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Petitioners

v.

RESEARCH CORPORATION TECHNOLOGIES, INC.,
Patent Owner

Case: IPR2014-01126

DECLARATION OF CLAYTON H. HEATHCOCK, PH.D. IN SUPPORT OF PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. RE 38,551

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TABLE OF CONTENTS

EXHIBITS REFERENCED IN THIS DECLARATION

Exhibit	Description
1001	U.S. Patent No. RE 38,551 to Kohn ("'551 patent") (reissue of U.S. Patent No. 5,773,475 ("'475 patent"))
1003	U.S. Patent No. 5,654,301 to Kohn and Watson (the "'301 patent")
1004	Jan. 28, 1998 Notice of Allowability (excerpt from prosecution history of '475 patent)
1005	Philippe LeGall, *2-Substituted-2-acetamido-N-benzylacetamides. Synthesis, Spectroscopic and Anticonvulsant Properties* (Dec. 1987) ("LeGall thesis")
1006	Apr. 10, 1998 Amendment Under 37 C.F.R. § 1.312 (excerpt from prosecution history of '475 patent)
1008	U.S. Patent No. 5,378,729 to Kohn and Watson ("'729 patent")
1009	Sergio Cortes et al., *Effect of Structural Modification of the Hydantoin Ring on Anticonvulsant Activity*, 28 J. Med. Chem. 601 (1985) ("Cortes")
1010	Harold Kohn et al., *Preparation and Anticonvulsant Activity of a Series of Functionalized α-Heteroatom-Substituted Amino Acids*, 34 J. Med. Chem. 2444 (1991) ("Kohn 1991")
1012	U.S. Provisional Patent Application No. 60/013,522 ("'522 prov. app.")
1014	Phillipe LeGall et al., *Synthesis of Functionalized Non-Natural Amino Acid Derivatives via Amidoalkylation Transformations*, 32 Int'l J. Peptide Protein Res. 279 (1988) ("LeGall 1988")
1015	R. L. M. Synge, *CCXXXIX. Experiments On Amino Acids. IV. The Methyl Ethers Of Some N-Acetyl-Hydroxyamino-*

Exhibit	Description
	Acids, 33 Biochem. J. 1931 (1939)
1016	M. Jaeger et al., *Enzymatic Resolution of O-Methyl-N-acetyl-DL-serine. Amino Acids. XXXII.*, 28 Croat. Chem. Acta 5 (1956)
1017	Judith D. Conley & Harold Kohn, *Functionalized DL-Amino Acid Derivatives. Potent New Agents for the Treatment of Epilepsy*, 30 J. Med. Chem. 567 (1987) ("Conley 1987")
1018	Judith D. Conley, *Functionalized Amino Acid Derivatives – Potent New Agents for the Treatment of Epilepsy: Synthesis, and Spectroscopic and Pharmacological Properties* (May 1986) ("Conley thesis")
1019	Harold Kohn & Judith D. Conley, *New Antiepileptic Agents*, 24 Chemistry in Britain 231 (March 1988) ("Kohn & Conley 1988")
1020	European Patent Application No. 0 194 464 ("'464 Application")
1021	Harold Kohn et al., *Marked Stereospecificity in a New Class of Anticonvulsants*, 457 Brain Res. 371 (1988) ("Kohn 1988")
1022	Harold Kohn et al., *Preparation and Anticonvulsant Activity of a Series of Functionalized α-Aromatic and α-Heteroaromatic Amino Acids*, 33 J. Med. Chem. 919 (1990) ("Kohn 1990")
1023	European Patent Application No. 0 263 506 ("'506 Application")
1024	European Patent Application No. 0 400 440 ("'440 Application")

Exhibit	Description
1025	Harold Kohn et al., *Synthesis and Anticonvulsant Activities of α-Heterocyclic α-Acetamido-N-Benzylacetamide Derivatives*, 36 J. Med. Chem. 3350 (1993) ("Kohn 1993")
1026	Harold Kohn et al., *Anticonvulsant Properties of N-Substituted α,α-Diamino Acid Derivatives*, 83 J. Pharmaceutical Sci. 689 (May 1994) ("Kohn 1994")
1027	C.W. Thornber, *Isosterism and Molecular Modification in Drug Design*, 8 Chemical Soc'y Revs. 563 (1979) ("Thornber 1979")
1028	Wilson & Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry, Ch. 2 (Delgado & Remers eds. 1991) ("W&G 1991")
1029	Richard B. Silverman, *The Organic Chemistry of Drug Design and Drug Action*, Ch. 2 (1992) ("Silverman 1992")
1030	Rosa Amoroso et al., *A New Route to the Synthesis of Amino Acids Through the Mercury Cyclization of Chiral Amidals*, 57 J. Org. Chem. 1082 (1992) ("Amoroso 1992")
1031	S. Cerrini et al., *Serine-Containing 10-Membered Cyclodepsipeptides*, 41 Int'l J. Peptide Protein Res. 282 (1993) ("Cerrini 1993")
1032	Svante Axelsson et al., *Versatile Synthesis of Stereospecifically Labelled D-Amino Acids via Labelled Aziridines*, J. Chem. Soc. Perkin Trans. 1 (1994) ("Axelsson 1994")
1033	Oliver Keil et al., *New Hydantoinases from Thermophilic Microorganisms – Synthesis of Enantiomerically Pure D-Amino Acids*, 6 Tetrahedron: Asymmetry 1257 (1995) ("Keil 1995")

Exhibit	Description
1034	Patrick Bardel et al., *Synthesis and Anticonvulsant Activities of α-Acetamido-N-Benzylacetamide Derivatives Containing an Electron-Deficient α-Heteroaromatic Substituent*, 37 J. Med. Chem. 4567 (1994) ("Bardel 1994")
1035	FDA, *Guideline for Industry: Dose-Response Information to Support Drug Registration* (Nov. 1994) ("FDA Dose-Response Guidance")
1036	R. Schmidt, *Dose-Finding Studies in Clinical Drug Development*, 34 Eur. J. Clin. Pharmacol. 15-19 (1988) ("Schmidt 1988")

1. I, Dr. Clayton H. Heathcock, hereby declare as follows:

I. INTRODUCTION AND QUALIFICATIONS

2. I am Emeritus Professor of the University of California at Berkeley and a chemist with over 50 years of experience in organic chemistry and medicinal chemistry.

3. I have been retained by Petitioners in connection with their request for *inter partes* review of U.S. Patent No. RE 38,551 ("the '551 patent"). A copy of the '551 patent has been designated Ex. 1001. I have reviewed and am familiar with the '551 patent.

4. I have been asked to provide my opinion regarding the validity of the claims of the '551 patent. This declaration includes a detailed discussion of my background and qualifications, the background of the technologies involved in and related to the '551 patent that would have been understood by a person of ordinary skill in the art ("POSA") at the time of the filing of the '551 patent, and various prior art references that disclose—either alone or in combination with each other—all of the relevant features of '551 patent claims 1-13. The bases and reasons for my opinions are set forth in this declaration.

A. Educational Background

5. I obtained my Bachelor of Science degree from Abilene Christian College, Texas in 1958 and my Ph.D. in Organic Chemistry from the University of

Colorado in 1963. The subject of my Ph.D. thesis was the synthesis of steroids that were modified by the incorporation of heterocyclic rings, mainly three-membered, nitrogen-containing structures called aziridines. I did my post-doctoral studies at Columbia University from 1963 to 1964, where I was an apprentice to Professor Gilbert Stork.

B. Career History and Relevant Industry Participation

6. I joined the University of California at Berkeley in 1964 as an Assistant Professor and have subsequently held a number of positions at the University of California, including: Associate Professor (1970-75); Professor (1975-2004); Vice-Chairman of the Department of Chemistry (1972-77); Chairman of the Department of Chemistry (1986-89); and Dean of the College of Chemistry (1999-2005 and January-June 2008). From 2005 through 2008, I was Chief Scientist of the Berkeley branch of the California Institute for Quantitative Biosciences (QB3), a research institute that was created to bring together the quantitative sciences at UC Berkeley and UC Santa Cruz and the clinical sciences at UC San Francisco to address and solve significant problems in human health.

7. During my tenure at the University of California at Berkeley, I taught both graduate and undergraduate courses in organic chemistry. One of the courses that I taught for a number of years was a course for graduate students on the subject of organic synthesis.

8. During my 41-year research career at the University of California, I trained more than 80 doctoral students and approximately 50 post-doctoral fellows. My relationship with these students and post-doctoral fellows was that of mentor-apprentice. I assigned research projects to them and met with them several times a week to discuss the results of their laboratory experiments and to decide on the next steps to take in the research. The majority of the students who did their research training in my laboratory are now employed as medicinal or process chemists in pharmaceutical and biotech companies, or have retired after occupying such positions during their careers.

9. During my active research career, my research subjects included the development of new synthesis strategies, biomimetic (nature-imitating) synthesis, natural products chemistry, and studies of the stereochemistry of carbon-carbon bond-forming reactions. My research projects were funded mainly by the National Institutes of Health and the National Science Foundation, but some were funded with direct grants from pharmaceutical companies.

10. I was elected a Fellow of the National Academy of Sciences (NAS) in 1995. I have been a member of the American Chemical Society for more than 50 years, and in 2009, I was selected as an inaugural Fellow of the American Chemical Society. I have received a number of awards for my work in organic chemistry including: Ernest Guenther Award, American Chemical Society (1986);

Award for Creative Work in Synthetic Organic Chemistry, American Chemical Society (1990); A.C. Cope Scholar, American Chemical Society (1990); Prelog Medal, ETH (Eidgenossische Technische Hochschule (Swiss Federal Institute of Technology) (1991); American Academy of Arts and Sciences (1991); Pfizer Award in Synthetic Organic Chemistry (1993); Centenary Medal, Royal Society of Chemistry (1996); H.C. Brown Award, American Chemical Society (2002); and Paul Gassman Award for Distinguished Service, American Chemical Society (2004).

11. I have consulted with a number of pharmaceutical and biotechnology companies including: Merck, Sharp & Dohme (1968-78); Abbott Laboratories (1986-1997); and Plexxikon, Inc. (2002-2011). In my work as a consultant, I typically met with individual medicinal chemists to review their current projects. In the cases of Abbott Laboratories and Plexxikon, I served as a member of their Scientific Advisory Boards and met regularly with top management to review and provide advice on their pharmaceutical development programs.

12. From 1979 to 1981, I was a member of the National Institutes of Health Medicinal Chemistry Study Section A (MCHA), and I chaired this group from 1981 to 1983. The MCHA reviewed research grant proposals submitted to the NIH in the area of medicinal chemistry and recommended the ones that should be funded.

13. I have published more than 275 scientific papers and patents relating to organic synthesis and medicinal chemistry.

14. Additional information regarding my background, qualifications, publications, and presentations is provided in my CV, which is included in Appendix A.

II. SCOPE OF ASSIGNMENT AND COMPENSATION

15. I have been asked to provide my opinions regarding the validity of claims 1-13 of the '551 patent. I have been asked to provide a detailed technical overview reflecting what I believe would have been known to a person of ordinary skill in the art at the time that the earliest priority application for the '551 patent was filed in March 1996.

16. I have been asked to focus my analysis on certain bases for invalidity (e.g., anticipation vs. obviousness). I reserve the right to form opinions on other bases for the invalidity of claims 1-13 of the '551 patent at a later time.

17. I am being compensated at my standard hourly consulting rate of $650 per hour for the time spent for the research, study, and writing required for this declaration. I am compensated at my standard hourly rate of $1,300 per hour for time spent giving testimony at deposition. My compensation is in no way contingent on the substance of my opinions or the outcome of this matter.

III. LEGAL PRINCIPLES USED IN MY ANALYSIS

18. I am not a patent attorney, nor have I independently researched the law of patent validity. Attorneys have explained certain legal principles to me that I have relied on in forming my opinions set forth in this Declaration.

A. Person of Ordinary Skill in the Art

19. I understand that U.S. Provisional Application No. 60/013,522, which the '551 patent claims priority to, was filed on March 15, 1996. Ex. 1012. For the purposes of my analysis, and in the absence of any information to the contrary, I have used the March 15, 1996 date as the relevant date for my analysis of the prior art.[1]

20. I understand that assessment of the validity of the claims of the '551 patent must be undertaken from the perspective of what would have been known and understood by someone of ordinary skill in the art as of the earliest priority date of the '551 patent. Based on my knowledge and expertise and the prior art cited in the '551 patent, it is my opinion that a POSA in the relevant art (medicinal chemistry) would include a person who has at least a Bachelor's or Master's degree, but more likely a Ph.D. degree in organic chemistry or medicinal chemistry, as well as having at least a few years of experience in medicinal

[1] However, if I were to use March 15, 1995, as the relevant date, my opinion would not be any different.

chemistry, including in the development of potential drug candidates. This person could have a lower level of formal education than a Ph.D. degree if such a person had more years of experience in medicinal chemistry and the development of potential drug candidates. This person would regularly peruse the literature of organic and medicinal chemistry and would know how to carry out library research using Chemical Abstracts and other library resources to find out more information about areas being researched. Included in the literature that would be regularly perused would be the patent literature in areas of interest. A POSA would know how to characterize potential drug candidates, both structurally and with regard to their biological properties. I have been informed that, from a patent law perspective, the POSA is a hypothetical person who is presumed to have knowledge of all of the relevant art at the relevant time. In addition, the POSA would know how to evaluate potential drugs for their *in vitro* and *in vivo* activity, and although he/she might not actually be set up to carry out those biological assays, he/she would know how to obtain such results from a qualified commercial testing laboratory, either within or outside his/her organization, or through a collaboration with a colleague elsewhere.

B. Prior Art

21. I have been informed that the law provides certain categories of information (known as prior art) that may be used to anticipate or render obvious

patent claims. The reference materials I discuss are prior art below because they were available to those of ordinary skill in the art as of March 15, 1996.[2]

C. Anticipation

22. I have been informed that a claim is not patentable when a single prior art reference describes every element of the claim, either expressly or inherently to a person of ordinary skill in the art. I understand that this is referred to as "anticipation." I have also been informed that, to anticipate a patent claim, the prior art reference need not use the same words as the claim, but it must describe the requirements of the claim with sufficient clarity that a person of skill in the art would be able to make and use the claimed invention based on the single prior art reference.

23. In addition, I was informed and understand that, in order to establish that an element of a claim is "inherent" in the disclosure of a prior art reference, it must be clear to one skilled in the art that the missing element is an inevitable part of what is explicitly described in the prior art, and that it would be recognized as necessarily present by a person of ordinary skill in the art.

[2] However, even if I were to consider the prior art as of March 15, 1995, which I understand any information published prior to that date is unequivocally prior art, the opinions on anticipation and obviousness expressed herein would be no different.

D. Obviousness

24. I have been informed that, even if every element of a claim is not found explicitly or implicitly in a single prior art reference, the claim may still be unpatentable if the differences between the claimed elements and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person of ordinary skill in the art. That is, the invention may be obvious to a person having ordinary skill in the art when seen in light of one or more prior art references.

25. I have been informed that the following four factors are considered when determining whether a patent claim is obvious: (1) the scope and content of the prior art; (2) the differences between the prior art and the claim; (3) the level of ordinary skill in the art; and (4) secondary considerations tending to prove obviousness or nonobviousness. These secondary considerations include: (i) long-felt need, (ii) unexpected results, (iii) skepticism of the invention, (iv) teaching away from the invention, (v) commercial success, (vi) praise by others for the invention, and (vii) copying by other companies. I have also been informed that there must be a connection between these secondary factors and the scope of the invention claimed in the patent.

26. To establish obviousness, I understand that it must be demonstrated that a POSA would have been motivated to combine the teachings of the prior art

references to achieve the claimed invention, and that the POSA would have had a reasonable expectation of success in doing so. Further, I understand that a sufficient motivation is that the claimed and prior art compounds possess a sufficiently close relationship to create an expectation, in light of the totality of the prior art, that the new compound will have similar properties to the old.

IV. SUMMARY OF MY OPINIONS

27. As set forth more fully herein, it is my opinion that claims 1-13 of the '551 patent are anticipated by U.S. Patent No. 5,654,301 (Ex. 1003) ("the '301 patent").

28. As set forth more fully herein, it is my opinion that claims 1-13 of the '551 patent are anticipated by Philippe LeGall, *2-Substituted-2-Acetamido-N-Benzylacetamides. Synthesis, Spectroscopic and Anticonvulsant Properties* (December 1987) (Ex. 1005) ("the LeGall thesis").

29. As set forth more fully herein, it is my opinion that claims 1-13 of the '551 patent would have been obvious to a POSA before March 15, 1996, based on the disclosures in the LeGall thesis (e.g., compound 107e) in view of other prior art, including U.S. Patent No. 5,378,729 (Ex. 1008) ("the '729 patent").

V. THE '551 PATENT

A. Overview of the '551 Patent – The Alleged Invention

30. The '551 patent describes its alleged invention as relating "to novel enantiomeric compounds and pharmaceutical compositions useful in the treatment of epilepsy and other CNS disorders."[3]

31. The compounds described in the '551 patent are a class of drugs referred to as "anticonvulsant drugs," compounds, or agents.[4] Anticonvulsant drugs are used to "control and prevent[] seizures associated with epilepsy or related central nervous system disorders."[5]

B. Overview of Claims 1-13 of the '551 Patent

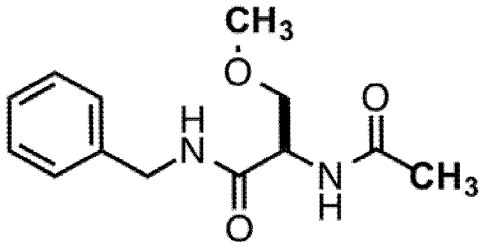
32. Claim 1 is the only independent claim of the '551 patent. Claims 2-13 are all dependent claims. I understand that a dependent claim incorporates all of the elements of the claims on which the dependent claim depends.

33. Claims 1-9 of the '551 patent are claims directed to chemical compounds that can be construed to cover the chemical compound lacosamide, which has the following chemical structure:

[3] Ex. 1001, col. 1:21-23.

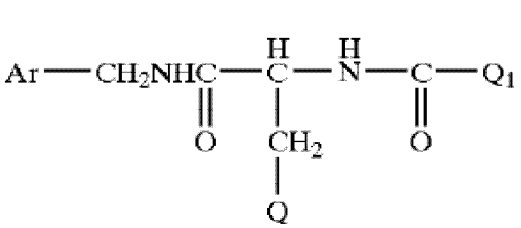
[4] *Id.* at col. 1:27-28.

[5] *Id.* at col. 1:27-29.



lacosamide

34. Lacosamide is the R-enantiomer of 2-acetamido-N-benzyl-3-methoxypropionamide and is the only compound claimed in claim 8 of the '551 patent. Claims 1 through 9 are recited as follows:

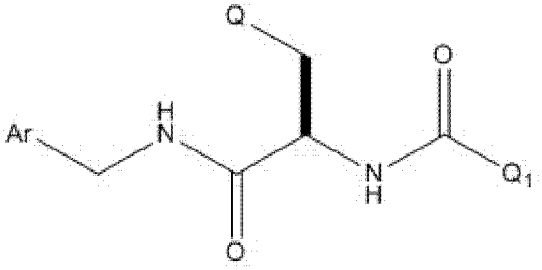
> 1. A compound in the R configuration having the formula:
>
> 
>
> wherein
>
> Ar is phenyl which is unsubstituted or substituted with at least one halo group;
>
> Q is lower alkoxy, and
>
> Q_1 is methyl.
>
> 2. The compound according to claim 1 which is substantially enantiopure.
>
> 3. The compound according to claim 1 wherein Q is lower alkoxy containing 1-3 carbon atoms.
>
> 4. The compound according to claim 3 wherein Q is methoxy.
>
> 5. The compound according to claim 1 wherein Ar is unsubstituted phenyl.
>
> 6. The compound according to claim 1 wherein halo is fluoro.

7. The compound according to claim 1 wherein Q is alkoxy containing 1-3 carbon atoms and Ar is unsubstituted phenyl.

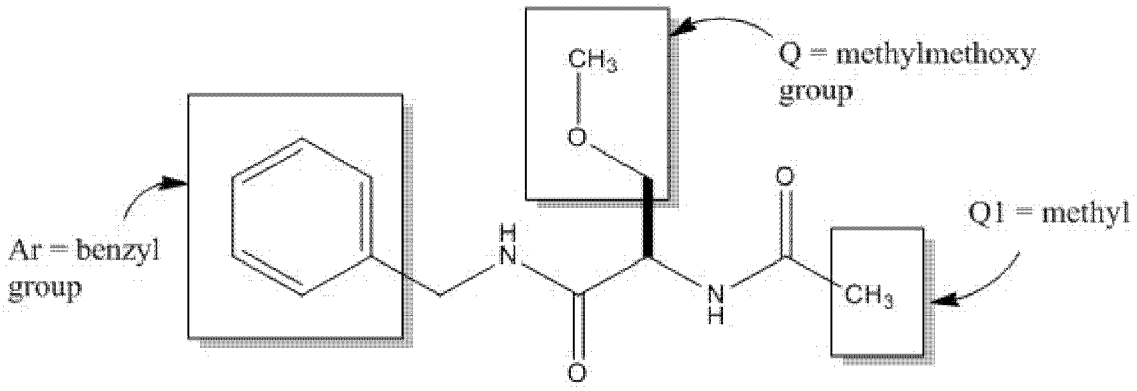
8. The compound according to claim 1 which is (R)-N-Benzyl 2-Acetamido-3-methoxypropionamide.

9. The compound according to claim 8 which contains at least 90% (w/w) R stereoisomer.

Claim 1 thus covers certain R enantiomers (referred to in the claims as R stereoisomers) depending on the substituents that are used for Ar, Q, and Q_1 below:



In particular, claim 1 covers the compound lacosamide (as part of the racemate, or as an isolated stereoisomer) when the Ar substituent is a benzyl group, Q is a methoxymethyl group, and Q_1 is a methyl group as shown in the following structure:



35. Claim 10 of the '551 patent is directed to "[a] therapeutic composition comprising an anticonvulsant effective amount" of the compounds recited in claims 1-9, including lacosamide. Claim 10 of the '551 patent recites:

> 10. A therapeutic composition comprising an anticonvulsant effective amount of a compound according to any one of claims 1-9 and a pharmaceutical carrier therefor.

36. Claims 11-13 of the '551 patent are directed to "method[s] of treating central nervous system disorders in an animal comprising administering … an anticonvulsant effective amount" of the compounds recited in claims 1-9, including lacosamide. Claims 11-13 of the '551 patent recite:

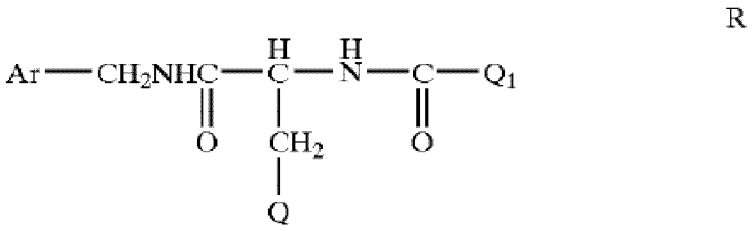
> 11. A method of treating central nervous system disorders in an animal comprising administering to said animal in need thereof an anticonvulsant effective amount of a compound according to any one of claims 1-9.
>
> 12. The method according to claim 11 wherein the animal is a mammal.
>
> 13. The method according to claim 12 wherein the mammal is a human.

C. Claim Construction of the '551 Patent

37. Claim 1 of the '551 patent claims compounds of the named chemical formula "in the R configuration," which refers to one of the two possible enantiomeric forms of the structure (discussed in more depth later). I understand this claim to include mixtures of enantiomeric compounds of the claimed formula

that include any amount of the relevant enantiomer with the R configuration. This construction is confirmed by claim 2, which provides a further limitation requiring that the compound be "substantially enantiopure." It is also confirmed by claim 9, which specifies the compound of claim 8, (R)-N-benzyl-2-acetamido-3-methoxypropionamide, contain at least 90% (w/w) R stereoisomer.

38. Claim 1 provides that "Ar is phenyl which is unsubstituted or substituted with at least one halo group":



Claim 6 further specifies that the "halo is fluoro." Under the broadest reasonable interpretation, claim 6 could be construed to include either (1) unsubstituted phenyl; or (2) phenyl substituted with at least one fluoro group. Under that construction, claim 6 would encompass lacosamide because lacosamide has unsubstituted phenyl in the Ar position.

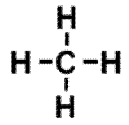
VI. TECHNICAL BACKGROUND

A. Representation of Chemical Structures

39. The pharmaceutical products of importance in this proceeding are organic chemical compounds. In order to fully understand my opinions, it is

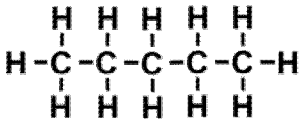
necessary to have a rudimentary understanding of some of the basic tenets of organic chemistry.[6]

40. Organic chemistry is the chemistry of compounds of carbon. Each carbon atom forms four bonds to other atoms and the most common other atom in organic compounds is hydrogen. Methane, CH_4, is the simplest example of a "hydrocarbon," a molecule composed solely of hydrogen and carbon. As shown in the following chemical structure, carbon (C) makes four bonds to other atoms and hydrogen (H) makes only one.



methane
CH_4

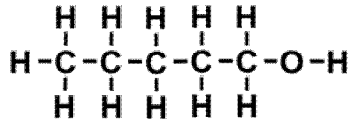
41. Carbon is an almost unique element in that it has the ability to form molecules by bonding to itself in the form of "chains" to give molecules such as the hydrocarbon depicted below:



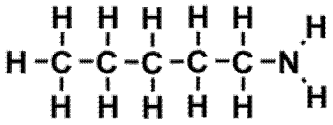
pentane
C_5H_{12}

[6] This background section on organic chemistry is a highly condensed version of portions of an introductory textbook coauthored by me: A. Streitwieser, Jr. and C. H. Heathcock, *Introduction to Organic Chemistry* (1985).

42. Although hydrogen is the most common "other atom" joined to carbon in organic compounds, a number of other atoms can occur in organic compounds. Examples are oxygen and nitrogen.



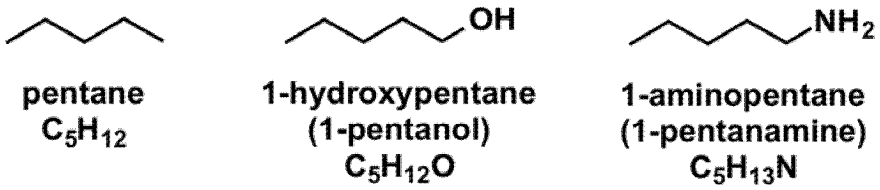
1-hydroxypentane
(1-pentanol)
$C_5H_{12}O$



1-aminopentane
(1-pentanamine)
$C_5H_{13}N$

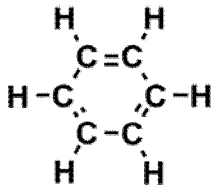
As shown in these two formulae, oxygen (O) makes two bonds to other atoms whereas nitrogen (N) makes three bonds to other atoms. The number of bonds to other atoms is called the "valence" of the atom. Thus, as shown in the examples so far, H has a valence of 1; O has a valence of 2; N has a valence of 3; and C has a valence of 4.

43. The following examples illustrate a "shorthand" that is commonly used by chemists in drawing chemical structures. In this shorthand, the individual carbons are not drawn but are represented by vertices in geometric depictions of chains or rings. In addition, the individual hydrogen atoms are not drawn and it is understood that there are enough hydrogens to give each carbon atom its valence of 4. The hydrogens attached to other atoms like oxygen and nitrogen are normally drawn. The following examples show how chemists would normally depict the simple example compounds shown in the preceding paragraphs:

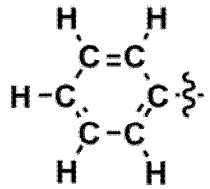


44. The hydrocarbons illustrated above in ¶¶40-41 (methane and pentane) are called "alkanes" and are said in the parlance of organic chemistry to be "saturated," meaning that they have as many hydrogens per carbon as they possibly can have, given the valences of carbon and hydrogen. Likewise, 1-hydroxypentane and 1-aminopentane have as many hydrogens as they possibly can have and they are also called "saturated."

45. Carbons can also join together in "rings," as illustrated by the compound benzene, which has a six-carbon ring. Derivatives of benzene, in which one or more of the hydrogen atoms are replaced by another atom, are called "phenyl" compounds. Benzene and its derivatives are examples of "unsaturated" compounds because they have carbon-carbon double bonds and therefore do not have the maximum number of hydrogens that are possible for six-carbon compounds.

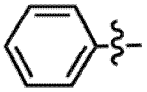


benzene
C_6H_6



phenyl group
C_6H_5-

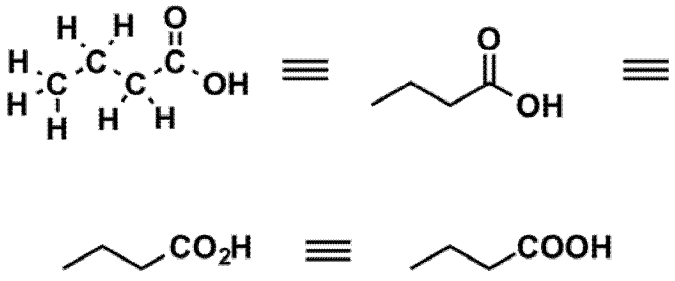
benzene



phenyl

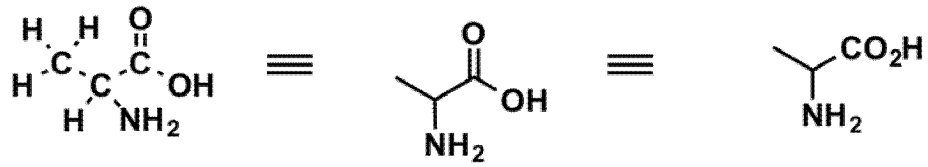
B. Amino Acids

46. As illustrated in ¶¶42-43, a compound having the grouping $–NH_2$ attached to a carbon framework is called an "amine" and the $–NH_2$ grouping is called an "amino group." Such groups are called "functional groups" and they tend to dictate the chemical reactivity of a compound, regardless of the number of carbons in the framework to which the functional group is attached. Another commonly encountered functional group is the carboxy group, $-CO_2H$, which is the typical group found in carboxylic acids. An example of a carboxylic acid, butanoic acid, is depicted below in four possible representations.



butanoic acid
$C_4H_8O_2$

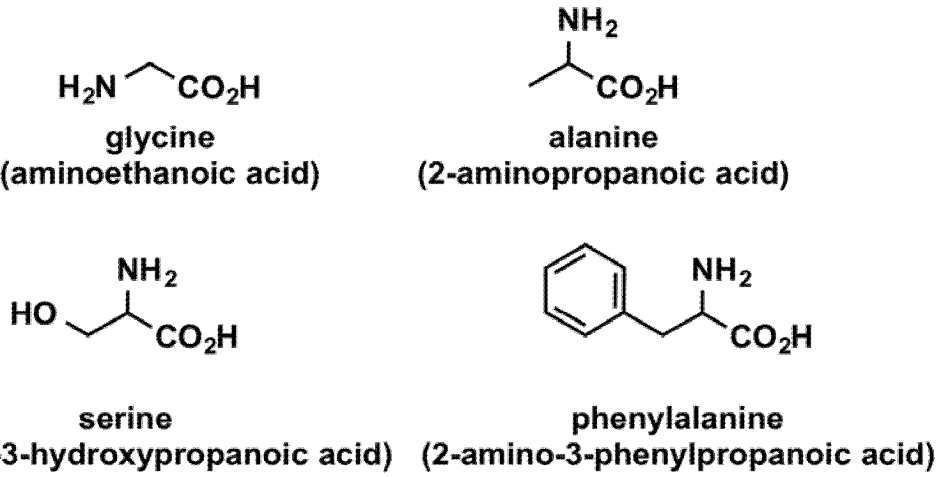
47. Many of the compounds of relevance in this proceeding are "bifunctional" compounds referred to as "amino acids" that have both an amino and a carboxy functional group. The chemistry of amino acids reflects the intrinsic chemical reactivity of both amines and carboxylic acids. An example, 2-aminopropanoic acid, is illustrated below in three possible representations.



2-aminopropanoic acid

48. Amino acids are an important group of biomolecules, constituting the basic building block units from which proteins are formed. There are 20 important natural amino acids; a few examples are depicted below.[7]

[7] A. Streitwieser, Jr. and C. H. Heathcock, *Introduction to Organic Chemistry* 926-928 (1985).

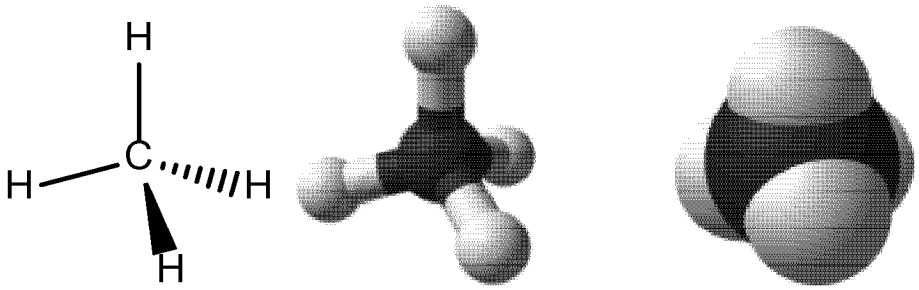


Note that serine is a "trifunctional" compound, having an OH group in addition to the NH_2 and CO_2H functional groups that make it an amino acid.

C. Stereochemistry

49. "Stereochemistry" refers to the three-dimensional aspect of chemical structures and the effect this dimensionality has on physical and chemical properties of molecules. Two molecules are stereoisomers of each other when they contain the same atoms bonded to the same other atoms, but where the configuration of those atoms in three dimensions differs.

50. Chemical structures are intrinsically three-dimensional, although we depict them as two-dimensional objects. An example is methane, CH_4, which has a three-dimensional structure that is illustrated in the following three representations:

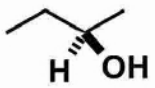


51. For example, there is only one form of 1-butanol but there are two forms of 2-butanol, which can only be interconverted by breaking and re-joining a bond:

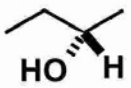
1-butanol **two different 2-butanols**

In these structures, the bold or hashed lines indicate that the OH or H projects away from the general plane of the compound toward the viewer (bold) or away from the viewer (hashed).

52. Compounds like 1-butanol, which have only one three-dimensional structure, are called "achiral." Compounds like 2-butanol are called "chiral." The two stereoisomers of a chiral compound like 2-butanol are called "enantiomers" and can be unambiguously named by a special stereochemical notation called the "sequence rule" or "RS convention." R-2-butanol and S-2-butanol are depicted below.

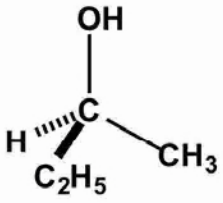


R-2-butanol



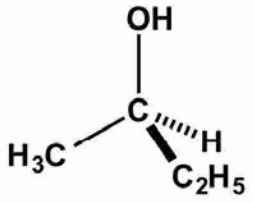
S-2-butanol

53. Enantiomers are mirror images of each other, like left and right hands.

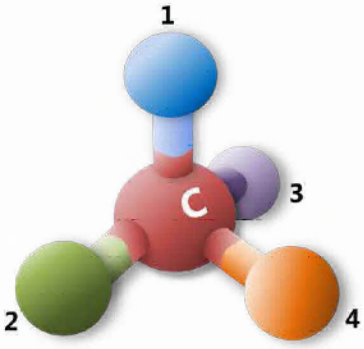


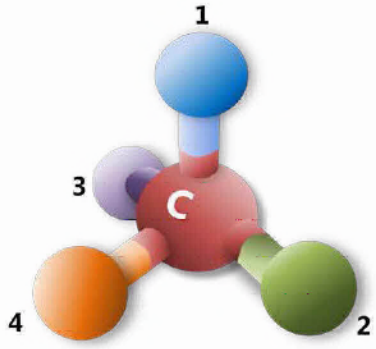
S-2-butanol

mirror plane

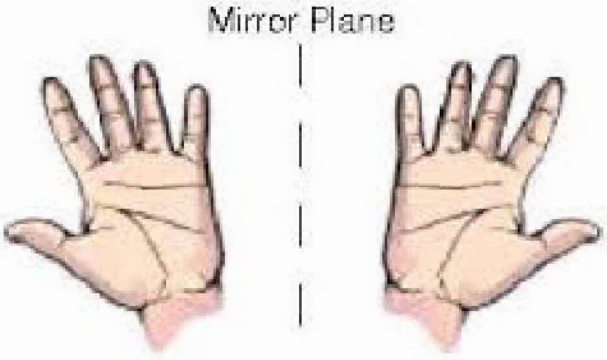


R-2-butanol





mirror plane



54. The convention used by chemists to label stereocenters as "R" or "S" has three steps:

i. Assigning each of the four different groups attached to the stereocenter a sequence rank, 1-4, using the sequence rule.

ii. Viewing the molecule along the bond from the stereocenter to the group with the lowest sequence rule rank, usually hydrogen.

iii. Noting whether the arc traced by the other three groups, from highest to lowest sequence rule rank, is clockwise or anti-clockwise. If the arc is clockwise the isomer is called R; if the arc is anti-clockwise the isomer is called S.

Application of this simple convention results in every enantiomeric pair having an unambiguous name. The POSA would know how to apply the sequence rule, using readily available tables that specify the relative ranking of any possible group of atoms.

55. Enantiomers may also be designated as "*d*" or "*l*" depending on whether a solution of the enantiomer rotates polarized light in a clockwise or counter-clockwise direction. There is no relationship between R/S and *d*/*l*; it is possible for a compound with the R configuration to rotate the plane of polarized light either in the clockwise (*d*) or counter-clockwise (*l*) direction.

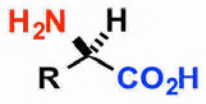
56. Enantiomers have identical physical properties (melting point, density, spectroscopy, or solubility in achiral solvents). As a consequence, it is not possible to separate a racemic mixture by purely physical methods like crystallization or differential solubility. However, enantiomers interact differently with other chiral substances and a racemate can be separated ("resolved") into its constituent enantiomeric forms by taking advantage of this difference. For

example, one cannot separate R- and S-2-butanol by distillation because the two enantiomers have the same boiling point. Likewise, one cannot separate them by chromatography using an achiral support like silica because the two enantiomers have the same exact binding energy to the achiral support. However, R- and S-2-butanol can be separated by chromatography using a chiral support because the two enantiomers interact differently with the molecules of the chiral support.

57. With the exception of glycine, all of the common naturally occurring amino acids are chiral molecules and have the same absolute configuration at the stereocenter:

alanine: R = CH_3
valine: R = $CH(CH_3)_2$
leucine: R = $CH_2CH(CH_3)_2$
isoleucine: R = $CH(CH_3)CH(CH_3)_2$
methionine: R = $CH_2CH_2SCH_3$
phenylalanine: R = $CH_2C_6H_5$
serine: R = CH_2OH

58. There is a traditional form of nomenclature whereby the α-amino acids are grouped into two families. Within each of these families, the relative orientation in space of the four groups attached to the stereocenter (the α-carbon) are the same. These families are called D- and L- respectively, regardless of the exact structure of the R group.



D-amino acid

L-amino acid

All of the naturally occurring amino acids depicted in ¶57 belong to the L family; e.g., L-alanine, L-valine, L-serine, etc. In most cases, including the compounds of importance in this proceeding, the L-amino acids have the S-configuration by application of the sequence rule. That is, L-alanine may also be called S-alanine, L-serine may also be called S-serine, etc. The enantiomers of the naturally occurring amino acids depicted in ¶57 belong to the D family and generally have the R-configuration; for example, D-alanine may also be called R-alanine, D-serine may also be called R-serine, etc.

59. An equal mixture of R and S enantiomers is called a "racemic mixture" or a "racemate." Racemates are sometimes indicated in nomenclature by a prefix such as *dl*, DL, or RS, showing that the actual compound is a 50/50 mixture of the two enantiomeric forms. That is, the racemic form of alanine might be called *dl*-alanine, DL-alanine, or RS-alanine.

60. Most drugs are chiral and only one of the two enantiomeric forms has biological activity. This is because the biological targets are chiral. In essence, the biological targets are like gloves and the chiral drugs are like right or left hands. Drugs are usually marketed as pure enantiomers. This was well known to a POSA before the "priority date" at issue here, March 15, 1996.

D. Background on Drug Development

61. The drug development process for a medicinal chemist in the mid-1990s typically began with a decision to enter a therapeutic area and seek a drug for treatment of a certain disease. For example, a pharmaceutical company might have decided to look for a drug that can be used to treat epilepsy, hypertension, diabetes, cardiovascular disease, or cancer. The project was typically assigned to an organic or medicinal chemist, or a team of scientists including such persons. The chemists would then review the scientific literature of the area, usually with the assistance of an experienced library staff. The information sought in this phase of the project would be an understanding of the basic biology that underlies the disease, and identification of patents and scientific publications that show what others have done to address the same issue.

62. Often the literature search would reveal one or more conceptual starting points, sometimes called "lead compounds." Such conceptual starting points would be compounds or structures that have, or were believed to possibly have, biological activity that could be useful in treating the disease of interest. Working from these conceptual starting points, the medicinal chemist would begin to make other compounds that were similar to a starting compound, but had slightly different structural features. These other compounds having slightly different structural features are sometimes referred to as "analogs." As each new

compound was made, its biological properties would be evaluated in a preclinical assay. One property sought to be optimized could be potency, such as the amount of a given compound required to achieve a particular biological effect. As the analog compounds are evaluated, the medicinal chemist discovers structure-activity relationships (SAR) for a given property, which allows the medicinal chemist to identify (a) which part of the molecule is responsible for activity; and (b) which substituents are better than others for that activity.

63. A common strategy for drug development of compounds with an activity of interest is to select development candidates based on a known active compound. This strategy involves identifying a new development candidate by starting with a compound that was already known to have the desired activity, and making small, conservative modifications to maintain that activity. This approach is regarded as "low-hanging fruit" because it often gives the medicinal chemist a significant head-start on the discovery and development process.

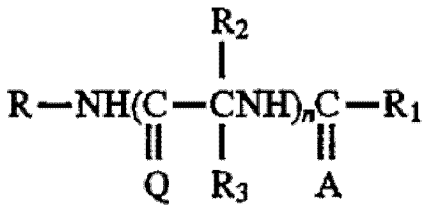
VII. CLAIMS 1-13 OF THE '551 PATENT ARE ANTICIPATED BY THE '301 PATENT

64. The '301 patent is a U.S. patent issuing from an application that was filed on January 12, 1993, naming inventors Harold L. Kohn and Darrell Watson.[8] I understand that this patent thus constitutes prior art to the '551 patent.

[8] Ex. 1003.

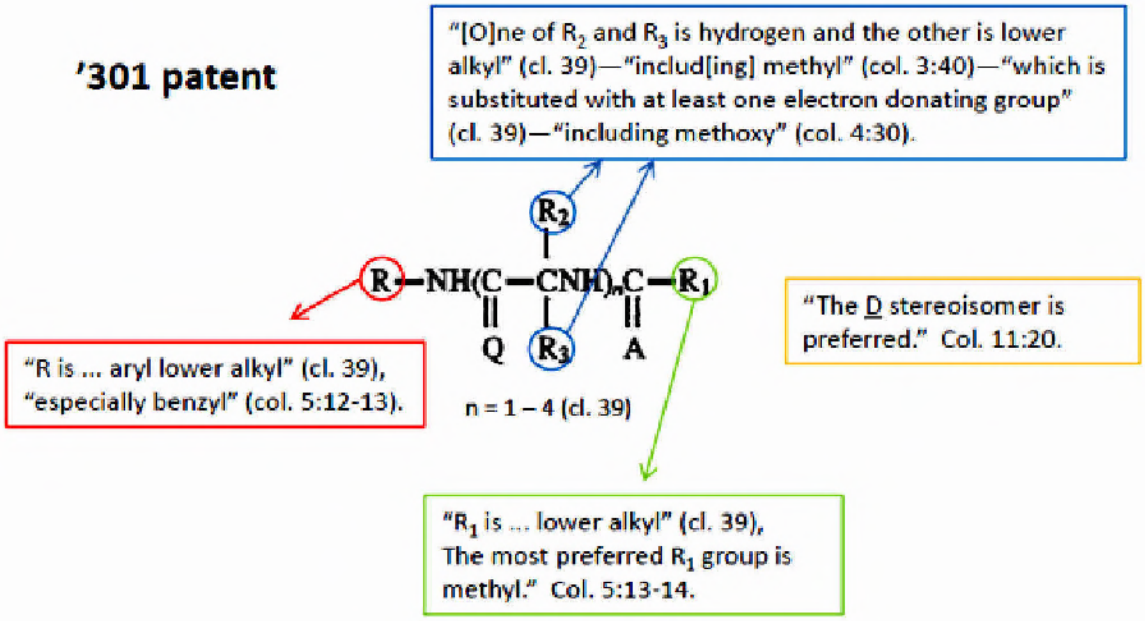
A. The '301 Patent Discloses Lacosamide

65. Claim 39 of the '301 patent covers a genus of compounds as follows:[9]

> 39. A compound of the formula
>
> 
>
> Or the pharmaceutically acceptable salts thereof wherein
>
> R is aryl, aryl lower alkyl, heterocyclic, heterocyclic lower alkyl, cycloalkyl or lower cycloalkyl lower alkyl, wherein R is unsubstituted or is substituted with at least one electron withdrawing group or an electron donating group;
>
> R_1 is hydrogen or lower alkyl and R_1 is unsubstituted or substituted with at least one electron withdrawing group or at least one electron donating group;
>
> A and Q are both O;
>
> one of R_2 and R_3 is hydrogen and the other is lower alkyl which is substituted with an electron donating group or a[n] electron withdrawing group and n is 1-4.

The genus of compounds claimed by claim 39 and described in the specification of the '301 patent includes lacosamide, as depicted below:

[9] *Id.* at cl. 39.



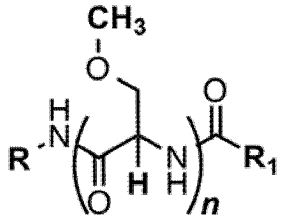
66. Dependent claims 40-44 further narrow the scope of claim 39 to subgenera by limiting the substituents attached at R_2 and R_3.[10] For example, claim 40 specifies that "one of R_2 and R_3 is hydrogen and the other is lower alkyl substituted with an electron donating group."[11] Claim 42 specifies that the other "of R_2 and R_3 is methyl substituted with an electron donating group."[12] Claim 43 specifies that the "electron donating group is lower alkoxy" and claim 44 requires

[10] *Id.* at cls. 40-44.

[11] *Id.* at cl. 40.

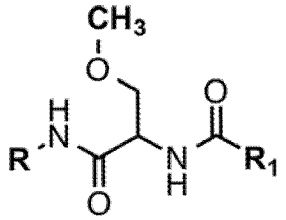
[12] *Id.* at cl. 42.

that lower alkoxy substituent be methoxy.[13] Thus, claim 44 of the '301 patent discloses that one of R_2 and R_3 is hydrogen and the other is methoxymethyl.



Kohn '301 Claim 44

67. Claim 45 further limits n to 1 and can depend from claim 44.[14] Claim 45 depending on claim 44 claims the following structure that covers lacosamide and its corresponding S enantiomer.



Kohn '301 Claim 45 (44)

Therefore, claims 38-45 all cover lacoasamide. Importantly, claim 44 specifies the methoxymethyl of lacosamide as a substituent at the α-carbon.

68. During prosecution of the '551 patent, I understand the examiner concluded that the '301 patent does not disclose the compounds claimed by the

[13] *Id.* at cls. 43, 44.

[14] *Id.* at cl. 45.

'551 patent, including lacosamide, because it does not "teach or suggest [sic] R_2, R_3 to be an ether, as against ether in herein claims."[15] That is a mistake. An ether describes a functional group characterized by a C-O-C linkage, an oxygen bonded to two carbons. Claim 44 of the '301 patent specifically identifies methoxymethyl as the substituent at R_2 or R_3, which is an ether.

69. I understand that the applicant agreed with the examiner, asserting that the '301 patent does not disclose "the basic structure wherein at least one of R_2, and R_3 is specifically alkoxymethyl, as specifically claimed."[16] This statement by the Applicant misconstrues basic chemistry principles. Claims 43 and 44 specifically claim compounds where one of R_2 or R_3 is alkoxymethyl. Claim 43 specifies that R_2 or R_3 is "methyl substituted with … lower alkoxy," which is alkoxymethyl.[17] Claim 44 further limits the species to methoxymethyl.[18]

B. The Preferences Disclosed by the '301 Patent Lead Directly to One Compound—Lacosamide—in Claim 44

70. The '301 patent provides clear preferences that serve to further limit the disclosure of the structure claimed in claim 44 of the '301 patent. First, "it is

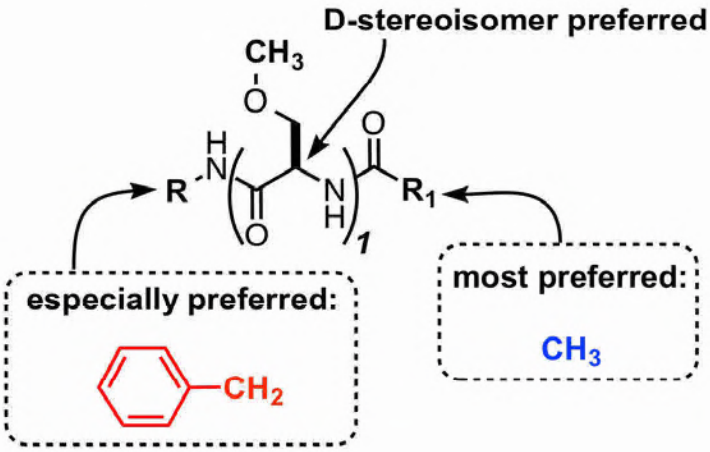
[15] Ex. 1004 at 2.

[16] Ex. 1006 at 2.

[17] Ex. 1003, '301 patent, cl. 43.

[18] *Id.* at cl. 44.

especially preferred that n is 1,"[19] which claim 45 recognizes for the purpose of the patent claim. Further, the '301 patent discloses that "[t]he preferred value[] of R is … especially benzyl, and … [t]he most preferred R_1 group is methyl."[20] The '301 patent also discloses that "[t]he D stereoisomer[21] is preferred."[22]



71. Furthermore, the '301 patent discloses that the R stereoisomer "can be prepared directly from [its] pure chiral intermediate" or "separated by recognized techniques known in the art" from a racemic mixture to obtain the R stereoisomer enantiomerically pure (≈ 100 % (w/w) R stereoisomer).[23] With respect to the

[19] *Id.* at 10:19.

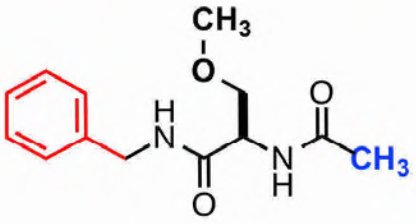
[20] *Id.* at 5:12-14.

[21] In the case of the compounds of the depicted genus, the D stereoisomers correspond to the R configuration, which a POSA would have known.

[22] Ex. 1003, '301 patent col. 11:20.

[23] *Id.* at 17:58-18:19.

structure of claim 44 in the '301 patent, following the stated preferences of the '301 patent discloses lacosamide to a POSA.

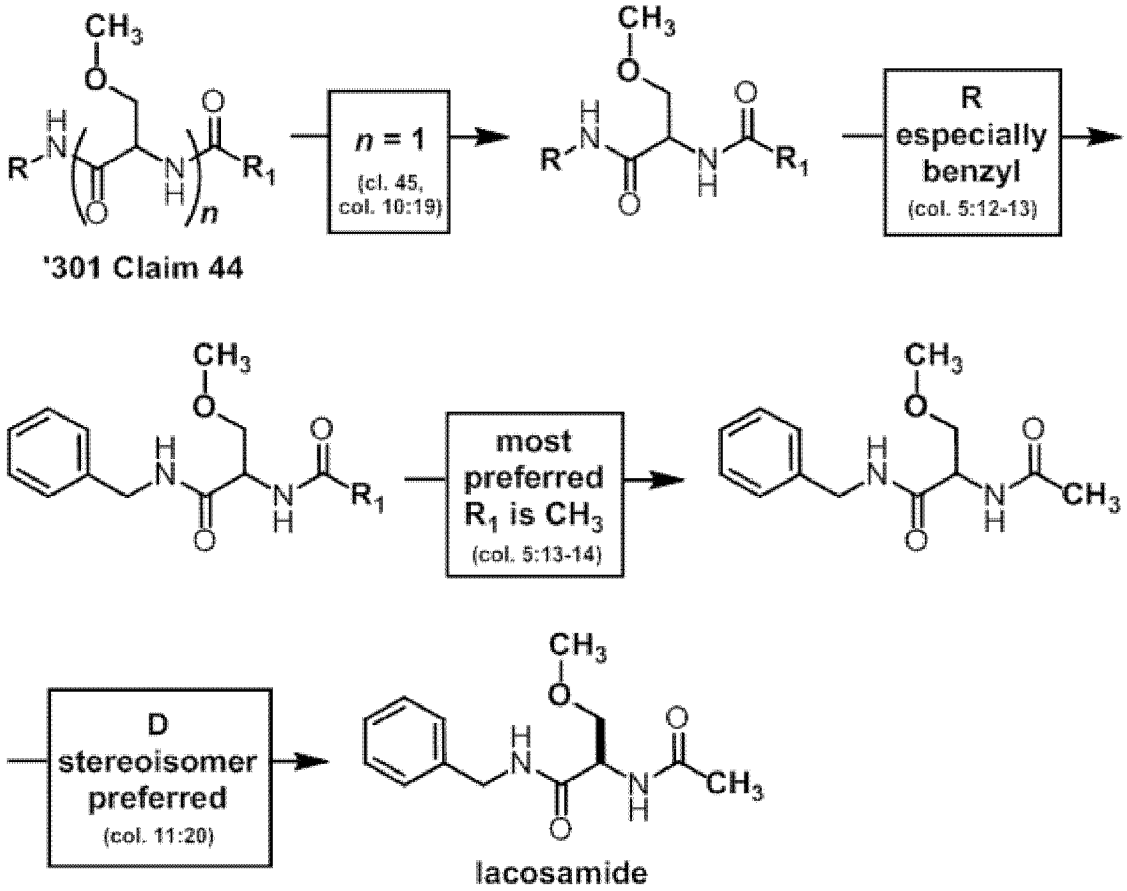


lacosamide

C. Claims 1-9 of the '551 Patent are Anticipated by the '301 Patent

72. I understand that the disclosure of a genus in a prior art reference can anticipate a later claim to a species within that genus if a POSA could "at once envisage each member" of the genus or a more limited class within the genus described by the reference. I understand that a pattern of specific preferences disclosed in connection with the description of a generic formula constitutes a description of a definite and limited class of compounds.

73. As described in Section VII.B, claim 44 alone and claim 45 dependent on claim 44 disclose a genus and a subgenus that include lacosamide. Application of the preferences identified in the '301 patent for the variables, n (i.e. 1), R (i.e. benzyl) and R_1 (i.e. methyl) and for the D stereoisomer (also the R stereoisomer) to claim 44 alone and claim 45 dependent on claim 44 discloses a definite and limited class, a single compound, i.e., lacosamide.



A POSA would have at once envisaged lacosamide from claim 44, and also from the subgenus claim 45 dependent on claim 44, when the preferences of the '301 patent are considered.

74. Claims 2 and 9 of the '551 patent place limits on enantiopurity of the R-enantiomer of the claimed compounds, including lacosamide. Claim 2 requires the R enantiomer to be "substantially enantiopure" whereas claim 9 contains "at least 90% (w/w) R stereoisomer." A POSA would have been enabled by the '301

patent disclosures to isolate the R enantiomer.[24] First, the '301 patent states that "[o]ptically pure functionalized amino acid derivatives can be prepared directly from the corresponding pure chiral intermediate."[25] As demonstrated below in ¶¶87-91, a POSA would have known how to synthesize lacosamide from its chiral intermediate. Second, the '301 patent discloses that racemic "mixtures of isomers can be separated in[to] [sic] the pure isomers by methods known to one skilled in the art."[26]

75. Furthermore, as described below in ¶87, the '551 patent admits that isolating enantiomers could be done using standard methods. Therefore, a POSA would be able to obtain an enantiomerically enriched sample of lacosamide that meets the requirements of claims 2 and 9 of the '551 patent.

76. Therefore, since claims 1-9 of the '551 patent all claim lacosamide with claims 2 and 9 requiring certain levels of enantiopurity, those claims are anticipated by the '301 patent.

D. Claim 10 of the '551 Patent is Anticipated by the '301 Patent

77. Claim 10 of the '551 patent claims a "therapeutic composition comprising an anticonvulsant effective amount" of the compounds claimed by

[24] Ex. 1003, col. 17:54-18:32.

[25] *Id.* at 17:60-62.

[26] *Id.* at 17:54-57; *see also id.* at 17:62-18:32.

claims 1-9 of the '551 patent, including lacosamide, "and a pharmaceutical carrier therefore."

78. The '301 patent discloses that "[t]he active ingredients of the therapeutic compositions and compounds of the present invention exhibit excellent anticonvulsant activity...."[27] Further, the '301 patent states that "[t]he principal active ingredient is compounded for convenient and effective administration in effective amounts with a suitable pharmaceutically acceptable carrier...."[28] The '301 patent also claims an "anti-convulsant composition comprising an anti-convulsant effective amount of" the claimed compounds including lacosamide "and a pharmaceutical carrier therefore."[29] Therefore, claim 10 of the '551 patent is anticipated by the '301 patent.

E. Claims 11-13 of the '551 Patent are Anticipated by the '301 Patent

79. Claims 11-13 of the '551 patent claim a "method of treating central nervous system disorders in an animal comprising administering ... an anticonvulsant effective amount" of the compounds of claims 1-9 including lacosamide. Claims 12 and 13 limit the animal to a mammal and human, respectively.

[27] *Id.* at 18:33-35.

[28] *Id.* at 20:31-35.

[29] *Id.* at cl. 46.

80. In addition to the disclosures above in Section VII.D, the '301 patent discloses that "the administration of an effective amount of the present compounds … can provide an excellent regime for the treatment of epilepsy, nervous anxiety, psychosis, insomnia, and other related central nervous system disorders."[30] The data provided to support this disclosure is *in vivo* testing in mice, a mammal.[31] The '551 patent relied exclusively on similar preclinical data in rodents to support its method of treating central nervous system disorders in humans in claim 13.[32] The '301 patent also claims "[a] method of treating CNS disorders in an animal comprising administering to said animal an anticonvulsive effective amount" of the claimed compounds including lacosamide.[33] Therefore, claims 11-13 of the '551 patent are anticipated by the '301 patent.

VIII. CLAIMS 1-13 OF THE '551 PATENT ARE ANTICIPATED BY THE LEGALL THESIS

81. The LeGall thesis is a University of Houston master's thesis authored by Phillipe LeGall dated December 1987, entitled "2-Substituted-2-Acetamido-N-Benzylacetamides. Synthesis, Spectroscopic and Anticonvulsant Properties." The

[30] Ex. 1003, col. 3:31-36.

[31] *Id.* at 79:59-87:62, Tbls. I-IV.

[32] Ex. 1001, col. 21:27-22:22.

[33] Ex. 1003, cl. 47.

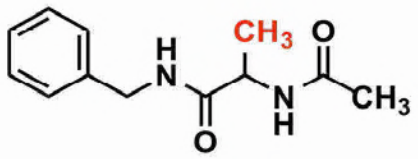
title would have informed a POSA of the generic structure of the compounds studied and described therein. In 1988, LeGall and several coworkers, including his Master's Advisor, Dr. Harold Kohn, published an article that was "[a]bstracted from [LeGall's] Masters dissertation" and directs the public to "[a]dditional structure proof and experimental and spectra data … in this reference."[34] The citation of the LeGall thesis in the 1988 article would have guided a POSA to the thesis for more extensive information relating to the compounds investigated by LeGall. Therefore, I understand the LeGall thesis was published well before March 15, 1996, and is prior art to the '551 patent.

A. The LeGall Thesis Discloses Racemic Lacosamide as an Anticonvulsant Compound

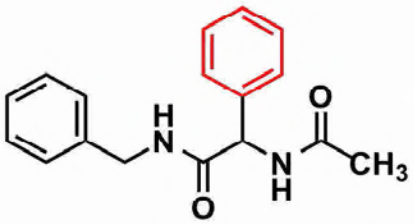
82. For the work on his Masters' thesis, LeGall set out to prepare "[s]elect functionalized amino acid derivatives of the potent anticonvulsant agent" AAB (α-methyl colored red) and APB (α-phenyl colored red):[35]

[34] Ex. 1014 at 279-291.

[35] Ex. 1005 at v. (Alternative names are provided in the illustration because these names are used in other prior art of relevance to this proceeding.)

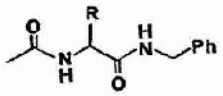


2-acetamido-*N*-benzylpropionamide (N-acetyl-alanine-N-benzylamide) (AAB)



α-acetamido-*N*-benzylphenylacetamide (N-acetyl-phenylglycine-N-benzylamide) (APB)

83. As part of the work for LeGall's Masters' thesis, he synthesized five "[c]ompounds 107a-e [that] were selected as polar analogues of the potent anticonvulsant" AAB (compound 68a), which he represented in the following table:[36]

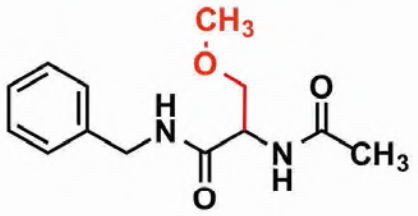


107

No.	R
68a	CH_3
107a	CN
107b	$CONH_2$
107c	$COOCH_2CH_3$
107d	CH_2OH
107e	CH_2OCH_3

[36] Ex. 1005 at 132-33 Tbl. 35. The structure of 107 can be drawn in the format used in the preceding paragraph for the illustration of AAB and APB where R replaces the substituents highlighted in red. In fact, compound 68a in the Table is AAB where R is CH_3.

Compound 107e (α-methoxymethyl colored red) is the racemate of lacosamide:



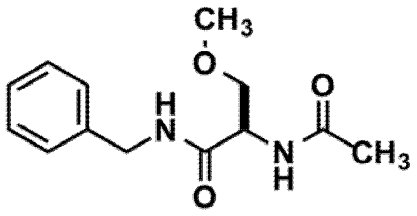
LeGall thesis compound 107e
(racemic lacosamide)

Compound 107e is a derivative of AAB that contains α-methoxymethyl instead of α-methyl. The LeGall thesis describes the conception, synthesis, and characterization of this compound.[37]

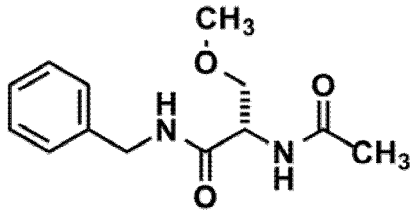
84. A POSA would have known that each of the compounds depicted in the table above depicting compounds 107a-e represent racemates that each consist of an equimolar mixture of the two possible enantiomers, which are depicted below for compound 107e. Therefore, the LeGall thesis discloses that compound 107e is a racemate, which therefore consists of a 50/50 mixture of the R enantiomer (lacosamide) along with the S enantiomer:[38]

[37] *Id.* at 132-33, 136-37.

[38] *Id.* at 135.



R-enantiomer of 107e
(lacosamide)



S-enantiomer of 107e

85. The LeGall thesis also teaches the anticonvulsant activity of compound 107e:

> "[t]he close structural analogy of this compound [107e] with 86b suggest[s] that … [it] may have *good anticonvulsant activity*."[39]

B. A POSA was Enabled by the LeGall Thesis and the Prior Art to Isolate the R Enantiomer, Lacosamide, in Pure Form

86. The LeGall thesis explains that for the five derivatives 107a-e that include racemic lacosamide (107e):

> "[i]n each case, the functionalized amino acid racemate was prepared rather than the individual enantiomers … [which] permitted the direct comparison of the observed biological data with that previously generated…"[40]

This statement tells a POSA that LeGall could have prepared the individual enantiomers separately. Further, the LeGall thesis notes that:

> "[t]he recent finding that the D-enantiomers[41] of 68a [AAB] and 68b [APB] were more active and less toxic than the corresponding racemates suggests

[39] *Id.* at 155 (emphasis added).

[40] *Id.* at 135.

> that the D-enantiomer of [other promising derivative compounds prepared by LeGall] may display even improved pharmacological properties."[42]

This disclosure along with what was known in the prior art would have enabled a POSA to isolate the enantiomers, including the R enantiomer of compound 107(e), i.e, lacosamide.

87. Indeed, the '551 patent and its priority application admit that lacosamide was "prepared by art recognized techniques from commercially available starting materials," and that "the optical purity of the product may be enhanced by further separation of the S enantiomer from the R enantiomer, by standard techniques known in the art, such as chiral chromatography using a standard chiral support known in the art."[43] In the case of lacosamide, the starting material is a derivative of serine. L-Serine is a naturally occurring amino acid and the corresponding D enantiomer had already been isolated. According to the '551 patent, "the racemic mixture" of lacosamide "can be resolved into the R isomer by standard techniques known in the art such as chiral chromatography."[44]

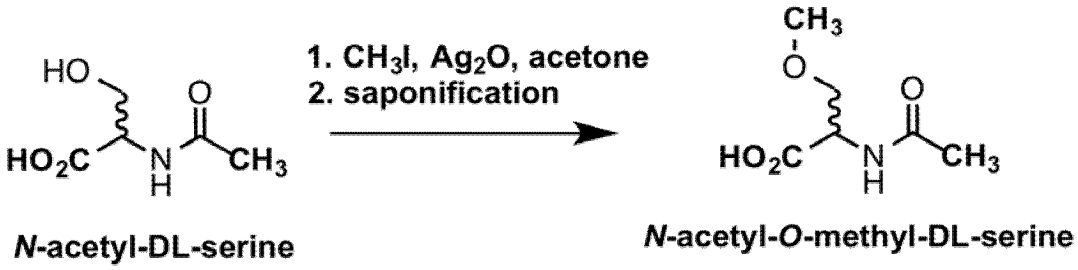
[41] In this case, the D-enantiomers referred to correspond to the R configuration, which a POSA would have known.

[42] Ex. 1005 at 164-65.

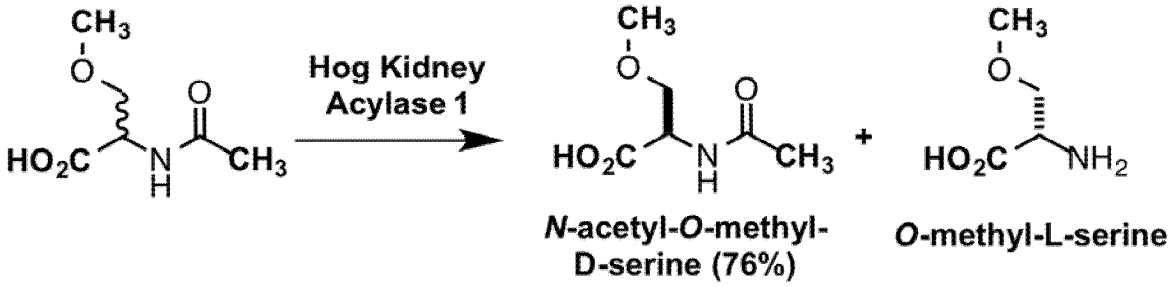
[43] Ex. 1001, col. 5:20-22, 8:50-54; Ex. 1012, '522 prov. app. col. 9:20-23.

[44] Ex. 1001, col. 8:59-61.

88. The following example demonstrates that given the structure of the racemate, 107(e), a POSA would have been enabled to isolate the R (or D) enantiomer, lacosamide. Racemic N-acetyl-O-methylserine was first prepared by Synge in 1939.[45]



In 1956, Jaeger and coworkers reported a method for deracemization, providing *N*-acetyl-*O*-methyl-D-serine:[46]

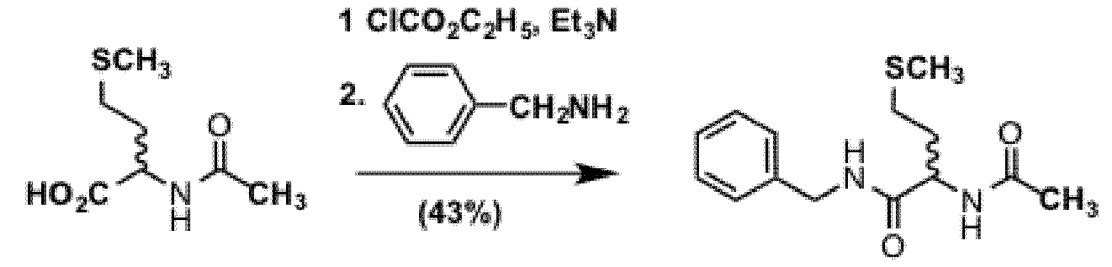


89. With this enantiomerically pure (D or R enantiomer) starting material thus readily available, it would only be necessary for the POSA to use a well-known standard method for making the N-benzylamide of an amino acid to obtain

[45] Ex. 1015 at 1934.

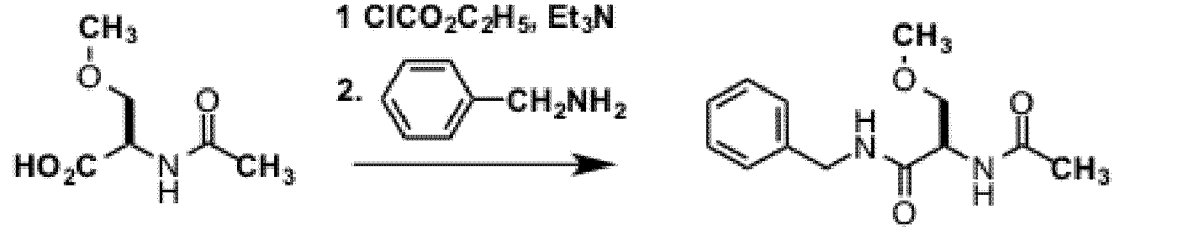
[46] Ex. 1016 at 6.

lacosamide, an enantiomerically pure R stereoisomer. For example, in their 1987 article, Conley and Kohn employed the following procedure for the synthesis of a related *N*-acetylamino acid benzamide in 43% yield:[47]



***N*-acetyl-*S*-methyl-DL-homocysteine** **N-acetyl-S-methyl-DL-homocysteinebenzamide**

90. By application of this reliable method to the *N*-acetyl-*O*-methyl-D-serine prepared by the method of Synge and Jaeger (see above), the enantiomerically pure R stereoisomer *N*-acetyl-*O*-methyl-D-serine benzamide (lacosamide) is enabled to a POSA.



***N*-acetyl-*O*-methyl-D-serine** **N-acetyl-O-methyl-D-serine benzamide (lacosamide)**

91. Furthermore, Kohn and coworkers taught that it is straightforward to prepare either D or L enantiomers from the relevant amino acid:

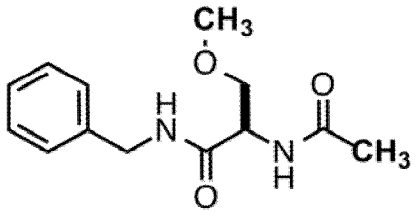
[47] Ex. 1017 at 567-574, Tbl. V (compound 1e).

> All of the compounds used in this study were synthesized from the appropriate chiral or D,L-amino acid, using procedures common for the preparation of peptides. The D- and L-enantiomers of AAB were prepared from the corresponding optically pure alanylmethyl ester hydrochlorides using the conditions employed for the racemate.[48]

As shown below in ¶152, the starting material necessary for the synthesis of lacosamide, D-serine, and derivatives thereof, was available by several methods.

C. Claims 1-9 of the '551 Patent are Anticipated by the LeGall Thesis

92. As set forth above, Claims 1-9 of the '551 patent are claims directed to chemical compounds that include lacosamide, which is the R enantiomer of racemic compound 107(e) in the LeGall thesis.



R-enantiomer of 107e
lacosamide

Therefore, claims 1-9 of the '551 patent are anticipated by the LeGall thesis.

93. As described above in ¶37, claims 1 and 3-8 cover compounds in which the R-enantiomer (lacosamide) is present in any amount in an enantiomeric mixture. Therefore, because the racemate 107e of the LeGall thesis is composed of

[48] Ex. 1021, Kohn 1988 at 371-72.

50% of the R-enantiomer (lacosamide), claims 1 and 3-8 are anticipated by the racemate 107e described in the LeGall thesis.

94. Claims 2 and 9 of the '551 patent place limits on enantiopurity of the R-enantiomer of the claimed compounds, including lacosamide. As described above in ¶¶87-91, because a POSA was enabled to isolate the R enantiomer of compound 107e in the LeGall thesis in enantiopure form, claims 2 and 9 are also anticipated by the LeGall thesis.

D. Claim 10 of the '551 Patent is Anticipated by the LeGall Thesis

95. Claim 10 of the '551 patent claims a "therapeutic composition comprising an anticonvulsant effective amount" of the compounds claimed by claims 1-9 of the '551 patent "and a pharmaceutical carrier therefore."

96. In the introduction of the LeGall thesis, the state of the art in the treatment of epilepsy is reviewed and LeGall refers to "the anticonvulsant properties of several N-benzyl amino acids," which he describes as "a new class of anticonvulsant drugs."[49] Compound 107e was prepared "[i]n an effort to further delineate the structure-activity relationship of this novel class of antiepileptic compounds."[50] The LeGall thesis further notes that "[t]he close structural analogy

[49] Ex. 1005 at 42.

[50] *Id.* at 43.

of [107e] with 86b suggest[s] that … [it] may have *good* anticonvulsant activity."[51] It was well within the ordinary skill of a POSA to determine an anticonvulsive effective amount of the referenced compounds. All that was necessary to a POSA would be to test the compound (107e) in the standard preclinical tests described in the LeGall thesis.[52]

97. Therefore, Claim 10, directed to a "therapeutic composition comprising an anticonvulsant effective amount of" compounds including lacosamide, is anticipated by the LeGall thesis, which discloses pharmaceutical compositions of the compounds of the thesis,[53] and discloses the making of pharmaceutical compositions for use as anticonvulsant therapeutic agents.

E. Claims 11-13 of the '551 Patent are Anticipated by the LeGall Thesis

98. Claims 11-13 of the '551 patent claim a "method of treating central nervous system disorders in an animal comprising administering … an anticonvulsant effective amount" of the compounds of claims 1-9, including lacosamide. Claims 12 and 13 limit the animal to a mammal and human, respectively.

[51] *Id.* at 155 (emphasis added).

[52] *Id.* at 102-03, 162-63.

[53] *See, e.g., id.* at 162.

99. As mentioned in ¶96, the introduction of the LeGall thesis reviews the state of the art in the treatment of epilepsy, which is a central nervous system disorder.[54] The LeGall thesis has a section on "clinical applications" which describes the drugs used at that time for the treatment of epilepsy in humans.[55] Compounds synthesized in the LeGall thesis were screened for anticonvulsant activity using tests in mice.[56] The '551 patent relied exclusively on similar preclinical data in rodents to support its method of treating central nervous system disorders in humans in claim 13.[57] The compounds described in the LeGall thesis were described as part of a "novel class of antiepileptic compounds."[58] Therefore, Claims 11-13, directed to a "method of treating central nervous system disorders" in animals, including humans, are anticipated by the LeGall thesis.

IX. CLAIMS 1-13 OF THE '551 PATENT ARE OBVIOUS

100. As I mentioned above, I understand I am to consider the following four factors to determine whether a patent claim is obvious: (1) the scope and content of the prior art; (2) the differences between the prior art and the claim;

[54] *See, e.g., id.* at 1.

[55] *Id.* at 25-30.

[56] *Id.* at 102-03, 162-63.

[57] Ex. 1001, col. 21:27-22:22.

[58] Ex. 1005 at 43.

(3) the level of ordinary skill in the art; and (4) secondary considerations tending to prove obviousness or nonobviousness. I discuss each factor below.

A. The Scope and Content of the Prior Art

101. As of March 15, 1996, a great deal of information had been published about the class of compounds claimed by the '551 patent. Based on what a POSA would have known from the LeGall thesis and other prior art, a POSA would have identified lacosamide as a compound with anticonvulsant activity with a reasonable expectation of success.

1. Structure-Activity Relationships Were Well-Known For The Class Of Compounds Covered By The '551 Patent

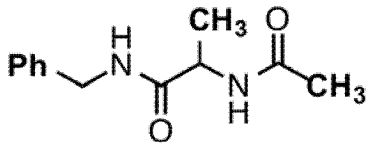
a. Sergio Cortes et al., Effect of Structural Modification of the Hydantoin Ring on Anticonvulsant Activity, 28 J. Med. Chem. 601-06 (1985) ("Cortes")

102. Cortes is prior art to the '551 patent because it was published in 1985, which obviously predates the March 15, 1996, priority date.

103. Cortes, which is co-authored by Dr. Kohn (the inventor listed on the '551 patent), describes the synthesis and anticonvulsant activity of several different types of nitrogen-containing compounds, including four amino acid derivatives.[59] Cortes reports that "[a]mong the most active compounds observed were the amino acid derivative N-acetyl-D,L-alanine benzylamide (6d) [AAB]) …. Compound 6d

[59] Ex. 1009 at 601 abstr.

proved to be slightly more potent … than phenacemide."[60] The following is the structure of compound 6d, AAB:[61]



N-acetyl-alanine-N-benzylamide
(Cortes 6d, AAB)

Cortes states that, based on this research, AAB was "slated for additional screening."[62]

b. Judith D. Conley, Functionalized Amino Acid Derivatives – Potent New Agents for the Treatment of Epilepsy: Synthesis, and Spectroscopic and Pharmacological Properties (May 1986) ("Conley Thesis")

104. The Conley thesis is a thesis authored by Judith Conley dated May 1986 presented in partial fulfillment of a Ph.D. from the University of Houston.[63] In 1987, Conley and her doctoral advisor Harold Kohn published an article that was "[a]bstracted from [Conley's] Ph.D. dissertation" and directs the public to "[a]dditional structure proof, discussion, and experimental and spectral data … in

[60] *Id.*

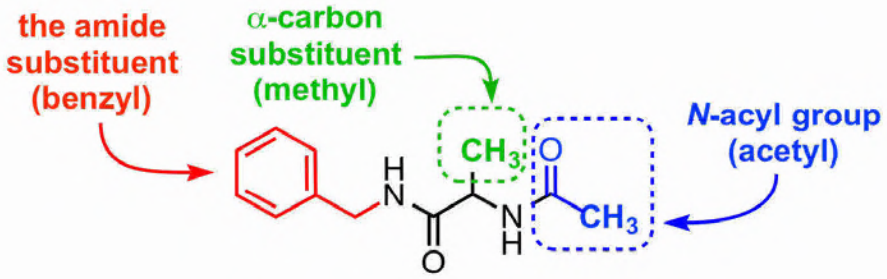
[61] *Id.* at 604, Tbl. IV.

[62] *Id.* at 604.

[63] Ex. 1018.

this reference."[64] The citation of the Conley thesis in the 1987 article would have guided a POSA to the thesis for more extensive information relating to the compounds investigated by Dr. Conley. Therefore, I understand that the Conley thesis was published well before March 15, 1996, and is prior art to the '551 patent.

105. The Conley thesis uses the AAB compound identified in Cortes 1985, which was "the most potent" compound identified by Cortes et al., as a "parent substrate" or starting point.[65] The thesis describes the modification of AAB and the anticonvulsant activity of derivative compounds and discloses structural analogs of AAB that were modified at three sites, "the α-carbon, the amide substituent, and the N-acyl group."[66]



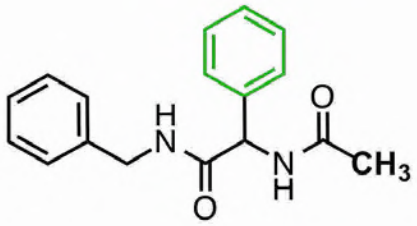
N-acetyl-alanine-N-benzylamide (AAB)

[64] Ex. 1017 at n.1.

[65] Ex. 1018 at 19, 26.

[66] *Id.* at 26.

For the compounds with modifications at the α-carbon, the Conley thesis shows that N-acetyl-DL-phenylglycine-N-benzylamide (53c) (APB) possessed "enhanced anticonvulsant activity" relative to AAB.[67] As demonstrated below, the difference between AAB and APB is that the α-carbon is substituted with a phenyl group instead of a methyl group:



N-acetyl-phenylglycine-N-benzylamide
(Conley thesis 53c, APB)

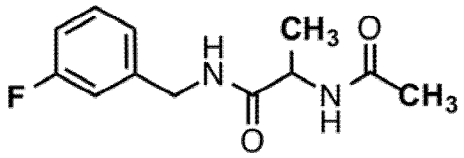
Dr. Conley also studied modifications of the N-acetyl group and the N-benzylamide.[68] It was found that "any increase in the size of the methyl group of the N-acetyl moiety … led to substrates that possessed decreased activity."[69] With respect to replacements of the N-benzylamide moiety, Dr. Conley did not find any with improved potency, although one, the m-flourobenzyl analog (compound 53l), had comparable potency:[70]

[67] *Id.* at 65-67.

[68] *Id.* at 67-70.

[69] *Id.* at 69.

[70] *Id.* at 68, Tbl. 20.



Conley compound 53l

106. The Conley thesis recognized that "[e]nantiomeric pairs exhibiting different biological activities are by no means a recent discovery."[71] Therefore, Dr. Conley investigated and reported the anticonvulsant activities of the enantiomers of the racemic compounds addressed in the thesis by synthesizing and testing for biological activity the "stereoisomers of those substrates possessing high anticonvulsant activities."[72] The Conley thesis identifies the D- and L-isomers of AAB and APB for evaluation because they "were the most active agents uncovered in the initial survey."[73] Based on the evaluation of the stereoisomers of AAB and APB, the Conley thesis taught that "the anticonvulsant activity displayed by the D-enantiomer[74] was equal to or greater than that observed in the racemate,

[71] *Id.* at 106.

[72] *Id.* at vii.

[73] *Id.* at 111-113.

[74] In this case, the D-enantiomer referred to corresponds the R configuration, which a POSA would have known.

while the L-isomer exhibited significantly lower levels of anticonvulsant activity than the racemic substance."[75]

c. Judith D. Conley & Harold Kohn, Functionalized DL-Amino Acid Derivatives. Potent New Agents for the Treatment of Epilepsy, 30 J. Med. Chem. 567-574 (1987) ("Conley 1987")

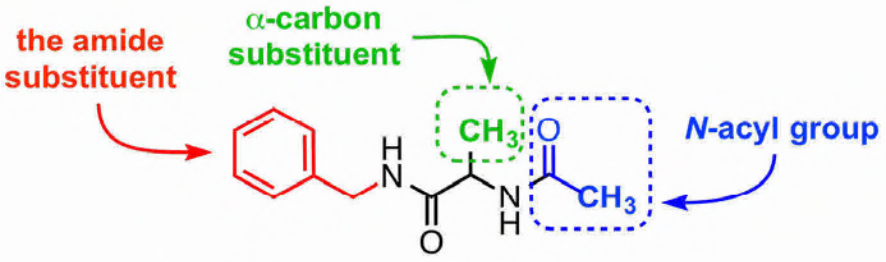
107. Conley 1987 is prior art to the '551 patent because it published in 1987, which is prior to March 15, 1996. Conley 1987 was abstracted from the Conley thesis and is highly duplicative of it.[76]

108. Conley 1987 demonstrated the importance a POSA would assign to the methyl group of the N-acetyl moiety and the benzyl group of the N-benzylamide moiety for anticonvulsant activity. Conley 1987 reported structural modifications to a parent compound AAB (1a) at three sites: the α-carbon, the amide substituent, and the N-acyl group.[77]

[75] *Id.* at viii.

[76] Ex. 1017 at n.1.

[77] *Id.* at 568.



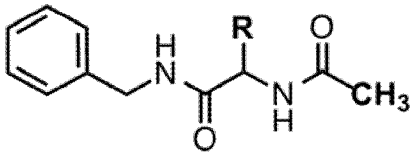
N-acetyl-alanine-N-benzylamide
Conley 1987 Cmpd 1a (AAB)

109. Each analog of AAB was tested for anticonvulsant activity.[78] Of the compounds that were modified at the α-carbon, "pronounced activity" was observed for N-acetyl-DL-phenylglycine-N-benzylamide (1d) (APB).[79] APB resulted from the substitution of a phenyl group instead of a methyl group at the α-carbon. Conley 1987 found that reduced CNS activity occurred as the size of the substituent on the α-carbon atom in 1a was decreased from a methyl group to a hydrogen (1b) or increased to either an isopropyl group (1c) or a thioalkyl group (1e).[80]

[78] *Id.* at 570.

[79] *Id.* at 571.

[80] *Id.*

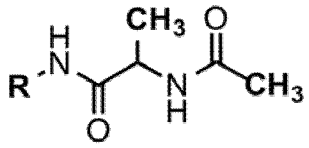


	MES
R = CH_3	3
R = H	2
R = $CH(CH_3)_2$	2
R = C_6H_5	4
R = $CH_2CH_2SCH_3$	2
R = $CH_2C_6H_5$	0

110. For the compounds that were modified at the carboxamide group, the "anticonvulsant activity in the MES test (the maximal electroshock seizure test)[81] was abolished when the size of the benzyl substituent in 1a was decreased to a methyl (1j) or increased to a benzhydryl (1k) or a glycine N-benzylamide (1n) group."[82]

[81] The MES results were reported by Conley and Kohn using a code whereby a test compound was given a rating of 0-4, where: 0 = no activity at 600 mg/kg; 1 = noticeable activity at 600 mg/kg; 2 = noticeable activity at 300 mg/kg; 3 = noticeable activity at 100 mg/kg; and 4 = noticeable activity at 30 mg/kg, Therefore, a larger number for MES means higher potency.

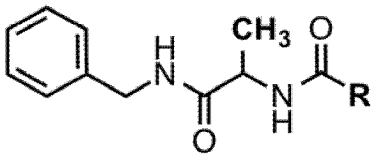
[82] *Id.* at 572.



	MES
R = $CH_2C_6H_5$	3
R = CH_3	0
R = $CH(C_6H_5)_2$	0
R = $CH_2C_6H_4$-m-OCH_3	2
R = $CH_2C_6H_4$-m-F	3
R = $CH_2CONHCH_2C_6H_5$	0

These results taught a POSA that modification of the benzyl moiety of the amide group did not result in improved anticonvulsant activity, although addition of a meta-F to the benzene ring gave an analog with comparable activity.

111. For the compounds that were modified at the N-acetyl moiety, "any increase in the size of the methyl group of the N-acetyl moiety in 1a led to compounds that possessed decreased activity in the MES test."[83]

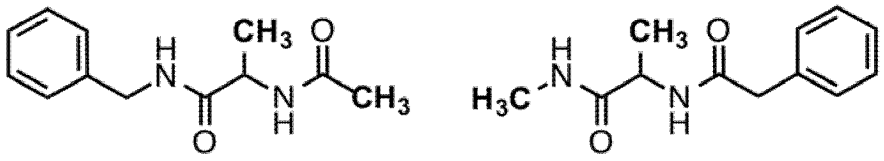


	MES
R = CH_3	3
R = $CH(CH_3)_2$	0
R = $C(CH_3)_3$	2
R = $CH_2CONHCH_3$	0

These results taught a POSA that alteration of the N-acetyl moiety did not result in improved anticonvulsant activity. Additionally, Conley 1987 discloses that

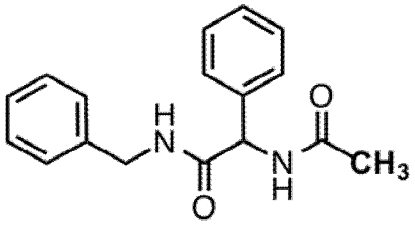
[83] *Id.*

transposition of the methyl group of the N-acetyl moiety and the benzyl group of the N-benzylamide moiety resulted in "compounds that were devoid of anticonvulsant activity."[84]

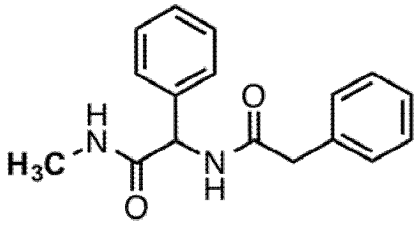


active

devoid of activity



active



devoid of activity

d. LeGall Thesis

112. I have discussed the disclosures of the LeGall thesis in detail in Section VII, which I have also considered for the purposes of this obviousness analysis. Of note, LeGall says in his thesis that he set out to prepare "analogues of the potent anticonvulsant agent" AAB from Cortes (referred to in the thesis as compound 68a), thus conducting the additional screening contemplated by Dr. Kohn and others as referenced in Cortes.[85]

[84] *Id.*

[85] *Id.* at 42, 132 & n.102.

e. Harold Kohn & Judith D. Conley, New Antiepileptic Agents, 24 Chemistry in Britain 231-234 (March 1988) ("Kohn & Conley 1988")

113. Kohn & Conley 1988 is prior art to the '551 patent because it published in 1988, which is prior to March 15, 1996.

114. Kohn & Conley 1988 was also based on research previously reported in the Conley thesis. Namely, Kohn & Conley 1988 reports the "[p]ronounced activity" of AAB, its fluorobenzylamide derivative, and APB.[86] The article also discloses that these compounds "were comparable to phenobarbital in the prevention of electroshock-induced seizures in mice and, perhaps more significantly, were less toxic after injection and oral administration than phenytoin or phenobarbital."[87] Based on a comparison with "the conventional antiepileptic agents," Kohn & Conley 1988 reported that "these compounds displayed significantly different activity profiles … suggesting that these compounds represented a new important class of anticonvulsant agents."[88] Kohn & Conley 1988 concluded that these functionalized amino acid compounds are "worthy of

[86] Ex. 1019 at 232.

[87] *Id.* at 232.

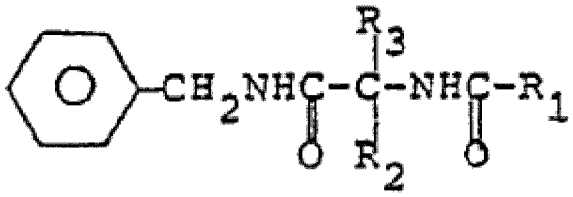
[88] *Id.*

further detailed inspection," and that "the anticonvulsant activity observed resided primarily in the D-stereoisomers[89]" of AAB and APB.[90]

f. European Patent Application No. 0 194 464 ("The '464 application")

115. The '464 application is prior art to the '551 patent because it published on September 17, 1986, which is prior to March 15, 1996.

116. The '464 application describes compounds "exhibiting anticonvulsant activity" that are "useful in the treatment of epilepsy and other central nervous system disorders" of the following general formula:[91]



I

The '464 application discloses that "R_1 is C_1-C_6 alkyl, R_2 and R_3, independently are hydrogen, C_1-C_6 alkyl or phenyl … wherein the benzyl moiety, R_1, R_2, and R_3 may be substituted by halo, nitro, carboxyl, carboalkoxyl, carboxamide, cyano or thiol, alkylthio, alkoxy, alkyl, amino or phenoxy."[92] This claimed genus includes AAB,

[89] In this case, the D-stereoisomers referred to correspond the R configuration, which a POSA would have known.

[90] *Id.* at 234.

[91] Ex. 1020 at 3:38-50.

[92] *Id.* at 3:51-54.

APB, and lacosamide.[93] The '464 application also describes the administration of the compounds of the invention with various pharmaceutical carriers for anticonvulsant activity.[94]

117. The '464 application discloses that "[t]he present compounds obviously exist in stereoisomeric forms and the products obtained thus can be mixtures of the isomers which can be resolved."[95] Consistent with the literature discussed above, the '464 application reports data showing that the D stereoisomer[96] was tenfold more potent than the L stereoisomer for the compounds reported.[97]

g. Harold Kohn et al., Marked Stereospecificity in a New Class of Anticonvulsants, 457 Brain Res. 371-375 (1988) ("Kohn 1988")

118. Kohn 1988 is prior art to the '551 patent because it published in 1988, which is prior to March 15, 1996.

[93] *Id.* at cl. 1.

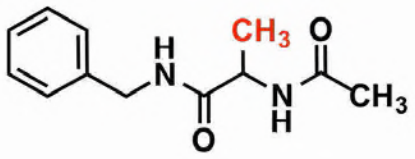
[94] *Id.* at 5:41-6:35; 5:30-32; 6:45-46.

[95] *Id.* at 5:27-28.

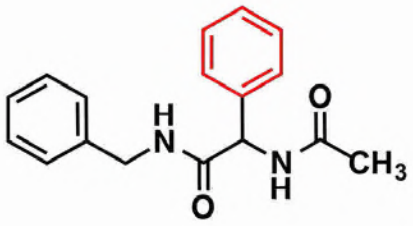
[96] In this case, the D-enantiomers for which data was reported correspond the R configuration, which a POSA would have known.

[97] *Id.* at 12, Tbl. 1.

119. Kohn 1988 reports studies of anticonvulsant potency of the racemates and individual enantiomers of N-acetyl-alanine-N-benzylamide ("AAB") and N-acetyl-phenylglycine-N-benzylamide ("APB"), which are depicted below, and which differ only in the substituent attached to the stereocenter (methyl in AAB and phenyl in APB):[98]



N-acetyl-DL-alanine-N-benzylamide (DL-AAB)



N-acetyl-DL-phenylglycine-N-benzylamide (DL-APB)

The main conclusions of the study were that "the anticonvulsant activity is due to the D-stereoisomer,[99] and the L-stereoisomer is virtually inactive as an anticonvulsant."[100]

[98] Ex. 1021 at 371, abstr.

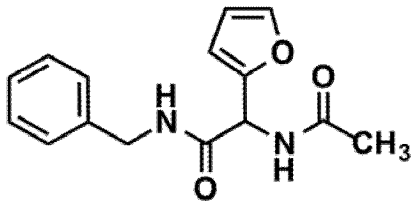
[99] In this case, the D-stereoisomers referred to correspond to the R configuration, which a POSA would have known.

[100] *Id.* at 371, abstr.; *see also id.* at 372-74.

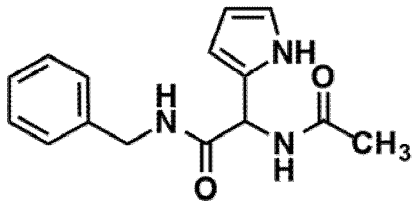
h. Harold Kohn et al., Preparation and Anticonvulsant Activity of a Series of Functionalized α-Aromatic and α-Heteroaromatic Amino Acids, 33 J. Med. Chem. 919-926 (1990) ("Kohn 1990")

120. Kohn 1990 is prior art to the '551 patent because it published in 1990, which is prior to March 15, 1996.

121. The Kohn 1990 study used APB as a starting point and explored replacement of the phenyl group attached to the α-carbon by a number of other aromatic or heteroaromatic groups.[101] After evaluating 23 analogs of APB, Kohn and coworkers concluded that "the most active compounds are (R,S)-α-acetamido-N-benzyl-2-furanacetamide (2g) and (R,S)-α-acetamido-N-benzyl-2-pyrroleacetamide (2i)," the structures of which are shown below:[102]



Kohn 1990 Furanyl Derivative (2g)



Kohn 1990 Pyrrolyl Derivative (2l)

On the basis of this SAR study, Kohn and coworkers concluded that "[e]vidence is presented that placement of a relatively small, electron-rich, heteroaromatic moiety at the α-site leads to a substantial enhancement in the anticonvulsant activity of the

[101] Ex. 1022 at 919.

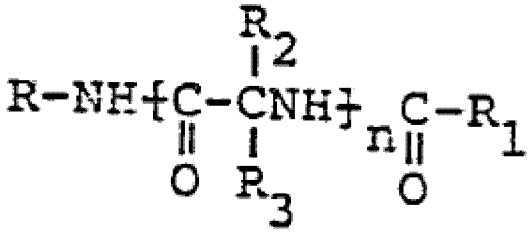
[102] *Id.* at 919 abstr., Tbl. I.

drug candidate" relative to APB.[103] As with AAB and APB, the "[e]valuation of the two individual enantiomers of 2g demonstrated that the anticonvulsant activity resided in the R stereoisomer."[104]

i. European Patent Application No. 0 263 506 ("The '506 application")

122. The '506 application is prior art to the '551 patent because it published on April 13, 1988, which is prior to March 15, 1996.

123. The '506 application discloses "compounds having central nervous system (CNS) activity which are useful in the treatment of epilepsy…having the following general formula:"[105]



The '506 application further discloses that R_2 can include lower alkyl groups, substituted or unsubstituted, where the substitution can be an alkoxy group, which

[103] *Id.* at 919, 922.

[104] *Id.* at 919, 922, Tbl. III.

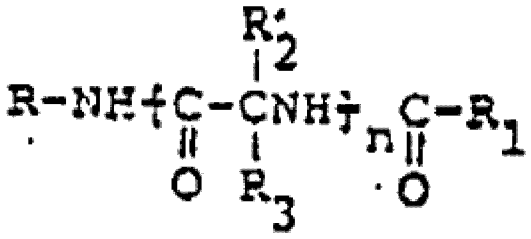
[105] Ex. 1023 at 2:2-10; *see also id.* 3:18-21, 8:8-10.

would include the methoxymethyl of lacosamide.[106] The '506 application reported the same data discussed above demonstrating that the D-enantiomer[107] possessed about tenfold greater anticonvulsant activity than the L-enantiomer.[108]

j. European Patent Application No. 0 400 440 ("The '440 application)

124. The '440 application is prior art to the '551 patent because it was published on December 5, 1990, which is prior to March 15, 1996.

125. The '440 application discloses "compounds exhibiting central nervous system (CNS) activity which are useful in the treatment of epilepsy…[of] the following general formula:"[109]



According to the '440 application, these compounds "exhibit excellent anticonvulsant activity."[110]

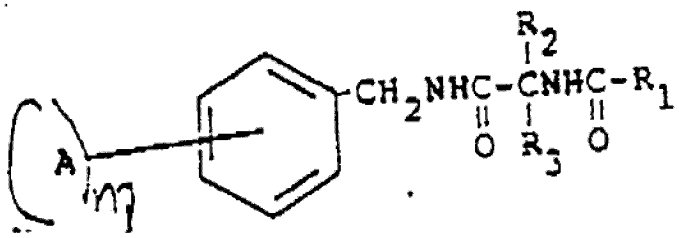
[106] *Id.* at 2:51 – 3:14.

[107] In this case, the D-enantiomers for which data was reported correspond to the R configuration, which a POSA would have known.

[108] *Id.* at 18, Tbl. 1.

[109] Ex. 1024 at 3:2-12.

126. The '440 application also states that "[p]referred compounds of the present invention have the following general formula:



wherein R_1 is H or lower alkyl .... [and] it is preferred that A is hydrogen."[111]

127. The '440 application stated that "[t]he present compounds obviously exist in stereoisomeric forms and the products obtained thus can be mixtures of the isomers, which can be resolved."[112] The '440 application then describes various art-recognized techniques for synthesizing and separating stereoisomers.[113] Table I reports the anticonvulsant activity for both the D and L stereoisomers of the 2-furanyl derivative,[114] showing that the D stereoisomer was much more potent than the L stereoisomer.[115]

[110] *Id.* at 11:27-29; *see also id.* at 4:25-28.

[111] *Id.* at 5:30-42.

[112] *Id.* at 10:57-58.

[113] *Id.* at 10:58-11:26.

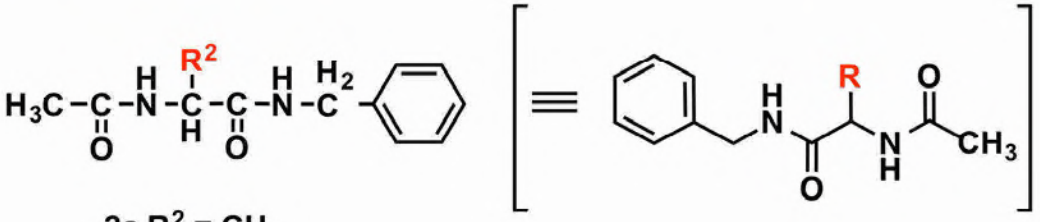
[114] In this case, the D-stereoisomer referred to corresponds to the R configuration, which a POSA would have known.

[115] *Id.* at Tbl. 1.

k. Harold Kohn et al., Preparation and Anticonvulsant Activity of a Series of Functionalized α-Heteroatom-Substituted Amino Acids, 34 J. Med. Chem. 2444-2452 (1991) ("Kohn 1991")

128. Kohn 1991 is prior art to the '551 patent because it was published in 1991, which is prior to March 15, 1996.

129. Kohn 1991 was a continuation of the work following the identification of the promising amino acid derivatives AAB, APB, the 2-pyrrolyl derivative, and the 2-furanyl derivative (2a-2d).[116]



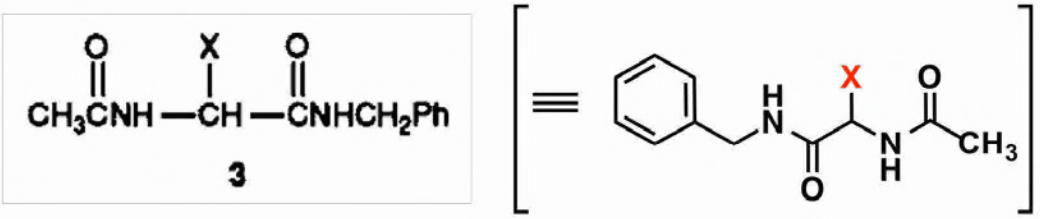
2a $R^2 = CH_3$
b R^2 = Ph
c R^2 = 2-pyrrolyl
d R^2 = 2-furanyl

Kohn 1991 describes the synthesis and testing of 26 amino acid derivatives for anticonvulsant activity, which "further define the structure-activity relationships for this class of amino acid derived anticonvulsant agents."[117] All 26 compounds

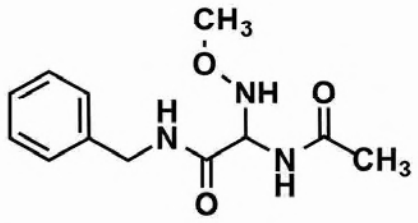
[116] Ex. 1010 at 2444.

[117] *Id.* at 2444.

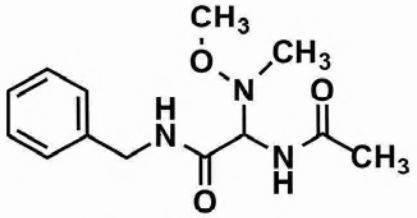
contain both an N-benzylamide moiety and an acetylated amino group, and vary only by the substituent at the α-carbon defined as X in the structure below:[118]



Of the 26 compounds tested, "[t]he most active compounds were (R,S)-2-acetamido-N-benzyl-2-(methoxyamino)acetamide (3l) and (R,S)-2-acetamido-N-benzyl-2-(methoxymethylamino)acetamide (3n)," the structures of which are represented below:[119]



Kohn 1991 methoxyamino derivative (3l)



Kohn 1991 methoxymethylamino derivative (3n)

130. Kohn 1991 reported that "[t]he anticonvulsant activities of racemic 3l … and 3n … were comparable to that of the (R,S)-2-furanyl derivative 2d … and phenytoin."[120] Kohn 1991 also describes "several important observations" about

[118] *Id.* at 2445, Tbl. 1.

[119] *Id.* at 2444, abstr., 2445, Tbl. 1.

[120] Ex. 1010 at 2447.

the structure-activity relationships of this class of compounds including that (1) "the α-amino … derivative[] displayed anticonvulsant activit[y] comparable to that observed for the α-methyl analogue"; (2) that there are "stringent steric requirements that exist for maximal anticonvulsant activity in this class of compounds"; and (3) "in the most potent analogues (2d, 3l, and 3n), a functionalized oxygen atom existed two atoms removed from the α-carbon atom."[121]

l. Harold Kohn et al., Synthesis and Anticonvulsant Activities of α-Heterocyclic α-Acetamido-N-Benzylacetamide Derivatives, 36 J. Med. Chem. 3350-3360 (1993) ("Kohn 1993")

131. Kohn 1993 is prior art to the '551 patent because it was published in 1993, which is prior to March 15, 1996.

132. Kohn 1993 reports the synthesis and anticonvulsant evaluation of an expanded set of C(α)-heteroaromatic analogs.[122] Kohn 1993 provides further support that "improved activity resulted by the positioning of a heteroatom two atoms removed from the C(α)-site."[123] The authors noted that they previously had observed that "the anticonvulsant activity … decreased in proceeding from oxygen

[121] *Id.* at 2447.

[122] Ex. 1025 at 3350, abstr.

[123] *Id.* at 3354.

to nitrogen to sulfur containing C(α)-heteroaromatic derivatives."[124] Moreover, Kohn 1993 "suggest[ed] that increased anticonvulsant activity generally accompanied the placement of a substituted (alkylated) heteroatom two atoms removed from the amino acid α-carbon."[125]

133. Kohn 1993 also prepared "several enantiopure congeners of (R)-4 [the 2-furanyl derivative] to demonstrate that this absolute configuration afforded compounds with marked anticonvulsant activity."[126] Kohn 1993 concluded that "the pharmacological stereospecificity that distinguishes this novel class of anticonvulsant agents was reaffirmed by the biological data … [in which Kohn 1993] noted a significant improvement in anticonvulsant activity of (R)-30 … versus the corresponding racemate."[127]

m. Harold Kohn et al., Anticonvulsant Properties of N-Substituted α,α-Diamino Acid Derivatives, 83 J. Pharmaceutical Sci. 689-691 (May 1994) ("Kohn 1994")

134. Kohn 1994 is prior art to the '551 patent because it was published in 1994, which is prior to March 15, 1996.

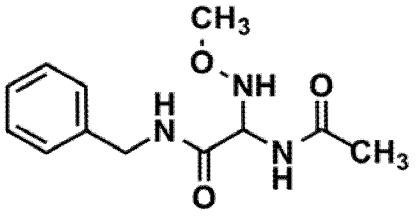
[124] *Id.* at 3354.

[125] *Id.* at 3354.

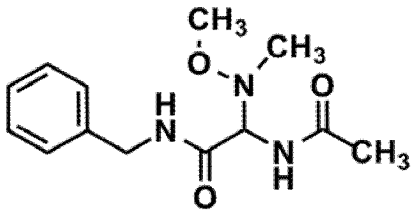
[126] *Id.* at 3350.

[127] *Id.* at 3355.

135. Kohn 1994 highlights the "potent anticonvulsant effects" of the methoxyamino derivative (2c) and the methoxymethylamino derivative (2d) reported in Kohn 1991:[128]

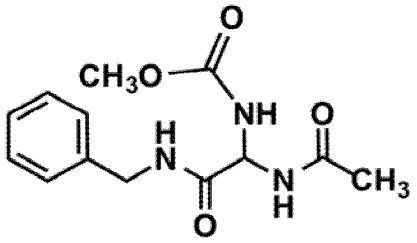


Methoxyamino derivative (2c)

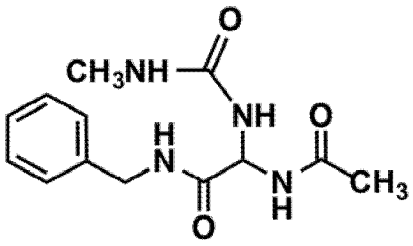


Methoxymethylamino derivative (2d)

The research reported by Kohn and coworkers in their 1994 publication was intended to find out the effect of conversion of the basic amino substituent at the stereocenter to a neutral derivative, such as carbamate 2e or urea 2g:[129]



Carbamate derivative (2e)



Urea derivative (2g)

A total of 10 such N-acyl derivatives were synthesized and evaluated. Most were inactive and all were significantly less potent than 2c and 2d.[130]

[128] Ex. 1026 at 689.

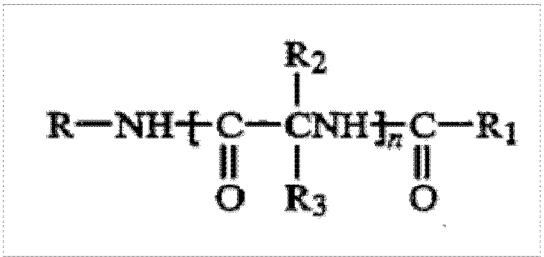
[129] *Id.* at 689.

[130] *Id.* at 691.

n. U.S. Patent No. 5,378,729 ("The '729 patent")

136. The '729 patent is prior art to the '551 patent because it issued on January 3, 1995, which is prior to March 15, 1996.

137. The '729 patent discloses "compounds … having central nervous system (CNS) activity which are useful in the treatment of epilepsy and other CNS disorders" of the following general formula:[131]



General formula describing compounds of the '729 patent

The '729 patent also discloses that "compounds of the present invention exhibit excellent anticonvulsant activity,"[132] that the compounds are administered with a "'"pharmaceutically acceptable carrier"'"[133] and that "[t]he use of such media and agents for pharmaceutical active substances is well known in the art."[134]

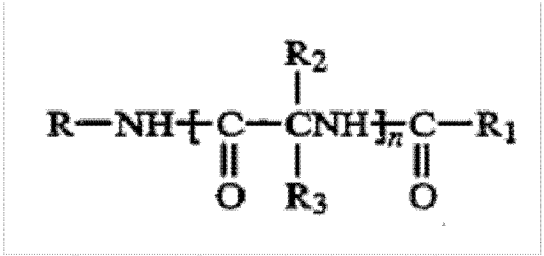
[131] Ex. 1008, col. 1:30-2:20.

[132] *Id.* at 16:5-7.

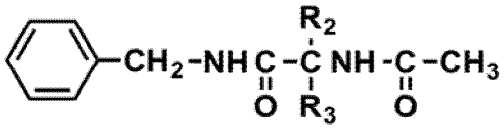
[133] *Id.* at 17:53-54.

[134] *Id.* at 17:54-58.

138. The '729 patent discloses that "[t]he preferred compounds are those wherein n is 1 …. The preferred value[] of R is … especially benzyl…. [and] The most preferred R_1 group is methyl."[135]



General formula describing compounds of the '729 patent



General formula of the '729 patent with preferred features

139. The '729 patent states that "[t]he present compounds obviously exist in stereoisomeric forms and the products obtained thus can be mixtures of the isomers, which can be resolved."[136] The '729 patent then describes various art-recognized techniques for synthesizing and separating stereoisomers.[137] The '729 patent also identifies that "[t]he D stereoisomer is preferred."[138] The biological data provided in Table I further support a preference for the D stereoisomer.[139] In the three instances where the D and L stereoisomers were both tested, AAB, APB,

[135] *Id.* at 5:14-19.

[136] *Id.* at 15:29-31; *see also id.* at 9:56-68.

[137] *Id.* at 15:31-16:4.

[138] *Id.* at 10:27.

[139] *Id.* at 58-61, Tbl. 1.

and the 2-furanyl derivative, the D stereoisomer[140] was at least tenfold more potent than the L stereoisomer.[141]

140. The '729 patent contains claims that cover lacosamide.[142] However, during the prosecution history of the '551 patent, as with the '301 patent, the applicant represented to the PTO that the '729 patent does not disclose lacosamide. Specifically, the applicant asserted that the '729 patent does not disclose "the basic structure wherein at least one of R_2, and R_3 is specifically alkoxymethyl, as specifically claimed."[143] However, this statement is incorrect and misconstrues basic chemistry principles because the '729 patent allows R_2 or R_3 to be alkoxymethyl, i.e., methylene substituted with methoxy.

o. Summary

141. A POSA would take away several important structure-activity relationships from the work published by Kohn and his coworkers. First, the class

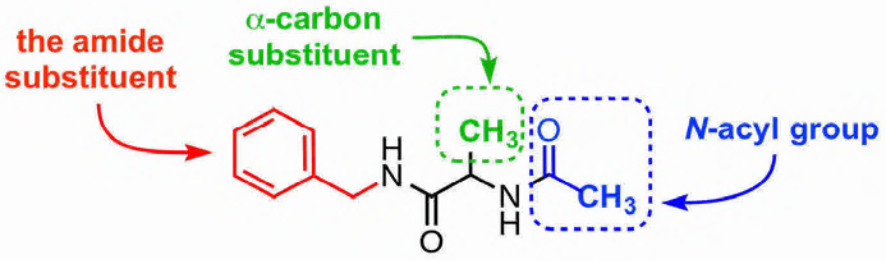
[140] In this case, the D-enantiomers for which data was reported correspond to the R configuration, which a POSA would have known.

[141] *Id.*

[142] *See*, *e.g.*, *id.* at cl. 1. Lacosamide is the R-enantiomer of the claimed compound where R is "aryl lower alkyl" (i.e., the "especially [preferred] benzyl" (col. 5:17-18)), R1 is "lower alkyl" (i.e., the "most preferred … methyl" (col. 5:17-18-19)), and one of R2 and R3 is "hydrogen" and the other "lower alkyl" (i.e., methylene) "substituted with … at least one electron donating substituent" (i.e., "methoxy" (col. 4:37)).

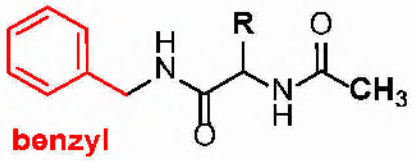
[143] Ex. 1006 at 2.

of compounds studied by Kohn et al., starting initially from AAB, had been modified at three positions, the α-carbon, the amide substituent, and the N-acyl group:[144]



N-acetyl-alanine-N-benzylamide
Conley 1987 Cmpd 1a (AAB)

142. Generally, modification of the benzyl (red in the structure below) substituent (except fluoro substitution) decreased the anticonvulsant activity of the series:[145]

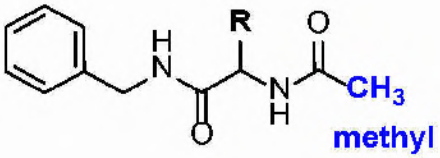


143. Modification of the N-acyl group to substituents other than methyl (blue in the structure below) resulted in decreased anticonvulsant activity:[146]

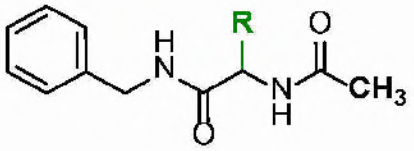
[144] Ex. 1017 at 568.

[145] *See, e.g., id.* at 572.

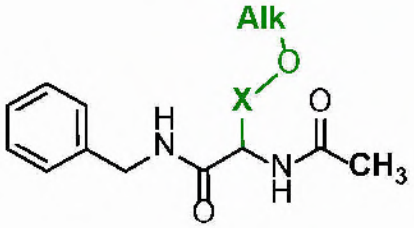
[146] *See, e.g., id.* at 572.



144. Modification of the R substituent (green in the structure below) could be used to modulate the anticonvulsant activity of the compounds:[147]



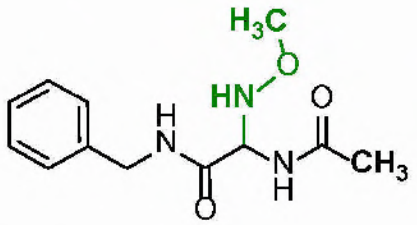
145. Kohn et al. had investigated a number of different R substituents and published "that increased anticonvulsant activity generally accompanied the placement of a substituted (alkylated) heteroatom two atoms removed from the amino acid α-carbon,"[148] which is displayed generically as follows:



A POSA would have been aware that as of March 1996, the most potent racemate identified was the compound where the R group was methoxyamino (highlighted in green below):

[147] *See, e.g.*, Ex. 1010, Ex. 1022, Ex. 1025, all discussed in detail above.

[148] Ex. 1025 at 3354.



Kohn 1991 methoxyamino derivative (3l)

146. Finally, a POSA would have been aware that Kohn and coworkers had published a preference for the D enantiomer as the stereoisomer in which the anticonvulsant activity primarily resides.[149] This preference was based on results finding stereospecific activity of compounds where the α-carbon is directly substituted with carbon (e.g., AAB, APB, 2-furanyl analog).[150]

2. The Substitution of Methyl for Amino Groups was Commonly Performed in the Prior Art

a. C.W. Thornber, Isosterism and Molecular Modification in Drug Design, 8 Chemical Soc'y Revs. 563 (1979) ("Thornber 1979")

147. Thornber 1979 is prior art to the '551 patent because it was published in 1979, which is prior to March 15, 1996.

148. Thornber 1979 defines bioisosteres as "groups or molecules which have chemical or physical similarities producing broadly similar biological

[149] *E.g.*, Ex. 1008, '729 patent col. 10:27.

[150] Ex. 1008, '729 patent Tbl. 1; Ex. 1021, Kohn 1988 at 371 abstr.; Ex. 1022, Kohn 1990 at 919, 922, Tbl. III.

properties"[151] and recognizes that methyl and amino groups are classical bioisosteres.[152]

b. Wilson & Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry, Ch. 2 (Delgado & Remers eds. 1991) ("W&G 1991")

149. W&G 1991 is prior art to the '551 patent because it was published in 1991, which is prior to March 15, 1996.

150. W&G 1991 discloses that "amine (-NH-) and methylene (-CH_2-) groups … are sufficiently alike in their steric nature to be frequently interchangeable in drugs."[153]

c. Richard B. Silverman, The Organic Chemistry of Drug Design and Drug Action, Ch. 2 (1992) ("Silverman 1992")

151. Silverman 1992 is prior art to the '551 patent because it was published in 1992, which is prior to March 15, 1996. Silverman 1992 recognizes that methyl and amino groups are classical bioisosteres.[154] "Bioisosteres are substituents or

[151] *Id.* at 563.

[152] Ex. 1027 at 564, Tbl. 1.

[153] Ex. 1028 at 30.

[154] Ex. 1029 at 19 (quotation from Ex. 1027), Tbl. 2.2.

groups that have chemical or physical similarities, and which produce broadly similar biological properties."[155]

3. The Prior Art Taught The Preparation Of Enantiomerically Pure D-Serine And Its Derivatives

152. The prior art discloses how to synthesize and isolate the D-enantiomer[156] of serine as well as its O-methyl derivative, as demonstrated by the following references which are all prior art to the '551 patent under because they published prior to March 15, 1996:

- Rosa Amoroso et al., "A New Route to the Synthesis of Amino Acids Through the Mercury Cyclization of Chiral Amidals," *57 J. Org. Chem.* 1082-1087 (1992) ("Amoroso 1992");

  Amoroso and coworkers reported a new synthetic procedure for the "preparation of enantiomerically pure amino acids through simple steps and under mild conditions."[157] One of the synthetic procedures illustrating the new method provided D-serine in 65% yield.

- S. Cerrini et al., "Serine-Containing 10-Membered Cyclodepsipeptides," *41 Int'l J. Peptide Protein Res.* 282-290 (1993) ("Cerrini 1993");

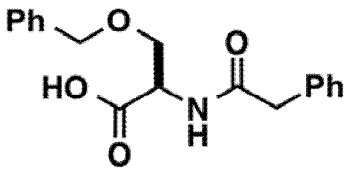
  Cerrini and coworkers described the preparation of a family of tripeptide lactones. One of the building blocks employed in this study was the following protected form of D-serine, in which the serine OH

[155] *Id.* at 19.

[156] In the case of D-serine and D-O-methylserine, the D-enantiomer corresponds to the R configuration, which a POSA would have known.

[157] Ex. 1030 at 1085.

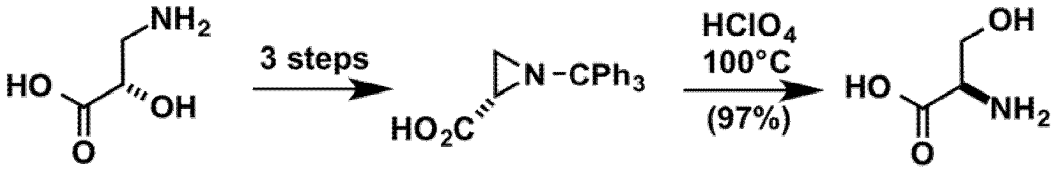
and NH_2 groups are protected as a benzyl ether and a phenylacetamide, respectively:[158]



D-serine derivative

- B. Svante Axelsson et al., "Versatile Synthesis of Stereospecifically Labelled D-Amino Acids via Labelled Aziridines…", *J. Chem. Soc. Perkin Trans. 1* 806-814 (1994) ("Axelsson 1994");

  Axelsson and coworkers developed a new method for stereospecific synthesis of amino acids; one of the examples was D-serine, which was prepared from the isomeric compound S-isoserine:[159]



S-isoserine

R-serine
(D-serine)

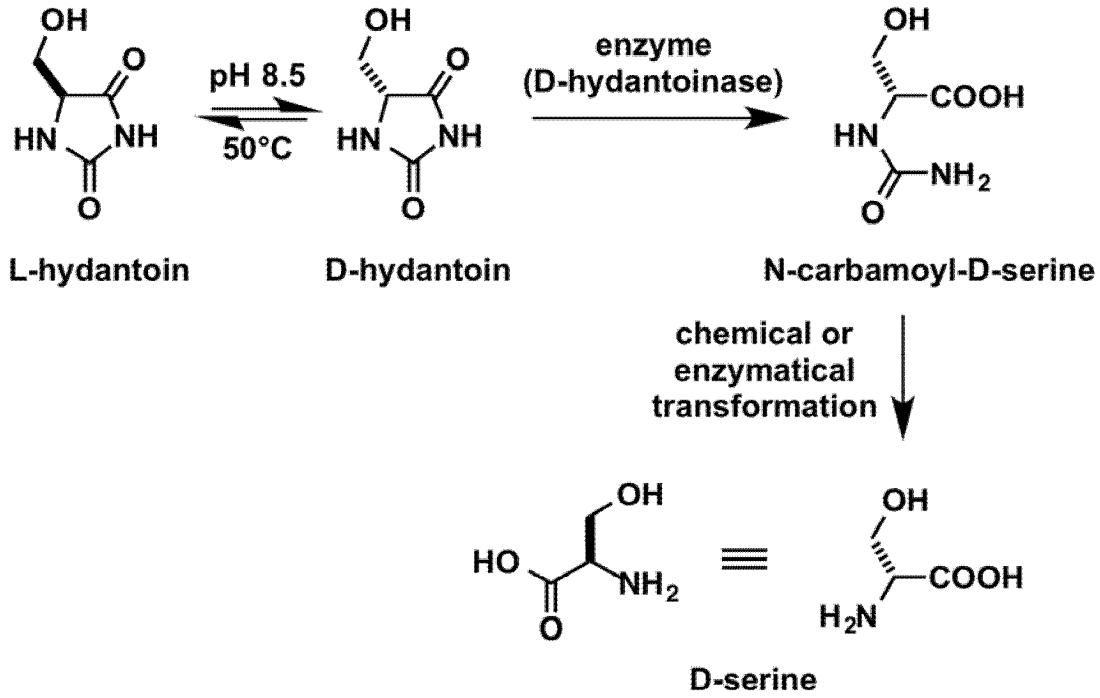
- Oliver Keil et al., "New Hydantoinases from Thermophilic Microorganisms – Synthesis of Enantiomerically Pure D-Amino Acids," *6 Tetrahedron: Asymmetry* 1257-1260 (1995) ("Keil 1995");

  In this article, Keil and coworkers reported that "14 D-α-amino acids were prepared from the corresponding racemic hydantoins by employing two novel hydantoinases from thermophilic

[158] Ex. 1031 at 288.

[159] Ex. 1032 at 809, 812.

microorganisms."[160] One of the examples, prepared in 97% enantiomeric purity, was D-serine.[161]



- M. Jaeger et al., Enzymatic Resolution of O-Methyl-N-Acetyl-DL-Serine. Amino Acids. XXXII., *28 Croat. Chem. ACTA* 5-8 (1956) ("Jaeger 1956");

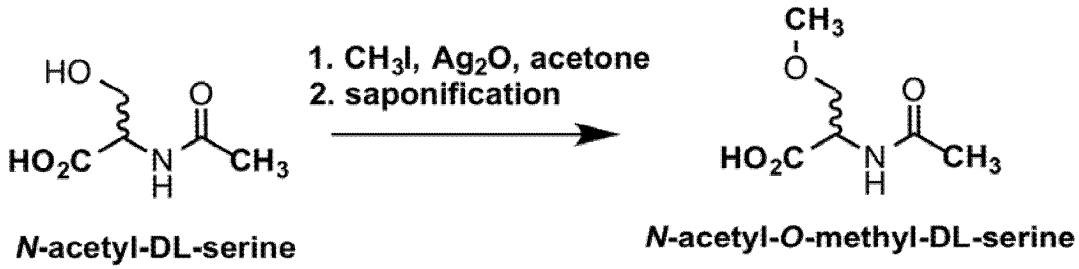
  As discussed in ¶88, Jaeger and coworkers[162] prepared *N*-acetyl-*O*-methyl-D-serine in 1956 by enzymatic deracemization of racemic N-acetyl-*dl*-serine, prepared by the method of Synge:[163]

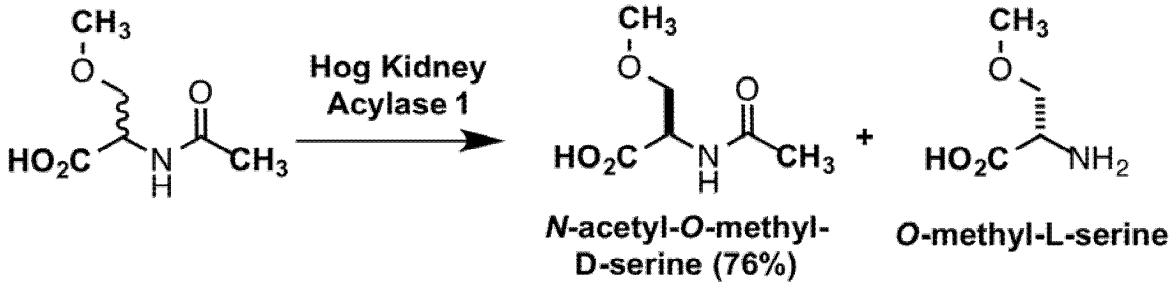
[160] Ex. 1033, abstr.

[161] *Id.* at Tbl., compound D-23.

[162] Ex. 1016 at 6.

[163] Ex. 1015 at 1934.



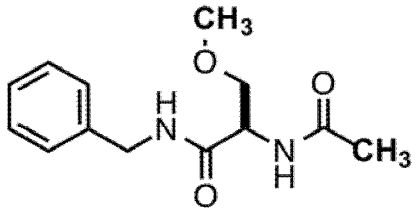


B. The Differences Between the Prior Art and Claims

153. In addition to anticipating claims 1-13 of the '551 patent, the same disclosures of the LeGall thesis described above make claims 1-13 of the '551 patent obvious in view of other prior art.

1. Claims 1 and 3-8 of the '551 Patent Would Have Been Obvious in View of the LeGall Thesis and Other Prior Art

154. As set forth above, Claims 1 and 3-8 of the '551 patent are claims directed to chemical compounds that include lacosamide. Lacosamide is the R enantiomer in racemic compound 107e in the LeGall thesis.



R-enantiomer of 107e
lacosamide

a. A POSA Would Understand that the LeGall Thesis Discloses Racemic Lacosamide, a 50/50 Mixture of Lacosamide and its S Enantiomer

155. The LeGall thesis identifies the synthesis of compound 107e as a "racemate … rather than the individual enantiomers."[164] Racemic compound 107e is a 50/50 mixture of the R-enantiomer lacosamide and an S-enantiomer. As described above in ¶37, claims 1 and 3-8 cover compounds in which the R-enantiomer is present in any amount in an enantiomeric mixture. Therefore, because the racemate 107e of the LeGall thesis contains 50% of the R-enantiomer (lacosamide), the LeGall thesis discloses lacosamide, a species of the compounds claimed by claims 1 and 3-7, and the compound specifically covered by claim 8. Other prior art confirms that a POSA would understand that compound 107(e) is a racemic mixture made up of half R stereoisomer (lacosamide) and half S stereoisomer. For example, the '729 patent, which covers compound 107e (see ¶140), recognizes that "[t]he compounds of the present invention are either the L-stereoisomer or the D-stereoisomer," and "may be found in mixtures of the L and D [or S and R] stereoisomer, e.g., racemic mixtures."[165]

[164] Ex. 1005 at 135.

[165] Ex. 1008, col. 10:22-28. The '729 patent also notes that "[i]t is well known in the art that the configuration around a chiral carbon … can also be described as R or S." *Id.* at 9:61-63.

b. A POSA Would Have Been Motivated to Select the Lacosamide Structure Disclosed in the LeGall Thesis as an Anticonvulsant Compound with a Reasonable Expectation of Success

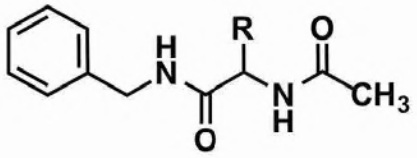
156. Not only does the LeGall thesis disclose racemic lacosamide (107e), it discloses *why* a POSA would be motivated to make and use the compound with a reasonable expectation of success. The structural analogy of compound 107e with another compound he identified to have good anticonvulsant activity led LeGall to believe that compound 107e "may have good anticonvulsant activity."[166] This would have motivated a POSA to make and use compound 107e of the LeGall thesis as an anticonvulsant compound that could be used to treat epilepsy and other central nervous system disorders. The reasonable expectation of success is demonstrated by LeGall's expectation that compound 107e would have "good anticonvulsant activity" based on its "close structural analogy" to another compound with anticonvulsant activity.[167]

157. The additional prior art confirms that a POSA would have been motivated to use the lacosamide structure identified in the LeGall thesis as an anticonvulsant compound. A POSA would be aware of the key structure-activity relationships of the class of compounds including lacosamide from the prior art.

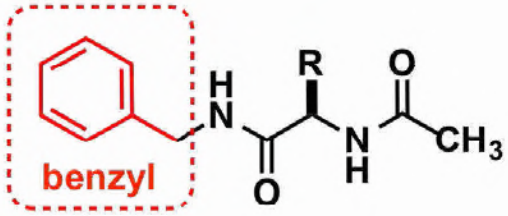
[166] Ex. 1005 at 155.

[167] *Id.*

158. First, a POSA would have been aware that the most promising compounds identified by Kohn and others in the prior art shared the following structure:



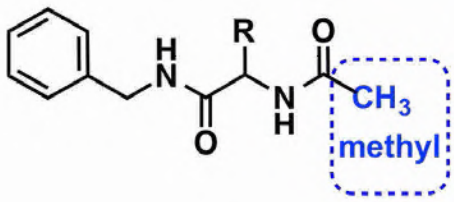
159. Kohn and coworkers direct a POSA to the above structure by the preferences that they identify after investigating the structure-activity relationships of the series of compounds. For example, Kohn and his collaborators identified a preference for "especially benzyl" as the substituent on one end of the amino chain:[168]



160. On the other end of the chain, the "most preferred" substitution of the acyl group is "methyl":[169]

[168] Ex. 1008, col. 5:17-18.

[169] *Id.* at 5:19; Ex. 1024 at 5:16.



161. Furthermore, Kohn and his collaborators also identified that it is "preferred that one of" the substituents on the α-carbon "is hydrogen,"[170] which leaves R (as represented above) at the α-carbon as the only variable.

162. That a POSA would have identified the above structure as promising is evidenced by the most promising compounds identified by Kohn and coworkers in prior art publications. After identifying AAB (R = methyl) as "among the most active compounds observed" with anticonvulsant activity,[171] Kohn and coworkers identified AAB as a "parent compound" from which "structural analogs" were made.[172] Upon further investigation, Kohn and coworkers identified APB (R = phenyl) which they found to have "enhanced anticonvulsant activity" relative to AAB.[173] Thereafter, the LeGall thesis reports the preparation and evaluation of "derivatives of the potent anticonvulsant agent [APB] and [AAB]," finding two

[170] *See, e.g.*, Ex. 1008, col. 6:12; *see also* Ex. 1024 at 5:26.

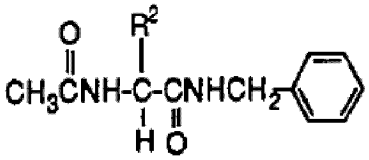
[171] Ex. 1009 at 601, abstr. (compound 6d).

[172] Ex. 1018 at vii, 26 (compound 30); Ex. 1017 at 568 abstr. (compound 1a).

[173] Ex. 1018 at 65-67 (compound 53c); Ex. 1017 at 571 (compound 1d).

derivatives (R = 2-furanyl, 2-pyrrolyl) that "were more potent than the parent" compound APB.[174]

163. Kohn 1991 is illustrative of how a POSA would have viewed the promise of the above structure. In Kohn 1991, Kohn and his coworkers continued to publish on additional derivatives using the structure and varying the R substituent. As a starting point, Kohn 1991 describes the above compounds, AAB, APB, the 2-pyrrolyl derivative, and the 2-furanyl derivative (compounds 2a-2d):[175]



2a $R^2 = CH_3$
b R^2 = Ph
c R^2 = 2-pyrrolyl
d R^2 = 2-furanyl

Kohn 1991 then describes "the synthesis and anticonvulsant properties of a novel series [26 compounds] of α-heteroatom-substituted amino acid derivatives."[176] These 26 compounds all share the above structure with various replacements for R (identified as R_2 in Kohn 1991). Kohn and coworkers reported that "[t]he most

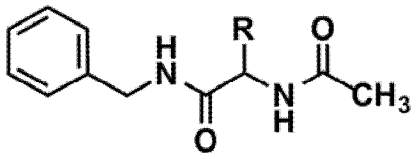
[174] Ex. 1005 at v, 103 (2-furanyl (compound 69a); 2-pyrrolyl (compound 69b); Ex. 1022 at 919 (2-furanyl (compound 2g); 2-pyrrolyl (compound 2i).

[175] Ex. 1010 at 2444.

[176] *Id.*

active compounds were [the methoxyamino derivative] (3l) and [the methoxymethylamino derivative] (3n),"[177] which had activity comparable with the 2-furanyl derivative.[178] These promising findings for the methoxyamino and methoxymethylamino derivatives "prompted [further] investigation of racemic N-substituted amino acid derivatives" all modified at the α-carbon substituent.[179]

164. Indeed, the compounds that Kohn published as having the most promising anticonvulsant activity and that prompted investigation of derivatives based on the same lead structure are shown in the table below:

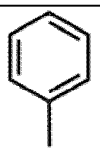
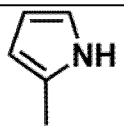
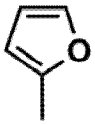
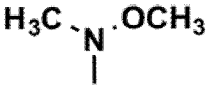


[177] *Id.* at 2444 abstr.

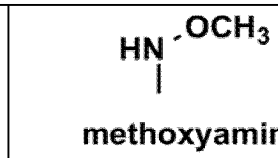
[178] *Id.* at 2447.

[179] Ex. 1026 at 689.

Table 1 – Compounds Of The Prior Art Kohn References

Prior Art Citation of Compound	R Substituent	Anticonvulsant Activity (ED_{50} mg/kg))[180] of Racemate (D,L)	Anticonvulsant Activity (ED_{50} (mg/kg)) of Stereoisomers
***N*-Acetyl-alanine-*N*-benzylamide (AAB) (Conley 1987 1a)**	 methyl	76.54	D- 54.80 (Kohn 1988) L- 548.37 (Kohn 1988)
N-Acetyl-phenylglycine-N-benzylamide (APB) (Kohn 1988)	 phenyl	32.1	D- 26.4 (Kohn 1988) L- > 300 (Kohn 1988)
2-pyrrolyl derivative (Kohn 1990 2i)	 2-pyrrolyl	16.1	[Not reported]
2-furanyl derivative (Kohn 1990 2g)	 2-furanyl	10.3	D- 3.3 (Kohn 1990) L- > 25 (Kohn 1990)
Methoxymethylamino derivative (Kohn 1991 3n)	 methoxymethylamino	6.7	[Not reported]

[180] Compounds with higher anticonvulsant efficacy have lower ED_{50}.

Methoxyamino derivative (Kohn 1991 3l)		6.2	[Not reported]

Of the compounds published by the Kohn studies summarized in Table 1, the racemic compound with the greatest anticonvulsive potency was the methoxyamino derivative 3l reported in Kohn 1991.

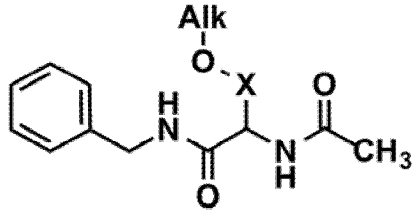
165. A POSA would have viewed the promise of compounds sharing the above structure favorably to other anticonvulsant compounds because of the anticonvulsant activity displayed by the series. Indeed, several analogs having the structure (2-furanyl, methoxyamino, methoxymethylamino) had favorable activity compared to phenytoin,[181] the most prescribed drug of the time for epilepsy.[182]

166. Based on the disclosures of the prior art, a POSA would have had a reasonable expectation that using a methoxymethyl substituent for R (as was used in compound 107e of the LeGall thesis) in the above structure would result in a compound with good anticonvulsant activity. A POSA would have understood

[181] Ex. 1005 at 103; Ex. 1022 at 922 abstr.; Ex. 1010 at 2444, 2445, Tbl. 1; Ex. 1034 at 4568.

[182] Ex. 1005 at 108 ("[P]henytoin is the most widely prescribed drug today for the treatment of epilepsies").

from the prior art that favorable activity occurs with an alkylated oxygen atom two atoms removed from the α-carbon atom:

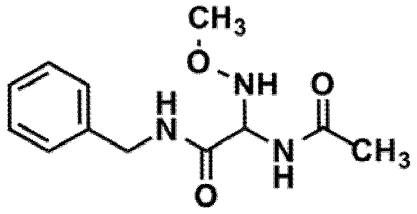


For example, Kohn 1991 teaches that "[i]mportantly, in the most potent analogues (2d, 3l, and 3n), a functionalized oxygen atom existed two atoms removed from the α-carbon atom"[183] and Kohn 1993 discloses additional derivatives which "provided support for [Kohn's] suggestion that increased anticonvulsant activity generally accompanied the placement of a substituted (alkylated) heteroatom two atoms removed from the amino acid α-carbon."[184]

167. A POSA would have known that the simplest alkylated oxygen atom is methoxy, where the "Alk" substituent above is methyl. Furthermore, a POSA would also have known that Kohn and his collaborators had identified the methoxyamino compound as the most active racemate:

[183] Ex. 1010 at 2447.

[184] Ex. 1025 at 3354; *see also* Ex. 1034 at 4568.



Kohn 1991 methoxyamino derivative (3l)

The methoxyamino compound has an oxygen atom two atoms removed from the α-carbon that is substituted with methyl, i.e., a methoxy group. In the methoxyamino compound, an amino group (-NH-) is substituted directly on the α-carbon (X in the general structure in ¶166).

168. A POSA would have had a reasonable expectation of maintaining activity with the substitution of methylene ($-CH_2-$) in place of the amino group (-NH-) for several reasons. Indeed, methylene ($-CH_2-$) and amino (-NH-) groups are classical isosteres that are generally known to be "interchangeable" and "produce broadly similar biological properties" when substituted for one another.[185]

169. More importantly, the prior art suggests that in the case of these particular amino acids, the substitution of methylene for amino would be expected to produce a compound with similar anticonvulsant activity. Kohn 1991 in and of itself illustrates this to a POSA. Kohn 1991 observes that the "α-amino …

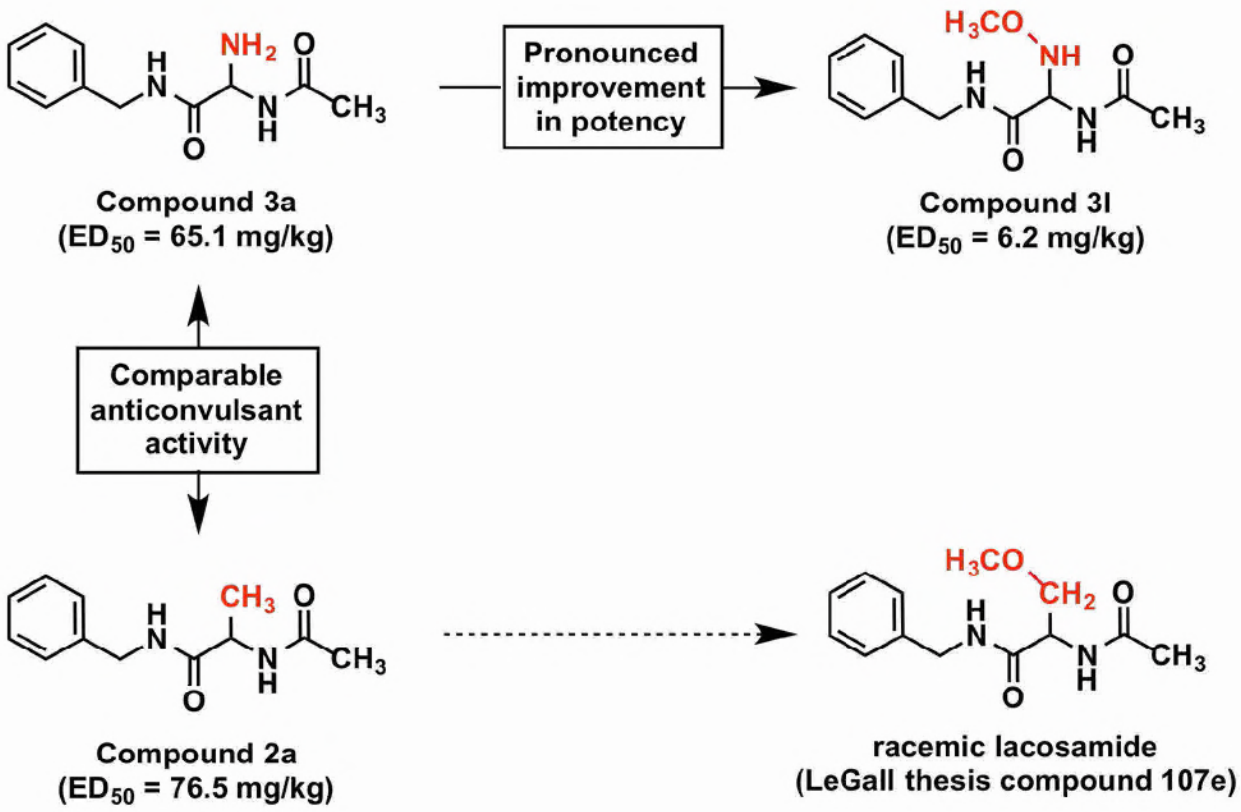
[185] Ex. 1028 at 30; Ex. 1029 at 19; Ex. 1027 at 563-64.

derivative[] … displayed anticonvulsant activit[y] comparable to that observed for the α-methyl analogue."[186]

170. The methoxyamino ($NHOCH_3$) compound, however, had an approximate *10-fold* increase in activity (ED_{50} of 6.2 vs. 65.1) relative to the unsubstituted amino (NH_2) compound.[187] A POSA likewise would have been motivated to substitute the methoxymethyl (CH_2OCH_3) for the methyl with a reasonable expectation that the compound, racemic lacosamide (compound 107e from the LeGall thesis) would also have promising anticonvulsant activity.

[186] Ex. 1010 at 2447; *see id.* at 2445 (Tbl. 1).

[187] *Id.* at 2445 (Tbl. 1).



171. A POSA would have had a reasonable expectation that compound 107e from the LeGall thesis, with its substitution of methoxymethyl for R (yielding lacosamide's structure), would have anticonvulsant activity consistent with LeGall's teaching that the structure "may have *good anticonvulsant activity*."[188] In addition, the '729 patent and its foreign counterpart applications and patents expressly teach that compounds within the formula disclosed—including the lacosamide structure—are useful anticonvulsant agents.[189] These patents disclose

[188] Ex. 1005 at 155 (emphasis added).

[189] *See, e.g.*, Ex. 1008. col. 1:30-35, cl. 132; Ex. 1003, cl. 47.

the use of these compounds, including lacosamide, as an anticonvulsant in the claimed methods of treating CNS disorders.[190] In addition, the expectation of success is further enhanced because the lacosamide structure employs *preferred* substituents of the formulas disclosed in the '729 patent.

172. Therefore, claims 1 and 3-8 of the '551 patent are obvious to a POSA in light of the LeGall thesis and other prior art.

2. Claims 2 and 9 of the '551 Patent Would Have Been Obvious in View of the LeGall Thesis and Other Prior Art

173. Claims 2 and 9 of the '551 patent place limits on enantiopurity of the R-enantiomer of the claimed compounds, including lacosamide. The only difference between compound 107e of the LeGall thesis and the requirements of claim 2 and 9 of the '551 patent is that compound 107e is a 50/50 racemic mixture of the R enantiomer (lacosamide) and the S enantiomer, whereas claims 2 and 9 require greater enantiopurity of the R enantiomer lacosamide. Claim 2 requires the R enantiomer to be "substantially enantiopure," whereas claim 9 requires "at least 90% (w/w) R stereoisomer."

174. The analysis set forth in ¶¶87-91 shows that a POSA would have been able to prepare lacosamide, i.e., the R enantiomer, in enantiopure form. In other

[190] Ex. 1008; Ex. 1003.

words, as discussed, the prior art enabled a POSA to obtain greater than 90% R stereoisomer lacosamide.

175. Furthermore, a POSA would have been motivated to isolate the pure R stereoisomer lacosamide, as demonstrated by the LeGall thesis itself. The LeGall thesis discloses that the D enantiomers (i.e., the R enantiomers) of similar racemic mixtures were actually tested and found to be more potent and less toxic than the corresponding L enantiomers (i.e., the S enantiomers). The LeGall thesis notes that "the D-enantiomer[191] of 68a [AAB] was 13 times more active than the L-isomer … [and that a] comparable difference in activity was also noted for two stereoisomers of" the phenyl derivative, APB (68b).[192] The LeGall thesis concludes that "[t]he recent finding that the D-enantiomers of 68a [AAB] and 68b [APB] were more active and less toxic than the corresponding racemates suggests that the D-enantiomer of [other promising derivative compounds prepared by LeGall] may display even improved pharmacological properties."[193] A POSA would have had a reasonable expectation that lacosamide, too, would have

[191] In this case, the D-enantiomer referred to corresponds to the R configuration, which a POSA would have known.

[192] Ex. 1005 at 42.

[193] *Id.* at 164-65.

improved pharmacological properties, including greater activity and less toxicity, and therefore would have been motivated to isolate the R enantiomer.

176. The prior art confirms the preference for the R stereoisomer of 107e. Indeed, the '729 patent, which covers the racemate 107e and lacosamide specifically, expressly states that "[t]he D stereoisomer is preferred."[194] Numerous other prior art references teach that, for compounds having the general structure of lacosamide, anticonvulsant activity resides primarily in the D stereoisomer. [195] Accordingly, a POSA would have been motivated to separate and evaluate the stereoisomers of 107e or otherwise isolate the D stereoisomer, which a POSA would expect to have the best activity.[196] As discussed, in the case of compound 107e of the LeGall thesis, the D stereoisomer (or R stereoisomer) is lacosamide.

177. Therefore, because a POSA would have been motivated to isolate the R stereoisomer of compound 107e of the LeGall thesis in enantiopure (i.e., pure R stereoisomer) form and would have been able to do so with a reasonable

[194] Ex. 1008, col. 10:27, *see also id.* at Tbl. 1.

[195] Ex. 1018 at viii (AAB & APB); Ex. 1019 at 234 (AAB & APB); Ex. 1020 at 12, Tbl. 1; Ex. 1021 at 371 (AAB & APB); Ex. 1022 at 919, 922, Tbl. III (furanyl derivative); Ex. 1023 at Tbl. 1; Ex. 1024 at Tbl. 1; Ex. 1010 at 2444; Ex. 1025 at 3352, Tbl. II, 3355 (Compound 30); Ex. 1005 at 42, 164-65.

[196] *See* Ex. 1018 at 111-13.

expectation of success, claims 2 and 9 are obvious over the LeGall thesis, either alone or in combination with other prior art.

3. Claim 10 of the '551 Patent Would Have Been Obvious in View of the LeGall Thesis and Other Prior Art

178. Claim 10 of the '551 patent claims a "therapeutic composition comprising an anticonvulsant effective amount" of the compounds claimed by claims 1-9 of the '551 patent, including lacosamide, "and a pharmaceutical carrier therefor."

179. The disclosures of the LeGall thesis described above in ¶¶96, 99 make obvious a therapeutic composition containing compound 107e and its R stereoisomer lacosamide. Even though the LeGall thesis did not actually report tests demonstrating the anticonvulsant activity of compound 107e, a POSA would have had a reasonable expectation that it would have such activity. The LeGall thesis expressly states that the compound "may have *good anticonvulsant activity*."[197] Therefore, a POSA would have been motivated to test compound 107e, as well as its R-stereoisomer (lacosamide), for anticonvulsant activity to identify "an anticonvulsive effective amount." FDA guidelines from 1994 disclose "[a] number of specific study designs … to assess dose-response," including for determining "the relationship of drug dosage[] or drug concentration" to both

[197] Ex. 1005 at 155 (emphasis added).

"clinical beneficial [and] undesirable effects."[198] Other prior art similarly explained how to conduct "dose-finding studies" for determining the effective amount of a drug.[199]

180. Furthermore, given that the purpose of LeGall's research was to study this "novel class of antiepileptic compounds,"[200] a POSA would have been motivated to include lacosamide in a therapeutic composition with a pharmaceutical carrier.[201]

181. The prior art as a whole confirms that a POSA would have been motivated to include compound 107e, and specifically its R stereoisomer lacosamide, in a therapeutic composition with a reasonable expectation of success. For example, the '729 patent explains that the genus of compounds including lacosamide "exhibit excellent anticonvulsant activity,"[202] and further teaches that "[t]he principal active ingredient is compounded for convenient and effective administration in effective amounts with a suitable pharmaceutically acceptable

[198] Ex. 1035, FDA, *Guideline for Industry: Dose-Response Information to Support Drug Registration* 9, 13 (Nov. 1994)

[199] *E.g.*, Ex. 1036, R. Schmidt, *Dose-Finding Studies in Clinical Drug Development*, 34 Eur. J. Clin. Pharmacol. 15-19 (1988).

[200] Ex. 1005 at 43.

[201] *See, e.g., id.* at 162.

[202] Ex. 1008,col. 16:5-8.

carrier."[203] A POSA would have been able to determine an anticonvulsant effective amount of compound 107e, and specifically lacosamide, through the routine tests on rodents described in the LeGall thesis, the '729 patent, throughout the prior art discussed above (*see* ¶¶102-140), and the '551 patent itself. [204]

182. Furthermore, a POSA would have known to use a "pharmaceutical carrier" in the therapeutic composition containing lacosamide. For example, the '729 patent discloses numerous "pharmaceutically acceptable carriers," including various "solvents, dispersion media, coatings, … absorption delaying agents, and the like,"[205] for formulating compounds including lacosamide into "tablets," "capsules, elixirs, suspensions, syrups"[206] or "for injectable use."[207] Indeed, the '729 patent recognizes that "[t]he use of such media and agents for pharmaceutical active substances is well known in the art."[208]

183. These disclosures are consistent with additional prior art references, each of which confirms that a POSA would have been motivated to formulate

[203] *Id.* at 18:12-16.

[204] Ex. 1001, col. 21:27-22:22.

[205] Ex. 1008, col. 17:53-58

[206] *Id.* at 16:33-37.

[207] *Id.* at col. 17:13.

[208] *Id.* at col. 17:56-58.

therapeutic compositions comprising anticonvulsant compounds that include lacosamide in an "anticonvulsant effective amount" with "a pharmaceutical carrier."[209]

184. Therefore, claim 10 is obvious in view of the LeGall thesis, either alone or in combination with other prior art, including the '729 patent.

4. Claims 11-13 of the '551 Patent Would Have Been Obvious in View of the LeGall Thesis and Other Prior Art

185. Claims 11-13 of the '551 patent claim a "method of treating central nervous system disorders in an animal comprising administering … an anticonvulsant effective amount" of the compounds of claims 1-9, including lacosamide. Claims 12 and 13 limit the animal to a mammal and to a human, respectively.

186. For the same reasons identified above in ¶¶179-181, a POSA would have been motivated with a reasonable expectation of success to administer an anticonvulsant effective amount of compound 107e of the LeGall thesis, and specifically its R stereoisomer lacosamide, to an animal, including a mammal or more specifically a human, in order to treat central nervous system disorders.

[209] *See, e.g.*, Ex. 1020 at 3:38-50, 5:30-32, 5:41-6:35, 6:45-46; Ex. 1023 at 2:2-10, 8:8-10, 8:19-9:27; Ex. 1024 at 3:2-12, 11:27-29, 11:38-12:43.

187. Other prior art confirms a POSA would have been motivated to use lacosamide to treat epilepsy—a "central nervous system disorder"—with a reasonable expectation of success. For example, the '729 patent explains that its covered compounds and compositions, including lacosamide, are "useful in the treatment of epilepsy and other CNS disorders."[210] Indeed, the '729 patent introduces its claimed invention by noting the "significant percentage of the population [i.e., humans] with epilepsy and related disorders"[211] and discloses the use of the compounds including lacosamide to treat "mammalian subjects."[212]

188. These disclosures are consistent with other prior art references that would further have motivated a POSA to administer "an anticonvulsant effective amount" of compounds that include lacosamide as part of a "method of treating central nervous system disorders."[213] Moreover, while the prior art does not specifically exemplify the use of such anticonvulsant compounds in humans, neither does the '551 patent. Because the '551 patent relies on screening tests

[210] Ex. 1008, col. 3:9-17.

[211] *Id.* at 3:1-4.

[212] *Id.* at 17:67.

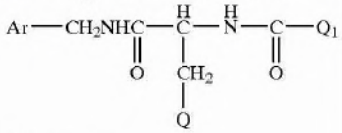
[213] *See, e.g.*, Ex. 1020 at 3:38-50, 5:30-32, 6:45-46; Ex. 1023 at 2:2-10, 3:18-21; 8:8-10; Ex. 1024 at 3:2-12, 4:25-28, 11:27-29.

performed on rodents to enable claim 13's method of treating humans, that claim is likewise enabled by the prior art, which discloses the same tests. [214]

189. Therefore, claims 11-13 are obvious in view of the LeGall thesis alone or in combination with other prior art including the '729 patent.

5. Claim Charts

190. To further evidence the obviousness of claims 1-13 of the '551 patent, I have prepared the following claim chart that charts the specific disclosures of the prior art that render these claims obvious.

'551 Patent Claims	Prior Art Reference Citations
1. A compound in the R configuration having the formula:  wherein Ar is phenyl which is unsubstituted or substituted with at least one halo group; Q is lower alkoxy, and Q_1 is methyl.	• Ex. 1005, LeGall thesis at v, vi, 42,45, 69, 102-04, 106, 108-09, 136-37, 153-55, 164-65, 279 • *Additional References for General Amino Acid Structure, Ar, and Q1:* ○ Ex. 1009, Cortes 1985 ○ Ex. 1017, Conley 1987 at 568-71 ○ Ex. 1018, Conley thesis at vii, 26, 65-67 ○ Ex. 1005, LeGall thesis at v, 103, 108 ○ Ex. 1022, Kohn 1990 at 919, 922 ○ Ex. 1026, Kohn 1994 at 689 ○ Ex. 1021, Kohn 1988 ○ Ex. 1034, Bardel 1994 at 4568 ○ Ex. 1008, '729 patent col. 5:14-19, 6:12 ○ Ex. 1024, '440 application at 5:15-16, 5:26

[214] Ex. 1001, col. 21:27-22:22.

	○ Ex. 1020, '464 application ○ Ex. 1010, Kohn 1991 at 2444, 2447, Tbl. 1 ○ Ex. 1019, Kohn & Conley 1988 at 234 • *Additional References For Selecting Methoxy At Q*: ○ Ex. 1010, Kohn 1991 at 2447, Tbl. 1 ○ Ex. 1025, Kohn 1993 at 3350, 3354 ○ Ex. 1034, Bardel 1994 at 4568 ○ Ex. 1028, W&G 1991 at 30 ○ Ex. 1029, Silverman 1992 at 19 ○ Ex. 1027, Thornber 1979 at 563, 564 Tbl. 1 ○ Ex. 1018, Conley thesis at vii, viii, 26, 65-69, 106, 111-13 ○ Ex. 1014, LeGall 1988 at 283 ○ Ex. 1022, Kohn 1990 at 919 ○ Ex. 1034, Bardel 1994 at 4567-68 ○ Ex. 1017, Conley 1987 at 567-72 ○ Ex. 1026, Kohn 1994 ○ Ex. 1021, Kohn 1988 at 371-72, 374

2. The compound according to claim 1 which is substantially enantiopure.	• Same as Claim 1 • *R (or D) Configuration References*: ○ Ex. 1005, LeGall thesis at 137 ○ Ex. 1018, Conley thesis at viii, 111-13 ○ Ex. 1019, Kohn & Conley 1988 at 234 ○ Ex. 1020, '464 application at 3:12, 14-19, Tbl. 1 ○ Ex. 1021, Kohn 1988 at 371-74 ○ Ex. 1022, Kohn 1990 at 919, 922, Tbl. III ○ Ex. 1023, '506 application at Tbl. 1 ○ Ex. 1024, '440 application at Tbl. 1 ○ Ex. 1010, Kohn 1991 at 2444 ○ Ex. 1008, '729 patent col. 10:27, Tbl. 1 ○ Ex. 1025, Kohn 1993 at 3352, Tbl. II, 3350-55 ○ Ex. 1032, Axelsson 1994 at 807, 809 (cmpd. 16), 812, 815 n.21 ○ Ex. 1030, Amoroso 1992 at 1085, 1087 ○ Ex. 1031, Cerrini 1993 at 283, 288 ○ Ex. 1033, Keil 1995 at 1259, Tbl.
3. The compound according to claim 1 wherein Q is lower alkoxy containing 1-3 carbon atoms.	Same as Claim 1
4. The compound according to claim 3 wherein Q is methoxy.	Same as Claim 1
5. The compound according to claim 1 wherein Ar is unsubstituted phenyl.	Same as Claim 1

6. The compound according to claim 1 wherein halo is fluoro.	Same as Claim 1
7. The compound according to claim 1 wherein Q is alkoxy containing 1-3 carbon atoms and Ar is unsubstituted phenyl.	Same as Claim 1
8. The compound according to claim 1 which is (R)-N-Benzyl 2-Acetamido-3-methoxypropionamide.	Same as Claim 1
9. The compound according to claim 8 which contains at least 90% (w/w) R stereoisomer.	Same as Claim 2
10. (element 1) A therapeutic composition comprising an anticonvulsant effective amount of a compound according to any one of claims 1-9	• Same as Claims 1 and 2 • Ex. 1020, '464 application at 3:38-50, 5:30-32, 6:45-46 • Ex. 1023, '506 application at 2:2-10, 3:18-21, 8:8-10 • Ex. 1024, '440 application at 3:2-12, 4:25-28, 11:27-29 • Ex. 1008, '729 patent col. 1:30-2:20, col. 3:35-39, col. 16:5-9, col. 18:12-15 • Ex. 1003, '301 patent col. 3:31-36, col. 18:33-37, col. 20:31-35, cl. 46 • Ex. 1035, FDA Dose-Response Guidance at 9, 13 • Ex. 1036, Schmidt 1988 at 15-19

10. (element 2) and a pharmaceutical carrier therefor.	• Ex. 1020, '464 application at 5:41-6:35; • Ex. 1023, '506 application at 8:19-9:27; • Ex. 1024, '440 application at 11:38-12:43; • Ex. 1008, '729 patent col. 17:53-58; • Ex. 1003, '301 patent col. 20:8-13; and • A person of ordinary skill in the art would, as a matter of routine, include an appropriate pharmaceutical carrier in the therapeutic composition.
11. A method of treating central nervous system disorders in an animal comprising administering to said animal in need thereof an anticonvulsant effective amount of a compound according to any one of claims 1-9.	• Same as Claims 1 and 2 • Ex. 1020, '464 application at 3:38-50, 5:30-32, 6:45-46; • Ex. 1023, '506 application at 2:2-10, 3:18-21, 8:8-10; • Ex. 1024, '440 application at 3:2-12, 4:25-28, 11:27-29; • Ex. 1008, '729 patent col. 1:30-2:20, col. 3:35-39, col. 16:5-9, col. 18:12-15; • Ex. 1003, '301 patent col. 3:31-36; col. 20:31-35; cl. 47. • Ex. 1035, FDA Dose-Response Guidance at 9, 13 • Ex. 1036, Schmidt 1988 at 15-19
12. The method according to claim 11 wherein the animal is a mammal.	Same as Claim 11
13. The method according to claim 12 wherein the mammal is a human.	Same as Claim 11

C. The Level of Ordinary Skill in the Art

191. In Section III.A, I gave my opinion on the POSA. I have considered the analysis of the obviousness of the claims of the '551 patent from the perspective of that POSA.

D. Secondary Considerations or Objective Indicia of Nonobviousness

192. I am not currently aware of any objective indicia that the claims of the '551 patent are not obvious.

193. In fact, I understand that many of the secondary considerations, such as commercial success and long-felt unmet need, are not probative of nonobviousness because a POSA would have been legally precluded from developing lacosamide as of the relevant priority date. Indeed, the '729 patent, issued on January 3, 1995, has claims covering lacosamide, and therefore would have legally precluded a POSA from developing the obvious compound as of the earliest claimed priority date, March 15, 1996.

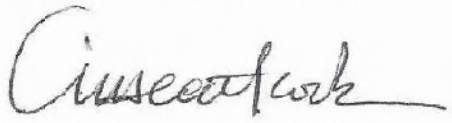
194. If the owners of the '551 patent offer any evidence they plan to rely upon for objective indicia of nonobviousness, I reserve the right to respond to that evidence.

X. CONCLUSION

195. In light of the foregoing, it is my opinion that claims 1-13 of the '551 patent were anticipated and made obvious by the prior art.

I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true. I further declare that these statements were made with the knowledge that willful false statements are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Respectfully submitted,

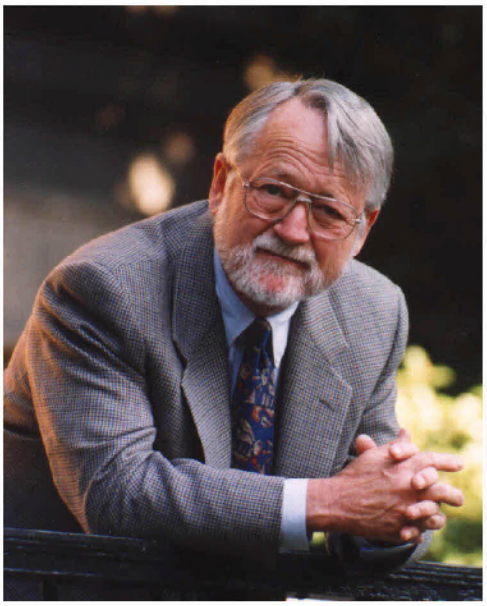


Clayton H. Heathcock

Dated: July 10, 2014

APPENDIX A

CLAYTON H. HEATHCOCK
Curriculum vitae



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education

San Antonio Public Schools, graduated from Brackenridge High School, 1954
Abilene Christian College; Abilene, TX; B.S., 1958
University of Colorado; Boulder, CO; Ph.D., 1963
Columbia University; New York City; Postdoctoral Fellow, 1963-64

Professional history

Champion Paper & Fibre Company, Pasadena, TX; Supervisor, Chemical Tests, 1958-60
University of California; Berkeley, CA; Assistant Professor, 1964-70; Associate Professor, 1970-75; Professor, 1975-2004
Vice-Chairman, 1972-77; Chairman, 1986-89; Dean, College of Chemistry, 1999-2005, Interim Dean, 2008; Gilbert Newton Lewis Professor, 2003-05; Chief Scientist, QB3 Berkeley, California Institute for Quantitative Biosciences, 2005-2008; Miller Research Professor, 1982-83, 1991-92; Emeritus Professor, 2005-present
Merck, Sharp & Dohme, Rahway, NJ; Consultant, 1968-78
Abbott Laboratories, Abbott Park, IL; Scientific Advisory Committee, 1986-1997
Medicinal Chemistry A Study Section (NIH); Member, 1979-81; Chair, 1981-83
Organic Chemistry Division of the American Chemical Society; Executive Committee, 1976-79, 1984-86; Chair, 1985
Organic Syntheses Editorial Board, 1980-88; Editor-in-Chief, 1986; Board of Directors, 1992-present
Chair, 1986 Gordon Conference on Stereochemistry
Editor-in-Chief, *Journal of Organic Chemistry*, 1989-1999
Chair, Chemistry Division, American Association for the Advancement of Science, 2000
Plexxikon, Scientific Advisory Board, 2002-2011

honors

National Science Foundation Predoctoral and Postdoctoral Fellow, 1961-64
Alfred P. Sloan Foundation Fellow, 1967-69
Humboldt United States Senior Scientist Award, 1978
Miller Research Professor, UC Berkeley, 1982-83, 1991-92
Ernest Guenther Award, American Chemical Society, 1986
Award for Creative Work in Synthetic Organic Chemistry, American Chemical Society, 1990
A. C. Cope Scholar Award, American Chemical Society, 1990
Prelog Medal, ETH, 1991
Fellow of the American Academy of Arts and Sciences, 1991
Pfizer Award in Synthetic Organic Chemistry, 1993
Fellow of the National Academy of Sciences, 1995
Centenary Medal, Royal Society of Chemistry, 1996
H. C. Brown Award, American Chemical Society, 2002
Paul Gassman Award for Distinguished Service, American Chemical Society, 2004
Fellow of the American Chemical Society (Inaugural Class), 2009

lectureships

Georgia Institute of Technology, DuPont Visiting Professor, 1975
University of Idaho, ITT Rayonier Lecturer, 1976
Rutgers University, Martin Friedman Lecturer, 1977
Emory University, Timmie Lecturer, 1978
University of New Hampshire, Iddles Lecture, 1982
University of Colorado, Liebig Lecture, 1982
University of Montreal, Merck Lecture, 1982
Texas Christian University, Dow Lecturer, 1983
University of Notre Dame, 1985 Reilly Lecturer
Yale University, Bergmann Lecturer, 1987
Greater Manchester Lectureship, University of Salford, 1987
Hope College, 1988 Parke-Davis Lecturer
Swiss Federal Institute of Technology, 1991 Prelog Lecturer
Massachusetts Institute of Technology, 1992 George Büchi Lecturer
University of Virginia; 1992 Robert Lutz Lecturer
Nottingham University 1992 SmithKline Beecham Lecturer
University of Rochester, Victor Chambers Lecturer, 1993
University of Illinois, 1994 C. S. Marvell Lectureship
University of Nebraska, Phi Lamda Upsilon, *Rho* Chapter Lectureship Award, 1995
University of Michigan, Warner-Lambert Lectureship, 1995
Royal Society of Chemistry Centenary Lecture, Edinburgh, Scotland, 1996
University of Sherbrooke, Bio-Mega/Boehringer Ingelheim Lecture, 1997
R. W. Johnson Research Institute, 1997 PRI Chemistry Lecture, 1997
Texas A&M, Frontiers in Science Lectures, 1997
University of Sydney & University of New South Wales, 1998 Howard Lectures
Kansas University, 50th Frank Burnett Dains Memorial Lecture, 1998
Texas Tech University, 1st Henry Shine Lecture, 1999
Ohio State University, Mack Memorial Award Lecture, 2000
University of Puerto Rico, Pfizer Lecture, 2000
University of California, Davis, R. B. Miller Memorial Lecturer, 2001
University of Texas, Mahler Lecture, 2002
Nagoya University, Hirata Memorial Symposium, 2002
A. I. Meyers Memorial Symposium, 2008
Presiding Officer, 100th Anniversary Symposium of the Organic Chemistry Division of the ACS, 2008

research interests

Total synthesis of natural products, biomimetic synthesis, development of new synthetic methods, acyclic stereocontrol

publications

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