(54) Titre : DERIVES DE DIAMANDOIDES POSSEDANT UNE ACTIVITE THERAPEUTIQUE
(54) Title: DIAMONDOD DERIVATIVES POSSESSING THERAPEUTIC ACTIVITY

(57) Abrégé/Abstract:
This invention relates to diamondoid derivatives which exhibit therapeutic activity. Specifically, the diamondoid derivatives herein exhibit therapeutic effects in the treatment of neurologic disorders. Also provided are methods of treatment, prevention and inhibition of neurologic disorders in a subject in need.
Title: DIAMONDOID DERIVATIVES POSSESSING THERAPEUTIC ACTIVITY

Abstract: This invention relates to diamondoid derivatives which exhibit therapeutic activity. Specifically, the diamondoid derivatives herein exhibit therapeutic effects in the treatment of neurologic disorders. Also provided are methods of treatment, prevention and inhibition of neurologic disorders in a subject in need.
BACKGROUND OF THE INVENTION

This application claims priority to U.S. Provisional Application No. 60/678,169, filed May 6, 2005 and U.S. Provisional Application No. 60/782,265, filed March 15, 2006 both of which are herein incorporated by reference in their entirety.

Field of the Invention

This invention relates to diamondoid derivatives which exhibit therapeutic activity. Specifically, the diamondoid derivatives herein exhibit therapeutic effects in the treatment of neurologic disorders. Also provided are methods of treatment, prevention and inhibition of neurologic disorders in a subject in need.

State of the Art

Neurologic disorders are among the most common in clinical medicine. Neurologic disorders can affect perception, memory, cognitive function, interaction with others, cause disturbances in language, and cause symptoms affecting the brain, spinal cord, nerves, and muscles. More serious neurologic disorders cause seizure, coma, loss of mobility, chronic pain, and even death. For example, in Western countries, stroke is the third most common cause of death and the second most common cause of neurologic disability after Alzheimer's disease. Neurologic disease remains the leading cause of institutional placement for loss of independence among adults. HARRISON'S PRINCIPLES OF INTERNAL MEDICINE, Isselbacher ed. 13th Ed. (1994) New York: McGraw-Hill, Inc.: 2203-2204.

Diamondoids are cage-shaped hydrocarbon molecules possessing rigid structures, resembling tiny fragments of a diamond crystal lattice. See Fort, Jr., et al., Adamantane: Consequences of the Diamondoid Structure, Chem. Rev., 64:277-300 (1964). Adamantane is the smallest member of the diamondoid series and consists of one diamond crystal subunit. Diamantane contains two diamond subunits, triamantane contain three, and so on.

Adamantane, which is currently commercially available, has been studied extensively with regard to thermodynamic stability and functionalization, as well as to properties of adamantane containing materials. It has been found that derivatives containing adamantane have certain pharmaceutical uses, including anti-viral properties and uses as blocking agents.
and protecting groups in biochemical syntheses. For example, *alpha*-methyl-1-adamantanemethylamine hydrochloride (Flumadine® (remantidine) Forest Pharmaceuticals, Inc.) and 1-aminoadamantane hydrochloride (Symmetrel® (amantadine) Endo Laboratories, Inc.) may be used to treat influenza. Adamantanes are also useful in the treatment of Parkinson diseases.

However, though research has addressed the application of adamantane derivatives, studies on derivatives of the other two lower diamondoids (diamantane or triamantane) are very limited. U.S. Patent No. 5,576,355 discloses the preparation of diamantane and diamantane alcohol, ketone, ketone derivatives, adamantyl amino acid, quaternary salt or combinations thereof which have antiviral properties. U.S. Patent No. 4,600,782 describes the preparation of substituted spiro[oxazolidine-5,2'-adamantane] compounds useful as antiinflammatory agent. U.S. Patent No. 3,657,273 discloses the preparation of antibiotic adamantane-1,3-dicarboxamides having antibacterial, antifungal, antialgal, antiprotozoal, and antiinflammatory properties, as well as having analgesic and antihypertensive properties.

A large body of evidence has shown that the neurotransmitter glutamate is a key mediator involved in both normal functions of the brain (*e.g.*, movement, learning and memory) and in pathological damage (*e.g.*, chronic and acute neurotoxicity, such as cell death following Alzheimer's dementia and stroke, respectively). Low affinity, uncompetitive inhibitors blocking the ion channel pore of glutaminergic NMDA receptors, such as the adamantane derivative memantine, have shown efficacy in treating a variety of neurological disorders. However, the therapeutic window between inhibition of pathological excess glutamate receptor activity and interference with normal glutaminergic function is narrow. New agents, compositions and methods for using these agents and compositions that inhibit and treat neurologic disorders are needed, which can be used alone or in combination with other agents.

**Structure, Function and Pharmacology of Glutamate Receptors**

Among the many chemicals mediating synaptic transmission between neurons, glutamate has secured a place as the primary excitatory neurotransmitter. Studies on the structure, function and pharmacology of glutamate receptors have shown that they are large multi-subunit transmembrane proteins that are subject to multiple, interacting types of regulation. They can be divided into two major families: ionotrophic and metabotropic. The ionotrophic family is composed of three major pharmacologically and genetically
defined sub-families of ligand-gated ion channels known as AMPA receptors (4 genes: GluR1-4), kainate receptors (5 genes: GluR5-7, KA1 and KA2) and NMDA receptors (7 genes: NR1, NR2A-D, NR3A and NR3B). The NMDA receptors (NRs) are unique in requiring two obligatory co-agonists, glutamate (binds NR2) and glycine (binds NR1), in order to open the ion channel and permit an influx of Ca²⁺ ions. The channel opening, or gating, is affected by binding of a number allosteric modulators: high affinity inhibition by Zn²⁺ (NR2A), current enhancement by low concentrations of polyamines such as spermine (NR1). Both of these effects are pH dependent (H⁺ ion effect) [reviewed in Mayer, M. L. and N. Armstrong (2004). "Structure and function of glutamate receptor ion channels." *Annu Rev Physiol* 66: 161-81.; Herin, G. A. and E. Aizenman (2004). "Amino terminal domain regulation of NMDA receptor function." *Eur J Pharmacol* 500(1-3): 101-11.; Mayer, M. L. (2005). "Glutamate receptor ion channels." *Curr Opin Neurobiol* 15(3): 282-8.; Kew, J. N. and J. A. Kemp (2005). "Iontropic and metabotropic glutamate receptor structure and pharmacology." *Psychopharmacology (Berl)* 179(1): 4-29.; Watkins, J. C. and D. E. Jane (2006). "The glutamate story." *Br J Pharmacol* 147 Suppl 1: S100-8.]. Furthermore, inhibition of resting NRs by endogenous Mg²⁺ binding in the pore channel provide the characteristic voltage dependence of Ca²⁺ ion flow, although the mechanistic details are still controversial [MacDonald 2006; Qian 2005; Vargas-Caballero 2004].


The NR sub-family of glutamate receptors in the brain (central nervous system, CNS) is crucial in maintaining normal cognitive functions. These include a) declarative memory
(conscious recollection of autobiographical events or facts), including consolidation of
memory from visual recognition or spatial learning; b) associative conditioning (such as
spatial learning in a water-maze escape task), including acquisition (encoding / consolidation)
of appetitive and aversive conditioning or extinction (when the reinforcer, e.g. food or shock,
associated with learning a particular task or response is withdrawn), but not maintenance of
already established performance, and; c) executive functions, such as retrieval (working
memory) and discriminative learning [Robbins & Murphy 2006].

During the same time period that the role of glutamate as a key excitatory
neurotransmitter was being discovered, its role in ‘excitotoxicity’ was also being defined.
The first experimental demonstration of the phenomena was in 1957 by Lucas and Newhouse
who injected glutamate subcutaneously into animals and found specific damage to retinal
ganglion cells, although the term ‘excitotoxicity’ was not developed until over 10 years later
by Olney. Since then, it has been seen that a variety of insults to the brain, from acute head
trauma and stroke to chronic progressive dementias such as Alzheimer’s and Parkinson’s,
involve excessive extracellular accumulation of glutamate and thus over-stimulation of
 glutamate receptors and neuronal cell death by over accumulation of Ca++. The concept thus
arose of neuroprotection as a property of drugs that could antagonize glutamate receptors in
order to limit excitotoxicity and preserve neuronal function. Based on these fundamental
studies a variety of therapeutic applications are being pursued for antagonists of glutamate
receptors, and NRs in particular [see reviews: Danysz W and Parsons CG, 2002
“Neuroprotective potential of ionotrophic glutamate receptor antagonists Neurotox Res 4:
119; Lipton SA, 2004 “Failures and successes of NMDA receptor antagonists” NeuroRx 1:
101; Lipton SA, 2006 “Paradigm shift in neuroprotection by NMDA receptor blockade:
Memantine and beyond” Nat Rev Drug Disc 5:160].

Despite the biochemical and pharmacologic complexities of how glutamate regulates
Ca++ ion flow into and out of neurons, the control of neurotransmission by NR is widely
recognized as an important potential means of treating many neurologic disorders. Perhaps
the most fruitful pharmacologic regulation of NR channel activity to date has come from
drugs that interact directly with the channel pore. Over a dozen such drugs (see table below)
are either undergoing clinical trials or marketed for a variety of indications [Bleich, S., K.
treatment in patients with moderate to severe Alzheimer disease already receiving donepezil:
a randomized controlled trial JAMA. Jan 21;291(3):317-24; Foster, A. C. and J. A. Kemp

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multicenter, randomized, double-blind, controlled clinical trials fail to demonstrate enhanced opioid analgesia or reduction in tolerance” Pain 115: 284-95; [(anon) 2005
“Dextromethorphan/quinidine: AVP 923, dextromethorphan/cytochrome P450-2D6 inhibitor, quinidine/dextromethorphan” Drugs R D. 6(3): 174-7]. Evidence of neuroprotection in models mimicking nerve-agent induced seizures, as may occur in wartime or from terrorist attack, has been obtained for memantine, MK-801, ketamine, gacyclidine (GK11) and HU-211 in animal models, but higher doses of MK-801 induced neuronal degeneration in some brain areas [Fihbert J el. al. 2005 Med Chem Biol Radiol Def online at http://jmedhchemdef.org].

Thus the need remains for improved agents, compositions and methods for using these agents and compositions that inhibit and treat neurologic disorders, which can be used alone or in concert with other agents.

**SUMMARY OF THE INVENTION**

The present invention provides diamondoid derivatives which exhibit pharmaceutical activity in the treatment, inhibition, and prevention of neurologic disorders. In particular, the present invention relates to derivatives of diamantane and triamantane, which may be used in the treatment, inhibition, and prevention of neurologic disorders. In its composition aspects, diamantane derivatives within the scope of the present invention include compounds of Formula I and II and triamantane derivatives within the scope of the present invention include compounds of Formula III.

In one of its composition aspects, this invention is directed to a compound of Formula I:

![Formula I](image_url)

wherein:
$R^1, R^2, R^5, R^8, R^9, R^{12}, R^{15},$ and $R^{16}$ are independently selected from the group consisting of hydrogen, hydroxy, lower alkyl, substituted lower alkyl, lower alkenyl, alkoxy, amino, nitroso, nitro, halo, cycloalkyl, carboxy, acyloxy, acyl, aminoacyl, and amincarbonyloxy;

$$R^3, R^4, R^6, R^7, R^{10}, R^{11}, R^{13}, R^{14}, R^{17}, R^{18}, R^{19} \text{ and } R^{20} \text{ are hydrogen;}$$

provided that at least two of $R^1, R^2, R^5, R^8, R^9, R^{12}, R^{15},$ and $R^{16}$ are not hydrogen;

and

that both $R^5$ and $R^{12}$ or $R^1$ and $R^8$ are not identical when the remaining of $R^1, R^2, R^5, R^9, R^{15},$ and $R^{16}$ are hydrogen;

and pharmaceutically acceptable salts thereof.

In one embodiment of the compounds of Formula I, at least three of $R^1, R^2, R^5, R^8, R^9, R^{12}, R^{15},$ and $R^{16}$ are not hydrogen. In another embodiment of the compounds of Formula I, at least four of $R^1, R^2, R^5, R^8, R^9, R^{12}, R^{15},$ and $R^{16}$ are not hydrogen. In yet another embodiment of the compounds of Formula I, five of $R^1, R^2, R^5, R^8, R^9, R^{12}, R^{15},$ and $R^{16}$ are not hydrogen.

In one preferred embodiment of the compounds of Formula I, $R^1$ and $R^5$ are aminoacyl and $R^2, R^8, R^9, R^{12}, R^{15},$ and $R^{16}$ are hydrogen or lower alkyl. In another preferred embodiment of the compounds of Formula I, $R^5$ is amino and two of $R^1, R^2, R^8$ and $R^{15}$ are lower alkyl, preferably methyl. In yet another embodiment of the compounds of Formula I, $R^5$ is amino and two of $R^1, R^2, R^8$ and $R^{15}$ are lower alkyl. In a preferred embodiment $R^1$ and $R^8$ are methyl and in another preferred embodiment $R^1$ and $R^{15}$ are methyl.

In a further embodiment of the compounds of Formula I, $R^9$ or $R^{15}$ is amino and $R^1$ is methyl. In another embodiment of the compounds of Formula I, $R^2$ or $R^{16}$ is amino and $R^1$ and $R^8$ are methyl.

In another embodiment of the compounds of Formula I, at least one of $R^1, R^2, R^5, R^8, R^9, R^{12}, R^{15},$ and $R^{16}$ is independently selected from the group consisting of amino, nitroso, nitro, and aminoacyl and at least one of the remaining of $R^1, R^2, R^5, R^8, R^9, R^{12}, R^{15},$ and $R^{16}$ are lower alkyl. In a preferred embodiment, at least two of the remaining of $R^1, R^2, R^5, R^8, R^9, R^{12}, R^{15},$ and $R^{16}$ are lower alkyl. In another preferred embodiment, three of the remaining of $R^1, R^2, R^5, R^8, R^9, R^{12}, R^{15},$ and $R^{16}$ are lower alkyl.

In an embodiment of the compounds of Formula I, at least one of $R^5$ and $R^{12}$ is independently selected from the group consisting of amino, nitroso, nitro, and aminoacyl and at least one of $R^1, R^2, R^8, R^9, R^{15},$ and $R^{16}$ is lower alkyl. In a preferred embodiment, at least
two of $R^1$, $R^2$, $R^8$, $R^9$, $R^{15}$, and $R^{16}$ are lower alkyl. In another preferred embodiment, three of
$R^1$, $R^2$, $R^8$, $R^9$, $R^{15}$, and $R^{16}$ are lower alkyl.

In an embodiment of the compounds of Formula I, at least one of $R^1$, $R^2$, $R^5$, $R^6$, $R^{12}$, $R^{15}$, and $R^{16}$ is substituted lower alkyl. In a preferred embodiment, two of $R^1$, $R^2$, $R^5$, $R^8$, $R^9$, $R^{12}$, $R^{15}$, and $R^{16}$ are substituted lower alkyl.

In another embodiment of the compounds of Formula I, at least one of $R^1$, $R^2$, $R^5$, $R^8$, $R^9$, $R^{12}$, $R^{15}$, and $R^{16}$ is substituted lower alkyl and at least one of the remaining of $R^1$, $R^2$, $R^5$, $R^8$, $R^9$, $R^{12}$, $R^{15}$, and $R^{16}$ are independently selected from the group consisting of amino, nitroso, nitro, and aminoacyl.

In another of its composition aspects, this invention is directed to a compound of Formula II:

![Formula II](attachment:image.png)

wherein:

$R^{21}$, $R^{22}$, $R^{25}$, $R^{28}$, $R^{29}$, $R^{32}$, $R^{35}$, and $R^{36}$ are independently selected from the group consisting of hydrogen or substituted lower alkyl;

$R^{23}$, $R^{24}$, $R^{26}$, $R^{27}$, $R^{30}$, $R^{31}$, $R^{33}$, $R^{34}$, $R^{37}$, $R^{38}$, $R^{39}$, and $R^{40}$ are hydrogen;

provided that at least at least one of $R^{21}$, $R^{22}$, $R^{25}$, $R^{28}$, $R^{29}$, $R^{32}$, $R^{35}$, and $R^{36}$ is substituted lower alkyl;

and pharmaceutically acceptable salts thereof.

In a preferred embodiment of the compounds of Formula II, the substituted lower alkyl group is substituted with one substitutent selected from the group consisting of amino, hydroxy, halo, nitroso, nitro, carboxy, acyloxy, acyl, aminoacyl, and aminocarbonyloxy. In a more preferred embodiment of the compounds of Formula II, the substituted lower alkyl group is substituted with one substitutent selected from the group consisting of amino, nitroso, nitro, and aminoacyl.
In one embodiment of the compounds of Formula II, \( R^{25} \) is substituted lower alkyl and \( R^{21}, R^{22}, R^{28}, R^{29}, R^{32}, R^{35}, \) and \( R^{36} \) are hydrogen.

In another embodiment of the compounds of Formula II, \( R^{35} \) and \( R^{32} \) are substituted lower alkyl.

In yet another embodiment of the compounds of Formula II, \( R^{21} \) is substituted lower alkyl and \( R^{22}, R^{25}, R^{28}, R^{29}, R^{32}, R^{35}, \) and \( R^{36} \) are hydrogen.

In one embodiment of the compounds of Formula II, \( R^{35} \) and \( R^{21} \) are substituted lower alkyl.

In another embodiment of the compounds of Formula II, \( R^{32} \) and \( R^{21} \) are substituted lower alkyl.

In yet another of its composition aspects, this invention is directed to a compound of Formula III:

![Formula III](image)

wherein:

\( R^{41}, R^{42}, R^{43}, R^{46}, R^{47}, R^{50}, R^{53}, R^{54}, R^{55}, \) and \( R^{58} \) are independently selected from the group consisting of hydrogen, hydroxy, lower alkyl, substituted lower alkyl, lower alkenyl, alkoxy, amino, nitroso, nitro, halo, cycloalkyl, carboxy, acyloxy, acyl, aminoacyl, and aminocarboxyloxy;

\( R^{44}, R^{45}, R^{48}, R^{49}, R^{51}, R^{52}, R^{56}, R^{57}, R^{59}, R^{60}, R^{61}, R^{62}, R^{63}, \) and \( R^{64} \) are hydrogen;

provided that at least one of \( R^{41}, R^{42}, R^{43}, R^{46}, R^{47}, R^{50}, R^{53}, R^{54}, R^{55}, \) and \( R^{58} \) is not hydrogen;

and pharmaceutically acceptable salts thereof.

In one embodiment of the compounds of Formula III, at least two of \( R^{41}, R^{42}, R^{43}, R^{46}, R^{47}, R^{50}, R^{53}, R^{54}, R^{55}, \) and \( R^{58} \) are not hydrogen. In another embodiment of the compounds of Formula III, at least three of \( R^{41}, R^{42}, R^{43}, R^{46}, R^{47}, R^{50}, R^{53}, R^{54}, R^{55}, \) and \( R^{58} \) are not hydrogen.
In one embodiment of the compounds of Formula III, \( R^{50} \) is selected from the group consisting of amino, nitroso, nitro, and aminoacyl and at least one of \( R^{41}, R^{42}, R^{43}, R^{46}, R^{47}, R^{50}, R^{51}, R^{54}, R^{55}, \) and \( R^{58} \) is lower alkyl. In a preferred embodiment, at least two of \( R^{41}, R^{42}, R^{47}, R^{50}, R^{53}, R^{54}, R^{55}, \) and \( R^{58} \) are lower alkyl.

In another aspect, this invention provides for a method for treating a neurologic disorder in a subject in need thereof, comprising administering a therapeutically effective amount of a compound of Formula Ia:

\[
\text{Formula Ia}
\]

wherein:

\[ R^1, R^2, R^5, R^8, R^9, R^{12}, R^{15}, \text{ and } R^{16} \text{ are independently selected from the group consisting of hydrogen, hydroxy, lower alkyl, substituted lower alkyl, lower alkenyl, alkoxy, amino, nitroso, nitro, halo, cycloalkyl, carboxy, acyloxy, acyl, aminoacyl, and aminocarbonyloxy;} \]

\[ R^3, R^4, R^6, R^7, R^{10}, R^{11}, R^{13}, R^{14}, R^{17}, R^{18}, R^{19}, \text{ and } R^{20} \text{ are hydrogen;} \]

provided that at least one of \( R^1, R^2, R^5, R^8, R^9, R^{12}, R^{15}, \text{ and } R^{16} \) are not hydrogen;

and pharmaceutically acceptable salts thereof.

In one embodiment of the compounds of Formula Ia, at least two of \( R^1, R^2, R^5, R^8, R^9, R^{12}, R^{15}, \text{ and } R^{16} \) are not hydrogen. In another embodiment of the compounds of Formula Ia, at least three of \( R^1, R^2, R^5, R^8, R^9, R^{12}, R^{15}, \text{ and } R^{16} \) are not hydrogen. In another embodiment of the compounds of Formula I, at least four of \( R^1, R^2, R^5, R^8, R^9, R^{12}, R^{15}, \text{ and } R^{16} \) are not hydrogen. In yet another embodiment of the compounds of Formula I, five of \( R^1, R^2, R^5, R^8, R^9, R^{12}, R^{15}, \text{ and } R^{16} \) are not hydrogen.

In another embodiment of the compounds of Formula Ia, \( R^1 \) and \( R^5 \) are aminoacyl and \( R^2, R^8, R^9, R^{12}, R^{15}, \text{ and } R^{16} \) are hydrogen or lower alkyl. In another preferred embodiment of the compounds of Formula Ia, \( R^{5} \) is amino and two of \( R^1, R^2, R^8 \) and \( R^{15} \) are lower alkyl, preferably methyl. In yet another embodiment of the compounds of Formula Ia, \( R^{5} \) is amino.
and two of \( R^1, R^2, R^8 \) and \( R^{15} \) are lower alkyl. In a further embodiment of the compounds of Formula Ia, \( R^9 \) or \( R^{15} \) is amino and \( R^1 \) is methyl. In another embodiment of the compounds of Formula Ia, \( R^2 \) is amino, \( R^1 \) is methyl, and \( R^8 \) or \( R^{15} \) is methyl.

In another embodiment of the compounds of Formula Ia, at least one of \( R^1, R^2, R^5, R^8, R^9, R^{12}, R^{15}, \) and \( R^{16} \) is independently selected from the group consisting of amino, nitroso, nitro, and aminoacyl and at least one of the remaining of \( R^1, R^2, R^5, R^8, R^9, R^{12}, R^{15}, \) and \( R^{16} \) are lower alkyl. In a preferred embodiment, at least two of the remaining of \( R^1, R^2, R^5, R^8, R^9, R^{12}, R^{15}, \) and \( R^{16} \) are lower alkyl. In another preferred embodiment, three of the remaining of \( R^1, R^2, R^5, R^8, R^9, R^{12}, R^{15}, \) and \( R^{16} \) are lower alkyl.

In one embodiment of the compounds of Formula Ia, at least one of \( R^5 \) and \( R^{12} \) is independently selected from the group consisting of amino, nitroso, nitro, and aminoacyl and at least one of \( R^1, R^2, R^8, R^9, R^{15}, \) and \( R^{16} \) is lower alkyl. In a preferred embodiment, at least two of \( R^1, R^2, R^8, R^9, R^{15}, \) and \( R^{16} \) are lower alkyl. In another preferred embodiment, three of \( R^1, R^2, R^8, R^9, R^{15}, \) and \( R^{16} \) are lower alkyl.

In one embodiment of the compounds of Formula Ia, at least one of \( R^1, R^2, R^5, R^8, R^9, R^{12}, R^{15}, \) and \( R^{16} \) is substituted lower alkyl. In a preferred embodiment, two of \( R^1, R^2, R^5, R^8, R^9, R^{12}, R^{15}, \) and \( R^{16} \) are substituted lower alkyl. In another preferred embodiment, \( R^5 \) is substituted lower alkyl and \( R^1, R^2, R^5, R^9, R^{12}, R^{15}, \) and \( R^{16} \) are hydrogen. In yet another preferred embodiment, \( R^5 \) and \( R^{12} \) are substituted lower alkyl. In another preferred embodiment, \( R^1 \) is substituted lower alkyl and \( R^2, R^5, R^8, R^9, R^{12}, R^{15}, \) and \( R^{16} \) are hydrogen. In yet another preferred embodiment, \( R^5 \) and \( R^1 \) are substituted lower alkyl. In another embodiment, \( R^{12} \) and \( R^1 \) are substituted lower alkyl.

In one embodiment of the compounds of Formula Ia, at least one of \( R^1, R^2, R^5, R^8, R^9, R^{12}, R^{15}, \) and \( R^{16} \) is substituted lower alkyl and at least one of the remaining of \( R^1, R^2, R^5, R^8, R^9, R^{12}, R^{15}, \) and \( R^{16} \) are independently selected from the group consisting of amino, nitroso, nitro, and aminoacyl.

In a preferred embodiment of the compounds of Formula Ia, the substituted lower alkyl group is substituted with one substituent selected from the group consisting of amino, hydroxy, halo, nitroso, nitro, carboxy, acyloxy, acyl, aminoacyl, and aminocarbonyloxy. In a more preferred embodiment, the substituted lower alkyl group is substituted with one substituent selected from the group consisting of amino, nitroso, nitro, and aminoacyl.

In yet another aspect, this invention provides for a method for treating a neurologic disorder in a subject in need thereof, comprising administering a therapeutically effective amount of a compound of Formula III as defined above.
In a preferred embodiment, the neurologic disorder is epilepsy, narcolepsy, neurodegenerative disorders, pain, and psychiatric disorders. Preferably, the neurodegenerative disorder may include Alzheimer's Disease, Parkinson's Disease, stroke, AIDS related dementia, traumatic brain injury (TBI), and Huntington's Disease. Preferably, the psychiatric disorder is substance abuse.

In another aspect, this invention provides pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of the compounds defined herein.

In yet another aspect, the present invention provides processes for preparing compounds of Formula I, Ia, II, and III.

**BRIEF DESCRIPTION OF THE FIGURES**

FIG. 1 illustrates synthetic pathways by which diamantane may be derivatized to provide a compound according to the present invention.

FIGs. 2-16 illustrate synthetic pathways by which derivatized diamantane and triamantane compounds may be prepared from diamantane and triamantane.

FIG. 17- is GC MS, \(^1\)H-NMR, or \(^{13}\)C-NMR data corresponding to the Examples.

FIG. 18 is the crystal structure of 1,6-dibromodiamantane.

FIGs. 19-32 are GC MS, HPLC, \(^1\)H-NMR, or \(^{13}\)C-NMR data corresponding to the Examples.

FIG. 33 shows the effect of diamantane compounds on NMDA evoked currents.

**DETAILED DESCRIPTION OF THE INVENTION**

As described above, this invention relates to diamandoid derivatives which exhibit pharmaceutical activity, useful for the treatment, inhibition, and/or prevention of neurologic conditions. However, prior to describing this invention in further detail, the following terms will first be defined.

**Definitions**

In accordance with this detailed description, the following abbreviations and definitions apply. It must be noted that as used herein, the singular forms “a”, “an”, and “the” include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to “compounds” includes a plurality of such compounds and reference to
“the dosage” includes reference to one or more dosages and equivalents thereof known to those skilled in the art, and so forth.

The publications discussed herein are provided solely for their disclosure prior to the filing date of the present application. Nothing herein is to be construed as an admission that the present invention is not entitled to antedate such publication by virtue of prior invention. Further, the dates of publication provided may be different from the actual publication dates, which may need to be independently confirmed.

Unless otherwise stated, the following terms used in the specification and claims have the meanings given below:

“Halo” means fluoro, chloro, bromo, or iodo.

“Nitro” means the group -NO₂.

“Nitroso” means the group –NO.

“Hydroxy” means the group -OH.

“Carboxy” means the group –COOH.

“Lower alkyl” refers to monovalent alkyl groups having from 1 to 6 carbon atoms including straight and branched chain alkyl groups. This term is exemplified by groups such as methyl, ethyl, iso-propyl, n-propyl, n-butyl, iso-butyl, sec-butyl, t-butyl, n-pentyl and the like.

“Substituted lower alkyl” means an alkyl group with one or more substituents, preferably one to three substituents, wherein the substitutents are selected from the group consisting of amino, nitroso, nitro, halo, hydroxy, carboxy, acyloxy, acyl, aminoacyl, and aminocarboxyloxy. “Lower alkenyl” means a linear unsaturated monovalent hydrocarbon radical of two to six carbon atoms or a branched monovalent hydrocarbon radical of three to eight carbon atoms containing at least one double bond, (-C=CH-). Examples of alkenyl groups include, but are not limited to, allyl, vinyl, 2-butenyl, and the like.

“Substituted lower alkenyl” means an alkenyl group with one or more substituents, preferably one to three substituents, wherein the substitutents are selected from the group consisting of amino, nitroso, nitro, halo, hydroxy, carboxy, acyloxy, acyl, aminoacyl, and aminocarboxyloxy.

The term “cycloalkyl” refers to cyclic alkyl groups of from 3 to 6 carbon atoms having a single cyclic ring including, by way of example, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.
“Alkoxy” refers to the group “lower alkyl-O-” which includes, by way of example, methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, tert-butoxy, sec-butoxy, n-pentoxy, 1,2-dimethylbutoxy, and the like.

“Amino” refers to the group NR\(^a\)R\(^b\), wherein R\(^a\) and R\(^b\) are independently selected from hydrogen, lower alkyl, substituted lower alkyl, and cycloalkyl.

“Acyloxy” refers to the groups H-C(O)O-, lower alkyl-C(O)O-, substituted lower alkyl-C(O)O-, lower alkenyl-C(O)O-, substituted lower alkenyl-C(O)O- and cycloalkyl-C(O)O-, wherein lower alkyl, substituted lower alkyl, lower alkenyl, substituted lower alkenyl, and cycloalkyl are as defined herein.

“Acyl” refers to the groups H-C(O)-, lower alkyl-C(O)-, substituted lower alkyl-C(O)-, lower alkenyl-C(O)-, substituted lower alkenyl-C(O)-, cycloalkyl-C(O)-, wherein lower alkyl, substituted lower alkyl, lower alkenyl, substituted lower alkenyl, and cycloalkyl are as defined herein.

“Aminocarbonyloxy” refers to the groups -NRC(O)lower alkyl, -NRC(O)substituted lower alkyl, -NRC(O)cycloalkyl, -NRC(O)lower alkenyl, and -NRC(O)substituted lower alkenyl, wherein R is hydrogen or lower alkyl and wherein lower alkyl, substituted lower alkyl, lower alkenyl, substituted lower alkenyl, and cycloalkyl are as defined herein.

“Aminocarbonyloxy” refers to the groups -NRC(O)O-lower alkyl, -NRC(O)O-substituted lower alkyl, -NRC(O)O-lower alkenyl, -NRC(O)O-substituted lower alkenyl, -NRC(O)O-cycloalkyl, wherein R is hydrogen or lower alkyl and wherein lower alkyl, substituted lower alkyl, lower alkenyl, substituted lower alkenyl, and cycloalkyl are as defined herein.

“Pharmaceutically acceptable carrier” means a carrier that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes a carrier that is acceptable for veterinary use as well as human pharmaceutical use. "A pharmaceutically acceptable carrier" as used in the specification and claims includes both one and more than one such carrier.

“Neurologic disorder” or “neurological disorder” means any condition, disease and/or disorder affecting or related to the central nervous system, the brain, nerves, and muscles.

These disorders include, but are not limited to, central nervous system disorders, disorders of the brain, disorders of nerves and muscles, psychiatric disorders, chronic fatigue disorders, and alcohol and/or drug dependency.

“Treating” or “treatment” of a disease includes:
(1) preventing the disease, i.e., causing the clinical symptoms of the disease not to develop in a mammal that may be exposed to or predisposed to the disease but does not yet experience or display symptoms of the disease,

(2) inhibiting the disease, i.e., arresting or reducing the development of the disease or its clinical symptoms, or

(3) relieving the disease, i.e., causing regression of the disease or its clinical symptoms.

A “therapeutically effective amount” means the amount of a compound that, when administered to a mammal for treating a disease, is sufficient to effect such treatment for the disease. The “therapeutically effective amount” will vary depending on the compound, the disease and its severity and the age, weight, etc., of the mammal to be treated.

“Pharmaceutically acceptable salt” refers to pharmaceutically acceptable salts of a compound of Formula I which salts are derived from a variety of organic and inorganic counter ions well known in the art and include, by way of example only, sodium, potassium, calcium, magnesium, ammonium, tetraalkylammonium, and the like; and when the molecule contains a basic functionality, salts of organic or inorganic acids, such as hydrochloride, hydrobromide, tartrate, mesylate, acetate, maleate, oxalate and the like. Preferably, the pharmaceutically acceptable salts are of inorganic acid salts, such as hydrochloride.

“Optional” or “optionally” means that the subsequently described event or circumstance may, but need not, occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, “aryl group optionally mono- or di- substituted with an alkyl group” means that the alkyl may but need not be present, and the description includes situations where the aryl group is mono- or disubstituted with an alkyl group and situations where the aryl group is not substituted with the alkyl group.

The term “mammal” refers to all mammals including humans, livestock, and companion animals.

The compounds of the present invention are generally named according to the IUPAC or CAS nomenclature system. Abbreviations which are well known to one of ordinary skill in the art may be used (e.g., “Ph” for phenyl, “Me” for methyl, “Et” for ethyl, “h” for hour or hours and “rt” for room temperature).

In naming the compounds of the present invention, the numbering scheme used for the diamantane ring system (C_{14}H_{20}) is as follows:
Positions 1, 2, 4, 6, 7, 9, 11, and 12 are bridgehead positions and the substituents at these positions are as defined for the compounds of Formula I, Ia, and II. It is to be understood that in naming the compounds based upon the above positions, the compounds may be racemic mixtures of enantiomers (e.g., the enantiomers 1,6-dimethyl-2-amino diamantane and 1,6-dimethyl-12-amino diamantane and the enantiomers 1-methyl-7-amino diamantane and 1-methyl-11-amino diamantane).

In naming the compounds of the present invention, the numbering scheme used for the triamantane ring system (C\textsubscript{18}H\textsubscript{24}) is as follows:

Positions 1, 2, 3, 4, 6, 7, 9, 11, 12, 13, and 15 are bridgehead positions and the substituents at these positions are as defined for the compounds of Formula III.

Diamantane derivatives within the scope of this invention, including those of Formula I, Ia, and II, include those set forth in Table I as follows. The substituents at positions 1, 2, 4, 6, 7, 9, 11, and 12 are defined in the Table. The substituents at positions 3, 5, 8, 10, 13, and 14 are all hydrogen.

Table I
Diamantane derivatives within the scope of this invention, including those of Formula I, Ia, and II, also include the following:
wherein R is independently amino, when amino preferably –NH₂, nitroso, nitro, or aminoacyl, when aminoacyl preferably acetamino. Preferably R is amino or aminoacyl.

Specific compounds within the scope of this invention include, for example, the following compounds: 4-aminodiamantane; 1-aminodiamantane; 1,6-diaminodiamantane; 4,9-diaminodiamantane, 1-methyl-7-aminodiamantane, 1-methyl-11-aminodiamantane, 1,6-dimethyl-2-aminodiamantane, 1,6-dimethyl-12-aminodiamantane, 1,6-dimethyl-4-aminodiamantane, 1,6-dimethyl-2,4-diaminodiamantane, 1,7-dimethyl-4-aminodiamantane, 4-acetaminodiamantane; 1-acetaminodiamantane; 1,6-diacetaminodiamantane; and 1,4-diacetaminodiamantane; and pharmaceutically acceptable salts thereof. Preferred pharmaceutically acceptable salts thereof include hydrochloride salts.

Triamantane derivatives within the scope of this invention include those as illustrated below. The substituents at positions 5, 8, 10, 14, 16, 17, and 18 are all hydrogen.
wherein R is independently amino, when amino preferably –NH₂, nitroso, nitro, or aminoacyl, when aminoacyl preferably acetamino.

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General Synthetic Schemes

Unsubstituted diamantane and triamantane may be synthesized by methods well known to those of skill in the art. For example, diamantane may be synthesized as described in Organic Syntheses, Vol 53, 30-34 (1973); Tetrahedron Letters, No. 44, 3877-3880 (1970); and Journal of the American Chemical Society, 87:4, 917-918 (1965). Triamantane may be synthesized as described in Journal of the American Chemical Society, 88:16, 3862-3863 (1966).

Furthermore, unsubstituted or alkylated diamantane and triamantane can be recovered from readily available feedstocks using methods and procedures well known to those of skill in the art. For example, unsubstituted or alkylated diamantane and triamantane can be isolated from suitable feedstock compositions by methods as described in U.S. Patent No. 5,414,189, herein incorporated by reference in its entirety. Furthermore, unsubstituted or alkylated diamantane and triamantane can be isolated from suitable feedstock compositions by methods as described for higher dendrimers in U.S. Patent No. 6,861,569, herein incorporated by reference in its entirety. It will be appreciated that where typical or preferred process conditions (i.e., reaction temperatures, times, solvents, pressures, etc.) are given, other process conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with feedstocks, but such conditions can be determined by one skilled in the art by routine optimization procedures. Suitable feedstocks are selected such that the feedstock comprises recoverable amounts of unsubstituted dendrimers selected from the group consisting of diamantane, triamanate, and mixtures thereof. Preferred feedstocks include, for example, natural gas condensates and refinery streams, including hydrocarbonaceous streams recoverable from cracking processes, distillations, coking, and

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the like. Preferred feedstocks include condensate fractions recovered from the Norphlet Formation in the Gulf of Mexico and from the LeDuc Formation in Canada.

Diamantane, isolated as described above, may be derivatized to provide a compound of Formula I, Ia, or II according to the present invention by synthetic pathways as illustrated in FIG. 1 and as described in further detail in the following examples.

Representative examples of derivatized diamantane and triamantane compounds may be prepared from diamantane and triamantane, isolated as described above, by synthetic pathways as illustrated in FIGs. 2-16, wherein D represents diamantane, triamantane, and their alkylated analogs.

The reagents used in preparing the compounds of Formula I, Ia, II, and III are either available from commercial suppliers such as Toronto Research Chemicals (North York, ON Canada), Aldrich Chemical Co. (Milwaukee, Wisconsin, USA), Bachem (Torrance, California, USA), Emka-Chemie, or Sigma (St. Louis, Missouri, USA) or are prepared by methods known to those skilled in the art following procedures set forth in references such as Fieser and Fieser's Reagents for Organic Synthesis, Volumes 1-15 (John Wiley and Sons, 1991), Rodd's Chemistry of Carbon Compounds, Volumes 1-5 and Supplementals (Elsevier Science Publishers, 1989), Organic Reactions, Volumes 1-40 (John Wiley and Sons, 1991), March's Advanced Organic Chemistry, (John Wiley and Sons, 4th Edition), and Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989). These schemes are merely illustrative of some methods by which the compounds of this invention can be synthesized, and various modifications to these schemes can be made and will be suggested to one skilled in the art having referred to this disclosure.

As it will be apparent to those skilled in the art, conventional protecting groups may be necessary to prevent certain functional groups from undergoing undesired reactions.

Suitable protecting groups for various functional groups, as well as suitable conditions for protecting and deprotecting particular function groups are well known in the art. For example, numerous protecting groups are described in T.W. Greene and G.M. Wuts, Protecting Groups in Organic Synthesis, Second Edition, Wiley, New York, 1991, and references cited therein.

The starting materials and the intermediates of the reaction may be isolated and purified if desired using conventional techniques, including but not limited to filtration, distillation, crystallization, chromatography, and the like. Such materials may be characterized using conventional means, including physical constants and spectral data.
FIG. 2 shows some representative primary derivatives of diamondoids and the corresponding reactions. As shown in FIG. 2, there are, in general, three major reactions for the derivatization of diamondoids sorted by mechanism: nucleophilic (S_N1-type) and electrophilic (S_E2-type) substitution reactions, and free radical reaction (details for such reactions and their use with adamantane are shown, for instance in, "Recent developments in the adamantane and related polycyclic hydrocarbons" by R. C. Bingham and P. v. R. Schleyer as a chapter of the book entitled "Chemistry of Adamantanes", Springer-Verlag, Berlin Heidelberg New York, 1971 and in; "Reactions of adamantanes in electrophilic media" by I. K. Moiseev, N. V. Makarova, M. N. Zemtsova published in Russian Chemical Review, 68(12), 1001-1020 (1999); "Cage hydrocarbons" edited by George A. Olah, John Wiley & Son, Inc., New York, 1990).

S_N1 reactions involve the generation of diamondoids carbocations (there are several different ways to generate the diamondoid carbocations, for instance, the carbocation is generated from a parent diamantane or trimantane, a hydroxylated diamantane or trimantane or a halogenated diamantane or trimantane, shown in FIG. 3), which subsequently react with various nucleophiles. Some representative examples are shown in FIG. 4. Such nucleophiles include, for instance, the following: water (providing hydroxylated diamantane or trimantane); halide ions (providing halogenated diamantane or trimantane); ammonia (providing aminated diamantane or trimantane); azide (providing azidylated diamantane or trimantane); nitriles (the Ritter reaction, providing aminated diamantane or trimantane after hydrolysis); carbon monoxide (the Koch-Haaf reaction, providing carboxylated diamantane or trimantane after hydrolysis); olefins (providing alkenylated diamantane or trimantane after deprotonation); and aromatic reagents (providing arylated diamantane or trimantane after deprotonation). The reaction occurs similarly to those of open chain alkyl systems, such as t-butyl, t-cumyl and cycloalkyl systems. Since tertiary (bridgehead) carbons of diamondoids are considerably more reactive than secondary carbons under S_N1 reaction conditions, substitution at the tertiary carbons is favored.

S_E2-type reactions (i.e., electrophile substitution of a C-H bond via a five-coordinate carbocation intermediate) include, for instance, the following reactions: hydrogen-deuterium exchange upon treatment with deuterated superacids (e.g., DF-SbF_5 or DSO_3F-SbF_5); nitration upon treatment with nitronium salts, such as NO_2^+BF_4^- or NO_2^+PF_6^- in the presence of superacids (e.g., CF_3SO_2H); halogenation upon, for instance, reaction with Cl_2^+AgSbF_6; alkylation of the bridgehead carbons under the Friedel-Crafts conditions (i.e., S_E2-type σ
alkylation); carboxylation under the Koch reaction conditions; and, oxygenation under \(\text{Se}_2\)-type \(\sigma\) hydroxylation conditions (\(e.g.\), hydrogen peroxide or ozone using superacid catalysis involving \(\text{H}_3\text{O}_2^+\) or \(\text{HO}_3^+\), respectively). Some representative \(\text{Se}_2\)-type reactions are shown in FIG. 5.

Of those \(\text{SN}1\) and \(\text{SN}2\) reactions, \(\text{SN}1\)-type reactions are the most frequently used for the derivatization of diamondoids. However, such reactions produce the derivatives mainly substituted at the tertiary carbons. Substitution at the secondary carbons of diamondoids is not easy in carbonium ion processes since secondary carbons are considerably less reactive than the bridgehead positions (tertiary carbons) in ionic processes. Free radical reactions provide a method for the preparation of a greater number of the possible isomers of a given diamondoids than might be available by ionic processes. The complex product mixtures and/or isomers which result, however, are generally difficult to separate.

FIG. 6 shows some representative pathways for the preparation of brominated diamantane or triamantane derivatives. Mono- and multi-brominated diamondoids are some of the most versatile intermediates in the derivative chemistry of diamondoids. These intermediates are used in, for example, the Koch-Haaf, the Ritter, and the Friedel-Crafts alkylation/arylation reactions. Brominated diamondoids are prepared by two different general routes. One involves direct bromination of diamantane or triamantane with elemental bromine in the presence or absence of a Lewis acid (\(e.g.\), \(\text{BBr}_3\)-\(\text{AlBr}_3\)) catalyst. The other involves the substitution reaction of hydroxylated diamantane or triamantane with hydrobromic acid.

Direct bromination of diamantane or triamantane is highly selective resulting in substitution at the bridgehead (tertiary) carbons. By proper choice of catalyst and conditions, one, two, three, four, or more bromines can be introduced sequentially into the molecule, all at bridgehead positions. Without a catalyst, the mono-bromo derivative is the major product with minor amounts of higher bromination products being formed. By use of suitable catalysts, however, di-, tri-, and tetra-, penta-, and higher bromide derivatives are isolated as major products in the bromination (\(e.g.\), adding catalyst mixture of boron bromide and aluminum bromide with different molar ratios into the bromine reaction mixture). Typically, tetrabromo or higher bromo derivatives are synthesized at higher temperatures in a sealed tube.

Bromination reactions of diamondoids are usually worked up by pouring the reaction mixture onto ice or ice water and adding a suitable amount of chloroform or ethyl ether or
carbon tetrachloride to the ice mixture. Excess bromine is removed by distillation under vacuum and addition of solid sodium disulfide or sodium hydrogen sulfide. The organic layer is separated and the aqueous layer is extracted by chloroform or ethyl ether or carbon tetrachloride for an additional 2-3 times. The organic layers are then combined and washed with aqueous sodium hydrogen carbonate and water, and finally dried.

To isolate the brominated derivatives, the solvent is removed under vacuum. Typically, the reaction mixture is purified by subjecting it to column chromatography on either alumina or silica gel using standard elution conditions (e.g., eluting with light petroleum ether, n-hexane, or cyclohexane or their mixtures with ethyl ether). Separation by preparative gas chromatography (GC) or high performance liquid chromatography (HPLC) is used where normal column chromatography is difficult and/or the reaction is performed on extremely small quantities of material.

Similarly to bromination reactions, diamantanes and triamantanes are chlorinated or photochlorinated to provide a variety of mono-, di-, tri-, or even higher chlorinated derivatives of the diamondoids. FIG. 7 shows some representative pathways for the synthesis of chlorinated diamondoid derivatives.

FIG. 8 shows some representative pathways for the synthesis of hydroxylated diamantane or triamantane. Direct hydroxylation is also effected on diamantane or triamantane upon treatment with N-hydroxyphthalimide and a binary co-catalyst in acetic acid. Hydroxylation is a very important way of activating the diamondoid nuclei for further derivatizations, such as the generation of diamondoid carbocations under acidic conditions, which undergo the S_N1 reaction to provide a variety of diamondoid derivatives. In addition, hydroxylated derivatives are very important nucleophilic agents, by which a variety of diamondoid derivatives are produced. For instance, the hydroxylated derivatives are esterified under standard conditions such as reaction with an activated acid derivative. Alkylation to prepare ethers is performed on the hydroxylated derivatives through nucleophilic substitution on appropriate alkyl halides.

The above described three core derivatives (hydroxylated diamondoids and halogenated, especially brominated and chlorinated, diamondoids), in addition to the parent diamondoids or substituted diamondoids directly separated from the feedstocks as described above, are most frequently used for further derivatizations of diamantane or triamantane, such as hydroxylated and halogenated derivatives at the tertiary carbons are very important precursors for the generation of diamondoid carbocations, which undergo the S_N1 reaction to provide a variety of diamondoid derivatives thanks to the tertiary nature of the bromide or...
chloride or alcohol and the absence of skeletal rearrangements in the subsequent reactions. Examples are given below.

FIG. 9 shows some representative pathways for the synthesis of carboxylated diamondoids, such as the Koch-Haaf reaction, starting from hydroxylated or brominated diamantane or triamantane. It should be mentioned that for most cases, using hydroxylated precursors get better yields than using brominated diamantane or triamantane. For instance, carboxylated derivatives are obtained from the reaction of hydroxylated derivatives with formic acid after hydrolysis. The carboxylated derivatives are further esterified through activation (e.g., conversion to acid chloride) and subsequent exposure to an appropriate alcohol. Those esters are reduced to provide the corresponding hydroxymethyl diamantanes or triamantanes (diamantane or triamantane substituted methyl alcohols, D-CH$_2$OH). Amide formation is also performed through activation of the carboxylated derivative and reaction with a suitable amine. Reduction of the diamondoid carboxamide with reducing agents (e.g., lithium aluminum hydride) provides the corresponding aminomethyl diamondoids (diamantane or triamantane substituted methylamines, D-CH$_2$NH$_2$).

FIG. 10 shows some representative pathways for the synthesis of acylaminated diamondoids, such as the Ritter reaction starting from hydroxylated or brominated diamondoids. Similarly to the Koch-Haaf reaction, using hydroxylated precursors get better yields than using brominated diamondoids in most cases. Acylaminated diamondoids are converted to amino derivatives after alkaline hydrolysis. Amino diamondoids are further converted to, without purification in most cases, amino diamondoid hydrochloride by introducing hydrochloride gas into the aminated derivatives solution. Amino diamondoids are some of very important precursors. They are also prepared from the reduction of nitrated compounds. FIG. 11 shows some representative pathways for the synthesis of nitro diamondoid derivatives. Diamondoids are nitrated by concentrated nitric acid in the presence of glacial acetic acid under high temperature and pressure. The nitrated diamondoids are reduced to provide the corresponding amino derivatives. In turn, for some cases, amino diamondoids are oxidized to the corresponding nitro derivatives if necessary. The amino derivatives are also synthesized from the brominated derivatives by heating them in the presence of formamidine and subsequently hydrolyzing the resultant amide.

Similarly to the hydroxylated compounds, amino diamondoids are acylated or alkylated. For instance, reaction of an amino diamondoid with an activated acid derivative produces the corresponding amide. Alkylation is typically performed by reacting the amine with a suitable carbonyl containing compound in the presence of a reducing agent (e.g.,
lithium aluminum hydride. The amino diamondoids undergo condensation reactions with carbamates such as appropriately substituted ethyl N-arylsulfonylcarbamates in hot toluene to provide, for instance, N-arylsulfonyl-N'-diamondoidylureas.

FIG. 12 presents some representative pathways for the synthesis of alkylated, alkenylated, alkynylated and arylated diamondoids, such as the Friedel-Crafts reaction. Ethynylated diamondoid derivatives are synthesized by reacting a brominated diamondoid with ethylene in the presence of AlBr₃ followed by dehydrogen bromide with potassium hydroxide (or the like). The ethynylated compound is transformed into the corresponding epoxide under standard reaction conditions (e.g., 3-chloroperbenzoic acid). Oxidative cleavage (e.g., ozonolysis) of the ethynylated diamondoid affords the related aldehyde. The ethynylated diamondoid derivatives are obtained by treating a brominated diamondoid with vinyl bromide in the presence of AlBr₃. The resultant product is dehydrogen bromide using KOH or potassium t-butoxide to provide the desired compound.

More reactions are illustrative of methods which can be used to functionalize diamondoids. For instance, fluorination of a diamondoid is carried out by reacting the diamondoid with a mixture of poly(hydrogen fluoride) and pyridine (30% Py, 70% HF) in the presence of nitronium tetrafluoroborate. Sulfur tetrafluoride reacts with a diamondoid in the presence of sulfur monochloride to afford a mixture of mono-, di-, tri- and even higher fluorinated diamondoids. Iodo diamondoids are obtained by a substitutive iodination of chloro, bromo or hydroxyl diamondoids.

Reaction of the brominated derivatives with hydrochloric acid in dimethylformamide (DMF) converts the compounds to the corresponding hydroxylated derivatives. Brominated or iodinated diamondoids are converted to thiolated diamondoids by way of, for instance, reacting with thioacetic acid to form diamondoid thioacetates followed by removal of the acetate group under basic conditions. Brominated diamondoids, e.g., D-Br, are heated under reflux with an excess (10 fold) of hydroxyalkylamine, e.g., HO-CH₂CH₂-NH₂, in the presence of a base, e.g., triethylamine, diamondoidyloxyalkylamine, e.g., D-O-CH₂CH₂-NH₂, is obtained. On acetylation of the amines with acetic anhydride and pyridine, a variety of N-acetyl derivatives are obtained. Direct substitution reaction of brominated diamondoids, e.g., D-Br, with sodium azide in dipolar aprotic solvents, e.g., DMF, to afford the azido diamondoids, e.g., D-N₃.

Diamondoid carboxylic acid hydrazides are prepared by conversion of diamondoid carboxylic acid into a chloroanhydride by thionyl chloride and condensation with isonicotinic or nicotinic acid hydrazide (FIG. 13).
Diamondoidones or “diamondoid oxides” are synthesized by photooxidation of diamondoids in the presence of peracetic acid followed by treatment with a mixture of chromic acid-sulfuric acid. Diamondoidones are reduced by, for instance, LiAlH₄, to diamondoidols hydroxylated at the secondary carbons. Diamondoidones also undergo acid-catalyzed (HCl-catalyzed) condensation reaction with, for example, excess phenol or aniline in the presence of hydrogen chloride to form 2,2-bis(4-hydroxyphenyl) diamondoids or 2,2-bis(4-aminophenyl) diamondoids.

Diamondoidones (e.g., D=O) are treated with RCN (R = hydrogen, alkyl, aryl, etc.) and reduced with LiAlH₄ to give the corresponding C-2-aminomethyl-C-2-D-OH, which are heated with COCl₂ or CS₂ to give afford the following derivatives shown in formula IV (where Z = O or S):

\[
\text{IV}
\]

Diamondoidones react with a suitable primary amine in an appropriate solvent to form the corresponding imines. Hydrogenation of the imines in ethanol using Pd/C as the catalyst at about 50°C to afford the corresponding secondary amines. Methylation of the secondary amines following general procedures (see, for instance, H. W. Geluk and V. G. Keiser, \textit{Organic Synthesis}, \textit{53}:8 (1973)) to give the corresponding tertiary amines. Quaternization of the tertiary amines by, for instance, slowly dropping CH₃I (excess) into an ethanol solution of the amine at around 35°C to form the corresponding quaternary amines.

C-2 derivatives of diamondoids, C-2 D-R' (R' = alkyl, alkoxy, halo, OH, Ph, COOH, CH₂COOH, NHCOCH₃, CF₃COOH) are prepared by nucleophilic substitution of diamondoid-C-2-spiro-C-3-diazirine in solution at 0-80°C in the presence of an acid catalyst.

N-sulfinyl diamondoids [D-(NSO)ₙ, n=1, 2, 3, 4,...] are prepared by refluxing the diamondoid-HCl with SOCl₂ in benzene for about half an hour to several hours affording mono-, di, tri-, or higher N-sulfinyl diamondoid derivatives.

Treatment of D-Br and/or D-Cl with HCONH₂ (wt. ratio not >1:2) at <195°C followed by hydrolysis of the formylamino diamondoids D-NHCHO with <20% HCl at <110°C affords the amino diamondoid hydrochloride D-NH₂HCl.

Diamondoid dicarboxamides are prepared by the reaction of diamondoid dicarbonyl chloride or diamondoid diacetyl chloride with aminoalkylamines. For instance, D-(COCl)₂
[from SOCl₂ and the corresponding dicarboxylic acid D-(COOH)₂] are treated with 
(CH₃)₂NCH₂CH₂CH₂NH₂ in C₅H₅N-C₆H₆ to give N,N'-bis(dimethylaminopropyl) 
diamondoid dicarboxamide.

Aminoethoxyacetylamino diamondoids are prepared from chloroacetamino 
diamondoids and HOCH₂CH₂NR'R''. Thus, for instance, amino diamondoids, D-NH₂, and 
ClCH₂COCl in benzene, is added to (CH₃)₂NCH₂CH₂ONa in xylene and refluxed for about 
10 hours to give aminoethoxyacetylamino diamondoids (R'=R''=CH₃).

Ritter reaction of C-3 D-OH and HCN gives D-NH₂; the preparation of D-NHCHO 
from diamondoids and HCN; the reaction of diamondoids with nitriles gives D-NHCHO and 
D-NH₂; the preparation of aza diamondoids from nitriles and compounds containing 
unsaturated OH groups, and SH groups, and so on.

Hydroxylated diamondoids, e.g., D-OH, react with COCl₂ or CS₂Cl₂ to afford the 
diamondoidyloxycarbonyl derivatives, e.g., D-O-C(O)Cl or D-O-C(S)Cl the former being an 
important blocking group in biochemical syntheses.

FIG. 14 shows representative reactions starting from D-NH₂ and D-CONH₂ and the 
corresponding derivatives.

FIG. 15 shows representative reactions starting from D-POCl₂ and the corresponding 
derivatives.

FIG. 16 shows representative reactions starting from D-SH or D-SOCl and the 
corresponding derivatives.

It is noted that many of the derivatizations described herein are merely exemplary and 
provide guidance to the skilled artisan for synthesizing diamantane and triamanate 
derivatives of the Formula I, Ia, II, and III according to the present invention.

Utility

The derivatives of diamantane and triamanate of the subject invention exhibit 
pharmaceutical activity, useful in the treatment, inhibition and/or prevention of neurologic 
disorders.

The diamantane and triamanate analogs of the present invention exhibit activity 
against neurologic disorders. Because diamantane and triamanate are larger than 
adamanate, the diffusivity of diamantane, triamanate and their derivatives will be lower 
than that of adamantane and its corresponding derivatives. This will lead to a slower release 
of the blocking agent from the ion channel.
In addition, substituting two amino groups onto the diamantane structure, as opposed to one amino group, improves the aqueous solubility, and decreases the lipid solubility, which will improve the bioavailability of the molecule. As diamantane and triamantane have rigid structures, they exhibit excellent bioavailability, as well as the ability to pass through the blood-brain barrier.

One mechanism of action of the present compounds includes the regulation of glutamate. Glutamate is the main neurotransmitter in the brain. Glutamatergic overstimulation results in neuronal damage and a condition termed excitotoxicity. The excitotoxicity leads to neuronal calcium overload and has been implicated in neurodegenerative disorders such as Alzheimer's disease. Glutamate stimulates a number of receptors, including the N-methyl-D-aspartate (NMDA) receptor. NMDA receptors are activated by concentrations of glutamate. In order to prevent excessive influx, the ion channel is blocked by a Mg++ under resting conditions.

Overexcitation of NMDA receptors by glutamate may play a role in Alzheimer's disease, as glutamate plays an integral role in the neural pathways associated with learning and memory, and is likely implicated or is affected by many neurologic disorders. The excitotoxicity produced by excessive amounts of glutamate is thought to contribute to neuronal cell death observed in Alzheimer's disease. The compounds of the subject invention are useful in selectively blocking the excitotoxic effects associated with excessive transmission of glutamate, while still allowing enough glutamate activation to preserve normal cell functioning.

For example, it was recently discovered that 1-amino-3,5-dimethyladamantane (Namenda™ (memantine) Forest Pharmaceuticals, Inc.) was effective at treating moderate to severe Alzheimer's disease. Numerous studies have demonstrated the effectiveness of memantine therapy including significant improvement in patients with vascular dementia and significant improvement in motor functions, cognition and social behaviors. However, although adamantanes such as amantadine and rimantadine have not shown great efficacy as NMDA channel blockers, the present diamantane and triamantane derivatives show improvement in this regard, especially as to regulating the Ca++ influx.

Memantine is a prototypical comparator in pre-clinical studies seeking new chemical entities which share a similar low affinity, uncompetitive mode of inhibition. Memantine was synthesized in the 1960s, although it's primary mode of action was not recognized as an NR inhibitor until the late 1980s. During this time an extensive clinical history has shown memantine to have some efficacy with minimal side effects [Rogawski, M. A. (2000). "Low
affinity channel blocking (uncompetitive) NMDA receptor antagonists as therapeutic agents—
toward an understanding of their favorable tolerability." Amino Acids 19(1): 133-49.; Lipton,
S. A. (2006), "Paradigm shift in neuroprotection by NMDA receptor blockade: memantine
and beyond." Nat Rev Drug Discov 5(2): 160-70]. This comparative approach to drug
discovery has demonstrated pre-clinical utility of compounds suitable for a broad spectrum of
neurologic disorders which are being pursued in the clinic to treat Parkinson’s disease
[Danysz, W., C. G. Parsons, et al. (1997). "Aminoadamantanes as NMDA receptor
antagonists and antiparkinsonian agents--preclinical studies." Neurosci Biobehav Rev 21(4):
action in Alzheimer’s disease and other neurologic disorders: low-affinity, uncompetitive
"The neuropathopharmacological basis for the use of memantine in the treatment of Alzheimer's
disease," CNS Drug Rev 9(3): 275-308.], a variety of acute and chronic neurologic insults
[Lipton, S. A. (2004). "Failures and successes of NMDA receptor antagonists: molecular
basis for the use of open-channel blockers like memantine in the treatment of acute and
chronic neurologic insults." NeuroRx 1(1): 101-10.], HIV-associated dementia or HAD
[Anderson ER 2004 Memantine protects hippocampal neuronal function in muringe human
"Could cholinesterase inhibitors and memantine alleviate HIV dementia?" J Acquir Immune
consequences for the central nervous system." Cell Death Differ 12 Suppl 1: 878-92.],
neuropathic pain [Parsons, C. G. (2001). "NMDA receptors as targets for drug action in
neuropathic pain." Eur J Pharmacol 429(1-3): 71-8.], and substance abuse [Danysz, W., C. G.
Parsons, et al. (2002). "Amino-alkyl-cyclohexanes as a novel class of uncompetitive NMDA
receptor antagonists." Curr Pharm Des 8(10): 835-43.]. Interestingly, although this search
strategy has been pursued with adamantane derivatives [Losi G 2006 “Functional in vitro
characterization of CR 3394: A novel voltage dependent N-methyl-D-aspartate (NMDA)
receptor antagonist” Neuropharmacol 50: 277.], most work has lead to a variety of chemical
structures which lack the adamantane nucleus [Parsons 2001 “NMDA receptors as targets for
drug action in neuropathic pain” Eur J Pharmacol 429: 71.; Danysz W and Parsons CG, 2002
"Neuroprotective potential of ionotrophic glutamate receptor antagonists Neurotox Res
4:119; Planells-Cases R et. al. 2002 “A novel N-methyl-D-aspartate receptor open channel
blocker with in vivo neuroprotectant activity” J Pharmacol Exp Thera 302: 163.]; Bleich S
et. al. 2003 “Glutamate and the glutamate receptor system: a target for drug action” Int J

The mechanistic understanding of why low affinity, uncompetitive NR antagonists are preferred clinical candidates is a subject of much experimentation and debate. No less than eight mechanisms are discussed in a recent review [Johnson JW and Kotermanski SE 2006 “Mechanism of action of memantine” Curr Opin Pharmacol 6:61].

1. the ability to bind only (or preferentially) to open channels;
2. the tendency to inhibit faster, or with higher affinity, at higher agonist concentrations;
3. a relatively low affinity of inhibition;
4. relatively fast unblocking kinetics;
5. relatively strong voltage dependence;
6. an ability to be trapped in some but not all receptors;
7. an ability to inhibit at two different sites;
8. and NMDAR subtype specificity, or lack thereof.

Current experiments are defining the role that specific amino acid residues lining the NR pore have on key functions affected by channel-binding inhibitors: gating and desensitization [Chen N et. al. 2004 “Site within N-methyl-D-aspartate receptor pore modulates channel gating” Mol Pharmacol 65:157; Yuan H et. al. 2005 “Conserved structural and functional control of N-methyl-d-aspartate receptor gating by transmembrane domain M3” J Biol Chem 280:29708. ; Thomas CG, et al. 2006 “Probing N-methyl-D-aspartate receptor desensitization with the substituted-cysteine accessibility method” Mol Pharmacol. 2006 Apr;69(4):1296-303]. There is also increasing evidence for two binding sites in the NR pore, one near the vestibule or pore entrance and a second deep within the pore near the selectivity filter, and evidence that inhibitors may bind each with differing affinities and functional consequences [Sobolevsky A and Koshelev 1998 “Two blocking sites of amino-adamantane derivatives in open N-methyl-d-aspartate channels” Biophysical J 74: 1305.; Kashiwagi K, et. al. 2002 “Channel blockers acting at N-methyl-D-aspartate receptors: Differential effects of mutation in the vestibule and ion channel pore” Mol Pharmacol 61:533; Chen H-S and Lipton SA 2005 “Pharmacological implications of two distinct mechanism of interaction of memantine with N-methyl-d-aspartate-gated channels” J Pharmacol Exp Ther 314:961; Bolshakov KV et. al. 2005 “Design of antagonists for NMDA and AMPA receptors” Neuropharmacol 42: 144.].
The compounds of the present invention may be used to treat, manage, and prevent neurologic disorders, including those associated with excessive activity of the NMDA receptor. If the NMDA receptor is activated by glutamate continuously, the influx of calcium increases which produces enhanced noise. This noise greatly reduces the chance of the receptor recognizing the relevant signal once it arrives, and cognitive and neuronal function decreases. The following neurologic diseases and conditions relate to the overexcitation of the NMDA receptor, and thus may be treated by the present compounds.

The term neurologic disorder embraces a collection of diseases and conditions, with each type consisting of numerous subsets. Preferred neurologic disorders to be treated, inhibited, and/or prevented with the triamantane and diamantane derivatives set forth herein, include but are not limited to, epilepsy, narcolepsy, neurodegenerative disorders, pain, and psychiatric disorders.

Pain includes both acute pain and chronic pain. Acute pain is pain that lasts or is anticipated to last a short time, typically less than one month. Chronic pain is pain persisting greater than one month beyond the resolution of an acute tissue injury, pain persisting or recurring for more than three months, or pain associated with tissue injury that is expected to continue. Pain may include neuropathic pain, including acute pain where the present compounds may also be used as an adjunct to other analgesic agents as well as administered alone.

Neurodegenerative disorders may include Alzheimer's Disease, Parkinson's Disease, stroke, AIDS related dementia, traumatic brain injury (TBI), and Huntington's Disease.

A stroke occurs when the blood supply to part of the brain is suddenly interrupted or when a blood vessel in the brain bursts, spilling blood into the spaces surrounding brain cells. Brain cells die when they no longer receive oxygen and nutrients from the blood or there is sudden bleeding into or around the brain. The symptoms of a stroke include sudden numbness or weakness, sudden confusion or trouble speaking or understanding speech; sudden trouble seeing in one or both eyes; sudden trouble with walking, dizziness, or loss of balance or coordination; or sudden severe headache with no known cause. Generally there are three treatment stages for stroke: prevention, including therapy immediately after the stroke, and post-stroke rehabilitation. The most popular classes of drugs used to prevent or treat stroke are antithrombotics (antiplatelet agents and anticoagulants) and thrombolytics. Recurrent stroke is frequent; about 25 percent of people who recover from their first stroke will have another stroke within five years.
TBI is characterized by is caused by a blow or jolt to the head or a penetrating head injury that disrupts the normal function of the brain. The severity of a TBI may be mild, resulting in only a brief change in mental status or consciousness to severe, with extended results including amnesia and unconsciousness or amnesia after the injury. Severe neural degeneration may occur following a brain injury, and is believed to evolve in a biphasic manner consisting of the primary mechanical insult and then a progressive secondary necrosis. Symptoms of a traumatic brain injury include functional changes affecting thinking, sensation, language, and/or emotions. Psychiatric disorders may include substance abuse. The substance abuse may include drug abuse and/or alcohol abuse.

Epilepsy is a recurrent, paroxysmal disorder of cerebral function characterized by sudden, brief attacks of altered consciousness, motor activity, sensory phenomena, or inappropriate behavior caused by excessive discharge of the cerebral neurons.

Narcolepsy is a recurrent disorder characterized by an pathologic increase in absolute sleep hours, usually by greater than 25 percent. See, for example, Xie et al., GABAB receptor-mediated modulation of hypocretin/orexin neurones in mouse hypothalamus. J Physiol, 2006, which as showing that NMDA responsive cells are implicated in narcolepsy. Narcolepsy is not definitively diagnosed in most patients until 10 to 15 years after the first symptoms appear. There is no cure for narcolepsy.

These diseases are divisible into two groups. In one group, the process inevitably produces dementia if it progresses through its full course; these are the conditions thought to affect the brain primarily or exclusively, such as Alzheimer's disease, Huntington's disease, and Parkinson-dementia complex. Other diseases may or may not produce dementia, depending upon whether or how the brain is affected. Examples are liver disease with portacaval encephalopathy, metabolic disorders such as hypothyroidism, or infectious disorders such as syphilis or acquired immune deficiency syndrome. Dementia, a clinical syndrome, can be produced by numerous pathological states that affect the brain. These pathological states can be divided into those that appear to be primary in the brain, such as Alzheimer's disease, and those which are outside the brain and affect it secondarily.

Certain chronic viral illnesses, such as human immunodeficiency virus, are known to produce dementia with great frequency. Thiamine deficiency produces Wernicke-Korsakoff's encephalopathy, which may cause Korsakoff's dementia. Thiamine deficiency is a preventable nutritional deficiency seen in the context of alcoholism, pernicious vomiting of pregnancy, depression, or any other condition in which this deficiency occurs.
Management of the underlying states can arrest and sometimes reverse the dementias of cardiovascular origin. Hypertension, especially severe hypertension, is one of the most frequent causes of dementia. Other causes are atherosclerosis and arteriosclerosis without hypertension, vasculitis, and emboli from the heart or elsewhere in the vascular system. Cardiac disease also produces dementia by single or repeated episodes of cerebral ischemia and hypoxia due to acute or intermittent disorders of cardiac function.

Alzheimer's Disease is the most common of all the dementing diseases. Other dementing diseases include those of the basal ganglia, (such as Parkinson's Disease and Huntington's Disease), of the cerebellum (cerebellar and spinocerebellar degenerations, olivopontocerebellar degeneration), and of the motor neurone (amyotrophic lateral sclerosis).

Pharmaceutical Formulations

In general, the compounds of the subject invention will be administered in a therapeutically effective amount by any of the accepted modes of administration for these compounds. The compounds can be administered by a variety of routes, including, but not limited to, oral, parenteral (e.g., subcutaneous, subdural, intravenous, intramuscular, intrathecal, intraperitoneal, intracerebral, intraarterial, or intralesional routes of administration), topical, intranasal, localized (e.g., surgical application or surgical suppository), rectal, and pulmonary (e.g., aerosols, inhalation, or powder). Accordingly, these compounds are effective as both injectable and oral compositions. Preferably, the compounds are administered by oral route. Also preferably, the compounds are administered by parenteral routes. The compounds can be administered continuously by infusion or by bolus injection. More preferably, the compounds are administered by intravenous routes.

Such compositions are prepared in a manner well known in the pharmaceutical art.

The actual amount of the compound of the subject invention, i.e., the active ingredient, will depend on a number of factors, such as the severity of the disease, i.e., the condition or disease to be treated, the age and relative health of the subject, the potency of the compound used, the route and form of administration, and other factors.

Toxicity and therapeutic efficacy of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD50 (the dose lethal to 50% of the population) and the ED50 (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD50/ED50. Compounds that exhibit large therapeutic indices are preferred.
The data obtained from cell culture assays and animal studies can be used in formulating a range of dosage for use in humans and other animal patients. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED$_{50}$ with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. For any compound used in the method of the invention, the therapeutically effective dose can be estimated initially from cell culture assays. A dose may be formulated in animal models to achieve a circulating plasma concentration range which includes the IC$_{50}$ (i.e., the concentration of the test compound which achieves a half-maximal inhibition of symptoms) as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Levels in plasma may be measured, for example, by high performance liquid chromatography. The effective blood level of the compounds of the subject invention is preferably greater than or equal to 40 ng/ml.

The amount of the pharmaceutical composition administered to the patient will vary depending upon what is being administered, the purpose of the administration, such as prophylaxis or therapy, the state of the patient, the manner of administration, and the like. In therapeutic applications, compositions are administered to a patient already suffering from a disease in an amount sufficient to cure or at least partially arrest the symptoms of the disease and its complications. An amount adequate to accomplish this is defined as “therapeutically effective dose.” Amounts effective for this use will depend on the disease condition being treated as well as by the judgment of the attending clinician depending upon factors such as the severity of the inflammation, the age, weight and general condition of the patient, and the like.

The compositions administered to a patient are in the form of pharmaceutical compositions described supra. These compositions may be sterilized by conventional sterilization techniques, or may be sterile filtered. The resulting aqueous solutions may be packaged for use as is, or lyophilized, the lyophilized preparation being combined with a sterile aqueous carrier prior to administration. The pH of the compound preparations typically will be between 3 and 11, more preferably from 5 to 9 and most preferably from 7 to 8. It will be understood that use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of pharmaceutical salts.

The active compound is effective over a wide dosage range and is generally administered in a pharmaceutically or therapeutically effective amount. The therapeutic dosage of the compounds of the present invention will vary according to, for example, the
particular use for which the treatment is made, the manner of administration of the compound, the health and condition of the patient, and the judgment of the prescribing physician. For example, for oral administration, the dose will typically be in the range of about 5 mg to about 300 mg per day, preferably about 100 mg to about 200 mg per day. For intravenous administration, the dose will typically be in the range of about 0.5 mg to about 50 mg per kilogram body weight, preferably about 2 mg to about 20 mg per kilogram body weight. Effective doses can be extrapolated from dose-response curves derived from in vitro or animal model test systems. Typically, the clinician will administer the compound until a dosage is reached that achieves the desired effect.

When employed as pharmaceuticals, the compounds of the subject invention are usually administered in the form of pharmaceutical compositions. This invention also includes pharmaceutical compositions, which contain as the active ingredient, one or more of the compounds of the subject invention above, associated with one or more pharmaceutically acceptable carriers or excipients. The excipient employed is typically one suitable for administration to human subjects or other mammals. In making the compositions of this invention, the active ingredient is usually mixed with an excipient, diluted by an excipient or enclosed within a carrier which can be in the form of a capsule, sachet, paper or other container. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders.

In preparing a formulation, it may be necessary to mill the active compound to provide the appropriate particle size prior to combining with the other ingredients. If the active compound is substantially insoluble, it ordinarily is milled to a particle size of less than 200 mesh. If the active compound is substantially water soluble, the particle size is normally adjusted by milling to provide a substantially uniform distribution in the formulation, e.g., about 40 mesh.

Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, sterile water, syrup, and methyl cellulose. The formulations can additionally include: lubricating agents such as talc,
magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl- and propylhydroxy-benzoates; sweetening agents; and flavoring agents. The compositions of the invention can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures known in the art.

The quantity of active compound in the pharmaceutical composition and unit dosage form thereof may be varied or adjusted widely depending upon the particular application, the manner or introduction, the potency of the particular compound, and the desired concentration. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient. The concentration of therapeutically active compound may vary from about 0.5 mg/ml to 500 g/ml.

Preferably, the compound can be formulated for parenteral administration in a suitable inert carrier, such as a sterile physiological saline solution. For example, the concentration of compound in the carrier solution is typically between about 1-100 mg/ml. The dose administered will be determined by route of administration. Preferred routes of administration include parenteral or intravenous administration. A therapeutically effective dose is a dose effective to produce a significant steroid tapering. Preferably, the amount is sufficient to produce a statistically significant amount of steroid tapering in a subject.

By way of example, for preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical excipient to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation is then subdivided into unit dosage forms of the type described above containing from, for example, 0.1 to about 500 mg of the active ingredient of the present invention.

The tablets or pills of the present invention may be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer, which serves to resist disintegration in the stomach and permit the inner component to
pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol, and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as corn oil, cottonseed oil, sesame oil, coconut oil, or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Syrups are preferred.

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as described supra. The compositions may be administered by the oral or nasal respiratory route for local or systemic effect. Compositions in preferably pharmaceutically acceptable solvents may be nebulized by use of inert gases. Nebulized solutions may be inhaled directly from the nebulizing device or the nebulizing device may be attached to a face mask tent, or intermittent positive pressure breathing machine. Solution, suspension, or powder compositions may be administered, preferably orally or nasally, from devices which deliver the formulation in an appropriate manner.

The compounds of this invention can be administered in a sustained release form. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing the protein, which matrices are in the form of shaped articles, e.g., films, or microcapsules. Examples of sustained-release matrices include polyesters, hydrogels (e.g., poly(2-hydroxyethyl-methacrylate) as described by Langer et al., J. Biomed. Mater. Res. 15: 167-277 (1981) and Langer, Chem. Tech. 12: 98-105 (1982) or poly(vinyl alcohol)), polylactides (U.S. Patent No. 3,773,919), copolymers of L-glutamic acid and gamma ethyl-L-glutamate (Sidman et al., Biopolymers 22: 547-556, 1983), non-degradable ethylene-vinyl acetate (Langer et al., supra), degradable lactic acid-glycolic acid copolymers such as the LUPRON DEPOT™ (i.e., injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), and poly-D-(-)-3-hydroxybutyric acid (EP 133,988).

The compounds of this invention can be administered in a sustained release form, for example a depot injection, implant preparation, or osmotic pump, which can be formulated in such a manner as to permit a sustained release of the active ingredient. Implants for sustained
release formulations are well-known in the art. Implants may be formulated as, including but not limited to, microspheres, slabs, with biodegradable or non-biodegradable polymers. For example, polymers of lactic acid and/or glycolic acid form an erodible polymer that is well-tolerated by the host. The implant is placed in proximity to the site of protein deposits (e.g., the site of formation of amyloid deposits associated with neurodegenerative disorders), so that the local concentration of active agent is increased at that site relative to the rest of the body.

The following formulation examples illustrate pharmaceutical compositions of the present invention.

**Formulation Example 1**

Hard gelatin capsules containing the following ingredients are prepared:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity (mg/capsule)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active Ingredient</td>
<td>30.0</td>
</tr>
<tr>
<td>Starch</td>
<td>305.0</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>5.0</td>
</tr>
</tbody>
</table>

The above ingredients are mixed and filled into hard gelatin capsules in 340 mg quantities.

**Formulation Example 2**

A tablet formula is prepared using the ingredients below:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity (mg/capsule)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active Ingredient</td>
<td>25.0</td>
</tr>
<tr>
<td>Cellulose, microcrystalline</td>
<td>200.0</td>
</tr>
<tr>
<td>Colloidal silicon dioxide</td>
<td>10.0</td>
</tr>
<tr>
<td>Stearic acid</td>
<td>5.0</td>
</tr>
</tbody>
</table>

The components are blended and compressed to form tablets, each weighing 240 mg.

**Formulation Example 3**

A dry powder inhaler formulation is prepared containing the following components:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Weight %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active Ingredient</td>
<td>5</td>
</tr>
</tbody>
</table>
Lactose 95

The active mixture is mixed with the lactose and the mixture is added to a dry powder inhaling appliance.

Formulation Example 4

Tablets, each containing 30 mg of active ingredient, are prepared as follows:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity (mg/capsule)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active Ingredient</td>
<td>30.0 mg</td>
</tr>
<tr>
<td>Starch</td>
<td>45.0 mg</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>35.0 mg</td>
</tr>
<tr>
<td>Polyvinylpyrrolidone (as 10% solution in water)</td>
<td>4.0 mg</td>
</tr>
<tr>
<td>Sodium carboxymethyl starch</td>
<td>4.5 mg</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>0.5 mg</td>
</tr>
<tr>
<td>Talc</td>
<td>1.0 mg</td>
</tr>
<tr>
<td>Total</td>
<td>120 mg</td>
</tr>
</tbody>
</table>

The active ingredient, starch and cellulose are passed through a No. 20 mesh U.S. sieve and mixed thoroughly. The solution of polyvinyl-pyrrolidone is mixed with the resultant powders, which are then passed through a 16 mesh U.S. sieve. The granules so produced are dried at 50° to 60°C and passed through a 16 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate, and talc, previously passed through a No. 30 mesh U.S. sieve, are then added to the granules, which after mixing, are compressed on a tablet machine to yield tablets each weighing 150 mg.
Formulation Example 5
Capsules, each containing 40 mg of medicament are made as follows:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>(mg/capsule)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active Ingredient</td>
<td>40.0 mg</td>
</tr>
<tr>
<td>Starch</td>
<td>109.0 mg</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>1.0 mg</td>
</tr>
<tr>
<td>Total</td>
<td>150.0 mg</td>
</tr>
</tbody>
</table>

The active ingredient, cellulose, starch, an magnesium stearate are blended, passed through a No. 20 mesh U.S. sieve, and filled into hard gelatin capsules in 150 mg quantities.

Formulation Example 6
Suppositories, each containing 25 mg of active ingredient are made as follows:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active Ingredient</td>
<td>25 mg</td>
</tr>
<tr>
<td>Saturated fatty acid glycerides</td>
<td>to 2,000 mg</td>
</tr>
</tbody>
</table>

The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2.0 g capacity and allowed to cool.

Formulation Example 7
Suspensions, each containing 50 mg of medicament per 5.0 ml dose are made as follows:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active Ingredient</td>
<td>50.0 mg</td>
</tr>
<tr>
<td>Xanthan gum</td>
<td>4.0 mg</td>
</tr>
<tr>
<td>Sodium carboxymethyl cellulose (11%)</td>
<td></td>
</tr>
<tr>
<td>Microcrystalline cellulose (89%)</td>
<td></td>
</tr>
<tr>
<td>Sucrose</td>
<td>1.75 g</td>
</tr>
<tr>
<td>Sodium benzoate</td>
<td>10.0 mg</td>
</tr>
<tr>
<td>Flavor and Color</td>
<td>q.v.</td>
</tr>
<tr>
<td>Purified water</td>
<td>to 5.0 ml</td>
</tr>
</tbody>
</table>

The medicament, sucrose and xanthan gum are blended, passed through a No. 10 mesh U.S. sieve, and then mixed with a previously made solution of the microcrystalline
cellulose and sodium carboxymethyl cellulose in water. The sodium benzoate, flavor, and color are diluted with some of the water and added with stirring. Sufficient water is then added to produce the required volume.

Formulation Example 8

Hard gelatin tablets, each containing 15 mg of active ingredient are made as follows:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity (mg/capsule)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active Ingredient</td>
<td>15.0 mg</td>
</tr>
<tr>
<td>Starch</td>
<td>407.0 mg</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>3.0 mg</td>
</tr>
<tr>
<td>Total</td>
<td>425.0 mg</td>
</tr>
</tbody>
</table>

The active ingredient, cellulose, starch, and magnesium stearate are blended, passed through a No. 20 mesh U.S. sieve, and filled into hard gelatin capsules in 560 mg quantities.

Formulation Example 9

An intravenous formulation may be prepared as follows:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active Ingredient</td>
<td>250.0 mg</td>
</tr>
<tr>
<td>Isotonic saline</td>
<td>1000 ml</td>
</tr>
</tbody>
</table>

Therapeutic compound compositions generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle or similar sharp instrument.

Formulation Example 10

A topical formulation may be prepared as follows:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active Ingredient</td>
<td>1-10 g</td>
</tr>
<tr>
<td>Emulsifying Wax</td>
<td>30 g</td>
</tr>
<tr>
<td>Liquid Paraffin</td>
<td>20 g</td>
</tr>
<tr>
<td>White Soft Paraffin</td>
<td>to 100 g</td>
</tr>
</tbody>
</table>

The white soft paraffin is heated until molten. The liquid paraffin and emulsifying wax are incorporated and stirred until dissolved. The active ingredient is added and stirring is continued until dispersed. The mixture is then cooled until solid.
Formulation Example 11

An aerosol formulation may be prepared as follows:

A solution of the candidate compound in 0.5% sodium bicarbonate/saline (w/v) at a concentration of 30.0 mg/mL is prepared using the following procedure:

**A. Preparation of 0.5% Sodium Bicarbonate / Saline Stock Solution: 100.0 mL**

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Gram / 100.0 mL</th>
<th>Final Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium Bicarbonate</td>
<td>0.5 g</td>
<td>0.5%</td>
</tr>
<tr>
<td>Saline</td>
<td>q.s. ad 100.0 mL</td>
<td>q.s. ad 100%</td>
</tr>
</tbody>
</table>

Procedure:

1. Add 0.5g sodium bicarbonate into a 100 mL volumetric flask.
2. Add approximately 90.0 mL saline and sonicate until dissolved.
3. Q.S. to 100.0 mL with saline and mix thoroughly.

**B. Preparation of 30.0 mg/mL Candidate Compound: 10.0 mL**

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Gram / 10.0 mL</th>
<th>Final Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candidate Compound</td>
<td>0.300 g</td>
<td>30.0 mg/mL</td>
</tr>
<tr>
<td>0.5% Sodium Bicarbonate / Saline Stock Solution</td>
<td>q.s. ad 10.0 mL</td>
<td>q.s. ad 100%</td>
</tr>
</tbody>
</table>

Procedure:

1. Add 0.300 g of the candidate compound into a 10.0 mL volumetric flask.
2. Add approximately 9.7 mL of 0.5% sodium bicarbonate / saline stock solution.
3. Sonicate until the candidate compound is completely dissolved.
4. Q.S. to 10.0 mL with 0.5% sodium bicarbonate / saline stock solution and mix thoroughly.

Another preferred formulation employed in the methods of the present invention employs transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the compounds of the present invention in controlled amounts. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art. See, e.g., U.S. Patent No. 5,023,252, issued June 11, 1991, herein incorporated by reference in its entirety for or all purposes. Such
patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

Direct or indirect placement techniques may be used when it is desirable or necessary to introduce the pharmaceutical composition to the brain. Direct techniques usually involve placement of a drug delivery catheter into the host's ventricular system to bypass the blood-brain barrier. One such implantable delivery system used for the transport of biological factors to specific anatomical regions of the body is described in U.S. Patent No. 5,011,472, which is herein incorporated by reference in its entirety for all purposes.

Indirect techniques, which are generally preferred, usually involve formulating the compositions to provide for drug latentiation by the conversion of hydrophilic drugs into lipid-soluble drugs. Latentiation is generally achieved through blocking of the hydroxy, carbonyl, sulfate, and primary amine groups present on the drug to render the drug more lipid soluble and amenable to transportation across the blood-brain barrier. Alternatively, the delivery of hydrophilic drugs may be enhanced by intra-arterial infusion of hypertonic solutions which can transiently open the blood-brain barrier.

According to one aspect of the invention, the compound may be administered alone, as a combination of compounds, or in combination with anti-alpha-4-antibodies. The compounds of the present invention may also be administered in combination with an immunosupressant, wherein the immunosuppressant is not a steroid, an anti-TNF composition, a 5-ASA composition, and combinations thereof, wherein the immunosuppressant, anti-TNF composition, and 5-ASA composition are typically used to treat the condition or disease for which the compound of the present invention is being administered. The immunosuppressant may be azathioprine, 6-mercaptopurine, methotrexate, or mycophenolate. The anti-TNF composition may be infliximab. The 5-ASA agent may be mesalamine or osalazine.

When administered in combination, the small compounds may be administered in the same formulation as these other compounds or compositions, or in a separate formulation. When administered in combinations, the steroid sparing agents may be administered prior to, following, or concurrently with the other compounds and compositions.

Pharmaceutical compositions of the invention are suitable for use in a variety of drug delivery systems. Suitable formulations for use in the present invention are found in Remington's Pharmaceutical Sciences, Mace Publishing Company, Philadelphia, PA, 17th ed. (1985).
In order to enhance serum half-life, the compounds may be encapsulated, introduced into the lumen of liposomes, prepared as a colloid, or other conventional techniques may be employed which provide an extended serum half-life of the compounds. A variety of methods are available for preparing liposomes, as described in, e.g., Szoka et al., U.S. Patent Nos. 4,235,871, 4,501,728 and 4,837,028 each of which is incorporated herein by reference in its entirety for all purposes.

The following synthetic and biological examples are offered to illustrate this invention and are not to be construed in any way as limiting the scope of this invention.

Example 1:

Preparation of Hydroxy, Amino, and Aminoacyl Derivatives of Diamantane

Experimental

Part I. GC-MS Instrumentation and Analytical Methods

Diamondoids and most of their derivatives can be conveniently detected and analyzed by gas chromatography-mass spectrometry (GC-MS) to confirm the presence of a diamondoid compound as well as its purity. Appropriate GC-MS systems include HP 5890 Series II Chromatography connected to an HP 5973 Series MSD (mass selective detector).

Detailed GC-MS Methods for the Analysis of Diamondoid Derivatives

1. Column details and dimensions

Column: HP-5ms 30M × 0.25 mm ID and 0.25 μm film thickness. In addition, we also used DB-1 column (15M × 0.25mm ID with film thickness of 0.1 μm), and we found that AT-1HT 15M × 0.25mm ID with film thickness 0.1 μm worked even better than the DB-1 columns.

2. Injector temperature, injection volume and split ratio

Injector temp.: 320°C; injection volume: 0.2 μL; splitless or split

3. Carrier gas flow rate

Flow rate: 1.2 mL/min.

4. Oven program

150°C hold for 1 min., then 10°C per min. to 320°C; hold at 320°C for 15 min.
5. Detector Temperature (if the analysis was run using FID detection)

320°C transfer temp.

6. MS conditions
Mode of analysis: EI mode; full scan with mass range of 50 to 550. SIM was not used.

7. Sample preparation conditions
Dissolve very little compound in suitable solvents.

**Part II. Reactions and Product Analysis**

*Hydroxylation Reaction of Diamantane to Prepare Hydroxyl Diamantanes*

![](image)

Scheme 1. Synthesis of diamantane alcohols

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Source/Cat. No.</th>
<th>MW</th>
<th>Amount</th>
<th>Moles</th>
<th>Eq.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diamantane</td>
<td>ChevronTexaco/2010780</td>
<td>188.31</td>
<td>300g</td>
<td>1.59</td>
<td>1.0</td>
</tr>
<tr>
<td>N-Hydroxyphthalimide</td>
<td>Aldrich/H53704</td>
<td>163.13</td>
<td>26.1g</td>
<td>0.59</td>
<td>0.1</td>
</tr>
<tr>
<td>Co(acac)2</td>
<td>Aldrich/22,712-9</td>
<td>257.15</td>
<td>2.04g</td>
<td>0.0079</td>
<td>0.005</td>
</tr>
<tr>
<td>Acetic acid</td>
<td>Aldrich/32009-9</td>
<td>60.05</td>
<td>2500mL</td>
<td>8.3 v.</td>
<td></td>
</tr>
<tr>
<td>Oxygen</td>
<td>Airgas</td>
<td>31.998</td>
<td>Excess</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**General Procedure**

A 4 liter, multi-neck reactor, fitted with mechanical stirrer, reflux condenser, thermometer, and gas inlet, was charged diamantane, N-hydroxyphthalimide (NHPi), Co(acac)₂ (cobalt (II) acetylacetonate), and acetic acid in quantities indicated in the above table. The mixture was stirred for about 23 hours at 75-100°C in a bubbling oxygen
atmosphere until all the diamantane was dissolved and resulted in a clear red solution without any visible solid in the flask. During the reaction, an additional portion (duplicate to triplicate) of NHPI and Co(acac)$_2$ were added as before. GCMS analysis of the reaction mixture showed significant proportion of diamantane mono-alcohols, dialcohols (diols), and tri-alcohols (triols) in the mixture and the reaction was continued as GCMS indicated increased yields of the alcohols until the desired yields were achieved or until GCMS analysis indicated no increase in the proportion of desired products was being achieved. Then the reaction was stopped and let the reaction mixture cool to room temperature. GCMS analysis of the resulting reaction mixture showed the total ion chromatogram (TIC) of the resulting reaction mixture confirming the presence of diamantane hydroxys in the mixture, shown in FIG. 17.

After the reaction mixture was cooled to room temperature (20°C), precipitated unreacted diamantane was removed by filtration (very little, if any), and the red colored reaction mixture was concentrated with rotary evaporator (rotovap) to give a dark red oily liquid. The dark red oily liquid was dissolved in dichloromethane (DCM). The DCM solution of the reaction mixture was first extracted with water for three times. The combined water layers were then back extracted with DCM for three times and the DCM layers were combined. The combined DCM layers were dried over Na$_2$SO$_4$, filtered, and evaporated to give a dark, brown oil, which was purified and separated into a series of diamantane diols and less polar products as described below by column chromatography.

The aqueous extract was concentrated with rotovap to afford a thick red oil. This material was then dissolved in ethanol and decolorizing charcoal added, stirring for 4 hours at room temperature. The mixture was filtered through celite and stripped to dryness to give a colorless oily liquid. This material was then dissolved in DCM/THF (2:1) and placed on the top of a large dry column of silica. The column was eluted with the same solvent mixture to remove a little less polar components and then eluted with THF/ethanol (4:1) to collect the triols. GC/MS: 218, 200, 236 (M$^+$).

A portion of the above crude oily mixture from DCM extract was dissolved into DCM and adsorbed onto double the mass of silica before placing on top of a large silica gel dry column (in this case: 200g crude mixed with 400g silica and the column has 1.2Kg of silica). The column was flushed first with DCM (2 L) and then eluted with 5-15% THF in DCM which resulted in the less polar components containing diamantanone, mono-alcohols, and mono-keto alcohols, amongst some other unidentified products, being quickly eluted off
together. Elution of the di-alcohols was then achieved using 20-50% THF. The 1,7-
dialcohol eluted first followed by the 1,4-/2,4- di-alcohol mixture.

Further purification of the 1,7-dialcohol was carried out as following: a 6g sample of
less pure 1,7-dialcohol was adsorbed onto silica and purified through a silica gel column,
eluting first with DCM (1 L) then running a gradient of 1-5% MeOH in DCM. Impurities of
higher and lower Rf spots were removed and the fractions containing predominantly the pure
product spots were combined and evaporated to dryness.

<table>
<thead>
<tr>
<th>Analysis of Diamantane-1,7-diol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rf=0.42 (DCM/THF, 95:5)</td>
</tr>
<tr>
<td>GC/MS: 202 (M-18&lt;sup&gt;+&lt;/sup&gt;)</td>
</tr>
<tr>
<td>&lt;sup&gt;1&lt;/sup&gt;H NMR (CDCl&lt;sub&gt;3&lt;/sub&gt;, 500 MHz): δ 3.9 (s, 2H), 2.25 (m, 4H), 1.9 (s, 2H), 1.55 (m, 10H), 1.4 (d, 2H)</td>
</tr>
<tr>
<td>&lt;sup&gt;13&lt;/sup&gt;C NMR (CDCl&lt;sub&gt;3&lt;/sub&gt;, 126 MHz): δ 72, 49, 45, 42, 40, 36, 32, 31, 27, 25</td>
</tr>
</tbody>
</table>

A further attempted separation of 2g of the two closely related diols (1,4- and 2,4-) was carried out using a silica gel column chromatography eluting with 10-20% THF/DCM. Partial separation of the two isomers was observed, enabling fractions containing predominatly upper and lower spots to be combined separately and evaporated to dryness. The top diol was believed to be the 1,4-isomer and the lower spot to be the 2,4-isomer. A very small amount of very pure 1,4-diol was obtained with a further very careful column chromatography. GC/MS: 202, 220(M<sup>+</sup>). Due to the extremely difficult nature of this separation, less pure 1,4- and 2,4-isomer were collected and characterized.

<table>
<thead>
<tr>
<th>Analysis of Diamantane-1,4-diol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rf=0.62 (DCM/THF, 80:20)</td>
</tr>
<tr>
<td>GC/MS: 202, 220(M&lt;sup&gt;+&lt;/sup&gt;)</td>
</tr>
<tr>
<td>&lt;sup&gt;1&lt;/sup&gt;H NMR (DMSO, 500 MHz): δ 4.0 (s, 2H), 2.0 (d, 2H), 1.8 (d, 2H), 1.7 (s, 2H), 1.5 (m, 10H), 1.1 (d, 2H)</td>
</tr>
<tr>
<td>&lt;sup&gt;13&lt;/sup&gt;C NMR (DMSO, 126 MHz): δ 68, 65, 45, 38, 36, 29</td>
</tr>
</tbody>
</table>
Further purification of the less polar mixtures containing keto, mono-alcohols, mono-keto alcohols was carried out as following: 50g of the less polar mixtures was adsorbed onto silica and placed on top of a large silica gel column. The column was eluted with DCM (100%) to DCM/THF (85/15) gradient elution. A series of separated samples were isolated and collected from this column, identifying fractions containing diamantanone, 1-hydroxyl diamantane, 4-hydroxyl diamantane. Or a silica gel column chromatography of a portion of the crude mixture containing less polar components using 0-10% MTBE in hexane gradient elution, afforded a sample of pure diamantanone.

The next identifiable sample to be collected from the crude mixture was the mono-alcohol with substitution at the 1 position, i.e., diamantane-1-ol. A silica column purification of the crude residences containing the 1-ol from other attempted purifications of the crude mixture was carried out using 1-20% MTBE (methyl tertiary-butyl ether) in hexane gradient elution. The desired compound eluted between 10-15% MTBE. Any pure fractions were evaporated to afford the 1-ol as a white solid.
Analysis of Diamantane-1-ol
R\text{f}=0.40 \text{ (hexane/MTBE, 75:25)}
GC/MS: 186, 204(M^+)
^{1}H \text{ NMR (CDCl}_3, 500 \text{ MHz): } \delta \text{ 3.2 (s, 1H), 2.0 (d, 2H), 1.9 (s, 1H), 1.85 (s, 2H), 1.65 (s, 1H), 1.55 (m, 10H), 1.3 (m, 2H)}
^{13}C \text{ NMR (CDCl}_3, 126\text{MHz): } \delta \text{ 71, 47, 43, 39.5, 38, 37.5, 36.5, 32, 30, 25}

The next identifiable sample to be collected from the crude mixture was the mono-alcohol with substitution at the 4 position, \textit{i.e.,} diamantane-4-ol. Several batches containing the crude 4-ol from previous columns (6.5g) were combined and adsorbed onto silica (15g) and placed on a silica gel column. Higher R\text{f} material was flushed off using a gradient of 2-10\% MTBE in hexane. Fractions containing the desired 4-ol were then collected and evaporated to dryness. GC-MS and NMR analyses of the sample indicated that there were still significant levels of impurity present that were not visible by TLC. A further silica column purification was carried out using 0-1\% MeOH in DCM gradient elution. Any pure fractions were combined and evaporated to dryness to afford the 4-ol as a white solid. Still some impurities were observed in proton NMR spectrum but no solvent system could be found yet to separate these from the target alcohol.

Analysis of Diamantane-4-ol
R\text{f}=0.36 \text{ (1\% MeOH in DCM)}
GC/MS: 204(M^+)
^{1}H \text{ NMR (CDCl}_3, 500 \text{ MHz): } \delta \text{ 2.0 (m, 6H), 1.7 (m, 12H), 1.45 (m, 1H)}
^{13}C \text{ NMR (CDCl}_3, 126 \text{MHz): } \delta \text{ 134, 123.5, 45.5, 40, 37, 36, 26}

After the diamantane-4-ol, there were a series of closely eluting spots believed to contain a mixture of keto alcohol isomers. Fractions containing keto-alcohols from the original column were combined, adsorbed onto silica and purified using a gradient of MTBE in hexane. The gradient was increased to 20\% MTBE until the desired compounds begin to elute. The polarity was gradually increased to 50:50. The products obtained were predominantly a mixture of keto-alcohols with other unresolved impurities. The combined
fractions containing keto-alcohol products were subjected to further purification using a
gradient elution of MeOH (0-2%) in DCM. Two samples were isolated that were purer than
before. The smaller sample contained mainly keto-alcohols and the larger, keto-alcohols with
another lower Rf impurity present on GC-MS. It is impossible to separate the various keto-
alcohol isomers by gravity column chromatography.

<table>
<thead>
<tr>
<th>Analysis of Diamantane Keto-Alcohol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rf=0.34 (1% MeOH in DCM)</td>
</tr>
<tr>
<td>GC/MS: 218 (M+), 200; GC/MS: 218 (M+), 200</td>
</tr>
<tr>
<td>1H NMR (CDCl3, 500 MHz): 8 3.2 (s, 1H), 2.5 (m, 1H), 2.4 (s, 1H), 2.25 (d, 2H), 1.75 (m, 12H)</td>
</tr>
</tbody>
</table>

**Acetamination of Diamantane Hydroxys to Prepare Acetaminated Diamantanes**

![Reaction Diagram]

R=NHCOCH3

Scheme 2. Synthesis of acetaminated diamantanes

7 g hydroxylated diamantane (mono- and di-hydroxyl mixtures) was dissolved in 25 mL acetonitrile (HPLC grade) while stirring at room temperature, 25 mL concentrated sulfuric acid was slowly added to the mixture, whereby the mixture heats up by the reaction (note: if H2SO4 added too fast, CH3CN will boil). The color of the mixture changed deeper and deeper as the reaction proceeds. After the mixture was stirred for 20 hours (the mixture became brownish with lots of solids precipitated), the mixture was poured onto 200 mL ice. Filtrating the water mixture by suction under an in house vacuum provided white to off-white solids, which were washed twice with water and then air dried to give 3 g of white solids.

GC-MS showed high purity of 1- and 4-acetamino diamantane isomer mixture with MW of 245. GC/MS: 245(M+); GC/MS: 245(M+).
The aqueous solution (400 mL) above was extracted with ethyl acetate for 3 times (3×200 mL) and combined the three extracts together to give a pale yellow clear solution, which was dried with Na₂SO₄. After filtration off the Na₂SO₄·xH₂O, the pale yellow ethyl acetate solution was concentrated under vacuum with rotovap to dryness to give 3 g of oil and solids mixture product. GC-MS analysis of the crude product showed mainly di-acetamino diamantane with minor mono-acetamino diamantane and other impurities, which could be further purified by washing with acetone. To another portion of the aqueous solution (120 mL) was added 100 mL water and extracted with CH₂Cl₂ for three times (3×100 mL). The combined CH₂Cl₂ extracts were then back extracted with water for three times (3×100 mL) and then dried with Na₂SO₄. After filtration, the CH₂Cl₂ solution was concentrated with rotovap to dryness to give an off-white solid, which GC-MS confirmed to be di-acetamino diamantane. The aqueous solution was extracted with CH₂Cl₂ for three times (3×100 mL). The combined CH₂Cl₂ extracts were dried with Na₂SO₄. Removing the solvent by rotovap gave 1.5 g brown liquid. 10 mL acetone was added into the liquid and a lot of solid was precipitated. The solid was collected by filtration and washed with acetone for three times (3×5 mL). note: after filtration, 670 mg of off-white solid was collected. GC-MS analysis of the solid showed di-acetamino diamantane, which was further purified by washing methanol and acetone) and air dried to afford a white solid, which was also characterized as pure di-acetamino diamantane. GC/MS: 302 (M⁺); GC/MS: 302 (M⁺).

Hydroxylation of Acetaminated Diamantanes to Prepare Aminated Diamantanes

![Chemical Diagram]

R=NHCOCH₃

Scheme 3. Synthesis of aminated diamantanes

To 3 g of 1- and 4-acetamino diamantane isomer mixture product was added 23 g diethylene glycol (b.p. 245 °C) and 2 g NaOH solid (20-40 mesh beads). The mixture was then heated to 200 °C and stirred for 5 hours (as the reaction proceeded and the temperature increased, the color of the mixture became deep dark red). The reaction mixture was then poured into 100 mL water. Filtration was conducted to collect the water insoluble solids and
washed with plenty of water and dried in air to give 400 mg solid product. GC-MS analysis showed the formation of 1- and 4-amino diamantane with some unreacted mono-acetamino diamantane. It indicated that the reaction needed a longer period of time to go to completion. GC/MS: 203(M⁺); GC/MS: 203(M⁺), 186.

Likewise, starting with 1-acetamino diamantane or 1,6-diacetamino diamantane afforded 1-amino diamantane or 1,6-diamino diamantane. GC/MS: 203 (M⁺); GC/MS: 218 (M⁺), respectively.

Example 2:

Preparation of 4-Aminodiamantane Using Trichloramine Reagent

The 4-amino derivative of diamantane was prepared by the method of Cahill (1) in which an aluminum chloride – NCl₃ adduct directs attack to the 4 position of diamantane.

Scheme 4. Synthesis of 4-aminodiamantane

This method uses the trichloramine reagent developed by Kovacic (2, 3), which has been previously used to prepare 1-amino diamantane (3, 4) as well as 4-aminodiamantane (1).

Materials

(Ordered from Sigma Aldrich, unless otherwise noted)

Diamantane (99.9%), FW 188.314, isolated by Shenggao Liu, ChevronTexaco
Dichloromethane (HPLC grade), from Fischer Scientific
1,2-dichloroethane [107-06-2], Cat. No. 27,057-1
Aluminum trichloride, FW133.34 [7446-70-0], Cat. No. 29,471-3
NaOH (50% in water, [1310-73-2], Cat. No. 41,541-3
HCl 37% [7647-01-0], Cat. No. 33,925-3
Na₂SO₄ anhydrous, granular [7757-82-6], 23,931-3

Materials Used to Prepare the Trichloramine (NCl₃) Reagent
Calcium hypochlorite, Ca(OCl)₂, FW 142.99 [7778-54-3], Cat. No. 21,138-9
Ammonium chloride, NH₄Cl, FW 53.49 [12125-02-9], Cat. No. 21,333-0
Hydrochloric acid (conc.) – see above
HPLC water – Fischer Scientific

5  Reagent for measuring NCl₃ content of the reagent

Sodium iodide, 95.5% [7681-82-5], Cat. No. 38,311-2
Sodium thiosulfate, 0.1N solution [10102-17-7], Cat. No. 31,954-6

Procedure used to prepare the trichloramine reagent (modified from ref. (2)):

1. 10 g (0.07mole) of Ca(OCl)₂ was suspended in 20 mL of HPLC grade water in a 250 mL 3-neck round-bottom flask (14/20 ground glass joints) with condenser, cooled (Kontes Article No. 633070-0050) addition funnel, thermometer in 14/20 adapter, and magnetic stirring bar.

2. The flask was cooled to ice bath temperatures (~ 4°C) and 30 mL of cold CH₂Cl₂, was added. With the flask and additional funnel at ~ 4°C, a solution of 2.2 g (0.04 mole) of NH₄Cl in 5 mL of concentrated HCl and 15 mL of HPLC grade water was slowly added to the flask over 30 min. (addition rate = 6 drops/min.) The in-flask thermometer read 40°F through-out the reaction. A bright yellow color appeared.

3. When the addition was completed, the reaction mixture was stirred an additional 15 min., and then the contents of the flask were poured into a 125 mL separatory funnel. The bottom bright yellow organic phase was separated, washed with HPLC water, and dried over anhydrous Na₂SO₄. (The reagent was stored at ice bath temperatures until used).

Procedure for titrating the trichloramine:

1. A 1.00 mL aliquot of the NCl₃ solution was added to 2 g of sodium iodide in 50 mL of 80% acetic acid.

2. 5.00 mL of this solution was titrated with 0.100 N sodium thiosulfate solution to reduce the liberated iodine to iodide. Two titrations were performed: #1 required 5.25 mL of the 0.100 N sodium thiosulfate, #2 : #1 required 5.30 mL of the 0.100 N sodium thiosulfate.

Procedure for preparing 4-aminodiamantane (modified from ref. (1)):
1. 1.00 g (5.32 mmol) of the diamantane was dissolved in 60 mL of dry 1,2-
dichloroethane and placed in a 3-neck 250 mL round-bottom flask (14/20 ground
glass joints) with condenser, cooled addition funnel (o-xylene/dry ice, -29°C), N₂
purge line/thermometer adapter and magnetic stirring bar, all placed inside a Dewar
cold bath containing o-xylene/dry ice (-29°C), behind a shield.

2. With the flask cold (-29°C), 0.75 g (5.5 mmol) of aluminum trichloride was added
with a slow N₂ purge.

3. 25 mL of cold (-29°C) CH₂Cl₂ was added to 5.32 mL of the cold NCl₃ reagent (-
29°C) CH₂Cl₂ and placed in the cooled (-29°C) addition funnel. This cold NCl₃-
CH₂Cl₂ solution was slowly added to the flask drop-wise over a 2 hr. time period.

4. The reaction mixture was brought to -10°C (ethylene glycol/ dry ice, -10.5°C) and
stirred at this temperature for 1 hr.

5. The reaction was then quenched by the rapid addition of 80 mL of cold (ice bath
temperature) 18% HCL with rapid N₂ purging (to remove the Cl₂ formed).

6. The aqueous layer was collected and washed once using 60 mL CH₂Cl₂ and 60 mL
diethylether.

7. The water solution was brought to pH of 9 by the addition of 50% NaOH, extracted
three times with 40 mL each of CH₂Cl₂, and the extract dried using anhydrous
Na₂SO₄.

8. The solvent was removed in a rotary evaporator and the product (white solid) stored
cold in absence of light and oxygen. Product yield was 130 mg.

9. GCMS analysis showed the product to be 79% 4-aminodiamantane (MS characteristic
of 4-aminodiamantane (1)), 8% 1-aminodiamantane, and 13%
aminochlorodiamantane. Specifically, the GCMS data for the reaction product
provided a total ion chromatogram showing GC peaks at 5.32, 5.41, and 7.35 min.,
and the mass spectrum of the component (79%) eluting at 5.32 min. showed it to be 4-
aminodiamantane (M⁺ = 203 m/z).

**Example 3:**

**Synthesis of 1,6-Dimethyl-4-aminodiamantane**

Two synthetic routes were designed for the synthesis of 1,6-dimethyl-4-aminodo-
diamantane, shown in Scheme 5 below.
Scheme 5. Synthesis of 1,6-dimethyl-4-aminodiamantane

Proceeding by Route A, the selective di-bromination at the medial positions C-1 and C-6 of diamantane is easier to control, and usually with high yields, when compared with Route B. However, synthesis of the target product via Route B was initially attempted because it was expected that the selective mono-bromination at the apical position C-4 of 1,6-dimethyl-diamantane in Route A would be difficult to control and the yield would not be satisfactory based on prior experience of the selective mono-bromination of diamantane at the apical C-4 position to synthesize 4-bromodiamantane. Therefore, proceeding by Route B, 10s of grams of 4-bromodiamantane and then 10s of grams of 4-azidodiamantane were produced. However, at the third reaction step (Step B3 in Scheme 1), an unexpected problem was encountered. When reacting 4-azidodiamantane reacted the neat bromine, the azide group was eliminated during the bromination reaction under conditions thought to be best suitable. Hence, synthesis via Route A was undertaken. Although the target product was successfully synthesized through the five-step Route A, the separation and purification of the intermediate 1,6-dimethyl-diamantane of Route A is difficult due to competing of the coupling reaction (methylolation) with the elimination of the two bromines of 1,6-dibromodiamantane. More details are set forth below.

**Step 1. Synthesis of 1,6-dibromodiamantane**

<table>
<thead>
<tr>
<th>Reagent</th>
<th>MW</th>
<th>Amount</th>
<th>Moles</th>
<th>Eq.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diamantane</td>
<td>188.3</td>
<td>10.0g</td>
<td>0.053</td>
<td>1</td>
</tr>
<tr>
<td>Neat Bromine</td>
<td>159.8</td>
<td>25.0ml</td>
<td>0.488</td>
<td>9.2</td>
</tr>
</tbody>
</table>
Under vigorous stirring, bromine (25.0 ml) was added dropwise to diamantane (10.0 g, 0.053 mole) in a 100 ml three-necked flask equipped with a thermometer and a gas outlet leading to a Na₂CO₃ solution and cooled in an ice-bath. The ice-bath was removed after the addition was completed in about 30 min. The reaction mixture was stirred for another 6 h at about 20°C. The mixture was then heated and refluxed for 24 h. After being cooled to room temperature, the mixture was poured onto frozen aqueous sodium hydrogen bisulfite solution. CHCl₃ (40.0 ml) was added and the organic layer was separated. The aqueous solution was extracted with CHCl₃ (3×20ml). The combined CHCl₃ solution was washed with water and dried with anhydrous CaCl₂. Evaporation under reduced pressure gave crude product (21.24g). Fractional recrystallization from CHCl₃ gave colorless crystals (8.30g, 0.024mol). The mother liquid was concentrated and the mixture was separated by flash column chromatography (silica gel; solvent: petroleum ether), an additional 0.35g 1,6-dibromodiamantane was obtained. The overall yield of the product 1,6-dibromodiamantane was 47.4%. m.p. 272°C. IR (cm⁻¹): 2900 (vs), 2854 (s), 1441 (m), 1286 (m), 1068 (m), 972, 877 (m), 795 (m), 715 (m). ¹H-NMR (CDCl₃, ppm): 2.48 (m, 8H), 2.36 (s, 4H), 1.95 (t, 2H), 1.69 (d, 4H). ¹³C-NMR (CDCl₃, ppm): 52.08, 48.91, 34.15, 30.44. The crystal structure of 1,6-dibromodiamantane with atom numbering is shown in Figure 18.

**Table 2**

Atomic coordinates (x 10⁶) and equivalent isotropic displacement parameters (Å² x 10³) for 1,6-dibromodiamantane. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

<table>
<thead>
<tr>
<th></th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>U(eq)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Br(1)</td>
<td>1818(1)</td>
<td>1655(1)</td>
<td>4984(1)</td>
<td>56(1)</td>
</tr>
<tr>
<td>C(1)</td>
<td>3646(5)</td>
<td>3646(5)</td>
<td>5320(3)</td>
<td>30(1)</td>
</tr>
<tr>
<td>C(2)</td>
<td>5730(5)</td>
<td>3192(5)</td>
<td>3192(5)</td>
<td>30(1)</td>
</tr>
<tr>
<td></td>
<td>5816(6)</td>
<td>2710(6)</td>
<td>3886(3)</td>
<td>41(1)</td>
</tr>
<tr>
<td>---</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
<td>-------</td>
</tr>
<tr>
<td>C(3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C(4)</td>
<td>5086(6)</td>
<td>4263(6)</td>
<td>3132(3)</td>
<td>43(1)</td>
</tr>
<tr>
<td>C(5)</td>
<td>2986(6)</td>
<td>4746(6)</td>
<td>3295(3)</td>
<td>40(1)</td>
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<td>C(6)</td>
<td>2918(5)</td>
<td>5216(5)</td>
<td>4529(3)</td>
<td>31(1)</td>
</tr>
<tr>
<td>C(7)</td>
<td>3571(6)</td>
<td>4169(6)</td>
<td>6550(3)</td>
<td>45(1)</td>
</tr>
</tbody>
</table>
Table 3

Bond lengths [Å] and angles [deg] for 1,6-dibromodiamantane

<table>
<thead>
<tr>
<th>Bond Lengths</th>
<th>Angstrom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Br(1)-C(1)</td>
<td>2.002(4)</td>
</tr>
<tr>
<td>C(1)-C(7)</td>
<td>1.521(5)</td>
</tr>
<tr>
<td>C(1)-C(6)</td>
<td>1.529(5)</td>
</tr>
<tr>
<td>C(1)-C(2)</td>
<td>1.529(5)</td>
</tr>
<tr>
<td>C(2)-C(3)</td>
<td>1.527(5)</td>
</tr>
<tr>
<td>C(2)-C(6)#1</td>
<td>1.547(5)</td>
</tr>
<tr>
<td>C(3)-C(4)</td>
<td>1.528(6)</td>
</tr>
<tr>
<td>C(4)-C(7)#1</td>
<td>1.522(6)</td>
</tr>
<tr>
<td>C(4)-C(5)</td>
<td>1.522(6)</td>
</tr>
<tr>
<td>C(5)-C(6)</td>
<td>1.526(5)</td>
</tr>
<tr>
<td>C(6)-C(2)#1</td>
<td>1.547(5)</td>
</tr>
<tr>
<td>C(7)-C(4)#1</td>
<td>1.522(6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bond Angles</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>C(7)-C(1)-C(6)</td>
<td>111.5(3)</td>
</tr>
<tr>
<td>C(7)-C(1)-C(2)</td>
<td>111.9(3)</td>
</tr>
<tr>
<td>C(6)-C(1)-C(2)</td>
<td>108.8(3)</td>
</tr>
<tr>
<td>C(7)-C(1)-Br(1)</td>
<td>105.7(2)</td>
</tr>
<tr>
<td>C(6)-C(1)-Br(1)</td>
<td>109.0(2)</td>
</tr>
<tr>
<td>C(2)-C(1)-Br(1)</td>
<td>109.9(2)</td>
</tr>
<tr>
<td>C(3)-C(2)-C(1)</td>
<td>112.2(3)</td>
</tr>
<tr>
<td>C(3)-C(2)-C(6)#1</td>
<td>110.3(3)</td>
</tr>
<tr>
<td>C(1)-C(2)-C(6)#1</td>
<td>107.0(3)</td>
</tr>
<tr>
<td>C(2)-C(3)-C(4)</td>
<td>109.2(3)</td>
</tr>
<tr>
<td>C(7)#1-C(4)-C(5)</td>
<td>108.9(4)</td>
</tr>
<tr>
<td>C(7)#1-C(4)-C(3)</td>
<td>109.0(3)</td>
</tr>
<tr>
<td>C(5)-C(4)-C(3)</td>
<td>110.3(3)</td>
</tr>
<tr>
<td>C(4)-C(5)-C(6)</td>
<td>109.9(3)</td>
</tr>
<tr>
<td>C(1)-C(6)-C(5)</td>
<td>111.6(3)</td>
</tr>
<tr>
<td>C(1)-C(6)-C(2)#1</td>
<td>107.2(3)</td>
</tr>
<tr>
<td>C(5)-C(6)-C(2)#1</td>
<td>110.3(3)</td>
</tr>
<tr>
<td>C(1)-C(7)-C(4)#1</td>
<td>108.9(3)</td>
</tr>
</tbody>
</table>

Symmetry transformations used to generate equivalent atoms:

#1 -x+1,-y+1,-z+1
### Table 4

Anisotropic displacement parameters (Å² x 10³) for 1,6-dibromodiamantane. The anisotropic displacement factor exponent takes the form: -2π² u h² a*² U11 + ... + 2 h k a* b² U12

<table>
<thead>
<tr>
<th></th>
<th>U11</th>
<th>U22</th>
<th>U33</th>
<th>U23</th>
<th>U13</th>
<th>U12</th>
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<tr>
<td>Br(1)</td>
<td>45(1)</td>
<td>38(1)</td>
<td>85(1)</td>
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<td>-14(1)</td>
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<tr>
<td>C(1)</td>
<td>30(2)</td>
<td>26(2)</td>
<td>34(2)</td>
<td>2(1)</td>
<td>6(1)</td>
<td>-3(1)</td>
</tr>
<tr>
<td>C(2)</td>
<td>32(2)</td>
<td>25(2)</td>
<td>32(2)</td>
<td>4(1)</td>
<td>2(1)</td>
<td>4(1)</td>
</tr>
<tr>
<td>C(3)</td>
<td>38(2)</td>
<td>41(2)</td>
<td>44(2)</td>
<td>-8(2)</td>
<td>7(2)</td>
<td>5(2)</td>
</tr>
<tr>
<td>C(4)</td>
<td>56(2)</td>
<td>53(3)</td>
<td>21(2)</td>
<td>-6(2)</td>
<td>7(2)</td>
<td>3(2)</td>
</tr>
<tr>
<td>C(5)</td>
<td>44(2)</td>
<td>44(2)</td>
<td>29(2)</td>
<td>0(2)</td>
<td>-8(2)</td>
<td>2(2)</td>
</tr>
<tr>
<td>C(6)</td>
<td>25(2)</td>
<td>31(2)</td>
<td>37(2)</td>
<td>1(2)</td>
<td>4(1)</td>
<td>1(1)</td>
</tr>
<tr>
<td>C(7)</td>
<td>47(2)</td>
<td>53(3)</td>
<td>37(2)</td>
<td>10(2)</td>
<td>18(2)</td>
<td>0(2)</td>
</tr>
</tbody>
</table>

### Table 5

Hydrogen coordinates (x 10⁴) and isotropic displacement parameters (Å² x 10³) for 1,6-dibromodiamantane

<table>
<thead>
<tr>
<th></th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>U(eq)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H(2A)</td>
<td>6181</td>
<td>2188</td>
<td>5600</td>
<td>36</td>
</tr>
<tr>
<td>H(3A)</td>
<td>4992</td>
<td>1692</td>
<td>3678</td>
<td>49</td>
</tr>
<tr>
<td>H(3B)</td>
<td>7162</td>
<td>2421</td>
<td>3788</td>
<td>49</td>
</tr>
<tr>
<td>H(4A)</td>
<td>5119</td>
<td>3954</td>
<td>2338</td>
<td>52</td>
</tr>
<tr>
<td>H(5A)</td>
<td>2110</td>
<td>3765</td>
<td>3077</td>
<td>48</td>
</tr>
<tr>
<td>H(5B)</td>
<td>2539</td>
<td>5737</td>
<td>2816</td>
<td>48</td>
</tr>
<tr>
<td>H(6A)</td>
<td>1557</td>
<td>5509</td>
<td>4627</td>
<td>37</td>
</tr>
<tr>
<td>H(7A)</td>
<td>4006</td>
<td>3177</td>
<td>7031</td>
<td>54</td>
</tr>
<tr>
<td>H(8A)</td>
<td>2227</td>
<td>4454</td>
<td>6654</td>
<td>54</td>
</tr>
</tbody>
</table>
Step 2. Synthesis of 1,6-dimethylidiamantane and other methylated diamantanes

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Amount</th>
<th>M.W.</th>
<th>moles</th>
<th>e.q.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,6-dibromodiamantane</td>
<td>10 g</td>
<td>346.3</td>
<td>0.029</td>
<td>1</td>
</tr>
<tr>
<td>CH₃MgI (freshly prepared)</td>
<td>33 g</td>
<td>165.9</td>
<td>0.2</td>
<td>6.9</td>
</tr>
<tr>
<td>Ethyl ether</td>
<td>200 ml</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CH₂Cl₂</td>
<td>100 ml</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mg</td>
<td>10 g</td>
<td>24</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>CH₃I</td>
<td>13 ml</td>
<td>146.9</td>
<td>0.2</td>
<td></td>
</tr>
</tbody>
</table>

Grignard reagent was freshly prepared by a common method. Mg (10 g, 0.4 mol) and CH₃I (13 ml, 0.2 mol) were stirred in ethyl ether (200 ml). The ethyl ether was then removed by evaporation under reduced pressure.

Under nitrogen atmosphere, 1,6-dibromodiamantane (10 g, 0.029 mol) and the freshly prepared Grignard reagent (33 g, 0.2 mol) were added to 100 ml anhydrous CH₂Cl₂. After refluxing for about 48 hours, the reaction was quenched by pouring the mixture onto ice, and extracted by CH₂Cl₂ (5×300ml). The combined extracts were dried and concentrated. The mixture was then subjected to column chromatography (silica gel; solvent: petroleum ether), however all methylated diamantanes eluted at almost the same time, showing poor separation by column chromatography. Therefore, only mixtures containing 1,6-dimethylidiamantane (5.30 g) were obtained. R₃= 0.98 (petroleum ether). ¹H-NMR (CDCl₃, 300MHz) δ (ppm): 2.07 (d, J=13.00 Hz, 6 H), 1.79 (m, 2 H), 1.66 (m, 1 H), 1.39 (s, 9 H), 0.91 (s, 6 H). ¹³C-NMR (CDCl₃, 75MHz) δ (pppm): 47.59, 42.91, 33.78, 33.24, 28.13, 26.15.

1,6-dimethylidiamantane was successfully synthesized by reacting the 1,6-dibromodiamantane with the Grignard reagent. ¹H-NMR showed that methyl groups (0.91ppm, s, 6H) were successfully bonded to the diamantane cage. The mixture should contain 1,6-dimethylidiamantane, 1-methyldiamantane, 1-methyl-6-bromodiamantane, and diamantane because, in principal, when the 1,6-dibromodiamantane reacted with the Grignard reagent, there should be at least four possible products (see below). Three of the products (1,6-dimethylidiamantane, 1-methyldiamantane, and diamantane) are similar non-polar compounds and, thus, it is difficult to separate them by column chromatography.

Consequently, it was decided to proceed to the next bromination reaction without further purification of the methylidiamantanes mixture.
Some possible alkylation products of 1,6-dibromodiamantane with the Grignard reagent

5

**Step 3. Synthesis of 1,6-dimethyldiamantane bromides mixture**

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Amount</th>
<th>M.W.</th>
<th>moles</th>
<th>e.q.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,6-dimethyldiamantane mixture</td>
<td>5 g</td>
<td>216.3</td>
<td>0.023</td>
<td>1.0</td>
</tr>
<tr>
<td>t-BuBr</td>
<td>4 g</td>
<td>137</td>
<td>0.03</td>
<td>1.30</td>
</tr>
<tr>
<td>AlBr₃</td>
<td>0.2 g</td>
<td>263</td>
<td>0.0008</td>
<td>0.03</td>
</tr>
<tr>
<td>Anhydrous cyclohexane</td>
<td>50 ml</td>
<td>84</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The mixture from step 2 containing 1,6-dimethyldiamantane (5.0 g, 0.023 mol) was dissolved in 50 ml anhydrous cyclohexane. t-BuBr (4 g, 0.03 mol) was then added to the solution. Under argon atmosphere, AlBr₃ (0.1 g) was added to the mixture, stirred for about 6 hours at about 0°C. Then a second batch of the AlBr₃ catalyst (0.1 g) was added. After stirring for an additional 2 hours, the reaction was quenched by pouring the reaction mixture into ice-water followed by extraction with CH₂Cl₂ (3×200ml). The combined CH₂Cl₂ extract was dried and concentrated. The product 1,6-dimethyl-2,4-dibromodiamantane (2.5 g, 0.007 mol) was crystallized out from the mother liquid. Rf=0.32 (petroleum ether). ¹H-NMR (CDCl₃, 300MHz) δ (ppm): 2.63 (d, J=12.83 Hz, 4 H), 2.27 (s, 5 H), 2.04 (m, 3 H), 1.62 (m, 4 H), 1.05 (m, 6 H). ¹³C-NMR (CDCl₃, 75MHz) δ (ppm): 63.70, 63.38, 56.77, 56.13, 49.07, 48.44, 45.09, 44.28, 43.81, 43.75, 40.52, 39.35, 37.76, 37.30, 25.92, 25.57. El⁺: 373 [M+H].

After filtration and collection of the 1,6-dimethyl-2,4-dibromodiamantane, the mother liquid was further concentrated by rota evaporation under reduced pressure. The concentrated mother liquid was subjected to flash column chromatography (silica gel; solvent: petroleum ether), resulting in a mixture (2.0 g) of 1,6-dimethyl-2-bromodiamantane and 1,6-dimethyl-4-bromodiamantane with other mono-methylated diamantane bromides, which are difficult to separate by column chromatography. Therefore, the methyl diamantane bromides mixture
was not further purified and was directly used for next reaction step in order to produce a variety of compounds with the hope of separating each of the methyl azidodiamantanes.

**Step 4. Synthesis of 1,6-dimethyl-2,4-diazidodiamantane**

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Amount</th>
<th>M.W.</th>
<th>moles</th>
<th>e.q.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,6-dimethyl-2,4-dibromodiamantane</td>
<td>1 g</td>
<td>372</td>
<td>0.003</td>
<td>1.0</td>
</tr>
<tr>
<td>TMSA</td>
<td>1.8 g</td>
<td>115</td>
<td>0.015</td>
<td>5.0</td>
</tr>
<tr>
<td>Anhydrous SnCl₄</td>
<td>1 ml</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1,6-dimethyl-2,4-dibromodiamantane (1.0 g, 0.003 mol) was dissolved in 20 ml anhydrous CH₂Cl₂, TMSA (1.8 g, 0.015 mol) and anhydrous SnCl₄ (1 ml) were then added to the solution. Under argon atmosphere, the reaction solution was heated to reflux for about 5 hours. It was quenched by pouring the reaction mixture into ice-water, and then extracted with CH₂Cl₂ (3×50 ml). The combined CH₂Cl₂ extracts were concentrated by rotavap under reduced pressure to collect the 1,6-dimethyl-2,4-diazido-diamantane. IR (KBr; cm⁻¹): 2923 (m), 2971 (m), 2095 (s, -N₃). Strong absorption at 2095 cm⁻¹ indicates the presence of the azide group. It was directly reduced to the diamine without purification.

**Step 5. Synthesis of 1,6-dimethyl-2,4-diaminodiamantane**

The above 1,6-dimethyl-2,4-diazidodiamantane mixture was dissolved in 20 ml methanol followed by adding Pd/C (50 mg) as the reducing reagent. The mixture was stirred in hydrogen atmosphere for about 12 hours, then concentrated by rotavap under reduced pressure giving the 1,6-dimethyl-2,4-diaminodiamantane as a white solid (200 mg, 0.0008 mol) without purification. \( R_f = 0.17 \) (MeOH:EA=1:3). \(^1\)H-NMR (CD₃OD, 300MHz) \( \delta \) (ppm): 1.89 (m, 4 H), 1.79 (s, 2 H), 1.68 (s, 1 H), 1.52 (m, 6 H), 0.87 (m, 1 H), 1.27 (d, \( J=10.03 \) Hz, 8 H), 1.38 (m, 6 H). \(^1\)C-NMR (CD₃OD, 75MHz) \( \delta \) (ppm): 54.68, 54.15, 48.55, 47.46, 46.27, 45.66, 44.82, 43.82, 40.99, 40.82, 40.39, 39.06, 36.08, 35.65, 27.04, 26.69. EI⁺: 246 [M]⁺. This product was a mixture of compounds and was designated as MDT-9. Figure 19 shows the GC-MS total ion chromatogram (TIC) for the final crude synthetic product of MDT-9.

**Step 6. Synthesis of 1,6-dimethyl-4-azidodiamantane mixture**
The mixture of 1,6-dimethyl-4-bromodiamantane and 1,6-dimethyl-2-
bromodiamantane with their mono-methylated analogs were reacted in the same way as the
1,6-dimethyl-2,4-dibromodiamantane described in Step 4 above. Therefore, more mixed
dimethyl or monomethyl azidodiamantane derivatives including the 1,6-dimethyl-2-
azidodiamantane and the 1,6-dimethyl-4-azidodiamantane were obtained. The mixture from
the bromination of 1,6-dimethylidiamantane mixture after removing the 1,6-dimethyl-2,4-
dibromodiamantane mainly contained 1,6-dimethyl-4-bromodiamantane, 1,6-dimethyl-2-
bromodiamantane and their mono-methyl bromides. It was directly reacted with TMSA
without further purification. After reacting with TMSA, four compounds from the reaction
mixture were separated by column chromatography on silica gel and all of them were
characterized to have the azide group by IR analysis, which showed a strong characteristic
absorption of the azide group at around 2095 cm\(^{-1}\). TLC showed only one spot for each
fraction, but the \(^1\)H- and \(^{13}\)C-NMR spectra were so complex that it is believed each fraction is
still a mixture. The four fractions were designated as 1,6-dimethyl-4-azidodiamantane, 1,6-
dimethyl-2-azidodiamantane, 1,6-dimethyl-mono-azidodiamantane, and 1,6- or 1,7-dimethyl-
mono-azidodiamantane based on preliminary \(^{13}\)C-NMR analysis. These four fractions were
not further purified.

**Step 7. Synthesis of 1,6-dimethyl-2-aminodiamantane mixture**

The above azidodiamantane mixture designated 1,6-dimethyl-2-azidodiamantane was
reduced by Pd/C in H\(_2\) environment to produce the corresponding amino compound mixture
as described in Step 5. Mass spectra showed that it was a 1,6-dimethyl mono-
aminodiamantane. TLC showed only one clear spot, but the \(^{13}\)C-NMR spectra were so
complex that it is believed the product is still a mixture containing compounds such as 1-
methyl-2-aminodiamantane. EI+: 231 [M]+. \(\dagger\). This product was designated as MDT-6.
Figure 20 shows the GC-MS total ion chromatogram (TIC) for the final crude synthetic
product of MDT-6.

**Step 8. Synthesis of 1,6-dimethyl-mono-aminodiamantane mixture**

The above azidodiamantane mixture designated 1,6-dimethyl-mono-azidodiamantane
was reduced by Pd/C in H\(_2\) environment to produce the corresponding amino compound
mixture as described in Step 5. Mass spectra showed that it was a dimethyl mono-
aminodiamantane. TLC showed only one clear spot, but the $^{13}$C-NMR spectra were so complex that it is believed the product is still a mixture. EI+: 231 [M]$.^+$

**Step 9. Synthesis of 1,6- or 1,7-dimethyl-mono-aminodiamantane mixture**

The above azidodiamantane mixture designated 1,6- or 1,7-dimethyl-mono-azidodiamantane was reduced by Pd/C in H$_2$ environment to produce the corresponding amino compound mixture as described in Step 5. Mass spectra showed a m/z at 231. TLC showed only one clear spot, but the $^{13}$C-NMR spectra were so complex that it is believed the product is still a mixture. EI+: 231 [M]$.^+$ During the multiple step reaction, it was observed that the methyl group may be rearranged to a different position. Therefore, the methylidiamantane mixtures may contain 1,7-dimethylidiamantane derivatives even though the starting precursor was 1,6-dibromodiamantane.

**Step 10. Synthesis of 1,6-dimethyl-4-aminodiamantane mixture**

The above azidodiamantane mixture designated 1,6-dimethyl-4-azidodiamantane was reduced by Pd/C in H$_2$ environment to produce the corresponding amino compound mixture as described in Step 5. TLC showed only one clear spot, but the $^{13}$C-NMR spectra were so complex that it is believed the product is still a mixture. This crude synthetic product is referred to herein as MDT-7. Mass spectrum (m/z: 231, 217, below) showed that it contained dimethyl mono-aminodiamantane with m/z at 231. In addition, the mass spectrum showed a strong peak at m/z 217 which represented a mono-methyl-mono-aminodiamantane.

**Example 4: Purification and structure of MDT-21, MDT-22 and MDT-23**

**Instrumentation/Equipment**

Gas Chromatographic Mass Spectral (GC-MS) analysis was performed on an Agilent model 6890 gas chromatograph equipped with an Agilent model 7683 autosampler and an Agilent model 5973 Network Mass Selective Detector. The GC was run in the splitless mode in an Agilent HP-MS5 column (30m by 0.25 mm I.D., 0.25μ phase thickness) with helium carrier gas at a flow rate of 1.2 mL/min (constant flow mode) and inlet pressure of 16 psi. During GC-MS analyses, the GC oven had a 1.0 min initial hold time at 150°C, followed by oven programming at 10°C/min to 320°C with a final hold time of 15 min. The GC-MS transfer line temperature was maintained at 320 °C. A solvent delay of 2.5 min was applied.
for GC-MS data accumulation. Trimethylsilyl (TMS) ether derivatives of the amines were prepared using standard procedures (N,O-bis-(trimethylsilyl)-trifluoroacetamidePierce (BSTFA), Pierce Chemical Company, Rockford, IL).

High-resolution mass spectra where measured on Micromass GCT TOFMS (time-of-flight mass spectrometer).

High Performance Liquid Chromatography (HPLC): the HPLC system consisted of a Waters Prep LC 4000 solvent pumping system (Waters Corporation, Milford, Massachusetts) in line with a Rheodyne Model 7125 sample injection valve (Rheodyne LLC, Cotati, California) fitted with a 50 microliter injection loop, used to inject samples into an in-line Hypercarb 10 mm I.D. by 250 mm long HPLC column (ThermoElectron Corporation, Bellefonte, Pennsylvania) containing 5- micron particle-size Hypercarb packing. The HPLC detector was a Waters Model 2410 Differential Refractometer, and HPLC chromatograms were collected using a Hewlett-Packard Chemstation Data system (Chemstation Rev. A.05.02 [273] software running on a Hewlett-Packard Vectra computer). Fractions were collected manually into Fisher 10 mm by 150 mm tubes and analyzed using the GCMS system described above. The mobile phase developed for the separation herein consisted of a mixture of methanol, water, and triethylamine, in the 95/5/1 volume ratios. A basic mobile phase prepared without inorganic salts made it possible to retrieve isolated methyldiamantane amines by simple solvent removal under a stream of dry nitrogen. Fisher solvents (Fisher Scientific, Chicago, Illinois) were consistently used for this application. It is desirable, in reversed-phase HPLC separations of amines, to use a high-pH material (in this case triethylamine) in the mobile phase to insure that amines remained unprotonated (uncharged) so that effective interactions with the hydrophobic HPLC column packing occur. A polar, water-containing mobile phase forces the methylated aminodiamantanes to interact with the hydrophobic stationary phase, thus effecting separation. A Hypercarb HPLC column was used because it is especially effective at providing separations of closely related isomer mixtures.

The Carbon-13 ($^{13}$C) and Hydrogen-1 ($^1$H) nuclear magnetic resonance (NMR) spectra were recorded for MDT-22 and MDT-23. The NMR spectra were recorded at room temperature on a Bruker AVANCE 500 spectrometer operating at 125.7537 MHz for $^{13}$C nuclei and 500.115 MHz for $^1$H nuclei. Both spectra were obtained using deuterated chloroform (CDCl$_3$) as the solvent and TMS as the reference.

*Separation and Purification*
The final crude synthesis product from step 10 of Example 3 was a mixture of diamantane compounds believed to include a dimethyl mono-aminodiamantane and a monomethyl-mono-aminodiamantane, among other compounds. This product is also designated herein as MDT-7. MDT-7 was subjected to further purification to provide fractions designated as MDT-21, MDT-22 and MDT-23, the details of which are provided below.

Gas Chromatographic Mass Spectral (GCMS) analysis of the reaction product MDT-7 showed three major components and some minor components including unmethylated, monomethyl-, dimethyl-, trimethyl-, tetramethyl-, pentamethyl-, and hexamethyl- monoaminodiamantanes. Figure 21 shows the GC-MS total ion chromatogram (TIC) for the final crude synthetic product of MDT-7. The TIC peaks corresponding to MDT-22 and MDT-23 are indicated on Figure 21. This crude synthetic product was then purified by HPLC using the method described above.

HPLC separations were run at a mobile phase flow rate of 1.5 mL/min. Figure 22 shows the HPLC chromatogram of the crude product (i.e., MDT-7). In Figure 22, 301 indicates the HPLC peak corresponding to the elution time of MDT-22 and 307 indicates the HPLC peak corresponding to the elution time of MDT-23.

A preparative HPLC isolation of MDT-21, MDT-22 and MDT-23 was undertaken using a high-sample loading of 43 mg of the crude product in the preparative HPLC runs. Five HPLC runs were made in which fractions were taken at elution times shown at 302, 303, 304, 305, and 306 in Figure 22. The fractions corresponding to 302 in Figure 22 from the various HPLC runs were combined into a single sample (15.1 mg) for MDT-21. This sample of MDT-21 was converted into the hydrochloride salt and submitted for biological testing. Figure 23 shows the GC-MS total ion chromatogram (TIC) for the final crude synthetic product of MDT-21.

A second HPLC fraction corresponding to cut 303 in Figure 22 from the series of preparative runs was collected and combined to give a total of 21 mg of a product enriched in MDT-22. This product was further purified using the same HPLC system, but at a lower sample loading (~3.5 mg per run) giving improved separations. Tight fractions were taken at the elution time corresponding to peak 301 in Figure 22. Five separate HPLC runs were carried-out. The early-eluting fractions rich in MDT-22 were combined to provide a single sample of MDT-22 (later-eluting fractions were retained for use in the preparation of a sample of MDT-23). This sample of MDT-22 was converted into the hydrochloride salt and submitted for biological testing.
A third HPLC fraction corresponding to cut 306 in Figure 22 from the 5 series of preparative runs was collected and combined to give a sample of MDT-23 (4.7mg). This sample was converted into the hydrochloride salt and submitted for biological testing. Figure 24 shows the GC-MS total ion chromatogram (TIC) of MDT-23 used for biological testing. Fractions 304 and 305 and late-eluting fractions retained from the final series of HPLC runs used to purify MDT-22, contained MDT-23. These fractions were further purified using the same HPLC system, but at a lower sample loading giving improved separations. Tight fractions were taken at the elution time corresponding to peak 307 in Figure 22. Fractions richest in MDT-23 were identified by GC-MS analyses, and were combined to provide a sample of MDT-23 submitted for structural analyses.

**Structure determination of MDT-22 and MDT-23**

Figures 25 and 26 show the GC-MS TIC trace and mass spectrum, respectively, of MDT-22. The peak corresponding to MDT-22 is indicated in the Figure 25 TIC. Figure 26 shows the mass spectrum of MDT-22 with a molecular ion at m/z 217 and base peak at m/z 120. High-resolution mass spectral analyses showed the molecular ion of MDT-22 to have a mass of 217.1900 (calculated 217.1830 for C\textsubscript{15}H\textsubscript{23}N). A sample of MDT-22 was derivatized to form the trimethylsilyl (TMS) ether. GC-MS analysis of the TMS product showed comparable purity to the GC-MS TIC of the MDT-22 free amine shown in Figure 25. The mass spectrum of the major TMS ether product showed a molecular ion of m/z 289, increased over the free amine by 72 mass units by the TMS moiety, further demonstrating the presence of the amine group in MDT-22.

The GCMS TIC of MDT-23 is shown in Figure 27 with the corresponding mass spectrum shown in Figure 28. The peak corresponding to MDT-23 is indicated in the Figure 27 TIC. Figure 28 shows the mass spectrum of MDT-23 with a molecular ion at m/z 231 and base peak at m/z 120. High-resolution mass spectral analyses showed the molecular ion of MDT-23 to have a mass of 231.2036 (calculated 231.1987 for C\textsubscript{16}H\textsubscript{25}N). A sample of MDT-23 was derivatized to form the trimethylsilyl (TMS) ether. GC-MS analysis of the TMS product showed comparable purity as the GC-MS TIC of the MDT-23 free amine shown in Figure 27. The mass spectrum of the major product showed a molecular ion of m/z 303, increased by 72 mass units by the TMS moiety, demonstrating the presence of the amine group in MDT-23.

**NMR Assignments:**

71
**MDT-22: 1-methyl-7-aminodiamantane**

The $^1$H- and $^{13}$C-NMR spectra of MDT-22 are shown in Figures 29 and 30, respectively.

![Molecule Diagram](image)

$^1$H NMR (CDCl$_3$, 298 K) $\delta$, ppm; 0.96 (s, 3H, CH$_3$), 1.92 (s, 2H, NH$_2$), 2.07 (d, 2H, H$_{13}$, J$_{13.9} = 12.3$ Hz), additional signals: 1.29 (m, 3H), 1.53 (m, 8H), 1.64 (m, 2H), 1.71 (m, 2H), 1.75 (m, 1H), signal of small water impurity over-lapping at 1.56 ppm.

$^{13}$C NMR (CDCl$_3$, 298 K) $\delta$, ppm; 25.88 (1-CH$_3$), 32.54 (7-NH$_2$), additional signals: 26.40, 36.37, 38.16, 40.19, 40.89, 46.63.

**MDT-23: 1,6-dimethyl-2-aminodiamantane**

Figures 31 and 32 show the $^1$H- and $^{13}$C-NMRs, respectively, of MDT-23.

![Molecule Diagram](image)

$^1$H NMR (CDCl$_3$, 298 K) $\delta$, ppm; 0.93 (s, 3H, CH$_3$), 0.96 (s, 3H, CH$_3$), 1.82 (s, 2H, NH$_2$), 1.96 (d, 2H, H$_{13}$, J$_{13.9} = 12.3$ Hz), 2.08 (d, 2H, H$_5$, J$_{5.4} = 12.3$ Hz), additional signals: 1.27 (m, 4H), 1.35 (s, 2H), 1.53 (m, 6H), 1.71 (m, 1H), signal of small water impurity over-lapping at 1.56 ppm.

$^{13}$C NMR (CDCl$_3$, 298 K) $\delta$, ppm; 26.95 (1-CH$_3$), 25.88 (6-CH$_3$), 55.83 (2-NH$_2$), additional signals: 27.87, 32.53, 41.67, 44.63, 45.88, 46.70, 47.62.

**Preparation of the hydrochloride salts from the free amines**

For testing, MDT-21, MDT-22 and MDT-23 were further converted into the water-soluble hydrochloride salt. The free amine was dissolved in dry diethyl ether, capped and place in an ice bath to cool. 1M HCl in diethyl ether was also capped and cooled in the ice
bath. The molar-equivalent of 1M HCl in diethyl ether was added to the solution of the free amine, and a white precipitate formed at varying rates depending on the composition of the amine and its concentration in the ether. For quantities of amine greater than ~10 mg, the solution containing the precipitate can be poured into a Millipore filter (0.5micron Teflon). The filtered precipitate is then washed with excess dry diethyl ether, dried on the filter and transferred to a tightly capped vial. For amounts smaller than ~10 mg, it can be difficult to retrieve the precipitate from the Millipore filter. In those cases, the precipitate was not filtered, but allowed to coagulate and settle to the bottom of the capped tube in which it was formed. The HCl-containing ether was then carefully decanted, and the precipitate resuspended in dry ether. This process was repeated until no acid could be detected (using pH paper) in the vapor emitted when the ether solution was slowly evaporated in a stream of dry nitrogen. When acid could no longer be detected, then the remaining ether was removed by evaporation in a gentle stream of dry nitrogen at ambient temperature, yielding a bright white, powdery solid.

**Example 5:**

**Binding analysis of diamondoid compounds**

**NMDA receptors (NMDARS)**

NMDARs are one of three subtypes of glutamate receptors, along with kainite and quisqualate receptors. The NMDAR appears to be unique in that activation is dependent upon simultaneous activation with glutamate and glycine, or perhaps D-serine (Dingledine et al., 1990, Mothe et al., 2000). These receptors are ligand-gated ion channels that have an important role in the regulation of synaptic function in the CNS. This regulatory role originates from their high permeability to Ca\(^{2+}\) ions upon receptor activation. Dysregulation of NMDAR-mediated calcium ion influx is implicated in many brain disorders, such as stroke, epilepsy, Huntington disease, Alzheimer disease and AIDS related dementia. In each of these diseases the common feature is the neuronal injury caused by the overstimulation of the glutamate receptors, especially of the NMDA subtype. NMDAR antagonists could therefore be of therapeutic use in several neurological disorders. Only those compounds that block the excessive activation of the NMDAR while leaving the normal function intact are useful in the clinic, as they will not cause unwanted side effects. For this reason, a non-competitive open-channel blocker would be an effective approach to maintain the normal physiological activity of the brain even in a diseased state.
A high affinity, selective PCP analog $[^3H]$MK-801 binds to an allosteric site on the NMDA receptor (Lodge and Anis 1982). Because of its high affinity, MK-801 has been widely used for binding studies in search for additional NMDAR antagonists.

**NMDA receptors in guinea pig brain**

Hartley guinea pigs were sacrificed, and their brains were quickly removed and weighed. The brains then were homogenized in 50 mM Tris HCl buffer, pH 7.7, using a Polytron homogenizer. The homogenate was centrifuged at 40,000 × g for 15 min, rehomogenized, and centrifuged again. The final pellet was resuspended in Tris-HCl, pH 7.7, at a final concentration of 6.67 mg original wet weight of tissue/ml. The radioligand used for the binding assay was $[^3H]$MK-801 (1 nM). The guinea pig brain membrane suspension (0.8 ml) was incubated in 5 mM Tris-HCl, pH 7.7, for 1 h at 25°C with 100 μl of radioligand and 100 μl of test compound at concentrations ranging from $10^{-3}$ to $10^{-8}$ M. Nonspecific binding was determined by incubation in the presence of 1 μM of the "cold" unlabeled MK-801. The samples were then filtered through glass fiber filters on a Tomtec cell harvester. The filters were washed 3 times with 3 ml of cold buffer. Filters were dried overnight and counted next day on a Wallac Betaplate Reader.

The binding experiments were conducted as follows. Competition curves with standard and test compounds included at least six concentrations, with at least four concentrations yielding greater than 20% but less than 80% inhibition. For each compound, graphs were prepared containing individual competition curves obtained for that compound. IC$_{50}$ values and Hill coefficients were calculated using the program Prism. $K_i$ values were calculated using the Chang Prusoff transformation:

$$K_i = \frac{IC_{50}}{1 + L/K_d}$$

where $L$ is radioligand concentration and $K_d$ is the binding affinity of the radioligand, as determined previously by saturation analysis. Experiments for those compounds were repeated if it was found to have an IC$_{50}$ value of less than 100 μM. In each experiment, one standard compound was simultaneously run on each 96 well plate. If the standard compound did not have an IC$_{50}$ value close to the established average for that compound (maximum 3-fold difference), the entire experiment was discarded.

**Results**

To establish this assay, a saturation experiment was conducted on guinea pig brain membranes, which provided a good correlation for the values obtained previously for rat
brain membranes (see Table 6). Even the affinity of the standard MK-801 was very close in both systems (2.84 nM in rats and 1.45 nM in the guinea pig).

Table 6

<table>
<thead>
<tr>
<th>Species</th>
<th>$K_d$ (nM)</th>
<th>$B_{max}$ (fmol/mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat</td>
<td>2.11</td>
<td>8655</td>
</tr>
<tr>
<td>Guinea pig</td>
<td>2.19</td>
<td>11730</td>
</tr>
</tbody>
</table>

Once this information was obtained we could proceed to test the other standards selected for these assays. The results are listed in Table 7. All of the standard compounds showed low affinity for the NMDARs, except MK-801. Each of these values correlates well with the binding affinities reported in the literature.

Table 7

$K_i$ values for selected standard compounds at the NMDA site

<table>
<thead>
<tr>
<th>Standard</th>
<th>$K_i$ (nM)</th>
<th>Hill Slope</th>
</tr>
</thead>
<tbody>
<tr>
<td>MK-801</td>
<td>1.45 ± 0.32</td>
<td>0.75 ± 0.05 (n=6)</td>
</tr>
<tr>
<td>Memantine</td>
<td>602 ± 27</td>
<td>0.95 ± 0.17 (n=3)</td>
</tr>
<tr>
<td>Amantadine</td>
<td>16,1437 ± 3,454</td>
<td>1.20 ± 0.45 (n=2)</td>
</tr>
<tr>
<td>NMDA</td>
<td>595,785 ± 82,446</td>
<td>0.80 ± 0.04 (n=2)</td>
</tr>
</tbody>
</table>

Following assay establishment, the test compounds were tested for binding affinities. The concentrations selected for the experiments were chosen according to what was found for memantine in our assay. The first task was to dissolve the compounds and make up the 10 mM stock solution for further experiments. Those compounds that were made into salt format were easy to dissolve in deionized water, but the other compounds were difficult to bring into solution. Several “assay friendly” solvents have been tried, such as moleculesol, acetic acid and propylene glycol followed by putting the vial into hot water. Several compounds (i.e., MDT-10, MDT-11, MDT-12, MDT-13, MDT-14, and MDT-15) went into
solution using this approach, however, some (i.e., MDT-17, MDT-19, and MDT-20) did not go into solution, or came out with time.

Table 8 sets forth the various diamondoid compounds tested, and Table 9 lists the results of the binding experiments.

<table>
<thead>
<tr>
<th>Identifier</th>
<th>Compound</th>
<th>Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDT-1</td>
<td>1-aminodiamantane</td>
<td>hydrochloride salt</td>
</tr>
<tr>
<td>MDT-2</td>
<td>1-aminodiamantane</td>
<td>hydrochloride salt</td>
</tr>
<tr>
<td>MDT-3</td>
<td>4-aminodiamantane</td>
<td>hydrochloride salt</td>
</tr>
<tr>
<td>MDT-4</td>
<td>1,6-diaminodiamantane</td>
<td>hydrochloride salt</td>
</tr>
<tr>
<td>MDT-5</td>
<td>4,9-diaminodiamantane</td>
<td>hydrochloride salt</td>
</tr>
<tr>
<td>MDT-6</td>
<td>Reaction product from step 7 of</td>
<td>free amine</td>
</tr>
<tr>
<td></td>
<td>Example 3</td>
<td></td>
</tr>
<tr>
<td>MDT-7</td>
<td>Reaction product from step 10 of</td>
<td>hydrochloride salt</td>
</tr>
<tr>
<td></td>
<td>Example 3</td>
<td></td>
</tr>
<tr>
<td>MDT-9</td>
<td>Reaction product from step 5 of</td>
<td>hydrochloride salt</td>
</tr>
<tr>
<td></td>
<td>Example 3</td>
<td></td>
</tr>
<tr>
<td>MDT-10</td>
<td>1-hydroxydiamantane</td>
<td>not ionizable</td>
</tr>
<tr>
<td>MDT-11</td>
<td>4-diamantanol</td>
<td>not ionizable</td>
</tr>
<tr>
<td>MDT-12</td>
<td>1,6-dihydroxydiamantane</td>
<td>not ionizable</td>
</tr>
<tr>
<td>MDT-13</td>
<td>1,7-dihydroxydiamantane</td>
<td>not ionizable</td>
</tr>
<tr>
<td>MDT-14</td>
<td>4,9-dihydroxydiamantane</td>
<td>not ionizable</td>
</tr>
<tr>
<td>MDT-15</td>
<td>9,15-dihydroxytriamantane</td>
<td>not ionizable</td>
</tr>
<tr>
<td>MDT-16</td>
<td>diamantane triols</td>
<td>not ionizable</td>
</tr>
<tr>
<td>MDT-17</td>
<td>1-diamantane carboxylic acid</td>
<td>free acid</td>
</tr>
<tr>
<td>MDT-19</td>
<td>1,6-diamantane dicarboxylic acid</td>
<td>free acid</td>
</tr>
<tr>
<td>MDT-20</td>
<td>4,9-diamantane dicarboxylic acid</td>
<td>free acid</td>
</tr>
<tr>
<td>MDT-21</td>
<td>HPLC-purified fraction of MDT-7</td>
<td>hydrochloride salt</td>
</tr>
<tr>
<td>MDT-22</td>
<td>Fraction enriched in 1-methyl-7-</td>
<td>hydrochloride salt</td>
</tr>
<tr>
<td></td>
<td>aminodiamantane</td>
<td></td>
</tr>
<tr>
<td>MDT-23</td>
<td>Fraction enriched in 1,6-dimethyl-2-</td>
<td>hydrochloride salt</td>
</tr>
<tr>
<td></td>
<td>aminodiamantane</td>
<td></td>
</tr>
</tbody>
</table>
Table 9

Kᵢ values and Hill coefficients for diamondoid compounds at the NMDA receptor in guinea pig brain membrane preparation

<table>
<thead>
<tr>
<th>Compound</th>
<th>Kᵢ (μM)</th>
<th>Hill Slope</th>
<th>Relative affinity*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memantine</td>
<td>0.60 ± 0.03</td>
<td>0.95 ± 0.17</td>
<td>1</td>
</tr>
<tr>
<td>MDT-1</td>
<td>5.83 ± 1.09</td>
<td>1.40 ± 0.24</td>
<td>0.103</td>
</tr>
<tr>
<td>MDT-2</td>
<td>6.40 ± 0.13</td>
<td>1.21 ± 0.00</td>
<td>0.094</td>
</tr>
<tr>
<td>MDT-3</td>
<td>34.60 ± 3.70</td>
<td>1.55 ± 0.10</td>
<td>0.017</td>
</tr>
<tr>
<td>MDT-4</td>
<td>99.56 ± 7.59</td>
<td>0.65 ± 0.06</td>
<td>0.006</td>
</tr>
<tr>
<td>MDT-5</td>
<td>268 ± 19</td>
<td>1.05 ± 0.30</td>
<td>0.002</td>
</tr>
<tr>
<td>MDT-6</td>
<td>4.59 ± 0.18</td>
<td>1.30 ± 0.07</td>
<td>0.131</td>
</tr>
<tr>
<td>MDT-7</td>
<td>9.88 ± 0.45</td>
<td>2.05 ± 0.34</td>
<td>0.061</td>
</tr>
<tr>
<td>MDT-9</td>
<td>22.53 ± 0.90</td>
<td>0.87 ± 0.14</td>
<td>0.027</td>
</tr>
<tr>
<td>MDT-10</td>
<td>40.83 ± 6.28</td>
<td>0.54 ± 0.07</td>
<td>0.015</td>
</tr>
<tr>
<td>MDT-11</td>
<td>&gt;100</td>
<td>---</td>
<td>-</td>
</tr>
<tr>
<td>MDT-12</td>
<td>7.76 ± 2.62</td>
<td>0.53 ± 0.13</td>
<td>0.077</td>
</tr>
<tr>
<td>MDT-13</td>
<td>&gt;100</td>
<td>---</td>
<td>-</td>
</tr>
<tr>
<td>MDT-14</td>
<td>&gt;100</td>
<td>---</td>
<td>-</td>
</tr>
<tr>
<td>MDT-15</td>
<td>&gt;100</td>
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<td>-</td>
</tr>
<tr>
<td>MDT-16</td>
<td>&gt;100</td>
<td>---</td>
<td>-</td>
</tr>
<tr>
<td>MDT-17</td>
<td>9.47 ± 3.89</td>
<td>1.09 ± 0.24</td>
<td>0.063</td>
</tr>
<tr>
<td>MDT-19</td>
<td>6.61 ± 1.90</td>
<td>0.81 ± 0.23</td>
<td>0.091</td>
</tr>
<tr>
<td>MDT-20</td>
<td>&gt;100</td>
<td>---</td>
<td>-</td>
</tr>
<tr>
<td>MDT-21</td>
<td>9.63 ± 0.80</td>
<td>0.97 ± 0.16</td>
<td>0.062</td>
</tr>
<tr>
<td>MDT-22</td>
<td>2.17 ± 0.90</td>
<td>0.47 ± 0.03</td>
<td>0.277</td>
</tr>
<tr>
<td>MDT-23</td>
<td>3.87 ± 0.07</td>
<td>0.83 ± 0.00</td>
<td>0.155</td>
</tr>
</tbody>
</table>

* Relative affinity was compared to that of Memantine.

All of the compounds that could be solubilized inhibited [³H]MK-801 to some extent. MDT-22 had the highest affinity, closely followed by MDT-23, MDT-6, and MDT-1. MDT-22 had binding affinity approximately one fourth that of memantine, MDT-23 had binding
affinity approximately one sixth that of memantine, with the other compounds mentioned having about an order of magnitude lower affinity than memantine.

Each of the diamonoids tested had some measurable affinity for NMDARs. The best compound, MDT-22, had affinity close to the clinically useful compound memantine. Other compounds had affinities within an order of magnitude of memantine. These results indicate that MDT-22, MDT-23, MDT-6, MDT-1, and the other diamonoid compounds may act as neuroprotectants.

References


Example 6:

Diamondoid compound modulation of NMDA-induced currents in mammalian cells using whole-cell voltage-clamp recordings

Cognitive disability characterizes the most common neurodegenerative diseases, i.e., Alzheimer’s (AD), Huntington’s, and Parkinson’s [1-5], and also is a prominent component of neuropsychiatric disorders such as schizophrenia, depression, anxiety, and chronic sleep disorders. Current medications are relatively ineffective in improving cognition [1, 6]. Moreover, most therapeutics are not disease modifying. Neuroprotective drugs tested in clinical trials, particularly those that block N-methyl-D-aspartate-sensitive glutamate receptors (NMDARs), have failed at least in part due to intolerable side effects. However, memantine was recently approved by the European Union and the US FDA for the treatment of dementia following the discovery of its clinically tolerated mechanism of action. The mechanism of action of memantine has been shown to preferentially block excessive NMDA receptor activity without disrupting normal activity [7].

The chemical structure of memantine is a low molecule of diamonoids. The present application describes additional diamonoid compounds for treatment of neurological disorders. At least some of these molecules are capable of modulating NMDA receptor-
induced currents and could be potentially neuroprotective through the modulation of NMDA receptor-mediated activity. The experiments below describe standard whole-cell-voltage-clamp recordings from mouse hypocretin (Hcrt) neurons, cells that are lost likely via excitotoxicity in narcoleptics, found in hypothalamic brain slices to investigate the effects of diamondoid compounds and compare with MK-801 and memantine.

Methods

Slice preparation

We prepared sections of the hypothalamus from day 21-26 Hcrt-EGFP (enhanced green fluorescent protein) mice as described previously [8]. Male and female Hcrt/EGFP mice, in which the human prepro-orexin promoter drives expression of EGFP were used for experiments. In brief, mice were anesthetized with isoflurane before decapitation. A block of tissue containing the hypothalamus was dissected and then sliced in the coronal plane (250 μm) using a vibratome (VT-1000S, Leica Instruments) in ice-cold sucrose solution (containing in mM: 220 sucrose, 2.5 KCl, 1.25 NaH₂PO₄, 6 MgCl₂, 1 CaCl₂, and 26 NaHCO₃). Slices were transferred to a holding chamber containing artificial cerebrospinal fluid (aCSF, in mM: 126 NaCl, 2.5 KCl, 1.2 NaH₂PO₄, 1.2 MgCl₂, 2.4 CaCl₂, 21.4 NaHCO₃ and 11.1 glucose) and allowed to recover at room temperature for at least 1 h. The slices were then individually transferred to the recording chamber and perfused at a rate of 2 ml/min with MgCl₂-free recording solution (containing in mM: 126 NaCl, 2.5 KCl, 2.4 CaCl₂, 1.2 NaH₂PO₄, 21.4 NaHCO₃, and 11 glucose). The MgCl₂-free solution also contained 10 μM glycine and 500 nM TTX (tetrodotoxin). All solutions had an osmolarity of 290-300 mOsm and were bubbled with 95% O₂ / 5% CO₂.

Whole-cell patch clamp recordings

Cells were visualized with an upright microscope (Leica DM LPSA, Leica Instruments) using both fluorescent microscopy and infrared illumination. Recording pipettes (8-10 M ohms) contained in mM: 145 KCl, 10 HEPES, 1.1 EGTA, 1 MgCl₂, 2 MgATP, 0.5 Na₂GTP, pH 7.2-7.4, 280-290 mOsm. Recording pipettes were advanced towards individual fluorescent cells in the slice under positive pressure and, on contact, tight seals between the pipette and the cell membrane (~ 1 G ohms) were made by negative pressure. The membrane patch was then ruptured by suction and membrane currents were monitored using an Axopatch 1D amplifier (Molecular Devices, formerly Axon Instruments). Neurons were voltage-clamped at -60mV.
Local NMDA application

NMDA evoked currents were elicited using an eight-channel local perfusion system (BPS-8, ALA-Scientific). The local perfusion needle was placed just above the tissue near the cell being recorded. Discrete currents were evoked by 80-180 ms application of 300 μM NMDA, immediately followed by a 540 ms application of MgCl₂-free recording solution. NMDA evoked currents were elicited every 20-30 seconds. The NMDA containing solution was made up from a 10 mM stock solution that was diluted to 300 μM in MgCl₂-free recording solution. As mentioned above, the MgCl₂-free solution also contained 10 μM glycine and 500 nM TTX.

Bath application of antagonists

All of the antagonists tested including MK-801, memantine, MDT-9, MDT-3, MDT-23 and MDT-22 (see Table 8 above for a description of the diamondoid compounds) were prepared as 10 mM stock solutions in ddH₂O. The stock solutions were then diluted to their final concentrations in MgCl₂-free recording solution. Following the establishment of a stable baseline (at least five consistent consecutive NMDA-evoked currents) the antagonists were applied to the slices via the bath using a 4-barrel gravity perfusion system (ALA-Scientific) at a rate of 2-3 ml/min.

Analysis

NMDA evoked currents were filtered at 1-2 kHz, digitized at 10 kHz and stored using pClamp 9.0 software (Molecular Devices). Peak amplitude values were determined using pClampfit software 9.0 (Molecular Devices). The percent inhibition produced by the antagonists was calculated as the change in NMDA-evoked current peak amplitude from baseline. All values are expressed as mean ± SEM. Statistical significance was assessed using one-tailed Student’s t-tests.

Results

To establish this assay we first demonstrated that local application of NMDA could produce inward currents in hypocretin neurons in the hypothalamus under voltage clamp at –60 mV in MgCl₂-free solution. It was further demonstrated that these currents were specific
to the application of NMDA since local application of control aCSF instead of NMDA did not induce an inward current in these neurons.

These initial studies demonstrated that the amplitude and kinetics (shape) of the NMDA evoked currents was dependent on the proximity of the local perfusion needle to the cell being recorded. Thus there were considerable differences in the responses between experiments. However, subsequent experiments demonstrated that the percent inhibition of NMDA evoked currents, induced by several NMDA receptor antagonists was similar between the cells.

The effect of known NMDA receptor antagonists was then tested on the inward current induced in hypocretin neurons by the local application of NMDA. Bath application of both MK-801 and memantine significantly inhibited the NMDA evoked currents. The parameters of the experiment did not allow differentiation of the control compounds based on voltage dependence or changes in the kinetics of the response but we were able to differentiate the compounds based on their potency. MK-801 (100 nM) produced a significant inhibition of the peak amplitude of NMDA evoked currents, 58 ± 9.4% (mean ± SEM, n=3). Memantine produced a concentration dependent and reversible inhibition of NMDA evoked currents, with 10 µM producing a 41.3 ± 10% (n=3) inhibition and 30 µM producing a 52.7 ± 7.4% (n=3) inhibition. Thus, consistent with the literature, there was a considerable difference in the potency of the two control compounds, with MK-801 being the most potent.

MDT-3, MDT-9, MDT-22 and MDT-23 were then tested to determine if they could inhibit the NMDA evoked currents. The effect of two concentrations (10 and 100 µM) of each compound on the peak amplitude of NMDA currents was examined.

Bath application of MDT-3 (10 and 100 µM) did not produce inhibition of NMDA evoked currents.

Bath application of 10 µM MDT-9 produced a small and statistically insignificant inhibition of the NMDA evoked currents (13.2 ± 9%, n=3). At 100 µM, MDT-9 still produced a small but significant inhibition of these currents (15.2 ± 4.8%, n=3).

In contrast, bath application of MDT-22 produced significant inhibition of the peak amplitude of NMDA evoked currents at both concentrations tested. The effect was concentration dependent with 10 µM producing a 19 ± 3.1% inhibition (n=4) and 100 µM producing a 45 ± 12.1% inhibition (n=2). The effect was reversible upon washout of the compound.
Bath application of 10 μM MDT-23 did not significantly inhibit NMDA evoked currents (11.6 ± 4.3%, n=3). In contrast, the highest concentration of MDT-23 tested (100 μM) did significantly inhibit the amplitude of NMDA currents (22.9 ± 9.3%, n=4). However, this inhibition was not reversible. NMDA currents did not return to baseline upon washout of this compound.

The percent inhibition produced by the two control compounds (MK-801 and memantine) and the four test compounds (MDT-3, MDT-9, MDT-22 and MDT-23) are summarized in Figure 33. Figure 33 is a summary bar graph demonstrating the % inhibition of the peak amplitude of NMDA evoked currents produced by all the compounds tested. The concentration used for each compound is listed under the corresponding bar. The asterisks indicate that the compound produced a significant inhibition p≤ 0.05. In all cases, except for MDT-3, the number of cells tested was between 3-4 for each compound. For MDT-3, n=1.

Of the four test compounds tested, MDT-22 produced substantial and significant inhibition of NMDA evoked currents in hypocretin neurons. The modulation of these currents was specific to the application of MDT-22 since it was reversible upon washout of the compound. In addition, the inhibition of NMDA evoked currents induced by MDT-22 was concentration dependent. Moreover, the percent inhibition produced by the 100 μM concentration of this compound was similar to the percent inhibition produced by the control antagonists MK-801 and memantine. MDT-22 is capable of modulating NMDA receptor-induced currents and could be potentially neuroprotective through the modulation of NMDA receptor-mediated activity. MDT-23 and MDT-9 also inhibited NMDA evoked current and, thus, are also potentially useful in this regard.

References


Example 7:
Assay for Neuronal Cell Function and Death

To test the diamondoid derivatives of the present invention for their ability to prevent neurotoxicity, neuronal cell death may be assayed as follows.

Under general anesthesia, the fluorescent dye granular blue (Mackromolecular Chemin, Umstadt, FRG) may be injected as approximately a 2% (w/v) suspension in saline into the superior colliculus of 4- to 6-day-old Long-Evans rats (Charles River Laboratory, Wilmington, Mass.). Two to six days later, the animals may be sacrificed by decapitation and enucleated, and the retinas quickly removed. The retinas may be dissociated by mild treatment with the enzyme papain and cultured in Eagle's minimum essential medium (MEM, catalog #1090, Gibco, Grand Island, N.Y.) supplemented with 0.7% (w/v) methylcellulose, 0.3% (w/v) glucose, 2 mM glutamine, 1 .mu.g/ml gentamicin, and 5% (v/v) rat serum, as described in Lipton et al., J. Physiol. 385:361, 1987. The cells are plated onto 75 mm.sup.2 glass coverslips coated with poly-L-lysine in 35 mm tissue culture dishes. The candidate diamondoid derivative is added (e.g., in a series of concentrations ranging from 1 nM-1 mM) in the presence or absence of compounds which activate the NMDA receptor-operated channel complex, and in high calcium, low magnesium medium (10 mM CaCl$_2$, 50 .mu.M MgCl$_2$) to enhance NMDA-receptor neurotoxicity in this preparation (Hahn et al., Proc. Natl. Acad. Sci. USA 85:6556, 1988; Levy et al., Neurology 40:852, 1990; Levy et al., Neurosci.
Lett. 110:291, 1990). The degree of survival (under these ionic conditions or with added
exogenous NMDA (200µM)) is compared to that in normal medium (1.8 mM CaCl₂, 0.8 mM
MgCl₂), which minimizes NMDA receptor-mediated injury in this preparation (Hahn et al.,
cited above). Incubations last 16-24 h at 37 degrees Celsius in an atmosphere of 5% CO₂/95%
air. The ability of retinal ganglion cells to take up and cleave fluorescein diacetate to
fluorescein is used as an index of their viability as described in detail in Hahn et al., (Proc.
Natl. Acad. Sci. USA 85:6556, 1988). Dye uptake and cleavage generally correlate well with
normal electrophysiological properties assayed with patch electrodes.

To perform the viability test, the cell-culture medium may be exchanged for
physiological saline containing 0.0005% fluorescein diacetate for 15-45 seconds, and then
cells may be rinsed in saline. Retinal ganglion cell neurons that do not contain the fluorescein
dye (and thus are not living) often remain visible under both phase-contrast and UV
fluorescence optics, the latter because of the continued presence of the marker dye granular
blue; other dead retinal ganglion cells disintegrate, leaving only cell debris. In contrast, the
viable retinal ganglion cells display not only a blue color in the UV light but also a yellow-
green fluorescence with filters appropriate for fluorescein. Thus, the use of two exchangeable
fluorescence filter sets permits the rapid determination of viable ganglion cells in the cultures.
The ganglion cells are often found as solitary neurons as well as neurons lying among other
cells in small clusters.

A diamondoid diamantane, or trimantane derivative may be tested for utility in the
method of the invention using any type of neuronal cell from the central nervous system, as
long as the cell can be isolated intact by conventional techniques. In addition to the retinal
cultures described above, hippocampal and cortical neurons may be used though any neuron
may be used that possesses NMDA receptors (e.g., neurons from other regions of the brain).
Such neurons may be prenatal or postnatal, and they may be from a human, rodent or other
mammals. In one example, retinal cultures may be produced from postnatal mammals, as
they are well-characterized and contain a central neuron (the retinal ganglion cell) that can be
unequivocally identified with fluorescent labels. A substantial portion of retinal ganglion
cells in culture display both functional synaptic activity and bear many, if not all, of the
neurotransmitter receptors found in the intact central nervous system.

Measurement of Intracellular Ca²⁺

The concentration of intracellular free Ca²⁺ ([Ca²⁺]) may be measured in neonatal
cortical neurons by digital imaging microscopy with the Ca²⁺ sensitive fluorescent dye fura 2,
as follows. The same cortical neuronal cultures as described above are used. During Ca\textsuperscript{2+} measurements, unless otherwise stated the fluid bathing the neurons consists of Hanks' balanced salts: 137.6 mM NaCl, 1 mM NaHCO\textsubscript{3}, 0.34 mM Na\textsubscript{2} HPO\textsubscript{4}, 0.44 mM KH\textsubscript{2} PO\textsubscript{4}, 5.36 mM KCl, 1.25 mM CaCl\textsubscript{2}, 0.5 mM MgSO\textsubscript{4}, 0.5 mM MgCl\textsubscript{2}, 5 mM Heps NaOH, 22.2 mM glucose, and sometimes with phenol red indicator (0.001% v/v); pH 7.2. NMDA (in the absence Mg\textsuperscript{2+}), glutamate, and other substances may be applied to the neurons by pressure ejection after dilution in this bath solution. Neuronal [Ca\textsuperscript{2+}]i is analyzed with fura 2-acetoxy-methyl ester (AM) as described [Gryniewicz, et al., J. Biol. Chem. 260:3440 (1985); Williams et al., Nature 318:558 (1985); Connor et al., J. Neurosci. 7:1384 (1987); Connor et al., Science 240:649 (1988); Cohan et al., J. Neurosci. 7:3588 (1987); Mattson, et al., ibid, 9:3728 (1989)]. After adding Eagle's minimum essential medium containing 10 \mu M fura 2-AM to the neurons, the cultures are incubated at 37 degrees Celsius in a 5% CO\textsubscript{2} /95% air humidified chamber and then rinsed. The dye is loaded, trapped, and deesterified within 1 hour, as determined by stable fluorescence ratios and the effect of the Ca\textsuperscript{2+} ionophore ionomycin on [Ca\textsuperscript{2+}]i is measured. During Ca\textsuperscript{2+} imaging, the cells may be incubated in a solution of Heps-buffered saline with Hanks' balanced salts. The [Ca\textsuperscript{2+}]i may be calculated from ratio images that are obtained by measuring the fluorescence at 500 nm that is excited by 350 and 380 nm light with a DAGE MTI 66 SIT or QUANTEK QX-100 Intensified CCD camera mounted on a Zeiss Axiovert 35 microscope. Exposure time for each picture is 500 milliseconds. Analysis may be performed with a Quantex (Sunnyvale, Calif.) QX7-210 image-processing system. As cells are exposed to ultraviolet light only during data collection (generally less than a total of 20 seconds per cell), bleaching of fura 2 is minimal. Delayed NMDA-receptor mediated neurotoxicity has been shown to be associated with an early increase in intracellular Ca\textsuperscript{2+} concentration.

Correlation Between Channel-Blocking and Anticonvulsive Action

The correlation between the action of the tested diamondoid derivatives at the NMDA receptor channel (in vitro) and the anticonvulsive effect (in vivo) has been tested. For this purpose an xy diagram of both test parameters can be plotted. It shows that there is a correlation between the blocking of the NMDA receptor channel and the anticonvulsive action of the diamondoid of formula (I), (II) or (III).

Protection Against Cerebral Ischemia

Both carotid arteries are occluded in rats for 10 minutes. At the same time the blood
pressure is reduced to 60-80 mg Hg by withdrawal of blood (Smith et al., 1984, *Acta Neurol. Scand.* 69: 385, 401). The ischemia is terminated by opening the carotids and reinfusion of the withdrawn blood. After seven days the brains of the test animals are histologically examined for cellular changes in the CA1-CA4 region of the hippocampus, and the percentage of destroyed neurons is determined. The action of the candidate diamondoid derivative is determined after a single administration of 5 mg/kg and 20 mg/kg one (1) hour prior to the ischemia.

**Example 8:**

**Treatment of Alzheimer’s Disease**

The patient of this example is an 80 year old female patient, presenting with Alzheimer’s Disease. Upon evaluation, she is administered tablets of a diamantane derivative at a dosage of 100 mg twice a day. After about two weeks of administration, her memory improves and she is able to accomplish household functions without assistance.
Example 9:

Treatment of Stroke

The patients of this example is a 50 year old male patient presenting at the hospital with symptoms indicating a stroke, including numbness and weakness on the left side of his body, trouble seeing and severe headache. He is parenterally administered a triamantane derivative. After two days, the symptoms of the stroke are abating and the patient exhibits greater recovery and freedom of movement than if he had not been given the triamantane derivative.

References


While the present invention has been described with reference to specific embodiments, this application is intended to cover those various changes and substitutions that may be made by those of ordinary skill in the art without departing from the spirit and scope of the appended claims.
WHAT IS CLAIMED IS:

1. A compound of Formula I:

\[
\text{Formula I}
\]

wherein:

- \( R^1, R^2, R^5, R^8, R^9, R^{12}, R^{15}, \) and \( R^{16} \) are independently selected from the group consisting of hydrogen, hydroxy, lower alkyl, substituted lower alkyl, lower alkenyl, alkoxy, amino, nitroso, nitro, halo, cycloalkyl, carboxy, acyloxy, acyl, aminoaacyl, and aminocarbonyloxy;
- \( R^3, R^4, R^6, R^7, R^{10}, R^{11}, R^{13}, R^{14}, R^{17}, R^{18}, R^{19} \) and \( R^{20} \) are hydrogen;
- provided that at least two of \( R^1, R^2, R^5, R^8, R^9, R^{12}, R^{15}, \) and \( R^{16} \) are not hydrogen;
- and that both \( R^5 \) and \( R^{12} \) or \( R^1 \) and \( R^8 \) are not identical when the remaining of \( R^1, R^2, R^5, R^9, R^{15}, \) and \( R^{16} \) are hydrogen;
- and pharmaceutically acceptable salts thereof.

2. The compound of claim 1, wherein at least three of \( R^1, R^2, R^5, R^8, R^{12}, R^{15}, \) and \( R^{16} \) are not hydrogen.

3. The compound of claim 1, wherein at least four of \( R^1, R^2, R^5, R^8, R^9, R^{12}, R^{15}, \) and \( R^{16} \) are not hydrogen.

4. The compound of claim 1, wherein five of \( R^1, R^2, R^5, R^8, R^9, R^{12}, R^{15}, \) and \( R^{16} \) are not hydrogen.
5. The compound of claim 1, wherein \( R^1 \) and \( R^5 \) are aminoacyl and \( R^2, R^8, R^9, R^{12}, R^{15} \), and \( R^{16} \) are hydrogen or lower alkyl.

6. The compound of claim 1, wherein \( R^5 \) is amino and two of \( R^1, R^2, R^8 \) and \( R^{15} \) are lower alkyl.

7. The compound of claim 6, wherein \( R^1 \) and \( R^8 \) are methyl.

8. The compound of claim 6, wherein \( R^1 \) and \( R^{15} \) are methyl.

9. The compound of claim 1, wherein \( R^9 \) or \( R^{15} \) is amino and \( R^1 \) is methyl.

10. The compound of claim 1, wherein \( R^2 \) or \( R^{16} \) is amino and \( R^1 \) and \( R^8 \) are methyl.

11. The compound of claim 1, wherein at least one of \( R^1, R^2, R^5, R^8, R^9, R^{12}, R^{15} \), and \( R^{16} \) is independently selected from the group consisting of amino, nitroso, nitro, and aminoacyl and at least one of the remaining of \( R^1, R^2, R^5, R^8, R^9, R^{12}, R^{15} \), and \( R^{16} \) are lower alkyl.

12. The compound of claim 11, wherein at least two of the remaining of \( R^1, R^2, R^5, R^8, R^9, R^{12}, R^{15} \), and \( R^{16} \) are lower alkyl.

13. The compound of claim 11, wherein three of the remaining of \( R^1, R^2, R^5, R^8, R^9, R^{12}, R^{15} \), and \( R^{16} \) are lower alkyl.

14. The compound of claim 11, wherein at least one of \( R^5 \) and \( R^{12} \) is independently selected from the group consisting of amino, nitroso, nitro, and aminoacyl and at least one of \( R^1, R^2, R^8, R^9, R^{15} \), and \( R^{16} \) is lower alkyl.

15. The compound of claim 14, wherein at least two of \( R^1, R^2, R^8, R^9, R^{15} \), and \( R^{16} \) are lower alkyl.
16. The compound of claim 14, wherein three of $R^1$, $R^2$, $R^8$, $R^9$, $R^{15}$, and $R^{16}$ are lower alkyl.

17. The compound of claim 1, wherein at least one of $R^1$, $R^2$, $R^5$, $R^8$, $R^9$, $R^{12}$, $R^{15}$, and $R^{16}$ is substituted lower alkyl.

18. The compound of claim 17, wherein two of $R^1$, $R^2$, $R^5$, $R^8$, $R^9$, $R^{12}$, $R^{15}$, and $R^{16}$ are substituted lower alkyl.

19. The compound of claim 1, wherein at least one of $R^1$, $R^2$, $R^5$, $R^8$, $R^9$, $R^{12}$, $R^{15}$, and $R^{16}$ is substituted lower alkyl and at least one of the remaining of $R^1$, $R^2$, $R^5$, $R^8$, $R^9$, $R^{12}$, $R^{15}$, and $R^{16}$ are independently selected from the group consisting of amino, nitroso, nitro, and aminoacyl.

20. A compound of Formula II:

\[ \text{Formula II} \]

\[ \text{wherein:} \]

\[ R^{21}, R^{22}, R^{25}, R^{28}, R^{29}, R^{32}, R^{35}, \text{and} \ R^{36} \text{ are independently selected from the group consisting of hydrogen or substituted lower alkyl;} \]

\[ R^{23}, R^{24}, R^{26}, R^{27}, R^{30}, R^{31}, R^{33}, R^{34}, R^{37}, R^{38}, R^{39}, \text{and} \ R^{40} \text{ are hydrogen;} \]

\[ \text{provided that at least at least one of} \ R^{21}, R^{22}, R^{25}, R^{28}, R^{29}, R^{32}, R^{35}, \text{and} \ R^{36} \text{ is substituted lower alkyl;} \]

\[ \text{and pharmaceutically acceptable salts thereof.} \]
21. The compound of claim 20, wherein \( R^{25} \) is substituted lower alkyl and \( R^{21} \), \( R^{22} \), \( R^{28} \), \( R^{29} \), \( R^{32} \), \( R^{35} \), and \( R^{36} \) are hydrogen.

22. The compound of claim 20, wherein \( R^{25} \) and \( R^{32} \) are substituted lower alkyl.

23. The compound of claim 20, wherein \( R^{21} \) is substituted lower alkyl and \( R^{22} \), \( R^{25} \), \( R^{28} \), \( R^{29} \), \( R^{32} \), \( R^{35} \), and \( R^{36} \) are hydrogen.

24. The compound of claim 20, wherein \( R^{25} \) and \( R^{21} \) are substituted lower alkyl.

25. The compound of claim 20, wherein \( R^{32} \) and \( R^{21} \) are substituted lower alkyl.

26. The compound of claim 20, wherein the substituted lower alkyl group is substituted with one substituent selected from the group consisting of amino, hydroxy, halo, nitroso, nitro, carboxy, acyloxy, acyl, aminoacyl, and aminocarbonyloxy.

27. The compound of claim 26, wherein the substituted lower alkyl group is substituted with one substituent selected from the group consisting of amino, nitroso, nitro, and aminoacyl.

28. A compound selected from the group consisting of 1,6-diaminodiamantane; 4,9-diaminodiamantane, 1-methyl-7-aminodiamantane, 1-methyl-11-aminodiamantane, 1,6-dimethyl-2-aminodiamantane, 1,6-dimethyl-12-aminodiamantane, 1,6-dimethyl-4-aminodiamantane, 1,6-dimethyl-2,4-diaminodiamantane, 1,7-dimethyl-4-aminodiamantane, 4-acetaminodiamantane; 1-acetaminodiamantane; 1,6-diacetaminodiamantane; and 1,4-diacetaminodiamantane; and pharmaceutically acceptable salts thereof.

29. A compound of Formula III:
wherein:

R^{41}, R^{42}, R^{43}, R^{46}, R^{47}, R^{50}, R^{53}, R^{54}, R^{55}, and R^{58} are independently selected from the group consisting of hydrogen, hydroxy, lower alkyl, substituted lower alkyl, lower alkenyl, alkoxy, amino, nitroso, nitro, halo, cycloalkyl, carboxy, acyloxy, acyl, aminoacyl, and aminocarbonyloxy;

R^{44}, R^{45}, R^{48}, R^{49}, R^{51}, R^{52}, R^{56}, R^{57}, R^{59}, R^{60}, R^{61}, R^{62}, R^{63}, and R^{64} are hydrogen;

provided that at least one of R^{41}, R^{42}, R^{43}, R^{46}, R^{47}, R^{50}, R^{53}, R^{54}, R^{55}, and R^{58} is not hydrogen;

and pharmaceutically acceptable salts thereof.

30. The compound of claim 29, wherein at least two of R^{41}, R^{42}, R^{43}, R^{46}, R^{47}, R^{50}, R^{53}, R^{54}, R^{55}, and R^{58} are not hydrogen.

31. The compound of claim 29, wherein at least three of R^{41}, R^{42}, R^{43}, R^{46}, R^{47}, R^{50}, R^{53}, R^{54}, R^{55}, and R^{58} are not hydrogen.

32. The compound of claim 29, wherein R^{50} is selected from the group consisting of amino, nitroso, nitro, and aminoacyl and at least one of R^{41}, R^{42}, R^{43}, R^{46}, R^{47}, R^{50}, R^{53}, R^{54}, R^{55}, and R^{58} is lower alkyl.

33. The compound of claim 32, wherein at least two of R^{41}, R^{42}, R^{43}, R^{46}, R^{47}, R^{50}, R^{53}, R^{54}, R^{55}, and R^{58} are lower alkyl.
34. A method for treating a neurologic disorder in a subject in need thereof, comprising administering a therapeutically effective amount of a compound of Formula Ia:

\[
\text{Formula Ia}
\]

wherein:

- $R^1$, $R^2$, $R^5$, $R^8$, $R^9$, $R^{12}$, $R^{15}$, and $R^{16}$ are independently selected from the group consisting of hydrogen, hydroxy, lower alkyl, substituted lower alkyl, lower alkenyl, alkoxy, amino, nitroso, nitro, halo, cycloalkyl, carboxy, acyloxy, acyl, aminoacyl, and aminocarbonyloxy;
- $R^3$, $R^4$, $R^6$, $R^7$, $R^{10}$, $R^{11}$, $R^{13}$, $R^{14}$, $R^{17}$, $R^{18}$, $R^{19}$ and $R^{20}$ are hydrogen;
- provided that at least one of $R^1$, $R^2$, $R^5$, $R^8$, $R^9$, $R^{12}$, $R^{15}$, and $R^{16}$ are not hydrogen;
- and pharmaceutically acceptable salts thereof.

35. The method of claim 34, wherein at least two of $R^1$, $R^2$, $R^5$, $R^8$, $R^9$, $R^{12}$, $R^{15}$, and $R^{16}$ are not hydrogen.

36. The method of claim 34, wherein at least three of $R^1$, $R^2$, $R^5$, $R^8$, $R^9$, $R^{12}$, $R^{15}$, and $R^{16}$ are not hydrogen.

37. The method of claim 34, wherein four of $R^1$, $R^2$, $R^5$, $R^8$, $R^9$, $R^{12}$, $R^{15}$, and $R^{16}$ are not hydrogen.

38. The method of claim 34, wherein $R^1$ and $R^2$ are aminoacyl and $R^3$, $R^8$, $R^9$, $R^{12}$, $R^{15}$, and $R^{16}$ are hydrogen or lower alkyl.
39. The method of claim 34, wherein R⁵ is amino and two of R¹, R², R⁸ and R¹⁵ are lower alkyl.

40. The method of claim 39, wherein R¹ and R⁸ are methyl.

41. The method of claim 39, wherein R¹ and R¹⁵ are methyl.

42. The method of claim 34, wherein R⁹ or R¹⁵ is amino and R¹ is methyl.

43. The method of claim 34, wherein R² is amino, R¹ is methyl, and R⁸ or R¹⁵ is methyl.

44. The method of claim 34, wherein at least one of R¹, R², R⁵, R⁸, R⁹, R¹², R¹⁵, and R¹⁶ is independently selected from the group consisting of amino, nitroso, nitro, and aminoacyl and at least one of the remaining of R¹, R², R⁵, R⁸, R⁹, R¹², R¹⁵, and R¹⁶ are lower alkyl.

45. The method of claim 44, wherein at least two of the remaining of R¹, R², R⁵, R⁸, R⁹, R¹², R¹⁵, and R¹⁶ are lower alkyl.

46. The method of claim 44, wherein three of the remaining of R¹, R², R⁵, R⁸, R⁹, R¹², R¹⁵, and R¹⁶ are lower alkyl.

47. The method of claim 44, wherein at least one of R⁵ and R¹² is independently selected from the group consisting of amino, nitroso, nitro, and aminoacyl and at least one of R¹, R², R⁸, R⁹, R¹⁵, and R¹⁶ is lower alkyl.

48. The method of claim 47, wherein at least two of R¹, R², R⁸, R⁹, R¹⁵, and R¹⁶ are lower alkyl.

49. The method of claim 47, wherein three of R¹, R², R⁸, R⁹, R¹⁵, and R¹⁶ are lower alkyl.
50. The method of claim 34, wherein at least one of \( R^1, R^2, R^5, R^8, R^9, R^{12}, R^{15} \), and \( R^{16} \) is substituted lower alkyl.

51. The method of claim 50, wherein two of \( R^1, R^2, R^5, R^8, R^9, R^{12}, R^{15}, \) and \( R^{16} \) are substituted lower alkyl.

52. The method of claim 34, wherein at least one of \( R^1, R^2, R^5, R^8, R^9, R^{12}, R^{15}, \) and \( R^{16} \) is substituted lower alkyl and at least one of the remaining of \( R^1, R^2, R^5, R^8, R^9, R^{12}, R^{15}, \) and \( R^{16} \) are independently selected from the group consisting of amino, nitroso, nitro, and aminoacyl.

53. The method of claim 34, wherein at least one of \( R^1, R^2, R^5, R^8, R^9, R^{12}, R^{15}, \) and \( R^{16} \) is a substituted lower alkyl.

54. The method of claim 53, wherein \( R^5 \) is substituted lower alkyl and \( R^1, R^2, R^8, R^9, R^{12}, R^{15} \), and \( R^{16} \) are hydrogen.

55. The method of claim 53, wherein \( R^5 \) and \( R^{12} \) are substituted lower alkyl.

56. The method of claim 53, wherein \( R^1 \) is substituted lower alkyl and \( R^2, R^5, R^8, R^9, R^{12}, R^{15}, \) and \( R^{16} \) are hydrogen.

57. The method of claim 53, wherein \( R^5 \) and \( R^1 \) are substituted lower alkyl.

58. The method of claim 53, wherein \( R^{12} \) and \( R^1 \) are substituted lower alkyl.

59. The method of claim 53, wherein the substituted lower alkyl group is substituted with one substituent selected from the group consisting of amino, hydroxy, halo, nitroso, nitro, carboxy, acyloxy, acyl, aminoacyl, and aminocarbonyloxy.

60. The method of claim 53, wherein the substituted lower alkyl group is substituted with one substituent selected from the group consisting of amino, nitroso, nitro, and aminoacyl.
61. The method of claim 34, wherein the compound of Formula 1a is selected from the group consisting of 4-aminodiamantane; 1-aminodiamantane; 1,6-diaminodiamantane; 4,9-diaminodiamantane, 1-methyl-7-aminodiamantane, 1-methyl-11-aminodiamantane, 1,6-dimethyl-2-aminodiamantane, 1,6-dimethyl-12-aminodiamantane, 1,6-dimethyl-4-aminodiamantane, 1,6-dimethyl-2,4-diaminodiamantane, 1,7-dimethyl-4-aminodiamantane, 4-acetaminodiamantane; 1-acetaminodiamantane; 1,6-diacetaminodiamantane; and 1,4-diacetaminodiamantane; and pharmaceutically acceptable salts thereof.

62. The method of claim 34, wherein the neurologic disorder is selected from the group consisting of pain, a neurodegenerative condition, a psychiatric condition, epilepsy, and narcolepsy.

63. The method of claim 62, wherein the pain is neuropathic pain.

64. The method of claim 62, wherein the neurodegenerative condition is selected from the group consisting of Alzheimer's Disease, Parkinson's Disease, stroke, AIDS related dementia, traumatic brain injury (TBI), and Huntington's Disease.

65. The method of claim 62, wherein the psychiatric condition is substance abuse.

66. The method of claim 65, wherein the substance abuse is alcohol abuse or drug abuse.

67. The method of claim 34, wherein the subject is a mammal.

68. The method of claim 67, wherein the mammal is a human.

69. The method of claim 34, wherein the compound is administered parenterally.

70. A pharmaceutical composition for the treatment of a neurologic disorder comprising a pharmaceutically effective amount of the compound of claim 34, and one or more pharmaceutically acceptable excipients or carriers.
71. A method for treating a neurologic disorder in a subject in need thereof, comprising administering a therapeutically effective amount of a compound of Formula III:

wherein:

$R^{41}, R^{42}, R^{43}, R^{46}, R^{47}, R^{50}, R^{53}, R^{54}, R^{55},$ and $R^{58}$ are independently selected from the group consisting of hydrogen, hydroxy, lower alkyl, substituted lower alkyl, lower alkenyl, alkoxy, amino, nitroso, nitro, halo, cycloalkyl, carboxy, acyloxy, acyl, aminoacyl, and aminocarbonyloxy;

$R^{44}, R^{45}, R^{48}, R^{49}, R^{51}, R^{52}, R^{56}, R^{57}, R^{59}, R^{60}, R^{61}, R^{62}, R^{63},$ and $R^{64}$ are hydrogen;

provided that at least one of $R^{41}, R^{42}, R^{43}, R^{46}, R^{47}, R^{50}, R^{53}, R^{54}, R^{55},$ and $R^{58}$ is not hydrogen;

and pharmaceutically acceptable salts thereof.

72. The method of claim 71, wherein at least two of $R^{41}, R^{42}, R^{43}, R^{46}, R^{47}, R^{50}, R^{53}, R^{54}, R^{55},$ and $R^{58}$ are not hydrogen.

73. The method of claim 71, wherein at least three of $R^{41}, R^{42}, R^{43}, R^{46}, R^{47}, R^{50}, R^{53}, R^{54}, R^{55},$ and $R^{58}$ are not hydrogen.

74. The method of claim 71, wherein $R^{50}$ is selected from the group consisting of amino, nitroso, nitro, and aminoacyl and at least one of $R^{41}, R^{42}, R^{43}, R^{46}, R^{47}, R^{50}, R^{53}, R^{54}, R^{55},$ and $R^{58}$ is lower alkyl.
75. The method of claim 71, wherein at least two of \( R^{41}, R^{42}, R^{43}, R^{46}, R^{47}, R^{50}, \)
\( R^{53}, R^{54}, R^{55}, \) and \( R^{58} \) are lower alkyl.

76. The method of claim 71, wherein the neurologic disorder wherein the
neurologic disorder is selected from the group consisting of pain, a neurodegenerative
condition, a psychiatric condition, epilepsy, and narcolepsy.

77. The method of claim 76, wherein the pain is neuropathic pain.

78. The method of claim 76, wherein the neurodegenerative condition is selected
from the group consisting of Alzheimer's Disease, Parkinson's Disease, stroke, AIDS related
dementia, traumatic brain injury (TBI), and Huntington's Disease.

79. The method of claim 76, wherein the psychiatric condition is substance abuse.

80. The method of claim 79, wherein the substance abuse is alcohol abuse or drug
abuse.

81. The method of claim 71, wherein the subject is a mammal.

82. The method of claim 81, wherein the mammal is a human.

83. The method of claim 71, wherein the compound is administered parenterally.

84. A pharmaceutical composition for the treatment of a neurologic disorder
comprising a pharmaceutically effective amount of the compound of claim 71, and one or
more pharmaceutically acceptable excipients or carriers.
FIG. 2

D → D-OH
   / \       \ FRR
  D-Cl → D-Br

CIR
   / \ S_{11}
  D-Br → D-Br

CIR=Cationic Reactions

FRR=Free Radical Reactions

D→D-SH
   / \       \  
  D-O → D-COOH

Br/AgSO_{4}

D→D-NH_{2}
   / \       \  
  D-CONH_{2} → D-CHO

D=Diamantane or Triamantane

D-CN
Representative Ways of Generation of Diamondoid Cations

\[ \text{D-OCOCl} \rightarrow \text{D-X} \overset{\text{SbF}_5}{\rightarrow} \text{D} + \rightarrow \text{D-H} + \rightarrow \text{D-OH} \]

\[ \text{SbF}_5 \]

\[ \text{D-NO} \rightarrow \text{D-CO} \rightarrow \text{D} + \rightarrow \text{D-OH} \]

\[ \text{X = Cl, F, Br} \]
FIG. 4

Representative $S_n1$ Reactions of Diamondoid Carbocations

$D^+$

- $D$-OH $\xrightarrow{H_2O}$
- $D$-OCH$_3$ $\xrightarrow{1) CH_3CN}$
- $D$-NHCOCH$_3$ $\xrightarrow{2) H_2O}$
- $D$-NH$_2$ $\xrightarrow{NH_3}$
- $D$-CH=CHR $\xrightarrow{1) CO}$
- $D$-COOH $\xrightarrow{2) H_2O}$
- $D$-Ar
- $D$-N$_3$ $\xrightarrow{N_3^-}$
- $D$-X $\xrightarrow{X^-}$
FIG. 5

Representative $S_{E2}$ Reactions of Diamondoids

\[
\begin{align*}
\text{D-OH} & \xrightarrow{H_2O_2/H_3O_2^+} \text{D} \\
\text{D-CHO} & \xrightarrow{HCO^+} \text{D} \\
\text{D-R} & \xrightarrow{R^+} \text{D} \\
\text{D-NO}_2 & \xrightarrow{NO_2^+} \text{D} \\
\text{D-X} & \xrightarrow{X_2/AgSbF_6} \text{D}
\end{align*}
\]
FIG. 6

D-(OH)$_n$ → D-Br$_2$

48% HBr
Reflux
e.g. n=2

D-Br → D

Br$_2$ (liq.)
r.t or reflux

D-Br$_3$ → D-Br$_4$

Br$_2$-AlBr$_3$
140 deg. C
sealed tube

BB$_3$-Br$_2$-AlBr$_3$ (trace)
reflux

Br$_2$-BB$_3$-AlBr$_3$
reflux, 80 deg. C

AlBr$_3$-Br$_2$
140 deg. C
sealed tube
FIG. 7

\[ \text{D-Cl} + \text{D-Cl}_2 \xrightarrow{\text{AlCl}_3/\text{CCl}_4, \text{r.t.}} \text{D} \xrightarrow{\text{AlCl}_3/\text{SOCl}_2, 75 \deg \text{C}} \text{D-Cl}_3 \]

hv  \hspace{1cm} \text{r.t.}  \hspace{1cm} \text{CCl}_4
\downarrow \hspace{1cm} \text{Cl}_2
\downarrow
\hspace{1cm}
\text{D-Cl}

(C-2 D-Cl + C-3 D-Cl)
FIG. 8

D-(Br)ₙ

D-OH

D-H₂O/THF

heat
e.g. n=1

K₂CO₃/AgNO₃

H₂SO₄-CrO₃

acetic acid (eq.)

CrO₃-D=1.5:1

D

hv

CH₃CO₂H

heat

AcOEt/CH₂Cl₂

C-2 D-OH + C-3 D-OH

D=O

RMgBr

D-R (C-2, R=alkyl)

OH

D-(OH)₂

D-(Br)ₙ

H₂O/THF

heat
e.g. n=2

K₂CO₃/AgNO₃

H₂SO₄-CrO₃

acetic acid (eq.)

CrO₃-D=6:1
FIG. 10

\[ \text{D-(COOH)}_n \xrightarrow{\text{CH}_3\text{CN}} \text{D-(NCOCH}_3\text{)}_n \xrightarrow{\text{KOH, diethylene glycol}} \text{D-(NH}_2\text{)}_n \]

1) H\text{SO}_4
2) CH\text{3CN}
3) H\text{2O}

or D-(OH)_n

(if use NaCN, then formylamino-D formed)
(CH\text{3CN can be also any RCN, R=alkyl, aryl, etc.})

\[ \text{D-(NH}_2\text{)}_n \xrightarrow{\text{ether, HCl gas}} \text{D-(NH}_2\text{)}_n\text{HCl} \]

\( n=1, 2, 3, 4, \ldots \)
FIG. 11

\[
\begin{align*}
D - \text{NH}_2 & \xrightarrow{\text{NO}_2, 175 \text{ deg. C}} D - \text{NO}_2 & & \xrightarrow{\text{Na}_2\text{S} \cdot 9\text{H}_2\text{O}} D - \text{NH}_2 \\
& \text{or HNO}_2\text{-Acetic acid (glacial)} \text{ with high temp and pressure} & & (140 \text{ deg. C} / 500 \text{ p.s.i.} \text{g} \text{N}_2) \\
D - \text{NO}_2 & \xrightarrow{\text{NO}_2, 200 \text{ deg. C}} D - (\text{NO}_2)_2 & & \xrightarrow{\text{Na}_2\text{S} \cdot 9\text{H}_2\text{O}} D - (\text{NH}_2)_2
\end{align*}
\]
FIG. 12
FIG. 13

\[ \text{D-COOH} \xrightarrow{\text{SOCl}_2/\text{ether}} \text{D-COCI} \xrightarrow{\text{CH}_2\text{N}_2} \text{D-COCHN}_2 \]
\[ \text{CH}_2\text{N}_2 \xrightarrow{\text{H}_2\text{NNH}_2\text{H}_2\text{O}} \text{D-CONH}_2 \]
\[ \text{D-CONH}_2 \xrightarrow{\text{NaN}_3} \text{D-CON}_2 \xrightarrow{\text{hv}} \text{C}_6\text{H}_5\text{-NH}_2 \]
\[ \text{R}^\prime\text{-NH}_2 \xrightarrow{\text{R}^\prime\text{=H or C}_6\text{H}_5} \text{D-CONHR}^\prime \]
\[ \text{NaOBr} \xrightarrow{\text{heat}} \text{D-CH}_3\text{CONH-C}_6\text{H}_5 \]
\[ \text{NaOBr} \xrightarrow{\text{heat}} \text{D-CH}_3\text{CONH-C}_6\text{H}_5 \]
\[ \text{D-CON}\xrightarrow{\text{NH}_2} \text{D-NCO} \xrightarrow{\text{R}^{\prime\prime}\text{-NH}_2} \text{D-NHCONHR}^{\prime\prime} \]
\[ \text{R}^{\prime\prime}\text{=C}_6\text{H}_5 \text{or D-C(O)} \]

\[ \text{H}_2\text{NNH}_2\text{H}_2\text{O} \]

\[ \text{D-CONHNH}_2 \]

\[ \text{D-COOCH}_3 \]

\[ \text{D-CH}_2\text{-OH} \]

\[ \text{LAIH}_4 \]

\[ \text{D-COOCH}_3 \]
FIG. 14

\[ \text{D-NH}_2 + \text{HCN} \rightarrow \text{D-NH-CH}_2-\text{CN} \rightarrow \text{D-NH-CH}_2-\text{COOH} \]

\[ \text{D-NHNH}_2 + \text{HCl} \rightarrow \text{D-N-CH}_2-\text{COOH} \]

\[ \text{D-CONH}_2 + \text{LiAlH}_4 \rightarrow \text{D-CH}_2\text{NH}_2 \]

\[ \text{Cl-SO}_2\text{-C}_6\text{H}_4\text{-CH}_3 \rightarrow \text{D-CH}_2\text{NH}_2 \]

\[ \text{Cl-CO-C}_6\text{H}_5 \rightarrow \text{D-CH}_2\text{NHCO-C}_6\text{H}_5 \]
FIG. 15

\[ \text{D-Br} \xrightarrow{[\text{AlBr}_3]} \text{D-POCl}_2 \xrightarrow{\text{C}_2\text{H}_5\text{OH}/\text{HCl}} \text{D-PO(OH)}_2 \]

\[ \text{LiAIH}_4 \xrightarrow{\text{H}_2\text{O}} \text{D-PH}_2 \xrightarrow{\text{H}_2\text{O}_2} \text{D-P(OH)}_2 \xrightarrow{\text{PO}_3} \text{D-PCl}_2 \]
FIG. 16

- D-SH → NaOH → D-S-C₂H₅ → H₂O₂ → D-SO₂-C₂H₅ → KOH
- D-SO₂Na → NH₄OH or NH₄R'' → D-SONR'R''
- D-SO₂CI → NH₂OH → D-SO₂NR'R''
- D-SO₂Cl → KOH → D-OH
- D-SO₂Cl → CH₂OH / Pyridine → D-Cl

(R³ = alkyl, aralkyl, etc.)
(R', R'' = H, Alkyl, Aryl, Aralkyl, etc.)
FIG. 17
Crystal structure of 1,6-dibromodiamantane with atom numbering
Fig. 21
Fig. 22
Fig. 23
Fig. 24

Ion Abundance

GCMS Time (min.) →
Fig. 25

MDT-22

Ion Abundance →

GCMS Time (min.) →
Fig. 26

Ion Abundance

m/z
FIG. 27

Ion Abundance

m/z

2.50 3.00 3.50 4.00 4.50 5.00 5.50 6.00 6.50 7.00 7.50 8.00 8.50 9.00 9.50

MDT-23
FIG. 28
FIG. 29

$^1$H NMR Spectrum of MDT-22

NH$_2$

Methyl

2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8 ppm
FIG. 30

$^{13}$C NMR Spectrum of MDT-22
FIG. 31

$^1\text{H}$ NMR Spectrum of MDT-23

NH$_2$

Methyl

Methyl

ppm
FIG. 32

$^{13}$C NMR Spectrum of MDT-23
Fig. 33

N.S.

% inhibition

[MK-801 (nM)] 100 - - - - - - -
[Memantine] - 10 30 - - - - - -
[MDT-9] - - - 10 100 - - - -
[MDT-3] - - - - 10 100 - - -
[MDT-23] - - - - - 10 100 - -
[MDT-22] - - - - - - 10 100 -