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# Vesicular Monoamine Transporter 2: Role as a Novel Target for Drug Development

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## Abstract

In the central nervous system, vesicular monoamine transporter 2 (VMAT2) is the only transporter that moves cytoplasmic dopamine (DA) into synaptic vesicles for storage and subsequent exocytotic release. Pharmacologically enhancing DA sequestration by VMAT2, and thus preventing the oxidation of DA in the cytoplasm, may be a strategy for treating diseases such as Parkinson's disease. VMAT2 may also be a novel target for the development of treatments for psychostimulant abuse. This review summarizes the possible role of VMAT2 as a therapeutic target, VMAT2 ligands reported in the literature, and the structure-activity relationship of these ligands, including tetrabenazine analogs, ketanserin analogs, lobeline analogs, and 3-amine-2-phenylpropene analogs. The molecular structure of VMAT2 and its relevance to ligand binding are briefly discussed.

**Keywords:** vesicular monoamine transporter 2, Parkinson's disease, psychostimulant abuse, tetrabenazine, ketanserin, lobeline

## Introduction

The vesicular monoamine transporter (VMAT), a member of the vesicular neurotransmitter transporter family, is responsible for the translocation of monoamines (serotonin, dopamine, norepinephrine, and histamine) from the cytoplasm into synaptic vesicles via a proton electrochemical gradient generated by the vacuolar type $H^+$-adenosine triphosphatase.[1] Two pharmacologically distinct VMAT isoforms, VMAT1 and VMAT2, have been cloned and described.[2-4] Adult human and rodent monoaminergic neurons of the central nervous system (CNS) and sympathetic postganglionic neurons express only VMAT2,[5-7] while VMAT1 is predominantly expressed in neuroendocrine cells such as chromaffin cells of the adrenal medulla and enterochromaffin cells of the intestinal tract.[5-7] VMAT2 is also expressed in at least 2 endocrine cell populations and in neurons.[6] Both VMAT1 and VMAT2 are more widely expressed during embryonic development.[8] Substrate recognition and inhibitor sensitivities for differences between VMAT1 and VMAT2 have been studied using membrane vesicles prepared from stable transformed cell lines from Chinese hamster ovaries (CHO) that express the respective proteins.[9] VMAT2 has a consistently higher affinity for all of the monoamine substrates tested, particularly histamine, and has a greater sensitivity than VMAT1 to the inhibitor tetrabenazine (TBZ).

The natural alkaloid reserpine and TBZ are considered 2 classical VMAT inhibitors.[10] Reserpine inhibits the transport of amines into chromaffin granules and synaptic storage vesicles[11,12] by binding with high affinity to VMAT, presumably at the amine recognition site. It has been suggested that TBZ, on the other hand, binds to a site on VMAT that is different from the substrate binding site at which reserpine interacts.[12-14]

## VMAT2 and Neuroprotection

Oxidative deamination of monoamines by monoamine oxidase is accompanied by the reduction of molecular oxygen to a toxic product, hydrogen peroxide.[15] Therefore, maintenance of low cytoplasmic concentrations of neurotransmitters by their reuptake into synaptic vesicles for storage is important to minimize their inherent toxicity.[16] Furthermore, storage of neurotransmitters in synaptic vesicles precludes their metabolism in the cytoplasmic compartment and reduces the synthetic demands on the cell.[16] In the central nervous system, VMAT2 is the only transporter that moves cytoplasmic dopamine (DA) into synaptic vesicles for storage and subsequent exocytotic release.[1]

Parkinson's disease is a degenerative, progressive disorder that dramatically affects neurons of the substantia nigra and the basal ganglia. The etiology of Parkinson's disease has not been elucidated, but exposure to endogenous or environmental toxins may contribute to the development of the disease.[17-21] In this regard, DA may play a role as an endogenous toxin, since the normal metabolism of DA produces hydrogen peroxide as a byproduct, and the formation of DA-associated reactive oxygen species may contribute to

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the loss of nigrostriatal DA neurons.[22] Accordingly, pharmacologically enhancing DA sequestration by VMAT2, and thus preventing the oxidation of DA in the cytoplasm, may be a strategy for treatment of Parkinson's disease.

Exposure to the neurotoxin *N*-methyl-4-phenyltetrahydropyridine (MPTP) results in clinical symptoms closely approximating Parkinson's disease.[17] *N*-Methyl-4-phenylpyridinium ($MPP^+$), the active toxic metabolite of MPTP, is a substrate for VMAT2.[23-27] VMAT2 sequesters $MPP^+$ in synaptic vesicles and thereby protects catecholamine-containing neurons from $MPP^+$-induced toxicity and degeneration.[3,28-32] CHO cells, which are normally sensitive to $MPP^+$ toxicity, because they lack a plasma membrane amine transporter, can be made relatively insensitive to $MPP^+$ toxicity by transfection with VMAT complementary DNA.[3] In addition, when the transfected CHO cells are treated with reserpine, which inhibits VMAT2 function, the cells then become sensitive to $MPP^+$ toxicity.[3] Other studies using heterozygous VMAT2 knockout mice show that the knockouts are more susceptible to the neurotoxic effects of MPTP compared with the wild-type mice.[28,30,33] Furthermore, heterozygous VMAT2 knockout mice are more sensitive to methamphetamine-induced neurotoxicity and are more vulnerable to the toxic effects of L-3,4-dihydroxyphenylalanine (L-DOPA, a DA precursor used to treat Parkinson's disease) compared with wild-type mice.[34,35] The latter results suggest that reduction in VMAT2 activity might attenuate the efficacy of L-DOPA therapy in Parkinson's patients. Finally, increased sequestration of DA in synaptic vesicles by VMAT2 has been suggested to be protective in Parkinson's disease.[36]

Recently, studies have suggested that pharmacological agents that increase VMAT2 activity are neuroprotective. For example, methylphenidate increases vesicular DA uptake in rats and prevents persistent dopaminergic deficits induced by high-dose methamphetamine administration.[37,38] Pramipexole, a DA D2/D3 agonist used as a therapy for Parkinson's disease, increases vesicular DA uptake and protects against the loss of nigrostriatal DA neurons in methamphetamine-, 3-acetylpyridine-, and ischemia-induced neurotoxicity.[39-41] Additionally, apomorphine, a DA D2/D3 agonist used in Europe as a treatment for Parkinson's disease and for impotence, increases vesicular DA uptake, and this mechanism has been suggested to be important for its associated neuroprotection.[42]

Taken together, the results of the above studies indicate that VMAT2 expression and function are important in counteracting the neurotoxicity of $MPP^+$ and perhaps of other environmental and endogenous neurotoxins that play an etiologic role in neurodegenerative disease.[21]

## VMAT2 and Psychostimulant Abuse

Psychostimulant-induced behavioral activation and reinforcement are mediated, at least in part, via interaction with neurotransmitter transporters that regulate synaptic DA concentrations.[43-45] Recent studies have demonstrated that psychostimulants alter VMAT2 function.[46,47] Cocaine inhibits DA transporter function, induces a rapid and reversible increase in vesicular DA uptake and dihydrotetrabenazine (DTBZ) binding, and causes a shift in the ratio of cytoplasmic to vesicular DA, all of which suggests that VMAT2 may be a novel target for the development of treatments for cocaine abuse.[48] Amphetamine and its analogs, such as methamphetamine, decrease vesicular DA sequestration by inhibiting vesicular uptake and promoting release from the vesicles.[49,50] Amphetamine diffuses across the vesicular membrane, decreasing the pH gradient, which results in the loss of free energy needed for monoamine sequestration.[49-52] Also, amphetamine that accumulates in the vesicles competes with monoamines for protons, resulting in an increase in the diffusion of uncharged monoamines out of the vesicle.[52] High-dose methamphetamine treatment decreases vesicular DA uptake and DTBZ binding, suggesting that there is a significant alteration in VMAT2 function and localization at the vesicular membrane.[53] VMAT2 heterologous knockout mice exhibit reduced amphetamine-conditioned place preference (reward) and enhanced sensitivity to the locomotor effects of apomorphine, ethanol, cocaine, and amphetamine.[28,54] VMAT2 knockout studies also indicate that VMAT2 plays an important role in mediating the behavioral effects of psychostimulants. Taken together, these results support the idea that VMAT2 should be considered as a valid target for the development of pharmacotherapies to treat psychostimulant abuse. Other evidence supporting the role of VMAT2 in psychostimulant pharmacology is the finding that benzoquinolizine derivatives, such as TBZ, which have high affinity for VMAT2, decrease locomotor activity and aggressiveness in monkeys[55] and decrease methamphetamine-induced hyperactivity in rodent animal models.[55]

## VMAT2 Ligands

### *TBZ and Its Analogs*

TBZ (**1**, Figure 1), a benzoquinolizine compound, has been shown to deplete cerebral monoamines in rat brain by reversibly inhibiting VMAT2.[56] First introduced in 1956 as an antipsychotic drug,[57] TBZ is currently used to treat hyperkinetic movement disorders, such as chorea associated with Huntington's disease, tics in Tourette's syndrome, and movement stereotypes in tardive dyskinesia.[58-60] The side effects associated with TBZ include sedation, depression, akathisia, and parkinsonism.[58] TBZ inhibits catecholamine uptake by VMAT2 with a $K_i$ of 3 nM[14] and acts as an inhibitor of both presynaptic and postsynaptic DA receptors in rat brain.[61] [$^{11}$C]TBZ (label on the 9-*O*-methyl group) has been synthesized[62] and used as an in vivo radioligand for positron emission tomography (PET) imaging of VMAT2.[63-66]

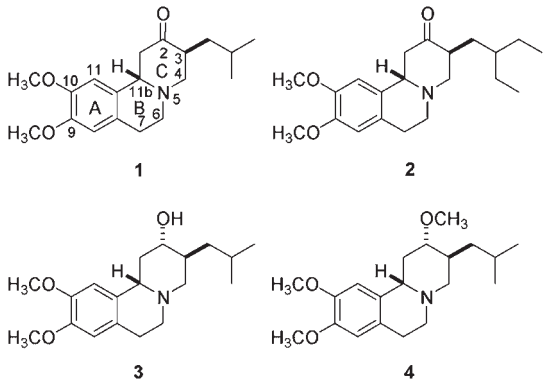


**Figure 1.** Structures of tetrabenazine and its analogs (**1-4**).

TBZ analogs have been synthesized with different alkyl groups at the C-3 position in the molecule, such as compound Ro 4-1632 (**2**, Figure 1). These analogs retain good amine-depleting activity.[55]

In vivo, TBZ is rapidly and extensively metabolized to its reduced form, DTBZ (**3**, Figure 1).[67] [$^3$H]DTBZ (label on the C-2 hydrogen) has been used as a selective radioligand in in vitro brain homogenate binding studies and in autoradiographic studies, and is reported to have a $K_d$ value of 3.0 nM.[13,14,68-70] [$^{11}$C]DTBZ (label on the 9-*O*-methyl group) has also been synthesized[71] and used for in vivo PET imaging of VMAT2.[66,72]

TBZ contains 2 chiral carbon centers at C-3 and C-11b; thus, theoretically, TBZ can exist as 4 possible stereoisomers (3R,11bR; 3S,11bS; 3R,11bS; and 3S,11bR). TBZ usually refers to the racemic compound, that is, a 1:1 mixture of the 3R,11bR and 3S,11bS isomers. Synthetic DTBZ, the product of hydride reduction of the 2-keto group of TBZ, can exist in 2 α-DTBZ forms (2R,3R,11bR, **3a**; and 2S,3S,11bS, **3b**, Figure 2) and 2 β-DTBZ forms (2S,3R,11bR, **3c**; and 2R,3S,11bS, **3d**, Figure 2). α-DTBZ and β-DTBZ can be separated by column chromatography, and the α-DTBZ isomer ($K_i$ = 6 nM) shows slightly higher binding affinity in vitro for rat brain VMAT2 than does β-DTBZ ($K_i$ = 20 nM).[73] The 2 enantiomers of α-DTBZ have been separated using chiral High Performance Liquid Chromatography (HPLC). The (+)-isomer (2R,3R,11bR, **3a**)[74] shows high affinity in vitro ($K_i$ = 0.97 nM) for rat VMAT2, whereas the (–)-isomer shows very low affinity for VMAT2 ($K_i$ = 2.2 μM). Thus the binding of α-DTBZ to VMAT2 is enantioselective, with the (+)-isomer having higher affinity.[75,76]

Another 4 possible DTBZ isomers (2S,3S,11bR, **3e**; 2R,3R,11bS, **3f**; 2R,3S,11bR, **3g**; 2S,3R,11bS, **3h**, Figure 3) have been synthesized and tested for inhibition of VMAT2 binding using rat vesicular membranes. Isomer **3g** showed the highest affinity ($K_i$ = 28 nM) in the [$^3$H]DTBZ binding assay.[77,78]

Methoxytetrabenazine (MTBZ) (**4**, Figure 1) is another TBZ analog with high affinity ($K_d$ = 3.9 nM) for VMAT2.[79] Similar to DTBZ, [$^3$H] and [$^{11}$C]MTBZ have also been synthesized[73] and used in in vitro and in vivo studies.[79-81]

Nucleophilic addition of organometallic reagents to the C-2 keto group of TBZ generated a series of 2-alkylated DTBZ analogs, such as the 2-Me, 2-Et, 2-Pr, 2-iso-Pr, and 2-iso-Bu derivatives (all racemic mixtures, Figure 4).[82-85] These compounds have been evaluated for inhibition of [$^3$H]MTBZ binding to VMAT2 in rat striatum.[85] The β-methyl compound **5a** showed the highest affinity ($K_i$ = 2.6 nM) in this series, with a nearly 5-fold higher affinity than its diastereomer **5b** ($K_i$ = 12 nM), which is consistent with the finding that α-DTBZ exhibits higher affinity for VMAT2 than does β-DTBZ.[73] Compound **5b** and compounds **6 to 9** all contain a β-hydroxyl group and showed a general decrease in binding affinity upon either lengthening or branching of the alkyl group at C-2.[85] These results indicate that analogs containing considerable steric bulk at position 2 can be tolerated. Thus, compound **10** (Figure 4), in which an $^{125}$I atom has been introduced for autoradiographic studies of VMAT2, has been synthesized.[86] (±)-Compound **10** can be separated by chiral HPLC into its optical isomers, and the first eluted enantiomer binds to VMAT2 with a $K_d$ of 0.22 nM.[87]

Structure-activity relationship (SAR) studies involving TBZ analogs have shown that quaternization of the amine nitrogen at position 5, aromatization of ring C, and elimination of the carbonyl group afforded compounds that were devoid

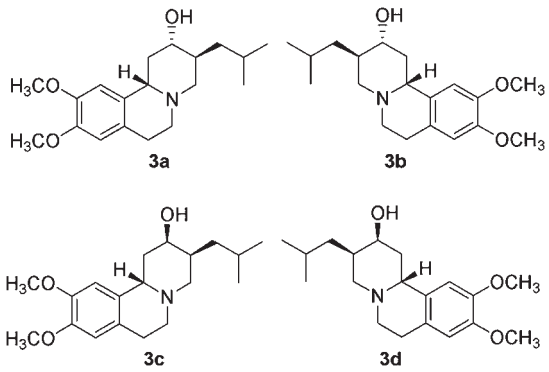


**Figure 2.** Stereoisomers of dihydrotetrabenazine (**3a-d**).

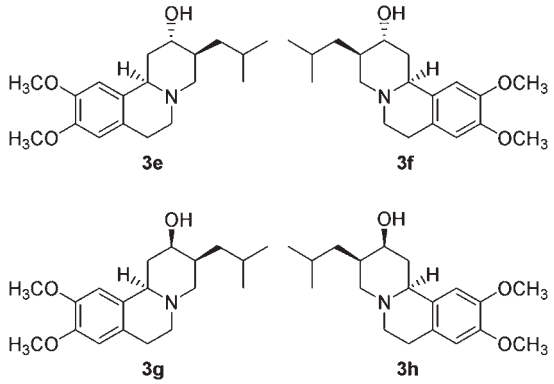


**Figure 3.** Stereoisomers of dihydrotetrabenazine (**3e-h**).

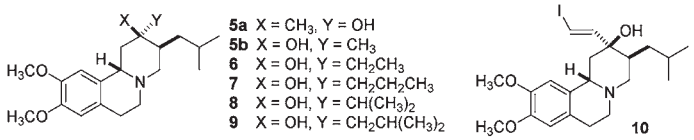


**Figure 4.** Structures of tetrabenazine analogs (**5a-b** and **6-10**).

of monoamine-depleting activity.[55,88] Thus, a basic amine nitrogen at position 5 is a prerequisite for TBZ-like activity.[89] Also, methoxy groups at positions 9 and 10 appear to be essential for TBZ-like activity; the methylenedioxy compound **11** (Figure 5) was 3 orders of magnitude less potent than Ro 4-1284 (**6**).[90]

Replacing the carbonyl oxygen in TBZ with a *bis*-methylthio group (compound **12**, Figure 5) affords a compound with similar activity to TBZ.[91] Olefination of the carbonyl group to afford compound **13** (Figure 5) ($EC_{50}$ = 14 nM) resulted in potent inhibition of [$^3$H]DTBZ binding.[92]

Based upon a limited number of TBZ analogs (**14-17**, Figure 6), a correlation between the lipophilicity of the analogs and their affinity for the DTBZ binding site has been established.[93] Compounds shown to have higher partition coefficients (octanol/buffer) generally exhibited a greater ability to inhibit the specific binding of [$^3$H]DTBZ ($IC_{50}$ = 6 nM for **14**, 47 nM for **17**, 110 nM for **16**, and 2500 nM for **15**) to VMAT2.[93] Accordingly, compound **20** (Figure 6), an iodinated and photosensitive derivative of TBZ, has been synthesized and exhibited an $IC_{50}$ of 428 nM to inhibit [$^3$H]DTBZ binding.[92] However, both its precursor (compound **18**, $IC_{50}$ = 8.1 nM) and the non-iodinated analog (**19**, $IC_{50}$ = 53 nM) of compound **20** showed higher affinity at VMAT2 than did compound **20**.[92]

Several derivatives of compound **16** (ie, compounds **21-24**, Figure 7) have been synthesized; of these, the amino compounds **21** and **22** retained affinity for VMAT2 ($K_i$ = 7.6 nM and 72.2 nM, respectively, in the [$^{125}$I]iodovinyl-TBZ binding assay), whereas the amido compounds **23** and **24** exhibited diminished affinity for VMAT2 ($K_i$ = 730 nM and >10 000 nM, respectively, in the [$^{125}$I]iodovinyl-TBZ binding assay).[94]

### *Ketanserin and Its Analogs*

Ketanserin (**25**, Figure 8), a well-known serotonin 5-HT2 receptor antagonist,[95] also binds to VMAT on chromaffin

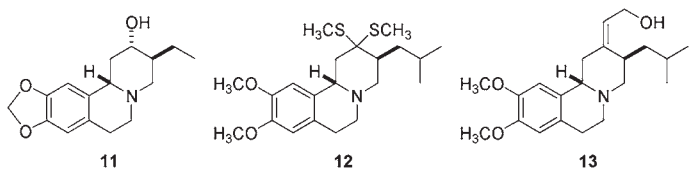


**Figure 5.** Structures of tetrabenazine analogs (**11-13**).

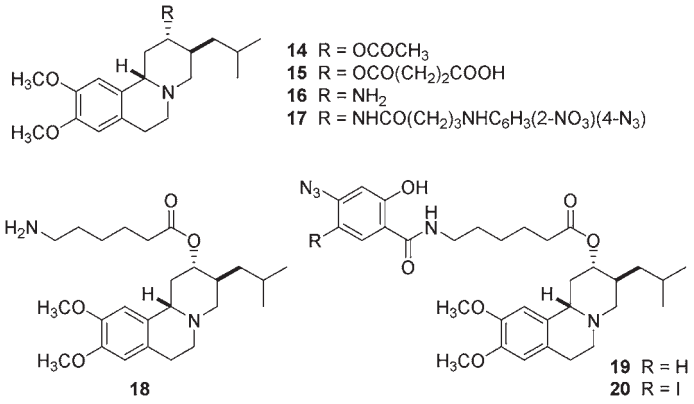


**Figure 6.** Structures of tetrabenazine analogs (**14-20**).

granules and synaptic vesicles.[96-98] In the studies by Darchen et al,[96] Henry et al,[97] and Leysen et al,[98] ketanserin competitively inhibited the binding of [$^3$H]DTBZ to VMAT2, and conversely, TBZ displaced [$^3$H]ketanserin binding. [$^3$H]Ketanserin binds to the TBZ binding site with a $K_d$ of 45 nM at 30ºC and a $K_d$ of 6 nM at 0ºC.[96]

A ketanserin derivative, 7-azidoketanserin (**26**, Figure 8), also binds to the TBZ binding site of bovine chromaffin granule membranes with a $K_i$ of 23 nM (inhibition of [$^3$H]DTBZ binding).[99] An iodinated azido derivative of ketanserin, 7-azido-8-iodoketanserin (**27**, Figure 8), binds to the same specific TBZ binding site as ketanserin with a $K_d$ of 5.5 nM at 0ºC[99]; 7-azido-8-[$^{125}$I]iodoketanserin has been successfully used for photoaffinity labeling of TBZ binding sites of different tissues, including rat striatum, rabbit platelets, human pheochromocytoma, and human adrenal medulla.[99]

Lengthening the distance between the piperidine and the benzoyleneurea moieties of the ketanserin molecule by addition of 2 methylene groups results in a compound (**28**, Figure 9) that exhibits a 20-fold decrease in affinity ($K_i$ = 950 nM) for the [$^3$H]DTBZ binding site.[96] Reducing the keto group of ketanserin (compound **29**, Figure 9) also decreases affinity ($K_i$ = 350 nM) for this site. Additionally, replacing the benzoyleneurea moiety with other heterocycles (eg, compounds **30-32**, Figure 9) also decreases affinity ($K_i$ = 950, 814, and 3600 nM, respectively) for the [$^3$H]DTBZ binding site. However, minor structural changes to the

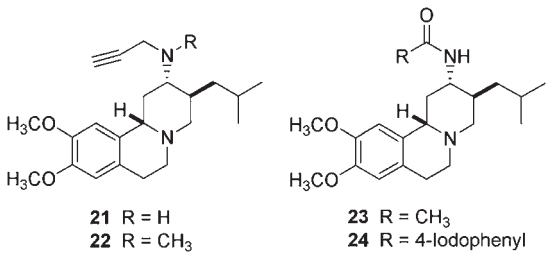


**Figure 7.** Structures of tetrabenazine analogs (**21-24**).

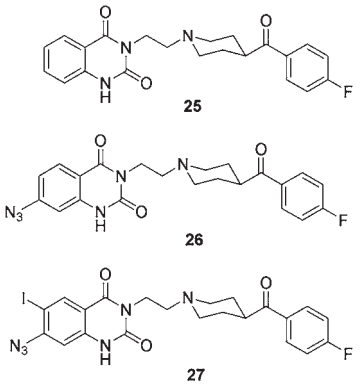


**Figure 8.** Structures of ketanserin and its analogs (**25-27**).

benzoyleneurea moiety, such as introducing a hydroxyl group into the ring (compound **33**, Figure 9) or replacing 1 of the oxygen atoms with a sulfur atom (compound **34**, Figure 9), retains the affinity ($K_i$ = 14 and 40 nM, respectively).[96]

### *Lobeline and Its Analogs*

A lipophilic alkaloid from *Lobelia inflata*, (–)-lobeline (lobeline, 2R,6S,10S-, **35**, Figure 10), displaces [$^3$H]nicotine binding from native nicotinic receptors in the CNS with high affinity ($K_i$ = 4-30 nM).[100-104] Although lobeline has no structural resemblance to nicotine, and SARs do not suggest a common pharmacophore,[105] it has many nicotinelike effects, such as tachycardia and hypertension,[106] bradycardia and hypotension in anesthetized rats,[107] anxiolytic activity,[108] and improvement of learning and memory.[109] In contrast to nicotine, lobeline only marginally supports self-administration in mice[110] and does not support self-administration in rats.[111] Additionally, chronic lobeline treatment does not increase locomotor activity in rats and does not produce conditioned place preference.[112,113] Thus, lobeline and nicotine have different effects in behavioral and

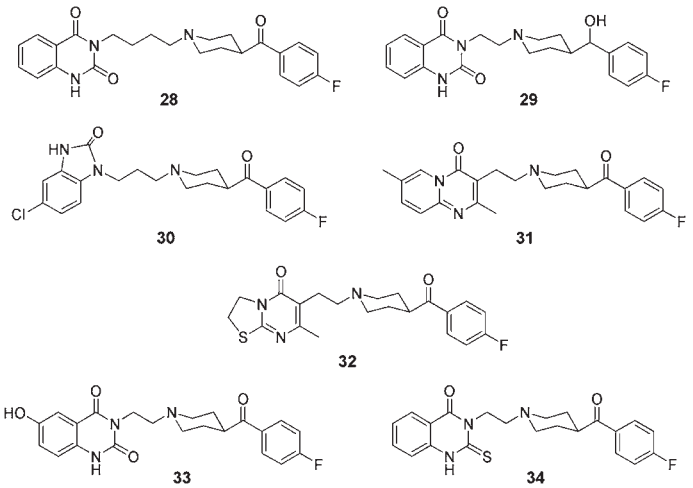


**Figure 9.** Structures of ketanserin analogs (**28-34**).

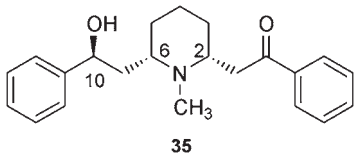


**Figure 10.** Structure of lobeline (**35**).

neurochemical studies, suggesting that they do not act via a common mechanism. Nevertheless, lobeline has often been considered to be a nicotinic receptor agonist. Conversely, we and others have established that lobeline acts as a potent, but nonselective, nicotinic receptor antagonist.[104,114-117] Lobeline inhibits nicotine-evoked [$^3$H]DA overflow from rat striatal slices with an $IC_{50}$ of 1 μM, suggesting that lobeline acts as an antagonist at nicotinic receptors mediating nicotine-evoked DA release (ie, α6β2β3* subtype).[116] Lobeline also inhibits nicotine-evoked $^{86}Rb^+$ efflux from rat thalamic synaptosomes with an $IC_{50}$ of 0.7 μM, indicating that lobeline is also an antagonist at α4β2* nicotinic receptors.[116] Moreover, lobeline also inhibits [$^3$H]methyllycaconitine binding to rat brain membranes with a $K_i$ of 6.26 μM, indicating that there is an interaction with the α7* nicotinic receptor subtype.[117] Lobeline has also been reported to be an antagonist ($IC_{50}$ of 8.5 μM) at human α7* nicotinic receptors expressed in *Xenopus* oocytes.[118]

In addition to interacting with nicotinic acetylcholine receptors (nAChRs), lobeline inhibits [$^3$H]DTBZ binding to VMAT2 with an $IC_{50}$ of 0.90 μM and inhibits [$^3$H]DA uptake into rat striatal vesicle preparations with an $IC_{50}$ of 0.88 μM.[119,120] Therefore, lobeline is a nonselective nAChR antagonist that also inhibits VMAT2 function. Importantly, lobeline has been shown to inhibit both the neurochemical and the behavioral effects of amphetamine in rodents.[111,121-123] The mechanism underlying the lobeline-induced inhibition of these effects has been suggested to be noncompetitive inhibition of VMAT2 function.[114] The observation that lobeline is not self-administered is consistent with findings that lobeline does not evoke DA release.[111,114,119] Furthermore, the observation that lobeline inhibits methamphetamine-evoked DA release from superfused rat striatal slices[116] is consistent with its ability to decrease methamphetamine self-administration in rats.[123] These studies clearly implicate VMAT2 as a potential target for the development of agents to treat methamphetamine abuse. Regardless, lobeline is a novel prototypical molecule from which subtype-selective nAChR ligands and selective VMAT2 inhibitors may be developed following appropriate structural modification.

Systematic structural modification of the lobeline molecule provided 2 non-oxygen-containing lobeline analogs: *N*-methyl-2,6-di-(*cis*-phenylethenyl)piperidine (*meso*-trans-diene [MTD], **36a**, Figure 11) and *N*-methyl-2,6-di-(*cis*-phenylethyl)piperidine (lobelane, **37a**, Figure 11). The latter

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