

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
9 February 2012 (09.02.2012)

PCT

(10) International Publication Number  
**WO 2012/019106 A2**

(51) International Patent Classification:  
C07C 33/18 (2006.01)

(21) International Application Number:  
PCT/US2011/046756

(22) International Filing Date:  
5 August 2011 (05.08.2011)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
61/371,221 6 August 2010 (06.08.2010) US

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(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, QA, 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: POSITIVE AND NEGATIVE MODULATORS OF NMDA RECEPTORS

(57) Abstract: Disclosed herein are compounds useful as modulators of an NMDA receptor. Further disclosed are methods of modulating an NMDA receptor using these compounds, and methods of treating various NMDA-receptor disorders, such as, for example, schizophrenia, post-traumatic stress disorder, Alzheimer's disease, and pain.



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**POSITIVE AND NEGATIVE MODULATORS OF NMDA RECEPTORS****CROSS-REFERENCE TO RELATED APPLICATIONS**

[0001] This application claims the benefit of U.S. provisional application no. 61/371,221, filed August 6, 2010, the disclosure of which is incorporated by reference in its entirety herein.

**STATEMENT OF U.S. GOVERNMENT INTEREST**

[0002] This invention was made with U.S. government support under Grant No. MH060252 awarded by the National Institutes of Health. The U.S. government has certain rights in the invention.

**BACKGROUND**

[0003] The primary excitatory neurotransmitter in the vertebrate central nervous system (CNS), L-glutamate, activates three distinct families of ligand-gated ion channels that are named for agonists by which they are selectively activated, NMDA (N-methyl-D-aspartate), AMPA ( $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) and kainate (1-3). While AMPA and kainate receptors underlie fast excitatory synaptic transmission in the CNS, NMDA receptor activation triggers diverse calcium-dependent intracellular responses that regulate distinct forms of synaptic plasticity such as long-term potentiation (LTP), long-term depression (LTD) and experience-dependent synaptic refinement (2-3).

[0004] Such NMDA receptor-mediated mechanisms are thought to play key roles in learning and memory, but also contribute to the expression of epilepsy, schizophrenia, drug addiction, mood disorders, post-traumatic stress disorder and neuropathic pain (4-6). Excessive NMDA receptor activation may also be a common mechanism causing neuronal cell death in stroke, traumatic brain injury and various neurodegenerative diseases such as Alzheimer's, Parkinson's, Huntington's, amyotrophic lateral sclerosis (ALS), and Creutzfeldt-Jakob disease (7-9). These findings have led to high expectations for clinical studies of NMDA receptor-based therapeutic agents. Unfortunately, the results from these studies have been largely disappointing due to adverse effects and limited therapeutic efficacy (7,10). To date, most NMDA receptor pharmacological agents tested in the clinic have been non-selective agents that cannot distinguish among NMDA receptor subtypes (7,11). Thus it has not been possible to optimize the therapeutic effect of NMDA receptor pharmacological agents while minimizing their adverse effects.

[0005] NMDA receptor complexes are composed of subunits from seven genes -- GluN1, GluN2A-GluN2D, and GluN3A-GluN3B (12-14). The majority of NMDA receptors are thought to be composed of two GluN1 subunits and two GluN2 subunits (15). L-Glutamate and a co-agonist (either glycine or D-serine), bind to homologous binding sites on GluN2 and GluN1 subunits, respectively, to cause the opening of the receptor's  $\text{Na}^+/\text{K}^+/\text{Ca}^{2+}$ -permeable ion channel (3). The influx of  $\text{Ca}^{2+}$  ions is thought to initiate many of the actions of NMDA receptors. Importantly, the GluN2 subunits have varied developmental profiles and anatomical distributions and confer distinct physiological, biochemical, and pharmacological properties to the NMDA receptor complex (13,16,17). Evidence suggests that specific NMDA receptor subunits have distinct, and sometimes opposing, roles in various physiological and pathophysiological actions (18-20). However, their specific roles have been difficult to study in the absence of highly-selective antagonists.

[0006] Currently, there are four functionally-distinct classes of compounds that are therapeutic candidates for the inhibition of NMDA receptor function, those that inhibit glutamate or glycine binding, block the ion channel, or compounds that inhibit the receptor by binding to an N-terminal regulatory domain (NTD) (21). Of these four drug targets, the first three drug binding sites are highly conserved in different NMDA receptor subtypes and it is only the NTD drug binding site for which there are compounds that fully distinguish GluN2 subunits. Presently, these latter compounds are limited to ones that are selective for GluN2B-containing receptors. Hence, the only subtype-selective agents that have been tested in the clinic are antagonists that selectively block GluN1/GluN2B receptors. While there are several potential therapeutic applications for positive modulators of NMDA receptor function, there are no such compounds available for clinical studies.

[0007] Thus, a need exists for NMDA receptor modulators that can (1) be either activators or inhibitors, (2) operate through an allosteric interaction with the NMDA receptor, and/or (3) be selective for one or more specific subunits (or subtypes) of the NMDA receptor.

## SUMMARY

[0008] Disclosed herein are modulators of an NMDA receptor. More specifically, disclosed herein are methods of modulating an NMDA receptor comprising contacting the NMDA receptor with a compound as disclosed herein. The modulation can be an increase in the NMDA receptor activity or a decrease in the NMDA receptor activity. The compound can interact with the NMDA receptor at an allosteric site on the NMDA receptor. In various cases, the compound does not compete for NMDA receptor binding with L-glutamate,

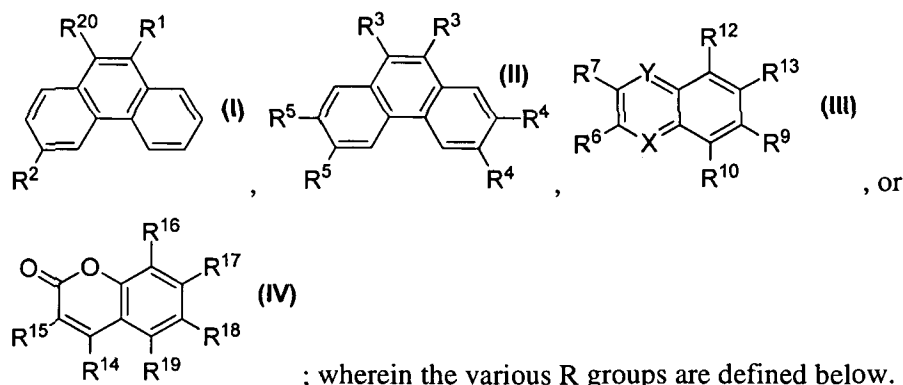
glycine, or both. In various embodiments, the NMDA receptor comprises NR2A, NR2B, NR2C, NR2D, or a combination thereof. The NMDA receptor can further comprise NR1, NR3A, NR3B, or a combination thereof. The compound can selectively modulate a receptor comprising a NR2A subunit (also referred to herein as selectively modulating NR2A). The compound can selectively modulate NR2B. The compound can selectively modulate NR2C. The compound can selectively modulate NR2D. In a specific set of embodiments, the compound increases NR2A activity and decreases NR2C, NR2D, or both NR2C and NR2D activity.

**[0009]** Further disclosed herein are methods of modulating the NMDA receptor by contacting with a compound as disclosed herein and further contacting with a second therapeutic agent. The second therapeutic agent can be a different NMDA receptor modulator or can be an mGluR2 modulator, mGluR3 modulator, mGluR5 modulator, or tissue plasminogen activator (TPA). In a specific set of embodiments, the second therapeutic agent is a TPA and the compound decreases NR2D activity.

**[0010]** The methods disclosed herein can be performed via administration of the compound to a subject. The compound can be administered as a composition comprising the compound and a carrier, excipient, diluents, or combination thereof. The composition can further comprise the optional second agent. The subject can be a mammal, or more specifically a human. The subject can suffer from an NMDA receptor modulated disorder. Contemplated disorders include a psychological disorder, post traumatic stress disorder, epilepsy, drug addiction, alcohol addiction, mood disorder, stroke, pain, a pain-related disorder, a prion disease, neurodegenerative disorder, dementia, HIV-related dementia, or a combination thereof. More specifically, the neurodegenerative disorder is Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, ALS, Creutzfeldt-Jakob Disease, or a combination thereof. In various embodiments, the psychological disorder is schizophrenia. In various embodiments, the subject suffers from a narcotic-related disorder.

**[0011]** The methods disclosed herein can be useful in enhancing cognitive function in the subject. In various embodiments, the subject suffers from a traumatic brain injury or stroke and the method improves the subject's recovery from the brain injury.

**[0012]** In various embodiments, the compound for the disclosed methods is one having a formula of any one of (I)-(IV):



**[0013]** For compounds of formula (I), in various embodiments, R<sup>1</sup> is H, halo, or alkyl, or more specifically iodo. In various embodiments, R<sup>1</sup> is alkylene-CO<sub>2</sub>H, alkylene-CO<sub>2</sub>alkyl, alkylene-OH, alkylene-cycloalkyl, heteroaryl aryl or alkylene-aryl. In various cases, R<sup>1</sup> is iodo, thienyl, thiomethyl, cyclopropyl, n-butyl, or n-pentyl. Additionally or alternatively, in various embodiments, R<sup>20</sup> is H, halo, or alkyl. In various embodiments, R<sup>20</sup> is alkylene-CO<sub>2</sub>H, alkylene-CO<sub>2</sub>alkyl, alkylene-OH, alkylene-cycloalkyl, or alkylene-aryl. Additionally or alternatively, in various embodiments, R<sup>2</sup> is CO<sub>2</sub>H. In various embodiments, R<sup>2</sup> is SO<sub>2</sub>NH<sub>2</sub>, SO<sub>3</sub>H, SO<sub>2</sub>H, alkylene-SO<sub>2</sub>H, alkylene-SO<sub>3</sub>H, alkylene-SO<sub>2</sub>NH<sub>2</sub>, C(O)NH-alkylene-SO<sub>2</sub>H, C(O)NH-alkylene-SO<sub>3</sub>H, or C(O)NH-alkylene-SO<sub>2</sub>NH<sub>2</sub>. In various embodiments, R<sup>2</sup> is P(O)(OH)(OH), P(O)(OH)(Oalkyl), P(O)(Oalkyl)(Oalkyl), P(O)(alkyl)(OH), alkylene-P(O)(OH)(OH), alkylene-P(O)(OH)(Oalkyl), alkylene-P(O)(Oalkyl)(Oalkyl), alkylene-P(O)(alkyl)(OH), C(O)NH-alkylene-P(O)(OH)(OH), C(O)NH-alkylene-P(O)(OH)(Oalkyl), C(O)NH-alkylene-P(O)(Oalkyl)(Oalkyl), or C(O)NH-alkylene-P(O)(alkyl)(OH).

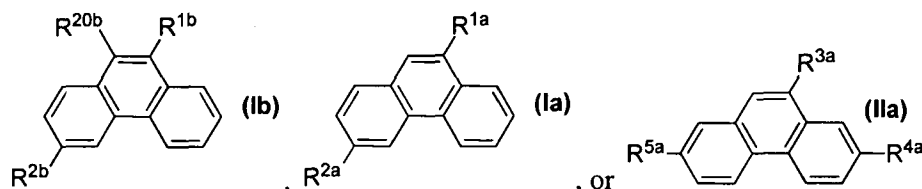
**[0014]** For compounds of formula (II), in various embodiments, each R<sup>4</sup> is independently H, halo, alkyl, or alkenyl. In various embodiments, each R<sup>4</sup> is independently alkylene-CO<sub>2</sub>H or alkylene-CO<sub>2</sub>alkyl. Additionally or alternatively, each R<sup>3</sup> is independently H, halo, alkyl, or alkenyl. In various embodiments, each R<sup>3</sup> is independently alkylenearyl or alkylene-cycloalkyl. In various cases, one R<sup>3</sup> is H and the other R<sup>3</sup> is iodo, thienyl, thiomethyl, cyclopropyl, n-butyl, or n-pentyl. Additionally or alternatively, in various embodiments, each R<sup>5</sup> is independently H, CO<sub>2</sub>H, or alkylene-CO<sub>2</sub>H.

**[0015]** For compounds of formula (III), in various embodiments, X is CR<sup>11</sup> and Y is CR<sup>8</sup>. Additionally or alternatively, in various embodiments, R<sup>6</sup> is CO<sub>2</sub>H, alkylene-CO<sub>2</sub>H, or alkylenylene-CO<sub>2</sub>H. In various embodiments, R<sup>6</sup> is SO<sub>2</sub>NH<sub>2</sub>, SO<sub>3</sub>H, SO<sub>2</sub>H, alkylene-SO<sub>2</sub>H, alkylene-SO<sub>3</sub>H, alkylene-SO<sub>2</sub>NH<sub>2</sub>, C(O)NH-alkylene-SO<sub>2</sub>H, C(O)NH-alkylene-SO<sub>3</sub>H, or

C(O)NH-alkylene-SO<sub>2</sub>NH<sub>2</sub>. In various embodiments, R<sup>6</sup> is P(O)(OH)(OH), P(O)(OH)(Oalkyl), P(O)(Oalkyl)(Oalkyl), P(O)(alkyl)(OH), alkylene-P(O)(OH)(OH), alkylene-P(O)(OH)(Oalkyl), alkylene-P(O)(Oalkyl)(Oalkyl), alkylene-P(O)(alkyl)(OH), C(O)NH-alkylene-P(O)(OH)(OH), C(O)NH-alkylene-P(O)(OH)(Oalkyl), C(O)NH-alkylene-P(O)(Oalkyl)(Oalkyl), or C(O)NH-alkylene-P(O)(alkyl)(OH). Additionally or alternatively, in various embodiments, R<sup>7</sup> is H. Additionally or alternatively, R<sup>10</sup> is H.

[0016] For compounds of formula (IV), in various embodiments, R<sup>15</sup> is CO<sub>2</sub>H, alkylene-CO<sub>2</sub>H, or alkenylene-CO<sub>2</sub>H. In various embodiments, R<sup>15</sup> is SO<sub>2</sub>NH<sub>2</sub>, SO<sub>3</sub>H, SO<sub>2</sub>H, alkylene-SO<sub>2</sub>H, alkylene-SO<sub>3</sub>H, alkylene-SO<sub>2</sub>NH<sub>2</sub>, C(O)NH-alkylene-SO<sub>2</sub>H, C(O)NH-alkylene-SO<sub>3</sub>H, or C(O)NH-alkylene-SO<sub>2</sub>NH<sub>2</sub>. In various embodiments, R<sup>15</sup> is P(O)(OH)(OH), P(O)(OH)(Oalkyl), P(O)(Oalkyl)(Oalkyl), P(O)(alkyl)(OH), alkylene-P(O)(OH)(OH), alkylene-P(O)(OH)(Oalkyl), alkylene-P(O)(Oalkyl)(Oalkyl), alkylene-P(O)(alkyl)(OH), C(O)NH-alkylene-P(O)(OH)(OH), C(O)NH-alkylene-P(O)(OH)(Oalkyl), C(O)NH-alkylene-P(O)(Oalkyl)(Oalkyl), or C(O)NH-alkylene-P(O)(alkyl)(OH). Additionally or alternatively, in various embodiments, R<sup>19</sup> and R<sup>18</sup> are each H or are each halo.

[0017] Also disclosed herein are compounds of formula (Ia), (Ib) or (IIa):



wherein the R groups are defined below. These compounds can be used in the disclosed methods of modulating an NMDA receptor.

[0018] For compounds of formula (Ib), in various embodiments, R<sup>1b</sup> is C<sub>4-20</sub>alkyl, or can be methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, t-butyl, pentyl, 2-methylpentyl, hexyl, or heptyl. In various embodiments, R<sup>1b</sup> is alkenyl, such as hept-1-ene-1-yl. In various embodiments, R<sup>1b</sup> is C<sub>3</sub>-C<sub>8</sub>cycloalkyl or alkylene-C<sub>3</sub>-C<sub>8</sub>cycloalkyl. In various embodiments, R<sup>1b</sup> is heteroaryl or aryl. In various embodiments, R<sup>1b</sup> is alkyleneamino. In various embodiments, R<sup>1b</sup> is alkylene-CO<sub>2</sub>H. In various embodiments, R<sup>1b</sup> is alkylene-OH. In various embodiments, R<sup>1b</sup> is alkylenearyl or alkenylenearyl. In various embodiments, R<sup>1b</sup> is thioalkyl or alkoxy.

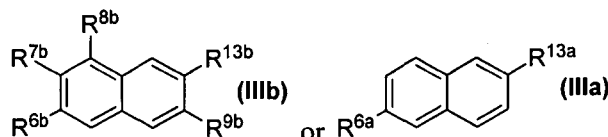
[0019] For compounds of formula (Ib), R<sup>2b</sup> can be CO<sub>2</sub>H. In various embodiments, R<sup>2b</sup> is alkylene-CO<sub>2</sub>H. In various embodiments, R<sup>2b</sup> is alkylene-CO<sub>2</sub>alkyl. In various

embodiments,  $R^{2b}$  is  $NH_2$ . In various embodiments,  $R^{2b}$  is  $C(O)NH$ -alkylenearyl. In various embodiments,  $R^{2b}$  is  $C(O)NH$ -alkyleneheteroaryl. In various embodiments,  $R^{2b}$  is  $C(O)NH$ -alkylene- $CO_2H$ . In various embodiments,  $R^{2b}$  is alkylene-OH. In various embodiments,  $R^{2b}$  is  $C(O)alkyl$ . In various embodiments,  $R^{2b}$  is  $NO_2$ . In various embodiments,  $R^{2b}$  is  $P(O)(OH)(OH)$ ,  $P(O)(OH)(Oalkyl)$ ,  $P(O)(Oalkyl)(Oalkyl)$ ,  $P(O)(alkyl)(OH)$ ,  $SO_2H$ ,  $SO_3H$ ,  $C(O)NHOH$ ,  $SO_2NH_2$ , tetrazole, alkylene- $P(O)(OH)(OH)$ , alkylene- $P(O)(OH)(Oalkyl)$ , alkylene- $P(O)(Oalkyl)(Oalkyl)$ , alkylene- $P(O)(alkyl)(OH)$ , alkylene- $SO_2H$ , alkylene- $SO_3H$ , alkylene- $C(O)NHOH$ , alkylene- $SO_2NH_2$ , alkylene-tetrazole,  $C(O)NH$ -alkylene- $P(O)(OH)(OH)$ ,  $C(O)NH$ -alkylene- $P(O)(OH)(Oalkyl)$ ,  $C(O)NH$ -alkylene- $P(O)(Oalkyl)(Oalkyl)$ ,  $C(O)NH$ -alkylene- $P(O)(alkyl)(OH)$ ,  $C(O)NH$ -alkylene- $SO_2H$ ,  $C(O)NH$ -alkylene- $SO_3H$ ,  $C(O)NH$ -alkylene- $C(O)NHOH$ ,  $C(O)NH$ -alkylene- $SO_2NH_2$ , or  $C(O)NH$ -alkylene-tetrazole.

**[0020]** For compounds of formula (Ia), in various embodiments,  $R^{1a}$  is bromo. In various embodiments,  $R^{1a}$  is iodo. Additionally or alternatively, for compounds of formula (Ia), in various embodiments,  $R^{2a}$  is  $C(O)$ -alkylene- $NH_2$ . In various embodiments,  $R^{2a}$  is  $C(O)$ -alkylene-heteroaryl.

**[0021]** For compounds of formula (IIa), in various embodiments,  $R^{3a}$  is bromo. In various embodiments,  $R^{3a}$  is iodo. Additionally or alternatively, in various embodiments,  $R^{4a}$  is heteroaryl. In various embodiments,  $R^{4a}$  is alkenylene- $CO_2H$ . In various embodiments,  $R^{4a}$  is alkenylene- $CO_2$ -alkyl. Additionally or alternatively, in various embodiments,  $R^{5a}$  is  $CO_2H$ . In various embodiments,  $R^{5a}$  is  $P(O)(OH)(OH)$ ,  $P(O)(OH)(Oalkyl)$ ,  $P(O)(Oalkyl)(Oalkyl)$ ,  $P(O)(alkyl)(OH)$ ,  $SO_2H$ ,  $SO_3H$ ,  $C(O)NHOH$ ,  $SO_2NH_2$ , tetrazole, alkylene- $P(O)(OH)(OH)$ , alkylene- $P(O)(OH)(Oalkyl)$ , alkylene- $P(O)(Oalkyl)(Oalkyl)$ , alkylene- $P(O)(alkyl)(OH)$ , alkylene- $SO_2H$ , alkylene- $SO_3H$ , alkylene- $C(O)NHOH$ , alkylene- $SO_2NH_2$ , alkylene-tetrazole,  $C(O)NH$ -alkylene- $P(O)(OH)(OH)$ ,  $C(O)NH$ -alkylene- $P(O)(OH)(Oalkyl)$ ,  $C(O)NH$ -alkylene- $P(O)(Oalkyl)(Oalkyl)$ ,  $C(O)NH$ -alkylene- $P(O)(alkyl)(OH)$ ,  $C(O)NH$ -alkylene- $SO_2H$ ,  $C(O)NH$ -alkylene- $SO_3H$ ,  $C(O)NH$ -alkylene- $C(O)NHOH$ ,  $C(O)NH$ -alkylene- $SO_2NH_2$ , or  $C(O)NH$ -alkylene-tetrazole.

**[0022]** Further disclosed herein are compounds of formulae (IIIa) or (IIIb):



wherein the various R groups are defined below.

### BRIEF DESCRIPTION OF THE FIGURES

**[0023]** Figure 1 shows voltage-clamped (-60 mV) current responses for GluN1/GluN2A (2A) and GluN1/GluN2D (2D) receptors evoked by 10  $\mu$ M glycine and 10  $\mu$ M L-glutamate (black bar) plus addition of a 100  $\mu$ M concentration of the indicated compound (grey bar); scale bars: x-axis = 17 s; y-axis = 200 nA. In the bottom of each panel is a dose-response curve for compound potentiation (values >1) or inhibition (values <1) of agonist responses by GluN1/GluN2A (filled square); GluN1/GluN2B (filled circle); GluN1/GluN2C (open square); and GluN1/GluN2D (open circle) receptors.

**[0024]** Figure 2A shows a schematic illustrating a GluN1/GluN2 dimer and the domain structure and binding sites for L-glutamate (hexagon), glycine (star), N-terminal domain (NTD) ligands (oval), and channel blockers (square).

**[0025]** Figure 2B shows UPB512 (100  $\mu$ M) inhibition of GluN1/GluN2D receptor responses at different membrane potentials, with the inset showing current traces for agonist (black bar) and UPB512 (grey bar) application, scale bars (x-axis seconds; y-axis mA): -60 mV (180 s, 1.1  $\mu$ A); +40 mV (72 s, 2.2  $\mu$ A).

**[0026]** Figures 2C and 2D show GluN1/GluN2C (2C) or GluN1/GluN2D (2D) receptors activated by increasing concentrations of glycine or glutamate in absence (filled symbols) and presence (open symbols) of 100  $\mu$ M concentrations of UPB512.

**[0027]** Figure 2E and 2F show UPB512 and UPB618 modulation of NMDA receptor responses evoked by low (10  $\mu$ M glutamate and 10  $\mu$ M glycine, open symbols) or high (300  $\mu$ M glutamate and 300  $\mu$ M glycine, filled symbols) agonist concentrations. UPB512 more effectively inhibited 2C (inverted triangles) and 2D (circles) receptor responses and more effectively potentiated 2A (squares) receptor responses evoked by high agonist concentrations than by low concentrations. UPB618 displays greater maximal inhibition of 2D receptor responses and decreased maximal inhibition of 2A receptor responses in the presence of high agonist concentrations.

**[0028]** Figure 3A, C, and E show compound activity tested on responses evoked by 10  $\mu$ M glutamate/10  $\mu$ M glycine of wild-type 2A and 2D receptors (dashed lines) or receptors without NTDs of both GluN1 and GluN2 subunits (solid lines)-2A <sup>$\Delta$ NTD</sup> and 2D <sup>$\Delta$ NTD</sup>.

**[0029]** Figures 3B, D, and F show compound activity tested on responses by wild-type 2A and 2C receptors (dashed lines) and by chimeric receptors (solid lines) where the GluN2A subunit has the GluN2C S1 (2A<sup>2CS1</sup>) or the GluN2C S2 (2A<sup>2CS2</sup>) domain.

[0030] Figure 4 shows the structure and shorthand name of several compounds that are NMDA receptor modulators, their activities are shown in Figure 5.

[0031] Figure 5 shows the inhibition activity of various compounds for specific NMDA receptors comprising NR1 subunits, and NR2A, NR2B, NR2C, or NR2D subunits.

[0032] Figure 6A shows a current trace indicating the effect of increasing concentrations of UBP552 (open bars) on GluN1/CluN2D receptor response evoked by agonists (Ag) 10  $\mu$ M glycine plus 10  $\mu$ M L-glutamate (solid bars).

[0033] Figures 6B-6H each shows the effect that a compound as disclosed herein has on the NMDA receptor activity (by NR2 subunit) evoked by 10  $\mu$ M L-glutamate and 10  $\mu$ M glycine with increasing concentration of the compound.

[0034] Figure 7 shows the effect of different L-glutamate or glycine concentrations and NTD-deletions on the inhibitory activity of UBP552; ( top panel) GluN1/GluN2A (2A) and (middle panel) GluN1/GluN2D (2D) receptor responses evoked by the indicated concentrations of glycine and L-glutamate ( $\mu$ M) and inhibited by increasing concentrations of UBP552; (bottom panel) UBP552 inhibition tested at wild-type GluN1/GluN2A and GluN1/GluN2D receptors (2A and 2D, respectively) and at these receptors with the NTD deleted on both the GluN1 and GluN2 subunits (2A <sup>$\Delta$ NTD</sup>, 2D <sup>$\Delta$ NTD</sup>).

[0035] Figure 8A shows a current trace indicating the effect of agonist (10  $\mu$ M L-glutamate plus 10  $\mu$ M glycine, black bar) and 100  $\mu$ M NMDA modulator NSC339614 (grey bar) on each of NR1/NR2A-NR1/NR2D.

[0036] Figure 8B shows the dose response for modulating activity of each of NR2A-NR2D in the presence of NSC339614.

[0037] Figure 9A shows UBP512 activity in the presence or absence of the zinc chelator TPEN (N,N,N',N'-tetrakis-(2-pyridylmethyl)ethylenediamine) or ZnCl<sub>2</sub>.

[0038] Figure 9B shows a dose response of increasing amounts of ZnCl<sub>2</sub> for inhibition of GluN1/GluN2A (2A) response in the presence (open squares) or absence (solid squares) of 100  $\mu$ M UBP512.

#### DETAILED DESCRIPTION

[0039] Provided herein are a novel class of NMDA modulators that interact with the NMDA receptor via an allosteric interaction. These modulators have greater subtype-selectivity than the other classes of NMDA receptor agents currently available for therapeutic

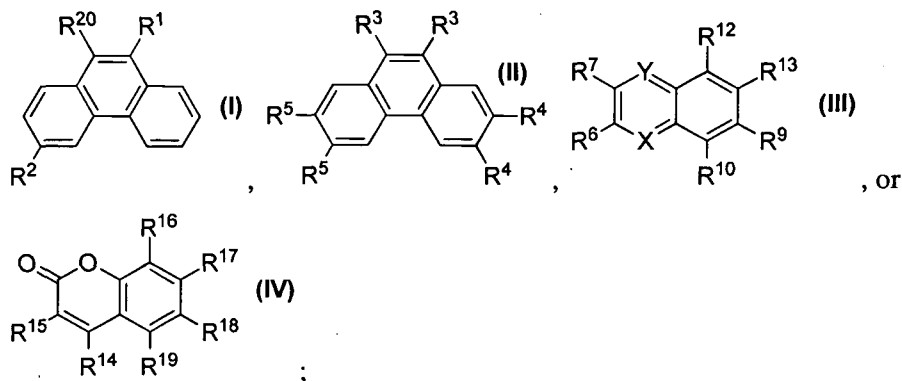
development. In various embodiments, the compound does not compete for binding to the NMDA receptor with the NMDA receptor ligands (e.g., L-glutamate, glycine, or both).

[0040] Because NMDA receptors are involved in a wide variety of psychiatric and neurological conditions, there are many potential applications of subtype-selective positive and negative NMDA receptor modulators. Most clinical interest has focused on the use of NMDA receptor blockers as neuroprotective agents. Over-activation of NMDA receptors causes an excessive influx of calcium ions leading to neuronal cell death in stroke, head injury, and probably, neurodegenerative diseases. Importantly, several studies have indicated that NMDA receptor subtypes differ in their ability to initiate cell death. GluN2B-containing NMDA receptors initiate cell death whereas GluN2A-containing receptors have been reported to contribute to neuroprotection signaling (19,20,27,28). This may correspond to an enrichment of GluN2A and GluN2B subunits in synaptic and extrasynaptic compartments, respectively (29,30), and the ability of synaptic NMDA receptors to promote neuroprotection while extrasynaptic NMDA receptor activation signals to neuronal cell death (31-33).

[0041] The compounds disclosed herein can modulate one or more of the subunits of a NMDA receptor, and in particular, modulate one or more of the NR2 subunits NR2A, NR2B, NR2C, and NR2D.

### NMDA Receptor Modulators

[0042] Disclosed herein are compounds that modulate a NMDA receptor. These compounds have a structure:



wherein

each R<sup>1</sup> and R<sup>20</sup> is independently H, halo, alkyl, alkenyl, alkynyl, alkoxy, amino, cycloalkyl, aryl, heteroaryl, alkyleneamino, CO<sub>2</sub>H, alkylene-CO<sub>2</sub>H, alkylene-CO<sub>2</sub>alkyl, alkylene-OH, alkylene-cycloalkyl, alkylenearyl, alkylenearyl, CHO, NO<sub>2</sub>, or thioalkyl;

R<sup>2</sup> is H, halo, R<sup>A</sup>, alkylene-R<sup>A</sup>, NH<sub>2</sub>, C(O)NH-alkylenearyl, C(O)NH-

alkyleneheteroaryl, C(O)NH-alkylene-R<sup>A</sup>, alkylene-OH, C(O)alkyl, C(O)alkylene-heteroaryl, or NO<sub>2</sub>,

each R<sup>3</sup> is independently H, alkyl, alkenyl, alkynyl, alkylenearyl, alkylene-cycloalkyl, OH, or halo;

each R<sup>4</sup> is independently H, halo, alkyl, alkenyl, alkynyl, alkylenearyl, alkylene-cycloalkyl, heteroaryl, alkenylene-CO<sub>2</sub>H, or alkenylene-CO<sub>2</sub>-alkyl,

each R<sup>5</sup> is independently H, R<sup>A</sup>, alkylene-R<sup>A</sup>, NH<sub>2</sub>, C(O)NH-alkylenearyl, C(O)NH-alkyleneheteroaryl, C(O)NH-alkylene-R<sup>A</sup>, alkylene-OH, C(O)alkyl, C(O)alkylene-heteroaryl, or NO<sub>2</sub>;

R<sup>6</sup> is H, R<sup>A</sup>, alkylene-R<sup>A</sup>, alkenylene-R<sup>A</sup>, OH, alkylene-OH, or amino;

R<sup>7</sup> is H, OH, alkoxy, CO<sub>2</sub>H, or amino;

Y is N or CR<sup>8</sup>;

R<sup>8</sup> is H, halo, OH, alkyl, or alkoxy;

R<sup>9</sup> is H, halo, OH, alkenyl, aryl, or alkyl;

R<sup>10</sup> is H, OH, alkyl, or halo;

or R<sup>9</sup> and R<sup>10</sup> together form an optional aromatic ring;

X is N or CR<sup>11</sup>;

R<sup>11</sup> is H, halo, OH, alkyl, alkoxy, or CO<sub>2</sub>H;

R<sup>12</sup> is H, OH, alkyl, alkoxy, amino, or halo;

R<sup>13</sup> is H, halo, alkyl, alkenyl, OH, alkylene-OH, amino, alkoxy, CO<sub>2</sub>H, CO<sub>2</sub>alkyl, OC(O)alkyl, aryl, heteroaryl, O-alkylenearyl, alkylenearyl, alkenylenearyl, alkenylene-CO<sub>2</sub>H, alkenylene-CO<sub>2</sub>alkyl, or O-alkylene-CO<sub>2</sub>alkyl;

or R<sup>12</sup> and R<sup>13</sup> together form an optional aromatic ring;

R<sup>14</sup> is H, alkyl, alkenyl, cycloalkyl, heteroaryl, alkyleneamino, CO<sub>2</sub>H, alkylene-CO<sub>2</sub>H, alkylene-OH, alkylenearyl, thioalkyl, aryl, alkynyl, alkylene-cycloalkyl, or halo;

R<sup>15</sup> is R<sup>A</sup>;

R<sup>16</sup> is H or halo;

R<sup>17</sup> is H, OH, amino, or alkoxy;

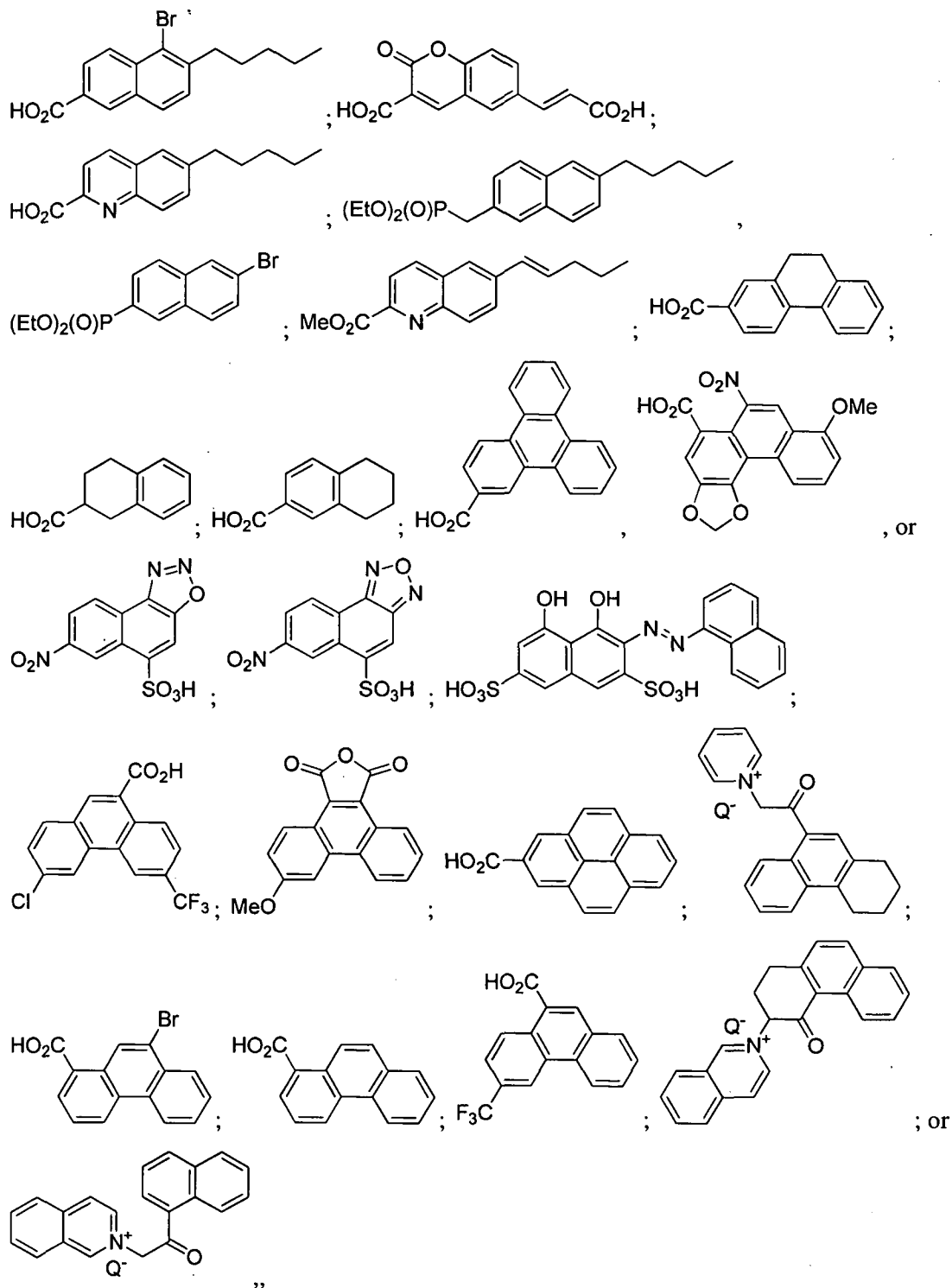
R<sup>18</sup> is H or halo;

R<sup>19</sup> is H or halo;

or R<sup>18</sup> and R<sup>19</sup> together form an optional aromatic ring; and

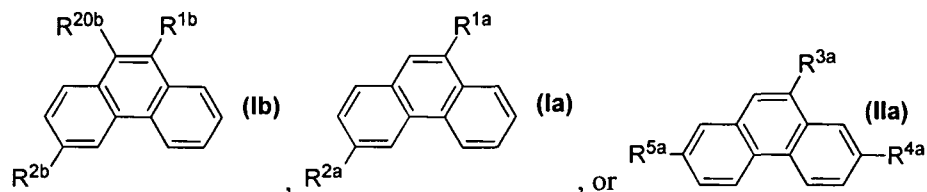
R<sup>A</sup> is CO<sub>2</sub>H, CO<sub>2</sub>alkyl, P(O)(OH)(OH), P(O)(OH)(Oalkyl), P(O)(Oalkyl)(Oalkyl), P(O)(alkyl)(OH), P(O)(alkyl)(OH), SO<sub>2</sub>H, SO<sub>3</sub>H, C(O)NHOH, SO<sub>2</sub>NH<sub>2</sub>, or tetrazole, or a salt, ester, solvate, tautomer, enantiomer, or hydrate thereof.

**[0043]** The modulator can be a compound having a structure as noted in Figure 4 (with the corresponding shorthand name) or have a structure:



or a salt, ester, solvate, tautomer, enantiomer, or hydrate thereof.

[0044] Further disclosed are compounds that are NMDA receptor modulators. These compounds can have a formula (Ia), (Ib), or (IIa):



$R^{1b}$  is iodo, alkyl, alkenyl, alkynyl, alkoxy, amino, cycloalkyl, aryl, heteroaryl, alkyleneamino, alkylene-CO<sub>2</sub>H, alkenylene-CO<sub>2</sub>alkyl, alkylene-OH, alkylene-cycloalkyl, alkylenearyl, alkenylenearyl, CHO, or thioalkyl;

$R^{2b}$  and  $R^{5a}$  are each independently  $R^A$ , alkylene- $R^A$ , NH<sub>2</sub>, C(O)NH-alkylenearyl, C(O)NH-alkyleneheteroaryl, C(O)NH-alkylene- $R^A$ , alkylene-OH, C(O)alkyl, or NO<sub>2</sub>;

$R^{1a}$  is halo;

$R^{2a}$  is C(O)alkylene-NH<sub>2</sub> or C(O)alkylene-heteroaryl;

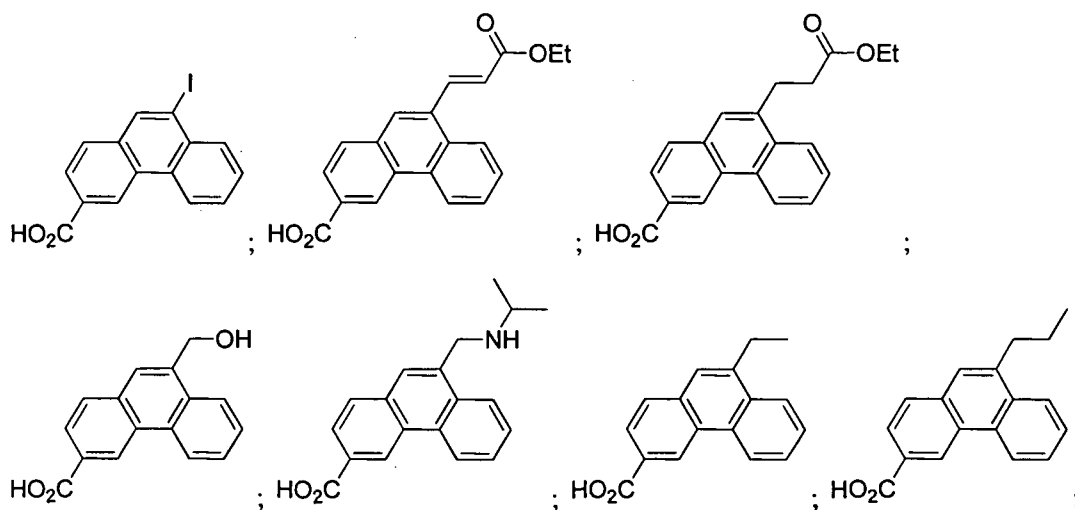
$R^{3a}$  is H or halo;

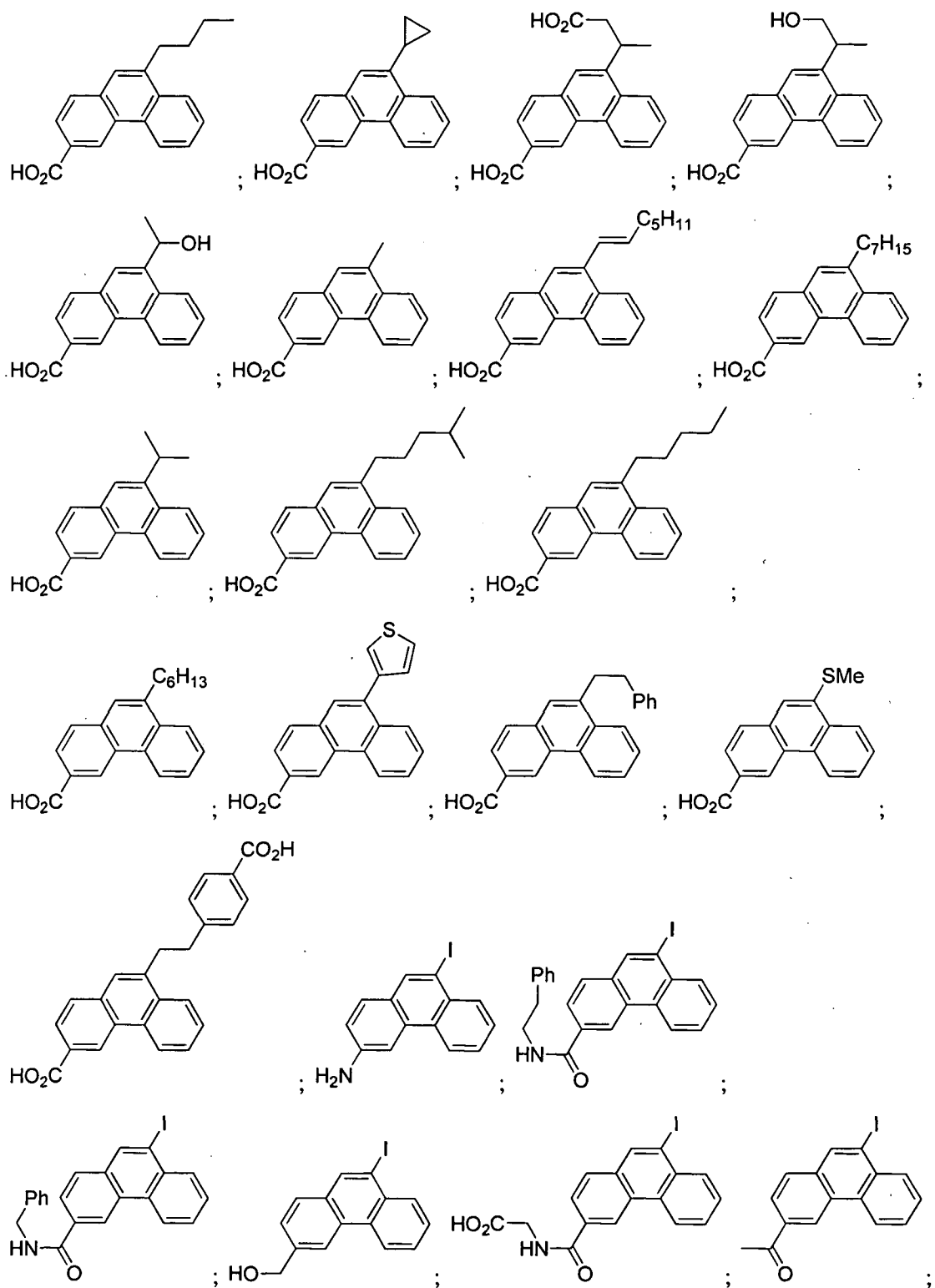
$R^{4a}$  is H, heteroaryl, alkenylene-CO<sub>2</sub>H, or alkenylene-CO<sub>2</sub>-alkyl;

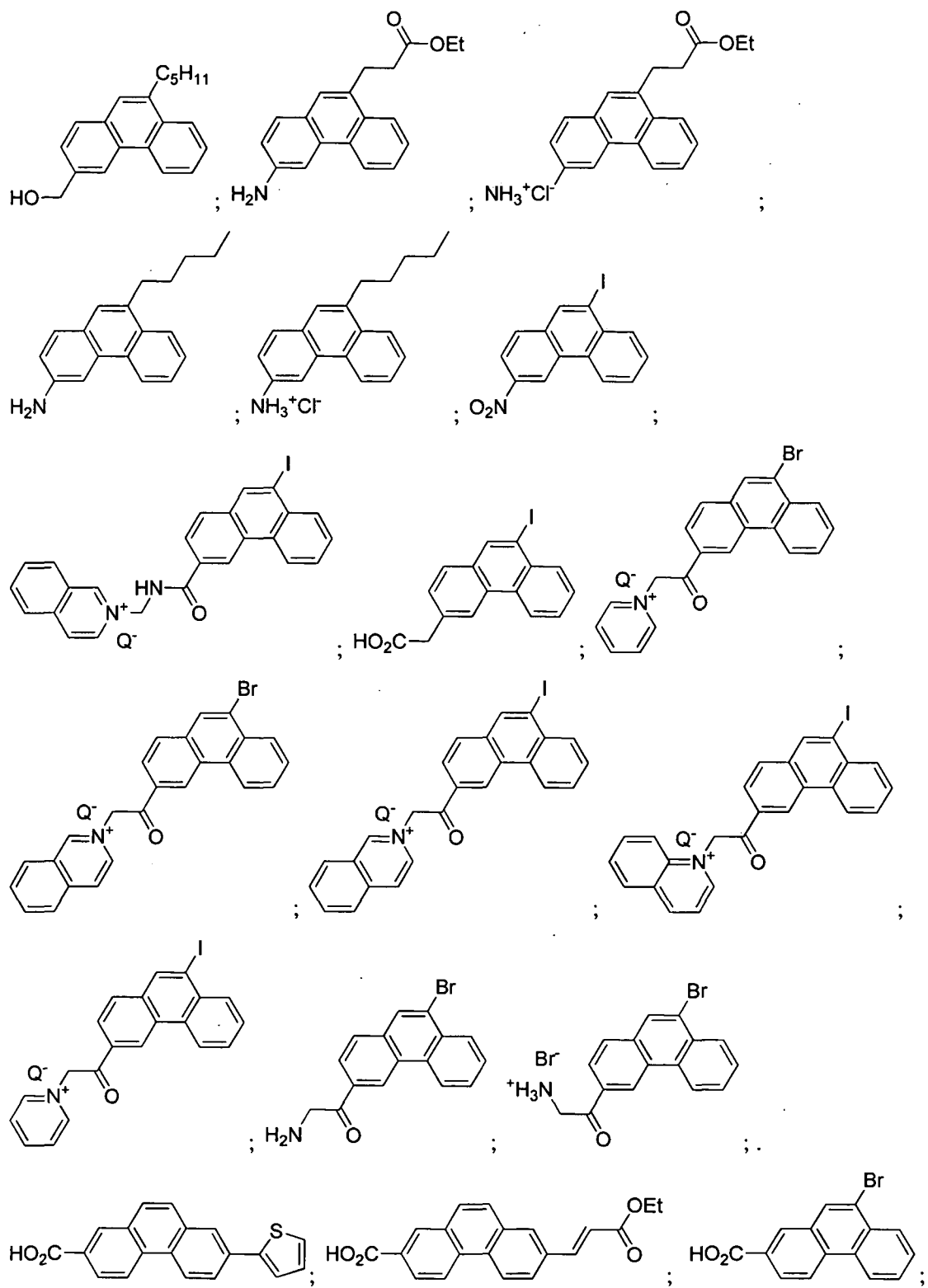
$R^{20b}$  is alkyl, alkenyl, alkynyl, NO<sub>2</sub>, amino, aryl or heteroaryl; and

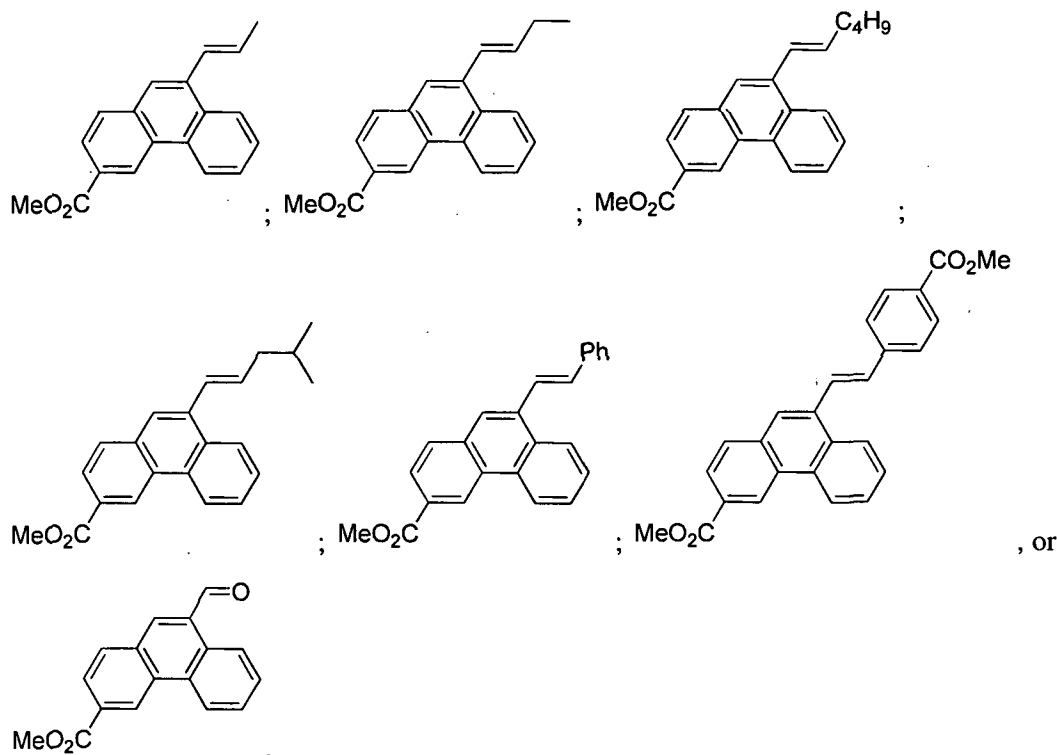
$R^A$  is CO<sub>2</sub>H, CO<sub>2</sub>alkyl, P(O)(OH)(OH), P(O)(OH)(Oalkyl), P(O)(Oalkyl)(Oalkyl), P(O)(alkyl)(OH), SO<sub>2</sub>H, SO<sub>3</sub>H, C(O)NHOH, SO<sub>2</sub>NH<sub>2</sub>, or tetrazole, with the proviso that  $R^{3a}$  and  $R^{4a}$  cannot each be H, or a salt, ester, solvate, tautomer, enantiomer, or hydrate thereof.

[0045] Specific compounds of formulae (Ib), (Ia), and (IIa) include



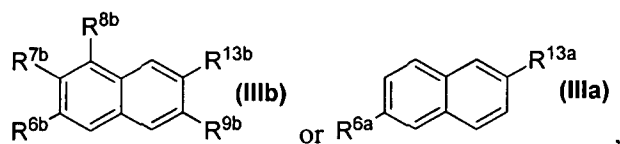






wherein Q is a pharmaceutically acceptable anion.

[0046] Further compounds disclosed herein have a formula (IIIb) or (IIIa):



wherein

R<sup>6b</sup> is R<sup>A</sup> or alkylene-R<sup>A</sup>;

R<sup>7b</sup> is OH, alkoxy, or CO<sub>2</sub>H;

R<sup>8b</sup> is H, halo, or C<sub>4</sub>-C<sub>20</sub>alkyl;

R<sup>9b</sup> is halo, alkenyl, aryl, or alkyl;

R<sup>13b</sup> is H, C<sub>4</sub>-C<sub>20</sub>alkyl, alkenyl, aryl, heteroaryl, alkenylenearyl, or alkenylenearyl;

R<sup>13a</sup> is C<sub>4</sub>-C<sub>20</sub>alkyl, alkenyl, alkenylene-CO<sub>2</sub>H, alkenylene-CO<sub>2</sub>alkyl, O-alkylene-CO<sub>2</sub>alkyl, or alkenylenearyl;

R<sup>6a</sup> is R<sup>A</sup>, alkylene-R<sup>A</sup>, or alkylene-OH;

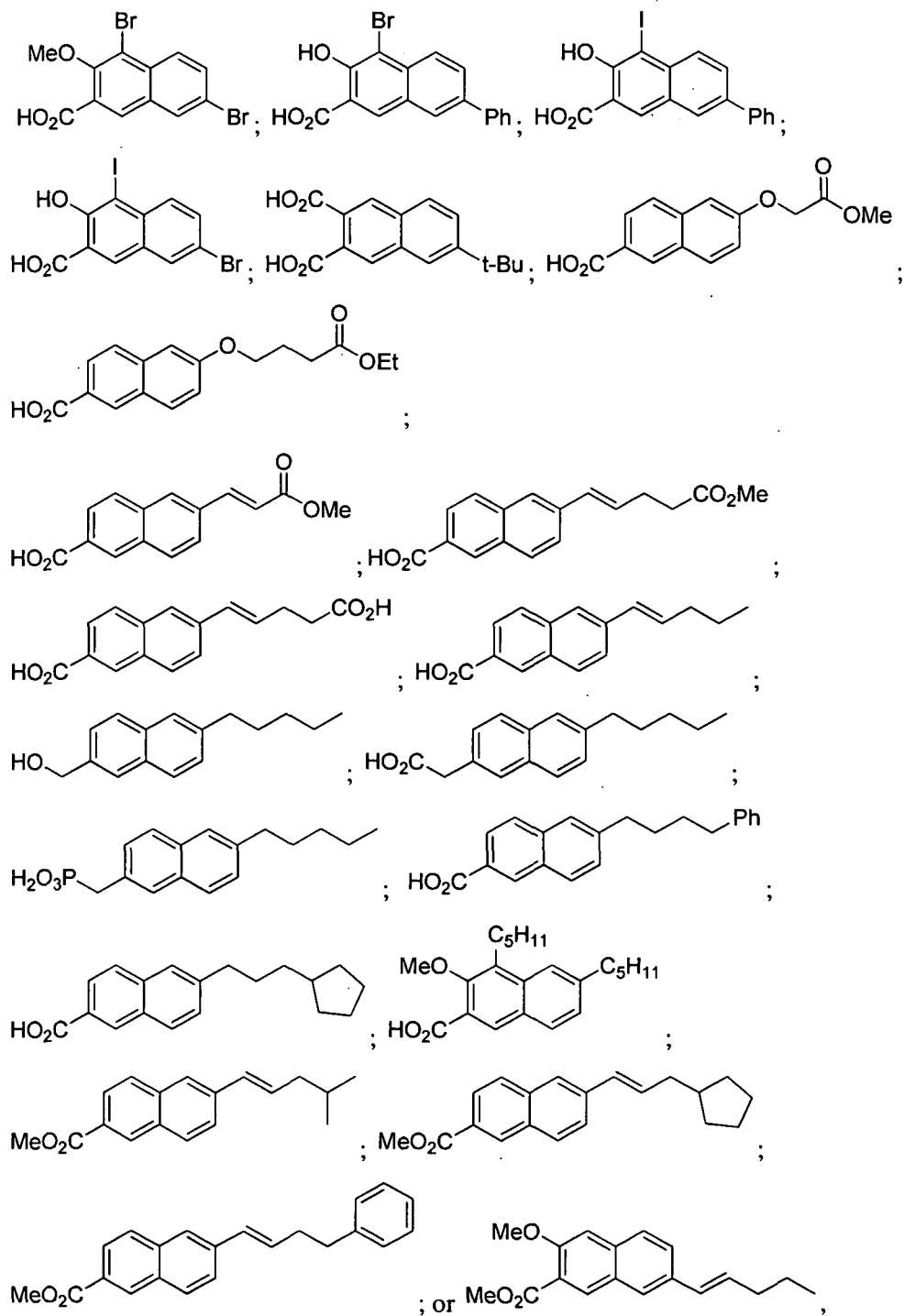
R<sup>A</sup> is CO<sub>2</sub>H, P(O)(OH)(OH), P(O)(OH)(Oalkyl), P(O)(Oalkyl)(Oalkyl),

P(O)(alkyl)(OH), SO<sub>2</sub>H, SO<sub>3</sub>H, C(O)NHOH, SO<sub>2</sub>NH<sub>2</sub>, or tetrazole,

with the proviso that when R<sup>13a</sup> is C<sub>4</sub>-C<sub>6</sub>alkyl, R<sup>6a</sup> is not CO<sub>2</sub>H or SO<sub>3</sub>H, and when R<sup>7b</sup>, R<sup>8b</sup>,

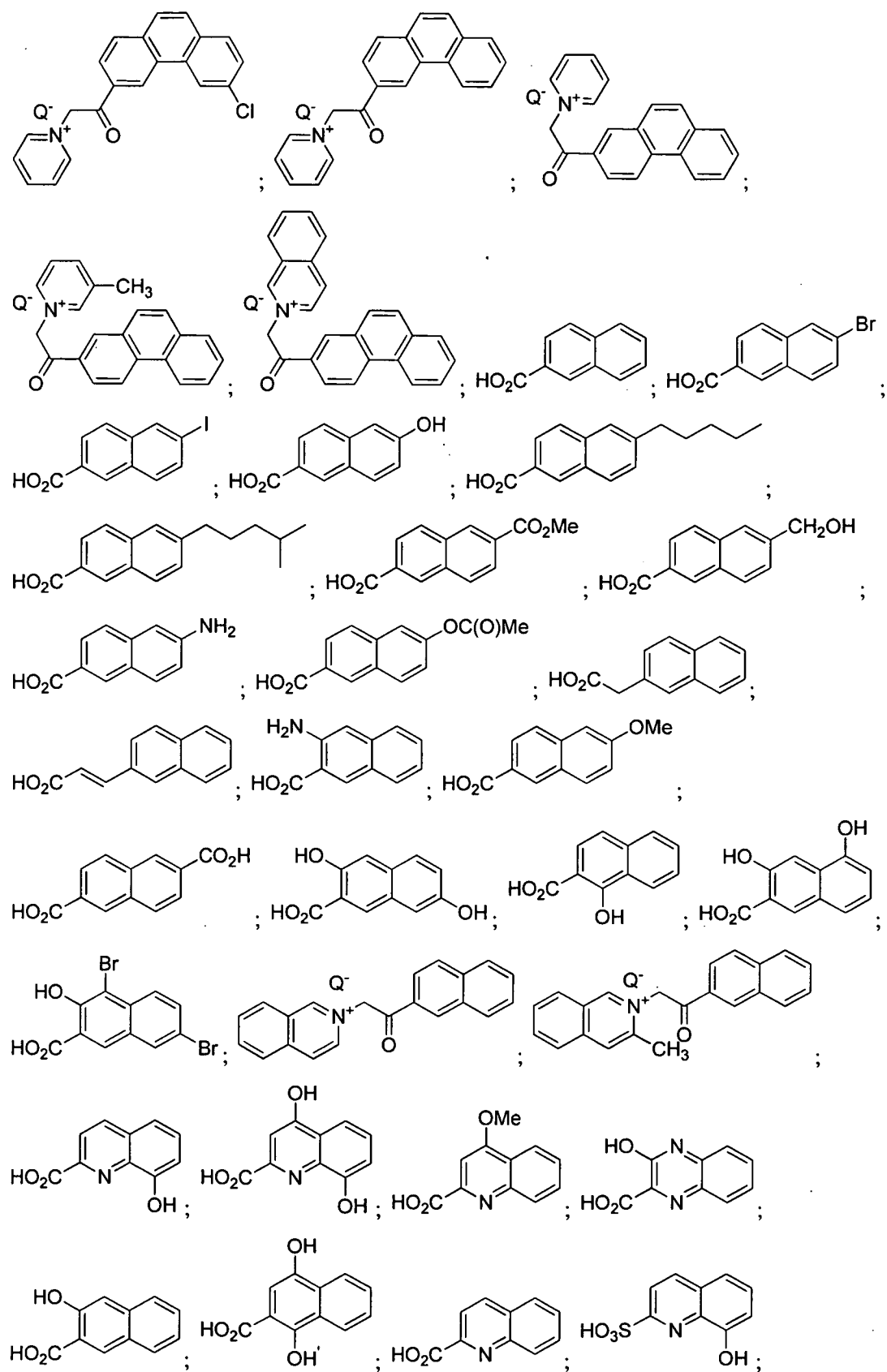
and R<sup>9b</sup> are each H and R<sup>13b</sup> is C<sub>4</sub>-C<sub>6</sub>alkyl, R<sup>6b</sup> is not CO<sub>2</sub>H or SO<sub>3</sub>H, or a salt, ester, solvate, tautomer, enantiomer, or hydrate thereof.

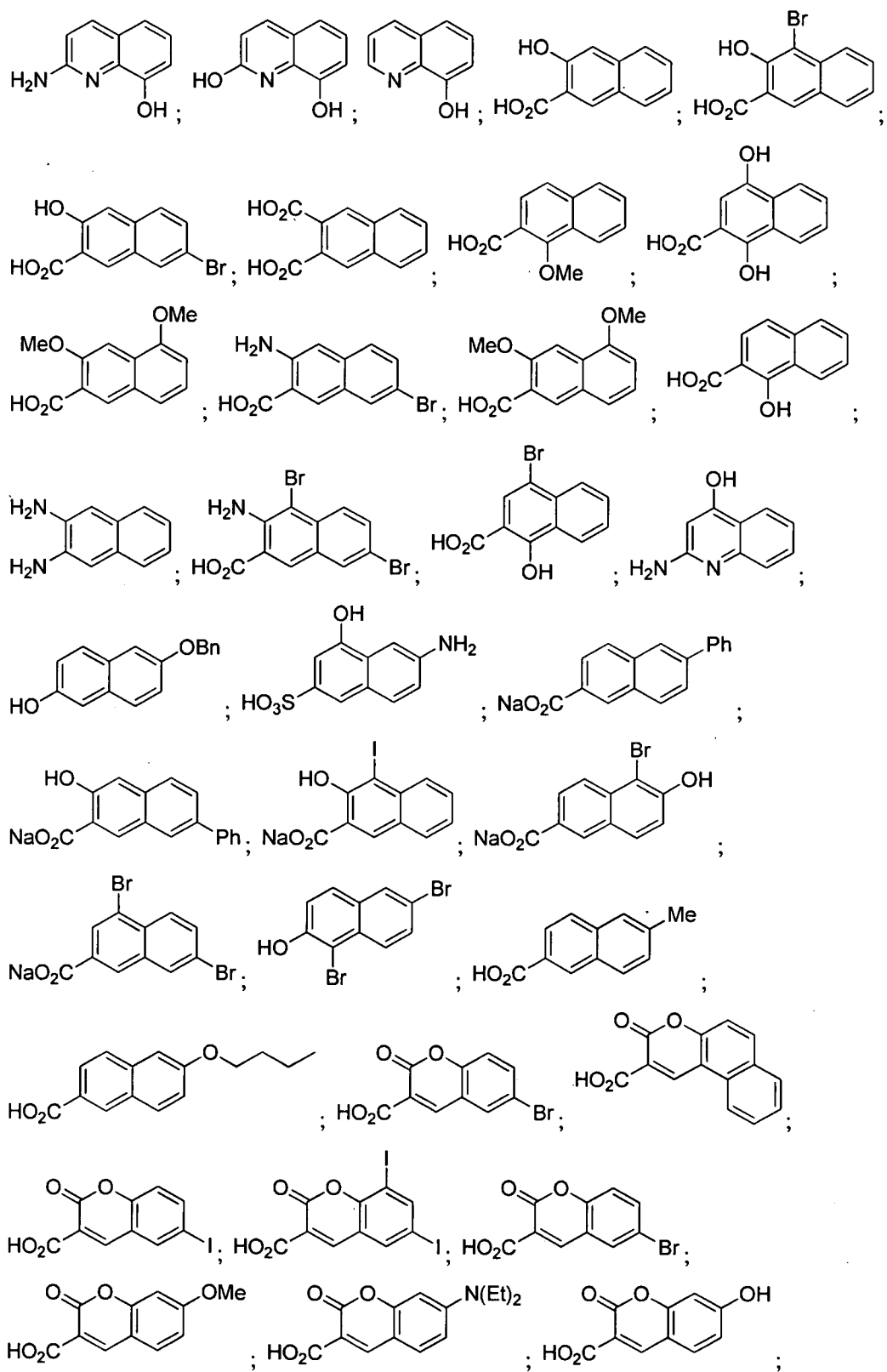
[0047] Specific compounds of formula (IIIb) or (IIIa) include

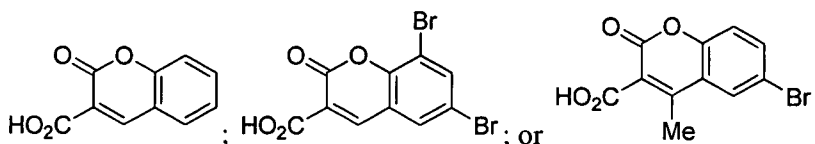


or a salt, ester, solvate, tautomer, enantiomer, or hydrate thereof.









wherein Q is a pharmaceutically acceptable anion,  
or a salt, ester, solvate, tautomer, enantiomer, or hydrate thereof.

**[0050]** As used herein, “alkyl” refers to monovalent alkyl groups having 1 to 20 carbon atoms. This term is exemplified by groups such as methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, t-butyl, hexyl and the like. Linear and branched alkyls are included. The alkyl group can be a specific number of carbon atoms, as exemplified by the use of  $C_x-C_y$ , where x and y are integers. The compounds disclosed herein can have a  $C_4-C_{20}$ alkyl or more specifically a  $C_4-C_{10}$ alkyl substituent.

**[0051]** As used herein, the term “alkylene” refers to an alkyl group having a substituent. For example, the term “alkylenearyl” refers to an alkyl group substituted with an aryl group.

**[0052]** As used herein, the term “cycloalkyl” refers to a cyclic hydrocarbon group, e.g., cyclopropyl, cyclobutyl, cyclohexyl, and cyclopentyl.

**[0053]** As used herein, the term “alkenyl” refers to an alkyl group having one or more carbon-carbon double bonds, and in particular  $C_4-C_{20}$  or  $C_4-C_{10}$  alkenyl groups, e.g., hept-1-ene-1-yl. Similarly, the term “alkenylene” refers to an alkenyl group having a substituent, such as alkenylenearyl, a alkenyl group with an aryl substituent.

**[0054]** The term “alkynyl” used herein refers to a straight or branched chain hydrocarbon group of two to ten carbon atoms containing at least one carbon triple bond including, but not limited to, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, and the like.

**[0055]** As used herein, the term “aryl” refers to a monocyclic or polycyclic aromatic group, preferably a monocyclic or bicyclic aromatic group, e.g., phenyl or naphthyl. Unless otherwise indicated, an aryl group can be unsubstituted or substituted with one or more, and in particular one to four groups independently selected from, for example, halo, alkyl, alkenyl,  $OCF_3$ ,  $NO_2$ , CN, NC, OH, alkoxy, amino,  $CO_2H$ ,  $CO_2$ alkyl, aryl, and heteroaryl. Exemplary aryl groups include, but are not limited to, phenyl, naphthyl, tetrahydronaphthyl, chlorophenyl, methylphenyl, methoxyphenyl, trifluoromethylphenyl, nitrophenyl, 2,4-methoxychlorophenyl, and the like.

**[0056]** As used herein, the term “heteroaryl” refers to a monocyclic or bicyclic ring system containing one or two aromatic rings and containing at least one nitrogen, oxygen, or sulfur

atom in an aromatic ring. Unless otherwise indicated, a heteroaryl group can be unsubstituted or substituted with one or more, and in particular one to four, substituents selected from, for example, halo, alkyl, alkenyl, OCF<sub>3</sub>, NO<sub>2</sub>, CN, NC, OH, alkoxy, amino, CO<sub>2</sub>H, CO<sub>2</sub>alkyl, aryl, and heteroaryl. In some cases, the heteroaryl group is substituted with one or more of alkyl and alkoxy groups. Examples of heteroaryl groups include, but are not limited to, thienyl, furyl, pyridyl, oxazolyl, quinolyl, thiophenyl, isoquinolyl, indolyl, triazinyl, triazolyl, isothiazolyl, isoxazolyl, imidazolyl, benzothiazolyl, pyrazinyl, pyrimidinyl, thiazolyl, and thiadiazolyl.

**[0057]** As used herein, the term “amino” refers to an unsubstituted, mono-substituted, or di-substituted nitrogen (e.g., -NH<sub>2</sub>, NHR, or NR<sub>2</sub>, where R is a substitution on the nitrogen). The amino group can be substituted with, e.g., alkyl, alkenyl, alkynyl, aryl, alkylenearyl, heteroaryl, or the like.

**[0058]** The term “alkoxy” used herein refers to an -Oalkyl group.

**[0059]** The term “thioalkyl” used herein refers to one or more thio groups appended to an alkyl group or an alkyl group appended via a sulfur atom (e.g., S-alkyl).

**[0060]** A substituent disclosed herein can optionally be substituted with another group. As used herein, a substituted group is derived from the unsubstituted parent structure in which there has been an exchange of one or more hydrogen atoms for another atom or group. A “substituent group,” as used herein, means a group selected from the following moieties:

(A) -OH, -NH<sub>2</sub>, -SH, -CN, -CF<sub>3</sub>, -NO<sub>2</sub>, oxo, halogen, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, unsubstituted alkoxy, unsubstituted aryloxy, trihalomethanesulfonyl, trifluoromethyl, and

(B) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, amino, amido, carbonyl, thiocarbonyl, alkoxycarbonyl, silyl, sulfonyl, sulfoxyl, alkoxy, aryloxy, and heteroaryl, substituted with at least one substituent selected from:

(i) -OH, -NH<sub>2</sub>, -SH, -CN, -CF<sub>3</sub>, -NO<sub>2</sub>, oxo, halogen, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, unsubstituted alkoxy, unsubstituted aryloxy, trihalomethanesulfonyl, trifluoromethyl, and

(ii) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, amino, amido, carbonyl, thiocarbonyl, alkoxycarbonyl, silyl, sulfonyl, sulfoxyl, alkoxy, aryloxy, and heteroaryl, substituted with at least one substituent selected from:

(a) -OH, -NH<sub>2</sub>, -SH, -CN, -CF<sub>3</sub>, -NO<sub>2</sub>, oxo, halogen, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, unsubstituted alkoxy, unsubstituted aryloxy, trihalomethanesulfonyl, trifluoromethyl, and

(b) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, amino, amido, carbonyl, thiocarbonyl, alkoxy carbonyl, silyl, sulfonyl, sulfoxyl, alkoxy, aryloxy, and heteroaryl, substituted with at least one substituent selected from -OH, -NH<sub>2</sub>, -SH, -CN, -CF<sub>3</sub>, -NO<sub>2</sub>, oxo, halogen, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, unsubstituted alkoxy, unsubstituted aryloxy, trihalomethanesulfonyl, trifluoromethyl.

[0061] Asymmetric carbon atoms can be present. All such isomers, including diastereomers and enantiomers, as well as the mixtures thereof, are intended to be included in the scope of the disclosure herein. In certain cases, compounds can exist in tautomeric forms. All tautomeric forms are intended to be included in the scope of the disclosure herein. Likewise, when compounds contain an alkenyl or alkenylene group, there exists the possibility of cis- and trans- isomeric forms of the compounds. Both cis- and trans- isomers, as well as the mixtures of cis- and trans- isomers, are contemplated.

[0062] The salts, e.g., pharmaceutically acceptable salts, of the disclosed therapeutics may be prepared by reacting the appropriate base or acid with a stoichiometric equivalent of the therapeutic.

[0063] Acids commonly employed to form pharmaceutically acceptable salts include inorganic acids such as hydrogen bisulfide, hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid and phosphoric acid, as well as organic acids such as para-toluenesulfonic acid, salicylic acid, tartaric acid, bitartaric acid, ascorbic acid, maleic acid, besylic acid, fumaric acid, gluconic acid, glucuronic acid, formic acid, glutamic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, lactic acid, oxalic acid, para-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid and acetic acid, as well as related inorganic and organic acids. Such pharmaceutically acceptable salts thus include anions, for example sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caprate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate,

dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, terephthalate, sulfonate, xylene sulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, O-hydroxybutyrate, glycolate, maleate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, and mandelate. In one embodiment, 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.

**[0064]** Pharmaceutically acceptable base addition salts may be formed with metals or amines, such as alkali and alkaline earth metals or organic amines. Pharmaceutically acceptable salts of compounds may also be prepared with a pharmaceutically acceptable cation. Suitable pharmaceutically acceptable cations are well known to those skilled in the art and include alkaline, alkaline earth, ammonium and quaternary ammonium cations. Carbonates or hydrogen carbonates are also possible. Examples of metals used as cations are sodium, potassium, magnesium, ammonium, calcium, or ferric, and the like. Examples of suitable amines include isopropylamine, trimethylamine, histidine, N,N'-dibenzylethylenediamine, chlorprocaine, choline, diethanolamine, dicyclohexylamine, ethylenediamine, N-methylglucamine, and procaine.

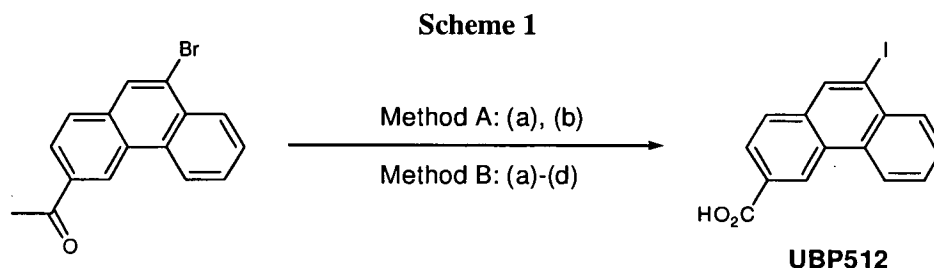
**[0065]** Similarly, pharmaceutically acceptable derivatives (e.g., esters), metabolites, hydrates, solvates and prodrugs of the therapeutic may be prepared by methods generally known to those skilled in the art. Thus, another embodiment provides compounds that are prodrugs of an active compound. In general, a prodrug is a compound which is metabolized *in vivo* (e.g., by a metabolic transformation such as deamination, dealkylation, de-esterification, and the like) to provide an active compound. A "pharmaceutically acceptable prodrug" means a compound which is, within the scope of sound medical judgment, suitable for pharmaceutical use in a patient without undue toxicity, irritation, allergic response, and the like, and effective for the intended use, including a pharmaceutically acceptable ester as well as a zwitterionic form, where possible, of the therapeutic. As used herein, the term "pharmaceutically acceptable ester" refers to esters that hydrolyze *in vivo* and include those that break down readily in the human body to leave the parent compound or a salt thereof. Suitable ester groups include, for example, those derived from pharmaceutically acceptable aliphatic carboxylic acids, particularly alkanolic, alkenolic, cycloalkanoic and alkanedioic acids, in which each alkyl or alkenyl moiety advantageously has not more than 6 carbon atoms. Representative examples of particular esters include, but are not limited to, formates,

acetates, propionates, butyrates, acrylates and ethylsuccinates. Examples of pharmaceutically-acceptable prodrug types are described in Higuchi and Stella, *Pro-drugs as Novel Delivery Systems*, Vol. 14 of the A.C.S. Symposium Series, and in Roche, ed., *Bioreversible Carriers in Drug Design*, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference.

[0066] The compounds and compositions described herein may also include metabolites. As used herein, the term "metabolite" means a product of metabolism of a compound of the embodiments or a pharmaceutically acceptable salt, analog, or derivative thereof, that exhibits a similar activity in vitro or in vivo to a disclosed therapeutic. The compounds and compositions described herein may also include hydrates and solvates. As used herein, the term "solvate" refers to a complex formed by a solute (herein, the therapeutic) and a solvent. Such solvents for the purpose of the embodiments preferably should not negatively interfere with the biological activity of the solute. Solvents may be, by way of example, water, ethanol, or acetic acid.

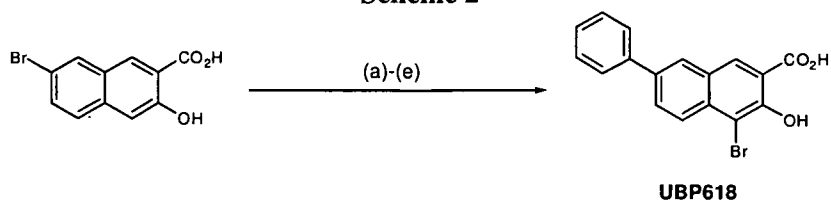
#### Synthesis of Compounds

[0067] The compounds disclosed herein can be synthesized through any means available to the synthetic chemist. Non-limiting examples of general schemes for preparing compounds disclosed herein is provided below.



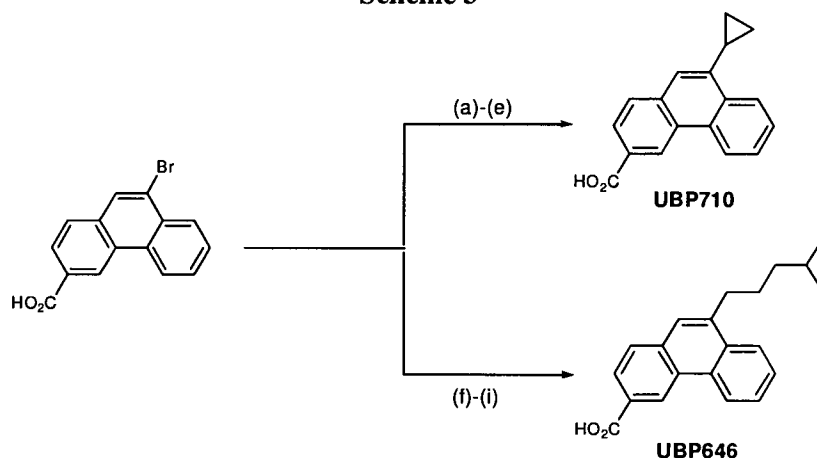
[0068] Method A: (a) NaI, CuI, N,N'-dimethylethylenediamine, dioxane, 110°C, 48 h; (b) (i) Br<sub>2</sub>, NaOH(aq), dioxane, 70°C, 1 h, (ii) HCl (aq). Method B: (a) ethylene glycol, TsOH, toluene, 110°C, 18 hr; (b) (i) n-BuLi, THF, -78°C, 1 hr; (ii) n-Bu<sub>3</sub>SnCl, -78°C; (c) (i) I<sub>2</sub>, DCM, 0°C, (ii) 2 M HCl (aq), acetone, 0.5 hr; (d) (i) Br<sub>2</sub>, NaOH (aq), dioxane, 70°C, 1 hr; (ii) conc HCl (aq).

Scheme 2



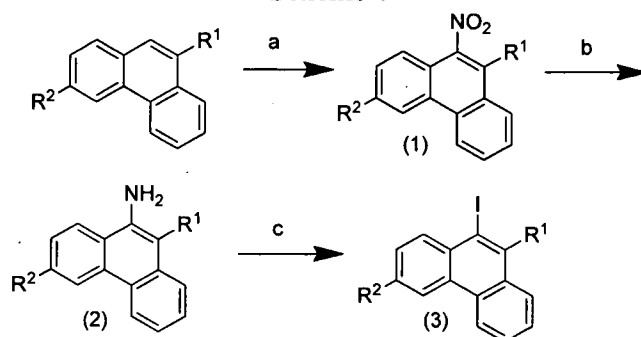
**[0069]** Reagents and conditions: (a) MeI, K<sub>2</sub>CO<sub>3</sub>, DMF, rt, 12 hr; (b) Ac<sub>2</sub>O, pyridine, DMAP, rt, 12 hr; (c) Ph-B(OH)<sub>2</sub>, K<sub>2</sub>CO<sub>3</sub>, Pd(dppf)Cl<sub>2</sub>, DME, 80°C, 3 hr; (d) (i) NaOH, THF/H<sub>2</sub>O, 70°C, 3 hr; (ii) 2 M HCl (aq); (e) Br<sub>2</sub>, AcOH, rt, 2 hr.

Scheme 3

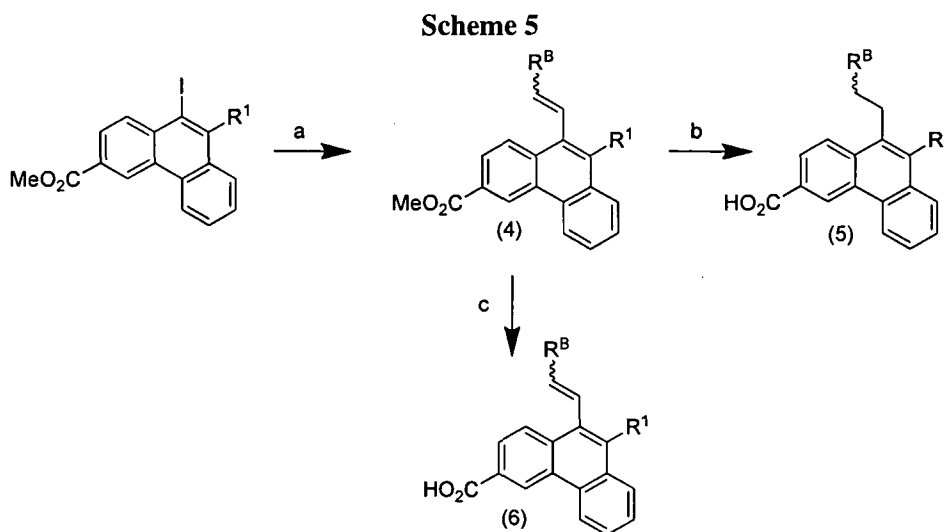


**[0070]** Reagents and conditions: (a) (i) Methyl acrylate, P(o-tolyl)<sub>3</sub>, TEA, Pd(OAc)<sub>2</sub>, DMF, 100°C, 18 hr; (ii) MeI, K<sub>2</sub>CO<sub>3</sub>, DMF, rt, 18 hr; (b) (i) OsO<sub>4</sub>, TMAO, t-BuOH/H<sub>2</sub>O, rt, 2 days; (ii) NaIO<sub>4</sub>; (c) CH<sub>3</sub>PPh<sub>3</sub>I, KHMDs, THF, 5 hr; (d) CH<sub>2</sub>I<sub>2</sub>, ZnEt<sub>2</sub>, DCM, 0°C, 18 hr; (e) (i) LiOH (aq), dioxane, rt, 18 hr; (ii) 1 M HCl (aq); (f) H<sub>2</sub>SO<sub>4</sub>, MeOH, 65°C, 48 hr; (g) 4-methyl-1-pentene, P(o-tolyl)<sub>3</sub>, TEA, Pd(OAc)<sub>2</sub>, DMF, 100°C, 18 hr; (h) H<sub>2</sub>, 10% Pd/C, EtOAc; (i) (i) NaOH (aq), dioxane, 70°C, 3 hr; (ii) 1 M HCl (aq).

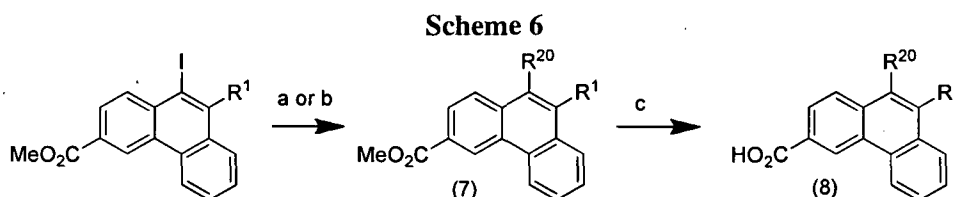
Scheme 4



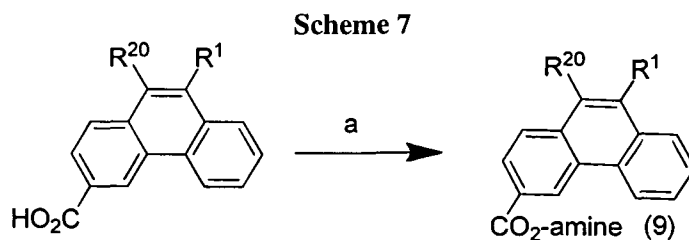
**[0071]** For formation of compounds of general structure (3), the chemical reactions in steps (a)-(c) use reagents as follows: a)  $\text{HNO}_3/\text{H}_2\text{SO}_4$ ; b)  $\text{SnCl}_2$ ,  $\text{HCl}$  (aq); c) (i)  $\text{NaNO}_2$ ,  $\text{HCl}$  (aq), ii)  $\text{KI}$  (aq).



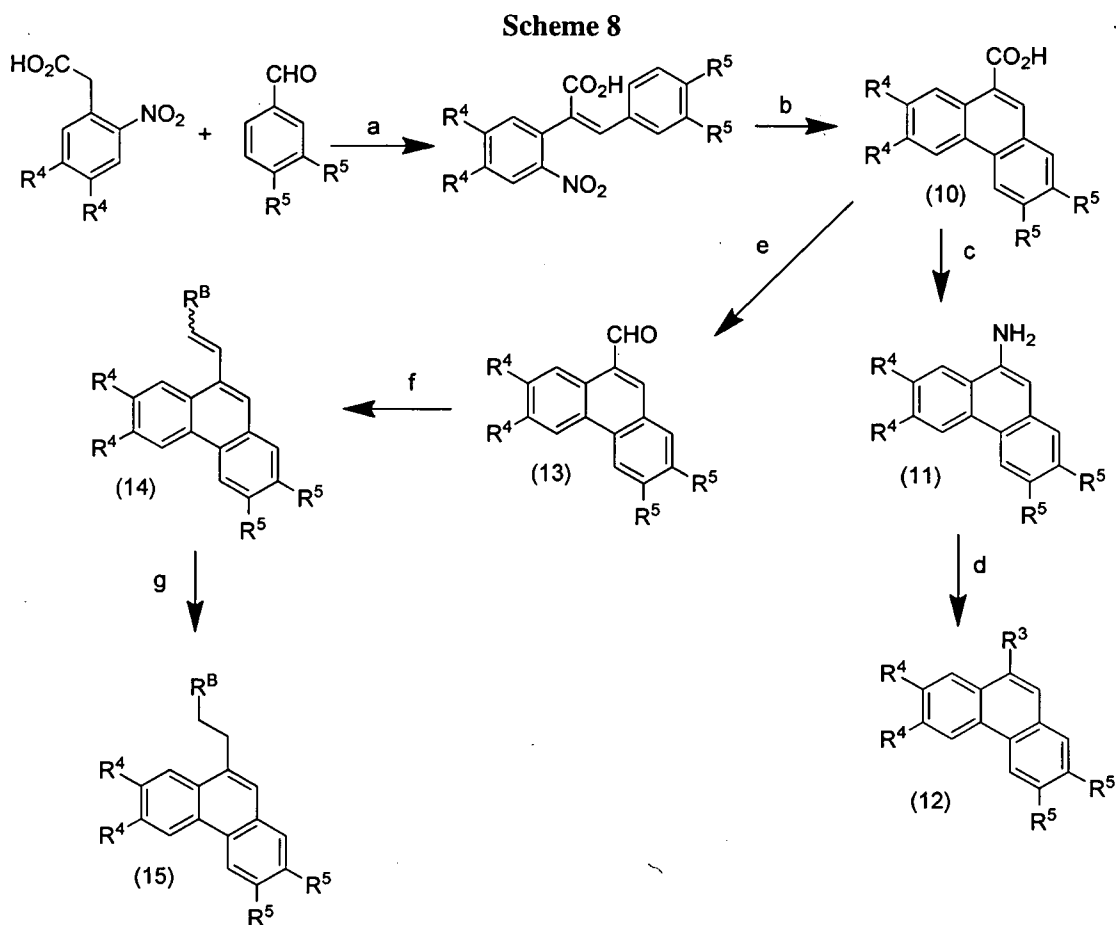
**[0072]** For formation of compounds of general structures (4)-(6), the chemical reactions in steps (a)-(c) use reagents as follows, where  $\text{R}^B$  represents an alkylene or alkenylene substituent for compounds as disclosed herein: a)  $\text{R}^B\text{-CH=CH}_2$ ,  $\text{Pd}(\text{OAc})_2$ ,  $\text{P}(\text{o-tolyl})_3$ , DMF; b) (i)  $\text{H}_2$ ,  $\text{Pd/C}$ , (ii)  $\text{NaOH}$ , dioxane/ $\text{H}_2\text{O}$ ; c)  $\text{NaOH}$ , dioxane/ $\text{H}_2\text{O}$ .



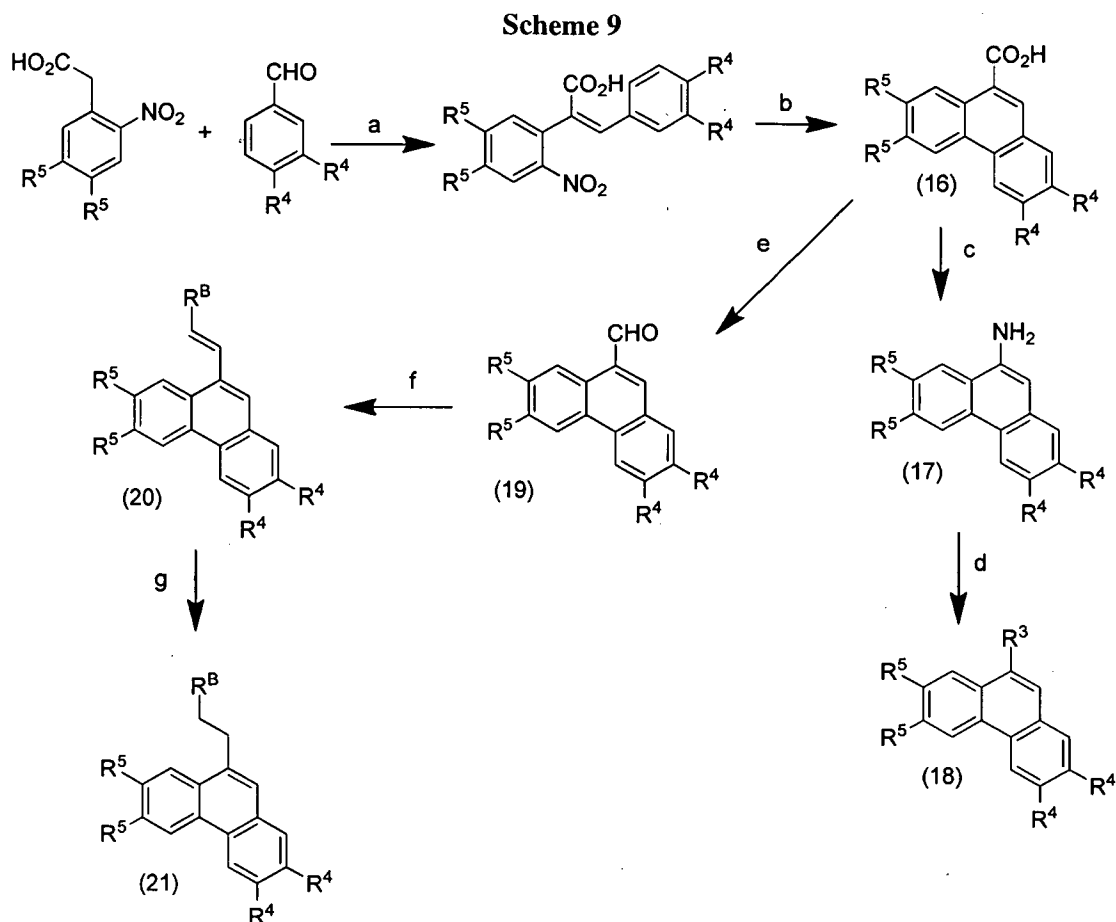
**[0073]** For formation of compounds of general structures (7) and (8), the chemical reactions in steps (a)-(c) use reagents as follows: a)  $\text{R}^B\text{-}\equiv$ ,  $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ ,  $\text{CuI}$ ,  $\text{Et}_3\text{N}$ , DMF; b) (i) aryl- $\text{B}(\text{OH})_2$  or heteroaryl- $\text{B}(\text{OH})_2$ ,  $\text{K}_2\text{CO}_3$ ,  $\text{Pd}(\text{dppf})\text{Cl}_2$ , DME; c)  $\text{NaOH}$ , dioxane/ $\text{H}_2\text{O}$ .



**[0074]** For formation of compounds of general structure (9), the chemical reaction in step (a) uses reagents as follows: (a) amine, DCC, HOBT, Hunigs base.

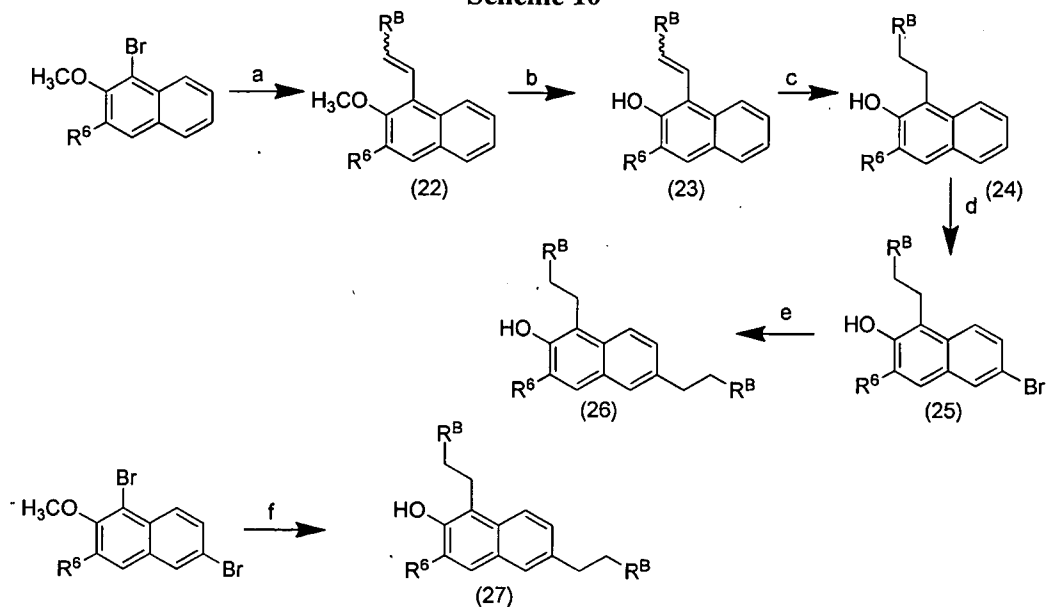


**[0075]** For formation of compounds of general structures (10)-(15), the chemical reactions in steps (a)-(g) use reagents as follows: a)  $Ac_2O$ ,  $Et_3N$  or  $Ac_2O$ ,  $K_2CO_3$ ; b) (i)  $FeSO_4$ ,  $NH_4OH$  (aq), (ii) isoamyl nitrite, ethanolic  $HCl$ , (iii)  $NaH_2PO_2$ , Cu bronze,  $H_2SO_4$  (aq); c) (i)  $SOCl_2$ , (ii)  $NH_4OH$ , (iii) diphenylphosphoryl azide; d) (i) isoamyl nitrite, ethanolic  $HCl$ , (ii)  $KI$ ,  $CuCl$  or  $CuBr$  for  $R^3=I$ ,  $Cl$  or  $Br$ , respectively; e) (i)  $SOCl_2$ , (ii)  $NaBH_4$ , dioxane, (iii)  $MnO_2$ ; f)  $R^BCH_2PPh_3I$ ,  $KHMDS$ ,  $THF$ ; g)  $Pd/C$ ,  $H_2$ .



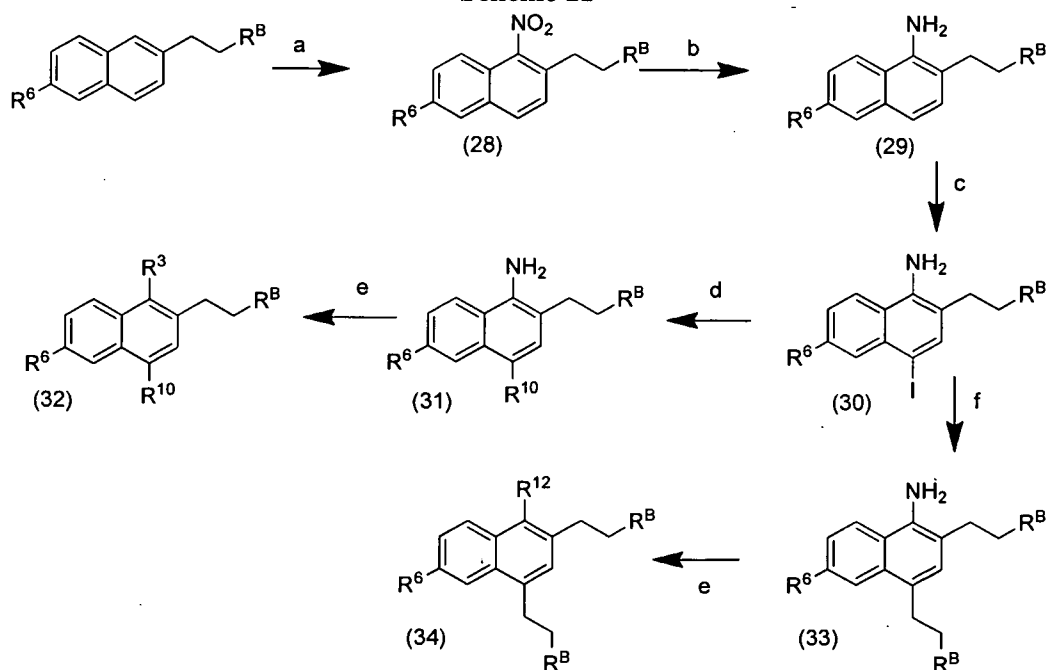
**[0076]** For formation of compounds of general structures (16)-(21), the chemical reactions in steps (a)-(g) use reagents as follows: a)  $\text{Ac}_2\text{O}$ ,  $\text{Et}_3\text{N}$  or  $\text{Ac}_2\text{O}$ ,  $\text{K}_2\text{CO}_3$ ; b) (i)  $\text{FeSO}_4$ ,  $\text{NH}_4\text{OH}$  (aq), (ii) isoamyl nitrite, ethanolic  $\text{HCl}$ , (iii)  $\text{NaH}_2\text{PO}_2$ , Cu bronze,  $\text{H}_2\text{SO}_4$  (aq); c) diphenylphosphoryl azide; d) (i) isoamyl nitrite, ethanolic  $\text{HCl}$ , (ii)  $\text{KI}$ ,  $\text{CuCl}$  or  $\text{CuBr}$ ; e) (i)  $\text{SOCl}_2$ , (ii)  $\text{NaBH}_4$ , dioxane, (iii)  $\text{MnO}_2$ ; f)  $\text{R}^B\text{CH}_2\text{PPh}_3\text{I}$ ,  $\text{KHMDs}$ ,  $\text{THF}$ ; g)  $\text{Pd/C}$ ,  $\text{H}_2$ .

Scheme 10

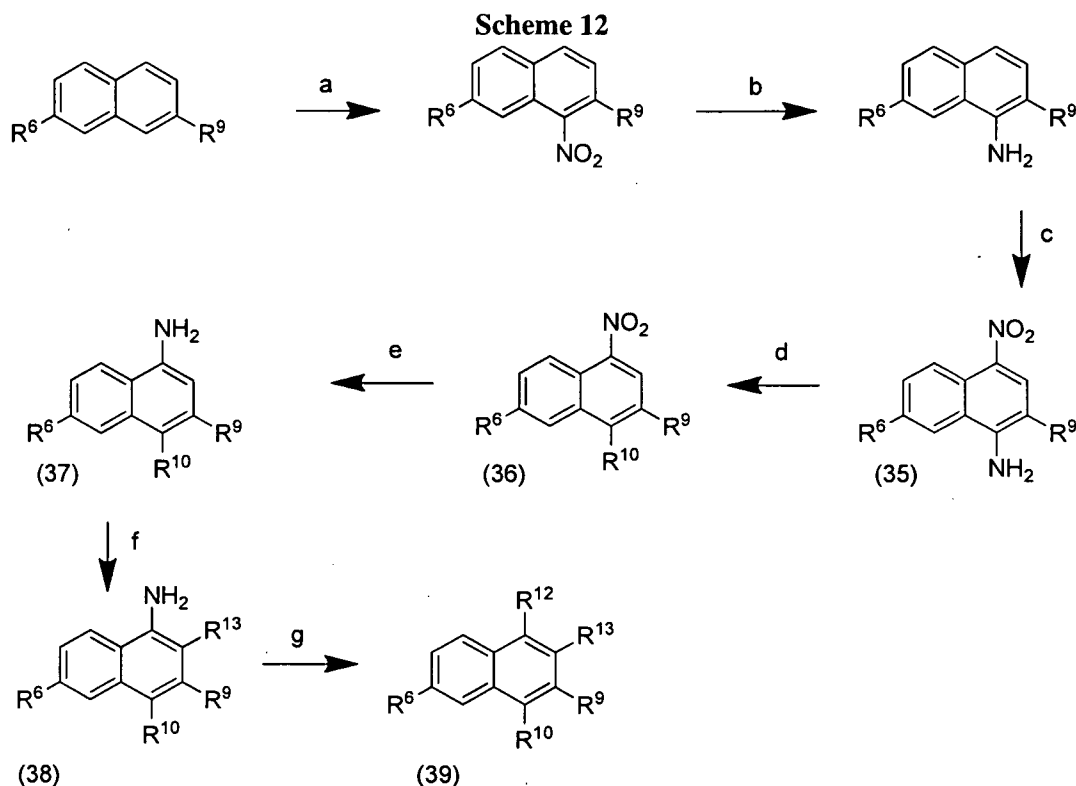


[0077] For formation of compounds of general structures (22)-(27), the chemical reactions in steps (a)-(f) use reagents as follows: a) R<sup>B</sup>-CH=CH<sub>2</sub>, Pd(OAc)<sub>2</sub>, P(o-tolyl)<sub>3</sub>, DMF; b) BBr<sub>3</sub>, DCM; c) H<sub>2</sub>, Pd/C; d) Br<sub>2</sub>, AcOH; e) (i) MeI, K<sub>2</sub>CO<sub>3</sub>, DMF, (ii) R<sup>B</sup>-CH=CH<sub>2</sub>, Pd(OAc)<sub>2</sub>, P(o-tolyl)<sub>3</sub>, DMF, (iii) H<sub>2</sub>, Pd/C, (iv) BBr<sub>3</sub>, DCM; f) (i) R<sup>B</sup>CH=CH<sub>2</sub>, Pd(OAc)<sub>2</sub>, P(o-tolyl)<sub>3</sub>, DMF (ii) H<sub>2</sub>, Pd/C, (iii) BBr<sub>3</sub>, DCM.

Scheme 11



[0078] For formation of compounds of general structures (28)-(34), the chemical reactions in steps (a)-(e) use reagents as follows: a)  $\text{HNO}_3$ ,  $\text{H}_2\text{SO}_4$ ; b)  $\text{H}_2$ , Pd/C; c)  $\text{I}_2$ , pyridine, dioxane; d)  $\text{R}^{10}\text{B}(\text{OH})_2$ ,  $\text{K}_2\text{CO}_3$ ,  $\text{Pd}(\text{dppf})\text{Cl}_2$ , DME; or  $\text{R}^{10}\text{-CH=CH}_2$ ,  $\text{Pd}(\text{OAc})_2$ ,  $\text{P}(\text{o-tolyl})_3$ , DMF and Pd/C,  $\text{H}_2$ ; e) (i) diazotization, (ii) for  $\text{R}^3$  or  $\text{R}^{12}$  halo treat with  $\text{CuCl}$ ,  $\text{CuBr}$  or  $\text{KI}$ , for  $\text{R}^3$  or  $\text{R}^{12}$  H treat with  $\text{NaH}_2\text{PO}_2$ , for  $\text{R}^3$  or  $\text{R}^{12}$  OH heat diazotized compound in aqueous  $\text{H}_2\text{SO}_4$ ; f) (i)  $\text{R}^B\text{-CH=CH}_2$ ,  $\text{Pd}(\text{OAc})_2$ ,  $\text{P}(\text{o-tolyl})_3$ , DMF, (ii) Pd/C,  $\text{H}_2$ .



[0079] For formation of compounds of general structures (35)-(39), the chemical reactions in steps (a)-(g) use reagents as follows: a)  $\text{HNO}_3$ ,  $\text{H}_2\text{SO}_4$ ; b)  $\text{H}_2$ , Pd/C or  $\text{SnCl}_2$ ,  $\text{HCl}$  (aq); c)  $\text{HNO}_3$ ,  $\text{H}_2\text{SO}_4$ ; d) (i) diazotisation, (ii) for  $\text{R}^{10}$  = halo treat with  $\text{CuCl}$ ,  $\text{CuBr}$  or  $\text{KI}$ , for  $\text{R}^{10}$  = H treat with  $\text{NaH}_2\text{PO}_2$ , for  $\text{R}^{10}$  = CN treat with  $\text{CuCN}$ , for  $\text{R}^{10}$  = alkyl, alkylenearyl, alkyleneheteroaryl or alkylene-cycloalkyl use a derivative of (36) where  $\text{R}^{10}$  = Br or I in Heck reaction, followed by catalytic hydrogenation, for  $\text{R}^{10}$  = aryl or heteroaryl use Suzuki reaction; e)  $\text{SnCl}_2$ ,  $\text{HCl}$  (aq); f) for  $\text{R}^{13}$  = halo, use  $\text{I}_2$ , pyridine, dioxane to introduce I,  $\text{Br}_2$  to introduce Br, for  $\text{R}^{13}$  = alkyl, alkylenearyl, alkyleneheteroaryl or alkylene-cycloalkyl use a derivative of (38) where  $\text{R}^{13}$  = Br or I in Heck reaction, followed by catalytic hydrogenation, for  $\text{R}^{13}$  = aryl or heteroaryl use Suzuki reaction; g) (i) diazotisation, (ii) for  $\text{R}^{12}$  = halo treat with  $\text{CuCl}$ ,  $\text{CuBr}$  or  $\text{KI}$ , for  $\text{R}^{12}$  = alkyl, alkylenearyl, alkyleneheteroaryl or alkylene-

cycloalkyl use a derivative of (39) where  $R^{10}$  = Br or I in Heck reaction, followed by catalytic hydrogenation, for  $R^{10}$  = aryl or heteroaryl use Suzuki reaction.

[0080] The above synthetic routes are meant to be illustrative on how a compound as disclosed herein can be prepared. However, it will be appreciated that the compounds can be prepared by any means available to the synthetic chemist.

#### **Methods of Modulating NMDA Receptor and Therapeutic Methods**

[0081] The compounds disclosed herein are modulators of the NMDA receptor. Modulation of the NMDA receptor occurs via contacting an NMDA receptor with a compound (or compounds) as disclosed herein. The contacting can be *in vivo* or *in vitro*.

[0082] The NMDA receptor comprises NR1, NR2, NR3, or a combination thereof. In various embodiments, the NMDA receptor comprises at least one NR2 subunit and a NR1 or NR3 subunit, at least one NR2 subunit and both an NR1 and NR3 subunit, or at least an NR1 and an NR3 subunit. The NR2 subunits can be, e.g., NR2A, NR2B, NR2C, or NR2D. The NR3 subunits can be, e.g., NR3A or NR3B. The NR2 subunits are alternatively referred to throughout as GluN2 (e.g., GluN2A, GluN2B). Some non-limiting examples of NMDA receptors contemplated include heterotetramers, such as, for example, 2 NR1 subunits and 2 NR2 subunits; 2 NR1 and 2 NR3 subunits; 2 NR1, 1 NR2 and 1 NR3 subunit.

[0083] Contacting an NMDA receptor with one or more of the compounds disclosed herein results in modulation of the NMDA receptor activity. The modulation can cause an increase (e.g., act as a potentiator) or a decrease (e.g., act as an antagonist or inhibitor) in NMDA receptor activity in response to agonist activation (e.g., L-glutamate and/or glycine or D-serine). The contacting can be by administering the compound or a composition comprising the compound. The compound (or composition) can be administered to an animal, for example a mammal. The mammal can be a marsupial, a rodent, dog, cat, horse, rabbit, pig, cow, deer, or human. Further description of the routes of administration and the composition of the compounds are found elsewhere in this disclosure.

[0084] The compounds disclosed herein can modulate the activity of the NMDA receptor by an allosteric interaction with the receptor. "Allosteric" refers to binding sites that are different from the primary substrate or ligand binding sites or domains (LBD). Binding of modulators to the allosteric site of the receptor can result in conformational changes which influence receptor function. In some embodiments, the compound does not compete with ligand(s) of the NMDA receptor (e.g., glutamate or glycine, or both) for binding to the

receptor, but can alter (e.g., increase or decrease) ligand binding, ligand affinity, ligand efficacy, and/or ligand avidity. Competitive binding can be determined using a suitable competitive binding assay, the choice of which is well within the skill of the ordinarily skilled artisan.

[0085] In some embodiments, a compound disclosed herein is a selective modulator for receptors comprising a specific subunit (also called subtype) of an NMDA receptor. For example, the compound can selectively modulate receptors comprising NR2A, NR2B, NR2C, or NR2D subunits. In some cases, the compound selectively modulates two, three, or four subunits of NMDA receptors. Modulation of any or each of the receptors comprising NR2A, NR2B, NR2C, and/or NR2D can be measured using an assay as described in the examples below.

[0086] Modulation of NMDA receptor activity has been implicated in a host of biological processes and disorders, as discussed below.

[0087] **Positive Modulation:** NMDA receptor positive allosteric modulators have distinct advantages over NMDA receptor agonists or partial agonists. It is possible to enhance some NMDA receptor signaling through the use of agonists or partial agonists. The NMDA receptor complex requires the binding of both L-glutamate and glycine or D-serine to achieve activation. L-Glutamate is the neurotransmitter that activates the NMDA receptor. It is released by synaptic vesicles from glutamate-using neurons. Glycine and/or D-serine are found at activating levels in the extracellular space. Their presence is thought to be near saturating, thus their addition may or may not enhance NMDA receptor function depending on the local concentrations of glycine/D-serine surrounding NMDA receptors. L-Glutamate itself, or other agents that activate by binding at the NMDA receptor's glutamate binding site are not therapeutically useful because they would simply activate all NMDA receptors they encounter. Thus, exogenous glutamate agents would not be able to activate the precise spatiotemporal pattern of NMDA receptor activation that mimics the normal patterns of brain activity. However, the positive allosteric modulators described herein do not activate NMDA receptors in the absence of L-glutamate or glycine. Nor do they activate NMDA receptors in the presence of L-glutamate alone or with glycine alone. Instead, they enhance the activity of just those receptors that are activated by both L-glutamate and glycine. Thus when added as a therapeutic agent, they would only have effects on NMDA receptors that are already being activated by L-glutamate and glycine/D-serine.

[0088] Another disadvantage of the enhancement of NMDA receptor function by the use of a glycine site agonist or partial agonist is that this binding site is on the common NR1 subunit, hence there will be very little specificity over the receptor subtypes being enhanced. Their activity, instead, would depend on the endogenous levels of glycine or D-serine near the receptor.

[0089] **Schizophrenia:** Provided herein is a method of treating schizophrenia using an NMDA receptor potentiator as disclosed herein. Evidence is now quite strong that hypofunction of NMDA receptor activity plays a key role in the expression of schizophrenia (51,52). NMDA receptor antagonists can cause both the positive and negative symptoms of schizophrenia (52) and enhancing NMDA receptor function by providing glycine agonists improves symptoms in schizophrenia patients (53). These findings are consistent with schizophrenia gene-linkage studies that have found associations with gene defects that result in reduced NMDA receptor activity (54). Currently available antipsychotic agents only address the positive symptoms of schizophrenia and not the negative and cognitive symptoms (52). Thus agents acting on the NMDA receptor system may have significantly improved therapeutic activity.

[0090] Schizophrenia etiology involves many different genes and there is evidence for patient subgroups. If the primary defect in a schizophrenia patient population results in a general decrease in NMDA receptor function, such as in defect with increased D-serine degradation, then a general NMDA receptor potentiator (e.g., UBP646, disclosed below) may be of use. However, some of the symptoms of schizophrenia may be due to NMDA receptor hypofunction of distinct populations of NMDA receptors. For example, genetic evidence suggests that a variation of the NR2B subunit may contribute to schizophrenia in some patients (55). Hence, selectively modulating this receptor population may have therapeutic benefit for schizophrenia. There is also evidence that GABAergic interneurons containing NR2C subunits have a special role in the symptoms of schizophrenia. In particular NR2C-containing NMDA receptors found on GABAergic interneurons of the reticular nucleus of the thalamus are critical to determining cortical-thalamic interactions (the generation of delta waves) that are known to be disturbed in schizophrenia (56). Along these lines, genetic evidence ties schizophrenia in some patients to the proteins neuroregulin1 and ErbB4. These proteins interact with NMDA receptors and are especially important for glutamate signaling on GABAergic interneurons. Hence, modulation of GluN2C-containing receptors (which are

frequently located on select populations on GABAergic interneurons) may have a beneficial effect on these populations of schizophrenic patients.

**[0091] Synaptic plasticity & cognitive enhancement:** NMDA receptor potentiators enhance synaptic plasticity, a major function of NMDA receptor activation. Hence, NMDA receptor potentiators can be useful in clinical conditions where synaptic plasticity is involved. Examples include post-traumatic stress disorder, enhancing cognition/plasticity in Alzheimer's disease, accelerating recovery of function after stroke or traumatic brain injury/spinal cord injury, and reversal of drug addiction.

**[0092]** Synaptic plasticity represents several different processes wherein specific temporal patterns of synaptic excitation can result in persistent changes in the strength of synaptic signaling. The most well characterized example is termed long term potentiation (LTP), where short bursts of electrical stimulation of a synaptic input at a high frequency (e.g. 100 Hz) results in a persistent enhancement of the electrically-evoked synaptic response. In contrast, stimulating the same pathway at a low frequency (1 to 3 Hz) is sometimes associated with a persistent depression of the magnitude of the synaptic response (long term depression, LTD). This ability to adjust the strength of signaling in the brain as a function of experience is thought to underlie learning and memory formation at the cellular level. In many forms of synaptic plasticity, it is the activation of NMDA receptors that serves as the trigger for initiating the molecular signals leading to LTP and to LTD. Accordingly, in a variety of learning paradigms, the blockade of NMDA receptors blocks learning as well as blocking the reversal of learning.

**[0093]** Thus, compounds as disclosed herein that potentiate NMDA receptor activity can enhance the ability to form LTP and LTD and thus enhance learning and memory. This can be seen as transgenic overexpression of the NR2B subunit in the mouse brain enhances learning ability (57). Likewise, D-serine, which can enhance the response of NMDA receptors to the neurotransmitter glutamate, can also enhance learning as well as reversal of learning (42,58). Such compounds may thus have use in improving cognition in dementia.

**[0094]** Post-traumatic stress is thought to be a form of "fear learning", a form of plasticity involving the emotional centers of the brain. The reversal of post-traumatic stress disorder has been reported to be enhanced by increasing NMDA receptor function (42) using glycine site agonists. Thus the ability to potentiate NMDA receptors can be useful in this condition. For post-traumatic stress disorder or fear conditioning, it is likely that specific subpopulations of NMDA receptors would be most relevant, though which populations remain to be defined.

Thus, the ability to enhance the function of select subpopulations would be an important advantage of subtype-selective potentiators.

**[0095]** In Alzheimer's disease, there is impaired synaptic plasticity, a loss of dendritic spines, and a loss of neurons in specific brain areas. This leads to impaired memory formation and memory retrieval and, consequently, cognitive decline. Thus, agents that can enhance the response of NMDA receptors in the remaining synaptic structures, should enhance synaptic plasticity and memory formation. The positive allosteric modulators described herein can be used to improve cognition in Alzheimer's patients and in other patients with dementia.

**[0096]** In Alzheimer's disease, NMDA receptors play a role in initiating the cell death promoted by the beta-amyloid protein. As described below, considerable research is now evaluating the role of specific NMDA receptor subtypes in initiation of the synaptic loss and cell death associated with NMDA receptors in Alzheimer's disease and the identification of other subpopulations of NMDA receptors that may be neuroprotective. Hence, a general NMDA receptor potentiator may acutely enhance function in Alzheimer's disease while accelerating the progression of the disease. However, a subtype-selective positive NMDA receptor modulator may improve cognition in Alzheimer's patients without accelerating disease progression. As mentioned below, the appropriate subtype-selective negative modulator may be useful for slowing the progression of the disease.

**[0097]** Studies of neurodegeneration in animal models indicates that some sub-populations of NMDA receptors promote neuroprotection by the activation of anti-oxidant pathways in the brain. In particular, synaptic NMDA receptors, in contrast to extrasynaptic NMDA receptors have been reported to improve neuronal survival. Along these lines, NR2A subunits which are often concentrated in the synapse, appear to be responsible for initiating the neuroprotection pathways. Hence, a positive allosteric modulator (such as, e.g., UBP512) which preferentially potentiates NR2A-containing NMDA receptors may have the ability to promote neuronal cell survival in Alzheimer's disease and other neurodegenerative conditions. This would be a positive effect on the disease progress and can have an additional beneficial acute effect on the cognitive symptoms by improving synaptic plasticity.

**[0098]** The activation of NMDA receptors is necessary during brain development to generate the correct afferent input between various brain regions. For example, NMDA receptor activation of cortical neurons is necessary for the nerve fibers terminating in the visual cortex to be segregated into eye-specific patches. In this process NMDA receptor

activation is used to both help stabilize the appropriate synapses and to actively remove inappropriate synapses. Thus, it is predicted that compounds that potentiate NMDA receptor activity would accelerate the process.

[0099] As an example plasticity enhancement, in developmentally-delayed childhood disorders, NMDA receptor potentiator drugs, in combination with training sessions, may lead to faster acquisition of skills. Similarly, in adult patients, in the recovery from brain injury or stroke, patients need to retrain parts of their brain. Potentiation of NMDA receptor activity would be expected to accelerate the formation of new circuits underlying functional recovery.

[0100] **NMDA receptor negative modulators:** Historically, most drug development and clinical interest regarding NMDA receptors has focused on the use of receptor blockers as neuroprotective agents. It is well established that over-activation of NMDA receptors can lead to neuronal cell death in stroke, head injury, and probably, neurodegenerative diseases. Various clinical studies have failed when using NMDA receptor blockers as neuroprotective agents. However, more recent animal model studies indicate that NMDA receptor subtypes differ in their ability to cause cell death and that some NMDA receptor populations act oppositely to promote cell survival. NR2B-containing NMDA receptors initiate cell death whereas NR2A-containing receptors have been reported to contribute to neuroprotection signaling in traumatic mechanical injury and ischemia models. This may correspond to an enrichment of NR2A and NR2B subunits in synaptic and extrasynaptic compartments, respectively, and the ability of synaptic NMDA receptors to promote neuroprotection while extrasynaptic NMDA receptor activation signals to neuronal cell death. Thus, the neuroprotective properties of GluN2B-selective antagonists have been actively studied.

[0101] **NR2D-selective inhibitors:** NR2D selective antagonists can be useful as neuroprotective agents in stroke, to prevent tPA-enhanced damage when used in treating stroke. Multiple lines of evidence also suggest that NR2D may have a special role in initiating cell death in various conditions. As mentioned above, extrasynaptic NMDA receptors may preferentially contribute to cell death (31). Thus, it is noteworthy that NR2D is found exclusively in the extrasynaptic compartment at some CNS synapses. Consistent with an excitotoxic role, NR2D knockout mice display reduced cerebral cortical damage, but unchanged hippocampal damage in the middle cerebral artery occlusion stroke model. Related to this observation, tissue plasminogen activator (TPA) – enhanced stroke damage in the cerebral cortex appears to be dependent specifically upon GluN2D subunits.

**[0102] NR2C and/or NR2D selective inhibitors:** NR2C and/or NR2D may play a specific role in white matter injury (39) and (specifically NR2D) a role in Creutzfeldt-Jakob disease (8) and Alzheimer's disease. Thus, compounds that are selective for NR2C and/or NR2D can be useful for treating white matter injury, multiple sclerosis, Creutzfeldt-Jakob disease, and Alzheimer's disease. Moreover, compounds with partial NR2D-selectivity, such as, for example, UBP512, may have neuroprotective actions in some brain regions without affecting the larger populations of NR2A- and NR2B-containing receptors.

**[0103] NMDA receptor selective negative modulators in treating neuropathic pain:** NR2-selective inhibitors of NMDA receptor signaling may also be useful for treating pain. NR2D subunits are involved in the expression of pain in the sciatic nerve ligation neuropathic pain model and in the prostaglandin PGF2- $\alpha$ -induced pain model while NR2A is important in the expression of tonic inflammatory pain (41). In addition to these studies, there are many reports that NR2B-containing NMDA receptors contribute to pain.

#### **NMDA Receptor Selectivity/Structure Activity Relationships**

**[0104]** For various compounds disclosed herein (e.g., UBP512, NSC339614, UBP710), there is a general separation of activities at NR2A/NR2B vs. NR2C/NR2D-containing receptors consistent with the relative degree of sequence homology. The agents can also distinguish between NR2A and NR2B (e.g., UBP512 and UBP608) and between NR2C and NR2D (e.g., UBP551 and UBP608). Thus, the corresponding pharmacophores for these agents appear to vary between the NR2 subunits, especially between 2A/B and 2C/D. The degree of selectivity by these compounds is already greater than that displayed by glutamate and glycine binding site antagonists and channel blockers. Thus, this class of agents are useful as subtype-selective agents.

**[0105]** Multiple lines of evidence suggest that NR2D may have a special role in initiating cell death in various conditions. Consistent with the hypothesis that extrasynaptic NMDA receptors preferentially contribute to cell death (31), NR2D is sometimes found exclusively in the extracellular compartment at some CNS synapses (30,36,37). Consistent with an excitotoxic role, GluN2D knockout mice display reduced cerebral cortical damage, but unchanged hippocampal damage in the middle cerebral artery occlusion stroke model. Also, due to the selective cleavage and activation of NR2D subunits; tissue plasminogen activator (TPA) – enhanced stroke damage in the cerebral cortex appears to be dependent upon NR2D subunits (38). NR2C and/or NR2D may also play a specific role in white matter injury (39). NR2D subunits may also have a specific role in Creutzfeldt-Jakob disease (8), and perhaps

Alzheimer's disease (40). Hence, compounds with partial NR2D-selectivity, such as UBP512, may have neuroprotective actions in some brain regions without affecting the larger populations of NR2A- and NR2B-containing receptors. NR2-selective inhibitors of NMDA receptor signaling may also be useful for treating pain. NR2D subunits are essential for the expression of pain in the sciatic nerve ligation neuropathic pain model and in the prostaglandin PGF2- $\alpha$ -induced pain models while NR2A is important in the expression of tonic inflammatory pain (41).

**[0106]** The compound class identified here has several additional therapeutic applications due to their ability to alternatively potentiate NMDA receptor activity. One intriguing possibility is that the potentiation of synaptic NMDA receptors containing the NR2A subunit may stimulate neuroprotective signaling pathways (19,28). In an in vivo context, direct agonist activation would activate inappropriate receptors while a potentiator should simply increase the response of endogenously-activated receptors, thus enhancing an appropriate biological response. Consequently, compounds that selectively potentiate NR2A subunits and not NR2B subunits, while inhibiting NR2D-containing receptors (e.g. UBP512) may have a combined pro-survival and neuroprotective properties. Such an activity may also have cognitive enhancement properties by promoting the formation of long-term potentiation.

**[0107]** NMDA receptor potentiators are useful in treating post-traumatic stress disorder and schizophrenia. The reversal of post-traumatic stress disorder has been reported to be enhanced by increasing NMDA receptor function (42). In the case of schizophrenia, this disease is thought to be associated with NMDA receptor hypofunction (6). Thus the ability to selectively potentiate the most appropriate subpopulations of NMDA receptors may be useful in these conditions.

**[0108]** The compounds disclosed herein do not have a T-shaped hydrophobic multi-ring system with a positive charge center commonly found in NMDA receptor channel blockers. They also do not have an extended structure with an aromatic ring containing a proton donor linked via a basic nitrogen to another aromatic ring – a structure that is typical of ifenprodil-like agents that act at the NTD (21).

**[0109]** Consistent with these structure-activity considerations, phenanthrene related compounds (e.g., UBP512) do not act as competitive ligands at either the L-glutamate or glycine binding sites. The compounds also do not have voltage-dependent activity expected for channel blockers, nor require the NTD for activity. UBP512 potentiating activity becomes inhibitory in NR1/NR2A receptors that have the GluN2A S2 domain replaced by

GluN2C's S2 domain (see Figure 3). Thus, UBP512 might be binding to this domain or this domain contributes to transducing the effect of UBP512 binding to its effect on receptor function.

[0110] The dimer interface between the ligand-binding domains may be the site of action for phenanthrene related compounds (e.g., UBP512). In the AMPA receptor family, several modulators have been identified that act at the dimer interface between the agonist ligand-binding domains. Site-directed mutagenesis and crystallography studies indicate that the inhibitory 2,3-benzodiazepines (e.g. GYKI-52466) bind at the dimer interface between the ligand-binding domains of adjacent subunits near to the membrane (pre-M1 and pre-M4) (43,44). The 2,3-benzodiazepines allosterically inhibit AMPA receptor activation by blocking the ligand-binding domain conformational changes being translated to changes in the transmembrane pore structure (43). Further from the membrane, but still in the ligand-binding dimer interface, the allosteric potentiators such as the benzothiadiazines (e.g., cyclothiazide) and pyrrolidinones (e.g., aniracetam) bind and reduce the desensitization of AMPA receptor activity (44,45). Consistent with this possible location, replacing the S2 domain of NR2A with that of NR2C eliminates the potentiating activity of UBP512.

[0111] The action of the compounds described herein also show similarity in action to the neurosteroid pregnenolone sulfate (PS). At high concentrations, PS potentiates NMDA receptor responses at receptors containing NR2A or NR2B subunits while inhibiting responses at receptors containing NR2C or NR2D subunits (46,47). It has been shown that PS both potentiates and inhibits at each of the four NR1/NR2 receptor complexes, but one activity can mask the other. Upon applying UBP512 to a steady state GluN1/GluN2A response, there is a transient inhibition followed by potentiation. Conversely, when washing off UBP710 after the potentiation of GluN1/GluN2D responses, there is a transient additional potentiation as though a fast-dissociating inhibitory action has been removed. For PS, the inhibitory and potentiating activities appear to represent distinct binding sites. These actions of PS involve the GluN2's S2 domain. Interestingly, the potentiating activity of PS is phosphorylation-state dependent, while the inhibitory activity is not (48). This may explain why the potentiating actions of NSC339614 and UBP710 displayed quantitative variations between different batches of cells.

[0112] **Naphthyl Compound Structure-Activity-Relationship:** The structure-activity relationships of a series of 2-naphthoic acid derivatives has been investigated to better define this novel drug-binding site for the development of improved pharmacological agents. A key

substituent was the acidic functional group (e.g., a carboxylic acid group or other R<sup>A</sup> group). In a molecule with otherwise optimal substituents, removal of the acidic group eliminated activity (e.g., UBP552 and UBP644). Affinity at all NMDA receptors was increased by halogen, aryl (e.g., phenyl), or hydroxy substitutions at multiple positions on the naphthalene ring in an additive manner. Both 1- and 6-halogenation of 2-hydroxy-3-naphthoic acid increase inhibitory activity and, when combined, result in relatively potent antagonists. In some embodiments, at the 1-position, a bromo group is preferred and at the 6-position, a phenyl group is preferred. In particular, 1-bromo-2-hydroxy-6-phenylnaphthalene-3-carboxylic acid (UBP618) is a particularly preferred compound.

**[0113]** Inhibitory activity of the 2-naphthoic acid derivatives is, for the most part, similar between the different GluN1/GluN2 receptors studied. However, the minimally substituted 2-naphthoic acid derivatives generally displayed greater potency at GluN1/GluN2A receptors. With further additions, compound activity was increased at all NMDA receptors, resulting in little subtype-selectivity. Subtype-selectivity is, however, affected by substitutions ortho to the carboxy group. Adding a hydroxyl group onto the 2-naphthoic acid structure reduced GluN2A activity while increasing activity at the other NMDA receptors (see, e.g., UBP519 and UBP558). Furthermore, substituting a hydroxy group into this position in the presence of 1,6-dibromo substitutions (see, e.g., UBP628 and UBP552) increased affinity 12-, 17-, and 33-fold at GluN1/GluN2B-D receptors respectively, but caused only a 3-fold increase in affinity at GluN2A-containing receptors, resulting in relatively potent, but non-selective blockade. The differential effect of the hydroxy group at this position on GluN1/GluN2A receptors may correspond to the enhanced GluN1/GluN2A-selectivity seen when an oxo group is placed at this position in UBP608. Without intending to be bound by theory, perhaps the oxo group acts as a hydrogen bond acceptor and enhances GluN2A inhibitory activity. In contrast, GluN2B, GluN2C, and GluN2D appear to preferentially interact with a hydrogen bond donor, such as, for example, the 2-hydroxy group in UBP552. Introduction of a negative charge at this position (UBP575) did not enhance activity, and may have reduced GluN1/GluN2D activity.

**[0114]** The initial studies indicated that the NTD is not necessary for the activity of UBP618 and that these compounds are not competitive antagonists or channel blockers. These findings were confirmed using UBP552. By analogy to AMPA receptor modulators such as GYKI-53655, these compounds may be binding in the ligand binding domain interface between GluN1 and GluN2 subunits and the linkers preceding the M1 and M4

segments (43). Replacing the segment 1 (S1), but not segment 2 (S2), of GluN2A with that of GluN2C reduced inhibitory activity of GluN2A-preferring UBP608. This site would appear then to be different from the binding site for the recently describe negative modulator QNZ46; inhibitory activity of this agent is determined by the S2 domain and not the S1 domain (60). Similar to that found for the allosteric AMPA receptor antagonists such as GYKI-53655, preliminary studies indicate that UBP552 has antagonist activity at AMPA receptors but not at kainate receptors.

[0115] Specific structural features underlie the ability of the antagonist compounds disclosed herein to fully block NMDA receptor responses. The compounds UBP617, UBP618, and UBP619 were the least able to fully block NMDA receptor responses at receptors containing GluN2A, GluN2B, or GluN2C subunits. Of the compounds tested, these were the only ones with a 6-phenyl substitution. Thus, while the phenyl ring increases affinity, at the same time it may be preventing a complete conformational movement that corresponds to channel closing. As this class of compounds is structurally similar to compounds with allosteric potentiating activity, it is also possible that the presence of a low affinity potentiating activity contributes to the incomplete blockade by UBP617, UBP618, and UBP619. In either case, blockers that cannot fully block NMDA responses may have an improved safety profile since they would be less able to cause excessive receptor blockade.

[0116] Modifications to the 2-naphthoic acid nucleus explored in this work reveal specific structure-activity relationships that underlie the potency of these compounds at NMDA receptors. The interactions defined here generally apply to all four of the GluN1/GluN2A-D receptors. Thus, the inhibitory binding site occupied by the 2-naphthoic acid derivatives may be largely conserved among the different NMDA receptor subtypes. However, compounds UBP608 and UBP628 demonstrate that there are elements in the binding pocket that are distinct between receptor subunit subtypes. The larger phenanthroic acid derivatives displayed greater subtype selectivity – perhaps due to the ability to probe subtype-specific regions of the drug binding pocket or perhaps to the ability to additionally bind to a distinct positive allosteric modulator binding site which displays greater subtype-selectivity. Further substitutions to expand the naphthoic acid structure may further increase both affinity and subtype selectivity.

[0117] The naphthoic acid compounds described here are negative allosteric modulators; they are not competitive antagonists and they do not require the N-terminal domain for activity. A potentially important feature of these compounds is that a specific structural

modification (phenyl substitution) leads to incomplete maximal inhibition at GluN2A and GluN2B-containing receptors. Thus, it appears possible to design compounds with varied maximal antagonist activity. Such compounds may have an improved safety profile due to their inability to fully block NMDA receptor activity.

#### **Dosing and Pharmaceutical Formulations**

**[0118]** The terms “therapeutically effective amount” and “prophylactically effective amount,” as used herein, refer to an amount of a compound sufficient to treat, ameliorate, or prevent the identified disease or condition, or to exhibit a detectable therapeutic, prophylactic, or inhibitory effect. The effect can be detected by, for example, an improvement in clinical condition, reduction in symptoms, or by any of the assays or clinical diagnostic tests described herein. The precise effective amount for a subject will depend upon the subject's body weight, size, and health; the nature and extent of the condition; and the therapeutic or combination of therapeutics selected for administration. Therapeutically and prophylactically effective amounts for a given situation can be determined by routine experimentation that is within the skill and judgment of the clinician.

**[0119]** Dosages of the therapeutic can alternately be administered as a dose measured in mg/kg. Contemplated mg/kg doses of the disclosed therapeutics include about 0.001 mg/kg to about 1000 mg/kg. Specific ranges of doses in mg/kg include about 0.1 mg/kg to about 500 mg/kg, about 0.5 mg/kg to about 200 mg/kg, about 1 mg/kg to about 100 mg/kg, about 2 mg/kg to about 50 mg/kg, and about 5 mg/kg to about 30 mg/kg.

**[0120]** As herein, the compounds described herein may be formulated in pharmaceutical compositions with a pharmaceutically acceptable excipient, carrier, or diluent. The compound or composition comprising the compound is administered by any route that permits treatment of the disease or condition. One route of administration is oral administration. Additionally, the compound or composition comprising the compound may be delivered to a patient using any standard route of administration, including parenterally, such as intravenously, intraperitoneally, intrapulmonary, subcutaneously or intramuscularly, intrathecally, topically, transdermally, rectally, orally, nasally or by inhalation. Slow release formulations may also be prepared from the agents described herein in order to achieve a controlled release of the active agent in contact with the body fluids in the gastro intestinal tract, and to provide a substantial constant and effective level of the active agent in the blood plasma. The crystal form may be embedded for this purpose in a polymer matrix of a biological degradable polymer, a water-soluble polymer or a mixture of both, and optionally

suitable surfactants. Embedding can mean in this context the incorporation of micro-particles in a matrix of polymers. Controlled release formulations are also obtained through encapsulation of dispersed micro-particles or emulsified micro-droplets via known dispersion or emulsion coating technologies.

**[0121]** Administration may take the form of single dose administration, or a compound as disclosed herein can be administered over a period of time, either in divided doses or in a continuous-release formulation or administration method (*e.g.*, a pump). However the compounds of the embodiments are administered to the subject, the amounts of compound administered and the route of administration chosen should be selected to permit efficacious treatment of the disease condition.

**[0122]** In an embodiment, the pharmaceutical compositions are formulated with one or more pharmaceutically acceptable excipient, such as carriers, solvents, stabilizers, adjuvants, diluents, etc., depending upon the particular mode of administration and dosage form. The pharmaceutical compositions should generally be formulated to achieve a physiologically compatible pH, and may range from a pH of about 3 to a pH of about 11, preferably about pH 3 to about pH 7, depending on the formulation and route of administration. In alternative embodiments, the pH is adjusted to a range from about pH 5.0 to about pH 8. More particularly, the pharmaceutical compositions may comprise a therapeutically or prophylactically effective amount of at least one compound as described herein, together with one or more pharmaceutically acceptable excipients. Optionally, the pharmaceutical compositions may comprise a combination of the compounds described herein, or may include a second active ingredient useful in the treatment or prevention of bacterial infection (*e.g.*, anti-bacterial or anti-microbial agents).

**[0123]** Formulations, *e.g.*, for parenteral or oral administration, are most typically solids, liquid solutions, emulsions or suspensions, while inhalable formulations for pulmonary administration are generally liquids or powders. A pharmaceutical composition can also be formulated as a lyophilized solid that is reconstituted with a physiologically compatible solvent prior to administration. Alternative pharmaceutical compositions may be formulated as syrups, creams, ointments, tablets, and the like.

**[0124]** The term “pharmaceutically acceptable excipient” refers to an excipient for administration of a pharmaceutical agent, such as the compounds described herein. The term refers to any pharmaceutical excipient that may be administered without undue toxicity.

[0125] Pharmaceutically acceptable excipients are determined in part by the particular composition being administered, as well as by the particular method used to administer the composition. Accordingly, there exists a wide variety of suitable formulations of pharmaceutical compositions (see, e.g., Remington's Pharmaceutical Sciences).

[0126] Suitable excipients may be carrier molecules that include large, slowly metabolized macromolecules such as proteins, polysaccharides, polylactic acids, polyglycolic acids, polymeric amino acids, amino acid copolymers, and inactive virus particles. Other exemplary excipients include antioxidants (*e.g.*, ascorbic acid), chelating agents (*e.g.*, EDTA), carbohydrates (*e.g.*, dextrin, hydroxyalkylcellulose, and/or hydroxyalkylmethylcellulose), stearic acid, liquids (*e.g.*, oils, water, saline, glycerol and/or ethanol) wetting or emulsifying agents, pH buffering substances, and the like. Liposomes are also included within the definition of pharmaceutically acceptable excipients.

[0127] The pharmaceutical compositions described herein are formulated in any form suitable for an intended method of administration. When intended for oral use for example, tablets, troches, lozenges, aqueous or oil suspensions, non-aqueous solutions, dispersible powders or granules (including micronized particles or nanoparticles), emulsions, hard or soft capsules, syrups or elixirs may be prepared. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions, and such compositions may contain one or more agents including sweetening agents, flavoring agents, coloring agents and preserving agents, in order to provide a palatable preparation.

[0128] Pharmaceutically acceptable excipients particularly suitable for use in conjunction with tablets include, for example, inert diluents, such as celluloses, calcium or sodium carbonate, lactose, calcium or sodium phosphate; disintegrating agents, such as cross-linked povidone, maize starch, or alginic acid; binding agents, such as povidone, starch, gelatin or acacia; and lubricating agents, such as magnesium stearate, stearic acid or talc.

[0129] Tablets may be uncoated or may be coated by known techniques including microencapsulation to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate alone or with a wax may be employed.

[0130] Formulations for oral use may be also presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example celluloses, lactose, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is

mixed with non-aqueous or oil medium, such as glycerin, propylene glycol, polyethylene glycol, peanut oil, liquid paraffin or olive oil.

**[0131]** In another embodiment, pharmaceutical compositions may be formulated as suspensions comprising a compound of the embodiments in admixture with at least one pharmaceutically acceptable excipient suitable for the manufacture of a suspension.

**[0132]** In yet another embodiment, pharmaceutical compositions may be formulated as dispersible powders and granules suitable for preparation of a suspension by the addition of suitable excipients.

**[0133]** Excipients suitable for use in connection with suspensions include suspending agents (e.g., sodium carboxymethylcellulose, methylcellulose, hydroxypropyl methylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth, gum acacia); dispersing or wetting agents (e.g., a naturally occurring phosphatide (e.g., lecithin), a condensation product of an alkylene oxide with a fatty acid (e.g., polyoxyethylene stearate), a condensation product of ethylene oxide with a long chain aliphatic alcohol (e.g., heptadecaethyleneoxycethanol), a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride (e.g., polyoxyethylene sorbitan monooleate)); and thickening agents (e.g., carbomer, beeswax, hard paraffin or cetyl alcohol). The suspensions may also contain one or more preservatives (e.g., acetic acid, methyl or n-propyl p-hydroxy-benzoate); one or more coloring agents; one or more flavoring agents; and one or more sweetening agents such as sucrose or saccharin.

**[0134]** The pharmaceutical compositions may also be in the form of oil-in water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, a mineral oil, such as liquid paraffin, or a mixture of these. Suitable emulsifying agents include naturally-occurring gums, such as gum acacia and gum tragacanth; naturally occurring phosphatides, such as soybean lecithin, esters or partial esters derived from fatty acids; hexitol anhydrides, such as sorbitan monooleate; and condensation products of these partial esters with ethylene oxide, such as polyoxyethylene sorbitan monooleate. The emulsion may also contain sweetening and flavoring agents. Syrups and elixirs may be formulated with sweetening agents, such as glycerol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, a flavoring or a coloring agent.

**[0135]** Additionally, the pharmaceutical compositions may be in the form of a sterile injectable preparation, such as a sterile injectable aqueous emulsion or oleaginous suspension. This emulsion or suspension may be formulated by a person of ordinary skill in

the art using those suitable dispersing or wetting agents and suspending agents, including those mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, such as a solution in 1,2-propane-diol.

**[0136]** The sterile injectable preparation may also be prepared as a lyophilized powder. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile fixed oils may be employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids (e.g., oleic acid) may likewise be used in the preparation of injectables.

**[0137]** To obtain a stable water-soluble dose form of a pharmaceutical composition, a pharmaceutically acceptable salt of a compound described herein may be dissolved in an aqueous solution of an organic or inorganic acid, such as 0.3 M solution of succinic acid, or more preferably, citric acid. If a soluble salt form is not available, the compound may be dissolved in a suitable co-solvent or combination of co-solvents. Examples of suitable co-solvents include alcohol, propylene glycol, polyethylene glycol 300, polysorbate 80, glycerin and the like in concentrations ranging from about 0 to about 60% of the total volume. In one embodiment, the active compound is dissolved in DMSO and diluted with water.

**[0138]** The pharmaceutical composition may also be in the form of a solution of a salt form of the active ingredient in an appropriate aqueous vehicle, such as water or isotonic saline or dextrose solution. Also contemplated are compounds which have been modified by substitutions or additions of chemical or biochemical moieties which make them more suitable for delivery (e.g., increase solubility, bioactivity, palatability, decrease adverse reactions, etc.), for example by esterification, glycosylation, PEGylation, etc.

**[0139]** In some embodiments, the compounds described herein may be formulated for oral administration in a lipid-based formulation suitable for low solubility compounds. Lipid-based formulations can generally enhance the oral bioavailability of such compounds.

**[0140]** As such, pharmaceutical compositions comprise a therapeutically or prophylactically effective amount of a compound described herein, together with at least one pharmaceutically acceptable excipient selected from the group consisting of medium chain fatty acids and propylene glycol esters thereof (e.g., propylene glycol esters of edible fatty acids, such as caprylic and capric fatty acids) and pharmaceutically acceptable surfactants, such as polyoxyl 40 hydrogenated castor oil.

[0141] In some embodiments, cyclodextrins may be added as aqueous solubility enhancers. Exemplary cyclodextrins include hydroxypropyl, hydroxyethyl, glucosyl, maltosyl and maltotriosyl derivatives of  $\alpha$ -,  $\beta$ -, and  $\gamma$ -cyclodextrin. A specific cyclodextrin solubility enhancer is hydroxypropyl-o-cyclodextrin (BPBC), which may be added to any of the above-described compositions to further improve the aqueous solubility characteristics of the compounds of the embodiments. In one embodiment, the composition comprises about 0.1% to about 20% hydroxypropyl-o-cyclodextrin, more preferably about 1% to about 15% hydroxypropyl-o-cyclodextrin, and even more preferably from about 2.5% to about 10% hydroxypropyl-o-cyclodextrin. The amount of solubility enhancer employed will depend on the amount of the compound of the invention in the composition.

### **Combination Therapy**

[0142] Further disclosed herein are methods of modulating a NMDA receptor activity by contacting with a compound as disclosed herein and a second therapeutic agent. The second therapeutic agent can be a different compound as disclosed herein or can be a therapeutic agent that has a different yet complimentary activity from the compounds disclosed herein. Other examples of contemplated second therapeutic agents include a mGluR2 modulator, mGluR3 modulator, mGluR5 modulator, AMPA receptor modulator, tissue plasminogen activator (TPA), or an NMDA receptor modulator of a different mechanism of action. One specific example of a contemplated combination therapy is a compound as disclosed herein that decreases NR2D activity and TPA. The second therapeutic agent can be co-formulated with the compound as disclosed herein or can be administered in a separate composition.

## **EXAMPLES**

### **Example 1 – NMDA Potentiators and Inhibitors**

[0143] A variety of structures containing either two or three fused aromatic rings were evaluated for their ability to modulate NMDA receptor responses evoked by 10  $\mu$ M L-glutamate and 10  $\mu$ M glycine. GluN1/GluN2A, GluN1/GluN2B, GluN1/GluN2C, and GluN1/GluN2D receptors were expressed in *Xenopus* oocytes and receptor activity was determined by two-electrode voltage clamp. Of the compounds screened, 6 compounds represent the different activities that were observed. UBP512 (9-iodo-3-carboxyphenanthrene) inhibited GluN1/GluN2C, and GluN1/GluN2D receptors, had minimal effect on GluN2B-containing receptors, and caused a small potentiation of GluN1/GluN2A receptors (as seen in Figure 1). Dose-response analysis (Figure 1A) confirmed the apparent selectivity of this compound. At 3-10  $\mu$ M, UBP512 weakly inhibited GluN1/GluN2A and

GluN1/GluN2B receptor responses (~10-15%). At higher doses, UBP512 potentiated GluN1/GluN2A receptor-mediated responses and inhibited responses at GluN1/GluN2C ( $IC_{50} = 51 \pm 11 \mu M$ , Hill coefficient =  $-1.3 \pm 0.3$ ) and GluN1/GluN2D receptors ( $IC_{50} = 46 \pm 6 \mu M$ , Hill coefficient =  $-1.35 \pm 0.1$ ). Under these conditions, UBP512's maximal inhibitory effect was  $69 \pm 6 \%$  and  $72 \pm 2 \%$  respectively. UBP512 did not have partial agonist activity; it did not evoke responses by itself or when paired with glycine or L-glutamate, as noted in Table 1. Compounds tested in Table 1 do not display agonist or partial agonist activity, nor alter the holding current. Compounds were tested for excitatory activity in the presence or absence of L-glutamate or glycine. Values represent % activation  $\pm$  s.e.m.,  $n = 4$ . G + E = 10  $\mu M$  glycine + 10  $\mu M$  L-glutamate, TC = test compound (100  $\mu M$ ), G = 10  $\mu M$  glycine, E = 10  $\mu M$  L-glutamate.

Table 1

|                  |           | UBP512         | UBP710         | UBP618         | UBP551         | NSC<br>339614   | UBP608         | UBP646        |
|------------------|-----------|----------------|----------------|----------------|----------------|-----------------|----------------|---------------|
| GluN1/<br>GluN2A | G + E     | 100.0          | 100.0          | 100.0          | 100.0          | 100.0           | 100.0          | 100.0         |
|                  | TC        | $-2.2 \pm 1.2$ | $2.7 \pm 3.3$  | $0.3 \pm 2.4$  | $-1.0 \pm 2.9$ | $-0.02 \pm 0.3$ | $0.2 \pm 0.2$  | $1.0 \pm 0.1$ |
|                  | TC +<br>G | $4.1 \pm 2.1$  | $7.6 \pm 4.8$  | $3.5 \pm 4.2$  | $7.2 \pm 3.3$  | $0.3 \pm 0.1$   | $0.1 \pm 0.2$  | $0.7 \pm 0.3$ |
|                  | TC +<br>E | $1.8 \pm 1.2$  | $0.03 \pm 1.2$ | $5.0 \pm 2.7$  | $-1.0 \pm 4.1$ | $0.4 \pm 0.9$   | $3.2 \pm 3.1$  | $1.8 \pm 0.6$ |
| GluN1/<br>GluN2D | G + E     | 100.0          | 100.0          | 100.0          | 100.0          | 100.0           | 100.0          | 100.0         |
|                  | TC        | $-1.4 \pm 1.9$ | $0.6 \pm 1.6$  | $-0.3 \pm 0.2$ | $0.1 \pm 0.5$  | $0.1 \pm 0.8$   | $1.4 \pm 2.3$  | $0.6 \pm 0.2$ |
|                  | TC +<br>G | $3.7 \pm 0.7$  | $3.2 \pm 2.1$  | $3.0 \pm 3.0$  | $0.4 \pm 1.3$  | $2.1 \pm 0.8$   | $3.3 \pm 1.7$  | $0.9 \pm 0.3$ |
|                  | TC +<br>E | $1.2 \pm 0.5$  | $-0.7 \pm 0.7$ | $0.7 \pm 0.4$  | $1.6 \pm 0.5$  | $1.8 \pm 0.3$   | $-1.2 \pm 0.7$ | $0.9 \pm 0.3$ |

[0144] In contrast to UBP512, UBP551 (3,5-dihydroxynaphthalene-2-carboxylic acid) inhibited responses at receptors containing GluN2A, GluN2B, or GluN2C subunits and potentiated activity at GluN1/GluN2D receptors (Figure 1B). UBP551 displayed  $IC_{50}$ s of  $9.7 \pm 0.2 \mu M$ ,  $9.4 \pm 0.6$ , and  $15 \pm 6 \mu M$  for receptors containing GluNA-C subunits, respectively, and Hill coefficients of  $1.4 \pm 0.1$ ,  $1.8 \pm 0.2$ ,  $1.2 \pm 0.3$ , with maximal inhibition of  $91 \pm 1.3\%$ ,  $83.9 \pm 7.1\%$ , and  $85.0 \pm 2.3\%$ . Maximal potentiation of GluN1/GluN2D responses was found at a concentration of 100  $\mu M$ ; higher concentrations resulted in reduced potentiating activity.

[0145] A different pattern of potentiation activity was observed for the compound NSC339614 (7-nitro-2-oxa-1,3-diaza-cyclopenta[a]naphthalene-5-sulfonic acid). This compound potentiated responses at both GluN1/GluN2C and GluN1/GluN2D receptors and had weak inhibitory activity at other NMDA receptors (Figure 8A and 8B). The potentiating

activity of NSC339614 did not saturate at 100  $\mu$ M since greater potentiation was observed at the highest dose tested, 300  $\mu$ M. However, the inhibitory activity was the same at 30  $\mu$ M and 300  $\mu$ M for GluN2A and GluN2B-containing receptors, suggesting that occupation at this site by NSC339614 does not fully inhibit receptor function – or that it is offset by a potentiating activity. In two of 15 cells tested, NSC339614 caused a weak inhibition of GluN1/GluN2C and GluN1/GluN2D receptor responses at 100  $\mu$ M and 300  $\mu$ M concentrations instead of potentiation. Thus, the ability of NSC339614 to potentiate GluN1/GluN2C and GluN1/GluN2D receptor responses may be state-dependent and not an intrinsic property of the receptor complex.

[0146] Two compounds, UBP608 (6-bromo-2-oxo-2H-chromene-3-carboxylic acid) and UBP618 (1-bromo-2-hydroxy-6-phenylnaphthalene-3-carboxylic acid) displayed only inhibitory activity when tested against 10  $\mu$ M L-glutamate plus 10  $\mu$ M glycine (Figure 1C, 1D, 6G, and 6H). UBP608 inhibited all NMDA receptors with greatest inhibitory activity at NR2A-containing receptors and least activity at GluN2D-containing receptors (Figure 1D and 6H). UBP608 fully inhibits (maximal inhibition =  $104 \pm 0.6$  %) GluN1/GluN2A responses with an  $IC_{50}$  of  $18.6 \pm 1.4$   $\mu$ M and a Hill coefficient =  $1.08 \pm 0.02$ . Several-fold higher concentrations of UBP608 were required to inhibit GluN1/GluN2B ( $IC_{50}$  =  $90 \pm 4$   $\mu$ M; Hill coefficient =  $1.25 \pm 0.06$ ) and GluN1/GluN2C responses ( $IC_{50}$  =  $68 \pm 9$   $\mu$ M, Hill coefficient =  $1.22 \pm 0.07$ ); GluN2D-containing receptors were least affected with an extrapolated  $IC_{50}$  of  $426 \pm 40$   $\mu$ M, Hill coefficient =  $1.16 \pm 0.1$ ).

[0147] UBP618 was a relatively potent, non-selective inhibitor at NMDA receptors (Figure 1C and 6G). UBP618 inhibited each of the NMDA receptors with a similar potency -  $IC_{50}$ s were GluN1/GluN2A:  $1.8 \pm 0.2$   $\mu$ M, Hill coefficient =  $0.98 \pm 0.07$ , maximal inhibition =  $82.8 \pm 3.9$  %; GluN1/GluN2B:  $2.4 \pm 0.1$   $\mu$ M, Hill coefficient =  $0.94 \pm 0.04$ , maximal inhibition =  $77.2 \pm 2.0$  %; GluN1/GluN2C:  $2.0 \pm 0.08$   $\mu$ M, Hill coefficient =  $0.98 \pm 0.05$ , maximal inhibition =  $78.0 \pm 2.5$  %; and GluN1/GluN2D:  $2.4 \pm 0.3$   $\mu$ M, Hill coefficient =  $1.48 \pm 0.15$ , maximal inhibition =  $77.5 \pm 2.5$  %.

[0148] Whereas NSC339614 preferentially potentiated NMDA receptors containing GluN2C and GluN2D subunits and weakly inhibits the others, UBP710 (9-cyclopropyl-2-carboxyphenanthrene) displayed greater activity in potentiating GluN2A and GluN2B-containing receptors (Figure 1E, 3E, and 3F). UBP710 consistently potentiated responses at receptors containing GluN2A and GluN2B subunits (approximately 50 - 150%) and frequently potentiated responses at GluN2C and GluN2D-containing receptors.

[0149] The structural features of these compounds do not conform to any known group of NMDA receptor antagonists or modulators. Thus, further studies were directed at defining the site of action of UBP512 as an example of an inhibitor and a potentiator. UBP512 is not a competitive antagonist at either the L-glutamate or glycine binding sites. The blockade by 100  $\mu$ M UBP512 could not be overcome by increasing concentrations of glycine (Figure 2C) or L-glutamate (Figure 2D). At the highest doses of L-glutamate in the presence of UBP512, there was a small reduction in receptor activation (Figure 2D). In converse experiments, UBP512 activity was tested with a range of concentrations in the presence of low (10  $\mu$ M) or high (300  $\mu$ M) concentrations of L-glutamate and glycine. High agonist concentrations did not significantly alter UBP512 potency for inhibition (GluN1/GluN2C and GluN1/GluN2D) or potentiation (GluN1/GluN2A) (Figure 2E). GluN1/GluN2C and GluN1/GluN2D receptor responses to high agonist concentrations (300  $\mu$ M L-glutamate / 300  $\mu$ M glycine) were inhibited by UBP512 with  $IC_{50}$ s of  $108 \pm 12$   $\mu$ M and  $53 \pm 6$   $\mu$ M, respectively. However, UBP512 now fully blocked GluN2C- and GluN2D-containing receptor responses ( $104 \pm 8$  % and  $97 \pm 7$  %, respectively), and increased Hill coefficients to near 2 ( $1.8 \pm 0.3$  and  $2.1 \pm 0.5$ , respectively). Increasing agonist concentrations also increased the magnitude of UBP512 potentiation of GluN1/GluN2A receptors (Figure 2E).

[0150] UBP512 does not appear to act as an NMDA receptor ion channel blocker. The ability of UBP512 to inhibit GluN1/GluN2D responses was not voltage-dependent (Figure 2B), suggesting that UBP 512 does not block by binding within the ion channel pore that is exposed to the transmembrane electric field.

[0151]  $Zn^{2+}$  is a high affinity negative modulator of GluN1/GluN2A receptors that binds to the N-terminal regulatory domain (NTD) of GluN2A (22,23). Thus, the selective potentiation of GluN2A-containing receptors could potentially be due to the reversal of  $Zn^{2+}$  inhibition by  $Zn^{2+}$  chelation. However, UBP512 potentiation was not affected by the presence of a potent  $Zn^{2+}$  chelator, nor by the addition of 100 nM  $Zn^{2+}$  (Figure 9A). Conversely, UBP512 addition did not alter the  $EC_{50}$ s for either the high affinity or the low affinity components of buffered (22)  $Zn^{2+}$  inhibition at GluN1/GluN2A receptors (Figure 9A). UBP512 also does not appear to cause potentiation by binding at the  $Zn^{2+}$  binding site, or elsewhere in the NTD, to cause an action opposite to that of  $Zn^{2+}$  binding. Removal of the NTD region of both GluN1 and GluN2 subunits enhances, rather than blocks, UBP512 potentiation of GluN1/GluN2A receptors. Likewise, NTD-deletion of GluN1/GluN2D

receptors does not eliminate UBP512 inhibitory activity, but does reduce UBP512 inhibitory potency a few-fold (Figure 3A).

**[0152]** Since the NTD region is not necessary for UBP512 activity, UBP512 is most likely binding on the remaining extracellular region that comprises the ligand-binding domain – either segment 1 (S2 domain) between the NTD and the first intra-membrane domain (M1) and/or on segment 2 (S2) the extracellular loop between the third (M3) and fourth (M4) intra-membrane domain. UBP512 was tested on GluN2A chimeras containing either the S1 or the S2 domain of GluN2C. GluN2A-containing NMDA receptors with the S1 domain of GluN2C were still potentiated by UBP512, but receptors with the S2 domain of GluN2C were inhibited instead of potentiated by UBP512 (Figure 3B). Thus, the S2 domain is important for the binding and/or the downstream actions of UBP512.

**[0153]** The other negative modulators described here (UBP608, UBP551, UBP618) are also unlikely to be competitive antagonists or partial agonists. UBP608 was the only compound that fully inhibited NMDA receptor responses (Figure 1D). Partial blockade by the other compounds could potentially be explained by partial agonist activity, however, these compounds had no excitatory activity alone or when paired with glycine or L-glutamate (Table 1). Direct testing of competition between agonists (L-glutamate and glycine) and the negative modulators (UBP608, UBP551, UBP618) indicate that these compounds are not competitive inhibitors, but that the L-glutamate and glycine binding sites interact with the modulatory binding site. Interestingly, high agonist concentrations promote a modest potentiating activity by 1 – 10  $\mu$ M of UBP608 and UBP551 at GluN1/GluN2A receptors. Compounds were still active at NMDA receptors lacking the NTD on GluN1/GluN2A or GluN1/GluN2D receptors; both inhibitory and potentiating activities remain after NTD-deletion, but NTD removal alters either the affinity of the drug binding sites or their ability to affect receptor function (Figure 3). This result is consistent with the close allosteric coupling between the NTD, the agonist ligand binding domain, and ion channel gating (24). The other inhibitory modulator's actions (UBP608 and UBP618) were mostly voltage-independent, receptor blockade was similar at -60 mV and +20mV or +40 mV.

**[0154]** Compounds: Synthesized compounds were purified and their structures verified by  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR, and mass spectroscopy. All compounds had elemental analyses where the determined percentages of C, H and N were less than 0.4 % different from theoretical values. Other compounds were obtained from either Sigma or the National Cancer Institute's

Developmental Therapeutics Program Open Chemical Repository <http://dtp.cancer.gov> (NSC339614).

[0155] NMDA receptor constructs: cDNA encoding the NMDAR1a subunit (GluN1a) was a generous gift of Dr. Shigetada Nakanishi (Kyoto, Japan). cDNA encoding the GluN2A, GluN2C and GluN2D were kindly provided by Dr. Peter Seeburg (Heidelberg, Germany) and the GluN2B [5'UTR] cDNA was the generous gift of Drs. Dolan Pritchett and David Lynch (Philadelphia, USA). GluN2A chimeras containing either the S1 (GluN2A<sup>2CS1</sup>) or the S2 domain (GluN2A<sup>2CS2</sup>) of GluN2C were constructed by overlap-extension PCR. In GluN2A<sup>2CS1</sup>, the GluN2C S1 domain, amino acids 352-535, replaced the corresponding sequence in GluN2A. In GluN2A<sup>2CS2</sup>, the region between M3 and M4, GluN2C amino acids 634-795, replaced the corresponding sequence in GluN2A. Constructs were verified by sequencing by the University of Nebraska Medical Center Sequencing Facility. The NTD-deleted NR1 (NR1<sup>ΔNTD</sup>) and the NTD-deleted NR2 constructs (NR2A<sup>ΔNTD</sup> and NR2D<sup>ΔNTD</sup>) were kindly provided by Dr. Bodo Laube (49) and Dr. Pierre Paoletti (50), respectively.

[0156] Plasmids were linearized with Not I (GluN1a, GluN2C, GluN2D, and NR1<sup>ΔNTD</sup>), EcoR I (GluN2A, GluN2A<sup>2CS1</sup>, and GluN2A<sup>2CS2</sup>) or Sal I (GluN2B, NR2A<sup>ΔNTD</sup> and NR2D<sup>ΔNTD</sup>) and transcribed *in vitro* with T7 (GluN1a, GluN2A, GluN2C, GluN2D, GluN2A<sup>2CS1</sup>, and GluN2A<sup>2CS2</sup>), SP6 (NR1<sup>ΔNTD</sup>, NR2A<sup>ΔNTD</sup>, NR2D<sup>ΔNTD</sup> and GluN2B) RNA polymerase using the mMessage mMachine transcription kits (Ambion, Austin, TX, USA).

[0157] NR subunit expression and electrophysiology in Xenopus oocytes: Oocytes from mature female *Xenopus laevis* (Xenopus One, Ann Arbor, MI, USA) were removed and isolated. NMDA receptor subunit RNAs were dissolved in sterile distilled H<sub>2</sub>O. GluN1a and GluN2 RNAs were mixed in a molar ratio of 1:1-3. 50 nl of the final RNA mixture was microinjected (15-30 ng total) into the oocyte cytoplasm. Oocytes were incubated in ND-96 solution at 17°C prior to electrophysiological assay (1-5 days).

[0158] Electrophysiological responses were measured using a standard two-microelectrode voltage clamp (Warner Instruments (Hamden, Connecticut) model OC-725B) designed to provide fast clamp of large cells. The recording buffer contained 116 mM NaCl, 2 mM KCl, 0.3 mM BaCl<sub>2</sub> and 5 mM HEPES, pH 7.4. Response magnitude was determined by the steady plateau response elicited by bath application of 10 μM L-glutamate plus 10 μM glycine at a holding potential of -60 mV unless stated otherwise. Response amplitudes for the four heteromeric complexes were generally between 0.1 to 3 μA. After obtaining a steady-state response to agonist application, test compounds were bath applied (Automate

Scientific 16-channel perfusion system) and the responses were digitized for quantification (Digidata 1440A and pClamp-10, Molecular Devices). Dose-response relationships were fit to a single-site with variable slope (GraphPad Prism, ISI Software, San Diego, CA, USA), using a nonlinear regression to calculate IC<sub>50</sub> or EC<sub>50</sub> and % maximal inhibition.

#### **Naphthoic acid derivative studies**

[0159] **NMDA receptor constructs:** GRIN1a cDNA encoding the NMDAR1a subunit (GluN1a) was a generous gift of Dr. Shigetada Nakanishi (Kyoto, Japan). cDNA encoding the GluN2A, GluN2C and GluN2D subunits (GRIN2A, GRIN2C, and GRIN2D) were kindly provided by Dr. Peter Seeburg (Heidelberg, Germany) and the GRIN2B cDNA was the generous gift of Drs. Dolan Pritchett and David Lynch (Philadelphia, USA). The NTD-deleted GluN1 (GRIN1<sup>ΔNTD</sup>) construct is described elsewhere (49) and the NTD-deleted GluN2 constructs (GRIN2A<sup>ΔNTD</sup> and GRIN2D<sup>ΔNTD</sup>) were kindly provided by Dr. Pierre Paoletti. Plasmids were linearized with Not I (GRIN1a, GRIN2C, GRIN2D, and GRIN1<sup>ΔNTD</sup>), EcoR I (GRIN2A) or Sal I (GRIN2B, GRIN2A<sup>ΔNTD</sup> and GRIN2D<sup>ΔNTD</sup>) and transcribed in vitro with T7 (GRIN1a, GRIN2A, GRIN2C, and GRIN2D) and SP6 (GRIN1<sup>ΔNTD</sup>, GRIN2A<sup>ΔNTD</sup>, GRIN2D<sup>ΔNTD</sup> and GRIN2B) RNA polymerase using the mMessage mMachine transcription kits (Ambion, Austin, TX, USA)

[0160] **GluN subunit expression and electrophysiology in *Xenopus* oocytes:** Oocytes from mature female *Xenopus laevis* (*Xenopus* One, Ann Arbor, MI, USA) were removed and isolated using procedures approved by the University of Nebraska Medical Center's Institutional Animal Care and Use Committee in compliance with the National Institutes of Health guidelines. NMDA receptor subunit RNAs were dissolved in sterile distilled H<sub>2</sub>O. GluN1a and GluN2 RNAs were mixed in a molar ratio of 1:1-3. 50 nl of the final RNA mixture was microinjected (15-30 ng total) into the oocyte cytoplasm. Oocytes were incubated in ND-96 solution for 1-5 days at 17°C prior to electrophysiological assay.

[0161] Electrophysiological responses were measured using a standard two-microelectrode voltage clamp model OC-725B (Warner Instruments, Hamden, Connecticut,) designed to provide fast clamp of large cells. The recording buffer contained 116 mM NaCl, 2 mM KCl, 0.3 mM BaCl<sub>2</sub> and 5 mM HEPES, pH 7.4. Response magnitude was determined by the steady plateau response elicited by bath application of 10 μM L-glutamate plus 10 μM glycine (unless stated otherwise) and held at a membrane potential of -60 mV. Response amplitudes for the four heteromeric complexes were generally between 0.1 to 3 μA. After obtaining a steady-state response to agonist application, test compounds were bath applied

(Automate Scientific 16-channel perfusion system) and the responses were digitized for analysis (Digidata 1440A and pClamp-10, Molecular Devices). Dose-response relationships were fit to a single-site with variable slope (GraphPad Prism, ISI Software), using a nonlinear regression to calculate  $IC_{50}$  and % maximal inhibition. All experiments were performed at least 4 times.  $IC_{50}$  and % maximal inhibition values were compared between drugs using ANOVA followed by a Newman-Keuls multiple comparison test.

**[0162] Compounds:** Structures of compounds synthesized and tested for this report are presented in Figure 4. 1,6-Dibromo-2-hydroxy-3-naphthoic acid (UBP552), 2-amino-1,6-dibromo-3-naphthoic acid (UBP597), and 2-amino-6-bromo-3-naphthoic acid (UBP606) were synthesized according to literature procedures (60,61). 1,6-Dibromo-3-naphthoic acid (UBP628), 1,6-dibromo-2-methoxy-3-naphthoic acid (UBP704), 2-hydroxy-1-iodo-3-naphthoic acid (UBP621), 6-bromo-2-hydroxy-1-iodo-3-naphthoic acid (UBP620), 2-hydroxy-6-phenyl-3-naphthoic acid (UBP617), 1-bromo-2-hydroxy-6-phenyl-3-naphthoic acid (UBP618), and 2-hydroxy-1-iodo-6-phenyl-3-naphthoic acid (UBP619) were synthesized and purified. After synthesis and purification, compound structure was verified by  $^1H$  NMR and mass spectroscopy. All novel compounds had elemental analyses in which the determined percentages for C, H, and N were less than 0.4% different from theoretical values. The other compounds were obtained from Sigma-Aldrich [2-naphthoic acid (UBP519), 2-hydroxy-3-naphthoic acid (UBP558), 2,3-dicarboxynaphthalene (UBP575), 6-bromo-2-oxo-2H-chromene-3-carboxylic acid (UBP608)], Alfa Aesar [3-amino-2-naphthoic acid (UBP596)], and Tokyo Chemical Industry UK Ltd [1-bromo-2-hydroxy-3-naphthoic acid (UBP573), 6-bromo-2-hydroxy-3-naphthoic acid (UBP574), 1,6-dibromo-2-naphthol (UBP644)].

**[0163] Compound activity at GluN1/GluN2A-D NMDA receptors** A series of 2-naphthoic acid derivatives were evaluated for their ability to inhibit the activation of GluN1/GluN2A-D NMDA receptors expressed in *Xenopus* oocytes using two-electrode voltage clamp at -60 mV. After obtaining a steady-state response to 10  $\mu M$  L-glutamate and 10  $\mu M$  glycine, the individual test compounds were then co-applied with the agonists.

**[0164]** The structures of the compounds tested are shown in Figure 4. With the exception of UB608, these compounds are derivatives of 2-naphthoic acid (UBP519). In initial studies, the ability of a 100  $\mu M$  concentration of each compound to inhibit NMDA receptor responses was evaluated (Figure 5). 2-Naphthoic acid weakly inhibited activity at GluN2A-containing receptors by approximately 30% and very weakly inhibited the other GluN2-

containing receptors (0 – 5% inhibition). 3-Substitution of 2-naphthoic acid had weak effects on compound activity at NMDA receptors. 2,3-Dicarboxynaphthalene (UBP575) displayed an activity that was generally similar to 2-naphthoic acid (UBP519). However, substituting with a 3-hydroxy group (UBP558) or a 3-amino group (UBP596) led to a small increase in activity at GluN1a/GluN2C and GluN1a/GluN2D receptors and reduced activity at GluN1/GluN2A receptors.

**[0165]** Next, the effect of halogen substitutions at the 1- and 6-positions of 2-hydroxy-3-naphthoic acid was assessed. 1-Bromo substitution (1-bromo-2-hydroxy-3-naphthoic acid, UBP573), enhanced inhibitory activity especially at GluN2C and GluN2D-containing receptors (Figure 5). 6-Bromo substitution (6-bromo-2-hydroxy-3-naphthoic acid, UBP574) enhanced inhibitory activity, with 100  $\mu$ M of compound causing approximately 40% inhibition at each of the 4 GluN2-containing receptors. These effects were at least additive with 100  $\mu$ M of the 1,6-dibromo-2-hydroxy-3-naphthoic acid derivative (UBP552) inhibiting more than 80% of the receptor responses (Figure 5). Dose-response analysis of UBP552 (Figure 6) confirmed that this compound is a relatively potent inhibitor with  $IC_{50}$  values of 3 to 7  $\mu$ M (Table 2) with a weak preference for GluN2D-containing receptors. Hill coefficients for the inhibition of NMDA receptor responses were generally between 1 and 2.

**[0166]** Of the 4 substituents on the naphthalene ring of UBP552, the 3-carboxy group makes the strongest contribution to activity. UBP644, which has the carboxy group substituted by hydrogen, was virtually inactive; 100  $\mu$ M UBP644 inhibited responses by less than 10%. The 2-hydroxy group in UBP552 was also important for high affinity. Substituting a hydrogen (UBP628) or a methoxy group (UBP704) for the 2-hydroxy of UBP552 reduced inhibitory activity (Figure 5). Relative to UBP552, UBP628 had weaker inhibitory activity especially at GluN1/GluN2B, GluN1/GluN2C and GluN1/GluN2D receptors. UBP628 displayed a 33-fold lower affinity for GluN1/GluN2D than did UBP552 but only a 3-fold lower affinity at GluN1/GluN2A (Figure 6, Table 2). Replacement of the hydroxy group by a methoxy group (UBP704) reduced activity equally at all NMDA receptors resulting in approximately 40% inhibition by 100  $\mu$ M of compound.

**[0167]** Since the 3-amino substitution in 3-amino-2-naphthoic acid (UBP596) increased inhibitory activity at all NMDA receptors except GluN1/GluN2A, the effect of halogenation of this structure was evaluated. Mono-bromination (2-amino-6-bromo-3-naphthoic acid, UBP606) and di-bromination (2-amino-1,6-dibromo-3-naphthoic acid, UBP597) increased

inhibitory activity at all NMDA receptors, but not to the extent that was seen for the 2-hydroxy substituted analogues (UBP574 and UBP552, respectively).

**[0168]** Substitution of the 1-bromo group in UBP573 for an iodo group (2-hydroxy-1-iodo-3-naphthoic acid, UBP621) led to an enhancement of NMDA receptor inhibitory activity; 100µM UBP621 inhibited NMDA receptor responses by 60 - 80 %. However, this enhancement in activity by 1-iodo substitution was not seen when activity was already enhanced by bromo- or phenyl-substitution at the 6-position (compare UBP620/UBP552 and UBP619/UBP618). Replacing the 6-bromo group of either UBP574 or UBP552 with a phenyl group, yielding UBP617 and UBP618, respectively, increased affinity for all NMDA receptors. Thus, of the combination of substitutions explored, UBP618 displayed the highest affinity for NMDA receptors and did not discriminate between NMDA receptor subtypes.

**[0169]** The comparison made above between UBP552 and UBP628 suggests that the 2-hydroxy group has a relatively small contribution to UBP552 affinity at GluN1/GluN2A receptors and a greater contribution to affinity at the other NMDA receptors. The compound UBP608, incorporates some of the features of UBP552 but replaces this 2-hydroxy group with an oxygen and eliminates the 1-bromo group by incorporation of a chromene ring. UBP608, like UBP628, displays a weak GluN1/GluN2A selectivity, with an IC<sub>50</sub> of 19 µM for GluN2A-containing receptors and 68 to 426 µM at other NMDA receptors.

Table 2

| Compound            | GluN1/GluN2A              |                           |                            | GluN1/GluN2B              |                            |                           | GluN1/GluN2C              |                           |                           | GluN1/GluN2D     |                           |                  |
|---------------------|---------------------------|---------------------------|----------------------------|---------------------------|----------------------------|---------------------------|---------------------------|---------------------------|---------------------------|------------------|---------------------------|------------------|
|                     | IC <sub>50</sub> (μM)     | % Max. Inh.               | IC <sub>50</sub>           | % Max. Inh.               | IC <sub>50</sub>           | % Max. Inh.               | IC <sub>50</sub>          | % Max. Inh.               | IC <sub>50</sub>          | % Max. Inh.      | IC <sub>50</sub>          | % Max. Inh.      |
| UBP608 <sup>a</sup> | 18.6 ± 1.4                | 106 ± 0.5                 | 89.5 ± 3.5                 | 100 <sup>b</sup>          | 68.3 ± 9.1                 | 100 <sup>b</sup>          | 426 ± 40 <sup>j</sup>     | 100 <sup>b</sup>          | 426 ± 40 <sup>j</sup>     | 100 <sup>b</sup> | 426 ± 40 <sup>j</sup>     | 100 <sup>b</sup> |
| UBP618 <sup>a</sup> | 1.76 ± 0.24 <sup>CH</sup> | 83.0 ± 4.0 <sup>CHi</sup> | 2.44 ± 0.11 <sup>CEH</sup> | 88.0 ± 2.0                | 2.00 ± 0.08 <sup>CEH</sup> | 87.3 ± 2.0 <sup>CHi</sup> | 2.4 ± 0.26 <sup>H</sup>   | 87.3 ± 2.0 <sup>CHi</sup> | 2.4 ± 0.26 <sup>H</sup>   | 92.0 ± 0.7       | 2.4 ± 0.26 <sup>H</sup>   | 92.0 ± 0.7       |
| UBP617              | 11.0 ± 5.2                | 71.5 ± 6.4 <sup>CgH</sup> | 97.8 ± 20.9                | 56.8 ± 5.2 <sup>CHH</sup> | 41.8 ± 8.4 <sup>H</sup>    | 105.5 ± 4.4               | 49.6 ± 6.0 <sup>DH</sup>  | 105.5 ± 4.4               | 49.6 ± 6.0 <sup>DH</sup>  | 98.6 ± 3.2       | 49.6 ± 6.0 <sup>DH</sup>  | 98.6 ± 3.2       |
| UBP619              | 5.48 ± 2.02 <sup>CH</sup> | 78.8 ± 2.5 <sup>CHi</sup> | 5.65 ± 1.10 <sup>CEH</sup> | 82.1 ± 3.1                | 4.95 ± 0.10 <sup>CEH</sup> | 77.3 ± 5.0 <sup>EH</sup>  | 2.8 ± 0.14 <sup>EH</sup>  | 77.3 ± 5.0 <sup>EH</sup>  | 2.8 ± 0.14 <sup>EH</sup>  | 97.0 ± 2.2       | 2.8 ± 0.14 <sup>EH</sup>  | 97.0 ± 2.2       |
| UBP620              | 3.17 ± 0.30 <sup>CH</sup> | 90.5 ± 7.4                | 9.06 ± 1.02 <sup>CEH</sup> | 90.6 ± 10.7               | 5.93 ± 1.56 <sup>CEH</sup> | 96.1 ± 2.3                | 5.36 ± 0.60 <sup>EH</sup> | 96.1 ± 2.3                | 5.36 ± 0.60 <sup>EH</sup> | 107.1 ± 4.3      | 5.36 ± 0.60 <sup>EH</sup> | 107.1 ± 4.3      |
| UBP628              | 19.3 ± 5.9                | 104.3 ± 4.3               | 88.2 ± 25.7                | 84.4 ± 12.5               | 84.1 ± 7.1                 | 103.0 ± 7.1               | 109.7 ± 11.0              | 103.0 ± 7.1               | 109.7 ± 11.0              | 112.4 ± 21.3     | 109.7 ± 11.0              | 112.4 ± 21.3     |
| UBP552              | 6.29 ± 0.88 <sup>CH</sup> | 105.6 ± 4.3               | 7.30 ± 1.21 <sup>CEH</sup> | 108.3 ± 2.0               | 5.04 ± 0.16 <sup>CEH</sup> | 101.5 ± 0.9               | 3.35 ± 0.18 <sup>EH</sup> | 101.5 ± 0.9               | 3.35 ± 0.18 <sup>EH</sup> | 103.6 ± 2.2      | 3.35 ± 0.18 <sup>EH</sup> | 103.6 ± 2.2      |

Compound potency (IC<sub>50</sub> ± s.e.m., μM) at NMDA receptor subtypes and extent of maximal inhibition (% Max. Inh.) ± s.e.m., n ≥ 4.

<sup>a</sup> Compounds UBP608 and UBP618 are shown here for comparison.

<sup>b</sup> % Maximal inhibition constrained to 100% to improve IC<sub>50</sub> estimate

<sup>c-i</sup> statistically different from UBP608 (c, C, C), UBP618 (d, D, D), UBP617 (e, E, E), UBP619 (f, F, F), UBP620 (g, G, G), UBP628 (h, H, H), and UBP552 (i, I, I) with p values < 0.05 (c-i), p < 0.01 (C-I), and p < 0.001 (C-I).

<sup>j</sup> extrapolated value, thus excluded from ANOVA.

[0170] Structural features underlying variations in maximal blockade A feature that distinguishes this class of antagonists from competitive NMDA receptor antagonists is the inability of some of these compounds to fully inhibit agonist responses (while not having partial agonist activity). UBP618 maximally inhibited GluN1/GluN2 receptor responses to 10  $\mu$ M L-glutamate and 10  $\mu$ M glycine by approximately 80 - 90% with GluN1/GluN2A having the lowest % maximal inhibition. As shown in Figure 6 and Table 2, the compounds tested here also differed in their ability to maximally inhibit NMDA receptor responses. Some compounds displayed a lower maximal inhibition at GluN1/GluN2A, GluN1/GluN2B, and GluN1/GluN2C receptors than at GluN1/GluN2D receptors. UBP617 had the lowest % maximal inhibition for both GluN1/GluN2A and GluN1/GluN2B receptors (71% and 57%, respectively) yet fully inhibited GluN1/GluN2C and GluN1/GluN2D receptor responses. The closely related compounds UBP618 and UBP619 also displayed relatively low % maximal inhibition at GluN1/GluN2A and GluN1/GluN2B receptors and displayed the two lowest % maximal inhibition of GluN1/GluN2C receptors. Thus specifically those compounds with a 6-phenyl group were less able to fully inhibit NMDA receptor responses, especially at receptors containing GluN2A, GluN2B and GluN2C subunits. UBP620 was intermediate in the ability to fully inhibit NMDA receptor responses (maximal inhibition of 90% at GluN1/GluN2A and GluN1/GluN2B receptors) while UBP552 was able to fully inhibit all receptor responses.

[0171] The effects of agonist concentration and the NTD on the activity of UBP552 It was discovered that increasing agonist concentration had opposite effects on the antagonist activity of UBP618 at GluN1/GluN2A and GluN1/GluN2D receptors (Figure 2F). In the presence of high agonist (L-glutamate and glycine) concentrations, UBP618 more effectively blocks GluN1/GluN2D receptor responses but more weakly inhibited GluN1/GluN2A receptor responses. It was next investigated whether agonist concentration also alters the activity of an antagonist that fully inhibits NMDA receptor responses. At GluN1/GluN2A receptors, increasing glycine and L-glutamate concentration 30-fold reduced UBP552 inhibitory potency 2-3 fold (from  $6.3 \pm 0.9 \mu\text{M}$  to  $15.5 \pm 1.7 \mu\text{M}$ ,  $p < 0.01$ ) (Figure 7). This, however, does not appear to represent competitive antagonist activity since such an increase in  $\text{IC}_{50}$  value is far less than expected for a competitive antagonist (~25-fold increase). In contrast to these results, increasing L-glutamate concentration from 0.3  $\mu\text{M}$  to 10  $\mu\text{M}$  or 300  $\mu\text{M}$  increased UBP552 inhibitory potency ~ 2-fold (from  $6.3 \pm 0.6 \mu\text{M}$  to  $3.4 \pm 0.2 \mu\text{M}$ ,  $p < 0.05$  and  $3.4 \pm 0.8 \mu\text{M}$ ,  $p < 0.05$ ) at GluN1/GluN2D receptors and caused a ~ 5% increase in maximal inhibition. Thus, UBP552, like UBP618, displays an uncompetitive antagonist

activity at GluN1/GluN2D receptors wherein higher agonist concentration increases antagonist activity while high agonist concentrations cause a small reduction in antagonist potency at GluN1/GluN2A receptors.

[0172] The role of the NTD in UBP552 activity was tested at GluN1/GluN2A and GluN1/GluN2D receptors by comparing wild-type receptors to those in which the NTD had been deleted on both the GluN1 and the GluN2 subunit. UBP552 was still able to inhibit GluN1/GluN2A and GluN1/GluN2D receptor responses in the absence of the NTD (Figure 7). However, NTD deletion increased the potency of UBP552 at inhibiting GluN1/GluN2A receptor responses and decreased the inhibitory potency at GluN1/GluN2D receptors. Thus, the NTD is not necessary for UBP552 activity, but does influence its actions.

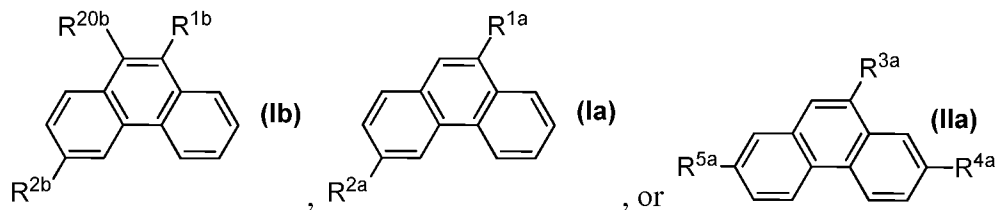
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**What is Claimed:**

1. A compound having a formula (Ib), (Ia), or (IIa):



$R^{1b}$  is iodo, alkyl, alkenyl, alkynyl, alkoxy, amino, cycloalkyl, aryl, heteroaryl, alkyleneamino, alkylene-CO<sub>2</sub>H, alkenylene-CO<sub>2</sub>alkyl, alkylene-OH, alkylene-cycloalkyl, alkylenearyl, alkenylenearyl, CHO, or thioalkyl;

$R^{2b}$  and  $R^{5a}$  are each independently  $R^A$ , alkylene- $R^A$ , NH<sub>2</sub>, C(O)NH-alkylenearyl, C(O)NH-alkyleneheteroaryl, C(O)NH-alkylene- $R^A$ , alkylene-OH, C(O)alkyl, or NO<sub>2</sub>;

$R^{1a}$  is halo;

$R^{2a}$  is C(O)alkylene-NH<sub>2</sub> or C(O)alkylene-heteroaryl;

$R^{3a}$  is H or halo;

$R^{4a}$  is H, heteroaryl, alkenylene-CO<sub>2</sub>H, or alkenylene-CO<sub>2</sub>-alkyl;

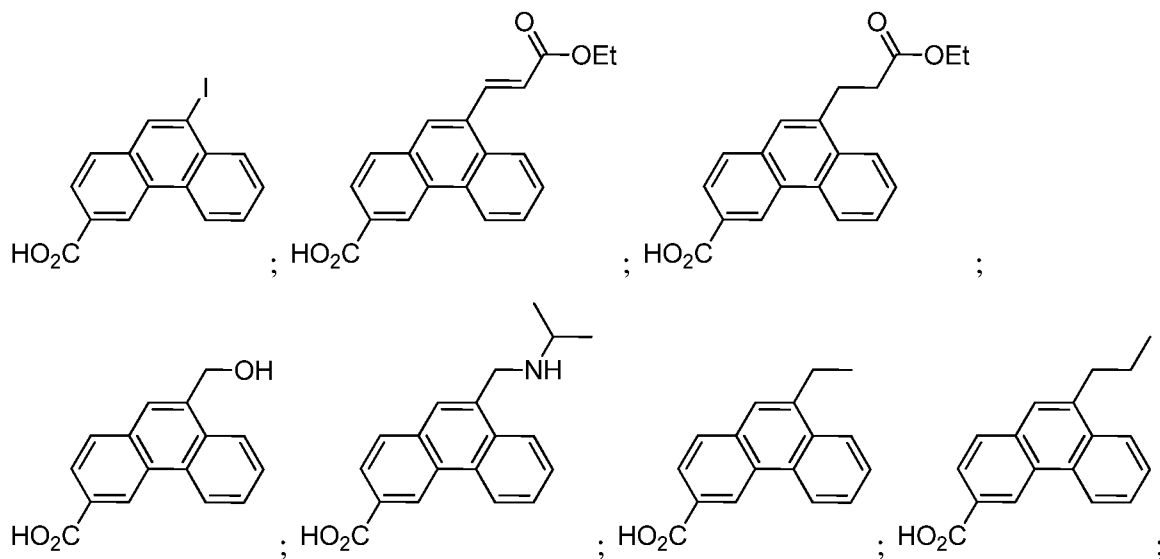
$R^{20b}$  is alkyl, alkenyl, alkynyl, NO<sub>2</sub>, amino, aryl or heteroaryl; and

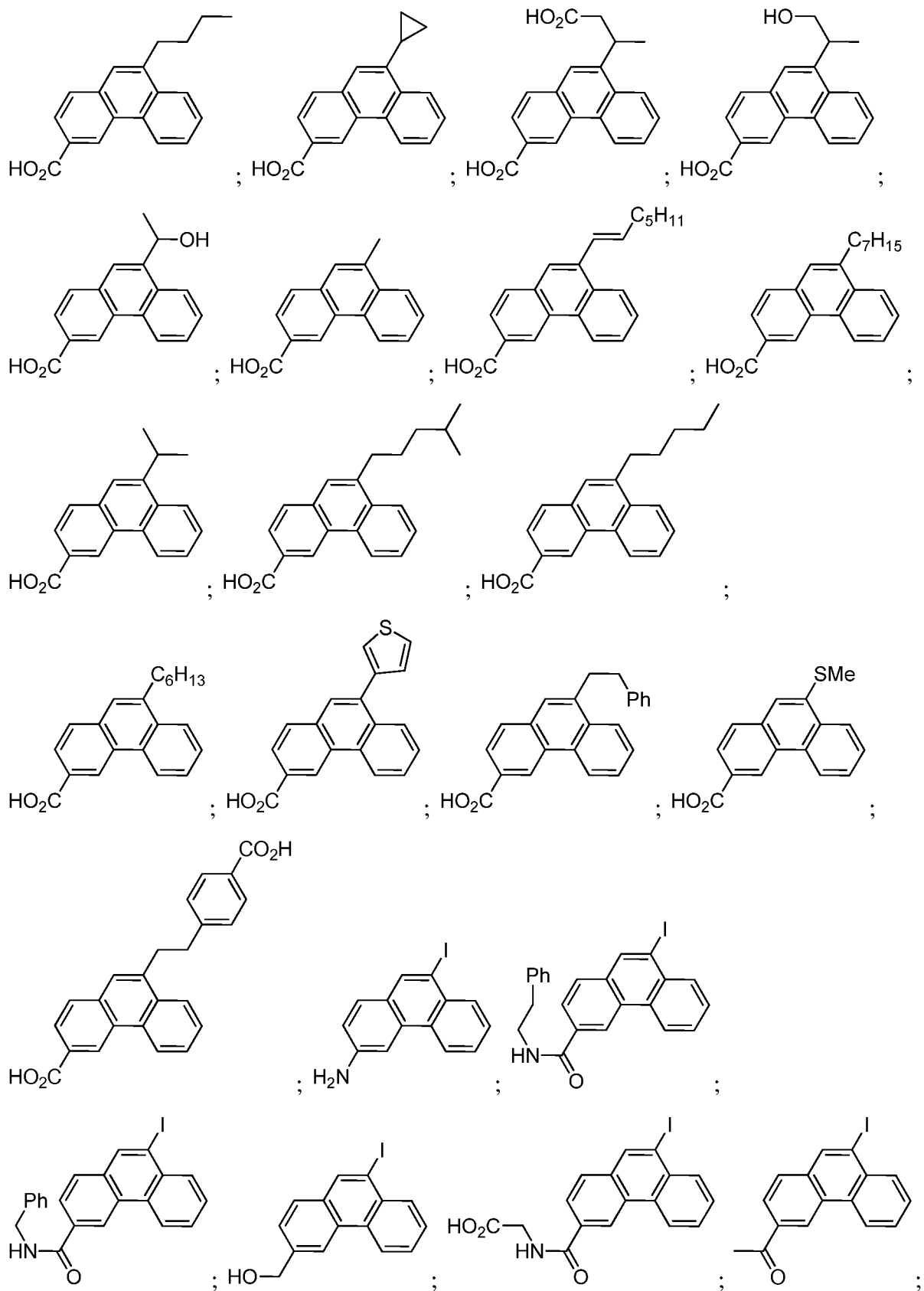
$R^A$  is CO<sub>2</sub>H, CO<sub>2</sub>alkyl, P(O)(OH)(OH), P(O)(OH)(Oalkyl), P(O)(Oalkyl)(Oalkyl), P(O)(alkyl)(OH), SO<sub>2</sub>H, SO<sub>3</sub>H, C(O)NHOH, SO<sub>2</sub>NH<sub>2</sub>, or tetrazole, with the proviso that  $R^{3a}$  and  $R^{4a}$  cannot each be H, or a salt, ester, solvate, tautomer, enantiomer, or hydrate thereof.

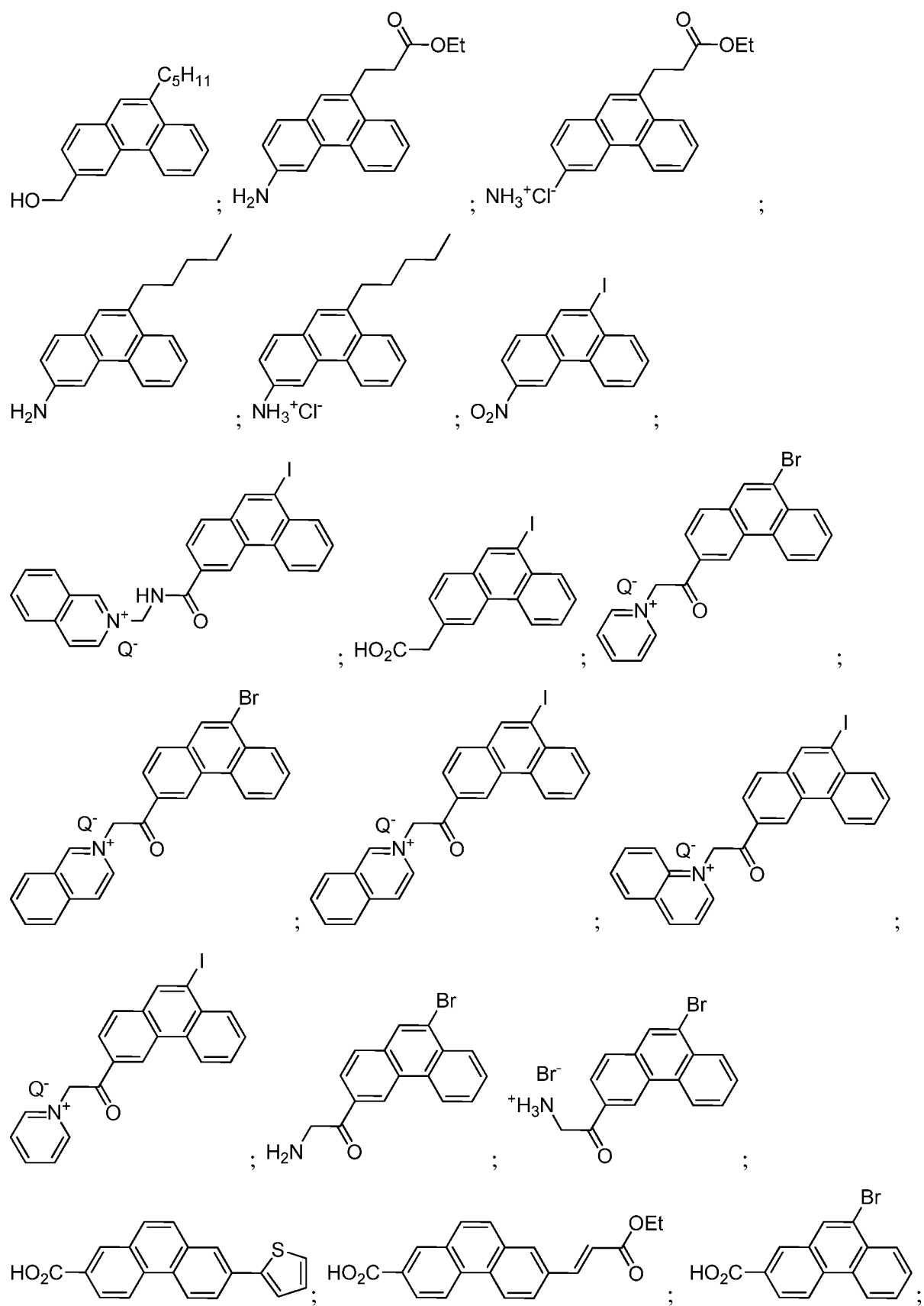
2. The compound of claim 1, wherein  $R^{1b}$  is C<sub>4-20</sub>alkyl.
3. The compound of claim 1, wherein  $R^{1b}$  is methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, t-butyl, pentyl, 2-methylpentyl, hexyl, or heptyl.
4. The compound of claim 1, wherein  $R^{1b}$  is alkenyl.
5. The compound of claim 4, wherein the alkenyl is hept-1-ene-1-yl.
6. The compound of claim 1, wherein  $R^{1b}$  is C<sub>3</sub>-C<sub>8</sub>cycloalkyl or alkylene-C<sub>3</sub>-C<sub>8</sub>cycloalkyl.
7. The compound of claim 1, wherein  $R^{1b}$  is heteroaryl or aryl.
8. The compound of claim 1, wherein  $R^{1b}$  is alkyleneamino.
9. The compound of claim 1, wherein  $R^{1b}$  is alkylene-CO<sub>2</sub>H.

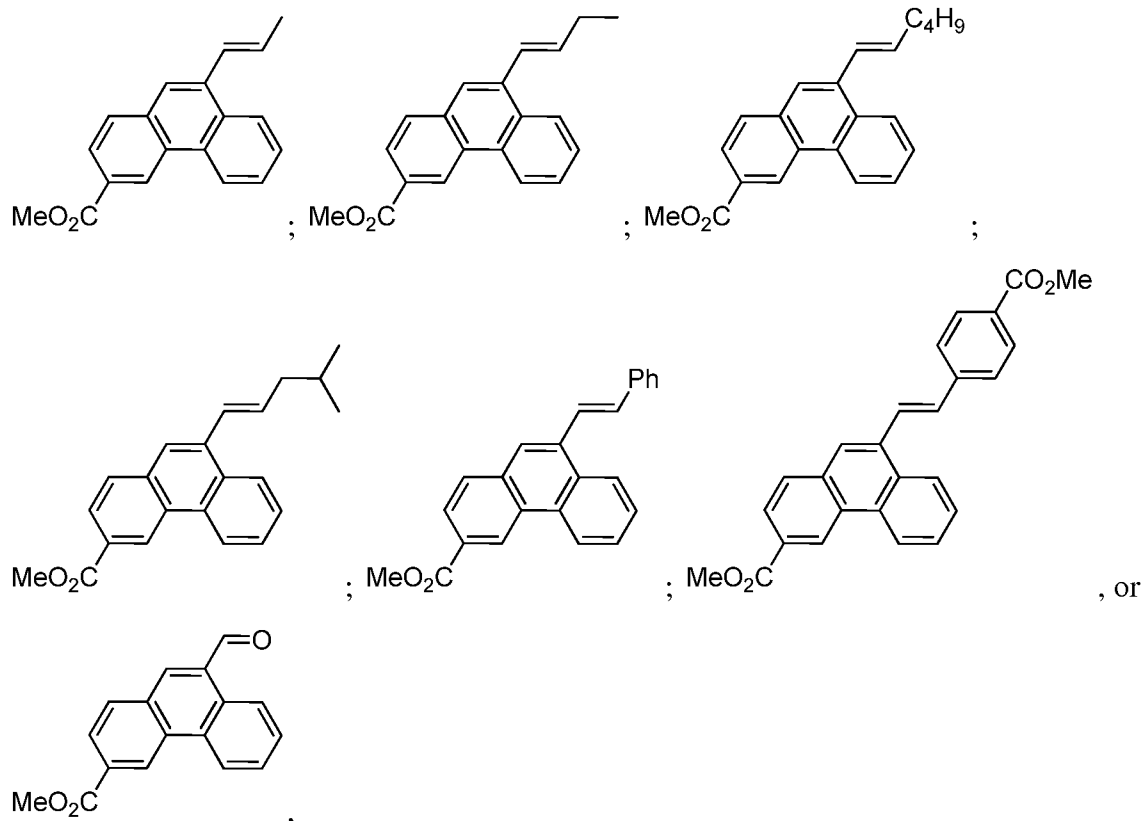
10. The compound of claim 1, wherein  $R^{1b}$  is alkylene-OH.
11. The compound of claim 1, wherein  $R^{1b}$  is alkylenearyl or alkenylenearyl.
12. The compound of claim 1, wherein  $R^{1b}$  is thioalkyl or alkoxy.
13. The compound of any one of claims 1-12, wherein  $R^{2b}$  is  $CO_2H$ .
14. The compound of any one of claims 1-12, wherein  $R^{2b}$  is alkylene- $CO_2H$ .
15. The compound of any one of claims 1-12, wherein  $R^{2b}$  is  $NH_2$ .
16. The compound of any one of claims 1-12, wherein  $R^{2b}$  is  $C(O)NH$ -alkylenearyl.
17. The compound of any one of claims 1-12, wherein  $R^{2b}$  is  $C(O)NH$ -alkyleneheteroaryl.
18. The compound of any one of claims 1-12, wherein  $R^{2b}$  is  $C(O)NH$ -alkylene- $CO_2H$ .
19. The compound of any one of claims 1-12, wherein  $R^{2b}$  is alkylene-OH.
20. The compound of any one of claims 1-12, wherein  $R^{2b}$  is  $C(O)alkyl$ .
21. The compound of any one of claims 1-12, wherein  $R^{2b}$  is  $NO_2$ .
22. The compound of any one of claims 1-12, wherein  $R^{2b}$  is  $P(O)(OH)(OH)$ ,  $P(O)(OH)(Oalkyl)$ ,  $P(O)(Oalkyl)(Oalkyl)$ ,  $P(O)(alkyl)(OH)$ ,  $SO_2H$ ,  $SO_3H$ ,  $C(O)NHOH$ ,  $SO_2NH_2$ , tetrazole, alkylene- $P(O)(OH)(OH)$ , alkylene- $P(O)(OH)(Oalkyl)$ , alkylene- $P(O)(Oalkyl)(Oalkyl)$ , alkylene- $P(O)(alkyl)(OH)$ , alkylene- $SO_2H$ , alkylene- $SO_3H$ , alkylene- $C(O)NHOH$ , alkylene- $SO_2NH_2$ , alkylene-tetrazole,  $C(O)NH$ -alkylene- $P(O)(OH)(OH)$ ,  $C(O)NH$ -alkylene- $P(O)(OH)(Oalkyl)$ ,  $C(O)NH$ -alkylene- $P(O)(Oalkyl)(Oalkyl)$ ,  $C(O)NH$ -alkylene- $P(O)(alkyl)(OH)$ ,  $C(O)NH$ -alkylene- $SO_2H$ ,  $C(O)NH$ -alkylene- $SO_3H$ ,  $C(O)NH$ -alkylene- $C(O)NHOH$ ,  $C(O)NH$ -alkylene- $SO_2NH_2$ , or  $C(O)NH$ -alkylene-tetrazole.
23. The compound of claim 1, wherein  $R^{1a}$  is bromo.
24. The compound of claim 1, wherein  $R^{1a}$  is iodo.
25. The compound of any one of claims 1, 23, and 24, wherein  $R^{2a}$  is  $C(O)$ -alkylene- $NH_2$ .
26. The compound of any one of claims 1, 23, and 24, wherein  $R^{2a}$  is  $C(O)$ -alkylene-heteroaryl.

27. The compound of claim 1, wherein R<sup>3a</sup> is bromo.
28. The compound of claim 1, wherein R<sup>3a</sup> is iodo.
29. The compound of claim 1, wherein R<sup>4a</sup> is heteroaryl.
30. The compound of claim 1, wherein R<sup>4a</sup> is alkenylene-CO<sub>2</sub>H.
31. The compound of claim 1, wherein R<sup>4a</sup> is alkenylene-CO<sub>2</sub>-alkyl.
32. The compound of any one of claims 1 and 27-31, wherein R<sup>5a</sup> is CO<sub>2</sub>H.
33. The compound of any one of claims 1 and 27-31, wherein R<sup>5a</sup> is  
P(O)(OH)(OH), P(O)(OH)(Oalkyl), P(O)(Oalkyl)(Oalkyl), P(O)(alkyl)(OH), SO<sub>2</sub>H, SO<sub>3</sub>H,  
C(O)NHOH, SO<sub>2</sub>NH<sub>2</sub>, tetrazole, alkylene-P(O)(OH)(OH), alkylene-P(O)(OH)(Oalkyl),  
alkylene-P(O)(Oalkyl)(Oalkyl), alkylene-P(O)(alkyl)(OH), alkylene-SO<sub>2</sub>H, alkylene-SO<sub>3</sub>H,  
alkylene-C(O)NHOH, alkylene-SO<sub>2</sub>NH<sub>2</sub>, alkylene-tetrazole, C(O)NH-alkylene-  
P(O)(OH)(OH), C(O)NH-alkylene-P(O)(OH)(Oalkyl), C(O)NH-alkylene-  
P(O)(Oalkyl)(Oalkyl), C(O)NH-alkylene-P(O)(alkyl)(OH), C(O)NH-alkylene-SO<sub>2</sub>H,  
C(O)NH-alkylene-SO<sub>3</sub>H, C(O)NH-alkylene-C(O)NHOH, C(O)NH-alkylene-SO<sub>2</sub>NH<sub>2</sub>, or  
C(O)NH-alkylene-tetrazole.
34. The compound of any one of claims 7, 17, 26, and 29, wherein the heteroaryl  
is thienyl, furyl, pyridyl, quinolyl, isoquinolyl, indolyl, triazinyl, triazolyl, isothiazolyl,  
isoxazolyl, imidazolyl, benzothiazolyl, pyrazinyl, pyrimidinyl, thiazolyl, or thiadiazolyl
35. The compound of claim 1, selected from



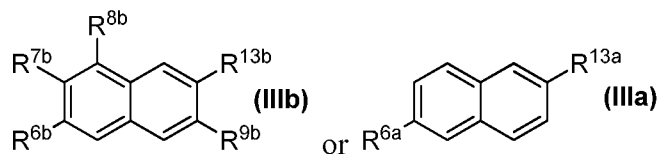






wherein Q is a pharmaceutically acceptable anion.

36. A compound having a formula (IIIb) or (IIIa):



wherein

R<sup>6b</sup> is R<sup>A</sup> or alkylene-R<sup>A</sup>;

R<sup>7b</sup> is OH, alkoxy, or CO<sub>2</sub>H;

R<sup>8b</sup> is H, halo, or C<sub>4</sub>-C<sub>20</sub>alkyl;

R<sup>9b</sup> is halo, alkenyl, aryl, or alkyl;

R<sup>13b</sup> is H, C<sub>4</sub>-C<sub>20</sub>alkyl, alkenyl, aryl, heteroaryl, alkenylenearyl, or alkenylenearyl;

R<sup>13a</sup> is C<sub>4</sub>-C<sub>20</sub>alkyl, alkenyl, alkenylene-CO<sub>2</sub>H, alkenylene-CO<sub>2</sub>alkyl, O-alkylene-CO<sub>2</sub>alkyl, or alkenylenearyl;

R<sup>6a</sup> is R<sup>A</sup>, alkylene-R<sup>A</sup>, or alkylene-OH;

R<sup>A</sup> is CO<sub>2</sub>H, P(O)(OH)(OH), P(O)(OH)(Oalkyl), P(O)(Oalkyl)(Oalkyl), P(O)(alkyl)(OH), SO<sub>2</sub>H, SO<sub>3</sub>H, C(O)NHOH, SO<sub>2</sub>NH<sub>2</sub>, or tetrazole;

with the proviso that when R<sup>13a</sup> is C<sub>4</sub>-C<sub>6</sub>alkyl, R<sup>6a</sup> is not CO<sub>2</sub>H or SO<sub>3</sub>H, and when R<sup>7b</sup>, R<sup>8b</sup>,

and R<sup>9b</sup> are each H and R<sup>13b</sup> is C<sub>4</sub>-C<sub>6</sub>alkyl, R<sup>6b</sup> is not CO<sub>2</sub>H or SO<sub>3</sub>H, or a salt, ester, solvate, tautomer, enantiomer, or hydrate thereof.

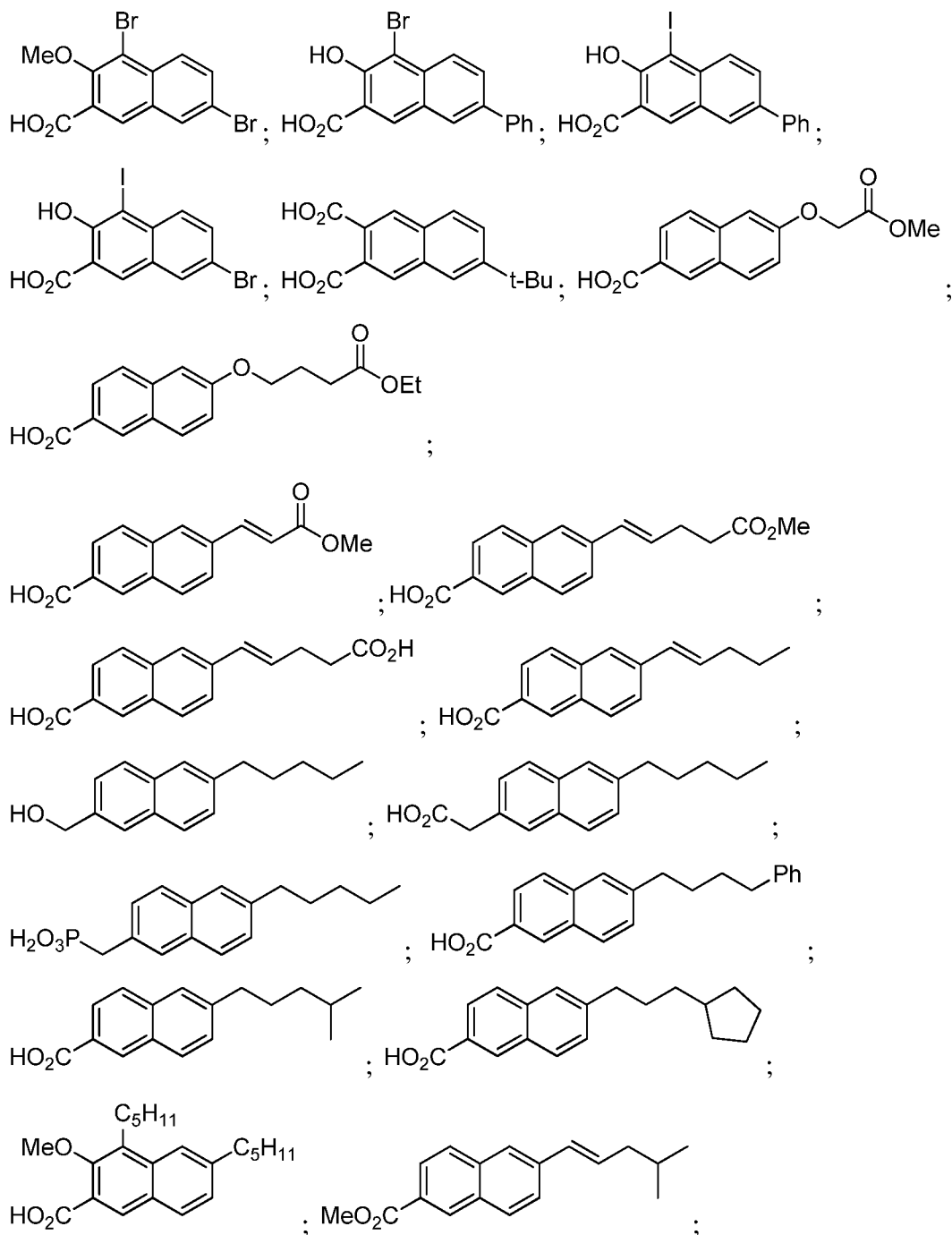
37. The compound of claim 36, wherein R<sup>7b</sup> is OH.
38. The compound of claim 36, wherein R<sup>7b</sup> is alkoxy.
39. The compound of claim 36, wherein R<sup>7b</sup> is CO<sub>2</sub>H.
40. The compound of any one of claims 36-39, wherein R<sup>8b</sup> is H.
41. The compound of any one of claims 36-39, wherein R<sup>8b</sup> is bromo.
42. The compound of any one of claims 36-39, wherein R<sup>8b</sup> is iodo.
43. The compound of any one of claims 36-42, wherein R<sup>9b</sup> is bromo.
44. The compound of any one of claims 36-42, wherein R<sup>9b</sup> is phenyl.
45. The compound of any one of claims 36-42, wherein R<sup>9b</sup> is t-butyl.
46. The compound of any one of claims 36-45, wherein R<sup>6b</sup> is CO<sub>2</sub>H.
47. The compound of any one of claims 36-45, wherein R<sup>6b</sup> is P(O)(OH)(OH), P(O)(OH)(Oalkyl), P(O)(Oalkyl)(Oalkyl), P(O)(alkyl)(OH), SO<sub>2</sub>H, SO<sub>3</sub>H, C(O)NHOH, SO<sub>2</sub>NH<sub>2</sub>, tetrazole, alkylene-P(O)(OH)(OH), alkylene-P(O)(OH)(Oalkyl), alkylene-P(O)(Oalkyl)(Oalkyl), alkylene-P(O)(alkyl)(OH), alkylene-SO<sub>2</sub>H, alkylene-SO<sub>3</sub>H, alkylene-C(O)NH<sub>2</sub>, or alkylene-SO<sub>2</sub>NH<sub>2</sub>, alkylene-tetrazole.
48. The compound of claim 35, wherein R<sup>6a</sup> is CO<sub>2</sub>H.
49. The compound of claim 35, wherein R<sup>6a</sup> is CH<sub>2</sub>CO<sub>2</sub>H.
50. The compound of claim 35, wherein R<sup>6a</sup> is alkylene-PO<sub>3</sub>H<sub>2</sub>.
51. The compound of claim 35, wherein R<sup>6a</sup> is P(O)(OH)(OH), P(O)(OH)(Oalkyl), P(O)(Oalkyl)(Oalkyl), P(O)(alkyl)(OH), SO<sub>2</sub>H, SO<sub>3</sub>H, C(O)NHOH, SO<sub>2</sub>NH<sub>2</sub>, tetrazole, alkylene-P(O)(OH)(OH), alkylene-P(O)(OH)(Oalkyl), alkylene-P(O)(Oalkyl)(Oalkyl), alkylene-P(O)(alkyl)(OH), alkylene-SO<sub>2</sub>H, alkylene-SO<sub>3</sub>H, alkylene-C(O)NHOH, or alkylene-SO<sub>2</sub>NH<sub>2</sub>, alkylene-tetrazole.
52. The compound of any one of claims 35 and 47-50, wherein R<sup>13a</sup> is C<sub>4</sub>-C<sub>10</sub>alkyl.
53. The compound of any one of claims 35 and 47-50, wherein R<sup>13a</sup> is alkenylene-CO<sub>2</sub>H.

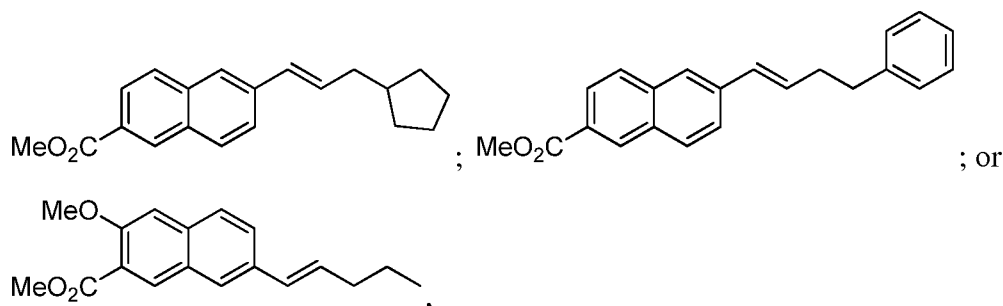
54. The compound of any one of claims 35 and 47-50, wherein R<sup>13a</sup> is alkenylene-CO<sub>2</sub>alkyl.

55. The compound of any one of claims 35 and 47-50, wherein R<sup>13a</sup> is O-alkylene-CO<sub>2</sub>alkyl.

56. The compound of any one of claims 35 and 47-50, wherein R<sup>13a</sup> is alkylenearyl.

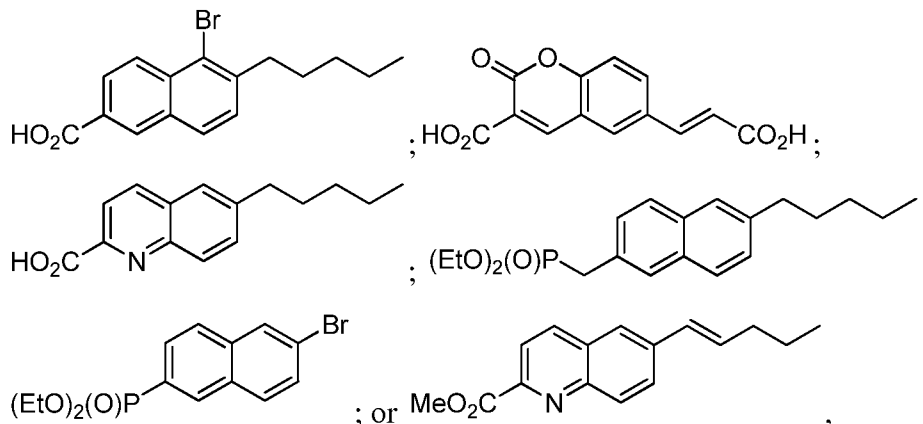
57. The compound of claim 35 selected from





or a salt, ester, solvate, tautomer, enantiomer, or hydrate thereof.

58. A compound selected from



or a salt, ester, solvate, tautomer, enantiomer, or hydrate thereof.

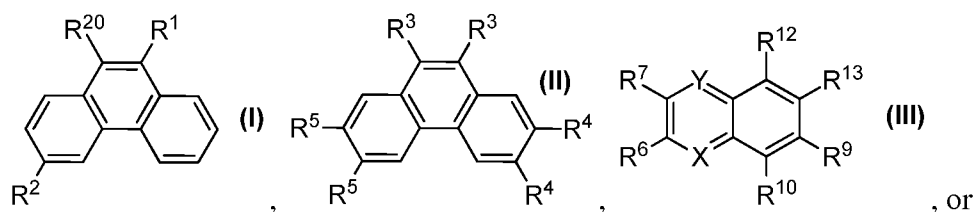
59. The compound of any one of claims 1-58, wherein the compound is a salt.

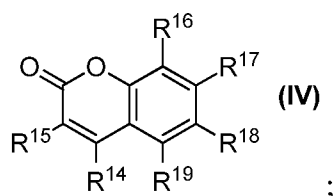
60. A composition comprising the compound of any one of claims 1-59 and a carrier, excipient, diluent, or combination thereof.

61. The composition of claim 60, further comprising one or more second therapeutic agents.

62. A method of modulating the activity of an NMDA receptor comprising contacting the NMDA receptor with one or more compounds of any one of claims 1-59 or the composition of claim 60 or 61.

63. A method of modulating the activity of an NMDA receptor comprising contacting the NMDA receptor with a compound of any one of formulae (I)-(IV):





wherein

each  $R^1$  and  $R^{20}$  is independently H, halo, alkyl, alkenyl, alkynyl, alkoxy, amino, cycloalkyl, aryl, heteroaryl, alkyleneamino,  $\text{CO}_2\text{H}$ , alkylene- $\text{CO}_2\text{H}$ , alkylene- $\text{CO}_2$ alkyl, alkylene-OH, alkylene-cycloalkyl, alkylenearyl, alkylenearyl, CHO,  $\text{NO}_2$ , or thioalkyl;

$R^2$  is H, halo,  $R^A$ , alkylene- $R^A$ ,  $\text{NH}_2$ ,  $\text{C}(\text{O})\text{NH}$ -alkylenearyl,  $\text{C}(\text{O})\text{NH}$ -alkyleneheteroaryl,  $\text{C}(\text{O})\text{NH}$ -alkylene- $R^A$ , alkylene-OH,  $\text{C}(\text{O})$ alkyl,  $\text{C}(\text{O})$ alkylene-heteroaryl, or  $\text{NO}_2$ ,

each  $R^3$  is independently H, alkyl, alkenyl, alkynyl, alkylenearyl, alkylene-cycloalkyl, OH, or halo;

each  $R^4$  is independently H, halo, alkyl, alkenyl, alkynyl, alkylenearyl, alkylene-cycloalkyl, heteroaryl, alkenylene- $\text{CO}_2\text{H}$ , or alkenylene- $\text{CO}_2$ -alkyl,

each  $R^5$  is independently H,  $R^A$ , alkylene- $R^A$ ,  $\text{NH}_2$ ,  $\text{C}(\text{O})\text{NH}$ -alkylenearyl,  $\text{C}(\text{O})\text{NH}$ -alkyleneheteroaryl,  $\text{C}(\text{O})\text{NH}$ -alkylene- $R^A$ , alkylene-OH,  $\text{C}(\text{O})$ alkyl,  $\text{C}(\text{O})$ alkylene-heteroaryl, or  $\text{NO}_2$ ;

$R^6$  is H,  $R^A$ , alkylene- $R^A$ , alkenylene- $R^A$ , OH, alkylene-OH, or amino;

$R^7$  is H, OH, alkoxy,  $\text{CO}_2\text{H}$ , or amino;

Y is N or  $\text{CR}^8$ ;

$R^8$  is H, halo, OH, alkyl, or alkoxy;

$R^9$  is H, halo, OH, alkenyl, aryl, or alkyl;

$R^{10}$  is H, OH, alkyl, or halo;

or  $R^9$  and  $R^{10}$  together form an optional aromatic ring;

X is N or  $\text{CR}^{11}$ ;

$R^{11}$  is H, halo, OH, alkyl, alkoxy, or  $\text{CO}_2\text{H}$ ;

$R^{12}$  is H, OH, alkyl, alkoxy, amino, or halo;

$R^{13}$  is H, halo, alkyl, alkenyl, OH, alkylene-OH, amino, alkoxy,  $\text{CO}_2\text{H}$ ,  $\text{CO}_2$ alkyl,  $\text{OC}(\text{O})$ alkyl, aryl, heteroaryl, O-alkylenearyl, alkylenearyl, alkenylenearyl, alkenylene- $\text{CO}_2\text{H}$ , alkenylene- $\text{CO}_2$ alkyl, or O-alkylene- $\text{CO}_2$ alkyl;

or  $R^{12}$  and  $R^{13}$  together form an optional aromatic ring;

$R^{14}$  is H, alkyl, alkenyl, cycloalkyl, heteroaryl, alkyleneamino,  $\text{CO}_2\text{H}$ , alkylene- $\text{CO}_2\text{H}$ , alkylene-OH, alkylenearyl, thioalkyl, aryl, alkynyl, alkylene-cycloalkyl, or halo;

$R^{15}$  is  $R^A$ ;

R<sup>16</sup> is H or halo;

R<sup>17</sup> is H, OH, amino, or alkoxy;

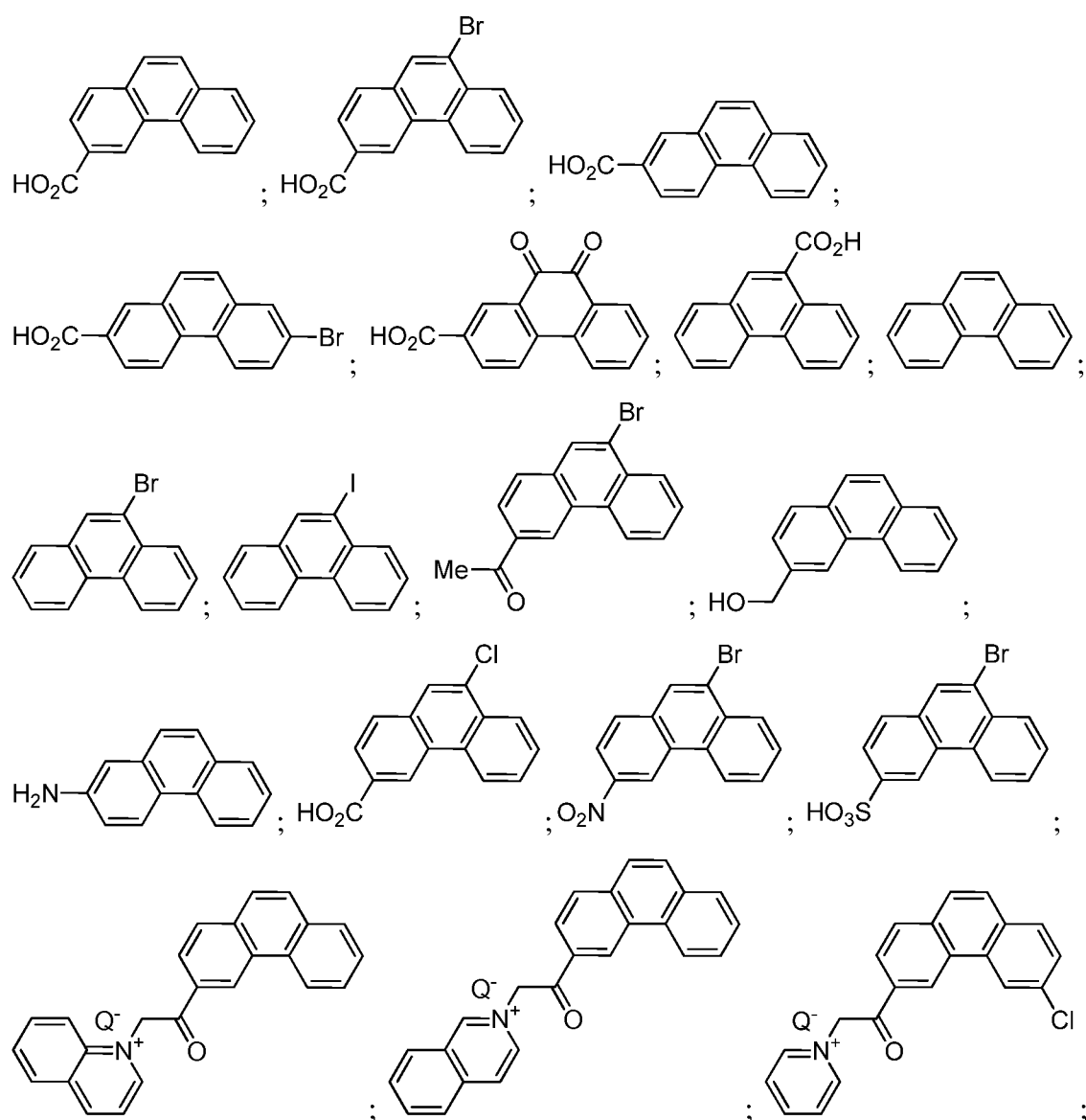
R<sup>18</sup> is H or halo;

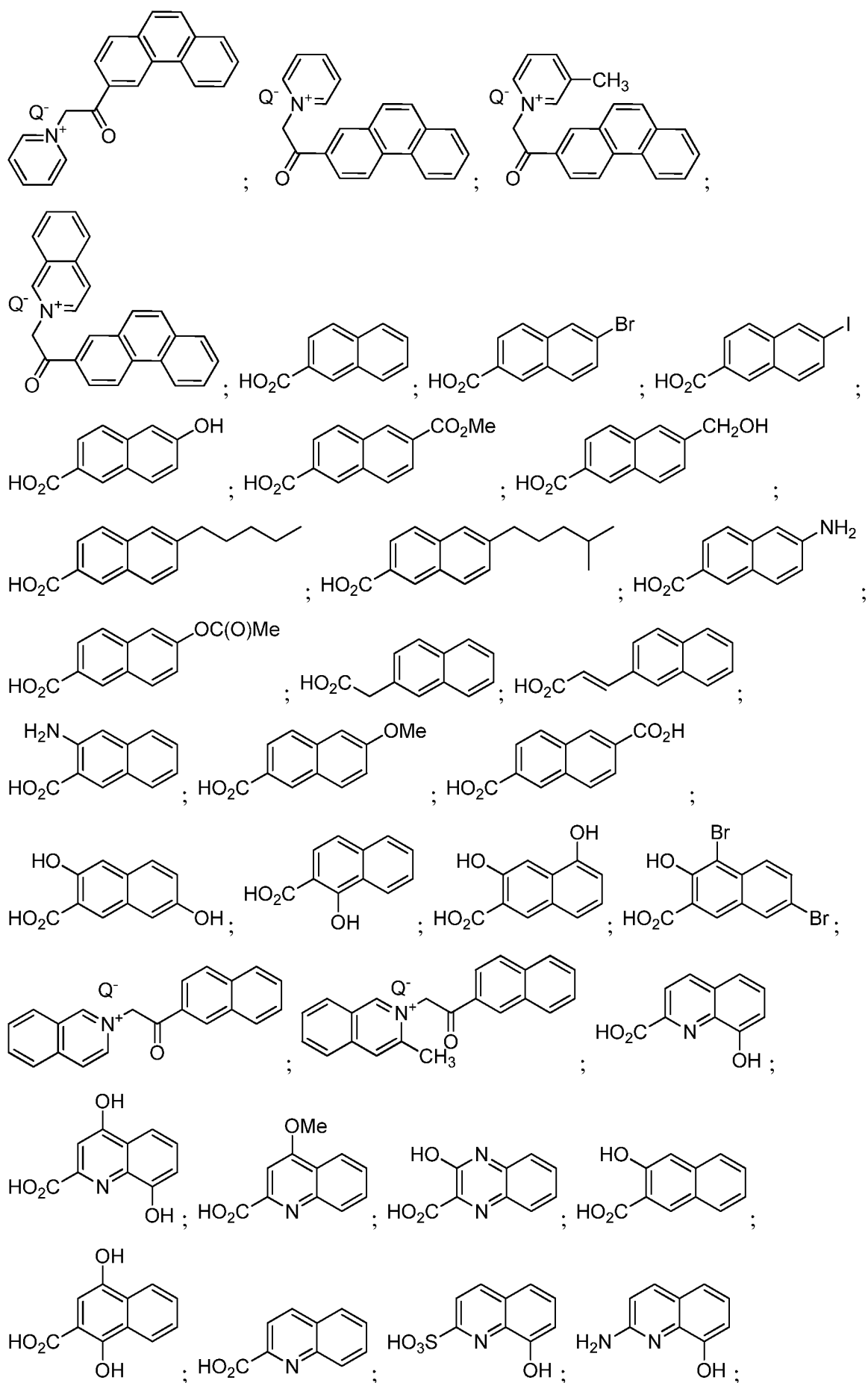
R<sup>19</sup> is H or halo;

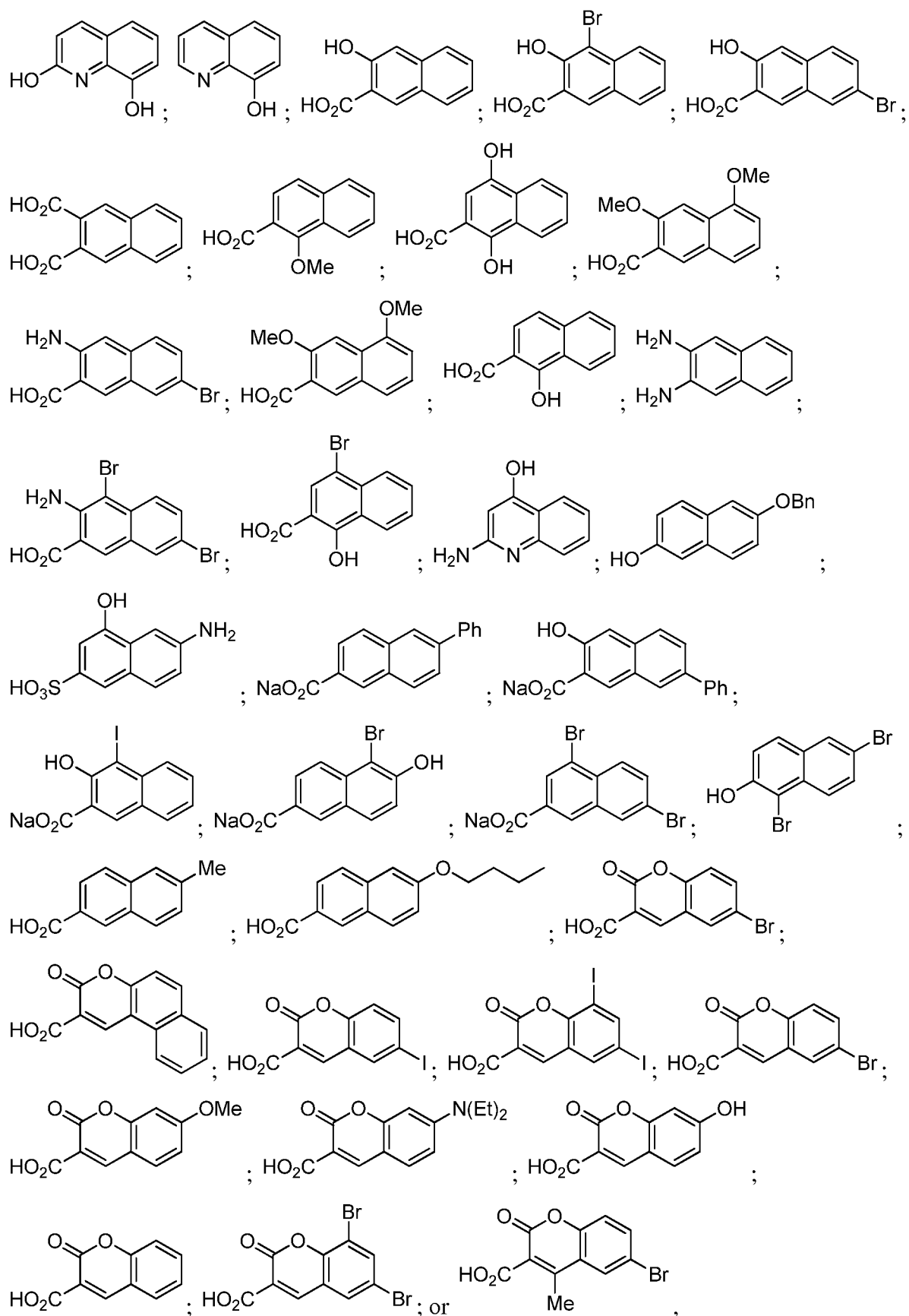
or R<sup>18</sup> and R<sup>19</sup> together form an optional aromatic ring; and

R<sup>A</sup> is CO<sub>2</sub>H, CO<sub>2</sub>alkyl, P(O)(OH)(OH), P(O)(OH)(Oalkyl), P(O)(Oalkyl)(Oalkyl), P(O)(alkyl)(OH), P(O)(alkyl)(OH), SO<sub>2</sub>H, SO<sub>3</sub>H, C(O)NHOH, SO<sub>2</sub>NH<sub>2</sub>, or tetrazole, or a salt, ester, solvate, tautomer, enantiomer, or hydrate thereof.

64. The method of claim 63, wherein the compound is selected from



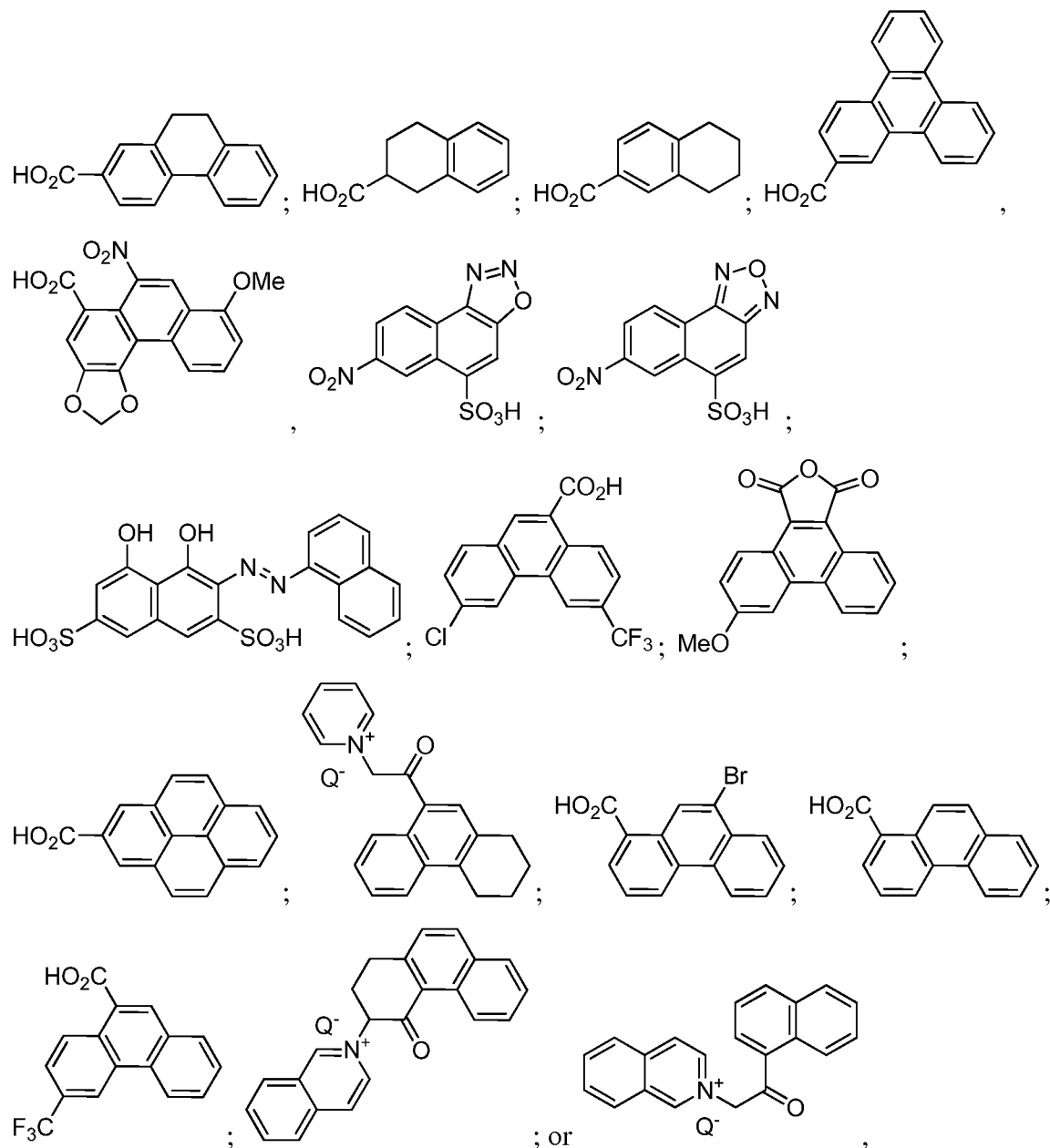




wherein Q is a pharmaceutically acceptable anion,

or a salt, ester, solvate, tautomer, enantiomer, or hydrate thereof.

65. A method of modulating the activity of an NMDA receptor comprising contacting the NMDA receptor with a compound selected from



or a salt, ester, solvate, tautomer, enantiomer, or hydrate thereof.

66. The method of any one of claims 62-65, wherein the compound interacts with the NMDA receptor at an allosteric site on the NMDA receptor.

67. The method of claim 66, wherein the compound does not compete for NMDA receptor binding with L-glutamate, glycine, or both.

68. The method of any one of claims 62-67, wherein the NMDA receptor comprises NR2A, NR2B, NR2C, NR2D, or a combination thereof.

69. The method of claim 68, wherein the NMDA receptor further comprises NR1, NR3A, NR3B, or a combination thereof.

70. The method of any one of claims 62-68, wherein the compound selectively modulates NR2A.

71. The method of any one of claims 62-68, wherein the compound selectively modulates NR2B.

72. The method of any one of claims 62-68, wherein the compound selectively modulates NR2C.

73. The method of any one of claims 62-68, wherein the compound selectively modulates NR2D.

74. The method of any one of claims 62-68, wherein the compound (a) increases NR2A activity and (b) decreases activity of NR2C, NR2D, or both.

75. The method of any one of claims 62-73, wherein the compound decreases the NMDA receptor activity.

76. The method of any one of claims 62-73, wherein the compound increases the NMDA receptor activity.

77. The method of any one of claims 62-76, further comprising contacting the NMDA receptor with a second therapeutic agent.

78. The method of claim 77, wherein the second therapeutic agent is a mGluR2 modulator, mGluR3 modulator, mGluR5 modulator, or tissue plasminogen activator (TPA).

79. The method of claim 78, wherein the second therapeutic agent is a TPA and the compound decreases NR2D activity.

80. The method of any one of claims 62-79, wherein contacting comprises administering the compound to a subject.

81. The method of claim 80, wherein the subject suffers from an NMDA receptor modulated disorder.

82. The method of claim 81, wherein the NMDA receptor modulated disorder is a psychological disorder, post traumatic stress disorder, epilepsy, drug addiction, alcohol addiction, mood disorder, stroke, pain, a pain-related disorder, a prion disease, neurodegenerative disorder, dementia, HIV-related dementia, or a combination thereof.

83. The method of claim 82, wherein the neurodegenerative disorder is Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, ALS, Creutzfeldt-Jakob Disease, or a combination thereof.
84. The method of claim 82, wherein the psychological disorder is schizophrenia.
85. The method of claim 80, wherein the compound enhances cognitive function in the subject.
86. The method of claim 80 or 85, wherein the subject suffers from a traumatic brain injury.
87. The method of claim 80, wherein the subject suffers from a narcotic-related disorder.
88. The method of any one of claims 80-87, wherein the subject is a mammal.
89. The method of claim 88, wherein the subject is human.

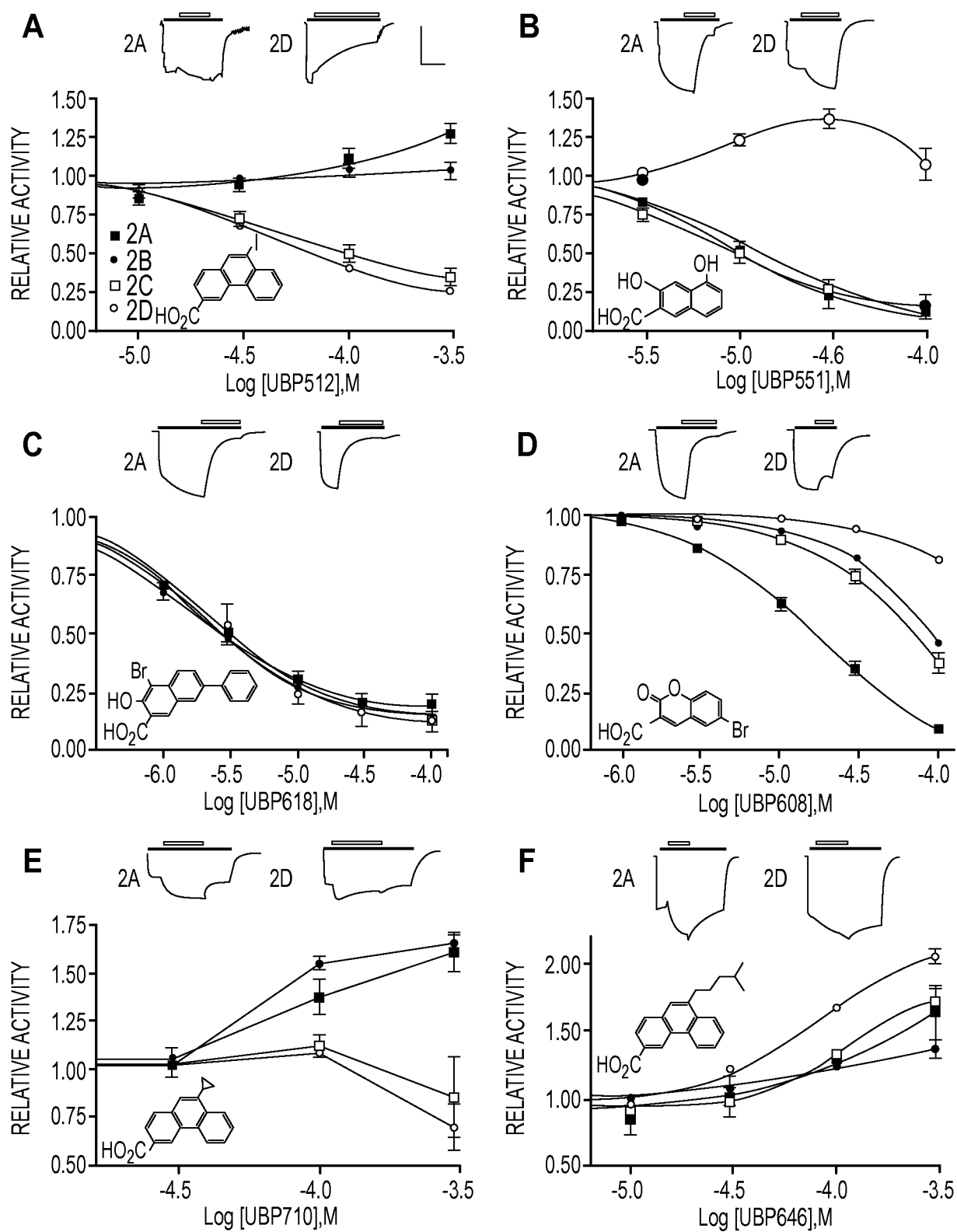


FIGURE 1

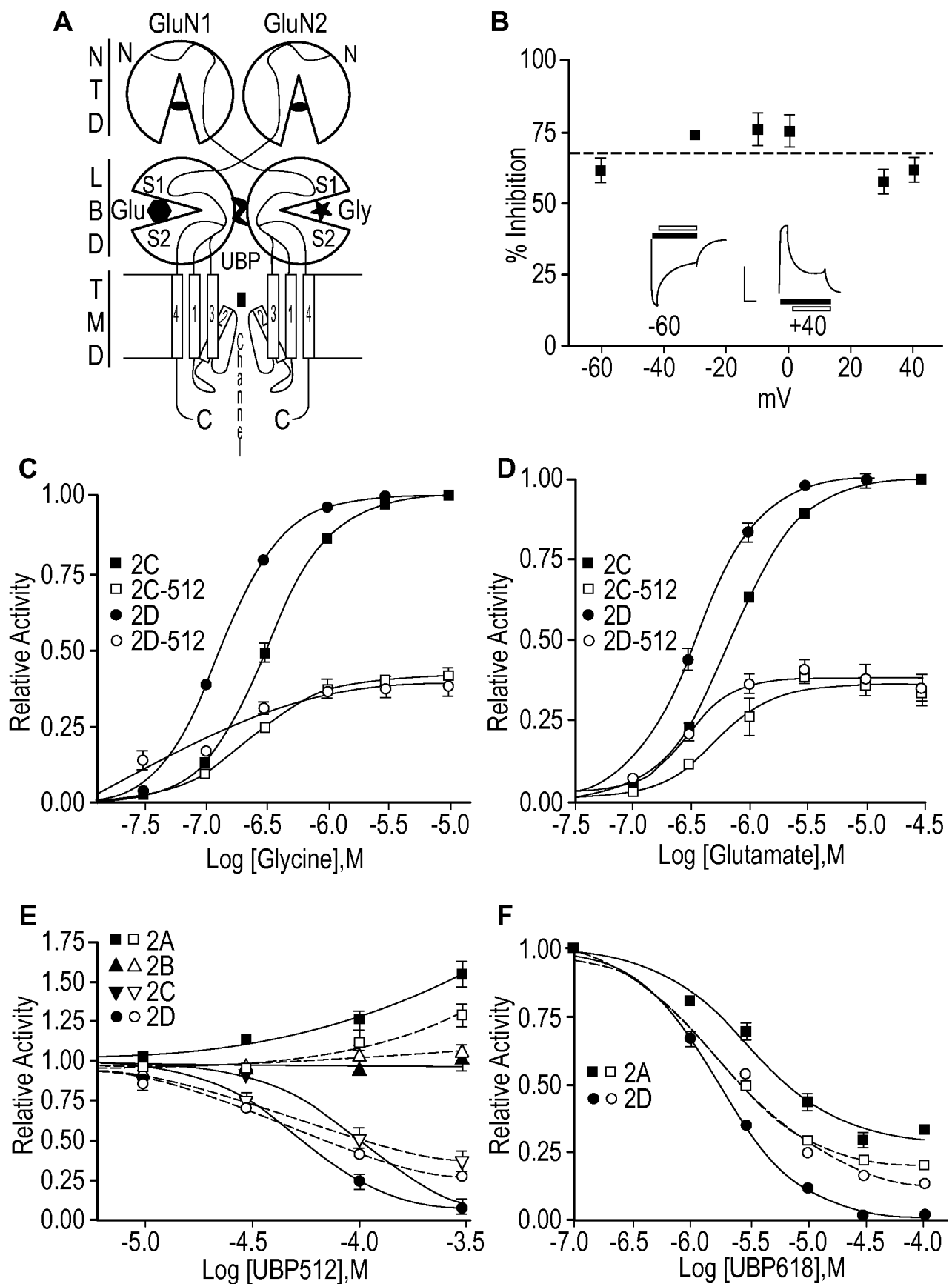


FIGURE 2

SUBSTITUTE SHEET (RULE 26)

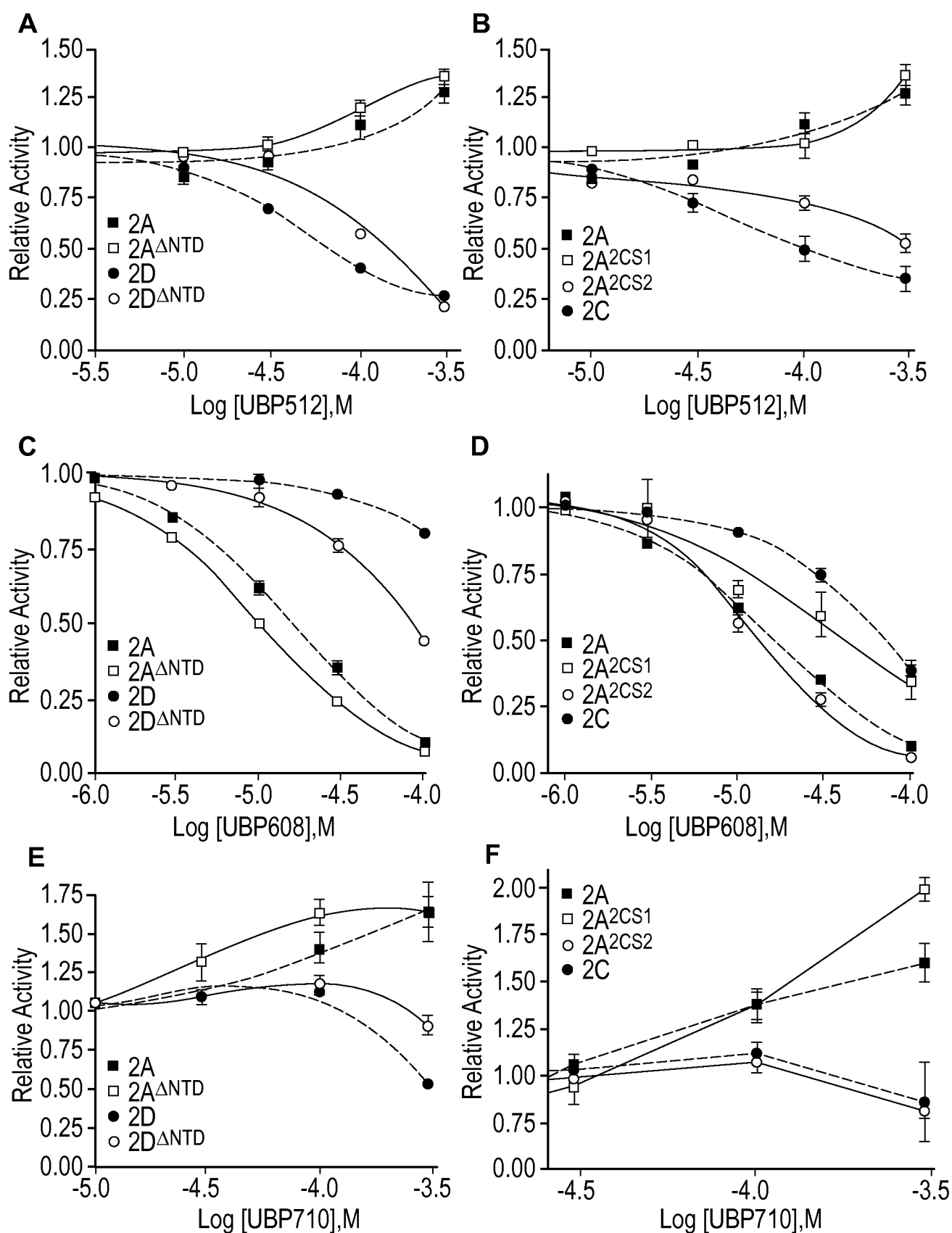


FIGURE 3

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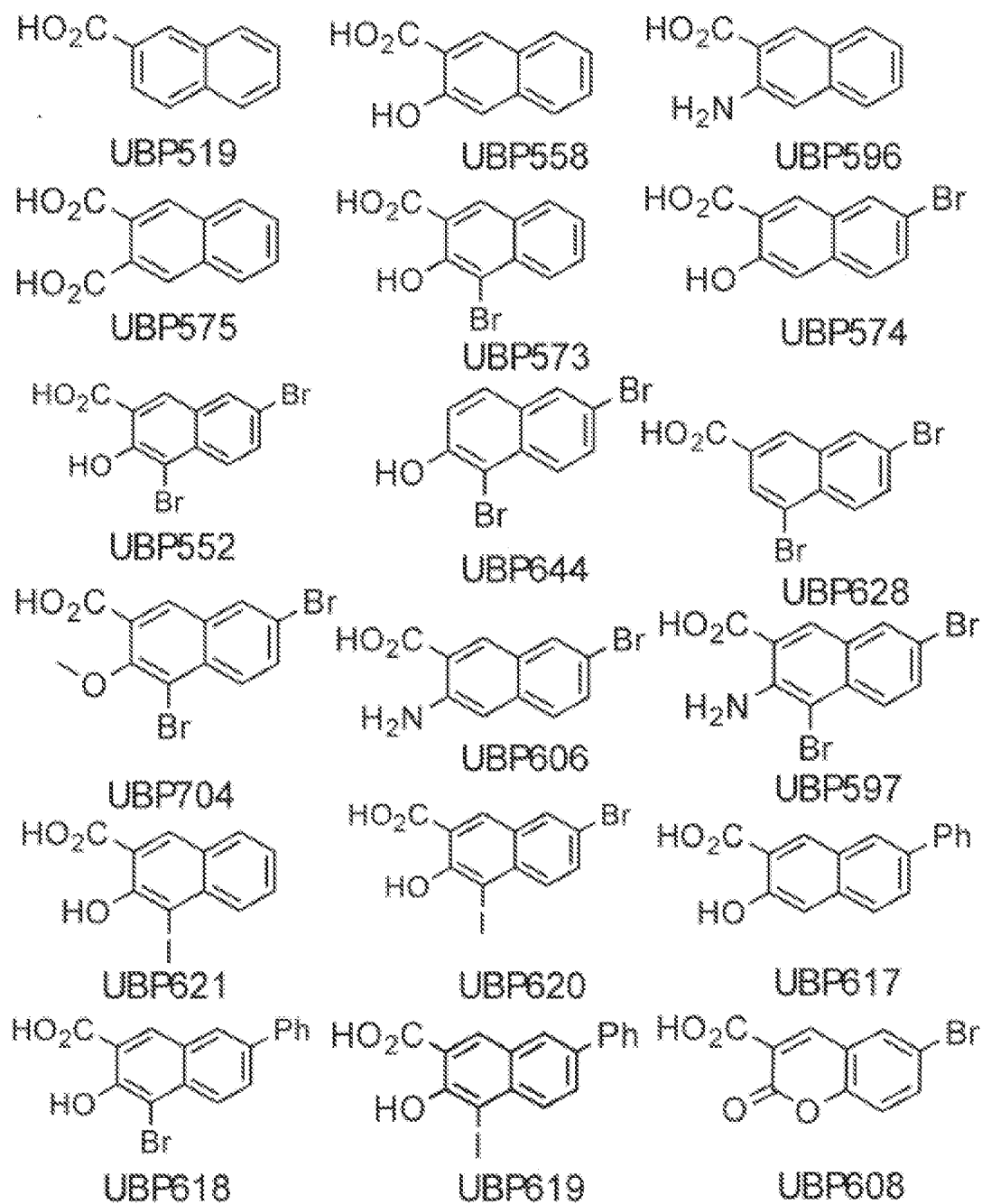


FIGURE 4

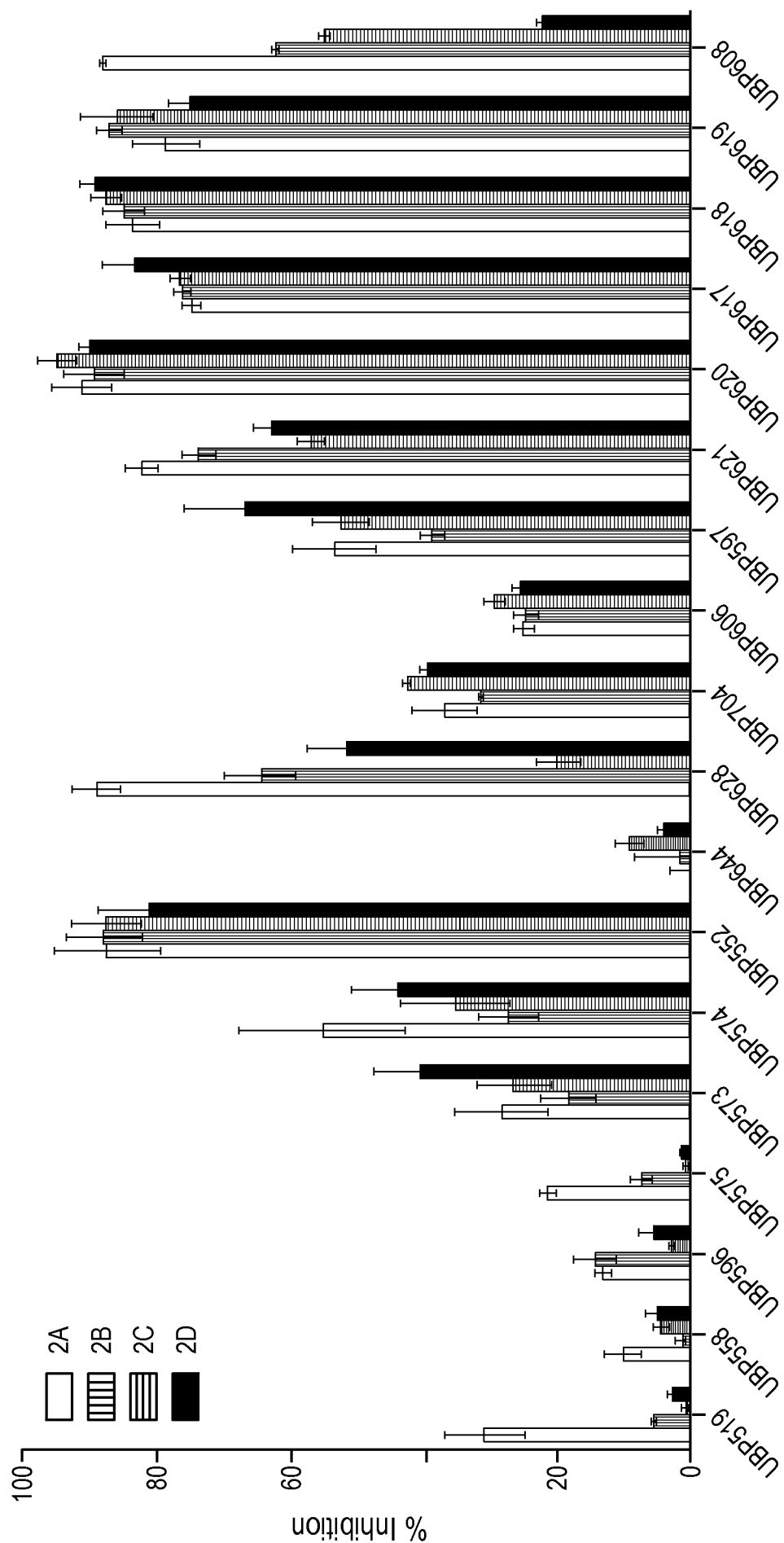


FIGURE 5

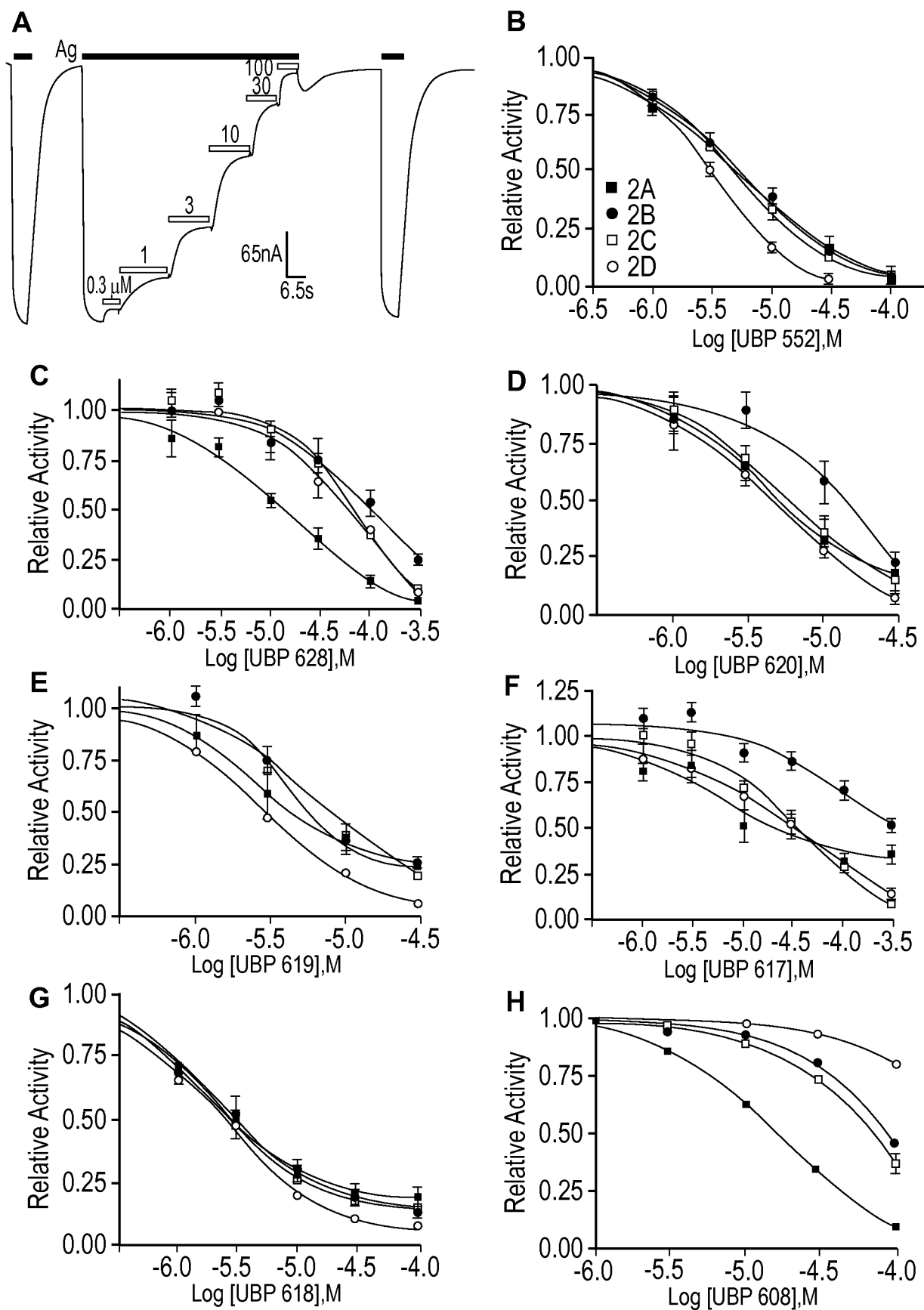
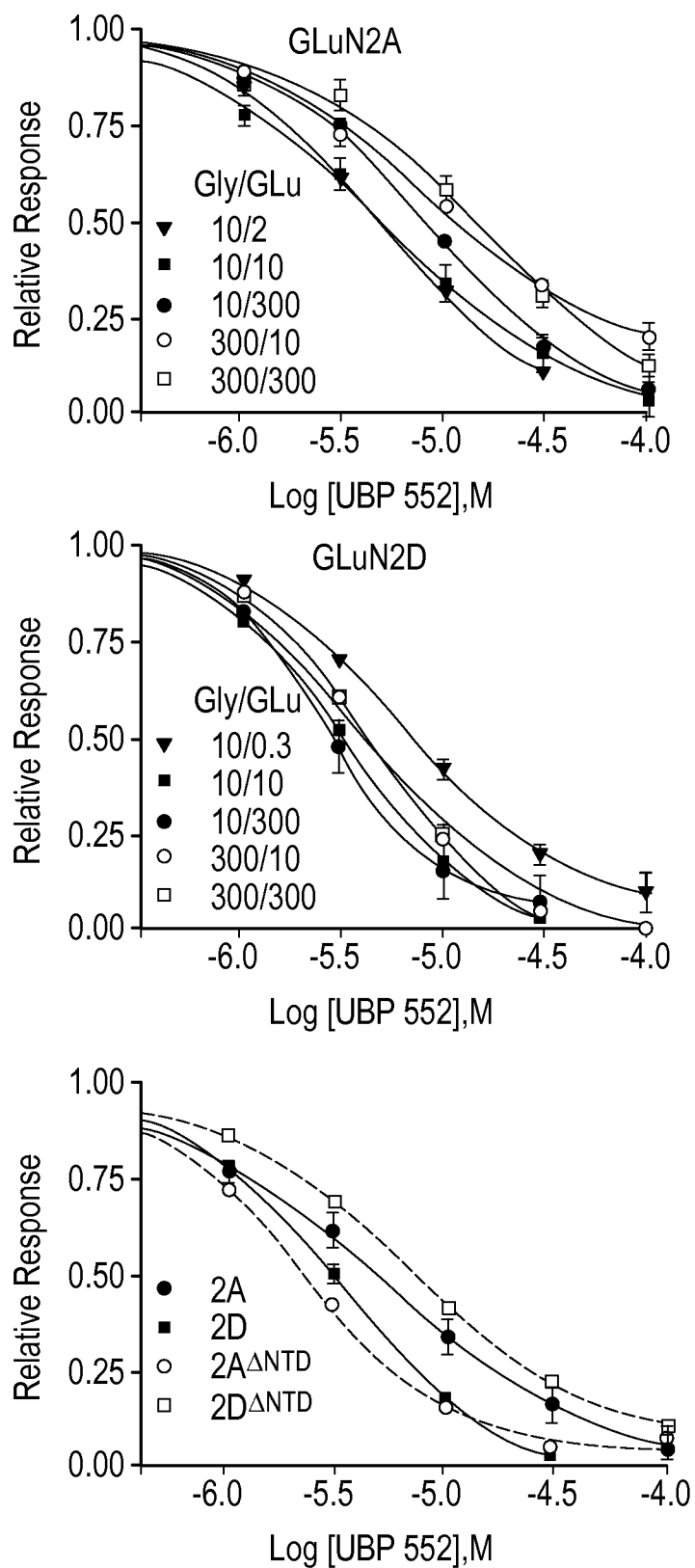


FIGURE 6

**FIGURE 7**

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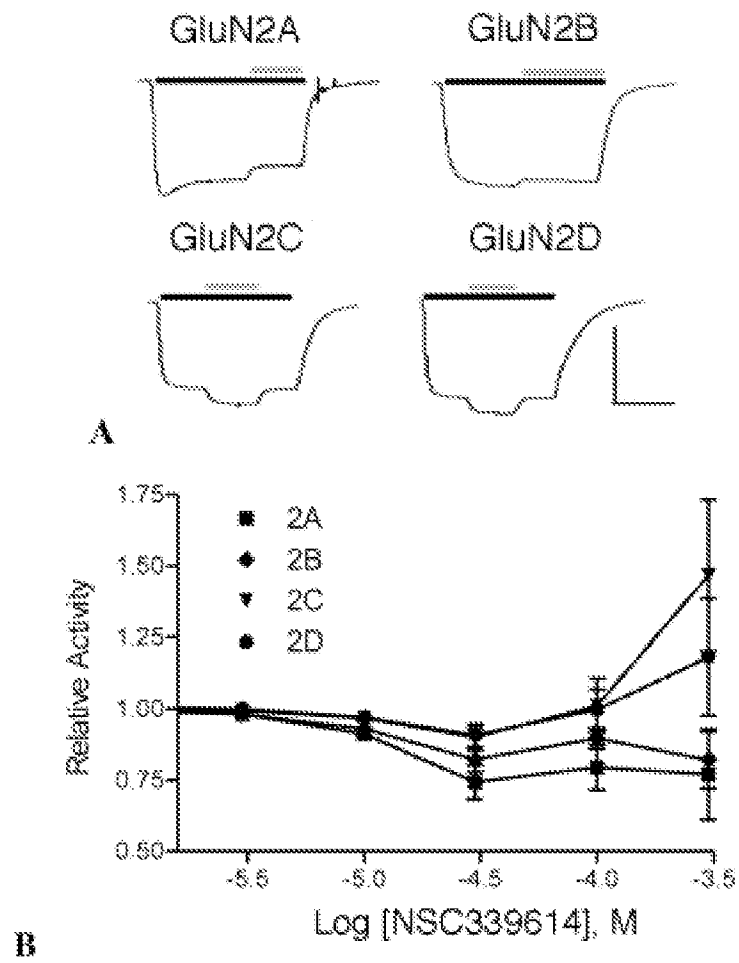


FIGURE 8

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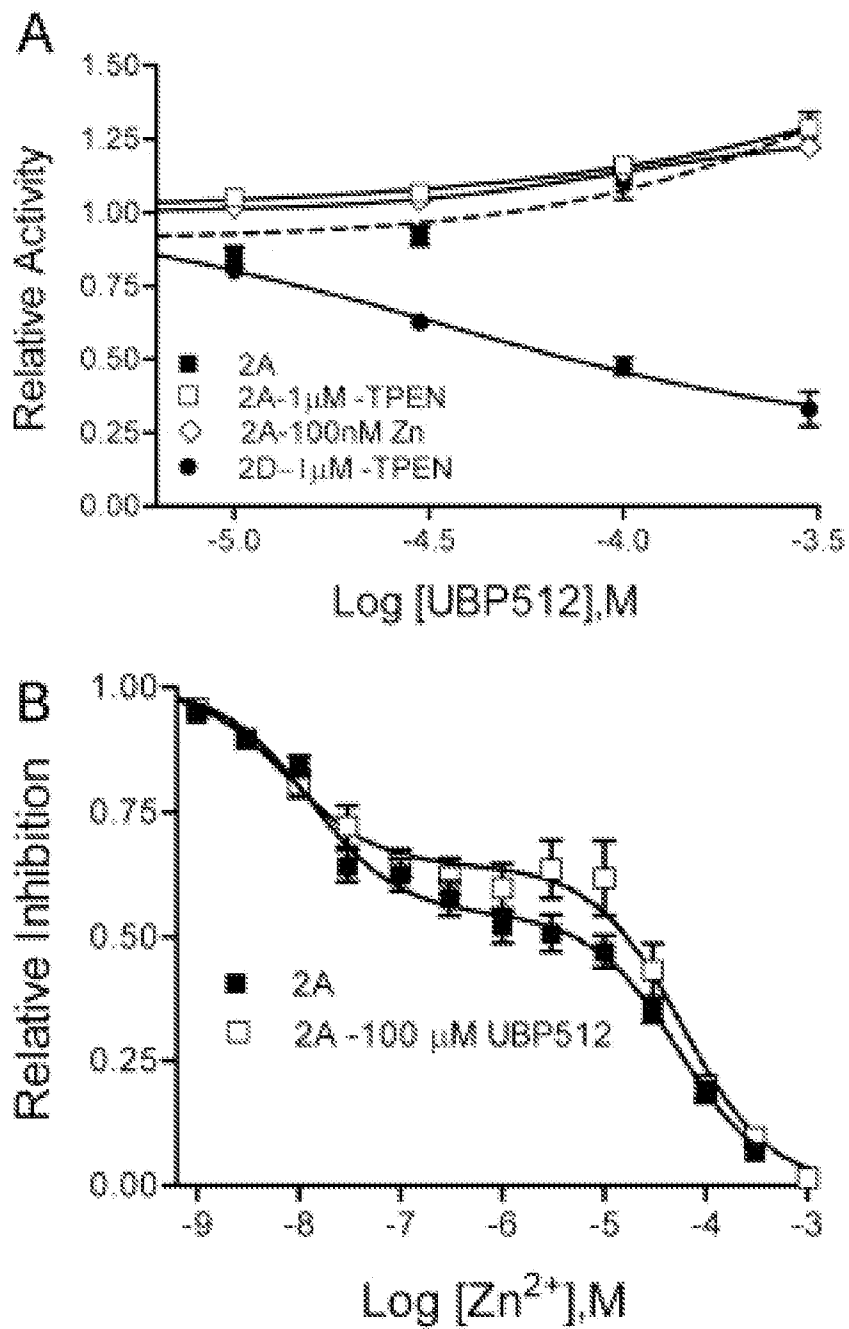


FIGURE 9