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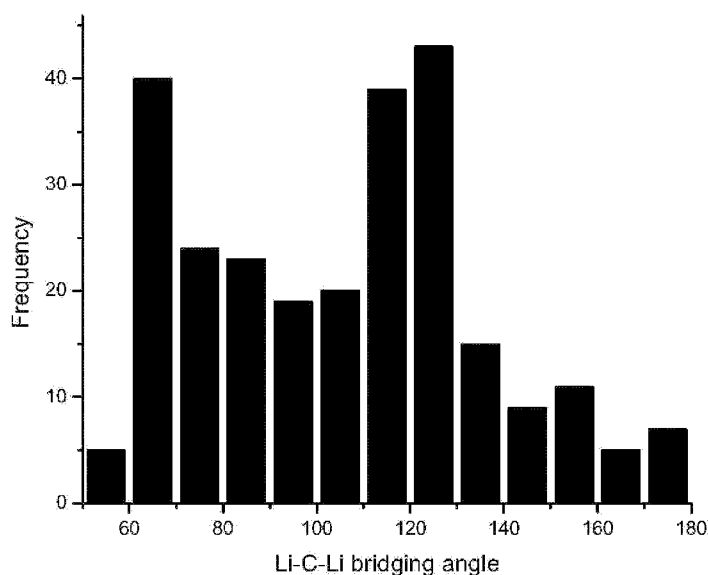
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[Continued on next page]

(54) Title: LITHIUM COMPOSITIONS



(57) **Abstract:** 2:1 cocrystals of amino acids and Li⁺ salts crystallize from hot water to afford water stable cationic networks based upon tetrahedral lithium cations: bilayered square grids, a lithium zeolitic metal-organic material (LiZMOM) and several lithium diamondoid metal-organic materials (LiDMOMs). The compositions may be used as a pharmaceutical for the treatment of suicidality and other disorders that require lithium to penetrate the blood brain barrier and exert therapeutic effects in the CNS. Advantageously, the novel cocrystal forms described herein may be used to lower the oral dose required to achieve therapeutic concentrations of lithium in the brain, thus reducing the peripheral toxicity and potentially broadening the therapeutic index in comparison to conventional lithium forms.

FIGURE 1



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PCT/US2012/030586**A. CLASSIFICATION OF SUBJECT MATTER****A61K 33/14(2006.01)i, A61K 33/10(2006.01)i, A61K 9/16(2006.01)i, A61K 9/20(2006.01)i, A61K 9/48(2006.01)i**

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)

A61K 33/14; A61K 9/14; A61K 31/19; A61K 31/60; A61K 31/00; A61K 31/55; A61K 31/522

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
eKOMPASS(KIPO internal) & Keywords: lithium co-crystal, lithium salt, amino acid, leucine, toxicity, therapeutic index**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	T. UMA DEVI et al. 'Synthesis, crystal growth and characterization of L-proline lithium chloride monohydrate: a new semiorganic nonlinear optical material' Crystal Growth & Design, 2009, Vol. 9, No. 3, pp. 1370-1374, ISSN 1528-7483.	15-20, 22-27, 29
A	See abstract; p. 1370 - p. 1371, left-column.	1-14, 21, 28
X	J. BARAN et al. 'Bis(glycine) lithium nitrate - a new non-centrosymmetric crystal: X-ray structure, vibrational spectra and DSC investigations' Journal of Molecular Structure, 2009, Vol. 927, No. 1/3, pp. 43-53, ISSN 0022-2860.	15-20, 22-27, 29
A	See abstract; p. 43 - p. 44, left-column.	1-14, 21, 28
A	US 2010-0204204 A1 (MICHAEL ZAWOROTKO et al.) 12 August 2010 See paragraphs [0098] - [0103], [0117] - [0119], [0138] - [0140], and [0148] - [0150]; claims 1-3.	1-29
A	US 2004-0176335 A1 (SCOTT L. CHILDS) 09 September 2004 See abstract; paragraphs [0058], [0059], [0064], [0075], [0195], [0196], [0198], [0201], [0202], and [0222]; claims 1 and 4-6; tables 2 and 3.	1-29

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2004-078163 A2 (TRANSFORM PHARMACEUTICALS, INC. et al.) 16 September 2004 See abstract; pp. 58-62; claims 1, 10, and 12; tables 2 and 4.	1-29

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2012/030586

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2010-0204204 A1	12.08.2010	EP 2167043 A2	31.03.2010
		US 2010-0173984 A1	08.07.2010
		WO 2008-153938 A2	18.12.2008
		WO 2008-153945 A2	18.12.2008
US 2004-0176335 A1	09.09.2004	US 2009-0281195 A1	12.11.2009
		US 2011-257430 A1	20.10.2011
		US 7452555 B2	18.11.2008
		US 8212079 B2	03.07.2012
WO 2004-078163 A2	16.09.2004	AU 2003-211021 A1	09.09.2003
		AU 2003-213719 A1	16.09.2003
		AU 2003-243354 A1	19.12.2003
		AU 2003-243699 A1	06.01.2004
		AU 2003-243699 B2	15.01.2009
		AU 2003-267231 A1	08.04.2004
		AU 2003-272270 A1	28.09.2004
		AU 2003-295846 A1	18.06.2004
		AU 2003-300452 A1	29.07.2004
		AU 2003-303591 A1	29.07.2004
		AU 2004-270238 A1	17.03.2005
		AU 2004-270238 B2	29.07.2010
		AU 2005-212229 A1	25.08.2005
		AU 2005-212229 B2	09.06.2011
		CA 2476422 A1	28.08.2003
		CA 2477923 A1	12.09.2003
		CA 2489984 A1	31.12.2003
		CA 2511881 A1	22.07.2004
		CA 2513746 A1	16.09.2004
		CA 2514733 A1	16.09.2004
		CA 2534664 A1	17.03.2005
		CA 2556106 A1	25.08.2005
		CN 100360117 C0	09.01.2008
		CN 101972240 A	16.02.2011
		CN 1646538 C0	27.07.2005
		CN 1668283 A	14.09.2005
		CN 1668283 C0	09.01.2008
		CN 1874993 A	06.12.2006
		CN 1874993 B	08.12.2010
		CN 1980888 A	13.06.2007
		CN 1980888 B	13.04.2011
		EP 1485388 A2	15.12.2004
		EP 1494998 A2	12.01.2005
		EP 1511490 A2	09.03.2005
		EP 1515703 A1	23.03.2005
		EP 1579198 A1	28.09.2005
		EP 1608339 A1	28.12.2005
		EP 1608339 B1	21.03.2012
		EP 1631260 A2	08.03.2006

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2012/030586

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		EP 1670753 A2	21.06.2006
		EP 1718607 A1	08.11.2006
		EP 1718640 A1	08.11.2006
		EP 1742941 A1	17.01.2007
		EP 2292213 A1	09.03.2011
		EP 2339328 A2	29.06.2011
		JP 2005-519112 A	30.06.2005
		JP 2005-524645 A	18.08.2005
		JP 2005-535602 A	24.11.2005
		JP 2006-500377 A	05.01.2006
		JP 2006-517527 A	27.07.2006
		JP 2007-507554 A	29.03.2007
		JP 2007-513867 A	31.05.2007
		JP 2007-522147 A	09.08.2007
		JP 2007-524596 A	30.08.2007
		JP 2007-525502 A	06.09.2007
		JP 2010-180239 A	19.08.2010
		JP 4842819 B2	21.12.2011
		JP 4906233 B2	28.03.2012
		JP 4917441 B2	18.04.2012
		JP 4923182 B2	25.04.2012
		KR 10-1184797 B1	20.09.2012
		KR 10-2005-0002826 A	10.01.2005
		KR 10-2005-0016596 A	21.02.2005
		KR 10-2006-0123613 A	01.12.2006
		US 2003-0166581 A1	04.09.2003
		US 2003-0224006 A1	04.12.2003
		US 2004-0019211 A1	29.01.2004
		US 2004-0053853 A1	18.03.2004
		US 2005-0025791 A1	03.02.2005
		US 2005-0070551 A1	31.03.2005
		US 2005-0169982 A1	04.08.2005
		US 2006-0052432 A1	09.03.2006
		US 2006-0134198 A1	22.06.2006
		US 2006-0140985 A1	29.06.2006
		US 2006-0148877 A1	06.07.2006
		US 2006-0223794 A1	05.10.2006
		US 2007-0015841 A1	18.01.2007
		US 2007-0021510 A1	25.01.2007
		US 2007-0026078 A1	01.02.2007
		US 2007-0059356 A1	15.03.2007
		US 2007-0293674 A1	20.12.2007
		US 2009-0018202 A1	15.01.2009
		US 2010-0210731 A1	19.08.2010
		US 2010-0279993 A1	04.11.2010
		US 2010-0311701 A1	09.12.2010
		US 6559293 B1	06.05.2003
		US 6699840 B2	02.03.2004
		US 7078526 B2	18.07.2006
		US 7351695 B2	01.04.2008

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2012/030586

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		US 7446107 B2	04.11.2008
		US 7566805 B2	28.07.2009
		US 7790905 B2	07.09.2010
		US 7927613 B2	19.04.2011
		US 8183290 B2	22.05.2012
		WO 03-070738 A2	28.08.2003
		WO 03-074474 A2	12.09.2003
		WO 03-101392 A2	11.12.2003
		WO 04-000284 A1	31.12.2003
		WO 2004-026235 A2	01.04.2004
		WO 2004-047752 A2	10.06.2004
		WO 2004-060347 A2	22.07.2004
		WO 2004-061433 A1	22.07.2004
		WO 2004-063152 A2	29.07.2004
		WO 2004-078161 A1	16.09.2004
		WO 2004-089313 A2	21.10.2004
		WO 2005-023198 A2	17.03.2005
		WO 2005-077894 A1	25.08.2005
		WO 2005-092884 A1	06.10.2005
		WO 2005-118577 A1	15.12.2005