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- (71) **Applicant (for all designated States except US):**
VIROBAY, INC. [US/US]; 1490 O'Brien Drive, Suite G, Menlo Park, CA 94025 (US).
- (72) **Inventor; and**
- (75) **Inventor/Applicant (for US only):** BOOTH, Robert [US/US]; 26700 Shady Oaks Court, Los Altos Hills, CA 94022 (US).
- (74) **Agents:** OSTOMEL, Todd A. et al.; Kilpatrick Townsend & Stockton LLP, Two Embarcadero Center, 8th Floor, San Francisco, CA 94111-3834 (US).
- (81) **Designated States (unless otherwise indicated, for every kind of national protection available):** AE, AG, AL, AM,

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(54) **Title:** CATHEPSIN INHIBITORS FOR TREATING MICROGLIA-MEDIATED NEURON LOSS IN THE CENTRAL NERVOUS SYSTEM

FIGURE 1

Cathepsin S Inhibitors
CNS PK: Rat

Time (hr)	VEY-A 50 mg/kg PO			VEY-B 50 mg/kg PO			VEY-C 50 mg/kg PO		
	Plasma (ng/mL)	CSF (ng/mL)	Brain (ng/g)	Plasma (ng/mL)	CSF (ng/mL)	Brain (ng/g)	Plasma (ng/mL)	CSF (ng/mL)	Brain (ng/g)
1	1768	75	33	10310	553	2260	3791	204	177
3	1975	311	23	10563	985	2528	2781	125	244

Results are expressed as mean from 3 rats per group
Assumes density of tissue is 1g/ml (typical assumption)

Cathepsin S Inhibitors
CNS PK: Mouse

Time (hr)	VEY-A 100 mg/kg PO			VEY-B 100 mg/kg PO			VEY-C 100 mg/kg PO		
	Plasma (ng/mL)	CSF (ng/mL)	Brain (ng/g)	Plasma (ng/mL)	CSF (ng/mL)	Brain (ng/g)	Plasma (ng/mL)	CSF (ng/mL)	Brain (ng/g)
3	1014	5	14	8087	60	2900	795	804	31

Time (hr)	VEY-D 100 mg/kg PO		
	Plasma (ng/mL)	CSF (ng/mL)	Brain (ng/g)
3	8493	96	210

Results are expressed as mean from 6 mice per group
Assumes density of wet brain tissue is 1g/ml

(57) **Abstract:** The present invention concerns methods of using Cathepsin S inhibitors and compounds of Formula I that are inhibitors of cathepsin S in treating CNS disorders, diseases, and injuries, particularly neurodegenerative conditions. The present invention is directed to pharmaceutical compositions comprising these compounds for treating CNS disorders.

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 12/42992

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A01N 55/02 (2012.01)

USPC - 514/186

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC: 514/186Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/186,112,613 (text search-see terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Dialog Classic, Google Scholar, Free Patents Online

Search Terms: microglial, inflammation or neuron loss, central nervous system, cathepsin S inhibitor, traumatic brain injury or concussion, neurotoxin, hypoxia, stroke or administering to a human subject, Parkinson's disease, Alzheimer's disease, senile dementia

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2004/0229209 A1 (Lynch et al.) 18 November 2004 (18.11.2004), para[0022],[0024],[0105] [0253]-[0254], [0289]	1-17 and 23-26
Y	US 2008/0293819 A1(Link et al.) 27 November 2008 (27.11.2008), para [0002], [0006]-[0007], [0018]-[0020], [0247], [0251],[0253],[0250]	1-26
Y	US 6,696,488 B2 (Wolfe et al.) 24 February 2004 (24.02.2004), (col19 ln 58-63), (col 20 ln 40- 52), (col 21 ln 1-22), (col 21 ln 54-61), (col 22 ln 49-51)	18-19, 23-26
Y	US 6,348,448 B1 (Tao et al.) 19 February 2002 (19.02.2002), (col 1 ln 14-16), (col 1 ln 19-46), (col 7 ln 17-24)	16-17, 20-26
Y	US 7,737,300 B2 (Li et al.) 15 June 2010 (15.06.2010), (col 1 ln 34-col2 ln 59), (col 18 ln 39-54)	3-4, 23-26

 Further documents are listed in the continuation of Box C.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

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Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774