UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AQUESTIVE THERAPEUTICS, INC.

Petitioner

v.

IONO PHARMA, LLC

Patent Owner

IPR2025-00874

U.S. Patent No. 11,021,437 B2

DECLARATION OF JARKKO RAUTIO, PH.D.

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I, Jarkko Rautio, Ph.D., do hereby make the following declaration:

AGREEMENT TO PROVIDE EXPERT TESTIMONY

1. I have agreed to provide expert testimony in support of Aquestive Therapeutics, Inc.´s ("Aquestive's") Petition for *Inter Partes* Review of U.S. Patent No. 11,021,437 B2. My *Curriculum Vitae* is attached hereto as Appendix A. My publications are attached as Appendix B.

2. I understand that this proceeding involves U.S. Patent No. 11,021,437 B2 ("Almoazen" or "the '437 Patent"), entitled "Pharmaceutical formulation for sublingual or buccal delivery of epinephrine or a pro-drug thereof" (Exhibit 1001).

3. I have reviewed, among other things, the '437 Patent which has five (5) claims. The '437 Patent claims are directed to epinephrine prodrugs[1] formulated in a film for sublingual or buccal administration.

4. I have been asked to provide my opinion regarding whether a person of ordinary skill in the art (a "POSA") at the relevant time would have understood that certain prior art references, alone or in combination, disclose or teach each of

[1] Prodrugs are bioreversible derivatives of drug molecules that undergo an enzymatic and/or chemical transformation in vivo to release the active parent drug, which can then exert the desired pharmacological effect.

the elements recited in the claims of the ‘437 patent. I have also been asked to provide my opinion regarding whether a POSA would have been motivated or had reasons to modify and/or combine prior art references to arrive at the elements recited in the challenged claims 1-3 of the ‘437 Patent. In my opinion, the references discussed below disclose or teach each of the elements recited in claims 1-3, and a POSA would have had strong and compelling reasons to modify and/or combine the prior art to arrive at claims 1-3 of the ‘437 Patent.

SUMMARY OF MY OPINION THAT CLAIMS 1-3 OF THE ‘437 PATENT ARE OBVIOUS AND GROUNDS THEREFOR

5. Based on my review and analyses of the ‘437 Patent, its prosecution history, the relevant prior art, and other publicly available information, claims 1-3 are unpatentable under 35 U.S.C. § 103 as obvious over the combination of any of the following three (3) sets of references (“Grounds”). A POSA would have had compelling reasons and would have been motivated to modify and/or combine the references identified in Grounds 1-3, and based on the reference’s disclosures would have arrived at the compounds formulated as a pharmaceutical composition in a unit dosage form configured for sublingual or buccal administration as recited in claims 1-3 of the ‘437 Patent.

6. As summarized below, Grounds 1-3 disclose all the material elements found in the '437 Patent claims 1-3, namely: (i) the recited prodrug compound and their associated half-lives ($t_{1/2}$) ranging from 1-6 minutes; (ii) the intrinsic log P value for these compounds (only claim 1); and (iii) the film containing the drug, *i.e.,* the unit dosage form, configured for sublingual or buccal administration in fast or rapidly dissolving films. Notwithstanding the foregoing, I rely on the actual words of the claims as properly construed for my opinion.

A. Ground 1 - Combination of Truelove 1 (Exhibit 1002), Ashraf (Exhibit 1003) and Almoazen Paper (Exhibit 1022)

1) First, U.S. Patent No. U.S. 3,809,714 (Exhibit 1002, "Truelove 1"), which though listed as a reference on the face of the '437 Patent, was never addressed by the Examiner, discloses several of the '437 Patent's claimed compounds, *i.e.,* ester prodrugs of epinephrine and their respective half-lives ($t_{1/2}$) of 1-6 minutes. (See, *e.g.,* ¶¶ 179 (Truelove 1 Relationship Chart), 180, below.)
2) Second, the publication by Ashraf and Sayeed entitled "Considerations in Developing Sublingual Tablets – An Overview" (Exhibit 1003, "Asraf") teaches that satisfactory absorption of drugs through oral mucosa has been

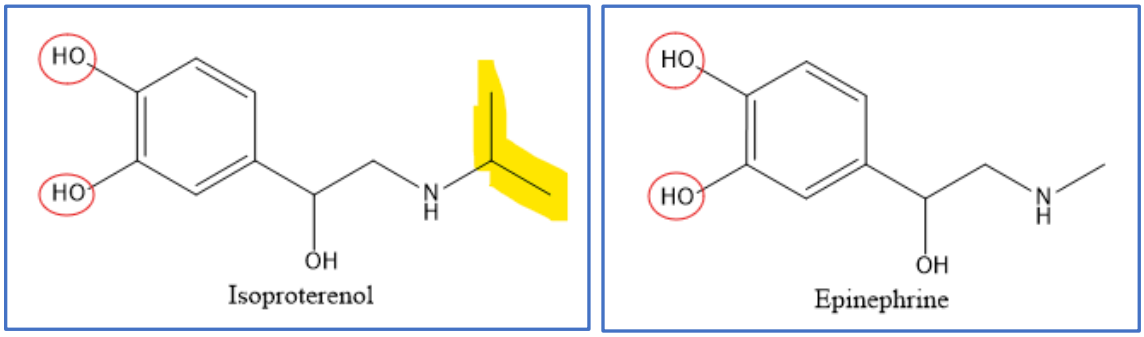
observed over a range of log P values of 1 to 5 (Exhibit 1003). Asraf also lists log P values of clinically used sublingually administered drugs which have log P values ranging between 0.94 and 4.9. (See ¶¶ 194-197, below.) The '437 Patent claims compounds having log P values in the range of about 0.5-6.0.

3) Third, the publication by Alayoubi, Haynes, Patil, Daihom, Helms & Almoazen entitled "Development of a fast dissolving film of epinephrine hydrochloride as a potential anaphylactic treatment for pediatrics" (Exhibit 1022, "Almoazen Paper"). The Almoazen Paper (Exhibit 1022) is not listed as a reference on the face of the '437 Patent. It discloses epinephrine in a unit dosage form configured for sublingual or buccal administration in rapidly or fast dissolving films, a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient. (See ¶¶ 181-193, below.)

B. Ground 2 - Combination of Truelove 3 (Exhibit 1008), Asraf (Exhibit 1003) and Almoazen Paper (Exhibit 1022)

1) First, Truelove 3 (Exhibit 1008) is not listed as a reference on the face of the '437 Patent. Truelove 3 discloses several of the '437 Patent's claimed ester promoieties used in forming its isoproterenol prodrugs and discloses their

respective half-lives ($t_{1/2}$) ranging from 1-6 minutes with the same ester promoieties as recited in challenged claims 1-3 of the '437 Patent. There is substantial structural similarity between the isoproterenol and epinephrine active drug compounds (molecules) and the position of the ester promoieties linked thereto, shown in circled -OH groups below. The difference in structures is highlighted in yellow.



(See, *e.g.*, ¶¶ 209 (Truelove 3 Relationship Chart), 210, below.)

Accordingly, a POSA would have readily expected that the half-lives ($t_{1/2}$) of epinephrine prodrugs recited in challenged claim 1-3 and the isoproterenol prodrugs of Truelove 3 would have been substantially the same, if not identical, because of the structural similarity between the isoproterenol and epinephrine molecules, the use of identical ester promoieties, and the positions of the promoieties on the active drug molecules. Thus, a POSA would have understood that Truelove 3 teaches the use of these ester moieties to form prodrugs and would have been motivated to use the

teachings of Truelove 3 with the active drug epinephrine to synthesize diester epinephrine prodrugs. Moreover, in view of the teachings of Truelove 3, a POSA would therefore have had a reasonable likelihood of success, without undue experimentation, of being able to achieve the compounds recited in the challenged claims and the claimed half-lives, *i.e.,* diester prodrugs of epinephrine and their respective half-lives ($t_{1/2}$) of 1-6 minutes. (See, *e.g.,* ¶¶ 215-217, below.)

2) Second, Ashraf (Exhibit 1003) teaches that satisfactory absorption of drugs through oral mucosa has been observed over a range of log P values of 1 to 5 (Exhibit 1003). Asraf also lists log P values of clinically used sublingually administered drugs which have log P values ranging between 0.94 and 4.9. (See ¶¶ 194-197, below.) The '437 Patent claims compounds having log P values in the range of about 0.5-6.0.

3) Third, the Almoazen Paper (Exhibit 1022) is <u>not</u> listed as a reference on the face of the '437 Patent. It discloses epinephrine in a unit dosage form configured for sublingual or buccal administration in rapidly or fast dissolving films, a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient. (See ¶¶ 181-193, below.)

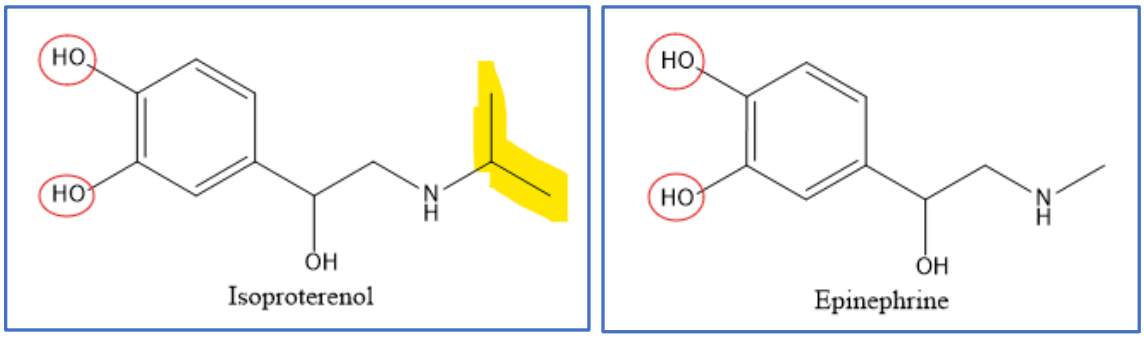
C. Ground 3 - Combination of Truelove 1 (Exhibit 1002), Truelove 3 (Exhibit 1008), Asraf (Exhibit 1003), Florence (Exhibit 1015), Fuchs (Exhibit 1004), Schobel (Exhibit 1021), and Almoazen Paper (Exhibit 1022)

Ground 3 combines the references of Grounds 1 and 2 with additional references, if for some reason, one or more of the Ground 1 and/or 2 references and/or their disclosures are challenged.

1) First, Truelove 1 (Exhibit 1002), which is listed as a reference on the face of the '437 Patent, was never addressed by the Examiner, discloses several of the '437 Patent's claimed ester promoieties used in forming prodrugs (see claims 1-3) and their respective half-lives ($t_{1/2}$) ranging from 1-6 minutes. A POSA would have understood that Truelove 1 teaches the use of these ester promoieties to form prodrugs and would have been motivated to use the teachings of Truelove 1 with the active drug epinephrine to synthesize diester epinephrine prodrugs. Moreover, in view of the teachings of Truelove 1, a POSA would therefore have had a reasonable likelihood of success, without undue experimentation, of being able to achieve the compounds recited in the challenged claims and the claimed half-lives, *i.e.,* diester prodrugs of epinephrine and their respective half-lives ($t_{1/2}$) of 1-6 minutes. (See, *e.g.,* ¶¶ 179 (Truelove 1 Relationship Chart), 180, below.)

2) Second, Truelove 3 (Exhibit 1008) is not listed as a reference on the face of

the ‘437 Patent. Truelove 3 discloses several of the ‘437 Patent’s claimed ester promoieties used in forming its isoproterenol prodrugs and discloses their respective half-lives ($t_{1/2}$) ranging from 1-6 minutes with the same ester promoieties as recited in challenged claims 1-3 of the ‘437 Patent. There is substantial structural similarity between the isoproterenol and epinephrine active drug compounds (molecules) and the position of the ester promoieties linked thereto, shown in circled -OH groups below. The difference in structures is highlighted in yellow.



Accordingly, a POSA would have readily expected that the half-lives ($t_{1/2}$) of epinephrine prodrugs recited in challenged claim 1-3 and the isoproterenol prodrugs of Truelove 3 would have been substantially the same, if not identical, because of the structural similarity between the isoproterenol and epinephrine molecules, the use of identical ester promoieties, and the positions of the promoieties on the active drug molecules. Thus, a POSA would have understood that Truelove 3 teaches the use of these ester

moieties to form prodrugs and would have been motivated to use the teachings of Truelove 3 with the active drug epinephrine to synthesize diester epinephrine prodrugs. Moreover, in view of the teachings of Truelove 3, a POSA would therefore have had a reasonable likelihood of success, without undue experimentation, of being able to achieve the compounds recited in the challenged claims and the claimed half-lives, *i.e.,* diester prodrugs of epinephrine and their respective half-lives ($t_{1/2}$) of 1-6 minutes. (See, *e.g.,* ¶¶ 209 (Truelove 3 Relationship Chart), 210, below.)

3) Third, Ashraf (Exhibit 1003) teaches that satisfactory absorption of drugs through oral mucosa has been observed over a range of log P values of 1 to 5 (Exhibit 1003). Asraf also lists log P values of clinically used sublingually administered drugs which have log P values ranging between 0.94 and 4.9. (See ¶¶ 194-197, below.). The '437 Patent claims compounds having log P values in the range of about 0.5-6.0. Florence (Exhibit 1015) discloses that ideal log P values for buccal cavity delivery range from 3.53 (dissociated) to 5.52 (undissociated).

4) Fourth, the Almoazen Paper (Exhibit 1022) is <u>not</u> listed as a reference on the face of the '437 Patent but discloses epinephrine in a unit dosage form configured for sublingual or buccal administration in rapidly or fast

dissolving films, a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient. (See ¶¶ 181-193, below.) Additionally, Fuchs (Exhibit 1004) discloses films which incorporate pharmaceutically active ingredients that can be administered mucosally. (See ¶¶ 198-201, below.) Moreover, Schobel (Exhibit 1021), which is not listed as a reference on the face of the '437 Patent, teaches the use and methods of making oral rapidly dissolving films for delivery of epinephrine compositions including epinephrine prodrugs to the oral mucosa. (See ¶¶ 234-240, below.)

EXHIBITS AND BASIS FOR OPINIONS GIVEN

7. In forming my opinion, I have relied on my own education, my professional and academic experience in the field of pharmacy, and specifically my experience related to prodrug design and development strategies, and my review of the following documents:

EXHIBIT NO.	EXHIBIT DESCRIPTION
1001	U.S. Patent No. 11,021,437 B2, entitled "Pharmaceutical Formulation For Sublingual Or Buccal Delivery Of Epinephrine Or A Pro - Drug Thereof", filed as application serial number 16/347,625 on November 9, 2017, Almoazen inventor, issued on June 1, 2021 ("the '437 Patent").

1002	U.S. Patent No. 3,809,714, entitled "Novel Ester Of [(Methylamino)Methyl] Benzyl Alcohol", Hussain and Truelove inventors, issued on May 7, 1974 ("the '714 Patent" or "Truelove 1").
1003	Ashraf M and Sayeed VA, "Considerations in Developing Sublingual Tablets – An Overview," *Pharmaceutical Technology* **38** (11) 2014 ("Asraf").
1004	U.S. Patent No. 4,136,145, entitled "Medicament Carriers In The Form Of Film Having Active Substance Incorporated Therein", Fuchs and Hilmann inventors, issued January 23, 1979 ("the '145 Patent" or "Fuchs").
1005	The Almoazen '437 Patent application prosecution history file for the '437 Patent, serial no. 16/347,625 ("the '437 FH" or "Almoazen File History").
1006	U.S. Patent No. 3,825,583, entitled "Ester Of 3-Hydroxy-α-[(Methylamino) Methyl]Benzyl Alcohol", Hussain and Truelove inventors, issued on July 23, 1974 ("the '583 Patent" or "Truelove 2").

1007	Hussain A and Truelove JE: "Prodrug Approaches to Enhancement of Physicochemical Properties of Drugs IV: Novel Epinephrine Prodrug", Journal of Pharmaceutical Sciences 65(10), 1976 ("Truelove Article" or "Truelove 4").
1008	U.S. Patent No. 3,868,461, entitled "Ester Of 3,4-Dihydroxy-Alpha (Isopropylamino) Methyl Benzyl Alcohol Composition And Anti-Asthma Use Thereof", Hussain and Truelove inventors, issued on February 25, 1975 ("the '461 Patent" or "Truelove 3").
1009	*The Merck Index*, 12th Ed., 1996, p. 613.
1011	USP certificate for epinephrine, dated 14 Aug 2017.
1012	The prescription information for the epinephrine used in the EpiPen.
1013	The Almoazen '437 Patent Provisional Application for Patent, serial no. 62,421,316, filed on November 13, 2016, Hassan Almoazen ("Almoazen Provisional Application").
1014	WO2018/089570 A1 (PCT/US2017/060761), entitled "Pharmaceutical Formulation For Sublingual Or Buccal

Delivery Of Epinephrine", Almoazen and Haynes, co-inventors ("Almoazen PCT Application").

1015 Florence AT and Attwood D, "Physicochemical Principles of Pharmacy", Fifth edition, Eds. Pharmaceutical Press (2011) ("Florence").

1016 U.S. Patent No. 4,145,441, entitled "Sympathomimetic Amines Exhibiting Anti-Hemorrhoidal Activity", Bodor inventor, issued March 20, 1979 ("the '441 Patent" or "Bodor").

1017 U.S. Patent Application Publication No. US 2007/0202163 A1, entitled "Fast-Disintegrating Epinephrine Tablets For Buccal Or Sublingual Administration", Rawas-Qalaji, *et al.,* inventors, published on August 30, 2007 ("Rawas-Qalaji").

1018 Ettmayer *et al.,* "Lessons Learned from Marketed and Investigational Prodrugs". Journal of Medicinal Chemistry 47(10), 2393-2404, 2004 ("Ettmayer").

1019 Rautio *et al.*, "Prodrugs: design and clinical applications". Nature Reviews Drug Discovery 7, 255-270, 2008 ("Rautio").

1020	Silverman RB., Chapter 8, "Prodrugs and drug delivery systems" in The Organic Chemistry of Drug Design and Drug Action. Academic Press, Inc. 1992 ("Silverman").
1021	U.S. Patent No. 11,191,737 B2, entitled "Enhanced Delivery Epinephrine Compositions", Schobel, *et al.* inventors, claiming benefit of provisional application No. 62/331,996, filed on May 5, 2016 ("Schobel").
1022	Alaadin Alayoubi, Lindsay Haynes, Hemlata Patil, Baher Daihom, Richard Helms & Hassan Almoazen (2016): "Development of a fast dissolving film of epinephrine hydrochloride as a potential anaphylactic treatment for pediatrics", Pharmaceutical Development and Technology, Early Online: 1-5, Published online 6 January 2016 ("Almoazen Paper").
1023	Baldessarini, *et al.,* "Hydrolysis of diester prodrugs of apomorphine", Biochemical Pharmacology. Vol. 26, pp. 1749-1756. Pergamon Press. 1977 ("Baldessarini").
1024	Kristoffersson, *et al.,* "Drug latentiation of terbutaline", Acta Pharm. Suecica 11, 427-438 (1974) ("Kristoffersson").

1025	Christrup, *et al.,* "Improvement of buccal delivery of morphine using the prodrug approach", Int J Pharma, 154, 1997, pp. 157-165 ("Christrup").
1029	Lieberman, *et al.,* "The diagnosis and management of anaphylaxis practice parameter: 2010 update", J Allergy Clin Immunol Sept. 2010 126(3):477-80.e1-42 ("Lieberman").
1030	Hansen, *et al.,* "Ketobemidone prodrugs for buccal delivery", Acta Pharm Nord, 3 (1991) 77-82 ("Hansen 1991").
1031	den Daas, et al., "Improvement of the oral bioavailability of the selective dopamine agonist N-0437 in rats: the in vitro and in vivo activity of eight ester prodrugs", Naunyn Schmiedeberg's Arch Pharmacol (1990) 341:186-91 ("den Daas").
1032	Hansen, *et al.,* "Ketobemidone prodrugs for buccal delivery: Prediction of the extent of saliva-catalyzed hydrolysis of various ester prodrugs under simulated in vivo condition", Int J Pharma, 88, 1992, pp. 229-235 ("Hansen 1992").
1033	A copy of the '437 Patent (Exhibit 1001) showing where material from the Almoazen Paper (Exhibit 1022) appears in highlighting.

1034	Roche, “Design of biopharmaceutical properties through prodrugs and analogs”, American Pharmaceut. Assoc., Washington, DC, 1977 (“Roche”).
1035	A copy of the Almoazen Paper (Exhibit 1022) highlighted to show where material from the Paper appears in the ‘437 Patent (Exhibit 1001).
1036	Morrison and Boyd, “Organic Chemistry”. 2nd Edition, Chapter Sections 18.1-18-4 (1970) (“Morrision and Boyd”).
1037	Streitwieser, et. al, “Introduction to Organic Chemistry”, 4th Edition, excerpts (1992) (“Streitweiser”).
1039	Stepensky, *et al.*, “Long-Term Stability Study of L-Adrenaline Injections: Kinetics of Sulfonation and Racemization Pathways of Drug Degradation”, J Pharm Sci 93:969–980 (2004) (“Stepensky”).
1040	Huttunen, K., Raunio, H., Rautio, J., “Prodrugs—from Serendipity to Rational Design”, *Pharmacol Rev* 63:750–771 (2011) (“Rautio II”).

1041	Senel & Hincal, "*Drug permeation enhancement via buccal route: possibilities and limitations*", J Contr Rel 72: 133-144, 2001("Senel").
1044	Kohn, et. al, "Clinical Comparison of Dipivalyl Epinephrine and Epinephrine in The Treatment Of Glaucoma", American Journal of Ophthalmology 87:196-201, 1979 ("Kohn").
1046	Journal of Medicinal Chemistry, "Manuscript Submission Requirements Checklist", https://researcher-resources.acs.org /publish/author_guidelines?coden=jmcmar#manuscript_submission_requirements_checklist, October 29, 2024 ("JMC Manuscript Requirements".

COMPENSATION

8. I am being compensated for my time at the rate of $330 per hour. My compensation is not contingent on the outcome of this proceeding.

QUALIFICATIONS AND EXPERIENCE

8. I am currently a Professor and Deputy Head of the School of Pharmacy at the University of Finland. I have been a full-time Professor since 2007 and in 2019 I became the Deputy Head of the School of Pharmacy.

9. I received my Ph.D. in Pharmaceutical Chemistry from the University of Kuopio in 2000 and in 2006 I earned the title of Docent (Associate Professor) in Pharmaceutical Chemistry from the same institution. Prior to receiving my Ph.D., I obtained my Licentiate in Pharmacy[2] in 1999 and my M.Sc. in Pharmacy in 1996.

10. My primary research interest is in the area of prodrug design and development. I have over two decades of experience in both industry and academia leading research teams regarding prodrug research and development. I have

[2] A Licentiate degree is a post-graduate, research degree above the master's degree and below the research doctoral degree.

received multiple grants for prodrug research. In these roles, I have led research teams in connection with the discovery and development of prodrugs, and this work included prodrug design and synthesis and *in vivo* and *in vitro* testing. Some of my work in industry includes consulting for GSK (formerly GlaxoSmithKline) and Novartis. Currently, my research is focused on prodrug methods for drug delivery and targeting.

11. I have also published in multiple peer-reviewed journals regarding original prodrug research. Additionally, I have several peer-reviewed reviews on prodrugs in journals such as *Nature Reviews in Drug Discovery, Chemical Society Reviews, Pharmacological Review* and *Advanced Drug Delivery Reviews*, as well as one edited book on prodrugs.

12. Of my more than 70 peer-reviewed research publications, 45 are directly related to prodrug research. I am the first author on 7 of these publications and the corresponding last author on 17 others. Throughout these projects, I have been deeply involved in designing study protocols and developing novel prodrugs. While much of the synthesis work has been performed by group members or collaborators, I personally synthesized the majority of prodrugs featured in my earliest publications, including those in my PhD dissertation.

13. The blend of academic and industrial experience has given me a comprehensive understanding of the prodrug field, from conceptual design to practical applications, helping to advance both the science and therapeutic utility of prodrugs.

14. I am a named inventor on several patents related to prodrugs. Additional information regarding my qualifications and background is outlined in my *Curriculum Vitae* and list of Publications attached as Appendices A and B, respectively.

RELEVANT CONSIDERATIONS

15. I am neither an attorney nor an expert in patent law. Nevertheless, I have been informed about certain legal standards and used my understanding of these standards to form my opinions and conclusions. My understanding of these standards is summarized here.

16. It is my understanding that a claimed invention is unpatentable if the differences between the invention and the prior art are such that the subject matter as a whole would have been obvious at the time the alleged invention was made to a person having ordinary skill in the art to which the subject matter pertains. It is my understanding that the obviousness analysis takes into account factual inquiries

including the level of a person of ordinary skill in the art, the scope and content of the prior art, and the differences between the prior art and the claimed subject matter.

17. It is my understanding that there are several accepted reasons for combining references or modifying a reference to demonstrate a patent claim would have been obvious to a POSA. Some of these rationales include the following: combining prior art elements according to known methods to yield predictable results; simple substitution of one known element for another to obtain predictable results; a predictable use of prior art elements according to their established functions; applying a known technique to a known device to yield predictable results; choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success; and some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.

18. It is my understanding that "a person of ordinary skill in the art", a "POSA", is not a specific, real individual, but rather a hypothetical individual or team of individuals working closely together, who is presumed to have known all relevant art at the time of the invention. In defining the POSA, I have been

informed to consider factors such as the educational level and years of experience, not only of the person or persons who have developed the invention that is the subject of the case, but also others working in the pertinent art at the time of the invention; the types of problems encountered in the art; the teachings of the prior art; patents and publications of other persons or companies; and the sophistication of the technology.

19. It is my understanding that claim terms are generally given their ordinary and customary meaning, and that when construing or interpreting patent claims, the ordinary and customary meaning of a claim term is what a POSA would have understood the term to mean at the time of the invention, *i.e.*, as of the effective filing date of the patent application. It is my understanding that the earliest possible effective filing date for the '437 Patent is no earlier than November 9, 2017, the filing of the Almoazen PCT Application (Exhibit 1014) as it provides the first disclosure of a half-life $t_{1/2}$ of 1-6 minutes, which is recited in challenged claims 1-3 of the 437 Patent. Nevertheless, my opinions, detailed below, would not change even if the effective date is November 13, 2016, the filing date of the Almoazen Provisional Application (Exhibit 1013).

20. It is my understanding that the proper construction of a patent claim can include consideration of the claim language itself, the patent's specification

(including, *e.g.*, documents incorporated by reference), other claims of the patent, and the patent's prosecution history, also referred to as the file history of the patent.

21. It is my understanding that the prosecution or file history of a patent is the record of all communications and documentations involved in the prosecution or patent examination process resulting in a patent.

THE PERSON OF ORDINARY SKILL IN THE ART ("POSA")

22. It is my understanding that the POSA is a hypothetical person considered to have normal skills and knowledge of all relevant prior art in the field to which the asserted patent relates at the time the invention was made, the effective filing date, though my opinions would not change if a different priority date were used.

23. I have assessed the level of ordinary skill in the art based upon my review of the '437 Patent, the prior art, and my own long standing career of working in the field prodrug discovery and development.

24. In my opinion, a POSA evaluating the '437 Patent and associated prior art would have had an advanced degree (*i.e.*, a Ph.D.) in fields relevant to drug design, such as pharmaceutical chemistry, medicinal chemistry, a medical degree, organic chemistry, or the equivalent, and at least 2-3 years of practical experience in the design of drugs. Alternatively, a POSA could have a lesser educational degree with

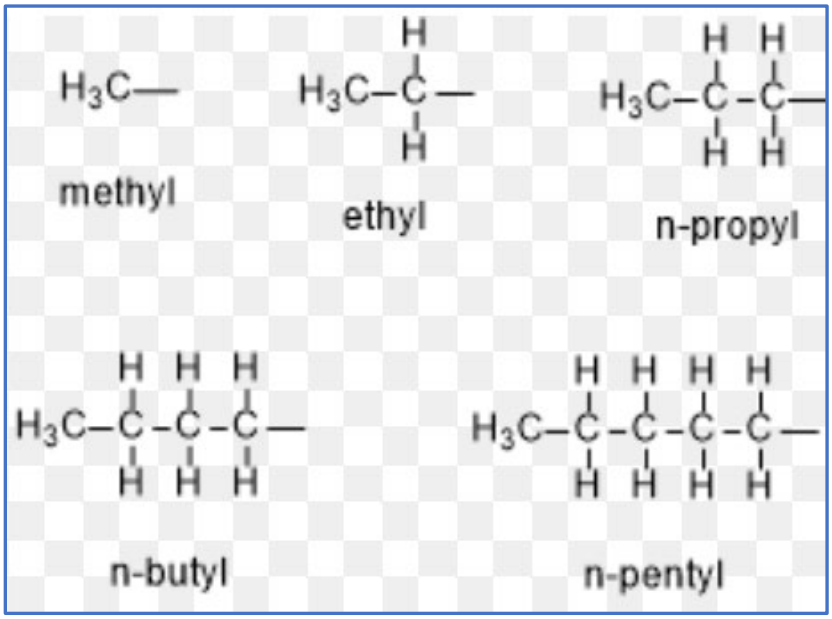
increased years (five to six years) of practical experience in research and development of pharmaceutical compounds. A POSA would have easily understood the prior-art references referred to herein and would have had the capability to draw reasonable inferences from those references. Such a person would have understood that the process relating to, *inter alia*, the development, design and testing of prodrugs requires a multidisciplinary approach. Accordingly, a POSA would have drawn upon not only his or her own expertise, but also could have also taken advantage of certain specialized skills of others, such as by consulting and collaborating with others, to solve any issues that develop in connection with the development, design and testing of prodrugs.

25. As of at least November 13, 2016 through today, I consider myself to be at least a POSA having the requisite education and experience as outlined above.

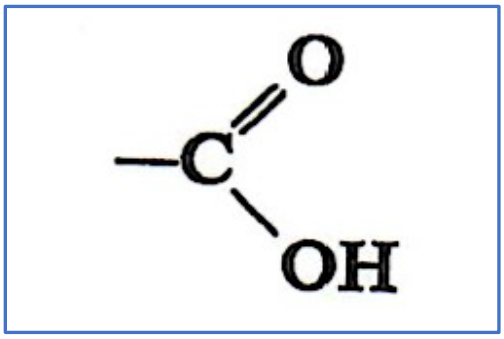
TERMINOLOGY AND TECHNOLOGY BACKGROUND

Terminology

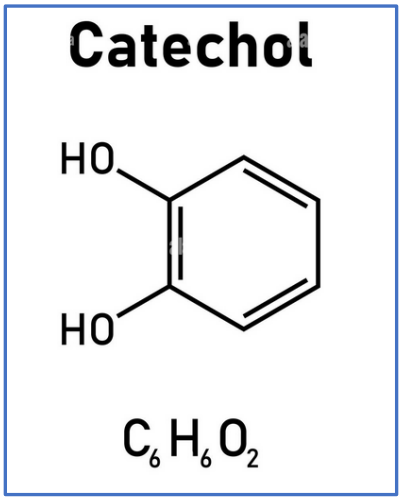
26. Alkyl Group, a chemical group have the structure C_nH_{2n+1}. Alkyls include methyl ($-CH_3$), ethyl ($-C_2H_5$), propyl ($-C_3H_7$), butyl ($-C_4H_9$), pentyl ($-C_5H_{11}$), and so on. For example:



27. Carboxyl groups: Carboxyl groups are a combination of two functional groups attached to a single carbon atom, namely, hydroxyl (single -OH) and carbonyl (=O), *i.e.,* -COOH, see structure below:



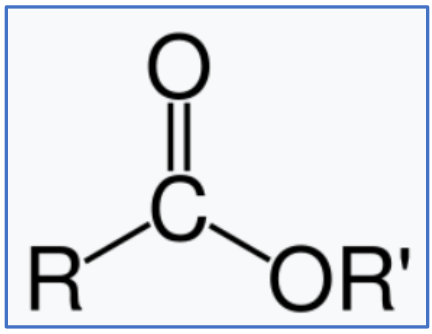
28. Catechol, a compound (1,2-dihydroxybenzene) comprising a benzene diol, see below.



29. ChemDraw® is a widely used software application designed for creating and editing chemical structures. I and others in the chemical field rely on ChemDraw® to, *inter alia,* accurately portray the structure and names of compounds. Key features of ChemDraw® include drawing chemical structures, calculating chemical properties of chemical structures, and generating systematic names for chemical structures (and vice versa). For example, the Journal of Medicinal Chemistry, one of the top peer-reviewed journals in medicinal chemistry, recommends using ChemDraw® for chemical structures in their Manuscript Submission Requirements Checklist (ChemDraw® with the ACS preferences selected is preferred). (See Exhibit 1046.) The structure-to-name and name-to-structure functionalities in ChemDraw® are highly reliable for most standard organic compounds. ChemDraw® follows IUPAC rules. IUPAC provides systematic rules for naming chemical compounds. Additionally, ChemDraw® can create structures from

chemical names that are not strictly IUPAC names. The software is capable of interpreting many common names, trade names, and abbreviations widely used in chemistry. The ChemDraw® molecule drawing program was used to generate the structures shown in my declaration.

30. Esters: a chemical moiety having the structure RCOOR′, see below, where R may be a hydrogen atom, an alkyl group, or an aryl group, and R′ may be an alkyl group or an aryl group but not a hydrogen atom. (If it were a hydrogen atom, the compound would be a carboxylic acid.)

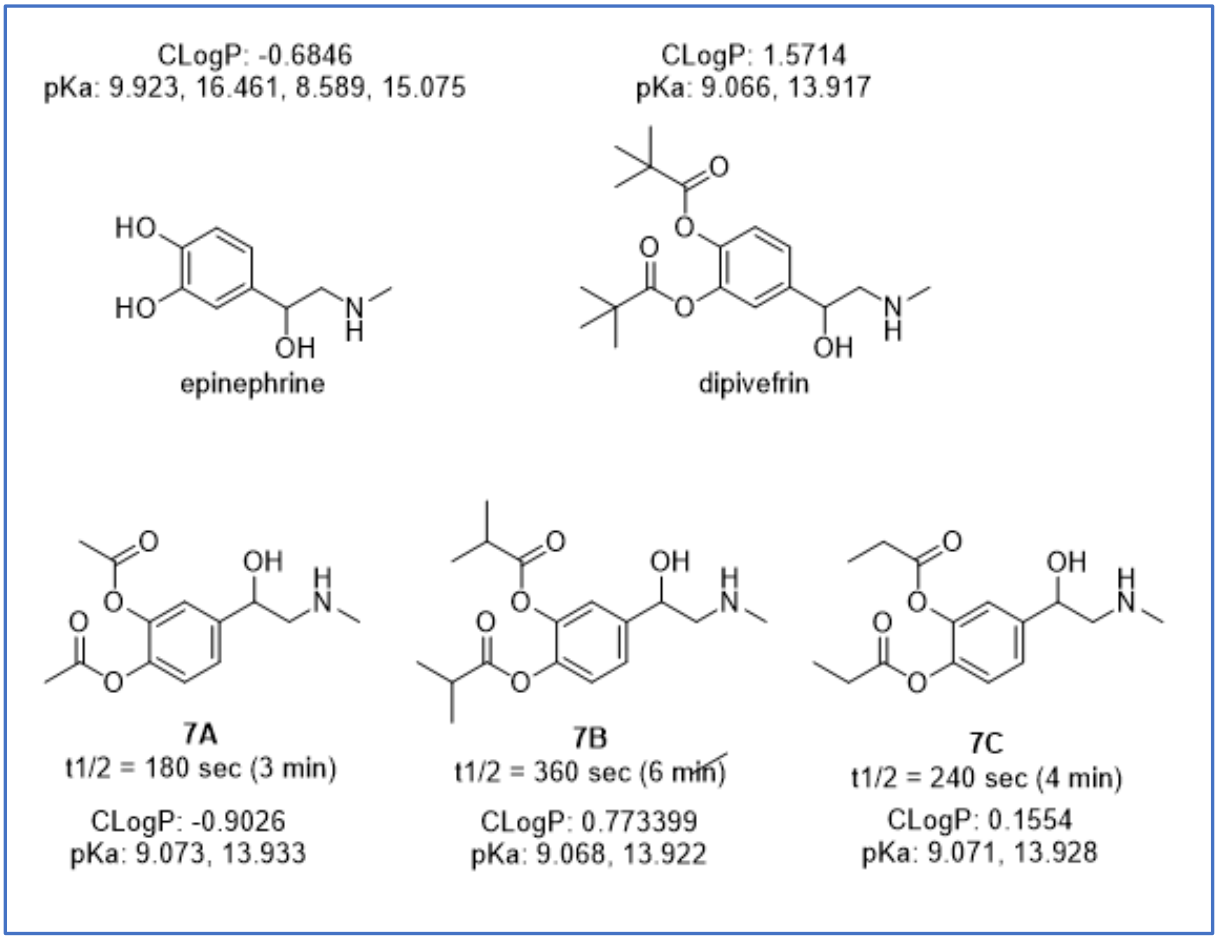


31. Enzymatic hydrolysis of diester prodrug of epinephrine, is the enzymatic cleavage of the ester groups to [re]form the parent drug, *e.g.,* epinephrine.

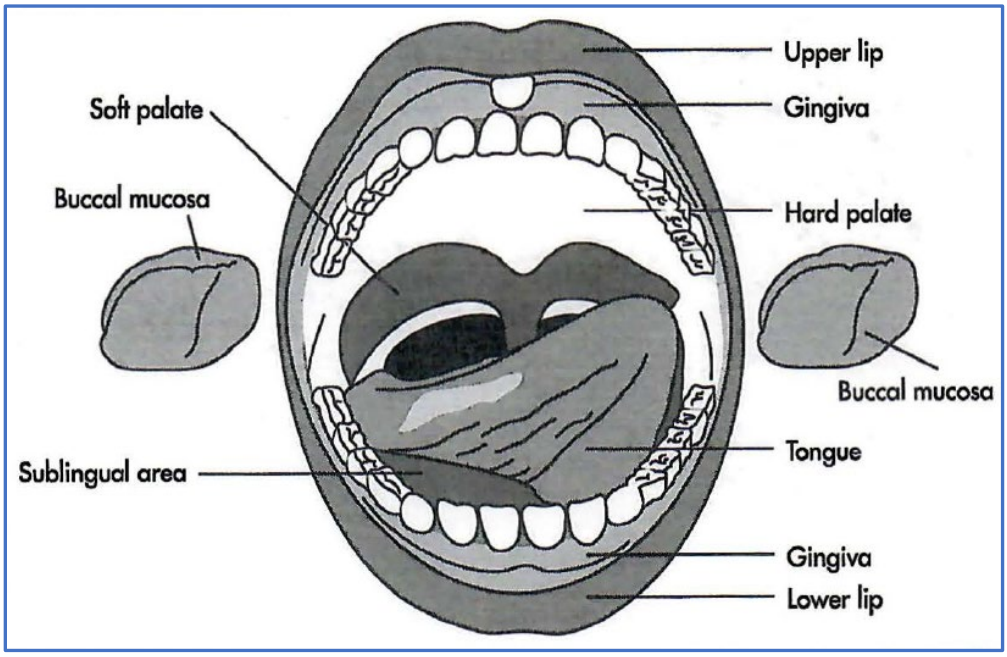
32. Lipophilicity, Log P, cLog P: Lipophilicity is the tendency of a compound to partition into a nonpolar lipid matrix rather than an aqueous matrix. A traditional method for assessing lipophilicity involves determining the partitioning of the compound between two immiscible nonpolar and polar liquid layers. Octanol is

commonly used as the nonpolar layer, while an aqueous buffer or water serves as the polar layer. The partition coefficient, P (typically expressed as its logarithmic value, log P), is calculated as the ratio of the concentration of the compound in the octanol phase to its concentration in the aqueous phase. A higher log P value indicates greater lipophilicity, meaning the compound has a higher tendency to dissolve in the lipid phase than in the aqueous phase. It is important to note that **P** represents the partition coefficient of the compound in its neutral form. In contrast, the **distribution coefficient** (D) takes into account both the ionic and neutral forms of the compound, providing a more comprehensive measure of how the compound distributes between the two phases under specific pH conditions. **cLogP** is a calculated version of the partition coefficient, where "c" denotes that the value is obtained through computational methods rather than experimental measurements. Several software programs are available to calculate cLogP, each using different algorithms and molecular descriptors. As a result, cLogP values can vary depending on the software used, reflecting differences in the underlying computational models and assumptions.

33. I obtained the following compound structures and their CLogP and pKa values shown below using ChemDraw®.



34. Oral Cavity: The oral cavity comprises the "buccal" (inside the cheeks) and "sublingual" (under the tongue) cavities, see below:



Florence, Exhibit 1015, Figure 9.15, p. 364.

35. Parent Drug: The parent drug is the pharmacologically active agent.

36. Prodrugs are bioreversible derivatives of pharmacologically active agents that require an enzymatic and/or chemical transformation in the body to release the active parent drug, which can then exert its desired pharmacological effect.

37. Promoiety: A functional group used to transiently modify the structure of pharmacologically active agents to improve physicochemical, biopharmaceutical or pharmacokinetic properties.

Technology Background

38. As discussed in the Terminology Section, prodrugs are bioreversible derivatives of pharmacologically active agents that require an enzymatic and/or chemical transformation in the body to release the active parent drug, which can then exert its desired pharmacological effect.

39. In a simplified representation of the prodrug concept, the drug-promoiety molecule serves as the prodrug, which is less pharmacologically active than the parent drug. A simplified illustration of the prodrug concept is illustrated in Figure 1 of Exhibit 1040, p. 751, copied below.

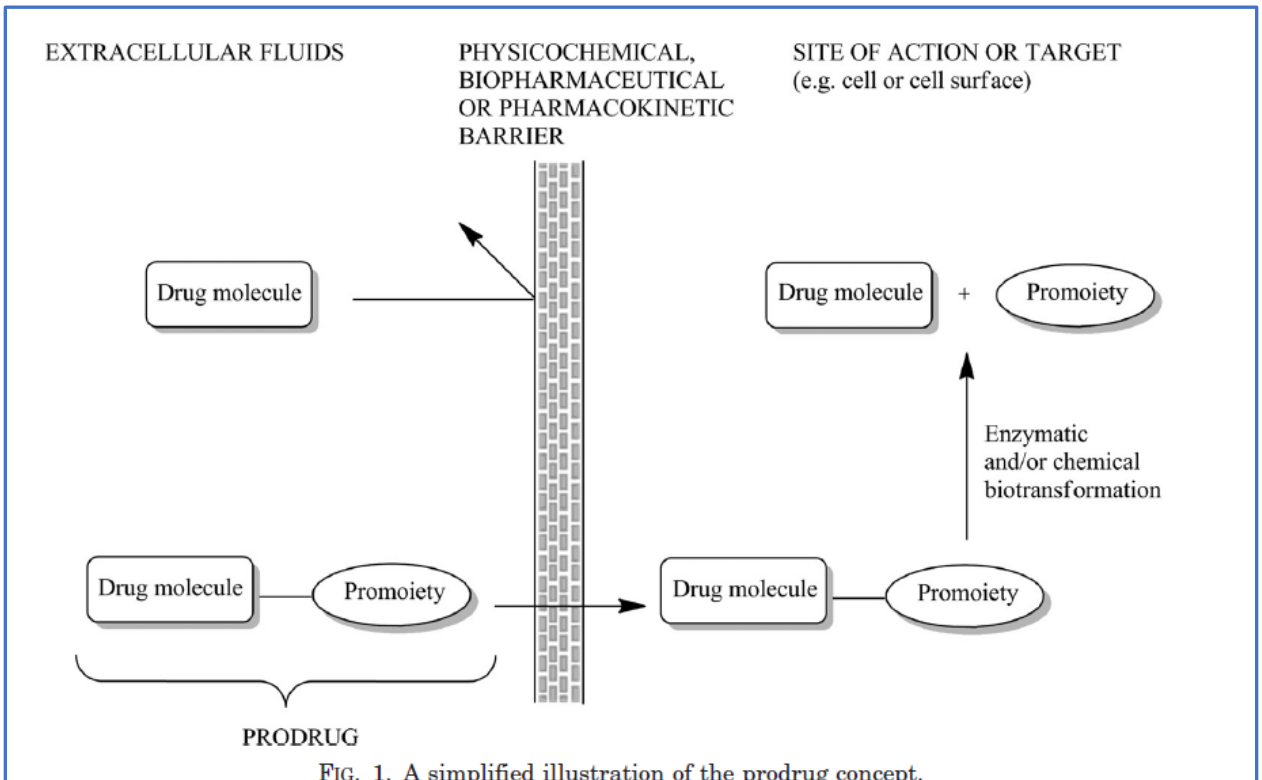


FIG. 1. A simplified illustration of the prodrug concept.

40. Prodrugs are a well-established concept used to overcome barriers to a drug's usefulness. They can be designed to address pharmaceutical, pharmacokinetic, or pharmacodynamic barriers such as poor chemical stability, low solubility, inadequate oral absorption, limited blood-brain barrier permeability, extensive presystemic metabolism, toxicity, and poor patient acceptability. *See*, *e.g.*, Exhibit 1018, Ettmayer, p. 2393 and Exhibit 1019, Rautio, p.255.

41. Intraoral drug delivery involves administering the drug directly into the oral cavity, typically sublingually, buccally or locally. Although the term buccal literally refers to administration to the mucosa of the cheek, the term is often used to describe all forms of intraoral drug delivery. (*See, e.g.,* Senel, Exhibit 1041, pp.133-136.)

42. Oral mucosal drug delivery offers several advantages, making it an attractive alternative to traditional methods like oral tablets or injections. Key benefits include **rapid absorption and onset of action, avoidance of first-pass metabolism,** and non-invasive administration, which **improves patient compliance.**

43. However, not all drugs are suitable for oral mucosal administration due to non-ideal physicochemical properties, such as poor lipophilicity. "For efficient absorption through the oral mucosa, the drug must be hydrophobic enough to

partition into the lipid bilayer, but not so hydrophobic such that once it is in the bilayer, it will not partition out again. Satisfactory oral absorption of drugs has been observed over a wide range of log P (octanol/water partition coefficient) values of 1 to 5."). (Asraf, Exhibit 1003, p. 35, 2nd col.) Similarly, from Florence and Attwood, the ideal log P values for buccal absorption typically fall within the range of 3.52 to 5.52. (*See*, *e.g.,* Florence and Attwood, Exhibit 1015, Table 9.1, p. 334.)

44. Prodrug strategies have successfully increased lipophilicity (higher log P values) and, consequently, enhanced the permeation of various drugs across the oral mucosa, enabling buccal/sublingual drug delivery. *See*, *e.g.*, Christrup, Exhibit 1025, discussed at ¶¶ 259-266, below, and Exhibit 1026, Hansen 1991, Exhibit 1030, discussed at ¶¶ 267-279, below.

45. Epinephrine, a catecholamine, is used to treat various conditions, such as anaphylaxis (with *l*-epinephrine being effective). Due to its high hydrophilicity (log P - 0.68) and poor lipophilicity,[3] epinephrine is poorly absorbed through the biological membranes like the oral mucosa. Epinephrine is also readily oxidized.

[3] '437 Patent, Exhibit 1001, 1:47.

Both hydrophilicity and susceptibility to oxidation are attributable to the two hydroxyl (catecholic) groups at positions 3 and 4 on the benzene ring.[4]

46. For a prodrug approach to be successful, a POSA considering sublingual or buccal administration of epinephrine would understand that to ensure rapid passage of epinephrine through the mucosal layer of the human mouth, it would be obvious to use a more lipophilic epinephrine prodrug to enhance its permeability through the mucosal layer.

47. The most common activation reaction for prodrugs is hydrolysis. (*See*, *e.g.*, Ettmayer, Exhibit 1018, p. 2394, Rautio, Exhibit 1019, p.256, and Silverman, Exhibit 1020, p. 355.) Further, the most common prodrug form for drugs containing alcohol functional group is an ester (Silverman, Exhibit 1020, p. 355.). This is due to several factors, which include: 1) esterases are ubiquitous, making the regeneration of the drug a straightforward process; 2) ester derivatives can be prepared with varying degrees of hydrophilicity or lipophilicity; and 3) ester stability can be readily modified by appropriate manipulation of electronic and steric factors (Silverman, Exhibit 1020, p. 355-356).

[4] For example of structure and representation of benzene ring see Exhibit 1036, pages from §§ 10.3 and 10.13.

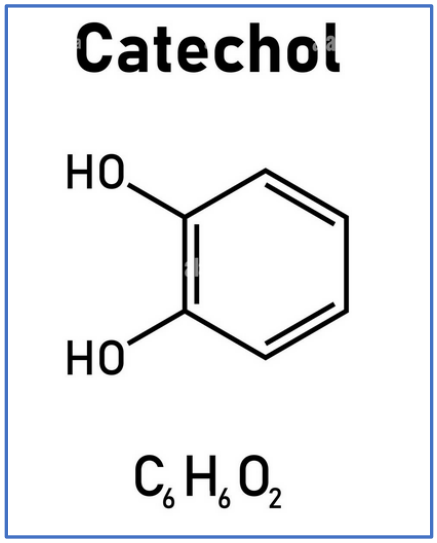
THE '437 PATENT (EXHIBIT 1001)

48. U.S. Patent No. 11,021,437 ("Almoazen" or "the '437 Patent"), entitled "*Pharmaceutical formulation for sublingual or buccal delivery of epinephrine or a pro-drug thereof*", issued on June 1, 2021, and claims priority to a provisional application filed on November 13, 2016. The '437 Patent has five (5) claims.

49. I have reviewed and considered the '437 Patent (Exhibit 1001) and its file history (Exhibit 1005) in view of the general knowledge in the relevant field measured from the relevant priority date for the '437 Patent from the perspective of a POSA as defined above. I have reviewed the '437 Patent, not for the purposes of using any hindsight in my analysis, but so that I could understand the nature of the alleged invention, the scope of the claims, and other matters relevant to my analysis.

50. The invention as stated the Almoazen '437 Patent is directed to the delivery of epinephrine, or an epinephrine prodrug administered sublingually or buccally via a rapidly dissolving film and relies on the prodrugs' modification of the physiochemical properties of epinephrine molecule to enhance as a way of enhancing the permeability through biological membranes. The Almoazen '437 Patent discloses that permeability can be increased by using a chemically modified catechol (1,2-dihydroxybenzene). Catechol (1,2-dihydroxybenzene) is shown

below.



The two hydroxyl (-OH) groups are chemically reacted to each form ester bonds with different alkyl groups. Notably, the addition of an alkyl group will enhance the lipophilicity of epinephrine (increase log P). (See Exhibit 1001, Abstract.)

51. The '437 Patent discloses its "rapidly dissolving film" as one made of a drug, a water-soluble polymer, a plasticizer, a saliva stimulating agent, a surfactant and other fillers.

> "The present invention further provides a pharmaceutical composition made of at least one compound or mixture of compounds of the invention in a pharmaceutically acceptable carrier thereof. The invention features a pharmaceutical composition in unit dosage form formulated for sublingual or buccal administration. The delivery systems include fast dissolving films, oral dissolving tablets, inhalation, and nasal delivery. In one embodiment, the unit

> dosage form of the present invention is a film for the delivery of epinephrine hydrochloride, as an anaphylactic treatment in a patient, such as for a pediatric or geriatric patient. A typical rapidly dissolving film is made of a drug, a water-soluble polymer, a plasticizer, a saliva stimulating agent, a surfactant and other fillers such as sweetening agents and flavors in case of bitter taste drugs. See e.g. A. Arya, A. Chandra, V. Sharma, and K. Pathak, "Fast dissolving oral films: An innovative drug delivery system and dosage form," *Int. ChemTech Res*., vol. 2, no. 1, pp. 576-583, 2010. D. P. Lettre, "Formulation and Evaluation of Rapidly Disintegrating Film of Levocetrizine Hydrochloride," *Pharmacia*, vol. 2, no. 2, pp. 208-220, 2010."

Almoazen, '437 Patent, Exhibit 1001, 7:19-39.

52. The '437 Patent disclosure is solely directed to epinephrine or a salt thereof, or an epinephrine prodrug or a salt thereof. "**For the present invention, the drug is epinephrine**, **a prodrug of epinephrine or a salt thereof. The typical dose of epinephrine for anaphylactic treatment is 0.3 to 0.5 mg in adults** and 0.01 mg/kg up to a maximum of 0.3 mg in children administered through intramuscular route." ('437 Patent, Exhibit 1001, 7:40-46 (emphasis supplied).)

53. The '437 Patent references epinephrine found in the EpiPen: "The administration of proper therapeutic agents, such as, epinephrine must be prompt. This is usually performed through the usage of auto-injectors such as EPIPEN …".

(Exhibit 1001, 1:50-53). The dose of epinephrine USP provided by the EpiPen is 0.3 mg, the same dose as disclosed for the '437 Patent's epinephrine. (See, e.g., Exhibit 1012, p. 1 of 19.)

54. Almoazen acknowledges that the Truelove 1 epinephrine diester compounds the '437 Patent discloses in its Figure 7 are also the diester epinephrine compounds of the '437 Patent present invention.[5] (Exhibit 1001, 4:5-38.) Indeed, Almoazen, while referring to Truelove 1's dipivalyl epinephrine compound, identifies it as shown in Almoazen Figure 7D, provides two tradenames for it, Dipivefrin and Propine and that its $t_{1/2}$ in human plasma was about 1,800 seconds (30 minutes).

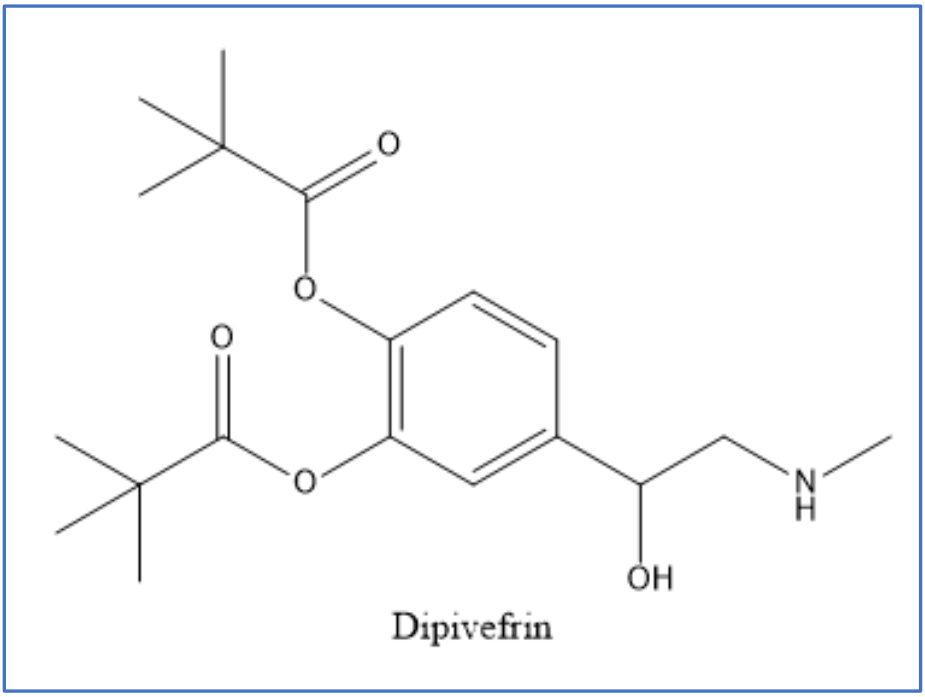
> "Anwar A. Hussain and James B. Truelove were granted patents **[Truelove 1 (Exhibit 1002) and Truelove 3 (Exhibit 1008)]** related to the synthesis of novel esters of [(methylamino)methyl] benzyl alcohol which is epinephrine. . . . Hussain et. al. **[Truelove 1]** synthesized four different prodrugs for this purpose (see structures **7**A, **7**B, **7**C, **7**D). These four molecules were tested in human, rabbit

[5] In the Almoazen Provisional Application the same Figure. 7 is represented as "show[ing] exemplary compounds of the present invention". Exhibit 1013, pdf. 18, [00017].

and horse plasmas and found that **3,4-dipivalyl-α-[(methylamino) methyl] benzyl alcohol hydrochloride (structure 7D)** shows the best penetration profile into the eye. . . . Dipivalyl-α-[(methylamino)] benzyl alcohol hydrochloride **(7D)** was further developed into a drug delivery system for glaucoma (**Dipivefrin or Propine**). Hussain and Truelove [**Truelove 1**] selected this prodrug for further development because of several physicochemical and biological qualities. The first quality was estimating the delay before onset of seizure for this prodrug was about 8-10 minutes [**Truelove 1, Table 1**], **the second quality was the rate of hydrolysis expressed as $t_{1/2}$ in human plasma was about 1,800 seconds** [**Truelove 1, Table 3**] and the third quality was the $t_{1/2}$ hydrolysis and oxidation in vitro was 700 and 300 days [**Truelove 1, Table 2**] respectively. In a separate publication (Journal of Pharmaceutical Sciences, Vol. 65, No. 10, October 1976, p: 1510-1512) **[Truelove 4 (Exhibit 1007)]**, Hussain et. al. shared the graphs for the in vitro hydrolysis of this particular prodrug using rabbit eye homogenate and compared the hydrolysis among three different plasmas (human, rabbit, rabbit eye homogenate)."

'437 Patent, Exhibit 1001, 2:5-39 (emphasis added).

55. While, as discussed below, Truelove 1 incorrectly names its dipivalyl epinephrine compound, Almoazen understood Truelove 1's disclosure, *e.g.,* when he named Truelove 1's compound by its trade name Dipivefrin. Shown below is the structure generated by ChemDraw® for Dipivefrin, which is the same compound as Exhibit 1001, Figure 7 and Truelove 1's dipivalyl epinephrine compound, see Exhibit 1002, Formulas 1 and 8.



Dipivefrin

56. According to the '437 Patent its "FIG . 7 shows Anwar A. Hussain and James E. Truelove compounds" (Exhibit 1001, 4:9-10), *i.e.,* the compounds disclosed in Exhibits 1002 and 1007.

57. The ‘437 Patent, in Figure 7 and the specification, discloses that the ‘437 Patent inventor understood what Truelove 1’s prodrug compounds were, not withstanding the incorrect nomenclature Truelove 1 used, and the ‘437 Patent provides correct names for each of those Truelove 1 epinephrine prodrug compounds.[6]

> “Now referring to **FIG. 7**, the compounds of the invention as shown in US patent 3,809,714 [Truelove 1, Exhibit 1002] and US patent 3,825,583 [Truelove 2, Exhibit 1006] hereby incorporated by reference.
> Representative molecules include:
> **7A** 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenlyene diacetate having a D [*sic,* C] Log P : -0.9026.
> **7B** 4-(1-hydroxy-2(methylamino)ethyl)-1,2-phenylene bis(2-methylpropanoate) having a C Log P: 0.773300.

[6] A POSA would have certainly recognized that there are a number of ways to correctly name these compounds and corresponding structures; the ‘437 Patent’s is but one of them. *See, e.g.,* Morrison and Boyd, Exhibit 1036, pp. 579-581, and Streitwieser, Exhibit 1037, pp. 483, 513-514.

7C 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenlyene dipropionate[7] having a C Log P: 0.1554.
7D 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,2-dimethylpropanoate) having a C Log P: 1.571.4. [*sic*][8] *If these molecules show fast permeability through the sublingual and buccal membranes and fast hydrolysis by the enzyme (half-life 1-6*

[7] The '437 Patent also refers to this compound as "4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene dipropanoate", see Fig. 7C. "4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene **dipropionate**" is the same compound as "4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenlyene **dipropanoate**", just using a different nomenclature. That is, "**dipropanoate"** names the same structure as **"dipropionate"**.

[8] As discussed below, see ¶ 62, these C Log P values, calculated Log P values, are slightly different than the Log P values disclosed in Table 2, the '437 Patent, 7:10-17, copied below.

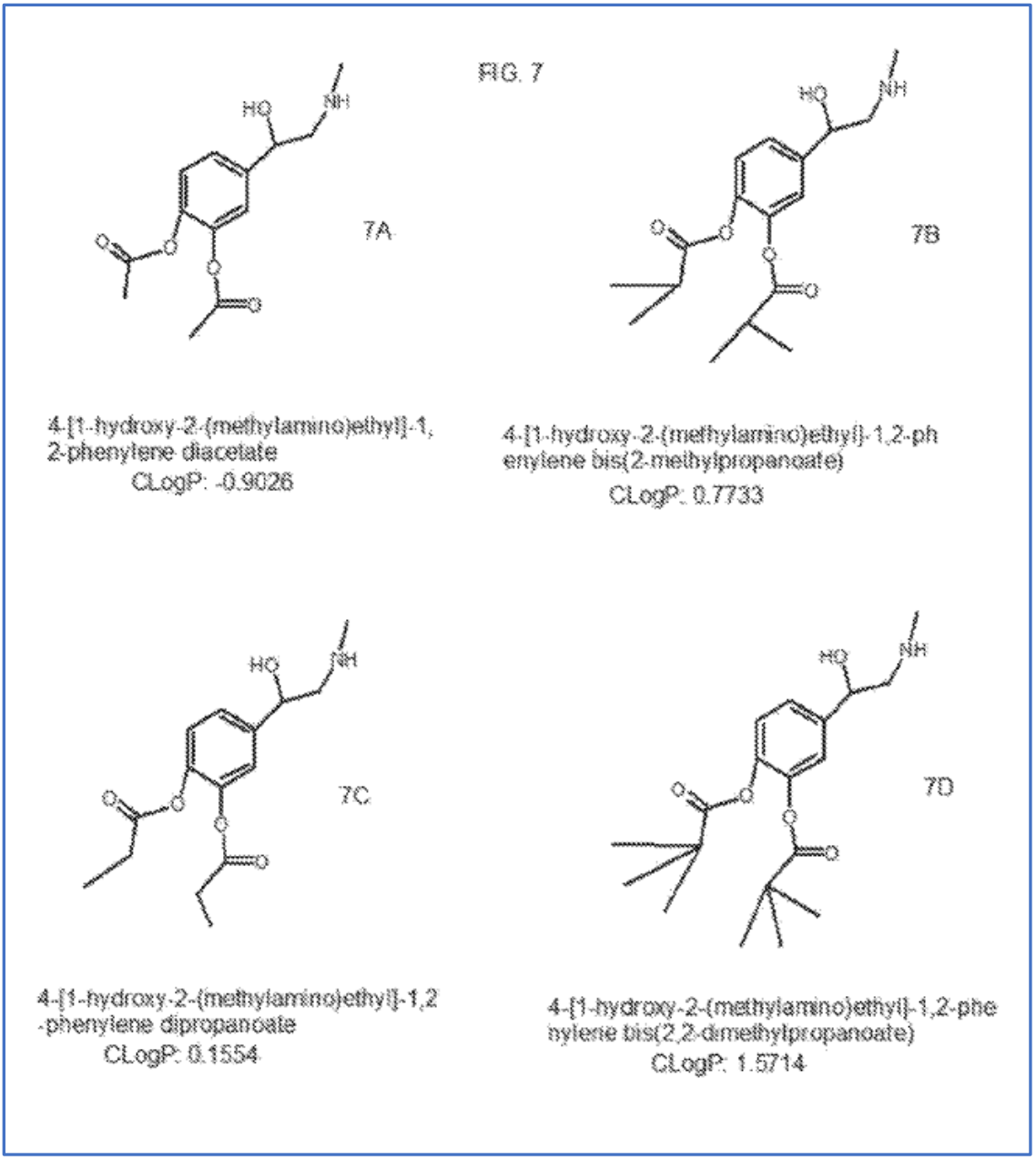
> *minutes)*[9] *a physical property of a compound that is useful to be formulated in a unit dosage form as a rapidly dissolving film*."[10] Almoazen '437 Patent, 6:42-52 (italics added, formatting changed for clarity).

58. Figure 7 of the '437 patent, showing the diester prodrug compounds of Truelove 1 as well as the '437 Patent's present invention compounds, along with the corresponding names, is copied below.

[9] As discussed in the section in which I discuss Truelove 1, see, e.g., ¶¶ 179 (Truelove 1 Relationship Chart), 180, it is noted that Truelove 1 discloses that several of its compounds, that are also shown in Figure 7 of the '437 Patent, have half-lives in the range of 1-6 minutes. See also Truelove 1, Exhibit 1002, Table 3, 9:28-38.

[10] The italicized sentence of the above quote from the '437 Patent (Exhibit 1001, 6:52-57) is different from the original language appearing in the Almoazen Provision Application (Exhibit 1013, p. 11 [00028]). The italicized sentence from the '437 Patent quoted above adds **NEW** subject matter namely a "*half-life 1-6 minutes*".

Fig. 7, '437 Patent, Exhibit 1001



59. The '437 Patent continues by stating that the subject matter of the invention includes uses of a pharmaceutical formulation in a patient in need of anaphylactic treatment, wherein the pharmaceutical formulation is made of a compound selected

from the group consisting of the Truelove 1 diester prodrug compounds shown in Figure 7. (*See* '437 Patent, Exhibit 1001, 6:57-67, copied below.)

> **"The subject matter includes: uses of a pharmaceutical formulation in a patient in need of anaphylactic treatment**, wherein the pharmaceutical formulation is made of **a compound selected from the group consisting** of 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene diacetate **[Fig. 7A, R = CH_3]**[11]; 4-(1-hydroxy-2(methylamino)ethyl)-1,2-phenylene bis(2-methylpropanoate) **[Fig. 7B, R = $CH(CH_3)_2$]**[12]; 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene dipropionate **[Fig. 7C, R = CH_2CH_3]**[13]; 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,2-dimethylpropanoate) **[Fig. 7D, R = $C(CH_3)_3$]**[14], and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient."

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[11] Figure 7A, where both R substituents are -CH_3, disclosed in Truelove 1, and in claims 2 and 3 of '437 Patent.

[12] Figure 7B, where both R substituents are -$CH(CH_3)_2$, disclosed in Truelove 1, and in claims 2 and 3 of '437 Patent.

[13] Figure 7C, where both R substituents are -CH_2CH_3, disclosed in Truelove 1, and in claims 2 and 3 of '437 Patent.

[14] Figure 7D, where both R substituents are -$C(CH_3)_3$, disclosed in Truelove 1.

Almoazen ‘437 Patent, Exhibit 1001, 6:57-7:10 (emphasis added).

60. The same Truelove 1 diester promoiety epinephrine prodrug compounds are also described as the subject matter of the invention which includes the pharmaceutical formulation itself. (*See* ‘437 Patent, Exhibit 1001, 6:67-7:10.)

Log P and CLog P

61. The ‘437 Patent discloses both Log P and CLogP (calculated Log P) values for epinephrine prodrugs and that Log P values include CLogP values.

> “**Table 1** shows exemplary prodrugs of epinephrine made by modifying the two hydroxyl (phenolic) groups in positions 3 and 4 on the benzene ring along with Log P values or a pharmaceutically acceptable salt thereof. **The prodrugs of epinephrine preferably have a Log P value in the range of about 0.5-6.0, and more preferably between 1.0-5.0. This range was listed as a table of marketed sublingual tablets and films in Ashraf** et. al “Considerations in developing sublingual tablets—An overview”, Pharmaceutical Technology, 2014, 38(11) [Exhibit 1003]. Log P is the logarithmic value of the ratio of two concentrations of a compound in a mixture of two immiscible liquids such as water and

> octanol at equilibrium Log P values can be calculated mathematically by the use of PERCEPTA PLATFORM software (ACS Labs, Toronto, Ontario, Canada)."

'437 Patent, Exhibit 1001, 5:3-42 (emphasis added).

For example, Table 1 discloses that the inherent Log P of claim 1's epinephrine compound with ester promoiety **R = -$CH_2CH_2CH_3$** is +0.8. See, '437 Patent, Table 1, 5:29.

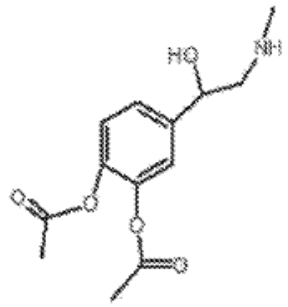
62. The Almoazen '437 Patent also includes Table 2 that includes Log P values for the Figure 7 epinephrine prodrug compounds (7A-7D).[15] I note that the Log P values provided in Table 2 are slightly different than the CLog P values provided in Figure 7, compare Fig. 7 (Exhibit 1001) with Table 2 (Exhibit 1001, 7:10-18), copied below.

[15] Table 2 is not referred in the text of the '437 Patent. The only references to Table 2 in the text of the '437 Patent appear to be references to Table 3, regarding the formulations of the films.

TABLE 2

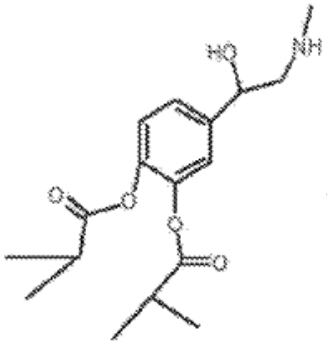
R	Log P
Structure 7A R=CH_3	−0.97
Structure 7C R=CH_2CH_3	+0.09
Structure 7B R=$CHCH_3CH_3$	+0.79
Structure 7D R=$CCH_3CH_3CH_3$	+1.49

FIG. 7



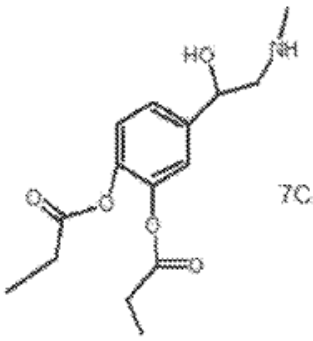
7A

4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene diacetate
CLogP: -0.9026



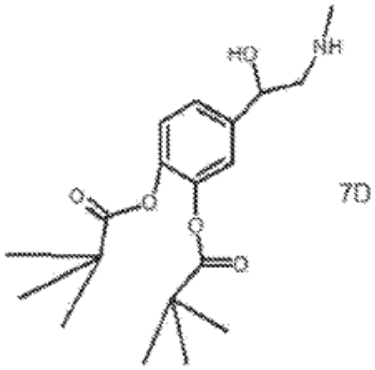
7B

4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene bis(2-methylpropanoate)
CLogP: 0.7733



7C

4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene dipropanoate
CLogP: 0.1554



7D

4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene bis(2,2-dimethylpropanoate)
CLogP: 1.5714

The Almoazen Provisional Application Does Not Disclose half-life values ranging from 1-6 minutes, thus these values are new additions to the '437 Patent

63. There is no disclosure of a fast rate of hydrolysis with a half-life $t_{1/2}$ 1-6 minutes in the Almoazen Provisional Application (Exhibit 1013) and only two (2) brief references to a fast hydrolysis with a half-life $t_{1/2}$ of 1-6 minutes in the '437 Patent Specification (see Exhibit 1001, 5:43-47 and 6:52-57). As to rate of hydrolysis, the Almoazen Provisional refers to Truelove 1's disclosure of a half-life $t_{1/2}$ of 1,800 seconds (Exhibit 1013, [0004], p. 3, pdf 14). The Almoazen Provisional Application provides no data or other information about the rate of hydrolysis nor does it provide a half-life or range of half-lives, but merely notes generally that:

> "The rate of hydrolysis of each ester can increase or decrease depending on how the atom in position R_4 influences the ester group. A pro-drug is selected for fast permeability through sublingual and buccal membranes and fast hydrolysis by the enzyme. *The molecule that shows fast permeability through the sublingual and buccal membranes and fast hydrolysis by the enzyme is a physical property of a compound that is useful to be formulated in a unit dosage form as a rapidly dissolving film*."

Almoazen Provisional Patent Application, Exhibit 1013, [00023], p. 9, pdf 20 (emphasis added).

> "*The molecule that shows fast permeability through the sublingual and buccal membranes and fast hydrolysis by the enzyme is a physical property of a compound that is useful to be formulated in a unit dosage form as a rapidly dissolving film.*"
>
> Almoazen Provisional Patent Application, Exhibit 1013, [00028], p. 11, pdf 22 (emphasis added).

64. The above quote from ¶ [00028] of the Almoazen Provisional follows the discussion of Figure 7 compounds of the present invention and the incorporation by reference of the Truelove 1 compounds found in both the Almoazen Provisional and the '437 Patent (*see* Exhibit 1001, 6:57-67, copied above). The Almoazen Provisional ¶ [00028] quote was amended so that the '437 Patent now discloses a half-life of 1-6 minutes. A comparison of portions of the Almoazen Provisional Application and the '437 Patent is provided below with the material deleted from the Almoazen Provisional underlined, and the new subject matter added to the '437 Patent shown in brackets and bold:

> "<u>The molecule that shows</u> [*If these molecules show*] fast permeability through the sublingual and buccal membranes and fast hydrolysis by the enzyme *[(half-life 1-6 minutes)]* <u>is</u> a physical property of a compound that is useful to be formulated in a unit dosage form as a rapidly dissolving film."

Almoazen Provisional Application, Exhibit 1013, [00028], p. 11, pdf. 22, compared with '437 Patent, Exhibit 1001, 6:52-57.

65. Finally, the other half-life ($t_{1/2}$) disclosure of 1-6 minutes in the '437 Patent specification at column 5, lines 43-47 corresponds to paragraph [00023] of the specification of the '437 Patent application as originally filed (see '437 FH, Exhibit 1005, pdf 333).[16] The corresponding paragraph from the Almoazen Provisional

[16] The timing of the inclusion of the "half-life $t_{1/2}$ range from 1-6 minutes" disclosure is relevant not only to an understanding the claims of the'437 Patent but to the priority (effective filing) date of the '437 Patent. Importantly, the "half-life" disclosure was relied on by Almoazen to support its claim amendments which added the following claim element: "wherein the compound is formulated in a unit dosage form as a rapidly dissolving film and has a half-life $t_{1/2}$ range from 1-6 minutes". **"Support for the amended claims is found at:** 'A pro-drug is a derivative of epinephrine selected for fast permeability through sub-lingual and buccal membranes (i.e., a compound that dissolves in the oral cavity) and fast hydrolysis (half-life $t_{1/2}$ range from 1-6 minutes) by plasma enzymes to form epinephrine when delivered.' **Para 00023** [of the '437 Patent application (Exhibit 1005), and not the Almoazen Provisional Application (Exhibit 1013) from which

Application is also a paragraph numbered [00023] (see Exhibit 1013, p. 9, pdf 20). The '437 Patent once again adds the new disclosure of a "*(half-life 1-6 minutes)"* to the disclosure in the Almoazen Provisional Application.

66. As noted above, the '437 Patent discloses no reason or data supporting the "half-life $t_{1/2}$ range from 1-6 minutes" claim limitation. Additionally, the '437 Patent provides no reason, data or support for either the lower or upper half-life $t_{1/2}$ limits for the formation of epinephrine in human plasma.

67. I want to emphasize that the '437 Patent does not include any experimental data or examples concerning its claimed prodrugs. In fact, the '437 Patent provides no example of the synthesis of any prodrug, much less those recited in its claimed prodrugs. The only half-life ($t_{1/2}$) data referenced in the '437 Patent is the half-life of 30 minutes for one ester promoiety disclosed in Truelove 1 (Exhibit 1002), incorrectly named pivalyl, but disclosing the structure of pivaloxy, and Truelove 4 (Exhibit 1007), correctly named as pivaloxy, and disclosing the same structure as shown in Truelove 1).

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the '437 Patent claims priority]". (See '437 FH, Exhibit 1013, pdf 39 and 45, pp. 2 and 5, emphasis added.)

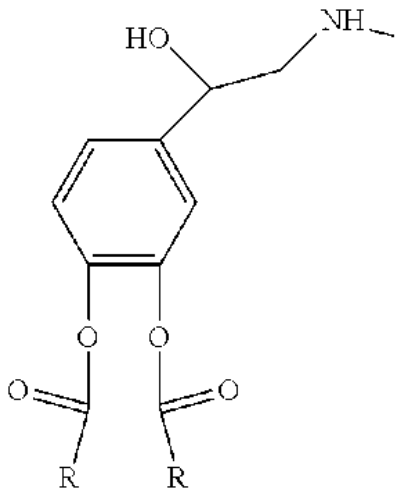
68. I also want to emphasize that one of the important factors a POSA would have considered when designing prodrugs is the safety of the drug's promoiety. Importantly, a POSA would have been aware that the chlorinated substituents recited in claims 4 and 5, upon release from the prodrug, would generate a potentially toxic by-product (2,2-dichloropropionic acid) which was known to act as a herbicide. Tellingly, the '437 Patent provides no information or data regarding the safety of its claimed chlorinated promoieties.

'437 PATENT CLAIMS

69. The '437 patent has five claims. The claimed compounds and ester promoieties that are relevant to my analysis are disclosed in the '437 Patent's Figures 5 and 7.

Claim 1 recites:

> Claim 1. A compound formulated as a pharmaceutical composition in a unit dosage form configured for sublingual or buccal administration of a Formula:

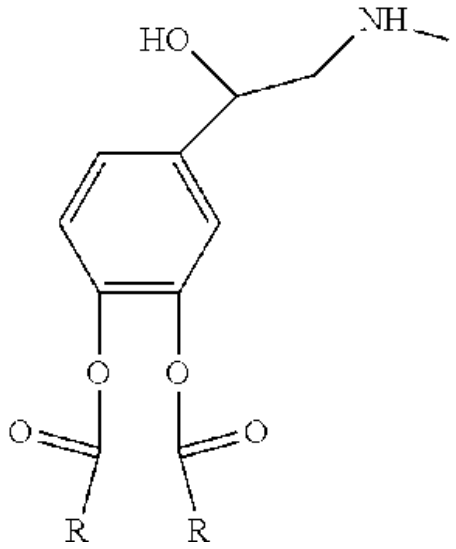


wherein R is selected from the group consisting of: —$CHCH_2$, —$CHCHCH_3$, —CH_2—CH_2—Cl, —$CHCH_2I$, —$CH(Cl)CH_2$ (Cl), —$CH(I)CH_2(I)$, —$CH(CH_3)CH_2(CH_3)$, —$CH_2C(CH_3)_3$, **—$CH_2CH_2CH_3$,**[17]—CH_2CI, —CH_2I, —CH_2F, H, CI, I, F, —$CH(CH_3)CH(CH_3)_2$, —$CH(Cl)CH(Cl)_2$, —$CH(I)CH(I)_2$, —$CH(F)CH(F)_2$, —CH_2CHCH_2, —$C(Cl)_2CH(Cl)_2$, —$C(I)_2CH(I)_2$, —$C(Cl)_3$, $C(I)_3$, —CH_2COCH_3, —CH_2COCl, —$CH_2CO(I)$, —CH_2OCH_3, —$CH(I)(CH_3)$, —$C(Cl)_2(CH_3)$, —$CH_2CH(CH_3)_2$, —$CH_2CH(Cl)_2$, —$CH_2CH(I)_2$, —$CH_2C(Cl)_3$, —$CH_2C(I)_3$, —$CH(Cl)_2$, —$CH(I)_2$, —$C(CH_3)_2CH(CH_3)_2$, —NH—$C(CH_3)$ 3, —NH—$CH(CH_3)_2$, —NH—CH_2CH_3, —NH—CH_3, —SCH_3, —SCH_2CH_3, —$SCH(CH_3)_2$, —$SC(CH_3)_3$, —$CH_2C_6H_5$ and —C_6H_5 or a pharmaceutically acceptable salt thereof, wherein said compound has a Log P value in the range of about 0.5-6.0 and wherein the compound is formulated in a unit dosage form as a rapidly dissolving film and has a half-life $t_{1/2}$ range from 1-6 minutes.

[17] R = -$CH_2CH_2CH_3$ (Figure 5G").

Claim 2 recites:

Claim 2. A compound of a Formula



wherein R is selected from the group consisting of: **CH_3, CH_2CH_3 and $CH(CH_3)_2$**[18] wherein the compound is formulated in a unit dosage form as a sublingual or buccal administration and wherein the compound is formulated in a unit dosage form as a rapidly dissolving film and has a half-life $t_{1/2}$ range from 1-6 minutes.

Claim 3 recites:

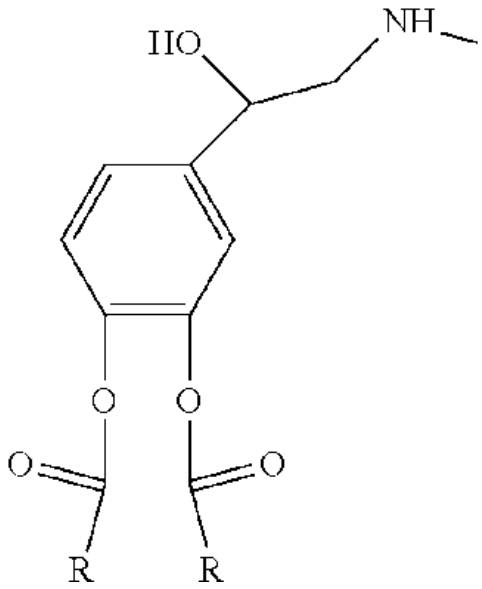
Claim 3. The compound of claim 2, wherein the compound is selected from the group consisting of: 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene

[18] R = -CH_3 (Figure 7A); R = -CH_2CH_3 (Figure 7C); R = -$CH(CH_3)_2$ (Figure 7B).

di-acetate[19]; 4-(1-hydroxy-2(methylamino)ethyl)-1,2-phenylene bis(2-methylpropanoate)[20]; 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene dipropionate[21]; and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein the compound is formulated in a unit dosage form as a rapidly dissolving film.

Claim 4 recites:

Claim 4. A compound formulated as a pharmaceutical composition in a unit dosage form configured for sublingual or buccal administration of a Formula:



[19] R = -CH_3 (Figure 7A).

[20] R = -$CH(CH_3)_2$ (Figure 7B).

[21] R = -CH_2CH_3 (Figure 7C).

wherein R is comprised of —$C(Cl)_2CH_3$.

Claim 5 recites:

Claim 5. The composition of claim 4 wherein the compound is formulated in a unit dosage form as a rapidly dissolving film and has a half-life $t_{1/2}$ range from 1-6 minutes.

PROSECUTION FILE HISTORY OF THE '437 PATENT (EXHIBIT 1005)

70. The prosecution file history associated with U.S. patent application serial number 16/347,625, was filed on May 6, 2019 and issued as the '437 Patent, it is referred to herein as Exhibit 1005.

71. I have reviewed the entire file history (Exhibit 1005) and provide the following summary of the application file history for the '437 patent.

72. On November 4, 2020, the Examiner issued a Restriction Requirement (Exhibit 1005, pdf pp. 151-158) requiring Applicant Almoazen to choose from 1 of 5 combinations of claims to prosecute. Applicant responded on December 1, 2020 (Exhibit 1005, pdf pp. 145-146, 149-150). In his response, Almoazen elected to prosecute claims directed to epinephrine prodrugs formulated for sublingual or buccal administration. Additionally, Almoazen stated: *"*to expedite review applicant elects the molecule which has the side group R = -$C(Cl)_2CH_3$. Support for this election is shown in Table 1, Claims 1 and 19." (Exhibit 1005, pdf p. 150.)

73. On December 24, 2020, the Examiner issued a Non-Final rejection rejecting claims 1, 3, and 19-21 under 35 U.S.C. § 103 as being unpatentable over Rawas-Qalaji *et al.* (US 2007/0202163 A1) ("Rawas-Qalaji") (Exhibit 1017) because of Bodor (U.S. Patent No. 4,145,441) ("Bodor") (Exhibit 1016). (See '437 FH, Exhibit 1005, pdf pp. 87-95. In particular, the Examiner observed: "Bodor explicitly teaches compound (7) 3-(trimethylaceloxy)-α-[(methylamino)methyl]benzyl alcohol (Exhibit 1016, col. 5, 1. 18) which corresponds to the claimed R being $-CH_2C(CH_3)_3$. Bodor establishes the claimed species as a known epinephrine compound." (Exhibit 1005, pdf p. 92.)

74. Notably, in the Office Action, the Examiner observed that the Log P value in the limitation of Applicant's claims was an inherent property of the compounds: "Furthermore, the claimed limitation of Log P value is deemed inherent to the claimed structures, unless evidence to the contrary." (Exhibit 1005, pdf p. 91.)

75. The Examiner also cited Rawas-Qalaji as teaching injectable epinephrine delivered in any suitable form including buccal and sublingual film and that the prodrugs (esters) differed only in the methyl substitutions on the R group, which the Examiner deemed to be obvious variations.

76. In the January 22, 2022 Response (Exhibit 1005, pdf pp. 73-87), Almoazen asserted that Bodor's compound 7 "is not epinephrine".

> "Bodor cites Compound (7) 3-(trimethylaceloxy)-a-(methylamino)methyl benzyl alcohol as an example.
> However, this compound is not epinephrine nor is it set out in the claims. It has only one phenolic group forming an ester with an alkyl group. The side chain $C(CH_3)_3$ is not listed in the claims. Bodor teaches compound 7 has the R group C(CH3)3. However, the R group claimed is: -CH2C(CH3)3, which is not the same compound. Thus, the disclosure in Bodor does not disclose or suggest the claimed compounds to one skilled in the art. Since the claimed compounds are not disclosed, the compounds of Bodor would not inherently have the claimed Log P value in the range of about 0.5-6.0."
> '437 FH, Exhibit 1005, pdf pp. 82-83.

77. Notably, in its January 22, 2021 Response, Almoazen did not argue or refute the Examiner's finding that the claim limitation of Log P value was inherent to the claimed structures, nor did Almoazen submit any evidence to the contrary. Instead, Almoazen argued that, although Rawas-Qalaji discloses buccal or sublingual administration, the industry still delivers epinephrine by injection due to GI tract issues. Almoazen further argued Bodor does not disclose the same compounds as Almoazen's claims, and further teaches treatment of hemorrhoids (topical application), not anaphylaxis. ('437 FH, Exhibit 1005, pdf pp. 82-83.) Finally, Almoazen argued that an alternative to delivery of epinephrine by injection

is a long-felt need in the industry. (Exhibit 1005, p. 84.) Almoazen submitted the Affidavit of Kafait U. Malik, a professor at the University of Tennessee Health Science Center in Memphis to support this argument (Exhibit 1005, pdf pp. 75-76).

78. On March 3, 2021, rejecting Almoazen's arguments as unpersuasive, the Examiner issued a Final Rejection finding the pending claims obvious in view of Rawas-Qalaji and Bodor (Exhibit 1005, pdf pp. 59-68). The Examiner stated that Almoazen had not provided objective evidence of the long-felt need in the industry and that Almoazen had not established that Rawas-Qalaji did not solve the problem. Addressing Almoazen's arguments regarding Bodor, the Examiner stated:

> "Bodor teaches compounds of formula (I) where R1 and R2 are acyl that is alkanoyl having 1-22 carbon atoms. This teaching overlaps the claimed R being -$CH_2CH_2CH_3$, amongst others."
>
> '437 FH, Exhibit 1005, pdf p. 64.

The Examiner also reiterated her previous rejections from the Non-Final Office Action (Exhibit 1005, pdf pp. 65-67).

79. On March 21, 2021, Almoazen, in responding to the Examiner's Final Rejection, amended the claims (Exhibit 1005, pdf pp. 39-51). Almoazen amended pending claims 1 and 19 (which appear as '437 Patent claims 1 and 2, respectively) to add the following language: "wherein the compound is formulated in a unit dosage form as a rapidly dissolving film and has **a half-life $t_{1/2}$ range from 1-6**

minutes." (Exhibit 1005, pdf pp. 39-40, emphasis added). Almoazen also added new claims 23 and 24 (which appear as Claims 4 and 5 in the '437 Patent). Independent claim 23 recites the structure of claim 1 where R is $-C(Cl)_2CH_3$. Claim 24, which depends on claim 23, recites the compound of claim 23 where the half-life $t_{½}$ range is 1-6 minutes.

80. When Almoazen amended the claims to include, *inter alia,* "wherein the compound is formulated in a unit dosage form as a rapidly dissolving film and has a half-life $t_{1/2}$ range from 1-6 minutes", Almoazen relied on the disclosure in paragraph [00023] found in the application appearing in the '437 Patent file history (Exhibit 1005):

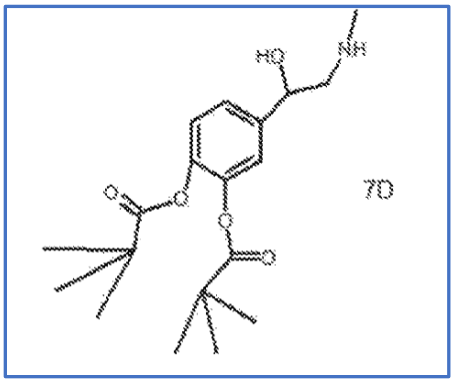
> "Support for the amended claims is found at: 'A pro-drug is a derivative of epinephrine selected for fast permeability through sub-lingual and buccal membranes (*i.e.,* a compound that dissolves in the oral cavity) and fast hydrolysis (half-life $t_{1/2}$ range from 1-6 minutes) by plasma enzymes to form epinephrine when delivered.' Para 00023".

'437 FH, Exhibit 1005, pdf 30, p. 5.

However, as discussed above, the corresponding paragraph from the Almoazen Provisional Application, which is also numbered paragraph [00023] (see Exhibit 1013, pdf 20, p. 9), does not disclose a "half-life $t_{1/2}$ range from 1-6 minutes".

81. Attempting to refute the obviousness rejection based on Bodor and Rawas-Qalaji, Almoazen *sua sponte* directed the Examiner in a misleading characterization of the Truelove´s references cited in column 2, lines 5-39 of the ‘437 Patent. There, Almoazen focused exclusively on the dipivalyl epinephrine prodrug compound, *i.e.,* the trimethyl derivative of epinephrine disclosed in Truelove 2 and 4, Exhibits 1002 and 1007 respectively.[22] By singling out a specific compound whose half-life ($t_{½}$) appears in Table 3 of Exhibit 1002, without referring to Table 3, Almoazen argued that the pending claims were patentable. He pointed to the trimethyl derivative of epinephrine compound in Exhibit 1002,

[22] Copied below is Figure 7D of the ‘437 Patent, which is the trimethyl derivative of epinephrine disclosed in Truelove 2 and 4.



which in Exhibit 1002, Table 3[23] demonstrated a hydrolysis half-life ($t_{½}$) in human plasma of 30 minutes, exceeding the 1-6 minute half-life range specified in the amended claims. Almoazen argued at '437 FH, Exhibit 1005, pdf pp. 47-48:

> "The claims have been amended to add the limitation of hydrolysis rate [a 1-6 minute half-life $t_{1/2}$]. This further differentiates the Bodor's patent [Exhibit 1016], compound 7 because Hussain [*see* Exhibit 1002 and Exhibit 1007] showed hydrolysis data for the trimethyl derivative of 30 minutes. This rate of hydrolysis is too long to treat anaphylaxis and as such Bodor teaches away from the presently claimed subject matter."

> "What we learned from Hussain-Truelove patent [Exhibit 1002, Table 3] is that higher carbon chain leads to higher hydrolysis half-life in plasma. The trimethyl alkyl derivative (compound 7) in Bodor's patent is similar in structure to Hussain´s [Exhibit 1002] trimethyl alkyl (Dipivifrin) which has 1800 second (30 minutes) half-life in plasma. For a successful epinephrine prodrug to be used

[23] As discussed below at ¶¶ 128-134, Truelove 1 (Exhibit 1002) incorrectly referred to the trimethyl derivative of epinephrine, *i.e.,* dipivalyl epinephrine, as L-3,4-**dipivalyl**-α-[(methylamino)-methyl-] benzyl alcohol hydroperchlorate, in its Table 3, when it should have been identified as L-3,4-**dipivaloxy**-α-[(methylamino)methyl] benzyl alcohol hydroperchlorate.

for anaphylaxis, the half-life should be 1-6 minutes. **It is surprising that substitution of methyl with chloro would lower the half-life since chloro is also hydrophobic**.[24] Furthermore, and to our knowledge no prodrug had similar structure or similar chloro substitution making the discovery of these compounds more novel and unexpected."

"As we indicated, the main objective of Hussain and Trulove's research was developing a prodrug that shows a good penetrating ability into the cornea as contrary to Epinephrine which is not lipid soluble and will not penetrate biological membranes. At the same time, Hussain-Truelove [Exhibits 1002 and 1007] wanted a prodrug design that hydrolyze in plasma at 30 minutes or more. Opposite to Hussain and Truelove [Exhibits 1002 and 1007] idea, and in order to treat anaphylaxis, we need to develop a prodrug that is capable of penetrating biological membranes such as sublingual tissues, but also hydrolyzes quickly."

'437 FH, Exhibit 1005, pdf pp. 47-48 (emphasis added).

[24] **It is not surprising** that the substitution of a chlorine group next to C(=O) on the alkyl chain of the ester results in faster hydrolysis. The chlorine pulls electron density away from the C(=O) putting more positive charge on the 'C' of the C(=O) making it a better target for nucleophilic attack leading to hydrolysis.

82. Addressing the Examiner's reliance on Bodor, Almoazen argued that Bodor covered thousands of compounds and changed the argument. Specifically, Almoazen argued that while the Bodor's compound 7 -- (3-(trimethylaceloxy)-α-[(methylamino) methyl]-benzyl alcohol) -- "is similar" to his "elected" species, CCl_2CH_3, it would not have been obvious to "change trimethyl [as disclosed in Bodor] to trichloro." (Exhibit 1005, pdf p. 47.)

83. Notably, Almoazen's so-called "elected species" CCl_2CH_3 is not a trichloro derivative.

84. Moreover, among the 50 epinephrine prodrug species recited in Claim 1, only two are trichloro derivatives (R = $-C(Cl)_3$, R = $-CH_2C(Cl)_3$). Additionally, there are no chlorinated derivatives recited in Claims 2 and 3.

85. Almoazen also argued that Rawas-Qalaji (i) does not refer to Log P, (ii) does not mention the ability of epinephrine to penetrate biological membranes and (iii) requires 40 mg of epinephrine in rabbits sublingually to mimic the AUC of the injection method.

86. Finally, Almoazen contended that the teaching of a wafer in Rawas-Qalaji was not the same as a film of as recited in the pending claims.

87. In the March 26, 2021, Examiner's Applicant-Initiated Interview Summary of an interview with Almoazen's counsel and Almoazen himself, the Examiner memorialized that during the interview, Almoazen emphasized that the proposed amended claims recited a half-life of 1-6 minutes and "argued that the prior art epinephrine prodrug has a half-life of 30 minutes." (Exhibit 1005, pdf pp. 24-25.) That is, Almoazen directed the Examiner solely to the "dipivalyl" compound in Truelove 1, which appears in Table 3, and not the other compounds with shorter half-lives. The interview summary included the following:

> "Applicant proposes amendment including the requirements of being a rapidly dissolving film and the substituents having a half life ranging from 1-6 minutes. **Applicant argued that prior art epinephrine prodrug has a half life of 30 minutes. It was suggested that this appears to be an unexpected result. It was suggested to further explain how the claimed substituents have the unexpected result of quicker hydrolysis.** It was also indicated that this on its face overcomes the prior art of record, however, that further search and consideration would be required to indicate allowance."

'437 FH, Exhibit 1005, pdf p. 25 (emphasis supplied).

88. On April 20, 2021, the Examiner issued a Notice of Allowance and Statement of Reasons for Allowance ('437 FH, Exhibit 1005, pdf pp. 8-16). In the

Reasons for Allowance, the Examiner withdrew her rejection of the claims based on Rawas-Qalaji and Bodor – not **on the basis of** Truelove 1. "Claims 1, 3 and 19-21 rejected under 35 U.S.C. 103 as being unpatentable over Rawas-Qalaji et al. (US 2007/0202163 A 1; cited in IDS) in view of Bodor (US 4,145,441; cited in IDS) is withdrawn." ('437 FH, Exhibit 1005, pdf. p. 13.)

89. The Examiner never cited or addressed Truelove 1 (Exhibit 1002), or for that matter any of the any of the other Truelove references mentioned in the '437 Patent (Exhibits 1002, 1006 and 1007). Additionally, the Examiner never challenged or even referred to Almoazen's characterizations of Truelove 1. Instead, the Examiner simply accepted and relied on Almoazen's misleading arguments regarding Truelove 1 and 4 as the basis for withdrawing the rejections, stating:

> "**Applicant [Almoazen] has amended claims and persuasively argued the unexpected result of the claimed epinephrine prodrug genus having a rapid half-life ranging from 1 to 6 minutes. Applicant points out that prior art prodrugs have 30 minute half-life. The instantly claimed genus is thus suitable for sublingual or buccal administration having a much shorter half-life.** Subsequent to persuasive arguments the rejection is withdrawn."
>
> '437 FH, Exhibit 1005, pdf. p. 14 (emphasis added).

90. In addition to withdrawing the rejections based on an erroneous understanding of the half-lives of prior art epinephrine prodrugs based on statements from Almoazen, the Examiner in allowing the claims to issue relied on her erroneous interpretation of Figure 9 to the effect that it showed that Almoazen's prodrug compound had a half-life falling within the claimed 1-6 minutes. Contrary to the Examiner's understanding, Figure 9 merely discloses how fast epinephrine is released from an Almoazen film containing only epinephrine (not an epinephrine prodrug) in 500 ml of simulated saliva at 37° C.

Statement of Reasons for Allowance

> "None of the prior art teaches in a single disclosure, nor fairly suggest in any combination, Applicants' claimed product of a compound of the claimed Formula, formulated as a pharmaceutical composition in a unit dosage form configured for sublingual or buccal administration. **Applicants have demonstrated novel compound structures in their disclosure as originally filed.[25]** Applicants' disclosure includes embodiments built around the claimed Formula and discloses the species embodiments and their Log P values. **Applicants'** disclose that epinephrine formulations have disintegrations times ranging from 10 to 30 seconds (see

[25] However, as discussed above ¶¶ 54-59, Almoazen admitted that its Figure 7 structures were from the prior art, namely Truelove 1 (Exhibit 1002).

> specification, p. 14, Table 5) and further **disclose exemplified embodiment of epinephrine release from hydrolysis where the half-life is within 4 minutes (see Drawings, Fig. 9).**"
>
> '437 FH, Exhibit 1005, pdf. p. 14 (emphasis added).

91. Almoazen was invited to correct any misunderstandings the Examiner might have: "Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled 'Comments on Statement of Reasons for Allowance.' " (Exhibit 1005, pdf. p. 14.) Although clearly invited to comment on the Examiner's statements, Almoazen chose not to do so.

ALMOAZEN PROVISIONAL APPLICATION (EXHIBIT 1013)

92. The '437 Patent incorporates by reference the Almoazen Provisional Application, serial no, 62/421,316 filed November 13, 2016. (Exhibit 1001, 1:8-12.)

93. It is my understanding that the Almoazen Provisional Application is considered part of the prosecution file history of the '437 Patent.

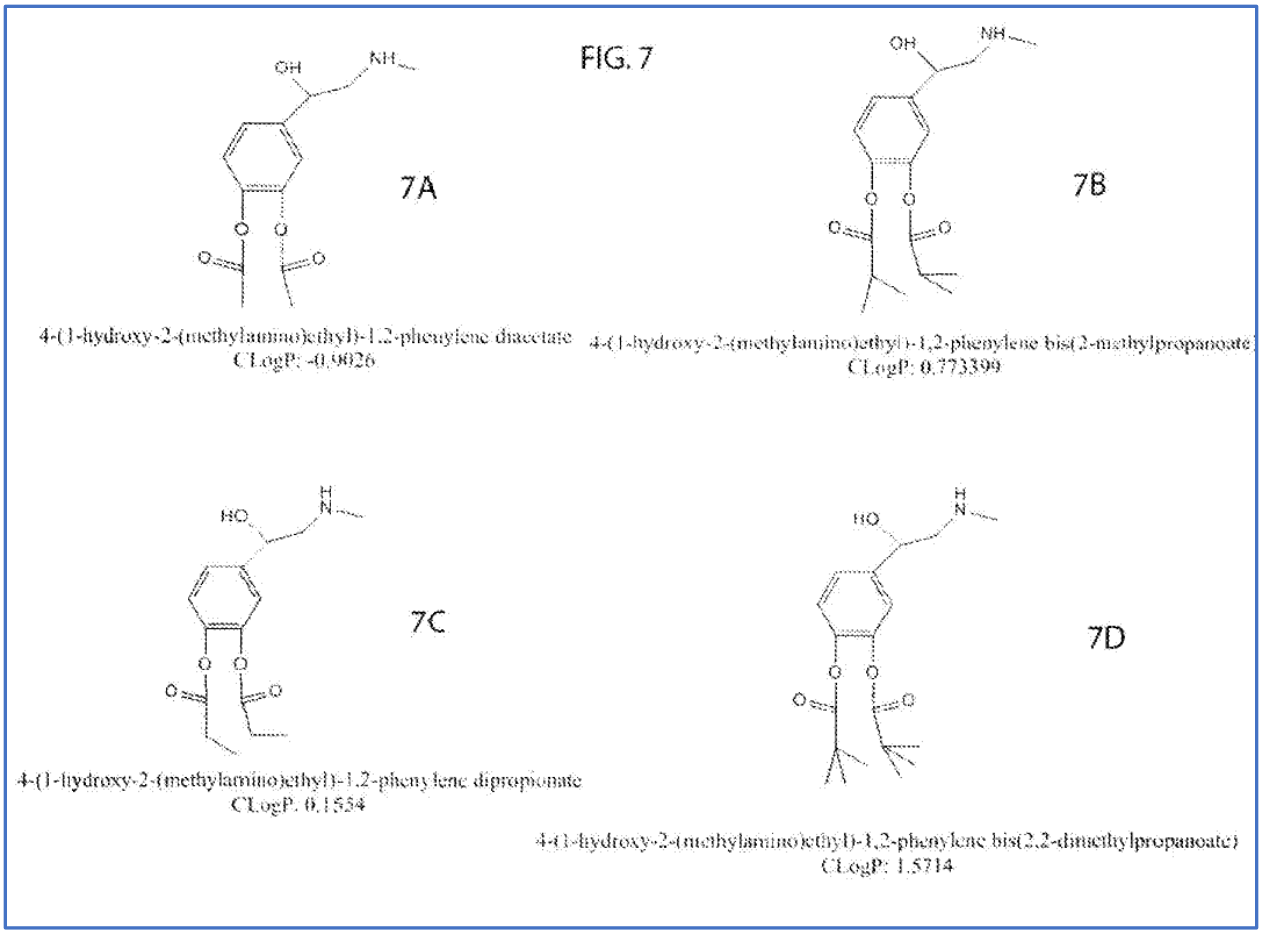
94. I note that the Almoazen Provisional Application contains an assignment from Lindsay Haynes. (Exhibit 1013, pdf p. 2.) Lindsay Haynes is identified as one of six (6) authors of the Almoazen Paper (Exhibit 1022).

95. In the assignment I also note the following statement: "Lindsay Haynes; an individual operating in Memphis, TN ("Assignor") has invented an EPINEPHRINE F1LM AND METHODS THEREOF ("Invention") therefore that is described in U.S. Patent Application No. 62/421,316, filed 11-13-2016 ("Patent") . . .". (Exhibit 1013, pdf. p. 2.)

96. Figure 7 from the Almoazen '437 Provisional Application is copied below. The same Figure 7[26] appears in the '437 Patent. In the Almoazen Provisional Application, **Figure 7 is described as showing compounds in accordance with Almoazen's invention.** "FIG. 7 shows exemplary compounds of the present invention." (Exhibit 1013, pdf. 18, [00017]. As noted earlier, the '437 Patent states that "FIG. **7** shows Anwar A. Hussain and James E. Truelove compounds". (Exhibit 1001, 4:9-10.)

[26] Figure 7 shows the epinephrine prodrug compounds from Truelove 1 (Exhibit 1002) and the epinephrine prodrug compound from Truelove 4 (Exhibit 1007).

Figure 7, Almoazen Provisional Application, Exhibit 1013, pdf. P. 45.



97. At paragraph [00028] of the Almoazen Provisional Application (Exhibit 1013), Almoazen incorporates Truelove 1, Exhibit 1002's compounds as compounds of the invention.

> "Now referring to **FIG. 7**, the compounds of the invention as shown in US patent 3,809,714 [Truelove 1, Exhibit 1002] and US patent 3,825,583 [Truelove 2, Exhibit 1006] hereby incorporated by reference. Representative molecules include: **7A** 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenlyene diacetate having a D[*sic*]LogP:

> -0.9026. **7B** 4-(1-hydroxy-2(methylamino)ethyl)-1,2-phenylene bis(2-methylpropanoate) having a ClogP: 0.773300. **7C** 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenlyene dipropionate having a CLogP: 0.1554. **7D** 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,2-dimethylpropanoate) having a CLogP: 1.5714. The molecule that shows fast permeability through the sublingual and buccal membranes and fast hydrolysis by the enzyme is a physical property of a compound that is useful to be formulated in a unit dosage form as a rapidly dissolving film."

Almoazen Provisional Application, Exhibit 1013, pdf. 22 [00028].

98. Other than stating that "fast hydrolysis by the enzyme is a physical property of a compound", the Almoazen Provisional Application provides no data or support for the half-lives of its the disclosed compounds. Importantly, the Almoazen Provisional Application does not disclose a "half-life $t_{1/2}$ range from 1-6 minutes" and does not provide any data supporting a "half-life $t_{1/2}$ range from 1-6 minutes" as recited in the claims of the '437 Patent.

ALMOAZEN PCT APPLICATION

99. The '437 Patent incorporates by reference the Almoazen PCT Application (Exhibit 1014), PCT/US2017/060761, filed November 9, 2017 (International Publication No. WO 2018/089570 A1). (See Exhibit 1001, 1:8-12.)

100. It is my understanding that that the Almoazen PCT Application is considered part of the prosecution file history of the ‘437 Patent.

101. In my review of this document, I observe that it identifies both Hassan Almoazen and Lindsay Haynes as inventors. (Exhibit 1014, first page.)

102. The Almoazen PCT Application discloses the half-life range recited in the ‘437 Patent. “[F]ast hydrolysis (half-life $t_{1/2}$ range from 1-6 minutes) by plasma enzymes to form epinephrine when delivered.” (Exhibit 1014, p. 7 [00023]; see also Exhibit 1014, p. 8 [00028].)

103. As discussed above, the Almoazen Provisional Application (Exhibit 1013), does not quantify or otherwise disclose what qualifies as fast hydrolysis of the claimed prodrugs, *i.e.,* a half-life $t_{1/2}$ range from 1-6 minutes. Thus, based on my review of the related applications listed in the ‘437 Patent (see Exhibit 1001, 1:7-12), the Almoazen PCT Application, filed November 9, 2017, contains the earliest disclosure of the “half-life $t_{1/2}$ range from 1-6 minute” for the ‘437 Patent’s claimed prodrugs.

CLAIM CONSTRUCTION

104. It is my understanding that the claims of a patent define the invention to which the patentee is entitled the right to exclude. I have been informed that claim terms are generally given their ordinary and customary meaning; in other words,

claim terms are generally defined by the meaning that the term would have had to a POSA as of the priority date of the Asserted Patent.

105. It is also my understanding that a claim term should be accorded the full breadth of its plain and ordinary meaning as understood by a POSA when read in the context of the specification and prosecution history and the prior art. In ascertaining the meaning of the claims, it is my understanding that, because the claims are directed to the invention described in the specification, the meaning of the claims cannot be divorced from the specification which necessarily informs the proper construction or interpretation of claim elements.

Half-life $t_{1/2}$ means the time for one half of the epinephrine to be formed from its prodrug in human plasma

106. The '437 Patent uses the methodology and disclosures of Truelove 1 (Exhibit 1002) and Truelove 4 (Exhibit 1007) to ascertain the half-life ($t_{1/2}$) of its claimed prodrugs. The '437 Patent's only reference to an actual determination of the half-life of an epinephrine prodrug is in connection with Truelove 1's 1,800 seconds (30 minutes) for its diester epinephrine prodrug, namely *l*-3,4-dipivalyl-α-[(methylamino)methyl]benzyl alcohol hydroperchlorate in human plasma, and Truelove 4's disclosure regarding the *in vitro* hydrolysis of the same epinephrine prodrug in human plasma (*see e.g.*, Exhibit 1001, 2:5-38).

107. Specifically, the ‘437 Patent discloses at Exhibit 1001, 2:25-38:

> “Hussain and Truelove [Truelove 1, Exhibit 1002] selected this prodrug for further development because of several physicochemical and biological qualities. The first quality was estimating the delay before onset of seizure for this prodrug was about 8-10 minutes, the **second quality was the rate of hydrolysis expressed as $t_{1/2}$ in human plasma was about 1,800 seconds** and the third quality was the $t_{1/2}$ hydrolysis and oxidation in vitro was 700 and 300 days respectively. In a separate publication (Journal of Pharmaceutical Sciences, Vol. 65, No. 10, October 1976, p: 1510-1512), Hussain et. al. [Truelove 4, Exhibit 1007] shared the graphs for the in vitro hydrolysis of this particular prodrug using rabbit eye homogenate and compared the hydrolysis among three different plasmas (human, rabbit, rabbit eye homogenate.”

‘437 Patent, Exhibit 1001, 2:25-38 (emphasis added).

108. Therefore, in addition to the Almoazen ‘437 Patent and its file history, a POSA would have considered the disclosure of Truelove 1 and Truelove 4 to understand the meaning of the ‘437 Patent’s half-life ($t_{1/2}$) range of 1-6 minutes as recited in the challenged claims (claims 1-3) of the ‘437 Patent.

109. Truelove 1 describes the results of the process of measuring the enzymatic rate of hydrolysis in various media at 37º C as the “$t_{1/2}$ life”, and reports those results in Table 3.

"The improved stability of the compound is demonstrated in various biological media by measuring its enzymatic rate of hydrolysis in various media at 37° C. and expressing this result as the $t_{1/2}$ life. The enzymatic rate of hydrolysis is measured at pH of about 7.5 and at a concentration of 0.5 mg./ml. of compound in media (a) horse serum cholinesterase, (b) rabbit serum, and human plasma. The results for the compound are listed in Table 3 [copied below], as are the results of other compounds treated in a like enzymatic environment. The free base compound was measured by using high pressure liquid chromatography."

Truelove 1, Exhibit 1002, '714 Patent, 9:15-25.

Truelove 1, Exhibit 1002, Table 3, '714 Patent, 9:26-37.

TABLE 3

Compound	Rate of hydrolysis in $t_{1/2}$ seconds		
	Horse	Rabbit	Human
L-3,4-diacetyl-α-[(methylamino)-methyl] benzyl alcohol hydroperchlorate	20	45	180
L-3,4-dipropionyl-α-[(methylamino)methyl] benzyl alcohol hydroperchlorate	50	90	240
L-3,4-dibutyryl-α-[(methylamino)-methyl] benzyl alcohol hydroperchlorate	100	160	360
L-3,4-dipivalyl-α-[(methylamino)-methyl] benzyl alcohol hydroperchlorate	600	720	1,800

110. Truelove 4 offers a POSA additional information regarding Truelove 1's process for determining the $t_{1/2}$ half-life.

> "**In Vitro Enzymatic Rate of Hydrolysis of Prodrug in Human or Rabbit Plasma** -- Blood samples (5 ml) were withdrawn and centrifuged immediately. Two milliliters of the plasma was transferred to a stoppered test tube and equilibrated to 37º. After equilibration, 0.2 ml of the 4-mg/ml solution of prodrug was added and the mixture was maintained at 37º. *Liberation of epinephrine was followed as already described*."

Truelove 4, Exhibit 1007, p. 1511, 2nd col. (emphasis added).

111. Truelove 4 also provides Table I, copied below, which discloses the half-life ($t_{1/2}$) of the fourth compound identified in Table 3 of Truelove 1, as the "dipivalyl" compound and the same compound in Truelove 4 as the "pivaloyl" compound. The table from Truelove 4 reports that by 28 minutes 47.5% of the epinephrine had formed and been released into the plasma. Accordingly, the data disclosed in Truelove 4, confirms the half-life ($t_{1/2}$) of 30 minutes (1,800 seconds) that is reported in Table 3 of Truelove 1 (Exhibit 1002).

Truelove 4, Exhibit 1007, Table 1, p. 1511, 2nd col. (highlighting added).

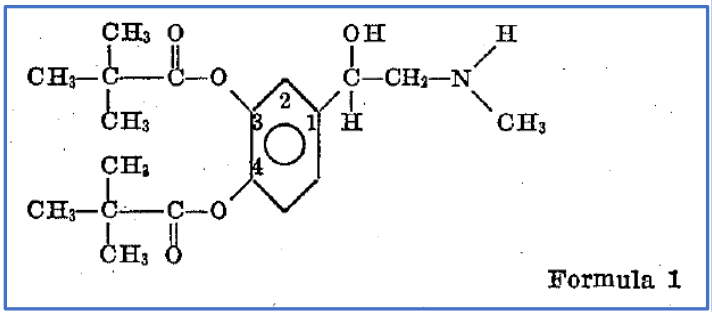
Table I—*In Vitro* Enzymatic Hydrolysis of the Prodrug

Minutes	Percent Hydrolysis in Rabbit Plasma	Percent Hydrolysis in Human Plasma	Percent Hydrolysis in Rabbit Eye Homogenate
0	0	0	0
3	12.3	—	—
8	47.7	—	—
10	—	8.0	—
13	58.0	—	—
18	—	24.1	—
20	—	—	2.3
22	96.0	—	—
28	—	47.5	—
32	100	—	—
40	—	—	5.3
45	—	85.8	—
60	—	95.1	18.2
90	—	100	34.0
105	—	—	42.5
150	—	—	68.9
190	—	—	81.8
285	—	—	100

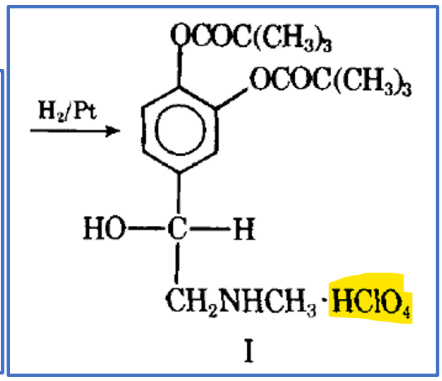
112. A comparison of the structures of Truelove 1's new inventive compound shown as Formula 1 (Exhibit 1002, 1:35-42)[27] and Compound 1 of Truelove 4

[27] Truelove 1's inventive compound is also referred to, shown and discussed as Formula 8. Formula 8 is shown in connection with the synthesis of Truelove 1's compound. (Exhibit 1002, 5:16-24, 68-75.)

(Exhibit 1007, p. 1511) illustrates that the only difference is that the Compound 1 structure is the salt form, as shown by the yellow highlighting, of non-salt or free-base structure depicted in Formula 1.



Truelove 1, Formula 1



Truelove 4, Compound I

113. Truelove 4 defines half-life ($t_{1/2}$) as the time for one-half of the parent epinephrine compound to be formed: "The results of the hydrolytic study with the rabbit eye homogenate, rabbit plasma, and human plasma are shown in Table I and Fig. 2. These data show that **the prodrug cleaves to epinephrine** at a reasonable rate." (Truelove 4, Exhibit 1007, p. 1512, 1st col., emphasis added.)

114. A POSA, reviewing either or both Truelove 1 and Truelove 4 in the context of the '437 Patent's specification, would have understood that the half-life measured in human plasma is the time for one-half of the parent epinephrine compound to form. Thus, "half-life $t_{1/2}$" as recited in the challenged claims should be construed as meaning the "time for one half of the epinephrine to be formed from its prodrug in human plasma". As will be detailed for example in ¶¶ 296-305,

below, a POSA would have understood that the half-lives of the salt and non-salt forms of the same epinephrine prodrugs would be essentially the same, if not identical. Finally, the half-lives determinations of the compounds disclosed in Truelove 1, Truelove 3 and Truelove 4 comply with this construction.

CONTENT OF THE PRIOR ART

115. The following references are some of the references I considered in forming my opinions. It is my understanding that a POSA is considered to have knowledge of all available prior art and my discussion of a subset of that prior art, or a particular section of a reference, is not intended to limit the POSA's knowledge for purposes of my analysis. Furthermore, the discussion below is not meant to be exhaustive and further details are provided in the analysis provided below.

Truelove 1 (Exhibit 1002) – Half-lives of Diester Prodrugs of Epinephrine.

116. U.S. Patent No. 3,809,714 ("Truelove 1" or "the '714 Patent"), entitled "*Novel ester of ((methylamino)methyl) benzyl alcohol*", issued on May 7, 1974, and describes "a novel and useful therapeutic ester of benzyl alcohol and to pharmaceutical compositions for using same" and discloses comparative esters of benzyl alcohol.

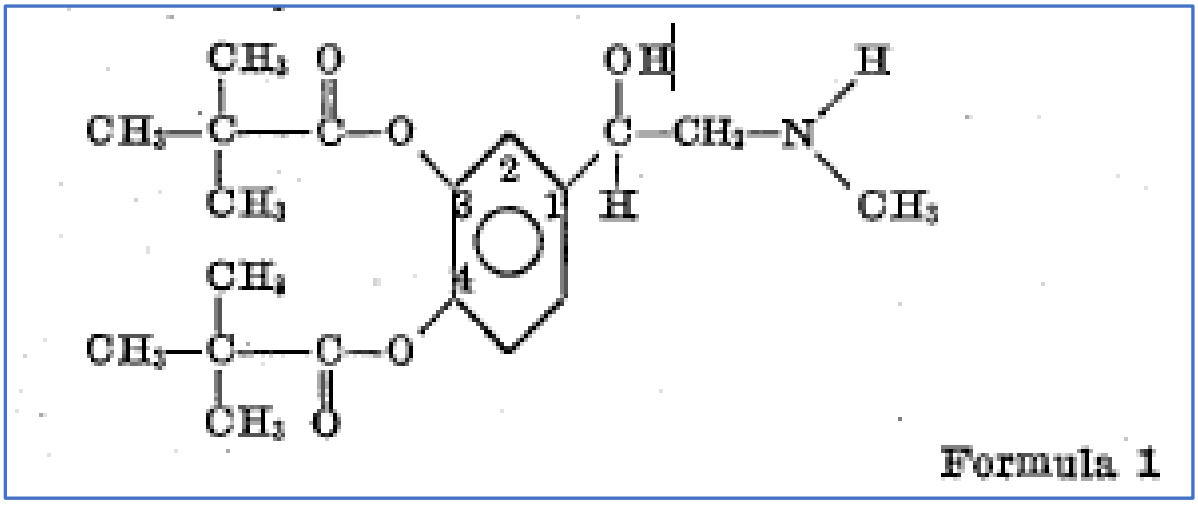
117. Truelove 1, though listed as a reference on the face of the '437 Patent, was never addressed by the Examiner, discloses several of the '437 Patent's claimed compounds, *i.e.,* ester prodrugs of epinephrine, and their respective half-lives ($t_{1/2}$). Three of Truelove 1's compounds have half-lives ($t_{1/2}$) ranging from 1-6 minutes as recited in the '437 Patent's challenged claims.

118. Truelove 1 recognized the pharmaceutical and medical need for a new and useful compound for the management of glaucoma, bronchial asthma and other sympathomimetic activities. Truelove 1 disclosed that the need existed because epinephrine, referred to as 3,4-dihydroxy-α-[(methylamino)methyl] benzyl alcohol, has several disadvantages including instability to both air and light and importantly "poor lipoid solubility attributed to its hydrophilic phenolic hydroxyl groups which tended to restrict the medical application of the drug." (*See, e.g.*, Exhibit 1002, 1:49-2:3.)

119. Truelove 1's stated purpose was to improve the chemical stability and lipid solubility of epinephrine by developing new ester prodrugs and pharmaceutically acceptable salts thereof. (*See, e.g.*, Exhibit 1002, 1:49-2:10.)

120. One of the objectives of Truelove 1 was to provide "3,4-dipivalyl-α-[(methylamino)methyl] benzyl alcohol hydroperchlorate" [28] also correctly referred to as "l- dipivalylepinephrine" as a therapeutic agent with "improved lipoid solubility for enhanced resorption when administered to warm blooded animal tissues" and which "can be administered per se or can be dispensed in ophthalmic, aerosol and other types of pharmaceutical formulations to warm blooded animals to produce a local or systemic physiological or pharmacological beneficial effect." (*See* Exhibit 1002, 2:28-39, 5:17-20.) The structure was also provided as Formula 1, copied below (Exhibit 1002, 2:50-58), see below, and as Formula 8 (Exhibit 1002, 5:68-75).

[28] As will be detailed below, see ¶¶ 128-134, a POSA would have understood the ester epinephrine prodrugs specially identified in Tables 1-3 of Truelove 1 are incorrectly identified as the ketone derivatives of the epinephrine analog (*e.g.,* "dipivalyl"), instead of ester prodrugs of epinephrine (*e.g.,* "dipivaloxy" or equivalently "dipivaloyloxy") which was the focus of the invention recited in Truelove 1.



121. Truelove 1's identification of Formula 1 (and for that matter Formula 8) as "dipivalylepinephrine" was correct as confirmed by Kohn, Exhibit 1044. Fig. 1, p. 196, reproduced below.

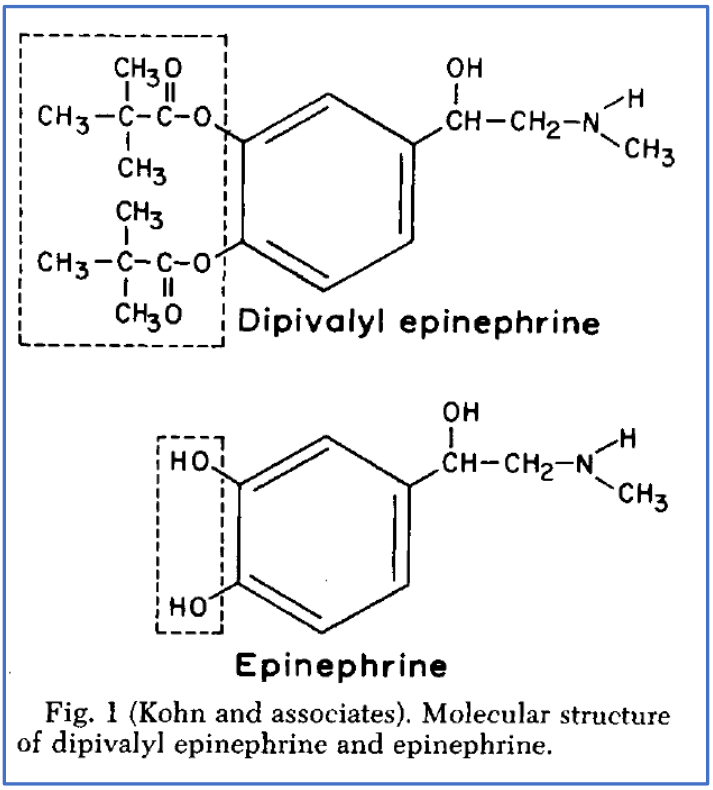
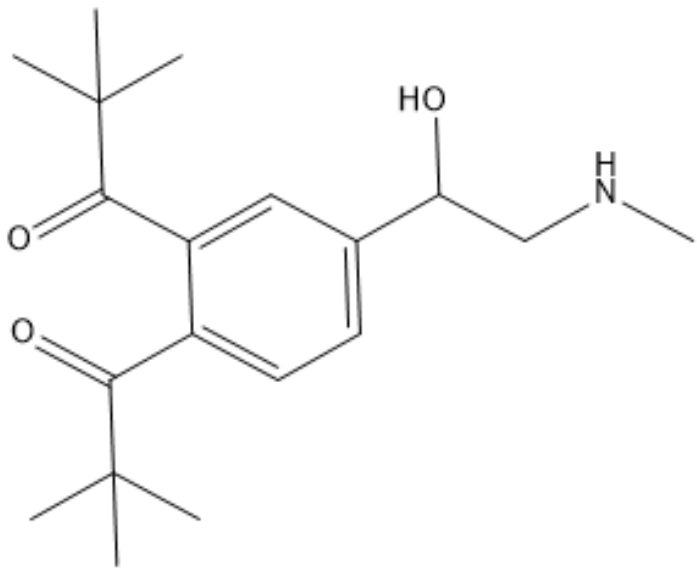


Fig. 1 (Kohn and associates). Molecular structure of dipivalyl epinephrine and epinephrine.

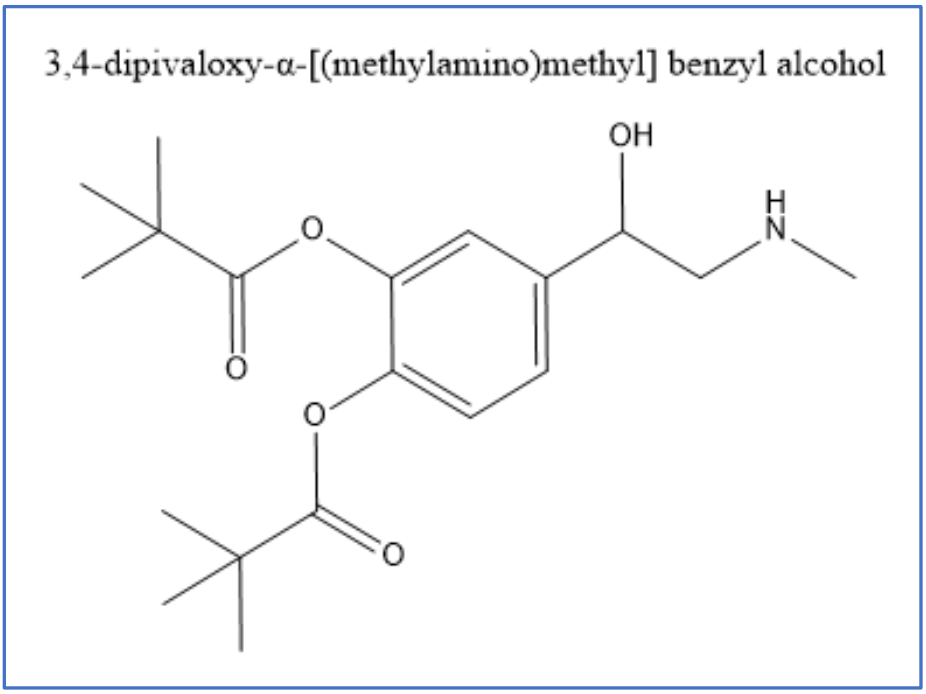
However, Truelove 1 mistakenly names its Formula 1 and Formula 8 structures as “3,4-dipivalyl-α-[(methylamino)methyl]benzyl alcohol”, which is not an ester derivative, but technically a ketone derivative of an epinephrine analog as shown by the structure below generated by ChemDraw®.

3,4-dipivalyl-α-[(methylamino)methyl]benzyl alcohol



Contrary to Truelove 1’s use of the wrong chemical name, POSA would have readily understood that the Formula 1 compound recited in Truelove 1 was the ester compound, “3,4-dipivaloyloxy-α-[(methylamino)methyl]benzyl alcohol”, as confirmed by the ChemDraw® generated structure and name shown below.

122. As generated by ChemDraw®, Truelove 1's Formula 1 (as well as Formula 8) are not the salts of "3,4-dipivalyl-α-[(methylamino)methyl] benzyl alcohol" but the salt of "3,4-dipivaloxy-α-[(methylamino)methyl] benzyl alcohol".



123. The synthesis of Truelove 1's compounds further confirms the identity of its compounds as ester derivatives of epinephrine. For example, Truelove 1 begins by generally disclosing the process for making the "dipivalyl" ester of epinephrine (Exhibit 1002, 2:68-4:36). Then, Truelove 1 provides in Examples 1 and 2, specific processes for synthesizing its epinephrine prodrug and making pharmaceutical preparations of that compound (Exhibit 1002, 4:36-8:7). Truelove 1 discloses pharmaceutically acceptable carriers and excipients for its epinephrine prodrug compound. (See, e.g., Exhibit 1002, 6:34-59.) Again, Truelove 1 refers to the

product of its synthesis as "l-dipivalylepinephrine" and its structure a Formula 8 (which is the same structure as Formula 1). (See Exhibit 1002, 5:17-22, 68-75.) These processes are instructive in making the other ester prodrugs of epinephrine that Truelove 1 recites.

124. Truelove 1 also discloses the pharmacological properties for the compound of the invention and related ester prodrugs of epinephrine in Tables 1-3. (*See* Exhibit 1002, 8:8-9:37.)

125. In Table 1, reproduced below, Truelove 1 reports the anti-asthmatic effects of four (4) ester prodrugs of epinephrine as compared to *l*-epinephrine. The recorded delay before onset of seizure ranged from 4 to 10 minutes. (*See* Exhibit 1002, Table 1, 8:33-64.)

Truelove 1, Exhibit 1002, Table 1

TABLE 1

Compound:	Delay before onset of seizure in minutes
Control	1–2
L - 3,4 - dihydroxy-α-[(methylamino)methyl] benzyl alcohol bitartrate	5.5
L - 3,4 - diacetyl - α-[(methylamino)methyl] benzyl alcohol hydroperchlorate	4
L - 3,4 - dipropionyl-α-[(methylamino)methyl] benzyl alcohol hydroperchlorate	5
L - 3,4-diisobutyryl-α-[(methylamino)methyl] benzyl alcohol hydroperchlorate	5
L - 3,4 - dipivalyl-α-[(methylamino)methyl] benzyl alcohol hydroperchlorate	8–10

126. In Table 2, reproduced below, Truelove 1 compares the chemical stability data for four (4) ester prodrugs of *l*-epinephrine to the parent *l*-epinephrine. This includes measurements of their (i) hydrolysis rates in a pH 4.5 acetate buffer solution at room temperature, expressed as $t_{1/2}$ days (excluding l-epinephrine); and (ii) rates of auto-oxidation in days of a 0.2% solution at a pH of 4 in an air oxidative environment. While the "dipivalyl" ester of epinephrine was the most stable of any of the compounds identified, nevertheless the other ester prodrugs were stable in the pH 4.5 acetate buffer solution for 30 to 50 days. (*See* Exhibit 1002, 8:65-9:14.)

Truelove 1, Exhibit 1002, Table 2

TABLE 2

Compound	Hydrolysis, $t_{1/2}$	Oxidation, days
L-3,4-dihydroxy-α-[(methylamino)methyl]benzyl alcohol bitartrate		15
L-3,4-diacetyl-α-[(methylamino)methyl]benzyl alcohol hydroperchlorate	30	20
L-3,4-dipropionyl-α-[methylamino)methyl]benzyl alcohol hydroperchlorate	34	35
L-3,4-diisobutyryl-α-[(methylamino)methyl]benzyl alcohol hydroperchlorate	50	35
L-3,4-dipivalyl-α-[(methylamino)methyl]benzyl alcohol hydroperchlorate	700	300

127. In Table 3, reproduced below, Truelove 1 discloses the rate of enzymatic hydrolysis of four (4) epinephrine ester prodrugs in various media at 37º C, and defines those rates as "the $t_{1/2}$ life." The enzymatic hydrolysis rate was measured at pH of about 7.5, at a concentration of 0.5 mg./ml. in, *inter alia,* human plasma. (*See* Exhibit 1002, 9:15-38.) Table 3 identifies three (3) prior art epinephrine prodrugs with half-lives ($t_{1/2}$) falling within the "half-life $t_{1/2}$ range from 1-6 minutes" recited in challenged claims 1, 2 and 3 of the '437 Patent.

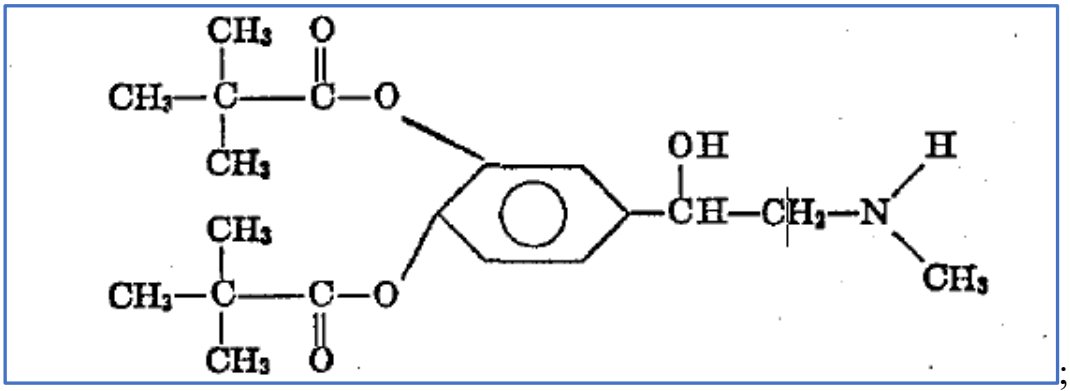
Truelove 1, Exhibit 1002, Table 3

TABLE 3

Compound	Rate of hydrolysis in $t_{1/2}$ seconds		
	Horse	Rabbit	Human
L-3,4-diacetyl-α-[(methylamino)-methyl] benzyl alcohol hydroperchlorate	20	45	150
L-3,4-dipropionyl-α-[(methylamino)methyl] benzyl alcohol hydroperchlorate	50	90	240
L-3,4-dibutyryl-α-[(methylamino)-methyl] benzyl alcohol hydroperchlorate	100	160	360
L-3,4-dipivalyl-α-[(methylamino)-methyl] benzyl alcohol hydroperchlorate	600	720	1,800

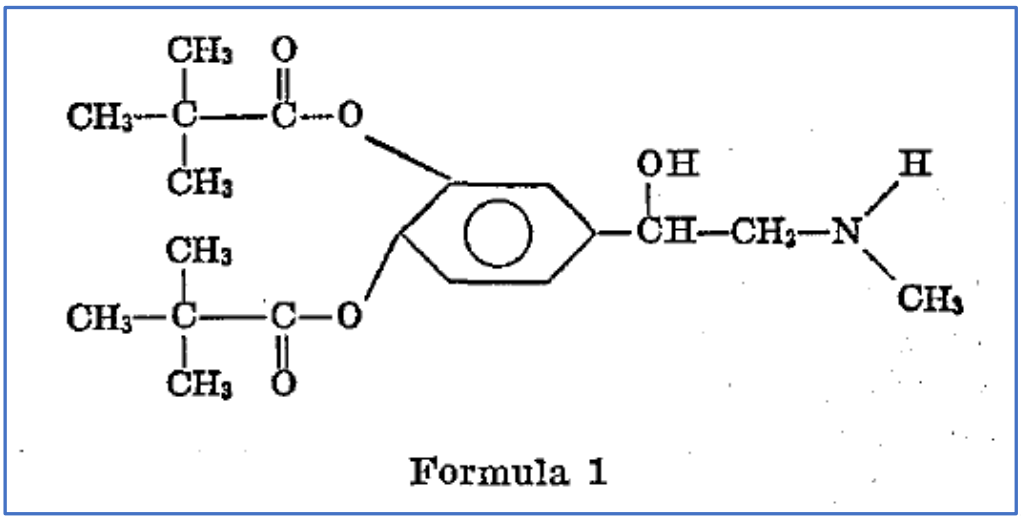
Truelove 1's Misidentification of Prodrugs

128. Truelove 1 is directed to epinephrine prodrugs with ester promoieties. Truelove 1's focus on ester promoieties of epinephrine cannot be overstated, for example: (i) Truelove 1 is entitled "Novel ester of ((methylamino)methyl) benzyl alcohol"; (ii) the Abstract provides "A novel ester of the general formula:



;

(iii) the Truelove 1 specification provides "[t]he present invention relates to both a novel and useful therapeutic ester of benzyl alcohol and to pharmaceutical compositions for using same. More particularly, Truelove 1 pertains to a new compound represented by Formula 1 copied below:



Formula 1;

(iv) the specification discloses "another object of the invention is to provide a novel and useful physicochemical ester of 3,4-dihydroxy-a- [(methylamino) methyl]benzyl alcohol [epinephrine] and its acceptable salts" (Exhibit 1002, 2:18-20).

129. Truelove 4, published after Truelove 1, correctly refers to the salt form of the Formula 1 ester prodrug as 3,4-dipivaloyloxy-α-(methylaminomethyl) benzyl alcohol perchlorate salt. (See Truelove 4, Exhibit 1007, p. 1510, 2nd col. and fn. 1.)

130. A POSA would have readily recognized that the ketone derivatives of α-[(methylamino methyl]benzyl alcohol (*i.e.,* 3,4-diacetyl, 3,4-dipropionyl, 3,4-dibutyryl, 3,4-diisobutyryl and 3,4-dipivalyl derivatives) listed in Truelove 1, Tables 1-3 are misidentified and misnamed, and should have instead been correctly identified as ester derivatives (*i.e.,* 3,4-diacetoxy, 3,4-dipropionoxy, 3,4-dibutyroxy, 3,4-diisobutyroxy and 3,4-dipivaloxy, or equivalently dipivaloyloxy) of α-[(methylamino methyl]benzyl alcohol. In other words, a POSA would have understood Truelove 1's ketone recitations of acetyl, propionyl, butyryl, isobutyryl and pivalyl promoieties, to be disclosing the acetoxy, propionoxy, butyroxy, isobutyroxy, dipivaloxy ester promoieties, respectively. See also following discussion.

131. Truelove 1's method of synthesizing the recited prodrugs is predicated on an esterification reaction. "Next, the hydroxyl groups of the product α-lower-3,4-dihydroxyacetophenone at positions C-3 and C-4 of the aryl ring are esterified by reacting an acylating agent with the hydroxyl group in an organic medium. Examples of acylating agents suitable for esterifying the hydroxyl groups include anhydrides, mixed anhydrides, the chloride of the appropriate alkanoic acid, and the like." (Truelove 1, Exhibit 1002, 3:15-22.)

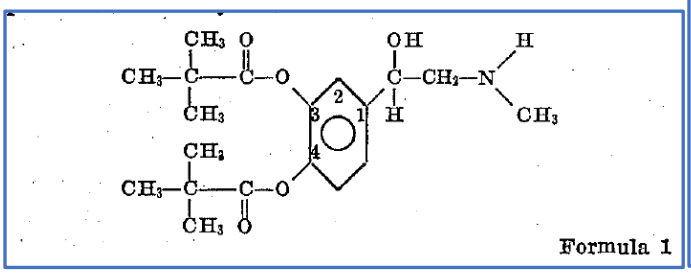
132. Moreover, further confirming the obvious misidentifications appearing in Truelove 1 is the fact that Truelove 3, filed after Truelove 1, correctly identifies the same prodrug promoiety compounds as esters. (*See, e.g.,* Truelove 3, Exhibit 1008, 1:9; 2:43; 10:4-72 (Tables 1-3).) Thus still further confirming that a POSA would have understood Truelove 1's misidentified ketone derivative compounds were ester derivative compounds.

133. Finally, the Almoazen '437 Patent clearly recognized that Truelove 1 disclosed the synthesis and half-lives of ester prodrugs of epinephrine, despite Truelove 1's misidentifying those compounds as ketone derivatives. As noted earlier, Almoazen specifically indicated that the structures depicted in Figures 7A-7D of the '437 Patent correspond to the **ester prodrugs of epinephrine** disclosed in Truelove 1.

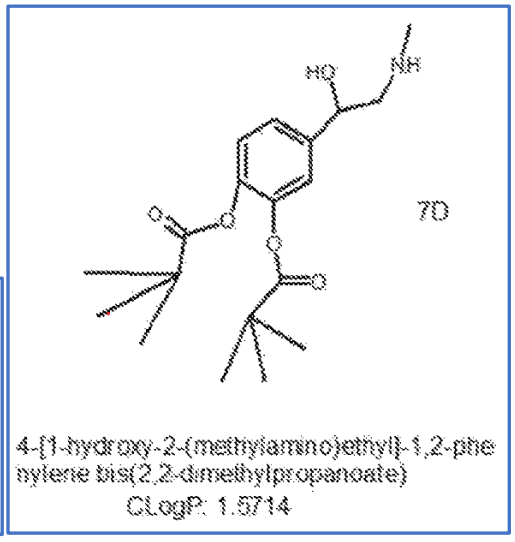
> "Anwar A. Hussain and James B. Truelove were granted patents [Truelove 1 (Exhibit 1002) and Truelove 3 (Exhibit 1008)] related to **the synthesis of novel esters of [(methylamino)methyl] benzyl alcohol** which is epinephrine. The purpose of the Hussain's et. al. invention was to develop a prodrug of epinephrine HCl with superior lipid solubility to enhance penetration through the cornea of the eye to treat glaucoma. Hussain et al. **[Truelove 1, Exhibit 1002] synthesized four different prodrugs for this purpose (see ['437 Patent] structures 7A, 7B, 7C, 7D)**."

‘437 Patent, Exhibit 1001, 2:5-12 (emphasis added).

134. Further supporting Almoazen understanding that Truelove 1 actually disclosed ester prodrugs and not ketone derivatives is that when after referring to Truelove 1’s “3,4-dipivalyl-α-[(methylamino)methyl]benzyl alcohol hydrochloride”, Almoazen correlates that compound to the structure depicted in Figure 7D of the ‘437 Patent. Moreover, Figure 7D employs an accurate naming convention for this compound, namely: 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,2-dimethylpropanoate). Finally, Almoazen’s ester prodrug shown in Figure 7D has the same structure as Truelove 1’s ester prodrug shown as Formula 1, see copies of each below.



Truelove 1, Exhibit 1002, 2:50-58.



‘437 Patent, Exhibit 1001, Fig. 7D.

The Half-Life of Salt and Non-Salt Forms of the Diester Prodrugs is Identical.

135. Finally, based on the presence of the term "hydroperchlorate" in the compounds identified in Table 3 of Truelove 1 and the presence of the term "hydrochloride" in the compounds identified in Table 3 of Truelove 3, the compounds so identified are the salt forms of the ester prodrugs whose half-lives are reported. While the salt form of ester prodrugs may slightly affect their dissolution rates, once dissolved, a POSA would have expected that the enzyme-mediated cleavage rates in the buffered medium or on the formation of the parent drug, used to determine their half-lives, would not have been impacted.

136. Challenged claims 1-3 of the '437 Patent claim the epinephrine prodrug in non-salt form (claim 1 also claims the salt form), whereas Truelove 1's Table 3 discloses the epinephrine prodrugs in their salt form.[29] However, a POSA would have understood that this difference would have had no effect on the compound's respective enzymatic hydrolysis half-life. This understanding stems, in part, from

[29] Truelove 4 also discloses one of the epinephrine prodrug salts from Truelove 1 Table 3.

the fact that Truelove 1 compounds are prepared as solutions[30] before exposure to hydrolyzing enzymes in plasma. The distinction between salt and non-salt forms could possibly impact dissolution rates, but once dissolved, a POSA would not have expected any impact on enzyme-mediated cleavage rates in the buffered medium and the formation of epinephrine, which is used to determine the half-life. Notably, the Almoazen '437 Patent does not report any hydrolysis data for any of compounds recited in challenged claims 1-3, other than the '437 Patent's reference to Truelove 1's half-life $t_{1/2}$ disclosures of the salt form of its ester prodrugs. See also discussion at ¶¶ 296-305, of Motivation to Combine section below.

137. Therefore, it is my opinion that Truelove 1's reported Table 3 half-lives for its "hydroperchlorate" compounds and Truelove 3's reported Table 3 half-lives for

[30] Truelove 4 disclosed that an aqueous solution of the prodrug was used. With respect to rabbit eye homogenate, "After equilibration, a 2-ml sample of the preparation was placed in another tube, mixed with 0.2 ml of a 4-mg/ml aqueous solution of the prodrug, flushed with nitrogen, and maintained at 37°." With respect to human plasma, "Two milliliters of the plasma" and "0.2 ml of the 4-mg/ml solution of prodrug was added". (Truelove 4, Exhibit 1007, p. 1511, 2nd col.)

its "hydrochloride" compounds, as disclosing the identical half-lives for the corresponding non-salt or free base form of those compounds.

Truelove 1 discloses Epinephrine Ester Prodrug where R = - CH_3 and half-life ($t_{1/2}$) = 3 minutes ('437 Patent claims 2 & 3).

Truelove 1, Table 3, EX1002, 9:26-38

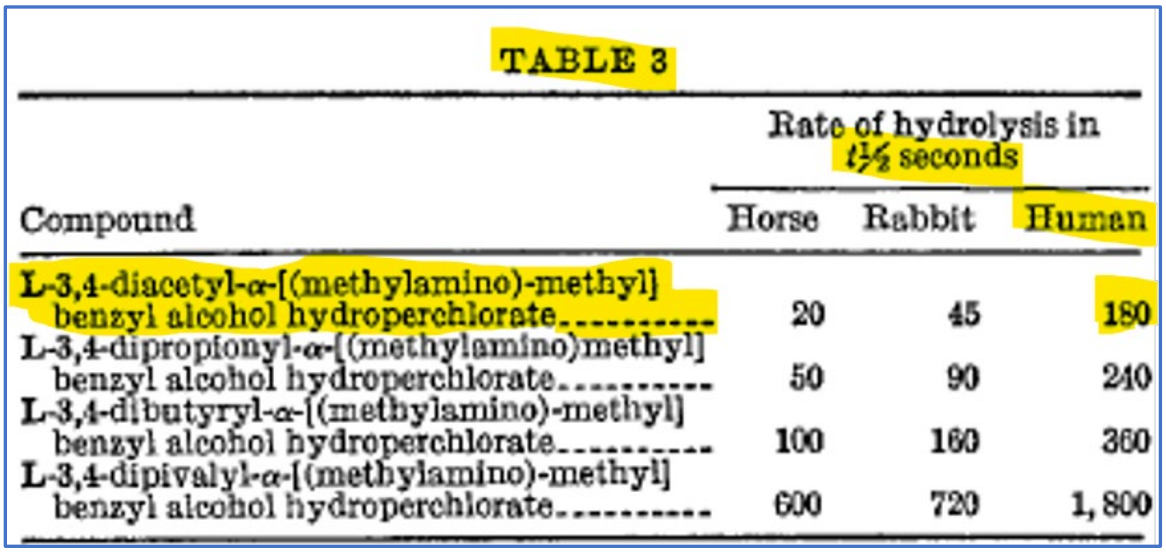


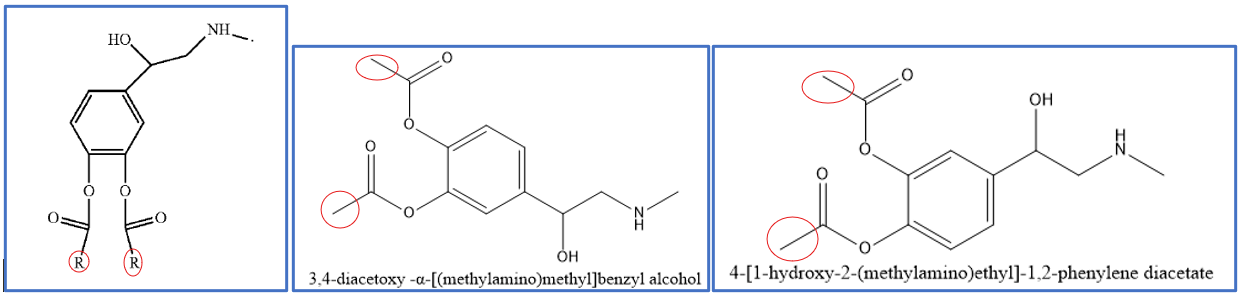
TABLE 3

Compound	Rate of hydrolysis in $t_{1/2}$ seconds		
	Horse	Rabbit	Human
L-3,4-diacetyl-α-[(methylamino)-methyl] benzyl alcohol hydroperchlorate	20	45	180
L-3,4-dipropionyl-α-[(methylamino)methyl] benzyl alcohol hydroperchlorate	50	90	240
L-3,4-dibutyryl-α-[(methylamino)-methyl] benzyl alcohol hydroperchlorate	100	160	360
L-3,4-dipivalyl-α-[(methylamino)-methyl] benzyl alcohol hydroperchlorate	600	720	1,800

138. As discussed above, see ¶¶ 128-134, a POSA would have understood that the identification of "L-3,4-**diacetyl**-α-[(methylamino)methyl] benzyl alcohol hydroperchlorate" in Table 3 of Truelove 1, though a misnomer, actually taught and disclosed the novel diester prodrug "L-3,4-**diacetoxy**-α-[(methylamino)methyl] benzyl alcohol hydroperchlorate."

139. A POSA would have understood the identification of the salt form of this ester prodrug was also a disclosure of the free base or non-salt form of this ester prodrug. (See ¶¶ 135-137.) Thus, a POSA would have understood, the

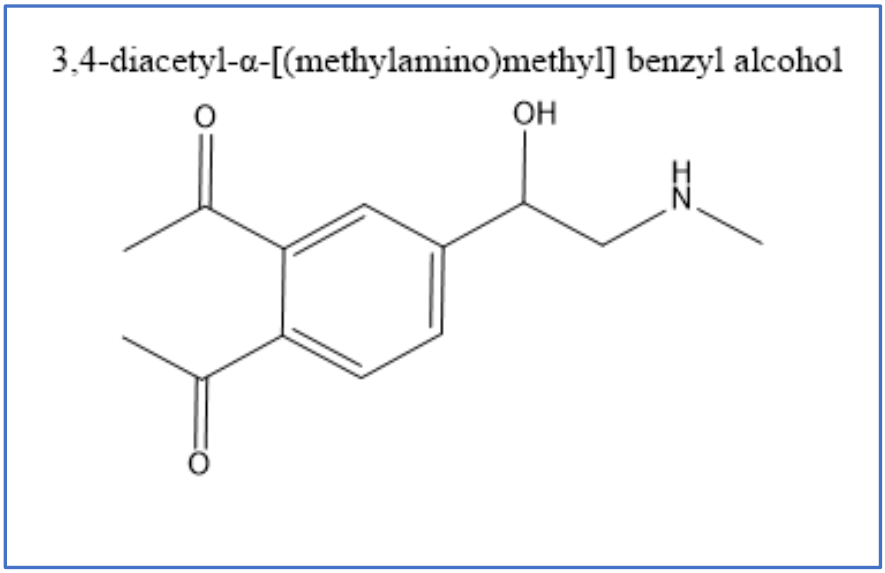
identification of "L-3,4-diacetyl-α-[(methylamino)methyl] benzyl alcohol hydroperchlorate" in Table 3 of Truelove 1 disclosed and taught the free base or non-salt form of the identified ester prodrug, namely: (i) the diester prodrug compound named "3,4-**diacetoxy**-α-[(methylamino)methyl] benzyl alcohol" and the same diester compound structure alternatively named "4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene diacetate" as claimed in claim 3 of the '437 Patent; and (ii) the diester prodrug compound having the structure where both R Groups (substituents) are -CH_3 as claimed in claim 2 of the '437 Patent. The free base or non-salt structures for this ester prodrug is shown below where both R groups are -CH_3. The first structure is from the claims of the '437 Patent, and the same second and third structures with alternative names from Truelove 1 were generated by ChemDraw®.



140. Specifically, a POSA would have understood Truelove 1's misidentification of this epinephrine prodrug in Table 3 was actually a disclosure of an ester prodrug

as well as the free base or non-salt structure of that ester prodrug, which a POSA could correctly identify and name for at least the following reasons.

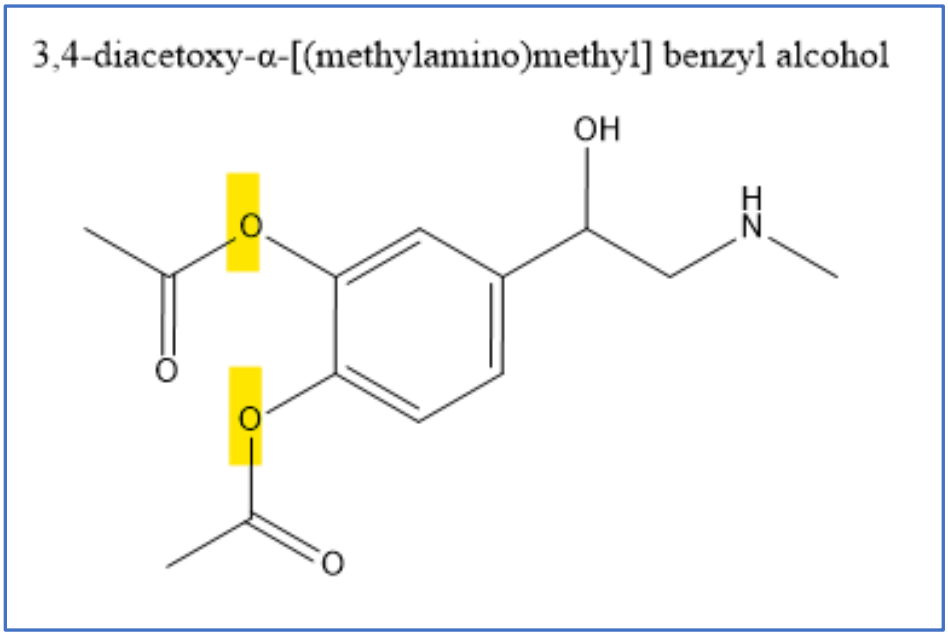
141. **First,** Truelove 1's invention is directed to novel ester prodrugs of epinephrine, see discussion above at ¶¶ 128-131, and a POSA would have appreciated that the compound identified as "L-3,4-**diacetyl**-α-[(methylamino)methyl] benzyl alcohol hydroperchlorate", in Table 3 of Truelove 1, was not a novel ester prodrug, but instead was incorrectly named and misidentified. In particular, Table 3 wrongly identified an epinephrine ketone derivative with the following free base or non-salt structure as generated by ChemDraw® shown below.



Ketone Derivative

A POSA would have recognized that this epinephrine ketone derivative could not function as a prodrug because it was unable to metabolize in human plasma into epinephrine and therefore is incapable of having a half-life $t_{1/2}$ which results in epinephrine. Basically, this is because while ketone groups can undergo oxidation and reduction, it would be highly unlikely for one to suddenly form a hydroxyl group attached to a benzyl ring. A POSA would not have expected known metabolic reactions to lead to such a transformation. Ar-O-CO-R (that is an aromatic ester) breaks down (hydrolyses) to Ar-OH. Ar-CO-R cannot hydrolyze to Ar-OH.

142. **Second,** to be a "novel ester" derivative of epinephrine as described in Truelove 1, the compound misidentified as "L-3,4-diacetyl-α-[(methylamino)methyl] benzyl alcohol hydroperchlorate" and its corresponding free base or non-salt structure would necessarily require the missing 2 oxygen atoms highlighted in the free base, or non-salt structure generated by ChemDraw® with highlighting added shown below.



Ester Derivative

Consequently, a POSA would have understood that the compound misidentified as "L-3,4-**diacetyl**-α-[(methylamino)methyl] benzyl alcohol hydroperchlorate" in Table 3 was instead a disclosure of "L-3,4-**diacetoxy**-α-[(methylamino)methyl] benzyl alcohol hydroperchlorate", which, in its free base or non-salt form can also be named "4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene diacetate." See ¶¶ 128-137 above.

143. **Third,** Figure 7A of the Almoazen '437 Patent, copied below, referred to the non-salt form of the ester derivative of epinephrine, identified in Table 3 (Truelove 1), by its structure and equivalent name: "4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene diacetate".

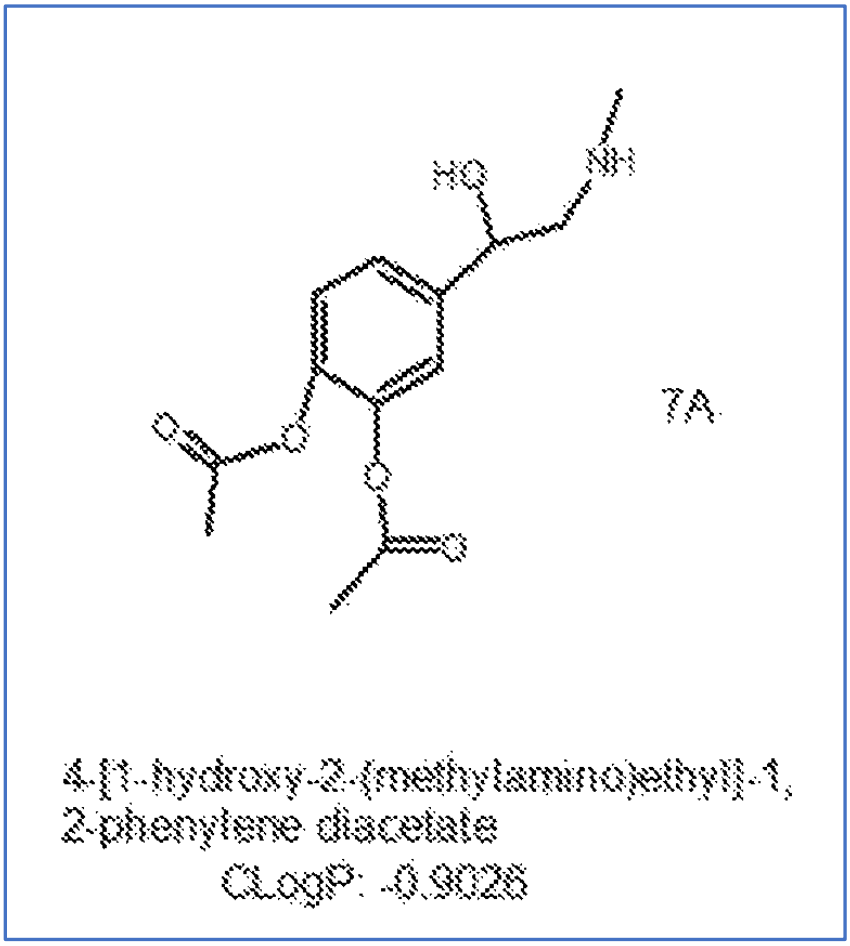
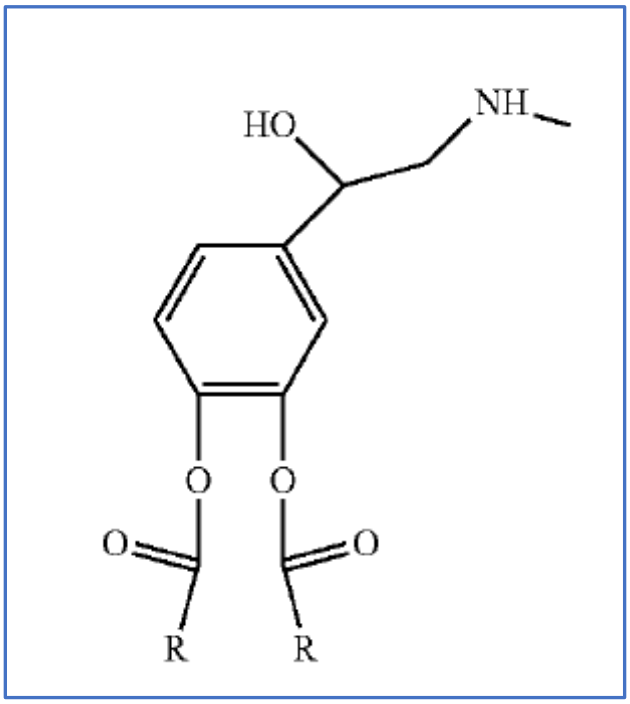


Exhibit 1001, Figure 7A (see also 6:42-57).

Thus, Truelove 1's disclosure of "L-3,4-**diacetyl**-α-[(methylamino)methyl] benzyl alcohol hydroperchlorate" compound in Table 3 of Truelove 1 would have been understood by a POSA as disclosing "L-3,4-**diacetoxy**-α-[(methylamino) methyl] benzyl alcohol hydroperchlorate", as well as its free base or non-salt form which can also be referred to as "4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene diacetate" – see Exhibit 1001, Figure 7A above.

144. In sum, a POSA would have understood Table 3's identification of the compound "L-3,4-diacetyl-α-[(methylamino)methyl] benzyl alcohol hydroperchlorate" was a misnomer and in fact disclosed the compound "L-3,4-diacetoxy-α-[(methylamino) methyl] benzyl alcohol hydroperchlorate". A POSA would have further understood that this correctly identified compound also disclosed its free base or non-salt ester prodrug structure, namely the structure reproduced below as claimed in claim 2 of the '437 Patent where both R Groups (substituents) as shown in the structure from claims 1 and 2 reproduced below are -CH_3.



A POSA would have further understood that this correctly identified compound also disclosed the epinephrine ester prodrug claimed in claim 3 of the '437 Patent

having the free base or non-salt structure identified as "4-[1-hydroxy-2-(methylamino) ethyl]-1,2-phenylene diacetate".

145. Finally, a POSA would have recognized that the identification of "L-3,4-diacetyl-α- [(methylamino)methyl] benzyl alcohol hydroperchlorate" in Table 3 with a half-life $t_{1/2}$ of approximately 180 seconds (3 minutes) was a disclosure of the claimed compound where the R Groups (substituents) are -CH_3 as recited in claim 2, which can be named "4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene diacetate" as recited in claim 3, and that the prodrug would have a half-life $t_{1/2}$ of approximately 180 seconds (3 minutes).

Truelove 1 discloses Epinephrine Ester Prodrug where R = -CH_2CH_3 and half-life ($t_{1/2}$) = 4 minutes ('437 Patent claims 2 & 3).

Truelove 1, Table 3, EX1002, 9:26-38

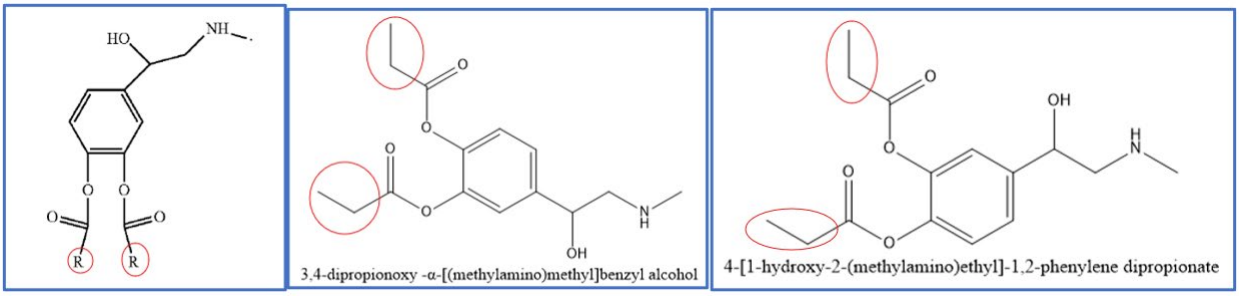
TABLE 3

Compound	Rate of hydrolysis in $t_{1/2}$ seconds		
	Horse	Rabbit	Human
L-3,4-diacetyl-α-[(methylamino)-methyl] benzyl alcohol hydroperchlorate	20	45	180
L-3,4-dipropionyl-α-[(methylamino)methyl] benzyl alcohol hydroperchlorate	50	90	240
L-3,4-dibutyryl-α-[(methylamino)-methyl] benzyl alcohol hydroperchlorate	100	160	360
L-3,4-dipivalyl-α-[(methylamino)-methyl] benzyl alcohol hydroperchlorate	600	720	1,800

146. As discussed above and below, see ¶¶ 128-137, a POSA would have understood that the identification of "L-3,4-**dipropionyl**-α-[(methylamino)methyl] benzyl alcohol hydroperchlorate" in Table 3 of Truelove 1, though a misnomer, actually taught and disclosed the novel ester prodrug "L-3,4-**dipropionoxy**-α-[(methylamino) methyl] benzyl alcohol hydroperchlorate."

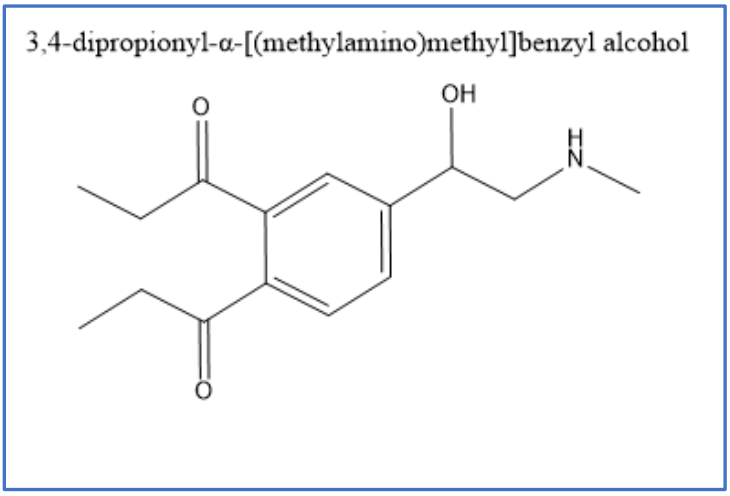
A POSA would have understood the identification of the salt form of this ester prodrug was also a disclosure of the free base or non-salt form of this ester prodrug. Thus, a POSA would have understood, the identification of "L-3,4-dipropionyl-α-[(methylamino)methyl]benzyl alcohol hydroperchlorate" in Table 3 of Truelove 1 disclosed and taught the free base or non-salt form of the identified ester prodrug, namely: (i) the diester prodrug compound named "3,4-dipropionoxy-α-[(methylamino) methyl] benzyl alcohol" and the same diester compound structure alternatively named "4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene dipropionate", recited in claim 3 of the '437 Patent; and (ii) the diester prodrug compound with a structure where both R Group (substituents) are -CH_2CH_3 as recited in claim 2 of the '437 Patent. The free base or non-salt structures for this ester prodrug are shown below where both R Groups (substituents) are -CH_2CH_3. From left to right, the first structure is from the claims of the '437 Patent, and the same second and third structures with alternative names

from Truelove 1 were generated by ChemDraw®.



147. Specifically, a POSA would have understood Truelove 1's misidentification of this epinephrine prodrug in Table 3 was actually a disclosure of an ester prodrug as well as the base or non-salt structure of that ester prodrug, which a POSA could correctly recognize and name for at least the following reasons.

148. **First,** Truelove 1's invention is directed to novel ester prodrugs of epinephrine, see discussion above at ¶¶ 128-131, and a POSA would have appreciated that the compound identified as "L-3,4-**dipropionyl**-α-[(methylamino)methyl]benzyl alcohol hydroperchlorate", in Table 3 of Truelove 1, was not a novel ester prodrug, but instead was incorrectly named and misidentified. In particular, Table 3 wrongly identified an inactive epinephrine ketone derivative with the following free base or non-salt structure as generated by ChemDraw® shown below.

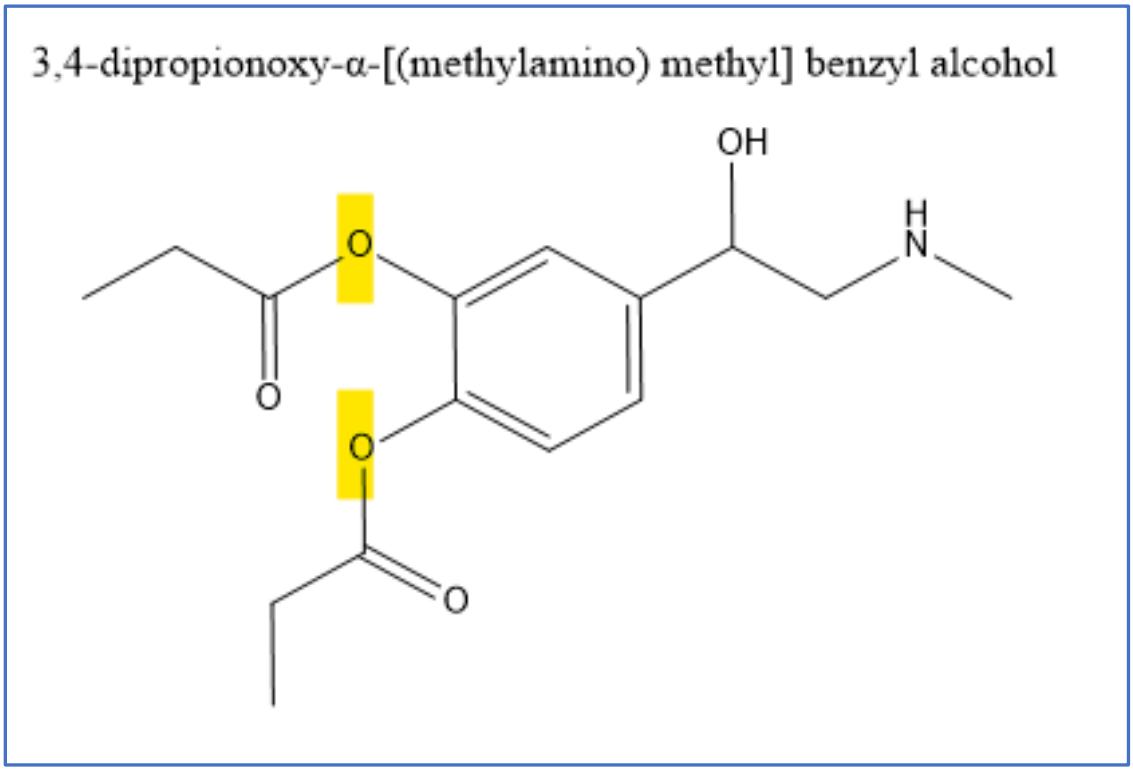


Ketone Derivative

A POSA would have recognized that this epinephrine ketone derivative could not function as a prodrug because it was unable to metabolize in human plasma into epinephrine and therefore is incapable of having a half-life $t_{1/2}$ which results in epinephrine. Basically, this is because while ketone groups can undergo oxidation and reduction, it would be highly unlikely for one to suddenly form a hydroxyl group attached to a benzyl ring. A POSA would not have expected known metabolic reactions to lead to such a transformation. Ar-O-CO-R (that is an aromatic ester) breaks down (hydrolyses) to Ar-OH. Ar-CO-R cannot hydrolyze to Ar-OH.

149. **Second,** to be a "novel ester" derivative of epinephrine as described in Truelove 1, the compound misidentified as "L-3,4-**dipropionyl**-α-[(methylamino)methyl] benzyl alcohol hydroperchlorate" and its corresponding free base or non-salt structure would necessarily require the missing two (2)

oxygen atoms highlighted in the structure generated by ChemDraw® with highlighting added shown below:



Ester Derivative

Consequently, a POSA would have understood that the compound misidentified as "L-3,4-**dipropionyl**-α-[(methylamino)methyl]benzyl alcohol hydroperchlorate" in Table 3 was instead actually a disclosure of "L-3,4-**dipropionoxy**-α-[(methylamino) methyl] benzyl alcohol hydroperchlorate", which, in its free base or non-salt form can also be named "4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene dipropionate." See ¶¶ 128-137 above.

Third, Figure 7C of the Almoazen '437 Patent, copied below, referred to the non-salt form of the ester derivative of epinephrine, identified in Table 3 (Truelove 1), by its equivalent name: "4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene dipropanoate [also referred to as dipropionate]."

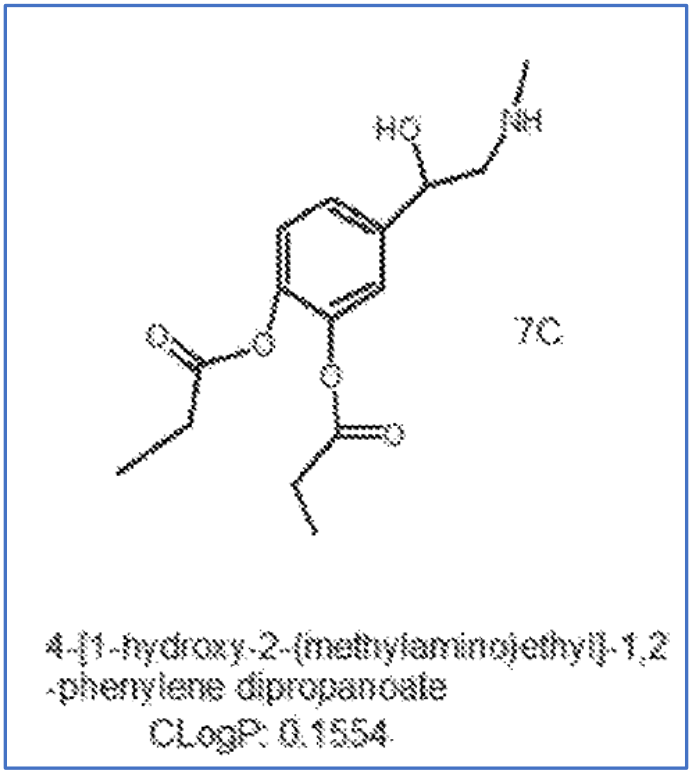
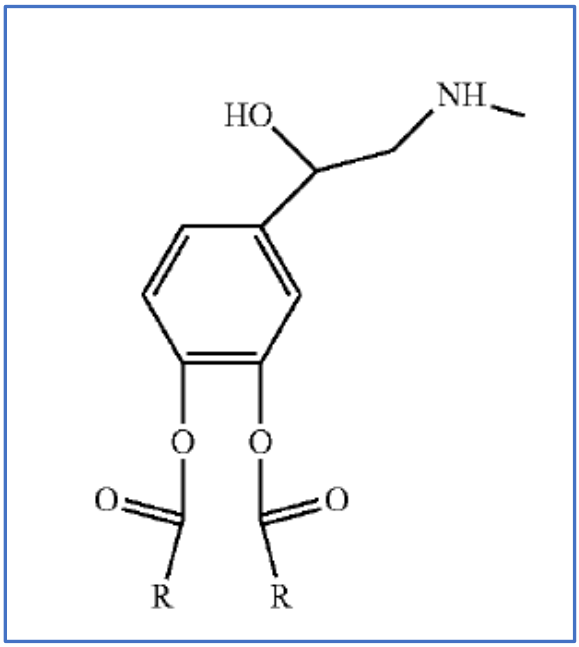


Exhibit 1001, Figure 7C(see also 6:42-57).

Thus, Truelove 1's disclosure of "L-3,4-**dipropionyl**-α-[(methylamino) methyl] benzyl alcohol hydroperchlorate" compound in Table 3 of Truelove 1 would have been understood by a POSA as actually disclosing "L-3,4-**dipropionoxy**-α-[(methylamino) methyl] benzyl alcohol hydroperchlorate", as well as its free base or non-salt form which can also be referred to as "4-[1-hydroxy-2-

(methylamino)ethyl]-1,2-phenylene dipropionate – see Exhibit 1001, Figure 7C above."

150. In sum, a POSA would have understood Table 3's identification of the compound "L-3,4-**dipropionyl**-α-[(methylamino) methyl] benzyl alcohol hydroperchlorate" was a misnomer and in fact disclosed the compound "L-3,4-**dipropionoxy**-α-[(methylamino) methyl] benzyl alcohol hydroperchlorate". A POSA would have further understood that this correctly identified compound also disclosed its free base or, non-salt ester prodrug structure, namely the structure reproduced below as claimed in claim 2 of the '437 Patent where both R Groups (substituents) as shown in the structure from claims 1 and 2 reproduced below are -CH_2CH_3.



A POSA would have further understood that this correctly identified compound also disclosed the epinephrine ester prodrug claimed in claim 3 of the '437 Patent having the free base or non-salt structure that can be identified as "4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene dipropionate".

151. Finally, a POSA would have recognized that the identification of "L-3,4-**dipropionyl**-α-[(methylamino) methyl] benzyl alcohol hydroperchlorate" in Table 3 with a half-life $t_{1/2}$ of 240 seconds (4 minutes) was a disclosure of the compound recited in claim 2 where both R Groups (substituents) are $-CH_2CH_3$ and that this compound could also be named "4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene dipropionate" as recited in claim 3, and that these compounds would have a half-life $t_{1/2}$ of approximately 240 seconds (4 minutes), which is within the range of from 1-6 minutes.

Truelove 1 discloses Epinephrine Ester Prodrug where R = -CH(CH$_3$)$_2$ ('437 Patent claims 2 & 3).

Truelove 1, Table 2, EX1002, 9:3-14

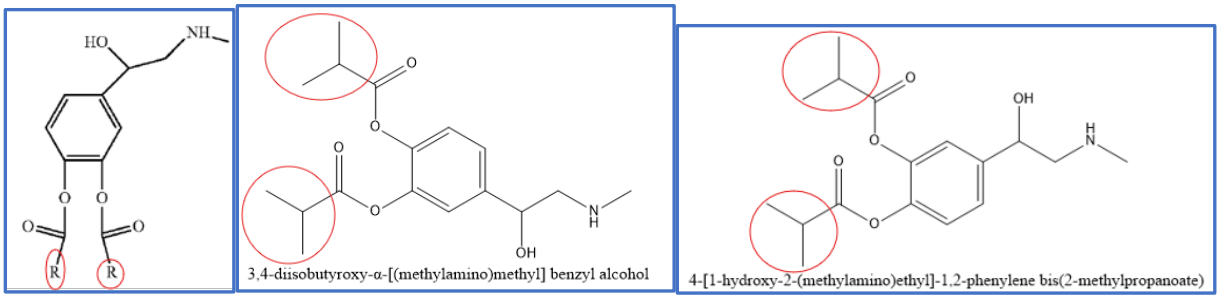
TABLE 2

Compound	Hydrolysis, $t_{1/2}$	Oxidation, days
L-3,4-dihydroxy-α-[(methylamino)methyl]benzyl alcohol bitartrate		15
L-3,4-diacetyl-α-[(methylamino)methyl]benzyl alcohol hydroperchlorate	30	20
L-3,4-dipropionyl-α-[methylamino)methyl]benzyl alcohol hydroperchlorate	34	35
L-3,4-diisobutyryl-α-[(methylamino)methyl]benzyl alcohol hydroperchlorate	50	35
L-3,4-dipivalyl-α-[(methylamino)methyl]benzyl alcohol hydroperchlorate	700	300

152. As discussed above and below, see ¶¶ 128-137, a POSA would have understood that the identification of "L-3,4-**diisobutyryl**-α-[(methylamino methyl] benzyl alcohol hydroperchlorate" in Table 2 of Truelove 1, though a misnomer, actually taught and disclosed the novel ester prodrug "L-3,4-**diisobutyroxy**-α-[(methylamino)methyl] benzyl alcohol hydroperchlorate."

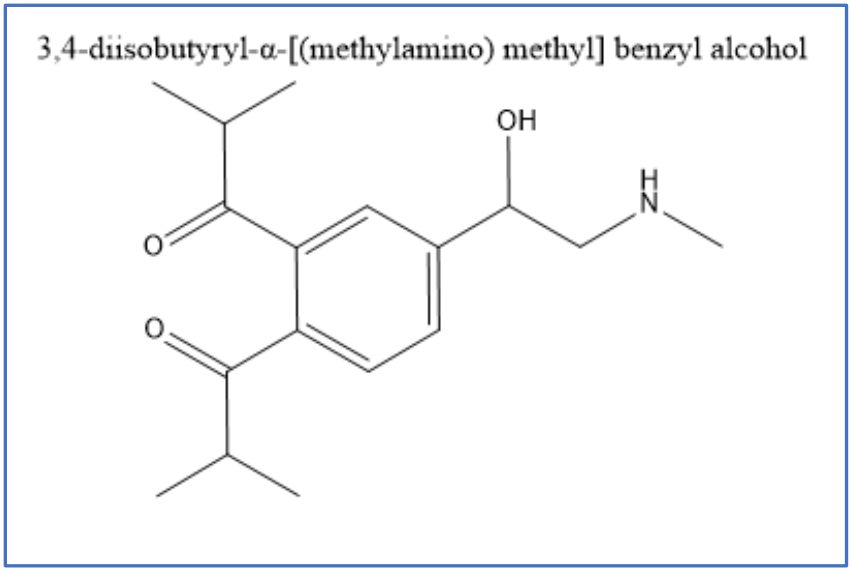
153. A POSA would have understood the identification of the salt form of this ester prodrug was also a disclosure of the free base or non-salt form of this ester prodrug. Thus, a POSA would have understood, the identification of "L-3,4-**diisobutyryl**-α-[(methylamino) methyl] benzyl alcohol hydroperchlorate" in Table 2 of Truelove 1 disclosed and taught the free base or non-salt form of the identified

ester prodrug, namely: (i) the diester prodrug compound named "3,4-**diisobutyroxy**-α-[(methylamino)methyl] benzyl alcohol" and the same diester compound structure alternatively named "4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene bis(2-methylpropanoate)", recited in claim 3 of the '437 Patent; and (ii) the diester prodrug compound with a structure where both R Groups (substituents) are - $CH(CH_3)_2$ as recited in challenged claim 2 of the '437 Patent. The free base or non-salt structure for this ester prodrug is shown below where both R Groups (substituents) are -$CH(CH_3)_2$. From left to right, the first structure is from the claims of the '437 Patent, and the same second and third structures with alternative names from Truelove 1 were generated by ChemDraw®.



154. Specifically, a POSA would have understood Truelove 1's misidentification of this epinephrine prodrug in Table 2 was actually a disclosure of an ester prodrug as well as the free base or non-salt form of that ester prodrug, which a POSA could correctly identify and name for at least the following reasons.

155. **First,** Truelove 1's invention is directed to novel ester prodrugs of epinephrine, see discussion above at ¶¶ 128-131, and a POSA would have appreciated that the compound identified as "L-3,4-**diisobutyryl**-α-[(methylamino methyl)] benzyl alcohol hydroperchlorate", in Table 2 of Truelove 1, was not a novel ester prodrug, but instead was incorrectly named and misidentified. In particular, Table 2 wrongly identified an inactive epinephrine ketone derivative with the following free base or non-salt structure as generated by ChemDraw® shown below.

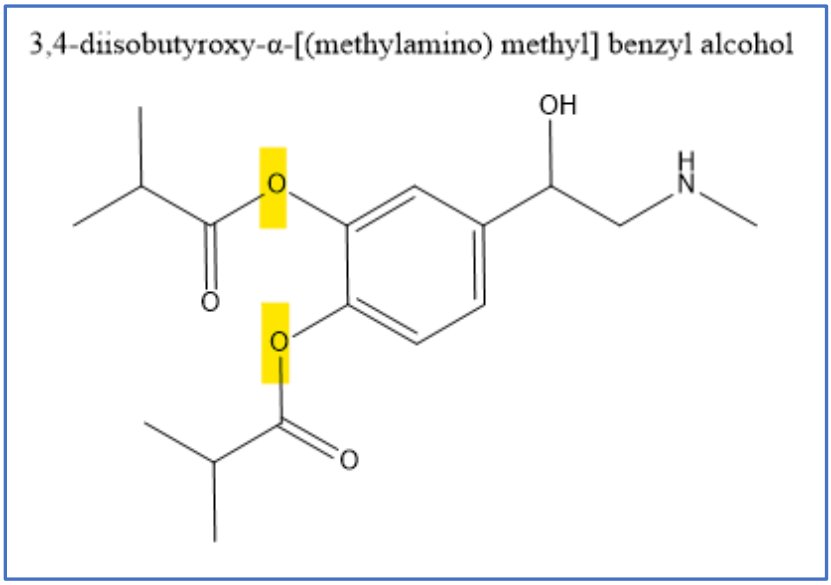


Ketone Derivative

A POSA would have recognized that this epinephrine ketone derivative could not function as a prodrug because it was unable to metabolize in human plasma into

epinephrine and therefore is incapable of having a half-life $t_{1/2}$ which results in epinephrine. Basically, this is because while ketone groups can undergo oxidation and reduction, it would be highly unlikely for one to suddenly form a hydroxyl group attached to a benzyl ring. A POSA would not have expected known metabolic reactions to lead to such a transformation. Ar-O-CO-R (that is an aromatic ester) breaks down (hydrolyses) to Ar-OH. Ar-CO-R cannot hydrolyze to Ar-OH.

156. **Second,** to be a "novel ester" derivative of epinephrine as described in Truelove 1, the compound misidentified as "L-3,4-**diisobutyryl**-α-(methylamino methyl] benzyl alcohol hydroperchlorate" and its corresponding free base or non-salt structure would necessarily require the missing two (2) oxygen atoms highlighted in the structure generated by ChemDraw® with highlighting added shown below.



Ester Derivative

Consequently, a POSA would have understood that the compound misidentified as "L-3,4-**diisobutyryl**-α-(methylamino methyl] benzyl alcohol hydroperchlorate" in Table 2 was instead a disclosure of "L-3,4-**diisobutyroxy**-α-[(methylamino) methyl] benzyl alcohol hydroperchlorate", which, in its free base or non-salt form can also be named "4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene bis(2-methylpropanoate)." See ¶¶ 128-137, above.

157. **Third,** Figure 7B of the Almoazen '437 Patent, copied below, demonstrates that the '437 Patent understood that Truelove 1 disclosed the base or non-salt form of the ester derivative of epinephrine, identified in Table 2 (Truelove 1), by its equivalent name: "4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene bis(2-methylpropanoate)."

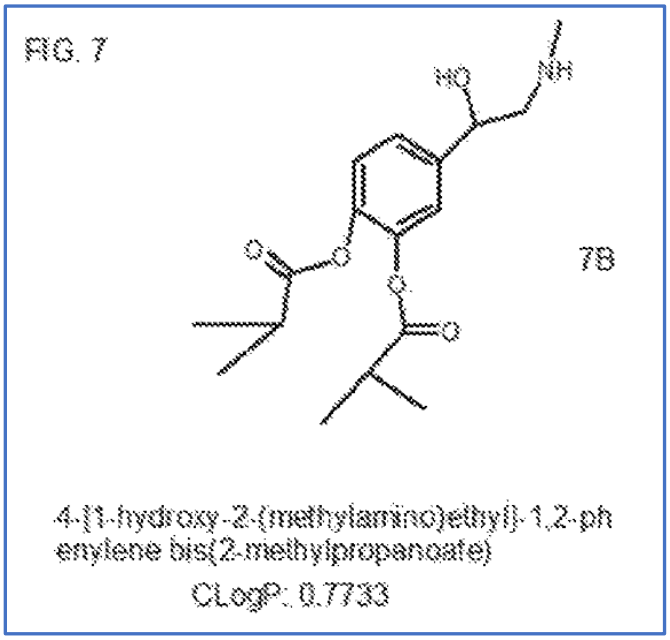
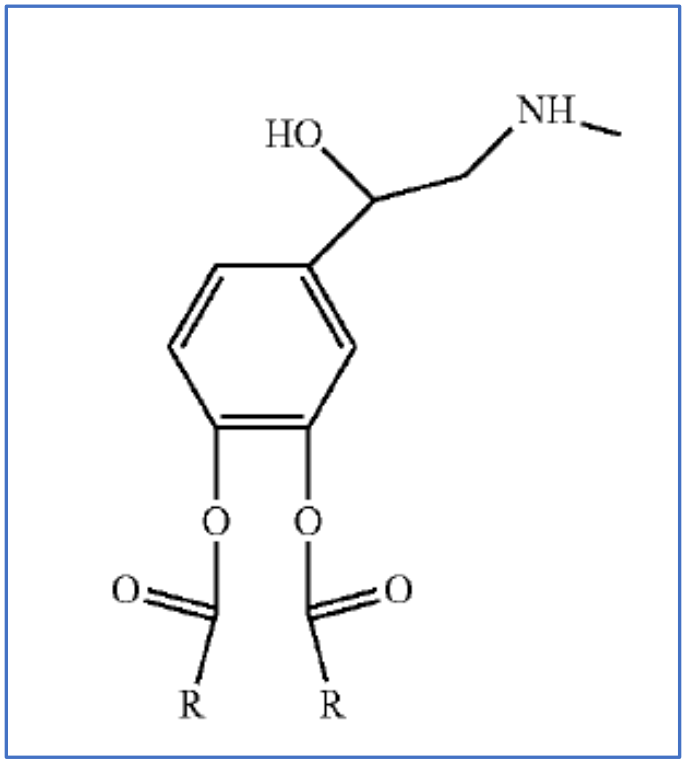


Exhibit 1001, Figure 7B (see also 6:42-57).

Thus, Truelove 1's identification of "L-3,4-**diisobutyryl**-α-(methylamino methyl] benzyl alcohol hydroperchlorate" compound in Table 2 of Truelove 1 would have been understood by a POSA as actually disclosing "L-3,4-**diisobutyroxy**-α-[(methylamino) methyl] benzyl alcohol hydroperchlorate", as well as its free base or non-salt form which can also be referred to as "4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene bis(2-methylpropanoate)" – see Exhibit 1001, Figure 7B above.

158. In sum, a POSA would have understood Table 2's identification of the compound "L-3,4-**diisobutyryl**-α-(methylamino methyl] benzyl alcohol hydroperchlorate" was a misnomer and in fact disclosed the compound "L-3,4-

diisobutyroxy-α-[(methylamino) methyl] benzyl alcohol hydroperchlorate". A POSA would have further understood that this correctly identified compound also disclosed its free base or, non-salt ester prodrug structure, namely the structure reproduced below as recited in claim 2 of the '437 Patent where both R Groups (substituents) as shown in the structure from claims 1 and 2 reproduced below are -$CH(CH_3)_2$.



159. A POSA would have further understood that this correctly identified compound also disclosed the epinephrine ester prodrug claimed in claim 3 of the '437 Patent having the free base or non-salt structure identified as "4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene bis(2-methylpropanoate)."

Truelove 1 discloses Epinephrine Ester Prodrug where R = -C(CH$_3$)$_3$ and half-life ($t_{1/2}$) = 30 minutes

Truelove 1, Table 3, EX1002, 9:26-38

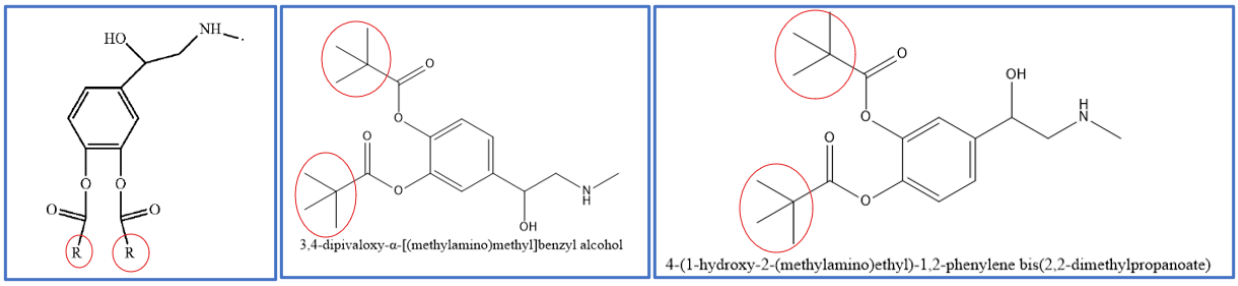
TABLE 3

Compound	Rate of hydrolysis in $t_{1/2}$ seconds		
	Horse	Rabbit	Human
L-3,4-diacetyl-α-[(methylamino)-methyl] benzyl alcohol hydroperchlorate	20	45	180
L-3,4-dipropionyl-α-[(methylamino)methyl] benzyl alcohol hydroperchlorate	50	90	240
L-3,4-dibutyryl-α-[(methylamino)-methyl] benzyl alcohol hydroperchlorate	100	160	360
L-3,4-dipivalyl-α-[(methylamino)-methyl] benzyl alcohol hydroperchlorate	600	720	1,800

160. As discussed above and below, see ¶¶ 128-137, a POSA would have understood that the identification of "L-3,4-**dipivalyl**-α-[(methylamino)methyl] benzyl alcohol hydroperchlorate" in Table 3 of Truelove 1, though a misnomer, actually taught and disclosed the novel ester prodrug "L-3,4-**dipivaloxy**-α-[(methylamino)methyl] benzyl alcohol hydroperchlorate."

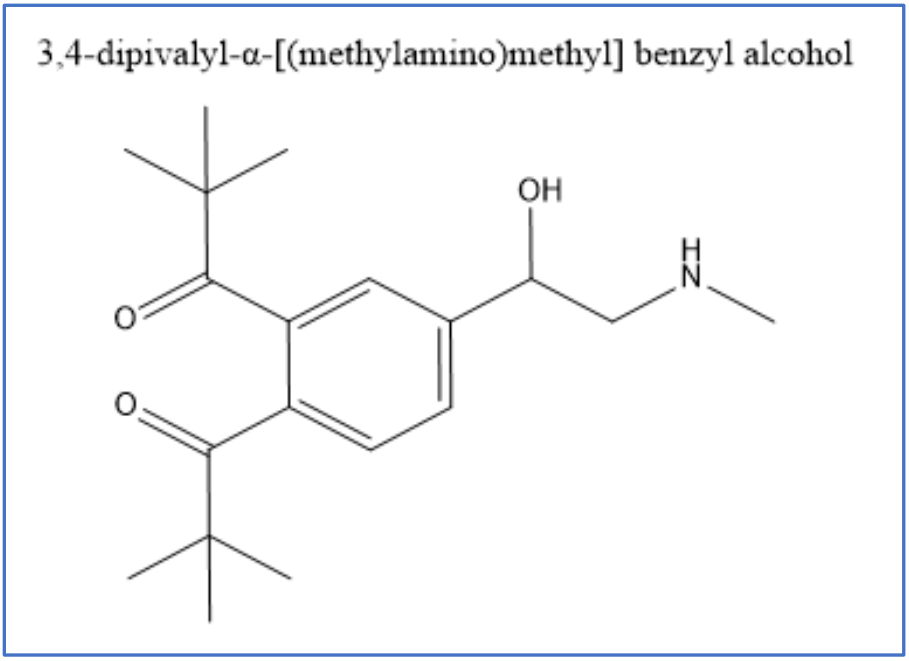
161. A POSA would have understood the identification of the salt form of this ester prodrug was also a disclosure of the free base or non-salt form of this ester prodrug. Thus, a POSA would have understood, the identification of "L-3,4-dipivalyl-α-[(methylamino)methyl] benzyl alcohol hydroperchlorate" in Table 3 of Truelove 1 disclosed and taught the free base or non-salt form of the identified

ester prodrug, namely: (i) the diester prodrug compound named "3,4-dipivaloxy-α-[(methylamino)methyl] benzyl alcohol" and the same diester compound structure alternatively named "4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene bis(2,2-dimethylpropanoate)", recited in claim 3 of the '437 Patent; and (ii) the prodrug with a structure where both R Groups (substituents) are -$C(CH_3)_3$. The free base or non-salt structure for this ester prodrug is shown below where both R Groups (substituents) are -$C(CH_3)_3$. The first structure is from the claims of the '437 Patent, and the same second and third structures with alternative names from Truelove 1 were generated by ChemDraw®.



162. Specifically, a POSA would have understood Truelove 1's misidentification of this epinephrine prodrug in Table 3 was actually a disclosure of an ester prodrug compound, as well as the free base or non-salt form of that ester prodrug compound, which a POSA could identify and correctly name for at least the following reasons.

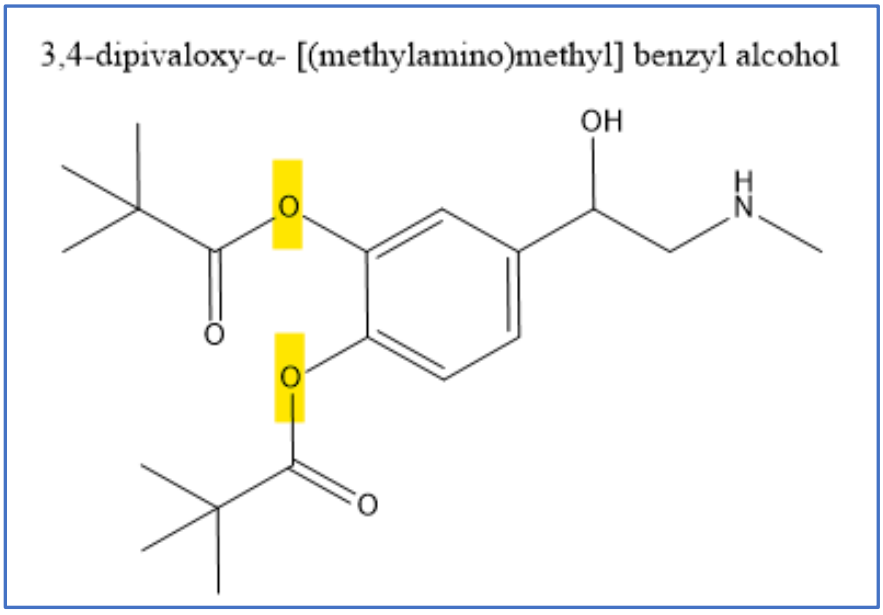
163. **First,** Truelove 1's invention is directed to novel ester prodrugs of epinephrine, see discussion above at ¶¶ 128-131, and a POSA would have appreciated that the compound identified as "L-3,4-dipivalyl-α-[(methylamino)methyl] benzyl alcohol hydroperchlorate", in Table 3 of Truelove 1, was not a novel ester prodrug, but instead was incorrectly named and misidentified. In particular, Table 3 wrongly identified an inactive epinephrine ketone derivative with the following free base or non-salt structure as generated by ChemDraw® shown below.



Ketone Derivative

A POSA would have recognized that this epinephrine ketone derivative could not function as a prodrug because it is unable to metabolize in human plasma into epinephrine and therefore is incapable of having a half-life $t_{1/2}$ which results in epinephrine. Basically, this is because while ketone groups can undergo oxidation and reduction, it would be highly unlikely for one to suddenly form a hydroxyl group attached to a benzyl ring. A POSA would not have expected known metabolic reactions to lead to such a transformation. Ar-O-CO-R (that is an aromatic ester) breaks down (hydrolyses) to Ar-OH. Ar-CO-R cannot hydrolyze to Ar-OH.

164. **Second,** to be a "novel ester" derivative of epinephrine as described in Truelove 1, the compound misidentified as "L-3,4-dipivalyl-α-[(methylamino)methyl] benzyl alcohol hydroperchlorate" and its corresponding free base or non-salt structure would necessarily require the missing 2 oxygen atoms highlighted in the structure generated by ChemDraw® with highlighting added shown below.



Ester Derivative

165. Consequently, a POSA would have understood that the compound misidentified as "L-3,4-**dipivalyl**-α-[(methylamino)methyl] benzyl alcohol hydroperchlorate" in Table 3 was instead a disclosure of "L-3,4-**dipivaloxy**-α-[(methylamino)methyl] benzyl alcohol hydroperchlorate", which, in its free base or non-salt form can also be named "4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene bis(2,2-dimethylpropanoate)." See ¶¶ 128-137, above.

166. **Third,** Figure 7D of the Almoazen '437 Patent, copied below, referred to the non-salt form of the ester derivative of epinephrine, identified in Table 3 (Truelove 1), by its equivalent name: "4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene bis(2,2-dimethylpropanoate)."

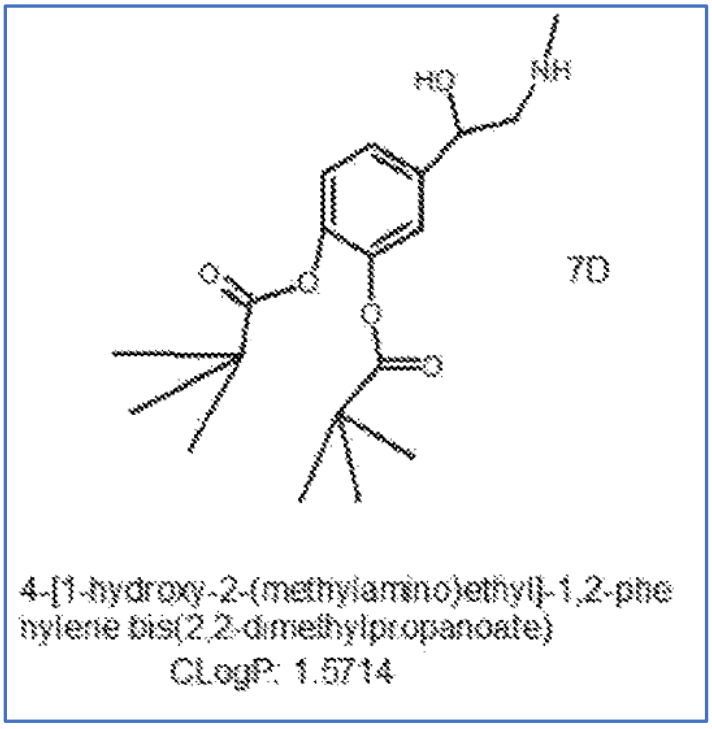
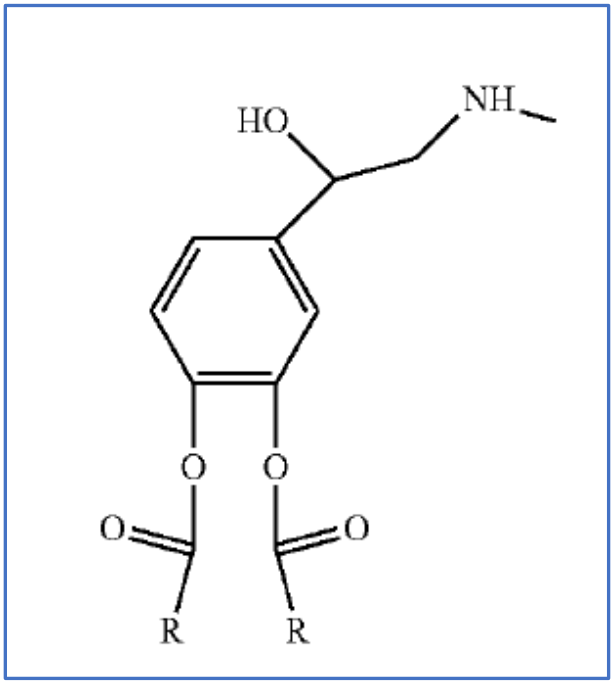


Exhibit 1001, Figure 7D (see also 6:42-57).

167. Thus, Truelove 1's disclosure of "L-3,4-**dipivalyl**-α-[(methylamino)methyl] benzyl alcohol hydroperchlorate" compound in Table 3 of Truelove 1 would have been understood by a POSA as disclosing "L-3,4-**dipivaloxy**-α-[(methylamino)methyl] benzyl alcohol hydroperchlorate", as well as its free base or, non-salt form which can also be called "4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene bis(2,2-dimethylpropanoate)" – see Exhibit 1001, Figure 7D above.

168. In sum, a POSA would have understood Table 3's identification of the compound "L-3,4-**dipivalyl**-α-[(methylamino)methyl] benzyl alcohol hydroperchlorate" was a misnomer and in fact disclosed "L-3,4-**dipivaloxy**-α-

[(methylamino)methyl] benzyl alcohol hydroperchlorate". A POSA would have further understood that this correctly identified compound also disclosed its free base or non-salt ester prodrug structure, namely the structure reproduced below where both R Groups (substituents) are -$C(CH_3)_3$.



A POSA would have further understood that this correctly identified compound also disclosed the free base or non-salt form of the epinephrine ester prodrug shown in Figure 7D of the '437 Patent and identified as "4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene bis(2,2-dimethylpropanoate)".

169. Finally, a POSA would have recognized that the identification of "L-3,4-di~~pivalyl~~pivaloxy-α-[(methylamino)methyl]benzyl alcohol hydroperchlorate" in Table 3 with a half-life $t_{1/2}$ of approximately 1800 seconds (30 minutes) was a

disclosure of the compound where both R Groups (substituents) are -$C(CH_3)_3$ and that it is also called "4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene bis(2,2-dimethylpropanoate)", and that this compound would have a half-life $t_{1/2}$ of 1800 seconds (30 minutes).

Truelove 1 discloses Epinephrine Ester Prodrug where R =-$CH_2CH_2CH_3$ ('437 Patent claim 1) and half-life ($t_{1/2}$) = 6 minutes.

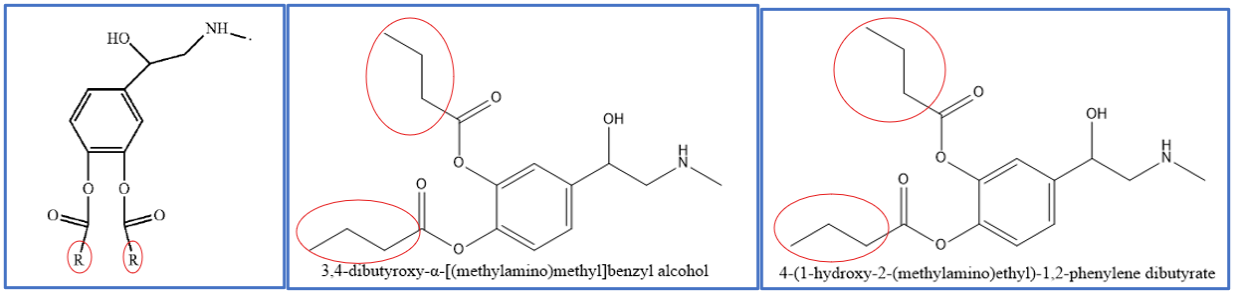
Truelove 1, Table 3, EX1002, 9:26-38

TABLE 3

Compound	Rate of hydrolysis in $t_{1/2}$ seconds		
	Horse	Rabbit	Human
L-3,4-diacetyl-α-[(methylamino)-methyl] benzyl alcohol hydroperchlorate	20	45	180
L-3,4-dipropionyl-α-[(methylamino)methyl] benzyl alcohol hydroperchlorate	50	90	240
L-3,4-dibutyryl-α-[(methylamino)-methyl] benzyl alcohol hydroperchlorate	100	160	360
L-3,4-dipivalyl-α-[(methylamino)-methyl] benzyl alcohol hydroperchlorate	600	720	1,800

170. As discussed above and below, see ¶¶ 128-137, a POSA would have understood that the identification of "L-3,4-**dibutyryl**-α-[(methylamino)methyl] benzyl alcohol hydroperchlorate" in Table 3 of Truelove 1, though a misnomer, actually taught and disclosed the novel ester prodrug "L-3,4-**dibutyroxy**-α-[(methylamino)methyl] benzyl alcohol hydroperchlorate."

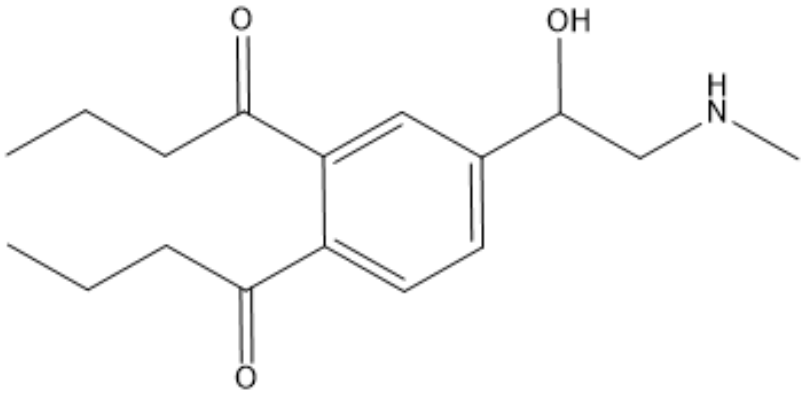
171. A POSA would have understood the identification of the salt form of this ester prodrug was also a disclosure of the free base or non-salt form of this ester prodrug compound. Thus, a POSA would have understood, the identification of "L-3,4-dibutyryl-α-[(methylamino)methyl] benzyl alcohol hydroperchlorate" in Table 3 of Truelove 1 disclosed and taught the free base or non-salt form of the identified ester prodrug, namely: (i) the diester prodrug compound named "3,4-dibutyroxy-α-[(methylamino)methyl] benzyl alcohol" and the same diester compound structure alternatively named "4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene dibutyrate"; and (ii) the diester prodrug with a structure where both R Groups (substituents) are $-CH_2CH_2CH_3$ as recited in challenged claim 1 of the '437 Patent. The base or non-salt structure for this ester prodrug is shown below where both R Groups (substituents) are $-CH_2CH_2CH_3$. The first structure is from claim 1 of the '437 Patent, and the same second and third structures with alternative names from Truelove 1 were generated by ChemDraw®.



172. Specifically, a POSA would have understood Truelove 1's misidentification of this epinephrine prodrug in Table 3 was actually a disclosure of an ester prodrug as well as base or the non-salt structure of that ester prodrug compound, which a POSA could correctly identify and name for at least the following reasons.

173. **First,** Truelove 1's invention is directed to novel ester prodrugs of epinephrine, see discussion above at ¶¶ 128-131, and a POSA would have appreciated that the compound identified as "L-3,4-**dibutyryl**-α-[(methylamino)methyl] benzyl alcohol hydroperchlorate", in Table 3 of Truelove 1, was not a novel ester prodrug, but instead was incorrectly named and misidentified. In particular, Table 3 wrongly identified an inactive epinephrine ketone derivative with the following free base or non-salt structure as generated by ChemDraw® shown below.

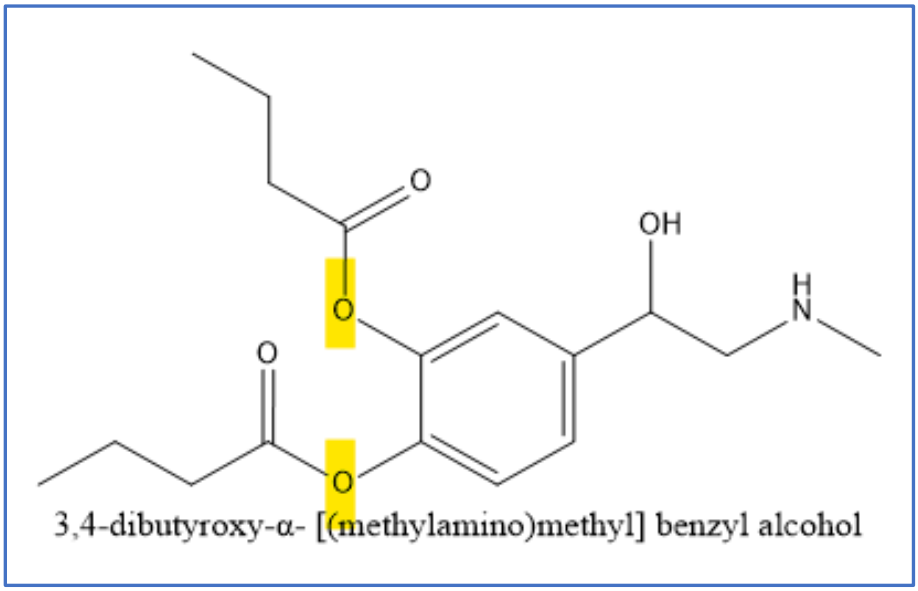
3,4-dibutyryl-α-[(methylamino)methyl] benzyl alcohol



Ketone Derivative

A POSA would have recognized that this epinephrine ketone derivative could not function as a prodrug because it is unable to metabolize in human plasma into epinephrine and therefore is incapable of having a half-life $t_{1/2}$ which results in epinephrine. Basically, this is because while ketone groups can undergo oxidation and reduction, it would be highly unlikely for one to suddenly form a hydroxyl group attached to a benzyl ring. A POSA would not have expected known metabolic reactions to lead to such a transformation. Ar-O-CO-R (that is an aromatic ester) breaks down (hydrolyses) to Ar-OH. Ar-CO-R cannot hydrolyze to Ar-OH.

174. **Second,** to be a "novel ester" derivative of epinephrine as described in Truelove 1, the compound misidentified as "L-3,4-**dibutyryl**-α-[(methylamino) methyl] benzyl alcohol hydroperchlorate" and its corresponding free base or non-salt structure would necessarily require the missing 2 oxygen atoms highlighted in the structure generated by ChemDraw® with highlighting added shown below.



Ester Derivative

Consequently, a POSA would have understood that the compound misidentified as "L-3,4-**dibutyryl**-α-[(methylamino)methyl] benzyl alcohol hydroperchlorate" in Table 3 was instead a disclosure of "L-3,4-**dibutyroxy**-α- [(methylamino)methyl] benzyl alcohol hydroperchlorate", which, in its free base or non-salt form can also be named "4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene dibutyrate." See ¶¶ 128-137, above.

175. **Third,** Figure 5G" of the Almoazen '437 Patent, copied below, referred to the free base or non-salt form of the ester derivative of epinephrine, identified in Table 3 (Truelove 1), by its equivalent name: "4-(1-hydroxy-2-(methylamino) ethyl)-1,2-phenylene dibutyrate".

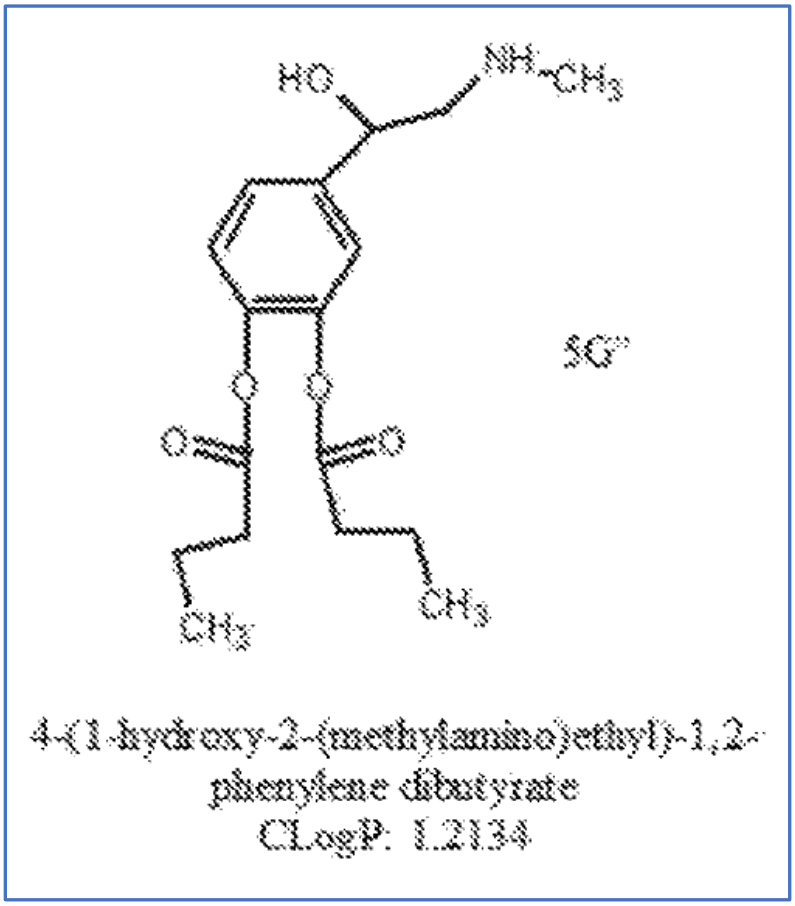
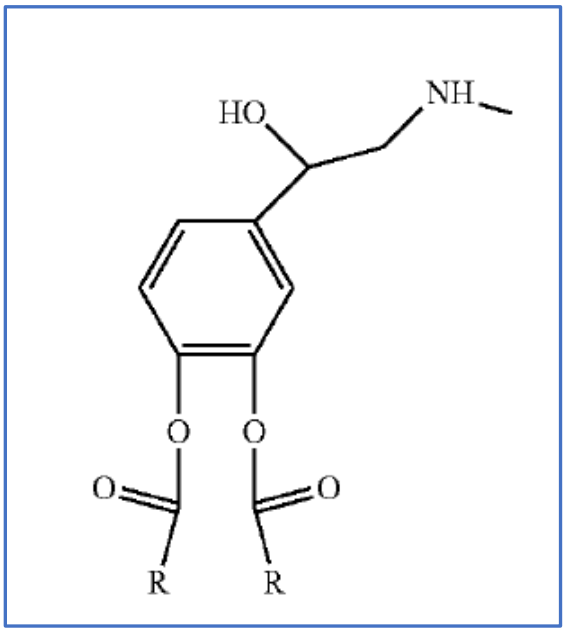


Exhibit 1001, Figure 5G" (see also 6:24-32).

Thus, Truelove 1's disclosure of "L-3,4-**dibutyryl**-α-[(methylamino)methyl] benzyl alcohol hydroperchlorate" compound in Table 3 of Truelove 1 would have been understood by a POSA as actually disclosing "L-3,4-**dibutyroxy**-α-[(methylamino)methyl] benzyl alcohol hydroperchlorate", as well as its free base or non-salt form which can also be referred to as "4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene dibutyrate" – see Exhibit 1001, Figure 5G" above.

176. In sum, a POSA would have understood Table 3's identification of the compound "L-3,4-**dibutyryl**-α-[(methylamino)methyl] benzyl alcohol hydroperchlorate" was a misnomer and in fact disclosed the compound "L-3,4-**dibutyroxy**-α- [(methylamino)methyl] benzyl alcohol hydroperchlorate". A POSA would have further understood that this this correctly identified compound also disclosed its free base or non-salt ester prodrug structure, namely the structure reproduced below as claimed in claim 1 of the '437 Patent where both R Groups (substituents) as shown in the structure from claim 1 reproduced below are -$(CH_2)_2CH_3$.



A POSA would have further understood that this correctly identified compound also disclosed the epinephrine ester promoiety having the free base or non-salt

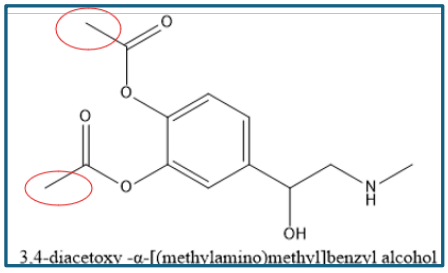
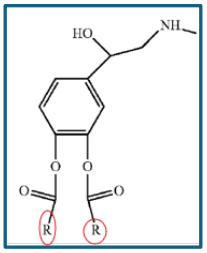
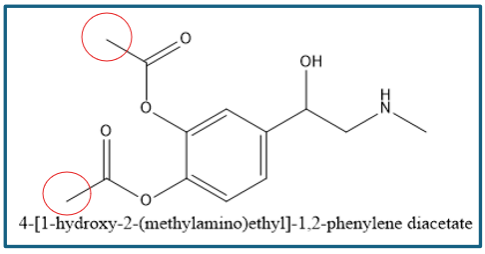
structure identified as "4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene dibutyrate".

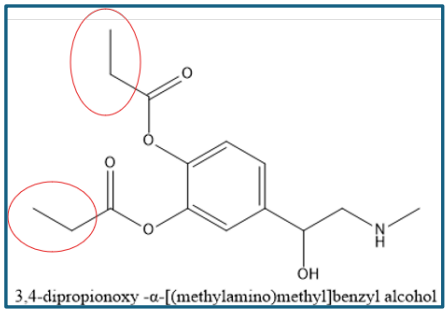
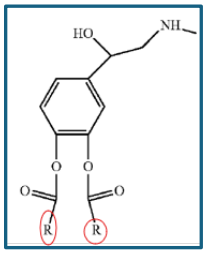
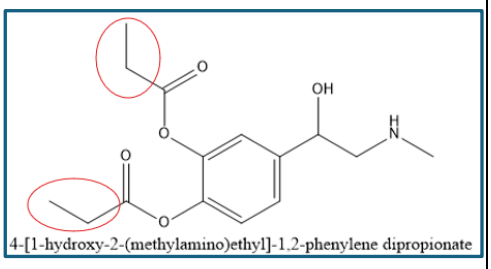
177. Finally, a POSA would have recognized that the identification of "L-3,4-**dibutyryl**-α-[(methylamino)methyl] benzyl alcohol hydroperchlorate" in Table 3 with a half-life $t_{1/2}$ of approximately 360 seconds (6 minutes) was a disclosure of the compound recited in claim 1 where both R Groups (substituents) are -$(CH_2)_2CH_3$ and named "4-(1-hydroxy-2-(methylamino) ethyl)-1,2-phenylene dibutyrate", and that this compound would have a half-life $t_{1/2}$ of approximately 360 seconds (6 minutes), thus falling within the range of from 1-6 minutes.

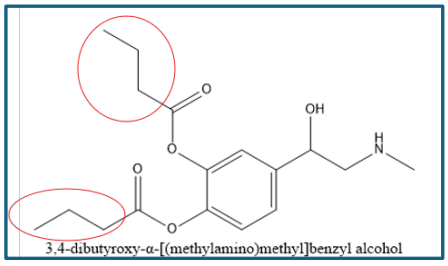
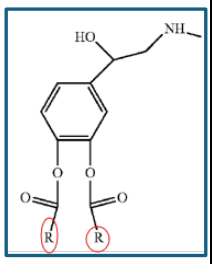
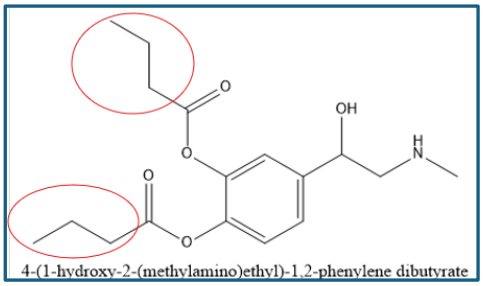
178. Additionally, a POSA would have understood that Truelove 1 teaches the use of all these ester promoieties to form prodrugs and would have been motivated to use the teachings of Truelove 1 with the active drug epinephrine to synthesize diester epinephrine prodrugs. Moreover, in view of the teachings of Truelove 1, a POSA would therefore have had a reasonable likelihood of success, without undue experimentation, of being able to achieve the compounds recited in the challenged claims and the claimed half-lives, *i.e.,* diester prodrugs of epinephrine and their respective half-lives ($t_{1/2}$) of 1-6 minutes. In the Relationship Chart that follows, I show Truelove 1's and Almoazen's identical diester compounds and focus on the free base or non-salt structures of the ester prodrugs, *i.e.,* without their salt forms.

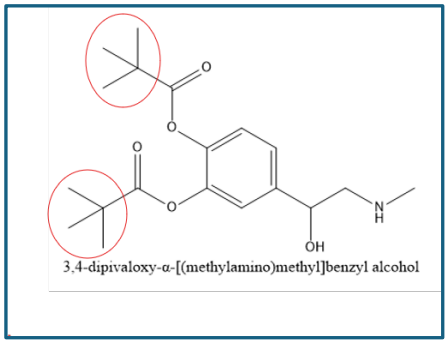
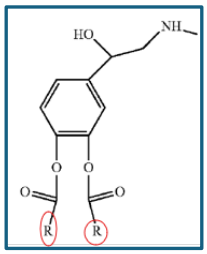
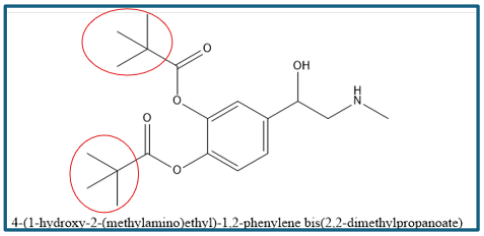
Structures were generated using ChemDraw®, which displayed the compound name as well.

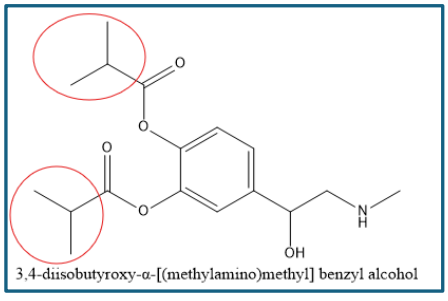
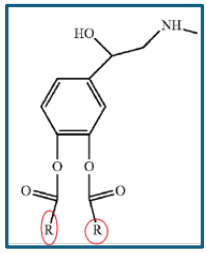
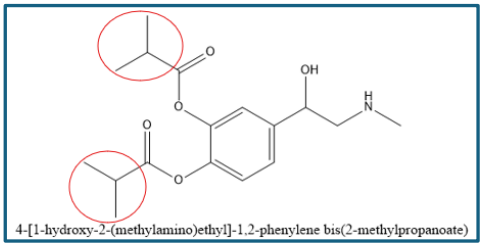
RELATIONSHIP CHART TRUELOVE 1'S AND ALMOAZEN'S IDENTICAL DIESTER COMPOUNDS

Truelove 1 (Exhibit 1002) Disclosed Compounds	**'437 Patent "R" Substituent Group**	**'437 Patent (Exhibit 1001) Compounds**
3,4-**di~~acetyl~~acetoxy**-α-[(methylamino)methyl] benzyl alcohol **$t_{1/2}$ = 180 seconds = 3 minutes** Above is the corrected name of the disclosed Truelove 1 compound and disclosed associated **$t_{1/2}$**. See Truelove 1, Table 3. The ChemDraw® generated compound structure and displayed compound name for the above compound is shown below.  	R = -CH_3 	4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene diacetate **$t_{1/2}$ = 1-6 minutes** Above is an alternative name of the Truelove 1 disclosed compound. The ChemDraw® generated compound structure and displayed compound name for the above named Almoazen compound is shown below. This structure, name and **$t_{1/2}$** are recited in claims 2 and 3 of the '437 Patent.  See also '437 Patent, Fig. 7A.

Truelove 1 (Exhibit 1002) Disclosed Compounds	**'437 Patent "R" Substituent Group**	**'437 Patent (Exhibit 1001) Compounds**
3,4-**di**~~propionyl~~**propionoxy**-α-[(methylamino)methyl] benzyl alcohol **$t_{1/2}$ = 240 seconds = 4 minutes** Above is the corrected name of the disclosed Truelove 1 compound and disclosed associated **$t_{1/2}$**. See Truelove 1, Table 3. The ChemDraw® generated compound structure and displayed compound name for the above compound is shown below.  3,4-dipropionoxy -α-[(methylamino)methyl]benzyl alcohol	Ⓡ = $-CH_2CH_3$  	4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene dipropionate **$t_{1/2}$ = 1-6 minutes** Above is an alternative name of the Truelove 1 disclosed compound. The ChemDraw® generated compound structure and displayed compound name for the above named Almoazen compound is shown below. This structure, name and **$t_{1/2}$** are recited in claims 2 and 3 of the '437 Patent.  4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene dipropionate See also '437 Patent, Fig. 7C. As in Fig. 7C., the above compound is alternatively named 4-[1-hydroxy-2-(methylamino) ethyl]-1,2-phenylene dipropanoate.

Truelove 1 (Exhibit 1002) Disclosed Compounds	**'437 Patent "R" Substituent Group**	**'437 Patent (Exhibit 1001) Compounds**
3,4-**di~~butyryl~~butyroxy**-α-[(methylamino)methyl] benzyl alcohol **$t_{1/2}$ = 360 seconds = 6 minutes** Above is the corrected name of the disclosed Truelove 1 compound and disclosed associated **$t_{1/2}$**. See Truelove 1, Table 3. The ChemDraw® generated compound structure and displayed compound name for the above compound is shown below.  3,4-dibutyroxy-α-[(methylamino)methyl]benzyl alcohol	R = $-(CH_2)_2CH_3$  	4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene dibutyrate **$t_{1/2}$ = 1-6 minutes** Above is an alternative name of the Truelove 1 disclosed compound. The ChemDraw® generated compound structure and displayed compound name for the above named Almoazen compound is shown below. This structure and **$t_{1/2}$** is recited in claim 1 of the '437 Patent.  4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene dibutyrate See also '437 Patent, Fig. 5G".

Truelove 1 (Exhibit 1002) Disclosed Compounds	**'437 Patent "R" Substituent Group**	**'437 Patent (Exhibit 1001) Compounds**
3,4-**di~~pivalyl~~pivaloxy**-α-[(methylamino)methyl]benzyl alcohol **$t_{1/2}$ = 1800 seconds = 30 minutes** Above is the corrected name of the disclosed Truelove 1 compound and disclosed associated **$t_{1/2}$**. See Truelove 1, Table 3. The ChemDraw® generated compound structure and displayed compound name for the above compound is shown below.  	R = $-C(CH_3)_3$ 	4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene bis(2,2-dimethylpropanoate) Above is an alternative name of the Truelove 1 disclosed compound. The ChemDraw® generated compound structure and displayed compound name for the above named Almoazen compound is shown below.  See also '437 Patent, Fig. 7D.

Truelove 1 (Exhibit 1002) Disclosed Compounds	**'437 Patent "R" Substituent Group**	**'437 Patent (Exhibit 1001) Compounds**
3,4-**di**~~isobutyryl~~**isobutyroxy** -α-[(methylamino)methyl] benzyl alcohol Above is the corrected name of the disclosed Truelove 1 compound. See Truelove 1, Tables 1 & 2. The ChemDraw® generated compound structure and displayed compound name for the above compound is shown below.  	Ⓡ = $-CH(CH_3)_2$ 	4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene bis(2-methylpropanoate) **$t_{1/2}$ = 1-6 minutes** Above is an alternative name of the Truelove 1 disclosed compound. Above is an alternative name of the Truelove 1 disclosed compound. The ChemDraw® generated compound structure and displayed compound name for the above named Almoazen compound is shown below. This structure, name and **$t_{1/2}$** are recited in claims 2 and 3 of the '437 Patent.  See also '437 Patent, Fig. 7B.

179. The **structures depicted in each of the rows in the above Relationship Chart are the same compounds although their presented orientations differ.** The reason that the orientation of the ChemDraw® structures presented in the right hand column do not entirely matchup with those in the left is that when presented with the name of a structure, the ChemDraw® program presents structures in an orientation that is based on its underlying naming algorithms. **Nevertheless, the structures in each of the rows in the above Relationship Chart are the same compounds**.

Almoazen Paper (Exhibit 1022)

180. The Almoazen Paper (Exhibit 1022) is an article co-authored by Alaadin Alayoubi, Lindsay Haynes, Hemlata Patil, Baher Daihom, Richard Helms & **Hassan Almoazen** (2016), and is entitled "Development of a fast dissolving film of epinephrine hydrochloride as a potential anaphylactic treatment for pediatrics". (Exhibit 1022, p. 1012.) It was published online on January 6, 2016.[31] One of the six (6) identified co-authors, **Hassan Almoazen,** is also identified as the inventor of the '437 Patent. The Almoazen Paper was not disclosed to the Patent Office by Almoazen during the prosecution of the '437 Patent, nor reviewed by the Examiner, nor is it listed on or disclosed in the '437 Patent.

181. The objective of the work reported in the Almoazen Paper, was to "develop a fast dissolving film [FDF] strip containing epinephrine HCl for the potential treatment of pediatric anaphylaxis." The Paper noted that the "study presents

[31] It is my understanding, because that as the Almoazen Paper, Exhibit 1022 was published on January 6, 2016 (more than a year before '437 Patent's earliest effective filing date of November 9, 2017 (see Almoazen PCT Application, Exhibit 1014)), it is proper for me to consider it as prior art to the '437 Patent, at least with respect to challenged claims 1-3.

potential proof for using FDFs as a replacement therapy of epinephrine injections for pediatrics." (Exhibit 1022, Abstract, p. 1012.) The Almoazen Paper discloses pharmaceutically acceptable carriers and excipients for its epinephrine compound. (See, e.g., Exhibit 1022, p. 1013, Table 1.)

182. The Almoazen Paper and the '437 Patent disclose identical information regarding epinephrine in a unit dosage form configured for sublingual or buccal administration in rapidly or fast dissolving films ("FDF").

183. In fact, at least the following portions of the '437 Patent appear to have been copied almost verbatim from the Almoazen Paper, namely: '437 Patent, Exhibit 1001, Figures 8 & 9; and '437 Patent, Exhibit 1001, columns/lines: 1:40-44, 4:11-15, 7:41-8:4, 8:8-33, 8:43-11:55.

184. To more clearly demonstrate the extent to which the '437 Patent copies from the Almoazen Paper, I have prepared Exhibit 1033 which is a copy of the Almoazen '437 Patent (Exhibit 1001) with material taken from the Almoazen Paper (Exhibit 1022) highlighted and I have also prepared Exhibit 1035 which is a copy of the Almoazen Paper (Exhibit 1022) with material from the Paper which appears in the Almoazen '437 Patent (Exhibit 1001) highlighted.

185. Several of the Tables in the '437 Patent were copied verbatim from the Almoazen Paper. In particular, Tables 3, 4 and 5 of the '437 Patent (Exhibit 1001)

are, respectively, identical to Tables 1, 2 and 3 the Almoazen Paper (Exhibit 1022). See, e.g., the two tables copied below.

Table 1, Almoazen Paper, Exhibit 1022, p. 1013.

Table 1. List of the compositions of the four FDFs formulations.

Ingredient (% w/w)	Use	F1	F2	F3	F4
Epinephrine HCl	Drug	5.9	5.9	5.9	5.9
Sodium metabisulfite	Antioxidant	5.9	5.9	5.9	5.9
Lycoat® RS720 (hydroxypropyl starch)	Film-forming polymer	20	25	27	30
Glycerin	Plasticizer	3	3	3	3
Tween 80	Surfactant	2	2	2	2
Citric acid monohydrate	Buffer; increases absorption in oral cavity	0.5	0.5	0.5	0.5
Sodium citrate monobasic	Buffer	0.5	0.5	0.5	0.5
Xylitol	Sweetener	10	10	10	10
Tutti Frutti	Flavor	6	6	6	6
Water		46.2	41.2	39.2	36.2

Table 3, Almoazen '437 Patent, Exhibit 1001, 8:51- 9:12.

TABLE 3

List of the cpmpositions of the four FDFs formulations

Ingredient (% w/w)	Use	F1	F2	F3	F4
Epinephrine HCl	Drug	5.9	5.9	5.9	5.9
Sodium Metabisulfite	Antioxidant	5.9	5.9	5.9	5.9
Lycoat 720 (hrydratypropyl starch)	Film-forming polymer	20	25	27	30
Glycerin	Plasticizer	3	3	3	3
Tween 80	Surfactant	2	2	2	2
Citric Acid Monohydrate	Buffer; increases absorption in oral cavity	0.5	0.5	0.5	0.5
Sodium Citrate Monobasic	Buffer	0.5	0.5	0.5	0.5
Xylitol	Sweetener	10	10	10	10
Tutti Fruiti	Flavor	6	6	6	6
Water		46.2	41.2	39.2	36.2

186. Two of the Figures in the ‘437 Patent are also copied from the Almoazen Paper. Specifically, Figures 8 and 9 of the ‘437 Patent are, respectively, exact copies of Figures 1 and 2 of the Almoazen Paper. See figures copied below.

Paper, Exhibit 1022, Figures 1&2 **‘437 Patent, Exhibit 1001, Figures 8&9**

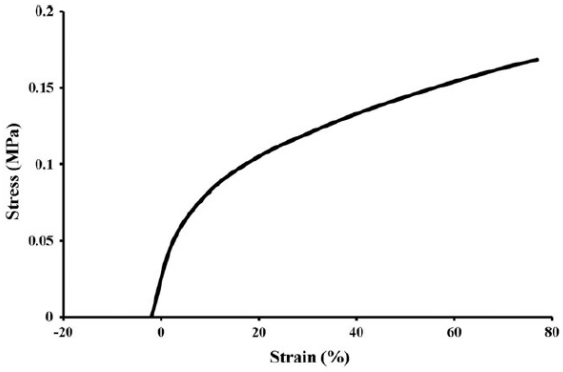
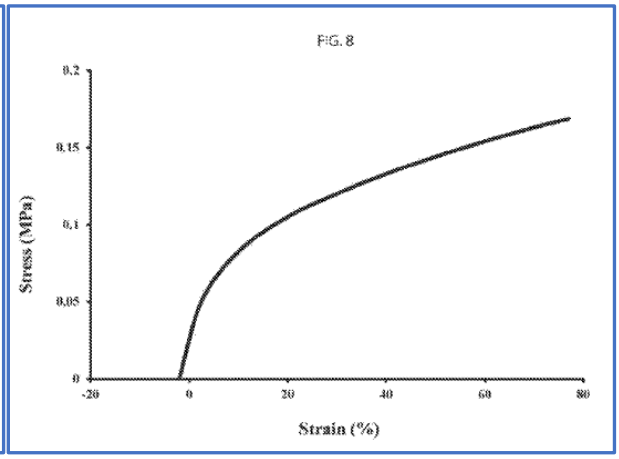


Figure 1. Stress–strain profile of the optimized epinephrine FDF.



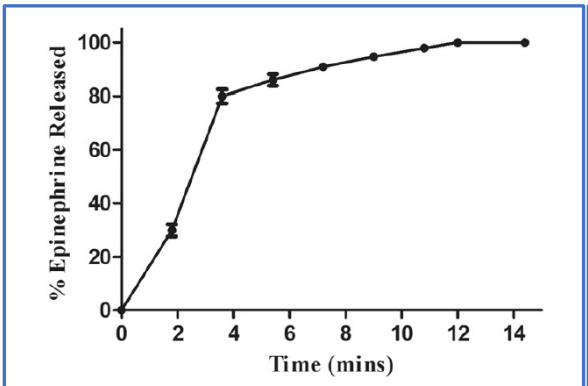
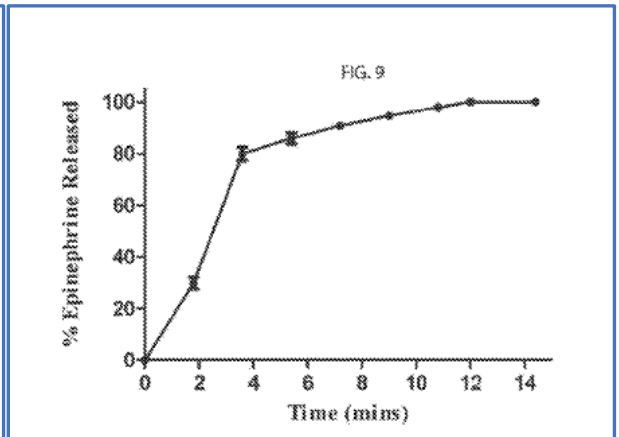


Figure 2. The release profile of the epinephrine from the optimized FDF in 500 ml simulated saliva at 37°C.



187. The ‘437 Patent’s Figure 9 (see above) and the ‘437 Patent’s Table 5 (see below), both copied from the Almoazen Paper, are referred to by the ‘437 Patent Application Examiner as supporting the Statement of Reasons for Allowance of the ‘437 Patent.

"**Statement of Reasons for Allowance**

"None of the prior art teaches in a single disclosure, nor fairly suggest in any combination, Applicants' claimed product of a compound of the claimed Formula, formulated as a pharmaceutical composition in a unit dosage form configured for sublingual or buccal administration. Applicants have demonstrated novel compound structures in their disclosure as originally filed. Applicants' disclosure includes embodiments built around the claimed Formula and discloses the species embodiments and their Log P values. **Applicants' disclose that epinephrine formulations have disintegrations times ranging from 10 to 30 seconds (see specification, p. 14, Table 5) and further disclose exemplified embodiment of epinephrine release from hydrolysis where the half-life is within 4 minutes (see Drawings, Fig. 9).**"

'437 FH, Exhibit 1005, pdf. p. 14 (emphasis added).

188. Additionally, as noted above, Table 5 of the '437 Patent, which was relied on by the Examiner in the Reasons for Allowance for showing disintegrations times ranging from 10 to 30 seconds, is identical to Table 3 of the Almoazen Paper. *Compare* '437 Patent, Table 5 *with* Almoazen Paper Table 3 copied below.

Table 5, Almoazen '437 Patent, Exhibit 1001, 10:41-53.

TABLE 5

In vivo taste and disintegration time evaluation of the optimized epinephrine FDF.

Volunteer	Bitterness	Tongue Constriction	Disintegration Time
1	None	None	~10 seconds
2	None	None	~10 seconds
3	Slight	None	~20 seconds
4	None	None	~30 seconds
5	Very slight	None	~20 seconds
6	None	None	~30 seconds

Table 3, Almoazen Paper, Exhibit 1022, p. 1016.

Table 3. *In vivo* taste and disintegration time evaluation of the optimized epinephrine FDF.

Volunteer	Bitterness	Tongue constriction	Disintegration time
1	None	None	~10 s
2	None	None	~10 s
3	Slight	None	~20 s
4	None	None	~30 s
5	Very slight	None	~20 s
6	None	None	~30 s

189. The Almoazen Paper concluded:

> "Four films with different polymer contents were evaluated in this study. The formulation with the highest concentration of the polymer Lycoat (30%) formed smooth and clear film. The optimized formulation showed good mechanical properties attaining high level

> of flexibility, thickness uniformity and rapid disintegration (20 s) and dissolution time (90% within 7.2 min). Moreover, a content uniformity of 93% was reported of different strips of the film. Furthermore, tasked masking of the bitterness of epinephrine was achieved based on the opinions of 6 volunteers. **Therefore, it was concluded that epinephrine was successfully incorporated into fast dissolving film strip for potential use in pediatrics. However, future research is needed, such as evaluation of the stability of the drug in film strips and performing animal studies, to determine the absorption rate of epinephrine HCl through the buccal cavity."**
>
> Almoazen Paper, Exhibit 1022, Conclusion, p. 1015 (emphasis added).

190. Almoazen discusses the importance of stabilizing epinephrine, in the same manner the Almoazen Paper does. (Compare, '437 Patent, Exhibit 1001, 9:26-35 with Almoazen Paper, Exhibit 1022, p. 1014, 2nd col.) The Almoazen Paper clearly noting that it is the epinephrine that needs be stabilized in the film and refers the reader to Stepensky, Exhibit 1039, for its discussion of L- Adrenaline (*l*-epinephrine). Stepensky notes that "**L-adrenaline** in solution **is inactivated by racemization** and oxidation or to reaction with auxiliary formulation components (e.g., sodium metabisulfite) employed as an antioxidant." (Exhibit 1039, p. 969,

emphasis added; *see also,* Merck Index, Exhibit 1009, p. 613, and USP Epinephrine, Exhibit 1012.)

191. The Almoazen Paper teaches compounds formulated in a unit dosage form as a rapidly dissolving film, a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, for sublingual or buccal administration.

192. Remarkably, despite the extensive material that was copied from the Almoazen Paper, it was not disclosed to the Patent Office by Almoazen during the prosecution of the '437 Patent, and not reviewed or considered by the Patent Examiner.

Ashraf (Exhibit 1003) – Log P values for satisfactory mucosal absorption

193. Ashraf and Sayeed's article, entitled "Considerations in Developing Sublingual Tablets – An Overview," was published in Pharmaceutical Technology Europe, in November 2014 ("Asraf") and discusses important physicochemical drug properties and formulation design considerations that play a crucial role in ensuring the quality and performance of sublingual tablets. Ashraf also discloses pharmaceutically acceptable carriers and excipients for its oral mucosa drugs. (See, e.g., Exhibit 1003, p. 36.)

194. Asraf was discussed in the '437 Patent in connection with preferred Log P values. (See '437 Patent, Exhibit 1003, 5:6-12.)

195. Ashraf discusses the physicochemical properties of drugs and includes Table II (Exhibit 1003, Table II, p. 35) that lists "the physicochemical properties of some commercially available drugs administered sublingually. These properties aid in their absorption via passive diffusion through the oral mucosa." The table includes partition coefficients and ionization constants of several drugs as described in the literature. Ashraf Table II is copied below.

Ashraf, Exhibit 1003, Table II, p. 35.

Table II: Physicochemical properties of sublingually administered drugs.

Drug	Molecular weight	Largest dose**	Water solubility	pKa	Log P
Nitroglycerin	227	0.6 mg	1.8 mg/mL	-5.6	0.94
Fentanyl citrate	336*	0.8 mg	0.025 mg/mL (citrate)	8.4	2.9
Buprenorphine	467.6	2–8 mg	Insoluble in water	8.24, 10.0	4.9
Asenapine maleate	285.8*	10 mg	3.7 mg/mL	8.6	4.9
Nicotine	162.234	4 mg	Slightly soluble	8.21	0.99
Ergotamine tartrate	583.68*	2 mg	Insoluble in water	6.3	2.4

* Molecular weight of the base.
**Largest dose for sublingual tablet.

196. Ashraf also states that "[f]or efficient absorption through the oral mucosa, the drug must be hydrophobic enough to partition into the lipid bilayer, but not so hydrophobic such that once it is in the bilayer, it will not partition out again. Satisfactory oral [mucosal] absorption of drugs has been observed over a wide range of log P (octanol/water partition coefficient) values of 1 to 5. As the log P value increases beyond 5, the solubility in saliva is usually not enough to provide adequate concentration for diffusion through the lipid bilayer". (*See* Exhibit 1003, p. 35, 2nd col.)

Fuchs (Exhibit 1004) – Films for mucosal drug delivery

197. U.S. Patent No. 4,136,145, ("the '145 Patent" or "Fuchs"), issued on January 23, 1979, and is entitled "*Medicament carriers in the form of film having active substance incorporated therein*". Fuchs provides twenty (20) "Examples" of films with various active ingredients and describes films that incorporate a pharmaceutical active ingredient, which can then be applied to the mucosal areas of the body. (*See* Exhibit 1004, 5:7-14:24.) The mucosal areas of the body include the oral mucosa comprising the sublingual and buccal areas of the mouth. *See, e.g.,* Florence, Exhibit 1015, p. 364. Almoazen characterizes Fuchs as follows:

> "Films that incorporate a pharmaceutically active ingredient are disclosed in U.S. Pat. No. 4,136,145 to Fuchs, et al. ("Fuchs"). These films can be formed into a sheet, dried and then cut into individual doses. Examples of specific uses disclosed by Fuchs include application of the films to mucosal membrane areas of the body, including the mouth, rectal, vaginal, nasal and ear areas. A drug delivery vehicle must provide a high level of uniformity with respect to the dosage delivered."

Almoazen, Exhibit 1001, 2:39-47.

198. Fuchs discloses "Pharmaceutical composition unit dosage forms adapted for enteral or topical administration are described, comprising a safe and effective

amount of a pharmaceutically active medicament compound dissolved or uniformly dispersed in a flexible, water-soluble film carrier therefor. Admixtures of medicament and carrier are drawn into a film, which can be cut to desired unit dosage content." (Exhibit 1004, Abstract.)

199. Fuchs also teaches that unit dosage films may be administered mucosally, for example, topically in body cavities such as the nose, rectum and vagina.

> "In principle, all pharmaceutically active medicaments used in human and veterinary medicine can be employed in accordance with the principles of the present invention. The dosages of active medicament employed are those conventionally used in the art for the particular medicament selected. For internal use, unit dosage forms adapted for oral administration are preferred. For external use, unit dosage forms adapted for either enteral or topical administration can be employed, e.g., for topical administration on the skin and in body cavities such as the nose, ears, rectum, vagina, etc."
>
> Fuchs, Exhibit 1004, 2:28-38.

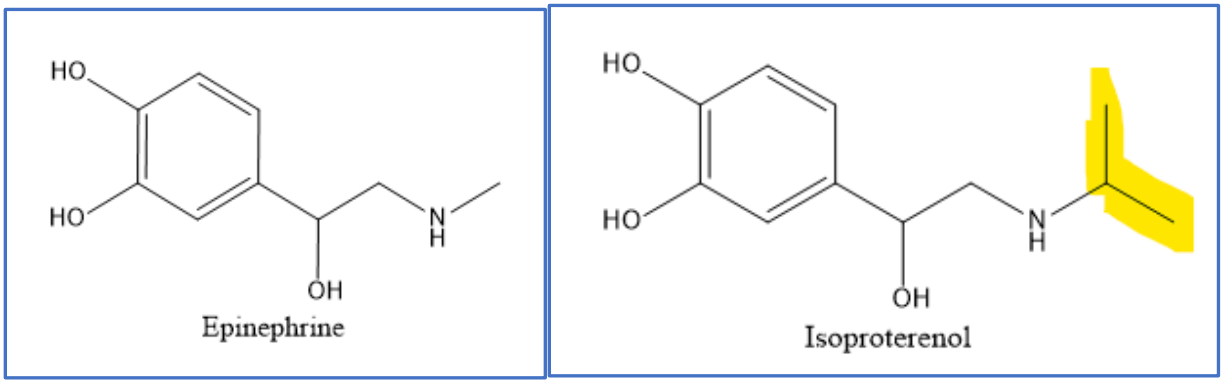
200. Fuchs also discloses compositions and methods for making the unit dosage films. (*See* Exhibit 1004, 2:65-5:6.) Fuchs discloses pharmaceutically acceptable carriers and excipients for pharmaceutical compounds. (See, e.g., Exhibit 1004, 1:10-14, 2:65-3:36.)

Truelove 3 (Exhibit 1008) – Half-lives of Diester Prodrugs of Isoproterenol

201. U.S. Patent No. 3,868,461 ("the '461 Patent" or "Truelove 3"), issued on February 25, 1975, and is entitled "*Ester of 3,4-dihydroxy-alpha (isopropylamino) methyl benzyl alcohol, composition and anti-asthma use thereof*". Truelove 3 was not identified on the "References Cited" section of the '437 Patent.

202. Truelove 3 discloses an ester of 3,4-dihydroxy-α-[(isopropylamino)methyl] benzyl alcohol, commonly known as isoproterenol. Truelove 3 discloses pharmaceutically acceptable carriers and excipients for its isoproterenol prodrug compound. (See, e.g., Exhibit 1008, 7:39-65.)

203. Isoproterenol has a very similar structure to epinephrine. See structures generated by ChemDraw® below, the difference in structures is highlighted in yellow.



204. Truelove 3 used the same methodology for determining the half-life ($t_{1/2}$) as was used by Truelove 1 and Truelove 4.

> "The rate of cleavage of these compounds to the parent drug is demonstrated in various biological media by measuring its enzymatic rate of hydrolysis in various media at 37C and expressing this result as the t seconds. The enzymatic rate of hydrolysis is measured at pH of about 7.5 and at a concentration of 0.5 mg/ml of compound in media (a) horse serum cholinesterase, (b) rabbit serum, and (c) human plasma. The results for the compound are listed in Table 3, as are the results of other compounds treated in a like enzymatic environment. The free base compound was measured by using high pressure liquid chromatography."
>
> Truelove 3, Exhibit 1008, 10:46-57.

205. Truelove 3, Table 3, copied below, provides the half-lives for several of its ester promoieties prodrugs of isoproterenol.

Truelove 3, Table 3, Exhibit 1008, 10:59-70

TABLE 3

Compound	Rate of Hydrolysis in $t_{1/2}$ Seconds Horse	Rabbit	Human
3,4-diacetoxy-α1[(isopropylamino)-methyl]benzyl alcohol hydrochloride	20	45	180
3,4-dipropionoxy-α-[(isopropylamino)-methyl]benzyl alcohol hydrochloride	50	90	240
3,4-dibutyroxy-α-[(isopropylamino)-methyl]benzyl alcohol hydrochloride	100	160	360
3,4-dipivaloxy-α1[(isopropylamino)-methyl]benzyl alcohol hydrochloride	600	720	1800

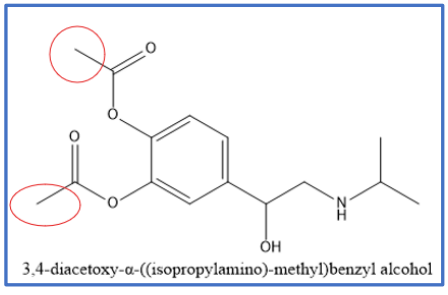
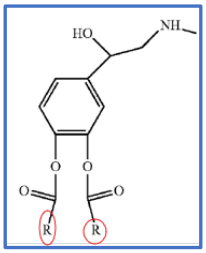
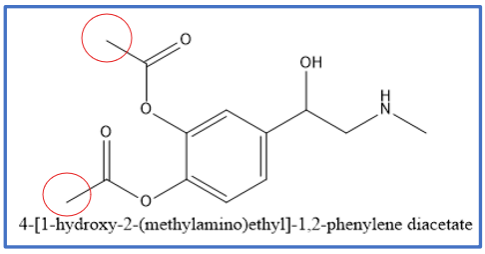
206. As more fully illustrated below in the Relationship Table below at ¶ 209, Truelove 3 also discloses compounds with many of the same R groups or substituents as the epinephrine ester prodrugs claimed in the ‘437 Patent. As discussed in ¶ 132 above, these same R groups or substituents are disclosed in Truelove 1.

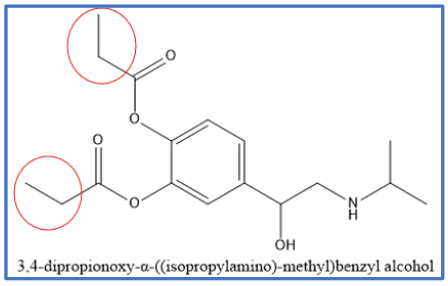
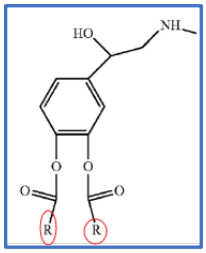
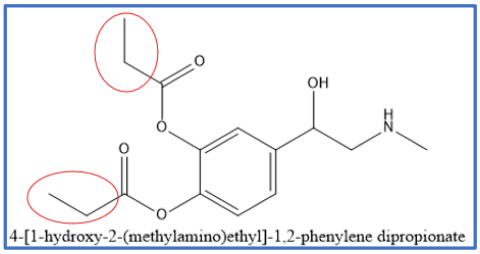
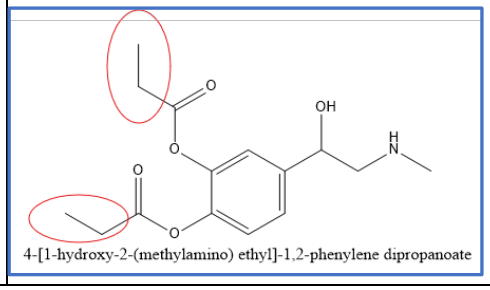
207. The compounds identified in Tables 1-3 of Truelove 3 are the salt form of isoproterenol, denoted by the term “hydrochloride.” When compared to the free base or non-salt form, the salt form of these compounds may slightly affect dissolution rates. However, once dissolved, a POSA would have expected that

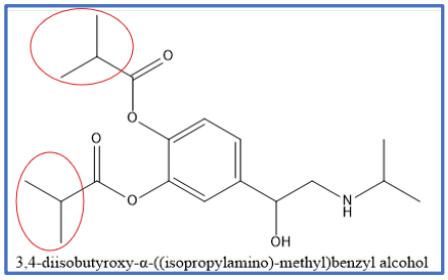
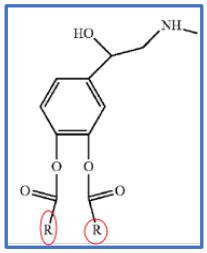
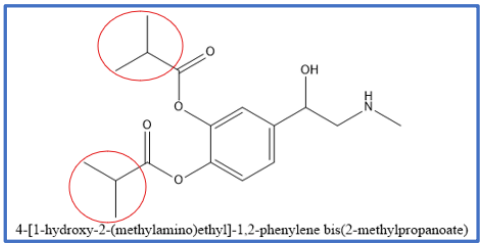
there would have been no impact on the enzyme-mediated cleavage rates in the buffered medium or on the formation of the epinephrine parent compound, which is used to determine the half-life.

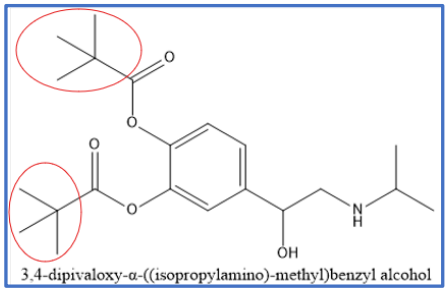
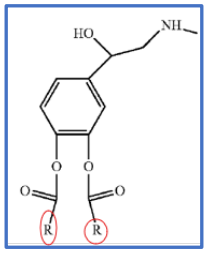
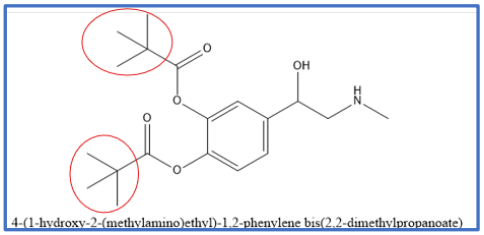
208. In the Relationship Chart that follows, I show Truelove 3's and Almoazen's identical diester compounds and focus on the free base or non-salt structures of the ester prodrugs, *i.e.,* without their salt forms. Structures were generated using ChemDraw®.

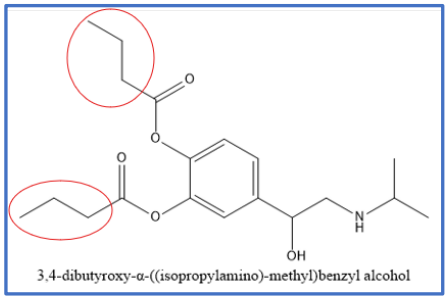
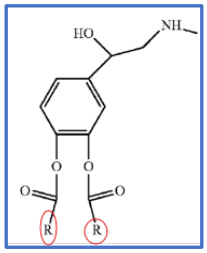
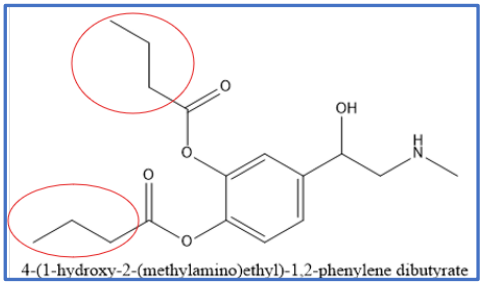
RELATIONSHIP CHART TRUELOVE 3'S AND ALMOAZEN'S IDENTICAL ESTER PROMOIETIES

Truelove 3 (Exhibit 1008) Prodrug	**'437 Patent "R" Group**	**'437 Patent (Exhibit 1001) Prodrug**
3,4-diacetoxy-α-((isopropylamino)-methyl)benzyl alcohol **$t_{1/2}$ = 180 seconds = 3 minutes** (disclosed in Truelove 3, Table 3)  3,4-diacetoxy-α-((isopropylamino)-methyl)benzyl alcohol	Promoiety R = -CH_3 	4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene diacetate Structure and name of compound recited in claims 2 and 3 are shown below.  4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene diacetate See also '437 Patent, Fig. 7A

Truelove 3 (Exhibit 1008) Prodrug	**'437 Patent "R" Group**	**'437 Patent (Exhibit 1001) Prodrug**
3,4-dipropionoxy-α-((isopropylamino)-methyl)benzyl alcohol **$t_{1/2}$ = 240 seconds = 4 minutes** (disclosed in Truelove 3, Table 3)  	Promoiety R= $-CH_2CH_3$ 	4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene dipropanoate [also dipropionate] Structure and name of compound recited in claims 2 and 3 are shown below.  See also '437 Patent, Fig. 7C and structure as generated by ChemDraw® for an alternative name below. 

Truelove 3 (Exhibit 1008) Prodrug	**'437 Patent "R" Group**	**'437 Patent (Exhibit 1001) Prodrug**
3,4-diisobutyroxy-α-((isopropylamino)-methyl)benzyl alcohol  	Promoiety R = $-CH(CH_3)_2$ 	4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene bis(2-methylpropanoate) Structure and name of compound recited in claims 2 and 3 are shown below.  See also '437 Patent, Fig. 7B

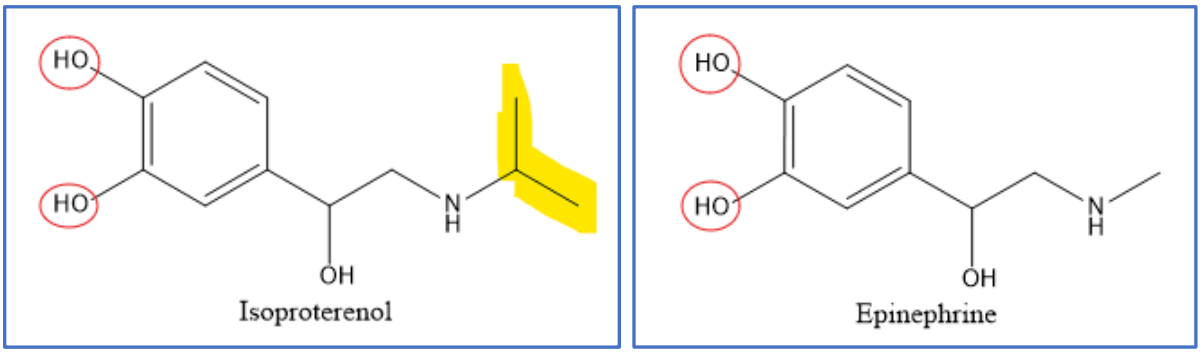
Truelove 3 (Exhibit 1008) Prodrug	**'437 Patent "R" Group**	**'437 Patent (Exhibit 1001) Prodrug**
3,4-dipivaloxy-α-((isopropylamino)-methyl)benzyl alcohol **$t_{1/2}$ = 1800 seconds = 30 minutes** (disclosed in Truelove 3, Table 3)  	Promoiety R = $-C(CH_3)_3$ 	4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene bis(2,2-dimethylpropanoate) Structure and name of compound disclosed in '437 Patent are shown below.  See also '437 Patent, Fig. 7D

Truelove 3 (Exhibit 1008) Prodrug	**'437 Patent "R" Group**	**'437 Patent (Exhibit 1001) Prodrug**
3,4-dibutyroxy-α-((isopropylamino)-methyl)benzyl alcohol **$t_{1/2}$ = 360 seconds = 6 minutes** (disclosed in Truelove 3, Table 3)  3,4-dibutyroxy-α-((isopropylamino)-methyl)benzyl alcohol	Promoiety R = $-(CH_2)_2CH_3$ 	4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene dibutyrate Structure and name of compound recited in claim 1 are shown below.  4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene dibutyrate See also '437 Patent, Fig. 5G"

209. The **structures depicted in each of the rows in the above Chart are the same compounds although their presented orientations differ.** The reason that the orientation of the ChemDraw® structures presented in the right hand column do not entirely matchup with those in the left is that when presented with the name of a structure, the ChemDraw® program presents structures in an orientation that is based on its underlying naming algorithms. **Nevertheless, the structures in each of the rows in the above Chart are the same compounds**.

210. As shown in the Relationship Chart above, Truelove 3 discloses isoproterenol prodrugs with several of the same ester promoieties used in forming '437 Patent's epinephrine prodrug compounds recited in challenged claims 1-3. Truelove 3 also discloses the prodrugs half-lives ($t_{1/2}$), several of which range from 1-6 minutes.

211. Importantly, there is substantial structural similarity between the isoproterenol and epinephrine active drug compounds and the position of the ester promoieties linked thereto, shown in circled -OH (hydroxyl) groups. The difference in structures is highlighted in yellow.



212. Accordingly, a POSA would have readily expected that the epinephrine prodrugs recited in challenged claims 1-3 and the isoproterenol prodrugs disclosed in Truelove 3 with the identical ester promoieties would have substantially the

same, if not identical, half-lives ($t_{1/2}$).[32] Basically, this is because of the structural similarity between the isoproterenol and epinephrine compounds, the use of identical ester promoieties, and the positions of the promoieties on the active drug compounds.

213. For example, a POSA would have understood that the location of isopropylamino (-NH-CH-$(CH_3)_2$) and methylamino (-NH-CH_3) substituents on the isoproterenol and epinephrine compounds, respectively, would have little or no steric influence on the cleavage of identical promoieties of those molecules and the formation of the active isoproterenol and epinephrine drug compounds.[33]

214. Because Truelove 3 teaches the use of some of the same ester promoieties recited in the '437 Patent's challenged claims 1-3 and discloses the half-lives of those prodrug compounds, a POSA seeking to synthesize epinephrine prodrugs with rapid

[32] However, I note that there is always some small degree of variability in hydrolysis rates even within a single prodrug study.

[33] This is confirmed by a comparison of the compounds and half-lives reported in Truelove 1, Table 3 and Truelove 3, Table 3. In particular, the epinephrine and isoproterenol prodrugs with identical ester promoieties are reported as having the same half-lives. *Compare* Exhibit 1002, 9:27-37 *with* Exhibit 1008, 10:58-70.

half-lives (*e.g.,* 6 minutes or less) would have been motivated by the disclosure and teachings of Truelove 3 to synthesize diester epinephrine prodrug compounds using the same Truelove 3 ester promoieties.

215. Moreover, in view of the disclosure and teachings of Truelove 3, a POSA would have had a reasonable likelihood of success, without undue experimentation, of being able to achieve the prodrug compounds and the claimed half-lives recited in challenged claims 1-3 *i.e.,* diester prodrugs of epinephrine and their respective half-lives ($t_{1/2}$) of 1-6 minutes.

216. Therefore, a POSA from the teachings of Truelove 3 would have understood that epinephrine prodrug with the following ester promoiety substituents ("R" groups) would have the same or nearly the same half-lives as follows:

(a) epinephrine prodrug ester promoiety with R= $-CH_3$ ('437 Patent claims 2 & 3) would have a half-life = $t_{1/2}$ = 180 seconds = 3 minutes (Truelove 3, Table 3);

(b) epinephrine prodrug ester promoiety with R = $-CH_2CH_3$ ('437 Patent claims 2 & 3) would have a half-life = $t_{1/2}$ = 240 seconds = 4 minutes (Truelove 3, Table 3);

(c) epinephrine prodrug ester promoiety with R = $-C(CH_3)_3$ would have a half-life = $t_{1/2}$ = 1800 seconds = 30 minutes (Truelove 3, Table 3); and

(d) epinephrine prodrug ester promoiety with R = -$CH_2CH_2CH_3$ ('437 Patent claim 1) would have a half-life = $t_{1/2}$ = 360 seconds = 6 minutes (Truelove 3, Table 3).

Truelove 4 (Exhibit 1007) – Half-life of a Diester Prodrug of Epinephrine

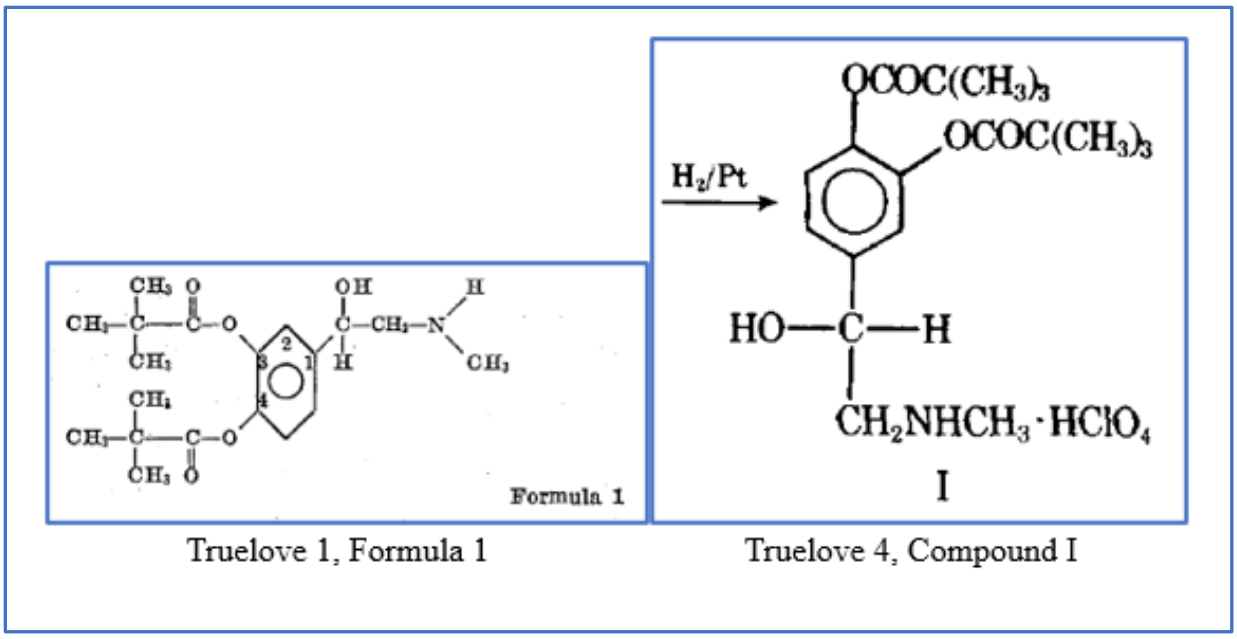
217. Truelove 4 (Exhibit 1007) is a publication by Hussain and Truelove entitled "*Prodrug Approaches to Enhancement of Physicochemical Properties of Drugs IV: Novel Epinephrine Prodrug*" ("Truelove 4", Exhibit 1007). Truelove 4 describes the synthesis and characterization of an ester prodrug correctly named as 3,4-dipivaloyloxy-α-(methylaminomethyl)benzyl alcohol perchlorate salt[34] (Exhibit 1007, p. 1510, 2nd col.) designed to overcome inefficient absorption of epinephrine through the lipoidal membranes of the eye. The same ester prodrug is disclosed in Truelove 1 though incorrectly named as "L-3,4-dipivalyl-α-[(methylamino)methyl] benzyl alcohol hydroperchlorate" (*see, e.g.,* Exhibit 1002, 2:47-69).

218. Truelove 4, published after Truelove 1, refers to this Truelove 1 compound and correctly refers to the salt form of the Truelove 1's Formula 1 diester

[34]Equivalently named "3,4-dipivaloxy-α-(methylaminomethyl)benzyl alcohol perchlorate salt".

promoiety prodrug as "3,4-dipivaloyloxy-α-(methylaminomethyl) benzyl alcohol perchlorate salt." (See Truelove 4, Exhibit 1007, p. 1510, 2nd col. and fn. 1.)

219. The structures of Formula 1 of Truelove 1 and Compound 1 of Truelove 4 are reproduced below. As is readily apparent, the only difference between the two structures is that Compound I is the salt form of Formula 1.



Truelove 1, Formula 1 Truelove 4, Compound I

220. Truelove 4 provides information regarding the assays used to carry out the enzymatic hydrolysis studies and determine the half-life ($t_{1/2}$) of its prodrug, giving essentially the same half-life ($t_{1/2}$) results that Truelove 1 provided for the same prodrug, see following discussion, and thus Truelove 4's methodology further informs that used in Truelove 1.

> "In Vitro Enzymatic Rate of Hydrolysis of Prodrug in Human or Rabbit Plasma -- Blood samples (5 ml) were withdrawn and

centrifuged immediately. Two milliliters of the plasma was transferred to a stoppered test tube and equilibrated to 37°. After equilibration, 0.2 ml of the 4-mg/ml solution of prodrug was added and the mixture was maintained at 37°. Liberation of epinephrine was followed as already described."

Truelove 4, Exhibit 1007, p. 1511, 2nd col.

221. Table 1 of Truelove 4, copied below, provides the half-life ($t_{1/2}$) of Truelove 1's compound. The table shows that by 28 minutes enough of the prodrug had hydrolyzed that 47.5% of the parent epinephrine had formed and been released into the plasma. Accordingly, the data disclosed in Truelove 4, confirms the half-life ($t_{1/2}$) of 30 minutes (1,800 seconds) that is reported in Table 3 of Truelove 1.

Truelove 4, Exhibit 1007, Table 1, p. 1511, 2nd col.

Table I—*In Vitro* Enzymatic Hydrolysis of the Prodrug

Minutes	Percent Hydrolysis in Rabbit Plasma	Human Plasma	Rabbit Eye Homogenate
0	0	0	0
3	12.3	—	—
8	47.7	—	—
10	—	8.0	—
13	58.0	—	—
18	—	24.1	—
20	—	—	2.3
22	96.0	—	—
28	—	47.5	—
32	100	—	—
40	—	—	5.3
45	—	85.8	—
60	—	95.1	18.2
90	—	100	34.0
105	—	—	42.5
150	—	—	68.9
190	—	—	81.8
285	—	—	100

222. The half-life ($t_{1/2}$) for Compound 1 of Truelove 4, namely 3,4-dipivaloyloxy-α-(methylaminomethyl)benzyl alcohol perchlorate salt, *i.e.,* epinephrine where both Almoazen claimed "R" Groups (substituents) are -$C(CH_3)_3$ (written as -$CCH_3CH_3CH_3$ in the '437 Patent) was approximately 30 minutes. Because the smaller alkyl group chains are expected to result in faster hydrolysis rates compared to larger alkyl groups, a POSA would have expected the half-life ($t_{1/2}$) in human plasma for epinephrine with ester promoieties with decreasing substitution on the carbon atom α to the carbonyl group to have a faster hydrolysis rate, *i.e.,* a shorter half-life ($t_{1/2}$). *See, e.g.,* den Daas, Baldessarini, Kristoffersson and Hansen 1991, discussed below.[35] Thus, a POSA would have expected that epinephrine

[35] While a POSA would have understood that the length of the alkyl group would affect to lipophilicity of the compound, *i.e.,* log P, as disclosed in the '437 Patent as long as the Log P fell within the range of approximately 0.5-6, the compound would be satisfactory for efficient absorption through the oral mucosa. '437 Patent, Exhibit 1001, 5:6-8. The '437 Patent provides at Table 2, Log P values for Figures A, B, C, & D. Figure 5G" provides CLogP = 1.2134 for that compound.

prodrugs with ester promoieties such as where the R groups are: R = -$CH(CH_3)_2$ [‘437 Patent, Figure 7B]; R = -CH_2CH_3 [‘437 Patent, Figure 7C]; R = -$CH_2CH_2CH_3$ [‘437 Patent, Figure 5G”]; and R = -CH_3 [‘437 Patent, Figure 7A] to each have a progressively faster hydrolysis rate, *i.e.,* a shorter half-life ($t_{1/2}$), and that epinephrine having these R groups would have half-lives ($t_{1/2}$) in human plasma of less than 6 minutes.

Florence (Exhibit 1015) – Range of log P values for buccal absorption

223. Florence (Exhibit 1015), entitled “Physicochemical Principles of Pharmacy” (Fifth edition, 2011), provides guidance on optimal log P_o values (the partition coefficient between octanol and water) for various absorbing membranes. According to Table 9.1 of this publication, the ideal log P_o values for buccal absorption typically range in bases from 3.52 (dissociated) to 5.52 (undissociated)

TABLE 2

R	Log P
Structure 7A R=CH_3	–0.97
Structure 7C R=CH_2CH_3	+0.09
Structure 7B R=$CHCH_3CH_3$	+0.79
Structure 7D R=$CCH_3CH_3CH_3$	+1.49

and in acids 4.19 (undissociated), varying based on the chemical characteristics of the absorbing molecule.

Florence, Table 9.1, Exhibit 1015, p. 350.

Table 9.1 Ideal lipophilic character of drugs (log P_o) in different regions of the body

System	Solute or drug	Log P_o (octanol/water) for maximal transport
Buccal cavity (human)	Bases	5.52 (undissociated)
		3.52 (dissociated)
	Acids	4.19 (undissociated)
Epidermis (human)	Steroids	3.34
Whole skin (rabbit)	Non-electrolytes	2.55
Small intestine (rat)	Sulfonamides	2.56–3.33
Stomach (rat)	Barbiturates	2.01
	Acids	1.97
Cornea (rabbit)	Steroids	2.8
Biliary excretion	Sulfathiazoles	0.60
Milk/plasma	Sulfonamides	0.53
Prostatic/plasma ratio	Sulfonamides	0.23

224. A POSA would have understood that Florence's disclosure of "ideal" log P values for buccal absorption, does not mean that Log P values outside of this "ideal" range will not effectively permeate across the mucosal membrane. In fact, Figure 9.16 of Florence shows the relationship between the Log P and mucosal/buccal permeability (%) and demonstrates absorption at higher log P values. For example, compounds having a log P of 1.5 seem to result in absorption from 0% up to 0.8%.

Florence, Figure 9.16, Exhibit 1015, p. 366.

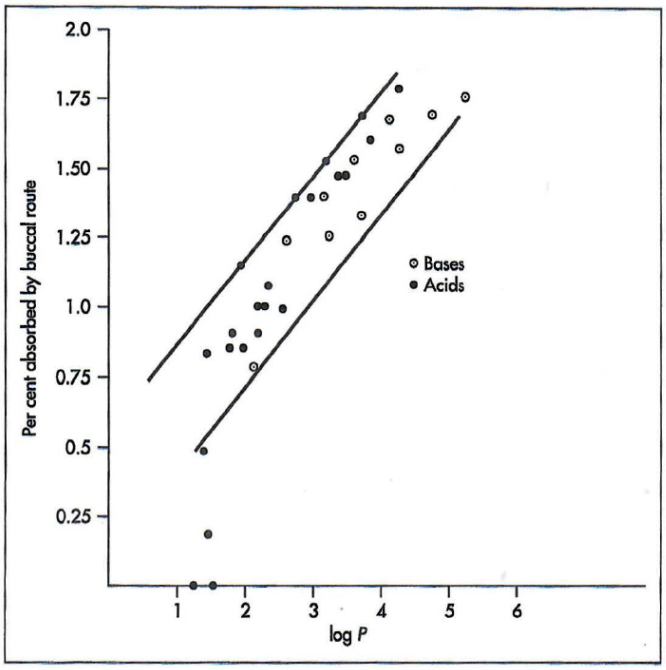


Figure 9.16 Relationship between the log *P* of solute and the percentage absorption through the buccal mucosa of human subjects for bases (○) and acids (●).

Plotted from data from Lien E *et al.*, *Drug Intell Clin Pharm*, 1971; 5: 38.

225. There is typically an upper log P value after which compounds tend to be poorly dissolved or get stuck to the lipophilic membrane which results in poor absorption through the membrane, *i.e.,* the parabolic curve when log P values are plotted against the absorption. Thus, there is an optimal log P point for absorption. (Florence, Exhibit 1015, 9.1.1, p. 350.)

226. For drugs that use the sublingual route a Log P of 1.6 to 3.3 is considered optimal.

> "It has been claimed that an oil/water partition coefficient in the range 40-2000 (log *P* of 1.6-3.3) is optimal for drugs to be used by the sublingual route. Drugs with a log *P* greater than 3.3 are so oil-soluble that it is difficult for sufficiently high levels of drug to be soluble in the aqueous salivary fluids. Drugs less lipophilic than those with a log *P* of 1 would not be absorbed to any great extent and would thus require large doses by this route."
>
> Florence, Exhibit 1015, p. 365.

Ettmayer (Exhibit 1018) - Many prodrugs are activated by hydrolysis to form the parent drug

227. Ettmayer (Exhibit 1018), entitled "Lessons Learned from Marketed and Investigational Prodrugs," teaches, among other things, that prodrugs are a well-known and established concept which can be used to overcome several various barriers to a drug's usefulness.

> "Prodrugs provide a rationale and opportunities to reach target physicochemical, pharmacokinetic, and pharmacodynamic properties. They can be designed to overcome pharmaceutical, pharmacokinetic, or pharmacodynamic barriers such as insufficient chemical stability, poor solubility, unacceptable taste or odor, irritation or pain, insufficient oral absorption, inadequate blood-brain barrier permeability, marked presystemic metabolism, and toxicity.
>
> Ettmayer, Exhibit 1018, p. 2393.

228. Ettmayer also teaches that "Approximately 49% of all marketed prodrugs are activated by hydrolysis . . .". (Exhibit 1018, p. 2393.)

Rautio (Exhibit 1019) – Prodrugs are an established tool for drug delivery.

229. Rautio (Exhibit 1019), entitled "*Prodrugs: design and clinical applications,*" and published in 2008, discloses that prodrugs have become an established tool for improving physicochemical, biopharmaceutical or pharmacokinetic properties of pharmacologically active agents. (Rautio, Exhibit 1019, p. 255.)

230. Rautio teaches that the hydroxyl (-OH) group is a common functional group for prodrug design (*i.e.,* group to which a promoiety can be attached) and that esters are most often used to enhance the lipophilicity and membrane permeability.

> "Some of the most common functional groups that are amenable to prodrug design include carboxylic, hydroxyl…".
>
> ****
>
> "Ester prodrugs are most often used to enhance the lipophilicity, and thus the passive membrane permeability…".

Rautio, Exhibit 1019, p. 256.

Silverman (Exhibit 1020) – Ester moieties are a common prodrug form for drugs containing alcohol functional groups such as epinephrine.

231. Silverman (Exhibit 1020), Chapter 8 of "Prodrugs and drug delivery systems" published in The Organic Chemistry of Drug Design and Drug Action, in 1992 ("Silverman") teaches, among other things, that the most common prodrug form for drugs containing alcohol functional groups is an ester. "A carrier-linked prodrug is a compound that contains an active drug linked to a carrier group that can be removed enzymatically, such as an ester which is hydrolyzed to an active carboxylic acid-containing drug." (*See, e.g.,* Exhibit 1020, p. 354.)

232. Silverman explains why the most common prodrug form for drugs containing alcohol or carboxylic functional groups is an ester.

> "There are several reasons why the most common prodrug form for drugs containing alcohol or carboxylic acid functional groups is an

> ester. First, esterases are ubiquitous, so metabolic regeneration of the drug is a facile process. Also, it is possible to prepare ester derivatives with virtually any degree of hydrophilicity or lipophilicity. Finally, a variety of stabilities of esters can be obtained by appropriate manipulation of electronic and steric factors. Therefore, a multitude of ester prodrugs, can be prepared to accommodate a wide variety of problems that require the prodrug approach."
>
> Silverman, Exhibit 1020, pp. 355-366.

Schobel (Exhibit 1021) – Film Delivery of Ester Prodrugs to Oral Mucosa

233. Schobel (Exhibit 1021), U.S. Patent No. 11,191,737 B2, is entitled "Enhanced delivery epinephrine compositions", and claims the benefit of provisional application No. 62/331,996, it was filed on May 5, 2016 ("Schobel"). It is my understanding that Schobel, based on its filing date, is prior art to the '437 Patent.

234. Schobel teaches that drug delivery through the buccal mucosa is limited by the barrier nature of the epithelium and that prodrugs may be employed to overcome the epithelium barrier. (Exhibit 1021, 7:26-33.)

235. Schobel describes three main classes of oral dissolving films, namely fast, moderate, and slow dissolving films. Schobel prefers to use films that are moderate

dissolving, that is, they dissolve in about 1 to about 30 minutes. (*See* Schobel, Exhibit 1021, 13:37-67.)

236. Schobel teaches the use and methods of making such oral dissolving films for delivery of pharmaceutical compositions to the oral mucosa. (*See generally* Exhibit 1021, 13:15-67, 16:57-27:2.)

237. Schobel discloses that in "general **a pharmaceutical composition can include** a polymeric matrix, **epinephrine in the polymeric matrix,** and an adrenergic receptor interacter. . . . In certain embodiments, the pharmaceutical composition can be a film further comprising a polymeric matrix, the pharmaceutically active component being contained in the polymeric matrix." (Exhibit 1021, 1:26-45 (emphasis added).) Schobel discloses pharmaceutically acceptable carriers and excipients for its pharmaceutical compositions, including epinephrine, having enhanced active component permeation properties. (See, e.g., Exhibit 1021, 2:20-3:29, 19:57-25:24, 26:14-35, 45:15-28.)

238. Moreover, the pharmaceutical composition can be a prodrug.

> A pharmaceutical composition can include one or more pharmaceutically active components. The pharmaceutically active component can be a single pharmaceutical component or a combination of pharmaceutical components. . . . **The pharmaceutically active component** can be the compound,

> pharmaceutically acceptable salt of a drug, **a prodrug,** a derivative, a drug complex or analog of a drug. **The term "prodrug" refers to a biologically inactive compound that can be metabolized in the body to produce a biologically active drug.**
>
> Exhibit 1021, 14:13-18 (emphasis added).

239. Schobel describes esters of epinephrine, *i.e.,* ester prodrugs of epinephrine. (*See, e.g.,* Exhibit 1021, 15:62-65 ("a composition including epinephrine or its salts or esters can have a biodelivery profile similar to that of epinephrine administered by injection, for example, using an EpiPen"); claim 1, 45:19-20 ("a pharmaceutically active component including epinephrine, a pharmaceutically acceptable salt or ester thereof"); claim 27, 46:45-46 ("a pharmaceutically active component including epinephrine, a pharmaceutically acceptable salt or ester thereof"); claim 28, 46:58-59 ("a pharmaceutically active component including epinephrine, a pharmaceutically acceptable salt or ester thereof").)

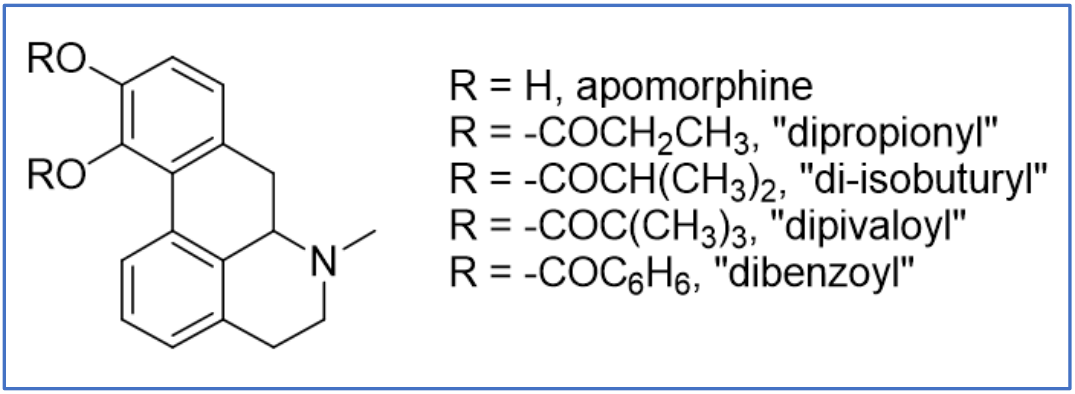
Baldessarini (Exhibit 1023) – Half-lives of Diester Prodrugs of Apomorphine in rat tissues

240. Baldessarini (Exhibit 1023), entitled "Hydrolysis of diester prodrugs of apomorphine," published in 1977 ("Baldessarini") reports, *inter alia*, that formation of free apomorphine from apomorphine diester prodrugs occurred in rat plasma. Baldessarini concluding that a POSA could control the rate of enzymatic

hydrolysis and thus formation of the parent drug by choosing the appropriate ester, where the shorter ester group would have expected to have the faster half-life and formed the parent drug quicker. "[The] apparent enzymatic reaction proceeded at rates varying inversely with the size of the ester substituent. These results support the suggestion that the rate of hydrolysis may be related to desirable prolongation of action of ester prodrugs of apomorphine." (Exhibit 1023, Abstract, p. 1749.)

241. Based just on Baldessarini, a POSA would have been aware of ester promoiety strategies for chemically modifying small molecules containing a catechol group to form prodrugs of the parent drugs. For example, a POSA would have been aware that Baldessarini discloses hydrolysis of various diester prodrugs of apomorphine in rat tissues along with their promoieties.

242. Shown below are the structures of Baldessarini's diester prodrugs.



243. Specifically, Baldessarini discloses that "the time course of hydrolysis of a series of esters of increasing molecular weight suggested that the rate of the

reaction bears an inverse relation to the size of the ester substituent (Fig. 4)…". (Exhibit 1023, p, 1753, 2nd col.) Thus, a POSA would have understood that smaller alkyl groups result in faster hydrolysis rates compared to larger alkyl groups.

244. Baldessarini's Figure 4 is reproduced below (diprop-APO highlighting added).

Baldessarini, Exhibit 1023, Figure 4, p. 1754

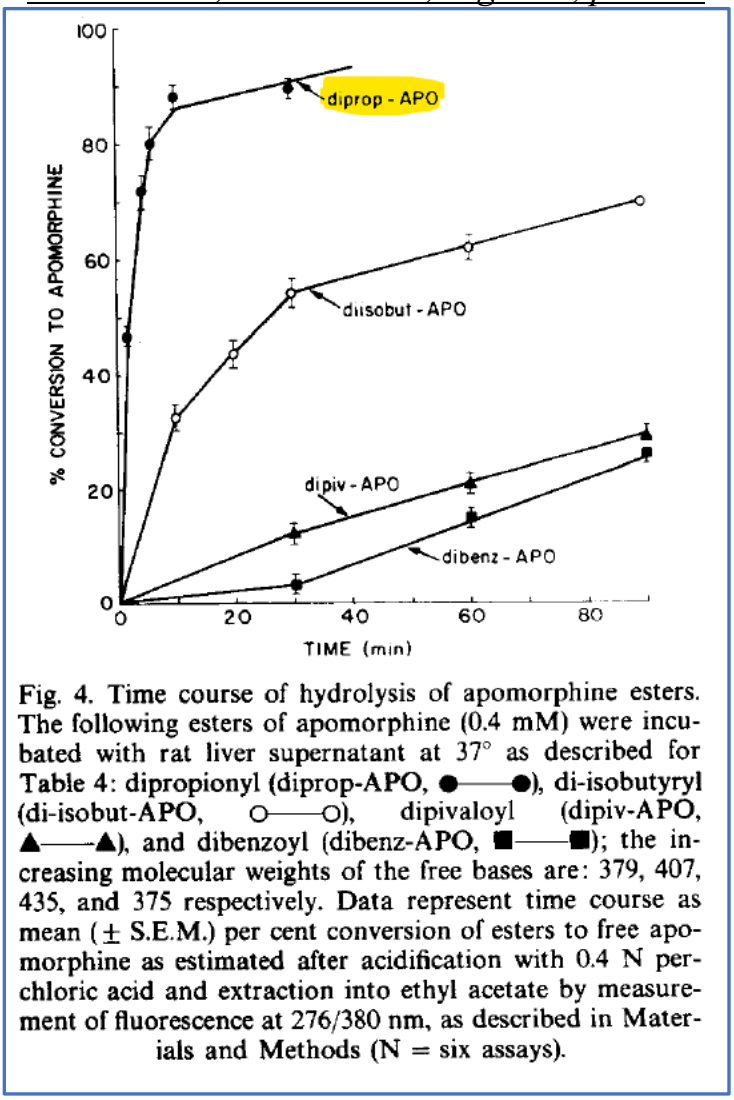


Fig. 4. Time course of hydrolysis of apomorphine esters. The following esters of apomorphine (0.4 mM) were incubated with rat liver supernatant at 37° as described for Table 4: dipropionyl (diprop-APO, ●——●), di-isobutyryl (di-isobut-APO, ○——○), dipivaloyl (dipiv-APO, ▲——▲), and dibenzoyl (dibenz-APO, ■——■); the increasing molecular weights of the free bases are: 379, 407, 435, and 375 respectively. Data represent time course as mean (± S.E.M.) per cent conversion of esters to free apomorphine as estimated after acidification with 0.4 N perchloric acid and extraction into ethyl acetate by measurement of fluorescence at 276/380 nm, as described in Materials and Methods (N = six assays).

245. For example, the hydrolysis rate of Baldessarini's dipropionyl ester (diprop-APO) to form 50% apomorphine (*i.e.,* its half-life), which corresponds to Almoazen '437 Patent, Exhibit 1001, Figure 7C's ester promoiety (R = $-CH_2CH_3$, which appears in claims 2 and 3), is less than five (5) minutes when incubated with rat liver homogenate. (See Exhibit 1023, Figure 4, p. 1754, copied above.) Even though the enzymatic assay used is different from human plasma assay, this would have informed a POSA that smaller straight and not branched alkyl groups, such as dipropionyl, result in faster hydrolysis rates compared to larger alkyl and branched groups, such as dipivaloyl group (corresponds to dipivefrin).

246. As discussed at ¶¶ 54-55 above, the '437 Patent refers to Truelove 1's ester prodrug as Dipivefrin and that it had a half-life $t_{1/2}$ of 1800 seconds [30 minutes]. (Exhibit 1001, 2:22-32.) However, as discussed above at ¶¶ 79-81, 87-90, Almoazen relied on Truelove 1's 30 minute half-life to overcome a claim rejection during the prosecution of the '437 Patent application. As noted by the Patent Examiner "Applicant has amended claims and persuasively argued the unexpected result of the claimed epinephrine prodrug genus having a rapid half-life ranging from 1 to 6 minutes. Applicant points out that prior art prodrugs have 30 minute half-life. The instantly claimed genus is thus suitable for sublingual or buccal administration having a much shorter half-life. Subsequent to persuasive arguments

the rejection is withdrawn." ('437 FH, Exhibit 1005, pdf. p. 14 (emphasis added).) Importantly, a POSA would have understood that argument to be faulty, as a POSA would have understood that the prodrug compounds disclosed in Truelove 1 with smaller straight and not branched alkyl groups would be expected to have shorter half-lives than 30 minutes.

Kristoffersson (Exhibit 1024) – Half-lives of Diester Prodrugs of Terbutaline in Human Serum[36]

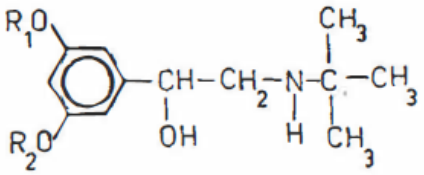
247. Kristofferson (Exhibit 1024) published in 1974 is entitled "Drug latentiation of terbutaline - *In vitro* serum esterase catalyzed hydrolysis of a series of acyl-substituted mono- and diesters of terbutaline" ("Kristoffersson"). (Exhibit 1024, p. 427.) "Latentiation" describes the alteration of drugs to derivatives (*i.e.,* prodrugs) from which parent drugs are regenerated by enzymatic attack. Kristoffersson provides data supporting the understanding that it would have been obvious to a

[36] Serum is plasma without the clotting factors (like fibrinogen). Plasma may contain as an additive an anticoagulant like EDTA or heparin to prevent any clotting. Plasma is typically used in hydrolysis studies even though it is known that anticoagulants can inhibit some hydrolytic enzymes. Likely no difference to hydrolysis rates of rapidly hydrolyzing ester prodrugs.

POSA to select in synthesizing prodrugs of the bronchodilator parent drug, terbutaline that small alkyl groups over larger and branched alkyl groups when designing rapidly hydrolyzing esters of epinephrine.

248. The structure of the parent drug terbutaline (R_1= R_2 = H) and the series of acyl substituted mono- and diesters of terbutaline studied by Kristofferson are shown below.

Terbutaline Structure (R_1= R_2 = H), Kristofferson, Exhibit 1024, p. 428.



KWD 2037: R_1 = R_2 = CH_3-CO
KWD 2074: R_1 = H,R_2 = CH_3-CO
KWD 2057: R_1 = R_2 = CH_3CH_2-CO
KWD 2058: R_1 = R_2 = $(CH_3)_2CH$-CO
KWD 2179: R_1 = H,R_2 = $(CH_3)_2CH$-CO
KWD 2170: R_1 = R_2 = $CH_3CH_2(CH_3)CH$-CO
KWD 2085: R_1 = R_2 = $(CH_3)_3C$-CO

249. Kristofferson's ester analogs to those disclosed or claimed in Almoazen '437 Patent are set forth below.

KWD 2037 = Analog of '437 Patent, Fig. 7A (Claims 2&3, R = -CH_3).
KWD 2057 = Analog of '437 Patent, Fig. 7C (Claims 2&3, R = -CH_2CH_3).
KWD 2058 = Analog of '437 Patent, Fig. 7B (Claims 2&3, R = -$CH(CH_3)_2$).
KWD 2085 = Analog of '437 Patent, Fig. 7D (Dipivefrine).

250. Kristofferson studied the in vitro hydrolysis of acyl-substituted diesters and monoesters of terbutaline in, among other things, diluted human serum and

concluded that "increased branching in the acyl moiety of esters lower the rate of hydrolysis".

> "The *in vitro* serum esterase catalyzed hydrolysis of a series of differently acyl-substituted diesters of terbutaline, i.e. 1-(3',5'-diacyloxyphenyl)-2-t-butylaminoethanols, together with some of their corresponding monoesters, have been studied in diluted serum from man, cat and dog. The kinetic behaviour of the esters in human serum support a mechanism for the esterase catalyzed reaction where acylation of the enzyme is rate-limiting. **It has also been found that the esterase catalyzed hydrolysis of the terbutaline esters is sensitive to steric hindrance, i.e. increased branching in the acyl moiety of the esters lower the rate of hydrolysis**."

Kristoffersson, Exhibit 1024, Summary, p. 427 (emphasis added).

251. Table 1 of Kristoffersson, copied below, demonstrates the hydrolysis rates (e.g. maximal rate, V_m) in human serum for diester to monoester were fastest for acetyl and propionyl esters (analogs to Almoazen, Figures 7A (both R Groups (substituents) are $-CH_3$) and 7C (both R Groups (substituents) are $-CH_2CH_3$), respectively), whereas the rate was significantly slower for isobutyryl (Almoazen, Figure 7B (both R Groups (substituents) are $-CH(CH_3)_2$)) and even more so for dipivaloyl ester (dipivefrin) (Figure 7D (both R Groups (substituents) are $-(CH_3)_3$)).

Table 1, Kristoffersson, Exhibit 1024, p. 431.

Table 1

Kinetic parameters for the human serum esterase-catalyzed hydrolysis of acyl-substituted terbutaline esters[a] in 0.061 M phosphate buffer pH 7.4 and serum diluted 1: 55 at 37.0°C.

Compound code No.	V_m $M\ sec^{-1} \cdot 10^8$	$(V_m)_{rel}$	K_m $M\ 10^5$	$\frac{V_m}{K_m}$ $sec^{-1} \cdot 10^3$	$\left(\frac{V_m}{K_m}\right)_{rel}$
KWD 2037 $R_1 = R_2 = CH_3CO$	71.1 ± 3.0	7.0	7.1 ± 0.7	10.0 ± 0.7	2.3
KWD 2074 $R_1 = H;\ R_2 = CH_3CO$	98.6 ± 1.9	9.8	4.9 ± 0.3	20.1 ± 0.8	4.7
KWD 2057 $R_1 = R_2 = CH_3CH_2CO$	73.6 ± 1.0	7.3	5.2 ± 0.2	14.0 ± 0.5	3.3
KWD 2058 $R_1 = R_2 = (CH_3)_2CHCO$	10.1 ± 0.1	1.0	2.3 ± 0.1	4.4 ± 0.2	1.0
KWD 2179 $R_1 = H;\ R_2 = (CH_3)_2CHCO$	89.2 ± 1.0	8.8	2.3 ± 0.1	38.1 ± 1.9	8.9
KWD 2085 $R_1 = R_2 = (CH_3)_3CCO$	0.17 ± 0.02	0.02	4.8 ± 1.7	0.04 ± 0.01	0.008
KWD 2170 $R_1 = R_2 = CH_3CH_2(CH_3)CH$	1.6 ± 0.1	0.16	2.6 ± 0.7	0.6 ± 0.1	0.15

[a] The rate constants for the diesters KWD 2037, 2057, 2058, 2085 and 2170 refer to hydrolysis of diester to monoester.

431

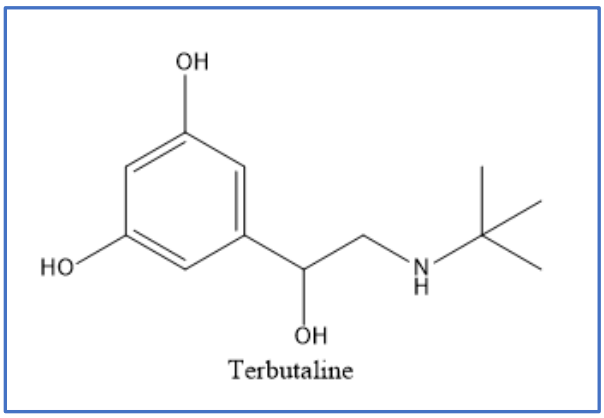
As noted earlier:

KWD 2037 = Analog of '437 Patent, Figure 7A (Claims 2 and 3, R = $-CH_3$).
KWD 2057 = Analog of '437 Patent, Figure 7C (Claims 2 and 3, R = $-CH_2CH_3$).
KWD 2058 = Analog of '437 Patent, Figure 7B (Claims 2 and 3, R = $-CH(CH_3)_2$).
KWD 2085 = Analog of '437 Patent, Figure 7D (Dipivefrine).

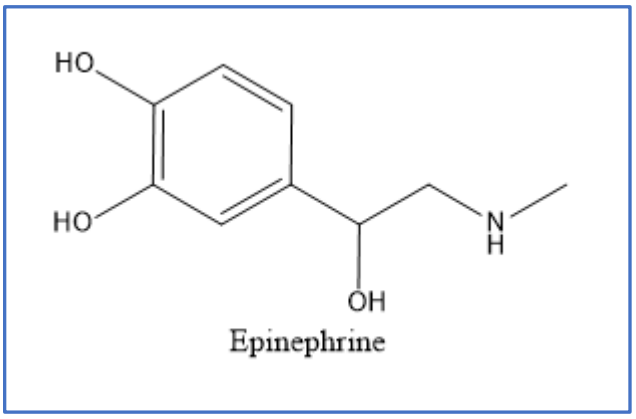
252. The hydrolysis experiments in Kristoffersson monitored the release of the phenolic compounds, *i.e.,* the parent compound terbutaline. Notably, the hydrolysis of both ester promoieties was, at least in one instance, so rapid that the monoester

could not be detected. "Also, in a preliminary experiment, no build-up of the monoester intermediate was found when the hydrolysis of KWD2058 in human serum was monitored…". (Exhibit 1024, p. 435, last paragraph.)

253. Based on Kristoffersson, it would have been obvious to a POSA to select small alkyl groups (substituents) over larger and branched alkyl groups when designing rapidly hydrolyzing esters of epinephrine. This would have been true, even though the parent drug in Kristoffersson, a bronchodilator terbutaline, contains two phenolic OH groups instead of the catechol group in epinephrine. The structures below were generated by ChemDraw®.



Terbutaline



Epinephrine

den Daas (Exhibit 1031) - Steric crowding around the ester group slows hydrolysis rate

254. den Daas (Exhibit 1031) is entitled "Improvement of the oral bioavailability of the selective dopamine agonist N-0437 in rats: the in vitro and in vivo activity of eight ester prodrugs".

255. den Daas discloses the general considerations necessary for an effective prodrug and the half-lives of acetyl (2), isobutyryl (3) and pivaloyl (4) prodrugs, corresponding to the '437 Patent's esters shown in, respectively, Figures, 7A (R = -CH_3), 7B (R = -$CH(CH_3)_2$) and 7D (R = -$C(CH_3)_3$).

Figure 1, den Daas, Exhibit 1031, p. 187, 1st column.

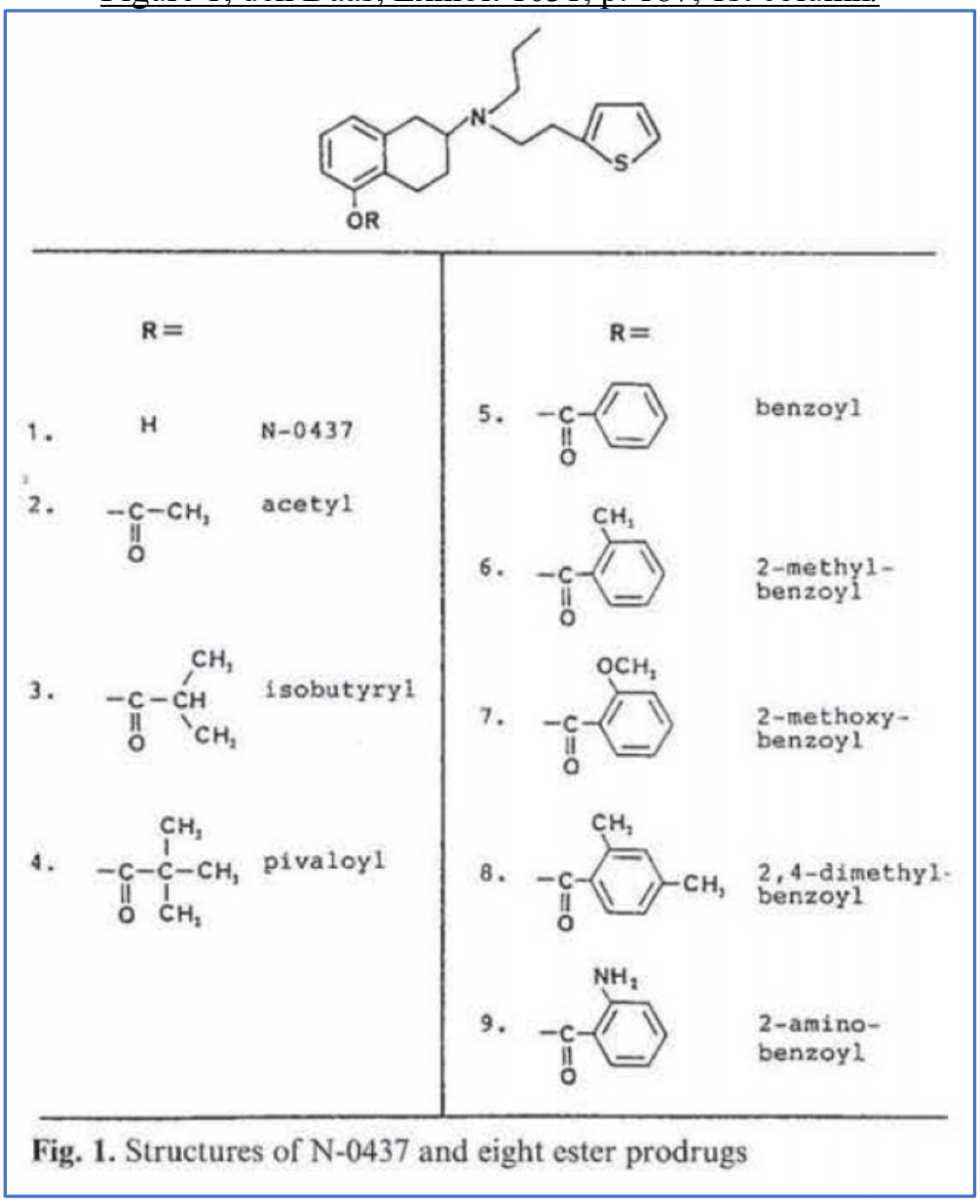


Fig. 1. Structures of N-0437 and eight ester prodrugs

256. den Daas teaches that there is an "expected" trend that straight alkyl group cleaves faster than branched: "The acetyl prodrug is hydrolyzed [in rat serum] very rapidly (half life ± 3 min) and has almost completely disappeared after 30 min. The total amount of prodrug conversion, calculated as the area under the curve (AUC),

is estimated to be ± 91 % of the original amount of N-0437. The hydrolysis rate of the isobutyryl ester is slower. It has a half life time of ± 21 min and a AUC of ± 85%. The prodrug with the lowest rate of hydrolysis of the aliphatic group is the pivaloyl ester with a half life of ± 92 min and a AUC of ±59%." (Exhibit 1031, p. 187 (2nd column).) The model drug, N-0437, is a phenol.

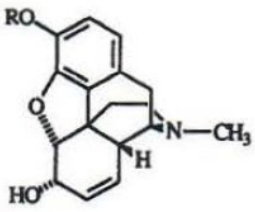
257. Finally, den Daas directly addresses the "expected" trend in hydrolysis rates, which is applicable across species. "**Concerning the hydrolysis rates of the compounds** we can divide them into two groups namely **the aliphatic** and aromatic **esters**. The former group **displayed the effects one would expect** i.e. **increasing substitution on the carbon atom α to the carbonyl group led to a decline in the hydrolysis rate**. This is due to an increase in steric crowding around the carbonyl function (Gould 1959) [Mechanism and structure in organic chemistry. Holt Rinehart and Winston, New York, pp 230 - 235]." (Exhibit 1031, p. 189 (2nd column, emphasis added).)

Christrup (Exhibit 1025) – Half-lives of Mono-ester Prodrugs of Morphine in Human Plasma

258. Christrup (Exhibit 1025),entitled "Improvement of buccal delivery of morphine using the prodrug approach," discloses that the buccal delivery of a less lipophilic parent drug (morphine) can be markedly improved by using ester prodrugs with higher lipophilicity. (Exhibit 1025, Abstract, 2-3 rows from bottom.)

259. Christrup provides the structure of morphine and the various esters investigated in the study in Scheme 1 copied below.

Scheme 1, Christrup, Exhibit 1025, p. 160.



	R	Name
I	—H	Morphine
II	—$COCH_3$	Morphine-3-acetate
III	—$COCH_2CH_3$	Morphine-3-propionate
IV	—$CO(CH_2)_4CH_3$	Morphine-3-hexanoate
V	—$CO(CH_2)_6CH_3$	Morphine-3-octanoate

Scheme 1. Chemical structure of morphine and the various esters investigated in this study. Compound, R and name, respectively: **I** H– morphine; **II** CH_3CO– morphine-3-acetate (M-3-A); **III** CH_3CH_2CO– morphine-3-propionate (M-3-P); **IV** $CH_3(CH_2)_4CO$– morphine-3-hexanoate (M-3-H); **V** $CH_3(CH_2)_6CO$– morphine-3-octanoate (M-3-O)

260. Christrup discloses the acetate ester promoiety (R = -CH_3). This same promoiety corresponds to Figure 7A of Almoazen '437 Patent and is recited in claims 2 and 3. Similarly, the propionate ester promoiety (R = -CH_2CH_3), is disclosed in Figure 7C of Almoazen and is recited in claims 2 and 3. As shown below, these promoieties rapidly hydrolyzed in human plasma diluted to 80%[37] and 10% with 0.05 M phosphate buffer pH 7.4. "In both the hydrolysis and bioactivation studies the hydrolysis of the morphine esters proceeded with quantitative formation of morphine." (Exhibit 1025, Section 3.1, p. 162.)

261. As shown in Table 1, copied below, where M-3-A is the acetate ester (R = -CH_3, which corresponds to Almoazen '437 Patent, Figure 7A, and is recited in claims 2 and 3) and M-3-P is the propionate ester (R = -CH_2CH_3, which corresponds to Almoazen, Figure 7C, and is recited in claims 2 and 3), Christrup

[37] General method for in vitro stability involves buffered plasma in which phosphate buffer (pH 7.4) is added to plasma (20-50% final volume) to adjust pH at 7.4. Diluted plasma contains enough enzymes when a test compound concentration is low, for example, in the micromolar range. Maintaining pH at 7.4 is important for enzyme activity.

teaches that the very short half-lives of hydrolysis of these two esters range from <0.2 to 0.8 minutes in both (80% and 10%) diluted plasma assays.

Table 1, Christrup, Exhibit 1025, p. 163

Table 1
Half-lives of hydrolysis of various morphine esters in 0.02 M phosphate buffer solutions (pH 7.4), in human plasma and in human saliva at 37°C

Compound	Buffer pH 7.4 (h)	Plasma 80% (min)	Plasma 10% (min)	Saliva 80%* (min)
M-3-A	34.9	<0.2	0.8	59.6 (15.4)
M-3-P	40.0	<0.2	0.3	16.0 (4.8)
M-3-H	~150	<0.2	0.2	nd**
M-3-O	nd**	0.4	nd**	nd**

Values are given as mean and (S.D.).
* Values corrected to a protein content of 1 mg/ml.
** Not determined.

262. Christrup observes that even though the half-lives were generally too fast to be accurately determined: "The bioactivation of M-3-A, M-3-P and M-3-H in human plasma both 80 and 10% proceeded too fast for the half-live to be accurately determined, however since the aim of these studies was merely to determine the rank order for the stability of the esters against enzymatic degradation in plasma, than to determine the exact half-lives no further studies were considered necessary." (Exhibit 1025, p. 162, 1st column.)

263. All the ester morphine prodrugs were able to permeate the porcine buccal mucosa while the morphine drug was not able to do so. (Christrup, Exhibit 1025, pp. 163-164.)

264. Christrup concludes that the ester morphine prodrugs with higher lipophilicity than the morphine drug increased the permeability of the bovine

buccal mucosa and hence buccal absorption of the drug. “The results obtained in the present study show that the permeation of morphine through porcine buccal mucosa and the buccal absorption of morphine in rats can be markedly improved by using ester prodrugs with higher lipophilicity.[38] However, under in vivo conditions, the enzymatic stability of the prodrugs in saliva do also play an important role for the overall improvement in absorption properties.” (Exhibit 1025, Conclusion, p. 164 , 2nd column.)

265. Even though the parent drug (morphine) in Christrup is a phenol, the know-how is directly applicable to catechol groups, such as that present in epinephrine. Again, increased lipophilicity is attributed to improved buccal permeability. Thus, a POSA would again have been aware of the benefits of using ester prodrugs for enhanced buccal permeability.

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38 While morphine has the experimental log P value of -0.06 determined between octanol and 0.05 M phosphate buffer pH 7.4, the acetate ester (M-3-A, R = $-CH_3$, which corresponds to Almoazen, Figure 7A, and is recited in claims 2 and 3) and the propionate ester (M-3-P, R = $-CH_2CH_3$, which corresponds to Almoazen, Figure 7C, and is recited in claims 2 and 3), have higher log P values of 0.17 and 0.66, respectively. See Exhibit 1025, Table 2, p. 163.

Hansen 1991 (Exhibit 1030) – Half-lives of Mono-ester Prodrugs of Ketobemidone in Human Plasma

266. Hansen 1991 (Exhibit 1030), is entitled "Ketobemidone prodrugs for buccal delivery" and states:

> "Various carboxylic acid and carbonate esters of the opioid analgesic ketobemidone were prepared and assessed as potential prodrugs with the aim of obtaining a ketobemidone formulation suitable for buccal or sublingual absorption. The chemical stability, enzymatic hydrolysis and lipophilicity characteristics of the esters were studied using HPLC assay procedures. **All esters were rapidly hydrolyzed in human plasma, the half-lives ranging between 0.03 and 1.8 min.** A marked enzymatic hydrolysis took place in whole human saliva, the half-lives of hydrolysis being in the range 3-295 min. All esters were more lipophilic than the parent ketobemidone, as determined by octanol-buffer partition experiments and by reversed-phase column chromatography. The relatively high resistance of the sterically hindered 3,3-dimethylbutyryl ester to undergo hydrolysis in saliva combined with its facile plasma-enzyme catalyzed conversion and high lipophilicity makes this ester the most promising prodrug candidate for buccal delivery."
>
> Hansen 1991, Exhibit 1030, Abstract, p. 77 (emphasis added).

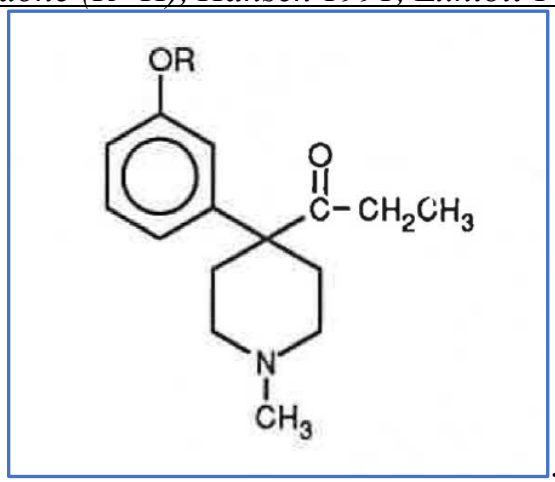
267. Even though Hansen 1991's parent drug ketobemidone, an opioid analgesic, is a phenol, the know-how is directly applicable to catechol groups, such as that

present in epinephrine.[39] Again, increased lipophilicity is attributed to improved buccal permeability. Thus, a POSA would again have been aware of the benefits of using ester prodrugs for enhanced buccal permeability and rapid release of the parent drug.

268. A POSA would have known that Hansen 1991's analgesic prodrug needed a short half-life and rapid release of the parent drug to be effective, *e.g.,* for rapid pain relief.

269. The structure of ketobemidone (R=H) from Hansen 1991 is copied below.

Ketobemidone (R=H), Hansen 1991, Exhibit 1030, p. 77.



.

270. Table 1,copied below, discloses the various esters studied by Hansen[40]

[39] As is true with respect to Christrup's phenol drug (Exhibit 1025).

[40]NB: The designations of the same prodrug ester moieties in Hansen 1991 (Exhibit 1030) differ from the designations given in Hansen 1992 (Exhibit 1032)

Table 1, Hansen 1991, Exhibit 1030, p. 78.

Table 1. *Physical and analytical data of various esters of ketobemidone*[a].

Ester	R	Melting point (°C)	Formula
II	$-COCH_3$	oil	$C_{17}H_{23}NO_3$
III	$-COC(CH_3)_3$	214–215	$C_{20}H_{30}ClNO_3$
IV	$-COCH_2C(CH_3)_3$	172–173	$C_{25}H_{35}NO_7$
V	$-COC_6H_5$	207–208	$C_{22}H_{26}ClNO_3$
VI	$-COOCH_3$	157–158	$C_{17}H_{24}ClNO_4$
VII	$-COOC_2H_5$	85– 86	$C_{18}H_{26}ClNO_4,H_2O$
VIII	$-COOCH(CH_3)_2$	171–172	$C_{19}H_{28}ClNO_4$
IX	$-COOCH_2CH(CH_3)_2$	159–160	$C_{20}H_{30}ClNO_4$
X	$-COOC_4H_9$	133–134	$C_{20}H_{30}ClNO_4$
XI	$-COOC_6H_{13}$	63– 64	$C_{22}H_{34}ClNO_4$

[a] The ester II was isolated as the free base and ester IV as the fumarate salt. All other esters are hydrochloric acid salts.

271. As noted in Hansen 1991, "[t]he esters of ketobemidone (II-XI) prepared include **alkyl esters (II-IV)**, an aryl ester (V) and several carbonate esters (i.e. carbonates) (VI-XI) containing both straight and branched alkyl chains. Such esters were expected to possess widely differing properties in terms of lipophilicity and chemical and enzymatic stability." (Exhibit 1030, pp. 78-79 (emphasis added).)

272. The alkyl esters II (O-Acetyl ketobemidone), III (O-Pivalyl ketobemidone) and IV (O-3,3-Dimethylbutyryl ketobemidone, disclosed in Hansen 1991 correspond to three of the '437 Patent mono-esters. Namely, the acetate ester (II: R = $-CH_3$, which corresponds to Almoazen '437 Patent, Figure 7A and **is recited in claims 2 and 3**), the pivaloyl ester (III: R = $-C(CH_3)_3$, which corresponds to

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discussed below. For example, Hansen 1992's prodrug ester moiety **II** is the same Hansen 1991's prodrug ester moiety **IV**.

Almoazen, Figure 7D) and the 3,3-dimethylbutyryl ester (also referred to as 3,3-dimethylbutyrate ester) (IV: R = -$CH_2C(CH_3)_3$, which **is recited in Almoazen '437 Patent, claim 1**).

273. Hansen 1991 tested "[t]he susceptibility of the ketobemidone esters to undergo enzymatic hydrolysis [that] was studied at 37°C in human plasma diluted to 80% with 0.01 M phosphate buffer solutions (pH = 7.40)". (Exhibit 1030, p. 80, 2nd column.)

274. Hansen 1991 taught that the hydrolysis in 80% human plasma of the three alkyl mono-esters disclosed in Almoazen were 0.05 minutes (II, R = -CH_3), 0.3 min (III: R = -$C(CH_3)_3$) and 1.8 minutes (IV, R = -$CH_2C(CH_3)_3$). (See Hansen 1991, Table 3 copied below.[41])

[41] Hansen 1991 also studied the half-life of ketobemidone ester prodrug IV (R = -$CH_2C(CH_3)_3$) in the plasma of different species and found differences. "The 3,3-dimethylbutyryl ester (IV) is hydrolyzed more rapidly in mouse, guinea pig and rabbit plasma than in human plasma but, surprisingly, markedly slower in rat plasma." Exhibit 1030, p. 80, 2nd column. *See also* Table 4, reproduced below. Nevertheless, while half-lives based on non-human plasma/tissue may provide

Table 3, Hansen 1991, Exhibit 1030, p. 80.

Table 3. *Half-lives for the hydrolysis of various ketobemidone esters in buffer solutions (pH 7.4), 80% human plasma and human whole saliva.*

Compound	Half-lives of hydrolysis (min)		
	pH 7.4 buffer[a]	80% human plasma[b]	whole saliva[b]
II	4.5 h (59 h)[b]	0.05	6.8
III	60 h	0.3	7.6
IV	60 h	1.8	295
V	11 h	0.08	4.0
VI	7.4 h (78 h)[b]	0.04	3.5
VII	10.3 h (162 h)[b]	0.03	5.1
VIII	35.6 h	0.04	4.9
IX	11.9 h	0.06	4.1
X	11.5 h	0.04	7.1
XI	11.8 h	0.11	4.4

[a] At 60°C
[b] At 37°C

different values, a POSA would have understood that these results disclose relevant trends, among, for example, the hydrolysis rates (half-lives) of different esters.

Table 4. *Half-lives of hydrolysis of two ketobemidone esters (IV and VIII) in 80% plasma solutions from various species (37°C).*

Plasma	Half-lives (min)	
	IV	VIII
Human	1.8	0.04
Rat	14.6	0.04
Mouse	0.7	0.03
Guinea pig	0.6	0.08
Rabbit	0.2	0.03

Hansen 1991, Exhibit 1030, p. 80.

275. Thus, this demonstrates the expected trend of progressively faster half-lives with progressively small alkyl chains. The absolute values are not important. But methyl ester hydrolyses 6 times faster than pivaloyl ester which is in line with Almoazen less than 6 min vs 30 min. Additionally, the $-CH_2$ group (in $-CH_2C(CH_3)_3$) slows hydrolysis down even further.

276. Hansen 1991 disclosed that the derivatization of the phenolic group in ketobemidone to form carboxylic acid or carbonate esters may be a useful prodrug approach. The esters are much more lipophilic than the parent drug, with at least one (IV: R = $-CH_2C(CH_3)_3$, which is recited in claim 1 of Almoazen '437 Patent, having a high resistance to being enzymatically hydrolyzed in saliva and thus making it a good candidate for buccal delivery. Hansen 1991, Exhibit 1030, p. 81, concludes:

> "The results obtained suggest that derivatization of the phenolic group in ketobemidone to form carboxylic acid or carbonate esters may be a useful prodrug approach. The esters are much more lipophilic than the parent drug and hence potentially more capable of penetrating the buccal mucosal barrier. Due to the presence of the tertiary amino group, the esters are readily soluble in water in the form of hydrochloric acid salts. Compared with the other esters, the 3,3-dimethylbutyryl ester IV shows a relatively high resistance to being enzymatically hydrolyzed by saliva. This property, along with

> its facile plasma-catalyzed hydrolysis and high lipophilicity, makes this ester the most promising prodrug for buccal delivery."
>
> Hansen 1991, Exhibit 1030, p. 81.

277. While Almoazen claims diesters and Hansen 1991 teaches monoesters, Hansen 1991 does support the rapid enzymatic hydrolysis of these monoesters in 80% human plasma and more importantly further supports the trend of quicker hydrolysis for shorter and linear alkyl esters in general.

278. Thus, a POSA would have considered these alkyl esters in forming prodrugs for the administration of epinephrine buccally or sublingually with more than a reasonable expectation that the prodrug would be lipophilic enough to allow for the quick passage in a substantial amount to the human bloodstream where it would be rapidly hydrolyzed to form the active drug.

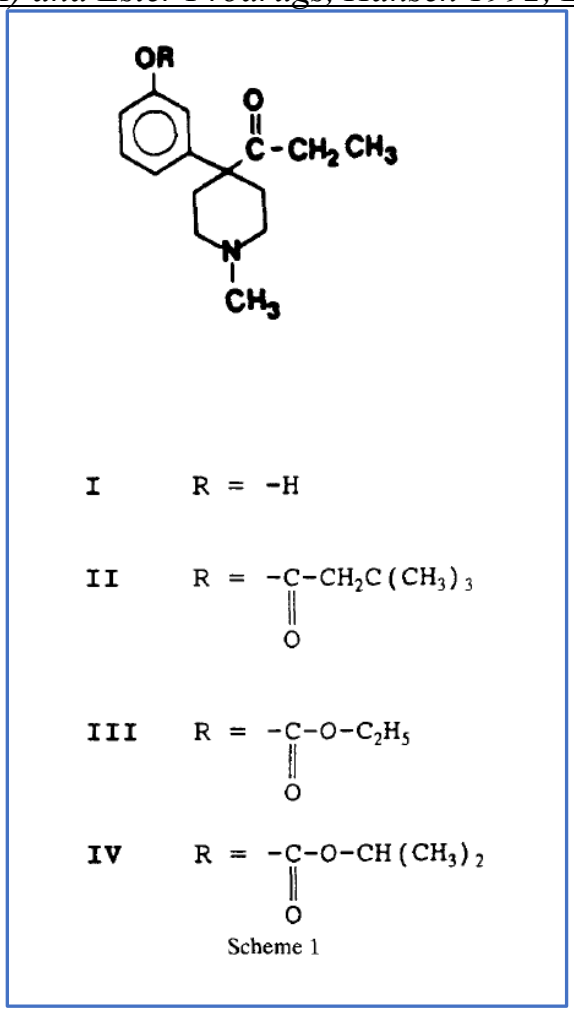
Hansen 1992 (Exhibit 1032) – Saliva Hydrolysis of Ketobemidone

279. Hansen 1992 (Exhibit 1032) is entitled "Ketobemidone prodrugs for buccal delivery: Prediction of the extent of saliva-catalyzed hydrolysis of various ester prodrugs under simulated in vivo condition". Hansen 1992 assessed the potential impact of saliva enzyme-catalyzed hydrolysis of ester prodrugs of ketobemidone on buccal or sublingual administration. (See Exhibit 1032, p. 229.)

280. Hansen 1992 studied the stability of three (3) ketobemidone ester prodrugs. "The primary objective of the present study was to provide information on the stability of various ketobemidone ester prodrugs (**II-IV**, Scheme 1) in human saliva at various prodrug concentrations including clinically relevant concentrations." (Exhibit 1032, p.230. See copy of Scheme 1 below.[42])

[42]NB: As discussed above, the designations of the same prodrug ester moieties in Hansen 1991 (Exhibit 1030) differ from the designations given in Hansen 1992 (Exhibit 1032) discussed below. For example, Hansen 1992's prodrug moiety **II** is the same as Hansen 1991's prodrug ester moiety **IV**.

Ketobemidone (R=H) and Ester Prodrugs, Hansen 1992, Exhibit 1032, p. 230.



Scheme 1

281. The authors erroneously - to my mind - call these compounds esters. **II** is carboxylic acid ester and III and IV carbonate esters. But as I discussed above, **III** and **IV** are carbonates. Nevertheless, Hansen 1992 is relevant as it discloses the same promoiety that is in the '437 Patent, Exhibit 1001.[43]

[43] Carbonates are typically less enzymatically stable than esters. Also, all carbonates (VI-XI) hydrolyze very rapidly in human plasma (see Table 3, Exhibit

282. Hansen 1992 studied buccal and sublingual tablets having either fast or slow disintegration rates containing the prodrugs. "The rapidly disintegrating sublingual tablets were placed under the tongue whereas the slowly disintegrating tablets were placed either sublingually or buccally (between the upper lip and gum)." (Exhibit 1032, p. 230, 2nd column.)

283. Hansen 1992 concluded that the hydrolysis of the ketobemidone prodrugs at drug doses corresponding to normal doses of ketobemidone hydrochloride by saliva in five (5) minutes occurred to only a "very minor extent" and stated:

> The amount of saliva normally secreted during 5 min is in the range of 1.5-4 ml. As can be seen from Fig. 5 [copied below], hydrolysis of a ketobemidone ester prodrug by saliva enzymes at pharmacologically relevant concentrations is only expected to occur to a very minor extent which in turn is due to the occurrence of zero-order kinetics at these ester concentrations.
> Hansen 1992, Exhibit 1032, p. 234.

1030, p. 80). The difference in structure between esters and carbonates is: (a) ester = -$OCOCH_3$ or -$COCH_3$ and (b) carbonate = -$OCOOCH_3$ or -$COOCH_3$.

Figure 5, Hydrolyzation of Prodrugs in Saliva, Hansen 1992, Exhibit 1032

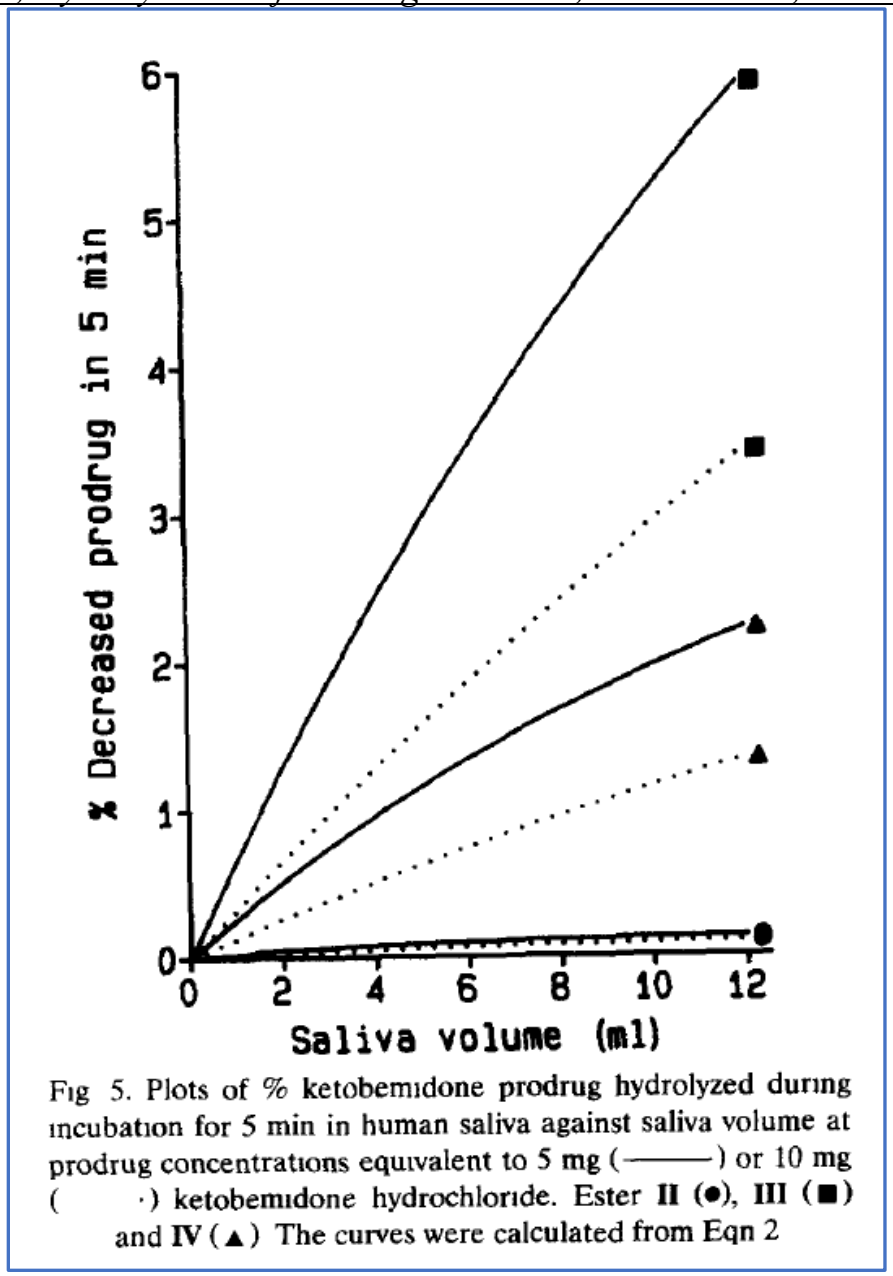


Fig 5. Plots of % ketobemidone prodrug hydrolyzed during incubation for 5 min in human saliva against saliva volume at prodrug concentrations equivalent to 5 mg (———) or 10 mg (·) ketobemidone hydrochloride. Ester II (●), III (■) and IV (▲) The curves were calculated from Eqn 2

284. A POSA would have understood that the impact of saliva on the Fig 5 prodrugs would have been extremely minimal.

Roche (Exhibit 1034)

285. Roche (Exhibit 1034) published in 1997 is entitled "Design of biopharmaceutical properties through prodrugs and analogs" ("Roche").

286. Copied below is Table I from Roche which lists various chemical fragments and their impact on Log P value. For example, adding a methyl group (CH_3) increases the Log P value either by 0.70 or 0.89 units depending on the method used.

Roche, Table I, Exhibit 1034, p. 50.

Table I

Compilation of f values

Fragment	f[a] (Nys & Rekker) Aliphat.	Aromat.	f(Leo, et al.) Aliphat.	Aromat.
H		0.19		0.23
CH_3		0.70		0.89
CH_2		0.52		0.66
CH		0.24		0.43
C		0.14		0.20
CH_2=CH		0.93		
CH=C		0.51		
F	-0.51	0.42	-0.38	0.37
Cl	0.06	0.93	0.06	0.94
Br	0.24	1.17	0.20	1.09
I	0.59	1.46	0.60	1.35
OH	-1.44	-0.37	-1.64	-0.40
O	-1.54	-0.46	-1.81	-0.57
COOH	-1.00	0.00	-1.09	-0.03
COO	-1.28	-0.40	-1.49	-0.56
NH_2	-1.38	-0.91	-1.54	-1.00
NH	-1.86	-0.93	-2.11	-1.03
N	-2.13	-1.07		
OCH_2COOH	1.21	-0.61		
NO_2	-1.06	-0.09	-1.26	-0.02
$CONH_2$	-1.99	-1.26	-2.18	-1.26
C=O	-1.69	-0.99	-1.90	-0.32
CF_3		1.28		
CN	-1.13	-0.20	-1.28	-0.34
SH	0.00	0.62		
S	-0.51	0.14	-0.79	0.03
OCH_3	-0.83	0.24		
C_6H_5		1.90		1.90
C_6H_4		1.73		
C_6H_3		1.48		
$C_{10}H_7$ (naphthalenyl)		3.17		
C_5H_4N (pyridinyl)		0.54		
C_4H_3O (furanyl)		1.22		
C_4H_3S (thienyl)		1.62		
C_4H_4N (pyrrolyl)		0.59		

287. Roche teaches the trend that increasing the number of alkyl groups results in higher lipophilicity and higher Log P value.

MOTIVATION TO COMBINE PRIOR ART REFERENCES

288. Disclosures of the salt form of prodrugs, such as found in Truelove 1 and Truelove 3, would have motivated a POSA to try the free base or non-salt form of the prodrug and the POSA would have had a reasonable expectation that the non-salt form would work at (i) penetrating the oral mucosa; and (ii) have the same or similar half-lives. See discussion below at ¶¶ 296-306, and also discussion at ¶¶ 135-137 above, in connection with Truelove 1 disclosure of the salt forms of epinephrine prodrugs.

289. Prodrugs are a well-known and established concept which can be used to overcome barriers to a drug's usefulness. It was known and understood that prodrugs could be designed and synthesized to overcome pharmaceutical, pharmacokinetic, or pharmacodynamic barriers such as insufficient chemical stability, poor solubility, insufficient oral absorption, inadequate blood-brain barrier permeability, marked presystemic metabolism, toxicity, and poor patient acceptability. (*See*, *e.g.*, Ettmayer, Exhibit 1018, p. 2393; Rautio, Exhibit 1019, p.255.)

290. A POSA would have appreciated that the most common reaction for activation of prodrugs is hydrolysis. (*See*, *e.g.*, Ettmayer, Exhibit 1018, p. 2394 and Rautio, Exhibit 1019, p.256, and Silverman, Exhibit 1020, p. 355.) Further,

the most common prodrug form for drugs containing alcohol functional groups is an ester (Silverman, Exhibit 1020, p. 355.). This is due to several factors, including: 1) esterases are ubiquitous which makes regeneration of the drug a facile process; 2) ester derivatives can be prepared with a range of hydrophilicity or lipophilicity; and 3) ester stability can be readily modified by appropriate manipulation of electronic and steric factors (Silverman, Exhibit 1020, p. 355-356).

291. A POSA would modify the catecholic hydroxyl groups of epinephrine by reacting them with various acid moieties to form simple acyl esters with different short alkyl chains. The addition of an alkyl group would enhance the lipophilicity of epinephrine (increasing its log P) and subsequently improve its permeability through biological membranes, such as the sublingual and buccal membranes in the oral cavity.

292. A POSA would consider references such as Truelove 1 (Exhibit 1002), Truelove 3 (Exhibit 1008), Truelove 4 (Exhibit 1007), Baldessarini (Exhibit 1023), Kristofferson (Exhibit 1024), den Daas (Exhibit 1031), Christrup (Exhibit 1025), and Hansen 1991 (Exhibit 1030), to identify suitable small alkyl promoieties for creating ester prodrugs of epinephrine that would rapidly convert to epinephrine in

the bloodstream after passing through the oral mucosa, effectively addressing conditions like anaphylaxis.

293. A POSA would also consider references detailing the half-lives of prodrugs with the same or similar diester promoieties and similarly structured drugs, such as those found, for example, in Truelove 1 (Exhibit 1002), Truelove 3 (Exhibit 1008), Truelove 4 (Exhibit 1007), and Hussain 1991 (Exhibit 1030).

294. The steps involved in the absorption of a compound from a formulation through the oral mucosa into systemic blood circulation are as follows:

1. **Release** of the compound from the formulation into saliva,
2. **Dissolution** of the compound into saliva,
3. **Transport** of the compound to the epithelial surface,
4. **Partitioning** of the compound into the superficial layers of the epithelium and **diffusion** through the epithelium,
5. **Partitioning** of the compound into and out of the basal lamina, and
6. **Diffusion** of the compound to the blood vessels.

295. A POSA would have been aware that while the more hydrophilic salt form of a prodrug may provide a faster dissolution rate into saliva, the more lipophilic free base (non-salt) form of the prodrug has a greater ability to partition into and penetrate lipid-rich biological membranes, such as the oral mucosa. Given the

importance of lipophilicity for effective mucosal absorption, a POSA would have been motivated to explore the free base form as a potential means to improve the permeability of the prodrug through the oral mucosa.

296. Additionally, a POSA would understand that the salt form of a prodrug would dissociate into its free base and ions before reaching the plasma. Therefore, the POSA would recognize that the non-salt or free base form of a prodrug would possess a similar hydrolysis rate in human plasma, which has its own buffering capacity.

297. A POSA would also understand that when the free base (non-salt) form of the prodrug or the salt form of the prodrug is directly exposed to an aqueous medium, such as plasma at a specific pH, the equilibrium between the free base and its ionic form is maintained, resulting in equivalent amounts of each. Consequently, the hydrolysis rate of the prodrug remains the same regardless of whether it is in the free base or salt form.

298. Challenged claims 1-3 of the ‘437 Patent are directed to diester epinephrine derivatives that can be administered sublingually or buccally. Claim 1 recites that the diester derivatives can include pharmaceutically acceptable salt forms of the claimed derivative. While independent claim 1 expressly recites pharmaceutically acceptable salt forms of the claimed compounds, independent claim 2 and

dependent claim 3, which depends from claim 2, do not expressly claim the pharmaceutically acceptable salt forms of the claimed derivative.

299. A POSA would have understood that the salt form of the claimed diester epinephrine prodrugs are soluble in aqueous media and would rapidly undergo dissociation into the free base or non-salt form of the claimed diester derivatives and acid radicals. Consequently, a POSA would have recognized that, once administered sublingually or buccally, both the free base or non-salt form and salt form of the claimed diester prodrugs would, for all practical purposes, be considered equivalent in terms of efficacy and the re-formation of the parent compound (*i.e.,* epinephrine) in the blood stream. See also discussion above at ¶¶ 135-137.

300. A POSA would have understood that disclosure of the salt forms of epinephrine and related prodrug compounds would have disclosed and made obvious the structure and half-lives ($t_{1/2}$) of the non-salt forms of the epinephrine and related prodrug compounds such as those recited in claims 2 and 3 of the ‘437 Patent.

301. Importantly, during prosecution of the ‘437 Patent, Almoazen made no distinction between the half-life ($t_{1/2}$) in human plasma of the salt and non-salt form of its prodrug compounds.

302. During prosecution, Almoazen relied on the 30-minute half-life ($t_{1/2}$) of the salt-form of one of the compounds disclosed in Truelove 1 to overcome a rejection of pending claims reciting both salt compounds (claim 1) and non-salt compounds (claim 2). Almoazen argued that Truelove 1's disclosure in Table 3 of a compound with a 30-minute half-life ($t_{1/2}$) supported his argument that the prior art did not disclose or teach both the recited salt and recited non-salt prodrugs compounds having half-lives ($t_{1/2}$) less than 30 minutes. See ¶¶ 79, 81, 87-90.

303. Without even mentioning Truelove 1 or addressing the substance of Truelove 1's disclosure, the Examiner simply accepted Almoazen's representations equating the half-lives ($t_{1/2}$) of both its recited salt and non-salt prodrug compounds and withdrew the pending rejection. See ¶¶ 89-90, above.

304. Almoazen's argument, which the Examiner accepted without question, relied on the premise that the claims under rejection, which encompassed both the salt and non-salt form of the prior art compounds, would have equivalent half-lives. Thus, Almoazen acknowledged, and a POSA would have understood, that the half-life ($t_{1/2}$) of prodrugs in salt and non-salt forms would have comparable, if not identical half-lives ($t_{1/2}$). Accordingly, a POSA would look, for example, to Truelove 1's Table 3 half-lives ($t_{1/2}$) and Truelove 3's Table 3 half-lives ($t_{1/2}$) as

disclosing the half-lives ($t_{1/2}$) of both the salt and non-salt forms of their disclosed prodrugs and that they would have comparable, if not identical half-lives ($t_{1/2}$).

305. A POSA would have recognized that the Log P (octanol-water partition coefficient) is a measure indicating hydrophilic or hydrophobic nature of a molecule, which is of great importance when delivering drugs through a mucosal layer. Therefore, the POSA would have considered references such as Ashraf, which discloses the Log P values of commercially marketed sublingually administered drugs and provides guidance on established and acceptable ranges of Log P for sublingual administration. (*See, e.g.,* Asraf, Exhibit 1003, Table II, p. 35.)

306. "For efficient absorption through the oral mucosa, the drug must be hydrophobic enough to partition into the lipid bilayer, but not so hydrophobic such that once it is in the bilayer, it will not partition out again. Satisfactory oral absorption of drugs has been observed over a wide range of log P (octanol/water partition coefficient) values of 1 to 5." (Asraf, Exhibit 1003, p. 35.)

307. Similarly, the POSA would have been aware, from Florence, that the ideal log P values for buccal absorption typically fall within the range of 3.52 to 5.52. (*See*, *e.g.,* Florence, Exhibit 1015, Table 9.1, p. 334.)

308. A POSA considering the sublingual or buccal administration of epinephrine would have understood that, to ensure rapid passage of epinephrine through the mucosal layer of the human mouth, it would have been obvious to use a lipophilic promoiety to increase the ability of an epinephrine prodrug with that promoiety to efficiently pass through the mucosal layer. The POSA would have considered disclosures such as Truelove 1 (Exhibit 1002) and the other Truelove patents and articles (e.g., Exhibits 1006, 1007 and 1008) to confirm the types of suitable ester promoieties of epinephrine that, after passage through the oral mucosal layer, would rapidly convert into epinephrine in the bloodstream and address conditions like anaphylaxis. (*See, e.g.,* Truelove 1, Exhibit 1002, Table 3, 9:26-37; and Truelove 4, Exhibit 1007, Table 1, p.1511.)

309. A POSA would also have considered references teaching the half-lives of prodrugs with the same or similar diester promoieties, as well as parent drugs having structures similar to or the same as epinephrine such as, for example, Truelove 1 (Exhibit 1002), Truelove 3 (Exhibit 1008) and Truelove 4 (Exhibit 1007).

310. A POSA would certainly have considered the Almoazen Paper (Exhibit 1022) which discloses epinephrine in a unit dosage form configured for sublingual or buccal administration in rapidly or fast dissolving films.

311. Finally, a POSA would have considered references such as Fuchs (Exhibit 1004) and Schobel (Exhibit 1021) which disclosed films designed for drug administration to human mucosa.

312. Fuchs explicitly discloses "unit dosage forms adapted for either enteral or topical administration can be employed, e.g., for topical administration on the skin and in body cavities such as the nose, ears, rectum, vagina, etc." (Fuchs, Exhibit 1004, 2:33-38.) Notably, the '437 Patent admits that Fuchs discloses "[f]ilms that incorporate a pharmaceutically active ingredient," those "films can be formed into a sheet, dried and then cut into individual doses" and that those films could be used for the "mucosal membrane areas of the body, including the mouth, rectal, vaginal, nasal and ear areas." ('437 Patent, Exhibit 1001, 2:39-47.)

313. A POSA would have considered Schobel as it teaches the use and methods of making oral rapidly dissolving films for delivery of epinephrine compositions including epinephrine prodrugs to the oral mucosa. (*See, e.g.,* Schobel, Exhibit 1021, 1:26-45 (epinephrine in films), 13:37-67 (rapidly dissolving films), 13:15-67 & 16:57-27:2 (oral dissolving films), 14:13-18 (drug in form of prodrug), 15:62-65 & 45:19-20 (ester prodrugs of epinephrine).)

314. A POSA would certainly have considered references such as den Daas (Exhibit 1031) regarding the general considerations necessary for an effective

prodrug and the half-lives of promoieties used in synthesizing prodrugs. For example, den Daas discloses that with respect to hydrolysis rates there is an "expected" trend that straight alkyl group cleaves faster than branched across species. "Concerning the hydrolysis rates of the compounds we can divide them into two groups namely the aliphatic and aromatic esters. The former group displayed the effects one would expect i.e. increasing substitution on the carbon atom α to the carbonyl group led to a decline in the hydrolysis rate. This is due to an increase in steric crowding around the carbonyl function . . .". (Den Dass, Exhibit 1031, p. 189, 2nd col.)

315. A POSA would have known that epinephrine should be administered as soon as the diagnosis of anaphylaxis is suspected. A POSA would have also recognized that anaphylaxis is a life-threatening event that needs to be addressed as rapidly as possible. Therefore, a POSA would have known, to be effective, an epinephrine prodrug must form epinephrine in the blood stream (human plasma) rapidly and if required, repeatedly. (*See, e.g.,* Lieberman, Exhibit 1029, pp. 477-478; 480.e10 ("Prompt recognition of signs and symptoms of anaphylaxis is crucial. If there is any doubt, it is generally better to administer epinephrine. . . . Epinephrine is the drug of choice, and the appropriate dose should be administered promptly at the onset of apparent anaphylaxis."), 480.e11 ("Epinephrine may be administered

every 5 to 10 minutes as necessary. If the clinician deems it appropriate, the 5 minute interval between injections can be liberalized to promote more frequent administration. . . . Epinephrine should be administered as soon as the diagnosis of anaphylaxis is suspected"); and Exhibit 1012, p. 1 ("EpiPen and EpiPen Jr are intended for immediate administration as emergency supportive therapy . . . ".).)

316. Based on the foregoing discussion, a POSA would have been motivated to combine the teachings of the prior art, in the various combinations as detailed below to arrive at compounds recited in claims 1-3 of the '437 Patent, and that the teachings of these prior art references would have provided the POSA with a reasonable expectation of success, without undue experimentation, to arrive at the challenged claimed compounds.

THE '437 PATENT CLAIM CHART

317. I have reviewed the '437 Patent Claim Chart attached hereto as Appendix C considering the prior art discussed previously and as further amplified below. In my opinion, a POSA would have been motivated to combine the various disclosures in the references found in each Ground and would have had a reasonable likelihood of success, without undue experimentation, separately for each Ground to arrive at the subject matter of claims 1-3 of the '437 Patent. Therefore, the '437 Claim Chart supports a finding that claims 1-3 of the '437

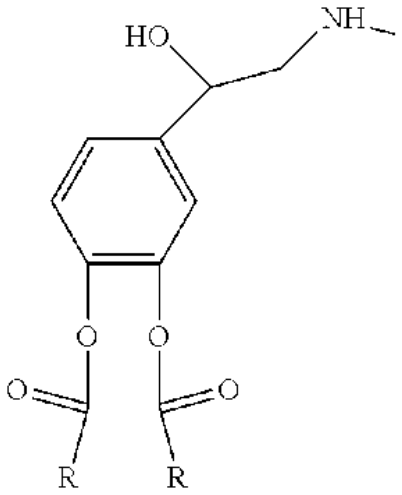
Patent would have been obvious to one skilled in the art. My opinions are discussed in more detail below.

GROUND 1
CLAIMS 1-3 ARE OBVIOUS IN VIEW OF TRUELOVE 1 (EXHIBIT 1002), ASHRAF (EXHIBIT 1003) AND ALMOAZEN PAPER (EXHIBIT 1022)

Claim 1 would have been obvious

318. Claim 1 recites in relevant part (emphasis added):

> A compound formulated as a pharmaceutical composition in a unit dosage form configured for sublingual or buccal administration of a Formula:



> wherein R is selected from the group consisting of: —$CHCH_2$, —$CHCHCH_3$, —CH_2—CH_2—Cl, —$CHCH_2I$, —$CH(Cl)CH_2$ (Cl), —$CH(I)CH_2(I)$, —$CH(CH_3)CH_2(CH_3)$, —$CH_2C(CH_3)_3$, **—$CH_2CH_2CH_3$**, —CH_2CI, … or a pharmaceutically acceptable salt thereof, wherein said compound has a Log P value in the range of about 0.5-6.0 and wherein the

compound is formulated in a unit dosage form as a rapidly dissolving film and has a half-life $t_{1/2}$ range from 1-6 minutes.

R Group "-$CH_2CH_2CH_3$"

319. The highlighted R group **-$CH_2CH_2CH_3$** in claim 1 above corresponds to the epinephrine ester prodrug named "4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene dibutyrate" and its structure is depicted in Figure 5G" of the '437 Patent. See also ¶¶ 171-178, 179 (Truelove 1 Relationship Chart),180, above, with respect to the following R Group discussion.

320. Truelove 1 discloses the epinephrine ester prodrug compound where R = **-$CH_2CH_2CH_3$** and the compound has a half-life ($t_{1/2}$) = 6 minutes as recited in claim 1. (See ¶¶ 171-178, above.) These disclosures appear in Table 3 of Truelove 1 (Exhibit 1002) copied below.

Truelove 1, Table 3, EX1002, 9:26-38

TABLE 3

Compound	Rate of hydrolysis in $t_{1/2}$ seconds		
	Horse	Rabbit	Human
L-3,4-diacetyl-α-[(methylamino)-methyl] benzyl alcohol hydroperchlorate	20	45	180
L-3,4-dipropionyl-α-[(methylamino)methyl] benzyl alcohol hydroperchlorate	50	90	240
L-3,4-dibutyryl-α-[(methylamino)-methyl] benzyl alcohol hydroperchlorate	100	160	360
L-3,4-dipivalyl-α-[(methylamino)-methyl] benzyl alcohol hydroperchlorate	600	720	1,800

321. A POSA would have understood that the identification of "L-3,4-**dibutyryl**-α-[(methylamino)methyl] benzyl alcohol hydroperchlorate" in Table 3 of Truelove 1, though a misnomer, actually taught and disclosed the novel ester prodrug "L-3,4-**dibutyroxy**-α- [(methylamino)methyl] benzyl alcohol hydroperchlorate."

322. A POSA would have understood that disclosure of "L-3,4-**dibutyroxy**-α-[(methylamino)methyl] benzyl alcohol hydroperchlorate" also taught the free base or non-salt form of the diester prodrug, namely "L-3,4-**dibutyroxy**-α-[(methylamino) methyl] benzyl alcohol" which is also known as "4-(1-hydroxy-2-(methylamino) ethyl)-1,2-phenylene dibutyrate".

323. The structure of "4-(1-hydroxy-2-(methylamino) ethyl)-1,2-phenylene dibutyrate" taken from Figure 5G" of the '437 Patent is shown below, disclosing the claimed R group "R = **-$CH_2CH_2CH_3$**".

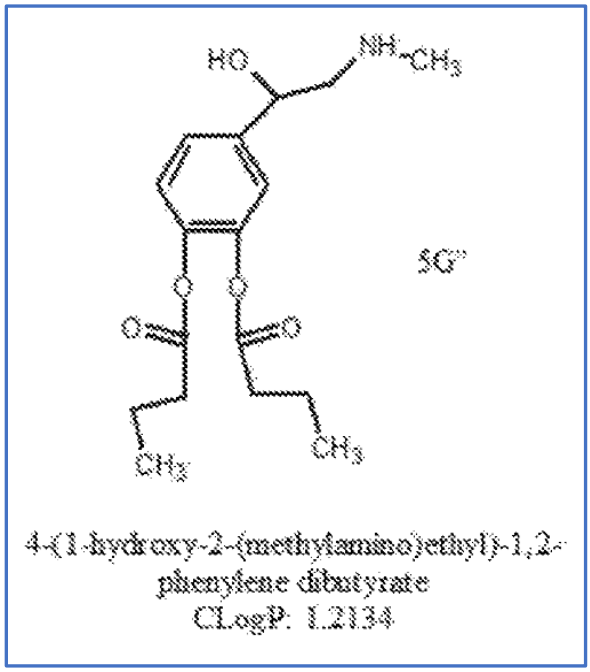
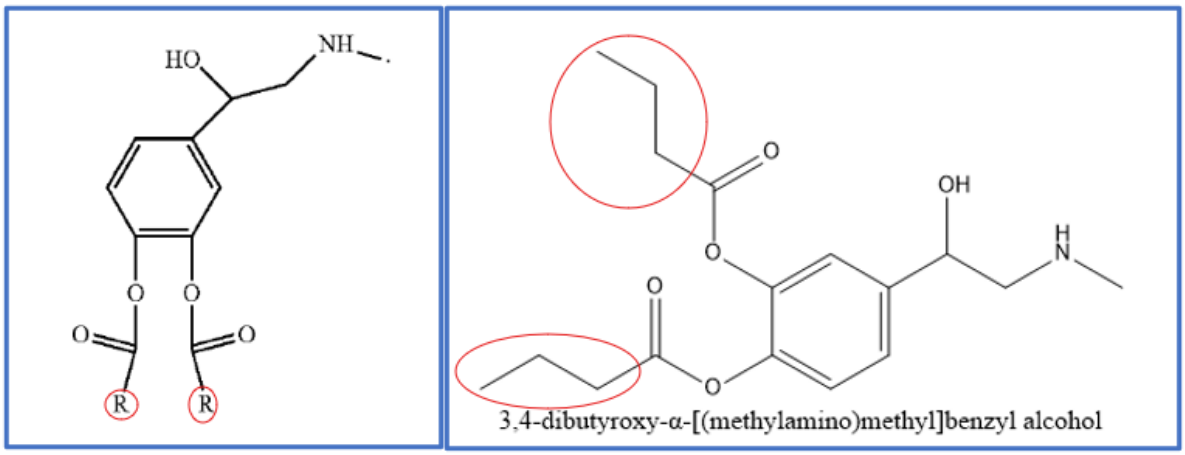


Exhibit 1001, Figure 5G" (see also 6:24-32).

324. Table 3 of Truelove 1 discloses one of the compounds recited in claim 1, namely, the compound where the R group is "R = **-$CH_2CH_2CH_3$**", and where the compound with this R group has a half-life $t_{1/2}$ is 360 seconds (6 minutes).

325. Claim 1 recites and shows a prodrug compound structure with an "R" group where "R = **-$CH_2CH_2CH_3$**". Shown below is a comparison of the recited structure with the structure generated by ChemDraw® that a POSA would have understood from Truelove 3 disclosure of "3,4-**dibutyroxy**-α-[(methylamino) methyl] benzyl alcohol" from Table 3.



326. Ashraf teaches that "Satisfactory oral [mucosal] absorption of drugs has been observed over a wide range of log P (octanol/water partition coefficient) values of 1 to 5." (Exhibit 1003, p. 35, 2nd col.) Ashraf also discloses some established acceptable ranges of Log P for sublingual and/or buccal administration, which Ashraf discloses are in the range of about 0.5 and 6. Exhibit 1003, Table II, p. 35. (See ¶¶ 194-197, above.)

327. Finally, the '437 patent admits that the Log P of the epinephrine compound of Claim 1 where the R group is "**-$CH_2CH_2CH_3$**" is +0.8 which falls within the Log P value of "in the range of about 0.5-6.0" as recited in claim 1. (See '437 Patent, Table 1, 5:29.)

328. The Almoazen Paper teaches everything that the '437 Patent does regarding epinephrine in a unit dosage form configured for sublingual or buccal administration in rapidly or fast dissolving films, including pharmaceutically

acceptable carriers or a pharmaceutically acceptable excipients. See Exhibit 1022, pp. 1012-1016. (See also, Exhibit 1033 visually showing the extent of the disclosure from the Almoazen Paper appearing in the '437 Paper and ¶¶ 181-193, above.)

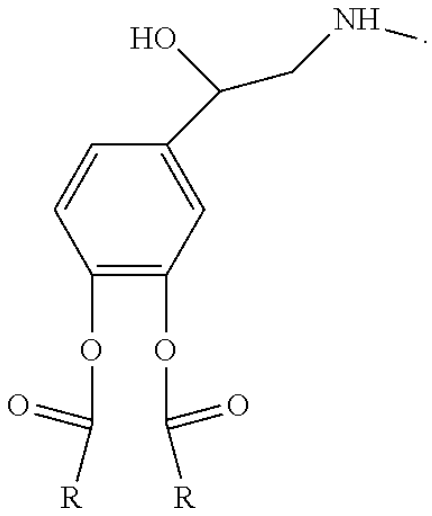
329. A POSA would have been motivated to combine the teachings of Truelove 1 (Exhibit 1002), Ashraf (Exhibit 1003) and the Almoazen Paper (Exhibit 1022), and without undue experimentation, a POSA would have had more than a reasonable expectation of success to arrive at the '437 Patent' to arrive at compound recited in claim 1 where the R groups is "**-$CH_2CH_2CH_3$**", where the compound is formulated as a pharmaceutical composition in a unit dosage form configured for sublingual or buccal administration as a rapidly dissolving film, and where the compound has a half-life $t_{1/2}$ within the range from 1-6 minutes and a Log P value in the range of about 0.5-6.0. See also discussion in Motivation to Combine Section, ¶¶ 289-317, above. Accordingly, claim 1 of the '437 Patent would have been obvious to a POSA based on the teachings of Truelove 1, Ashraf, and the Almoazen Paper.

Claim 2 would have been obvious

330. The discussion regarding the obviousness of claim 1 above is incorporated into this discussion of the obviousness of claim 2.

331. Claim 2 recites (emphasis added):

A compound of a Formula



wherein R is selected from the group consisting of: **CH_3**, **CH_2CH_3** and $CH(CH_3)_2$ wherein the compound is formulated in a unit dosage form as a sublingual or buccal administration and wherein the compound is formulated in a unit dosage form as a rapidly dissolving film and has a half-life $t_{1/2}$ range from 1-6 minutes.

332. Unlike claim 1, claim 2 does not specifically recite a compound "or a pharmaceutically acceptable salt thereof". However, as discussed above at ¶¶ 135-137, a POSA would have understood that disclosure of the salt form of a prodrug in the prior art, was also a disclosure of the free base or non-salt form, for purposes of informing a POSA that it would have been obvious to try the non-salt form of the prodrug for purposes the salt form was intended to accomplish and a POSA

would have expected, without undue experimentation, the non-salt form to achieve the desired effect. (See also, Motivation to Combine section at ¶¶ 296-305.)

R Groups "CH_3" and "CH_2CH_3"

333. The highlighted R group -**CH_3**[44] in claim 2 above corresponds to the epinephrine ester prodrug named "4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene diacetate" and its structure is depicted in Figure 7A of the '437 Patent. The highlighted R group -**CH_2CH_3**[45] in claim 2 above corresponds to the epinephrine ester prodrug named "4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene dipropionate" and its structure is depicted in Figure 7C of the '437 Patent. See also ¶¶ 138-145 (R = -CH_3), 146-152 (R = -CH_2CH_3) and Truelove 1 Relationship Chart (¶¶ 179-180), above, with respect to the following R Groups discussion.

334. Truelove 1 discloses the epinephrine ester prodrugs where R = **-CH_3** with a half-life ($t_{1/2}$) = 3 minutes as claimed in claim 2. Truelove 1 also discloses the epinephrine ester prodrugs where R = **-CH_2CH_3** with a half-life ($t_{1/2}$) = 4 minutes

[44] Both R Groups (substituents) are "-CH_3"; see '437 Patent Figure 7A.

[45] Both R Groups (substituents) are "-CH_2CH_3"; see '437 Patent Figure 7C.

as claimed in claim 2. These disclosures appear in Table 3 of Truelove 1 (Exhibit 1002) copied below.

Truelove 1, Table 3, EX1002, 9:26-38

TABLE 3

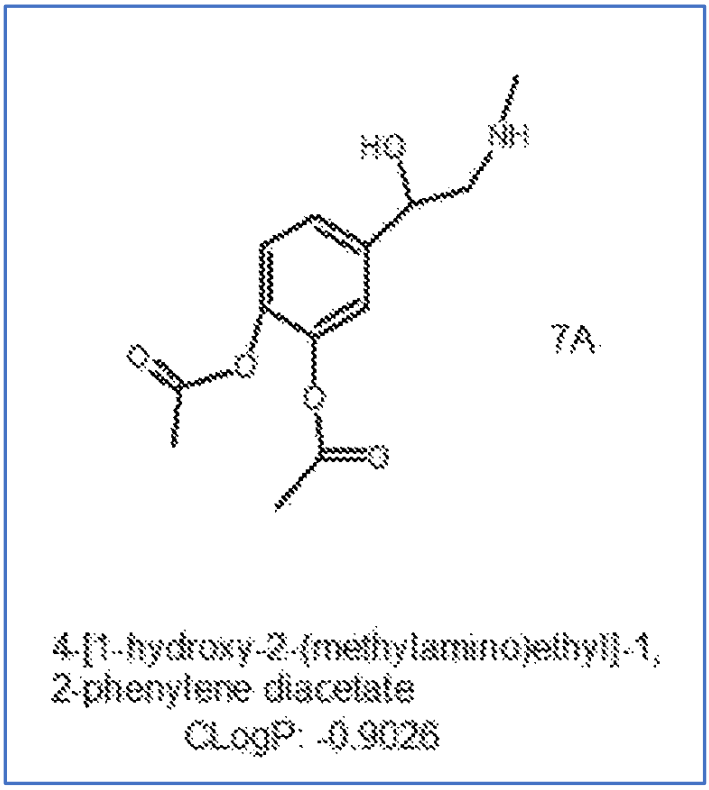
Compound	Rate of hydrolysis in $t_{1/2}$ seconds		
	Horse	Rabbit	Human
L-3,4-diacetyl-α-[(methylamino)-methyl] benzyl alcohol hydroperchlorate	20	45	180
L-3,4-dipropionyl-α-[(methylamino)methyl] benzyl alcohol hydroperchlorate	50	90	240
L-3,4-dibutyryl-α-[(methylamino)-methyl] benzyl alcohol hydroperchlorate	100	160	360
L-3,4-dipivalyl-α-[(methylamino)-methyl] benzyl alcohol hydroperchlorate	600	720	1,800

335. A POSA would have understood that the identification of "L-3,4-**diacetyl**-α-[(methylamino)methyl] benzyl alcohol hydroperchlorate" in Table 3 of Truelove 1, though a misnomer, taught and disclosed the novel ester prodrug "L-3,4-**diacetoxy**-α-[(methylamino)methyl] benzyl alcohol hydroperchlorate." Also. a POSA would have understood that the identification of "L-3,4-**dipropionyl**-α-[(methylamino)methyl] benzyl alcohol hydroperchlorate" in Table 3 of Truelove 1, though a misnomer, taught and disclosed the novel ester prodrug "L-3,4-**dipropionoxy**-α-[(methylamino) methyl] benzyl alcohol hydroperchlorate."

336. Further, a POSA would have understood that disclosure of "L-3,4-**diacetoxy**-α-[(methylamino)methyl] benzyl alcohol hydroperchlorate" also taught

and disclosed the free base or non-salt form of the ester prodrug, namely "L-3,4-**diacetoxy**-α-[(methylamino)methyl] benzyl alcohol" which is also known as "4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene diacetate".

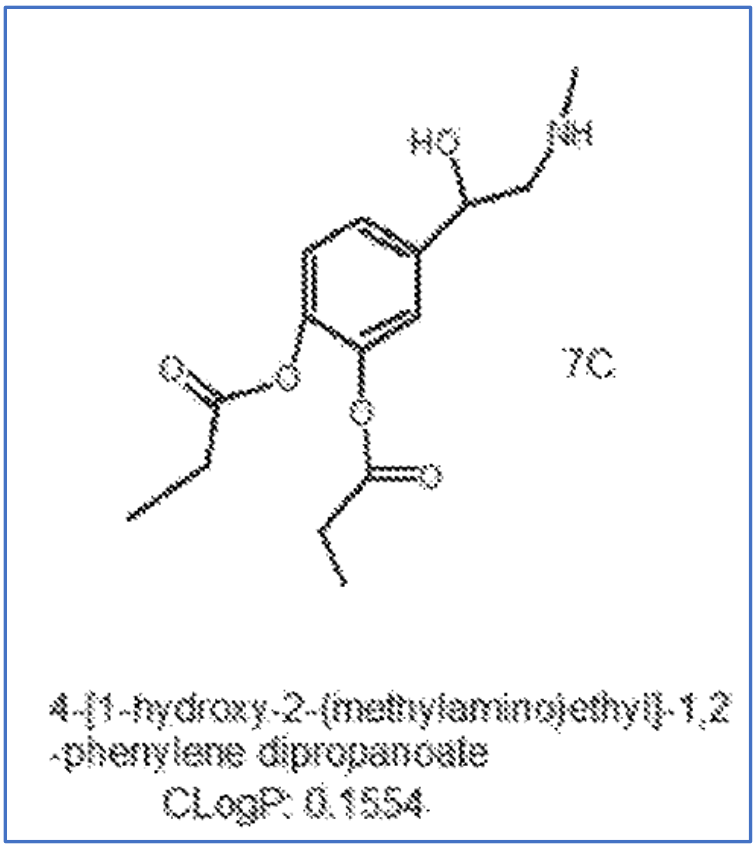
337. The structure of "4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene diacetate" depicted in Figure 7A of the '437 Patent is shown below, disclosing the claimed R group "R = **-CH_3**".



338. A POSA would have understood that disclosure of "L-3,4-**dipropionoxy**-α-[(methylamino) methyl] benzyl alcohol hydroperchlorate" also taught disclosure of the free base or non-salt form of the ester prodrug, namely "L-3,4-**dipropionoxy**-

α-[(methylamino) methyl] benzyl alcohol" which is also known as "4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene dipropionate".

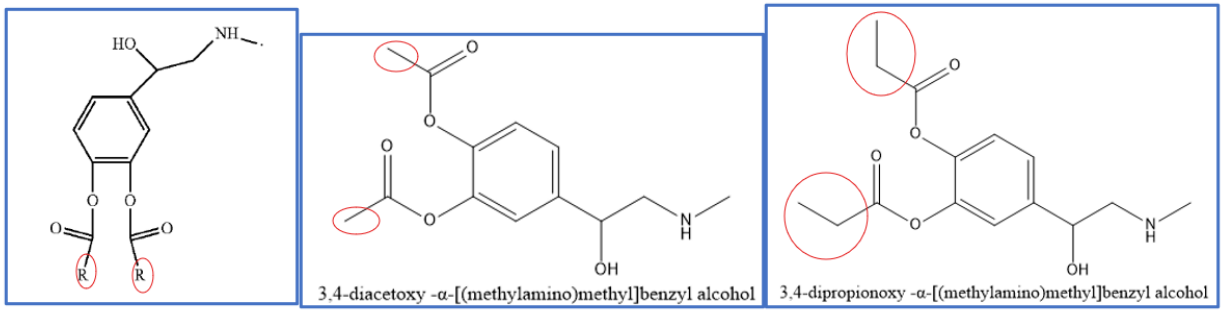
339. The structure of "4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene dipropanoate [also dipropionate]" depicted in Figure 7C of the '437 Patent is shown below, disclosing the claimed R group "R = **-CH_2CH_3**".



340. Table 3 of Truelove 1 discloses two of the compounds recited in claim 2, namely: (i) the compound where the R group is "R = **-CH_3**", and where this compound has a half-life $t_{1/2}$ of 180 seconds (3 minutes); and (ii) the compound

where the R group is "R = **-CH_2CH_3**", and where this compound has a half-life $t_{1/2}$ of 240 seconds (4 minutes).

341. Claim 2 recites and shows a prodrug compound structure with an "R" group where "R = **-CH_3**" and "R = **-CH_2CH_3**". Shown below is a comparison of the recited claim 2 structure with the structure generated by ChemDraw® that a POSA would have understood from Truelove 3 disclosure of "3,4-**diacetoxy**-α-[(methylamino)methyl] benzyl alcohol" and "3,4-**dipropionoxy**-α-[(methylamino) methyl] benzyl alcohol" from Table 3.



342. The Almoazen Paper teaches everything that the '437 Patent does regarding epinephrine in a unit dosage form configured for sublingual or buccal administration in rapidly or fast dissolving films. (See Exhibit 1022, pp. 1012-1016; and Exhibit 1033 (visually showing the extent of the disclosure from the Almoazen Paper appearing in the '437 Paper); and see also ¶¶ 181-193, above., above.)

343. A POSA would have been motivated to combine the teachings of Truelove 1 (Exhibit 1002) and the Almoazen Paper (Exhibit 1022), and without undue experimentation, a POSA would have had more than a reasonable expectation of success to arrive at the '437 Patent' to arrive at compounds recited in claim 2 where the R groups are "**-CH_3**" and "**-CH_2CH_3**", where the compound is formulated in a unit dosage form as a rapidly dissolving film for sublingual or buccal administration, and wherein the compounds have a half-life $t_{1/2}$ within the range from 1-6 minutes. See also discussion in Motivation to Combine Section, ¶¶ 289-317, above. Accordingly, claim 2 of the '437 Patent would have been obvious to a POSA based on the teachings of Truelove 1 and the Almoazen Paper.

Claim 3 would have been obvious

344. The discussions regarding the obviousness of claims 1 and 2 above are incorporated into this discussion of the obviousness of claim 3.

345. Claim 3 recites (emphasis added):

> The compound of claim 2, wherein the compound is selected from the group consisting of: **4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene di-acetate**;[46] 4-(1-hydroxy-2(methylamino) ethyl)-1,2-phenylene bis(2-methylpropanoate); **4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene dipropionate**;[47] and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein the compound is formulated in a unit dosage form as a rapidly dissolving film.

346. Claim 3 depends from claim 2 and adds the chemical names for the compounds whose structures are recited in claim 2.

347. Claim 3 also adds the following language to claim 2, namely "a pharmaceutically acceptable carrier **or** a pharmaceutically acceptable excipient" (emphasis added). This limitation is met by the films disclosed in the Almoazen Paper (Exhibit 1022), see ¶¶ 181-193, above.)

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[46] Both R groups are "-CH_3"; '437 Patent Figure 7A.

[47] Both R groups are "-CH_2CH_3"; '437 Patent Figure 7C.

348. Finally, claim 3 adds the following language to claim 2, namely "wherein the compound is formulated in a unit dosage form as a rapidly dissolving film". However, this language is an exact quote from claim 2 and thus adds nothing to the claim limitations of claim 3.

349. The highlighted chemical names "**4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene di-acetate"** and **"4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene dipropionate"** recited in claim 3, were discussed in relation to the obviousness of claim 2 for the compounds whose R groups are "**-CH_3**" and "**-CH_2CH_3**". Thus the structures and their names are one and the same, see discussion below.

350. As discussed with respect to the obviousness of claim 2, the epinephrine ester prodrug compound named "4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene diacetate" corresponds to R Group = "**-CH_3"** and its structure is depicted in Figure 7A of the '437 Patent.

351. As also discussed with respect to the obviousness of claim 2, the epinephrine ester prodrug named "4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene dipropionate" corresponds to R group = "**-CH_2CH_3"** and its structure is depicted in Figure 7C of the '437 Patent.

352. The disclosure of these named compounds appears in Table 3 of Truelove 1 (Exhibit 1002) copied below.

Truelove 1, Table 3, EX1002, 9:26-38

TABLE 3

Compound	Rate of hydrolysis in $t_{1/2}$ seconds		
	Horse	Rabbit	Human
L-3,4-diacetyl-α-[(methylamino)-methyl] benzyl alcohol hydroperchlorate	20	45	180
L-3,4-dipropionyl-α-[(methylamino)methyl] benzyl alcohol hydroperchlorate	50	90	240
L-3,4-dibutyryl-α-[(methylamino)-methyl] benzyl alcohol hydroperchlorate	100	160	360
L-3,4-dipivalyl-α-[(methylamino)-methyl] benzyl alcohol hydroperchlorate	600	720	1,800

353. A POSA would have understood that the identification of "L-3,4-**diacetyl**-α-[(methylamino)methyl] benzyl alcohol hydroperchlorate" in Table 3 of Truelove 1, though a misnomer, actually taught and disclosed the novel ester prodrug compound "L-3,4-**diacetoxy**-α-[(methylamino)methyl] benzyl alcohol hydroperchlorate." See also ¶¶ 138-145 (R = -CH_3), 146-152 (R = -CH_2CH_3) and Truelove 1 Relationship Chart (¶¶ 179-180), above, with respect to the following R Groups discussion.

354. A POSA would have understood that the identification of "L-3,4-**dipropionyl**-α-[(methylamino)methyl] benzyl alcohol hydroperchlorate" in Table 3 of Truelove 1, though a misnomer, actually taught and disclosed the novel ester

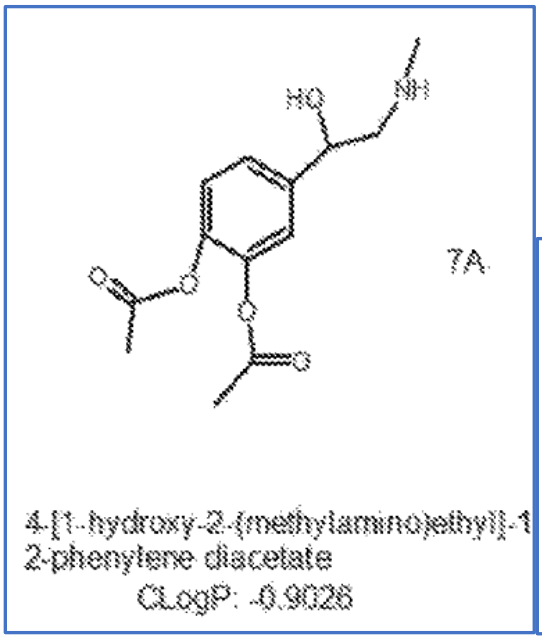
prodrug "L-3,4-**dipropionoxy**-α-[(methylamino) methyl] benzyl alcohol hydroperchlorate."

355. A POSA would have understood that Truelove 1's disclosure of "L-3,4-**diacetoxy**-α-[(methylamino)methyl] benzyl alcohol hydroperchlorate" also taught disclosure of the free base or non-salt form of the ester prodrug, namely "L-3,4-**diacetoxy**-α-[(methylamino)methyl] benzyl alcohol" which is also known as **"4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene diacetate"**, the compound identified by name and recited in claim 3.

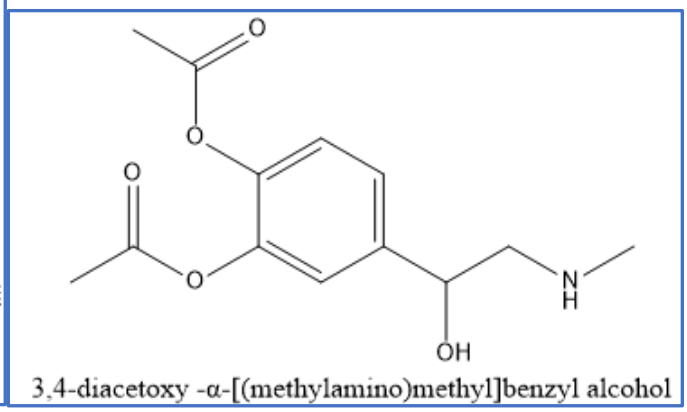
356. A POSA would have understood that disclosure of "L-3,4-**dipropionoxy**-α-[(methylamino) methyl] benzyl alcohol hydroperchlorate" also taught disclosure of the free base or non-salt form of the ester prodrug, namely "L-3,4-**dipropionoxy**-α-[(methylamino) methyl] benzyl alcohol" which is also known as **"4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene dipropionate"**, the compound identified by name and recited in claim 3.

357. Claim 3 recites the prodrug compounds "4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene di-acetate" and "4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene dipropionate". Shown below is a comparison of the recited claim 3 named compounds and their structures from the '437 Patent Figure 7 (Figures 7A and 7C, respectively) with disclosures a POSA would have

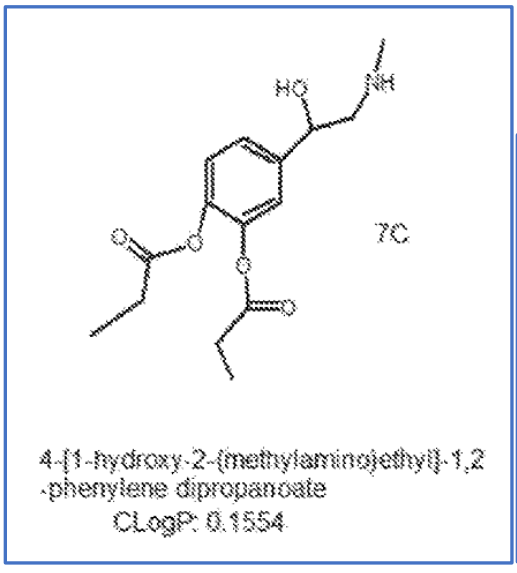
understood from Truelove 3 disclosure of the compounds "3,4-**diacetoxy**-α-[(methylamino)methyl] benzyl alcohol" and "3,4-**dipropionoxy**-α-[(methylamino) methyl] benzyl alcohol" from Truelove 1, Table 3 as generated by ChemDraw®.



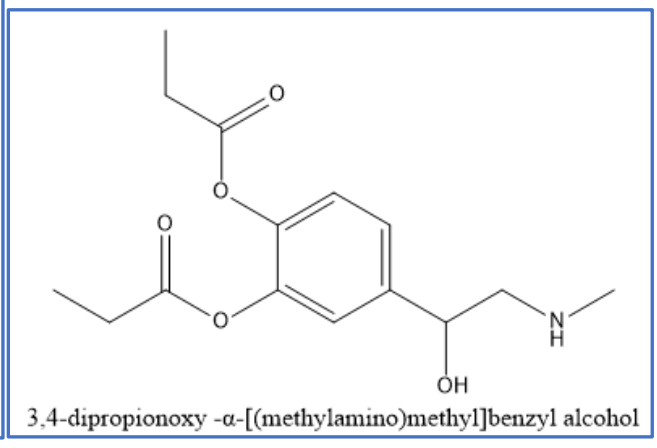
437 Patent, Fig. 7A



Truelove 1, Table 3 Disclosure



437 Patent, Fig. 7C



Truelove 1, Table 3 Disclosure

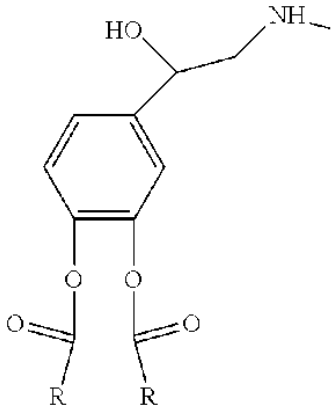
358. A POSA would have been motivated to combine the teachings of Truelove 1 (Exhibit 1002) and the Almoazen Paper (Exhibit 1022), and without undue experimentation, a POSA would have had more than a reasonable expectation of success to arrive at the '437 Patent' to arrive at the following named compounds recited in claim 3, namely "**4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene di-acetate"** and **"4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene dipropionate"**, where the compound is formulated in a unit dosage form as a rapidly dissolving film, a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, for sublingual or buccal administration, and wherein the compounds have a half-life $t_{1/2}$ within the range from 1-6 minutes. See also discussion in Motivation to Combine Section, ¶¶ 289-317, above. Accordingly, claim 3 of the '437 Patent would have been obvious to a POSA based on the teachings of Truelove 1 and the Almoazen Paper.

GROUND 2
CLAIMS 1-3 ARE OBVIOUS IN VIEW OF TRUELOVE 3 (EXHIBIT 1008), ASRAF (EXHIBIT 1003) AND ALMOAZEN PAPER (EXHIBIT 1022)

Claim 1 would have been obvious

359. Claim 1 recites in relevant part (emphasis added):

A compound formulated as a pharmaceutical composition in a unit dosage form configured for sublingual or buccal administration of a Formula:



wherein R is selected from the group consisting of: —$CHCH_2$, —$CHCHCH_3$, —CH_2—CH_2—Cl, —$CHCH_2$I, —$CH(Cl)CH_2$ (Cl), —$CH(I)CH_2(I)$, —$CH(CH_3)CH_2(CH_3)$, —$CH_2C(CH_3)_3$, **—$CH_2CH_2CH_3$**, —CH_2CI, … or a pharmaceutically acceptable salt thereof, wherein said compound has a Log P value in the range of about 0.5-6.0 and wherein the compound is formulated in a unit dosage form as a rapidly dissolving film and has a half-life $t_{1/2}$ range from 1-6 minutes.

R Group "-$CH_2CH_2CH_3$"

360. The highlighted R group **-$CH_2CH_2CH_3$** in claim 1 above corresponds to the epinephrine ester prodrug named "4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene dibutyrate" and its structure is depicted in Figure 5G" of the '437 Patent. See ¶ 209 and Truelove 3 Relationship Chart (¶¶ 209-210), above, with respect to the following R Group discussion.

361. The structure of "4-(1-hydroxy-2-(methylamino) ethyl)-1,2-phenylene dibutyrate" taken from Figure 5G" of the '437 Patent is shown below, disclosing the claimed R group "R = **-$CH_2CH_2CH_3$**". (See also ¶¶ _____, above.)

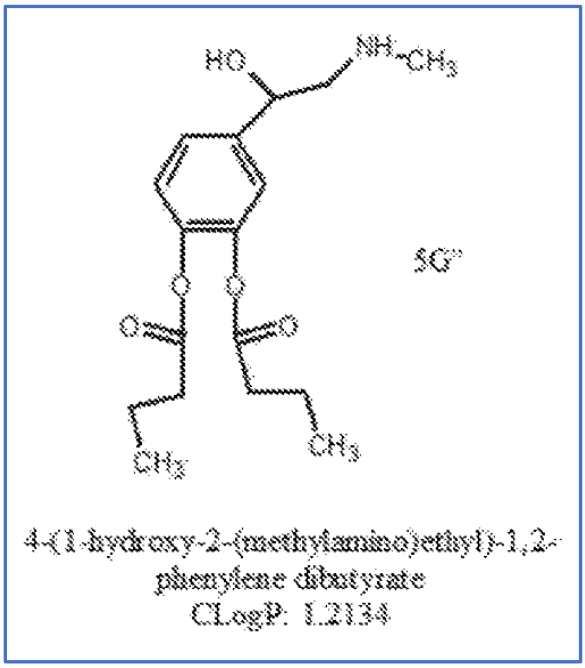


Exhibit 1001, Figure 5G" (see also 6:24-32).

362. Table 3 of Truelove 3 (Exhibit 1008) is copied below.

Truelove 3, Table 3, Exhibit 1008, 10:59-70

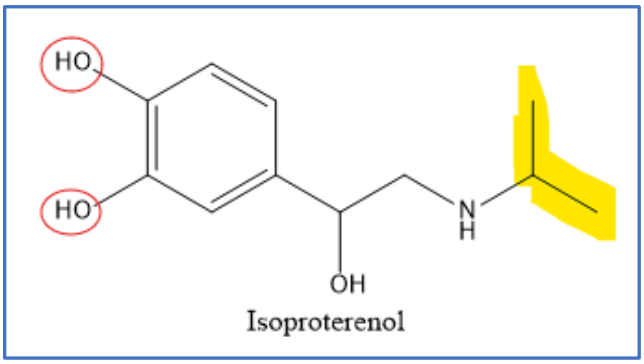
TABLE 3

Compound	Rate of Hydrolysis in $t_{1/2}$ Seconds Horse	Rabbit	Human
3,4-diacetoxy-α1[(isopropylamino)-methyl]benzyl alcohol hydrochloride	20	45	180
3,4-dipropionoxy-α-[(isopropylamino)-methyl]benzyl alcohol hydrochloride	50	90	240
3,4-dibutyroxy-α-[(isopropylamino)-methyl]benzyl alcohol hydrochloride	100	160	360
3,4-dipivaloxy-α1[(isopropylamino)-methyl]benzyl alcohol hydrochloride	600	720	1800

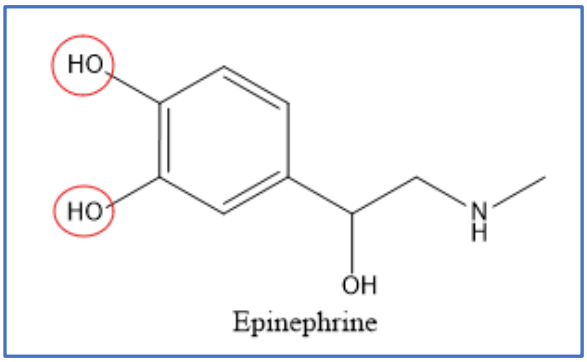
363. Table 3 of Truelove 3 (Exhibit 1008) in disclosing the isoproterenol ester prodrug compound "3,4-dibutyroxy-α-((isopropylamino)-methyl)benzyl alcohol hydrochloride" discloses one of the ester promoieties namely where R = -**$CH_2CH_2CH_3$** recited in claim 1, notably the isoproterenol ester prodrug compound with this R group has a half-life $t_{1/2}$ is 360 seconds (6 minutes).

364. As discussed above at ¶¶ 204, there is substantial structural similarity between the isoproterenol and epinephrine active drug compounds and the position

of the ester promoieties linked thereto, shown in circled -OH (hydroxyl) groups shown below. The difference in structures is highlighted in yellow.

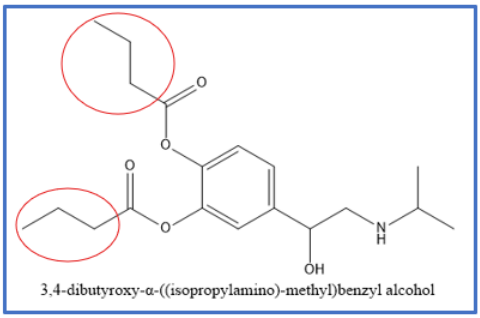
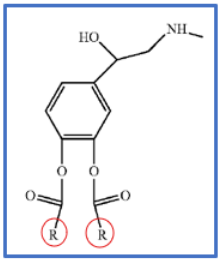
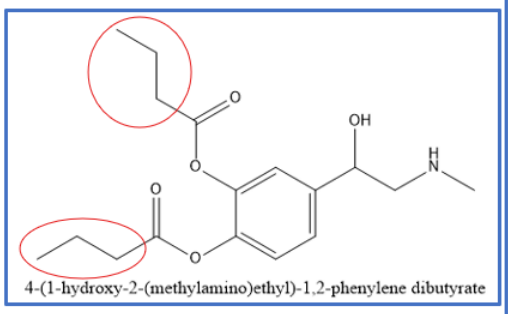


Isoproterenol



Epinephrine

365. A POSA would have understood disclosure of the salt form of the prodrug or drug as being a disclosure of the free or non-salt form of the prodrug or drug. The free base or non-salt structures of Almoazen's epinephrine prodrug "4-(1-hydroxy-2-(methylamino) ethyl)-1,2-phenylene dibutyrate", whose structure is recited in claim 1, and Truelove 3's isoproterenol prodrug "3,4-dibutyroxy-α-((isopropylamino)-methyl)benzyl alcohol hydrochloride" whose free base or non-salt structure is "3,4-dibutyroxy-α-((isopropylamino)-methyl)benzyl alcohol" are very similar to each other. See also ¶¶ 202-217, above; and the structures below, with the R groups of the ester promoieties circled.

3,4-dibutyroxy-α-((isopropylamino)-methyl)benzyl alcohol **$t_{1/2}$ = 360 seconds = 6 minutes** (disclosed in Truelove 3, Table 3)  	Promoiety R = $-(CH_2)_2CH_3$ 	4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene dibutyrate Structure and name of compound recited in claim 1 are shown below.  See also '437 Patent, Fig. 5G"

366. A POSA would have readily expected that the half-life ($t_{1/2}$) of epinephrine prodrug recited in challenged claim 1, whose structure is named "4-(1-hydroxy-2-(methylamino) ethyl)-1,2-phenylene dibutyrate" and the isoproterenol prodrug disclosed in Truelove 3, whose free base or non-salt structure is "3,4-dibutyroxy-α-((isopropylamino)-methyl)benzyl alcohol", having the same identical ester promoieties would have substantially the same, if not identical, half-lives ($t_{1/2}$), *i.e.,* 6 minutes. Basically, this is because of the structural similarity between the

isoproterenol and epinephrine compounds, the use of identical ester promoieties, and the positions of the promoieties on the active drug compounds.

367. Because Truelove 3 teaches the use of some of the same ester promoieties recited in challenged claims 1-3, and discloses the half-lives of those prodrug compounds, a POSA seeking to synthesize epinephrine prodrugs with rapid half-lives (*e.g.,* 6 minutes or less) would have been motivated by the disclosures and teachings of Truelove 3 to synthesize diester epinephrine prodrug compounds using the same Truelove 3 ester promoieties would have had a reasonable likelihood of success, without undue experimentation, of being able to achieve the prodrug compounds and the claimed half-lives recited in the challenged claims.

368. Basically, a POSA would have known: (i) epinephrine has been used to treat anaphylaxis; (ii) epinephrine needs to be administered rapidly; (iii) the ester isoproterenol prodrugs exhibit rapid half-lives; (iv) epinephrine and isoproterenol actives have similar structures; and (iv) based on that structural similarity, a POSA would have substituted the same esters disclosed in Truelove 3 at the same positions of the epinephrine active to achieve epinephrine prodrugs with the same or substantially the same rapid half-lives.

369. Moreover, in view of the disclosure of Truelove 3, regarding "3,4-dibutyroxy-α-((isopropylamino)-methyl)benzyl alcohol hydrochloride", a POSA

would have had a reasonable likelihood of success, without undue experimentation, of being able to achieve the epinephrine prodrug recited in challenged claim 1, whose structure is named "4-(1-hydroxy-2-(methylamino) ethyl)-1,2-phenylene dibutyrate", and a POSA would have expected it to have the same or almost same half-life of 6 minutes recited in challenged claim 1 of the '437 Patent. (See also ¶¶ 202-217, above.)

370. Ashraf teaches that "Satisfactory oral [mucosal] absorption of drugs has been observed over a wide range of log P (octanol/water partition coefficient) values of 1 to 5." (Exhibit 1003, p. 35, 2nd col.) Ashraf also discloses some established acceptable ranges of Log P for sublingual and/or buccal administration, which Ashraf discloses are in the range of about 0.5 and 6. Exhibit 1003, Table II, p. 35. (See also ¶¶ 194-197, above.)

371. Finally, the '437 patent admits that the Log P of the epinephrine compound of Claim 1 where the R group is "**-$CH_2CH_2CH_3$**" is +0.8 which falls within the Log P value of "in the range of about 0.5-6.0" as recited in claim 1. (See '437 Patent, Table 1, 5:29.)

372. As discussed above at ¶¶ 181-193, the Almoazen Paper teaches everything that the '437 Patent does regarding epinephrine in a unit dosage form configured for sublingual or buccal administration in rapidly or fast dissolving films, including

pharmaceutically acceptable carriers or a pharmaceutically acceptable excipients. (See Exhibit 1022, pp. 1012-1016; and Exhibit 1033 (visually showing the extent of the disclosure from the Almoazen Paper appearing in the '437 Paper).

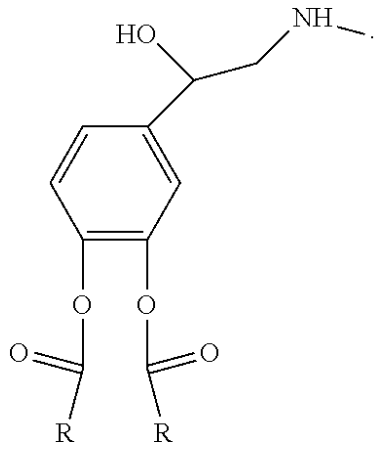
373. A POSA would have been motivated to combine the teachings of Truelove 3 (Exhibit 1008), Ashraf (Exhibit 1003) and the Almoazen Paper (Exhibit 1022), and without undue experimentation, a POSA would have had more than a reasonable expectation of success to arrive at the '437 Patent' to arrive at compound recited in claim 1 where the R group is "**-$CH_2CH_2CH_3$**", where the compound is formulated as a pharmaceutical composition in a unit dosage form configured for sublingual or buccal administration as a rapidly dissolving film, and where the compound has a half-life $t_{1/2}$ within the range from 1-6 minutes and a Log P value in the range of about 0.5-6.0. (See also discussion in Motivation to Combine Section, at ¶¶ 289-317 above.) Accordingly, claim 1 of the '437 Patent would have been obvious to a POSA based on the teachings of Truelove 3, Ashraf, and the Almoazen Paper.

Claim 2 would have been obvious

374. The discussion regarding the obviousness of claim 1 above and the discussion of the obviousness of claim 3 below are incorporated into this discussion of the obviousness of claim 2.

375. Claim 2 recites (emphasis added):

A compound of a Formula



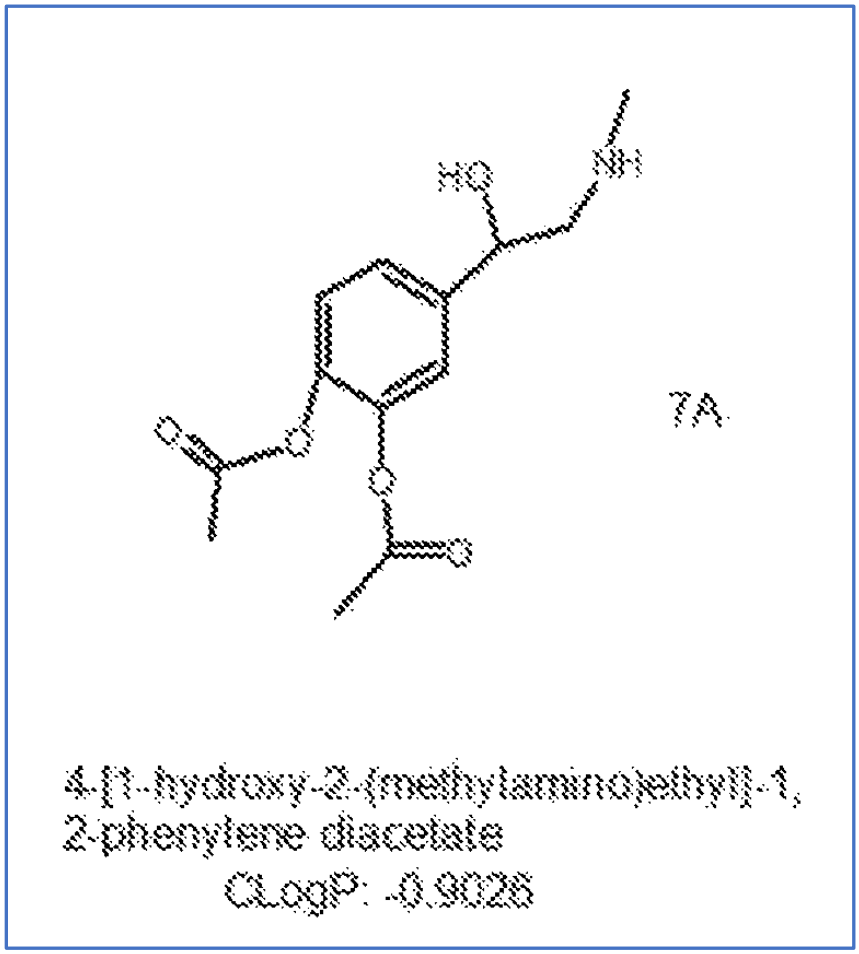
wherein R is selected from the group consisting of: **CH_3**, **CH_2CH_3** and $CH(CH_3)_2$ wherein the compound is formulated in a unit dosage form as a sublingual or buccal administration and wherein the compound is formulated in a unit dosage form as a rapidly dissolving film and has a half-life $t_{1/2}$ range from 1-6 minutes.

376. Unlike claim 1, claim 2 does not specifically recite a compound "or a pharmaceutically acceptable salt thereof". However, as discussed above at ¶¶ 135-137, a POSA would have understood that disclosure of the salt form of a prodrug in the prior art, was also a disclosure of the free base or non-salt form, for purposes of informing a POSA that it would have been obvious to try the non-salt form of the prodrug for purposes the salt form was intended to accomplish and a POSA

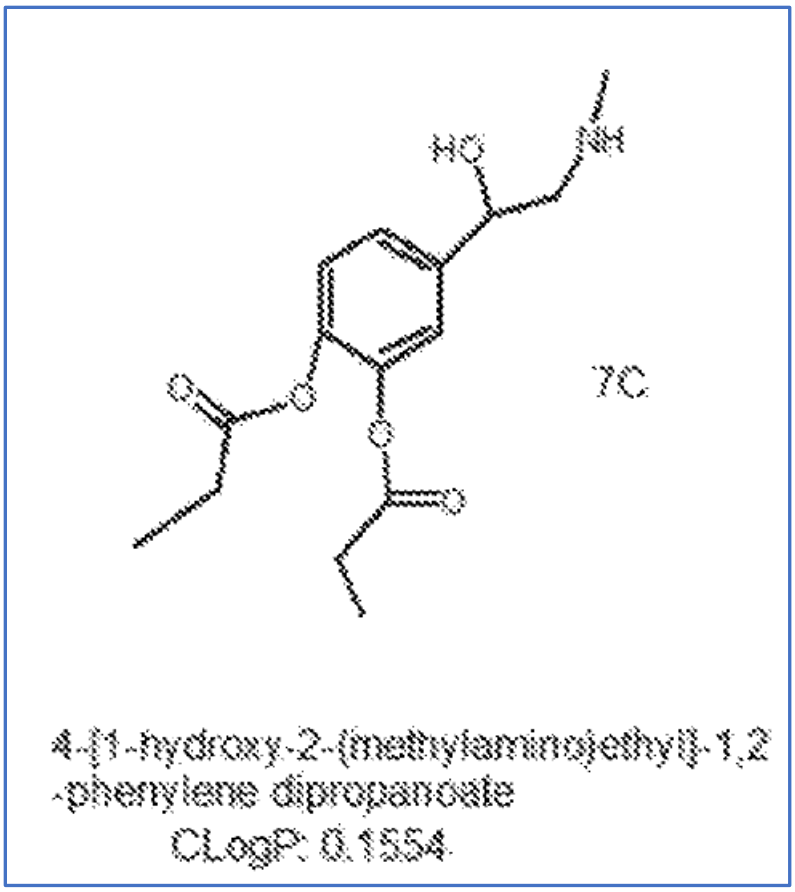
would have expected, without undue experimentation, the non-salt form to achieve the desired effect. (See also, Motivation to Combine section at ¶¶ 296-305.)

R Groups "CH_3" and "CH_2CH_3"

377. The structure of "4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene diacetate" depicted in Figure 7A of the '437 Patent is shown below, disclosing the claimed R group "R = **-CH_3**". See also ¶¶ 209 (Truelove 3 Relationship Chart), 210, above.



378. The structure of "4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene dipropanoate [also dipropionate]" depicted in Figure 7C of the '437 Patent is shown below, disclosing the claimed R group "R = **-CH_2CH_3**". See also ¶¶ 209 (Truelove 3 Relationship Chart), 210, above.



379. Table 3 of Truelove 3 (Exhibit 1008) is copied below.

Truelove 3, Table 3, Exhibit 1008, 10:59-70

TABLE 3

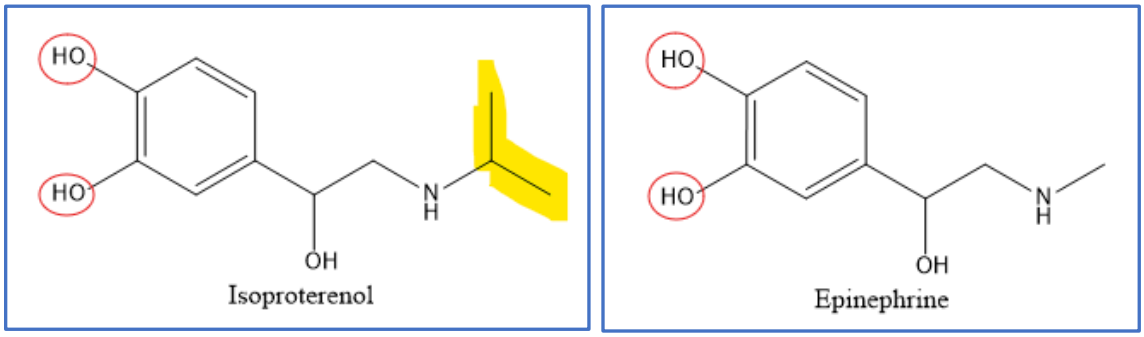
Compound	Rate of Hydrolysis in $t_{1/2}$ Seconds Horse	Rabbit	Human
3,4-diacetoxy-α[(isopropylamino)-methyl]benzyl alcohol hydrochloride	20	45	180
3,4-dipropionoxy-α-[(isopropylamino)-methyl]benzyl alcohol hydrochloride	50	90	240
3,4-dibutyroxy-α-[(isopropylamino)-methyl]benzyl alcohol hydrochloride	100	160	360
3,4-dipivaloxy-α[(isopropylamino)-methyl]benzyl alcohol hydrochloride	600	720	1800

380. Table 3 of Truelove 3 (Exhibit 1008) in disclosing the isoproterenol ester prodrug compound "3,4-diacetoxy-α-((isopropylamino)-methyl)benzyl alcohol hydrochloride", discloses the ester promoieties where R = **-CH_3** as recited in claim 2. Notably the isoproterenol ester prodrug compound with the R group R = **-CH_3** has a half-life ($t_{1/2}$) = 3 minutes as claimed in claim 2. See also ¶¶ 202-217, above for this paragraph and the paragraphs to following regarding Truelove 3. above.)

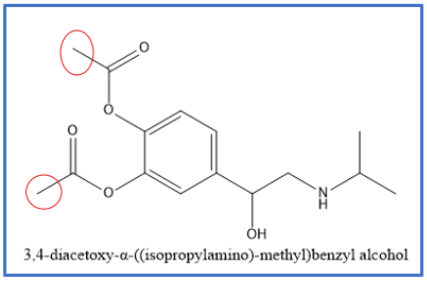
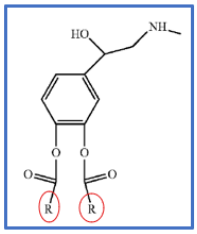
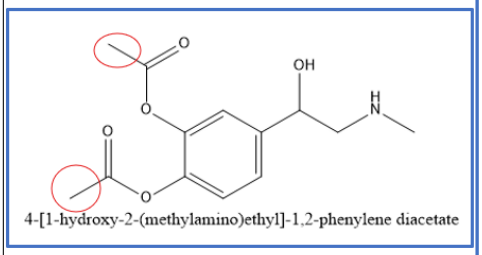
381. Table 3 of Truelove 3 (Exhibit 1008) in disclosing the isoproterenol ester prodrug compound "3,4-dipropionoxy-α-((isopropylamino)-methyl)benzyl alcohol hydrochloride", discloses the ester promoieties where R = **-CH_2CH_3** as recited in

claim 2. Notably the isoproterenol ester prodrug compound with the R group R = -**CH_2CH_3** has a half-life ($t_{1/2}$) = 4 minutes as claimed in claim 2.

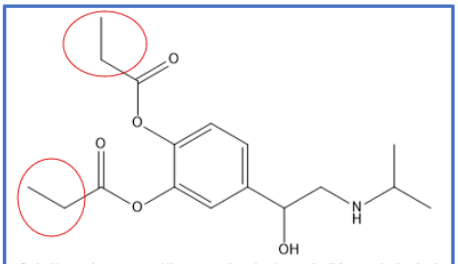
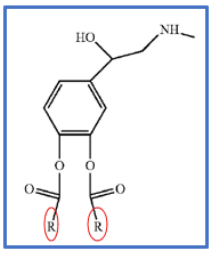
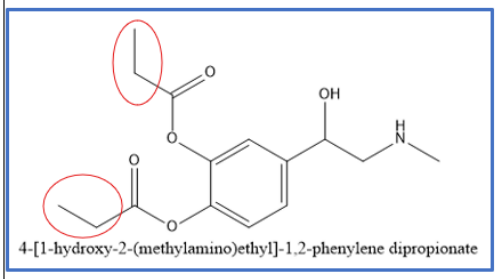
382. As discussed above there is substantial structural similarity between the isoproterenol and epinephrine active drug compounds and the position of the ester promoieties linked thereto, shown in circled -OH (hydroxyl) groups. The difference in structures is highlighted in yellow.



383. A POSA would have understood disclosure of the salt form of the prodrug or drug as being a disclosure of the free or non-salt form of the prodrug or drug. The free base or non-salt structures of Almoazen's epinephrine prodrug "4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene diacetate", whose structure is recited in claim 2, and Truelove 3's isoproterenol prodrug "3,4-diacetoxy-α-((isopropylamino)-methyl)benzyl alcohol hydrochloride" whose free base or non-salt structure is "3,4-diacetoxy-α-((isopropylamino)-methyl)benzyl alcohol" are very similar to each other. (See also the structures below, with the R groups of the ester promoieties circled.)

3,4-diacetoxy-α-((isopropylamino)-methyl)benzyl alcohol **$t_{1/2}$ = 180 seconds = 3 minutes** (disclosed in Truelove 3, Table 3)  3,4-diacetoxy-α-((isopropylamino)-methyl)benzyl alcohol	Promoiety R = -CH_3 	4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene diacetate Structure and name of compound recited in claims 2 and 3 are shown below.  4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene diacetate See also '437 Patent, Fig. 7A

384. A POSA would have also understood disclosure of the salt form of the prodrug or drug as being a disclosure of the free or non-salt form of the prodrug or drug. The free base or non-salt structures of Almoazen's epinephrine prodrug "4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene dipropionate", whose structure is recited in claim 2, and Truelove 3's isoproterenol prodrug "3,4-dipropionoxy-α-((isopropylamino)-methyl)benzyl alcohol hydrochloride" whose free base or non-salt structure is "3,4-dipropionoxy-α-((isopropylamino)-methyl)benzyl alcohol" are very similar to each other. (See also the structures below, with the R groups of the ester promoieties circled.)

3,4-dipropionoxy-α-((isopropylamino)-methyl)benzyl alcohol **$t_{1/2}$ = 240 seconds = 4 minutes** (disclosed in Truelove 3, Table 3)	Promoiety R= $-CH_2CH_3$	4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene dipropanoate [also dipropionate] Structure and name of compound recited in claims 2 and 3 are shown below.
		 See also '437 Patent, Fig. 7C

385. A POSA would have readily expected that the half-life ($t_{1/2}$) of epinephrine prodrug recited in challenged claim 2, whose structure is named "4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene diacetate" and the isoproterenol prodrug disclosed in Truelove 3, whose free base or non-salt structure is "3,4-diacetoxy-α-((isopropylamino)-methyl)benzyl alcohol", having the same identical ester promoieties would have substantially the same, if not identical, half-lives ($t_{1/2}$), *i.e.,* 3 minutes. Basically, this is because of the structural similarity between the isoproterenol and epinephrine compounds, the use of identical ester promoieties, and the positions of the promoieties on the active drug compounds. .

386. A POSA would have readily expected that the half-life ($t_{1/2}$) of epinephrine prodrug recited in challenged claim 2, whose structure is named "4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene dipropionate" and the isoproterenol prodrug disclosed in Truelove 3, whose free base or non-salt structure is "3,4-dipropionoxy-α-((isopropylamino)-methyl)benzyl alcohol", having the same identical ester promoieties would have substantially the same, if not identical, half-lives ($t_{1/2}$), *i.e.,* 4 minutes. Again, this is because of the structural similarity between the isoproterenol and epinephrine compounds, the use of identical ester promoieties, and the positions of the promoieties on the active drug compounds..

387. Because Truelove 3 teaches the use of some of the same ester promoieties recited in the '437 Patent's challenged claims 1-3 and discloses the half-lives of those prodrug compounds, a POSA seeking to synthesize epinephrine prodrugs with rapid half-lives (*e.g.,* 6 minutes or less) would have been motivated by the disclosures and teachings of Truelove 3 to synthesize diester epinephrine prodrug compounds using the same Truelove 3 ester promoieties would have had a reasonable likelihood of success, without undue experimentation, of being able to achieve the prodrug compounds and the claimed half-lives recited in the challenged claims..

388. Basically, a POSA would have known: (i) epinephrine has been used to treat anaphylaxis; (ii) epinephrine needs to be administered rapidly; (iii) the ester isoproterenol prodrugs exhibit rapid half-lives; (iv) epinephrine and isoproterenol actives have similar structures; and (iv) based on that structural similarity, a POSA would have substituted the same esters disclosed in Truelove 3 at the same positions of the epinephrine active to achieve epinephrine prodrugs with the same or substantially the same rapid half-lives.

389. Moreover, in view of the disclosure of Truelove 3, regarding (i) "3,4-diacetoxy-α-((isopropylamino)-methyl)benzyl alcohol hydrochloride" and (ii) "3,4-dipropionoxy-α-((isopropylamino)-methyl)benzyl alcohol hydrochloride" a POSA would have had a reasonable likelihood of success, without undue experimentation, of being able to achieve the epinephrine prodrugs recited in challenged claim 2, whose structures are named (i) "4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene diacetate" and (ii) "4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene dipropionate", respectively, and a POSA would have expected it to have the same or almost same half-life of (i) 3 and (ii) 4 minutes, respectively, and thus fall within the range of 1-6 minutes recited in challenged claim 2 of the '437 Patent. (See also ¶¶ 209 (Truelove 3 Relationship Chart), 210, above.)

390. As discussed above at ¶¶ 181-193, the Almoazen Paper teaches everything that the ‘437 Patent does regarding epinephrine in a unit dosage form configured for sublingual or buccal administration in rapidly or fast dissolving films, including pharmaceutically acceptable carriers or a pharmaceutically acceptable excipients. See Exhibit 1022, pp. 1012-1016. (See Exhibit 1022, pp. 1012-1016; and Exhibit 1033 (visually showing the extent of the disclosure from the Almoazen Paper appearing in the ‘437 Paper).

391. A POSA would have been motivated to combine the teachings of Truelove 3 (Exhibit 1008) and the Almoazen Paper (Exhibit 1022), and without undue experimentation, a POSA would have had more than a reasonable expectation of success to arrive at the ‘437 Patent’ to arrive at compound recited in claim 1 where the R groups are “**CH_3**” **and** “**CH_2CH_3**”, where the compound is formulated as a pharmaceutical composition in a unit dosage form configured for sublingual or buccal administration as a rapidly dissolving film, and where the compound has a half-life $t_{1/2}$ within the range from 1-6 minutes. (See also discussion in Motivation to Combine Section, at ¶¶ 289-317, above.) Accordingly, claim 2 of the ‘437 Patent would have been obvious to a POSA based on the teachings of Truelove 3 and the Almoazen Paper.

Claim 3 would have been obvious

392. The discussions regarding the obviousness of claims 1 and 2 above are incorporated into this discussion of the obviousness of claim 3.

393. Claim 3 recites (emphasis added):

> The compound of claim 2, wherein the compound is selected from the group consisting of: **4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene di-acetate**;[48] **4-(1-hydroxy-2(methylamino) ethyl)-1,2-phenylene bis(2-methylpropanoate)**; **4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene dipropionate**;[49] and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein the compound is formulated in a unit dosage form as a rapidly dissolving film.

394. Claim 3 depends from claim 2 and adds the chemical names for the compounds whose structures are recited in claim 2.

395. Claim 3 also adds the following language to claim 2, namely "a pharmaceutically acceptable carrier **or** a pharmaceutically acceptable excipient" (emphasis added). This limitation is met by the films disclosed in the Almoazen Paper (Exhibit 1022) as discussed with respect to claim 2 above.

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[48] Both R Groups are "-CH_3"; '437 Patent Figure 7A.

[49] Both R Groups are "-CH_2CH_3"; '437 Patent Figure 7C.

396. Finally, claim 3 adds the following language to claim 2, namely "wherein the compound is formulated in a unit dosage form as a rapidly dissolving film". However, this language is an exact quote from claim 2 and thus adds nothing to the claim limitations of claim 3.

397. The highlighted chemical names "**4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene di-acetate"** and **"4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene dipropionate"** recited claim 3, were discussed in relation to the obviousness of claim 2 for the compounds whose R groups are "-**CH_3**" and "-**CH_2CH_3**". Thus the structures and their names are one and the same, see discussion below. (See also ¶¶ 209 (Truelove 3 Relationship Chart), 210, above, with respect to tis paragraph and the following paragrapghs.)

398. As discussed with respect to the obviousness of claim 2, the epinephrine ester prodrug compound named "4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene diacetate" corresponds to R Group = "-**CH_3"** and its structure is depicted in Figure 7A of the '437 Patent.

399. As also discussed with respect to the obviousness of claim 2, the epinephrine ester prodrug named "4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene dipropanoate [also dipropionate]" corresponds to R group = "-**CH_2CH_3"** and its structure is depicted in Figure 7C of the '437 Patent.

400. Finally, as disclosed with respect to the obviousness of claim 2, in view of the disclosure of Truelove 3, regarding (i) "3,4-diacetoxy-α-((isopropylamino)-methyl)benzyl alcohol hydrochloride" and (ii) "3,4-dipropionoxy-α-((isopropylamino)-methyl)benzyl alcohol hydrochloride" a POSA would have had a reasonable likelihood of success, without undue experimentation, of being able to achieve the epinephrine prodrugs recited in challenged claim 2, whose structures are named (i) "4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene diacetate" and (ii) "4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene dipropionate", respectively.

401. As discussed above at ¶¶ 181-193, the Almoazen Paper teaches everything that the '437 Patent does regarding epinephrine in a unit dosage form configured for sublingual or buccal administration in rapidly or fast dissolving films, including pharmaceutically acceptable carriers or a pharmaceutically acceptable excipients. See Exhibit 1022, pp. 1012-1016. (See also, Exhibit 1033 visually showing the extent of the disclosure from the Almoazen Paper appearing in the '437 Paper.)

402. A POSA would have been motivated to combine the teachings of Truelove 3 (Exhibit 1008) and the Almoazen Paper (Exhibit 1022), and without undue experimentation, a POSA would have had more than a reasonable expectation of success to arrive at the '437 Patent' to arrive at compounds recited in claim 3, and

named “4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene diacetate” and “4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene dipropionate”, where the R groups are “**CH_3**” **and** “**CH_2CH_3**”, respectively, and where the compound is formulated as a pharmaceutical composition in a unit dosage form as a rapidly dissolving film, a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, for sublingual or buccal administration. (See also discussion in Motivation to Combine Section, at ¶¶ 189-317, above.) Accordingly, claim 3 of the ‘437 Patent would have been obvious to a POSA based on the teachings of Truelove 3 and the Almoazen Paper.

GROUND 3
CLAIMS 1-3 ARE OBVIOUS IN VIEW OF TRUELOVE 1 (EXHIBIT 1002), TRUELOVE 3 (EXHIBIT 1008), ASRAF (EXHIBIT 1003), ALMOAZEN PAPER (EXHIBIT 1022), FUCHS (EXHIBIT 1004), SCHOBEL (EXHIBIT 1021) and FLORENCE (1015).

403. The discussions regarding the application of the prior art to the challenged claims 1-3 of the '437 Patent as discussed in Grounds 1 and 2 are hereby incorporated by reference.

404. A POSA would have had a reasonable likelihood of success, without undue experimentation, of combining the disclosures of Truelove 1 (disclosing challenged claims 1-3's epinephrine prodrug compounds, their names and their half-lives), Asraf (disclosing challenged claim 1's Log P range) and the Almoazen Paper (disclosing challenged claims 1-3's film limitation) and would have been motivated to do so to arrive at least one of the compounds recited in claim 1. Likewise, a POSA would have had a reasonable likelihood of success, without undue experimentation, of combining the disclosures of Truelove 1 and the Almoazen Paper and would have been motivated to do so to obtain compounds recited in claims 2-3.

405. However, should Patent Owner successfully challenge Truelove 1 as used in Ground 1 is not applicable to demonstrating the obviousness of challenged claims

1-3. Then a POSA would still have found challenged claims 1-3 obvious, when the POSA would also have considered Truelove 1's disclosure of ester promoieties in combination with the other prior art cited in this Ground 3, and the use of these ester promoieties in forming prodrugs, especially of epinephrine.

406. A POSA would have had a reasonable likelihood of success, without undue experimentation, of combining the disclosures of Truelove 3 (disclosing challenged claims 1-3's epinephrine prodrug compounds, their names and their half-lives by disclosing the ester promoieties of its isoproterenol prodrugs and their half-lives), Ashraf (disclosing challenged claim 1's Log P range) and the Almoazen Paper (disclosing challenged claims 1-3's film limitation) and would have been motivated to do so to arrive at least one of the compounds recited in claim 1. Likewise, a POSA would have had a reasonable likelihood of success, without undue experimentation, of combining the disclosures of Truelove 3 and the Almoazen Paper and would have been motivated to do so to achieve compounds recited in claims 2-3.

407. However, should Patent Owner successfully challenge Truelove 3 as used in Ground 2 is not applicable to demonstrating the obviousness of challenged claims 1-3. Then a POSA would still have found challenged claims 1-3 obvious, when the POSA would also have considered Truelove 3's disclosure of ester promoieties in

combination with the other prior art cited in this Ground 3, and the use of these ester promoieties in forming prodrugs.

408. Moreover, should Patent Owner disingenuously argue that the Almoazen Paper is not applicable to demonstrating the obviousness of challenged claims 1-3, as it is not prior art, then Fuchs (which is referenced in the '437 Patent but is also admitted prior art) and/or Schobel (which was not cited in the '437 Patent) disclose the film limitation. (See also ¶¶ 198-201, 234-240, above.)

409. Fuchs (Exhibit 1004) is admitted prior art ('437 Patent, Exhibit 1001, 2:39-47), teaches films that incorporate a pharmaceutical active ingredient, cut into individual doses, which can then be applied to the mucosal areas of the body. The mucosal areas of the body include the sublingual and buccal areas of the mouth. Fuchs also discloses compositions and methods for making the unit dosage films (Exhibit 1004, 2:65-5:6) and provides many examples of various suitable film compositions having various characteristics (Exhibit 1004, 5:7-14:24). (See also ¶¶ 198-201, above.) Thus, Fuchs discloses unit dosage formulations and forms as a water soluble film, a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, for sublingual or buccal administration..

410. Schobel (Exhibit 1021) teaches the use and methods of making oral rapidly dissolving films for delivery of epinephrine compositions including epinephrine

prodrugs to the oral mucosa. (*See, e.g.,* Exhibit 1021, 1:26-45 (epinephrine in films), 13:37-67 (rapidly dissolving films), 13:15-67 & 16:57-27:2 (oral dissolving films), 14:13-18 (drug in form of prodrug), 15:62-65 & 45:19-20 (ester prodrugs of epinephrine); and ¶¶ 234-240, above.). Thus, Schobel discloses epinephrine in compounds formulated in a unit dosage form as a rapidly or fast dissolving film, a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, for sublingual or buccal administration.

411. Further, should Patent Owner disingenuously argue that Ashraf is not applicable to demonstrating the obviousness of challenged claim 1, as it was discussed in the '437 Patent as admitted prior art; then Florence, which was neither cited nor discussed in the '437 Patent, also makes obvious the claimed Log P range limitation. (See also ¶¶ 224-227, above.)

412. Florence (Exhibit 1015) teaches the ideal log P values for buccal absorption typically range in bases from 3.52 to 5.52 and in acids 4.19, varying based on the chemical characteristics of the absorbing molecule. (See Exhibit 1015, Table 9.1, p. 350.) Florence's ideal log P range of from 3.52 to 5.52 which falls within the range of Log P values (*i.e.,* 0.5-6.0) recited in claim 1.

413. Thus, a POSA would have had a reasonable likelihood of success, without undue experimentation, of combining the disclosures of Truelove 1, Truelove 3,

Asraf, Florence, Fuchs, Schobel, and the Almoazen Paper and would have been motivated to do so (see Motivation to Combine section at ¶¶ 289-317, above) to arrive at all of the limitations recited in challenged claim 1. Likewise, a POSA would have had a reasonable likelihood of success, without undue experimentation, of combining the disclosures of Truelove 1, Truelove 3, Fuchs, Schobel, Florence and the Almoazen Paper and would have been motivated to do so (see Motivation to Combine section at ¶¶ 289-317, above) to arrive at all of the limitations recited in challenged claims 2 and 3. Thus, claims 1-3 of U.S. Patent No. 11,021,437 are unpatentable as they would have been obvious to a POSA in view of the prior art.

NO LONG-FELT NEED

414. In my opinion, I have not seen any evidence that a long-felt need existed for the compounds recited in the challenged claims. For example, during the prosecution of the '437 Patent a declaration was submitted asserting without pointing to any evidence opining that "effective sublingual or buccal administration of a pharmaceutical composition to treat anaphylaxis would meet a long felt need in the medical field." ('437 FH, Exhibit 1005, pdf p.75.) The Patent Examiner dismissed this assertion of alleged "long felt need" and stated "Applicant's argument

is found unpersuasive due to not providing objective evidence of establishing a long-felt need. . . . Applicant has not presented objective evidence that this a need that has been persistent and recognized by those of ordinary skill in the art . . . ." ('437 FH, Exhibit 1005, pdf p.63.) Additionally, the '437 Patent provides no data supporting any claim that an epinephrine prodrug needed to form epinephrine in human plasma within 1-6 minutes. In fact, Dipivefrin or Propine was available as a drug delivery system for epinephrine, albeit for administration to the mucosa of the eye. (*See, e.g.,* '437 Patent, Exhibit 1001, 2:24-25.). Additionally, the '437 Patent discloses that the EpiPen, *inter alia,* was available and effective for administering epinephrine to treat anaphylaxis ('437 Patent, Exhibit 1001, 1:50-55).

CONCLUSION

415. First, a POSA would have had a reasonable likelihood of success, without undue experimentation, of combining the disclosures of Truelove 1, Asraf and the Almoazen Paper and would have been motivated to do so to arrive at least one of the compounds recited in claim 1. Likewise, a POSA would have had a reasonable likelihood of success, without undue experimentation, of combining the disclosures of Truelove 1 and the Almoazen Paper and would have been motivated to do so to achieve compounds recited in claims 2-3. Thus, claims 1-3 of U.S. Patent No.

11,021,437 are unpatentable as they would have been obvious to a POSA in view of the prior art.

416. Second, a POSA would have had a reasonable likelihood of success, without undue experimentation, of combining the disclosures of Truelove 3, Asraf and the Almoazen Paper and would have been motivated to do so to arrive at least one of the compounds recited in claim 1. Likewise, a POSA would have had a reasonable likelihood of success, without undue experimentation, of combining the disclosures of Truelove 3 and the Almoazen Paper and would have been motivated to do so to achieve compounds recited in claims 2-3. Thus, claims 1-3 of U.S. Patent No. 11,021,437 are unpatentable as they would have been obvious to a POSA in view of the prior art.

417. Third, a POSA would have had a reasonable likelihood of success, without undue experimentation, of combining the disclosures of Truelove 1, Truelove 3, Asraf, Florence, Fuchs, Schobel, and the Almoazen Paper and would have been motivated to do so to arrive at least one of the compounds recited in claim 1. Likewise, a POSA would have had a reasonable likelihood of success, without undue experimentation, of combining the disclosures of Truelove 1, Truelove 3, Fuchs, Schobel, Florence and the Almoazen Paper and would have been motivated to do so to achieve compounds recited in claims 2-3. Thus, claims 1-3 of U.S.

Patent No. 11,021,437 are unpatentable as they would have been obvious to a POSA in view of the prior art.

418. I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

Executed on this the 5th day of May, 2025.

Jarkko Rautio, Ph.D

APPENDIX A - ***CURRICULUM VITAE - JARKKO RAUTIO, PH.D. (PHARM.)***

1. Personal details and the date of the CV

- Rautio, Jarkko Tapani
- orcid.org/0000-0003-2172-3980 ⊥ researchgate.net/profile/Jarkko_Rautio

2. Degrees

- 1 June 2006, Title of Docent, Pharmaceutical Chemistry, University of Kuopio
- 20 September 2000, Ph.D., Pharmaceutical Chemistry, University of Kuopio
- 31 August 1999, Licentiate in Pharmacy, Pharmaceutical Chemistry, University of Kuopio
- 22 August 1996, M.Sc. in Pharmacy, Pharmaceutical Chemistry, University of Kuopio
- 2 June 1990, Matriculation Examination, Kallavesi high school, Kuopio

3. Current employment

- 1.8.2019 – present, Deputy Head of the School of Pharmacy, University of Eastern Finland (UEF)
- 16.11.2007 – present, Professor in Pharmaceutical Chemistry, School of Pharmacy, UEF

4. Previous work experience

- 1.8.2015 – 14.8.2019, Head of the Pharmaceutical Chemistry discipline, School of Pharmacy, UEF
- 8/2010 – 7/2011, Visiting scientist, Metabolic disease drug discovery group, DMPK, GlaxoSmithKline, Inc., RTP, NC, USA
- 1.2.2009 – 31.7.2009, Research Fellow of the Academy of Finland, University of Kuopio
- 1.3.2007 – 15.11.2007, Senior Assistant, University of Kuopio
- 1.1.2007 – 28.2.2007, Professor in Pharmaceutical Chemistry, University of Kuopio
- 1.1.2005 – 31.12.2006, Postdoctoral researcher of the Academy of Finland (2nd term), University of Kuopio
- 6/2004 – 7/2005, Visiting scientist, Preclinical Drug Metabolism and Pharmacokinetics (DMPK), GlaxoSmithKline, Inc., RTP, NC, USA
- 1.8.2002 – 31.12.2004, Postdoctoral researcher of the Academy of Finland

(1st term), University of Kuopio
- 1.1/2002 – 31.7.2002, Assistant, University of Kuopio
- 1.10.2001–31.12.2001, The Project leader, University of Kuopio
- 10/2000 – 10/2001, Postdoctoral researcher, University of Maryland, MD, USA
- 1.9.1998 – 31.9.2000, Assistant, University of Kuopio
- 1.5.1996 – 31.8.1998, Researcher, University of Kuopio

5. Research funding and grants

- Funding for research group since 2004 as a principal investigator: 3 905 665 €
  - Academy of Finland (LAT1-targeted boron carriers for BNCT), 1.1.2024–31.12.2027, 497 191 €
  - Innovo Pharmaceuticals, Inc. (prodrug research), 6/2021-5/2022, 20937 € & 4/2023-12/2023, 18913 €
  - Higher Council for Innovation & Excellence, Palestine (prodrug research), 9/2022-8/2023, 30 891 €
  - Higher Council for Innovation & Excellence, Palestine (prodrug research), 11/2019-12/2021, 37 726 €
  - Academy of Finland (302000), 1.9.2017-31.8.2021, 441 492 €
  - Finnish National Agency for Education (EDUFI), 2017 & 2018, 18 000 € (10 500 + 7 500)
  - Pharmaceutical company (CNS prodrug design and discovery), 2016, 49 242 €
  - Cancer Foundation, 2015, 20 000 €
  - Päivikki and Sakari Sohlberg Foundation, 2015, 35 000 €
  - Finnish Funding Agency for Technology and Innovation (Commercialization of prodrug expertise), 1.9.2014–30.4.2016, 200 000 €
  - Finnish Funding Agency for Technology and Innovation (Initialization of commercialization of metformin prodrug), 1.5.2010–31.7.2011, 190 000 €
  - Finnish Funding Agency for Technology and Innovation (Cancergel), 1.3.2010–1.4.2013, 247 198 €
  - Academy of Finland (Novel LAT1-mediated prodrugs: potential approach for improved brain drug targeting), 1.1.2010–31.12.2013, 372 060 €
  - Pharmaceutical company (Prodrug design and discovery), 1.1–31.12.2009, 99 357 €

- Pharmaceutical company (Prodrug design and discovery), 1.6.2008–1.9.2008, 46 227 €
- Finnish Funding Agency for Technology and Innovation (Carrier-mediated transporter mechanisms in efficient CNS drug Delivery), 1.5.2008–30.4.2010, 322 000 €
- University of Kuopio (Prodrug design and discovery), 12.6.2006–31.12.2007, 25 000 €
- Pharmaceutical company (Prodrug design and discovery), 1.9.2006–1.5.2008), 188 704 €
- Finnish Funding Agency for Technology and Innovation (Water-soluble and cytochrome P450 mediated prodrugs), 1.1.2005–31.03.2007, 247 440 €
- Finnish Funding Agency for Technology and Innovation (Water-soluble and cytochrome P450 mediated prodrugs), 1.1.2004–31.12.2004, 117 640 €

- As a co-applicant since 2001: 1 523 347 €
  - Cancer foundation (Delivery agents for BNCT), 2019-2021, 200 000 € (50 000 € for UEF), PI Adj. prof. Ekholm (Univ. of Helsinki)
  - Nordforsk (Nordic University Hubs), 2018-2023 (2 866 579 NOK for UEF) 302 000 €, PI Prof. Rantanen (Univ. of Copenhagen)
  - Pharmaceutical company, 2017-2018, 230 000 €, PI PhD Nevalainen
  - Finnish Funding Agency for Technology and Innovation (Improvement of suicide gene therapy of brain tumours and brain penetration of nucleoside analogues), PI: Prof. Markus Forsberg, 1.7.2010–30.6.2012, 578 747 €
  - Finnish Funding Agency for Technology and Innovation (Carrier-mediated transporter mechanisms in efficient CNS drug Delivery), PI: Prof. Tomi Järvinen, 101900 €
  - Finnish Funding Agency for Technology and Innovation (Drug targeting via prodrug-technology), PI: Prof. Tomi Järvinen, 1.1.2001–31.12.2003, 260 700 €

- Personal Grants since 1996: 350 500 €
  - Academy of Finland (salary), 1.8.2002–31.12.2006, 186 800 €
  - Academy of Finland (research), 1.8.2002–31.12.2006, 60 600 €
  - Various foundations (postdoctoral studies in USA), 2000-2001 and 2004-2005, 91 600 €
  - Various foundations (Ph.D. studies), 1996–2000, 11 500 €

6. Research output

- Total number of publications – complete list of publications as a separate appendix
  - 95 original peer-reviewed publications (including 18 peer-reviewed reviews), 3 submitted manuscripts, 5 editorials/viewpoints, 6 book chapters, 2 books (Finnish pharmaceutical chemistry textbooks), 1 edited book (Prodrugs and Targeted Delivery, Wiley-VCH, 2011), 3 audiovisual talks and 5 patent families in total.
  - Publications for example in ***Nature Reviews Drug Discovery*** **(IF = 84.694) 1211 citations** (published in 2008) and **298** citations (published in 2018), *Pharmacological Review* (IF = 25.468, 395 citations), and *Advanced Drug Delivery Reviews* (IF = 15.447, 212 & 112 citations).
  - Total number of citations according to Web of Science® (15 January 2025) is 4,893 (4,635 excluding self-citations) and **h-index is 31**.

7. Research supervision and leadership experience

- Supervision of post-doc researchers
  - PhD Juulia Järvinen, 2025-
  - PhD Diego Rodriguez, 2024-
  - PhD Juri Timonen, 2016-2018
  - PhD Mikko Gynther, 2012–2014
  - PhD Kristiina Huttunen, 2011–2013
  - PhD Krista Laine, 2005–2007
  - PhD Jukka Leppänen, 2004–2006

- Supervision of doctoral students
  - Katayan Bahrami, ongoing, principal supervisor
  - Seyedhamed Maljaei, ongoing, co-supervisor
  - Jussi Kärkkäinen, ongoing, co-supervisor
  - Juulia Järvinen, graduated in 2024, principal supervisor
  - Lauri Peura, graduated in 2013, principal supervisor
  - Niina Tani, graduated in 2013, co-supervisor
  - Mikko Gynther, graduated in 2010, principal supervisor
  - Anne Mannila, graduated in 2009, co-supervisor
  - Kristiina Huttunen, graduated in 2009, principal supervisor
  - Hanna Kumpulainen, graduated in 2007, co-supervisor
  - Antti Mäntylä, graduated in 2004, co-supervisor

- Supervision of Master and Bachelor students
  - 14 Master and 50 Bachelor students

8. Teaching merits

- Teaching
  - Approximately 75 hours of lectures and 15 hours of small group teaching a year at the UEF in the following courses: Pharmaceutical Chemistry (responsible teacher), Introduction to Pharmaceutical Research and Development, Advanced Physical Pharmacy. Approximately 700 hrs lectures and 900 hrs small group teaching in total.
  - Lectures on physicochemical properties at the University of Turku (8 h) as well as on prodrugs and cyclodextrins at the University of Helsinki (3 h) annually 2010-2019..
  - Organizing and lecturing in a one-day course on "Discovery of prodrugs" at 4 pharma companies in 2015 and 2 companies in 2016 (Prof. Rautio the only instructor).
  - Organizing and lecturing in a four-day course on physicochemical properties and prodrugs at the University of Khon Kaen (Thailand) in 2009.
  - Organizing and lecturing in graduate school courses on prodrugs in 2006 and 2012 at the UEF.
  - Organizing and lecturing in AAPS short course on prodrugs in 2012.
  - In total, teaching experience of ca. 500 hours in lectures and ca. 850 hours in small group teaching.
- Textbooks
  - Co-author in a textbook "Essentials of Pharmaceutical Chemistry" (Farmaseuttisen kemian perusteet), Rautio, Laine, Jarho, Wallen, Vuorensola, Wikberg ja Lindeke, Fortis ry. Kuopio 2013.
  - Co-author in a textbook "Introduction to Medicinal Chemistry" (Lääkeainekemian perusteet), Gynther, Järvinen, Rautio, Savolainen, Fortis ry, Kuopio, 2002.

9. Other key academic merits

- Acting as expert evaluator in Professorship application (7):
  - Government College University, Lahore, Pakistan, April 2022
  - Johns Hopkins University School of Medicine, May 2019
  - School of Pharmacy, University of Eastern Finland, April 2015 and August 2015

- Faculty of Pharmacy, The University of Jordan, 2013
- The College of Pharmacy, King Saud bin Abdulaziz University for Health Sciences, 2013
- Faculty of Pharmacy, **The University of Jordan, 2012**

- Acting as opponent of a doctoral dissertation (3):
  - Aarhus University, Department of Chemistry, Denmark, 2023
  - University of Iceland, Faculty of Pharmaceutical Sciences, Iceland, 2022
  - Khon Kaen University, Thailand, 2017

- Acting as Pre-examiner of a doctoral dissertation (6):
  - University of Catania, Italy, 2024
  - Åbo Akademi University, 2023
  - University of Helsinki, 2007 & 2023
  - Government College University, Lahore, Pakistan, 2019, 2020 & 2021

- Acting as evaluator in evaluation of applications for the Title of Docent (1):
  - Åbo Akademi University, Turku, 2017

- Peer review of grant proposals (28):
  - Finnish Cultural Foundation, 2022
  - Orion Research Foundation, 2022, 2023, 2024
  - University of Helsinki, 2019, 2020, 2021, 2022
  - University of Turku, 2019, 2020, 2021, 2022
  - Finnish Pharmaceutical Society, yearly since 2010
  - National Science Centre, Poland 2013, 2017, 2018 & 2020
  - Breast Cancer Now, UK, 2017
  - Netherlands Organisation for Scientific Research (NWO), Netherlands, 2017
  - Åbo Akademi University, Finland 2015, 2016, 2021 & 2022
  - Cancer Research Wales, 2016
  - Research Development Fund of Xi'an Jiaotong-Liverpool University (China) 2014
  - German-Israeli Foundation for Scientific Research and Development 2013
  - Scientific Research Support Fund (Jordan) 2013
  - Estonian Science Foundation 2011
  - The Medical Research Council Career Development Award (UK) 2010
  - The Icelandic Centre for Research 2010
  - Qatar Nation Research Fund 2009

- Peer review of miscellaneous proposals (1):
  - Doctoral programme at the University of Vienna, 2018

- Memberships and positions of trust in scientific communities:
  - Doctoral Programme in Drug Research (DPDR) at School of Pharmacy, UEF
    - ✓ Director, 1/2018 – present
    - ✓ Vice-Director, 1/2014 – 12/2017
  - Director of FinPharmaNet (national Doctoral Programme in Drug Research, https://www.helsinki.fi/en/networks/finpharmanet/finpharmanetsuoen) 6/2018 – 6/2020
  - Finnish Pharmaceutical Society (http://pro.tsv.fi/finpharmsociety/engl/index.html)
    - ✓ Chairman of the Board 4/2020 - present
    - ✓ Board member 5/2013 – 3/2020
  - American Association of Pharmaceutical Scientists (AAPS):
    - ✓ AAPS Prodrug Focus Group: Co-founder in 2004, Chair-elect 2004 – 2005, Chair 2005 – 2006, Steering committee member 2006 – 2016
    - ✓ AAPS Physical Pharmacy and Biopharmaceutics Section: International outreach committee member 2010 – 2016
  - CRS Nordic Chapter (Controlled Release Society): Board member 1/2014 – 6/2022
  - Drug Research and Development Centre (Kuopio, Finland): Steering committee member 8/2008–8/2010 and 8/2011–present
  - EUFEPS council member 4/2020 - present
  - European Federation for Medicinal Chemistry (EFMC) steering group member 3/2013 – present
  - European Technology Platform on Nanomedicine: Scientific expert 9/2006 - 2018
  - Kuopio Innovation HealthBIO (Kuopio, Finland): Steering committee member 2008 – 2010

- Membership in editorial advisory board for the following scientific journals:
  - Molecules (2008 – 2024)
  - Therapeutic Delivery (2009 – 2023)

- Referee for the following 44 scientific journals:
  - AAPS Journal; Acta Pharmacologica Sinica; ACS Medicinal Chemistry

Letters; Amino Acids; Archiv der Pharmazie; Asian Journal of Pharmaceutics; Bioorganic & Medical Chemistry; Biopharmaceutics & Drug Disposition; Brain Research Bulletin, Chemical Biology & Drug Design; ChemMedChem; *Current Medicinal Chemistry;* Current Pharmaceutical Design; Die Pharmazie; Drug Design, Drug Development and Industrial Pharmacy, Drug Design, Development and Therapy; Drug Discovery Today; Drug Metabolism and Disposition; Drug Metabolism Reviews; European Journal of Clinical Pharmacology; European Journal of Medicinal Chemistry; European Journal of Pharmaceutical Sciences; Expert Opinion On Drug Delivery; Expert Opinion On Drug Discovery; Frontiers in Pharmacology; Future Medicinal Chemistry; International Journal of Molecular Sciences; International Journal of Pharmaceutics; Journal of Controlled Release; Journal of Medicinal Chemistry; Journal of Pharmaceutical Sciences; Journal of Taibah University for Science; MedChemComm; Medicinal Chemistry; Melanoma Management, Molecular Pharmaceutics; Molecules; Nanomedicine; Nature Communications; Pharmaceutical Research; Pharmaceutics; Recent Patents on Nanomedicine; The Protein Journal

- Administrative positions:
  - Deputy head of the School of Pharmacy, University of Eastern Finland, 8/2020 – present
  - Head of the Doctoral programme in Drug Research, School of Pharmacy, University of Eastern Finland, 1/2018 – present
  - Head of the Pharmaceutical Chemistry discipline, School of Pharmacy, University of Eastern Finland, 5/2008–7/2010 and 9/2015 – 8/2019

- Significant invited international lectures
  - ACS 2022
  - EFMC 2021
  - Plenary presentation in 1st Spring Virtual Meeting on Medicinal Chemistry, May 26, 2021
  - CRS Italy Chapter Annual Workshop, Catania, Italy, November 7-9, 2019
  - Keynote lecture at 2nd RSC Anglo-Nordic MedChem symposium, Snekkersten, Denmark, June 11-14, 2019
  - CRS Nordic Chapter, Drug Transporters Symposium in Kuopio, June 11, 2017
  - 6th BBBB Conference on Pharmaceutical Sciences, Helsinki, September 10-12, 2015
  - AAPS short course “Prodrug strategies in drug design” in 2012, Chicago, IL

- AAPS roundtable "Prodrug approaches for organ specific targeted therapy" in 2008, Atlanta, GA

- Organizing scientific conferences:
  - Host, organizer: FinPharmaNet Annual Meeting 2021, 2023
  - Organizer committee: CRS Nordic Chapter, Drug Transporters Symposium in Kuopio, June 11, 2017
  - Organizer committee: 6th BBBB Conference on Pharmaceutical Sciences, Helsinki, September 10-12, 2015
  - Organizer committee: FinMedChem, Helsinki, August 24-27, 2015
  - Organizer committee: CRS Nordic Chapter, Drug Transport and Delivery Symposium in Helsinki, August 26-27, 2014
  - Organizer, moderator and speaker in an AAPS short course "Prodrug strategies in drug design" in 2012
  - Moderator and speaker in an AAPS minisymposium "Prodrugs – towards better drugs" in 2009
  - Organizer, moderator and speaker in an AAPS roundtable "Prodrug approaches for organ specific targeted therapy" in 2008
  - Organizer and moderator in an AAPS roundtable "Transporters as Prodrug Carriers for Oral Drug Delivery" in 2008
  - Organizer and moderator in an AAPS roundtable "Tumor-activated Prodrug and Tumor-targeting Technologies ADEPT, GDEPT and PDEPT to Increase Drug Efficacy and Reduce Drug Toxicity" in 2007
  - Organizer and moderator in an AAPS roundtable "Prodrug Approaches for Site-Specific Cellular Targets" in 2007
  - Organizer and moderator in an AAPS roundtable "Strategies & Technologies for Topical and Transdermal Drug Delivery" in 2006

10. Scientific and societal impact of research

- 5 patent families (2021, 2020, 2009, 2007, 1998), 1 invention disclosure (2020)
- ACS webinar "Prodrugs in Medicinal Chemistry" at www.acs.org/acswebinars, Nov 26 2019
- Rautio, J. (2022, July 31). Prodrug strategies to overcome problems in drug therapy [Video file]. In *The Biomedical & Life Sciences Collection, Henry Stewart Talks*. Retrieved August 7, 2022, from https://hstalks.com/bs/5019/
- HSTalks "Prodrugs and Drug Delivery" at

https://hstalks.com/t/2644/prodrugs-and-drug-delivery, Sep 23, 2013

APPENDIX B – PUBLICATIONS - JARKKO RAUTIO, PH.D. (PHARM.)

A Peer-reviewed scientific articles: A1 Journal articles

1. N Ivanova, C Agca, Y Agca, EG Noble, MM Forsberg, J Rautio, J Leppänen, SN Whitehead, DF Cechetto: Impact of a novel anti-inflammatory ketoprofen-lysine prodrug on cerebral pathology and cognition in a comorbid APP21 transgenic rat with diet-induced metabolic syndrome (submitted)

2. S Imlimthan, K Bahrami, H Pehkonen, A Centanni, AB Montaser, A Värä, J Matović, H Liljenbäck, T Auchynnikava, KM Huttunen, A Roivainen, A Airaksinen, FS Ekholm, O Monni, J Rautio, M Sarparanta, Mirkka: Biological Evaluation of a Glucose-Based Boron Carrier as a Potential Agent for Boron Neutron Capture Therapy (submitted)

3. R Lombardo, S Rizzo, J Rautio, R Pignatello: Green techniques to develop food-grade Resveratrol Eudraguard® Biotic/Control microparticles as a shield against stress conditions (submitted)

4. M Retini, J Järvinen, K Bahrami, J Tampio, F Bartoccini, P Riihelä, H Pehkonen, A Värä, T Laitinen, KM Huttunen, J Rautio, G Piersanti, JM Timonen: Asymmetric synthesis and biological evaluation of both enantiomers of 5- and 6-boronotryptophan as potential boron delivery agents for boron neutron capture therapy (BNCT). *ACS Medicinal Chemistry Letters* **2024** https://doi.org/10.1021/acsmedchemlett.4c00241

5. J Matovic, J Järvinen, I Sokka, S Imlimthan, O Aitio, M Sarparanta, J Rautio, F Ekholm: Towards New Delivery Agents for Boron Neutron Capture Therapy: Synthesis and In Vitro Evaluation of a Set of Fluorinated Carbohydrate Derivatives. Molecules **2024**, 29, 4263. https://doi.org/10.3390/molecules29174263

6. K Kaimuangpak, T Srisongkram, M Lehtonen, J Rautio, N Weerapreeyakul: The metabolic response of HepG2 cells to extracellular vesicles derived from *Raphanus sativus* L. var. *caudatus* Alef microgreens probed by chemometrics-assisted LC-MS/MS analysis. *Food Chemistry* **2024**, https://doi.org/10.1016/j.foodchem.2024.140833

7. E Zingale, S Masuzzo, T Lajunen, M Reinisalo, J Rautio, R Pignatello: Protective role and enhanced intracellular uptake of CUR in retinal cells using self-emulsifying drug delivery systems (SNEDDS) (submitted)

8. R Lombardo, M Ruponen, J Rautio, R Lampinen, KM Kanninen, AM Koivisto, E Penttilä, H Löppönen, S Demartis, P Giunchedi, G Rassu, ME Fragalà, R

Pignatello: A technological comparison of freeze-dried poly-ε-caprolactone (PCL) and poly (lactic-co-glycolic acid) (PLGA) nanoparticles loaded with clozapine for nose-to-brain delivery. *Journal of Drug Delivery Science and Technology* 93: 105419, **2024** https://doi.org/10.1016/j.jddst.2024.105419

9. K Bahrami, J Kärkkäinen, S Bibi, J Huttunen, J Tampio, AB Montaser, CL Moody, M Lehtonen, J Rautio, RT Wheelhouse, KM Huttunen: Specific transport of temozolomide does not override DNA repair-mediated chemoresistance. *European Journal of Pharmaceutical Sciences* 195: 106661, **2024** https://doi.org/10.1016/j.ejps.2023.106661

10. E Zingale, A Bonaccorso, AG D'Amico, R Lombardo, V D'Agata, J Rautio, R Pignatello: Formulating Resveratrol and Melatonin Self-Nano-emulsifying Drug Delivery Systems (SNEDDS) for ocular administration using Design of Experiments. *Pharmaceutics* **2024**, *16*(1), 125; https://doi.org/10.3390/pharmaceutics16010125

11. J Järvinen, AB Montaser, SK Adla, J Leppänen, M Lehtonen, K-S Vellonen, T Laitinen, A Jalkanen, WF Elmquist, J Timonen, KM Huttunen, J Rautio: Improving brain targeting with two novel prodrugs of palbociclib. *European Journal of Pharmaceutical Sciences* 192: 106637, **2023** https://doi.org/10.1016/j.ejps.2023.106637

12. T Auchynnikava, A Äärelä, H Liljenbäck, J Järvinen, P Andriana, L Kovacs, J Rautio, J Rajander, P Virta, A Roivainen, X-G Li, AJ Airaksinen: Tetrazine glycoconjugate for pretargeted PET imaging of trans-cyclooctene functionalized molecular spherical nucleic acids. ACS Omega **2023**, 8, 48, 45326–45336. https://doi.org/10.1021/acsomega.3c04041

13. AK Tonduru, SH Maljaei, SK Adla, L Anamea, C Espada, IF Santos, AB Montaser, J Rautio, T Kronenberger, A Poso, KM Huttunen: Targeting astrocytes by Organic anion transporting polypeptide 1C1 (OATP1C1) - utilizing *L*-Thyroxine-derived prodrugs. *Journal of Medical Chemistry* **2023**. https://doi.org/10.1021/acs.jmedchem.3c01026

14. R Lombardo, M Ruponen, J Rautio, C Ghelardini, L Di Cesare Mannelli, L Calosi, De Bani, R Lampinen, KM Kanninen, AM Koivisto, E Penttilä, H Löppönen, R Pignatello: Development of lyophilised Eudragit® Retard nanoparticles for the sustained release of clozapine via intranasal administration. *Pharmaceutics* 15(5): 1554, **2023**. https:// doi: 10.3390/pharmaceutics15051554

15. J Borregaard Eriksen, JJ Christiansen, A Bauer-Brandl, M Ruponen, J Rautio, M Brandl: *In-vitro* dynamic dissolution/bioconversion/permeation of fosamprenavir using a novel tool with an artificial biomimetic permeation

barrier and microdialysis-sampling. *European Journal of Pharmaceutical Sciences* 181(1), 106366, **2023** https://doi.org/10.1016/j.ejps.2022.106366

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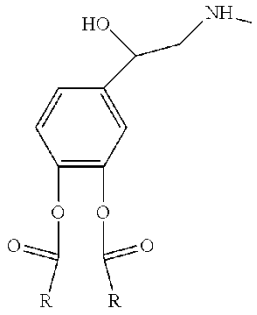
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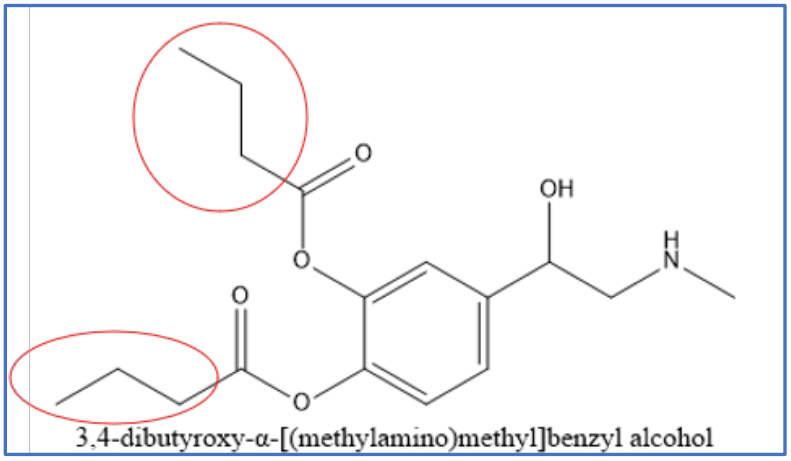
APPENDIX C - ALMOAZEN '437 PATENT CLAIM CHART

In the following claim chart, the following shorthand is used: first the ground number, e.g., G1 stands for Ground 1; then the '437 Patent claim number, followed by the claim limitation, e.g., 1A stands for claim 1's first claim limitation. Thus, G1-1A stands for Ground 1 – Claim 1, first (A) claim limitation.

GROUND 1

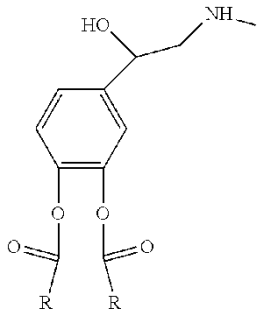
GROUND 1 **Truelove 1 (EX1002), Almoazen Paper (EX1022) and Ashraf (EX1003)**	
CLAIMS [**G**round # - **C**laim **ID**]	**REFERENCES**
Claim 1. [G1-1A] A compound formulated as a pharmaceutical composition in a unit dosage form configured for sublingual or buccal administration	**Truelove 1 (EX1002)** "[T]he new compound and its non-toxic salts are administered in the form of . . . buccal patches. . . ." (EX1002, 6:29-32.) **Almoazen Paper (EX1022)** "*Objective*: To develop a fast dissolving film ["FDF"] strip containing epinephrine HCl for the potential treatment of pediatric anaphylaxis." (EX1022, Abstract, p.1012.) "Fast dissolving films (FDF) . . . are very thin strips that disintegrate or dissolve very rapidly in the oral cavity releasing the medication to be absorbed through the oro-mucosal route." (EX1022, p.1012.)

GROUND 1 Truelove 1 (EX1002), Almoazen Paper (EX1022) and Ashraf (EX1003)	
CLAIMS [**G**round # - **C**laim **ID**]	**REFERENCES**
[G1-1B] of a Formula:  wherein R is selected from the group consisting of: — *** **-$CH_2CH_2CH_3$,** *** or a pharmaceutically acceptable salt thereof,	"The formulations compositions of the FDFs are mentioned in **Table 1.**" (EX1022, p.1013, emphasis added.) **Ashraf (EX1003)** Ashraf discloses pharmaceutically acceptable carriers and excipients for its oral mucosa drugs. (EX1003, p.36.) ********** **Truelove 1 (EX1002)** Truelove 1, Table 3, EX1002, 9:26-38, copied below, **TABLE 3** Rate of hydrolysis in $t_{1/2}$ seconds Compound / Horse / Rabbit / Human L-3,4-diacetyl-α-[(methylamino)-methyl] benzyl alcohol hydroperchlorate ---------- 20 / 45 / 180 L-3,4-dipropionyl-α-[(methylamino)methyl] benzyl alcohol hydroperchlorate ---------- 50 / 90 / 240 L-3,4-dibutyryl-α-[(methylamino)-methyl] benzyl alcohol hydroperchlorate ---------- 100 / 160 / 360 L-3,4-dipivalyl-α-[(methylamino)-methyl] benzyl alcohol hydroperchlorate ---------- 600 / 720 / 1,800 discloses "3,4-dibutyryl-α-[(methylamino)methyl] benzyl alcohol hydroperchlorate". A POSA would have recognized that as Truelove 1 was directed to and discloses diester derivatives of epinephrine, not the named ketone derivative, Truelove 1 was disclosing, as corrected, both (i) the salt "3,4-**di~~butyryl~~butyroxy** -α-[(methylamino) methyl] benzyl alcohol hydroperchlorate" and (ii) the non-salt "3,4-**di~~butyryl~~butyroxy**-α-[(methylamino) methyl] benzyl alcohol" compounds. The POSA would have further understood that "3,4-

GROUND 1 Truelove 1 (EX1002), Almoazen Paper (EX1022) and Ashraf (EX1003)	
CLAIMS [**G**round # - **C**laim **ID**]	**REFERENCES**
[G1-1C] wherein said compound has a **Log P value in the range of about 0.5-6.0** and	**dibutyroxy**-α-[(methylamino) methyl] benzyl alcohol" discloses, as recited in claim 1, the compound with the following ChemDraw® generated compound structure and displayed compound name having the circled R substituent Group **-$CH_2CH_2CH_3$** which POSA would have substantially the same, if not identical half-life **$t_{1/2}$ of 360 seconds or 6 minutes** as disclosed in Table 3.  3,4-dibutyroxy-α-[(methylamino)methyl]benzyl alcohol ********** **Ashraf (EX1003)** "Satisfactory oral [mucosal] absorption of drugs has been observed over a wide range of **log P** (octanol/water partition coefficient) **values of 1 to 5**." (EX1003, p.35, 2nd col., emphasis added). The inherent Log P of the claim 1 epinephrine compound with ester promoiety **R = -$CH_2CH_2CH_3$** is +0.8. See, '437 Patent (EX1001), Table 1, 5:29.

GROUND 1 Truelove 1 (EX1002), Almoazen Paper (EX1022) and Ashraf (EX1003)	
CLAIMS [**G**round # - **C**laim **ID**]	**REFERENCES**
[G1-1D] wherein the compound is formulated in a unit dosage form as a rapidly dissolving film and	********** **Truelove 1 (EX1002), Almoazen Paper (EX1022) & Ashraf (EX1003)** See discussion for [G1-1A] above.
[G1-1E] has a half-life $t_{1/2}$ range from 1-6 minutes.	********** **Truelove 1 (EX1002)** See discussion in [G1-1B] above.

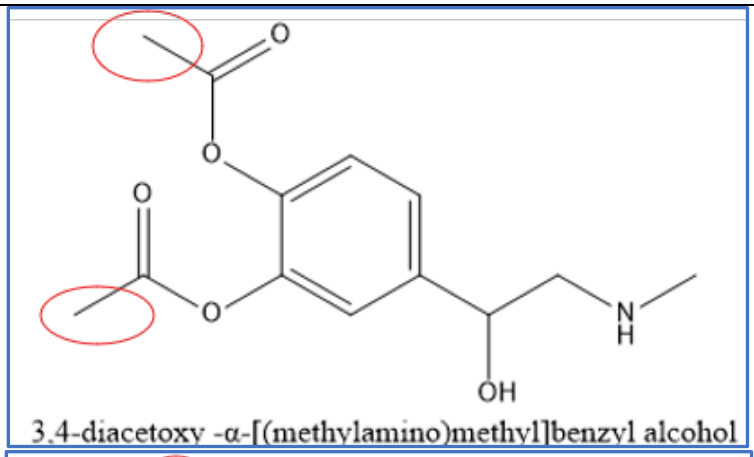
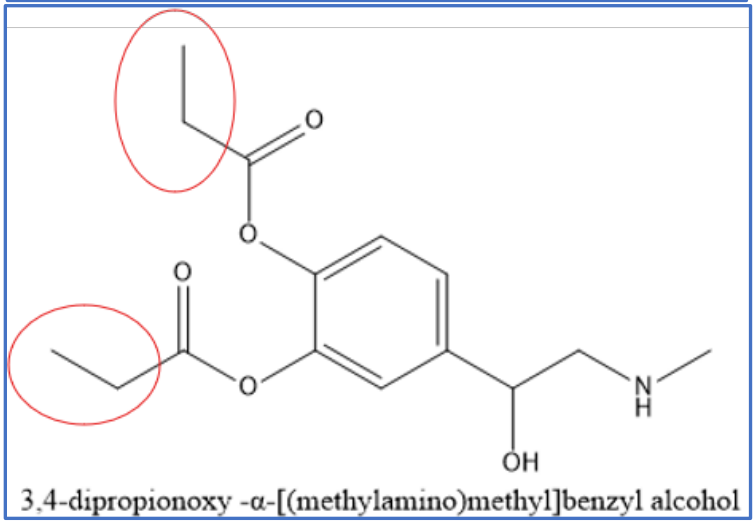
<table>
<tr><th colspan="2">GROUND 1
Truelove 1 (EX1002), Almoazen Paper (EX1022) and Ashraf (EX1003)</th></tr>
<tr><th>CLAIMS
[Ground # - Claim ID]</th><th>REFERENCES</th></tr>
<tr><td></td><td></td></tr>
<tr><td>Claim 2.

[G1-2A]
A compound of a Formula
 

wherein R is selected from the group consisting of: CH₃, CH₂CH₃ and CH(CH₃)₂</td><td>Truelove 1 (EX1002)

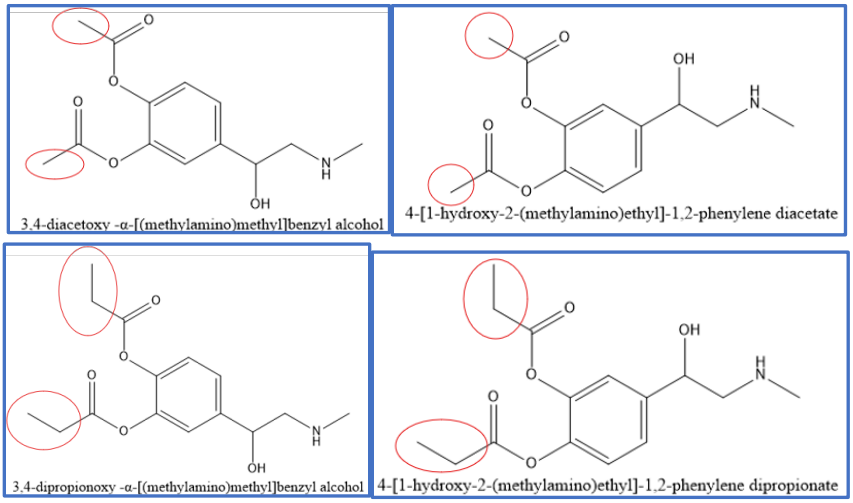
Truelove 1, Table 3, EX1002, 9:26-38, copied below

TABLE 3
<table><tr><th></th><th colspan="3">Rate of hydrolysis in $t_{1/2}$ seconds</th></tr><tr><th>Compound</th><th>Horse</th><th>Rabbit</th><th>Human</th></tr><tr><td>L-3,4-diacetyl-α-[(methylamino)-methyl] benzyl alcohol hydroperchlorate</td><td>20</td><td>45</td><td>180</td></tr><tr><td>L-3,4-dipropionyl-α-[(methylamino)methyl] benzyl alcohol hydroperchlorate</td><td>50</td><td>90</td><td>240</td></tr><tr><td>L-3,4-dibutyryl-α-[(methylamino)-methyl] benzyl alcohol hydroperchlorate</td><td>100</td><td>160</td><td>360</td></tr><tr><td>L-3,4-dipivalyl-α-[(methylamino)-methyl] benzyl alcohol hydroperchlorate</td><td>600</td><td>720</td><td>1,800</td></tr></table>
discloses the salt form and thus the non-salt form of the following corrected named diester compounds, namely “3,4- di<s>acetyl</s>acetoxy-α-[(methylamino)methyl] benzyl alcohol” and “3,4- di<s>propionyl</s>propionoxy-α-[(methylamino)methyl]benzyl alcohol”. A POSA would have understood these compounds to have the ChemDraw® structures and displayed name as shown below with R substituent Groups -CH₃ and -CH₂CH₃, as recited in [G1-2A] circled, and that Table 3 also discloses that these diester epinephrine prodrug compounds would have substantially the same, if not identical half-lives $t_{1/2}$ of 3 minutes and 4 minutes, respectively.</td></tr>
</table>

GROUND 1 Truelove 1 (EX1002), Almoazen Paper (EX1022) and Ashraf (EX1003)	
CLAIMS [**G**round # - **C**laim **ID**]	**REFERENCES**
	 3,4-diacetoxy -α-[(methylamino)methyl]benzyl alcohol  3,4-dipropionoxy -α-[(methylamino)methyl]benzyl alcohol

GROUND 1 Truelove 1 (EX1002), Almoazen Paper (EX1022) and Ashraf (EX1003)	
CLAIMS [**G**round # - **C**laim **ID**]	**REFERENCES**
[G1-2B] wherein the compound is formulated in a unit dosage form as a sublingual or buccal administration and wherein the compound is formulated in a unit dosage form as a rapidly dissolving film and	********** **Truelove 1 (EX1002), Almoazen Paper (EX1022) & Ashraf (EX1003)** See discussed in [G1-1A] above for [G1-2B] disclosure.
[G1-2C] has a half-life $t_{1/2}$ range from 1-6 minutes.	********** **Truelove 1 (EX1002)** See discussion in [G1-2B] above.

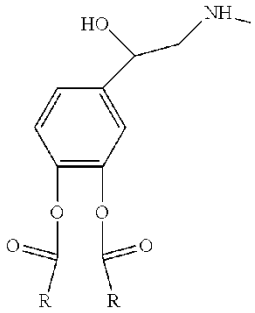
GROUND 1 Truelove 1 (EX1002), Almoazen Paper (EX1022) and Ashraf (EX1003)	
CLAIMS [**G**round # - **C**laim **ID**]	**REFERENCES**
Claim 3. [G1-3A] The compound of claim 2,	See discussion for Ground 1, claim 2 above.
[G1-3B] wherein the compound is selected from the group consisting of: **4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene di-acetate**; 4-(1-hydroxy-2(methylamino)ethyl)-1,2-phenylene bis(2-methylpropanoate); **4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene dipropionate**; and	********** **Truelove 1 (EX1002)** As discussed in [G1-2A] above, Truelove 1, Table 3, EX1002, 9:26-38, copied below TABLE 3 Rate of hydrolysis in $t_{1/2}$ seconds Compound — Horse — Rabbit — Human L-3,4-diacetyl-α-[(methylamino)-methyl] benzyl alcohol hydroperchlorate — 20 — 45 — 180 L-3,4-dipropionyl-α-[(methylamino)methyl] benzyl alcohol hydroperchlorate — 50 — 90 — 240 L-3,4-dibutyryl-α-[(methylamino)-methyl] benzyl alcohol hydroperchlorate — 100 — 160 — 360 L-3,4-dipivalyl-α-[(methylamino)-methyl] benzyl alcohol hydroperchlorate — 600 — 720 — 1,800 discloses the corrected named diester compounds, namely "3,4-**di~~acetyl~~acetoxy**-α-[(methylamino) methyl] benzyl alcohol" and "3,4-**di~~propionyl~~ propionoxy**-α-[(methylamino)methyl]benzyl alcohol."

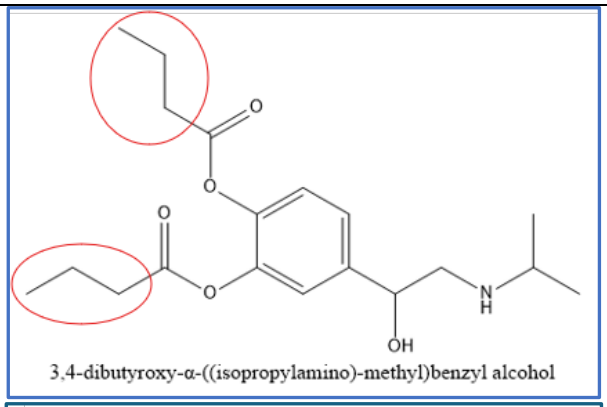
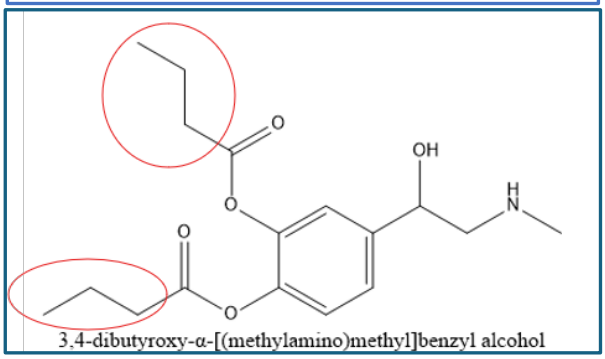
GROUND 1 Truelove 1 (EX1002), Almoazen Paper (EX1022) and Ashraf (EX1003)	
CLAIMS [**G**round # - **C**laim **ID**]	**REFERENCES**
	A POSA would have understood that "3,4-**diacetoxy**-α-[(methylamino) methyl] benzyl alcohol" has the alternative name of "4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene diacetate", and that "3,4-**dipropionoxy**-α-[(methylamino)methyl] benzyl alcohol" has the alternative name of "4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene dipropionate". See, e.g., ChemDraw generated structures and displayed names below. 
[G1-3C] a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein the compound is formulated in a unit	********** **Truelove 1 (EX1002), Almoazen Paper (EX1022) & Ashraf (EX1003)** See discussion for [G1-1A] above.

GROUND 1 Truelove 1 (EX1002), Almoazen Paper (EX1022) and Ashraf (EX1003)	
CLAIMS [**G**round # - **C**laim **ID**]	**REFERENCES**
dosage form as a rapidly dissolving film.	

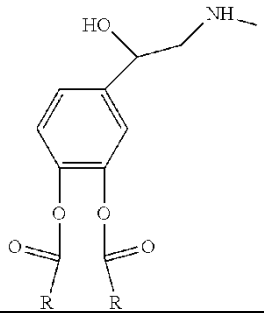
GROUND 2

GROUND 2 Truelove 3 (EX1008), Almoazen Paper (EX1022) and Ashraf (EX1003)	
CLAIMS [**G**round # - **C**laim **ID**]	**REFERENCES**
Claim 1. [G2-1A] A compound formulated as a pharmaceutical composition in a unit dosage form configured for sublingual or buccal administration [G2-1B] of a Formula:	**Truelove 3 (EX1008)** "The new compound and its non-toxic salts are thus administrable in the form of . . . buccal patches. . . . ". (EX1008, 7:35-39.) **Almoazen Paper (EX1022) & Ashraf (EX1003)** See Almoazen Paper & Ashraf discussion in [G1-1A] above. ********** **Truelove 3 (EX1008)** Truelove 3, Table 3, EX1008, 10:58-70, copied below,

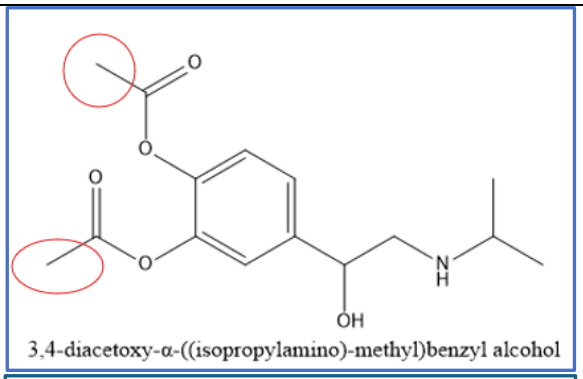
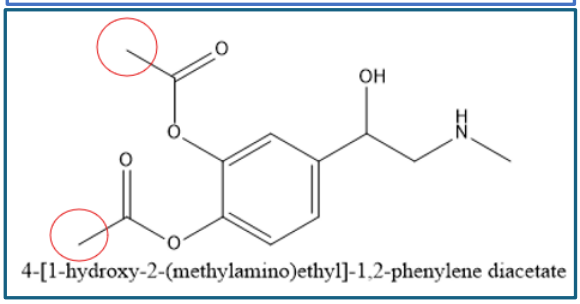
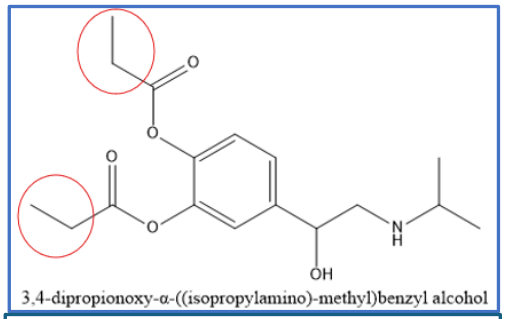
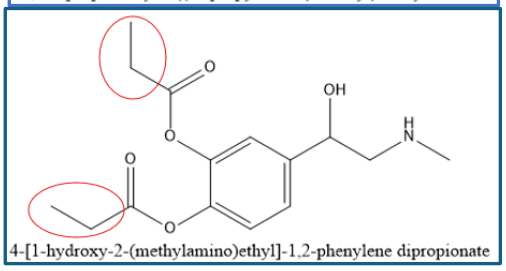
GROUND 2 Truelove 3 (EX1008), Almoazen Paper (EX1022) and Ashraf (EX1003)	
CLAIMS [Ground # - Claim ID]	**REFERENCES**
 wherein R is selected from the group consisting of: — *** **-$CH_2CH_2CH_3$**, *** or a pharmaceutically acceptable salt thereof,	TABLE 3 Rate of Hydrolysis in $t_{1/2}$ Seconds Compound — Horse — Rabbit — Human 3,4-diacetoxy-α1[(isopropylamino)-methyl]benzyl alcohol hydrochloride — 20 — 45 — 180 3,4-dipropionoxy-α-[(isopropylamino)-methyl]benzyl alcohol hydrochloride — 50 — 90 — 240 3,4-dibutyroxy-α-[(isopropylamino)-methyl]benzyl alcohol hydrochloride — 100 — 160 — 360 3,4-dipivaloxy-α1[(isopropylamino)-methyl]benzyl alcohol hydrochloride — 600 — 720 — 1800 discloses the diester isoproterenol compound "3,4-dibutyroxy-α-[(isopropylamino)-methyl]benzyl alcohol hydrochloride" as well as its non-salt form "3,4-dibutyroxy-α-[(isopropylamino)-methyl]benzyl alcohol". A POSA would have understood that this compound in both salt and non-salt form corresponds to diester isoproterenol compounds where R substituents of the ester promoieties are **-$CH_2CH_2CH_3$**. See ChemDraw® generated compound structure and displayed compound name below for the non-salt form for both isoproterenol (top) and epinephrine (bottom) with, in each case, the R Group **-$CH_2CH_2CH_3$** circled.

GROUND 2 Truelove 3 (EX1008), Almoazen Paper (EX1022) and Ashraf (EX1003)	
CLAIMS [Ground # - Claim **ID**]	**REFERENCES**
	 3,4-dibutyroxy-α-((isopropylamino)-methyl)benzyl alcohol  3,4-dibutyroxy-α-[(methylamino)methyl]benzyl alcohol Because of isoproterenol's and epinephrine's structural similarity, a POSA would have understood that Truelove 3's disclosure of this diester isoproterenol compound and its associated half-life $t_{1/2}$ teaches that the same ester promoiety with R substituent $-CH_2CH_2CH_3$ could be used to form the epinephrine prodrug compound "3,4-dibutyroxy-α-[(methylamino)-methyl]benzyl alcohol", shown above, which has the same structure as recited in Claim 1 and which would have substantially the same, if not identical **$t_{1/2}$ of 360 seconds or 6 minutes.** The $t_{1/2}$ of 360 seconds or 6 minutes falls within the claim limitation [G2-1E] below of a half-life $t_{1/2}$ range from 1-6 minutes.

GROUND 2 Truelove 3 (EX1008), Almoazen Paper (EX1022) and Ashraf (EX1003)	
CLAIMS [**G**round # - **C**laim **ID**]	**REFERENCES**
[G2-1C] wherein said compound has a **Log P value in the range of about 0.5-6.0** and	********** **Ashraf (EX1003)** "Satisfactory oral [mucosal] absorption of drugs has been observed over a wide range of **log P** (octanol/water partition coefficient) **values of 1 to 5**." (EX1003, p. 35, 2nd col., emphasis added). The inherent Log P of the claim 1 epinephrine compound with ester promoiety **R = -$CH_2CH_2CH_3$** is +0.8. See, '437 Patent (EX1001), Table 1, 5:29..
[G2-1D] wherein the compound is formulated in a unit dosage form as a rapidly dissolving film and	********** **Truelove 3 (EX1008) & Almoazen Paper (EX1022)** See discussion in [G2-1A] above.
[G2-1E.] has a **half-life $t_{1/2}$ range from 1-6 minutes**.	********** **Truelove 3 (EX1008)** See discussion in [G2-1B] above for the disclosure in Truelove 3, Table 3 of

GROUND 2 Truelove 3 (EX1008), Almoazen Paper (EX1022) and Ashraf (EX1003)	
CLAIMS [Ground # - Claim **ID**]	**REFERENCES**
	compound where both R substituents of the ester promoieties of epinephrine are **$-CH_2CH_2CH_3$** as disclosing to a POSA a epinephrine prodrug compound with a **half-life $t_{1/2}$ of 6 minutes.**
Claim 2. A compound of a Formula 	**Truelove 3 (EX1008)** Truelove 3, Table 3. Exhibit 1008, 10:58-70, copied below, TABLE 3 Rate of Hydrolysis in $t_{1/2}$ Seconds Compound — Horse — Rabbit — Human 3,4-diacetoxy-α1[(isopropylamino)-methyl]benzyl alcohol hydrochloride — 20 — 45 — 180 3,4-dipropionoxy-α-[(isopropylamino)-methyl]benzyl alcohol hydrochloride — 50 — 90 — 240 3,4-dibutyroxy-α-[(isopropylamino)-methyl]benzyl alcohol hydrochloride — 100 — 160 — 360 3,4-dipivaloxy-α1[(isopropylamino)-methyl]benzyl alcohol hydrochloride — 600 — 720 — 1800

GROUND 2 Truelove 3 (EX1008), Almoazen Paper (EX1022) and Ashraf (EX1003)	
CLAIMS [**G**round # - **C**laim **ID**]	**REFERENCES**
wherein R is selected from the group consisting of: **CH_3**, **CH_2CH_3** and $CH(CH_3)_2$	discloses the salt form and thus the non-salt form of "3,4 diacetoxy-α-((isopropylamino)-methyl)benzyl alcohol" and "3,4-dipropionoxy-α-((isopropylamino)-methyl)benzyl alcohol". A POSA would have understood that these compounds in both salt and non-salt form correspond to diester isoproterenol compounds where the R substituents of the ester promoieties are -**CH_3** and -**CH_2CH_3**, respectively. Because of isoproterenol's and epinephrine's structural similarity, see structures below, a POSA would have understood that Truelove 3's disclosure of these diester isoproterenol prodrug compounds and their associated half-lives $t_{1/2}$ teaches that the same ester promoieties with R substituents -**CH_3** and -**CH_2CH_3**, could be used to form the epinephrine prodrug compounds of Claim 2, namely "4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene diacetate" and "4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene dipropionate". See ChemDraw® generated compound structures (showing their structural similarity) and displayed compound names for the non-salt form for isoproterenol (**top**) and epinephrine (**bottom**) prodrug compounds: with R = -**CH_3** group circled below -

GROUND 2 Truelove 3 (EX1008), Almoazen Paper (EX1022) and Ashraf (EX1003)	
CLAIMS [Ground # - Claim **ID**]	**REFERENCES**
	 3,4-diacetoxy-α-((isopropylamino)-methyl)benzyl alcohol  4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene diacetate with R = **-CH_2CH_3** group circled below -  3,4-dipropionoxy-α-((isopropylamino)-methyl)benzyl alcohol  4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene dipropionate

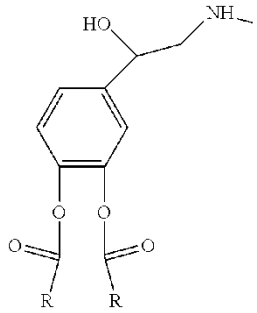
GROUND 2 Truelove 3 (EX1008), Almoazen Paper (EX1022) and Ashraf (EX1003)	
CLAIMS [**G**round # - **C**laim **ID**]	**REFERENCES**
	Thus, a POSA would have expected that the epinephrine prodrugs with the same ester promoieties as the isoproterenol prodrug compounds would have a similar if not identical half-lives of **$t_{1/2}$ = 180 seconds (3 minutes) and $t_{1/2}$ = 240 seconds (4 minutes), respectively**. These half-lives fall within the claim limitation [G2-2C] below of a half-life $t_{1/2}$ range from 1-6 minutes.
	**********
[G2-2B] wherein the compound is formulated in a unit dosage form as a sublingual or buccal administration and wherein the compound is formulated in a unit dosage form as a rapidly dissolving film and	**Truelove 3 (EX1008), Almoazen Paper (EX1022) & Ashraf (EX1003)** See discussed in [G2-1A] above for [G2-2B] disclosure.

GROUND 2 Truelove 3 (EX1008), Almoazen Paper (EX1022) and Ashraf (EX1003)	
CLAIMS [**G**round # - **C**laim **ID**]	**REFERENCES**
[G2-2C] has a **half-life $t_{1/2}$ range from 1-6 minutes**.	********** **Truelove 3 (EX1008)** See discussion in [G2-1B] above for the disclosure in Truelove 3, Table 3 of compounds where R substituents of the ester promoieties are **-CH_3** and **-CH_2CH_3**, as disclosing to a POSA that epinephrine prodrugs with these ester promoieties have half-lives of **$t_{1/2}$ = 180 seconds (3 minutes) and $t_{1/2}$ = 240 seconds (4 minutes), respectively.**
Claim 3. [G2-3A] The compound of claim 2,	See discussion for Ground 2, claim 2 above.
[G2-3B] wherein the compound is selected from the group consisting of:	********** As discussed in [G2-2A] above, Truelove 3, Table 3. Exhibit 1008, 10:58-70, discloses diester promoieties that a POSA would have understood

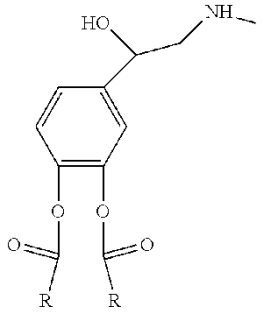
GROUND 2 Truelove 3 (EX1008), Almoazen Paper (EX1022) and Ashraf (EX1003)	
CLAIMS [**G**round # - **C**laim **ID**]	**REFERENCES**
4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene di-acetate; 4-(1-hydroxy-2(methylamino)ethyl) -1,2-phenylene bis(2-methylpropanoate) [diisobutyryl]; **4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene dipropionate**; and	could be used to form the epinephrine prodrug compounds "4-[1-hydroxy-2-(methylamino)ethyl] -1,2-phenylene diacetate" and "4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene dipropionate".
[G2-3C] a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein the compound is formulated in a unit dosage form as a rapidly dissolving film.	********** **Truelove 3 (EX1008), Almoazen Paper (EX1022) & Ashraf (EX1003)** See discussion above got [G2-1A] above.

GROUND 3

GROUND 3 – Truelove 1, Truelove 3, Almoazen Paper, Ashraf, Fuchs, Florence and Schobel	
CLAIMS [**G**round # - **C**laim **ID**]	**REFERENCES**
Claim 1. [G3-1A] A compound formulated as a pharmaceutical composition in a unit dosage form configured for sublingual or buccal administration	**Truelove 1 (EX1002) , Truelove 3 (EX1008), Almoazen Paper (EX1022) & Ashraf (EX1003)** See discussions in [G1-1A] and [G2-1A] above. **Fuchs (EX1004)** Fuchs (EX1004) teaches unit dosage films (EX1004, 2:65-5:6) and provides many examples of various suitable film compositions having various characteristics (EX1004, 5:7-14:24). See also, EX1001, 2:39-46. **Schobel (EX1021)** Schobel (EX1021) teaches the use and methods of making oral rapidly dissolving films for delivery of epinephrine compositions including epinephrine prodrugs to the oral mucosa. *See, e.g.,* EX1021, 1:17-46 (epinephrine in films), 13:37-67 (rapidly dissolving films), 13:15-67 & 16:57-27:2 (oral dissolving films), 14:13-18 (drug in form of prodrug), 15:62-65 & 45:19-20 (ester prodrugs of epinephrine).

GROUND 3 – Truelove 1, Truelove 3, Almoazen Paper, Ashraf, Fuchs, Florence and Schobel	
CLAIMS [**G**round # - **C**laim **ID**]	**REFERENCES**
[G3-1B] of a Formula:  wherein R is selected from the group consisting of: — *** **$CH_2CH_2CH_3$**, *** or a pharmaceutically acceptable salt thereof,	********** **Truelove 1 (EX1002) & Truelove 3 (EX1008)** A POSA would have understood that Truelove 1, Table 3 and Truelove 3, Table 3 each disclose the diester promoiety where the R substituent is - **$CH_2CH_2CH_3$**, and that this promoiety could be used to form the recited epinephrine prodrug compound. See discussions in [G1-1A] and [G2-1A] above.
[G3-1C] wherein said compound has a **Log P value in the range of about 0.5-6.0** and	********** **Ashraf (EX1003)** "Satisfactory oral [mucosal] absorption of drugs has been observed over a wide range of **log P** (octanol/water partition coefficient) **values of 1 to 5**." (EX1003, p. 35, 2nd col., emphasis added).

GROUND 3 – Truelove 1, Truelove 3, Almoazen Paper, Ashraf, Fuchs, Florence and Schobel	
CLAIMS [**G**round # - **C**laim **ID**]	**REFERENCES**
	The inherent Log P of the claim 1epinephrine compound with the ester promoiety **R = -$CH_2CH_2CH_3$** is +0.8. See, '437 Patent (EX1001), Table 1, 5:29. **Florence (EX1015)** Florence (EX1015) at Table 9.1, p. 350, teaches that the ideal log P values for buccal absorption typically range in bases from 3.52 (dissociated) to 5.52 (undissociated) and in acids 4.19 (undissociated), varying based on the chemical characteristics of the absorbing molecule. ********** **Truelove 1 (EX1002) , Truelove 3 (EX1008), Almoazen Paper (EX1022) & Ashraf (EX1003)**
[G3-1D] wherein the compound is formulated in a unit dosage form as a rapidly dissolving film and	See discussions in [G1-1A] and [G2-1A] above. **Fuchs (EX1004) & Schobel (EX1021)** See discussion in [G3-1A] above. **********
[G3-1E] has a **half-life $t_{1/2}$ range from 1-6 minutes**.	**Truelove 1 (EX1002) & Truelove 3 (EX1008)** See discussions in [G1-1E] and [G2-1E] above.

GROUND 3 – Truelove 1, Truelove 3, Almoazen Paper, Ashraf, Fuchs, Florence and Schobel	
CLAIMS [**G**round # - **C**laim **ID**]	**REFERENCES**
Claim 2. [G3-2A] A compound of a Formula  wherein R is selected from the group consisting of: **CH_3**, **CH_2CH_3** and $CH(CH_3)_2$	**Truelove 1 (EX1002) & Truelove 3 (EX1008)** A POSA would have understood that Truelove 1, Table 3 and Truelove 3, Table 3 each disclose the diester promoieties where the R substituents are - **CH_3** and -**CH_2CH_3**, and that these promoieties could be used to form the recited epinephrine prodrug compounds. See discussions in [G1-2A] and [G2-2A] above.

GROUND 3 – Truelove 1, Truelove 3, Almoazen Paper, Ashraf, Fuchs, Florence and Schobel	
CLAIMS [**G**round # - **C**laim **ID**]	**REFERENCES**
[G3-2B] wherein the compound is formulated in a unit dosage form as a sublingual or buccal administration and wherein the compound is formulated in a unit dosage form as a rapidly dissolving film and	********** **Truelove 1 (EX1002) , Truelove 3 (EX1008), Almoazen Paper (EX1022) & Ashraf (EX1003)** See discussions in [G1-1A] and [G2-1A] above. **Fuchs (EX1004) & Schobel (EX1021)** See discussion in [G3-1A] above.
[G3-2C] has a **half-life $t_{1/2}$ range from 1-6 minutes**.	********** **Truelove 1 (EX1002) & Truelove 3 (EX1008)** See discussions in [G1-1C] and [G2-1C] above.

GROUND 3 – Truelove 1, Truelove 3, Almoazen Paper, Ashraf, Fuchs, Florence and Schobel	
CLAIMS [**G**round # - **C**laim **ID**]	**REFERENCES**
Claim 3. [G3-3A] The compound of claim 2,	See discussion for Ground 2, claim 2 above.
[G3-3B] wherein the compound is selected from the group consisting of: **4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene di-acetate**; 4-(1-hydroxy-2(methylamino)ethyl)-1,2-phenylene bis(2-methylpropanoate); **4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene dipropionate**; and	********** **Truelove 1 (EX1002) & Truelove 3 (EX1008)** See discussion in [G1-3B] and [G2-3B] above that EX1002, Table 3 and EX1008, Table 3 disclose the ester promoieties that would form the following recited compounds: "4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene di-acetate" and "4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene dipropionate".

GROUND 3 – Truelove 1, Truelove 3, Almoazen Paper, Ashraf, Fuchs, Florence and Schobel	
CLAIMS [**G**round # - **C**laim **ID**]	**REFERENCES**
[G3-3C] a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein the compound is formulated in a unit dosage form as a rapidly dissolving film.	********** **Truelove 1 (EX1002) , Truelove 3 (EX1008), Almoazen Paper (EX1022) & Ashraf (EX1003)** See discussions in [G1-1A] and [G2-1A] above. **Fuchs (EX1004) & Schobel (EX1021)** See discussion in [G3-1A] above.