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Review Article

# Dementia, Dopamine and Medicinal Chemistry Drug Design

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## Abstract

Neurodegenerative and neurological diseases that afflict those in mid to late life have steadily become a common cause of mortality worldwide as elderly populations have continued to grow. Epidemiological reviews of these neurodegenerative diseases show that associated deaths have increased within the last 25 years. Evidence supports neurodegenerative diseases, especially Alzheimer's Disease (AD) and Parkinson's Disease (PD) are linked to dementia symptoms in afflicted patients. Although AD and PD have different etiologies, and have some pathological differences, they also share similar neurodegenerative sequela, such as glial activation and dopamine (DA) dysregulation. The aim of this review is to discuss basic AD and PD pathophysiology and the role of DA regulation in these two neurodegenerative diseases. Currently available and novel approaches for the treatment of AD and PD will be discussed, focusing on those that modulate DA. Finally, the therapeutic potential of ligands for the translocator protein (TSPO) will be considered as they may be a beneficial approach for treating AD and PD.

**Keywords:** neurodegeneration, Alzheimer's disease, Parkinson's disease, translocator protein, neuroinflammation

## Introduction

Neurodegenerative and neurological diseases that afflict those in mid to late life have steadily become a common cause of mortality worldwide as elderly populations have continued to grow. Epidemiological reviews of these neurodegenerative diseases show that associated deaths have increased within the last 25 years, having increased worldwide by more than 35%.[1,2] Evidence supports neurodegenerative diseases, especially Alzheimer's Disease (AD) and Parkinson's Disease (PD) are linked to dementia symptoms in afflicted patients.[3,4] Although AD and PD have different etiologies, and have some pathological differences, they also share similar neurodegenerative sequela, such as glial activation and DA dysregulation.[3,5,6] Glial cell activation within neurodegenerative diseases is linked to increased neuroinflammation, decreased myelination and white matter volume, as well as enhanced neurological and cognitive deficits.[3,5] As healthy neurons succumb to disease, neurotransmitter release becomes dysregulated and less or more of a

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neurotransmitter is present within the brain.[3,5] With regard to both AD and PD, this is especially true of the neurotransmitter DA, and both diseases are linked to decreased DA levels.[3,5] The aim of this review is to discuss basic AD and PD pathophysiology and the role of DA regulation in these neurodegenerative diseases. This paper will then discuss current pharmacotherapies for AD and PD that focuses on DA regulation. Novel medicinal chemistry approaches for central nervous system DA modulation, as well as multi-target ligands, which may be therapeutically advantageous in AD and PD treatment, are also discussed. Finally, consideration of the translocator protein (TSPO), a protein found within immune cells, will be given as a potential approach for treating aberrant glial cell activation and neuroinflammation. Not discussed within this review are novel gene therapy related approaches as these exceed the scope of this focused review. For further review over AD and PD related gene therapy, please see reviews by Tedeschi and colleagues[7] and Shalaby and El-Agnaf[8], respectively. Likewise, AD- or PD-specific protein therapeutic targets will not be covered. For AD- and PD-specific protein therapeutic targets, please see the reviews by Wang and colleagues[9] and Jankovic and Tan[10], respectively.

## Alzheimer's Disease (AD)

AD is the most common neurodegenerative disease that contributes to approximately 60-80% of all dementia cases globally, impacting an estimated 55 million people worldwide, and with forecasts projecting 78 million being affected by the year 2030.[11,12] AD is distinguished by the extracellular accumulation of β-amyloid (βA) plaques and intracellular aggregation of neurofibrillary tangles (NFTs).[13] Clinical presentations of AD will typically follow a gradual decline in patient memory and cognition, often exhibiting amnesia of recent episodic memories in early AD.[11] Patients with late-stage AD will continue to exhibit amnesia, though significantly more severe than in early stages, alongside declining cognitive function that affects communication, behavior, and executive motor function.[14]

AD is commonly associated with the elderly, as approximately 90-95% of AD patients are over the age of 65.[15] However, early-onset AD can affect patients younger than 65, as early as 40 years old, and is associated with a familial history of AD.[13] This familial contribution is likely due to autosomal dominant inheritance of mutations at presenilin 1, presenilin 2, or amyloid precursor protein (*APP*), which are present in 13% of patients diagnosed with early-onset AD.[13,16] A family history of AD can contribute to patient risk of both early-onset and sporadic AD, with up to 3.5-fold increases in risk when first-degree relatives are positively diagnosed with AD.[17] The risk of sporadic development of AD also has proposed genetic contributions with allelic variations of the polymorphic apolipoprotein E increasing the risk of dementia by 25% among AD patients.[18,19]

The current prevalent consensus of AD pathogenesis is the amyloid hypothesis, which suggests that the imbalanced accumulation of βA plaques and resulting aggregation of NFTs result in AD development. While the normal physiological function is not well understood, the cleavage of the transmembrane *APP* via proteolytic cleavage enzymes β-secretase

and γ-secretase, which includes presenilin, produce insoluble βA peptides.[20,21] These peptides are undetectable in the brains of healthy young adults. However, increased buildup occurs in older individuals because of pathological aging, those experiencing mild cognitive impairment, and those with a familial history of AD.[21] In these patients βA polymerizes, producing amyloid fibrils that aggregate into toxic amyloid plaques. This aggregation activates kinases such as Glycogen Synthase kinase-3 β and cyclin-dependent kinase 5 which results in the hyperphosphorylation of τ protein.[22-25] This hyperphosphorylation of τ leads to oligomerization, resulting in tubule subunit destabilization that results in τ filaments, which are the components that aggregate into NFTs.[3]

The aggregation of these β-amyloid plaques and NFTs result in synaptic damage, impeded neuronal signaling, oxidative stress, and neuroinflammation (Fig. 1). Factors such as increased release of inflammatory cytokines and chemokines,

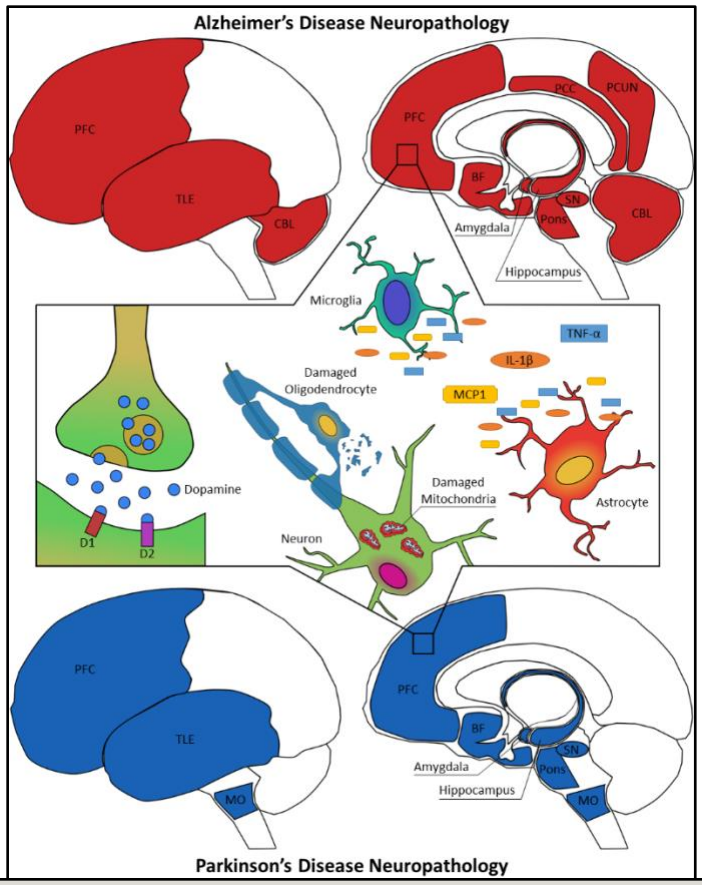


**Figure 1.** Neuropathological distribution of brain regions affected by Alzheimer's disease (red) or Parkinson's disease (blue). Such regions experience heavy neurodegeneration and inflammation with glial cells expressing various inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and chemokines such as monocyte chemoattractant protein 1 (MCP1). Such inflammation contributes to an extracellular environment that lends itself to neuronal damage, mitochondrial dysfunction, oligodendrocyte dysfunction, demyelination, and altered dopamine signaling. D1 – DA 1 receptors, D2 – DA 2 receptors, PFC – prefrontal cortex, TLE – temporal lobe, CBL – cerebellum, MO – medulla oblongata, BF – basal forebrain, PCC – posterior cingulate cortex, PCUN – precuneus, SN – substantia nigra.

neuronal mitochondrial damage, direct neuronal stress, oligodendrocyte damage, along with the direct activation of toll-like receptors by βA plaques, result in glial activation[3] with activated astrocytes and microglia being observed in higher densities near senile plaques.[26-28] In normal physiological conditions, glial cells eliminate these β-amyloid oligomers and NFT fibrils. However, patients that develop AD have reduced glial clearance capacity due to pathological aging, an overabundance of βA plaques and NFTs, and increased cytokine concentrations that downregulate the expression of βA-phagocytosis receptors.[3] Along with the neurodegenerative pathology associated with AD, demyelination, and loss of oligodendrocyte function may contribute to white matter degeneration in AD and may be the result of βA toxicity and AD associated inflammatory stress. [29-31] Contributions from phosphorylated τ may also result in AD associated inflammation and demyelination due to the formation of NFTs in both astrocytes and oligodendrocytes that hinder function.[32,33]

While the amyloid hypothesis of AD pathogenesis maintains widespread acceptance, shifts in the conceptualization of AD onset suggest similar changes for currently homogenous therapeutic approaches. Multiple phase 3 clinical trials have found repeated failure with such approaches attempting to ameliorate cognitive decline in patients with AD associated dementia.[34] Indeed, increasing understanding of the diverse pathology of AD and its vast network of interactive components downstream of amyloid aggregation strongly suggests that future therapeutic development should focus on potential targets other than just amyloid aggregation alone. Thus, novel approaches, such as selective alterations that occur in neurochemical signaling within the AD brain are attractive leads that may provide potential therapeutic benefits.

**Parkinson's Disease (PD)**

Following AD in terms of prevalence is PD with an estimated number of 930,000 patients 45 years and older in the United States in 2020.[4] Unlike AD, where cognitive decline and dementias form the basis of clinical diagnosis, PD is based primarily on the loss of motor function with features such as resting tremors and bradykinesia (slow movements or freezing). However, non-motor components such as behavioral changes and anosmia (loss of smell) can develop years prior to the exhibition of impaired motor function, with symptoms such as autonomic dysfunction and impaired cognition associated with dementias being exhibited later in disease progression.[5,6] Instances of PD are considered sporadic, with genetic mutations and environmental factors being associated with PD etiology.[35] Current neuropathogenic mechanisms of PD include genomic factors, epigenetic changes, toxic factors, oxidative stress, neuroinflammatory reactions, and ubiquitin-proteasome system dysfunction; providing sufficient detail for the vast array of these mechanisms extends beyond the scope of this review and further review of Cacabelos and Simon et al. is suggested. [5,36]

Motor dysfunction associated with PD results from the selective loss of dopaminergic neurons within the substantia nigra pars compacta. It is hallmarked by the aggregation of α-synuclein that forms Lewy bodies. While the normal physiological function of α-synuclein is not well understood, it is thought to regulate synaptic vesicle trafficking and subsequent neurotransmitter release.[37-39] Conformational changes and protein misfolding of α-synuclein result in abnormal

aggregation that forms Lewy bodies.[10,37] Factors that influence α-synuclein misfolding include oxidative stress, impaired protein clearance, mitochondrial dysfunction, and neuroinflammation (Fig. 1), all of which can contribute further to PD-related neurodegeneration.[10] Neurodegeneration and promoting factors also contribute to glial cell activation, particularly astrocytes, that contribute further to PD pathology due to the release of neurotoxic chemokines and cytokines such as tumor necrosis factor-α and interleukin-1β.[40-42] Additionally, pathological α-synuclein contributes to the formation of A1 astrocytes, a neurotoxic subtype that has been observed to accumulate in post-mortem PD brains and is capable of inducing neuronal cell death both *in vitro* and *in vivo.* [42-44]
Oligodendrocytes have also been observed to accumulate α-synuclein in post-mortem PD brains and may contribute to hindered oligodendrocyte function and demyelination, likely contributing further to neuronal degeneration observed in PD pathology.[43,45]

Non-motor morbidities comprise an essential component of PD clinical presentation, despite not being present alongside motor symptoms in the early stages of the disease. Indeed, PD exhibits comorbidities with dementia in over 25% of patients and depression in over 30% of patients. [46] Mild cognitive impairment is found in approximately 20% of patients upon PD diagnosis, though clinical profiles of this early impairment is commonly non-amnestic and single-domain. [47-48]

PD-associated dementia manifests late in patients and involves impairment of more than one cognitive domain, unlike early mild cognitive impairment. By the time PD-associated dementia is diagnosed, it is often accompanied by autonomic dysfunctions, severe motor disorders, and shifts in behavior.[47] It is observed that various regions associated with motor function, cognitive processes, and emotion experience PD neurodegeneration, though no particular sequence has been determined regarding a proposed order in which brain regions experience this neurodegeneration.[49]

Clinical trials aiming to improve patient quality of life have shown continued success with the recent approvals by the FDA of therapeutics providing symptomatic relief, though treatment of PD associated dementia remains a prominent challenge yet to be overcome with ongoing clinical trials.[50] Promise with current preclinical strategies support the potential to treat PD associated dementia with augmentation of neurotransmitter deficits with the use of acetylcholinesterase inhibitors, glutamatergic agents, and DA agonists.[51]

## Dopaminergic System

DA is a catecholamine neurotransmitter synthesized from the amino acid tyrosine. Five different DA receptors ($D_1$, $D_2$, $D_3$, $D_4$, and $D_5$) are known, are part of the G-protein-coupled receptor family, and produce both stimulatory and inhibitory effects.[52] Despite the characterization of these five DA receptors, *in vitro* and *in vivo* studies using selective pharmacological probes indicate that these receptors can be functionally separated into two distinct subgroups ($D_1$-like and $D_2$-like). $D_1$ receptors ($D_1$, $D_5$) are coupled to $G_S$ protein and stimulate cAMP release.[53,54] Meanwhile, $D_2$-like ($D_2$, $D_3$, $D_4$) are $G_i$ protein coupled and inhibit cAMP.[53,54] The ventral tegmental area (VTA) and substantia nigra (SN) are two very important sources of DA in the brain.[53,55-57] The VTA projects to the nucleus accumbens (NA), amygdala prefrontal cortex (PFC), and hippocampus giving rise to the mesolimbic

DA pathways. Dopaminergic signaling along the mesolimbic pathways plays an important role in learning and memory.[55,58] The hippocampus and VTA form a functional loop in which novelty-dependent signals results in DA release within the hippocampus. DA release in the hippocampus enhances the neuronal processes associated with memory formation and learning; thus, DA plays an important role in memory encoding.[59] DA release within the NA is linked to purposive behaviors (i.e., orientation), incentive salience (i.e., wanting), as well as motivation, and the NA can mediate signaling to limbic and motor systems.[60-62] The SN is connected to the caudate and putamen forming the nigrostriatal pathway.[58,63] Dopaminergic signaling along the nigrostriatal pathway has been found to signal whether a voluntary movement should be commenced or halted. DA signaling pathways seem to play an important role in two of the most common neurodegenerative diseases, AD and PD.

## Dopamine Relevance in Alzheimer's Disease

Postmortem analysis of AD brain tissue provided initial evidence suggesting disruptions in dopaminergic pathways. The radiolabeled ligand, [$^{125}$I] epidepride, binds with high affinity and specificity to central $D_2$-like receptors. [64,65] Receptor autography with [$^{125}$I] epidepride was employed to measure $D_2$ receptors within the hippocampus and amygdala of AD-patient brains as well as brains collected postmortem from non-AD individuals. Compared to brains taken from non-AD patients, brains collected from AD patients had a 76% reduction in $D_2$ receptor binding in the hippocampus and a 47% decrease in the amygdala.[66] Bands of highly concentrated $D_2$ receptors were observed in the temporal cortex of non-AD patients [67]. However, these $D_2$ receptor bands were found to be absent in brain tissue taken from postmortem AD patients.[68]

*In vivo* studies are largely consistent with postmortem studies and confirm DA signaling disruptions in living AD patients. A recent meta-analysis of the literature which used 17 studies comparing *in vivo* DA concentration and DA receptor density between living AD patients and healthy controls is supportive of this finding.[68] Most of the studies included in the analysis employed high performance liquid chromatography to measure DA concentration, while positron emission tomography (PET) and single-photon emission computed tomography (SPECT) were used for $D_1$ and $D_2$ receptor quantification. DA concentrations were significantly lower in AD than in healthy controls. The meta-analysis also found that both $D_1$ and $D_2$ receptors were decreased in AD patients compared to healthy controls. However, a decrease in $D_2$ receptor was found to have a higher rank correlation with AD.[69] N-omega-fluoropropyl-2beta-carboxymethoxy-3beta-(4-iodophenyl) tropane (FP-CIT) is an imaging agent that targets the dopamine transporter (DAT), FP-CIT has been shown to be representative of DA uptake. In experiments by Sala and colleagues, FT-CIT was measured using SPECT. AD patients had decreased binding of FP-CIT-SPECT in the ventral striatum, hippocampus, and cingulate cortex (mesolimbic pathway). However, no alterations along the nigrostriatal pathway were observed when AD patients were compared to healthy age-paired volunteers.[70]

As mentioned above, the VTA is heavily innervated by DA neurons and is involved in higher cognitive functions, motivation, and reward. Long-term potentiation (LTP), or a

long duration increase in excitatory synaptic transmission efficacy typically follows brief, high-frequency electrical stimulation delivery. LTP within the hippocampus is a mechanism of synaptic plasticity and is considered to be the neural basis of learning and memory.[71] DA release in the hippocampus enhances LTP.[59] In live humans it can be challenging to record direct electrophysiological LTP measurements, but methods have been developed to measure LTP indirectly. One such method measures LTP-like activity produced by motor-evoked potentials in the dorsal interosseous muscles following repetitive transcranial magnetic stimulation in the motor cortex. In AD patients LTP-like activity was markedly reduced but was rescued following 4-week treatment with $D_2$ receptor agonist, rotigotine.[72] Transgenic animal models are important to better understand AD pathology. In correlation to human studies, transgenic AD animal models have repeatedly shown decreases in LTP.[73-78] A widely used transgenic model of AD is Tg2576, which overexpresses a muted amyloid precursor protein (APP). Mutations in the APP have been found in patients with early-onset familial AD. A recent study using the Tg2576 mice line, found that degeneration of DA neurons in the VTA occurs prior to the appearance of A-B plaque in the hippocampus [79]. Neuronal degeneration in the VTA seems to be responsible for neuropsychiatric symptoms in AD in both human and animal studies.[79,80] However, DA-related therapies have not been employed in animal experiments, which in turn presents an understudied area that may produce impactful insights into AD pathology and novel therapeutic targets.

DA is the rate-limiting precursor for norepinephrine and epinephrine synthesis. Disruptions in DA signaling associated with AD would theoretically produce a chain reaction impacting norepinephrine and epinephrine. This was confirmed in 1981 by Cross and colleagues.[81] They measured levels of the enzyme DA-beta-hydroxylase, which converts DA to norepinephrine, in post-mortem brain tissue. The study focused on three regions (frontal cortex, temporal cortex, and hippocampus) and tissue was analyzed from five different cohorts: healthy control, Alzheimer's disease, multi-infarct dementia, depression, and terminal coma patients. Tissues taken from AD patients displayed significant DA-beta-hydroxylase deficits within all three brain regions when compared to healthy controls. None of the other groups displayed significant alterations in any regions tested.

## Dopamine Relevance in Parkinson's Disease

The role of DA as a CNS neurotransmitter involved in movement was introduced in seminal papers by Carlsson and colleagues in 1957 and 1958.[82,83] Soon after the initial papers, a study of DA in 8 different species was done by Bertler and Rosengren.[84] It was reported that DA was present in all species tested, and DA was heavily localized within the corpus striatum.[84] Inspired by initial DA research, Ehringer & Hornykiewicz set out to investigate DA in the brains of patients that were diagnosed with PD prior to their deaths. [85] They found that the concentrations of DA in the caudate and putamen were extremely reduced.[85] The caudate and putamen received dopaminergic innervations from the SN.[58,63] More recently, Kordower and colleagues, investigated the timeline of DA neuronal degeneration in patients diagnosed with PD 1-27 years prior to death.[86] They measured optical densities of DA innervation in the striatum and stereological estimates of tyrosine hydroxylase-immunoreactivity and melanin-containing neurons. They found that time significantly impacted DA marker

loss within the first 4 years after diagnosis; after 4 years DA markers were completely lost.[86] Another post-mortem study using autoradiography investigated DA dysfunction in the brains of patients diagnosed with PD. In the caudal putamen of PD diagnosed brains, [$^3$H]Mazindol binding to DAT was 75% below controls. DA concentration was 90% lower in PD tissue compared to controls. However, [$^3$H]–raclopride binding to $D_2$ receptors was increased.[87] The increased binding sensitivity of $D_2$ receptors could be a sign of neuronal loss.

These postmortem findings have been validated by *in vivo* imaging studies using positron emission tomography (PET). [$^{11}$C]–raclopride binding was significantly increased in the striatum and cerebellum of PD patients. This suggests that denervation of $D_2$ receptors in early PD results in increased receptor binding sensitivity.[88] SPECT studies have also confirmed markedly decreased DAT activity in the SN but only moderately decreased activity within the VTA.[89-92] Overall, the literature seems to suggest that the differential manifestation of clinical symptoms among neurodegenerative diseases is dependent on the region and the degree of DA receptor loss. The mesolimbic DA pathways are more relevant to cognitive, personality, and mood disturbances which are characteristic of AD. Meanwhile, dopaminergic degeneration along the nigrostriatal pathway is associated with movement disturbances which are characteristic of PD. Within the SN two separate circuits can be identified, ventrolateral SN and medial SN. The ventrolateral area projects to the dorsal putamen and is associated with akinetic symptoms, the medial area projects to the caudate nucleus and is linked to dyskinetic symptoms.

DA replacement has been an important target for pharmacotherapies since the 1960 study by Ehringer and Hornykiewicz.[85] A major caveat lies in the point that DA is not able to cross the blood-brain barrier due to polarity. However, its precursor L-Dopa readily crosses the blood-brain barrier via the large amino acid transporter, and once in the brain, the enzyme DOPA decarboxylase converts L-Dopa into DA.[93] Indeed, administration of L-Dopa is effective at reducing the motor signs and symptoms of PD symptoms by rescuing DA in the brain.[94,95] As a therapeutic, L-Dopa is incredibly effective initially, but within a few years, it produces additional motor disturbances which include abnormal and abrupt movements. It is important to mention that current pharmacotherapies do not delay or prevent the progression of PD, they only serve as symptomatic treatments. Recently, DA agonists have been prescribed either alone or concomitantly with L-Dopa.[96-98] Given that L-Dopa results in fluctuations and dyskinesias in >90% of users within 5-10 years there is an incredible need to develop new pharmacotherapies that are more effective and with fewer side effects.[99] Compounds that directly or indirectly impact DA signaling are promising targets.

## Medicinal Chemistry Approaches to Target Aberrant Dopamine Signaling Related to Dementia

Traditionally, medicinal chemists have effectively employed a single-target approach to drug discovery, relying on the identification of highly selective compounds acting on a single target. However, the etiology of neurodegenerative diseases (AD and PD) encompasses a network of multiple pathways. Thus, the need for poly-pharmacological agents in the treatment of complex disorders becomes apparent.[100] As outlined in the current review DA plays an

important role in the pathogenesis of AD and PD. The neurotransmitter serotonin closely interacts with DA and is also involved in the pathology of AD and PD. Thus, modulation of their levels is viewed as a promising approach for managing them. Kappa Opioid Receptor (KOR) and Translocator Protein (TSPO) related ligands have been found to indirectly impact DA system suggesting their therapeutic potential in the settings of PD and AD.

**Kappa Opioid Receptor (KOR)**

KOR can be found on presynaptic axons of the mesolimbic and nigrostriatal DA pathways. KOR is important for maintaining DA homeostasis and neuroplasticity.[101,102] Acute administration of the KOR agonists U-50488 (Fig. 2) and Salvinorin A have been shown to inhibit DA release in the mesolimbic and nigrostriatal pathways by acting on presynaptic KOR located on DA neurons.[103-107] However, repeated administration of U-50488 leads to increased presynaptic DA release along the mesolimbic and nigrostriatal in response to a DA agonist (amphetamine and cocaine) and $K^+$ stimulation in the NA.[108-111] These studies suggest KOR ligands can be used to restore basal physiological levels of dopamine in dopamine-deficient pathologies.[112] Preclinical research of KOR agonists/antagonists have produced ambivalent results. For example, in olfactory bulbectomized mice U-50488 was found to restore cognitive impairment in the passive avoidance test.[113] On the other hand, Paris et al. showed that U-50488 can also inhibit novel object recognition in mice.[114] Thus, both agonist and antagonist KOR ligands should be evaluated for their effect on symptoms associated with neurodegenerative diseases, such as dementia.

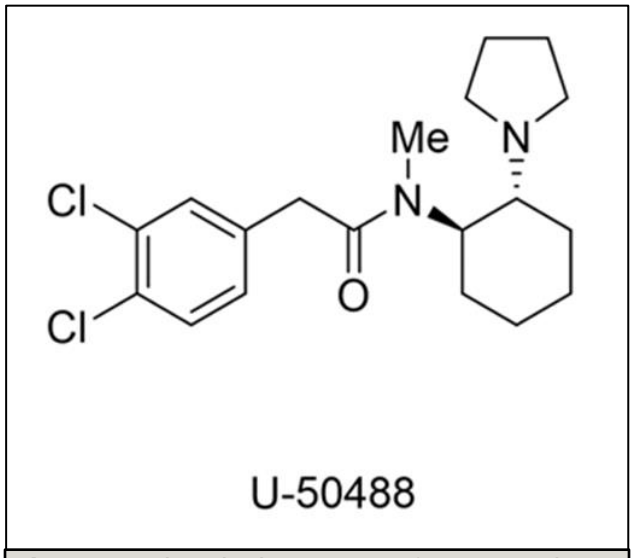


**Figure 2.** Chemical structure of U-50488 (KOR agonist)

Like most of the known opioid ligands, KOR ligands originate from natural sources. For example, Salvinorin A (Fig. 3), derived from *S. divinorum*, is one of the most well-known KOR ligands, widely studied in the field of medicinal chemistry. Salvinorin A is a selective high efficacy agonist of KOR.

Structure-activity relationship studies on this ligand identified key functional groups required for the observed selectivity and activity, including substitution at C2 and ketone group in ring A. Substitution of C2 acetate group with bulkier ethyl of *i*Propyl group abolished the original activity, whereas modifications at this position with thiocyanate **4** or bromoacetate **5** improved the affinity to KOR by 3-fold and 1.2-fold, respectively. The introduction of a H-bond donor in place of the ketone group on ring A **6**, lead to a significant 280-fold reduction in the affinity of Salvinorin A for KOR. It is of particular interest that this modification resulted in a transition from agonist to antagonist activity at KOR.[115]

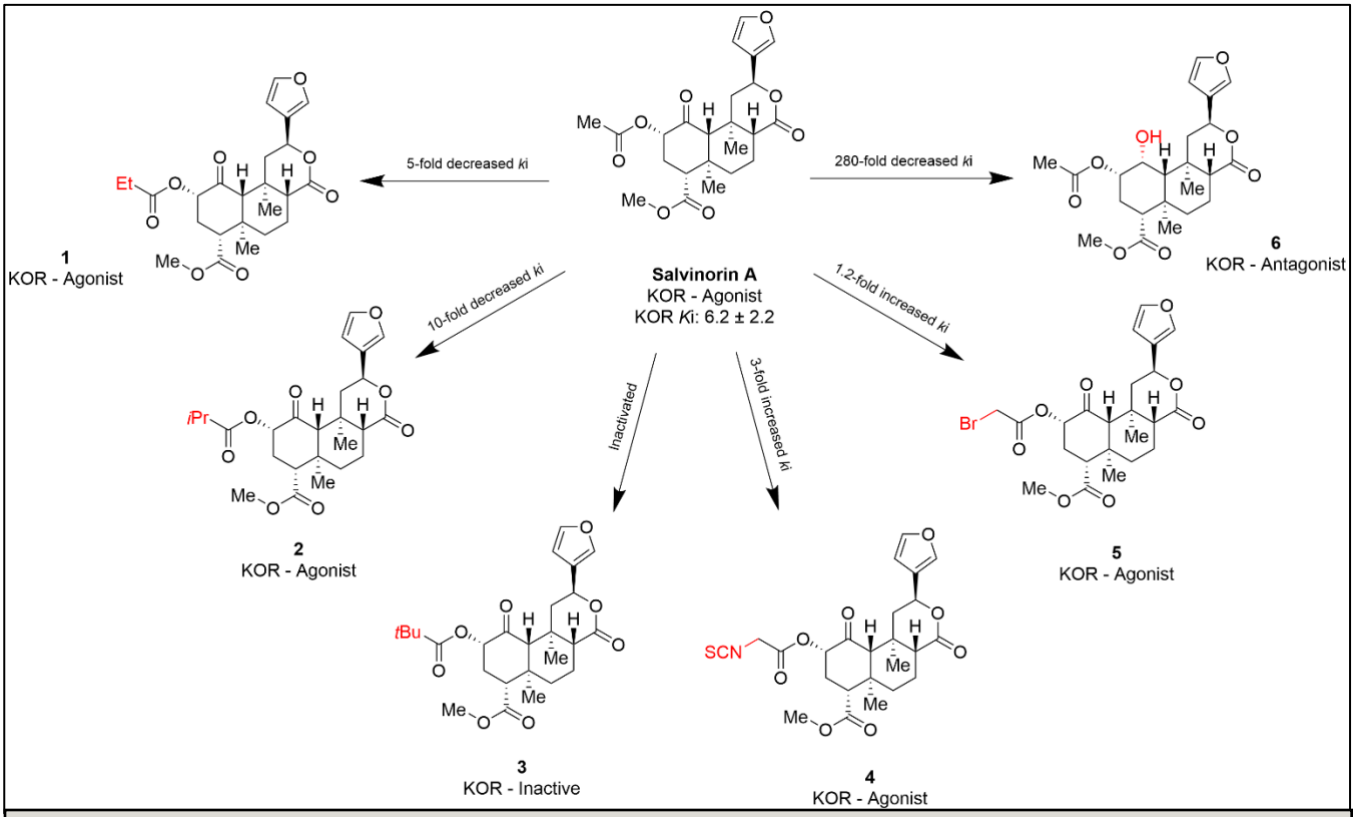


**Figure 3.** Structural modifications of Salvinorin A.

In addition to standard medicinal chemistry approaches, *in silico* screening techniques are widely used to develop novel KOR ligands. In a work carried out by Zheng et al., crystal structure of KOR−JDTic (PDB 4DJH) was used to screen 4.5 million commercially available compounds by using ICM VLS procedure with partial flexibility in the binding pocket.[116] In this work, the authors could identify 11 sub-micromolar hit compounds based on 4 distinct novel chemotypes, a few with antagonistic action with the best $K_i$ = 0.09 μM (**7**) and few with agonistic action with the best $K_i$ = 0.16 μM (**8**) (Fig. 4). Currently, KOR ligand chemotypes are largely limited to morphinans, and non-morphinan natural or semisynthetic chemotypes like diterpenes (e.g. Salvinorin A), and JDTic analogues.[116] Derivatives of these analogues represent KOR ligands differ in degrees of potency, and affinity towards KOR. However, the full understanding of agonist pharmacophore vs antagonist pharmacophore in these chemical classes of KOR ligands is yet to be gained.

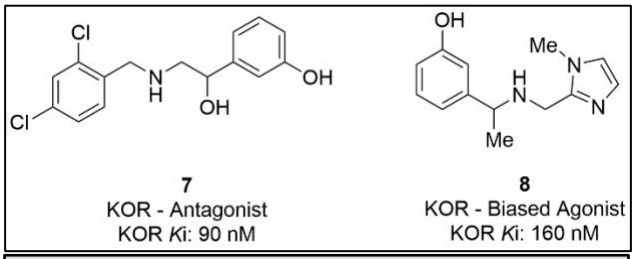


**Figure 4.** Examples of novel KOR antagonist and biased agonist identified by using computational screening techniques.

## Allosteric Modulation of Dopamine $D_1$ Receptor

In a work done by Hao et al., it is demonstrated that the PAM of $D_1$ receptor can be a potential candidate for treatment of

Lewy Body Dementia, a subtype of dementia characterized by abnormal deposition of a protein called alpha-synuclein in nerve cells of the brain, by increasing $D_1$ receptor potency.[117] In this work, LY3154207 (Fig. 4) is introduced as PAM of human $D_1$ receptor with $EC_{50}$ of 3.0±0.3 nM. To determine if LY3154207 has a different *in vivo* behavior than a $D_1$ orthosteric agonist, the authors used the locomotor activity test in mice as the primary *in vivo* efficacy model. However, due to low PAM potency and efficacy of LY3154207 at the mouse $D_1$ receptor, a transgenic mouse in which human $D_1$ ($hD_1$) receptor was replaced with its murine counterpart, was generated. In the locomotor activity assay, total ambulation counts were collected for 60 min after dosing and SKF-82958 ($D_1$ agonist) was used as a positive control in different doses (0.1 – 60 mg/kg, *s.c.*). In the case of SKF-82958, a bell-shaped curve was observed with the response starting to taper off at 10 mg/kg. LY3154207 (1 – 240 mg/kg, *p.o.*) was also tested. Despite exhibiting a similar response to the $D_1$ agonist SKF82958 in the lower dose range, higher doses of LY3154207 did not decrease locomotor responses. Thus, the authors concluded that LY3154207 differs in type of action from the $D_1$ agonist SKF82958. Besides this, the authors tested LY3154207 *in vivo* in a mouse model of early-stage PD in which the animals still have functional DA neurons required for $D_1$ PAM to function. In this model, DA was partially depleted by pretreating the mice with a low dose of reserpine (0.3 mg/kg, *s.c.*).

In this test, it was observed that pretreatment with reserpine could partially inhibit the exploratory behavior of $hD_1$ mice (not previously habituated to the activity cages). However, treatment with LY3154207 could reverse the reduced locomotor activity induced by reserpine, with full reversal at 6 mg/kg. With this result, the authors introduce LY3154207 as a potential therapeutic option for motor symptoms in early PD patients. This compound recently underwent phase II clinical trials. Importantly, LY3154207 failed to meet primary and secondary cognition end points but improved motor symptoms associated with PD.[118]

**Multi-target ligands (Dopamine - Serotonin)**

There is an increased interest in the development of multi-target drugs for the treatment of dementia and associated neurodegenerative disorders. This also includes targeting dementia-related psychological symptoms, such as psychosis, depression, and anxiety. Compound **9** (Fig. 5) was initially tested in functional *in vitro* assay against the receptors of interest.[100] This compound was found to be a partial $D_2$ receptor agonist (EC50 = 56 ± 9.3 nM), full antagonist of 5-$HT_6$ receptor ($K_B$ = 5.6 ± 3.2 nM), and antagonist (36% at 1.0 × $10^{-6}$ M test concentration) and agonist (92% at 1.0 × $10^{-6}$ M test conc.) of 5-$HT_7$ and 5-$HT_{1A}$, respectively. Considering the safety profile of compound **11**, after obtaining concentration-response curve of hERG binding, this compound was tested in a battery of preclinical assays, including the forced swim test, passive avoidance test, scopolamine-induced cognitive dysfunction test, and the locomotor test. The authors report that compound **9** could significantly reverse MK-801-induced hyperactivity at minimum effective dose of 0.125 mg/kg. In addition, it demonstrated greater potency than classical antidepressants imipramine and citalopram as well as the anxiolytic drug diazepam at a dose range of 0.625−1.25 mg/kg. The authors also stated that compound **9** did not induce catalepsy (ED50 > 100 mg/kg) and did not inhibit locomotor

activity (up to 10 mg/kg). Lastly, compound **9** (0.3125 mg/kg) exhibited memory-enhancing properties in the passive avoidance test. With these results, compound **9** may have utility as a lead compound in the development of novel compounds to treat both dementia-related cognitive impairment as well as non-cognitive psychological dementia-related symptoms.

of compound **10** besides evaluating its safety profile, enabled the authors to report compound **10** as a novel chemotype, a potential treatment option for dementia patients. Unlike compounds **9** and **10** that are simultaneously acting on multiple targets, Kolaczkowski et al., introduced compound **11** (Fig. 5), acting on $D_2$ receptor (partial agonist) and 5-$HT_6$R (antagonist).[120]

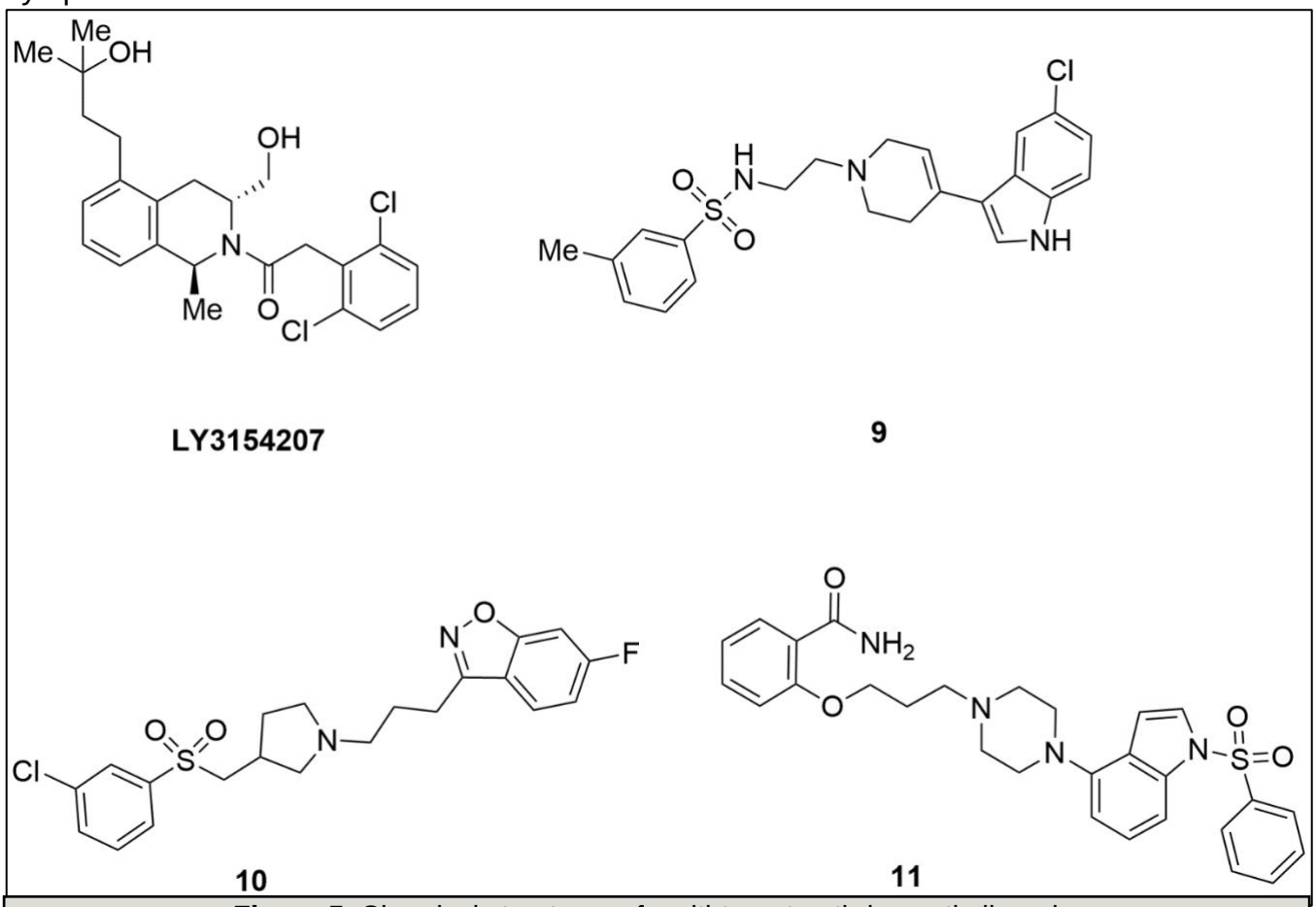


**Figure 5.** Chemical structures of multi-target anti-dementia ligands.

In another similar study, Marcinkowska et al., identified compound **10** (Fig. 5), with multi-target biological profile, and memory enhancing activity in the novel object recognition test, suggesting its implication in the treatment of dementia associate symptoms.[119] The main receptors modulated by **10** are $D_2$, 5-$HT_6$, 5-$HT_7$, and 5-$HT_{2A}$ proteins. *In vitro* and *in vivo* profiling

The findings of *in vivo* testing of this compound in rats showed that compound **11** has antidepressant and anxiolytic properties, at doses lower than the reference compounds. With this, the authors introduce compound **11** a promising lead for structure-activity relation studies with therapeutic implications for dementia as well as non-cognitive psychological dementia-related

symptoms.

**Translocator Protein (TSPO)**

Another potential target for the treatment of AD and PD symptoms is translocator protein (TSPO). This protein exhibits potential therapeutic effects by maintaining cholesterol homeostasis in the body and the brain, regulating mitochondrial functions, as well as oxidative stress, and apoptosis.[121] A TSPO ligand has been found to ameliorate DA degeneration and preserve DA metabolism in a preclinical neurotoxic model of PD.[122] Additionally, because TSPO ligands are known to act on microglia, and other immune cells, this target may be involved in other processes that contribute to the etiology of AD and PD such as regulation of neuroinflammation, βA accumulation, and brain steroidogenesis.[123-125] In a recently conducted study, Christensen et al., demonstrated that in a mouse genetic AD model, the TSPO antagonist PK-11195 (Fig. 6) significantly enhanced the time female mice spent in the open arms in the elevated plus maze, suggesting that TSPO inhibition may reverse AD-related cognitive impairment. outcomes.[126]

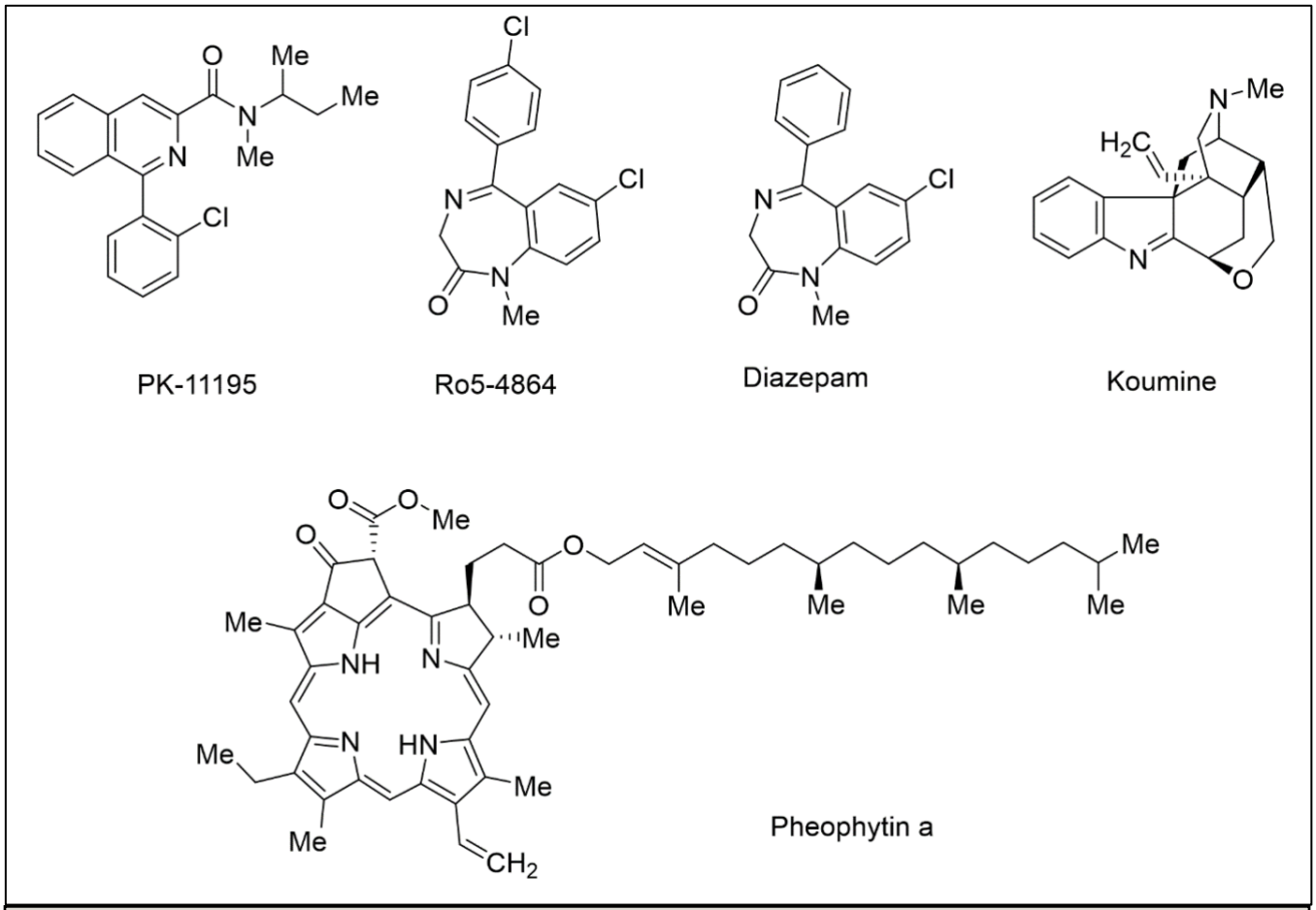


**Figure 6.** Chemical structure of PK-11195 (TSPO antagonist), Ro5-4864 (TSPO agonist), diazepam (TSPO agonist), Koumine (TSPO PAM), and Pheophytin a.

A wide variety of TSPO ligands and allosteric modulators have been reported so far, originating from natural sources or already existing chemotypes, but have yet to be

tested in models of AD, PD, and associated psychological symptoms. Pheophytin a (Fig. 6) is a photosynthetic pigment, obtained from a seagrass *Syringodium isoetifolium.* Shailaja V.L. et al. have tested the anti-cancer properties of pheophytin a, *in vitro* and evaluated its cytotoxicity on A549 (lung adenocarcinomic cells).[127] The results of this work demonstrated the anti-cancer properties of pheophytin a ($IC_{50}$: 22.9 µM) against A549 cell, and that this compound binds to TSPO. Work carried out by Xiong et al., Koumine (Fig. 6), a monomer compound, abundantly present in the alkaloid extract of *Gelsemium elegans*, is presented as positive allosteric modulator (PAM) of TSPO ($K_D$: 0.86 ± 0.07 nM).[128]

potency to induce benzodiazepine associated side effects.

The authors introduced **12 (***K*i: 4.9 nM) (Fig. 7) as a TSPO ligand inducing benzodiazepine-like side effects including motor impairment. However, further structural modification of **12** resulted in the development of **13** (*K*i: 8.6 nM) (Fig. 7) with high binding affinity and good selectivity for TSPO with acceptable pharmacokinetic profile. The authors used **13** (1 mg/kg, *p.o.*) in rat Vogel conflict model to evaluate its anxiolytic properties. The findings of *in vivo* testing of **13**, indicated that this compound could significantly increase the number of shocks in the model.

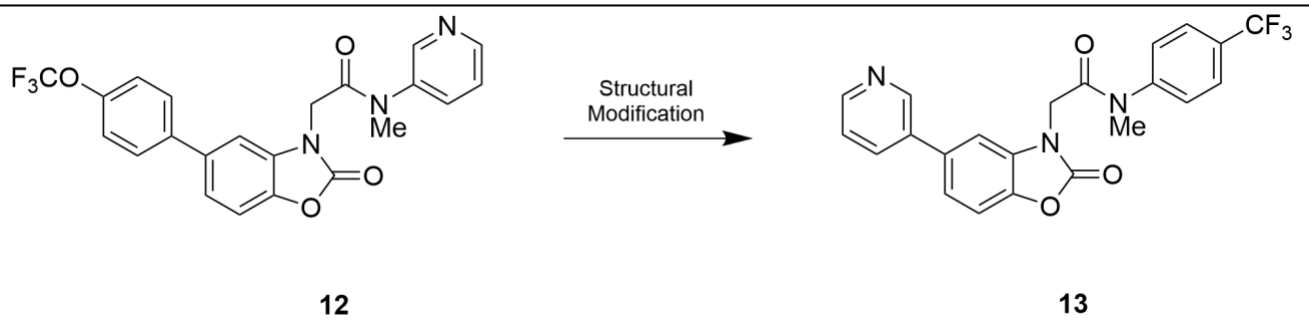


**Figure 7.** TSPO ligands synthetized by opening the diazepine ring in the structure of Ro5-4864.

Previously, TSPO was known as peripheral benzodiazepine receptor (PBR), and was identified as a discrete receptor for diazepam. Diazepam (Fig. 6) and Ro5-4864 share structural similarities, and both are TSPO ligands. Accordingly, Fukaya et al, designed and synthesized a library of TSPO ligands by opening the diazepine ring in the structure of Ro5-4864. In this work, several ligands were identified with nanomolar range binding affinities towards TSPO.[129] However, the lack of selectivity of the ligands (off-target activity) towards TSPO reported in this work (in this study, here or herein), is a good demonstrative of challenges associated with the development of TSPO ligands, as non-selective ligands have the

Moreover, the compound did not induce motor impairment in the horizontal rotarod test, memory impairment, and decrease of locomotor even at the high dose (100 mg/kg, *p.o.*).

Despite all advances made so far, there are currently no pharmacotherapies available to treat AD and PD. The need for additional and even multi-target compounds becomes obvious considering the plethora of behavioral and psychological symptoms associated with neurodegenerative diseases. As outlined in this review, dopaminergic neurodegeneration plays a critical role in the pathophysiology of AD and PD. Therefore, direct or indirect DA

regulation is an attractive approach to target the diseases. KOR ligands can restore basal levels of the neurotransmitter. Allosteric modulators can also be designed to help enhance and regulate the activity of DA. Given the complex etiologies of AD and PD and the wide variety of symptoms ligands with multiple targets are also being investigated.

Additionally, in this review we also described how TSPO ligands have neuroprotective properties and their effects on animal models of AD and PD. Continued development of compounds by medicinal chemists acting on different targets, should help determine the most efficacious compounds with optimized structure-activity properties for the treatment of dementia associated symptoms.

**Table 1.** Summary of *in vitro* characterization data of compounds discussed

| Target | Drug/ compound | Type of action | EC50/IC50/$K_i$/$K_D$/$K_B$ | Reference |
|---|---|---|---|---|
| KOR | **Salvinorin A** | Agonist | $K_i$ = 6.2 nM | Roach JJ. et al.[115] |
| | **1** | Agonist | $K_i \cong$ 31 nM | |
| | **2** | Agonist | $K_i \cong$ 62 nM | |
| | **4** | Agonist | $K_i \cong$ 2 nM | |
| | **5** | Agonist | $K_i \cong$ 7.5 nM | |
| | **6** | Antagonist | $K_i \cong$ 1.73 μM | |
| | **7** | Antagonist | $K_i$ = 0.09 μM | Zheng Z. et al.[116] |
| | **8** | Inverse agonist | $K_i$ = 0.16 μM | |
| DA $D_1$R | **LY3154207** | PAM | $EC_{50:}$ 3.0 nM | Junliang H. et al.[117] |
| DA $D_2$R\5-$HT_6$\5-$HT_7$\5-$HT_{1A}$ | **9** | Partial agonist\antagonist\ antagonist\agonist | DA $D_2$: EC50 = 56 nM<br>5-$HT_{6:}$ $K_B$ = 5.6 nM | Adam B. et al.[100] |
| DA $D_2$R\5-$HT_6$\5-$HT_7$\5-$HT2_A$ | **10** | Antagonist | DA $D_2$: p$K_B$ = 7.34 nM<br>5-$HT_6$: p$K_B$ = 7.12 nM<br>5-$HT_7$: p$K_B$ = 7.36 nM<br>5-$HT2_A$: p$K_B$ = 7.81 nM | Monika M. et al.[119] |
| DA $D_2$R\5-$HT_6$ | **11** | Partial agonist \antagonist | DA $D_2$: $K_i$ = 6.3 nM<br>5-$HT_6$: $K_i$ = 1 nM | Marcin K. et al.[120] |
| TSPO | **Pheophytin a** | - | $IC_{50}$: 22.9 μM | Shailaja V.L. et al.[127] |
| | **Koumine** | PAM | $K_D$: 0.86 nM | Bojun X. et al.[128] |
| | **12** | - | *K*i: 4.9 nM | Takayuki F. et al.[129] |
| | **13** | - | *K*i: 8.6 nM | |

**Table 2.** Summary of *in vivo* characterization data of drugs/compounds discussed

| Target | Drug/ compound | Animal/ Disease Model | Dose/conc. (route) | *In-vivo* experiments outcomes |
|---|---|---|---|---|
| DA $D_1R$ | **LY3154207**[117, 118] | Mouse/model of early-stage Parkinson's Disease | 6 – 30 mg/kg (*p.o.*) | Failed to meet primary and secondary cognition end points but improved motor symptoms associated with PD |
| DA $D_2R$\5-$HT_6$\5-$HT_7$\5-$HT_{1A}$ | **9**[100] | Mouse /forced swim test | 1.25 mg/kg (*i.p.*) | More potent antidepressants properties than imipramine and citalopram |
| | | Mouse /passive avoidance test | 0.3125 mg/kg (*i.p.*) | Showed memory-enhancing properties |
| | | Mouse/four-plate test | 0.625 mg/kg (*i.p.*) | More potent anxiolytic properties than diazepam |
| DA $D_2R$\5-$HT_6$\5-$HT_7$\5-$HT2_A$ | **10**[119] | Rat/forced swim test | 0.1 mg/kg (*i.p.*) | More potent antidepressants properties than imipramine or escitalopram |
| | | Rat/Vogel conflict drinking test | > 10 mg/kg (*i.p.*) | No statistically significant anxiolytic effect was observed in dose range administered |
| DA $D_2R$\5-$HT_6$ | **11**[120] | Rat/forced swim test | 1 mg/kg (*i.p.*) | Potent antidepressants properties were observed |
| | | Rat/Vogel conflict drinking test | 1 mg/kg (*i.p.*) | Potent anxiolytic properties were observed |
| | | Rat/open field test | 1 mg/kg (*i.p.*) | Potent anxiolytic properties were observed |
| TSPO | **Koumine**[128] | Mouse /formalin-induced inflammatory pain model | 2 – 10 mg/kg (*s.c.*) | Inhibited the second-phase nociceptive response |
| | | Rat/Collagen-Induced Arthritis (CIA) Model | 1 mg/kg (*s.c.*) | Increased Ro5-4864-mediated analgesic and anti-edematogenic effects (0.125–1.0 and 0.25 mg/kg, *i.p.*) |
| | | Rat/Chronic Constriction Injury (CCI) Model | 1.4 and 7.0 mg/kg (*s.c.*) | Antinociceptive effect |
| | **13**[129] | Rat/Vogel-type conflict model | 1 mg/kg (*p.o.*) | Indicated anxiolytic effect |

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## References

1. Feigin VL, Abajobir AA, Abate KH, et al. Global, regional, and national burden of neurological disorders during 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet Neurol*. 2017;16(11):877-897. doi:10.1016/s1474-4422(17)30299-5

2. Lilienfeld DE, Perl DP. Projected neurodegenerative disease mortality in the United States, 1990-2040. *Neuroepidemiology*. 1993;12(4):219-28. doi:10.1159/000110320

3. Tiwari S, Atluri V, Kaushik A, Yndart A, Nair M. Alzheimer's disease: pathogenesis, diagnostics, and therapeutics. *Int J Nanomedicine*. 2019;14:5541-5554. doi:10.2147/IJN.S200490

4. Marras C, Beck JC, Bower JH, et al. Prevalence of Parkinson's disease across North America. *NPJ Parkinsons Dis*. 2018;4(1):1-7. doi:10.1038/s41531-018-0058-0

5. Simon DK, Tanner CM, Brundin P. Parkinson disease epidemiology, pathology, genetics and pathophysiology. *Clin Geriar Med*. 2020;36(1):1-12. doi:10.1016/j.cger.2019.08.002

6. Sung VW, Nicholas AP. Nonmotor symptoms in Parkinson's disease: expanding the view of parkinson's disease beyond a pure motor, pure dopaminergic problem. *Neurolo Clin*. 2013;31(3, Suppl):S1-S16. doi:10.1016/j.ncl.2013.04.013

7. Tedeschi DV, da Cunha AF, Cominetti MR, Pedroso RV. Efficacy of gene therapy to restore cognition in Alzheimer's disease: a systematic review. *Curr Gene Ther*. 2021;21(3):246-257. doi:10.2174/1566523221666210120091146

8. Shalaby KE, El-Agnaf OMA. Gene-based therapeutics for Parkinson's disease. *Biomedicines*. 2022;10(8):1790. doi:10.3390/biomedicines10081790

9. Wang T, Liu X-h, Guan J, et al. Advancement of multi-target drug discoveries and promising applications in the field of Alzheimer's disease. *Eur J Med Chem.* 2019;169:200-223. doi:https://doi.org/10.1016/j.ejmech.2019.02.076

10. Jankovic J, Tan EK. Parkinson's disease: etiopathogenesis and treatment. *J Neurol Neurosurg Psychiatry*. 2020;91(8):795-808. doi:10.1136/jnnp-2019-322338

11. Erkkinen MG, Kim M-O, Geschwind MD. Clinical neurology and epidemiology of the major neurodegenerative diseases. *Cold Spring Harb Perspect Biol*. 2018;10(4):a033118. doi:10.1101/cshperspect.a033118

12. International AsD. World Alzheimer Report 2021: Journey through the diagnosis of dementia. 2021:314. *World Alzheimer Report*. 2021.

13. Scheltens P, Strooper BD, Kivipelto M, et al. Alzheimer's disease. *Lancet.* 2021;397(10284):1577-1590. doi:10.1016/S0140-6736(20)32205-4

14. Atri A. The Alzheimer's disease clinical spectrum: diagnosis and management. *Med Clin North Am*. 2019;103(2):263-293. doi:10.1016/j.mcna.2018.10.009

15. Ayodele T, Rogaeva E, Kurup JT, Beecham G, Reitz C. Early-onset alzheimer's disease: what is missing in research? *Curr Neurol Neurosci Rep*. 2021;21(2):4. doi:10.1007/s11910-020-01090-y

16. Campion D, Dumanchin C, Hannequin D, et al. Early-onset autosomal dominant Alzheimer disease: prevalence, genetic heterogeneity, and mutation spectrum. *Am J of Hum Genet*. 1999;65(3):664-670. doi:10.1086/302553

17. Van Duijn CM, Clayton D, Chandra V, et al. Familial aggregation of Alzheimer's disease and related disorders: a collaborative re-analysis of case-control studies. *Int J Epidemiol*. 1991;20(Suppl 2):S13-S20. doi:10.1093/ije/20.Supplement_2.S13

18. Jarvik G, Larson EB, Goddard K, Schellenberg GD, Wijsman EM. Influence of apolipoprotein E genotype on the transmission of Alzheimer disease in a community-based sample. *Am J Hum Genet*. 1996;58(1):191-200.

19. Slooter AJC, Cruts M, Hofman A, et al. The impact of APOE on myocardial infarction, stroke, and dementia: The Rotterdam Study. *Neurology*. 2004;62(7):1196-1198. doi:10.1212/01.WNL.0000118302.66674.E1

20. Crews L, Masliah E. Molecular mechanisms of neurodegeneration in Alzheimer's disease. *Hum Mol Genet*. 2010;19(R1):R12-R20. doi:10.1093/hmg/ddq160

21. Dickson D, Weller RO. *Neurodegeneration: The Molecular Pathology of Dementia and Movement Disorders*. John Wiley & Sons; 2011:497.

22. Baum L, Hansen L, Masliah E, Saitoh T. Glycogen synthase kinase 3 alteration in

alzheimer disease is related to neurofibrillary tangle formation. *Mol Chel Neuropathol*. 1996;29(2):253-261. doi:10.1007/BF02815006

23. Rockenstein E, Torrance M, Adame A, et al. Neuroprotective effects of regulators of the glycogen synthase kinase-3β signaling pathway in a transgenic model of Alzheimer's disease are associated with reduced amyloid precursor protein phosphorylation. *J Neurosci*. 2007;27(8):1981-1991. doi:10.1523/JNEUROSCI.4321-06.2007

24. Cruz JC, Tsai L-H. A Jekyll and Hyde kinase: roles for Cdk5 in brain development and disease. *Curr Opin Neurobiol*. 2004;14(3):390-394. doi:10.1016/j.conb.2004.05.002

25. Cruz JC, Kim D, Moy LY, et al. p25/Cyclin-dependent kinase 5 induces production and intraneuronal accumulation of amyloid β in vivo. *J Neurosci*. 2006;26(41):10536-10541. doi:10.1523/JNEUROSCI.3133-06.2006

26. Fakhoury M. Microglia and astrocytes in Alzheimer's disease: implications for therapy. *Curr Neuropharmacol*. 2018;16(5):508-518. doi:10.2174/1570159X15666170720095240

27. Shao Y, Gearing M, Mirra SS. Astrocyte-apolipoprotein E associations in senile plaques in Alzheimer disease and vascular lesions: a regional immunohistochemical study. *J Neuropathol Exp Neurol*. 1997;56(4):376-381. doi:10.1097/00005072-199704000-00006

28. Zotova E, Holmes C, Johnston D, Neal JW, Nicoll JaR, Boche D. Microglial alterations in human Alzheimer's disease following Aβ42 immunization. *Neuropathol Appl Neurobiol*. 2011;37(5):513-524. doi:10.1111/j.1365-2990.2010.01156.x

29. Desai MK, Mastrangelo MA, Ryan DA, Sudol KL, Narrow WC, Bowers WJ. Early oligodendrocyte/myelin pathology in Alzheimer's disease mice constitutes a novel therapeutic target. *Am J Pathol*. 2010;177(3):1422-1435. doi:10.2353/ajpath.2010.100087

30. Lee J-T, Xu J, Lee J-M, et al. Amyloid-β peptide induces oligodendrocyte death by activating the neutral sphingomyelinase–ceramide pathway. *J Cell Biol*. 2004;164(1):123-131. doi:10.1083/jcb.200307017

31. Nasrabady SE, Rizvi B, Goldman JE, Brickman AM. White matter changes in Alzheimer's disease: a focus on myelin and oligodendrocytes. *Acta Neuropathol Commun*. 2018;6:22. doi:10.1186/s40478-018-0515-3

32. Ballatore C, Lee VM-Y, Trojanowski JQ. Tau-mediated neurodegeneration in Alzheimer's disease and related disorders. *Nat Rev Neurosci*. 2007;8(9):663-672. doi:10.1038/nrn2194

33. McAleese KE, Firbank M, Dey M, et al. Cortical tau load is associated with white matter hyperintensities. *Acta Neuropathol Commun*. 2015;3:60. doi:10.1186/s40478-015-0240-0

34. Cummings JL, Morstorf T, Zhong K. Alzheimer's disease drug-development pipeline: few candidates, frequent failures. *Alzheimers Res Ther*. 2014;6(4):37. doi:10.1186/alzrt269

35. Rokad D, Ghaisas S, Harischandra DS, et al. Role of neurotoxicants and traumatic brain injury in α-synuclein protein misfolding and aggregation. *Brain Res Bull*. 2017;133:60-70. doi:10.1016/j.brainresbull.2016.12.003

36. Cacabelos R. Parkinson's disease: from pathogenesis to pharmacogenomics. *Int J of Mol Sci*. 2017;18(3):551. doi:10.3390/ijms18030551

37. Burré J, Sharma M, Südhof TC. Cell biology and pathophysiology of α-synuclein. *Cold Spring Harb Perspect Med*. 2018;8(3):a024091. doi:10.1101/cshperspect.a024091

38. Scott DA, Tabarean I, Tang Y, Cartier A, Masliah E, Roy S. A pathologic cascade leading to synaptic dysfunction in α-synuclein-induced neurodegeneration. *J Neurosci*. 2010;30(24):8083-8095. doi:10.1523/JNEUROSCI.1091-10.2010

39. Vargas KJ, Makani S, Davis T, Westphal CH, Castillo PE, Chandra SS. Synucleins regulate the kinetics of synaptic vesicle endocytosis. *J Neurosci*. 2014;34(28):9364-9376. doi:10.1523/JNEUROSCI.4787-13.2014

40. Lau LT, Yu AC. Astrocytes produce and release interleukin-1, interleukin-6, tumor necrosis factor alpha and interferon-gamma following traumatic and metabolic injury. *J Neurotrauma*. 2001;18(3):351-359. doi:10.1089/08977150151071035

41. Leal MC, Casabona JC, Puntel M, Pitossi FJ. Interleukin-1β and tumor necrosis factor-α: reliable targets for protective therapies in Parkinson's disease? *Front Cell Neurosci*. 2013;7:53. doi:10.3389/fncel.2013.00053

42. Liddelow SA, Guttenplan KA, Clarke LE, et al. Neurotoxic reactive astrocytes are induced by activated microglia. *Nature*. 2017;541(7638):481-487. doi:10.1038/nature21029

43. Wakabayashi K, Hayashi S, Yoshimoto M, Kudo H, Takahashi H. NACP/alpha-synuclein-positive filamentous inclusions in astrocytes and oligodendrocytes of Parkinson's disease brains. *Acta Neuropathol*. 2000;99(1):14-20. doi:10.1007/pl00007400

44. Yun SP, Kam T-I, Panicker N, et al. Block of A1 astrocyte conversion by microglia is neuroprotective in models of Parkinson's disease. *Nat Med*. 2018;24(7):931-938. doi:10.1038/s41591-018-0051-5

45. Kam T-I, Hinkle JT, Dawson TM, Dawson VL. Microglia and astrocyte dysfunction in Parkinson's disease. *Neurobiol Dis*. 2020;144:105028. doi:10.1016/j.nbd.2020.105028

46. Riedel O, Bitters D, Amann U, Garbe E, Langner I. Estimating the prevalence of Parkinson's disease (PD) and proportions of patients with associated dementia and depression among the older adults based on secondary claims data. *Int J Geriatr Psychiatry*. 2016;31(8):938-943. doi:10.1002/gps.4414

47. Zhang Q, Aldridge GM, Narayanan NS, Anderson SW, Uc EY. Approach to cognitive impairment in Parkinson's disease. *Neurotherapeutics*. 2020;17(4):1495-1510. doi:10.1007/s13311-020-00963-x

48. Litvan I, Aarsland D, Adler C, et al. MDS task force on mild cognitive impairment in parkinson's disease: critical review of PD-MCI. *Mov Disord*. 2011;26(10):1814-1824. doi:10.1002/mds.23823

49. Giguère N, Burke Nanni S, Trudeau L-E. On cell loss and selective vulnerability of neuronal populations in parkinson's disease. *Front Neurol*. 2018;9:455. doi:10.3389/fneur.2018.00455

50. McFarthing K, Rafaloff G, Baptista MAS, Wyse RK, Stott SRW. Parkinson's disease drug therapies in the clinical trial pipeline: 2021 update. *J Parkinsons Dis*. 2021;11(3):891-903. doi:10.3233/JPD-219006

51. Borovac JA. Side effects of a dopamine agonist therapy for Parkinson's disease: a mini-review of clinical pharmacology. *Yale J Biol Med*. 2016;89(1):37-47.

52. Kumar U, Patel SC. Immunohistochemical localization of dopamine receptor subtypes (D1R-D5R) in Alzheimer's disease brain. *Brain Res*. 2007;1131(1):187-196. doi:10.1016/j.brainres.2006.10.049

53. Bates MD, Gingrich JA, Bunzow JR, et al. Molecular characterization of dopamine receptors. *Am J Hyperten.* 1990;2(6 Pt 2):29S-33S. doi:10.1093/ajh/3.6.29s

54. Björklund A, Dunnett SB. Dopamine neuron systems in the brain: an update. *Trends Neurosci.* 2007;30(5):194-202. doi:10.1016/j.tins.2007.03.006.

55. Alcaro A, Huber R, Panksepp J. Behavioral functions of the mesolimbic dopaminergic system: an affective neuroethological perspective. *Brain Res Rev*. 2007;56(2):283-283. doi:10.1016/J.BRAINRESREV.2007.07.014

56. Farahimanesh S, Moradi M, Nazari-Serenjeh F, Zarrabian S, Haghparast A. Role of D1-like and D2-like dopamine receptors within the ventral tegmental area in stress-induced and drug priming-induced reinstatement of morphine seeking in rats. *Behav Pharmacol*. 2018;29(5):426-436. doi:10.1097/FBP.0000000000000381

57. Pasterkamp RJ, Smidt MP, Burbach JPH. Development and Engineering of Dopamine Neurons. *Adv Exp Med Biol.* 2009;651:v-vi.

58. Prasad AA, Pasterkamp RJ. Axon guidance in the dopamine system. *Adv Exp Med Biol*. 2009;651:91-100. doi:10.1007/978-1-4419-0322-8_9

59. Lisman JE, Grace AA. The Hippocampal-VTA Loop: controlling the entry of information into long-term memory. *Neuron*. 2005;46(5):703-713. doi:10.1016/J.NEURON.2005.05.002

60. Bromberg-Martin ES, Matsumoto M, Hikosaka O. Dopamine in motivational control: rewarding, aversive, and alerting. *Neuron*. 2010;68(5):815-834. doi:10.1016/J.NEURON.2010.11.022

61. Mogenson GJ, Jones DL, Yim CY. From motivation to action: functional interface between the limbic system and the motor system. *Prog Neurobiol*. 1980;14(2-3):69-97. doi:10.1016/0301-0082(80)90018-0

62. Saddoris MP, Cacciapaglia F, Wightman RM, Carelli RM. Differential dopamine release dynamics in the nucleus accumbens core and shell reveal complementary signals for error prediction and incentive motivation. *J Neurosci.* 2015;35(33):11572-11582. doi:10.1523/JNEUROSCI.2344-15.2015

63. Pariyadath V, Gowin JL, Stein EA. Resting state functional connectivity analysis for addiction medicine: from individual loci to complex networks. *Prog Brain Res*. 2016;224:155-173. doi:10.1016/BS.PBR.2015.07.015

64. Joyce JN, Janowsky A, Neve KA. Characterization and distribution of [125I]epidepride binding to dopamine D2 receptors in basal ganglia and cortex of human brain. *J Pharmacol Exp Ther.* 1991;257(3):1253-1263.

65. Neve KA, Henningsen RA, Kinzie JM, et al. Sodium-dependent isomerization of dopamine D-2 receptors characterized using [125I]epidepride, a high-affinity substituted benzamide ligand. *J Pharmacol Exp Ther*. 1990;252(3):1108-1116.

66. Joyce JN, Kaeger C, Ryoo H, Goldsmith S. Dopamine D2 receptors in the hippocampus and amygdala in Alzheimer's disease. *Neurosci Lett.* 1993;154(1-2):171-174. doi:10.1016/0304-3940(93)90199-u

67. Goldsmith SK, Joyce JN. Dopamine D2 receptors are organized in bands in normal human temporal cortex. *Neuroscience*. 1996;74(2):435-451. doi:10.1016/0306-4522(96)00132-7

68. Joyce JN, Myers AJ, Gurevich E. Dopamine D2 receptor bands in normal human temporal cortex are absent in Alzheimer's disease. *Brain Res.* 1998;784(1-2):7-17. doi:10.1016/s0006-8933(97)01005-6

69. Pan X, Kaminga AC, Wen SW, Wu X, Acheampong K, Liu A. Dopamine and dopamine receptors in Alzheimer's disease: A systematic review and network meta-analysis. *Front Aging Neurosci*. 2019;11:175. doi:10.3389/FNAGI.2019.00175

70. Sala A, Caminiti SP, Presotto L, et al. In vivo human molecular neuroimaging of dopaminergic vulnerability along the Alzheimer's disease phases. *Alzheimers Res Ther*. 2021;13(1):1-12. doi:10.1186/S13195-021-00925-1

71. Bliss TVP, Collingridge GL. A synaptic model of memory: long-term potentiation in the hippocampus. *Nature*. 1993;361(6407):31-39. doi:10.1038/361031A0

72. Koch G, Di Lorenzo F, Bonnì S, et al. Dopaminergic modulation of cortical plasticity in Alzheimer's disease patients. *Neuropsychopharmacology*. 2014;39(11):2654-2661. doi:10.1038/npp.2014.119

73. Chapman PF, White GL, Jones MW, et al. Impaired synaptic plasticity and learning in aged amyloid precursor protein transgenic mice. *Nat Neurosci*. 1999;2(3):271-276. doi:10.1038/6374

74. Kamenetz F, Tomita T, Hsieh H, et al. APP processing and synaptic function. *Neuron*. 2003;37(6):925-937. doi:10.1016/S0896-6273(03)00124-7

75. Lanté F, Chafai M, Raymond EF, et al. Subchronic glucocorticoid receptor inhibition rescues early episodic memory and synaptic plasticity deficits in a mouse model of Alzheimer's disease. 2015;40(7):1772-1781. doi:10.1038/NPP.2015.25

76. Nalbantoglu J, Tirado-Santiago G, Lahsaïni A, et al. Impaired learning and LTP in mice expressing the carboxy terminus of the Alzheimer amyloid precursor protein. *Nature*. 1997;387(6632):500-505. doi:10.1038/387500A0

77. Oddo S, Caccamo A, Shepherd JD, et al. Triple-transgenic model of Alzheimer's disease with plaques and tangles: intracellular Abeta and synaptic dysfunction. *Neuron*. 2003;39(3):409-421. doi:10.1016/S0896-6273(03)00434-3

78. Richards JG, Higgins GA, Ouagazzal AM, et al. PS2APP transgenic mice, coexpressing

hPS2mut and hAPPswe, show age-related cognitive deficits associated with discrete brain amyloid deposition and inflammation. *J Neurosci.* 2003;23(26):8989-9003. doi:10.1523/JNEUROSCI.23-26-08989.2003

79. Nobili A, Latagliata EC, Viscomi MT, et al. Dopamine neuronal loss contributes to memory and reward dysfunction in a model of Alzheimer's disease. *Nat Commun*. 2017;8:14727 doi:10.1038/ncomms14727

80. Mitchell RA, Herrmann N, Lanctôt KL. The role of dopamine in symptoms and treatment of apathy in Alzheimer's disease. *CNS Neurosc Ther*. 2011;17(5):411-411. doi:10.1111/J.1755-5949.2010.00161.X

81. Cross AJ, Crow TJ, Perry EK, Perry RH, Blessed G, Tomlinson BE. Reduced dopamine-beta-hydroxylase activity in Alzheimer's disease. *Br Med J (Clin Res Ed).* 1981;282(6258):93-94. doi:10.1136/bmj.282.6258.93

82. Carlsson A, Lindqvist M, Magnusson T. 3,4-Dihydroxyphenylalanine and 5-hydroxytryptophan as reserpine antagonists. *Nature*. 1957;180(4596):1200. doi:10.1038/1801200A0

83. Carlsson A, Lindqvist M, Magnusson T, Waldeck B. On the Presence of 3-Hydroxytyramine in Brain. *Science*. 1958;127(3296):471. doi:10.1126/SCIENCE.127.3296.471.A

84. Bertler Å, Rosengren E. Occurrence and distribution of dopamine in brain and other tissues. *Experientia*. 1959;15(1):10-11. doi:10.1007/BF02157069

85. Ehringer H, Hornykiewicz O. [Distribution of noradrenaline and dopamine (3-hydroxytyramine) in the human brain and their behavior in diseases of the extrapyramidal system]. *Klin Wochenschr*. 1960;38(24):1236-1239. doi:10.1007/BF01485901

86. Kordower JH, Olanow CW, Dodiya HB, et al. Disease duration and the integrity of the nigrostriatal system in Parkinson's disease. *Brain.* 2013;136(Pt 8):2419-2431. doi:10.1093/BRAIN/AWT192

87. Piggott MA, Marshall EF, Thomas N, et al. Striatal dopaminergic markers in dementia with Lewy bodies, Alzheimer's and Parkinson's diseases: rostrocaudal distribution. *Brain.* 1999;122(Pt 8):1449-1468. doi:10.1093/brain/122.8.1449

88. Rinne UK, Laihinen A, Rinne JO, Naågren K, Bergman J, Ruotsalainen U. Positron emission tomography demonstrates dopamine D2 receptor supersensitivity in the striatum of patients with early Parkinson's disease. *Mov Disord*. 1990;5(1):55-59. doi:10.1002/MDS.870050114

89. Booij J, Speelman JD, Horstink MWIM, Wolters EC. The clinical benefit of imaging striatal dopamine transporters with [123I]FP-CIT SPET in differentiating patients with presynaptic parkinsonism from those with other forms of Parkinsonism. *Eur J Nucl Med*. 2001;28(3):266-272. doi:10.1007/S002590000460

90. Booij J, Tissingh G, Boer GJ, et al. [123I]FP-CIT SPECT shows a pronounced decline of striatal dopamine transporter labelling in early and advanced Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 1997;62(2):133-140. doi:10.1136/jnnp.62.2.133

91. Brucke T, Djamshidian S, Bencsits G, Pirker W, Asenbaum S, Podreka I. SPECT and PET imaging of the dopaminergic system in Parkinson's disease. *J Neurol*. 2000;247 Suppl 4(4):IV/2-7. doi:10.1007/PL00007769

92. Tissingh G, Booij J, Bergmans P, et al. Iodine-123-N-ω-Fluoropropyl-2β-Carbomethoxy-3β-(4-Iodophenyl)Tropane SPECT in healthy controls and early-stage, drug-naive Parkinson's disease. J *Nucl Med*. 1998;39(7):1143-1148.

93. Platt J, Mador RT, Phys IL, Seitz F. Possible dopamine derivatives capable of crossing the blood-brain barrier in relation to Parkinsonism. *Nature*. 1970;228(5269):358. doi:10.1038/228358a0

94. Everett GM, Borcherding JW. L-Dopa: Effect on concentrations of dopamine, norepinephrine, and serotonin in brains of mice. *Science*. 1970;168(3933):849-850. doi:10.1126/SCIENCE.168.3933.849

95. Lewitt PA. Levodopa for the treatment of Parkinson's disease. *N Engl J Med.* 2008;359(23):2468-2476. doi:10.1056/NEJMCT0800326

96. DeMaagd G, Philip A. Part 2: Introduction to the pharmacotherapy of Parkinson's disease, with a focus on the use of dopaminergic agents. *P T*. 2015;40(9):590-590.

97. Hisahara S, Shimohama S. Dopamine receptors and Parkinson's disease. *Int J Med Chem*. 2011;2011:1-16. doi:10.1155/2011/403039

98. Perez-Lloret S, Rascol O. Dopamine receptor agonists for the treatment of early or advanced Parkinson's disease. *CNS Drugs*. 2010;24(11):941-968. doi:10.2165/11537810-000000000-00000

99. Lang AE, Obeso JA. Challenges in Parkinson's disease: restoration of the nigrostriatal dopamine system is not enough. *Lancet Neurol*. 2004;3(5):309-316. doi:10.1016/S1474-4422(04)00740-9

100. Bucki A, Marcinkowska M, Sniecikowska J, et al. Novel 3-(1,2,3,6-Tetrahydropyridin-4-yl)-1H-indole-based multifunctional ligands with antipsychotic-like, mood-modulating, and procognitive activity. *J Med Chem*. 2017;60(17):7483-7501. doi:10.1021/acs.jmedchem.7b00839

101. Hawes SL, Salinas AG, Lovinger DM, Blackwell KT. Long-term plasticity of corticostriatal synapses is modulated by pathway-specific co-release of opioids through kappa-opioid receptors. *J Physiol*. 2017;595(16):5637-5652. doi:10.1113/JP274190

102. Tejeda HA, Wu J, Kornspun AR, et al. Pathway- and cell-specific kappa-opioid receptor modulation of excitation-inhibition balance differentially gates D1 and D2 accumbens neuron activity. *Neuron*. 2017;93(1):147-163. doi:10.1016/j.neuron.2016.12.005

103. Xi ZX, Fuller SA, Stein EA. Dopamine release in the nucleus accumbens during heroin self-administration is modulated by kappa opioid receptors: an in vivo fast-cyclic voltammetry study. *J Pharmacol Exp Ther*. 1998;284(1):151-61.

104. Maisonneuve IM, Archer S, Glick SD. U50,488, a kappa opioid receptor agonist, attenuates cocaine-induced increases in extracellular dopamine in the nucleus accumbens of rats. *Neurosci Lett*. 1994;181(1-2):57-60. doi:10.1016/0304-3940(94)90559-2

105. Devine DP, Leone P, Pocock D, Wise RA. Differential involvement of ventral tegmental mu, delta and kappa opioid receptors in modulation of basal mesolimbic dopamine release: in vivo microdialysis studies. *J Pharmacol Exp Ther*. 1993;266(3):1236-46.

106. Manzanares J, Lookingland KJ, Moore KE. Kappa opioid receptor-mediated regulation of dopaminergic neurons in the rat brain. *J Pharmacol Exp Ther*. 1991;256(2):500-5.

107. Di Chiara G, Imperato A. Opposite effects of mu and kappa opiate agonists on dopamine release in the nucleus accumbens and in the dorsal caudate of freely moving rats. *J Pharmacol Exp Ther*. 1988;244(3):1067-80.

108. Heidbreder CA, Schenk S, Partridge B, Shippenberg TS. Increased responsiveness of mesolimbic and mesostriatal dopamine neurons to cocaine following repeated administration of a selective kappa-opioid receptor agonist. *Synapse*. 1998;30(3):255-62. doi:10.1002/(SICI)1098-2396(199811)30:3<255::AID-SYN3>3.0.CO;2-A

109. Escobar Adel P, Cornejo FA, Andres ME, Fuentealba JA. Repeated treatment with the kappa opioid receptor agonist U69593 reverses enhanced K+ induced dopamine release in the nucleus accumbens, but not the expression of locomotor sensitization in amphetamine-sensitized rats. *Neurochem Int*. 2012;60(4):344-9. doi:10.1016/j.neuint.2012.01.014

110. Fuentealba JA, Gysling K, Magendzo K, Andres ME. Repeated administration of the selective kappa-opioid receptor agonist U-69593 increases stimulated dopamine extracellular levels in the rat nucleus accumbens. *J Neurosci Res*. 2006;84(2):450-9. doi:10.1002/jnr.20890

111. Fuentealba JA, Gysling K, Andres ME. Increased locomotor response to amphetamine induced by the repeated administration of the selective kappa-opioid receptor agonist U-69593. *Synapse*. 2007;61(9):771-7. doi:10.1002/syn.20424

112. Trifilieff P, Martinez D. Kappa-opioid receptor signaling in the striatum as a potential modulator of dopamine transmission in cocaine dependence. *Front Psychiatry*. 2013;4:44. doi:10.3389/fpsyt.2013.00044

113. Takahashi K, Nakagawasai O, Sugawara M, et al. Kappa opioid receptor agonist administration in olfactory bulbectomized mice restores cognitive impairment through cholinergic neuron activation. *Biol Pharm Bull*. 2018;41(6):957-960. doi:10.1248/bpb.b18-00115

114. Paris JJ, Reilley KJ, McLaughlin JP. Kappa opioid receptor-mediated disruption of novel object recognition: relevance for psychostimulant treatment. *J Addict Res Ther*. 2011;S4doi:10.4172/2155-6105.S4-007

115. Roach JJ, Shenvi RA. A review of salvinorin analogs and their kappa-opioid receptor activity. *Bioorg Med Chem Lett*. 2018;28(9):1436-1445. doi:10.1016/j.bmcl.2018.03.029

116. Zheng Z, Huang XP, Mangano TJ, et al. Structure-based discovery of new antagonist and biased agonist chemotypes for the kappa opioid receptor. *J Med Chem*. 2017;60(7):3070-3081. doi:10.1021/acs.jmedchem.7b00109

117. Mages K, Grassmann F, Jägle H, et al. The agonistic TSPO ligand XBD173 attenuates the glial response thereby protecting inner retinal neurons in a murine model of retinal ischemia. *J Neuroinflammation*. 2019;16(1)doi:10.1186/s12974-019-1424-5

118. Gong J, Szego EM, Leonov A, et al. Translocator protein ligand protects against neurodegeneration in the mptp mouse model of Parkinsonism. *J Neurosci*. 2019;39(19):3752-3769. doi:10.1523/JNEUROSCI.2070-18.2019

119. Barresi E, Robello M, Costa B, et al. An update into the medicinal chemistry of translocator protein (TSPO) ligands. *Eur J Med Chem*. 2021;209:112924. doi:10.1016/j.ejmech.2020.112924

120. Barron AM, Garcia-Segura LM, Caruso D, et al. Ligand for translocator protein reverses pathology in a mouse model of Alzheimer's disease. J *Neurosci*. 2013;33(20):8891-8897. doi:10.1523/jneurosci.1350-13.2013

121. Christensen A, Pike CJ. TSPO ligand PK11195 improves Alzheimer-related outcomes in aged female 3xTg-AD mice. *Neurosci Lett*. 2018;683:7-12. doi:10.1016/j.neulet.2018.06.029

122. Shailaja VL, Christina VS, Mohanapriya CD, et al. A natural anticancer pigment,Pheophytin a,from a seagrass acts as a high affinity human mitochondrial translocator protein (TSPO) ligand, in silico, to reduce mitochondrial membrane Potential (psimit) in adenocarcinomic A549 cells. *Phytomedicine*. 2019;61:152858. doi:10.1016/j.phymed.2019.152858

123. Xiong B, Jin G, Xu Y, et al. Identification of koumine as a translocator protein 18 kDa positive allosteric modulator for the treatment of inflammatory and neuropathic pain. *Front Pharmacol*. 2021;12:692917. doi:10.3389/fphar.2021.692917

124. Fukaya T, Ishiyama T, Baba S, Masumoto S. Identification of a novel benzoxazolone derivative as a selective, orally active 18 kDa translocator protein (TSPO) ligand. *J Med Chem*. 2013;56(20):8191-5. doi:10.1021/jm401325r

125. Hao J, Beck JP, Schaus JM, et al. Synthesis and pharmacological characterization of 2-(2,6-dichlorophenyl)-1-((1S,3R)-5-(3-hydroxy-3-methylbutyl)-3-(hydroxymethyl)-1 -methyl-3,4-dihydroisoquinolin-2(1H)-yl)ethan-1-one (LY3154207), a potent, subtype selective, and orally available positive allosteric modulator of the human dopamine D1 receptor. *J Med Chem*. 2019;62(19):8711-8732. doi:10.1021/acs.jmedchem.9b01234

126. Marcinkowska M, Bucki A, Sniecikowska J, et al. Multifunctional arylsulfone and arylsulfonamide-based ligands with prominent mood-modulating activity and benign safety profile, targeting neuropsychiatric symptoms of dementia. *J Med Chem*. 2021;64(17):12603-12629. doi:10.1021/acs.jmedchem.1c00497

127. Kolaczkowski M, Marcinkowska M, Bucki A, et al. Novel 5-HT6 receptor antagonists/D2 receptor partial agonists targeting behavioral and psychological symptoms of dementia. *Eur J Med Chem*. 2015;92:221-35. doi:10.1016/j.ejmech.2014.12.045