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(54) **AMINO ACID LIPIDS AND USES THEREOF**

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(52) **U.S. Cl.** **514/44 R**; 514/44 A; 514/785; 514/788; 514/943; 554/53; 560/168; 564/159

(58) **Field of Classification Search** None
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,844,884 A 7/1989 Tur
5,141,751 A * 8/1992 Tomikawa et al. 424/450
5,310,542 A 5/1994 Au et al.
5,357,026 A 10/1994 Younes
5,376,640 A * 12/1994 Miyazaki et al. 514/12
5,504,228 A 4/1996 Morelle et al.
5,658,885 A 8/1997 Lee et al.
5,820,873 A * 10/1998 Choi et al. 424/283.1
5,831,005 A 11/1998 Zuckerman et al.
5,849,276 A 12/1998 Guskey et al.
5,908,777 A * 6/1999 Lee et al. 435/320.1
5,935,936 A 8/1999 Fasbender et al.
5,965,188 A 10/1999 Bland et al.
5,977,301 A 11/1999 Zuckerman et al.
5,980,935 A 11/1999 Kirpotin et al.

6,335,468 B1 1/2002 Hatajima et al.
6,379,965 B1 4/2002 Boutin
6,458,381 B1 10/2002 Sourovoï et al.
6,656,499 B1 12/2003 Foldvari et al.
6,749,863 B1 6/2004 Chang et al.
6,815,432 B2 11/2004 Wheeler et al.
6,858,225 B2 2/2005 Semple et al.
6,897,196 B1 * 5/2005 Szoka et al. 514/1
7,312,206 B2 12/2007 Panzner et al.
7,335,509 B2 2/2008 Huang et al.
7,341,738 B2 3/2008 Semple et al.
7,371,404 B2 5/2008 Panzner et al.
2003/0130237 A1 7/2003 Miller et al.
2004/0131666 A1 7/2004 Panzner et al.
2004/0204377 A1 10/2004 Rana
2005/0064595 A1 3/2005 MacLachlan et al.
2005/0186586 A1 8/2005 Zamore et al.
2005/0222396 A1 * 10/2005 Bao et al. 534/11
2005/0239687 A1 10/2005 Divita
2005/0265955 A1 * 12/2005 Raman et al. 424/78.12
2005/0287627 A1 12/2005 Hashimoto et al.
2006/0009507 A1 1/2006 Miller et al.
2006/0211637 A1 9/2006 Scaria et al.
2007/0129305 A1 6/2007 Divita
2007/0260055 A1 11/2007 Rana
2008/0020058 A1 1/2008 Chen et al.
2008/0286866 A1 * 11/2008 Quay et al. 435/375

FOREIGN PATENT DOCUMENTS

DE 2064480 7/1971
DE 4311806 A1 6/1994
EP 0136879 A2 4/1985
EP 0320976 A1 6/1989
EP 0490379 A2 12/1991
EP 0763592 A1 3/1997
EP 0805147 A1 5/1997
EP 1060739 A1 12/2000

(Continued)

OTHER PUBLICATIONS

Epand, R. et al., "Properties of lipoamino acids incorporated into membrane bilayers," *Biochimica et Biophysica Acta*, v. 1373, No. 1, pp. 67-75, Elsevier, 1998. Heyes, J. et al., "Cationic lipid saturation influences intracellular delivery of encapsulated nucleic acids," *Journal of Controlled Release*, v. 107, No. 2, pp. 276-287, Elsevier, 2005. MacDonald, M. et al., "Physical and Biological Properties of Cationic Triesters of Phosphatidylcholine," *Biophysical Journal*, v. 77, pp. 2612-2629, 1999. Reshetnyak, Y. et al., "Translocation of molecules into cells by pH-dependent insertion of a transmembrane helix," *PNAS*, v. 103, No. 17, pp. 6460-6465, 2006. Rossi, J., "SNALPing siRNAs in vivo," *Gene Therapy*, v. 13, pp. 583-584, Nature Publishing Group, 2005. Saleh, M. et al., "The endocytic pathway mediates cell entry of dsRNA to induce RNAi silencing," *Nature Cell Biology*, v. 8, No. 8, pp. 793-802, 2006. Hafez, I. et al. "Tunable pH-Sensitive Liposomes Composed of Mixtures of Cationic and Anionic Lipids," *Biophysical Journal*, v. 79, No. 3, pp. 1438-1446, 2000.

(Continued)

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(57) **ABSTRACT**

This disclosure provides a range of amino acid lipid compounds and compositions useful for drug delivery, therapeutics, and the diagnosis and treatment of diseases and conditions. The amino acid lipid compounds and compositions can be used for delivery of various agents such as nucleic acid therapeutics to cells, tissues, organs, and subjects.



FOREIGN PATENT DOCUMENTS

EP	1264591	A2	12/2002
EP	1325735	A2	7/2003
EP	PCT/US2008/078627	R	10/2009
EP	PCT/US2009/060930	R	8/2010
FR	WO02053583	A	7/2002
GB	2355013		11/2001
JP	63-189288	A	8/1988
JP	02088549		3/1990
JP	04026662		1/1992
JP	2000128725		5/2000
JP	2000128725		9/2000
WO	9101724	A1	2/1991
WO	9403468	A1	2/1994
WO	9640737	A1	12/1996
WO	9705865	A1	2/1997
WO	WO9725070	A	7/1997
WO	9743363	A1	11/1997
WO	9915506	A1	4/1999
WO	9933787	A1	8/1999
WO	9952936	A2	10/1999
WO	0015206	A2	3/2000
WO	0073471	A1	12/2000
WO	0171022	A2	9/2001
WO	0198362	A2	12/2001
WO	02072068	A2	9/2002
WO	02002538	A1	10/2002
WO	02078448	A1	10/2002
WO	03024402	A2	3/2003
WO	03091276	A2	11/2003
WO	03091276	A3	11/2003
WO	03106636	A2	12/2003
WO	2005032494	A2	4/2005
WO	2005039629	A2	5/2005
WO	2005068488	A1	7/2005
WO	2005105152		10/2005
WO	2005102997	A1	11/2005
WO	2006001381	A1	5/2006
WO	2006082978	A1	10/2006
WO	2007001455		1/2007
WO	2007027742	A2	3/2007
WO	2007039736	A1	4/2007
WO	2008042973		4/2008
WO	WO2009046220	A2	4/2009

OTHER PUBLICATIONS

Wang, K. et al. "Synthesis and in vitro Behavior of Multivalent Cationic Lipopeptide for DNA Delivery and Release in HeLa Cells," *Bioconjugate Chemistry*, v. 18, No. 6, pp. 1735-1738, American Chemical Society, 2007.

Gonzalez, H. et al., "New Class of Polymers for the Delivery of Macromolecular Therapeutics," *Bioconjugate Chemistry*, v. 10, pp. 1068-1074, 1999.

Thomas, M., et al., "Non-viral siRNA delivery to the lung" *Advanced Drug Delivery Reviews* 59 (2007) pp. 124-133.

Thomas, M., et al., "Full deacylation of polyethylenimine dramatically boosts its gene delivery efficiency and specificity to mouse lung" *PNAS*, v. 102 No. 16, 2005.

Prata, C., et al., "Lipophilic Peptides for Gene Delivery" *Bioconjugate Chem.*, vol. 19, No. 2, 2008.

Rudraksh, S., et al., "Molecular modeling of arginine-glycine-aspartic acid (RGD) analogs Relevance to Transepithelial transport" *J Pharm Pharmaceut Sci (www.ualberta.ca/~csps)* 4(1):32-41, 2001.

Opal, S., et al., "Lipopolyamines as a therapeutic strategy in experimental Gram-negative bacterial sepsis" *Journal of Endotoxin Research*, v. 7, No. 1, pp. 35-39, 2001.

Ma, B., et al. "Lipoplex morphologies and their influences on transfection efficiency in gene delivery" *Journal of Controlled Release*, 123, pp. 184-194, 2007.

Yaghmur, A., et al., "Tuning Curvature and Stability of Monoolein Bilayers by Designer Lipid-Like Peptide Surfactants" *PLoS ONE* 2(5): e479. doi:10.1371/journal.pone.0000479, (2007).

David, S., et al. "Lipopolyamines: Novel Antiendotoxin Compounds That Reduce Mortality in Experimental Sepsis Caused by Gram-

Negative Bacteria" *Antimicrobial Agents and Chemotherapy*, v.43 No. 4, pp. 912-919, 1999.

Bedford, M., et al. "Arginine Methylation: An Emerging Regulator of Protein Function" *Molecular Cell*, v. 18, pp. 263-272, 2005.

Vavrova K, et al., "Synthetic ceramide analogues as skin permeation enhancers: structure-activity relationships" *Bioorganic & Medicinal Chemistry*, Elsevier Science LTD, v. 11, No. 24, pp. 5381-5390, 2003.

Fan, G., et al., "Synthesis of alpha-galactosyl ceramide and the related glycolipids for evaluation of their activities on mouse splenocytes" *Tetrahedron*, Elsevier Science Publishers, v. 61, No. 7, pp. 1855-1862, 2005.

Polidori, A., et al., "Vesicles and other supramolecular systems made from double-tailed synthetic glycolipids derived from galactosylated tris (hydroxymethyl) aminomethane" *Chemistry and Physics of Lipids*, v. 77, No. 2, pp. 225-251, 1995.

Tonges, L., et al., "Stearylated octaarginine and artificial virus-like particles for transfection of siRNA into primary rat neurons" *RNA*, v. 12, No. 7, pp. 1431-1438, 2006.

Sommerdijk, M., et al., "Boomerang shaped aggregates from histidine surfactant" *Chem. Commun.*, pp. 455-456, 1997.

Heyes, J., et al., "Synthesis of novel cationic lipids: Effect of structural modification on the efficiency of gene transfer" *Journal of Medicinal Chemistry*, US American Chemical Society, v. 45, No. 1, pp. 99-114, 2002.

Kumar, V., et al. "Single histidine residue in head-group region is sufficient to impart remarkable gene transfection properties to cationic lipids: Evidence for histidine-mediated membrane fusion at acidic pH" *Gene Therapy*, Macmillan Press Ltd., v. 10, No. 15, pp. 1206, 2003.

Martin, B., et al., "The design of cationic lipids for gene delivery" *Current Pharmaceutical Design*, v.11, No. 3, pp. 375-394, 2005.

Sommerdijk, M., et al., "Supramolecular expression of chirality in assemblies of gemini surfactants" *Chem. Comm.*, pp. 1423-1424, 1997.

Gao, H., et al., "Synthesis of a novel series of cationic lipids that can act as efficient gene delivery vehicles through systematic heterocyclic substitution of cholesterol derivatives" *Gene Therapy*, v. 8, No. 11, pp. 855-863, 2001.

Meekel, A., et al., "Synthesis of pyridium amphiphiles used for transfection and some characteristics of amphiphile/DNA complex formation" *European Journal of Organic Chemistry*, Wiley-Vch, No. 4, pp. 665-673, 2000.

Karmali, P., et al., "Cationic liposomes as non-viral carriers of gene medicines: Resolved issues, open questions, and future promises" *Medicinal Research Reviews*, v. 27, No. 5, pp. 696-722, 2006.

Gascon, A., et al., "Cationic lipids as gene transfer agents: a patent review" *Expert Opin. Ther. Patents*, v. 18, No. 5, pp. 515-521, 2008.

Futaki, *Bioconjugate Chemistry*, 2001; vol. 12(6): 1005-1011.

Khalil, *Gene Therapy*, 2004 ; vol. 11(7): 636-644.

Mitchell, *Journal of Peptide Research*, 2000 ; vol. 56(5): 318-325.

Leng, *Cancer Gene Therapy*, 2005 ; vol. 12(8): 682-690.

Fan, *European Food Research and Technology*, 2007; vol. 227(1): 167-174.

Frederiksen, *Journal of Pharmaceutical Sciences*, 1997; vol. 86(8): 921-928.

Gabizon, *Journal of Liposome Research*, 2006; vol. 16(3): 175-183.

Mainardes, *Current Drug Delivery*, 2006; vol. 3(3): 275-285.

Maitani, *International Journal of Pharmaceutics*, 2007; vol. 342(1-2): 33-39.

Maitani, *Journal of Liposome Research*, 2001; vol. 11(1): 115-125.

Pons, *International Journal of Pharmaceutics*, 1993; vol. 95(1-3): 51-56.

Sharma, *International Journal of Pharmaceutics*, 1997; vol. 154(2): 123-140.

Skalko, *European Journal of Pharmaceutical Sciences*, 1996; vol. 4(6): 359-366.

* cited by examiner

FIG. 1

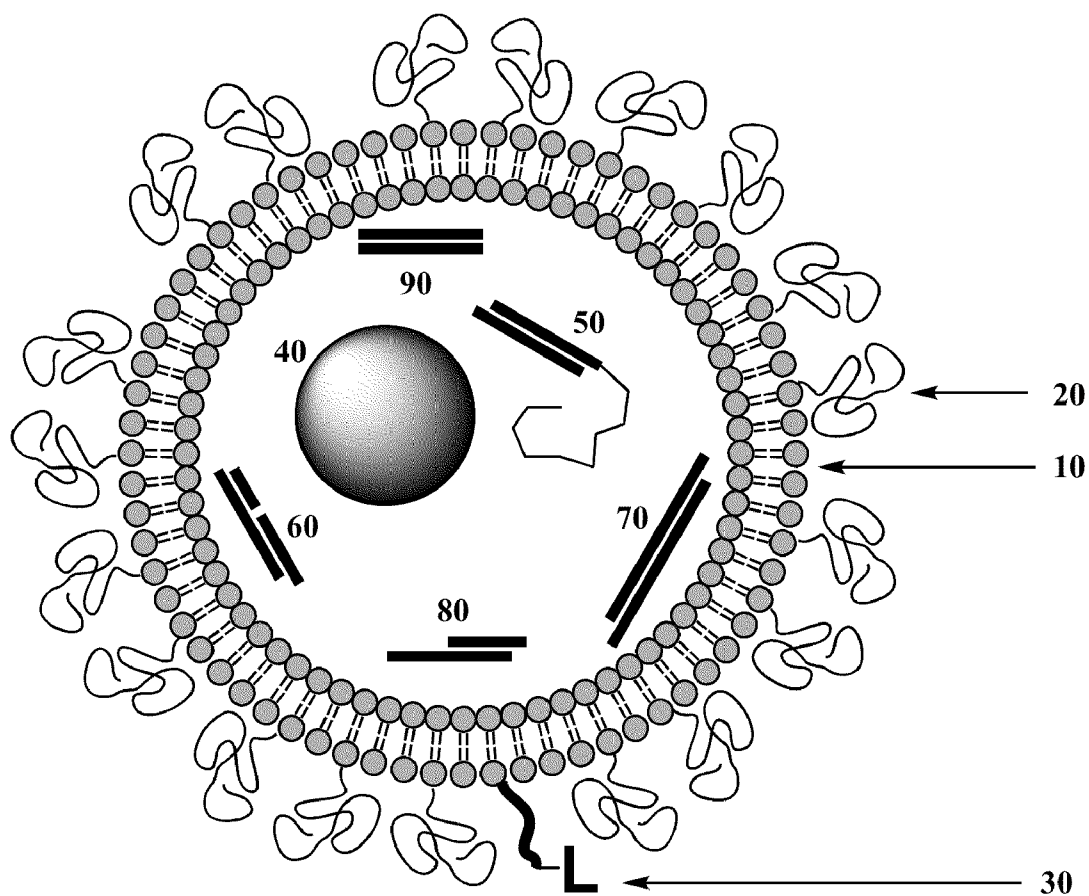


FIG. 2

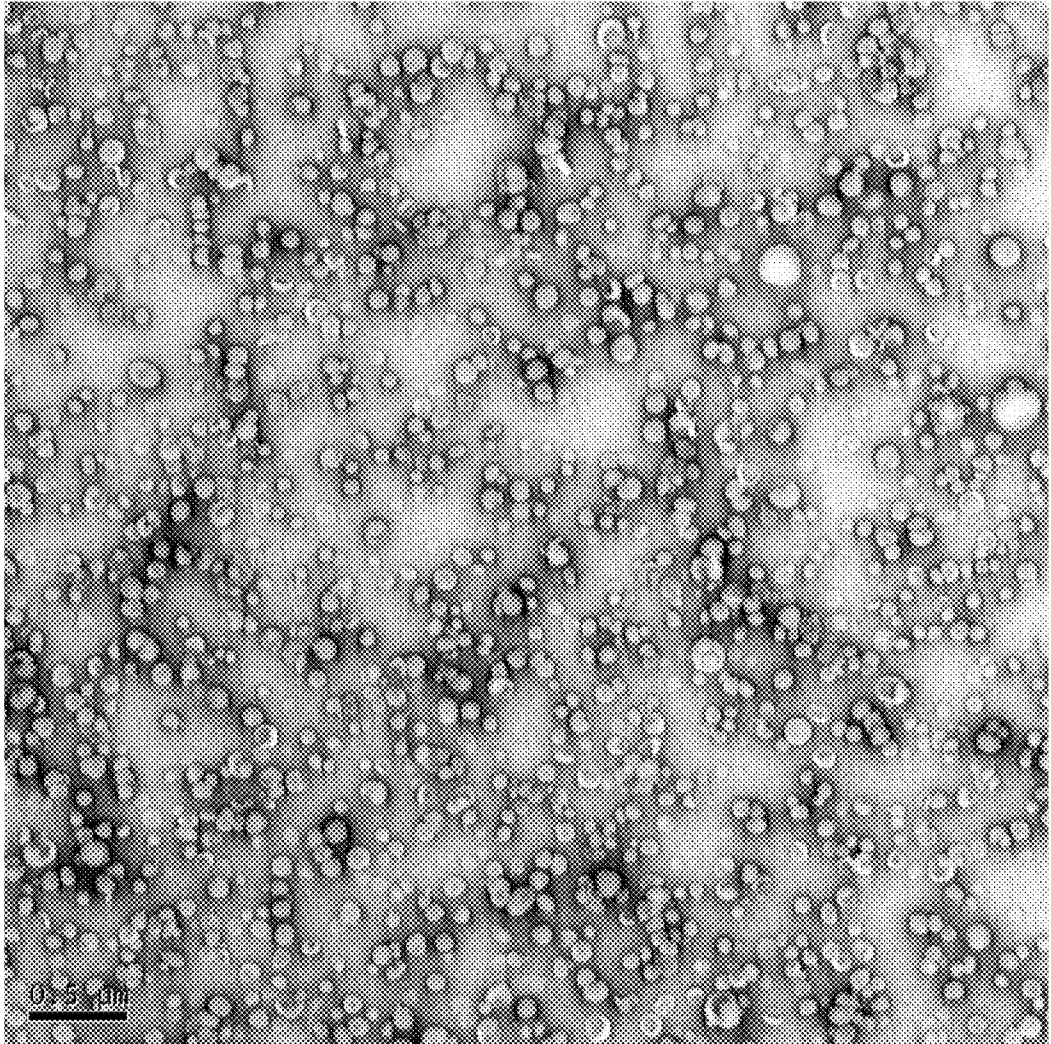
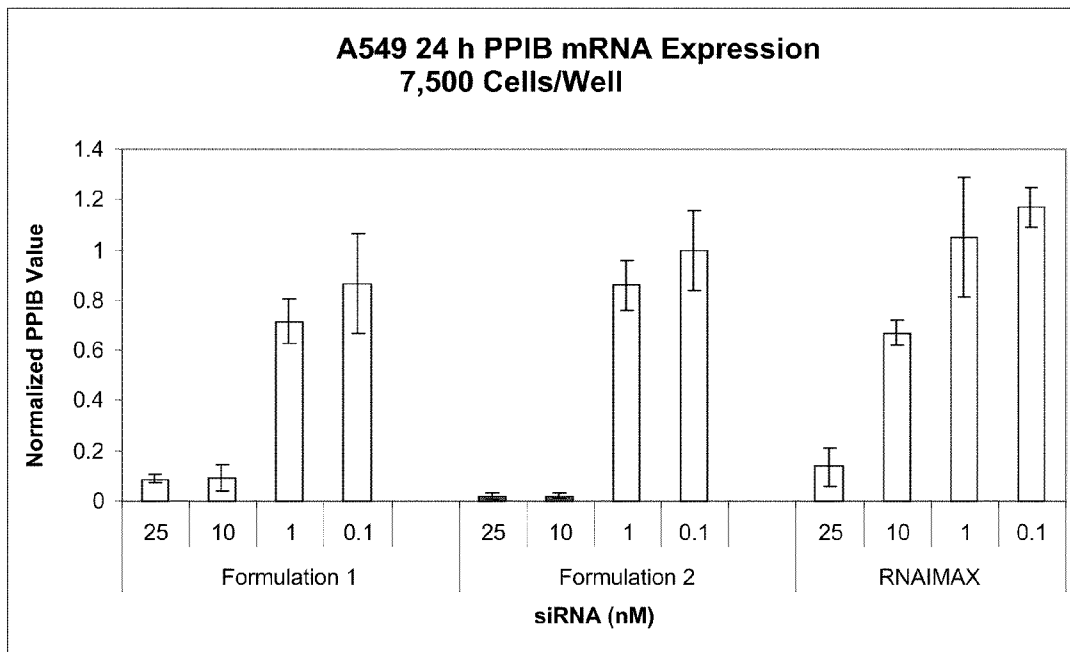


FIG. 3



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