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(54) Title: PEPTIDOMIMETIC GALANIN RECEPTOR MODULATORS

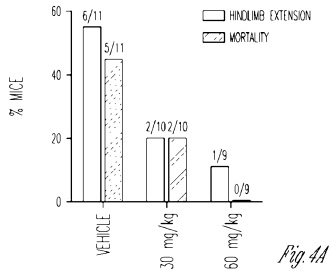



*Fig. 4A*

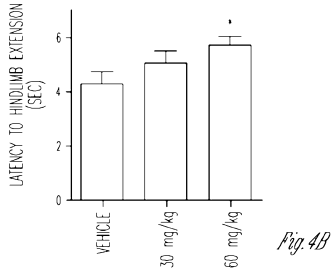



*Fig. 4B*

(57) Abstract: Potent and effective modulators of galanin receptors such as Ga1R1 and Ga1R2 are provided. Methods of preparation and methods of use are further provided. The compounds of the invention may be effective for treatment of malconditions in human patients including epilepsy or seizure disorders, mood disorders including depression and anxiety spectrum disorders; drug addiction including addiction to alcohol or tobacco; autistic spectrum diseases and pervasive development disorders; Alzheimer's disease or other dementias; cognition disorders; cerebral or myocardial stroke; demyelinating diseases including multiple sclerosis, Guillain-Barre syndrome and Charcot-Marie-Tooth disease; neurodegenerative diseases including Parkinson's disease, Lou Gehrig's diseases, Huntington's disease, and HIV dementia; neurotrauma; diabetes, obesity, metabolic syndrome and feeding disorders; solid tumors and leukemia/lymphoma; pain; neuropathies; sleeping disorders and regulation; neuroprotection; and inflammation.

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# PEPTIDOMIMETIC GALANIN RECEPTOR MODULATORS

## CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the priority of U.S. Ser. No. 61/363,727, filed July 13, 2010, and of U.S. Ser. No. 61/468,277, filed March 28, 2011, the disclosures of which are incorporated by reference herein in their entireties.

## STATEMENT OF GOVERNMENT SUPPORT

This work was supported by Grants Number NS063580 and MH084512 from the National Institutes of Health. The government has certain rights in this invention.

## BACKGROUND

The neuropeptide galanin (1) is widely expressed in the central nervous system (2-4), where it regulates a variety of physiological and pathological processes, including pain, learning and memory, mood, addiction, and food intake (5-16). In addition, a critical role for galanin in seizure control has been suggested. Galanin has been shown to exhibit potent anticonvulsant effect in both acute and chronic seizure models in rodents. Intrahippocampal injected galanin strongly and irreversibly attenuated the status epilepticus induced by perforant path stimulation in rats (17). Mice with null mutation of galanin were more susceptible to develop status epilepticus after perforant path stimulation or systemic kainic acid injection, and exhibited more severe seizures following pentylenetetrazol injection (18). In contrast, mice that overexpress galanin under a dopamine-beta-hydroxylase promoter had increased resistance to seizure induction in these three models (18). A separate line of transgenic mice that overexpress galanin under the platelet-derived growth factor β promoter was found to exhibit delayed epileptogenesis induced by kindling stimulations (19). Moreover, galanin delivered to the rat brain via adeno-associated viral vectors has been shown to suppress kainic acid induced seizures (20, 21), attenuate inferior collicular stimulation induced wild running seizure (21), and delay kindling development (22).

The aforementioned anticonvulsant effects of galanin are most likely mediated through galanin receptor type 1 (GalR1) and type 2 (GalR2). GalR1 knockout mice

exhibited spontaneous seizures (23) and they developed more severe seizures when subjected to perforant path stimulation and Li-pilocarpine injection (24). Down-regulation of GalR2 expression in the rat hippocampus with an anti-GalR2 peptide nucleic acid antisense significantly increased the severity of perforant path stimulation induced status epilepticus (25). Both GalR1 and GalR2 are G protein coupled receptors that are expressed at high levels in the hippocampus (26, 27). GalR1 receptor is predominantly coupled to Gi mediating suppression of forskolin stimulated cAMP accumulation. In addition to weakly coupled to Gi, GalR2 is found to couple to Gq resulting in membrane lipid turnover and inositol phosphate (IP) accumulation (28). Consequently, GalR1 and GalR2 represent novel pharmacological targets for treatment of seizures and epilepsy.

The pharmacological potential of GalR1 and GalR2 agonists has been well recognized over the past 20 years but there have been great difficulties in finding receptor subtype selective, systemically active, non-peptide type galanin receptor ligands. Two systemically active non- peptide galanin receptor agonists, Galnon and Galmic from Langel and Rebek groups (17, 29), became important pharmacological tools for studying the pharmacology of galanin signaling and represented prototypic compounds for design of improved non-peptide ligands. Peptide analogues shorter than the endogenous galanin with receptor subtype selectivity were synthesized and characterized (36, 44, 45).

Galanin is a 29 aminoacid (30 aminoacid in humans) neuropeptide, known to inhibit the neuronal firing and/or release of norepinephrine, serotonin, dopamine, glutamate, and acetylcholine. These actions of galanin are mediated through at least three known G-protein coupled receptor (GPCR) subtypes (GalR1, GalR2, and GalR3), expressed in midbrain monoamine-producing nuclei as well as their forebrain projections sites including amygdala, hippocampus, septum, and hypothalmus, suggesting that galanin may play a role in mediating various higher-order behavioral functions. Such functions can include epilepsy or seizure disorders, mood disorders including depression and anxiety spectrum disorders, drug addiction including addiction to alcohol or tobacco, autistic spectrum diseases and pervasive development disorders, Alzheimer's disease or other dementias, and cognition disorders.

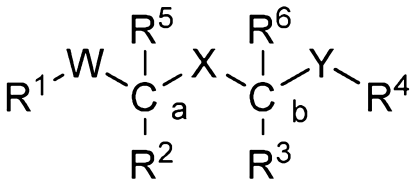
Other conditions wherein modulation of galanin receptors can have therapeutic effect can include cerebral or myocardial stroke, demyelinating diseases including multiple sclerosis, Guillain-Barre syndrome and Charcot-Marie-Tooth disease, neurodegenerative diseases including Parkinson's disease, Lou Gehrig's diseases, Huntington's disease, and HIV dementia, neurotrauma, diabetes, obesity, metabolic syndrome and feeding disorders, solid tumors and leukemia/lymphoma, pain, neuropathies, sleeping disorders and regulation, neuroprotection, and inflammation.

## SUMMARY

The application is directed in various embodiments to compounds that at an effective concentration *in vivo*, such as in a human patient, can modulate the action of a receptor of galanin; to pharmaceutical formulations and combinations of the compounds; to use of the compounds for modulating oxytocin and/or vasopressin receptors; and to treatment of malconditions in patients wherein modulation of a galanin receptor(s) is (are) medically indicated.

In various embodiments, the invention provides a compound of any of the following formulas.

In various embodiments, the invention provides a galanin receptor-modulatory compound of formula (I):



(I)

wherein W, X and Y are each independently ($C_1$-$C_5$)alkylene, $(CH_2)_{0-2}O(CH_2)_{0-2}$, $(CH_2)_{0-2}C(=O)(CH_2)_{0-2}$, $(CH_2)_{0-2}CR_2(CH_2)_{0-2}$, $(CH_2)_{0-2}C(OR)(R)(CH_2)_{0-2}$, $O(CR_2)_nO$ wherein n is 1 to 4, $(CH_2)_{0-2}N(R)(CH_2)_{0-2}$, $(CH_2)_{0-2}S(CH_2)_{0-2}$, $(CH_2)_{0-2}SO(CH_2)_{0-2}$, $(CH_2)_{0-2}SO_2(CH_2)_{0-2}$, $(CH_2)_{0-2}SO_2N(R)(CH_2)_{0-2}$, $(CH_2)_{0-2}SO_3(CH_2)_{0-2}$, $(CH_2)_{0-2}C(=O)C(=O)(CH_2)_{0-2}$, $(CH_2)_{0-2}C(=O)CH_2C(=O)$ $(CH_2)_{0-2}$, $(CH_2)_{0-2}C(=S)(CH_2)_{0-2}$, $(CH_2)_{0-2}C(=O)O(CH_2)_{0-2}$, $(CH_2)_{0-2}OC(=O)(CH_2)_{0-2}$, $(CH_2)_{0-2}OC(=O)O(CH_2)_{0-2}$, $(CH_2)_{0-2}C(=O)N(R)(CH_2)_{0-2}$,

$(CH_2)_{0-2}OC(=O)N(R)(CH_2)_{0-2}$, $(CH_2)_{0-2}C(=S)N(R)(CH_2)_{0-2}$, $(CH_2)_{0-2}NHC(=O)(CH_2)_{0-2}$, $(CH_2)_{0-2}N(R)N(R)C(=O)(CH_2)_{0-2}$, $(CH_2)_{0-2}N(R)N(R)C(=O)O(CH_2)_{0-2}$, $(CH_2)_{0-2}N(R)N(R)C(=O)N(R)(CH_2)_{0-2}$, $(CH_2)_{0-2}N(R)SO_2(CH_2)_{0-2}$, $(CH_2)_{0-2}N(R)SO_2N(R)(CH_2)_{0-2}$, $(CH_2)_{0-2}N(R)C(=O)O(CH_2)_{0-2}$, $(CH_2)_{0-2}N(R)C(=O)(CH_2)_{0-2}$, $(CH_2)_{0-2}N(R)C(=S)(CH_2)_{0-2}$, $(CH_2)_{0-2}N(R)C(=O)N(R)(CH_2)_{0-2}$, $(CH_2)_{0-2}N(R)C(=S)N(R)(CH_2)_{0-2}$, $(CH_2)_{0-2}N(C(=O)R)C(=O)(CH_2)_{0-2}$, $(CH_2)_{0-2}N(OR)(CH_2)_{0-2}$, $(CH_2)_{0-2}C(=NH)N(R)(CH_2)_{0-2}$, $(CH_2)_{0-2}C(=O)N(OR)(CH_2)_{0-2}$, or $(CH_2)_{0-2}C(=NOR)(CH_2)_{0-2}$; or any of W, X, and Y is a bond provided that only one of W, X, and Z is a bond;

$R^1$, $R^2$, and $R^3$ are each independently alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl; provided that any alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl is substituted with 0-4 J, and wherein any $R^2$ can be bonded to $C_a$ either directly or via a linker comprising O, NR, C(=O)NR, OC(=O)NR, or $S(O)_q$, and wherein any $R^3$ can be bonded to $C_b$ either directly or via a linker comprising O, NR, C(=O)NR, OC(=O)NR, or $S(O)_q$, wherein q is 0, 1, or 2; or wherein $R^1$ and $R^2$ together with W and $C_a$ form a heterocyclyl ring substituted with 0-4 J which can be fused with cycloalkyl, aryl or heteroaryl;

$R^4$ is aryl or heteroaryl, substituted with 0-4 J;

$R^5$ and $R^6$ are each independently H or methyl;

J is independently at each occurrence R, F, Cl, Br, I, OR, CN, $CF_3$, $OCF_3$, =O, =S, C(O), S(O), methylenedioxy, ethylenedioxy, $N(R)_2$, SR, SOR, $SO_2R$, $SO_2N(R)_2$, $SO_3R$, C(O)R, C(O)C(O)R, $C(O)CH_2C(O)R$, C(S)R, C(O)OR, OC(O)R, OC(O)OR, $C(O)N(R)_2$, $OC(O)N(R)_2$, $C(S)N(R)_2$, $(CH_2)_{0-2}NHC(O)R$, N(R)N(R)C(O)R, N(R)N(R)C(O)OR, $N(R)N(R)CON(R)_2$, $N(R)SO_2R$, $N(R)SO_2N(R)_2$, N(R)C(O)OR, N(R)C(O)R, N(R)C(S)R, $N(R)C(O)N(R)_2$, $N(R)C(S)N(R)_2$, N(COR)COR, N(OR)R, $C(=NH)N(R)_2$, C(O)N(OR)R, or C(=NOR)R;

R is independently at each occurrence hydrogen, alkyl, alkoxy, haloalkyl, haloalkoxy, alkenyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl, wherein any alkyl, alkoxy, haloalkyl, haloalkoxy, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl,

heteroaryl, or heteroarylalkyl is substituted with 0-4 J; or wherein two R groups together with a nitrogen atom or with two adjacent nitrogen atoms to which they are bonded can together form a three to eight membered heterocyclyl substituted with 0-4 J; optionally further comprising 1-3 additional ring heteroatoms selected from the group consisting of O, N, and $S(O)_q$;

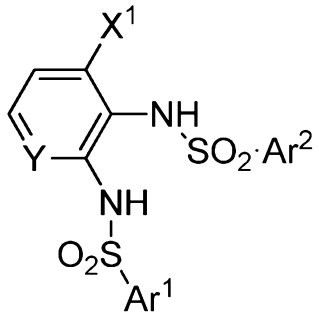
wherein any cycloalkyl, aryl, heterocyclyl, or heteroaryl can be fused, bridged, or in a spiro configuration with one or more additional optionally substituted cycloalkyl, aryl, heterocyclyl, and heteroaryl, monocyclic, bicyclic or polycyclic, saturated, partially unsaturated, or aromatic rings;

including all stereoisomers thereof and all isotopically labeled forms thereof;

or any salt, hydrate, solvate, prodrug, or metabolite thereof;

provided that the compound is not a peptide comprising only ribosomal amino acid residues, or a derivative thereof.

In various embodiments, the invention provides a galanin receptor-modulatory compound of formula (II)



(II)

wherein:

Y is CH or N;

$X^1$ is H or alkyl, or $X^1$, the carbon atom to which it is bonded, an adjacent carbon atom bearing an N atom, and the N atom, together form a pyrrole ring fused to the ring containing Y, to provide an indole or aza-indole ring system;

$Ar^1$ and $Ar^2$ are each independently aryl or heteroaryl, wherein any aryl or heteroaryl is optionally mono- or indepdendently multi-substituted with J;

J is independently at each occurrence R, F, Cl, Br, I, OR, CN, $CF_3$, $CF_2H$, $OCF_3$, $OCF_2H$, =O, =S, methylenedioxy, ethylenedioxy, $N(R)_2$, SR, SOR, $SO_2R$, $SO_2N(R)_2$, $SO_3R$, C(O)R, C(O)C(O)R, $C(O)CH_2C(O)R$, C(S)R, C(O)OR, OC(O)R, OC(O)OR,

$C(O)N(R)_2$, $OC(O)N(R)_2$, $C(S)N(R)_2$, $(CH_2)_{0-2}NHC(O)R$, $N(R)N(R)C(O)R$, $N(R)N(R)C(O)OR$, $N(R)N(R)CON(R)_2$, $N(R)SO_2R$, $N(R)SO_2N(R)_2$, $N(R)C(O)OR$, $N(R)C(O)R$, $N(R)C(S)R$, $N(R)C(O)N(R)_2$, $N(R)C(S)N(R)_2$, $N(COR)COR$, $N(OR)R$, $C(=NH)N(R)_2$, $C(O)N(OR)R$, or $C(=NOR)R$;

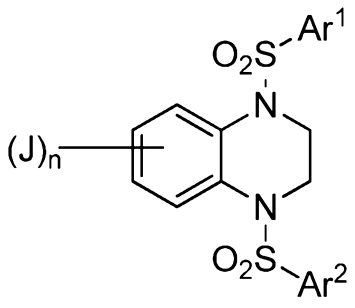
R is independently at each occurrence hydrogen, alkyl, alkoxy, haloalkyl, haloalkoxy, alkenyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl, wherein any alkyl, alkoxy, haloalkyl, haloalkoxy, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl is substituted with 0-4 J; or wherein two R groups together with a nitrogen atom or with two adjacent nitrogen atoms to which they are bonded can together form a three to eight membered heterocyclyl substituted with 0-4 J; optionally further comprising 1-3 additional ring heteroatoms selected from the group consisting of O, N, and $S(O)_q$;

wherein any cycloalkyl, aryl, heterocyclyl, or heteroaryl can be fused, bridged, or in a spiro configuration with one or more additional optionally substituted cycloalkyl, aryl, heterocyclyl, and heteroaryl, monocyclic, bicyclic or polycyclic, saturated, partially unsaturated, or aromatic rings;

including all stereoisomers thereof and all isotopically labeled forms thereof;

or any salt, hydrate, solvate, prodrug, or metabolite thereof.

In various embodiments, the invention provides a galanin receptor-modulatory compound of formula (III)




(III)

wherein $Ar^1$ and $Ar^2$ are each independently selected aryl or heteroaryl, wherein any aryl or heteroaryl is mono- or independently multi-substituted with J;

n is 0, 1, 2, or 3;

J is independently at each occurrence R, F, Cl, Br, I, OR, CN, $CF_3$, $CF_2H$, $OCF_3$, $OCF_2H$, =O, =S, methylenedioxy, ethylenedioxy, $N(R)_2$, SR, SOR, $SO_2R$, $SO_2N(R)_2$, $SO_3R$, C(O)R, C(O)C(O)R, $C(O)CH_2C(O)R$, C(S)R, C(O)OR, OC(O)R, OC(O)OR, $C(O)N(R)_2$, $OC(O)N(R)_2$, $C(S)N(R)_2$, $(CH_2)_{0-2}NHC(O)R$, N(R)N(R)C(O)R, N(R)N(R)C(O)OR, $N(R)N(R)CON(R)_2$, $N(R)SO_2R$, $N(R)SO_2N(R)_2$, N(R)C(O)OR, N(R)C(O)R, N(R)C(S)R, $N(R)C(O)N(R)_2$, $N(R)C(S)N(R)_2$, N(COR)COR, N(OR)R, $C(=NH)N(R)_2$, C(O)N(OR)R, or C(=NOR)R;

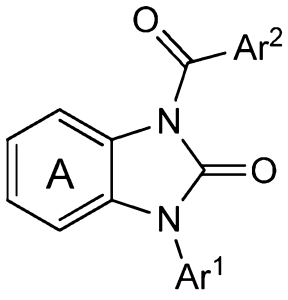
R is independently at each occurrence hydrogen, alkyl, alkoxy, haloalkyl, haloalkoxy, alkenyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl, wherein any alkyl, alkoxy, haloalkyl, haloalkoxy, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl is substituted with 0-4 J; or wherein two R groups together with a nitrogen atom or with two adjacent nitrogen atoms to which they are bonded can together form a three to eight membered heterocyclyl substituted with 0-4 J; optionally further comprising 1-3 additional ring heteroatoms selected from the group consisting of O, N, and $S(O)_q$;

wherein any cycloalkyl, aryl, heterocyclyl, or heteroaryl can be fused, bridged, or in a spiro configuration with one or more additional optionally substituted cycloalkyl, aryl, heterocyclyl, and heteroaryl, monocyclic, bicyclic or polycyclic, saturated, partially unsaturated, or aromatic rings;

including all stereoisomers thereof and all isotopically labeled forms thereof;

or any salt, hydrate, solvate, prodrug, or metabolite thereof.

In various embodiments, the invention provides a galanin receptor-modulatory compound of formula (IV)




(IV)

wherein $Ar^1$ and $Ar^2$ is each independently aryl, heteroaryl, fused cyclalkylaryl, fused heterocyclylaryl, fused cycloalkylheteroaryl, or fused heterocyclylheteroaryl, any of which is substituted with 0-4 J groups;

the ring labeled "A" comprises 0, 1, or 2 N atoms, and is substituted with 0-3 $R^1$ groups, wherein $R^1$ is (C1-C10) straight chain alkyl, (C3-C10)branched chain alkyl, (C3-C12)cycloalkyl or bicycloalkyl, OH, $NR_2$, CN, $CO_2R$, heterocyclylalkyl, heterobicycloalkyl, halo, nitro, alkoxy, cycloalkyloxy, perhaloalkyl, perhaloalkoxy, aryl, or heteroaryl wherein any alkyl cycloalkyl, bicycloalkyl, heterocyclylalkyl, heterobicyclylalkyl, alkoxy, aryl, or heteroaryl is optionally mono- or independently multi-substituted with J;

J is independently at each occurrence R, F, Cl, Br, I, OR, CN, $CF_3$, $CF_2H$, $OCF_3$, $OCF_2H$, =O, =S, methylenedioxy, ethylenedioxy, $N(R)_2$, SR, SOR, $SO_2R$, $SO_2N(R)_2$, $SO_3R$, C(O)R, C(O)C(O)R, $C(O)CH_2C(O)R$, C(S)R, C(O)OR, OC(O)R, OC(O)OR, $C(O)N(R)_2$, $OC(O)N(R)_2$, $C(S)N(R)_2$, $(CH_2)_{0-2}NHC(O)R$, N(R)N(R)C(O)R, N(R)N(R)C(O)OR, $N(R)N(R)CON(R)_2$, $N(R)SO_2R$, $N(R)SO_2N(R)_2$, N(R)C(O)OR, N(R)C(O)R, N(R)C(S)R, $N(R)C(O)N(R)_2$, $N(R)C(S)N(R)_2$, N(COR)COR, N(OR)R, $C(=NH)N(R)_2$, C(O)N(OR)R, or C(=NOR)R;

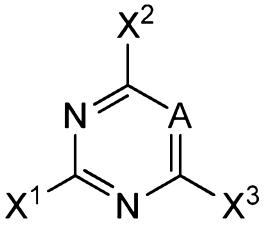
R is independently at each occurrence hydrogen, alkyl, alkoxy, haloalkyl, haloalkoxy, alkenyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl, wherein any alkyl, alkoxy, haloalkyl, haloalkoxy, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl is substituted with 0-4 J; or wherein two R groups together with a nitrogen atom or with two adjacent nitrogen atoms to which they are bonded can together form a three to eight membered heterocyclyl substituted with 0-4 J; optionally further comprising 1-3 additional ring heteroatoms selected from the group consisting of O, N, and $S(O)_q$;

wherein any cycloalkyl, aryl, heterocyclyl, or heteroaryl can be fused, bridged, or in a spiro configuration with one or more additional optionally substituted cycloalkyl, aryl, heterocyclyl, and heteroaryl, monocyclic, bicyclic or polycyclic, saturated, partially unsaturated, or aromatic rings;

including all stereoisomers thereof and all isotopically labeled forms thereof;

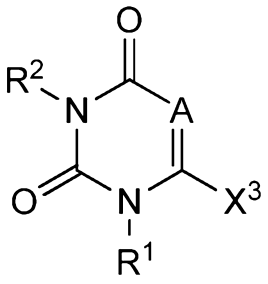
or any salt, hydrate, solvate, prodrug, or metabolite thereof.

In various embodiments, the invention provides a galanin receptor-modulating compound of formula (VA)



(VA)

or (IVB)



(VB)

wherein

A is N or CR', wherein R' is H, optionally substituted (C1-C6)alkyl, or $NR^3R^4$;

$X^1$, $X^2$ and $X^3$ are each independently H, halo, cyano, $NR^3R^4$, $N(R^3)S(O)_qAr^1$, $N(R^3)C(=O)Ar^1$, or $OR^5$, wherein q is 0, 1, or 2;

$R^1$ and $R^2$ are each independently optionally substituted aralkyl;

$R^3$ and $R^4$ are each independently H, alkyl, cycloalkyl or bicycloalkyl, aryl, heterocyclyl, or heteroaryl, wherein any alkyl, cycloalkyl or bicycloalkyl, aryl, heterocyclyl, or heteroaryl is substituted with 0-3 J and any alkyl, cycloalkyl or bicycloalkyl, aryl, heterocyclyl, or heteroaryl can be bonded directly to a nitrogen atom which bears $R^3$ or $R^4$ or can be bonded to the nitrogen atom via M, wherein M is $(CH_2)_n$, $S(O)_q(CH_2)_n$, $(CH_2)_nN(R)C(O)$, or $(CH_2)_nC(O)N(R)$, wherein n is 0-9 and q is 0, 1, or 2; or $R^3$ and $R^4$ together with a nitrogen atom to which they are bonded form a heterocyclyl optionally further comprising 1 or 2 additional heteroatoms selected from O, $S(O)_q$, or $NR^3$, wherein the heterocyclyl is substituted with 0-3 J;

$R^5$ is H, alkyl, cycloalkyl, aryl, heterocyclyl, or heteroaryl, any of which non-hydrogen groups is optionally mono- or independently multi-substituted with J;

$Ar^1$ is aryl or heteroaryl, optionally mono- or independently multi-substituted with J;

J is independently at each occurrence R, F, Cl, Br, I, OR, CN, $CF_3$, $CF_2H$, $OCF_3$, $OCF_2H$, =O, =S, methylenedioxy, ethylenedioxy, $N(R)_2$, SR, SOR, $SO_2R$, $SO_2N(R)_2$, $SO_3R$, C(O)R, C(O)C(O)R, $C(O)CH_2C(O)R$, C(S)R, C(O)OR, OC(O)R, OC(O)OR, $C(O)N(R)_2$, $OC(O)N(R)_2$, $C(S)N(R)_2$, $(CH_2)_{0-2}NHC(O)R$, N(R)N(R)C(O)R, N(R)N(R)C(O)OR, $N(R)N(R)CON(R)_2$, $N(R)SO_2R$, $N(R)SO_2N(R)_2$, N(R)C(O)OR, N(R)C(O)R, N(R)C(S)R, $N(R)C(O)N(R)_2$, $N(R)C(S)N(R)_2$, N(COR)COR, N(OR)R, $C(=NH)N(R)_2$, C(O)N(OR)R, or C(=NOR)R;

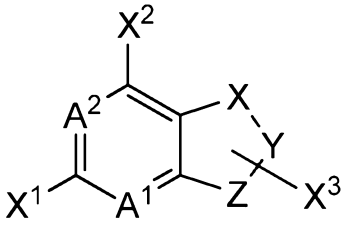
R is independently at each occurrence hydrogen, alkyl, alkoxy, haloalkyl, haloalkoxy, alkenyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl, wherein any alkyl, alkoxy, haloalkyl, haloalkoxy, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl is substituted with 0-4 J; or wherein two R groups together with a nitrogen atom or with two adjacent nitrogen atoms to which they are bonded can together form a three to eight membered heterocyclyl substituted with 0-4 J; optionally further comprising 1-3 additional ring heteroatoms selected from the group consisting of O, N, and $S(O)_q$;

wherein any cycloalkyl, aryl, heterocyclyl, or heteroaryl can be fused, bridged, or in a spiro configuration with one or more additional optionally substituted cycloalkyl, aryl, heterocyclyl, and heteroaryl, monocyclic, bicyclic or polycyclic, saturated, partially unsaturated, or aromatic rings;

including all stereoisomers thereof and all isotopically labeled forms thereof;

or any salt, hydrate, solvate, prodrug, or metabolite thereof.

In various embodiments, the invention provides a galanin receptor-modulatory compound of formula (VI)




(VI)

wherein:

$A^1$ and $A^2$ are each independently N or CR', wherein R' is H, optionally substituted (C1-C6)alkyl, or $NR^3R^4$;

X, Y, and Z are each independently N or NR' or CR' or $C(R')_2$ provided that the bond between X and Y, and the bond between Y and Z, can each be a double bond or a single bond provided there is one double bond and one single bond between X and Y and Y and Z;

$X^1$ and $X^2$ is each independently H, halo, cyano, $NR^3R^4$, $Ar^1$, $Ar^1S(O)_q$, or $OR^5$, $N(R^3)S(O)_qAr^1$, or $N(R^3)C(=O)Ar^1$;

$Ar^1$ is optionally substituted aryl or heteroaryl;

$R^3$ and $R^4$ are each independently H, alkyl, cycloalkyl or bicycloalkyl, aryl, heterocyclyl, or heteroaryl, wherein any alkyl, cycloalkyl or bicycloalkyl, aryl, heterocyclyl, or heteroaryl is substituted with 0-3 J and any alkyl, cycloalkyl or bicycloalkyl, aryl, heterocyclyl, or heteroaryl can be bonded directly to a nitrogen atom which bears $R^3$ or $R^4$ or can be bonded to the nitrogen atom via M, wherein M is $(CH_2)_n$, $S(O)_q(CH_2)_n$, $(CH_2)_nN(R)C(O)$, or $(CH_2)_nC(O)N(R)$, wherein n is 0-9 and q is 0, 1, or 2; or $R^3$ and $R^4$ together with a nitrogen atom to which they are bonded form a heterocyclyl optionally further comprising 1 or 2 additional heteroatoms selected from O, $S(O)_q$, or $NR^3$, wherein the heterocyclyl is substituted with 0-3 J;

$R^5$ is H, alkyl, cycloalkyl, aryl, heterocyclyl, or heteroaryl, any of which non-hydrogen groups is optionally mono- or independently multi-substituted with J;

J is independently at each occurrence R, F, Cl, Br, I, OR, CN, $CF_3$, $CF_2H$, $OCF_3$, $OCF_2H$, =O, =S, methylenedioxy, ethylenedioxy, $N(R)_2$, SR, SOR, $SO_2R$, $SO_2N(R)_2$, $SO_3R$, C(O)R, C(O)C(O)R, $C(O)CH_2C(O)R$, C(S)R, C(O)OR, OC(O)R, OC(O)OR, $C(O)N(R)_2$, $OC(O)N(R)_2$, $C(S)N(R)_2$, $(CH_2)_{0-2}NHC(O)R$, N(R)N(R)C(O)R, N(R)N(R)C(O)OR, $N(R)N(R)CON(R)_2$, $N(R)SO_2R$, $N(R)SO_2N(R)_2$, N(R)C(O)OR, N(R)C(O)R, N(R)C(S)R, $N(R)C(O)N(R)_2$, $N(R)C(S)N(R)_2$, N(COR)COR, N(OR)R, $C(=NH)N(R)_2$, C(O)N(OR)R, or C(=NOR)R;

R is independently at each occurrence hydrogen, alkyl, alkoxy, haloalkyl, haloalkoxy, alkenyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl, wherein any alkyl, alkoxy, haloalkyl, haloalkoxy, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl,

heteroaryl, or heteroarylalkyl is substituted with 0-4 J; or wherein two R groups together with a nitrogen atom or with two adjacent nitrogen atoms to which they are bonded can together form a three to eight membered heterocyclyl substituted with 0-4 J; optionally further comprising 1-3 additional ring heteroatoms selected from the group consisting of O, N, and $S(O)_q$;

wherein any cycloalkyl, aryl, heterocyclyl, or heteroaryl can be fused, bridged, or in a spiro configuration with one or more additional optionally substituted cycloalkyl, aryl, heterocyclyl, and heteroaryl, monocyclic, bicyclic or polycyclic, saturated, partially unsaturated, or aromatic rings;

including all stereoisomers thereof and all isotopically labeled forms thereof;

or any salt, hydrate, solvate, prodrug, or metabolite thereof.

In various embodiments, the compound is a modulator of a galanin receptor, and can be a selective modulator of GalR1 or of GalR2 or of GalR3.

In various embodiements, the invention provides a pharmaceutical composition comprising a compound of the invention and a pharmaceutically acceptable excipient.

In various embodiments, the invention provides a method of modulation a galanin receptor comprising contacting the receptor with an effective amount or concentration of a compound of the invention. The contacting can take place *in vivo* in a human patient.

In various embodiments, the invention provides a method of treatment of a malcondition in a patient for which modulation of a galanin receptor is medically indicated, comprising administering to the patient a compound of the invention in a dose, at a frequency, and for a duration sufficient to provide a beneficial effect to the patient. For example, the malcondition can be epilepsy or seizure disorders; mood disorders including depression and anxiety spectrum disorders; drug addiction including addiction to alcohol or tobacco; autistic spectrum diseases and pervasive development disorders; Alzheimer's disease or other dementias; cognition disorders; cerebral or myocardial stroke; demyelinating diseases including multiple sclerosis, Guillain-Barre syndrome and Charcot-Marie-Tooth disease; neurodegenerative diseases including Parkinson's disease, Lou Gehrig's diseases, Huntington's disease, and HIV dementia; neurotrauma; diabetes, obesity, metabolic syndrome and feeding disorders; solid tumors and leukemia/lymphoma; pain; neuropathies; sleeping disorders and regulation; neuroprotection; and inflammation.

## BRIEF DESCRIPTION OF THE FIGURES

Figure 1 is a series of graphs showing CYM2503, a compound of formula (I), mediated potentiation of the agonist stimulated GalR2 activation and the lack of affinity of CYM2503 for GalR2 orthosteric site in HEK293-GalR2 cells. IP1 accumulation was used as an index of GalR2 activation. A) CYM2503 potentiated the effect of 100 nM galanin. B) CYM2503 shifted the galanin dose response curve to the left. C) $^{125}$I porcine galanin, at 0.15 nM, was not displaced by CYM2503 at up to 100 μM concentration. As a comparison, unlabeled rat galanin displaced $^{125}$I porcine galanin with an IC50 of 10.1 nM in the same experiment. D) Lack of effect of CYM2503 on IP1 accumulation. CYM2503 at concentrations up to 100 μM did not change baseline IP1 level. As a comparison, rat galanin stimulated IP1 production in the same experiment. All data shown were from one experiment performed in triplicate and are typical of 2-6 independent experiments giving similar results.

Figure 2 is a series of graphs showing that CYM2503 exhibited no affinity for GalR1 and it did not modulate GalR1 signaling. Agonist-induced inhibition of forskolin-stimulated cAMP production in CHO-GalR1 cells was used as an index of GalR1 activation. Forskolin was used at a concentration of 4 μM. A) $^{125}$I porcine galanin, at 0.1 nM, were not displaced by CYM2503 at up to 100 μM concentration. As a comparison, unlabeled rat galanin displaced $^{125}$I porcine galanin with an IC50 of 5.4 nM in the same experiment. B) Rat galanin inhibited forskolin-stimulated cAMP accumulation with an IC50 of 7.8 pM in CHO-GalR1 cells, while it had no effect in the parent CHO cell line that does not express GalR1. C) Lack of effect of CYM2503 on cAMP accumulation. CYM2503 at concentrations up to 100 μM had no effect on forskolin-stimulated cAMP production. D) CYM2503 did not shift the galanin dose response curve. The data shown here were from one experiment performed in triplicate and are typical of 3-4 independent experiments giving similar results.

Figure 3 is a series of graphs showing the anticonvulsant effect of CYM2503 in the Li-pilocarpine model in mice. A) Experimental paradigm. B) Examples of electrographic seizure activity and spikes induced by Li-pilocarpine. C) Statistic analysis of EEG. Data

are mean ± SEM. * p<0.05, ANOVA followed by Dunnett's multiple comparison to respective controls, n=6-10. LEV: levetiracetam 50 mg/kg, i.p.

Figure 4 is a series of graphs showing that CYM2503 protected mice in the electroshock induced seizure model. A 15 minute pretreatment with 60 mg/kg, i.p.: A) decreased the percent of mice that developed hindlimb extension and decreased the mortality. The number of animals in each group is shown above the bar graph. B) increased the latency to hindlimb extension. Data are mean ± SEM. *p<0.05, one way ANOVA followed by Dunnett's multiple comparison to vehicle, n =9-11.

## DETAILED DESCRIPTION

### Definitions

As used in the specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise.

The term "about" as used herein, when referring to a numerical value or range, allows for a degree of variability in the value or range, for example, within 10%, or within 5% of a stated value or of a stated limit of a range.

As used herein, "individual" (as in the subject of the treatment) means both mammals and non-mammals. Mammals include, for example, humans; non-human primates, e.g. apes and monkeys; and non-primates, e.g. dogs, cats, cattle, horses, sheep, and goats. Non-mammals include, for example, fish and birds.

The term "disease" or "disorder" or "malcondition" are used interchangeably, and are used to refer to diseases or conditions wherein a galanin receptor plays a role in the biochemical mechanisms involved in the disease or malcondition such that a therapeutically beneficial effect can be achieved by acting on the kinase. "Acting on" galanin receptor can include binding to a galanin receptor and/or inhibiting the bioactivity of a galanin receptor.

The expression "effective amount", when used to describe therapy to an individual suffering from a disorder, refers to the amount of a compound of the invention that is effective to inhibit or otherwise act on a galanin receptor in the individual's tissues wherein a galanin receptor involved in the disorder is active, wherein such inhibition or other action occurs to an extent sufficient to produce a beneficial therapeutic effect.

A "galanin receptor-modulatory compound" is a compound that can act upon the receptors that are adapted in vivo to bind galanin and exert a biochemical or physiological effect. Typically such receptors are termed G-protein coupled receptor (GPCRs) because the initial transduction effect of a ligand binding to the receptor is an alteration in the bioactivity of the G protein to which the receptor is coupled. A "modulary" effect on a receptor, or "receptor modulation", can be an agonistic or an antagonist effect, reversible or irreversible, acting at a ligand binding site, a cofactor binding site, or an allosteric binding site. Modulation can occur by directly blocking binding of a native ligand for a galanin receptor, i.e., a galanin peptide, such as by occupation of the ligand binding site on the receptor protein, or by enhancing binding or the effect of binding of a native ligand, or by allosterically altering the receptor such that binding or the effect thereof is diminished or increased relative to the state in the absence of the receptor-modulatory compound.

A compound is a "selective modulator" of a galanin receptor when it exerts its effect on one of GalR1, GalR2, or GalR3 at a significantly lower concentration than a concentration at which it exerts an effect an another of the galanin receptors.

Phrases such as "under conditions suitable to provide" or "under conditions sufficient to yield" or the like, in the context of methods of synthesis, as used herein refers to reaction conditions, such as time, temperature, solvent, reactant concentrations, and the like, that are within ordinary skill for an experimenter to vary, that provide a useful quantity or yield of a reaction product. It is not necessary that the desired reaction product be the only reaction product or that the starting materials be entirely consumed, provided the desired reaction product can be isolated or otherwise further used.

"Substantially" as the term is used herein means completely or almost completely; for example, a composition that is "substantially free" of a component either has none of the component or contains such a trace amount that any relevant functional property of the composition is unaffected by the presence of the trace amount, or a compound is "substantially pure" is there are only negligible traces of impurities present.

"Treating" or "treatment" within the meaning herein refers to an alleviation of symptoms associated with a disorder or disease, or inhibition of further progression or worsening of those symptoms, or prevention or prophylaxis of the disease or disorder, or curing the disease or disorder. Similarly, as used herein, an "effective amount" or a

"therapeutically effective amount" of a compound of the invention refers to an amount of the compound that alleviates, in whole or in part, symptoms associated with the disorder or condition, or halts or slows further progression or worsening of those symptoms, or prevents or provides prophylaxis for the disorder or condition. In particular, a "therapeutically effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired therapeutic result. A therapeutically effective amount is also one in which any toxic or detrimental effects of compounds of the invention are outweighed by the therapeutically beneficial effects.

By "chemically feasible" is meant a bonding arrangement or a compound where the generally understood rules of organic structure are not violated; for example a structure within a definition of a claim that would contain in certain situations a pentavalent carbon atom that would not exist in nature would be understood to not be within the claim. The structures disclosed herein, in all of their embodiments are intended to include only "chemically feasible" structures, and any recited structures that are not chemically feasible, for example in a structure shown with variable atoms or groups, are not intended to be disclosed or claimed herein.

When a substituent is specified to be an atom or atoms of specified identity, "or a bond", a configuration is referred to when the substituent is "a bond" that the groups that are immediately adjacent to the specified substituent are directly connected to each other in a chemically feasible bonding configuration.

All chiral, diastereomeric, racemic forms of a structure are intended, unless a particular stereochemistry or isomeric form is specifically indicated. Compounds used in the present invention can include enriched or resolved optical isomers at any or all asymmetric atoms as are apparent from the depictions, at any degree of enrichment. Both racemic and diastereomeric mixtures, as well as the individual optical isomers can be isolated or synthesized so as to be substantially free of their enantiomeric or diastereomeric partners, and these are all within the scope of the invention.

The inclusion of an isotopic form of one or more atoms in a molecule that is different from the naturally occurring isotopic distribution of the atom in nature is referred to as an "isotopically labeled form" of the molecule. All isotopic forms of atoms are included as options in the composition of any molecule, unless a specific isotopic form of

an atom is indicated. For example, any hydrogen atom or set thereof in a molecule can be any of the isotopic forms of hydrogen, i.e., protium ($^{1}H$), deuterium ($^{2}H$), or tritium ($^{3}H$) in any combination. Similarly, any carbon atom or set thereof in a molecule can be any of the isotopic form of carbons, such as $^{11}C$, $^{12}C$, $^{13}C$, or $^{14}C$, or any nitrogen atom or set thereof in a molecule can be any of the isotopic forms of nitrogen, such as $^{13}N$, $^{14}N$, or $^{15}N$. A molecule can include any combination of isotopic forms in the component atoms making up the molecule, the isotopic form of every atom forming the molecule being independently selected. In a multi-molecular sample of a compound, not every individual molecule necessarily has the same isotopic composition. For example, a sample of a compound can include molecules containing various different isotopic compositions, such as in a tritium or $^{14}C$ radiolabeled sample where only some fraction of the set of molecules making up the macroscopic sample contains a radioactive atom. It is also understood that many elements that are not artificially isotopically enriched themselves are mixtures of naturally occurring isotopic forms, such as $^{14}N$ and $^{15}N$, $^{32}S$ and $^{34}S$, and so forth. A molecule as recited herein is defined as including isotopic forms of all its constituent elements at each position in the molecule. As is well known in the art, isotopically labeled compounds can be prepared by the usual methods of chemical synthesis, except substituting an isotopically labeled precursor molecule. The isotopes, radiolabeled or stable, can be obtained by any method known in the art, such as generation by neutron absorption of a precursor nuclide in a nuclear reactor, by cyclotron reactions, or by isotopic separation such as by mass spectrometry. The isotopic forms are incorporated into precursors as required for use in any particular synthetic route. For example, $^{14}C$ and $^{3}H$ can be prepared using neutrons generated in a nuclear reactor. Following nuclear transformation, $^{14}C$ and $^{3}H$ are incorporated into precursor molecules, followed by further elaboration as needed.

The term "amino protecting group" or "N-protected" as used herein refers to those groups intended to protect an amino group against undesirable reactions during synthetic procedures and which can later be removed to reveal the amine. Commonly used amino protecting groups are disclosed in Protective Groups in Organic Synthesis, Greene, T.W.; Wuts, P. G. M., John Wiley & Sons, New York, NY, (3rd Edition, 1999). Amino protecting groups include acyl groups such as formyl, acetyl, propionyl, pivaloyl, t-

butylacetyl, 2-chloroacetyl, 2-bromoacetyl, trifluoroacetyl, trichloroacetyl, o-nitrophenoxyacetyl, α-chlorobutyryl, benzoyl, 4-chlorobenzoyl, 4-bromobenzoyl, 4-nitrobenzoyl, and the like; sulfonyl groups such as benzenesulfonyl, p-toluenesulfonyl and the like; alkoxy- or aryloxy-carbonyl groups (which form urethanes with the protected amine) such as benzyloxycarbonyl (Cbz), p-chlorobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 3,5-dimethoxybenzyloxycarbonyl, 2,4-dimethoxybenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitro-4,5-dimethoxybenzyloxycarbonyl, 3,4,5-trimethoxybenzyloxycarbonyl, 1-(p-biphenylyl)-1-methylethoxycarbonyl, α,α-dimethyl-3,5-dimethoxybenzyloxycarbonyl, benzhydryloxycarbonyl, t-butyloxycarbonyl (Boc), diisopropylmethoxycarbonyl, isopropyloxycarbonyl, ethoxycarbonyl, methoxycarbonyl, allyloxycarbonyl (Alloc), 2,2,2-trichloroethoxycarbonyl, 2-trimethylsilylethyloxycarbonyl (Teoc), phenoxycarbonyl, 4-nitrophenoxycarbonyl, fluorenyl-9-methoxycarbonyl (Fmoc), cyclopentyloxycarbonyl, adamantyloxycarbonyl, cyclohexyloxycarbonyl, phenylthiocarbonyl and the like; aralkyl groups such as benzyl, triphenylmethyl, benzyloxymethyl and the like; and silyl groups such as trimethylsilyl and the like. Amine protecting groups also include cyclic amino protecting groups such as phthaloyl and dithiosuccinimidyl, which incorporate the amino nitrogen into a heterocycle. Typically, amino protecting groups include formyl, acetyl, benzoyl, pivaloyl, t-butylacetyl, phenylsulfonyl, Alloc, Teoc, benzyl, Fmoc, Boc and Cbz. It is well within the skill of the ordinary artisan to select and use the appropriate amino protecting group for the synthetic task at hand.

The term "hydroxyl protecting group" or "O-protected" as used herein refers to those groups intended to protect an OH group against undesirable reactions during synthetic procedures and which can later be removed to reveal the amine. Commonly used hydroxyl protecting groups are disclosed in Protective Groups in Organic Synthesis, Greene, T.W.; Wuts, P. G. M., John Wiley & Sons, New York, NY, (3rd Edition, 1999). Hydroxyl protecting groups include acyl groups such as formyl, acetyl, propionyl, pivaloyl, t-butylacetyl, 2-chloroacetyl, 2-bromoacetyl, trifluoroacetyl, trichloroacetyl, o-nitrophenoxyacetyl, α-chlorobutyryl, benzoyl, 4-chlorobenzoyl, 4-bromobenzoyl,

4-nitrobenzoyl, and the like; sulfonyl groups such as benzenesulfonyl, p-toluenesulfonyl and the like; acyloxy groups (which form urethanes with the protected amine) such as benzyloxycarbonyl (Cbz), p-chlorobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 3,5-dimethoxybenzyloxycarbonyl, 2,4-dimethoxybenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitro-4,5-dimethoxybenzyloxycarbonyl, 3,4,5-trimethoxybenzyloxycarbonyl, 1-(p-biphenylyl)-1-methylethoxycarbonyl, α,α-dimethyl-3,5-dimethoxybenzyloxycarbonyl, benzhydryloxycarbonyl, t-butyloxycarbonyl (Boc), diisopropylmethoxycarbonyl, isopropyloxycarbonyl, ethoxycarbonyl, methoxycarbonyl, allyloxycarbonyl (Alloc), 2,2,2-trichloroethoxycarbonyl, 2-trimethylsilylethyloxycarbonyl (Teoc), phenoxycarbonyl, 4-nitrophenoxycarbonyl, fluorenyl-9-methoxycarbonyl (Fmoc), cyclopentyloxycarbonyl, adamantyloxycarbonyl, cyclohexyloxycarbonyl, phenylthiocarbonyl and the like; aralkyl groups such as benzyl, triphenylmethyl, benzyloxymethyl and the like; and silyl groups such as trimethylsilyl and the like. It is well within the skill of the ordinary artisan to select and use the appropriate hydroxyl protecting group for the synthetic task at hand.

In general, "substituted" refers to an organic group as defined herein in which one or more bonds to a hydrogen atom contained therein are replaced by one or more bonds to a non-hydrogen atom such as, but not limited to, a halogen (i.e., F, Cl, Br, and I); an oxygen atom in groups such as hydroxyl groups, alkoxy groups, aryloxy groups, aralkyloxy groups, oxo(carbonyl) groups, carboxyl groups including carboxylic acids, carboxylates, and carboxylate esters; a sulfur atom in groups such as thiol groups, alkyl and aryl sulfide groups, sulfoxide groups, sulfone groups, sulfonyl groups, and sulfonamide groups; a nitrogen atom in groups such as amines, hydroxylamines, nitriles, nitro groups, N-oxides, hydrazides, azides, and enamines; and other heteroatoms in various other groups. Non-limiting examples of substituents that can be bonded to a substituted carbon (or other) atom include F, Cl, Br, I, OR', $OC(O)N(R')_2$, CN, NO, $NO_2$, $ONO_2$, azido, $CF_3$, $OCF_3$, R', O (oxo), S (thiono), methylenedioxy, ethylenedioxy, $N(R')_2$, SR', SOR', $SO_2R'$, $SO_2N(R')_2$, $SO_3R'$, C(O)R', C(O)C(O)R', $C(O)CH_2C(O)R'$, C(S)R', C(O)OR', OC(O)R', $C(O)N(R')_2$, $OC(O)N(R')_2$, $C(S)N(R')_2$, $(CH_2)_{0-2}N(R')C(O)R'$, $(CH_2)_{0-2}N(R')N(R')_2$, N(R')N(R')C(O)R', N(R')N(R')C(O)OR', $N(R')N(R')CON(R')_2$, $N(R')SO_2R'$,

$N(R')SO_2N(R')_2$, $N(R')C(O)OR'$, $N(R')C(O)R'$, $N(R')C(S)R'$, $N(R')C(O)N(R')_2$, $N(R')C(S)N(R')_2$, $N(COR')COR'$, $N(OR')R'$, $C(=NH)N(R')_2$, $C(O)N(OR')R'$, or $C(=NOR')R'$ wherein R' can be hydrogen or a carbon-based moiety, and wherein the carbon-based moiety can itself be further substituted.

When a substituent is monovalent, such as, for example, F or Cl, it is bonded to the atom it is substituting by a single bond. When a substituent is more than monovalent, such as O, which is divalent, it can be bonded to the atom it is substituting by more than one bond, i.e., a divalent substituent is bonded by a double bond; for example, a C substituted with O forms a carbonyl group, C=O, which can also be written as "CO", "C(O)", or "C(=O)", wherein the C and the O are double bonded. When a carbon atom is substituted with a double-bonded oxygen (=O) group, the oxygen substituent is termed an "oxo" group. When a divalent substituent such as NR is double-bonded to a carbon atom, the resulting C(=NR) group is termed an "imino" group. When a divalent substituent such as S is double-bonded to a carbon atom, the results C(=S) group is termed a "thiocarbonyl" group.

Alternatively, a divalent substituent such as O or S can be connected by two single bonds to two different carbon atoms. For example, O, a divalent substituent, can be bonded to each of two adjacent carbon atoms to provide an epoxide group, or the O can form a bridging ether group, termed an "oxy" group, between adjacent or non-adjacent carbon atoms, for example bridging the 1,4-carbons of a cyclohexyl group to form a [2.2.1]-oxabicyclo system. Further, any substituent can be bonded to a carbon or other atom by a linker, such as $(CH_2)_n$ or $(CR'_2)_n$ wherein n is 1, 2, 3, or more, and each R' is independently selected. Similarly, a methylenedioxy group can be a substituent when bonded to two adjacent carbon atoms, such as in a phenyl ring.

C(O) and $S(O)_2$ groups can be bound to one or two heteroatoms, such as nitrogen, rather than to a carbon atom. For example, when a C(O) group is bound to one carbon and one nitrogen atom, the resulting group is called an “amide” or “carboxamide.” When a C(O) group is bound to two nitrogen atoms, the functional group is termed a urea. When a $S(O)_2$ group is bound to one carbon and one nitrogen atom, the resulting unit is termed a “sulfonamide.” When a $S(O)_2$ group is bound to two nitrogen atoms, the resulting unit is termed a “sulfamate.”

Substituted alkyl, alkenyl, alkynyl, cycloalkyl, and cycloalkenyl groups as well as other substituted groups also include groups in which one or more bonds to a hydrogen atom are replaced by one or more bonds, including double or triple bonds, to a carbon atom, or to a heteroatom such as, but not limited to, oxygen in carbonyl (oxo), carboxyl, ester, amide, imide, urethane, and urea groups; and nitrogen in imines, hydroxyimines, oximes, hydrazones, amidines, guanidines, and nitriles.

Substituted ring groups such as substituted cycloalkyl, aryl, heterocyclyl and heteroaryl groups also include rings and fused ring systems in which a bond to a hydrogen atom is replaced with a bond to a carbon atom. Therefore, substituted cycloalkyl, aryl, heterocyclyl and heteroaryl groups can also be substituted with alkyl, alkenyl, and alkynyl groups as defined herein.

By a "ring system" as the term is used herein is meant a moiety comprising one, two, three or more rings, which can be substituted with non-ring groups or with other ring systems, or both, which can be fully saturated, partially unsaturated, fully unsaturated, or aromatic, and when the ring system includes more than a single ring, the rings can be fused, bridging, or spirocyclic. By "spirocyclic" is meant the class of structures wherein two rings are fused at a single tetrahedral carbon atom, as is well known in the art.

As to any of the groups described herein, which contain one or more substituents, it is understood, of course, that such groups do not contain any substitution or substitution patterns which are sterically impractical and/or synthetically non–feasible. In addition, the compounds of this disclosed subject matter include all stereochemical isomers arising from the substitution of these compounds.

Selected substituents within the compounds described herein are present to a recursive degree. In this context, “recursive substituent” means that a substituent may recite another instance of itself. Because of the recursive nature of such substituents, theoretically, a large number may be present in any given claim. One of ordinary skill in the art of medicinal chemistry and organic chemistry understands that the total number of such substituents is reasonably limited by the desired properties of the compound intended. Such properties include, by of example and not limitation, physical properties such as molecular weight, solubility or log P, application properties such as activity against the intended target, and practical properties such as ease of synthesis.

Recursive substituents are an intended aspect of the disclosed subject matter. One of ordinary skill in the art of medicinal and organic chemistry understands the versatility of such substituents. To the degree that recursive substituents are present in a claim of the disclosed subject matter, the total number should be determined as set forth above.

Alkyl groups include straight chain and branched alkyl groups and cycloalkyl groups having from 1 to about 20 carbon atoms, and typically from 1 to 12 carbons or, in some embodiments, from 1 to 8 carbon atoms. Examples of straight chain alkyl groups include those with from 1 to 8 carbon atoms such as methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, n-heptyl, and n-octyl groups. Examples of branched alkyl groups include, but are not limited to, isopropyl, iso-butyl, sec-butyl, t-butyl, neopentyl, isopentyl, and 2,2-dimethylpropyl groups. Representative substituted alkyl groups can be substituted one or more times with any of the groups listed above, for example, amino, hydroxy, cyano, carboxy, nitro, thio, alkoxy, and halogen groups.

Cycloalkyl groups are cyclic alkyl groups such as, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl groups. In some embodiments, the cycloalkyl group can have 3 to about 8-12 ring members, whereas in other embodiments the number of ring carbon atoms range from 3 to 4, 5, 6, or 7. Cycloalkyl groups further include polycyclic cycloalkyl groups such as, but not limited to, norbornyl, adamantyl, bornyl, camphenyl, isocamphenyl, and carenyl groups, and fused rings such as, but not limited to, decalinyl, and the like. Cycloalkyl groups also include rings that are substituted with straight or branched chain alkyl groups as defined above. Representative substituted cycloalkyl groups can be mono-substituted or substituted more than once, such as, but not limited to, 2,2-, 2,3-, 2,4- 2,5- or 2,6-disubstituted cyclohexyl groups or mono-, di- or tri-substituted norbornyl or cycloheptyl groups, which can be substituted with, for example, amino, hydroxy, cyano, carboxy, nitro, thio, alkoxy, and halogen groups. The term "cycloalkenyl" alone or in combination denotes a cyclic alkenyl group.

The terms "carbocyclic," "carbocyclyl," and "carbocycle" denote a ring structure wherein the atoms of the ring are carbon, such as a cycloalkyl group or an aryl group. In some embodiments, the carbocycle has 3 to 8 ring members, whereas in other embodiments the number of ring carbon atoms is 4, 5, 6, or 7. Unless specifically

indicated to the contrary, the carbocyclic ring can be substituted with as many as N-1 substituents wherein N is the size of the carbocyclic ring with, for example, alkyl, alkenyl, alkynyl, amino, aryl, hydroxy, cyano, carboxy, heteroaryl, heterocyclyl, nitro, thio, alkoxy, and halogen groups, or other groups as are listed above. A carbocyclyl ring can be a cycloalkyl ring, a cycloalkenyl ring, or an aryl ring. A carbocyclyl can be monocyclic or polycyclic, and if polycyclic each ring can be independently be a cycloalkyl ring, a cycloalkenyl ring, or an aryl ring.

(Cycloalkyl)alkyl groups, also denoted cycloalkylalkyl, are alkyl groups as defined above in which a hydrogen or carbon bond of the alkyl group is replaced with a bond to a cycloalkyl group as defined above.

Alkenyl groups include straight and branched chain and cyclic alkyl groups as defined above, except that at least one double bond exists between two carbon atoms. Thus, alkenyl groups have from 2 to about 20 carbon atoms, and typically from 2 to 12 carbons or, in some embodiments, from 2 to 8 carbon atoms. Examples include, but are not limited to vinyl, $-CH=CH(CH_3)$, $-CH=C(CH_3)_2$, $-C(CH_3)=CH_2$, $-C(CH_3)=CH(CH_3)$, $-C(CH_2CH_3)=CH_2$, cyclohexenyl, cyclopentenyl, cyclohexadienyl, butadienyl, pentadienyl, and hexadienyl among others.

Cycloalkenyl groups include cycloalkyl groups having at least one double bond between 2 carbons. Thus for example, cycloalkenyl groups include but are not limited to cyclohexenyl, cyclopentenyl, and cyclohexadienyl groups. Cycloalkenyl groups can have from 3 to about 8-12 ring members, whereas in other embodiments the number of ring carbon atoms range from 3 to 5, 6, or 7. Cycloalkyl groups further include polycyclic cycloalkyl groups such as, but not limited to, norbornyl, adamantyl, bornyl, camphenyl, isocamphenyl, and carenyl groups, and fused rings such as, but not limited to, decalinyl, and the like, provided they include at least one double bond within a ring. Cycloalkenyl groups also include rings that are substituted with straight or branched chain alkyl groups as defined above.

(Cycloalkenyl)alkyl groups are alkyl groups as defined above in which a hydrogen or carbon bond of the alkyl group is replaced with a bond to a cycloalkenyl group as defined above.

Alkynyl groups include straight and branched chain alkyl groups, except that at least one triple bond exists between two carbon atoms. Thus, alkynyl groups have from 2 to about 20 carbon atoms, and typically from 2 to 12 carbons or, in some embodiments, from 2 to 8 carbon atoms. Examples include, but are not limited to –C≡CH, -C≡C($CH_3$), -C≡C($CH_2CH_3$), -$CH_2$C≡CH, -$CH_2$C≡C($CH_3$), and -$CH_2$C≡C($CH_2CH_3$) among others.

The term "heteroalkyl" by itself or in combination with another term means, unless otherwise stated, a stable straight or branched chain alkyl group consisting of the stated number of carbon atoms and one or two heteroatoms selected from the group consisting of O, N, and S, and wherein the nitrogen and sulfur atoms may be optionally oxidized and the nitrogen heteroatom may be optionally quaternized. The heteroatom(s) may be placed at any position of the heteroalkyl group, including between the rest of the heteroalkyl group and the fragment to which it is attached, as well as attached to the most distal carbon atom in the heteroalkyl group. Examples include: -O-$CH_2$-$CH_2$-$CH_3$, -$CH_2$-$CH_2CH_2$-OH, -$CH_2$-$CH_2$-NH-$CH_3$, -$CH_2$-S-$CH_2$-$CH_3$, -$CH_2CH_2$-S(=O)-$CH_3$, and -$CH_2CH_2$-O-$CH_2CH_2$-O-$CH_3$. Up to two heteroatoms may be consecutive, such as, for example, -$CH_2$-NH-$OCH_3$, or –$CH_2$-$CH_2$-S-S-$CH_3$.

A "cycloheteroalkyl" ring is a cycloalkyl ring containing at least one heteroatom. A cycloheteroalkyl ring can also be termed a "heterocyclyl," described below.

The term "heteroalkenyl" by itself or in combination with another term means, unless otherwise stated, a stable straight or branched chain monounsaturated or di-unsaturated hydrocarbon group consisting of the stated number of carbon atoms and one or two heteroatoms selected from the group consisting of O, N, and S, and wherein the nitrogen and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. Up to two heteroatoms may be placed consecutively. Examples include -CH=CH-O-$CH_3$, -CH=CH-$CH_2$-OH, -$CH_2$-CH=N-$OCH_3$, -CH=CH-N($CH_3$)-$CH_3$, -$CH_2$-CH=CH-$CH_2$-SH, and and -CH=CH-O-$CH_2CH_2$-O-$CH_3$.

Aryl groups are cyclic aromatic hydrocarbons that do not contain heteroatoms in the ring. Thus aryl groups include, but are not limited to, phenyl, azulenyl, heptalenyl, biphenyl, indacenyl, fluorenyl, phenanthrenyl, triphenylenyl, pyrenyl, naphthacenyl, chrysenyl, biphenylenyl, anthracenyl, and naphthyl groups. In some embodiments, aryl groups contain about 6 to about 14 carbons in the ring portions of the groups. Aryl groups

can be unsubstituted or substituted, as defined above. Representative substituted aryl groups can be mono-substituted or substituted more than once, such as, but not limited to, 2-, 3-, 4-, 5-, or 6-substituted phenyl or 2-8 substituted naphthyl groups, which can be substituted with carbon or non-carbon groups such as those listed above.

Aralkyl groups are alkyl groups as defined above in which a hydrogen or carbon bond of an alkyl group is replaced with a bond to an aryl group as defined above. Representative aralkyl groups include benzyl and phenylethyl groups and fused (cycloalkylaryl)alkyl groups such as 4-ethyl-indanyl. Aralkenyl group are alkenyl groups as defined above in which a hydrogen or carbon bond of an alkyl group is replaced with a bond to an aryl group as defined above.

Heterocyclyl groups or the term "heterocyclyl" includes aromatic and non-aromatic ring compounds containing 3 or more ring members, of which, one or more is a heteroatom such as, but not limited to, N, O, and S. Thus a heterocyclyl can be a cycloheteroalkyl, or a heteroaryl, or if polycyclic, any combination thereof. In some embodiments, heterocyclyl groups include 3 to about 20 ring members, whereas other such groups have 3 to about 15 ring members. A heterocyclyl group designated as a $C_2$-heterocyclyl can be a 5-ring with two carbon atoms and three heteroatoms, a 6-ring with two carbon atoms and four heteroatoms and so forth. Likewise a $C_4$-heterocyclyl can be a 5-ring with one heteroatom, a 6-ring with two heteroatoms, and so forth. The number of carbon atoms plus the number of heteroatoms sums up to equal the total number of ring atoms. A heterocyclyl ring can also include one or more double bonds. A heteroaryl ring is an embodiment of a heterocyclyl group. The phrase “heterocyclyl group” includes fused ring species including those comprising fused aromatic and non-aromatic groups. For example, a dioxolanyl ring and a benzdioxolanyl ring system (methylenedioxyphenyl ring system) are both heterocyclyl groups within the meaning herein. The phrase also includes polycyclic ring systems containing a heteroatom such as, but not limited to, quinuclidyl. Heterocyclyl groups can be unsubstituted, or can be substituted as discussed above. Heterocyclyl groups include, but are not limited to, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, pyrrolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, thiazolyl, pyridinyl, thiophenyl, benzothiophenyl, benzofuranyl, dihydrobenzofuranyl, indolyl, dihydroindolyl, azaindolyl, indazolyl, benzimidazolyl, azabenzimidazolyl, benzoxazolyl,

benzothiazolyl, benzothiadiazolyl, imidazopyridinyl, isoxazolopyridinyl, thianaphthalenyl, purinyl, xanthinyl, adeninyl, guaninyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, quinoxalinyl, and quinazolinyl groups. Representative substituted heterocyclyl groups can be mono-substituted or substituted more than once, such as, but not limited to, piperidinyl or quinolinyl groups, which are 2-, 3-, 4-, 5-, or 6-substituted, or disubstituted with groups such as those listed above.

Heteroaryl groups are aromatic ring compounds containing 5 or more ring members, of which, one or more is a heteroatom such as, but not limited to, N, O, and S; for instance, heteroaryl rings can have 5 to about 8-12 ring members. A heteroaryl group is a variety of a heterocyclyl group that possesses an aromatic electronic structure. A heteroaryl group designated as a $C_2$-heteroaryl can be a 5-ring with two carbon atoms and three heteroatoms, a 6-ring with two carbon atoms and four heteroatoms and so forth. Likewise a $C_4$-heteroaryl can be a 5-ring with one heteroatom, a 6-ring with two heteroatoms, and so forth. The number of carbon atoms plus the number of heteroatoms sums up to equal the total number of ring atoms. Heteroaryl groups include, but are not limited to, groups such as pyrrolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, thiazolyl, pyridinyl, thiophenyl, benzothiophenyl, benzofuranyl, indolyl, azaindolyl, indazolyl, benzimidazolyl, azabenzimidazolyl, benzoxazolyl, benzothiazolyl, benzothiadiazolyl, imidazopyridinyl, isoxazolopyridinyl, thianaphthalenyl, purinyl, xanthinyl, adeninyl, guaninyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, quinoxalinyl, and quinazolinyl groups. Heteroaryl groups can be unsubstituted, or can be substituted with groups as is discussed above. Representative substituted heteroaryl groups can be substituted one or more times with groups such as those listed above.

Additional examples of aryl and heteroaryl groups include but are not limited to phenyl, biphenyl, indenyl, naphthyl (1-naphthyl, 2-naphthyl), N-hydroxytetrazolyl, N-hydroxytriazolyl, N-hydroxyimidazolyl, anthracenyl (1-anthracenyl, 2-anthracenyl, 3-anthracenyl), thiophenyl (2-thienyl, 3-thienyl), furyl (2-furyl, 3-furyl) , indolyl, oxadiazolyl, isoxazolyl, quinazolinyl, fluorenyl, xanthenyl, isoindanyl, benzhydryl, acridinyl, thiazolyl, pyrrolyl (2-pyrrolyl), pyrazolyl (3-pyrazolyl), imidazolyl (1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl), triazolyl (1,2,3-triazol-1-yl, 1,2,3-triazol-2-yl 1,2,3-triazol-4-yl, 1,2,4-triazol-3-yl), oxazolyl (2-oxazolyl, 4-oxazolyl, 5-

oxazolyl), thiazolyl (2-thiazolyl, 4-thiazolyl, 5-thiazolyl), pyridyl (2-pyridyl, 3-pyridyl, 4-pyridyl), pyrimidinyl (2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl), pyrazinyl, pyridazinyl (3- pyridazinyl, 4-pyridazinyl, 5-pyridazinyl), quinolyl (2-quinolyl, 3-quinolyl, 4-quinolyl, 5-quinolyl, 6-quinolyl, 7-quinolyl, 8-quinolyl), isoquinolyl (1-isoquinolyl, 3-isoquinolyl, 4-isoquinolyl, 5-isoquinolyl, 6-isoquinolyl, 7-isoquinolyl, 8-isoquinolyl), benzo[b]furanyl (2-benzo[b]furanyl, 3-benzo[b]furanyl, 4-benzo[b]furanyl, 5-benzo[b]furanyl, 6-benzo[b]furanyl, 7-benzo[b]furanyl), 2,3-dihydro-benzo[b]furanyl (2-(2,3-dihydro-benzo[b]furanyl), 3-(2,3-dihydro-benzo[b]furanyl), 4-(2,3-dihydro-benzo[b]furanyl), 5-(2,3-dihydro-benzo[b]furanyl), 6-(2,3-dihydro-benzo[b]furanyl), 7-(2,3-dihydro-benzo[b]furanyl), benzo[b]thiophenyl (2-benzo[b]thiophenyl, 3-benzo[b]thiophenyl, 4-benzo[b]thiophenyl, 5-benzo[b]thiophenyl, 6-benzo[b]thiophenyl, 7-benzo[b]thiophenyl), 2,3-dihydro-benzo[b]thiophenyl, (2-(2,3-dihydro-benzo[b]thiophenyl), 3-(2,3-dihydro-benzo[b]thiophenyl), 4-(2,3-dihydro-benzo[b]thiophenyl), 5-(2,3-dihydro-benzo[b]thiophenyl), 6-(2,3-dihydro-benzo[b]thiophenyl), 7-(2,3-dihydro-benzo[b]thiophenyl), indolyl (1-indolyl, 2-indolyl, 3-indolyl, 4-indolyl, 5-indolyl, 6-indolyl, 7-indolyl), indazole (1-indazolyl, 3-indazolyl, 4-indazolyl, 5-indazolyl, 6-indazolyl, 7-indazolyl), benzimidazolyl (1-benzimidazolyl, 2-benzimidazolyl, 4-benzimidazolyl, 5-benzimidazolyl, 6-benzimidazolyl, 7-benzimidazolyl, 8-benzimidazolyl), benzoxazolyl (1-benzoxazolyl, 2-benzoxazolyl), benzothiazolyl (1-benzothiazolyl, 2-benzothiazolyl, 4-benzothiazolyl, 5-benzothiazolyl, 6-benzothiazolyl, 7-benzothiazolyl), carbazolyl (1-carbazolyl, 2-carbazolyl, 3-carbazolyl, 4-carbazolyl), 5H-dibenz[b,f]azepine (5H-dibenz[b,f]azepin-1-yl, 5H-dibenz[b,f]azepine-2-yl, 5H-dibenz[b,f]azepine-3-yl, 5H-dibenz[b,f]azepine-4-yl, 5H-dibenz[b,f]azepine-5-yl), 10,11-dihydro-5H-dibenz[b,f]azepine (10,11-dihydro-5H-dibenz[b,f]azepine-1-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-2-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-3-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-4-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-5-yl), and the like.

Heterocyclylalkyl groups are alkyl groups as defined above in which a hydrogen or carbon bond of an alkyl group as defined above is replaced with a bond to a heterocyclyl group as defined above. Representative heterocyclyl alkyl groups include, but are not

limited to, furan-2-yl methyl, furan-3-yl methyl, pyridine-3-yl methyl, tetrahydrofuran-2-yl ethyl, and indol-2-yl propyl.

Heteroarylalkyl groups are alkyl groups as defined above in which a hydrogen or carbon bond of an alkyl group is replaced with a bond to a heteroaryl group as defined above.

The term “alkoxy" refers to an oxygen atom connected to an alkyl group, including a cycloalkyl group, as are defined above. Examples of linear alkoxy groups include but are not limited to methoxy, ethoxy, propoxy, butoxy, pentyloxy, hexyloxy, and the like. Examples of branched alkoxy include but are not limited to isopropoxy, sec-butoxy, tert-butoxy, isopentyloxy, isohexyloxy, and the like. Examples of cyclic alkoxy include but are not limited to cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, and the like. An alkoxy group can include one to about 12-20 carbon atoms bonded to the oxygen atom, and can further include double or triple bonds, and can also include heteroatoms. For example, an allyloxy group is an alkoxy group within the meaning herein. A methoxyethoxy group is also an alkoxy group within the meaning herein, as is a methylenedioxy group in a context where two adjacent atoms of a structures are substituted therewith.

The terms “halo” or “halogen” or "halide" by themselves or as part of another substituent mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom, preferably, fluorine, chlorine, or bromine.

A “haloalkyl” group includes mono-halo alkyl groups, poly-halo alkyl groups wherein all halo atoms can be the same or different, and per-halo alkyl groups, wherein all hydrogen atoms are replaced by halogen atoms, such as fluoro. Examples of haloalkyl include trifluoromethyl, 1,1-dichloroethyl, 1,2-dichloroethyl, 1,3-dibromo-3,3-difluoropropyl, perfluorobutyl, and the like.

A "haloalkoxy" group includes mono-halo alkoxy groups, poly-halo alkoxy groups wherein all halo atoms can be the same or different, and per-halo alkoxy groups, wherein all hydrogen atoms are replaced by halogen atoms, such as fluoro. Examples of haloalkoxy include trifluoromethoxy, 1,1-dichloroethoxy, 1,2-dichloroethoxy, 1,3-dibromo-3,3-difluoropropoxy, perfluorobutoxy, and the like.

The term "($C_x$-$C_y$)perfluoroalkyl," wherein x < y, means an alkyl group with a minimum of x carbon atoms and a maximum of y carbon atoms, wherein all hydrogen atoms are replaced by fluorine atoms. Preferred is -($C_1$-$C_6$)perfluoroalkyl, more preferred is -($C_1$-$C_3$)perfluoroalkyl, most preferred is $–CF_3$.

The term "($C_x$-$C_y$)perfluoroalkylene," wherein x < y, means an alkyl group with a minimum of x carbon atoms and a maximum of y carbon atoms, wherein all hydrogen atoms are replaced by fluorine atoms. Preferred is -($C_1$-$C_6$)perfluoroalkylene, more preferred is -($C_1$-$C_3$)perfluoroalkylene, most preferred is $–CF_2–$.

The terms "aryloxy" and "arylalkoxy" refer to, respectively, an aryl group bonded to an oxygen atom and an aralkyl group bonded to the oxygen atom at the alkyl moiety. Examples include but are not limited to phenoxy, naphthyloxy, and benzyloxy.

An "acyl" group as the term is used herein refers to a group containing a carbonyl moiety wherein the group is bonded via the carbonyl carbon atom. The carbonyl carbon atom is also bonded to another carbon atom, which can be part of an alkyl, aryl, aralkyl cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl group or the like. In the special case wherein the carbonyl carbon atom is bonded to a hydrogen, the group is a "formyl" group, an acyl group as the term is defined herein. An acyl group can include 0 to about 12-20 additional carbon atoms bonded to the carbonyl group. An acyl group can include double or triple bonds within the meaning herein. An acryloyl group is an example of an acyl group. An acyl group can also include heteroatoms within the meaning here. A nicotinoyl group (pyridyl-3-carbonyl) group is an example of an acyl group within the meaning herein. Other examples include acetyl, benzoyl, phenylacetyl, pyridylacetyl, cinnamoyl, and acryloyl groups and the like. When the group containing the carbon atom that is bonded to the carbonyl carbon atom contains a halogen, the group is termed a "haloacyl" group. An example is a trifluoroacetyl group.

The term "amine" includes primary, secondary, and tertiary amines having, e.g., the formula $N(group)_3$ wherein each group can independently be H or non-H, such as alkyl, aryl, and the like. Amines include but are not limited to $R\text{-}NH_2$, for example, alkylamines, arylamines, alkylarylamines; $R_2NH$ wherein each R is independently selected, such as dialkylamines, diarylamines, aralkylamines, heterocyclylamines and the like; and $R_3N$ wherein each R is independently selected, such as trialkylamines, dialkylarylamines,

alkyldiarylamines, triarylamines, and the like. The term "amine" also includes ammonium ions as used herein.

An "amino" group is a substituent of the form $-NH_2$, -NHR, $-NR_2$, $-NR_3^+$, wherein each R is independently selected, and protonated forms of each, except for $-NR_3^+$, which cannot be protonated. Accordingly, any compound substituted with an amino group can be viewed as an amine. An "amino group" within the meaning herein can be a primary, secondary, tertiary or quaternary amino group. An "alkylamino" group includes a monoalkylamino, dialkylamino, and trialkylamino group.

An "ammonium" ion includes the unsubstituted ammonium ion $NH_4^+$, but unless otherwise specified, it also includes any protonated or quaternarized forms of amines. Thus, trimethylammonium hydrochloride and tetramethylammonium chloride are both ammonium ions, and amines, within the meaning herein.

The term “amide” (or “amido”) includes C- and N-amide groups, i.e., $-C(O)NR_2$, and –NRC(O)R groups, respectively. Amide groups therefore include but are not limited to primary carboxamide groups ($-C(O)NH_2$) and formamide groups (-NHC(O)H). A "carboxamido" group is a group of the formula $C(O)NR_2$, wherein R can be H, alkyl, aryl, etc.

The term "azido" refers to an $N_3$ group. An "azide" can be an organic azide or can be a salt of the azide ($N_3^-$) anion. The term "nitro" refers to an $NO_2$ group bonded to an organic moiety. The term "nitroso" refers to an NO group bonded to an organic moiety. The term nitrate refers to an $ONO_2$ group bonded to an organic moiety or to a salt of the nitrate ($NO_3^-$) anion.

The term “urethane” (“carbamoyl” or “carbamyl”) includes N- and O-urethane groups, i.e., -NRC(O)OR and $–OC(O)NR_2$ groups, respectively.

The term “sulfonamide” (or “sulfonamido”) includes S- and N-sulfonamide groups, i.e., $-SO_2NR_2$ and $–NRSO_2R$ groups, respectively. Sulfonamide groups therefore include but are not limited to sulfamoyl groups ($-SO_2NH_2$). An organosulfur structure represented by the formula –S(O)(NR)– is understood to refer to a sulfoximine, wherein both the oxygen and the nitrogen atoms are bonded to the sulfur atom, which is also bonded to two carbon atoms.

The term “amidine” or “amidino” includes groups of the formula -C(NR)$NR_2$. Typically, an amidino group is –C(NH)$NH_2$.

The term “guanidine” or “guanidino” includes groups of the formula -NRC(NR)$NR_2$. Typically, a guanidino group is –NHC(NH)$NH_2$.

A "salt" as is well known in the art includes an organic compound such as a carboxylic acid, a sulfonic acid, or an amine, in ionic form, in combination with a counterion. For example, acids in their anionic form can form salts with cations such as metal cations, for example sodium, potassium, and the like; with ammonium salts such as $NH_4^+$ or the cations of various amines, including tetraalkyl ammonium salts such as tetramethylammonium, or other cations such as trimethylsulfonium, and the like. A "pharmaceutically acceptable" or "pharmacologically acceptable" salt is a salt formed from an ion that has been approved for human consumption and is generally non-toxic, such as a chloride salt or a sodium salt. A "zwitterion" is an internal salt such as can be formed in a molecule that has at least two ionizable groups, one forming an anion and the other a cation, which serve to balance each other. For example, amino acids such as glycine can exist in a zwitterionic form. A "zwitterion" is a salt within the meaning herein. The compounds of the present invention may take the form of salts. The term “salts” embraces addition salts of free acids or free bases which are compounds of the invention. Salts can be "pharmaceutically-acceptable salts." The term “pharmaceutically-acceptable salt” refers to salts which possess toxicity profiles within a range that affords utility in pharmaceutical applications. Pharmaceutically unacceptable salts may nonetheless possess properties such as high crystallinity, which have utility in the practice of the present invention, such as for example utility in process of synthesis, purification or formulation of compounds of the invention.

Suitable pharmaceutically-acceptable acid addition salts may be prepared from an inorganic acid or from an organic acid. Examples of inorganic acids include hydrochloric, hydrobromic, hydriodic, nitric, carbonic, sulfuric, and phosphoric acids. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, examples of which include formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic,

4-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, trifluoromethanesulfonic, 2-hydroxyethanesulfonic, p-toluenesulfonic, sulfanilic, cyclohexylaminosulfonic, stearic, alginic, β-hydroxybutyric, salicylic, galactaric and galacturonic acid. Examples of pharmaceutically unacceptable acid addition salts include, for example, perchlorates and tetrafluoroborates.

Suitable pharmaceutically acceptable base addition salts of compounds of the invention include, for example, metallic salts including alkali metal, alkaline earth metal and transition metal salts such as, for example, calcium, magnesium, potassium, sodium and zinc salts. Pharmaceutically acceptable base addition salts also include organic salts made from basic amines such as, for example, *N*,*N*'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. Examples of pharmaceutically unacceptable base addition salts include lithium salts and cyanate salts. Although pharmaceutically unacceptable salts are not generally useful as medicaments, such salts may be useful, for example as intermediates in the synthesis of Formula (I) compounds, for example in their purification by recrystallization. All of these salts may be prepared by conventional means from the corresponding compound according to Formula (I) by reacting, for example, the appropriate acid or base with the compound according to Formula (I). The term "pharmaceutically acceptable salts" refers to nontoxic inorganic or organic acid and/or base addition salts, see, for example, Lit et al., Salt Selection for Basic Drugs (1986), *Int J. Pharm.*, **33**, 201-217, incorporated by reference herein.

A "hydrate" is a compound that exists in a composition with water molecules. The composition can include water in stoichiometic quantities, such as a monohydrate or a dihydrate, or can include water in random amounts. As the term is used herein a "hydrate" refers to a solid form, i.e., a compound in water solution, while it may be hydrated, is not a hydrate as the term is used herein.

A "solvate" is a similar composition except that a solvent other that water replaces the water. For example, methanol or ethanol can form an "alcoholate", which can again be stoichiometic or non-stoichiometric. As the term is used herein a "solvate" refers to a solid

form, i.e., a compound in solution in a solvent, while it may be solvated, is not a solvate as the term is used herein.

A "prodrug" as is well known in the art is a substance that can be administered to a patient where the substance is converted in vivo by the action of biochemicals within the patients body, such as enzymes, to the active pharmaceutical ingredient. Examples of prodrugs include esters of carboxylic acid groups, which can be hydrolyzed by endogenous esterases as are found in the bloodstream of humans and other mammals. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

As used herein, the statement that "the compound is not a peptide comprising only ribosomal amino acid residues, or a derivative thereof" refers to the condition that the compound is not a peptide that could be formed on a ribosome *in vivo* or *in vitro* using only the naturally occurring ribosomal amino acids as are well known in the art, i.e., those amino acids that are coded in DNA by codons for which transfer RNAs exist in the living organism. A "peptide", as is well known in the art, is a linear polyamide formed from head-to-tail polymerization of alpha-amino acids. Thus, a peptide comprising only ribosomal amino acids" can be termed a "natural peptide." The compounds of the present invention can be structural analogs of peptides, but encompass at least some portions of the molecule that do not correspond to a ribosomal amino acid residue. A "derivative thereof" as the term is used herein refers to a chemical derivative of a natural peptide that is readily prepared from the natural peptide, e.g., by N-terminus acetylation, benzylation, or carboxyalkylation, or C-terminus esterification, or sidechain reaction such as any of the above listed depending on the chemical nature of the side chain.

In addition, where features or aspects of the invention are described in terms of Markush groups, those skilled in the art will recognize that the invention is also thereby described in terms of any individual member or subgroup of members of the Markush group. For example, if a group X is described as selected from the set consisting of bromine, chlorine, and iodine, claims for X being bromine and claims for X being bromine and chlorine are fully described. Moreover, where features or aspects of the invention are described in terms of Markush groups, those skilled in the art will recognize that the invention is also thereby described in terms of any combination of individual members or

subgroups of members of Markush groups. Thus, for example, if X is described as selected from the group consisting of bromine, chlorine, and iodine, and Y is described as selected from the group consisting of methyl, ethyl, and propyl, claims for X being bromine and Y being methyl are fully described.

If a value of a variable that is necessarily an integer, e.g., the number of carbon atoms in an alkyl group or the number of substituents on a ring, is described as a range, e.g., 0-4, what is meant is that the value can be any integer between 0 and 4 inclusive, i.e., 0, 1, 2, 3, or 4.

In various embodiments, the compound or set of compounds, such as are used in the inventive methods, can be any one of any of the combinations and/or sub-combinations of the above-listed embodiments.

In various embodiments, a compound as shown in any of the Examples, or among the exemplary compounds, is provided. Provisos may apply to any of the disclosed categories or embodiments wherein any one or more of the other above disclosed embodiments or species may be excluded from such categories or embodiments.

The present invention further embraces isolated compounds of the invention, such as compounds of any of formulas (I) – (VI). The expression "isolated compound" refers to a preparation of a compound of the invention, or a mixture of compounds the invention, wherein the isolated compound has been separated from the reagents used, and/or byproducts formed, in the synthesis of the compound or compounds. "Isolated" does not mean that the preparation is technically pure (homogeneous), but it is sufficiently pure to compound in a form in which it can be used therapeutically. Preferably an "isolated compound" refers to a preparation of a compound of the invention or a mixture of compounds of the invention, which contains the named compound or mixture of compounds of the invention in an amount of at least 10 percent by weight of the total weight. Preferably the preparation contains the named compound or mixture of compounds in an amount of at least 50 percent by weight of the total weight; more preferably at least 80 percent by weight of the total weight; and most preferably at least 90 percent, at least 95 percent or at least 98 percent by weight of the total weight of the preparation.The compounds of the invention and intermediates may be isolated from their reaction mixtures and purified by standard techniques such as filtration, liquid-liquid

extraction, solid phase extraction, distillation, recrystallization or chromatography, including flash column chromatography, or HPLC.

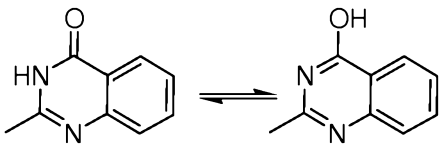
Isomerism and Tautomerism in Compounds of the Invention

*Tautomerism*

Within the present invention it is to be understood that a compound of the formula (I) or a salt thereof may exhibit the phenomenon of tautomerism whereby two chemical compounds that are capable of facile interconversion by exchanging a hydrogen atom between two atoms, to either of which it forms a covalent bond. Since the tautomeric compounds exist in mobile equilibrium with each other they may be regarded as different isomeric forms of the same compound. It is to be understood that the formulae drawings within this specification can represent only one of the possible tautomeric forms. However, it is also to be understood that the invention encompasses any tautomeric form, and is not to be limited merely to any one tautomeric form utilized within the formulae drawings. The formulae drawings within this specification can represent only one of the possible tautomeric forms and it is to be understood that the specification encompasses all possible tautomeric forms of the compounds drawn not just those forms which it has been convenient to show graphically herein. For example, tautomerism may be exhibited by a pyrazolyl group bonded as indicated by the wavy line. While both substituents would be termed a 4-pyrazolyl group, it is evident that a different nitrogen atom bears the hydrogen atom in each structure.




Such tautomerism can also occur with substituted pyrazoles such as 3-methyl, 5-methyl, or 3,5-dimethylpyrazoles, and the like. Another example of tautomerism is amido-imido (lactam-lactim when cyclic) tautomerism, such as is seen in heterocyclic compounds bearing a ring oxygen atom adjacent to a ring nitrogen atom. For example, the equilibrium:

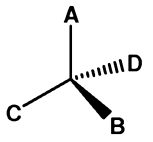



is an example of tautomerism. Accordingly, a structure depicted herein as one tautomer is intended to also include the other tautomer.

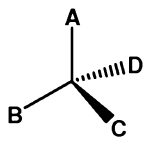
*Optical Isomerism*

It will be understood that when compounds of the present invention contain one or more chiral centers, the compounds may exist in, and may be isolated as pure enantiomeric or diastereomeric forms or as racemic mixtures. The present invention therefore includes any possible enantiomers, diastereomers, racemates or mixtures thereof of the compounds of the invention.

The isomers resulting from the presence of a chiral center comprise a pair of non-superimposable isomers that are called "enantiomers." Single enantiomers of a pure compound are optically active, *i.e.*, they are capable of rotating the plane of plane polarized light. Single enantiomers are designated according to the *Cahn-Ingold-Prelog* system. The priority of substituents is ranked based on atomic weights, a higher atomic weight, as determined by the systematic procedure, having a higher priority ranking. Once the priority ranking of the four groups is determined, the molecule is oriented so that the lowest ranking group is pointed away from the viewer. Then, if the descending rank order of the other groups proceeds clockwise, the molecule is designated *(R)* and if the descending rank of the other groups proceeds counterclockwise, the molecule is designated *(S)*. In the example in Scheme 14, the *Cahn-Ingold-Prelog* ranking is A > B > C > D. The lowest ranking atom, D is oriented away from the viewer.




(R) configuration




(S) configuration

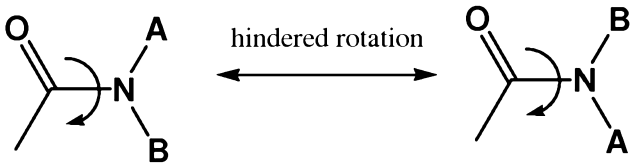
The present invention is meant to encompass diastereomers as well as their racemic and resolved, diastereomerically and enantiomerically pure forms and salts thereof. Diastereomeric pairs may be resolved by known separation techniques including normal and reverse phase chromatography, and crystallization.

"Isolated optical isomer" means a compound which has been substantially purified from the corresponding optical isomer(s) of the same formula. Preferably, the isolated isomer is at least about 80%, more preferably at least 90% pure, even more preferably at least 98% pure, most preferably at least about 99% pure, by weight.

Isolated optical isomers may be purified from racemic mixtures by well-known chiral separation techniques. According to one such method, a racemic mixture of a compound of the invention, or a chiral intermediate thereof, is separated into 99% wt.% pure optical isomers by HPLC using a suitable chiral column, such as a member of the series of DAICEL® CHIRALPAK® family of columns (Daicel Chemical Industries, Ltd., Tokyo, Japan). The column is operated according to the manufacturer's instructions.

*Rotational Isomerism*

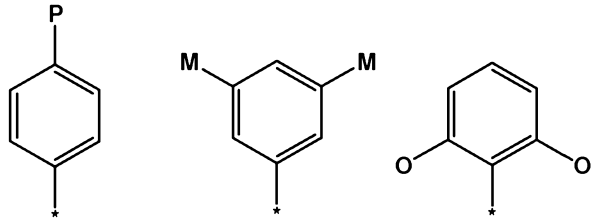
It is understood that due to chemical properties (*i.e.*, resonance lending some double bond character to the C-N bond) of restricted rotation about the amide bond linkage (as illustrated below) it is possible to observe separate rotamer species and even, under some circumstances, to isolate such species (see below). It is further understood that certain structural elements, including steric bulk or substituents on the amide nitrogen, may enhance the stability of a rotamer to the extent that a compound may be isolated as, and exist indefinitely, as a single stable rotamer. The present invention therefore includes any possible stable rotamers of formula (I) which are biologically active in the treatment of cancer or other proliferative disease states.




*Regioisomerism*

The preferred compounds of the present invention have a particular spatial arrangement of substituents on the aromatic rings, which is related to the structure activity relationship demonstrated by the compound class. Often such substitution arrangement is denoted by a numbering system; however, numbering systems are often not consistent between different ring systems. In six-membered aromatic systems, the spatial

arrangements are specified by the common nomenclature "para" for 1,4-substitution, "meta" for 1,3-substitution and "ortho" for 1,2-substitution as shown below.



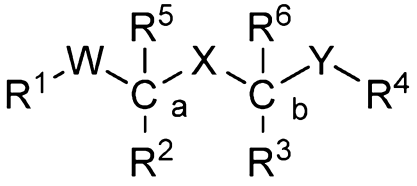

"para-" "meta-" "ortho-"

## Description

***Compounds of the Invention***

The invention is directed to compounds that can be potent modulators of galanin receptors of various types, to methods of use of the compounds, and to methods of preparation of the compounds, as well as to pharmaceutical compositions including the compounds.

In various embodiments, the invention provides a galanin receptor-modulatory compound of formula (I):




(I)

wherein W, X and Y are each independently $(C_1\text{-}C_5)$alkylene, $(CH_2)_{0\text{-}2}O(CH_2)_{0\text{-}2}$, $(CH_2)_{0\text{-}2}C(=O)(CH_2)_{0\text{-}2}$, $(CH_2)_{0\text{-}2}CR_2(CH_2)_{0\text{-}2}$, $(CH_2)_{0\text{-}2}C(OR)(R)(CH_2)_{0\text{-}2}$, $O(CR_2)_nO$ wherein n is 1 to 4, $(CH_2)_{0\text{-}2}N(R)(CH_2)_{0\text{-}2}$, $(CH_2)_{0\text{-}2}S(CH_2)_{0\text{-}2}$, $(CH_2)_{0\text{-}2}SO(CH_2)_{0\text{-}2}$, $(CH_2)_{0\text{-}2}SO_2(CH_2)_{0\text{-}2}$, $(CH_2)_{0\text{-}2}SO_2N(R)(CH_2)_{0\text{-}2}$, $(CH_2)_{0\text{-}2}SO_3(CH_2)_{0\text{-}2}$, $(CH_2)_{0\text{-}2}C(=O)C(=O)(CH_2)_{0\text{-}2}$,

$(CH_2)_{0\text{-}2}C(=O)CH_2C(=O)$ $(CH_2)_{0\text{-}2}$, $(CH_2)_{0\text{-}2}C(=S)(CH_2)_{0\text{-}2}$, $(CH_2)_{0\text{-}2}C(=O)O(CH_2)_{0\text{-}2}$, $(CH_2)_{0\text{-}2}OC(=O)(CH_2)_{0\text{-}2}$, $(CH_2)_{0\text{-}2}OC(=O)O(CH_2)_{0\text{-}2}$, $(CH_2)_{0\text{-}2}C(=O)N(R)(CH_2)_{0\text{-}2}$, $(CH_2)_{0\text{-}2}OC(=O)N(R)(CH_2)_{0\text{-}2}$, $(CH_2)_{0\text{-}2}C(=S)N(R)(CH_2)_{0\text{-}2}$, $(CH_2)_{0\text{-}2}NHC(=O)(CH_2)_{0\text{-}2}$, $(CH_2)_{0\text{-}2}N(R)N(R)C(=O)(CH_2)_{0\text{-}2}$, $(CH_2)_{0\text{-}2}N(R)N(R)C(=O)O(CH_2)_{0\text{-}2}$, $(CH_2)_{0\text{-}2}N(R)N(R)C(=O)N(R)(CH_2)_{0\text{-}2}$, $(CH_2)_{0\text{-}2}N(R)SO_2(CH_2)_{0\text{-}2}$,

$(CH_2)_{0-2}N(R)SO_2N(R)(CH_2)_{0-2}$, $(CH_2)_{0-2}N(R)C(=O)O(CH_2)_{0-2}$, $(CH_2)_{0-2}N(R)C(=O)(CH_2)_{0-2}$, $(CH_2)_{0-2}N(R)C(=S)(CH_2)_{0-2}$, $(CH_2)_{0-2}N(R)C(=O)N(R)(CH_2)_{0-2}$, $(CH_2)_{0-2}N(R)C(=S)N(R)(CH_2)_{0-2}$, $(CH_2)_{0-2}N(C(=O)R)C(=O)(CH_2)_{0-2}$, $(CH_2)_{0-2}N(OR)(CH_2)_{0-2}$, $(CH_2)_{0-2}C(=NH)N(R)(CH_2)_{0-2}$, $(CH_2)_{0-2}C(=O)N(OR)(CH_2)_{0-2}$, or $(CH_2)_{0-2}C(=NOR)(CH_2)_{0-2}$; or any of W, X, and Y is a bond provided that only one of W, X, and Z is a bond;

$R^1$, $R^2$, and $R^3$ are each independently alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl; provided that any alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl is substituted with 0-4 J, and wherein any $R^2$ can be bonded to $C_a$ either directly or via a linker comprising O, NR, C(=O)NR, OC(=O)NR, or $S(O)_q$, and wherein any $R^3$ can be bonded to $C_b$ either directly or via a linker comprising O, NR, C(=O)NR, OC(=O)NR, or $S(O)_q$, wherein q is 0, 1, or 2; or wherein $R^1$ and $R^2$ together with W and $C_a$ form a heterocyclyl ring substituted with 0-4 J which can be fused with cycloalkyl, aryl or heteroaryl;

$R^4$ is aryl or heteroaryl, substituted with 0-4 J;

$R^5$ and $R^6$ are each independently H or methyl;

J is independently at each occurrence R, F, Cl, Br, I, OR, CN, $CF_3$, $OCF_3$, =O, =S, methylenedioxy, ethylenedioxy, $N(R)_2$, SR, SOR, $SO_2R$, $SO_2N(R)_2$, $SO_3R$, C(O)R, C(O)C(O)R, $C(O)CH_2C(O)R$, C(S)R, C(O)OR, OC(O)R, OC(O)OR, $C(O)N(R)_2$, $OC(O)N(R)_2$, $C(S)N(R)_2$, $(CH_2)_{0-2}NHC(O)R$, N(R)N(R)C(O)R, N(R)N(R)C(O)OR, $N(R)N(R)CON(R)_2$, $N(R)SO_2R$, $N(R)SO_2N(R)_2$, N(R)C(O)OR, N(R)C(O)R, N(R)C(S)R, $N(R)C(O)N(R)_2$, $N(R)C(S)N(R)_2$, N(COR)COR, N(OR)R, $C(=NH)N(R)_2$, C(O)N(OR)R, or C(=NOR)R;

R is independently at each occurrence hydrogen, alkyl, alkoxy, haloalkyl, haloalkoxy, alkenyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl, wherein any alkyl, alkoxy, haloalkyl, haloalkoxy, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl is substituted with 0-4 J; or wherein two R groups together with a nitrogen atom or with two adjacent nitrogen atoms to which they are bonded can together form a three to eight membered heterocyclyl substituted with 0-4 J;

optionally further comprising 1-3 additional ring heteroatoms selected from the group consisting of O, N, and $S(O)_q$;

wherein any cycloalkyl, aryl, heterocyclyl, or heteroaryl can be fused, bridged, or in a spiro configuration with one or more additional optionally substituted cycloalkyl, aryl, heterocyclyl, and heteroaryl, monocyclic, bicyclic or polycyclic, saturated, partially unsaturated, or aromatic rings;

including all stereoisomers thereof and all isotopically labeled forms thereof;

or any salt, hydrate, solvate, prodrug, or metabolite thereof;

provided that the compound is not a peptide comprising only ribosomal amino acid residues, or a derivative thereof.

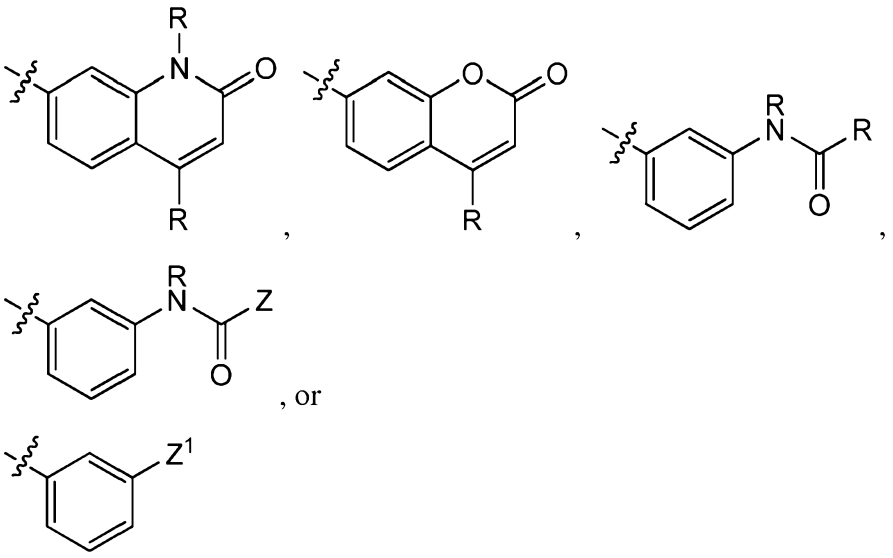
For example, in various embodiments, a compound of formula (I) is provided wherein W is $CH_2$ or a bond, and X and Y are both C(=O)NR.

For example, in various embodiments, a compound of formula (I) is provided wherein $R^1$ comprises at least six carbon atoms.

For example, in various embodiments, a compound of formula (I) is provided wherein $R^1$ is cyclohexyl, cyclohexylmethyl, indolyl, pyridyl, cyclohexyloxycarbonyl, benzyloxy, benzylthio, naphthyl, methyl, isopropyl, isobutyl, imidazolyl, or aralkyl imidazolyl.

For example, in various embodiments, a compound of formula (I) is provided wherein $R^2$ or $R^3$, or both, is $(CH_2)_nNRH$ or $(CH_2)_nNR\text{-}C(=O)OR$, wherein n is 0, 1, 2, 3, or 4 and each independently selected R is as defined above. More specifically, for $R^2$ or $R^3$, or both, NR can be NH and OR can be O-t-butyl or O-fluorenylmethylene.

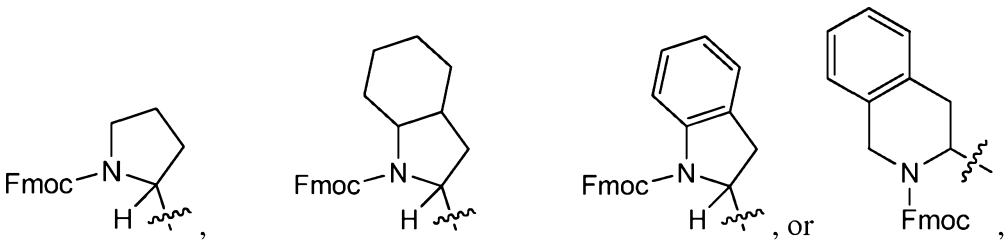
For example, in various embodiments, a compound of formula (I) is provided wherein $R^4$ is any of



wherein Z is alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, alkynyl, heterocyclylalkyl, or heteroarylalkyl; $Z^1$ is $NR_2$, $-C(R)=C(CN)_2$, C(=O)R, heterocyclylalkyl, or heteroarylalkyl; and each independently selected R is as defined in claim 1, and wherein a wavy line indicates a point of attachment.

In various embodiments, the invention provides a compound of formula (I) wherein $R^5$ and $R^6$ are both H.

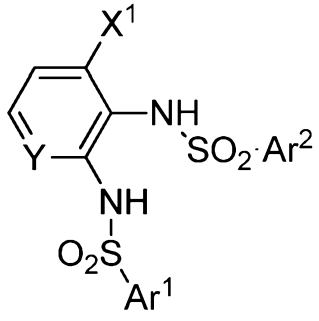
In various embodiments, the invention provides a compound of formula (I) wherein $R^1$ and $R^2$ together with W and $C_a$ comprise any of the following heterocyclyl groups



wherein a wavy line indicates a point of attachment.

In various embodiments, the compound of formula (I) can be any of the examplary compounds shown in Table 1, below, or a salt thereof.

For example, in various embodiments, the galanin receptor-modulatory compound is of formula (II)



(II)

wherein:

Y is CH or N;

$X^1$ is H or alkyl, or $X^1$, the carbon atom to which it is bonded, an adjacent carbon atom bearing an N atom, and the N atom, together form a pyrrole ring fused to the ring containing Y, to provide an indole or aza-indole ring system;

$Ar^1$ and $Ar^2$ are each independently aryl or heteroaryl, wherein any aryl or heteroaryl is optionally mono- or indepdendently multi-substituted with J;

J is independently at each occurrence R, F, Cl, Br, I, OR, CN, $CF_3$, $CF_2H$, $OCF_3$, $OCF_2H$, =O, =S, methylenedioxy, ethylenedioxy, $N(R)_2$, SR, SOR, $SO_2R$, $SO_2N(R)_2$, $SO_3R$, C(O)R, C(O)C(O)R, $C(O)CH_2C(O)R$, C(S)R, C(O)OR, OC(O)R, OC(O)OR, $C(O)N(R)_2$, $OC(O)N(R)_2$, $C(S)N(R)_2$, $(CH_2)_{0-2}NHC(O)R$, N(R)N(R)C(O)R, N(R)N(R)C(O)OR, $N(R)N(R)CON(R)_2$, $N(R)SO_2R$, $N(R)SO_2N(R)_2$, N(R)C(O)OR, N(R)C(O)R, N(R)C(S)R, $N(R)C(O)N(R)_2$, $N(R)C(S)N(R)_2$, N(COR)COR, N(OR)R, $C(=NH)N(R)_2$, C(O)N(OR)R, or C(=NOR)R;

R is independently at each occurrence hydrogen, alkyl, alkoxy, haloalkyl, haloalkoxy, alkenyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl, wherein any alkyl, alkoxy, haloalkyl, haloalkoxy, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl is substituted with 0-4 J; or wherein two R groups together with a nitrogen atom or with two adjacent nitrogen atoms to which they are bonded can together form a three to eight membered heterocyclyl substituted with 0-4 J; optionally further comprising 1-3 additional ring heteroatoms selected from the group consisting of O, N, and $S(O)_q$;

wherein any cycloalkyl, aryl, heterocyclyl, or heteroaryl can be fused, bridged, or in a spiro configuration with one or more additional optionally substituted cycloalkyl,

aryl, heterocyclyl, and heteroaryl, monocyclic, bicyclic or polycyclic, saturated, partially unsaturated, or aromatic rings;

including all stereoisomers thereof and all isotopically labeled forms thereof;

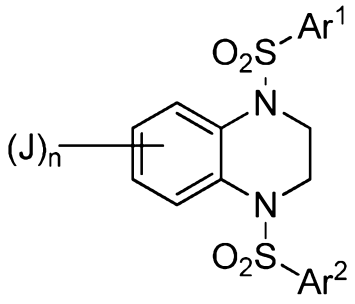
or any salt, hydrate, solvate, prodrug, or metabolite thereof.

For example, in various embodiments, a compound of formula (II) is provided wherein at least one of $Ar^1$ or $Ar^2$ is benzothienyl. Or, alternatively, $Ar^1$ can be phenyl substituted with halo, haloalkyl, or haloalkoxy.

For example, in various embodiments, a compound of formula (II) is provided wherein Y is N.

In various embodiments, the compound of formula (II) can be any of the examplary compounds shown in Table 2, below, or a salt thereof.

In various embodiments, the invention provides a galanin receptor-modulatory compound of formula (III)



(III)

wherein $Ar^1$ and $Ar^2$ are each independently selected aryl or heteroaryl, wherein any aryl or heteroaryl is mono- or independently multi-substituted with J;

n is 0, 1, 2, or 3;

J is independently at each occurrence R, F, Cl, Br, I, OR, CN, $CF_3$, $CF_2H$, $OCF_3$, $OCF_2H$, =O, =S, methylenedioxy, ethylenedioxy, $N(R)_2$, SR, SOR, $SO_2R$, $SO_2N(R)_2$, $SO_3R$, C(O)R, C(O)C(O)R, $C(O)CH_2C(O)R$, C(S)R, C(O)OR, OC(O)R, OC(O)OR, $C(O)N(R)_2$, $OC(O)N(R)_2$, $C(S)N(R)_2$, $(CH_2)_{0-2}NHC(O)R$, N(R)N(R)C(O)R, N(R)N(R)C(O)OR, $N(R)N(R)CON(R)_2$, $N(R)SO_2R$, $N(R)SO_2N(R)_2$, N(R)C(O)OR, N(R)C(O)R, N(R)C(S)R, $N(R)C(O)N(R)_2$, $N(R)C(S)N(R)_2$, N(COR)COR, N(OR)R, $C(=NH)N(R)_2$, C(O)N(OR)R, or C(=NOR)R;

R is independently at each occurrence hydrogen, alkyl, alkoxy, haloalkyl, haloalkoxy, alkenyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl, wherein any alkyl, alkoxy, haloalkyl, haloalkoxy, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl is substituted with 0-4 J; or wherein two R groups together with a nitrogen atom or with two adjacent nitrogen atoms to which they are bonded can together form a three to eight membered heterocyclyl substituted with 0-4 J; optionally further comprising 1-3 additional ring heteroatoms selected from the group consisting of O, N, and $S(O)_q$;

wherein any cycloalkyl, aryl, heterocyclyl, or heteroaryl can be fused, bridged, or in a spiro configuration with one or more additional optionally substituted cycloalkyl, aryl, heterocyclyl, and heteroaryl, monocyclic, bicyclic or polycyclic, saturated, partially unsaturated, or aromatic rings;

including all stereoisomers thereof and all isotopically labeled forms thereof;

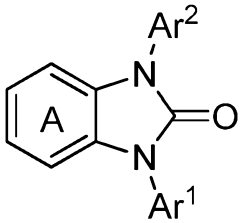
or any salt, hydrate, solvate, prodrug, or metabolite thereof.

For example, in various embodiments, a compound of formula (III) is provided wherein at least one of $Ar^1$ and $Ar^2$ is benzothienyl. Alternatively, at least one of $Ar^1$ and $Ar^2$ can be chlorophenyl, trifluoromethylphenyl, or cyanophenyl.

For example, in various embodiments, a compound of formula (III) is provided wherein n = 0.

In various embodiments, the compound of formula (III) can be any of the examplary compounds shown in Table 3, below, or a salt thereof.

In various embodiments, the invention provides a galanin receptor-modulatory compound of formula (IV)




(IV)

wherein $Ar^1$ and $Ar^2$ is each independently hydrogen, aryl, heteroaryl, fused cycloalkyl-aryl, fused heterocyclyl-aryl, fused cycloalkyl-heteroaryl, or fused heterocyclyl-heteroaryl, any of which is substituted with 0-4 J groups, wherein Ar1 and

Ar2 can each be bonded directly to the nitrogen atom, or can be bonded via group Q, wherein Q is $(CH_2)_n$, $S(O)_q(CH_2)_n$, C(=O) $(CH_2)_n$, $(CH_2)_nN(R)C(O)$, or $(CH_2)_nC(O)N(R)$, wherein n is 0-9 and q is 0, 1, or 2, provided that at least one of $Ar^1$ and $Ar^2$ is non-hydrogen;

the ring labeled "A" comprises 0, 1, or 2 ring N atoms, and is substituted with 0-3 $R^1$ groups, wherein $R^1$ is (C1-C10) straight chain alkyl, (C3-C10)branched chain alkyl, (C3-C12)cycloalkyl or bicycloalkyl, OH, $NR^3R^4$, CN, $CO_2R^5$, heterocyclylalkyl, heterobicycloalkyl, halo, nitro, alkoxy, cycloalkyloxy, perhaloalkyl, perhaloalkoxy, aryl, or heteroaryl wherein any alkyl cycloalkyl, bicycloalkyl, heterocyclylalkyl, heterobicyclylalkyl, alkoxy, aryl, or heteroaryl is optionally mono- or independently multi-substituted with J;

$R^3$ and $R^4$ are each independently H, alkyl, cycloalkyl or bicycloalkyl, aryl, heterocyclyl, or heteroaryl, wherein any alkyl, cycloalkyl or bicycloalkyl, aryl, heterocyclyl, or heteroaryl is substituted with 0-3 J and any alkyl, cycloalkyl or bicycloalkyl, aryl, heterocyclyl, or heteroaryl can be bonded directly to a nitrogen atom which bears $R^3$ or $R^4$ or can be bonded to the nitrogen atom via M, wherein M is $(CH_2)_n$, $S(O)_q(CH_2)_n$, $(CH_2)_nN(R)C(O)$, or $(CH_2)_nC(O)N(R)$, wherein n is 0-9 and q is 0, 1, or 2; or $R^3$ and $R^4$ together with a nitrogen atom to which they are bonded form a heterocyclyl optionally further comprising 1 or 2 additional heteroatoms selected from O, $S(O)_q$, or $NR^3$, wherein the heterocyclyl is substituted with 0-3 J;

$R^5$ is H, alkyl, cycloalkyl, aryl, heterocyclyl, or heteroaryl, any of which non-hydrogen groups is optionally mono- or independently multi-substituted with J;

J is independently at each occurrence R, F, Cl, Br, I, OR, CN, $CF_3$, $CF_2H$, $OCF_3$, $OCF_2H$, =O, =S, methylenedioxy, ethylenedioxy, $N(R)_2$, SR, SOR, $SO_2R$, $SO_2N(R)_2$, $SO_3R$, C(O)R, C(O)C(O)R, $C(O)CH_2C(O)R$, C(S)R, C(O)OR, OC(O)R, OC(O)OR, $C(O)N(R)_2$, $OC(O)N(R)_2$, $C(S)N(R)_2$, $(CH_2)_{0-2}NHC(O)R$, N(R)N(R)C(O)R, N(R)N(R)C(O)OR, $N(R)N(R)CON(R)_2$, $N(R)SO_2R$, $N(R)SO_2N(R)_2$, N(R)C(O)OR, N(R)C(O)R, N(R)C(S)R, $N(R)C(O)N(R)_2$, $N(R)C(S)N(R)_2$, N(COR)COR, N(OR)R, $C(=NH)N(R)_2$, C(O)N(OR)R, or C(=NOR)R;

R is independently at each occurrence hydrogen, alkyl, alkoxy, haloalkyl, haloalkoxy, alkenyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl,

heterocyclylalkyl, heteroaryl, or heteroarylalkyl, wherein any alkyl, alkoxy, haloalkyl, haloalkoxy, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl is substituted with 0-4 J; or wherein two R groups together with a nitrogen atom or with two adjacent nitrogen atoms to which they are bonded can together form a three to eight membered heterocyclyl substituted with 0-4 J; optionally further comprising 1-3 additional ring heteroatoms selected from the group consisting of O, N, and $S(O)_q$;

wherein any cycloalkyl, aryl, heterocyclyl, or heteroaryl can be fused, bridged, or in a spiro configuration with one or more additional optionally substituted cycloalkyl, aryl, heterocyclyl, and heteroaryl, monocyclic, bicyclic or polycyclic, saturated, partially unsaturated, or aromatic rings;

including all stereoisomers thereof and all isotopically labeled forms thereof;

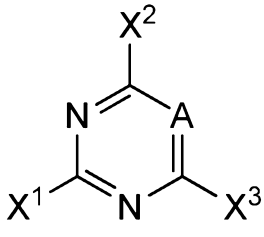
or any salt, hydrate, solvate, prodrug, or metabolite thereof.

For example, in various embodiments, the invention provides a compound of formula (IV) wherein at least one Q is sulfonyl, carbonyl, or methylene.

In various embodiments, the invention provides a compound of formula (IV) wherein $Ar^1$ or $Ar^2$, or both, is a J-substituted phenyl group. Alternatively, $Ar^1$ or $Ar^2$, or both, can be a J-substituted pyridyl group.

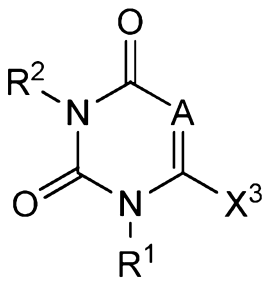
In various embodiments, the compound of formula (IV) can be any of the examplary compounds shown in Table 4, below, or a salt thereof.

In various embodiments, the invention provides a galanin receptor-modulating compound of formula (VA)



(VA)

or (IVB)



(VB)

wherein

A is N or CR', wherein R' is H, optionally substituted (C1-C6)alkyl, or $NR^3R^4$;

$X^1$, $X^2$ and $X^3$ are each independently H, halo, cyano, $NR^3R^4$, $N(R^3)S(O)_qAr^1$, $N(R^3)C(=O)Ar^1$, or $OR^5$, wherein q is 0, 1, or 2;

$R^1$ and $R^2$ are each independently optionally substituted aralkyl;

$R^3$ and $R^4$ are each independently H, alkyl, cycloalkyl or bicycloalkyl, aryl, heterocyclyl, or heteroaryl, wherein any alkyl, cycloalkyl or bicycloalkyl, aryl, heterocyclyl, or heteroaryl is substituted with 0-3 J and any alkyl, cycloalkyl or bicycloalkyl, aryl, heterocyclyl, or heteroaryl can be bonded directly to a nitrogen atom which bears $R^3$ or $R^4$ or can be bonded to the nitrogen atom via M, wherein M is $(CH_2)_n$, $S(O)_q(CH_2)_n$, $(CH_2)_nN(R)C(O)$, or $(CH_2)_nC(O)N(R)$, wherein n is 0-9 and q is 0, 1, or 2; or $R^3$ and $R^4$ together with a nitrogen atom to which they are bonded form a heterocyclyl optionally further comprising 1 or 2 additional heteroatoms selected from O, $S(O)_q$, or $NR^3$, wherein the heterocyclyl is substituted with 0-3 J;

$R^5$ is H, alkyl, cycloalkyl, aryl, heterocyclyl, or heteroaryl, any of which non-hydrogen groups is optionally mono- or independently multi-substituted with J;

$Ar^1$ is aryl or heteroaryl, optionally mono- or independently multi-substituted with J;

J is independently at each occurrence R, F, Cl, Br, I, OR, CN, $CF_3$, $CF_2H$, $OCF_3$, $OCF_2H$, =O, =S, methylenedioxy, ethylenedioxy, $N(R)_2$, SR, SOR, $SO_2R$, $SO_2N(R)_2$, $SO_3R$, C(O)R, C(O)C(O)R, $C(O)CH_2C(O)R$, C(S)R, C(O)OR, OC(O)R, OC(O)OR, $C(O)N(R)_2$, $OC(O)N(R)_2$, $C(S)N(R)_2$, $(CH_2)_{0-2}NHC(O)R$, N(R)N(R)C(O)R, N(R)N(R)C(O)OR, $N(R)N(R)CON(R)_2$, $N(R)SO_2R$, $N(R)SO_2N(R)_2$, N(R)C(O)OR, N(R)C(O)R, N(R)C(S)R, $N(R)C(O)N(R)_2$, $N(R)C(S)N(R)_2$, N(COR)COR, N(OR)R, $C(=NH)N(R)_2$, C(O)N(OR)R, or C(=NOR)R;

R is independently at each occurrence hydrogen, alkyl, alkoxy, haloalkyl, haloalkoxy, alkenyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl, wherein any alkyl, alkoxy, haloalkyl, haloalkoxy, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl is substituted with 0-4 J; or wherein two R groups together with a nitrogen atom or with two adjacent nitrogen atoms to which they are bonded can together form a three to eight membered heterocyclyl substituted with 0-4 J; optionally further comprising 1-3 additional ring heteroatoms selected from the group consisting of O, N, and $S(O)_q$;

wherein any cycloalkyl, aryl, heterocyclyl, or heteroaryl can be fused, bridged, or in a spiro configuration with one or more additional optionally substituted cycloalkyl, aryl, heterocyclyl, and heteroaryl, monocyclic, bicyclic or polycyclic, saturated, partially unsaturated, or aromatic rings;

including all stereoisomers thereof and all isotopically labeled forms thereof;

or any salt, hydrate, solvate, prodrug, or metabolite thereof.

For example, in various embodiments, a compound of formula (VA) is provided wherein $X^1$, $X^2$, and $X^3$ are each independently $NR^3R^4$. Or, in various embodiments, $X^1$ and $X^2$ can each independently be $NR^3R^4$ and $X^3$ can be halo, or $X^1$ can be halo and $X^2$ and $X^3$ can each independently be $NR^3R^4$. Alternatively, $X^1$ can alkoxy, and $X^2$ and $X^3$ can each independently be $NR^3R^4$ or halo in a compound of formula (VA).

For example, in various embodiments, a compound of formula (VA) is provided wherein $X^1$ is H, $NR^3R^4$, $OR^5$, halo, optionally substituted arylsulfonamido, or optionally substituted arylcarboxamido. In various embodiments, $X^2$ can be heterocyclyl, optionally substituted arylamino, or dialkylamino. Also, $X^3$ can be hydrogen, halo, cyano, $NR^3R4$ wherein $R^3$ is H or alkyl and $R^4$ is aryl or heteroaryl wherein the aryl or heteroaryl is independently substituted with 0-3 J, or $NR^3R^4$ wherein $NR^3R^4$ forms an optionally substituted heterocyclyl.

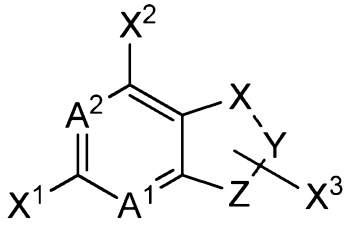
For example, in various embodiments, a compound of formula (VA) is provided wherein two of $X^1$, $X^2$ and $X^3$ are arylamino and a third is heterocyclyl. Or, for a compound of formula (VA), one of $X^1$, $X^2$ and $X^3$ can be arylcarboxamido, and another one can be heterocyclyl or aryl amino.

In various embodiments for a compound of formula (VA), at least one of $X^1$, $X^2$, or $X^3$ can be p-methyloxyphenylamino, m-methoxyphenylamino, pyrrolidinyl, cyclohexylamino, methoxy, piperidinyl, chloro, m-fluoro-p-methoxyphenylamino, 4-($CF_3$-pyridyl)-1,4-diazepan-1-yl preferably 4-(3-$CF_3$-pyrid-2-yl)-1,4-diazepan-1-yl, p-chlorophenylamino, p-ethoxyphenylamino, p-isopropoxyphenylamino, p-methoxyphenylsulfonamido, 3,4,-dichlorobenzamido, benzamido, 4-(p-methoxyphenylsulfonamido)-1,4-diazepan-1-yl, or 4-($CF_3$-pyridyl)-piperazin-1-yl preferably 4-(3-CF3-pyrid-2-yl)-piperazin-1-yl.

For example, in various embodiments, a compound of formula (VB) is provided wherein $R^1$ is benzyl optionally substituted with J, preferably $R^1$ is p-methoxybenzyl. Furthermore, $R^2$ can be benzyl optionally substituted with J, preferably $R^2$ is p-ethylbenzyl. In various embodiments, $X^3$ can H or $NH_2$.

In various embodiments, the compound of formula (VA) or (VB) can be any of the examplary compounds shown in Table 5, below, or a salt thereof.

In various embodiments, the invention provides a galanin receptor-modulatory compound of formula (VI)




(VI)

wherein:

$A^1$ and $A^2$ are each independently N or CR', wherein R' is H, optionally substituted (C1-C6)alkyl, or $NR^3R^4$;

X, Y, and Z are each independently N or NR' or CR' or $C(R')_2$ provided that the bond between X and Y, and the bond between Y and Z, can each be a double bond or a single bond provided there is one double bond and one single bond between X and Y and Y and Z;

$X^1$ and $X^2$ is each independently H, halo, cyano, $NR^3R^4$, $Ar^1$, $Ar^1S(O)_q$, or $OR^5$, $N(R^3)S(O)_qAr^1$, or $N(R^3)C(=O)Ar^1$;

$Ar^1$ is optionally substituted aryl or heteroaryl;

$R^3$ and $R^4$ are each independently H, alkyl, cycloalkyl or bicycloalkyl, aryl, heterocyclyl, or heteroaryl, wherein any alkyl, cycloalkyl or bicycloalkyl, aryl, heterocyclyl, or heteroaryl is substituted with 0-3 J and any alkyl, cycloalkyl or bicycloalkyl, aryl, heterocyclyl, or heteroaryl can be bonded directly to a nitrogen atom which bears $R^3$ or $R^4$ or can be bonded to the nitrogen atom via M, wherein M is $(CH_2)_n$, $S(O)_q(CH_2)_n$, $(CH_2)_nN(R)C(O)$, or $(CH_2)_nC(O)N(R)$, wherein n is 0-9 and q is 0, 1, or 2; or $R^3$ and $R^4$ together with a nitrogen atom to which they are bonded form a heterocyclyl optionally further comprising 1 or 2 additional heteroatoms selected from O, $S(O)_q$, or $NR^3$, wherein the heterocyclyl is substituted with 0-3 J;

$R^5$ is H, alkyl, cycloalkyl, aryl, heterocyclyl, or heteroaryl, any of which non-hydrogen groups is optionally mono- or independently multi-substituted with J;

J is independently at each occurrence R, F, Cl, Br, I, OR, CN, $CF_3$, $CF_2H$, $OCF_3$, $OCF_2H$, =O, =S, methylenedioxy, ethylenedioxy, $N(R)_2$, SR, SOR, $SO_2R$, $SO_2N(R)_2$, $SO_3R$, C(O)R, C(O)C(O)R, $C(O)CH_2C(O)R$, C(S)R, C(O)OR, OC(O)R, OC(O)OR, $C(O)N(R)_2$, $OC(O)N(R)_2$, $C(S)N(R)_2$, $(CH_2)_{0-2}NHC(O)R$, N(R)N(R)C(O)R, N(R)N(R)C(O)OR, $N(R)N(R)CON(R)_2$, $N(R)SO_2R$, $N(R)SO_2N(R)_2$, N(R)C(O)OR, N(R)C(O)R, N(R)C(S)R, $N(R)C(O)N(R)_2$, $N(R)C(S)N(R)_2$, N(COR)COR, N(OR)R, $C(=NH)N(R)_2$, C(O)N(OR)R, or C(=NOR)R;

R is independently at each occurrence hydrogen, alkyl, alkoxy, haloalkyl, haloalkoxy, alkenyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl, wherein any alkyl, alkoxy, haloalkyl, haloalkoxy, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl is substituted with 0-4 J; or wherein two R groups together with a nitrogen atom or with two adjacent nitrogen atoms to which they are bonded can together form a three to eight membered heterocyclyl substituted with 0-4 J; optionally further comprising 1-3 additional ring heteroatoms selected from the group consisting of O, N, and $S(O)_q$;

wherein any cycloalkyl, aryl, heterocyclyl, or heteroaryl can be fused, bridged, or in a spiro configuration with one or more additional optionally substituted cycloalkyl, aryl, heterocyclyl, and heteroaryl, monocyclic, bicyclic or polycyclic, saturated, partially unsaturated, or aromatic rings;

including all stereoisomers thereof and all isotopically labeled forms thereof; or any salt, hydrate, solvate, prodrug, or metabolite thereof.

For example, in various embodiments, a compound of formula (VI) is provided wherein $X^1$ is halo, optionally substituted aryl, or optionally substituted arylamino; preferably chloro, p-methoxyphenyl, or p-methoxyphenylamino. For example, in various embodiments, a compound of formula (VI) is provided wherein $X^2$ is heterocyclyl; preferably morpholinyl, or piperidinyl.

In various embodiments, for the compound of formula (VI) X can be CH, or Y and Z can each be N, or both. In various embodiments, Z can be NR' and R' can optionally be substituted phenyl.

In various embodiments, the compound of formula (VI) can be any of the examplary compounds shown in Table 6, below, or a salt thereof.

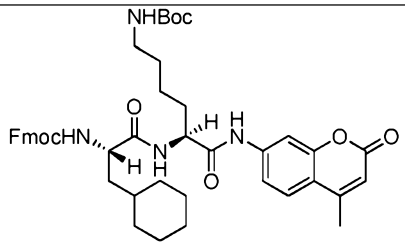
In various embodiments, the invention provides any of the compounds shown below in the list of Exemplary Compounds of the Invention of Tables 1-6.

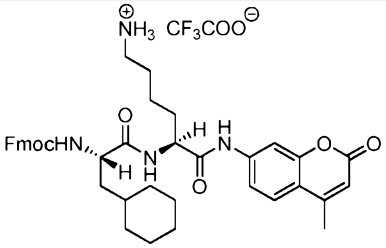
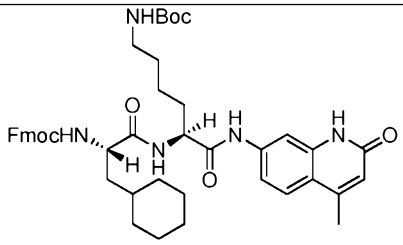
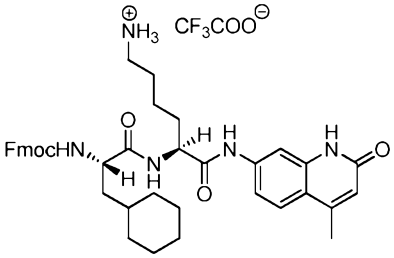
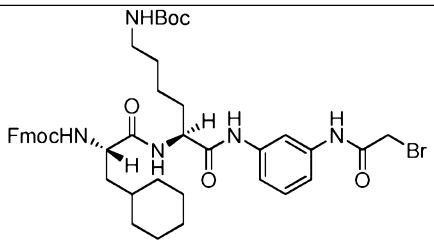
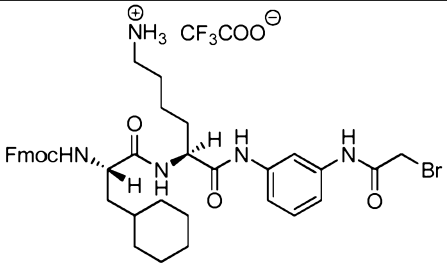
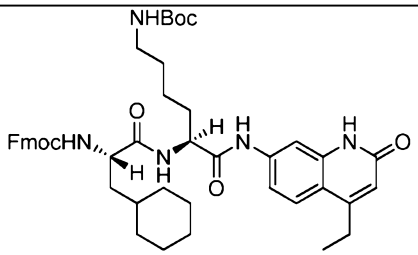
**Table 1: Exemplary Compounds of the Invention and Related Biodata—Formula (I)**

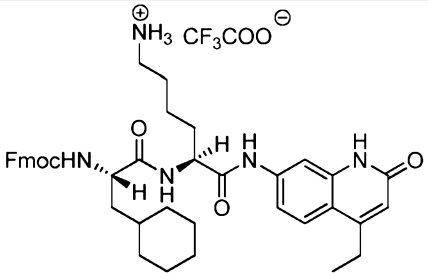
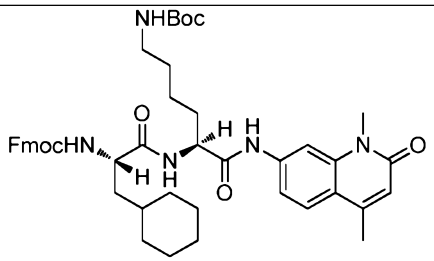
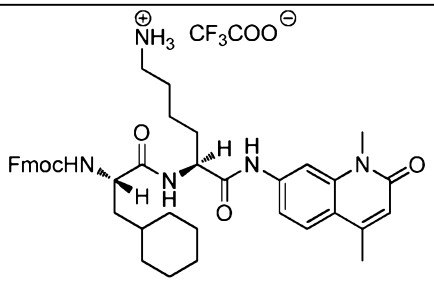
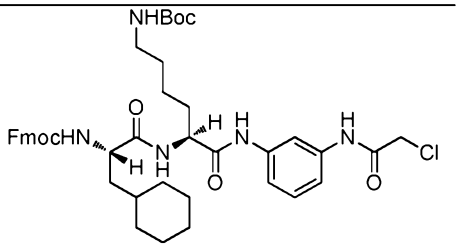
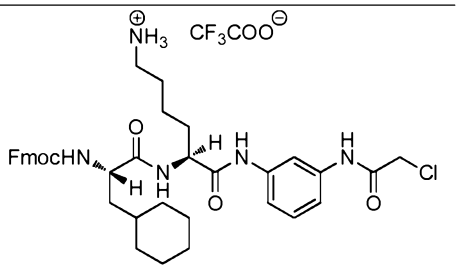
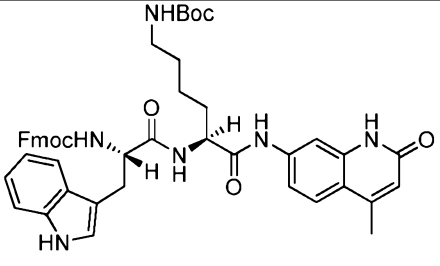
note: Fmoc refers to 9-fluorenylmethoxycarbonyl, tBoc to t-butoxycarbonyl

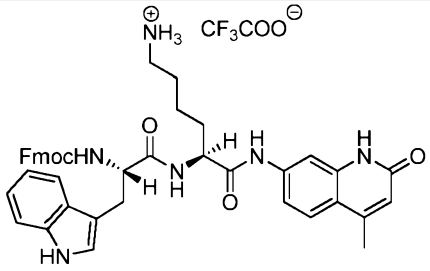
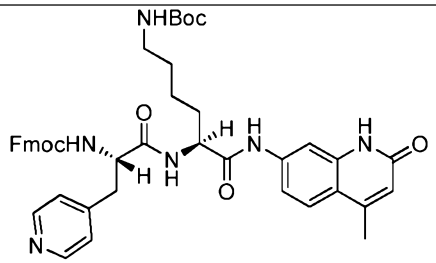
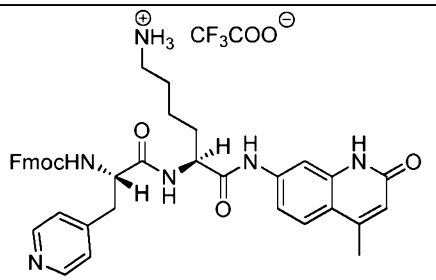
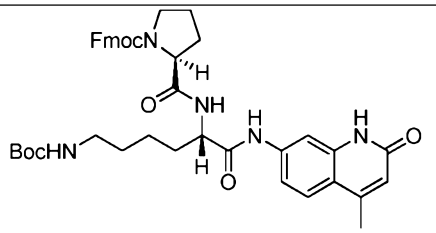
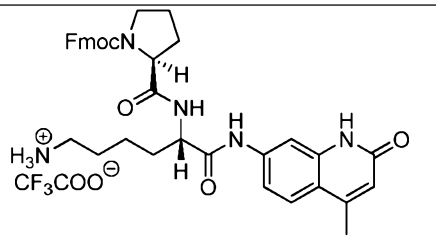
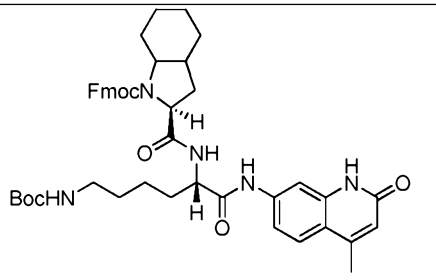
Chemical names were assigned by ChemDraw (CambridgeSoft, Inc.) except where indicated (*).

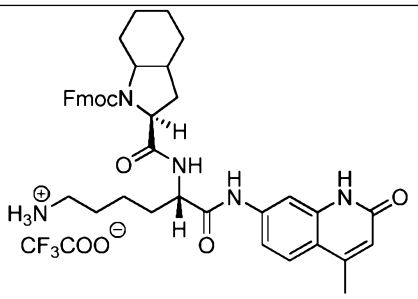
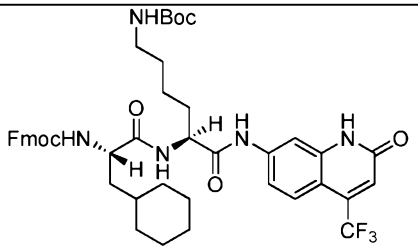
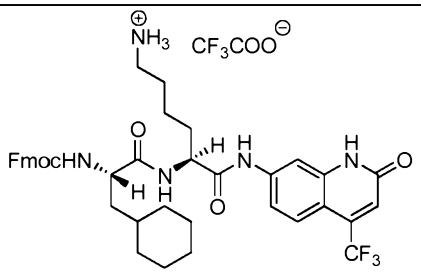
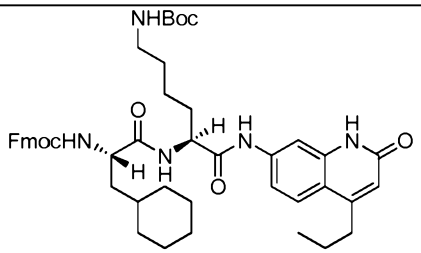
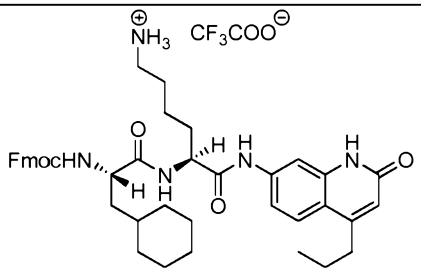
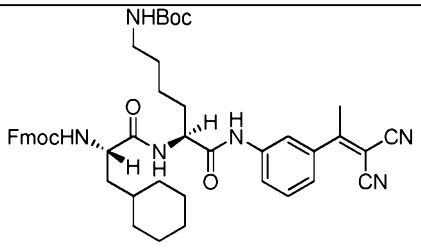
When a compound is shown as a salt (e.g., a trifluoroacetate salt), all salt and non-salt (neutral, free base, zwitterionic, etc.) forms of the organic structure are intended.

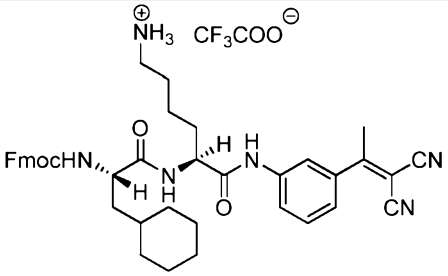
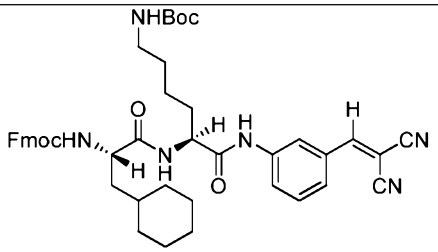
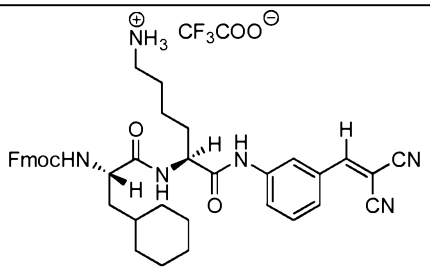
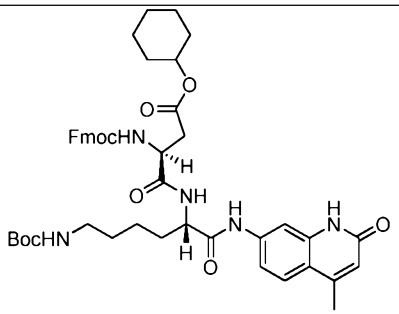
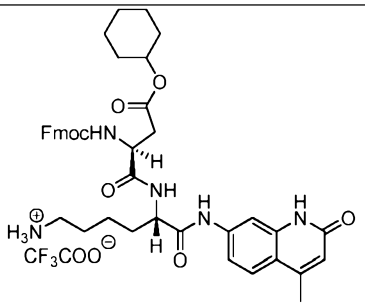
| Serial Number / TSRI number | Chemical Name | Chemical Structure |
|---|---|---|
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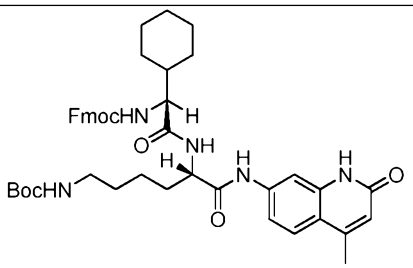
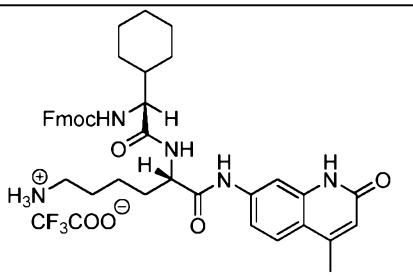
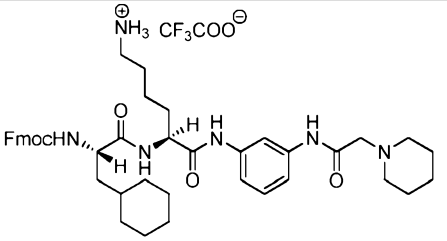
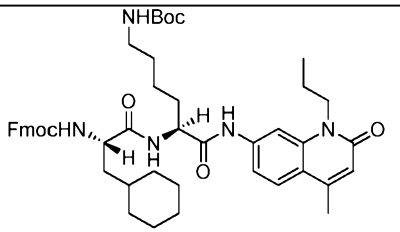
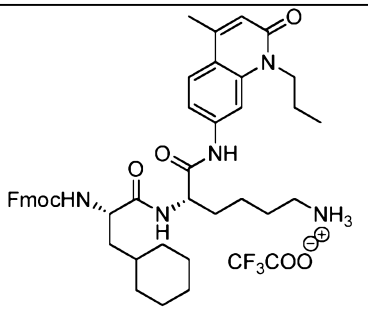
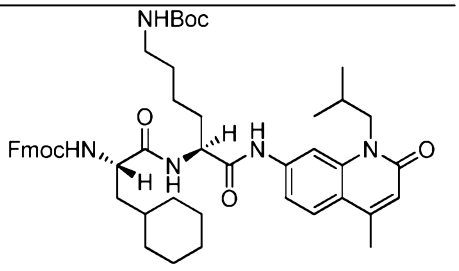
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|---|---|---|
| 2<br>2502 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-amino-1-((4-methyl- 2-oxo-2H-chromen-7-yl)amino)-1-oxohexan-2-yl)amino)-3-cyclohexyl-1-oxopropan-2-yl)carbamate |  |
| 3<br>2503 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-(tert-butoxycarbonyl)amino-1-((4-methyl-2-oxo-1,2-dihydroquinolin-7-yl)amino)-1-oxohexan-2-yl)amino)-3-cyclohexyl-1-oxopropan-2-yl)carbamate |  |
| 4<br>2504 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-amino-1-((4-methyl-2-oxo-1,2-dihydroquinolin-7-yl)amino)-1-oxohexan-2-yl)amino)-3-cyclohexyl-1-oxopropan-2-yl)carbamate |  |
| 5<br>2505 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-(tert-butoxycarbonyl)amino-1-((3-(2-bromoacetamido)phenyl)amino)-1-oxohexan-2-yl)amino)-3-cyclohexyl-1-oxopropan-2-yl)carbamate |  |
| 6<br>2506 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-amino-1-((3-(2-bromoacetamido)phenyl)amino)-1-oxohexan-2-yl)amino)-3-cyclohexyl-1-oxopropan-2-yl)carbamate |  |
| 7<br>2507 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-(tert-butoxycarbonyl)amino-1-((4-ethyl-2-oxo-1,2-dihydroquinolin-7-yl)amino)-1-oxohexan-2-yl)amino)-3-cyclohexyl-1-oxopropan-2-yl)carbamate |  |

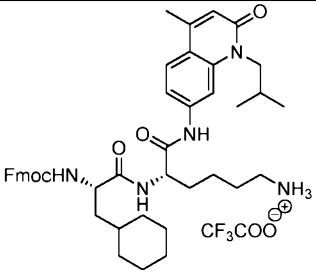
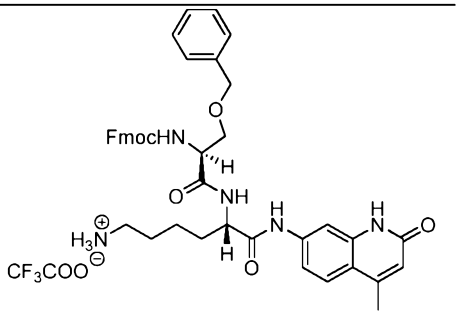
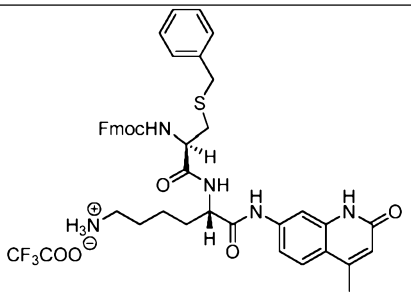
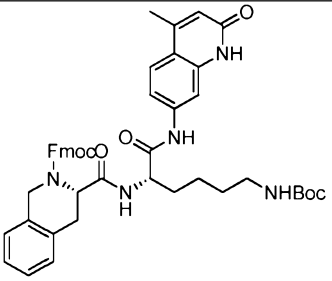
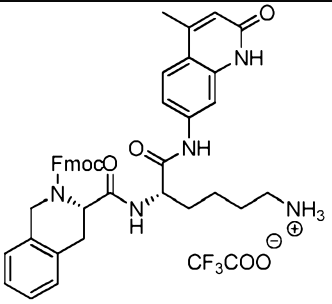
| | | |
|---|---|---|
| 8<br>2508 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-amino-1-((4-ethyl-2-oxo-1,2-dihydroquinolin-7-yl)amino)-1-oxohexan-2-yl)amino)-3-cyclohexyl-1-oxopropan-2-yl)carbamate |  |
| 9<br>2509 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-(tert-butoxycarbonyl)amino-1-((1,4-dimethyl-2-oxo-1,2-dihydroquinolin-7-yl)amino)-1-oxohexan-2-yl)amino)-3-cyclohexyl-1-oxopropan-2-yl)carbamate |  |
| 10<br>2510 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-amino-1-((1,4-dimethyl-2-oxo-1,2-dihydroquinolin-7-yl)amino)-1-oxohexan-2-yl)amino)-3-cyclohexyl-1-oxopropan-2-yl)carbamate |  |
| 11<br>2511 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-(tert-butoxycarbonyl)amino-1-((3-(2-chloroacetamido)phenyl)amino)-1-oxohexan-2-yl)amino)-3-cyclohexyl-1-oxopropan-2-yl)carbamate |  |
| 12<br>2512 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-amino-1-((3-(2-chloroacetamido)phenyl)amino)-1-oxohexan-2-yl)amino)-3-cyclohexyl-1-oxopropan-2-yl)carbamate |  |
| 13<br>2533 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-(tert-butoxycarbonyl)amino-1-((4-methyl-2-oxo-1,2-dihydroquinolin-7-yl)amino)-1-oxohexan-2-yl)amino)-3-(1H-indol-3-yl)-1-oxopropan-2-yl)carbamate |  |

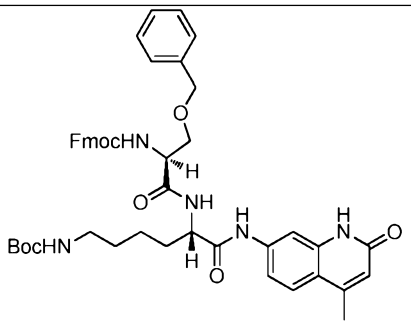
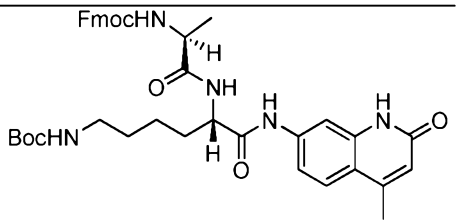
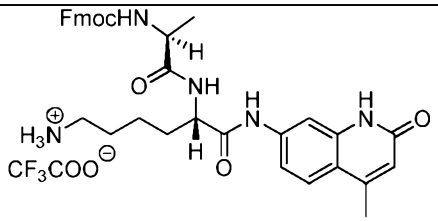
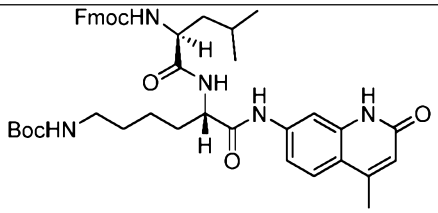
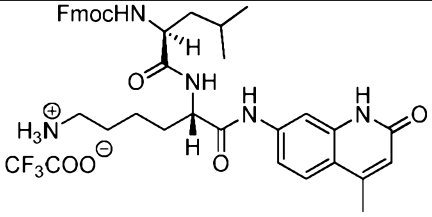
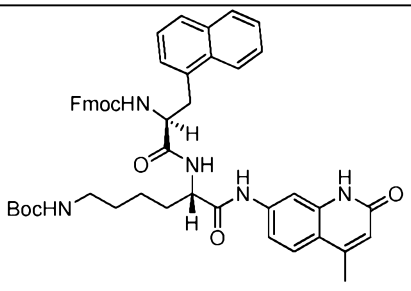
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|---|---|---|
| 14<br>2514 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-amino-1-((4-methyl-2-oxo-1,2-dihydroquinolin-7-yl)amino)-1-oxohexan-2-yl)amino)-3-(1H-indol-3-yl)-1-oxopropan-2-yl)carbamate |  |
| 15<br>2515 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-(tert-butoxycarbonyl)amino-1-((4-methyl-2-oxo-1,2-dihydroquinolin-7-yl)amino)-1-oxohexan-2-yl)amino)-1-oxo-3-(pyridin-4-yl)propan-2-yl)carbamate |  |
| 16<br>2516 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-amino-1-((4-methyl-2-oxo-1,2-dihydroquinolin-7-yl)amino)-1-oxohexan-2-yl)amino)-1-oxo-3-(pyridin-4-yl)propan-2-yl)carbamate |  |
| 17<br>2517 | (S)-(9H-fluoren-9-yl)methyl2-(((S)-6-(tert-butoxycarbonyl)amino-1-((4-methyl-2-oxo-1,2-dihydroquinolin-7-yl)amino)-1-oxohexan-2-yl)carbamoyl)pyrrolidine-1-carboxylate |  |
| 18<br>2518 | (S)-(9H-fluoren-9-yl)methyl2-(((S)-6-amino-1-((4-methyl-2-oxo-1,2-dihydroquinolin-7-yl)amino)-1-oxohexan-2-yl)carbamoyl)pyrrolidine-1-carboxylate |  |
| 19<br>2519 | (2S)-(9H-fluoren-9-yl)methyl2-(((S)-6-(tert-butoxycarbonyl)amino-1-((4-methyl-2-oxo-1,2-dihydroquinolin-7-yl)amino)-1-oxohexan-2-yl)carbamoyl)octahydro-1H-indole-1-carboxylate |  |

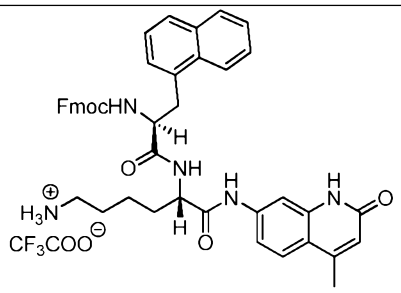
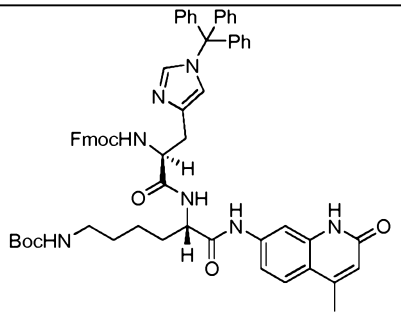
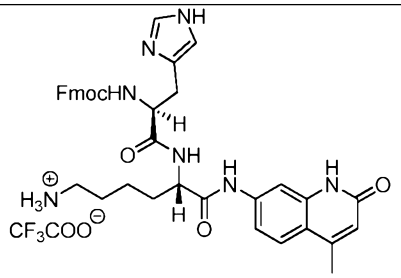
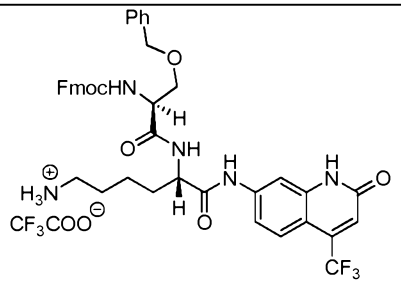
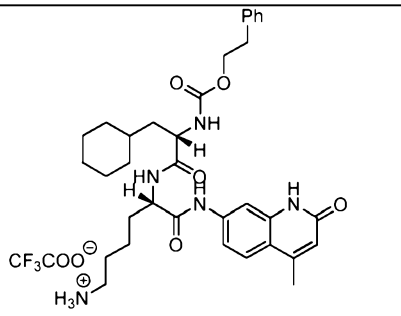
| | | |
|---|---|---|
| 20<br>2520 | (2S)-(9H-fluoren-9-yl)methyl2-(((S)-6-amino-1-((4-methyl-2-oxo-1,2-dihydroquinolin-7-yl)amino)-1-oxohexan-2-yl)carbamoyl)octahydro-1H-indole-1-carboxylate |  |
| 21<br>2521 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-(tert-butoxycarbonyl)amino-1-oxo-1-((2-oxo-4-(trifluoromethyl)-1,2-dihydroquinolin-7-yl)amino)hexan-2-yl)amino)-3-cyclohexyl-1-oxopropan-2-yl)carbamate |  |
| 22<br>2522 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-amino-1-oxo-1-((2-oxo-4-(trifluoromethyl)-1,2-dihydroquinolin-7-yl)amino)hexan-2-yl)amino)-3-cyclohexyl-1-oxopropan-2-yl)carbamate |  |
| 23<br>2523 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-(tert-butoxycarbonyl)amino-1-oxo-1-((2-oxo-4-propyl-1,2-dihydroquinolin-7-yl)amino)hexan-2-yl)amino)-3-cyclohexyl-1-oxopropan-2-yl)carbamate |  |
| 24<br>2524 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-amino-1-oxo-1-((2-oxo-4-propyl-1,2-dihydroquinolin-7-yl)amino)hexan-2-yl)amino)-3-cyclohexyl-1-oxopropan-2-yl)carbamate |  |
| 25<br>2525 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-(tert-butoxycarbonyl)amino-1-((3-(1,1-dicyanoprop-1-en-2-yl)phenyl)amino)-1-oxohexan-2-yl)amino)-3-cyclohexyl-1-oxopropan-2-yl)carbamate |  |

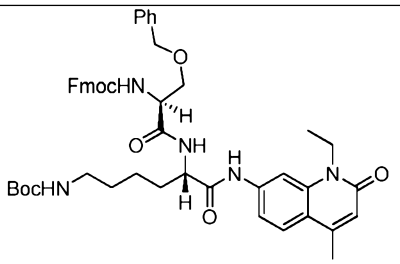
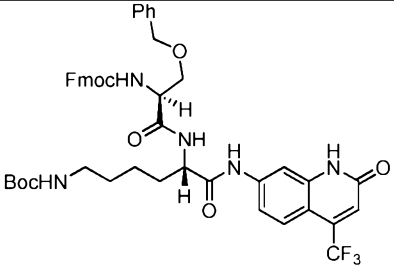
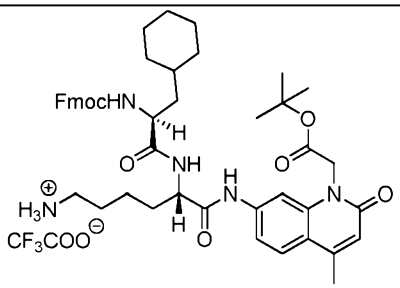
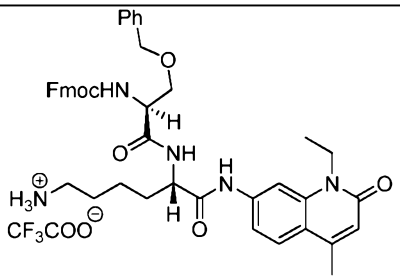
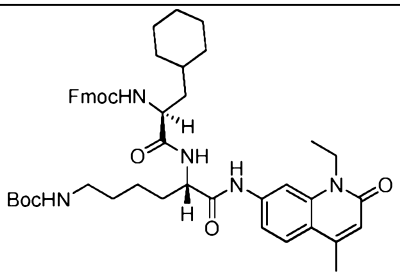
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| 26<br>2526 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-amino-1-((3-(1,1-dicyanoprop-1-en-2-yl)phenyl)amino)-1-oxohexan-2-yl)amino)-3-cyclohexyl-1-oxopropan-2-yl)carbamate |  |
| 27<br>2527 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-(tert-butoxycarbonyl)amino-1-((3-(2,2-dicyanovinyl)phenyl)amino)-1-oxohexan-2-yl)amino)-3-cyclohexyl-1-oxopropan-2-yl)carbamate |  |
| 28<br>2528 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-amino-1-((3-(2,2-dicyanovinyl)phenyl)amino)-1-oxohexan-2-yl)amino)-3-cyclohexyl-1-oxopropan-2-yl)carbamate |  |
| 29<br>2529 | (S)-cyclohexyl-3-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-4-(((S)-6-(tert-butoxycarbonyl)amino-1-((4-methyl-2-oxo-1,2-dihydroquinolin-7-yl)amino)-1-oxohexan-2-yl)amino)-4-oxobutanoate |  |
| 30<br>2530 | (S)-cyclohexyl-3-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-4-(((S)-6-amino-1-((4-methyl-2-oxo-1,2-dihydroquinolin-7-yl)amino)-1-oxohexan-2-yl)amino)-4-oxobutanoate |  |

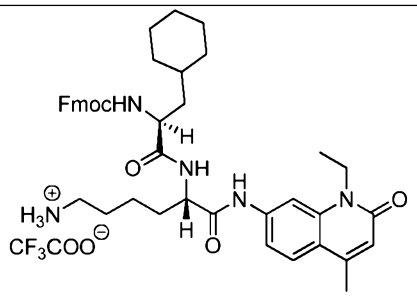
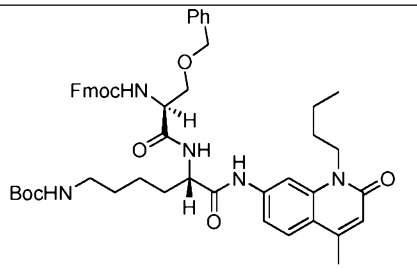
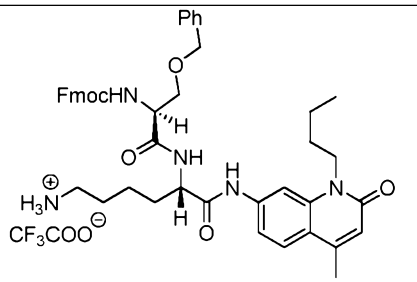
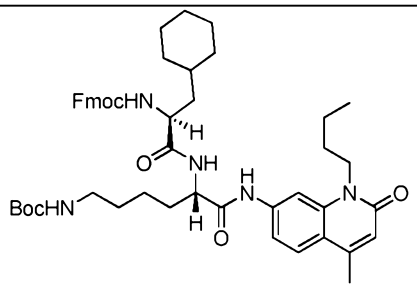
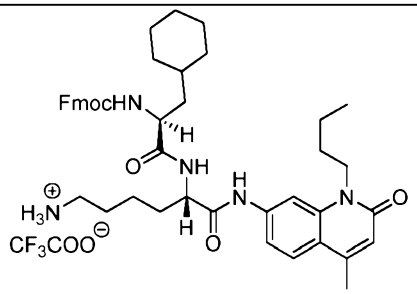
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| 31<br>2531 | (9H-fluoren-9-yl)methyl((S)-2-(((S)-6-(tert-butoxycarbonyl)amino-1-((4-methyl-2-oxo-1,2-dihydroquinolin-7-yl)amino)-1-oxohexan-2-yl)amino)-1-cyclohexyl-2-oxoethyl)carbamate |  |
| 32<br>2532 | (9H-fluoren-9-yl)methyl((S)-2-(((S)-6-amino-1-((4-methyl-2-oxo-1,2-dihydroquinolin-7-yl)amino)-1-oxohexan-2-yl)amino)-1-cyclohexyl-2-oxoethyl)carbamate |  |
| 33<br>2513 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-amino-1-oxo-1-((3-(2-(piperidin-1-yl)acetamido)phenyl)amino)hexan-2-yl)amino)-3-cyclohexyl-1-oxopropan-2-yl)carbamate |  |
| 34<br>2534 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-(tert-butoxycarbonyl)amino-1-((4-methyl-2-oxo-1-propyl-1,2-dihydroquinolin-7-yl)amino)-1-oxohexan-2-yl)amino)-3-cyclohexyl-1-oxopropan-2-yl)carbamate |  |
| 35<br>2535 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-amino-1-((4-methyl-2-oxo-1-propyl-1,2-dihydroquinolin-7-yl)amino)-1-oxohexan-2-yl)amino)-3-cyclohexyl-1-oxopropan-2-yl)carbamate |  |
| 36<br>2536 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-(tert-butoxycarbonyl)amino-1-((1-isobutyl-4-methyl-2-oxo-1,2-dihydroquinolin-7-yl)amino)-1-oxohexan-2-yl)amino)-3-cyclohexyl-1-oxopropan-2-yl)carbamate |  |

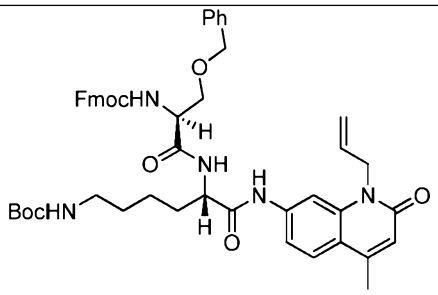
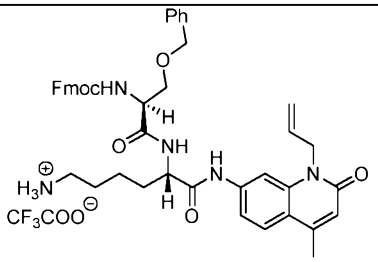
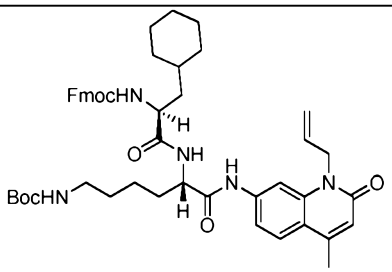
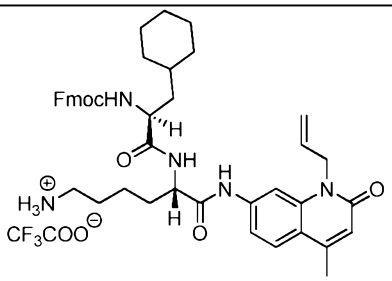
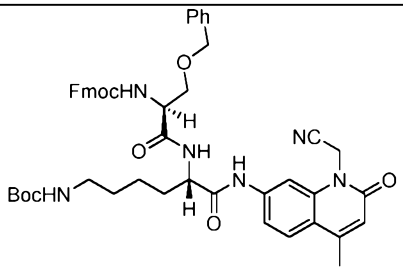
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| 37<br>2537 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-amino-1-((1-isobutyl-4-methyl-2-oxo-1,2-dihydroquinolin-7-yl)amino)-1-oxohexan-2-yl)amino)-3-cyclohexyl-1-oxopropan-2-yl)carbamate |  |
| 38<br>2538 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-amino-1-((4-methyl-2-oxo-1,2-dihydroquinolin-7-yl)amino)-1-oxohexan-2-yl)amino)-3-(benzyloxy)-1-oxopropan-2-yl)carbamate |  |
| 39<br>2539 | (9H-fluoren-9-yl)methyl((R)-1-(((S)-6-amino-1-((4-methyl-2-oxo-1,2-dihydroquinolin-7-yl)amino)-1-oxohexan-2-yl)amino)-3-(benzylthio)-1-oxopropan-2-yl)carbamate |  |
| 40<br>2540 | (S)-(9H-fluoren-9-yl)methyl3-(((S)-6-(tert-butoxycarbonyl)amino-1-((4-methyl-2-oxo-1,2-dihydroquinolin-7-yl)amino)-1-oxohexan-2-yl)carbamoyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate |  |
| 41<br>2541 | (S)-(9H-fluoren-9-yl)methyl3-(((S)-6-amino-1-((4-methyl-2-oxo-1,2-dihydroquinolin-7-yl)amino)-1-oxohexan-2-yl)carbamoyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate |  |

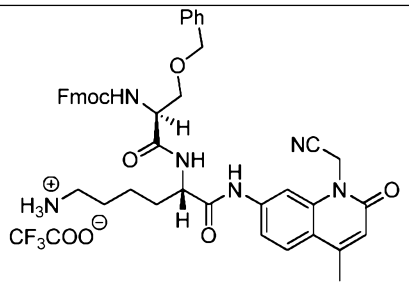
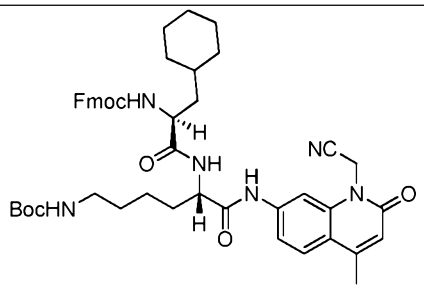
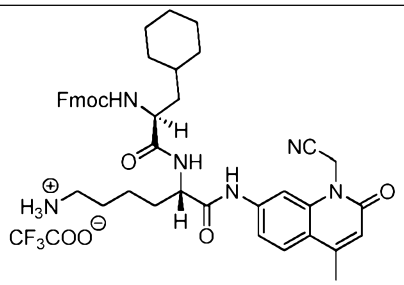
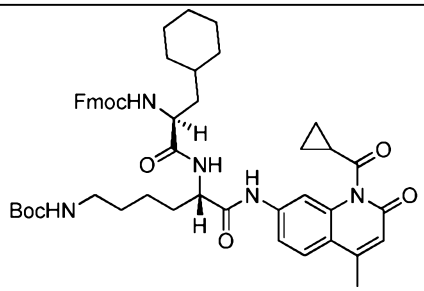
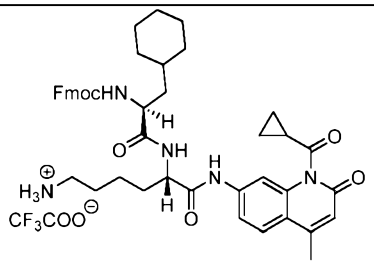
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| 42<br>2542 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-(tert-butoxycarbonyl)amino-1-((4-methyl-2-oxo-1,2-dihydroquinolin-7-yl)amino)-1-oxohexan-2-yl)amino)-3-(benzyloxy)-1-oxopropan-2-yl)carbamate |  |
| 43<br>2543 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-(tert-butoxycarbonyl)amino-1-((4-methyl-2-oxo-1,2-dihydroquinolin-7-yl)amino)-1-oxohexan-2-yl)amino)-1-oxopropan-2-yl)carbamate |  |
| 44<br>2544 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-amino-1-((4-methyl-2-oxo-1,2-dihydroquinolin-7-yl)amino)-1-oxohexan-2-yl)amino)-1-oxopropan-2-yl)carbamate |  |
| 45<br>2545 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-(tert-butoxycarbonyl)amino-1-((4-methyl-2-oxo-1,2-dihydroquinolin-7-yl)amino)-1-oxohexan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)carbamate |  |
| 46<br>2546 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-amino-1-((4-methyl-2-oxo-1,2-dihydroquinolin-7-yl)amino)-1-oxohexan-2-yl)amino)-4-methyl-1-oxopentan-2-yl)carbamate |  |
| 47<br>2547 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-(tert-butoxycarbonyl)amino-1-((4-methyl-2-oxo-1,2-dihydroquinolin-7-yl)amino)-1-oxohexan-2-yl)amino)-3-(naphthalen-1-yl)-1-oxopropan-2-yl)carbamate |  |

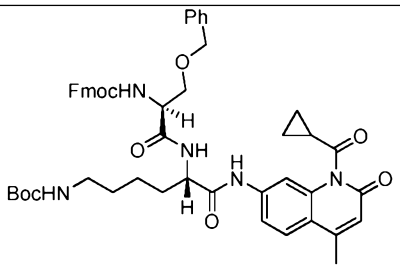
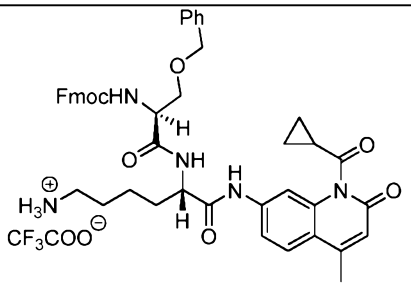
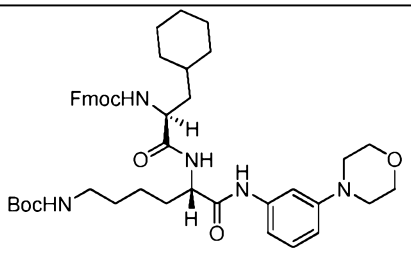
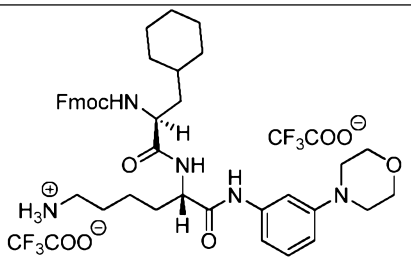
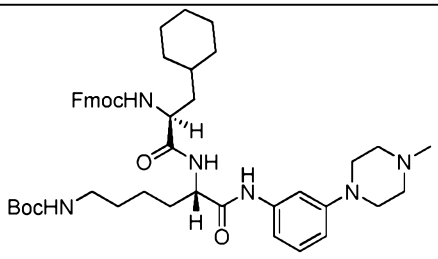
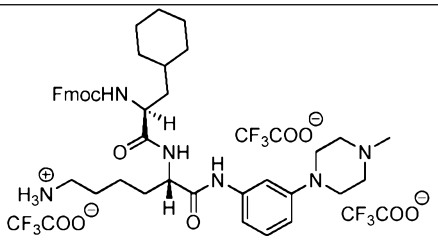
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| 48<br>2548 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-amino-1-((4-methyl-2-oxo-1,2-dihydroquinolin-7-yl)amino)-1-oxohexan-2-yl)amino)-3-(naphthalen-1-yl)-1-oxopropan-2-yl)carbamate |  |
| 49<br>2549 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-(tert-butoxycarbonyl)amino-1-((4-methyl-2-oxo-1,2-dihydroquinolin-7-yl)amino)-1-oxohexan-2-yl)amino)-1-oxo-3-(1-trityl-1H-imidazol-4-yl)propan-2-yl)carbamate |  |
| 50<br>2550 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-amino-1-((4-methyl-2-oxo-1,2-dihydroquinolin-7-yl)amino)-1-oxohexan-2-yl)amino)-3-(1H-imidazol-4-yl)-1-oxopropan-2-yl)carbamate |  |
| 51<br>2552 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-amino-1-oxo-1-((2-oxo-4-(trifluoromethyl)-1,2-dihydroquinolin-7-yl)amino)hexan-2-yl)amino)-3-(benzyloxy)-1-oxopropan-2-yl)carbamate |  |
| 52<br>2552 | phenethyl((S)-1-(((S)-6-amino-1-((4-methyl-2-oxo-1,2-dihydroquinolin-7-yl)amino)-1-oxohexan-2-yl)amino)-3-cyclohexyl-1-oxopropan-2-yl)carbamate |  |

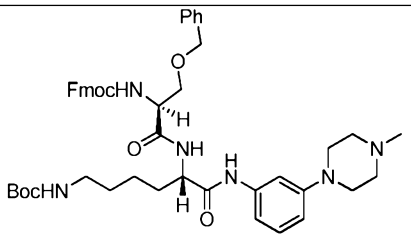
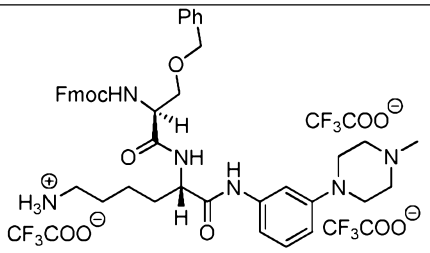
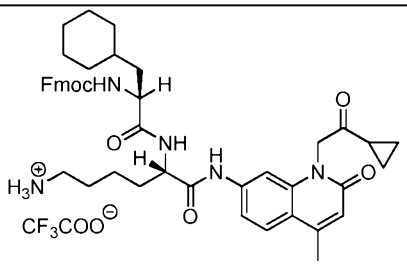
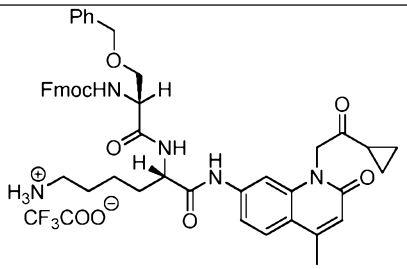
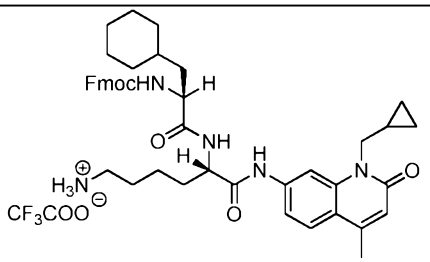
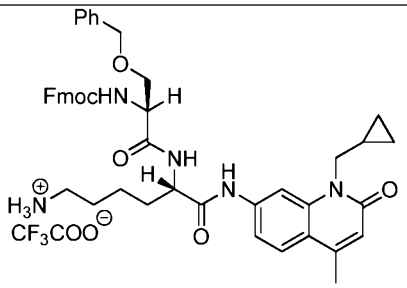
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| 53<br>2553 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-(tert-butoxycarbonyl)amino-1-((1-ethyl-4-methyl-2-oxo-1,2-dihydroquinolin-7-yl)amino)-1-oxohexan-2-yl)amino)-3-(benzyloxy)-1-oxopropan-2-yl)carbamate |  |
| 54<br>2554 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-(tert-butoxycarbonyl)amino-1-oxo-1-((2-oxo-4-(trifluoromethyl)-1,2-dihydroquinolin-7-yl)amino)hexan-2-yl)amino)-3-(benzyloxy)-1-oxopropan-2-yl)carbamate |  |
| 55<br>2555 | tert-butyl2-(7-((S)-2-((S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-cyclohexylpropanamido)-6-aminohexanamido)-4-methyl-2-oxoquinolin-1(2H)-yl)acetate |  |
| 56<br>2556 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-amino-1-((1-ethyl-4-methyl-2-oxo-1,2-dihydroquinolin-7-yl)amino)-1-oxohexan-2-yl)amino)-3-(benzyloxy)-1-oxopropan-2-yl)carbamate |  |
| 57<br>2557 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-(tert-butoxycarbonyl)amino-1-((1-ethyl-4-methyl-2-oxo-1,2-dihydroquinolin-7-yl)amino)-1-oxohexan-2-yl)amino)-3-cyclohexyl-1-oxopropan-2-yl)carbamate |  |

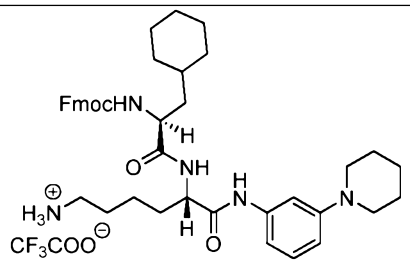
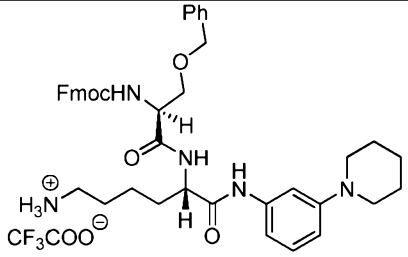
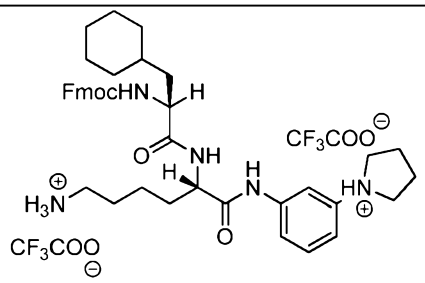
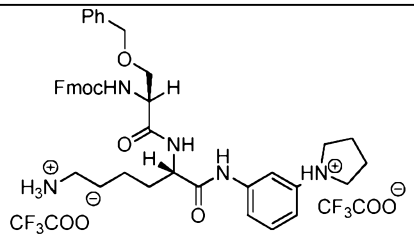
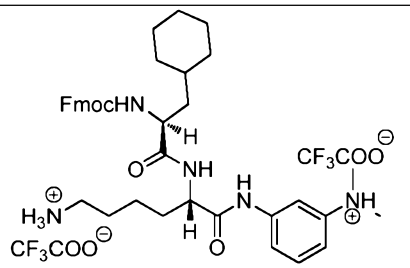
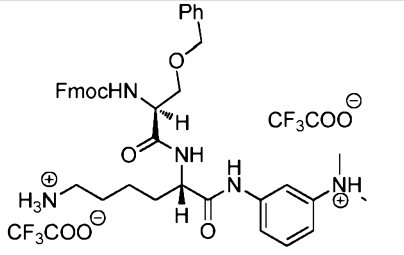
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| 58<br>2558 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-amino-1-((1-ethyl-4-methyl-2-oxo-1,2-dihydroquinolin-7-yl)amino)-1-oxohexan-2-yl)amino)-3-cyclohexyl-1-oxopropan-2-yl)carbamate |  |
| 59<br>2559 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-(tert-butoxycarbonyl)-1-((1-butyl-4-methyl-2-oxo-1,2-dihydroquinolin-7-yl)amino)-1-oxohexan-2-yl)amino)-3-(benzyloxy)-1-oxopropan-2-yl)carbamate |  |
| 60<br>2560 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-amino-1-((1-butyl-4-methyl-2-oxo-1,2-dihydroquinolin-7-yl)amino)-1-oxohexan-2-yl)amino)-3-(benzyloxy)-1-oxopropan-2-yl)carbamate |  |
| 61<br>2561 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-(tert-butoxycarbonyl)amino-1-((1-butyl-4-methyl-2-oxo-1,2-dihydroquinolin-7-yl)amino)-1-oxohexan-2-yl)amino)-3-cyclohexyl-1-oxopropan-2-yl)carbamate |  |
| 62<br>2562 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-amino-1-((1-butyl-4-methyl-2-oxo-1,2-dihydroquinolin-7-yl)amino)-1-oxohexan-2-yl)amino)-3-cyclohexyl-1-oxopropan-2-yl)carbamate |  |

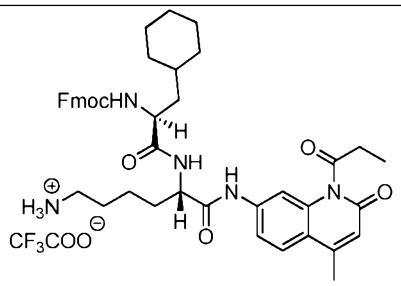
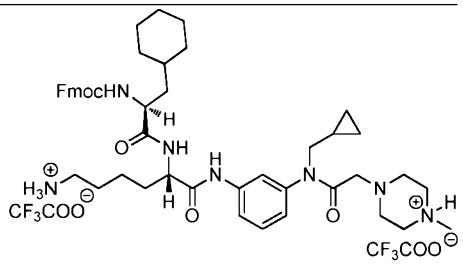
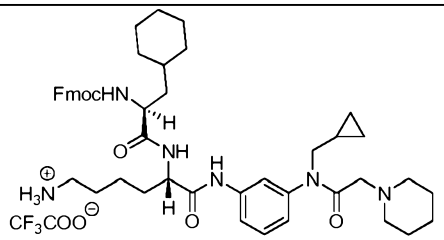
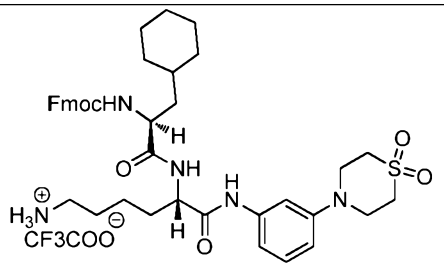
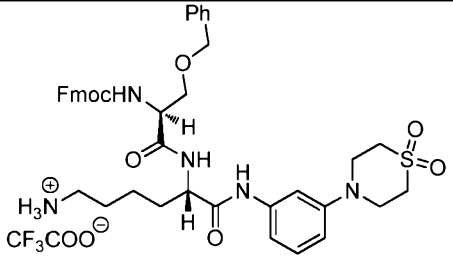
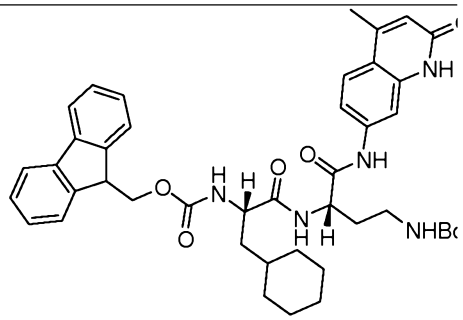
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| 65<br>2565 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-1-((1-allyl-4-methyl-2-oxo-1,2-dihydroquinolin-7-yl)amino)-6-(tert-butoxycarbonyl)amino-1-oxohexan-2-yl)amino)-3-(benzyloxy)-1-oxopropan-2-yl)carbamate |  |
| 66<br>2566 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-1-((1-allyl-4-methyl-2-oxo-1,2-dihydroquinolin-7-yl)amino)-6-amino-1-oxohexan-2-yl)amino)-3-(benzyloxy)-1-oxopropan-2-yl)carbamate |  |
| 67<br>2567 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-1-((1-allyl-4-methyl-2-oxo-1,2-dihydroquinolin-7-yl)amino)-6-(tert-butoxycarbonyl)amino-1-oxohexan-2-yl)amino)-3-cyclohexyl-1-oxopropan-2-yl)carbamate |  |
| 68<br>2568 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-1-((1-allyl-4-methyl-2-oxo-1,2-dihydroquinolin-7-yl)amino)-6-amino-1-oxohexan-2-yl)amino)-3-cyclohexyl-1-oxopropan-2-yl)carbamate |  |
| 69<br>2569 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-(tert-butoxycarbonyl)amino-1-((1-(cyanomethyl)-4-methyl-2-oxo-1,2-dihydroquinolin-7-yl)amino)-1-oxohexan-2-yl)amino)-3-(benzyloxy)-1-oxopropan-2-yl)carbamate |  |

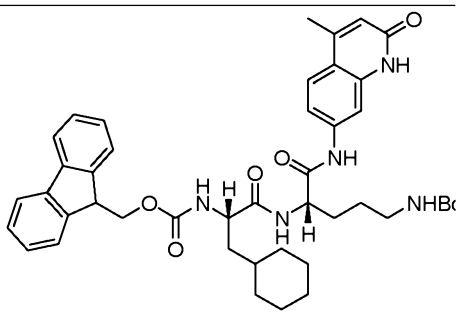
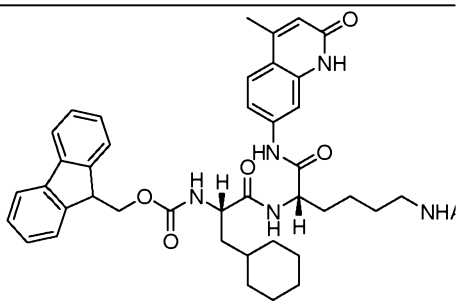
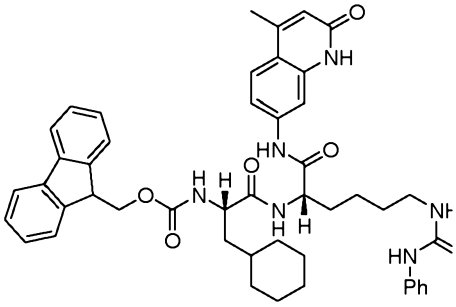
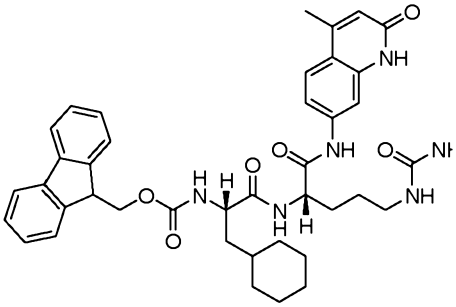
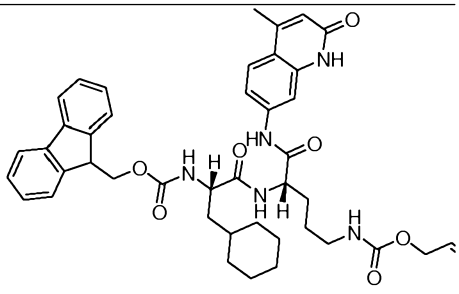
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| 70<br>2570 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-amino-1-((1-(cyanomethyl)-4-methyl-2-oxo-1,2-dihydroquinolin-7-yl)amino)-1-oxohexan-2-yl)amino)-3-(benzyloxy)-1-oxopropan-2-yl)carbamate |  |
| 71<br>2571 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-(tert-butoxycarbonyl)amino-1-((1-(cyanomethyl)-4-methyl-2-oxo-1,2-dihydroquinolin-7-yl)amino)-1-oxohexan-2-yl)amino)-3-cyclohexyl-1-oxopropan-2-yl)carbamate |  |
| 72<br>2572 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-amino-1-((1-(cyanomethyl)-4-methyl-2-oxo-1,2-dihydroquinolin-7-yl)amino)-1-oxohexan-2-yl)amino)-3-cyclohexyl-1-oxopropan-2-yl)carbamate |  |
| 73<br>2573 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-(tert-butoxycarbonyl)amino-1-((1-(cyclopropanecarbonyl)-4-methyl-2-oxo-1,2-dihydroquinolin-7-yl)amino)-1-oxohexan-2-yl)amino)-3-cyclohexyl-1-oxopropan-2-yl)carbamate |  |
| 74<br>2574 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-amino-1-((1-(cyclopropanecarbonyl)-4-methyl-2-oxo-1,2-dihydroquinolin-7-yl)amino)-1-oxohexan-2-yl)amino)-3-cyclohexyl-1-oxopropan-2-yl)carbamate |  |

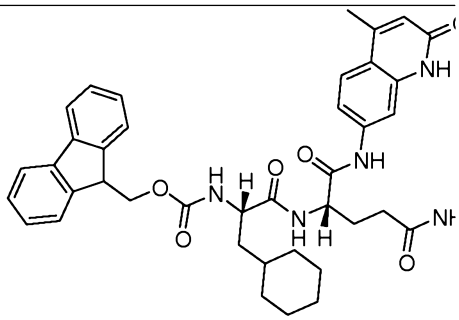
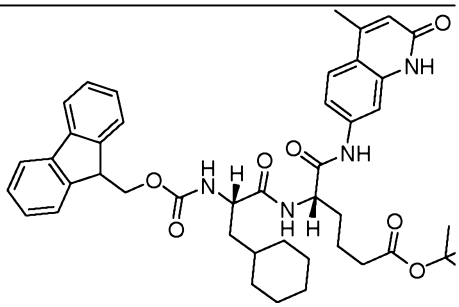
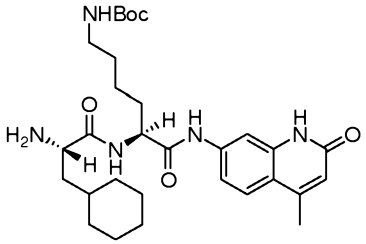
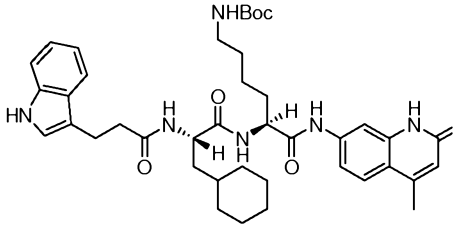
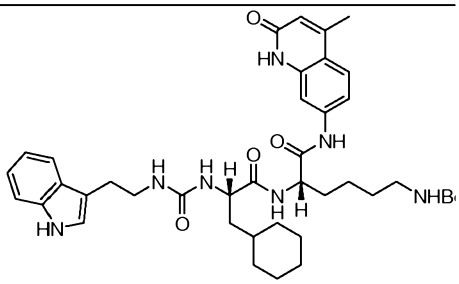
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| 75<br>2575 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-(tert-butoxycarbonyl)amino-1-((1-(cyclopropanecarbonyl)-4-methyl-2-oxo-1,2-dihydroquinolin-7-yl)amino)-1-oxohexan-2-yl)amino)-3-(benzyloxy)-1-oxopropan-2-yl)carbamate |  |
| 76<br>2576 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-amino-1-((1-(cyclopropanecarbonyl)-4-methyl-2-oxo-1,2-dihydroquinolin-7-yl)amino)-1-oxohexan-2-yl)amino)-3-(benzyloxy)-1-oxopropan-2-yl)carbamate |  |
| 77<br>2577 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-(tert-butoxycarbonyl)amino-1-((3-morpholinophenyl)amino)-1-oxohexan-2-yl)amino)-3-cyclohexyl-1-oxopropan-2-yl)carbamate |  |
| 78<br>2578 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-amino-1-((3-morpholinophenyl)amino)-1-oxohexan-2-yl)amino)-3-cyclohexyl-1-oxopropan-2-yl)carbamate |  |
| 79<br>2579 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-(tert-butoxycarbonyl)amino-1-((3-(4-methylpiperazin-1-yl)phenyl)amino)-1-oxohexan-2-yl)amino)-3-cyclohexyl-1-oxopropan-2-yl)carbamate |  |
| 80<br>2580 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-amino-1-((3-(4-methylpiperazin-1-yl)phenyl)amino)-1-oxohexan-2-yl)amino)-3-cyclohexyl-1-oxopropan-2-yl)carbamate |  |

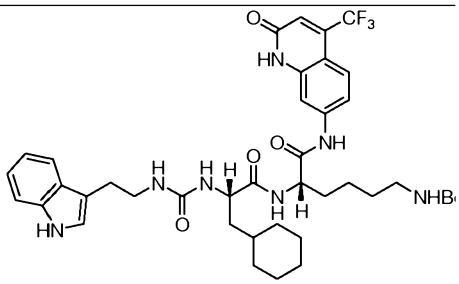
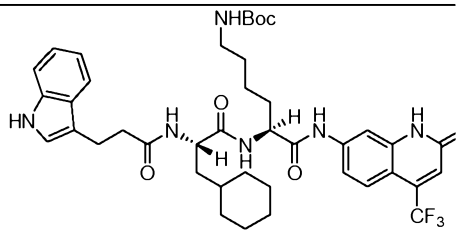
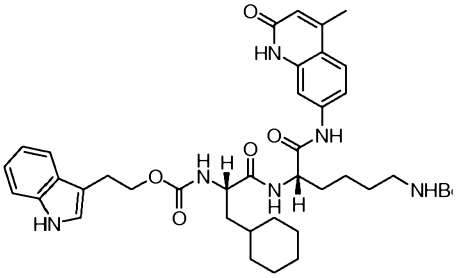
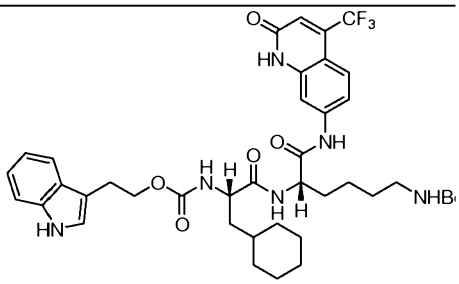
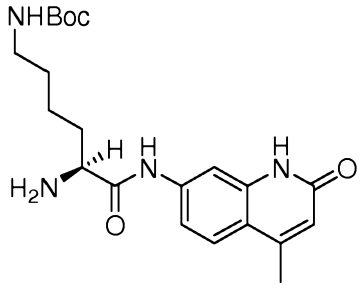
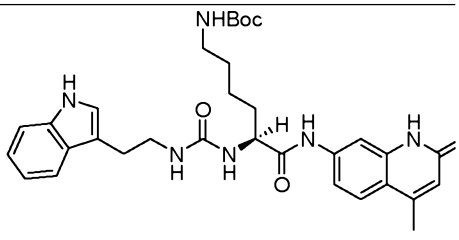
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|---|---|---|
| 81<br>2581 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-(tert-butoxycarbonyl)amino-1-((3-(4-methylpiperazin-1-yl)phenyl)amino)-1-oxohexan-2-yl)amino)-3-(benzyloxy)-1-oxopropan-2-yl)carbamate |  |
| 82<br>2582 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-amino-1-((3-(4-methylpiperazin-1-yl)phenyl)amino)-1-oxohexan-2-yl)amino)-3-(benzyloxy)-1-oxopropan-2-yl)carbamate |  |
| 83<br>2583 | (9H-fluoren-9-yl)methyl(1-(((S)-6-amino-1-((1-(2-cyclopropyl-2-oxoethyl)-4-methyl-2-oxo-1,2-dihydroquinolin-7-yl)amino)-1-oxohexan-2-yl)amino)-3-cyclohexyl-1-oxopropan-2-yl)carbamate |  |
| 84<br>2584 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-amino-1-((1-(2-cyclopropyl-2-oxoethyl)-4-methyl-2-oxo-1,2-dihydroquinolin-7-yl)amino)-1-oxohexan-2-yl)amino)-3-(benzyloxy)-1-oxopropan-2-yl)carbamate |  |
| 85<br>2585 | (9H-fluoren-9-yl)methyl(1-(((S)-6-amino-1-((1-(cyclopropylmethyl)-4-methyl-2-oxo-1,2-dihydroquinolin-7-yl)amino)-1-oxohexan-2-yl)amino)-3-cyclohexyl-1-oxopropan-2-yl)carbamate |  |
| 86<br>2586 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-amino-1-((1-(cyclopropylmethyl)-4-methyl-2-oxo-1,2-dihydroquinolin-7-yl)amino)-1-oxohexan-2-yl)amino)-3-(benzyloxy)-1-oxopropan-2-yl)carbamate |  |

| | | |
|---|---|---|
| 87<br>2587 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-amino-1-oxo-1-((3-(piperidin-1-yl)phenyl)amino)hexan-2-yl)amino)-3-cyclohexyl-1-oxopropan-2-yl)carbamate |  |
| 88<br>2588 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-amino-1-oxo-1-((3-(piperidin-1-yl)phenyl)amino)hexan-2-yl)amino)-3-(benzyloxy)-1-oxopropan-2-yl)carbamate |  |
| 89<br>2589 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-amino-1-oxo-1-((3-(pyrrolidin-1-yl)phenyl)amino)hexan-2-yl)amino)-3-cyclohexyl-1-oxopropan-2-yl)carbamate |  |
| 90<br>2590 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-amino-1-oxo-1-((3-(pyrrolidin-1-yl)phenyl)amino)hexan-2-yl)amino)-3-(benzyloxy)-1-oxopropan-2-yl)carbamate |  |
| 91<br>2591 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-amino-1-((3-(dimethylamino)phenyl)amino)-1-oxohexan-2-yl)amino)-3-cyclohexyl-1-oxopropan-2-yl)carbamate |  |
| 92<br>2592 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-amino-1-((3-(dimethylamino)phenyl)amino)-1-oxohexan-2-yl)amino)-3-(benzyloxy)-1-oxopropan-2-yl)carbamate |  |

| | | |
|---|---|---|
| 93<br>2593 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-amino-1-((4-methyl-2-oxo-1-propionyl-1,2-dihydroquinolin-7-yl)amino)-1-oxohexan-2-yl)amino)-3-cyclohexyl-1-oxopropan-2-yl)carbamate |  |
| 94<br>2594 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-amino-1-((3-(N-(cyclopropylmethyl)-2-(4-methylpiperazin-1-yl)acetamido)phenyl)amino)-1-oxohexan-2-yl)amino)-3-cyclohexyl-1-oxopropan-2-yl)carbamate |  |
| 95<br>2595 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-amino-1-((3-(N-(cyclopropylmethyl)-2-(piperidin-1-yl)acetamido)phenyl)amino)-1-oxohexan-2-yl)amino)-3-cyclohexyl-1-oxopropan-2-yl)carbamate |  |
| 96<br>2596 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-amino-1-((3-(1,1-dioxidothiomorpholino)phenyl)amino)-1-oxohexan-2-yl)amino)-3-cyclohexyl-1-oxopropan-2-yl)carbamate |  |
| 97<br>2597 | (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-amino-1-((3-(1,1-dioxidothiomorpholino)phenyl)amino)-1-oxohexan-2-yl)amino)-3-(benzyloxy)-1-oxopropan-2-yl)carbamate |  |
| 98<br>2632 | (9H-fluoren-9-yl)methyl (S)-1-((S)-4-(t-butoxycarbonylamino)-1-(4-methyl-2-oxo-1,2-dihydroquinolin-7-ylamino)-1-oxobutan-2-ylamino)-3-cyclohexyl-1-oxopropan-2-ylcarbamate * |  |

| | | |
|---|---|---|
| 99<br>2633 | (9H-fluoren-9-yl)methyl (S)-1-((S)-5-(t-butoxycarbonylamino)-1-(4-methyl-2-oxo-1,2-dihydroquinolin-7-ylamino)-1-oxopentan-2-ylamino)-3-cyclohexyl-1-oxopropan-2-ylcarbamate * |  |
| 100<br>2634 | (9H-fluoren-9-yl)methyl (S)-1-((S)-6-acetamido-1-(4-methyl-2-oxo-1,2-dihydroquinolin-7-ylamino)-1-oxohexan-2-ylamino)-3-cyclohexyl-1-oxopropan-2-ylcarbamate |  |
| 101<br>2635 | (9H-fluoren-9-yl)methyl (S)-3-cyclohexyl-1-((S)-1-(4-methyl-2-oxo-1,2-dihydroquinolin-7-ylamino)-1-oxo-6-(3-phenylureido)hexan-2-ylamino)-1-oxopropan-2-ylcarbamate |  |
| 102<br>2636 | (9H-fluoren-9-yl)methyl (S)-3-cyclohexyl-1-((S)-1-(4-methyl-2-oxo-1,2-dihydroquinolin-7-ylamino)-1-oxo-5-ureidopentan-2-ylamino)-1-oxopropan-2-ylcarbamate |  |
| 103<br>2637 | (9H-fluoren-9-yl)methyl (S)-1-((S)-5-allyloxycarbonylamino-1-(4-methyl-2-oxo-1,2-dihydroquinolin-7-ylamino)-1-oxopentan-2-ylamino)-3-cyclohexyl-1-oxopropan-2-ylcarbamate * |  |

| | | |
|---|---|---|
| 104<br>2638 | (9H-fluoren-9-yl)methyl (S)-1-((S)-5-amino-1-(4-methyl-2-oxo-1,2-dihydroquinolin-7-ylamino)-1,5-dioxopentan-2-ylamino)-3-cyclohexyl-1-oxopropan-2-ylcarbamate |  |
| 105<br>2639 | (S)-tert-butyl 5-((S)-2-(((9H-fluoren-9-yl)methoxy)carbonylamino)-3-cyclohexylpropanamido)-6-(4-methyl-2-oxo-1,2-dihydroquinolin-7-ylamino)-6-oxohexanoate |  |
| 106<br>2640 | tert-butyl (S)-5-((S)-2-amino-3-cyclohexylpropanamido)-6-(4-methyl-2-oxo-1,2-dihydroquinolin-7-ylamino)-6-oxohexylcarbamate |  |
| 107<br>2641 | tert-butyl (S)-5-((S)-2-(3-(1H-indol-3-yl)propanamido)-3-cyclohexylpropanamido)-6-(4-methyl-2-oxo-1,2-dihydroquinolin-7-ylamino)-6-oxohexylcarbamate |  |
| 108<br>2642 | tert-butyl (S)-5-((S)-2-(3-(2-(1H-indol-3-yl)ethyl)ureido)-3-cyclohexylpropanamido)-6-(4-methyl-2-oxo-1,2-dihydroquinolin-7-ylamino)-6-oxohexylcarbamate |  |

| | | |
|---|---|---|
| 109<br>2643 | tert-butyl (S)-5-((S)-2-(3-(2-(1H-indol-3-yl)ethyl)ureido)-3-cyclohexylpropanamido)-6-oxo-6-(2-oxo-4-(trifluoromethyl)-1,2-dihydroquinolin-7-ylamino)hexylcarbamate |  |
| 110<br>2644 | tert-butyl (S)-5-((S)-2-(3-(1H-indol-3-yl)propanamido)-3-cyclohexylpropanamido)-6-oxo-6-(2-oxo-4-(trifluoromethyl)-1,2-dihydroquinolin-7-ylamino)hexylcarbamate |  |
| 111<br>2645 | tert-butyl (S)-5-((S)-2-(3-(1H-indol-3-yl)ethoxycarbonylamino)-3-cyclohexylpropanamido)-6-oxo-6-(2-oxo-4-(methyl)-1,2-dihydroquinolin-7-ylamino)hexylcarbamate * |  |
| 112<br>2646 | tert-butyl (S)-5-((S)-2-(3-(1H-indol-3-yl)ethoxycarbonylamino)-3-cyclohexylpropanamido)-6-oxo-6-(2-oxo-4-(trifluoromethyl)-1,2-dihydroquinolin-7-ylamino)hexylcarbamate |  |
| 113<br>2647 | (S)-tert-butyl 5-amino-6-(4-methyl-2-oxo-1,2-dihydroquinolin-7-ylamino)-6-oxohexylcarbamate |  |
| 114<br>2648 | (S)-tert-butyl 5-(3-(2-(1H-indol-3-yl)ethyl)ureido)-6-(4-methyl-2-oxo-1,2-dihydroquinolin-7-ylamino)-6-oxohexylcarbamate |  |

**Biological Activity of Examplary Compounds of Formula (I)**

Table 1A: Positive Allosteric Modulators for GalR2 receptor; compounds of formula (I)

IP1 production stimulated by compound plus 100 nM galanin was measured in HEK293 cells stably expressing GalR2 receptor with a FRET based IP-One Tb kit (Cisbio).

| Binding | | Allosteric modulation |
|---|---|---|
| $GalR_1$ | $GalR_2$ | $EC_{50}$(μM) at a galanin concentration of 100nM |
| $IC_{50}$ (μM) | $IC_{50}$(μM) | |
| 9.83 | 84.37 | - |
| - | - | 1 |
| - | - | 2.4 |
| 10.15 | 13.36 | - |
| - | - | 4.9 |
| 14.5 | - | - |
| - | - | 11 |
| - | - | 3.3 |
| - | - | 11.2 |
| 9.83 | - | - |
| 34.8 | - | - |
| 10.5 | - | - |
| 11.4 | 13.27 | - |
| 31.33 | 11.09 | - |
| 18.63 | - | - |
| 11.47 | 21.43 | - |
| 11.31 | 27.95 | - |
| - | - | 2.6 |
| 11.7 | 10.99 | - |
| 9.75 | 20.82 | - |
| - | 28.19 | - |

| | | |
|---|---|---|
| - | 19.58 | - |
| 6.04 | - | - |
| 8.13 | - | - |
| 17.46 | - | - |
| 19.08 | - | - |
| 6.39 | - | - |
| 4.68 | - | - |
| 8.67 | - | 1.9 |
| 8.27 | - | - |
| 14.41 | - | 0.48 |
| 23.28 | - | - |
| 18.28 | - | - |
| 20.85 | - | - |
| 12.58 | - | - |
| 29.55 | - | - |
| 11.67 | - | - |
| 11.81 | - | - |

Table 1B: Effects of CYM2503, a compound of formula (I), on the establishment of SE and on mortality in rat Li-pilocarpine SE model

| | Dose (mg/kg, i.p.) | Number of rats tested | Rats with SE | Mortality at 4 hrs | Mortality at 24 hrs |
|---|---|---|---|---|---|
| Vehicle | -- | 5 | 5 (100%) | 2 (40%) | 5 (100%) |
| LEV | 50 | 4 | 4 (100%) | 1 (25%) | 4 (100%) |
| CYM2503 | 60 | 5 | 4 (80%) | 0 (0%) | 0 (0%) |

SE: status epilepticus; LEV: levetiracetam

A compound of the invention of formula (I), termed CYM2503, has been identified by the inventors herein as a GalR2 positive allosteric modulator compound. CYM2503 potentiated the galanin stimulated IP1 accumulation in HEK293 cells stably expressing GalR2 receptors, while it exhibited no detectable affinity for the $^{125}$I galanin binding site of GalR2 receptor, an effect consistent with that of a positive allosteric modulator. In the rat

Li-pilocarpine status epilepticus model, CYM2503, injected intraperitoneally, increased the latency to first electrographic seizure and the latency to first stage 3 behavioral seizure; decreased the latency to the establishment of status epilepticus; dramatically decreased the mortality. In a lithium-pilocarpine seizure model in mice, CYM2503 increased the latency to first electrographic seizure and decreased the total time in seizure. CYM2503 also attenuated electroshock induced seizures in mice.

CYM2503 potentiated GalR2 signaling

A compound of the invention, termed CYM2503, was first identified from screening of a chemical library for modulators of the GalR2 receptor. The endogenous ligand galanin stimulated IP1 production in HEK293-GalR2 cells was employed as a functional index of GalR2 receptor activation. In the absence of CYM2503, galanin stimulated IP1 accumulation in HEK293-GalR2 cells with an EC 50 of 0.3 ± 0.6 μM (mean ± SEM, n=10). The initial screen was carried out in the presence of 100 nM galanin, CYM2503 was found to concentration dependently potentiate the effect of 100 nM galanin with an EC 50 of 0.69 ± 2.7 μM (n=2) and an efficacy of 9.7- ± 3.2-fold potentiation (Figure 1A).

We then tested the effect of CYM2503 on the galanin concentration response curve. As shown in Figure 1B, CYM2503 shifted the galanin concentration response curve to the left. EC 50 was shifted by 50.4 - ± 17.8 (mean ± SEM, n=4), with 100 μM CYM2503. Smaller shifts of 12.5- ± 3.2-fold and 3.4- ± 0.7-fold were seen with 10 μM and 1 μM CYM2503, respectively. CYM2503 also increased the maximal galanin response by up to 25 ± 9%.

In HEK293-GalR2 cells, CYM2503, by itself, did not stimulate IP1 production in the absence of galanin (Figure 1D). In $^{125}$I-galanin competitive binding assay to membranes prepared from HEK293-GalR2 cells, CYM2503 at concentrations up to 100 μM failed to displace $^{125}$I-galanin from its binding sites on GalR2 (Figure 1C). The lack of affinity of CYM2503 at the orthosteric site of the GalR2 as well as the absence of baseline agonist-like activity suggests CYM2503 might be a putative GalR2 allosteric modulator with no intrinsic activity.

CYM2503 had no effect on GalR1 signaling

CYM2503 exhibited no affinity for the galanin binding site on GalR1 receptor (Figure 2A) at up to 100 μM. A FRET (fluorescence resonance energy transfer) based cAMP assay was then used to test if CYM2503 modulates GalR1 signaling. Inhibition of forskolin-stimulated cAMP accumulation in CHO-GalR1 cells by the endogenous ligand galanin was employed as a functional index of GalR1 receptor activation. In this assay, galanin suppressed forskolin-stimulated cAMP accumulation with an IC50 of 7.3 ± 6.8 pM (Figure 2, mean ± SEM, n = 10), which is about two orders of magnitude lower than the observed affinity for GalR1 (Kd = 0.23 ± 0.45 nM). To ensure that the observed inhibitory effect of galanin on cAMP is indeed mediated by the GalR1 receptor, we compared the galanin response in CHO-GalR1 cells to that in the master CHO cell line, which was used to construct the CHO-GalR1 stable cell line. As shown in Figure 1B, galanin had no effect on forskolin-stimulated cAMP production in CHO cells that are lacking the rat GalR1 transgene, confirming that the cAMP response to galanin in CHO-GalR1 cells is indeed mediated by GalR1 receptor. CYM2503 did not shift the galanin dose response curve in cAMP assay (Figure 2D) and it, by itself, had no effect on forskolin-stimulated cAMP production in CHO-GalR1 cells (Figure 2C).

Anticonvulsant effect of CYM2503 in mice

Pilocarpine at the dose of 150 mg/kg s.c. induced brief episodes of electrographic seizures with an average duration of 0.7 ± 0.4 min (mean ± SEM, n = 32) in LiCl (3 mEq/kg, i.p. 16-20 hrs prior to pilocarpine) and methylscopolamine (1 mg/kg, s.c., 30 min prior to pilocarpine) pretreated mice. Seizure started about 30 min after pilocarpine injection and, by 8 hrs, all mice were seizure free. Only a few mice developed status epilepticus (3/30) at this pilocarpine dose. All EEG tracings were analyzed up to 8 hr.

Pretreatment with CYM2503 (15 min prior to pilocarpine) attenuated Li-pilocarpine induced seizures in mice (Figure 3). The effects were significant at 60 mg/kg i.p. (Figure 3C): the latency to first electrographic seizure was prolonged by approximately 5-fold, from 36.7 ± 8.0 min in vehicle group to 180.7 ± 76.2 min ($p<0.05$, mean ± SEM, n=9); total time in seizures decreased from 9.5 ± 1.9 min in vehicle group to 0.2 ± 0.06 min ($p<0.05$, n=9); the total number of spikes decreased by 50%, from 614.4 ± 52.52 in vehicle group to 341.3 ± 34.2 ($p<0.05$, n=9); total number of seizure episodes decreased from 13.9

± 1.1 in vehicle group to 4.4 ± 1.7 ($p<0.05$, n=9). Overall, the effects of CYM2503 (60 mg/kg, i.p.) were comparable to that of levetiracetam (50 mg/kg i.p.) in this seizure model.

The electroshock seizure model is frequently used to predict anticonvulsant drug efficacy against generalized tonic-clonic seizures (35). Under the test conditions, about 55% (6/11) of mice in the vehicle-treated group developed hindlimb extension and the mortality was about 45% (5/11) (Figure 4A). Fifteen minutes pretreatment with CYM2503 at concentrations of 30 mg/kg i.p. and 60 mg/kg i.p. decreased the percentage of mice exhibited hindlimb extension from 55% (6/11) to 20% to (2/10); decreased the mortality from 45% (5/11) to 0% (0/9) (Figure 4A). The latency to hindlimb extension was prolonged by pretreatment with 60 mg/kg CYM2503, from 4.2 ± 0.42 seconds in vehicle group to 5.7 ± 0.27 seconds in CYM2503 treated group (Figure 4B, $p<0.05$, n=9-11).

Anticonvulsant effect of CYM2503 in Li-pilocarpine status epilepticus model in rats

Intraperitoneal injection of CYM2503 (60 mg/kg, i.p.), similarly to levetiracetam (50 mg/kg, i.p.), increased the latency to first electrographic seizure by 2-fold, from 18.0 ± 4.1 min in the vehicle group to 34.4 ± 3.0 min (mean ± SEM, $p< 0.05$, n=5); increased the latency to generalized seizure (>stage 3) by 2-fold, from 18.1 ± 4.1 min in vehicle group to 35.6 ± 5.9 min ($p<0.05$); increased the latency to the establishment of status epilepticus 2-fold, from 0.40 ± 0.05 hr in vehicle group to 0.72 ± 0.06 hr ($p<0.01$). In the vehicle-treated group, 100% (5/5) rats developed status epilepticus and in the CYM2503-treated group 80% (4/5) developed status epilepticus (Table 1, below). There appeared to be a great survival benefit of CYM2503, as the 24 hr mortality was 0% (0/5) in CYM2503-treated rats compared to 100% (5/5) in vehicle-treated rats.

CYM2503 can potentiate galanin response at GalR2 receptor by increasing the potency of galanin, as well as maximal response in HEK293 cells stably expressing GalR2 receptors. The lack of the affinity of CYM2503 for orthosteric site of GalR2 and the lack of effect of CYM2503 on baseline IP turnover suggest CYM2503 is a positive allosteric modulator of GalR2 without intrinsic activity. The specificity of the effect of CYM2503 was evidenced by its lack of effect on galanin response at GalR1 receptor and its lack of GalR1-like signaling and affinity for GalR1 in CHO cells stably expressing GalR1 receptors. Furthermore, CYM2503 was systemically active in attenuating seizures in Li-pilocarpine model in both mice and rats, and in electroshock induced seizures in mice.

GalR2 signaling represents a potent anticonvulsant and anti-epileptic mechanism. In addition to attenuating acute seizures (25), intrahippocampal infusion of the GalR2 preferring ligand galanin (2-11) was recently shown to completely prevent the occurrence of full kindled seizures (36). It is known that GalR2 is expressed at the highest level in the dentate gyrus of hippocampus and it has been shown that heightened neuronal activity and seizure trigger the release of galanin into hippocampus from projections originating from septal basal forebrain complex, locus coeruleus, and hypothalamus (18, 26, 37-39). At the same time, seizure activity induces de novo galanin expression in the entire hippocampus, as well as in the interneurons of the dentate gyrus (22, 39). Thus, the presence of intact GalR2 signaling during ictal and peri-ictal period lends a theoretic support for developing GalR2 positive allosteric modulators to treat seizures. In addition to an anticonvulsant effect, enhanced GalR2 signaling by positive allosteric modulators such as CYM2503 might provide the added benefit of neuroprotection during seizures (25).

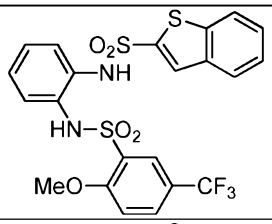
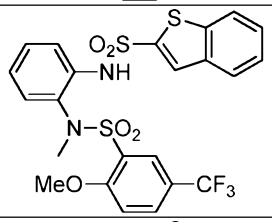
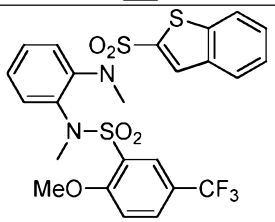
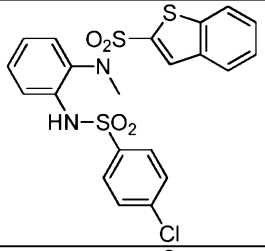
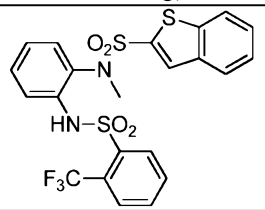
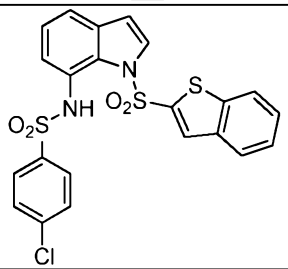
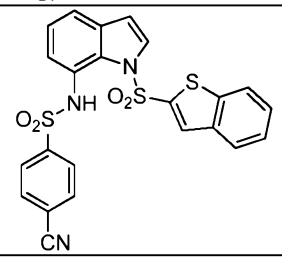
The Li-pilocarpine model is a widely used animal model for temporal lobe seizure/epilepsy. In rats, it is a very robust model for status epilepticus (39, 40). Although CYM2503 did not seem to block the establishment of status epilepticus, it increased the latency to seizure and to status epilepticus. More importantly, it appeared to decrease the mortality dramatically (Table 1). Centrally or peripherally mediated cardiovascular and respiratory failure is a significant cause of death in Li-pilocarpine induced status epilepticus. As GalR2 is expressed in the heart (41) and galanin has been shown to regulate cardiac function via peripheral mechanisms (42, 43), it would be of interest to explore the direct effect of CYM2503 and/or GalR2 agonist on parameters of cardiac function in the future.

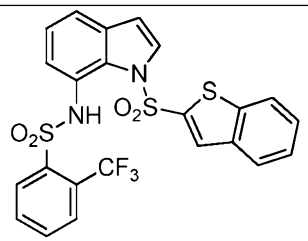
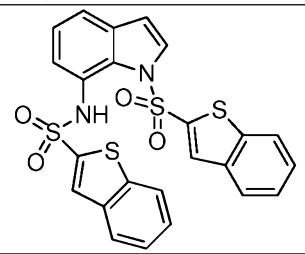
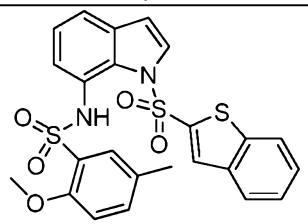
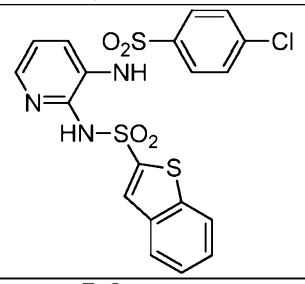
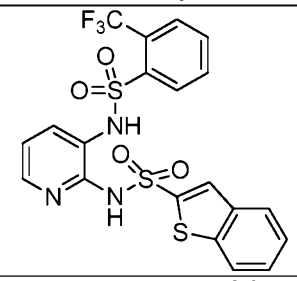
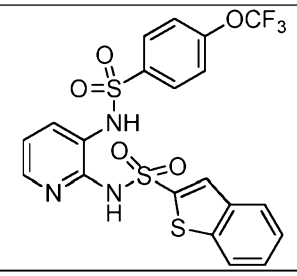
The Li-pilocarpine model in mice has also been employed as a model for status epilepticus by several researchers (35), but great variations have been observed with this model, perhaps due to its high sensitivity to strain differences and to subtle changes in experimental condition (35). The Li-pilocarpine (pilocarpine 150 mg/kg, s.c.) seizure model was used to test the anticonvulsant efficacy of the CYM2503 in mice, and it was found that CYM2503 at 60 mg/kg was comparable to levetiracetam (50 mg/kg) in increasing latency to first electrographic seizure and decreasing total time in seizure. The present study was performed with C57Bl/6 mice obtained from the Scripps Research

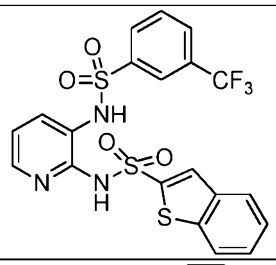
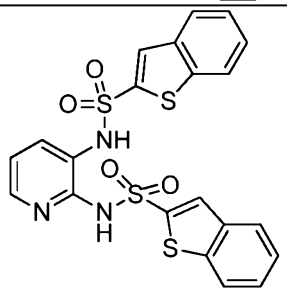
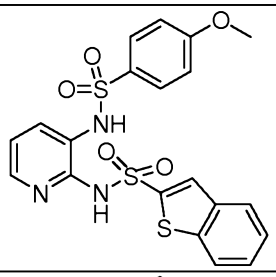
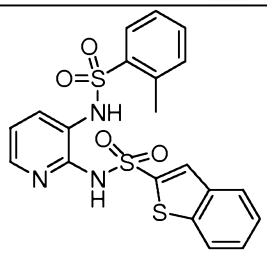
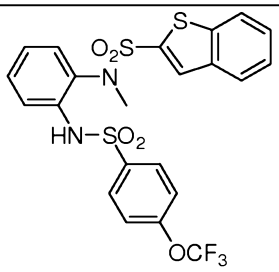
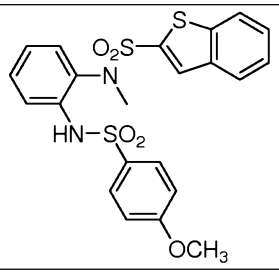
Institute local colony. Compound of the invention CYM2503, a non-peptide type, positive allosteric modulator of GalR2, exhibited potent anticonvulsant activity upon systemic administration in acute seizure models in both rats and mice.

5

**Table 2: Exemplary Compounds of the Invention—Formula (II)**

| | | |
|---|---|---|
| 115<br>2598 | N-(2-(2-methoxy-5-(trifluoromethyl)phenylsulfonamido)phenyl)benzo[b]thiophene-2-sulfonamide |  |
| 116<br>2599 | N-(2-(2-methoxy-N-methyl-5-(trifluoromethyl)phenylsulfonamido)phenyl)benzo[b]thiophene-2-sulfonamide |  |
| 117<br>2600 | N-(2-(2-methoxy-N-methyl-5-(trifluoromethyl)phenylsulfonamido)phenyl)-N-methylbenzo[b]thiophene-2-sulfonamide |  |
| 118<br>2601 | N-(2-(4-chlorophenylsulfonamido)phenyl)-N-methylbenzo[b]thiophene-2-sulfonamide |  |
| 119<br>2602 | N-methyl-N-(2-(2-(trifluoromethyl)phenylsulfonamido)phenyl)benzo[b]thiophene-2-sulfonamide |  |
| 120<br>2603 | N-(1-(benzo[b]thiophen-2-ylsulfonyl)-1H-indol-7-yl)-4-chlorobenzenesulfonamide |  |
| 121<br>2604 | N-(1-(benzo[b]thiophen-2-ylsulfonyl)-1H-indol-7-yl)-4-cyanobenzenesulfonamide |  |

| | | |
|---|---|---|
| 122<br>2605 | N-(1-(benzo[b]thiophen-2-ylsulfonyl)-1H-indol-7-yl)-2-(trifluoromethyl)benzenesulfonamide |  |
| 123<br>2606 | N-(1-(benzo[b]thiophen-2-ylsulfonyl)-1H-indol-7-yl)benzo[b]thiophene-2-sulfonamide |  |
| 124<br>2607 | N-(1-(benzo[b]thiophen-2-ylsulfonyl)-1H-indol-7-yl)-2-methoxy-5-methylbenzenesulfonamide |  |
| 131<br>2614 | N-(3-(4-chlorophenylsulfonamido)pyridin-2-yl)benzo[b]thiophene-2-sulfonamide |  |
| 132<br>2615 | N-(3-(2-(trifluoromethyl)phenylsulfonamido)pyridin-2-yl)benzo[b]thiophene-2-sulfonamide |  |
| 133<br>2616 | N-(3-(4-(trifluoromethoxy)phenylsulfonamido)pyridin-2-yl)benzo[b]thiophene-2-sulfonamide |  |

| | | |
|---|---|---|
| 134<br>2617 | N-(3-(3-(trifluoromethyl)phenylsulfonamido)pyridin-2-yl)benzo[b]thiophene-2-sulfonamide |  |
| 135<br>2618 | N,N'-(pyridine-2,3-diyl)bis(benzo[b]thiophene-2-sulfonamide) |  |
| 137<br>2626 | N-(3-(4-methoxyphenylsulfonamido)pyridin-2-yl)benzo[b]thiophene-2-sulfonamide |  |
| 138<br>2627 | N-(3-(2-methylphenylsulfonamido)pyridin-2-yl)benzo[b]thiophene-2-sulfonamide |  |
| 139<br>2628 | N-methyl-N-(2-(4-(trifluoromethoxy)phenylsulfonamido)phenyl)benzo[b]thiophene-2-sulfonamide |  |
| 140<br>2629 | N-(2-(4-methoxyphenylsulfonamido)phenyl)-N-methylbenzo[b]thiophene-2-sulfonamide |  |

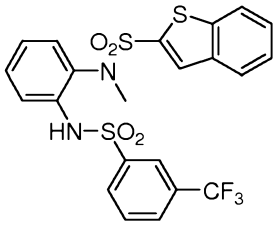
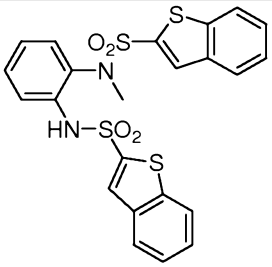
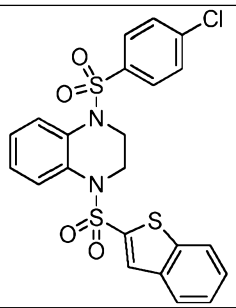
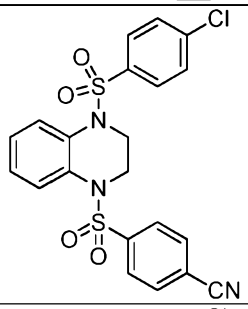
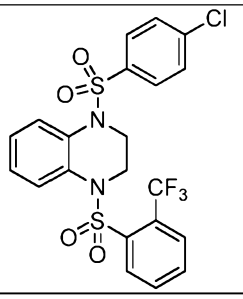
| | | |
|---|---|---|
| 141<br>2630 | N-methyl-N-(2-(3-(trifluoromethyl)phenylsulfonamido)phenyl)benzo[b]thiophene-2-sulfonamide |  |
| 142<br>2631 | N-(2-(benzo[b]thiophene-2-sulfonamido)phenyl)-N-methylbenzo[b]thiophene-2-sulfonamide |  |

**Table 3: Exemplary Compounds of the Invention—Formula (III)**

| | | |
|---|---|---|
| 125<br>2608 | 1-(benzo[b]thiophen-2-ylsulfonyl)-4-((4-chlorophenyl)sulfonyl)-1,2,3,4-tetrahydroquinoxaline |  |
| 126<br>2609 | 4-((4-((4-chlorophenyl)sulfonyl)-3,4-dihydroquinoxalin-1(2H)-yl)sulfonyl)benzonitrile |  |
| 127<br>2610 | 1-((4-chlorophenyl)sulfonyl)-4-((2-(trifluoromethyl)phenyl)sulfonyl)-1,2,3,4-tetrahydroquinoxaline |  |

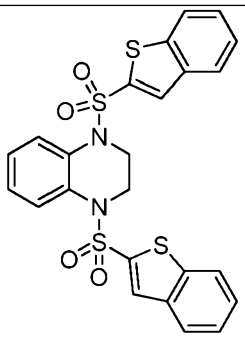
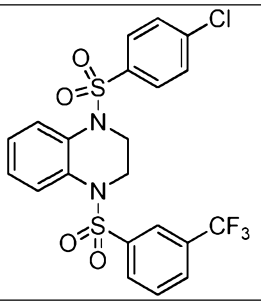
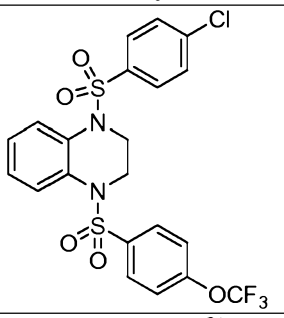
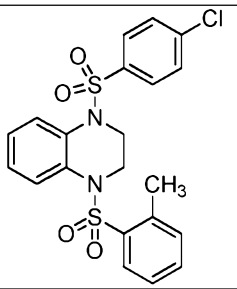
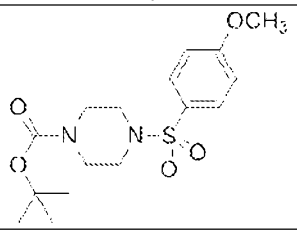
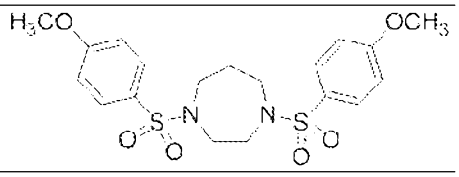
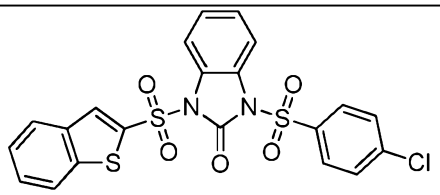
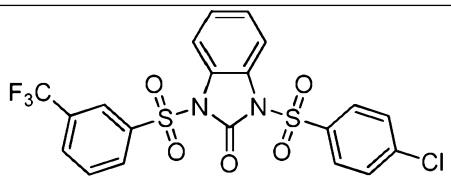
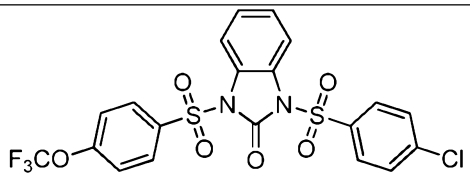
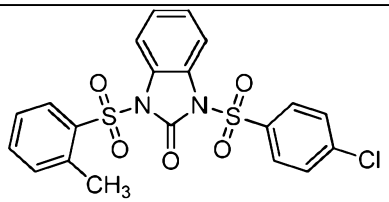
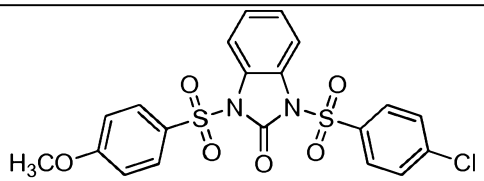
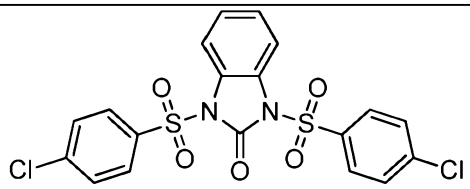
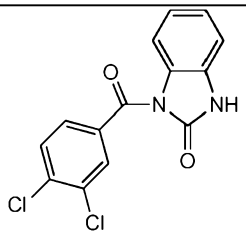
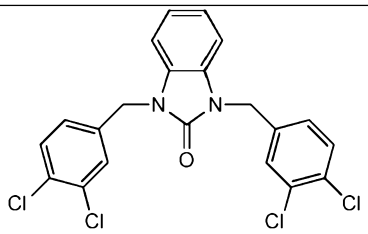
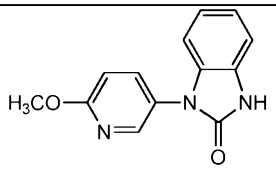
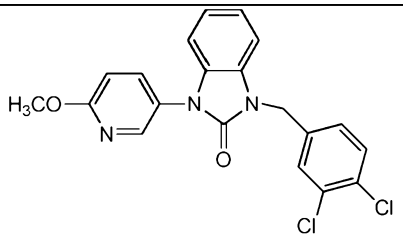
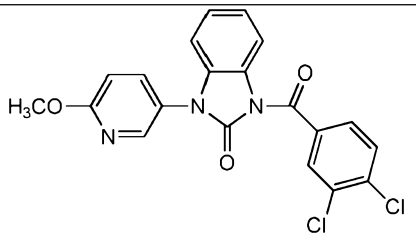
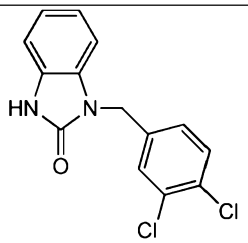
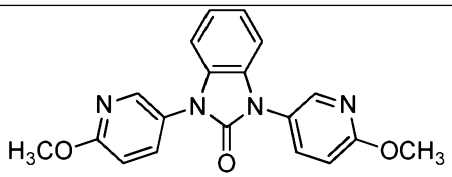
| | | |
|---|---|---|
| 128<br>2611 | 1,4-bis(benzo[b]thiophen-2-ylsulfonyl)-1,2,3,4-tetrahydroquinoxaline |  |
| 129<br>2612 | 1-((4-chlorophenyl)sulfonyl)-4-((3-(trifluoromethyl)phenyl)sulfonyl)-1,2,3,4-tetrahydroquinoxaline |  |
| 130<br>2613 | 1-((4-chlorophenyl)sulfonyl)-4-((4-(trifluoromethoxy)phenyl)sulfonyl)-1,2,3,4-tetrahydroquinoxaline |  |
| 136<br>2624 | 1-((4-chlorophenyl)sulfonyl)-4-(o-tolylsulfonyl)-1,2,3,4-tetrahydroquinoxaline |  |
| 136A<br>2319 | tert-butyl 4-((4-methoxyphenyl)sulfonyl)piperazine-1-carboxylate |  |
| 136B<br>2320 | 1,4-bis((4-methoxyphenyl)sulfonyl)-1,4-diazepane |  |

**Table 4: Exemplary Compounds of the Invention—Formula (IV)**

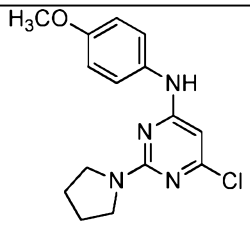
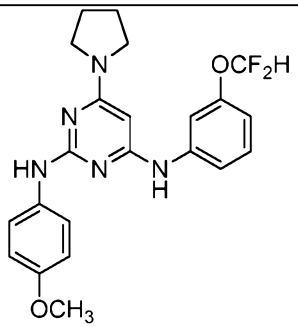
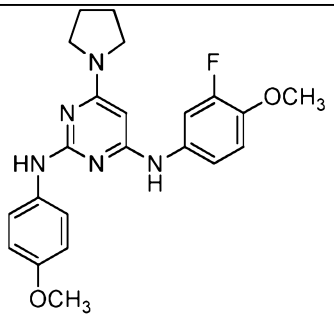
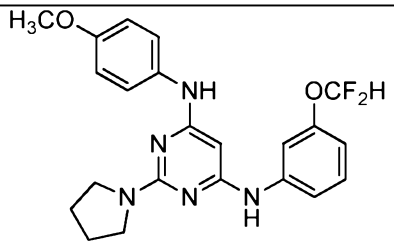
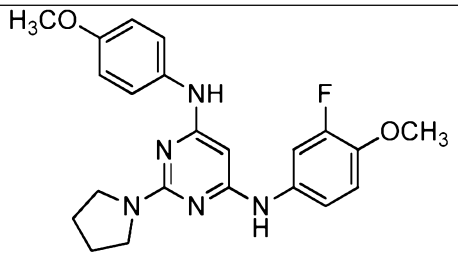
| | | |
|---|---|---|
| 143<br>2619 | 1-(benzo[b]thiophen-2-ylsulfonyl)-3-((4-chlorophenyl)sulfonyl)-1H-benzo[d]imidazol-2(3H)-one |  |
| 144<br>2620 | 1-((4-chlorophenyl)sulfonyl)-3-((3-(trifluoromethyl)phenyl)sulfonyl)-1H-benzo[d]imidazol-2(3H)-one |  |
| 145<br>2621 | 1-((4-chlorophenyl)sulfonyl)-3-((4-(trifluoromethoxy)phenyl)sulfonyl)-1H-benzo[d]imidazol-2(3H)-one |  |
| 146<br>2622 | 1-((4-chlorophenyl)sulfonyl)-3-(o-tolylsulfonyl)-1H-benzo[d]imidazol-2(3H)-one |  |
| 147<br>2623 | 1-((4-chlorophenyl)sulfonyl)-3-((4-methoxyphenyl)sulfonyl)-1H-benzo[d]imidazol-2(3H)-one |  |
| 148<br>2625 | 1,3-bis((4-chlorophenyl)sulfonyl)-1H-benzo[d]imidazol-2(3H)-one |  |
| 148A<br>2004 | 1-(3,4-dichlorobenzoyl)-1H-benzo[d]imidazol-2(3H)-one |  |

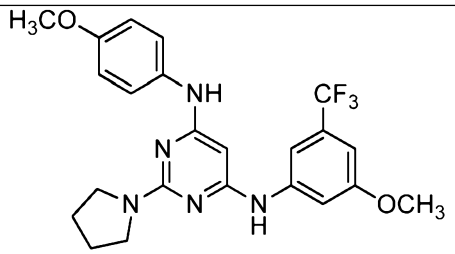
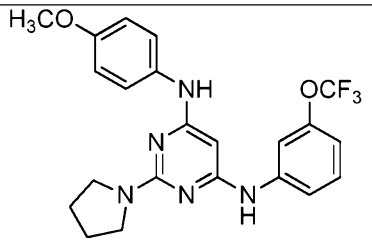
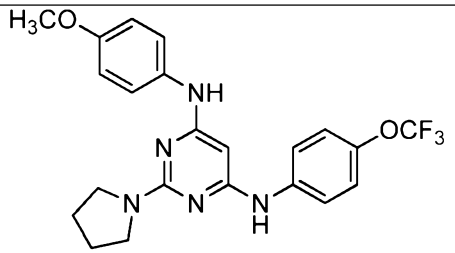
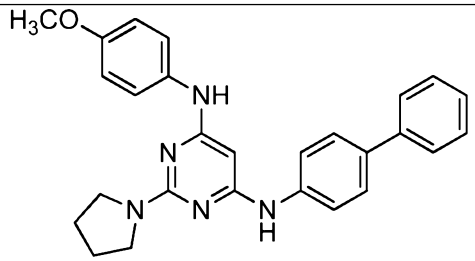
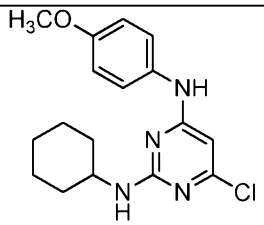
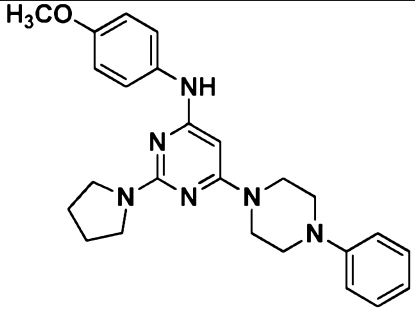
| | | |
|---|---|---|
| 148B 2005 | 1,3-bis (3,4-dichlorobenzyl)-1H-benzo[d]imidazol-2(3H)-one |  |
| 148C 2007 | 1-(6-methoxypyrid-3-yl)-1H-benzo[d]imidazol-2(3H)-one |  |
| 148D 2008 | 1(3,4-dichlorobenzyl)-3-(6-methoxypyrid-3-yl)-1H-benzo[d]imidazol-2(3H)-one |  |
| 148E 2009 | 1-(3,4-dichlorobenzoyl)-3-(6-methoxypyrid-3-yl)-1H-benzo[d]imidazol-2(3H)-one |  |
| 148F 2129 | 1-(3,4-dichlorobenzyl)-1H-benzo[d]imidazol-2(3H)-one |  |
| 148G 2379 | 1,3-bis(6-methoxypyrid-3-yl)-1H-benzo[d]imidazol-2(3H)-one |  |

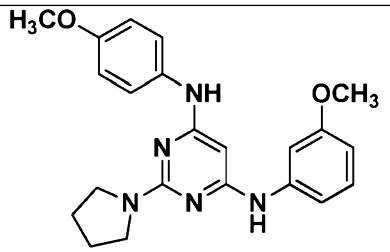
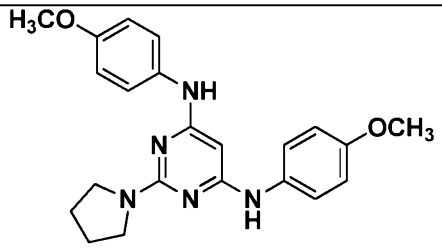
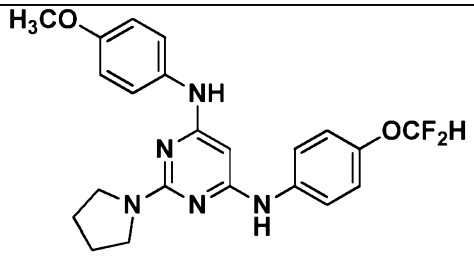
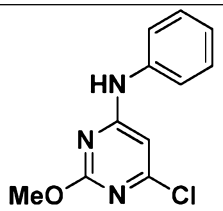
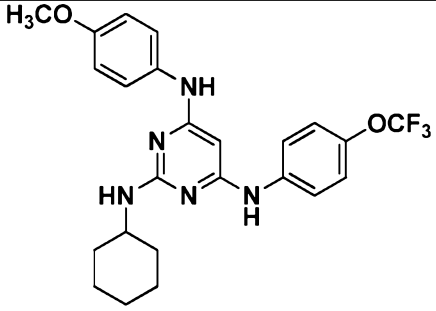
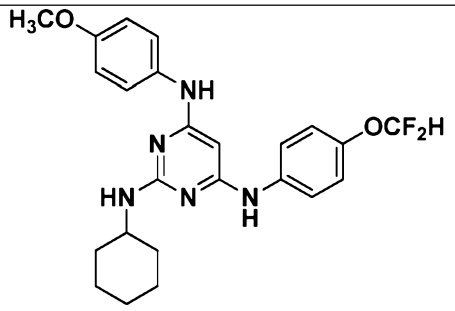
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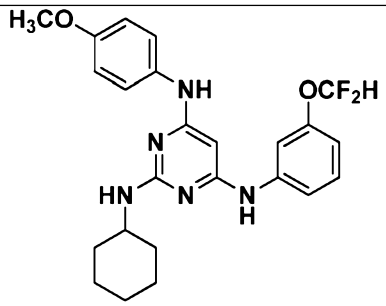
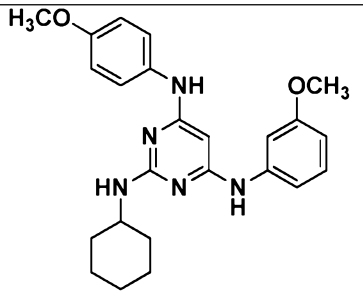
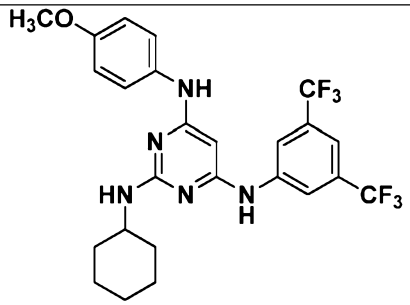
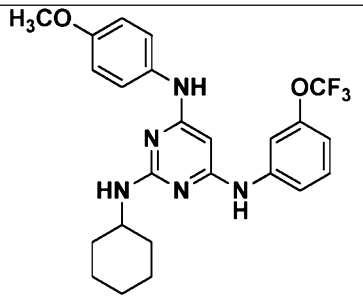
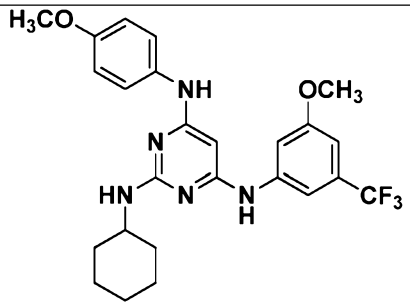
GalR2 $EC_{50}$ = 2.727 μM

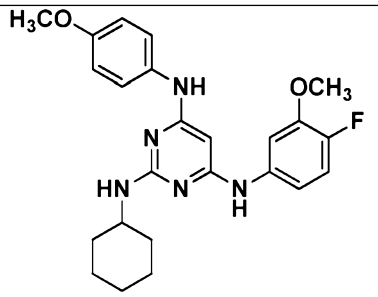
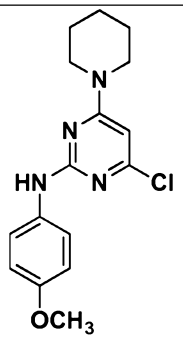
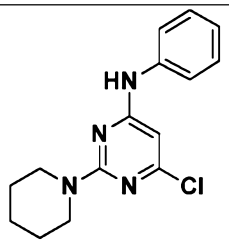
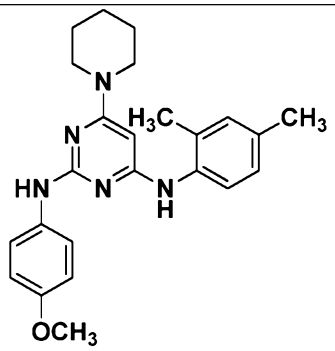
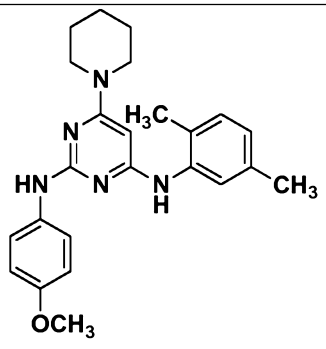
**Table 5: Exemplary Compounds of the Invention—Formula (VA / VB)**

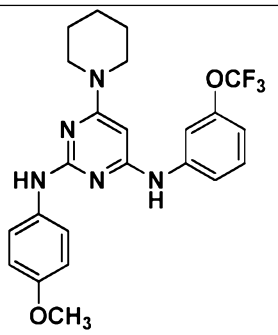
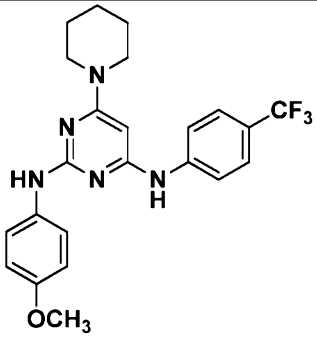
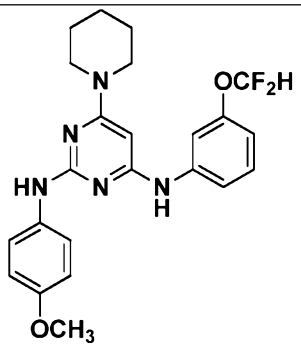
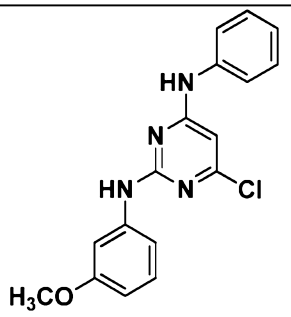
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| 151<br>2204 |  |
| 152<br>2205 |  |
| 153<br>2206 |  |

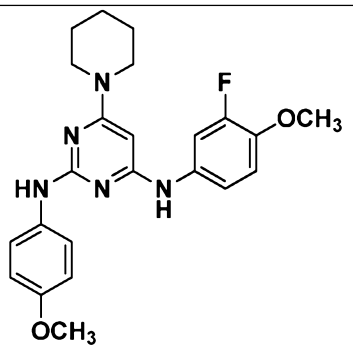
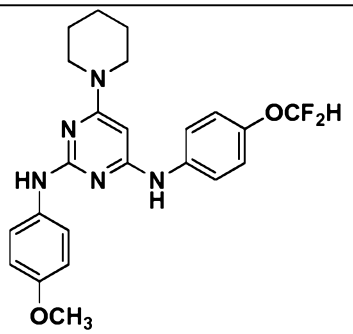
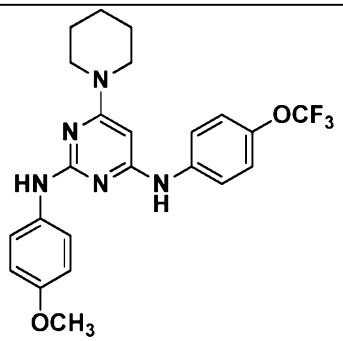
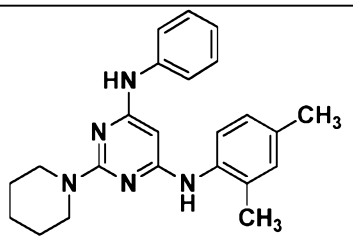
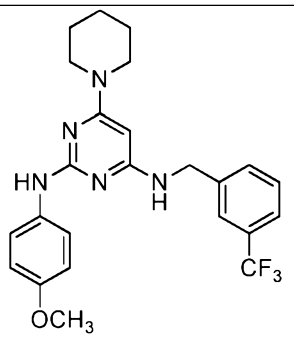
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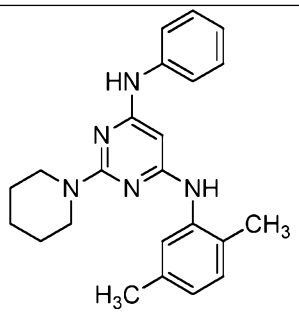
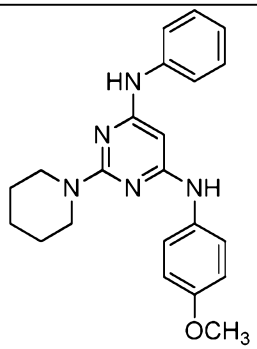
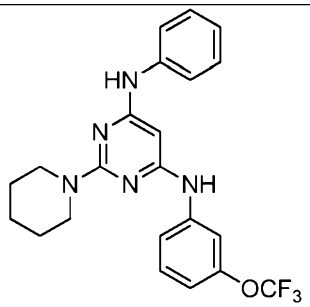
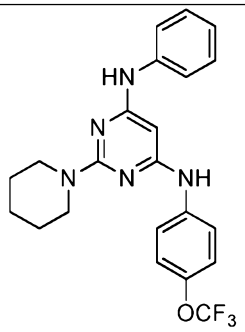
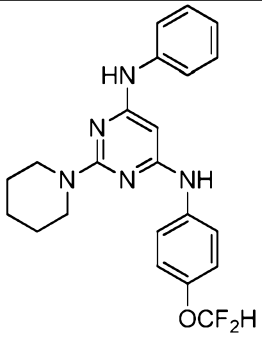
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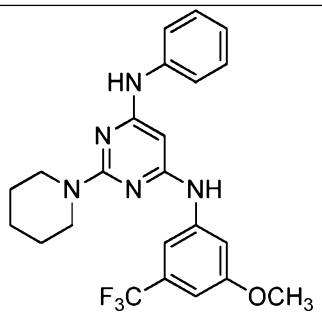
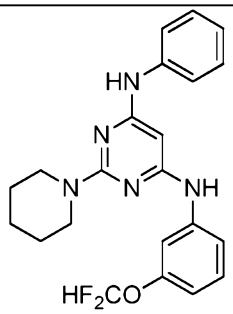
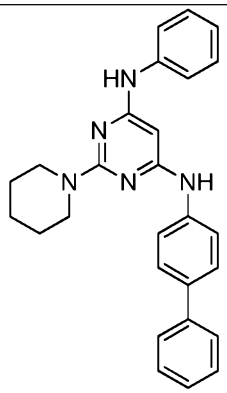
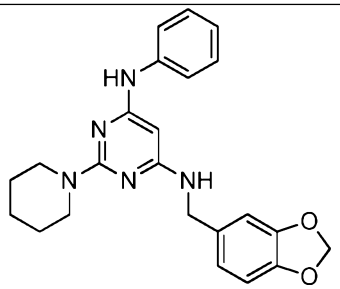
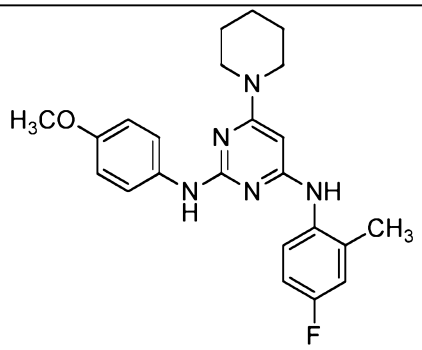
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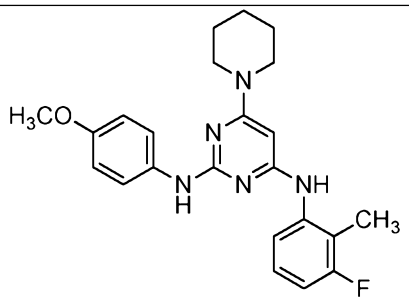
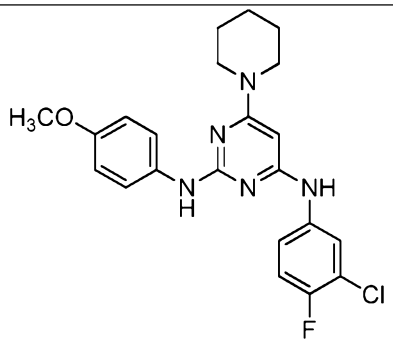
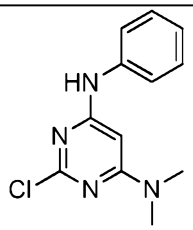
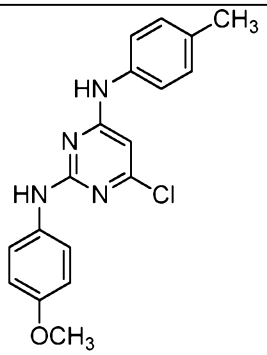
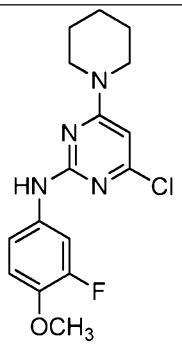
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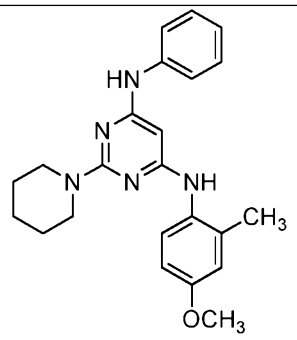
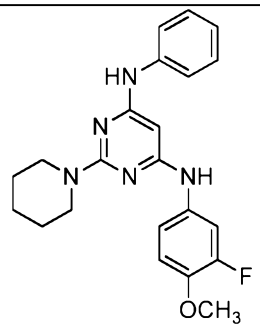
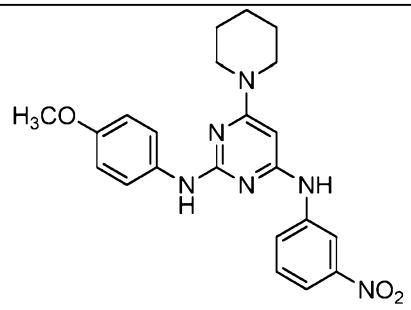
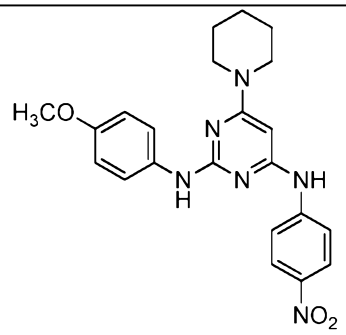
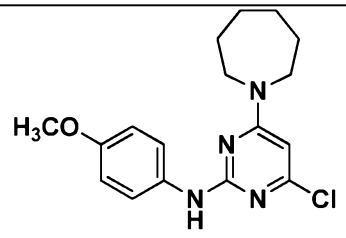
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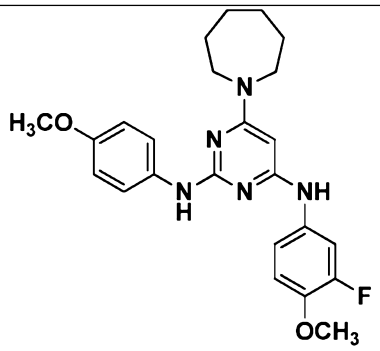
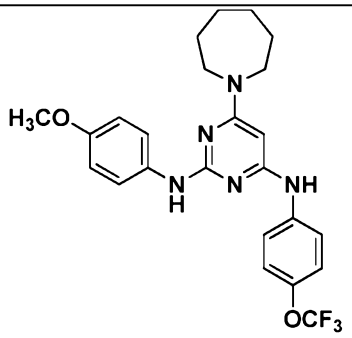
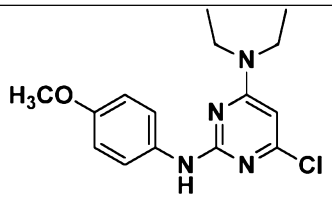
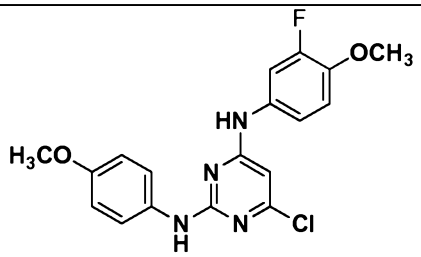
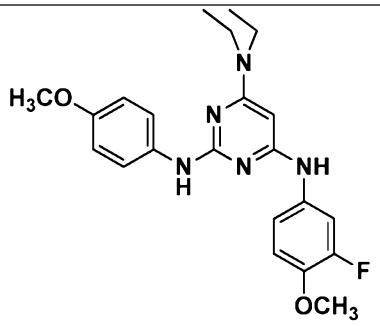
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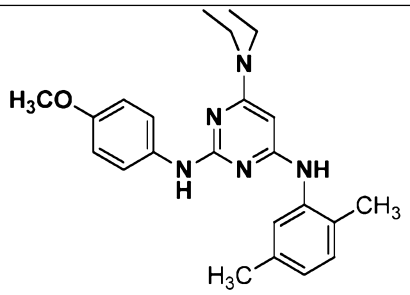
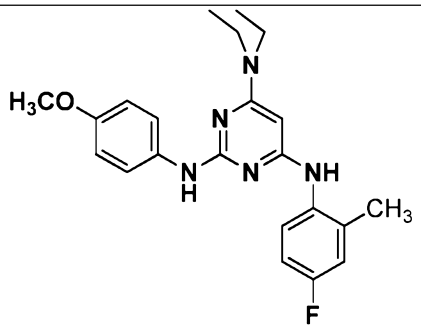
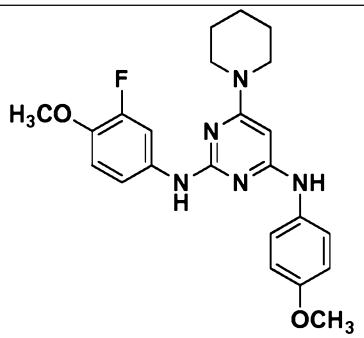
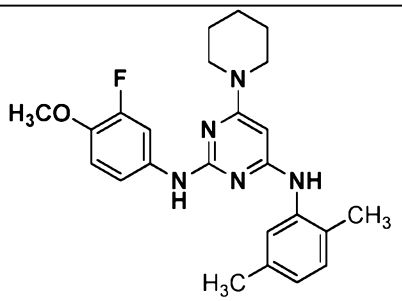
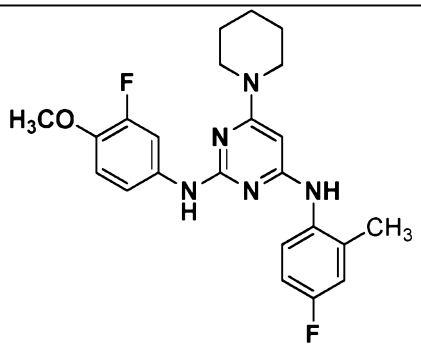
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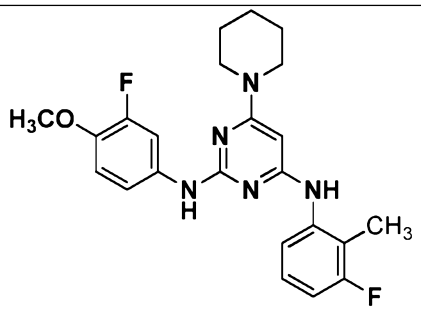
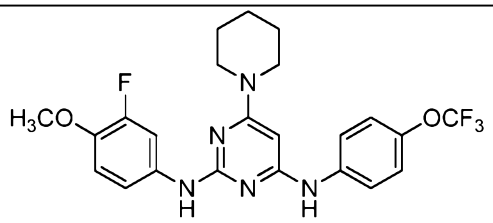
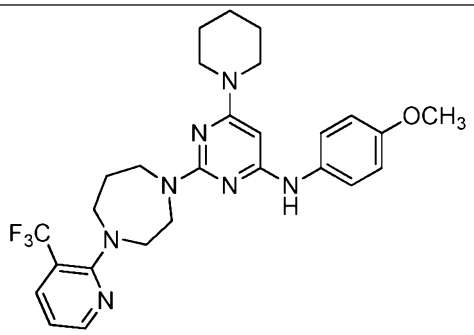
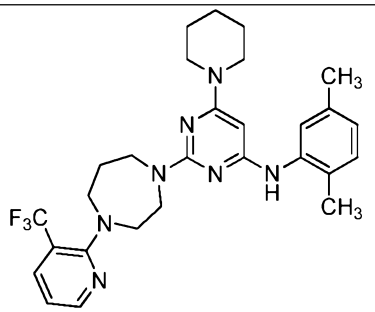
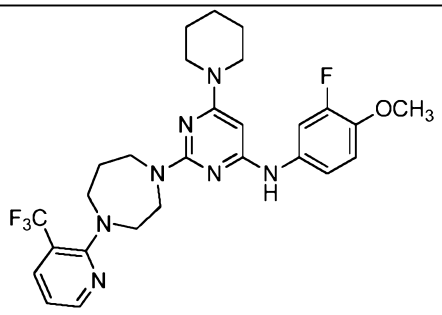
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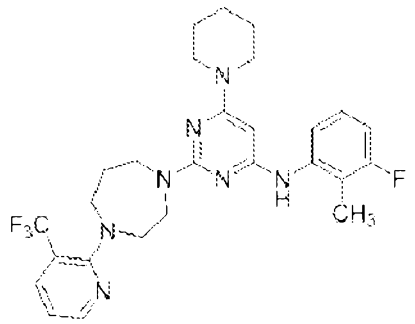
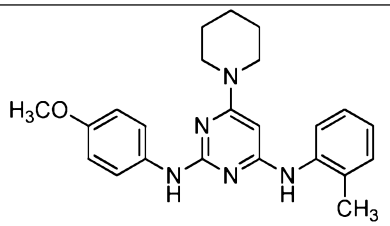
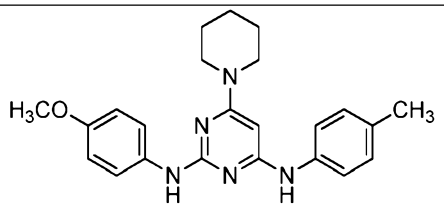
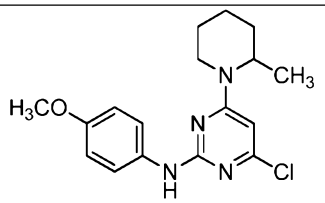
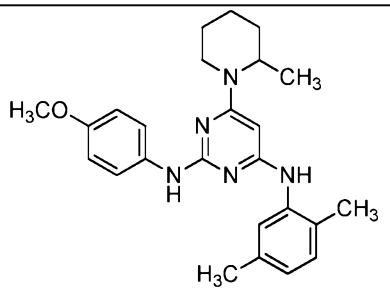
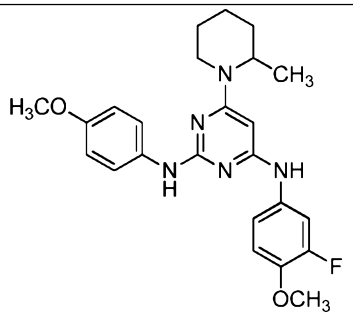
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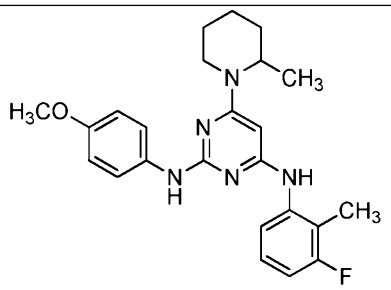
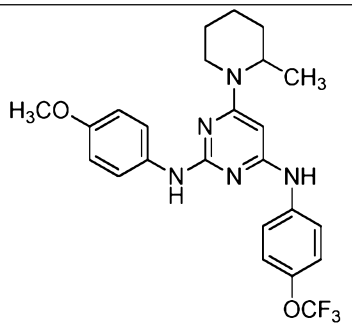
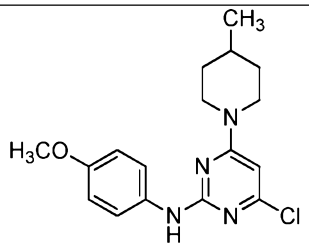
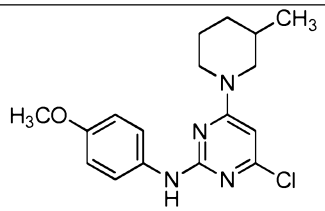
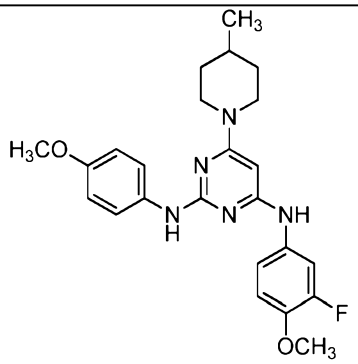
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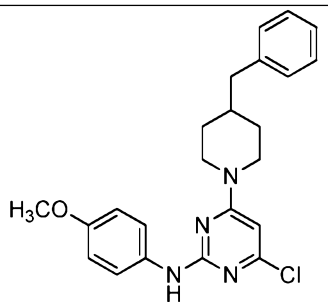
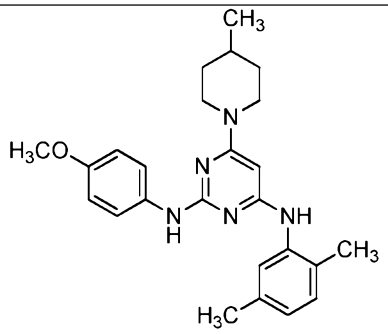
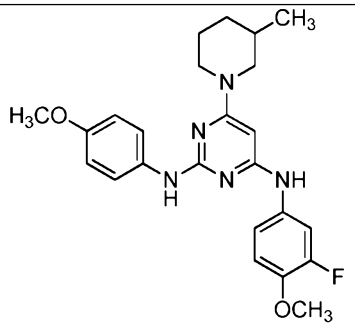
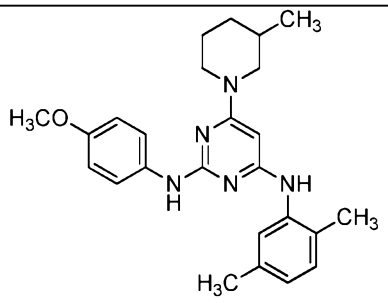
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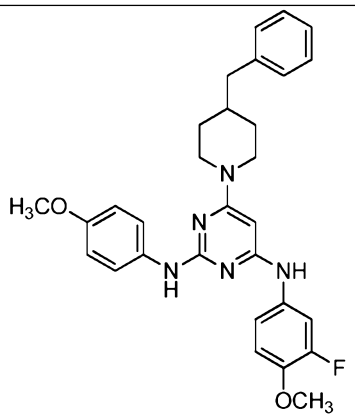
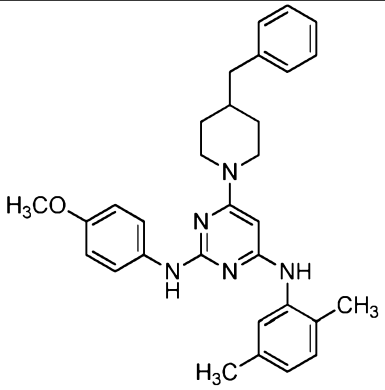
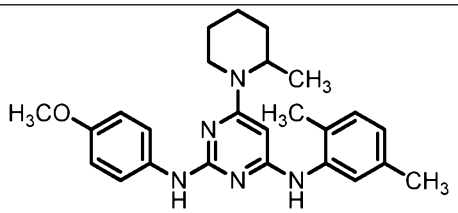
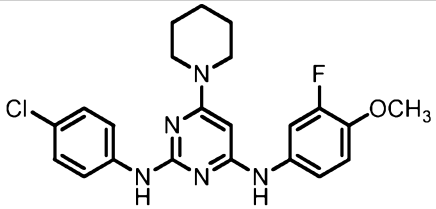
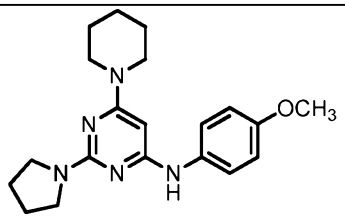
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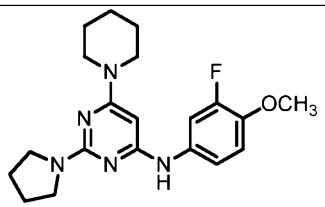
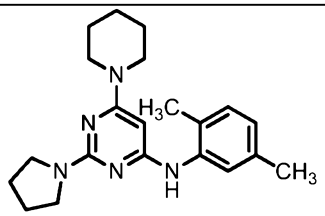
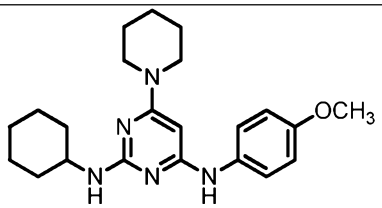
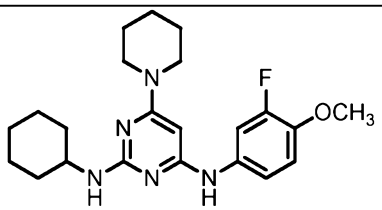
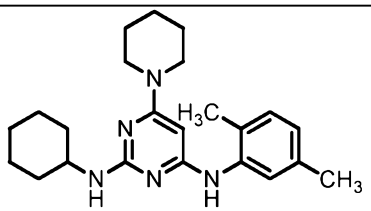
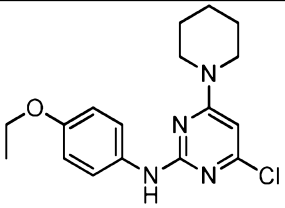
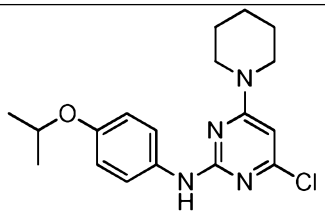
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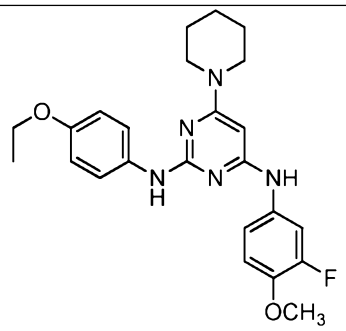
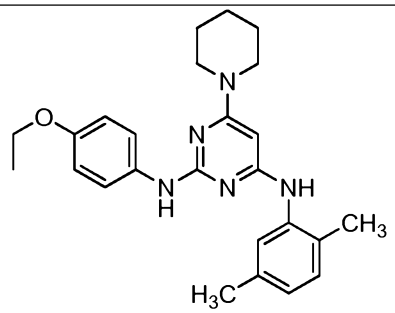
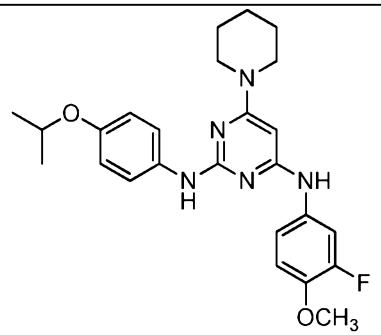
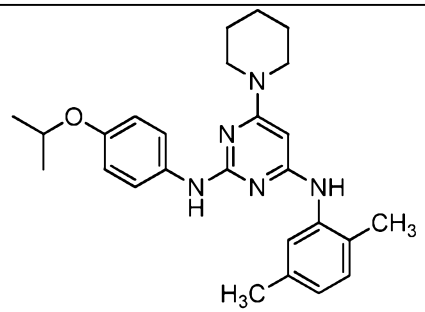
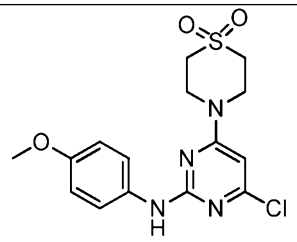
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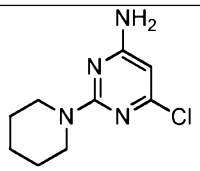
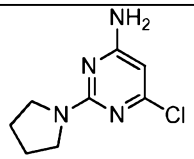
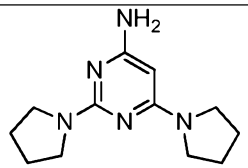
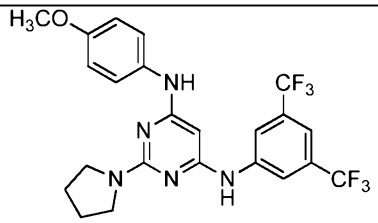
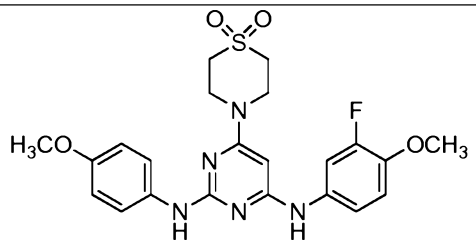
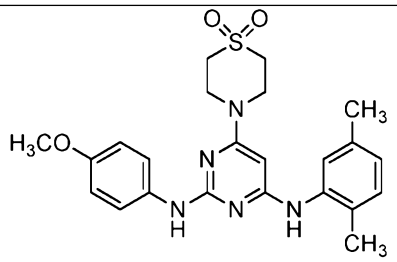
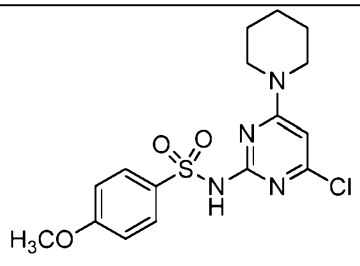
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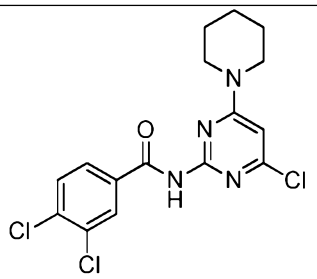
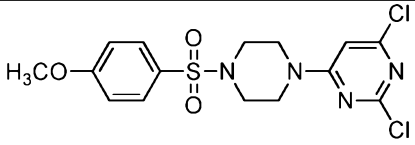
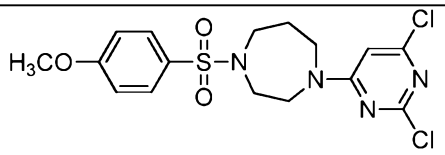
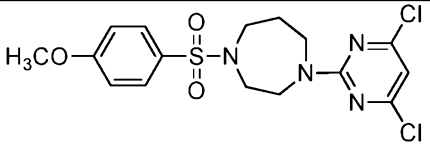
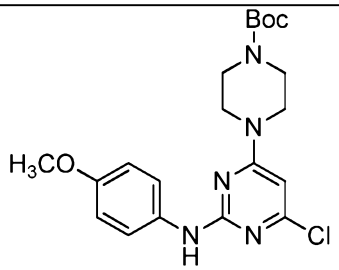
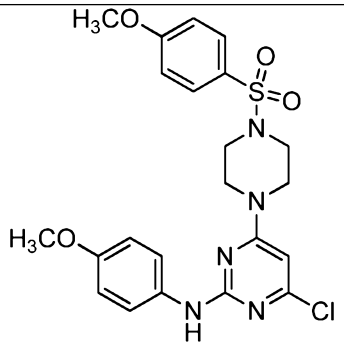
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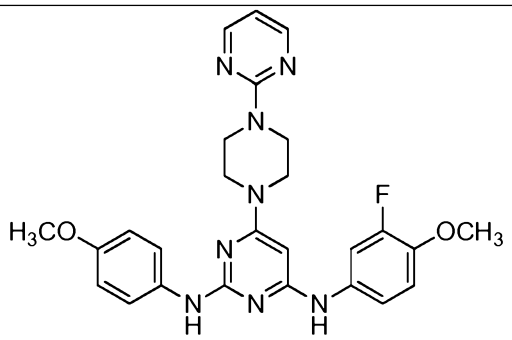
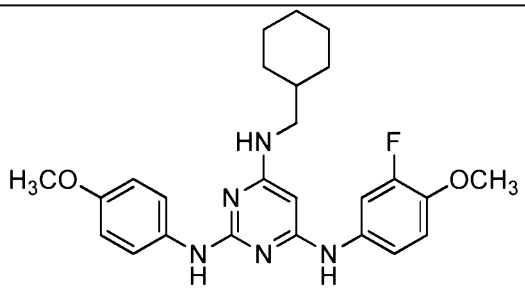
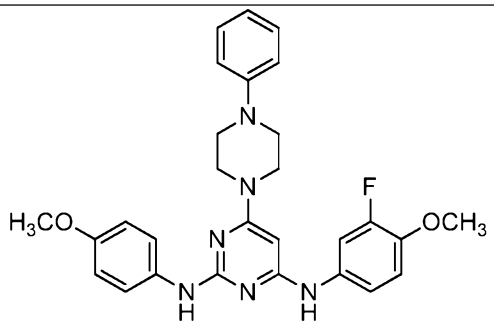
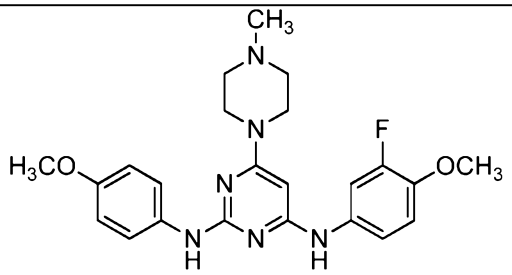
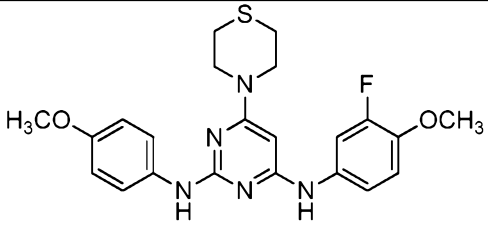
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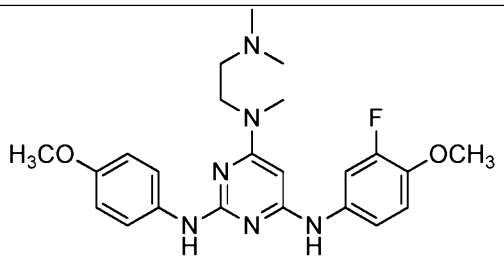
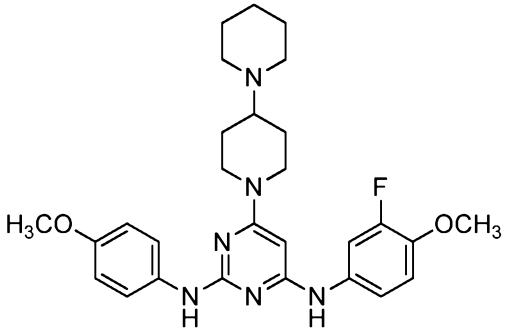
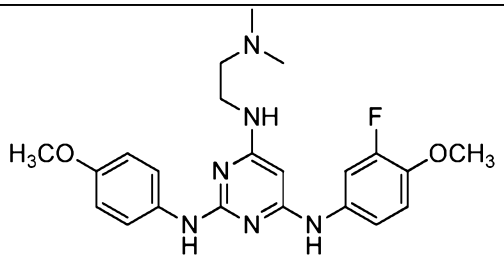
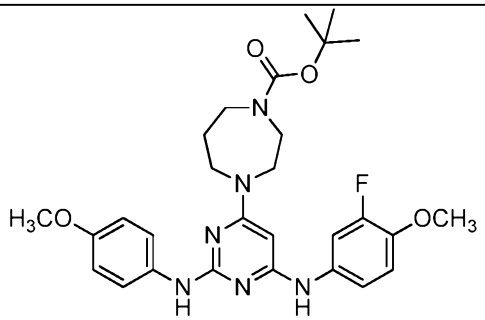
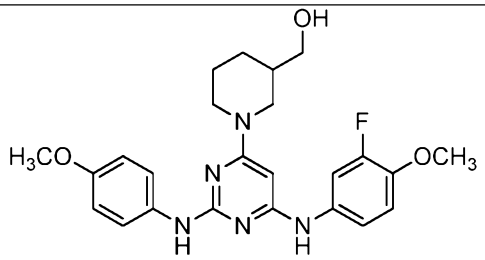
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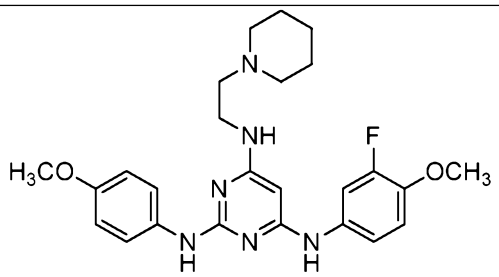
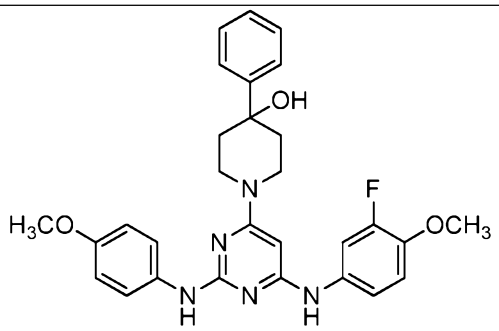
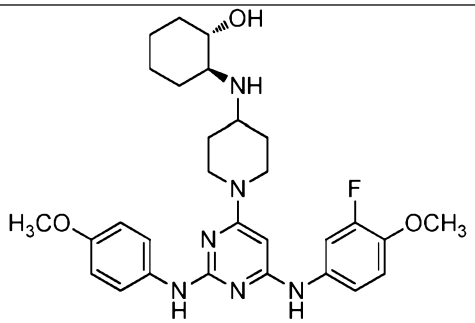
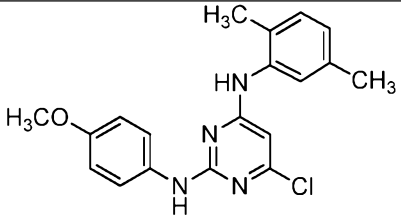
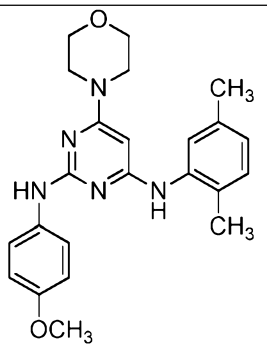
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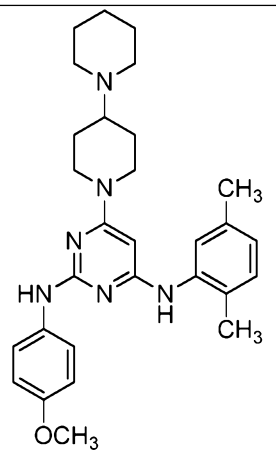
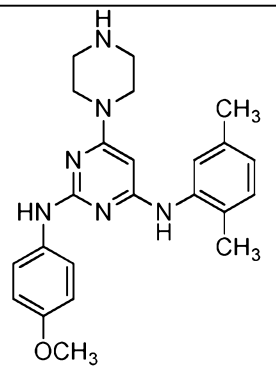
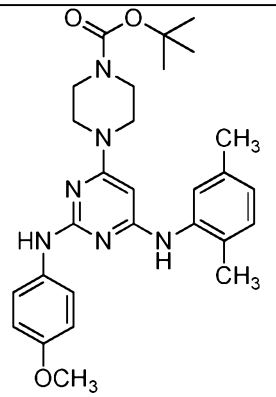
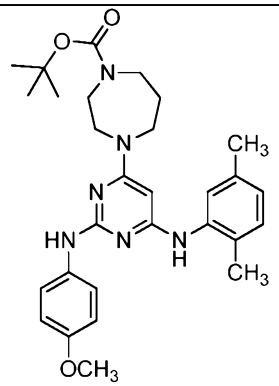
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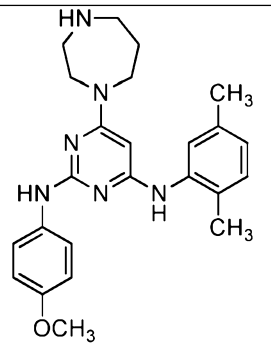
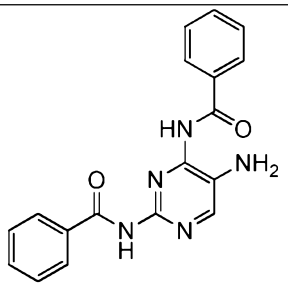
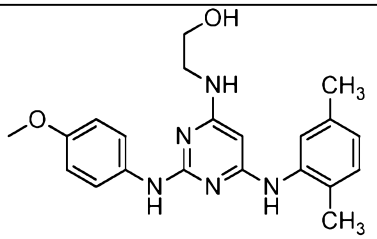
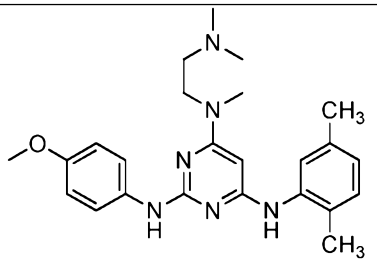
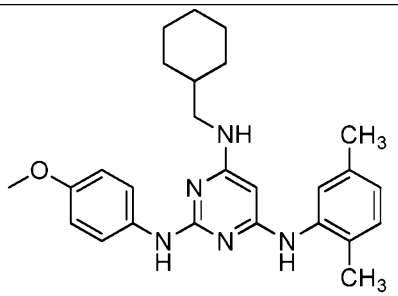
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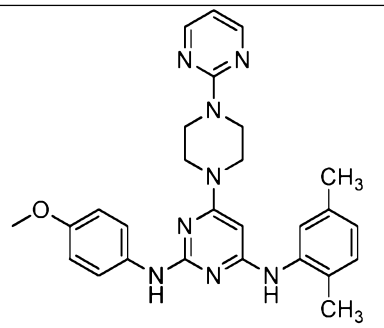
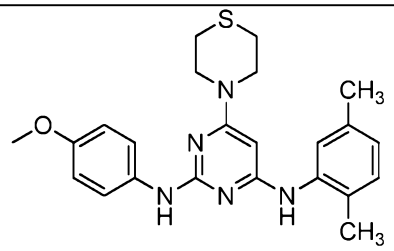
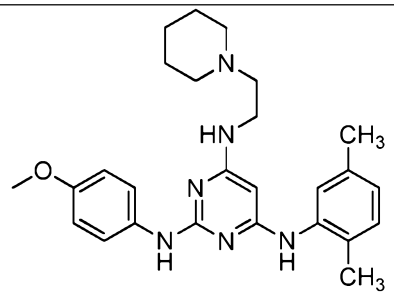
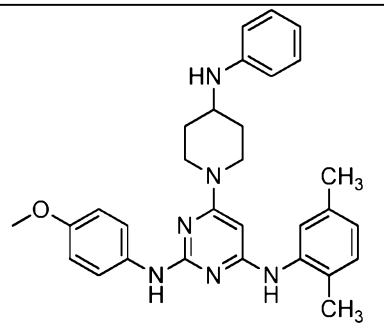
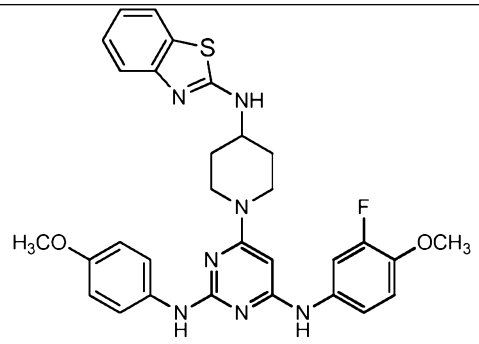
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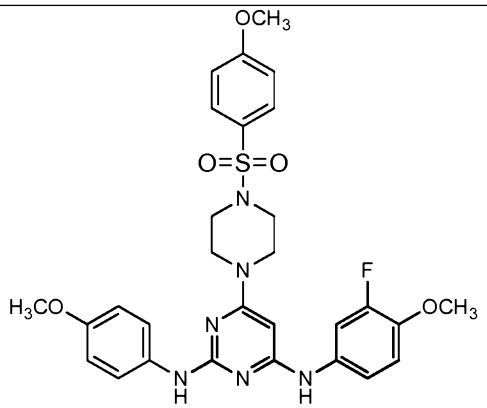
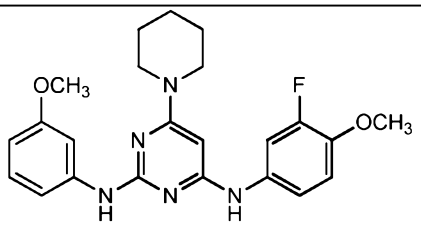
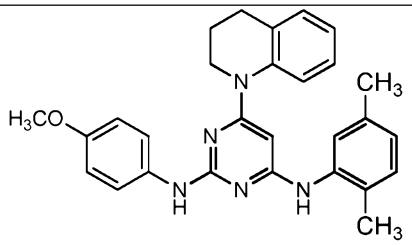
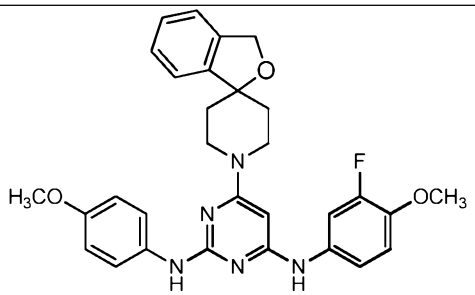
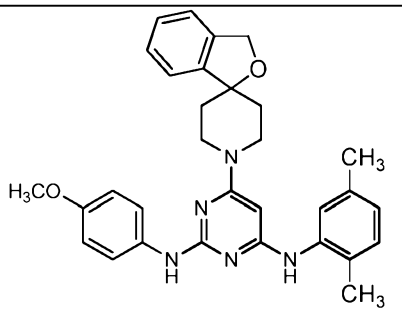
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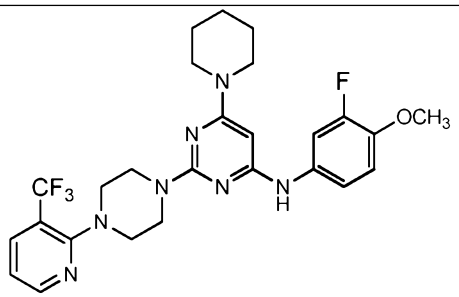
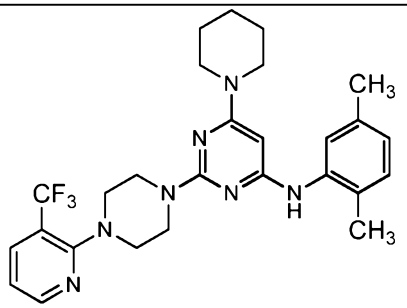
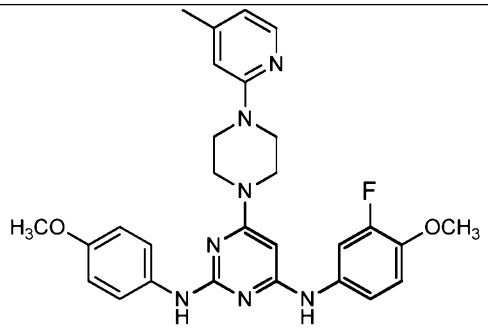
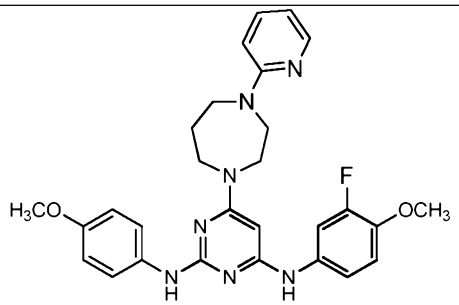
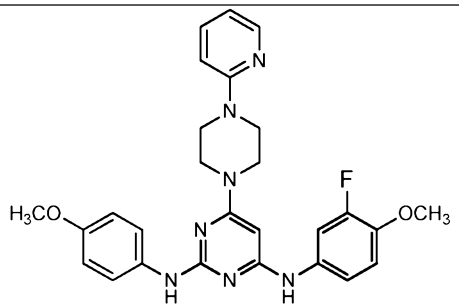
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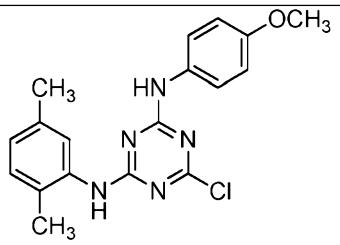
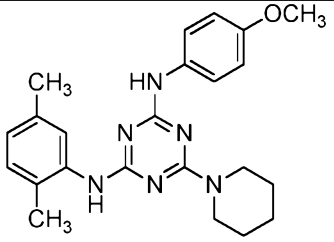
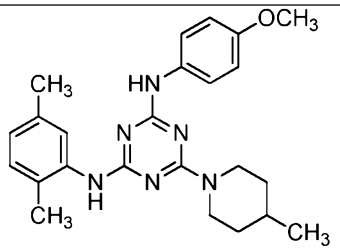
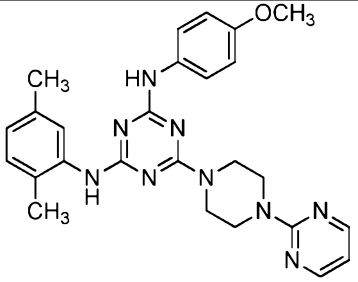
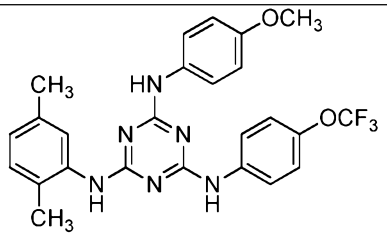
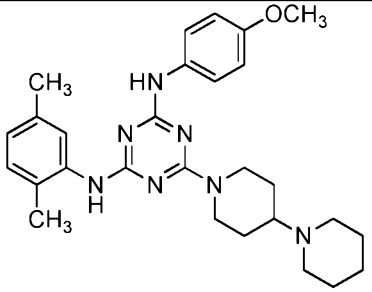
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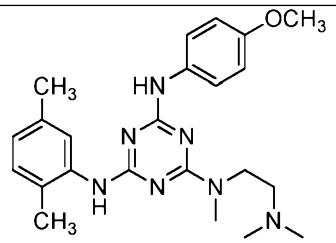
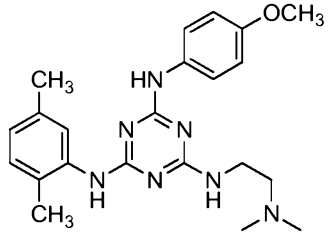
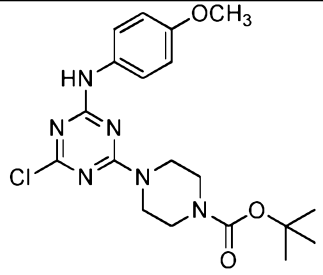
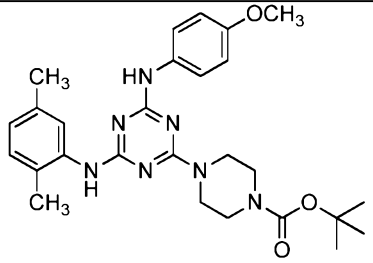
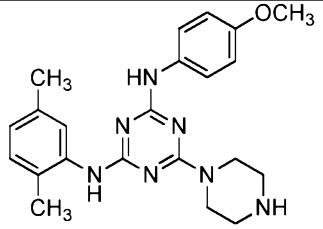
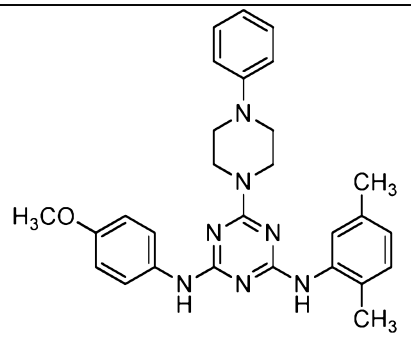
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| 288<br>2365 |  |

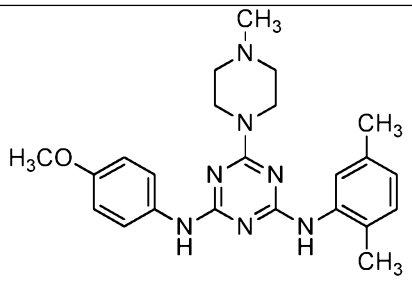
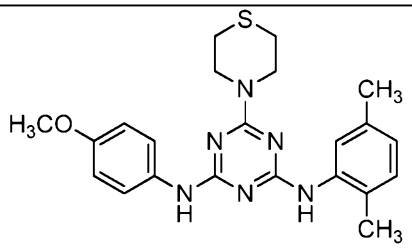
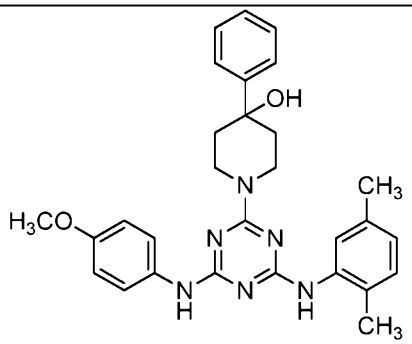
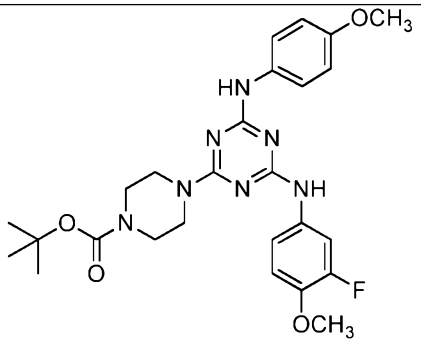
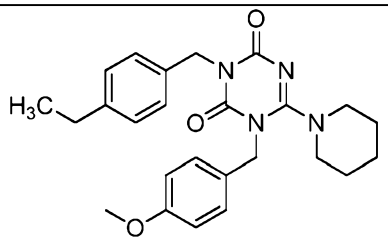
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| 293<br>2380 |  |

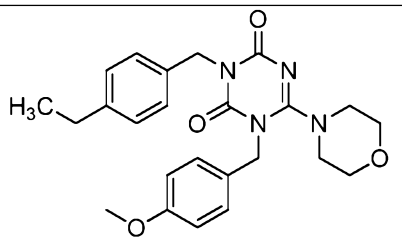
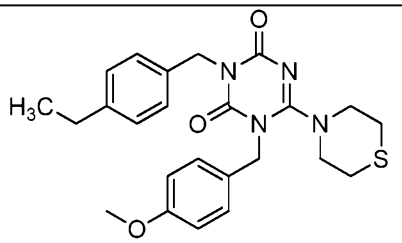
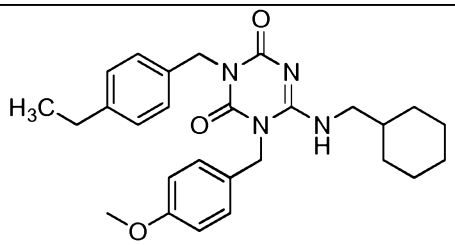
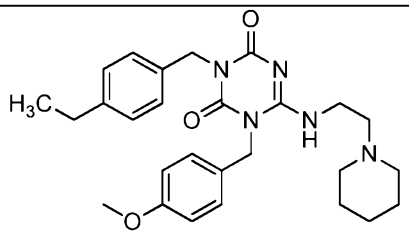
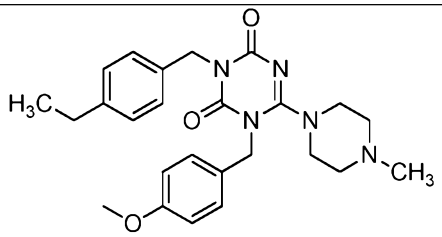
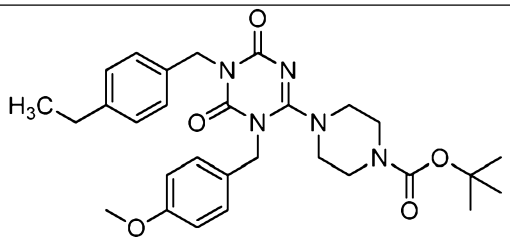
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| 296<br>2384 |  |
| 297<br>2385 |  |
| 298<br>2386 |  |

| | |
|---|---|
| 299<br>2387 |  |
| 300<br>2388 |  |
| 301<br>2389 |  |
| 302<br>2390 |  |
| 303<br>2391 |  |

| | |
|---|---|
| 304<br>2326 |  |
| 305<br>2327 |  |
| 306<br>2328 |  |
| 307<br>2329 |  |
| 308<br>2330 |  |
| 309<br>2331 |  |

| | |
|---|---|
| 310<br>2332 |  |
| 311<br>2333 |  |
| 312<br>2334 |  |
| 313<br>2335 |  |
| 314<br>2336 |  |
| 315<br>2350 |  |

| | |
|---|---|
| 316<br>2351 |  |
| 317<br>2352 |  |
| 318<br>2353 |  |
| 319<br>2355 |  |
| 320<br>2370 |  |

| | |
|---|---|
| 321<br>2371 |  |
| 322<br>2372 |  |
| 323<br>2373 |  |
| 324<br>2374 |  |
| 325<br>2375 |  |
| 326<br>2376 |  |

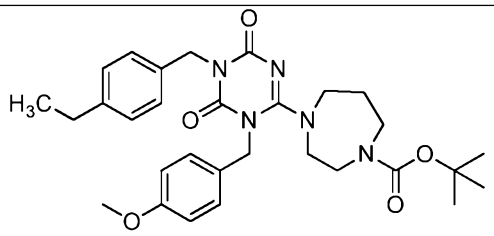
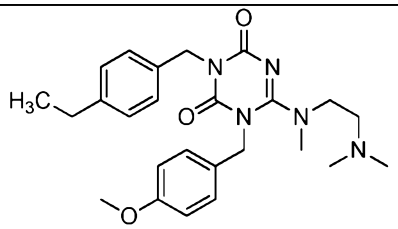
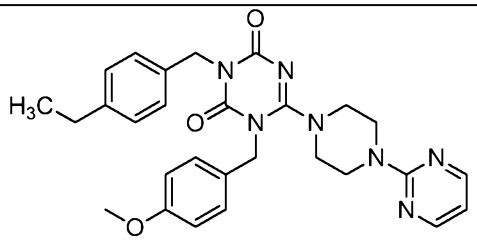
| | |
|---|---|
| 327<br>2377 |  |
| 328<br>2378 |  |
| 329<br>2381 |  |

Table 5A: Exemplary Biodata for Compounds of Formula (VA / VB):

Each line represent data for a single compound from Table 5, above.

| GalR1 (μM) | | GalR2 (μM) | |
|---|---|---|---|
| IC50 | EC50 | IC50 | EC50 |
| 12.8 | NA | 3.33 | NA |
| 4.57 | NA | 0.93 | NA |
| | NA | 8.04 | NA |
| 27.53 | NA | 12.55 | NA |
| 5.93 | NA | 1.06 | NA |
| 5.62 | NA | 1.75 | NA |
| 5.03 | NA | 0.77 | NA |
| 6.82 | NA | 0.55 | NA |
| NA | NA | 1.18 | NA |
| NA | NA | 0.44 | NA |
| NA | NA | 0.38 | NA |
| NA | NA | 0.78 | NA |
| NA | NA | 0.54 | NA |
| NA | NA | 0.43 | NA |
| NA | NA | 0.33 | NA |
| NA | NA | 1.93 | NA |
| NA | NA | 4.57 | NA |
| 8.59 | NA | 1.09 | NA |
| 34.86 | NA | 6.62 | NA |

| | | | |
|---|---|---|---|
| NA | NA | 3.38 | NA |
| 6.934 | NA | 4.15 | NA |
| NA | NA | 3.69 | NA |
| NA | NA | 0.98 | NA |
| NA | NA | 0.38 | NA |
| NA | NA | 4.18 | NA |
| 6.774 | NA | 8.652 | NA |
| 5.488 | NA | 0.772 | NA |
| NA | NA | 2.851 | NA |
| NA | NA | 2.655 | NA |
| NA | NA | 2.588 | NA |
| 14.82 | NA | 5.888 | NA |
| 3.353 | NA | 1.92 | NA |
| 3.902 | NA | 2.084 | NA |
| 6.329 | NA | 2.033 | NA |
| 1.307 | NA | 0.561 | NA |
| 11.26 | NA | --- | 0.196 |
| 6.78 | NA | 1.34 | NA |
| 10.85 | NA | --- | NA |

| | | | |
|---|---|---|---|
| 56.49% @10 µM | NA | 66.16% @10µM | 0.100 |
| 7.933 | NA | ---- | NA |
| NA | NA | 8.106 | NA |
| NA | NA | 2.10 | NA |
| NA | NA | 11.22 | NA |
| NA | NA | 5.378 | NA |
| NA | NA | 4.86 | NA |

Table 5B: Further exemplary biodata for compounds of formula (VA/VB).

Each line provides data for an exemplary compound of the invention of formula (VA / VB) as shown in Table 5, above.

Gal R2, $IC_{50}$ = 32.02 µM

Gal R2, $IC_{50}$ = 24.13 µM

Gal R2, $IC_{50}$ = 8.10 µM

Gal R2, $IC_{50}$ = 49.77 µM

Gal R2, $IC_{50}$ = 2.10 µM

Gal R1, $IC_{50}$ = 17.33 µM

Gal R1 = 5.446 µM; Gal R2 = 5.14 µM

Gal R1 = 21.44 µM; Gal R2 = 21.66 µM

Gal R1 = 3.844 µM; Gal R1 = 3.838 µM

Gal R1 = 6.815 µM; Gal R2 = 24.85 µM

Gal R2 = 36.42 µM

Gal R1 = 16.01 µM

Gal R1 = 24.30 µM

Gal R1 = 2.829 µM ; Gal R2 = 9.069 µM

Gal R2 = 9.8 µM

Gal R1 = 11.21 µM

Gal R1 = 4.318 μM; Gal R2 = 2.279 μM

Gal R1 = 527.45 μM

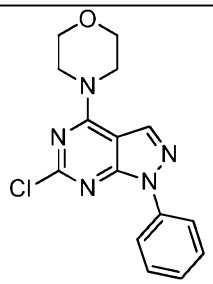
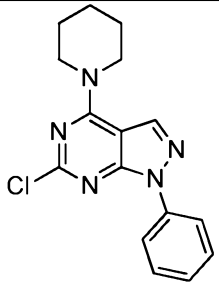
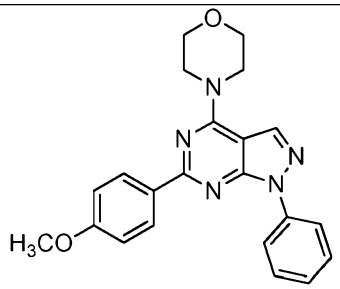
GalR1 = 21.26 μM

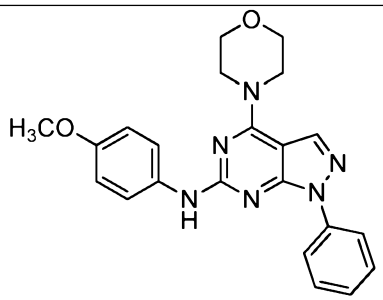
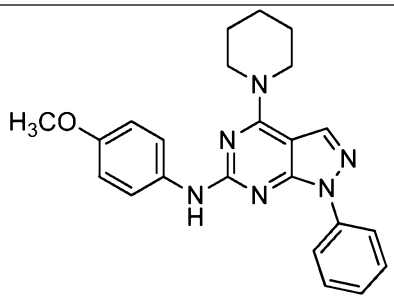
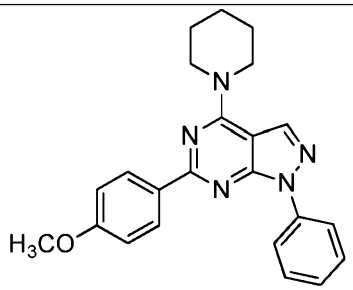
GalR2 = 6.84 μM

GalR2 = 4.47 μM

GalR1 = 7.55 μM

**Table 6: Exemplary Compounds of the Invention—Formula (VI)**

| | |
|---|---|
| 330<br>2313 |  |
| 331<br>2314 |  |
| 332<br>2315 |  |

| | |
|---|---|
| 333<br>2316 |  |
| 334<br>2317 |  |
| 335<br>2318 |  |

In various embodiments, the invention provides a compound of the invention wherein the compound is a modulator of a galanin receptor. Compounds of the invention can be potent modulators of a galanin receptor, of which there are believed to be more than one type. In various embodiments, the compound is a selective modulator of GalR1 or of GalR2, two known classes or forms of galanin receptors. As discussed below, it is within ordinary skill to determine if a compound of the invention is a modulator of a galanin receptor using the methods described herein in combination with the knowledge of a the skilled practitioner. Tables are provided above showing biodata obtained from exemplary compounds of the invention indicating potent bioactivity of the inventive compounds with respect to a galanin receptor.

*Pharmaceutical Compositions*

In various embodiments, the invention provides a pharmaceutical composition comprising a compound of the invention and a pharmaceutically acceptable excipient.

A composition of the compounds of the invention, can provide the compound alone or in combination with another medicament. As set forth herein, compounds of the invention include stereoisomers, tautomers, solvates, prodrugs, pharmaceutically acceptable salts and mixtures thereof. Compositions containing a compound of the invention can be prepared by conventional techniques, e.g. as described in Remington: *The Science and Practice of Pharmacy*, 19th Ed., 1995, incorporated by reference herein. The compositions can appear in conventional forms, for example capsules, tablets, aerosols, solutions, suspensions or topical applications.

Typical compositions include a compound of the invention and a pharmaceutically acceptable excipient which can be a carrier or a diluent. For example, the active compound will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which can be in the form of an ampoule, capsule, sachet, paper, or other container. When the active compound is mixed with a carrier, or when the carrier serves as a diluent, it can be solid, semi-solid, or liquid material that acts as a vehicle, excipient, or medium for the active compound. The active compound can be adsorbed on a granular solid carrier, for example contained in a sachet. Some examples of suitable carriers are water, salt solutions, alcohols, polyethylene glycols, polyhydroxyethoxylated castor oil, peanut oil, olive oil, gelatin, lactose, terra alba, sucrose, dextrin, magnesium carbonate, sugar, cyclodextrin, amylose, magnesium stearate, talc, gelatin, agar, pectin, acacia, stearic acid or lower alkyl ethers of cellulose, silicic acid, fatty acids, fatty acid amines, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, polyoxyethylene, hydroxymethylcellulose and polyvinylpyrrolidone. Similarly, the carrier or diluent can include any sustained release material known in the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax.

The formulations can be mixed with auxiliary agents which do not deleteriously react with the active compounds. Such additives can include wetting agents, emulsifying and suspending agents, salt for influencing osmotic pressure, buffers and/or coloring

substances preserving agents, sweetening agents or flavoring agents. The compositions can also be sterilized if desired.

The route of administration can be any route which effectively transports the active compound of the invention to the appropriate or desired site of action, such as oral, nasal, pulmonary, buccal, subdermal, intradermal, transdermal or parenteral, e.g., rectal, depot, subcutaneous, intravenous, intraurethral, intramuscular, intranasal, ophthalmic solution or an ointment, the oral route being preferred.

If a solid carrier is used for oral administration, the preparation can be tabletted, placed in a hard gelatin capsule in powder or pellet form or it can be in the form of a troche or lozenge. If a liquid carrier is used, the preparation can be in the form of a syrup, emulsion, soft gelatin capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension or solution.

Injectable dosage forms generally include aqueous suspensions or oil suspensions which can be prepared using a suitable dispersant or wetting agent and a suspending agent Injectable forms can be in solution phase or in the form of a suspension, which is prepared with a solvent or diluent. Acceptable solvents or vehicles include sterilized water, Ringer's solution, or an isotonic aqueous saline solution. Alternatively, sterile oils can be employed as solvents or suspending agents. Preferably, the oil or fatty acid is non-volatile, including natural or synthetic oils, fatty acids, mono-, di- or tri-glycerides.

For injection, the formulation can also be a powder suitable for reconstitution with an appropriate solution as described above. Examples of these include, but are not limited to, freeze dried, rotary dried or spray dried powders, amorphous powders, granules, precipitates, or particulates. For injection, the formulations can optionally contain stabilizers, pH modifiers, surfactants, bioavailability modifiers and combinations of these. The compounds can be formulated for parenteral administration by injection such as by bolus injection or continuous infusion. A unit dosage form for injection can be in ampoules or in multi-dose containers.

The formulations of the invention can be designed to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art. Thus, the formulations can also be formulated for controlled release or for slow release.

Compositions contemplated by the present invention can include, for example, micelles or liposomes, or some other encapsulated form, or can be administered in an extended release form to provide a prolonged storage and/or delivery effect. Therefore, the formulations can be compressed into pellets or cylinders and implanted intramuscularly or subcutaneously as depot injections. Such implants can employ known inert materials such as silicones and biodegradable polymers, e.g., polylactide-polyglycolide. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides).

For nasal administration, the preparation can contain a compound of the invention, dissolved or suspended in a liquid carrier, preferably an aqueous carrier, for aerosol application. The carrier can contain additives such as solubilizing agents, e.g., propylene glycol, surfactants, absorption enhancers such as lecithin (phosphatidylcholine) or cyclodextrin, or preservatives such as parabens.

For parenteral application, particularly suitable are injectable solutions or suspensions, preferably aqueous solutions with the active compound dissolved in polyhydroxylated castor oil.

Tablets, dragees, or capsules having talc and/or a carbohydrate carrier or binder or the like are particularly suitable for oral application. Preferable carriers for tablets, dragees, or capsules include lactose, corn starch, and/or potato starch. A syrup or elixir can be used in cases where a sweetened vehicle can be employed.

A typical tablet that can be prepared by conventional tabletting techniques can contain:

| | | |
|---|---|---|
| Core: | | |
| | Active compound (as free compound or salt thereof) | 250 mg |
| | Colloidal silicon dioxide (Aerosil)® | 1.5 mg |
| | Cellulose, microcryst. (Avicel)® | 70 mg |
| | Modified cellulose gum (Ac-Di-Sol)® | 7.5 mg |
| | Magnesium stearate | Ad. |
| Coating: | | |
| | HPMC approx. | 9 mg |
| | *Mywacett 9-40 T approx. | 0.9 mg |

*Acylated monoglyceride used as plasticizer for film coating.

A typical capsule for oral administration contains compounds of the invention (250 mg), lactose (75 mg) and magnesium stearate (15 mg). The mixture is passed through a 60 mesh sieve and packed into a No. 1 gelatin capsule. A typical injectable preparation is produced by aseptically placing 250 mg of compounds of the invention into a vial, aseptically freeze-drying and sealing. For use, the contents of the vial are mixed with 2 mL of sterile physiological saline, to produce an injectable preparation.

*Pharmaceutical Uses*

In various embodiments, the invention provides a method of modulation a galanin receptor comprising contacting the receptor with an effective amount or concentration of a compound of the invention. More specifically, the contacting can be *in vivo* in a human patient. In various embodiments, the amount or concentration of the compound can be effective to selectively modulate GalR1 or GalR2; i.e., the amount or concentration is sufficient to act on one class of receptor but not the other, or not other classes of galanin receptors. In other embodiments, an effective amount or concentration of a compound of the invention in the body of a human patient can effectively modulate both GalR1 and GalR2, or can modulate other classes of galanin receptor.

In various embodiments, the invention provides a method of treatment of a malcondition in a patient for which modulation of a galanin receptor is medically

indicated, comprising administering to the patient a compound of any of formulas (I), (II), (III), (IV), (VA), (VB), or (VI) in a dose, at a frequency, and for a duration sufficient to provide a beneficial effect to the patient. More specifically, the malcondition can comprise epilepsy or seizure disorders, mood disorders including depression and anxiety spectrum disorders; drug addiction including addiction to alcohol or tobacco; autistic spectrum diseases and pervasive development disorders; Alzheimer's disease or other dementias; cognition disorders; cerebral or myocardial stroke; demyelinating diseases including multiple sclerosis, Guillain-Barre syndrome and Charcot-Marie-Tooth disease; neurodegenerative diseases including Parkinson's disease, Lou Gehrig's diseases, Huntington's disease, and HIV dementia; neurotrauma; diabetes, obesity, metabolic syndrome and feeding disorders; solid tumors and leukemia/lymphoma; pain; neuropathies; sleeping disorders and regulation; neuroprotection; and inflammation.

In various embodiments, the invention provides a use of a compound of any of formulas (I), (II), (III), (IV), (VA), (VB), or (VI) in treatment of a malcondition in a human patient. For example, modulation of any galanin receptor is medically indicated for treatment of the malcondition. More specifically, the malcondition can comprise epilepsy or seizure disorders, mood disorders including depression and anxiety spectrum disorders; drug addiction including addiction to alcohol or tobacco; autistic spectrum diseases and pervasive development disorders; Alzheimer's disease or other dementias; cognition disorders; cerebral or myocardial stroke; demyelinating diseases including multiple sclerosis, Guillain-Barre syndrome and Charcot-Marie-Tooth disease; neurodegenerative diseases including Parkinson's disease, Lou Gehrig's diseases, Huntington's disease, and HIV dementia; neurotrauma; diabetes, obesity, metabolic syndrome and feeding disorders; solid tumors and leukemia/lymphoma; pain; neuropathies; sleeping disorders and regulation; neuroprotection; and inflammation.

For example, a compound of the invention termed CYM2503 has been identified by the inventors herein as a GalR2 positive allosteric modulator compound. CYM2503 potentiated the galanin stimulated IP1 accumulation in HEK293 cells stably expressing GalR2 receptors, while it exhibited no detectable affinity for the $^{125}$I galanin binding site of GalR2 receptor, an effect consistent with that of a positive allosteric modulator. In the rat Li-pilocarpine status epilepticus model, CYM2503, injected intraperitoneally, increased

the latency to first electrographic seizure and the latency to first stage 3 behavioral seizure; decreased the latency to the establishment of status epilepticus; dramatically decreased the mortality. In a lithium-pilocarpine seizure model in mice, CYM2503 increased the latency to first electrographic seizure and decreased the total time in seizure. CYM2503 also attenuated electroshock induced seizures in mice.

The compounds of the invention can be administered to a mammal, especially a human in need of such treatment, prevention, elimination, alleviation or amelioration of a malcondition. Such mammals include also animals, both domestic animals, e.g. household pets, farm animals, and non-domestic animals such as wildlife.

The compounds of the invention are effective over a wide dosage range. For example, in the treatment of adult humans, dosages from about 0.05 to about 5000 mg, preferably from about 1 to about 2000 mg, and more preferably between about 2 and about 2000 mg per day can be used. A typical dosage is about 10 mg to about 1000 mg per day. In choosing a regimen for patients it can frequently be necessary to begin with a higher dosage and when the condition is under control to reduce the dosage. The exact dosage will depend upon the activity of the compound, mode of administration, on the therapy desired, form in which administered, the subject to be treated and the body weight of the subject to be treated, and the preference and experience of the physician or veterinarian in charge.

Generally, the compounds of the invention are dispensed in unit dosage form including from about 0.05 mg to about 1000 mg of active ingredient together with a pharmaceutically acceptable carrier per unit dosage.

Usually, dosage forms suitable for oral, nasal, pulmonal or transdermal administration include from about 125 μg to about 1250 mg, preferably from about 250 μg to about 500 mg, and more preferably from about 2.5 mg to about 250 mg, of the compounds admixed with a pharmaceutically acceptable carrier or diluent.

Dosage forms can be administered daily, or more than once a day, such as twice or thrice daily. Alternatively dosage forms can be administered less frequently than daily, such as every other day, or weekly, if found to be advisable by a prescribing physician.

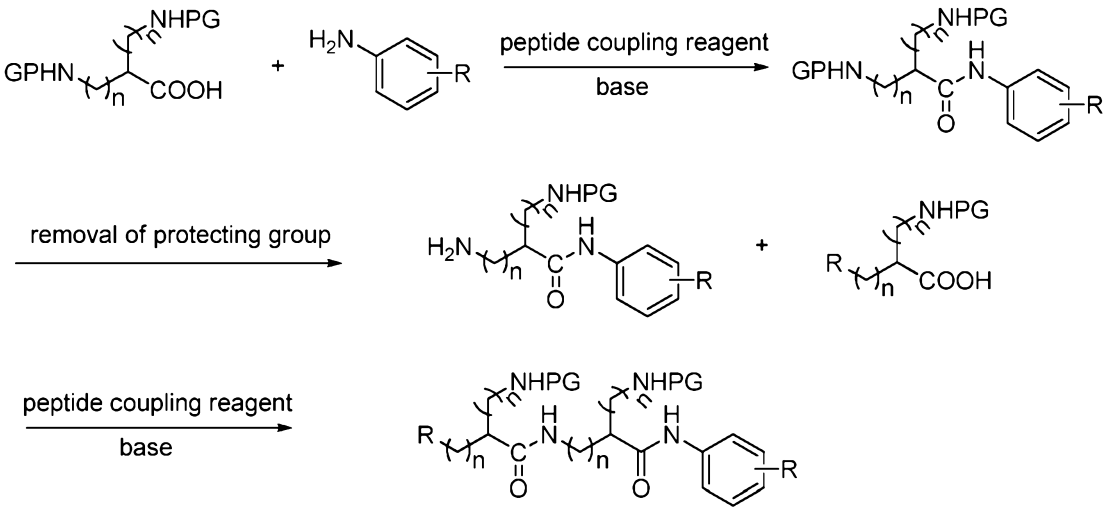
Representative exemplary compounds of the invention and associated biodata are shown above in Tables 1-6.

**Methods of Synthesis**

Compounds of the invention can be prepared by the person of ordinary skill using the procedures provided herein in conjunction with the knowledge of the skilled practitioner.

Method for general synthesis of peptidomimetics

As an example; an N-Protected or N,N'-protected aminoacid or carboxylic acid (1 mmol) in a solvent such as DMF was treated with suitable anilines and amines (1 mmol) , in the presence of a peptide coupling reagent (e.g., HATU) and a base (e.g., DIPEA). The mixture was heated to 70 °C for 10 h or until completion of the reaction. The solvent was removed in vacuo and the residue dissolved in an organic solvent like EtOAc (50 mL). The organic layer was washed with brine and water, and then dried over magnesium sulfate and concentrated under reduced pressure to afford the crude product, which was purified by column chromatography to afford the desired pure product. The protecting group was removed with either base or acid depending on the nature of the protecting group (see Green, protecting groups in Organic Chemistry), followed by coupling with another amino acid, or amine (1 mmol) to give the desired products.

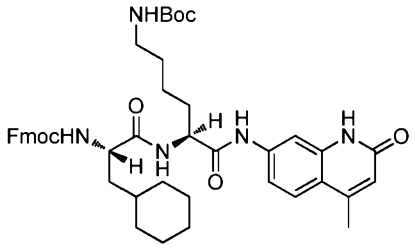



For exemplary compound **3**, Fmoc-Lys(Boc)-OH in DMF was treated with suitable anilines and substituted anilines, HATU, and DIPEA . The mixture was heated to 70 °C for 10 h. After completion of the coupling, the solvent was removed and the residue was dissolved in EtOAc (50 mL). The organic layer was washed with brine and water, and then dried over magnesium sulfate and concentrated under reduced pressure to afford the crude

product. The residue was purified by column chromatography (DCM-MeOH) to provide Fmoc-Lys(Boc)-substituted anilines. The Fmoc group was removed with Piperidine/DMF (10/90 v/v), followed by coupling of Fmoc-Cha-OH to give compound **3**.

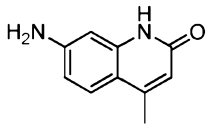
Synthetic Procedure for Compound **3**

*(9H-fluoren-9-yl)methyl((S)-1-(((S)-6-(tert-butoxycarbonyl)amino-1-((4-methyl-2-oxo-1,2-dihydroquinolin-7-yl)amino)-1-oxohexan-2-yl)amino)-3-cyclohexyl-1-oxopropan-2-yl)carbamate*




Step 1.

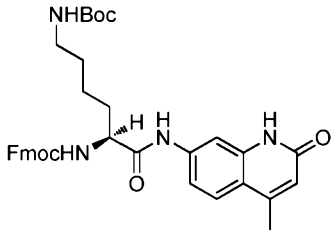
*7-amino-4-methylquinolin-2(1H)-one.*




A mixture of phenylenediamine (2 mmol), methyl 3-oxobutanoate (2 mmol), and water (2 mL) were added into a 20-mL glass tube with a magnetic stirring bar and covered with a plastic cap. The synthesis was carried out at 150 °C for 80 min under 90 W of microwave irradiation using a Biotage Corp. AB Initiator microwave reactor with an automated Explorer unit. Completion of the reaction was checked by TLC at the end of 80 min. All products were left at 4 °C overnight, collected by suction filtration, washed with water and then hexane, and dried. 7-amino-4-methylquinolin-2(1H)-one was used for next step without further purification.

Step 2.

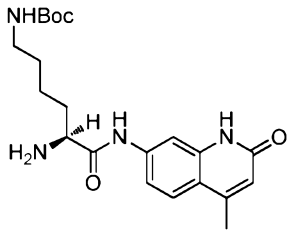
*(S)-(9H-fluoren-9-yl)methyl tert-butyl(6-((4-methyl-2-oxo-1,2-dihydroquinolin -7-yl) amino)-6-oxohexane-1,5-diyl)dicarbamate*




Fmoc-Lys(Boc)-OH (1 mmol) in DMF (20 mL) was added 7-amino-4-methylquinolin-2 (1H)-one (1 mmol), HATU (1 mmol), and DIPEA (1 mmol). The mixture was heated to 50 °C for 10 h. After completion of the reaction, the solvent was removed and the residue was dissolved in EtOAc (50 mL). The organic layer was washed with brine and water, and then dried over magnesium sulfate and concentrated under reduced pressure to afford the crude product. The residue was purified by column chromatography (DCM-MeOH) to provide (S)-(9H-fluoren-9-yl)methyl tert-butyl(6-((4-methyl-2-oxo-1,2-dihydroquinolin-7-yl)amino)-6- oxohexane-1,5-diyl)dicarbamate

Step 3.

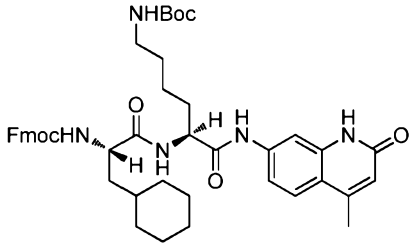
*(S)-tert-butyl (5-amino-6-((4-methyl-2-oxo-1,2-dihydroquinolin-7-yl)amino) -6-oxohexyl)carbamate*




(S)-(9H-fluoren-9-yl)methyl tert-butyl(6-((4-methyl-2-oxo-1,2-dihydroquinolin-7-yl)amino)-6- oxohexane-1,5-diyl)dicarbamate (1 mmol) in DMF (10 mL) was added piperidine (1 mL). The resulting mixture was stirred at r.t. for 1 h. After completion of the reaction, the solvent was removed and the residue was dissolved in DCM (50 mL), The organic layer was washed with brine and water, and then dried over magnesium sulfate and concentrated under reduced pressure to afford the crude product. The residue was purified by column chromatography (DCM-MeOH) to give (S)-tert-butyl (5-amino-6-((4-methyl-2-oxo-1,2-dihydroquinolin-7-yl)amino) -6- oxohexyl)carbamate.

Step 4.

*(9H-fluoren-9-yl)methyl((S)-1-(((S)-6-(tert-butoxycarbonyl)amino-1-((4-methyl -2-oxo-1,2-dihydroquinolin-7-yl)amino)-1-oxohexan-2-yl)amino)-3-cyclohexyl-1-oxopropan-2-yl)carbamate*




Fmoc-3-cyclohexyl-L-alanine (1 mmol) in DMF (20 mL) was added (S)-tert-butyl (5-amino -6-((4-methyl-2-oxo-1,2-dihydroquinolin-7-yl)amino) -6- oxohexyl)carbamate. (1 mmol), HATU (1 mmol), and DIPEA (1 mmol). The mixture was stirred at r.t. for 10 h. After completion of the reaction, the solvent was removed and the residue was dissolved in EtOAc (50 mL). The organic layer was washed with brine and water, and then dried over magnesium sulfate and concentrated under reduced pressure to afford the crude product. The residue was purified by column chromatography (DCM-MeOH) to provide (9H-fluoren-9-yl)methyl((S)-1-(((S)-6-(tert-butoxy carbonyl)amino-1-((4-methyl-2-oxo-1,2-dihydroquinolin-7-yl)amino)-1-oxohexan-2-yl)amino)-3- cyclohexyl-1-oxopropan-2-yl)carbamate

**Biological Materials and methods**

Animals

All mice used in the experiments were 8-week-old male C57BL/6 obtained from the Scripps Research Institute. Male Wistar rats weighing 240-260 g were obtained from Simonsen Laboratories (Gilroy, CA). The animals were housed at a 12 hr light/dark cycle with *ad libitum* access to water and food. Animal care, maintenance, and experimental procedures were according to the *National Institutes of Health Guide for the Care and Use of Laboratory Animals*.

Materials

All cell culture supplies were from Invitrogen (Carlsbad, San Diego). LiCl and pilocarpine HCl were from Sigma-Aldrich (Saint Louis, MO). Methylscopolamine was from Pfaltz & Bauer (Waterbury, CT). 2-Hydroxypropyl-$\beta$-cyclodextrin (HBC) was

purchased from Acros Organics (Fair Lawn, NJ). $^{125}$I porcine galanin and rat galanin were from PerkinElmer (Massachusetts) and Biopeptide (San Diego, CA), respectively.

Cell lines

The cDNA encoding rat GalR1 and rat GalR2 receptor was generated by RT-PCR with total RNA prepared from rat hypothalamus and cloned into a TA vector (Invitrogen). The entire coding sequence of each receptor was subcloned into pCMV vector (Clontech) and verified by sequencing. After transfecting CHO cells and HEK293 cells with the pCMV vectors containing rat GalR1 and rat GalR2 receptor coding sequences, respectively, cell lines were selected by the antibiotics G418, followed by limited dilution to obtain single clones. Ten clones from each cell line were screened with $^{125}$I porcine galanin binding ($^{125}$I porcine galanin 0.1 nM; 5 μM cold rat galanin as competitor) and clones with highest binding (one for each cell type) were expanded and used in subsequent experiments. $^{125}$I galanin saturation binding assays were performed on the CHO-GalR1 and HEK293-GalR2 cell lines selected by the screening. Nonlinear regression analysis of specific binding data indicated a Bmax of 1411 ± 267 fmol/mg membrane protein and a Kd value of 0.23 ± 0.45 nM in the CHO-GalR1 cells; a Bmax of 497 ± 60 fmol/mg membrane protein and a Kd of 2.0 ± 1.2 nM in the HEK293-GalR2 cells (mean ± SEM, n=3).

Radioligand binding assay

Ligand competition binding of $^{125}$I porcine galanin to the membrane preparations (29) was performed in a volume of 150 μL in a 96 well plate. Cell membranes were diluted in Hepes buffer containing 25 mM Hepes, pH 7.4, 10 mM MgCl2, 1mM CaCl2, 0.5% BSA, 1x protease inhibitor. $^{125}$I porcine galanin was diluted in Tris buffer (50 mM Tris-HCl, pH 7.4, 14 mM MgCl2, 2.45% BSA). Compounds and rat galanin were diluted in 20% DMSO. Eighty μl cell membrane (2.5 μg for GalR1 and 5 μg for GalR2 binding), 55 μl $^{125}$I porcine galanin and 15 μl compound/galanin preparations were combined and incubations were carried out at room temperature for 1 h. $^{125}$I porcine galanin was used at 0.1 nM and 0.15 nM for GalR1 and GalR2 binding respectively. The reactions were terminated by rapid vacuum filtration through glass fiber filters (Packard, Meriden, CT), which had been pretreated with 0.3% polyethylenimine. After three washes with cold PBS (pH 7.4) containing 0.01% (vol/vol) Triton X-100, the filter was counted with Cobra II

auto-γ-counting systems (Packard Bioscience). All data were analyzed by nonlinear regression (GraphPad Prism, San Diego, CA).

cAMP assay and IP1 assay

cAMP and IP1 levels were measured with a cAMP dynamic 2 kit and a IP-One Tb kit (both from Cisbio, Bedford, MA), respectively, following the manufacturer's instruction. Assays were performed in 384-well plates and 2500 cells/well and 7500 cells/well were used in cAMP and IP1 assay, respectively. The signal was quantified with TECAN Infinite F500. Assays were performed in triplicates and the results were analyzed by nonlinear regression (GraphPad).

Li-pilocarpine seizure experiment in the mice

Under isoflurane anesthesia, mice were surgically implanted with recording electrodes according to stereotaxic guidance as previously described in detail (46, 47). Electrodes were fabricated with Teflon-insulated, 0.25-mm outside diameter wire (Plastics One, Roanoke, VA). Two small holes were drilled on the skull over right and left parietal lobes for implantation of recording electrode and reference electrode, respectively. The biopotential lead wires were attached to small stainless steel screws (#80 × 1/8 in., Small Parts, Miami Lakes, FL). The electrodes were then connected to a multipin socket and secured to the skull by acrylic dental cement. Mice were allowed to recover for 3-5 days before the experiment.

Mice were injected with LiCl (3 mEq/kg, i.p.), followed 16-20 hrs later with pilocarpine HCl (150 mg/kg, s.c.) to induce seizure. Methylscopolamine (1 mg/kg, s.c.) was injected 30 min prior to pilocarpine to protect mice from peripheral cholinergic effects. Vehicle or compound (vehicle was 40% HBC + 2% DMSO, i.p.) was injected 15 min prior to pilocarpine. Reference drug was levetiracetam (50 mg/kg). Levetiracetam is a newer generation anticonvulsant/antiepileptic drug with novel mechanism of action and with fewer side effects compared to the older generations of anticonvulsants. Similarly to the GalR1 and GalR2 signaling mediated anticonvulsant action, levetiracetam might exert its anticonvulsant effects by inhibiting the release of excitatory neurotransmitters (48). Furthermore, Levetiracetam was previously shown to suppress Li-pilocarpine induced seizure in mice and rats (48, 49), thus it is a suitable comparator in this seizure

model. EEG was recorded with BIOPAC Recording System (Biopac system Inc, Santa Barbara, CA) with a sampling frequency of 200 Hz and a filter setting of 0.5 Hz high pass and 100 Hz low pass. Seizures were defined as clusters of spikes with the frequency of 3 Hz or more and duration of 3 sec or longer.

Mouse electroshock seizure model

Mice were administered vehicle (40% HBS + 2% DMSO) or CYM2503 i.p. 15 min prior to electroshock. The electroshock was delivered through auricular electrodes (unidirectional rectangular pulse 0.5 msec, 100 pulses/sec, 3s, 35 mA; Pulse Generator 57800-001 from UGO Basile, Collegeville, PA) while holding the mouse in supine position in a researcher's hand. Full tonic extension of both hind limbs was taken as the endpoint. The experiment was performed between 2 to 5 PM. All mice were videotaped and the latency to hindlimb extension was scored by a person who was blind to the treatment. If extension did not occur within 6 seconds, a value of 6 seconds was recorded (50).

Lithium-pilocarpine seizures in rats

Male Wistar rats weighing 240-260 g were implanted under isoflurane anesthesia with stainless steel skull screws to serve as epidural EEG electrodes. A ground screw was placed in the rostrum and two others, one on each side, were placed approximately 1mm anterior to lambda and 1 mm from the midline. A tripolar electrode was connected to skull screws and anchored with dental cement. After surgery, animals were placed in an observation chamber on a temperature pad until they recovered. Animals were allowed to recover for 7 to 10 days and were then given 3 mEq/kg LiCl s.c. 16 hours prior to initiating seizures. For recordings, which began 15 min before pilocarpine injection, EEG electrodes were connected to tethered cables with swivel mounts (Plastics One, Roanoke, VA), which fed the amplified signal to a monitoring and recording system. Seizures were initiated by the s.c. injection of 60 mg/kg pilocarpine and 1 mg/kg methylscopolamine. Test compounds and vehicle were injected i.p. immediately before pilocarpine. Vehicle consisted of 2.5% DMSO in 40% HBC. Levetiracetam was used at 50 mg/kg. EEG was continuously recorded for 18 to 24 hours using a BIOPAC (Santa Barbara, CA) MP100 work station. Seizures were defined as a discharge lasting at least 3 s, with a mean frequency higher than 3 Hz, coefficient of variation $\geq$65, and amplitude 2.7 times higher

than baseline. Scoring of behavioral seizures used a modified Racine scale (51). Other measurements were performed by inspection or by computer analysis of the recordings using Stellate Harmonie software, as previously described (52).

Statistical analysis

Seizure data were analyzed by one-way ANOVA followed by Dunnett's post-hoc comparison of the test compounds to vehicle.

Evaluations

It is within ordinary skill to evaluate any compound disclosed and claimed herein for effectiveness in modulation of a galanin receptor and in the various cellular assays using the procedures described above or found in the scientific literature. Accordingly, the person of ordinary skill can prepare and evaluate any of the claimed compounds without undue experimentation.

Any compound found to be an effective modulator of a galanin receptor can likewise be tested in animal models and in human clinical studies using the skill and experience of the investigator to guide the selection of dosages and treatment regimens.

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While the invention has been described and exemplified in sufficient detail for those skilled in this art to make and use it, various alternatives, modifications, and improvements will be apparent to those skilled in the art without departing from the spirit and scope of the claims.

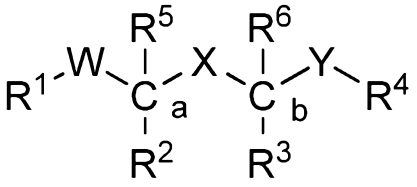
All patents and publications referred to herein are incorporated by reference herein to the same extent as if each individual publication was specifically and individually indicated to be incorporated by reference in its entirety.

The terms and expressions which have been employed are used as terms of description and not of limitation, and there is no intention that in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the invention claimed. Thus, it should be understood that although the present invention has been specifically disclosed by preferred embodiments and optional features, modification and variation of the concepts herein disclosed may be resorted to by those skilled in the art, and that such modifications and variations are considered to be within the scope of this invention as defined by the appended claims.

## CLAIMS

What is claimed is:

1. A galanin receptor-modulatory compound of formula (I):



(I)

wherein W, X and Y are each independently ($C_1$-$C_5$)alkylene, $(CH_2)_{0-2}O(CH_2)_{0-2}$, $(CH_2)_{0-2}C(=O)(CH_2)_{0-2}$, $(CH_2)_{0-2}CR_2(CH_2)_{0-2}$, $(CH_2)_{0-2}C(OR)(R)(CH_2)_{0-2}$, $O(CR_2)_nO$ wherein n is 1 to 4, $(CH_2)_{0-2}N(R)(CH_2)_{0-2}$, $(CH_2)_{0-2}S(CH_2)_{0-2}$, $(CH_2)_{0-2}SO(CH_2)_{0-2}$, $(CH_2)_{0-2}SO_2(CH_2)_{0-2}$, $(CH_2)_{0-2}SO_2N(R)(CH_2)_{0-2}$, $(CH_2)_{0-2}SO_3(CH_2)_{0-2}$, $(CH_2)_{0-2}C(=O)C(=O)(CH_2)_{0-2}$, $(CH_2)_{0-2}C(=O)CH_2C(=O)$ $(CH_2)_{0-2}$, $(CH_2)_{0-2}C(=S)(CH_2)_{0-2}$, $(CH_2)_{0-2}C(=O)O(CH_2)_{0-2}$, $(CH_2)_{0-2}OC(=O)(CH_2)_{0-2}$, $(CH_2)_{0-2}OC(=O)O(CH_2)_{0-2}$, $(CH_2)_{0-2}C(=O)N(R)(CH_2)_{0-2}$, $(CH_2)_{0-2}OC(=O)N(R)(CH_2)_{0-2}$, $(CH_2)_{0-2}C(=S)N(R)(CH_2)_{0-2}$, $(CH_2)_{0-2}NHC(=O)(CH_2)_{0-2}$, $(CH_2)_{0-2}N(R)N(R)C(=O)(CH_2)_{0-2}$, $(CH_2)_{0-2}N(R)N(R)C(=O)O(CH_2)_{0-2}$, $(CH_2)_{0-2}N(R)N(R)C(=O)N(R)(CH_2)_{0-2}$, $(CH_2)_{0-2}N(R)SO_2(CH_2)_{0-2}$, $(CH_2)_{0-2}N(R)SO_2N(R)(CH_2)_{0-2}$, $(CH_2)_{0-2}N(R)C(=O)O(CH_2)_{0-2}$, $(CH_2)_{0-2}N(R)C(=O)$ $(CH_2)_{0-2}$, $(CH_2)_{0-2}N(R)C(=S)(CH_2)_{0-2}$, $(CH_2)_{0-2}N(R)C(=O)N(R)(CH_2)_{0-2}$, $(CH_2)_{0-2}N(R)C(=S)N(R)(CH_2)_{0-2}$, $(CH_2)_{0-2}N(C(=O)R)C(=O)(CH_2)_{0-2}$, $(CH_2)_{0-2}N(OR)(CH_2)_{0-2}$, $(CH_2)_{0-2}C(=NH)N(R)(CH_2)_{0-2}$, $(CH_2)_{0-2}C(=O)N(OR)$ $(CH_2)_{0-2}$, or $(CH_2)_{0-2}C(=NOR)$ $(CH_2)_{0-2}$; or any of W, X, and Y is a bond provided that only one of W, X, and Z is a bond;

$R^1$, $R^2$, and $R^3$ are each independently alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl; provided that any alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl is substituted with 0-4 J, and wherein any $R^2$ can be bonded to $C_a$ either directly or via a linker comprising O, NR, C(=O)NR, OC(=O)NR, or $S(O)_q$, and wherein any $R^3$ can be bonded to $C_b$ either

directly or via a linker comprising O, NR, C(=O)NR, OC(=O)NR, or $S(O)_q$, wherein q is 0, 1, or 2; or wherein $R^1$ and $R^2$ together with W and $C_a$ form a heterocyclyl ring substituted with 0-4 J which can be fused with cycloalkyl, aryl or heteroaryl;

$R^4$ is aryl or heteroaryl, substituted with 0-4 J;

$R^5$ and $R^6$ are each independently H or methyl;

J is independently at each occurrence R, F, Cl, Br, I, OR, CN, $CF_3$, $OCF_3$, =O, =S, methylenedioxy, ethylenedioxy, $N(R)_2$, SR, SOR, $SO_2R$, $SO_2N(R)_2$, $SO_3R$, C(O)R, C(O)C(O)R, $C(O)CH_2C(O)R$, C(S)R, C(O)OR, OC(O)R, OC(O)OR, $C(O)N(R)_2$, $OC(O)N(R)_2$, $C(S)N(R)_2$, $(CH_2)_{0-2}NHC(O)R$, N(R)N(R)C(O)R, N(R)N(R)C(O)OR, $N(R)N(R)CON(R)_2$, $N(R)SO_2R$, $N(R)SO_2N(R)_2$, N(R)C(O)OR, N(R)C(O)R, N(R)C(S)R, $N(R)C(O)N(R)_2$, $N(R)C(S)N(R)_2$, N(COR)COR, N(OR)R, $C(=NH)N(R)_2$, C(O)N(OR)R, or C(=NOR)R;

R is independently at each occurrence hydrogen, alkyl, alkoxy, haloalkyl, haloalkoxy, alkenyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl, wherein any alkyl, alkoxy, haloalkyl, haloalkoxy, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl is substituted with 0-4 J; or wherein two R groups together with a nitrogen atom or with two adjacent nitrogen atoms to which they are bonded can together form a three to eight membered heterocyclyl substituted with 0-4 J; optionally further comprising 1-3 additional ring heteroatoms selected from the group consisting of O, N, and $S(O)_q$;

wherein any cycloalkyl, aryl, heterocyclyl, or heteroaryl can be fused, bridged, or in a spiro configuration with one or more additional optionally substituted cycloalkyl, aryl, heterocyclyl, and heteroaryl, monocyclic, bicyclic or polycyclic, saturated, partially unsaturated, or aromatic rings;

including all stereoisomers thereof and all isotopically labeled forms thereof;

or a salt thereof;

provided that the compound is not a peptide comprising only ribosomal amino acid residues, or a derivative thereof.

2. The compound of claim 1 wherein W is $CH_2$ or a bond, and X and Y are both C(=O)NR.

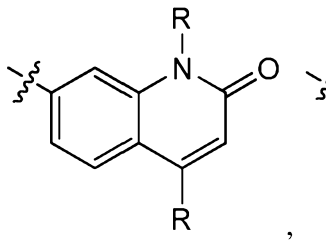
3. The compound of claim 1 or 2 wherein $R^1$ comprises at least six carbon atoms.

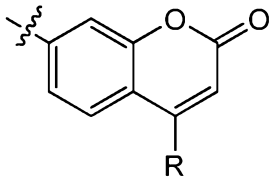
4. The compound of claim 1 wherein $R^1$ is cyclohexyl, cyclohexylmethyl, indolyl, pyridyl, cyclohexyloxycarbonyl, benzyloxy, benzylthio, naphthyl, methyl, isopropyl, isobutyl, imidazolyl, or aralkyl imidazolyl.

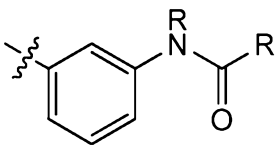
5. The compound of claim 1 wherein $R^2$ or $R^3$, or both, is $(CH_2)_nNRH$ or $(CH_2)_nNR$-C(=O)OR, wherein n is 0, 1, 2, 3, or 4 and each independently selected R is as defined in claim 1.

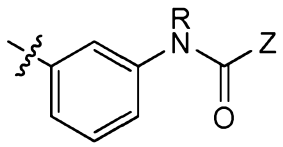
6. The compound of claim 5 wherein for $R^2$ or $R^3$, or both, NR is NH and OR is O-t-butyl or O-fluorenylmethylene.

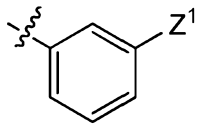
7. The compound of claim 1 wherein $R^4$ is any of



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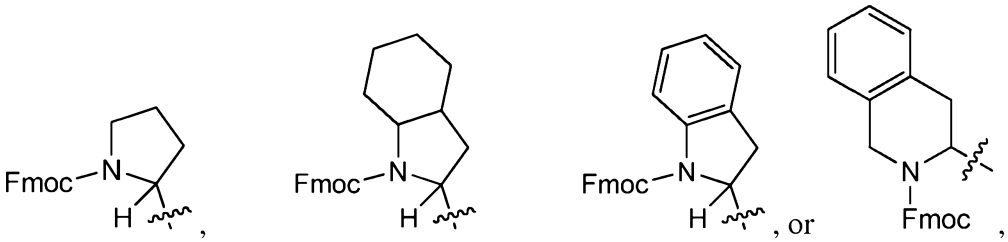
, or



wherein Z is alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, alkynyl, heterocyclylalkyl, or heteroarylalkyl; $Z^1$ is $NR_2$, -C(R)=C$(CN)_2$, C(=O)R, heterocyclylalkyl, or

heteroarylalkyl; and each independently selected R is as defined in claim 1, and wherein a wavy line indicates a point of attachment.

8. The compound of claim 1 wherein $R^5$ and $R^6$ are both H.

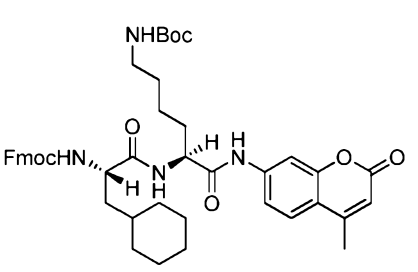
9. The compound of claim 1 wherein $R^1$ and $R^2$ together with W and $C_a$ comprise any of the following heterocyclyl groups



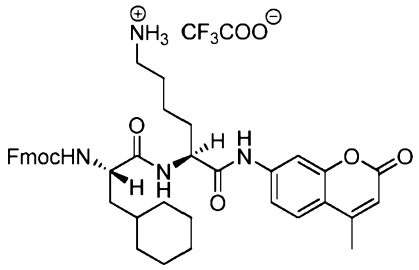

, , , or ,

wherein a wavy line indicates a point of attachment.

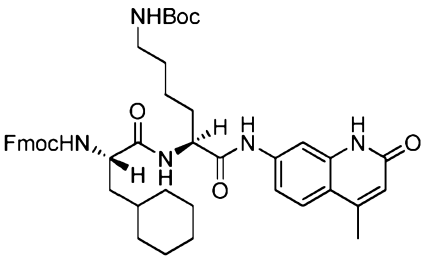
10. The compound of claim 1 wherein the compound is any of the following:



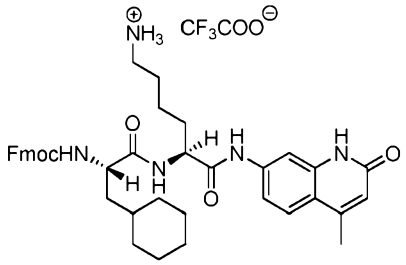

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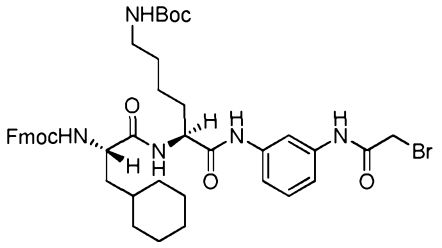

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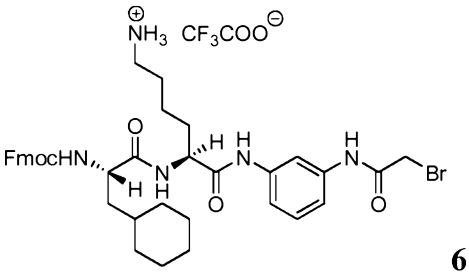

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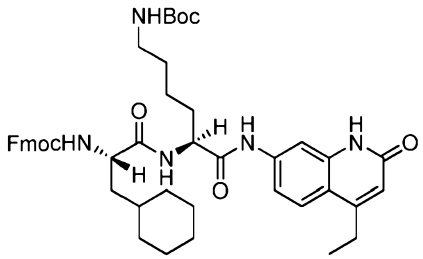

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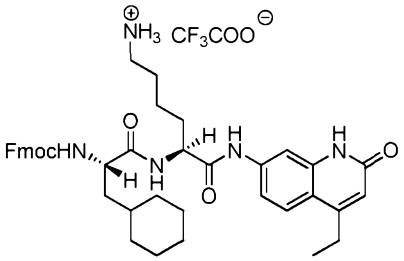

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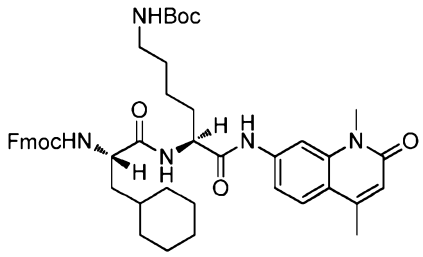

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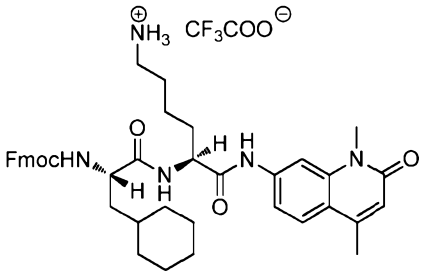

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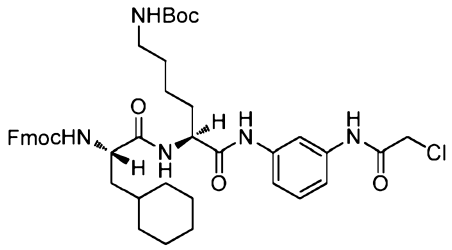

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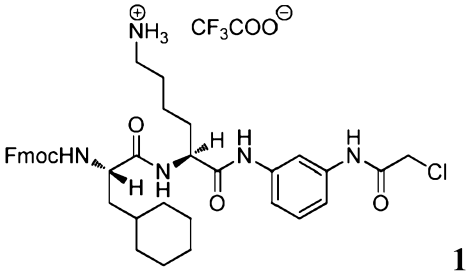

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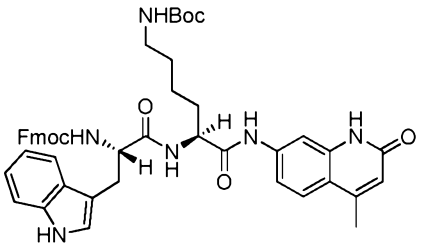

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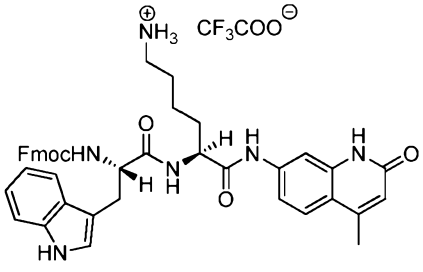

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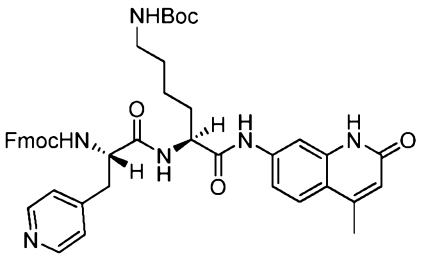

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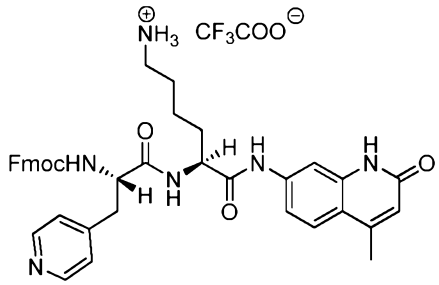
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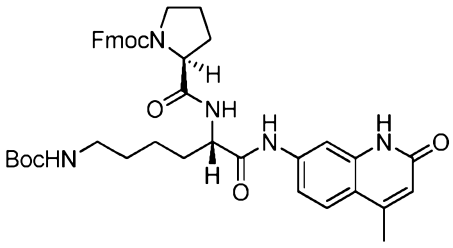
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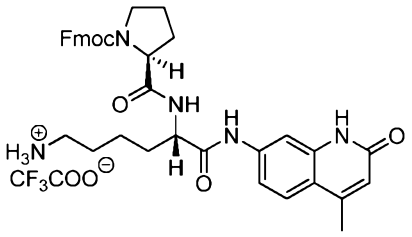
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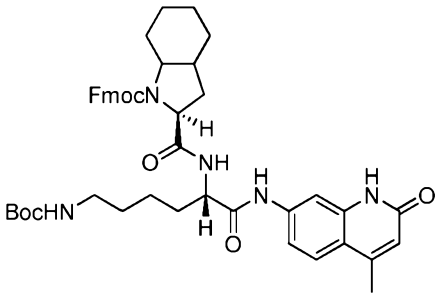
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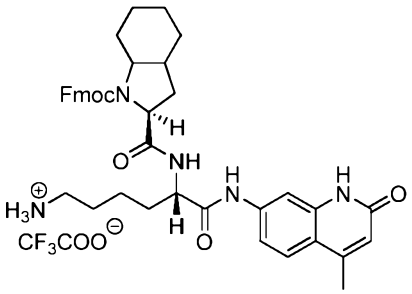
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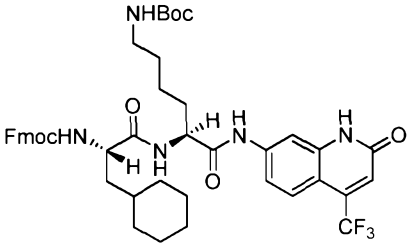
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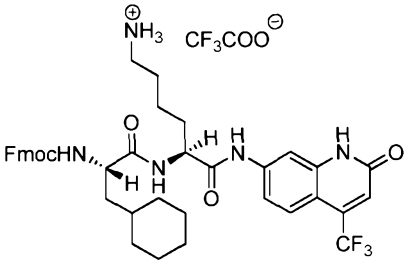
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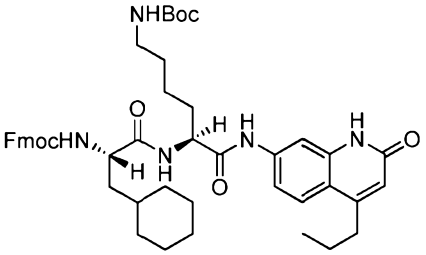
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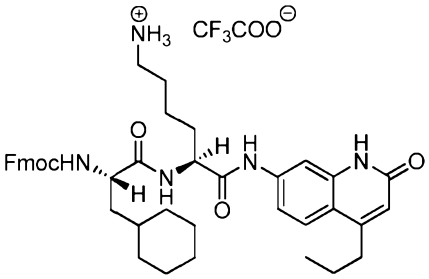

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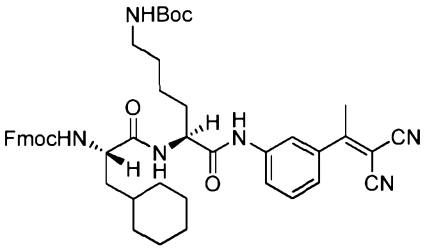

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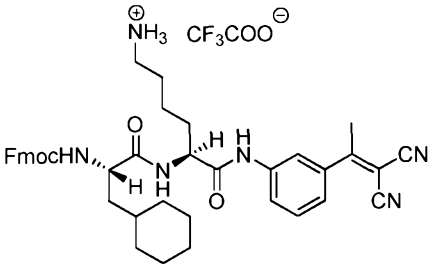

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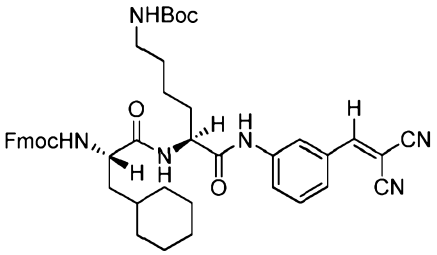

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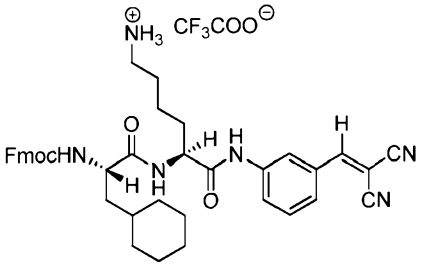

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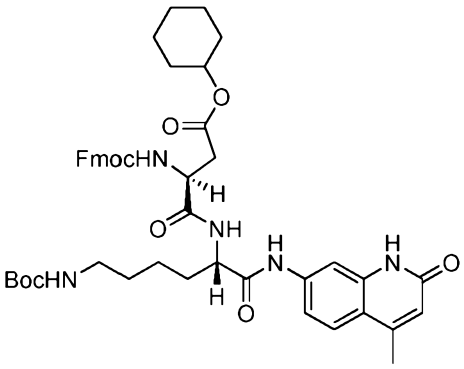

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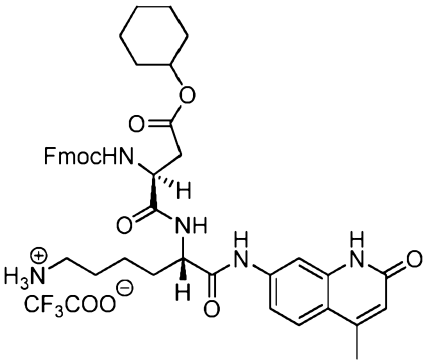

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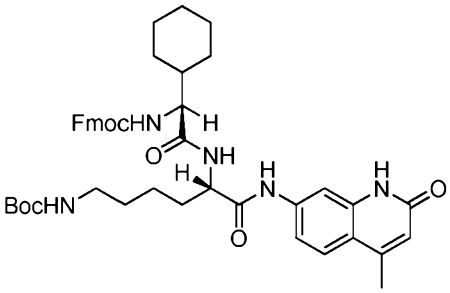

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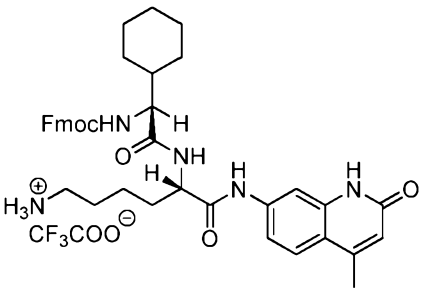
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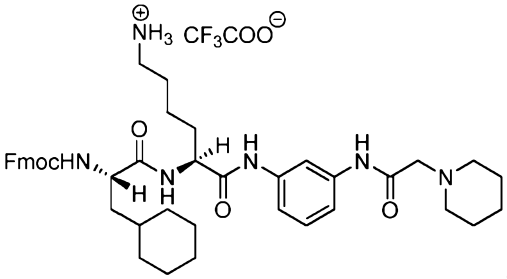
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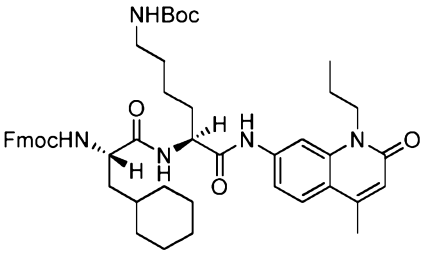
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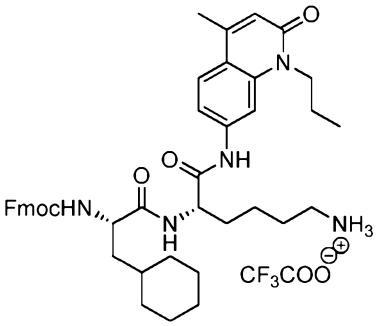
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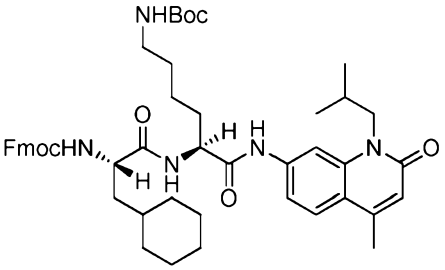
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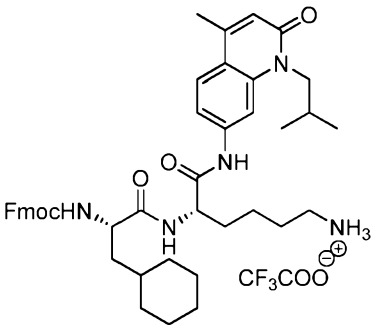
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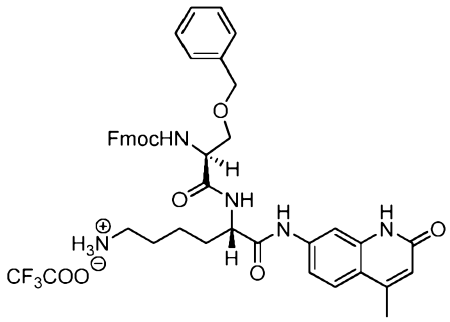
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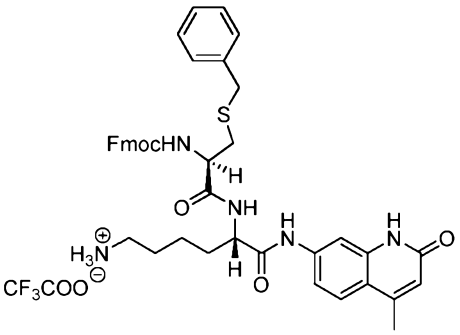
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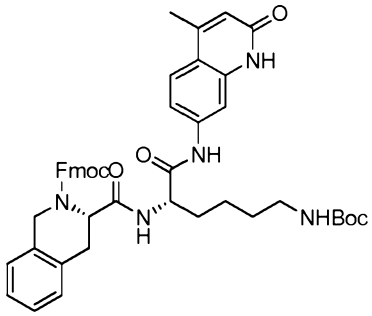
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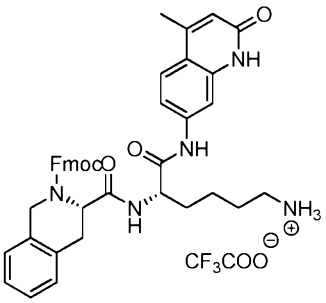
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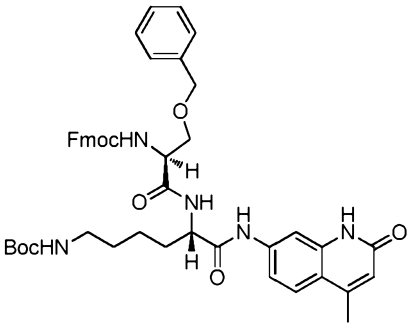
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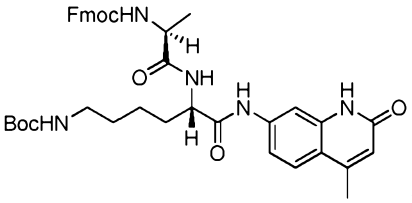
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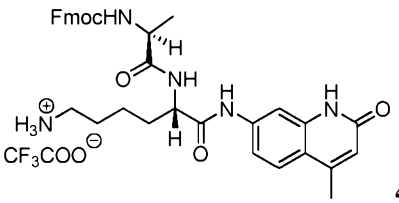
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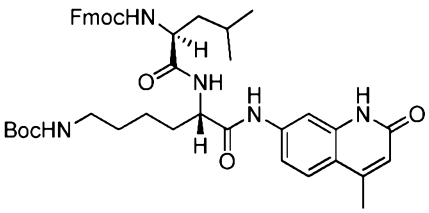
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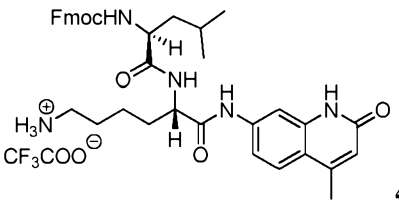
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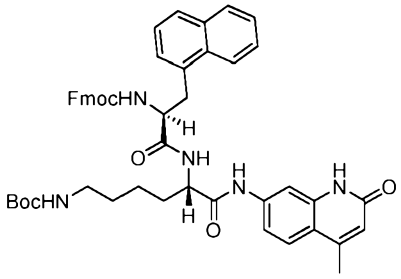
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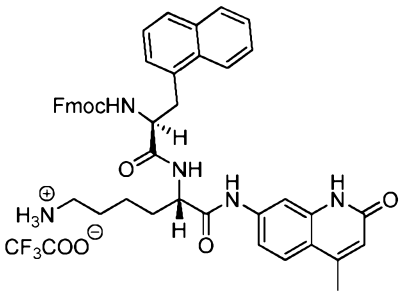
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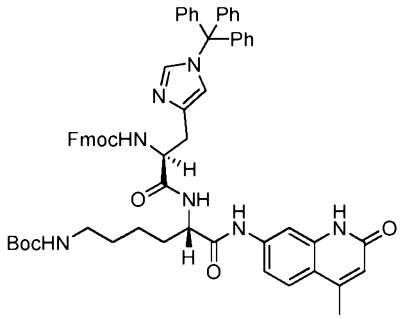
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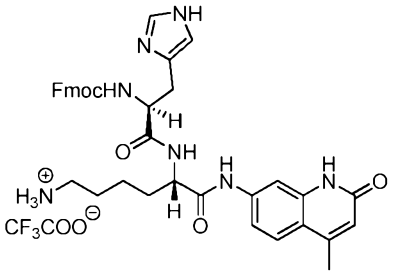

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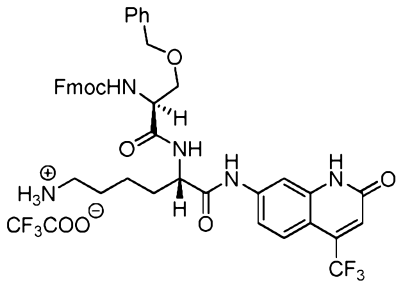

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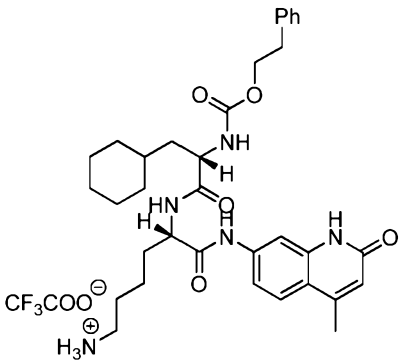

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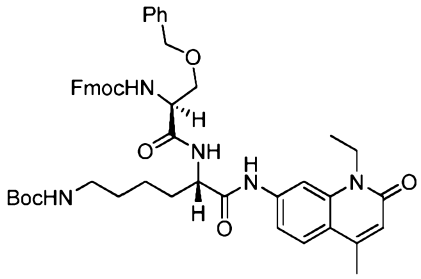

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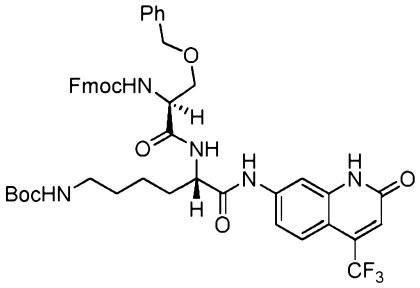

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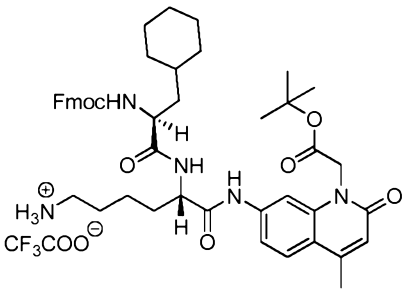

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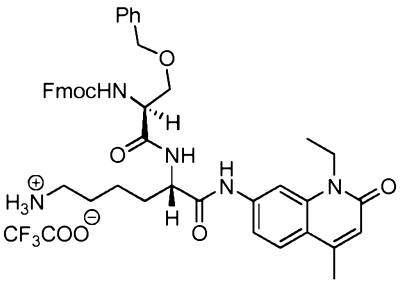

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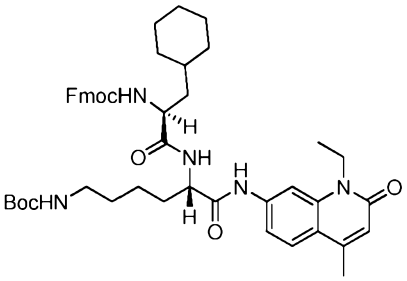

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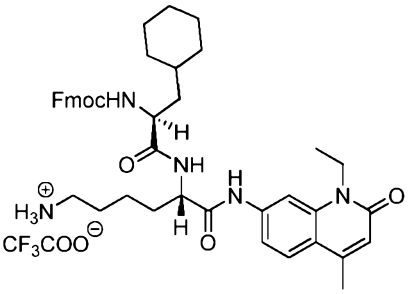
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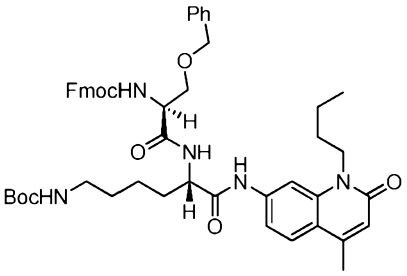
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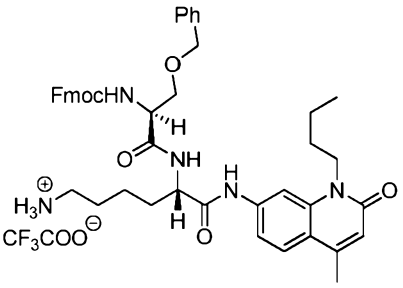
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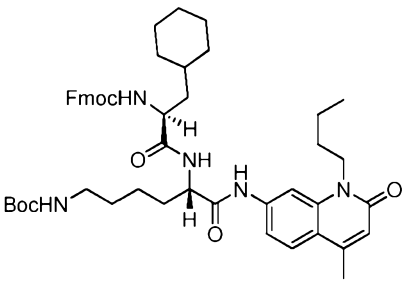
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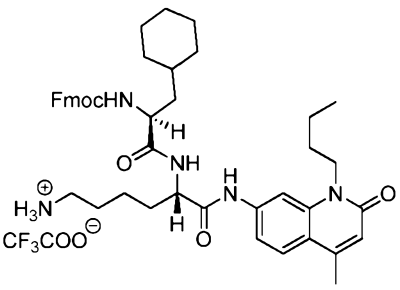
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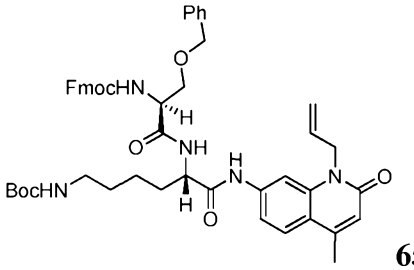
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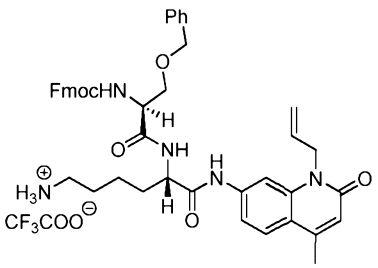
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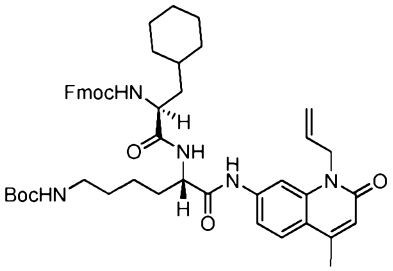
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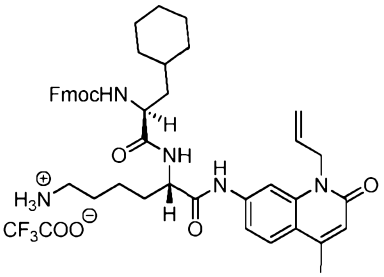

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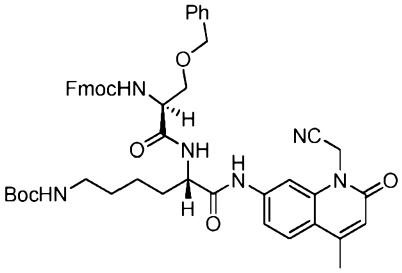

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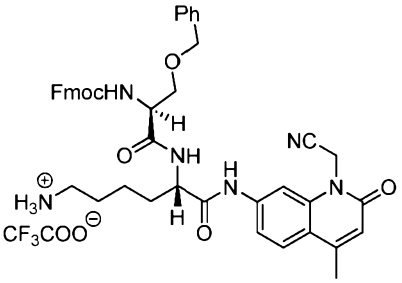

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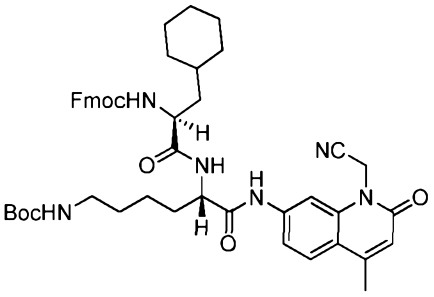

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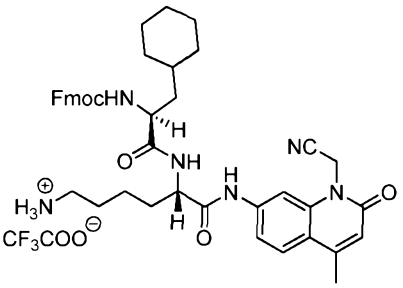

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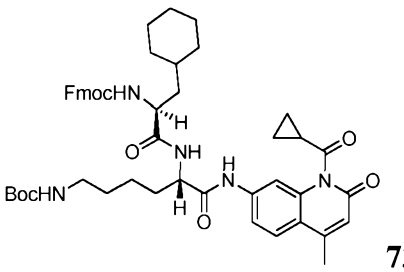

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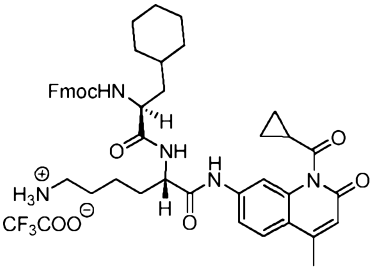

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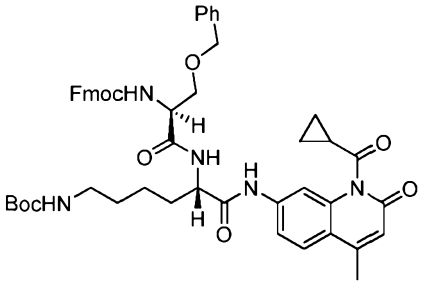

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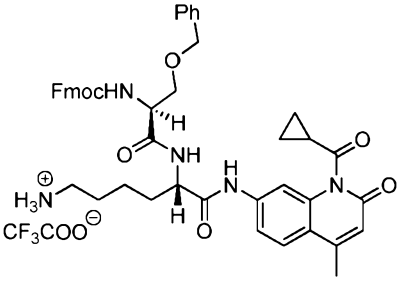

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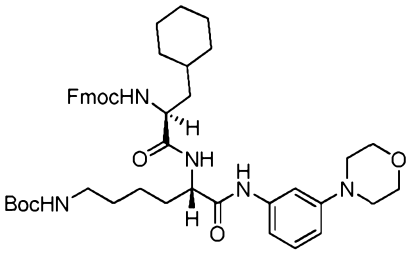

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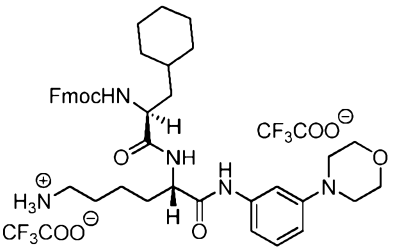
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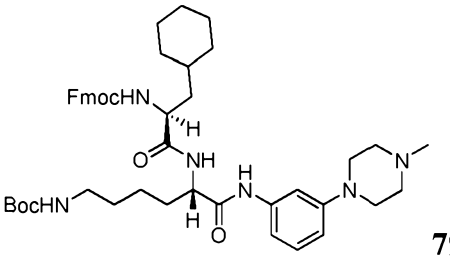
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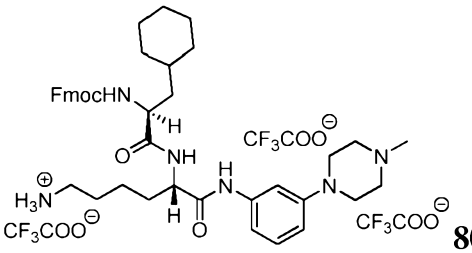
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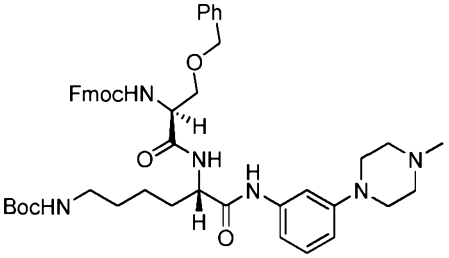
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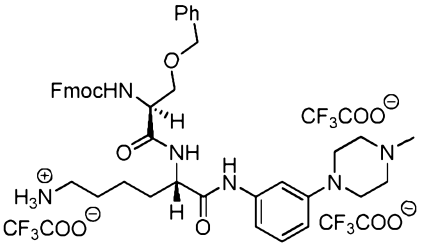
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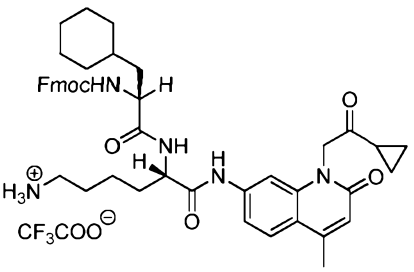
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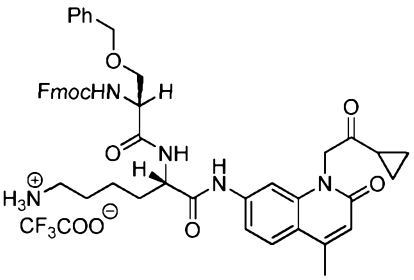
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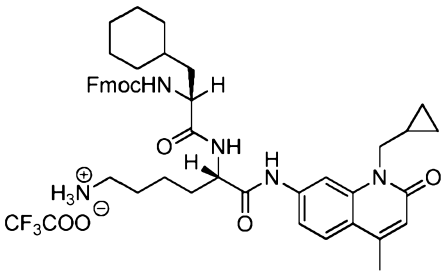
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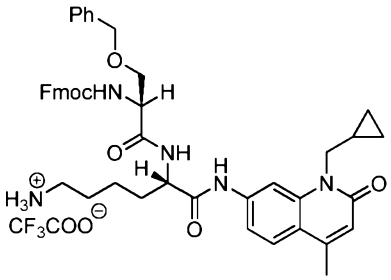
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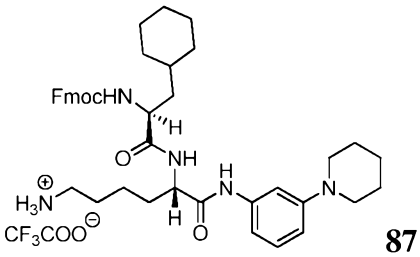
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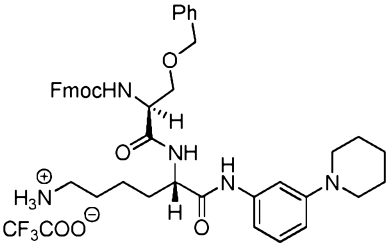
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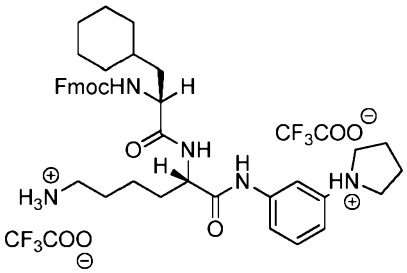
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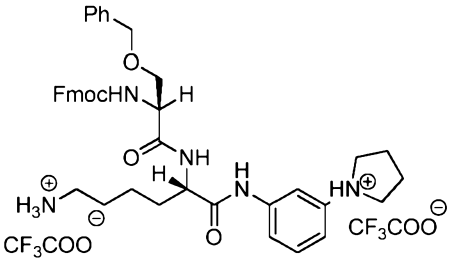
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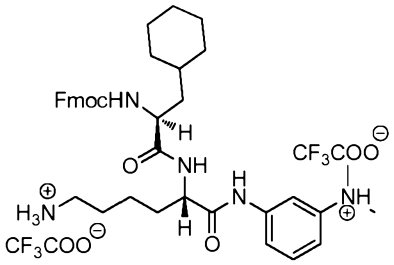
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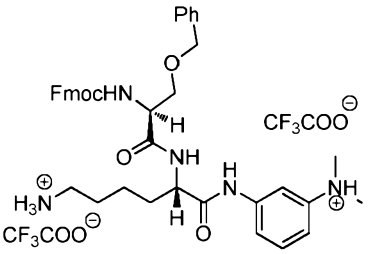
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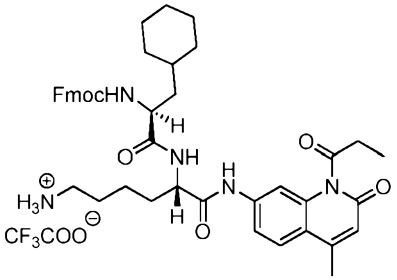
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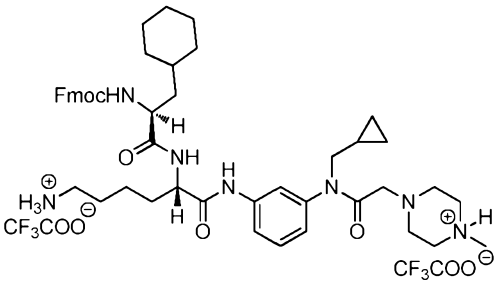
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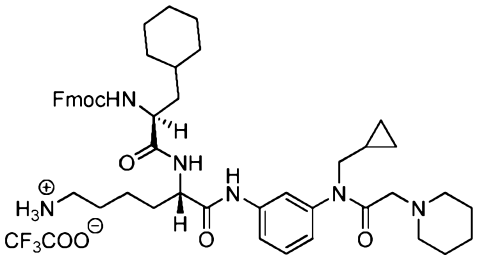
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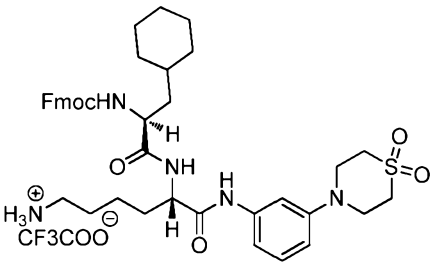
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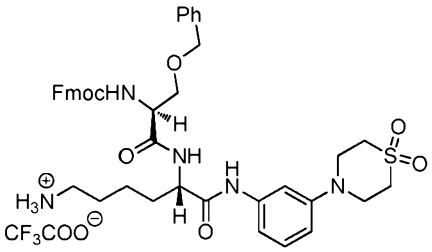
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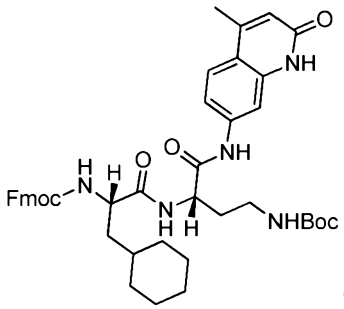

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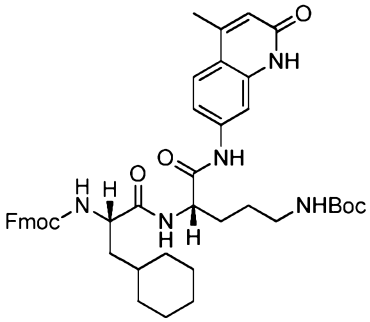

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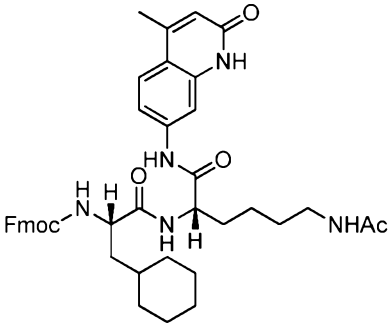

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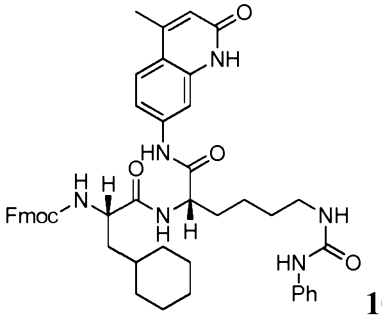

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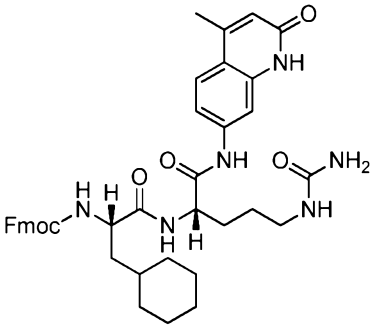

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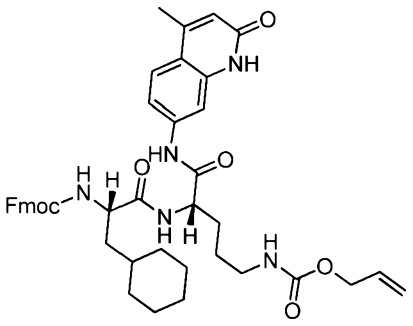

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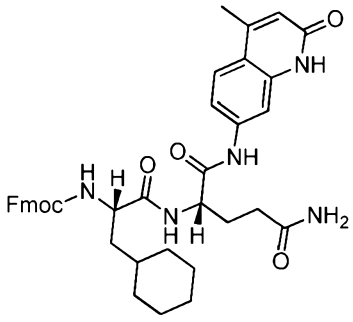

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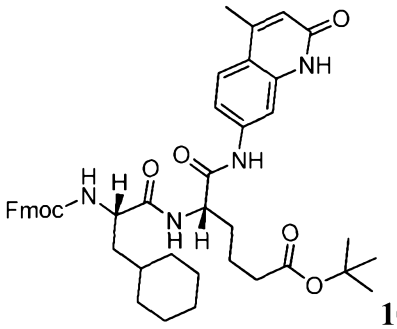

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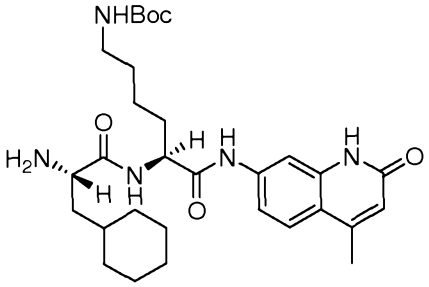

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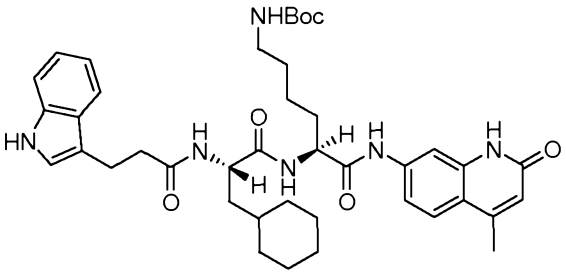

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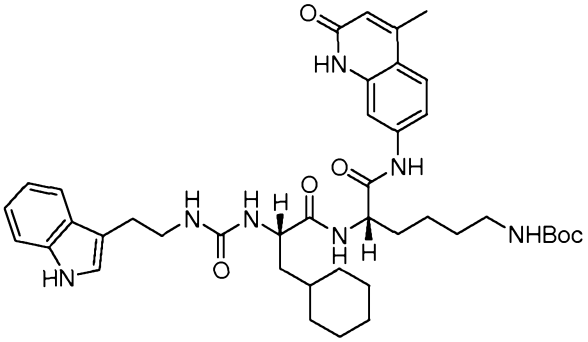
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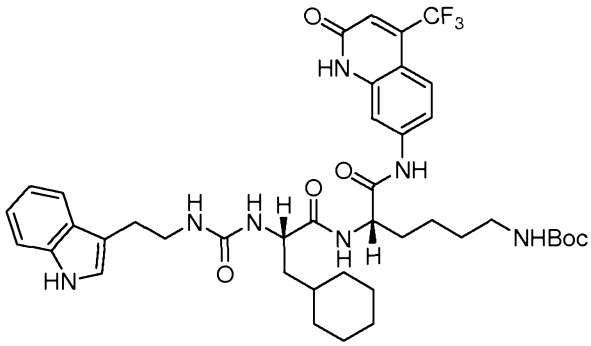
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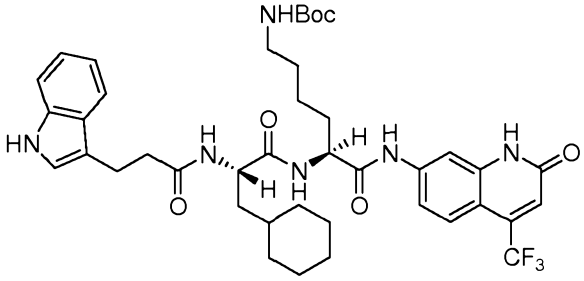
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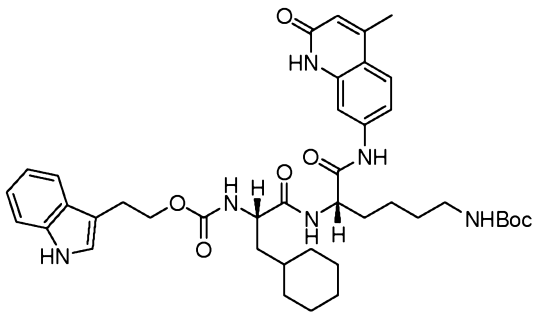
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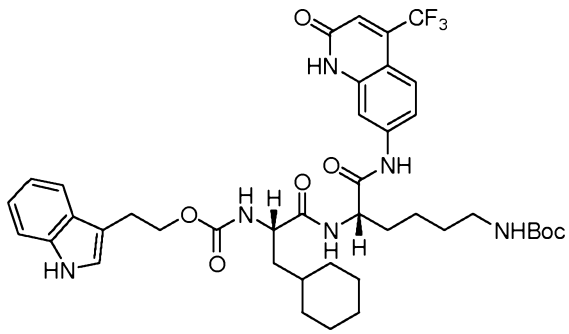
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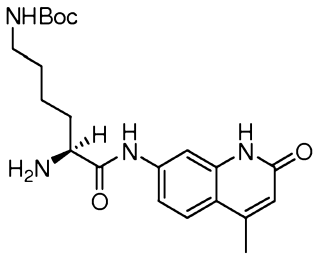
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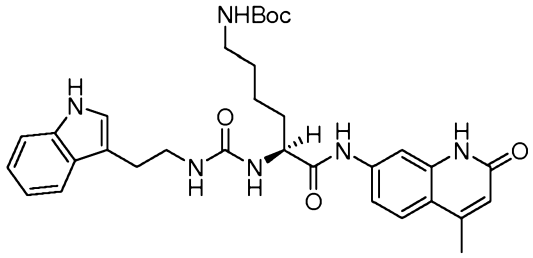
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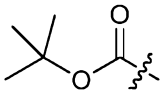


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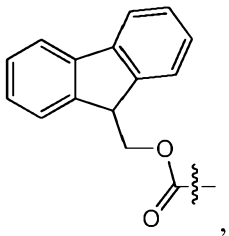
114

wherein Boc signifies



,

and Fmoc signifies

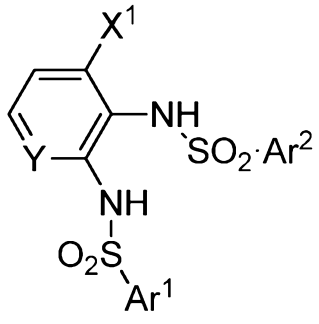


,

wherein a wavy line indicates a point of attachment;

or a salt thereof.

11. A galanin receptor-modulatory compound of formula (II)



(II)

wherein:

Y is CH or N;

$X^1$ is H or alkyl, or $X^1$, the carbon atom to which it is bonded, an adjacent carbon atom bearing an N atom, and the N atom, together form a pyrrole ring fused to the ring containing Y, to provide an indole or aza-indole ring system;

$Ar^1$ and $Ar^2$ are each independently aryl or heteroaryl, wherein any aryl or heteroaryl is optionally mono- or indepdendently multi-substituted with J;

J is independently at each occurrence R, F, Cl, Br, I, OR, CN, $CF_3$, $CF_2H$, $OCF_3$, $OCF_2H$, =O, =S, methylenedioxy, ethylenedioxy, $N(R)_2$, SR, SOR, $SO_2R$, $SO_2N(R)_2$, $SO_3R$, C(O)R, C(O)C(O)R, $C(O)CH_2C(O)R$, C(S)R, C(O)OR, OC(O)R, OC(O)OR, $C(O)N(R)_2$, $OC(O)N(R)_2$, $C(S)N(R)_2$, $(CH_2)_{0-2}NHC(O)R$, N(R)N(R)C(O)R, N(R)N(R)C(O)OR, $N(R)N(R)CON(R)_2$, $N(R)SO_2R$, $N(R)SO_2N(R)_2$, N(R)C(O)OR, N(R)C(O)R, N(R)C(S)R, $N(R)C(O)N(R)_2$, $N(R)C(S)N(R)_2$, N(COR)COR, N(OR)R, $C(=NH)N(R)_2$, C(O)N(OR)R, or C(=NOR)R;

R is independently at each occurrence hydrogen, alkyl, alkoxy, haloalkyl, haloalkoxy, alkenyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl, wherein any alkyl, alkoxy, haloalkyl, haloalkoxy, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl is substituted with 0-4 J; or wherein two R groups together with a nitrogen atom or with two adjacent nitrogen atoms to which they are bonded can together form a three to eight membered heterocyclyl substituted with 0-4 J; optionally further comprising 1-3 additional ring heteroatoms selected from the group consisting of O, N, and $S(O)_q$;

wherein any cycloalkyl, aryl, heterocyclyl, or heteroaryl can be fused, bridged, or in a spiro configuration with one or more additional optionally substituted cycloalkyl, aryl, heterocyclyl, and heteroaryl, monocyclic, bicyclic or polycyclic, saturated, partially unsaturated, or aromatic rings;

including all stereoisomers thereof and all isotopically labeled forms thereof;

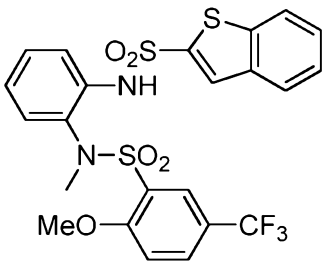
or any salt, hydrate, solvate, prodrug, or metabolite thereof.

12. The compound of claim 11 wherein at least one of $Ar^1$ or $Ar^2$ is benzothienyl.

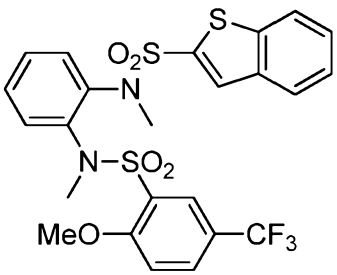
13. The compound of claim 11 wherein $Ar^1$ is phenyl substituted with halo, haloalkyl, or haloalkoxy.

14. The compound of claim 11 wherein Y is N.

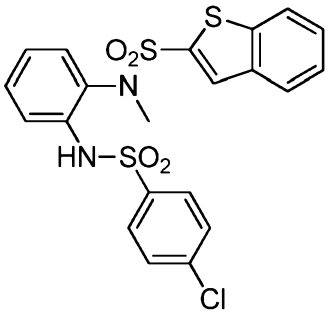
15. The compound of claim 11 wherein the compound is any of the following:



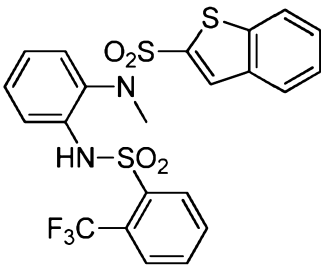

**115**



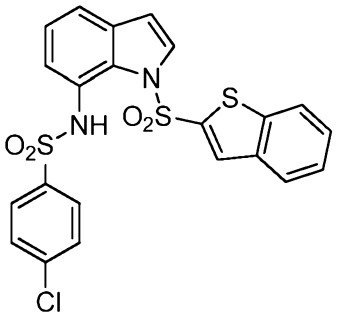

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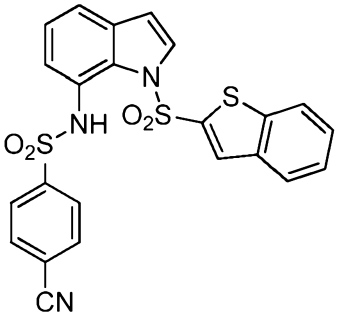

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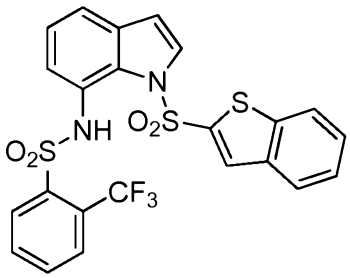

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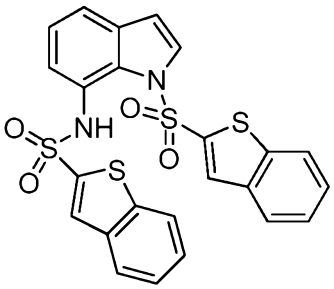
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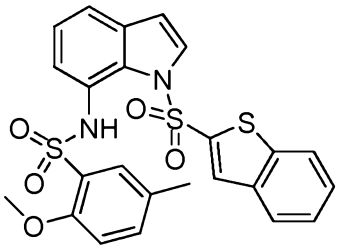
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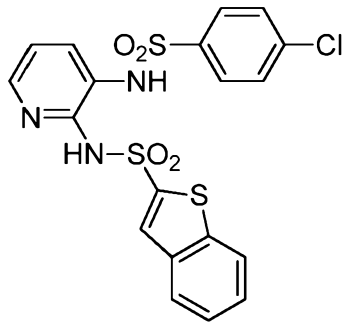
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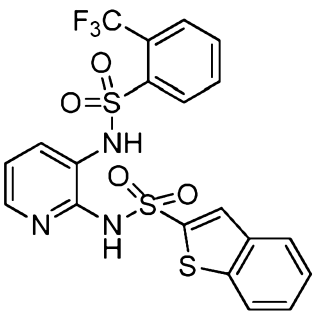
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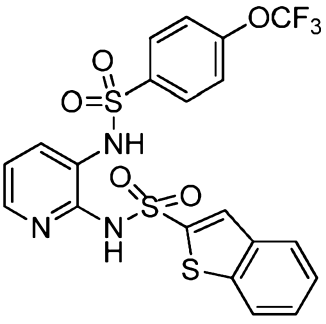
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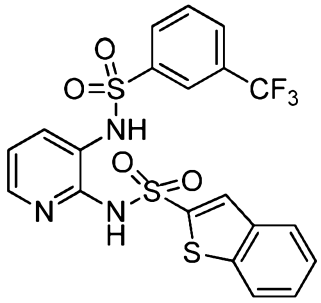
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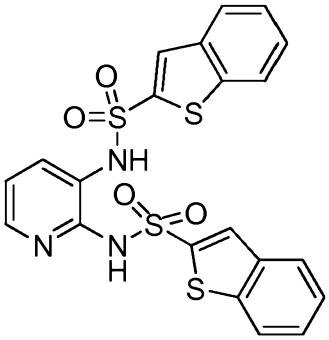
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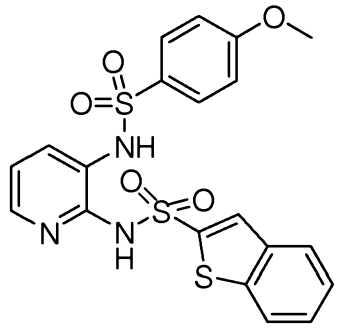
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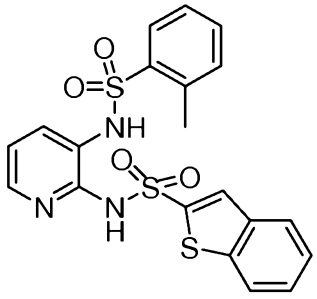
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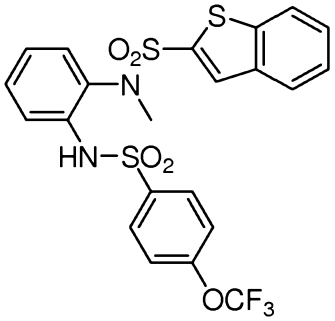
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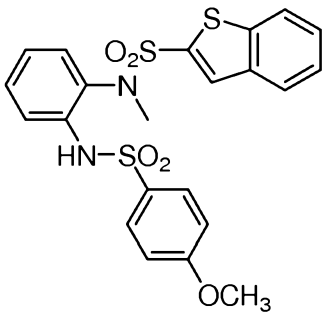
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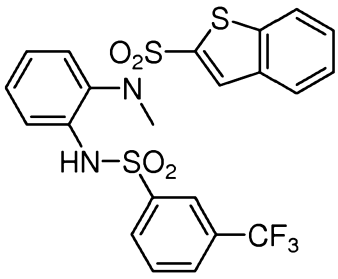
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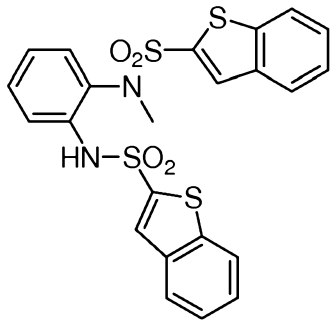
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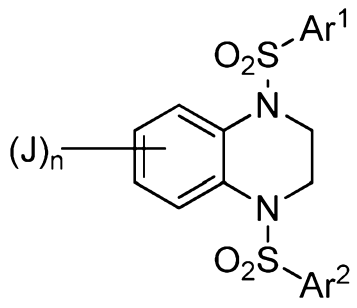
141



142

or a salt thereof.

16. A galanin receptor-modulatory compound of formula (III)



(III)

wherein $Ar^1$ and $Ar^2$ are each independently selected aryl or heteroaryl, wherein any aryl or heteroaryl is mono- or independently multi-substituted with J;

n is 0, 1, 2, or 3;

J is independently at each occurrence R, F, Cl, Br, I, OR, CN, $CF_3$, $CF_2H$, $OCF_3$, $OCF_2H$, =O, =S, methylenedioxy, ethylenedioxy, $N(R)_2$, SR, SOR, $SO_2R$, $SO_2N(R)_2$, $SO_3R$, C(O)R, C(O)C(O)R, $C(O)CH_2C(O)R$, C(S)R, C(O)OR, OC(O)R, OC(O)OR, $C(O)N(R)_2$, $OC(O)N(R)_2$, $C(S)N(R)_2$, $(CH_2)_{0-2}NHC(O)R$, N(R)N(R)C(O)R, N(R)N(R)C(O)OR, $N(R)N(R)CON(R)_2$, $N(R)SO_2R$, $N(R)SO_2N(R)_2$, N(R)C(O)OR, N(R)C(O)R, N(R)C(S)R, $N(R)C(O)N(R)_2$, $N(R)C(S)N(R)_2$, N(COR)COR, N(OR)R, $C(=NH)N(R)_2$, C(O)N(OR)R, or C(=NOR)R;

R is independently at each occurrence hydrogen, alkyl, alkoxy, haloalkyl, haloalkoxy, alkenyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl, wherein any alkyl, alkoxy, haloalkyl, haloalkoxy, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl is substituted with 0-4 J; or wherein two R groups

together with a nitrogen atom or with two adjacent nitrogen atoms to which they are bonded can together form a three to eight membered heterocyclyl substituted with 0-4 J; optionally further comprising 1-3 additional ring heteroatoms selected from the group consisting of O, N, and $S(O)_q$;

wherein any cycloalkyl, aryl, heterocyclyl, or heteroaryl can be fused, bridged, or in a spiro configuration with one or more additional optionally substituted cycloalkyl, aryl, heterocyclyl, and heteroaryl, monocyclic, bicyclic or polycyclic, saturated, partially unsaturated, or aromatic rings;

including all stereoisomers thereof and all isotopically labeled forms thereof;

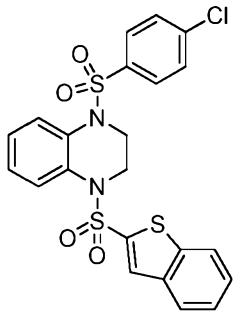
or a salt thereof.

17. The compound of claim 16, wherein at least one of $Ar^1$ and $Ar^2$ is benzothienyl.

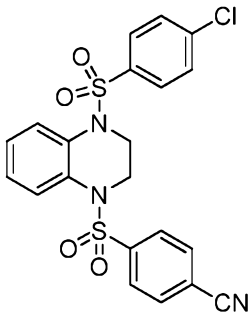
18. The compound of claim 16, wherein at least one of $Ar^1$ and $Ar^2$ is chlorophenyl, trifluoromethylphenyl, or cyanophenyl.

19. The compound of claim 16, wherein n = 0.

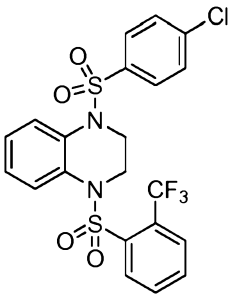
20. The compound of claim 16, wherein the compound is any of the following:



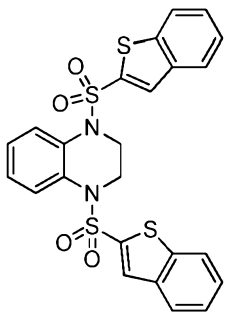

**124**



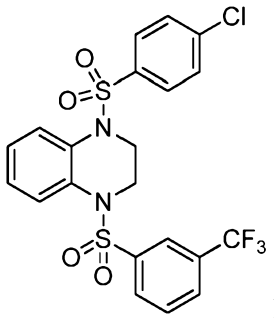

**125**



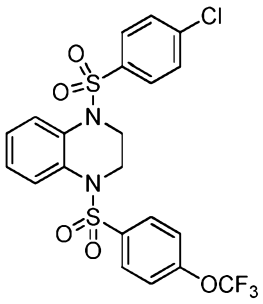

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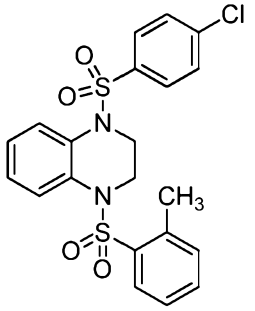

**127**



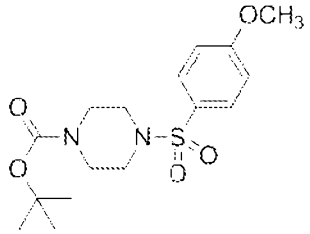
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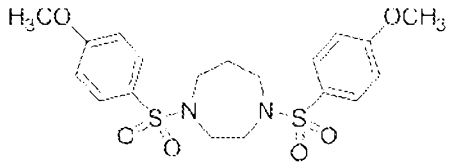
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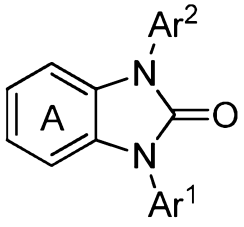
136A



136B

or a salt thereof.

21. A galanin receptor-modulatory compound of formula (IV)



(IV)

wherein $Ar^1$ and $Ar^2$ is each independently hydrogen, aryl, heteroaryl, fused cycloalkyl-aryl, fused heterocyclyl-aryl, fused cycloalkyl-heteroaryl, or fused heterocyclyl-heteroaryl, any of which is substituted with 0-4 J groups, wherein Ar1 and Ar2 can each be bonded directly to the nitrogen atom, or can be bonded via group Q, wherein Q is $(CH_2)_n$, $S(O)_q(CH_2)_n$, $C(=O)$ $(CH_2)_n$, $(CH_2)_nN(R)C(O)$, or $(CH_2)_nC(O)N(R)$, wherein n is 0-9 and q is 0, 1, or 2, provided that at least one of $Ar^1$ and $Ar^2$ is non-hydrogen;

the ring labeled "A" comprises 0, 1, or 2 ring N atoms, and is substituted with 0-3 $R^1$ groups, wherein $R^1$ is (C1-C10) straight chain alkyl, (C3-C10)branched chain alkyl, (C3-C12)cycloalkyl or bicycloalkyl, OH, $NR^3R^4$, CN, $CO_2R^5$, heterocyclylalkyl, heterobicycloalkyl, halo, nitro, alkoxy, cycloalkyloxy, perhaloalkyl, perhaloalkoxy, aryl, or heteroaryl wherein any alkyl cycloalkyl, bicycloalkyl, heterocyclylalkyl, heterobicyclylalkyl, alkoxy, aryl, or heteroaryl is optionally mono- or independently multi-substituted with J;

$R^3$ and $R^4$ are each independently H, alkyl, cycloalkyl or bicycloalkyl, aryl, heterocyclyl, or heteroaryl, wherein any alkyl, cycloalkyl or bicycloalkyl, aryl, heterocyclyl, or heteroaryl is substituted with 0-3 J and any alkyl, cycloalkyl or bicycloalkyl, aryl, heterocyclyl, or heteroaryl can be bonded directly to a nitrogen atom which bears $R^3$ or $R^4$ or can be bonded to the nitrogen atom via M, wherein M is $(CH_2)_n$, $S(O)_q(CH_2)_n$, $(CH_2)_nN(R)C(O)$, or $(CH_2)_nC(O)N(R)$, wherein n is 0-9 and q is 0, 1, or 2; or $R^3$ and $R^4$ together with a nitrogen atom to which they are bonded form a heterocyclyl optionally further comprising 1 or 2 additional heteroatoms selected from O, $S(O)_q$, or $NR^3$, wherein the heterocyclyl is substituted with 0-3 J;

$R^5$ is H, alkyl, cycloalkyl, aryl, heterocyclyl, or heteroaryl, any of which non-hydrogen groups is optionally mono- or independently multi-substituted with J;

J is independently at each occurrence R, F, Cl, Br, I, OR, CN, $CF_3$, $CF_2H$, $OCF_3$, $OCF_2H$, =O, =S, methylenedioxy, ethylenedioxy, $N(R)_2$, SR, SOR, $SO_2R$, $SO_2N(R)_2$, $SO_3R$, C(O)R, C(O)C(O)R, $C(O)CH_2C(O)R$, C(S)R, C(O)OR, OC(O)R, OC(O)OR, $C(O)N(R)_2$, $OC(O)N(R)_2$, $C(S)N(R)_2$, $(CH_2)_{0-2}NHC(O)R$, N(R)N(R)C(O)R, N(R)N(R)C(O)OR, $N(R)N(R)CON(R)_2$, $N(R)SO_2R$, $N(R)SO_2N(R)_2$, N(R)C(O)OR, N(R)C(O)R, N(R)C(S)R, $N(R)C(O)N(R)_2$, $N(R)C(S)N(R)_2$, N(COR)COR, N(OR)R, $C(=NH)N(R)_2$, C(O)N(OR)R, or C(=NOR)R;

R is independently at each occurrence hydrogen, alkyl, alkoxy, haloalkyl, haloalkoxy, alkenyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl, wherein any alkyl, alkoxy, haloalkyl, haloalkoxy, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl is substituted with 0-4 J; or wherein two R groups together with a nitrogen atom or with two adjacent nitrogen atoms to which they are bonded can

together form a three to eight membered heterocyclyl substituted with 0-4 J; optionally further comprising 1-3 additional ring heteroatoms selected from the group consisting of O, N, and $S(O)_q$;

wherein any cycloalkyl, aryl, heterocyclyl, or heteroaryl can be fused, bridged, or in a spiro configuration with one or more additional optionally substituted cycloalkyl, aryl, heterocyclyl, and heteroaryl, monocyclic, bicyclic or polycyclic, saturated, partially unsaturated, or aromatic rings;

including all stereoisomers thereof and all isotopically labeled forms thereof;

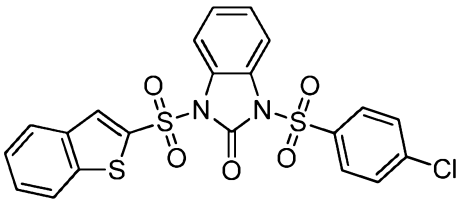
or a salt thereof.

22. The compound of claim 21 wherein at least one Q is sulfonyl, carbonyl, or methylene.

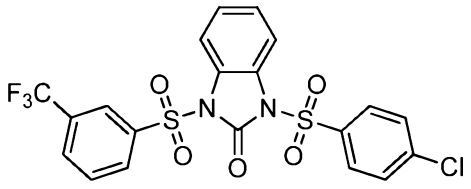
23. The compound of claim 21 wherein $Ar^1$ or $Ar^2$, or both, is a J-substituted phenyl group.

24. The compound of claim 21 wherein $Ar^1$ or $Ar^2$, or both, is a J-substituted pyridyl group.

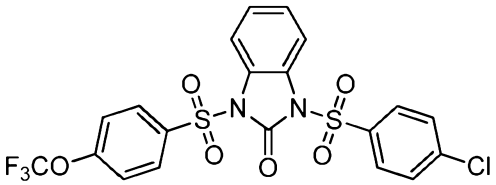
25. The compound of claim 21 comprising any of the following:



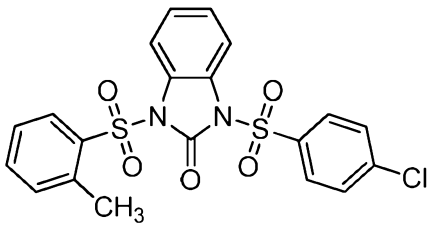
**143**



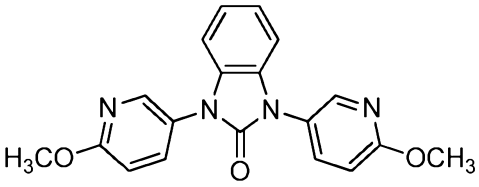
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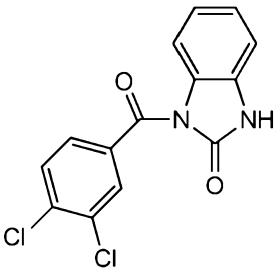


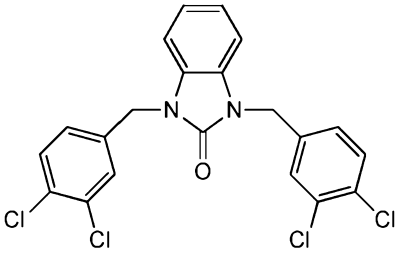
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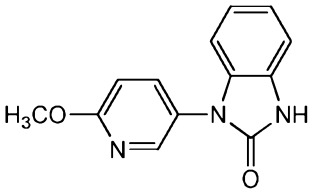


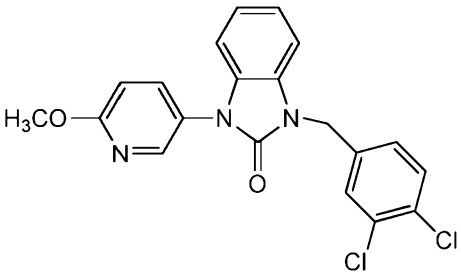
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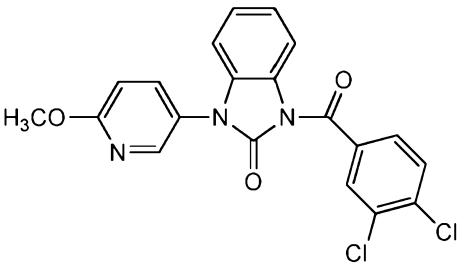

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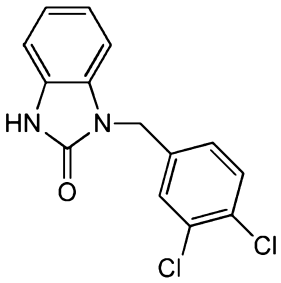

148A

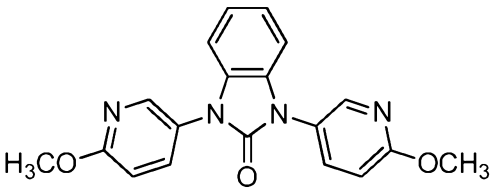

148B


148C


148D

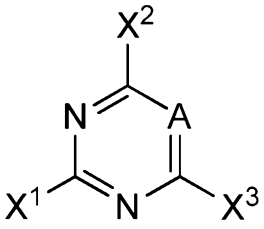

148E


148F


148G

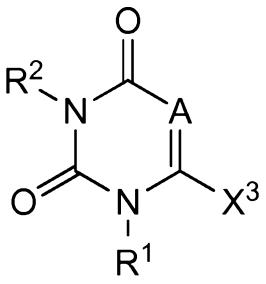
or a salt thereof.

26. A galanin receptor-modulating compound of formula (VA)



(VA)

or (IVB)



(VB)

wherein

A is N or CR', wherein R' is H, optionally substituted (C1-C6)alkyl, or $NR^3R^4$;

$X^1$, $X^2$ and $X^3$ are each independently H, halo, cyano, $NR^3R^4$, $N(R^3)S(O)_qAr^1$, $N(R^3)C(=O)Ar^1$, or $OR^5$, wherein q is 0, 1, or 2;

$R^1$ and $R^2$ are each independently optionally substituted aralkyl;

$R^3$ and $R^4$ are each independently H, alkyl, cycloalkyl or bicycloalkyl, aryl, heterocyclyl, or heteroaryl, wherein any alkyl, cycloalkyl or bicycloalkyl, aryl, heterocyclyl, or heteroaryl is substituted with 0-3 J and any alkyl, cycloalkyl or bicycloalkyl, aryl, heterocyclyl, or heteroaryl can be bonded directly to a nitrogen atom which bears $R^3$ or $R^4$ or can be bonded to the nitrogen atom via M, wherein M is $(CH_2)_n$, $S(O)_q(CH_2)_n$, $(CH_2)_nN(R)C(O)$, or $(CH_2)_nC(O)N(R)$, wherein n is 0-9 and q is 0, 1, or 2; or $R^3$ and $R^4$ together with a nitrogen atom to which they are bonded form a heterocyclyl optionally further comprising 1 or 2 additional heteroatoms selected from O, $S(O)_q$, or $NR^3$, wherein the heterocyclyl is substituted with 0-3 J;

$R^5$ is H, alkyl, cycloalkyl, aryl, heterocyclyl, or heteroaryl, any of which non-hydrogen groups is optionally mono- or independently multi-substituted with J;

$Ar^1$ is aryl or heteroaryl, optionally mono- or independently multi-substituted with J;

J is independently at each occurrence R, F, Cl, Br, I, OR, CN, $CF_3$, $CF_2H$, $OCF_3$, $OCF_2H$, =O, =S, methylenedioxy, ethylenedioxy, $N(R)_2$, SR, SOR, $SO_2R$, $SO_2N(R)_2$, $SO_3R$, C(O)R, C(O)C(O)R, $C(O)CH_2C(O)R$, C(S)R, C(O)OR, OC(O)R, OC(O)OR, $C(O)N(R)_2$, $OC(O)N(R)_2$, $C(S)N(R)_2$, $(CH_2)_{0-2}NHC(O)R$, N(R)N(R)C(O)R, N(R)N(R)C(O)OR, $N(R)N(R)CON(R)_2$, $N(R)SO_2R$, $N(R)SO_2N(R)_2$, N(R)C(O)OR, N(R)C(O)R, N(R)C(S)R, $N(R)C(O)N(R)_2$, $N(R)C(S)N(R)_2$, N(COR)COR, N(OR)R, $C(=NH)N(R)_2$, C(O)N(OR)R, or C(=NOR)R;

R is independently at each occurrence hydrogen, alkyl, alkoxy, haloalkyl, haloalkoxy, alkenyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl, wherein any alkyl, alkoxy, haloalkyl, haloalkoxy, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl is substituted with 0-4 J; or wherein two R groups together with a nitrogen atom or with two adjacent nitrogen atoms to which they are bonded can together form a three to eight membered heterocyclyl substituted with 0-4 J; optionally further comprising 1-3 additional ring heteroatoms selected from the group consisting of O, N, and $S(O)_q$;

wherein any cycloalkyl, aryl, heterocyclyl, or heteroaryl can be fused, bridged, or in a spiro configuration with one or more additional optionally substituted cycloalkyl, aryl, heterocyclyl, and heteroaryl, monocyclic, bicyclic or polycyclic, saturated, partially unsaturated, or aromatic rings;

including all stereoisomers thereof and all isotopically labeled forms thereof;

or a salt thereof.

27. The compound of formula (VA) of claim 26 wherein $X^1$, $X^2$, and $X^3$ are each independently $NR^3R^4$.

28. The compound of formula (VA) of claim 26 wherein $X^1$ and $X^2$ are each independently $NR^3R^4$ and $X^3$ is halo, or $X^1$ is halo and $X^2$ and $X^3$ are each independently $NR^3R^4$.

29. The compound of formula (VA) of claim 26 wherein $X^1$ is alkoxy, and $X^2$ and $X^3$ are each independently $NR^3R^4$ or halo.

30. The compound of formula (VA) of claim 26 wherein $X^1$ is H, $NR^3R^4$, $OR^5$, halo, optionally substituted arylsulfonamido, or optionally substituted arylcarboxamido.

31. The compound of formula (VA) of claim 26 wherein $X^2$ is heterocyclyl, optionally substituted arylamino, or dialkylamino.

32. The compound of formula (VA) of claim 26, wherein $X^3$ is hydrogen, halo, cyano, $NR^3R4$ wherein $R^3$ is H or alkyl and $R^4$ is aryl or heteroaryl wherein the aryl or heteroaryl is independently substituted with 0-3 J, or $NR^3R^4$ wherein $NR^3R^4$ forms an optionally substituted heterocyclyl.

33. The compound of formula (VA) of claim 26 wherein two of $X^1$, $X^2$ and $X^3$ are arylamino and a third is heterocyclyl.

34. The compound of formula (VA) of claim 26 wherein one of $X^1$, $X^2$ and $X^3$ is arylcarboxamido, and one is heterocyclyl or aryl amino.

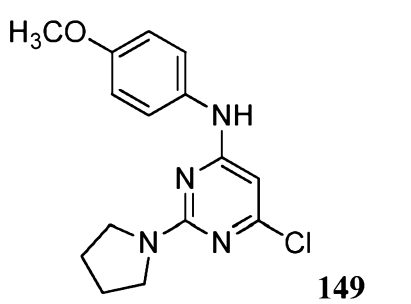
35. The compound of formula (VA) of claim 26 wherein at least one of $X^1$, $X^2$, or $X^3$ is p-methyloxyphenylamino, m-methoxyphenylamino, pyrrolidinyl, cyclohexylamino, methoxy, piperidinyl, chloro, m-fluoro-p-methoxyphenylamino, 4-($CF_3$-pyridyl)-1,4-diazepan-1-yl preferably 4-(3-$CF_3$-pyrid-2-yl)-1,4-diazepan-1-yl, p-chlorophenylamino, p-ethoxyphenylamino, p-isopropoxyphenylamino, p-methoxyphenylsulfonamido, 3,4,-dichlorobenzamido, benzamido, 4-(p-methoxyphenylsulfonamido)-1,4-diazepan-1-yl, or 4-($CF_3$-pyridyl)-piperazin-1-yl preferably 4-(3-CF3-pyrid-2-yl)-piperazin-1-yl.

36. The compound of formula (VB) of claim 26 wherein $R^1$ is benzyl optionally substituted with J, preferably $R^1$ is p-methoxybenzyl.

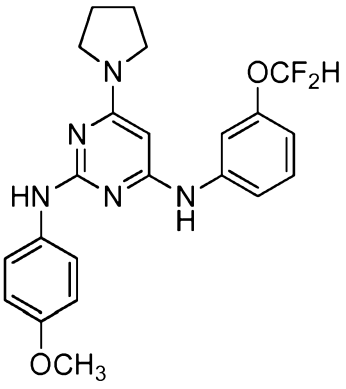
37. The compound of formula (VB) of claim 26 wherein $R^2$ is benzyl optionally substituted with J, preferably $R^2$ is p-ethylbenzyl.

38. The compound of formula (VB) of claim 26 wherein $X^3$ is H or $NH_2$.

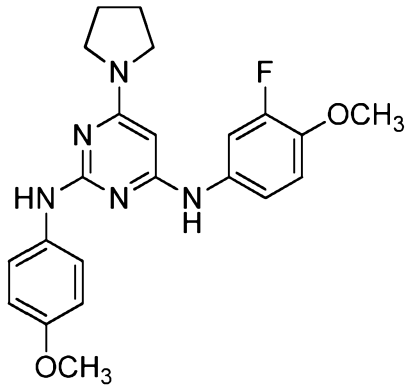
39. The compound of formula (VA) of claim 26 wherein the compound is any of the following:



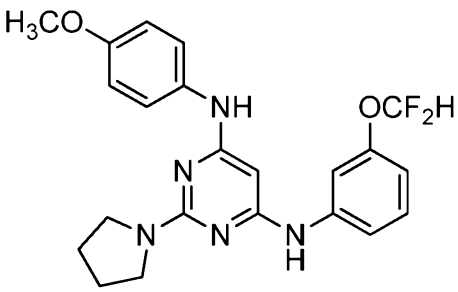
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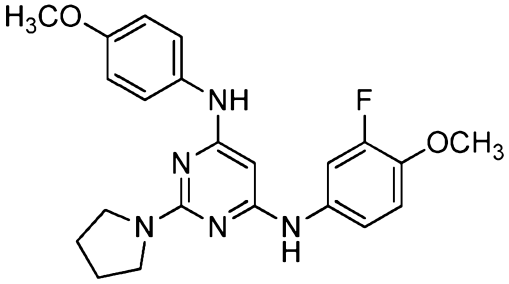
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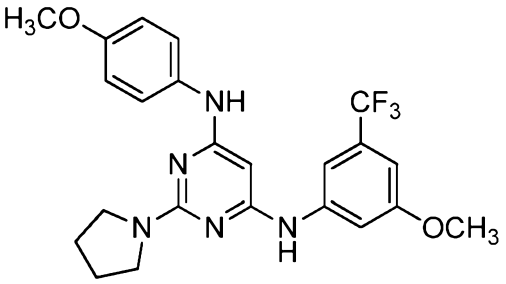
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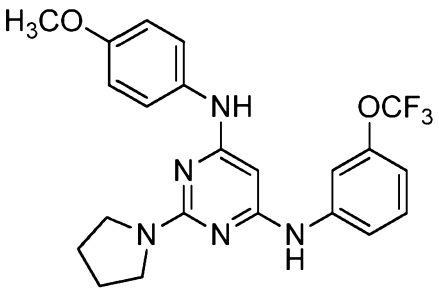
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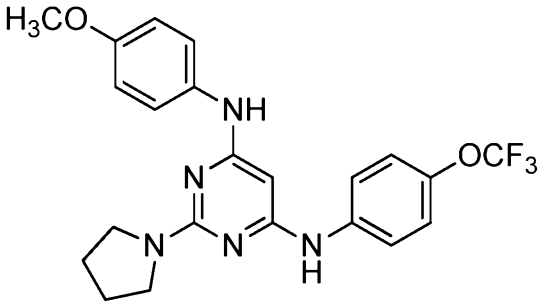
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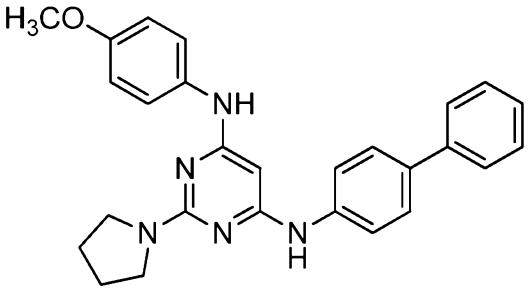
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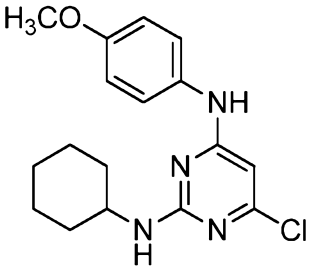
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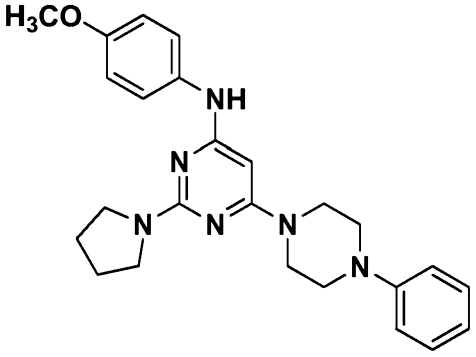
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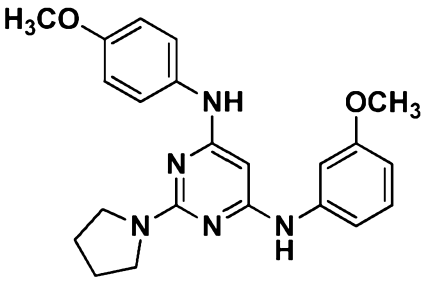
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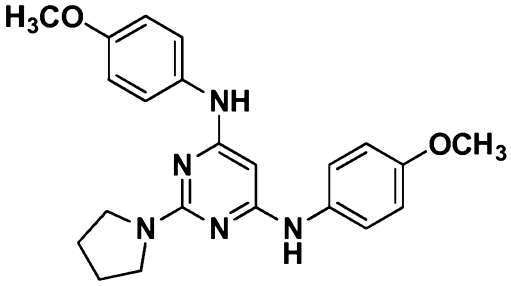
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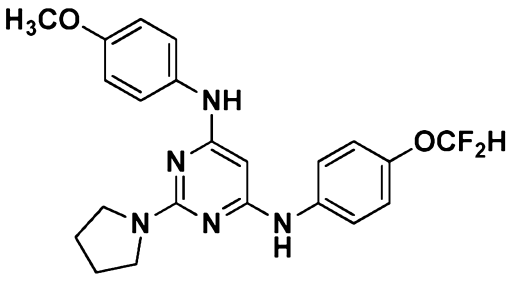
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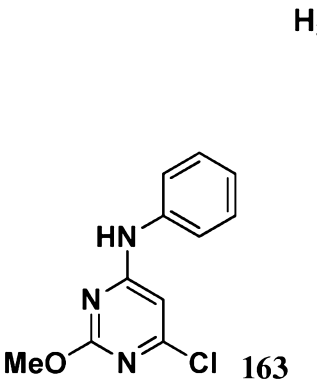
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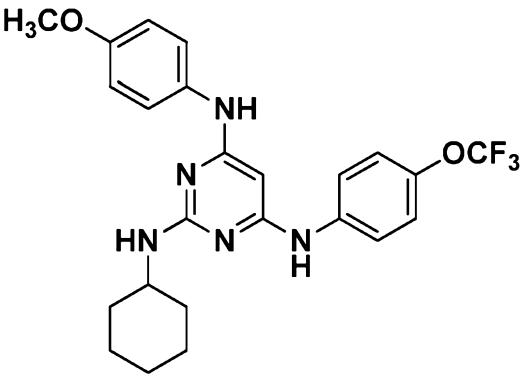
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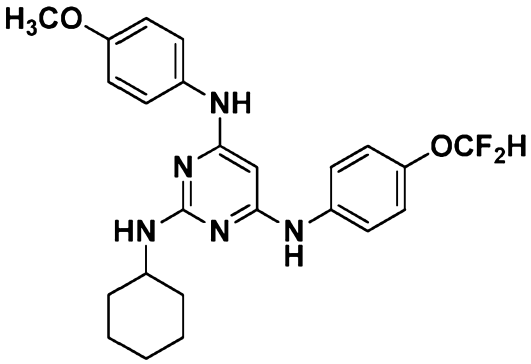
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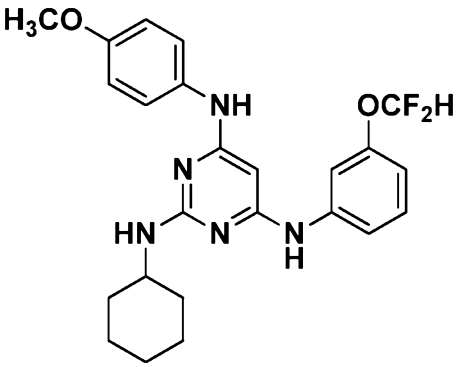
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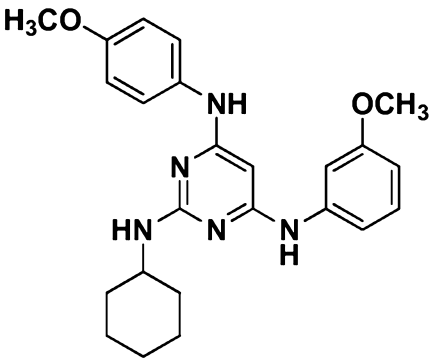
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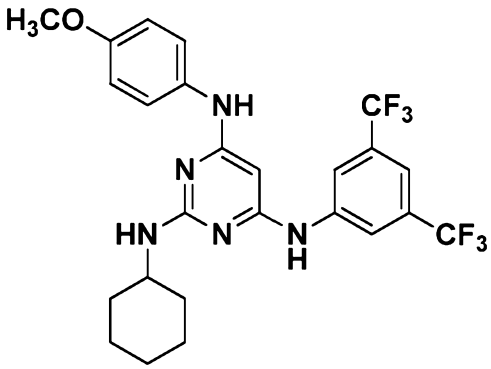
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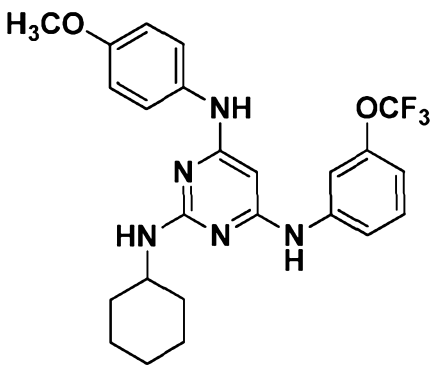
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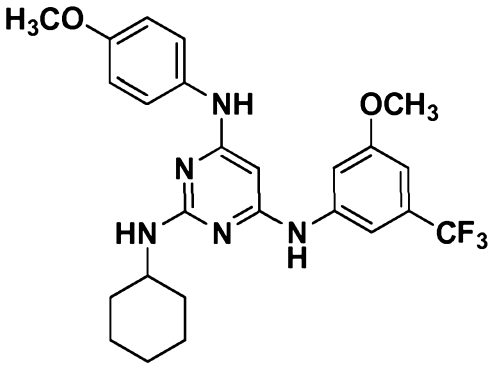
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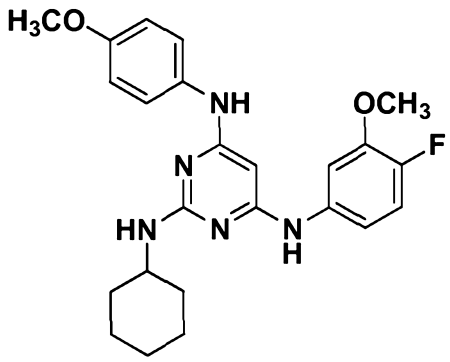
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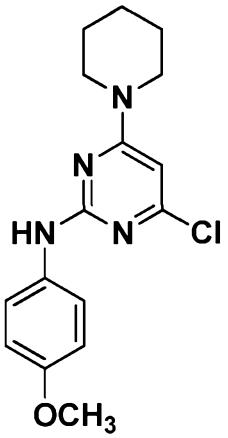

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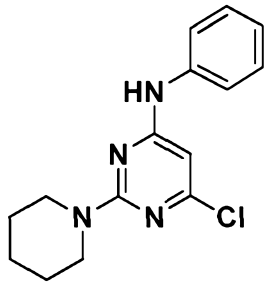

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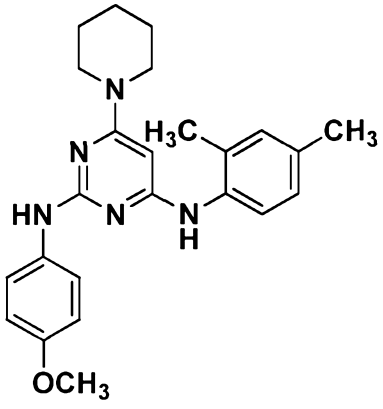

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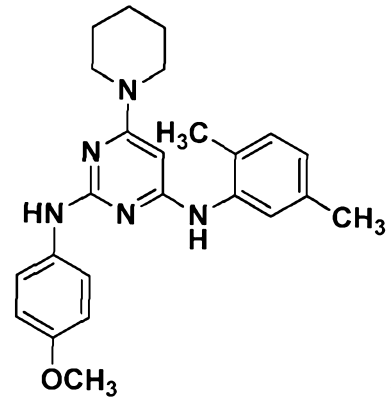

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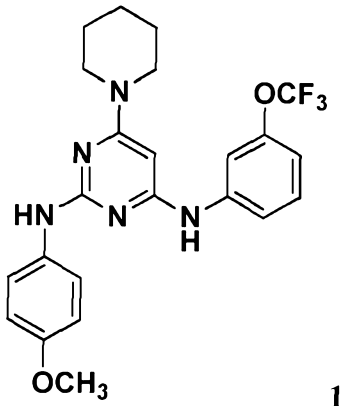

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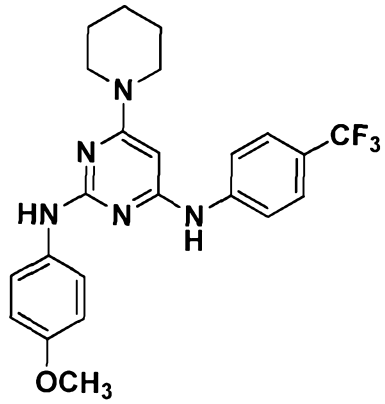

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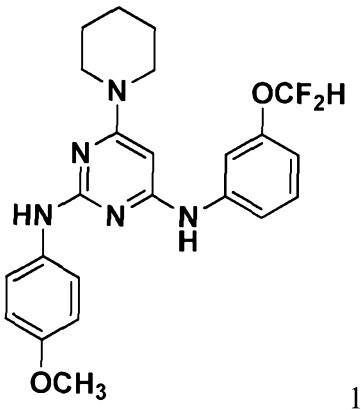
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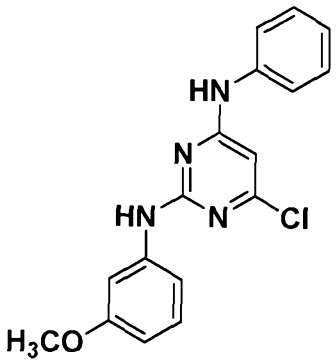


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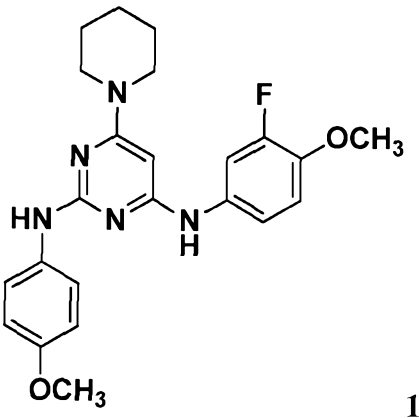


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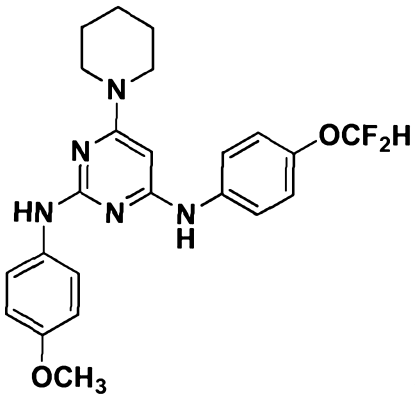




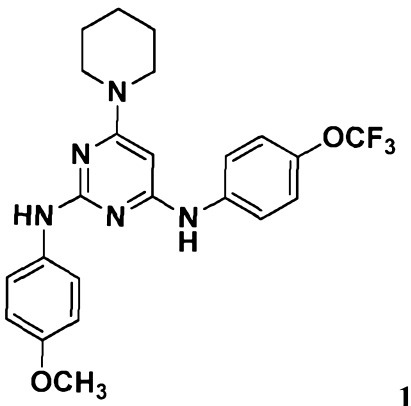
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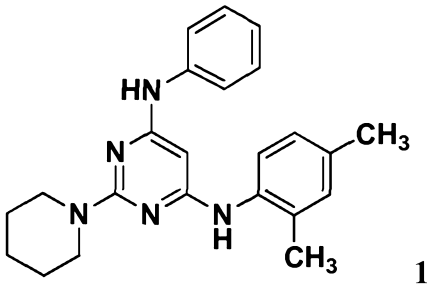
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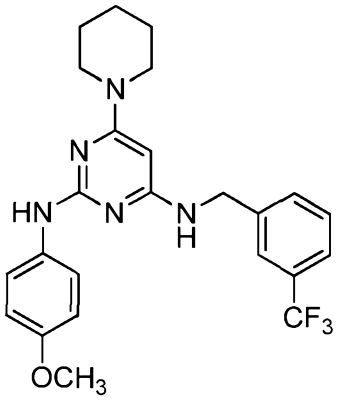
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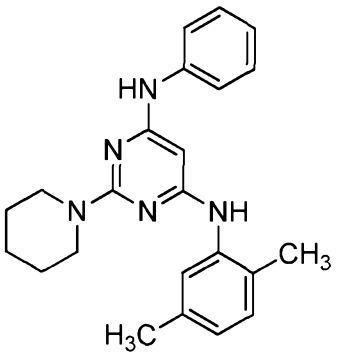
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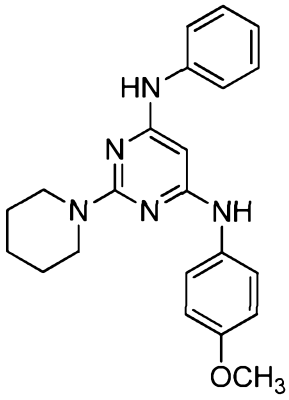
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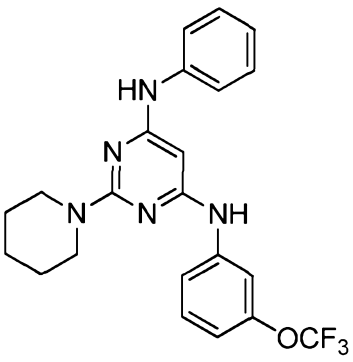
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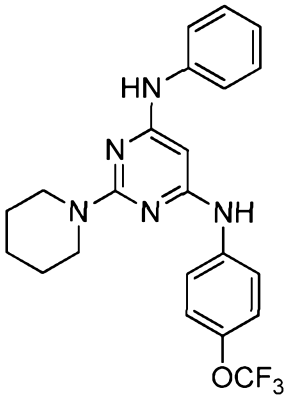
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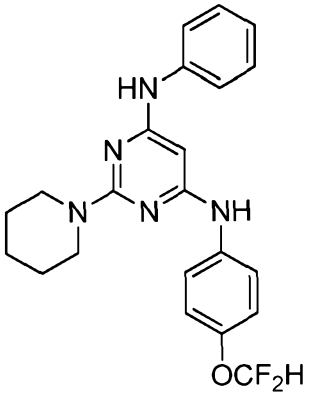
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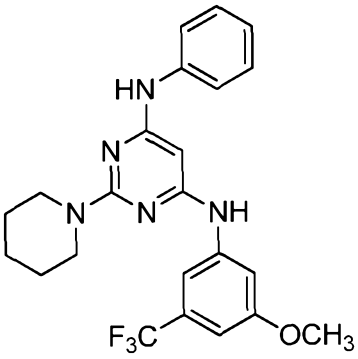
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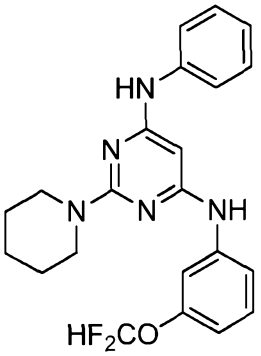
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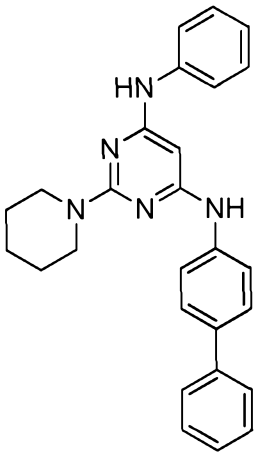

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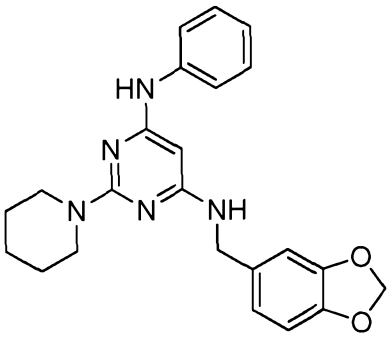

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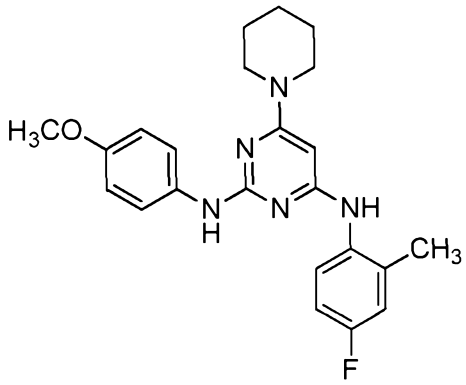

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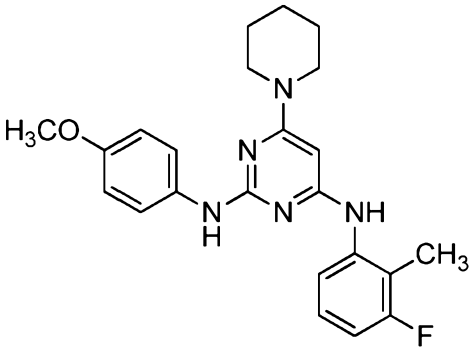

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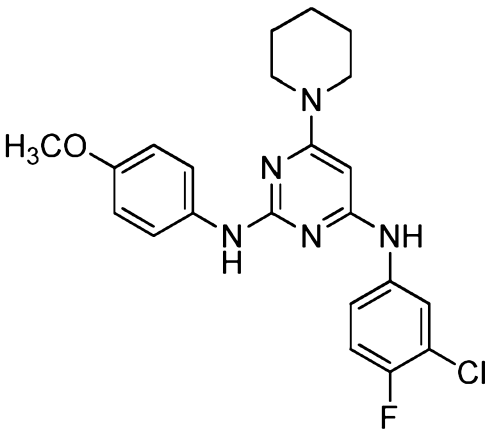

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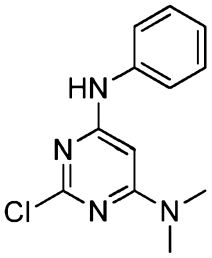

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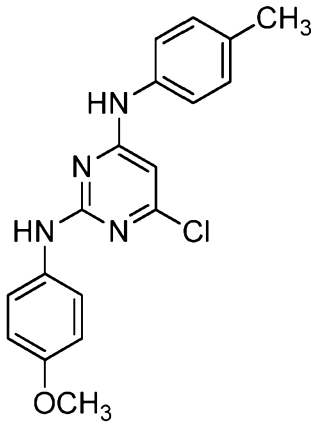
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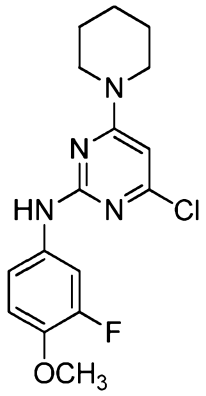
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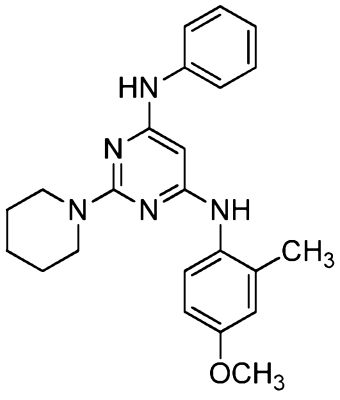
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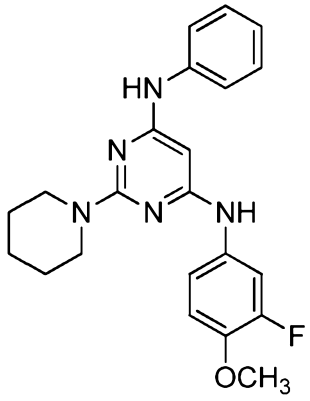
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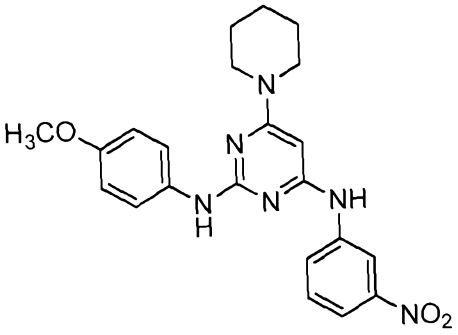
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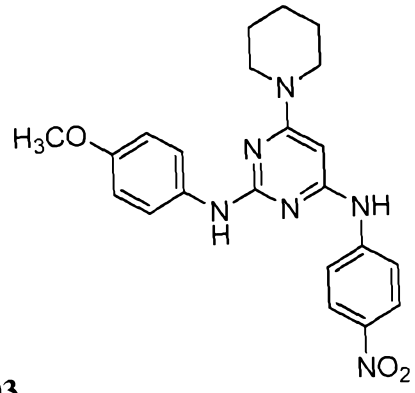
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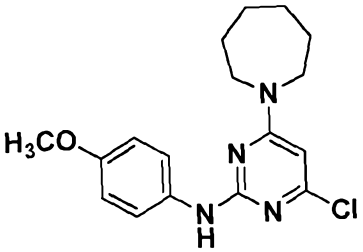
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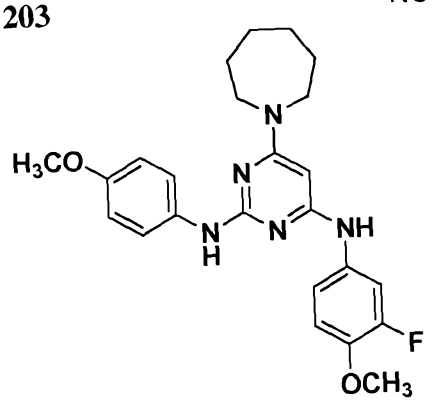

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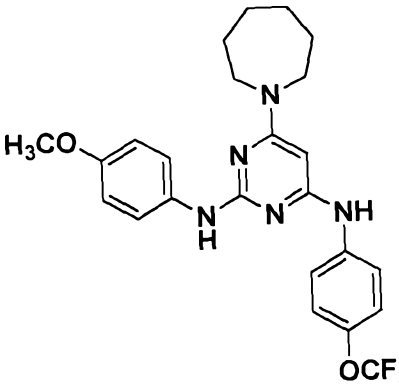

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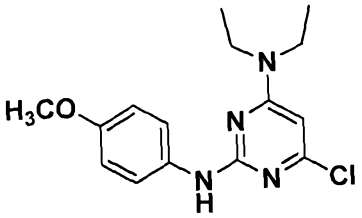

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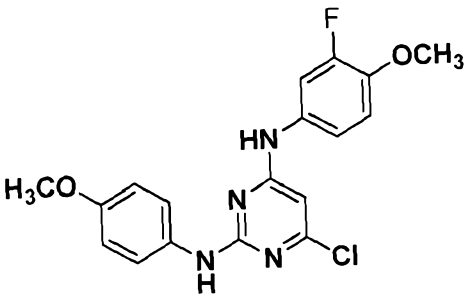

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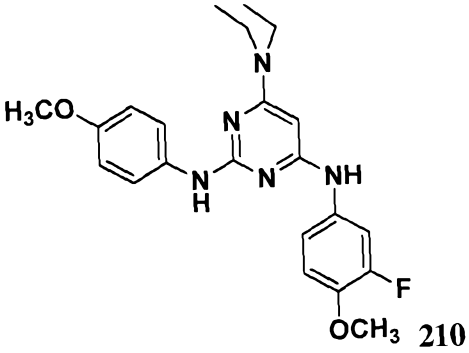

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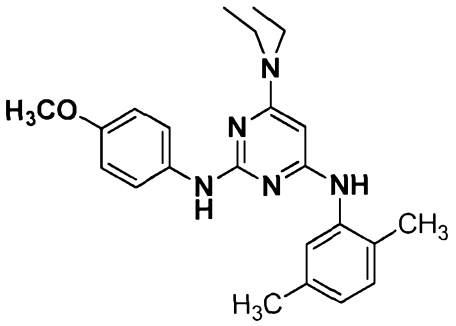

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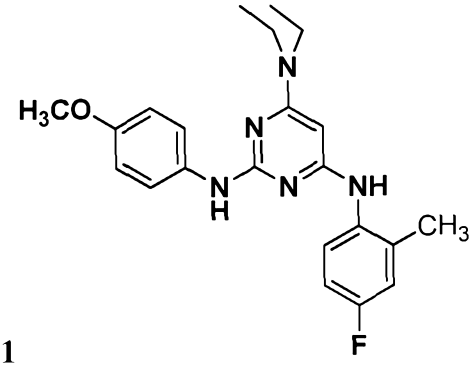

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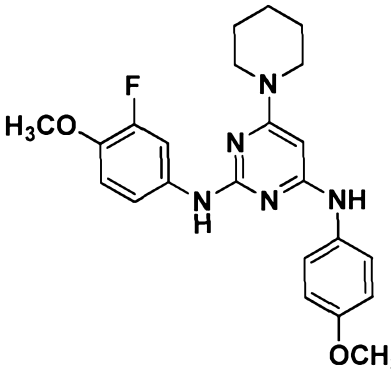

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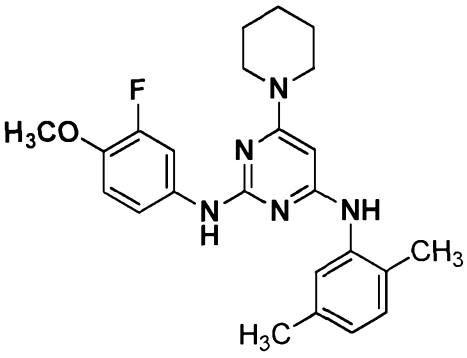
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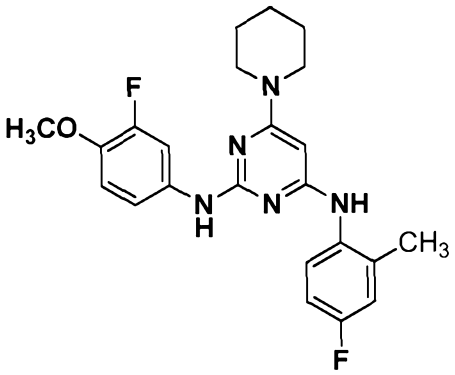
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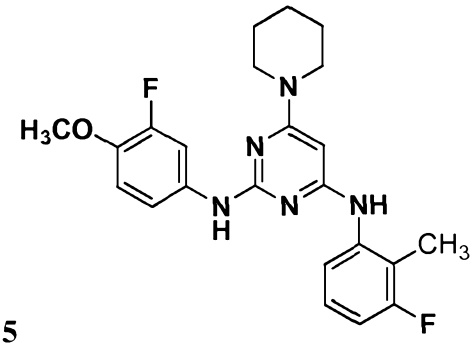


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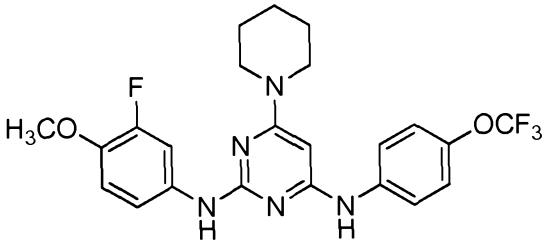
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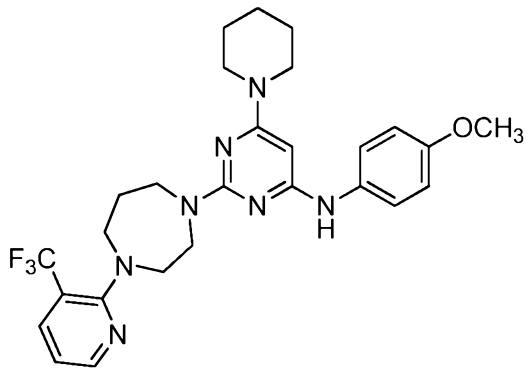


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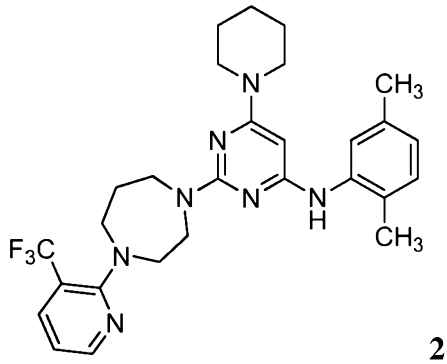
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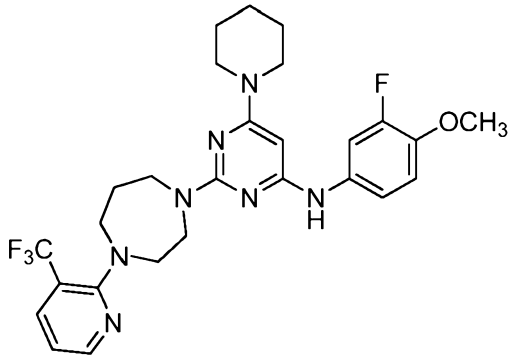
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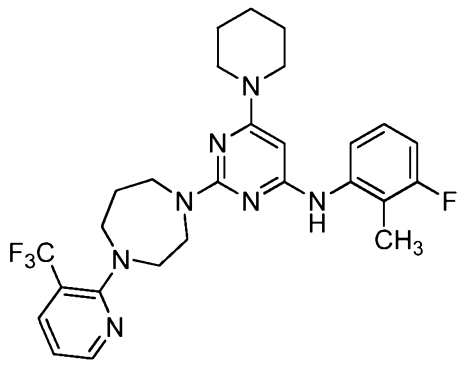
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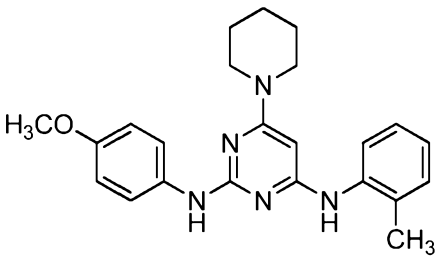
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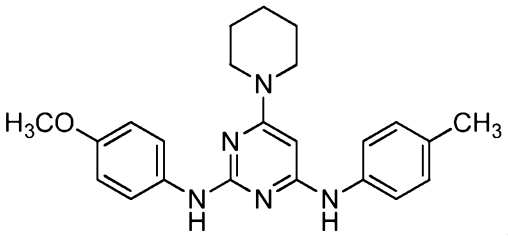
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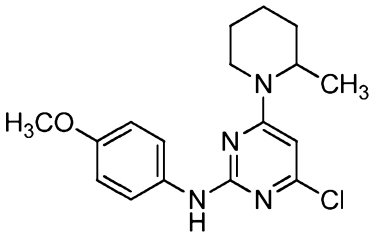
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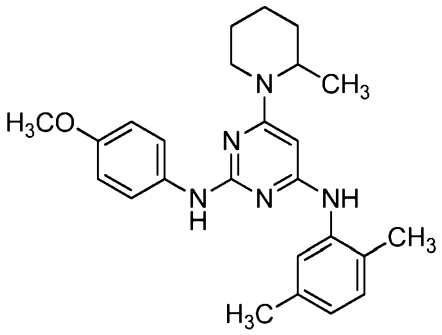

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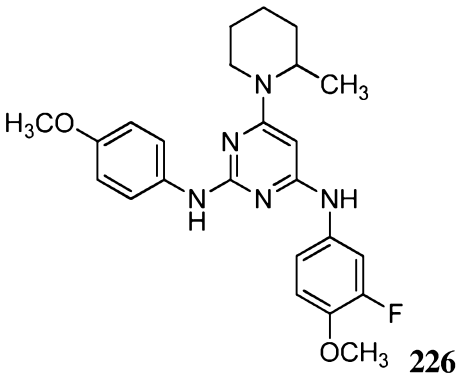

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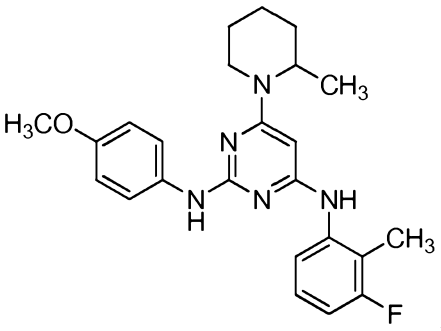

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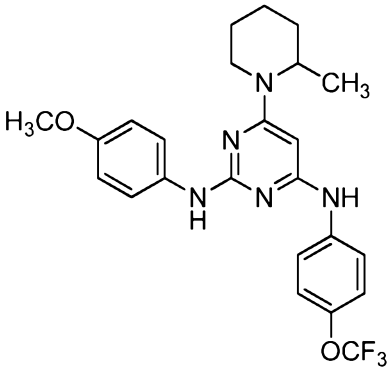

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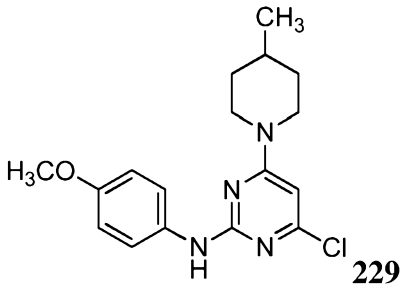

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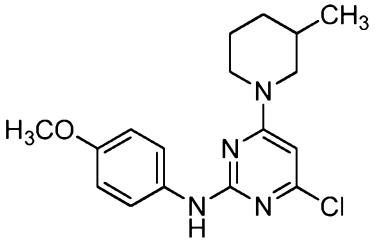

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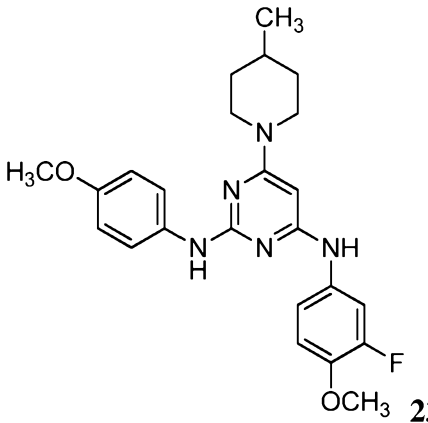

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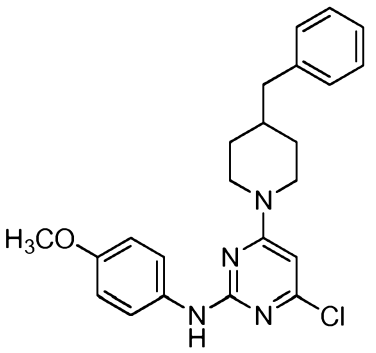

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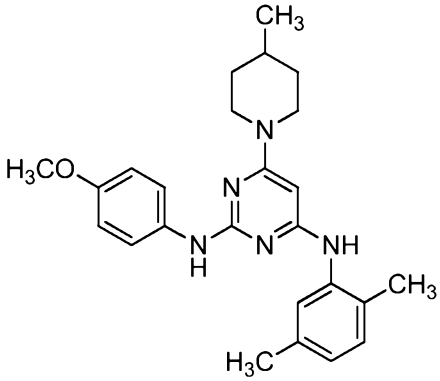
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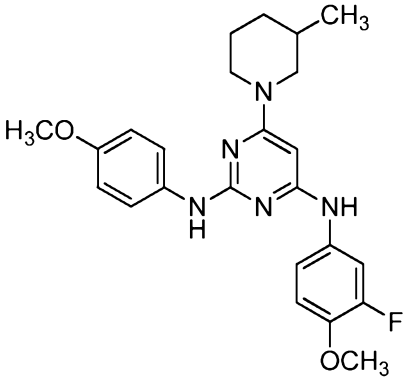
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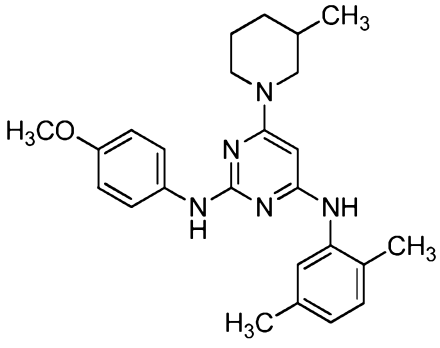
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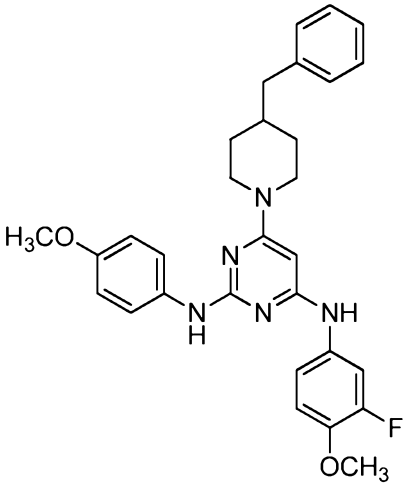
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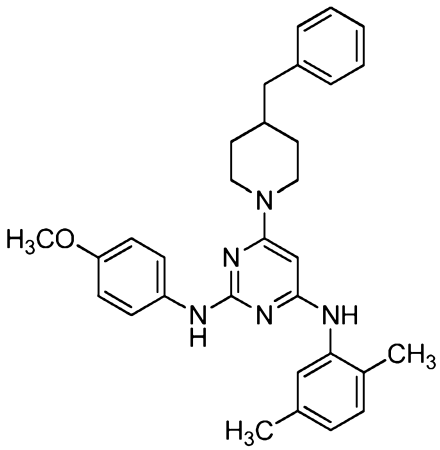
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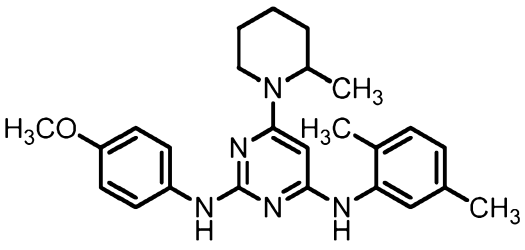
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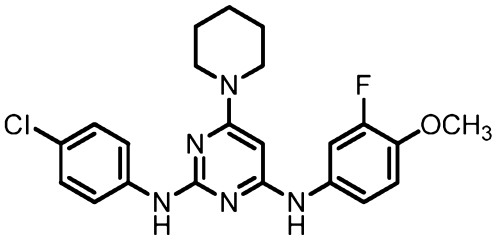


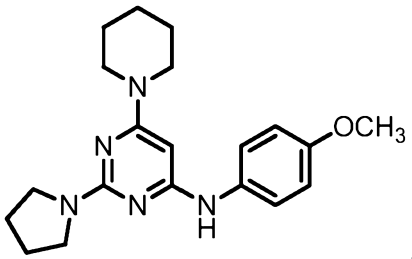
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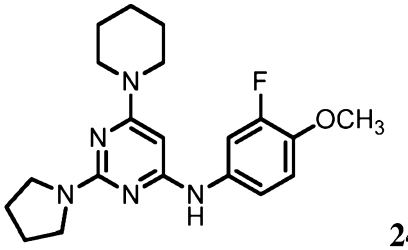


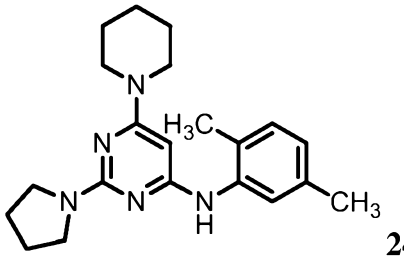
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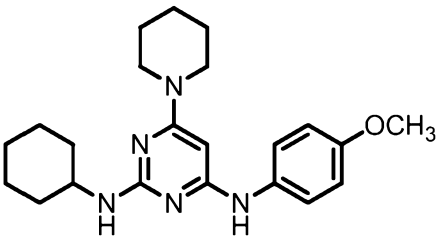

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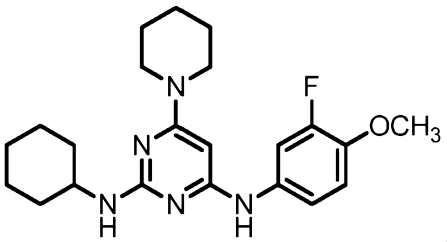

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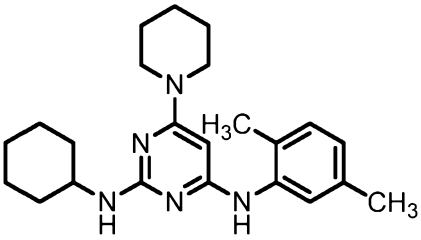

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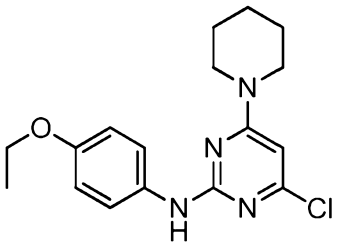

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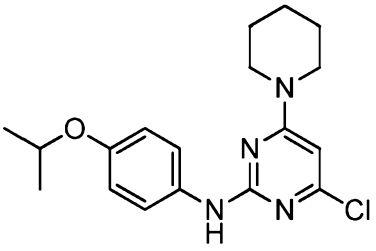

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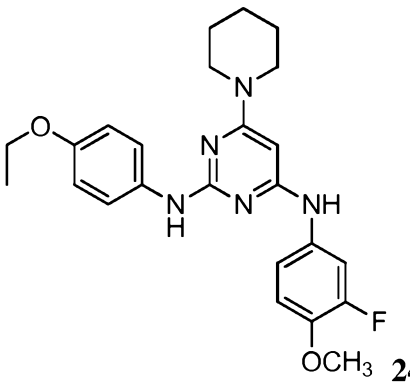

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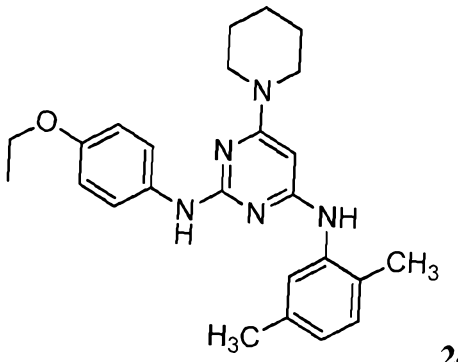

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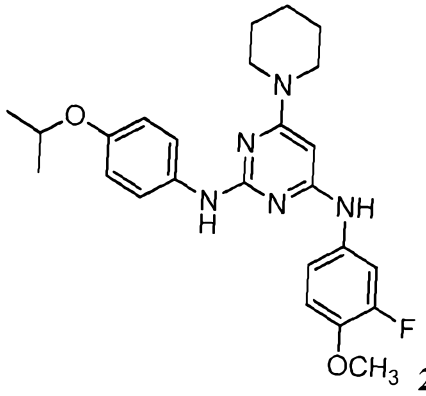

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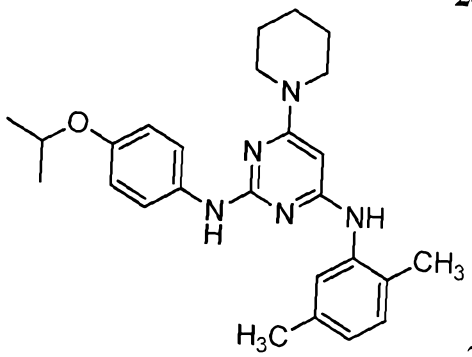

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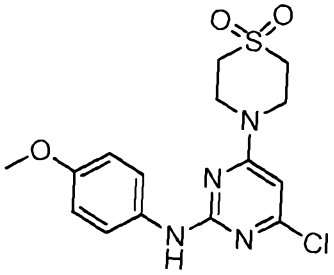
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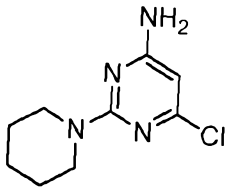
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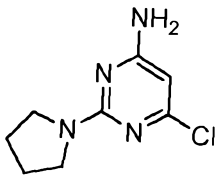
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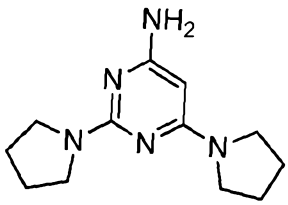
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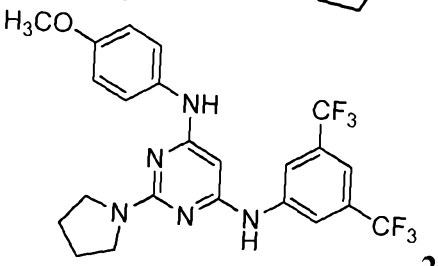
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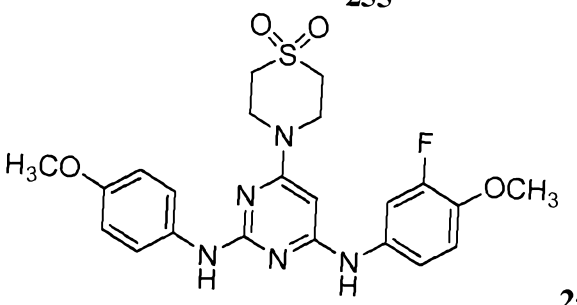
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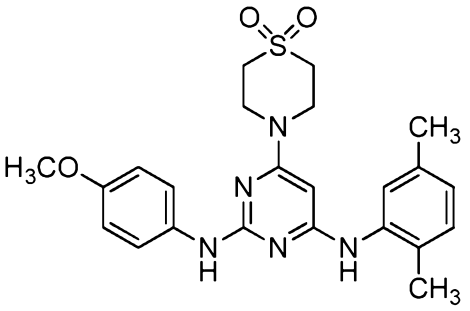
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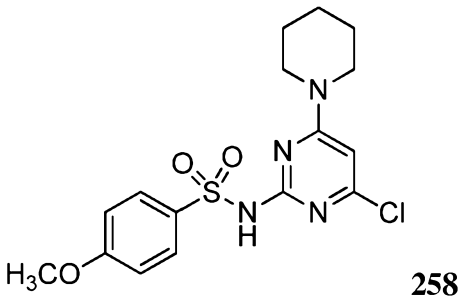


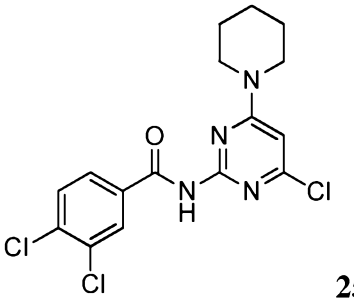
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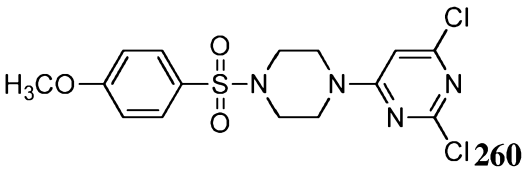


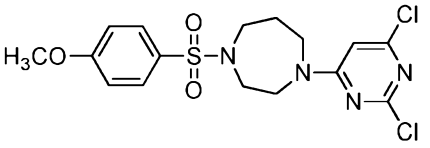
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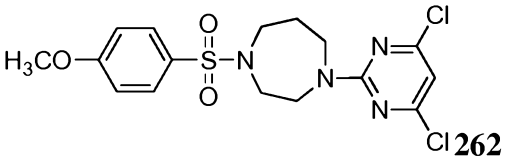

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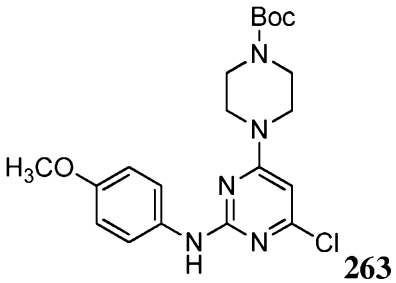

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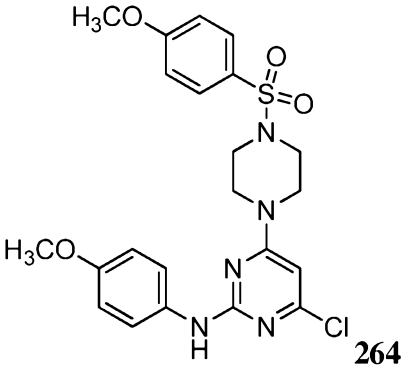

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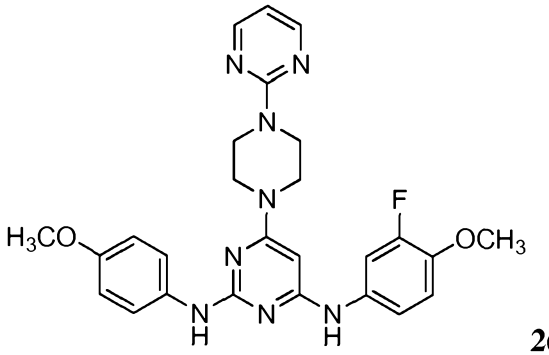

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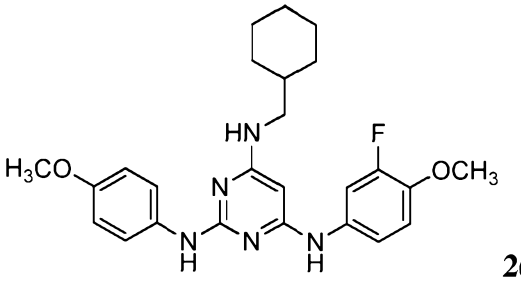

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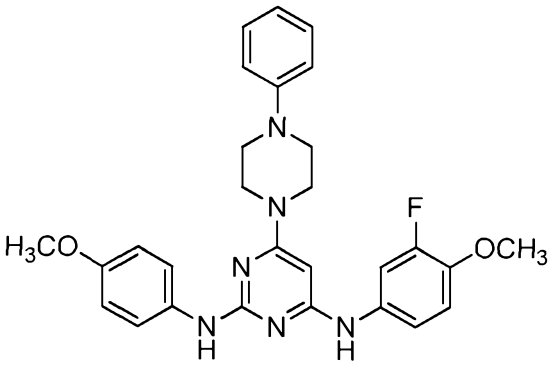

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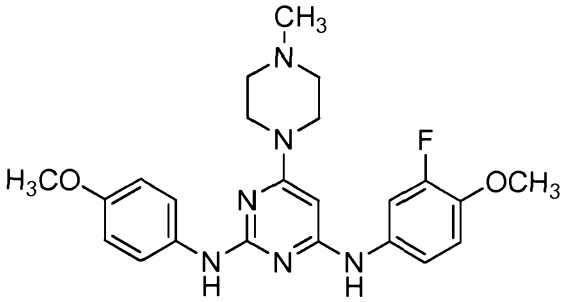
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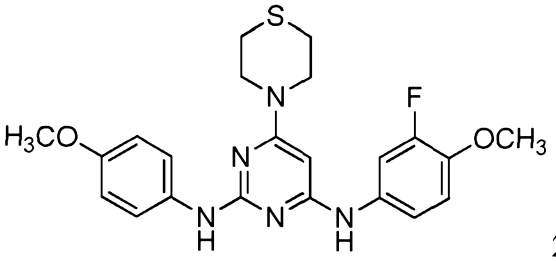


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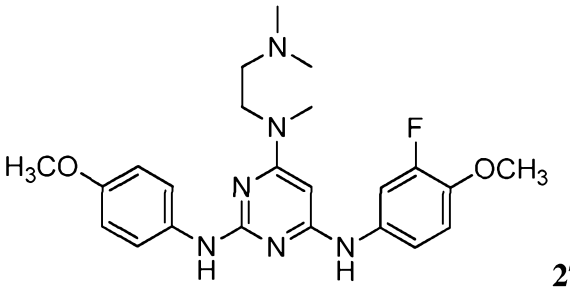
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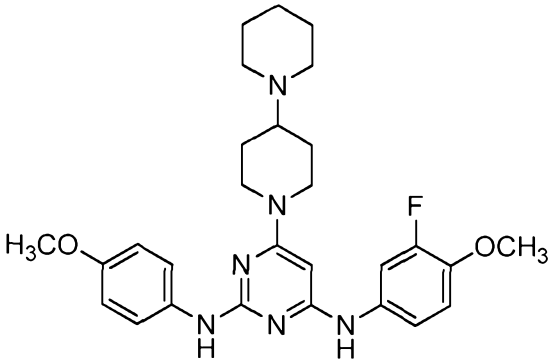


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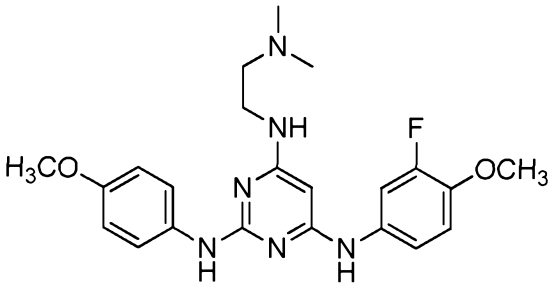
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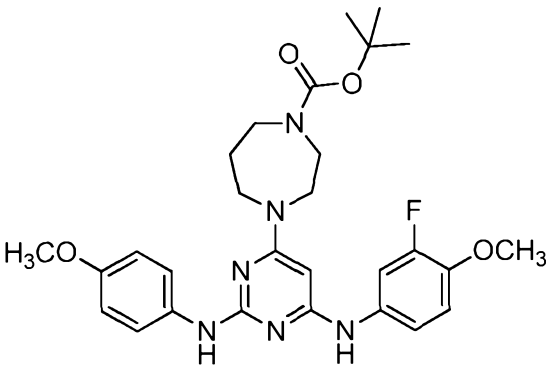


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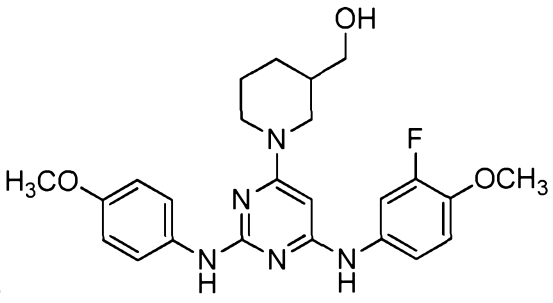


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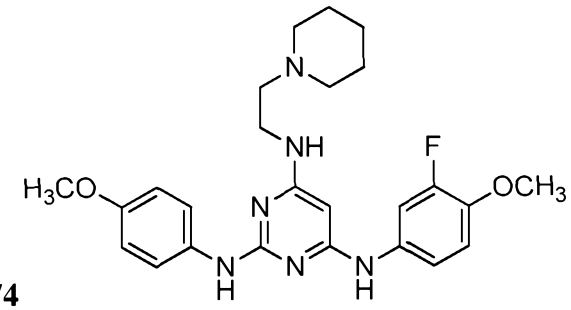
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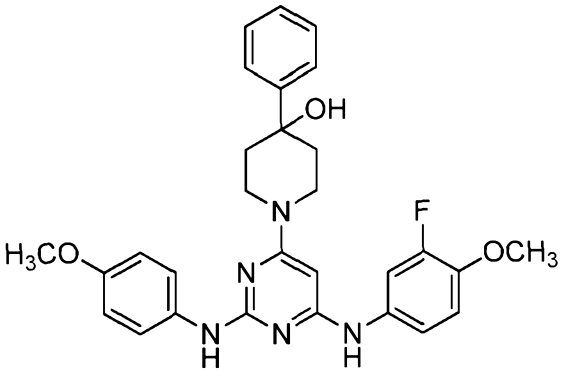


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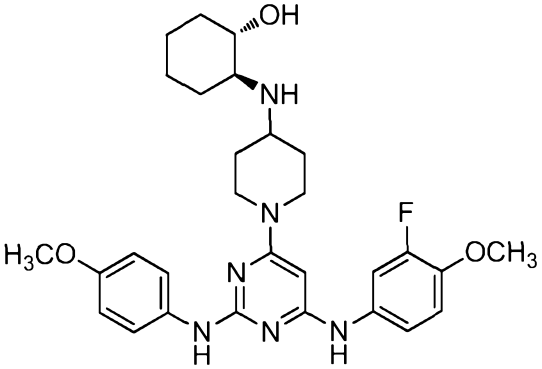


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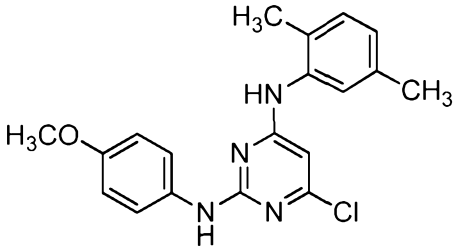
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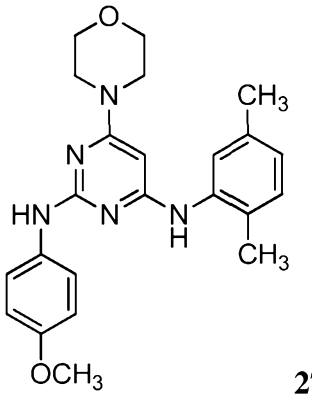


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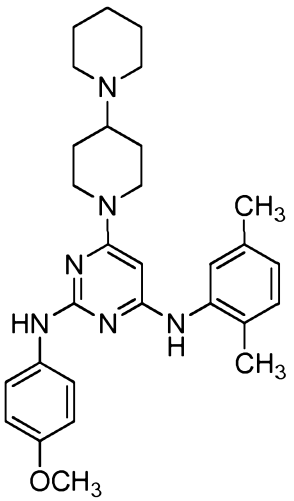


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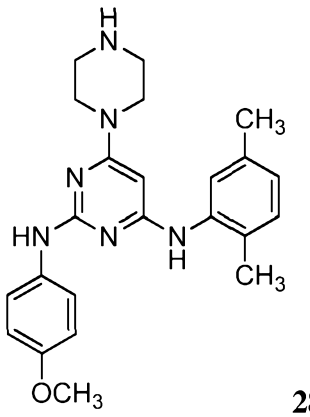
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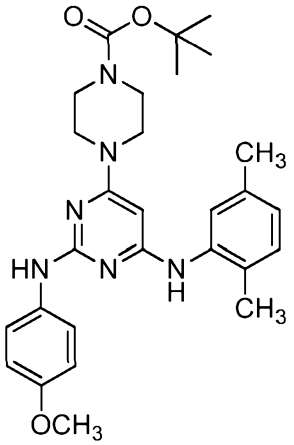
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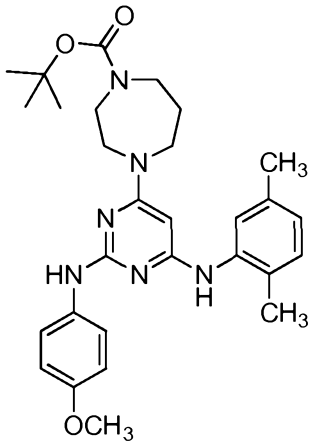
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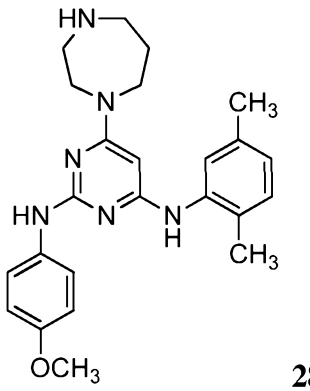
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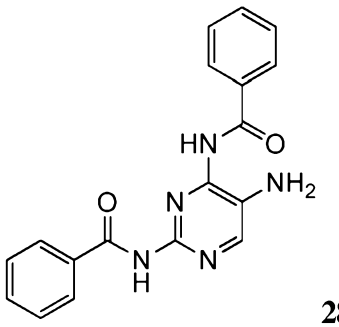
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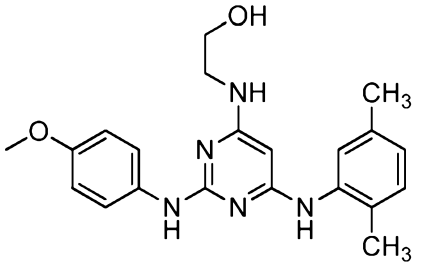
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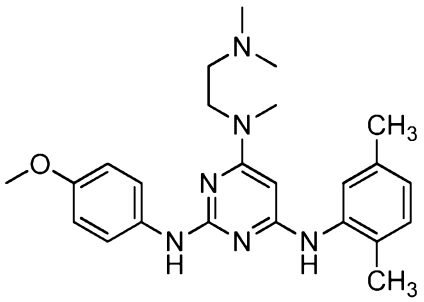
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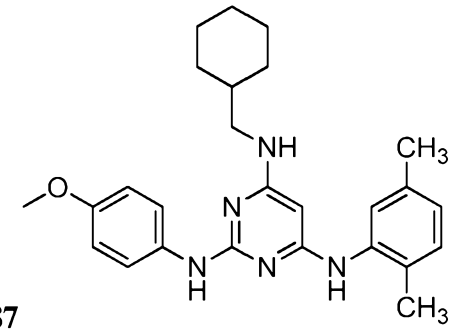
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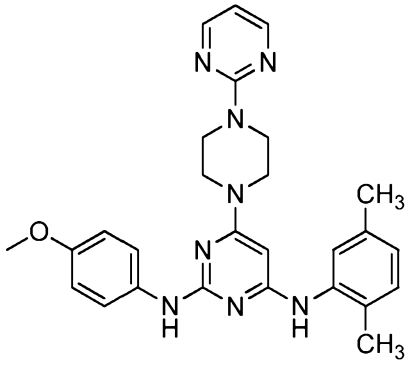
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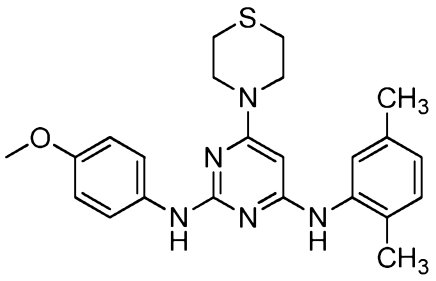
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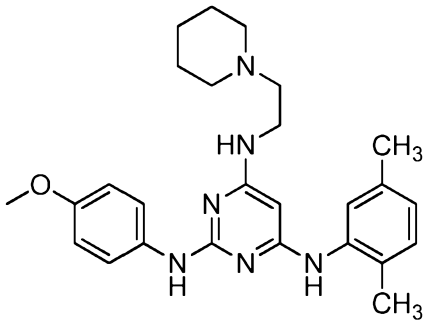
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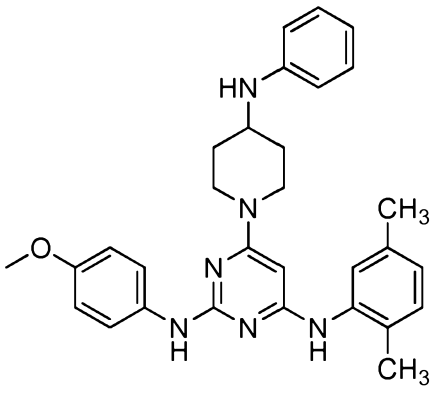
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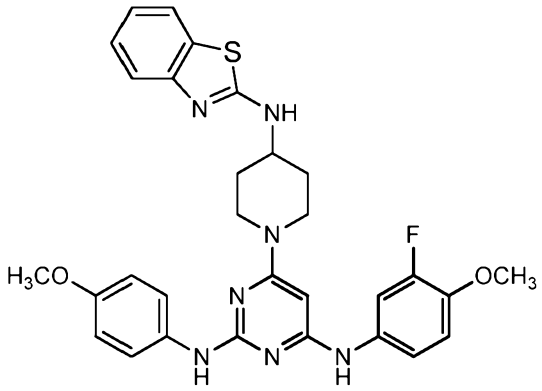
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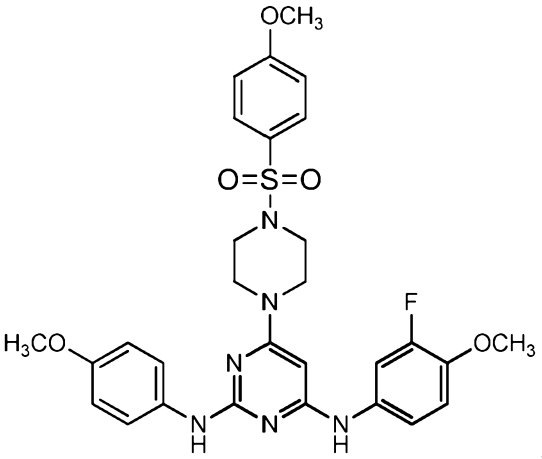
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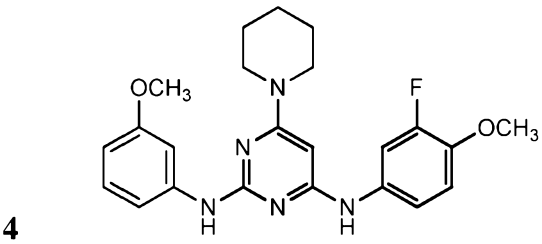
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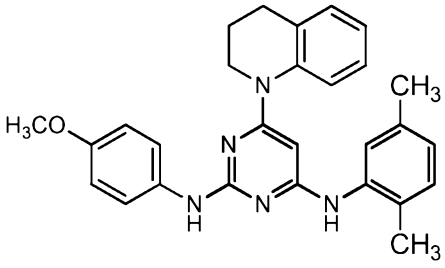


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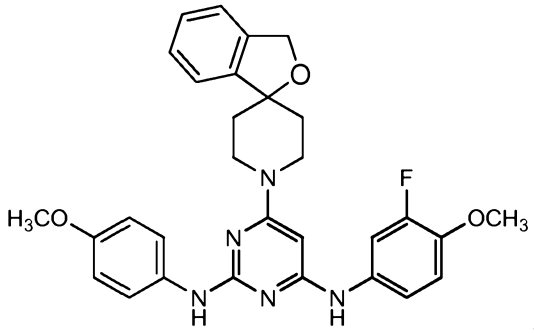


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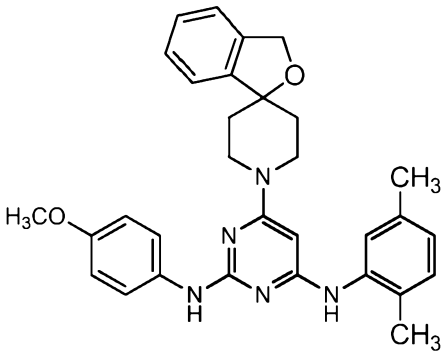
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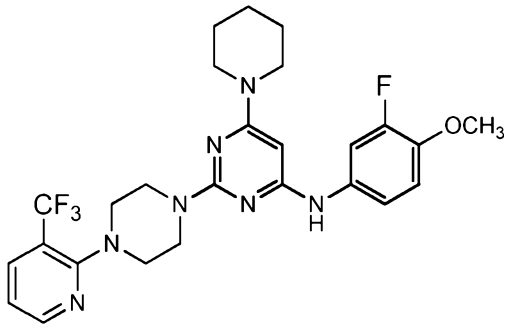
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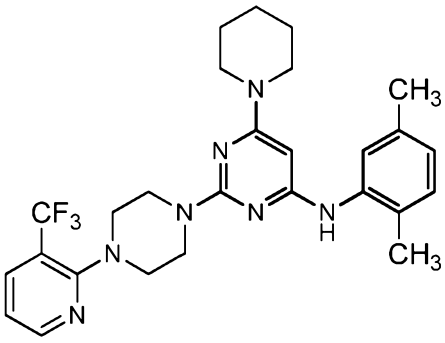
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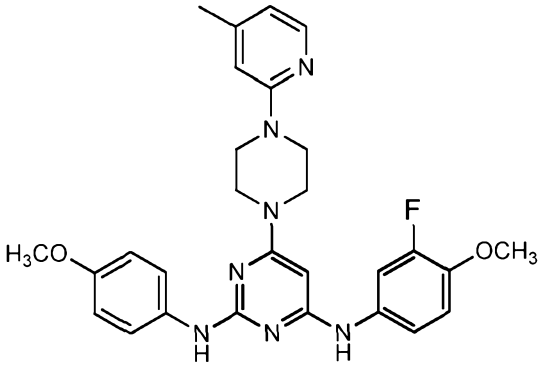
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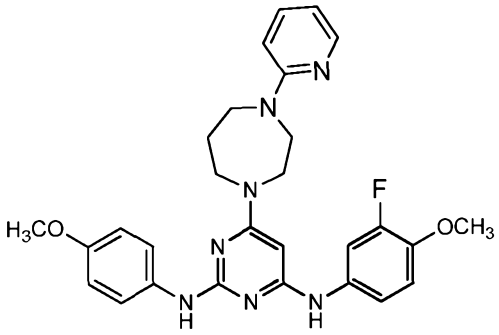
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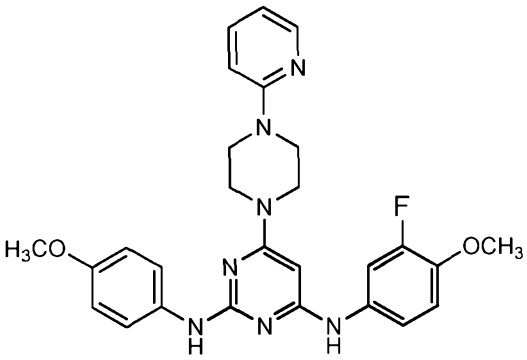
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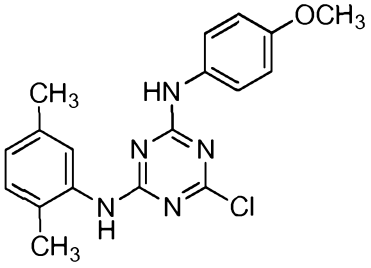
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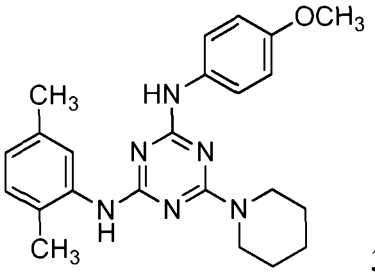
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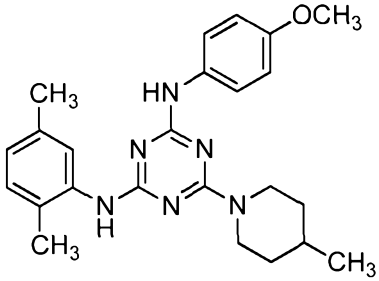
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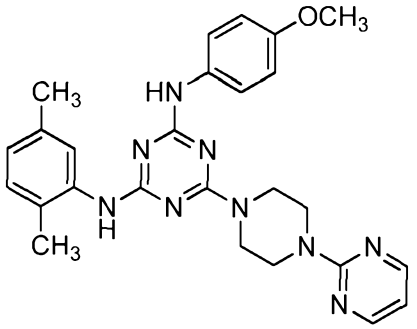
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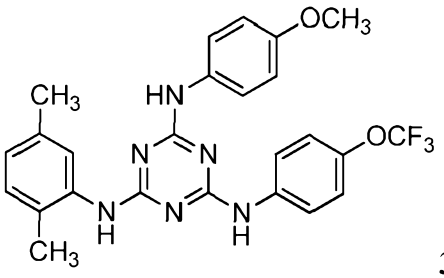
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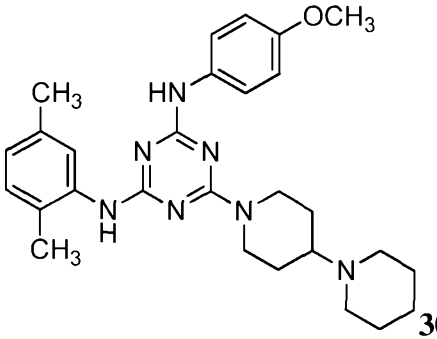
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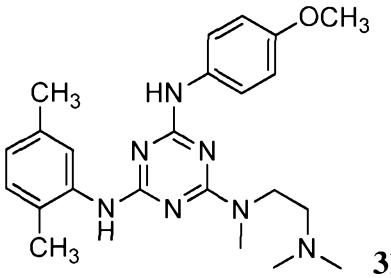
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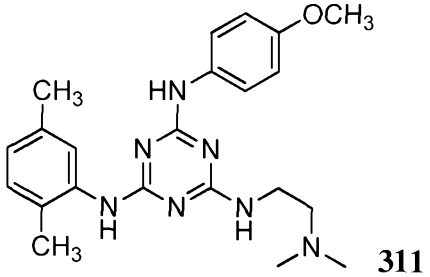
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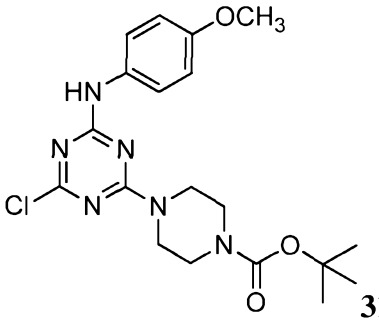
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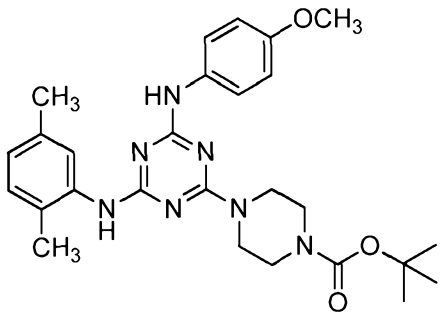
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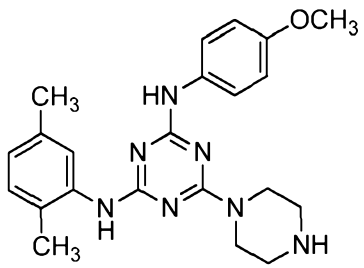
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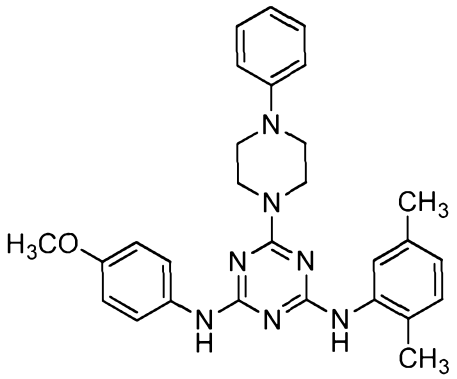
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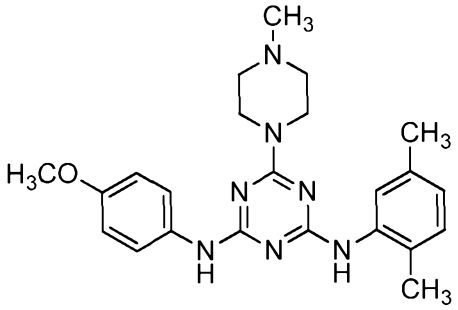
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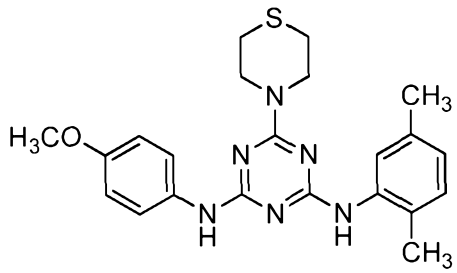
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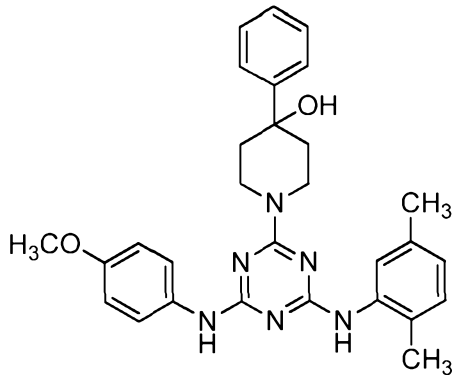
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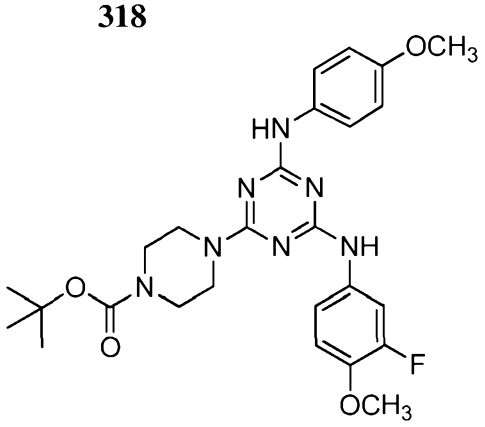
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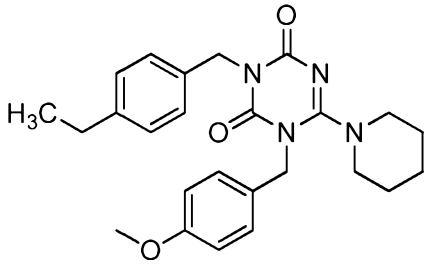
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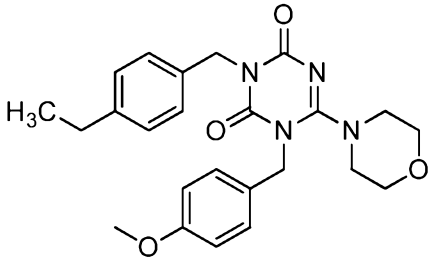
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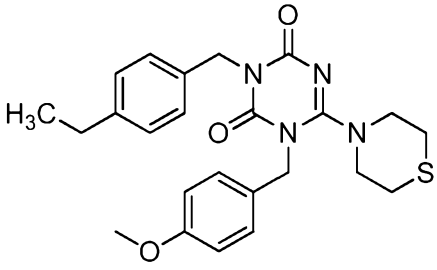
40. The compound of formula (VB) of claim 26 wherein the compound is any of the following:



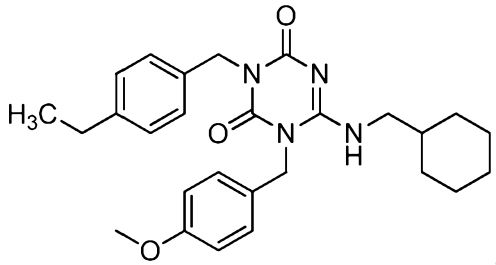
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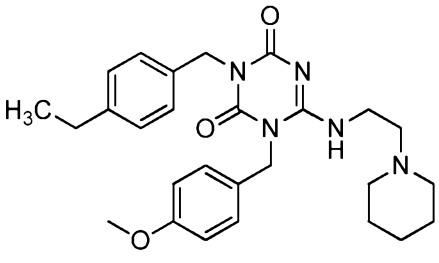
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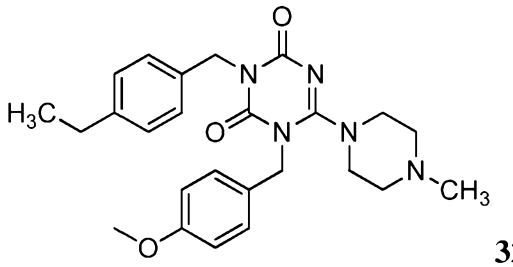
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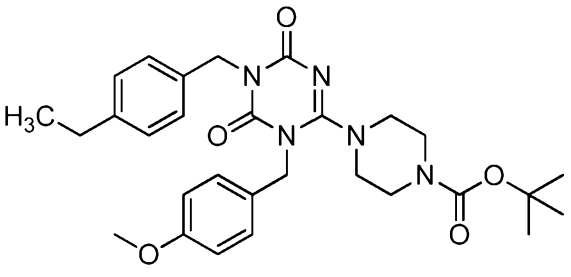
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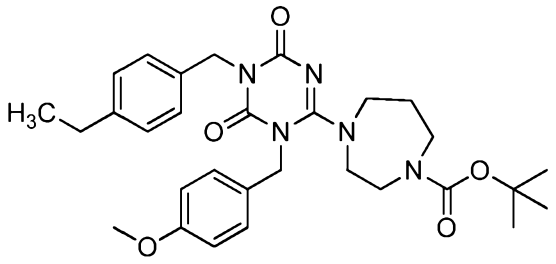
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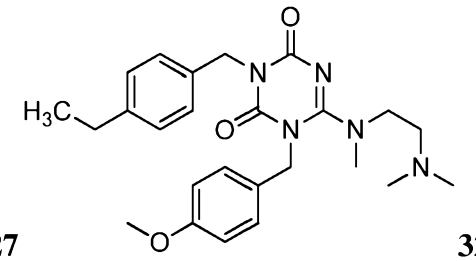
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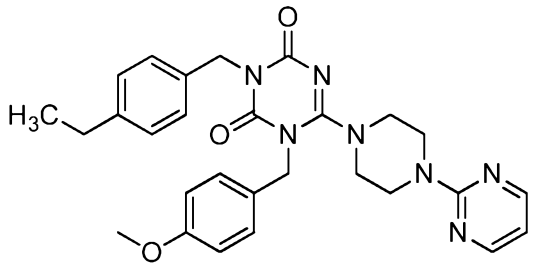
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327



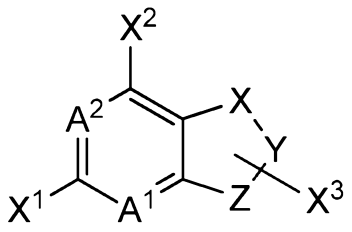
328



329

or a salt thereof.

41. A galanin receptor-modulatory compound of formula (VI)



(VI)

wherein:

$A^1$ and $A^2$ are each independently N or CR', wherein R' is H, optionally substituted (C1-C6)alkyl, or $NR^3R^4$;

X, Y, and Z are each independently N or NR' or CR' or $C(R')_2$ provided that the bond between X and Y, and the bond between Y and Z, can each be a double bond or a single bond provided there is one double bond and one single bond between X and Y and Y and Z;

$X^1$ and $X^2$ is each independently H, halo, cyano, $NR^3R^4$, $Ar^1$, $Ar^1S(O)_q$, or $OR^5$, $N(R^3)S(O)_qAr^1$, or $N(R^3)C(=O)Ar^1$;

$Ar^1$ is optionally substituted aryl or heteroaryl;

$R^3$ and $R^4$ are each independently H, alkyl, cycloalkyl or bicycloalkyl, aryl, heterocyclyl, or heteroaryl, wherein any alkyl, cycloalkyl or bicycloalkyl, aryl, heterocyclyl, or heteroaryl is substituted with 0-3 J and any alkyl, cycloalkyl or bicycloalkyl, aryl, heterocyclyl, or heteroaryl can be bonded directly to a nitrogen atom

which bears $R^3$ or $R^4$ or can be bonded to the nitrogen atom via M, wherein M is $(CH_2)_n$, $S(O)_q(CH_2)_n$, $(CH_2)_nN(R)C(O)$, or $(CH_2)_nC(O)N(R)$, wherein n is 0-9 and q is 0, 1, or 2; or $R^3$ and $R^4$ together with a nitrogen atom to which they are bonded form a heterocyclyl optionally further comprising 1 or 2 additional heteroatoms selected from O, $S(O)_q$, or $NR^3$, wherein the heterocyclyl is substituted with 0-3 J;

$R^5$ is H, alkyl, cycloalkyl, aryl, heterocyclyl, or heteroaryl, any of which non-hydrogen groups is optionally mono- or independently multi-substituted with J;

J is independently at each occurrence R, F, Cl, Br, I, OR, CN, $CF_3$, $CF_2H$, $OCF_3$, $OCF_2H$, =O, =S, C(O), S(O), methylenedioxy, ethylenedioxy, $N(R)_2$, SR, SOR, $SO_2R$, $SO_2N(R)_2$, $SO_3R$, C(O)R, C(O)C(O)R, $C(O)CH_2C(O)R$, C(S)R, C(O)OR, OC(O)R, OC(O)OR, $C(O)N(R)_2$, $OC(O)N(R)_2$, $C(S)N(R)_2$, $(CH_2)_{0-2}NHC(O)R$, N(R)N(R)C(O)R, N(R)N(R)C(O)OR, $N(R)N(R)CON(R)_2$, $N(R)SO_2R$, $N(R)SO_2N(R)_2$, N(R)C(O)OR, N(R)C(O)R, N(R)C(S)R, $N(R)C(O)N(R)_2$, $N(R)C(S)N(R)_2$, N(COR)COR, N(OR)R, $C(=NH)N(R)_2$, C(O)N(OR)R, or C(=NOR)R;

R is independently at each occurrence hydrogen, alkyl, alkoxy, haloalkyl, haloalkoxy, alkenyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl, wherein any alkyl, alkoxy, haloalkyl, haloalkoxy, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl is substituted with 0-4 J; or wherein two R groups together with a nitrogen atom or with two adjacent nitrogen atoms to which they are bonded can together form a three to eight membered heterocyclyl substituted with 0-4 J; optionally further comprising 1-3 additional ring heteroatoms selected from the group consisting of O, N, and $S(O)_q$;

wherein any cycloalkyl, aryl, heterocyclyl, or heteroaryl can be fused, bridged, or in a spiro configuration with one or more additional optionally substituted cycloalkyl, aryl, heterocyclyl, and heteroaryl, monocyclic, bicyclic or polycyclic, saturated, partially unsaturated, or aromatic rings;

including all stereoisomers thereof and all isotopically labeled forms thereof;

or a salt thereof.

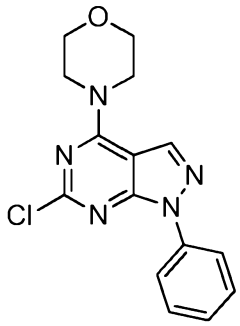
42. The compound of claim 41 wherein $X^1$ is halo, optionally substituted aryl, or optionally substituted arylamino; preferably chloro, p-methoxyphenyl, or p-methoxyphenylamino.

43. The compound of claim 41 wherein $X^2$ is heterocyclyl; preferably morpholinyl, or piperidinyl.

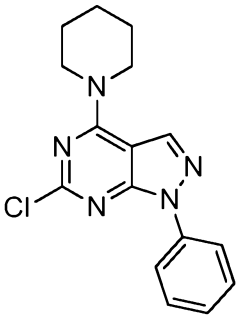
44. The compound of claim 41 wherein X is CH, or Y and Z are each N, or both.

45. The compound of claim 41 wherein Z is NR' and R' is optionally substituted phenyl.

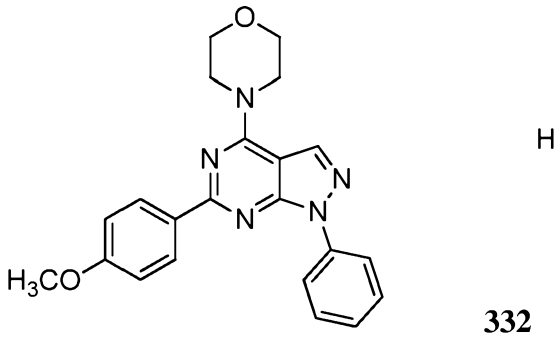
46. The compound of claim 41 wherein the compound is any of the following:



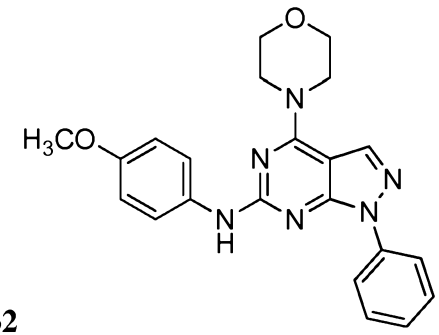
**330**



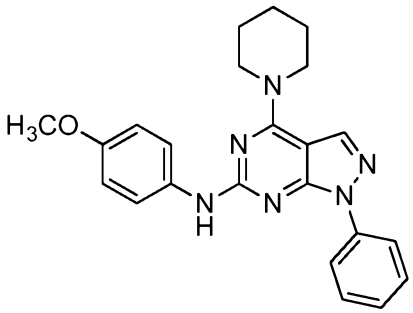
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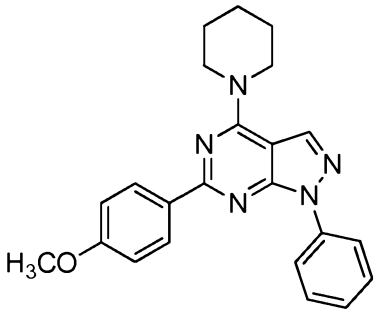
**332**



**333**



**334**



**335**

or a salt thereof.

47. The compound of any one of claims 1, 11, 16, 21, 26, or 41 wherein the compound is a modulator of a galanin receptor.

48. The compound of claim 47 wherein the compound is a selective modulator of GalR1 or of GalR2 or of GalR3.

49. A pharmaceutical composition comprising a compound of any one of claims 1, 11, 16, 21, 26, or 41 and a pharmaceutically acceptable excipient.

50. A method of modulation a galanin receptor comprising contacting the receptor with an effective amount or concentration of a compound of any one of claims 1, 11, 16, 21, 26, or 41.

51. The method of claim 50 wherein the contacting is *in vivo* in a human patient.

52. The method of claim 50 wherein the amount or concentration of the compound is effective to selectively modulate GalR1 or GalR2.

53. A method of treatment of a malcondition in a patient for which modulation of a galanin receptor is medically indicated, comprising administering to the patient a compound of any one of claims 1, 11, 16, 21, 26, or 41 in a dose, at a frequency, and for a duration sufficient to provide a beneficial effect to the patient.

54. The method of claim 53 wherein the malcondition comprises epilepsy or seizure disorders, mood disorders including depression and anxiety spectrum disorders; drug addiction including addiction to alcohol or tobacco; autistic spectrum diseases and pervasive development disorders; Alzheimer's disease or other dementias; cognition disorders; cerebral or myocardial stroke; demyelinating diseases including multiple sclerosis, Guillain-Barre syndrome and Charcot-Marie-Tooth disease; neurodegenerative diseases including Parkinson's disease, Lou Gehrig's diseases, Huntington's disease, and HIV dementia; neurotrauma; diabetes, obesity, metabolic syndrome and feeding disorders; solid tumors and leukemia/lymphoma; pain; neuropathies; sleeping disorders and regulation; neuroprotection; and inflammation.

55. Use of a compound of any one of claims 1, 11, 16, 21, 26, or 41 in treatment of a malcondition in a human patient.

56. The use of claim 55 wherein modulation of any galanin receptor is medically indicated for treatment of the malcondition.

57. The use of claim 55 wherein the malcondition comprises epilepsy or seizure disorders, mood disorders including depression and anxiety spectrum disorders; drug addiction including addiction to alcohol or tobacco; autistic spectrum diseases and pervasive development disorders; Alzheimer's disease or other dementias; cognition disorders; cerebral or myocardial stroke; demyelinating diseases including multiple sclerosis, Guillain-Barre syndrome and Charcot-Marie-Tooth disease; neurodegenerative diseases including Parkinson's disease, Lou Gehrig's diseases, Huntington's disease, and HIV dementia; neurotrauma; diabetes, obesity, metabolic syndrome and feeding disorders;

solid tumors and leukemia/lymphoma; pain; neuropathies; sleeping disorders and regulation; neuroprotection; and inflammation.

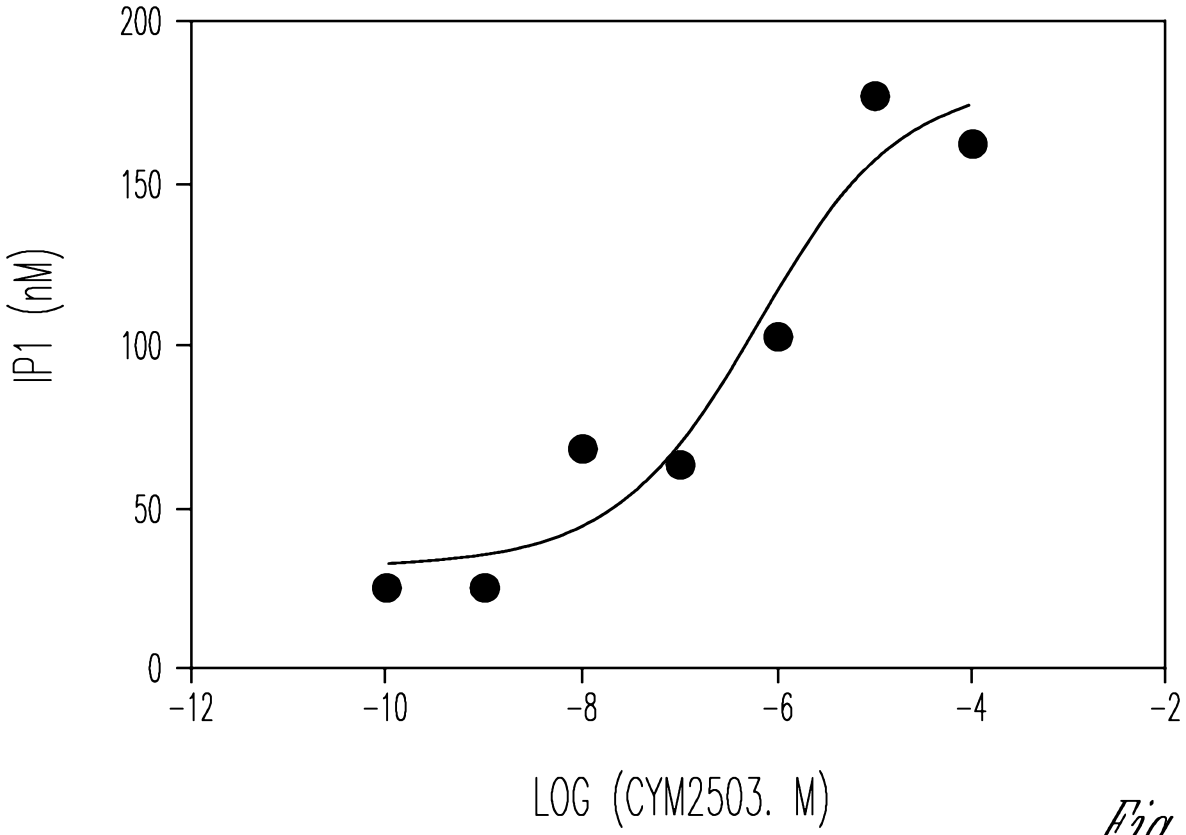

200
150
100
50
0
IP1 (nM)
-12
-10
-8
-6
-4
-2
LOG (CYM2503. M)

*Fig. 1A*

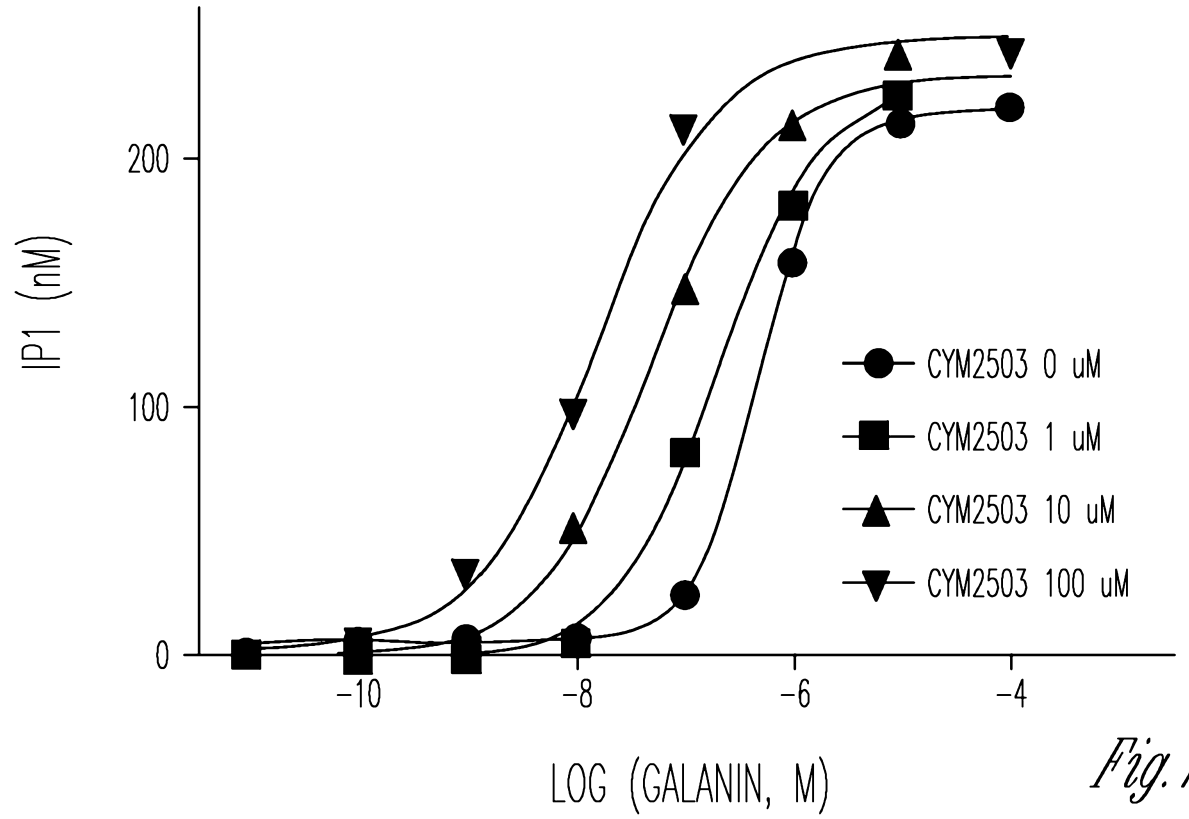

200
100
0
IP1 (nM)
-10
-8
-6
-4
LOG (GALANIN, M)
CYM2503 0 uM
CYM2503 1 uM
CYM2503 10 uM
CYM2503 100 uM

*Fig. 1B*

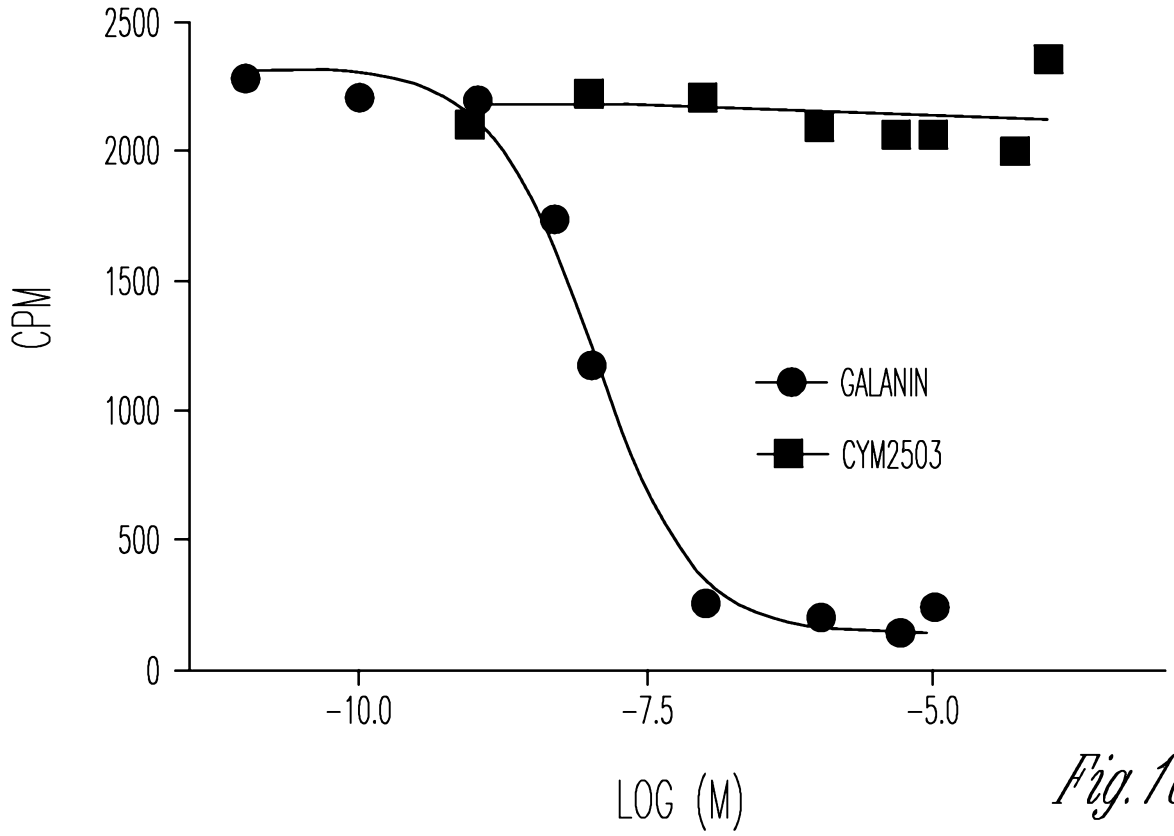

2500
2000
1500
1000
500
0
CPM
GALANIN
CYM2503
-10.0
-7.5
-5.0
LOG (M)

*Fig. 1C*

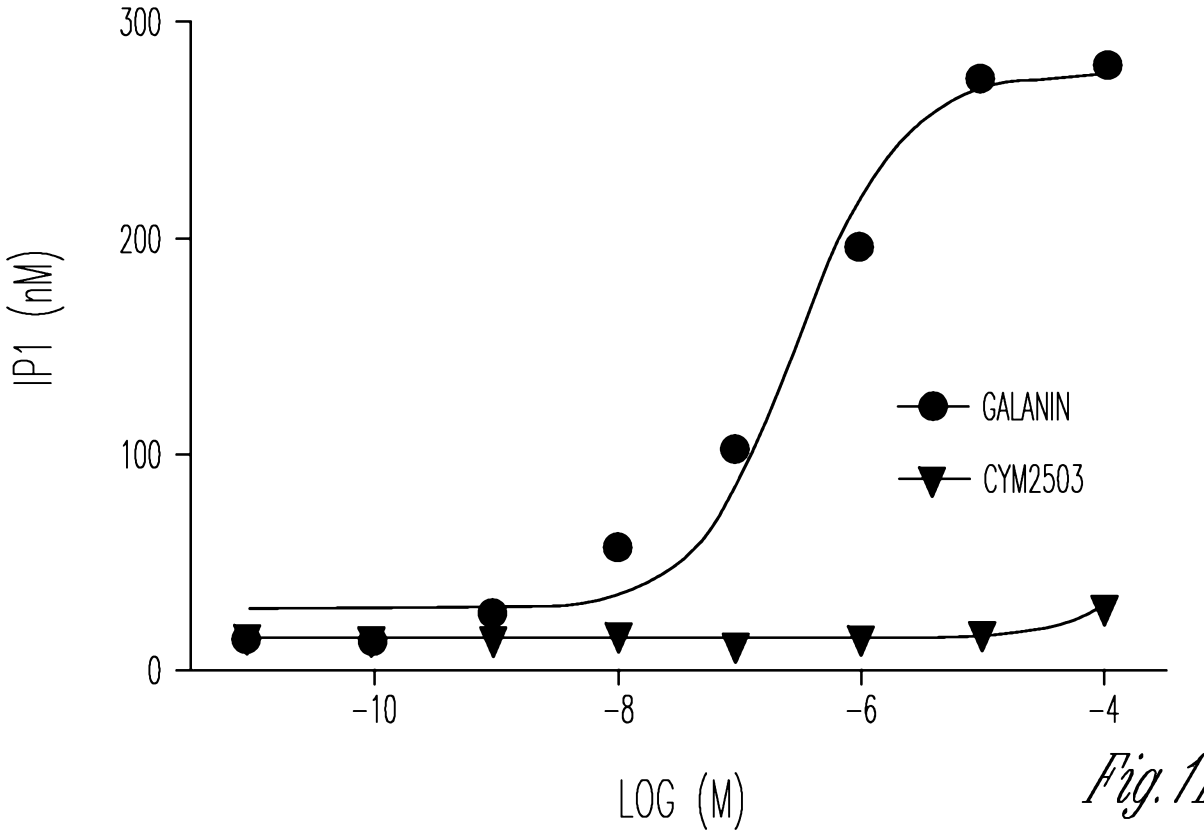

300
200
100
0
IP1 (nM)
GALANIN
CYM2503
-10
-8
-6
-4
LOG (M)

*Fig. 1D*

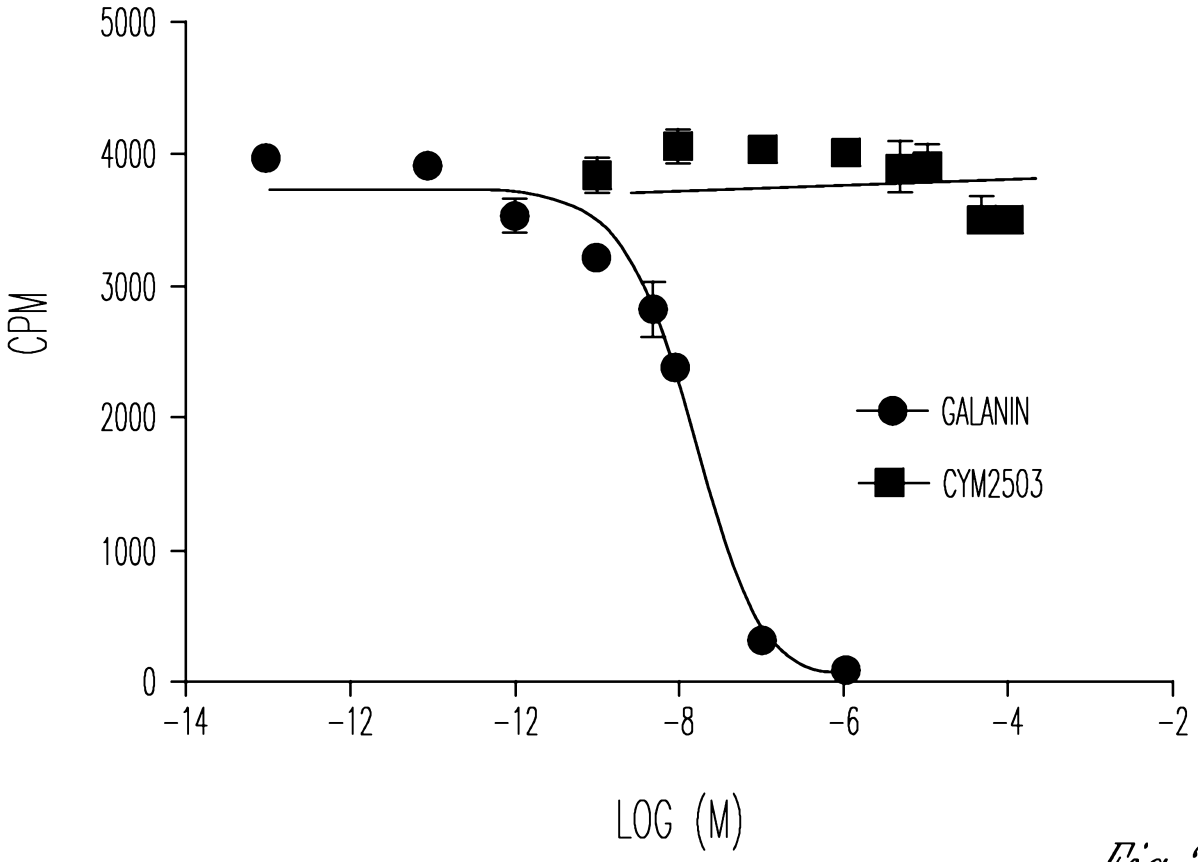

5000
4000
3000
2000
1000
0
CPM
−14
−12
−12
−8
−6
−4
−2
LOG (M)
GALANIN
CYM2503

*Fig.2A*

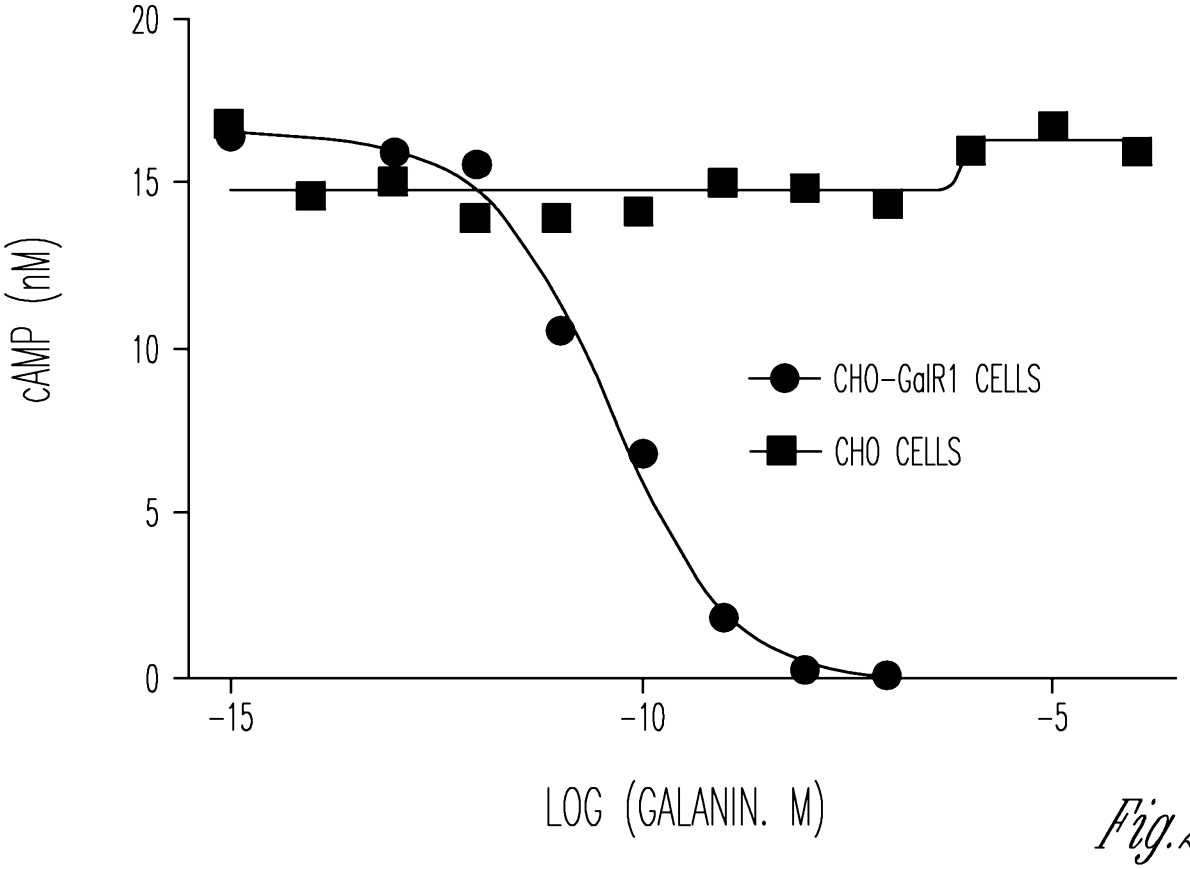

20
15
10
5
0
cAMP (nM)
−15
−10
−5
LOG (GALANIN. M)
CHO-GalR1 CELLS
CHO CELLS

*Fig.2B*

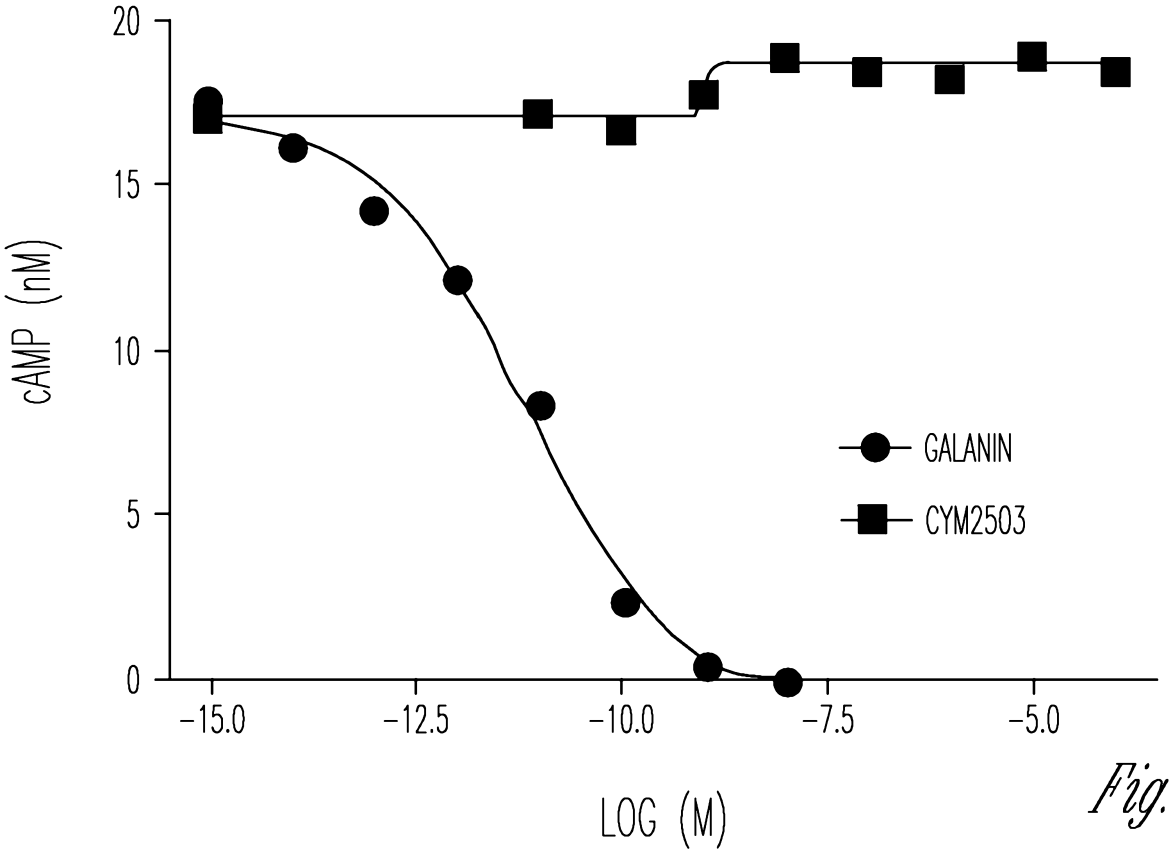

20
15
10
5
0
cAMP (nM)
−15.0
−12.5
−10.0
−7.5
−5.0
LOG (M)
GALANIN
CYM2503

*Fig.2C*

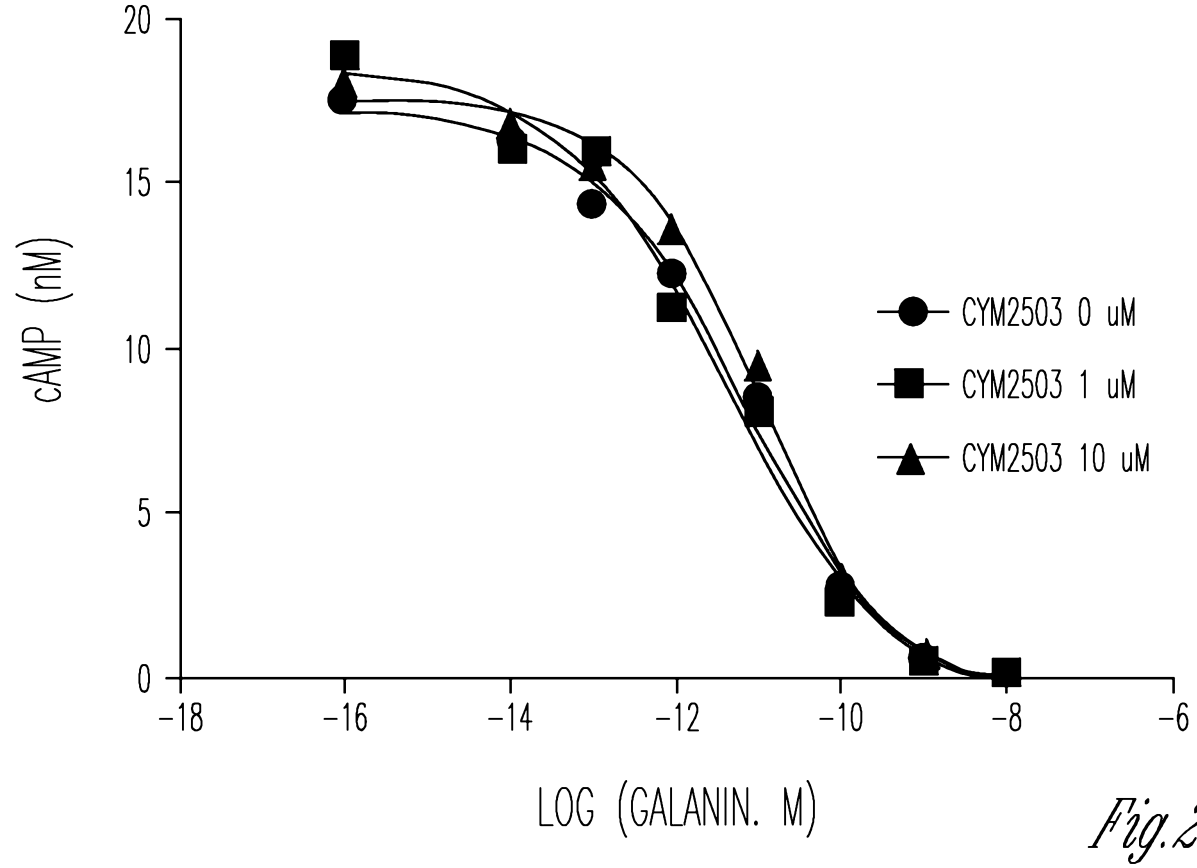

20
15
10
5
0
cAMP (nM)
−18
−16
−14
−12
−10
−8
−6
LOG (GALANIN. M)
CYM2503 0 uM
CYM2503 1 uM
CYM2503 10 uM

*Fig.2D*

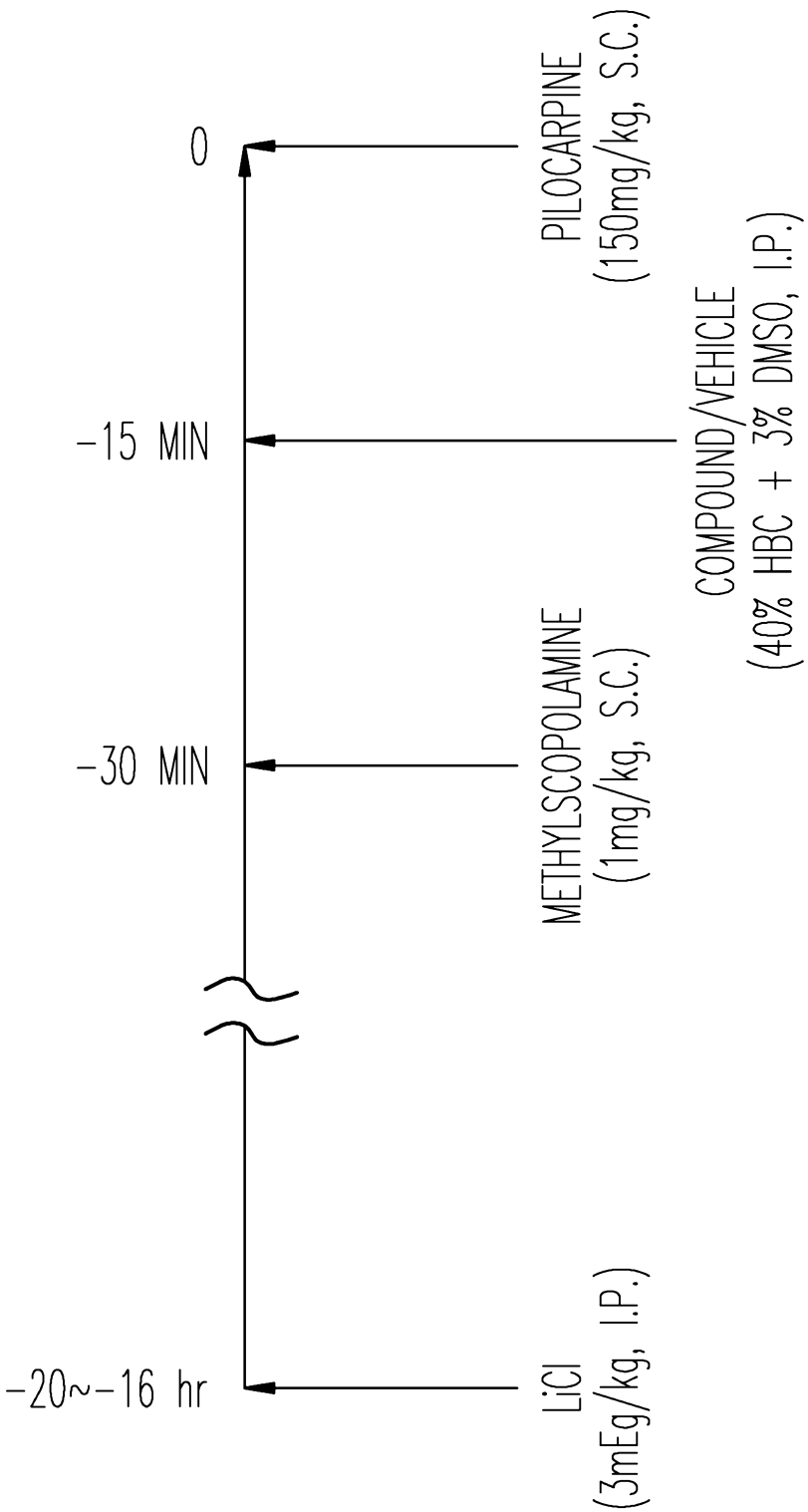

0
PILOCARPINE
(150mg/kg, S.C.)
-15 MIN
COMPOUND/VEHICLE
(40% HBC + 3% DMSO, I.P.)
-30 MIN
METHYLSCOPOLAMINE
(1mg/kg, S.C.)
-20~-16 hr
LiCl
(3mEg/kg, I.P.)

*Fig. 3A*

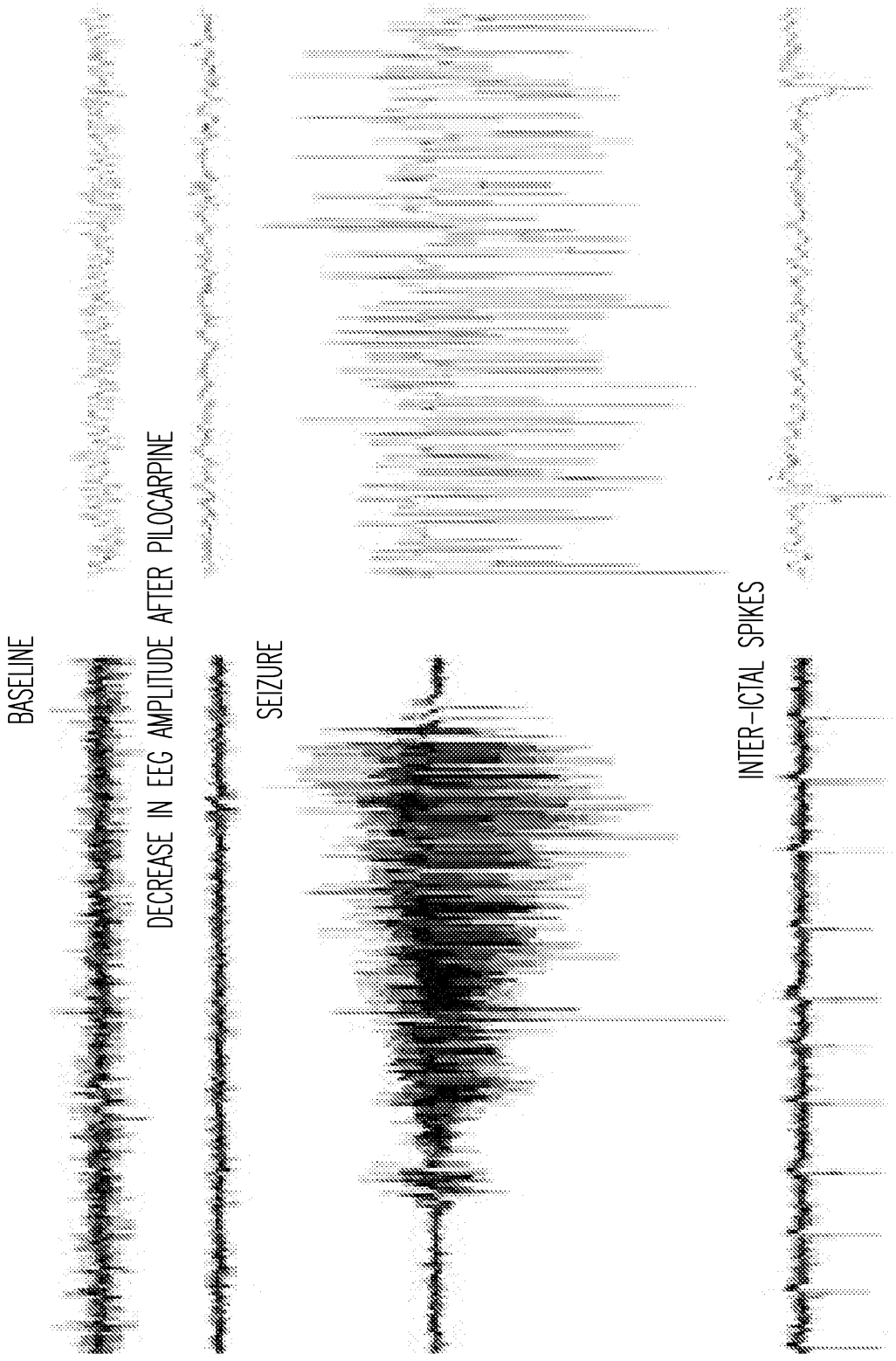

BASELINE
DECREASE IN EEG AMPLITUDE AFTER PILOCARPINE
SEIZURE
INTER-ICTAL SPIKES

Fig. 3B

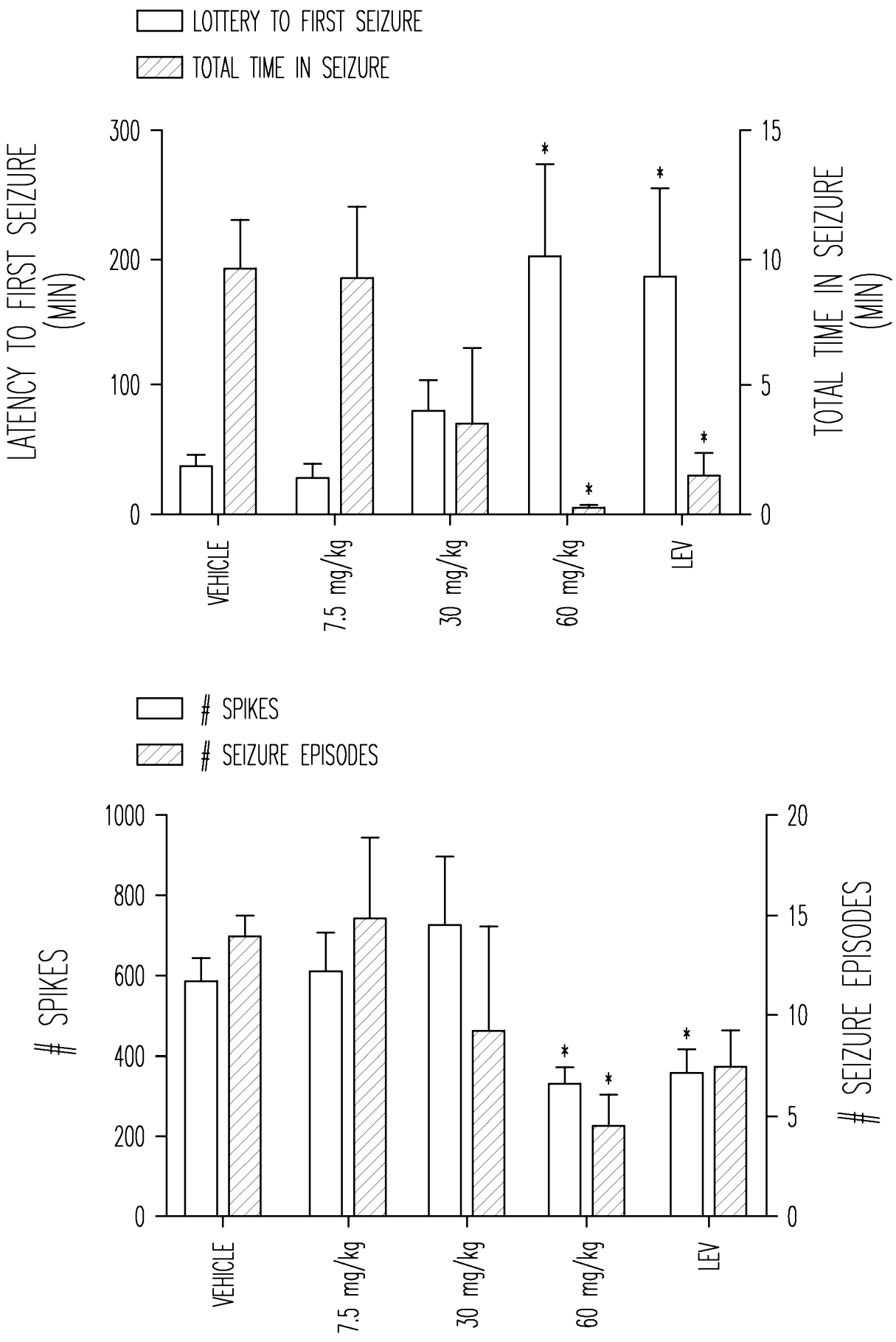

LOTTERY TO FIRST SEIZURE
TOTAL TIME IN SEIZURE
LATENCY TO FIRST SEIZURE (MIN)
TOTAL TIME IN SEIZURE (MIN)
300
200
100
0
15
10
5
0
VEHICLE
7.5 mg/kg
30 mg/kg
60 mg/kg
LEV
# SPIKES
# SEIZURE EPISODES
1000
800
600
400
200
0
20
15
10
5
0
VEHICLE
7.5 mg/kg
30 mg/kg
60 mg/kg
LEV

Fig. 3C

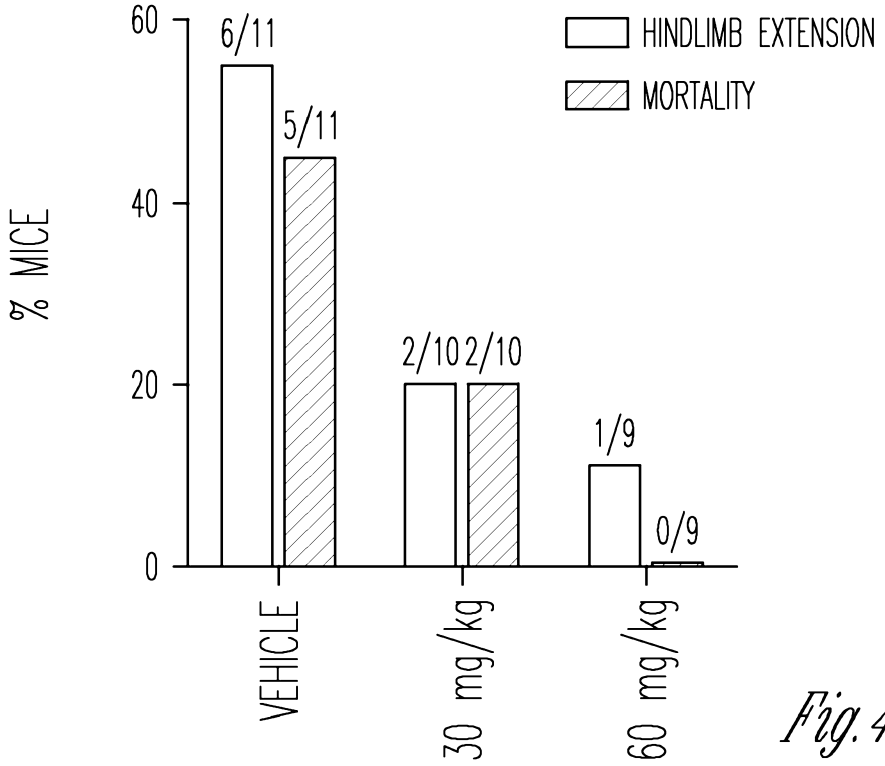

60
40
20
0
% MICE
6/11
5/11
2/10
2/10
1/9
0/9
HINDLIMB EXTENSION
MORTALITY
VEHICLE
30 mg/kg
60 mg/kg

*Fig. 4A*

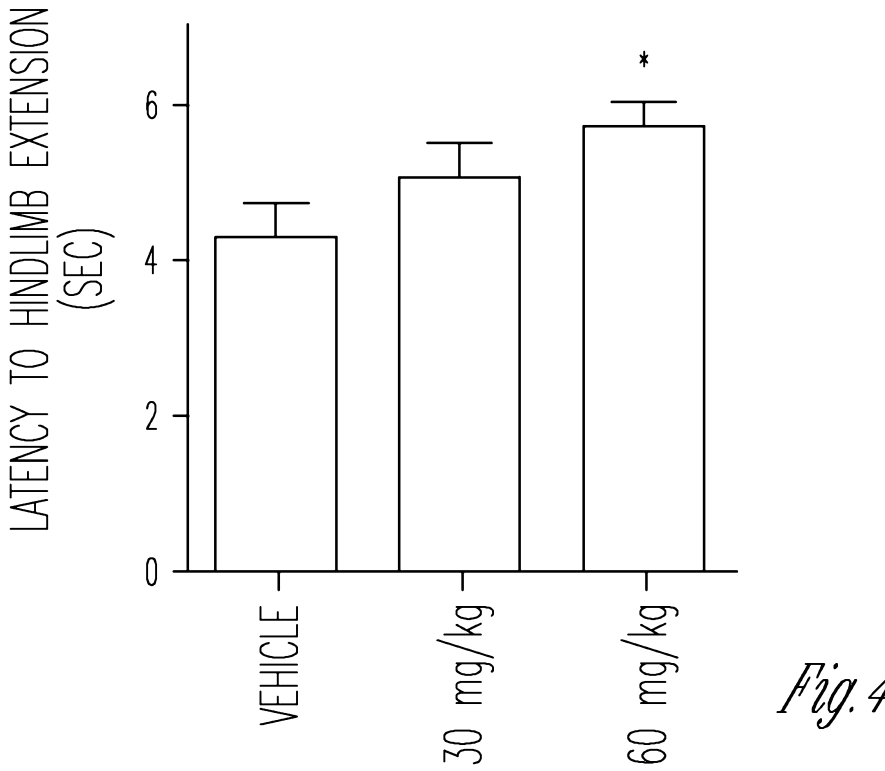

LATENCY TO HINDLIMB EXTENSION (SEC)
6
4
2
0
*
VEHICLE
30 mg/kg
60 mg/kg

*Fig. 4B*