

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
17 November 2011 (17.11.2011)

PCT

(10) International Publication Number
WO 2011/143444 A2

(51) International Patent Classification:

C07D 471/10 (2006.01) **A61K 31/438** (2006.01)
C07D 211/52 (2006.01) **A61K 31/445** (2006.01)
C07D 211/58 (2006.01) **A61P 25/00** (2006.01)
C07D 401/04 (2006.01)

(21) International Application Number:

PCT/US2011/036272

(22) International Filing Date:

12 May 2011 (12.05.2011)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

61/334,802 14 May 2010 (14.05.2010) US

(71) Applicants (for all designated States except US): **PRESIDENT AND FELLOWS OF HARVARD COLLEGE** [US/US]; 17 Quincy Street, Cambridge, MA 02138 (US). **SHANGHAI INSTITUTE OF ORGANIC CHEMISTRY** [CN/CN]; Chinese Academy Of Sciences, 345 Lingling Road, Shanghai, 200032 (CN).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **YUAN, Junying** [CN/CN]; 22 Fairlee Road, Newton, MA 02468U (US). **YUAN, Chengye** [CN/CN]; 393 Zaojiaband Road, Building 2, Room 6b, Shanghai, 200032 (CN). **CHEN, Gang** [CN/CN]; No. 6, Group 6, Weijiatang Village, Xinzhuang Town, Changshu County, Suzhou City, Jiangsu Province, 215552 (CN). **XIA, Hong-guang** [CN/CN]; 538 Xiao Mu

Qiao Road, Building 1, Room 1102, Shanghai, 200032 (CN).

(74) Agents: **SMITH, DeAnn, F.** et al.; Patent Group, Foley Hoag LLP, 155 Seaport Boulevard, Boston, MA 02210-2600 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— without international search report and to be republished upon receipt of that report (Rule 48.2(g))

(54) Title: DIPHENYLBUTYPIPERIDINE AUTOPHAGY INDUCERS

(57) Abstract: Autophagy inducing compounds, methods of their preparation and use, and kits containing said compounds are disclosed herein.



WO 2011/143444 A2

Diphenylbutylpiperidine Autophagy Inducers

RELATED APPLICATIONS

This application claims the benefit of priority to United States Provisional Patent
5 Application serial number 61/334,802, filed May 14, 2010, the contents of which are
hereby incorporated by reference.

GOVERNMENT SUPPORT

This invention was made with U.S. Government support under National Institutes of
Health Grant Nos. AG012859 and AG027916. The government has certain rights in the
10 invention.

BACKGROUND

Autophagy is a lysosome-dependent process whereby proteins or damaged
organelles within a cell are degraded (Klionsky, DJ., and Emr, S. D. (2000). Science. 290:
1717-21). During this process, an autophagosome having a double membrane encloses the
15 component of the cell to be degraded, the autophagosome then fuses with a lysosome which
carries out the function of degradation, which results in the recycling of amino acids. This
system of degradation and recycling has been conserved to a high degree by evolution and
is of key importance in development, growth, aging, illness, death, and other biological
processes. Together, the autophagy-lysosome pathway and the ubiquitin-proteasome
20 pathway form the two principal degradation systems of eukaryotic cells; however, the two
pathways have different functions in the cell. Autophagy is primarily involved in the
degradation of long-lived proteins, protein aggregates, and cellular organelles and other
cellular components. Thus, in addition to taking part in various important physiological
processes, autophagy appears to have great significance for the treatment of various
25 diseases caused by misfolded protein aggregates in specific tissues and cells.

Under ordinary circumstances, autophagy is maintained at a very low basal level
within a cell, but when confronted with starvation or other stress conditions, the level of
autophagy is rapidly up-regulated. Seventeen autophagy-related genes (abbreviated "ATG"
genes) have already been confirmed through the analysis of yeast genes (Klionsky, D.J.,
30 Cregg, J.M., Dunn, W.A., et al. (2003) Dev Cell. 5: 539-45). The proteins encoded by these
seventeen genes can be divided into four types, comprising several kinds of serine-
threonine kinase (Atg1, Atg13, Atg17) that are involved in regulating upstream autophagy
signals (such as mTOR); proteins that are involved in regulating lipase/kinase signal

compounds during the initiation stage of the autophagy process (Atg6, Atg14, Vps34, and Vps15); two types of new ubiquitin-like conjugation systems (the Atg8 and Atg12 systems) that are involved in autophagosome formation; and proteins (Atg2, Atg9, and Atg18) that assist ATG molecules bound to an autophagosome during the autophagosome formation process to dissociate from the mature autophagosome. The vast majority of ATG genes in yeast have homologues in high-level eukaryotic biological cells (Mizushima, N. and Klionsky, DJ. (2007) *Annu Rev Nutr.* 27: 19-40). For example, in mammalian cells, the inhibition of autophagy under non-starvation conditions is mediated by target of rapamycin (mTOR) kinase (Lum, J.J., DeBerardinis, R.J., and Thompson, CB. (2005) *Nat Rev Mol Cell Biol.* 6: 439-48). By contrast, C3 PI3 kinase, the homologue of yeast Vps34 protein in mammalian cells, is required for the initiation of autophagy.

Autophagy can be induced by many factors both from within and outside the cell, including starvation, nutrient deprivation, bacterial infection, damage to cellular organelles, and protein mismatching. At present, only the mechanism underlying starvation-induced autophagy is understood with relative clarity. However, at the same time, it has been demonstrated that a number of intracellular signaling molecules, such as AMPK, mTOR, C3PI3K, and MAPK, are also involved in autophagy regulation.

Autophagy has been proposed to play complex roles in development and treatment of cancers. Activation of autophagy may promote tumor cell survival under metabolic stress and function as a tumor suppression mechanism by preventing necrotic cell death and subsequent inflammation which favors tumor growth (White, E. (2008). *Autophagic cell death unraveled: Pharmacological inhibition of apoptosis and autophagy enables necrosis.* *Autophagy* 4, 399-401). On the other hand, inhibition of autophagy may lead to genome instability through unknown mechanisms which might explain the increased frequency of beclin 1 heterozygosity in multiple lines of cancers (Qu, X., Yu, J., Bhagat, G., Furuya, N., Hibshoosh, H., Troxel, A., Rosen, J., Eskelinen, E.L., Mizushima, N., Ohsumi, Y., et al. (2003). Promotion of tumorigenesis by heterozygous disruption of the beclin 1 autophagy gene. *J Clin Invest* 112, 1809-1820; and Yue, Z., Jin, S., Yang, C., Levine, A.J., and Heintz, N. (2003). Beclin 1, an autophagy gene essential for early embryonic development, is a haploinsufficient tumor suppressor. *Proc Natl Acad Sci U S A* 100, 15077-15082) and decreased expression of autophagy-related proteins in malignant epithelial ovarian cancer (Shen, Y., Li, D.D., Wang, L.L., Deng, R., and Zhu, X.F. (2008). Decreased expression of

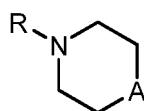
autophagy-related proteins in malignant epithelial ovarian cancer. *Autophagy* 4, 1067-8). Thus, chronic suppression of autophagy may stimulate tumorigenesis.

The proposed role of autophagy in anticancer therapy is opposite to that during tumorigenesis. Once a tumor is formed, acute inhibition of autophagy might be beneficial for the therapeutic goal by promoting radiosensitization and chemosensitization (Amaravadi, R.K., and Thompson, C.B. (2007). The roles of therapy-induced autophagy and necrosis in cancer treatment. *Clin Cancer Res* 13, 7271-7279). In an animal model of cancer therapy, inhibition of therapy-induced autophagy either with shRNA against a key autophagy gene ATG5 or with anti-malarial drug chloroquine enhanced cell death and tumor regression of Myc-driven tumors in which either activated p53 or alkylating chemotherapy was used to drive tumor cell death (Amaravadi, R.K., Yu, D., Lum, J.J., Bui, T., Christophorou, M.A., Evan, G.I., Thomas-Tikhonenko, A., and Thompson, C.B. (2007). Autophagy inhibition enhances therapy-induced apoptosis in a Myc-induced model of lymphoma. *J Clin Invest* 117, 326-336). Chloroquine causes a dose-dependent accumulation of large autophagic vesicles and enhances alkylating therapy-induced cell death to a similar degree as knockdown of ATG5. In another example, resistance to TRAIL was found to be reversed by a common approach of targeting specific components of autophagic process, such as Beclin1 or Vps34, for inhibition (Hou, W., Han, J., Lu, C., Goldstein, L.A., and Rabinowich, H. (2008). Enhancement of tumor-TRAIL susceptibility by modulation of autophagy. *Autophagy* 4, 940-943). In the case of chronic myelogenous leukemia (CML), inhibition of autophagy by chloroquine markedly enhanced death of a CML cell line, K562, induced by imatinib. Furthermore, imatinib-resistant cell lines, BaF3/T315I and BaF3/E255K, can be induced to die by co-treatment with imatinib and chloroquine. Thus, inhibition of autophagy sensitizes tumor cells to imatinib-induced cell death. The block of autophagy has been proposed to be a new strategy for the treatment of CML (Mishima, Y., Terui, Y., Taniyama, A., Kuniyoshi, R., Takizawa, T., Kimura, S., Ozawa, K., and Hatake, K. (2008). Autophagy and autophagic cell death are next targets for elimination of the resistance to tyrosine kinase inhibitors. *Cancer Sci* 99, 2200-8). These studies suggest that autophagy can promote resistance to DNA-damaging therapy. Since chloroquine is a blocker of lysosomes, it will be interesting to see if specific inhibitors targeting different steps of autophagy process also have the same effect in enhancing the effect of chemotherapies in cell-based assays and animal models.

In addition, autophagy has also been shown to play an important role in mediating cellular damage induced by acute pancreatitis. Autodigestion of the pancreas by its own prematurely activated digestive proteases is thought to be an important event in the onset of acute pancreatitis. A conditional knockout mouse that lacks the autophagy-related (Atg) gene Atg5 in the pancreatic acinar cells has shown significantly reduced severity of acute pancreatitis induced by cerulein (Ohmuraya, M., and Yamamura, K. (2008). Autophagy and acute pancreatitis: a novel autophagy theory for trypsinogen activation. *Autophagy* 4, 1060-1062). Thus autophagy exerts a detrimental effect in pancreatic acinar cells by activation of trypsinogen to trypsin. Inhibitors of autophagy may provide important new therapeutics for acute pancreatitis.

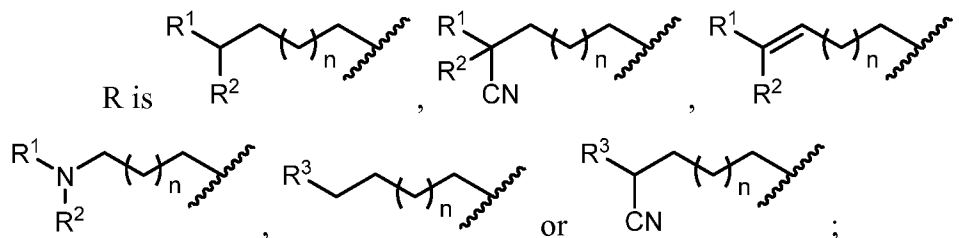
SUMMARY

One aspect of the present invention relates to an autophagy inducing compound represented by compounds of formula I:



I

or pharmaceutically acceptable salt, solvate, hydrate, prodrug, chemically-protected form, enantiomer or stereoisomer thereof; wherein, independently for each occurrence,

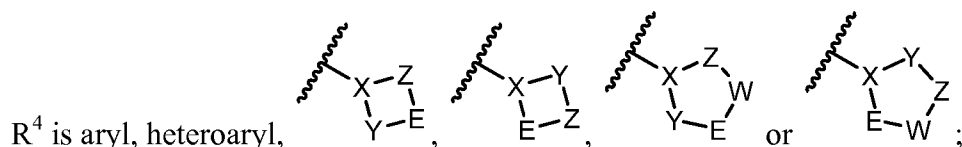
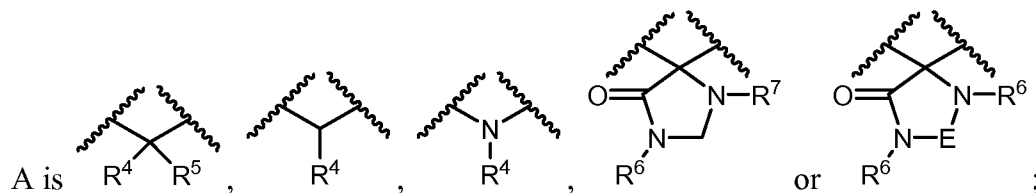


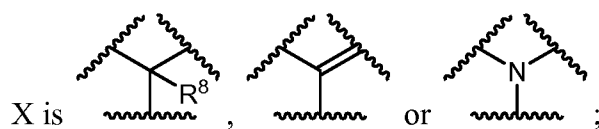
R^1 is aryl or heteroaryl;

R^2 is aryl or heteroaryl;

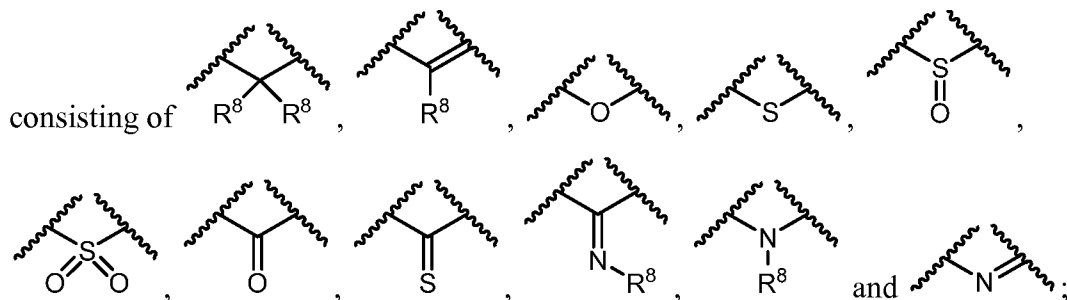
R^3 is fluorenyl or fluorenyl-like;

n is 0, 1, 2 or 3;





W, Y and Z are independently for each occurrence selected from the group



5 E is arylene or heteroarylene;

R⁵ is hydroxy, alkyloxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, silyloxy, alkylcarbonyloxy, arylcarbonyloxy, heteroarylcarbonyloxy, aralkylcarbonyloxy, heteroaralkylcarbonyloxy, cyano, amino or amido;

R⁶ is hydrogen or alkyl;

10 R⁷ is aryl or heteroaryl; and

R⁸ is hydrogen or alkyl.

Another aspect of the invention relates to a pharmaceutical composition comprising an autophagy inducing compound in an amount effective for treating an autophagy associated disease, wherein the compound is selected from at least one compound of

15 formula I, or a pharmaceutically acceptable salt, solvate, hydrate, prodrug, chemically-protected form, enantiomer or stereoisomer thereof. In certain embodiments, the composition further comprises a pharmaceutically acceptable carrier. In certain embodiments, the autophagy associated disease is a disease caused by misfolded protein aggregates. In certain embodiments, the disease caused by misfolded protein aggregates is

20 selected from the group consisting of: Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease, spinocerebellar ataxia, oculopharyngeal muscular dystrophy, prion diseases, fatal familial insomnia, alpha-1 antitrypsin deficiency, dentatorubral pallidoluysian atrophy, frontal temporal dementia, progressive supranuclear palsy, x-linked spinobulbar muscular atrophy, and neuronal intranuclear hyaline inclusion

25 disease. In certain embodiments, the disease associated with misfolded protein aggregates is a chronic disease. In yet another embodiment of this aspect, the autophagy associated disease is cancer.

Another aspect of the present invention relates to a method of inducing autophagy in a cell, the method comprising contacting the cell with an autophagy inducing compound in an amount effective to induce autophagy in the cell. In certain embodiments, the autophagy inducing compound is selected from at least one compound of formula I, or a

5 pharmaceutically acceptable salt, solvate, hydrate, prodrug, chemically-protected form, enantiomer or stereoisomer thereof. In certain embodiments, the cell is present in a subject. In certain embodiments, the cell is present in an in vitro cell culture. In certain embodiments, the cell is contacted with an autophagy inducing compound at a concentration of about 0.1 μ M to about 15.0 μ M. In certain embodiments, the cell is
10 contacted with an autophagy inducing compound at a concentration of about 3.0 μ M to about 9.0 μ M. In certain embodiments, the cell is selected from the group consisting of neural cells, glial cells, such as astrocytes, oligodendrocytes, ependymal cells, Schwann cells, lymphatic cells, epithelial cells, endothelial cells, lymphocytes, cancer cells, and haematopoietic cells.

15 Another aspect of the invention relates to a method of treating an autophagy associated disease in a subject; the method includes administering to the subject an autophagy inducing compound in an amount effective to treat the disease, or a composition comprising the compound, thereby treating the disease in the subject. In certain embodiments, the autophagy associated disease is a disease caused by misfolded protein
20 aggregates. In certain embodiments, the disease caused by misfolded protein aggregates is selected from the group including: Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease, spinocerebellar ataxia, oculopharyngeal muscular dystrophy, prion diseases, fatal familial insomnia, alpha-1 antitrypsin deficiency, dentatorubral pallidoluysian atrophy, frontal temporal dementia, progressive supranuclear
25 palsy, x-linked spinobulbar muscular atrophy, and neuronal intranuclear hyaline inclusion disease. In certain embodiments, the disease associated with misfolded protein aggregates is a chronic disease. In yet another embodiment of this aspect, the autophagy associated disease is cancer. In certain embodiments, the autophagy inducing compound is selected from at least one compound of formula I and pharmaceutically acceptable salts thereof. In
30 certain embodiments, the autophagy inducing compound is administered at a concentration of about 0.1 μ M to about 15.0 μ M. In certain embodiment, the autophagy inducing compound is administered at a concentration of about 3.0 μ M to about 9.0 μ M.

Another aspect of the invention relates to a kit which includes: (i) a pharmaceutical composition comprising an autophagy inducing compound and (ii) instructions for administering the composition to a subject for the treatment of an autophagy associated disease. In certain embodiments, the autophagy inducing compound is selected from at least one compound of formula I and pharmaceutically acceptable salts thereof.

Additional aspects, embodiments, and advantages of the invention are discussed below in detail.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 depicts DPBPs autophagy regulators: Fluspirilene (**1**), Pimozide (**2**), Trifluoperazine (**3**) and Penfluridol (**4**).

Figure 2 depicts a synthetic route to compounds **36-41** and **45-54**. Reagents and conditions: (a) THF, Reflux; (b) EtOH, Con. HCl, Reflux; (c) CBr₄, Ph₃P, CH₂Cl₂, 0 °C-RT; (d) Pd/C, H₂, EtOH, RT; and (e) piperidines, NaCO₃, KI, CH₃CN, Reflux.

Figure 3 depicts a synthetic route to compounds **42-44** and **55-57**. Reagents and conditions: (a) Et₂O, Reflux; (b) MgBr₂, Et₂O, Reflux; (c) Pd/C, H₂, EtOH, RT; and (d) piperidines, NaCO₃, KI, CH₃CN, Reflux.

Figure 4 depicts a synthetic route to compounds **67-76**. Reagents and conditions: (a) THF, Reflux; (b) EtOAc, 3M HCl RT; and (c) diphenylbutyl bromide, NaCO₃, KI, CH₃CN, Reflux.

Figure 5 depicts a synthetic route to compounds **77-90**. Reagents and conditions: (a) acetyl chloride, CHCl₃, 0 °C-RT; and (b) Con. H₂SO₄, CH₃CN, RT.

Figures 6 to 11 depicts tables of EC₅₀ values for selected autophagy inducers.

Figure 12 depicts DPBP autophagy regulators: Pimozide (**2**), and DPBPs scaffolds, wherein the piperidines have 6,5-fused rings, P-1-56 and P-2-56, or 6,6-fused rings, P-1-66 and P-2-66 at their 4-position (wherein W, X, Y and Z are as defined herein).

Figures 13 and 14 depict tables of EC₅₀ values for selected autophagy inducers

Figures 15 and 16 depict a synthetic route to compounds **142-150**, **152**, **153**, **156-58**, **160** and **161**. Reagents and conditions: (a) NaH, DMF, 90 °C; (b) TFA, CH₂Cl₂, 0 °C-RT; (c) NaBH(OAc)₃, DCE, RT; (d) (Cl₃CO)₃CO, py., THF; (e) KOH, MeOH, Reflux; (f) Pd/C, H₂, EtOH, RT; (g) NaBH₃CN, AcOH; and (h) N-Boc piperidone, NaBH(OAc)₃, DCE, RT.

Figure 17 depicts a synthetic route to compounds **163-180**. Reagents and conditions: (a) PPA, 180 °C; (b) BH₃.THF; (c) N-Boc piperidone, NaBH(OAc)₃, DCE, RT; (d)TFA, CH₂Cl₂, 0 °C-RT; (e) DMF, 90 °C; and (f) DEAD, Ph₃P, THF.

Figures 18 and 19 depict tables of EC₅₀ values for selected P-1-56 autophagy inducers.

Figure 20 depicts a table of EC₅₀ values for selected P-2-56 autophagy inducers.

Figures 21 and 22 depict a synthetic route to compounds **218-223**. Reagents and conditions: (a) NaBH₃CN, BF₃.Et₂O; (b) N-Boc piperidone, NaBH(OAc)₃, DCE, RT; (c) TFA, CH₂Cl₂, 0 °C-RT; (d) TsOH, toluene; (e) LiAlH₄, dioxane; (f) CDI, CH₃CN, Reflux; (g) Pd(OH)₂/H₂, MeOH; (h) sulfamide, pyridine, Reflux; (i) HCOOH, Reflux; (j) NaNO₂, concd HCl; and (k) CS₂,EtOH, Reflux.

Figures 23 and 24 depict a synthetic route to compounds **224-233**. Reagents and conditions: (a) NaBH₄, NiCl₂, MeOH; (b) N-Boc piperidone, NaBH(OAc)₃, DCE, RT; (c) TFA, CH₂Cl₂, 0 °C-RT; (d) NaBH₄, MeOH; (e) CDI, CH₃CN, Reflux; (f) Pd(OH)₂/H₂, MeOH; (h) NaNO₂, concd HCl; (i) CH(OMe)₃, concd HCl, Reflux; (j) ClCO₂Et, Reflux; (k) KOH, EtOH, Reflux; (l) Pd-C, H₂, EtOH; (m) sulfamide, pyridine, Reflux; and (n) CS₂,EtOH, Reflux.

Figure 25 depicts a table of EC₅₀ values for selected P-1-66 autophagy inducers.

Figures 26 and 27 depict tables of EC₅₀ values for selected P-2-66 autophagy inducers.

Figure 28 depicts a table of EC₅₀ values for selected autophagy inducers.

Figure 29 depicts compounds **238** and **239** and their autophagy EC₅₀ values.

DETAILED DESCRIPTION

In certain embodiments, the invention relates to autophagy inducing compounds that are useful in treating or preventing autophagy associated diseases, e.g., diseases caused by misfolded protein aggregates. One aspect of the invention relates to diphenylbutylpiperidines which have autophagy inducing activity. Another aspect of the invention relates to an effective synthetic route to a diphenylbutyl bromide intermediate useful in the preparation of compounds of the invention. Another aspect of the invention relates to novel diphenylbutylpiperidines which have improved autophagy inducing activity when compared to known diphenylbutylpiperidines. For example, modification of compounds **1** and **4** resulted in up to about a 10-fold increase in autophagy inducing activity (e.g., compound **48**). Another aspect of the invention relates to compounds derived from

compound **2**, in which different 5,6- and 6,6-ring systems are substituted at the 4-position of piperidine ring, as shown in Figure 12 (Klionsky, D.J.; Emr, S.D. *Science*. **2000**, 290, 1717; and Levine B, Yuan J. *J Clin Invest*. **2005**, 115, 2679).

DEFINITIONS

5 The articles “a” and “an” are used herein to refer to one or to more than one (i.e., to at least one) of the grammatical object of the article. By way of example, “an element” means one element or more than one element.

 The phrase “and/or,” as used herein in the specification and in the claims, should be understood to mean “either or both” of the elements so conjoined, i.e., elements that are
10 conjunctively present in some cases and disjunctively present in other cases. Multiple elements listed with “and/or” should be construed in the same fashion, i.e., “one or more” of the elements so conjoined. Other elements may optionally be present other than the elements specifically identified by the “and/or” clause, whether related or unrelated to those elements specifically identified. Thus, as a non-limiting example, a reference to “A and/or
15 B”, when used in conjunction with open-ended language such as “comprising” can refer, in one embodiment, to A only (optionally including elements other than B); in another embodiment, to B only (optionally including elements other than A); in yet another embodiment, to both A and B (optionally including other elements); etc.

 As used herein in the specification and in the claims, “or” should be understood to
20 have the same meaning as “and/or” as defined above. For example, when separating items in a list, “or” or “and/or” shall be interpreted as being inclusive, i.e., the inclusion of at least one, but also including more than one, of a number or list of elements, and, optionally, additional unlisted items. Only terms clearly indicated to the contrary, such as “only one of” or “exactly one of,” or, when used in the claims, “consisting of,” will refer to the
25 inclusion of exactly one element of a number or list of elements. In general, the term “or” as used herein shall only be interpreted as indicating exclusive alternatives (i.e., “one or the other but not both”) when preceded by terms of exclusivity, such as “either,” “one of,” “only one of,” or “exactly one of.” “Consisting essentially of,” when used in the claims, shall have its ordinary meaning as used in the field of patent law.

30 As used herein in the specification and in the claims, the phrase “at least one,” in reference to a list of one or more elements, should be understood to mean at least one element selected from any one or more of the elements in the list of elements, but not necessarily including at least one of each and every element specifically listed within the

list of elements and not excluding any combinations of elements in the list of elements.

This definition also allows that elements may optionally be present other than the elements specifically identified within the list of elements to which the phrase “at least one” refers,

whether related or unrelated to those elements specifically identified. Thus, as a non-

5 limiting example, “at least one of A and B” (or, equivalently, “at least one of A or B,” or, equivalently “at least one of A and/or B”) can refer, in one embodiment, to at least one, optionally including more than one, A, with no B present (and optionally including elements other than B); in another embodiment, to at least one, optionally including more than one, B, with no A present (and optionally including elements other than A); in yet
10 another embodiment, to at least one, optionally including more than one, A, and at least one, optionally including more than one, B (and optionally including other elements); etc.

It should also be understood that, unless clearly indicated to the contrary, in any methods claimed herein that include more than one step or act, the order of the steps or acts of the method is not necessarily limited to the order in which the steps or acts of the method
15 are recited.

In the claims, as well as in the specification above, all transitional phrases such as “comprising,” “including,” “carrying,” “having,” “containing,” “involving,” “holding,” “composed of,” and the like are to be understood to be open-ended, i.e., to mean including but not limited to. Only the transitional phrases “consisting of” and “consisting essentially of” shall be closed or semi-closed transitional phrases, respectively, as set forth in the
20 United States Patent Office Manual of Patent Examining Procedures, Section 2111.03.

Numerous values and ranges are recited in connection with various embodiments of the present invention, e.g., amount of a compound of formula (I) or (II) present in a composition. It is to be understood that all values and ranges which fall between the values and ranges listed are intended to be encompassed by the present invention unless explicitly
25 stated otherwise. The term “about” as used herein in association with parameters, ranges and amounts, means that the parameter or amount is within + 1% of the stated parameter or amount.

The term “autophagy” refers to the catabolic process involving the degradation of a
30 cell's own components; such as, long lived proteins, protein aggregates, cellular organelles, cell membranes, organelle membranes, and other cellular components. The mechanism of autophagy may include: (i) the formation of a membrane around a targeted region of the cell, separating the contents from the rest of the cytoplasm, (ii) the fusion of the resultant

vesicle with a lysosome and the subsequent degradation of the vesicle contents. For example, the term autophagy may refer to one of the mechanisms by which a starving cell re-allocates nutrients from unnecessary processes to more essential processes. Also, for example, autophagy may inhibit the progression of some diseases and play a protective role against infection by intracellular pathogens.

As used herein, the term "compound" is intended to mean a substance made up of molecules that further consist of atoms. A compound generally refers to a chemical entity, whether in the solid, liquid or gaseous phase, and whether in a crude mixture or purified and isolated. Compounds encompass the chemical compound itself as well as, where applicable: amorphous and crystalline forms of the compound, including polymorphic forms, said forms in mixture or in isolation; free acid and free base forms of the compound; isomers of the compound, including geometric isomers, optical isomers, and tautomeric isomers, said optical isomers to include enantiomers and diastereomers, chiral isomers and non-chiral isomers, said optical isomers to include isolated optical isomers or mixtures of optical isomers including racemic and non-racemic mixtures; said geometric isomers to include transoid and cisoid forms, where an isomer may be in isolated form or in admixture with one or more other isomers; isotopes of the compound, including deuterium- and tritium-containing compounds, and including compounds containing radioisotopes, including therapeutically- and diagnostically-effective radioisotopes; multimeric forms of the compound, including dimeric, trimeric, etc. forms; salts of the compound, including acid addition salts and base addition salts, including organic counterions and inorganic counterions, and including zwitterionic forms, where if a compound is associated with two or more counterions, the two or more counterions may be the same or different; and solvates of the compound, including hemisolvates, monosolvates, disolvates, etc., including organic solvates and inorganic solvates, said inorganic solvates including hydrates; where if a compound is associated with two or more solvent molecules, the two or more solvent molecules may be the same or different

The term "autophagy inducing compound" refers to a compound that induces autophagy in a cell. The term autophagy inducing compound, as used herein, comprises the specific compounds disclosed herein.

The term "misfolded protein aggregates" refers to a mass of misfolded proteins, wherein said proteins have not adopted the appropriate three-dimensional structure, i.e.,

tertiary structure. For example, the misfolded proteins may have clustered together to form an assemblage of misfolded proteins.

The term "autophagy associated disease" includes a disease that can be treated by the induction of autophagy. Examples of such diseases include diseases caused by misfolded protein aggregates. The term "disease caused by misfolded protein aggregates" is intended to include any disease, disorder or condition associated with or caused by misfolded protein aggregates. For example, such diseases include Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease, spinocerebellar ataxia, oculopharyngeal muscular dystrophy, prion diseases, fatal familial insomnia, alpha-1 antitrypsin deficiency, dentatorubral pallidoluysian atrophy, frontal temporal dementia, progressive supranuclear palsy, x-linked spinobulbar muscular atrophy, and neuronal intranuclear hyaline inclusion disease. The term "autophagy associated disease" also includes cancer e.g., any cancer wherein the induction of autophagy would inhibit cell growth and division, reduce mutagenesis, remove mitochondria and other organelles damaged by reactive oxygen species or kill developing tumor cells. Autophagy associated diseases can be chronic diseases.

The term "chronic disease" refers to a persistent and lasting disease or medical condition, or one that has developed slowly.

The term "effective" amount refers to the amount of an autophagy inducing compound of the present invention required to treat or prevent an autophagy associated disease, e.g., a disease associated with misfolded protein aggregates. The effective amount of an autophagy inducing compound of the invention used to practice the invention for therapeutic or prophylactic treatment of autophagy associated diseases varies depending upon the manner of administration, the age, body weight, and general health of the subject. An effective amount of an autophagy inducing compound, as defined herein may vary according to factors such as the disease state, age, and weight of the subject, and the ability of the autophagy inducing compound to elicit a desired response in the subject. Dosage regimens may be adjusted to provide the optimum therapeutic response. An effective amount is also one in which any toxic or detrimental effects (e.g., side effects) of the autophagy inducing compound are outweighed by the therapeutically beneficial effects. A therapeutically effective amount of an autophagy inducing compound (i.e., an effective dosage) may range from about 0.001 to 30 mg/kg body weight, preferably about 0.01 to 25 mg/kg body weight, more preferably about 0.1 to 20 mg/kg body weight, and even more

preferably about 1 to 10 mg/kg, 2 to 9 mg/kg, 3 to 8 mg/kg, 4 to 7 mg/kg, or 5 to 6 mg/kg body weight. The skilled artisan will appreciate that certain factors may influence the dosage required to effectively treat a subject, including but not limited to the severity of the disease or disorder, previous treatments, the general health and/or age of the subject, and other diseases present. Moreover, treatment of a subject with a therapeutically effective amount of an autophagy inducing compound can include a single treatment or, preferably, can include a series of treatments. In one example, a subject is treated with an autophagy inducing compound in the range of between about 0.1 to 20 mg/kg body weight, one time per week for between about 1 to 10 weeks, preferably between 2 to 8 weeks, more preferably between about 3 to 7 weeks, and even more preferably for about 4, 5, or 6 weeks. It will also be appreciated that the effective dosage of an autophagy inducing compound used for treatment may increase or decrease over the course of a particular treatment.

The term "pharmaceutical composition" refers to a composition containing an autophagy inducing compound of the invention formulated with one or more pharmaceutical-grade excipients in a manner that conforms with the requirements of a governmental agency regulating the manufacture and sale of pharmaceuticals as part of a therapeutic regimen for the treatment or prevention of disease in a mammal (e.g., manufactured according to GMP regulations and suitable for administration to a human).

Pharmaceutical compositions can be formulated, for example, for oral administration in unit dosage form (e.g., a tablet, capsule, caplet, gelcap, or syrup); for topical administration (e.g., as a cream, gel, lotion, or ointment); for intravenous administration (e.g., as a sterile solution free of particulate emboli and in a solvent system suitable for intravenous use); or any other formulation described herein.

The term "pharmaceutically acceptable carrier" refers to any such carriers known to those skilled in the art to be suitable for the particular mode of administration. For example, the term "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like, that may be used as a media for a pharmaceutically acceptable substance. In addition, the active materials can also be mixed with other active materials that do not impair the desired action, or with materials that supplement the desired action, or have another action. The autophagy inducing compounds may be formulated as the sole

pharmaceutically active ingredient in the composition or may be combined with other active ingredients.

As used herein, the term "treating" refers to administering a pharmaceutical composition for prophylactic and/or therapeutic purposes. To "prevent disease" refers to prophylactic treatment of a subject who is not yet ill, but who is susceptible to, or otherwise at risk of, a particular disease. To "treat disease" or use for "therapeutic treatment" refers to administering treatment to a subject already suffering from a disease to improve or stabilize the subject's condition. Thus, in the claims and embodiments, treating is the administration to a subject either for therapeutic or prophylactic purposes.

The term "subject" includes humans, and non-human animals amenable to therapy, e.g., preferably mammals and animals susceptible to an autophagy associated disease, such as a disease associated with misfolded protein aggregates, including non-human primates, transgenic animals, mice, rats, dogs, cats, rabbits, pigs, chickens, sheep, horses, and cows. Preferably, the subject is a human subject

The definition of each expression, e.g., alkyl, m, n, and the like, when it occurs more than once in any structure, is intended to be independent of its definition elsewhere in the same structure.

It will be understood that "substitution" or "substituted with" includes 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 which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, or other reaction.

The term "substituted" is also 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, aromatic and nonaromatic substituents of organic compounds. Illustrative substituents include, for example, those described herein below. The permissible substituents may be one or more and the same or different for appropriate organic compounds. For purposes of this invention, the heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms. This invention is not intended to be limited in any manner by the permissible substituents of organic compounds.

The term "lower" when appended to any of the groups listed below indicates that the group contains less than seven carbons (i.e. six carbons or less). For example "lower alkyl" refers to an alkyl group containing 1-6 carbons, and "lower alkenyl" refers to an alkenyl group containing 2-6 carbons.

5 The term "saturated," as used herein, pertains to compounds and/or groups which do not have any carbon-carbon double bonds or carbon-carbon triple bonds.

The term "unsaturated," as used herein, pertains to compounds and/or groups which have at least one carbon-carbon double bond or carbon-carbon triple bond.

10 The term "aliphatic," as used herein, pertains to compounds and/or groups which are linear or branched, but not cyclic (also known as "acyclic" or "open-chain" groups).

The term "cyclic," as used herein, pertains to compounds and/or groups which have one ring, or two or more rings (e.g., spiro, fused, bridged).

15 The term "aromatic" refers to a planar or polycyclic structure characterized by a cyclically conjugated molecular moiety containing $4n+2$ electrons, wherein n is the absolute value of an integer. Aromatic molecules containing fused, or joined, rings also are referred to as bicyclic aromatic rings. For example, bicyclic aromatic rings containing heteroatoms in a hydrocarbon ring structure are referred to as bicyclic heteroaryl rings.

The term "hydrocarbon" as used herein refers to an organic compound consisting entirely of hydrogen and carbon.

20 For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 67th Ed., 1986-87, inside cover.

25 The term "heteroatom" as used herein is art-recognized and refers to an atom of any element other than carbon or hydrogen. Illustrative heteroatoms include boron, nitrogen, oxygen, phosphorus, sulfur and selenium.

The term "alkyl" means an aliphatic or cyclic hydrocarbon radical containing from 1 to 12 carbon atoms. Representative examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, 2-methylcyclopentyl, and 1-cyclohexylethyl.

30 The term "alkylene" is art-recognized, and as used herein pertains to a bidentate moiety obtained by removing two hydrogen atoms of an alkyl group, as defined above.

The term "alkenyl" as used herein means a straight or branched chain hydrocarbon containing from 2 to 10 carbons and containing at least one carbon-carbon double bond

formed by the removal of two hydrogens. Representative examples of alkenyl include, but are not limited to, ethenyl, 2-propenyl, 2-methyl-2-propenyl, 3-butenyl, 4-pentenyl, 5-hexenyl, 2-heptenyl, 2-methyl-1-heptenyl, and 3-decenyl.

The term "alkynyl" as used herein means a straight or branched chain hydrocarbon group containing from 2 to 10 carbon atoms and containing at least one carbon-carbon triple bond. Representative examples of alkynyl include, but are not limited, to acetylenyl, 1-propynyl, 2-propynyl, 3-butyne, 2-pentyne, and 1-butyne.

The term "carbocyclyl" as used herein means monocyclic or multicyclic (e.g., bicyclic, tricyclic, etc.) hydrocarbons containing from 3 to 12 carbon atoms that is completely saturated or has one or more unsaturated bonds, and for the avoidance of doubt, the degree of unsaturation does not result in an aromatic ring system (e.g. phenyl). Examples of carbocyclyl groups include 1-cyclopropyl, 1-cyclobutyl, 2-cyclopentyl, 1-cyclopentenyl, 3-cyclohexyl, 1-cyclohexenyl and 2-cyclopentenylmethyl.

The term "heterocyclyl", as used herein include non-aromatic, ring systems, including, but not limited to, monocyclic, bicyclic and tricyclic rings, which can be completely saturated or which can contain one or more units of unsaturation, for the avoidance of doubt, the degree of unsaturation does not result in an aromatic ring system, and have 3 to 12 atoms including at least one heteroatom, such as nitrogen, oxygen, or sulfur. For purposes of exemplification, which should not be construed as limiting the scope of this invention, the following are examples of heterocyclic rings: azepines, azetidiny, morpholinyl, oxopiperidinyl, oxopyrrolidinyl, piperazinyl, piperidinyl, pyrrolidinyl, quinclidinyl, thiomorpholinyl, tetrahydropyranyl and tetrahydrofuranyl. The heterocyclyl groups of the invention are substituted with 0, 1, 2, 3, 4 or 5 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, fluoroalkyl, hydroxy, alkoxy, alkylenoxy, alkynyloxy, carbocycloxy, heterocycloxy, haloalkoxy, fluoroalkoxy, sulfhydryl, alkylthio, haloalkylthio, fluoroalkylthio, alkyenylthio, alkynylthio, sulfonic acid, alkylsulfonyl, haloalkylsulfonyl, fluoralkylsulfonyl, alkenylsulfonyl, alkynylsulfonyl, alkoxysulfonyl, haloalkoxysulfonyl, fluoralkoxysulfonyl, alkenyloxysulfonyl, alkynyloxysulfonyl, aminosulfonyl, sulfinic acid, alkylsulfinyl, haloalkylsulfinyl, fluoralkylsulfinyl, alkenylsulfinyl, alkynylsulfinyl, alkoxysulfinyl, haloalkoxysulfinyl, fluoralkoxysulfinyl, alkenyloxysulfinyl, alkynyloxysulfinyl, aminosulfinyl, formyl, alkylcarbonyl, haloalkylcarbonyl, fluoroalkylcarbonyl, alkenylcarbonyl, alkynylcarbonyl, carboxy, alkoxycarbonyl, haloalkoxycarbonyl,

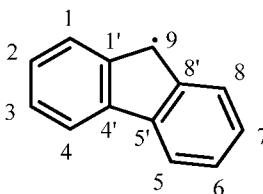
fluoroalkoxycarbonyl, alkenyloxycarbonyl, alkynyloxycarbonyl, alkylcarbonyloxy, haloalkylcarbonyloxy, fluoroalkylcarbonyloxy, alkenylcarbonyloxy, alkynylcarbonyloxy, alkylsulfonyloxy, haloalkylsulfonyloxy, fluroralkylsulfonyloxy, alkenylsulfonyloxy, alkynylsulfonyloxy, haloalkoxysulfonyloxy, fluroralkoxysulfonyloxy, alkenyloxysulfonyloxy, alkynyloxysulfonyloxy, alkylsulfinyloxy, haloalkylsulfinyloxy, fluroralkylsulfinyloxy, alkenylsulfinyloxy, alkynylsulfinyloxy, alkoxysulfinyloxy, haloalkoxysulfinyloxy, fluroralkoxysulfinyloxy, alkenyloxysulfinyloxy, alkynyloxysulfinyloxy, aminosulfinyloxy, amino, amido, aminosulfonyl, aminosulfinyl, cyano, nitro, azido, phosphinyl, phosphoryl, silyl, silyloxy, and any of said substituents bound to the heterocyclyl group through an alkylene moiety (e.g. methylene).

The term "aryl," as used herein means a phenyl group, naphthyl or anthracenyl group. The aryl groups of the present invention can be optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, fluoroalkyl, hydroxy, alkoxy, alkyenyloxy, alkynyloxy, carbocycloxy, heterocycloxy, haloalkoxy, fluoroalkyloxy, sulfhydryl, alkylthio, haloalkylthio, fluoroalkylthio, alkyenylthio, alkynylthio, sulfonic acid, alkylsulfonyl, haloalkylsulfonyl, fluroralkylsulfonyl, alkenylsulfonyl, alkynylsulfonyl, alkoxysulfonyl, haloalkoxysulfonyl, fluroralkoxysulfonyl, alkenyloxysulfonyl, alkynyloxysulfonyl, aminosulfonyl, sulfinic acid, alkylsulfinyl, haloalkylsulfinyl, fluroralkylsulfinyl, alkenylsulfinyl, alkynylsulfinyl, alkoxysulfinyl, haloalkoxysulfinyl, fluroralkoxysulfinyl, alkenyloxysulfinyl, alkynyloxysulfinyl, aminosulfinyl, formyl, alkylcarbonyl, haloalkylcarbonyl, fluoroalkylcarbonyl, alkenylcarbonyl, alkynylcarbonyl, carboxy, alkoxycarbonyl, haloalkoxycarbonyl, fluoroalkoxycarbonyl, alkenyloxycarbonyl, alkynyloxycarbonyl, alkylcarbonyloxy, haloalkylcarbonyloxy, fluoroalkylcarbonyloxy, alkenylcarbonyloxy, alkynylcarbonyloxy, alkylsulfonyloxy, haloalkylsulfonyloxy, fluroralkylsulfonyloxy, alkenylsulfonyloxy, alkynylsulfonyloxy, haloalkoxysulfonyloxy, fluroralkoxysulfonyloxy, alkenyloxysulfonyloxy, alkynyloxysulfonyloxy, alkylsulfinyloxy, haloalkylsulfinyloxy, fluroralkylsulfinyloxy, alkenylsulfinyloxy, alkynylsulfinyloxy, alkoxysulfinyloxy, haloalkoxysulfinyloxy, fluroralkoxysulfinyloxy, alkenyloxysulfinyloxy, alkynyloxysulfinyloxy, aminosulfinyloxy, amino, amido, aminosulfonyl, aminosulfinyl, cyano, nitro, azido, phosphinyl, phosphoryl, silyl, silyloxy, and any of said substituents bound to the aryl group through a methylene, ethylene or propylene moiety.

The term "arylene," is art-recognized, and as used herein pertains to a bidentate moiety obtained by removing two hydrogen atoms from adjacent carbons of an aryl ring, as defined above.

The term "arylalkyl" or "aralkyl" as used herein means an aryl group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of aralkyl include, but are not limited to, benzyl, 2-phenylethyl, 3-phenylpropyl, and 2-naphth-2-ylethyl.

The term "fluorenyl" as used herein refers to a radical having the chemical formula and numbering scheme indicated below:



10

In this numbering scheme, 9 indicates the bridgehead carbon atom. The remaining carbon atoms available to accept substituents are indicated by numbers 1-4 on one phenyl group of the ligand, and numbers 5-8 on the other phenyl group of the fluorenyl group. The fluorenyl groups of the invention are substituted with 0, 1, 2, 3, 4, 5, 6, 7 or 8 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, fluoroalkyl, hydroxy, alkoxy, alkyenyloxy, alkynyloxy, carbocycloxy, heterocycloxy, haloalkoxy, fluoroalkyloxy, sulfhydryl, alkylthio, haloalkylthio, fluoroalkylthio, alkyenylthio, alkynylthio, sulfonic acid, alkylsulfonyl, haloalkylsulfonyl, fluroralkylsulfonyl, alkenylsulfonyl, alkynylsulfonyl, alkoxy sulfonyl, haloalkoxy sulfonyl, fluroralkoxy sulfonyl, alkenyloxysulfonyl, alkynyloxysulfonyl, aminosulfonyl, sulfinic acid, alkylsulfinyl, haloalkylsulfinyl, fluroralkylsulfinyl, alkenylsulfinyl, alkynylsulfinyl, alkoxy sulfinyl, haloalkoxy sulfinyl, fluroralkoxy sulfinyl, alkenyloxysulfinyl, alkynyloxysulfinyl, aminosulfinyl, formyl, alkylcarbonyl, haloalkylcarbonyl, fluoroalkylcarbonyl, alkenylcarbonyl, alkynylcarbonyl, carboxy, alkoxy carbonyl, haloalkoxy carbonyl, fluoroalkoxy carbonyl, alkenyloxycarbonyl, alkynyloxycarbonyl, alkylcarbonyloxy, haloalkylcarbonyloxy, fluoroalkylcarbonyloxy, alkenylcarbonyloxy, alkynylcarbonyloxy, alkylsulfonyloxy, haloalkylsulfonyloxy, fluroralkylsulfonyloxy, alkenylsulfonyloxy, alkynylsulfonyloxy, haloalkoxy sulfonyloxy, fluroralkoxy sulfonyloxy, alkenyloxysulfonyloxy, alkynyloxysulfonyloxy, alkylsulfinyloxy, haloalkylsulfinyloxy, fluroralkylsulfinyloxy, alkenylsulfinyloxy, alkynylsulfinyloxy, alkoxy sulfinyloxy,

30

haloalkoxysulfinyloxy, fluroralkoxysulfinyloxy, alkenyloxysulfinyloxy, alkynyloxysulfinyloxy, aminosulfinyloxy, amino, amido, aminosulfonyl, aminosulfinyl, cyano, nitro, azido, phosphinyl, phosphoryl, silyl, silyloxy, and any of said substituents bound to the fluorenyl group through an alkylene moiety (e.g. methylene).

5 The term "fluorenyl-like" as used herein refers to a fluorenyl radical, as described above, wherein 0, 1, 2, 3 or 4 of the carbons, excluding the C-9 carbon, is/are replaced with a nitrogen; and/or the bond between the C-4' and C-5' carbons is replaced with -S-, -O-, -N(H)-, -CH₂- or -CH₂CH₂-. The fluorenyl-like groups of the invention are substituted, on the aromatic rings or on the atoms between C-4' and C-5', with 0, 1, 2, 3, 4, 5, 6, 7 or 8
10 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, fluoroalkyl, hydroxy, alkoxy, alkyenyloxy, alkynyloxy, carbocycloxy, heterocycloxy, haloalkoxy, fluoroalkyloxy, sulfhydryl, alkylthio, haloalkylthio, fluoroalkylthio, alkyenylthio, alkynylthio, sulfonic acid, alkylsulfonyl, haloalkylsulfonyl, fluroralkylsulfonyl, alkenylsulfonyl, alkynylsulfonyl, alkoxysulfonyl, haloalkoxysulfonyl,
15 fluroralkoxysulfonyl, alkenyloxysulfonyl, alkynyloxysulfonyl, aminosulfonyl, sulfinic acid, alkylsulfinyl, haloalkylsulfinyl, fluroralkylsulfinyl, alkenylsulfinyl, alkynylsulfinyl, alkoxysulfinyl, haloalkoxysulfinyl, fluroralkoxysulfinyl, alkenyloxysulfinyl, alkynyloxysulfinyl, aminosulfinyl, formyl, alkylcarbonyl, haloalkylcarbonyl, fluoroalkylcarbonyl, alkenylcarbonyl, alkynylcarbonyl, carboxy, alkoxycarbonyl,
20 haloalkoxycarbonyl, fluoroalkoxycarbonyl, alkenyloxycarbonyl, alkynyloxycarbonyl, alkylcarbonyloxy, haloalkylcarbonyloxy, fluoroalkylcarbonyloxy, alkenylcarbonyloxy, alkynylcarbonyloxy, alkylsulfonyloxy, haloalkylsulfonyloxy, fluroralkylsulfonyloxy, alkenylsulfonyloxy, alkynylsulfonyloxy, haloalkoxysulfonyloxy, fluroralkoxysulfonyloxy, alkenyloxysulfonyloxy, alkynyloxysulfonyloxy, alkylsulfinyloxy, haloalkylsulfinyloxy,
25 fluroralkylsulfinyloxy, alkenylsulfinyloxy, alkynylsulfinyloxy, alkoxysulfinyloxy, haloalkoxysulfinyloxy, fluroralkoxysulfinyloxy, alkenyloxysulfinyloxy, alkynyloxysulfinyloxy, aminosulfinyloxy, amino, amido, aminosulfonyl, aminosulfinyl, cyano, nitro, azido, phosphinyl, phosphoryl, silyl, silyloxy, and any of said substituents bound to the fluorenyl-like group through an alkylene moiety (e.g. methylene).

30 The term "heteroaryl" as used herein include aromatic ring systems, including, but not limited to, monocyclic, bicyclic and tricyclic rings, and have 3 to 12 atoms including at least one heteroatom, such as nitrogen, oxygen, or sulfur. For purposes of exemplification, which should not be construed as limiting the scope of this invention: azaindolyl,

benzo(b)thienyl, benzimidazolyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzothiadiaazolyl, benzotriazolyl, benzoxadiazolyl, furanyl, imidazolyl, imidazopyridinyl, indolyl, indolinyl, indazolyl, isoindolinyl, isoxazolyl, isothiazolyl, isoquinolinyl, oxadiazolyl, oxazolyl, purinyl, pyranyl, pyrazinyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrrolyl, pyrrolo[2,3-d]pyrimidinyl, pyrazolo[3,4-d]pyrimidinyl, quinolinyl, quinazolinyl, triazolyl, thiazolyl, thiophenyl, tetrahydroindolyl, tetrazolyl, thiadiazolyl, thienyl, thiomorpholinyl, triazolyl or tropanyl. The heteroaryl groups of the invention are substituted with 0, 1, 2, 3, 4 or 5 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, fluoroalkyl, hydroxy, alkoxy, alkyenyloxy, alkynyloxy, carbocycloxy, heterocycloxy, haloalkoxy, fluoroalkyloxy, sulfhydryl, alkylthio, haloalkylthio, fluoroalkylthio, alkyenylthio, alkynylthio, sulfonic acid, alkylsulfonyl, haloalkylsulfonyl, fluoralkylsulfonyl, alkenylsulfonyl, alkynylsulfonyl, alkoxysulfonyl, haloalkoxysulfonyl, fluoralkoxysulfonyl, alkenyloxysulfonyl, alkynyloxysulfonyl, aminosulfonyl, sulfinic acid, alkylsulfinyl, haloalkylsulfinyl, fluoralkylsulfinyl, alkenylsulfinyl, alkynylsulfinyl, alkoxysulfinyl, haloalkoxysulfinyl, fluoralkoxysulfinyl, alkenyloxysulfinyl, alkynyloxysulfinyl, aminosulfinyl, formyl, alkylcarbonyl, haloalkylcarbonyl, fluoroalkylcarbonyl, alkenylcarbonyl, alkynylcarbonyl, carboxy, alkoxycarbonyl, haloalkoxycarbonyl, fluoroalkoxycarbonyl, alkenyloxycarbonyl, alkynyloxycarbonyl, alkylcarbonyloxy, haloalkylcarbonyloxy, fluoroalkylcarbonyloxy, alkenylcarbonyloxy, alkynylcarbonyloxy, alkylsulfonyloxy, haloalkylsulfonyloxy, fluoralkylsulfonyloxy, alkenylsulfonyloxy, alkynylsulfonyloxy, haloalkoxysulfonyloxy, fluoralkoxysulfonyloxy, alkenyloxysulfonyloxy, alkynyloxysulfonyloxy, alkylsulfinyloxy, haloalkylsulfinyloxy, fluoralkylsulfinyloxy, alkenylsulfinyloxy, alkynylsulfinyloxy, alkoxysulfinyloxy, haloalkoxysulfinyloxy, fluoralkoxysulfinyloxy, alkenyloxysulfinyloxy, alkynyloxysulfinyloxy, aminosulfinyloxy, amino, amido, aminosulfonyl, aminosulfinyl, cyano, nitro, azido, phosphinyl, phosphoryl, silyl, silyloxy, and any of said substituents bound to the heteroaryl group through an alkylene moiety (e.g. methylene).

The term "heteroarylene," is art-recognized, and as used herein pertains to a bidentate moiety obtained by removing two hydrogen atoms from adjacent atoms of a heteroaryl ring, as defined above.

The term "heteroarylalkyl" or "heteroaralkyl" as used herein means a heteroaryl, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined

herein. Representative examples of heteroarylalkyl include, but are not limited to, pyridin-3-ylmethyl and 2-(thien-2-yl)ethyl.

The term "halo" or "halogen" means -Cl, -Br, -I or -F.

5 The term "haloalkyl" means an alkyl group, as defined herein, wherein at least one hydrogen is replaced with a halogen, as defined herein. Representative examples of haloalkyl include, but are not limited to, chloromethyl, 2-fluoroethyl, trifluoromethyl, pentafluoroethyl, and 2-chloro-3-fluoropentyl.

The term "fluoroalkyl" means an alkyl group, as defined herein, wherein all the hydrogens are replaced with fluorines.

10 The term "hydroxy" as used herein means an -OH group.

The term "alkoxy" as used herein means an alkyl group, as defined herein, appended to the parent molecular moiety through an oxygen atom. Representative examples of alkoxy include, but are not limited to, methoxy, ethoxy, propoxy, 2-propoxy, butoxy, tert-butoxy, pentyloxy, and hexyloxy. The terms "alkenyloxy", "alkynyloxy", "carbocycloxy", and
15 "heterocycloxy" are likewise defined.

The term "haloalkoxy" as used herein means an alkoxy group, as defined herein, wherein at least one hydrogen is replaced with a halogen, as defined herein. Representative examples of haloalkoxy include, but are not limited to, chloromethoxy, 2-fluoroethoxy, trifluoromethoxy, and pentafluoroethoxy. The term "fluoroalkyloxy" is likewise defined.

20 The term "aryloxy" as used herein means an aryl group, as defined herein, appended to the parent molecular moiety through an oxygen. The term "heteroaryloxy" as used herein means a heteroaryl group, as defined herein, appended to the parent molecular moiety through an oxygen. The terms "heteroaryloxy" is likewise defined.

The term "arylalkoxy" or "arylalkyloxy" as used herein means an arylalkyl group, as
25 defined herein, appended to the parent molecular moiety through an oxygen. The term "heteroarylalkoxy" is likewise defined. Representative examples of aryloxy and heteroarylalkoxy include, but are not limited to, 2-chlorophenylmethoxy, 3-trifluoromethylphenylethoxy, and 2,3-dimethylpyridinylmethoxy.

The term "sulfhydryl" or "thio" as used herein means a -SH group.

30 The term "alkylthio" as used herein means an alkyl group, as defined herein, appended to the parent molecular moiety through a sulfur. Representative examples of alkylthio include, but are not limited, methylthio, ethylthio, tert-butylthio, and hexylthio.

The terms "haloalkylthio", "fluoroalkylthio", "alkenylthio", "alkynylthio", "carbocycylthio", and "heterocycylthio" are likewise defined.

5 The term "arylthio" as used herein means an aryl group, as defined herein, appended to the parent molecular moiety through an sulfur. The term "heteroarylthio" is likewise defined.

The term "arylalkylthio" or "aralkylthio" as used herein means an arylalkyl group, as defined herein, appended to the parent molecular moiety through an sulfur. The term "heteroarylalkylthio" is likewise defined.

The term "sulfonyl" as used herein refers to $-S(=O)_2-$ group.

10 The term "sulfonic acid" as used herein refers to $-S(=O)_2OH$.

The term "alkylsulfonyl" as used herein means an alkyl group, as defined herein, appended to the parent molecular moiety through a sulfonyl group, as defined herein. Representative examples of alkylsulfonyl include, but are not limited to, methylsulfonyl and ethylsulfonyl. The terms "haloalkylsulfonyl", "fluoroalkylsulfonyl", "alkenylsulfonyl", "alkynylsulfonyl", "carbocycylsulfonyl", "heterocycylsulfonyl", "arylsulfonyl", "aralkylsulfonyl", "heteroarylsulfonyl" and "heteroaralkylsulfonyl" are likewise defined.

15 The term "alkoxysulfonyl" as used herein means an alkoxy group, as defined herein, appended to the parent molecular moiety through a sulfonyl group, as defined herein. Representative examples of alkoxysulfonyl include, but are not limited to, methoxysulfonyl, ethoxysulfonyl and propoxysulfonyl. The terms "haloalkoxysulfonyl", "fluoroalkoxysulfonyl", "alkenylloxysulfonyl", "alkynylloxysulfonyl", "carbocycylloxysulfonyl", "heterocycylloxysulfonyl", "aryloxysulfonyl", "aralkylloxysulfonyl", "heteroaryloxysulfonyl" and "heteroaralkylloxysulfonyl" are likewise defined.

25 The terms triflyl, tosyl, mesyl, and nonafllyl are art-recognized and refer to trifluoromethanesulfonyl, *p*-toluenesulfonyl, methanesulfonyl, and nonafluorobutanesulfonyl groups, respectively. The terms triflate, tosylate, mesylate, and nonaflate are art-recognized and refer to trifluoromethanesulfonate ester, *p*-toluenesulfonate ester, methanesulfonate ester, and nonafluorobutanesulfonate ester functional groups and molecules that contain said groups, respectively.

30 The term "aminosulfonyl" as used herein means an amino group, as defined herein, appended to the parent molecular moiety through a sulfonyl group.

The term "sulfinyl" as used herein refers to -S(=O)- group. Sulfinyl groups are as defined above for sulfonyl groups. The term "sulfinic acid" as used herein refers to -S(=O)OH.

The term "oxy" refers to a -O- group.

5 The term "carbonyl" as used herein means a -C(=O)- group.

The term "thiocarbonyl" as used herein means a -C(=S)- group.

The term "formyl" as used herein means a -C(=O)H group.

The term "alkylcarbonyl" as used herein means an alkyl group, as defined herein, appended to the parent molecular moiety through a carbonyl group, as defined herein.

10 Representative examples of alkylcarbonyl include, but are not limited to, acetyl, 1-oxopropyl, 2,2-dimethyl-1-oxopropyl, 1-oxobutyl, and 1-oxopentyl. The terms "haloalkylcarbonyl", "fluoroalkylcarbonyl", "alkenylcarbonyl", "alkynylcarbonyl", "carbocycylcarbonyl", "heterocycylcarbonyl", "arylcarbonyl", "aralkylcarbonyl", "heteroarylcarbonyl", and "heteroaralkylcarbonyl" are likewise defined.

15 The term "carboxy" as used herein means a -CO₂H group.

The term "alkoxycarbonyl" as used herein means an alkoxy group, as defined herein, appended to the parent molecular moiety through a carbonyl group, as defined herein. Representative examples of alkoxycarbonyl include, but are not limited to, methoxycarbonyl, ethoxycarbonyl, and tert-butoxycarbonyl. The terms

20 "haloalkoxycarbonyl", "fluoroalkoxycarbonyl", "alkenyloxycarbonyl", "alkynyloxycarbonyl", "carbocycloxy carbonyl", "heterocycloxy carbonyl", "aryloxycarbonyl", "aralkyloxycarbonyl", "heteroaryloxycarbonyl", and "heteroaralkyloxycarbonyl" are likewise defined.

The term "alkylcarbonyloxy" as used herein means an alkylcarbonyl group, as defined herein, appended to the parent molecular moiety through an oxygen atom. Representative examples of alkylcarbonyloxy include, but are not limited to, acetyloxy, ethylcarbonyloxy, and tert-butylcarbonyloxy. The terms "haloalkylcarbonyloxy", "fluoroalkylcarbonyloxy", "alkenylcarbonyloxy", "alkynylcarbonyloxy", "carbocycylcarbonyloxy", "heterocycylcarbonyloxy", "arylcarbonyloxy", "aralkylcarbonyloxy", "heteroarylcarbonyloxy", and "heteroaralkylcarbonyloxy" are likewise defined.

30 The term "alkylsulfonyloxy" as used herein means an alkylsulfonyl group, as defined herein, appended to the parent molecular moiety through an oxygen atom. The

terms "haloalkylsulfonyloxy", "fluoroalkylsulfonyloxy", "alkenylsulfonyloxy",
 "alkynylsulfonyloxy", "carbocycylsulfonyloxy", "heterocycylsulfonyloxy",
 "arylsulfonyloxy", "aralkylsulfonyloxy", "heteroarylsulfonyloxy",
 "heteroaralkylsulfonyloxy", "haloalkoxysulfonyloxy", "fluoroalkoxysulfonyloxy",
 5 "alkenyloxysulfonyloxy", "alkynyloxysulfonyloxy", "carbocycyloxysulfonyloxy",
 "heterocycyloxysulfonyloxy", "aryloxysulfonyloxy", "aralkyloxysulfonyloxy",
 "heteroaryloxysulfonyloxy" and "heteroaralkyloxysulfonyloxy"

The term "amino" as used herein refers to -NH_2 and substituted derivatives thereof wherein one or both of the hydrogens are independently replaced with substituents selected
 10 from the group consisting of alkyl, haloalkyl, fluoroalkyl, alkenyl, alkynyl, carbocycyl, heterocycyl, aryl, aralkyl, heteroaryl, heteroaralkyl, alkylcarbonyl, haloalkylcarbonyl, fluoroalkylcarbonyl, alkenylcarbonyl, alkynylcarbonyl, carbocycylcarbonyl, heterocycylcarbonyl, arylcarbonyl, aralkylcarbonyl, heteroarylcarbonyl, heteroaralkylcarbonyl and the sulfonyl and sulfinyl groups defined above; or when both
 15 hydrogens together are replaced with an alkylene group (to form a ring which contains the nitrogen). Representative examples include, but are not limited to methylamino, acetylamino, and dimethylamino.

The term "amido" as used herein means an amino group, as defined herein, appended to the parent molecular moiety through a carbonyl.

20 The term "cyano" as used herein means a $\text{-C}\equiv\text{N}$ group.

The term "nitro" as used herein means a -NO_2 group.

The term "azido" as used herein means a -N_3 group.

The term "phosphinyl" as used herein includes -PH_3 and substituted derivatives thereof wherein one, two or three of the hydrogens are independently replaced with
 25 substituents selected from the group consisting of alkyl, haloalkyl, fluoroalkyl, alkenyl, alkynyl, carbocycyl, heterocycyl, aryl, aralkyl, heteroaryl, heteroaralkyl, alkoxy, haloalkoxy, fluoroalkoxy, alkenyloxy, alkynyloxy, carbocycyloxy, heterocycyloxy, aryloxy, aralkyloxy, heteroaryloxy, heteroaralkyloxy, and amino.

The term "phosphoryl" as used herein refers to -P(=O)OH_2 and substituted
 30 derivatives thereof wherein one or both of the hydroxyls are independently replaced with substituents selected from the group consisting of alkyl, haloalkyl, fluoroalkyl, alkenyl, alkynyl, carbocycyl, heterocycyl, aryl, aralkyl, heteroaryl, heteroaralkyl, alkoxy,

haloalkoxy, fluoroalkyloxy, alkenyloxy, alkynyloxy, carbocycloxy, heterocycloxy, aryloxy, aralkyloxy, heteroaryloxy, heteroaralkyloxy, and amino.

The term "silyl" as used herein includes H₃Si- and substituted derivatives thereof wherein one, two or three of the hydrogens are independently replaced with substituents selected from alkyl, haloalkyl, fluoroalkyl, alkenyl, alkynyl, carbocycyl, heterocycyl, aryl, aralkyl, heteroaryl, and heteroaralkyl. Representative examples include trimethylsilyl (TMS), tert-butyldiphenylsilyl (TBDPS), tert-butyldimethylsilyl (TBS/TBDMS), triisopropylsilyl (TIPS), and [2-(trimethylsilyl)ethoxy]methyl (SEM).

The term "silyloxy" as used herein means a silyl group, as defined herein, is appended to the parent molecule through an oxygen atom.

The abbreviations Me, Et, Ph, Tf, Nf, Ts, and Ms represent methyl, ethyl, phenyl, trifluoromethanesulfonyl, nonafluorobutanesulfonyl, *p*-toluenesulfonyl and methanesulfonyl, respectively. A more comprehensive list of the abbreviations utilized by organic chemists of ordinary skill in the art appears in the first issue of each volume of the *Journal of Organic Chemistry*; this list is typically presented in a table entitled *Standard List of Abbreviations*.

AUTOPHAGY INDUCING COMPOUNDS

One aspect of the invention relates to autophagy inducing compounds. Recently, a high-throughput image-based screen was used to identify seven FDA-approved drugs which can induce autophagy without inducing cell death (see International Patent Application publication number WO/2009/049242, which is hereby incorporated by reference in its entirety). These compounds are discussed below.

Fluspirilene, an FDA-approved phenothiazine tranquilizer (antipsychotic drug), has been used to treat schizophrenia (Meijer, A.J. and Codogno, P. *Int J Biochem Cell Biol.* **2004**, 36, 2445-62). This molecule may function by blocking adrenaline and dopamine transport in the central nervous system (Janssen, P.A., Niemegeers, C.J., Schellekens, K.H., *et al. Arzneimittelforschung* **1970**, 20, 1689-98).

Trifluoperazine is another FDA-approved tranquilizer, which, like fluspirilene, can effectively treat acute schizophrenia (Janssen, P. A., Niemegeers, C.J., Schellekens, K.H., *et al. Arzneimittelforschung* **1970**, 20, 1689-98). In addition, trifluoperazine has also been reported to inhibit calmodulin activity and mitochondrial permeability transition pore (MTP), and to reduce the toxic effect that expanded polyglutamine associated with

Huntington's disease has on cells (Stokes, H. B. *Dis Nerv Syst.* **1975**, 36, 102-5). In addition, it has also been found that it is a calcium ion channel blocker.

Pimozide is an FDA-approved tranquilizer used in the treatment of chronic schizophrenia. It may act on central aminergic receptors. At high doses, this compound may
5 also affect the degradation of norepinephrine.

Three additional autophagy inducing agents nifedipine, nifedipine, and amiodarone are all FDA-approved drugs for the treatment of cardiovascular disorders, including high blood pressure, angina pectoris, arrhythmia, and the like. Moreover, these compounds have been used to inhibit intracellular Ca^{2+} current. Among them, nifedipine
10 acts as an inhibitor of Type-T Ca^{2+} current in cardiac myocytes. As a dihydropyridine-type Ca^{2+} channel blocker, nifedipine is frequently used to treat chronic angina pectoris, high blood pressure, and Raynaud's phenomenon. Amiodarone is another highly effective anti-arrhythmia drug. It also blocks Ca^{2+} channels.

Loperamide is a heterocyclic piperidine derivative. As an FDA-approved drug to
15 treat diarrhea, it can effectively improve gastrointestinal symptoms. Loperamide can block high-voltage-activated Ca^{2+} channels and reactions to N-methyl-D-aspartate in the hippocampal neurons of rabbits and mice (Girotti, F., Carella, F., Scigliano, G., *et al. J Neurol Neurosurg Psychiatry* **1984**, 47: 848-52). In addition, loperamide can also block voltage-dependant Ca^{2+} channels in cultured dorsal root ganglions (Church, J. Fletcher, E.J.,
20 Abdel-Hamid, K. *et al. Mol Pharmacol.* **1995**, 45: 747-57).

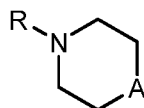
Penitrem A, a fungal neurotoxin discovered in ryegrass, can selectively block Ca^{2+} -activated K^{+} channels (100% blockage is achieved by 10-nM penitrem A). It has been reported that this compound may possess marked neurotoxicity and can cause severe tremors or ataxia (Hagiwara, K., Nakagawasai, O., Murata, A., *et al. Neurosci Res.* **2003**,
25 46, 493-7); however the results presented in International Patent Application publication number WO/2009/049242 show that this drug does not destroy H4.

Interestingly, five of these compounds were previously known to have activity in inhibiting intracellular Ca^{2+} . Few studies have proposed the possible involvement of intracellular Ca^{2+} in regulating autophagy. Williams *et al.* reported that L-type Ca^{2+} channel
30 antagonists, the K^{+} ATP channel opener minoxidil, and the G_i signaling activator clonidine could induce autophagy in mTOR-independent manner (Williams, A.; Sarkar, S.; Cuddon, P.; Ttofi, E.K.; Saiki, S.; Siddiqi, F. H.; *et al. Chem Biol.* **2008**, 4, 295). Recently, the activity of fluspirilene in inhibiting Ca^{2+} flux was confirmed. Further, it was shown that

calpains play an important role in controlling the levels of autophagy in normal living cells by regulating the levels of ATG5 (Xia, H.; Zhang, L.; Chen, G.; Zhang, t.; Liu, J.; Jin, M.; Ma, X.; Ma, D.; Yuan, J. *Autophagy*. **2010**, 6, 1).

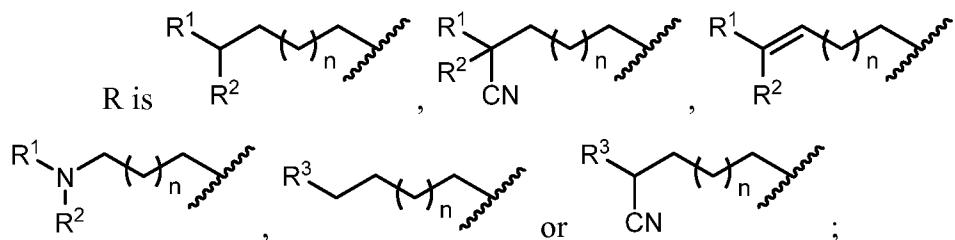
Three of these compounds -- Fluspirilene (**1**), Pimozide (**2**), Trifluoperazine (**3**) -- belong to a class of compounds known as the diphenylbutylpiperidines, or DPBPs (see Figure 1). DPBPs were originally antagonists of the D₂ receptor and were clinically used to treat various forms of psychosis (Seeman, P.; Lee, T.; Chau-Wong, M; Wong, K. *Nature*. **1976**, 261, 717). However, more recently, increasing evidence suggested that DPBPs are also potent antagonists of calcium channels (Gould, R.J.; Murphy, K.M.M.; Reynolds, I.J.; Snyder, S.H. *Proc. Natl. Acad. Sci. U.S.A.* **1983**, 80, 5122; Grantham, C.J.; Main, M. J.; Cannell, M. B. *Br. J. Pharmacol.* **1994**, 111, 483; Sah, D. W. Y.; Bean, B.P.; *Mol Pharmacol.* **1994**, 45, 4; Enyeart, J. J; Biagi, B. A.; Day, R. N.; Sheu, S. S; Maurer, R.A. *J. Biol. Chem.* **1990**, 265, 16373; Galizzi, J.P.; Fosset, M.; Romey, G.; Laudron, P.; Lazdunski, M. *Proc Natl. Acad. Sci. U.S.A.* **1986**, 83, 7513; and King, V. F.; Garcia, M. L.; Shevell, J. L.; Slaughter, R. S.; Kaczorowski, G. J. *J. Biol. Chem.* **1989**, 264, 5633). Penfluridol (**4**), one of common DPBPs, which is not in the above screening library, has also been found to be a good autophagy inducer (EC₅₀ = 3.2 μm).

One aspect of the invention relates to a compound represented by formula I:



I

or pharmaceutically acceptable salt, solvate, hydrate, prodrug, chemically-protected form, enantiomer or stereoisomer thereof; wherein, independently for each occurrence,

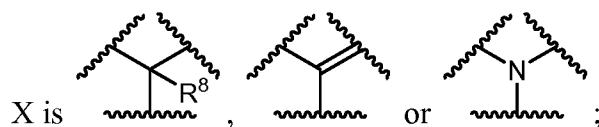
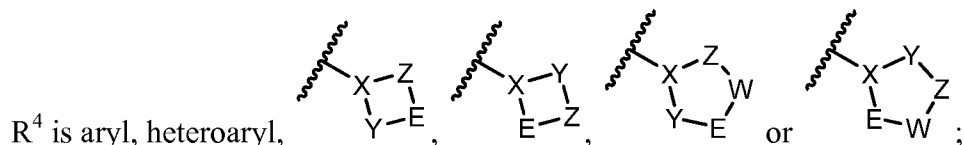
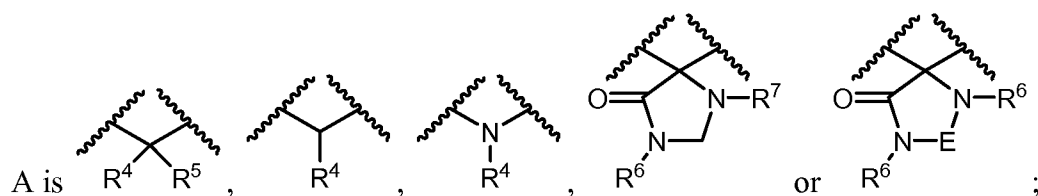


R¹ is aryl or heteroaryl;

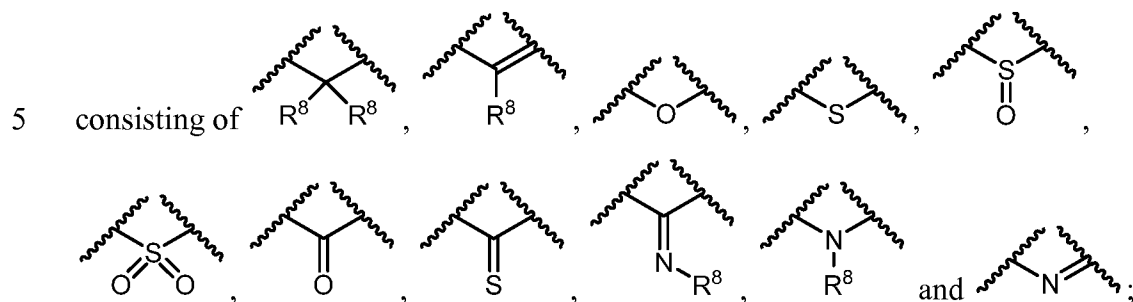
R² is aryl or heteroaryl;

R³ is fluorenyl or fluorenyl-like;

n is 0, 1, 2 or 3;



W, Y and Z are independently for each occurrence selected from the group



E is arylene or heteroarylene;

R⁵ is hydroxy, alkyloxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, silyloxy, alkylcarbonyloxy, arylcarbonyloxy, heteroarylcarbonyloxy, aralkylcarbonyloxy,

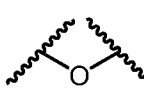
10 heteroaralkylcarbonyloxy, cyano, amino or amido;

R⁶ is hydrogen or alkyl;

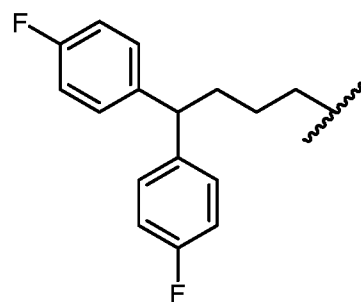
R⁷ is aryl or heteroaryl; and

R⁸ is hydrogen or alkyl.

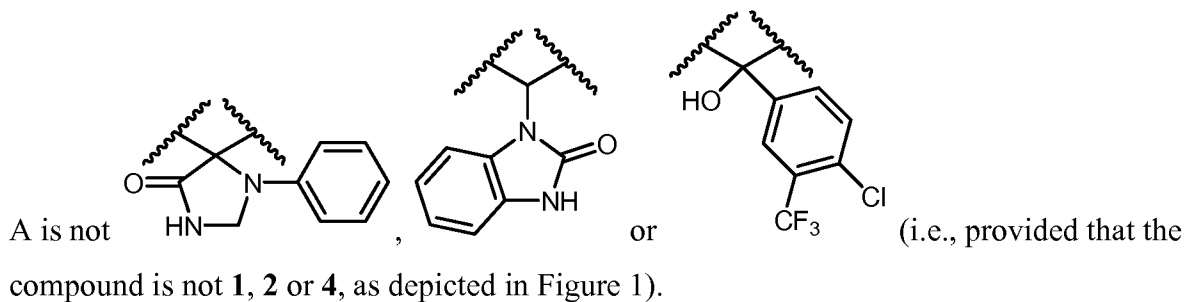
As one of skill in the art will appreciate, W, X, Y and Z (as defined above) need to
15 be selected so that each single bond (represented by “-”) is connected to an adjacent single bond, and each double bond (represented by “=”) is connected to an adjacent double bond. One of skill in the art will also appreciate that certain selections of W, X, Y and Z, such as

when W, X, Y and Z are all  , result in non-sensical compounds. In other words, the selection of W, X, Y and Z must be in accordance with permitted valence and result in a
20 stable compound.

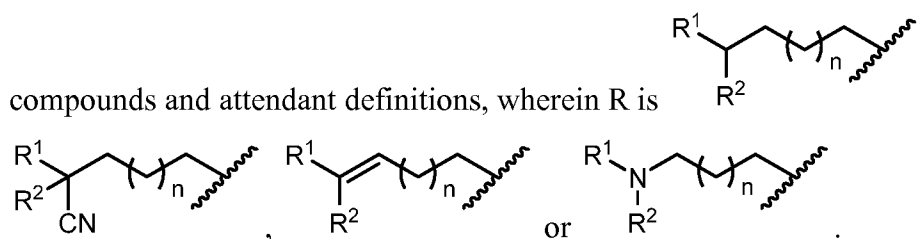
In certain embodiments, the invention relates to any of the aforementioned



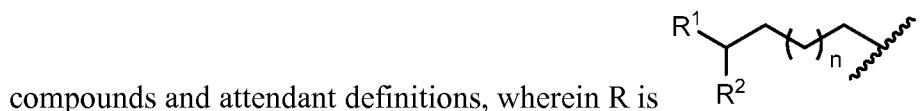
compounds and attendant definitions, provided that when R is



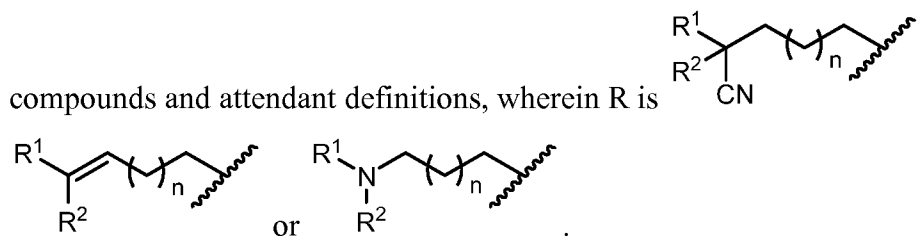
5 In certain embodiments, the invention relates to any of the aforementioned



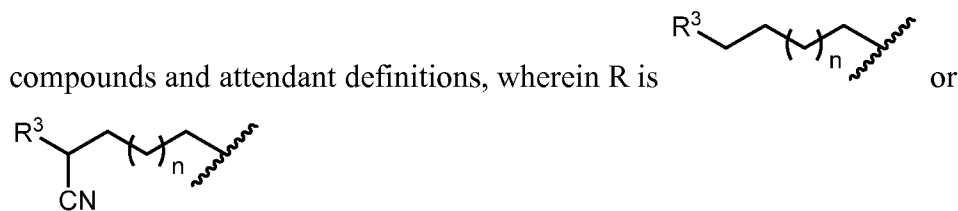
In certain embodiments, the invention relates to any of the aforementioned



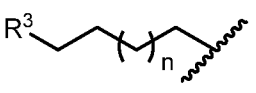
10 In certain embodiments, the invention relates to any of the aforementioned



In certain embodiments, the invention relates to any of the aforementioned



In certain embodiments, the invention relates to any of the aforementioned

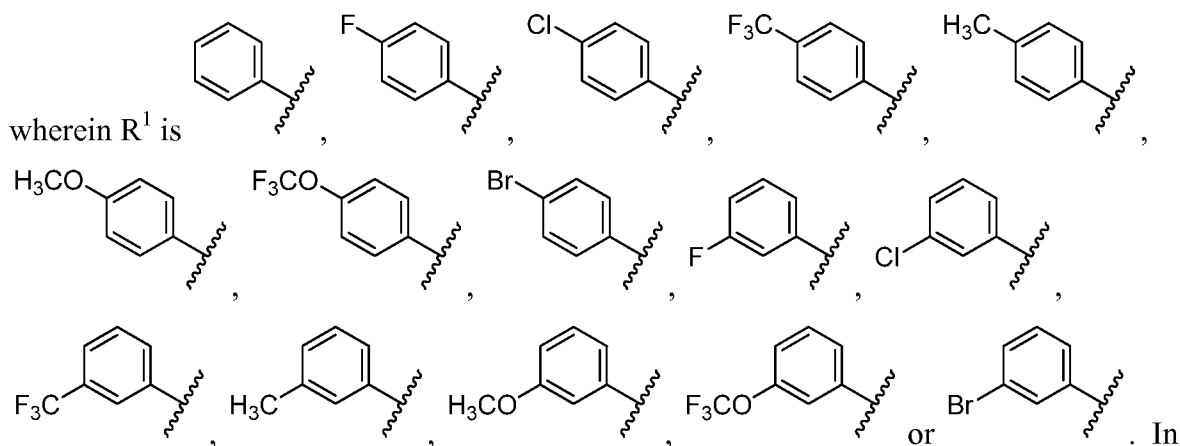
compounds and attendant definitions, wherein R is  .

In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions, wherein R¹ is aryl. In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions, wherein R¹ is heteroaryl.

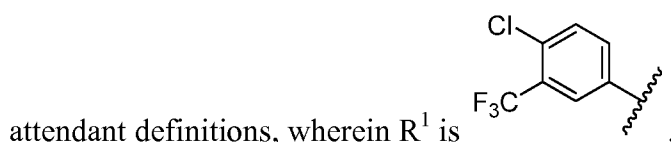
In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions, wherein R¹ is phenyl substituted with 0-5 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, fluoroalkyl, hydroxy, alkoxy, alkyenyloxy, alkynyloxy, carbocycloxy, heterocycloxy, haloalkoxy, fluoroalkyloxy, sulfhydryl, alkylthio, haloalkylthio, fluoroalkylthio, alkyenylthio, alkynylthio, sulfonic acid, alkylsulfonyl, haloalkylsulfonyl, fluroralkylsulfonyl, alkenylsulfonyl, alkynylsulfonyl, alkoxysulfonyl, haloalkoxysulfonyl, fluroralkoxysulfonyl, alkenyloxysulfonyl, alkynyloxysulfonyl, aminosulfonyl, sulfinic acid, alkylsulfinyl, haloalkylsulfinyl, fluroralkylsulfinyl, alkenylsulfinyl, alkynylsulfinyl, alkoxysulfinyl, haloalkoxysulfinyl, fluroralkoxysulfinyl, alkenyloxysulfinyl, alkynyloxysulfinyl, aminosulfinyl, formyl, alkylcarbonyl, haloalkylcarbonyl, fluoroalkylcarbonyl, alkenylcarbonyl, alkynylcarbonyl, carboxy, alkoxycarbonyl, haloalkoxycarbonyl, fluoroalkoxycarbonyl, alkenyloxycarbonyl, alkynyloxycarbonyl, alkylcarbonyloxy, haloalkylcarbonyloxy, fluoroalkylcarbonyloxy, alkenylcarbonyloxy, alkynylcarbonyloxy, alkylsulfonyloxy, haloalkylsulfonyloxy, fluroralkylsulfonyloxy, alkenylsulfonyloxy, alkynylsulfonyloxy, haloalkoxysulfonyloxy, fluroralkoxysulfonyloxy, alkenyloxysulfonyloxy, alkynyloxysulfonyloxy, alkylsulfinyloxy, haloalkylsulfinyloxy, fluroralkylsulfinyloxy, alkenylsulfinyloxy, alkynylsulfinyloxy, alkoxysulfinyloxy, haloalkoxysulfinyloxy, fluroralkoxysulfinyloxy, alkenyloxysulfinyloxy, alkynyloxysulfinyloxy, aminosulfinyloxy, amino, amido, aminosulfonyl, aminosulfinyl, cyano, nitro, azido, phosphinyl, phosphoryl, silyl, silyloxy, and any of said substituents bound to the phenyl group through an alkylene moiety. In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions, wherein R¹ is a 3-substituted phenyl. In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions, wherein R¹ is a 4-substituted phenyl. In certain embodiments, the invention relates to any of the aforementioned

compounds and attendant definitions, wherein R^1 is a 3-substituted phenyl. In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions, wherein R^1 is a 3,4-disubstituted phenyl.

In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions, wherein R^1 is phenyl substituted 0-5 substituents independently selected from the group consisting of halo, alkyl, haloalkyl, alkoxy and haloalkoxy. In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions, wherein R^1 is phenyl substituted in the 3- or 4-position with halo, alkyl, haloalkyl, alkoxy or haloalkoxy. In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions, wherein R^1 is 3-alkyl-4-halophenyl or 3-haloalkyl-4-halophenyl. In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions,



In certain embodiments, the invention relates to any of the aforementioned compounds and



In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions, wherein R^2 is aryl. In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions, wherein R^2 is heteroaryl.

In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions, wherein R^2 is phenyl substituted with 0-5 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, fluoroalkyl, hydroxy, alkoxy, alkyenyloxy, alkynyloxy, carbocycloxy, heterocycloxy, haloalkoxy, fluoroalkyloxy, sulfhydryl, alkylthio, haloalkylthio, fluoroalkylthio,

- alkenyylthio, alkynylthio, sulfonic acid, alkylsulfonyl, haloalkylsulfonyl, fluroralkylsulfonyl, alkenylsulfonyl, alkynylsulfonyl, alkoxy sulfonyl, haloalkoxy sulfonyl, fluroralkoxy sulfonyl, alkenyloxy sulfonyl, alkynyloxy sulfonyl, aminosulfonyl, sulfinic acid, alkylsulfinyl, haloalkylsulfinyl, fluroralkylsulfinyl, alkenylsulfinyl, alkynylsulfinyl,
- 5 alkoxy sulfinyl, haloalkoxy sulfinyl, fluroralkoxy sulfinyl, alkenyloxy sulfinyl, alkynyloxy sulfinyl, aminosulfinyl, formyl, alkylcarbonyl, haloalkylcarbonyl, fluoroalkylcarbonyl, alkenylcarbonyl, alkynylcarbonyl, carboxy, alkoxy carbonyl, haloalkoxy carbonyl, fluoroalkoxy carbonyl, alkenyloxy carbonyl, alkynyloxy carbonyl, alkylcarbonyloxy, haloalkylcarbonyloxy, fluoroalkylcarbonyloxy, alkenylcarbonyloxy,
- 10 alkynylcarbonyloxy, alkylsulfonyloxy, haloalkylsulfonyloxy, fluroralkylsulfonyloxy, alkenylsulfonyloxy, alkynylsulfonyloxy, haloalkoxy sulfonyloxy, fluroralkoxy sulfonyloxy, alkenyloxy sulfonyloxy, alkynyloxy sulfonyloxy, alkylsulfinyloxy, haloalkylsulfinyloxy, fluroralkylsulfinyloxy, alkenylsulfinyloxy, alkynylsulfinyloxy, alkoxy sulfinyloxy, haloalkoxy sulfinyloxy, fluroralkoxy sulfinyloxy, alkenyloxy sulfinyloxy,
- 15 alkynyloxy sulfinyloxy, aminosulfinyloxy, amino, amido, aminosulfonyl, aminosulfinyl, cyano, nitro, azido, phosphinyl, phosphoryl, silyl, silyloxy, and any of said substituents bound to the phenyl group through an alkylene moiety. In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions, wherein R^2 is a 3-substituted phenyl. In certain embodiments, the invention relates to any
- 20 of the aforementioned compounds and attendant definitions, wherein R^2 is a 4-substituted phenyl. In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions, wherein R^2 is a 3-substituted phenyl. In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions, wherein R^2 is a 3,4-disubstituted phenyl.
- 25 In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions, wherein R^2 is phenyl substituted 0-5 substituents independently selected from the group consisting of halo, alkyl, haloalkyl, alkoxy and haloalkoxy. In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions, wherein R^2 is phenyl substituted in the 3- or 4-
- 30 position with halo, alkyl, haloalkyl, alkoxy or haloalkoxy. In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions, wherein R^2 is 3-alkyl-4-halophenyl or 3-haloalkyl-4-halophenyl. In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions,

wherein R^2 is

In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions, wherein R^2 is

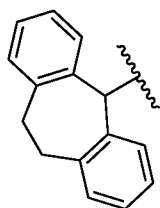
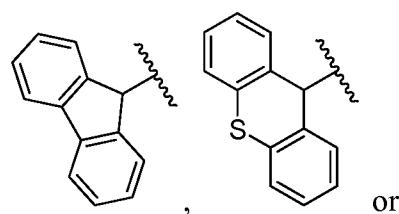
5 attendant definitions, wherein R^2 is

In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions, wherein R^1 and R^2 are the same. In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions, wherein R^1 and R^2 are not the same.

10 In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions, wherein R^3 is fluorenyl. In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions, wherein R^3 is fluorenyl-like.

In certain embodiments, the invention relates to any of the aforementioned

15 compounds and attendant definitions, wherein R^3 is

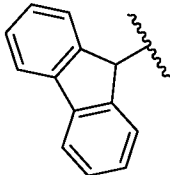
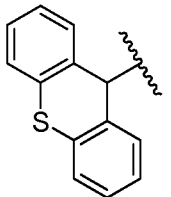
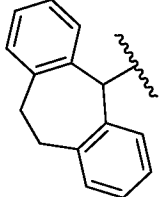


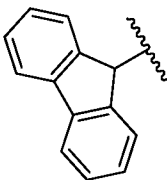
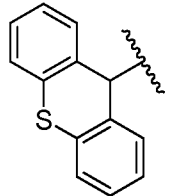
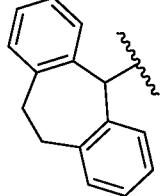
substituted with 0-8 substituents independently selected from the group

consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, fluoroalkyl, hydroxy, alkoxy, alkenyloxy, alkynyloxy, carbocycloxy, heterocycloxy, haloalkoxy, fluoroalkyloxy, sulfhydryl, alkylthio, haloalkylthio, fluoroalkylthio, alkyenylthio, alkynylthio, sulfonic acid,

20 alkylsulfonyl, haloalkylsulfonyl, fluoroalkylsulfonyl, alkenylsulfonyl, alkynylsulfonyl,

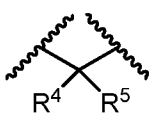
alkoxysulfonyl, haloalkoxysulfonyl, fluoralkoxysulfonyl, alkenyloxysulfonyl, alkynyloxysulfonyl, aminosulfonyl, sulfinic acid, alkylsulfinyl, haloalkylsulfinyl, fluoralkylsulfinyl, alkenylsulfinyl, alkynylsulfinyl, alkoxyulfinyl, haloalkoxyulfinyl, fluoralkoxyulfinyl, alkenyloxysulfinyl, alkynyloxysulfinyl, aminosulfinyl, formyl, alkylcarbonyl, haloalkylcarbonyl, fluoroalkylcarbonyl, alkenylcarbonyl, alkynylcarbonyl, carboxy, alkoxy carbonyl, haloalkoxy carbonyl, fluoroalkoxy carbonyl, alkenyloxycarbonyl, alkynyloxycarbonyl, alkylcarbonyloxy, haloalkylcarbonyloxy, fluoroalkylcarbonyloxy, alkenylcarbonyloxy, alkynylcarbonyloxy, alkylsulfonyloxy, haloalkylsulfonyloxy, fluoralkylsulfonyloxy, alkenylsulfonyloxy, alkynylsulfonyloxy, haloalkoxysulfonyloxy, fluoralkoxysulfonyloxy, alkenyloxysulfonyloxy, alkynyloxysulfonyloxy, alkylsulfinyloxy, haloalkylsulfinyloxy, fluoralkylsulfinyloxy, alkenylsulfinyloxy, alkynylsulfinyloxy, alkoxyulfinyloxy, haloalkoxyulfinyloxy, fluoralkoxyulfinyloxy, alkenyloxysulfinyloxy, alkynyloxysulfinyloxy, aminosulfinyloxy, amino, amido, aminosulfonyl, aminosulfinyl, cyano, nitro, azido, phosphinyl, phosphoryl, silyl, silyloxy, and any of said substituents

bound to the ,  or  through an alkylene moiety. In certain embodiments, the invention relates to any of the aforementioned compounds and

attendant definitions, wherein R^3 is ,  or  substituted with 0-8 substituents independently selected from the group consisting of halo, alkyl, haloalkyl, alkoxy and haloalkoxy.

In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions, wherein n is 0. In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions, wherein n is 1. In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions, wherein n is 2. In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions, wherein n is 3.

In certain embodiments, the invention relates to any of the aforementioned

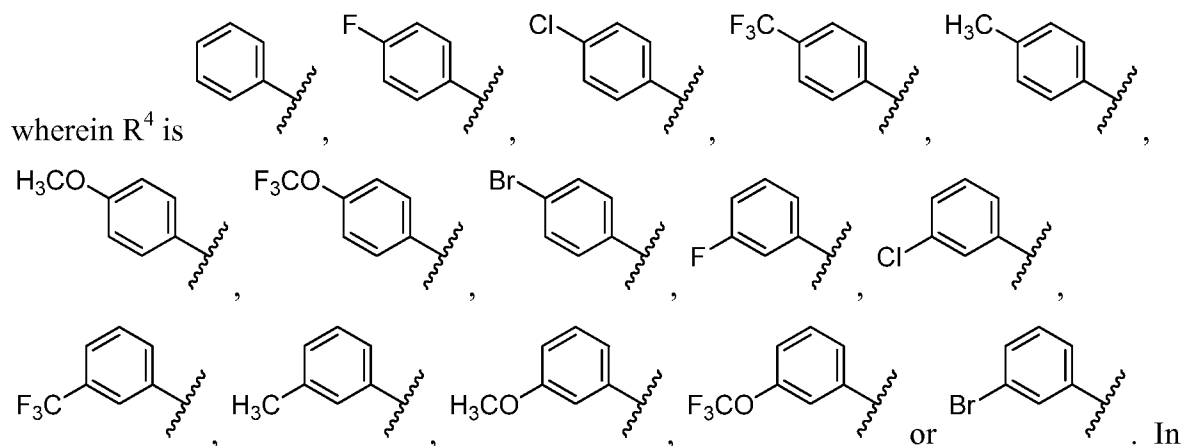
compounds and attendant definitions, wherein A is .

In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions, wherein R⁴ is aryl. In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions, wherein R⁴ is heteroaryl.

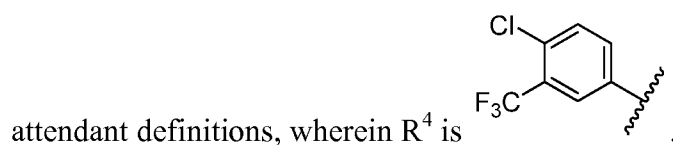
In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions, wherein R⁴ is phenyl substituted with 0-5 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, fluoroalkyl, hydroxy, alkoxy, alkyenyloxy, alkynyloxy, carbocycloxy, heterocycloxy, haloalkoxy, fluoroalkyloxy, sulfhydryl, alkylthio, haloalkylthio, fluoroalkylthio, alkyenylthio, alkynylthio, sulfonic acid, alkylsulfonyl, haloalkylsulfonyl, fluroralkylsulfonyl, alkenylsulfonyl, alkynylsulfonyl, alkoxysulfonyl, haloalkoxysulfonyl, fluroralkoxysulfonyl, alkenyloxysulfonyl, alkynyloxysulfonyl, aminosulfonyl, sulfinic acid, alkylsulfinyl, haloalkylsulfinyl, fluroralkylsulfinyl, alkenylsulfinyl, alkynylsulfinyl, alkoxysulfinyl, haloalkoxysulfinyl, fluroralkoxysulfinyl, alkenyloxysulfinyl, alkynyloxysulfinyl, aminosulfinyl, formyl, alkylcarbonyl, haloalkylcarbonyl, fluoroalkylcarbonyl, alkenylcarbonyl, alkynylcarbonyl, carboxy, alkoxycarbonyl, haloalkoxycarbonyl, fluoroalkoxycarbonyl, alkenyloxycarbonyl, alkynyloxycarbonyl, alkylcarbonyloxy, haloalkylcarbonyloxy, fluoroalkylcarbonyloxy, alkenylcarbonyloxy, alkynylcarbonyloxy, alkylsulfonyloxy, haloalkylsulfonyloxy, fluroralkylsulfonyloxy, alkenylsulfonyloxy, alkynylsulfonyloxy, haloalkoxysulfonyloxy, fluroralkoxysulfonyloxy, alkenyloxysulfonyloxy, alkynyloxysulfonyloxy, alkylsulfinyloxy, haloalkylsulfinyloxy, fluroralkylsulfinyloxy, alkenylsulfinyloxy, alkynylsulfinyloxy, alkoxysulfinyloxy, haloalkoxysulfinyloxy, fluroralkoxysulfinyloxy, alkenyloxysulfinyloxy, alkynyloxysulfinyloxy, aminosulfinyloxy, amino, amido, aminosulfonyl, aminosulfinyl, cyano, nitro, azido, phosphinyl, phosphoryl, silyl, silyloxy, and any of said substituents bound to the phenyl group through an alkylene moiety. In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions, wherein R⁴ is a 3-substituted phenyl. In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions, wherein R⁴ is a 4-substituted phenyl. In certain embodiments, the invention relates to any of the aforementioned

compounds and attendant definitions, wherein R^4 is a 3-substituted phenyl. In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions, wherein R^4 is a 3,4-disubstituted phenyl.

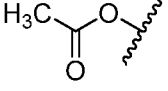
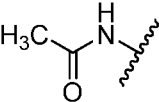
In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions, wherein R^4 is phenyl substituted 0-5 substituents independently selected from the group consisting of halo, alkyl, haloalkyl, alkoxy and haloalkoxy. In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions, wherein R^4 is phenyl substituted in the 3- or 4-position with halo, alkyl, haloalkyl, alkoxy or haloalkoxy. In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions, wherein R^4 is 3-alkyl-4-halophenyl or 3-haloalkyl-4-halophenyl. In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions,



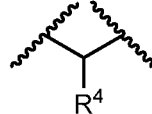
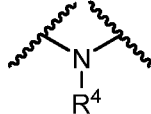
certain embodiments, the invention relates to any of the aforementioned compounds and



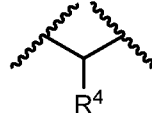
In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions, wherein R^5 is hydroxy, alkyloxy, alkylcarbonyloxy, cyano or amino. In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions, wherein R^5 is hydroxy, alkyloxy or alkylcarbonyloxy. In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions, wherein R^5 is amino. In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions, wherein R^5 is cyano. In certain embodiments, the invention relates to any of the

aforementioned compounds and attendant definitions, wherein R^5 is , , , or .

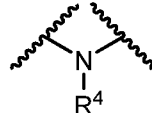
In certain embodiments, the invention relates to any of the aforementioned

compounds and attendant definitions, wherein A is  or .

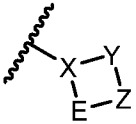
5 In certain embodiments, the invention relates to any of the aforementioned

compounds and attendant definitions, wherein A is .

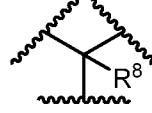
In certain embodiments, the invention relates to any of the aforementioned

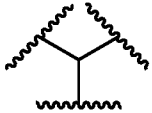
compounds and attendant definitions, wherein A is .

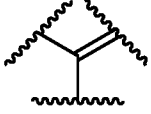
In certain embodiments, the invention relates to any of the aforementioned

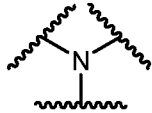
10 compounds and attendant definitions, wherein R^4 is .

In certain embodiments, the invention relates to any of the aforementioned

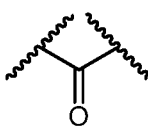
compounds and attendant definitions, wherein X is . In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions,

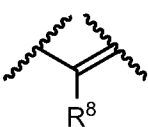
wherein X is . In certain embodiments, the invention relates to any of the

15 aforementioned compounds and attendant definitions, wherein X is . In certain embodiments, the invention relates to any of the aforementioned compounds and attendant

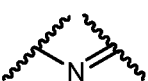
definitions, wherein X is .

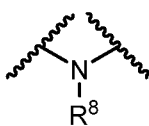
In certain embodiments, the invention relates to any of the aforementioned

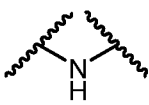
compounds and attendant definitions, wherein Y is . In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions,

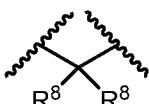
wherein Y is . In certain embodiments, the invention relates to any of the

5 aforementioned compounds and attendant definitions, wherein Y is . In certain embodiments, the invention relates to any of the aforementioned compounds and attendant

definitions, wherein Y is . In certain embodiments, the invention relates to any

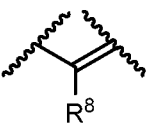
of the aforementioned compounds and attendant definitions, wherein Y is . In certain embodiments, the invention relates to any of the aforementioned compounds and

10 attendant definitions, wherein Y is . In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions, wherein Y is

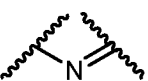
. In certain embodiments, the invention relates to any of the aforementioned

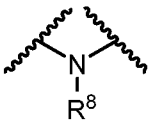
compounds and attendant definitions, wherein Y is .

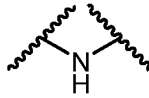
In certain embodiments, the invention relates to any of the aforementioned

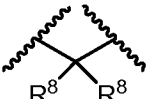
15 compounds and attendant definitions, wherein Z is . In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions,

wherein Z is . In certain embodiments, the invention relates to any of the

aforementioned compounds and attendant definitions, wherein Z is . In certain embodiments, the invention relates to any of the aforementioned compounds and attendant

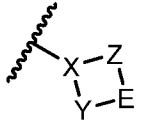
definitions, wherein Z is . In certain embodiments, the invention relates to any

of the aforementioned compounds and attendant definitions, wherein Z is . In certain embodiments, the invention relates to any of the aforementioned compounds and

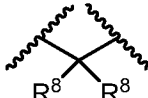
attendant definitions, wherein Z is . In certain embodiments, the invention
5 relates to any of the aforementioned compounds and attendant definitions, wherein Z is



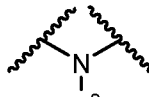
In certain embodiments, the invention relates to any of the aforementioned

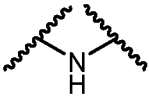
compounds and attendant definitions, wherein R⁴ is .

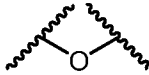
In certain embodiments, the invention relates to any of the aforementioned

10 compounds and attendant definitions, wherein Y is . In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions,

wherein Y is . In certain embodiments, the invention relates to any of the

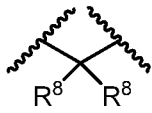
aforementioned compounds and attendant definitions, wherein Z is . In certain embodiments, the invention relates to any of the aforementioned compounds and attendant

15 definitions, wherein Z is . In certain embodiments, the invention relates to any

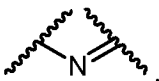
of the aforementioned compounds and attendant definitions, wherein Y is . In certain embodiments, the invention relates to any of the aforementioned compounds and

attendant definitions, wherein Y is .

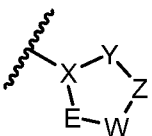
In certain embodiments, the invention relates to any of the aforementioned

compounds and attendant definitions, wherein Z is . In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions,

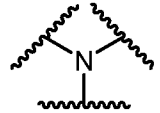
wherein Z is . In certain embodiments, the invention relates to any of the

5 aforementioned compounds and attendant definitions, wherein Y is .

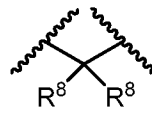
In certain embodiments, the invention relates to any of the aforementioned

compounds and attendant definitions, wherein R⁴ is .

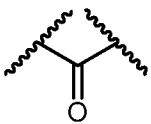
In certain embodiments, the invention relates to any of the aforementioned

compounds and attendant definitions, wherein X is .

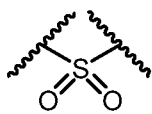
10 In certain embodiments, the invention relates to any of the aforementioned

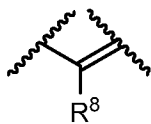
compounds and attendant definitions, wherein Y is . In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions,

wherein Y is . In certain embodiments, the invention relates to any of the

aforementioned compounds and attendant definitions, wherein Y is . In certain

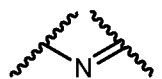
15 embodiments, the invention relates to any of the aforementioned compounds and attendant

definitions, wherein Y is . In certain embodiments, the invention relates to any

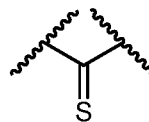
of the aforementioned compounds and attendant definitions, wherein Y is . In certain embodiments, the invention relates to any of the aforementioned compounds and

attendant definitions, wherein Y is . In certain embodiments, the invention

relates to any of the aforementioned compounds and attendant definitions, wherein Y is

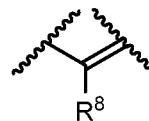


. In certain embodiments, the invention relates to any of the aforementioned



compounds and attendant definitions, wherein Y is

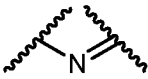
In certain embodiments, the invention relates to any of the aforementioned

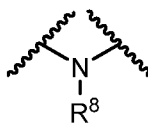


- 5 compounds and attendant definitions, wherein Z is . In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions,

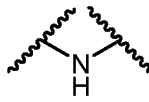


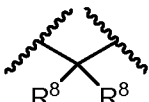
wherein Z is . In certain embodiments, the invention relates to any of the

aforementioned compounds and attendant definitions, wherein Z is . In certain embodiments, the invention relates to any of the aforementioned compounds and attendant



- 10 definitions, wherein Z is . In certain embodiments, the invention relates to any

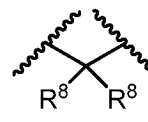
of the aforementioned compounds and attendant definitions, wherein Z is . In certain embodiments, the invention relates to any of the aforementioned compounds and

attendant definitions, wherein Z is . In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions, wherein Z is

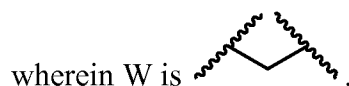


15

In certain embodiments, the invention relates to any of the aforementioned

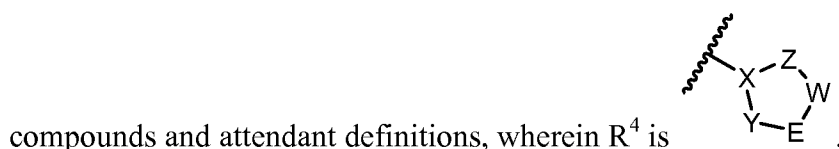


compounds and attendant definitions, wherein W is . In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions,

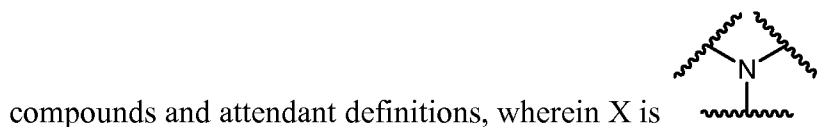


wherein W is

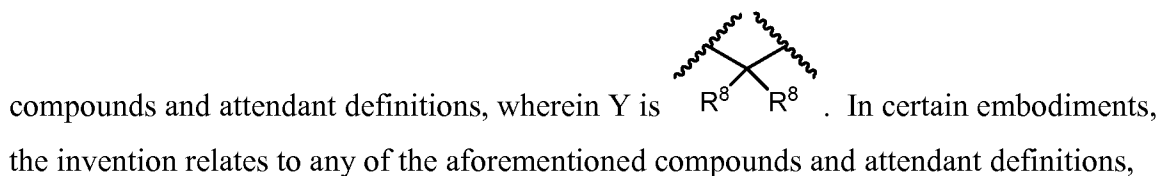
In certain embodiments, the invention relates to any of the aforementioned



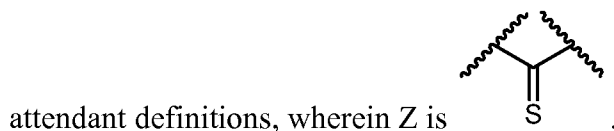
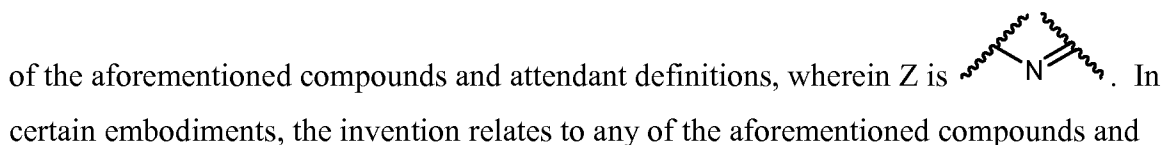
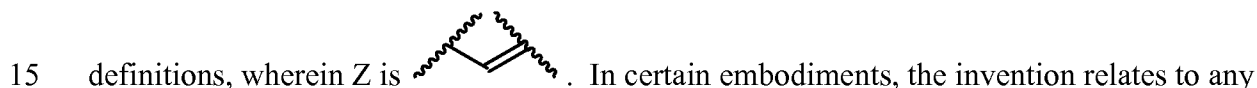
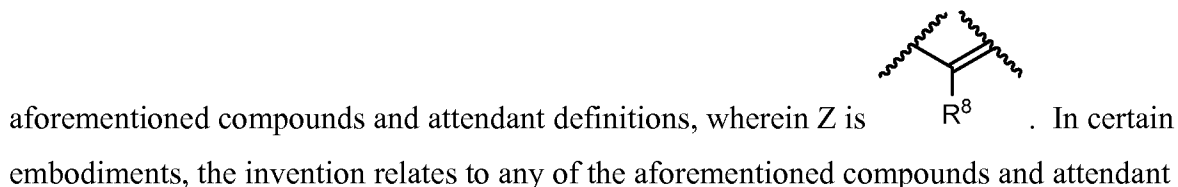
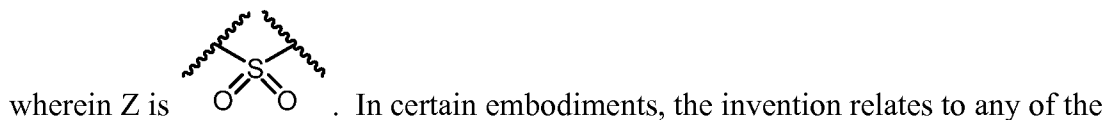
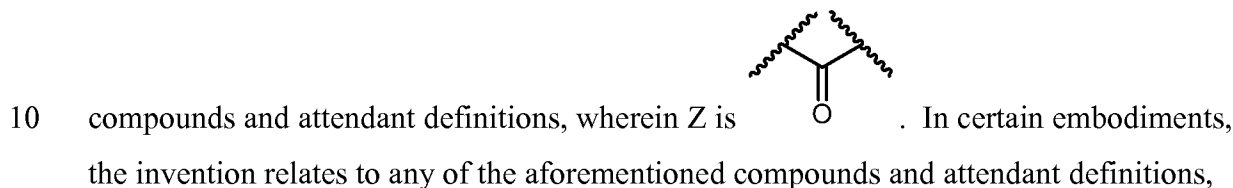
In certain embodiments, the invention relates to any of the aforementioned



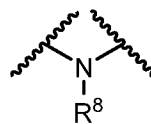
5 In certain embodiments, the invention relates to any of the aforementioned

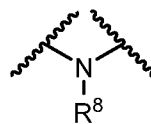


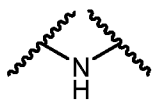
In certain embodiments, the invention relates to any of the aforementioned

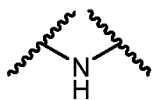


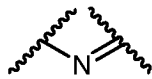
In certain embodiments, the invention relates to any of the aforementioned



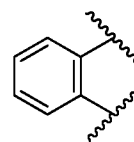
compounds and attendant definitions, wherein W is . In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions,

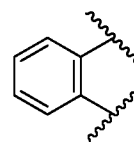


wherein W is . In certain embodiments, the invention relates to any of the

5 aforementioned compounds and attendant definitions, wherein W is .

In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions, wherein E is arylene. In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions, wherein E is heteroarylene. In certain embodiments, the invention relates to any of the



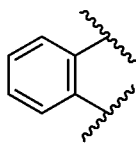
10 aforementioned compounds and attendant definitions, wherein E is  substituted with 0-4 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, fluoroalkyl, hydroxy, alkoxy, alkyenyloxy, alkynyloxy, carbocycloxy, heterocycloxy, haloalkoxy, fluoroalkyloxy, sulfhydryl, alkylthio, haloalkylthio, fluoroalkylthio, alkyenylthio, alkynylthio, sulfonic acid, alkylsulfonyl, haloalkylsulfonyl, fluroralkylsulfonyl, alkenylsulfonyl, alkynylsulfonyl, alkoxysulfonyl, haloalkoxysulfonyl, fluroralkoxysulfonyl, alkenyloxysulfonyl, alkynyloxysulfonyl, aminosulfonyl, sulfinic acid, alkylsulfinyl, haloalkylsulfinyl, fluroralkylsulfinyl, alkenylsulfinyl, alkynylsulfinyl, alkoxysulfinyl, haloalkoxysulfinyl, fluroralkoxysulfinyl, alkenyloxysulfinyl, alkynyloxysulfinyl, aminosulfinyl, formyl, alkylcarbonyl, haloalkylcarbonyl, fluoroalkylcarbonyl, alkenylcarbonyl, alkynylcarbonyl, carboxy, alkoxycarbonyl, haloalkoxycarbonyl, fluoroalkoxycarbonyl, alkenyloxycarbonyl, alkynyloxycarbonyl, alkylcarbonyloxy, haloalkylcarbonyloxy, fluoroalkylcarbonyloxy, alkenylcarbonyloxy, alkynylcarbonyloxy, alkylsulfonyloxy, haloalkylsulfonyloxy, fluroralkylsulfonyloxy, alkenylsulfonyloxy, alkynylsulfonyloxy, haloalkoxysulfonyloxy, fluroralkoxysulfonyloxy, alkenyloxysulfonyloxy, alkynyloxysulfonyloxy, alkylsulfinyloxy, haloalkylsulfinyloxy, fluroralkylsulfinyloxy, alkenylsulfinyloxy, alkynylsulfinyloxy, alkoxysulfinyloxy, haloalkoxysulfinyloxy, fluroralkoxysulfinyloxy, alkenyloxysulfinyloxy, alkynyloxysulfinyloxy, aminosulfinyloxy, amino, amido, aminosulfonyl, aminosulfinyl,

15

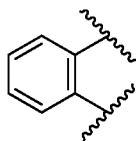
20

25

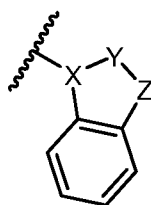
cyano, nitro, azido, phosphinyl, phosphoryl, silyl, silyloxy, and any of said substituents



bound to the through an alkylene moiety. In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions, wherein E is

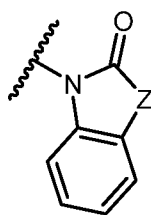


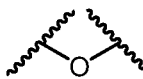
5 In certain embodiments, the invention relates to any of the aforementioned

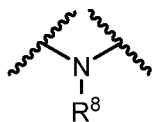


compounds and attendant definitions, wherein R^4 is

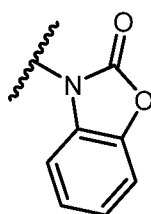
In certain embodiments, the invention relates to any of the aforementioned



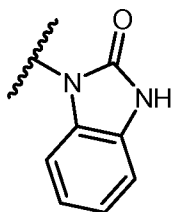
compounds and attendant definitions, wherein R^4 is ; and Z is  or



. In certain embodiments, the invention relates to any of the aforementioned

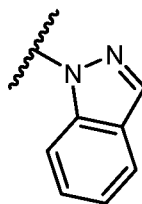


10 compounds and attendant definitions, wherein R^4 is . In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions,

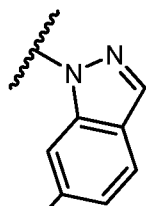


wherein R^4 is

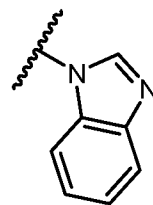
In certain embodiments, the invention relates to any of the aforementioned



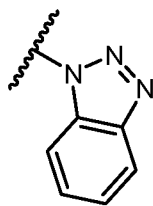
compounds and attendant definitions, wherein R^4 is . In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions,



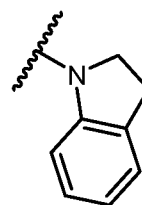
wherein R^4 is O_2N . In certain embodiments, the invention relates to any of the



5 aforementioned compounds and attendant definitions, wherein R^4 is . In certain embodiments, the invention relates to any of the aforementioned compounds and attendant

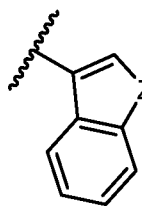


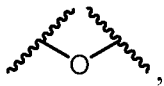
definitions, wherein R^4 is . In certain embodiments, the invention relates to any

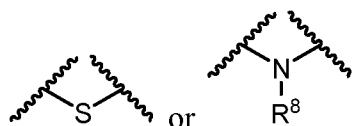


of the aforementioned compounds and attendant definitions, wherein R^4 is .

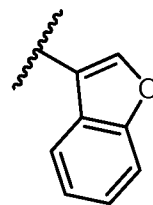
In certain embodiments, the invention relates to any of the aforementioned



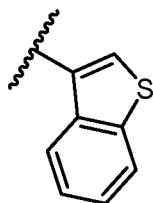
10 compounds and attendant definitions, wherein R^4 is ; and Z is ,



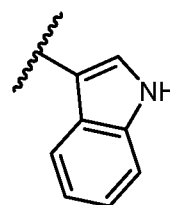
. In certain embodiments, the invention relates to any of the



aforementioned compounds and attendant definitions, wherein R^4 is . In certain embodiments, the invention relates to any of the aforementioned compounds and attendant

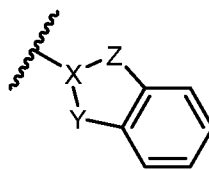


definitions, wherein R^4 is . In certain embodiments, the invention relates to any



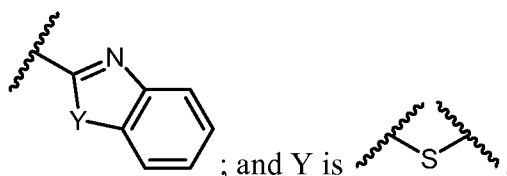
of the aforementioned compounds and attendant definitions, wherein R^4 is .

5 In certain embodiments, the invention relates to any of the aforementioned

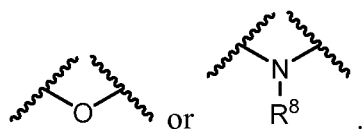


compounds and attendant definitions, wherein R^4 is .

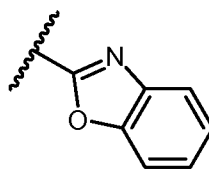
In certain embodiments, the invention relates to any of the aforementioned



compounds and attendant definitions, wherein R^4 is

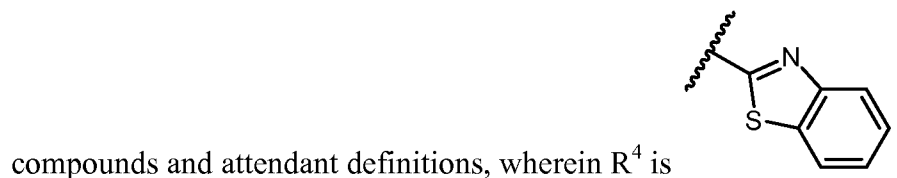


10 In certain embodiments, the invention relates to any of the aforementioned

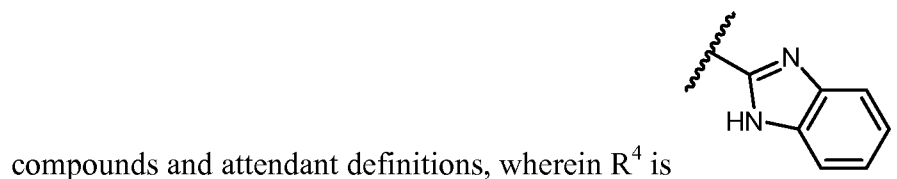


compounds and attendant definitions, wherein R^4 is .

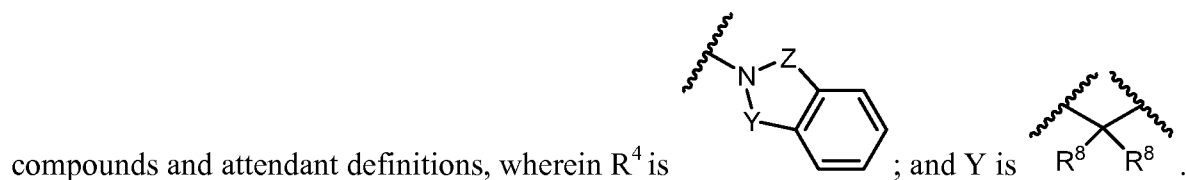
In certain embodiments, the invention relates to any of the aforementioned



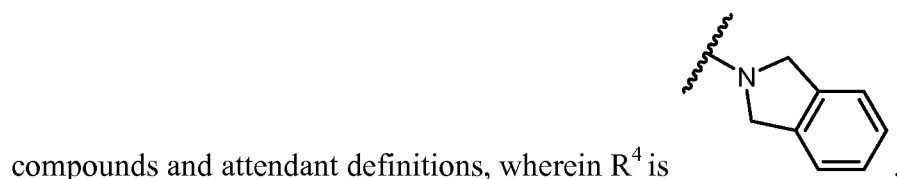
In certain embodiments, the invention relates to any of the aforementioned



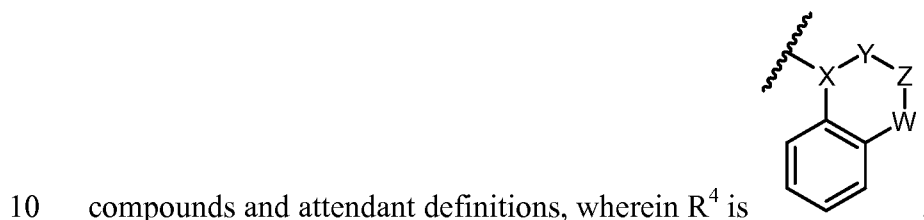
5 In certain embodiments, the invention relates to any of the aforementioned



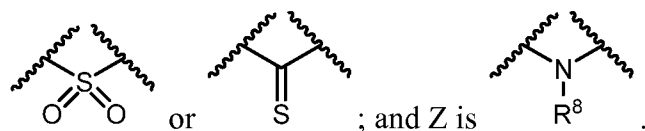
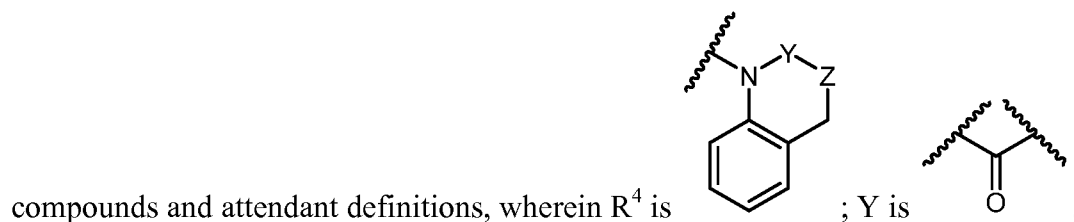
In certain embodiments, the invention relates to any of the aforementioned



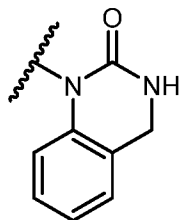
In certain embodiments, the invention relates to any of the aforementioned



In certain embodiments, the invention relates to any of the aforementioned

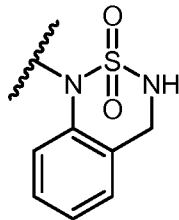


In certain embodiments, the invention relates to any of the aforementioned



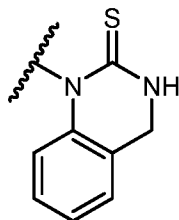
compounds and attendant definitions, wherein R^4 is

In certain embodiments, the invention relates to any of the aforementioned



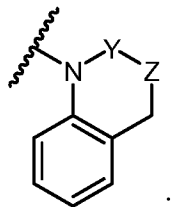
compounds and attendant definitions, wherein R^4 is

5 In certain embodiments, the invention relates to any of the aforementioned

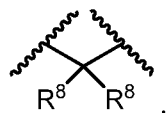
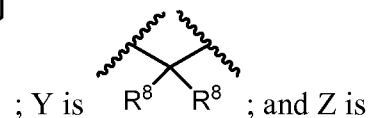


compounds and attendant definitions, wherein R^4 is

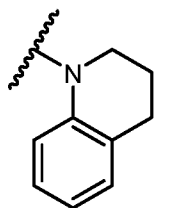
In certain embodiments, the invention relates to any of the aforementioned



compounds and attendant definitions, wherein R^4 is

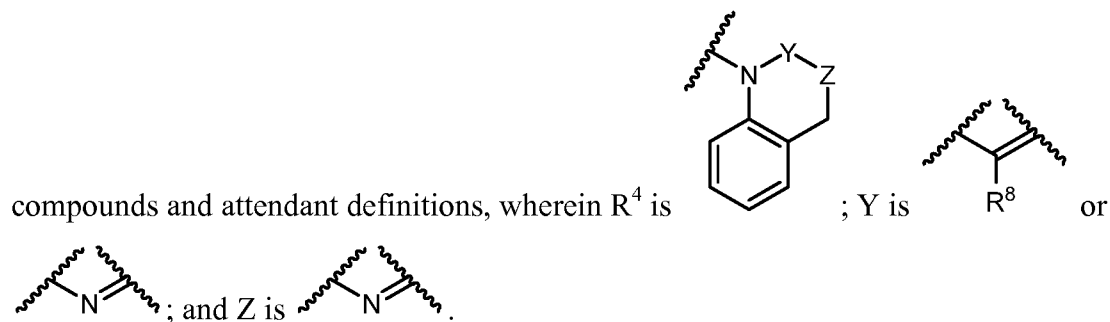


10 In certain embodiments, the invention relates to any of the aforementioned

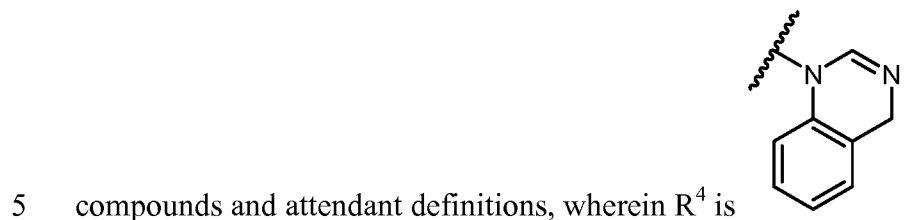


compounds and attendant definitions, wherein R^4 is

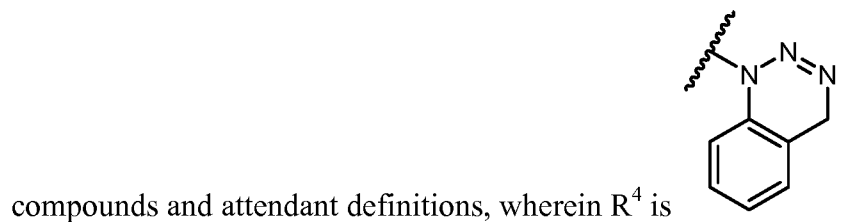
In certain embodiments, the invention relates to any of the aforementioned



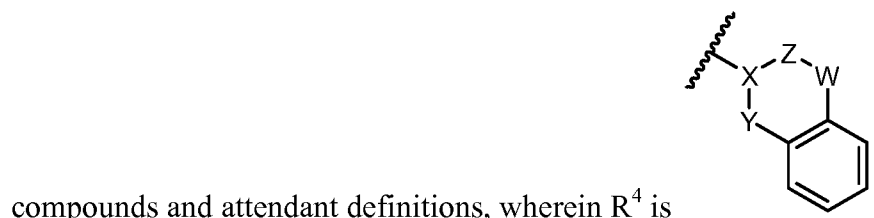
In certain embodiments, the invention relates to any of the aforementioned



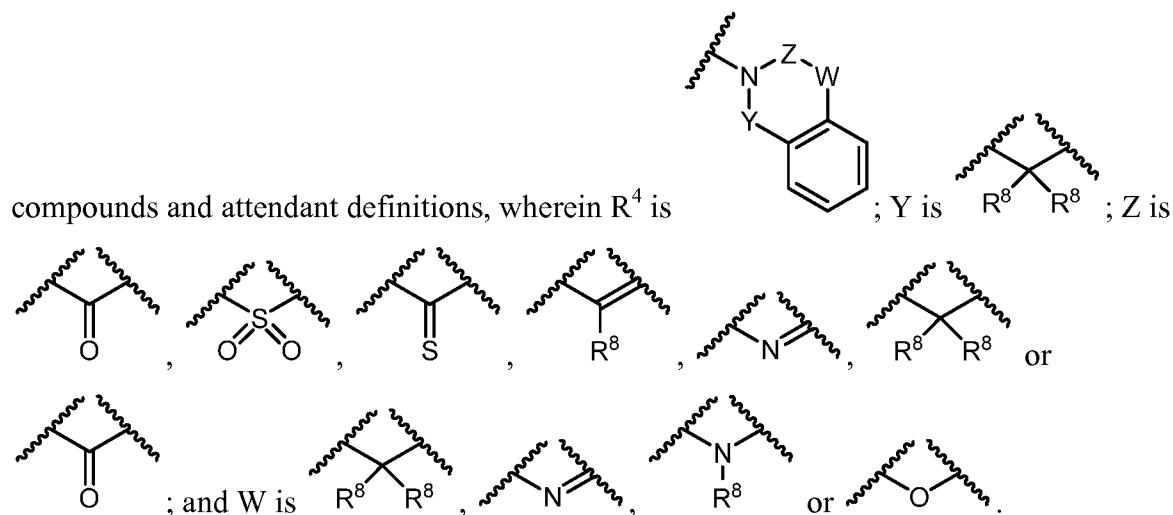
In certain embodiments, the invention relates to any of the aforementioned



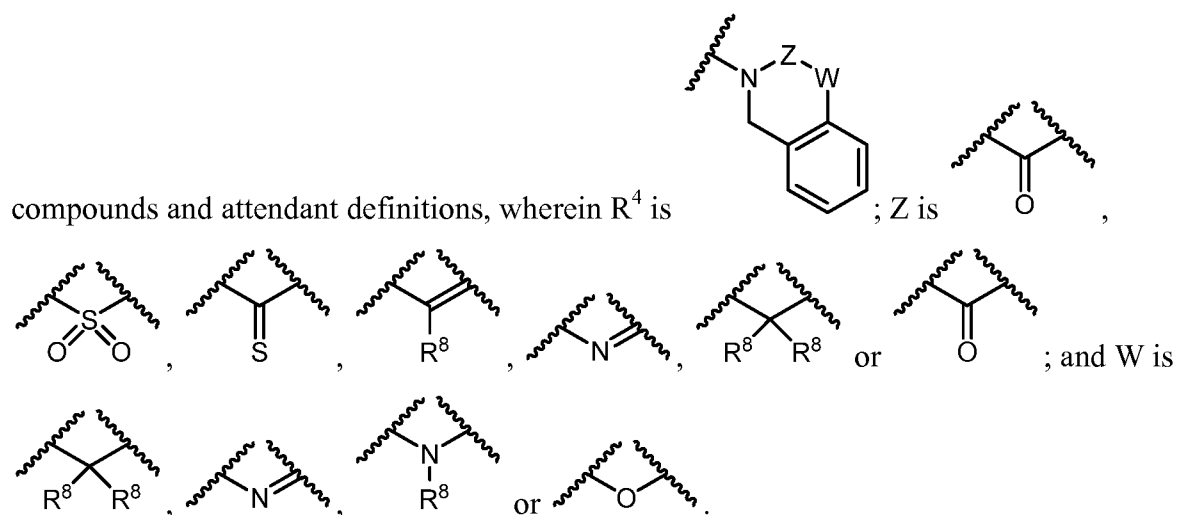
In certain embodiments, the invention relates to any of the aforementioned



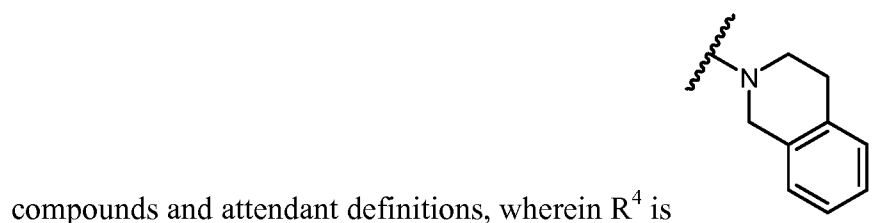
10 In certain embodiments, the invention relates to any of the aforementioned



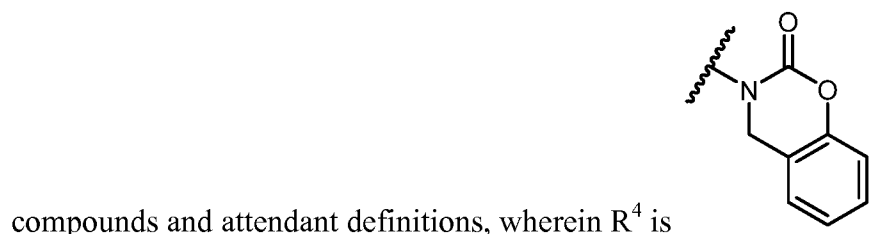
In certain embodiments, the invention relates to any of the aforementioned



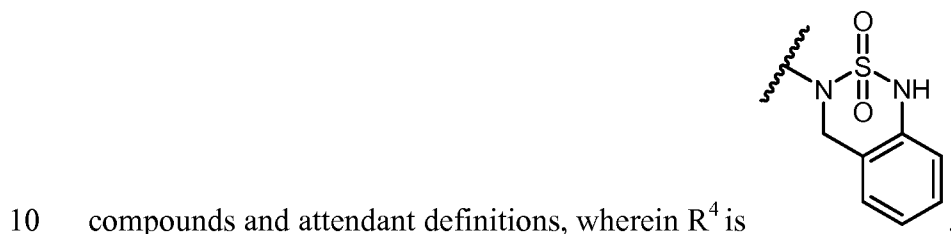
5 In certain embodiments, the invention relates to any of the aforementioned



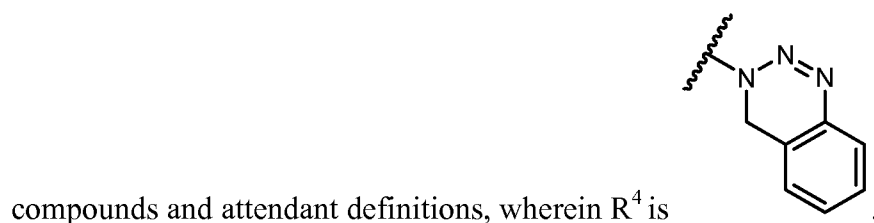
In certain embodiments, the invention relates to any of the aforementioned



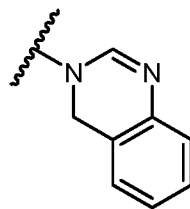
In certain embodiments, the invention relates to any of the aforementioned



In certain embodiments, the invention relates to any of the aforementioned

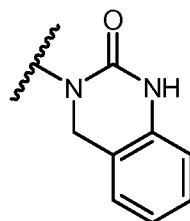


In certain embodiments, the invention relates to any of the aforementioned



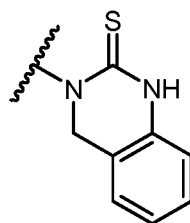
compounds and attendant definitions, wherein R^4 is

In certain embodiments, the invention relates to any of the aforementioned



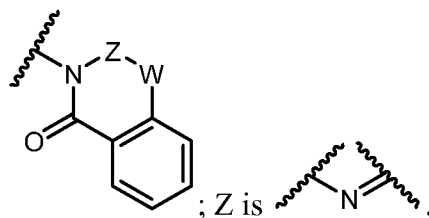
compounds and attendant definitions, wherein R^4 is

5 In certain embodiments, the invention relates to any of the aforementioned

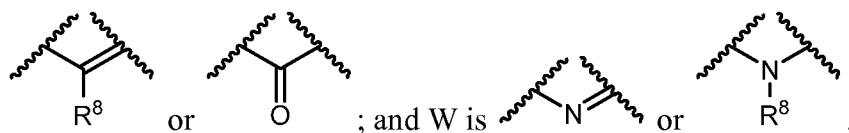


compounds and attendant definitions, wherein R^4 is

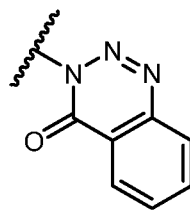
In certain embodiments, the invention relates to any of the aforementioned



compounds and attendant definitions, wherein R^4 is

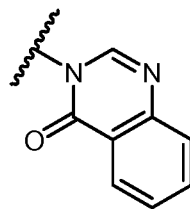


10 In certain embodiments, the invention relates to any of the aforementioned



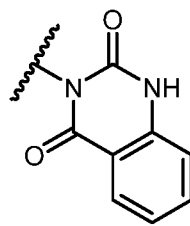
compounds and attendant definitions, wherein R^4 is

In certain embodiments, the invention relates to any of the aforementioned



compounds and attendant definitions, wherein R^4 is

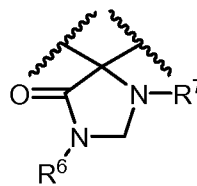
In certain embodiments, the invention relates to any of the aforementioned



compounds and attendant definitions, wherein R^4 is

- 5 In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions, wherein R^8 is hydrogen.

In certain embodiments, the invention relates to any of the aforementioned



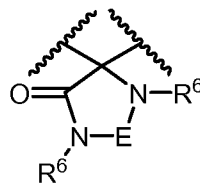
compounds and attendant definitions, wherein A is

- 10 In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions, wherein R^6 is hydrogen. In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions, wherein R^6 is alkyl. In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions, wherein R^6 is methyl.

- 15 In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions, wherein R^7 is aryl. In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions, wherein heteroaryl. In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions, wherein R^7 is phenyl substituted with 0-5 substituents independently selected from the group consisting of alkyl, alkenyl, alkynyl, halo, haloalkyl, fluoroalkyl, hydroxy, alkoxy, alkyenyloxy, alkynyloxy, carbocycloxy, heterocycloxy, haloalkoxy, fluoroalkyloxy, sulfhydryl, alkylthio, haloalkylthio, fluoroalkylthio, alkyenylthio, alkynylthio, sulfonic acid, alkylsulfonyl, haloalkylsulfonyl, fluoroalkylsulfonyl, alkenylsulfonyl, alkynylsulfonyl, alkoxysulfonyl, haloalkoxysulfonyl, fluoroalkoxysulfonyl, alkenyloxysulfonyl, alkynyloxysulfonyl, aminosulfonyl, sulfinic acid,
- 20

alkylsulfinyl, haloalkylsulfinyl, fluoralkylsulfinyl, alkenylsulfinyl, alkynylsulfinyl, alkoxy sulfinyl, haloalkoxy sulfinyl, fluoralkoxy sulfinyl, alkenyloxy sulfinyl, alkynyloxy sulfinyl, aminosulfinyl, formyl, alkylcarbonyl, haloalkylcarbonyl, fluoroalkylcarbonyl, alkenylcarbonyl, alkynylcarbonyl, carboxy, alkoxy carbonyl, haloalkoxy carbonyl, fluoroalkoxy carbonyl, alkenyloxy carbonyl, alkynyloxy carbonyl, alkylcarbonyloxy, haloalkylcarbonyloxy, fluoroalkylcarbonyloxy, alkenylcarbonyloxy, alkynylcarbonyloxy, alkylsulfonyloxy, haloalkylsulfonyloxy, fluoralkylsulfonyloxy, alkenylsulfonyloxy, alkynylsulfonyloxy, haloalkoxy sulfonyloxy, fluoralkoxy sulfonyloxy, alkenyloxy sulfonyloxy, alkynyloxy sulfonyloxy, alkylsulfinyloxy, haloalkylsulfinyloxy, fluoralkylsulfinyloxy, alkenylsulfinyloxy, alkynylsulfinyloxy, alkoxy sulfinyloxy, haloalkoxy sulfinyloxy, fluoralkoxy sulfinyloxy, alkenyloxy sulfinyloxy, alkynyloxy sulfinyloxy, aminosulfinyloxy, amino, amido, aminosulfonyl, aminosulfinyl, cyano, nitro, azido, phosphinyl, phosphoryl, silyl, silyloxy, and any of said substituents bound to the phenyl group through an alkylene moiety. In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions, wherein R⁷ is phenyl.

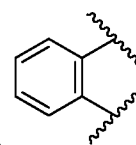
In certain embodiments, the invention relates to any of the aforementioned



compounds and attendant definitions, wherein A is

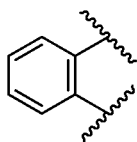
In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions, wherein R⁶ is hydrogen. In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions, wherein R⁶ is alkyl. In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions, wherein R⁶ is methyl.

In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions, wherein E is arylene. In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions, wherein E is heteroarylene. In certain embodiments, the invention relates to any of the

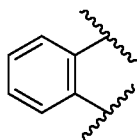


aforementioned compounds and attendant definitions, wherein E is substituted with 0-4 substituents independently selected from the group consisting of alkyl, alkenyl,

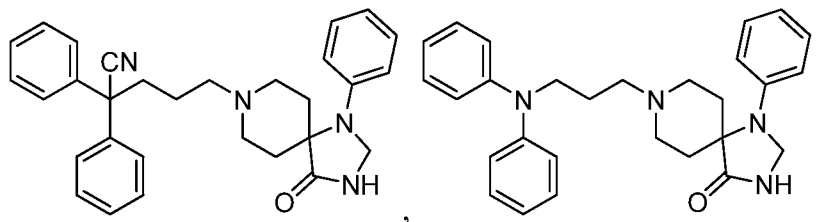
alkynyl, halo, haloalkyl, fluoroalkyl, hydroxy, alkoxy, alkyenyloxy, alkynyloxy, carbocycloxy, heterocycloxy, haloalkoxy, fluoroalkyloxy, sulfhydryl, alkylthio, haloalkylthio, fluoroalkylthio, alkyenylthio, alkynylthio, sulfonic acid, alkylsulfonyl, haloalkylsulfonyl, fluroralkylsulfonyl, alkenylsulfonyl, alkynylsulfonyl, alkoxysulfonyl, haloalkoxysulfonyl, fluroralkoxysulfonyl, alkenyloxysulfonyl, alkynyloxysulfonyl, aminosulfonyl, sulfinic acid, alkylsulfinyl, haloalkylsulfinyl, fluroralkylsulfinyl, alkenylsulfinyl, alkynylsulfinyl, alkoxysulfinyl, haloalkoxysulfinyl, fluroralkoxysulfinyl, alkenyloxysulfinyl, alkynyloxysulfinyl, aminosulfinyl, formyl, alkylcarbonyl, haloalkylcarbonyl, fluoroalkylcarbonyl, alkenylcarbonyl, alkynylcarbonyl, carboxy, alkoxycarbonyl, haloalkoxycarbonyl, fluoroalkoxycarbonyl, alkenyloxycarbonyl, alkynyloxycarbonyl, alkylcarbonyloxy, haloalkylcarbonyloxy, fluoroalkylcarbonyloxy, alkenylcarbonyloxy, alkynylcarbonyloxy, alkylsulfonyloxy, haloalkylsulfonyloxy, fluroralkylsulfonyloxy, alkenylsulfonyloxy, alkynylsulfonyloxy, haloalkoxysulfonyloxy, fluroralkoxysulfonyloxy, alkenyloxysulfonyloxy, alkynyloxysulfonyloxy, alkylsulfinyloxy, haloalkylsulfinyloxy, fluroralkylsulfinyloxy, alkenylsulfinyloxy, alkynylsulfinyloxy, alkoxysulfinyloxy, haloalkoxysulfinyloxy, fluroralkoxysulfinyloxy, alkenyloxysulfinyloxy, alkynyloxysulfinyloxy, aminosulfinyloxy, amino, amido, aminosulfonyl, aminosulfinyl, cyano, nitro, azido, phosphinyl, phosphoryl, silyl, silyloxy, and any of said substituents

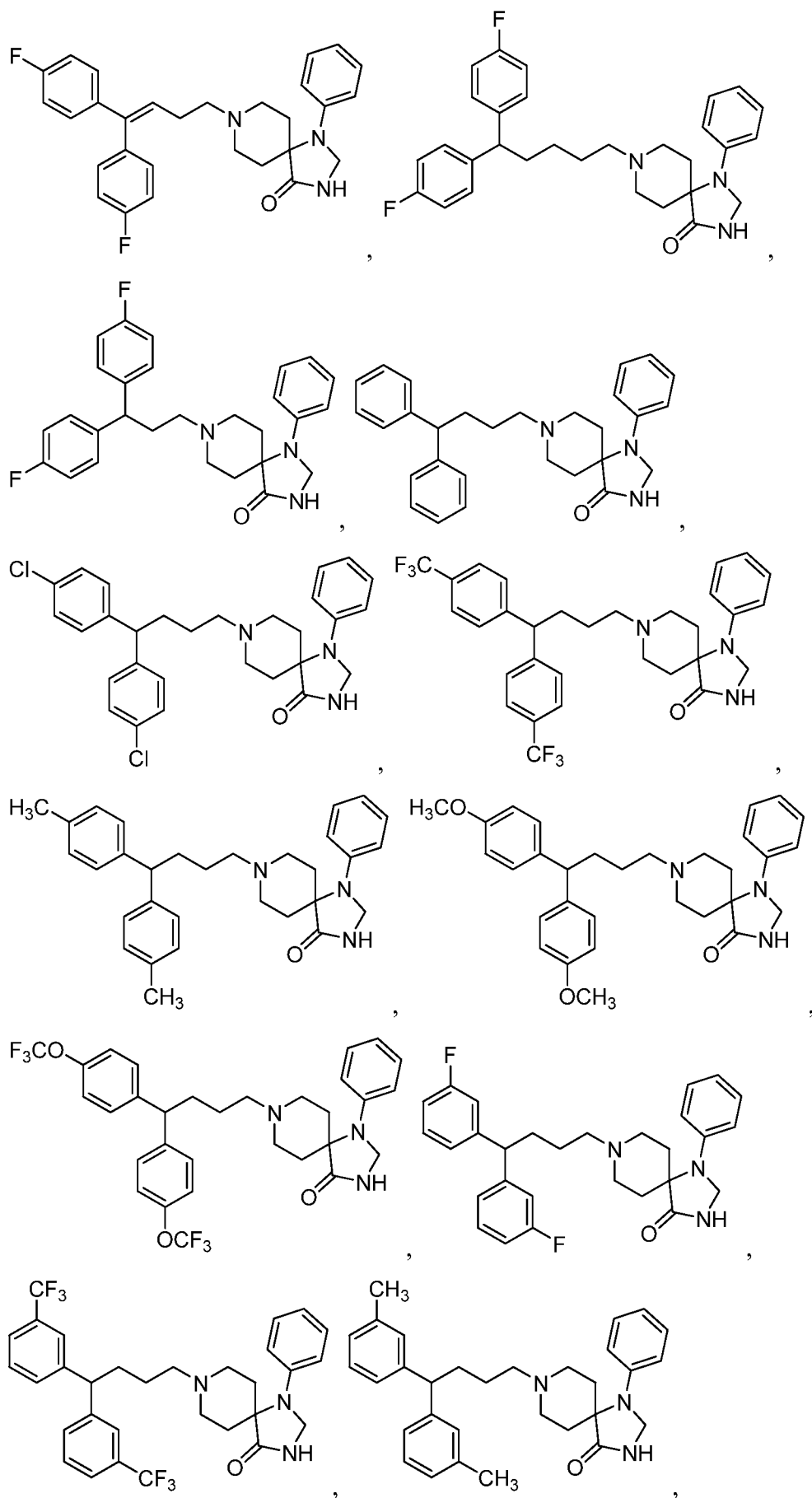


bound to the through an alkylene moiety. In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions, wherein E is

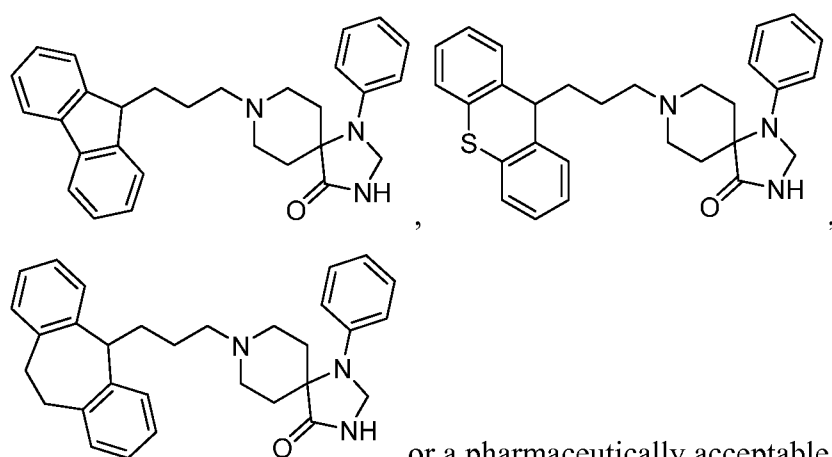


In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions, wherein the compound is



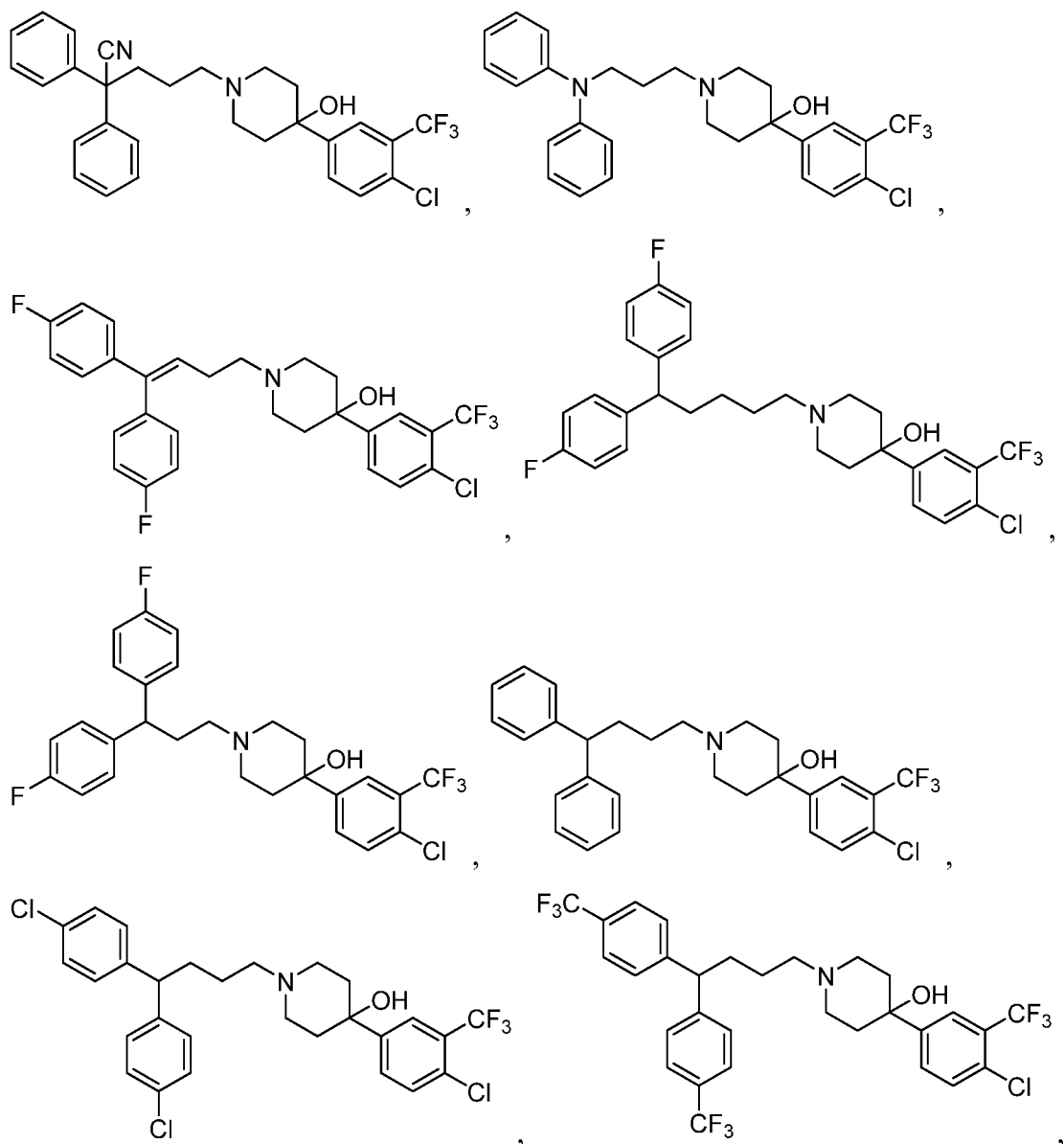


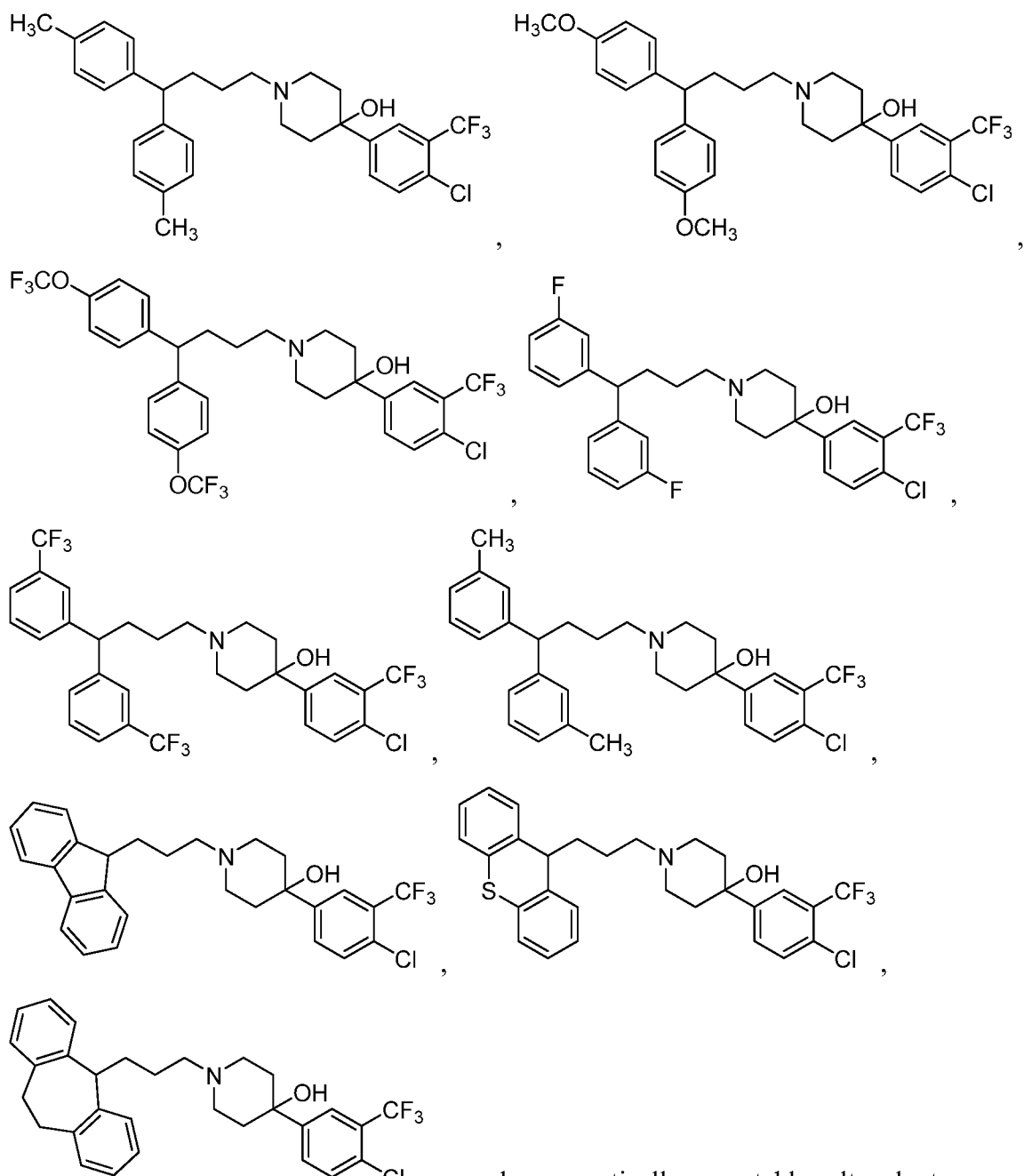
5



or a pharmaceutically acceptable salt, solvate or hydrate thereof.

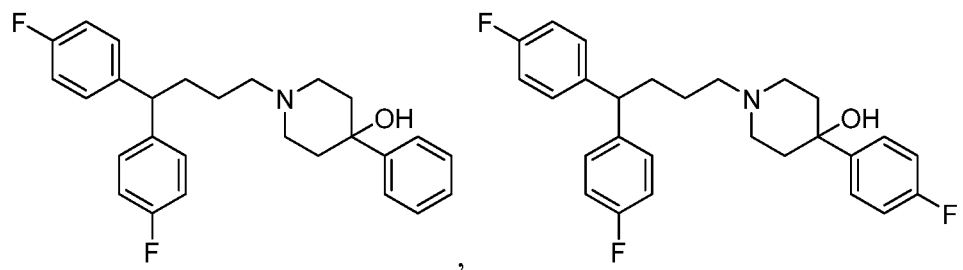
In certain embodiments, the invention relates to any of the aforementioned
5 compounds and attendant definitions, wherein the compound is

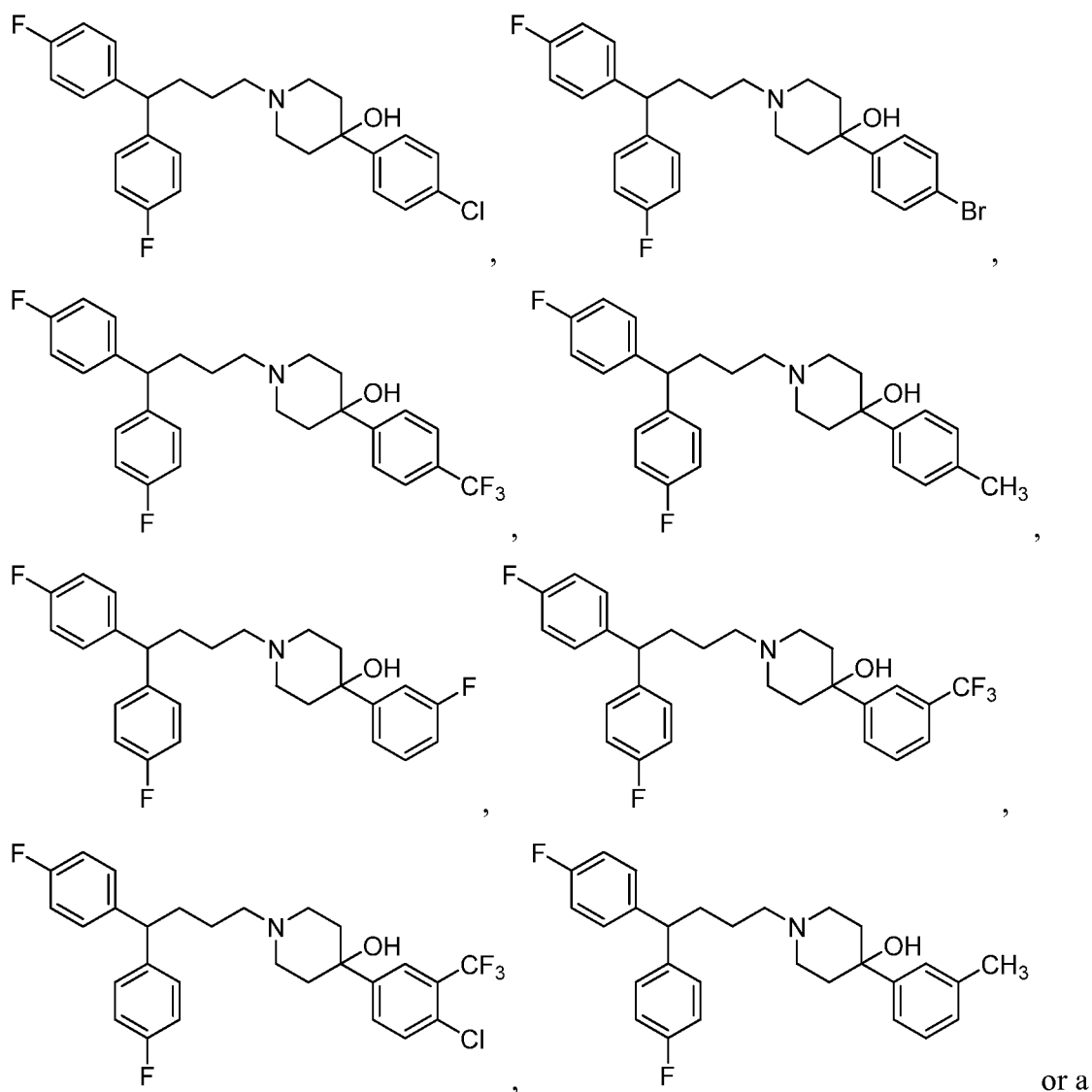




or a pharmaceutically acceptable salt, solvate or hydrate thereof.

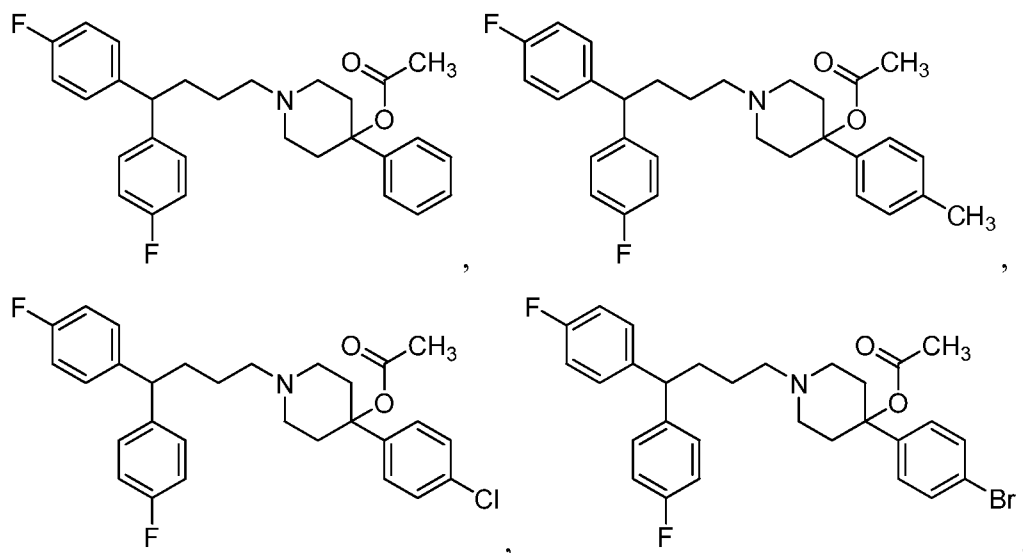
In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions, wherein the compound is

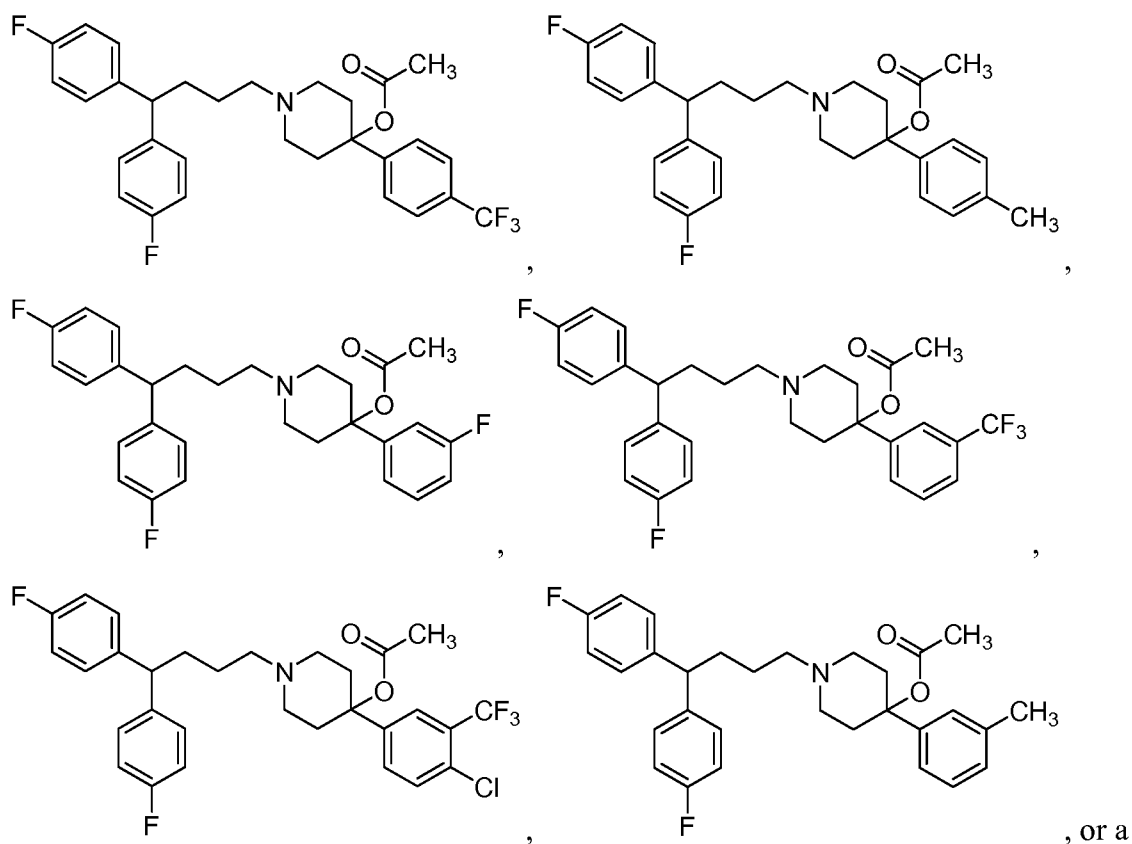




5 pharmaceutically acceptable salt, solvate or hydrate thereof.

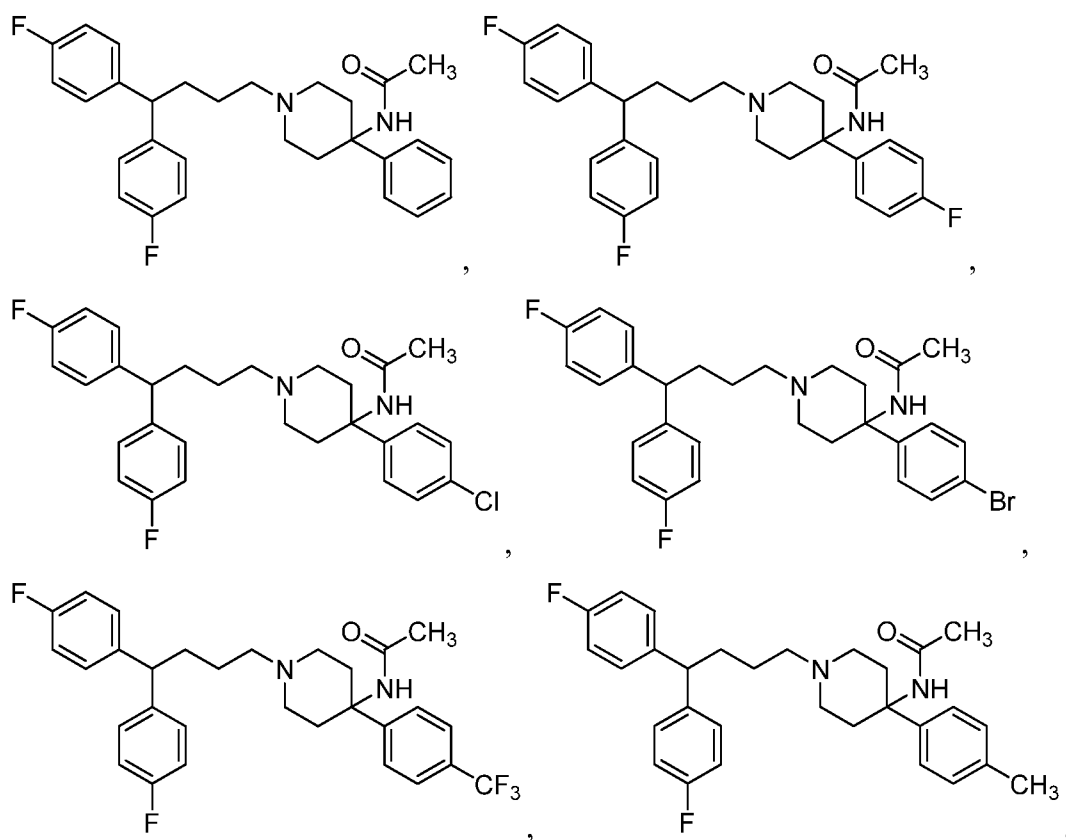
In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions, wherein the compound is

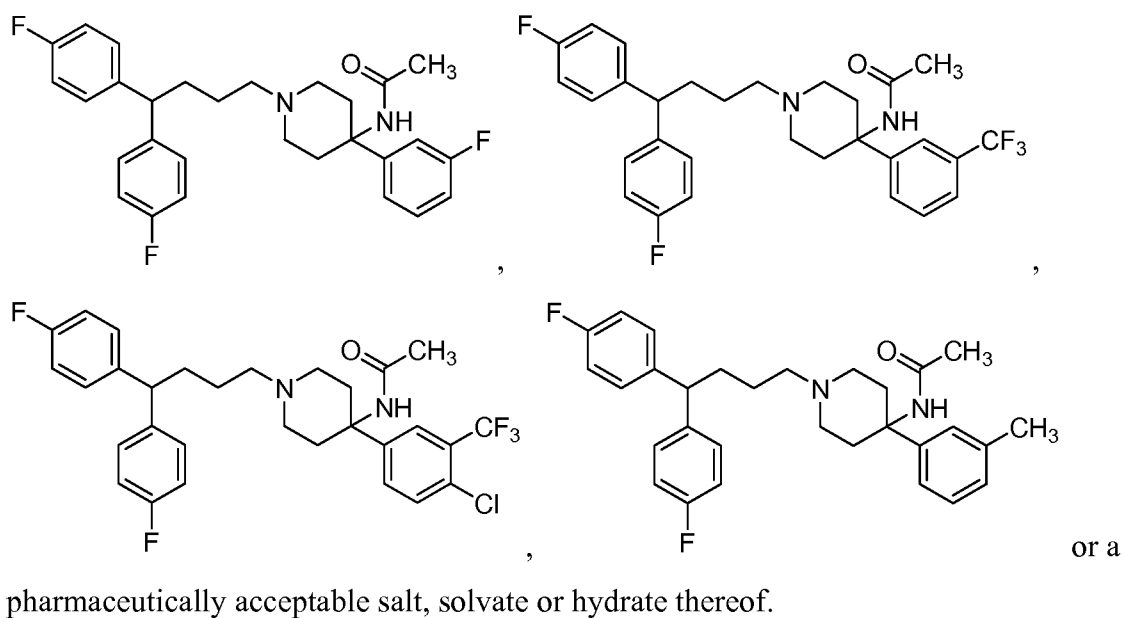




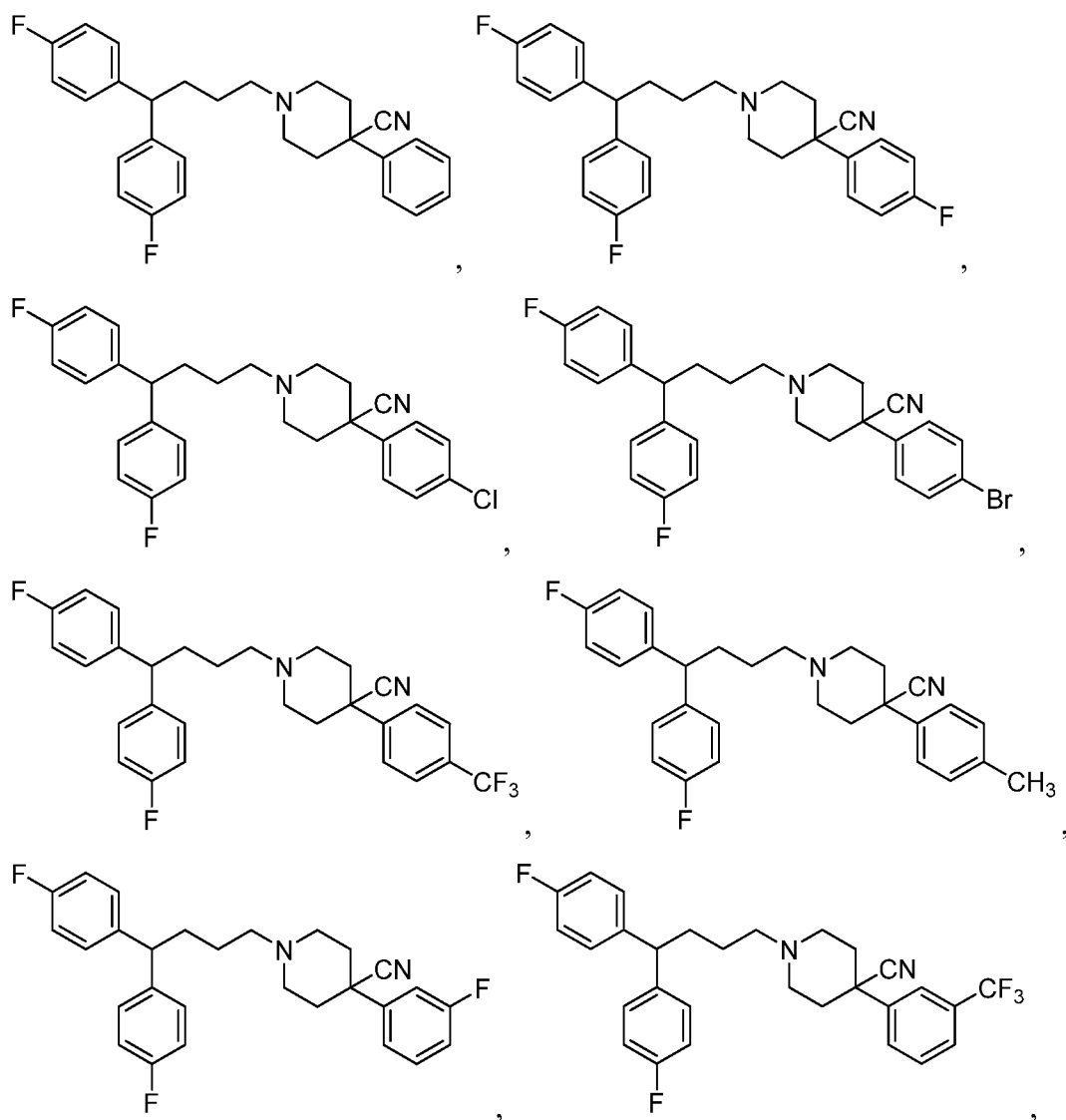
pharmaceutically acceptable salt, solvate or hydrate thereof.

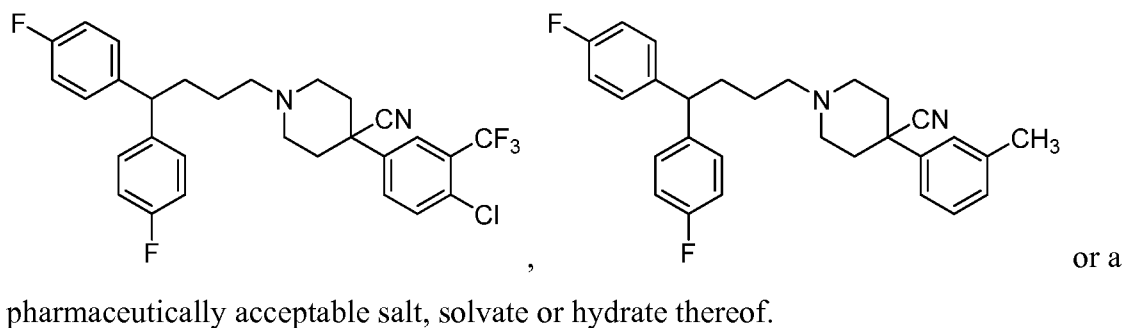
5 In certain embodiments, the invention relates to any of the aforementioned
compounds and attendant definitions, wherein the compound is



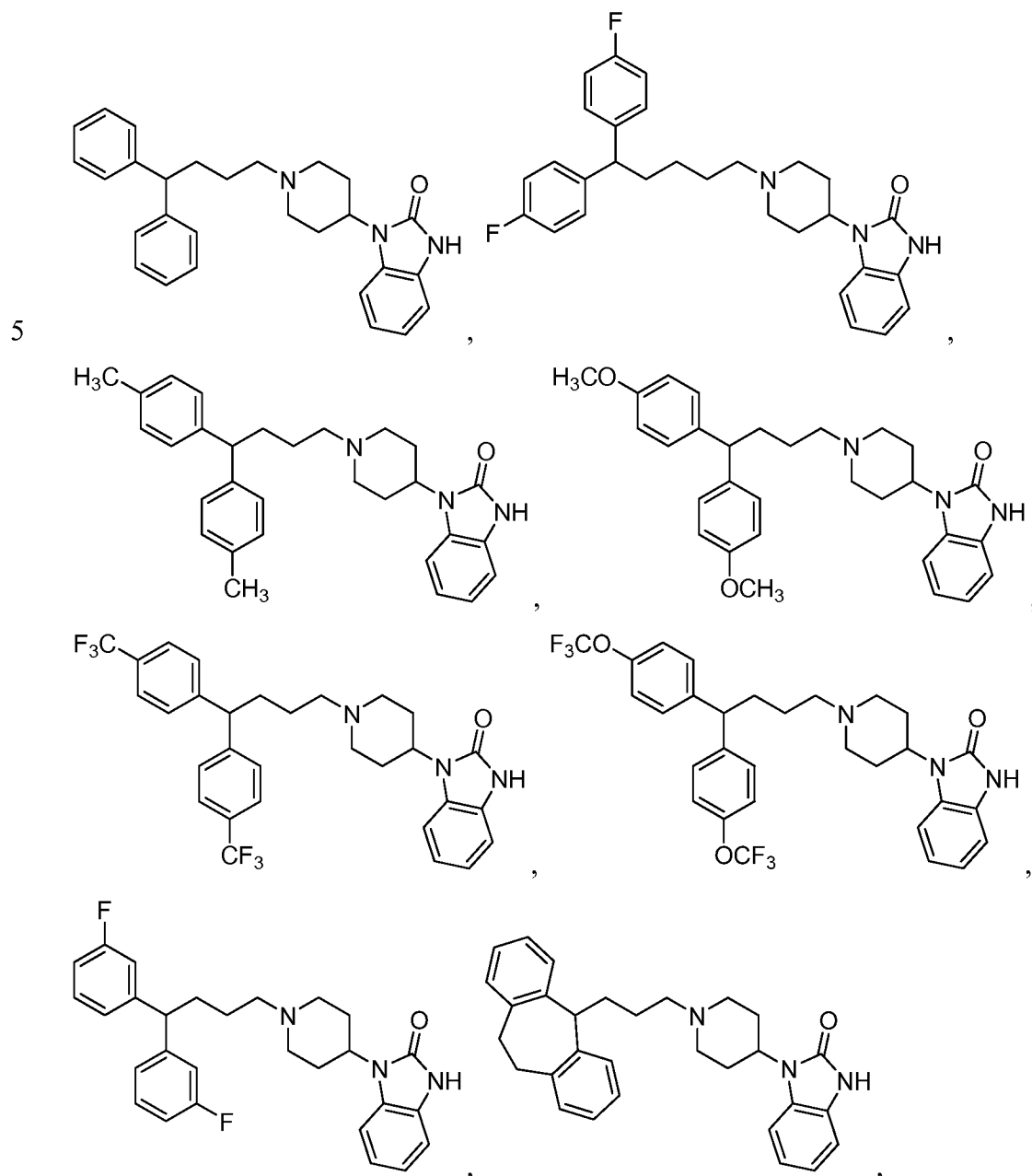


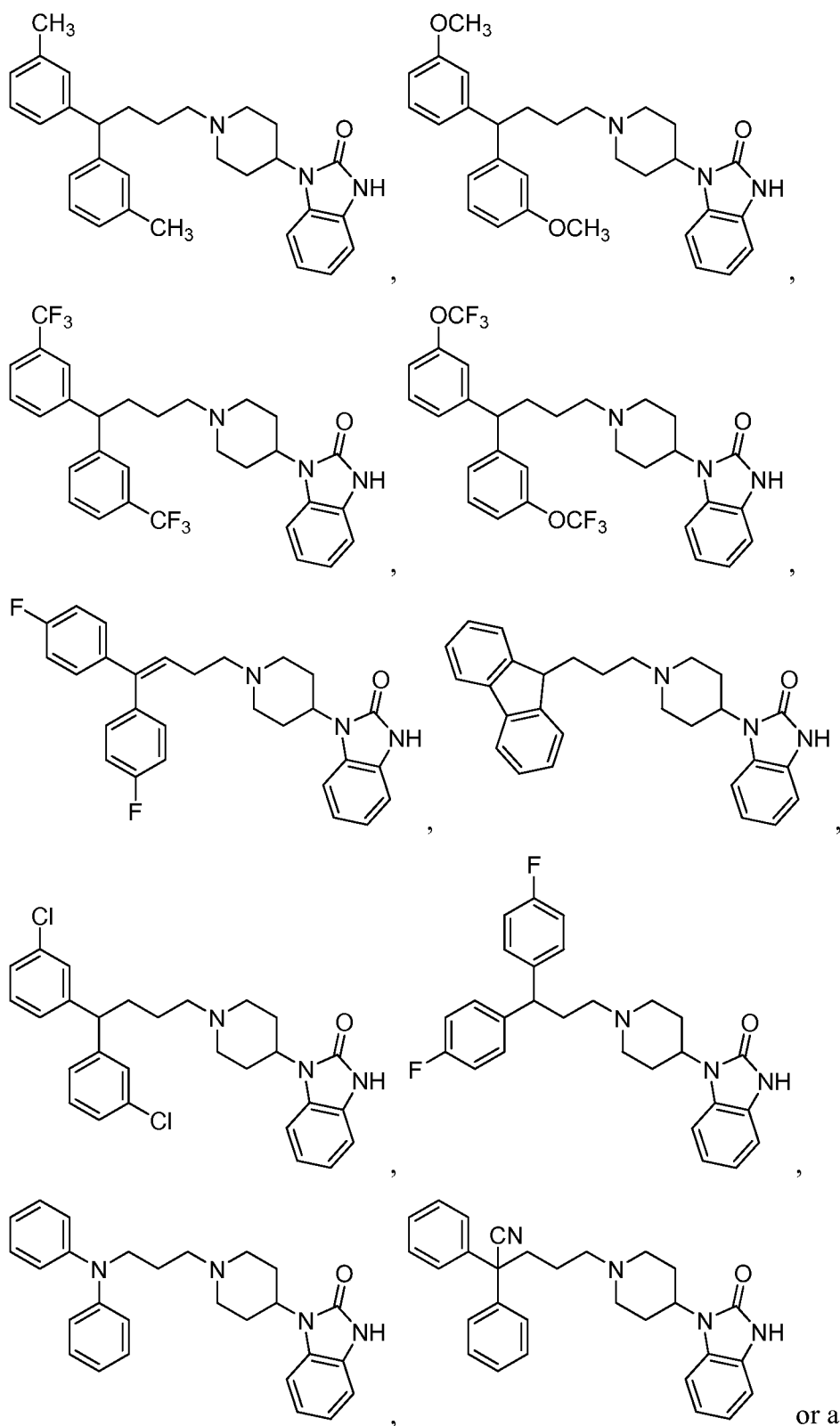
In certain embodiments, the invention relates to any of the aforementioned
 5 compounds and attendant definitions, wherein the compound is





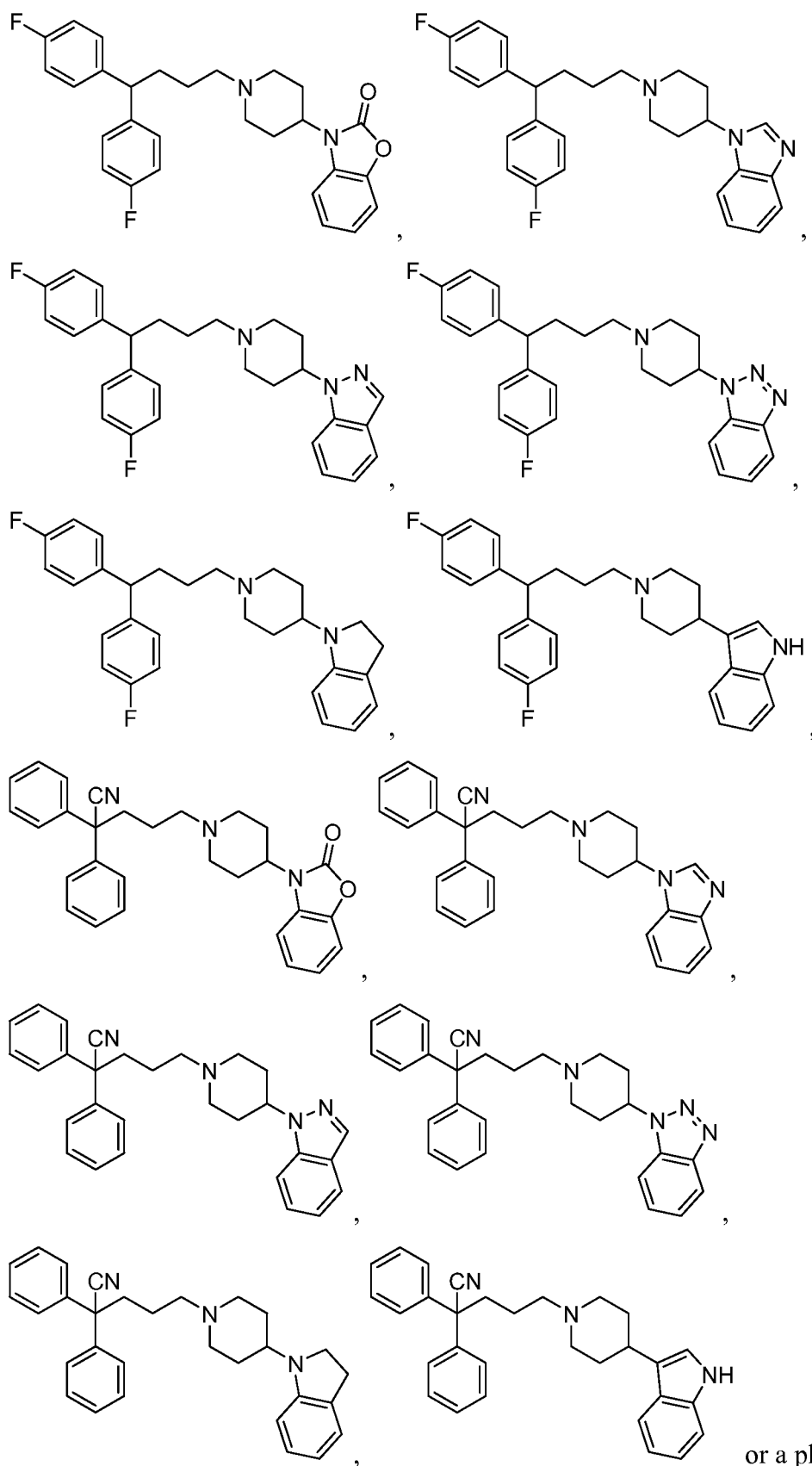
In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions, wherein the compound is





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

In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions, wherein the compound is

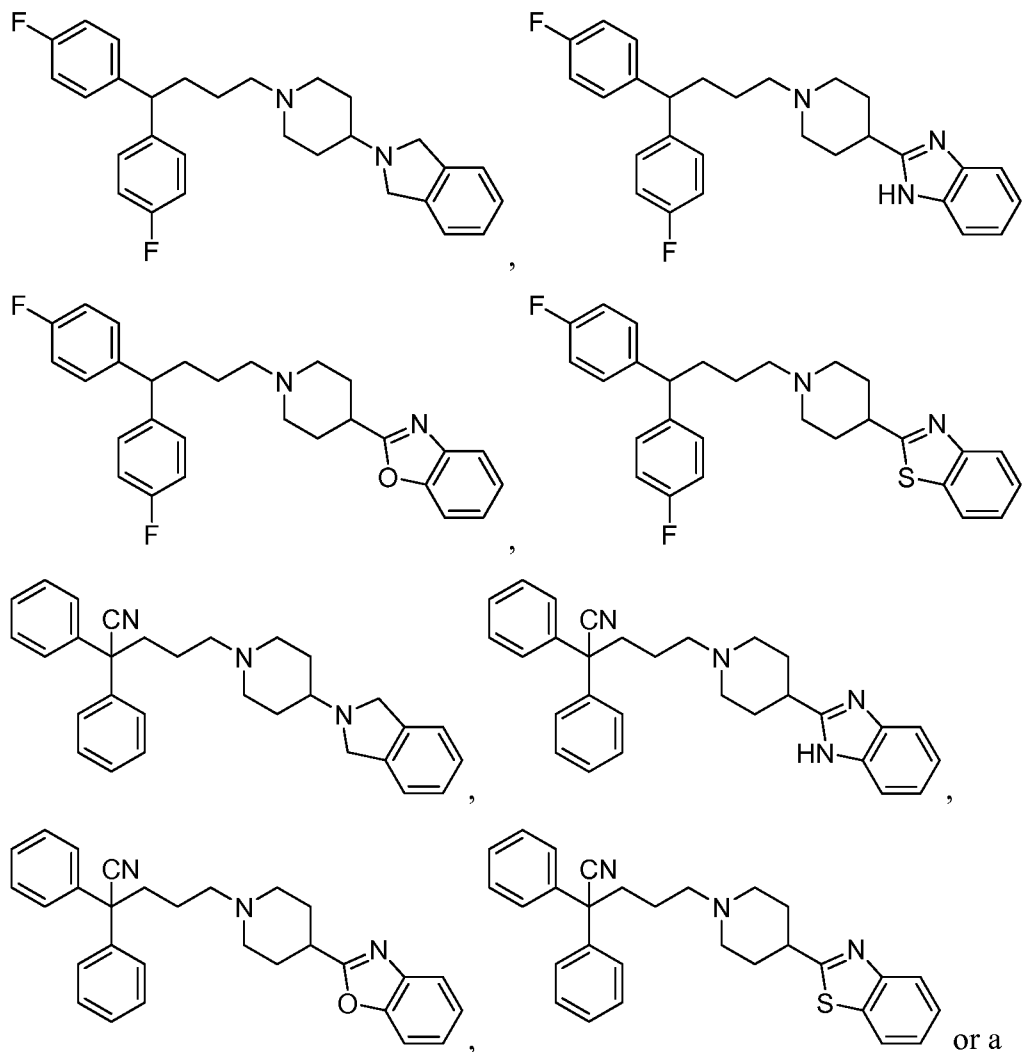


5

or a pharmaceutically

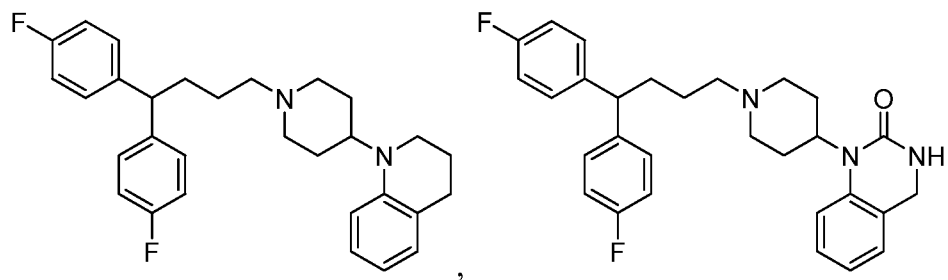
acceptable salt, solvate or hydrate thereof.

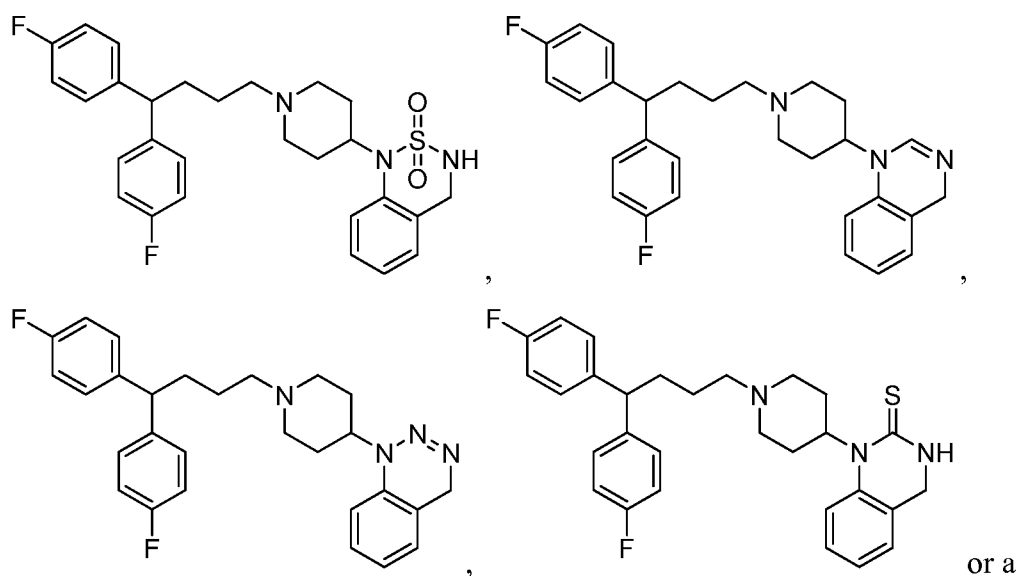
In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions, wherein the compound is



pharmaceutically acceptable salt, solvate or hydrate thereof.

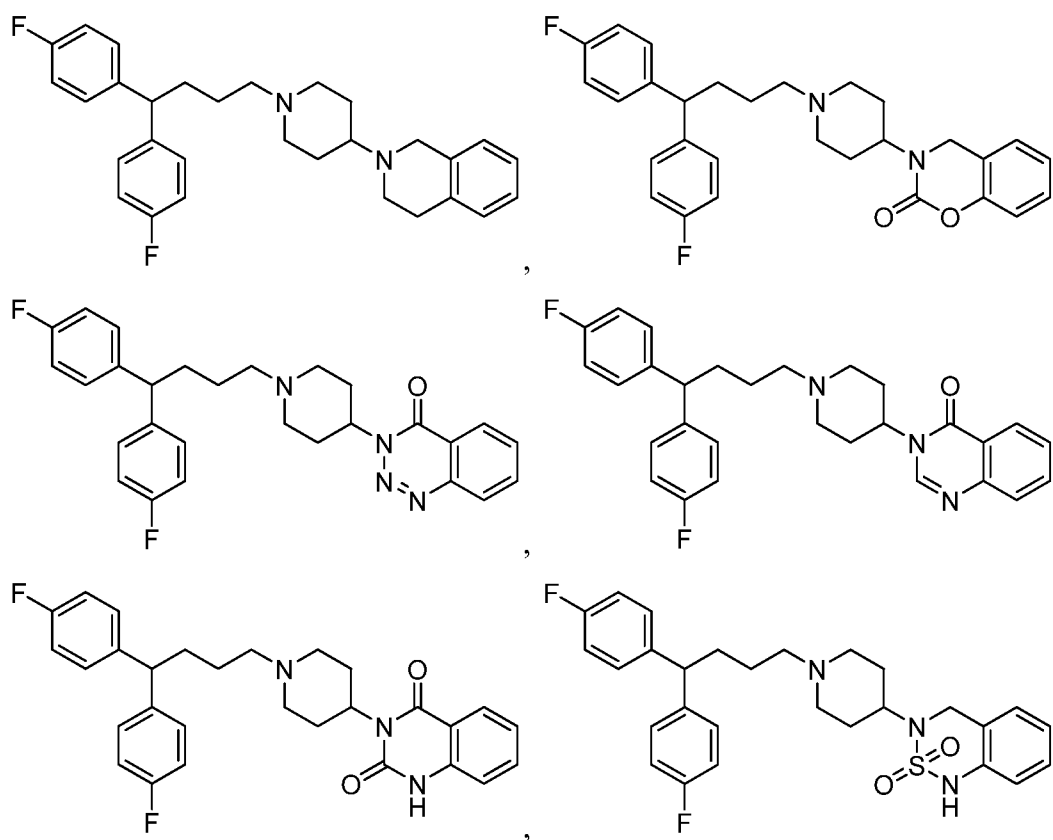
In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions, wherein the compound is

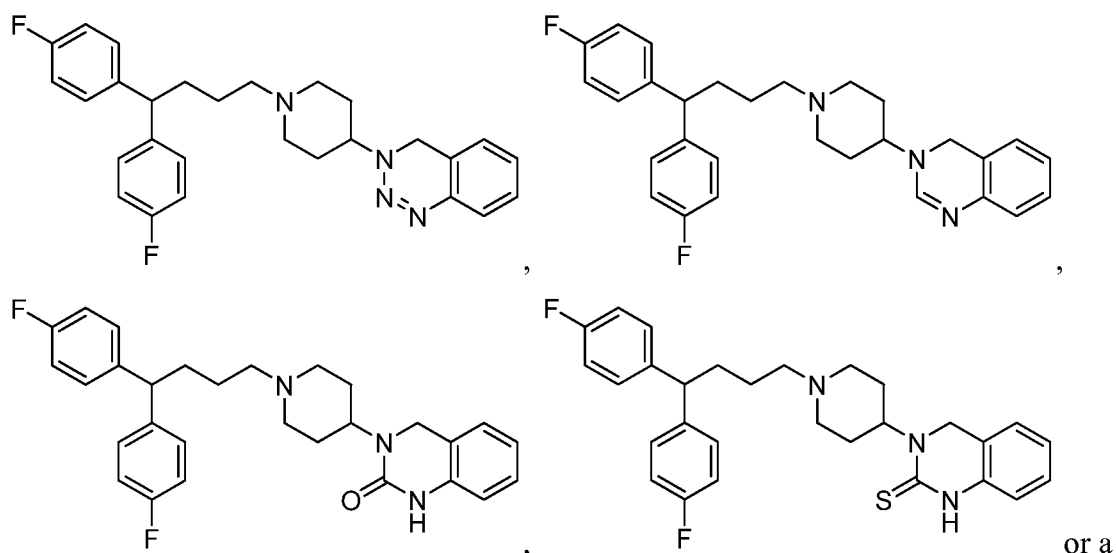




pharmaceutically acceptable salt, solvate or hydrate thereof.

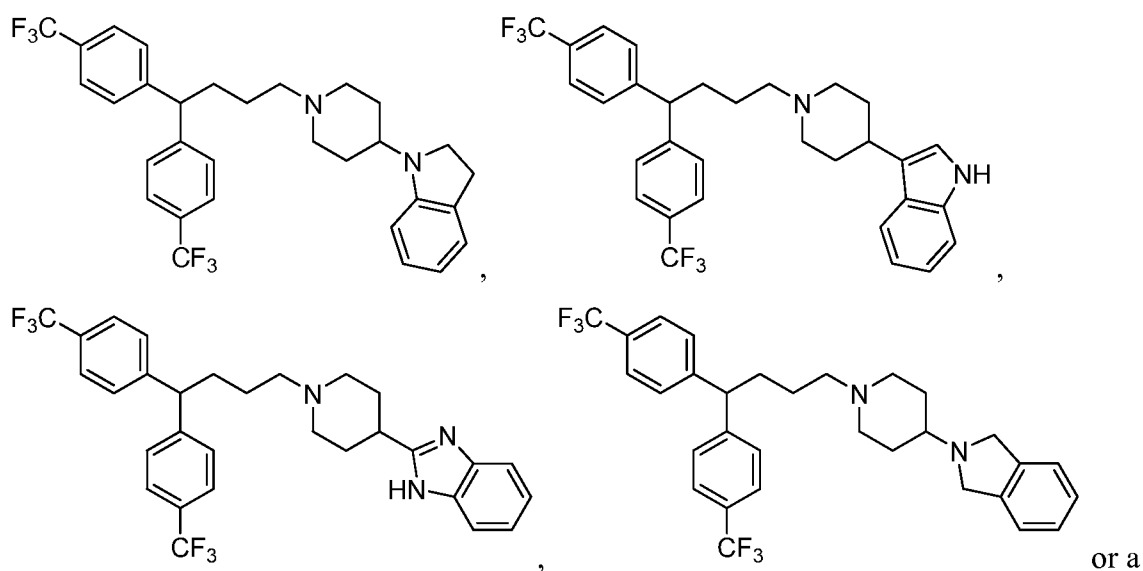
In certain embodiments, the invention relates to any of the aforementioned
 5 compounds and attendant definitions, wherein the compound is





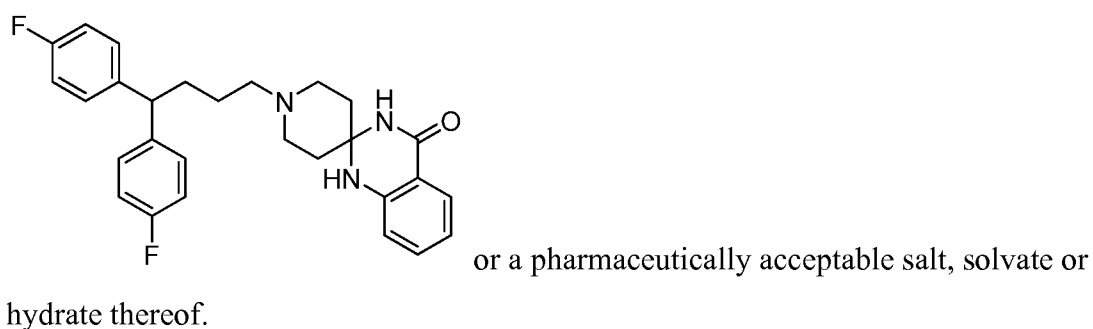
pharmaceutically acceptable salt, solvate or hydrate thereof.

- In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions, wherein the compound is
- 5

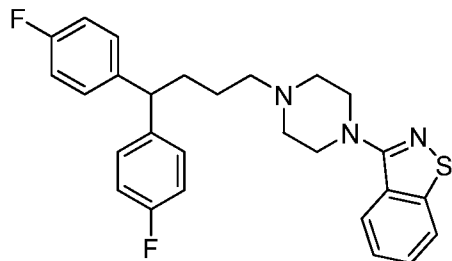


pharmaceutically acceptable salt, solvate or hydrate thereof.

- In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions, wherein the compound is
- 10



In certain embodiments, the invention relates to any of the aforementioned compounds and attendant definitions, wherein the compound is



or a pharmaceutically acceptable salt, solvate or hydrate thereof.

5 Many of the compounds of the invention may be provided as salts with pharmaceutically compatible counterions (*i.e.*, pharmaceutically acceptable salts). A “pharmaceutically acceptable salt” means any non-toxic salt that, upon administration to a recipient, is capable of providing, either directly or indirectly, a compound or a prodrug of a compound of this invention. A “pharmaceutically acceptable counterion” is an ionic
10 portion of a salt that is not toxic when released from the salt upon administration to a recipient. Pharmaceutically compatible salts may be formed with many acids, including but not limited to hydrochloric, sulfuric, acetic, lactic, tartaric, malic, succinic, etc. Salts tend to be more soluble in aqueous or other protonic solvents than are the corresponding free base forms.

15 Acids commonly employed to form pharmaceutically acceptable salts include inorganic acids such as hydrogen bisulfide, hydrochloric, hydrobromic, hydroiodic, sulfuric and phosphoric acid, as well as organic acids such as para-toluenesulfonic, salicylic, tartaric, bitartaric, ascorbic, maleic, besylic, fumaric, gluconic, glucuronic, formic, glutamic, methanesulfonic, ethanesulfonic, benzenesulfonic, lactic, oxalic, para-
20 bromophenylsulfonic, carbonic, succinic, citric, benzoic and acetic acid, and related inorganic and organic acids. Such pharmaceutically acceptable salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caprate, heptanoate,
25 propionate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, terephthalate, sulfonate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, β -hydroxybutyrate, glycolate, maleate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate,

naphthalene-2-sulfonate, mandelate and the like salts. Preferred pharmaceutically acceptable acid addition salts include those formed with mineral acids such as hydrochloric acid and hydrobromic acid, and especially those formed with organic acids such as maleic acid.

5 Suitable bases for forming pharmaceutically acceptable salts with acidic functional groups include, but are not limited to, hydroxides of alkali metals such as sodium, potassium, and lithium; hydroxides of alkaline earth metal such as calcium and magnesium; hydroxides of other metals, such as aluminum and zinc; ammonia, and organic amines, such as unsubstituted or hydroxy-substituted mono-, di-, or trialkylamines; dicyclohexylamine; 10 tributyl amine; pyridine; N-methyl,N-ethylamine; diethylamine; triethylamine; mono-, bis-, or tris-(2-hydroxy-lower alkyl amines), such as mono-, bis-, or tris-(2-hydroxyethyl)amine, 2-hydroxy-tert-butylamine, or tris-(hydroxymethyl)methylamine, N,N-di-lower alkyl-N-(hydroxy lower alkyl)-amines, such as N,N-dimethyl-N-(2-hydroxyethyl)amine, or tri-(2-hydroxyethyl)amine; N-methyl-D-glucamine; and amino acids such as arginine, lysine, and 15 the like.

Certain compounds of the invention and their salts may exist in more than one crystal form and the present invention includes each crystal form and mixtures thereof.

Certain compounds of the invention and their salts may also exist in the form of solvates, for example hydrates, and the present invention includes each solvate and 20 mixtures thereof.

Certain compounds of the invention may contain one or more chiral centers, and exist in different optically active forms. When compounds of the invention contain one chiral center, the compounds exist in two enantiomeric forms and the present invention includes both enantiomers and mixtures of enantiomers, such as racemic mixtures. The 25 enantiomers may be resolved by methods known to those skilled in the art, for example by formation of diastereoisomeric salts which may be separated, for example, by crystallization; formation of diastereoisomeric derivatives or complexes which may be separated, for example, by crystallization, gas-liquid or liquid chromatography; selective reaction of one enantiomer with an enantiomer-specific reagent, for example enzymatic 30 esterification; or gas-liquid or liquid chromatography in a chiral environment, for example on a chiral support for example silica with a bound chiral ligand or in the presence of a chiral solvent. It will be appreciated that where the desired enantiomer is converted into another chemical entity by one of the separation procedures described above, a further step

may be used to liberate the desired enantiomeric form. Alternatively, specific enantiomers may be synthesized by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting one enantiomer into the other by asymmetric transformation.

5 When a compound of the invention contains more than one chiral center, it may exist in diastereoisomeric forms. The diastereoisomeric compounds may be separated by methods known to those skilled in the art, for example chromatography or crystallization and the individual enantiomers may be separated as described above. The present invention includes each diastereoisomer of compounds of the invention and mixtures thereof.

10 Certain compounds of the invention may exist in different tautomeric forms or as different geometric isomers, and the present invention includes each tautomer and/or geometric isomer of compounds of the invention and mixtures thereof.

 Certain compounds of the invention may exist in different stable conformational forms which may be separable. Torsional asymmetry due to restricted rotation about an
15 asymmetric single bond, for example because of steric hindrance or ring strain, may permit separation of different conformers. The present invention includes each conformational isomer of compounds of the invention and mixtures thereof.

 Certain compounds of the invention may exist in zwitterionic form and the present invention includes each zwitterionic form of compounds of the invention and mixtures
20 thereof.

 The present invention also includes pro-drugs. As used herein the term "pro-drug" refers to an agent which is converted into the parent drug in vivo by some physiological chemical process (e.g., a prodrug on being brought to the physiological pH is converted to the desired drug form). Pro-drugs are often useful because, in some situations, they may be
25 easier to administer than the parent drug. They may, for instance, be bioavailable by oral administration whereas the parent drug is not. The prodrug may also have improved solubility in pharmacological compositions over the parent drug. An example, without limitation, of a pro-drug would be a compound of the present invention wherein it is administered as an ester (the "pro-drug") to facilitate transmittal across a cell membrane
30 where water solubility is not beneficial, but then it is metabolically hydrolyzed to the carboxylic acid once inside the cell where water solubility is beneficial. Pro-drugs have many useful properties. For example, a pro-drug may be more water soluble than the ultimate drug, thereby facilitating intravenous administration of the drug. A pro-drug may

also have a higher level of oral bioavailability than the ultimate drug. After administration, the prodrug is enzymatically or chemically cleaved to deliver the ultimate drug in the blood or tissue.

Exemplary pro-drugs upon cleavage release the corresponding free acid, and such hydrolyzable ester-forming residues of the compounds of this invention include but are not limited to carboxylic acid substituents (e.g., $-\text{C}(\text{O})_2\text{H}$ or a moiety that contains a carboxylic acid) wherein the free hydrogen is replaced by $(\text{C}_1\text{-C}_4)\text{alkyl}$, $(\text{C}_2\text{-C}_{12})\text{alkanoyloxymethyl}$, $(\text{C}_4\text{-C}_9)1\text{-(alkanoyloxy)ethyl}$, 1-methyl-1-(alkanoyloxy)-ethyl having from 5 to 10 carbon atoms, alkoxycarbonyloxymethyl having from 3 to 6 carbon atoms, 1-(alkoxycarbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-methyl-1-(alkoxycarbonyloxy)ethyl having from 5 to 8 carbon atoms, N-(alkoxycarbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxycarbonyl)amino)ethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N- $(\text{C}_1\text{-C}_2)\text{alkylamino}(\text{C}_2\text{-C}_3)\text{alkyl}$ (such as β -dimethylaminoethyl), carbamoyl- $(\text{C}_1\text{-C}_2)\text{alkyl}$, N,N-di $(\text{C}_1\text{-C}_2)\text{-alkylcarbamoyl-}(\text{C}_1\text{-C}_2)\text{alkyl}$ and piperidino-, pyrrolidino- or morpholino $(\text{C}_2\text{-C}_3)\text{alkyl}$.

Other exemplary pro-drugs release an alcohol or amine of a compound of the invention wherein the free hydrogen of a hydroxyl or amine substituent is replaced by $(\text{C}_1\text{-C}_6)\text{alkanoyloxymethyl}$, 1- $((\text{C}_1\text{-C}_6)\text{alkanoyloxy})\text{ethyl}$, 1-methyl-1- $((\text{C}_1\text{-C}_6)\text{alkanoyloxy})\text{ethyl}$, $(\text{C}_1\text{-C}_6)\text{alkoxycarbonyl-oxymethyl}$, N- $(\text{C}_1\text{-C}_6)\text{alkoxycarbonylamino-methyl}$, succinoyl, $(\text{C}_1\text{-C}_6)\text{alkanoyl}$, α -amino $(\text{C}_1\text{-C}_4)\text{alkanoyl}$, arylactyl and α -aminoacyl, or α -aminoacyl- α -aminoacyl wherein said α -aminoacyl moieties are independently any of the naturally occurring L-amino acids found in proteins, $-\text{P}(\text{O})(\text{OH})_2$, $-\text{P}(\text{O})(\text{O}(\text{C}_1\text{-C}_6)\text{alkyl})_2$ or glycosyl (the radical resulting from detachment of the hydroxyl of the hemiacetal of a carbohydrate).

The phrase "protecting group" as used herein means temporary substituents which protect a potentially reactive functional group from undesired chemical transformations. Examples of such protecting groups include esters of carboxylic acids, silyl ethers of alcohols, and acetals and ketals of aldehydes and ketones, respectively. The field of protecting group chemistry has been reviewed (Greene, T.W.; Wuts, P.G.M. *Protective Groups in Organic Synthesis*, 2nd ed.; Wiley: New York, 1991). Protected forms of the inventive compounds are included within the scope of this invention.

The term “chemically protected form,” as used herein, pertains to a compound in which one or more reactive functional groups are protected from undesirable chemical reactions, that is, are in the form of a protected or protecting group (also known as a masked or masking group). It may be convenient or desirable to prepare, purify, and/or handle the active compound in a chemically protected form.

By protecting a reactive functional group, reactions involving other unprotected reactive functional groups can be performed, without affecting the protected group; the protecting group may be removed, usually in a subsequent step, without substantially affecting the remainder of the molecule. See, for example, *Protective Groups in Organic Synthesis* (T. Green and P. Wuts, Wiley, 1991), and *Protective Groups in Organic Synthesis* (T. Green and P. Wuts; 3rd Edition; John Wiley and Sons, 1999).

For example, a hydroxy group may be protected as an ether (-OR) or an ester (-OC(=O)R), for example, as: a t-butyl ether; a benzyl, benzhydryl (diphenylmethyl), or trityl (triphenylmethyl) ether; a trimethylsilyl or t-butyldimethylsilyl ether; or an acetyl ester (-OC(=O)CH₃, -OAc).

For example, an aldehyde or ketone group may be protected as an acetal or ketal, respectively, in which the carbonyl group (C(=O)) is converted to a diether (C(OR)₂), by reaction with, for example, a primary alcohol. The aldehyde or ketone group is readily regenerated by hydrolysis using a large excess of water in the presence of acid.

For example, an amine group may be protected, for example, as an amide (-NRC(=O)R) or a urethane (-NRC(=O)OR), for example, as: a methyl amide (-NHC(=O)CH₃); a benzyloxy amide (-NHC(=O)OCH₂C₆H₅NHCbz); as a t-butoxy amide (-NHC(=O)OC(CH₃)₃, -NHBoc); a 2-biphenyl-2-propoxy amide (-NHC(=O)OC(CH₃)₂C₆H₄C₆H₅NHBoc), as a 9-fluorenylmethoxy amide (-NHFmoc), as a 6-nitroveratryloxy amide (-NHNVoc), as a 2-trimethylsilylethyloxy amide (-NHTEoc), as a 2,2,2-trichloroethyloxy amide (-NHTroc), as an allyloxy amide (-NHAlloc), as a 2-(phenylsulfonyl)ethyloxy amide (-NHPsec); or, in suitable cases (e.g., cyclic amines), as a nitroxide radical.

For example, a carboxylic acid group may be protected as an ester or an amide, for example, as: a benzyl ester; a t-butyl ester; a methyl ester; or a methyl amide.

For example, a thiol group may be protected as a thioether (-SR), for example, as: a benzyl thioether; or an acetamidomethyl ether (-SCH₂NHC(=O)CH₃). tamoxifen.

As discussed below, the foregoing autophagy inducing compounds are useful in the treatment of autophagy associated diseases, such as neurodegenerative diseases caused by mismatched proteins, such as polyglutamine expansion diseases, and can be prepared so as to be useful for the treatment of diseases caused by misfolded protein aggregates and other autophagy-related diseases.

METHODS OF PREPARING DIARYL- OR DIHETEROARYLBUTYL HALIDES

One aspect of the invention relates to a method of preparing diphenylbutyl bromides comprising the steps of reacting at least two equivalents of an aryl magnesium bromide with one equivalent of a γ -butyrolactone to first open the lactone and form a compound containing a primary alcohol and an aryl ketone, and then react with the resultant aryl ketone, thereby forming a tertiary alcohol; dehydrating the tertiary alcohol to form an alkene; hydrogenating the alkene; and converting the primary alcohol to a halide, such as a bromide. Another aspect of the invention relates to the use of a heteroaryl magnesium bromide instead of an aryl magnesium bromide. Another aspect of the invention relates to the use of another carbanion, such as a lithiate. In another aspect of the invention, instead of forming a halide, in the last step, a tosylate or other sulfonate leaving group may be formed.

METHODS OF USE

One aspect the invention provides a method for inhibiting autophagy in a subject for whom inhibition of autophagy is beneficial, comprising administering to the subject a compound of the invention such that autophagy activity in the subject is altered and treatment or prevention is achieved. In certain embodiments, the subject is a human.

The term "treating" as used herein, encompasses the administration and/or application of one or more compounds described herein, to a subject, for the purpose of providing prevention of or management of, and/or remedy for a condition. "Treatment" for the purposes of this disclosure, may, but does not have to, provide a cure; rather, "treatment" may be in the form of management of the condition. When the compounds described herein are used to treat unwanted proliferating cells, including cancers, "treatment" includes partial or total destruction of the undesirable proliferating cells with minimal destructive effects on normal cells. A desired mechanism of treatment of unwanted rapidly proliferating cells, including cancer cells, at the cellular level is apoptosis.

The term "preventing" as used herein includes either preventing or slowing the onset of a clinically evident unwanted cell proliferation altogether or preventing or slowing

the onset of a preclinically evident stage of unwanted rapid cell proliferation in individuals at risk. Also intended to be encompassed by this definition is the prevention or slowing of metastasis of malignant cells or to arrest or reverse the progression of malignant cells. This includes prophylactic treatment of those at risk of developing precancers and cancers. Also
5 encompassed by this definition is the prevention or slowing of restenosis in subjects that have undergone angioplasty or a stent procedure.

The term "subject" for purposes of treatment includes any human or animal subject who has been diagnosed with, has symptoms of, or is at risk of developing a disorder wherein inhibition of autophagy would be beneficial. For methods of prevention the subject
10 is any human or animal subject. To illustrate, for purposes of prevention, a subject may be a human subject who is at risk of or is genetically predisposed to obtaining a disorder characterized by unwanted, rapid cell proliferation, such as cancer. The subject may be at risk due to exposure to carcinogenic agents, being genetically predisposed to disorders characterized by unwanted, rapid cell proliferation, and so on. Besides being useful for
15 human treatment, the compounds described herein are also useful for veterinary treatment of mammals, including companion animals and farm animals, such as, but not limited to dogs, cats, horses, cows, sheep, and pigs.

Another aspect of the invention relates to methods for treating autophagy associated diseases caused by misfolded protein aggregates, in a subject, comprising the step of
20 administering to a subject an autophagy inducing compound in an amount effective to treat or prevent the disease. The methods and compositions of the present invention can be used to treat, for example, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease, spinocerebellar ataxia, oculopharyngeal muscular dystrophy, prion diseases, fatal familial insomnia, alpha-1 antitrypsin deficiency,
25 dentatorubral pallidoluysian atrophy, frontal temporal dementia, progressive supranuclear palsy, x-linked spinobulbar muscular atrophy, and neuronal intranuclear hyaline inclusion disease or any other diseases caused by misfolded protein aggregates described herein.

Another aspect of the invention relates to methods for treating autophagy associated diseases caused by protein aggregates, in a subject, comprising the step of administering to
30 a subject an autophagy inducing compound in an amount effective to treat or prevent the disease. The methods and compositions of the present invention can be used to treat, for example, diabetes. Deposition of amyloid, derived from the polypeptide hormone islet amyloid polypeptide (IAPP; 'amylin') is the single most typical islet alteration in type 2

diabetes. Islet amyloid is a polymerization product of a novel β -cell regulatory product. Similar to the situation in Alzheimer's disease, it has been argued that the amyloid may not be of importance since there is no strict correlation between the degree of islet amyloid infiltration and the disease. However, amyloid is important in subjects where islets have
5 been destroyed by pronounced islet amyloid deposits. Even when there is less islet amyloid the deposits are widely spread, and β -cells show ultrastructural signs of cell membrane destruction. It is suggested that type 2 diabetes is heterogeneous and that in one major subtype aggregation of IAPP into amyloid fibrils is determining the progressive loss of β -cells. Interestingly, development of islet amyloid may be an important event in the loss of
10 β -cell function after islet transplantation into type 1 diabetic subjects. In certain embodiments, the disease is type I diabetes. In certain embodiments, the disease is type II diabetes.

The methods and compositions of the present invention may also be used to treat other diseases associated with autophagy. Such diseases may include cancer. Preferably, the
15 cancer may be any cancer wherein the induction of autophagy would inhibit cell growth and division, reduce mutagenesis, remove mitochondria and other organelles damaged by reactive oxygen species or kill developing tumor cells. For example, the cancer may be cancer of the breast, liver, prostate, stomach, colon, GI tract, pancreases, skin, head, neck, throat, bladder, eye, esophagus, lung, kidney, or brain.

20 One aspect of the invention relates to a method of treating or preventing cancer, comprising the step of administering to a subject in need thereof a therapeutically effective amount of one or more compounds of formula I, or a pharmaceutically acceptable salt, biologically active metabolite, solvate, hydrate, prodrug, enantiomer or stereoisomer thereof.

25 Suppression of autophagy has been proposed to be a new anticancer therapy by promoting radiosensitization and chemosensitization. In an animal model of cancer therapy, inhibition of therapy-induced autophagy either with shRNA against a key autophagy gene ATG5 or with anti-malarial drug chloroquine enhanced cell death and tumor regression of Myc-driven tumors in which either activated p53 or alkylating chemotherapy was used to
30 drive tumor cell death (Amaravadi, R.K., et al., Autophagy inhibition enhances therapy-induced apoptosis in a Myc-induced model of lymphoma. J Clin Invest, 2007. 117(2): p. 326-36). Chloroquine causes a dose-dependent accumulation of large autophagic vesicles and enhances alkylating therapy-induced cell death to a similar degree as knockdown of

ATG5. In the case of chronic myelogenous leukemia (CML), chloroquine markedly enhanced death of a CML cell line, K562, induced by imatinib. Furthermore, imatinib-resistant cell lines, BaF3/T315I and BaF3/E255K, can be induced to die by co-treatment with imatinib and chloroquine. These studies suggest that inhibiting autophagy may
 5 potentiate conventional chemotherapy.

The National Cancer Institute alphabetical list of cancer includes: Acute Lymphoblastic Leukemia, Adult; Acute Lymphoblastic Leukemia, Childhood; Acute Myeloid Leukemia, Adult; Adrenocortical Carcinoma; Adrenocortical Carcinoma, Childhood; AIDS-Related Lymphoma; AIDS-Related Malignancies; Anal Cancer;
 10 Astrocytoma, Childhood Cerebellar; Astrocytoma, Childhood Cerebral; Bile Duct Cancer, Extrahepatic; Bladder Cancer; Bladder Cancer, Childhood; Bone Cancer, Osteosarcoma/Malignant Fibrous Histiocytoma; Brain Stem Glioma, Childhood; Brain Tumor, Adult; Brain Tumor, Brain Stem Glioma, Childhood; Brain Tumor, Cerebellar Astrocytoma, Childhood; Brain Tumor, Cerebral Astrocytoma/Malignant Glioma,
 15 Childhood; Brain Tumor, Ependymoma, Childhood; Brain Tumor, Medulloblastoma, Childhood; Brain Tumor, Supratentorial Primitive Neuroectodermal Tumors, Childhood; Brain Tumor, Visual Pathway and Hypothalamic Glioma, Childhood; Brain Tumor, Childhood (Other); Breast Cancer; Breast Cancer and Pregnancy; Breast Cancer, Childhood; Breast Cancer, Male; Bronchial Adenomas/Carcinoids, Childhood; Carcinoid
 20 Tumor, Childhood; Carcinoid Tumor, Gastrointestinal; Carcinoma, Adrenocortical; Carcinoma, Islet Cell; Carcinoma of Unknown Primary; Central Nervous System Lymphoma, Primary; Cerebellar Astrocytoma, Childhood; Cerebral Astrocytoma/Malignant Glioma, Childhood; Cervical Cancer; Childhood Cancers; Chronic Lymphocytic Leukemia; Chronic Myelogenous Leukemia; Chronic Myeloproliferative
 25 Disorders; Clear Cell Sarcoma of Tendon Sheaths; Colon Cancer; Colorectal Cancer, Childhood; Cutaneous T-Cell Lymphoma; Endometrial Cancer; Ependymoma, Childhood; Epithelial Cancer, Ovarian; Esophageal Cancer; Esophageal Cancer, Childhood; Ewing's Family of Tumors; Extracranial Germ Cell Tumor, Childhood; Extragonadal Germ Cell Tumor; Extrahepatic Bile Duct Cancer; Eye Cancer, Intraocular Melanoma; Eye Cancer,
 30 Retinoblastoma; Gallbladder Cancer; Gastric (Stomach) Cancer; Gastric (Stomach) Cancer, Childhood; Gastrointestinal Carcinoid Tumor; Germ Cell Tumor, Extracranial, Childhood; Germ Cell Tumor, Extragonadal; Germ Cell Tumor, Ovarian; Gestational Trophoblastic Tumor; Glioma, Childhood Brain Stem; Glioma, Childhood Visual Pathway and

Hypothalamic; Hairy Cell Leukemia; Head and Neck Cancer; Hepatocellular (Liver) Cancer, Adult (Primary); Hepatocellular (Liver) Cancer, Childhood (Primary); Hodgkin's Lymphoma, Adult; Hodgkin's Lymphoma, Childhood; Hodgkin's Lymphoma During Pregnancy; Hypopharyngeal Cancer; Hypothalamic and Visual Pathway Glioma,

5 Childhood; Intraocular Melanoma; Islet Cell Carcinoma (Endocrine Pancreas); Kaposi's Sarcoma; Kidney Cancer; Laryngeal Cancer; Laryngeal Cancer, Childhood; Leukemia, Acute Lymphoblastic, Adult; Leukemia, Acute Lymphoblastic, Childhood; Leukemia, Acute Myeloid, Adult; Leukemia, Acute Myeloid, Childhood; Leukemia, Chronic Lymphocytic; Leukemia, Chronic Myelogenous; Leukemia, Hairy Cell; Lip and Oral

10 Cavity Cancer; Liver Cancer, Adult (Primary); Liver Cancer, Childhood (Primary); Lung Cancer, Non-Small Cell; Lung Cancer, Small Cell; Lymphoblastic Leukemia, Adult Acute; Lymphoblastic Leukemia, Childhood Acute; Lymphocytic Leukemia, Chronic; Lymphoma, AIDS-Related; Lymphoma, Central Nervous System (Primary); Lymphoma, Cutaneous T-Cell; Lymphoma, Hodgkin's, Adult; Lymphoma, Hodgkin's, Childhood; Lymphoma,

15 Hodgkin's During Pregnancy; Lymphoma, Non-Hodgkin's, Adult; Lymphoma, Non-Hodgkin's, Childhood; Lymphoma, Non-Hodgkin's During Pregnancy; Lymphoma, Primary Central Nervous System; Macroglobulinemia, Waldenstrom's; Male Breast Cancer; Malignant Mesothelioma, Adult; Malignant Mesothelioma, Childhood; Malignant Thymoma; Medulloblastoma, Childhood; Melanoma; Melanoma, Intraocular; Merkel Cell

20 Carcinoma; Mesothelioma, Malignant; Metastatic Squamous Neck Cancer with Occult Primary; Multiple Endocrine Neoplasia Syndrome, Childhood; Multiple Myeloma/Plasma Cell Neoplasm; Mycosis Fungoides; Myelodysplastic Syndromes; Myelogenous Leukemia, Chronic; Myeloid Leukemia, Childhood Acute; Myeloma, Multiple; Myeloproliferative Disorders, Chronic; Nasal Cavity and Paranasal Sinus Cancer; Nasopharyngeal Cancer;

25 Nasopharyngeal Cancer, Childhood; Neuroblastoma; Non-Hodgkin's Lymphoma, Adult; Non-Hodgkin's Lymphoma, Childhood; Non-Hodgkin's Lymphoma During Pregnancy; Non-Small Cell Lung Cancer; Oral Cancer, Childhood; Oral Cavity and Lip Cancer; Oropharyngeal Cancer; Osteosarcoma/Malignant Fibrous Histiocytoma of Bone; Ovarian Cancer, Childhood; Ovarian Epithelial Cancer; Ovarian Germ Cell Tumor; Ovarian Low

30 Malignant Potential Tumor; Pancreatic Cancer; Pancreatic Cancer, Childhood; Pancreatic Cancer, Islet Cell; Paranasal Sinus and Nasal Cavity Cancer; Parathyroid Cancer; Penile Cancer; Pheochromocytoma; Pineal and Supratentorial Primitive Neuroectodermal Tumors, Childhood; Pituitary Tumor; Plasma Cell Neoplasm/Multiple Myeloma; Pleuropulmonary

Blastoma; Pregnancy and Breast Cancer; Pregnancy and Hodgkin's Lymphoma; Pregnancy and Non-Hodgkin's Lymphoma; Primary Central Nervous System Lymphoma; Primary Liver Cancer, Adult; Primary Liver Cancer, Childhood; Prostate Cancer; Rectal Cancer; Renal Cell (Kidney) Cancer; Renal Cell Cancer, Childhood; Renal Pelvis and Ureter,

5 Transitional Cell Cancer; Retinoblastoma; Rhabdomyosarcoma, Childhood; Salivary Gland Cancer; Salivary Gland Cancer, Childhood; Sarcoma, Ewing's Family of Tumors; Sarcoma, Kaposi's; Sarcoma (Osteosarcoma)/Malignant Fibrous Histiocytoma of Bone; Sarcoma, Rhabdomyosarcoma, Childhood; Sarcoma, Soft Tissue, Adult; Sarcoma, Soft Tissue, Childhood; Sezary Syndrome; Skin Cancer; Skin Cancer, Childhood; Skin Cancer

10 (Melanoma); Skin Carcinoma, Merkel Cell; Small Cell Lung Cancer; Small Intestine Cancer; Soft Tissue Sarcoma, Adult; Soft Tissue Sarcoma, Childhood; Squamous Neck Cancer with Occult Primary, Metastatic; Stomach (Gastric) Cancer; Stomach (Gastric) Cancer, Childhood; Supratentorial Primitive Neuroectodermal Tumors, Childhood; T-Cell Lymphoma, Cutaneous; Testicular Cancer; Thymoma, Childhood; Thymoma, Malignant;

15 Thyroid Cancer; Thyroid Cancer, Childhood; Transitional Cell Cancer of the Renal Pelvis and Ureter; Trophoblastic Tumor, Gestational; Unknown Primary Site, Cancer of, Childhood; Unusual Cancers of Childhood; Ureter and Renal Pelvis, Transitional Cell Cancer; Urethral Cancer; Uterine Sarcoma; Vaginal Cancer; Visual Pathway and Hypothalamic Glioma, Childhood; Vulvar Cancer; Waldenstrom's Macroglobulinemia; and

20 Wilms' Tumor. The methods of the present invention may be useful to treat such types of cancer.

Another aspect of the invention relates to a method of treating or preventing acute pancreatitis, comprising the step of administering to a subject in need thereof a therapeutically effective amount of one or more compounds of formula I, or a

25 pharmaceutically acceptable salt, biologically active metabolite, solvate, hydrate, prodrug, enantiomer or stereoisomer thereof.

Pancreatitis is an inflammation of the pancreas mediated by the release of digestive enzymes that eventually lead to the destruction of the organ itself. Pancreatitis can be a severe, life-threatening illness with many complications. In severe cases, bleeding, tissue

30 damage to the heart, lungs and kidneys, and infection may occur. About 80,000 cases of acute pancreatitis occur annually in the United States; about 20 percent of them are severe. There is no known treatment for pancreatitis. The current approaches for managing

pancreatitis involve waiting for it to resolve on its own and the treatment of heart, lungs and kidney complications if that occur.

Autophagy has been shown to play an important role in mediating cellular damage induced by acute pancreatitis. Autodigestion of the pancreas by its own prematurely activated digestive proteases is believed to be important for the onset of acute pancreatitis. Although lysosomal hydrolases are known to play a key role in pancreatic trypsinogen activation, it remains unclear where and how trypsinogen meets these lysosomal enzymes. Recently, autophagy has been proposed to play a key role in the release of pancreatic digestive enzymes in animal models of pancreatitis (Hashimoto, D., et al., Involvement of autophagy in trypsinogen activation within the pancreatic acinar cells. *J Cell Biol*, 2008. 181(7): p. 1065-72; and Ohmuraya, M. and K. Yamamura, Autophagy and acute pancreatitis: a novel autophagy theory for trypsinogen activation. *Autophagy*, 2008. 4(8): p. 1060-2.) In Atg5^{-/-} mice, which are defective for a key autophagy gene Atg5, the severity of acute pancreatitis induced by cerulein is greatly reduced with a significantly decreased level of trypsinogen activation. Thus, activation of autophagy may exert a detrimental effect in pancreatic acinar cells by mediating the activation of trypsinogen to trypsin. Inhibition of autophagy may provide a unique opportunity for blocking trypsinogen activation in acute pancreatitis. Development of an autophagy inhibitor may provide a first-in-class inhibitor for acute pancreatitis.

Recent studies have established a role for autophagy in cellular defense against intracellular pathogens including bacteria, such as *Coxiella burnetii*, *Mycobacterium tuberculosis*, *Streptococcus pyogenes*, *Shigella* spp. and *Salmonella typhimurium*, as well as viruses and protozoa which use autophagosomes to proliferate, such as dengue viruses, hepatitis (A, B & C) viruses, poliovirus, rhinovirus, SARS coronavirus, and West Nile viruses. The execution of autophagy is regulated by upstream signal transduction systems that are influenced by largely physiological factors such as nutrient status, growth factors/cytokines, and hypoxia. The pharmacological induction of autophagy is a therapeutic strategy in which this effector of innate immunity would be triggered or amplified to defend against intracellular pathogens.

Another aspect of the invention relates to a method of treating or preventing a disease caused by an intracellular pathogen, comprising the step of administering to a subject in need thereof a therapeutically effective amount of one or more compounds of formula I, or a pharmaceutically acceptable salt, biologically active metabolite, solvate,

hydrate, prodrug, enantiomer or stereoisomer thereof. See, for example, US Patent Application Publication No. 2009/0111799 to Chen et al. (hereby incorporated by reference in its entirety).

In certain embodiments, the intracellular pathogen is selected from the group
5 consisting of Group A streptococcus, *Listeria monocytogenes*, *Mycobacterium tuberculosis*, *Vibrio cholerae*, *Salmonella enterica*, *Staphylococcus aureus*, *Bacillus anthracis*, *Burkholderia pseudomallei*, *Helicobacter pylori*, *Pseudomonas syringae*, *Toxoplasma gondii*, Sindbis virus, Vesicular stomatitis virus and Herpes simplex virus.

COMBINATION THERAPY

10 The methods of the invention further include administering to a subject a therapeutically effective amount of an autophagy inducing compound in combination with another pharmaceutically active compound known to treat an autophagy associated disease; or a compound that may potentiate the autophagy inducing activity of the autophagy
15 inducing compound. Other pharmaceutically active compounds that may be used can be found in Harrison's Principles of Internal Medicine, Thirteenth Edition, Eds. T.R. Harrison et al. McGraw-Hill N.Y., NY; and the Physicians Desk Reference 50th Edition 1997, Oradell New Jersey, Medical Economics Co., the complete contents of which are expressly incorporated herein by reference. The combination therapy contemplated by the invention includes, for example, administration of a compound of the invention, or a
20 pharmaceutically acceptable salt thereof, and additional agent(s) in a single pharmaceutical formulation as well as administration of a compound of the invention, or a pharmaceutically acceptable salt thereof, and additional agent(s) in separate pharmaceutical formulations. In other words, co-administration shall mean the administration of at least two agents to a subject so as to provide the beneficial effects of the combination of both agents. For
25 example, the agents may be administered simultaneously or sequentially over a period of time.

It should further be understood that the combinations included within the invention are those combinations useful for their intended purpose. The agents set forth below are illustrative for purposes and not intended to be limited. The combinations, which are part
30 of this invention, can be the compounds of the present invention and at least one additional agent selected from the lists below. The combination can also include more than one additional agent, e.g., two or three additional agents if the combination is such that the formed composition can perform its intended function.

For example, one aspect of the invention relates to the use of an autophagy inhibitor (e.g., a compound of formula I) in combination with an anti-angiogenesis inhibitors for the treatment of cancers. It is known that anti-angiogenesis inhibitors have the promise to inhibit tumor growth by suppressing the growth of blood vessels in tumors which are required for supporting tumor survival and growth. For example, the angiostatic agent endostatin and related chemicals can suppress the building of blood vessels and reduce tumor growth. Several hundred clinical trials of anti-angiogenesis drugs are now under way. In tests with patients, anti-angiogenesis therapies are able to suppress tumor growth with relatively few side effects. However, anti-angiogenesis therapy alone may not be insufficient to prolong patient survival; combination with a conventional chemotherapy may therefore be beneficial. Specifically, autophagy inhibitors may provide a new option to work alone or in combination with anti-angiogenesis therapy.

Endostatin has been shown to induce autophagy in endothelial cells by modulating Beclin 1 and beta-catenin levels (Nguyen, T.M., et al., Endostatin induces autophagy in endothelial cells by modulating Beclin 1 and beta-catenin levels. J Cell Mol Med, 2009). As disclosed herein, it has been found that inhibition of autophagy selectively kills a subset of cancer cells under starvation condition. Therefore, it is proposed that anti-angiogenesis therapy may induce additional metabolic stress to sensitize cancer cells to autophagy inhibitors, which are not normally cytotoxic. Thus, a combination of anti-angiogenesis therapy and anti-autophagy therapy may provide a new option for treatment of cancers without cytotoxicity to normal cells (Ramakrishnan, S., et al., *Autophagy and angiogenesis inhibition*. Autophagy, 2007. 3(5): p. 512-5).

Non-limiting examples of anti-angiogenesis agents with which a compound of the invention of the invention can be combined include, for example, the following: bevacizumab (Avastin®), carboxyamidotriazole, TNP-470, CM101, IFN- α , IL-12, platelet factor-4, suramin, SU5416, thrombospondin, VEGFR antagonists, angiostatic steroids with heparin, Cartilage-Derived Angiogenesis Inhibitory Factor, matrix metalloproteinase inhibitors, angiostatin, endostatin, 2-methoxyestradiol, tecogalan, thrombospondin, prolactin, α V β 3 inhibitors and linomide.

In addition, as described in US Patent Application Publication No. 2008/0269259 to Thompson et al. (hereby incorporated by reference in its entirety), autophagy inhibitors can be used to treat a subject who has been identified as having a glycolysis dependent cancer by combining one or more autophagy inhibitors with one or more anti-cancer compounds

which converts glycolysis dependent cancer to cells incapable of glycolysis. Examples of anti-cancer compounds which convert glycolysis dependent cancer to cells incapable of glycolysis: Alkylating Agents; Nitrosoureas; Antitumor Antibiotics; Corticosteroid Hormones; Anti-estrogens; Aromatase Inhibitors; Progestins; Anti-androgens; LHRH agonists; Kinase Inhibitors; and Antibody therapies; for example, busulfan, cisplatin, carboplatin, chlorambucil, cyclophosphamide, ifosfamide, dacarbazine (DTIC), mechlorethamine (nitrogen mustard), melphalan, carmustine (BCNU), lomustine (CCNU), dactinomycin, daunorubicin, doxorubicin (Adriamycin), idarubicin, mitoxantrone, prednisone, dexamethasone, tamoxifen, fulvestrant, anastrozole, letrozole, megestrol acetate, bicalutamide, flutamide, leuprolide, goserelin, gleevac, Iressa, Tarceva, Herceptin, Avastin, L-asparaginase and tretinoin.

PHARMACEUTICAL COMPOSITIONS

The invention features compositions, kits, and methods for treating or preventing a disease or condition associated with diseases caused by misfolded protein aggregates or additional autophagy-related diseases by administering a compound of the invention (i.e., an autophagy inducing compound). Compounds of the present invention may be administered by any appropriate route for treatment or prevention of a disease or condition associated with misfolded protein aggregates or additional autophagy-related diseases.

These may be administered to humans, domestic pets, livestock, or other animals with a pharmaceutically acceptable diluent, carrier, or excipient, in unit dosage form.

Administration may be topical, parenteral, intravenous, intra-arterial, subcutaneous, intramuscular, intracranial, intraorbital, ophthalmic, intraventricular, intracapsular, intraspinal, intracisternal, intraperitoneal, intranasal, aerosol, by suppositories, or oral administration.

Therapeutic formulations may be in the form of liquid solutions or suspensions; for oral administration, formulations may be in the form of tablets or capsules; and for intranasal formulations, in the form of powders, nasal drops, ear drops, or aerosols.

Methods well known in the art for making formulations are found, for example, in "Remington: The Science and Practice of Pharmacy" (20th ed., ed. A.R. Gennaro, 2000, Lippincott Williams & Wilkins). Formulations for parenteral administration may, for example, contain excipients, sterile water, or saline, polyalkylene glycols such as polyethylene glycol, oils of vegetable origin, or hydrogenated naphthalenes. Biocompatible, biodegradable lactide polymer, lactide/glycolide copolymer, or polyoxyethylene-

polyoxypropylene copolymers may be used to control the release of the compounds.

Nanoparticulate formulations (e.g., biodegradable nanoparticles, solid lipid nanoparticles, liposomes) may be used to control the biodistribution of the compounds. Other potentially useful parenteral delivery systems include ethylene-vinyl acetate copolymer particles,

5 osmotic pumps, implantable infusion systems, and liposomes. Formulations for inhalation may contain excipients, for example, lactose, or may be aqueous solutions containing, for example, polyoxyethylene-9-lauryl ether, glycolate and deoxycholate, or may be oily solutions for administration in the form of nasal drops, or as a gel. The concentration of the compound in the formulation will vary depending upon a number of factors, including the
10 dosage of the drug to be administered, and the route of administration.

The compound may be optionally administered as a pharmaceutically acceptable salt, such as a non-toxic acid addition salts or metal complexes that are commonly used in the pharmaceutical industry. Examples of acid addition salts include organic acids such as acetic, lactic, pamoic, maleic, citric, malic, ascorbic, succinic, benzoic, palmitic, suberic,
15 salicylic, tartaric, methanesulfonic, toluenesulfonic, or trifluoro acetic acids or the like; polymeric acids such as tannic acid, carboxymethyl cellulose, or the like; and inorganic acid such as hydrochloric acid, hydrobromic acid, sulfuric acid phosphoric acid, or the like. Metal complexes include zinc, iron, and the like.

Administration of compounds in controlled release formulations is useful where the
20 autophagy inducing compound has (i) a narrow therapeutic index (e.g., the difference between the plasma concentration leading to harmful side effects or toxic reactions and the plasma concentration leading to a therapeutic effect is small; generally, the therapeutic index, TI, is defined as the ratio of median lethal dose (LD_{50}) to median effective dose (ED_{50})); (ii) a narrow absorption window in the gastro-intestinal tract; or (iii) a short
25 biological half-life, so that frequent dosing during a day is required in order to sustain the plasma level at a therapeutic level.

Many strategies can be pursued to obtain controlled release in which the rate of release outweighs the rate of metabolism of the therapeutic compound. For example, controlled release can be obtained by the appropriate selection of formulation parameters
30 and ingredients, including, e.g., appropriate controlled release compositions and coatings. Examples include single or multiple unit tablet or capsule compositions, oil solutions, suspensions, emulsions, microcapsules, microspheres, nanop articles, patches, and liposomes.

Formulations for oral use include tablets containing the active ingredient(s) in a mixture with non-toxic pharmaceutically acceptable excipients. These excipients may be, for example, inert diluents or fillers (e.g., sucrose and sorbitol), lubricating agents, glidants, and antiadhesives (e.g., magnesium stearate, zinc stearate, stearic acid, silicas, hydrogenated vegetable oils, or talc).

Formulations for oral use may also be provided in unit dosage form as chewable tablets, tablets, caplets, or capsules (i.e., as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium).

The formulations can be administered to human subjects in therapeutically effective amounts. Typical dose ranges are from about 0.01 $\mu\text{g/kg}$ to about 2 mg/kg of body weight per day. The preferred dosage of drug to be administered is likely to depend on such variables as the type and extent of the disorder, the overall health status of the particular subject, the specific compound being administered, the excipients used to formulate the compound, and its route of administration. Routine experiments may be used to optimize the dose and dosing frequency for any particular compound.

In one embodiment, the autophagy inducing compound is administered at a concentration in the range from about 0.001 $\mu\text{g/kg}$ to greater than about 500 mg/kg . For example, the concentration may be 0.001 $\mu\text{g/kg}$, 0.01 $\mu\text{g/kg}$, 0.05 $\mu\text{g/kg}$, 0.1 $\mu\text{g/kg}$, 0.5 $\mu\text{g/kg}$, 1.0 $\mu\text{g/kg}$, 10.0 $\mu\text{g/kg}$, 50.0 $\mu\text{g/kg}$, 100.0 $\mu\text{g/kg}$, 500 $\mu\text{g/kg}$, 1.0 mg/kg , 5.0 mg/kg , 10.0 mg/kg , 15.0 mg/kg , 20.0 mg/kg , 25.0 mg/kg , 30.0 mg/kg , 35.0 mg/kg , 40.0 mg/kg , 45.0 mg/kg , 50.0 mg/kg , 60.0 mg/kg , 70.0 mg/kg , 80.0 mg/kg , 90.0 mg/kg , 100.0 mg/kg , 150.0 mg/kg , 200.0 mg/kg , 250.0 mg/kg , 300.0 mg/kg , 350.0 mg/kg , 400.0 mg/kg , 450.0 mg/kg , to greater than about 500.0 mg/kg or any incremental value thereof. It is to be understood that all values and ranges between these values and ranges are meant to be encompassed by the present invention.

In another embodiment, the autophagy inducing compound is administered in doses that range from 0.01 μM to greater than or equal to 500 μM . For example, the dose may be 0.01 μM , 0.02 μM , 0.05 μM , 0.1 μM , 0.15 μM , 0.2 μM , 0.5 μM , 0.7 μM , 1.0 μM , 3.0 μM , 5.0 μM , 7.0 μM , 10.0 μM , 15.0 μM , 20.0 μM , 25.0 μM , 30.0 μM , 35.0 μM , 40.0 μM , 45.0 μM , 50.0 μM , 60.0 μM , 70.0 μM , 80.0 μM , 90.0 μM , 100.0 μM , 150.0 μM , 200.0 μM , 250.0 μM , 300.0 μM , 350.0 μM , 400.0 μM , 450.0 μM , to greater than about 500.0 μM or

any incremental value thereof. It is to be understood that all values and ranges between these values and ranges are meant to be encompassed by the present invention.

In yet another embodiment, the autophagy inducing compound is administered at concentrations that range from 0.10 µg/ml to 500.0 µg/ml. For example, the concentration may be 0.10 µg/ml, 0.50 µg/ml, 1 µg/ml, 2.0 µg/ml, 5.0 µg/ml, 10.0 µg/ml, 20 µg/ml, 25 µg/ml, 30 µg/ml, 35 µg/ml, 40 µg/ml, 45 µg/ml, 50 µg/ml, 60.0 µg/ml, 70.0 µg/ml, 80.0 µg/ml, 90.0 µg/ml, 100.0 µg/ml, 150.0 µg/ml, 200.0 µg/ml, 250.0 µg/ml, 300.0 µg/ml, 350.0 µg/ml, 400.0 µg/ml, 450.0 µg/ml, to greater than about 500.0 µg/ml or any incremental value thereof. It is to be understood that all values and ranges between these values and ranges are meant to be encompassed by the present invention.

KITS

In one aspect, the present invention discloses a kit which includes a pharmaceutical composition comprising an autophagy inducing compound of the present invention (e.g. a compound of formula I) and instructions for administering the composition to a subject for the treatment or prevention of an autophagy associated disease, e.g., a disease caused by misfolded protein aggregates. In one embodiment of this aspect, the pharmaceutical composition may include one or more autophagy inducing compounds. In certain embodiment, the pharmaceutical composition may comprise a pharmaceutically acceptable carrier.

EXEMPLIFICATION

The invention now being generally described, it will be more readily understood by reference to the following, which is included merely for purposes of illustration of certain aspects and embodiments of the present invention, and is not intended to limit the invention.

25 **Example 1** -- Synthesis and SAR of Diphenylbutylpiperidines Autophagy Inducers Based on Fluspirilene (1), and Penfluridol (4)

Diphenylbutylpiperidines compounds, such as those described below, can be prepared by S_N2 substitution of diphenylbutyl halide compounds with piperidines (as described in Janneke, W.; Hulshof, H. F.; Vischer, H.P.; Verheij, S. A.; Fratantoni, Martine, J. S.; Iwan, J. P. *Bioorg. Med. Chem. Lett.* **2006**, 14, 7213). As a key intermediate, synthetic routes to diphenylbutyl bromide **10** have been reported (see Janneke, W.; Hulshof, H. F.; Vischer, H.P.; Verheij, S. A.; Fratantoni, Martine, J. S.; Iwan, J. P. *Bioorg. Med. Chem. Lett.* **2006**, 14, 7213; Sindelar, K.; Rajsner, M.; Cervena, I.; Valenta, V.; Jilek, J. O.; Kakac,

B.; Holubek, J.; Svatek, E.; Miksik, F.; Protiva, M. *Collect. Czech. Chem. Commun.* **1973**, 38, 3879; Carlo, B.; Mauro, M.; Stefano, P.; Francesco, P. P. *Tetrahedron*, **2001**, 57, 1631; and Hulshof, J. W.; Casarosa, P.; Wiro, M. P. B.; Kuusisto, L. M.; van der Goot, H.; Smit, M. J.; de Esch, I. J. P.; Leurs, R. *J. Med. Chem.* **2005**, 48, 6461). In addition, herein is also disclosed a new synthetic route to diphenylbutyl halide compounds, as described in Figure 2. Treatment of Grignard reagents of bromobenzene derivative **5** with (γ -)butyrolactone **6** gave dihydroxyl compound **7**, which was converted to dehydrated compound **8** in the acidic conditions. Hydrogenation of **8** followed by bromination with triphenylphosphine and carbon tetrabromide gave intermediate **10**. This route has several advantages: the raw materials are very cheap; and the diphenylbutyl chain with different substituents on the diphenyl ring can be easily prepared.

Three bromobutyl tricyclic compounds were prepared as described in Figure 3. Treatment of Grignard reagents of bromocyclopropane **12** with tricyclic ketone compound **11** gave cyclopropyldiphenyldiphenylmethanol **13**, which was converted to rearranging compounds **14** by MgBr_2 . Subsequent hydrogenation of **14** gave the desired compound **15**.

Synthetic efforts also focused on changing substituents in the 4-position of piperidine ring (Figures 4 and 5). Grignard reaction of bromobenzene derivatives **16** with N-Boc piperidone gave compound **18**. Deprotection of Boc group with trifluoroacetic acid gave mainly dehydrated products. After screening different reaction conditions, it was determined that piperidine **19** could be prepared by treatment with 3M HCl with ethyl acetate as solvents under room temperature. Subsequently, the free hydroxyl group of compounds **67-72** and **76** was protected by acetyl group and substituted by acetamide group via a Ritter reaction (Janneke, W.; Hulshof, H. F.; Vischer, H.P.; Verheij, S. A.; Fratantoni, Martine, J. S.; Iwan, J. P. *Bioorg. Med. Chem. Lett.* **2006**, 14, 7213; and Miroslav, R.; Antonnin, D.; Miroslav, P. *Collection Czechoslovak Chem. Commun.* **1981**, 46, 1530).

Figures 6 and 7 contain the results of incorporating various chemical moieties into the butyl linkers between the diphenyl moiety and the piperidine. Autophagy inducing activity may be determined as described in International Patent Application publication number WO/2009/049242. For compounds **20-22**, modification of the linker decreased the autophagy inducing activity, as compared to compound **1**. Interestingly, compound **31** showed the same activity as compound **30**. Compounds **23** and **33**, which contain amide linkages, showed no autophagy activity, perhaps due to *in vivo* hydrolysis. Also,

compounds **24-27**, wherein one of the biphenyl phenyl rings is replaced with a hydrogen, showed no activity, suggesting that the diphenyl moiety is essential.

In addition, the number of methylenes between the piperidine and the biphenyl was investigated. It was found that the addition of one methylene group in the structure of **1**, giving compound **28**, decreased the activity of the compound 2-fold. In contrast, compound **34** showed a small increased activity. Shortening of the methylene group, gave compounds **29** and **35**, which both had about equipotent activity as compared to the butyl-containing compounds, suggesting that the length of the linker may be varied (e.g., a 2-4 carbon chain).

As part of the structure-activity relationship studies, variation in the substitution on diphenyl ring were also explored (Figure 8). Compound **36** and **45** (i.e. those without substitutions on diphenyl ring) showed lowest activity in this series. For compounds **37-41**, different substitutions in the *para*-position of diphenyl ring showed no improved activity comparable to compound **1**. However, compounds **47-50** (having various substitutions in the *para*-position) showed promising results. For example, compound **48** (wherein R is CF₃) showed a 10-fold increase in autophagy inducing activity. Compounds wherein R is 4-CF₃, 2-CH₃, 4-CH₃ and 3-CH₃ were shown to be five to ten times potent as compound **2**. It was also observed that the electronic nature of the substituents on the diphenyl moiety have little effect on the bio-activities, while the steric effect of the substitutions show a significant influence (e.g. compounds with larger substitutions have higher bio-activity). However, compounds with very large substituents have decreased bio-activity.

Additional compounds, wherein the two phenyl rings were connected to form a tricyclic moieties, resulting in a more rigid compound, showed different results. Compounds **42-44** showed decreased activity comparable to compound **1**; and compound **56** showed about a 4-fold decrease in activity. However, compound **55** and **57** showed a small increase in autophagy inducing activity

Results of modifications of substituents at the 4-position on the piperidine (Figure 9) suggest that a saturated piperidine ring is essential. Compounds **58-60** (piperazines) and compound **61** (morphine) showed no activity. In addition, compound **62** with unsaturated piperidine and compound **63** losing hydroxyl group also showed no activity. As previously reported, modification of hydroxyl group, protected with acetyl group (compound **65**) and substituted by acetamide group (compound **66**), showed good results (Janneke, W.; Hulshof, H. F.; Vischer, H.P.; Verheij, S. A.; Fratanoni, Martine, J. S.; Iwan, J. P. *Bioorg.*

Med. Chem. Lett. **2006**, 14, 7213). However, compounds wherein the hydroxyl group is replaced with a cyano group show little inducing activity. These results suggest that the six-membered ring must have the appropriate confirmation and the hydroxyl, or related, group may interact with the target protein through hydrogen bonding.

Encouraged by above results, compounds containing substitutions on the phenyl ring in the 4-position of the piperidine ring were prepared (Figure 10). Compound **70** with R is bromo displayed the best result in this series. Compounds **68**, **71**, **72** with *para*-substituents on the phenyl showed better results comparable to compounds **73**, **74**, **75** with meta-substituents, while compound **67**, without substituents on the phenyl ring, showed decreased activity. It was also observed that compounds containing electron withdrawing substituents have higher bio-activity than compounds with electron donating substituents. Moreover, compounds with larger substituents have improved results.

It is believed that the 4-hydroxyl group is thought to be a site of potential metabolic toxicity (Castagnoli, N. Jr.; Rimoldi, J. M.; Bloomquist, J.; Castagnoli, K. P. *Chem. Res. Toxicol.* **1997**, 10, 924). Therefore, compounds wherein the hydroxyl at the four position of the piperidine was replaced by other moieties (Figure 11) were also prepared. The introduction of an ester group in compounds **77-83** did not result in compounds with a higher activity comparable to compounds **67-72** and **76**, while introduction of an amide group in compounds **84-90** showed good results. As mentioned above, compound **63**, wherein R¹ is hydrogen showed no activity. Compound **91**, wherein R¹ is cyano and R² is hydrogen showed no higher activity.

Example 2 -- Synthesis and SAR of Diphenylbutylpiperidines Autophagy Inducers Based on Pimozide (2)

Diphenylbutylpiperidines compounds, such as those described herein, can be prepared by S_N2 substitution of halodiphenylbutyl compounds with piperidines (as described in Janneke, W.; Hulshof, H. F.; Vischer, H.P.; Verheij, S. A.; Fratantoni, Martine, J. S.; Iwan, J. P. *Bioorg. Med. Chem. Lett.* **2006**, 14, 7213).

As part of structure-activity relationship studies, modification of left-hand side of compound **2** were explored (Figures 13 and 14). Interestingly, compound **109** showed 2-fold increase in the activity of inducing autophagy

Modifications of the right-hand side of compound **2** were also explored. For example, synthetic variations on the P-1-56 fused ring scaffold are described in Figures 15 and 16. Reductive amination of N-Bocpiperidone with o-aminophenol was followed by

cyclization with triphosgene and removal the Boc group. Substitution of the MsO group of piperidine **114** with compounds **113**, **116** or **118** (6,5-fused heterocycles) followed by deprotection of Boc group by TFA afforded the desired compound **115**, **117** or **119** (He, Y.; Yang, J., et al. *Bioorg. Med. Chem. Lett.* **2004**, 14, 695). Reductive amination of N-

- 5 Bocpiperidone **121** with o-aminophenol **120** followed by cyclization of **122** with triphosgene and deprotection the Boc group yielded compound **123** (Flyren, K.; Bergquist, L. O.; et al. *Bioorg. Med. Chem. Lett.* **2007**, 17, 3421). Treatment of piperidone **125** with indole gave compound **126**, which was converted to compound **127** by hydrogenation. Reductive amination of **121** with indoline, prepared by reduction of indole, and
10 deprotection gave compound **130**.

Cyclization of compounds **120**, **131** or **132** with 4-piperidinecarboxylic acid **133** give the desired compounds **134**, **135** or **136** (He, Y.; Yang, J., et al. *Bioorg. Med. Chem. Lett.* **2004**, 14, 695). Reductive amination of N-Boc piperidone with isoindoline prepared by reduction of phthalimide **137** and deprotection of the Boc group gave compound **138**.

- 15 Substitution of MsO group of piperidine **141** with phthalimide potassium salt followed by deprotection of Boc group afforded the desired compound **142**. Treatment of 4-hydroxy piperidine **144** with 1,2,3-benzotriazole by Mitsunobu reaction followed by deprotection afforded two compounds **145** and **146** (Ruckle, T.; Biamonte, M., et al. *J. Med. Chem.* **2004**, 47, 6921). Cyclization of compounds **121**, **131** or **132** with 4-piperidine carboxylic
20 acid gave compounds **134**, **135** or **136** (respectively).

- Figures 18 and 19 showed the biological activity of selected P-1-56 compounds. As mentioned above, compound **109** showed 2-fold increased potent activity comparable to compound **2**. A series of compounds with CN group have also been prepared; interestingly, some showed good results (**147** vs **155**, **151** vs **159**, **153** vs **161**) while some did not (**149** vs
25 **157**, **150** vs **158**, **152** vs **160**). In the left series, compounds **149**, **150**, **152** and **153** showed 3 to 5-fold increased activity comparable to compound **2**, while compounds **148**, **151** and **154** showed no activity. In the right series, compounds **157**, **158** and **160** showed 3 to 7-fold increased activity comparable to compound **2**, while compounds **156** and **162** showed no activity. All of the above results indicate that the 4-position of piperidine ring can tolerate
30 6,5-fused heterocycle groups.

The biological activity results of P-2-56 compounds is shown in Figure 20. These results suggested that compounds **163** and **166** are comparable to compound **2**, while compounds **169** and **178** showed about a 4-fold increase in activity. However, compounds

164, **165**, **170** and **177** showed no activity. Comparing the three isoelectronic compounds at the bottom of Figure 20, compound **166** showed the best result, while compounds **167** and **168** showed the same results. In contrast, compound **178** also showed the best result, while compounds **179** and **180** showed no activity.

5 Encouraged by the biological activity results of DPBPs with 6,5-fused ring linked to the piperidine ring, compounds with 6,6-fused ring shown in Figures **21-24** were also prepared. Reductive amination of N-Boc piperidone with compound **182**, prepared by reduction of isoquinoline **137**, and deprotection of the Boc group gave compound **183**. Cyclization of anthranilamide **184** with N-benzylpiperidone **185** followed by reduction of
10 compound **186** afforded intermediate compound **187** (Takai, H.; Obase, H.; Nakamizo, N.; Teranishi, M.; Kubo, K.; Shuto, K.; Kasuya, Y.; Shigenobl, K.; Hashikami, M.; Karashima, N. *Chem. Pharm. Bull.* **1985**, 33, 1116). Cyclization **187** with CDI and deprotection of the Boc group gave compound **189**. Cyclization **187** with different reagents gave compounds **191**, **193**, **195** and **197** (Takai, H.; Obase, H.; Nakamizo, N.; Teranishi, M.; Kubo, K.;
15 Shuto, K.; Kasuya, Y.; Shigenobl, K.; Hashikami, M.; Karashima, N. *Chem. Pharm. Bull.* **1985**, 33, 1116; and Takai, H.; Obase, H.; Nakamizo, N.; Teranishi, M.; Kubo, K.; Shuto, K.; Hashimoto, T. *Chem. Pharm. Bull.* **1985**, 33, 1104).

The biological activity results of P-2-66 compounds is shown in Figures 23 and 24. Reductive amination of N-Boc piperidone with compound **199**, prepared by reduction of
20 quinoline **198**, and deprotection of the Boc group gave compound **200**. Treatment of salicylaldehyde **201** with compound **202**, followed cyclization with CDI and deprotection of Bn group gave compound **205** (Takai, H.; Obase, H.; Nakamizo, N.; Teranishi, M.; Kubo, K.; Shuto, K.; Hashimoto, T. *Chem. Pharm. Bull.* **1985**, 33, 1104). Ring opening of compound **206** with **202** afforded intermediate **203** (Takai, H.; Obase, H.; Nakamizo, N.;
25 Teranishi, M.; Karasawa, A.; Kubo, K.; Shuto, K.; Kasuya, T. *Chem. Pharm. Bull.* **1986**, 34, 1907). Cyclization **203** with different reagents gave compounds **205**, **207** and **209**. Reductive amination of compound **210** with **211**, followed by deprotection of the Boc group, gave compound **212**. Cyclization **212** with different reagents gave compounds **213-217** (Takai, H.; Obase, H.; Nakamizo, N.; Teranishi, M.; Kubo, K.; Shuto, K.; Hashimoto,
30 T. *Chem. Pharm. Bull.* **1985**, 33, 1104).

Compounds **234-237**, which combined variations in both the left-hand side and right-hand side, we prepared and tested (Figure 28). Compounds **238** and **239** were also prepared and tested (Figure 29). Compound **239** (with a spiro structure) showed better

results than Fluspirilene; this compound was easily prepared and has good solubility properties.

INCORPORATION BY REFERENCE

5 All publications and patents mentioned herein are hereby incorporated by reference in their entirety as if each individual publication or patent was specifically and individually indicated to be incorporated by reference. In case of conflict, the present application, including any definitions herein, will control.

EQUIVALENTS

10 While specific embodiments of the subject invention have been discussed, the above specification is illustrative and not restrictive. Many variations of the invention will become apparent to those skilled in the art upon review of this specification. The appended claims are not intended to claim all such embodiments and variations, and the full scope of the invention should be determined by reference to the claims, along with their full scope of equivalents, and the specification, along with such variations.

15

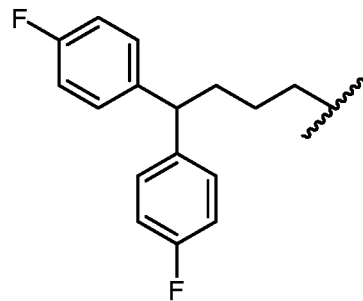
E is arylene or heteroarylene;

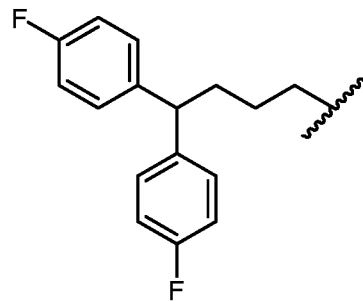
R⁵ is hydroxy, alkyloxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, silyloxy, alkylcarbonyloxy, arylcarbonyloxy, heteroarylcarbonyloxy, aralkylcarbonyloxy, heteroaralkylcarbonyloxy, cyano, amino or amido;

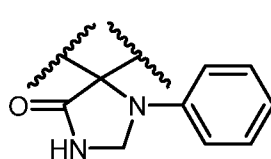
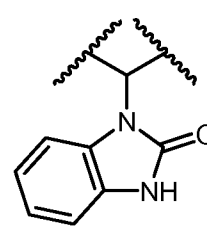
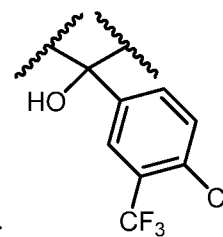
R⁶ is hydrogen or alkyl;

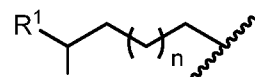
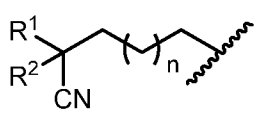
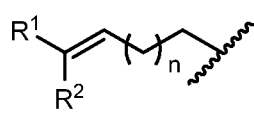
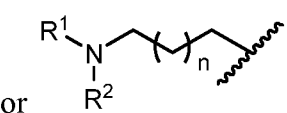
R⁷ is aryl or heteroaryl; and

R⁸ is hydrogen or alkyl.

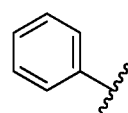
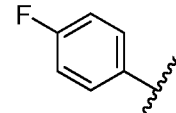
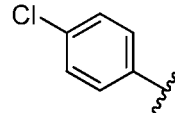
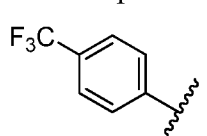
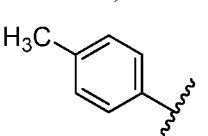
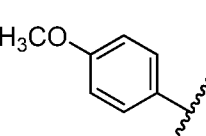
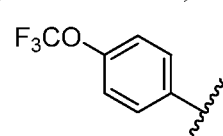


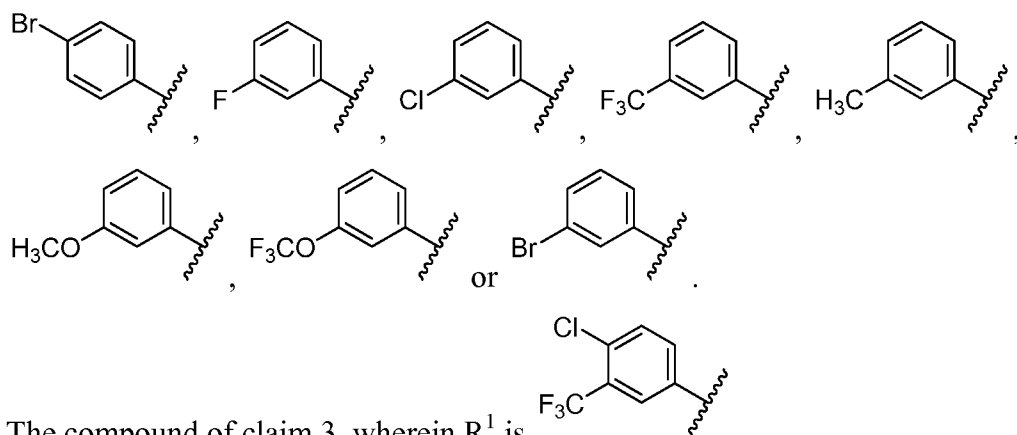
2. The compound of claim 1, provided that when R is , A

is not ,  or  (i.e., provided that the compound is not **1**, **2** or **4**, as depicted in Figure 1).

3. The compound of claim 1 or 2, wherein R is , ,  or .

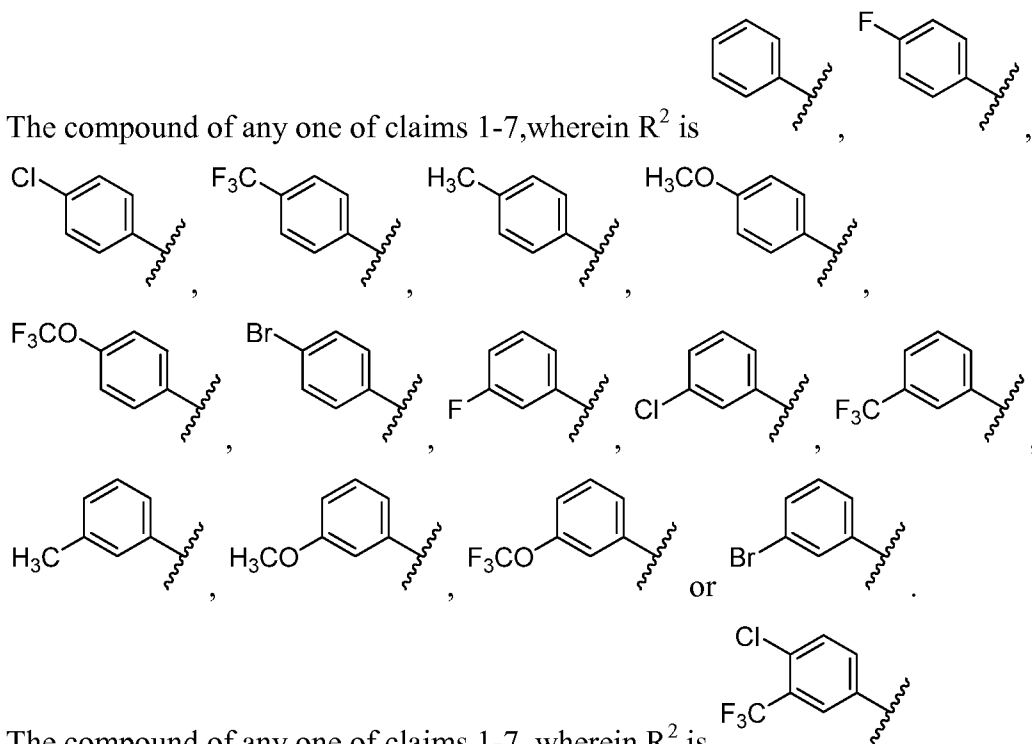
4. The compound of claim 3, wherein R¹ is aryl.
5. The compound of claim 3, wherein R¹ is phenyl substituted 0-5 substituents independently selected from the group consisting of halo, alkyl, haloalkyl, alkoxy and haloalkoxy.

6. The compound of claim 3, wherein R¹ is , , , , , , .



7. The compound of claim 3, wherein R^1 is
8. The compound of any one of claims 1-7, wherein R^2 is aryl.
9. The compound of any one of claims 1-7, wherein R^2 is phenyl substituted 0-5 substituents independently selected from the group consisting of halo, alkyl, haloalkyl, alkoxy and haloalkoxy.

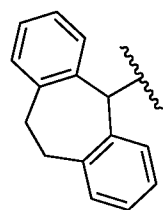
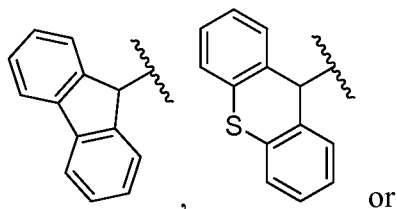
10. The compound of any one of claims 1-7, wherein R^2 is



11. The compound of any one of claims 1-7, wherein R^2 is
12. The compound of any one of claims 1-11, wherein R^1 and R^2 are the same.

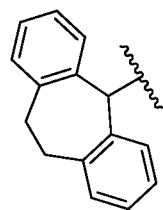
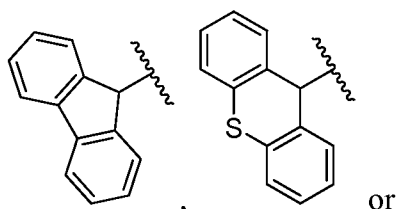
13. The compound of claim 1 or 2, wherein R is
-

14. The compound of claims 13, wherein R^3 is



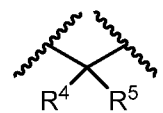
substituted with 0-8 substituents independently selected from the group consisting of halo, alkyl, haloalkyl, alkoxy and haloalkoxy.

15. The compound of claims 13, wherein R^3 is



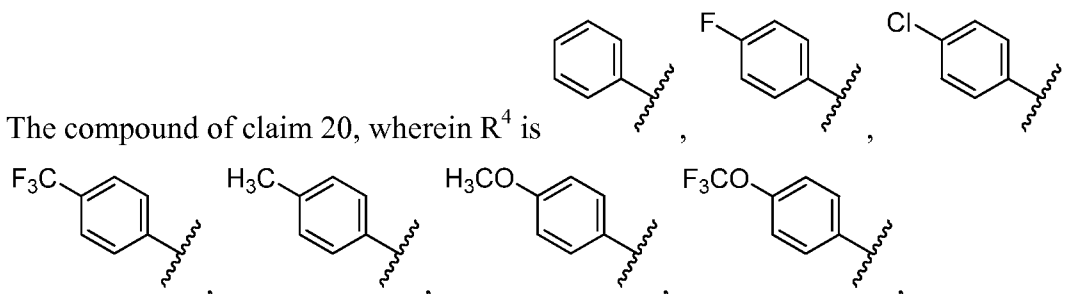
16. The compound of any one of claims 1-15, wherein n is 0.
 17. The compound of any one of claims 1-15, wherein n is 1.
 18. The compound of any one of claims 1-15, wherein n is 2.
 19. The compound of any one of claims 1-15, wherein n is 3.

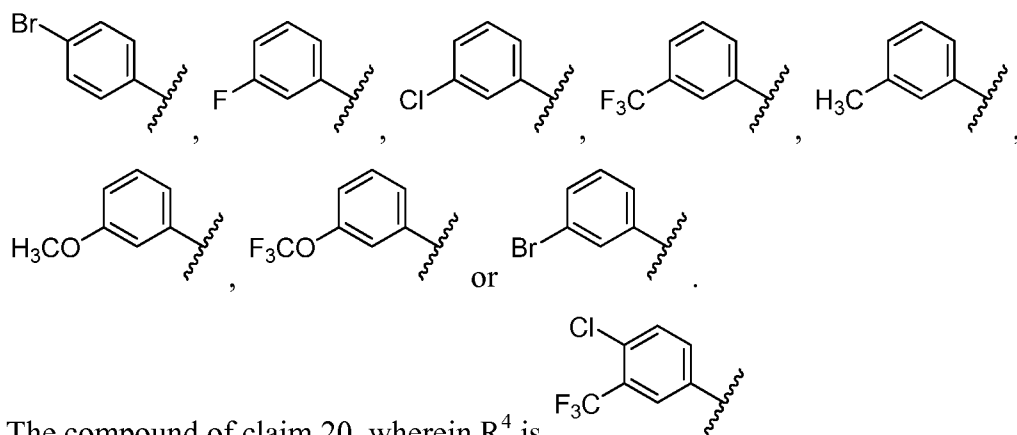
20. The compound of any one of claims 1-19, wherein A is



21. The compound of claim 20, wherein R^4 is aryl.
 22. The compound of claim 20, wherein R^4 is phenyl substituted 0-5 substituents independently selected from the group consisting of halo, alkyl, haloalkyl, alkoxy and haloalkoxy.

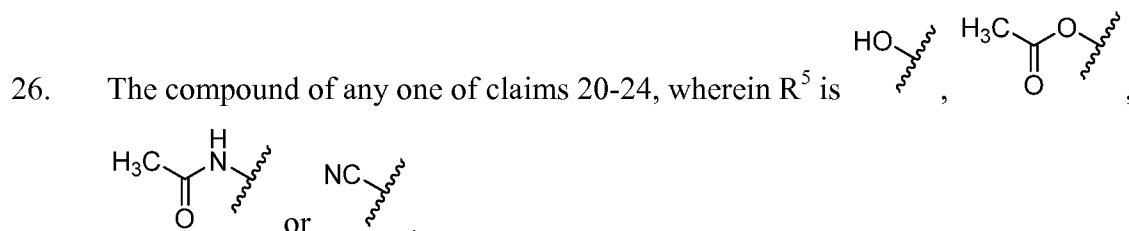
23. The compound of claim 20, wherein R^4 is



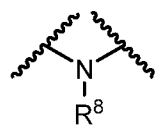
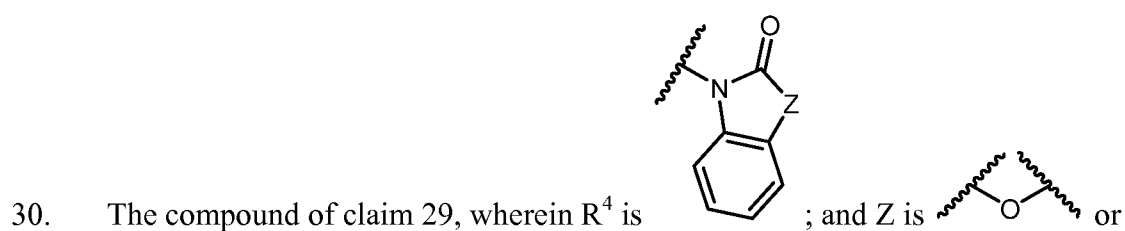
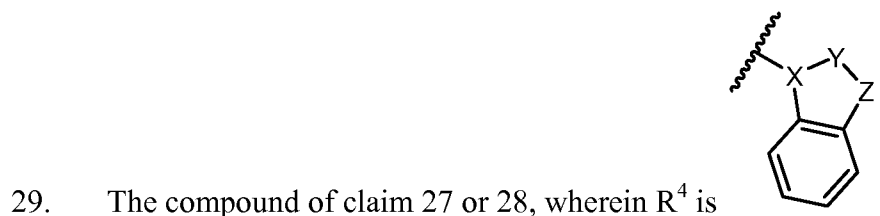
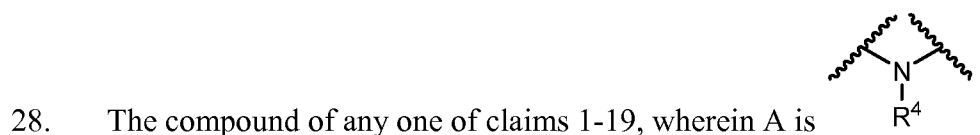
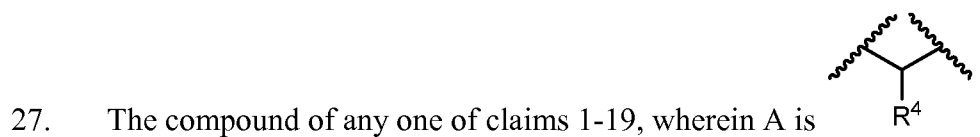


24. The compound of claim 20, wherein R^4 is

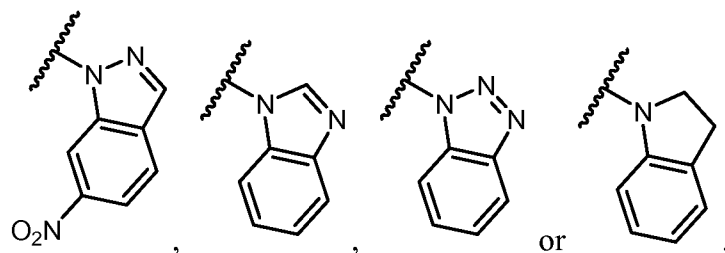
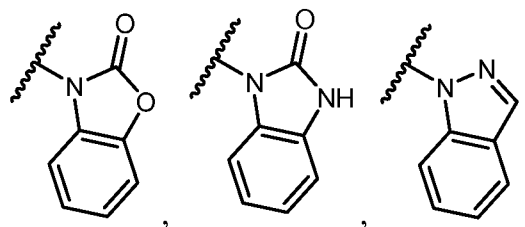
25. The compound of any one of claims 20-24, wherein R^5 is hydroxy, alkyloxy, alkylcarbonyloxy, cyano or amino.



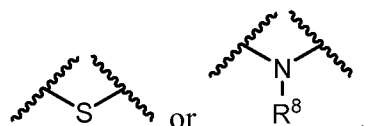
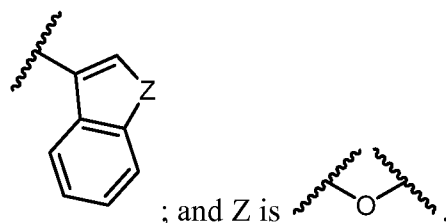
26. The compound of any one of claims 20-24, wherein R^5 is



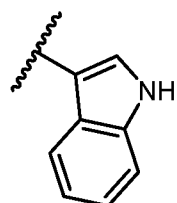
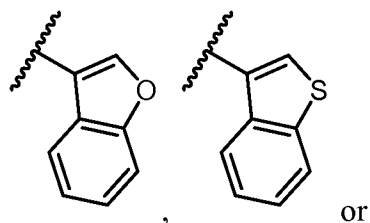
31. The compound of claim 29, wherein R^4 is



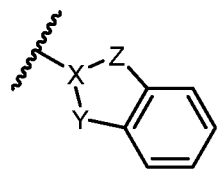
32. The compound of claim 27 or 28, wherein R^4 is



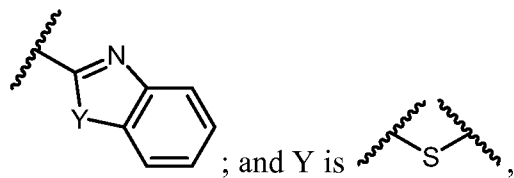
33. The compound of claim 32, wherein R^4 is

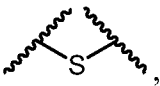


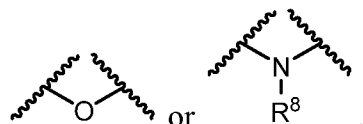
34. The compound of claim 27 or 28, wherein R^4 is



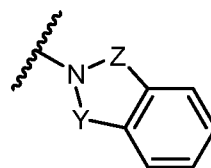
35. The compound of claim 34, wherein R^4 is



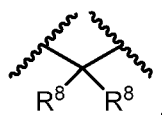
; and Y is ,



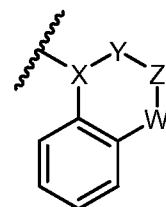
36. The compound of claim 27 or 28, wherein R^4 is



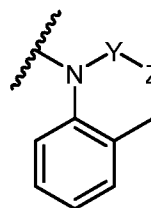
; and Y is

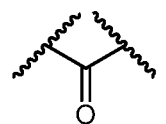


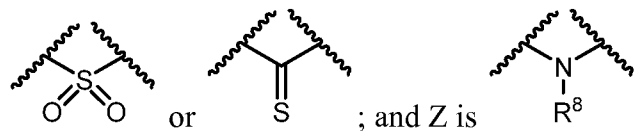
37. The compound of claim 27 or 28, wherein R^4 is



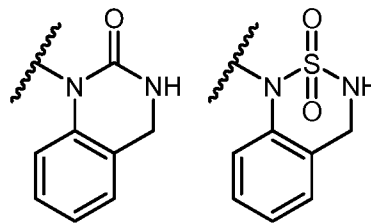
38. The compound of claim 27, wherein R^4 is

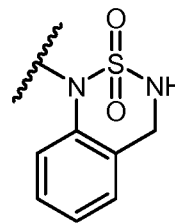


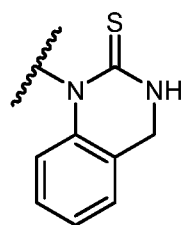
; Y is ,

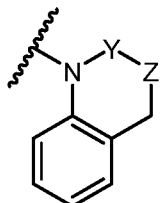
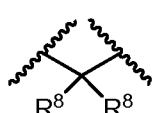


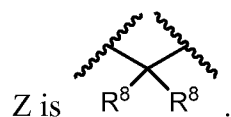
39. The compound of claim 37, wherein R^4 is

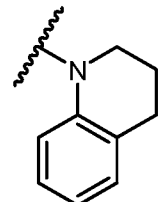


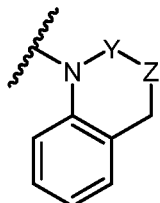
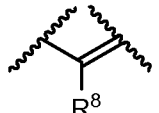
,  or



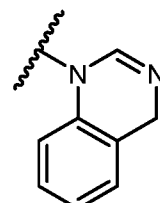
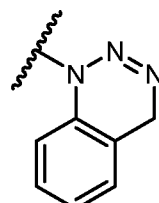
40. The compound of claim 27 or 28, wherein R^4 is ; Y is ; and

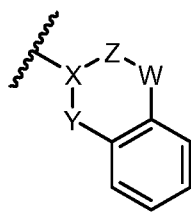


41. The compound of claim 40, wherein R^4 is .

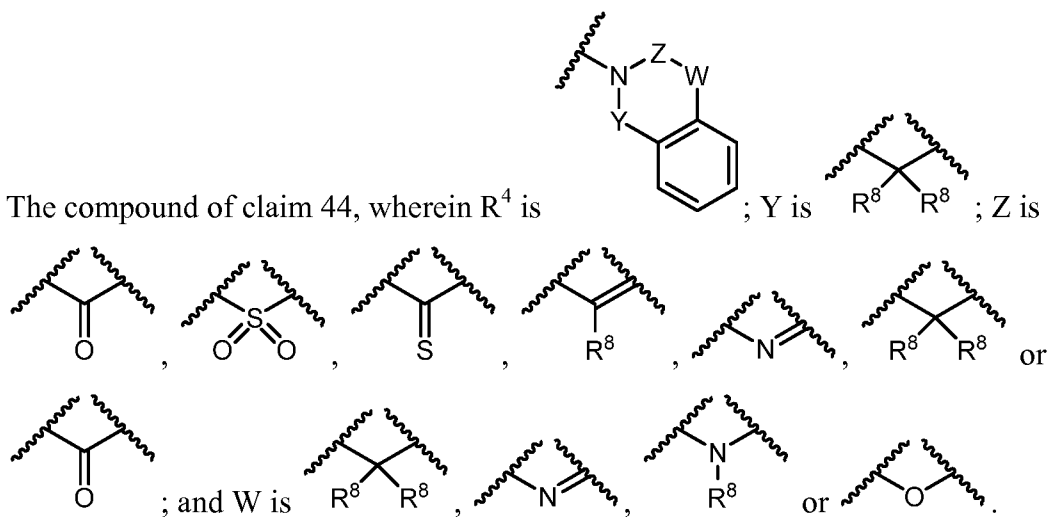
42. The compound of claim 27 or 28, wherein R^4 is ; Y is  or



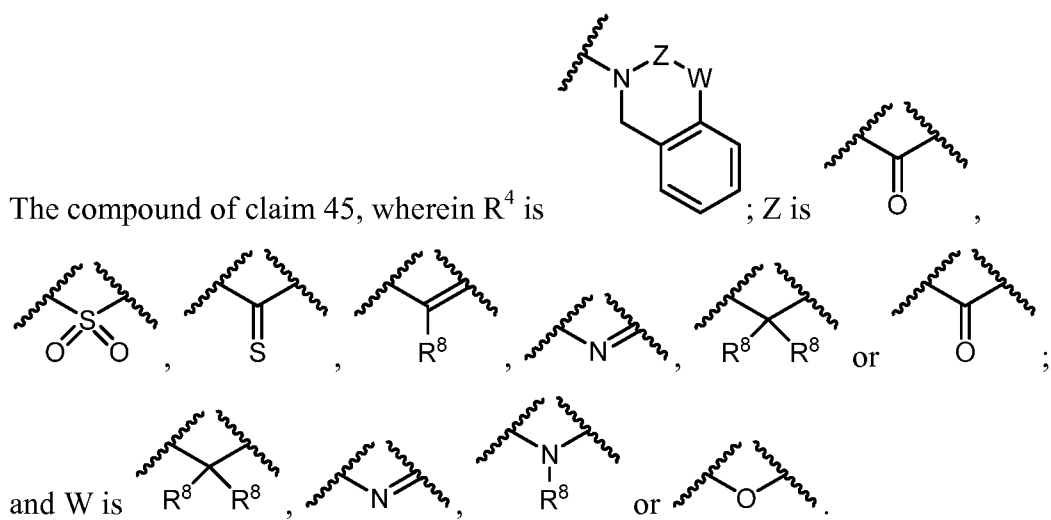
43. The compound of claim 42, wherein R^4 is  or .

44. The compound of claim 27 or 28, wherein R^4 is .

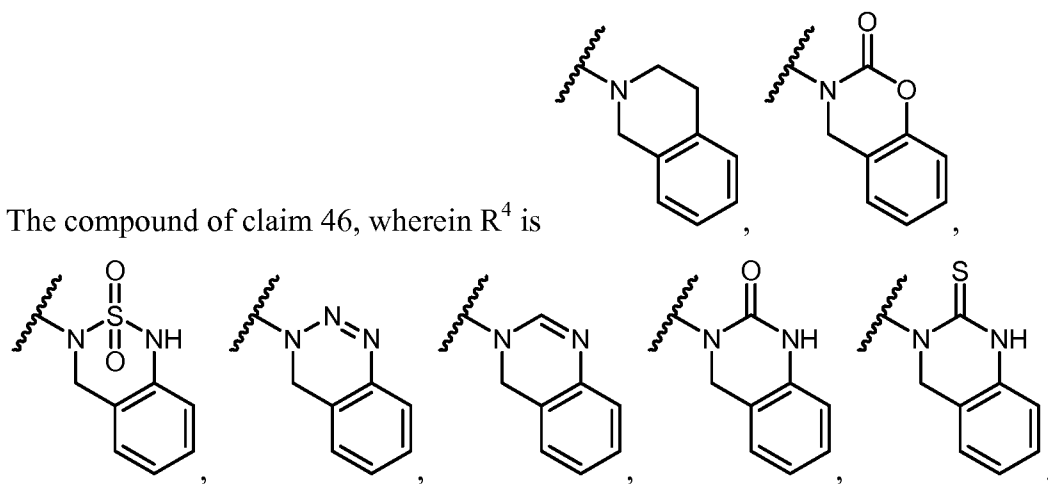
45. The compound of claim 44, wherein R^4 is



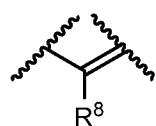
46. The compound of claim 45, wherein R^4 is



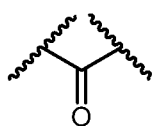
47. The compound of claim 46, wherein R^4 is



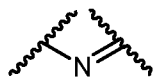
48. The compound of claim 45, wherein R^4 is



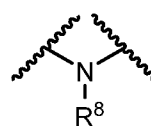
or



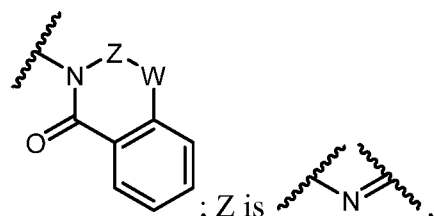
; and W is



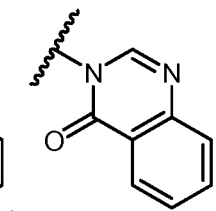
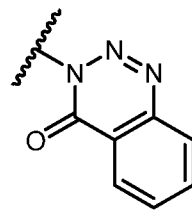
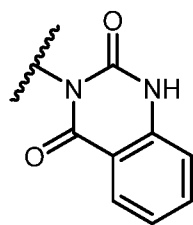
or



.

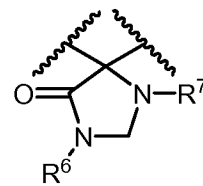


49. The compound of claim 48, wherein R^4 is

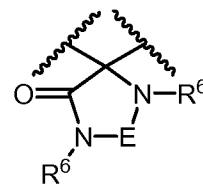


50. The compound of any one of claims 1-49, wherein R^8 is hydrogen.

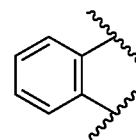
51. The compound of any one of claims 1-19, wherein A is



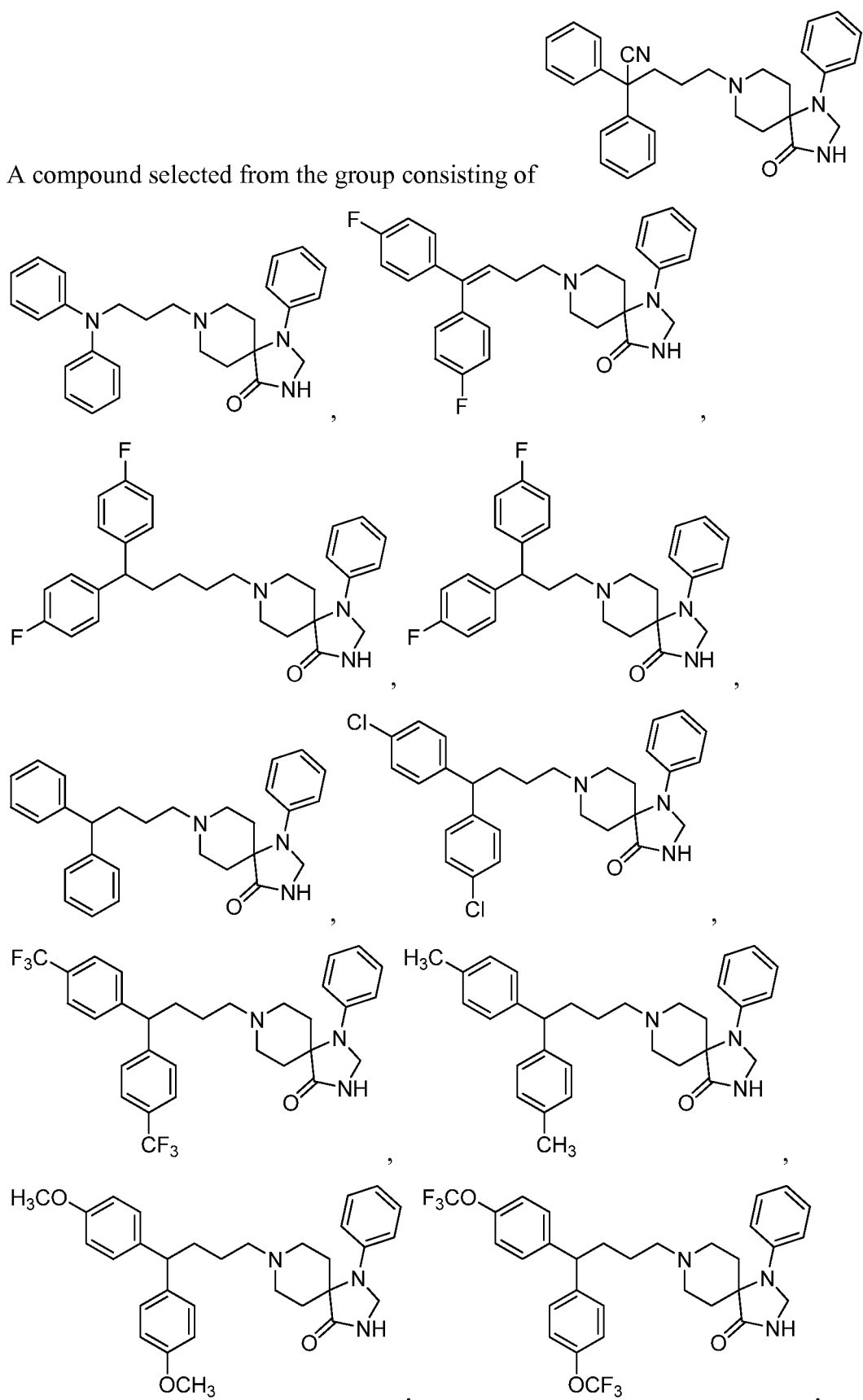
52. The compound of any one of claims 1-19, wherein A is

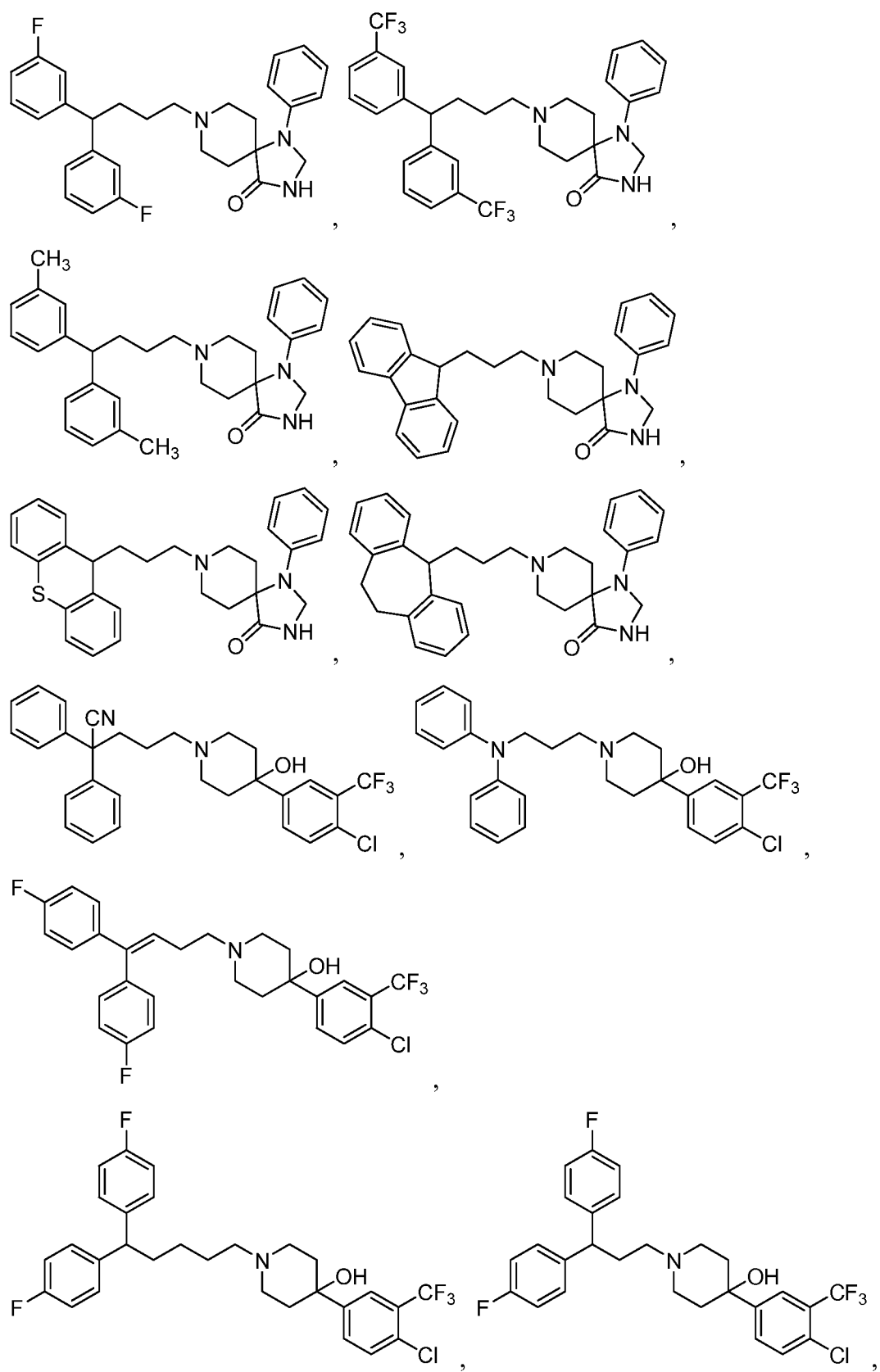


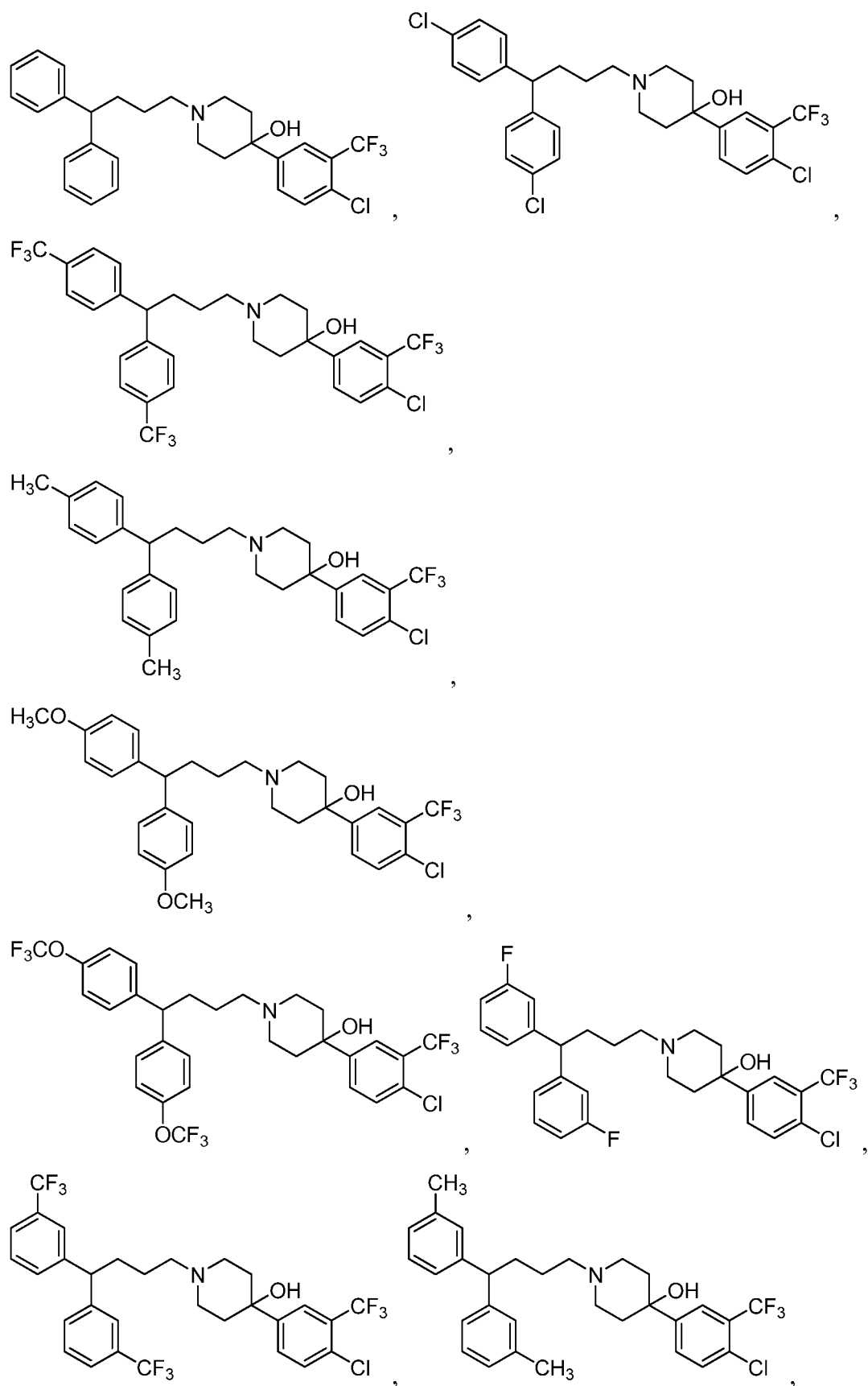
53. The compound of any one of claims 1-52, wherein E is

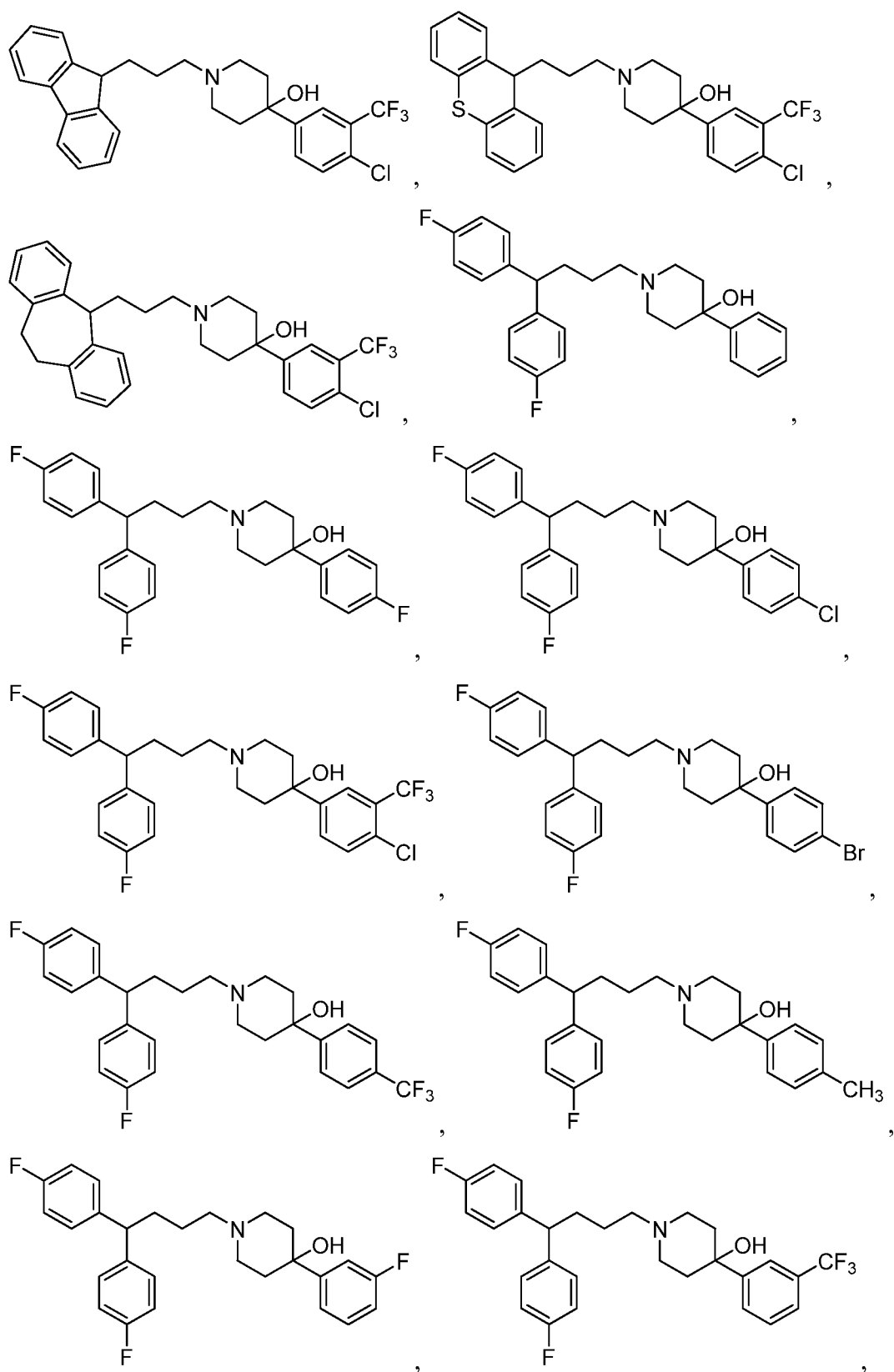


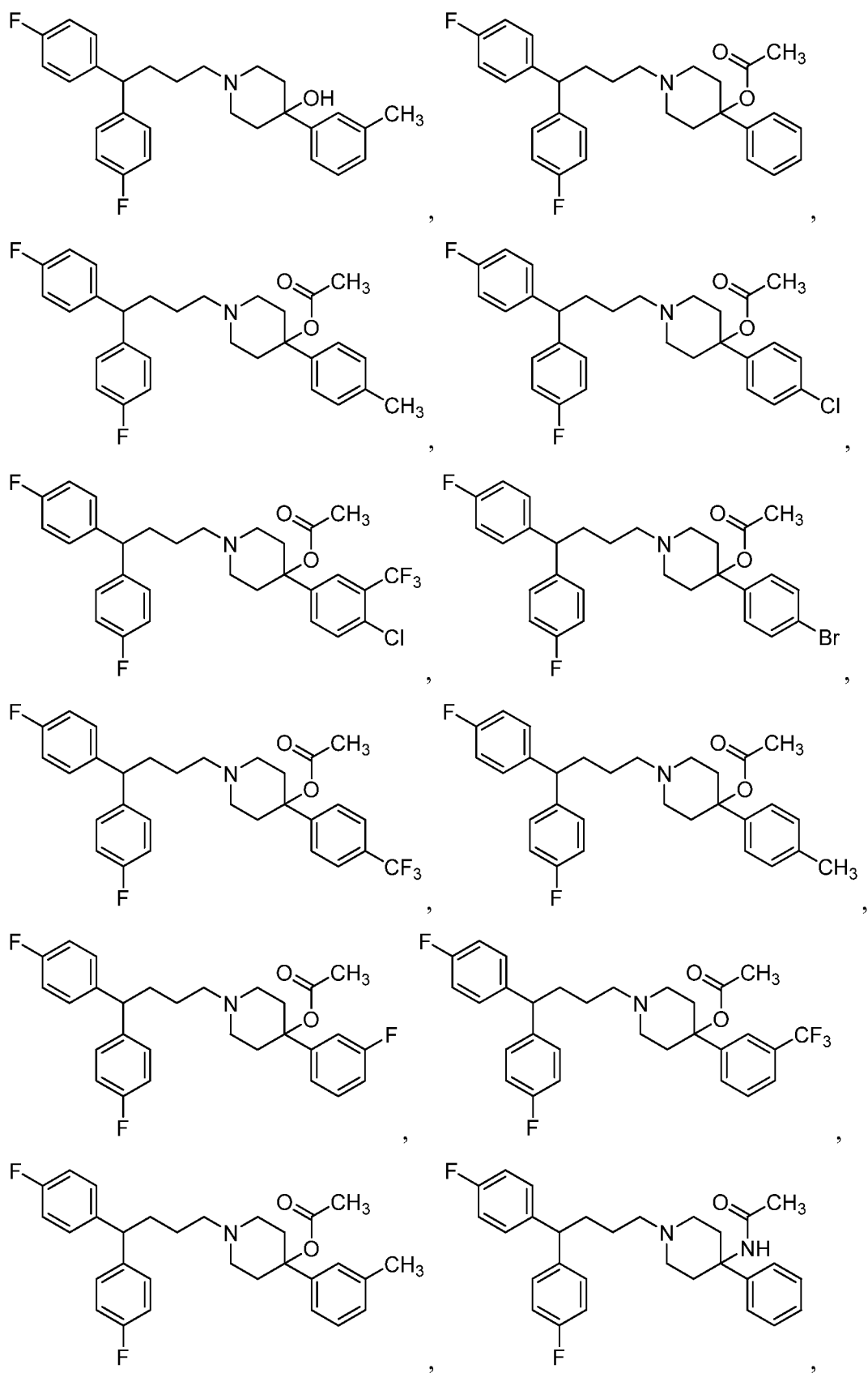
54. A compound selected from the group consisting of

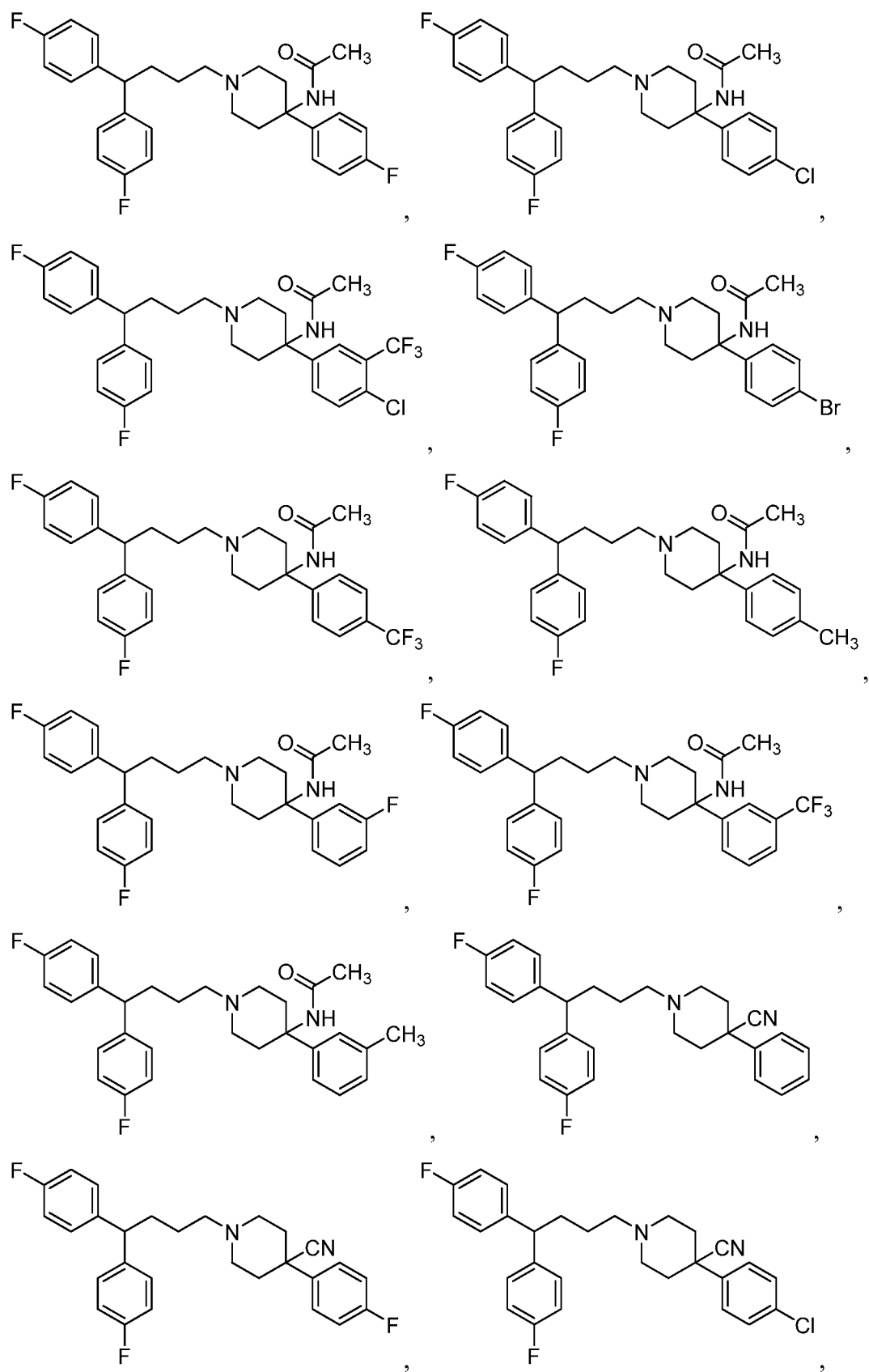


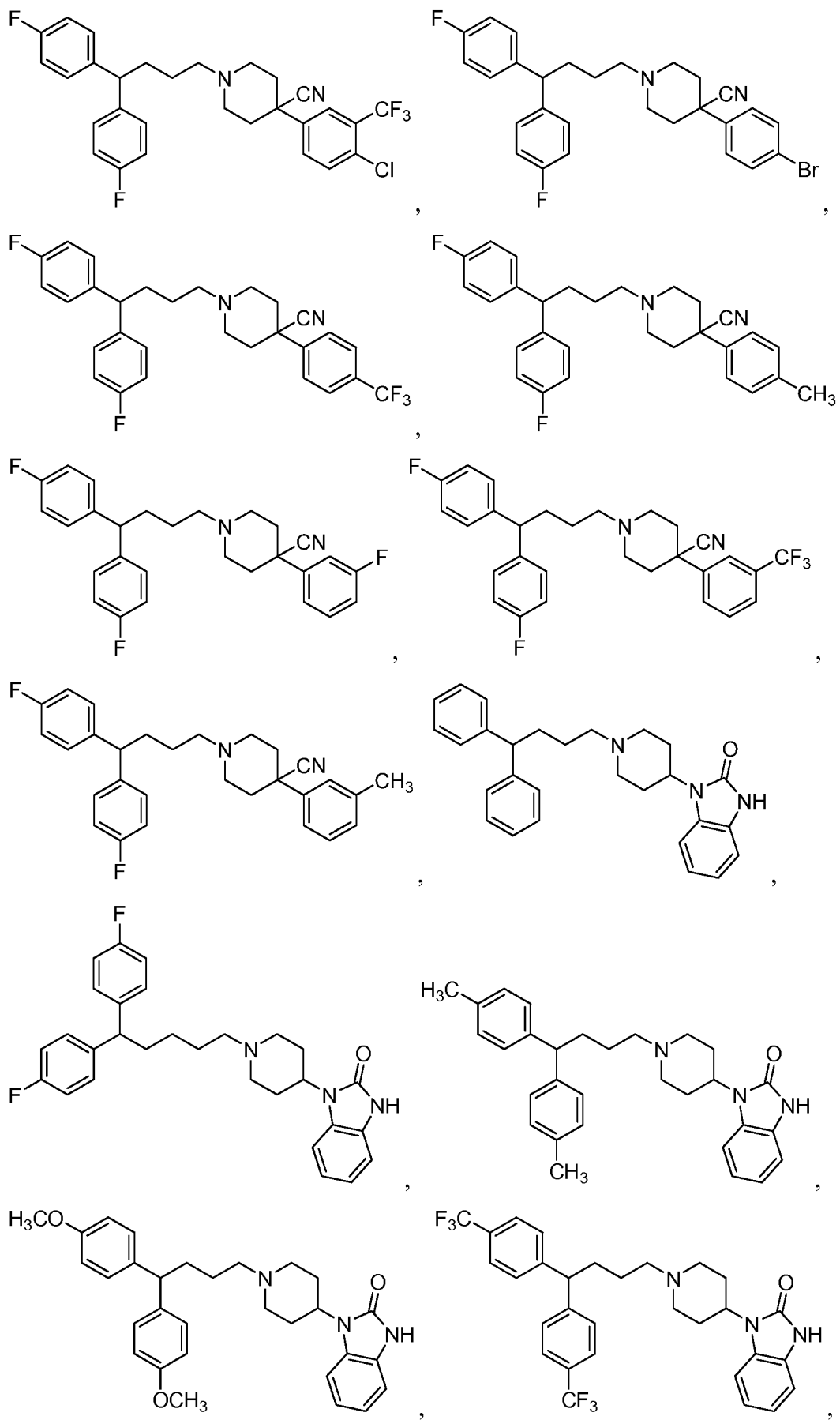


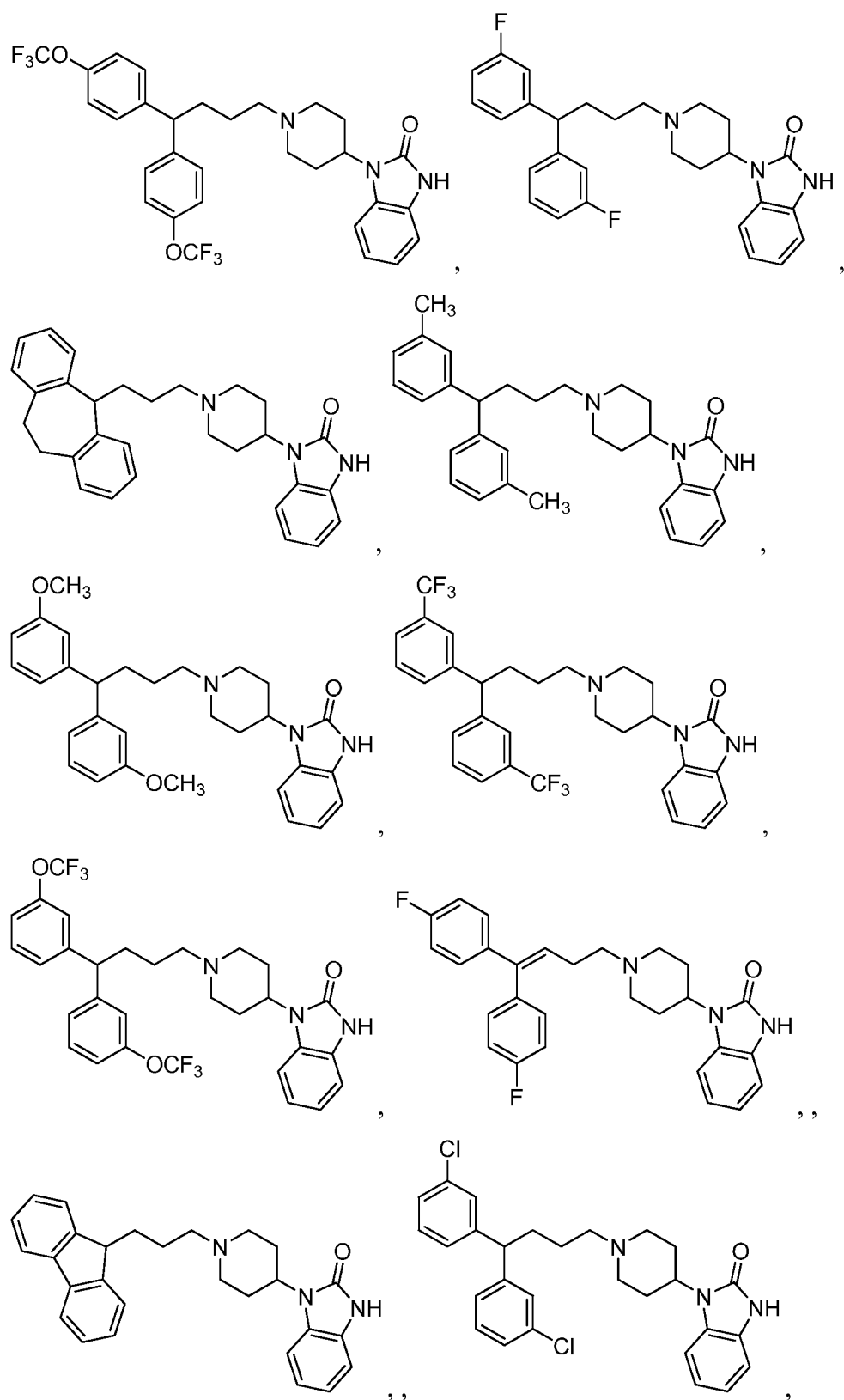


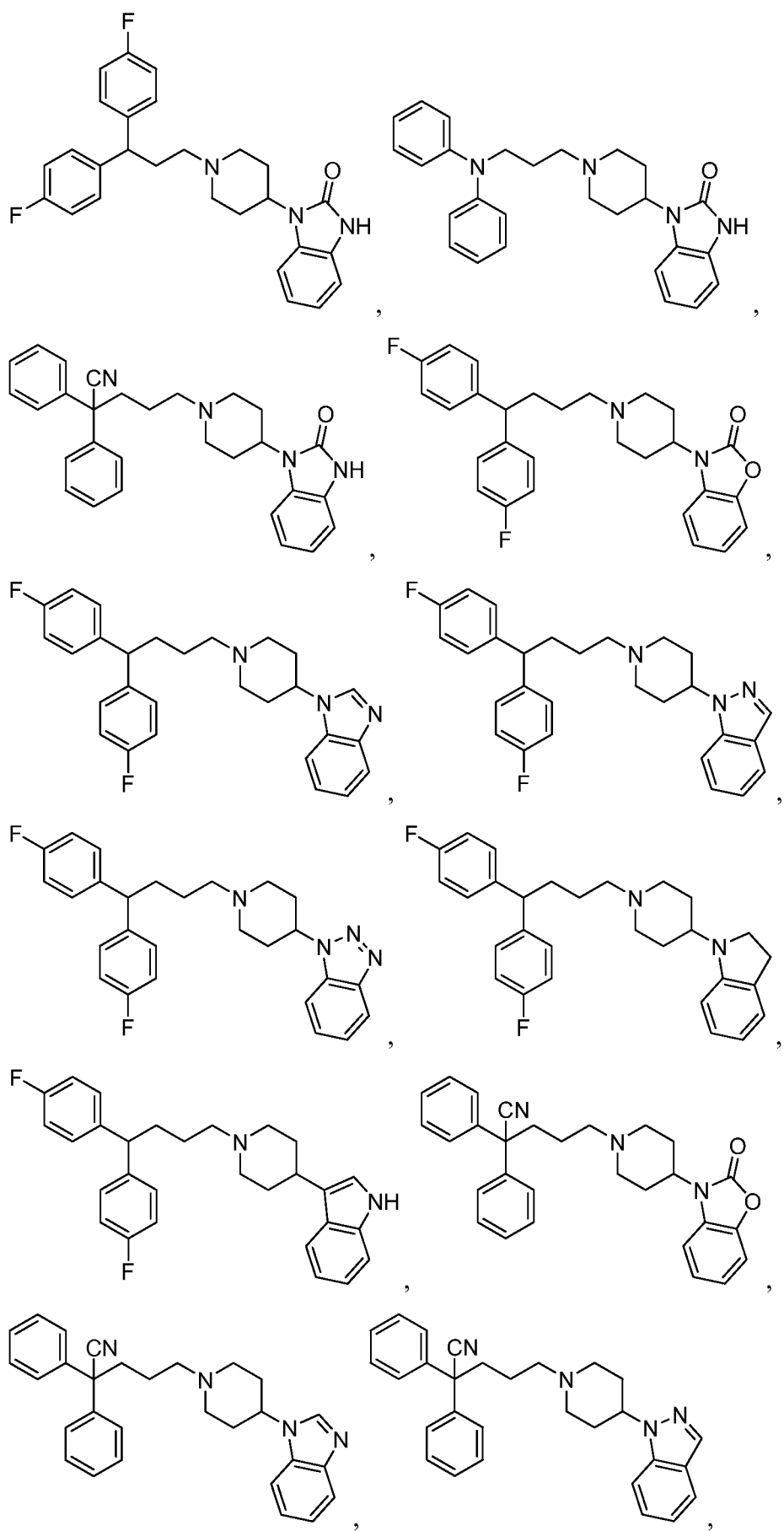


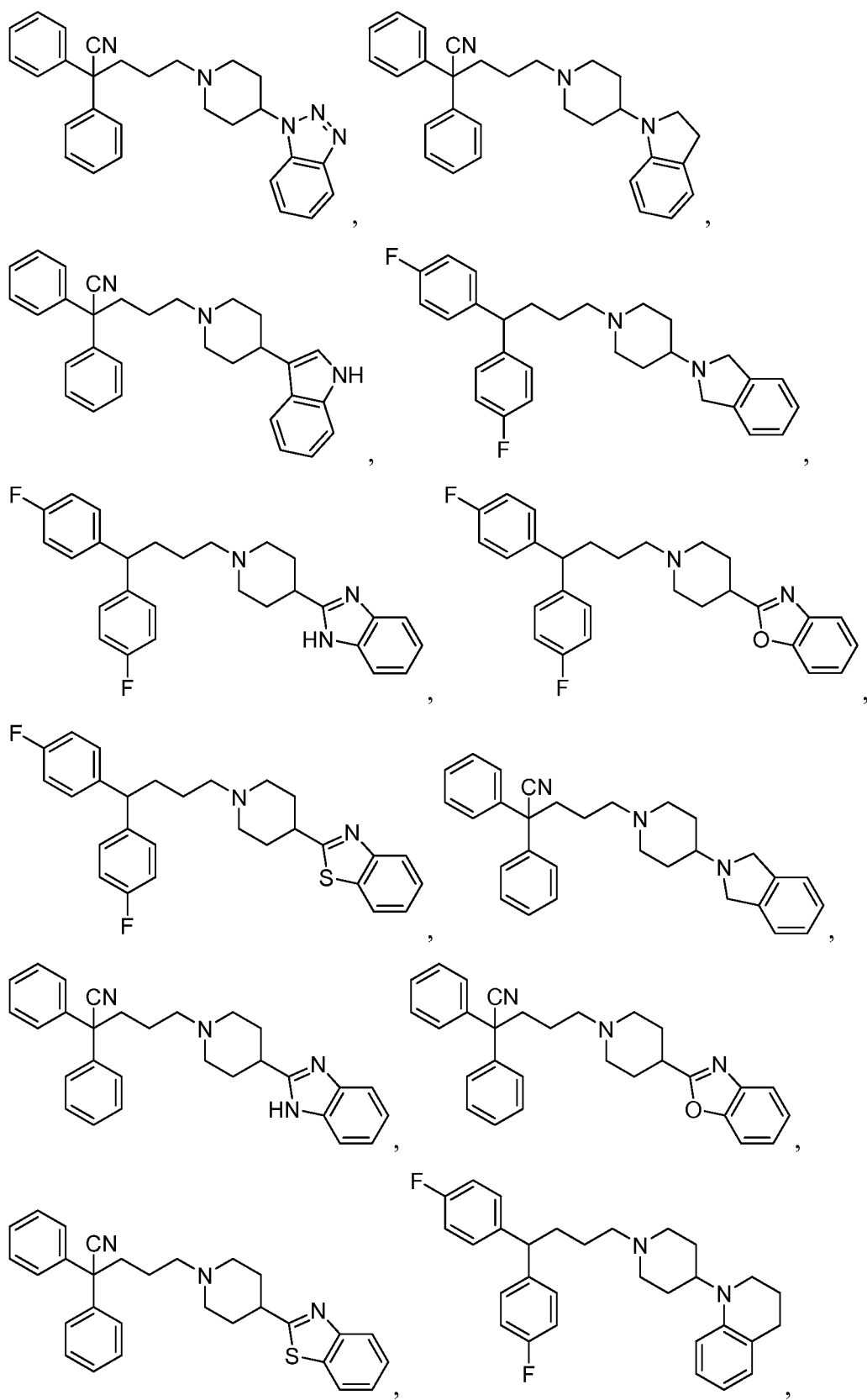


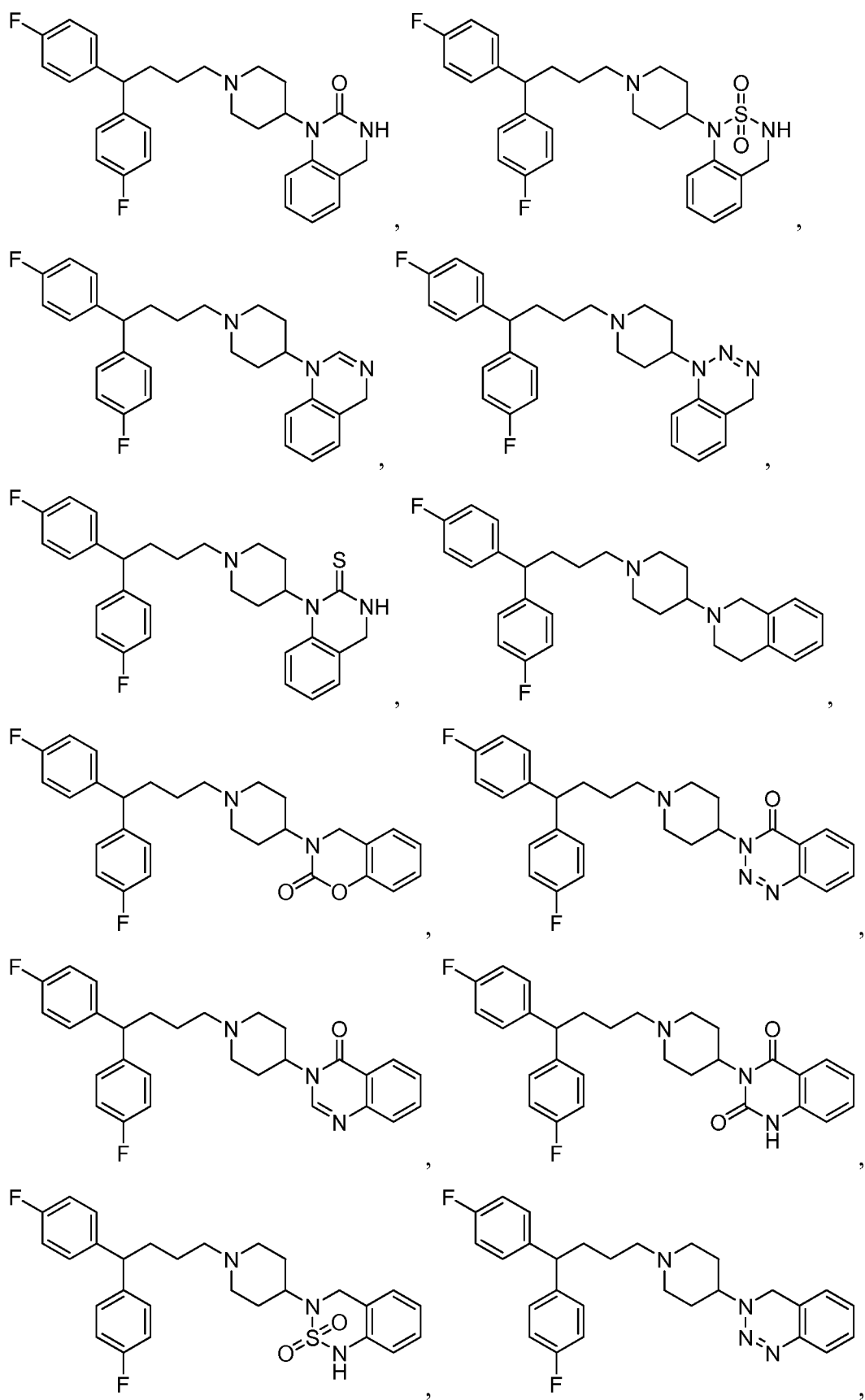


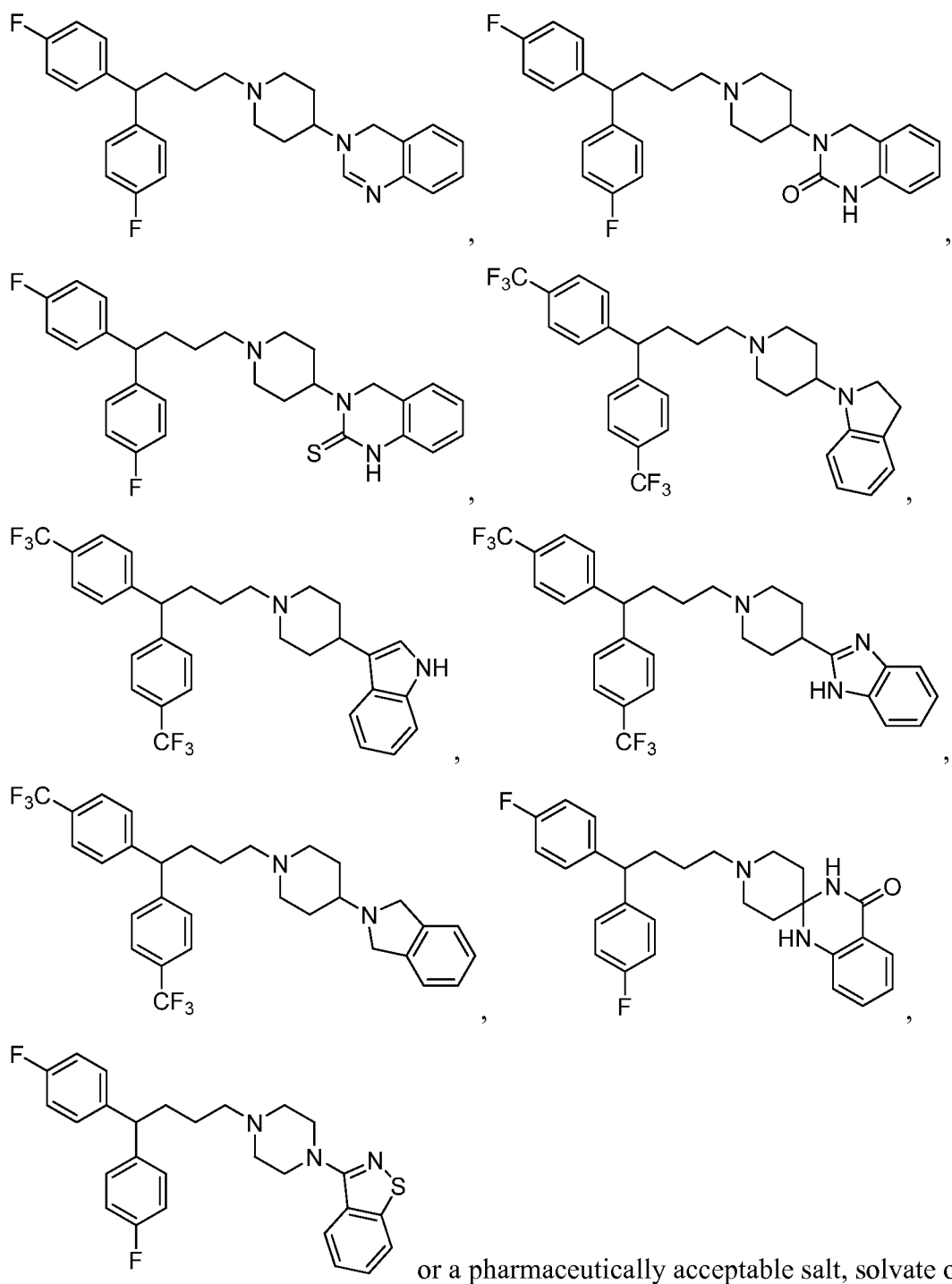












or a pharmaceutically acceptable salt, solvate or

hydrate thereof.

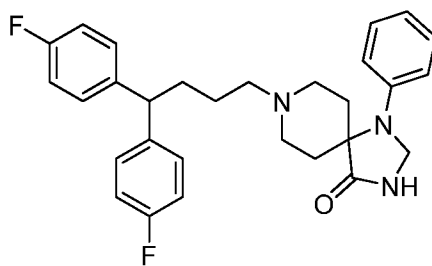
55. A pharmaceutical composition comprising an autophagy inducing compound in an amount effective for treating an autophagy associated disease, wherein the compound is selected from at least one compound of any one of claims 1-54; and a pharmaceutically acceptable carrier.

56. A method of inducing autophagy in a cell, the method comprising contacting the cell with an autophagy inducing compound of any one of claims 1-54 in an amount effective to induce autophagy in the cell.
57. The method of claim 56, wherein the cell is present in a subject.
58. The method of claim 56, wherein the cell is present in an in vitro cell culture.
59. The method of any one of claims 56-58, wherein the cell is selected from the group consisting of neural cells, glial cells, such as astrocytes, oligodendrocytes, ependymal cells, Schwann cells, lymphatic cells, epithelial cells, endothelial cells, lymphocytes, cancer cells, and haematopoietic cells.
60. A method of treating an autophagy associated disease in a subject, comprising the step of administering to the subject an autophagy inducing compound of any one of claims 1-54 or a composition of claim 55, in an amount effective to treat the disease, thereby treating the disease in the subject.
61. The method of claim 60, wherein the autophagy associated disease is a disease caused by misfolded protein aggregates.
62. The method of claim 60, wherein the disease caused by misfolded protein aggregates is selected from the group consisting of: Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease, spinocerebellar ataxia, oculopharyngeal muscular dystrophy, prion diseases, fatal familial insomnia, alpha-1 antitrypsin deficiency, dentatorubral pallidoluysian atrophy, frontal temporal dementia, progressive supranuclear palsy, x-linked spinobulbar muscular atrophy, and neuronal intranuclear hyaline inclusion disease..
63. The method of claim 60, the disease associated with misfolded protein aggregates is a chronic disease.
64. The method of claim 60, the autophagy associated disease is cancer.
65. The method of claim 60, the autophagy associated disease is diabetes.
66. A method of treating a disease caused by an intracellular pathogen, comprising the step of administering to a subject in need thereof a therapeutically effective amount of compound of any one of claims 1-54 or a composition of claim 55, in an amount effective to treat the disease, thereby treating the disease in the subject.
67. The method of claim 66, wherein the intracellular pathogen is selected from the group consisting of Group A streptococcus, *Listeria monocytogenes*, *Mycobacterium tuberculosis*, *Vibrio cholerae*, *Salmonella enterica*, *Staphylococcus*

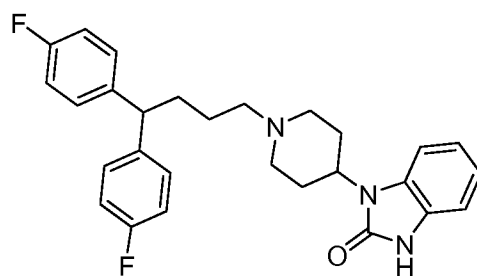
aureus, *Bacillus anthracis*, *Burkholderia pseudomallei*, *Helicobacter pylori*, *Pseudomonas syringae*, *Toxoplasma gondii*, Sindbis virus, Vesicular stomatitis virus and Herpes simplex virus.

68. A kit which includes: (i) a pharmaceutical composition comprising a compound of any one of claims 1-54; and (ii) instructions for administering the composition to a subject for the treatment of an autophagy associated disease.

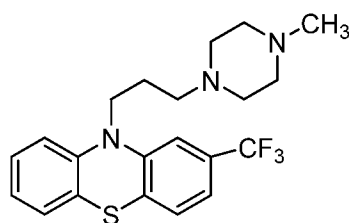
Figure 1



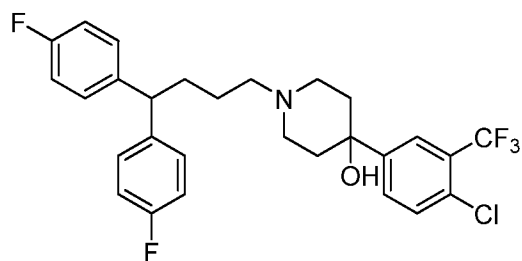
1



2



3



4

Figure 2

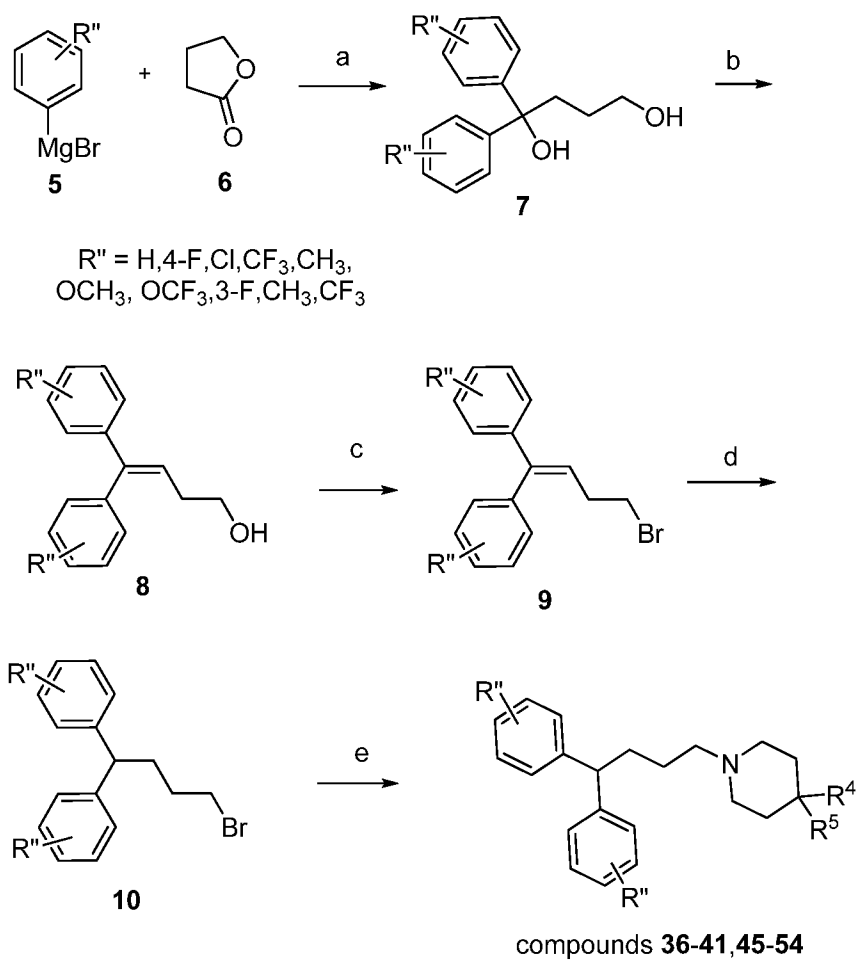


Figure 3

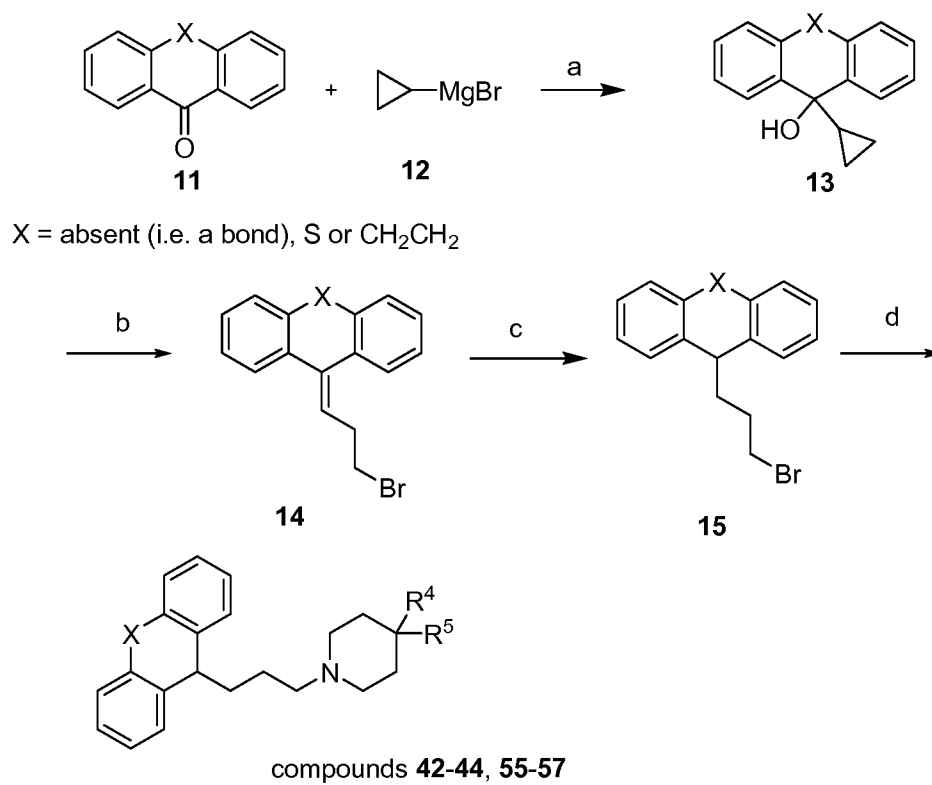


Figure 4

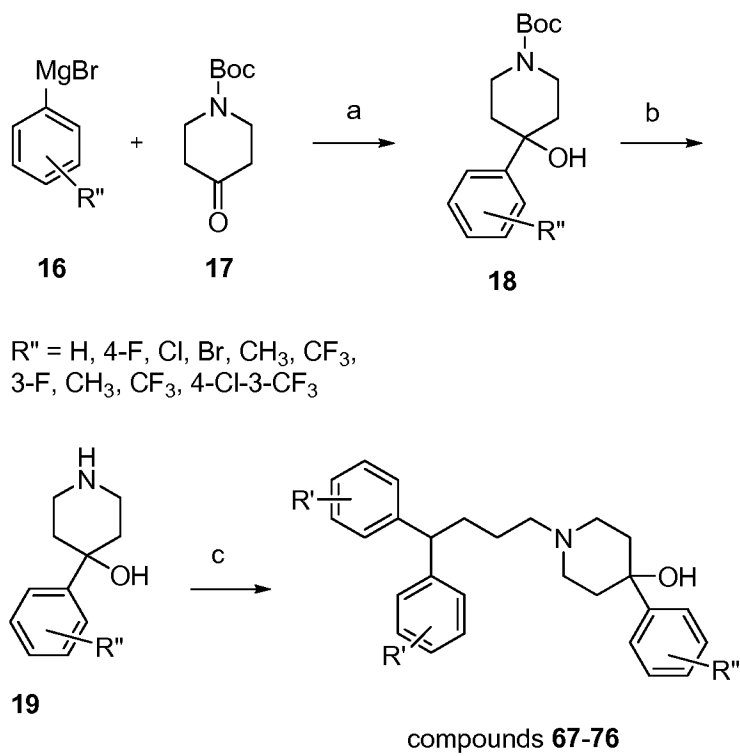


Figure 5

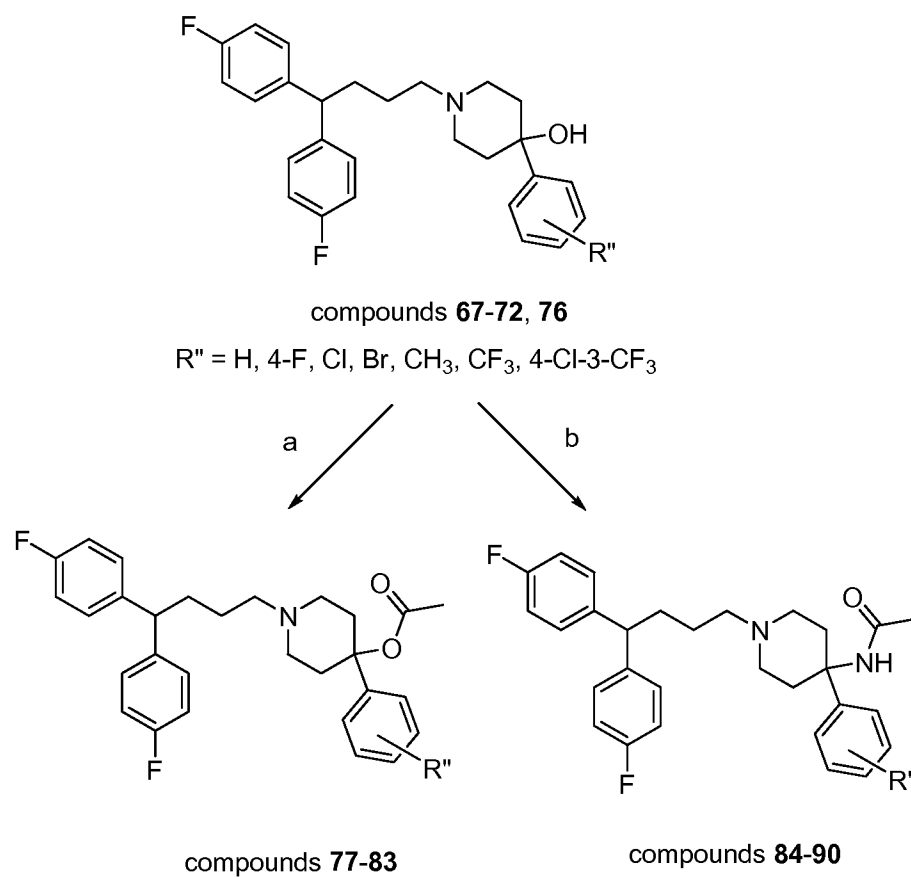


Figure 6

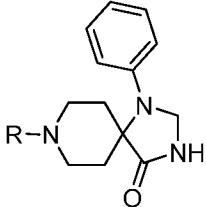
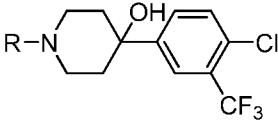
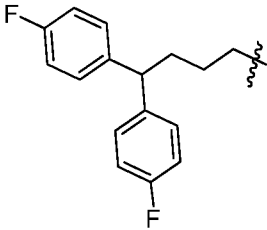
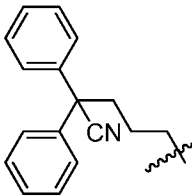
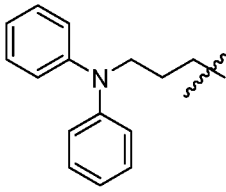
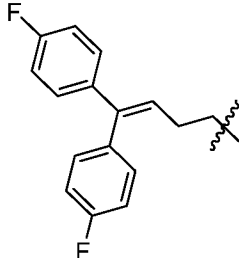
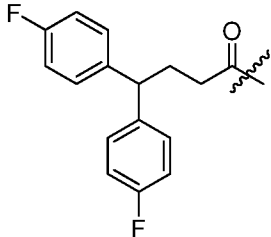
R		
	compound/EC ₅₀ (um)	compound/EC ₅₀ (um)
	1 / 2.4	30 / 3.2
	20 / 14.8	31 / 3.2
	21 / 24.9	/
	22 / 6.2	32 / 4.3
	23 / >50	33 / >50

Figure 7

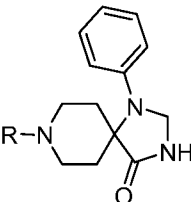
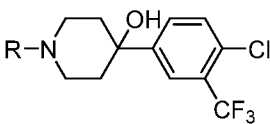
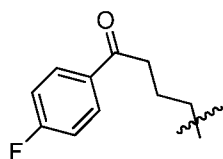
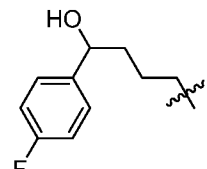
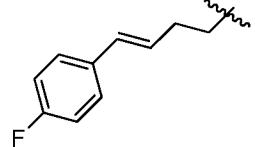
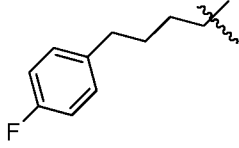
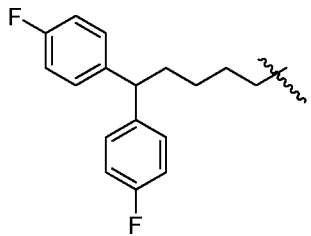
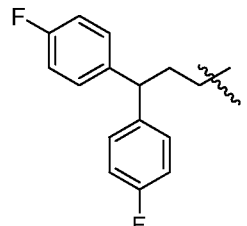
R		
	compound/EC ₅₀ (um)	compound/EC ₅₀ (um)
	24 / >50	/
	25 / >50	/
	26 / >50	/
	27 / >50	/
	28 / 4.7	34 / 2.7
	29 / 2.1	35 / 4.5

Figure 8

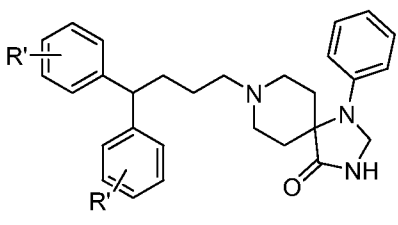
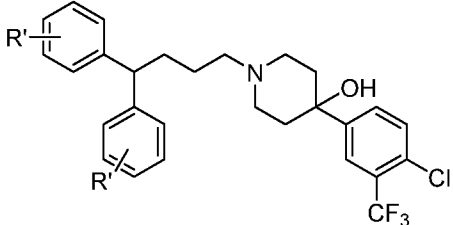
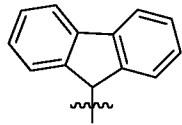
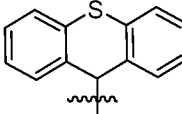
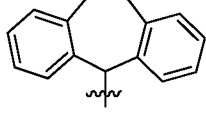
 		
R'	compound/EC ₅₀ (um)	compound/EC ₅₀ (um)
H	36 / 34.6	45 / 5.1
4-F	1 / 2.4	4 / 3.2
4-Cl	38 / 4.2	47 / 2.4
4-CF ₃	39 / 3.7	48 / 0.28
4-CH ₃	40 / 3.1	49 / 0.29
4-OCH ₃	41 / 4.6	50 / 1.2
4-OCF ₃	—	51 / 0.97
3-F	—	52 / 2.2
3-CF ₃	—	53 / 0.65
3-CH ₃	—	54 / 0.29
<i>or the two phenyl rings can form a tricycle:</i>		
	42 / 7.9	55 / 2.6
	43 / >50	56 / 14.4
	44 / 5.1	57 / 2.6

Figure 9

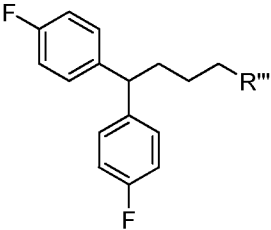
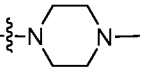
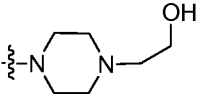
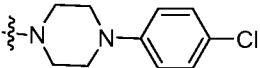
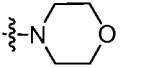
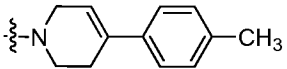
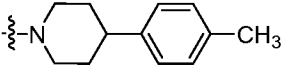
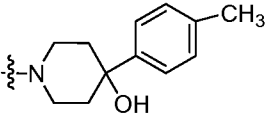
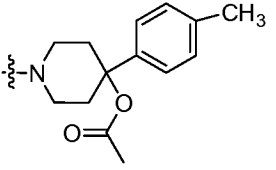
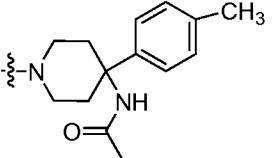
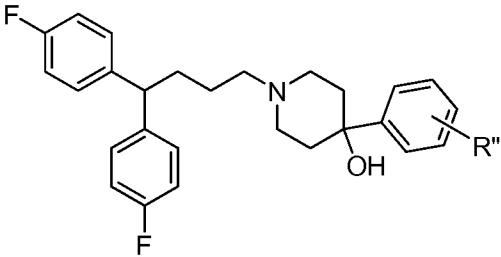
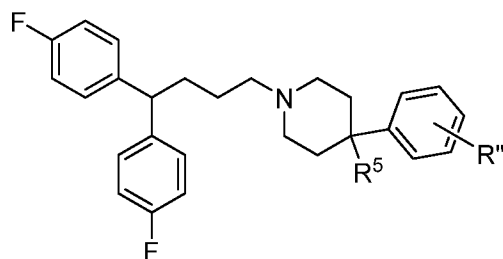
		
compound	R'''	EC ₅₀ (um)
58		>50
59		>50
60		>50
61		>50
62		>50
63		>50
64		6.4
65		4.4
66		2.2

Figure 10



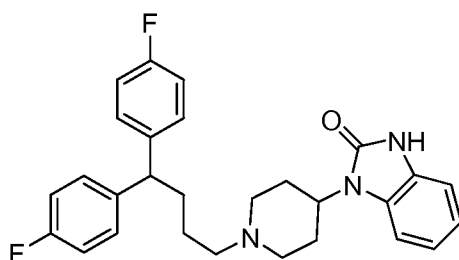
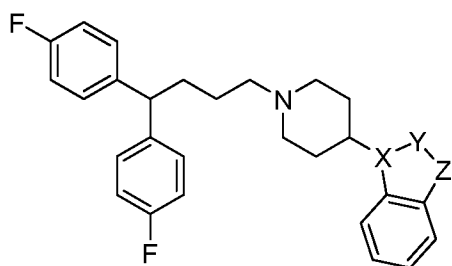
compound	R''	EC ₅₀ (um)
67	H	12.0
68	4-F	6.1
69	4-Cl	7.7
70	4-Br	2.2
71	4-CF ₃	4.2
72	4-CH ₃	6.4
73	3-F	10.1
74	3-CF ₃	6.7
75	3-CH ₃	24.6
4	3-CF ₃ -4-Cl	3.2

Figure 11

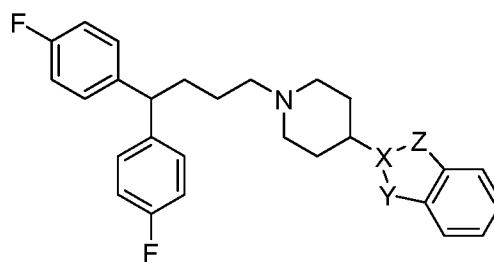


compound	R ⁵	R''	EC ₅₀ (μm)
77	-OC(=O)CH ₃	H	> 50
78		4-F	5.4
79		4-Cl	5.0
80		4-Br	2.6
81		4-CF ₃	4.5
65		4-CH ₃	4.4
83		3-CF ₃ -4-Cl	6.3
84	-N(H)C(=O)CH ₃	H	6.2
85		4-F	3.0
86		4-Cl	3.0
87		4-Br	2.5
88		4-CF ₃	3.5
66		4-CH ₃	2.2
90		3-CF ₃ -4-Cl	4.0
92	-OH	H	12.0
93		4-F	6.1
94		4-Cl	7.7
95		4-Br	2.2
96		4-CF ₃	4.2
97		4-CH ₃	6.4
98		3-CF ₃ -4-Cl	3.2
63	H	4-CH ₃	> 50
91	CN	H	10.5

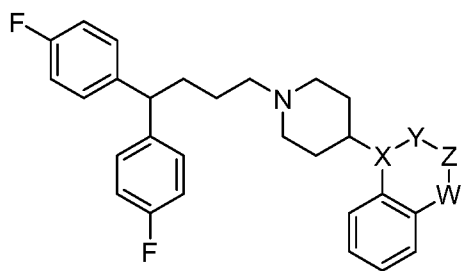
Figure 12

**2**

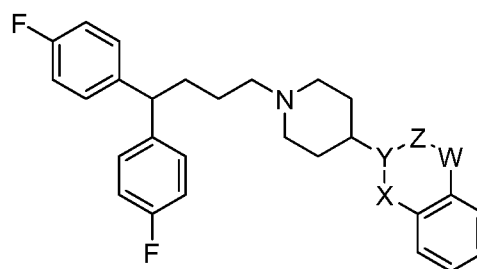
P-1-56 scaffold
compounds **2**, **109**, **147-162**



P-2-56 scaffold
compounds **163-180**

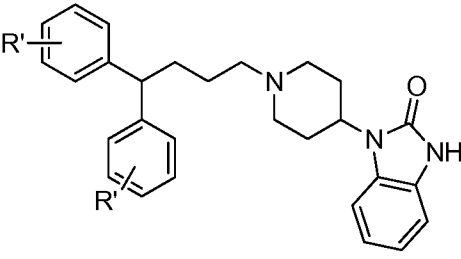


P-1-66 scaffold
compounds **218-223**



P-2-66 scaffold
compounds **224-233**

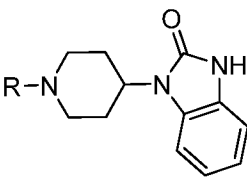
Figure 13



The chemical structure shows a benzimidazole ring system. A piperidine ring is attached to the nitrogen of the benzimidazole. A propyl chain connects the piperidine ring to a central carbon atom. This central carbon is also bonded to two phenyl rings, each with an R' substituent at the para position.

compound	R'	EC ₅₀ (um)
105	H	5.0
2	4-F	5.4
106	4-CH ₃	2.1
107	4-OCH ₃	2.4
108	3-F	0.58

Figure 14



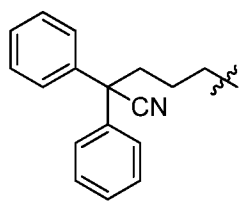
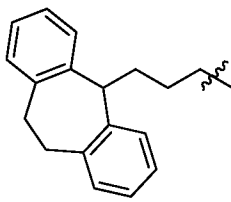
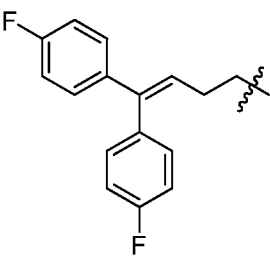
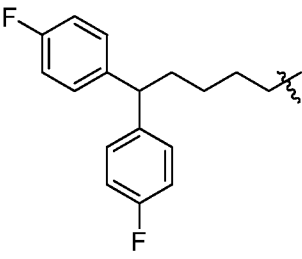
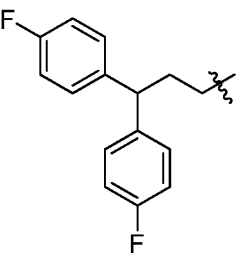
compound	R	EC ₅₀ (um)
109		8.2
110		4.8
111		2.3
112		4.6
300		

Figure 15

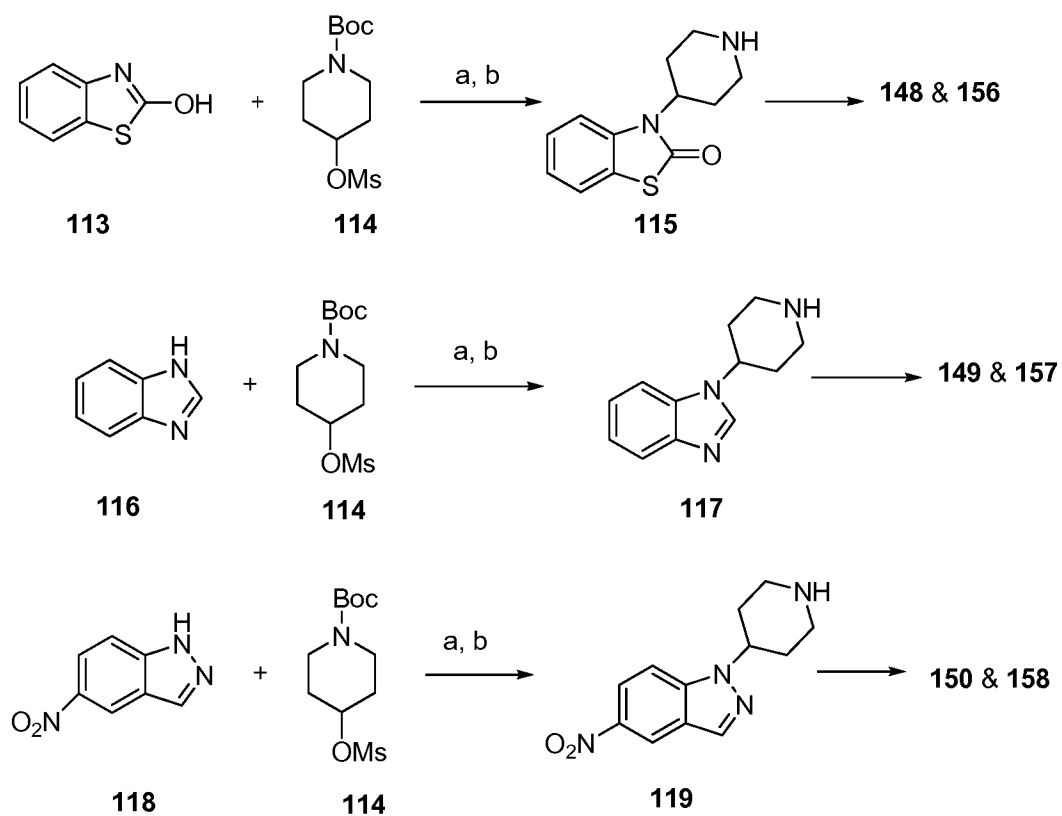


Figure 16

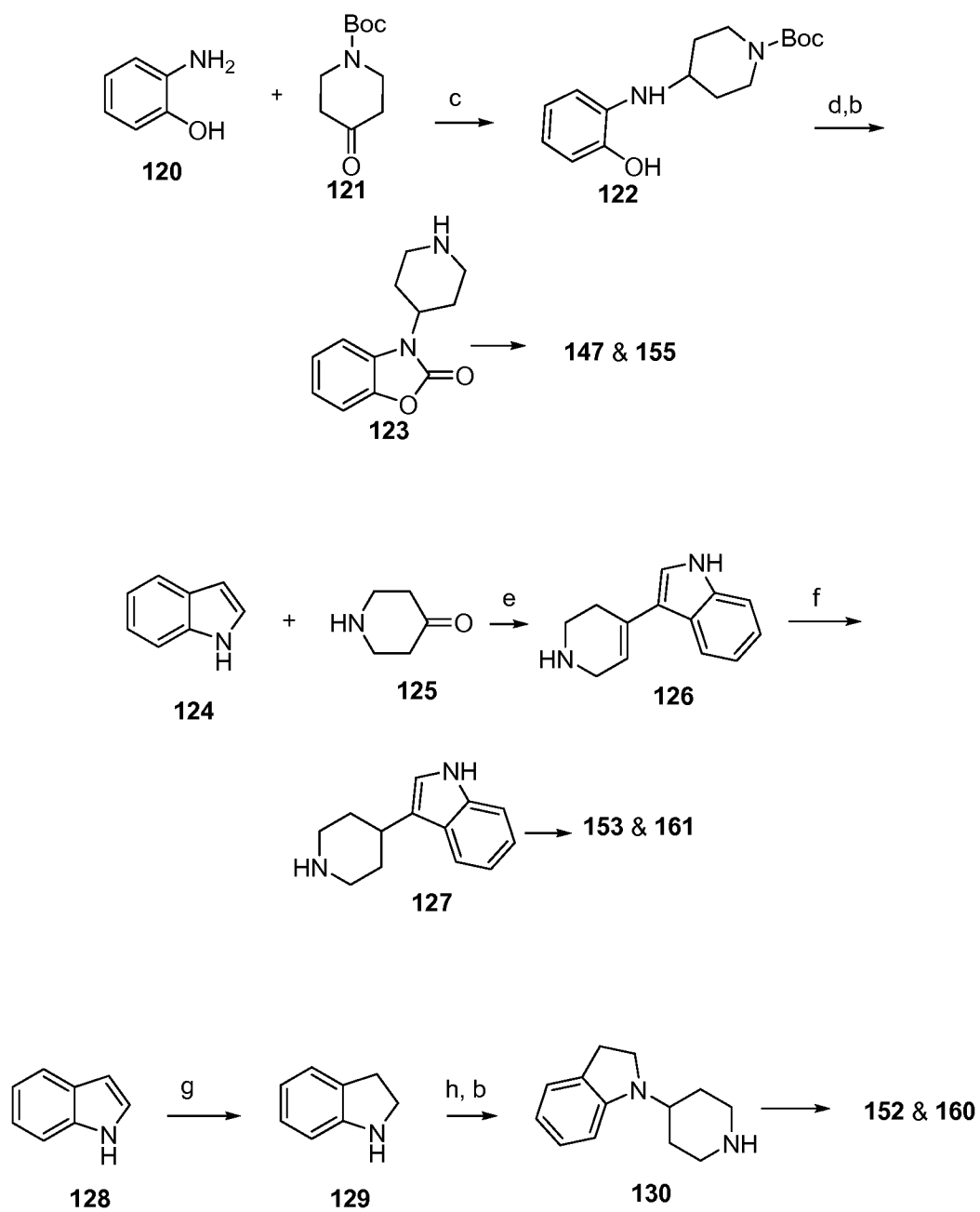


Figure 17

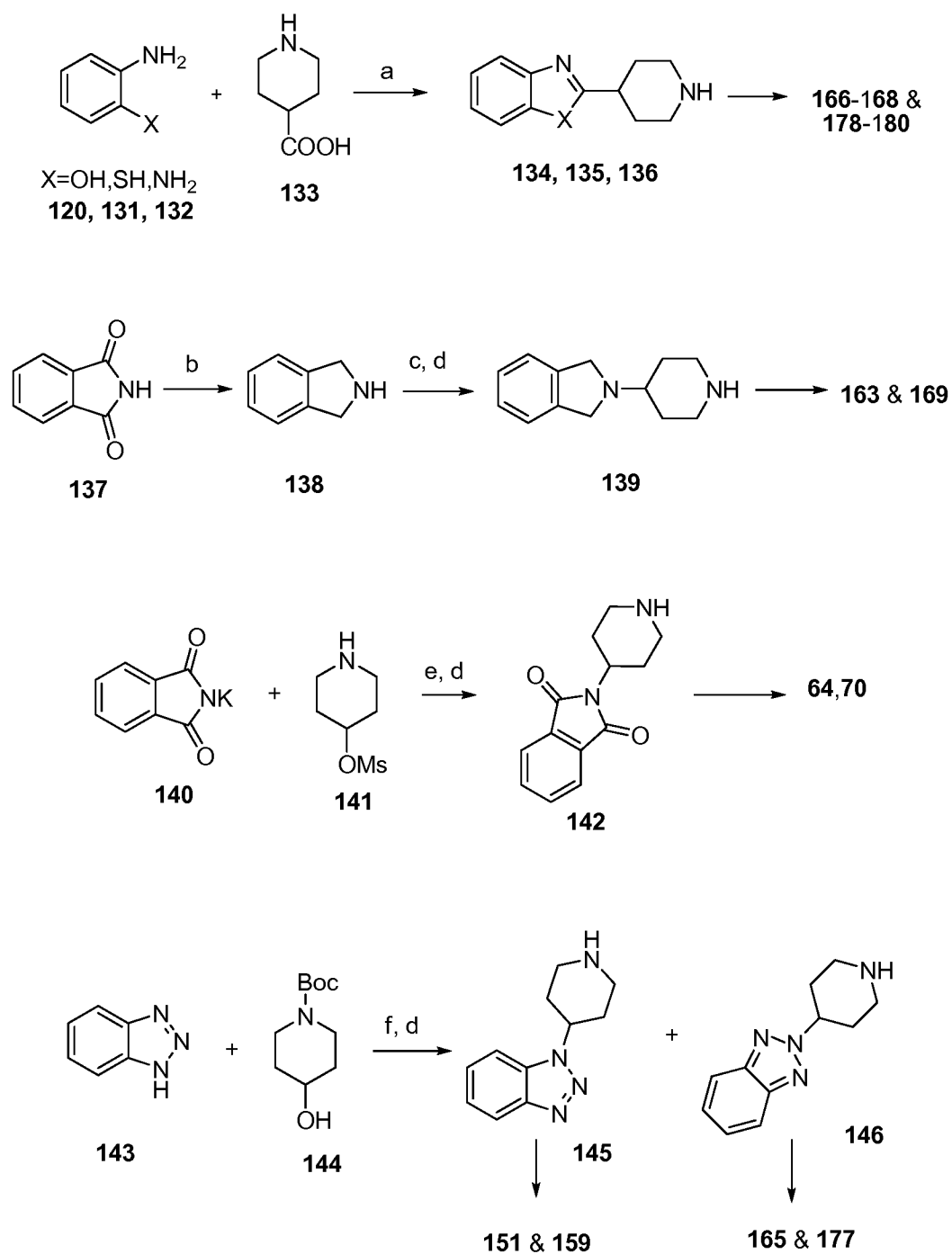


Figure 18

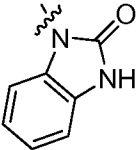
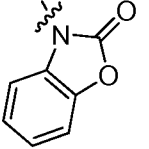
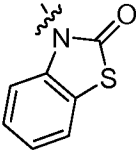
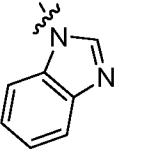
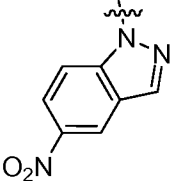
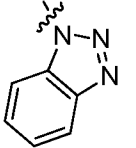
R ⁴	compound/EC ₅₀ (um)	compound/EC ₅₀ (um)
	2 /5.4	19 /8.2
	147 /8.2	155 /12.0
	148 / > 50	156 / > 50
	149 /4.2	157 /5.2
	150 /4.5	158 /6.3
	151 / > 50	159 /9.8

Figure 19

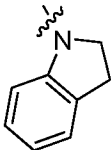
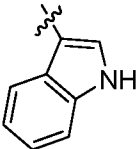
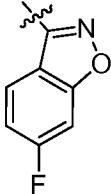
R^4	compound/ EC_{50} (μ m)	compound/ EC_{50} (μ m)
	152 /3.8	160 /4.5
	153 /6.4	161 /2.6
	154 / >50	162 / >50

Figure 20

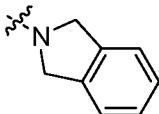
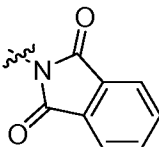
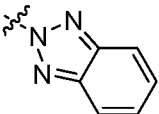
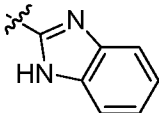
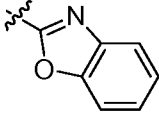
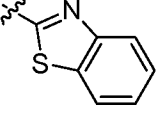
R^4	compound/ EC_{50} (μ m)	compound/ EC_{50} (μ m)
	163 /4.1	169 /7.1
	164 / >50	170 / >50
	165 / >50	177 / >50
	166 /4.0	178 /8.5
	167 /11.2	179 / >50
	168 /10.6	180 / >50

Figure 21

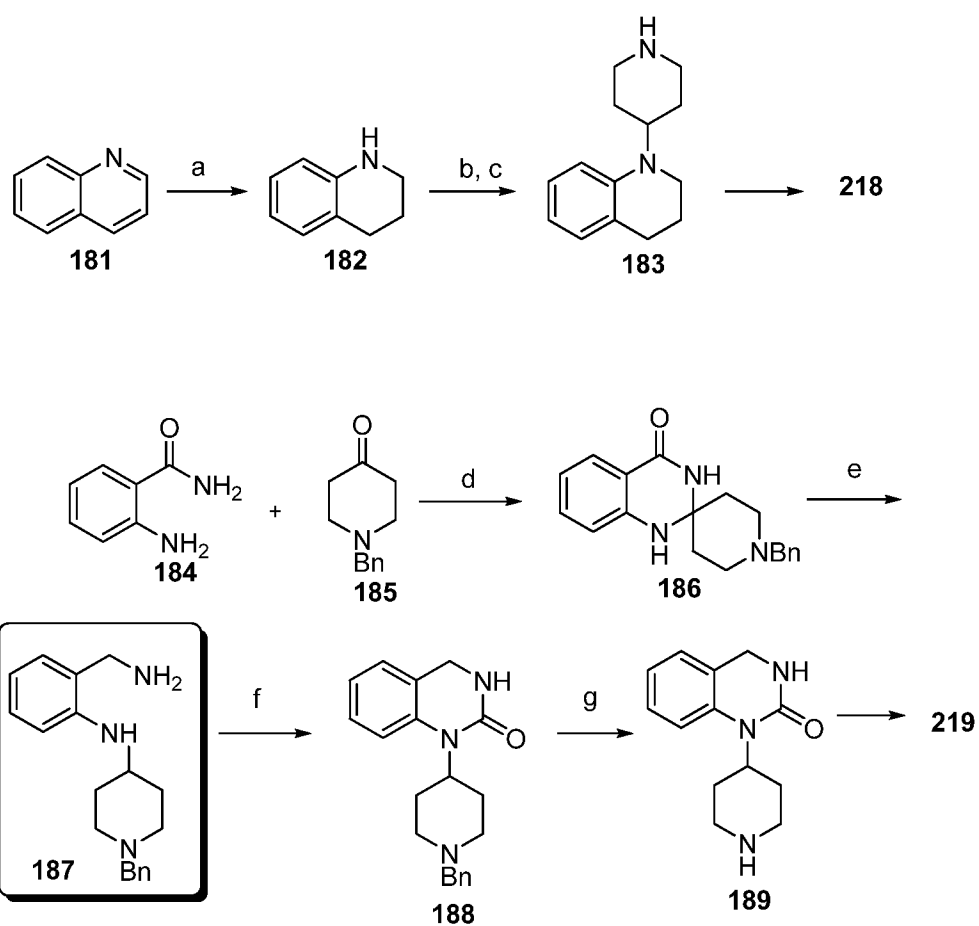


Figure 22

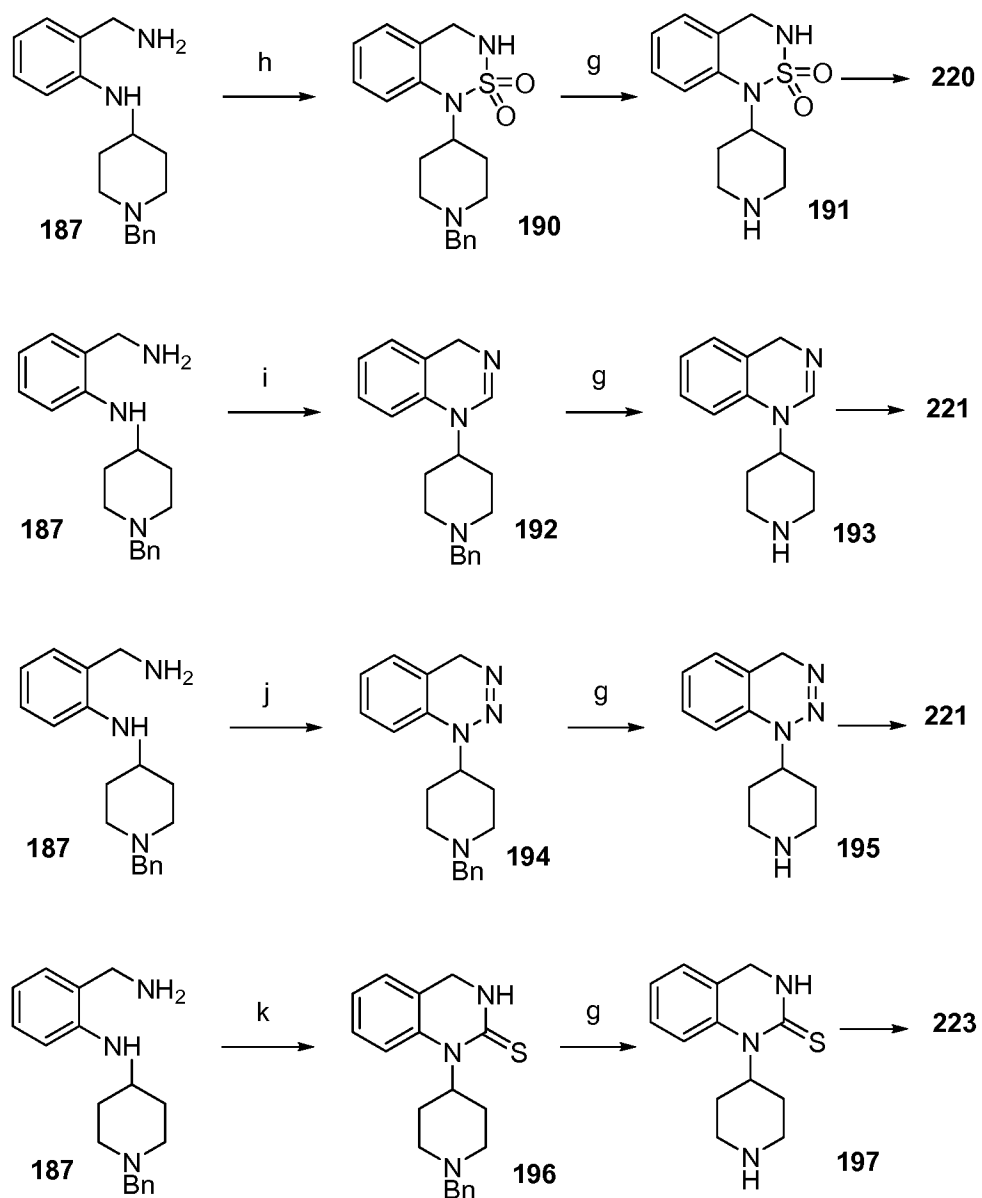


Figure 23

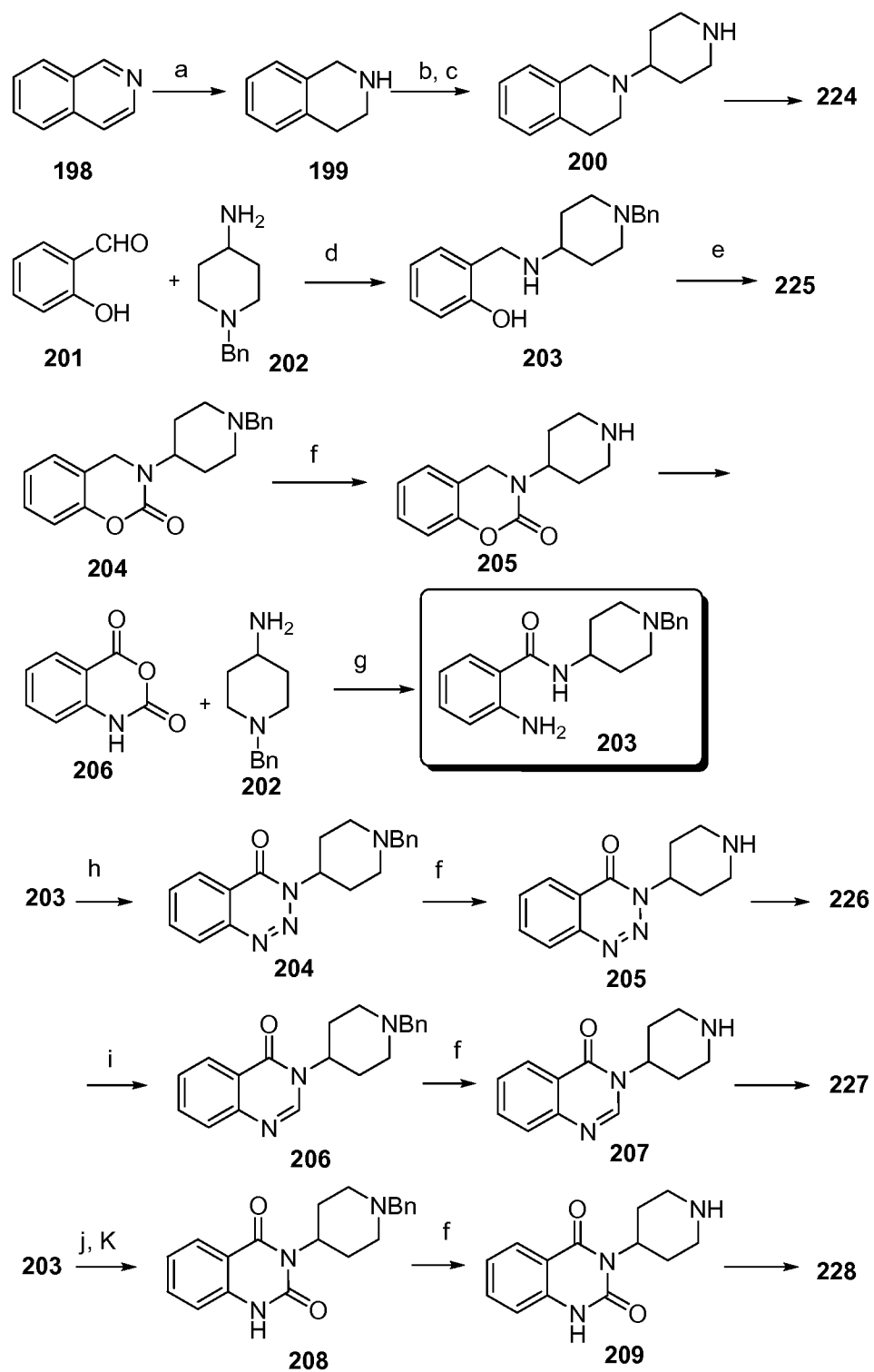


Figure 24

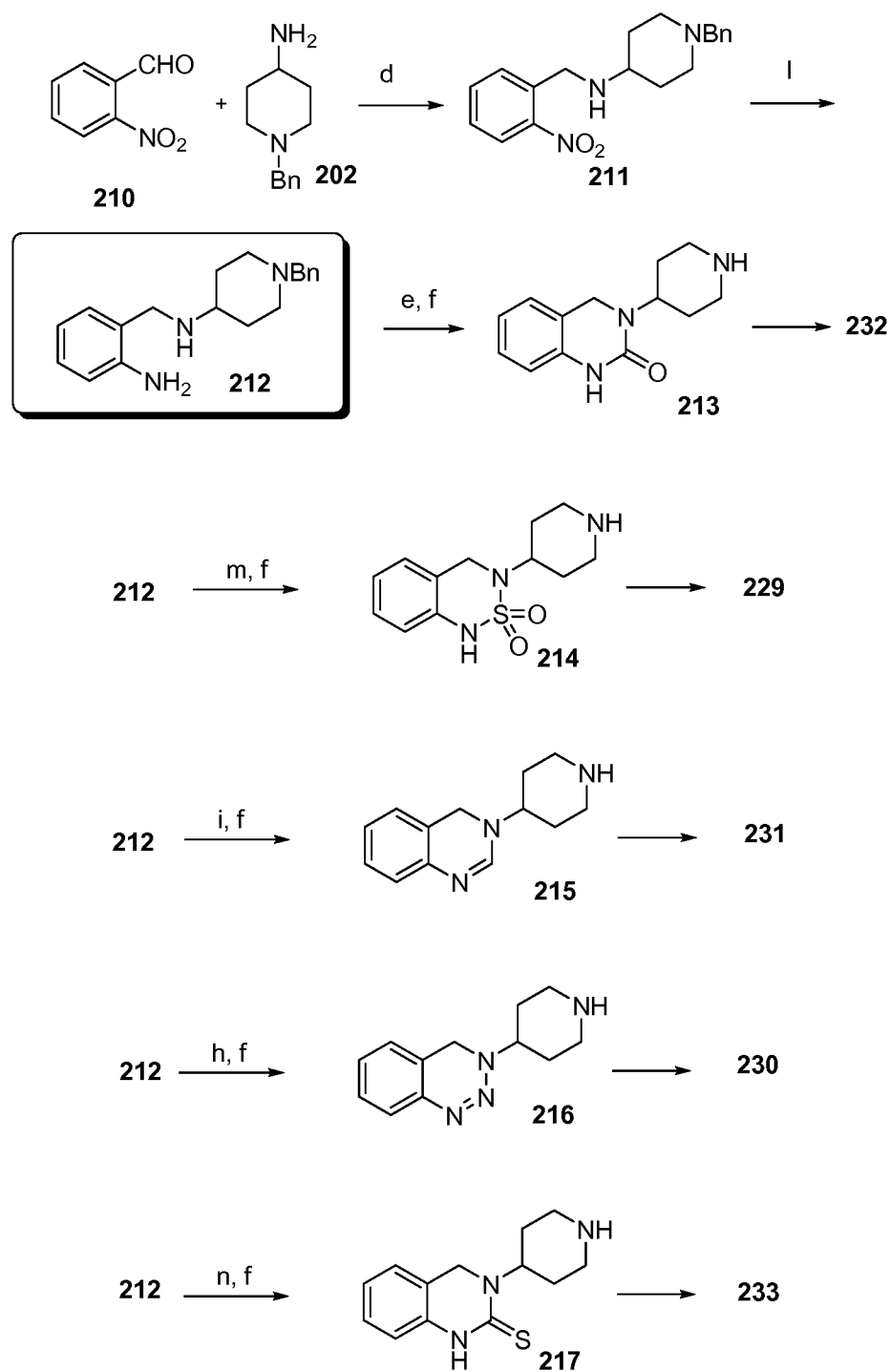


Figure 25

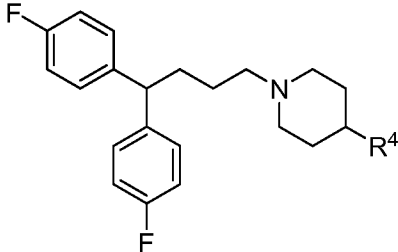
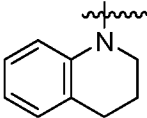
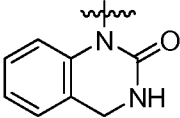
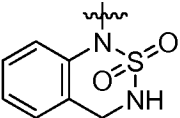
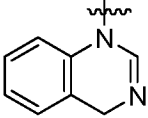
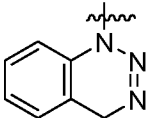
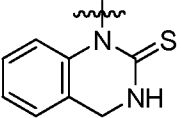
		
compound	R ⁴	EC ₅₀ (um)
218		
219		2.9
220		10.2
221		
222		
223		

Figure 26

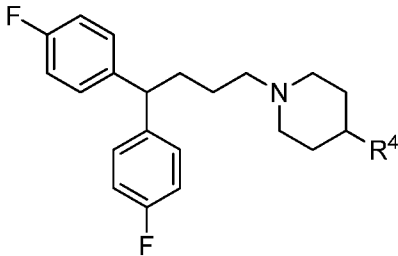
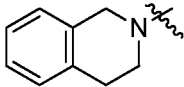
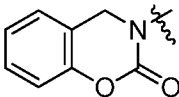
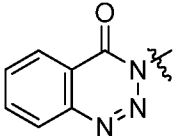
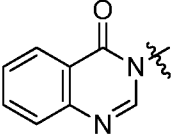
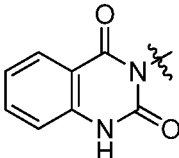
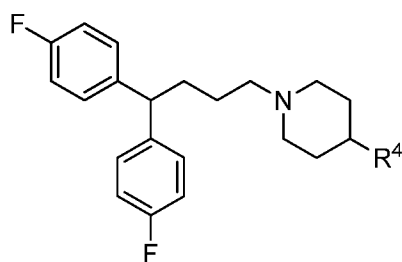
		
compound	R ⁴	EC ₅₀ (um)
224		6.0
225		4.1
226		7.8
227		
228		2.8

Figure 27



compound	R ⁴	EC ₅₀ (μm)
----------	----------------	-----------------------

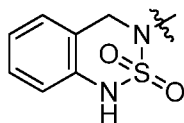
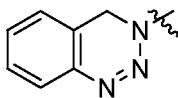
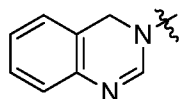
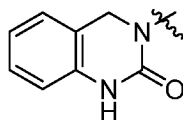
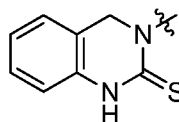
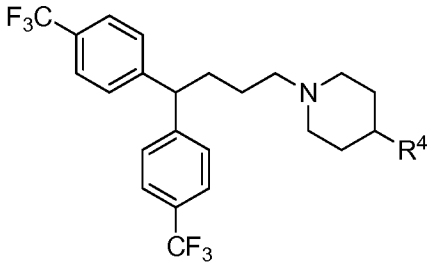
22921.72302312321.3233

Figure 28



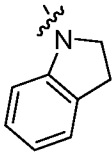
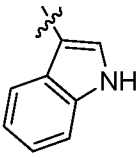
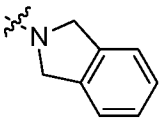
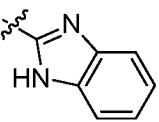
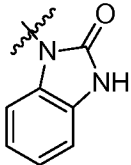
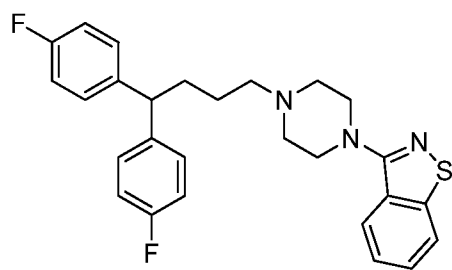
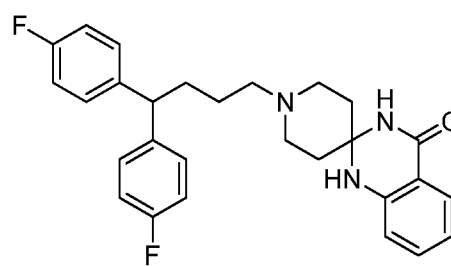
compound	R ⁴	EC ₅₀ (um)
234		1.2
235		0.45
236		1.5
237		0.90
		1.2

Figure 29

**238** $EC_{50} = 10.1 \mu\text{m}$ **239** $EC_{50} = 1.9 \mu\text{m}$