

Occurrence of Morpholine in Central Nervous System Drug Discovery

Elena Lenci, Lorenzo Calugi, and Andrea Trabocchi*

Cite This: *ACS Chem. Neurosci.* 2021, 12, 378–390

Read Online

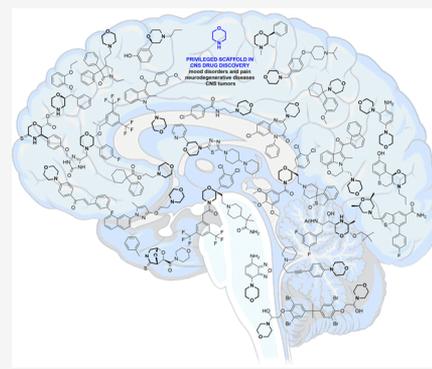
ACCESS |

Metrics & More

Article Recommendations

ABSTRACT: Developing drugs for the central nervous system (CNS) requires fine chemical modifications, as a strict balance between size and lipophilicity is necessary to improve the permeability through the blood-brain barrier (BBB). In this context, morpholine and its analogues represent valuable heterocycles, due to their conformational and physicochemical properties. In fact, the presence of a weak basic nitrogen atom and of an oxygen atom at the opposite position provides a peculiar pK_a value and a flexible conformation to the ring, thus allowing it to take part in several lipophilic–hydrophilic interactions, and to improve blood solubility and brain permeability of the overall structure. In CNS-active compounds, morpholines are used (1) to enhance the potency through molecular interactions, (2) to act as a scaffold directing the appendages in the correct position, and (3) to modulate pharmacokinetic/pharmacodynamic (PK/PD) properties. In this perspective, selected morpholine-containing CNS drug candidates are discussed to reveal the active pharmacophores accountable for the (1) modulation of receptors involved in mood disorders and pain, (2) bioactivity toward enzymes and receptors responsible for neurodegenerative diseases, and (3) inhibition of enzymes involved in the pathology of CNS tumors. The medicinal chemistry/pharmacological activity of morpholine derivatives is discussed, in the effort to highlight the importance of morpholine ring interactions in the active site of different targets, particularly reporting binding features retrieved from PDB data, when available.

KEYWORDS: brain, blood-brain barrier, Alzheimer's disease, Parkinson's disease, cancer, enzyme inhibitor



INTRODUCTION

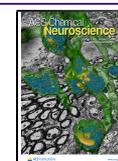
The development of treatments for central nervous system (CNS) disorders is accompanied by challenging tasks and difficulties, as compared to other therapeutic areas. In general, the chance for CNS drug candidates to reach the market is about 50% lower than that for other drug applications, and their development costs are 30% higher relative to most other areas of drug discovery.¹ It is not surprising that several Big Pharma companies have reduced research in this area in recent years, despite the multibillion-dollar interest in developing drugs for diseases such as Alzheimer's, Parkinson's, depression, anxiety, schizophrenia, and stroke, that are of paramount importance in the context of an aging global population.² The high cost and low approval rate of CNS drugs is mainly related to the fact that the majority of neuropsychiatric leads fail in the pricey Phase III of clinical trials. The reasons for the neurofailures are numerous, ranging from the inadequate understanding of the biology behind CNS (brain and spinal cord) to the lack of reliable animal models, and also due to complications associated with the blood-brain barrier (BBB), a dynamic and selective membrane that restricts the flow to foreign agents, thus requiring fine chemical modifications of drug candidates. Generally, large size, high topological polar surface area, and a high degree of hydrogen bonding are not

compatible with the passive diffusion of the molecules through the BBB,³ thus limiting the use of antibodies and peptides as orally administered CNS drugs.^{4–7} This is complicated in some patients with neurodegenerative conditions, where BBB is altered, thus affecting further drug permeability uptake.⁸ A balance between decreasing size and increasing lipophilicity is necessary to improve the penetrability of a drug,^{9,10} while simultaneously ensuring that P-glycoprotein-mediated efflux or plasma-mediated or fatty tissue-mediated drug sequestration are not activated.¹¹ Thus, even though drugs affecting the CNS were the first to be discovered by humans thousands of years ago, there is still room for improving the exploration of the CNS-relevant chemical space.¹² Among the many different N-containing heterocycles, morpholine represents one of the most useful scaffolds for the development of CNS drug candidates, thanks to its well-balanced lipophilic–hydrophilic profile, the reduced pK_a value, and the chairlike flexible

Received: November 13, 2020

Accepted: January 11, 2021

Published: January 18, 2021



conformation. This heterocycle has been the object of a plethora of research studies, and several review papers have been reported regarding synthetic methodologies for its preparation,^{13–16} as well as the different biological activities displayed by compounds in which it is found.^{17–22} In fact, morpholine is used to modulate the pharmacokinetic/pharmacodynamic (PK/PD) properties of the overall structure, as the presence of a weak basic nitrogen at the opposite position of the oxygen atom provides to the ring a pK_a value similar to the pH of blood, thus enhancing solubility and brain permeability. Also, it can be added to enhance the potency toward a target protein, as the oxygen atom can form hydrogen bonds, while the relatively electron-deficient ring can establish hydrophobic interactions.²³ Finally, the flexible conformation resulting from the equilibrium between the chairlike and skew-boat topologies provides the optimal features for a suitable scaffold directing the appendages in the right position.^{24,25} Morpholine has also an improved CYP3A4 profile, prolonged bioavailability, and optimal clearance, being oxidized easily into nontoxic derivatives.^{17–22} A plethora of morpholine derivatives have already been present in the market for several decades (Figure 1). Just to give some

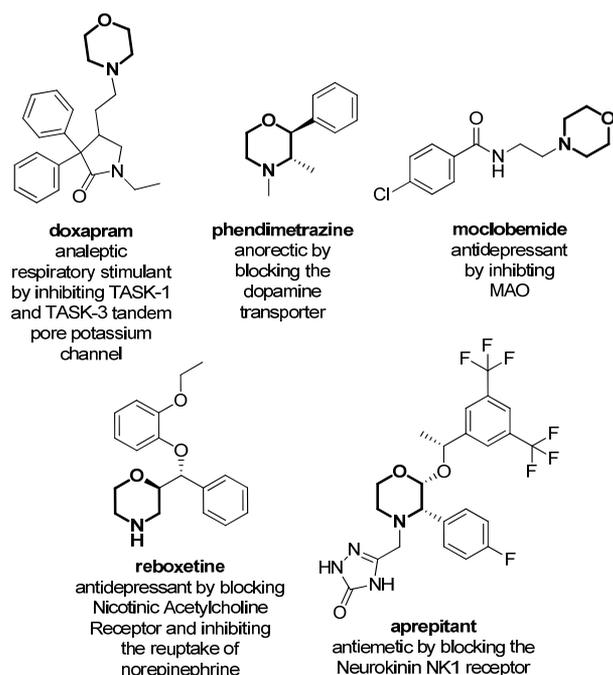


Figure 1. Approved morpholine-containing CNS drugs.

examples, doxapram (1976),²⁶ phendimetrazine (1979),²⁷ moclobemide (1992),²⁸ reboxetine (1997),²⁹ and aprepitant (2003)^{30–32} are drugs with applications in several CNS diseases, mainly as anxiolytics and/or antidepressants.

Several morpholine-containing pharmacophores have been identified as responsible for the selective interaction with specific molecular targets, such as aryl-morpholines interacting with PI3K kinase family³³ or morpholine–azaindoles with cannabinoid receptors.³⁴ They are structurally similar to endogenous neurotransmitters (as in the case of aryl-morpholines) and it has been demonstrated that they play a key role in improving the crossing of the blood-brain barrier. Although the biological activity of morpholine derivatives has been reviewed elsewhere,^{17–22} herein selected morpholine-

containing CNS drug candidates are discussed to reveal the active pharmacophores accountable for the modulation of (1) receptors involved in mood disorders and pain, (2) enzymes and receptors responsible for neurodegenerative diseases, and (3) enzymes involved in the pathology of CNS tumors. The medicinal chemistry/pharmacological activity of morpholine derivatives is discussed, in the effort to highlight the importance of morpholine ring interactions in the active site of different targets, particularly reporting the binding features retrieved from PDB data, when available. The role of the morpholine ring is highlighted using different colors, depending on whether it acts as (1) interacting element (red), (2) scaffold (blue), or (3) PK/PD modulator (green) and, when appropriate, by comparing morpholine-containing compounds with analogues that lack this ring.

■ BIOLOGICAL ACTIVITY OF MORPHOLINE DERIVATIVES IN MOOD DISORDERS AND PAIN

The human nervous system comprises millions of neurons, that communicate quickly between each other thanks to the action of a plethora of different receptors. Three different classes of receptors have been identified in the CNS, many of them involved in the pathological development of different disorders. Although their classification still needs to be clearly understood, neurotransmitter receptors can be divided into ionotropic receptors, ligand-gated ion channels that are excited by the binding of neurotransmitters activating the passage of different ions, and metabotropic receptors, often G protein-coupled receptors that respond to the binding of the neurotransmitter by activating a signal transduction pathway inside the cell. For some of the most important classes of neurotransmitter receptors involved in the regulation of mood disorders and pain control, morpholine derivatives are found to be able to desensitize or downregulate their mode of action, as they usually present structural similarity with their endogenous ligands (Figure 2). In some cases, a precise pharmacophore

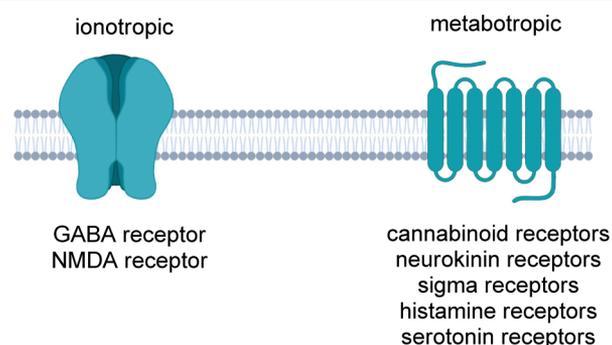


Figure 2. Neuroreceptors as molecular targets of morpholine-containing compounds.

containing the morpholine ring can be identified, whereas in some other cases, the morpholine ring plays a key role by improving the overall pharmacokinetic profile and the brain permeability of the final compound.

Cannabinoid receptors interact endogenously with several different ligands, and their partial agonism is of interest for the development of therapeutics for pain management, inflammation, obesity, and substance abuse disorders.^{35,36} Of the many different compounds that can act as agonists toward the two main CB1 and CB2 receptors, aminoalkylindoles (AAI) are

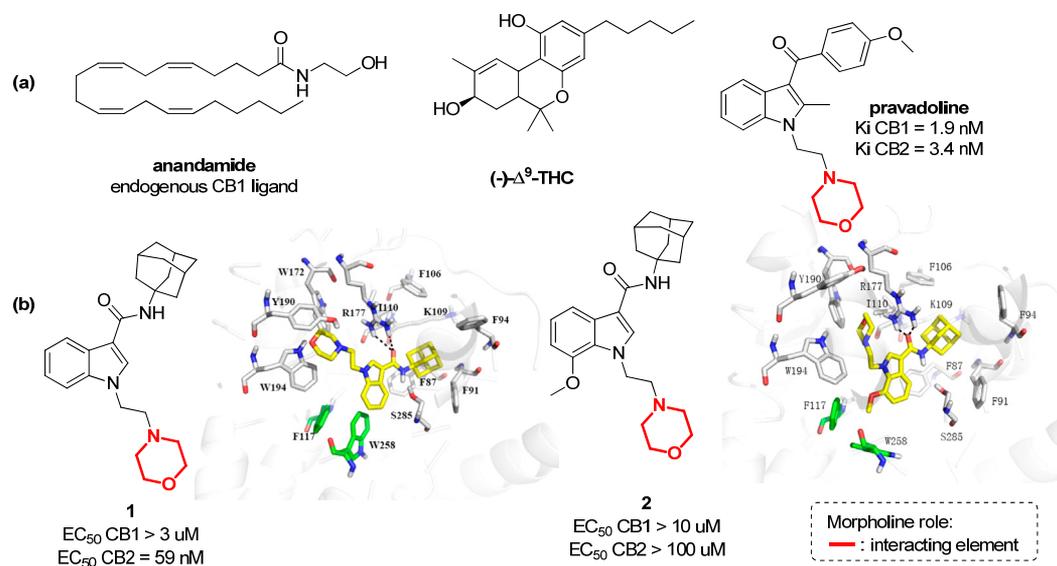


Figure 3. Structure of endogenous cannabinoid receptor ligands, $(-)\text{-}\Delta^9\text{-THC}$ and pravadoline. (b) Structure of a selective CB2 receptor agonist (compound 1) and antagonist (compound 2) and their interactions in the CB2 binding site (Adapted with permission from ref 39. Copyright (2017) American Chemical Society.).

very active, such as pravadoline, discovered serendipitously in the 1990s,^{37,38} or compounds 1 and 2,³⁹ although they do not share any obvious structural similarity with the classical cannabinoid $(-)\text{-}\Delta^9\text{-THC}$ or with endogenous fatty acid ethanolamide ligands (such as anandamide) (Figure 3).⁴⁰ The crystal structures of the human CB1 receptor⁴¹ and CB2 receptor⁴² have been resolved only in recent years and provided important insights for the development of selective CB2 receptor agonists. In fact, while the CB1 receptor is mainly found in the central nervous system and its inhibition can produce addictive effects, the selective targeting of the CB2 receptor, being found only in the peripheral immune system and in diseased brain cells, has a much more desirable therapeutic value for pain relief, anti-inflammatory activity, and inhibition of cough without addictive side effects.^{43–46} Recent studies have highlighted how the substitution pattern of the indole core plays a key role in the selectivity among the two receptors. In particular, bulky substituents at position 3 of the indole ring can increase the selectivity for the CB2 receptor, as in compound 1 (Figure 3b).³⁹ The *N*-morpholinoethyl moiety occupies the deep hydrophobic pocket surrounded by conserved aromatic residues (Trp172, Tyr190, and Trp194) in the fourth transmembrane domain,³⁴ which have been identified as crucial residues for ligand recognition,⁴⁷ while the indole moiety creates arene–H interactions with F87. The introduction of a methoxy group at position 7 of the indole core, as in compound 2, results in a switch from agonist to antagonist activity for the CB2 receptor,⁴² possibly due to a different binding mode to the CB2 receptor. The presence of the methoxy group may force the rotation of the indole ring, producing the loss of the interaction with the crucial tryptophan residues (Figure 3b).

The *N*-morpholinoethyl moiety is found to be important also for the modulation of other metabotropic receptors, such as sigma receptors ($\sigma 1R$ and $\sigma 2R$)⁴⁸ and serotonin receptors (5-hydroxytryptamine, 5-HT),⁴⁹ molecular targets involved in the regulation of drug dependence, amnesia, depression, and cognition, and in the endocrine system modulation. A comprehensive overview of morpholine-containing antagonists

of sigma and serotonin receptors is reported by Kouronakis,¹⁷ and two selected examples of them are reported in Figure 4.

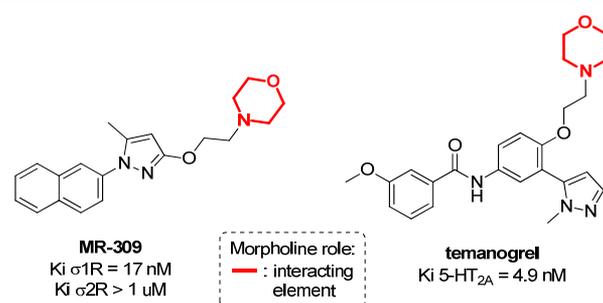


Figure 4. Structure of sigma and serotonin receptor antagonists containing the *N*-morpholinoethyl moiety.

MR-309 is a sigma receptor antagonist, where the presence of *N*-morpholinoethyl in the molecular structure has been balanced by the addition of a naphthyl group, to provide the desirable lipophilicity required for CNS permeability.⁵⁰ MR-309 has a potential therapeutic application in those patients affected by spinal cord injury (SCI) that develop central neuropathic pain (CNP), by reducing the expression of extracellular pain mediators (TNF- α and IL-1 β) and intracellular signaling cascades (ERK/pERK).⁵¹ As $\sigma 1R$ can regulate the *N*-methyl-D-aspartate receptor (NMDAR), that has been implicated in the treatment of ischemic stroke, this compound may be used also for the treatment of cerebral ischemia, as demonstrated by the reduction of cerebral infarct size and neurological deficits in mice with middle cerebral artery occlusion (MCAO) after intravenous treatment with MR-309.⁵² In addition, temanogrel (APD791) is a potent inverse agonist of the serotonin receptor, in which the *N*-morpholinoethyl moiety provides selectivity for the 5-HT_{2A} isoform versus the 5-HT_{2B} and 5-HT_{2c} receptors (Figure 4).⁵³ As 5-HT_{2A} is involved in the reduction of thrombus formation, by inhibiting the inositol phosphate accumulation, temanogrel

entered Phase I clinical trial as a potential antiplatelet agent.^{54,55}

Another class of GPCR metabotropic receptors that play a key role in the CNS is the family of tachykinin or neurokinin receptors (NK1, NK2, and NK3), that are involved in a variety of conditions, including migraine, asthma, nausea, analgesia, inflammation, emesis, pruritus, and bronchoconstriction. The endogenous ligands of these receptors are Substance P (SP), and neurokinins A (NKA) and B (NKB), that are small peptides sharing the conserved C-terminal structural motif FxGLM-NH₂.^{56,57} After 80 years of research around substance P antagonists (SPAs), a morpholine-containing compound (aprepitant) became the first approved oral drug for the treatment of chemotherapy-induced nausea and vomiting (CINV).^{30–32} The crystal structure of aprepitant complexed with the NK1 receptor has been reported (Figure 5),⁵⁸ thus

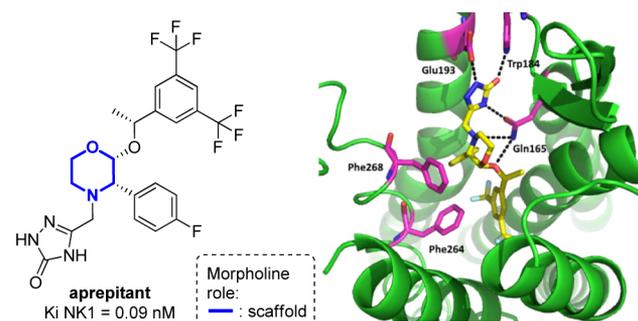


Figure 5. Crystal structure of the human neurokinin 1 receptor in complex with aprepitant (left) and detailed interactions with the receptor, viewed from the extracellular side above helix I (right, PDB: 6HLO).⁵⁹

revealing the importance of the morpholine ring, acting as a scaffold able to direct the three interacting arms in the correct positions. Specifically, the 1*H*-1,2,4-triazol-5(4*H*)-one moiety is found establishing hydrogen bonds with Glu193, Trp184, and Gln165, the latter interacting also with morpholine, and the two substituted phenyl rings found interacting with Phe264 and Phe 268.

Histamine H₃ receptor, regulating histamine levels in different areas of the CNS (cerebral cortex, striatum, and hypothalamus), is a molecular target with potential application for the treatment not only of allergic disorders, but also of schizophrenia, insomnia, and metabolic diseases, such as obesity and diabetes.^{60,61} Several different histamine H₃ receptor modulators contain a morpholine ring, as this nucleus is often added to improve the pharmacokinetic properties of the overall compound, especially addressing the half-life and the distribution in CNS tissues. For example, the substitution of the piperidine ring with a morpholine in a series of (4-aminobutyn-1-yl)benzylamines H₃ antagonists results in the improvement of potency and CNS druggability, as shown by JNJ-10181457 possessing a shorter plasma half-life and a higher ability to penetrate the BBB, with brain concentration values that roughly parallel those found in plasma (Figure 6).⁶²

Similarly, morpholine is contained in different mGlu₂ (metabotropic Glutamate receptor 2) negative allosteric modulators (NAM) to increase their pharmacokinetic properties. mGlu₂ is another metabotropic receptor that is broadly expressed in the CNS and represents an important therapeutic target for mood disorders (anxiety, depression, schizophrenia, addiction), as well as for neurodegenerative diseases such as

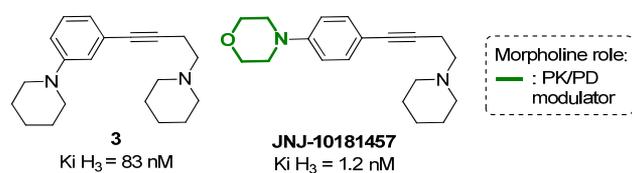


Figure 6. Structure of a histamine H₃ receptor antagonist in comparison with the morpholine-containing analogue JNJ-10181457.

Alzheimer's disease (AD) and Parkinson's disease (PD).^{63–65} First-generation mGlu₂ NAMs were characterized by poor physicochemical properties (e.g., high lipophilicity, poor solubility) and very low CNS penetration (as shown by the value of rat brain:plasma partition ratios K_p , that is, 0.30 for compounds 4 and 5, Figure 7a). Recently, a novel mGlu₂

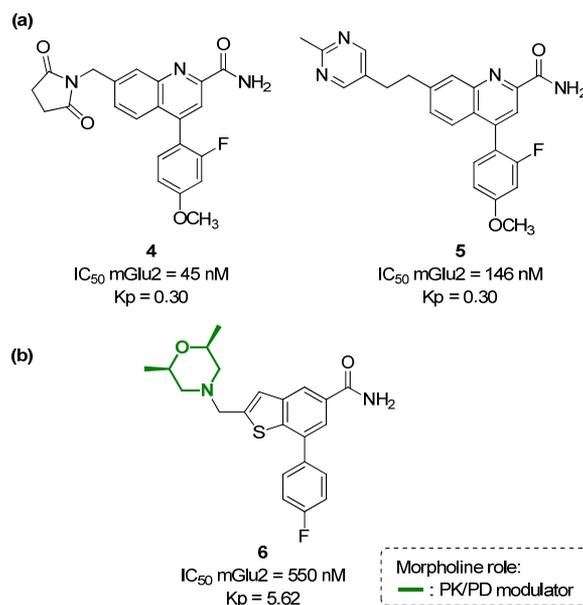


Figure 7. (a) Structure of first-generation mGlu₂ NAMs and (b) structure of a morpholine-containing compound able to modulate the mGlu₂ receptor.

NAM based on the thieno[3,2-*b*]pyridine-5-carboxamide core (compound 6) has been developed, showing that the introduction of 2,5-dimethylmorpholine allowed the compound to be highly CNS penetrant (K_p = 5.62), with moderate predicted hepatic clearance in microsomes and *in vivo* efficacy (Figure 7b).⁶⁶

Morpholine chemotypes can be found also in antagonists or agonists of ionotropic neurotransmitter receptors, even though few examples are known in the literature. Even in this case, different roles for the morpholine nucleus can be evinced, namely, as a key interacting element or as a suitable appendage to better modulate the pharmacokinetic properties. For example, in the case of GABA (γ -aminobutyric acid) receptor, it has been recently reported how the introduction of morpholine to a 1,5-benzodiazepine derivative (such as clobazam) can increase the anxiolytic activity, by modulating the overall pharmacokinetic profile of compound 7 (Figure 8).⁶⁷ On the contrary, in the case of NMDA (*N*-methyl-D-aspartate) receptor, a calcium channel target for achieving analgesic and antipyretic effects, the phencyclidine analogue 8 with agonist activity (Figure 8) possesses a morpholine instead

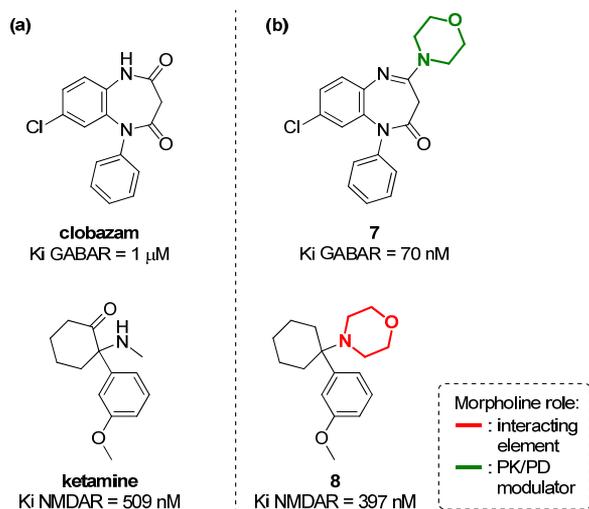


Figure 8. Structure of (a) compounds able to modulate ionotropic receptors (GABA and NMDA receptors), in comparison with (b) morpholine-containing analogues.

of a methylamino group (as in ketamine), resulting in the morpholine moiety directly interacting with the receptor as a pharmacophoric element.⁶⁸

■ BIOLOGICAL ACTIVITY OF MORPHOLINE DERIVATIVES IN NEURODEGENERATIVE DISEASES

Parkinson's disease (PD) is a long-term progressive degenerative disorder that affects more than 10 million people worldwide, with a variety of clinical symptoms related to the motor system, such as shaking, rigidity, slowness of movement, and difficulty with walking.⁶⁹ Although many pharmacological agents have been specifically developed over the past decades, there is still no cure for Parkinson's disease, but only some treatments that can alleviate motor symptoms, even though with undesirable adverse effects. Thus, there is still a relevant and unmet clinical need for treatments that offer disease modification and that addresses symptoms resistant to levodopa.⁷⁰ In this context, morpholine containing compounds represent powerful therapeutic agents, being able to target different receptors and enzymes involved in the pathological development of the disease. For example, mutations in LRRK2 (encoding leucine-rich repeat kinase 2) are the most common autosomal dominant mutations responsible for the development of either familial and sporadic PD, leading to an increase of LRRK2 kinase activity in neurons, mitochondrial DNA dysfunction, autophagy, inflammatory response, and apoptosis.⁷¹ Selective LRRK2 kinase inhibitors with favorable drug-like properties, such as MLI-2 (Figure 9a), may represent an alternative therapy for PD. This compound, possessing a 2,5-dimethylmorpholine ring, is able to inhibit LRRK2 with a IC_{50} of 0.76 nM and a 295-fold selectivity over 300 kinases, and showed good brain permeability and a good tolerance in different animal models, including MitoPark mice.⁷² Starting from the structure of MLI-2, compound 9 was recently developed and labeled with fluorine-18 (¹⁸F), in order to obtain a positron emission tomography (PET) tracer for the visualization of LRRK2 in the brain (Figure 9a).⁷³ Other important molecular targets involved in PD are dopamine receptors.^{74,75} These GPCR receptors are classified in two different subtypes, D₁-like receptors (D1 and D5) and D₂-like

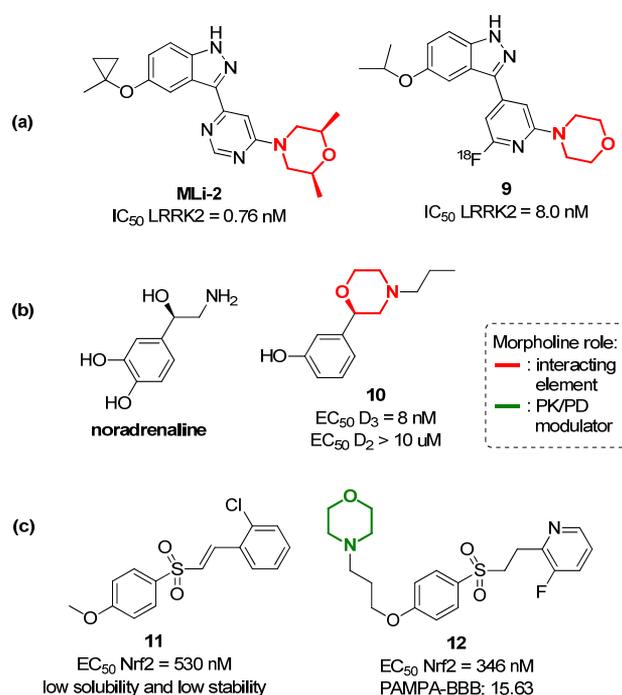


Figure 9. Structure of morpholine-containing compounds able to modulate molecular targets involved in Parkinson's disease, such as (a) LRRK2 kinase, (b) dopamine receptors, and (c) Nrf2 transcription factor.

receptors (D₂, D₃, and D₄), that show a different distribution in the CNS system.^{74,75} D₂ receptors are mainly found in basal ganglia neurons at the supraspinal level and are involved in adenylyl cyclase and phosphatidylinositol hydrolysis activity, as well as in the release of arachidonic acid. On the contrary, D₃ receptors are present only in a few areas of the brain, such as the limbic system, which is associated with cognition and emotion. A dysregulation of either D₂ and D₃ receptors is found in a number of CNS disorders. Nevertheless, the selective inhibition of D₃ over D₂ is crucial, as an increase of D₃ receptors was observed in PD-affected brains, while D₂ receptors are not altered and provoke diverse side effects if activated.⁷⁶ In this context, the *N*-morpholinopropyl moiety, as already seen for other metabotropic receptors, being functionalized with an aryl group in the 2-position has been widely used for the development of selective D₃ receptor agonists, such as compound 10 that shows structural similarity to noradrenaline (Figure 9b).⁷⁷ The *N*-morpholinopropyl moiety is also found in compound 12, a nuclear factor erythroid 2-related factor 2 (Nrf2)⁷⁸ inhibitor able to attenuate the loss of dopaminergic neurons.⁷⁹ Even in this case, previously developed lead compound 11 exhibited undesirable drug-like properties,⁸⁰ and the introduction of a morpholine ring resulted in the improvement of the activity (EC_{50}) and the CNS permeability (as proved by PAMPA-BBB assay) (Figure 9c).

Alzheimer's disease (AD) is the most common cause of dementia, with over 50 million affected people worldwide, a number that is expected to reach 152 million in 2050.⁸¹ Even though the molecular mechanisms behind Alzheimer's pathogenesis is far from being completely unveiled, the amyloid cascade hypothesis remains one of the less debated.^{82–84} Several different molecular targets are involved in this process, and most of them have been studied for the development of

novel therapeutic agents. For example, β -Secretase (BACE-1) is the enzyme that cleaves the extracellular domain of the Amyloid Precursor Protein (APP) into a *N*-terminal fragment C99, which is then processed by γ -secretase into the pathogenic neurotoxic peptides $A\beta_{40}$ and $A\beta_{42}$.⁸⁵ Thus, either β - and γ -secretases have been devised as therapeutic targets of clear importance, although their inhibition proved to be challenging, in particular, for the development of compounds able to pass efficiently the BBB.⁸⁶ Morpholines were shown to be important molecular scaffolds for the inhibition of BACE-1. For example, compound **13**, a hydroxyethylamine-based peptide isostere, provided the right flexible architecture to fit perfectly into the active site of BACE-1, thus orienting its substituents toward the S1, S1', and S2' pockets, and showing capabilities for BBB entrance (Figure 10a).⁸⁷ The synclinal relationship between the endocyclic

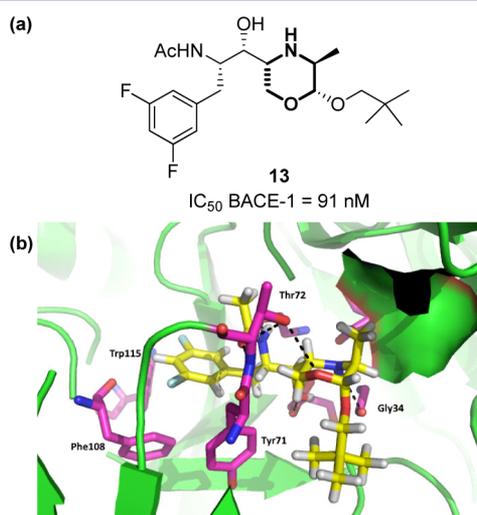


Figure 10. (a) Structure of compound **13**, and (b) its interactions within the active site of BACE-1 (PDB: 6BFX).⁸⁷

oxygen and the first exocyclic carbon atoms was found to be the preferred conformation of morpholine in solution due to the exoanomeric effect. In this orientation, the methyl group of morpholine is oriented toward S1 (Figure 10b). The morpholine ring was also found to establish polar interactions with its nitrogen atom pointing toward the carbonyl group of Gly34, and with Thr72 on the flap region taking advantage of the oxygen atom.

In addition, the morpholine moiety possessing the amidino group in position 3 (1,4-oxazin-3-amine) was found to be a crucial molecular platform for the inhibition of this enzyme. Just to give an example, compound **14**, developed by Rambouts and co-workers, inhibits BACE-1 with IC_{50} of 22 nM (Figure 11a).⁸⁸ The morpholine ring is important for presenting the two nitrogen atoms of the amidino group in the right position to interact with the catalytic aspartic acids (Asp32 and Asp228) and to address other interacting sites (i.e., the oxygen atom establishing a hydrogen bond with the OH group of Thr72 and with the NH group of Arg235). The long hydrophobic chain provided by the amide-tethered biaryl system can efficiently address the S1 and S3 pockets, with the NH of the amide bond interacting with Gly230, and the two aromatic rings establishing π -stacking interactions with Tyr71, Phe108, Trp76, and Trp115 (Figure 11a). An important issue in the development of BACE-1 inhibitors is the right

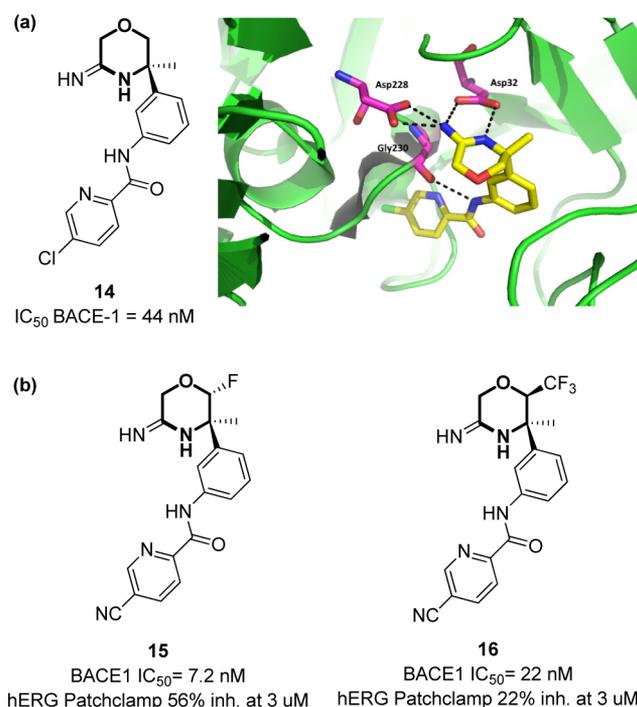


Figure 11. (a) Structure of compound **14** and key interactions within the active site of BACE-1 (PDB: 5CLM).⁸⁸ (b) Lead optimization of compound **14** into compounds **15** and **16**.

optimization of the structure to allow good brain permeation through the BBB, and subsequent efforts of the same authors were directed through the reduction of the amidino pK_a value to modulate the overall cLogP of the compounds. The authors found that the substitution of the chlorine atom with a CN group and the introduction of a fluorine atom at C-2 position can increase the inhibition potency as well as the CNS permeation (compound **15**, Figure 11b).⁸⁹ An additional challenge of BACE-1 inhibitors is to avoid the inhibition of hERG, which causes cardiotoxicity as a severe side effect.⁹⁰ In this view, the authors demonstrated that the replacement of the 2-fluoro substituent by a CF_3 group (compound **16**) resulted in a reduced hERG inhibition, with an improved cardiovascular safety profile to allow the entrance of compound **16** into clinical trials (Figure 11b).⁸⁹

Our efforts in this field consist of the development of morpholine-containing peptidomimetics able to inhibit BACE-1. We recently reported how a bicyclic morpholine containing acetal scaffold decorated with a $C=S$ bond was found to be active as a BACE-1 inhibitor (compound **17**, Figure 12).⁹¹ Docking studies revealed the importance of the morpholine appendage for interacting with polar and apolar residues and of the sulfur atom for addressing the flap region.^{92,93} Successively,

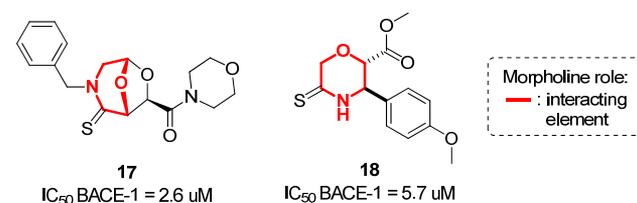


Figure 12. Structure of morpholine derivatives **17** and **18** developed as BACE-1 inhibitors.

we developed C-2 substituted morpholine derivatives containing a thioamide group, identifying compound **18** with micromolar activity against BACE-1. According to molecular docking calculations, the binding mode of this compound was characterized by the thioamide moiety experiencing interactions with catalytic Asp228 and by the phenyl substituent interacting with aromatic residues on the flap region (Figure 12).⁹⁴

$A\beta_{40}$ and $A\beta_{42}$ peptides are known to be the main toxic factors for neuronal injury and death in Alzheimer's disease (AD), due to the ion-channel formation, free radical generation, and interaction with various proteins (e.g., apolipoprotein E and mitochondrial hydroxyacyl-CoA dehydrogenase).⁹⁵ The presence of these peptides can be reduced by inhibiting γ -secretase, the enzyme that processes the N-terminal fragment C99 of the APP protein into these peptides.⁹⁵ This enzyme can be inhibited by the 2,6-disubstituted morpholine *N*-arylsulfonamide **20**, a compound able to reduce $A\beta$ levels in Tg CRND8 mice (Figure 13a).⁹⁶

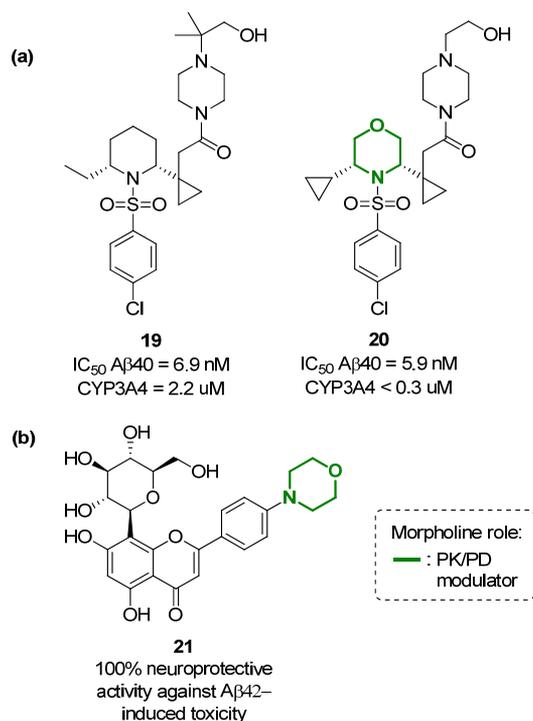


Figure 13. Structure of morpholine-containing compounds involved in the reduction of amyloid β ($A\beta$) peptides for the treatment of Alzheimer's disease by inhibiting γ -secretase or reducing $A\beta_{42}$ -induced cell toxicity.

The replacement of the piperidine scaffold with a morpholine ring in a previous series of compounds⁹⁷ resulted in an overall improvement of potency and CYP3A4 liability (see compound **19** in Figure 13a). The introduction of morpholine was found beneficial also in a class of C-glucosyl chromen-4-ones, as the *p*-morpholinyl flavone **21** stood out for its ability to interact with $A\beta_{42}$ peptides, reducing $A\beta_{42}$ -induced cell death in AD and neuroblastoma model systems (Figure 13b).⁹⁸

Finally, another molecular target that has been recently proposed due to its involvement in the amyloid cascade is δ -secretase, also known as asparagine endopeptidase (AEP) or

legumain.⁹⁹ This lysosomal cysteine proteinase cleaves both amyloid precursor protein (APP) and tau, two major pathogenic players in AD. APP is the peptide that is also demolished by β - and γ -secretase, while tau is cleaved into SET fragments, small peptides that inhibit the activity of protein phosphatase 2A (PP2A). Recently, a high-throughput screening to find δ -secretase inhibitors resulted in the identification of 7-morpholinobenzo[*c*][1,2,5]oxadiazol-4-amine (compound **22**, Figure 14a) and a 2,4-dimorpholinoaniline (compound **23**,

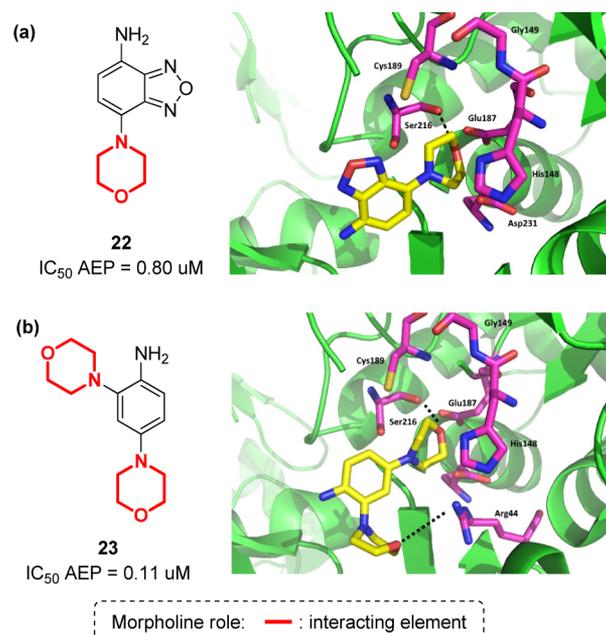


Figure 14. (a) Structure of compound **22** and its interaction in the active site of δ -secretase (PDB: 5LUB);⁵⁹ (b) structure of compound **23** and its interaction in the active site of δ -secretase (PDB: 5LUA).⁵⁹

Figure 14b) as nontoxic and potent δ -secretase inhibitors, able to reduce tau and APP cleavage in *in vivo* murine models.¹⁰⁰ The crystal structure of δ -secretase in complex with these two compounds revealed the importance of morpholine for the interaction, both in the active site and in the regulatory allosteric exosite of δ -secretase. Specifically, the morpholine ring in compound **22** was found to be interacting within the S1 pocket with Cys189, Gly149, and His148 (Figure 14a), and the benzofurazan moiety interacting with Ser215 and Tyr217 of the S2 pocket, with fewer contact points as compared to those found in the interaction with the allosteric site. Compound **23**, not possessing the benzofurazan core, was developed to increase the preference of the inhibitor for the active site and not for the allosteric one. As shown in Figure 14b, compound **23** is able not only to maintain the interaction with Cys189, Gly149, and His148 at the S1 site typical of the morpholine ring, but also to mimic the canonical P2–S2 and P3–S3 interactions found in the active site, with an increased binding affinity for δ -secretase.

Although not strictly related to the amyloid cascade hypothesis, there has been reported evidence regarding the involvement of acetylcholine, norepinephrine, dopamine, and serotonin levels in the etiology of Alzheimer's disease.^{101,102} Thus, acetylcholinesterase (AChE), monoamine oxidase (MAO-A and MAO-B), and the M1 acetylcholine receptor, responsible for the regulation of such biogenic amines in the CNS, are considered interesting therapeutic targets in AD drug

discovery. The morpholine ring is frequently observed in acetylcholinesterase (AChE) and MAO inhibitors, thus confirming the importance of this heterocycle in providing useful interactions with different receptors.¹⁰³ For example, compound **25** is a dual inhibitor of acetylcholinesterase (AChE) and monoamine oxidase B (MAO-B) with good BBB permeability, representing a promising lead compound for the prevention and treatment of AD (Figure 15b).¹⁰⁴ Again,

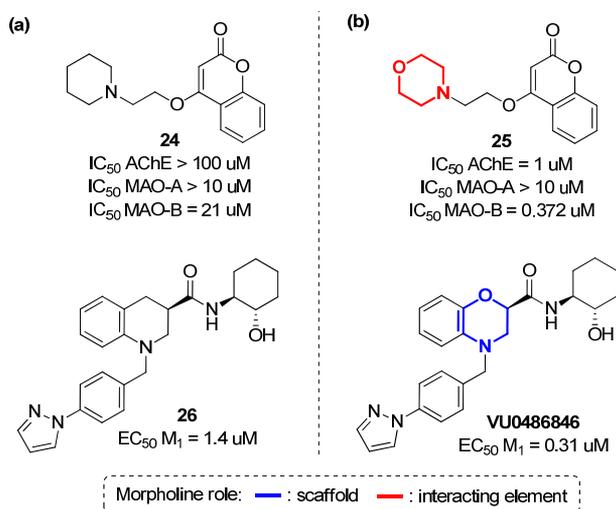


Figure 15. Structure of (a) compounds able to modulate molecular targets (acetylcholinesterase enzyme (AChE), monoamine oxidase (MAO-A and MAO-B) and M1 acetylcholine receptor) involved in the regulation of several biogenic amines, in comparison with (b) morpholine-containing analogues.

the replacement of the piperidine ring with morpholine resulted in a 100-fold enhancement of the activity toward MAO-B, as evinced by molecular modeling studies that revealed how the morpholine ring interacts in the entrance cavity, directing the coumarin scaffold in the substrate cavity. In addition, the benzomorpholine compound VU0486846 is able to activate the M1 subtype of muscarinic acetylcholine receptor through a positive allosteric modulation (PAM), showing a potential recovery of cognition in AD animal models (Figure 15b).¹⁰⁵ This compound was developed by a scaffold hopping screening campaign, and showed good CNS penetration, with no classic cholinergic adverse events in the prefrontal cortex (PFC), as evinced by the absence of any interaction with the orthosteric acetylcholine (ACh) site and no seizure liability at high brain exposures.¹⁰⁶

■ BIOLOGICAL ACTIVITY OF MORPHOLINE DERIVATIVES ON CNS TUMORS

The development of morpholine containing anticancer drugs with minimal or no side effects is an active field in drug discovery,^{17–22} and this is especially true in the case of CNS tumors, including astrocytoma, glioblastoma, medulloblastoma, ependymal, and meningeal tumors. Targeted therapy is one of the most effective ways to treat those type of cancers, and especially for CNS tumors, major targets that can be addressed with morpholine-containing compounds are the kinases involved in cell cycle regulation, namely, phosphatidylinositol 3-kinase (PI3K)^{107,108} and the mammalian target of rapamycin (mTOR1 and mTOR2).^{109,110} In particular, the PI3K-mTOR pathway has attracted much attention to the scientific

community involved in CNS drug discovery, as an over-activated PI3K/mTOR pathway has been related not only to aberrant cancer cell growth, but also to several neurodegenerative pathways.^{111,112} Thus, the development of brain penetrant dual pan-PI3K/mTOR inhibitors may enable the identification of novel agents for the treatment of brain metastasis and brain tumors. Many morpholine-containing PI3K inhibitors have been developed over the last decades,^{113–116,17,22} with a particular recurrence of morpholino-pyrimidine,¹¹³ morpholino-triazine,¹¹⁴ and morpholinopyrimidine-5-carbonitrile.¹¹⁵ Just to give some examples, NVP-BKM120 is a compound able to inhibit all four class I PI3K isoforms with 50-fold selectivity over the other protein kinases (Figure 16a).¹¹⁷ As shown by the crystal structure of this

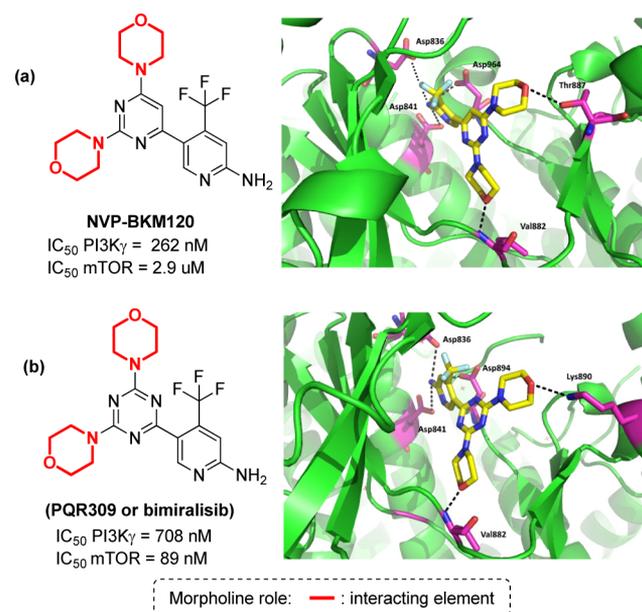


Figure 16. (a) Structure of compound NVP-BKM120 and its interaction pattern in the active site of PI3K γ (PDB: 3SD5).⁵⁹ (b) Structure of compound PQR309 and its interaction pattern in the active site of PI3K γ (PDB: 5OQ4).⁵⁹

compound, one morpholine ring interacts with the hinge valine Val882 through its oxygen atom, a key interaction established by several PI3K inhibitors in the ATP-binding site. The second morpholine interacts with Thr887, though it was added as a double substitution to maintain the capacity of interacting with the key Val882, considering that morpholine is highly susceptible to *in vivo* oxidation. The NH₂ group of the aminopyridine ring forms hydrogen bonds with the carboxylic group of aspartates Asp836, Asp841, and Asp964. Starting from this compound, Beaufils and co-workers replaced the pyrimidine ring with a triazine ring, developing PQR309 (also called bimiralisib), a compound able to inhibit all PI3K kinases of class I as well as mTOR kinase (Figure 16b).¹¹⁸ This compound is orally active, crosses the blood-brain barrier, and displays favorable pharmacokinetic parameters in several animal models, thus demonstrating its potential for the treatment of brain tumors or CNS metastasis. The crystal structure revealed the same interaction of one morpholine oxygen atom with Val882, with the other morpholine establishing a hydrogen bond with Lys890, and maintaining those interactions of the aminopyridine NH₂ group with Asp964, whereas the triazine ring was found interacting

through π - π stacking interactions with Phe961, Tyr867, and Phe965.

Although the dual inhibition of PI3K and mTOR enzyme is of potential interest for the development of anticancer drugs, the selective inhibition of the mTOR complex over the PI3K family is of special relevance in the field of CNS drug discovery. In fact, for several dual inhibitors (including PQR309) it has been observed that when mTOR1 is inhibited, class IA PI3Ks are overactivated, resulting in a mTOR2-dependent increase in the PKB/Akt activity.^{119–121} Compounds targeting both mTOR1 and mTOR2, without significantly inhibiting PI3K family, are expected to provide a more efficient blockade of growth factors, as well as to display a beneficial effect in Alzheimer's and Parkinson's diseases,^{122,123} mostly because the inhibition of mTOR promotes the removal of toxic protein complexes by inducing autophagy. The crystal structure of mTOR has been reported by Yang and co-workers,¹²⁴ in complex with PI-103, a morpholine-containing compound that is able to inhibit both mTOR and class I PI3K kinase (Figure 17). This study revealed that the active site of

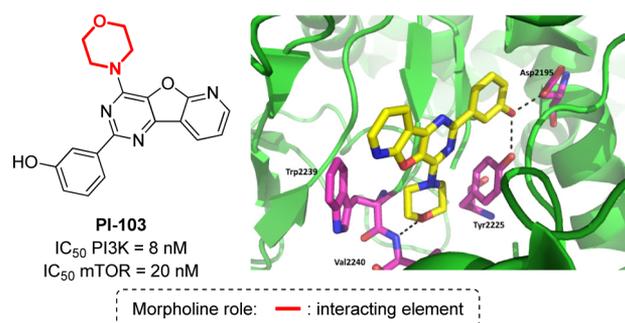


Figure 17. Crystal structure of PI-103 in complex with mTOR (PDB: 4JT6).⁵⁹

this enzyme is remarkably similar to canonical PI3K kinases. Thus, the hinge interaction with valine (here Val2240) is conserved, as well as the presence of several hydrophobic residues. Thus, PI-103 does not provide any selectivity for this catalytic cleft, as the morpholine ring makes the classical hydrogen bonds to the “hinge” Val2240 and Cys2243, while the *m*-phenol group binds to the inner pocket establishing two hydrogen bonds with Tyr2225 and Asp2195 side chains at the back of the cleft (Figure 17). In addition, the central aromatic scaffolds establish a π -stacking interaction with Trp2239.

As mTOR has a deeper pocket as compared to PI3K, the introduction of substituents on the morpholine ring, such as an ethylene bridge between positions 3 and 5 or a methyl group at position 3, have been studied in order to develop selective and highly brain penetrant mTOR kinase inhibitors.¹²⁵ In particular, the introduction of the bridged morpholine moiety is often beneficial for CNS candidates, as they are effective in decreasing lipophilicity, partly because of an enhancement of the polar surface area resulting from conformational changes.^{24,126} For example, PQR620, containing two 3,5-bridged morpholines, inhibits mTOR kinase potently and selectively, and showed antitumor effects *in vitro* and *in vivo*, with promising benefits in CNS indications due to its brain/plasma distribution ratio.¹²⁷ Similarly, compound 27, possessing two 3-methylmorpholines, is a potent, orally available, and specific ATP-competitive mTOR inhibitor with selectivity against all Class I PI3K isoforms and other kinases (Figure

18).¹²⁸ In particular, the thiazolopyrimidine 27 was found to be brain-penetrant and active in neuronal cell-based models of

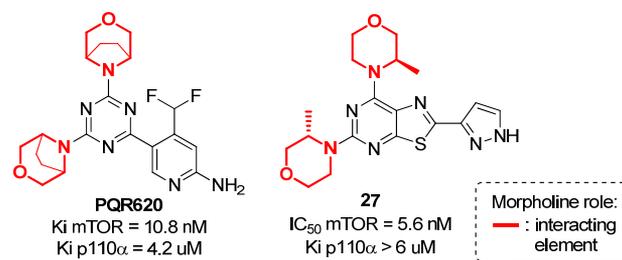


Figure 18. Structure of morpholine-containing compounds able to selectively inhibit mTOR complex over the PI3K kinase family.

mTOR hyperactivity, significantly improving the survival rate of mice with neuronal-specific ablation of the *Tsc1* gene. Molecular docking studies revealed the importance of the pyrazole moiety of compound 27 in providing additional hydrogen-bonding interactions with catalytic Lys2187 and Asp2195 residues, in addition to the interaction of the morpholine oxygen atom with Val2240.

CONCLUSION

Developing drugs for the central nervous system (CNS) require fine chemical modifications, as a strict balance between size and lipophilicity is necessary to improve the permeability through the blood-brain barrier (BBB). In this context, morpholine and its analogues represent valuable heterocycles, due to their conformational and physicochemical properties. In fact, the presence of a weak basic nitrogen, at the opposite position of the oxygen atom, provide to the ring a peculiar pK_a value and a flexible conformation, thus allowing it to take part in several lipophilic–hydrophilic interactions, and to improve blood solubility and brain permeability of the overall structure. Herein, the analysis of selected morpholine-containing CNS drug candidates revealed the active pharmacophores accountable for the modulation of different molecular targets, that have been subdivided in three classes: (1) receptors involved in mood disorders and pain; (2) enzymes and receptors responsible for neurodegenerative diseases; and (3) enzymes involved in the pathology of CNS tumors. This analysis allowed us to highlight the cases when morpholine contributes in the overall drug structure by (1) directly interacting with key residues in the binding site of the target, (2) having a scaffolding function to direct the appendages in the right position, or (3) improving the overall pharmacokinetic profile, specifically relating to the half-life and the distribution in CNS tissues/brain permeability of the final compound. For the first two cases, several examples reporting binding features retrieved from PDB data allowed us to highlight the key role of the morpholine chemotype in establishing key interactions. For the latter, we compared morpholine-containing compounds with analogues lacking this ring, in order to evaluate not only the potency but also the PK/PD properties relevant for the CNS drug discovery. The morpholine ring has attracted the attention of a large area of the medicinal chemistry community for the development of compounds with a plethora of different biological activities, as demonstrated by the increasing number of research articles and review papers. We do expect in the future that the morpholine chemotype will be taken into

account increasingly for drug development in the field of CNS drug discovery.

AUTHOR INFORMATION

Corresponding Author

Andrea Trabocchi – Department of Chemistry “Ugo Schiff”,
University of Florence, 50019 Sesto Fiorentino, Florence,
Italy; orcid.org/0000-0003-1774-9301;
Email: andrea.trabocchi@unifi.it

Authors

Elena Lenci – Department of Chemistry “Ugo Schiff”,
University of Florence, 50019 Sesto Fiorentino, Florence,
Italy; orcid.org/0000-0001-7408-2828

Lorenzo Calugi – Department of Chemistry “Ugo Schiff”,
University of Florence, 50019 Sesto Fiorentino, Florence,
Italy; orcid.org/0000-0002-8652-9751

Complete contact information is available at:

<https://pubs.acs.org/10.1021/acscchemneuro.0c00729>

Author Contributions

All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

Airalzh Onlus-COOP Italia (fellowship to LC), MIUR (“Progetto Dipartimenti di Eccellenza 2018-2022” allocated to Department of Chemistry “Ugo Schiff”) and Fondazione Cassa di Risparmio di Pistoia e Pescia (Bando Giovani@Ricerca scientifica 2018, fellowship to EL) are acknowledged for financial support.

REFERENCES

- (1) Kesselheim, A. S., Hwang, T. J., and Franklin, J. M. (2015) Two decades of new drug development for central nervous system disorders. *Nat. Rev. Drug Discovery* 14, 815–816.
- (2) Gribkoff, V. K., and Kaczmarek, L. K. (2017) The need for new approaches in CNS drug discovery. *Neuropharmacology* 120, 11–19.
- (3) Ghose, A. K., Herberich, T., Hudkins, R. L., Dorsey, B. D., and Mallamo, J. P. (2012) Knowledge-based, central nervous system (CNS) lead selection and lead optimization for CNS drug discovery. *ACS Chem. Neurosci.* 3, 50–68.
- (4) Lalatsa, A., Schatzlein, A. G., and Uchegbu, I. F. (2014) Strategies to deliver peptide drugs to the brain. *Mol. Pharmaceutics* 11, 1081–1093.
- (5) Lau, J. L., and Dunn, M. K. (2018) Therapeutic peptides: historical perspectives, current development trends, and future directions. *Bioorg. Med. Chem.* 26, 2700–2707.
- (6) Neves, V., Aires-Da-Silva, F., Corte-Real, S., and Castanho, M. A. R. B. (2016) Antibody approaches to treat brain diseases. *Trends Biotechnol.* 34, 36–48.
- (7) Ryan, P., Patel, B., Makwana, V., Jadhav, H. R., Kiefel, M., Davey, A., Reekie, T. A., Rudrawar, S., and Kassiou, M. (2018) Peptides, peptidomimetics, and carbohydrate-peptide conjugates as amyloidogenic aggregation inhibitors for Alzheimer’s disease. *ACS Chem. Neurosci.* 9, 1530–1551.
- (8) Sweeney, M. D., Sagare, A. P., and Zlokovic, B. V. (2018) Blood-brain barrier breakdown in Alzheimer disease and other neurodegenerative disorders. *Nat. Rev. Neurol.* 14, 133–150.
- (9) Wager, T. T., Chandrasekaran, R. Y., Hou, X., Troutman, M. D., Verhoest, P. R., Villalobos, A., and Will, Y. (2010) Defining desirable central nervous system drug space through the alignment of molecular properties, in vitro ADME, and safety attributes. *ACS Chem. Neurosci.* 1, 420–434.
- (10) Wager, T. T., Hou, X., Verhoest, P. R., and Villalobos, A. (2016) Central nervous system multiparameter optimization desirability: application in drug discovery. *ACS Chem. Neurosci.* 7, 767–775.
- (11) Rankovic, Z. (2015) CNS drug design: balancing physicochemical properties for optimal brain exposure. *J. Med. Chem.* 58, 2584–2608.
- (12) Danon, J. J., Reekie, T. A., and Kassiou, M. (2019) Challenges and opportunities in central nervous system drug discovery. *Trends Chem.* 1, 612–624.
- (13) Wijtmans, R., Vink, M. K. S., Schoemaker, H. E., van Delft, F. L., Blaauw, R. H., and Rutjes, F. P. J. T. (2004) Biological relevance and synthesis of C-substituted morpholine derivatives. *Synthesis* 2004, 641–662.
- (14) Ilaš, J., Anderluh, P. Š., Dolenc, M. S., and Kikelj, D. (2005) Recent advances in the synthesis of 2H-1,4-benzoxazin-3-(4H)-ones and 3,4-dihydro-2H-1,4-benzoxazines. *Tetrahedron* 61, 7325–7348.
- (15) Pal’chikov, V. A. (2013) Morpholines. Synthesis and biological activity. *Russ. J. Org. Chem.* 49, 787–814.
- (16) Tzara, A., Xanthopoulos, D., and Kourounakis, A. P. (2020) Morpholine as a scaffold in medicinal chemistry: an update on synthetic strategies. *ChemMedChem* 15, 392–403.
- (17) Kourounakis, A. P., Xanthopoulos, D., and Tzara, A. (2020) Morpholine as a privileged structure: a review on the medicinal chemistry and pharmacological activity of morpholine containing bioactive molecules. *Med. Res. Rev.* 40, 709–752.
- (18) Al-Ghorbani, M., Begum, B., Zabiulla, A., Mamatha, S. V., and Khanum, S. A. (2015) Piperazine and morpholine: synthetic preview and pharmaceutical applications. *J. Chem. Pharm. Res.* 7, 281–301.
- (19) Naim, M. J., Alam, O., Alam, M. J., Alam, P., and Shrivastava, N. (2015) A review on pharmacological profile of morpholine derivatives. *Int. J. Pharmacol. Pharm. Sci.* 3, 40–51.
- (20) Rupak, K., Vulichi, S. R., and Suman, K. (2016) Emphasizing morpholine and its derivatives (maid): typical candidate of pharmaceutical importance. *Int. J. Chem. Sci.* 14, 1777–1788.
- (21) Arshad, F., Khan, M. F., Akhtar, W., Alam, M. M., Nainwal, L. M., Kaushik, S. K., Akhter, M., Parvez, S., Hasan, S. M., and Shaquiquzzaman, M. (2019) Revealing quinquennial journey of morpholine: a SAR based review. *Eur. J. Med. Chem.* 167, 324–356.
- (22) Kumari, A., and Singh, R. K. (2020) Morpholine as ubiquitous pharmacophore in medicinal chemistry: deep insight into the structure-activity relationship (SAR). *Bioorg. Chem.* 96, 103578.
- (23) Rekká, E. A., and Kourounakis, P. N. (2010) Medicinal chemistry of 2,2,4-substituted morpholines. *Curr. Med. Chem.* 17, 3422–3430.
- (24) Hocine, S., Berger, G., and Hanessian, S. (2020) Design and synthesis of backbone-fused, conformationally constrained morpholine-proline chimeras. *J. Org. Chem.* 85, 4237–4247.
- (25) Baskar, R., Baby, C., Moni, M. S., and Subramanian, K. (2013) Synthesis, characterization and dynamic NMR studies of a novel chalcone based N-substituted morpholine derivative. *J. Mol. Struct.* 1040, 90–97.
- (26) Cotten, J. F., Keshavaprasad, B., Laster, M. J., Eger, E. I., and Yost, C. S. (2006) The ventilator stimulant doxapram inhibits TASK tandem pore (K2P) potassium channel function but does not affect minimum alveolar anesthetic concentration. *Anesth. Analg.* 102, 779–785.
- (27) Stoops, W. W., Strickland, J. C., Alcorn, J. L., Hays, L. R., Rayapati, A. O., Lile, J. A., and Rush, C. R. (2019) Influence of phendimetrazine maintenance on the reinforcing, subjective, performance, and physiological effects of intranasal cocaine. *Psychopharmacology* 236, 2569–2577.
- (28) Bonnet, U. (2003) Moclobemide: therapeutic use and clinical studies. *CNS Drug Rev.* 9, 97–140.
- (29) Naidu, C., and Kulkarni, J. (2019) Psychosis induced by antidepressant treatment with reboxetine. *Aust. N. Z. J. Psychiatry* 53, 1227–1228.

- (30) Walsh, S. L., Heilig, M., Nuzzo, P. A., Henderson, P., and Lofwall, M. R. (2013) Effects of the NK1 antagonist, aprepitant, on response to oral and intranasal oxycodone in prescription opioid abusers. *Addict. Biol.* 18, 332–343.
- (31) Hale, J. J., Mills, S. G., MacCoss, M., Finke, P. E., Cascieri, M. A., Sadowski, S., Ber, E., Chicchi, G. G., Kurtz, M., Metzger, J., et al. (1998) Structural optimization affording 2-(R)-(1-(R)-3, 5-bis-(trifluoromethyl) phenylethoxy)-3-(S)-(4-fluoro)phenyl-4- (3-oxo-1,2,4-triazol-5-yl)methylmorpholine, a potent, orally active, long acting morpholine acetal human NK-1 receptor antagonist. *J. Med. Chem.* 41, 4607–4614.
- (32) Hargreaves, R., Arjona Ferreira, J. C., Hughes, D., Brands, J., Hale, J., Mattson, B., and Mills, S. (2011) Development of aprepitant, the first neurokinin-1 receptor antagonist for the prevention of chemotherapy-induced nausea and vomiting. *Ann. N. Y. Acad. Sci.* 1222, 40–48.
- (33) Hobbs, H., Bravi, G., Campbell, I., Convery, M., Davies, H., Inglis, G., Pal, S., Peace, S., and Redmond, J. (2019) and Summers, D. Discovery of 3-oxabicyclo[4.1.0]heptane, a non-nitrogen containing morpholine isostere, and its application in novel inhibitors of the PI3K-AKT-mTOR pathway. *J. Med. Chem.* 62, 6972–6984.
- (34) Li, J., Ji, J., Xu, R., and Li, R. (2019) Indole compounds with N-ethyl morpholine moieties as CB2 receptor agonists for anti-inflammatory management of pain: synthesis and biological evaluation. *MedChemComm* 10, 1935–1947.
- (35) Sugiura, T., and Waku, K. (2002) Cannabinoid receptors and their endogenous ligands. *J. Biochem.* 132, 7–12.
- (36) Janero, D. R., Vadivel, S. K., and Makriyannis, A. (2009) Pharmacotherapeutic modulation of the endocannabinoid signalling system in psychiatric disorders: drug-discovery strategies. *Int. Rev. Psychiatry* 21, 122–133.
- (37) Cushman, M., Nagarathnam, D., Gopal, D., He, H. M., Lin, C. M., and Hamel, E. (1992) Synthesis and evaluation of analogs of (Z)-1-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethene as potential cytotoxic and antimetabolic agents. *J. Med. Chem.* 35, 2293.
- (38) Haubrich, D. R., Ward, S. J., Baizman, E., Bell, M. R., Bradford, J., Ferrari, R., Miller, M., Perrone, M., Pierson, A. K., Saelens, J. K., et al. (1990) Pharmacology of pravadoline: a new analgesic agent. *J. Pharmacol Exp Ther.* 255, 511–522.
- (39) Shi, Y., Duan, Y. H., Ji, Y. Y., Wang, Z. L., Wu, Y. R., Gunosewoyo, H., Xie, X. Y., Chen, J. Z., Yang, F., Li, J., et al. (2017) Amidoalkylindoles as potent and selective cannabinoid type 2 receptor agonists with in vivo efficacy in a mouse model of multiple sclerosis. *J. Med. Chem.* 60, 7067–7083.
- (40) Reggio, P. H. (2010) Endocannabinoid binding to the cannabinoid receptors: what is known and what remains unknown. *Curr. Med. Chem.* 17, 1468–1486.
- (41) Hua, T., Vemuri, K., Pu, M., Qu, L., Han, G. W., Wu, Y., Zhao, S., Shui, W., Li, S., et al. (2016) Crystal structure of the human cannabinoid receptor CB1. *Cell* 167, 750–762.
- (42) Li, X., Hua, T., Vemuri, K., Ho, J.-H., Wu, X., Wu, L., Popov, P., Benchama, O., Zvonok, N., et al. (2019) Crystal structure of the human cannabinoid receptor CB2. *Cell* 176, 459–467.
- (43) Howlett, A. C. (2002) The cannabinoid receptors. *Prostaglandins Other Lipid Mediators* 68, 619–631.
- (44) Rajesh, M., Mukhopadhyay, P., Haskó, G., Huffman, J. W., Mackie, K., and Pacher, P. (2008) CB2 cannabinoid receptor agonists attenuate TNF- α -induced human vascular smooth muscle cell proliferation and migration. *Br. J. Pharmacol.* 153, 347–357.
- (45) Picone, R. P., and Kendall, D. A. (2015) Minireview: from the bench, toward the clinic: therapeutic opportunities for cannabinoid receptor modulation. *Mol. Endocrinol.* 29, 801–813.
- (46) Soethoudt, M., Grether, U., Fingerle, J., Grim, T. W., Fezza, F., de Petrocellis, L., Ullmer, C., Rothenhäusler, B., Perret, C., van Gils, N., et al. (2017) Cannabinoid CB 2 receptor ligand profiling reveals biased signalling and off-target activity. *Nat. Commun.* 8, 13958.
- (47) Rhee, M. H., Nevo, I., Bayewitch, M. L., Zagoory, O., and Vogel, Z. (2000) Functional role of tryptophan residues in the fourth transmembrane domain of the CB(2) cannabinoid receptor. *J. Neurochem.* 75, 2485–2491.
- (48) Su, T. P., Su, T. C., Nakamura, Y., and Tsai, S. Y. (2016) The sigma-1 receptor as a pluripotent modulator in living systems. *Trends Pharmacol. Sci.* 37, 262–278.
- (49) McCorvy, J. D., and Roth, B. L. (2015) Structure and function of serotonin G protein-coupled receptors. *Pharmacol. Ther.* 150, 129–142.
- (50) Díaz, J. L., Cuberes, R., Berrocal, J., Contijoch, M., Christmann, U., Fernández, A., Port, A., Holenz, J., Buschmann, H., Laggner, C., et al. (2012) Synthesis and biological evaluation of the 1-arylpyrazole class of $\sigma(1)$ receptor antagonists: identification of 4-{2-[5-methyl-1-(naphthalen-2-yl)-1H-pyrazol-3-yloxy]ethyl}morpholine (S1RA, E-52862). *J. Med. Chem.* 55, 8211–8224.
- (51) Castany, S., Codony, X., Zamanillo, D., Merlos, M., Verdú, E., and Boadas-Vaello, P. (2019) Repeated sigma-1 receptor antagonist MR309 administration modulates central neuropathic pain development after spinal cord injury in mice. *Front. Pharmacol.* 10, 222.
- (52) Sánchez-Blázquez, P., Pozo-Rodríguez, A., Merlos, M., and Garzón, J. (2018) The sigma-1 receptor antagonist, S1RA, reduces stroke damage, ameliorates post-stroke neurological deficits and suppresses the overexpression of MMP-9. *Mol. Neurobiol.* 55, 4940–4951.
- (53) Xiong, Y., Teegarden, B. R., Choi, J. S., Strah-Pleyne, S., Decaire, M., Jayakumar, H., Dosa, P. I., Casper, M. D., Pham, L., Feichtinger, K., et al. (2010) Discovery and structure-activity relationship of 3-methoxy N-(3-(1-methyl-1H-pyrazol-5-yl)-4-(2-morpholinoethoxy)phenyl)benzamide (APD791): a highly selective 5-hydroxytryptamine_{2A} receptor inverse agonist for the treatment of arterial thrombosis. *J. Med. Chem.* 53, 4412–4421.
- (54) Przyklenk, K., Frelinger, A. L., Linden, M. D., Whittaker, P., Li, Y., Barnard, M. R., Adams, J., Morgan, M., Al-Shamma, H., and Michelson, A. D. (2010) Targeted inhibition of the serotonin 5HT_{2A} receptor improves coronary patency in an in vivo model of recurrent thrombosis. *J. Thromb. Haemostasis* 8, 331–340.
- (55) Seo, H. J., Park, E.-J., Kim, M. J., Kang, S. Y., Lee, S. H., Kim, H. J., Lee, K. N., Jung, M. E., Lee, M., Kim, M. S., et al. (2011) Design and synthesis of novel arylpiperazine derivatives containing the imidazole core targeting 5-HT(2A) receptor and 5-HT transporter. *J. Med. Chem.* 54, 6305–6318.
- (56) Quartara, L., and Maggi, C. A. (1997) The tachykinin NK1 receptor. Part I: Ligands and mechanisms of cellular activation. *Neuropeptides* 31, 537–563.
- (57) Steinhoff, M. S., von Mentzer, B., Geppetti, P., Pothoulakis, C., and Bunnett, N. W. (2014) Tachykinins and their receptors: contributions to physiological control and the mechanisms of disease. *Physiol. Rev.* 94, 265–301.
- (58) Schöppe, J., Ehrenmann, J., Klenk, C., Rucktooa, P., Schütz, M., Doré, A. S., and Plücker, A. (2019) Crystal structures of the human neurokinin 1 receptor in complex with clinically used antagonists. *Nat. Commun.* 10, 17.
- (59) Edited with PyMOL 0.99rc6, DeLano Scientific LLC; Palo Alto, CA, USA, 2006.
- (60) Celanire, S., Wijtman, M., Talaga, P., Leurs, R., and de Esch, I. J. P. (2005) Histamine H3 receptor antagonists reach out for the clinic. *Drug Discovery Today* 10, 1613–1627.
- (61) Gemkow, M. J., Davenport, A. J., Harich, S., Ellenbroek, B. A., Cesura, A., and Hallett, D. (2009) The histamine H3 receptor as a therapeutic drug target for CNS disorders. *Drug Discovery Today* 14, 509–515.
- (62) Dvorak, C. A., Apodaca, R., Xiao, W., Jablonowski, J. A., Bonaventure, P., Dugovic, C., Shelton, J., Lord, B., Miller, K., Dvorak, L. K., et al. (2009) Diamine-based human histamine H3 receptor antagonists: (4-aminobutyn-1-yl) benzylamines. *Eur. J. Med. Chem.* 44, 4098–4106.
- (63) Niswender, C. M., and Conn, P. J. (2010) Metabotropic glutamate receptors: physiology, pharmacology, and disease. *Annu. Rev. Pharmacol. Toxicol.* 50, 295–322.

- (64) Crupi, R., Impellizzeri, D., and Cuzzocrea, S. (2019) Role of metabotropic glutamate receptors in neurological disorders. *Front. Mol. Neurosci.* 12, 20.
- (65) Chaki, S., Ago, Y., Palucha-Paniewiera, A., Matrisciano, F., and Pilc, A. (2013) mGlu2/3 and mGlu5 receptors: potential targets for novel antidepressants. *Neuropharmacology* 66, 40–52.
- (66) Childress, E. S., Wieting, J. M., Felts, A. S., Breiner, M. M., Long, M. F., Luscombe, V. B., Rodriguez, A. L., Cho, H. P., Blobaum, A. L., Niswender, C. M., et al. (2019) Discovery of novel central nervous system penetrant metabotropic glutamate receptor subtype 2 (mGlu2) negative allosteric modulators (NAMs) based on functionalized pyrazolo[1,5-a]pyrimidine-5-carboxamide and thieno[3,2-b]-pyridine-5-carboxamide cores. *J. Med. Chem.* 62, 378–384.
- (67) Gatta, E., Cupello, A., Di Braccio, M., Grossi, G., Ferruzzi, R., Roma, G., and Robello, M. (2010) New 1,5-benzodiazepine compounds: activity at native GABA(A) receptors. *Neuroscience* 166, 917–923.
- (68) Colestock, T., Wallach, J., Mansi, M., Filemban, N., Morris, H., Elliott, S. P., Westphal, F., Brandt, S. D., and Adejare, A. (2018) Syntheses, analytical and pharmacological characterizations of the 'legal high' 4-[1-(3-methoxyphenyl)cyclohexyl]morpholine (3-MeO-PCMo) and analogues. *Drug Test. Anal.* 10, 272–283.
- (69) Szeto, J. Y. Y., Walton, C. C., Rizos, A., Martinez-Martin, P., Halliday, G. M., Naismith, S. L., Chaudhuri, K. R., and Lewis, S. J. G. (2020) Dementia in long-term Parkinson's disease patients: a multicentre retrospective study. *NPJ. Parkinsons Dis.* 6, 20.
- (70) Elkouzi, A., Vedam-Mai, V., Eisinger, R. S., and Okun, M. S. (2019) Emerging therapies in Parkinson disease — repurposed drugs and new approaches. *Nat. Rev. Neurol.* 15, 204–223.
- (71) Martin, I., Kim, J. W., Dawson, V. L., and Dawson, T. M. (2014) LRRK2 pathobiology in Parkinson's disease. *J. Neurochem.* 131, 554–565.
- (72) Fell, M. J., Mirescu, C., Basu, K., Cheewatrakoolpong, B., et al. (2015) MLI-2, a potent, selective, and centrally active compound for exploring the therapeutic potential and safety of LRRK2 kinase inhibition. *J. Pharmacol. Exp. Ther.* 355, 397–409.
- (73) Mori, W., Yamasaki, T., Hattori, Y., Zhang, Y., Kumata, K., Fujinaga, M., Hanyu, M., Nengaki, N., Zhang, H., and Zhang, M.-R. (2020) Radiosynthesis and evaluation of 4-(6-[¹⁸F]Fluoro-4-(5-isopropoxy-1H-indazol-3-yl)pyridin-2-yl)-morpholine as a novel radiotracer candidate targeting leucine-rich repeat kinase 2. *RSC Med. Chem.* 11, 676–684.
- (74) Lindsley, C. W., and Hopkins, C. R. (2017) Return of D4 dopamine receptor antagonists in drug discovery. *J. Med. Chem.* 60, 7233–7243.
- (75) Mishra, A., Singh, S., and Shukla, S. (2018) Physiological and functional basis of dopamine receptors and their role in neurogenesis: possible implication for Parkinson's disease. *J. Exp. Neurosci.* 12, 1179069518779829.
- (76) Mach, R. H., and Luedtke, R. R. (2018) Challenges in the development of dopamine D2- and D3-selective radiotracers for PET imaging studies. *J. Labelled Compd. Radiopharm.* 61, 291–298.
- (77) Blagg, J., Allerton, C. M., Batchelor, D. V., Baxter, A. D., Burring, D. J., Carr, C. L., Cook, A. S., Nichols, C. L., Phipps, J., Sanderson, V. G., et al. (2007) Design and synthesis of a functionally selective D3 agonist and its in vivo delivery via the intranasal route. *Bioorg. Med. Chem. Lett.* 17, 6691–6696.
- (78) Todorovic, M., Wood, S. A., and Mellick, G. D. (2016) Nrf2: a modulator of Parkinson's disease? *J. Neural Transm.* 123, 611–619.
- (79) Choi, J. W., Kim, S., Park, J.-H., Kim, H. J., Shin, S. J., Kim, J. W., Woo, S. Y., Lee, C., Han, S. M., Lee, J., et al. (2019) Optimization of vinyl sulfone derivatives as potent nuclear factor erythroid 2-related factor 2 (Nrf2) activators for Parkinson's disease therapy. *J. Med. Chem.* 62, 811–830.
- (80) Woo, S. Y., Kim, J. H., Moon, M. K., Han, S. H., Yeon, S. K., Choi, J. W., Jang, B. K., Song, H. J., Kang, Y. G., Kim, J. W., et al. (2014) Discovery of vinyl sulfones as a novel class of neuroprotective agents toward Parkinson's disease therapy. *J. Med. Chem.* 57, 1473–1487.
- (81) Alzheimer's Disease International (2019) *World Alzheimer Report 2019: Attitudes to dementia*, Alzheimer's Disease International, London.
- (82) Beyreuther, K., and Masters, C. L. (1991) Amyloid precursor protein (APP) and beta A4 amyloid in the etiology of Alzheimer's disease: precursor-product relationships in the derangement of neuronal function. *Brain Pathol.* 1, 241–251.
- (83) Hardy, J., and Selkoe, D. J. (2002) The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. *Science* 297, 353–356.
- (84) Selkoe, D. J., and Hardy, J. (2016) The amyloid hypothesis of Alzheimer's disease at 25 years. *EMBO Mol. Med.* 8, 595–560.
- (85) Sisodia, S. S., and St George-Hyslop, P. H. (2002) Gamma-secretase, notch, abeta and Alzheimer's disease: where do the presenilins fit in? *Nat. Rev. Neurosci.* 3, 281–290.
- (86) Hu, X., Das, B., Hou, H., He, W., and Yan, R. (2018) BACE1 deletion in the adult mouse reverses preformed amyloid deposition and improves cognitive functions. *J. Exp. Med.* 215, 927–940.
- (87) Bueno, A. B., Agejas, J., Broughton, H., Dally, R., Durham, T. B., Espinosa, J. F., González, R., Hahn, P. J., Marcos, A., Rodríguez, R., et al. (2017) Optimization of hydroxyethylamine transition state isosteres as aspartic protease inhibitors by exploiting conformational preferences. *J. Med. Chem.* 60, 9807–9820.
- (88) Rombouts, F. J. R., Tresadern, G., Delgado, O., Martínez-Lamenca, C., Van Gool, M., García-Molina, A., Alonso de Diego, S. A., Oehlrich, D., Prokopcova, H., Alonso, J. M., et al. (2015) 1,4-Oxazine β -secretase 1 (BACE1) inhibitors: from hit generation to orally bioavailable brain penetrant leads. *J. Med. Chem.* 58, 8216–8235.
- (89) Gijzen, H. J. M., Alonso de Diego, S. A., De Cleyn, M., García-Molina, A., Macdonald, G. J., Martínez-Lamenca, C., Oehlrich, D., Prokopcova, H., Rombouts, F. J. R., Surkyn, M., et al. (2018) Optimization of 1,4-oxazine β -secretase 1 (BACE1) inhibitors toward a clinical candidate. *J. Med. Chem.* 61, 5292–5303.
- (90) Brodney, M. A., Beck, E. M., Butler, C. R., Barreiro, G., Johnson, E. F., Riddell, D., Parris, K., Nolan, E. C., Fan, Y., Atchison, K., et al. (2015) Utilizing structures of CYP2D6 and BACE1 complexes to reduce risk of drug-drug interactions with a novel series of centrally efficacious BACE1 inhibitors. *J. Med. Chem.* 58, 3223–3252.
- (91) Innocenti, R., Lenci, E., Menchi, G., Pupi, A., and Trabocchi, A. (2017) Design and synthesis of bicyclic acetals as Beta Secretase (BACE1) inhibitors. *Bioorg. Med. Chem.* 25, 5077–5083.
- (92) Mundlapati, V. R., Gautam, S., Sahoo, D. K., Ghosh, A., and Biswal, H. S. (2017) Thioamide, a hydrogen bond acceptor in proteins and nucleic Acids. *J. Phys. Chem. Lett.* 8, 4573–4579.
- (93) van Bergen, L. A. H., Alonso, M., Palló, A., Nilsson, L., De Proft, F., and Messens, J. (2016) Revisiting sulfur H-bonds in proteins: the example of peroxiredoxin AhpE. *Sci. Rep.* 6, 30369.
- (94) Calugi, L., Lenci, E., Innocenti, R., and Trabocchi, A. (2020) Synthesis of morpholine derivatives using the Castagnoli-Cushman reaction as BACE1 inhibitors: unexpected binding activity of cyclic thioamides. *Bioorg. Med. Chem. Lett.* 30, 127211.
- (95) Wiley, J. C., Hudson, M., Kanning, K. C., Schecterson, L. C., and Bothwell, M. (2005) Familial Alzheimer's disease mutations inhibit gamma-secretase-mediated liberation of beta-amyloid precursor protein carboxy-terminal fragment. *J. Neurochem.* 94, 1189–1201.
- (96) Josien, H., Bara, T., Rajagopalan, M., Clader, J. W., Greenlee, W. J., Favreau, L., Hyde, L. A., Nomeir, A. A., Parker, E. M., Song, L., et al. (2009) Novel orally active morpholine N-arylsulfonamides γ -secretase inhibitors with low CYP 3A4 liability. *Bioorg. Med. Chem. Lett.* 19, 6032–6037.
- (97) Josien, H., Bara, T., Rajagopalan, M., Asberom, T., Clader, J. W., Favreau, L., Greenlee, W. J., Hyde, L. A., Nomeir, A. A., Parker, E. M., et al. (2007) Small conformationally restricted piperidine N-arylsulfonamides as orally active γ -secretase inhibitors. *Bioorg. Med. Chem. Lett.* 17, 5330–5335.

- (98) de Matos, A. M., Martins, A., Man, T., Evans, D., Walter, M., Oliveira, M. C., López, O., Fernandez-Bolaños, J. G., Dätwyler, P., Ernst, B., et al. (2019) Design and synthesis of CNS-targeted flavones and analogues with neuroprotective potential against H₂O₂- and Aβ₁₋₄₂-induced toxicity in SH-SY5Y human neuroblastoma cells. *Pharmaceuticals* 12, 98.
- (99) Zhang, Z., Song, M., Liu, X., Kang, S., Duong, D. M., Seyfried, N. T., Cao, X., Cheng, L., Sun, Y. E., Ping Yu, S., et al. (2015) Delta-secretase cleaves amyloid precursor protein and regulates the pathogenesis in Alzheimer's disease. *Nat. Commun.* 6, 8762.
- (100) Zhang, Z., Obianyo, O., Dall, E., Du, Y., Fu, H., Liu, X., Kang, S. S., Song, M., Yu, S. P., Cabrele, C., et al. (2017) Inhibition of delta-secretase improves cognitive functions in mouse models of Alzheimer's disease. *Nat. Commun.* 8, 14740.
- (101) Francis, P. T. (2005) The interplay of neurotransmitters in Alzheimer's disease. *CNS Spectr.* 10, 6–9.
- (102) Cai, Z. (2014) Monoamine oxidase inhibitors: promising therapeutic agents for Alzheimer's disease (Review). *Mol. Med. Rep.* 9, 1533–1541.
- (103) Manera, C., Martinelli, A., Nencetti, S., Romagnoli, F., Rossello, A., Giannaccini, G., Scatizzi, R., Cozzini, P., and Domiano, P. (1994) X-ray analysis, theoretical studies and adrenergic biopharmacological properties of 1-(2,5 dimethoxyphenyl)-2- aminoethanol and its morpholine analogue. *Eur. J. Med. Chem.* 29, 519–525.
- (104) Repsold, B. P., Malan, S. F., Joubert, J., and Oliver, D. W. (2018) Multi-targeted directed ligands for Alzheimer's disease: design of novel lead coumarin conjugates. *SAR QSAR Environ. Res.* 29, 231–255.
- (105) Bertron, J. L., Cho, H. P., Garcia-Barrantes, P. M., Panarese, J. D., Salovich, J. M., Nance, K. D., Engers, D. W., Rook, J. M., Blobaum, A. L., Niswender, C. M., et al. (2018) The discovery of VU0486846: steep SAR from a series of M1 PAMs based on a novel benzomorpholine core. *Bioorg. Med. Chem. Lett.* 28, 2175–2179.
- (106) Rook, J. M., Bertron, J. L., Cho, H. P., Garcia-Barrantes, P. M., Moran, S. P., Maksymetz, J. T., Nance, K. D., Dickerson, J. W., Remke, D. H., Chang, S., et al. (2018) A novel M1 PAM VU0486846 exerts efficacy in cognition models without displaying agonist activity or cholinergic toxicity. *ACS Chem. Neurosci.* 9, 2274–2285.
- (107) Yang, J., Nie, J., Ma, X., Wei, Y., Peng, Y., and Wei, X. (2019) Targeting PI3K in cancer: mechanisms and advances in clinical trials. *Mol. Cancer* 18, 26.
- (108) Liu, P., Cheng, H., Roberts, T. M., and Zhao, J. J. (2009) Targeting the phosphoinositide 3-kinase pathway in cancer. *Nat. Rev. Drug Discovery* 8, 627–644.
- (109) Saxton, R. A., and Sabatini, D. M. (2017) mTOR signaling in growth, metabolism, and disease. *Cell* 168, 960–976.
- (110) Pópulo, H., Lopes, J. M., and Soares, P. (2012) The mTOR signalling pathway in human cancer. *Int. J. Mol. Sci.* 13, 1886–1918.
- (111) Heras-Sandoval, D., Avila-Muñoz, E., and Arias, C. (2011) The phosphatidylinositol 3-kinase/mTOR pathway as a therapeutic target for brain aging and neurodegeneration. *Pharmaceuticals* 4, 1070–1087.
- (112) Heras-Sandoval, D., Pérez-Rojas, J. M., Hernández-Damián, J., and Pedraza-Chaverri, J. (2014) The role of PI3K/AKT/mTOR pathway in the modulation of autophagy and the clearance of protein aggregates in neurodegeneration. *Cell. Signalling* 26, 2694–2701.
- (113) Zhu, W., Sun, C., Xu, S., Wu, C., Wu, J., Xu, M., Zhao, H., Chen, L., Zeng, W., and Zheng, P. (2014) Design, synthesis, anticancer activity and docking studies of novel 4-morpholino-7,8-dihydro-5H-thiopyrano-[4,3-d]pyrimidine derivatives as mTOR inhibitors. *Bioorg. Med. Chem.* 22, 6746–6754.
- (114) Liu, K. K.-C., Bailey, S., Dinh, D. M., Lam, H., Li, C., Wells, P. A., Yin, M. J., and Zou, A. (2012) Conformationally-restricted cyclic sulfones as potent and selective mTOR kinase inhibitors. *Bioorg. Med. Chem. Lett.* 22, 5114–5117.
- (115) Helwa, A. A., Gedawy, E. M., Taher, A. T., El-Ansary, A. K., and Abou-Seri, S. M. (2020) Synthesis and biological evaluation of novel pyrimidine-5-carbonitriles featuring morpholine moiety as antitumor agents. *Future Med. Chem.* 12, 403–421.
- (116) Zask, A., Kaplan, J., Verheijen, J. C., Richard, D. J., Curran, K., Brooijmans, N., Bennett, E. M., Toral-Barza, L., Hollander, I., Ayrál-Kaloustian, S., et al. (2009) Morpholine derivatives greatly enhance the selectivity of mammalian target of rapamycin (mTOR) inhibitors. *J. Med. Chem.* 52, 7942–7945.
- (117) Maira, S.-M., Pecchi, S., Huang, A., et al. (2012) Identification and characterization of NVP-BKM120, an orally available pan-class I PI3-kinase inhibitor. *Mol. Cancer Ther.* 11, 317–328.
- (118) Beaufils, F., Cmiljanovic, N., Cmiljanovic, V., et al. (2017) 5-(4,6-Dimorpholino-1,3,5-triazin-2-yl)-4-(trifluoromethyl)pyridin-2-amine (PQR309), a potent, brain-penetrant, orally bioavailable, pan-class I PI3K/mTOR inhibitor as clinical candidate in oncology. *J. Med. Chem.* 60, 7524–7538.
- (119) Shimobayashi, M., and Hall, M. N. (2014) Making new contacts: the mTOR network in metabolism and signalling crosstalk. *Nat. Rev. Mol. Cell Biol.* 15, 155–162.
- (120) Saxton, R. A., and Sabatini, D. M. (2017) mTOR signaling in growth, metabolism, and disease. *Cell* 168, 960–976.
- (121) Laplante, M., and Sabatini, D. M. (2012) mTOR signaling in growth control and disease. *Cell* 149, 274–293.
- (122) Crino, P. B., Nathanson, K. L., and Henske, E. P. (2006) The tuberous sclerosis complex. *N. Engl. J. Med.* 355, 1345–1356.
- (123) Talboom, J. S., Velazquez, R., and Oddo, S. (2015) The mammalian target of rapamycin at the crossroad between cognitive aging and Alzheimer's disease. *NPJ. Aging Mech. Dis.* 1, 15008.
- (124) Yang, H., Rudge, D. G., Koos, J. D., Vaidialingam, B., Yang, H. J., and Pavletich, N. P. (2013) mTOR kinase structure, mechanism and regulation. *Nature* 497, 217–223.
- (125) Rupak, K., Vulichi, S. R., and Suman, K. (2016) Emphasizing morpholine and its derivatives (MAID): A typical candidates of pharmaceutical importance. *Int. J. Chem. Sci.* 14, 1777–1788.
- (126) Degorce, S. L., Bodnarchuk, M. S., Cumming, I. A., and Scott, J. S. (2018) Lowering lipophilicity by adding carbon: one-carbon bridges of morpholines and piperazines. *J. Med. Chem.* 61, 8934–8943.
- (127) Rageot, D., Bohnacker, T., Melone, A., et al. (2018) Discovery and preclinical characterization of 5 - [4,6-Bis({3-oxa-8-azabicyclo[3.2.1]octan-8-yl})-1,3,5-triazin-2-yl]-4-(difluoromethyl)pyridin-2-amine (PQR620), a highly potent and selective mTORC1/2 inhibitor for cancer and neurological disorders. *J. Med. Chem.* 61, 10084–10105.
- (128) Bonazzi, S., Goold, C. P., Gray, A., Thomsen, N. M., Nunez, J., Karki, R. G., Gorde, A., Biag, J. D., Malik, H. A., Sun, Y., et al. (2020) Discovery of a brain-penetrant ATP-competitive inhibitor of the mechanistic target of rapamycin (mTOR) for CNS disorders. *J. Med. Chem.* 63, 1068–1083.