactions involving Val135, Val208, Phe214, Ala222, Phe327, Phe328, and Val354 residues [488].

The internal validation or cross-validation consists in the elimination of one (Leave-One-Out cross-validation, LOO) or more (Leave Some-Out cross-validation, LSO; Leave-Many-Out cross-validation, LMO) ligands of the training set. The reconstruction of QSAR models is based on the remaining ligands of the training set using the combination of descriptor variables previously selected, and the pharmacological activity of the eliminated ligand(s) is predicted from the rebuilt QSAR model. Afterward, the same methodology is repeated until all or a definite portion of the ligands have been removed once. The external validation consists in the prediction of biological/pharmacological activity using a group of ligands that are not included in the training set (test set) and the same descriptor variables are employed in the generation of the QSAR model [501].

The 3D QSAR CoMFA and CoMSIA methodologies have emerged as fundamental tools for design and molecular optimization of drug candidates targeting GPCRs. The CoMFA methodology provides information of whether differences in steric (Lennard-Jones potential functions) and electrostatic components (Coulomb potential functions) for field calculation of a training set of molecules in a given alignment can be correlated with differences in biological/pharmacological activity [502-504]. A comparable 3D QSAR-based methodology, CoMSIA, was developed based on arbitrary descriptors named similarity indices. In opposition to CoMFA, CoMSIA applies a smoother potential based on Gaussian functions, allowing the calculation of various similarity indices, such as steric, electrostatic, hydrophobic, hydrogen bond acceptor, and hydrogen bond donor parameters, that covers more extensively than the steric and electrostatic fields calculated by CoMFA, the most significant contributing factors for the binding free energy of ligands towards a putative target [505]. In both methodologies, the 3D alignment of the chemical structures of ligands is required and should reveal the maximum superimposition of steric, electrostatic, hydrophobic, hydrogen bond acceptor, and hydrogen bond donor parameters that a database of ligands adopt when interacting with a specific therapeutic target. Each ligand on the training set is aligned to a template which exhibits a common molecular substructure and the aligned ligands are placed inside virtual 3D grid boxes. Subsequently, the interaction energies are calculated between the ligands and molecular fragments (molecular probes) at each

grid point. Applying an appropriate statistical method for regression analysis, usually by PLS, the 3D-QSAR model is constructed to describe the variation of biological/pharmacological activity with the variation of CoMFA/CoMSIA interaction fields and the predictive ability of 3D-QSAR model is corroborated by cross-validation and prediction of activity of test set. The generated CoMFA/CoMSIA is typically represented as color-coded contoured 3D maps, which displays specific volumes of space where the magnitudes of steric, electrostatic, hydrophobic, hydrogen bond acceptor and hydrogen bond donor parameters are positively or negatively correlated with the pharmacological activity [502-505]. This type of graphical representation can be presumed as a model of the binding site in which a training set of ligands is supposed to interact. Table 3 emphasizes the distinct ligand- and pharmacophore-based design approaches applied for the aforementioned GPCR-derived therapeutic targets potentially involved in PD.

3. RELEVANT FEATURES IN GPCR-LIGAND INTERACTIONS

3.1. Impact of Structural Water Molecules in GPCR-mediated Interactions

Ubiquitous when considering biological interactions, water molecules display different and important roles in protein-protein interactions in general, and in GPCR associated interactions in particular. These molecules are not to be overlooked when considering drug design for either orthosteric or allosteric purpose. By forming a 'water pocket' network, they can play an important role on the transition between active and inactive states, by deforming TM7 and potentiating hydrogen bonds that stabilize the structure on the inactive state [22]. In the case of rhodopsin, water molecules tend to be clustered in the vicinity of the binding pockets, near highly conserved residues [330]. Furthermore, internal water networks connecting to the ligand binding site have found to be highly conserved, even for receptors from different subfamilies of GPCRs, in particular, A_{2A}AR and DOR, with associated recurring motifs [562]. The direct involvement of the structural water molecules in the interaction of ligands with GPCRs can be a major bottleneck for an efficient design of drug candidates without the proper structural data information, since the replacement of water molecules

Table 3. Ligand- and pharmacophore-based drug design methodologies reported for ligands targeting GPCRs potentially involved in PD.

Dopamine D ₂ Receptor (D ₂ R) Agonists			
Entry	Method(s)	Ligand(s)	Results/Conclusions
1	CoMFA using SYBYL 6.8 QSAR module [434]	Aminoindans, aminotetralins, dopamine analogs, ergolines, apomorphine, phenylpiperidines, benzo[<i>f</i>]quinolines	CoMFA maps showed that bulky substituents with low electronegativity on the fused piperidine ring nitrogen and small substituents with low electronegativity on the aromatic ring are favorable features for agonist activity [506].
2	CoMFA and CoMSIA using SYBYL 8.0 [434] and MOE v. 2011.10 [507] programs	(<i>S</i>)-6-((2-(4-Phenylpiperazine-1-yl)-ethyl)(propyl)amino)-5,6,7,8-tetrahydronaphthalene-1-ol analogs	The key features for ligand activity are divided into two groups: near the aminotetralin head group and at/near the phenyl ring bound to piperazine moiety. Near the aminotetralin head group, the presence of bulky groups on 5-methoxy group of aminotetralin moiety is beneficial for activity; the introduction of bulky groups near the <i>N</i> -propyl group of aminotetralin moiety is expected to decrease the activity; the presence of electronegative substituents at 7-position of aminotetralin group and hydrophilic groups near the <i>N</i> -propyl group is predicted to enhance activity; a beneficial effect for activity is also expected upon the introduction of hydrogen bond donor groups near the 5- and 7-positions and near the <i>N</i> -propyl group of aminotetralin moiety. The presence of bulky substituents at 6-, 7-, and 8- positions of quinoline ring, electropositive groups on 3-position, and hydrophilic substituents on quinoline ring is favorable for activity. The introduction of hydrophilic substituents around the piperazine ring and hydrogen bond donor groups on the nitrogen atom of piperazine ring enhances the binding affinity [508].
3	Pharmacophore modeling using Discovery Studio software [416]	Arylpiperazines	Pharmacophore model including key features for ligand activity: (i) salt bridge interactions between the basic nitrogen atom of piperazine ring and the receptor; (ii) one or more aromatic interactions involving arylpiperazine substructure; (iii) hydrogen bond interaction between the oxygen atom of methoxy group and the receptor; (iv) possibility of hydrogen bond interaction involving the linker part [417].
4	Pharmacophore modeling using MOE v. 2005.06 [509]	Aminotetralins, apomorphine, quinolines	Pharmacophore model including key features for ligand activity: (i) one excluded volume covering the projected feature Asp; (ii) one positively charged nitrogen atom interacting with Ser; (iii) one hydrogen bond donor feature interacting with Asp; (iv) one aromatic ring feature [510].
Dopamine D ₃ Receptor (D ₃ R) Agonists			
Entry	Method(s)	Ligand(s)	Results/Conclusions
5	HQSAR and CoMFA using SYBYL 6.6 program [434]	Piperazinylalkylisoxazole analogues	The best HQSAR model was constructed using Atom, Bond, Connectivity, Donor and Acceptor (A/B/C/DA) as fragment type, 257 as hologram length, and 4–7 as fragment size. CoMFA models showed that the electrostatic parameters are the most contributing factor for D ₃ R agonist affinity of these ligands [511].
6	CoMFA using SYBYL-X 1.3 program [434]	Library of 34 structurally diverse D ₃ R agonists	Two representative molecules were used to analyze the key features for D ₃ R binding affinity. <i>N</i> -((1 <i>S</i> ,4 <i>r</i>)-4-(2-(((<i>S</i>)-2-Amino-4,5,6,7-tetrahydrobenzo[<i>d</i>]thiazol-6-yl)(propyl)amino)ethyl)cyclohexyl)-3-(5-methyl-1,2,4-oxadiazol-3-yl)benzamide: (i) the presence of bulky groups near the 2- and 3-position in pyridine ring enhances the binding affinity and near the 4-position of pyridine ring is expected to reduce the activity; (ii) the presence of electropositive groups near the 2-position and electronegative groups near the 4- and 5-position in pyridine ring may enhance activity. <i>N</i> -((1 <i>S</i> ,4 <i>r</i>)-4-(2-(((<i>S</i>)-2-Amino-4,5,6,7-tetrahydrobenzo[<i>d</i>]thiazol-6-yl)(propyl)amino)ethyl)cyclohexyl)-2-chloropyridine-3-sulfonamide: (i) the introduction of bulky and electronegative substituents near the 5-position of the benzene ring is expected to increase agonist activity; (ii) the introduction of electropositive groups near methyl position of 1,2,4-oxadiazole ring is favorable for activity [424].
7	CoMFA and CoMSIA using SYBYL 7.2 program [434]	Library of 41 structurally diverse D ₃ R agonists	The hydrophobic interactions are the most important contributing factor for D ₃ R agonist activity. Hydrogen bonding also contributes largely to the binding affinity and may confer receptor subtype selectivity [512].

(Table 3) contd....

Dopamine D ₃ Receptor (D ₃ R) Agonists			
Entry	Method(s)	Ligand(s)	Results/Conclusions
8	CoMFA and CoMSIA using SYBYL 8.0 [434] and MOE v. 2011.10 [507] programs	(S)-6-((2-(4-Phenylpiperazine-1-yl)-ethyl)(propyl)amino)-5,6,7,8-tetrahydronaphthalene-1-ol analogs	The key features for ligand activity are divided into two groups: near the aminotetralin head group and at/near the phenyl ring bound to piperazine moiety. Regarding the aminotetralin head group, the introduction of bulky substituents around 7- and 8-positions, hydrophobic and hydrophilic substituents on phenyl and cyclohexyl rings of aminotetralin moiety, respectively, is favorable for activity. The presence of bulky groups near the <i>N</i> -propyl group of aminotetralin moiety is expected to reduce the binding affinity to D ₃ R. The introduction of both hydrogen bond donor and acceptor substituents near piperazine ring is predicted to be favorable for agonist activity [508].
9	Pharmacophore modeling using Chem-X software	(R)-(+)-PD-128907, (R)-(+)-7-OH-DPAT, BP-897, (S)-(-)-3-PPP, pramipexole, (+)-UH-232, (S)-(-)-DS-121, quinolorane, (-)-quinpirole, ropinirole	Pharmacophore model including common key features for these ligands: (i) one aromatic ring and one sp ³ nitrogen bound to a propyl group and to two additional sp ³ carbons; (ii) the distance between the aromatic ring center and the basic sp ³ nitrogen within these compounds was found to be on approximately 5.16 ± 0.16 Å [419].
Adenosine A _{2A} Receptor (A _{2A} AR) Antagonists			
Entry	Method(s)	Ligand(s)	Results/Conclusions
10	HQSAR using SYBYL 7.2 program [434]	2-(Furan-2-yl)-[1,2,4]triazolo[1,5- <i>f</i>]pyrimidin-5-amines, 2-(furan-2-yl)-[1,2,4]triazolo[1,5- <i>a</i>]pyrazin-8-amines, 2-(furan-2-yl)-[1,2,4]triazolo[1,5- <i>a</i>][1,3,5]triazin-7-amines	The best HQSAR model includes the combination of fragment parameters A/B/C/DA, with a size fragment of 7-10 and a hologram length of 199. The structure features that contribute positively for the activity are: (i) for 2-(furan-2-yl)-[1,2,4]triazolo[1,5- <i>f</i>]pyrimidin-5-amines, the presence of a substituent at C ³ of phenyl ring; (ii) for 2-(furan-2-yl)-[1,2,4]triazolo[1,5- <i>a</i>]pyrazin-8-amines, a short length of carbon chain between the piperazine moiety and the methylated nitrogen atom [446].
11	CoMFA using SYBYL 6.3 program [434]	Flavonoids	The key features for high affinity to A _{2A} AR are: (i) the presence of bulky substituents at C ² , C ⁷ , and C ⁸ of chromone ring; (ii) the absence of high electron density groups at the <i>para</i> position of phenyl ring [513].
12	CoMFA using SYBYL-X 1.1.1 program [434]	Substituted thieno[2,3- <i>d</i>]pyrimidines	The key features for A _{2A} AR antagonistic activity are: (i) the presence of bulky substituents in the thiophene ring and small substituents in the pyrimidine ring; (ii) electropositive substituents between positions 1 and 2 and at position 4 of benzene ring located at pyrimidine ring; (iii) electronegative substituents at position 2 of the benzene ring located at the pyrimidine ring [429].
13	CoMFA and CoMSIA using DRAGON software [514]	Pyrimidine and triazine derivatives, pyrazolo[3,4- <i>d</i>]pyrimidines, pyrrolo[2,3- <i>d</i>]pyrimidines, triazolo[4,5- <i>d</i>]pyrimidines, 6-arylpurines, thieno[3,2- <i>d</i>]pyrimidines	For pyrimidine and triazine derivatives, the key features for A _{2A} AR antagonistic activity are: (i) the presence of a limitedly bulky, electronegative, and hydrophobic group at C ⁶ ; (ii) the presence of a small, electronegative, and hydrophilic group at C ² ; (iii) a limitedly bulky, electronegative, and hydrophilic group (non hydrogen bond donor group) at C ⁴ . For pyrazolo[3,4- <i>d</i>]pyrimidines, pyrrolo[2,3- <i>d</i>]pyrimidines, triazolo[4,5- <i>d</i>]pyrimidines, and 6-arylpurines, the key features for A _{2A} AR antagonistic activity are: (i) the presence of a small, and electronegative group (hydrogen bond acceptor group) at C ⁶ ; (ii) a hydrogen bond donor group at C ² ; (iii) a hydrogen bond acceptor group at N ³ . For thieno[3,2- <i>d</i>]pyrimidines, the key features for A _{2A} AR antagonistic activity are: (i) the presence of a limitedly bulky, electronegative, and hydrophilic group (hydrogen bond donor group) at C ⁶ , a small and electronegative group (hydrogen bond donor group) [445].
14	Pharmacophore modeling and GFA-based QSAR using Cerius ² [418] and LigandScout programs [515]	4-Arylthieno[3,2- <i>d</i>]-pyrimidines	Molecular connectivity index (SC-2), molecular surface area (AREA), graph-theoretical (WIENER), and molecular flexibility (PHI-MAG) descriptors influenced the activity of ligands against A _{2A} AR. Pharmacophore model including key features for ligand activity: (i) the presence of one hydrogen bond donor feature (amino group interacts with Asn253), two hydrophobic features (one group interacts with Leu85, Phe168, Met177, Trp246, and Leu249 residues; other group interacts with Leu269 and Met270 residues) [98].
15	Pharmacophore modeling and QSAR using PHASE 3.2 module of Schrodinger suite [516]	Library of 46 A _{2A} AR antagonists	Pharmacophore model including key features for ligand activity: (i) one hydrogen bond acceptor feature; (ii) one hydrogen bond donor feature; (iii) one hydrophobic feature; (iv) two aromatic ring features [430].

(Table 3) contd....

Adenosine A _{2A} Receptor (A _{2A} AR) Antagonists			
Entry	Method(s)	Ligand(s)	Results/Conclusions
16	Pharmacophore modeling using CATALYST 4.11 software package [517]	Xanthine derivatives (KW6002, KF17837, BS-DMPX) Non-xanthine derivatives (7-substituted 5-amino-2-(2-furyl)pyrazolo[4,3- <i>e</i>]-1,2,4-triazolo[1,5- <i>c</i>]pyrimidines and piperazine derivatives of [1,2,4]triazolo[1,5- <i>a</i>]triazine)	Pharmacophore models for xanthine and non-xanthine derivatives including key features for ligand activity: (i) two hydrophobic features; (ii) one hydrogen bond acceptor feature; (iii) one aromatic ring feature [445].
17	Pharmacophore modeling using PHASE 2.0 module of Schrodinger suite [516]	Library of 68 A _{2A} AR antagonists	Pharmacophore model 1 including key features for ligand activity: (i) two hydrogen bond acceptor features; (ii) two aromatic ring features; (iii) one hydrogen bond donor feature. Pharmacophore model 2 including key features for ligand activity: (i) two hydrogen bond acceptor features; (ii) one hydrogen bond donor feature; (iii) one aromatic ring; (iv) one hydrophobic feature [518].
18	Pharmacophore modeling using CATALYST 4.10 software package [517]	7-Substituted 5-amino-2-(2-furyl)pyrazolo[4,3- <i>e</i>]-1,2,4-triazolo[1,5- <i>c</i>]pyrimidines	Pharmacophore model including key features for ligand activity: (i) one ring aromatic feature; (ii) one positively ionizable feature; (iii) one hydrogen bond acceptor lipid feature; (iv) one hydrophobic feature [519].
19	Pharmacophore modeling using CATALYST 4.11 program [517]	1,2,4-Triazole derivatives, pyrazolotriazolopyrimidines, trifluoropyrimidines, 9-ethyladenine derivatives, thioacyhydrazones	Pharmacophore model including key features for ligand activity: (i) one hydrogen bond donor feature; (ii) three hydrophobic features; (iii) one aromatic ring feature [520].
20	Pharmacophore modeling using PHASE module of Schrodinger suite [516]	Library of 751 A _{2A} AR antagonists	Pharmacophore model including key features for ligand activity: (i) one hydrogen bond acceptor feature; (ii) one hydrogen bond donor feature; (iv) two aromatic ring features [521].
21	Pharmacophore modeling using FLAPPharm program [522]	Istradefyline, MSX-2, SYN-115, BIIB014, SCH-442416, ZM-241385, ST-1535, preladenant	Pharmacophore model including key features for ligand activity: (i) three hydrogen bond acceptor features; (ii) one hydrogen bond donor feature; (iii) hydrophobic features. The proposed pharmacophore is predicted to interact Glu169 and Asn253 [523].
22	Pharmacophore modeling using CATALYST 4.11 program [517]	7-Substituted 5-amino-2-(2-furyl)pyrazolo[4,3- <i>e</i>]-1,2,4-triazolo[1,5- <i>c</i>]pyrimidines, piperazine derivatives of triazolotriazine and triazolopyrimidines	Pharmacophore model including key features for ligand activity: (i) two hydrophobic features, and one aromatic ring hydrophobic feature for 7-substituted 5-amino-2-(2-furyl)pyrazolo[4,3- <i>e</i>]-1,2,4-triazolo[1,5- <i>c</i>]pyrimidines; (ii) one hydrogen bond acceptor feature, two hydrophobic features, and one aromatic ring hydrophobic feature for piperazine derivatives of triazolotriazine and triazolopyrimidines [432].
M ₁ muscarinic acetylcholine receptor (mAChR ₁) antagonists / negative allosteric modulators (NAMs)			
Entry	Method(s)	Ligand(s)	Results/Conclusions
23	Pharmacophore modeling and 3D-QSAR using CATALYST 4.10 program [517]	α -Substituted 2,2-diphenylpropionates	The stereoelectronic properties including total energies, bond distances, valence angles, torsion angles, HOMO-LUMO energies, reactivity indices, vibrational frequencies of ether and carbonyl moieties, and nitrogen atom proton influences the binding affinity of these ligands. Pharmacophore model including key features for ligand activity: (i) one aromatic ring feature; (ii) one hydrogen bond donor; (iii) basic nitrogen species at a distance of ~4Å from the hydrogen bond acceptor [524].
24	Pharmacophore modeling using PHASE module of Schrodinger suite [516]	Trihexylphenidyl, atropine, darifenacin, 4-DAMP, propantheline, pirenzepine	Pharmacophore model including the common molecular features: (i) molecular weight: 289.37–426.55; (ii) polar surface area: 23.47–68.78 Å ² ; (iii) hydrogen bond acceptors: 1–3; (iv) hydrogen bond donors: 0–1; (v) rotatable bonds: 2–7; (vi) AlogP: 1.68–4.53 [525].
25	Pharmacophore modeling using CATALYST 4.10 program [517]	Caramiphen, indocaramiphen, nitrocaramiphen, atropine, dicyclomine, methoctramine, oxybutynin	Pharmacophore model including key features for ligand activity: (i) two hydrogen bond acceptor features; (ii) one aliphatic hydrophobic feature; (iii) one aromatic ring feature [526].
Metabotropic Glutamate Receptor 4 (mGluR ₄) agonists / positive allosteric modulators (PAMs)			
Entry	Method(s)	Ligand(s)	Results/Conclusions
26	Pharmacophore modeling using APEX-3D software (MSI) [527]	(<i>S</i>)-Glu, (<i>S</i>)-Asp, (<i>S</i>)-AP4, (<i>S</i>)-SOP, (2 <i>S</i>)-4CH ₂ Glu, (<i>S</i>)-Gla, (2 <i>S</i>)-CCG-I, (2 <i>SR</i> ,3 <i>RS</i>)-CPrAP4, (2 <i>SR</i> ,3 <i>SR</i>)-CPrAP4, (1 <i>S</i> ,3 <i>S</i>)-ACPD, (2 <i>SR</i> ,4 <i>SR</i>)-CpeAP4, (2 <i>SR</i> ,4 <i>RS</i>)-CpeAP4, ACPT-I, (+)-ACPT-III	Pharmacophore model including key features for ligand activity: (i) the presence of two hydrogen bond donor groups; (ii) the presence of three hydrogen bond acceptor groups. Additional regions are predicted to interact with mGluR ₄ , including the oxygen atom of phosphonic and phosphoric groups of (<i>S</i>)-Glu analogues, the carboxylic groups of (<i>S</i>)-Glu, ACPT-I, and (+)-ACPT-III, and the presence of cycloalkyl rings of CPrAP4, CpeAP4, ACPT-I, and (+)-ACPT-III [527].

Metabotropic Glutamate Receptor 5 (mGluR ₅) Antagonists / Negative Allosteric Modulators (NAMs)			
Entry	Method(s)	Ligand(s)	Results/Conclusions
27	Pharmacophore modeling using Accelrys Discovery Studio 4.0 (DS) software [528]	Pyridyl and phenyl substituted oxadiazoles, 5-aryl-3-acylpyridinyl-pyrazoles, 1-aryl-4-acylpyridinyl-imidazoles, aryl azetidiny oxadiazoles, N-aryl pyrrolidinonyl oxadiazoles	Pharmacophore model including common key features: (i) one hydrogen bond acceptor feature; (ii) one hydrophobic feature; (iii) two hydrophobic aromatic features; (iv) two excluded volumes [465].
5-Hydroxytryptamine Receptor 1A (5-HT _{1A} R) Agonists			
Entry	Method(s)	Ligand(s)	Results/Conclusions
28	QSAR using 2D molecular descriptors by MOE v. 2004.0314 programs [529]	2-[ω -(4-Arylpiperazin-1-yl)alkyl]perhydropyrrolo-[1,2-c]imidazoles, 2-[ω -(4-arylpiperazin-1-yl)alkyl]perhydroimidazo[1,5- α]pyridines	Steric parameters contribute most significantly to the 5-HT _{1A} R agonist activity. The number of rotatable bonds, partial charge descriptors, subdivided surface area descriptors, and an indicator variable for carbonyl oxygens also influence the 5-HT _{1A} R agonist activity of the ligands [530].
29	CoMFA using SYBYL 5.5 program [434]	Arylpiperazines, (aryloxy)propanolamines, tetrahydropyridyl indoles	Arylpiperazines: the introduction of steric groups is favorable close to the aromatic ring and unfavorable near the basic nitrogen atom. The presence of electronegative substituents near the <i>ortho</i> position of the aromatic ring is beneficial for activity. (Aryloxy)propanolamines: the introduction of bulky and electronegative substituents close to the <i>ortho</i> and <i>meta</i> positions of the aromatic ring is beneficial for the activity. The presence of bulky and electropositive groups near the <i>para</i> position of the aromatic ring is favorable as well as the introduction of electropositive substituents near the basic nitrogen atom. Tetrahydropyridylindoles: the steric parameters contribute most significantly to the activity. The introduction of bulky and hydrogen bond donor groups at 5-position of indole ring is predicted to be beneficial for the activity [531].
30	CoMFA using SYBYL 5.5 program [434]	3-(1,2,5,6-Tetrahydropyridin-4-yl)indole derivatives	The steric parameters contribute most significantly to the 5-HT _{1A} R agonist activity. The presence of bulky substituents in the plane of indole 5-position is beneficial for 5-HT _{1A} R activity, whereas bulky substituents located out of a plane is expected to decrease the activity. There is also a preference for coplanarity between indole and tetrahydropyridine rings. Using as a reference a 5-CONH ₂ analog, the presence of oxygen and hydrogen atoms of carboxamide moiety contributes positively to 5-HT _{1A} R activity [532].
31	CoMFA using SYBYL 6.0 program [434]	Bicyclohydantoin-phenylpiperazines	The electrostatic parameters contribute most significantly to the 5-HT _{1A} R agonist activity. The key features for agonist activity are: (i) the introduction of bulky substituents at <i>ortho</i> and <i>meta</i> positions of the phenyl ring; (ii) the introduction of electron-withdrawing substituents at <i>ortho</i> and <i>meta</i> positions of the phenyl ring. The presence of bulky and electron-withdrawing substituents is expected to have a negative effect on activity [533].
32	Pharmacophore modeling and CoMFA using DISCO [534] and SYBYL programs [434]	Pyridazinothiazepines, pyridazinoxazepines	Pharmacophore model including common key features for ligand activity: (i) two hydrophobic ring features (phenyl and 3(2 <i>H</i>)-pyridazinone rings); (ii) four hydrogen bond donor features (<i>N</i> atom of protonated amine, <i>N</i> ¹ atom and the two lone pairs of <i>O</i> atom of carbonyl group of 3(2 <i>H</i>)-pyridazinone ring); (iii) two hydrogen bond acceptor features (<i>O</i> atom of carbonyl group and <i>N</i> ¹ atom of 3(2 <i>H</i>)-pyridazinone ring); (iv) <i>O</i> atom of carbonyl group interacting to the <i>N</i> atom of oxazepine or thiazepine rings), using as reference the ligand GYKI16527 [535].
33	Pharmacophore modeling and CoMFA using GALAHAD program [536-538]	Arylpiperazines	Pharmacophore model including common key features for ligand activity: (i) one hydrogen bond acceptor feature; (ii) one positively charged group; (iii) one aromatic ring feature; (iv) one hydrophobic feature. The steric parameters contribute most significantly to the 5-HT _{1A} R agonist activity. The introduction of bulky substituents, as benzothio-phenyl, and electropositive substituents attached to benzothio-phenyl ring may enhance activity. Moreover, the presence of electronegative substituents surrounding the dihydrobenzodioxepin ring may have a positive effect on activity [539].

(Table 3) contd....

5-Hydroxytryptamine Receptor 1A (5-HT _{1A} R) Agonists			
Entry	Method(s)	Ligand(s)	Results/Conclusions
34	Pharmacophore modeling using CATALYST 4.6 program [517]	(2-Alkoxy)phenylpiperazine derivatives of 1-(2-hydroxy-3-(4-aryl piperazin-1-yl)propyl)-5,5-diphenylimidazolidine-2,4-dione with alkyl or ester substituents at N ³ of the hydantoin ring	Pharmacophore model including common key features for ligand activity: (i) one hydrogen bond acceptor; (ii) one positively charged group; (iii) one aromatic ring feature; (iv) one hydrophobic feature. The inter-feature distance range between hydrogen bond acceptor and hydrophobic features is [5.53-5.62 Å], between hydrogen bond acceptor and positively charged group is [5.13-6.00 Å], between hydrogen bond acceptor and aromatic ring is [10.08-11.68 Å], between hydrophobic feature and positively charged group is [7.60-8.08 Å], between hydrophobic and aromatic ring features is [12.24-13.91 Å], and between positively charged group and aromatic ring feature is [5.68-5.69 Å] [540, 541].
35	Pharmacophore modeling using Accelrys Discovery Studio versions 3.5 (DS) software [542]	(R)-8-OH-DPAT, quetiapine, olanzapine, ziprasidone, 5-methyl urapidil, BMY14802, JB788, S14671, F15599, F13714, 1,3-dioxolane derivatives, pyridyl-fused 3-amino chroman derivatives, 1-(meta-trifluoromethylphenyl) piperazines	Pharmacophore modeling including common key features for ligand activity: (i) one positively ionizable group; (ii) one hydrogen bond acceptor feature; (iii) three hydrophobic features; (iv) seven excluded volumes [543].
36	Pharmacophore modeling using GRID 22 program [544]	8-OH-DPAT, buspirone, vilazodone, aripiprazole, F-13640	Pharmacophore modeling including common key features for ligand activity: (i) two hydrophobic features surrounded by TM5/TM6 and by TM2/TM7/ECL2; (ii) one positive ionizable feature interacting with Asp; (iii) one hydrogen bond acceptor feature interacting with Tyr; (iv) three excluded volumes [162].
5-Hydroxytryptamine Receptor 2A (5-HT _{2A} R) Antagonists			
Entry	Method(s)	Ligand(s)	Results/Conclusions
37	QSAR performed by GRID 22 [544] and GOLPE 4.6.0 programs [545] and using GRID/GOLPE descriptors	Butyrophenones	The interaction of hydrophobic groups in two areas, one at the bottom of the pocket near Leu163 and the other in the center near the side chains of Val and Phe residues, is expected to increase the binding affinity. The interaction of these ligands near the oxygen atom of Asp residue, the indolic nitrogen of Trp residue, at the bottom near the Ser residue, the side chain of Asn residue, and close to other Ser and Trp residues are favorable for antagonistic activity [546].
38	QSAR performed by MDL QSAR software package, version 2.2 (Symyx) using electronic and molecular parameters [547]	1-Benzhydryl-piperazines and 1-aryl piperazines with xanthine moiety at N ⁴	The binding affinity of these ligands to 5-HT _{2A} R correlates positively with the lipophilicity of ligands, the largest negative charge associated to O ⁶ atom of xanthine moiety, and with the partial atomic charge of N ⁴ atom of piperazine moiety [547].
39	QSAR by DRAGON software (version 1.11-2001) [514] and using DRAGON descriptors	2-Alkyl-4-aryl-pyrimidine fused heterocycles	A lower number of rotatable bonds, a more hydrophobic nature of the ligands, and lower polar surface area are expected to be favorable for binding affinity [548].
40	CoMFA using SYBYL 5.5 program [434]	3-(1,2,5,6-Tetrahydropyridine-4-yl)indole derivatives	The introduction of bulky substituents around the 5-position of indole ring is unfavorable for activity, whereas the presence of bulky groups at the N ¹ position of pyridine ring and at the N ¹ position of the indole ring is expected to be beneficial for activity. The introduction of electronegative substituents around the 5-position of the indole ring and of electropositive substituents above 5- and 6-carbons of the indole ring may increase the activity [532].
41	CoMFA using SYBYL 7.0 program [434]	Hexahydro- and octahydropyrido[1,2-c]pyrimidine derivatives	The introduction of bulky substituents in the proximity to the <i>para</i> position in the benzene ring attached to the piperazine ring and the absence of substituents at <i>ortho</i> position may enhance activity. The presence of bulky groups placed in the proximity of piperazine ring and at the C ⁴ position of the imide moiety is also beneficial for activity. The introduction of electronegative substituents in imide and piperazine moieties may increase the affinity [549].

(Table 3) contd....

5-Hydroxytryptamine Receptor 2A (5-HT _{2A} R) Antagonists			
Entry	Method(s)	Ligand(s)	Results/Conclusions
42	CoMSIA using SYBYL 7.2 program [434]	Tetrahydrofuran derivatives, benzamides, 3-aminoethyl-1-tetralones, piperazines, benzothiazepines, pyrrolbenzodiazepines, clozapine, flupentixol, haloperidol, loxapine, mesoridazine, olanzapine, quetiapine, risperidone, sertindole, thiothixene, thioridazine, compazine, ziprasidone	The electrostatic, hydrophobic, and hydrogen bond donor parameters contribute most significantly to the binding affinity towards 5-HT _{2A} , comparing to steric and hydrogen bond acceptor parameters [550].
43	Pharmacophore modeling using MOE v. 2007.09 program [551]	Ketanserin, risperidone, ritanserin, spiperone, clozapine, sertindole, setoperone, chlorpromazine, cyproheptadine, tefludazine, 5H-thiazolo[3,2- <i>a</i>]pyrimidine-5-one derivatives	Pharmacophore model including common key features for 5-HT _{2A} antagonist activity: (i) two hydrogen bond acceptor features; (ii) one aromatic ring or hydrophobic feature with two parallel features for π orbital accommodation; (iii) one aromatic ring feature with one hydrogen bond donor group; (iv) one hydrophobic feature [552].
44	Pharmacophore modeling using MOE v. 2008.10 program [553]	Thiophene derivatives	Pharmacophore model including the common key features for ligand activity: (i) one aromatic ring feature; (ii) one positively ionizable group containing a nitrogen atom; (iii) one hydrogen bond acceptor feature; (iv) one hydrophobic or aromatic feature attached to the positively ionizable group. The inter-feature distance range between the positively ionizable group and the hydrogen acceptor group is [6.6-10.3 Å], between aromatic ring feature and the hydrogen bond acceptor feature is [3.1-3.8 Å], between aromatic ring feature and the positively ionizable group is [7.4-8.8 Å], and the angle between the positively ionizable group and the plane of aromatic ring feature is [141.0-152.9 Å] ^o [554].
45	Pharmacophore modeling using MOE v. 2008.10 programs [553]	4-Nitroindole derivatives	Pharmacophore model including the common key features for ligand activity: (i) two aromatic ring features; (ii) one positively ionizable group; (iii) one hydrophobic feature [555].
46	Pharmacophore modeling using GRID 22 software [544]	Ketanserin	Pharmacophore model including the key features for ligand activity: (i) one positively ionizable amino group; (ii) two hydrophobic features; (iii) one hydrophobic feature [480].
5-Hydroxytryptamine receptor 2C (5-HT _{2C} R) antagonists			
Entry	Method(s)	Ligand(s)	Results/Conclusions
47	QSAR by DRAGON software (v.1.11-2001) [514] and using Dragon descriptors	Isoindoline	The binding affinity of these ligands are correlated to several atomic descriptors, in particular, the eigenvalue n.2 and the eigenvalue n.5 of the Burden matrix, atomic van der Waals volume to path length 2 and 8 of the Moran autocorrelations and path length 2 of Geary autocorrelation, polarizability to the highest eigenvalue n.1 and n.6 of the Burden matrix, and Sanderson electronegativity to path length 4 of Geary autocorrelation descriptors [556].
48	QSAR by D-CENT QSAR program [557, 558] using quantum chemical parameters	<i>N</i> -Benzylphenethylamines	The binding affinity was correlated negatively with total atomic electrophilic superdelocalizability of atom 3 and atom 13, the orbital electrophilic superdelocalizability of the highest occupied molecular orbital localized on atom 20, and the local atomic electronic chemical potential of atom 22. On the other hand, the binding affinity was correlated positively with Fukui index of the second highest occupied molecular orbital localized on atom 15 and Fukui index of the lowest vacant molecular orbital localized on atom 17 [559].
49	CoMFA using SYBYL 7.0 program [434]	Library of 24 structurally diverse 5-HT _{2C} R antagonists	The introduction of bulky substituents in the regions where methyl and propyl groups are located may enhance activity, whereas the presence of bulky groups in the proximity of indole group is expected to decrease activity. The presence of electronegative substituents near the amide moiety and positively charged groups is favorable for antagonistic activity [488].
50	Pharmacophore modeling using Accelrys Discovery Studio version 2.1 (DS) software [560]	Library of 24 structurally diverse 5-HT _{2C} R antagonists	Pharmacophore model including the common key features for ligand activity: (i) three hydrophobic features; (ii) one positively ionizable group; (iii) one hydrogen acceptor feature [488].
51	Pharmacophore modeling using CATALYST 4.6 program [517]	Diaryl substituted pyrrolidinones and pyrrolones	Pharmacophore model including the common key features for ligand activity: (i) one positively ionizable group; (ii) one hydrogen bond acceptor feature; (iii) one aromatic ring feature; (iv) three hydrophobic features [561].

in the ligand binding site may induce a dramatic modification of Structure-Activity Relationships (SAR) [562]. Interestingly, the inclusion of structural water molecules in crystallographic structures without the knowledge of structural water positions can lead to an improvement of virtual screening enrichment of active drug candidates over decoys [563]. Apart from experimental approaches, such as X-ray crystallography and NMR, MD simulations have been employed to predict the involvement of water molecules in GPCR-ligand interactions and to study the water networks within receptors in different activation states [564].

Homology modeling approaches, in particular, have found to significantly decrease in accuracy when the participation of structural water molecules is not considered. Hence, it is essential to always assess the number and the characteristics of the water-contacts of the GPCR in study [565]. In docking, the water molecules associated to the binding pockets can be determinant in the development of drug candidates that may establish distinct types of interactions with the protein target [44]. Several docking tools take into account the intervention of water molecules in protein-ligand interaction, such as Yet Another Docking Approach (YADA) [566], which considers the explicitly structural water molecules at the binding site and improves the prediction scores by up to 24%. Another docking software, Molegro Virtual Docker (MVD) [567], incorporates water molecules in protein-ligand complexes and considers that water molecules exhibit the same flexibility of the ligand. During the docking simulations, MVD solvates the ligands with the maximum number of water molecules, and these are then retained or excluded depending on energy contributions. Each water molecule is flexible on/off part of the ligand and is treated with the same flexibility as the ligand. To facilitate the removal of the water molecules, a constant (positive) entropy penalty value is introduced *per* included water. This approach has found to be successful in docking simulations when the water molecules are included in ligands containing hydrogen bonding groups [567]. Also, a more recent approach incorporated Quantum Mechanics/Molecular Mechanics (QM/MM) calculations with an implicit solvent for application to GPCR-targeted drug discovery, by considering the ligands and protein residues in the binding site as QM described regions [568].

In addition to the above-mentioned tools, alternative software packages are used to model water molecules, such as GRID [544], Hydrophobic INteractions (HINT) [569], SuperStar [570], Just Add Water Molecules (JAWM) [571], WaterMap [572, 573], water Potential of Mean Forces (wPMF) [574], Water Fingerprints for Ligand And Proteins (WaterFLAP) [522], among others. Overall, water molecules should be taken into consideration, since they may influence the ligand binding affinity, the binding free energy, and the protein mobility.

3.2. Analysis of the Ligand-binding Site of Potential GPCR-derived Therapeutic Targets

Even though computational methods have proven to be effective to solve structural aspects of GPCR-ligand complexes, they rely on experimental work as both validations

and as a starting point. Recently, the determination of 3D structures of GPCR-ligand complexes had substantially increased, shedding light on important patterns governing the interactions that lead to the formation and stabilization of these complexes. Among all the aforementioned GPCR-derived therapeutic targets of PD, the X-ray structure of five GPCRs (D₃R, A_{2A}AR, mGluR₂, mGluR₃, and mGluR₅) has been determined in complex with small-molecule modulators. Table 4 represents an overview of all known 3D structures of ligands in complex with GPCR-derived therapeutic targets of PD available on PDB and the important interacting residues involved in the GPCR-ligand interaction. Relevant interactions were retrieved from the G-Protein-Coupled Receptor database (GPCRdb) [575] for D₃R, A_{2A}AR and mGluR₅, and from the PDBeMOTIF for mGluR₂ and mGluR₃. The analysis of the ligand-binding site of the distinct GPCR-derived therapeutic targets of PD, reveals the presence of residue patterns underlying the GPCR-ligand interaction. The majority of A_{2A}AR ligands makes hydrophobic interactions with Leu85 in TM3. Interestingly, the A_{2A}AR agonists and the A_{2A}AR antagonist 4-(3-amino-5-phenyl-1,2,4-triazin-6-yl)-2-chlorophenol interact with Val83 in TM3. In ECL2, the A_{2A}AR modulators establish aromatic interactions with Phe168. More specifically, the A_{2A}AR agonists make π - π interactions with the Phe168 and hydrogen bond interactions with Glu169. Considering the TM6 domain, the analysis of the Table 4 shows that the A_{2A}AR ligands make hydrophobic interactions with Trp248 and Leu249, π - π interactions with His250, and hydrogen bond interactions with Asn253. Some A_{2A}AR antagonists establish hydrophobic interactions with Met177 in TM5 and π - π interactions with His264 located on ECL2. Similarly, to TM6, a considerable number of residues located in the TM7 domain are involved in the A_{2A}AR-ligand interaction. Interestingly, the A_{2A}AR agonists make hydrogen bond interactions with Ser277 and His278, while the A_{2A}AR antagonists make hydrophobic interactions with Met270. In addition, some antagonists bind to Leu267, to Tyr271, and to Ile274. The structural details of agonists CGS21680 and 5'-(N-ethylcarboxamido)adenosine, and the antagonists ZM241385 and 4-(3-amino-5-phenyl-1,2,4-triazine-6-yl)-2-chlorophenol in complex with A_{2A}AR are represented in Fig. (4A, 4B), Fig. (5A, and 5B), respectively. The mGluR₂ orthosteric agonists mentioned on Table 4 make hydrogen bond interactions with Arg61, Ser145, Ala166, Tyr168, and Asp295 residues and van der Waals interactions with Arg57, Ser167, Tyr216, and Lys377 residues mainly located on the extracellular Amino-Terminal Domain (ATD). The structural details of the binding modes of mGluR₂ orthosteric agonists are represented in Fig. (6A and 6B). Similarly, the mGluR₃ orthosteric agonists interact with residues located on the extracellular ATD. The mGluR₃ agonists make hydrogen bond and van der Waals interactions with Arg64, Arg68, Tyr150, Ser151, Ala172, Ser173, Thr174, and Lys389 residues. The structural details of the binding pose of glutamate (Fig. 7A) and DCG-IV (Fig. 7B) in complex with mGluR₃ are represented. While mGluR₂ and mGluR₃ orthosteric agonists interact with their receptors on extracellular ATD, the mGluR₅ NAM binds exclusively to the TM domains (TM2, TM3, TM4, and TM7 domains for mavoglurant; TM3, TM5, TM6, and TM7 domains for HTL14242 and 3-chloro-4-

Table 4. Residues involved in the interaction of ligands with potential GPCR-derived therapeutic targets of PD for which structural data information is available on PDB.

Receptor	Main Ligand(s)/ Binding Partners	Localization of the Interacting Residues on GPCR Structure									
Dopamine D₃ Receptor (D₃R)											
3PBL [294]	Eticlopride (antagonist)	Extracellular ATD: -									
		TM1: -	TM2: -	ECL1: -	TM3: Asp110 (HB and SB); Val111 (HP)	TM4: -	ECL2: Ile183 (HP)	TM5: -	TM6: Phe345 (AR); Phe346 (HP); His349 (HB)	ECL3: -	TM7: -
Adenosine A_{2A} receptor (A_{2A}AR)											
2YDO [240]	Adeosine (agonist)	Extracellular ATD: -									
		TM1: -	TM2: -	ECL1: -	TM3: -	TM4: -	ECL2: Phe168 (AR); Glu169 (HB)	TM5: -	TM6: Trp246 (HP); Leu249 (HP); Asn253 (HB)	ECL3: -	TM7: Ser277 (HB); H278 (2HB)
2YDV [240]	5'-(N-Ethylcarboxamido)adenosine (agonist)	Extracellular ATD: -									
		TM1: -	TM2: -	ECL1: -	TM3: Val84 (HP); Val85 (HP); Thr88 (HB);	TM4: -	ECL2: Phe168 (AR); Glu169 (HB)	TM5: -	TM6: Trp246 (HP); Leu249 (HP); His250 (HB); Asn253 (2HB)	ECL3: -	TM7: Ser277 (HB); His278 (HB)
3EML [44]	ZM241385 (antagonist)	Extracellular ATD: -									
		TM1: -	TM2: -	ECL1: -	TM3: Leu85 (AR)	TM4: -	ECL2: -	TM5: Met177 (HP)	TM6: Trp246 (HP); Leu249 (HP); His250 (AR); Asn253 (HB)	ECL3: His264 (AR)	TM7: Lys267 (HP); Met270 (HP)
3PWH [241]	ZM241385 (antagonist)	Extracellular ATD: -									
		TM1: -	TM2: -	ECL1: -	TM3: -	TM4: -	ECL2: Phe168 (AR)	TM5: Met177 (HP)	TM6: Leu249 (HP); His250 (AR); Asn253 (HB)	ECL3: -	TM7: Tyr271 (HP); Ile274 (HP)
3QAK [43]	UK-432097 (agonist)	Extracellular ATD: -									
		TM1: -	TM2: -	ECL1: -	TM3: Val84 (HP); Leu85 (HP)	TM4: -	ECL2: Phe168 (AR); Glu169 (2HB)	TM5: -	TM6: Trp246 (HP); Leu249 (HP); His250 (HB); Asn253 (HB)	ECL3: -	TM7: Met270 (HP); Tyr271 (HB and AR); Ile274 (HP); Ser277 (HB); His278 (2HB)
3REY [241]	Xanthine amine congener (antagonist)	Extracellular ATD: -									
		TM1: -	TM2: -	ECL1: -	TM3: -	TM4: -	ECL2: Phe168 (HP)	TM5: Met177 (HP)	TM6: Asn253 (HB)	ECL3: -	TM7: Met270 (HP); Ile274 (HP)
3RFM [241]	Caffeine (antagonist)	Extracellular ATD: -									
		TM1: -	TM2: -	ECL1: -	TM3: -	TM4: -	ECL2: Phe168 (HP)	TM5: -	TM6: -	ECL3: -	TM7: Ile274 (HP)

(Table 4) contd....

Receptor	Main Ligand(s)/ Binding Partners	Localization of the Interacting Residues on GPCR Structure									
Adenosine A_{2A} Receptor (A_{2A}AR)											
3UZA [243]	6-(2,6-Dimethylpyridin-4-yl)-5-phenyl-1,2,4-triazin-3-amine (antagonist)	Extracellular ATD: -									
		TM1: -	TM2: -	ECL1: -	TM3: -	TM4: -	ECL2: Phe168 (HP)	TM5: Met177 (HP)	TM6: Leu249 (HP); His250 (AR); Asn253 (2HB)	ECL3: -	TM7: Ile274 (HP)
3UZC [243]	4-(3-Amino-5-phenyl-1,2,4-triazin-6-yl)-2-chlorophenol (antagonist)	Extracellular ATD: -									
		TM1: -	TM2: -	ECL1: -	TM3: Val84 (HP); Leu85 (HP)	TM4: -	ECL2: Phe168 (AR)	TM5: Met177 (HP)	TM6: Trp246 (HP); Leu249 (HP); His250 (AR); Asn253 (2HB)	ECL3: -	TM7: Ile274 (HP); His278 (HB)
3VG9 [242]	ZM241385 (antagonist)	Extracellular ATD: -									
		TM1: -	TM2: -	ECL1: -	TM3: Leu85 (HP)	TM4: -	ECL2: Phe168 (HP)	TM5: -	TM6: Trp246 (HP); Leu249 (HP); His250 (AR); Asn253 (HB)	ECL3: -	TM7: Met270 (HP); Tyr271 (HP)
3VGA [242]	ZM241385 (antagonist)	Extracellular ATD: -									
		TM1: -	TM2: -	ECL1: -	TM3: Leu85 (HP)	TM4: -	ECL2: Phe168 (AR)	TM5: Met177 (HP)	TM6: Leu249 (HP); His250 (AR)	ECL3: -	TM7: Met270 (HP)
4E1Y [244]	ZM241385 (antagonist)	Extracellular ATD: -									
		TM1: -	TM2: -	ECL1:-	TM3: -	TM4: -	ECL2: Phe168 (AR); Glu169 (HB)	TM5: Met177 (HP)	TM6: Trp246 (HP); Leu249 (HP); His250 (AR); Asn253 (3HB)	ECL3: His264 (AR)	TM7: Leu267 (HP); Met270 (HP)
4UG2 [245]	CGS21680 (agonist)	Extracellular ATD: -									
		TM1: -	TM2: Ser67 (HB)	ECL1: -	TM3: Val84 (HP); Leu85 (HP); Thr88 (HB)	TM4: -	ECL2: Phe168 (AR); Glu169 (HB)	TM5: -	TM6: Trp246 (HP); Leu249 (HP); His250 (HB); Asn253 (2HB)	ECL3: -	TM7: Met270 (HP); Ile274 (HP); Ser277 (HB); His278 (2HB)
4UHR [245]	CGS21680 (agonist)	Extracellular ATD: -									
		TM1: -	TM2: -	ECL1: -	TM3: Val84 (HP); Leu85 (HP); Thr88 (HB)	TM4: -	ECL2: Phe168 (AR)	TM5: -	TM6: Trp246 (HP); Leu249 (HP); His250 (HB); Asn253 (HB)	ECL3: -	TM7: Ile274 (HP); Ser277 (HB); His278 (2HB)
5G53 [246]	5'-(N-Ethylcarboxamido)adenosine (agonist)	Extracellular ATD: -									
		TM1: -	TM2: -	ECL1: -	TM3: Val84 (HP); Leu85 (HP); Thr88 (HB)	TM4: -	ECL2: Phe168 (AR); Glu169 (HB)	TM5: -	TM6: Trp246 (HP); Leu249 (HP); His250 (HB); Asn253 (2HB)	ECL3: -	TM7: Ser277 (HB); His278 (2HB)
5IU4 [247]	ZM241385 (antagonist)	Extracellular ATD: -									
		TM1: -	TM2: -	ECL1: -	TM3: Leu85 (HP)	TM4: -	ECL2: Phe168 (AR); Glu169 (HB)	TM5: Met177 (HP)	TM6: Trp246 (HP); Leu249 (HP); His250 (AR); Asn253 (3HB)	ECL3: His264 (AR)	TM7: Met270 (HP)

(Table 4) contd....

Receptor	Main Ligand(s)/ Binding Partners	Localization of the Interacting Residues on GPCR Structure									
Adenosine A_{2A} Receptor (A_{2A}AR)											
5IU7 [247]	2-(Furan-2-yl)-N ⁶ -(2-(4-phenylpiperidin-1-yl)ethyl)-1,2-dihydro-[1,2,4]triazolo[1,5-a][1,3,5]triazine-5,7-diamine (antagonist)	Extracellular ATD: -									
		TM1: -	TM2: -	ECL1: -	TM3: Leu85 (HP)	TM4: -	ECL2: Phe168 (AR); Glu169 (HB)	TM5: Met177 (HP)	TM6: Trp246 (HP); Leu249 (HP); His250 (AR); Asn253 (3HB)	ECL3: His264 (AR)	TM7: Met270 (HP)
5IU8 [247]	2-(Furan-2-yl)-N ⁶ -(2-(4-phenylpiperidin-1-yl)ethyl)-1,2-dihydro-[1,2,4]triazolo[1,5-a][1,3,5]triazine-5,7-diamine (antagonist)	Extracellular ATD: -									
		TM1: -	TM2: -	ECL1: -	TM3: Leu85 (HP)	TM4: -	ECL2: Phe168 (AR); Glu169 (HB)	TM5: Met177 (HP)	TM6: Trp246 (HP); Leu249 (HP); His250 (AR); Asn253 (2HB)	ECL3: -	TM7: Met270 (HP)
5IUA [247]	2-(Furan-2-yl)-N ⁶ -(3-(4-phenylpiperazin-1-yl)propyl)-1,2-dihydro-[1,2,4]triazolo[1,5-a][1,3,5]triazine-5,7-diamine (antagonist)	Extracellular ATD: -									
		TM1: -	TM2: -	ECL1: -	TM3: Leu85 (HP)	TM4: -	ECL2: Phe168 (AR); Glu169 (HB)	TM5: Met177 (HP)	TM6: Trp246 (HP); Leu249 (HP); His250 (AR); Asn253 (HB)	ECL3: -	TM7: Leu267 (HP); Met270 (HP)
5IUB [247]	N ⁶ -(2-(4-(2,4-Difluorophenyl)piperazin-1-yl)ethyl)-2-(furan-2-yl)-1,2-dihydro-[1,2,4]triazolo[1,5-a][1,3,5]triazine-5,7-diamine (antagonist)	Extracellular ATD: -									
		TM1: -	TM2: -	ECL1: -	TM3: Leu85 (HP)	TM4: -	ECL2: Phe168 (AR); Glu169 (HB)	TM5: Met177 (HP)	TM6: Trp246 (HP); Leu249 (HP); His250 (AR); Asn253 (3HB)	ECL3: His264 (AR); Ala265	TM7: Leu267 (HB); Met270 (HP); Ile274 (HP)
5K2A [249]	ZM241385 (antagonist)	Extracellular ATD: -									
		TM1: -	TM2: -	ECL1: -	TM3: -	TM4: -	ECL2: Phe168 (AR); Glu169 (HB)	TM5: Met177 (HP)	TM6: Trp246 (HP); Leu249 (HP); His250 (AR); Asn253 (3HB)	ECL3: His264 (AR); Ala265	TM7: Leu267 (HP); Met270 (HP)
5K2B [249]	ZM241385 (antagonist)	Extracellular ATD: -									
		TM1: -	TM2: -	ECL1: -	TM3: -	TM4: -	ECL2: Phe168 (AR); Glu169 (HB)	TM5: -	TM6: Trp246 (HP); Leu249 (HP); His250 (AR); Asn253 (3HB)	ECL3: -	TM7: Leu267 (HP); Met270 (HP)
5K2C [249]	ZM241385 (antagonist)	Extracellular ATD: -									
		TM1: -	TM2: -	ECL1: -	TM3: -	TM4: -	ECL2: Phe168 (AR); Glu169 (HB)	TM5: Met177 (HP)	TM6: Leu249 (AR); His250 (AR); Asn253 (3HB)	ECL3: His264 (AR)	TM7: Met270 (HP)
5K2D [249]	ZM241385 (antagonist)	Extracellular ATD: -									
		TM1: -	TM2: -	ECL1: -	TM3: -	TM4: -	ECL2: Phe168 (AR); Glu169 (HB)	TM5: Met177 (HP)	TM6: Leu249 (HP); His250 (AR); Asn253 (3HB)	ECL3: His264 (AR)	TM7: Met270 (HP)
5UIG [252]	5-Amino-N-[(2-methoxyphenyl)methyl]-2-(3-methylphenyl)-2H-1,2,3-triazole-4-carboximidamide (antagonist)	Extracellular ATD: -									
		TM1: -	TM2: -	ECL1: -	TM3: Leu85 (HP)	TM4: -	ECL2: Phe168 (AR)	TM5: Met177 (HP)	TM6: Trp246 (HP); Leu249 (HP); His250 (AR)	ECL3: -	TM7: Tyr271 (HP); Ile274 (HP)

(Table 4) contd....

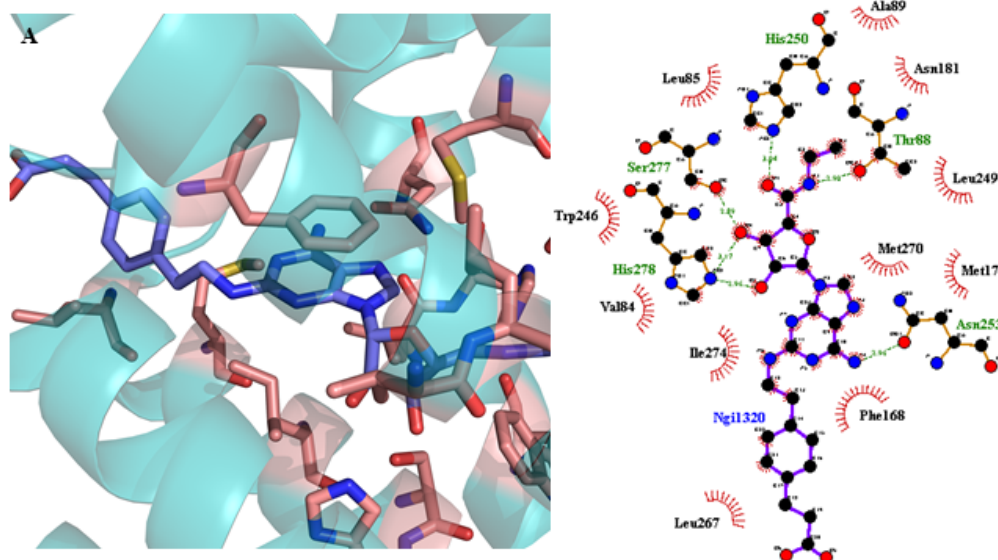
Receptor	Main Ligand(s)/ Binding Partners	Localization of the Interacting Residues on GPCR Structure									
Metabotropic Glutamate Receptor 2 (mGluR₂)											
5CNI [379]	Glutamate (agonist)	Extracellular ATD: Arg57 (VdW); Arg61 (HB); Tyr144 (VdW); Ser145 (HB); Ala166 (HB); Ser167 (VdW); Thr168 (HB); Tyr216 (VdW); Asp295 (HB); Lys377 (VdW)									
		TM1: -	TM2: -	ECL1: -	TM3: -	TM4: -	ECL2: -	TM5: -	TM6: -	ECL3: -	TM7: -
5CNJ [379]	LY2812223 (agonist)	Extracellular ATD: Arg57 (VdW); Arg61 (HB); Ser143 (VdW); Tyr144 (SB); Ser145 (HB); Ala166 (HB); Ser167 (VdW); Thr168 (HB); Tyr216 (VdW); Arg271 (VdW); Ser272 (VdW); Glu273 (VdW); Asp295 (HB); Gly296 (VdW); Lys377 (VdW) – chain A Arg57 (VdW); Arg61 (HB); Ser143 (VdW); Tyr144 (VdW); Ser145 (HB); Ala166 (VdW); Ser167 (VdW); Thr168 (HB); Tyr216 (VdW); Arg271 (VdW); Ser272 (VdW); Glu273 (VdW); Asp295 (HB); Gly296 (VdW); Lys377 (VdW) – chain B									
		TM1: -	TM2: -	ECL1: -	TM3: -	TM4: -	ECL2: -	TM5: -	TM6: -	ECL3: -	TM7: -
Metabotropic Glutamate Receptor 3 (mGluR₃)											
2E4U [380]	Glutamate (agonist)	Extracellular ATD: Arg64 (VdW); Arg68 (HB); Ser149 (VdW); Tyr150 (VdW); Ser151 (HB); Ala172 (VdW); Ser173 (VdW); Thr174 (HB); Tyr222 (VdW); Asp301 (HB); Lys389 (VdW)									
		TM1: -	TM2: -	ECL1: -	TM3: -	TM4: -	ECL2: -	TM5: -	TM6: -	ECL3: -	TM7: -
2E4V [380]	DCG-IV (agonist)	Extracellular ATD: Arg64 (VdW); Arg68 (HB); Ser149 (VdW); Tyr150 (VdW); Ser151 (HB); Ala172 (VdW); Ser173 (VdW); Thr174 (HB); Tyr222 (VdW); Arg277 (VdW); Ser278 (HB); Asp301 (HB); Gly302 (VdW); Lys389 (VdW)									
		TM1: -	TM2: -	ECL1: -	TM3: -	TM4: -	ECL2: -	TM5: -	TM6: -	ECL3: -	TM7: -
2E4W [380]	1S,3S-ACPD (agonist)	Extracellular ATD: Arg64 (VdW); Arg68 (HB); Ser149 (VdW); Tyr150 (VdW); Ser151 (HB); Ala172 (HB); Ser173 (VdW); Thr174 (HB); Tyr222 (VdW); Asp301 (HB); Gly302 (VdW); Lys389 (VdW)									
		TM1: -	TM2: -	ECL1: -	TM3: -	TM4: -	ECL2: -	TM5: -	TM6: -	ECL3: -	TM7: -
2E4X [380]	1S,3R-ACPD (agonist)	Extracellular ATD: Arg64 (VdW); Arg68 (HB); Ser149 (VdW); Tyr150 (VdW); Ser151 (HB); Ala172 (HB); Ser173 (VdW); Thr174 (HB); Tyr222 (VdW); Asp301 (HB); Gly302 (VdW); Lys389 (VdW)									
		TM1: -	TM2: -	ECL1: -	TM3: -	TM4: -	ECL2: -	TM5: -	TM6: -	ECL3: -	TM7: -
2E4Y [380]	2R,4R-APDC (agonist)	Extracellular ATD: Arg64 (SB); Arg68 (HB); Ser149 (HB); Tyr150 (VdW); Ser151 (HB); Ala172 (HB); Ser173 (VdW); Thr174 (VdW); Tyr222 (VdW); Asp301 (HB) – chain A Arg64 (HB); Arg68 (HB); Tyr150 (VdW); Ser151 (HB); Ala172 (VdW); Ser173 (VdW); Thr174 (HB); Tyr222 (SB); Asp301 (HB); Gly302 (VdW); Lys389 (VdW) – chain B									
		TM1: -	TM2: -	ECL1: -	TM3: -	TM4: -	ECL2: -	TM5: -	TM6: -	ECL3: -	TM7: -
5CNK [379]	Glutamate (agonist)	Extracellular ATD: Arg64 (VdW); Arg68 (HB); Ser149 (VdW); Tyr150 (VdW); Ser151 (HB); Ala172 (HB); Thr174 (VdW); Tyr222 (VdW); Asp301 (HB); Lys389 (HB) – chain A Arg64 (VdW); Arg68 (HB); Ser149 (VdW); Tyr150 (VdW); Ser151 (HB); Ala172 (HB); Thr174 (VdW); Tyr222 (VdW); Asp301 (HB); Lys389 (HB) – chain B									
		TM1: -	TM2: -	ECL1: -	TM3: -	TM4: -	ECL2: -	TM5: -	TM6: -	ECL3: -	TM7: -
5CNM [379]	LY2812223 (agonist)	Extracellular ATD: Arg64 (VdW); Arg68 (HB); Tyr150 (VdW); Ser151 (HB); Ala172 (HB); Ser173 (VdW); Thr174 (VdW); Lys389 (HB)									
		TM1: -	TM2: -	ECL1: -	TM3: -	TM4: -	ECL2: -	TM5: -	TM6: -	ECL3: -	TM7: -
Metabotropic Glutamate Receptor 5 (mGluR₅)											
4009 [381]	Mavoglurant (NAM)	Extracellular ATD: -									
		TM1: -	TM2: Ile625 (HP)	ECL1: -	TM3: Ile651 (HP); Pro655 (HP); Tyr659 (HP)	TM4: Leu744 (HP); Asn747 (HB)	ECL2: -	TM5: -	TM6: -	ECL3: -	TM7: Ser805 (2HB); Val806 (HP); Ser809 (HB); Ala810 (HP)
5CGC [382]	3-Chloro-4-fluoro-5-[6-(1H-pyrazol-1-yl)pyrimidin-4-yl]benzotrile (NAM)	Extracellular ATD: -									
		TM1: -	TM2: -	ECL1: -	TM3: Ile651 (HP); Pro655 (HP)	TM4: -	ECL2: -	TM5: Leu744 (HP)	TM6: Trp785 (AR); Phe788 (HP)	ECL3: -	TM7: Val806 (HP); Ser809 (HB); Ala810 (HP)

(Table 4) contd....

Receptor	Main Ligand(s)/ Binding Partners	Localization of the Interacting Residues on GPCR Structure									
Metabotropic Glutamate Receptor 5 (mGluR₅)											
5CGD [382]	HTL14242 (NAM)	Extracellular ATD: -									
		TM1: -	TM2: Ile625 (HP)	ECL1: -	TM3: Ile651 (HP); Pro655 (HP)	TM4: -	ECL2: -	TM5: Leu744 (HP)	TM6: Trp785 (HP); Phe788 (AR)	ECL3: -	TM7: Val806 (HP); Ser809 (HB)

Among all the aforementioned GPCR-derived therapeutic targets of PD, the X-ray structure of five GPCRs (D₃R, A_{2A}AR, mGluR₂, mGluR₃, and mGluR₅) has been determined in complex with small-molecule modulators. Relevant interactions were retrieved from the GPCRdb [575] and are divided into Hydrogen Bonds (HB), Salt Bridges (SB), Hydrophobic (HP), and Aromatic interactions (AR). For mGluR₂ and mGluR₃, the information related to ligand interaction was gathered using PDBMOTIF [576], an online tool designed to analyse protein-ligand interaction by detecting Hydrogen Bonds (HB) and Van der Waals (VdW) interactions.

Complex: A_{2A}AR – CGS21680 (agonist)



Complex: A_{2A}AR – 5'-(N-Ethylcarboxamido)adenosine (agonist)

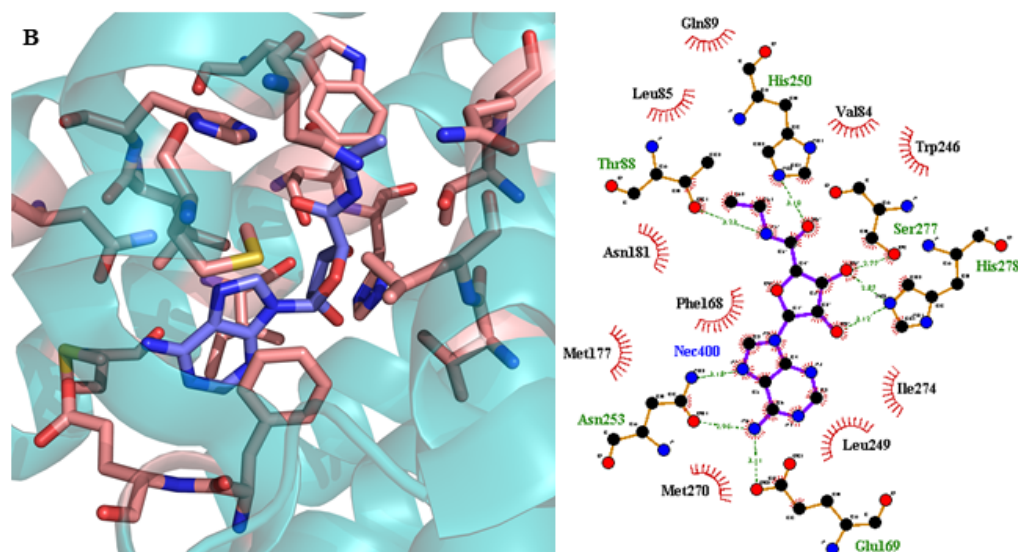


Fig. (4). Structural detail of the interaction between A_{2A}AR and agonists. A) Complex between A_{2A}AR and CGS21680 (PDBid 4UHR [245]); B) Complex between A_{2A}AR and 5'-(N-ethylcarboxamido)adenosine (PDBid 5G53 [246]).

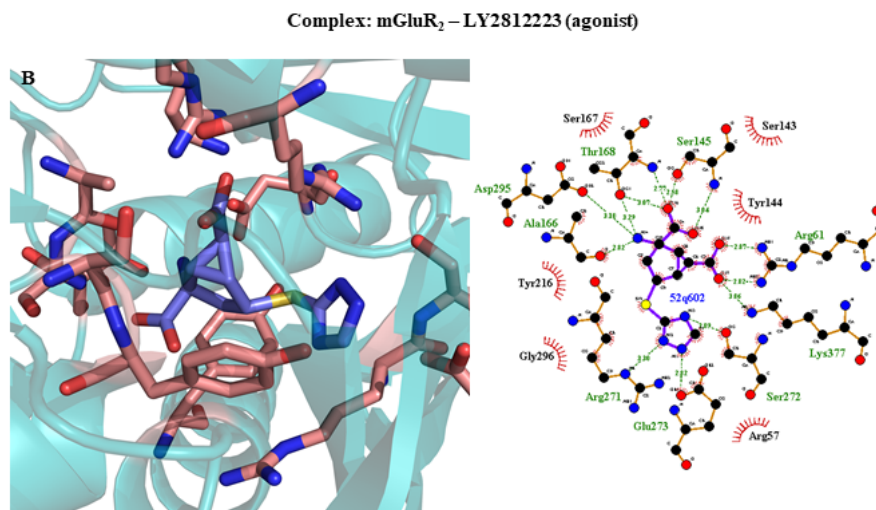


Fig. (6). Structural detail of the interaction between mGluR₂ and orthosteric agonists. A) Complex between mGluR₂ and glutamate (PDBid 5CNI [379]); B) Complex between mGluR₂ and LY2812223 (PDBid 5CNJ [379]).

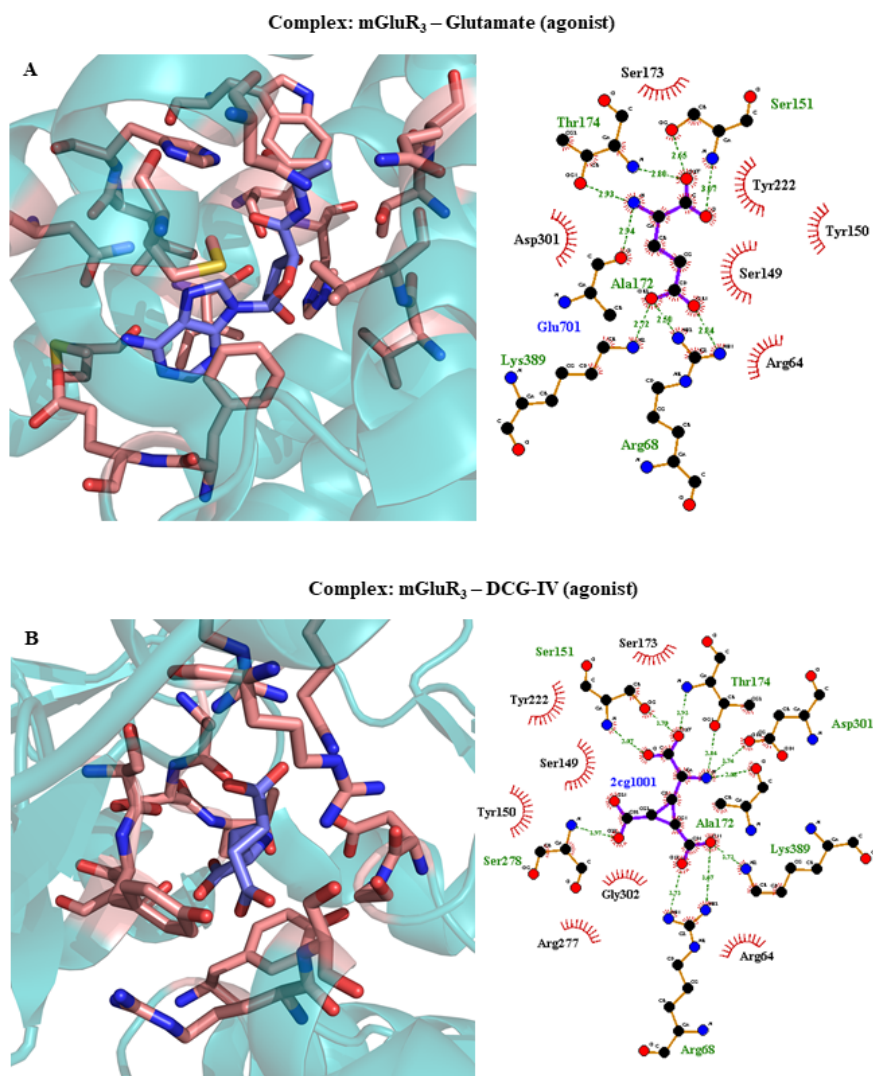


Fig. (7). Structural detail of the interaction between mGluR₃ and orthosteric agonists. A) Complex between mGluR₃ and glutamate (PDBid 2E4U [380]); B) Complex between mGluR₃ and DCG-IV (PDBid 2E4V [380]).

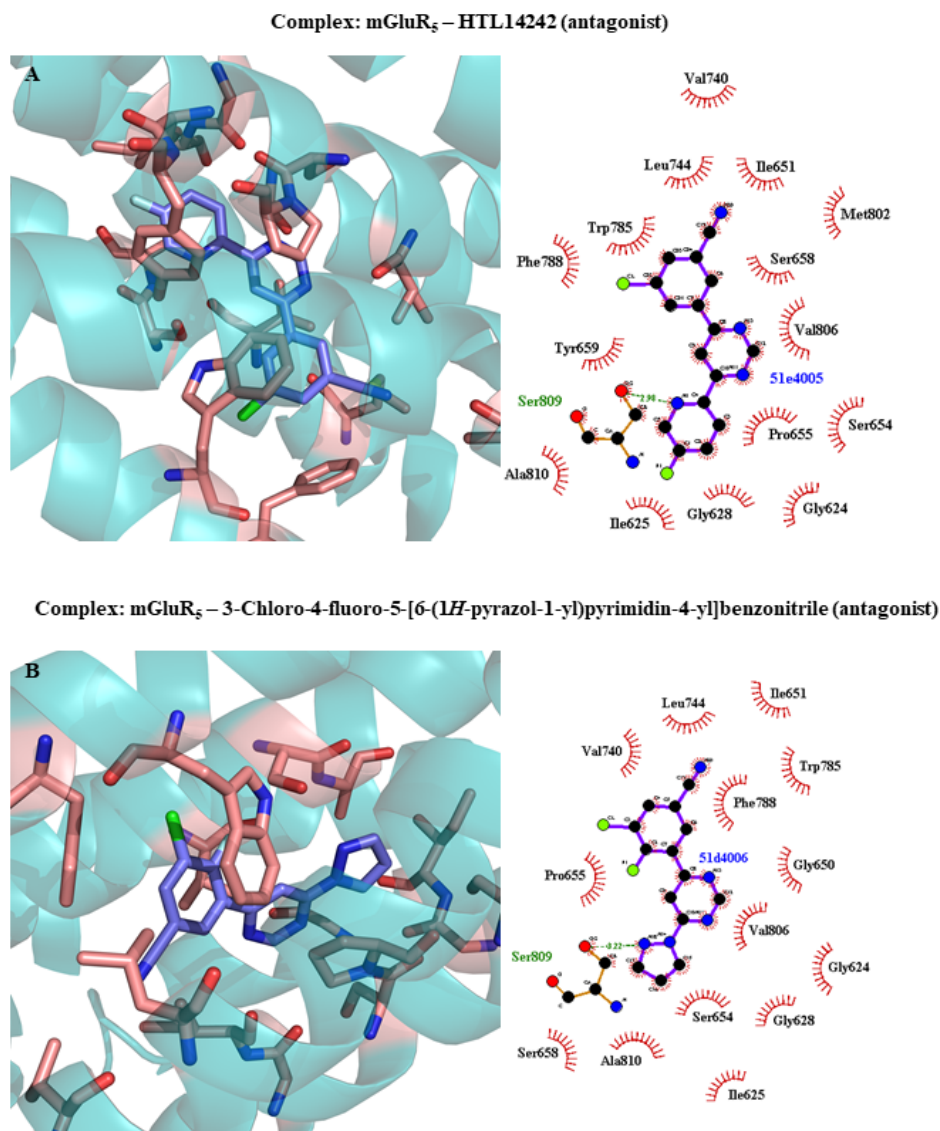


Fig. (8). Structural detail of the interaction between mGluR₅ and antagonists/NAM. A) Complex between mGluR₅ and HTL14242 (PDBid 5CGD [382]); B) Complex between mGluR₂ and 3-chloro-4-fluoro-5-[6-(1H-pyrazol-1-yl)pyrimidin-4-yl]benzotrile (PDBid 5CGC [382]).

fluoro-5-[6-(1H-pyrazole-1-yl)pyrimidin-4-yl]benzotrile). In TM3, the mGluR₅ NAM makes hydrophobic interactions with Ile651 and Pro655. The structural details of the binding modes of mGluR₂ orthosteric agonists are represented in Fig. (6A and 6B). Similarly, the mGluR₃ orthosteric agonists interact with residues located on the extracellular ATD. The mGluR₃ agonists make hydrogen bond and van der Waals interactions with Arg64, Arg68, Tyr150, Ser151, Ala172, Ser173, Thr174, and Lys389 residues. The structural details of the binding pose of glutamate (Fig. 7A) and DCG-IV (Fig. 7B) in complex with mGluR₃ are represented. While mGluR₂ and mGluR₃ orthosteric agonists interact with their receptors on extracellular ATD, the mGluR₅ NAM binds exclusively to the TM domains (TM2, TM3, TM4, and TM7 domains for mavoglurant; TM3, TM5, TM6, and TM7 domains for HTL14242 and 3-chloro-4-fluoro-5-[6-(1H-pyrazole-1-yl)pyrimidin-4-yl]benzotrile). In TM3, the mGluR₅ NAM makes hydrophobic interactions with Ile651 and Pro655.

Additionally, in TM7 domains, the mGluR₅ NAM makes hydrophobic interactions with Val806 and hydrogen bond interactions with Ser809. A representation of the binding conformation of HTL14242 and 3-chloro-4-fluoro-5-[6-(1H-pyrazol-1-yl)pyrimidin-4-yl]benzotrile is shown in Fig. (8A and 8B), respectively.

CONCLUSION

GPCRs are practically ubiquitous proteins and drug targets, making them of high interest when dealing with a wide range of emerging diseases as PD. Drug discovery efforts targeting alternative therapeutic targets have been made to reduce the occurrence of these side effects. In fact, the pharmacological activation/inhibition of all the aforementioned GPCR subtypes with small-molecule drug candidates may reduce L-DOPA induced dyskinesias. This raises the need

for novel and subtype-selective drug candidates useful for PD therapy.

The design of receptor subtype ligands that interact with the orthosteric binding site of GPCRs has proven to be ineffective, specifically for muscarinic acetylcholine receptors and metabotropic glutamate receptors, because of the high homology across binding sites of different GPCR subtypes, leading to a decreased subtype selectivity and specificity and unfavorable side effect profiles. Taking this into account, allosteric modulators are preferable to target subtype specific GPCRs by interacting with a protein region that is both larger and more diverse. Experimentally, these structure-based drug design methodologies have the advantage of understanding drug-GPCR interactions at a molecular level, which is vital for the development of new and reliable pharmacophore models. Nevertheless, the drug design of GPCR modulators based on orthosteric or allosteric binding site requires prior structural data information, which is scarce for the majority of GPCRs. In fact, future drugs acting on GPCRs are likely to rely on ligand-based computational methodologies to tackle missing structural data information. Overall, these *in silico* approaches have been extremely relevant in early stages of drug discovery, particularly in lead optimization of drug candidates, in order to determine the most favorable molecular modifications for the identification of more potent and subtype-selective GPCR modulators targeting PD. Another aspect of extreme importance in drug discovery process of GPCR modulators resides in their pharmacokinetic and toxicological profile since usually, drug candidates with a favorable pharmacodynamic profile fail to advance at late stages of drug discovery process due to their unfavorable pharmacokinetic properties and toxicity. A drug design strategy that perfectly combines favorable pharmacodynamic properties of small molecule GPCR modulators with encouraging pharmacokinetic properties (*e.g.* blood-brain barrier permeability, brain exposure, *etc*) is crucial for the development of promising antiparkinsonian agents with potential clinical efficacy.

LIST OF ABBREVIATIONS

5-HTR	=	5-HydroxyTryptamine Receptor	APJR	=	Apelin Receptor
6-OHDA	=	6-HydroxyDopamine	AR	=	Adenosine Receptor
AADC	=	Aromatic L-Amino acid DeCarboxylase	ATD	=	Amino-Terminal Domain
AC	=	Adenylyl Cyclase	ATR	=	AngioTensin II Receptor
AD	=	Alzheimer's Disease	AutoDock	=	Automated Docking
ADGRG1	=	ADhesion G-protein coupled Receptor G1	β AR	=	β -Adrenergic Receptor
ADGRL3	=	ADhesion G-protein coupled Receptor L3	BBB	=	Blood-Brain Barrier
ADHD	=	Attention Deficit Hyperactivity Disorder	CAChe	=	Computer-Aided Chemistry consulting
AMPA	=	α -Amino-3-hydroxy-5-Methyl-4-isoxazolePropionic Acid	cAMP	=	cyclic Adenosine MonoPhosphate
ANN	=	Artificial Neural Networks	CADD	=	Computer-Assisted Drug Design
APEX-3D	=	Activity Prediction EXpert system-3D	CBR	=	Cannabinoid Receptor
			CCR	=	CC Chemokine Receptor
			CDocker	=	CHARMm-based Docker
			cGMP	=	cyclic Guanosine MonoPhosphate
			CNS	=	Central Nervous System
			CoMFA	=	Comparative Molecular Field Analysis
			CoMSIA	=	Comparative Molecular Similarity Index Analysis
			COMT	=	Catechol-O-MethylTransferase
			CRF	=	Corticotropin Releasing Factor
			CRFR	=	Corticotropin Releasing Factor Receptor
			CRLR	=	Calcitonin Receptor-Like Receptor
			CXCR	=	CXC Chemokine Receptor
			CV	=	Cross-Validation
			DAG	=	DiAcylGlycerol
			DISCO	=	DIcrete Surface Charge Optimization
			DOR	=	δ -Opioid Receptor
			DR	=	Dopamine Receptor
			ECL	=	ExtraCellular Loop
			ETR	=	EndoThelin Receptor
			FFAR	=	Free Fatty Acid Receptor
			FLAP	=	Fingerprints for Ligands And Proteins
			FlexiDock	=	Flexible Docking
			FLRT2	=	Fibronectin Leucin-Rich Transmembrane protein 2
			FN3	=	FibroNectin type III domain
			FSH	=	Follicle-Stimulating Hormone
			FSHR	=	Follicle-Stimulating Hormone Receptor
			GABA	=	γ -AminoButyric Acid
			GABAR	=	γ -AminoButyric Acid Receptor

GALAHAD	=	Genetic Algorithm with Linear Assignment of Hypermolecular Alignment of Database	N/OFQR	=	Nociceptin/Orphanin FQ Receptor
GDP	=	Guanosine DiPhosphate	NAM	=	Negative Allosteric Modulator
GFA	=	Genetic Function Approximation	NMDA	=	<i>N</i> -Methyl-D-Aspartate
GLIDE	=	Grid-based LIgand-Docking with Energetics	NMR	=	Nuclear Magnetic Resonance
GLPR	=	Glucagon-Like Peptide Receptor	NTSR	=	Neurotensin Receptor
GOLD	=	Genetic Optimization for Ligand Docking	OXR	=	OreXin Receptor
GOLPE	=	General Optimal Linear PLS Estimation	P2YR	=	Purinergic P2Y Receptor
GPCR	=	G-Protein Coupled Receptors	PAM	=	Positive Allosteric Modulator
GPCRdb	=	G-Protein Coupled Receptors database	PAR	=	Protease-Activated Receptor
GRK	=	G-protein coupled Receptor Kinase	PD	=	Parkinson's Disease
GTP	=	Guanosine TriPhosphate	PHASE	=	PHarmacophore Alignment and Scoring Engine
HINT	=	Hydrophobic INteractions	PKA	=	Protein Kinase A
HQSAR	=	Hologram Quantitative Structure-Activity Relationship	PKC	=	Protein Kinase C
HR	=	Histamine Receptor	PLC	=	PhosphoLipase C
ICL	=	IntraCellular Loop	PLS	=	Partial Least Square
ICM	=	Internal Coordinate Mechanics	PNS	=	Peripheral Nervous System
iGluR	=	Ionotropic Glutamate Receptor	PTHR	=	ParaThyroid Hormone-related peptide Receptor
IP ₃	=	Inositol-1,4,5-triPhosphate	PTHrP	=	ParaThyroid Hormone-related Peptide
JAWM	=	Just Add Water Molecules	QM/MM	=	Quantum Mechanics/Molecular Mechanics
KA	=	Kainic Acid	QSAR	=	Quantitative Structure-Activity Relationship
KOR	=	κ -Opioid Receptor	RAMP	=	Receptor-Activity Modifying Protein
LDA	=	Linear Discriminant Analysis	REM	=	Rapid Eye Movement
LibDock	=	Library Docking	RGS	=	Regulators of G-protein Signaling
LPAR	=	LysoPhosphatidic Acid Receptor	RHO	=	Rhodopsin
L-DOPA	=	L-3,4-Dihydroxyphenylalanine LevoDOPA	S1PR	=	Sphingosine-1-Phosphate Receptor
mAChR	=	Muscarinic AcetylCholine Receptor	SAR	=	Structure-Activity Relationships
MAO-B	=	MonoAmino Oxidase-B	Smo	=	Smoothened Receptor
MD	=	Molecular Dynamics	SNc	=	Substantia Nigra pars compacta
mGluR	=	Metabotropic Glutamate Receptor	SNr	=	Substantia Nigra pars reticulata
ML	=	Machine Learning	STN	=	SubThalamic Nucleus
MLR	=	Multiple Linear Regression	SVM	=	Support Vector Machines
MOE	=	Molecular Operating Environment	TM	=	TransMembrane
MOR	=	μ -Opioid Receptor	TSHR	=	Thyroid-Stimulating Hormone Receptor
MPTP	=	1-Methyl-4-Phenyl-1,2,3,6-TetrahydroPyridine	Unc5D	=	Unc5D guidance receptor
MVD	=	Molegro Virtual Docker	US28	=	Cytomegalovirus-encoded chemokine Receptor
			VFT	=	Venus FlyTrap
			VIPR	=	Vasoactive Intestinal Peptide Receptor

VR = Vasopressin Receptor
 wPMF = water Potential of Mean Forces
 YADA = Yet Another Docking Approach

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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