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(54) **Title:** SUBSTITUTED 1H-PYRROLO[3,2-C]QUINOLIN-4(5H)-ONE ANALOGS AS POSITIVE ALLOSTERIC MODULATORS OF THE MUSCARINIC ACETYLCHOLINE RECEPTOR M4

(57) **Abstract:** In one aspect, the invention relates to substituted 1H-pyrrolo[3,2-c]quinolin-4(5H)-one analogs, derivatives thereof, and related compounds, which are useful as positive allosteric modulators of the muscarinic acetylcholine receptor; synthetic methods for making the compounds; pharmaceutical compositions comprising the compounds; and methods of treating neurological and psychiatric disorders associated with muscarinic acetylcholine receptor dysfunction using the compounds and compositions. In a further aspect, the muscarinic acetylcholine receptor is muscarinic acetylcholine receptor M4 (mAChR M4). This abstract is intended as a scanning tool for purposes of searching in the particular art and is not intended to be limiting of the present invention.



**SUBSTITUTED 1H-PYRROLO[3,2-C]QUINOLIN-4(5H)-ONE ANALOGS AS
POSITIVE ALLOSTERIC MODULATORS OF THE MUSCARINIC
ACETYLCHOLINE RECEPTOR M4**

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This Application claims the benefit of U.S. Provisional Application No. 61/483,700, filed on May 8, 2011, which is incorporated herein by reference in entirety.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH

[0002] This invention was made with government support under grant numbers MH87965, MH86601, MH82867, MH73676, MH89870, NS65867, MH77607, MH84659 and MH74427 awarded by the National Institutes of Health. The United States government has certain rights in the invention.

BACKGROUND

[0003] Cholinergic neurotransmission involves the activation of nicotinic acetylcholine receptors (nAChRs) or the muscarinic acetylcholine receptors (mAChRs) by the binding of the endogenous orthosteric agonist acetylcholine (ACh). Conditions associated with cognitive impairment, such as Alzheimer's disease, are accompanied by a reduction of acetylcholine content in the brain. This is believed to be the result of degeneration of cholinergic neurons of the basal forebrain, which widely innervate multiple areas of the brain, including the association cortices and hippocampus, that are critically involved in higher processes. Clinical data supports that cholinergic hypofunction contributes to the cognitive deficits of patients suffering from schizophrenia. Efforts to increase acetylcholine levels have focused on increasing levels of choline, the precursor for acetylcholine synthesis, and on blocking acetylcholinesterase (AChE), the enzyme that metabolizes acetylcholine. As a result, acetylcholinesterase (AChE) inhibitors, which inhibit the hydrolysis of ACh, have been approved in the United States for use in the palliative, but not disease-modifying, treatment of the cognitive deficits in AD patients.

[0004] Attempts to augment central cholinergic function through the administration of choline or phosphatidylcholine have not been successful. AChE inhibitors have shown

therapeutic efficacy, but have been found to have frequent cholinergic side effects due to peripheral acetylcholine stimulation, including abdominal cramps, nausea, vomiting, and diarrhoea. These gastrointestinal side effects have been observed in about a third of the patients treated. In addition, some AChE inhibitors, such as tacrine, have also been found to cause significant hepatotoxicity with elevated liver transaminases observed in about 30% of patients. The adverse effects of AChE inhibitors have severely limited their clinical utility. An alternative approach to pharmacologically target cholinergic hypofunction is the activation of mAChRs, which are widely expressed throughout the body.

[0005] The mAChRs are members of the family A GPCRs and include five subtypes, designated M₁-M₅. The M₁, M₃ and M₅ subtypes mainly couple to G_q and activate phospholipase C, whereas the M₂ and M₄ subtypes mainly couple to G_{i/o} and associated effector systems. These five distinct mAChR subtypes have been identified in the mammalian central nervous system where they are prevalent and differentially expressed. M₁-M₅ have varying roles in cognitive, sensory, motor and autonomic functions. Thus, without wishing to be bound by a particular theory, it is believed that selective agonists of mAChR subtypes that regulate processes involved in cognitive function could prove superior to be superior therapeutics for treatment of psychosis, schizophrenia and related disorders. The muscarinic M₄ receptor has been shown to have a major role in cognitive processing and is believed to have a major role in the pathophysiology of psychotic disorders, including schizophrenia.

[0006] Evidence suggests that the most prominent adverse effects of AChE inhibitors and other cholinergic agents are mediated by activation of peripheral M₂ and M₃ mAChRs and include bradycardia, GI distress, excessive salivation, and sweating. In contrast, M₄ has been viewed as the most likely subtype for mediating the effects of muscarinic acetylcholine receptor dysfunction in psychotic disorders, including schizophrenia, cognition disorders, and neuropathic pain. Because of this, considerable effort has been focused on developing selective M₄ agonists for treatment of these disorders. Unfortunately, these efforts have been largely unsuccessful because of an inability to develop compounds that are highly selective for the mAChR M₄. Because of this, mAChR agonists that have been tested in clinical studies induce a range adverse effects by activation of peripheral mAChRs. To fully understand the physiological roles of individual mAChR subtypes and to further explore the therapeutic utility of mAChR ligands in psychosis, including schizophrenia, cognition

disorders and other disorders, it can be important to develop compounds that are highly selective activators of mAChR M₄ and other individual mAChR subtypes.

[0007] Previous attempts to develop agonists that are highly selective for individual mAChR subtypes have failed because of the high conservation of the orthosteric ACh binding site. To circumvent problems associated with targeting the highly conserved orthosteric ACh binding site, it is believed that developing compounds that act at allosteric sites on mAChRs that are removed from the orthosteric site and are less highly- conserved. This approach is proving to be highly successful in developing selective ligands for multiple GPCR subtypes. In the case of mAChRs, a major goal has been to develop allosteric ligands that selectively increase activity of mAChR M₄ or other mAChR subtypes. Allosteric activators can include allosteric agonists, that act at a site removed from the orthosteric site to directly activate the receptor in the absence of ACh as well as positive allosteric modulators (PAMs), which do not activate the receptor directly but potentiate activation of the receptor by the endogenous orthosteric agonist ACh. Also, it is possible for a single molecule to have both allosteric potentiator and allosteric agonist activity.

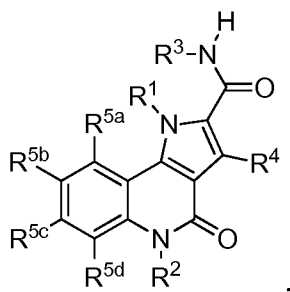
[0008] Recently, muscarinic agonists including xanomeline have been shown to be active in animal models with similar profiles to known antipsychotic drugs, but without causing catalepsy (Bymaster et al., Eur. J. Pharmacol. 1998, 356, 109, Bymaster et al., Life Sci. 1999, 64, 527; Shannon et al., J. Pharmacol. Exp. Ther. 1999, 290, 901; Shannon et al., Schizophrenia Res. 2000, 42, 249.). Further, xanomeline was shown to reduce psychotic behavioral symptoms such as delusions, suspiciousness, vocal outbursts, and hallucinations in Alzheimer's disease patients (Bodick et al., Arch. Neurol. 1997, 54, 465.), however treatment induced side effects, e.g., gastrointestinal effects, have severely limited the clinical utility of this compound.

[0009] Despite advances in muscarinic acetylcholine receptor research, there is still a scarcity of compounds that are both potent, efficacious, and selective activators of the M₄ mAChR and also effective in the treatment of neurological and psychiatric disorders associated with cholinergic activity and diseases in which the muscarinic M₄ receptor is involved. These needs and other needs are satisfied by the present invention.

SUMMARY

[0010] In accordance with the purpose(s) of the invention, as embodied and broadly described herein, the invention, in one aspect, relates to compounds useful as positive allosteric modulators (*i.e.*, potentiators) of the muscarinic acetylcholine receptor M₄ (mAChR M₄), methods of making same, pharmaceutical compositions comprising same, and methods of treating neurological and psychiatric disorders associated with muscarinic acetylcholine receptor dysfunction using same.

[0011] Disclosed are compounds having a structure represented by a formula:

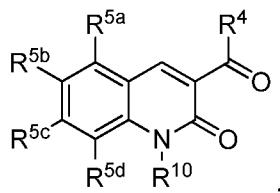


wherein R¹ is selected from hydrogen, C2-C8 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, and Cy¹; wherein Cy¹ is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy¹ is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein R² is selected from hydrogen, C1-C8 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, and Cy²; wherein Cy² is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy² is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein R³ is selected from C1-C8 alkyl, Cy³, and Ar¹; wherein Ar¹ is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar¹ is heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy³ is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino,

C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy³ is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein R⁴ is selected from hydrogen, halogen, hydroxyl, cyano, amino, C1-C8 alkyl, C1-C6 alkoxy, C1-C6 alkylamino, C1-C6 dialkylamino, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, Cy⁴, and Ar²; wherein Ar² is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar² is heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy⁴ is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy⁴ is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein each of R^{5a}, R^{5b}, R^{5c}, and R^{5d} is independently selected from hydrogen, halogen, hydroxyl, cyano, amino, CONR⁶R⁷, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 alkylamino, C1-C6 dialkylamino, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, Cy⁵, and Ar³, wherein Ar³ is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar³ is heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy⁵ is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy⁵ is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein each of R⁶ and R⁷ is independently selected from hydrogen, C1-C6 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, aryl and heteroaryl; or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof.

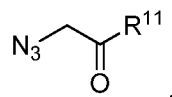
[0012] Also disclosed are pharmaceutical compositions comprising a therapeutically effective amount of a disclosed compound and a pharmaceutically acceptable carrier.

[0013] Also disclosed are synthetic method comprising the steps of: (a) providing a compound having a structure represented by a formula:

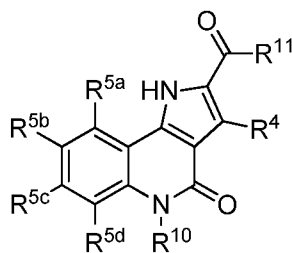


wherein R^4 is selected from hydrogen, hydroxyl, amino, C1-C8 alkyl, C1-C6 alkoxy, C1-C6 alkylamino, C1-C6 dialkylamino, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, Cy^4 , and Ar^2 ; wherein Ar^2 is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar^2 is heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy^4 is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy^4 is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein each of R^{5a} , R^{5b} , R^{5c} , and R^{5d} is independently selected from hydrogen, halogen, hydroxyl, cyano, amino, $-CONR^6R^7$, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 alkylamino, C1-C6 dialkylamino, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, Cy^5 , and Ar^3 , wherein Ar^3 is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar^3 is heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy^5 is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy^5 is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein each of R^6 and R^7 is independently selected from hydrogen, C1-C6 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, aryl and heteroaryl; wherein R^{10} is selected from an amino-protecting group and R^2 , which is selected from hydrogen, C1-C8 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, and Cy^2 ; and wherein Cy^2 is

C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy² is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; (b) reacting with a compound having a structure represented by a formula:



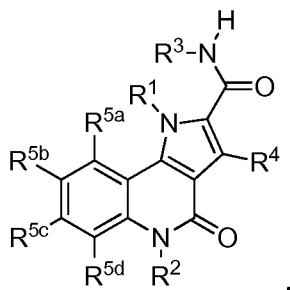
wherein R¹¹ is hydroxyl, -NH₂, -NHR³, or an optionally substituted group selected from C1-C10 alkoxy, C3-C8 cycloalkoxy, phenoxy, benzyloxy, heteroaryloxy, and C3-C8 heterocycloalkoxy; wherein R³ is selected from C1-C8 alkyl, Cy³, and Ar¹; wherein Ar¹ is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar¹ is monocyclic heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; and wherein Cy³ is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy³ is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; and (c) cyclizing to form a product having a structure represented by a formula:



[0014] Also disclosed are the products of the disclosed methods.

[0015] Also disclosed are pharmaceutical compositions comprising a therapeutically effective amount of a product of a disclosed synthetic method and a pharmaceutically acceptable carrier.

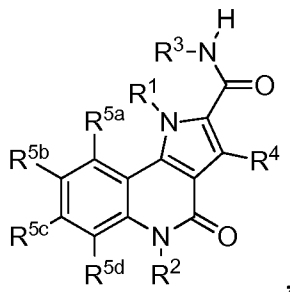
[0016] Disclosed are methods for the treatment of a neurological and/or psychiatric disorder associated with muscarinic acetylcholine receptor dysfunction in a mammal comprising the step of administering to the mammal a therapeutically effective amount of least one compound having a structure represented by a formula:



wherein R^1 is selected from hydrogen, C1-C8 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, and Cy^1 ; wherein Cy^1 is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy^1 is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein R^2 is selected from hydrogen, C1-C8 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, and Cy^2 ; wherein Cy^2 is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy^2 is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein R^3 is selected from C1-C8 alkyl, Cy^3 , and Ar^1 ; wherein Ar^1 is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar^1 is monocyclic heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy^3 is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy^3 is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein

R^4 is selected from hydrogen, halogen, hydroxyl, cyano, amino, C1-C8 alkyl, C1-C6 alkoxy, C1-C6 alkylamino, C1-C6 dialkylamino, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, Cy^4 , and Ar^2 ; wherein Ar^2 is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar^2 is heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy^4 is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy^4 is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein each of R^{5a} , R^{5b} , R^{5c} , and R^{5d} is independently selected from hydrogen, halogen, hydroxyl, cyano, amino, $CONR^6R^7$, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 alkylamino, C1-C6 dialkylamino, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, Cy^5 , and Ar^3 , wherein Ar^3 is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar^3 is heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy^5 is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy^5 is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein each of R^6 and R^7 is independently selected from hydrogen, C1-C6 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, aryl and heteroaryl; or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof.

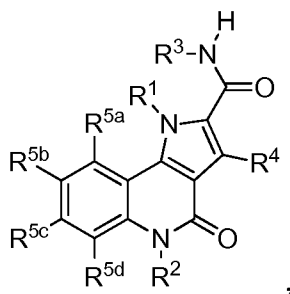
[0017] Also disclosed are methods for potentiation of muscarinic acetylcholine receptor activity in a mammal comprising the step of administering to the mammal a therapeutically effective amount of least one compound having a structure represented by a formula:



wherein R^1 is selected from hydrogen, C1-C8 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, and Cy^1 ; wherein Cy^1 is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy^1 is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein R^2 is selected from hydrogen, C1-C8 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, and Cy^2 ; wherein Cy^2 is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy^2 is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein R^3 is selected from C1-C8 alkyl, Cy^3 , and Ar^1 ; wherein Ar^1 is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar^1 is monocyclic heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy^3 is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy^3 is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein R^4 is selected from hydrogen, halogen, hydroxyl, cyano, amino, C1-C8 alkyl, C1-C6 alkoxy, C1-C6 alkylamino, C1-C6 dialkylamino, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, Cy^4 , and Ar^2 ; wherein Ar^2 is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar^2 is heteroaryl substituted with 0-3 substituents independently selected from halogen,

cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy⁴ is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy⁴ is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein each of R^{5a}, R^{5b}, R^{5c}, and R^{5d} is independently selected from hydrogen, halogen, hydroxyl, cyano, amino, CONR⁶R⁷, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 alkylamino, C1-C6 dialkylamino, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, Cy⁵, and Ar³, wherein Ar³ is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar³ is heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy⁵ is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy⁵ is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein each of R⁶ and R⁷ is independently selected from hydrogen, C1-C6 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, aryl and heteroaryl; or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof.

[0018] Also disclosed are methods for partial agonism of muscarinic acetylcholine receptor activity in a mammal comprising the step of administering to the mammal a therapeutically effective amount of least one compound having a structure represented by a formula:

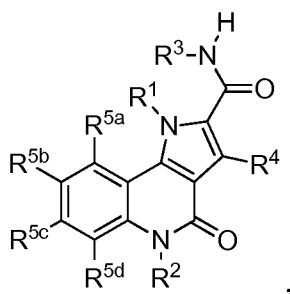


wherein R¹ is selected from hydrogen, C1-C8 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, and Cy¹; wherein Cy¹ is C3-C8 cycloalkyl substituted with 0-3 substituents selected from

halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy¹ is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein R² is selected from hydrogen, C1-C8 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, and Cy²; wherein Cy² is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy² is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein R³ is selected from C1-C8 alkyl, Cy³, and Ar¹; wherein Ar¹ is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar¹ is monocyclic heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy³ is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy³ is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein R⁴ is selected from hydrogen, halogen, hydroxyl, cyano, amino, C1-C8 alkyl, C1-C6 alkoxy, C1-C6 alkylamino, C1-C6 dialkylamino, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, Cy⁴, and Ar²; wherein Ar² is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar² is heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy⁴ is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy⁴ is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein each of R^{5a}, R^{5b}, R^{5c}, and R^{5d} is independently selected from hydrogen, halogen, hydroxyl,

cyano, amino, CONR^6R^7 , C1-C6 alkyl, C1-C6 alkoxy, C1-C6 alkylamino, C1-C6 dialkylamino, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, Cy^5 , and Ar^3 , wherein Ar^3 is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar^3 is heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy^5 is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy^5 is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein each of R^6 and R^7 is independently selected from hydrogen, C1-C6 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, aryl and heteroaryl; or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof.

[0019] Also disclosed are methods for enhancing cognition in a mammal comprising the step of administering to the mammal an effective amount of least one compound having a structure represented by a formula:

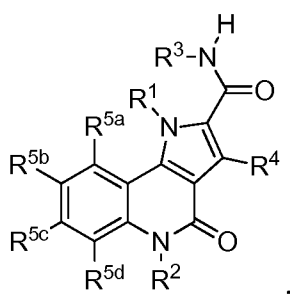


wherein R^1 is selected from hydrogen, C1-C8 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, and Cy^1 ; wherein Cy^1 is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy^1 is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein R^2 is selected from hydrogen, C1-C8 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, and Cy^2 ; wherein Cy^2 is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl,

or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy² is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein R³ is selected from C1-C8 alkyl, Cy³, and Ar¹; wherein Ar¹ is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar¹ is monocyclic heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy³ is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy³ is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein R⁴ is selected from hydrogen, halogen, hydroxyl, cyano, amino, C1-C8 alkyl, C1-C6 alkoxy, C1-C6 alkylamino, C1-C6 dialkylamino, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, Cy⁴, and Ar²; wherein Ar² is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar² is heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy⁴ is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy⁴ is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein each of R^{5a}, R^{5b}, R^{5c}, and R^{5d} is independently selected from hydrogen, halogen, hydroxyl, cyano, amino, CONR⁶R⁷, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 alkylamino, C1-C6 dialkylamino, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, Cy⁵, and Ar³, wherein Ar³ is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar³ is heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy⁵ is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl,

C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy⁵ is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein each of R⁶ and R⁷ is independently selected from hydrogen, C1-C6 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, aryl and heteroaryl; or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof.

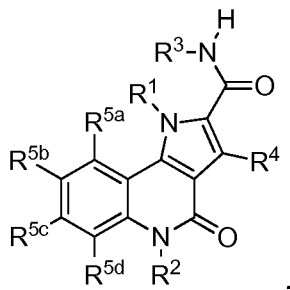
[0020] Also disclosed are methods for modulating muscarinic acetylcholine receptor activity in a mammal comprising the step of administering to the mammal an effective amount of least one compound having a structure represented by a formula:



wherein R¹ is selected from hydrogen, C1-C8 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, and Cy¹; wherein Cy¹ is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy¹ is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein R² is selected from hydrogen, C1-C8 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, and Cy²; wherein Cy² is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy² is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein R³ is selected from C1-C8 alkyl, Cy³, and Ar¹; wherein Ar¹ is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar¹ is monocyclic heteroaryl substituted with 0-3 substituents independently selected from halogen,

cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy³ is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy³ is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein R⁴ is selected from hydrogen, halogen, hydroxyl, cyano, amino, C1-C8 alkyl, C1-C6 alkoxy, C1-C6 alkylamino, C1-C6 dialkylamino, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, Cy⁴, and Ar²; wherein Ar² is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar² is heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy⁴ is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy⁴ is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein each of R^{5a}, R^{5b}, R^{5c}, and R^{5d} is independently selected from hydrogen, halogen, hydroxyl, cyano, amino, CONR⁶R⁷, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 alkylamino, C1-C6 dialkylamino, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, Cy⁵, and Ar³, wherein Ar³ is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar³ is heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy⁵ is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy⁵ is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein each of R⁶ and R⁷ is independently selected from hydrogen, C1-C6 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, aryl and heteroaryl; or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof.

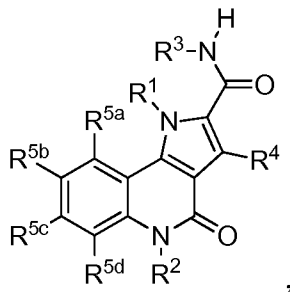
[0021] Also disclosed are methods for modulating muscarinic acetylcholine receptor activity in at least one cell, comprising the step of contacting the at least one cell with an effective amount of least one compound having a structure represented by a formula:



wherein R^1 is selected from hydrogen, C1-C8 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, and Cy^1 ; wherein Cy^1 is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy^1 is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein R^2 is selected from hydrogen, C1-C8 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, and Cy^2 ; wherein Cy^2 is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy^2 is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein R^3 is selected from C1-C8 alkyl, Cy^3 , and Ar^1 ; wherein Ar^1 is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar^1 is monocyclic heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy^3 is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy^3 is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein R^4 is selected from hydrogen, halogen, hydroxyl, cyano, amino, C1-C8 alkyl, C1-C6 alkoxy,

C1-C6 alkylamino, C1-C6 dialkylamino, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, Cy^4 , and Ar^2 ; wherein Ar^2 is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar^2 is heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy^4 is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy^4 is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein each of R^{5a} , R^{5b} , R^{5c} , and R^{5d} is independently selected from hydrogen, halogen, hydroxyl, cyano, amino, $CONR^6R^7$, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 alkylamino, C1-C6 dialkylamino, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, Cy^5 , and Ar^3 , wherein Ar^3 is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar^3 is heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy^5 is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy^5 is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein each of R^6 and R^7 is independently selected from hydrogen, C1-C6 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, aryl and heteroaryl; or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof.

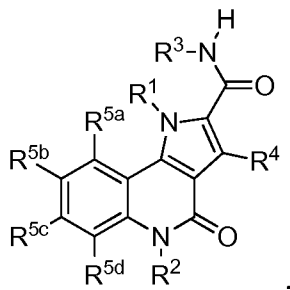
[0022] Also disclosed are uses of a compound having a structure represented by a formula:



wherein R^1 is selected from hydrogen, C1-C8 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, and Cy^1 ; wherein Cy^1 is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy^1 is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein R^2 is selected from hydrogen, C1-C8 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, and Cy^2 ; wherein Cy^2 is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy^2 is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein R^3 is selected from C1-C8 alkyl, Cy^3 , and Ar^1 ; wherein Ar^1 is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar^1 is monocyclic heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy^3 is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy^3 is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein R^4 is selected from hydrogen, halogen, hydroxyl, cyano, amino, C1-C8 alkyl, C1-C6 alkoxy, C1-C6 alkylamino, C1-C6 dialkylamino, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, Cy^4 , and Ar^2 ; wherein Ar^2 is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar^2 is heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy^4 is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy^4 is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-

C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein each of R^{5a} , R^{5b} , R^{5c} , and R^{5d} is independently selected from hydrogen, halogen, hydroxyl, cyano, amino, CONR^6R^7 , C1-C6 alkyl, C1-C6 alkoxy, C1-C6 alkylamino, C1-C6 dialkylamino, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, Cy^5 , and Ar^3 , wherein Ar^3 is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar^3 is heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy^5 is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy^5 is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein each of R^6 and R^7 is independently selected from hydrogen, C1-C6 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, aryl and heteroaryl; or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof.

[0023] Also disclosed are pharmaceutical compositions comprising a pharmaceutically acceptable carrier and an effective amount of a compound represented by a formula:

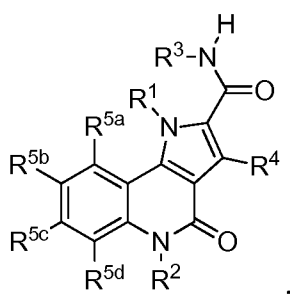


wherein R^1 is selected from hydrogen, C1-C8 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, and Cy^1 ; wherein Cy^1 is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy^1 is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein R^2 is selected from hydrogen, C1-C8 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, and Cy^2 ; wherein Cy^2 is C3-C8 cycloalkyl substituted with 0-3 substituents

selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy² is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein R³ is selected from C1-C8 alkyl, Cy³, and Ar¹; wherein Ar¹ is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar¹ is monocyclic heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy³ is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy³ is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein R⁴ is selected from hydrogen, halogen, hydroxyl, cyano, amino, C1-C8 alkyl, C1-C6 alkoxy, C1-C6 alkylamino, C1-C6 dialkylamino, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, Cy⁴, and Ar²; wherein Ar² is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar² is heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy⁴ is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy⁴ is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein each of R^{5a}, R^{5b}, R^{5c}, and R^{5d} is independently selected from hydrogen, halogen, hydroxyl, cyano, amino, CONR⁶R⁷, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 alkylamino, C1-C6 dialkylamino, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, Cy⁵, and Ar³, wherein Ar³ is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar³ is heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy⁵ is C3-C8 cycloalkyl

substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy⁵ is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein each of R⁶ and R⁷ is independently selected from hydrogen, C1-C6 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, aryl and heteroaryl; or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof.

[0024] Also disclosed are kits comprising at least one compound having a structure represented by a formula:



wherein R¹ is selected from hydrogen, C1-C8 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, and Cy¹; wherein Cy¹ is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy¹ is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein R² is selected from hydrogen, C1-C8 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, and Cy²; wherein Cy² is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy² is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein R³ is selected from C1-C8 alkyl, Cy³, and Ar¹; wherein Ar¹ is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar¹ is monocyclic heteroaryl substituted with 0-3 substituents independently selected from halogen,

cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy³ is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy³ is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein R⁴ is selected from hydrogen, halogen, hydroxyl, cyano, amino, C1-C8 alkyl, C1-C6 alkoxy, C1-C6 alkylamino, C1-C6 dialkylamino, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, Cy⁴, and Ar²; wherein Ar² is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar² is heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy⁴ is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy⁴ is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein each of R^{5a}, R^{5b}, R^{5c}, and R^{5d} is independently selected from hydrogen, halogen, hydroxyl, cyano, amino, CONR⁶R⁷, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 alkylamino, C1-C6 dialkylamino, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, Cy⁵, and Ar³, wherein Ar³ is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar³ is heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy⁵ is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy⁵ is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein each of R⁶ and R⁷ is independently selected from hydrogen, C1-C6 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, aryl and heteroaryl; or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof, and one or more of:

- a. at least one agent known to increase mAChR M₄ activity;
- b. at least one agent known to decrease mAChR M₄ activity;
- c. at least one agent known to treat a disorder associated with cholinergic activity;
- d. instructions for treating a disorder associated with cholinergic activity;
- e. instructions for treating a disorder associated with M₁ receptor activity; or
- f. instructions for administering the compound in connection with cognitive or behavioral therapy.

[0025] Also disclosed are methods for the manufacture of a medicament to activate the mAChR M₄ in a mammal comprising combining at least one disclosed compound or at least one disclosed product with a pharmaceutically acceptable carrier or diluent.

[0026] Also disclosed are uses of a disclosed compound or a disclosed product in the manufacture of a medicament for the treatment of a disorder associated with muscarinic acetylcholine receptor dysfunction in a mammal.

[0027] While aspects of the present invention can be described and claimed in a particular statutory class, such as the system statutory class, this is for convenience only and one of skill in the art will understand that each aspect of the present invention can be described and claimed in any statutory class. Unless otherwise expressly stated, it is in no way intended that any method or aspect set forth herein be construed as requiring that its steps be performed in a specific order. Accordingly, where a method claim does not specifically state in the claims or descriptions that the steps are to be limited to a specific order, it is no way intended that an order be inferred, in any respect. This holds for any possible non-express basis for interpretation, including matters of logic with respect to arrangement of steps or operational flow, plain meaning derived from grammatical organization or punctuation, or the number or type of aspects described in the specification.

BRIEF DESCRIPTION OF THE FIGURES

[0028] The accompanying figures, which are incorporated in and constitute a part of this specification, illustrate several aspects and together with the description serve to explain the principles of the invention.

[0029] Figure 1 is a schematic illustration of ligand binding to the orthosteric site and an allosteric site in the muscarinic acetylcholine receptor.

[0030] Additional advantages of the invention will be set forth in part in the description which follows, and in part will be obvious from the description, or can be learned by practice of the invention. The advantages of the invention will be realized and attained by means of the elements and combinations particularly pointed out in the appended claims. It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as claimed.

DESCRIPTION

[0031] The present invention can be understood more readily by reference to the following detailed description of the invention and the Examples included therein.

[0032] Before the present compounds, compositions, articles, systems, devices, and/or methods are disclosed and described, it is to be understood that they are not limited to specific synthetic methods unless otherwise specified, or to particular reagents unless otherwise specified, as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular aspects only and is not intended to be limiting. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, example methods and materials are now described.

[0033] All publications mentioned herein are incorporated herein by reference to disclose and describe the methods and/or materials in connection with which the publications are cited. The publications discussed herein are provided solely for their disclosure prior to the filing date of the present application. Nothing herein is to be construed as an admission that the present invention is not entitled to antedate such publication by virtue of prior invention. Further, the dates of publication provided herein can be different from the actual publication dates, which can require independent confirmation.

A. DEFINITIONS

[0034] As used herein, nomenclature for compounds, including organic compounds, can be given using common names, IUPAC, IUBMB, or CAS recommendations for nomenclature. When one or more stereochemical features are present, Cahn-Ingold-Prelog rules for

stereochemistry can be employed to designate stereochemical priority, *E/Z* specification, and the like. One of skill in the art can readily ascertain the structure of a compound if given a name, either by systemic reduction of the compound structure using naming conventions, or by commercially available software, such as CHEMDRAWTM (Cambridgesoft Corporation, U.S.A.).

[0035] 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. Thus, for example, reference to “a functional group,” “an alkyl,” or “a residue” includes mixtures of two or more such functional groups, alkyls, or residues, and the like.

[0036] Ranges can be expressed herein as from “about” one particular value, and/or to “about” another particular value. When such a range is expressed, a further aspect includes from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by use of the antecedent “about,” it will be understood that the particular value forms a further aspect. It will be further understood that the endpoints of each of the ranges are significant both in relation to the other endpoint, and independently of the other endpoint. It is also understood that there are a number of values disclosed herein, and that each value is also herein disclosed as “about” that particular value in addition to the value itself. For example, if the value “10” is disclosed, then “about 10” is also disclosed. It is also understood that each unit between two particular units are also disclosed. For example, if 10 and 15 are disclosed, then 11, 12, 13, and 14 are also disclosed.

[0037] References in the specification and concluding claims to parts by weight of a particular element or component in a composition denotes the weight relationship between the element or component and any other elements or components in the composition or article for which a part by weight is expressed. Thus, in a compound containing 2 parts by weight of component X and 5 parts by weight component Y, X and Y are present at a weight ratio of 2:5, and are present in such ratio regardless of whether additional components are contained in the compound.

[0038] A weight percent (wt. %) of a component, unless specifically stated to the contrary, is based on the total weight of the formulation or composition in which the component is included.

[0039] As used herein, the terms “optional” or “optionally” means that the subsequently described event or circumstance can or can not occur, and that the description includes instances where said event or circumstance occurs and instances where it does not.

[0040] As used herein, the term “orthosteric site” refers to the primary binding site on a receptor that is recognized by the endogenous ligand or agonist for that receptor. For example, the orthosteric site in the mAChR M₄ receptor is the site that acetylcholine binds.

[0041] As used herein, the term “mAChR M₄ receptor positive allosteric modulator” refers to any exogenously administered compound or agent that directly or indirectly augments the activity of the mAChR M₄ receptor in the presence or in the absence of acetylcholine in an animal, in particular a mammal, for example a human. In one aspect, a mAChR M₄ receptor positive allosteric modulator increases the activity of the mAChR M₄ receptor in a cell in the presence of extracellular acetylcholine. The cell can be Chinese hamster ovary (CHO-K1) cells transfected with human mAChR M₄. The cell can be Chinese hamster ovary (CHO-K1) cells transfected with rat mAChR M₄ receptor. The cell can be Chinese hamster ovary (CHO-K1) cells transfected with a mammalian mAChR M₄. The term “mAChR M₄ receptor positive allosteric modulator” includes a compound that is a “mAChR M₄ receptor allosteric potentiator” or a “mAChR M₄ receptor allosteric agonist,” as well as a compound that has mixed activity comprising pharmacology of both an “mAChR M₄ receptor allosteric potentiator” and an “mAChR M₄ receptor allosteric agonist”. The term “mAChR M₄ receptor positive allosteric modulator” also includes a compound that is a “mAChR M₄ receptor allosteric enhancer.”

[0042] As used herein, the term “mAChR M₄ receptor allosteric potentiator” refers to any exogenously administered compound or agent that directly or indirectly augments the response produced by the endogenous ligand (such as acetylcholine) when the endogenous ligand binds to the orthosteric site of the mAChR M₄ receptor in an animal, in particular a mammal, for example a human. The mAChR M₄ receptor allosteric potentiator binds to a site other than the orthosteric site, that is, an allosteric site, and positively augments the response of the receptor to an agonist or the endogenous ligand. In one aspect, an allosteric potentiator does not induce desensitization of the receptor, activity of a compound as an mAChR M₄ receptor allosteric potentiator provides advantages over the use of a pure mAChR M₄ receptor

allosteric agonist. Such advantages can include, for example, increased safety margin, higher tolerability, diminished potential for abuse, and reduced toxicity.

[0043] As used herein, the term “mAChR M₄ receptor allosteric enhancer” refers to any exogenously administered compound or agent that directly or indirectly augments the response produced by the endogenous ligand (such as acetylcholine) in an animal, in particular a mammal, for example a human. In one aspect, the allosteric enhancer increases the affinity of the natural ligand or agonist for the orthosteric site. In another aspect, an allosteric enhancer increases the agonist efficacy. The mAChR M₄ receptor allosteric potentiator binds to a site other than the orthosteric site, that is, an allosteric site, and positively augments the response of the receptor to an agonist or the endogenous ligand. An allosteric enhancer has no effect on the receptor by itself and requires the presence of an agonist or the natural ligand to realize a receptor effect.

[0044] As used herein, the term “mAChR M₄ receptor allosteric agonist” refers to any exogenously administered compound or agent that directly augments the activity of the mAChR M₄ receptor in the absence of the endogenous ligand (such as acetylcholine) in an animal, in particular a mammal, for example a human. The mAChR M₄ receptor allosteric agonist binds to a site that is distinct from the orthosteric acetylcholine site of the mAChR M₄ receptor and influences the binding of an agonist or the natural ligand to the orthosteric site of the mAChR M₄ receptor. Because it does not require the presence of the endogenous ligand, activity of a compound as an mAChR M₄ receptor allosteric agonist provides advantages over the use of a pure mAChR M₄ receptor allosteric potentiator, such as more rapid onset of action.

[0045] As used herein, the terms “mAChR M₄ receptor neutral allosteric ligand” and “silent allosteric modulator” (or “SAM”), can be used interchangeably and refer to any exogenously administered compound or agent that binds to an allosteric site without affecting the binding or function of agonists or the natural ligand at the orthosteric site in an animal, in particular a mammal, for example a human. However, a neutral allosteric ligand can block the action of other allosteric modulators that act via the same site.

[0046] As used herein, the term “subject” can be a vertebrate, such as a mammal, a fish, a bird, a reptile, or an amphibian. Thus, the subject of the herein disclosed methods can be a human, non-human primate, horse, pig, rabbit, dog, sheep, goat, cow, cat, guinea pig or

rodent. The term does not denote a particular age or sex. Thus, adult and newborn subjects, as well as fetuses, whether male or female, are intended to be covered. In one aspect, the subject is a mammal. A patient refers to a subject afflicted with a disease or disorder. The term “patient” includes human and veterinary subjects. In some aspects of the disclosed methods, the subject has been diagnosed with a need for treatment of one or more neurological and/or psychiatric disorder associated with muscarinic acetylcholine receptor dysfunction prior to the administering step. In some aspects of the disclosed method, the subject has been diagnosed with a need for positive allosteric modulation of muscarinic acetylcholine receptor activity prior to the administering step. In some aspects of the disclosed method, the subject has been diagnosed with a need for partial agonism of muscarinic acetylcholine receptor activity prior to the administering step. In some aspects of the disclosed method, the subject has been diagnosed with a psychotic disorder, e.g. schizophrenia, a cognitive disorder, or neuropathic pain prior to the administering step. In some aspects of the disclosed method, the subject has been identified with a disorder treatable by activation of the mAChR M₄ receptor and/or or a need for activation/agonism of mAChR M₄ activity prior to the administering step. In some aspects of the disclosed method, the subject has been identified with anxiety or a related disorder prior to the administering step. In one aspect, a subject can be treated prophylactically with a compound or composition disclosed herein, as discussed herein elsewhere.

[0047] As used herein, the term “treatment” refers to the medical management of a patient with the intent to cure, ameliorate, stabilize, or prevent a disease, pathological condition, or disorder. This term includes active treatment, that is, treatment directed specifically toward the improvement of a disease, pathological condition, or disorder, and also includes causal treatment, that is, treatment directed toward removal of the cause of the associated disease, pathological condition, or disorder. In addition, this term includes palliative treatment, that is, treatment designed for the relief of symptoms rather than the curing of the disease, pathological condition, or disorder; preventative treatment, that is, treatment directed to minimizing or partially or completely inhibiting the development of the associated disease, pathological condition, or disorder; and supportive treatment, that is, treatment employed to supplement another specific therapy directed toward the improvement of the associated disease, pathological condition, or disorder. In various aspects, the term covers any treatment of a subject, including a mammal (e.g., a human), and includes: (i) preventing the disease

from occurring in a subject that can be predisposed to the disease but has not yet been diagnosed as having it; (ii) inhibiting the disease, i.e., arresting its development; or (iii) relieving the disease, i.e., causing regression of the disease. In one aspect, the subject is a mammal such as a primate, and, in a further aspect, the subject is a human. The term “subject” also includes domesticated animals (e.g., cats, dogs, etc.), livestock (e.g., cattle, horses, pigs, sheep, goats, etc.), and laboratory animals (e.g., mouse, rabbit, rat, guinea pig, fruit fly, etc.).

[0048] As used herein, the term “prevent” or “preventing” refers to precluding, averting, obviating, forestalling, stopping, or hindering something from happening, especially by advance action. It is understood that where reduce, inhibit or prevent are used herein, unless specifically indicated otherwise, the use of the other two words is also expressly disclosed.

[0049] As used herein, the term “diagnosed” means having been subjected to a physical examination by a person of skill, for example, a physician, and found to have a condition that can be diagnosed or treated by the compounds, compositions, or methods disclosed herein. For example, “diagnosed with a disorder treatable by modulation of mAChR M₄” means having been subjected to a physical examination by a person of skill, for example, a physician, and found to have a condition that can be diagnosed or treated by a compound or composition that can modulate mAChR M₄. As a further example, “diagnosed with a need for modulation of mAChR M₄” refers to having been subjected to a physical examination by a person of skill, for example, a physician, and found to have a condition characterized by mAChR M₄ activity. Such a diagnosis can be in reference to a disorder, such as a neurodegenerative disease, and the like, as discussed herein. For example, the term “diagnosed with a need for positive allosteric modulation of muscarinic acetylcholine receptor activity” refers to having been subjected to a physical examination by a person of skill, for example, a physician, and found to have a condition that can be diagnosed or treated by positive allosteric modulation of muscarinic acetylcholine receptor activity. For example, “diagnosed with a need for partial agonism of muscarinic acetylcholine receptor activity” means having been subjected to a physical examination by a person of skill, for example, a physician, and found to have a condition that can be diagnosed or treated by partial agonism of muscarinic acetylcholine receptor activity. For example, “diagnosed with a need for treatment of one or more neurological and/or psychiatric disorder associated with acetylcholine dysfunction” means having been subjected to a physical examination by a

person of skill, for example, a physician, and found to have one or more neurological and/or psychiatric disorder associated with acetylcholine dysfunction.

[0050] As used herein, the phrase “identified to be in need of treatment for a disorder,” or the like, refers to selection of a subject based upon need for treatment of the disorder. For example, a subject can be identified as having a need for treatment of a disorder (e.g., a disorder related to mAChR M₄ activity dysfunction) based upon an earlier diagnosis by a person of skill and thereafter subjected to treatment for the disorder. It is contemplated that the identification can, in one aspect, be performed by a person different from the person making the diagnosis. It is also contemplated, in a further aspect, that the administration can be performed by one who subsequently performed the administration.

[0051] As used herein, the terms “administering” and “administration” refer to any method of providing a pharmaceutical preparation to a subject. Such methods are well known to those skilled in the art and include, but are not limited to, oral administration, transdermal administration, administration by inhalation, nasal administration, topical administration, intravaginal administration, ophthalmic administration, intraaural administration, intracerebral administration, rectal administration, sublingual administration, buccal administration, and parenteral administration, including injectable such as intravenous administration, intra-arterial administration, intramuscular administration, and subcutaneous administration. Administration can be continuous or intermittent. In various aspects, a preparation can be administered therapeutically; that is, administered to treat an existing disease or condition. In further various aspects, a preparation can be administered prophylactically; that is, administered for prevention of a disease or condition.

[0052] The term “contacting” as used herein refers to bringing a disclosed compound and a cell, target muscarinic acetylcholine receptor, or other biological entity together in such a manner that the compound can affect the activity of the target (e.g., spliceosome, cell, etc.), either directly; i.e., by interacting with the target itself, or indirectly; i.e., by interacting with another molecule, co-factor, factor, or protein on which the activity of the target is dependent.

[0053] As used herein, the terms “effective amount” and “amount effective” refer to an amount that is sufficient to achieve the desired result or to have an effect on an undesired condition. For example, a “therapeutically effective amount” refers to an amount that is sufficient to achieve the desired therapeutic result or to have an effect on undesired

symptoms, but is generally insufficient to cause adverse side effects. The specific therapeutically effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration; the route of administration; the rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed and like factors well known in the medical arts. For example, it is well within the skill of the art to start doses of a compound at levels lower than those required to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved. If desired, the effective daily dose can be divided into multiple doses for purposes of administration. Consequently, single dose compositions can contain such amounts or submultiples thereof to make up the daily dose. The dosage can be adjusted by the individual physician in the event of any contraindications. Dosage can vary, and can be administered in one or more dose administrations daily, for one or several days. Guidance can be found in the literature for appropriate dosages for given classes of pharmaceutical products. In further various aspects, a preparation can be administered in a “prophylactically effective amount”; that is, an amount effective for prevention of a disease or condition.

[0054] As used herein, “EC₅₀,” is intended to refer to the concentration of a substance (e.g., a compound or a drug) that is required for 50% agonism of a biological process, or component of a process, including a protein, subunit, organelle, ribonucleoprotein, etc. In one aspect, an EC₅₀ can refer to the concentration of a substance that is required for 50% agonism *in vivo*, as further defined elsewhere herein. In a further aspect, EC₅₀ refers to the concentration of agonist that provokes a response halfway between the baseline and maximum response. In a yet further aspect, the response is *in vitro*. In a still further aspect, the response is in Chinese hamster ovary (CHO-K1) cell transfected with human mAChR M₄. In a yet further aspect, the response is a Chinese hamster ovary (CHO-K1) cell transfected with rat mAChR M₄. In an even further aspect, the response is in a Chinese hamster ovary (CHO-K1) cell transfected with a mammalian mAChR M₄.

[0055] As used herein, “IC₅₀,” is intended to refer to the concentration of a substance (e.g., a compound or a drug) that is required for 50% inhibition of a biological process, or component of a process, including a protein, subunit, organelle, ribonucleoprotein, etc. In one aspect, an

IC₅₀ can refer to the concentration of a substance that is required for 50% inhibition *in vivo*, as further defined elsewhere herein. In a further aspect, IC₅₀ refers to the half maximal (50%) inhibitory concentration (IC) of a substance. In a yet further aspect, the inhibition is measured *in vitro*. In a still further aspect, the inhibition is measured in a Chinese hamster ovary (CHO-K1) cell transfected with human mAChR M₄. In a yet further aspect, the inhibition is measured in a Chinese hamster ovary (CHO-K1) cell transfected with rat mAChR M₄. In an even further aspect, the inhibition is measured in a Chinese hamster ovary (CHO-K1) cell transfected with a mammalian mAChR M₄.

[0056] The term “pharmaceutically acceptable” describes a material that is not biologically or otherwise undesirable, i.e., without causing an unacceptable level of undesirable biological effects or interacting in a deleterious manner.

[0057] As used herein, the term “derivative” refers to a compound having a structure derived from the structure of a parent compound (e.g., a compound disclosed herein) and whose structure is sufficiently similar to those disclosed herein and based upon that similarity, would be expected by one skilled in the art to exhibit the same or similar activities and utilities as the claimed compounds, or to induce, as a precursor, the same or similar activities and utilities as the claimed compounds. Exemplary derivatives include salts, esters, amides, salts of esters or amides, and N-oxides of a parent compound.

[0058] As used herein, the term “pharmaceutically acceptable carrier” refers to sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, as well as sterile powders for reconstitution into sterile injectable solutions or dispersions just prior to use. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol and the like), carboxymethylcellulose and suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants. These compositions can also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms can be ensured by the inclusion of various antibacterial and antifungal agents such as paraben, chlorobutanol, phenol, sorbic acid and the like. It can also be desirable to include isotonic agents such as sugars, sodium

chloride and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the inclusion of agents, such as aluminum monostearate and gelatin, which delay absorption. Injectable depot forms are made by forming microencapsule matrices of the drug in biodegradable polymers such as polylactide-polyglycolide, poly(orthoesters) and poly(anhydrides). Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissues. The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable media just prior to use. Suitable inert carriers can include sugars such as lactose. Desirably, at least 95% by weight of the particles of the active ingredient have an effective particle size in the range of 0.01 to 10 micrometers.

[0059] A residue of a chemical species, as used in the specification and concluding claims, refers to the moiety that is the resulting product of the chemical species in a particular reaction scheme or subsequent formulation or chemical product, regardless of whether the moiety is actually obtained from the chemical species. Thus, an ethylene glycol residue in a polyester refers to one or more $\text{-OCH}_2\text{CH}_2\text{O-}$ units in the polyester, regardless of whether ethylene glycol was used to prepare the polyester. Similarly, a sebacic acid residue in a polyester refers to one or more $\text{-CO(CH}_2)_8\text{CO-}$ moieties in the polyester, regardless of whether the residue is obtained by reacting sebacic acid or an ester thereof to obtain the polyester.

[0060] As used herein, the term “substituted” is contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, and aromatic and nonaromatic substituents of organic compounds. Illustrative substituents include, for example, those described below. The permissible substituents can be one or more and the same or different for appropriate organic compounds. For purposes of this disclosure, the heteroatoms, such as nitrogen, can have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms. This disclosure is not intended to be limited in any manner by the permissible substituents of organic compounds. Also, the terms “substitution” or “substituted with”

include the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, *e.g.*, a compound that does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc. It is also contemplated that, in certain aspects, unless expressly indicated to the contrary, individual substituents can be further optionally substituted (*i.e.*, further substituted or unsubstituted).

[0061] In defining various terms, “A¹,” “A²,” “A³,” and “A⁴” are used herein as generic symbols to represent various specific substituents. These symbols can be any substituent, not limited to those disclosed herein, and when they are defined to be certain substituents in one instance, they can, in another instance, be defined as some other substituents.

[0062] The term “alkyl” as used herein is a branched or unbranched saturated hydrocarbon group of 1 to 24 carbon atoms, such as methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *s*-butyl, *t*-butyl, *n*-pentyl, isopentyl, *s*-pentyl, neopentyl, hexyl, heptyl, octyl, nonyl, decyl, dodecyl, tetradecyl, hexadecyl, eicosyl, tetracosyl, and the like. The alkyl group can be cyclic or acyclic. The alkyl group can be branched or unbranched. The alkyl group can also be substituted or unsubstituted. For example, the alkyl group can be substituted with one or more groups including, but not limited to, alkyl, cycloalkyl, alkoxy, amino, ether, halide, hydroxy, nitro, silyl, sulfo-oxo, or thiol, as described herein. A “lower alkyl” group is an alkyl group containing from one to six (*e.g.*, from one to four) carbon atoms.

[0063] Throughout the specification “alkyl” is generally used to refer to both unsubstituted alkyl groups and substituted alkyl groups; however, substituted alkyl groups are also specifically referred to herein by identifying the specific substituent(s) on the alkyl group. For example, the term “halogenated alkyl” or “haloalkyl” specifically refers to an alkyl group that is substituted with one or more halide, *e.g.*, fluorine, chlorine, bromine, or iodine. The term “alkoxyalkyl” specifically refers to an alkyl group that is substituted with one or more alkoxy groups, as described below. The term “alkylamino” specifically refers to an alkyl group that is substituted with one or more amino groups, as described below, and the like. When “alkyl” is used in one instance and a specific term such as “alkylalcohol” is used in another, it is not meant to imply that the term “alkyl” does not also refer to specific terms such as “alkylalcohol” and the like.

[0064] This practice is also used for other groups described herein. That is, while a term such as “cycloalkyl” refers to both unsubstituted and substituted cycloalkyl moieties, the substituted moieties can, in addition, be specifically identified herein; for example, a particular substituted cycloalkyl can be referred to as, *e.g.*, an “alkylcycloalkyl.” Similarly, a substituted alkoxy can be specifically referred to as, *e.g.*, a “halogenated alkoxy,” a particular substituted alkenyl can be, *e.g.*, an “alkenylalcohol,” and the like. Again, the practice of using a general term, such as “cycloalkyl,” and a specific term, such as “alkylcycloalkyl,” is not meant to imply that the general term does not also include the specific term.

[0065] The term “cycloalkyl” as used herein is a non-aromatic carbon-based ring composed of at least three carbon atoms. Examples of cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, norbornyl, and the like. The term “heterocycloalkyl” is a type of cycloalkyl group as defined above, and is included within the meaning of the term “cycloalkyl,” where at least one of the carbon atoms of the ring is replaced with a heteroatom such as, but not limited to, nitrogen, oxygen, sulfur, or phosphorus. The cycloalkyl group and heterocycloalkyl group can be substituted or unsubstituted. The cycloalkyl group and heterocycloalkyl group can be substituted with one or more groups including, but not limited to, alkyl, cycloalkyl, alkoxy, amino, ether, halide, hydroxy, nitro, silyl, sulfo-oxo, or thiol as described herein.

[0066] The term “polyalkylene group” as used herein is a group having two or more CH₂ groups linked to one another. The polyalkylene group can be represented by the formula —(CH₂)_a—, where “a” is an integer of from 2 to 500.

[0067] The terms “alkoxy” and “alkoxyl” as used herein to refer to an alkyl or cycloalkyl group bonded through an ether linkage; that is, an “alkoxy” group can be defined as —OA¹ where A¹ is alkyl or cycloalkyl as defined above. “Alkoxy” also includes polymers of alkoxy groups as just described; that is, an alkoxy can be a polyether such as —OA¹—OA² or —OA¹—(OA²)_a—OA³, where “a” is an integer of from 1 to 200 and A¹, A², and A³ are alkyl and/or cycloalkyl groups.

[0068] The term “alkenyl” as used herein is a hydrocarbon group of from 2 to 24 carbon atoms with a structural formula containing at least one carbon-carbon double bond. Asymmetric structures such as (A¹A²)C=C(A³A⁴) are intended to include both the *E* and *Z* isomers. This can be presumed in structural formulae herein wherein an asymmetric alkene is

present, or it can be explicitly indicated by the bond symbol C=C. The alkenyl group can be substituted with one or more groups including, but not limited to, alkyl, cycloalkyl, alkoxy, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, heteroaryl, aldehyde, amino, carboxylic acid, ester, ether, halide, hydroxy, ketone, azide, nitro, silyl, sulfo-oxo, or thiol, as described herein.

[0069] The term “cycloalkenyl” as used herein is a non-aromatic carbon-based ring composed of at least three carbon atoms and containing at least one carbon-carbon double bond, *i.e.*, C=C. Examples of cycloalkenyl groups include, but are not limited to, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclopentadienyl, cyclohexenyl, cyclohexadienyl, norbornenyl, and the like. The term “heterocycloalkenyl” is a type of cycloalkenyl group as defined above, and is included within the meaning of the term “cycloalkenyl,” where at least one of the carbon atoms of the ring is replaced with a heteroatom such as, but not limited to, nitrogen, oxygen, sulfur, or phosphorus. The cycloalkenyl group and heterocycloalkenyl group can be substituted or unsubstituted. The cycloalkenyl group and heterocycloalkenyl group can be substituted with one or more groups including, but not limited to, alkyl, cycloalkyl, alkoxy, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, heteroaryl, aldehyde, amino, carboxylic acid, ester, ether, halide, hydroxy, ketone, azide, nitro, silyl, sulfo-oxo, or thiol as described herein.

[0070] The term “alkynyl” as used herein is a hydrocarbon group of 2 to 24 carbon atoms with a structural formula containing at least one carbon-carbon triple bond. The alkynyl group can be unsubstituted or substituted with one or more groups including, but not limited to, alkyl, cycloalkyl, alkoxy, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, heteroaryl, aldehyde, amino, carboxylic acid, ester, ether, halide, hydroxy, ketone, azide, nitro, silyl, sulfo-oxo, or thiol, as described herein.

[0071] The term “cycloalkynyl” as used herein is a non-aromatic carbon-based ring composed of at least seven carbon atoms and containing at least one carbon-carbon triple bond. Examples of cycloalkynyl groups include, but are not limited to, cycloheptynyl, cyclooctynyl, cyclononyl, and the like. The term “heterocycloalkynyl” is a type of cycloalkenyl group as defined above, and is included within the meaning of the term “cycloalkynyl,” where at least one of the carbon atoms of the ring is replaced with a heteroatom such as, but not limited to, nitrogen, oxygen, sulfur, or phosphorus. The

cycloalkynyl group and heterocycloalkynyl group can be substituted or unsubstituted. The cycloalkynyl group and heterocycloalkynyl group can be substituted with one or more groups including, but not limited to, alkyl, cycloalkyl, alkoxy, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, heteroaryl, aldehyde, amino, carboxylic acid, ester, ether, halide, hydroxy, ketone, azide, nitro, silyl, sulfo-oxo, or thiol as described herein.

[0072] The term “aryl” as used herein is a group that contains any carbon-based aromatic group including, but not limited to, benzene, naphthalene, phenyl, biphenyl, phenoxybenzene, and the like. The term “aryl” also includes “heteroaryl,” which is defined as a group that contains an aromatic group that has at least one heteroatom incorporated within the ring of the aromatic group. Examples of heteroatoms include, but are not limited to, nitrogen, oxygen, sulfur, and phosphorus. Likewise, the term “non-heteroaryl,” which is also included in the term “aryl,” defines a group that contains an aromatic group that does not contain a heteroatom. The aryl group can be substituted or unsubstituted. The aryl group can be substituted with one or more groups including, but not limited to, alkyl, cycloalkyl, alkoxy, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, heteroaryl, aldehyde, amino, carboxylic acid, ester, ether, halide, hydroxy, ketone, azide, nitro, silyl, sulfo-oxo, or thiol as described herein. The term “biaryl” is a specific type of aryl group and is included in the definition of “aryl.” Biaryl refers to two aryl groups that are bound together *via* a fused ring structure, as in naphthalene, or are attached *via* one or more carbon-carbon bonds, as in biphenyl.

[0073] The term “aldehyde” as used herein is represented by the formula —C(O)H . Throughout this specification “C(O)” is a short hand notation for a carbonyl group, *i.e.*, C=O .

[0074] The terms “amine” or “amino” as used herein are represented by the formula $\text{—NA}^1\text{A}^2$, where A^1 and A^2 can be, independently, hydrogen or alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein.

[0075] The term “alkylamino” as used herein is represented by the formula —NH(—alkyl) where alkyl is as described herein. Representative examples include, but are not limited to, methylamino group, ethylamino group, propylamino group, isopropylamino group, butylamino group, isobutylamino group, (sec-butyl)amino group, (tert-butyl)amino group, pentylamino group, isopentylamino group, (tert-pentyl)amino group, hexylamino group, and the like.

[0076] The term “dialkylamino” as used herein is represented by the formula —N(—alkyl)_2 where alkyl is as described herein. Representative examples include, but are not limited to, dimethylamino group, diethylamino group, dipropylamino group, diisopropylamino group, dibutylamino group, diisobutylamino group, di(sec-butyl)amino group, di(tert-butyl)amino group, dipentylamino group, diisopentylamino group, di(tert-pentyl)amino group, dihexylamino group, N-ethyl-N-methylamino group, N-methyl-N-propylamino group, N-ethyl-N-propylamino group and the like.

[0077] The term “carboxylic acid” as used herein is represented by the formula —C(O)OH .

[0078] The term “ester” as used herein is represented by the formula —OC(O)A^1 or —C(O)OA^1 , where A^1 can be alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein. The term “polyester” as used herein is represented by the formula $\text{—(A}^1\text{O(O)C—A}^2\text{—C(O)O)}_a\text{—}$ or $\text{—(A}^1\text{O(O)C—A}^2\text{—OC(O))}_a\text{—}$, where A^1 and A^2 can be, independently, an alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group described herein and “a” is an interger from 1 to 500. “Polyester” is as the term used to describe a group that is produced by the reaction between a compound having at least two carboxylic acid groups with a compound having at least two hydroxyl groups.

[0079] The term “ether” as used herein is represented by the formula A^1OA^2 , where A^1 and A^2 can be, independently, an alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group described herein. The term “polyether” as used herein is represented by the formula $\text{—(A}^1\text{O—A}^2\text{O)}_a\text{—}$, where A^1 and A^2 can be, independently, an alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group described herein and “a” is an integer of from 1 to 500. Examples of polyether groups include polyethylene oxide, polypropylene oxide, and polybutylene oxide.

[0080] The term “halide” as used herein refers to the halogens fluorine, chlorine, bromine, and iodine.

[0081] The term “heterocycle,” as used herein refers to single and multi-cyclic aromatic or non-aromatic ring systems in which at least one of the ring members is other than carbon. Heterocycle includes pyridine, pyrimidine, furan, thiophene, pyrrole, isoxazole, isothiazole, pyrazole, oxazole, thiazole, imidazole, oxazole, including, 1,2,3-oxadiazole, 1,2,5-oxadiazole and 1,3,4-oxadiazole, thiadiazole, including, 1,2,3-thiadiazole, 1,2,5-thiadiazole, and 1,3,4-

thiadiazole, triazole, including, 1,2,3-triazole, 1,3,4-triazole, tetrazole, including 1,2,3,4-tetrazole and 1,2,4,5-tetrazole, pyridine, pyridazine, pyrimidine, pyrazine, triazine, including 1,2,4-triazine and 1,3,5-triazine, tetrazine, including 1,2,4,5-tetrazine, pyrrolidine, piperidine, piperazine, morpholine, azetidine, tetrahydropyran, tetrahydrofuran, dioxane, and the like.

[0082] The term “hydroxyl” as used herein is represented by the formula —OH .

[0083] The term “ketone” as used herein is represented by the formula $\text{A}^1\text{C}(\text{O})\text{A}^2$, where A^1 and A^2 can be, independently, an alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein.

[0084] The term “azide” as used herein is represented by the formula —N_3 .

[0085] The term “nitro” as used herein is represented by the formula —NO_2 .

[0086] The term “nitrile” as used herein is represented by the formula —CN .

[0087] The term “silyl” as used herein is represented by the formula $\text{—SiA}^1\text{A}^2\text{A}^3$, where A^1 , A^2 , and A^3 can be, independently, hydrogen or an alkyl, cycloalkyl, alkoxy, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein.

[0088] The term “sulfo-oxo” as used herein is represented by the formulas $\text{—S}(\text{O})\text{A}^1$, $\text{—S}(\text{O})_2\text{A}^1$, $\text{—OS}(\text{O})_2\text{A}^1$, or $\text{—OS}(\text{O})_2\text{OA}^1$, where A^1 can be hydrogen or an alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein.

Throughout this specification “S(O)” is a short hand notation for S=O . The term “sulfonyl” is used herein to refer to the sulfo-oxo group represented by the formula $\text{—S}(\text{O})_2\text{A}^1$, where A^1 can be hydrogen or an alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein. The term “sulfone” as used herein is represented by the formula $\text{A}^1\text{S}(\text{O})_2\text{A}^2$, where A^1 and A^2 can be, independently, an alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein. The term “sulfoxide” as used herein is represented by the formula $\text{A}^1\text{S}(\text{O})\text{A}^2$, where A^1 and A^2 can be, independently, an alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein.

[0089] The term “thiol” as used herein is represented by the formula —SH .

[0090] “ R^1 ,” “ R^2 ,” “ R^3 ,” “ R^n ,” where n is an integer, as used herein can, independently, possess one or more of the groups listed above. For example, if R^1 is a straight chain alkyl group, one of the hydrogen atoms of the alkyl group can optionally be substituted with a

hydroxyl group, an alkoxy group, an alkyl group, a halide, and the like. Depending upon the groups that are selected, a first group can be incorporated within second group or, alternatively, the first group can be pendant (*i.e.*, attached) to the second group. For example, with the phrase “an alkyl group comprising an amino group,” the amino group can be incorporated within the backbone of the alkyl group. Alternatively, the amino group can be attached to the backbone of the alkyl group. The nature of the group(s) that is (are) selected will determine if the first group is embedded or attached to the second group.

[0091] As described herein, compounds of the invention may contain “optionally substituted” moieties. In general, the term “substituted,” whether preceded by the term “optionally” or not, means that one or more hydrogens of the designated moiety are replaced with a suitable substituent. Unless otherwise indicated, an “optionally substituted” group may have a suitable substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. Combinations of substituents envisioned by this invention are preferably those that result in the formation of stable or chemically feasible compounds. It is also contemplated that, in certain aspects, unless expressly indicated to the contrary, individual substituents can be further optionally substituted (*i.e.*, further substituted or unsubstituted).

[0092] The term “stable,” as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and, in certain aspects, their recovery, purification, and use for one or more of the purposes disclosed herein.

[0093] Suitable monovalent substituents on a substitutable carbon atom of an “optionally substituted” group are independently halogen; $-(CH_2)_{0-4}R^\circ$; $-(CH_2)_{0-4}OR^\circ$; $-O(CH_2)_{0-4}R^\circ$; $-O-(CH_2)_{0-4}C(O)OR^\circ$; $-(CH_2)_{0-4}CH(OR^\circ)_2$; $-(CH_2)_{0-4}SR^\circ$; $-(CH_2)_{0-4}Ph$, which may be substituted with R° ; $-(CH_2)_{0-4}O(CH_2)_{0-1}Ph$ which may be substituted with R° ; $-CH=CHPh$, which may be substituted with R° ; $-(CH_2)_{0-4}O(CH_2)_{0-1}$ -pyridyl which may be substituted with R° ; $-NO_2$; $-CN$; $-N_3$; $-(CH_2)_{0-4}N(R^\circ)_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)R^\circ$; $-N(R^\circ)C(S)R^\circ$; $-(CH_2)_{0-4}N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)C(S)NR^\circ_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)OR^\circ$; $-N(R^\circ)N(R^\circ)C(O)R^\circ$; $-N(R^\circ)N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)N(R^\circ)C(O)OR^\circ$; $-(CH_2)_{0-4}C(O)R^\circ$; $-C(S)R^\circ$; $-(CH_2)_{0-4}C(O)OR^\circ$; $-(CH_2)_{0-4}C(O)SR^\circ$; $-(CH_2)_{0-4}C(O)OSiR^\circ_3$; $-(CH_2)_{0-4}OC(O)R^\circ$; $-OC(O)(CH_2)_{0-4}SR^\circ$; $SC(S)SR^\circ$; $-(CH_2)_{0-4}SC(O)R^\circ$; $-(CH_2)_{0-4}C(O)NR^\circ_2$; $-C(S)NR^\circ_2$; $-$

$C(S)SR^{\circ}$; $-SC(S)SR^{\circ}$; $-(CH_2)_{0-4}OC(O)NR^{\circ}_2$; $-C(O)N(OR^{\circ})R^{\circ}$; $-C(O)C(O)R^{\circ}$; $-C(O)CH_2C(O)R^{\circ}$; $-C(NOR^{\circ})R^{\circ}$; $-(CH_2)_{0-4}SSR^{\circ}$; $-(CH_2)_{0-4}S(O)_2R^{\circ}$; $-(CH_2)_{0-4}S(O)_2OR^{\circ}$; $-(CH_2)_{0-4}OS(O)_2R^{\circ}$; $-S(O)_2NR^{\circ}_2$; $-(CH_2)_{0-4}S(O)R^{\circ}$; $-N(R^{\circ})S(O)_2NR^{\circ}_2$; $-N(R^{\circ})S(O)_2R^{\circ}$; $-N(OR^{\circ})R^{\circ}$; $-C(NH)NR^{\circ}_2$; $-P(O)_2R^{\circ}$; $-P(O)R^{\circ}_2$; $-OP(O)R^{\circ}_2$; $-OP(O)(OR^{\circ})_2$; SiR°_3 ; $-(C_{1-4}$ straight or branched alkylene) $O-N(R^{\circ})_2$; or $-(C_{1-4}$ straight or branched alkylene) $C(O)O-N(R^{\circ})_2$, wherein each R° may be substituted as defined below and is independently hydrogen, C_{1-6} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, $-CH_2$ -(5-6 membered heteroaryl ring), or a 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of R° , taken together with their intervening atom(s), form a 3-12-membered saturated, partially unsaturated, or aryl mono- or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, which may be substituted as defined below.

[0094] Suitable monovalent substituents on R° (or the ring formed by taking two independent occurrences of R° together with their intervening atoms), are independently halogen, $-(CH_2)_{0-2}R^{\bullet}$, $-(haloR^{\bullet})$, $-(CH_2)_{0-2}OH$, $-(CH_2)_{0-2}OR^{\bullet}$, $-(CH_2)_{0-2}CH(OR^{\bullet})_2$; $-O(haloR^{\bullet})$, $-CN$, $-N_3$, $-(CH_2)_{0-2}C(O)R^{\bullet}$, $-(CH_2)_{0-2}C(O)OH$, $-(CH_2)_{0-2}C(O)OR^{\bullet}$, $-(CH_2)_{0-2}SR^{\bullet}$, $-(CH_2)_{0-2}SH$, $-(CH_2)_{0-2}NH_2$, $-(CH_2)_{0-2}NHR^{\bullet}$, $-(CH_2)_{0-2}NR^{\bullet}_2$, $-NO_2$, $-SiR^{\bullet}_3$, $-OSiR^{\bullet}_3$, $-C(O)SR^{\bullet}$, $-(C_{1-4}$ straight or branched alkylene) $C(O)OR^{\bullet}$, or $-SSR^{\bullet}$ wherein each $R^{\bullet}$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently selected from C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Suitable divalent substituents on a saturated carbon atom of R° include $=O$ and $=S$.

[0095] Suitable divalent substituents on a saturated carbon atom of an "optionally substituted" group include the following: $=O$, $=S$, $=NNR^*_2$, $=NNHC(O)R^*$, $=NNHC(O)OR^*$, $=NNHS(O)_2R^*$, $=NR^*$, $=NOR^*$, $-O(C(R^*_2))_{2-3}O-$, or $-S(C(R^*_2))_{2-3}S-$, wherein each independent occurrence of R^* is selected from hydrogen, C_{1-6} aliphatic which may be substituted as defined below, or an unsubstituted 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Suitable divalent substituents that are bound to vicinal substitutable

carbons of an “optionally substituted” group include: $-\text{O}(\text{CR}^*)_{2-3}\text{O}-$, wherein each independent occurrence of R^* is selected from hydrogen, C_{1-6} aliphatic which may be substituted as defined below, or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0096] Suitable substituents on the aliphatic group of R^* include halogen, $-\text{R}^\bullet$, $-(\text{haloR}^\bullet)$, $-\text{OH}$, $-\text{OR}^\bullet$, $-\text{O}(\text{haloR}^\bullet)$, $-\text{CN}$, $-\text{C}(\text{O})\text{OH}$, $-\text{C}(\text{O})\text{OR}^\bullet$, $-\text{NH}_2$, $-\text{NHR}^\bullet$, $-\text{NR}^{\bullet 2}$, or $-\text{NO}_2$, wherein each $\text{R}^\bullet$ is unsubstituted or where preceded by “halo” is substituted only with one or more halogens, and is independently C_{1-4} aliphatic, $-\text{CH}_2\text{Ph}$, $-\text{O}(\text{CH}_2)_{0-1}\text{Ph}$, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0097] Suitable substituents on a substitutable nitrogen of an “optionally substituted” group include $-\text{R}^\dagger$, $-\text{NR}^{\dagger 2}$, $-\text{C}(\text{O})\text{R}^\dagger$, $-\text{C}(\text{O})\text{OR}^\dagger$, $-\text{C}(\text{O})\text{C}(\text{O})\text{R}^\dagger$, $-\text{C}(\text{O})\text{CH}_2\text{C}(\text{O})\text{R}^\dagger$, $-\text{S}(\text{O})_2\text{R}^\dagger$, $-\text{S}(\text{O})_2\text{NR}^{\dagger 2}$, $-\text{C}(\text{S})\text{NR}^{\dagger 2}$, $-\text{C}(\text{NH})\text{NR}^{\dagger 2}$, or $-\text{N}(\text{R}^\dagger)\text{S}(\text{O})_2\text{R}^\dagger$; wherein each $\text{R}^\dagger$ is independently hydrogen, C_{1-6} aliphatic which may be substituted as defined below, unsubstituted $-\text{OPh}$, or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of $\text{R}^\dagger$, taken together with their intervening atom(s) form an unsubstituted 3–12–membered saturated, partially unsaturated, or aryl mono- or bicyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

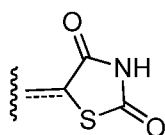
[0098] Suitable substituents on the aliphatic group of $\text{R}^\dagger$ are independently halogen, $-\text{R}^\bullet$, $-(\text{haloR}^\bullet)$, $-\text{OH}$, $-\text{OR}^\bullet$, $-\text{O}(\text{haloR}^\bullet)$, $-\text{CN}$, $-\text{C}(\text{O})\text{OH}$, $-\text{C}(\text{O})\text{OR}^\bullet$, $-\text{NH}_2$, $-\text{NHR}^\bullet$, $-\text{NR}^{\bullet 2}$, or $-\text{NO}_2$, wherein each $\text{R}^\bullet$ is unsubstituted or where preceded by “halo” is substituted only with one or more halogens, and is independently C_{1-4} aliphatic, $-\text{CH}_2\text{Ph}$, $-\text{O}(\text{CH}_2)_{0-1}\text{Ph}$, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0099] The term “leaving group” refers to an atom (or a group of atoms) with electron withdrawing ability that can be displaced as a stable species, taking with it the bonding electrons. Examples of suitable leaving groups include halides and sulfonate esters, including, but not limited to, triflate, mesylate, tosylate, brosylate, and halides.

[00100] The terms “hydrolysable group” and “hydrolysable moiety” refer to a functional group capable of undergoing hydrolysis, e.g., under basic or acidic conditions. Examples of hydrolysable residues include, without limitation, acid halides, activated carboxylic acids, and various protecting groups known in the art (see, for example, “Protective Groups in Organic Synthesis,” T. W. Greene, P. G. M. Wuts, Wiley-Interscience, 1999).

[00101] The term “organic residue” defines a carbon containing residue, i.e., a residue comprising at least one carbon atom, and includes but is not limited to the carbon-containing groups, residues, or radicals defined hereinabove. Organic residues can contain various heteroatoms, or be bonded to another molecule through a heteroatom, including oxygen, nitrogen, sulfur, phosphorus, or the like. Examples of organic residues include but are not limited alkyl or substituted alkyls, alkoxy or substituted alkoxy, mono or di-substituted amino, amide groups, etc. Organic residues can preferably comprise 1 to 18 carbon atoms, 1 to 15, carbon atoms, 1 to 12 carbon atoms, 1 to 8 carbon atoms, 1 to 6 carbon atoms, or 1 to 4 carbon atoms. In a further aspect, an organic residue can comprise 2 to 18 carbon atoms, 2 to 15, carbon atoms, 2 to 12 carbon atoms, 2 to 8 carbon atoms, 2 to 4 carbon atoms, or 2 to 4 carbon atoms.

[00102] A very close synonym of the term “residue” is the term “radical,” which as used in the specification and concluding claims, refers to a fragment, group, or substructure of a molecule described herein, regardless of how the molecule is prepared. For example, a 2,4-thiazolidinedione radical in a particular compound has the structure:



regardless of whether thiazolidinedione is used to prepare the compound. In some embodiments the radical (for example an alkyl) can be further modified (i.e., substituted alkyl) by having bonded thereto one or more “substituent radicals.” The number of atoms in a given radical is not critical to the present invention unless it is indicated to the contrary elsewhere herein.

[00103] “Organic radicals,” as the term is defined and used herein, contain one or more carbon atoms. An organic radical can have, for example, 1-26 carbon atoms, 1-18 carbon atoms, 1-12 carbon atoms, 1-8 carbon atoms, 1-6 carbon atoms, or 1-4 carbon atoms. In a

further aspect, an organic radical can have 2-26 carbon atoms, 2-18 carbon atoms, 2-12 carbon atoms, 2-8 carbon atoms, 2-6 carbon atoms, or 2-4 carbon atoms. Organic radicals often have hydrogen bound to at least some of the carbon atoms of the organic radical. One example, of an organic radical that comprises no inorganic atoms is a 5, 6, 7, 8-tetrahydro-2-naphthyl radical. In some embodiments, an organic radical can contain 1-10 inorganic heteroatoms bound thereto or therein, including halogens, oxygen, sulfur, nitrogen, phosphorus, and the like. Examples of organic radicals include but are not limited to an alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, mono-substituted amino, di-substituted amino, acyloxy, cyano, carboxy, carboalkoxy, alkylcarboxamide, substituted alkylcarboxamide, dialkylcarboxamide, substituted dialkylcarboxamide, alkylsulfonyl, alkylsulfinyl, thioalkyl, thiohaloalkyl, alkoxy, substituted alkoxy, haloalkyl, haloalkoxy, aryl, substituted aryl, heteroaryl, heterocyclic, or substituted heterocyclic radicals, wherein the terms are defined elsewhere herein. A few non-limiting examples of organic radicals that include heteroatoms include alkoxy radicals, trifluoromethoxy radicals, acetoxo radicals, dimethylamino radicals and the like.

[00104] “Inorganic radicals,” as the term is defined and used herein, contain no carbon atoms and therefore comprise only atoms other than carbon. Inorganic radicals comprise bonded combinations of atoms selected from hydrogen, nitrogen, oxygen, silicon, phosphorus, sulfur, selenium, and halogens such as fluorine, chlorine, bromine, and iodine, which can be present individually or bonded together in their chemically stable combinations. Inorganic radicals have 10 or fewer, or preferably one to six or one to four inorganic atoms as listed above bonded together. Examples of inorganic radicals include, but not limited to, amino, hydroxy, halogens, nitro, thiol, sulfate, phosphate, and like commonly known inorganic radicals. The inorganic radicals do not have bonded therein the metallic elements of the periodic table (such as the alkali metals, alkaline earth metals, transition metals, lanthanide metals, or actinide metals), although such metal ions can sometimes serve as a pharmaceutically acceptable cation for anionic inorganic radicals such as a sulfate, phosphate, or like anionic inorganic radical. Inorganic radicals do not comprise metalloids elements such as boron, aluminum, gallium, germanium, arsenic, tin, lead, or tellurium, or the noble gas elements, unless otherwise specifically indicated elsewhere herein.

[00105] Compounds described herein can contain one or more double bonds and, thus, potentially give rise to cis/trans (E/Z) isomers, as well as other conformational isomers.

Unless stated to the contrary, the invention includes all such possible isomers, as well as mixtures of such isomers.

[00106] Unless stated to the contrary, a formula with chemical bonds shown only as solid lines and not as wedges or dashed lines contemplates each possible isomer, *e.g.*, each enantiomer and diastereomer, and a mixture of isomers, such as a racemic or scalemic mixture. Compounds described herein can contain one or more asymmetric centers and, thus, potentially give rise to diastereomers and optical isomers. Unless stated to the contrary, the present invention includes all such possible diastereomers as well as their racemic mixtures, their substantially pure resolved enantiomers, all possible geometric isomers, and pharmaceutically acceptable salts thereof. Mixtures of stereoisomers, as well as isolated specific stereoisomers, are also included. During the course of the synthetic procedures used to prepare such compounds, or in using racemization or epimerization procedures known to those skilled in the art, the products of such procedures can be a mixture of stereoisomers.

[00107] Many organic compounds exist in optically active forms having the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L or R and S are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d and l or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or meaning that the compound is levorotatory. A compound prefixed with (+) or d is dextrorotatory. For a given chemical structure, these compounds, called stereoisomers, are identical except that they are non-superimposable mirror images of one another. A specific stereoisomer can also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture. Many of the compounds described herein can have one or more chiral centers and therefore can exist in different enantiomeric forms. If desired, a chiral carbon can be designated with an asterisk (*). When bonds to the chiral carbon are depicted as straight lines in the disclosed formulas, it is understood that both the (R) and (S) configurations of the chiral carbon, and hence both enantiomers and mixtures thereof, are embraced within the formula. As is used in the art, when it is desired to specify the absolute configuration about a chiral carbon, one of the bonds to the chiral carbon can be depicted as a wedge (bonds to atoms above the plane) and the other can be depicted as a series or wedge of short parallel lines is (bonds to atoms below the

plane). The Cahn-Ingold-Prelog system can be used to assign the (R) or (S) configuration to a chiral carbon.

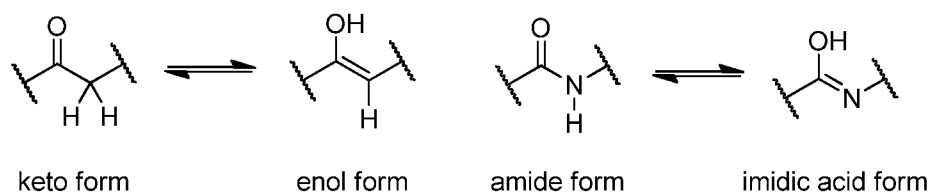
[00108] Compounds described herein comprise atoms in both their natural isotopic abundance and in non-natural abundance. The disclosed compounds can be isotopically-labelled or isotopically-substituted compounds identical to those described, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number typically found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{35}S , ^{18}F and ^{36}Cl , respectively. Compounds further comprise prodrugs thereof, and pharmaceutically acceptable salts of said compounds or of said prodrugs which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically-labelled compounds of the present invention, for example those into which radioactive isotopes such as ^3H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^3H , and carbon-14, i.e., ^{14}C , isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium, i.e., ^2H , can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labelled compounds of the present invention and prodrugs thereof can generally be prepared by carrying out the procedures below, by substituting a readily available isotopically labelled reagent for a non- isotopically labelled reagent.

[00109] The compounds described in the invention can be present as a solvate. In some cases, the solvent used to prepare the solvate is an aqueous solution, and the solvate is then often referred to as a hydrate. The compounds can be present as a hydrate, which can be obtained, for example, by crystallization from a solvent or from aqueous solution. In this connection, one, two, three or any arbitrary number of solvate or water molecules can combine with the compounds according to the invention to form solvates and hydrates. Unless stated to the contrary, the invention includes all such possible solvates.

[00110] The term “co-crystal” means a physical association of two or more molecules which owe their stability through non-covalent interaction. One or more components of this

molecular complex provide a stable framework in the crystalline lattice. In certain instances, the guest molecules are incorporated in the crystalline lattice as anhydrides or solvates, see e.g. “Crystal Engineering of the Composition of Pharmaceutical Phases. Do Pharmaceutical Co-crystals Represent a New Path to Improved Medicines?” Almarasson, O., et. al., The Royal Society of Chemistry, 1889-1896, 2004. Examples of co-crystals include p-toluenesulfonic acid and benzenesulfonic acid.

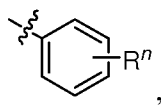
[00111] It is also appreciated that certain compounds described herein can be present as an equilibrium of tautomers. For example, ketones with an α -hydrogen can exist in an equilibrium of the keto form and the enol form.



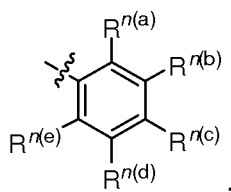
Likewise, amides with an N-hydrogen can exist in an equilibrium of the amide form and the imidic acid form. Unless stated to the contrary, the invention includes all such possible tautomers.

[00112] It is known that chemical substances form solids which are present in different states of order which are termed polymorphic forms or modifications. The different modifications of a polymorphic substance can differ greatly in their physical properties. The compounds according to the invention can be present in different polymorphic forms, with it being possible for particular modifications to be metastable. Unless stated to the contrary, the invention includes all such possible polymorphic forms.

[00113] In some aspects, a structure of a compound can be represented by a formula:



which is understood to be equivalent to a formula:



wherein n is typically an integer. That is, R^n is understood to represent five independent substituents, $R^{n(a)}$, $R^{n(b)}$, $R^{n(c)}$, $R^{n(d)}$, $R^{n(e)}$. By “independent substituents,” it is meant that each R substituent can be independently defined. For example, if in one instance $R^{n(a)}$ is halogen, then $R^{n(b)}$ is not necessarily halogen in that instance.

[00114] Certain materials, compounds, compositions, and components disclosed herein can be obtained commercially or readily synthesized using techniques generally known to those of skill in the art. For example, the starting materials and reagents used in preparing the disclosed compounds and compositions are either available from commercial suppliers such as Aldrich Chemical Co., (Milwaukee, Wis.), Acros Organics (Morris Plains, N.J.), Fisher Scientific (Pittsburgh, Pa.), or Sigma (St. Louis, Mo.) or are prepared by methods known to those skilled in the art following procedures set forth in references such as Fieser and Fieser's Reagents for Organic Synthesis, Volumes 1-17 (John Wiley and Sons, 1991); Rodd's Chemistry of Carbon Compounds, Volumes 1-5 and Supplementals (Elsevier Science Publishers, 1989); Organic Reactions, Volumes 1-40 (John Wiley and Sons, 1991); March's Advanced Organic Chemistry, (John Wiley and Sons, 4th Edition); and Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989).

[00115] The following abbreviations are used herein. AcOEt: ethyl acetate. AcOH: acetic acid. ACN: acetonitrile. BuOH: 1-butanol. DIPEA or DIEA: diisopropylethylamine. DMAP: 4-dimethylaminopyridine. DCM: dichloromethane. DCE: 1,2-dichloroethane. DIPE: diisopropylether. DIPEA: N,N-diisopropylethylamine. DMF: N,N-dimethyl formamide. DMSO: dimethylsulfoxide. EDC: 1-ethyl-3-[3-dimethylaminopropyl]carbodiimide hydrochloride. EtOAc: ethyl acetate. EtOH: ethanol. h: Hours. HPLC: high-performance liquid chromatography. HOBt: 1-hydroxybenzotriazole. iPrOH: 2-propanol. LC-MS or LCMS: liquid chromatography/mass spectrometry. $[M+H]^+$: protonated mass of the free base of the compound. M. p.: melting point. MeCN: Acetonitrile. MeOH: methanol. Min: Minutes. NMR: nuclear magnetic resonance. RP: reversed phase. Rt: retention time (in minutes). RT: Room temperature. TEA: triethylamine. THF: tetrahydrofuran. TMEDA: N,N,N',N'-tetramethylethylenediamine.

[00116] Unless otherwise expressly stated, it is in no way intended that any method set forth herein be construed as requiring that its steps be performed in a specific order. Accordingly, where a method claim does not actually recite an order to be followed by its steps or it is not

otherwise specifically stated in the claims or descriptions that the steps are to be limited to a specific order, it is no way intended that an order be inferred, in any respect. This holds for any possible non-express basis for interpretation, including: matters of logic with respect to arrangement of steps or operational flow; plain meaning derived from grammatical organization or punctuation; and the number or type of embodiments described in the specification.

[00117] Disclosed are the components to be used to prepare the compositions of the invention as well as the compositions themselves to be used within the methods disclosed herein.

These and other materials are disclosed herein, and it is understood that when combinations, subsets, interactions, groups, etc. of these materials are disclosed that while specific reference of each various individual and collective combinations and permutation of these compounds can not be explicitly disclosed, each is specifically contemplated and described herein. For example, if a particular compound is disclosed and discussed and a number of modifications that can be made to a number of molecules including the compounds are discussed, specifically contemplated is each and every combination and permutation of the compound and the modifications that are possible unless specifically indicated to the contrary. Thus, if a class of molecules A, B, and C are disclosed as well as a class of molecules D, E, and F and an example of a combination molecule, A-D is disclosed, then even if each is not individually recited each is individually and collectively contemplated meaning combinations, A-E, A-F, B-D, B-E, B-F, C-D, C-E, and C-F are considered disclosed. Likewise, any subset or combination of these is also disclosed. Thus, for example, the sub-group of A-E, B-F, and C-E would be considered disclosed. This concept applies to all aspects of this application including, but not limited to, steps in methods of making and using the compositions of the invention. Thus, if there are a variety of additional steps that can be performed it is understood that each of these additional steps can be performed with any specific embodiment or combination of embodiments of the methods of the invention.

[00118] It is understood that the compositions disclosed herein have certain functions.

Disclosed herein are certain structural requirements for performing the disclosed functions, and it is understood that there are a variety of structures that can perform the same function that are related to the disclosed structures, and that these structures will typically achieve the same result.

B. COMPOUNDS

[00119] In one aspect, the invention relates to compounds useful as positive allosteric modulators of the muscarinic acetylcholine receptor M₄ (mAChR M₄). More specifically, in one aspect, the present invention relates to compounds that allosterically modulate mAChR M₄ receptor activity, affecting the sensitivity of mAChR M₄ receptors to agonists without acting as orthosteric agonists themselves. The compounds can, in one aspect, exhibit subtype selectivity.

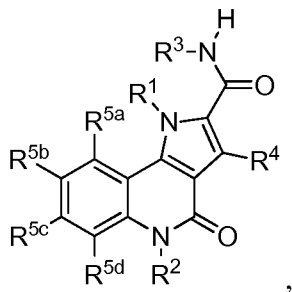
[00120] In one aspect, the disclosed compounds exhibit positive allosteric modulation of mAChR M₄ response to acetylcholine as an increase in response to non-maximal concentrations of acetylcholine in Chinese hamster ovary (CHO-K1) cells transfected with rat mAChR M₄ in the presence of the compound, compared to the response to acetylcholine in the absence of the compound. In further aspect, the Chinese hamster ovary (CHO-K1) cells are transfected with human mAChR M₄. In yet a further aspect, Chinese hamster ovary (CHO-K1) cells are transfected with mAChR M₄ of a mammal.

[00121] In one aspect, the compounds of the invention are useful in the treatment neurological and psychiatric disorders associated with muscarinic acetylcholine receptor dysfunction and other diseases in which muscarinic acetylcholine receptors are involved, as further described herein. In a further aspect, the muscarinic acetylcholine receptor dysfunction is mAChR M₄ dysfunction.

[00122] It is contemplated that each disclosed derivative can be optionally further substituted. It is also contemplated that any one or more derivative can be optionally omitted from the invention. It is understood that a disclosed compound can be provided by the disclosed methods. It is also understood that the disclosed compounds can be employed in the disclosed methods of using.

1. STRUCTURE

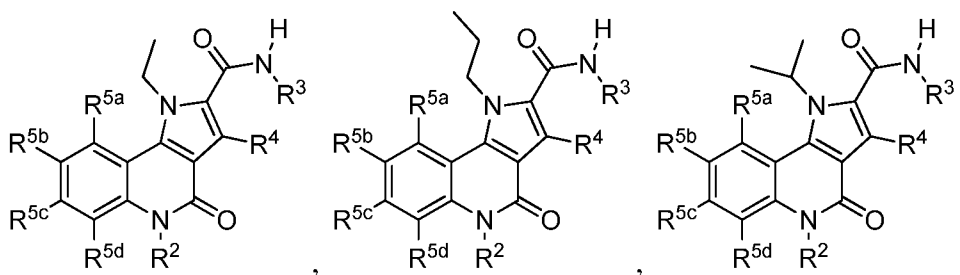
[00123] In one aspect, the invention relates to a compound having a structure represented by a formula:

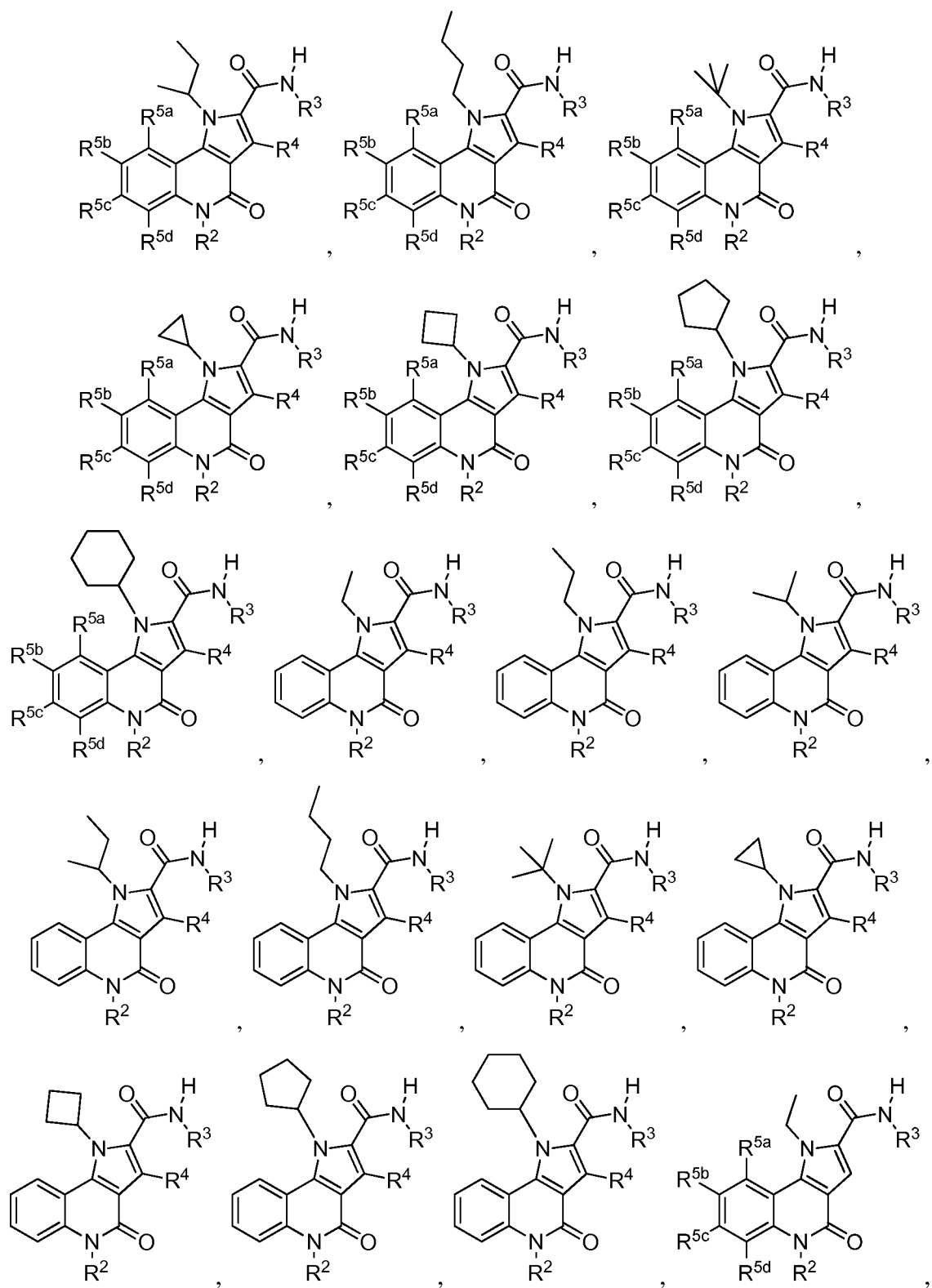


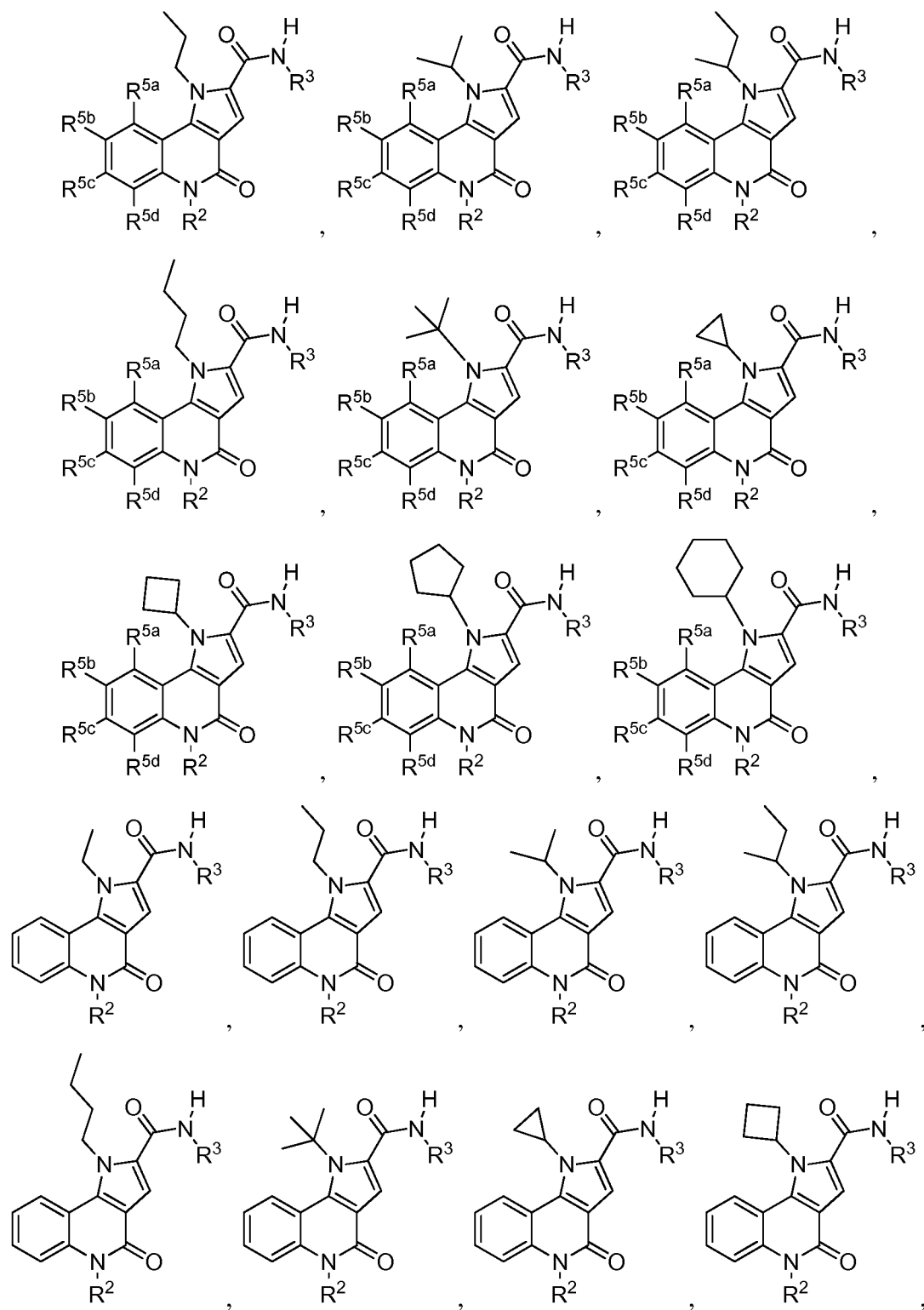
wherein R^1 is selected from hydrogen, C2-C8 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, and Cy^1 ; wherein Cy^1 is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy^1 is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein R^2 is selected from hydrogen, C1-C8 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, and Cy^2 ; wherein Cy^2 is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy^2 is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein R^3 is selected from C1-C8 alkyl, Cy^3 , and Ar^1 ; wherein Ar^1 is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar^1 is heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy^3 is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy^3 is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein R^4 is selected from hydrogen, halogen, hydroxyl, cyano, amino, C1-C8 alkyl, C1-C6 alkoxy, C1-C6 alkylamino, C1-C6 dialkylamino, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, Cy^4 , and Ar^2 ; wherein Ar^2 is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar^2 is heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-

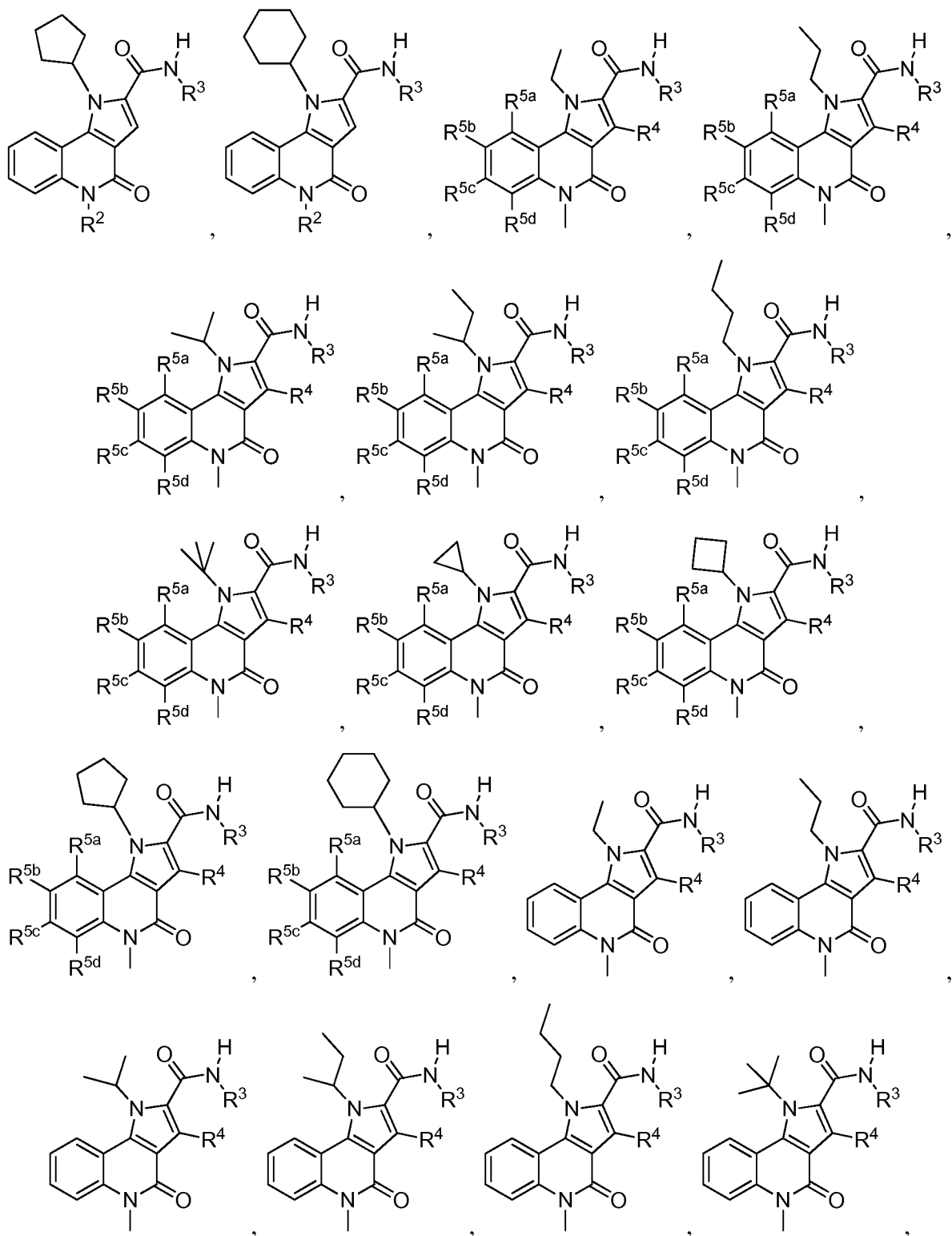
C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy⁴ is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy⁴ is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein each of R^{5a}, R^{5b}, R^{5c}, and R^{5d} is independently selected from hydrogen, halogen, hydroxyl, cyano, amino, CONR⁶R⁷, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 alkylamino, C1-C6 dialkylamino, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, Cy⁵, and Ar³, wherein Ar³ is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar³ is heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy⁵ is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy⁵ is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein each of R⁶ and R⁷ is independently selected from hydrogen, C1-C6 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, aryl and heteroaryl; or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof.

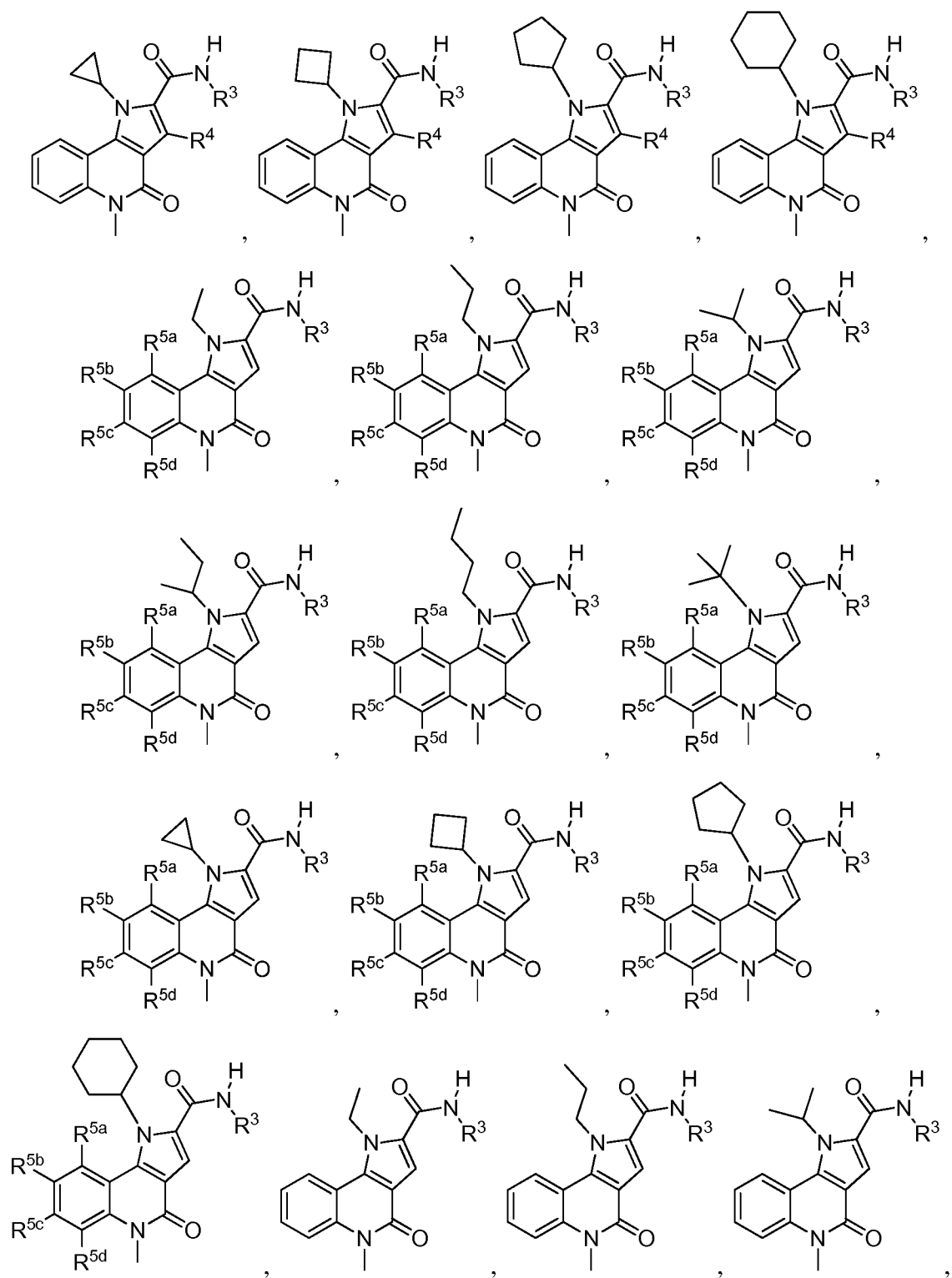
[00124] In a further aspect, a compound can have a structure listed below. In a further aspect, a compound can be selected from two or more of the structures listed below.

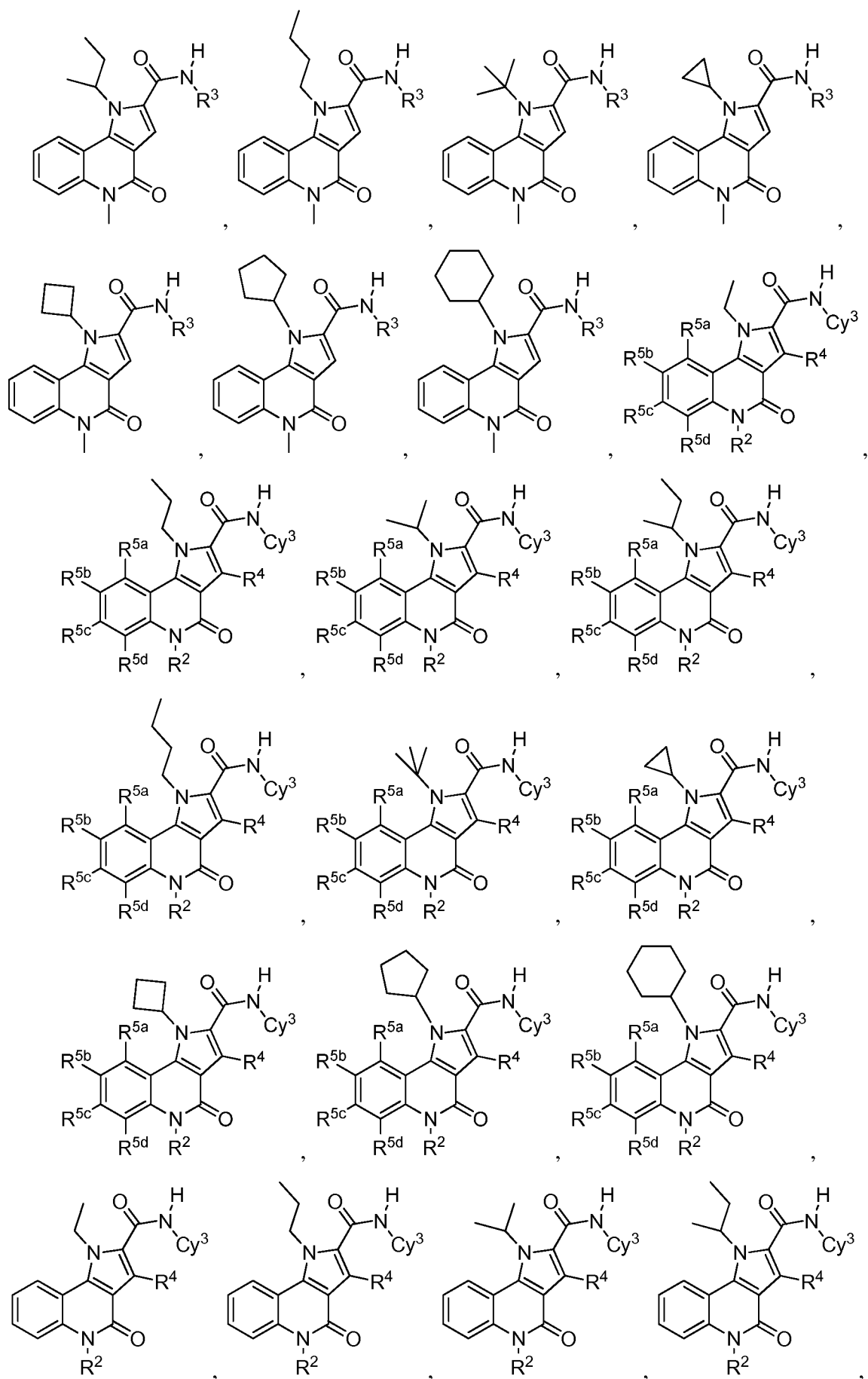


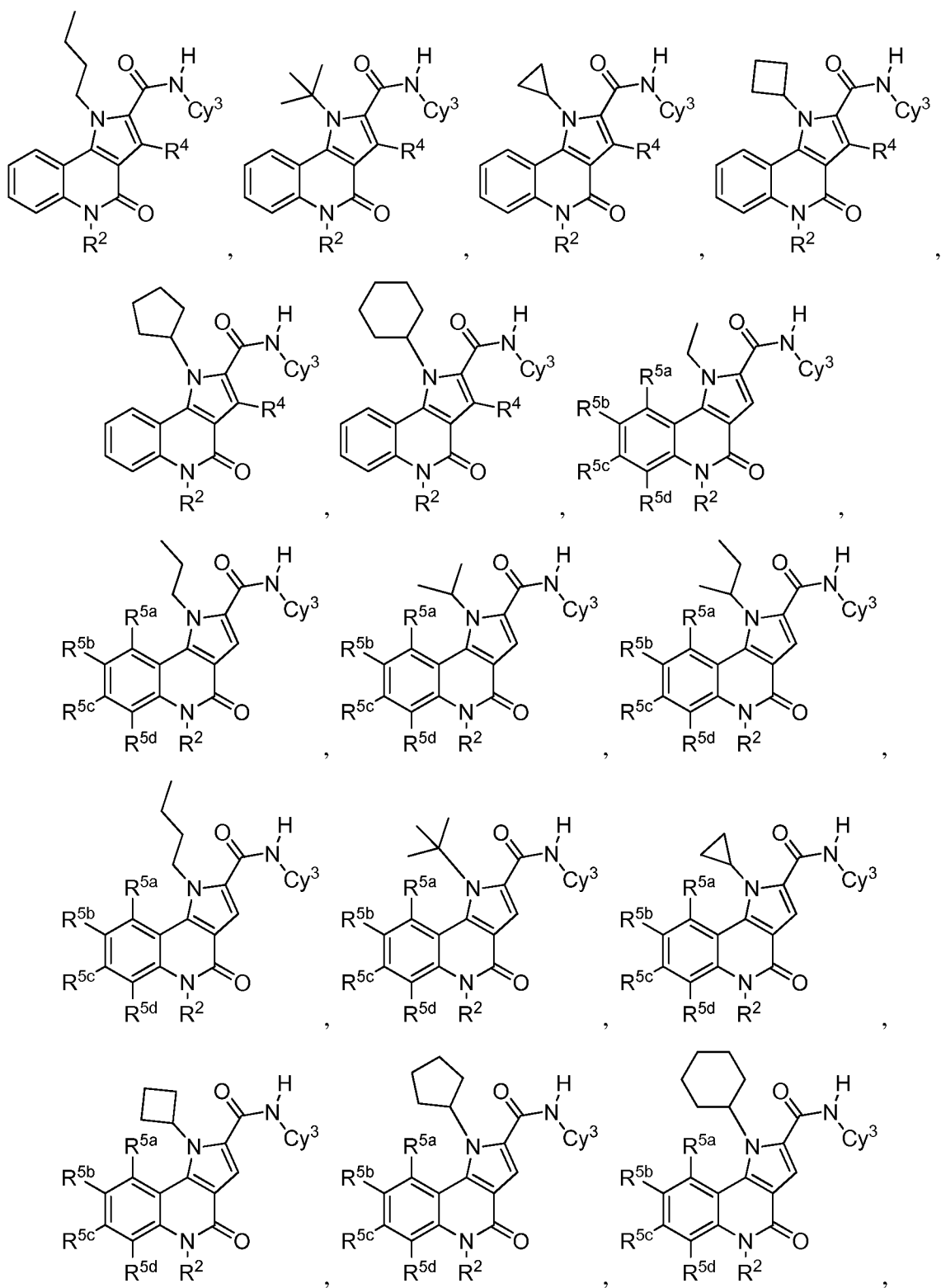


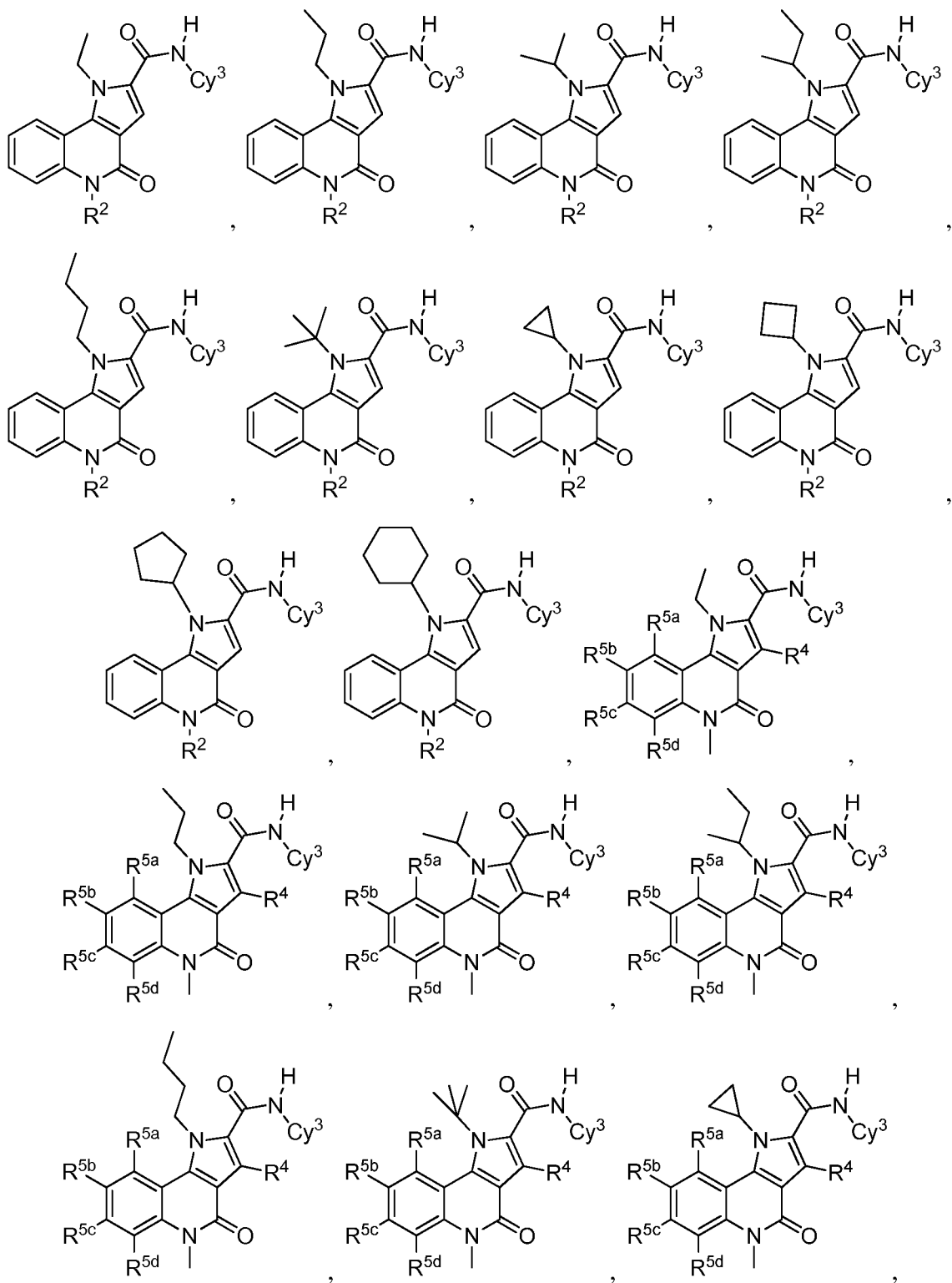


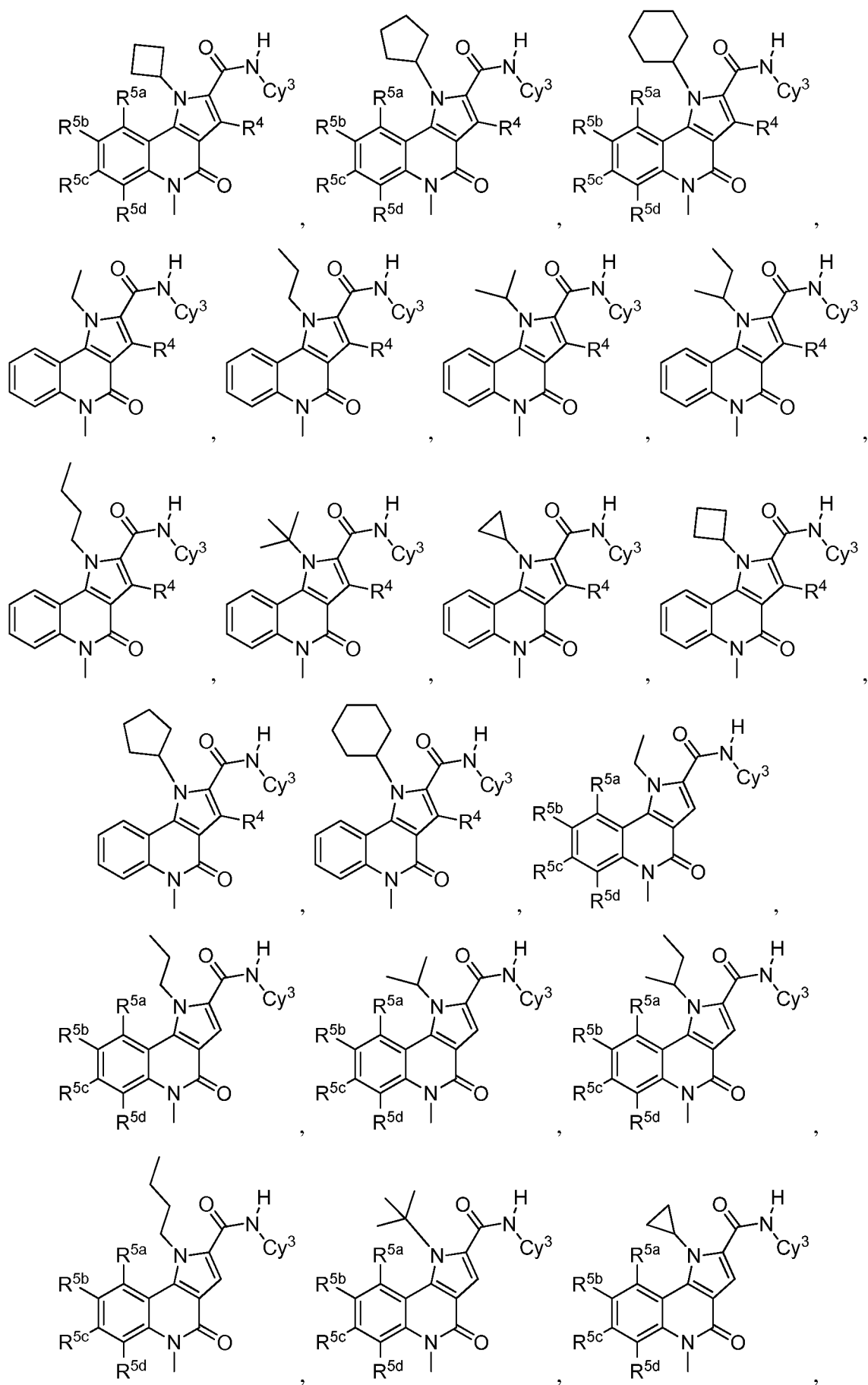


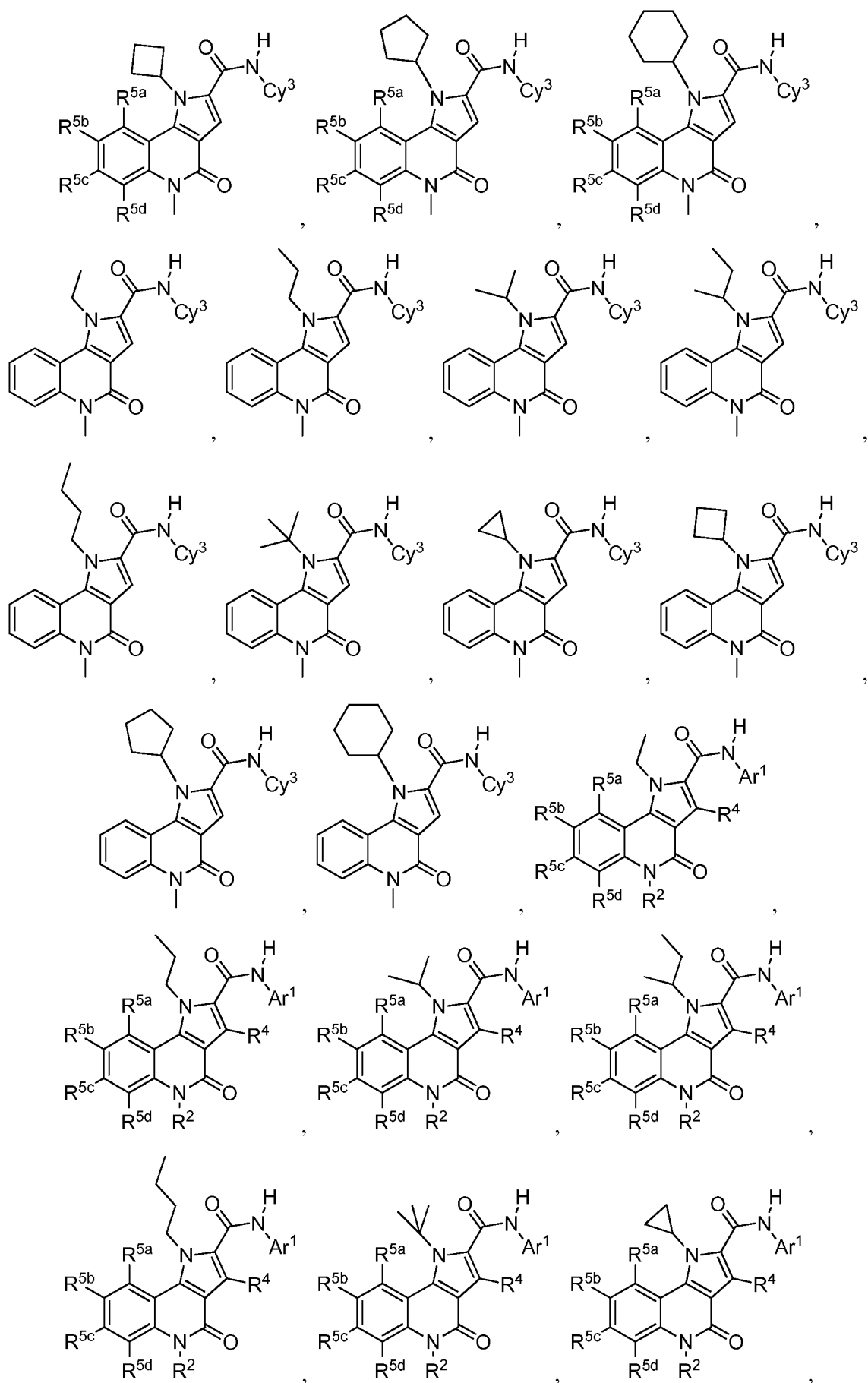


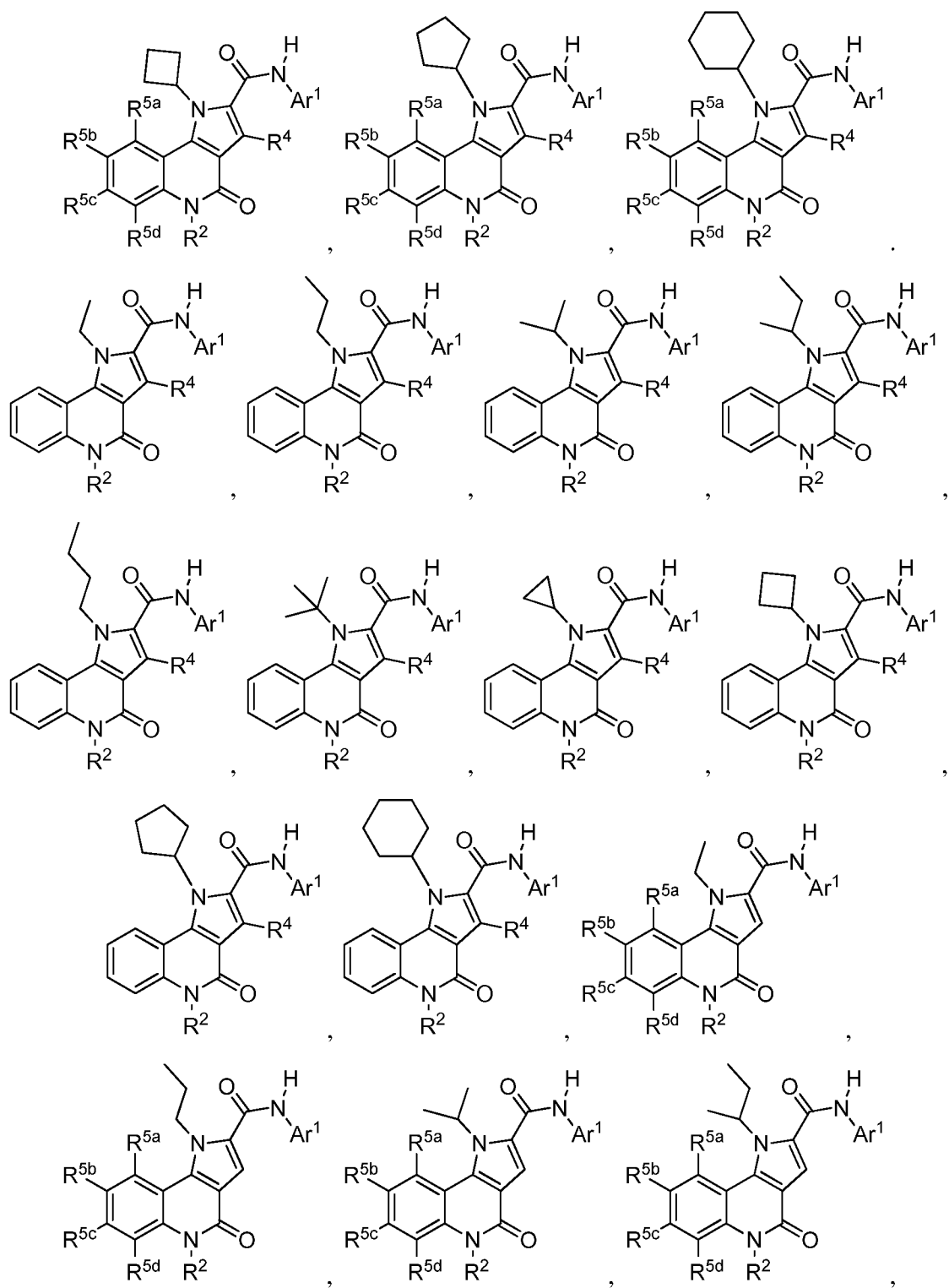


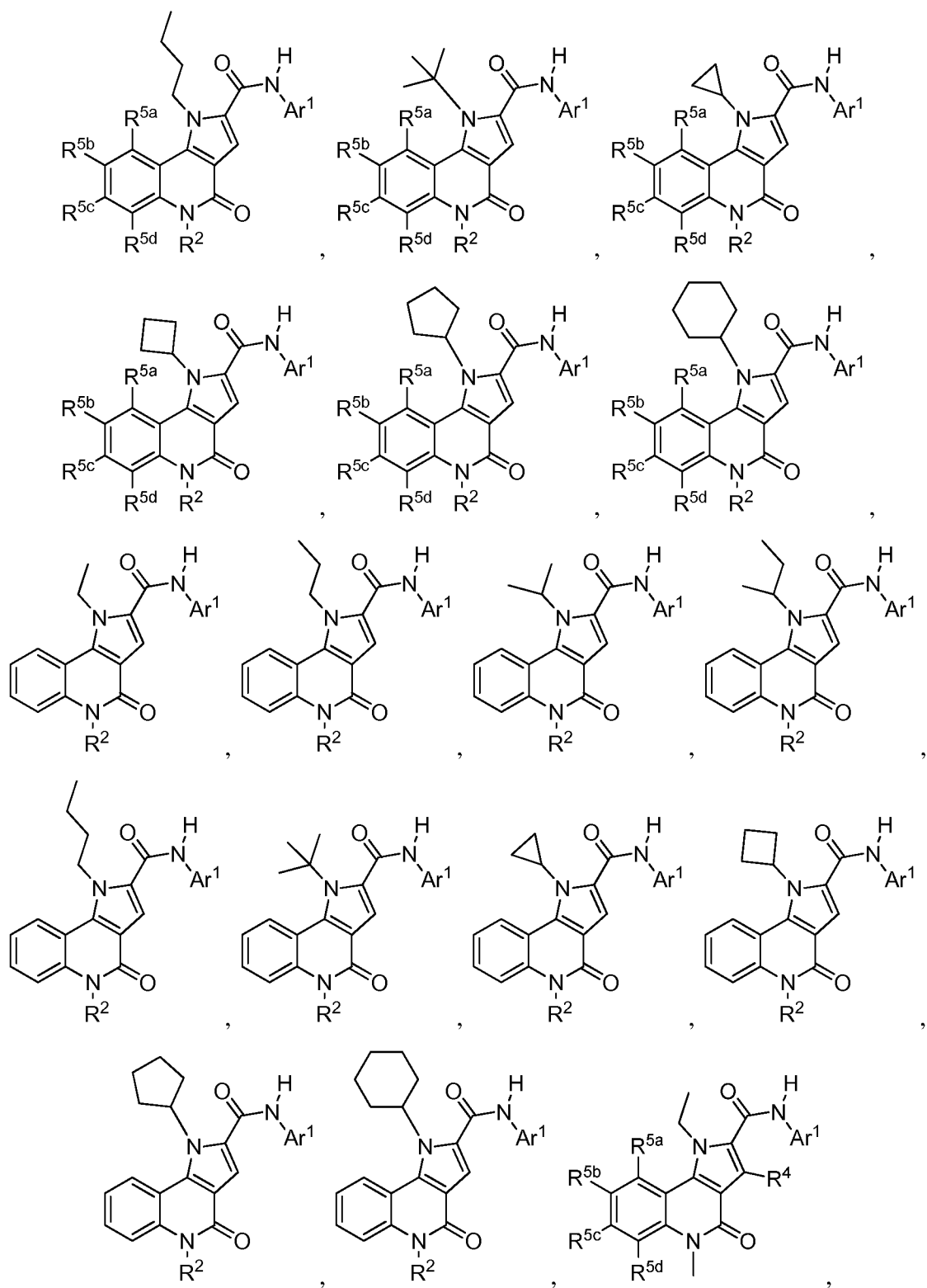


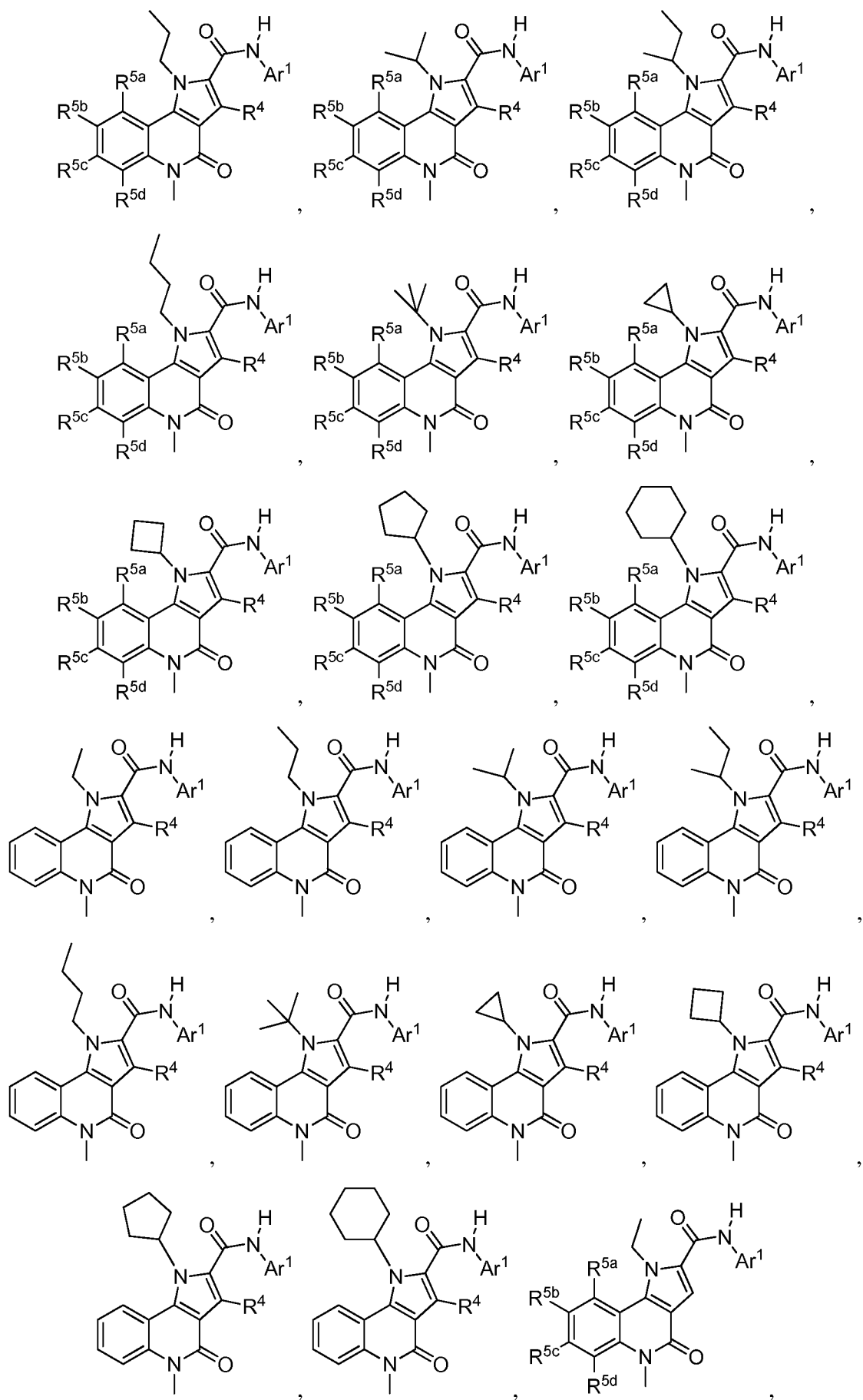


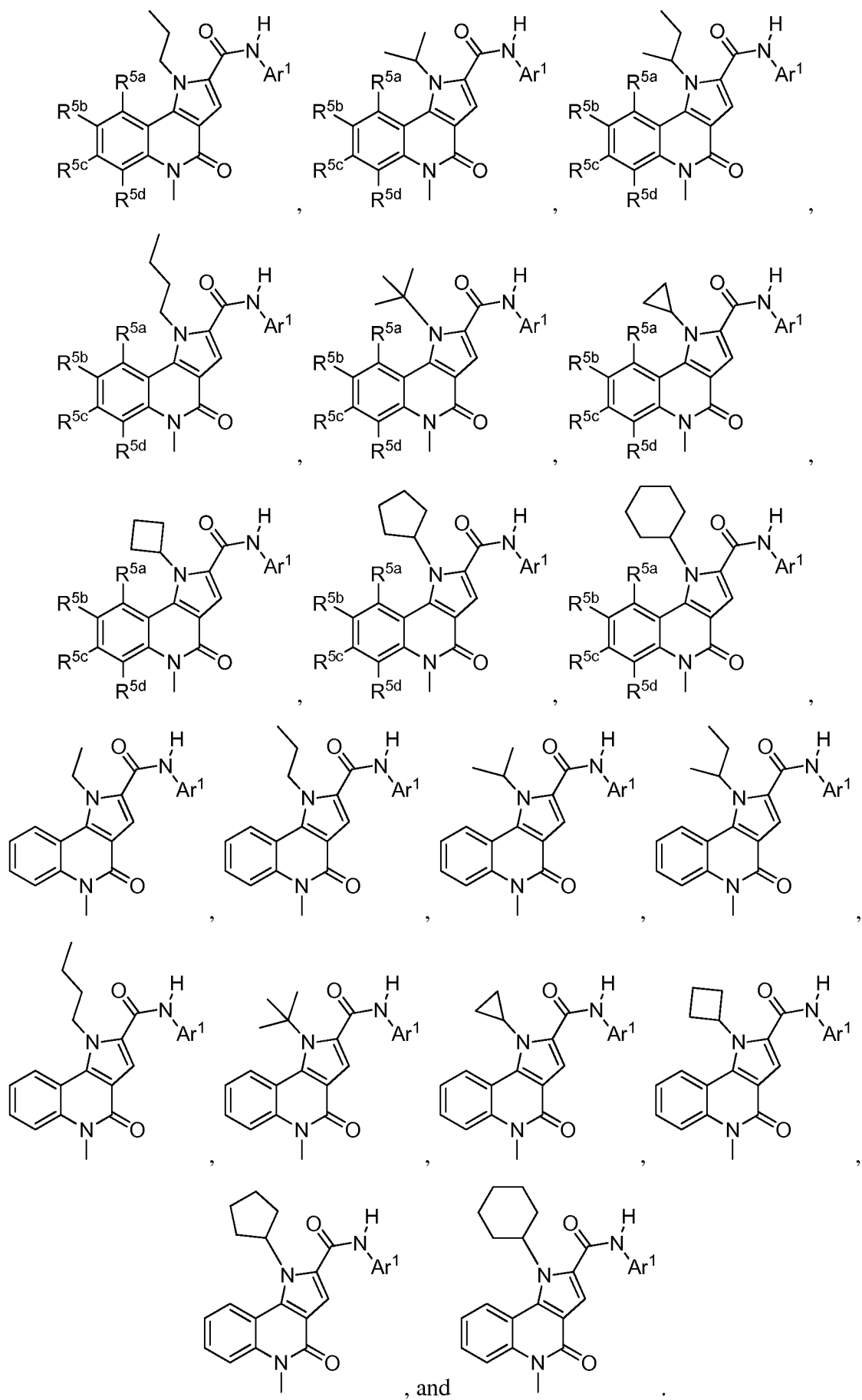




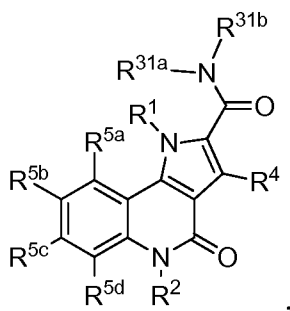








[00125] In one aspect, the invention relates to a compound having a structure represented by a formula:



wherein R^1 is selected from hydrogen, C2-C8 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, and Cy^1 ; wherein Cy^1 is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy^1 is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein R^2 is selected from hydrogen, C1-C8 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, and Cy^2 ; wherein Cy^2 is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy^2 is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein each of R^{31a} and R^{31b} is independently selected from hydrogen, C1-C8 alkyl, Cy^3 , and Ar^1 ; wherein Ar^1 is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar^1 is heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy^3 is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy^3 is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein R^4 is selected from hydrogen, halogen, hydroxyl, cyano, amino, C1-C8 alkyl, C1-C6 alkoxy, C1-C6 alkylamino, C1-C6

dialkylamino, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, Cy⁴, and Ar²; wherein Ar² is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar² is heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy⁴ is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy⁴ is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein each of R^{5a}, R^{5b}, R^{5c}, and R^{5d} is independently selected from hydrogen, halogen, hydroxyl, cyano, amino, CONR⁶R⁷, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 alkylamino, C1-C6 dialkylamino, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, Cy⁵, and Ar³, wherein Ar³ is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar³ is heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy⁵ is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy⁵ is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein each of R⁶ and R⁷ is independently selected from hydrogen, C1-C6 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, aryl and heteroaryl; or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof.

a. AR¹ GROUPS

[00126] In one aspect, Ar¹ is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar¹ is heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl. In a further aspect, Ar¹ is unsubstituted. In a further aspect, Ar¹ has 1, 2, or 3 substituents. In a further aspect, Ar¹ is substituted with 1-3 groups independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6

polyhaloalkyl. In a further aspect, Ar¹ is substituted with 0-3 halogens. In a further aspect, Ar¹ is substituted with 1-3 halogens. In a further aspect, Ar¹ is substituted with 1-3 groups selected from halogen, methyl, trifluoromethyl, ethyl, propyl, and butyl. In a further aspect, Ar¹ is substituted with 1-3 groups selected from cyano, halogen, methyl, trifluoromethyl, ethyl, propyl, and butyl. In a further aspect, Ar¹ is substituted with 1-3 groups selected from methoxy, trifluoromethoxy, ethoxy, propyloxy, or butyloxy.

[00127] In a further aspect, Ar¹ is phenyl. In a further aspect, Ar¹ is phenyl with 1-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl.

[00128] In a further aspect, Ar¹ is heteroaryl. In a further aspect, Ar¹ is pyrrolyl, imidazolyl, furanyl, thiophenyl, pyridinyl, pyridazinyl, pyrimidinyl, or pyrazinyl. In a further aspect, Ar¹ is pyridinyl, pyridazinyl, pyrimidinyl, or pyrazinyl. In a further aspect, Ar¹ is pyridinyl, pyridazinyl, pyrimidinyl, or pyrazinyl and has 1-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl.

[00129] In various further aspects, Ar¹ can be a bicyclic/heteroaryl selected from naphthyl, indene, indole, benzofuran, benzothiophene, quinoline, isoquinoline, tetrahydroquinoline, indazole, oxindole, benzimidazole, azaindole, azabenzofuran, benzoxazole, and benzothiazole.

b. AR² GROUPS

[00130] In one aspect, Ar² is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar² is heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl. In a further aspect, Ar² is unsubstituted. In a further aspect, Ar² has 1, 2, or 3 substituents. In a further aspect, Ar² is substituted with 1-3 groups independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl. In a further aspect, Ar² is substituted with 0-3 halogens. In a further aspect, Ar² is substituted with 1-3 halogens. In a further aspect, Ar² is substituted with 1-3 groups selected from halogen, methyl, trifluoromethyl, ethyl, propyl, and butyl. In a further aspect, Ar² is substituted with 1-3 groups selected from cyano, halogen, methyl, trifluoromethyl,

ethyl, propyl, and butyl. In a further aspect, Ar² is substituted with 1-3 groups selected from methoxy, trifluoromethoxy, ethoxy, propyloxy, or butyloxy.

[00131] In a further aspect, Ar² is phenyl. In a further aspect, Ar² is phenyl with 1-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl.

[00132] In a further aspect, Ar² is heteroaryl. In a further aspect, Ar² is pyrrolyl, imidazolyl, furanyl, thiophenyl, pyridinyl, pyridazinyl, pyrimidinyl, or pyrazinyl. In a further aspect, Ar² is pyridinyl, pyridazinyl, pyrimidinyl, or pyrazinyl. In a further aspect, Ar² is pyridinyl, pyridazinyl, pyrimidinyl, or pyrazinyl and has 1-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl.

[00133] In various further aspects, Ar² can be a bicyclic/heteroaryl selected from naphthyl, indene, indole, benzofuran, benzothiophene, quinoline, isoquinoline, tetrahydroquinoline, indazole, oxindole, benzimidazole, azaindole, azabenzofuran, benzoxazole, and benzothiazole.

c. AR³ GROUPS

[00134] In one aspect, Ar³ is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar³ is heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl. In a further aspect, Ar³ is unsubstituted. In a further aspect, Ar³ has 1, 2, or 3 substituents. In a further aspect, Ar³ is substituted with 1-3 groups independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl. In a further aspect, Ar³ is substituted with 0-3 halogens. In a further aspect, Ar³ is substituted with 1-3 halogens. In a further aspect, Ar³ is substituted with 1-3 groups selected from halogen, methyl, trifluoromethyl, ethyl, propyl, and butyl. In a further aspect, Ar³ is substituted with 1-3 groups selected from cyano, halogen, methyl, trifluoromethyl, ethyl, propyl, and butyl. In a further aspect, Ar³ is substituted with 1-3 groups selected from methoxy, trifluoromethoxy, ethoxy, propyloxy, or butyloxy.

[00135] In a further aspect, Ar³ is phenyl. In a further aspect, Ar³ is phenyl with 1-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl.

[00136] In a further aspect, Ar³ is heteroaryl. In a further aspect, Ar³ is pyrrolyl, imidazolyl, furanyl, thiophenyl, pyridinyl, pyridazinyl, pyrimidinyl, or pyrazinyl. In a further aspect, Ar³ is pyridinyl, pyridazinyl, pyrimidinyl, or pyrazinyl. In a further aspect, Ar³ is pyridinyl, pyridazinyl, pyrimidinyl, or pyrazinyl and has 1-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl.

[00137] In various further aspects, Ar³ can be a bicyclic/heteroaryl selected from naphthyl, indene, indole, benzofuran, benzothiophene, quinoline, isoquinoline, tetrahydroquinoline, indazole, oxindole, benzimidazole, azaindole, azabenzofuran, benzoxazole, and benzothiazole.

d. CY¹ GROUPS

[00138] In one aspect, Cy¹ is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy¹ is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino. In a further aspect, Cy¹ is unsubstituted.

[00139] In a further aspect, Cy¹ is C3-C8 cycloalkyl. In a further aspect, Cy¹ is C3-C8 cycloalkyl with 1-3 substituents independently selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino.

[00140] In a further aspect, Cy¹ is C3-C8 heterocycloalkyl with 1-3 substituents independently selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino.

[00141] In a further aspect, Cy¹ is aziridinyl, oxiranyl, thiiranyl, azetidiny, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, oxazolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperazinyl,

hexahydropyrimidinyl, hexahydropyridazinyl, morpholinyl, oxazinanyl, azepanyl, oxepanyl, thiepanyl, azocanyl, oxocanyl, or thiocanyl. In a further aspect, Cy¹ is aziridinyl, oxiranyl, thiiranyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, oxazolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperazinyl, hexahydropyrimidinyl, hexahydropyridazinyl, morpholinyl, or oxazinanyl. In a further aspect, Cy¹ is aziridinyl, oxiranyl, thiiranyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, oxazolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperazinyl, hexahydropyrimidinyl, hexahydropyridazinyl, morpholinyl, or oxazinanyl and has 1-3 substituents independently selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino.

[00142] In a further aspect, Cy¹ is substituted with 1-3 groups independently selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino. In a further aspect, Cy¹ is substituted with 0-3 halogens. In a further aspect, Cy¹ is substituted with 1-3 halogens. In a further aspect, Cy¹ is substituted with 1-3 groups selected from halogen, methyl, trifluoromethyl, ethyl, propyl, and butyl. In a further aspect, Cy¹ is substituted with 1-3 groups selected from halogen, hydroxyl, cyano, amino, methyl, trifluoromethyl, ethyl, propyl, and butyl. In a further aspect, Cy¹ is substituted with 1-3 groups selected from methoxy, trifluoromethoxy, ethoxy, propyloxy, or butyloxy.

e. CY² GROUPS

[00143] In one aspect, Cy² is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy² is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino. In a further aspect, Cy² is unsubstituted.

[00144] In a further aspect, Cy² is C3-C8 cycloalkyl. In a further aspect, Cy² is C3-C8 cycloalkyl with 1-3 substituents independently selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino.

[00145] In a further aspect, Cy^2 is C3-C8 heterocycloalkyl with 1-3 substituents independently selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino.

[00146] In a further aspect, Cy^2 is aziridinyl, oxiranyl, thiiranyl, azetidiny, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, oxazolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperazinyl, hexahydropyrimidinyl, hexahydropyridazinyl, morpholinyl, oxazinanyl, azepanyl, oxepanyl, thiepanyl, azocanyl, oxocanyl, or thiocanyl. In a further aspect, Cy^2 is aziridinyl, oxiranyl, thiiranyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, oxazolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperazinyl, hexahydropyrimidinyl, hexahydropyridazinyl, morpholinyl, or oxazinanyl. In a further aspect, Cy^2 is aziridinyl, oxiranyl, thiiranyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, oxazolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperazinyl, hexahydropyrimidinyl, hexahydropyridazinyl, morpholinyl, or oxazinanyl and has 1-3 substituents independently selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino.

[00147] In a further aspect, Cy^2 is substituted with 1-3 groups independently selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino. In a further aspect, Cy^2 is substituted with 0-3 halogens. In a further aspect, Cy^2 is substituted with 1-3 halogens. In a further aspect, Cy^2 is substituted with 1-3 groups selected from halogen, methyl, trifluoromethyl, ethyl, propyl, and butyl. In a further aspect, Cy^2 is substituted with 1-3 groups selected from halogen, hydroxyl, cyano, amino, methyl, trifluoromethyl, ethyl, propyl, and butyl. In a further aspect, Cy^2 is substituted with 1-3 groups selected from methoxy, trifluoromethoxy, ethoxy, propyloxy, or butyloxy.

f. CY^3 GROUPS

[00148] In one aspect, Cy^3 is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy^3 is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano,

amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino. In a further aspect, Cy³ is unsubstituted.

[00149] In a further aspect, Cy³ is C3-C8 cycloalkyl. In a further aspect, Cy³ is C3-C8 cycloalkyl with 1-3 substituents independently selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino.

[00150] In a further aspect, Cy³ is C3-C8 heterocycloalkyl with 1-3 substituents independently selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino.

[00151] In a further aspect, Cy³ is aziridinyl, oxiranyl, thiiranyl, azetidiny, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, oxazolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperazinyl, hexahydropyrimidinyl, hexahydropyridazinyl, morpholinyl, oxazinanyl, azepanyl, oxepanyl, thiepanyl, azocanyl, oxocanyl, or thiocanyl. In a further aspect, Cy³ is aziridinyl, oxiranyl, thiiranyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, oxazolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperazinyl, hexahydropyrimidinyl, hexahydropyridazinyl, morpholinyl, or oxazinanyl. In a further aspect, Cy³ is aziridinyl, oxiranyl, thiiranyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, oxazolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperazinyl, hexahydropyrimidinyl, hexahydropyridazinyl, morpholinyl, or oxazinanyl and has 1-3 substituents independently selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino.

[00152] In a further aspect, Cy³ is substituted with 1-3 groups independently selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino. In a further aspect, Cy³ is substituted with 0-3 halogens. In a further aspect, Cy³ is substituted with 1-3 halogens. In a further aspect, Cy³ is substituted with 1-3 groups selected from halogen, methyl, trifluoromethyl, ethyl, propyl, and butyl. In a further aspect, Cy³ is substituted with 1-3 groups selected from halogen, hydroxyl, cyano, amino, methyl, trifluoromethyl, ethyl, propyl,

and butyl. In a further aspect, Cy³ is substituted with 1-3 groups selected from methoxy, trifluoromethoxy, ethoxy, propyloxy, or butyloxy.

g. CY⁴ GROUPS

[00153] In one aspect, Cy⁴ is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy⁴ is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino. In a further aspect, Cy⁴ is unsubstituted.

[00154] In a further aspect, Cy⁴ is C3-C8 cycloalkyl. In a further aspect, Cy⁴ is C3-C8 cycloalkyl with 1-3 substituents independently selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino.

[00155] In a further aspect, Cy⁴ is C3-C8 heterocycloalkyl with 1-3 substituents independently selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino.

[00156] In a further aspect, Cy⁴ is aziridinyl, oxiranyl, thiiranyl, azetidiny, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, oxazolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperazinyl, hexahydropyrimidinyl, hexahydropyridazinyl, morpholinyl, oxazinanyl, azepanyl, oxepanyl, thiepanyl, azocanyl, oxocanyl, or thiocanyl. In a further aspect, Cy⁴ is aziridinyl, oxiranyl, thiiranyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, oxazolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperazinyl, hexahydropyrimidinyl, hexahydropyridazinyl, morpholinyl, or oxazinanyl. In a further aspect, Cy⁴ is aziridinyl, oxiranyl, thiiranyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, oxazolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperazinyl, hexahydropyrimidinyl, hexahydropyridazinyl, morpholinyl, or oxazinanyl and has 1-3 substituents independently selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino.

[00157] In a further aspect, Cy⁴ is substituted with 1-3 groups independently selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino. In a further aspect, Cy⁴ is substituted with 0-3 halogens. In a further aspect, Cy⁴ is substituted with 1-3 halogens. In a further aspect, Cy⁴ is substituted with 1-3 groups selected from halogen, methyl, trifluoromethyl, ethyl, propyl, and butyl. In a further aspect, Cy⁴ is substituted with 1-3 groups selected from halogen, hydroxyl, cyano, amino, methyl, trifluoromethyl, ethyl, propyl, and butyl. In a further aspect, Cy⁴ is substituted with 1-3 groups selected from methoxy, trifluoromethoxy, ethoxy, propyloxy, or butyloxy.

h. CY⁵ GROUPS

[00158] In one aspect, Cy⁵ is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy⁵ is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino. In a further aspect, Cy⁵ is unsubstituted.

[00159] In a further aspect, Cy⁵ is C3-C8 cycloalkyl. In a further aspect, Cy⁵ is C3-C8 cycloalkyl with 1-3 substituents independently selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino.

[00160] In a further aspect, Cy⁵ is C3-C8 heterocycloalkyl with 1-3 substituents independently selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino.

[00161] In a further aspect, Cy⁵ is aziridinyl, oxiranyl, thiiranyl, azetidiny, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, oxazolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperazinyl, hexahydropyrimidinyl, hexahydropyridazinyl, morpholinyl, oxazinanyl, azepanyl, oxepanyl, thiepanyl, azocanyl, oxocanyl, or thiocanyl. In a further aspect, Cy⁵ is aziridinyl, oxiranyl, thiiranyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, oxazolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperazinyl, hexahydropyrimidinyl, hexahydropyridazinyl, morpholinyl, or oxazinanyl. In a further aspect,

Cy⁵ is aziridinyl, oxiranyl, thiiranyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, oxazolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperazinyl, hexahydropyrimidinyl, hexahydropyridazinyl, morpholinyl, or oxazinanyl and has 1-3 substituents independently selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino.

[00162] In a further aspect, Cy⁵ is substituted with 1-3 groups independently selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino. In a further aspect, Cy⁵ is substituted with 0-3 halogens. In a further aspect, Cy⁵ is substituted with 1-3 halogens. In a further aspect, Cy⁵ is substituted with 1-3 groups selected from halogen, methyl, trifluoromethyl, ethyl, propyl, and butyl. In a further aspect, Cy⁵ is substituted with 1-3 groups selected from halogen, hydroxyl, cyano, amino, methyl, trifluoromethyl, ethyl, propyl, and butyl. In a further aspect, Cy⁵ is substituted with 1-3 groups selected from methoxy, trifluoromethoxy, ethoxy, propyloxy, or butyloxy.

i. R¹ GROUPS

[00163] In one aspect, wherein R¹ is selected from hydrogen, C1-C8 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, and Cy¹. In a further aspect, R¹ is selected from C1-C8 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, and Cy¹. In a further aspect, R¹ is selected from hydrogen, C2-C8 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, and Cy¹. In a further aspect, R¹ is selected from C2-C8 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, and Cy¹.

[00164] In a further aspect, R¹ is C1-C8 alkyl, for example, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, or octyl. In a further aspect, R¹ is C2-C8 alkyl, for example, ethyl, propyl, butyl, pentyl, hexyl, heptyl, or octyl.

[00165] In a further aspect, R¹ is C1-C6 haloalkyl, for example, methyl, ethyl, propyl, butyl, pentyl, or hexyl, substituted with a halogen selected from fluoro, chloro, bromo, and iodo.

[00166] In a further aspect, R¹ is C1-C6 polyhaloalkyl, for example, methyl, ethyl, propyl, butyl, pentyl, or hexyl, substituted with 2 or more (e.g., 2, 3, 4, or 5) halogens independently selected from fluoro, chloro, bromo, and iodo. Polyhaloalkyl includes trifluoromethyl, perfluoroethyl, trichloromethyl, and perchloroethyl.

[00167] In a further aspect, R^1 is Cy^1 .

j. R^2 GROUPS

[00168] In one aspect, R^2 is selected from hydrogen, C1-C8 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, and Cy^2 . In a further aspect, R^2 is selected from C1-C8 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, and Cy^2 .

[00169] In a further aspect, R^2 is C1-C8 alkyl, for example, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, or octyl. In a further aspect, R^2 is C1-C6 haloalkyl, for example, methyl, ethyl, propyl, butyl, pentyl, or hexyl, substituted with a halogen selected from fluoro, chloro, bromo, and iodo. In a further aspect, R^2 is C1-C6 polyhaloalkyl, for example, methyl, ethyl, propyl, butyl, pentyl, or hexyl, substituted with 2 or more (e.g., 2, 3, 4, or 5) halogens independently selected from fluoro, chloro, bromo, and iodo. Polyhaloalkyl includes trifluoromethyl, perfluoroethyl, trichloromethyl, and perchloroethyl.

[00170] In a further aspect, R^2 is Cy^2 .

k. R^3 GROUPS

[00171] In one aspect, R^3 is selected from C1-C8 alkyl, Cy^3 , and Ar^1 . In a further aspect, R^3 is selected from C1-C8 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, and Cy^3 .

[00172] In a further aspect, R^3 is C1-C8 alkyl, for example, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, or octyl. In a further aspect, R^3 is C1-C6 haloalkyl, for example, methyl, ethyl, propyl, butyl, pentyl, or hexyl, substituted with a halogen selected from fluoro, chloro, bromo, and iodo. In a further aspect, R^3 is C1-C6 polyhaloalkyl, for example, methyl, ethyl, propyl, butyl, pentyl, or hexyl, substituted with 2 or more (e.g., 2, 3, 4, or 5) halogens independently selected from fluoro, chloro, bromo, and iodo. Polyhaloalkyl includes trifluoromethyl, perfluoroethyl, trichloromethyl, and perchloroethyl.

[00173] In a further aspect, R^3 is Cy^3 . In a further aspect, R^3 is Ar^1 .

l. R^{31} GROUPS

[00174] In one aspect, each of R^{31a} and R^{31b} is independently selected from hydrogen, C1-C8 alkyl, Cy^3 , and Ar^1 . In a further aspect, each of R^{31a} and R^{31b} is independently selected from hydrogen, C1-C8 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, and Cy^3 .

[00175] In a further aspect, each of R^{31a} and R^{31b} is independently selected from hydrogen and C1-C8 alkyl, for example, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, or octyl. In yet a further aspect, each of R^{31a} and R^{31b} is independently selected from hydrogen and C1-C6 haloalkyl, for example, methyl, ethyl, propyl, butyl, pentyl, or hexyl, substituted with a halogen selected from fluoro, chloro, bromo, and iodo. In a still further aspect, each of R^{31a} and R^{31b} is independently selected from hydrogen and C1-C6 polyhaloalkyl, for example, methyl, ethyl, propyl, butyl, pentyl, or hexyl, substituted with 2 or more (e.g., 2, 3, 4, or 5) halogens independently selected from fluoro, chloro, bromo, and iodo. Polyhaloalkyl includes trifluoromethyl, perfluoroethyl, trichloromethyl, and perchloroethyl.

[00176] In a further aspect, each of R^{31a} and R^{31b} is independently selected from hydrogen and Cy^3 . In a still further aspect, each of R^{31a} and R^{31b} is independently selected from hydrogen and Ar^1 .

[00177] In a further aspect, R^{31a} is hydrogen and R^{31b} is C1-C8 alkyl, for example, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, or octyl. In yet a further aspect, R^{31a} is hydrogen and R^{31b} is C1-C6 haloalkyl, for example, methyl, ethyl, propyl, butyl, pentyl, or hexyl, substituted with a halogen selected from fluoro, chloro, bromo, and iodo. In a still further aspect, R^{31a} is hydrogen and R^{31b} is C1-C6 polyhaloalkyl, for example, methyl, ethyl, propyl, butyl, pentyl, or hexyl, substituted with 2 or more (e.g., 2, 3, 4, or 5) halogens independently selected from fluoro, chloro, bromo, and iodo. Polyhaloalkyl includes trifluoromethyl, perfluoroethyl, trichloromethyl, and perchloroethyl.

[00178] In a further aspect, R^{31a} is hydrogen and R^{31b} is Cy^3 . In a still further aspect, R^{31a} is hydrogen and R^{31b} is Ar^1 .

m. R^4 GROUPS

[00179] In one aspect, R^4 is selected from hydrogen, halogen, hydroxyl, cyano, amino, C1-C8 alkyl, C1-C6 alkoxy, C1-C6 alkylamino, C1-C6 dialkylamino, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, Cy^4 , and Ar^2 . In a further aspect, R^4 is selected from halogen, hydroxyl, cyano, amino, C1-C8 alkyl, C1-C6 alkoxy, C1-C6 alkylamino, C1-C6 dialkylamino, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, Cy^4 , and Ar^2 .

[00180] In a further aspect, R^4 is C1-C8 alkyl, for example, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, or octyl. In a further aspect, R^4 is C1-C6 alkoxy, for example methoxyl, ethoxyl, propoxyl, butoxyl, pentoxyl, or hexoxyl.

[00181] In a further aspect, R^4 is C1-C6 alkylamino, for example, methylamino, ethylamino, propylamino, isopropylamino, butylamino, isobutylamino, (sec-butyl)amino, (tert-butyl)amino, pentylamino, isopentylamino, (tert-pentyl)amino, or hexylamino group. In a further aspect, R^4 is C1-C6 dialkylamino, for example, dimethylamino, diethylamino, dipropylamino, diisopropylamino, dibutylamino, diisobutylamino, di(sec-butyl)amino, di(tert-butyl)amino, dipentylamino, diisopentylamino, di(tert-pentyl)amino, dihexylamino, N-ethyl-N-methylamino, N-methyl-N-propylamino, or N-ethyl-N-propylamino.

[00182] In a further aspect, R^4 is C1-C6 haloalkyl, for example, methyl, ethyl, propyl, butyl, pentyl, or hexyl, substituted with a halogen selected from fluoro, chloro, bromo, and iodo. In a further aspect, R^4 is C1-C6 polyhaloalkyl, for example, methyl, ethyl, propyl, butyl, pentyl, or hexyl, substituted with 2 or more (e.g., 2, 3, 4, or 5) halogens independently selected from fluoro, chloro, bromo, and iodo. Polyhaloalkyl includes trifluoromethyl, perfluoroethyl, trichloromethyl, and perchloroethyl.

[00183] In a further aspect, R^4 is Cy^4 . In a further aspect, R^4 is Ar^2 .

n. R^{41} GROUPS

[00184] In one aspect, R^{41} is selected from hydrogen, C1-C6 alkyl and C3-C8 cycloalkyl. In a further aspect, R^{41} is selected from C1-C6 alkyl and C3-C8 cycloalkyl.

[00185] In a further aspect, R^{41} is C1-C8 alkyl, for example, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, or octyl. In a still further aspect, R^{41} is selected from methyl, ethyl, and propyl. In a yet further aspect, R^{41} is methyl. In an even further aspect, R^{41} is C3-C8 cycloalkyl, for example, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

o. R^5 GROUPS

[00186] In one aspect, each of R^{5a} , R^{5b} , R^{5c} , and R^{5d} is independently selected from hydrogen, halogen, hydroxyl, cyano, amino, $-CONR^6R^7$, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 alkylamino, C1-C6 dialkylamino, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, Cy^5 , and Ar^3 . In a further aspect, each of R^{5a} , R^{5b} , R^{5c} , and R^{5d} is independently selected from halogen, hydroxyl, cyano, amino, $-CONR^6R^7$, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 alkylamino, C1-C6 dialkylamino, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, Cy^5 , and Ar^3 . In a further aspect, each of R^{5a} , R^{5b} , R^{5c} , and R^{5d} is independently selected from fluoro, chloro, bromo, and iodo. In a

further aspect, each of R^{5a} , R^{5b} , R^{5c} , and R^{5d} is independently selected from hydroxyl, cyano, and amino.

[00187] In a further aspect, each of R^{5a} , R^{5b} , R^{5c} , and R^{5d} is independently C1-C6 alkyl, for example, methyl, ethyl, propyl, butyl, pentyl, or hexyl. In a further aspect, each of R^{5a} , R^{5b} , R^{5c} , and R^{5d} is independently C1-C6 alkoxy, for example methoxyl, ethoxyl, propoxyl, butoxyl, pentoxyl, or hexoxyl.

[00188] In a further aspect, each of R^{5a} , R^{5b} , R^{5c} , and R^{5d} is independently C1-C6 alkylamino, for example, methylamino, ethylamino, propylamino, isopropylamino, butylamino, isobutylamino, (sec-butyl)amino, (tert-butyl)amino, pentylamino, isopentylamino, (tert-pentyl)amino, or hexylamino group. In a further aspect, each of R^{5a} , R^{5b} , R^{5c} , and R^{5d} is independently C1-C6 dialkylamino, for example, dimethylamino, diethylamino, dipropylamino, diisopropylamino, dibutylamino, diisobutylamino, di(sec-butyl)amino, di(tert-butyl)amino, dipentylamino, diisopentylamino, di(tert-pentyl)amino, dihexylamino, N-ethyl-N-methylamino, N-methyl-N-propylamino, or N-ethyl-N-propylamino.

[00189] In a further aspect, each of R^{5a} , R^{5b} , R^{5c} , and R^{5d} is independently C1-C6 haloalkyl, for example, methyl, ethyl, propyl, butyl, pentyl, or hexyl, substituted with a halogen selected from fluoro, chloro, bromo, and iodo. In a further aspect, each of R^{5a} , R^{5b} , R^{5c} , and R^{5d} is independently C1-C6 polyhaloalkyl, for example, methyl, ethyl, propyl, butyl, pentyl, or hexyl, substituted with 2 or more (e.g., 2, 3, 4, or 5) halogens independently selected from fluoro, chloro, bromo, and iodo. Polyhaloalkyl includes trifluoromethyl, perfluoroethyl, trichloromethyl, and perchloroethyl.

[00190] In a further aspect, each of R^{5a} , R^{5b} , R^{5c} , and R^{5d} is independently Cy^5 . In a further aspect, each of R^{5a} , R^{5b} , R^{5c} , and R^{5d} is independently Ar^3 .

[00191] In one aspect, R^{5a} is hydrogen. In one aspect, R^{5b} is hydrogen. In one aspect, R^{5c} is hydrogen. In one aspect, R^{5d} is hydrogen. In a further aspect, all of R^{5a} , R^{5b} , R^{5c} , and R^{5d} are hydrogen.

[00192] In a further aspect, each of R^{5b} , R^{5c} , and R^{5d} is hydrogen, while R^{5a} is selected from halogen, hydroxyl, cyano, amino, $-CONR^6R^7$, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 alkylamino, C1-C6 dialkylamino, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, Cy^5 , and Ar^3 . In a further aspect, each of R^{5a} , R^{5c} , and R^{5d} is hydrogen, while R^{5b} is selected from halogen,

hydroxyl, cyano, amino, $-\text{CONR}^6\text{R}^7$, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 alkylamino, C1-C6 dialkylamino, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, Cy^5 , and Ar^3 . In a further aspect, each of R^{5a} , R^{5b} , and R^{5d} is hydrogen, while R^{5c} is selected from halogen, hydroxyl, cyano, amino, $-\text{CONR}^6\text{R}^7$, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 alkylamino, C1-C6 dialkylamino, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, Cy^5 , and Ar^3 . In a further aspect, each of R^{5a} , R^{5b} , and R^{5c} is hydrogen, while R^{5d} is selected from halogen, hydroxyl, cyano, amino, $-\text{CONR}^6\text{R}^7$, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 alkylamino, C1-C6 dialkylamino, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, Cy^5 , and Ar^3 .

[00193] In one aspect, R^{5c} and R^{5d} are hydrogen, while one or both of R^{5a} and R^{5b} is selected from halogen, hydroxyl, cyano, amino, $-\text{CONR}^6\text{R}^7$, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 alkylamino, C1-C6 dialkylamino, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, Cy^5 , and Ar^3 . In a further aspect, R^{5a} and R^{5b} are hydrogen, while one or both of R^{5c} and R^{5d} is selected from halogen, hydroxyl, cyano, amino, $-\text{CONR}^6\text{R}^7$, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 alkylamino, C1-C6 dialkylamino, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, Cy^5 , and Ar^3 . In a further aspect, R^{5a} and R^{5d} are hydrogen, while one or both of R^{5b} and R^{5c} is selected from halogen, hydroxyl, cyano, amino, $-\text{CONR}^6\text{R}^7$, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 alkylamino, C1-C6 dialkylamino, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, Cy^5 , and Ar^3 . In a further aspect, R^{5b} and R^{5c} are hydrogen, while one or both of R^{5a} and R^{5d} is selected from halogen, hydroxyl, cyano, amino, $-\text{CONR}^6\text{R}^7$, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 alkylamino, C1-C6 dialkylamino, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, Cy^5 , and Ar^3 . In a further aspect, R^{5a} and R^{5c} are hydrogen, while one or both of R^{5b} and R^{5d} is selected from halogen, hydroxyl, cyano, amino, $-\text{CONR}^6\text{R}^7$, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 alkylamino, C1-C6 dialkylamino, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, Cy^5 , and Ar^3 . In a further aspect, R^{5b} and R^{5d} are hydrogen, while one or both of R^{5a} and R^{5c} is selected from halogen, hydroxyl, cyano, amino, $-\text{CONR}^6\text{R}^7$, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 alkylamino, C1-C6 dialkylamino, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, Cy^5 , and Ar^3 .

p. R^6 GROUPS

[00194] In one aspect, R^6 is selected from hydrogen, C1-C6 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, aryl and heteroaryl. In a further aspect, R^6 is selected from C1-C6 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, aryl and heteroaryl.

[00195] In a further aspect, R⁶ is C1-C6 alkyl, for example, methyl, ethyl, propyl, butyl, pentyl, or hexyl. In a further aspect, R⁶ is C1-C6 haloalkyl, for example, methyl, ethyl, propyl, butyl, pentyl, or hexyl, substituted with a halogen selected from fluoro, chloro, bromo, and iodo. In a further aspect, R⁶ is C1-C6 polyhaloalkyl, for example, methyl, ethyl, propyl, butyl, pentyl, or hexyl, substituted with 2 or more (e.g., 2, 3, 4, or 5) halogens independently selected from fluoro, chloro, bromo, and iodo. Polyhaloalkyl includes trifluoromethyl, perfluoroethyl, trichloromethyl, and perchloroethyl.

[00196] In a further aspect, R⁶ is aryl selected from phenyl and naphthyl.

[00197] In a further aspect, R⁶ is heteroaryl selected from oxazolyl, isoxazolyl, pyrazolyl, furanyl, pyranal, imidazolyl, thiophenyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, tetrazinyl, benzofuranyl, benzothiophene, indolyl, indazolyl, quinolinyl, naphthyridinyl, benzothiazolyl, benzooxazolyl, benzoimidazolyl, and benzotriazolyl.

[00198] In a further aspect, R⁶ is aryl or heteroaryl, and wherein R⁶ is substituted with 0-3 groups. In a further aspect, R⁶ is aryl or heteroaryl, and wherein R⁶ is substituted with 1-2 groups. In various further aspects, the groups are independently selected from cyano, acyl, fluoro, chloro, bromo, iodo, methyl, ethyl, propyl, butyl, pentyl, hexyl, hydroxyl, acetoxyl, methoxyl, ethoxyl, propoxyl, and butoxyl.

q. R⁷ GROUPS

[00199] In one aspect, R⁷ is selected from hydrogen, C1-C6 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, aryl and heteroaryl. In a further aspect, R⁷ is selected from C1-C6 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, aryl and heteroaryl.

[00200] In a further aspect, R⁷ is C1-C6 alkyl, for example, methyl, ethyl, propyl, butyl, pentyl, or hexyl. In a further aspect, R⁷ is C1-C6 haloalkyl, for example, methyl, ethyl, propyl, butyl, pentyl, or hexyl, substituted with a halogen selected from fluoro, chloro, bromo, and iodo. In a further aspect, R⁷ is C1-C6 polyhaloalkyl, for example, methyl, ethyl, propyl, butyl, pentyl, or hexyl, substituted with 2 or more (e.g., 2, 3, 4, or 5) halogens independently selected from fluoro, chloro, bromo, and iodo. Polyhaloalkyl includes trifluoromethyl, perfluoroethyl, trichloromethyl, and perchloroethyl.

[00201] In a further aspect, R⁷ is aryl selected from phenyl and naphthyl.

[00202] In a further aspect, R^7 is heteroaryl selected from oxazolyl, isoxazolyl, pyrazolyl, furanyl, pyranyl, imidazolyl, thiophenyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, tetrazinyl, benzofuranyl, benzothiophene, indolyl, indazolyl, quinoliny, naphthyridinyl, benzothiazolyl, benzooxazolyl, benzoimidazolyl, and benzotriazolyl.

[00203] In a further aspect, R^7 is aryl or heteroaryl, and wherein R^7 is substituted with 0-3 groups. In a further aspect, R^7 is aryl or heteroaryl, and wherein R^7 is substituted with 1-2 groups. In various further aspects, the groups are independently selected from cyano, acyl, fluoro, chloro, bromo, iodo, methyl, ethyl, propyl, butyl, pentyl, hexyl, hydroxyl, acetoxyl, methoxyl, ethoxyl, propoxyl, and butoxyl.

r. R^{10} GROUPS

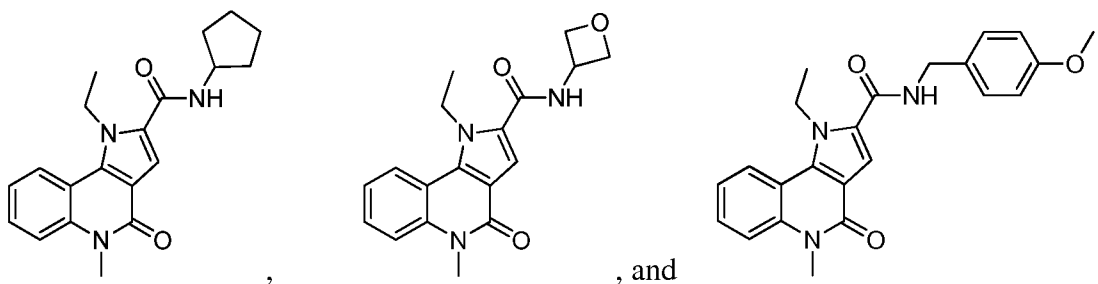
[00204] In one aspect, R^{10} is selected from an amino-protecting group and R^2 . In a further aspect, R^{10} is an amino-protecting group. In a further aspect, R^{10} is R^2 .

s. R^{11} GROUPS

[00205] In one aspect, R^{11} is hydroxyl, $-NH_2$, $-NHR^3$, or an optionally substituted group selected from C1-C10 alkoxyl, C3-C8 cycloalkoxyl, phenoxy, benzyloxy, heteroaryloxy, and C3-C8 heterocycloalkoxyl. In a further aspect, R^{11} is hydroxyl, $-NH_2$, or an optionally substituted group selected from C1-C10 alkoxyl, C3-C8 cycloalkoxyl, phenoxy, benzoyl, heteroaryloxy, and C3-C8 heterocycloalkoxyl. In a further aspect, R^{11} is $-NHR^3$.

t. EXAMPLE COMPOUNDS

[00206] In one aspect, a compound can be present as one or more of the following structures:



[00207] It is understood that the disclosed compounds can be used in connection with the disclosed methods, compositions, kits, and uses.

2. MUSCARINIC ACETYLCHOLINE RECEPTOR M₄ ACTIVITY

[00208] The human muscarinic acetylcholine receptor M₄ (mAChR M₄) is a protein of 479 amino acids encoded by the CHRM4 gene. The molecular weight of the unglycosylated protein is about 54 kDa and it is a transmembrane GPCR. As described above, the mAChR M₄ is a member of the GPCR Class 1 family, or the rhodopsin-like GPCRs, which are characterized by structural feature similar to rhodopsin such as seven transmembrane segments. The muscarinic acetylcholine receptors have the N-terminus oriented to the extracellular face of the membrane and the C-terminus located on the cytoplasmic face. A schematic of the structure of mAChR M₄ is shown in Figure 1, with the transmembrane segments shown as cylindrical shapes (which span the lipid bilayer of the cell membrane). The orthosteric binding for natural ligand, acetylcholine, for mAChRs is within a pocket located in the transmembrane segments as depicted in Figure 1.

[00209] In one aspect, the disclosed compounds potentiate the agonist response (e.g., acetylcholine) of mAChR M₄. In a further aspect, the disclosed compounds increase mAChR M₄ response to non-maximal concentrations of agonist in the presence of compound compared to the response to agonist in the absence of compound. The potentiation of mAChR M₄ activity, can be demonstrated by methodology known in the art. For example, activation of mAChR M₄ activity can be determined by measurement of calcium flux in response to agonist, e.g. acetylcholine, in cells loaded with a Ca²⁺-sensitive fluorescent dye (e.g., Fluo-4). In a further aspect, the calcium flux was measured as an increase in fluorescent static ratio. In a yet further aspect, positive allosteric modulator activity was analyzed as a concentration-dependent increase in the EC₂₀ acetylcholine response (i.e. the response of mAChR M₄ at a concentration of acetylcholine that yields 20% of the maximal response). Rat assay results were found to correlate well with human assay results.

[00210] In one aspect, the disclosed compounds activate mAChR M₄ response as an increase in calcium fluorescence in mAChR M₄-transfected CHO-K1 cells in the presence of the compound, compared to the response of equivalent CHO-K1 cells in the absence of the compound. For example, a disclosed compound can have an EC₅₀ of less than about 10 μ M, of less than about 5 μ M, of less than about 1 μ M, of less than about 500 nM, of less than about 100 nM, or of less than about 50 nM.

[00211] In one aspect, the disclosed compounds exhibit potentiation of mAChR M₄ response to acetylcholine as an increase in response to non-maximal concentrations of acetylcholine in CHO-K1 cells transfected with a mammalian mAChR M₄ in the presence of the compound, compared to the response to acetylcholine in the absence of the compound. For example, CHO-K1 cells can be transfected with human mAChR M₄. For example, CHO-K1 cells can be transfected with rat mAChR M₄. For example, a compound can exhibit positive allosteric modulation of mAChR M₄ with an EC₅₀ of less than about 10,000 nM, of less than about 5,000 nM, of less than about 1,000 nM, of less than about 500 nM, or of less than about 100 nM. Alternatively, the disclosed compounds exhibit potentiation of mAChR M₄ response to acetylcholine as an increase in response to non-maximal concentrations of acetylcholine in CHO-K1 cells transfected with human mAChR M₄ in the presence of the compound, compared to the response to acetylcholine in the absence of the compound. For example, a compound can exhibit positive allosteric modulation of mAChR M₄ with an EC₅₀ of less than about 10,000 nM, of less than about 5,000 nM, of less than about 1,000 nM, of less than about 500 nM, of less than about 100 nM, or of less than about 50 nM.

[00212] Without wishing to be bound by a particular theory, the disclosed compounds and products of the disclosed methods are believed to bind to an allosteric site distinct from the orthosteric binding site. Further, without wishing to be bound by particular theory, the disclosed compounds and products of the disclosed methods bind to an allosteric site that comprises portions of one or more extracellular loops and transmembrane segments distinct from the orthosteric binding site. For example, a disclosed compound can bind at the binding site as illustrated in Figure 1.

[00213] Previous attempts to develop agonists that are highly selective for individual mAChR subtypes have failed because of the high conservation of the orthosteric ACh binding site. To circumvent problems associated with targeting the highly conserved orthosteric ACh binding site, it is believed that developing compounds that act at allosteric sites on mAChRs that are removed from the orthosteric site and are less highly- conserved.

[00214] In various further aspects, the compound activates mAChR M₄ response in mAChR M₄-transfected CHO-K1 cells with an EC₅₀ less than the EC₅₀ for one or more of mAChR M₁, M₂, M₃ or M₅-transfected CHO-K1 cells. That is, a disclosed compound can have selectivity for the mAChR M₄ receptor vis-à-vis one or more of the mAChR M₁, M₂,

M₃ or M₅ receptors. For example, in one aspect, a disclosed compound can activate mAChR M₄ response with an EC₅₀ of 5-fold less than that for mAChR M₁, of 10-fold less than that for mAChR M₁, of 20-fold less than that for mAChR M₁, of 30-fold less than that for mAChR M₁, or of 50-fold less than that for mAChR M₁. In a further aspect, a disclosed compound can activate mAChR M₄ response with an EC₅₀ of 5-fold less than that for mAChR M₂, of 10-fold less than that for mAChR M₂, of 20-fold less than that for M₂, of 30-fold less than that for mAChR M₂, or of 50-fold less than that for mAChR M₂. In a further aspect, a disclosed compound can activate mAChR M₄ response with an EC₅₀ of 5-fold less than that for mAChR M₃, of 10-fold less than that for mAChR M₃, of 20-fold less than that for M₃, of 30-fold less than that for mAChR M₃, or of 50-fold less than that for mAChR M₃. In a further aspect, a disclosed compound can activate mAChR M₄ response with an EC₅₀ of 5-fold less than that for mAChR M₅, of 10-fold less than that for mAChR M₅, of 20-fold less than that for mAChR M₅, of 30-fold less than that for mAChR M₅, or of 50-fold less than that for mAChR M₅. In a further aspect, a disclosed compound can activate mAChR M₄ response with an EC₅₀ of 5-fold less than that for the mAChR M₁, M₂, M₃, or M₅ receptors, of 10-fold less than that for the mAChR M₁, M₂, M₃, or M₅ receptors, of 20-fold less than that for the mAChR M₁, M₂, M₃, or M₅ receptors, of 30-fold less than that for the M₁, M₂, M₃, or M₅ receptors, or of 50-fold less than that for the mAChR M₁, M₂, M₃, or M₅ receptors.

[00215] In various further aspects, the compound activates mAChR M₄ response in M₄-transfected CHO-K1 cells with an EC₅₀ of less than about 10 μM and exhibits a selectivity for the M₄ receptor vis-à-vis one or more of the mAChR M₁, M₂, M₃, or M₅ receptors. For example, in one aspect, the compound can have an EC₅₀ of less than about 10 μM, of less than about 5 μM, of less than about 1 μM, of less than about 500 nM, of less than about 100 nM, or of less than about 50 nM; and the compound can also activate mAChR M₄ response with an EC₅₀ of 5-fold less than that for mAChR M₁, of 10-fold less than that for mAChR M₁, of 20-fold less than that for mAChR M₁, of 30-fold less than that for mAChR M₁, or of 50-fold less than that for mAChR M₁. In a further aspect, the compound can have an EC₅₀ of less than about 10 μM, of less than about 5 μM, of less than about 1 μM, of less than about 500 nM, of less than about 100 nM, or of less than about 50 nM; and the compound can also activate mAChR M₄ response with an EC₅₀ of 5-fold less than that for mAChR M₂, of 10-fold less than that for mAChR M₂, of 20-fold less than that for mAChR M₂, of 30-fold less than that for mAChR M₂, or of 50-fold less than that for mAChR M₂. In a further aspect, the

compound can have an EC_{50} of less than about 10 μ M, of less than about 5 μ M, of less than about 1 μ M, of less than about 500 nM, of less than about 100 nM, or of less than about 50 nM; and the compound can also activate mAChR M_4 response with an EC_{50} of 5-fold less than that for mAChR M_3 , of 10-fold less than that for mAChR M_3 , of 20-fold less than that for mAChR M_3 , of 30-fold less than that for mAChR M_3 , or of 50-fold less than that for mAChR M_3 . In a further aspect, the compound can have an EC_{50} of less than about 10 μ M, of less than about 5 μ M, of less than about 1 μ M, of less than about 500 nM, of less than about 100 nM, or of less than about 50 nM; and the compound can also activate mAChR M_4 response with an EC_{50} of 5-fold less than that for mAChR M_5 , of 10-fold less than that for mAChR M_5 , of 20-fold less than that for mAChR M_5 , of 30-fold less than that for mAChR M_5 , or of 50-fold less than that for mAChR M_5 . In a further aspect, the compound can have an EC_{50} of less than about 10 μ M, of less than about 5 μ M, of less than about 1 μ M, of less than about 500 nM, of less than about 100 nM, or of less than about 50 nM; and the compound can also activate mAChR M_4 response with an EC_{50} of 5-fold less than that for the mAChR M_1 , M_2 , M_3 , or M_5 receptors, of 10-fold less than that for the mAChR M_1 , M_2 , M_3 , or M_5 receptors, of 20-fold less than that for the mAChR M_1 , M_2 , M_3 , or M_5 receptors, of 30-fold less than that for the mAChR M_1 , M_2 , M_3 , or M_5 receptors, or of 50-fold less than that for the mAChR M_1 , M_2 , M_3 , or M_5 receptors.

[00216] In vivo efficacy for disclosed compounds can be measured in a number of preclinical rat behavioral models where known, clinically useful antipsychotics display similar positive responses. For example, disclosed compounds are anticipated to reverse amphetamine-induced hyperlocomotion in male Sprague-Dawley rats at doses ranging from 1 to 100 mg/kg p.o.

C. METHODS OF MAKING THE COMPOUNDS

[00217] In one aspect, the invention relates to methods of making compounds useful as positive allosteric activators of the mAChR M_4 receptor, which can be useful in the treatment neurological and psychiatric disorders associated with muscarinic acetylcholine dysfunction and other diseases in which muscarinic acetylcholine receptors are involved.

[00218] The compounds of this invention can be prepared by employing reactions as shown in the disclosed schemes, in addition to other standard manipulations that are known in the literature, exemplified in the experimental sections or clear to one skilled in the art. For

clarity, examples having a fewer substituent can be shown where multiple substituents are allowed under the definitions disclosed herein. Thus, the following examples are provided so that the invention might be more fully understood, are illustrative only, and should not be construed as limiting.

[00219] In one aspect, the disclosed compounds comprise the products of the synthetic methods described herein. In a further aspect, the disclosed compounds comprise a compound produced by a synthetic method described herein. In a still further aspect, the invention comprises a pharmaceutical composition comprising a therapeutically effective amount of the product of the disclosed methods and a pharmaceutically acceptable carrier. In a still further aspect, the invention comprises a method for manufacturing a medicament comprising combining at least one compound of any of disclosed compounds or at least one product of the disclosed methods with a pharmaceutically acceptable carrier or diluent.

[00220] In a further aspect, the compound produced exhibits positive allosteric modulation of mAChR M₄ response to acetylcholine as an increase in response to non-maximal concentrations of acetylcholine in CHO-K1 cells transfected with rat mAChR M₄ in the presence of the compound, compared to the response to acetylcholine in the absence of the compound. In a further aspect, CHO-K1 cells are transfected with human mAChR M₄. In yet a further aspect, human embryonic kidney cells are transfected with mammalian mAChR M₄.

[00221] In a further aspect, the compound produced exhibits positive allosteric modulation of mAChR M₄ with an EC₅₀ of less than about 10,000 nM. In a still further aspect, the compound exhibits positive allosteric modulation of mAChR M₄ with an EC₅₀ of less than about 5,000 nM. In an even further aspect, the compound exhibits positive allosteric modulation of mAChR M₄ with an EC₅₀ of less than about 1,000 nM. In a further aspect, the compound exhibits positive allosteric modulation of mAChR M₄ with an EC₅₀ of less than about 500 nM. In a yet further aspect, the compound exhibits positive allosteric modulation of mAChR M₄ with an EC₅₀ of less than about 100 nM. In a further aspect, the compound exhibits positive allosteric modulation of mAChR M₄ with an EC₅₀ of between from about 10,000 nM to about 1 nM. In a yet further aspect, the compound exhibits positive allosteric modulation of mAChR M₄ with an EC₅₀ of between from about 1,000 nM to about 1 nM. In a still further aspect, the compound exhibits positive allosteric modulation of mAChR M₄ with an EC₅₀ of between from about 100 nM to about 1 nM. In an even further aspect, the

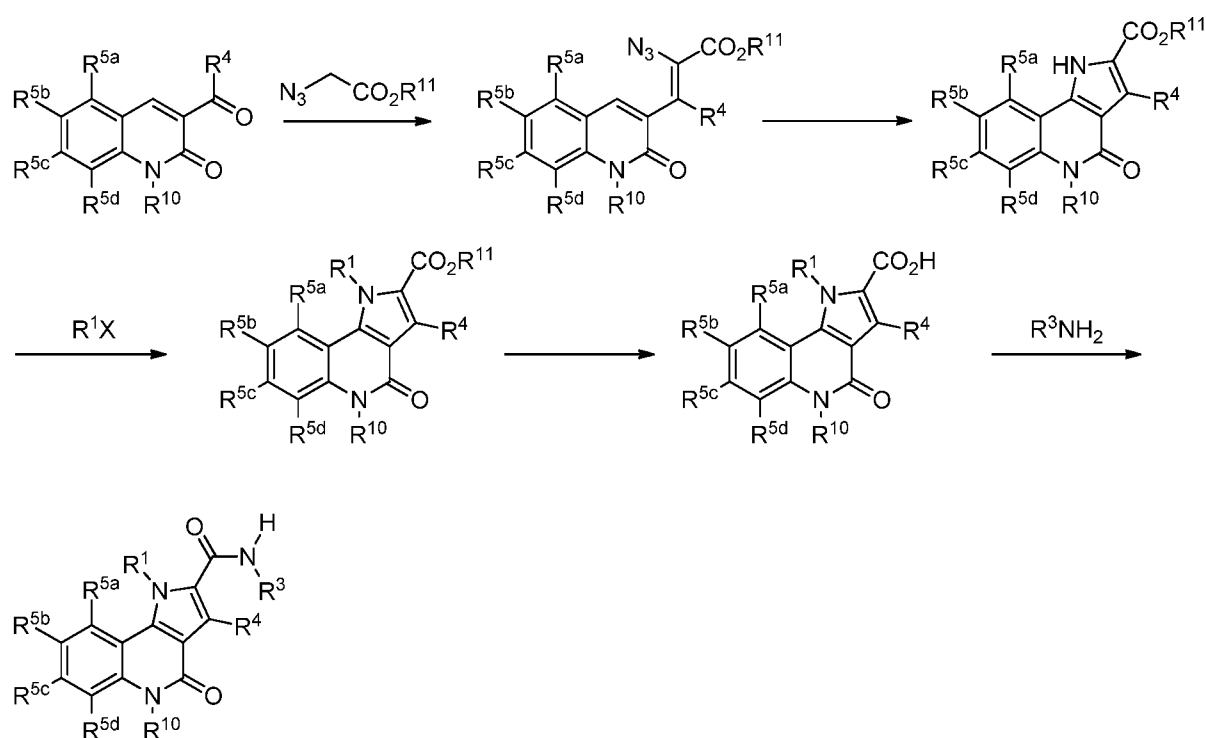
compound exhibits positive allosteric modulation of mAChR M₄ with an EC₅₀ of between from about 10 nM to about 1 nM.

[00222] In a further aspect, the compound produced is a positive allosteric modulator of human and rat mAChR M₄ and were selective for mAChR M₄ compared to the other four subtypes of muscarinic acetylcholine receptors (mAChR M₁, M₂, M₃ and M₅).

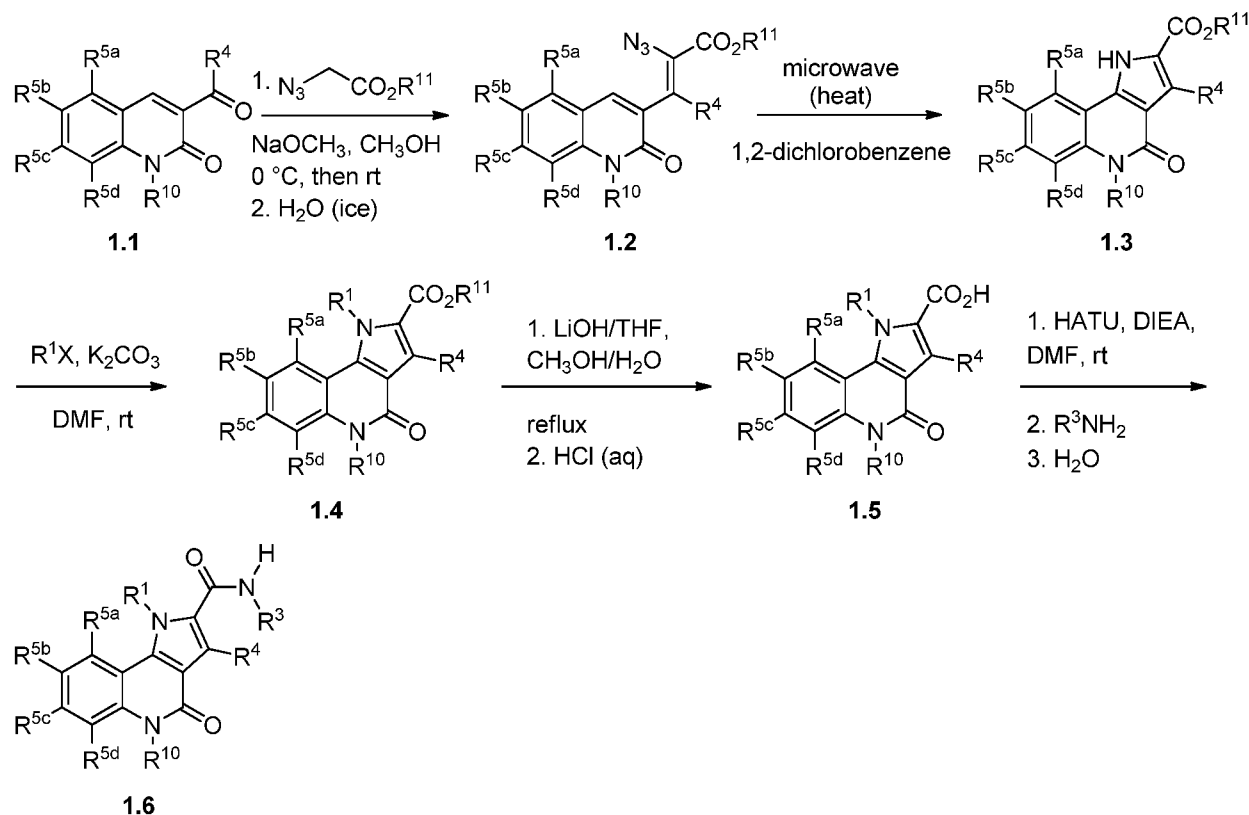
[00223] It is contemplated that each disclosed method can further comprise additional steps, manipulations, and/or components. It is also contemplated that any one or more step, manipulation, and/or component can be optionally omitted from the invention. It is understood that a disclosed method can be used to provide the disclosed compounds. It is also understood that the products of the disclosed methods can be employed in the disclosed compositions, kits, and uses.

1. ROUTE I

[00224] In one aspect, substituted 1*H*-pyrrolo[3,2-*c*]quinolin-4(5*H*)-one analogs of the present invention can be prepared generically by the synthetic scheme as shown below.



[00225] Compounds are represented in generic form, with substituents as noted in compound descriptions elsewhere herein. A more specific example is set forth below.



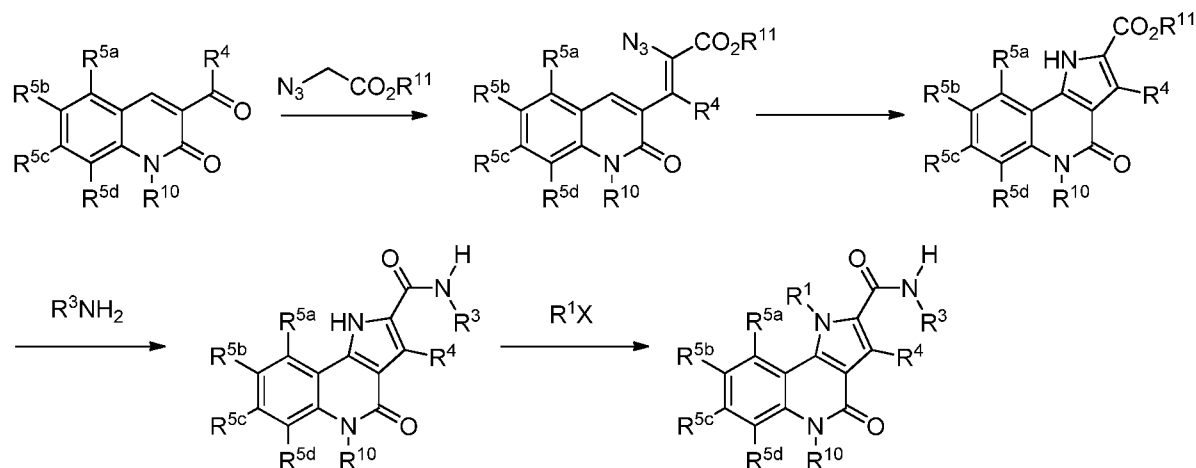
[00226] In one aspect, Route I begins with a suitable substituted 2-oxo-1,2-dihydroquinoline-3-carbaldehyde (**1.1**) and ethyl 2-azidocarboxylic acid derivative. Suitable 2-oxo-1,2-dihydroquinoline-3-carbaldehydes and ethyl 2-azidocarboxylic acid derivatives are commercially available or can be readily prepared by one skilled in the art according to methods described in the literature (Taylor, E. C. Jr.; Crovetti, A. J. *Organic Syntheses* 1956, 36). For example, one suitable ethyl 2-azidocarboxylic acid derivative is ethyl 2-azidoacetate. The reaction of the carbaldehyde and ethyl 2-azidocarboxylic acid derivative is typically carried out in a suitable solvent such as methanol. To the reaction a suitable base is added, e.g. an alkoxide such as NaOCH_3 , as the reaction is maintained at a low temperature, e.g. about 0°C . The reaction is then warmed to about room temperature and the reaction carried for a time sufficient to complete the reaction, e.g. about two hours. The product, a compound of type **1.2**, is isolated and then dissolved in an appropriate solvent, e.g. 1,2-dichlorobenzene, and heated. In some cases, the reaction is heated by microwave irradiation at suitable temperature, e.g. about 140°C , for a time sufficient to complete the reaction, e.g. about 20 minutes, to provide compounds of type **1.3** as shown above.

[00227] In one aspect, compounds of type **1.4** can be prepared by reaction of compounds of type **1.3** with a suitable aminoalkylating reagent, e.g. an alkyl halide or cycloalkyl halide. In a typical reaction, a compound of type **1.3** is dissolved or suspended in a suitable solvent, e.g. DMF, to which is added a suitable base, e.g. potassium carbonate, and a suitable alkyl halide, e.g. iodomethane or another alkyl or cycloalkyl with an iodo group. The reaction is carried out at a suitable temperature, e.g. room temperature, and for a time suitable, e.g. about 12 hours, to complete the reaction. The product, a compound of type **1.4**, is isolated by methods known to one skilled in the art (e.g. extraction, washing, drying, and concentration under a vacuum).

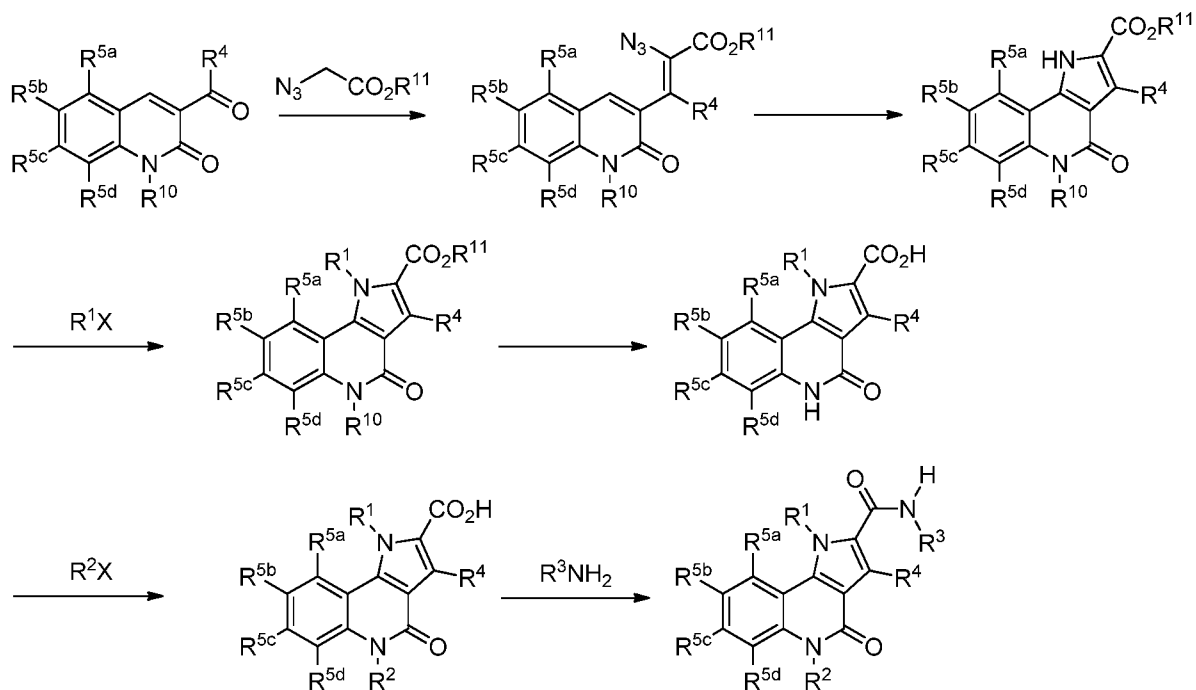
[00228] In one aspect, compounds of type **1.5** can be prepared by conversion of an ester of compound type **1.4** to the corresponding carboxylic acid. For example, a reaction of this type is commonly carried out by dissolving or suspending the ester (**1.4**) in a suitable solvent, e.g. THF/methanol (3:1 ratio), to which is added a suitable base, e.g. lithium hydroxide, and the mixture heated at reflux for a time sufficient, e.g. about one hour, to complete the reaction. The mixture is then neutralized and the product (**1.5**) isolated.

[00229] In one aspect, amidation of compounds of type **1.5** can provide compounds of type **1.6**. For example, a mixture of a suitable carboxylic acid (**1.5**), HATU, and DIEA is prepared in a suitable solvent, e.g. DMF, and the mixture stirred at a suitable temperature, e.g. room temperature, for a suitable time, e.g. about 10 minutes, before addition of the a suitable amine. The amine is allowed to react at a suitable temperature, e.g. room temperature, for a time sufficient to complete the reaction, e.g. about 15 minutes. The product (**1.6**) is isolated by methods known to one skilled in the art.

[00230] In a further aspect, the order of steps can be appropriately modified by one skilled in the art. For example, using methods similar to those described above, substituted 1*H*-pyrrolo[3,2-*c*]quinolin-4(5*H*)-one analogs can be of the present invention can be prepared generically by the synthetic scheme as shown below.

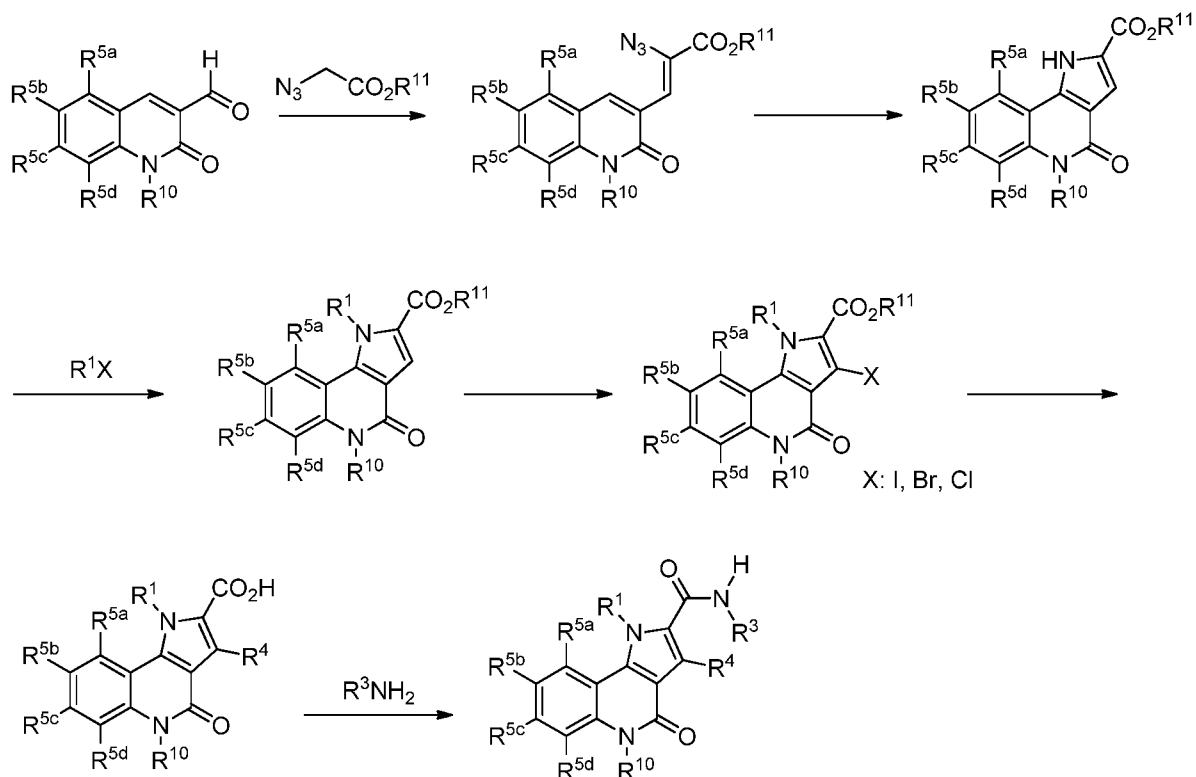


[00231] In one aspect, in the foregoing synthetic schemes, R^{10} is not an amino protecting group and is equivalent to R^2 . Alternatively, in some cases, the synthesis of the desired substituted 1*H*-pyrrolo[3,2-*c*]quinolin-4(5*H*)-one analogs will be carried out wherein R^{10} is a suitable amino protecting group, e.g. Boc or Fmoc, which is removed in the course of synthesis, e.g. acid hydrolysis (under conditions appropriate for the protecting group and other synthetic considerations). After removal, the amine is alkylated under suitable reaction conditions, e.g. reaction with a suitable alkyl halide or cycloalkyl halide, under suitable reaction conditions, e.g. as described above. The synthetic scheme described above can be modified to allow inclusion of the deprotection step and alkylation of the resulting amine. For example, when R^{10} is an amine protecting group, substituted 1*H*-pyrrolo[3,2-*c*]quinolin-4(5*H*)-one analogs of the present invention can be prepared generically by the synthetic scheme as shown below.

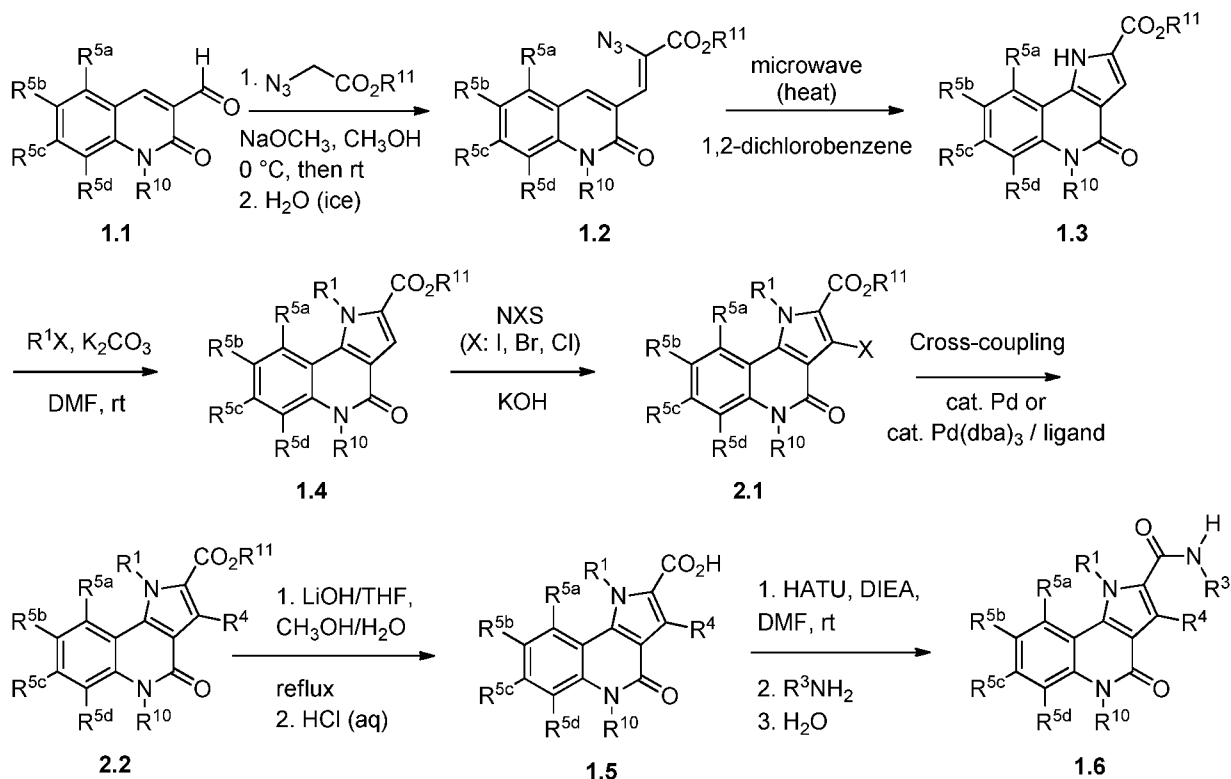


2. ROUTE II

[00232] In one aspect, substituted 1H-pyrrolo[3,2-c]quinolin-4(5H)-one analogs of the present invention can be prepared generically by the synthetic scheme as shown below.

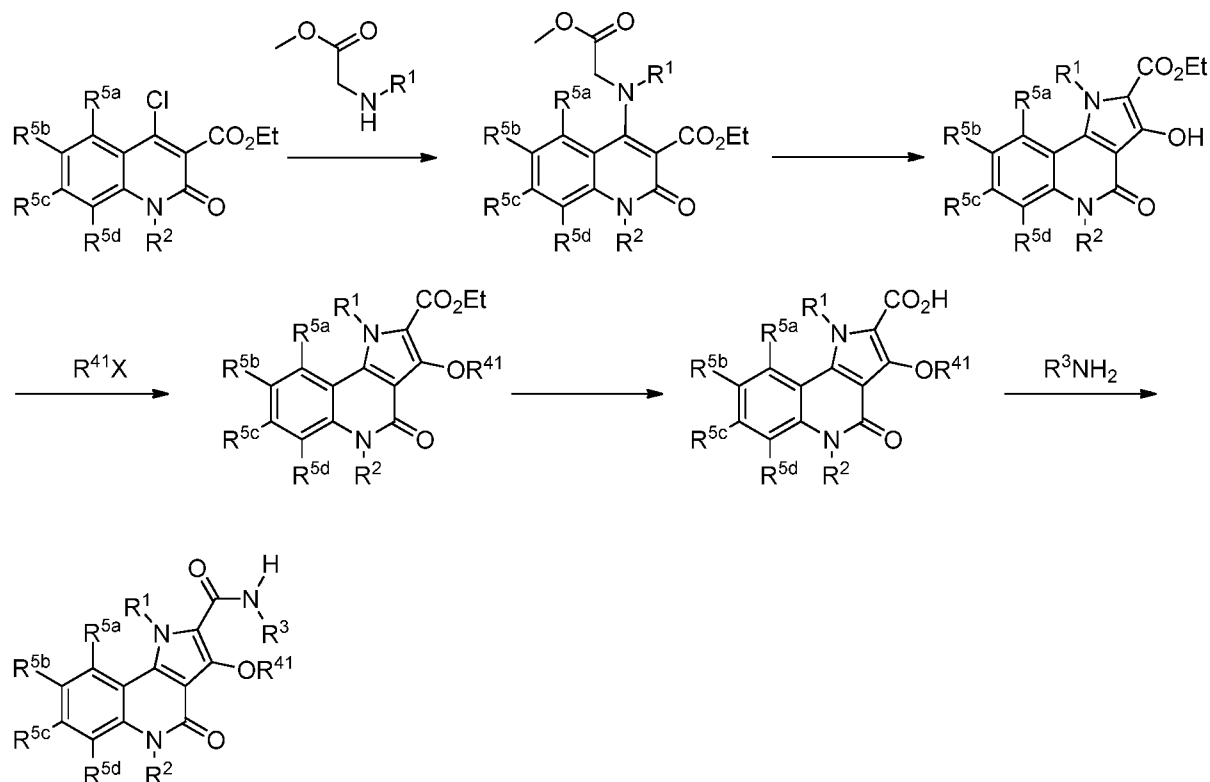


[00233] Compounds are represented in generic form, with substituents as noted in compound descriptions elsewhere herein. A more specific example is set forth below.

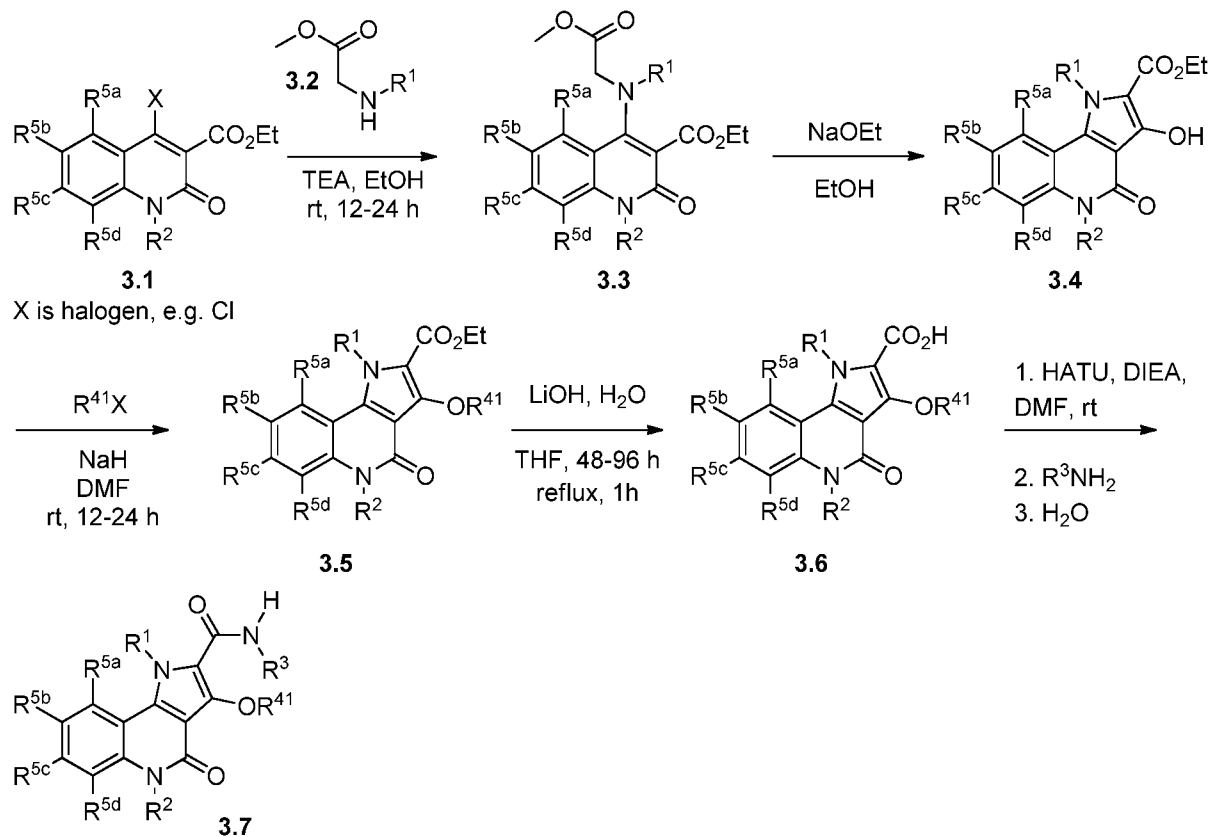


[00234] In one aspect, compounds of type **1.6** can be prepared with the R^4 substituent introduced as shown the generic and specific examples above. The steps distinct from those in Route I are halogenation of the pyrrole ring using a N-halosuccinimide (e.g. N-bromosuccinimide) with the reaction carried out in a suitable inert solvent at a suitable temperature in the presence of base, e.g. potassium hydroxide. The person skilled in the art can choose from a diverse spectrum of cross-coupling chemistry to utilize to introduce appropriate R^4 groups to the pyrrole ring. Cross-coupling can be typically accomplished with cat. Pd or cat Pd(dba)₃ with a suitable ligand, although in some cases the use of copper catalysts (Cu(0) or Cu(I)) can be used as needed. The rest of the synthetic scheme can proceed using methods similar to those described above or as modified as determined by one skilled in the art.

[00235] In a further aspect, compounds of type **1.6** wherein R^4 is an alkoxy group can be prepared by the synthetic scheme shown below.

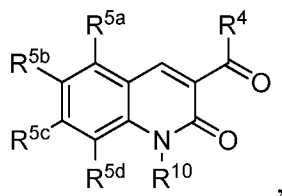


[00236] Compounds are represented in generic form, with substituents as noted in compound descriptions elsewhere herein. More specific examples are set forth below.



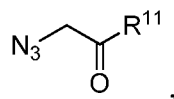
[00237] In one aspect, the preparation of the alkoxy derivatives shown above begins with a suitable substituted 4-halo-2-oxo-1,2-dihydroquinoline-3-carboxylate (**3.1**) and a suitable methyl 2-(alkylamino)acetate derivative (**3.2**). Suitable substituted 4-halo-2-oxo-1,2-dihydroquinoline-3-carboxylates and methyl 2-(alkylamino)acetate derivatives are commercially available or can be readily prepared by one skilled in the art according to methods described in the literature (Taylor, E. C. Jr.; Crovetti, A. J. *Organic Syntheses* 1956, 36). For example, suitable methyl 2-(alkylamino)acetate derivatives are methyl 2-(methylamino)acetate and methyl 2-(ethylamino)acetate. The reaction of the carboxylate and methyl 2-(alkylamino)acetate derivative is typically carried out in a suitable solvent such as ethanol. To the reaction a suitable base is added, e.g. triethylamine, as the reaction is maintained at ambient temperature, e.g. about 20-30 °C. The product, a compound of type **3.3**, is isolated and then dissolved in an appropriate solvent, e.g. ethanol, and treated with a suitable base, e.g. sodium ethoxide. In some cases, the reaction is heated, e.g. about 40-60 °C, for a time sufficient to complete the reaction, e.g. about 12-24 h, to provide compounds of type **3.4** as shown above. Following isolation, a compound of type **3.4** is dissolved in a suitable solvent, e.g. DMF, along with a suitable base, e.g. sodium hydride or DBU, and a suitable haloalkyl, e.g. iodomethane. The reaction is reacted at ambient temperature for a suitable period of time, e.g. 12-24 h, to provide a compound of type **3.5**. Subsequent steps leading to compounds of type **3.7** are similar to those described above in Route I.

[00238] In one aspect, the invention relates to a synthetic method comprising the steps of:
(a) providing a compound having a structure represented by a formula:



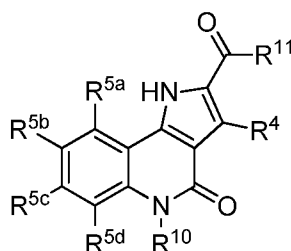
wherein R^4 is selected from hydrogen, halogen, hydroxyl, cyano, amino, C1-C8 alkyl, C1-C6 alkoxy, C1-C6 alkylamino, C1-C6 dialkylamino, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, Cy^4 , and Ar^2 ; wherein Ar^2 is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar^2 is heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy^4 is C3-C8 cycloalkyl substituted with 0-3 substituents selected

from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy⁴ is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein each of R^{5a}, R^{5b}, R^{5c}, and R^{5d} is independently selected from hydrogen, halogen, hydroxyl, cyano, amino, -CONR⁶R⁷, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 alkylamino, C1-C6 dialkylamino, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, Cy⁵, and Ar³, wherein Ar³ is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar³ is heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy⁵ is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy⁵ is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein each of R⁶ and R⁷ is independently selected from hydrogen, C1-C6 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, aryl and heteroaryl; wherein R¹⁰ is selected from an amino-protecting group and R², which is selected from hydrogen, C1-C8 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, and Cy²; and wherein Cy² is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy² is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; (b) reacting with a compound having a structure represented by a formula:



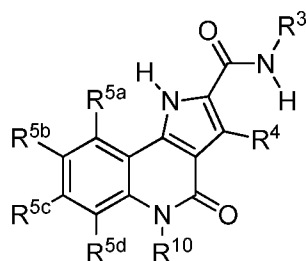
wherein R¹¹ is hydroxyl, -NH₂, -NHR³, or an optionally substituted group selected from C1-C10 alkoxy, C3-C8 cycloalkoxy, phenoxy, benzyloxy, heteroaryloxy, and C3-C8 heterocycloalkoxy; wherein R³ is selected from C1-C8 alkyl, Cy³, and Ar¹; wherein Ar¹ is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6

alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar¹ is monocyclic heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; and wherein Cy³ is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy³ is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; and (c) cyclizing to form a product having a structure represented by a formula:

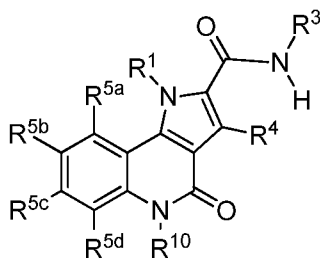


[00239] In a further aspect, R¹⁰ is an amino-protecting group, the method further comprising converting R¹⁰ to R².

[00240] In a further aspect, R¹¹ is hydroxyl, -NH₂, or an optionally substituted group selected from C1-C10 alkoxy, C3-C8 cycloalkoxy, phenoxy, benzoyl, heteroaryoxy, and C3-C8 heterocycloalkoxy; the method further comprising converting R¹¹ to -NHR³ to yield a product having a structure represented by a formula:

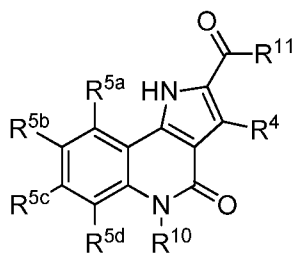


In a still further aspect, the method further comprises alkylating the product produced above with R¹X, wherein X is a leaving group, to yield:

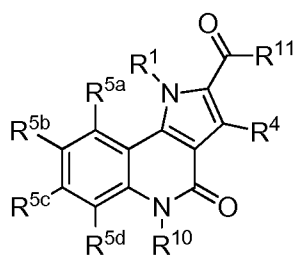


wherein R¹ is selected from C1-C8 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, and Cy¹; wherein Cy¹ is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy¹ is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino. In a yet further aspect, R¹ is selected from C2-C8 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, and Cy¹.

[00241] In a further aspect, the method comprises the step of alkylating the product,

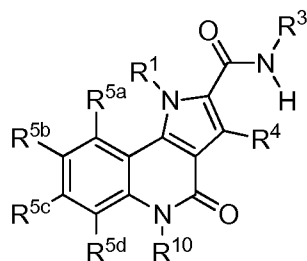


with R¹X, wherein X is a leaving group, to yield:



wherein R¹ is selected from C1-C8 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, and Cy¹; wherein Cy¹ is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy¹ is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6

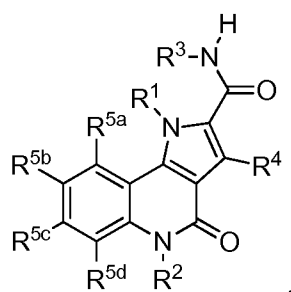
dialkylamino. In a still further aspect, R^1 is selected from C2-C8 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, and Cy^1 . In a yet further aspect, R^{11} is hydroxyl, $-NH_2$, or an optionally substituted group selected from C1-C10 alkoxy, C3-C8 cycloalkoxy, phenoxy, benzoyl, heteroaryoxy, and C3-C8 heterocycloalkoxy; the method further comprising converting R^{11} to $-NHR^3$ to yield a product having a structure represented by a formula:



D. PHARMACEUTICAL COMPOSITIONS

[00242] In one aspect, the invention relates to pharmaceutical compositions comprising the disclosed compounds. That is, a pharmaceutical composition can be provided comprising a therapeutically effective amount of at least one disclosed compound, at least one product of a disclosed method, or a pharmaceutically acceptable salt, solvate, hydrate, or polymorph thereof, and a pharmaceutically acceptable carrier.

[00243] In one aspect, the invention relates to pharmaceutical compositions comprising a pharmaceutically acceptable carrier and an effective amount of a compound represented by a formula:



wherein R^1 is selected from hydrogen, C1-C8 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, and Cy^1 ; wherein Cy^1 is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy^1 is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6

dialkylamino; wherein R^2 is selected from hydrogen, C1-C8 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, and Cy^2 ; wherein Cy^2 is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy^2 is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein R^3 is selected from C1-C8 alkyl, Cy^3 , and Ar^1 ; wherein Ar^1 is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar^1 is monocyclic heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy^3 is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy^3 is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein R^4 is selected from hydrogen, halogen, hydroxyl, cyano, amino, C1-C8 alkyl, C1-C6 alkoxy, C1-C6 alkylamino, C1-C6 dialkylamino, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, Cy^4 , and Ar^2 ; wherein Ar^2 is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar^2 is heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy^4 is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy^4 is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein each of R^{5a} , R^{5b} , R^{5c} , and R^{5d} is independently selected from hydrogen, halogen, hydroxyl, cyano, amino, $CONR^6R^7$, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 alkylamino, C1-C6 dialkylamino, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, Cy^5 , and Ar^3 , wherein Ar^3 is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar^3 is heteroaryl substituted

with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy⁵ is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy⁵ is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein each of R⁶ and R⁷ is independently selected from hydrogen, C1-C6 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, aryl and heteroaryl; or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof.

[00244] In a further aspect, the effective amount is a therapeutically effective amount. In a still further aspect, the effective amount is a prophylactically effective amount.

[00245] In a further aspect, the pharmaceutical composition comprises a disclosed compound. In a yet further aspect, the pharmaceutical composition comprises a product of a disclosed method of making.

[00246] In a further aspect, the pharmaceutical composition exhibits positive allosteric modulation of mAChR M₄ with an EC₅₀ of less than about 10,000 nM. In a still further aspect, the pharmaceutical composition exhibits positive allosteric modulation of mAChR M₄ with an EC₅₀ of less than about 5,000 nM. In an even further aspect the pharmaceutical composition exhibits positive allosteric modulation of mAChR M₄ with an EC₅₀ of less than about 1,000 nM. In a further aspect, the pharmaceutical composition exhibits positive allosteric modulation of mAChR M₄ with an EC₅₀ of less than about 500 nM. In a yet further aspect, the pharmaceutical composition exhibits positive allosteric modulation of mAChR M₄ with an EC₅₀ of less than about 100 nM. In a further aspect, the pharmaceutical composition exhibits positive allosteric modulation of mAChR M₄ with an EC₅₀ of between from about 10,000 nM to about 1 nM. In a yet further aspect, the pharmaceutical composition exhibits positive allosteric modulation of mAChR M₄ with an EC₅₀ of between from about 1,000 nM to about 1 nM. In a still further aspect, the pharmaceutical composition exhibits positive allosteric modulation of mAChR M₄ with an EC₅₀ of between from about 100 nM to about 1 nM. In an even further aspect, the pharmaceutical composition exhibits positive allosteric modulation of mAChR M₄ with an EC₅₀ of between from about 10 nM to about 1 nM.

[00247] In one aspect, the pharmaceutical composition is used to treat a mammal. In a yet further aspect, the mammal is a human. In a further aspect, the mammal has been diagnosed with a need for treatment of the disorder prior to the administering step. In a further aspect, the mammal has been identified to be in need of treatment of the disorder. In a further aspect, the pharmaceutical composition is used to treat a neurological and/or psychiatric disorder. In a yet further aspect, the disorder is associated with muscarinic acetylcholine receptor dysfunction. In a still further aspect, the disorder is associated with mAChR M₄ dysfunction.

[00248] In a further aspect, the pharmaceutical composition is used to treat a psychotic disorder. In a still further aspect, the psychotic disorder is selected from schizophrenia, psychotic disorder NOS, brief psychotic disorder, schizophreniform disorder, schizoaffective disorder, delusional disorder, shared psychotic disorder, catastrophic schizophrenia, postpartum psychosis, psychotic depression, psychotic break, tardive psychosis, myxedematous psychosis, occupational psychosis, menstrual psychosis, secondary psychotic disorder, bipolar I disorder with psychotic features, and substance-induced psychotic disorder. In a yet further aspect, the psychotic disorder is a psychosis associated with an illness selected from major depressive disorder, affective disorder, bipolar disorder, electrolyte disorder, neurological disorder, hypoglycemia, AIDS, lupus, and post-traumatic stress disorder. In a yet further aspect, the neurological disorder is selected from brain tumor, dementia with Lewy bodies, multiple sclerosis, sarcoidosis, Lyme disease, syphilis, Alzheimer's disease, Parkinson's disease, and anti-NMDA receptor encephalitis.

[00249] In a further aspect, the psychotic disorder is selected from schizophrenia, brief psychotic disorder, schizophreniform disorder, schizoaffective disorder, delusional disorder, and shared psychotic disorder. In a still further aspect, the schizophrenia is selected from catastrophic schizophrenia, catatonic schizophrenia, paranoid schizophrenia, residual schizophrenia, disorganized schizophrenia, and undifferentiated schizophrenia. In a yet further aspect, the disorder is selected from schizoid personality disorder, schizotypal personality disorder, and paranoid personality disorder.

[00250] In a further aspect, the pharmaceutical composition is used to treat a cognitive disorder. In a still further aspect, the cognitive disorder is selected from amnesia, dementia, delirium, amnestic disorder, substance-induced persisting delirium, dementia due to HIV disease, dementia due to Huntington's disease, dementia due to Parkinson's disease,

Parkinsonian-ALS demential complex, dementia of the Alzheimer's type, age-related cognitive decline, and mild cognitive impairment.

[00251] In a further aspect, the pharmaceutical composition is used to treat a disorder selected from conduct disorder, disruptive behavior disorder, psychotic episodes of anxiety, anxiety associated with psychosis, psychotic mood disorders such as severe major depressive disorder; mood disorders associated with psychotic disorders, acute mania, depression associated with bipolar disorder, mood disorders associated with schizophrenia, behavioral manifestations of mental retardation, conduct disorder, autistic disorder; movement disorders, Tourette's syndrome, akinetic-rigid syndrome, movement disorders associated with Parkinson's disease, tardive dyskinesia, drug induced and neurodegeneration based dyskinesias, attention deficit hyperactivity disorder, cognitive disorders, dementias, and memory disorders.

[00252] In certain aspects, the disclosed pharmaceutical compositions comprise the disclosed compounds (including pharmaceutically acceptable salt(s) thereof) as an active ingredient, a pharmaceutically acceptable carrier, and, optionally, other therapeutic ingredients or adjuvants. The instant compositions include those suitable for oral, rectal, topical, and parenteral (including subcutaneous, intramuscular, and intravenous) administration, although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active ingredient is being administered. The pharmaceutical compositions can be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of pharmacy.

[00253] As used herein, the term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids. When the compound of the present invention is acidic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic bases, including inorganic bases and organic bases. Salts derived from such inorganic bases include aluminum, ammonium, calcium, copper (-ic and -ous), ferric, ferrous, lithium, magnesium, manganese (-ic and -ous), potassium, sodium, zinc and the like salts. Particularly preferred are the ammonium, calcium, magnesium, potassium and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, as well as cyclic amines and substituted amines such as naturally occurring and synthesized substituted amines. Other

pharmaceutically acceptable organic non-toxic bases from which salts can be formed include ion exchange resins such as, for example, arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like.

[00254] As used herein, the term “pharmaceutically acceptable non-toxic acids”, includes inorganic acids, organic acids, and salts prepared therefrom, for example, acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid and the like. Preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, and tartaric acids.

[00255] In practice, the compounds of the invention, or pharmaceutically acceptable salts thereof, of this invention can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier can take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral (including intravenous). Thus, the pharmaceutical compositions of the present invention can be presented as discrete units suitable for oral administration such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient. Further, the compositions can be presented as a powder, as granules, as a solution, as a suspension in an aqueous liquid, as a non-aqueous liquid, as an oil-in-water emulsion or as a water-in-oil liquid emulsion. In addition to the common dosage forms set out above, the compounds of the invention, and/or pharmaceutically acceptable salt(s) thereof, can also be administered by controlled release means and/or delivery devices. The compositions can be prepared by any of the methods of pharmacy. In general, such methods include a step of bringing into association the active ingredient with the carrier that constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both. The product can then be conveniently shaped into the desired presentation.

[00256] Thus, the pharmaceutical compositions of this invention can include a pharmaceutically acceptable carrier and a compound or a pharmaceutically acceptable salt of the compounds of the invention. The compounds of the invention, or pharmaceutically acceptable salts thereof, can also be included in pharmaceutical compositions in combination with one or more other therapeutically active compounds.

[00257] The pharmaceutical carrier employed can be, for example, a solid, liquid, or gas. Examples of solid carriers include lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid. Examples of liquid carriers are sugar syrup, peanut oil, olive oil, and water. Examples of gaseous carriers include carbon dioxide and nitrogen.

[00258] In preparing the compositions for oral dosage form, any convenient pharmaceutical media can be employed. For example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like can be used to form oral liquid preparations such as suspensions, elixirs and solutions; while carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like can be used to form oral solid preparations such as powders, capsules and tablets. Because of their ease of administration, tablets and capsules are the preferred oral dosage units whereby solid pharmaceutical carriers are employed. Optionally, tablets can be coated by standard aqueous or nonaqueous techniques

[00259] A tablet containing the composition of this invention can be prepared by compression or molding, optionally with one or more accessory ingredients or adjuvants. Compressed tablets can be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets can be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent.

[00260] The pharmaceutical compositions of the present invention comprise a compound of the invention (or pharmaceutically acceptable salts thereof) as an active ingredient, a pharmaceutically acceptable carrier, and optionally one or more additional therapeutic agents or adjuvants. The instant compositions include compositions suitable for oral, rectal, topical, and parenteral (including subcutaneous, intramuscular, and intravenous) administration,

although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active ingredient is being administered. The pharmaceutical compositions can be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of pharmacy.

[00261] Pharmaceutical compositions of the present invention suitable for parenteral administration can be prepared as solutions or suspensions of the active compounds in water. A suitable surfactant can be included such as, for example, hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof in oils. Further, a preservative can be included to prevent the detrimental growth of microorganisms.

[00262] Pharmaceutical compositions of the present invention suitable for injectable use include sterile aqueous solutions or dispersions. Furthermore, the compositions can be in the form of sterile powders for the extemporaneous preparation of such sterile injectable solutions or dispersions. In all cases, the final injectable form must be sterile and must be effectively fluid for easy syringability. The pharmaceutical compositions must be stable under the conditions of manufacture and storage; thus, preferably should be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (*e.g.*, glycerol, propylene glycol and liquid polyethylene glycol), vegetable oils, and suitable mixtures thereof.

[00263] Pharmaceutical compositions of the present invention can be in a form suitable for topical use such as, for example, an aerosol, cream, ointment, lotion, dusting powder, mouth washes, gargles, and the like. Further, the compositions can be in a form suitable for use in transdermal devices. These formulations can be prepared, utilizing a compound of the invention, or pharmaceutically acceptable salts thereof, via conventional processing methods. As an example, a cream or ointment is prepared by mixing hydrophilic material and water, together with about 5 wt% to about 10 wt% of the compound, to produce a cream or ointment having a desired consistency.

[00264] Pharmaceutical compositions of this invention can be in a form suitable for rectal administration wherein the carrier is a solid. It is preferable that the mixture forms unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in

the art. The suppositories can be conveniently formed by first admixing the composition with the softened or melted carrier(s) followed by chilling and shaping in moulds.

[00265] In addition to the aforementioned carrier ingredients, the pharmaceutical formulations described above can include, as appropriate, one or more additional carrier ingredients such as diluents, buffers, flavoring agents, binders, surface-active agents, thickeners, lubricants, preservatives (including anti-oxidants) and the like. Furthermore, other adjuvants can be included to render the formulation isotonic with the blood of the intended recipient. Compositions containing a compound of the invention, and/or pharmaceutically acceptable salts thereof, can also be prepared in powder or liquid concentrate form.

[00266] In the treatment conditions which require positive allosteric modulation of mAChR M₄ receptor activity an appropriate dosage level will generally be about 0.01 to 500 mg per kg patient body weight per day and can be administered in single or multiple doses. Preferably, the dosage level will be about 0.1 to about 250 mg/kg per day; more preferably 0.5 to 100 mg/kg per day. A suitable dosage level can be about 0.01 to 250 mg/kg per day, about 0.05 to 100 mg/kg per day, or about 0.1 to 50 mg/kg per day. Within this range the dosage can be 0.05 to 0.5, 0.5 to 5.0 or 5.0 to 50 mg/kg per day. For oral administration, the compositions are preferably provided in the form of tablets containing 1.0 to 1000 milligrams of the active ingredient, particularly 1.0, 5.0, 10, 15, 20, 25, 50, 75, 100, 150, 200, 250, 300, 400, 500, 600, 750, 800, 900 and 1000 milligrams of the active ingredient for the symptomatic adjustment of the dosage of the patient to be treated. The compound can be administered on a regimen of 1 to 4 times per day, preferably once or twice per day. This dosing regimen can be adjusted to provide the optimal therapeutic response.

[00267] It is understood, however, that the specific dose level for any particular patient will depend upon a variety of factors. Such factors include the age, body weight, general health, sex, and diet of the patient. Other factors include the time and route of administration, rate of excretion, drug combination, and the type and severity of the particular disease undergoing therapy.

[00268] The present invention is further directed to a method for the manufacture of a medicament for modulating muscarinic acetylcholine receptor activity (*e.g.*, treatment of one or more neurological and/or psychiatric disorder associated with muscarinic acetylcholine

receptor dysfunction such as mAChR M₄ dysfunction) in mammals (*e.g.*, humans) comprising combining one or more disclosed compounds, products, or compositions with a pharmaceutically acceptable carrier or diluent. Thus, in one aspect, the invention relates to a method for manufacturing a medicament comprising combining at least one disclosed compound or at least one disclosed product with a pharmaceutically acceptable carrier or diluent.

[00269] The disclosed pharmaceutical compositions can further comprise other therapeutically active compounds, which are usually applied in the treatment of the above mentioned pathological conditions.

[00270] It is understood that the disclosed compositions can be prepared from the disclosed compounds. It is also understood that the disclosed compositions can be employed in the disclosed methods of using.

E. METHODS OF USING THE COMPOUNDS AND COMPOSITIONS

[00271] Also provided is a method of use of a disclosed compound, composition, or medicament. In one aspect, the method of use is directed to the treatment of a disorder. In a further aspect, the disclosed compounds can be used as single agents or in combination with one or more other drugs in the treatment, prevention, control, amelioration or reduction of risk of the aforementioned diseases, disorders and conditions for which the compound or the other drugs have utility, where the combination of drugs together are safer or more effective than either drug alone. The other drug(s) can be administered by a route and in an amount commonly used therefore, contemporaneously or sequentially with a disclosed compound. When a disclosed compound is used contemporaneously with one or more other drugs, a pharmaceutical composition in unit dosage form containing such drugs and the disclosed compound is preferred. However, the combination therapy can also be administered on overlapping schedules. It is also envisioned that the combination of one or more active ingredients and a disclosed compound can be more efficacious than either as a single agent.

[00272] In one aspect, the compounds can be coadministered with anti-Alzheimer's agents, beta-secretase inhibitors, gamma-secretase inhibitors, orthosteric muscarinic agonists, muscarinic potentiators, cholinesterase inhibitors, HMG-CoA reductase inhibitors, NSAIDs and anti-amyloid antibodies. In a further aspect, the compounds can be administered in combination with sedatives, hypnotics, anxiolytics, antipsychotics (typical and atypical),

selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), 5-HT₂ antagonists, GlyT1 inhibitors and the like such as, but not limited to: risperidone, clozapine, haloperidol, fluoxetine, prazepam, xanomeline, lithium, phenobarbital, and salts thereof and combinations thereof.

[00273] The pharmaceutical compositions and methods of the present invention can further comprise other therapeutically active compounds as noted herein which are usually applied in the treatment of the above mentioned pathological conditions.

1. TREATMENT METHODS

[00274] The compounds disclosed herein are useful for treating, preventing, ameliorating, controlling or reducing the risk of a variety of disorders associated with selective mAChR M₄ receptor activation. For example, a treatment can include selective mAChR M₄ receptor activation to an extent effective to affect cholinergic activity. Thus, a disorder can be associated with cholinergic activity, for example cholinergic hypofunction. Thus, provided is a method of treating or preventing a disorder in a subject comprising the step of administering to the subject at least one disclosed compound; at least one disclosed pharmaceutical composition; and/or at least one disclosed product in a dosage and amount effective to treat the disorder in the subject.

[00275] Also provided is a method for the treatment of one or more disorders associated with mAChR M₄ receptor activity in a subject comprising the step of administering to the subject at least one disclosed compound; at least one disclosed pharmaceutical composition; and/or at least one disclosed product in a dosage and amount effective to treat the disorder in the subject.

[00276] Also provided is a method for the treatment of a disorder in a mammal comprising the step of administering to the mammal at least one disclosed compound, composition, or medicament.

[00277] In one aspect, the disclosed compounds have utility in treating a variety of neurological and psychiatric disorders associated with the mAChR M₄ receptor, including one or more of the following conditions or diseases: schizophrenia (paranoid, disorganized, catatonic or undifferentiated), psychotic disorder NOS, brief psychotic disorder, schizophreniform disorder, schizoaffective disorder, delusional disorder, shared psychotic disorder, catastrophic schizophrenia, postpartum psychosis, psychotic depression, psychotic

break, tardive psychosis, myxedematous psychosis, occupational psychosis, menstrual psychosis, secondary psychotic disorder, bipolar I disorder with psychotic features, and substance-induced psychotic disorder. In a yet further aspect, the psychotic disorder is a psychosis associated with an illness selected from major depressive disorder, affective disorder, bipolar disorder, electrolyte disorder, Alzheimer's disease, neurological disorder, hypoglycemia, AIDS, lupus, and post-traumatic stress disorder. In a yet further aspect, the neurological disorder is selected from brain tumor, dementia with Lewy bodies, multiple sclerosis, sarcoidosis, Lyme disease, syphilis, Alzheimer's disease, Parkinson's disease, and anti-NMDA receptor encephalitis. In an even further aspect, the psychotic disorder is due to a general medical condition and substance-induced or drug-induced (phencyclidine, ketamine and other dissociative anaesthetics, amphetamine and other psychostimulants and cocaine),

[00278] In one aspect, the present invention provides a method for treating cognitive disorders, comprising: administering to a patient in need thereof an effective amount of a compound of the present invention. In a further aspect, cognitive disorders include dementia (associated with Alzheimer's disease, ischemia, multi-infarct dementia, trauma, vascular problems or stroke, HIV disease, Parkinson's disease, Huntington's disease, Pick's disease, Creutzfeldt- Jacob disease, perinatal hypoxia, other general medical conditions or substance abuse); delirium, amnestic disorders or age-related cognitive decline. At present, the text revision of the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) (2000, American Psychiatric Association, Washington DC) provides a diagnostic tool that includes cognitive disorders including dementia, delirium, amnestic disorders and age-related cognitive decline. As used herein, the term "cognitive disorders" includes treatment of those mental disorders as described in DSM-IV-TR. The skilled artisan will recognize that there are alternative nomenclatures, nosologies and classification systems for mental disorders, and that these systems evolve with medical and scientific progress. Thus the term "cognitive disorders" is intended to include like disorders that are described in other diagnostic sources.

[00279] In a further specific aspect, the present invention provides a method for treating schizophrenia or psychosis comprising: administering to a patient in need thereof an effective amount of a compound of the present invention. Particular schizophrenia or psychosis pathologies are paranoid, disorganized, catatonic or undifferentiated schizophrenia and substance-induced psychotic disorder. At present, the text revision of the fourth edition of the

Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) (2000, American Psychiatric Association, Washington DC) provides a diagnostic tool that includes paranoid, disorganized, catatonic or undifferentiated schizophrenia and substance-induced psychotic disorder. As used herein, the term “schizophrenia or psychosis” includes treatment of those mental disorders as described in DSM-W-TR. The skilled artisan will recognize that there are alternative nomenclatures, nosologies and classification systems for mental disorders, and that these systems evolve with medical and scientific progress. Thus the term “schizophrenia or psychosis” is intended to include like disorders that are described in other diagnostic sources.

[00280] In a still further aspect, the present invention provides a method for treating pain, comprising administering to a patient in need thereof an effective amount of a compound of the present invention. Particular pain embodiments are bone and joint pain (osteoarthritis), repetitive motion pain, dental pain, cancer pain, myofascial pain (muscular injury, fibromyalgia), perioperative pain (general surgery, gynecological), chronic pain and neuropathic pain.

[00281] The compounds are further useful in a method for the prevention, treatment, control, amelioration, or reduction of risk of the diseases, disorders and conditions noted herein. The compounds are further useful in a method for the prevention, treatment, control, amelioration, or reduction of risk of the aforementioned diseases, disorders and conditions in combination with other agents.

[00282] In various aspects, the present invention provides a method for treating Huntington's disease comprising administering to a patient in need thereof an effective amount of a compound of the present invention. Huntington's disease (HD) is a neurodegenerative disorder associated with a wide range of progressively worsening symptoms including chorea, motor dysfunction, seizures, impaired cognitive function, memory deficits, dementia, depression, anxiety and a range of other psychiatric disorders. Without wishing to be bound by a particular theory, it is believed that these conditions result from a genetic condition wherein the CAG-repeat region of the huntingtin gene (HTT) contains an abnormally large number of CAG repeats, which then gives rise to a mutated form of the huntingtin protein (mHtt). The mutated huntingtin protein can be toxic to a variety of cells, including, but not limited to, neuronal cells in the brain. It has been reported

that the mAChR M₄ receptor is selectively co-localized with dopamine receptors on medial striatal spiny projection neurons and in the dorsal and ventral striatum (Jeon, J., et al., J. Neurosci., 2010, 30(6), 2396-2405). Without wishing to be bound by a particular theory, based on the role of dopamine and its function in various regions of the brain related to movement and psychiatric conditions, the disclosed compounds of the present invention can be beneficial in patients with Huntington's disease.

[00283] In one aspect, the disclosed compounds can be used in combination with one or more other drugs in the treatment, prevention, control, amelioration, or reduction of risk of diseases or conditions for which disclosed compounds or the other drugs can have utility, where the combination of the drugs together are safer or more effective than either drug alone. Such other drug(s) can be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with a compound of the present invention. When a compound of the present invention is used contemporaneously with one or more other drugs, a pharmaceutical composition in unit dosage form containing such other drugs and a disclosed compound is preferred. However, the combination therapy can also include therapies in which a disclosed compound and one or more other drugs are administered on different overlapping schedules. It is also contemplated that when used in combination with one or more other active ingredients, the disclosed compounds and the other active ingredients can be used in lower doses than when each is used singly.

[00284] Accordingly, the pharmaceutical compositions include those that contain one or more other active ingredients, in addition to a compound of the present invention.

[00285] The above combinations include combinations of a disclosed compound not only with one other active compound, but also with two or more other active compounds. Likewise, disclosed compounds can be used in combination with other drugs that are used in the prevention, treatment, control, amelioration, or reduction of risk of the diseases or conditions for which disclosed compounds are useful. Such other drugs can be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with a compound of the present invention. When a compound of the present invention is used contemporaneously with one or more other drugs, a pharmaceutical composition containing such other drugs in addition to a disclosed compound is preferred. Accordingly, the

pharmaceutical compositions include those that also contain one or more other active ingredients, in addition to a compound of the present invention.

[00286] The weight ratio of a disclosed compound to the second active ingredient can be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used. Thus, for example, when a compound of the present invention is combined with another agent, the weight ratio of a disclosed compound to the other agent will generally range from about 1000:1 to about 1:1000, preferably about 200:1 to about 1:200. Combinations of a compound of the present invention and other active ingredients will generally also be within the aforementioned range, but in each case, an effective dose of each active ingredient should be used.

[00287] In such combinations a disclosed compound and other active agents can be administered separately or in conjunction. In addition, the administration of one element can be prior to, concurrent to, or subsequent to the administration of other agent(s).

[00288] Accordingly, the disclosed compounds can be used alone or in combination with other agents which are known to be beneficial in the subject indications or other drugs that affect receptors or enzymes that either increase the efficacy, safety, convenience, or reduce unwanted side effects or toxicity of the disclosed compounds. The subject compound and the other agent can be coadministered, either in concomitant therapy or in a fixed combination.

[00289] In one aspect, the compound can be employed in combination with anti-Alzheimer's agents, beta-secretase inhibitors, gamma-secretase inhibitors, HMG-CoA reductase inhibitors, NSAID's including ibuprofen, vitamin E, and anti-amyloid antibodies. In another embodiment, the subject compound can be employed in combination with sedatives, hypnotics, anxiolytics, antipsychotics, antianxiety agents, cyclopyrrolones, imidazopyridines, pyrazolopyrimidines, minor tranquilizers, melatonin agonists and antagonists, melatonergic agents, benzodiazepines, barbiturates, 5HT-2 antagonists, and the like, such as: adinazolam, allobarbitol, alonimid, alprazolam, amisulpride, amitriptyline, amobarbital, amoxapine, aripiprazole, bentazepam, benzoctamine, brotizolam, bupropion, busprione, butabarbital, butalbital, capuride, carbocloral, chloral betaine, chloral hydrate, clomipramine, clonazepam, cloperidone, clorazepate, chlordiazepoxide, clorethate, chlorpromazine, clozapine, cyprazepam, desipramine, dexclamol, diazepam, dichloralphenazone, divalproex, diphenhydramine, doxepin, estazolam, ethchlorvynol, etomidate, fenobam, flunitrazepam,

flupentixol, fluphenazine, flurazepam, fluvoxamine, fluoxetine, fosazepam, glutethimide, halazepam, haloperidol, hydroxyzine, imipramine, lithium, lorazepam, lormetazepam, maprotiline, mecloqualone, melatonin, mephobarbital, meprobamate, methaqualone, midaflur, midazolam, nefazodone, nisobamate, nitrazepam, nortriptyline, olanzapine, oxazepam, paraldehyde, paroxetine, pentobarbital, perlapine, perphenazine, phenelzine, phenobarbital, prazepam, promethazine, propofol, protriptyline, quazepam, quetiapine, reclazepam, risperidone, roletamide, secobarbital, sertraline, suproclone, temazepam, thioridazine, thiothixene, tracazolate, tranlycypromaine, trazodone, triazolam, trepipam, tricetamide, triclofos, trifluoperazine, trimetozine, trimipramine, uldazepam, venlafaxine, zaleplon, ziprasidone, zolazepam, Zolpidem, and salts thereof, and combinations thereof, and the like, or the subject compound can be administered in conjunction with the use of physical methods such as with light therapy or electrical stimulation.

[00290] In a further aspect, the compound can be employed in combination with levodopa (with or without a selective extracerebral decarboxylase inhibitor such as carbidopa or benserazide), anticholinergics such as biperiden (optionally as its hydrochloride or lactate salt) and trihexyphenidyl (benzhexol) hydrochloride, COMT inhibitors such as entacapone, MOA-B inhibitors, antioxidants, A2a adenosine receptor antagonists, cholinergic agonists, NMDA receptor antagonists, serotonin receptor antagonists and dopamine receptor agonists such as alentemol, bromocriptine, fenoldopam, lisuride, naxagolide, pergolide and pramipexole. It will be appreciated that the dopamine agonist can be in the form of a pharmaceutically acceptable salt, for example, alentemol hydrobromide, bromocriptine mesylate, fenoldopam mesylate, naxagolide hydrochloride and pergolide mesylate. Lisuride and pramipexol are commonly used in a non-salt form.

[00291] In a further aspect, the compound can be employed in combination with a compound from the phenothiazine, thioxanthene, heterocyclic dibenzazepine, butyrophenone, diphenylbutylpiperidine and indolone classes of neuroleptic agent. Suitable examples of phenothiazines include chlorpromazine, mesoridazine, thioridazine, acetophenazine, fluphenazine, perphenazine and trifluoperazine. Suitable examples of thioxanthenes include chlorprothixene and thiothixene. An example of a dibenzazepine is clozapine. An example of a butyrophenone is haloperidol. An example of a diphenylbutylpiperidine is pimozide. An example of an indolone is molindolone. Other neuroleptic agents include loxapine, sulpiride and risperidone. It will be appreciated that the neuroleptic agents when used in combination

with the subject compound can be in the form of a pharmaceutically acceptable salt, for example, chlorpromazine hydrochloride, mesoridazine besylate, thioridazine hydrochloride, acetophenazine maleate, fluphenazine hydrochloride, flurphenazine enathate, fluphenazine decanoate, trifluoperazine hydrochloride, thiothixene hydrochloride, haloperidol decanoate, loxapine succinate and molindone hydrochloride. Perphenazine, chlorprothixene, clozapine, haloperidol, pimozide and risperidone are commonly used in a non-salt form. Thus, the subject compound can be employed in combination with acetophenazine, alentemol, aripiprazole, amisulpride, benzhexol, bromocriptine, biperiden, chlorpromazine, chlorprothixene, clozapine, diazepam, fenoldopam, fluphenazine, haloperidol, levodopa, levodopa with benserazide, levodopa with carbidopa, lisuride, loxapine, mesoridazine, molindolone, naxagolide, olanzapine, pergolide, perphenazine, pimozide, pramipexole, quetiapine, risperidone, sulpiride, tetrabenazine, trihexyphenidyl, thioridazine, thiothixene, trifluoperazine or ziprasidone.

[00292] In one aspect, the compound can be employed in combination with an anti-depressant or anti-anxiety agent, including norepinephrine reuptake inhibitors (including tertiary amine tricyclics and secondary amine tricyclics), selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), reversible inhibitors of monoamine oxidase (RIMAs), serotonin and noradrenaline reuptake inhibitors (SNRIs), corticotropin releasing factor (CRF) antagonists, α -adrenoreceptor antagonists, neurokinin-1 receptor antagonists, atypical anti-depressants, benzodiazepines, 5-HT_{1A} agonists or antagonists, especially 5-HT_{1A} partial agonists, and corticotropin releasing factor (CRF) antagonists. Specific agents include: amitriptyline, clomipramine, doxepin, imipramine and trimipramine; amoxapine, desipramine, maprotiline, nortriptyline and protriptyline; fluoxetine, fluvoxamine, paroxetine and sertraline; isocarboxazid, phenelzine, tranlycypromine and selegiline; moclobemide; venlafaxine; duloxetine; aprepitant; bupropion, lithium, nefazodone, trazodone and viloxazine; alprazolam, chlordiazepoxide, clonazepam, chlorazepate, diazepam, halazepam, lorazepam, oxazepam and prazepam; buspirone, flesinoxan, gepirone and ipsapirone, and pharmaceutically acceptable salts thereof.

[00293] In the treatment of conditions which require activation of mAChR M₄ an appropriate dosage level will generally be about 0.01 to 500 mg per kg patient body weight per day which can be administered in single or multiple doses. Preferably, the dosage level will be about 0.1 to about 250 mg/kg per day; more preferably about 0.5 to about 100 mg/kg per day. A

suitable dosage level can be about 0.01 to 250 mg/kg per day, about 0.05 to 100 mg/kg per day, or about 0.1 to 50 mg/kg per day. Within this range the dosage can be 0.05 to 0.5, 0.5 to 5 or 5 to 50 mg/kg per day. For oral administration, the compositions are preferably provided in the form of tablets containing 1.0 to 1000 milligrams of the active ingredient, particularly 1.0, 5.0, 10, 15, 20, 25, 50, 75, 100, 150, 200, 250, 300, 400, 500, 600, 750, 800, 900, and 1000 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. The compounds can be administered on a regimen of 1 to 4 times per day, preferably once or twice per day. This dosage regimen can be adjusted to provide the optimal therapeutic response. It will be understood, however, that the specific dose level and frequency of dosage for any particular patient can be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

[00294] Thus, in one aspect, the invention relates to a method for activating mAChR M₄ receptor activity in at least one cell comprising the step of contacting the at least one cell with at least one disclosed compound or at least one product of a disclosed method in an amount effective to activate mAChR M₄ in the at least one cell. In a further aspect, the cell is mammalian, for example, human. In a further aspect, the cell has been isolated from a subject prior to the contacting step. In a further aspect, contacting is via administration to a subject.

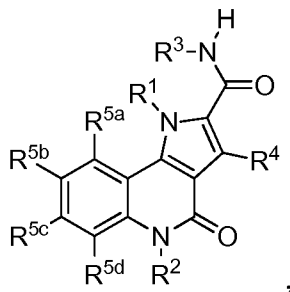
[00295] In a further aspect, the invention relates to a method for activating mAChR M₄ activity in a subject comprising the step of administering to the subject at least one disclosed compound or at least one product of a disclosed method in a dosage and amount effective to activating mAChR M₄ activity in the subject. In a further aspect, the subject is mammalian, for example, human. In a further aspect, the mammal has been diagnosed with a need for mAChR M₄ agonism prior to the administering step. In a further aspect, the mammal has been diagnosed with a need for mAChR M₄ activation prior to the administering step. In a further aspect, the method further comprises the step of identifying a subject in need of mAChR M₄ agonism.

[00296] In a further aspect, the invention relates to a method for the treatment of a disorder associated with selective mAChR M₄ activation, for example, a disorder associated with cholinergic activity, in a mammal comprising the step of administering to the mammal at least one disclosed compound or at least one product of a disclosed method in a dosage and amount effective to treat the disorder in the mammal. In a further aspect, the mammal is a human. In a further aspect, the mammal has been diagnosed with a need for treatment for the disorder prior to the administering step. In a further aspect, the method further comprises the step of identifying a subject in need of treatment for the disorder.

[00297] In one aspect, the disorder can be selected from psychosis, schizophrenia, conduct disorder, disruptive behavior disorder, bipolar disorder, psychotic episodes of anxiety, anxiety associated with psychosis, psychotic mood disorders such as severe major depressive disorder; mood disorders associated with psychotic disorders, acute mania, depression associated with bipolar disorder, mood disorders associated with schizophrenia, behavioral manifestations of mental retardation, conduct disorder, autistic disorder; movement disorders, Tourette's syndrome, akinetic-rigid syndrome, movement disorders associated with Parkinson's disease, tardive dyskinesia, drug induced and neurodegeneration based dyskinesias, attention deficit hyperactivity disorder, cognitive disorders, dementias, and memory disorders. In a further aspect, the disorder is Alzheimer's disease. In a further aspect, the disorder is a neurological and/or psychiatric disorder associated with muscarinic acetylcholine receptor dysfunction. In a still further aspect, muscarinic acetylcholine receptor dysfunction is mAChR M₄ dysfunction.

**a. TREATING A DISORDER ASSOCIATED WITH MUSCARINIC
ACETYLCHOLINE RECEPTOR ACTIVITY**

[00298] In one aspect, the invention relates to a method for the treatment of a neurological and/or psychiatric disorder associated with muscarinic acetylcholine receptor dysfunction in a mammal comprising the step of administering to the mammal an effective amount of least one compound having a structure represented by a formula:

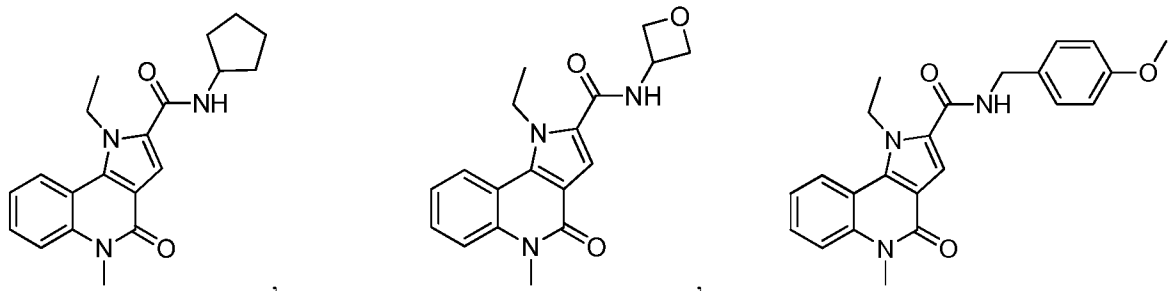


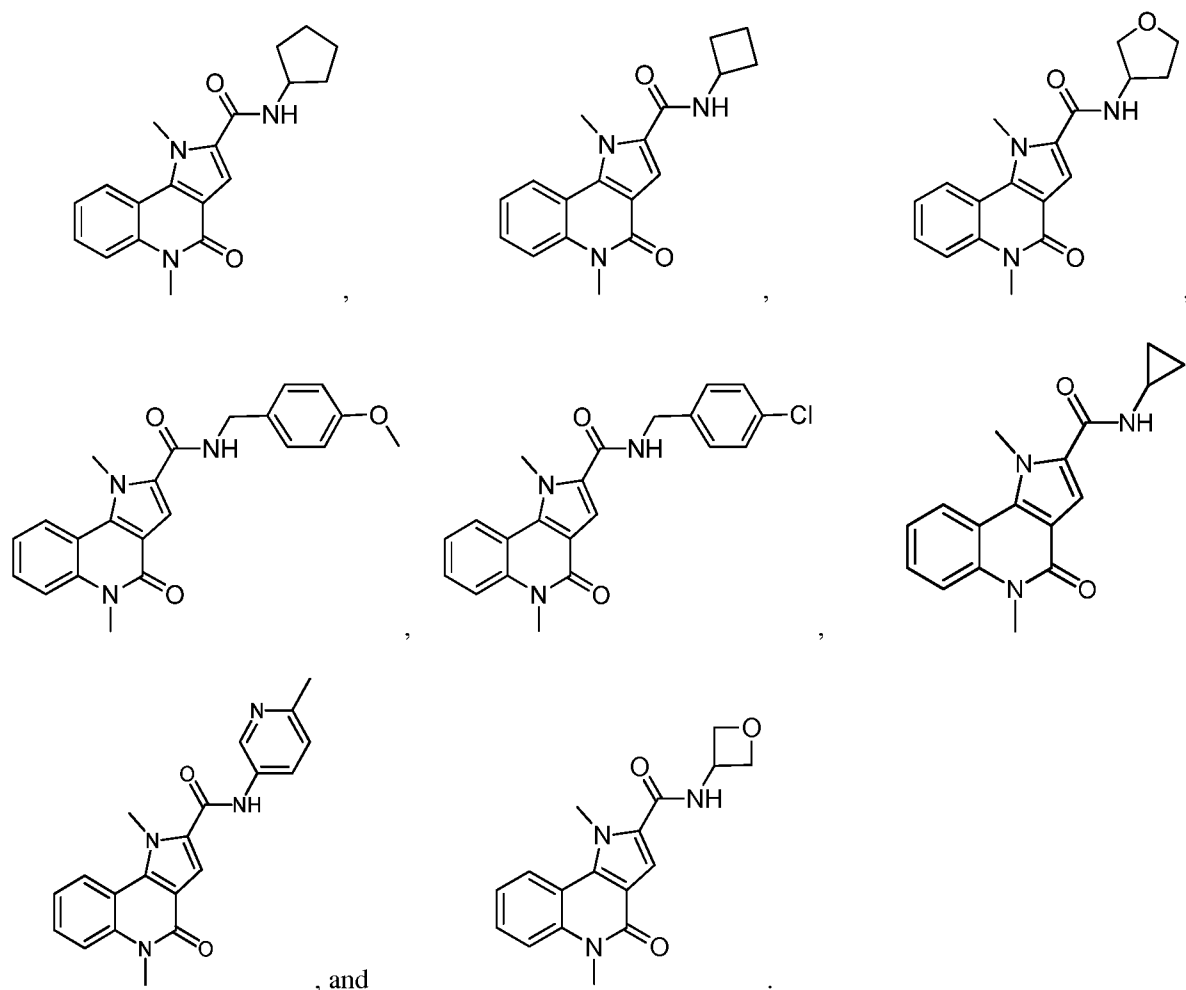
wherein R^1 is selected from hydrogen, C1-C8 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, and Cy^1 ; wherein Cy^1 is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy^1 is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein R^2 is selected from hydrogen, C1-C8 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, and Cy^2 ; wherein Cy^2 is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy^2 is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein R^3 is selected from C1-C8 alkyl, Cy^3 , and Ar^1 ; wherein Ar^1 is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar^1 is monocyclic heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy^3 is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy^3 is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein R^4 is selected from hydrogen, halogen, hydroxyl, cyano, amino, C1-C8 alkyl, C1-C6 alkoxy, C1-C6 alkylamino, C1-C6 dialkylamino, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, Cy^4 , and Ar^2 ; wherein Ar^2 is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar^2 is heteroaryl substituted with 0-3 substituents independently selected from halogen,

cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy⁴ is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy⁴ is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein each of R^{5a}, R^{5b}, R^{5c}, and R^{5d} is independently selected from hydrogen, halogen, hydroxyl, cyano, amino, CONR⁶R⁷, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 alkylamino, C1-C6 dialkylamino, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, Cy⁵, and Ar³, wherein Ar³ is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar³ is heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy⁵ is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy⁵ is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein each of R⁶ and R⁷ is independently selected from hydrogen, C1-C6 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, aryl and heteroaryl; or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof.

[00299] In a further aspect, the compound administered is a disclosed compound or a product of a disclosed method of making a compound. In a still further aspect, an effective amount is a therapeutically effective amount.

[00300] In a further aspect, the compound administered is selected from:





[00301] In a further aspect, the compound exhibits positive allosteric modulation of mAChR M_4 with an EC_{50} of less than about 10,000 nM. In a still further aspect, the compound exhibits positive allosteric modulation of mAChR M_4 with an EC_{50} of less than about 5,000 nM. In an even further aspect, the compound exhibits positive allosteric modulation of mAChR M_4 with an EC_{50} of less than about 1,000 nM. In a further aspect, the compound exhibits positive allosteric modulation of mAChR M_4 with an EC_{50} of less than about 500 nM. In a yet further aspect, the compound exhibits positive allosteric modulation of mAChR M_4 with an EC_{50} of less than about 100 nM. In a further aspect, the compound exhibits positive allosteric modulation of mAChR M_4 with an EC_{50} of between from about 10,000 nM to about 1 nM. In a yet further aspect, the compound exhibits positive allosteric modulation of mAChR M_4 with an EC_{50} of between from about 1,000 nM to about 1 nM. In a still further aspect, the compound exhibits positive allosteric modulation of mAChR M_4 with an EC_{50} of between from about 100 nM to about 1 nM. In an even further aspect, the compound exhibits positive

allosteric modulation of mAChR M₄ with an EC₅₀ of between from about 10 nM to about 1 nM.

[00302] In one aspect, the mammal is a human. In a further aspect, the mammal has been diagnosed with a need for treatment of the disorder prior to the administering step. In a further aspect, the method further comprises the step of identifying a mammal in need of treatment of the disorder. In a further aspect, the disorder is a neurological and/or psychiatric disorder associated with muscarinic acetylcholine receptor dysfunction. In a still further aspect, the muscarinic acetylcholine receptor dysfunction is mAChR M₄ dysfunction.

[00303] In a further aspect, the disorder is selected from a Alzheimer's disease, Parkinson's disease, Huntington's disease, a neurological disorder, a pain disorder and a psychotic disorder. In a still further aspect, the disorder is selected from a Alzheimer's disease, Parkinson's disease, Huntington's disease, a pain disorder and a psychotic disorder. In a yet further aspect, the disorder is Alzheimer's disease. In an even further aspect, the disorder is Parkinson's disease. In a still further aspect, the disorder is Huntington's disease. In a yet further aspect, the disorder is a pain disorder. In an even further aspect, the disorder is a neurological disorder.

[00304] In a further aspect, the disorder is a psychotic disorder. In a still further aspect, the psychotic disorder is selected from schizophrenia, psychotic disorder NOS, brief psychotic disorder, schizophreniform disorder, schizoaffective disorder, delusional disorder, shared psychotic disorder, catastrophic schizophrenia, postpartum psychosis, psychotic depression, psychotic break, tardive psychosis, myxedematous psychosis, occupational psychosis, menstrual psychosis, secondary psychotic disorder, bipolar I disorder with psychotic features, and substance-induced psychotic disorder. In a yet further aspect, the psychotic disorder is a psychosis associated with an illness selected from major depressive disorder, affective disorder, bipolar disorder, electrolyte disorder, neurological disorder, hypoglycemia, AIDS, lupus, and post-traumatic stress disorder. In a yet further aspect, the neurological disorder is selected from brain tumor, dementia with Lewy bodies, multiple sclerosis, sarcoidosis, Lyme disease, syphilis, Alzheimer's disease, Parkinson's disease, and anti-NMDA receptor encephalitis. In a yet further aspect, the psychotic disorder is selected from schizophrenia, brief psychotic disorder, schizophreniform disorder, schizoaffective disorder, delusional disorder, and shared psychotic disorder. In a still further aspect, the schizophrenia is selected

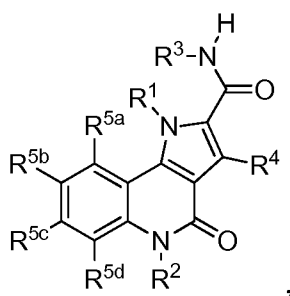
from catastrophic schizophrenia, catatonic schizophrenia, paranoid schizophrenia, residual schizophrenia, disorganized schizophrenia, and undifferentiated schizophrenia. In a yet further aspect, the disorder is selected from schizoid personality disorder, schizotypal personality disorder, and paranoid personality disorder.

[00305] In a further aspect, the disorder is a cognitive disorder. In a still further aspect, the cognitive disorder is selected from amnesia, dementia, delirium, amnestic disorder, substance-induced persisting delirium, dementia due to HIV disease, dementia due to Huntington's disease, dementia due to Parkinson's disease, Parkinsonian-ALS demential complex, dementia of the Alzheimer's type, age-related cognitive decline, and mild cognitive impairment.

[00306] In a further aspect, disorder is selected from conduct disorder, disruptive behavior disorder, psychotic episodes of anxiety, anxiety associated with psychosis, psychotic mood disorders such as severe major depressive disorder; mood disorders associated with psychotic disorders, acute mania, depression associated with bipolar disorder, mood disorders associated with schizophrenia, behavioral manifestations of mental retardation, conduct disorder, autistic disorder; movement disorders, Tourette's syndrome, akinetic-rigid syndrome, movement disorders associated with Parkinson's disease, tardive dyskinesia, drug induced and neurodegeneration based dyskinesias, attention deficit hyperactivity disorder, cognitive disorders, dementias, and memory disorders.

b. POTENTIATION OF MUSCARINIC ACETYLCHOLINE RECEPTOR ACTIVITY

[00307] In one aspect, the invention relates to a method for potentiation of muscarinic acetylcholine receptor activity in a mammal comprising the step of administering to the mammal an effective amount of least one compound having a structure represented by a formula:



wherein R^1 is selected from hydrogen, C1-C8 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, and Cy^1 ; wherein Cy^1 is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy^1 is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein R^2 is selected from hydrogen, C1-C8 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, and Cy^2 ; wherein Cy^2 is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy^2 is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein R^3 is selected from C1-C8 alkyl, Cy^3 , and Ar^1 ; wherein Ar^1 is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar^1 is monocyclic heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy^3 is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy^3 is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein R^4 is selected from hydrogen, halogen, hydroxyl, cyano, amino, C1-C8 alkyl, C1-C6 alkoxy, C1-C6 alkylamino, C1-C6 dialkylamino, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, Cy^4 , and Ar^2 ; wherein Ar^2 is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar^2 is heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy^4 is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy^4 is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-

C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein each of R^{5a} , R^{5b} , R^{5c} , and R^{5d} is independently selected from hydrogen, halogen, hydroxyl, cyano, amino, $CONR^6R^7$, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 alkylamino, C1-C6 dialkylamino, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, Cy^5 , and Ar^3 , wherein Ar^3 is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar^3 is heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy^5 is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy^5 is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein each of R^6 and R^7 is independently selected from hydrogen, C1-C6 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, aryl and heteroaryl; or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof.

[00308] In a further aspect, the compound administered is a disclosed compound or a product of a disclosed method of making a compound. In a still further aspect, an effective amount is a therapeutically effective amount.

[00309] In a further aspect, the compound exhibits potentiation of mAChR M_4 with an EC_{50} of less than about 10,000 nM. In a still further aspect, the compound exhibits potentiation of mAChR M_4 with an EC_{50} of less than about 5,000 nM. In an even further aspect, the compound exhibits potentiation of mAChR M_4 with an EC_{50} of less than about 1,000 nM. In a further aspect, the compound exhibits potentiation of mAChR M_4 with an EC_{50} of less than about 500 nM. In a yet further aspect, the compound potentiation of mAChR M_4 with an EC_{50} of less than about 100 nM. In a further aspect, the compound exhibits potentiation of mAChR M_4 with an EC_{50} of between from about 10,000 nM to about 1 nM. In a yet further aspect, the compound exhibits potentiation of mAChR M_4 with an EC_{50} of between from about 1,000 nM to about 1 nM. In a still further aspect, the compound exhibits potentiation of mAChR M_4 with an EC_{50} of between from about 100 nM to about 1 nM. In an even further aspect, the compound exhibits potentiation of mAChR M_4 with an EC_{50} of between from about 10 nM to about 1 nM.

[00310] In one aspect, the mammal is a human. In a further aspect, the mammal has been diagnosed with a need for potentiation of muscarinic acetylcholine receptor activity prior to the administering step. In a further aspect, the method further comprises the step of identifying a mammal in need of potentiating muscarinic acetylcholine receptor activity. In a further aspect, the potentiation of muscarinic acetylcholine receptor activity is associated with muscarinic acetylcholine receptor dysfunction. In a still further aspect, the muscarinic acetylcholine receptor dysfunction is mAChR M₄ dysfunction.

[00311] In a further aspect, the potentiation of muscarinic acetylcholine receptor activity is potentiation of mAChR M₄ activity. In a yet further aspect, the potentiation of mAChR M₄ activity treats a disorder associated with mAChR M₄ activity in the mammal. In a still further aspect, the mammal has been diagnosed with a need for treatment of the disorder prior to the administering step. In an even further aspect, treatment further comprises the step of identifying a mammal in need of treatment of the disorder.

[00312] In a further aspect, potentiation of muscarinic acetylcholine receptor activity in a mammal is associated with the treatment of a neurological and/or psychiatric disorder associated with muscarinic acetylcholine receptor dysfunction. In a yet further aspect, the muscarinic acetylcholine receptor dysfunction is mAChR M₄ dysfunction. In a still further aspect, the disorder is a psychotic disorder. In an even further aspect, the disorder is a neurological disorder.

[00313] In a further aspect, the disorder is selected from a Alzheimer's disease, Parkinson's disease, Huntington's disease, a neurological disorder, a pain disorder and a psychotic disorder. In a still further aspect, the disorder is selected from a Alzheimer's disease, Parkinson's disease, Huntington's disease, a pain disorder and a psychotic disorder. In a yet further aspect, the disorder is Alzheimer's disease. In an even further aspect, the disorder is Parkinson's disease. In a still further aspect, the disorder is Huntington's disease. In a yet further aspect, the disorder is a pain disorder.

[00314] In a further aspect, the disorder is a psychotic disorder. In a still further aspect, the psychotic disorder is selected from schizophrenia, psychotic disorder NOS, brief psychotic disorder, schizophreniform disorder, schizoaffective disorder, delusional disorder, shared psychotic disorder, catastrophic schizophrenia, postpartum psychosis, psychotic depression, psychotic break, tardive psychosis, myxedematous psychosis, occupational psychosis,

menstrual psychosis, secondary psychotic disorder, bipolar I disorder with psychotic features, and substance-induced psychotic disorder. In a yet further aspect, the psychotic disorder is a psychosis associated with an illness selected from major depressive disorder, affective disorder, bipolar disorder, electrolyte disorder, neurological disorder, hypoglycemia, AIDS, lupus, and post-traumatic stress disorder. In a yet further aspect, the neurological disorder is selected from brain tumor, dementia with Lewy bodies, multiple sclerosis, sarcoidosis, Lyme disease, syphilis, Alzheimer's disease, Parkinson's disease, and anti-NMDA receptor encephalitis. In a further aspect, the psychotic disorder is selected from schizophrenia, brief psychotic disorder, schizophreniform disorder, schizoaffective disorder, delusional disorder, and shared psychotic disorder. In a still further aspect, the schizophrenia is selected from catastrophic schizophrenia, catatonic schizophrenia, paranoid schizophrenia, residual schizophrenia, disorganized schizophrenia, and undifferentiated schizophrenia. In a yet further aspect, the disorder is selected from schizoid personality disorder, schizotypal personality disorder, and paranoid personality disorder.

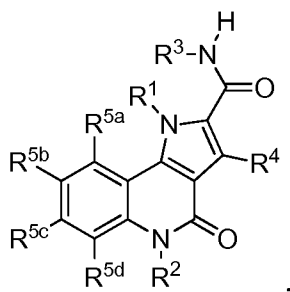
[00315] In a further aspect, the disorder is a cognitive disorder. In a still further aspect, the cognitive disorder is selected from amnesia, dementia, delirium, amnestic disorder, substance-induced persisting delirium, dementia due to HIV disease, dementia due to Huntington's disease, dementia due to Parkinson's disease, Parkinsonian-ALS demential complex, dementia of the Alzheimer's type, age-related cognitive decline, and mild cognitive impairment.

[00316] In a further aspect, disorder is selected from conduct disorder, disruptive behavior disorder, psychotic episodes of anxiety, anxiety associated with psychosis, psychotic mood disorders such as severe major depressive disorder; mood disorders associated with psychotic disorders, acute mania, depression associated with bipolar disorder, mood disorders associated with schizophrenia, behavioral manifestations of mental retardation, conduct disorder, autistic disorder; movement disorders, Tourette's syndrome, akinetic-rigid syndrome, movement disorders associated with Parkinson's disease, tardive dyskinesia, drug induced and neurodegeneration based dyskinesias, attention deficit hyperactivity disorder, cognitive disorders, dementias, and memory disorders.

c. PARTIAL AGONISM OF MUSCARINIC ACETYLCHOLINE RECEPTOR

ACTIVITY

[00317] In one aspect, the invention relates to a method for partial agonism of muscarinic acetylcholine receptor activity in a mammal comprising the step of administering to the mammal a therapeutically effective amount of least one compound having a structure represented by a formula:



wherein R¹ is selected from hydrogen, C1-C8 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, and Cy¹; wherein Cy¹ is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy¹ is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein R² is selected from hydrogen, C1-C8 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, and Cy²; wherein Cy² is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy² is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein R³ is selected from C1-C8 alkyl, Cy³, and Ar¹; wherein Ar¹ is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar¹ is monocyclic heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy³ is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy³ is C3-C8 heterocycloalkyl substituted with 0-3

substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein R^4 is selected from hydrogen, halogen, hydroxyl, cyano, amino, C1-C8 alkyl, C1-C6 alkoxy, C1-C6 alkylamino, C1-C6 dialkylamino, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, Cy^4 , and Ar^2 ; wherein Ar^2 is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar^2 is heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy^4 is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy^4 is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein each of R^{5a} , R^{5b} , R^{5c} , and R^{5d} is independently selected from hydrogen, halogen, hydroxyl, cyano, amino, $CONR^6R^7$, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 alkylamino, C1-C6 dialkylamino, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, Cy^5 , and Ar^3 , wherein Ar^3 is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar^3 is heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy^5 is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy^5 is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein each of R^6 and R^7 is independently selected from hydrogen, C1-C6 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, aryl and heteroaryl; or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof.

[00318] In a further aspect, the compound administered is a disclosed compound or a product of a disclosed method of making a compound. In a still further aspect, an effective amount is a therapeutically effective amount.

[00319] In a further aspect, the compound exhibits partial agonism of mAChR M₄ with an EC₅₀ of less than about 10,000 nM. In a still further aspect, the compound exhibits partial agonism of mAChR M₄ with an EC₅₀ of less than about 5,000 nM. In an even further aspect, the compound exhibits partial agonism of mAChR M₄ with an EC₅₀ of less than about 1,000 nM. In a further aspect, the compound exhibits partial agonism of mAChR M₄ with an EC₅₀ of less than about 500 nM. In a yet further aspect, the compound partial agonism of mAChR M₄ with an EC₅₀ of less than about 100 nM. In a further aspect, the compound exhibits partial agonism of mAChR M₄ with an EC₅₀ of between from about 10,000 nM to about 1 nM. In a yet further aspect, the compound exhibits partial agonism of mAChR M₄ with an EC₅₀ of between from about 1,000 nM to about 1 nM. In a still further aspect, the compound exhibits partial agonism of mAChR M₄ with an EC₅₀ of between from about 100 nM to about 1 nM. In an even further aspect, the compound exhibits partial agonism of mAChR M₄ with an EC₅₀ of between from about 10 nM to about 1 nM.

[00320] In one aspect, the mammal is a human. In a further aspect, the mammal has been diagnosed with a need for partial agonism of muscarinic acetylcholine receptor activity prior to the administering step. In a further aspect, the method further comprises the step of identifying a mammal in need of partial agonism of muscarinic acetylcholine receptor activity. In a further aspect, the partial agonism of muscarinic acetylcholine receptor activity is associated with muscarinic acetylcholine receptor dysfunction. In a still further aspect, the muscarinic acetylcholine receptor dysfunction is mAChR M₄ dysfunction.

[00321] In a further aspect, the partial agonism of muscarinic acetylcholine receptor activity is partial agonism of mAChR M₄ activity. In a yet further aspect, the partial agonism of mAChR M₄ activity treats a disorder associated with mAChR M₄ activity in the mammal. In a still further aspect, the mammal has been diagnosed with a need for treatment of the disorder prior to the administering step. In an even further aspect, treatment further comprises the step of identifying a mammal in need of treatment of the disorder.

[00322] In a further aspect, partial agonism of muscarinic acetylcholine receptor activity in a mammal is associated with the treatment of a neurological and/or psychiatric disorder associated with a muscarinic acetylcholine receptor dysfunction. In a yet further aspect, the muscarinic acetylcholine receptor dysfunction is mAChR M₄ dysfunction. In a still further

aspect, the disorder is a psychotic disorder. In a yet further aspect, the disorder is a neurological disorder.

[00323] In a further aspect, the disorder is selected from a Alzheimer's disease, Parkinson's disease, Huntington's disease, a neurological disorder, a pain disorder and a psychotic disorder. In a still further aspect, the disorder is selected from a Alzheimer's disease, Parkinson's disease, Huntington's disease, a pain disorder and a psychotic disorder. In a yet further aspect, the disorder is Alzheimer's disease. In an even further aspect, the disorder is Parkinson's disease. In a still further aspect, the disorder is Huntington's disease. In a yet further aspect, the disorder is a pain disorder.

[00324] In a further aspect, the disorder is a psychotic disorder. In a still further aspect, the psychotic disorder is selected from schizophrenia, psychotic disorder NOS, brief psychotic disorder, schizophreniform disorder, schizoaffective disorder, delusional disorder, shared psychotic disorder, catastrophic schizophrenia, postpartum psychosis, psychotic depression, psychotic break, tardive psychosis, myxedematous psychosis, occupational psychosis, menstrual psychosis, secondary psychotic disorder, bipolar I disorder with psychotic features, and substance-induced psychotic disorder. In a yet further aspect, the psychotic disorder is a psychosis associated with an illness selected from major depressive disorder, affective disorder, bipolar disorder, electrolyte disorder, neurological disorder, hypoglycemia, AIDS, lupus, and post-traumatic stress disorder. In a yet further aspect, the neurological disorder is selected from brain tumor, dementia with Lewy bodies, multiple sclerosis, sarcoidosis, Lyme disease, syphilis, Alzheimer's disease, Parkinson's disease, and anti-NMDA receptor encephalitis. In a further aspect, the psychotic disorder is selected from schizophrenia, brief psychotic disorder, schizophreniform disorder, schizoaffective disorder, delusional disorder, and shared psychotic disorder. In a still further aspect, the schizophrenia is selected from catastrophic schizophrenia, catatonic schizophrenia, paranoid schizophrenia, residual schizophrenia, disorganized schizophrenia, and undifferentiated schizophrenia. In a yet further aspect, the disorder is selected from schizoid personality disorder, schizotypal personality disorder, and paranoid personality disorder.

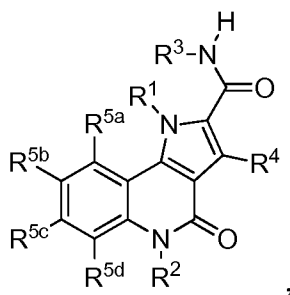
[00325] In a further aspect, the disorder is a cognitive disorder. In a still further aspect, the cognitive disorder is selected from amnesia, dementia, delirium, amnestic disorder, substance-induced persisting delirium, dementia due to HIV disease, dementia due to

Huntington's disease, dementia due to Parkinson's disease, Parkinsonian-ALS demential complex, dementia of the Alzheimer's type, age-related cognitive decline, and mild cognitive impairment.

[00326] In a further aspect, disorder is selected from conduct disorder, disruptive behavior disorder, psychotic episodes of anxiety, anxiety associated with psychosis, psychotic mood disorders such as severe major depressive disorder; mood disorders associated with psychotic disorders, acute mania, depression associated with bipolar disorder, mood disorders associated with schizophrenia, behavioral manifestations of mental retardation, conduct disorder, autistic disorder; movement disorders, Tourette's syndrome, akinetic-rigid syndrome, movement disorders associated with Parkinson's disease, tardive dyskinesia, drug induced and neurodegeneration based dyskinesias, attention deficit hyperactivity disorder, cognitive disorders, dementias, and memory disorders.

d. ENHANCING COGNITION

[00327] In one aspect, the invention relates to a method for enhancing cognition in a mammal comprising the step of administering to the mammal an effective amount of least one compound having a structure represented by a formula



wherein R^1 is selected from hydrogen, C1-C8 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, and Cy^1 ; wherein Cy^1 is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy^1 is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein R^2 is selected from hydrogen, C1-C8 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, and Cy^2 ; wherein Cy^2 is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl,

or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy² is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein R³ is selected from C1-C8 alkyl, Cy³, and Ar¹; wherein Ar¹ is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar¹ is monocyclic heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy³ is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy³ is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein R⁴ is selected from hydrogen, halogen, hydroxyl, cyano, amino, C1-C8 alkyl, C1-C6 alkoxy, C1-C6 alkylamino, C1-C6 dialkylamino, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, Cy⁴, and Ar²; wherein Ar² is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar² is heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy⁴ is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy⁴ is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein each of R^{5a}, R^{5b}, R^{5c}, and R^{5d} is independently selected from hydrogen, halogen, hydroxyl, cyano, amino, CONR⁶R⁷, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 alkylamino, C1-C6 dialkylamino, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, Cy⁵, and Ar³, wherein Ar³ is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar³ is heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy⁵ is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl,

C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy⁵ is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein each of R⁶ and R⁷ is independently selected from hydrogen, C1-C6 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, aryl and heteroaryl; or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof.

[00328] In a further aspect, the compound administered is a disclosed compound or a product of a disclosed method of making a compound. In a still further aspect, an effective amount is a therapeutically effective amount.

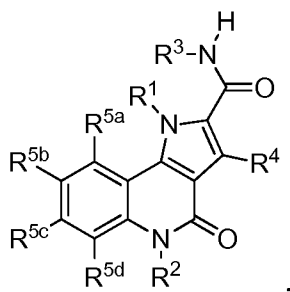
[00329] In a further aspect, the compound exhibits positive allosteric modulation of mAChR M₄ with an EC₅₀ of less than about 10,000 nM. In a still further aspect, the compound exhibits positive allosteric modulation of mAChR M₄ with an EC₅₀ of less than about 5,000 nM. In an even further aspect, the compound exhibits positive allosteric modulation of mAChR M₄ with an EC₅₀ of less than about 1,000 nM. In a further aspect, the compound exhibits positive allosteric modulation of mAChR M₄ with an EC₅₀ of less than about 500 nM. In a yet further aspect, the compound exhibits positive allosteric modulation of mAChR M₄ with an EC₅₀ of less than about 100 nM. In a further aspect, the compound exhibits positive allosteric modulation of mAChR M₄ with an EC₅₀ of between from about 10,000 nM to about 1 nM. In a yet further aspect, the compound exhibits positive allosteric modulation of mAChR M₄ with an EC₅₀ of between from about 1,000 nM to about 1 nM. In a still further aspect, the compound exhibits positive allosteric modulation of mAChR M₄ with an EC₅₀ of between from about 100 nM to about 1 nM. In an even further aspect, the compound exhibits positive allosteric modulation of mAChR M₄ with an EC₅₀ of between from about 10 nM to about 1 nM.

[00330] In one aspect, the mammal is a human. In a further aspect, the mammal has been diagnosed with a need for cognition enhancement prior to the administering step. In a further aspect, the method further comprises the step of identifying a mammal in need of cognition enhancement. In a further aspect, the need for cognition enhancement is associated with muscarinic acetylcholine receptor dysfunction. In a yet further aspect, the muscarinic acetylcholine receptor dysfunction is mAChR M₄ dysfunction.

[00331] In a further aspect, the cognition enhancement is a statistically significant increase in Novel Object Recognition. In a further aspect, the cognition enhancement is a statistically significant increase in performance of the Wisconsin Card Sorting Test.

e. MODULATING MUSCARINIC ACETYLCHOLINE RECEPTOR ACTIVITY IN A MAMMAL

[00332] In one aspect, the invention relates to a modulating muscarinic acetylcholine receptor activity in a mammal comprising the step of administering to the mammal an effective amount of least one compound having a structure represented by a formula:



wherein R¹ is selected from hydrogen, C1-C8 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, and Cy¹; wherein Cy¹ is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy¹ is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein R² is selected from hydrogen, C1-C8 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, and Cy²; wherein Cy² is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy² is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein R³ is selected from C1-C8 alkyl, Cy³, and Ar¹; wherein Ar¹ is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar¹ is monocyclic heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy³ is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano,

amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy³ is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein R⁴ is selected from hydrogen, halogen, hydroxyl, cyano, amino, C1-C8 alkyl, C1-C6 alkoxy, C1-C6 alkylamino, C1-C6 dialkylamino, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, Cy⁴, and Ar²; wherein Ar² is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar² is heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy⁴ is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy⁴ is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein each of R^{5a}, R^{5b}, R^{5c}, and R^{5d} is independently selected from hydrogen, halogen, hydroxyl, cyano, amino, CONR⁶R⁷, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 alkylamino, C1-C6 dialkylamino, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, Cy⁵, and Ar³, wherein Ar³ is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar³ is heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy⁵ is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy⁵ is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein each of R⁶ and R⁷ is independently selected from hydrogen, C1-C6 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, aryl and heteroaryl; or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof.

[00333] In a further aspect, the compound administered is a disclosed compound or a product of a disclosed method of making a compound. In a still further aspect, an effective amount is a therapeutically effective amount.

[00334] In one aspect, modulating is increasing. In a further aspect, modulating is potentiation. In a further aspect, modulating is partial agonism.

[00335] In a further aspect, an effective amount is a therapeutically effective amount.

[00336] In a further aspect, the compound exhibits modulation of mAChR M₄ with an EC₅₀ of less than about 10,000 nM. In a still further aspect, the compound exhibits modulation of mAChR M₄ with an EC₅₀ of less than about 5,000 nM. In an even further aspect, the compound exhibits modulation of mAChR M₄ with an EC₅₀ of less than about 1,000 nM. In a further aspect, the compound exhibits modulation of mAChR M₄ with an EC₅₀ of less than about 500 nM. In a yet further aspect, the compound modulation of mAChR M₄ with an EC₅₀ of less than about 100 nM. In a further aspect, the compound exhibits modulation of mAChR M₄ with an EC₅₀ of between from about 10,000 nM to about 1 nM. In a yet further aspect, the compound exhibits modulation of mAChR M₄ with an EC₅₀ of between from about 1,000 nM to about 1 nM. In a still further aspect, the compound exhibits modulation of mAChR M₄ with an EC₅₀ of between from about 100 nM to about 1 nM. In an even further aspect, the compound exhibits modulation of mAChR M₄ with an EC₅₀ of between from about 10 nM to about 1 nM.

[00337] In one aspect, the mammal is a human. In a further aspect, the mammal has been diagnosed with a need for modulation of muscarinic acetylcholine receptor activity prior to the administering step. In a further aspect, the method further comprises the step of identifying a mammal in need of modulating muscarinic acetylcholine receptor activity. In a further aspect, the modulation of muscarinic acetylcholine receptor activity is associated with muscarinic acetylcholine receptor dysfunction. In a still further aspect, the muscarinic acetylcholine receptor dysfunction is mAChR M₄ dysfunction.

[00338] In a further aspect, the modulation of muscarinic acetylcholine receptor activity is modulation of mAChR M₄ activity. In a yet further aspect, the modulation of mAChR M₄ activity treats a disorder associated with mAChR M₄ activity in the mammal. In a still further aspect, the mammal has been diagnosed with a need for treatment of the disorder prior to the

administering step. In an even further aspect, treatment further comprises the step of identifying a mammal in need of treatment of the disorder.

[00339] In a further aspect, modulation of muscarinic acetylcholine receptor activity in a mammal is associated with the treatment of a neurological and/or psychiatric disorder associated with a muscarinic acetylcholine receptor dysfunction. In a yet further aspect, the muscarinic acetylcholine receptor dysfunction is mAChR M₄ dysfunction. In a still further aspect, the disorder is a psychiatric disorder. In an even further aspect, the disorder is a neurological disorder.

[00340] In a further aspect, the disorder is selected from a Alzheimer's disease, Parkinson's disease, Huntington's disease, a neurological disorder, a pain disorder and a psychotic disorder. In a still further aspect, the disorder is selected from a Alzheimer's disease, Parkinson's disease, Huntington's disease, a pain disorder and a psychotic disorder. In a yet further aspect, the disorder is Alzheimer's disease. In an even further aspect, the disorder is Parkinson's disease. In a still further aspect, the disorder is Huntington's disease. In a yet further aspect, the disorder is a pain disorder.

[00341] In a further aspect, the disorder is a psychotic disorder. In a still further aspect, the psychotic disorder is selected from schizophrenia, psychotic disorder NOS, brief psychotic disorder, schizophreniform disorder, schizoaffective disorder, delusional disorder, shared psychotic disorder, catastrophic schizophrenia, postpartum psychosis, psychotic depression, psychotic break, tardive psychosis, myxedematous psychosis, occupational psychosis, menstrual psychosis, secondary psychotic disorder, bipolar I disorder with psychotic features, and substance-induced psychotic disorder. In a yet further aspect, the psychotic disorder is a psychosis associated with an illness selected from major depressive disorder, affective disorder, bipolar disorder, electrolyte disorder, neurological disorder, hypoglycemia, AIDS, lupus, and post-traumatic stress disorder. In a yet further aspect, the neurological disorder is selected from brain tumor, dementia with Lewy bodies, multiple sclerosis, sarcoidosis, Lyme disease, syphilis, Alzheimer's disease, Parkinson's disease, and anti-NMDA receptor encephalitis. In a further aspect, the psychotic disorder is selected from schizophrenia, brief psychotic disorder, schizophreniform disorder, schizoaffective disorder, delusional disorder, and shared psychotic disorder. In a still further aspect, the schizophrenia is selected from catastrophic schizophrenia, catatonic schizophrenia, paranoid schizophrenia, residual

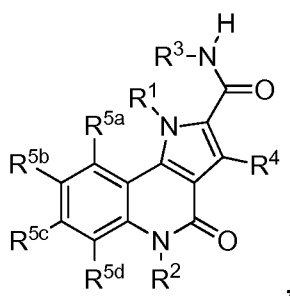
schizophrenia, disorganized schizophrenia, and undifferentiated schizophrenia. In a yet further aspect, the disorder is selected from schizoid personality disorder, schizotypal personality disorder, and paranoid personality disorder.

[00342] In a further aspect, the disorder is a cognitive disorder. In a still further aspect, the cognitive disorder is selected from amnesia, dementia, delirium, amnesic disorder, substance-induced persisting delirium, dementia due to HIV disease, dementia due to Huntington's disease, dementia due to Parkinson's disease, Parkinsonian-ALS demential complex, dementia of the Alzheimer's type, age-related cognitive decline, and mild cognitive impairment.

[00343] In a further aspect, disorder is selected from conduct disorder, disruptive behavior disorder, psychotic episodes of anxiety, anxiety associated with psychosis, psychotic mood disorders such as severe major depressive disorder; mood disorders associated with psychotic disorders, acute mania, depression associated with bipolar disorder, mood disorders associated with schizophrenia, behavioral manifestations of mental retardation, conduct disorder, autistic disorder; movement disorders, Tourette's syndrome, akinetic-rigid syndrome, movement disorders associated with Parkinson's disease, tardive dyskinesia, drug induced and neurodegeneration based dyskinesias, attention deficit hyperactivity disorder, cognitive disorders, dementias, and memory disorders.

f. MODULATING MUSCARINIC ACETYLCHOLINE RECEPTOR ACTIVITY IN CELLS

[00344] In one aspect, the invention relates to a method for modulating muscarinic acetylcholine receptor activity in at least one cell, comprising the step of contacting the at least one cell with an effective amount of least one compound having a structure represented by a formula:



wherein R^1 is selected from hydrogen, C1-C8 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, and Cy^1 ; wherein Cy^1 is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy^1 is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein R^2 is selected from hydrogen, C1-C8 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, and Cy^2 ; wherein Cy^2 is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy^2 is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein R^3 is selected from C1-C8 alkyl, Cy^3 , and Ar^1 ; wherein Ar^1 is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar^1 is monocyclic heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy^3 is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy^3 is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein R^4 is selected from hydrogen, halogen, hydroxyl, cyano, amino, C1-C8 alkyl, C1-C6 alkoxy, C1-C6 alkylamino, C1-C6 dialkylamino, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, Cy^4 , and Ar^2 ; wherein Ar^2 is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar^2 is heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy^4 is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy^4 is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-

C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein each of R^{5a} , R^{5b} , R^{5c} , and R^{5d} is independently selected from hydrogen, halogen, hydroxyl, cyano, amino, $CONR^6R^7$, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 alkylamino, C1-C6 dialkylamino, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, Cy^5 , and Ar^3 , wherein Ar^3 is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar^3 is heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy^5 is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy^5 is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein each of R^6 and R^7 is independently selected from hydrogen, C1-C6 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, aryl and heteroaryl; or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof.

[00345] In a further aspect, the compound administered is a disclosed compound or a product of a disclosed method of making a compound. In a still further aspect, an effective amount is a therapeutically effective amount.

[00346] In one aspect, modulating is increasing. In a further aspect, modulating is potentiation. In a further aspect, modulating is partial agonism.

[00347] In a further aspect, an effective amount is a therapeutically effective amount.

[00348] In a further aspect, the compound exhibits modulation of mAChR M_4 with an EC_{50} of less than about 10,000 nM. In a still further aspect, the compound exhibits modulation of mAChR M_4 with an EC_{50} of less than about 5,000 nM. In an even further aspect, the compound exhibits modulation of mAChR M_4 with an EC_{50} of less than about 1,000 nM. In a further aspect, the compound exhibits modulation of mAChR M_4 with an EC_{50} of less than about 500 nM. In a yet further aspect, the compound modulation of mAChR M_4 with an EC_{50} of less than about 100 nM. In a further aspect, the compound exhibits modulation of mAChR M_4 with an EC_{50} of between from about 10,000 nM to about 1 nM. In a yet further aspect, the compound exhibits modulation of mAChR M_4 with an EC_{50} of between from about 1,000

nM to about 1 nM. In a still further aspect, the compound exhibits modulation of mAChR M₄ with an EC₅₀ of between from about 100 nM to about 1 nM. In an even further aspect, the compound exhibits modulation of mAChR M₄ with an EC₅₀ of between from about 10 nM to about 1 nM.

[00349] In one aspect, the cell is mammalian. In a further aspect, the cell is human. In a further aspect, the cell has been isolated from a mammal prior to the contacting step.

[00350] In a further aspect, contacting is via administration to a mammal. In a further aspect, the mammal has been diagnosed with a need for modulation of muscarinic acetylcholine receptor activity prior to the administering step. In a further aspect, the method further comprises the step of identifying a mammal in need of modulating muscarinic acetylcholine receptor activity. In a further aspect, the modulation of muscarinic acetylcholine receptor activity is associated with muscarinic acetylcholine receptor dysfunction. In a still further aspect, the muscarinic acetylcholine receptor dysfunction is mAChR M₄ dysfunction.

[00351] In a further aspect, the modulation of muscarinic acetylcholine receptor activity is modulation of mAChR M₄ activity. In a yet further aspect, the modulation of mAChR M₄ activity treats a disorder associated with mAChR M₄ activity in the mammal. In a still further aspect, the mammal has been diagnosed with a need for treatment of the disorder prior to the administering step. In an even further aspect, treatment further comprises the step of identifying a mammal in need of treatment of the disorder.

[00352] In a further aspect, modulation of muscarinic acetylcholine receptor activity in at least one cell is associated with the treatment of a neurological and/or psychiatric disorder associated with muscarinic acetylcholine receptor dysfunction. In a yet further aspect, the muscarinic acetylcholine receptor dysfunction is mAChR M₄ dysfunction. In a still further aspect, the disorder is a psychiatric disorder. In an even further aspect, the disorder is a neurological disorder.

[00353] In a further aspect, the disorder is selected from a Alzheimer's disease, Parkinson's disease, Huntington's disease, a neurological disorder, a pain disorder and a psychotic disorder. In a still further aspect, the disorder is selected from a Alzheimer's disease, Parkinson's disease, Huntington's disease, a pain disorder and a psychotic disorder. In a yet further aspect, the disorder is Alzheimer's disease. In an even further aspect, the disorder is

Parkinson's disease. In a still further aspect, the disorder is Huntington's disease. In a yet further aspect, the disorder is a pain disorder. In an even further aspect, the disorder is a neurological disorder.

[00354] In a further aspect, the disorder is a psychotic disorder. In a still further aspect, the psychotic disorder is selected from schizophrenia, psychotic disorder NOS, brief psychotic disorder, schizophreniform disorder, schizoaffective disorder, delusional disorder, shared psychotic disorder, catastrophic schizophrenia, postpartum psychosis, psychotic depression, psychotic break, tardive psychosis, myxedematous psychosis, occupational psychosis, menstrual psychosis, secondary psychotic disorder, bipolar I disorder with psychotic features, and substance-induced psychotic disorder. In a yet further aspect, the psychotic disorder is a psychosis associated with an illness selected from major depressive disorder, affective disorder, bipolar disorder, electrolyte disorder, neurological disorder, hypoglycemia, AIDS, lupus, and post-traumatic stress disorder. In a yet further aspect, the neurological disorder is selected from brain tumor, dementia with Lewy bodies, multiple sclerosis, sarcoidosis, Lyme disease, syphilis, Alzheimer's disease, Parkinson's disease, and anti-NMDA receptor encephalitis. In a further aspect, the psychotic disorder is selected from schizophrenia, brief psychotic disorder, schizophreniform disorder, schizoaffective disorder, delusional disorder, and shared psychotic disorder. In a still further aspect, the schizophrenia is selected from catastrophic schizophrenia, catatonic schizophrenia, paranoid schizophrenia, residual schizophrenia, disorganized schizophrenia, and undifferentiated schizophrenia. In a yet further aspect, the disorder is selected from schizoid personality disorder, schizotypal personality disorder, and paranoid personality disorder.

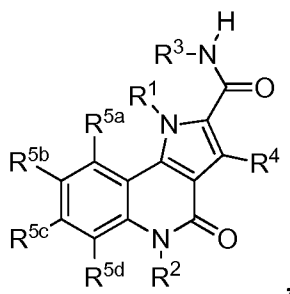
[00355] In a further aspect, the disorder is a cognitive disorder. In a still further aspect, the cognitive disorder is selected from amnesia, dementia, delirium, amnestic disorder, substance-induced persisting delirium, dementia due to HIV disease, dementia due to Huntington's disease, dementia due to Parkinson's disease, Parkinsonian-ALS demential complex, dementia of the Alzheimer's type, age-related cognitive decline, and mild cognitive impairment.

[00356] In a further aspect, disorder is selected from conduct disorder, disruptive behavior disorder, psychotic episodes of anxiety, anxiety associated with psychosis, psychotic mood disorders such as severe major depressive disorder; mood disorders associated with psychotic

disorders, acute mania, depression associated with bipolar disorder, mood disorders associated with schizophrenia, behavioral manifestations of mental retardation, conduct disorder, autistic disorder; movement disorders, Tourette's syndrome, akinetic-rigid syndrome, movement disorders associated with Parkinson's disease, tardive dyskinesia, drug induced and neurodegeneration based dyskinesias, attention deficit hyperactivity disorder, cognitive disorders, dementias, and memory disorders.

2. COTHERAPEUTIC METHODS

[00357] The present invention is further directed to administration of a selective mAChR M₄ activator for improving treatment outcomes in the context of cognitive or behavioral therapy. That is, in one aspect, the invention relates to a cotherapeutic method comprising the step of administering to a mammal an effective amount and dosage of at least one compound having a structure represented by a formula:



wherein R¹ is selected from hydrogen, C1-C8 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, and Cy¹; wherein Cy¹ is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy¹ is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein R² is selected from hydrogen, C1-C8 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, and Cy²; wherein Cy² is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy² is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein R³ is selected from C1-C8 alkyl, Cy³, and Ar¹; wherein Ar¹ is phenyl substituted with 0-3 substituents independently selected from halogen,

cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar¹ is monocyclic heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy³ is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy³ is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein R⁴ is selected from hydrogen, halogen, hydroxyl, cyano, amino, C1-C8 alkyl, C1-C6 alkoxy, C1-C6 alkylamino, C1-C6 dialkylamino, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, Cy⁴, and Ar²; wherein Ar² is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar² is heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy⁴ is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy⁴ is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein each of R^{5a}, R^{5b}, R^{5c}, and R^{5d} is independently selected from hydrogen, halogen, hydroxyl, cyano, amino, CONR⁶R⁷, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 alkylamino, C1-C6 dialkylamino, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, Cy⁵, and Ar³, wherein Ar³ is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar³ is heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy⁵ is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy⁵ is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein each of R⁶ and R⁷ is independently selected from hydrogen, C1-C6 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl,

aryl and heteroaryl; or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof.

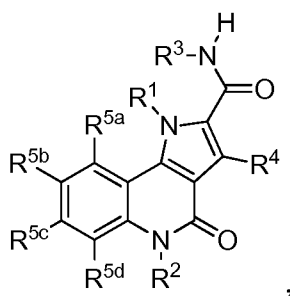
[00358] In a further aspect, administration improves treatment outcomes in the context of cognitive or behavioral therapy. Administration in connection with cognitive or behavioral therapy can be continuous or intermittent. Administration need not be simultaneous with therapy and can be before, during, and/or after therapy. For example, cognitive or behavioral therapy can be provided within 1, 2, 3, 4, 5, 6, 7 days before or after administration of the compound. As a further example, cognitive or behavioral therapy can be provided within 1, 2, 3, or 4 weeks before or after administration of the compound. As a still further example, cognitive or behavioral therapy can be provided before or after administration within a period of time of 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 half-lives of the administered compound.

[00359] It is understood that the disclosed cotherapeutic methods can be used in connection with the disclosed compounds, compositions, kits, and uses.

3. MANUFACTURE OF A MEDICAMENT

[00360] In one aspect, the invention relates methods for the manufacture of a medicament for modulating the activity mACHR M₄ (*e.g.*, treatment of one or more neurological and/or psychiatric disorder associated with muscarinic acetylcholine receptor dysfunction such as mACHR M₄ dysfunction) in mammals (*e.g.*, humans) comprising combining one or more disclosed compounds, products, or compositions or a pharmaceutically acceptable salt, solvate, hydrate, or polymorph thereof, with a pharmaceutically acceptable carrier.

[00361] In one aspect, the invention relates to a medicament comprising one or more compounds having a structure represented by a formula:



wherein R¹ is selected from hydrogen, C1-C8 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, and Cy¹; wherein Cy¹ is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6

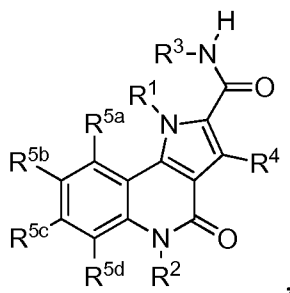
polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy¹ is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein R² is selected from hydrogen, C1-C8 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, and Cy²; wherein Cy² is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy² is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein R³ is selected from C1-C8 alkyl, Cy³, and Ar¹; wherein Ar¹ is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar¹ is monocyclic heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy³ is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy³ is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein R⁴ is selected from hydrogen, halogen, hydroxyl, cyano, amino, C1-C8 alkyl, C1-C6 alkoxy, C1-C6 alkylamino, C1-C6 dialkylamino, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, Cy⁴, and Ar²; wherein Ar² is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar² is heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy⁴ is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy⁴ is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein each of R^{5a}, R^{5b}, R^{5c}, and R^{5d} is independently selected from hydrogen, halogen, hydroxyl, cyano, amino, CONR⁶R⁷, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 alkylamino, C1-C6

dialkylamino, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, Cy⁵, and Ar³, wherein Ar³ is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar³ is heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy⁵ is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy⁵ is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein each of R⁶ and R⁷ is independently selected from hydrogen, C1-C6 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, aryl and heteroaryl; or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof.

4. USE OF COMPOUNDS

[00362] Also provided are the uses of the disclosed compounds and products. In one aspect, the use relates to a treatment of a disorder in a mammal. In one aspect, the use is characterized in that the mammal is a human. In one aspect, the use is characterized in that the disorder is a neurological and/or psychiatric disorder associated with muscarinic acetylcholine receptor dysfunction. In one aspect, the use relates to positive allosteric modulation of muscarinic acetylcholine receptor activity in a mammal. In a further aspect, the muscarinic acetylcholine receptor is mAChR M₄.

[00363] In one aspect, the invention relates to use of a compound having a structure represented by a formula:



wherein R¹ is selected from hydrogen, C1-C8 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, and Cy¹; wherein Cy¹ is C3-C8 cycloalkyl substituted with 0-3 substituents selected from

halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy¹ is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein R² is selected from hydrogen, C1-C8 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, and Cy²; wherein Cy² is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy² is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein R³ is selected from C1-C8 alkyl, Cy³, and Ar¹; wherein Ar¹ is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar¹ is monocyclic heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy³ is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy³ is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein R⁴ is selected from hydrogen, halogen, hydroxyl, cyano, amino, C1-C8 alkyl, C1-C6 alkoxy, C1-C6 alkylamino, C1-C6 dialkylamino, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, Cy⁴, and Ar²; wherein Ar² is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar² is heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy⁴ is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy⁴ is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein each of R^{5a}, R^{5b}, R^{5c}, and R^{5d} is independently selected from hydrogen, halogen, hydroxyl,

cyano, amino, CONR⁶R⁷, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 alkylamino, C1-C6 dialkylamino, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, Cy⁵, and Ar³, wherein Ar³ is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar³ is heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy⁵ is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy⁵ is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein each of R⁶ and R⁷ is independently selected from hydrogen, C1-C6 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, aryl and heteroaryl; or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof.

[00364] In a further aspect, a use relates to potentiation of muscarinic acetylcholine receptor activity in a mammal. In a further aspect, a use relates to partial agonism of muscarinic acetylcholine receptor activity in a mammal. In a further aspect, a use relates to enhancing cognition in a mammal. In a further aspect, a use relates to modulating mAChR M₄ activity in a mammal. In a still further aspect, a use relates to modulating mAChR M₄ activity in a cell. In a yet further aspect, use relates to partial allosteric modulation of mAChR M₄. In an even further aspect, the mammal is a human.

[00365] In a further aspect, the disorder is selected from a Alzheimer's disease, Parkinson's disease, Huntington's disease, a neurological disorder, a pain disorder and a psychotic disorder. In a still further aspect, the disorder is selected from a Alzheimer's disease, Parkinson's disease, Huntington's disease, a pain disorder and a psychotic disorder. In a yet further aspect, the disorder is Alzheimer's disease. In an even further aspect, the disorder is Parkinson's disease. In a still further aspect, the disorder is Huntington's disease. In a yet further aspect, the disorder is a pain disorder. In an even further aspect, the disorder is a neurological disorder. In a still further aspect, the disorder is a psychiatric disorder.

[00366] In a further aspect, a use is associated with the treatment of a psychotic disorder. In a still further aspect, the psychotic disorder is selected from schizophrenia, psychotic disorder

NOS, brief psychotic disorder, schizophreniform disorder, schizoaffective disorder, delusional disorder, shared psychotic disorder, catastrophic schizophrenia, postpartum psychosis, psychotic depression, psychotic break, tardive psychosis, myxedematous psychosis, occupational psychosis, menstrual psychosis, secondary psychotic disorder, bipolar I disorder with psychotic features, and substance-induced psychotic disorder. In a yet further aspect, the psychotic disorder is a psychosis associated with an illness selected from major depressive disorder, affective disorder, bipolar disorder, electrolyte disorder, neurological disorder, hypoglycemia, AIDS, lupus, and post-traumatic stress disorder. In a yet further aspect, the neurological disorder is selected from brain tumor, dementia with Lewy bodies, multiple sclerosis, sarcoidosis, Lyme disease, syphilis, Alzheimer's disease, Parkinson's disease, and anti-NMDA receptor encephalitis. In a further aspect, the psychotic disorder is selected from schizophrenia, brief psychotic disorder, schizophreniform disorder, schizoaffective disorder, delusional disorder, and shared psychotic disorder. In a still further aspect, the schizophrenia is selected from catastrophic schizophrenia, catatonic schizophrenia, paranoid schizophrenia, residual schizophrenia, disorganized schizophrenia, and undifferentiated schizophrenia. In a yet further aspect, the disorder is selected from schizoid personality disorder, schizotypal personality disorder, and paranoid personality disorder.

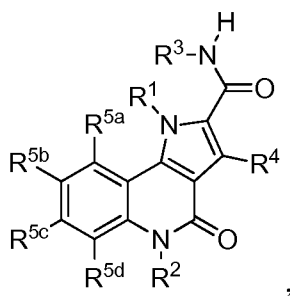
[00367] In a further aspect, the disorder is a cognitive disorder. In a still further aspect, the cognitive disorder is selected from amnesia, dementia, delirium, amnestic disorder, substance-induced persisting delirium, dementia due to HIV disease, dementia due to Huntington's disease, dementia due to Parkinson's disease, Parkinsonian-ALS demential complex, dementia of the Alzheimer's type, age-related cognitive decline, and mild cognitive impairment.

[00368] In a further aspect, disorder is selected from conduct disorder, disruptive behavior disorder, psychotic episodes of anxiety, anxiety associated with psychosis, psychotic mood disorders such as severe major depressive disorder; mood disorders associated with psychotic disorders, acute mania, depression associated with bipolar disorder, mood disorders associated with schizophrenia, behavioral manifestations of mental retardation, conduct disorder, autistic disorder; movement disorders, Tourette's syndrome, akinetic-rigid syndrome, movement disorders associated with Parkinson's disease, tardive dyskinesia, drug induced and neurodegeneration based dyskinesias, attention deficit hyperactivity disorder, cognitive disorders, dementias, and memory disorders.

[00369] It is understood that the disclosed uses can be employed in connection with the disclosed compounds, methods, compositions, and kits. In a further aspect, the invention relates to the use of a disclosed compound or a disclosed product in the manufacture of a medicament for the treatment of a disorder associated with muscarinic acetylcholine receptor dysfunction in a mammal. In a still further aspect, the muscarinic acetylcholine receptor dysfunction is mAChR M₄ dysfunction. In a yet further aspect, the disorder is a neurological and/or psychiatric disorder.

5. Kits

[00370] In one aspect, the invention relates to kits comprising at least one disclosed compound or at least one product of a disclosed method and at least one agent known to have M₁ receptor agonist activity. Also disclosed are kits comprising at least one compound having a structure represented by a formula:



wherein R¹ is selected from hydrogen, C1-C8 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, and Cy¹; wherein Cy¹ is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy¹ is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein R² is selected from hydrogen, C1-C8 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, and Cy²; wherein Cy² is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy² is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein R³ is selected from C1-C8 alkyl, Cy³, and Ar¹; wherein Ar¹ is phenyl substituted with 0-3 substituents independently selected from halogen,

cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar¹ is monocyclic heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy³ is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy³ is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein R⁴ is selected from hydrogen, halogen, hydroxyl, cyano, amino, C1-C8 alkyl, C1-C6 alkoxy, C1-C6 alkylamino, C1-C6 dialkylamino, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, Cy⁴, and Ar²; wherein Ar² is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar² is heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy⁴ is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy⁴ is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein each of R^{5a}, R^{5b}, R^{5c}, and R^{5d} is independently selected from hydrogen, halogen, hydroxyl, cyano, amino, CONR⁶R⁷, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 alkylamino, C1-C6 dialkylamino, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, Cy⁵, and Ar³, wherein Ar³ is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar³ is heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy⁵ is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy⁵ is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein each of R⁶ and R⁷ is independently selected from hydrogen, C1-C6 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl,

aryl and heteroaryl; or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof, and one or more of:

- a. at least one agent known to increase mAChR M₄ activity;
- b. at least one agent known to decrease mAChR M₄ activity;
- c. at least one agent known to treat a disorder associated with cholinergic activity;
- d. instructions for treating a disorder associated with cholinergic activity;
- e. instructions for treating a disorder associated with M₄ receptor activity; or
- f. instructions for administering the compound in connection with cognitive or behavioral therapy.

[00371] In a further aspect, the kit comprises a disclosed compound or a product of a disclosed method.

[00372] In a further aspect, the at least one compound and the at least one agent are co-formulated. In a still further aspect, the at least one compound and the at least one agent are co-packaged.

[00373] The kits can also comprise compounds and/or products co-packaged, co-formulated, and/or co-delivered with other components. For example, a drug manufacturer, a drug reseller, a physician, a compounding shop, or a pharmacist can provide a kit comprising a disclosed compound and/or product and another component for delivery to a patient.

[00374] It is contemplated that the disclosed kits can be used in connection with the disclosed methods of making, the disclosed methods of using, and/or the disclosed compositions.

6. NON-MEDICAL USES

[00375] Also provided are the uses of the disclosed compounds and products as pharmacological tools in the development and standardization of in vitro and in vivo test systems for the evaluation of the effects of modulators of mAChR M₄ related activity in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents of mAChR M₄.

F. EXPERIMENTAL

[00376] The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how the compounds, compositions, articles, devices and/or methods claimed herein are made and evaluated, and are intended to be purely exemplary of the invention and are not intended to limit the scope of what the inventors regard as their invention. Efforts have been made to ensure accuracy with respect to numbers (e.g., amounts, temperature, etc.), but some errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, temperature is in °C or is at ambient temperature, and pressure is at or near atmospheric.

[00377] Several methods for preparing the compounds of this invention are illustrated in the following Examples. Starting materials and the requisite intermediates are in some cases commercially available, or can be prepared according to literature procedures or as illustrated herein.

[00378] The following exemplary compounds of the invention were synthesized. The Examples are provided herein to illustrate the invention, and should not be construed as limiting the invention in any way. The Examples are typically depicted in free base form, according to the IUPAC naming convention.

1. GENERAL METHODS

[00379] ¹H NMR spectra were recorded either on a Bruker DPX-400 or on a Bruker AV-500 spectrometer with standard pulse sequences, operating at 400 MHz and 500 MHz respectively. Chemical shifts (δ) are reported in parts per million (ppm) downfield from tetramethylsilane (TMS), which was used as internal standard. Coupling constants (J-values) are expressed in Hz units.

[00380] Microwave assisted reactions were performed in a single-mode reactor: EmrysTM Optimizer microwave reactor (Personal Chemistry A.B., currently Biotage).

[00381] Flash column chromatography was performed using ready-to-connect cartridges from: (a) ISCO, on irregular silica gel, particle size 15-40 μ m (normal layer disposable flash columns) on a Companion system from ISCO, Inc.; or, (b) Merck, on irregular silica gel, particle size 15-40 μ m (normal layer disposable flash columns) on an SPOT or LAFLASH system from Armen Instrument.

[00382] Analytical HPLC was performed on an HP1100 with UV detection at 214 and 254 nm along with ELSD detection and low resolution mass spectra using an Agilent 1200 series 6130 mass spectrometer.

2. LC-MS METHODS

[00383] The UPLC (Ultra Performance Liquid Chromatography) measurement was performed using an Acquity UPLC (Waters) system comprising a sampler organizer, a binary pump with degasser, a four column's oven, a diode-array detector (DAD) and a column as specified below. Column flow was used without split to the MS detector. The MS detector was configured with an ESCI dual ionization source (electrospray combined with atmospheric pressure chemical ionization). Nitrogen was used as the nebulizer gas. The source temperature was maintained at 140 °C. Data acquisition was performed with MassLynx-Openlynx software. [M+H]⁺, means the protonated mass of the free base of the compound and where indicated R_t means retention time (in minutes).

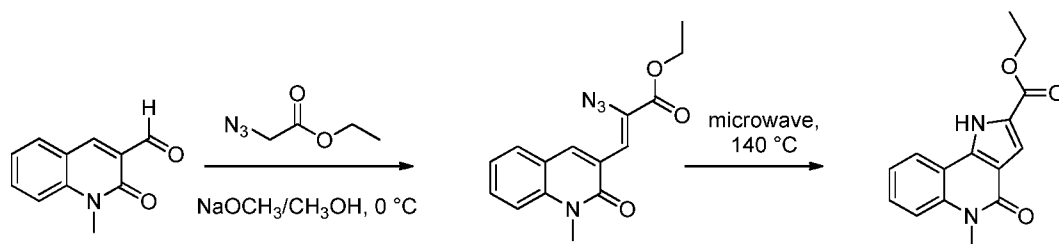
[00384] In the LC-MS analysis, reversed phase UPLC was carried out on a BEH-C18 column (1.7 µm, 2.1 x 50 mm) from Waters, with a flow rate of 1.0 mL/min, at 50 °C without split to the MS detector. The gradient conditions used are: 95 % A (0.5 g/l ammonium acetate solution + 5 % acetonitrile), 5 % B (acetonitrile), to 40 % A, 60 % B in 3.8 minutes, to 5 % A, 95 % B in 4.6 minutes, kept till 5.0 minutes. Injection volume was 2.0 µl. Low-resolution mass spectra (single quadrupole, SQD detector) were acquired by scanning from 100 to 1000 in 0.1 seconds using an inter-channel delay of 0.08 second. The capillary needle voltage was 3 kV. The cone voltage was 25 V for positive ionization mode and 30 V for negative ionization mode.

3. GENERAL SYNTHETIC METHODS

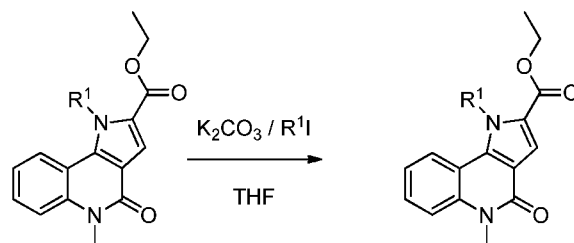
[00385] The general schemes described below were used to synthesize the compounds shown in Table 1.

[00386] **General Scheme 1.** To the reaction mixture of 1-methyl-2-oxo-1,2-dihydroquinoline-3-carbaldehyde and ethyl 2-azidoacetate (1:1 molar ratio) in CH₃OH was added NaOCH₃ (1 M in CH₃OH; about 1-3 equivalents of base added) at 0 °C. The reaction mixture was stirred at room temperature for 2 h, then poured into crushed ice and left for 1 h at 4 °C. The product was obtained by filtration and dried under vacuum. The ethyl 2-azido-3-

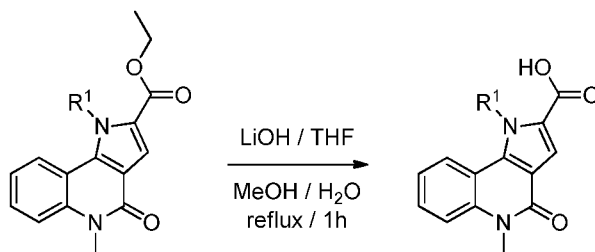
(2-oxo-1,2-dihydroquinolin-3-yl)acrylate was dissolved in 1,2-dichlorobenzene then reaction mixture was irradiated in microwave at 140 °C for 20 min. The reaction mixture was cooled to room temperature then filtered to afford a solid product (ethyl 5-methyl-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxylate). The generalized reaction scheme is given below.



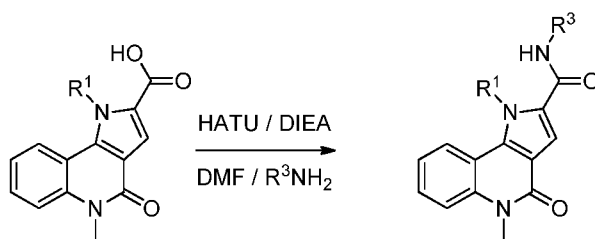
[00387] General Scheme 2. To a suspension of ester (about 0.1 M; prepared using General Scheme 1 described above) in DMF was added potassium carbonate (about 1-3 equivalent weights) and either iodomethane or iodoethane (about 1-2 equivalents) as required for the desired final product shown in Table 1. After 12 h at room temperature, water and ethyl acetate were added and the mixture was filtered through Celite. The ethyl acetate layer was separated, washed with water and saturated brine solution, dried over Na_2SO_4 and concentrated under vacuum to give an orange powder. The material was used without further purification. The generalized reaction scheme is given below, with R^1 either methyl or ethyl as required to provide the product shown in Table 1.



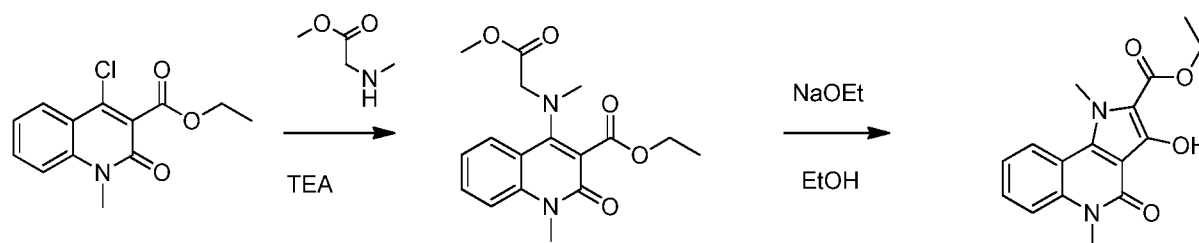
[00388] General Scheme 3. To a suspension of ester (about 0.1 M; prepared using General Scheme 2 described above) in THF/ CH_3OH (3:1) was added a solution of LiOH (about 10 equivalents) in water. The mixture was heated to reflux for 1h. The pH was adjusted to 2-3 with 2N HCl . The solid was filtered and dried under vacuum. The material was used without purification in the next reaction step. The generalized reaction scheme is given below.



[00389] General Scheme 4. A mixture of the carboxylic acid (about 0.1 M; prepared using General Scheme 3 described above), HATU (about 1.2 equivalents), DIEA (about 1-3 equivalents) and DMF was stirred at room temperature for about 10 min before the addition of the amine (about 1.2 equivalents). After about 15 min, water (10 mL) was added, the mixture was stirred for 10 min and filtered to give the desired compound as a yellow solid. The solid was dried in a vacuum oven for about 10 h. The generalized reaction scheme is given below, with R^3 as required to provide the product shown in Table 1.

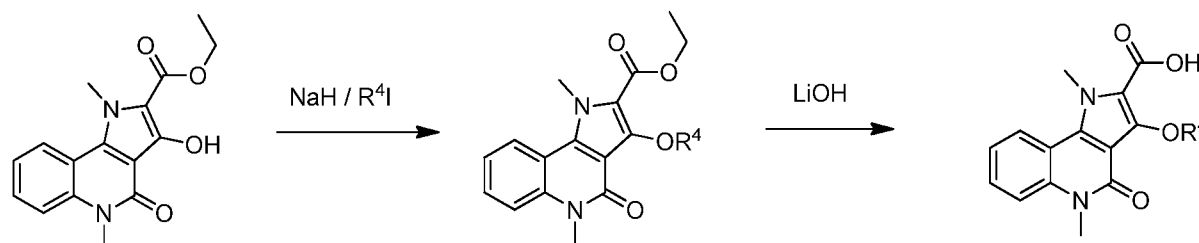


[00390] General Scheme 5. A solution of ethyl 4-chloro-1-methyl-2-oxo-1,2-dihydroquinoline-3-carboxylate (1.0 g, 3.77mmol), methyl 2-(methylamino)acetate (1.05 g, 7.54 mmol), TEA (1.07 mL, 7.9 mmol) in ethanol (10 mL) was stirred for about 18 h at room temperature. The mixture was poured onto ice and then extracted with ethyl acetate. The organic phase was extracted with 1N HCl, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford crude ethyl 4-((2-methoxy-2-oxoethyl)(methyl)amino)-1-methyl-2-oxo-1,2-dihydroquinoline-3-carboxylate. The crude material was dissolved in ethanol (25 mL) and treated with sodium ethoxide (21% in denatured ethanol; 1.17 mL, 3.14 mmol). The resulting mixture was heated at about 55 °C for about 18 h. The mixture was cooled and poured onto ice, and the resulting solution was acidified with 1 N HCl to pH of about 7. The resulting solid material was recovered by filtration, washed with water, and then dried to afford ethyl 3-hydroxy-1,5-dimethyl-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxylate. ^1H NMR (DMSO- d_6) δ 9.0 (m, 1H), 8.3 (m, 1H, $J = 8.3$ Hz), 7.6 (m, 2H), 7.3 (m, 1H), 4.3 (q, 2H), 4.2 (s, 3H), 3.8 (s, 3H), 1.3 (t, 3H, $J = 5.5$ Hz). The generalized reaction scheme is given below.

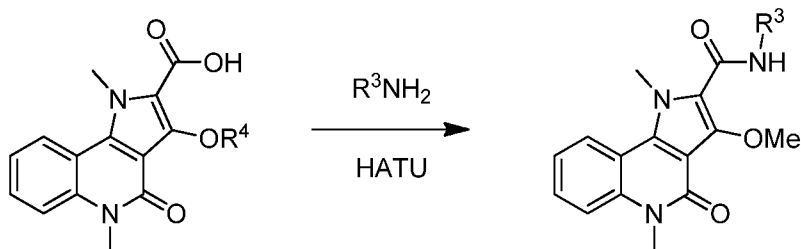


[00391] General Scheme 6. The following reaction is described in terms of preparation of 3-methoxy-1,5-dimethyl-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxylic acid, such that in the general scheme below, R^4 is methyl. However, reactants other than MeI can be used in the reaction to provide alternative alkoxy ($-OR^4$) derivatives as required. Briefly, ethyl 3-hydroxy-1,5-dimethyl-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxylate (prepared as described above in General Procedure 5; 0.25 g, 0.8 mmol), DBU (0.13 mL, 0.91 mmol) and iodomethane (0.1 mL) were dissolved in DMF (5 mL) and stirred at room temperature for about 18 h. The solution was then poured onto ice and the resulting solid recovered by filtration. The solid was washed with water and dried to afford ethyl 3-methoxy-1,5-dimethyl-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxylate. ^1H NMR (DMSO- d_6) δ 8.3 (d, 1H, $J=11$ Hz), 7.6 (m, 2H), 7.3 (m, 1H), 4.3 (q, 2H $J=7.8$ Hz), 4.2 (s, 3H), 3.9 (s, 3H), 3.6 (s, 3H), 1.3 (t, 3H, $J=9.8$ Hz). The crude material (120 mg, 0.38 mmol) was dissolved in THF (5 mL) and treated with aqueous LiOH (3.2 mg, 0.76 mmol in 1 mL water). The mixture was stirred at room temperature for about 72 h. LiOH (5 mg, 0.2 mmol) was added to the solution and then heated to reflux for one hour. The solution was cooled and the solvent removed under reduced pressure. The mixture was diluted with water, extracted with ethyl acetate, and then acidified with the addition of 1 N HCl. The resulting solid material collected by filtration, washed with water and dried under vacuum to afford 3-methoxy-1,5-dimethyl-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxylic acid.

[00392] The generalized reaction scheme is given below, with R^4 as required to provide the product shown in Table 1.



[00393] General Scheme 7. The following reaction is described in terms of preparation of 3-methoxy-1,5-dimethyl-N-(oxetan-3-yl)-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide, such that in the general scheme below R^3 is oxetanyl. However, reactants other than oxetan-3-amine can be used in the reaction to provide alternative amide derivatives ($-NHR^3$) as required. Briefly, A solution of 3-methoxy-1,5-dimethyl-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxylic acid (34 mg, 0.12 mmol) in DMF (1 mL) was treated with DIEA (0.15 mL, 0.87 mmol) and HATU (140 mg, 0.36 mmol). The resulting solution was stirred for 15 min and then treated with oxetan-3-amine (11 mg, 0.14 mmol). The mixture was stirred at room temperature for about 18 h and then poured onto 15 mL of ice. The resulting solid was washed with water and dried under vacuum to afford 3-methoxy-1,5-dimethyl-N-(oxetan-3-yl)-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide. LC=98% @ 254 nm, RT=0.91 min, MS=342(m+1); ; ^1H NMR (DMSO- d_6) δ 8.6 (d, 1H, $J=6.6$ Hz), 8.3(d, 1H, $J=8.1$ Hz), 7.6 (m, 2H), 7.3 (m, 1H), 5.0(m, 1H), 4.7 (t, 2H, $J=7.0$ Hz), 4.6 (t, 2H, $J=6.9$ Hz), 4.2(s, 3H), 4.0 (s, 3H), 3.7 (s, 3H); HRMS calculated for $C_{18}H_{20}N_3O_4$ (M+H) $^+$ m/z : 342.1454, measured: 342.1452. The generalized reaction scheme is given below, with R^3 as required to provide the product shown in Table 1.



4. SYNTHESIS OF SUBSTITUTED 1H-PYRROLO[3,2-c]QUINOLIN-4(5H)-ONE ANALOGS

[00394] Representative substituted 1H-pyrrolo[3,2-c]quinolin-4(5H)-one analogs were synthesized using the general procedures described above. Compounds that were synthesized are given below with LC-MS data and activity (Table 1). Compounds 1-10 were prepared with >98% purity and Compounds 11-21 was prepared with >95% purity. Activity for the representative compounds in Table 1 was determined in the mAChR M_4 cell-based functional assay as described below and the EC_{50} is shown in Table 2.

Table 1.

No.	Structure	Name	Rt (min) (LC-MS)	M+H
1		N-cyclopentyl-1-ethyl-5-methyl-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide	1.12	338
2		1-ethyl-5-methyl-N-(oxetan-3-yl)-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide	0.92	326
3		1-ethyl-N-(4-methoxybenzyl)-5-methyl-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide	1.14	390
4		N-cyclopentyl-1,5-dimethyl-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide	0.75	324
5		N-cyclobutyl-1,5-dimethyl-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide	0.75	310
6		1,5-dimethyl-4-oxo-N-(tetrahydrofuran-3-yl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide	0.67	326
7		N-(4-methoxybenzyl)-1,5-dimethyl-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide	0.64	376

No.	Structure	Name	Rt (min) (LC-MS)	M+H
8		N-(4-chlorobenzyl)-1,5-dimethyl-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide	0.81	380
9		N-cyclopropyl-1,5-dimethyl-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide	1.20	296
10		1,5-dimethyl-N-(6-methylpyridin-3-yl)-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide	0.54	347
11		1,5-dimethyl-N-(oxetan-3-yl)-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide	0.64	310
12		1,5-dimethyl-4-oxo-N-(2-(piperidin-1-yl)ethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide	---	367
13		1,5-dimethyl-N-(2-(1-methylpyrrolidin-2-yl)ethyl)-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide	---	367
14		3-methoxy-1,5-dimethyl-4-oxo-N-(tetrahydrofuran-3-yl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide	---	356

No.	Structure	Name	Rt (min) (LC-MS)	M+H
15		3-methoxy-1,5-dimethyl-4-oxo-N-(pyridin-4-ylmethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide	---	377
16		3-methoxy-1,5-dimethyl-N-(oxetan-3-yl)-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide	---	342
17		1-isobutyl-5-methyl-N-(oxetan-3-yl)-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide	---	354
18		3-methoxy-1,5,8-trimethyl-4-oxo-N-(pyridin-3-ylmethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide	---	391
19		3-methoxy-1,5,8-trimethyl-N-(3-methyloxetan-3-yl)-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide	---	370
20		3-methoxy-1,5,8-trimethyl-N-(oxetan-3-yl)-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide	---	356
21		3-methoxy-1,5,8-trimethyl-4-oxo-N-(pyridin-4-ylmethyl)-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide	---	391

[00395] NMR data for compound 11 given in Table 1 (1,5-dimethyl-N-(oxetan-3-yl)-4-oxo-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-2-carboxamide) was as follows: ¹H-NMR (400 MHz, DMSO-d₆) δ 9.17 (d, *J* = 6.5 Hz, 1H), 8.37 (d, *J* = 8.3 Hz, 1H), 7.62 (m, 2H), 7.51 (s, 1H), 7.36 (dt, *J* = 8.2, 1.3 Hz, 1H), 5.01 (m, 1H), 4.78 (t, *J* = 6.9 Hz, 2H), 4.62 (t, *J* = 6.5 Hz, 2H), 4.38 (s, 3H), 3.70 (s, 3H); LC-MS: 310 [M+H], *R*_t 0.64 min.

5. CELL LINES EXPRESSING MUSCARINIC ACETYLCHOLINE RECEPTORS

[00396] Chinese hamster ovary (CHO-K1) cells stably expressing rat (r)M₁ were purchased from the American Type Culture Collection and cultured according to their indicated protocol. CHO cells stably expressing human (h)M₂, hM₃, and hM₅ were described previously (Levey AI, et al., (1991) J Neurosci 11:3218 –3226.); hM₁ and hM₄ cDNAs were purchased from Missouri S&T cDNA Resource; rM₄ cDNA was provided by T. I. Bonner (National Institutes of Health, Bethesda, MD). rM₂ and rM₃ were cloned from a rat brain cDNA library and sequence verified. hM₁, rM₂, rM₃, hM₄, and rM₄ cDNAs were used to stably transfect CHO-K1 cells purchased from the American Type Culture Collection using Lipofectamine2000. To make stable rM₂, hM₂, hM₄, and rM₄ cell lines for use in calcium mobilization assays, these cells also were stably transfected with a chimeric G-protein (G_{qi5}) (provided by B.R. Conklin, University of California, San Francisco) using Lipofectamine 2000. rM₁, hM₁, rM₃, hM₃, rM₅, and hM₅ cells were grown in Ham's F-12 medium containing 10% heat-inactivated fetal bovine serum (FBS), 20mM HEPES, and 50μg/mL G418 sulfate. rM₂-G_{qi5}, hM₂-G_{qi5}, and hM₄-G_{qi5} cells were grown in the same medium also containing 500 μg/mL Hygromycin B. Stable rM₄-G_{qi5} cells were grown in DMEM containing 10% heat-inactivated FBS, 20 mM HEPES, 400 μg/mL G418 sulfate, and 500 μg/mL Hygromycin B.

6. CELL-BASED FUNCTIONAL ASSAY OF MUSCARINIC ACETYLCHOLINE RECEPTOR ACTIVITY

[00397] For high throughput measurement of agonist-evoked increases in intracellular calcium, CHO-K1 cells stably expressing the target muscarinic receptor were plated in growth medium lacking G418 and hygromycin at 15,000 cells/20 μL/well in Greiner 384-well black-walled, tissue culture (TC)-treated, clear-bottom plates (VWR). Cells were incubated overnight at 37 °C and 5% CO₂. The next day, cells were washed using an ELX 405 (BioTek) with four washes (80μL) of assay buffer then aspirated to 20μL. Next, 20μL of 16μM Fluo-4/acetoxymethyl ester (Invitrogen, Carlsbad, CA) prepared as a 2.3 mM stock in DMSO and

mixed in a 1:1 ratio with 10% (w/v) Pluronic F-127 and diluted in assay buffer was added to the wells and the cell plates were incubated for 50 min at 37 °C and 5% CO₂. Dye was removed by washing with the ELX 405 (four 80µL washes of assay buffer) then aspirated to 20µL. Compound master plates were formatted in an 11 point CRC format (1:3 dilutions) in 100% DMSO with a starting concentration of 10mM using the BRAVO liquid handler (Agilent). Test compound CRCs were then transferred to daughter plates (240nL) using the Echo acoustic plate reformatter (Labcyte, Sunnyvale, CA) and then diluted into assay buffer (40µL) to a 2× stock using a Thermo Fisher Combi (Thermo Fisher Scientific, Waltham, MA).

[00398] Calcium flux was measured using the Functional Drug Screening System (FDSS) 6000 (Hamamatsu Corporation, Tokyo, Japan) as an increase in the fluorescent static ratio. Compounds were applied to cells (20µL, 2X) using the automated system of the FDSS 6000 at 4 s into the 300 s protocol and the data were collected at 1 Hz. At 144 s into the 300s protocol, 10 µL of an EC₂₀ concentration of the muscarinic receptor agonist acetylcholine was added (5X), followed by the addition of 12 µL an EC₈₀ concentration of acetylcholine at the 230 s time point (5X). Agonist activity was analyzed as a concentration-dependent increase in calcium mobilization upon compound addition. Positive allosteric modulator activity was analyzed as a concentration-dependent increase in the EC₂₀ acetylcholine response. Antagonist activity was analyzed as a concentration-dependent decrease in the EC₈₀ acetylcholine response. Concentration-response curves were generated using a four-parameter logistical equation in XLfit curve fitting software (IDBS, Bridgewater, NJ) for Excel (Microsoft, Redmond, WA) or Prism (GraphPad Software, Inc., San Diego, CA).

[00399] The above described assay was also operated in a second mode where an appropriate fixed concentration of the present compounds were added to the cells after establishment of a fluorescence baseline for about 3 seconds, and the response in cells was measured. 140 s later the appropriate concentration of agonist was added and readings taken for an additional 106 s. Data were reduced as described above and the EC₅₀ values for the agonist in the presence of test compound were determined by nonlinear curve fitting. A decrease in the EC₅₀ value of the agonist with increasing concentrations of the present compounds (a leftward shift of the agonist concentration-response curve) is an indication of the degree of muscarinic positive allosteric modulation at a given concentration of the present compound. An increase in the EC₅₀ value of the agonist with increasing concentrations of the present compounds (a

rightward shift of the agonist concentration response curve) is an indication of the degree of muscarinic antagonism at a given concentration of the present compound. The second mode also indicates whether the present compounds also affect the maximum response of the muscarinic receptor to agonists.

7. ACTIVITY OF COMPOUNDS IN CELL-BASED ASSAYS

[00400] Substituted 1*H*-pyrrolo[3,2-*c*]quinolin-4(5*H*)-one analogs were synthesized as described above. Activity (EC_{50} and E_{max}) was determined in the mAChR M_4 cell-based functional assay as described above and the data are shown in Table 2. The compound number corresponds to the compound numbers used in Table 1.

TABLE 2.

No.	EC_{50} (μ M)	E_{max} (%)*	No.	EC_{50} (μ M)	E_{max} (%)*
1	1.34	53	12	>10	0
2	0.96	72	13	>10	0
3	> 10	0	14	0.99	54
4	2.6	79	15	1.20	51
5	1.01	67	16	1.70	67
6	2.75	71	17	3.50	18
7	0.52	33	18	>10	0
8	>10	0	19	0.85	42
9	1.52	78	20	1.20	49
10	>10	0	21	1.00	44
11	1.02	86			

* %ACh maximum at 30 μ M.

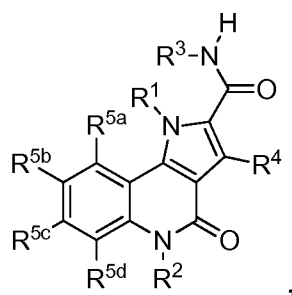
[00401] For compounds showing low potency (as indicated by a lack of a plateau in the concentration response curve) but greater than a 20% increase in ACh response, a potency of > 10 μ M ($pEC_{50} < 5$) is estimated.

[00402] The selectivity of Compounds 1, 5, 6 and 11 for mAChR M₄ compared to mAChR M₁, M₂, M₃ and M₅ was determined using the cell-based functional assay described below. The EC₅₀ for each of mAChR M₁, M₂, M₃ and M₅ was greater than at least 30 μ M for these four compounds (i.e., there was no receptor response up to a concentration of about 30 μ M, the upper limit of compound used in the assay).

8. PROPHETIC *IN VIVO* EFFECTS

[00403] Generally clinically relevant antipsychotic agents (both typical and atypical) display efficacy in preclinical behavior challenge models. *In vivo* effects of the disclosed compounds described in the preceding examples and in the specification are expected to be shown in various animal behavioural challenge models known to the skilled person, such as amphetamine-induced or phencyclidine (PCP)-induced hyperlocomotion, and other models, such as NMDA receptor antagonist MK-801-induced locomotor activity. These models are typically conducted in rodent, such as rat or mouse, but may be conducted in other animal species as is convenient to the study goals. Compounds, products, and compositions disclosed herein are expected to show *in vivo* effects in various animal behavioural challenge models known to the skilled person, such as amphetamine-induced or phencyclidine (PCP)-induced hyperlocomotion in rodent, and other models, such as NMDA receptor antagonist MK-801-induced locomotor activity. These models are typically conducted in rodent, such as rat or mouse, but may be conducted in other animal species as is convenient to the study goals.

[00404] For example, compounds having a structure represented by a formula:



wherein R¹ is selected from hydrogen, C1-C8 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, and Cy¹; wherein Cy¹ is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy¹ is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl,

C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein R^2 is selected from hydrogen, C1-C8 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, and Cy^2 ; wherein Cy^2 is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy^2 is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein R^3 is selected from C1-C8 alkyl, Cy^3 , and Ar^1 ; wherein Ar^1 is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar^1 is monocyclic heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy^3 is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy^3 is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein R^4 is selected from hydrogen, halogen, hydroxyl, cyano, amino, C1-C8 alkyl, C1-C6 alkoxy, C1-C6 alkylamino, C1-C6 dialkylamino, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, Cy^4 , and Ar^2 ; wherein Ar^2 is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar^2 is heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy^4 is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy^4 is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein each of R^{5a} , R^{5b} , R^{5c} , and R^{5d} is independently selected from hydrogen, halogen, hydroxyl, cyano, amino, $CONR^6R^7$, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 alkylamino, C1-C6 dialkylamino, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, Cy^5 , and Ar^3 , wherein Ar^3 is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl,

C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar³ is heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy⁵ is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy⁵ is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein each of R⁶ and R⁷ is independently selected from hydrogen, C1-C6 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, aryl and heteroaryl; or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof. are expected to show such *in vivo* effects.

[00405] One suitable method to assess the anti-psychotic effect of the disclosed compounds will be described herein, i.e. the amphetamine-induced hyperlocomotor activity assay. Other models known to one skilled in the art as described above can also be used to determine the anti-psychotic, cognitive, or neuropathic pharmacological effects of the disclosed compounds.

[00406] The amphetamine-induced hyperlocomotor activity studies are conducted using male Sprague-Dawley rats (Harlan Sprague-Dawley, Inc., Indianapolis, IN) weighing 270 to 300 g. Subject animals are housed in pairs in a large colony room under a 12-h light/12-h dark cycle (lights on at 6:00 AM) with food and water provided ad libitum. Test sessions are performed between 6:00 AM and 6:00 PM. Dose groups consisted of 8 to 16 rats per dose group. Doses of test compound are injected in a 1.0 ml/kg volume. Each test compound is prepared in a suitable vehicle formulation, e.g. the test compound can be dissolved in 10% Tween 80 and double deionized water with the pH adjusted to approximately 7.0 using 1 N NaOH.

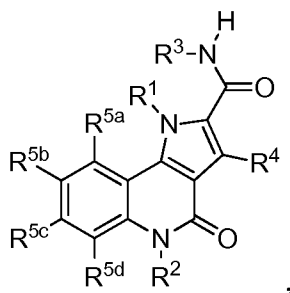
[00407] The studies are conducted using a SmartFrame Open Field System (Kinder Scientific., San Diego, CA) equipped with 32 horizontal (x- and y-axes) infrared photobeams located 1 cm above the floor of the chamber. Changes in ambulation or locomotor activity were measured as the number of total photobeam breaks, expressed in 5-min intervals, and were recorded with a Pentium I computer equipped with the Motor Monitor System software (Kinder Scientific).

[00408] Rats are placed in the open-field chambers for a 30-min habituation interval (data not shown), followed by a pretreatment for 30 minutes with vehicle or a suitable dose of test compound administered by i.p. injection or alternatively by oral gavage dose. Suitable doses for use in this study are from about 1 mg/kg to about 100 mg/kg. Next, all rats receive an injection of 1 mg/kg s.c. amphetamine, and locomotor activity is measured for an additional 60 min. Data are analyzed by a one-way ANOVA with comparison with the vehicle + amphetamine control group using Dunnett's test. Calculations are performed using JMP version 5.1.2 (SAS Institute Inc., Cary, NC) statistical software.

[00409] The effects of a test compound on motor performance are evaluated using a rotorod (Columbus Instruments, Columbus, OH). All rats are given an initial training trial of 120 s, followed by two additional training trials of 85 s, approximately 10 min apart, using a rotorod (7.5 cm in diameter) rotating at a constant speed of 20 revolutions/min. After initial training trials, a baseline trial of 85 s is conducted, and any rats that did not reach the 85-s criteria were excluded from the study. Rats are then pretreated for 30 min i.p. or oral gavage, as appropriate, with vehicle or dose of test compound, e.g. about 30, 50, or 100 mg/kg, and then the time each animal remains on the rotorod is recorded; animals not falling off of the rotorod are given a maximal score of 85 s. Data are analyzed by a one-way ANOVA, with comparison to the vehicle control group using Dunnett's test. Calculations are performed using JMP version 5.1.2 (SAS Institute Inc.) statistical software.

9. PROPHETIC PHARMACEUTICAL COMPOSITION EXAMPLES

[00410] "Active ingredient" as used throughout these examples, relates to one or more compounds having a structure represented by a formula:



wherein R^1 is selected from hydrogen, C1-C8 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, and Cy^1 ; wherein Cy^1 is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6

polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy¹ is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein R² is selected from hydrogen, C1-C8 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, and Cy²; wherein Cy² is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy² is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein R³ is selected from C1-C8 alkyl, Cy³, and Ar¹; wherein Ar¹ is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar¹ is monocyclic heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy³ is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy³ is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein R⁴ is selected from hydrogen, halogen, hydroxyl, cyano, amino, C1-C8 alkyl, C1-C6 alkoxy, C1-C6 alkylamino, C1-C6 dialkylamino, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, Cy⁴, and Ar²; wherein Ar² is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar² is heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy⁴ is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy⁴ is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein each of R^{5a}, R^{5b}, R^{5c}, and R^{5d} is independently selected from hydrogen, halogen, hydroxyl, cyano, amino, CONR⁶R⁷, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 alkylamino, C1-C6

dialkylamino, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, Cy⁵, and Ar³, wherein Ar³ is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar³ is heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; wherein Cy⁵ is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy⁵ is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; wherein each of R⁶ and R⁷ is independently selected from hydrogen, C1-C6 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, aryl and heteroaryl; or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof. The following examples of the formulation of the compounds of the present invention in tablets, suspension, injectables and ointments are prophetic. Typical examples of recipes for the formulation of the invention are as given below.

a. TABLETS

[00411] A tablet can be prepared as follows:

Component	Amount
Active ingredient	5 to 50 mg
Di-calcium phosphate	20 mg
Lactose	30 mg
Talcum	10 mg
Magnesium stearate	5
Potato starch	add to make total weight 200 mg

[00412] In this Example, active ingredient can be replaced with the same amount of any of the compounds according to the present invention, in particular by the same amount of any of the exemplified compounds.

b. SUSPENSION

[00413] An aqueous suspension is prepared for oral administration so that each 1 milliliter contains 1 to 5 mg of one of the active compounds, 50 mg of sodium carboxymethyl cellulose, 1 mg of sodium benzoate, 500 mg of sorbitol and water ad 1 ml.

c. INJECTABLE

[00414] A parenteral composition is prepared by stirring 1.5 % by weight of active ingredient of the invention in 10% by volume propylene glycol in water.

d. OINTMENT

[00415] An ointment can be prepared as follows:

Component	Amount
Active ingredient	5 to 1000 mg
Stearyl alcohol	3 g
Lanoline	5 g
White petroleum	15 g
Water	add to make total weight 100 g

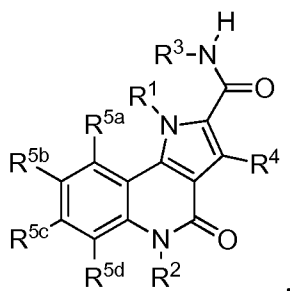
[00416] In this Example, active ingredient can be replaced with the same amount of any of the compounds according to the present invention, in particular by the same amount of any of the exemplified compounds.

[00417] It will be apparent to those skilled in the art that various modifications and variations can be made in the present invention without departing from the scope or spirit of the invention. Other aspects of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims.

CLAIMS

What is claimed is:

1. A compound having a structure represented by a formula:



wherein R^1 is selected from hydrogen, C2-C8 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, and Cy^1 ;

wherein Cy^1 is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy^1 is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino;

wherein R^2 is selected from hydrogen, C1-C8 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, and Cy^2 ;

wherein Cy^2 is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy^2 is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino;

wherein R^3 is selected from C1-C8 alkyl, $-(C1-C8 \text{ alkyl})-Cy^3$, $-(C1-C8 \text{ alkyl})-Ar^1$, Cy^3 , and Ar^1 ;

wherein Ar^1 is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar^1 is heteroaryl substituted with 0-3 substituents independently

selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl;

wherein Cy^3 is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy^3 is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino;

wherein R^4 is selected from hydrogen, halogen, hydroxyl, cyano, amino, C1-C8 alkyl, C1-C6 alkoxy, C1-C6 alkylamino, C1-C6 dialkylamino, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, Cy^4 , and Ar^2 ;

wherein Ar^2 is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar^2 is heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl;

wherein Cy^4 is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy^4 is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino;

wherein each of R^{5a} , R^{5b} , R^{5c} , and R^{5d} is independently selected from hydrogen, halogen, hydroxyl, cyano, amino, $CONR^6R^7$, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 alkylamino, C1-C6 dialkylamino, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, Cy^5 , and Ar^3 ,

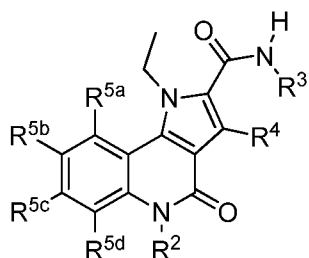
wherein Ar^3 is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar^3 is heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl;

wherein Cy^5 is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy^5 is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino;

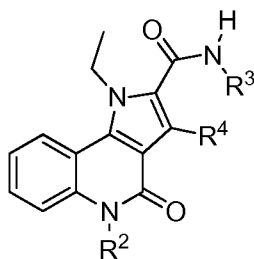
wherein each of R^6 and R^7 is independently selected from hydrogen, C1-C6 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, aryl and heteroaryl;

or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof.

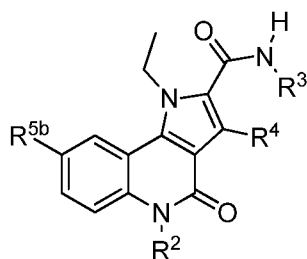
2. The compound of claim 1, wherein Ar^1 is unsubstituted.
3. The compound of claim 1, wherein Ar^1 is phenyl.
4. The compound of claim 1, wherein Ar^1 is heteroaryl.
5. The compound of claim 1, wherein Cy^3 is unsubstituted.
6. The compound of claim 1, wherein Cy^3 is C3-C8 cycloalkyl.
7. The compound of claim 1, wherein Cy^3 is C3-C8 heterocycloalkyl with 1-3 substituents independently selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino.
8. The compound of claim 1, wherein Cy^3 is aziridinyl, oxiranyl, thiiranyl, azetidiny, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, oxazolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperazinyl, hexahydropyrimidinyl, hexahydropyridazinyl, morpholinyl, oxazinanyl, azepanyl, oxepanyl, thiepanyl, azocanyl, oxocanyl, or thiocanyl.
9. The compound of claim 1, having a structure represented by a formula:



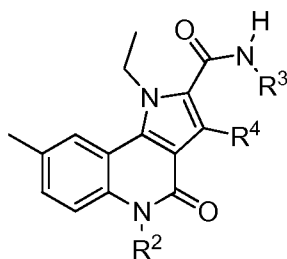
10. The compound of claim 1, having a structure represented by a formula:



11. The compound of claim 1, having a structure represented by a formula:

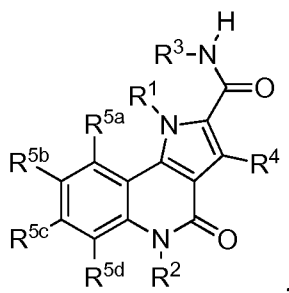


12. The compound of claim 1, having a structure represented by a formula:



13. A pharmaceutical composition comprising a therapeutically effective amount of a compound of any of claims 1-12 and a pharmaceutically acceptable carrier.

14. A method for the treatment of a neurological and/or psychiatric disorder associated with muscarinic acetylcholine receptor dysfunction in a mammal comprising the step of administering to the mammal a therapeutically effective amount of at least one compound having a structure represented by a formula:



wherein R¹ is selected from hydrogen, C1-C8 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, and Cy¹;

wherein Cy¹ is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy¹ is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino;

wherein R² is selected from hydrogen, C1-C8 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, and Cy²;

wherein Cy² is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy² is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino;

wherein R³ is selected from C1-C8 alkyl, Cy³, and Ar¹;

wherein Ar¹ is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar¹ is monocyclic heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl;

wherein Cy³ is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy³ is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino;

wherein R⁴ is selected from hydrogen, halogen, hydroxyl, cyano, amino, C1-C8 alkyl, C1-C6 alkoxy, C1-C6 alkylamino, C1-C6 dialkylamino, C1-C6 haloalkyl, C1-C6

polyhaloalkyl, Cy⁴, and Ar²;

wherein Ar² is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar² is heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl;

wherein Cy⁴ is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy⁴ is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino;

wherein each of R^{5a}, R^{5b}, R^{5c}, and R^{5d} is independently selected from hydrogen, halogen, hydroxyl, cyano, amino, CONR⁶R⁷, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 alkylamino, C1-C6 dialkylamino, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, Cy⁵, and Ar³,

wherein Ar³ is phenyl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl; or Ar³ is heteroaryl substituted with 0-3 substituents independently selected from halogen, cyano, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, and C1-C6 polyhaloalkyl;

wherein Cy⁵ is C3-C8 cycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino; or Cy⁵ is C3-C8 heterocycloalkyl substituted with 0-3 substituents selected from halogen, hydroxyl, cyano, amino, C1-C6 alkyl, C1-C6 alkoxy, C1-C6 haloalkyl, or C1-C6 polyhaloalkyl, C1-C6 alkylamino, and C1-C6 dialkylamino;

wherein each of R⁶ and R⁷ is independently selected from hydrogen, C1-C6 alkyl, C1-C6 haloalkyl, C1-C6 polyhaloalkyl, aryl and heteroaryl;

or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof.

15. The method of claim 14, wherein the mammal is a human.

16. The method of claim 14, wherein the mammal has been diagnosed with a need for treatment of the disorder prior to the administering step.
17. The method of claim 14, further comprising the step of identifying a mammal in need of treatment of the disorder.
18. The method of claim 14, wherein the disorder is a neurological and/or psychiatric disorder associated with mAChR M₄ dysfunction.
19. The method of claim 14, wherein the disorder is selected from a Alzheimer's disease, Parkinson's disease, Huntington's disease, a neurological disorder, a pain disorder and a psychotic disorder.
20. The method of claim 19, wherein the psychotic disorder is selected from schizophrenia, psychotic disorder NOS, brief psychotic disorder, schizophreniform disorder, schizoaffective disorder, delusional disorder, shared psychotic disorder, catastrophic schizophrenia, postpartum psychosis, psychotic depression, psychotic break, tardive psychosis, myxedematous psychosis, occupational psychosis, menstrual psychosis, secondary psychotic disorder, bipolar I disorder with psychotic features, and substance-induced psychotic disorder.

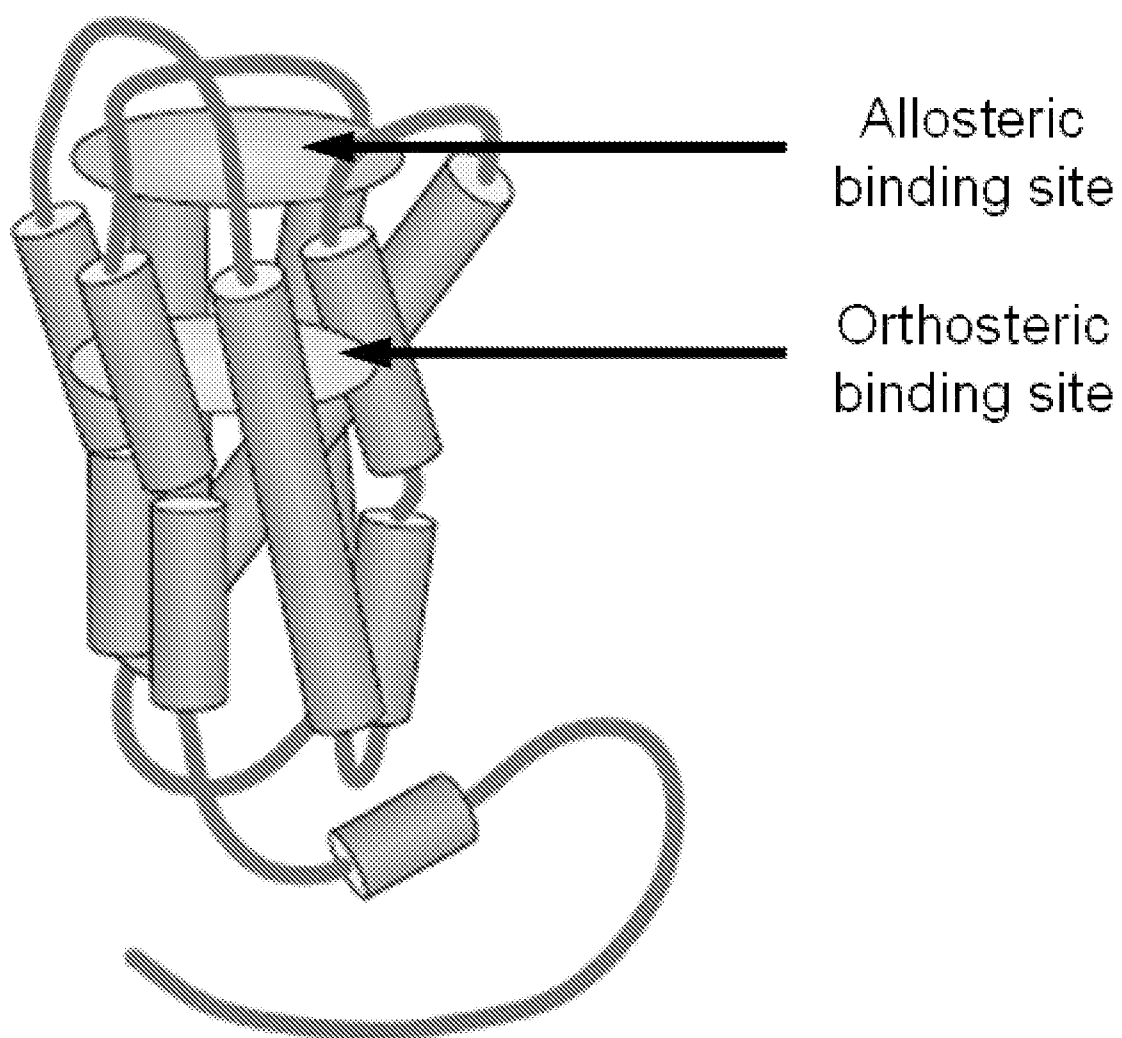


Figure 1

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 12/36925

A. CLASSIFICATION OF SUBJECT MATTER IPC(8) - A01N 43/38, 43/42; A61K 31/40, 31/44 (2012.01) USPC - 514/291; 514/411 According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC(8): A01N 43/38, 43/42; A61K 31/40, 31/44 (2012.01) USPC: 514/291; 514/411 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched IPC(8): A61K 31/497, 43/38; C07D 413/00, 401/00, 455/04 (2012.01) USPC: 514/253.03, 410; 544/126, 361; 546/80 Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) PubWEST, SureChem, PubChem, GoogleScholar, ScienceDirect muscarinic acetylcholine receptor dysfunction, mAChR M4, nicotinic acetylcholine receptors, Alzheimer's disease, Parkinson's disease, Huntington's disease, a neurological disorder, a pain disorder, a psychotic disorder, 4,5-dihydro-1H-pyrrolo[2,3-f]quinoline, AChE inhibitor		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ----- 14-20	US 2009/0227561 A1 (FUJI et al.) 10 September 2009 (10.09.2009) para[0035] compound I' is subpara[5], para[0043], para[0048], para[0049], para[0066], para[0298], para[1667]	1-13 ----- 14-20
Y	WO/2006/024517 A1 (BENTLEY et al.) 9 March 2006 (09.03.2006) page 3, ln 15- page 3, ln 25, page 13, ln 25-30, page 29, ln 5-10, page 29, ln 20-25, page 33, ln 24, page 34, ln 10-15, page 44, 25-30, page 91, ln 20-25	14- 20
Y	Yohannes et al. Deconstructing cytosine: The syntheses of (+)-cyfusine and (+)-cyclopropylcyfusine, fused ring analogs of cytosine. Bioorganic & Medicinal Chemistry Letters, 2008, Vol.18, pp 2316-2319. page 2316, Fig. 1, page 2318, Fig. 3 and Scheme 2	14- 20
A	US 7,501,438 B2 (RONSHEIM et al.) 10 March 2009 (10.03.2009) col 1, ln 50-65, col 2, ln 5-10, col 8, ln 50-65, col 16, ln 15-20	1-20
☐ Further documents are listed in the continuation of Box C. ☐		
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 18 July 2012 (18.07.2012)		Date of mailing of the international search report 07 AUG 2012
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201		Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774