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(54) **METHODS AND COMPOSITIONS FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS**
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WO WO 02/078683 10/2002
WO WO 02/079235 10/2002
WO WO 02/098912 12/2002
WO WO 03/072125 9/2003
WO WO2003/072754 9/2003
WO WO2004/069165 8/2004
WO WO 2004/071436 8/2004
WO WO2005/087797 9/2005

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OTHER PUBLICATIONS

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

Amarante et al., "The κ -opioid agonist (\pm)-bremazocine elicits peripheral antinociception by activation of the L-arginine/nitric oxide/cyclic GMP pathway" *European Journal of Pharmacology*, vol. 454: pp. 19-23 (2002).

Arita et al., "Purification and characterization of a heat-stable enterotoxin of *Vibrio mimicus*" *FEMS Microbiology Letters*, vol. 79/1: pp. 105-110 (1991).

Camilleri, "Management of the Irritable Bowel Syndrome" *Gastroenterology* 120:652-668, 2001.

Chan et al., "Amino Acid Sequence of Heat-stable Enterotoxin Produced by *Escherichia coli* Pathogenic for Man" *The Journal of Biological Chemistry*, vol. 256, No. 15: pp. 7744-7746 (1981).

Drossman, D.A., "The functional gastrointestinal disorders and the Rome II process" *Gut* 45:Supp. II:111-113, 1999.

Drossman, D.A., "Psychosocial aspects of the functional gastrointestinal disorders" *Gut* 45:Supp. II:1125-1130, 1999.

Drossman et al., "U.S. Householder Survey of Functional Gastrointestinal Disorders" *Digestive Diseases and Sciences* 38(9):1569-1580, 1993.

Forte et al., "Lymphoguanlylin: Cloning and Characterization of a Unique Member of the Guanylin Peptide Family" *Endocrinology*, vol. 140, No. 4: pp. 1800-1806 (1999).

Giannella, "*Escherichia coli* heat-stable enterotoxins, guanylins, and their receptors: What are they and what do they do?" *The Journal of Laboratory and Clinical Medicine*, vol. 125, No. 2: pp. 173-181 (1995).

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Related U.S. Application Data

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A61K 38/00 (2006.01)

(52) **U.S. Cl.** **514/14; 530/300**

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

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,140,102 A 8/1992 Currie 530/326
5,395,490 A 3/1995 Hoff 204/132
5,489,670 A 2/1996 Currie et al.
5,969,097 A 10/1999 Wiegand et al.
6,060,037 A 5/2000 Waldman
7,304,036 B2 12/2007 Currie et al.
7,371,727 B2* 5/2008 Currie et al. 514/14
2003/0073628 A1 4/2003 Shailubhai et al.
2003/0232013 A1 12/2003 Sieckman et al.
2004/0121961 A1 6/2004 Masferrer
2004/0152868 A1 8/2004 Larsen et al.
2004/0258687 A1 12/2004 Waldman et al.
2004/0266989 A1 12/2004 Currie et al.
2005/0032684 A1 2/2005 Cetin et al.
2006/0281682 A1 12/2006 Currie et al.
2009/0005534 A1 1/2009 Currie et al.
2009/0062207 A1 3/2009 Currie et al.
2009/0191611 A1 7/2009 Currie et al.

FOREIGN PATENT DOCUMENTS

EP 1012188 6/2000
WO WO 99/14239 3/1999
WO WO 01/25266 4/2001

(Continued)

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Assistant Examiner—Roy Teller

(74) *Attorney, Agent, or Firm*—Honigman Miller Cohen & Schwartz LLP; Jonathan P. O'Brien; Kelly T. Murphy

(57) **ABSTRACT**

The present invention features compositions and related methods for treating IBS and other gastrointestinal disorders and conditions (e.g., gastrointestinal motility disorders, functional gastrointestinal disorders, gastroesophageal reflux disease (GERD), Crohn's disease, ulcerative colitis, inflammatory bowel disease, functional heartburn, dyspepsia (including functional dyspepsia or nonulcer dyspepsia), gastroparesis, chronic intestinal pseudo-obstruction (or colonic pseudo-obstruction), and disorders and conditions associated with constipation, e.g., constipation associated with use of opiate pain killers, post-surgical constipation (post-operative ileus), and constipation associated with neuropathic disorders as well as other conditions and disorders using peptides and other agents that activate the guanylate cyclase C (GC-C) receptor.



OTHER PUBLICATIONS

- Ginnella, "Escherichia coli heat-stable enterotoxins, guanylin, and their receptors: What are they and what do they do?," *The Journal of Laboratory and Clinical Medicine*, vol. 125:173-181.
- Gualillo et al., "Ghrelin, a widespread hormone: insights into molecular and cellular regulation of its expression and mechanism of action" *FEBS Letters*, vol. 552: pp. 105-109 (2003).
- Guarino et al., "Citrobacter freundii Produces an 18-Amino-Acid Heat-Stable Enterotoxin Identical to the 18-Amino-Acid Escherichia coli Heat-Stable Enterotoxin (ST 1a)" *Infection and Immunity*, vol. 57, No. 2: pp. 649-652 (1989).
- Huang et al., "Nucleotide sequence of a gene encoding the novel Yersinia enterocolitica heat-stable enterotoxin that includes a pro-region-like sequence in its mature toxin molecule" *Microbial Pathogenesis*, vol. 22: pp. 89-97 (1997).
- Jain et al., "Sildenafil-induced peripheral analgesia and activation of the nitric oxide-cyclic GMP pathway" *Brain Research*, vol. 909: pp. 170-178 (2001).
- Kim et al., "Changes in ghrelin and ghrelin receptor expression according to feeding status" *NeuroReport*, vol. 14, No. 10: pp. 1317-1320 (2003).
- Lazaro-Ibanez et al., "Participation of the nitric oxide-cyclic GMP-ATP-sensitive K⁺ channel pathway in the antinociceptive action of ketorolac" *European Journal of Pharmacology*, vol. 426: pp. 39-44 (2001).
- Moseley et al., "Isolation and Nucleotide Sequence Determination of a Gene Encoding a Heat-Stable Enterotoxin of Escherichia coli" *Infection and Immunity*, vol. 39, No. 3: pp. 1167-1174 (1983).
- Nzegwu et al., "Luminal capsaicin inhibits fluid secretion induced by enterotoxin E. coli STa, but not by carbachol, in vivo in rat small and large intestines" *Experimental Physiology*, vol. 81, No. 2: pp. 313-315 (1996).
- Ringel, et al., "Irritable Bowel Syndrome" *Annu. Rev. Med.* 52:319-38, 2001.
- Rolfe et al., "Enterotoxin Escherichia coli STa activates a nitric oxide-dependent myenteric plexus secretory reflex in the rat ileum" *The Journal of Physiology*, vol. 475, No. 3: pp. 531-537 (1994).
- Rolfe et al., "Vagotomy inhibits the jejunal fluid secretion activated by luminal ileal Escherichia coli STa in the rat in vivo" *Gut*, vol. 44: pp. 615-619 (1999).
- Santos-Neto, et al., "Guanylin and its Lysine-Containing Analogue in the Isolated Perfused Rat Kidney" *Pharmacol. & Toxicol.* 92:114-120, 2003.
- Shailubhai, "Therapeutic applications of guanylate cyclase-C receptor agonists" *Drug Discovery & Development*, vol. 5 No. 2: pp. 261-268 (2002).
- So et al., "Nucleotide Sequence of the Bacterial Transposon Tn1681 Encoding a Heat-Stable (ST) Toxin and Its Identification in Enterotoxigenic Escherichia coli Strains" *Proceedings of the National Academy of Sciences of the U.S.A.*, vol. 77, No. 7 [Part 2: Biological Sciences]: pp. 4011-4015 (1980).
- Soares, et al., "Dibutyl-cyclic GMP induces peripheral antinociception via activation of ATP-sensitive K⁺ channels in the RAT PGE₂-induced hyperalgesic paw" *British Journal of Pharmacology*, vol. 134: pp. 127-131 (2001).
- Takao et al., "Amino acid sequence of heat-stable enterotoxin produced by Vibrio cholerae non-01" *FEBS*, vol. 193, No. 2: pp. 250-254 (1985).
- Takao et al., "Isolation, primary structure and synthesis of heat-stable enterotoxin produced by Yersinia enterocolitica" *European Journal of Biochemistry*, vol. 152, No. 1: pp. 199-206 (1985).
- Talley, et al., "Irritable Bowel Syndrome in a Community: Symptom Subgroups, Risk." *Am. J. of Epidemiology* 142(1):76-83, 1995.
- Talley, et al., "Medical Costs in Community Subjects with Irritable Bowel Syndrome" *Gastroenterology* 109(6):1736-1741, 1995.
- Vaandrager et al., "Structure and function of the heat-stable enterotoxin receptor/guanylyl cyclase C" *Molecular and Cellular Biochemistry*, vol. 230, Nos. 1&2: pp. 73-83 (2002).
- GenBank Accession No. QHECIB; GI:69638; Aimoto et al., Jun. 18, 1999.
- GenBank Accession No. P01559; GI:123711; So et al., Oct. 25, 2004.
- GenBank Accession No. AAA24653; GI:147878; Sekizaki et al., Apr. 26, 1993.
- GenBank Accession No. P01560; GI:123707; Chan et al., Jun. 15, 2004.
- GenBank Accession No. AAA27561; GI:295439; Ogawa et al., Jun. 12, 1993.
- GenBank Accession No. P04429; GI:123712; Ogawa et al., Jun. 15, 2004.
- GenBank Accession No. S34671; GI:421286; Rossolini et al., Apr. 12, 1995.
- GenBank Accession No. CAA52209; GI:395161; Guglielmetti et al., Jul. 27, 2005.
- GenBank Accession No. A54534; GI:628844; Arita et al., May 3, 1996.
- GenBank Accession No. AAL02159; GI:15592919; Teixeira et al., Sep. 13, 2001.
- GenBank Accession No. AAA18472; GI:487395; Mikulskis et al., May 26, 1994.
- GenBank Accession No. S25659; GI:282047; Takao et al., Oct. 15, 1999.
- GenBank Accession No. P74977; GI:3913874; Ramamurthy et al., Jun. 15, 2004.
- GenBank Accession No. BAA23656; GI:2662339; Huang et al., Feb. 13, 1999.
- GenBank Accession No. P31518; GI:399947; Ibrahim et al., Mar. 15, 2004.
- GenBank Accession No. P07965; GI:3915589; Stieglitz et al., Jun. 15, 2004.
- Abandonment for U.S. Appl. No. 10/766,735 dated Nov. 28, 2007.
- Abandonment for U.S. Appl. No. 10/845,895 dated Mar. 9, 2009.
- Office Action for U.S. Appl. No. 11/054,071 dated Jul. 6, 2009.
- Notice of Allowance for U.S. Appl. No. 11/930,696 dated Aug. 7, 2009.
- Forte, L., "Uroguanylin and guanylin peptides; pharmacology and experimental therapeutics", *Pharmacology & Therapeutics*, vol. 104, (2004), pp. 137-162.

* cited by examiner

LCMS ANALYSIS OF RECOMBINANT PEPTIDE VARIANTS

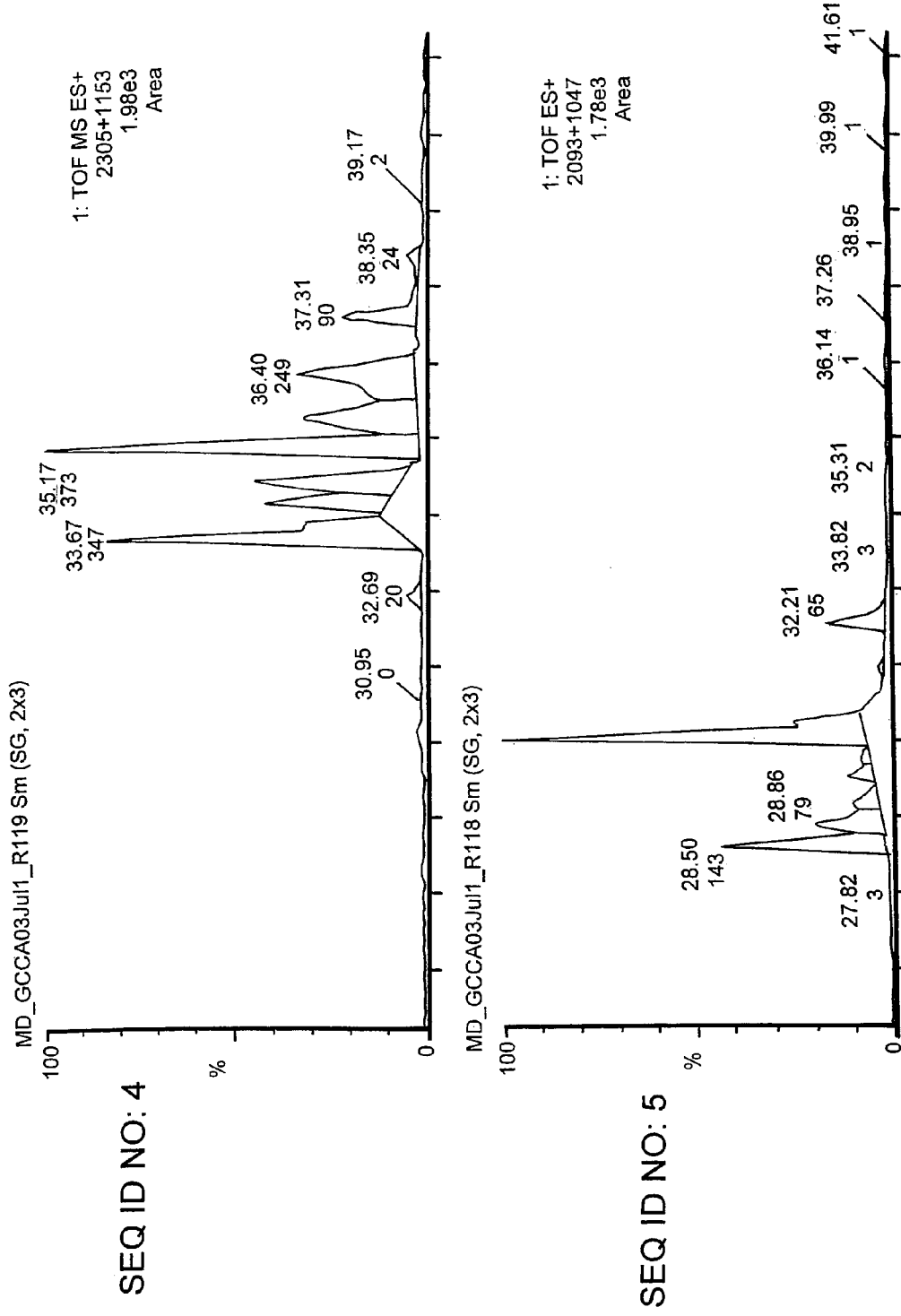


FIG. 1A

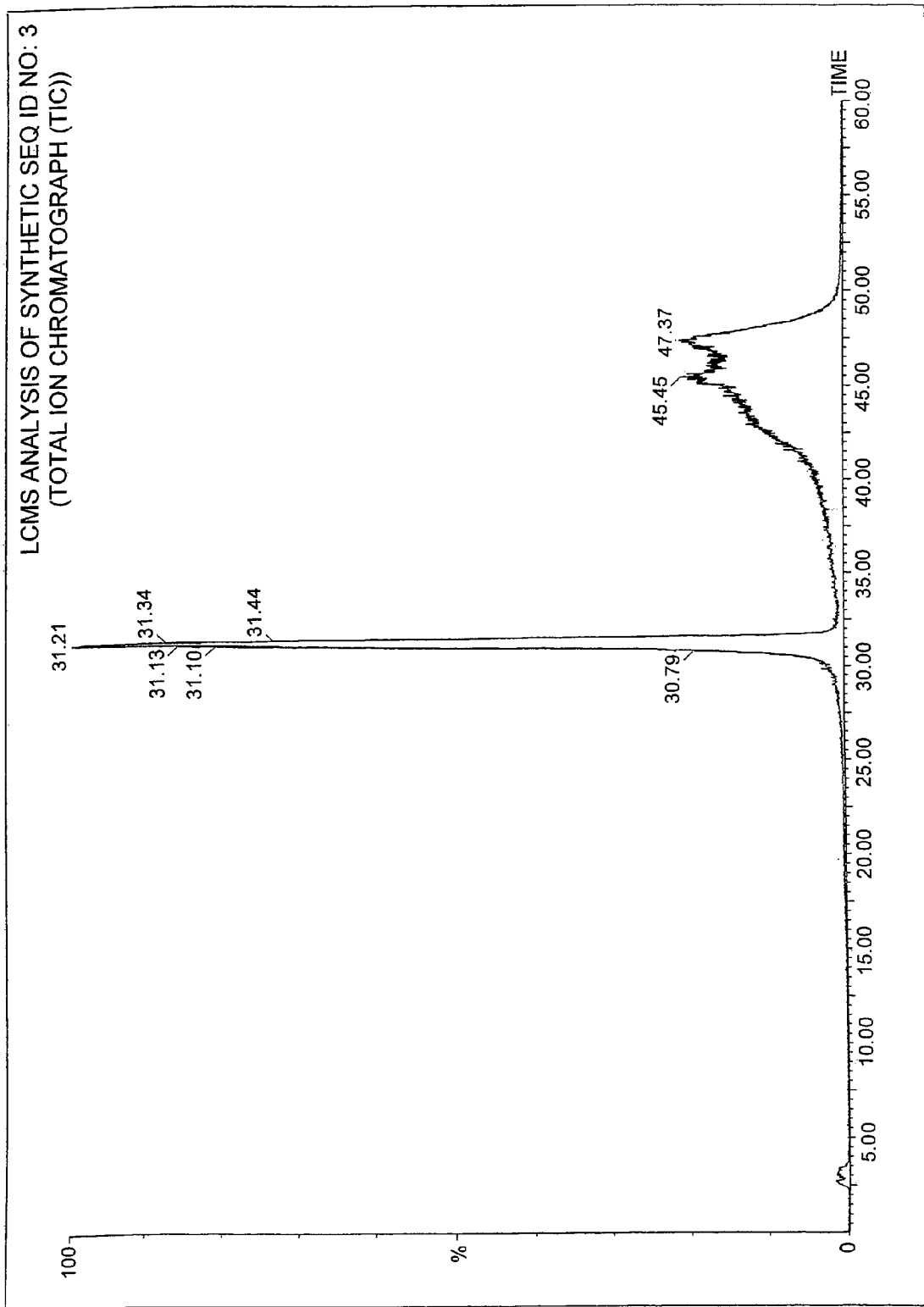


FIG. 1B

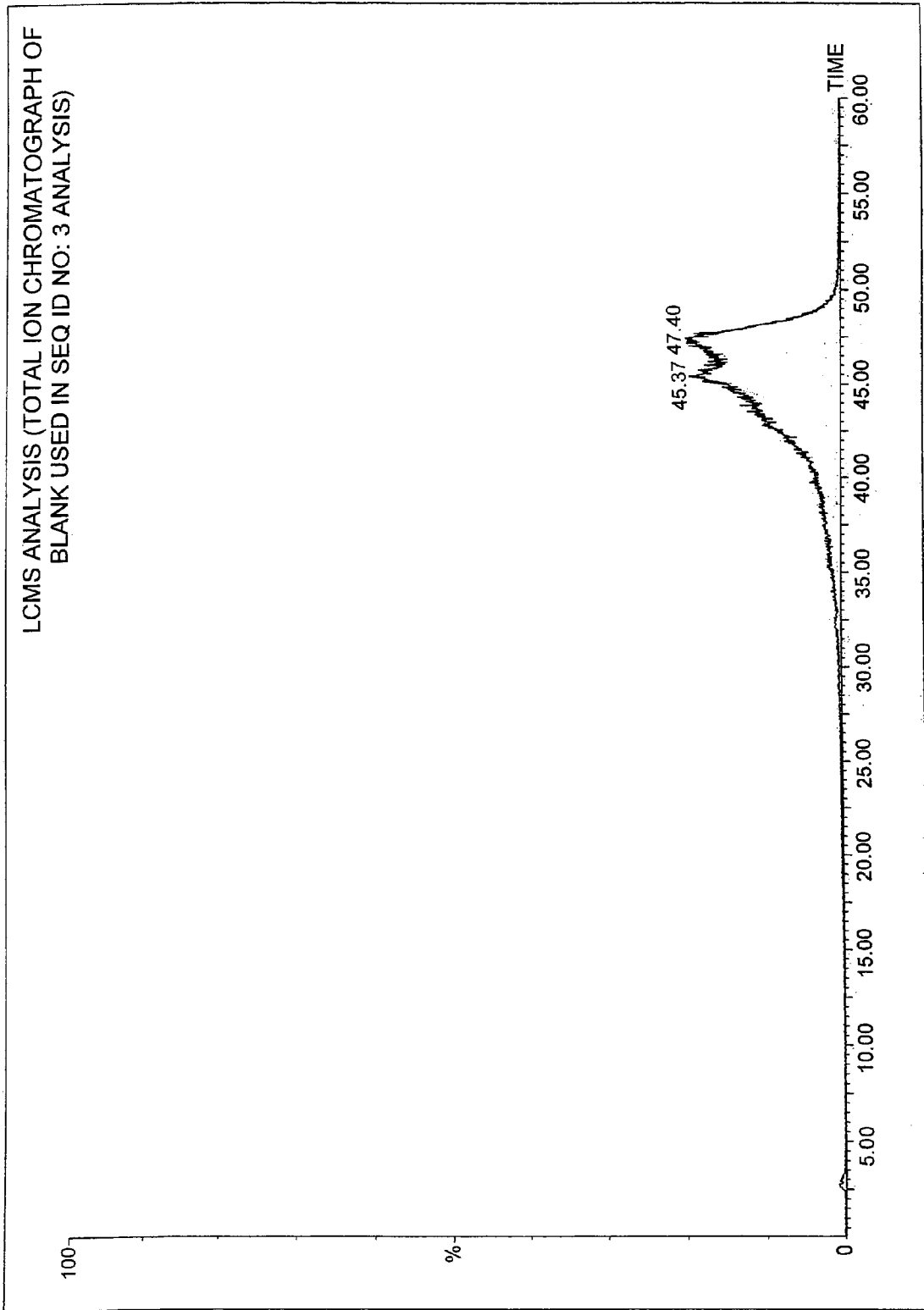


FIG. 1C

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