



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|------------------------------|-------------|----------------------|---------------------|------------------|
| 13/039,105 | 03/02/2011 | Genesis M. BACANI | PRD2962USDIV1 | 1145 |
| 27777 | 7590 | 12/16/2016 | EXAMINER | |
| JOSEPH F. SHIRTZ | | | OTTON, ALICIA L | |
| JOHNSON & JOHNSON | | | ART UNIT | |
| ONE JOHNSON & JOHNSON PLAZA | | | PAPER NUMBER | |
| NEW BRUNSWICK, NJ 08933-7003 | | | 1626 | |
| | | | NOTIFICATION DATE | DELIVERY MODE |
| | | | 12/16/2016 | ELECTRONIC |

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

jnjuspatent@corus.jnj.com
lhowd@its.jnj.com
pair_jnj@firsttofile.com

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte GENESIS M. BACANI, DIEGO BROGGINI, EUGENE Y. CHEUNG, CHRISTA C. CHROVIAN, XIAOHU DENG, ANNE M. FOURI, LAURENT GOMEZ, CHERYL A. GRICE, AARON M. KEARNEY, ADRIENNE M. LANDRY-BAYLE, ALICE LEE-DUTRA, JIMMY T. LIANG, SUSANNE LOCHNER, NEELAKANDHA S. MANI, ALEJANDRO SANTILLÁN JR., KATHLEEN SAPPEY, KIA SEPASSI, VIRGINIA M. TANIS, ALVAH T. WICKBOLDT, JOHN J.M. WIENER, and HARTMUT ZINSER¹

Appeal 2015-005029
Application 13/039,105
Technology Center 1600

Before MELANIE L. McCOLLUM, JOHN G. NEW, and RACHEL H. TOWNSEND, *Administrative Patent Judges*.

TOWNSEND, *Administrative Patent Judge*.

DECISION ON APPEAL

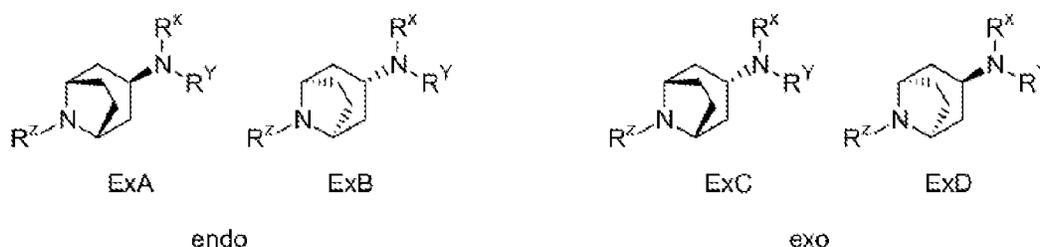
This is an appeal under 35 U.S.C. § 134 involving claims to a method for synthesizing an endo amine from an oxime in a single step acetylation-reduction, which have been rejected as obvious. We have jurisdiction under 35 U.S.C. § 6(b).

¹ Appellants identify the Real Party in Interest as Janssen Pharmaceutica NV. (Appeal Br. 3.)

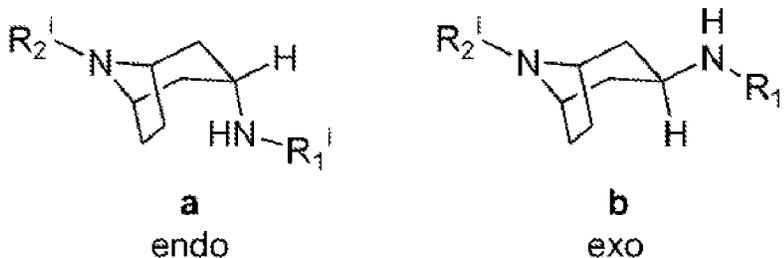
We affirm.

STATEMENT OF THE CASE

“Compounds that incorporate amines such as ExA, ExB, ExC, and ExD, which are listed below, are described as ‘endo’ or ‘exo’ in their chemical name to denote the orientation of the two-methylene bridge with respect to the functionalized exocyclic amine.” (Spec. 21.)



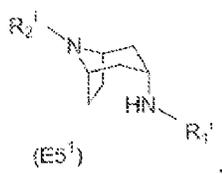
Bicyclic substituted 8-aza-bicyclo[3.2.1]oct-3-ylamines such as depicted below (endo **a** and exo **b**) are integral intermediates utilized in a variety of drugs. (Spec. 66.)



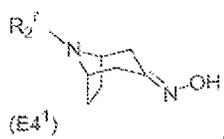
“Several methods have been developed to synthesize endo and/or exo substituted 8-aza-bicyclo[3.2.1]oct-3-ylamines **a** and **b**, but a highly selective synthesis of the endo form is desirable.” (*Id.*) Appellants’ invention is directed to such a selective synthesis method. (*Id.*)

Claims 1–5 are on appeal. Claim 1 is representative and reads as follows:

1. A method for synthesizing an endo amine E5¹



comprising an acetylation-reduction of oxime E4¹



by reacting said oxime E4¹ with a carboxylic acid anhydride and hydrogen in the presence of a hydrogenation catalyst, wherein

R₁ⁱ is one of C₁₋₆alkylC(O)-, arylC(O)- where said moiety C₁₋₆alkyl is linear or branched, and said aryl and said C₁₋₆alkyl moieties are optionally and independently substituted with at least one substituent in the group of halo and linear or branched C₁₋₆alkyl;

R₂ⁱ is one of C₁₋₁₀alkyl, -CH₂aryl, -S(O)₂aryl, and -S(O)₂C₁₋₆alkyl, where said C₁₋₁₀alkyl moiety is linear or branched, and said C₁₋₁₀alkyl and said aryl moieties are optionally substituted with at least one substituent in the group of halo and C₁₋₆alkyl;

R₂ⁱ is one of H and R₂^{i'}; and

wherein endo amine E5¹ is obtained in high selectivity with respect to the exo isomer of said amine.

(Appeal Br. 16.)

The following ground of rejection by the Examiner is before us on review:

Claims 1–5 under 35 U.S.C. § 103 as unpatentable over Hutt,² Bagley,³ and Tafesh.⁴

DISCUSSION

The Examiner finds that Hutt teaches a method of making both the endo and exo forms of 3-acetyl-8-azabicyclo[3.2.1]octane of the bicyclo formula E

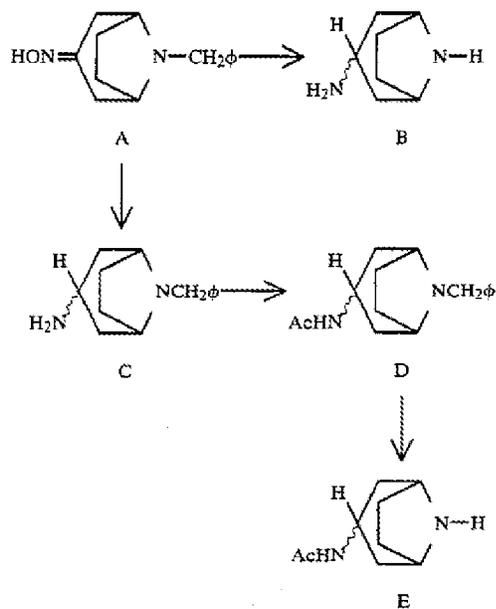


from the known starting material 8-(phenylmethyl)-8-azabicyclo[3.2.1]octan-3-one oxime. (Final Action 4; Ans. 4.) The reaction sequence is summarily depicted in Hutt as follows:

² Hutt et al., US 4,571,396, issued Feb. 18, 1986.

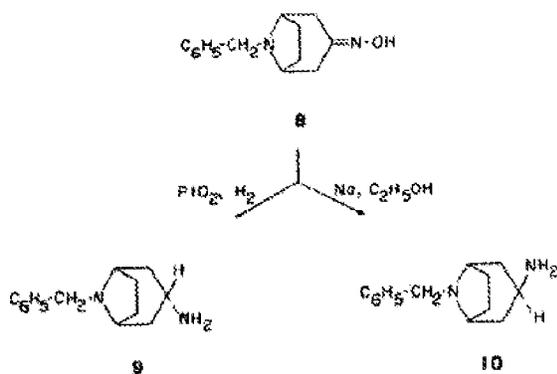
³ Bagley et al., *Isomeric Tropane Analogues of Histamine H₂-Receptor Antagonists*, 19 J. Heterocyclic Chem., 485–488 (1982).

⁴ Tafesh et al., US 5,220,063, issued June 15, 1993.



, but is noted to be

described in detail in Bagley as follows:



, where the oxime

(structure A in Hutt or structure 8 in Bagley) is reduced using platinum oxide-hydrogen to obtain the endo reduced form or is reduced with sodium and ethanol to obtain the exo reduced form and then is subsequently acylated. (Final Action 5; Ans. 5–6.) The Examiner further explains that, while Bagley describes the subsequent acylation of the reduced forms, Hutt teaches a different acylation by reaction “with acetyl chloride and acetonitrile at room temperature for two hours, which yielded the 3-

reaction with formation of the acylated endo product in high selectivity” (Appeal Br. 8) is unavailing. “[O]ne cannot show non-obviousness by attacking references individually where ... the rejections are based on combinations of references.” *In re Keller*, 642 F.2d 413, 426 (CCPA 1981). The Examiner relied upon Tafesh for suggesting a one-step acetylation-reduction reaction was obvious to convert the oxime compounds disclosed in Hutt. Thus, it is of no moment that neither Hutt nor Bagley teach or suggest a one-step acetylation-reduction reaction.

Moreover, we do not find persuasive Appellants’ argument that Tafesh does not support modification of the Hutt process to a single step reduction-acylation process that has endo selectivity. (Appeal Br. 9; Reply Br. 9–10.) According to Appellants, the modification is not supported because Tafesh does not teach isomeric selectivity of its one-step process. (*Id.*) We do not disagree with Appellants that Tafesh does not describe isomeric selectivity of its process—the compounds reacted and produced in Tafesh are not bridged heterocycles capable of exhibiting the isomerism of the compound in Hutt. However, we do not find that fact to be material.

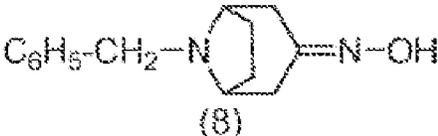
Tafesh teaches that, in the one-step acetylation-reduction reaction of an oxime, a hydrogenation catalyst that is a transition metal catalyst is employed along with a “sufficient quantity” of hydrogen and a carboxylic acid anhydride acyl donor. (Tafesh 4:17–51.) One of the transition metal hydrogenation catalysts that may be selected is platinum (Tafesh 4:45–51), which is the same catalyst that Hutt/Bagley teaches achieves endo selectivity (Bagley 485–86). Bagley teaches that the processing steps after reduction of the oxime would not be expected to change the endo configuration. (*Id.*)

(noting that after reducing the oxime “[t]he remaining synthetic transformations involved in conversion of the primary amines 9 [the endo configuration] and 10 [the exo configuration] (Scheme II) would not be expected to alter configuration at C-3”).) And indeed, Appellants’ Specification recognizes that Bagley describes “selective *endo* reduction of oxime E4.” (Spec. 69.) We find the modification of the Hutt method with the Tafesh one-step process that would be a more efficient process in requiring a single step would also inherently achieve the same endo specificity claimed in light of Tafesh’s teaching of using the same catalyst that Hutt/Bagley teaches achieves endo selectivity.

The motivation to combine the prior art does not have to be for the same reasons as that of Appellants to establish obviousness. *In re Kemps*, 97 F.3d 1427, 1430 (Fed. Cir. 1996); *In re Lintner*, 458 F.2d 1013, 1016 (CCPA 1972) (“The fact that appellant uses sugar for a different purpose does not alter the conclusion that its use in a prior art composition would be prima facie obvious from the purpose disclosed in the references.”). The reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. *Id.* In other words, whether or not Tafesh teaches endo selectivity, it teaches an efficient acylating-reduction reaction to be used with an oxime, which Bagley indicates would inherently result in endo selectivity for an azobicyclic oxime structure like the one recited in claim 1.

Appellants’ argument that the compounds of Tafesh have “steric differences” and “electronic differences” as compared to the Hutt compounds and thus one of ordinary skill in the art would not have a

reasonable expectation of success in substituting a one-step acylation-reduction reaction for the two part reaction taught in Hutt (Appeal Br. 9–10) is unavailing. The oxime moiety of Hutt to be reduced, like Tafesh, includes a nitrogen that is double bonded to a branched carbon; it is not a double bond, for example, embedded in a cyclic structure. (See, Appeal Br. 8 (providing a comparison chart, (excerpted below):

| | |
|--|--|
| Bagley (p. 485, right column; p. 486, left column) |  (8) |
| Tafesh (col. 4) | $\begin{array}{c} \text{O} \quad \text{N-R}_1 \\ \parallel \quad \parallel \\ \text{Ar-C-C-R}_2 \end{array}$ |

Hutt teaches that the same hydrogenation catalyst used in Tafesh is capable of reducing the oxime on an azobicyclo ring in the presence of hydrogen and to do so with a specific isomeric configuration. Other than asserting there are structural differences (the Tafesh compound does not exhibit isomerism) and electronic differences (the Tafesh compound is “comparatively much more electron-withdrawing versus [the] azobicyclo moiety”) (Appeal Br. 9–10), Appellants have not provided evidence that would countermand the expectation of success supplied in light of the teaching of Hutt and Tafesh that the reduction at the oxime moiety projecting from the azobicyclo ring, like the oxime moiety projecting from the linear carbon chain of the Tafesh oxime molecule (that includes an aromatic ring compound at one end of the

structure like the Hutt compound), is capable of being reduced using the same hydrogenation catalyst, whether in a single step acylation-reduction reaction or as a separate step prior to acylation.

Appellants argument that the “reaction conditions” are different between Tafesh and Hutt is also unpersuasive in light of the fact that claim 1 does not recite reaction conditions, and it would have been obvious to one of skill in the art to optimize temperature and pressure conditions to effect a single step reaction as compared to the two-step reaction taught by Hutt. *In re Antonie*, 559 F.2d 618, 620 (CCPA 1977) (“[T]he discovery of an optimum value of a variable in a known process is normally obvious.”)

Appellants’ position that “conventional synthetic methodologies at the time of the invention were found to lead to poor endo selectivity and/or mixtures with impurity ketones and/or dimers” (Appeal Br. 10; Reply Br. 10) and thus the claimed invention involves unpredictable technology is also unpersuasive. As the Examiner aptly explained, Appellants’ disclosure referring to “conventional synthetic conditions” does not make clear what these conditions were that led to poor selectivity, and Hutt/Bagley teaches a reduction process using a platinum hydrogenation catalyst with sufficient hydrogen results in good selectivity for the endo isomer. (Ans. 11; Hutt 18 (Example I (noting use without further purification)).) Bagley indicates that after reducing the oxime in the manner that Hutt uses, further reactions are not expected to change the isomeric form. (Bagley 486.) And Hutt exemplifies that expectation. (Hutt 17–18 (Examples F-I).) And indeed, Appellants’ Specification recognizes that Bagley describes “selective *endo* reduction of oxime E4.” (Spec. 69.) Consequently, Bagley and Hutt suggest

that selectivity for the endo isomer of an oxime is dependent on using the transition metal hydrogenation catalyst and there is insufficient reason provided by Appellants to lead one not to expect this selectivity when using that catalyst in a single step reduction-acylation reaction, such as is taught by Tafesh, for oximes using the same catalyst other than a difference in structures between the oxime of Tafesh and Hutt. However, as noted above, the fact that there is a difference in structure does not explain why one of ordinary skill in the art would not expect the reaction to proceed precisely as suggested by Hutt, with endo specificity due to the use of the transition metal hydrogenation catalyst.

We also do not find persuasive Appellants' argument that the Examiner's rejection is based on improper hindsight reconstruction because it "rel[ies] on features of the invention," *i.e.*, reducing the number of synthetic steps (Reply Br. 12; Appeal Br. 11.) A single step acylation-reduction of an oxime is not knowledge "gleaned only from the [Appellants'] disclosure," but rather is taught by Tafesh. Thus, as the Examiner properly noted, the "reconstruction" here in making the obviousness rejection was proper as it took into account "knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned **only** from the [Appellants'] disclosure." *In re McLaughlin*, 443 F.2d 1392, 1395 (CCPA 1971) (emphasis added).

Claims 2–5 have not been argued separately and therefore fall with claim 1. 37 C.F.R. § 41.37(c)(1)(iv).

Appeal 2015-005029
Application 13/039,105

SUMMARY

We affirm the rejection of claims 1–5 under 35 U.S.C. § 103 as unpatentable over Hutt, Bagley, and Tafesh.

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED