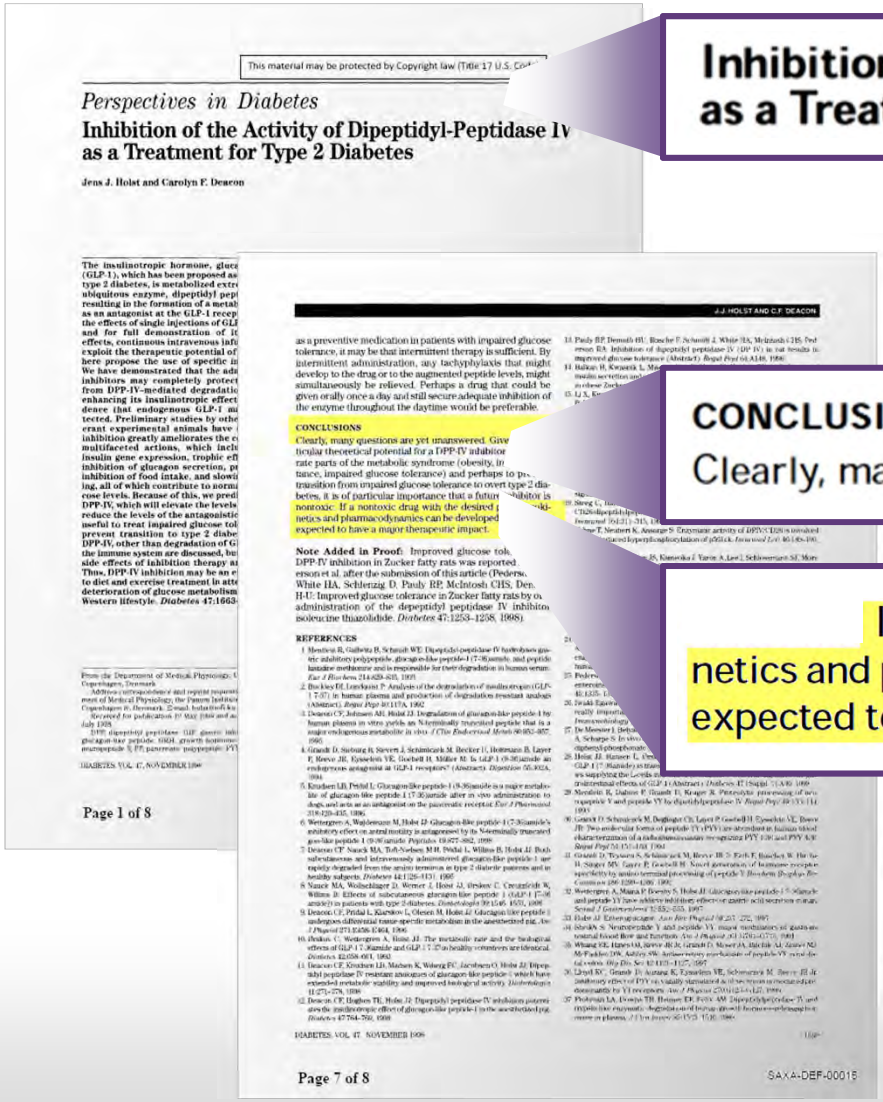
Mylan Pharmaceuticals Inc.,
v.
AstraZeneca AB

Case IPR2015-01340

Patent RE44,186

Holst and Deacon (1998)



Perspectives in Diabetes

Inhibition of the Activity of Dipeptidyl-Peptidase IV as a Treatment for Type 2 Diabetes

Jens J. Holst and Carolyn F. Deacon

Page 1 of 8

J.J. HOLST AND C.F. DEACON

CONCLUSIONS

Clearly, many questions are yet unanswered. Given ... particular theoretical potential for a DPP-IV inhibitor ... rate parts of the metabolic syndrome (obesity, ... tance, impaired glucose tolerance) and perhaps to ... transition from impaired glucose tolerance to overt type 2 dia... betes, it is of particular importance that a future ... inhibitor is nontoxic. If a nontoxic drug with the desired ... netics and pharmacodynamics can be developed ... expected to have a major therapeutic impact.

Note Added in Proof: Improved glucose tol... DPP-IV inhibition in Zucker fatty rats was reported ... erson et al. after the submission of this article (Pederse... White HA, Schlenzig D, Pauly RP, McIntosh CHS, Den... H-U: Improved glucose tolerance in Zucker fatty rats by o... administration of the dipeptidyl peptidase IV inhibito... isoleucine thiazolidide. *Diabetes* 47:1253–1258, 1998).

REFERENCES

Page 7 of 8

SAXA-DEF-00018

Inhibition of the Activity of Dipeptidyl-Peptidase IV as a Treatment for Type 2 Diabetes

CONCLUSIONS

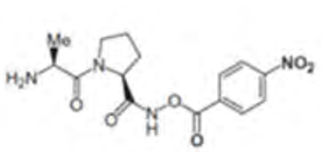
Clearly, many questions are yet unanswered.

If a nontoxic drug with the desired pharmacokinetics and pharmacodynamics can be developed, it would be expected to have a major therapeutic impact.

Ex. 2005 at 7

Ex. 2056 ¶ 86; *see also* Paper 7 at 9; *see* Paper 28 at 6 (citing Ex. 2057 ¶¶ 37-39)

Prior Art DPP-4 Inhibitors: None FDA-Approved



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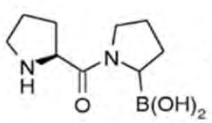

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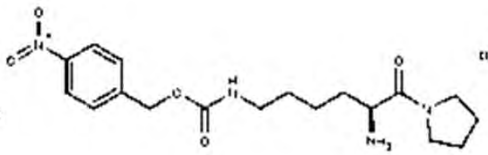

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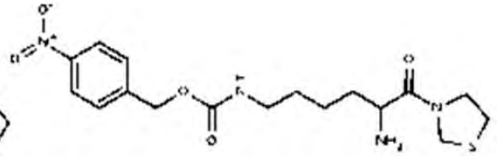

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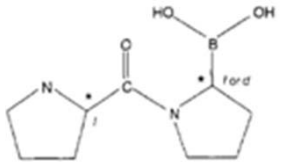

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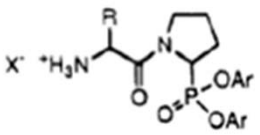

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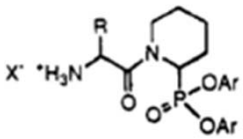

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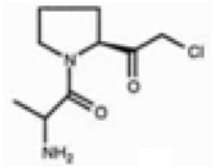

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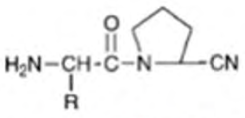

Arg(PMC)-Pyrr-2-CN
Arg-Pyrr-2-CN
Ala-Pyrr-2-CN
Phe-Pyrr-2-CN

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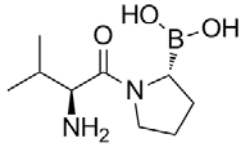

PT-100 (Talabostat)

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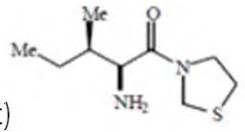

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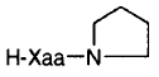

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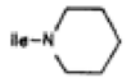

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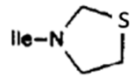

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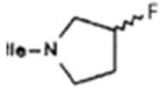

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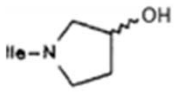

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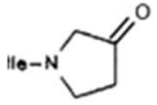

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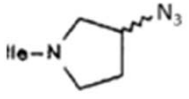

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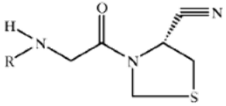

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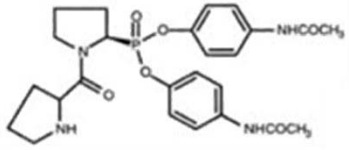

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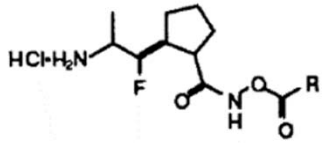

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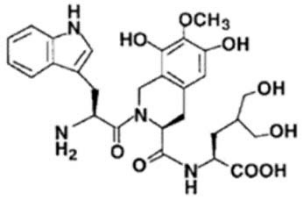

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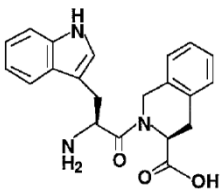

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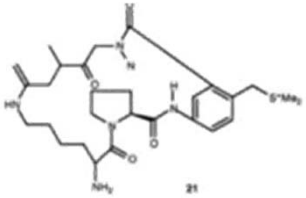

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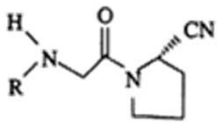

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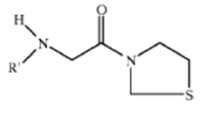

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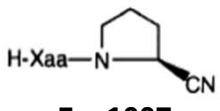

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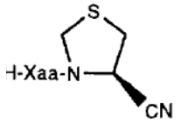

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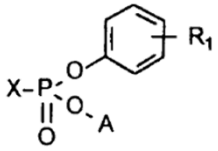

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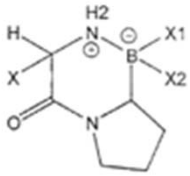

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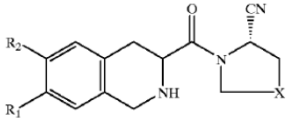
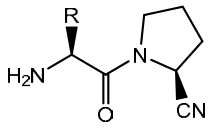


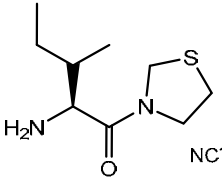
X is CH_2, S, O, or $C(CH_3)_2$

Ex. 2156



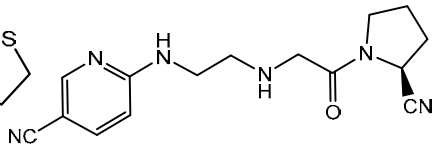
Ashworth I

Ex. 1007



P32/98

Ex. 2009



NVP-DPP728

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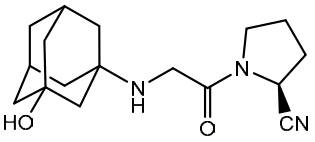
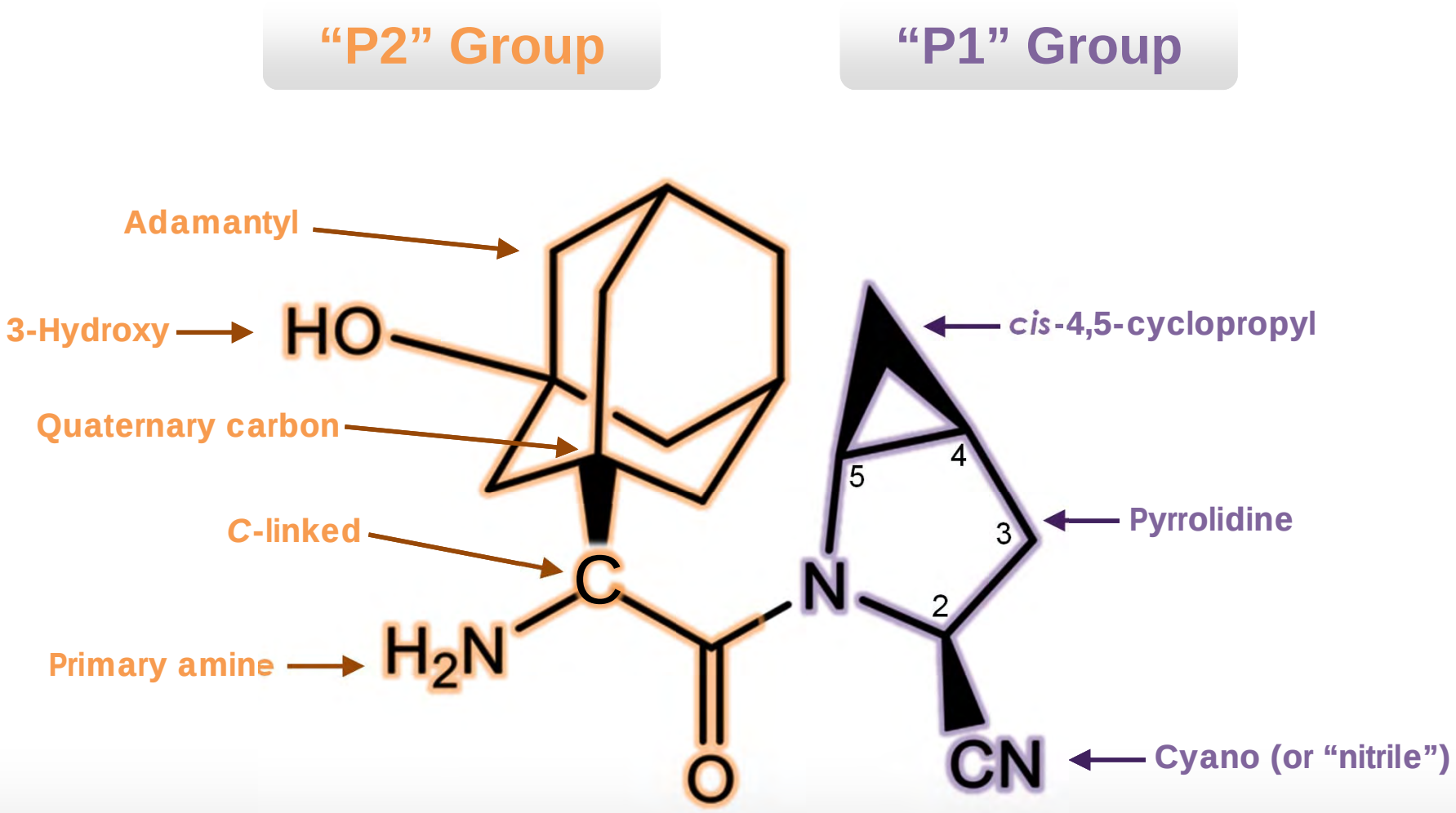


Vildagliptin

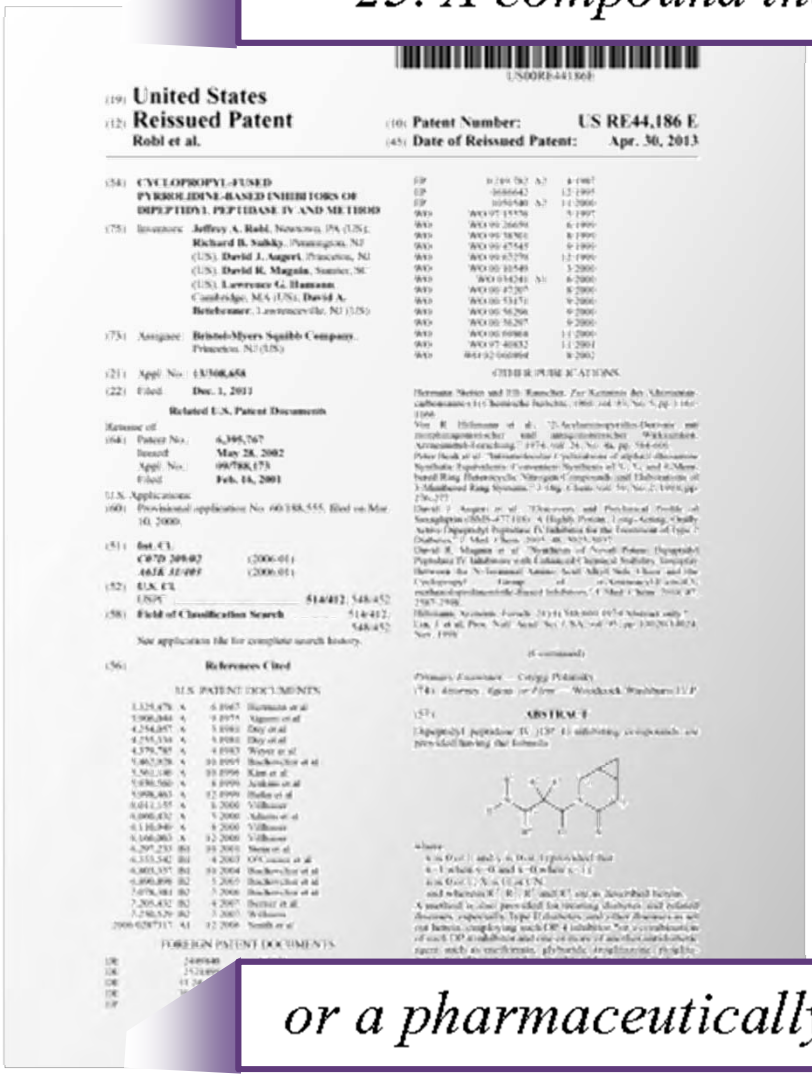
Ex. 2013

Saxagliptin



Claim 25

25. A compound that is



(19) **United States**
(12) **Reissued Patent**
Robl et al.

(10) **Patent Number: US RE44,186 E**
(45) **Date of Reissued Patent: Apr. 30, 2013**

(54) **CYCLOPROPYL-FUSED PYRROLIDINE-BASED INHIBITORS OF DIPEPTIDYL PEPTIDASE IV AND METHOD**

(75) Inventors: **Jeffrey A. Robl**, Newtown, PA (US); **Richard B. Sulsky**, Pennington, NJ (US); **David J. Augeri**, Princeton, NJ (US); **David R. Magnin**, Sumter, SC (US); **Lawrence G. Hamann**, Cambridge, MA (US); **David A. Betebenner**, Lawrenceville, NJ (US)

(73) Assignee: **Bristol-Myers Squibb Company**, Princeton, NJ (US)

(21) Appl. No.: **13/308,658**

(22) Filed: **Dec. 1, 2011**

Related U.S. Patent Documents

Reissue of:
(64) Patent No.: **6,395,767**
Issued: **May 28, 2002**
Appl. No.: **09/788,173**
Filed: **Feb. 16, 2001**

U.S. Applications:
(60) Provisional application No. 60/188,555, filed on Mar. 10, 2000.

(51) **Int. Cl.**
C07D 209/02 (2006.01)
A61K 31/401 (2006.01)

(52) **U.S. Cl.**
USPC **514/412**; 548/452

(58) **Field of Classification Search**
..... 514/412; 548/452
See application file for complete search history.

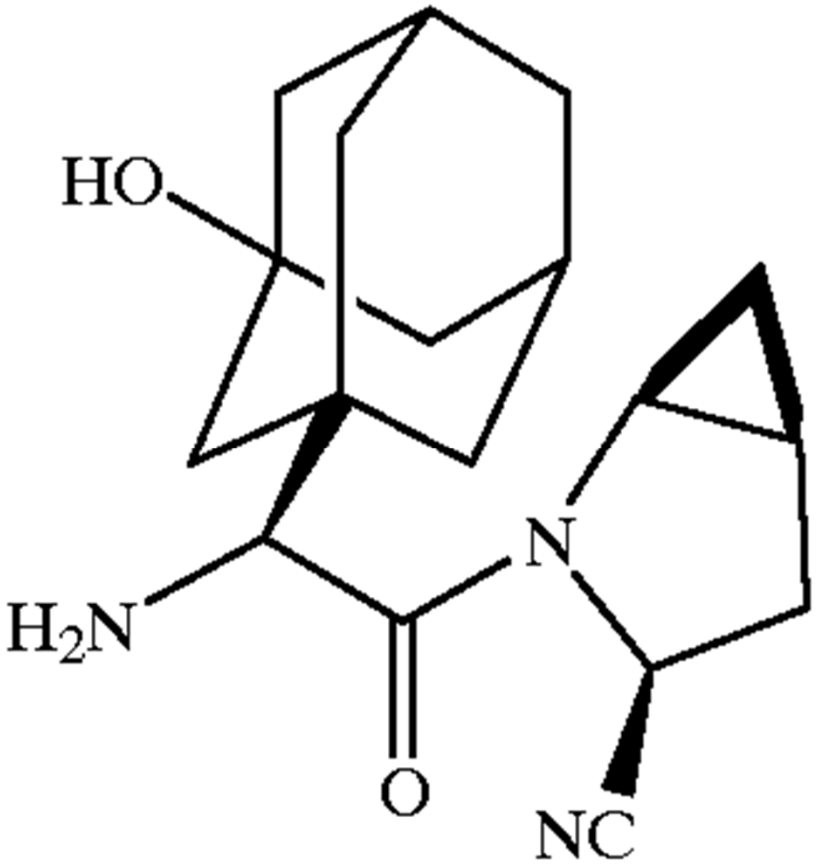
(56) **References Cited**

U.S. PATENT DOCUMENTS

FOREIGN PATENT DOCUMENTS

OTHER PUBLICATIONS

(57) **ABSTRACT**



or a pharmaceutically acceptable salt thereof.

Ex. 1001; Paper 28 at 19

The Experts

Dr. Weber

ANN E WEBER, PHD PAGE 1

ANN E WEBER, PHD

103 Chestnut Street, Apt. 217, Cranford, NJ 07016 | (732) 771-4704 | weberan8@gmail.com

PROFESSIONAL SUMMARY

Accomplished independent consultant and former pharmaceutical executive with a passion for discovering innovative therapeutics to address unmet medical needs. Over 28 years of industrial experience focused on small molecule and peptide drug discovery across therapeutic areas leading to over 40 development candidates, including JANUVIA® (sitagliptin), a treatment for patients with Type 2 diabetes (T2DM), and MARIZEV® (omarigliptin), a once-weekly treatment for T2DM recently approved in Japan; vibegron for the treatment of overactive bladder is in late stage clinical trials. Highly collaborative scientific leader in drug discovery and early development, recognized for building strong teams, setting strategy and managing change. Noted for strong interpersonal skills, talent development, and commitment to advancing women in chemistry.

EXPERIENCE

ANN WEBER PHARMA CONSULTING
December 2015 – present
Independent consultant to biotech and pharma for all aspects of drug discovery including target and lead identification, lead optimization, and development candidate nomination

MERCK & CO
August 1987 – November 2015

Vice President – Lead Optimization Chemistry, Kenilworth, NJ and Boston, MA
November 2013 – November 2015
Responsible for delivering the lead optimization pipeline to the clinic, particularly in the areas of cardiometabolic diseases, infectious diseases, neurological disorders, oncology and asthma; talent recruitment, management and development for department of ~100 lead optimization chemists in Kenilworth and Boston, working in small-molecule and peptide modalities; Cubist integration team co-lead for Discovery Research

Vice President – Kenilworth Discovery Chemistry Site Head, Kenilworth, NJ
September 2011 – October 2013
Discovery of innovative therapeutic agents to treat patients with cardiovascular disease, diabetes, infectious diseases, and neurological disorders; leadership of chemists at Kenilworth site working in Lead Identification, Lead Optimization, and Automated Synthesis & Purification; Joint Steering Committee for Theravance collaboration; leadership and executive sponsorship of strategic initiatives; Six Sigma Executive Black Belt

Vice President – Rahway Discovery Chemistry Site Head, Rahway, NJ
February 2010 – August 2011
Primary focus on the development of new therapies for cardiovascular disease and metabolic disorders; provided leadership for department of ~200 medicinal chemists during re-organization activities following Schering Plough merger; established Rahway Women in Chemistry Lunch, providing networking and leadership opportunities for emerging women leaders across the internal chemistry organization, sponsored the first Merck Women in Chemistry Symposium

Executive Director, Medicinal Chemistry, Rahway, NJ
July 2005 – January 2010
Scientific oversight for teams that identified clinical candidates in the fields of obesity, diabetes, urinary incontinence, and pain; discovery of omarigliptin (approved in Japan Sept 2015), a once weekly agent for diabetes, and vibegron (licensed to Kyorin at Phase III) for urinary incontinence; Diabetes & Obesity Research Licensing Committee; Joint Research Committees for Metabasis and Neuromed collaborations; leadership of Early

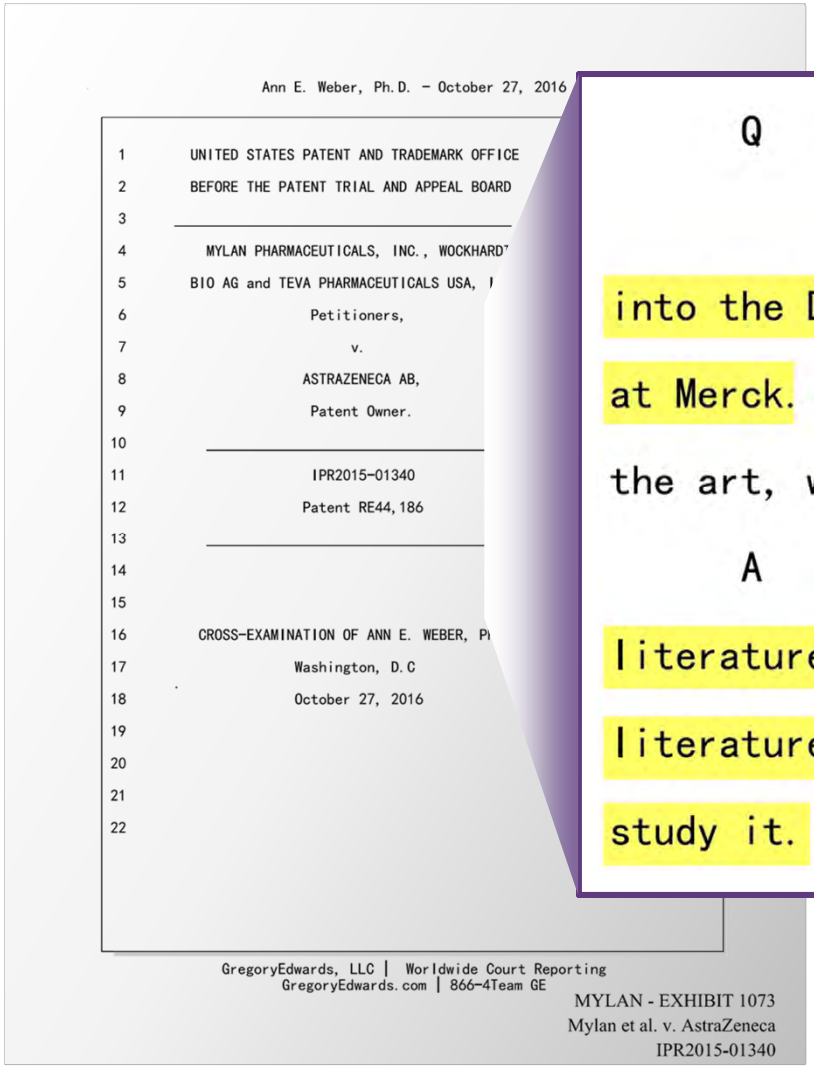
Page 1 of 17

AstraZeneca Exhibit 2210
Mylan v. AstraZeneca
IPR2015-01340

Ex. 2210

- Co-lead of program core team that identified JANUVIA® (sitagliptin)
- Authored/co-authored thirty-eight publications relating to DPP-4 inhibitors
- Co-inventor of thirty-three patents relating to DPP-4 inhibitors
- Presented forty-eight times on DPP-4 inhibitors
- Chaired two symposiums relating to DPP-4 inhibitors
- Vice President of Lead Optimization Chemistry at Merck

Dr. Weber



Ann E. Weber, Ph.D. - October 27, 2016

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS, INC., WOCKHARDT
BIO AG and TEVA PHARMACEUTICALS USA, I

Petitioners,

v.

ASTRAZENECA AB,

Patent Owner.

IPR2015-01340

Patent RE44,186

CROSS-EXAMINATION OF ANN E. WEBER, PI

Washington, D.C

October 27, 2016

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MYLAN - EXHIBIT 1073
Mylan et al. v. AstraZeneca
IPR2015-01340

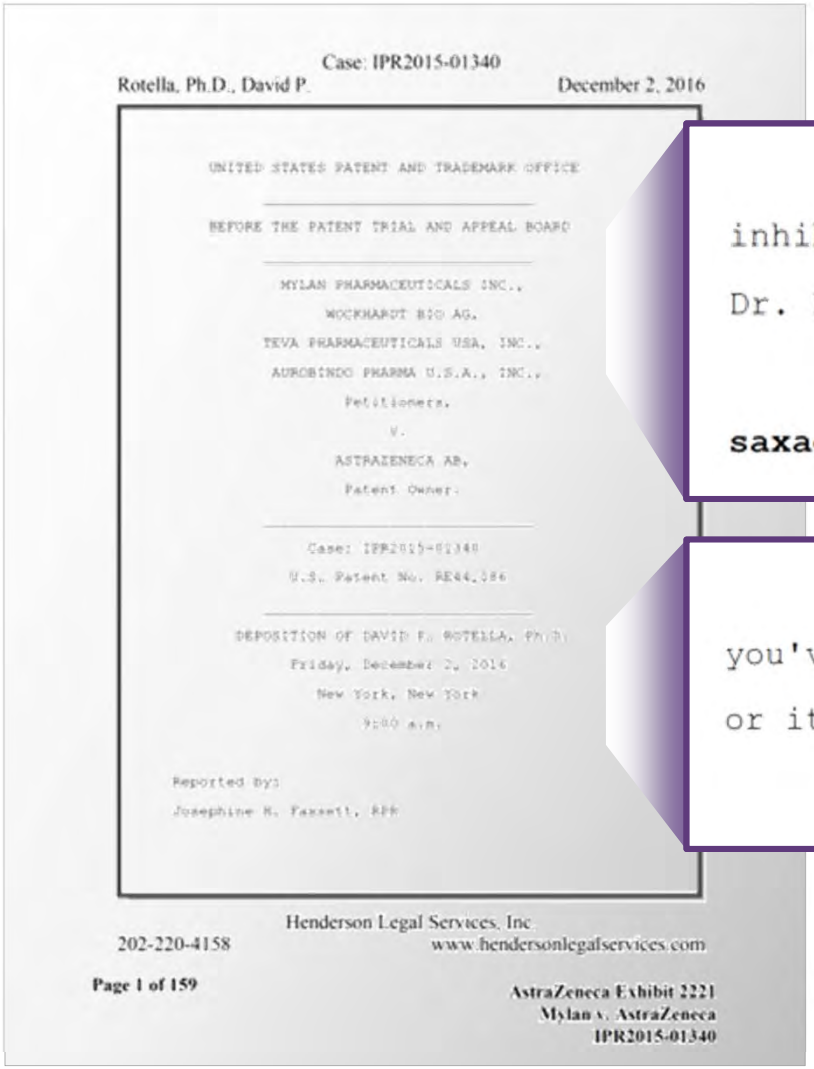
Q Okay.

Now, you had testified that you came into the DPP-4 field, inhibitor field around 2000 at Merck. To get your arms around the state of the art, what was the first thing you did?

A The first thing I did was survey the literature, both the journals and the patent literature, collect all the prior art. Review and study it.

Ex. 1073 (Weber Redirect) at 111:11-19

Dr. Rotella



Case: IPR2015-01340
Rotella, Ph.D., David P. December 2, 2016

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC.,
WOCKHARDT BIO AG,
TEVA PHARMACEUTICALS USA, INC.,
AUROBINDO PHARMA U.S.A., INC.,
Petitioners,
v.
ASTRAZENECA AB,
Patent Owner.

Case: IPR2015-01340
U.S. Patent No. RE44,186

DEPOSITION OF DAVID P. ROTELLA, Ph.D.
Friday, December 2, 2016
New York, New York
9:00 a.m.

Reported by:
Josephine M. Fassett, RPR

Henderson Legal Services, Inc.
202-220-4158 www.hendersonlegalservices.com

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AstraZeneca Exhibit 2221
Mylan v. AstraZeneca
IPR2015-01340

The first work you did on DPP-4 inhibitors was when you joined the group with Dr. Robl and Dr. Hamann at BMS, correct?

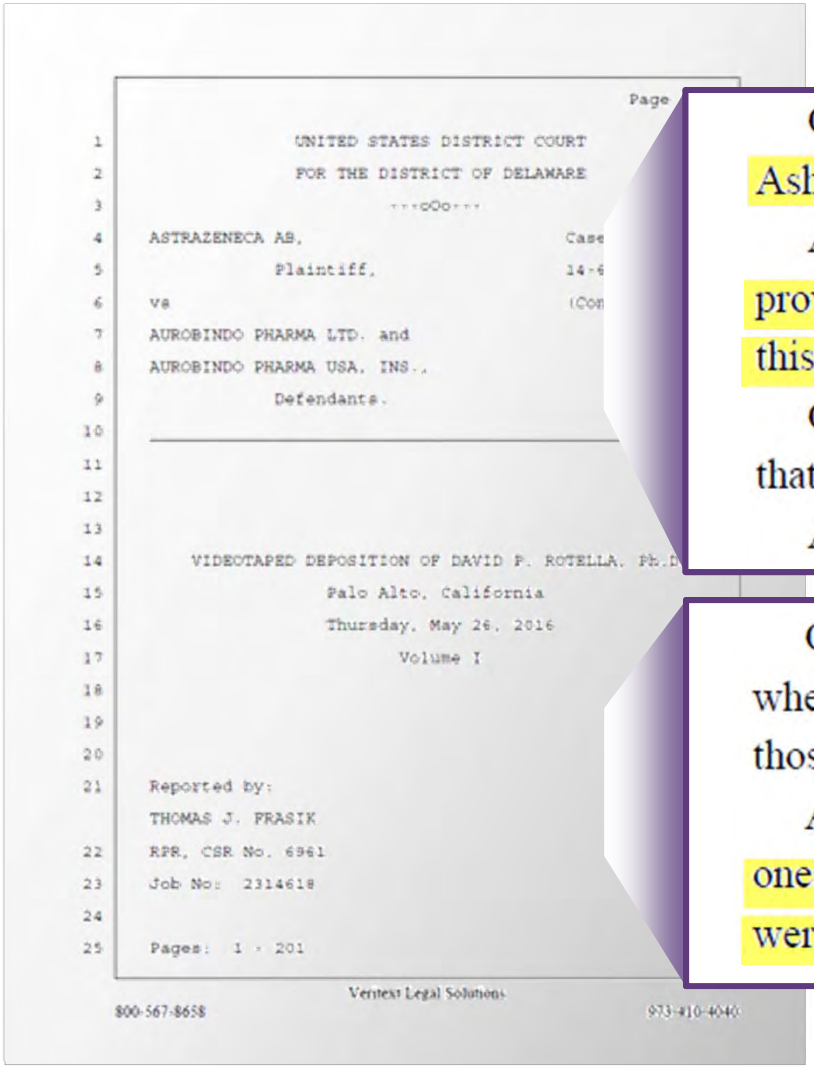
A. Subsequent to the discovery of saxagliptin, yes.

Q. Okay. And none of the work that you've done since leaving BMS is related to DPP-4 or its inhibition, correct?

A. None of my research work.

Paper 62 at Observation 31; Ex. 2221 at 109:4-8, 116:22-25

Dr. Rotella



Page

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE
---oOo---

ASTRAZENECA AB,
Plaintiff,
vs
AURORINDO PHARMA LTD. and
AURORINDO PHARMA USA, INS.,
Defendants.

VIDEOTAPED DEPOSITION OF DAVID P. ROTELLA, Ph.D.
Palo Alto, California
Thursday, May 26, 2016
Volume I

Reported by:
THOMAS J. PRASIK
RPR, CSR No. 6961
Job No: 2314618

Pages: 1 - 201

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Q. All right. How did you become familiar with Ashworth One, if you recall?

A. That was part of the information that I was provided with by Bristol Myers when I began to work on this program as a medicinal chemist.

Q. Okay. And how about the Hanessian publication that you've identified, the 1997 one?

A. The same.

Q. Were there other materials you were provided when you began working on this program at BMS beyond those two, if you recall?

A. Well, I'm reasonably certain that all of the ones I identified were part of the literature that we were provided with as a part of working on that program.

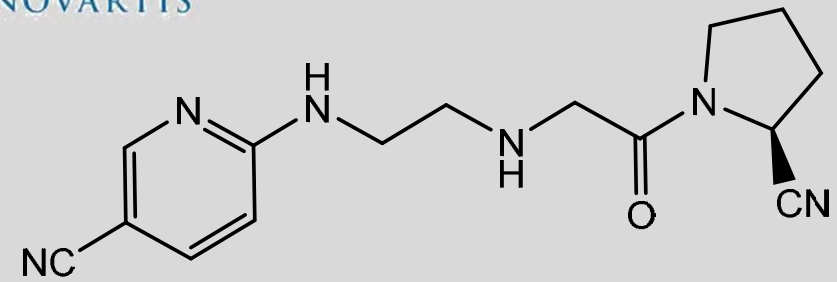
Paper 62 at Observation 31; Ex. 2174 at 125:10-25; Ex. 2221 at 109:14-113:6

Lead Compound Selection

The Principal Prior Art

Clinical Trial Compounds

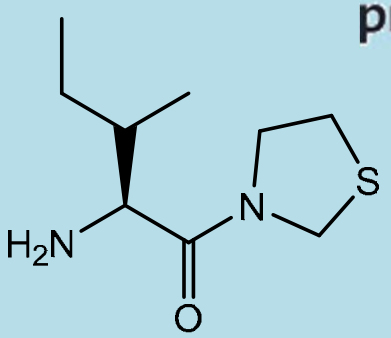
NOVARTIS



NVP-DPP728

Ex. 2016

probiodrug

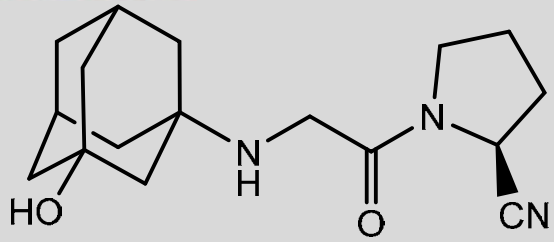


P32/98

Ex. 2078

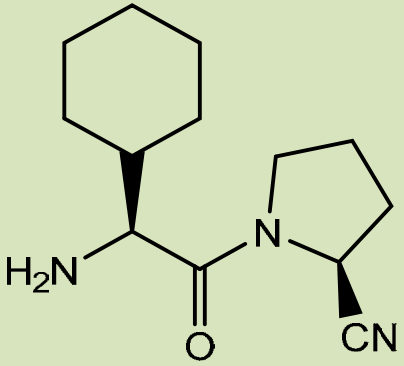
Other Compounds

NOVARTIS



Villhauer-063
Ex. 1

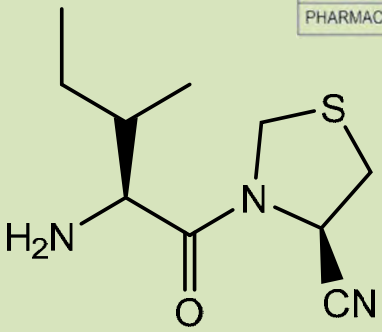
Ex. 2013



Ashworth I
Compound 25

Ex. 1007

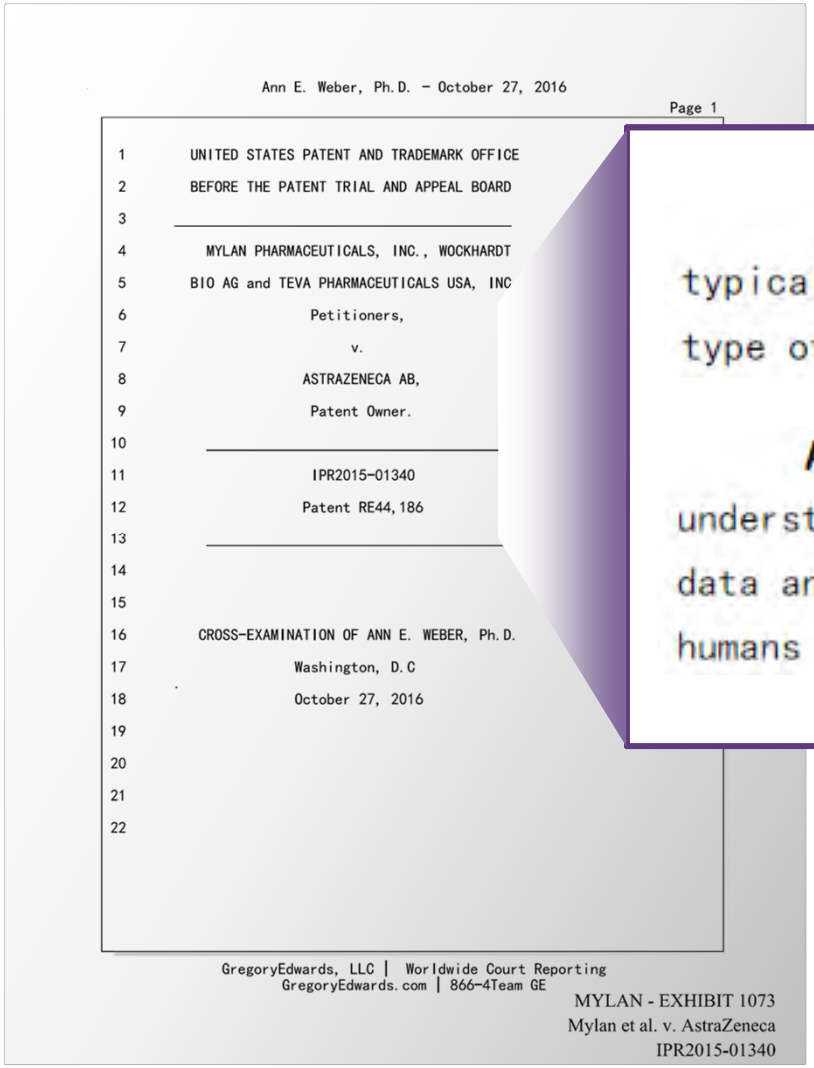
FERRING PHARMACEUTICALS



Ashworth II
Compound 3

Ex. 2001

Dr. Weber



Ann E. Weber, Ph.D. - October 27, 2016

Page 1

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS, INC., WOCKHARDT BIO AG and TEVA PHARMACEUTICALS USA, INC

Petitioners,

v.

ASTRAZENECA AB,

Patent Owner.

IPR2015-01340

Patent RE44,186

CROSS-EXAMINATION OF ANN E. WEBER, Ph.D.

Washington, D.C

October 27, 2016

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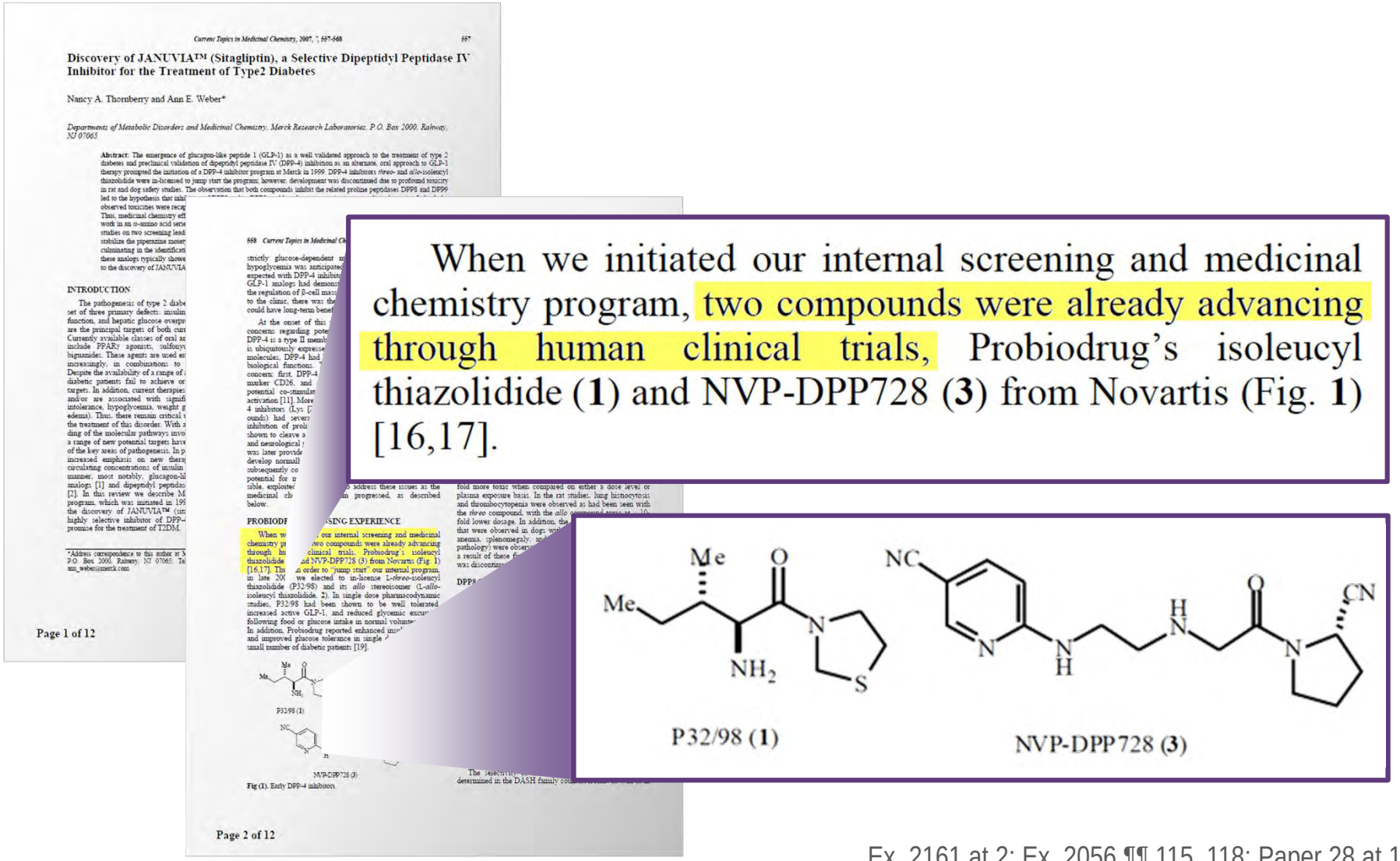
MYLAN - EXHIBIT 1073
Mylan et al. v. AstraZeneca
IPR2015-01340

As a medicinal chemist is there a typical hierarchy to ascribe an importance to that type of data, and if so what is it?

A Absolutely. A medicinal chemist would understand that in vivo data would trump in vitro data and that human clinical data, so data in humans would trump any preclinical in vivo data.

Ex. 1073 (Weber Redirect) at 114:5-14

Weber (2007): Discovery of Januvia™



Current Topics in Medicinal Chemistry, 2007, 7, 557-568 557

Discovery of JANUVIA™ (Sitagliptin), a Selective Dipeptidyl Peptidase IV Inhibitor for the Treatment of Type2 Diabetes

Nancy A. Thornberry and Ann E. Weber*

Departments of Metabolic Disorders and Medicinal Chemistry, Merck Research Laboratories, P.O. Box 2000, Rahway, NJ 07065

Abstract: The emergence of glucagon-like peptide 1 (GLP-1) as a well validated approach to the treatment of type 2 diabetes and preclinical validation of dipeptidyl peptidase IV (DPP-4) inhibition as an alternate, oral approach to GLP-1 therapy prompted the initiation of a DPP-4 inhibitor program at Merck in 1999. DPP-4 inhibitors *threo*- and *allo*-isoleucyl thiazolidide were in-licensed to jump start the program; however, development was discontinued due to profound toxicity in rat and dog safety studies. The observation that both compounds inhibit the related proline peptidases DP8 and DP9 led to the hypothesis that inhi... observed toxicities were recap... Thus, medicinal chemistry eff... work in an α-amino acid serie... studies on two screening lead... stabilize the piperazine moiet... culminating in the identificat... these analogs typically showe... to the discovery of JANUVIA...

INTRODUCTION

The pathogenesis of type 2 diabe... set of three primary defects: insulin... function, and hepatic glucose overpr... are the principal targets of both curr... Currently available classes of oral ag... include PPARγ agonists, sulfonyl... biguanides. These agents are used en... increasingly, in combinations to... Despite the availability of a range of ... diabetic patients fail to achieve or... targets. In addition, current therapies... and/or are associated with signif... intolerance, hypoglycemia, weight g... edema). Thus, there remain critical ... the treatment of this disorder. With a... ding of the molecular pathways invo... a range of new potential targets have... of the key areas of pathogenesis. In p... increased emphasis on new thera... circulating concentrations of insulin... manner, most notably, glucagon-li... analogs [1] and dipeptidyl peptidas... [2]. In this review we describe M... program, which was initiated in 19... the discovery of JANUVIA™ (sit... highly selective inhibitor of DPP-... promise for the treatment of T2DM.

*Address correspondence to this author at ... P.O. Box 2000, Rahway, NJ 07065. Te... ann_weber@merck.com

Page 1 of 12

558 Current Topics in Medicinal Ch...

strictly glucose-dependent m... hypoglycemia was anticipated... expected with DPP-4 inhibit... GLP-1 analogs had demonst... the regulation of β-cell mass... to the clinic, there was the... could have long-term benef...

At the onset of this ... concerns regarding pote... DPP-4 is a type II membr... is ubiquitously expresse... molecules, DPP-4 had ... biological functions. ... concern: first, DPP-4 ... marker CD26, and ... potential co-stimulat... activation [11]. More... 4 inhibitors (Lys [... ounds) had severe ... inhibition of prol... shown to cleave a ... and neurological ... was later provide... develop normall... subsequently co... potential for u... sible, exploste... medicinal ch... below.

PROBIODR... SING EXPERIENCE

When w... our internal screening and medicinal chemistry p... two compounds were already advancing through hu... clinical trials, Probiodrug's isoleucyl thiazolidide ... and NVP-DPP728 (3) from Novartis (Fig. 1) [16,17]. Th... In order to "jump start" our internal program, in late 20... we elected to in-license *L-threo*-isoleucyl thiazolidide (P32/98) and its *allo* stereoisomer (*L-allo*-isoleucyl thiazolidide, 2). In single dose pharmacodynamic studies, P32/98 had been shown to be well tolerated, increased active GLP-1, and reduced glycemic excu... following food or glucose intake in normal volunte... In addition, Probiodrug reported enhanced insu... and improved glucose tolerance in single ... small number of diabetic patients [19].

P32/98 (1)

NVP-DPP728 (3)

Fig (1). Early DPP-4 inhibitors.

The selectivity ... determined in the DASH family ...

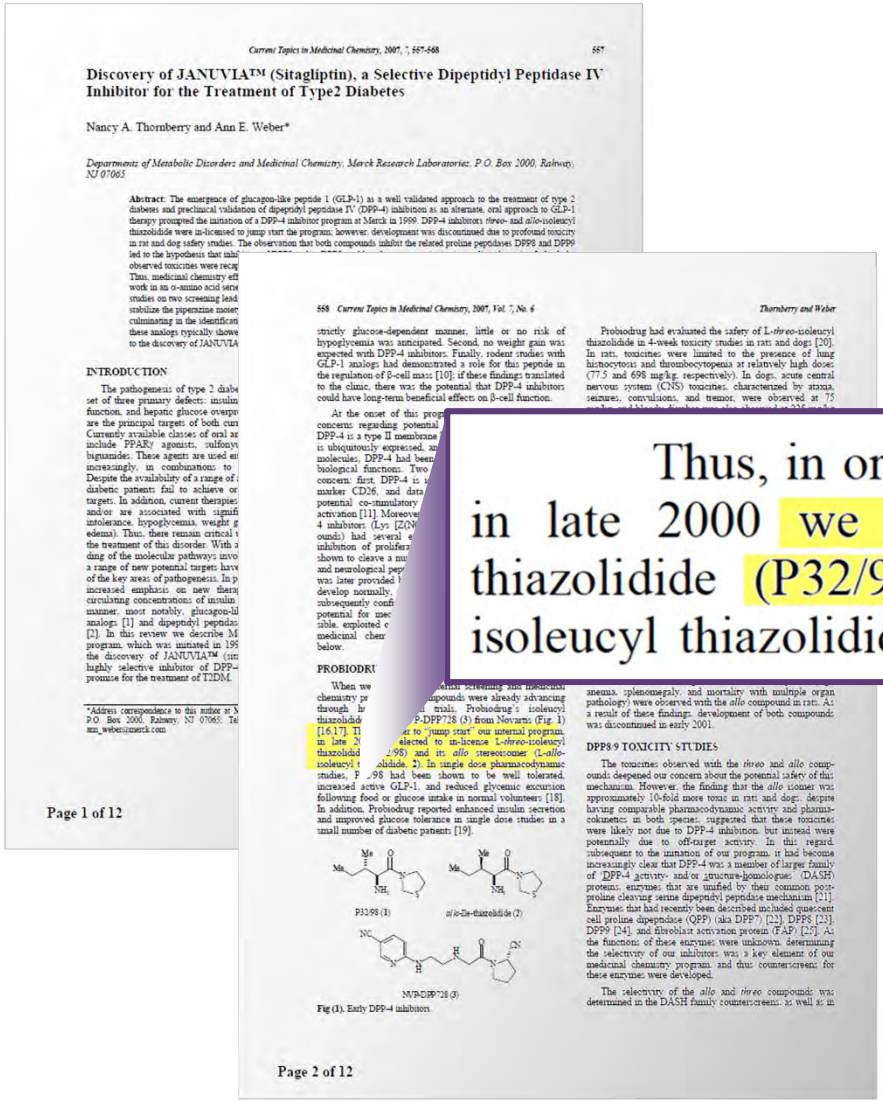
Page 2 of 12

When we initiated our internal screening and medicinal chemistry program, two compounds were already advancing through human clinical trials, Probiodrug's isoleucyl thiazolidide (**1**) and NVP-DPP728 (**3**) from Novartis (Fig. **1**) [16,17].

P32/98 (**1**) NVP-DPP728 (**3**)

Ex. 2161 at 2; Ex. 2056 ¶¶ 115, 118; Paper 28 at 16

Weber (2007): Discovery of Januvia™



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INTRODUCTION

The pathogenesis of type 2 diabe… set of three primary defects: insulin… function, and hepatic glucose overpr… are the principal targets of both curr… Currently available classes of oral ag… include PPARγ agonists, sulfonyl… biguanides. These agents are used en… increasingly, in combinations to… Despite the availability of a range of … diabetic patients fail to achieve or… targets. In addition, current therapies… and/or are associated with signifi… intolerance, hypoglycemia, weight g… edema). Thus, there remain critical … the treatment of this disorder. With a… ding of the molecular pathways invo… a range of new potential targets have… of the key areas of pathogenesis. In p… increased emphasis on new thera… circulating concentrations of insulin… manner, most notably, glucagon-li… analogs [1] and dipeptidyl peptidas… [2]. In this review we describe M… program, which was initiated in 19… the discovery of JANUVIA™ (sit… highly selective inhibitor of DPP-… promise for the treatment of T2DM.

*Address correspondence to this author at … P.O. Box 2000, Rahway, NJ 07065. Te… ann_weber@merck.com

strictly glucose-dependent manner, little or no risk of hypoglycemia was anticipated. Second, no weight gain was expected with DPP-4 inhibitors. Finally, rodent studies with GLP-1 analogs had demonstrated a role for this peptide in the regulation of β-cell mass [10]; if these findings translated to the clinic, there was the potential that DPP-4 inhibitors could have long-term beneficial effects on β-cell function.

At the onset of this prog… concerns regarding potential… DPP-4 is a type II membrane… is ubiquitously expressed, an… molecules, DPP-4 had been… biological functions. Two… concern: first, DPP-4 is i… marker CD26, and data… potential co-stimulatory… activation [11]. Moreove… 4 inhibitors (Lys [Z(O… ounds) had several a… inhibition of prolifer… shown to cleave a mu… and neurological pep… was later provided … develop normally, … subsequently confi… potential for mec… sible, exploited … medicinal chem… below.

PROBIODRU…

When we … chemistry pr… through … trials, Probiodrug's isoleucyl thiazolidide … P-DPP728 (3) from Novartis (Fig. 1) [16,17]. Th… s to "jump start" our internal program, in late … elected to in-license L-*threo*-isoleucyl thiazolidid… 2/98) and its *allo* stereoisomer (L-*allo*-isoleucyl t… olidide, 2). In single dose pharmacodynamic studies, P…/98 had been shown to be well tolerated, increased active GLP-1, and reduced glycemic excursion following food or glucose intake in normal volunteers [18]. In addition, Probiodrug reported enhanced insulin secretion and improved glucose tolerance in single dose studies in a small number of diabetic patients [19].

P32/98 (1) *allo*-Ile-thiazolidide (2)

NVP-DPP728 (3)

Fig (1). Early DPP-4 inhibitors.

anemia, splenomegaly, and mortality with multiple organ pathology) were observed with the *allo* compound in rats. As a result of these findings, development of both compounds was discontinued in early 2001.

DPP8/9 TOXICITY STUDIES

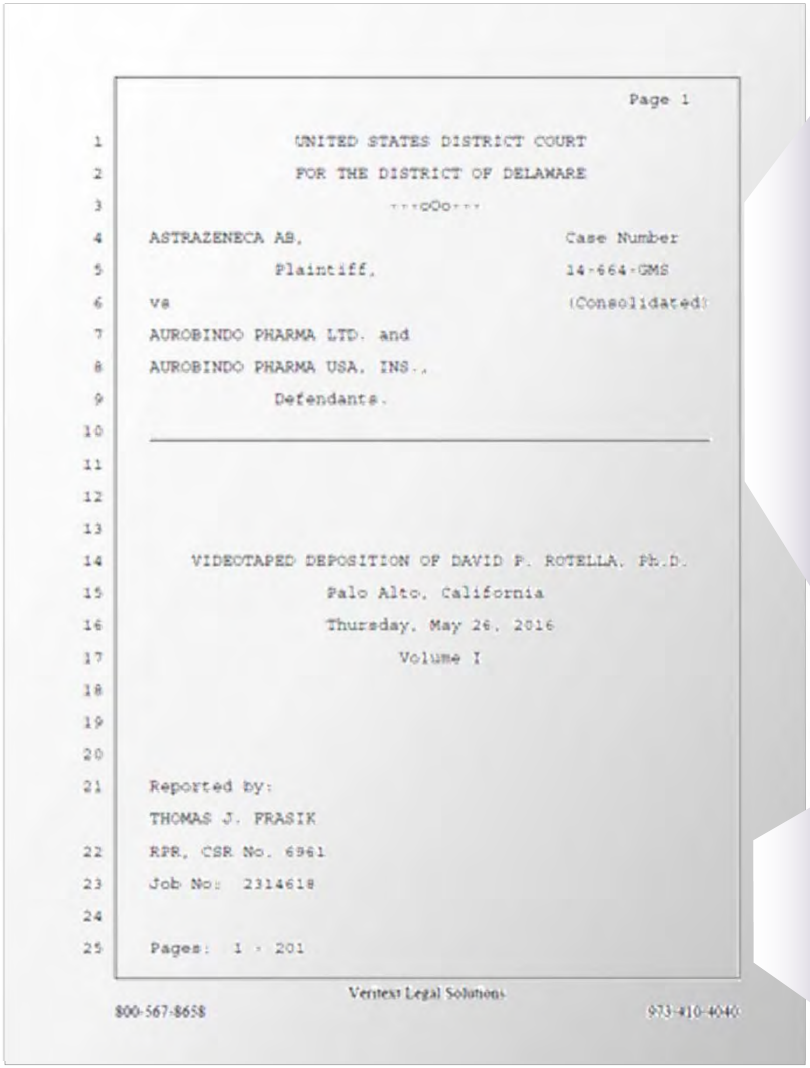
The toxicities observed with the *threo* and *allo* compounds deepened our concern about the potential safety of this mechanism. However, the finding that the *allo* isomer was approximately 10-fold more toxic in rat and dog, despite having comparable pharmacodynamic activity and pharmacokinetics in both species, suggested that these toxicities were likely not due to DPP-4 inhibition, but instead were potentially due to off-target activity. In this regard, subsequent to the initiation of our program, it had become increasingly clear that DPP-4 was a member of larger family of DPP-4 activity- and or structure-homologues (DASH) proteins, enzymes that are unified by their common prolyl-proline cleaving serine dipeptidyl peptidase mechanism [21]. Enzymes that had recently been described included quiescent cell proline dipeptidase (QPP) (aka DPP7) [22], DPP8 [23], DPP9 [24], and fibroblast activation protein (FAP) [25]. As the functions of these enzymes were unknown, determining the selectivity of our inhibitors was a key element of our medicinal chemistry program, and thus counterscreens for these enzymes were developed.

The selectivity of the *allo* and *threo* compounds was determined in the DASH family counterscreens. As well as in

Thus, in order to "jump start" our internal program, in late 2000 we elected to in-license L-*threo*-isoleucyl thiazolidide (P32/98) and its *allo* stereoisomer (L-*allo*-isoleucyl thiazolidide, **2**).

Ex. 2161 at 2; Ex. 2056 ¶ 118

Dr. Rotella



Page 1

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE
---oOo---

ASTRAZENECA AB,
Plaintiff,
vs
AUROBINDO PHARMA LTD. and
AUROBINDO PHARMA USA, INC.,
Defendants.

Case Number
14-664-GMS
(Consolidated)

VIDEOTAPED DEPOSITION OF DAVID P. ROTELLA, Ph.D.
Palo Alto, California
Thursday, May 26, 2016
Volume I

Reported by:
THOMAS J. PRASIK
RPR, CSR No. 6961
Job No: 2314618

Pages: 1 - 201

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Q. Okay. Did you consider whether P32/98 was an appropriate compound for the commencement of further development to find a DPP4 inhibitor?

MS. STEINER: Objection to form.

THE WITNESS: I was aware of the existence of this molecule at the time this report was prepared, and that was based on information that I obtained at Bristol Myers during the course of this program. I also knew at the time that this report was prepared that this molecule failed or did not progress in clinical trials. And so it's difficult to separate what you know now versus what was known in 2000 and, for that reason, this was a molecule that I did not consider.

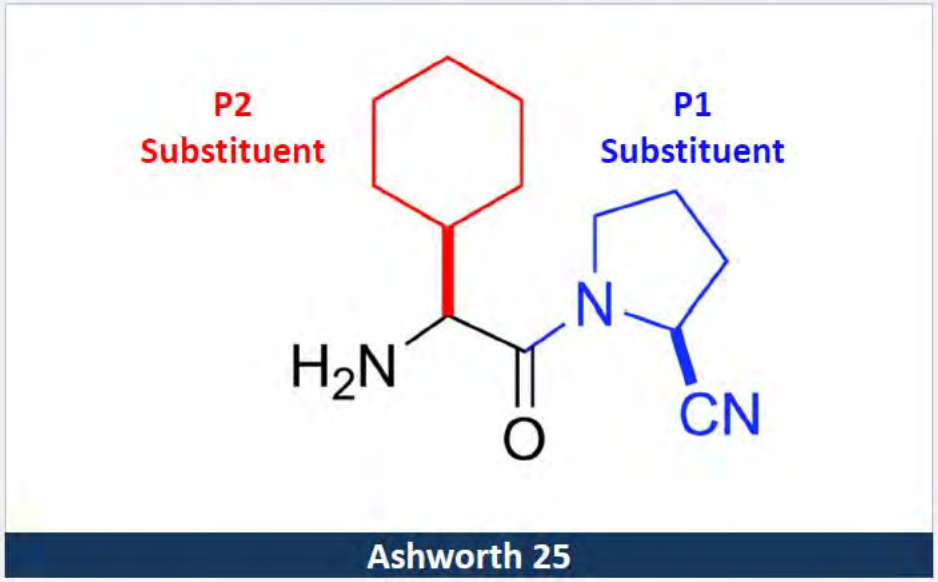
Q. Okay. Did you consider in forming your opinions whether NVP-DPP728 was an appropriate starting point for the development of new DPP4 inhibitors?

A. Again, it's difficult for me to separate, given that this molecule did not progress. It is one that I was unlikely to consider.

Paper 28 at 24; Ex. 2174 at 63:18-64:5, 65:18-23

Mylan Demonstrative Exhibit

Ashworth 25 is a Pertinent Lead Compound



Ashworth 25

- ✓ **Potency:** $K_i < 2$ nM
- ✓ **Solution Stability:** $t_{1/2} > 48$ hours

Source: EX1007 (Ashworth I) at 1166.

4

Rothenberg (2000): Ex. 2012


diabetes

A JOURNAL OF THE AMERICAN DIABETES ASSOCIATION

ABSTRACT BOOK
60th Scientific Sessions
Friday, June 9 – Tuesday, June 13, 2000

60th Scientific Sessions
San Antonio

Page 1 of 2

Abstracts from the ADA 60th Scientific Sessions

ORALS

158-OR

159-OR

160-OR

A numeral beside an author's name indicates a disability of interest. See page 93

A39

Page 2 of 2

BMS-Onglyza 007425

160-OR

Treatment with a DPP-IV Inhibitor, NVP-DPP728, Increases Prandial Intact GLP-1 Levels and Reduces Glucose Exposure in Humans

PAUL ROTHENBERG,[1, 2] JYOTI KALBAG, HAROLD SMITH, RONALD GINGERICH, JERRY NEDELMAN, EDWIN VILLHAUER, JAMES MCLEOD, THOMAS HUGHES, *East Hanover, NJ; St. Charles, MO*

NVP-DPP728 is a highly selective, orally active inhibitor of dipeptidyl peptidase-IV (DPP-IV) designed to augment the glucose-lowering activity of endogenously secreted GLP-1. Recent studies have demonstrated that NVP-DPP728 prevents N-terminal degradative inactivation of GLP-1 and improves glucose tolerance in insulin-resistant rats. The present crossover trial evaluated the single dose pharmacodynamics of NVP-DPP728 administered to 12 healthy normoglycemic volunteers. After an overnight fast, subjects were administered 100 mg NVP-DPP728 or placebo, followed 30 minutes later by a 1000 kcal solid meal (23g protein, 42g fat, 36g carbohydrate, standard FDA breakfast). Blood samples were obtained predose and for up to 24 hours after each dose for analysis of plasma glucose and insulin levels and also for active, undegraded GLP-1 levels by direct ELISA (Linco Research). NVP-DPP728 increased peak plasma levels of active GLP-1 (15±2 vs. 9±2 pmol/l, $p = 0.018$) and also increased active GLP-1 prandial exposures, $AUC_{GLP\text{-}1(0\text{-}4h)}$ (28±4 vs. 14±4 pmol.l^{-1}.h^{-1}, $p < 0.0001$). Prandial glucose excursions above baseline were reduced by NVP-DPP728 relative to placebo (12±3 vs. 20±4 mg.dl^{-1}.h^{-1}, respectively, $p = 0.04$), while glucose excursions below baseline were unchanged (-22±4 vs. -16±4, p=0.3). Insulin excursions were not affected. No clinically significant adverse events were observed. In addition, administration of NVP-DPP728 to fasting individuals was unaccompanied by clinically significant changes in plasma glucose levels.

Thus NVP-DPP728 increased prandial active GLP-1 levels with concomitant reduction in prandial glucose exposure in normal subjects without causing hypoglycemia. These results provide the first direct clinical demonstration that DPP-IV inhibition is a viable new pharmacological approach for potentiating endogenous GLP-1 activity, and support the investigation of the glucose-lowering potential of NVP-DPP728 for the treatment of type 2 diabetics.

Paper 28 at 14; Ex. 2012 at 2

Demuth 2000: Ex. 2010


diabetes

A JOURNAL OF THE AMERICAN DIABETES ASSOCIATION

ABSTRACT BOOK
60th Scientific Sessions
Friday, June 9 – Tuesday, June 13, 2000

60th Scientific Sessions
San Antonio

Page 1 of 3

Page 3 of 3

413-P

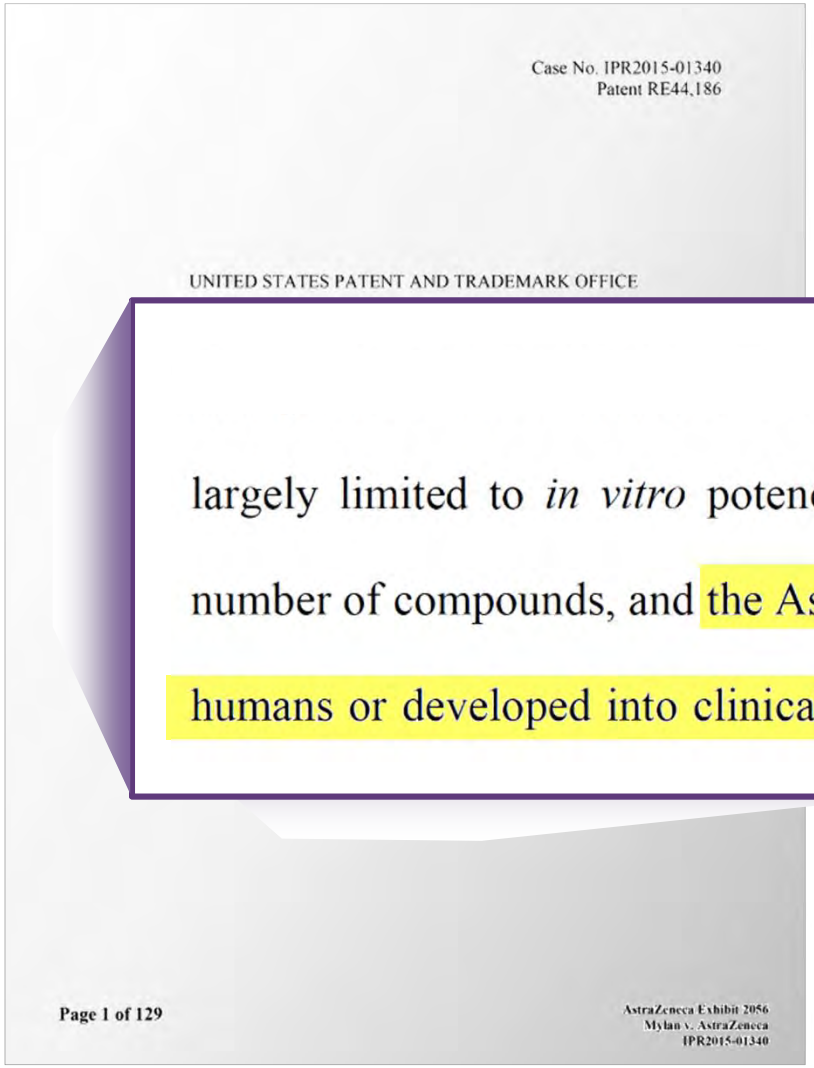
Single Dose Treatment of Diabetic Patients by the DP IV Inhibitor P32/98

HANS-U. DEMUTH, TORSTEN HOFFMANN, KONRAD GLUND, CHRISTOPHER H. S. MCINTOSH, RAYMOND A. PEDERSON, KATJA FUECKER, SABINE FISCHER, MARKOLF HANEFELD, *Halle (Saale), Germany; Vancouver, Canada; Dresden, Germany*

The DP IV inhibitor Di-[3N-((2S,3S)-2-amino-3-methyl-pentanoyl) 1,3-thiazolidine] fumarate (P32/98) improves glucose tolerance (Gt) by an incretin-mediated enhanced insulin response in normal and diabetic rodents, as well as in human volunteers. Within the clinical program, a pilot study in diabetic patients on different therapies was designed. Goal of the open investigation was the evaluation of patients response to a single dose of 60 mg P32/98 15 min prior to an OGTT (75 g) after over-night fasting and 12 hour post-medication (diet, acarbose, metformin, glibenclamide or insulin). Patients (n=20, men) were allocated according to there current medication to 5 groups, each receiving placebo and OGTT at the beginning of the experiment. Seven days later, again after over-night fasting and 12 hours post-medication, 15 min prior OGTT one tablet containing 60 mg P32/98 was administered. Glucose response was recorded every 15 min in an interval of -15 to 300 min. Blood samples were taken to all that time points for determination of P32/98, glucose, insulin, proinsulin, C-peptide, GLP-1, glucagon, FFA and leptin. As expected, a profound Gt improvement caused by P32/98 was observed in patients being treated with acarbose or glibenclamide. In these cases the glucose tolerance improvement was 20.6% and 31.3%, respectively. These values parallel the elevated insulin responses observed after P32/98 treatment in these patients. In contrast, in diabetics on insulin therapy, the acute Gt improvement after a single dose of P32/98 was 8.8% only (assessed by area under the Gt curve). Whether insulin resistance can be reduced or islet responsiveness will improve, mediated by DP IV inhibition, remains to be proven by longer term application of P32/98 in such patients.

Paper 28 at 14; Ex. 2010

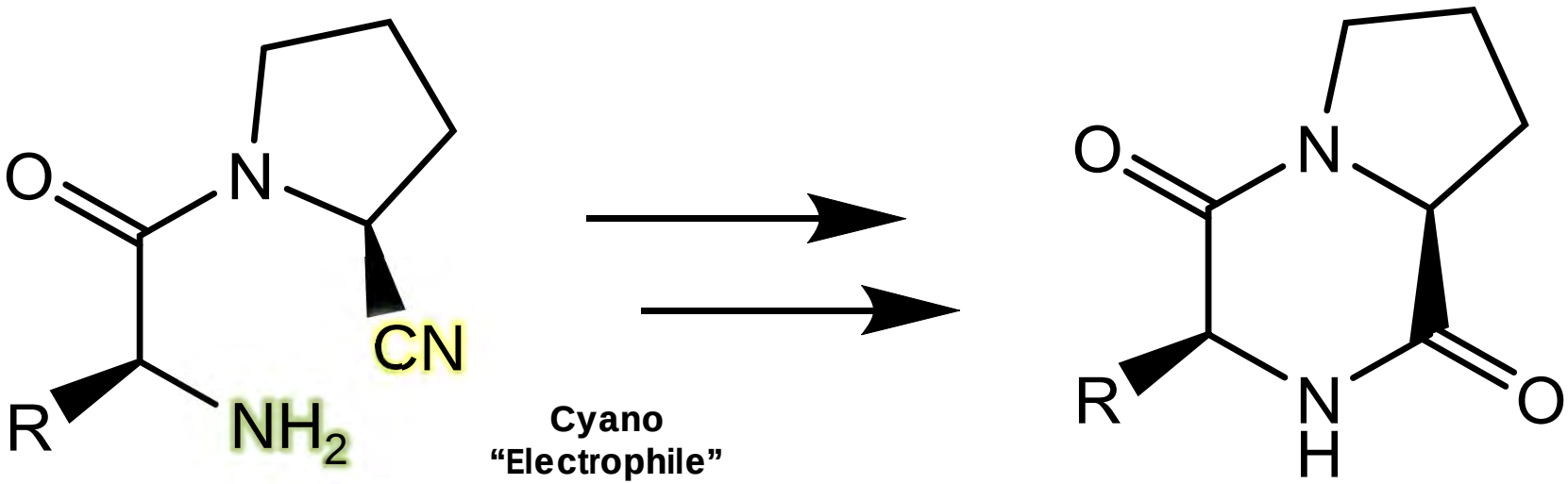
Dr. Weber



Ashworth provides data largely limited to *in vitro* potency and room temperature stability for a limited number of compounds, and the Ashworth series of compounds were never tested in humans or developed into clinically useful inhibitors.

Paper 28 at 11, 24; Ex. 2056 ¶ 171

Intramolecular Cyclization



Amine
"Nucleophile"

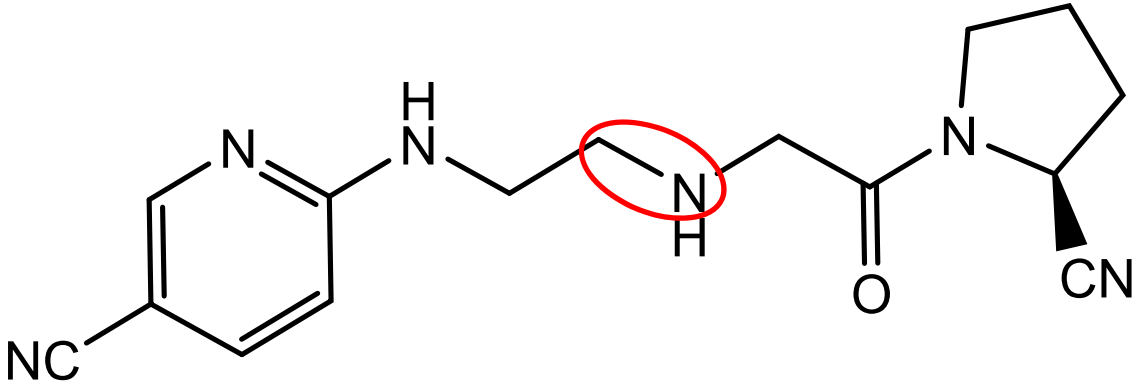
Active

Inactive

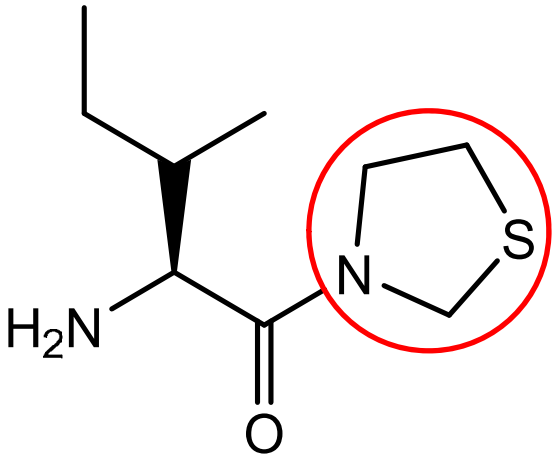
Paper 28 at 8; Ex. 2056 ¶ 116

DPP-4 Inhibitors in the Clinic (2000)

Dr. Weber's Lead Compounds



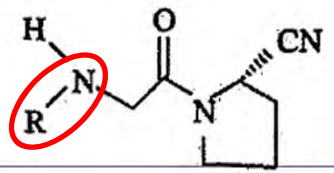
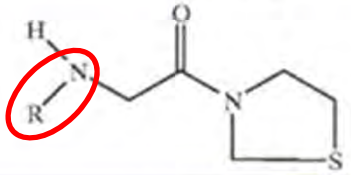
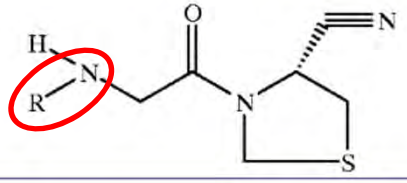
NVP-DPP728



P32/98

Paper 28 at 14-16, 23-26; Ex. 2010; Ex. 2012; Ex. 2226

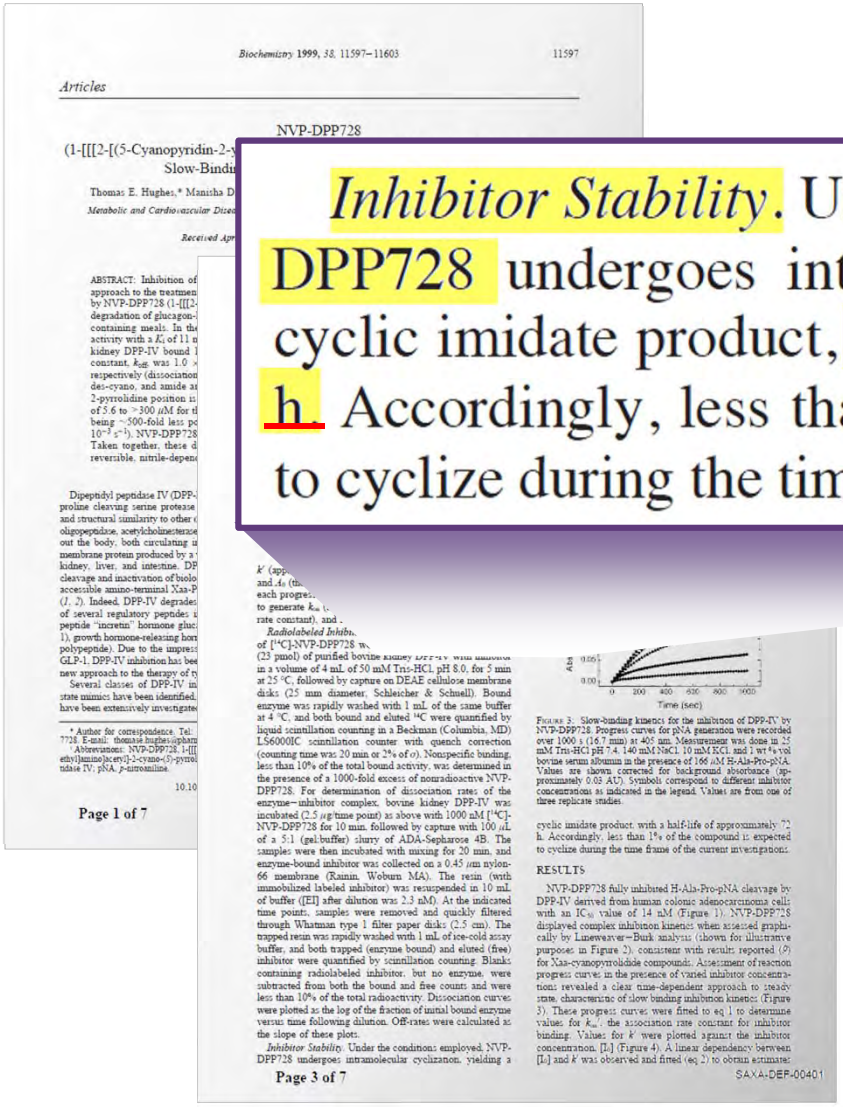
Villhauer's DPP-4 Inhibitor Compounds

Exhibit #	Reference	Structure
Ex. 1008	WO 98/19998	
Ex. 2157	6,107,317	
Ex. 2158	6,110,949	

Paper 28 at 12; Ex. 2056 ¶ 113

Hughes (1999): Ex. 2016

Inhibitor Stability. Under the conditions employed, NVP-DPP728 undergoes intramolecular cyclization, yielding a cyclic imidate product, with a half-life of approximately 72 h. Accordingly, less than 1% of the compound is expected to cyclize during the time frame of the current investigations.



Biochemistry 1999, 38, 11597–11603 11597

Articles

NVP-DPP728

Page 1 of 7

Page 3 of 7

SAXA-DEF-00401

Ex. 2016 at 3; Ex. 2056 ¶¶ 144, 190; Paper 28 at 12

Dr. Weber

UNITED STATES PATENT AND TRADEMARK

BEFORE THE PATENT TRIAL AND AP

MYLAN PHARMACEUTICA
Petitioner,

v.

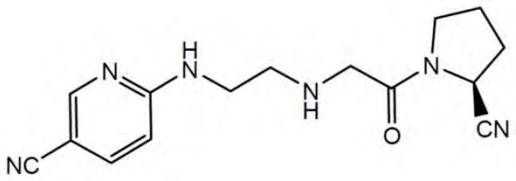
ASTRAZENECA AB
Patent Owner.

Case IPR2015-01340
Patent RE44,186

PATENT OWNER'S RESPONSE

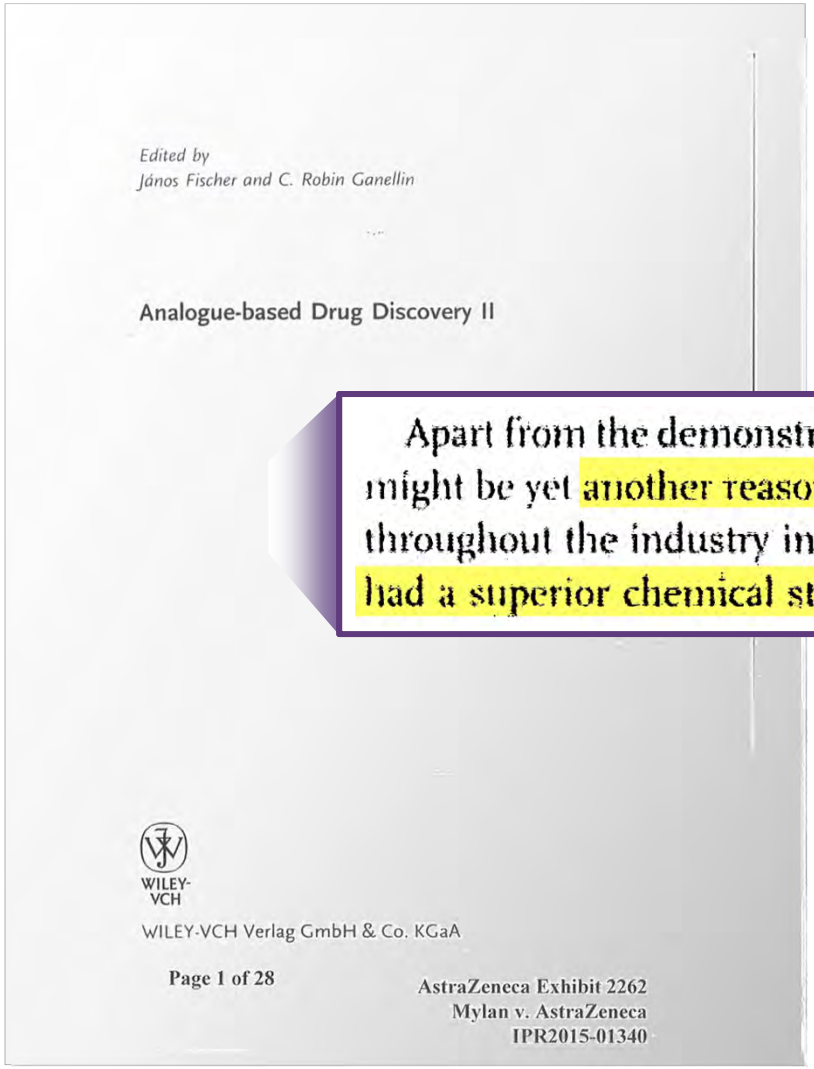
125. Various researchers published different structural solutions to the problem of intramolecular cyclization:

- Villhauer used a backbone with a secondary amine and reported less than 1% cyclization. (Ex. 2016 at 11599.)



Paper 28 at 11-12; Ex. 2056 ¶ 125

Peters and Mattei (2010): Ex. 2262



Edited by
János Fischer and C. Robin Ganellin

Analogue-based Drug Discovery II

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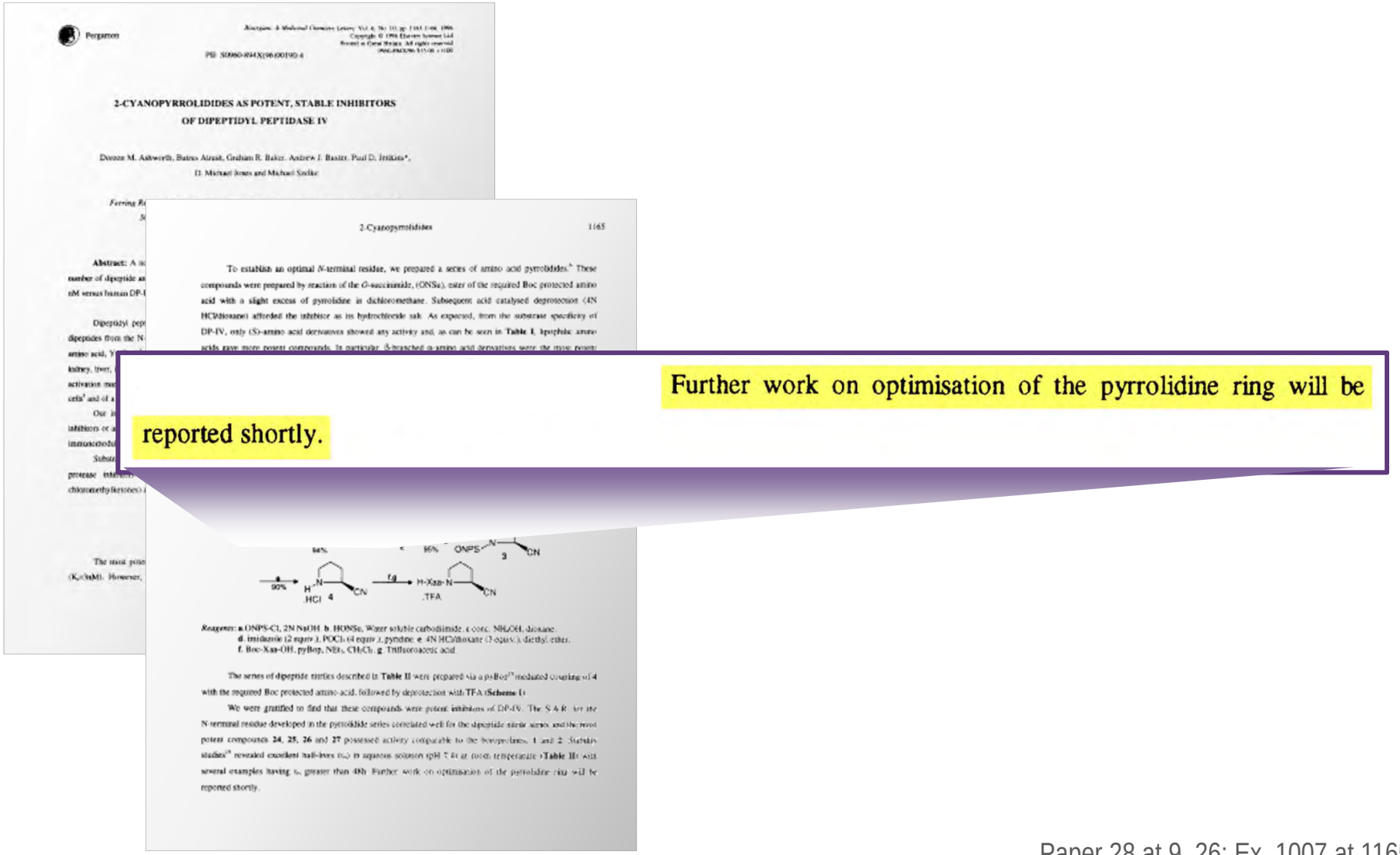
Page 1 of 28

AstraZeneca Exhibit 2262
Mylan v. AstraZeneca
IPR2015-01340

Apart from the demonstrated clinical efficacy and the facile synthetic access, there might be yet another reason why the *N*-alkylglycine inhibitors became very popular throughout the industry in the following years: it was generally perceived that they had a superior chemical stability.

Paper 62 at Observation 9; Ex. 2262 at 9; Ex. 2174 at 77:5-80:14

Ashworth I (1996): Ex. 1007



Pergamon

2-CYANOPYRROLIDIDES AS POTENT, STABLE INHIBITORS OF DIPEPTIDYL PEPTIDASE IV

Dorcas M. Ashworth, Bahra Atrash, Graham R. Baker, Andrew J. Baxter, Paul D. Jenkins*, D. Michael Jones and Michael Szelke

2-Cyanopyrrolidides 1165

To establish an optimal *N*-terminal residue, we prepared a series of amino acid pyrrolidides.[5] These compounds were prepared by reaction of the *O*-succinimide, (ONSu), ester of the required Boc protected amino acid with a slight excess of pyrrolidine in dichloromethane. Subsequent acid catalysed deprotection (4N HCl/dioxane) afforded the inhibitor as its hydrochloride salt. As expected, from the substrate specificity of DP-IV, only (S)-amino acid derivatives showed any activity and, as can be seen in **Table I**, lipophilic amino acids gave more potent compounds. In particular, β-branched α-amino acid derivatives were the most potent

Further work on optimisation of the pyrrolidine ring will be reported shortly.

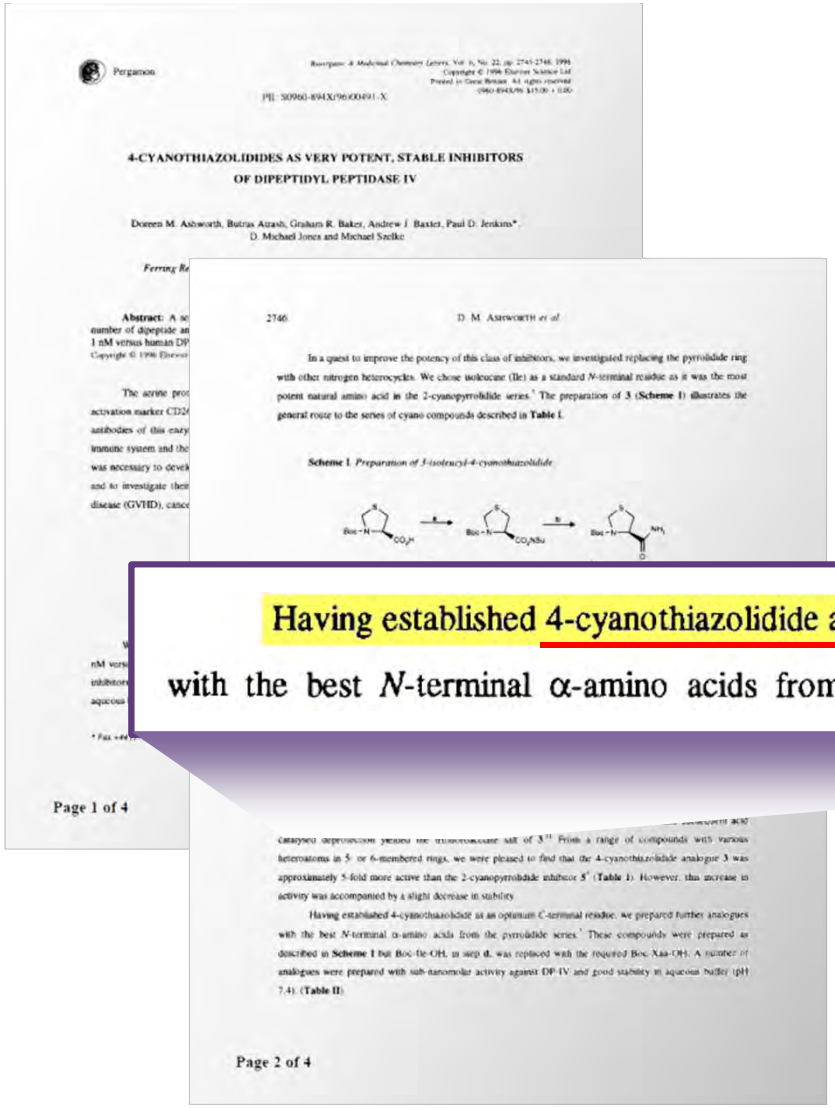
Reagents: a ONPS-Cl, 2N NaOH b. HONSu, Water soluble carbodiimide, c conc. NH_4OH, dioxane, d. imidazole (2 equiv.), $POCl_3$ (4 equiv.), pyridine e. 4N HCl/dioxane (3 equiv.), diethyl ether, f. Boc-Xaa-OH, pyBop, NEt_3, CH_2Cl_2 g. Trifluoroacetic acid.

The series of dipeptide nitriles described in **Table II** were prepared via a prBop[17] mediated coupling of 4 with the required Boc protected amino acid, followed by deprotection with TFA (**Scheme 1**).

We were gratified to find that these compounds were potent inhibitors of DP-IV. The S.A.R. for the N-terminal residue developed in the pyrrolidide series correlated well for the dipeptide nitrile series and the most potent compounds **24**, **25**, **26** and **27** possessed activity comparable to the boropeptides, **1** and **2**. Stability studies[18] revealed excellent half-lives ($t_{1/2}$) in aqueous solution (pH 7.4) at room temperature (**Table II**) with several examples having $t_{1/2}$ greater than 48h. Further work on optimisation of the pyrrolidine ring will be reported shortly.

Paper 28 at 9, 26; Ex. 1007 at 1165

Ashworth II (1996): Ex. 2001



Pergamon

4-CYANOTHIAZOLIDIDES AS VERY POTENT, STABLE INHIBITORS OF DIPEPTIDYL PEPTIDASE IV

Doreen M. Ashworth, Butrus Atrash, Graham R. Baker, Andrew J. Baxter, Paul D. Jenkins*, D. Michael Jones and Michael Szelke

Page 1 of 4

2746 D. M. Ashworth *et al.*

In a quest to improve the potency of this class of inhibitors, we investigated replacing the pyrrolidide ring with other nitrogen heterocycles. We chose isoleucine (Ile) as a standard *N*-terminal residue as it was the most potent natural amino acid in the 2-cyanopyrrolidide series.[7] The preparation of **3** (**Scheme 1**) illustrates the general route to the series of cyano compounds described in **Table 1**.

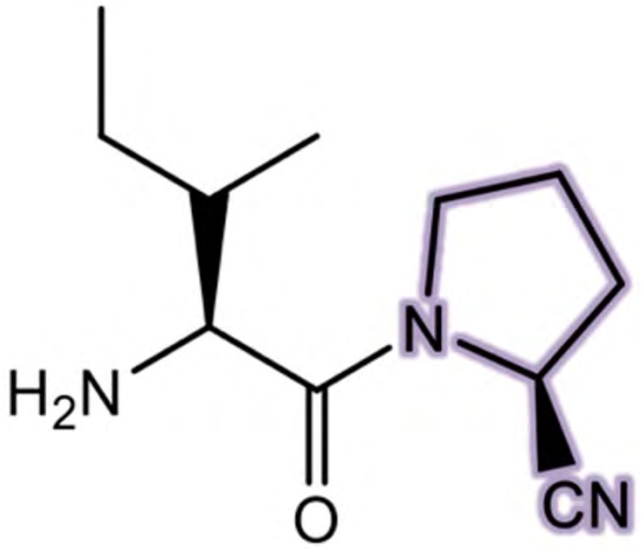
Scheme 1 *Preparation of 3-isoleucyl-4-cyanothiazolidide*

Having established 4-cyanothiazolidide as an optimum *C*-terminal residue, we prepared further analogues with the best *N*-terminal α-amino acids from the pyrrolidide series.[7] These compounds were prepared as described in **Scheme 1** but Boc-Ile-OH, in step **d**, was replaced with the required Boc-Xaa-OH. A number of analogues were prepared with sub-nanomolar activity against DP-IV and good stability in aqueous buffer (pH 7.4). (**Table II**)

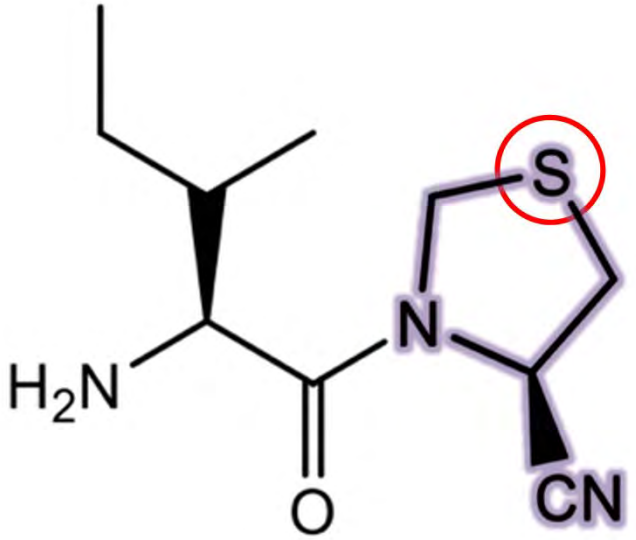
Page 2 of 4

Paper 28 at 9-10, 27; Ex. 2001 at 2

Ashworth II (1996): Ex. 2001



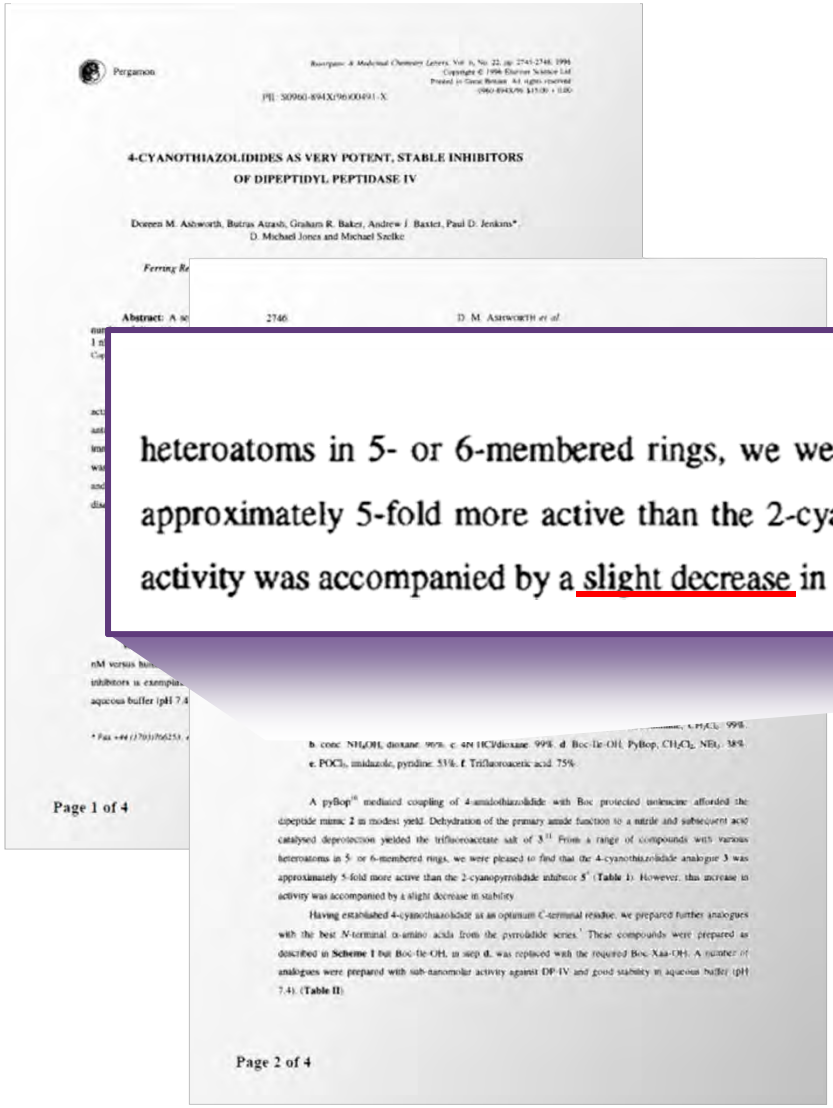
Compound 5
K_i = 2.2 nM ± 0.50



Compound 3
K_i = 0.41 nM ± 0.15

Paper 28 at 9, 27; Ex. 2056 ¶¶ 107-108; Ex. 2001 at 3, Table I; Ex. 2231

Ashworth II (1996): Ex. 2001



Pergamon

4-CYANOTHIAZOLIDIDES AS VERY POTENT, STABLE INHIBITORS OF DIPEPTIDYL PEPTIDASE IV

Doreen M. Ashworth, Butrus Atrash, Graham R. Baker, Andrew J. Baxter, Paul D. Jenkins*, D. Michael Jones and Michael Szelke

Page 1 of 4

b. conc. NH_4OH, dioxane. 90%. c. 4N HCl/dioxane. 99%. d. Boc-Ile-OH, PyBop, CH_2Cl_2, NEt_3. 38%. e. $POCl_3$, imidazole, pyridine. 53%. f. Trifluoroacetic acid. 75%.

A pyBop[16] mediated coupling of 4-amidothiazolidide with Boc protected isoleucine afforded the dipeptide mimic **2** in modest yield. Dehydration of the primary amide function to a nitrile and subsequent acid catalysed deprotection yielded the trifluoroacetate salt of **3**.[11] From a range of compounds with various heteroatoms in 5- or 6-membered rings, we were pleased to find that the 4-cyanothiazolidide analogue **3** was approximately 5-fold more active than the 2-cyanopyrrolidide inhibitor **5**[7] (**Table 1**). However, this increase in activity was accompanied by a slight decrease in stability.

Having established 4-cyanothiazolidide as an optimum C-terminal residue, we prepared further analogues with the best *N*-terminal α-amino acids from the pyrrolidide series.[7] These compounds were prepared as described in **Scheme 1** but Boc-Ile-OH, in step **d**, was replaced with the required Boc-Xaa-OH. A number of analogues were prepared with sub-nanomolar activity against DP-IV and good stability in aqueous buffer (pH 7.4). (**Table II**).

Page 2 of 4

From a range of compounds with various heteroatoms in 5- or 6-membered rings, we were pleased to find that the 4-cyanothiazolidide analogue **3** was approximately 5-fold more active than the 2-cyanopyrrolidide inhibitor **5**[7] (**Table I**). However, this increase in activity was accompanied by a slight decrease in stability.

Villhauer-949: Ex. 2158

US006110949A

United States Patent [19]
Villhauer

[11] **Patent Number: 6,110,949**
[45] **Date of Patent: *Aug. 29, 2000**

[54] **N-(SUBSTITUTED GLYCYL)-4-CYANOTHIAZOLIDINES, PHARMACEUTICAL COMPOSITIONS CONTAINING THEM AND THEIR USE IN INHIBITING DIPEPTIDYL PEPTIDASE-IV**

[75] Inventor: **Edwin Bernard Villhauer**, Morristown, N.J.

[73] Assignee: **Novartis AG**, Basel, Switzerland

[*] Notice: This patent issued on a continued prosecution application filed under 37 CFR 1.53(d), and is subject to the twenty year patent term provisions of 35 U.S.C. 154(a)(2).

[21] Appl. No.: **09/339,503**

[22] Filed: **Jun. 24, 1999**

[51] **Int. Cl.**[7] **C07D 207/00**
[52] **U.S. Cl.** **514/365**, 548/200
[58] **Field of Search** 548/200, 514/365

[56] **References Cited**

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Primary Examiner—Robert Gerstl
Attorney, Agent, or Firm—Joseph J. Borovian

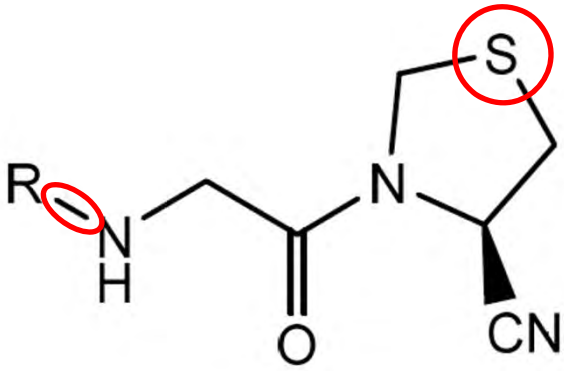
[57] **ABSTRACT**

The invention discloses certain N-(substituted glycyl)-4-cyanothiazolidines, pharmaceutical compositions containing said compounds as an active ingredient thereof, and the use of said compounds in inhibiting dipeptidyl peptidase-IV.

38 Claims, No Drawings

Page 1 of 11

AstraZeneca Exhibit 2158
Mylan v. AstraZeneca
IPR2015-01340

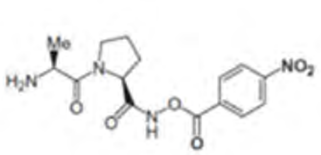


Cyanothiazolidine

Paper 62 at Observation 13; Ex. 2158; Ex. 2056 ¶ 113

Cyclopropanation

Prior Art DPP-4 Inhibitors: None FDA-Approved



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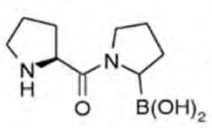

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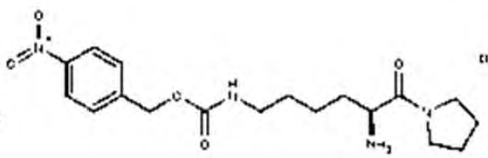

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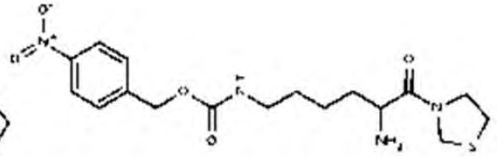

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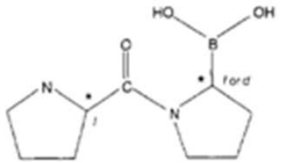

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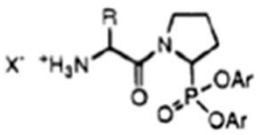

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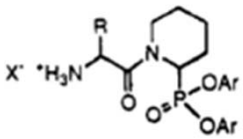

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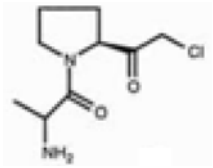

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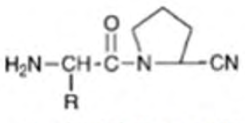

Arg(PMC)-Pyrr-2-CN
Arg-Pyrr-2-CN
Ala-Pyrr-2-CN
Phe-Pyrr-2-CN

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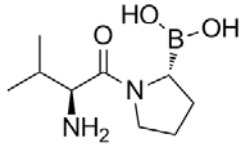

PT-100 (Talabostat)

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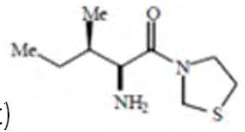

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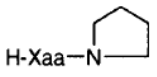

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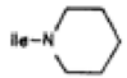

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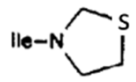

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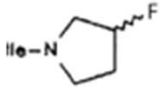

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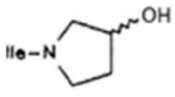

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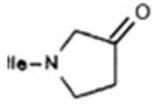

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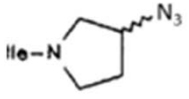

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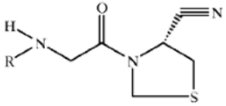

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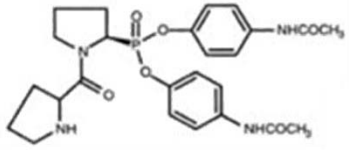

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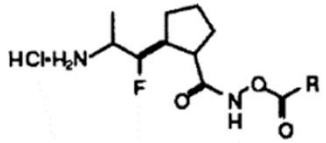

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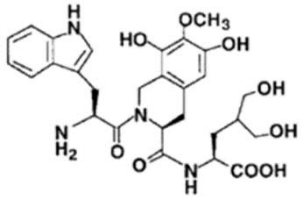

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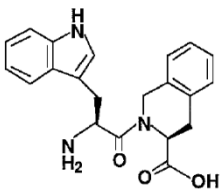

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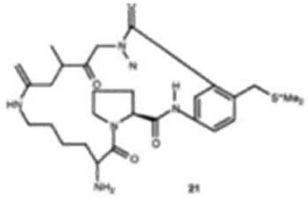

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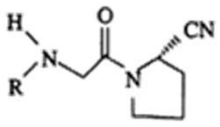

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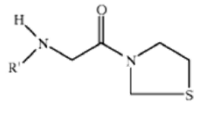

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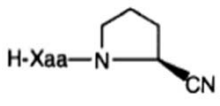
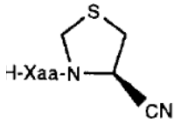
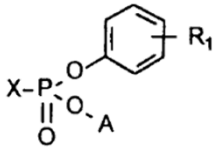


Ex. 1007



Ex. 2001



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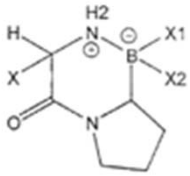

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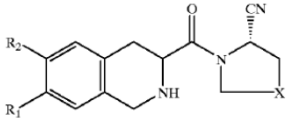
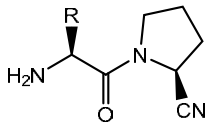


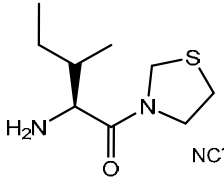
X is CH_2, S, O, or $C(CH_3)_2$

Ex. 2156



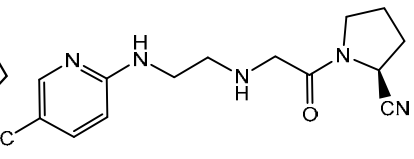
Ashworth I

Ex. 1007



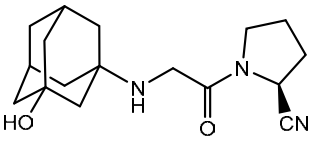
P32/98

Ex. 2009



NVP-DPP728

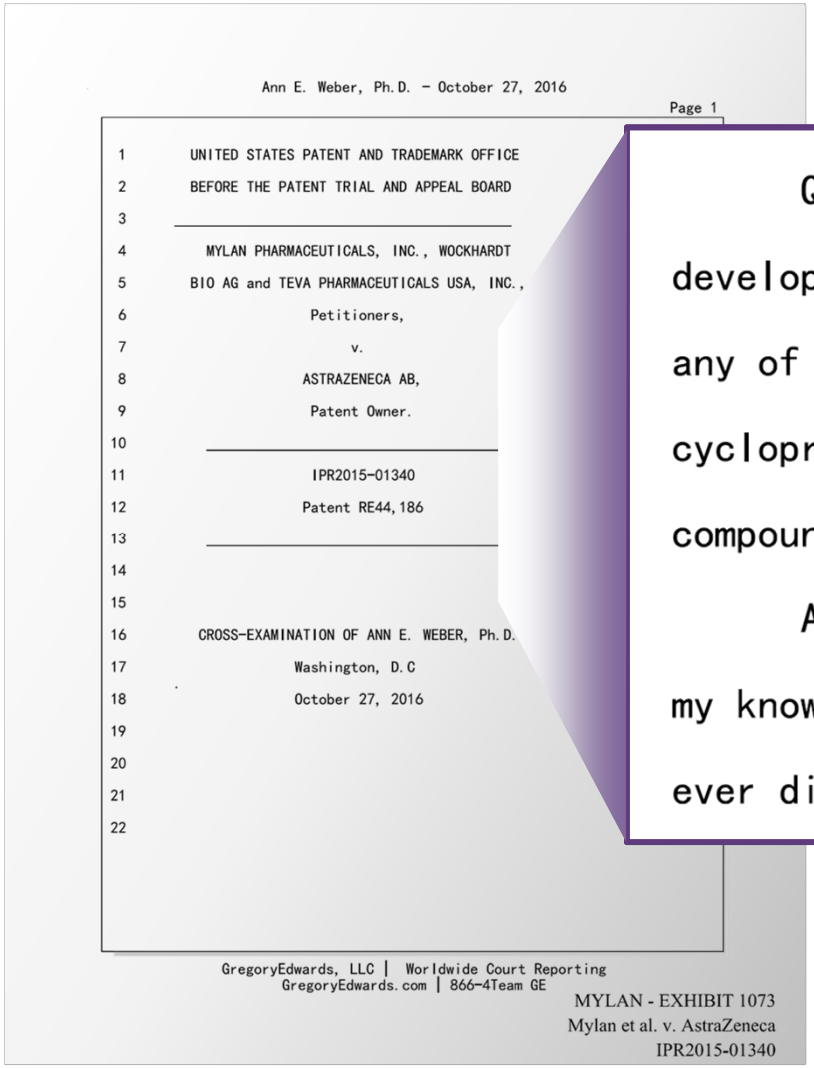
Ex. 2016



Vildagliptin

Ex. 2013

Dr. Weber



Ann E. Weber, Ph.D. - October 27, 2016

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS, INC., WOCKHARDT BIO AG and TEVA PHARMACEUTICALS USA, INC.,

Petitioners,

v.

ASTRAZENECA AB,

Patent Owner.

IPR2015-01340

Patent RE44,186

CROSS-EXAMINATION OF ANN E. WEBER, Ph.D.

Washington, D.C

October 27, 2016

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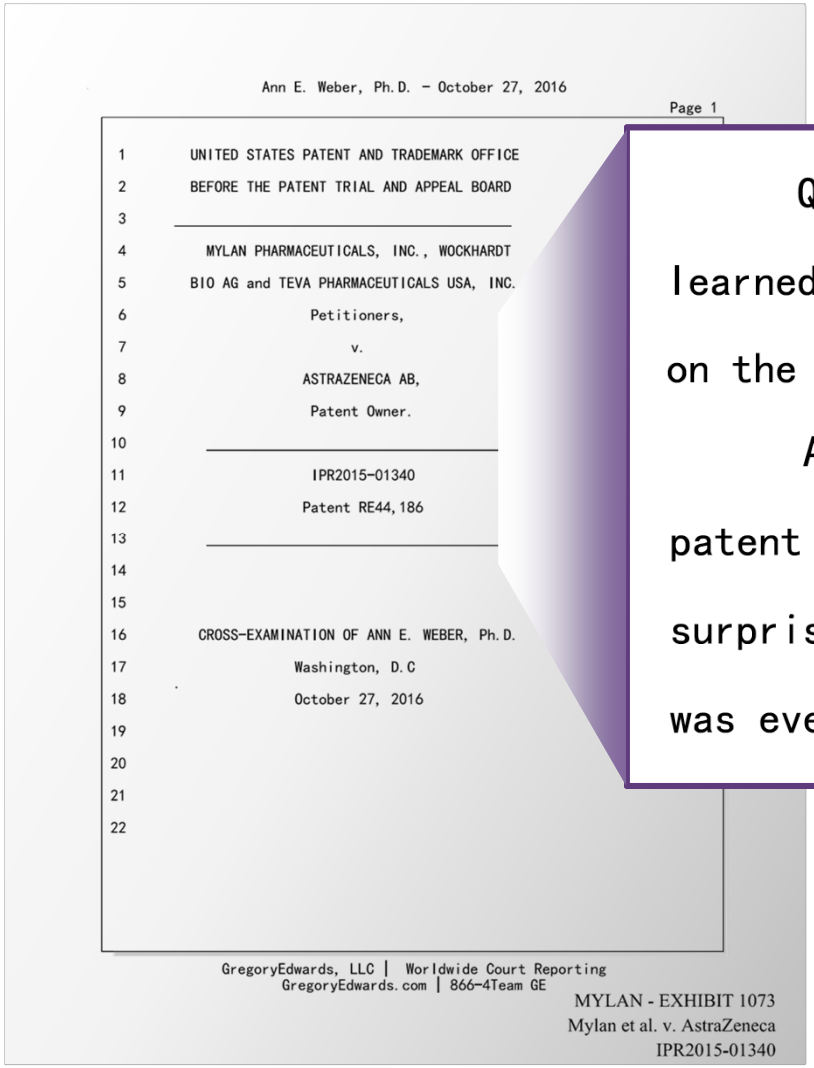
MYLAN - EXHIBIT 1073
Mylan et al. v. AstraZeneca
IPR2015-01340

Q In the course of your work in developing DPP-4 inhibitors at Merck, did you or any of your colleagues consider adding a cyclopropyl group at the P1 position of your DPP-4 compounds?

A No, we never did, and to the best of my knowledge nobody other than the chemists at BMS ever did that.

Ex. 1073 (Weber Redirect) at 117:4-11; Ex. 2056 ¶ 187; Paper 28 at 37

Dr. Weber



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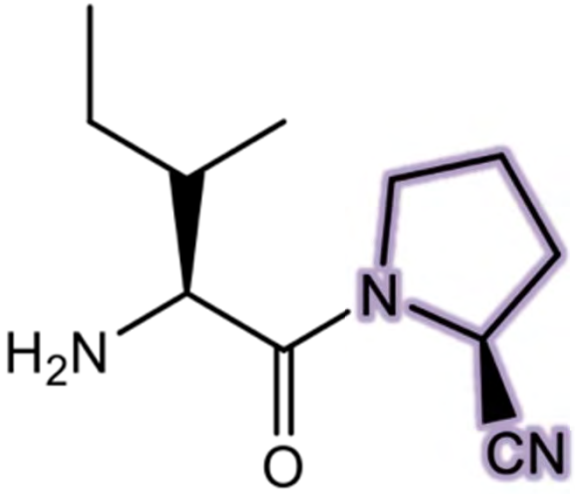
MYLAN - EXHIBIT 1073
Mylan et al. v. AstraZeneca
IPR2015-01340

Q What was your reaction when you first learned that saxagliptin had a cyclopropyl group on the pyrrolidine ring?

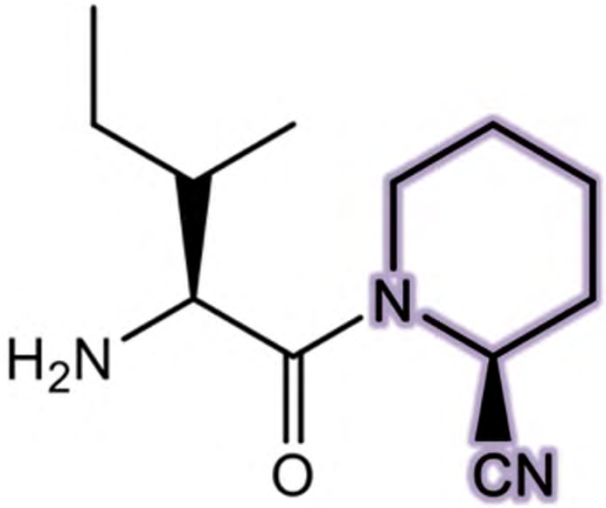
A I was very surprised when I saw the patent when it was first published. I was first surprised that they had actually tried it, and I was even more surprised that it worked.

Ex. 1073 (Weber Redirect) 117:12-20; Ex. 2056 ¶ 187; see Paper 28 at 37

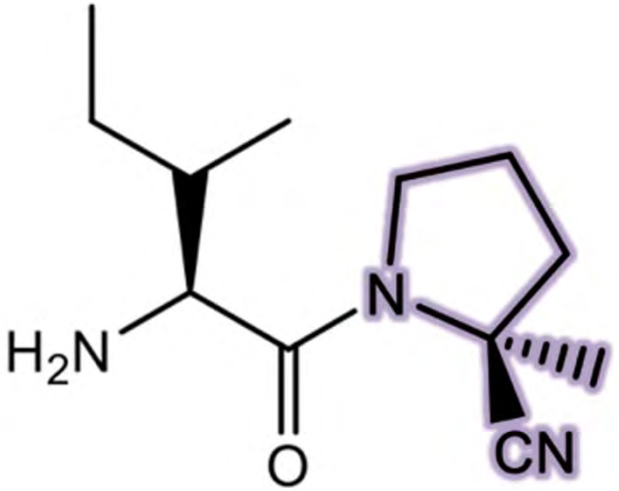
Ashworth II (1996): Ex. 2001



Compound 5
K_i = 2.2 nM
5-membered ring



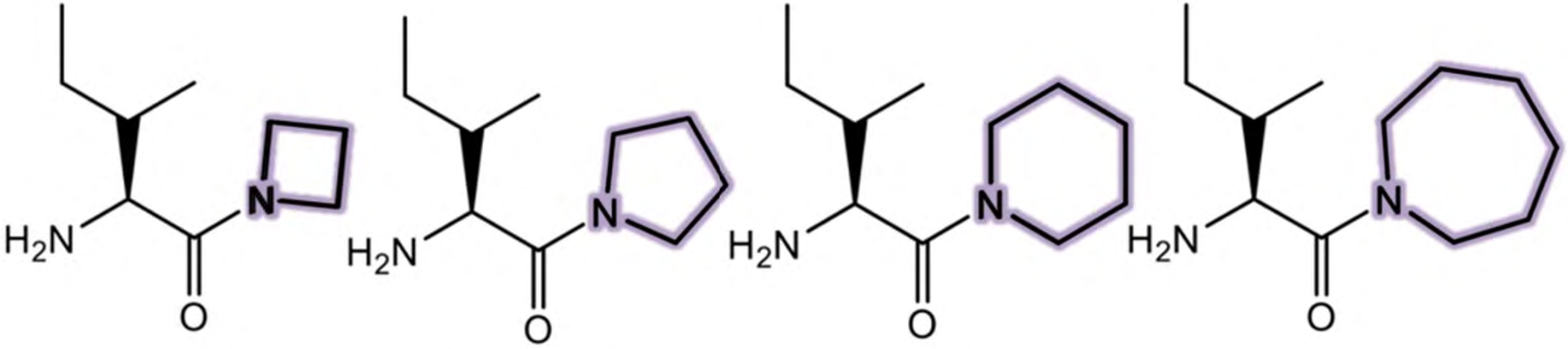
Compound 8
K_i = 260 nM
6-membered ring



Compound 11
K_i = 4200 nM
2-methyl

Paper 28 at 10; Ex. 2056 ¶¶ 107-108, 173-174; Ex. 2001 at 3, Table I; Ex. 2230

Augustyns (1997): Ex. 2151



Compound 8b
IC_{50} = 270 µM
4-membered ring

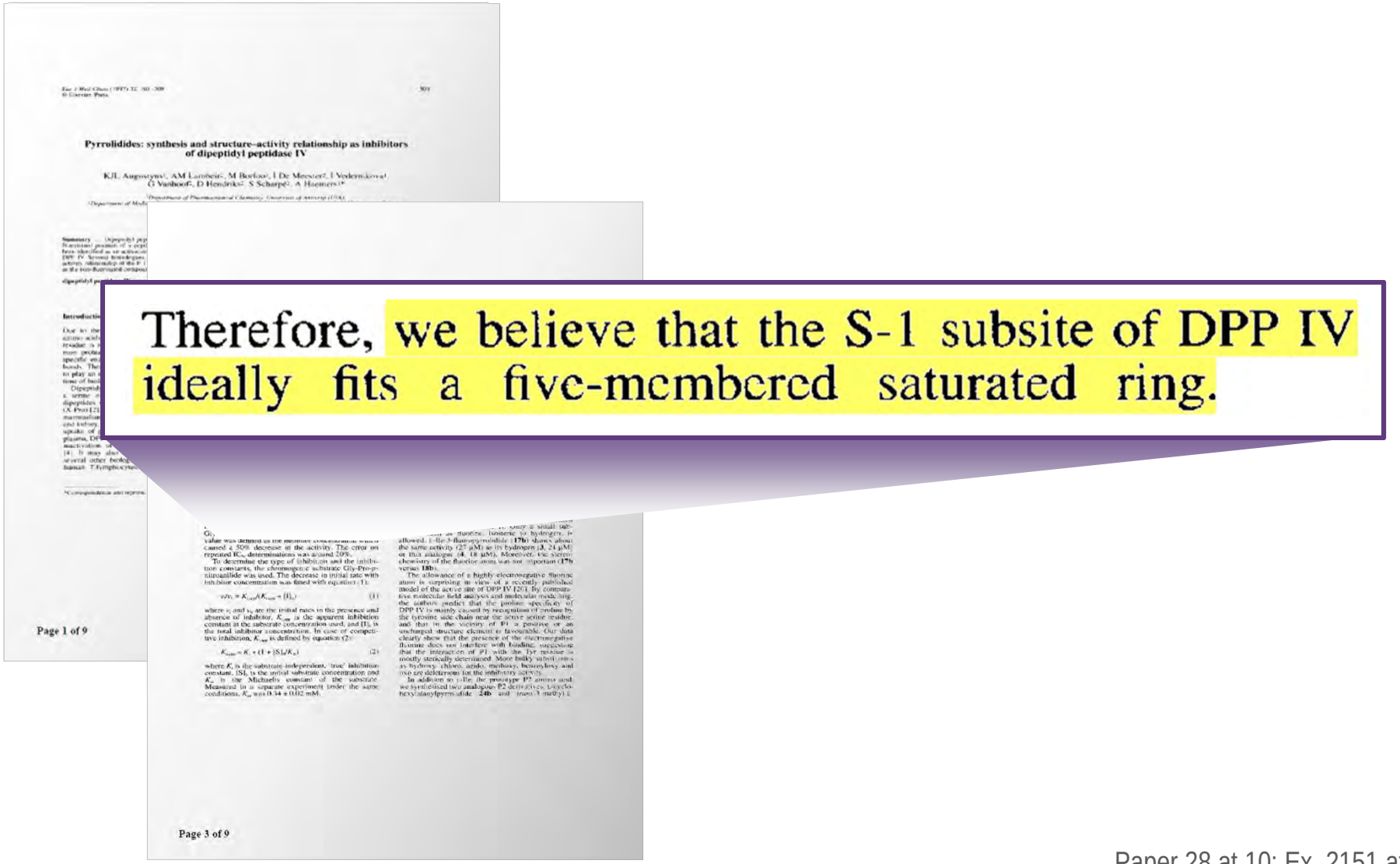
Compound 3
IC_{50} = 21 µM
5-membered ring

Compound 6b
IC_{50} = 510 µM
6-membered ring

Compound 7b
IC_{50} = 2700 µM
7-membered ring

Paper 28 at 10; Ex. 2151 at 2, 4; Ex. 2228

Augustyns (1997): Ex. 2151



Pyrrolidides: synthesis and structure–activity relationship as inhibitors of dipeptidyl peptidase IV

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Therefore, we believe that the S-1 subsite of DPP IV ideally fits a five-membered saturated ring.

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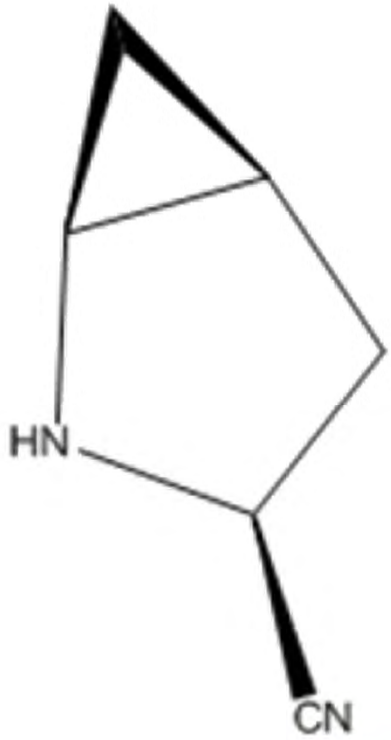
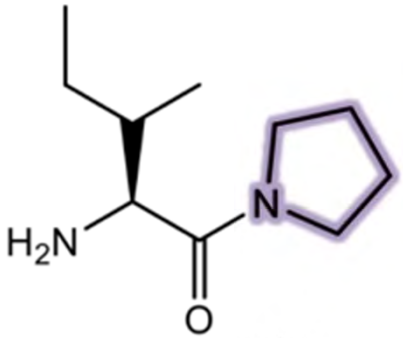
Standard IUPAC Name



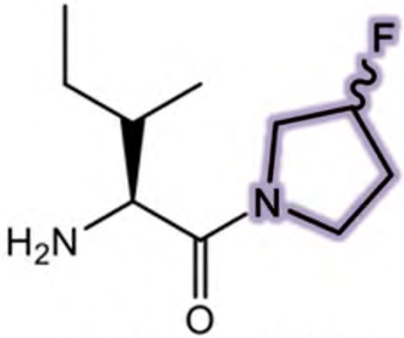
(1*S*,3*S*,5*S*)-2-azabicyclo[3.1.0]hexane-3-carbonitrile

Ex. 2221 at 30:14-31:20; Ex. 2258; Paper 62 at Observation 10

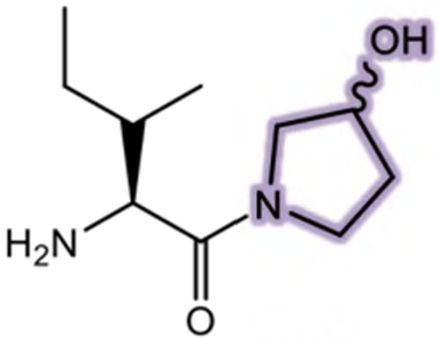
Augustyns (1997): Ex. 2151



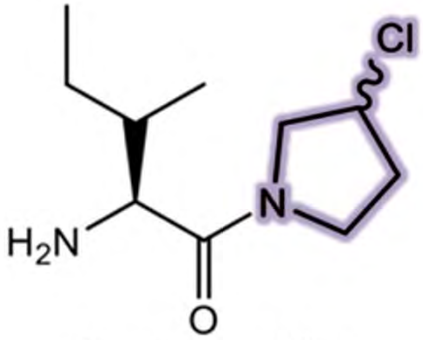
Compound 3
IC_{50} = 21 µM



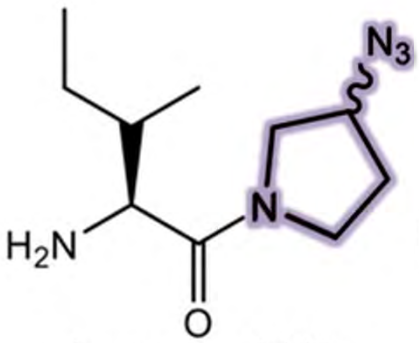
Compound 17b
IC_{50} = 27 µM



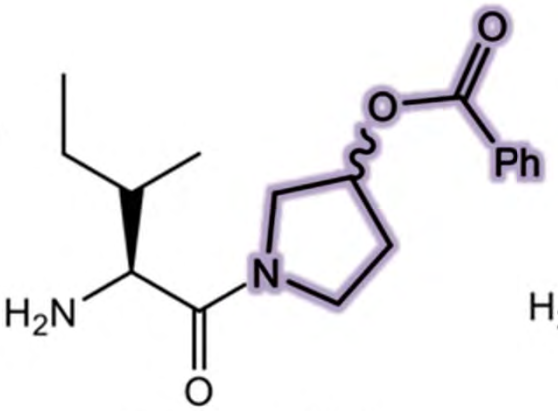
Compound 16b
IC_{50} = 740 µM



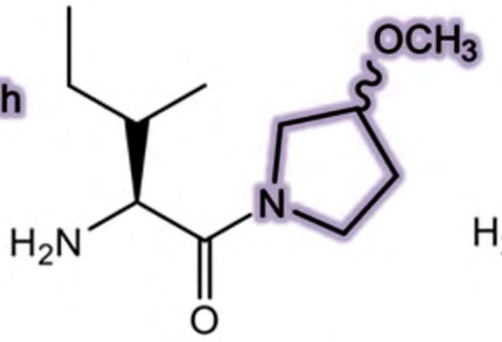
Compound 19b
IC_{50} = 610 µM



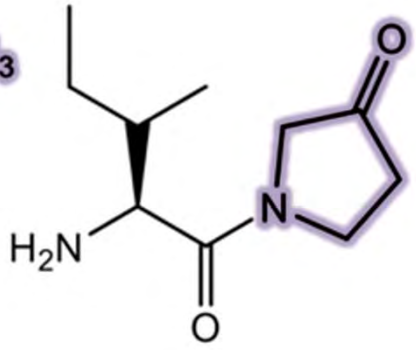
Compound 20b
IC_{50} = 1070 µM



Compound 21b
IC_{50} = 6200 µM



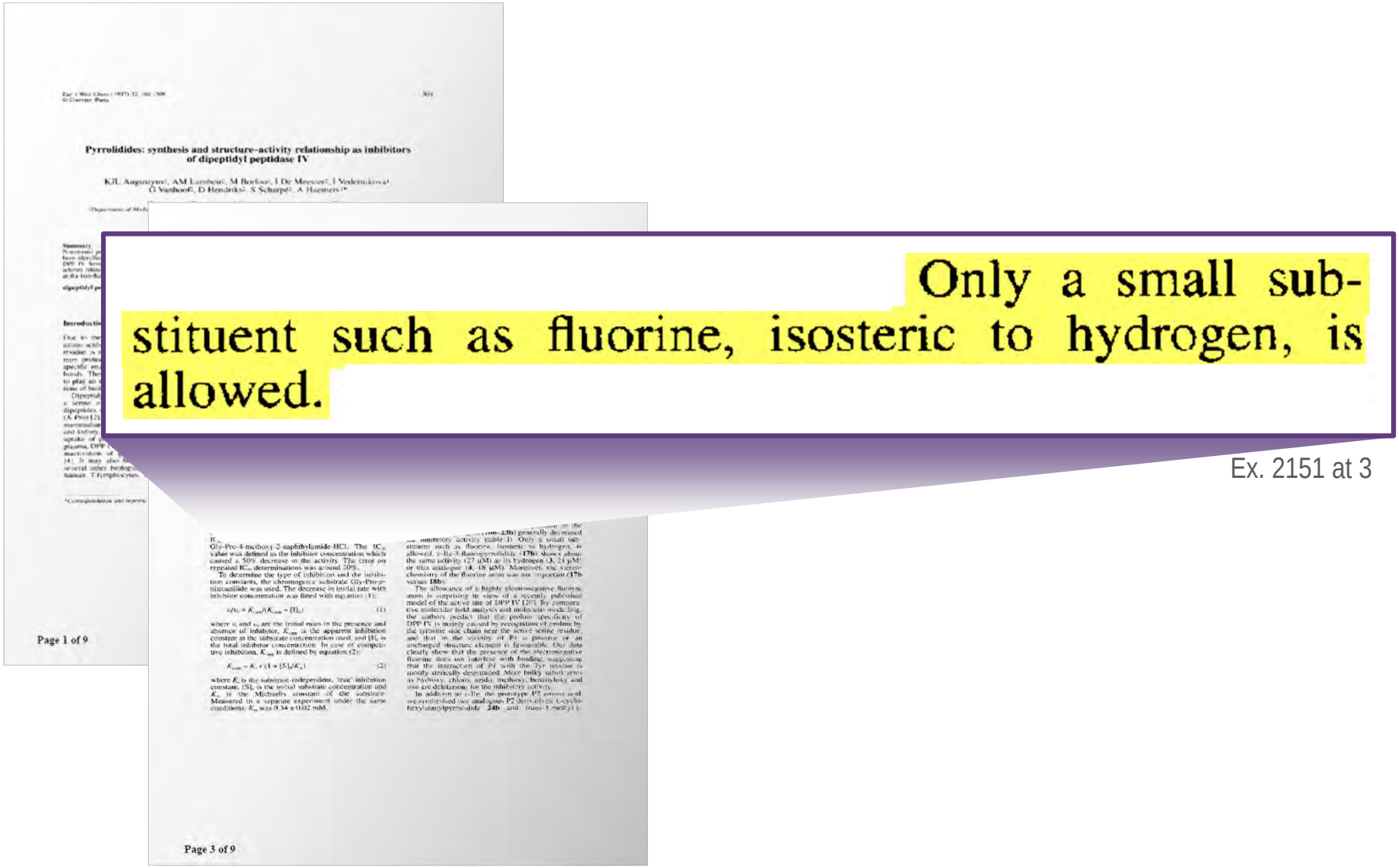
Compound 22b
IC_{50} = >10,000 µM



Compound 23b
IC_{50} = 320 µM

Paper 28 at 10; Ex. 2151 at 2, 4; Ex. 2229

Augustyns (1997): Ex. 2151



Pyrrolidides: synthesis and structure–activity relationship as inhibitors of dipeptidyl peptidase IV

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Only a small substituent such as fluorine, isosteric to hydrogen, is allowed.

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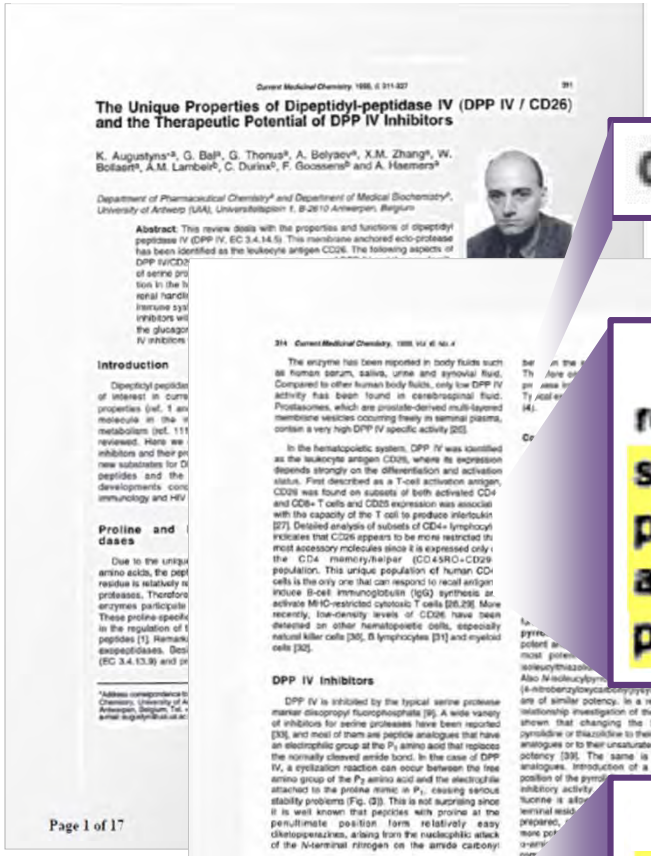
Ex. 2151 at 3

Augustyns (1999): Ex. 2007



The Unique Properties of Dipeptidyl-peptidase IV (DPP IV / CD26) and the Therapeutic Potential of DPP IV Inhibitors

K. Augustyns[a], G. Bal[a], G. Thonus[a], A. Belyaev[a], X.M. Zhang[a], W. Bollaert[a], A.M. Lambeir[b], C. Durinx[b], F. Goossens[b] and A. Haemers[a]

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DPP IV Inhibitors

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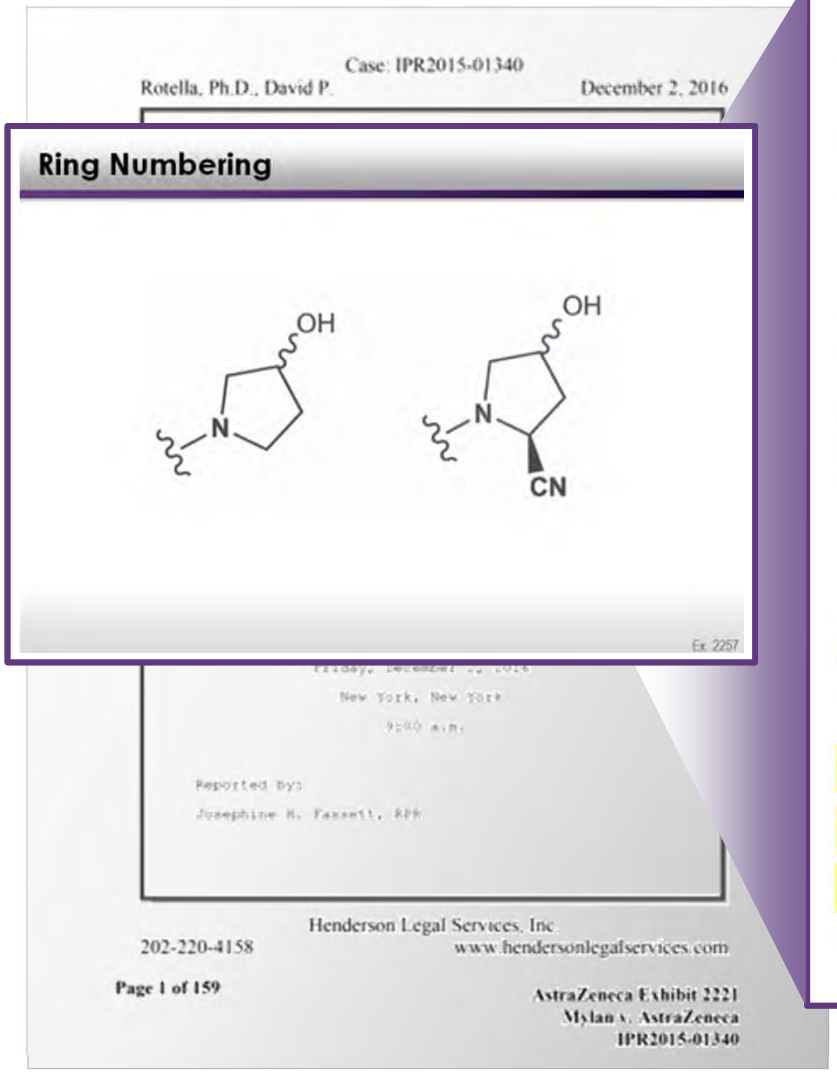
SAXA-DEF-00202

Competitive Reversible Inhibitors

In a recent structure-activity relationship investigation of these compounds it was shown that changing the 5-membered ring of pyrrolidine or thiazolidine to their 4-, 6-, or 7-membered analogues or to their unsaturated analogues decreases potency [39].

Introduction of a substituent at the 3-position of the pyrrolidine ring generally decreased the inhibitory activity. Only a small substituent such as fluorine is allowed (7).

Dr. Rotella



Q. Okay. And if the figure on the left -- or I guess I'll ask you: Does the figure on the left show the substitution of the OH in the so-called 3-position on that pyrrolidine ring?

A. Yes, it does.

Q. Okay. And if the OH were moved one position to the right, that would still be in what's called the 3-position in that ring, correct?

* * *

A. Yes. That is the -- that would also be a 3-position.

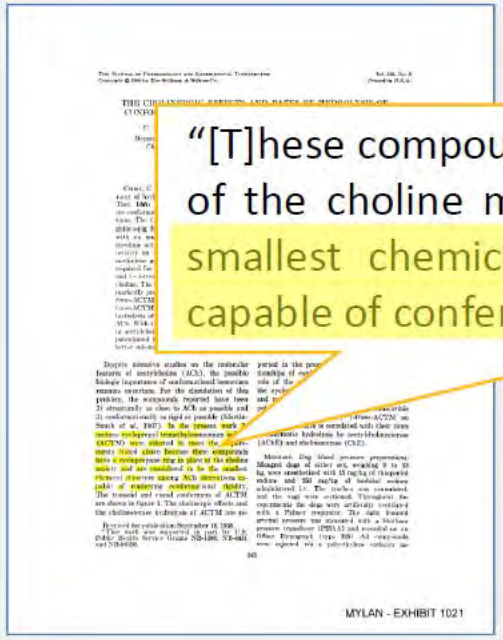
Q. Okay. So when Augustyns says he substituted at the 3-position, that would imply that putting the substituent in either -- on either one of those carbons was a problem, right?

A. Yes. Yes.

Paper 62 at Observation 14; Ex. 2221 at 52:10-18, 53:3-11; Ex. 2257

Mylan Demonstrative Exhibit

Cyclopropanation Has Minimal Effect on Ring Size

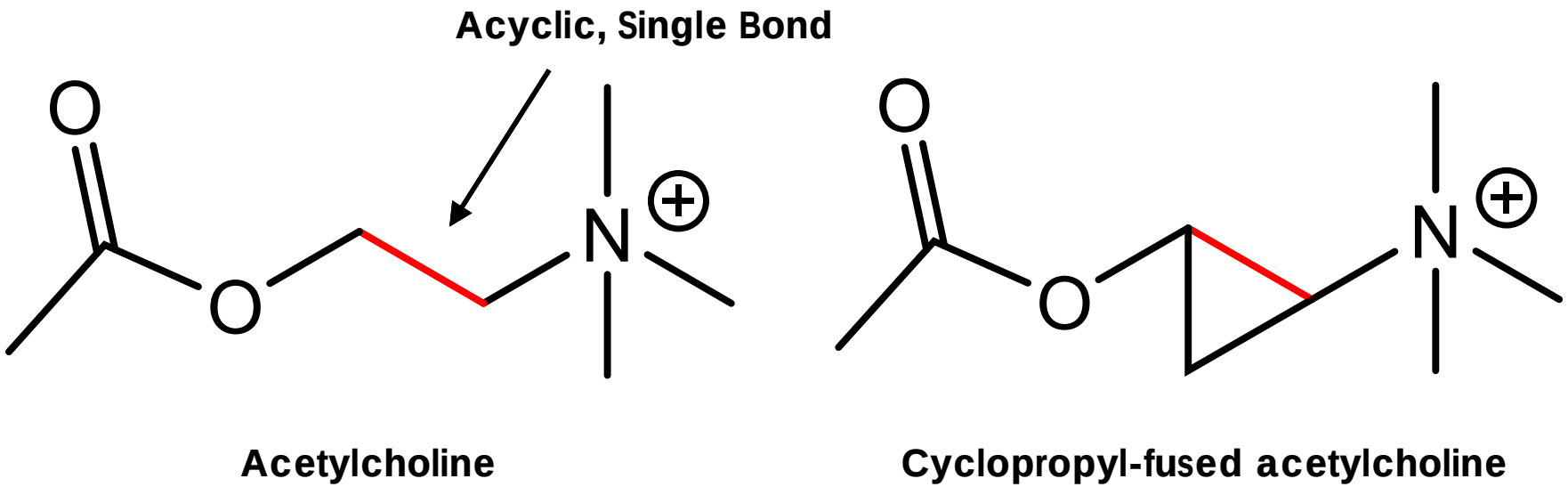


"[T]hese compounds have a cyclopropane ring in place of the choline moiety and are considered to be the smallest chemical structure among Ach derivatives capable of conferring conformational rigidity."

Source: EX1021 (Chiou) at 243; EX1003 (Rotella Decl.), ¶135; Pet. at 22.

18

Chiou: Ex. 1021

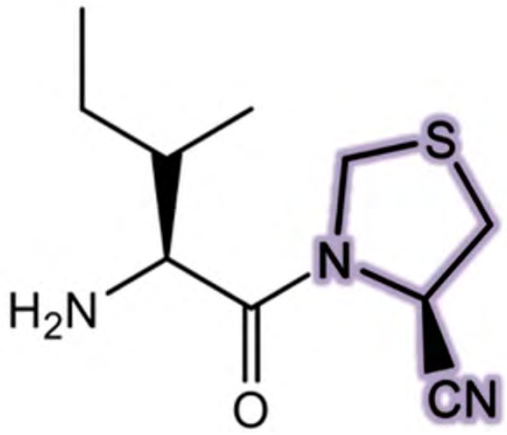


Acetylcholine

Cyclopropyl-fused acetylcholine

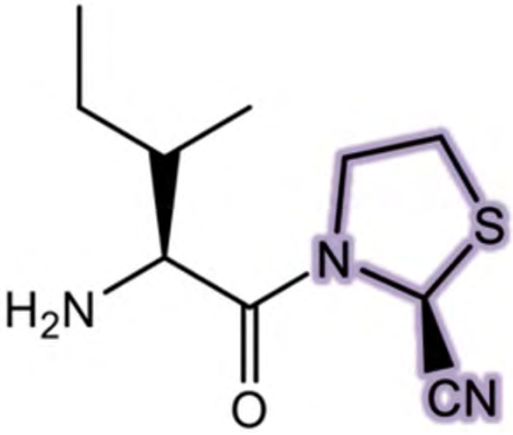
Paper 28 at 31; Ex. 1021 at 243; Ex. 2056 ¶¶ 177-178

Ashworth II (1996): Ex. 2001



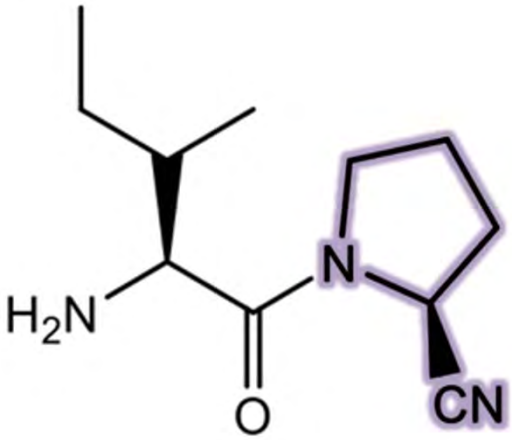
Compound 3

K_i = 0.41 nM ± 0.15



Compound 4

K_i = 1.70 nM ± 0.50

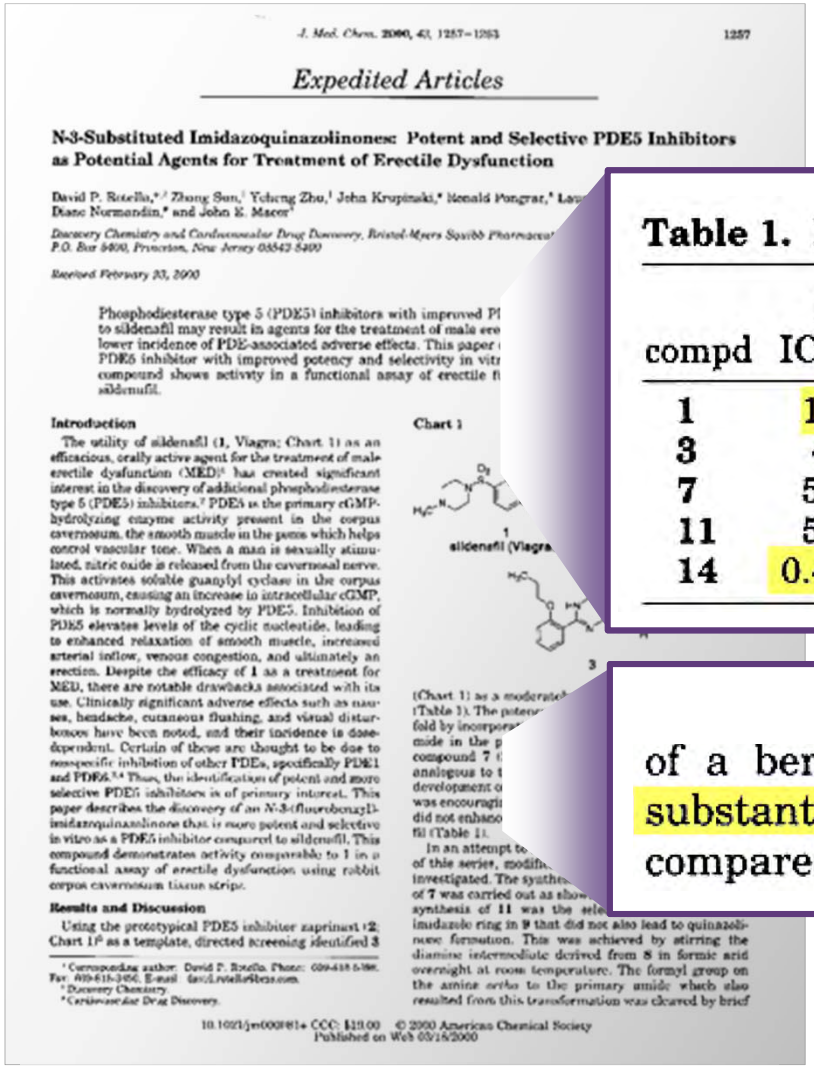


Compound 5

K_i = 2.2 nM ± 0.50

Ex. 2001 at 3, Table I; Ex. 2232

Rotella: Ex. 2254



J. Med. Chem. 2000, 43, 1257−1263 1257

Expedited Articles

N-3-Substituted Imidazoquinazolinones: Potent and Selective PDE5 Inhibitors as Potential Agents for Treatment of Erectile Dysfunction

David P. Rotella,*,† Zhong Sun,† Yuheng Zhu,† John Krupinski,‡ Ronald Pongrac,‡ Lan Diane Normandin,‡ and John E. Macor†

Discovery Chemistry and Cardiovascular Drug Discovery, Bristol-Myers Squibb Pharmaceutical Research Institute, P.O. Box 4000, Princeton, New Jersey 08543-5400

Received February 23, 2000

Phosphodiesterase type 5 (PDE5) inhibitors with improved P… to sildenafil may result in agents for the treatment of male ere… lower incidence of PDE-associated adverse effects. This paper … PDE5 inhibitor with improved potency and selectivity in vitr… compound shows activity in a functional assay of erectile f… sildenafil.

Introduction

The utility of sildenafil (**1**, Viagra; Chart 1) as an efficacious, orally active agent for the treatment of male erectile dysfunction (MED)[1] has created significant interest in the discovery of additional phosphodiesterase type 5 (PDE5) inhibitors.[2] PDE5 is the primary cGMP-hydrolyzing enzyme activity present in the corpus cavernosum, the smooth muscle in the penis which helps control vascular tone. When a man is sexually stimulated, nitric oxide is released from the cavernosal nerve. This activates soluble guanylyl cyclase in the corpus cavernosum, causing an increase in intracellular cGMP, which is normally hydrolyzed by PDE5. Inhibition of PDE5 elevates levels of the cyclic nucleotide, leading to enhanced relaxation of smooth muscle, increased arterial inflow, venous congestion, and ultimately an erection. Despite the efficacy of **1** as a treatment for MED, there are notable drawbacks associated with its use. Clinically significant adverse effects such as nausea, headache, cutaneous flushing, and visual disturbances have been noted, and their incidence is dose-dependent. Certain of these are thought to be due to nonspecific inhibition of other PDEs, specifically PDE1 and PDE6.[3,4] Thus, the identification of potent and more selective PDE5 inhibitors is of primary interest. This paper describes the discovery of an *N*-3-(fluorobenzyl)-imidazoquinazolinone that is more potent and selective in vitro as a PDE5 inhibitor compared to sildenafil. This compound demonstrates activity comparable to **1** in a functional assay of erectile dysfunction using rabbit corpus cavernosum tissue strips.

Results and Discussion

Using the prototypical PDE5 inhibitor zaprinast (**2**, Chart 1)[5] as a template, directed screening identified **3**

Chart 1

1 sildenafil (Viagra

3

(Chart 1) as a moderate… (Table 1). The poten… fold by incorpora… mide in the p… compound **7** … analogous to … development o… was encouragi… did not enhanc… fil (Table 1).

In an attempt to … of this series, modifi… investigated. The synthe… of **7** was carried out as show… synthesis of **11** was the sele… imidazole ring in **9** that did not also lead to quinazoli… none formation. This was achieved by stirring the diamine intermediate derived from **8** in formic acid overnight at room temperature. The formyl group on the amine ortho to the primary amide which also resulted from this transformation was cleaved by brief

* Corresponding author: David P. Rotella. Phone: 609-818-3486. Fax: 609-818-3450. E-mail: david.rotella@bms.com.
† Discovery Chemistry.
‡ Cardiovascular Drug Discovery.

10.1021/jm000081+ CCC: $19.00 © 2000 American Chemical Society
Published on Web 03/16/2000

Table 1. PDE5 IC_{50} and Selectivity Ratios for Other PDEs[a]

compd	PDE5 IC_{50} (nM)[b]	IC_{50} ratio PDE1/5	PDE2/5	PDE3/5	PDE4/5	PDE6/5
1	1.6 ± 0.5	140	$>10^4$	3500	2600	8
3	44 ± 19	200	360	300	100	1
7	5.3 ± 0.6	90	1300	5900	1600	2
11	5.3 ± 1.1	3400	$>10^4$	8800	600	20
14	0.48 ± 0.1	$>10^5$	$>10^5$	$>10^5$	4200	60

Addition of a benzyl moiety at N-3 of this template confers substantial improvement in PDE selectivity and potency compared to sildenafil.

Paper 62 at Observation 11; Ex. 2221 at 36:1-38:3; Ex. 2254 at 2

Dr. Rotella

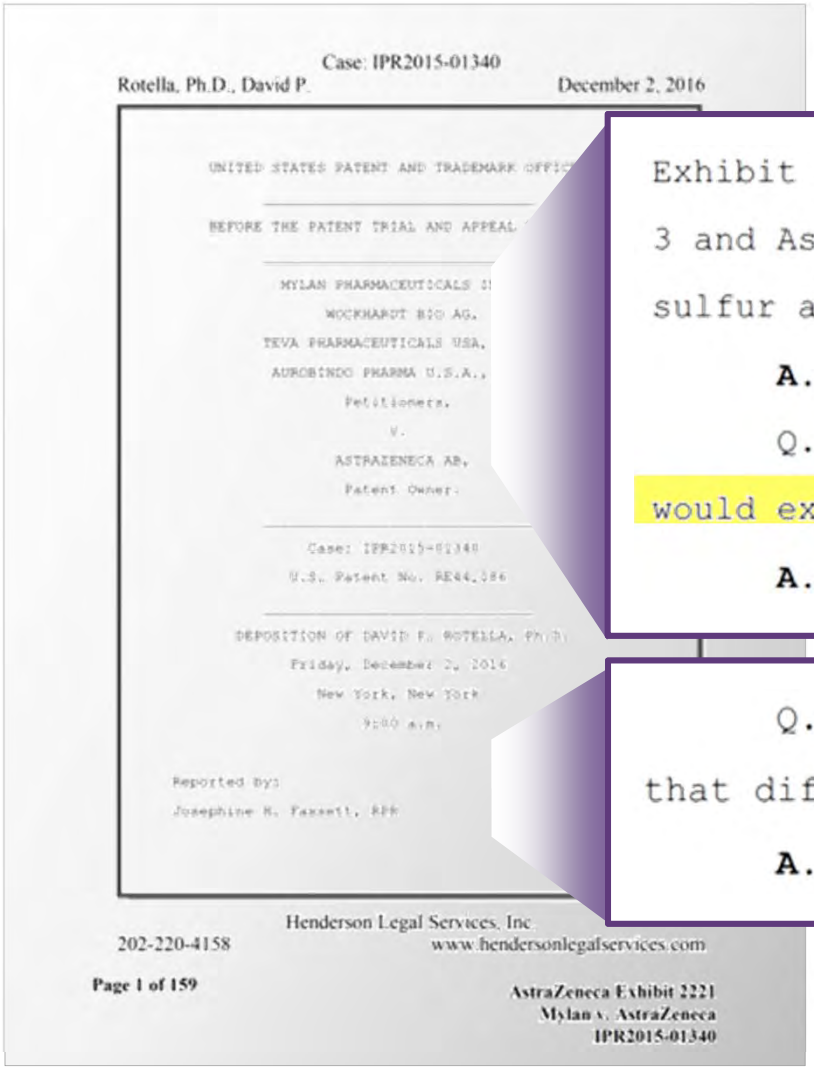


Exhibit 2232, when we look at Ashworth II compound 3 and Ashworth II compound 4, they both have a sulfur atom in the ring, correct?

A. Yes, they do.

Q. Okay. So both of those rings you would expect to be the same size, right?

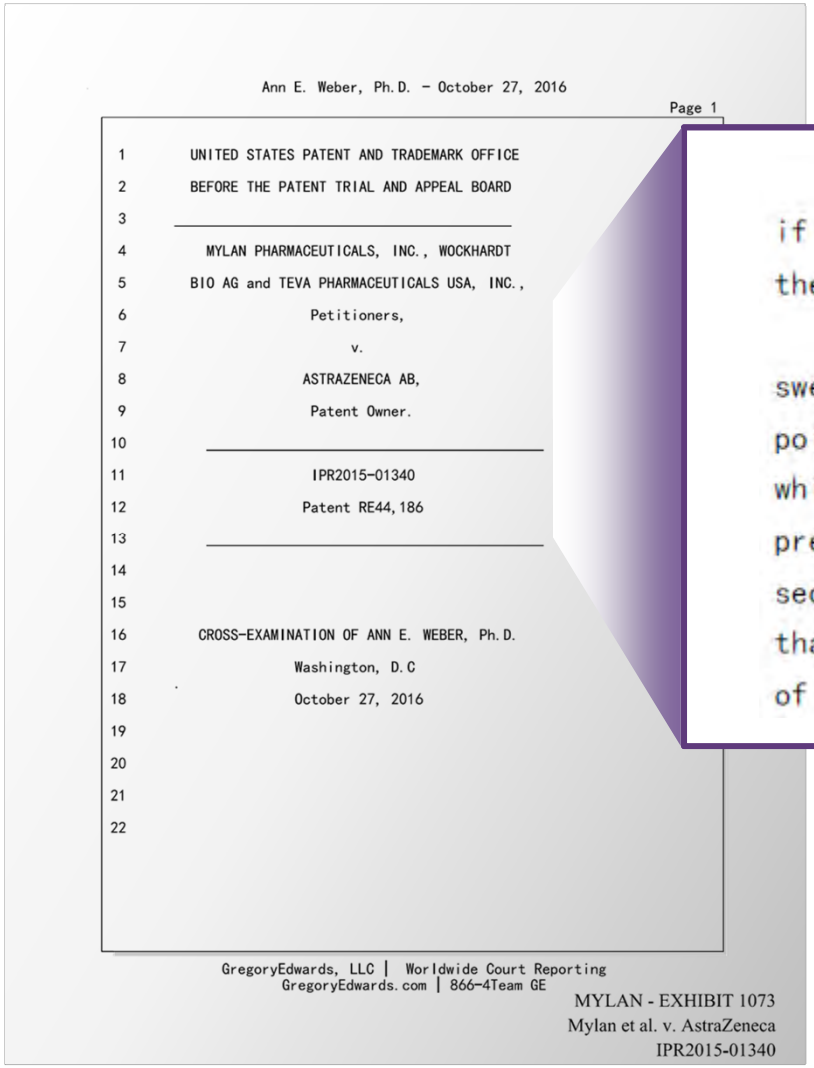
A. Yes.

Q. Okay. So whatever's responsible for that difference, it's not size, right?

A. I don't know what the difference is.

Paper 62 at Observation 12; Ex. 2221 at 38:6-12, 38:16-18

Dr. Weber



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IPR2015-01340

Patent RE44,186

CROSS-EXAMINATION OF ANN E. WEBER, Ph.D.

Washington, D.C

October 27, 2016

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MYLAN - EXHIBIT 1073
Mylan et al. v. AstraZeneca
IPR2015-01340

In your review of the prior art what, if any, support for such a sweet spot argument is there?

A I didn't find any support for such a sweet spot argument. And in particular I would point to Augustyns 2 which clearly shows that while the thiazolidine slightly larger ring is preferred in one position it is not preferred in a second position, indicating that something other than size is contributing to the greater potency of that compound.

Ex. 1073 (Weber Redirect) at 104:3-13, 121:14-122:1 (correcting Augustyns 2 to Ashworth II)

Villhauer-949: Ex. 2158

US006110949A

United States Patent [19]
Villhauer

[11] **Patent Number: 6,110,949**
[45] **Date of Patent: *Aug. 29, 2000**

[54] **N-(SUBSTITUTED GLYCYL)-4-CYANOTHIAZOLIDINES, PHARMACEUTICAL COMPOSITIONS CONTAINING THEM AND THEIR USE IN INHIBITING DIPEPTIDYL PEPTIDASE-IV**

[75] Inventor: **Edwin Bernard Villhauer**, Morristown, N.J.

[73] Assignee: **Novartis AG**, Basel, Switzerland

[*] Notice: This patent issued on a continued prosecution application filed under 37 CFR 1.53(d), and is subject to the twenty year patent term provisions of 35 U.S.C. 154(a)(2).

[21] Appl. No.: **09/339,503**

[22] Filed: **Jun. 24, 1999**

[51] **Int. Cl.**[7] **C07D 207/00**
[52] **U.S. Cl.** **514/365**, 548/200
[58] **Field of Search** 548/200, 514/365

[56] **References Cited**

U.S. PATENT DOCUMENTS

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FOREIGN PATENT DOCUMENTS

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90/12005 10/1990 WIPO .
91/16339 10/1991 WIPO .
93/08259 4/1993 WIPO .
95/11689 5/1995 WIPO .
95/13069 5/1995 WIPO .
95/15309 6/1995 WIPO .
95/29190 11/1995 WIPO .
95/29691 11/1995 WIPO .
95/34538 12/1995 WIPO .
98/19998 5/1998 WIPO .
99/38501 8/1999 WIPO .

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Primary Examiner—Robert Gerstl
Attorney, Agent, or Firm—Joseph J. Borovian

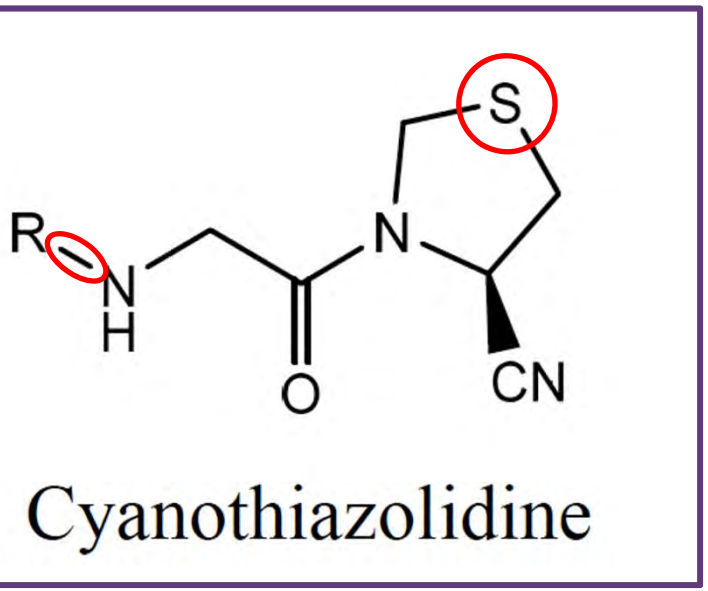
[57] **ABSTRACT**

The invention discloses certain N-(substituted glycyl)-4-cyanothiazolidines, pharmaceutical compositions containing said compounds as an active ingredient thereof, and the use of said compounds in inhibiting dipeptidyl peptidase-IV.

38 Claims, No Drawings

Page 1 of 11

AstraZeneca Exhibit 2158
Mylan v. AstraZeneca
IPR2015-01340



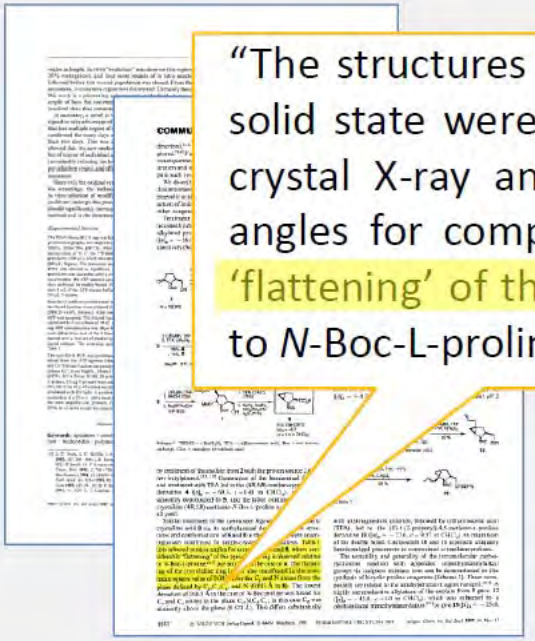
Cyanothiazolidine

Paper 62 at Observation 13; Ex. 2158; Ex. 2056 ¶ 113

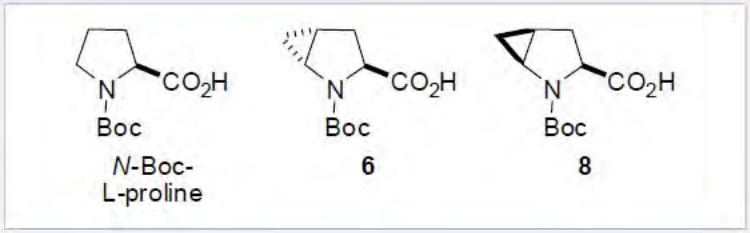
Teachings of Hanessian

Mylan Demonstrative Exhibit

Cyclopropanation Modulates Proline Conformation



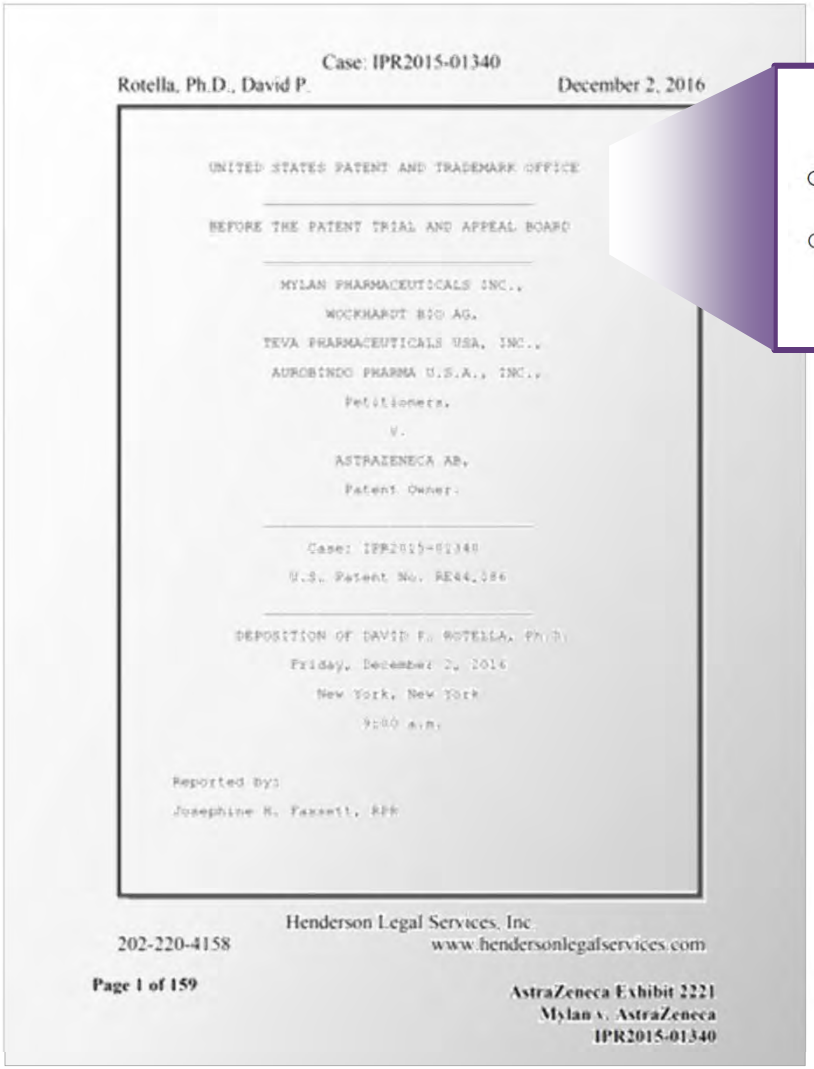
"The structures and conformations of **6** and **8** in the solid state were unambiguously confirmed by single-crystal X-ray analysis. Table 1 lists selected torsion angles for compounds **6** and **8**, where considerable 'flattening' of the pyrrolidine ring is observed relative to *N*-Boc-L-proline[.]"



Source: EX1010 (Hanessian '97) at 1882; EX1003 (Rotella Decl.), ¶135.

13

Dr. Rotella



Case: IPR2015-01340
Rotella, Ph.D., David P. December 2, 2016

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC.,
WOCKHARDT BIO AG,
TEVA PHARMACEUTICALS USA, INC.,
AUROBINDO PHARMA U.S.A., INC.,
Petitioners,
v.
ASTRAZENECA AB,
Patent Owner.

Case: IPR2015-01340
U.S. Patent No. RE44,186

DEPOSITION OF DAVID P. ROTELLA, Ph.D.
Friday, December 2, 2016
New York, New York
9:00 a.m.

Reported by:
Josephine M. Fassett, RPR

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202-220-4158 www.hendersonlegalservices.com

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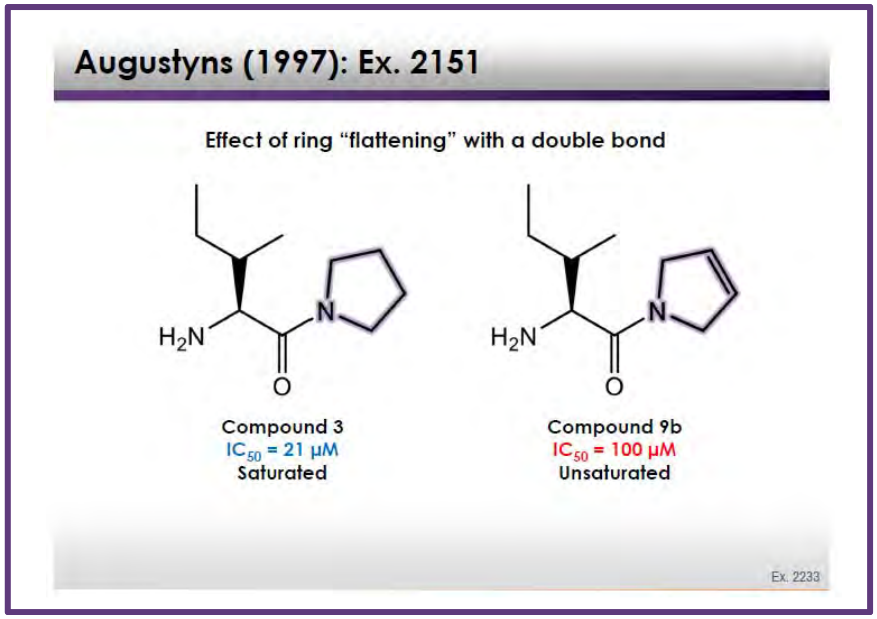
AstraZeneca Exhibit 2221
Mylan v. AstraZeneca
IPR2015-01340

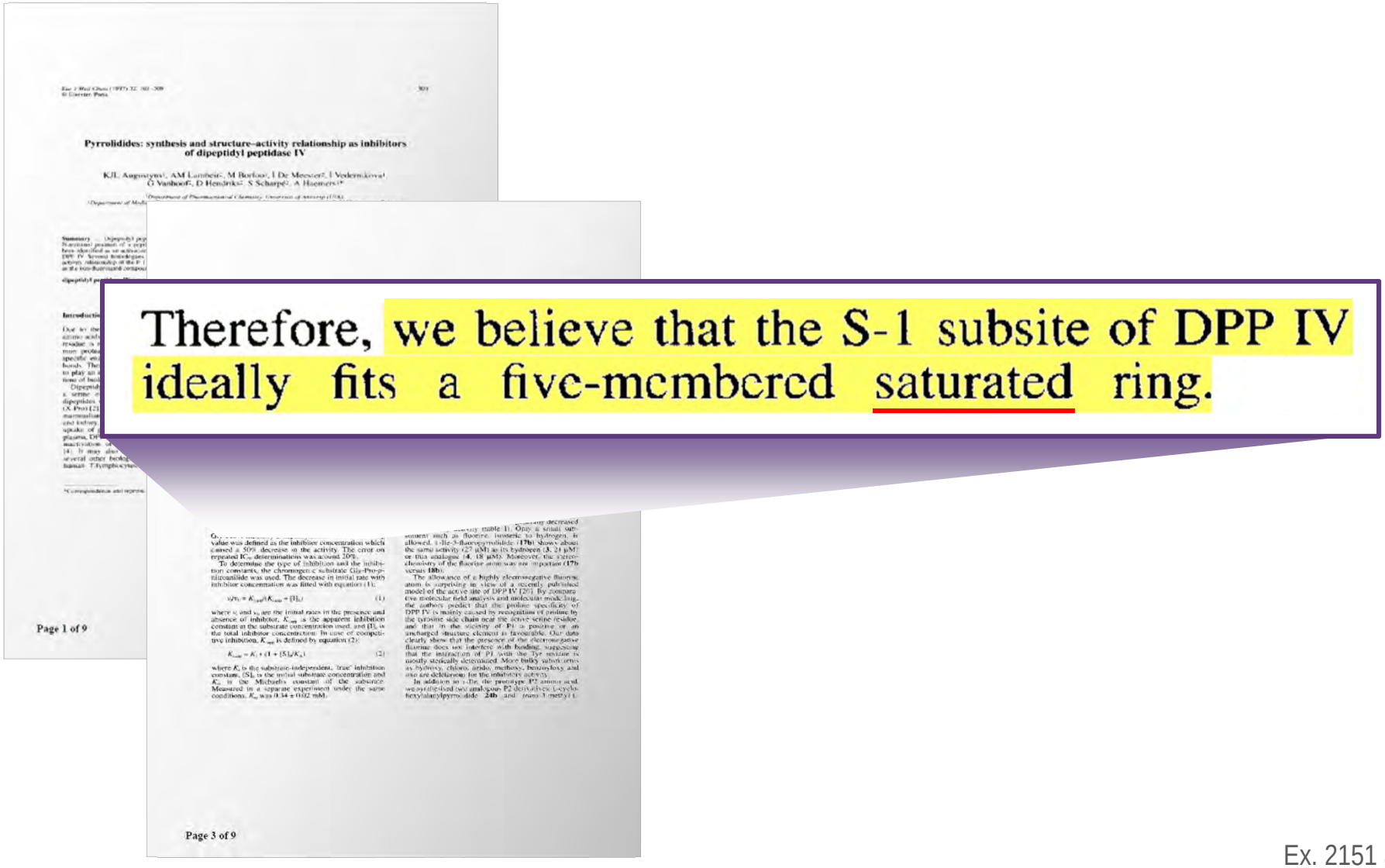
You would agree that introducing a double bond into that ring would flatten the ring, correct?

A. Yes, it would flatten the ring.



Paper 62 at Observation 15; Ex. 2221 at 58:21-24; Ex. 2151; Ex. 2233

Augustyns (1997): Ex. 2151



Pyrrolidides: synthesis and structure–activity relationship as inhibitors of dipeptidyl peptidase IV

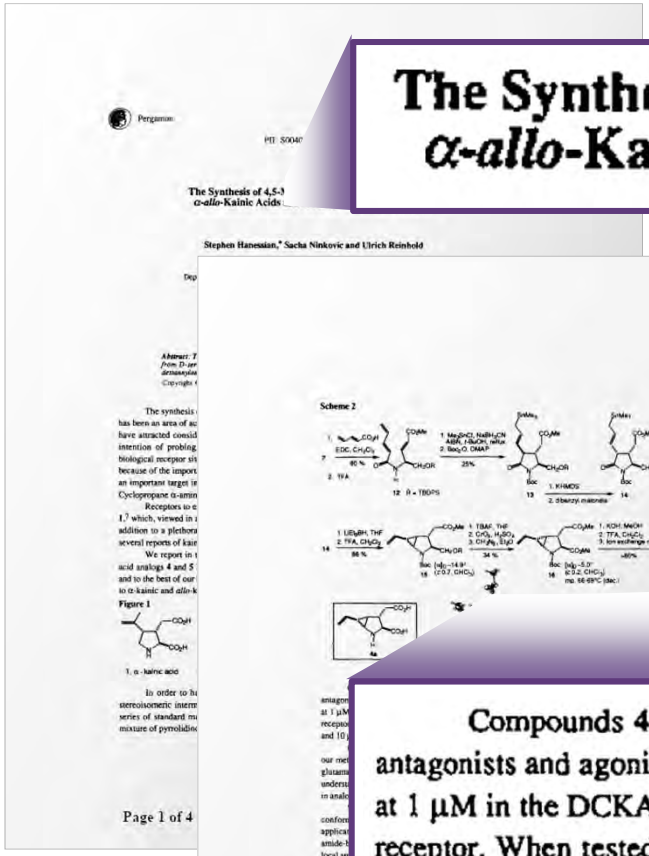
Page 1 of 9

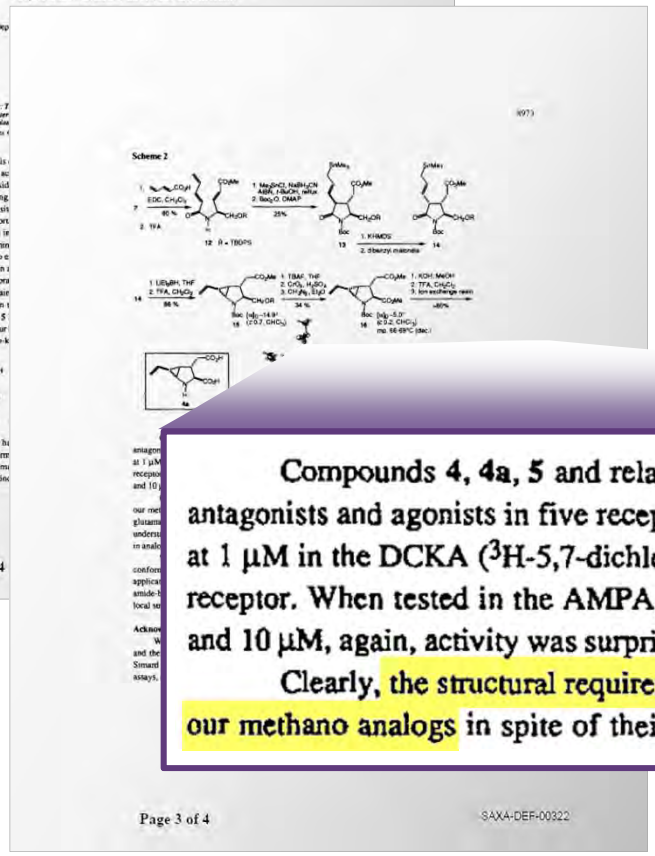
Page 3 of 9

Therefore, we believe that the S-1 subsite of DPP IV ideally fits a five-membered saturated ring.

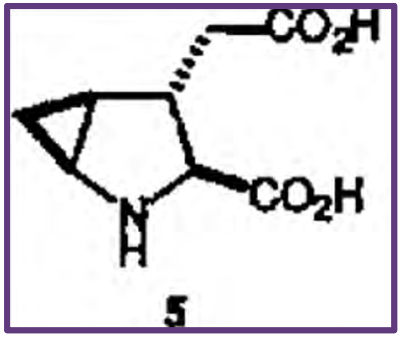
Ex. 2151 at 3

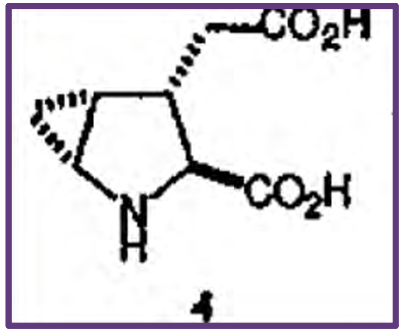
Hanessian (1996): Ex. 2043





The Synthesis of 4,5-Methano Congeners of α-Kainic and *α-allo*-Kainic Acids as Probes for Glutamate Receptors



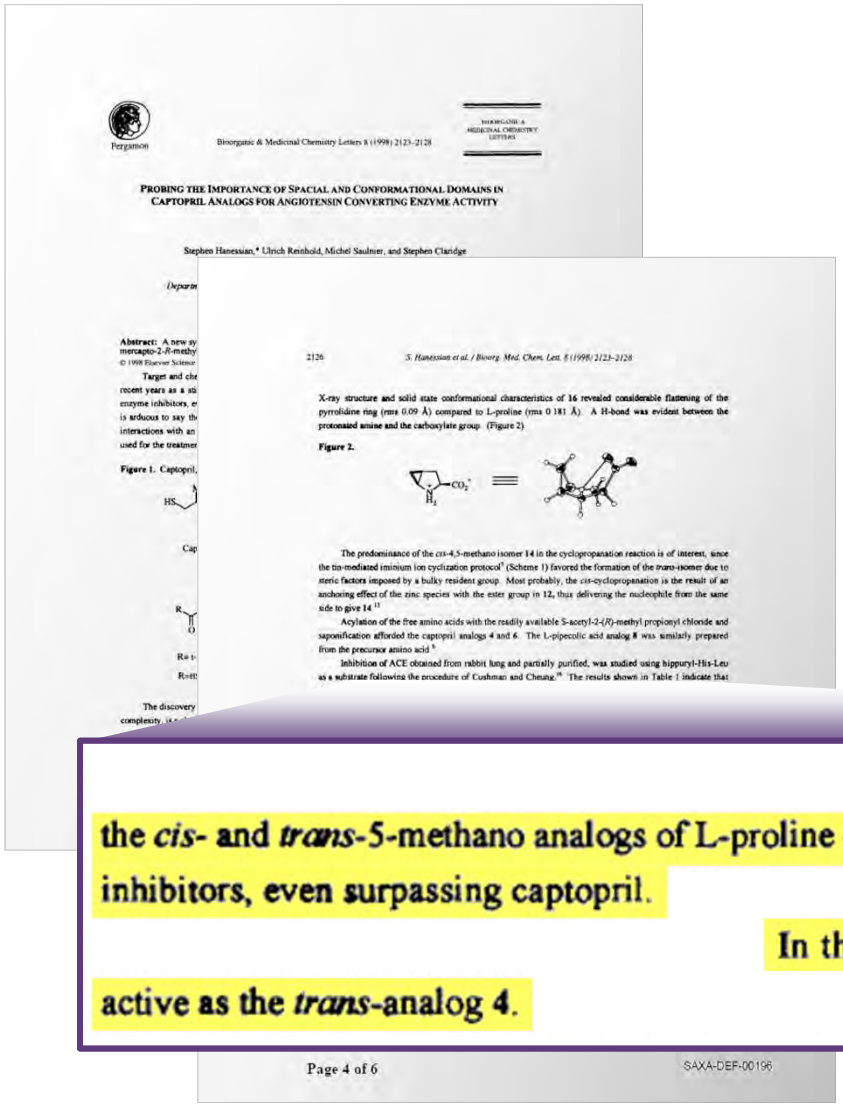


Compounds **4**, **4a**, **5** and related amino acids from another series[11] were tested for their binding as antagonists and agonists in five receptor assays.[5a] Unfortunately, no significant binding affinity was found at 1 μM in the DCKA (^{3}H-5,7-dichlorokynurenic acid) assay for the glycine recognition site of the NMDA receptor. When tested in the AMPA, kainate, and other receptor binding assays at concentrations of 1 μM and 10 μM, again, activity was surprisingly low compared to standards.[17]

Clearly, the structural requirements for effective binding to these receptors have not been satisfied by our methano analogs in spite of their novel structures.

Ex. 2043 at 3; Paper 62 at Observation 16; Ex. 2221, 62:1-63:3

Hanessian (1998): Ex. 2028



Pergamon

Bioorganic & Medicinal Chemistry Letters 8 (1998) 2123–2128

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

PROBING THE IMPORTANCE OF SPACIAL AND CONFORMATIONAL DOMAINS IN CAPTOPRIL ANALOGS FOR ANGIOTENSIN CONVERTING ENZYME ACTIVITY

Stephen Hanessian,* Ulrich Reinhold, Michel Saulnier, and Stephen Claridge

Abstract: A new sy
mercapto-2-R-methy
© 1998 Elsevier Science

Target and che
recent years as a sti
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interactions with an
used for the treatmer

Figure 1. Captopril,

The discovery
complexity, it s

2126 S. Hanessian et al. / Bioorg. Med. Chem. Lett. 8 (1998) 2123–2128

X-ray structure and solid state conformational characteristics of 16 revealed considerable flattening of the pyrrolidine ring (rms 0.09 Å) compared to L-proline (rms 0.181 Å). A H-bond was evident between the protonated amine and the carboxylate group. (Figure 2).

Figure 2.

The predominance of the *cis*-4,5-methano isomer 14 in the cyclopropanation reaction is of interest, since the tin-mediated iminium ion cyclization protocol[3] (Scheme 1) favored the formation of the *trans*-isomer due to steric factors imposed by a bulky resident group. Most probably, the *cis*-cyclopropanation is the result of an anchoring effect of the zinc species with the ester group in 12, thus delivering the nucleophile from the same side to give 14.[11]

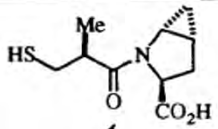
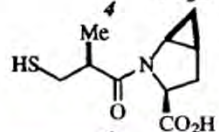
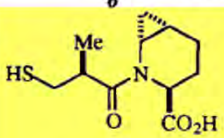
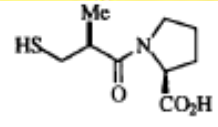
Acylation of the free amino acids with the readily available S-acetyl-2-(*R*)-methyl propionyl chloride and saponification afforded the captopril analogs 4 and 6. The L-pipecolic acid analog 8 was similarly prepared from the precursor amino acid.[5]

Inhibition of ACE obtained from rabbit lung and partially purified, was studied using hippuryl-His-Leu as a substrate following the procedure of Cushman and Cheung.[16] The results shown in Table 1 indicate that

Page 4 of 6

SAXA-DEF-00196

Table 1 Inhibition Tests on Angiotensin Converting Enzyme (ACE)[a]

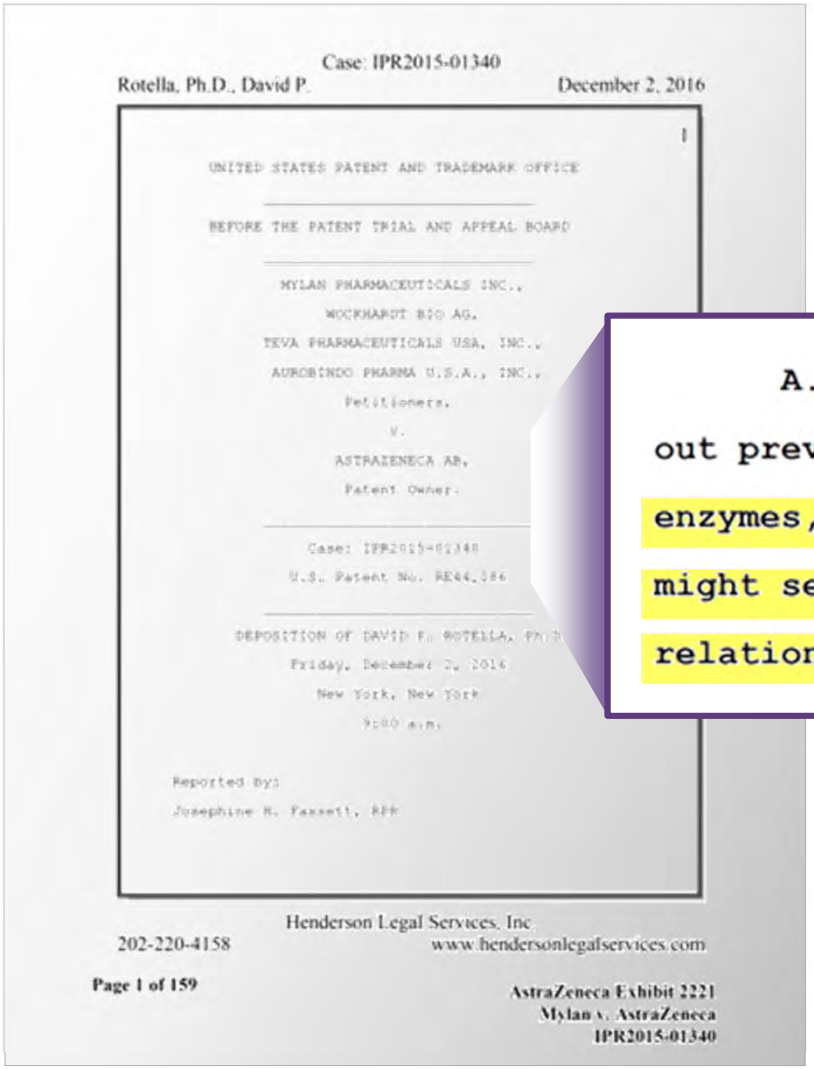
Compound	IC_{50}
 **4**	7.6 (± 0.7 nM)
 **6**	6.6 (± 0.3 nM)
 **8**	5.3 (± 0.2 nM)
 **1**, Captopril	13.0 (± 1.0 nM)

The results shown in Table 1 indicate that the *cis*- and *trans*-5-methano analogs of L-proline **4**,**6**, and the *trans*-L-pipecolic acid analog **8** are highly potent inhibitors, even surpassing captopril.

In this respect it is of interest that the *cis*-analog **6** is equally as active as the *trans*-analog **4**.

Paper 62 at Observation 16; Ex. 2028

Dr. Rotella



Case: IPR2015-01340
Rotella, Ph.D., David P. December 2, 2016

UNITED STATES PATENT AND TRADEMARK OFFICE

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MYLAN PHARMACEUTICALS INC.,
WOCKHARDT BIO AG,
TEVA PHARMACEUTICALS USA, INC.,
AUROBINDO PHARMA U.S.A., INC.,
Petitioners,
v.
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Patent Owner.

Case: IPR2015-01340
U.S. Patent No. RE44,186

DEPOSITION OF DAVID P. ROTELLA, PhD
Friday, December 2, 2016
New York, New York
9:00 a.m.

Reported by:
Josephine M. Fassett, RPR

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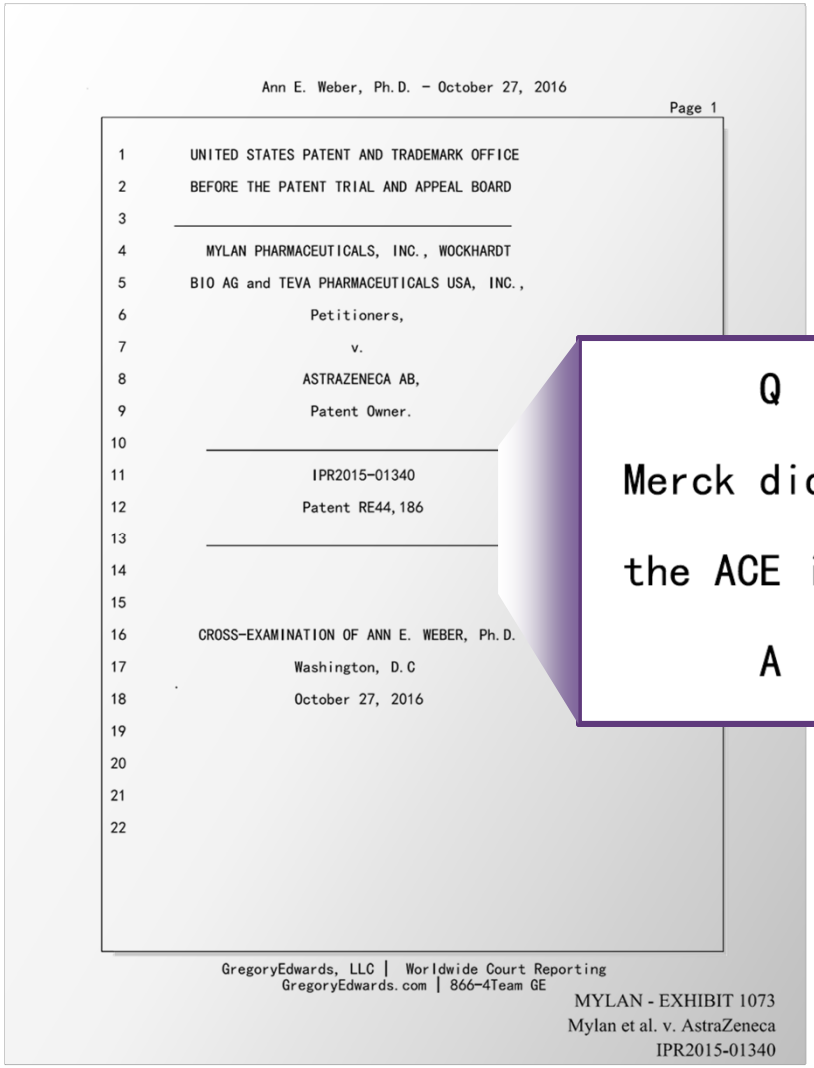
AstraZeneca Exhibit 2221
Mylan v. AstraZeneca
IPR2015-01340

A. That's correct. And, as you pointed out previously, DPP-4 and ACE are different enzymes, and so it's reasonable to expect that you might see a difference in structure activity relationships between the two enzymes.

Paper 62 at Observation 16; Ex. 2221 at 65:19-23

Dr. Weber



Ann E. Weber, Ph.D. - October 27, 2016

Page 1

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS, INC., WOCKHARDT BIO AG and TEVA PHARMACEUTICALS USA, INC.,

Petitioners,

v.

ASTRAZENECA AB,

Patent Owner.

IPR2015-01340

Patent RE44,186

CROSS-EXAMINATION OF ANN E. WEBER, Ph.D.

Washington, D.C

October 27, 2016

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MYLAN - EXHIBIT 1073
Mylan et al. v. AstraZeneca
IPR2015-01340

Q In your work on DPP-4 inhibitors at Merck did you or your colleagues look to any of the ACE inhibitor art for guidance?

A No, we absolutely never did that.

Ex. 1073 (Weber Redirect) at 118:11-119:5; *see* Ex. 2056 ¶ 187; *see also* Paper 28 at 37

Mylan's Position on Stability

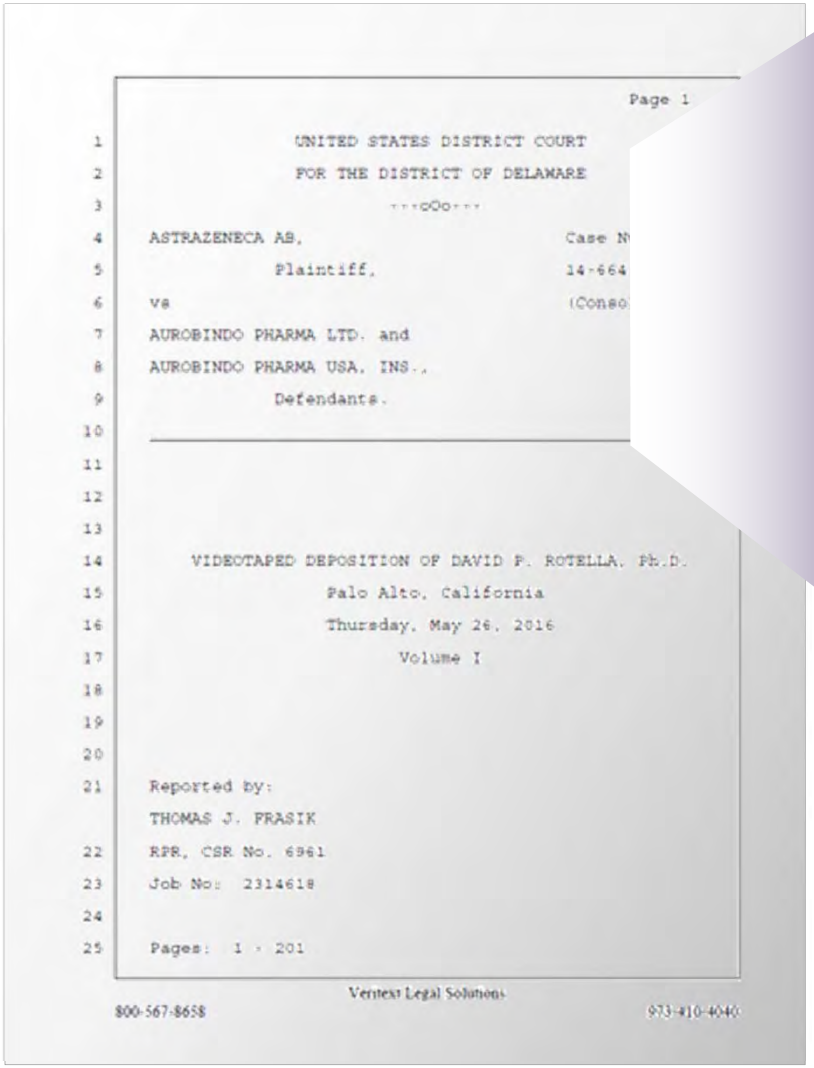
As evidenced by Ashworth I and II, there was significant interest in the art for DP-IV inhibitors like compound **25**, as a result of its favorable potency and stability. Ashworth II tried to optimize these compounds, including compound **25**.

Motivation to modify:

at 1163. Similarly, Augustyns teaches, "[I]n the case of [DP-IV], a cyclization reaction can occur between the free amino group of the P_2 amino acid and the electrophile attached to the proline mimic in P_1, causing serious stability problems" and further that this issue was "not surprising [and] well known." Ex. 2007 at 314. Based on these teachings, there was clear motivation to modify DP-IV inhibitors like compound **25** to improve their stability. Pet. at 24-25.

Paper 28 at 28-29; Paper 11 at 4, 5

Dr. Rotella



Page 1

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE
---oOo---

ASTRAZENECA AB,
Plaintiff,
vs
AURODINDO PHARMA LTD. and
AURODINDO PHARMA USA, INS.,
Defendants.

Case N
14-664
(Conso

VIDEOTAPED DEPOSITION OF DAVID P. ROTELLA, Ph.D.
Palo Alto, California
Thursday, May 26, 2016
Volume I

Reported by:
THOMAS J. PRASIK
RPR, CSR No. 6961
Job No: 2314618

Pages: 1 - 201

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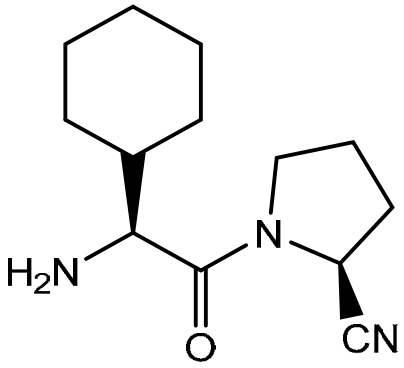
Q. Well, what is the objective of putting the cyclopropane on the molecule, in your opinion?

A. There are two possible objectives based on the data -- there are at least two possible objectives based on the data available surrounding compound 25.

Q. And what are they?

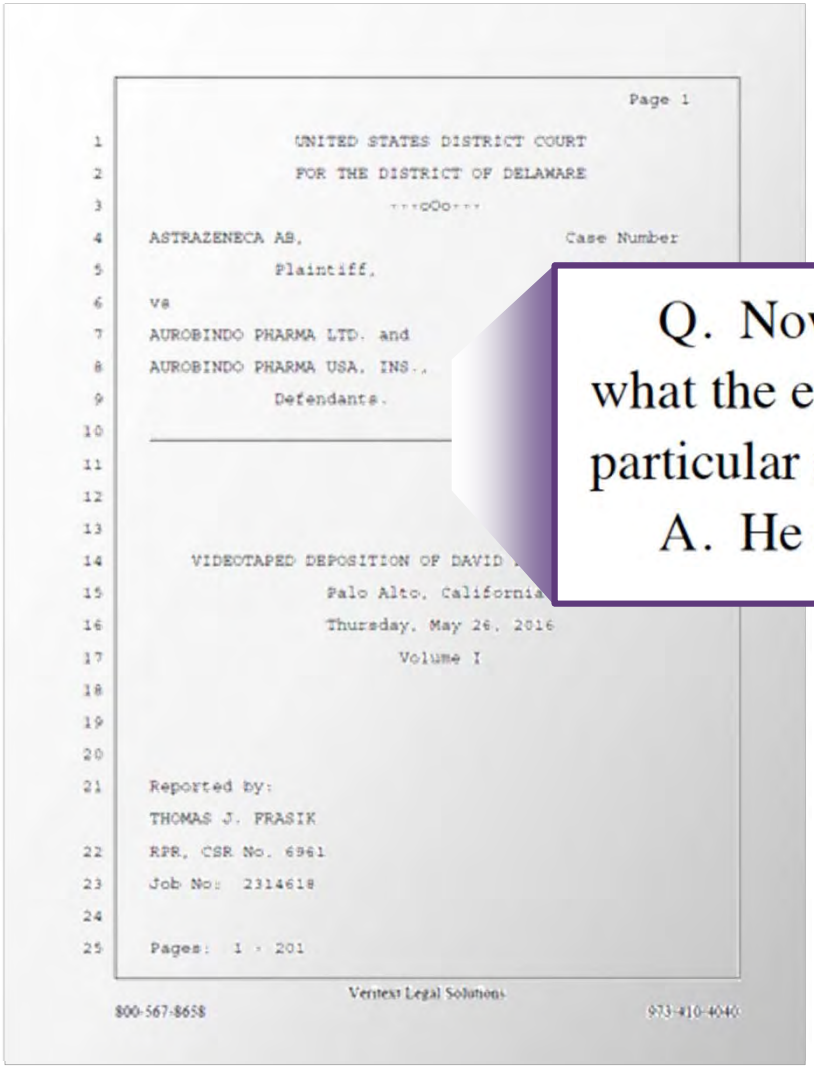
A. One would be to explore whether or not you could improve potency. A second would be whether or not you could improve solution stability. One might also explore how that -- those changes, either by themselves or in combination with two changes, might also improve or change -- sorry -- to improve solid-state stability. Furthermore, since nothing is known, at least at this point in time, about other properties associated with compound 25, you'd want to understand what those properties were and adjust them as need be. Generally speaking, those properties are things that we call, collectively, pharmaceutical properties.



Ashworth I Compound 25

Paper 28 at 25; Ex. 2174 at 115:21-116:13

Dr. Rotella



Page 1

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE
---oOo---

ASTRAZENECA AB,
Plaintiff,
vs
AURORINDO PHARMA LTD. and
AURORINDO PHARMA USA, INS.,
Defendants.

Case Number

VIDEOTAPED DEPOSITION OF DAVID
Palo Alto, California
Thursday, May 26, 2016
Volume I

Reported by:
THOMAS J. PRASIK
RPR, CSR No. 6961
Job No: 2314618

Pages: 1 - 201

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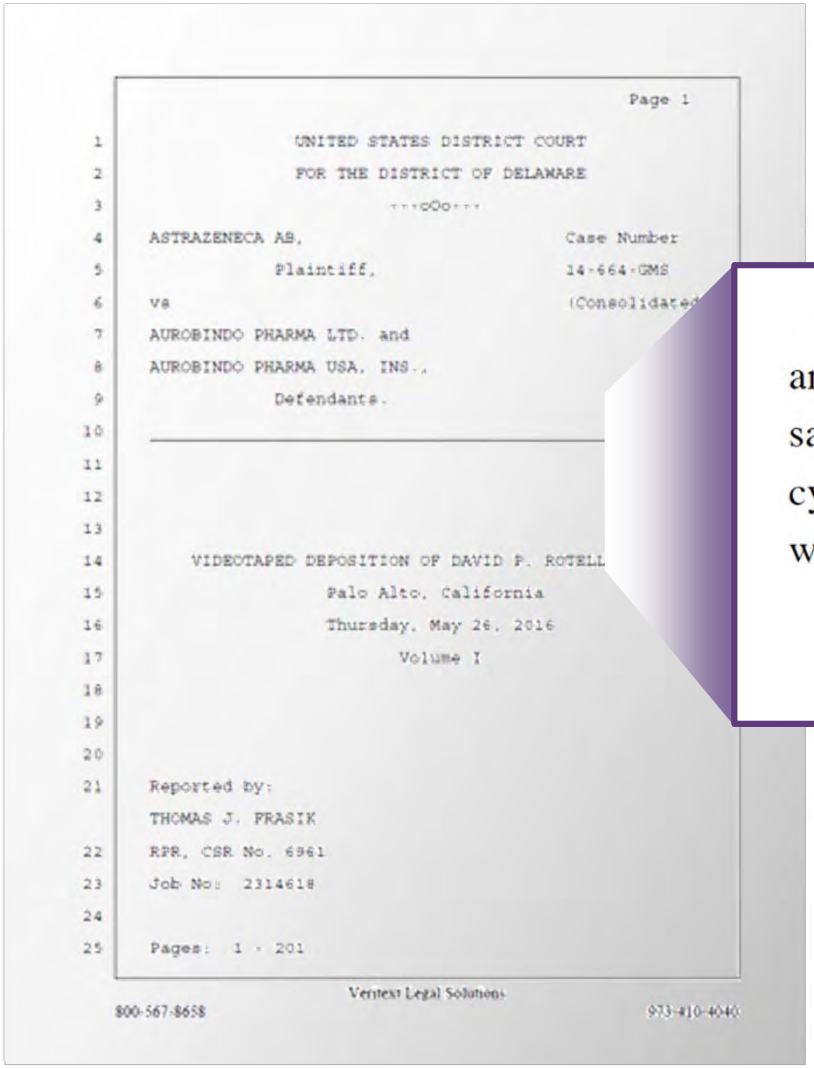
Q. Now, Hanessian doesn't tell you in this article what the effect of that flattening is going to be in any particular system; correct?

A. He does not.

Paper 28 at 33; Ex. 2174 at 127:1-4

Dr. Rotella



Page 1

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE
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ASTRAZENECA AB,
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Defendants.

Case Number
14-664-GMS
(Consolidated

VIDEOTAPED DEPOSITION OF DAVID P. ROTELL
Palo Alto, California
Thursday, May 26, 2016
Volume I

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THOMAS J. PRASIK
RPR, CSR No. 6961
Job No: 2314618

Pages: 1 - 201

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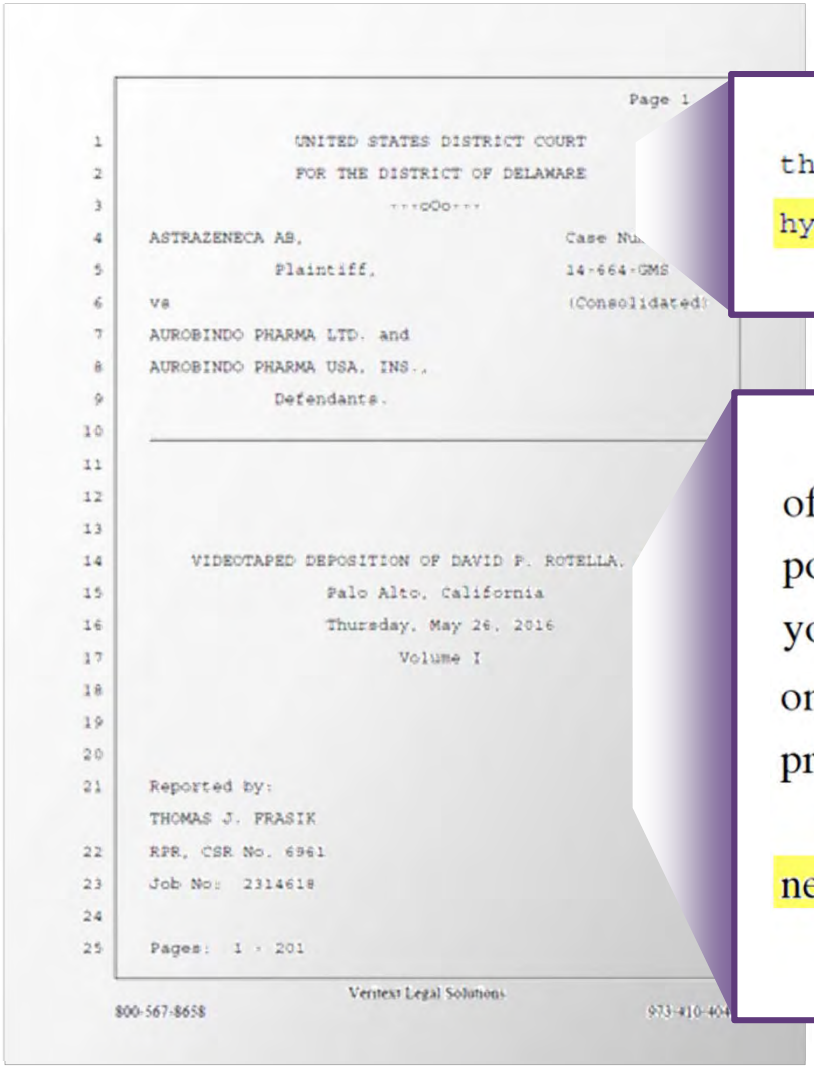
Q. Now, I think we can agree that there wasn't anything in the literature prior to the invention of saxagliptin that actually suggested that cyclopropanation of an Ashworth One-type DPP4 inhibitor would improve its stability; correct?

MS. STEINER: Objection to form.

THE WITNESS: That is true.

Paper 28 at 32; Ex. 2174 at 142:3-9

Dr. Rotella



Page 1

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE
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ASTRAZENECA AB,
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(Consolidated)

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Reported by:
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RPR, CSR No. 6961
Job No: 2314618

Pages: 1 - 201

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Q. Okay. And just to be clear, fusing a ring to that pyrrolidine ring does involve replacing two of the hydrogen atoms with something else; correct?

A. It does.

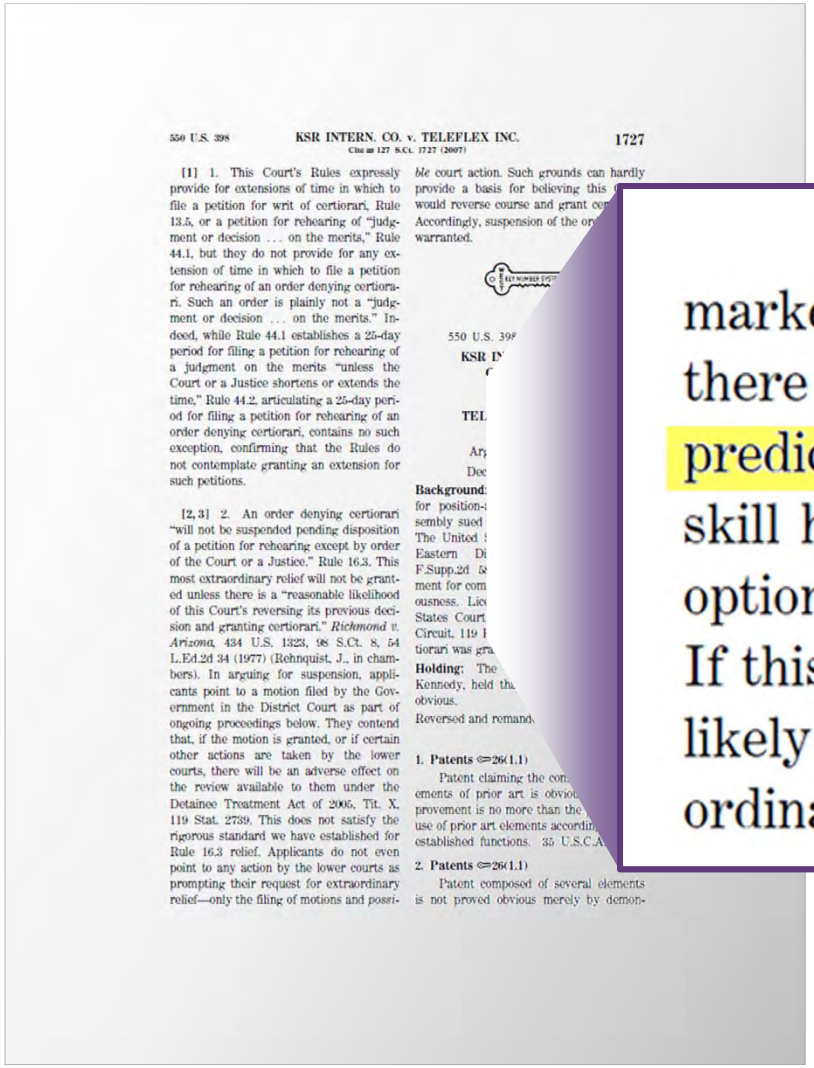
And in the process of that modification of orientation in space, you may observe effects on potency, you may observe effects on solution stability, you may observe other effects on other properties that one might measure in connection with a drug discovery project.

Q. And those effects might be either positive or negative; correct?

A. They might be, yes.

Paper 28 at 32-33; Ex. 2174 at 119:10-13, 119:22-120:5

KSR Int'l Co. v. Teleflex Inc.



550 U.S. 398 KSR INTERN. CO. v. TELEFLEX INC. 1727
Cite as 127 S.Ct. 1727 (2007)

[1] 1. This Court's Rules expressly provide for extensions of time in which to file a petition for writ of certiorari, Rule 13.5, or a petition for rehearing of "judgment or decision ... on the merits," Rule 44.1, but they do not provide for any extension of time in which to file a petition for rehearing of an order denying certiorari. Such an order is plainly not a "judgment or decision ... on the merits." Indeed, while Rule 44.1 establishes a 25-day period for filing a petition for rehearing of a judgment on the merits "unless the Court or a Justice shortens or extends the time," Rule 44.2, articulating a 25-day period for filing a petition for rehearing of an order denying certiorari, contains no such exception, confirming that the Rules do not contemplate granting an extension for such petitions.

[2, 3] 2. An order denying certiorari "will not be suspended pending disposition of a petition for rehearing except by order of the Court or a Justice." Rule 16.3. This most extraordinary relief will not be granted unless there is a "reasonable likelihood of this Court's reversing its previous decision and granting certiorari." *Richmond v. Arizona*, 434 U.S. 1323, 98 S.Ct. 8, 54 L.Ed.2d 34 (1977) (Rehnquist, J., in chambers). In arguing for suspension, applicants point to a motion filed by the Government in the District Court as part of ongoing proceedings below. They contend that, if the motion is granted, or if certain other actions are taken by the lower courts, there will be an adverse effect on the review available to them under the Detainee Treatment Act of 2005, Tit. X, 119 Stat. 2739. This does not satisfy the rigorous standard we have established for Rule 16.3 relief. Applicants do not even point to any action by the lower courts as prompting their request for extraordinary relief—only the filing of motions and *possible* court action. Such grounds can hardly provide a basis for believing this C would reverse course and grant cer Accordingly, suspension of the or warranted.

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Background:
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States Court
Circuit, 119 F
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Holding: The
Kennedy, held tha
obvious.
Reversed and remand

1. Patents ⇐26(1.1)
Patent claiming the com
ements of prior art is obviou
provement is no more than the
use of prior art elements accordi
established functions. 35 U.S.C.A

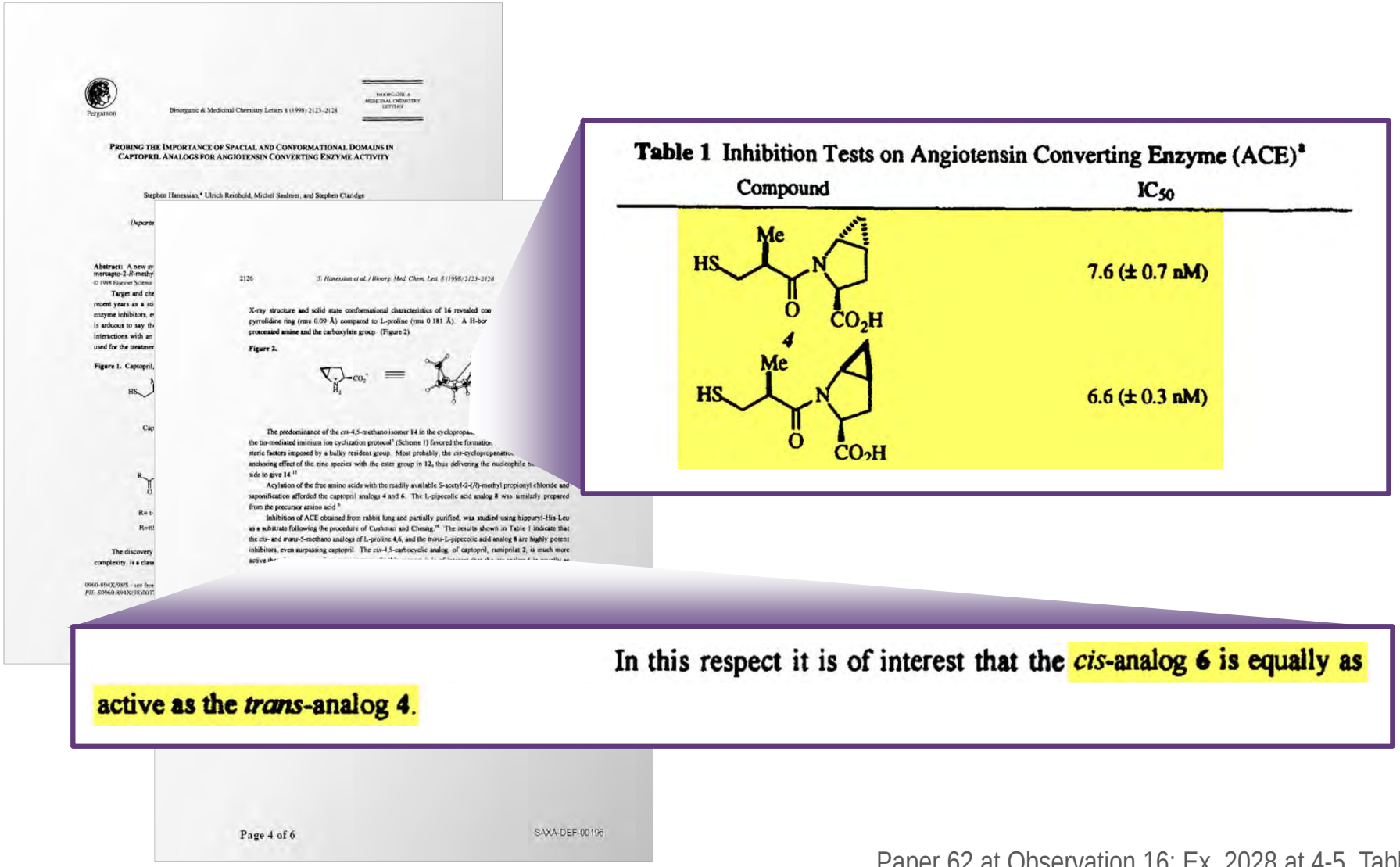
2. Patents ⇐26(1.1)
Patent composed of several elements is not proved obvious merely by demon-

When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.

127 S. Ct. 1727, 1742 (2007)

Effects of Cyclopropanation in DPP-4 Inhibitors

Hanessian (1998): Ex. 2028



Pergamon

Bioorganic & Medicinal Chemistry Letters 8 (1998) 2123–2128

PROBING THE IMPORTANCE OF SPACIAL AND CONFORMATIONAL DOMAINS IN CAPTOPRIL ANALOGS FOR ANGIOTENSIN CONVERTING ENZYME ACTIVITY

Stephen Hanessian,* Ulrich Reinhold, Michel Saulnier, and Stephen Claridge

2126 S. Hanessian et al. / Bioorg. Med. Chem. Lett. 8 (1998) 2123–2128

X-ray structure and solid state conformational characteristics of 16 revealed con pyrrolidine ring (rms 0.09 Å) compared to L-proline (rms 0.181 Å). A H-bor protonated amine and the carboxylate group. (Figure 2).

Figure 2.

The predominance of the *cis*-4,5-methano isomer 14 in the cyclopropa... the tin-mediated iminium ion cyclization protocol[3] (Scheme 1) favored the formation... steric factors imposed by a bulky resident group. Most probably, the *cis*-cyclopropanatio... anchoring effect of the zinc species with the ester group in 12, thus delivering the nucleophile h... side to give 14.[11]

Acylation of the free amino acids with the readily available S-acetyl-2-(*R*)-methyl propionyl chloride and saponification afforded the captopril analogs 4 and 6. The L-pipecolic acid analog 8 was similarly prepared from the precursor amino acid.[5]

Inhibition of ACE obtained from rabbit lung and partially purified, was studied using hippuryl-His-Leu as a substrate following the procedure of Cushman and Cheung.[16] The results shown in Table 1 indicate that the *cis*- and *trans*-5-methano analogs of L-proline 4,6, and the *trans*-L-pipecolic acid analog 8 are highly potent inhibitors, even surpassing captopril. The *cis*-4,5-carbocyclic analog of captopril, ramiprilat 2, is much more active th...

Page 4 of 6 SAXA-DEF-00196

Table 1 Inhibition Tests on Angiotensin Converting Enzyme (ACE)[a]

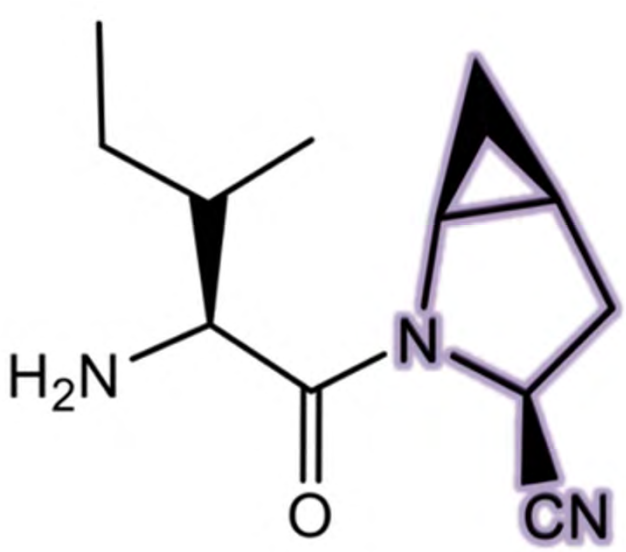
Compound	IC_{50}
4	7.6 (± 0.7 nM)
6	6.6 (± 0.3 nM)

In this respect it is of interest that the *cis*-analog **6** is equally as active as the *trans*-analog **4**.

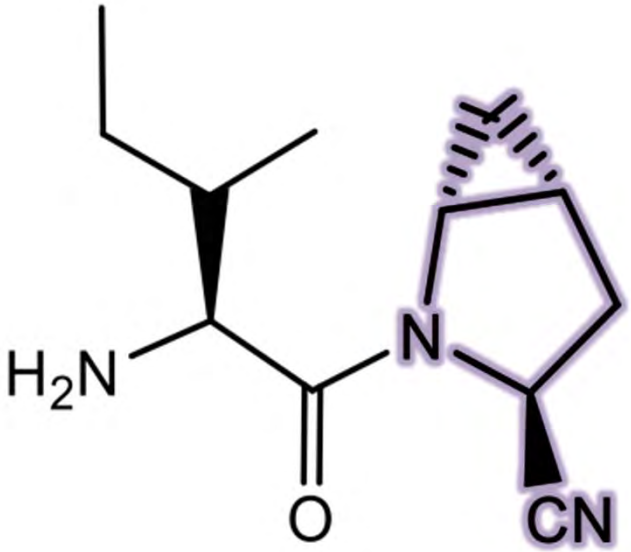
Paper 62 at Observation 16; Ex. 2028 at 4-5, Table 1

Effects of Cyclopropanation: Magnin (2004)

Effect of ORIENTATION



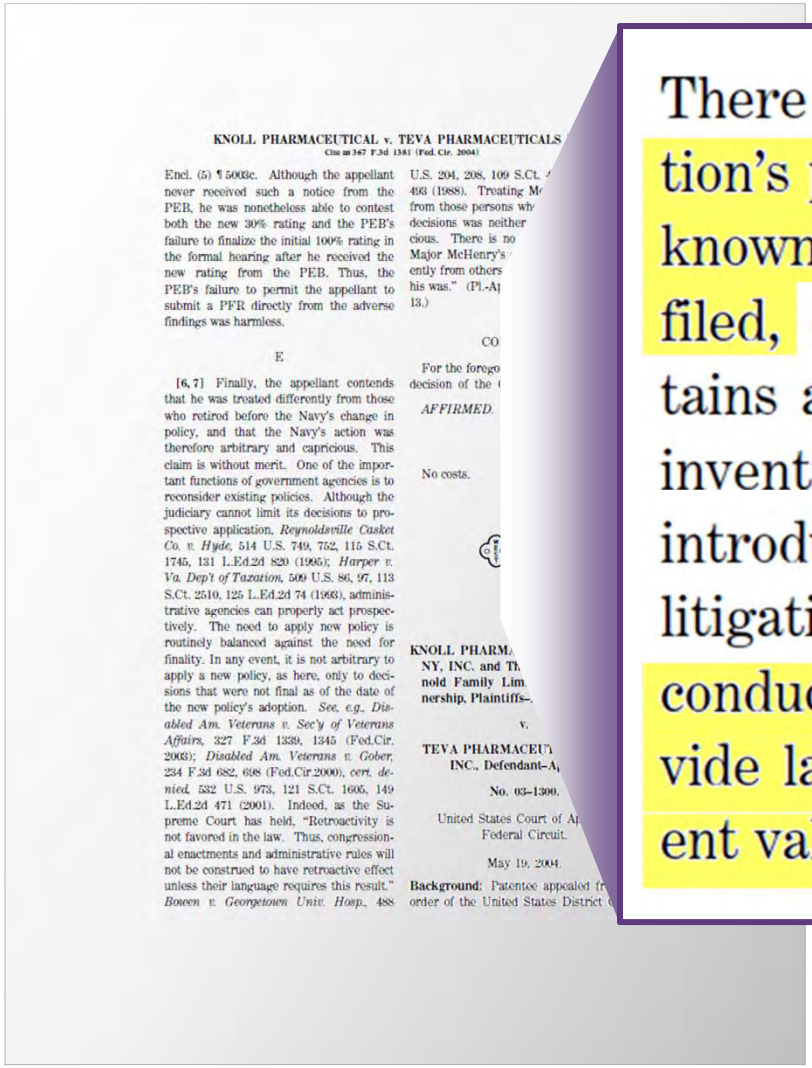
Compound 24 (*cis*-4,5)
K_i = 25 nM



Compound 22 (*trans*-4,5)
K_i = 1620 nM

Paper 62 at Observation 17; Ex. 2002 at 3; Ex. 2234

Knoll Pharm. Co. v. Teva Pharm. USA, Inc.



KNOLL PHARMACEUTICAL v. TEVA PHARMACEUTICALS
Cite as 367 F.3d 1381 (Fed. Cir. 2004)

Encl. (5) ¶ 5003c. Although the appellant never received such a notice from the PEB, he was nonetheless able to contest both the new 30% rating and the PEB's failure to finalize the initial 100% rating in the formal hearing after he received the new rating from the PEB. Thus, the PEB's failure to permit the appellant to submit a PFR directly from the adverse findings was harmless.

E

[6, 7] Finally, the appellant contends that he was treated differently from those who retired before the Navy's change in policy, and that the Navy's action was therefore arbitrary and capricious. This claim is without merit. One of the important functions of government agencies is to reconsider existing policies. Although the judiciary cannot limit its decisions to prospective application, *Reynoldsville Casket Co. v. Hyde*, 514 U.S. 749, 752, 115 S.Ct. 1745, 131 L.Ed.2d 820 (1995); *Harper v. Va. Dep't of Taxation*, 509 U.S. 86, 97, 113 S.Ct. 2510, 125 L.Ed.2d 74 (1993), administrative agencies can properly act prospectively. The need to apply new policy is routinely balanced against the need for finality. In any event, it is not arbitrary to apply a new policy, as here, only to decisions that were not final as of the date of the new policy's adoption. *See, e.g., Disabled Am. Veterans v. Sec'y of Veterans Affairs*, 327 F.3d 1339, 1345 (Fed.Cir. 2003); *Disabled Am. Veterans v. Gober*, 234 F.3d 682, 698 (Fed.Cir.2000), *cert. denied*, 532 U.S. 973, 121 S.Ct. 1605, 149 L.Ed.2d 471 (2001). Indeed, as the Supreme Court has held, "Retroactivity is not favored in the law. Thus, congressional enactments and administrative rules will not be construed to have retroactive effect unless their language requires this result." *Bowen v. Georgetown Univ. Hosp.*, 488 U.S. 204, 208, 109 S.Ct. 468, 102 L.Ed.2d 493 (1988). Treating M... from those persons wh... decisions was neither ...cious. There is no Major McHenry's ...ently from others ...his was." (Pl.-A... 13.)

CO...

For the forego... decision of the ...

AFFIRMED.

No costs.

KNOLL PHARM... NY, INC. and Th... nold Family Lim... nership, Plaintiffs-...

v.

TEVA PHARMACEU... INC., Defendant-A...

No. 03-1300.

United States Court of A... Federal Circuit.

May 19, 2004.

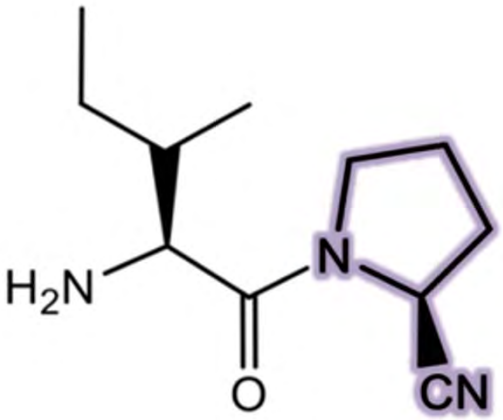
Background: Patentee appealed fr... order of the United States District ...

There is no requirement that an invention's properties and advantages were fully known before the patent application was filed, or that the patent application contains all of the work done in studying the invention, in order for that work to be introduced into evidence in response to litigation attack. Nor is it improper to conduct additional experiments and provide later-obtained data in support of patent validity.

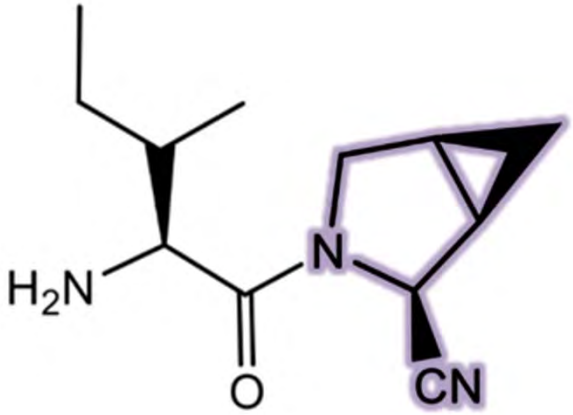
367 F.3d 1381, 1385 (Fed. Cir. 2004)

Effects of Cyclopropanation: Magnin (2004)

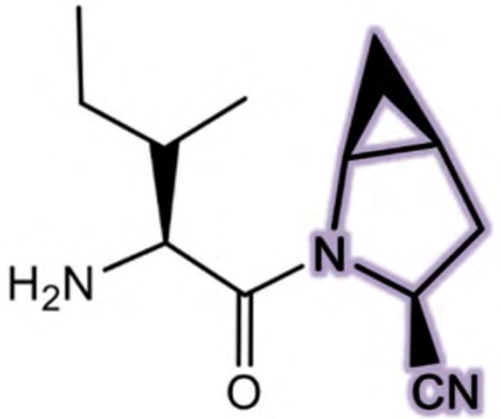
Effect of LOCATION on Stability



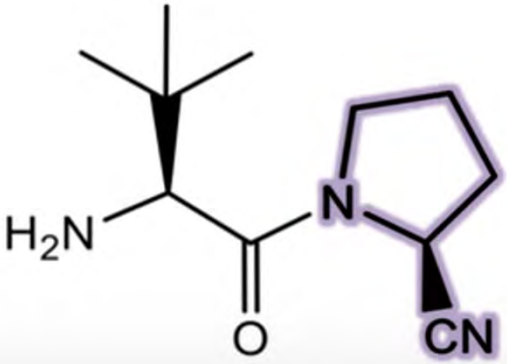
Compound 21
$t_{½}$ = 5 h



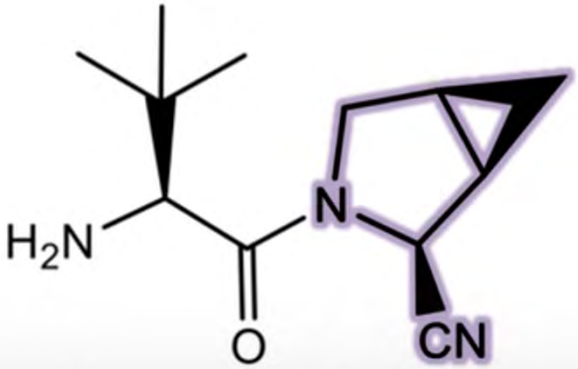
Compound 25 (*cis*-3,4)
$t_{½}$ = 4 h



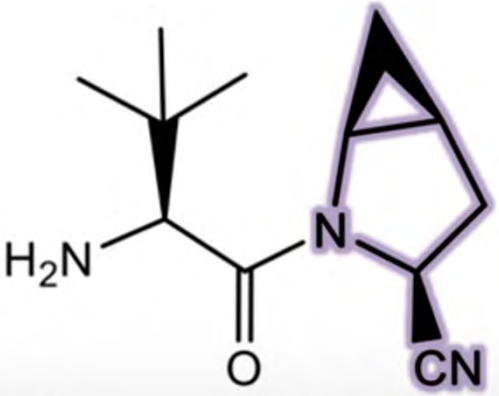
Compound 24 (*cis*-4,5)
$t_{½}$ = 22 h



Compound 28
$t_{½}$ = 27 h



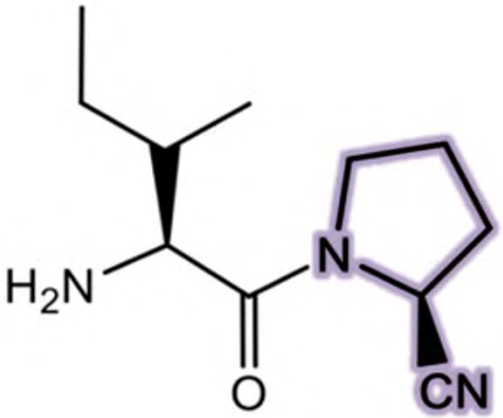
Compound 30 (*cis*-3,4)
$t_{½}$ = 4 h



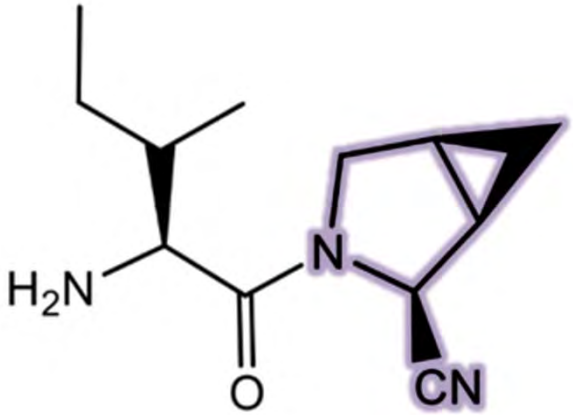
Compound 29 (*cis*-4,5)
$t_{½}$ = 42 h

Effects of Cyclopropanation: Magnin (2004)

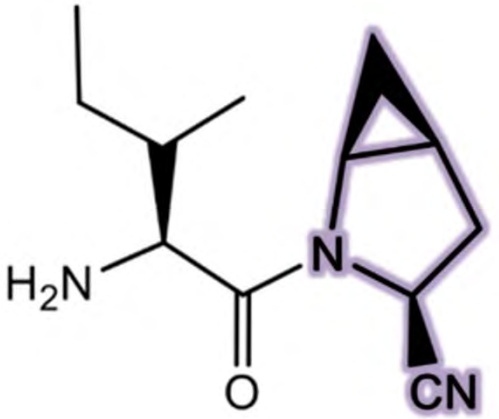
Effect of LOCATION on Potency



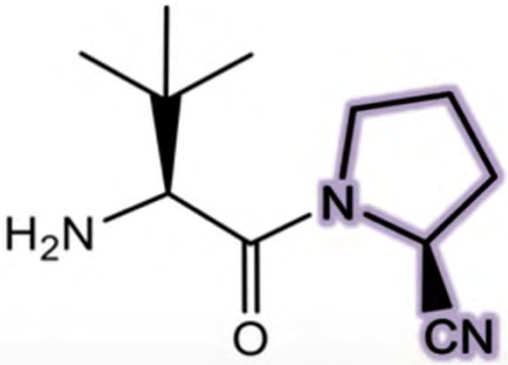
Compound 21
K_i = 2 nM



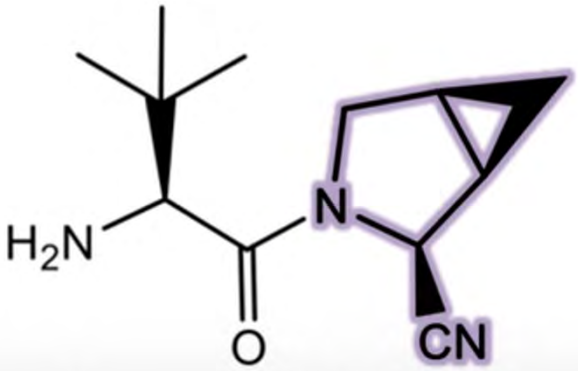
Compound 25 (*cis*-3,4)
K_i = 15 nM



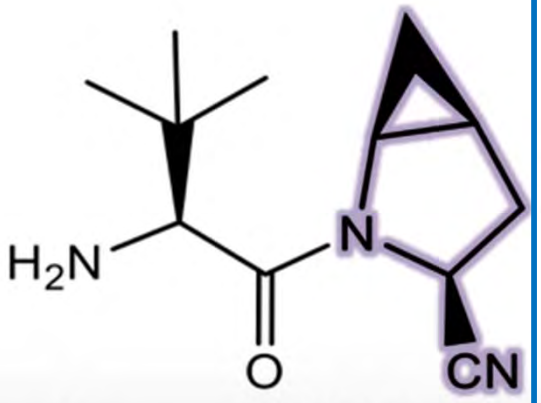
Compound 24 (*cis*-4,5)
K_i = 25 nM



Compound 28
K_i = 8 nM



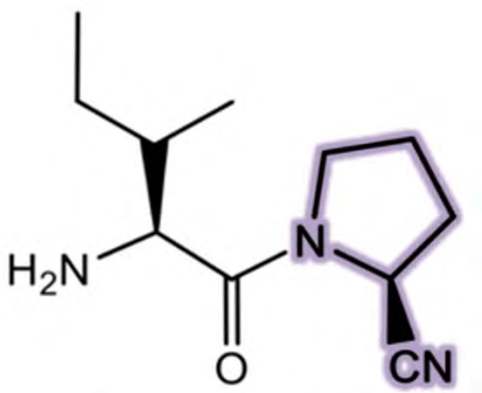
Compound 30 (*cis*-3,4)
K_i = 14 nM



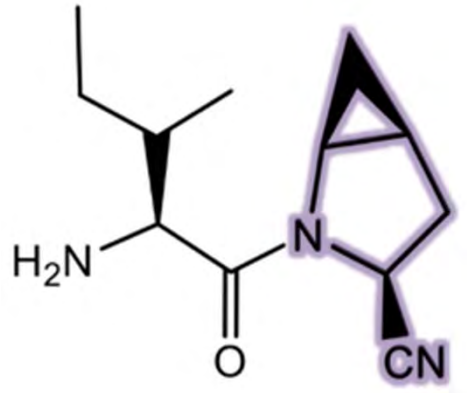
Compound 29 (*cis*-4,5)
K_i = 7 nM

Effects of Cyclopropanation: Magnin (2004)

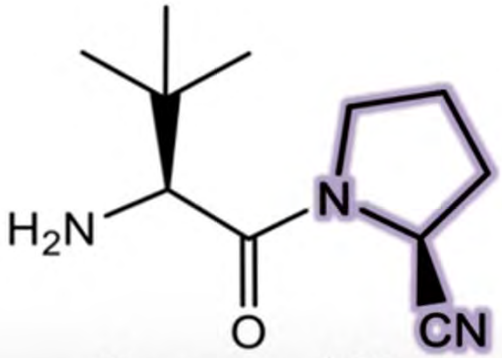
Effect of the P2 GROUP



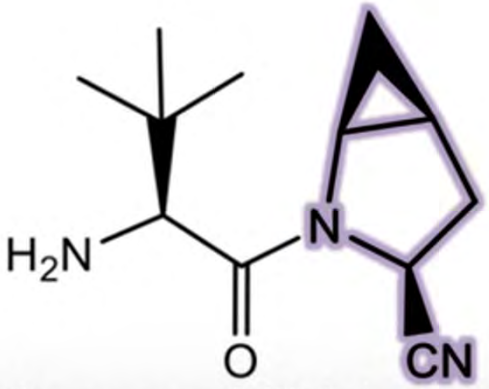
Compound 21
K_i = 2 nM



Compound 24 (*cis*-4,5)
K_i = 25 nM



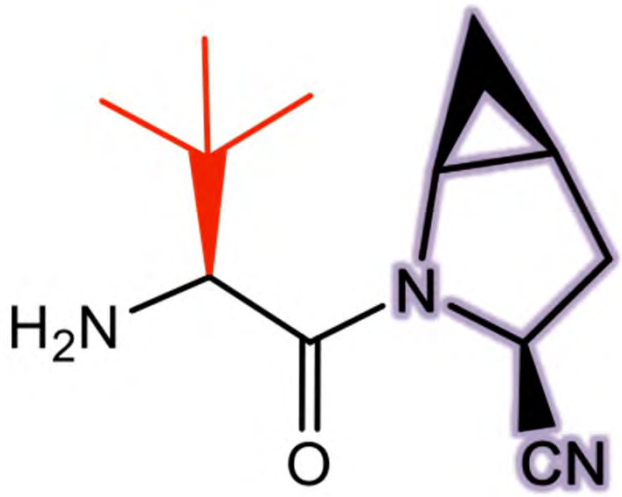
Compound 28
K_i = 8 nM



Compound 29 (*cis*-4,5)
K_i = 7 nM

Effects of Cyclopropanation: Magnin (2004)

Effect on Stability and Potency From *Cis*-4,5-Cyclopropyl + Quaternary Carbon

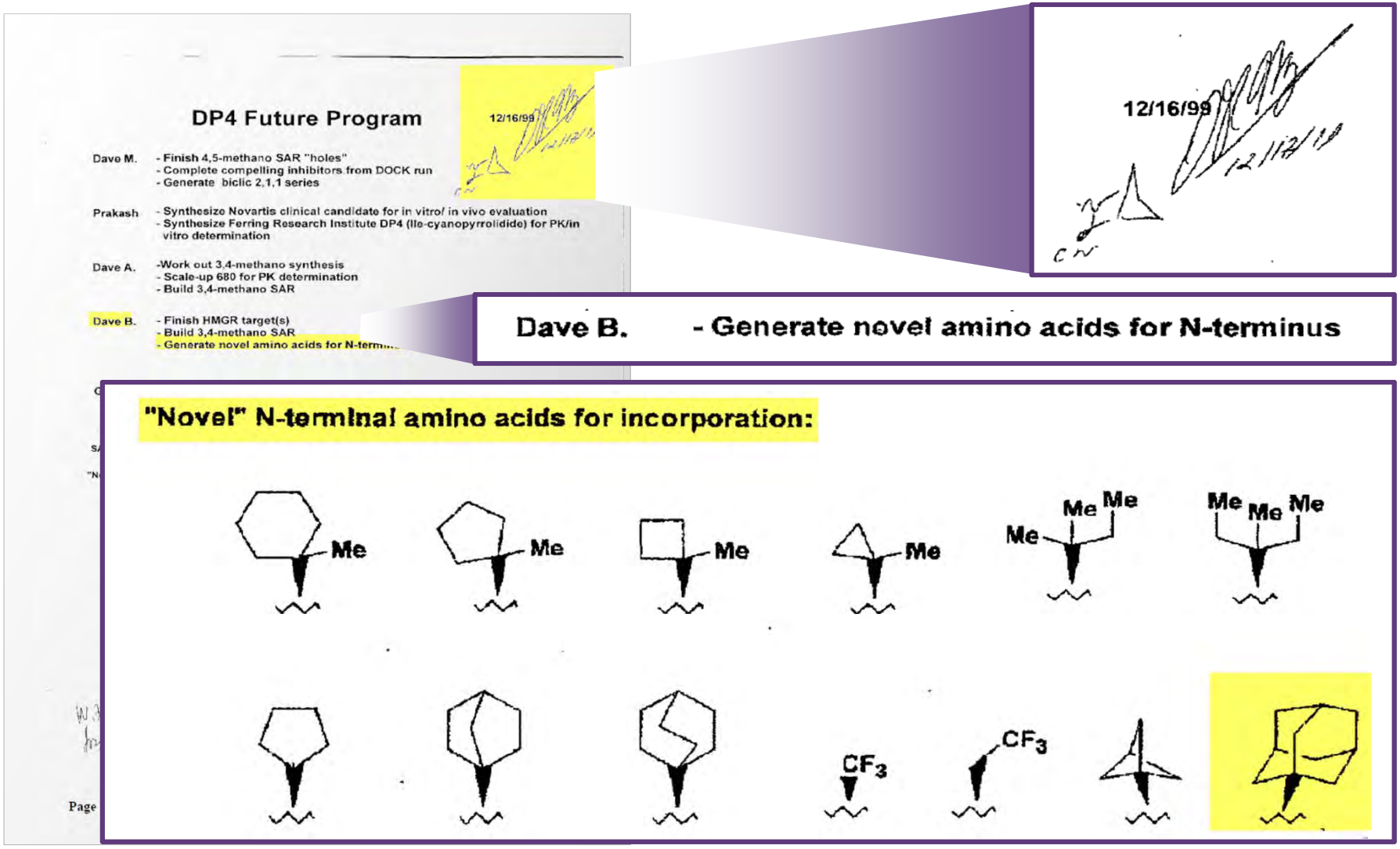


Compound 29 (*cis*-4,5)

K_i = 7 nM

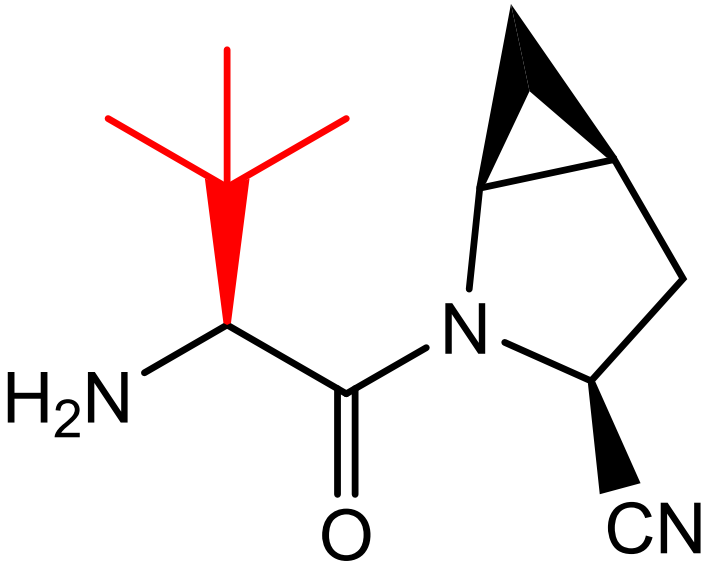
$t_{½}$ = 42 h

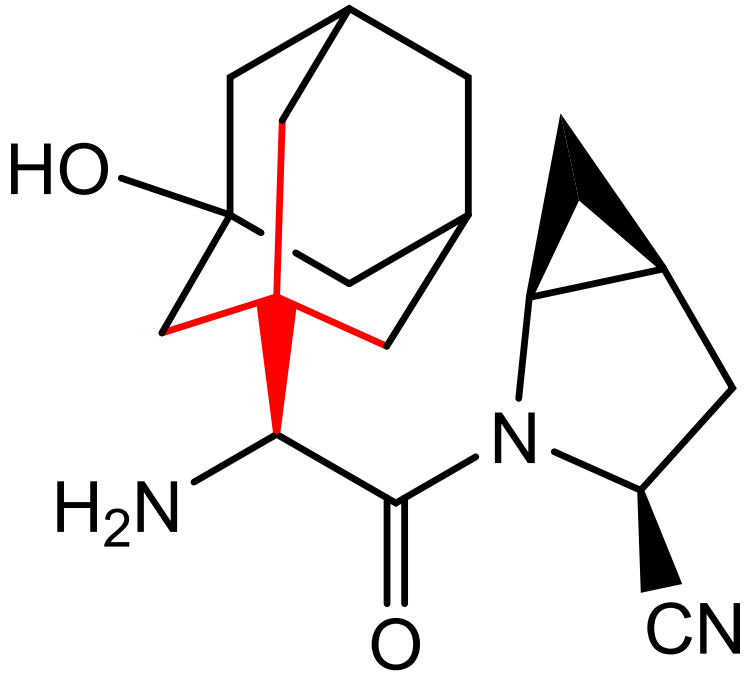
December 16, 1999: Ex. 2187



Ex. 2187; Ex. 2173 ¶ 11

Cis-4,5-Cyclopropyl + Quaternary Carbon





Saxagliptin

Ashworth II (1996): Ex. 2001

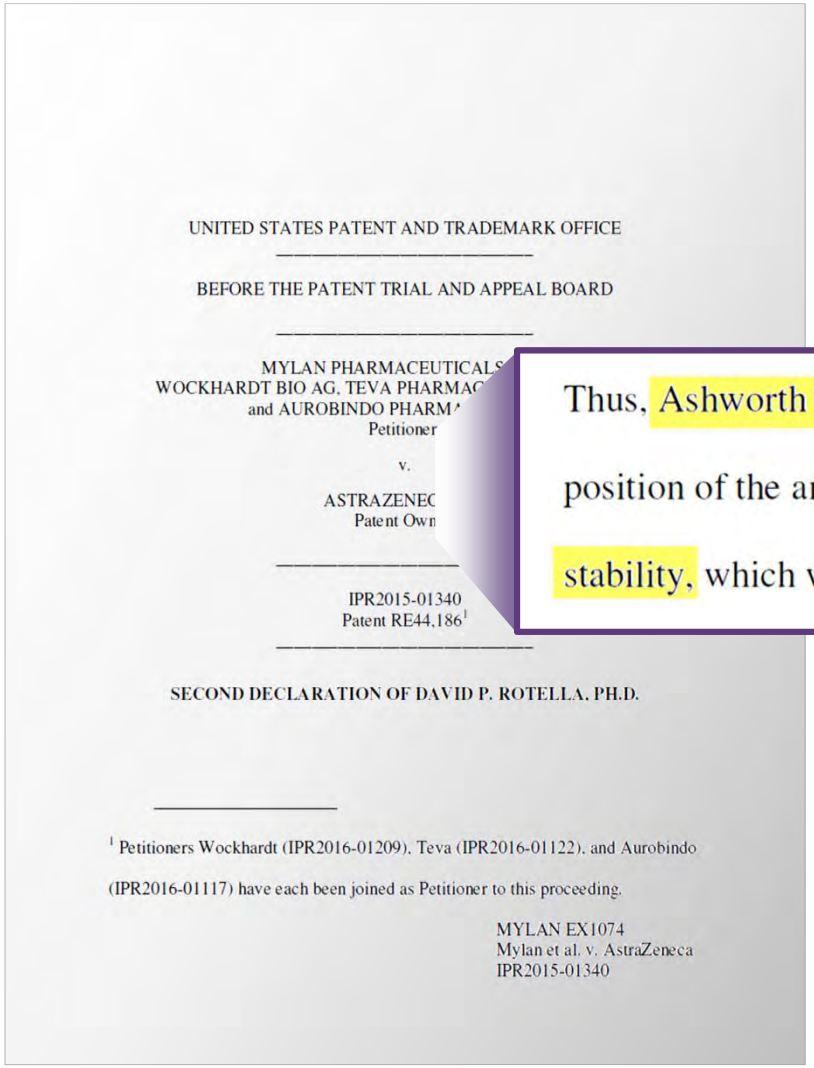
Having established 4-cyanothiazolidide as an optimum *C*-terminal residue, we prepared further analogues with the best *N*-terminal α-amino acids from the pyrrolidide series.[7] These compounds were prepared as described in **Scheme I** but Boc-Ile-OH, in step **d**, was replaced with the required Boc-Xaa-OH. A number of analogues were prepared with sub-nanomolar activity against DP-IV and good stability in aqueous buffer (pH 7.4). (**Table II**)

Compound N°	Xaa	K_i (nM)[8]	$t_{1/2}$ (h)[9]
3	Ile	0.41 ± 0.15	27
13	Cyclopentylglycine	0.50 ± 0.10	5
14	Cyclohexylglycine	0.80 ± 0.20	16
15	Lys(Cbz)	5.00 ± 1.00	>48

Ex. 2001 at 2, 4, Table II

Selection of an “Adamantyl” P2 Group

Declaration of Dr. Rotella



UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS
WOCKHARDT BIO AG, TEVA PHARMA
and AUROBINDO PHARM
Petitioner

v.

ASTRAZENEC
Patent Own

IPR2015-01340
Patent RE44,186[1]

SECOND DECLARATION OF DAVID P. ROTELLA, PH.D.

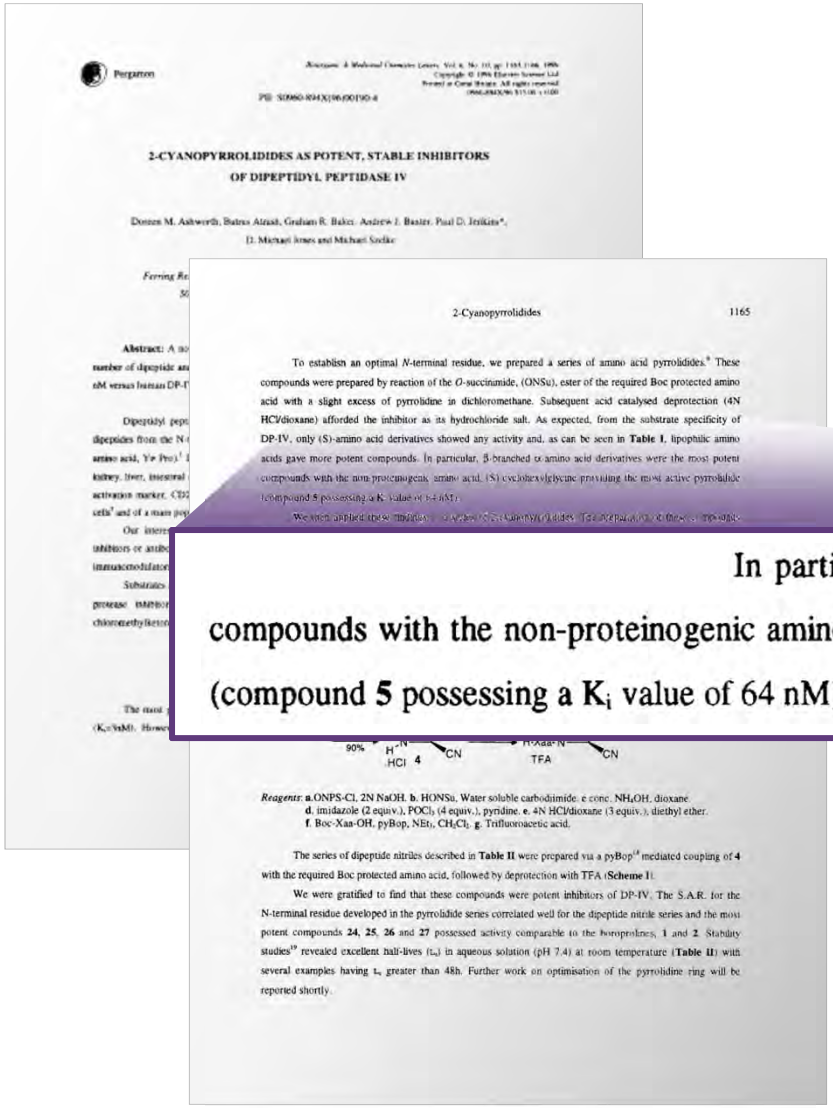
[1] Petitioners Wockhardt (IPR2016-01209), Teva (IPR2016-01122), and Aurobindo (IPR2016-01117) have each been joined as Petitioner to this proceeding.

MYLAN EX1074
Mylan et al. v. AstraZeneca
IPR2015-01340

Thus, Ashworth I teaches that increasing the bulk of the substituent at the 2-position of the amino acyl cyanopyrrolidine can improve both potency and stability, which would have motivated a person of ordinary skill in the art to

Ex. 1074 ¶ 19

Ashworth I (1996): Ex. 1007



2-CYANOPYRROLIDIDES AS POTENT, STABLE INHIBITORS OF DIPEPTIDYL PEPTIDASE IV

2-Cyanopyrrolidides 1165

To establish an optimal *N*-terminal residue, we prepared a series of amino acid pyrrolidides.[9] These compounds were prepared by reaction of the *O*-succinimide, (ONSu), ester of the required Boc protected amino acid with a slight excess of pyrrolidine in dichloromethane. Subsequent acid catalysed deprotection (4N HCl/dioxane) afforded the inhibitor as its hydrochloride salt. As expected, from the substrate specificity of DP-IV, only (S)-amino acid derivatives showed any activity and, as can be seen in **Table I**, lipophilic amino acids gave more potent compounds. In particular, β-branched α-amino acid derivatives were the most potent compounds with the non-proteinogenic amino acid, (S)-cyclohexylglycine providing the most active pyrrolidide (compound **5** possessing a K_i value of 64 nM).

Reagents: **a**. ONPS-Cl, 2N NaOH. **b**. HONSu, Water soluble carbodiimide. **c** conc. NH_4OH, dioxane. **d**. imidazole (2 equiv.), $POCl_3$ (4 equiv.), pyridine. **e**. 4N HCl/dioxane (3 equiv.), diethyl ether. **f**. Boc-Xaa-OH, pyBop, NEt_3, CH_2Cl_2. **g**. Trifluoroacetic acid.

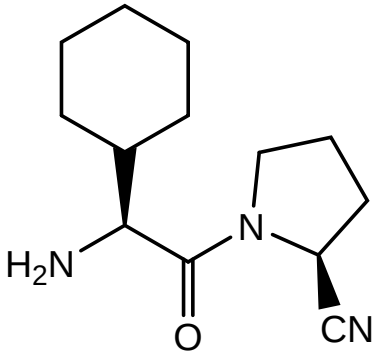
The series of dipeptide nitriles described in **Table II** were prepared via a pyBop[14] mediated coupling of **4** with the required Boc protected amino acid, followed by deprotection with TFA (**Scheme 1**).

We were gratified to find that these compounds were potent inhibitors of DP-IV. The S.A.R. for the N-terminal residue developed in the pyrrolidide series correlated well for the dipeptide nitrile series and the most potent compounds **24**, **25**, **26** and **27** possessed activity comparable to the boroprolines, **1** and **2**. Stability studies[19] revealed excellent half-lives ($t_{1/2}$) in aqueous solution (pH 7.4) at room temperature (**Table II**) with several examples having $t_{1/2}$ greater than 48h. Further work on optimisation of the pyrrolidine ring will be reported shortly.

In particular, β-branched α-amino acid derivatives were the most potent compounds with the non-proteinogenic amino acid, (S)-cyclohexylglycine providing the most active pyrrolidide (compound **5** possessing a K_i value of 64 nM).

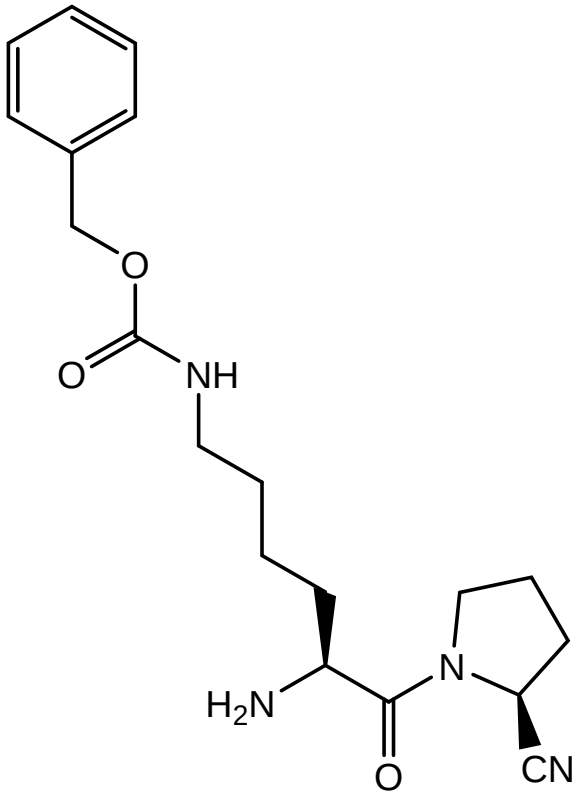
Ex. 1007 at 1165

Ashworth I's largest P2 group is less stable



Compound 25

$t_{½}$ > 48 h



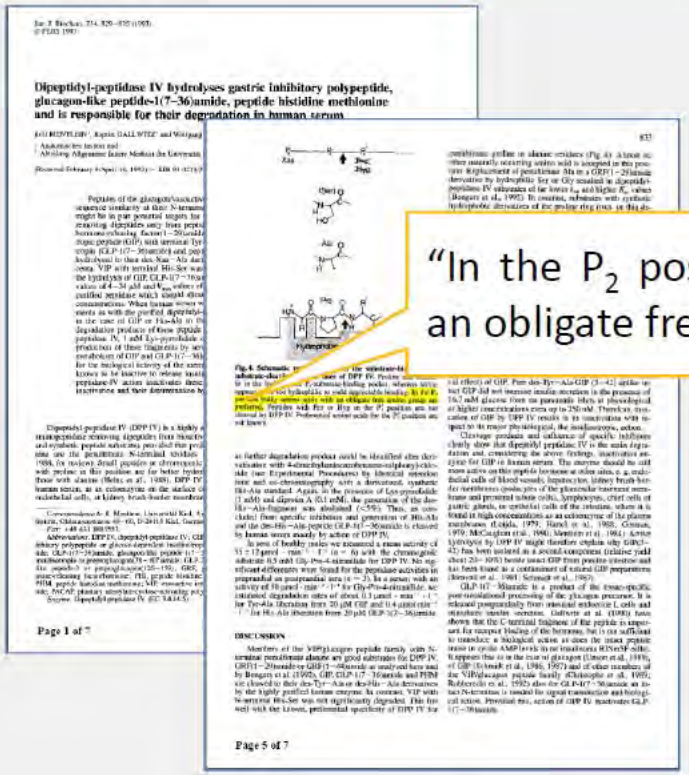
Compound 28

$t_{½}$ = 24 h

Paper 62 at Observation 3; Paper 28 at 46; Ex. 2261; Ex. 1007 at 4, Table II

Mylan Demonstrative Exhibit

Mentlein: Bulky Groups are Preferred at P2



Dipeptidyl-peptidase IV hydrolyses gastric inhibitory polypeptide, glucagon-like peptide-1(7–36)amide, peptide histidine methionine and is responsible for their degradation in human serum

Page 1 of 7

Page 5 of 7

"In the P_2 position bulky amino acids with an obligate free amino group are preferred."

Source: EX2096 (Mentlein) at 833; EX1074 (Second Rotella Decl.), ¶19.

33

Mentlein (1993): Ex. 2096

Eur. J. Biochem. *214*, 829–835 (1993)
© FEBS 1993

Dipeptidyl-peptidase IV hydrolyses gastric inhibitory poly glucagon-like peptide-1(7–36)amide, peptide histidine met and is responsible for their degradation in human serum

Rolf MENTLEIN[1], Baptist GALLWITZ[2] and Wolfgang E. SCHMIDT[2]

[1] Anatomisches Institut and
[2] Abteilung Allgemeine Innere Medizin der Universität Kiel, Germany

(Received February 9/April 16, 1993) – EJB 93 0215/3

Peptides of the glucagon/vasoactive-intestinal-peptide (VIP) peptide family share a consi… sequence similarity at their N-terminus. They either start with Tyr-Ala, His-Ala or His-Ser wi… might be in part potential targets for dipeptidyl-peptidase IV, a highly specialized aminopeptidas… removing dipeptides only from peptides with N-terminal penultimate proline or alanine. Growth-hormone-releasing factor(1–29)amide and gastric inhibitory peptide/glucose-dependent insulinotropic peptide (GIP) with terminal Tyr-Ala as well as glucagon-like peptide-1(7–36)amide/insulinotropin [GLP-1(7–36)amide] and peptide histidine methionine (PHM) with terminal His-Ala were hydrolysed to their des-Xaa–Ala derivatives by dipeptidyl-peptidase IV purified from human placenta. VIP with terminal His-Ser was not significantly degraded by the peptidase. The kinetics of the hydrolysis of GIP, GLP-1(7–36)amide and PHM were analyzed in detail. For these peptides K_m values of 4–34 μM and V_{max} values of 0.6–3.8 μmol · min^{-1} · mg protein^{-1} were determined for the purified peptidase which should allow their enzymic degradation also at physiological, nanomolar concentrations. When human serum was incubated with GIP or GLP-1(7–36)amide the same fragments as with the purified dipeptidyl-peptidase IV, namely the des-Xaa–Ala peptides and Tyr-Ala in the case of GIP or His-Ala in the case of GLP-1(7–36)amide, were identified as the main degradation products of these peptide hormones. Incorporation of inhibitors specific for dipeptidyl-peptidase IV, 1 mM Lys-pyrrolidide or 0.1 mM diprotin A (Ile-Pro-Ile), completely abolished the production of these fragments by serum. It is concluded that dipeptidyl-peptidase IV initiates the metabolism of GIP and GLP-1(7–36)amide in human serum. Since an intact N-terminus is obligate for the biological activity of the members of the glucagon/VIP peptide family [e. g. GIP(3–42) is known to be inactive to release insulin in the presence of glucose as does intact GIP], dipeptidyl-peptidase-IV action inactivates these peptide hormones. The relevance of this finding for their inactivation and their determination by immunoassays is discussed.

Dipeptidyl-peptidase IV (DPP IV) is a highly specialized aminopeptidase removing dipeptides from bioactive peptides and synthetic peptide substrates provided that proline or alanine are the penultimate N-terminal residues (Mentlein, 1988, for review). Small peptides or chromogenic substrates with proline in this position are far better hydrolysed than those with alanine (Heins et al., 1988). DPP IV occurs in human serum, as an ectoenzyme on the surface of capillary endothelial cells, at kidney brush-border membranes, on the surface of hepatocytes (here termed also GP110 or OX-61 antigen), on the surface of a subset of T-lymphocytes and thymocytes (here termed CD 26, or thymocyte-activating molecule) and other sites (Loijda, 1979; Nausch and Heymann, 1985; Mentlein et al., 1984; McCaughan et al., 1990). The enzyme has been shown to be responsible for the degradation and inactivation of circulating peptides with penultimate proline, like substance P (Heymann and Mentlein, 1978; Ahmad et al., 1992), but also for growth-hormone-releasing factor (GRF) with penultimate alanine (Frohman et al., 1989; Kubiak, 1989; Boulanger et al., 1992). [Ala^{15}]GRF(1–29)amide with penultimate Ala is even a comparably good substrate as a synthetic Pro^{2}-containing derivative for purified DPP IV (Bongers et al., 1992). This suggests that the conformation or chain length may greatly influence the cleavage of peptides with penultimate proline/alanine-residues by DPP IV.

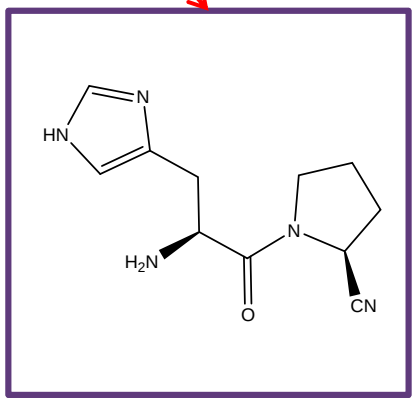
We therefore evaluated whether or not other peptide hormones related to GRF might be substrates for DPP IV, and whether this probable proteolytic degradation might be of relevance in the circulation. GRF belongs to the glucagon/

Correspondence to R. Mentlein, Universität Kiel, Anatomisches Institut, Olshausenstrasse 40–60, D-24118 Kiel, Germany
Fax: +49 431 8801557.

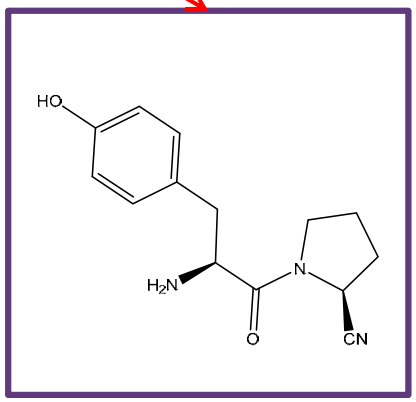
Abbreviations. DPP IV, dipeptidyl-peptidase IV; GIP, gastric inhibitory polypeptide or glucose-dependent insulinotropic polypeptide; GLP-1(7–36)amide, glucagon-like peptide-1(7–36)amide or insulinotropin or preproglucagon(78–107)amide; GLP-2, glucagon-like peptide-2 or preproglucagon(126–159); GRF, growth-hormone-releasing factor/hormone; PHI, peptide histidine isoleucine; PHM, peptide histidine methionine; VIP, vasoactive intestinal peptide; PACAP, pituitary adenylate-cyclase-activating polypeptide.

Enzyme. Dipeptidyl peptidase IV (EC 3.4.14.5).

				5					10			
Tyr	Ala	Asp	Ala	Ile	–	Phe	Thr	Asn	Ser	Tyr	…-29	*h* GRF(1-29)amide
–	–	Glu	Gly	Thr	–	Ile	Ser	Asp	–		…-42	*h* GIP
His	–	Glu	Gly	Thr	–	Thr	Ser	Asp	Val		…-30	*h* GLP-1(7-36)amide
His	–	–	Gly	Ser	–	Ser	Asp	Glu	Met		…-34	*h* GLP-2
His	–	–	Gly	Val	–	–	Ser	Asp	Phe		…-27	*h* PHM-27
His	–	–	Gly	Val	–	–	Ser	Asp	–		…-27	*r* PHI-27



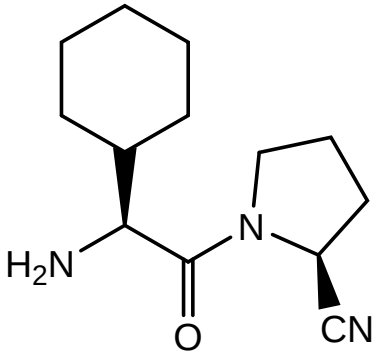
Histidine



Tyrosine

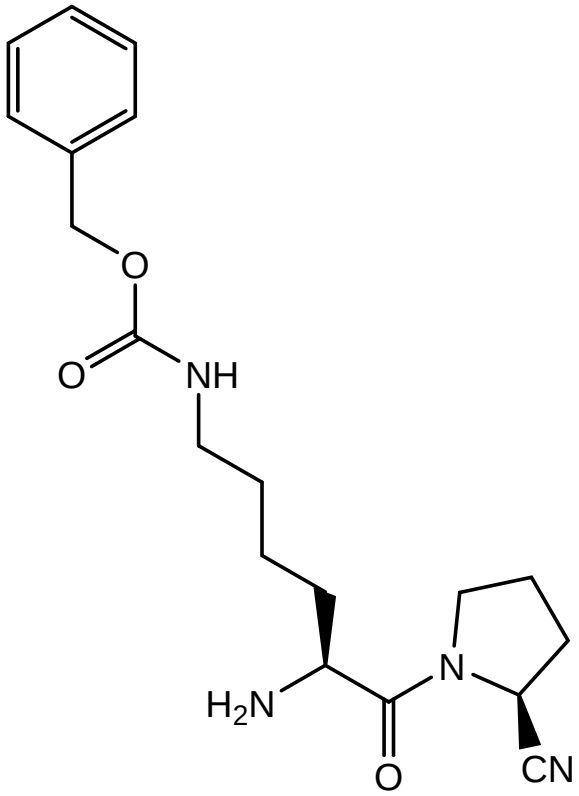
Ex. 2096, 2 (Figure 1); Ex. 2056, ¶¶ 57, 90

Ashworth I's largest P2 group is less stable



Compound 25

$t_{½}$ > 48 h

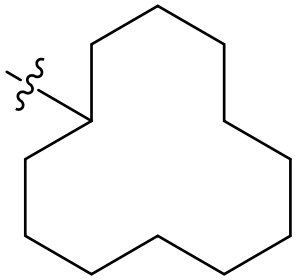


Compound 28

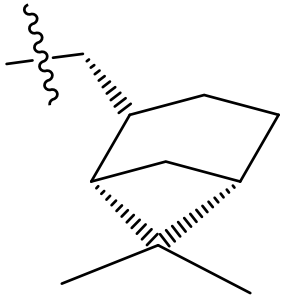
$t_{½}$ = 24 h

Paper 62 at Observation 3; Paper 28 at 46; Ex. 2261; Ex. 1007 at 4, Table II

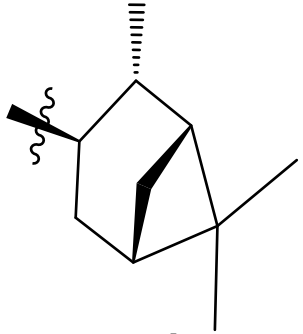
Villhauer-1998's large alkyl groups



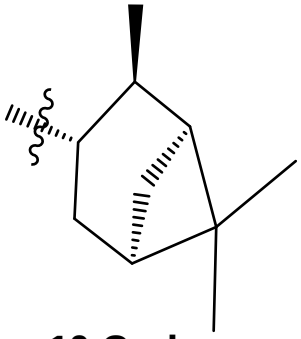
12 Carbons
Ex. 57



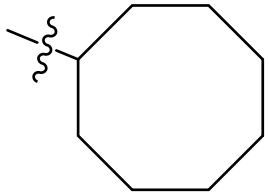
10 Carbons
Ex. 25



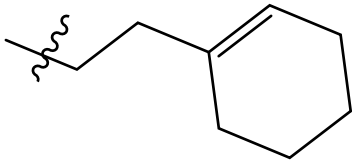
10 Carbons
Ex. 33



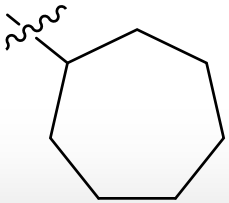
10 Carbons
Ex. 44



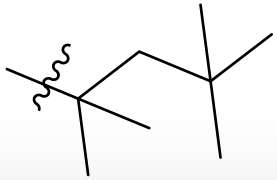
8 Carbons
Ex. 58



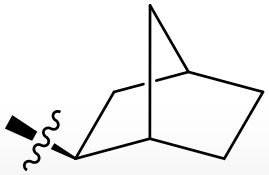
8 Carbons
Ex. 27



8 Carbons
Ex. 48



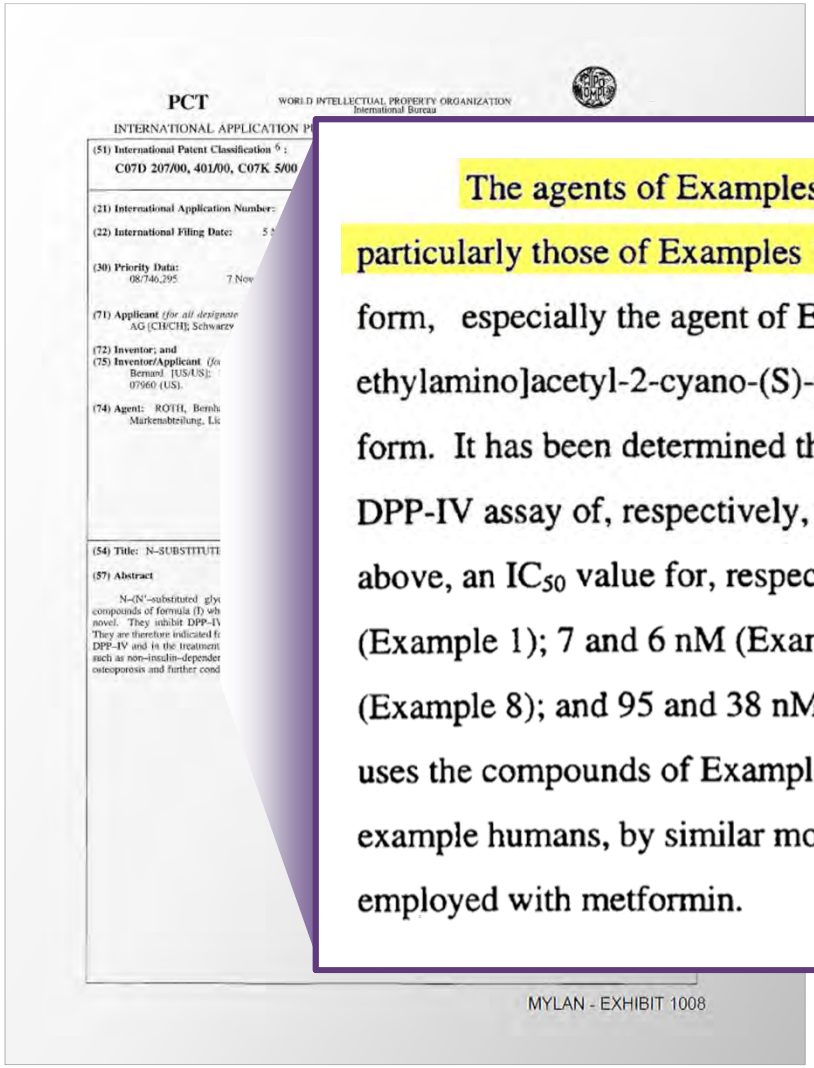
7 Carbons
Ex. 24



7 Carbons
Ex. 29

Paper 28 at 45; Ex. 2056 ¶ 203; Ex. 1008 at 11-16

Villhauer-1998: Ex. 1008


PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION P

(51) International Patent Classification 6 :
C07D 207/00, 401/00, C07K 5/00

(21) International Application Number:

(22) International Filing Date:

(30) Priority Data:
08/746,295

(71) Applicant (for all designate
AG (CH/CH); Schwarzv

(72) Inventor; and
(75) Inventor/Applicant (fo
Bernard [US/US];
07960 (US).

(74) Agent: ROTH, Bernh
Markenabteilung, Li

(54) Title: N-SUBSTITUTE

(57) Abstract

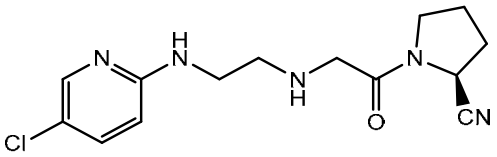
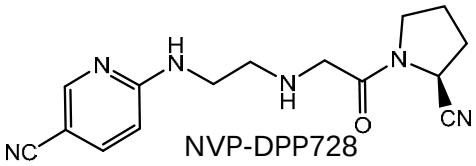
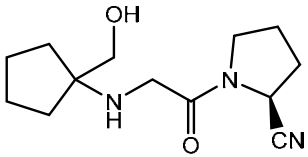
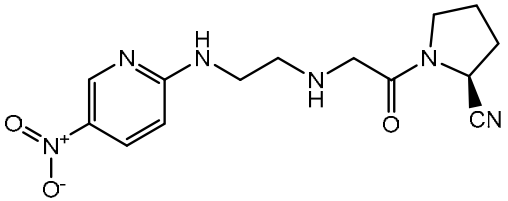
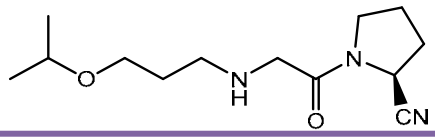
N-(N'-substituted gly
compounds of formula (I) wh
novel. They inhibit DPP-IV
They are therefore indicated f
DPP-IV and in the treatment
such as non-insulin-dependen
osteoporosis and further cond

MYLAN - EXHIBIT 1008

The agents of Examples 1, 3, 5, 8 and 12 are the preferred agents of the invention, particularly those of Examples 1, 3, 5 and 12, preferably in hydrochloride acid addition salt form, especially the agent of Example 3, namely 1-[2-[(5-cyanopyridin-2-yl)amino]-ethylamino]acetyl-2-cyano-(S)-pyrrolidine, preferably in dihydrochloride acid addition salt form. It has been determined that in hydrochloride form they have an IC_{50} value in the Caco-2 DPP-IV assay of, respectively, 36, 22, 26, 8 and 279 nM, and in the modified Kubota assay above, an IC_{50} value for, respectively, human and rat plasma DPP-IV, of 27 and 22 nM (Example 1); 7 and 6 nM (Example 3); 37 and 18 nM (Example 5); 12 and 11 nM (Example 8); and 95 and 38 nM (Example 12). It is, therefore, indicated that for the above uses the compounds of Examples 1, 3, 5, 8 and 12 may be administered to larger mammals, for example humans, by similar modes of administration at similar dosages than conventionally employed with metformin.

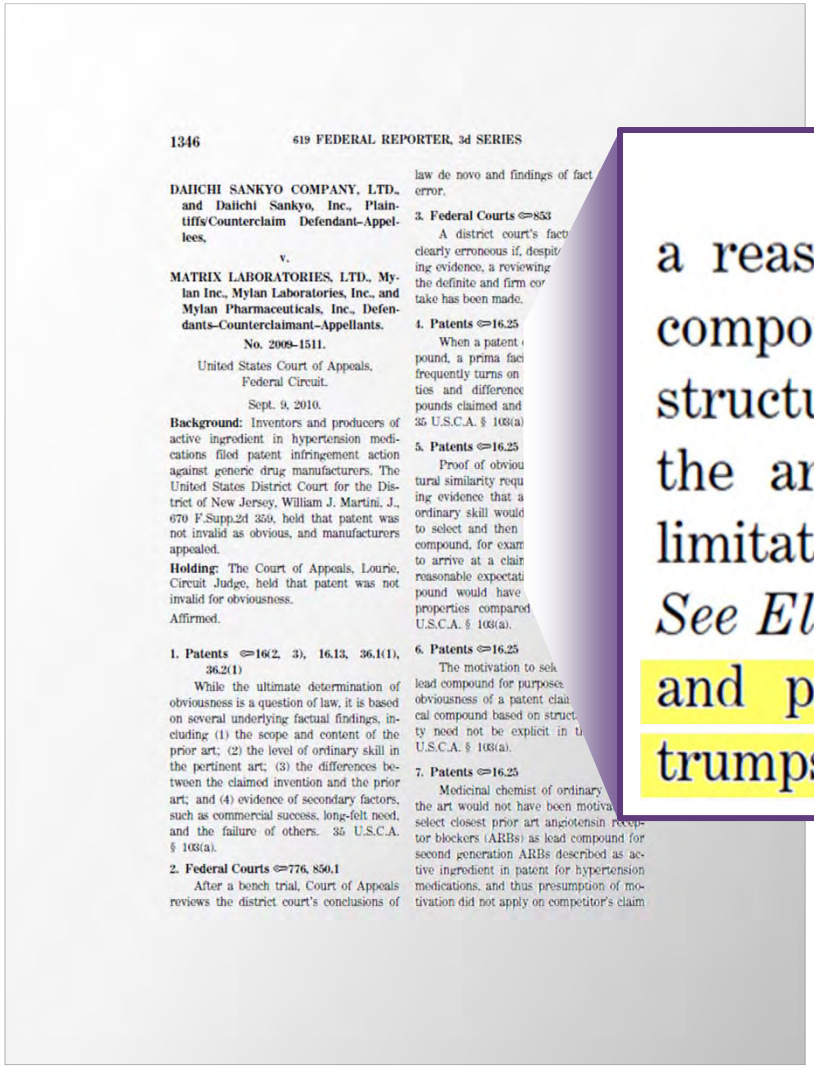
Ex. 1008 at 23

Villhauer-1998: Ex. 1008

Example	Structure	Increase of Insulin Response at 10 µmol/kg	Human Plasma DPP-4 IC_{50} (nM)	Rat Plasma DPP-4 IC_{50} (nM)	Caco-2 DPP-4 (nM)
Ex. 1		61%	27	22	36
Ex. 3	 NVP-DPP728	66%	7	6	22
Ex. 5		108%	37	18	26
Ex. 8		144%	12	11	8
Ex. 12		59%	95	38	279

Ex. 1008 at 19, 21; Ex. 2056 ¶¶ 201-202

Daiichi Sankyo Co. v. Matrix Labs., Ltd.



1346 619 FEDERAL REPORTER, 3d SERIES

DAIICHI SANKYO COMPANY, LTD., and Daiichi Sankyo, Inc., Plaintiffs/Counterclaim Defendant–Appellees,

v.

MATRIX LABORATORIES, LTD., Mylan Inc., Mylan Laboratories, Inc., and Mylan Pharmaceuticals, Inc., Defendants–Counterclaimant–Appellants.

No. 2009–1511.

United States Court of Appeals, Federal Circuit.

Sept. 9, 2010.

Background: Inventors and producers of active ingredient in hypertension medications filed patent infringement action against generic drug manufacturers. The United States District Court for the District of New Jersey, William J. Martini, J., 670 F.Supp.2d 359, held that patent was not invalid as obvious, and manufacturers appealed.

Holding: The Court of Appeals, Lourie, Circuit Judge, held that patent was not invalid for obviousness.

Affirmed.

1. Patents ⇐16(2, 3), 16.13, 36.1(1), 36.2(1)

While the ultimate determination of obviousness is a question of law, it is based on several underlying factual findings, including (1) the scope and content of the prior art; (2) the level of ordinary skill in the pertinent art; (3) the differences between the claimed invention and the prior art; and (4) evidence of secondary factors, such as commercial success, long-felt need, and the failure of others. 35 U.S.C.A. § 103(a).

2. Federal Courts ⇐776, 850.1

After a bench trial, Court of Appeals reviews the district court's conclusions of law de novo and findings of fact error.

3. Federal Courts ⇐853

A district court's fact clearly erroneous if, despit ing evidence, a reviewing the definite and firm co take has been made.

4. Patents ⇐16.25

When a patent pound, a prima fac frequently turns on ties and differenc pounds claimed and 35 U.S.C.A. § 103(a)

5. Patents ⇐16.25

Proof of obviou tural similarity requ ing evidence that a ordinary skill would to select and then compound, for exam to arrive at a clai reasonable expectati pound would have properties compared U.S.C.A. § 103(a).

6. Patents ⇐16.25

The motivation to sel lead compound for purposes obviousness of a patent clai cal compound based on struct ty need not be explicit in t U.S.C.A. § 103(a).

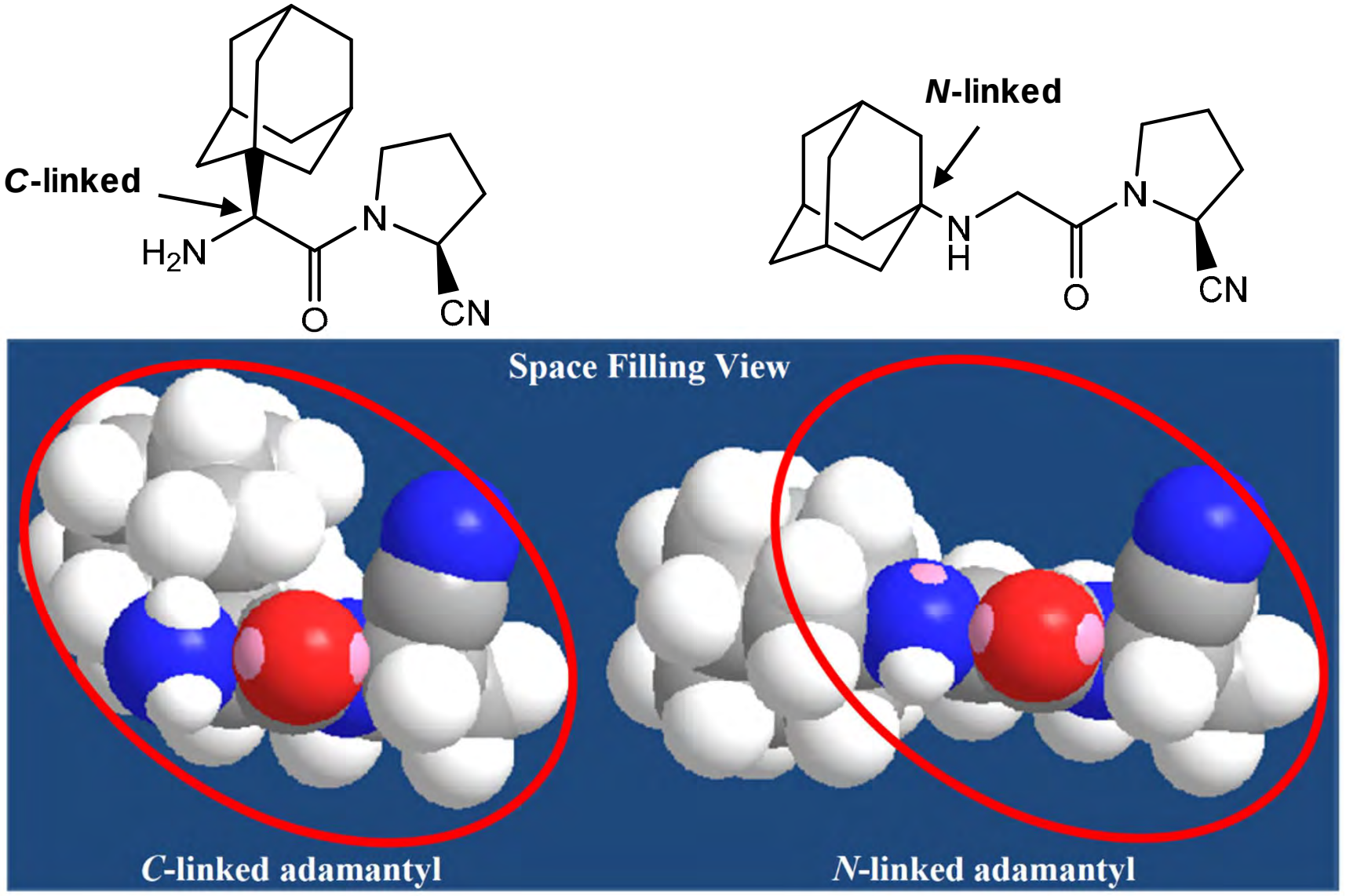
7. Patents ⇐16.25

Medicinal chemist of ordinary the art would not have been motiva select closest prior art angiotensin recep tor blockers (ARBs) as lead compound for second generation ARBs described as active ingredient in patent for hypertension medications, and thus presumption of motivation did not apply on competitor's claim

Accordingly, proving a reason to select a compound as a lead compound depends on more than just structural similarity, but also knowledge in the art of the functional properties and limitations of the prior art compounds. *See Eli Lilly*, 471 F.3d at 1377–79. Potent and promising activity in the prior art trumps mere structural relationships.

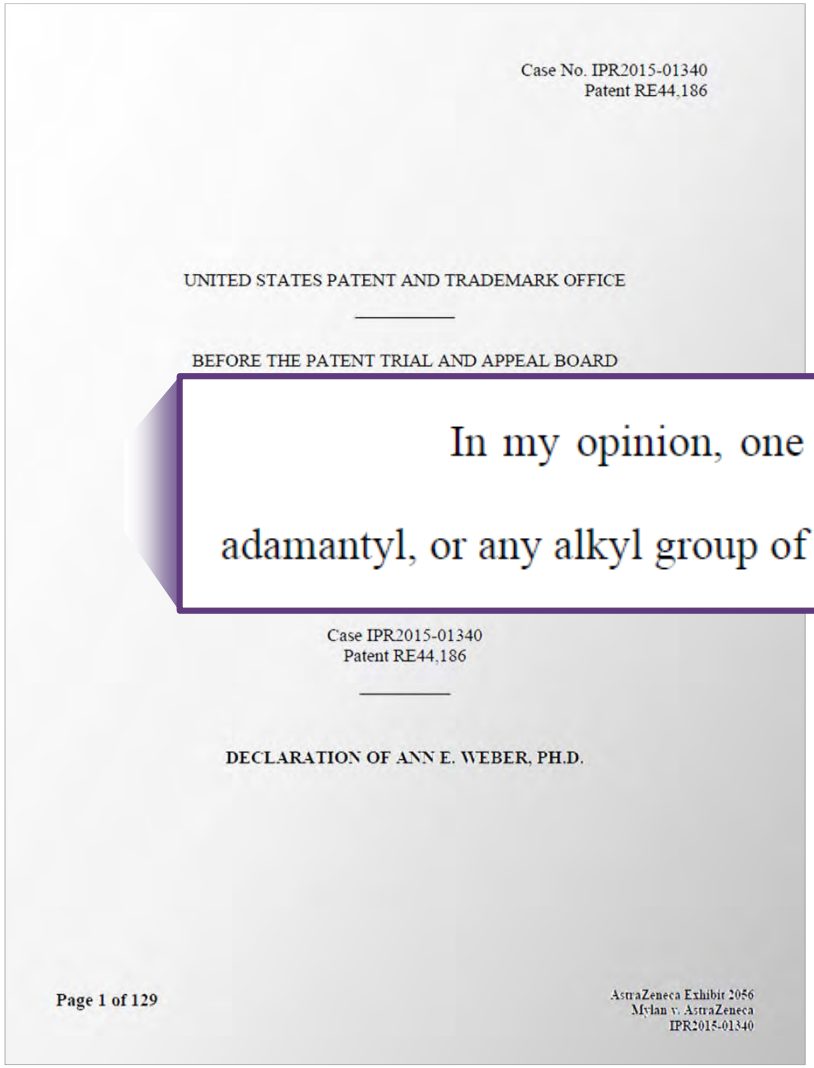
619 F.3d 1346, 1354 (Fed. Cir. 2010)

C-linked v. *N*-linked



Paper 62 at Observation 7; Ex. 2056 ¶ 200; Ex. 2259

Dr. Weber Declaration



Case No. IPR2015-01340
Patent RE44,186

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Case IPR2015-01340
Patent RE44,186

DECLARATION OF ANN E. WEBER, PH.D.

Page 1 of 129

AstraZeneca Exhibit 2056
Mylan v. AstraZeneca
IPR2015-01340

In my opinion, one of skill in the art would not have considered the adamantyl, or any alkyl group of Villhauer-1998, apart from its *N*-linkage.

Paper 28 at 42-43; Ex. 2056 ¶ 197

Dr. Weber

UNITED STATES PATENT AND TRADEMARK

BEFORE THE PATENT TRIAL AND AP

MYLAN PHARMACEUTICA
Petitioner,

v.

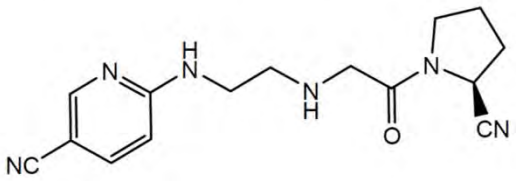
ASTRAZENECA AB
Patent Owner.

Case IPR2015-01340
Patent RE44,186

PATENT OWNER'S RESPONSE

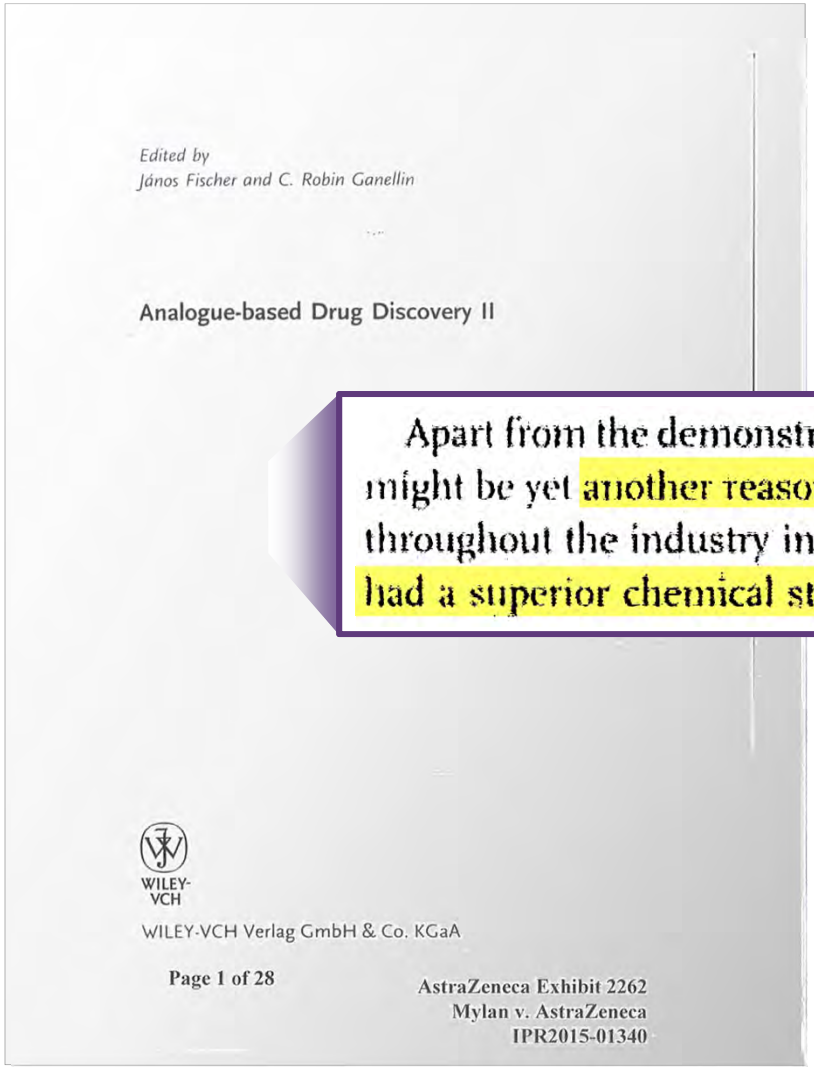
125. Various researchers published different structural solutions to the problem of intramolecular cyclization:

- Villhauer used a backbone with a secondary amine and reported less than 1% cyclization. (Ex. 2016 at 11599.)



Paper 28 at 11-12; Ex. 2056 ¶ 125

Peters and Mattei (2010): Ex. 2262



Edited by
János Fischer and C. Robin Ganellin

Analogue-based Drug Discovery II

WILEY-VCH

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Page 1 of 28

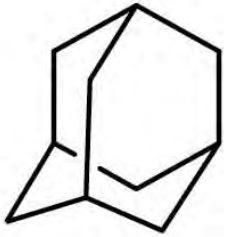
AstraZeneca Exhibit 2262
Mylan v. AstraZeneca
IPR2015-01340

Apart from the demonstrated clinical efficacy and the facile synthetic access, there might be yet another reason why the *N*-alkylglycine inhibitors became very popular throughout the industry in the following years: it was generally perceived that they had a superior chemical stability.

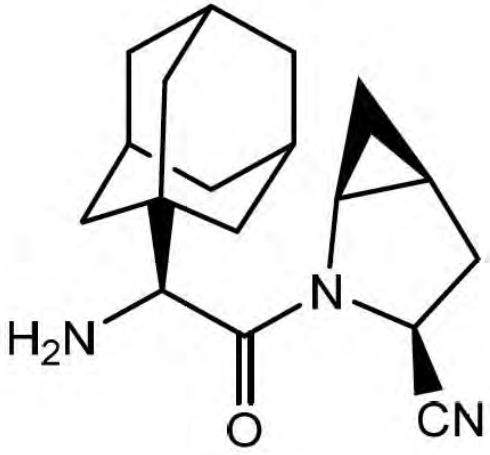
Paper 62 at Observation 9; Ex. 2262 at 9; Ex. 2174 at 77:5-80:14

Hydroxylating an Adamantyl P2 Group

Substrate Differences & Potential Oxidation Sites



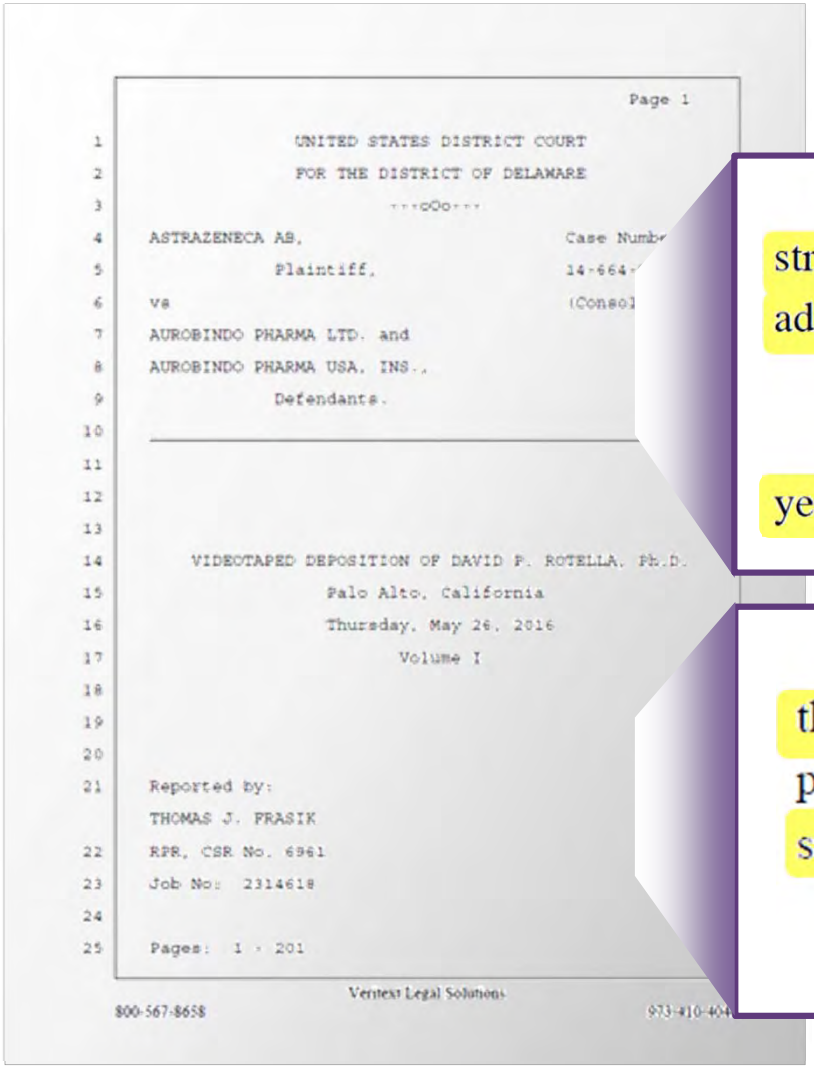
Adamantane



Deshydroxy saxagliptin

Paper 28 at 52; Ex. 2056 ¶ 212; Ex. 2174 at 164:19-165:3

Dr. Rotella



Page 1

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE
---oOo---

ASTRAZENECA AB,
Plaintiff,
vs
AURODINDO PHARMA LTD. and
AURODINDO PHARMA USA, INS.,
Defendants.

Case Numb
14-664-
(Consol

VIDEOTAPED DEPOSITION OF DAVID P. ROTELLA, Ph.D.
Palo Alto, California
Thursday, May 26, 2016
Volume I

Reported by:
THOMAS J. PRASIK
RPR, CSR No. 6961
Job No: 2314618

Pages: 1 - 201

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973-410-404

Q. And the presence and nature of that other structure can affect the metabolic fate of that adamantane ring; correct?

MS. STEINER: Objection. Form.

THE WITNESS: Depending on the modifications, yes.

Q. And adamantane is, by itself, not the molecule that's described in the Villhauer WO 98/19998 publication or in the patent in suit describing saxagliptin; correct?

MS. STEINER: Objection to form.

THE WITNESS: That's correct.

Paper 28 at 52; Ex. 2174 at 164:19-24, 165:4-9

Hoffman (Ex. 1016)

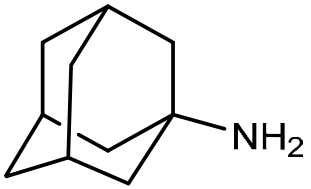
Pharmacokinetics and Metabolism of Rimantadine Hydrochloride in Mice and Dogs

HOWARD E. HOFFMAN,[1]* JANET C. GAYLORD,[2] JOHN W. BLASECKI,[3] LAMAAT M. SHALABY,[4] AND CHARLES C. WHITNEY, JR.[5]

Medical Research, Pharmaceuticals Division, Medical Products Department, E. I. du Pont de Nemours & Co., Inc., Barley Mill Plaza 26/1230, Wilmington, Delaware 19898[1]; Drug Metabolism Section, Pharmaceuticals Division, Medical Products Department, E. I. du Pont de Nemours & Co., Inc., Stine-Haskell Research Center, Newark, Delaware 19714[2]; Chemotherapy Research Section, Pharmaceuticals Division, Medical Products Department, E. I. du Pont de Nemours & Co., Inc., Glenolden Laboratory, Glenolden, Pennsylvania 19036[3]; and Agricultural Products Department[4] and Analytical Research and Development, Pharmaceuticals Division,[5] Experimental Station, E. I. du Pont de Nemours & Co., Inc., Wilmington, Delaware 19898

Received 11 April 1988/Accepted 16 August 1988

Pharmacokinetics and Metabolism of Rimantadine Hydrochloride in Mice and Dogs



Amantadine

The metabolism of amantadine is less clear. Recent studies by Koppel and Denzer (5) have shown small quantities of eight metabolites recovered from a patient under a therapeutic dosing regimen. A major metabolic pathway was N acetylation, with several other unusual metabolic pathways observed. However, no metabolites were detected with a hydroxylated adamantane ring system.

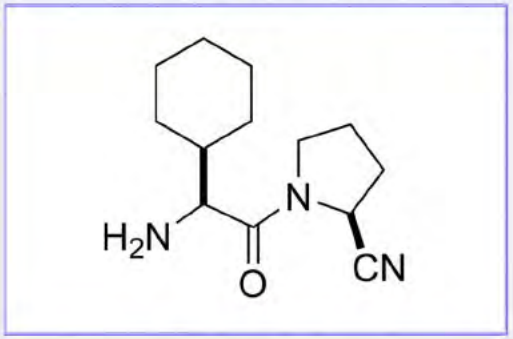
Ex. 1016 at 1703; Ex. 2056 ¶ 215; Ex. 2174 at 168:8-21; Paper 28 at 53

Mylan Demonstrative Exhibit

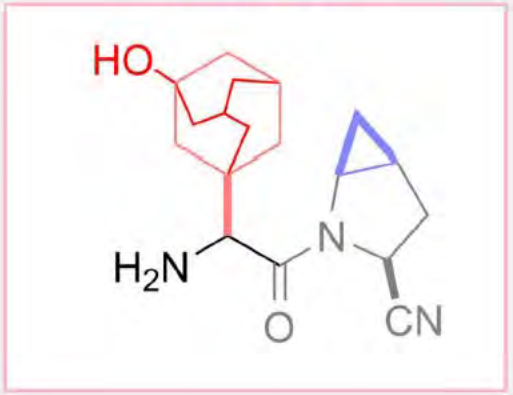
Summary of Structural Differences

- **Cyclopropanation of the pyrrolidine ring**
  - EX1007: Ashworth I
  - EX1010: Hanessian
- **Replace cyclohexyl ring with hydroxyadamantyl**
  - EX1007: Ashworth I
  - EX1008: Villhauer WO 98
  - EX1009: Raag

Ashworth 25

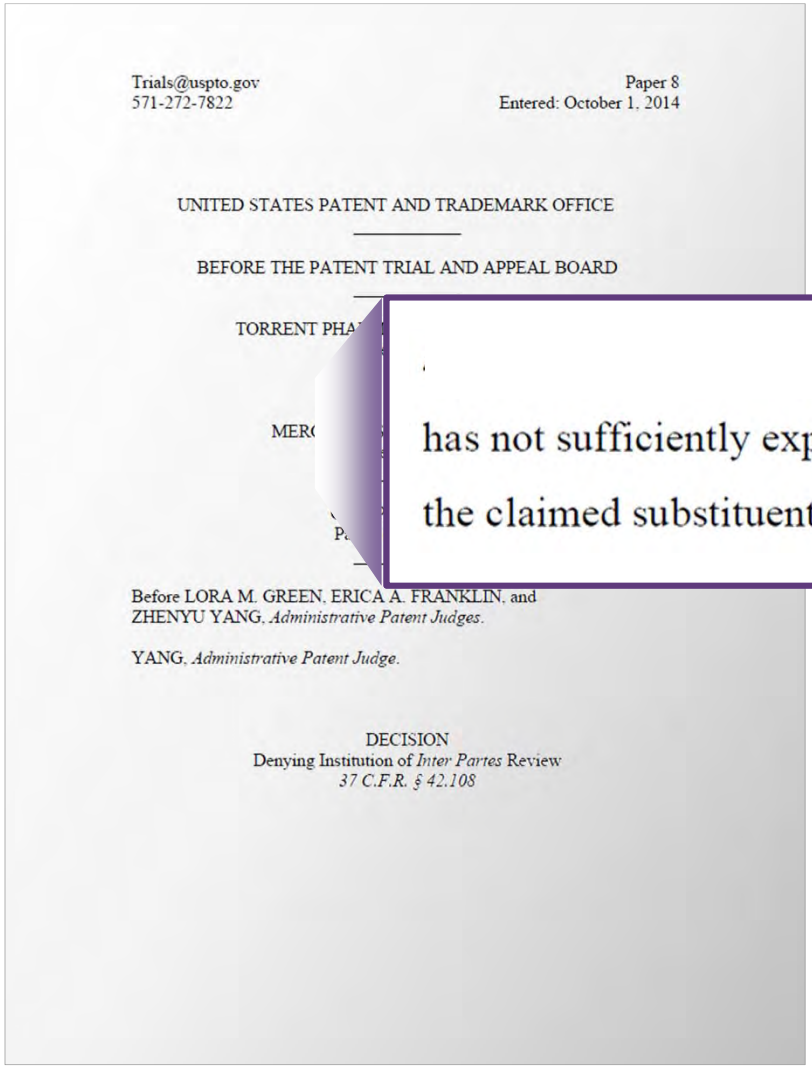


Saxagliptin



11

Torrent Pharm. Ltd. v. Merck Frosst Canada & Co.



Trials@uspto.gov
571-272-7822

Paper 8
Entered: October 1, 2014

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

TORRENT PHA

MERC

P

Before LORA M. GREEN, ERICA A. FRANKLIN, and ZHENYU YANG, *Administrative Patent Judges*.

YANG, *Administrative Patent Judge*.

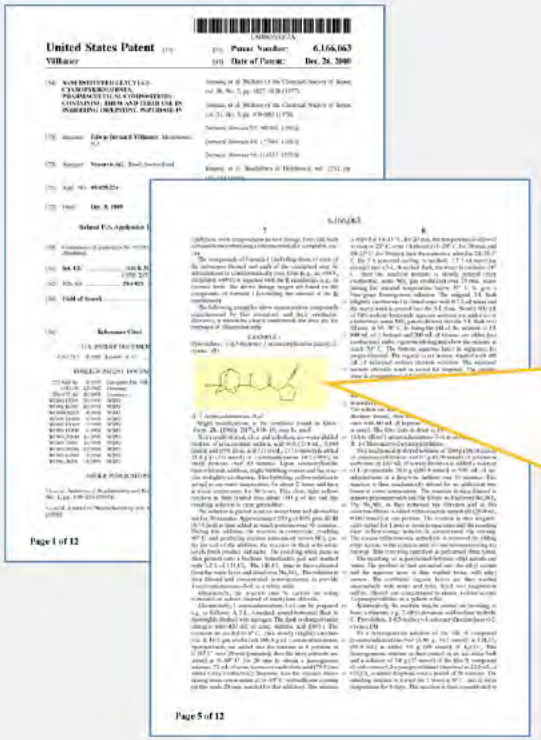
DECISION
Denying Institution of *Inter Partes* Review
37 C.F.R. § 42.108

Petitioner has not sufficiently explained why one skilled in the art would have selected the claimed substituents at each of the six independent positions *all at once*.

IPR2014-00559, Paper 8 at 9 (PTAB Oct. 1, 2014)

Mylan Demonstrative Exhibit

Hydroxyadamantyl at P2 was Known in DPP-4 Inhibitors


United States Patent

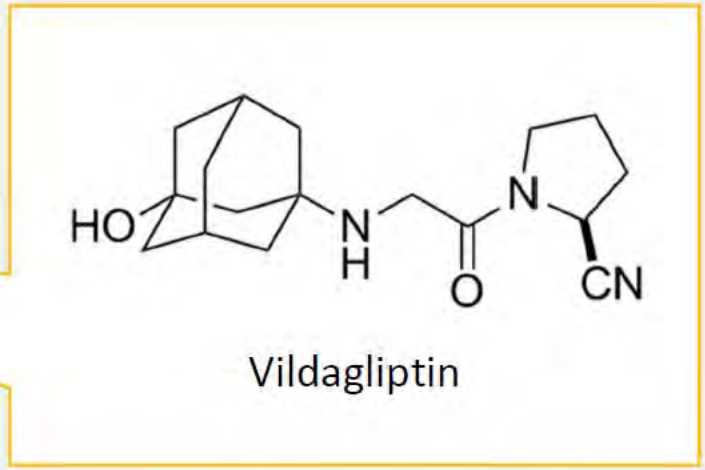
Villhauer

Patent Number: 6,166,063

Date of Patent: Dec. 26, 2000

Page 1 of 12

Page 5 of 12



Vildagliptin

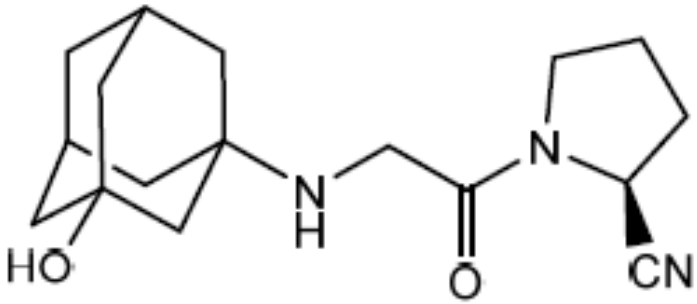
Source: EX2013 (Villhauer 2000), 7:15-27; Pet. Reply at 14.

31

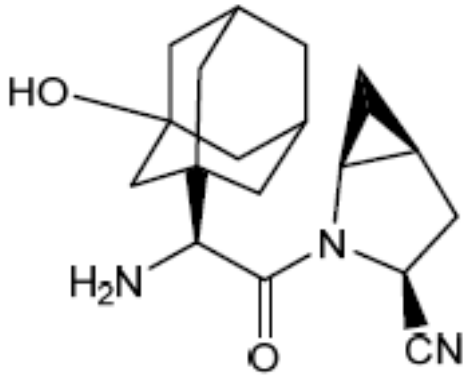
Unexpected Results

Vildagliptin and Saxagliptin

Vildagliptin



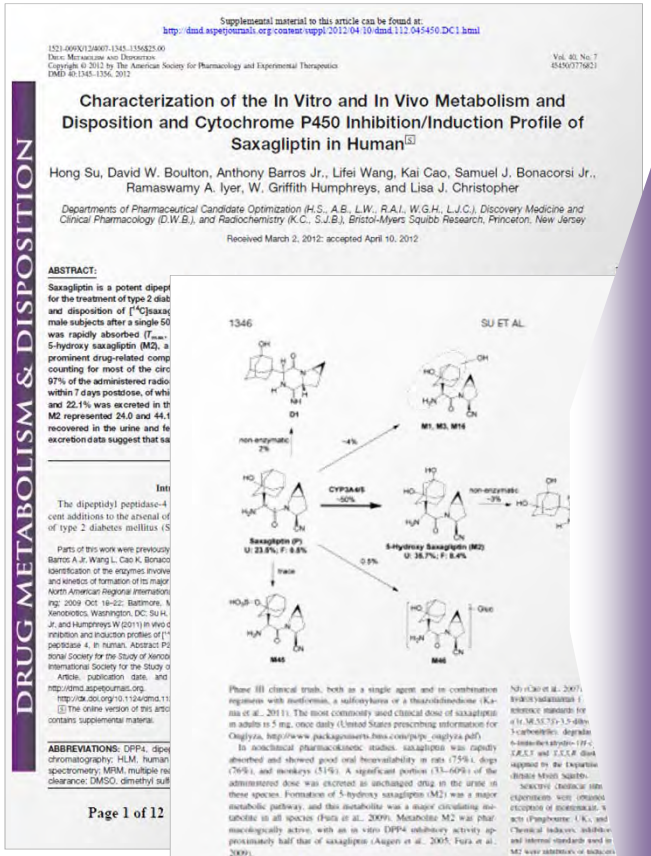
Saxagliptin



Villhauer '063 Patent – Ex. 1
Ex. 2013

Paper 28 at 15; Paper 62 at Observation 22; Ex. 2176 at 3, 4; Ex. 2241; Ex. 2056 at ¶ 234

Su (2012): Ex. 2045



Supplemental material to this article can be found at:
http://dmd.aspetjournals.org/content/suppl/2012/04/10/dmd.112.045450.DC1.html

1521-009X/12/4007-1345-1356$25.00
DRUG METABOLISM AND DISPOSITION
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DMD 40:1345–1356, 2012

Vol. 40, No. 7
0450/3776821

DRUG METABOLISM & DISPOSITION

Characterization of the In Vitro and In Vivo Metabolism and Disposition and Cytochrome P450 Inhibition/Induction Profile of Saxagliptin in Human

Hong Su, David W. Boulton, Anthony Barros Jr., Lifei Wang, Kai Cao, Samuel J. Bonacorsi Jr., Ramaswamy A. Iyer, W. Griffith Humphreys, and Lisa J. Christopher

Departments of Pharmaceutical Candidate Optimization (H.S., A.B., L.W., R.A.I., W.G.H., L.J.C.), Discovery Medicine and Clinical Pharmacology (D.W.B.), and Radiochemistry (K.C., S.J.B.), Bristol-Myers Squibb Research, Princeton, New Jersey

Received March 2, 2012; accepted April 10, 2012

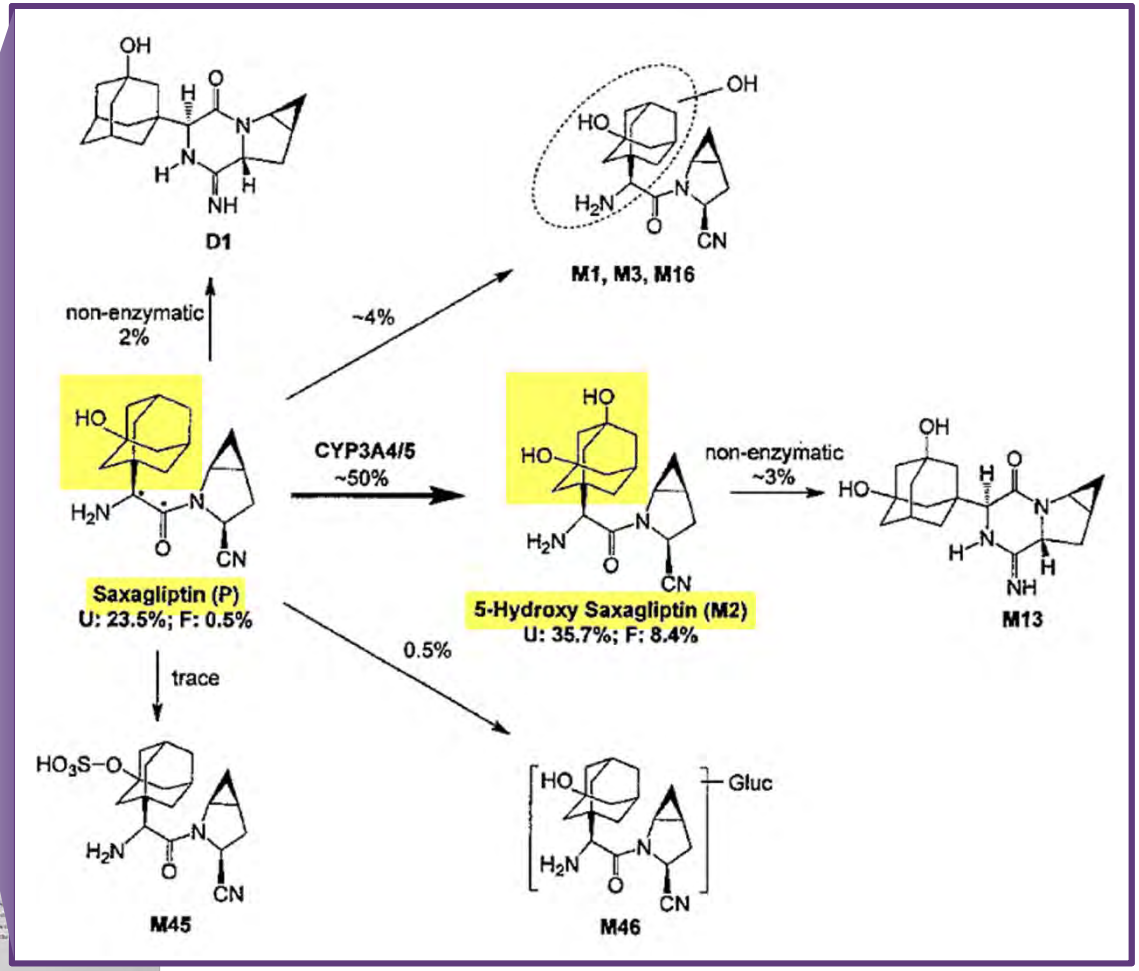
ABSTRACT:

Page 1 of 12

1346 SU ET AL.

Page 2 of 12

Metabolism of Saxagliptin



Paper 28 at 62-63; Ex. 2056 ¶¶ 236-240; Ex. 2045 at 2

He (2009): Ex. 2046

Metabolism of Vildagliptin

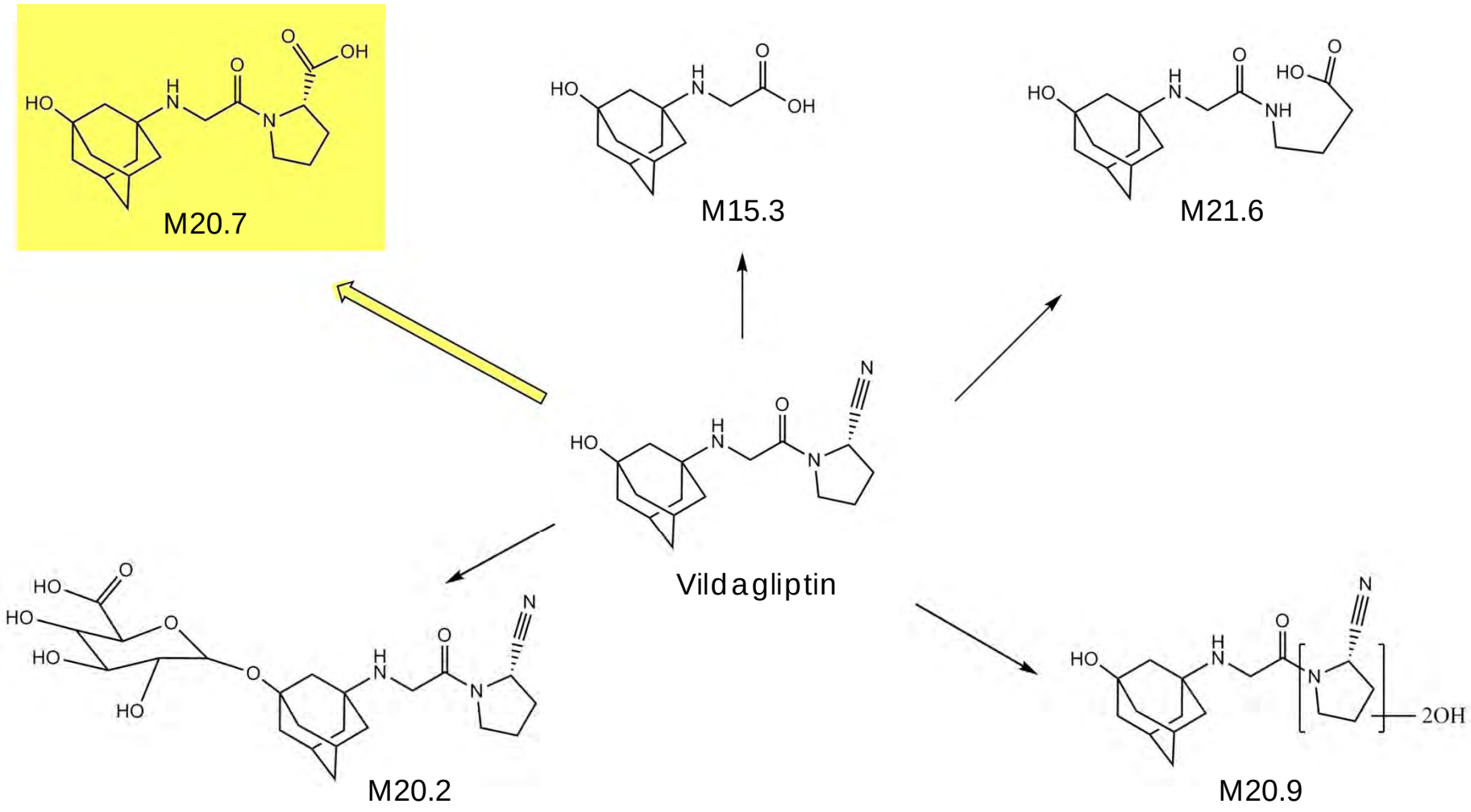
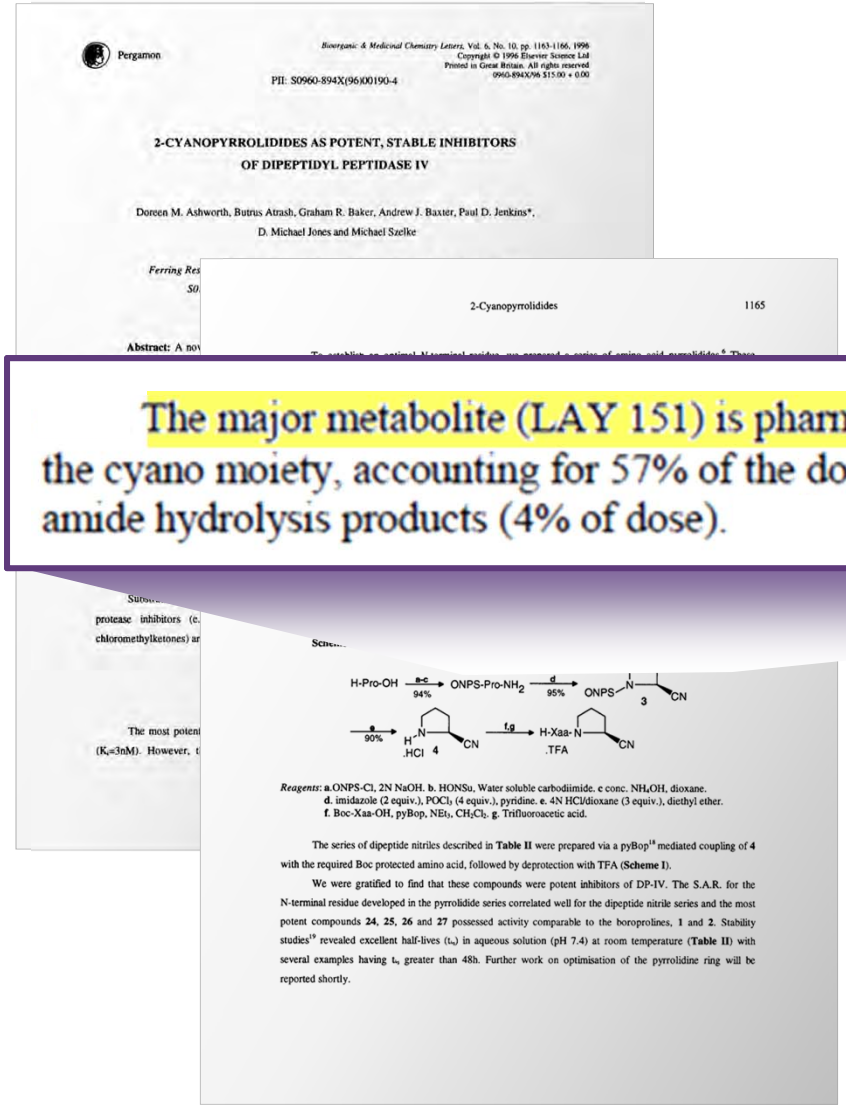


FIG. 5. Metabolism of vildagliptin in humans. The major route is indicated by a large arrow.

Novartis' Galvus (Vildagliptin) European Label: Ex. 2080



Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 6, No. 10, pp. 1163-1166, 1996
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0960-894X/96 $15.00 + 0.00

PII: S0960-894X(96)00190-4

2-CYANOPYRROLIDIDES AS POTENT, STABLE INHIBITORS OF DIPEPTIDYL PEPTIDASE IV

Doreen M. Ashworth, Butrus Atrash, Graham R. Baker, Andrew J. Baxter, Paul D. Jenkins*, D. Michael Jones and Michael Szelke

2-Cyanopyrrolidides 1165

protease inhibitors (e.
chloromethylketones) ar

The most potent
(K_i=3nM). However, t

H-Pro-OH —(a-c, 94%)→ ONPS-Pro-NH_2 —(d, 95%)→ ONPS-(3)-CN

—(e, 90%)→ (4) .HCl —(f,g)→ H-Xaa-(3)-CN .TFA

Reagents: **a**.ONPS-Cl, 2N NaOH. **b**. HONSu, Water soluble carbodiimide. **c** conc. NH_4OH, dioxane. **d**. imidazole (2 equiv.), $POCl_3$ (4 equiv.), pyridine. **e**. 4N HCl/dioxane (3 equiv.), diethyl ether. **f**. Boc-Xaa-OH, pyBop, NEt_3, CH_2Cl_2. **g**. Trifluoroacetic acid.

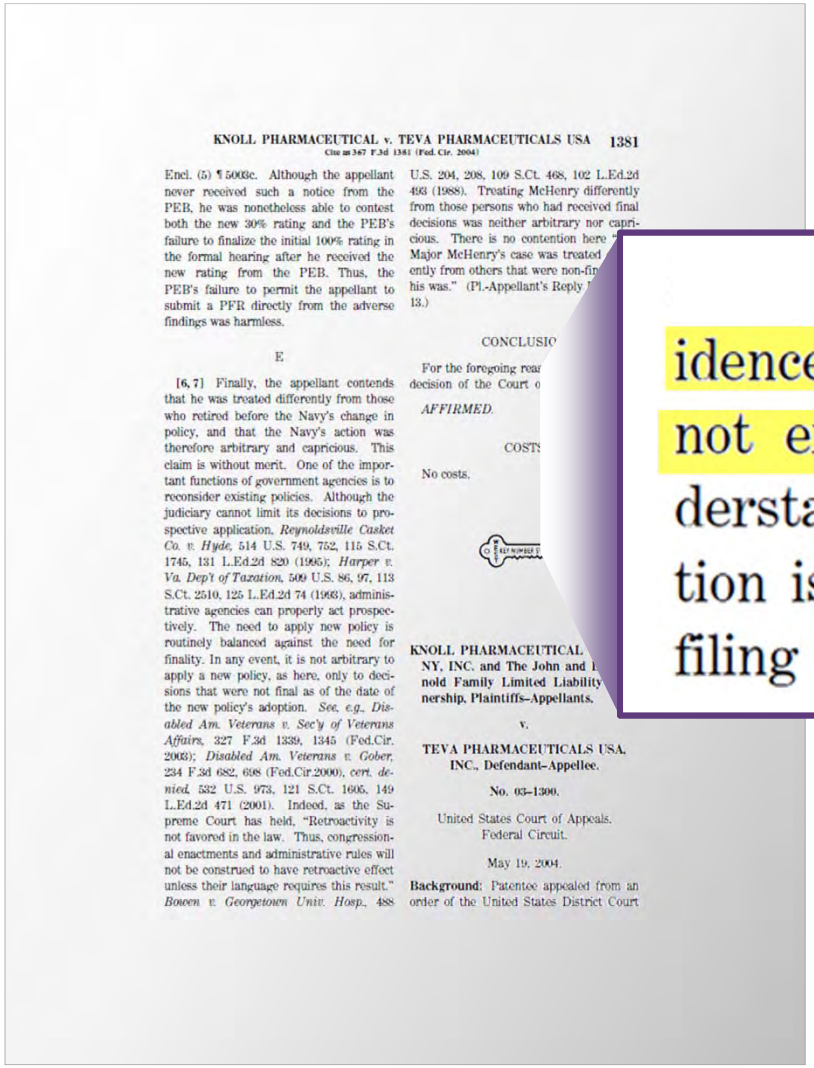
The series of dipeptide nitriles described in **Table II** were prepared via a pyBop[18] mediated coupling of **4** with the required Boc protected amino acid, followed by deprotection with TFA (**Scheme I**).

We were gratified to find that these compounds were potent inhibitors of DP-IV. The S.A.R. for the N-terminal residue developed in the pyrrolidide series correlated well for the dipeptide nitrile series and the most potent compounds **24**, **25**, **26** and **27** possessed activity comparable to the boroprolines, **1** and **2**. Stability studies[19] revealed excellent half-lives ($t_{1/2}$) in aqueous solution (pH 7.4) at room temperature (**Table II**) with several examples having $t_{1/2}$ greater than 48h. Further work on optimisation of the pyrrolidine ring will be reported shortly.

The major metabolite (LAY 151) is pharmacologically inactive and is the hydrolysis product of the cyano moiety, accounting for 57% of the dose, followed by the glucuronide (BQS867) and the amide hydrolysis products (4% of dose).

Paper 28 at 62-63; Ex. 2056 ¶ 241; Ex. 2080 at 15

Knoll Pharm. Co. v. Teva Pharm. USA, Inc.



KNOLL PHARMACEUTICAL v. TEVA PHARMACEUTICALS USA 1381
Cite as 367 F.3d 1381 (Fed. Cir. 2004)

Encl. (5) ¶ 5003c. Although the appellant never received such a notice from the PEB, he was nonetheless able to contest both the new 30% rating and the PEB's failure to finalize the initial 100% rating in the formal hearing after he received the new rating from the PEB. Thus, the PEB's failure to permit the appellant to submit a PFR directly from the adverse findings was harmless.

E

[6, 7] Finally, the appellant contends that he was treated differently from those who retired before the Navy's change in policy, and that the Navy's action was therefore arbitrary and capricious. This claim is without merit. One of the important functions of government agencies is to reconsider existing policies. Although the judiciary cannot limit its decisions to prospective application, *Reynoldsville Casket Co. v. Hyde*, 514 U.S. 749, 752, 115 S.Ct. 1745, 131 L.Ed.2d 820 (1995); *Harper v. Va. Dep't of Taxation*, 509 U.S. 86, 97, 113 S.Ct. 2510, 125 L.Ed.2d 74 (1993), administrative agencies can properly act prospectively. The need to apply new policy is routinely balanced against the need for finality. In any event, it is not arbitrary to apply a new policy, as here, only to decisions that were not final as of the date of the new policy's adoption. *See, e.g., Disabled Am. Veterans v. Sec'y of Veterans Affairs*, 327 F.3d 1339, 1345 (Fed.Cir. 2003); *Disabled Am. Veterans v. Gober*, 234 F.3d 682, 698 (Fed.Cir.2000), *cert. denied*, 532 U.S. 973, 121 S.Ct. 1605, 149 L.Ed.2d 471 (2001). Indeed, as the Supreme Court has held, "Retroactivity is not favored in the law. Thus, congressional enactments and administrative rules will not be construed to have retroactive effect unless their language requires this result." *Bowen v. Georgetown Univ. Hosp.*, 488 U.S. 204, 208, 109 S.Ct. 468, 102 L.Ed.2d 493 (1988). Treating McHenry differently from those persons who had received final decisions was neither arbitrary nor capricious. There is no contention here "
Major McHenry's case was treated
ently from others that were non-fi
his was." (Pl.-Appellant's Reply
13.)

CONCLUSIO

For the foregoing rea
decision of the Court o

AFFIRMED.

COST

No costs.

KNOLL PHARMACEUTICAL
NY, INC. and The John and
nold Family Limited Liability
nership, Plaintiffs–Appellants.

v.

TEVA PHARMACEUTICALS USA, INC., Defendant–Appellee.

No. 03–1300.

United States Court of Appeals, Federal Circuit.

May 19, 2004.

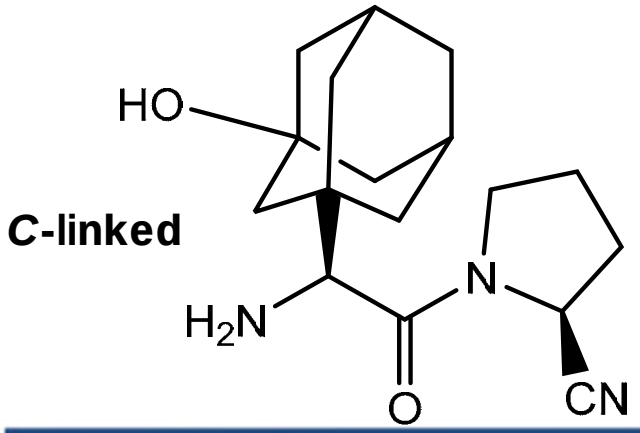
Background: Patentee appealed from an order of the United States District Court

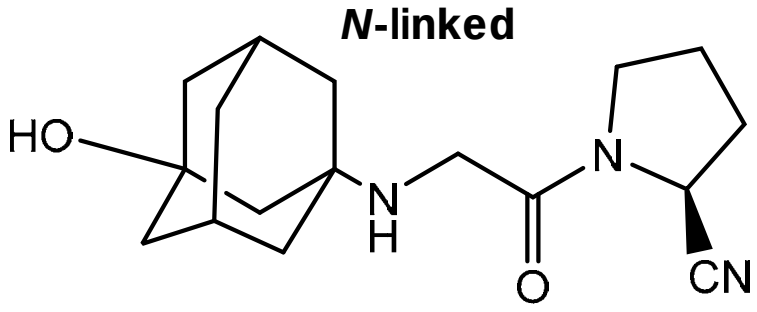
Ev-

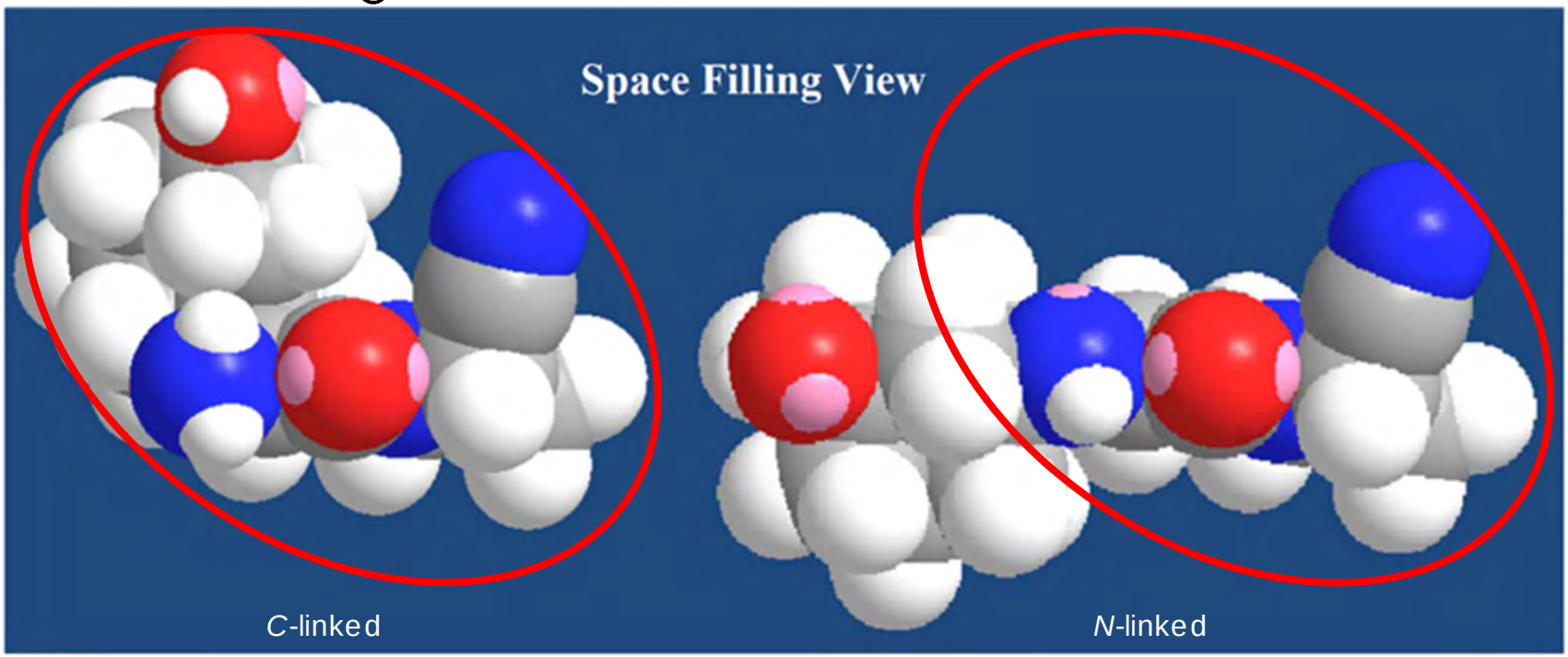
idence developed after the patent grant is not excluded from consideration, for understanding of the full range of an invention is not always achieved at the time of filing the patent application.

367 F.3d 1381, 1385 (Fed. Cir. 2004)

C-linked v. *N*-linked

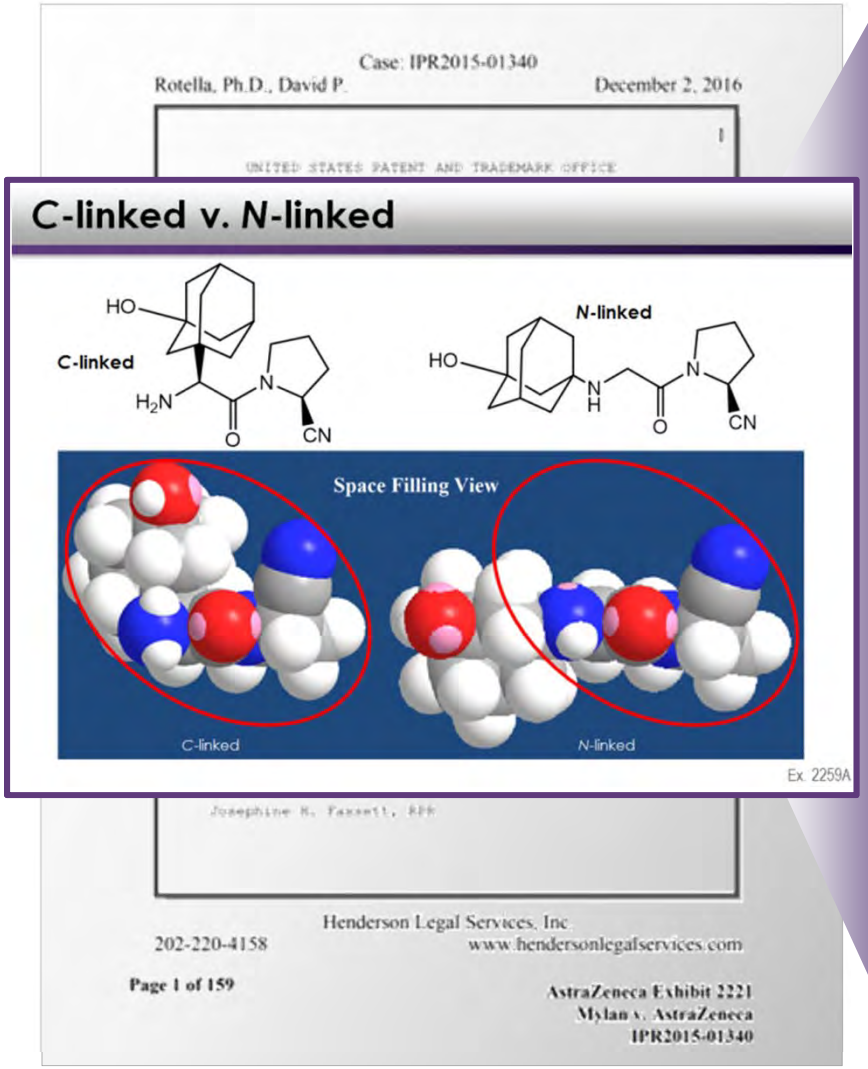






Paper 62 at Observation 21; *cf.* Ex. 2056 ¶ 200; Ex. 2259A

Dr. Rotella



Q. Would it be fair to say that you could not predict that the N-linked hydroxy adamantyl molecule illustrated here would have its P2 group binding to the enzyme in the same way as the hydroxy adamantyl in the C-linked molecule as illustrated here?

MR. TORCZON: Objection. Scope.

A. I offer no opinion on what position in space the P2 group in the N-linked molecule occupies in space.

Q. My question was a little different.

My question was whether you could have predicted that they would bind to the enzyme in the same way?

MR. TORCZON: Same objection.

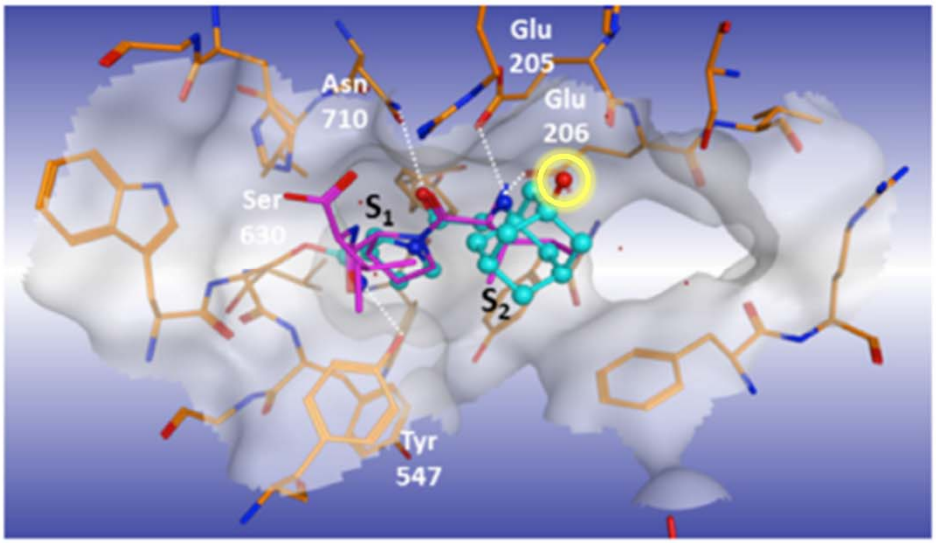
A. Again, my -- my answer is the same. I mean, you, you -- in the DPP-4 field at the time there were no crystal structures and so one has no way of knowing how these various groups fit into and interact with the enzyme.

Paper 62 at Observation 21; Ex. 2221 at 83:8-84:2; Ex. 2259A

Nabeno (2013): Ex. 2176

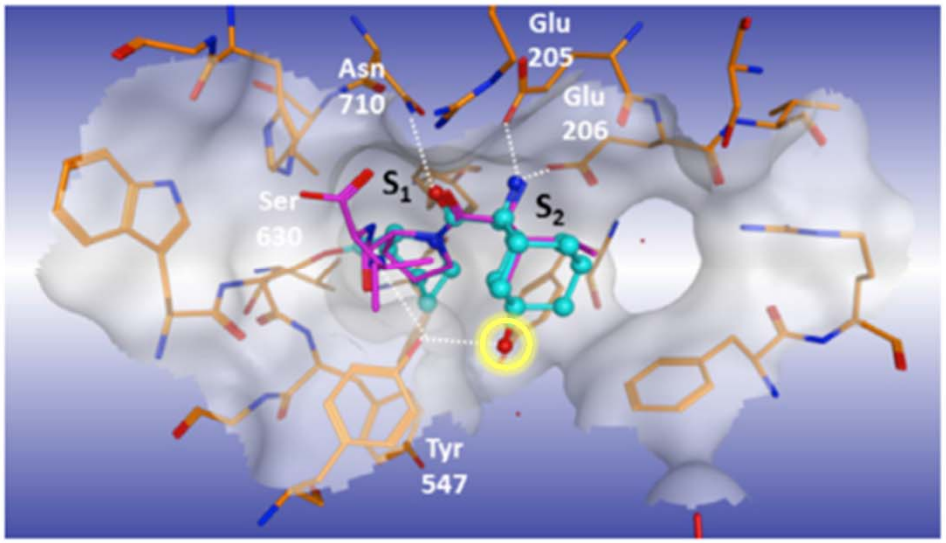
Binding Interactions of Vildagliptin and Saxagliptin

Vildagliptin



The hydroxyl group on the adamantyl moiety forms hydrogen bonds with His126 and Ser209 via the water molecules.

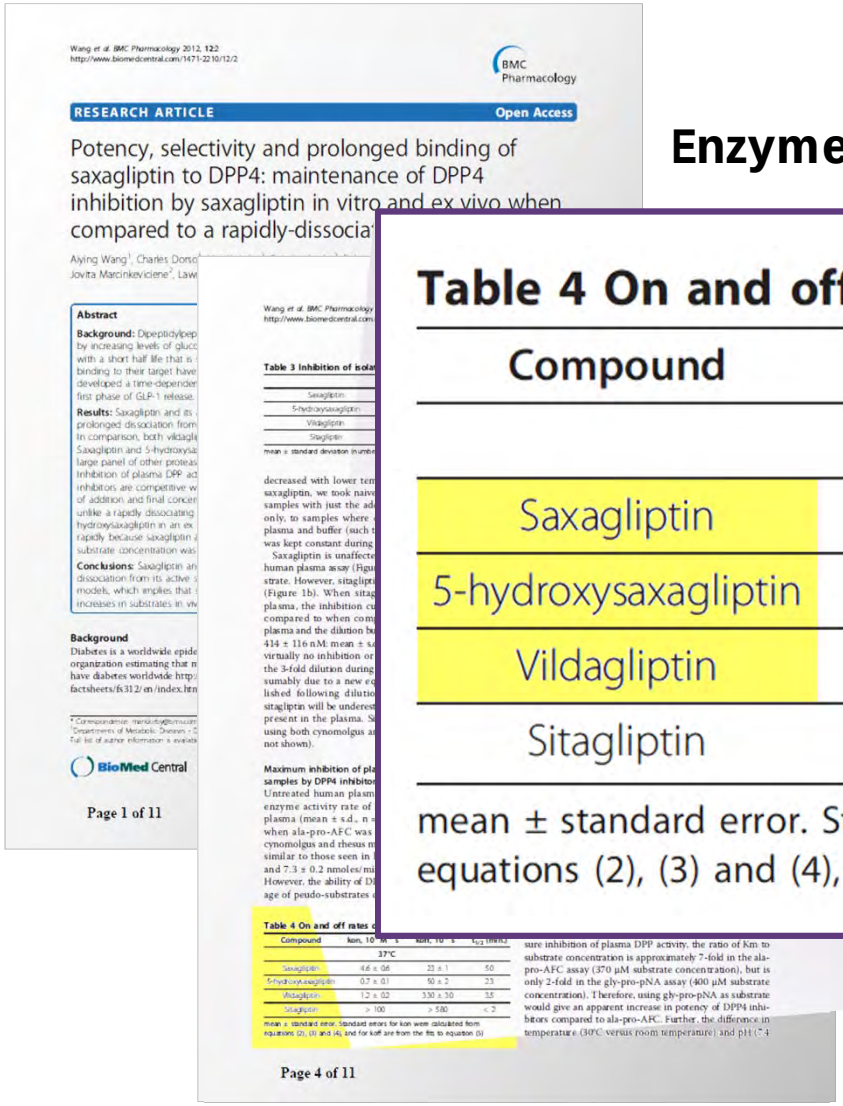
Saxagliptin



Although it was originally intended to enhance the chemical stability of the cyanopyrrolidine [3], introduction of the cyclopropane moiety afforded an additional hydrophobic interaction with the side chain of Tyr666 in the S_1 subsite. Moreover, the direct hydrogen bond between the hydroxyl group of saxagliptin and the side chain of Tyr547 may also contribute to its higher potency.

Paper 28 at 63-64; Paper 62 at Observation 22; Ex. 2176 at 3, 4; Ex. 2241; Ex. 2056 ¶ 244

Wang (2012): Ex. 2018


Wang et al. BMC Pharmacology 2012, 12:2
http://www.biomedcentral.com/1471-2210/12/2

BMC Pharmacology

RESEARCH ARTICLE Open Access

Potency, selectivity and prolonged binding of saxagliptin to DPP4: maintenance of DPP4 inhibition by saxagliptin in vitro and ex vivo when compared to a rapidly-dissocia

Aiying Wang[1], Charles Dorso
Jovita Marcinkeviciene[1], Law

Abstract

Background: Dipeptidylpep
by increasing levels of gluc
with a short half life that is
binding to their target have
developed a time-dependen
first phase of GLP-1 release.

Results: Saxagliptin and its
prolonged dissociation from
In comparison, both vildagli
Saxagliptin and 5-hydroxysa
large panel of other protea
Inhibition of plasma DPP ac
inhibitors are competitive w
of addition and final concer
unlike a rapidly dissociating
hydroxysaxagliptin in an ex
rapidly because saxagliptin
substrate concentration was

Conclusions: Saxagliptin an
dissociation from its active
models, which implies that
increases in substrates in vi

Background

Diabetes is a worldwide epide
organization estimating that n
have diabetes worldwide: http:
factsheets/fs312/en/index.htm

BioMed Central

Page 1 of 11

Wang et al. BMC Pharmacology
http://www.biomedcentral.com

Table 3 Inhibition of isola

decreased with lower tem
saxagliptin, we took naive
samples with just the ad
only, to samples where
plasma and buffer (such t
was kept constant during
Saxagliptin is unaffecte
human plasma assay (Figu
strate. However, sitaglipt
(Figure 1b). When sitag
plasma, the inhibition cu
compared to when com
plasma and the dilution bu
414 ± 116 nM; mean ± s
virtually no inhibition or
the 3-fold dilution during
sumably due to a new e
lished following dilutio
sitagliptin will be underest
present in the plasma. S
using both cynomolgus a
not shown).

Maximum inhibition of pla
samples by DPP4 inhibitor
Untreated human plasm
enzyme activity rate of
plasma (mean ± s.d., n =
when ala-pro-AFC was
cynomolgus and rhesus m
similar to those seen in
and 7.3 ± 0.2 nmoles/mi
However, the ability of D
age of pseudo-substrates

Table 4 On and off rates o

Compound	kon, 10^5 M^{-1} s^{-1}	koff, 10^{-5} s^{-1}	$t_{1/2}$ (min.)
	37°C		
Saxagliptin	4.6 ± 0.6	23 ± 1	50
5-hydroxysaxagliptin	0.7 ± 0.1	50 ± 2	23
Vildagliptin	1.2 ± 0.2	330 ± 30	3.5
Sitagliptin	> 100	> 580	< 2

mean ± standard error. Standard errors for kon were calculated from equations (2), (3) and (4), and for koff are from the fits to equation (5)

sure inhibition of plasma DPP activity, the ratio of Km to substrate concentration is approximately 7-fold in the ala-pro-AFC assay (370 μM substrate concentration), but is only 2-fold in the gly-pro-pNA assay (400 μM substrate concentration). Therefore, using gly-pro-pNA as substrate would give an apparent increase in potency of DPP4 inhibitors compared to ala-pro-AFC. Further, the difference in temperature (30°C versus room temperature) and pH (7.4

Page 4 of 11

Enzyme Binding of Saxagliptin and Vildagliptin

Table 4 On and off rates of DPP4 inhibitors at 37°C

Compound	kon, 10^5 M^{-1} s^{-1}	koff, 10^{-5} s^{-1}	$t_{1/2}$ (min.)
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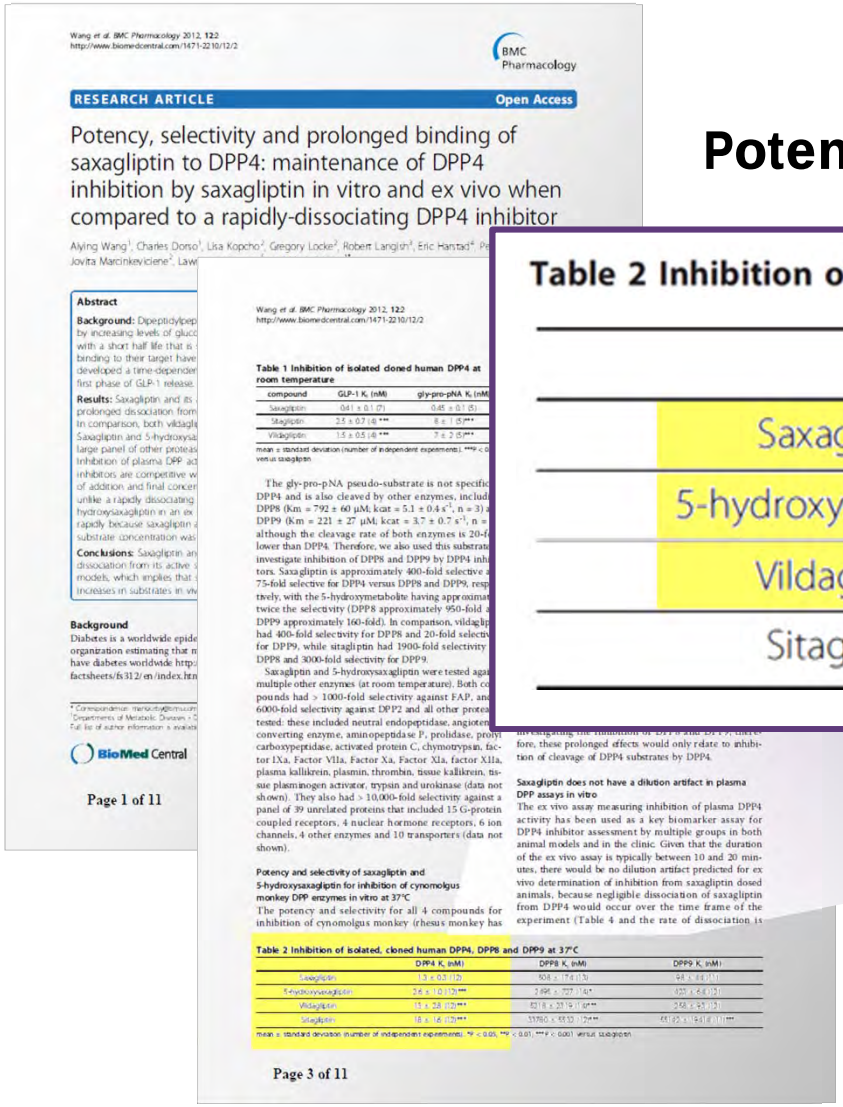
mean ± standard error. Standard errors for kon were calculated from equations (2), (3) and (4), and for koff are from the fits to equation (5)

Paper 28 at 61; Ex. 2018 at 4; Ex. 2056 ¶¶ 235-236

Wang (2012): Ex. 2018



Wang et al. BMC Pharmacology 2012, 12:2
http://www.biomedcentral.com/1471-2210/12/2

BMC Pharmacology

RESEARCH ARTICLE Open Access

Potency, selectivity and prolonged binding of saxagliptin to DPP4: maintenance of DPP4 inhibition by saxagliptin in vitro and ex vivo when compared to a rapidly-dissociating DPP4 inhibitor

Aiying Wang[1], Charles Dorso[1], Lisa Kopcho[2], Gregory Locke[2], Robert Langish[3], Eric Hanstad[4], Pe
Jovita Marcinkeviciene[1], Law

Abstract

Background: Dipeptidylpep
by increasing levels of gluc
with a short half life that is
binding to their target have
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Results: Saxagliptin and its
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hydroxysaxagliptin in an ex
rapidly because saxagliptin
substrate concentration was

Conclusions: Saxagliptin an
dissociation from its active
models, which implies that
increases in substrates in vi

Background

Diabetes is a worldwide epide
organization estimating that n
have diabetes worldwide http:
factsheets/fs312/en/index.htm

* Correspondence: mansouty@bms.com
Departments of Metabolic Diseases, 2
Full list of author information is availa

BioMed Central

Page 1 of 11

Wang et al. BMC Pharmacology 2012, 12:2
http://www.biomedcentral.com/1471-2210/12/2

Table 1 Inhibition of isolated cloned human DPP4 at room temperature

compound	GLP-1 K_i (nM)	gly-pro-pNA K_i (nM)
Saxagliptin	0.61 ± 0.1 (7)	0.45 ± 0.1 (5)
Sitagliptin	2.5 ± 0.7 (4) ***	8 ± 1 (5)***
Vildagliptin	1.5 ± 0.5 (4) ***	7 ± 2 (5)***

mean ± standard deviation (number of independent experiments). *** $P < 0.001$ versus saxagliptin

The gly-pro-pNA pseudo-substrate is not specific
DPP4 and is also cleaved by other enzymes, includ
DPP8 (Km = 792 ± 60 μM; kcat = 5.1 ± 0.4 s^{-1}, n = 3) a
DPP9 (Km = 221 ± 27 μM; kcat = 3.7 ± 0.7 s^{-1}, n =
although the cleavage rate of both enzymes is 20-f
lower than DPP4. Therefore, we also used this substrat
investigate inhibition of DPP8 and DPP9 by DPP4 inh
tors. Saxagliptin is approximately 400-fold selective a
75-fold selective for DPP4 versus DPP8 and DPP9, resp
tively, with the 5-hydroxymetabolite having approxima
twice the selectivity (DPP8 approximately 950-fold a
DPP9 approximately 160-fold). In comparison, vildagli
had 400-fold selectivity for DPP8 and 20-fold selectiv
for DPP9, while sitagliptin had 1900-fold selectivity
DPP8 and 3000-fold selectivity for DPP9.

Saxagliptin and 5-hydroxysaxagliptin were tested aga
multiple other enzymes (at room temperature). Both co
pounds had > 1000-fold selectivity against FAP, an
6000-fold selectivity against DPP2 and all other protea
tested; these included neutral endopeptidase, angioten
converting enzyme, aminopeptidase P, prolidase, prolyl
carboxypeptidase, activated protein C, chymotrypsin, fac-
tor IXa, Factor VIIa, Factor Xa, Factor XIa, factor XIIa,
plasma kallikrein, plasmin, thrombin, tissue kallikrein, tis-
sue plasminogen activator, trypsin and urokinase (data not
shown). They also had > 10,000-fold selectivity against a
panel of 39 unrelated proteins that included 15 G-protein
coupled receptors, 4 nuclear hormone receptors, 6 ion
channels, 4 other enzymes and 10 transporters (data not
shown).

Potency and selectivity of saxagliptin and 5-hydroxysaxagliptin for inhibition of cynomolgus monkey DPP enzymes in vitro at 37°C

The potency and selectivity for all 4 compounds for
inhibition of cynomolgus monkey (rhesus monkey has

Table 2 Inhibition of isolated, cloned human DPP4, DPP8 and DPP9 at 37°C

	DPP4 K_i (nM)	DPP8 K_i (nM)	DPP9 K_i (nM)
Saxagliptin	1.3 ± 0.3 (12)	908 ± 174 (13)	94 ± 44 (11)
5-hydroxysaxagliptin	2.6 ± 1.0 (12)***	2496 ± 727 (14)*	420 ± 64 (12)*
Vildagliptin	13 ± 2.8 (12)***	8218 ± 2179 (12)**	2458 ± 95 (12)*
Sitagliptin	18 ± 1.6 (12)***	33780 ± 8533 (12)**	44192 ± 1461 (11)***

mean ± standard deviation (number of independent experiments). * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ versus saxagliptin

fore, these prolonged effects would only relate to inhibi-
tion of cleavage of DPP4 substrates by DPP4.

Saxagliptin does not have a dilution artifact in plasma DPP assays in vitro

The ex vivo assay measuring inhibition of plasma DPP4
activity has been used as a key biomarker assay for
DPP4 inhibitor assessment by multiple groups in both
animal models and in the clinic. Given that the duration
of the ex vivo assay is typically between 10 and 20 min-
utes, there would be no dilution artifact predicted for ex
vivo determination of inhibition from saxagliptin dosed
animals, because negligible dissociation of saxagliptin
from DPP4 would occur over the time frame of the
experiment (Table 4 and the rate of dissociation is

Page 3 of 11

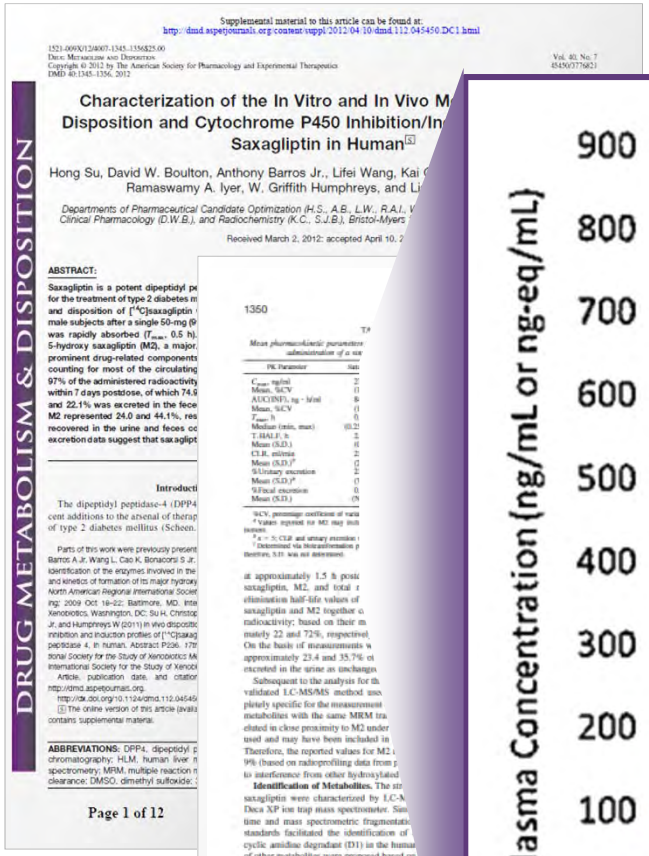
Potency of Saxagliptin and Vildagliptin

Table 2 Inhibition of isolated, cloned human DPP4, DPP8 and DPP9 at 37°C

	DPP4 K_i (nM)
Saxagliptin	1.3 ± 0.3 (12)
5-hydroxysaxagliptin	2.6 ± 1.0 (12)***
Vildagliptin	13 ± 2.8 (12)***
Sitagliptin	18 ± 1.6 (12)***

Paper 28 at 61; Ex. 2018 at 3; Ex. 2056 ¶ 235

Su (2012): Ex. 2045


Supplemental material to this article can be found at:
http://dmd.aspetjournals.org/content/suppl/2012/04/10/dmd.112.045450.DC1.html

1521-009X/12/4007-1345–1356$25.00
DRUG METABOLISM AND DISPOSITION
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DMD 40:1345–1356, 2012

Vol. 40, No. 7
45450/3776821

DRUG METABOLISM & DISPOSITION

Characterization of the In Vitro and In Vivo M
Disposition and Cytochrome P450 Inhibition/In
Saxagliptin in Human

Hong Su, David W. Boulton, Anthony Barros Jr., Lifei Wang, Kai
Ramaswamy A. Iyer, W. Griffith Humphreys, and Li

Departments of Pharmaceutical Candidate Optimization (H.S., A.B., L.W., R.A.I., V
Clinical Pharmacology (D.W.B.), and Radiochemistry (K.C., S.J.B.), Bristol-Myers

Received March 2, 2012; accepted April 10, 2

ABSTRACT:

Saxagliptin is a potent dipeptidyl pe
for the treatment of type 2 diabetes m
and disposition of [14C]saxagliptin
male subjects after a single 50-mg (9
was rapidly absorbed (T_{max}, 0.5 h).
5-hydroxy saxagliptin (M2), a major
prominent drug-related components
counting for most of the circulating
97% of the administered radioactivity
within 7 days postdose, of which 74.9
and 22.1% was excreted in the feces
M2 represented 24.0 and 44.1%, res
recovered in the urine and feces co
excretion data suggest that saxagliptin

Introducti

The dipeptidyl peptidase-4 (DPP4
cent additions to the arsenal of therap
of type 2 diabetes mellitus (Scheen,

Parts of this work were previously present
Barros A Jr, Wang L, Cao K, Bonacorsi S Jr,
identification of the enzymes involved in the
and kinetics of formation of its major hydroxy
North American Regional International Societ
ing; 2009 Oct 18–22; Baltimore, MD. Inte
Xenobiotics, Washington, DC: Su H, Christop
Jr, and Humphreys W (2011) In vivo disposit
inhibition and induction profiles of [14C]saxag
peptidase 4, in human. Abstract P226. 17t
tional Society for the Study of Xenobiotics M
International Society for the Study of Xenobi
Article, publication date, and citation
http://dmd.aspetjournals.org.
http://dx.doi.org/10.1124/dmd.112.04545
The online version of this article (avail
contains supplemental materia

ABBREVIATIONS: DPP4, dipeptidyl p
chromatography; HLM, human liver
spectrometry; MRM, multiple reaction
clearance; DMSO, dimethyl sulfoxide;

Page 1 of 12

1350

Mean pharmacokinetic parameters
administration of a sa

PK Parameter

C_{max}, ng/ml
Mean, %CV
AUC(INF), ng · h/ml
Mean, %CV
T_{max}, h
Median (min, max)
T_HALF, h
Mean (S.D.)
CLR, ml/min
Mean (S.D.)[a]
%Urinary excretion
Mean (S.D.)[a]
%Fecal excretion
Mean (S.D.)

%CV, percentage coefficient of varia
[a] Values reported for M2 may incl
increases.
[b] n = 5; CLR and urinary excretion
[c] Determined via metabolite/formation p
therefore, S.D. was not determined.

at approximately 1.5 h post
saxagliptin, M2, and total r
elimination half-life values of
saxagliptin and M2 together c
radioactivity; based on their m
mately 22 and 72%, respectivel
On the basis of measurements
approximately 23.4 and 35.7% o
excreted in the urine as unchanged

Subsequent to the analysis for th
validated LC-MS/MS method use
pletely specific for the measurement
metabolites with the same MRM tra
eluted in close proximity to M2 under
used and may have been included in
Therefore, the reported values for M2
9% (based on radioprofiling data from p
to interference from other hydroxylated

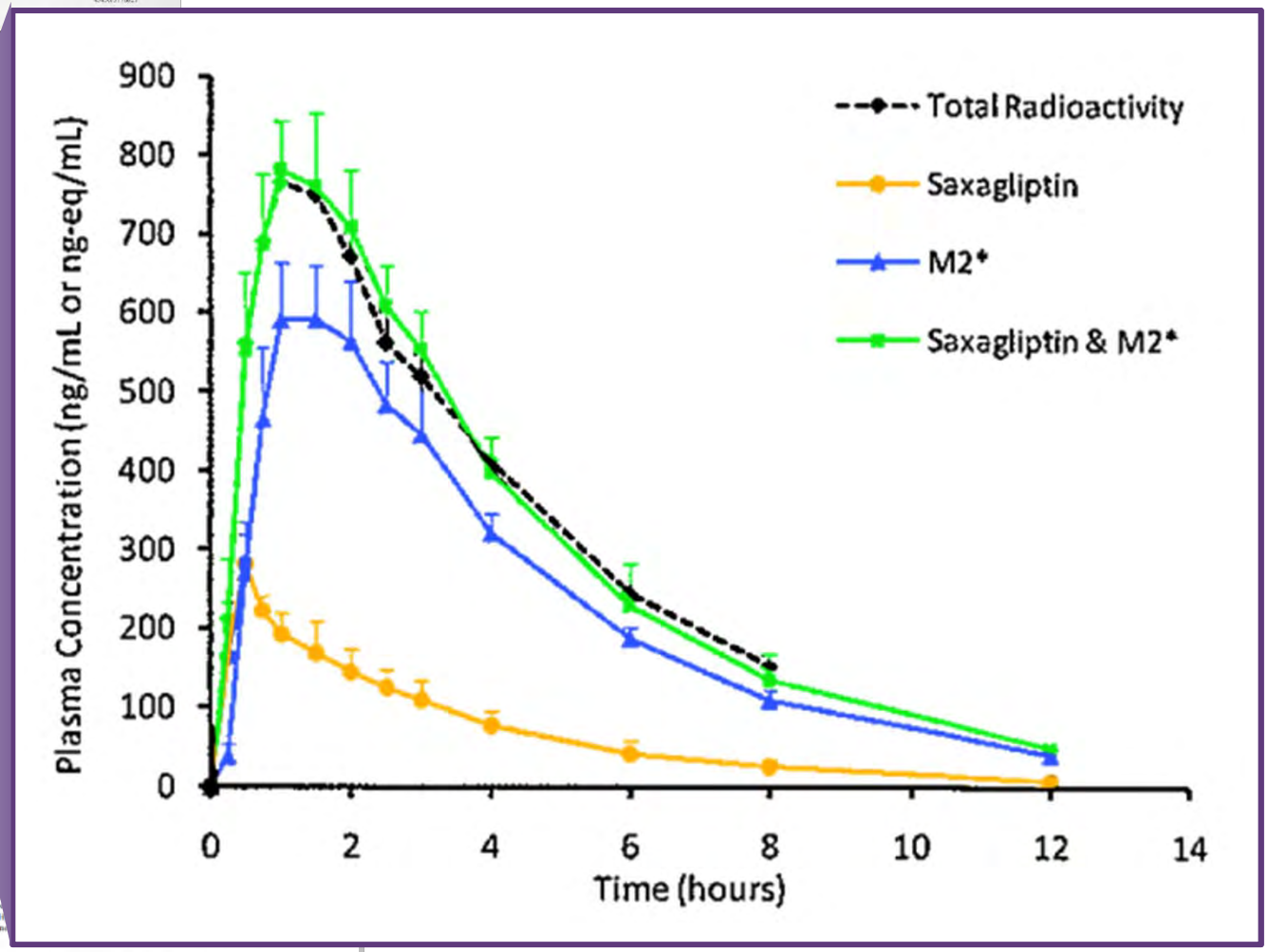
Identification of Metabolites. The str
saxagliptin were characterized by LC-M
Duca XP ion trap mass spectrometer. Sim
time and mass spectrometric fragmentati
standards facilitated the identification of
cyclic amidine degradant (D1) in the human
of other metabolites were proposed based on
fragmentation patterns relative to saxagliptin
reference standards. The mass spectrometric da
tural elucidation of the metabolites are summa

Saxagliptin had a protonated molecule [M+H
major MS^2 fragment at m/z 180 resulting fr
carbon-carbon bond between the carbonyl carbo
the methanamine group. The metabolites generall
fragmentation, enabling the localization of structura
either the amino-methyl-adamantyl group or the fr
bimethrile moiety.

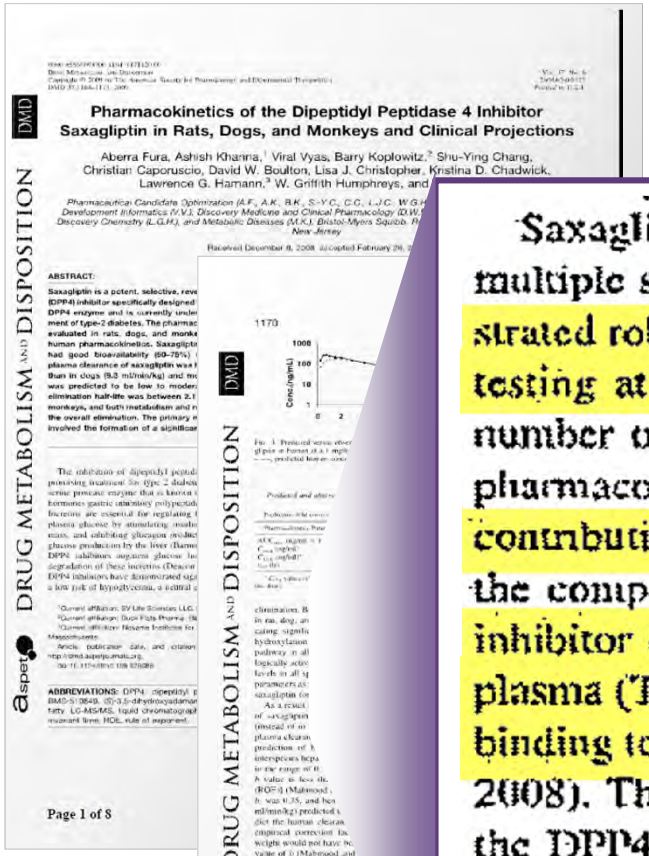
Metabolite M2 had a protonated molecule [M+H
Da higher than saxagliptin). The product ion mass s
a major MS^2 fragment at m/z 196, consistent with h
the amino-methyl-adamantyl group. Like M2, metab
and M16 each had a protonated molecular ion [M+H
(16 Da higher than saxagliptin) and a major MS^2 fragm

Page 6 of 12

Pharmacokinetics of Saxagliptin



Fura (2009): Ex. 2073

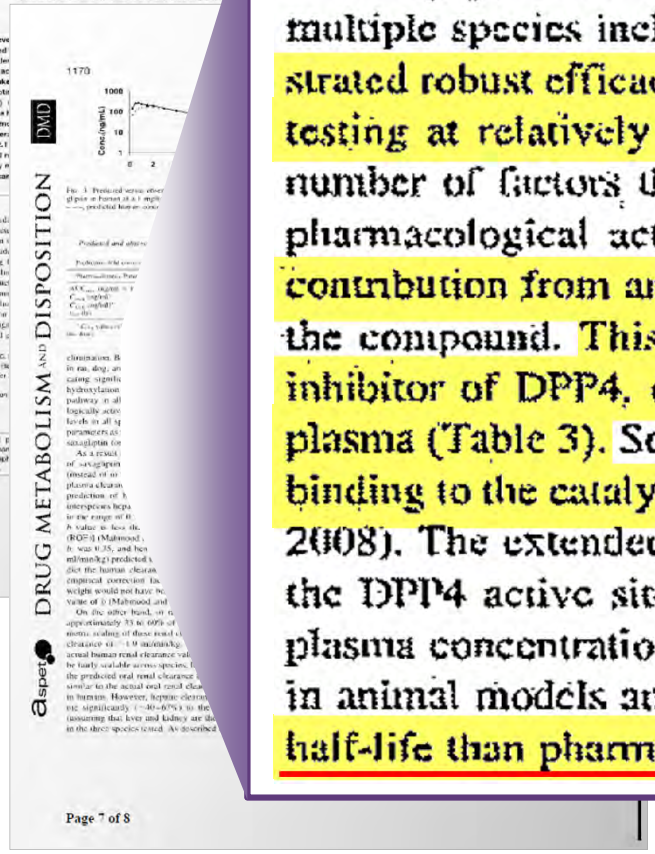


Pharmacokinetics of the Dipeptidyl Peptidase 4 Inhibitor Saxagliptin in Rats, Dogs, and Monkeys and Clinical Projections

Aberra Fura, Ashish Khanna, Viral Vyas, Barry Koplowitz, Shu-Ying Chang, Christian Caporuscio, David W. Boulton, Lisa J. Christopher, Kristina D. Chadwick, Lawrence G. Hamann, W. Griffith Humphreys, and

DRUG METABOLISM AND DISPOSITION

Page 1 of 8



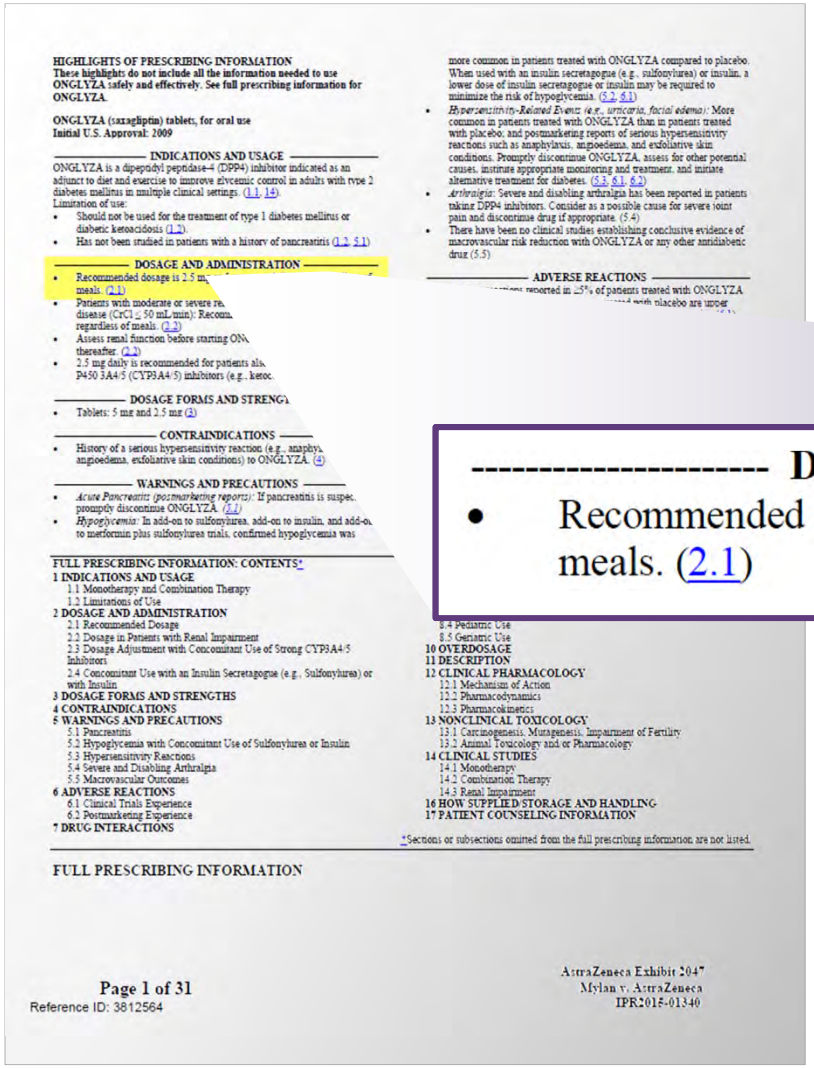
DRUG METABOLISM AND DISPOSITION

Page 7 of 8

Saxagliptin has a plasma pharmacokinetic half-life of 2 to 5 h in multiple species including humans. However, saxagliptin has demonstrated robust efficacy in clinical trials as well as in preclinical animal testing at relatively low doses after once-daily dosing. There are a number of factors that could contribute to the sustained duration of pharmacological action of saxagliptin. First, there is likely to be a contribution from an active metabolite, M2, to the overall efficacy of the compound. This metabolite, which is also a potent and specific inhibitor of DPP4, circulates in significant concentrations in human plasma (Table 3). Second, both saxagliptin and M2 display prolonged binding to the catalytic site of DPP4 (Kirby et al., 2008; Metzler et al., 2008). The extended rate of dissociation of saxagliptin and M2 from the DPP4 active site would be expected to give hysteresis between plasma concentration and DPP4 inhibition, which has been observed in animal models and humans, providing a longer pharmacodynamic half-life than pharmacokinetic half-life for the compound.

Paper 28 at 63; Ex. 2073 at 7; Ex. 2221 at 95:7-19; Ex. 2056 ¶ 238

Saxagliptin Label: Ex. 2047



HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ONGLYZA safely and effectively. See full prescribing information for ONGLYZA.

ONGLYZA (saxagliptin) tablets, for oral use
Initial U.S. Approval: 2009

INDICATIONS AND USAGE
ONGLYZA is a dipeptidyl peptidase-4 (DPP4) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus in multiple clinical settings. (1.1, 14)
Limitation of use:
- Should not be used for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis (1.2).
- Has not been studied in patients with a history of pancreatitis (1.2, 5.1)

DOSAGE AND ADMINISTRATION
- Recommended dosage is 2.5 m… meals. (2.1)
- Patients with moderate or severe re… disease (CrCl ≤ 50 mL/min): Recom… regardless of meals. (2.2)
- Assess renal function before starting ON… thereafter. (2.2)
- 2.5 mg daily is recommended for patients als… P450 3A4/5 (CYP3A4/5) inhibitors (e.g., ketoc…

DOSAGE FORMS AND STRENG…
- Tablets: 5 mg and 2.5 mg (3)

CONTRAINDICATIONS
- History of a serious hypersensitivity reaction (e.g., anaphy… angioedema, exfoliative skin conditions) to ONGLYZA. (4)

WARNINGS AND PRECAUTIONS
- *Acute Pancreatitis (postmarketing reports):* If pancreatitis is suspec… promptly discontinue ONGLYZA. (5.1)
- *Hypoglycemia:* In add-on to sulfonylurea, add-on to insulin, and add-o… to metformin plus sulfonylurea trials, confirmed hypoglycemia was more common in patients treated with ONGLYZA compared to placebo. When used with an insulin secretagogue (e.g., sulfonylurea) or insulin, a lower dose of insulin secretagogue or insulin may be required to minimize the risk of hypoglycemia. (5.2, 5.1)
- *Hypersensitivity-Related Events (e.g., urticaria, facial edema):* More common in patients treated with ONGLYZA than in patients treated with placebo, and postmarketing reports of serious hypersensitivity reactions such as anaphylaxis, angioedema, and exfoliative skin conditions. Promptly discontinue ONGLYZA, assess for other potential causes, institute appropriate monitoring and treatment, and initiate alternative treatment for diabetes. (5.3, 5.1, 6.2)
- *Arthralgia:* Severe and disabling arthralgia has been reported in patients taking DPP4 inhibitors. Consider as a possible cause for severe joint pain and discontinue drug if appropriate. (5.4)
- There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with ONGLYZA or any other antidiabetic drug (5.5)

ADVERSE REACTIONS
…reported in ≥5% of patients treated with ONGLYZA … with placebo are upper …

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

Page 1 of 31
Reference ID: 3812564

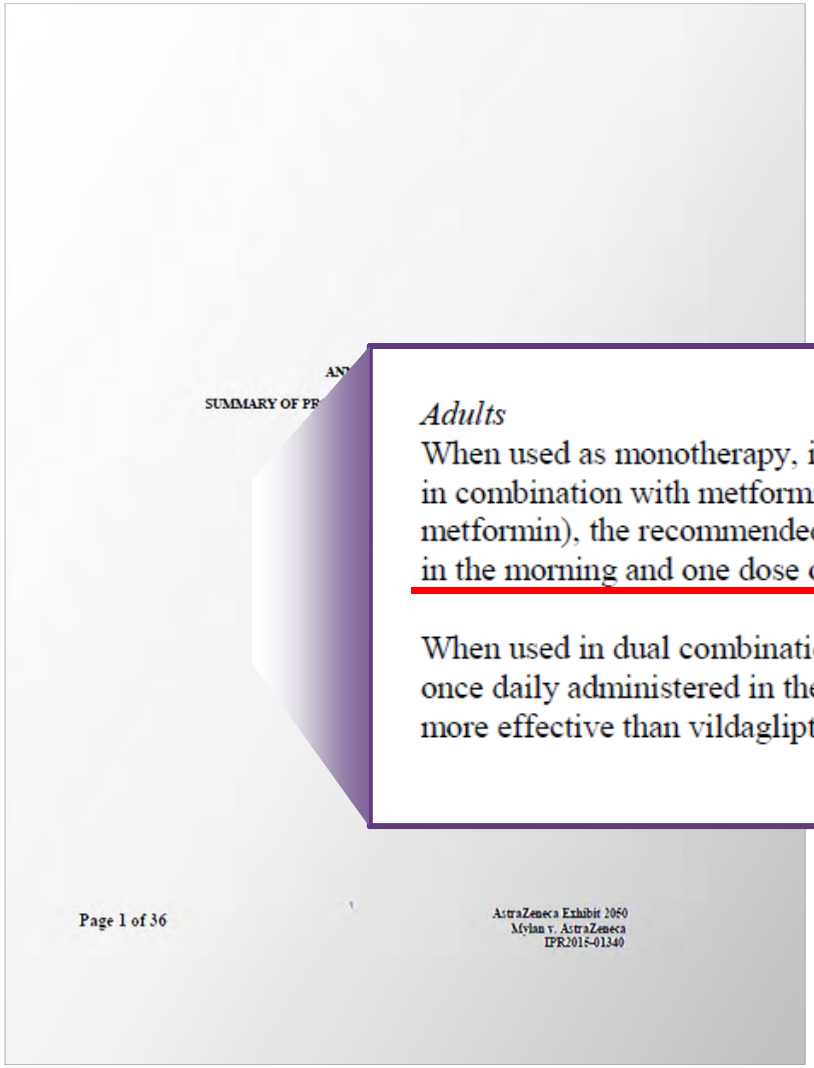
AstraZeneca Exhibit 2047
Mylan v. AstraZeneca
IPR2018-01340

---------- **DOSAGE AND ADMINISTRATION** ----------

- Recommended dosage is 2.5 mg or 5 mg once daily taken regardless of meals. (2.1)

Paper 7 at 53-54; Ex. 2047 at 1; Ex. 2056 ¶ 248; Paper 28 at 64 (citing Ex. 2057 ¶¶ 78-85)

Galvus Label: Ex. 2050



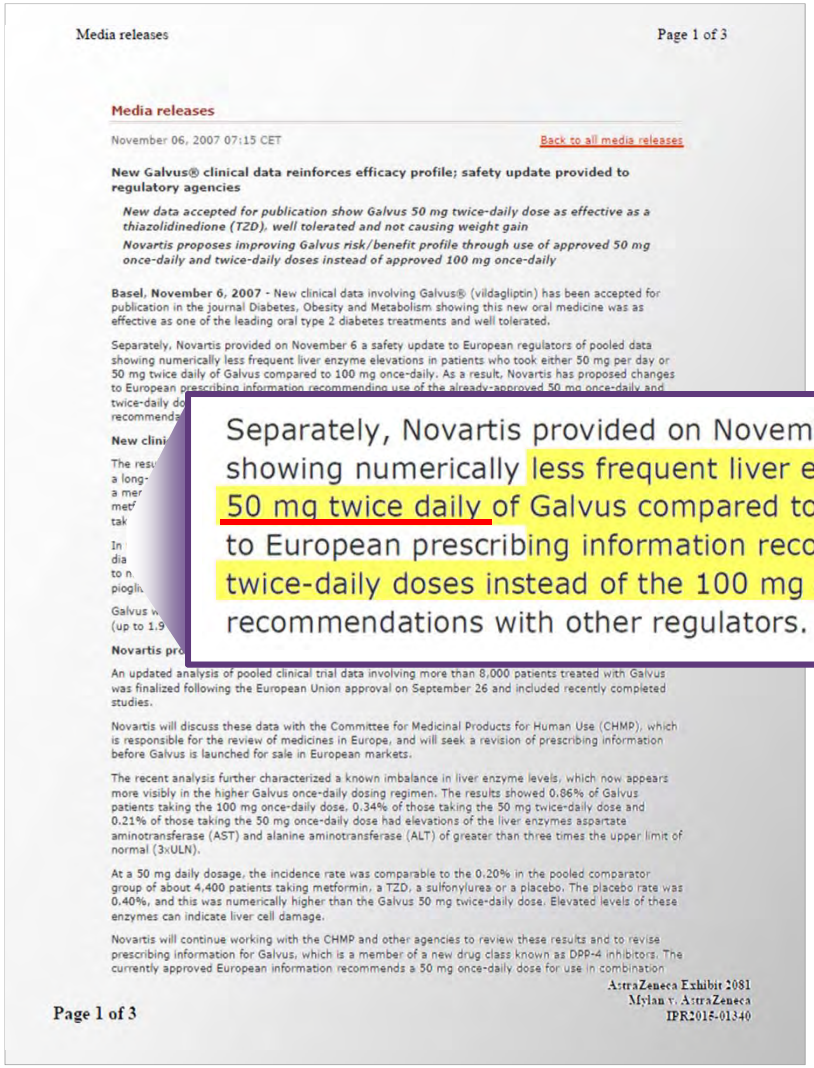
Adults

When used as monotherapy, in combination with metformin, in combination with thiazolidinedione, in combination with metformin and a sulphonylurea, or in combination with insulin (with or without metformin), the recommended daily dose of vildagliptin is 100 mg, administered as one dose of 50 mg in the morning and one dose of 50 mg in the evening.

When used in dual combination with a sulphonylurea, the recommended dose of vildagliptin is 50 mg once daily administered in the morning. In this patient population, vildagliptin 100 mg daily was no more effective than vildagliptin 50 mg once daily.

Ex. 2050 at 3; Paper 28, 15, 59, 65 ; Ex. 2057 ¶ 68

Novartis' Galvus (Vildagliptin) European Press Release (2007): Ex. 2081



Media releases Page 1 of 3

Media releases

November 06, 2007 07:15 CET Back to all media releases

New Galvus® clinical data reinforces efficacy profile; safety update provided to regulatory agencies

New data accepted for publication show Galvus 50 mg twice-daily dose as effective as a thiazolidinedione (TZD), well tolerated and not causing weight gain

Novartis proposes improving Galvus risk/benefit profile through use of approved 50 mg once-daily and twice-daily doses instead of approved 100 mg once-daily

Basel, November 6, 2007 - New clinical data involving Galvus® (vildagliptin) has been accepted for publication in the journal Diabetes, Obesity and Metabolism showing this new oral medicine was as effective as one of the leading oral type 2 diabetes treatments and well tolerated.

Separately, Novartis provided on November 6 a safety update to European regulators of pooled data showing numerically less frequent liver enzyme elevations in patients who took either 50 mg per day or 50 mg twice daily of Galvus compared to 100 mg once-daily. As a result, Novartis has proposed changes to European prescribing information recommending use of the already-approved 50 mg once-daily and twice-daily do
recommend

New clini

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Novartis pr

An updated analysis of pooled clinical trial data involving more than 8,000 patients treated with Galvus was finalized following the European Union approval on September 26 and included recently completed studies.

Novartis will discuss these data with the Committee for Medicinal Products for Human Use (CHMP), which is responsible for the review of medicines in Europe, and will seek a revision of prescribing information before Galvus is launched for sale in European markets.

The recent analysis further characterized a known imbalance in liver enzyme levels, which now appears more visibly in the higher Galvus once-daily dosing regimen. The results showed 0.86% of Galvus patients taking the 100 mg once-daily dose, 0.34% of those taking the 50 mg twice-daily dose and 0.21% of those taking the 50 mg once-daily dose had elevations of the liver enzymes aspartate aminotransferase (AST) and alanine aminotransferase (ALT) of greater than three times the upper limit of normal (3xULN).

At a 50 mg daily dosage, the incidence rate was comparable to the 0.20% in the pooled comparator group of about 4,400 patients taking metformin, a TZD, a sulfonylurea or a placebo. The placebo rate was 0.40%, and this was numerically higher than the Galvus 50 mg twice-daily dose. Elevated levels of these enzymes can indicate liver cell damage.

Novartis will continue working with the CHMP and other agencies to review these results and to revise prescribing information for Galvus, which is a member of a new drug class known as DPP-4 inhibitors. The currently approved European information recommends a 50 mg once-daily dose for use in combination

AstraZeneca Exhibit 2081
Mylan v. AstraZeneca
IPR2015-01340

Page 1 of 3

Separately, Novartis provided on November 6 a safety update to European regulators of pooled data showing numerically less frequent liver enzyme elevations in patients who took either 50 mg per day or 50 mg twice daily of Galvus compared to 100 mg once-daily. As a result, Novartis has proposed changes to European prescribing information recommending use of the already-approved 50 mg once-daily and twice-daily doses instead of the 100 mg once-daily dose. Novartis will discuss the data and recommendations with other regulators.

Paper 28 at 15, 59, 65; Ex. 2081 at 1; Ex. 2056 ¶ 248

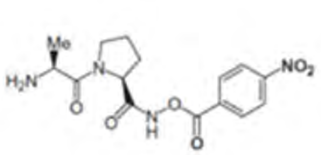
Long-Felt Need and Failures of Others

Oral Treatments From the Late 1990s

Class	Compounds	Side Effects
Sulfonylureas/Meglitinides	Tolbutamide Chlorpropamide Tolazamide Acetohexamide Glyburide Glipizide Glimepiride Repaglinide Nateglinide	Hypoglycemia Weight gain
Biguanides	Metformin	Lactic acidosis Gastrointestinal distress
TZDs	Rosiglitazone Pioglitazone	Edema Weight gain Fractures Hepatic toxicity
Alpha-Glucosidase Inhibitors	Acarbose Miglitol	Gastrointestinal distress Hepatic toxicity

Paper 28 at 5; Ex. 2057 ¶ 34, Table 2; Ex. 2063 at 8-9, 17; Ex. 2067 at 2-7

Prior Art DPP-4 Inhibitors: None FDA-Approved



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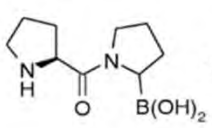
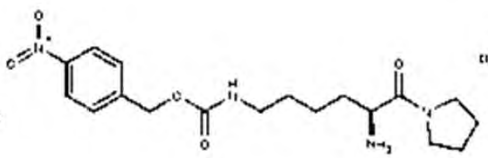


Ex. 2008



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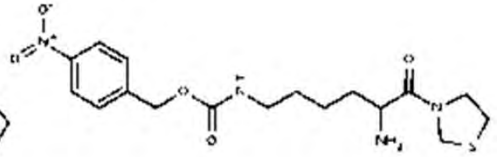

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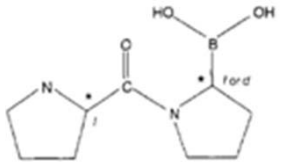

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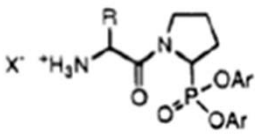

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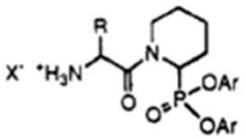

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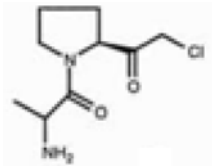

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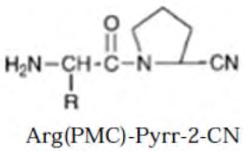
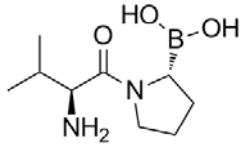


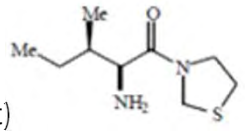
Arg(PMC)-Pyrr-2-CN
Arg-Pyrr-2-CN
Ala-Pyrr-2-CN
Phe-Pyrr-2-CN

Ex. 2042



PT-100 (Talabostat)

Ex. 2150



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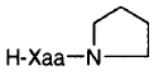

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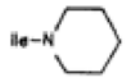

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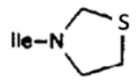

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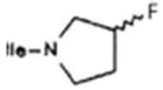

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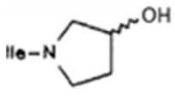

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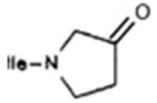
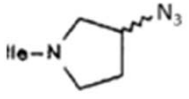
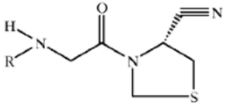


Ex. 2151



Ex. 2151



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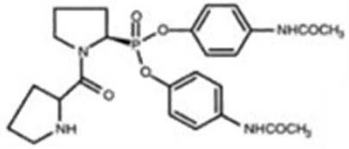
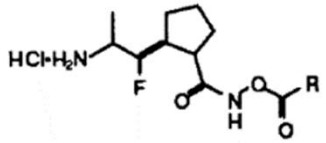
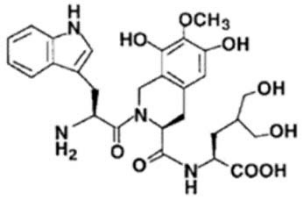


Ex. 2007



Ex. 1015



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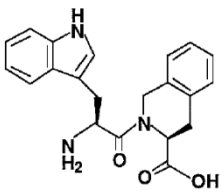
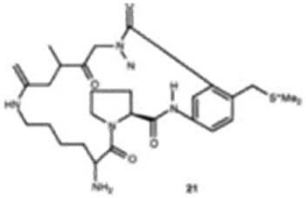
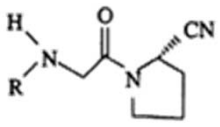


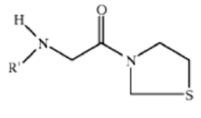
Ex. 2152



Ex. 2017



Ex. 1008



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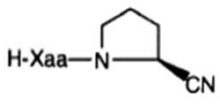
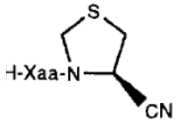
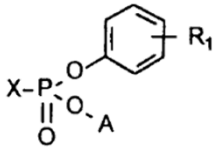


Ex. 1007



Ex. 2001



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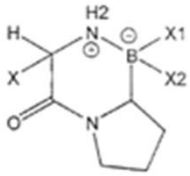

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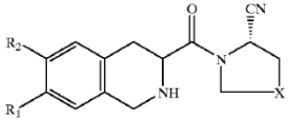
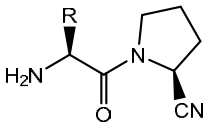


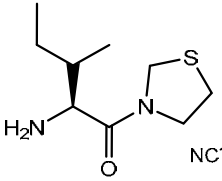
X is CH_2, S, O, or $C(CH_3)_2$

Ex. 2156



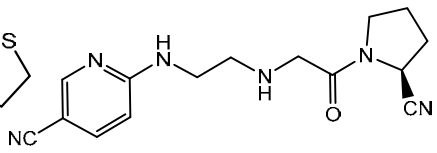
Ashworth I

Ex. 1007



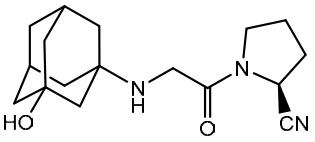
P32/98

Ex. 2009



NVP-DPP728

Ex. 2016



Vildagliptin

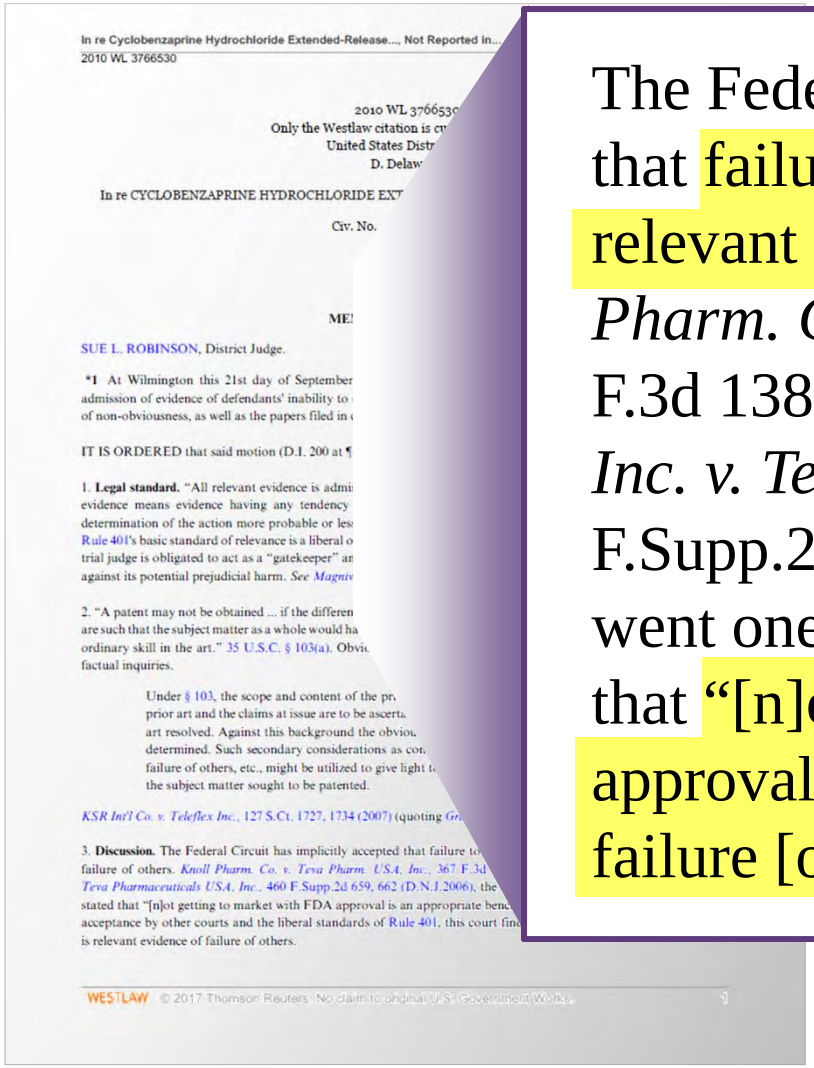
Ex. 2013

Clinical Failures of Others

DPP-4 Inhibitor	Developer	Clinical Phase	FDA Status
LAF-237 (vildagliptin)	Novartis AG	3	Discontinued
GW823093C (denagliptin)	GlaxoSmithKline PLC	3	Discontinued
PHX 1149 (dutogliptin)	Phenomix Corp. and Forrest Laboratories, Inc.	3	Discontinued
PT-630	Point Therapeutics, Inc.	3	Discontinued
AMG-222	Amgen Inc.	2	Discontinued
NVP-DPP728	Novartis AG	2	Discontinued
PSN-9301	Probiodrug AG, Prosidion Ltd., and OSI Pharmaceuticals, Inc.	2	Discontinued
P32/98	Probiodrug AG	2	Discontinued
R-1438	F. Hoffmann-La Roche Ltd.	2	Discontinued
TA-6666	Mitsubishi Tanabe Pharma Corp.	2	Discontinued
TS-021	Taisho Pharmaceutical Co., Ltd. and Eli Lilly and Co.	2	Discontinued
SSR-162339	Sanofi-Aventis U.S. LLC	1	Discontinued
SYR-619	Takeda Pharmaceutical Co. Ltd.	1	Discontinued

See Paper 28 at 59; Ex. 2057 ¶ 66, Table 4; Ex. 2086

In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.



In re Cyclobenzaprine Hydrochloride Extended-Release..., Not Reported in...
2010 WL 3766530

2010 WL 3766530
Only the Westlaw citation is cu
United States Distr
D. Delaw

In re CYCLOBENZAPRINE HYDROCHLORIDE EXT

Civ. No.

ME

SUE L. ROBINSON, District Judge.

*1 At Wilmington this 21st day of September
admission of evidence of defendants' inability to
of non-obviousness, as well as the papers filed in

IT IS ORDERED that said motion (D.I. 200 at ¶

1. **Legal standard.** "All relevant evidence is admi
evidence means evidence having any tendency
determination of the action more probable or les
Rule 401's basic standard of relevance is a liberal o
trial judge is obligated to act as a "gatekeeper" ar
against its potential prejudicial harm. *See Magniv*

2. "A patent may not be obtained ... if the differen
are such that the subject matter as a whole would ha
ordinary skill in the art." 35 U.S.C. § 103(a). Obvi
factual inquiries.

Under § 103, the scope and content of the pr
prior art and the claims at issue are to be ascerta
art resolved. Against this background the obviou
determined. Such secondary considerations as con
failure of others, etc., might be utilized to give light t
the subject matter sought to be patented.

KSR Int'l Co. v. Teleflex Inc., 127 S.Ct. 1727, 1734 (2007) (quoting *Gr*

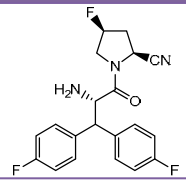
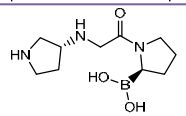
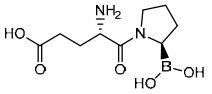
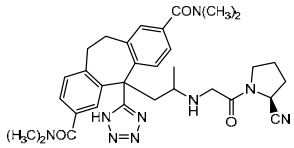
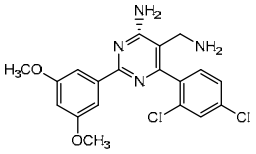
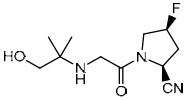
3. **Discussion.** The Federal Circuit has implicitly accepted that failure to
failure of others. *Knoll Pharm. Co. v. Teva Pharm. USA, Inc.*, 367 F.3d
Teva Pharmaceuticals USA, Inc., 460 F.Supp.2d 659, 662 (D.N.J.2006), the
stated that "[n]ot getting to market with FDA approval is an appropriate benc
acceptance by other courts and the liberal standards of Rule 401, this court find
is relevant evidence of failure of others.

WESTLAW © 2017 Thomson Reuters. No claim to original U.S. Government Works.

The Federal Circuit has implicitly accepted that failure to obtain FDA approval is relevant evidence of failure of others. *Knoll Pharm. Co. v. Teva Pharm. USA, Inc.*, 367 F.3d 1381, 1385 (Fed.Cir.2004). In *Pfizer Inc. v. Teva Pharmaceuticals USA, Inc.*, 460 F.Supp.2d 659, 662 (D.N.J.2006), the court went one step further, and expressly stated that "[n]ot getting to market with FDA approval is an appropriate benchmark for failure [of others]."

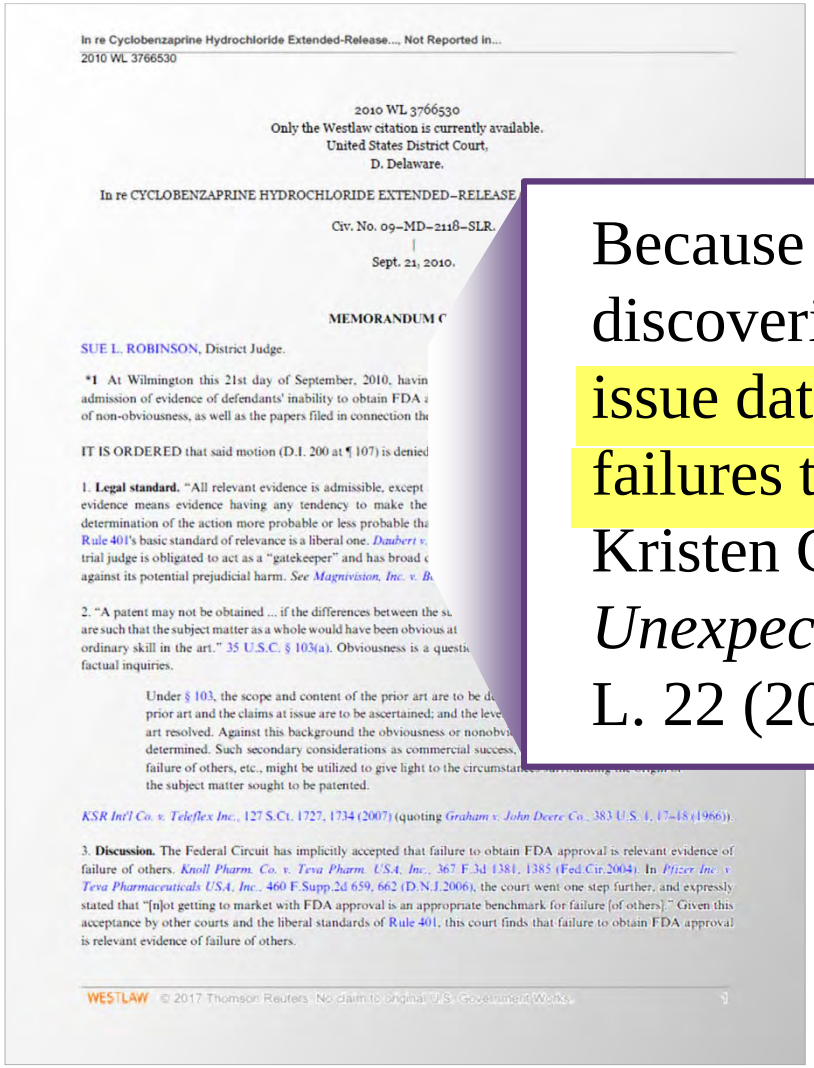
No. CIV. 09-MD-2118-SLR,
2010 WL 3766530, at *1 (D. Del. Sept. 21, 2010)

Post Invention Compounds Not FDA Approved

DDP-4 Inhibitor	Developer	Structure	FDA Status
GW823093C (denagliptin)	GlaxoSmithKline PLC		Discontinued
PHX1149T (dutogliptin)	Phenomix Corp. and Forrest Laboratories, Inc.		Discontinued
PT-630	Point Therapeutics, Inc.		Discontinued
AMG-222	Amgen Inc.		Discontinued
PSN-9301	Probiodrug AG, Prosidion Ltd., and OSI Pharmaceuticals, Inc.		Discontinued
R-1438	F. Hoffmann-La Roche Ltd.		Discontinued
TA-6666	Mitsubishi Tanabe Pharma Corp.		Discontinued
TS-021	Taisho Pharmaceutical Co., Ltd. and Eli Lilly and Co.		Discontinued

Paper 62 at Observation 30; Ex. 2056 ¶¶ 253-54; Ex. 2247

In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.



In re Cyclobenzaprine Hydrochloride Extended-Release..., Not Reported in...
2010 WL 3766530

2010 WL 3766530
Only the Westlaw citation is currently available.
United States District Court,
D. Delaware.

In re CYCLOBENZAPRINE HYDROCHLORIDE EXTENDED–RELEASE

Civ. No. 09–MD–2118–SLR.

Sept. 21, 2010.

MEMORANDUM C

SUE L. ROBINSON, District Judge.

*1 At Wilmington this 21st day of September, 2010, havin
admission of evidence of defendants' inability to obtain FDA
of non-obviousness, as well as the papers filed in connection th

IT IS ORDERED that said motion (D.I. 200 at ¶ 107) is denied

1. **Legal standard.** "All relevant evidence is admissible, except
evidence means evidence having any tendency to make the
determination of the action more probable or less probable tha
Rule 401's basic standard of relevance is a liberal one. *Daubert v.*
trial judge is obligated to act as a "gatekeeper" and has broad
against its potential prejudicial harm. *See Magnivision, Inc. v. B*

2. "A patent may not be obtained ... if the differences between the s
are such that the subject matter as a whole would have been obvious at
ordinary skill in the art." 35 U.S.C. § 103(a). Obviousness is a questi
factual inquiries.

> Under § 103, the scope and content of the prior art are to be d
> prior art and the claims at issue are to be ascertained; and the leve
> art resolved. Against this background the obviousness or nonobv
> determined. Such secondary considerations as commercial success,
> failure of others, etc., might be utilized to give light to the circumstan
> the subject matter sought to be patented.

KSR Int'l Co. v. Teleflex Inc., 127 S.Ct. 1727, 1734 (2007) (quoting *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966)).

3. **Discussion.** The Federal Circuit has implicitly accepted that failure to obtain FDA approval is relevant evidence of failure of others. *Knoll Pharm. Co. v. Teva Pharm. USA, Inc.*, 367 F.3d 1381, 1385 (Fed.Cir.2004). In *Pfizer Inc. v. Teva Pharmaceuticals USA, Inc.*, 460 F.Supp.2d 659, 662 (D.N.J.2006), the court went one step further, and expressly stated that "[n]ot getting to market with FDA approval is an appropriate benchmark for failure [of others]." Given this acceptance by other courts and the liberal standards of Rule 401, this court finds that failure to obtain FDA approval is relevant evidence of failure of others.

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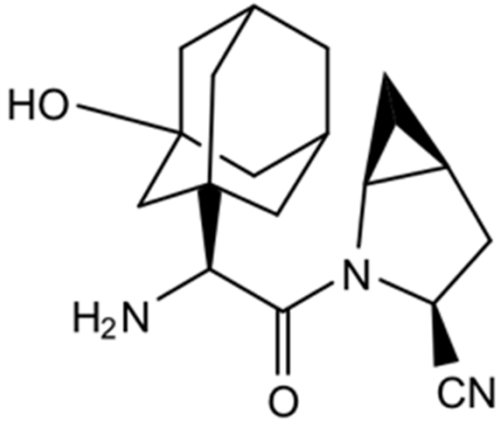
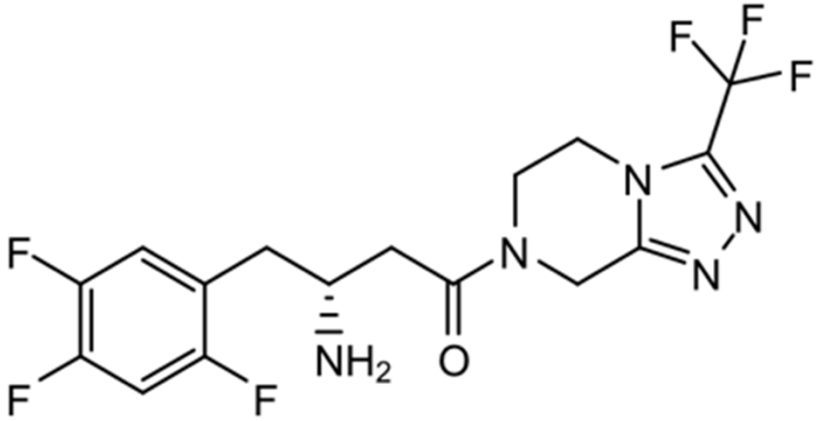
Because science necessarily builds upon past discoveries, failure of others after a patent's issue date may be more persuasive than failures that occur before. *See generally* Kristen C. Buteau, *Denuterated Drugs: Unexpectedly Nonobvious*, 10 J. High Tech. L. 22 (2009).

No. CIV. 09-MD-2118-SLR,
2010 WL 3766530, at *2 (D. Del. Sept. 21, 2010)

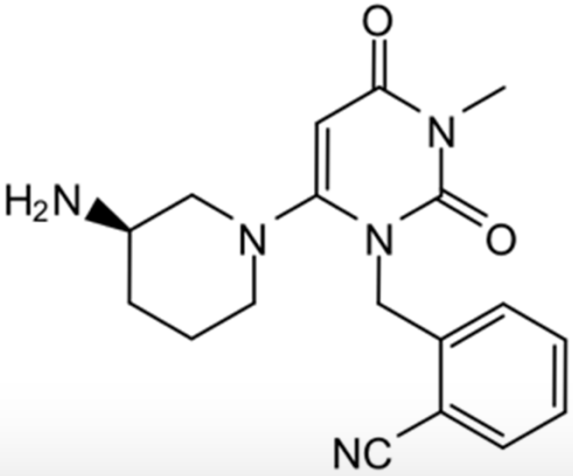
FDA Approved DPP-4 inhibitors (2016)



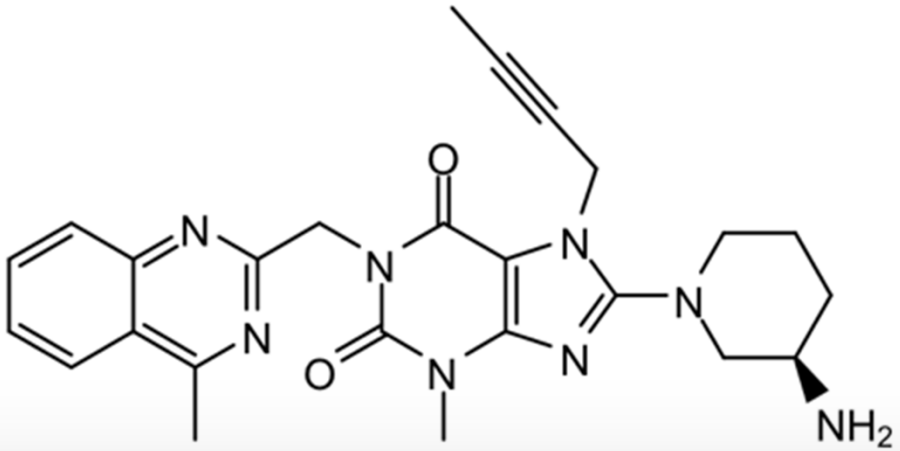
Saxagliptin
First Invented



Sitagliptin



Alogliptin



Linagliptin

Paper 62 at Observation 29; Ex. 2047; Ex. 2049; Ex. 2079; Ex. 2077; Ex. 2245

Procter & Gamble Co. v. Teva Pharm. USA, Inc.

PROCTER & GAMBLE CO. v. TEVA PHARMACEUTICALS USA 989
Cite as 566 F.3d 989 (Fed. Cir. 2009)

The PROCTER & GAMBLE COMPANY, Plaintiff-Appellee,

v.

TEVA PHARMACEUTICALS USA, INC., Defendant-Appellant.

Nos. 2008-1404, 2008-1405, 2008-1406.

United States Court of Appeals, Federal Circuit.

May 13, 2009.

Background: Owner of patent claiming compound risedronate, the active ingredient of an osteoporosis drug, brought infringement action against competitor. The United States District Court for the District of Delaware, Joseph J. Farnan, Jr., J., 536 F.Supp.2d 476, in a bench trial, entered judgment in favor of patent owner. Competitor appealed.

Holdings: The Court of Appeals, Huff, District Judge, sitting by designation, held that:

(1) district court did not clearly err in finding that competitor failed to establish prima facie case of obviousness;

(2) district court did not commit clear error in concluding that secondary considerations supported a finding of non-obviousness of patent claiming risedronate;

(3) patent claiming an intermittent dosing method for treating osteoporosis qualified as prior art; and

(4) patent claiming risedronate was not invalid based on obviousness-type double patenting.

Affirmed.

Appellants' Motion to Supplement the Record on Appeal.

1. Patents ⇐324.5, 324.55(2)
On appeal from a patent bench trial, the court of appeals reviews a district court's conclusions of law de novo and findings of fact for clear error.

2. Patents ⇐324.5
Whether the subject matter of a patent is obvious is a question of
reviewed de novo.

3. Patents ⇐324.55(4)
Factual determina
issue of a patent's
viewed for clear e

4. Patents ⇐11
The evident
supporting a cor
is one of clear

5. Patents ⇐32
Non-statuto
legal question r

6. Patents ⇐112.
Patents are pre

7. Patents ⇐16.5(1), 3
A party seeking to in
based on obviousness must
clear and convincing evidence
artisan would have been motivated
bine the teachings of the prior art refer-
ences to achieve the claimed invention, and
that the skilled artisan would have had a
reasonable expectation of success in doing
so.

8. Patents ⇐16(2, 3), 36.1(3), 36.2(1)
The determination of whether a patent is obvious turns on underlying factual inquiries involving: (1) the scope and content of prior art, (2) differences between claims and prior art, (3) the level of ordinary skill in pertinent art, and (4) second-

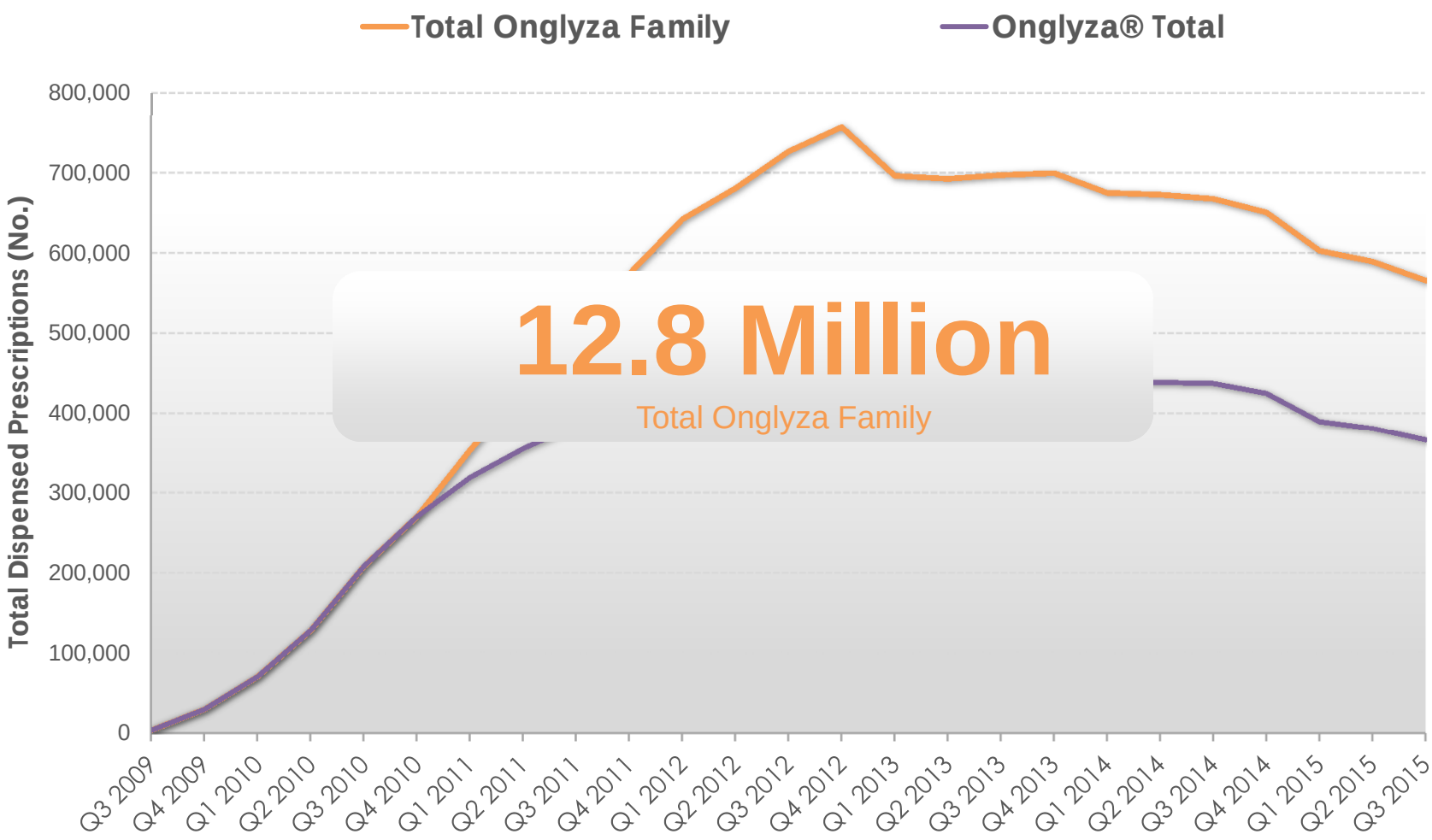
Under *Monarch*, we look to the filing date of the challenged invention to assess the presence of a long-felt and unmet need.

566 F.3d 989, 998 (Fed. Cir. 2009)

Commercial Success

U.S. Total Dispensed Prescriptions for Onglyza Family Products

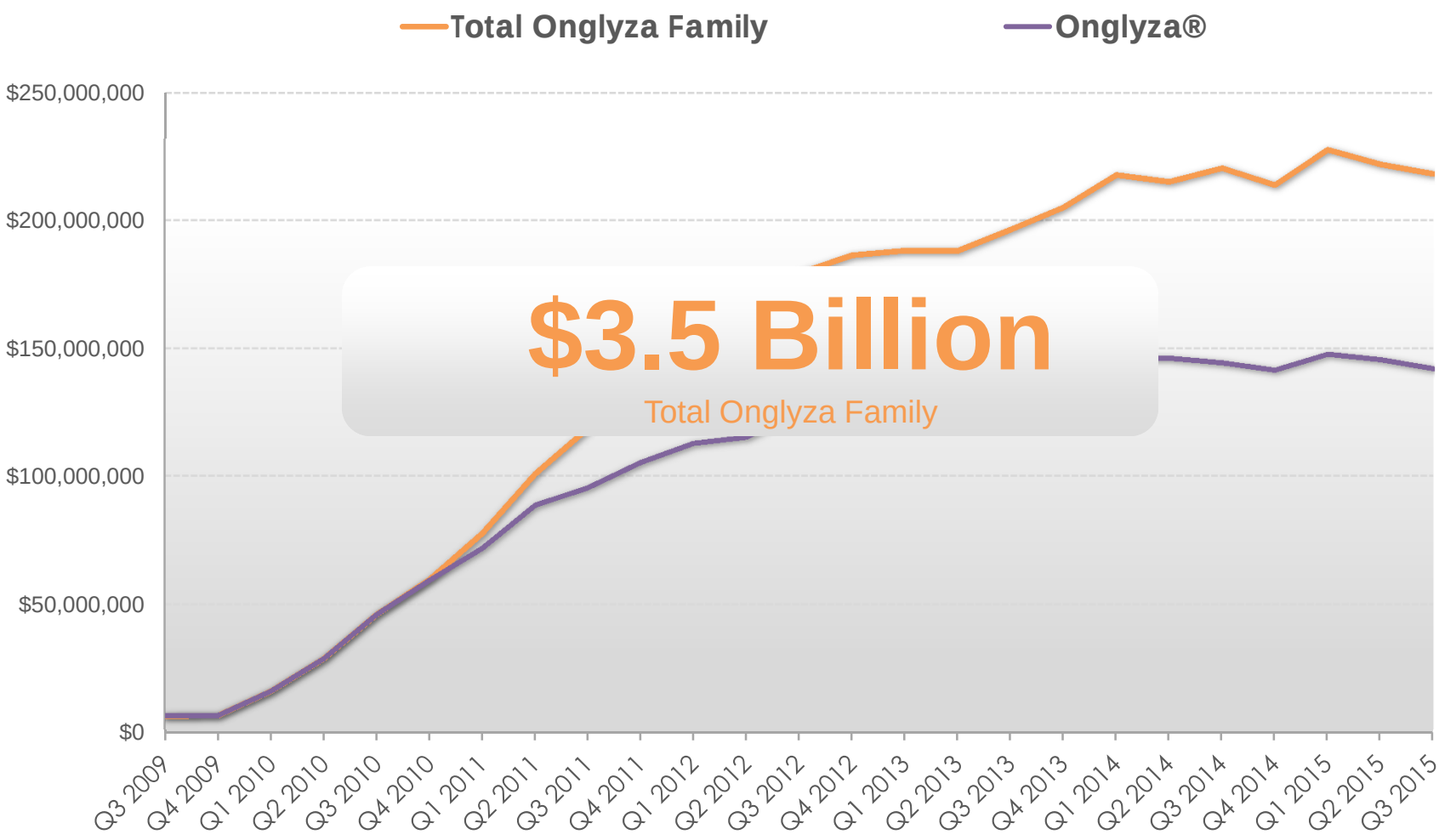
Q3 2009 through Q3 2015



Paper 28 at 66; Ex. 2059A ¶ 33, Table 2(a), Fig. 1; Ex. 2117

U.S. Sales of Onglyza Family Products in Dollars

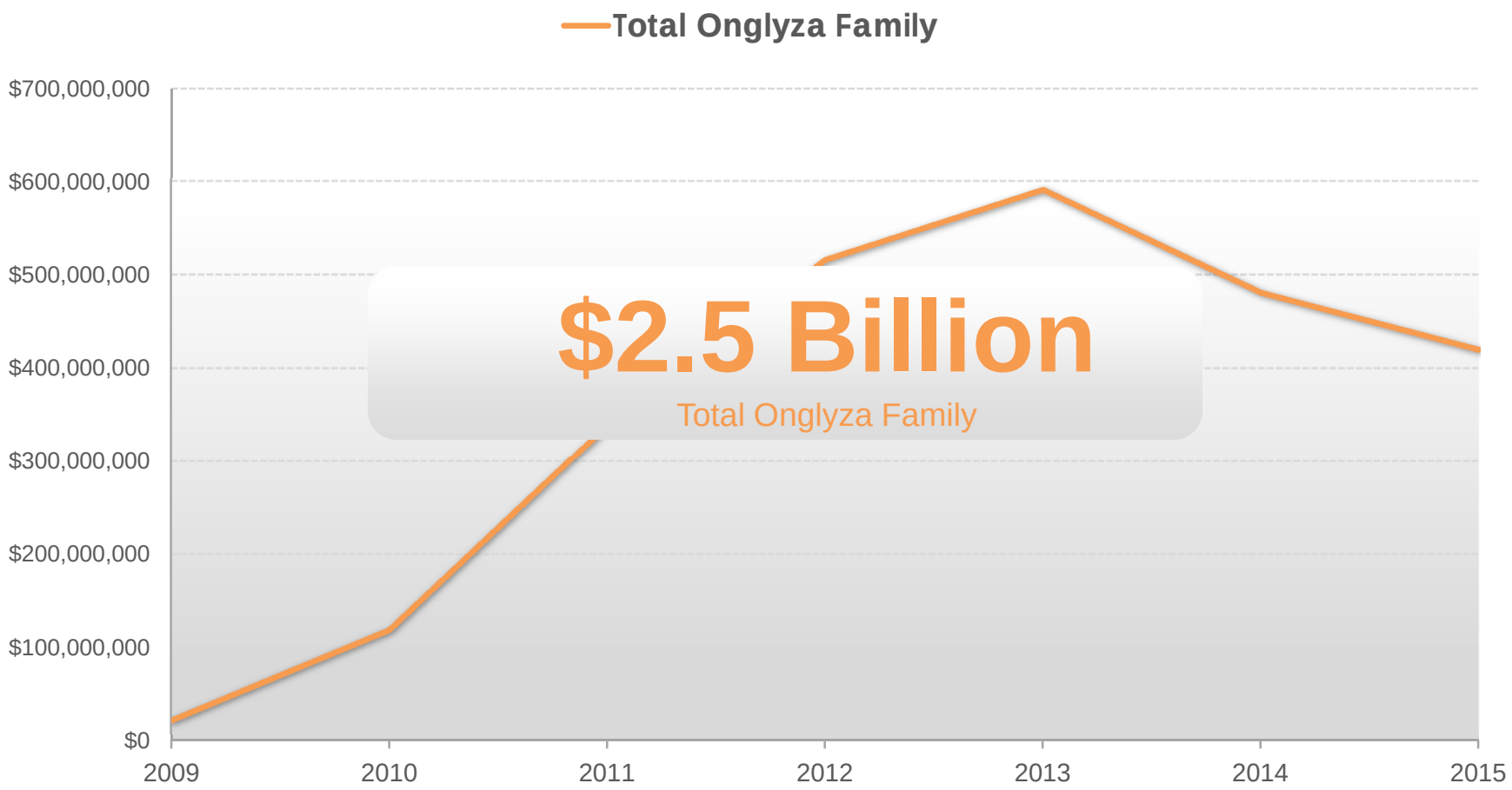
Q3 2009 through Q3 2015



Paper 28 at 66; Ex. 2059A ¶ 34, Table 3, Fig. 2; Ex. 2118

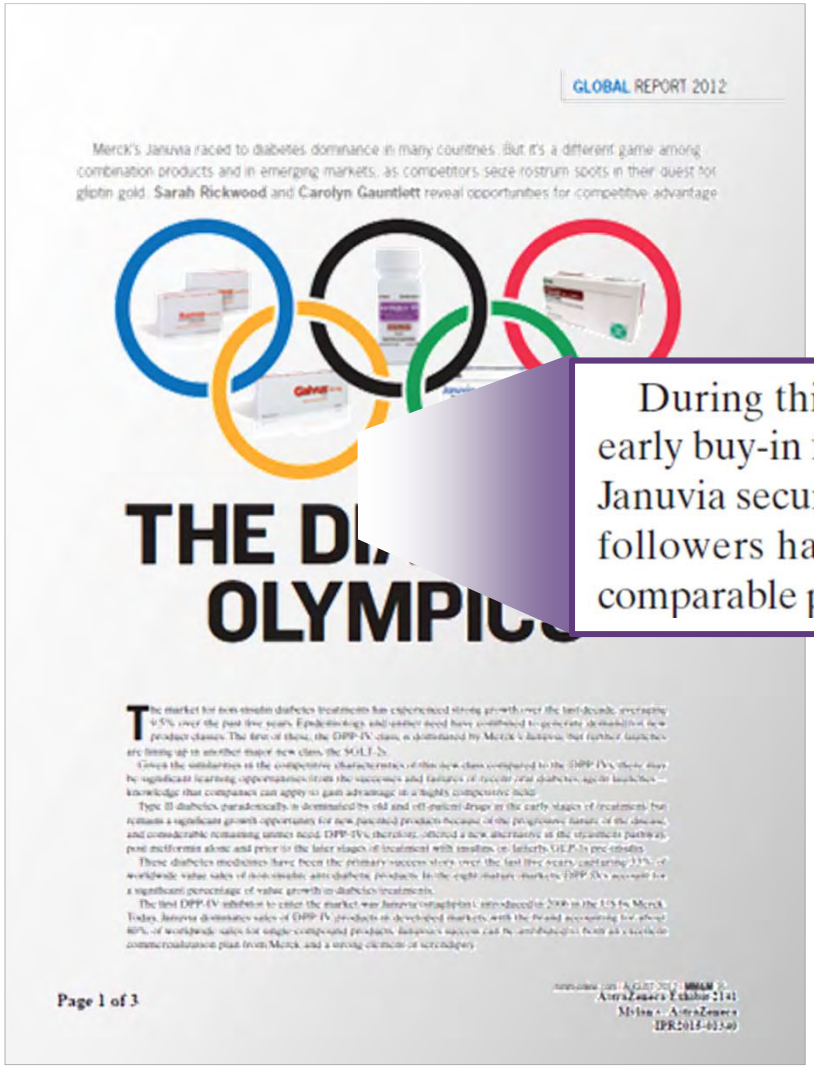
U.S. Net Revenues from Sales of Onglyza Family Products

Q3 2009 through Q3 2015



Ex. 2059A ¶ 35, Table 4, Fig. 3; Exs. 2004, 2111-2115, 2108

First-Mover Advantage



GLOBAL REPORT 2012

Merck's Januvia raced to diabetes dominance in many countries. But it's a different game among combination products and in emerging markets, as competitors seize rostrum spots in their quest for gliptin gold. **Sarah Rickwood** and **Carolyn Gauntlett** reveal opportunities for competitive advantage

THE DI…
OLYMPIC…

Page 1 of 3

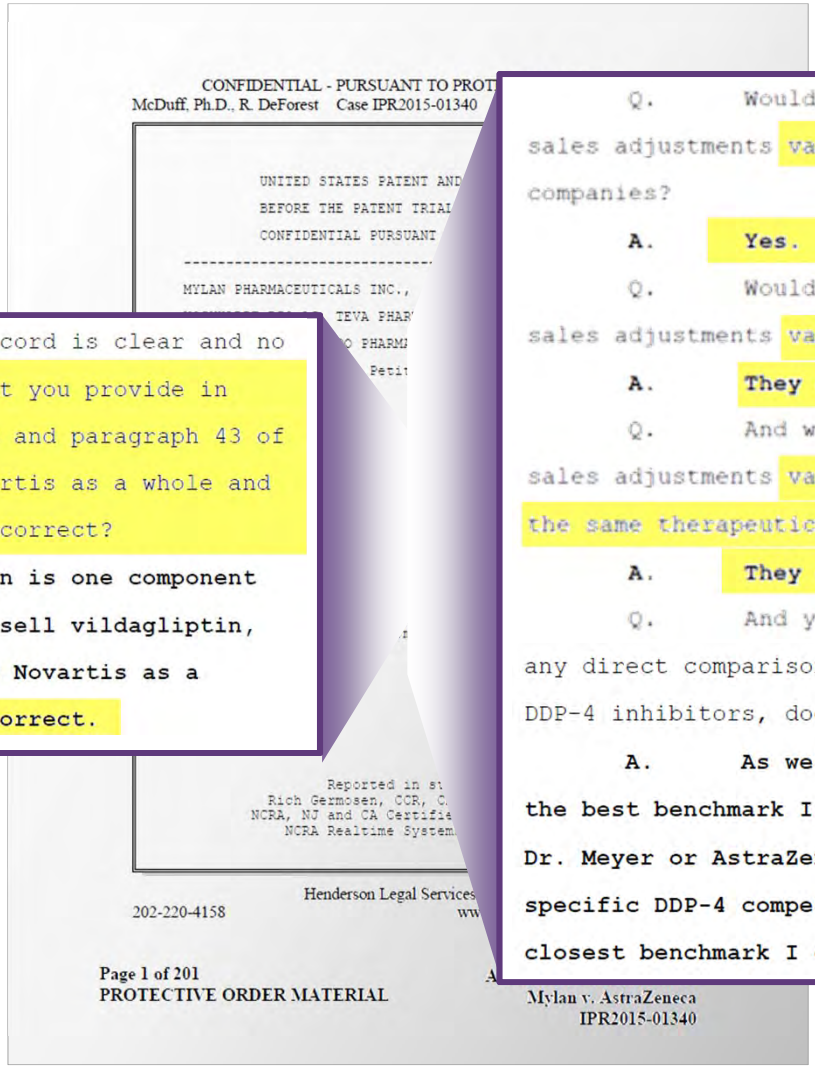
AstraZeneca Exhibit 2141
Mylan v. AstraZeneca
IPR2015-01340

During this time, Merck aggressively promoted Januvia to gain early buy-in from stakeholders and to build a positive brand image. Januvia secured its place as "the" gliptin, an image followers have found hard to challenge despite comparable promotional spending.

Ex. 2141 at 2

Paper 28 at 67; Ex. 2059A ¶¶ 42-43

Dr. McDuff



Q. So just so the record is clear and no one is confused, the numbers that you provide in paragraph 42 of your declaration and paragraph 43 of your declaration pertain to Novartis as a whole and not vildagliptin in particular; correct?

A. Well, vildagliptin is one component of that figure as Novartis does sell vildagliptin, but the figures reported are for Novartis as a company as a benchmark, that's correct.

Ex. 2220 at 134:8-16

Q. Would you agree that gross to net sales adjustments vary across pharmaceutical companies?

A. Yes.

Q. Would you agree that gross to net sales adjustments vary across therapeutic areas?

A. They can, yes.

Q. And would you agree that gross to net sales adjustments vary across products even within the same therapeutic class?

A. They can, yes.

Q. And your declaration doesn't provide any direct comparison of net sales adjustments among DDP-4 inhibitors, does it?

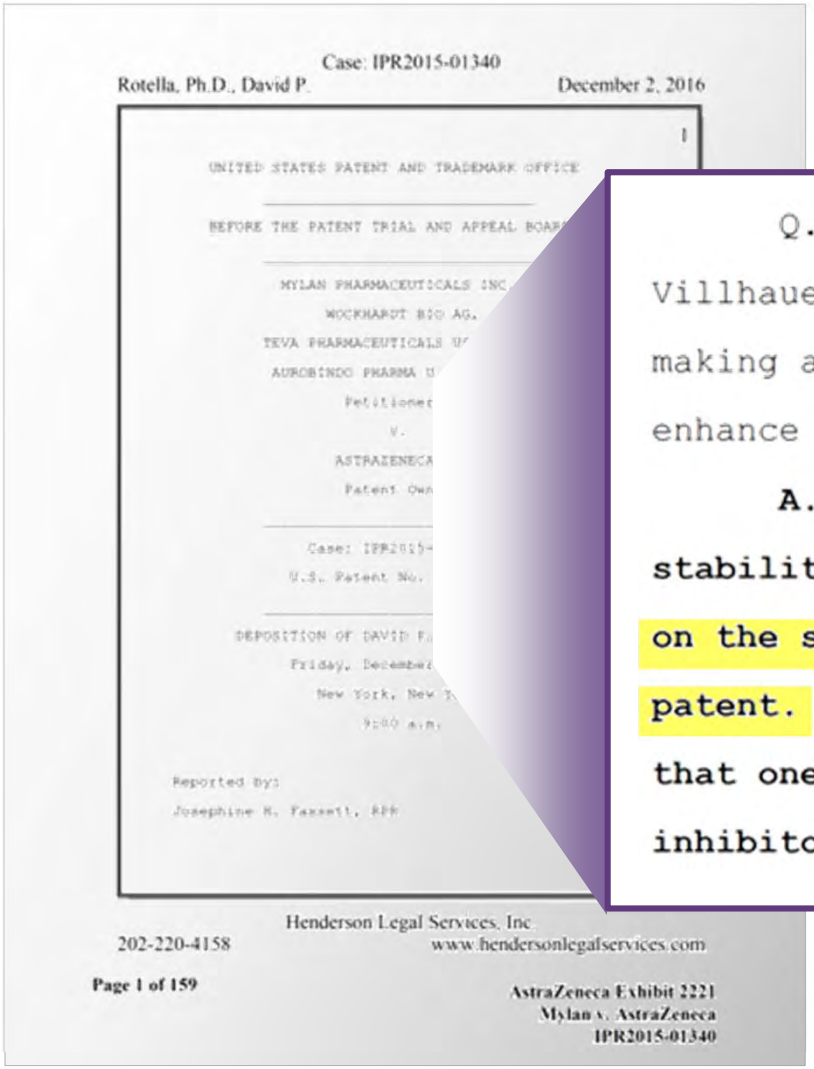
A. As we've been discussing, I provided the best benchmark I was aware of. I'm not aware of Dr. Meyer or AstraZeneca providing information for specific DDP-4 competitors, yet I've evaluated the closest benchmark I could find.

Ex. 2220 at 136:14-137:7

Paper 61 at Observation 15

Back Up

Dr. Rotella

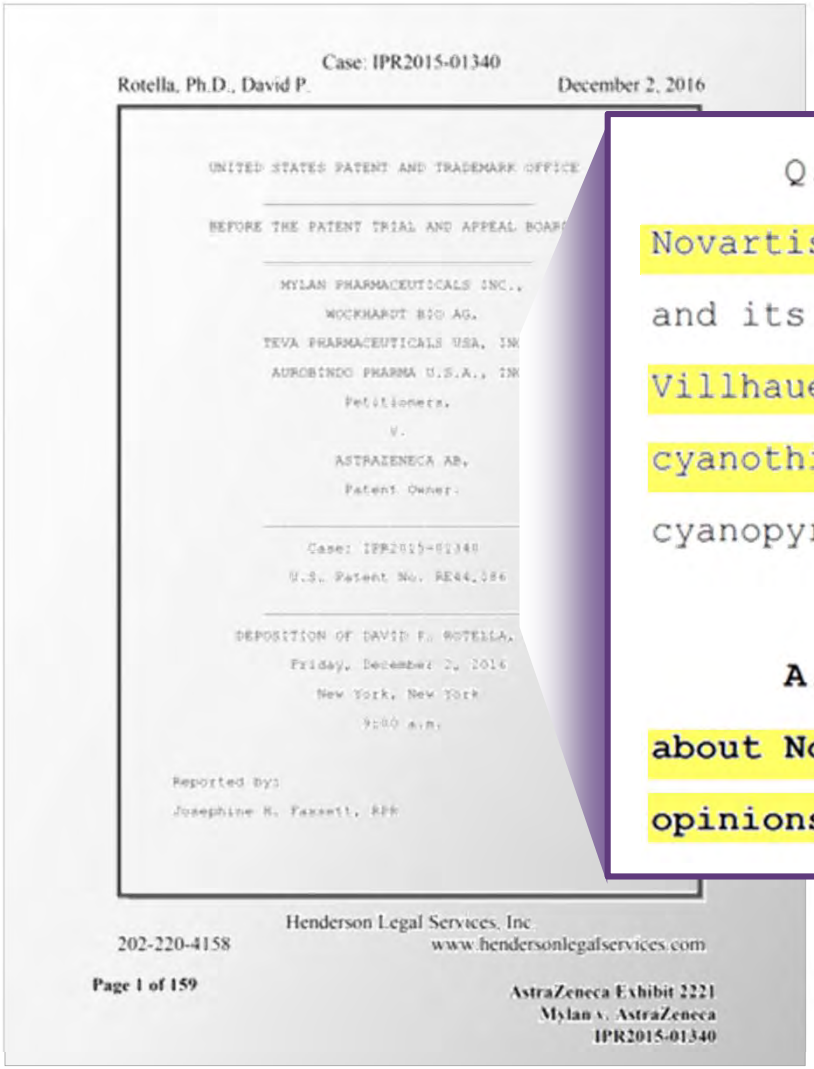


Q. Okay. Now, the N-linkage in the Villhauer DPP-4 inhibitors that Novartis was making and publishing on was generally believed to enhance the stability of those molecules, correct?

A. I wasn't asked to comment on the stability, and I wasn't asked to provide opinions on the stability of molecules in the Villhauer patent. But I'll note that stability is a feature that one has to pay attention to in a DPP-4 inhibitor that contains a cyano functional group.

Paper 62 at Observation 8; Ex. 2221 at 24:7-16

Dr. Rotella



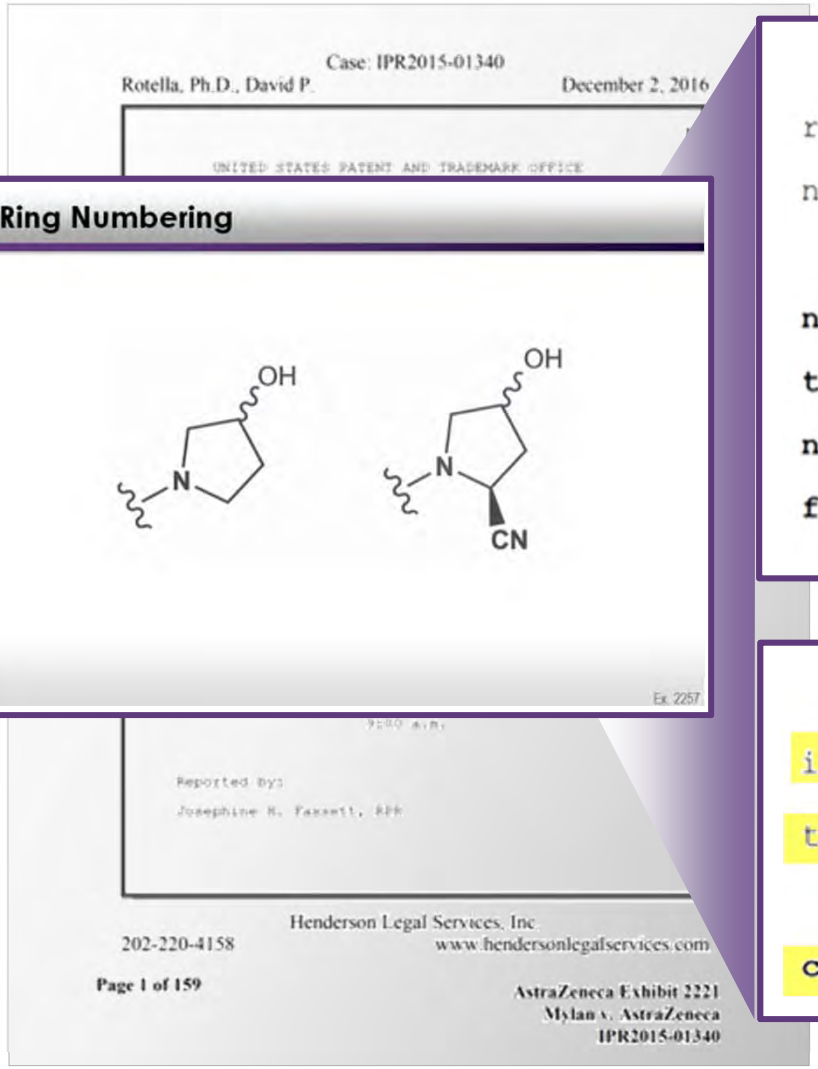
Q. The fact of the matter is that Novartis itself faced with the work of Ashworth and its own work, proposed instead to combine Villhauer type P2 groups with the cyanothiazolidine of Ashworth II, not a cyanopyrrolidine of Ashworth I, correct?

MR. TORCZON: Objection.

A. I was not asked to opine on anything about Novartis's approach, conclusions or opinions.

Paper 62 at Observation 13; Ex. 2221 at 43:12-21

Dr. Rotella



Q. Okay. Now, in the molecule on the right where we've added in the cyano group, what number carbon is the hydroxyl on now?

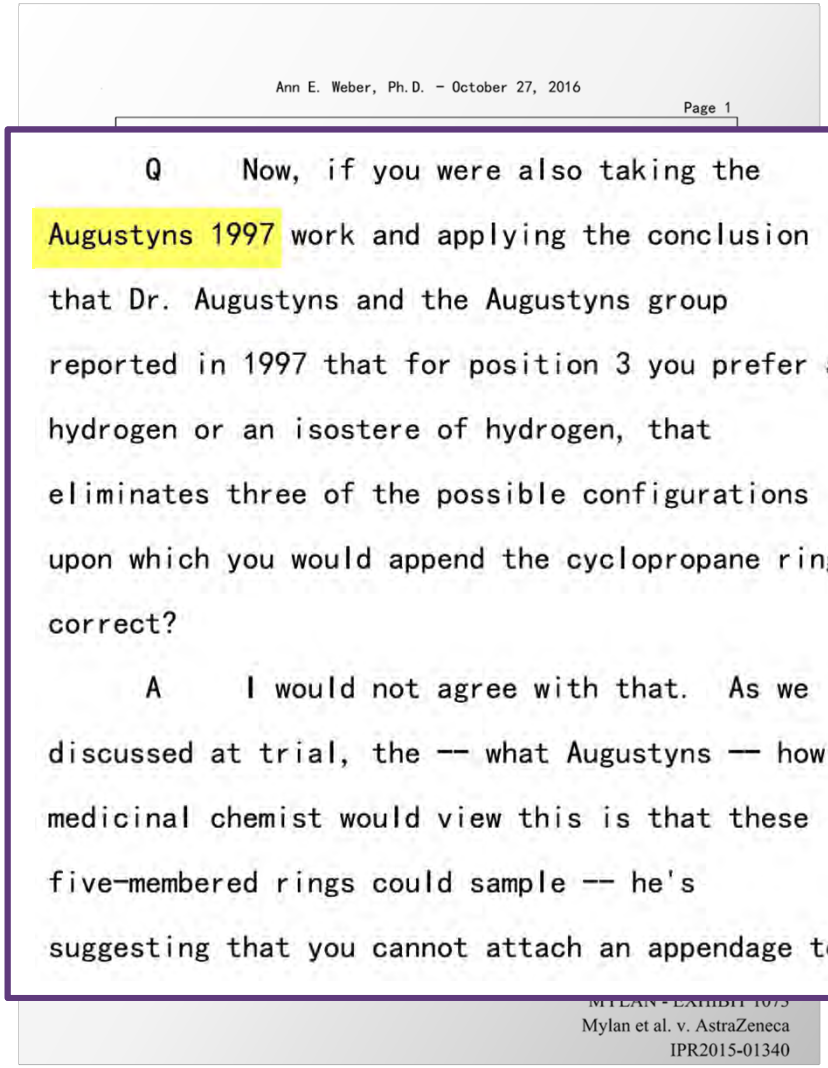
A. Well, I am not an expert in nomenclature, but my interpretation would be that that hydroxyl group would be at the 4-position, numbering in a counterclockwise manner starting from nitrogen.

Q. So that even though the number given in the name is different, the hydroxyl is still in the same place, right?

A. Relative to the nitrogen atom, that's correct.

Paper 62 at Observation 14; Ex. 2221 at 53:12-54:3; Ex. 2257

Dr. Weber



Ann E. Weber, Ph.D. - October 27, 2016

Page 1

Q Now, if you were also taking the Augustyns 1997 work and applying the conclusion that Dr. Augustyns and the Augustyns group reported in 1997 that for position 3 you prefer a hydrogen or an isostere of hydrogen, that eliminates three of the possible configurations upon which you would append the cyclopropane ring, correct?

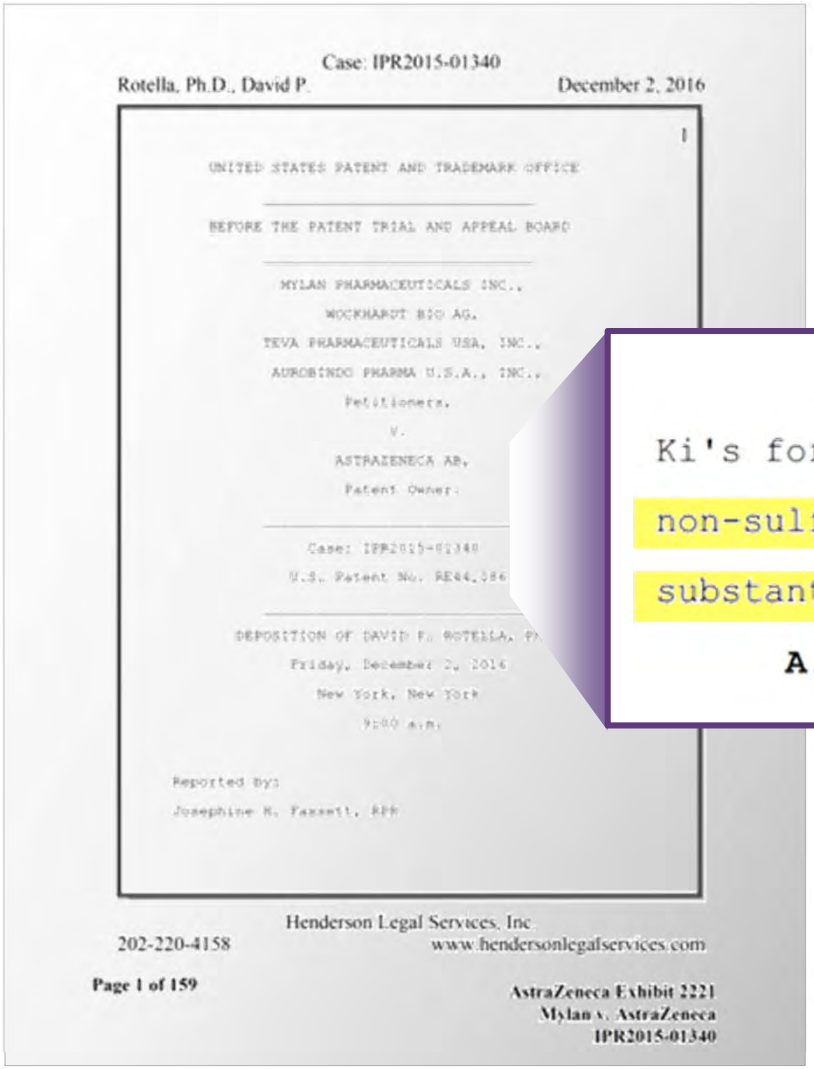
A I would not agree with that. As we discussed at trial, the -- what Augustyns -- how a medicinal chemist would view this is that these five-membered rings could sample -- he's suggesting that you cannot attach an appendage to a carbon that is not attached to the nitrogen. In other words, while his compounds are 3 substituted, the enzyme actually samples two configurations of that compound, of these compounds because the ring can flip over, so essentially you're sampling the 3- and the 4-position.

So a medicinal chemist would view these data and would understand that Augustyns was suggesting that putting an appendage, substituting at one of the two carbons that is not attached to nitrogen would not be preferred.

MYLAN - EXHIBIT 1073
Mylan et al. v. AstraZeneca
IPR2015-01340

Ex. 1073 (Weber Cross-Examination) 85:2-86:4; Ex. 2056 ¶¶ 112, 174-176; Paper 28 at 10, 35-36

Dr. Rotella



Case: IPR2015-01340
Rotella, Ph.D., David P. December 2, 2016

1

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TEVA PHARMACEUTICALS USA, INC.,
AUROBINDO PHARMA U.S.A., INC.,
Petitioners,
v.
ASTRAZENECA AB,
Patent Owner.

Case: IPR2015-01340
U.S. Patent No. RE44,186

DEPOSITION OF DAVID P. ROTELLA, PH
Friday, December 2, 2016
New York, New York
9:00 a.m.

Reported by:
Josephine M. Fassett, RPR

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AstraZeneca Exhibit 2221
Mylan v. AstraZeneca
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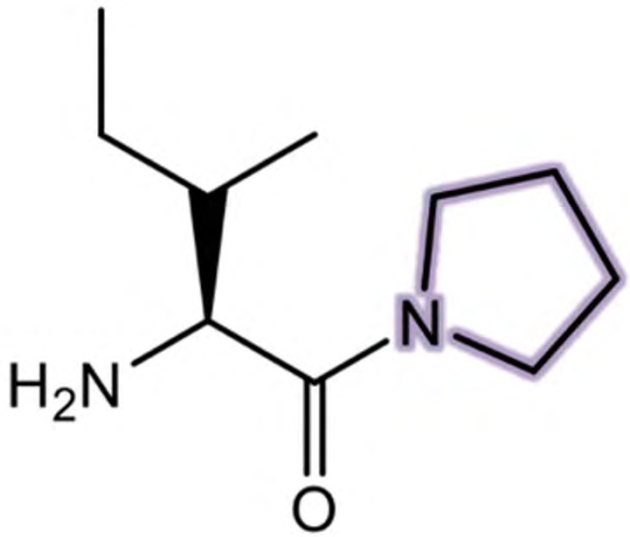
So you would agree with me that the Ki's for the sulfur containing compound 4 and the non-sulfur containing compound 5 are not substantially different, correct?

A. Yes, I would.

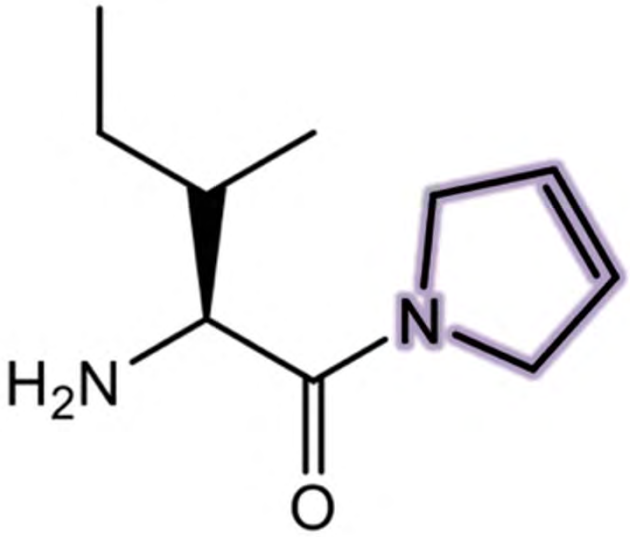
Paper 62 at Observation 11; Ex. 2221 at 35:15-19

Augustyns (1997): Ex. 2151

Effect of ring "flattening" with a double bond



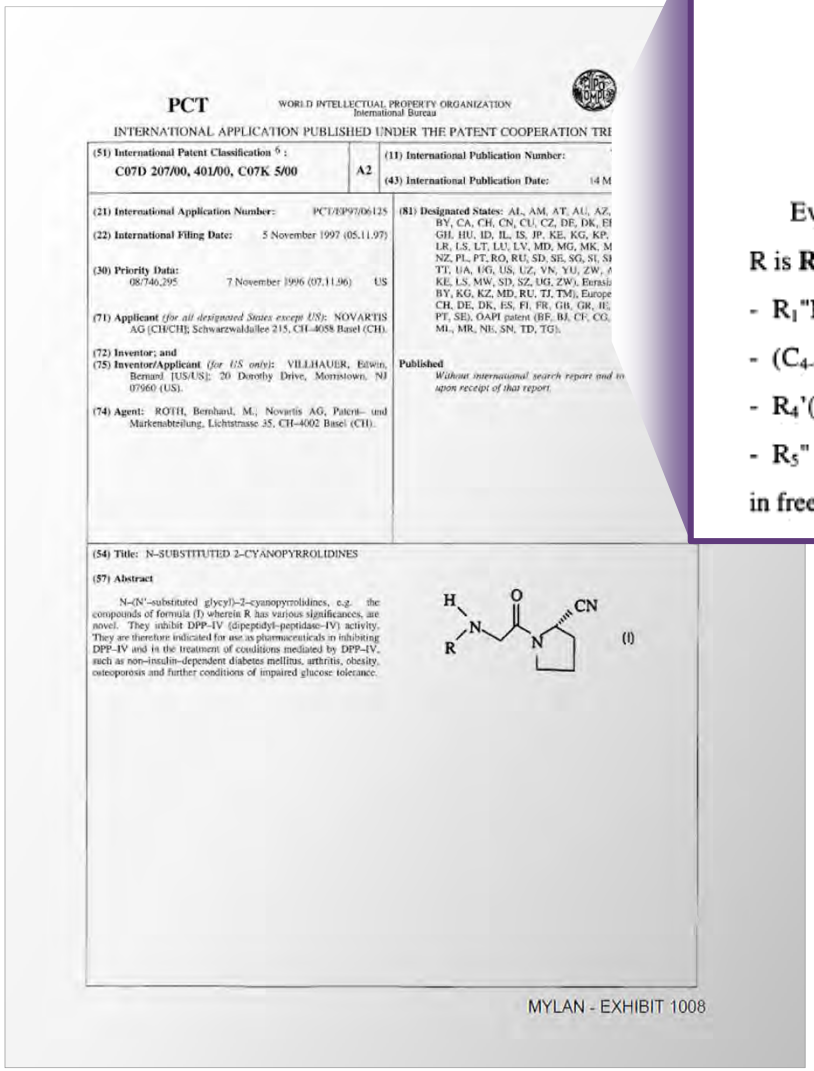
Compound 3
IC_{50} = 21 µM
Saturated



Compound 9b
IC_{50} = 100 µM
Unsaturated

Paper 28 at 10; Ex. 2151 at 2, 4; Ex. 2233

Villhauer-1998: Ex. 1008



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(71) Applicant (for all designated States except US): NOVARTIS AG [CH/CH]; Schwarzwaldallee 215, CH-4058 Basel (CH).

(72) Inventor; and

(75) Inventor/Applicant (for US only): VILLHAUER, Edwin, Bernard [US/US]; 20 Dorothy Drive, Morristown, NJ 07960 (US).

(74) Agent: ROTH, Bernhard, M.; Novartis AG, Patent- und Markenabteilung, Lichtstrasse 35, CH-4002 Basel (CH).

(81) Designated States: AL, AM, AT, AU, AZ, BY, CA, CH, CN, CU, CZ, DE, DK, EE, GH, HU, ID, IL, IS, JP, KE, KG, KP, LR, LS, LT, LU, LV, MD, MG, MK, MN, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published

Without international search report and to be republished upon receipt of that report.

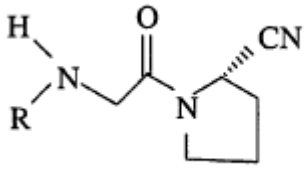
(54) Title: N-SUBSTITUTED 2-CYANOPYRROLIDINES

(57) Abstract

N-(N'-substituted glycyl)-2-cyanopyrrolidines, e.g. the compounds of formula (I) wherein R has various significances, are novel. They inhibit DPP-IV (dipeptidyl-peptidase-IV) activity. They are therefore indicated for use as pharmaceuticals in inhibiting DPP-IV and in the treatment of conditions mediated by DPP-IV, such as non-insulin-dependent diabetes mellitus, arthritis, obesity, osteoporosis and further conditions of impaired glucose tolerance.

(I)

MYLAN - EXHIBIT 1008



I

Even more preferred compounds of the invention are the compounds of formula I wherein R is **R"'** (**compounds Ic**), whereby R"' is:

- R_1"$NH(CH_2)_2$- wherein R_1" is as defined above;
- (C_{4-6})cycloalkyl monosubstituted in 1-position with hydroxymethyl;
- R_4'$(CH_2)_3$- wherein R_4' is as defined above; or
- R_5" wherein R_5" is adamantyl;

in free form or in acid addition salt form.

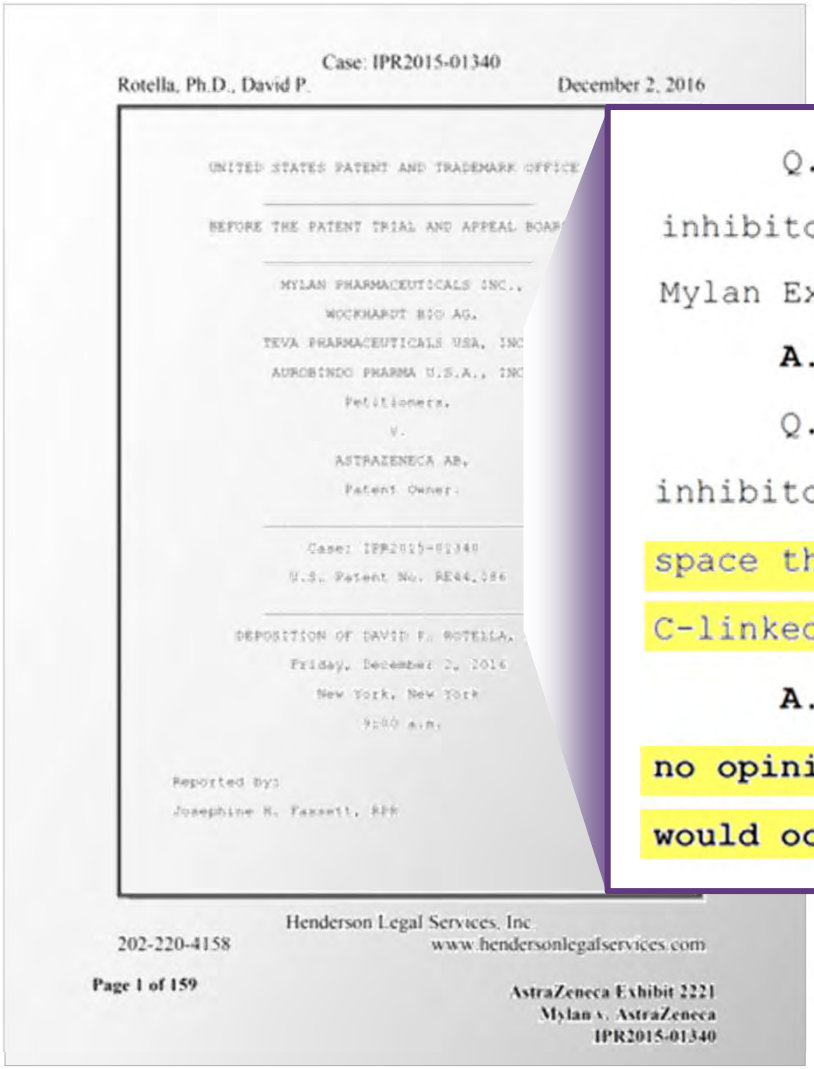
Ex. 1008 at 2, 5

Q. Okay. And just so that we don't have to quarrel about it later. Can we agree that the number of different molecules that are embraced by the description in that paragraph is in the many of hundreds?

A. That's true. This is a generic description that is commonly used in patents to describe classes of compounds.

Ex. 2221 at 21:7-14; Paper 62 at Observation 6

Dr. Rotella



Q. Okay. Now, all of the DPP-4 inhibitors in the Villhauer 19998 publication, Mylan Exhibit 1008, are N-linked, correct?

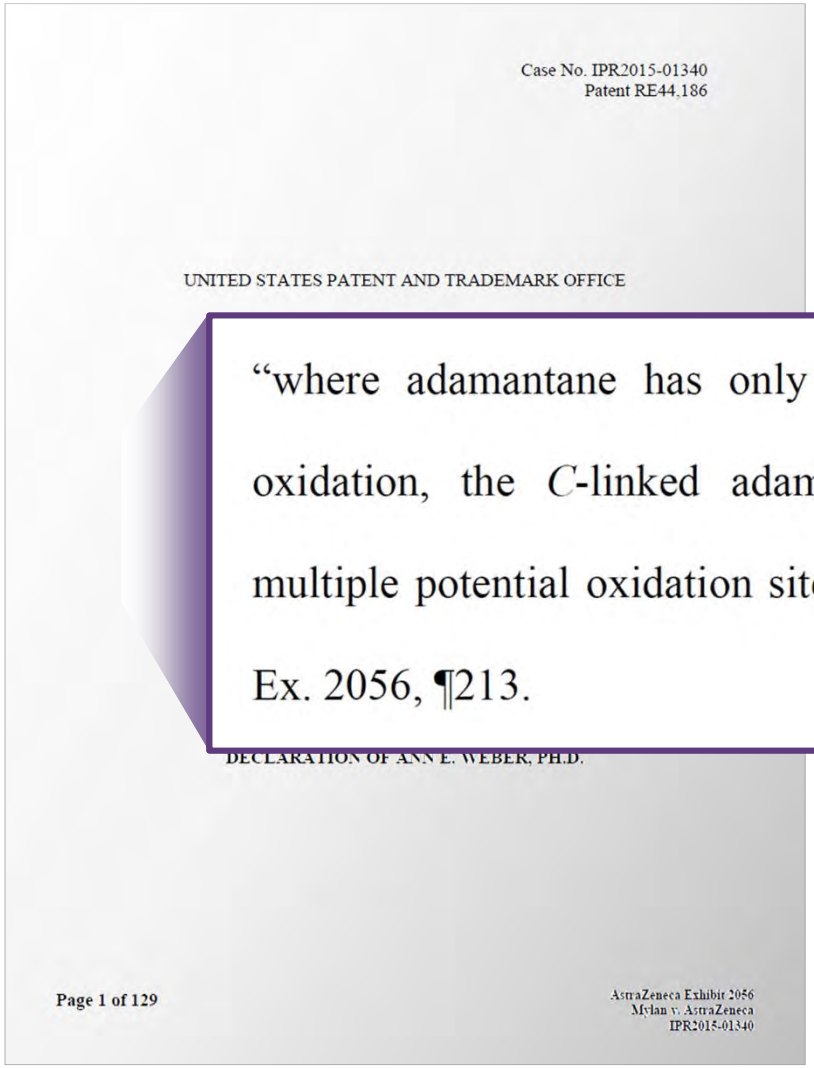
A. That's correct.

Q. And, as such, those P2 groups of those inhibitors will occupy a different position in space than they would were those P2 groups C-linked, correct?

A. That's unknown. I would -- and I have no opinion on that, on what position those groups would occupy in space.

Ex. 2221 at 22:23-23:8; Paper 62 at Observation 7

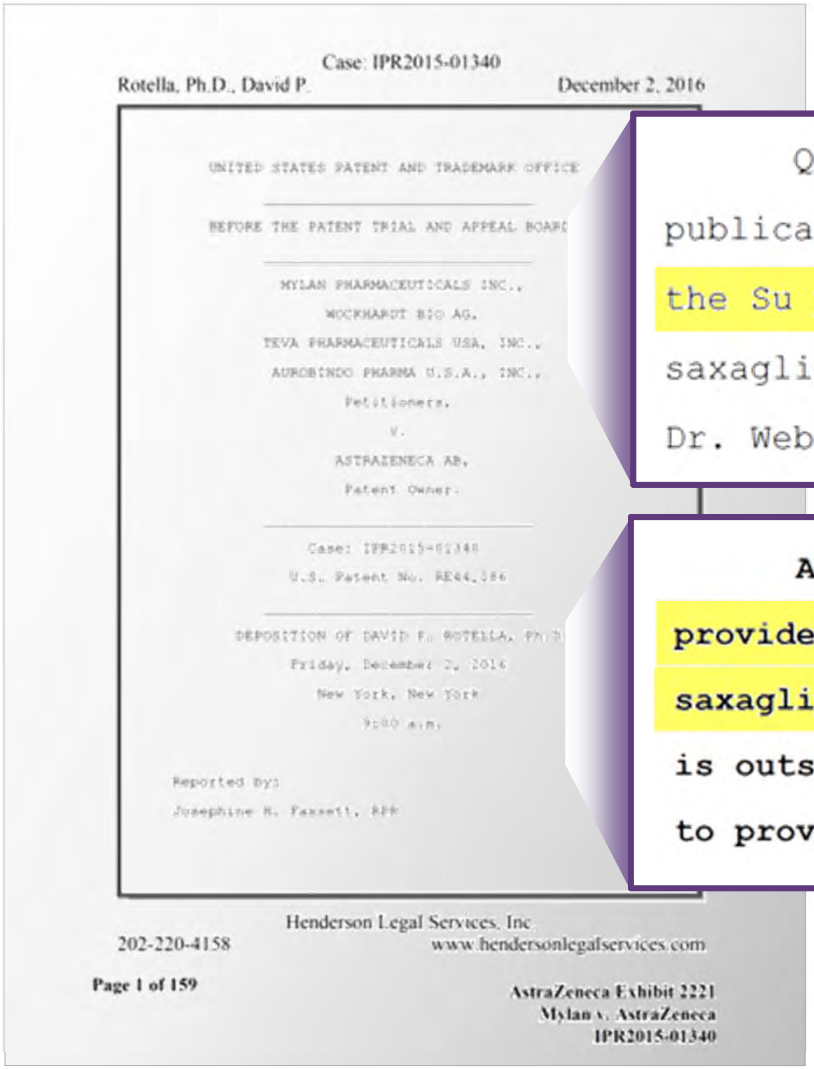
Dr. Weber Declaration



"where adamantane has only two types of unique carbon atoms capable of oxidation, the *C*-linked adamantyl cyclopropyl-fused cyanopyrrolidines have multiple potential oxidation sites, some of which are not on the adamantyl ring." Ex. 2056, ¶213.

Paper 28 at 52; Ex. 2056 ¶ 213

Dr. Rotella

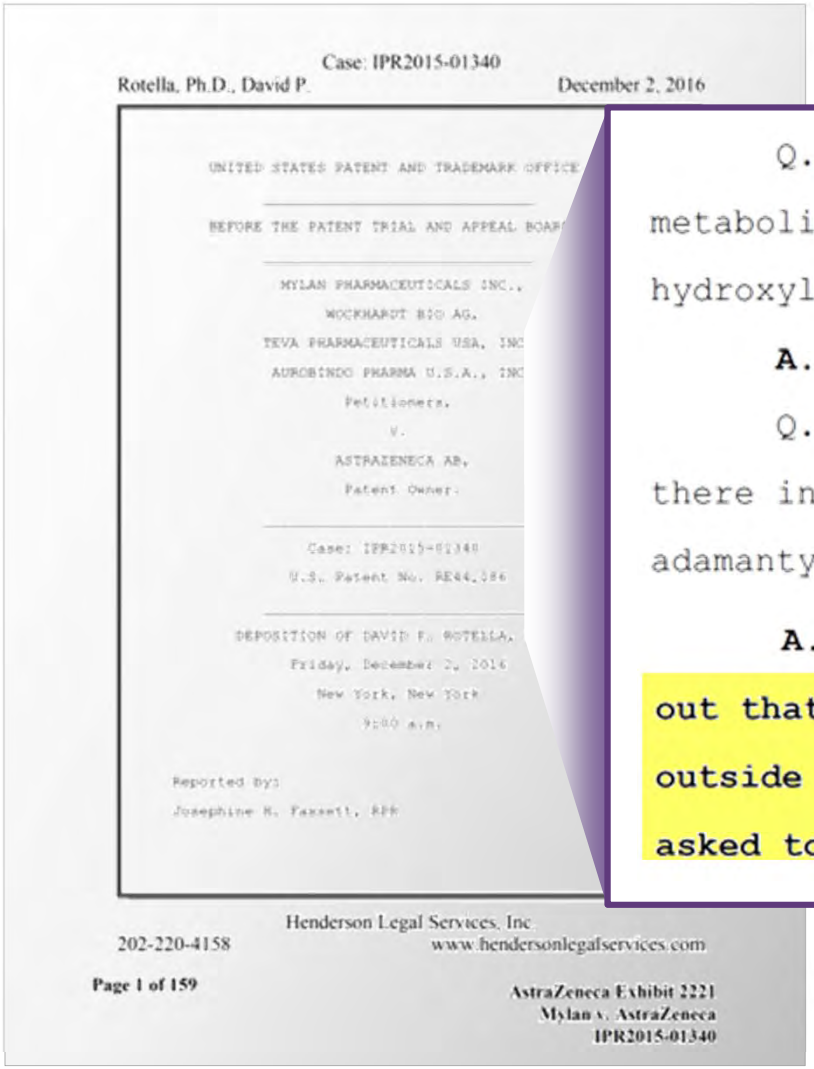


Q. Okay. I'd like to show you a publication marked as AstraZeneca Exhibit 2045, the Su publication relating to the publication of saxagliptin as among the materials cited by Dr. Weber.

A. Once again, this -- I was not asked to provide an opinion on the metabolism of saxagliptin. This paper was published in 2012 and is outside the scope of materials that I was asked to provide opinions on.

Paper 62 at Observations 23, 24; Ex. 2221 at 89:17-21, 90:7-11

Dr. Rotella



Case: IPR2015-01340
Rotella, Ph.D., David P. December 2, 2016

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Petitioners,
v.
ASTRAZENECA AB,
Patent Owner.

Case: IPR2015-01340
U.S. Patent No. RE44,186

DEPOSITION OF DAVID P. ROTELLA,
Friday, December 2, 2016
New York, New York
9:00 a.m.

Reported by:
Josephine M. Fassett, RPR

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202-220-4158 www.hendersonlegalservices.com

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AstraZeneca Exhibit 2221
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Q. Okay. And according to He, the major metabolite of vildagliptin does not involve hydroxylation on the adamantyl group, correct?

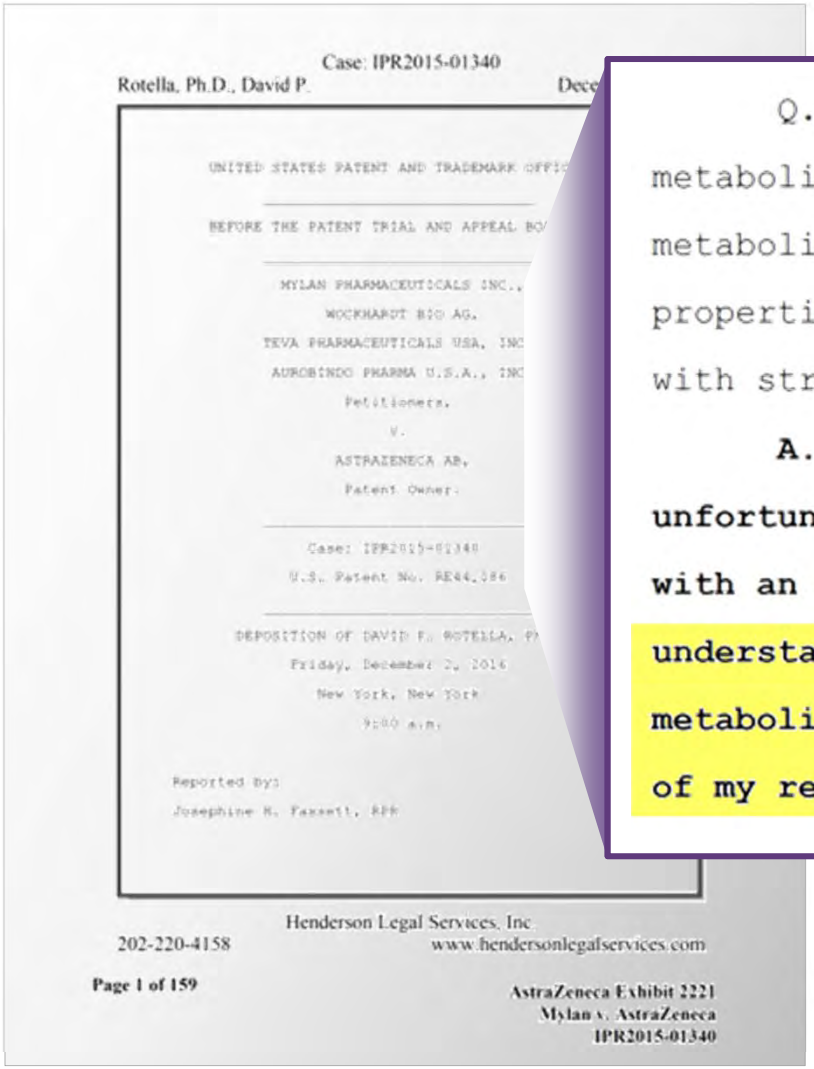
A. Yes, that's correct.

Q. And, in fact, none of the metabolites there involve further hydroxylation of the adamantyl group, correct?

A. That's correct. I would like to point out that this paper was published in 2009 and is outside the scope of the matters on which I was asked to provide opinions.

Paper 62 at Observation 23; Ex. 2221 at 88:19-89:4

Dr. Rotella

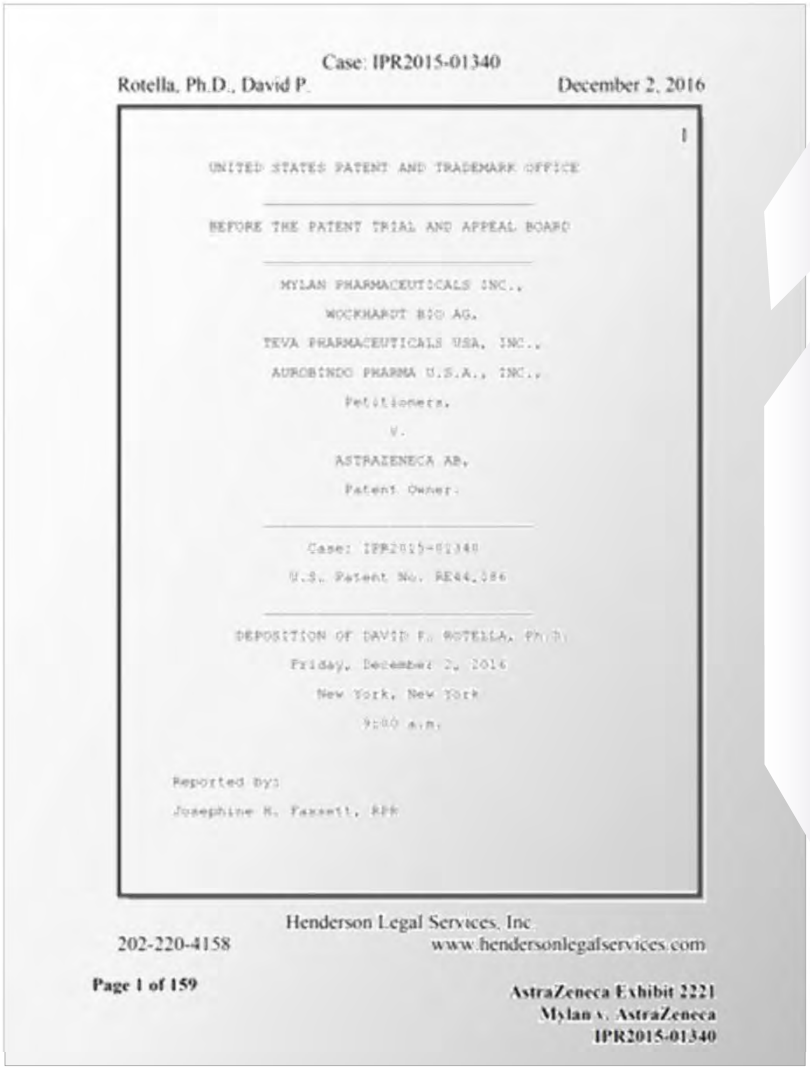


Q. Do you agree that the different metabolic fate and different properties of the metabolites suggests that the metabolic fate and properties of the metabolites vary unpredictably with structure?

A. And, once again, the question is unfortunately too general for me to provide you with an answer. And, furthermore, describing or understanding or providing an opinion on the metabolism of these molecules is outside the scope of my responsibilities in this declaration.

Paper 62 at Observation 24; Ex. 2221 at 91:1-11

Dr. Rotella



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New York, New York
9:00 a.m.

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I'd like to show you the Nabeno publication that's been marked as AstraZeneca Exhibit 2176.

Q. And you have no quarrel with the conclusion Nabeno drew here with respect to saxagliptin that introduction of the cyclopropane moiety afforded an additional hydrophobic interaction with the side chain of Tyrosine 666 in the S1 subsite, correct?

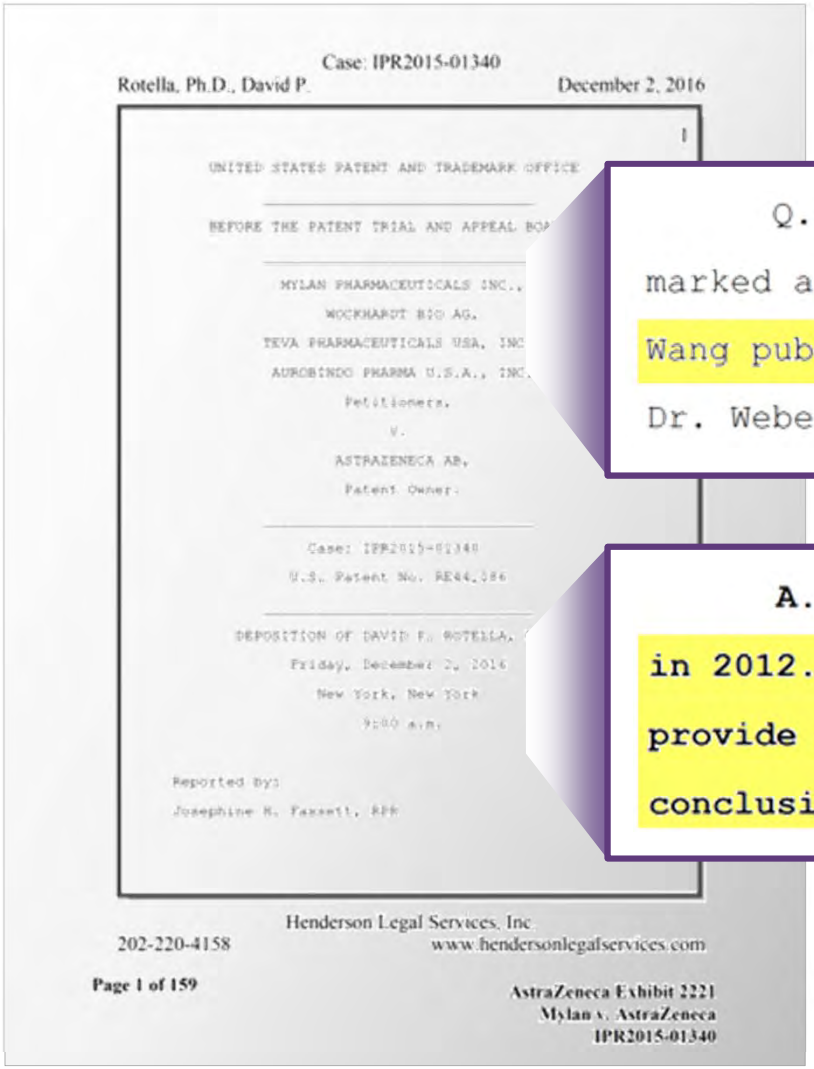
A. I have no opinion on that. I wasn't asked to -- this is outside the scope of what I was asked to consider in this proceeding.

Q. So I assume you have no quarrel with the next statement that Nabeno made that, moreover, the direct hydrogen bond between the hydroxyl group of saxagliptin and the side chain of Tyrosine 547 may also contribute to its higher potency, correct?

A. I have no opinion on that statement. I'm not prepared to offer an opinion on that statement.

Paper 62 at Observation 22; Ex. 2221 at 84:21-23, 86:4-21

Dr. Rotella

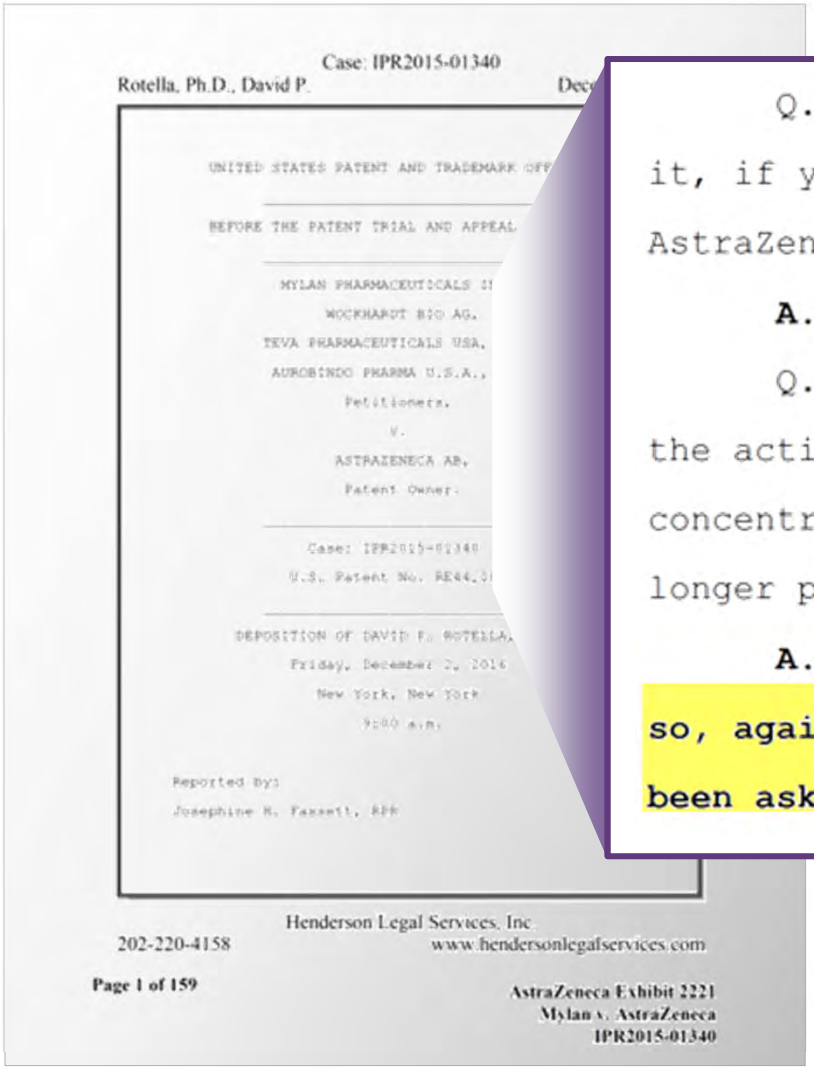


Q. Okay. I'd like to show you a document marked as AstraZeneca Exhibit 2018, which is the Wang publication. Again, a publication cited by Dr. Weber.

A. Once again, this paper was published in 2012. I have not reviewed it, and I will provide no opinions on any of the data or conclusions in this paper.

Paper 62 at Observation 25; Ex. 2221 at 92:18-21, 93:20-23

Dr. Rotella



Q. Okay. Just because they pay me to do it, if you would turn to in the Su article, AstraZeneca 2045, to Figure 2 on page 6 of 12.

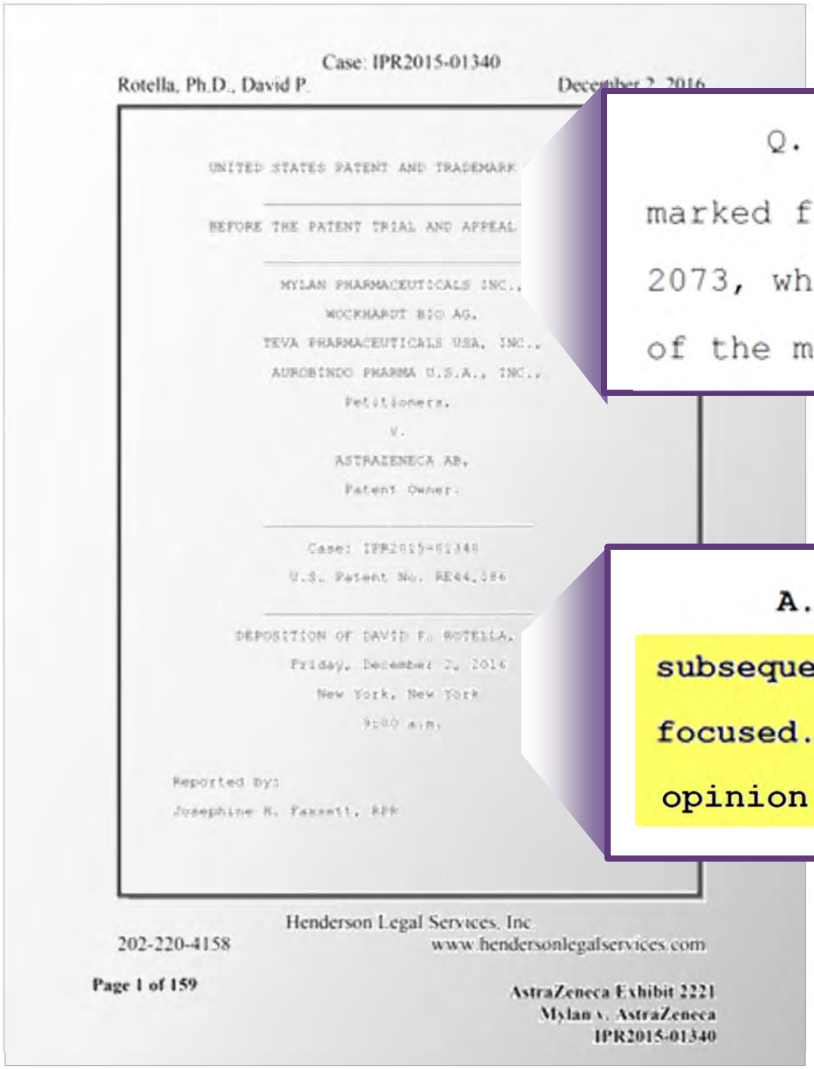
A. (Complies.)

Q. That figure as drawn illustrates that the active metabolite M2 is present in higher concentrations than saxagliptin itself over a longer period of time, correct?

A. This is the first I'm seeing this and so, again, this is outside the scope of what I've been asked to offer opinions on.

Paper 62 at Observation 24; Ex. 2221 at 91:12-22

Dr. Rotella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Petitioners,
v.
ASTRAZENECA AB,
Patent Owner.

Case: IPR2015-01340
U.S. Patent No. RE44,186

DEPOSITION OF DAVID P. ROTELLA,
Friday, December 2, 2016
New York, New York
9:00 a.m.

Reported by:
Josephine M. Fassett, RPR

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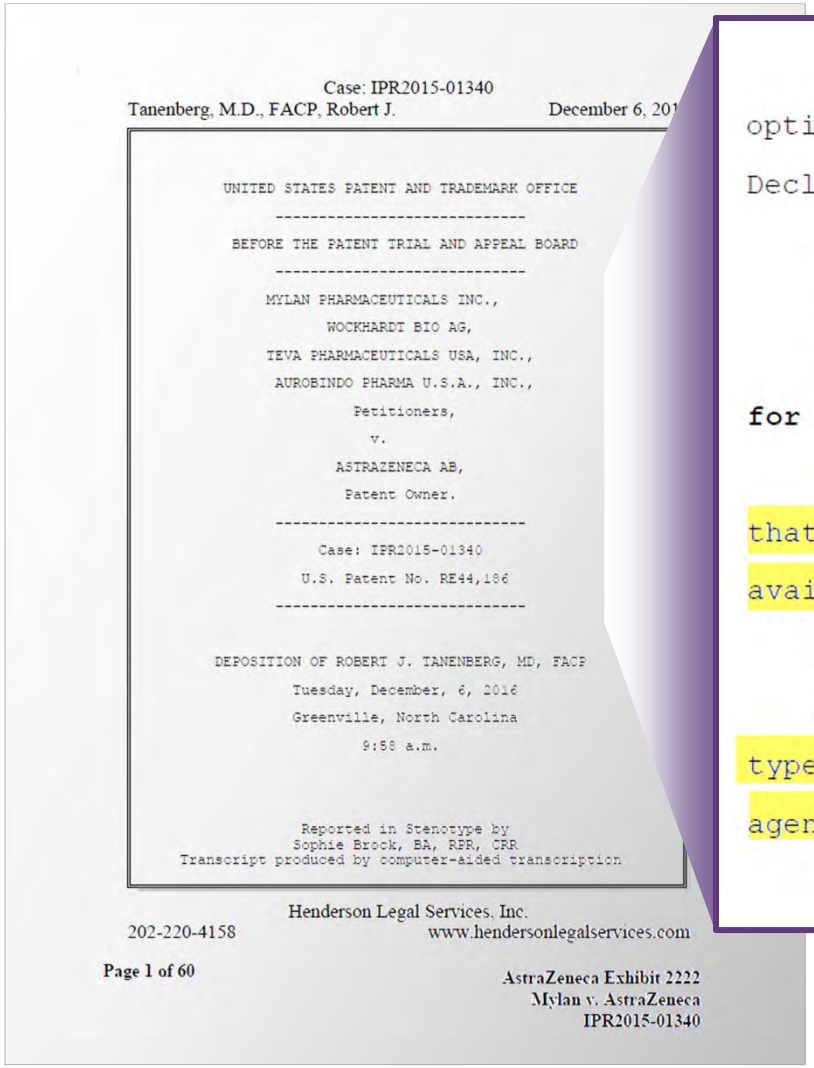
Q. I'd like to show you a document that's marked for identification as AstraZeneca Exhibit 2073, which is the Fura publication. Another one of the materials cited by Dr. Weber.

A. Once again, this paper was published subsequent to the period in time that I was focused. I haven't read this paper and I offer no opinion on the conclusions drawn in this paper.

Paper 62 at Observation 26; Ex. 2221 at 94:25-95:3, 95:23-96:1

Dr. Tanenberg



Case: IPR2015-01340
Tanenberg, M.D., FACP, Robert J. December 6, 201

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AUROBINDO PHARMA U.S.A., INC.,
Petitioners,
v.
ASTRAZENECA AB,
Patent Owner.

Case: IPR2015-01340
U.S. Patent No. RE44,186

DEPOSITION OF ROBERT J. TANENBERG, MD, FACP
Tuesday, December, 6, 2016
Greenville, North Carolina
9:58 a.m.

Reported in Stenotype by
Sophie Brock, BA, RPR, CRR
Transcript produced by computer-aided transcription

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AstraZeneca Exhibit 2222
Mylan v. AstraZeneca
IPR2015-01340

Prior to 2000, the available treatment options listed in Table 2 of Dr. Lenhard's Declaration -- these were the oral --

A. Yes.

Q. -- treatment options that were available?

A. Right. Because insulin has been available for almost 100 years.

Q. And do you have any issue with the statement that there are shortcomings for each of these available treatment options?

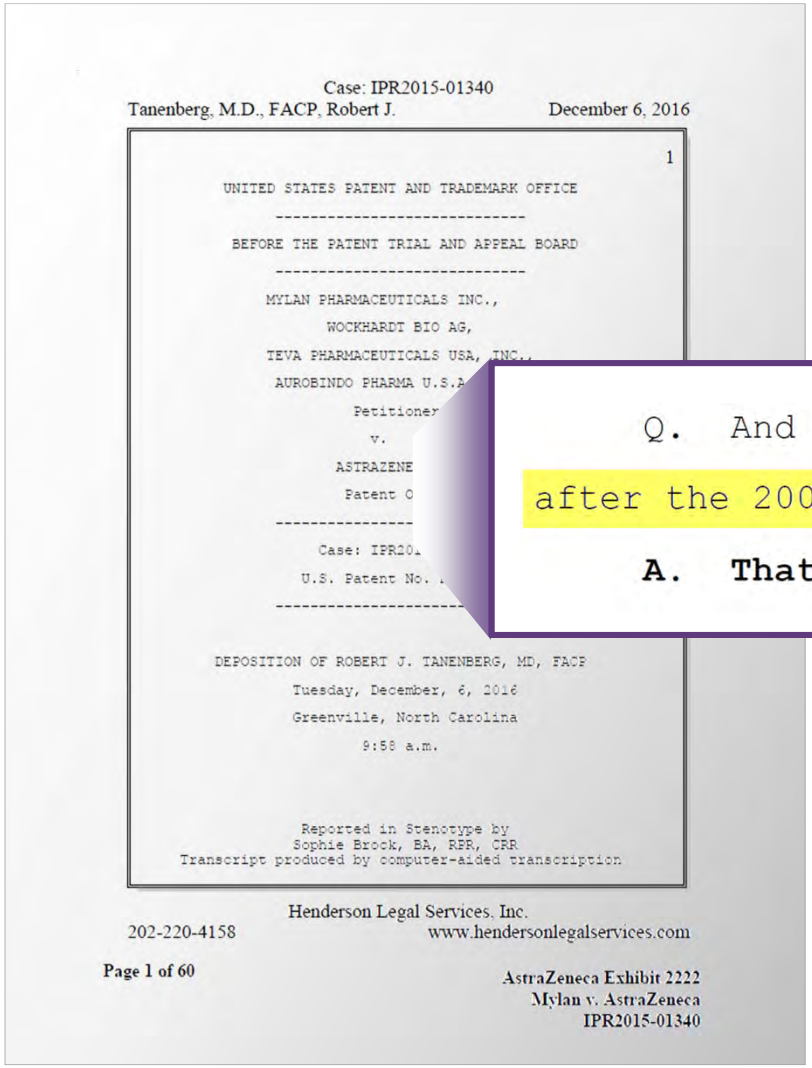
A. No.

Q. And do you agree that most patients with type 2 diabetes will eventually need two or more oral agents and/or insulin to maintain good control?

A. Yes.

Paper 63 at Observation 8; Ex. 2222 at 40:23-41:12

Dr. Tanenberg



Case: IPR2015-01340
Tanenberg, M.D., FACP, Robert J. December 6, 2016

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MYLAN PHARMACEUTICALS INC.,
WOCKHARDT BIO AG,
TEVA PHARMACEUTICALS USA, INC.,
AURO[illegible]
Petitioner
v.
ASTRAZENE[illegible]
Patent O[illegible]

Case: IPR20[illegible]
U.S. Patent No. [illegible]

DEPOSITION OF ROBERT J. TANENBERG, MD, FACP
Tuesday, December, 6, 2016
Greenville, North Carolina
9:58 a.m.

Reported in Stenotype by
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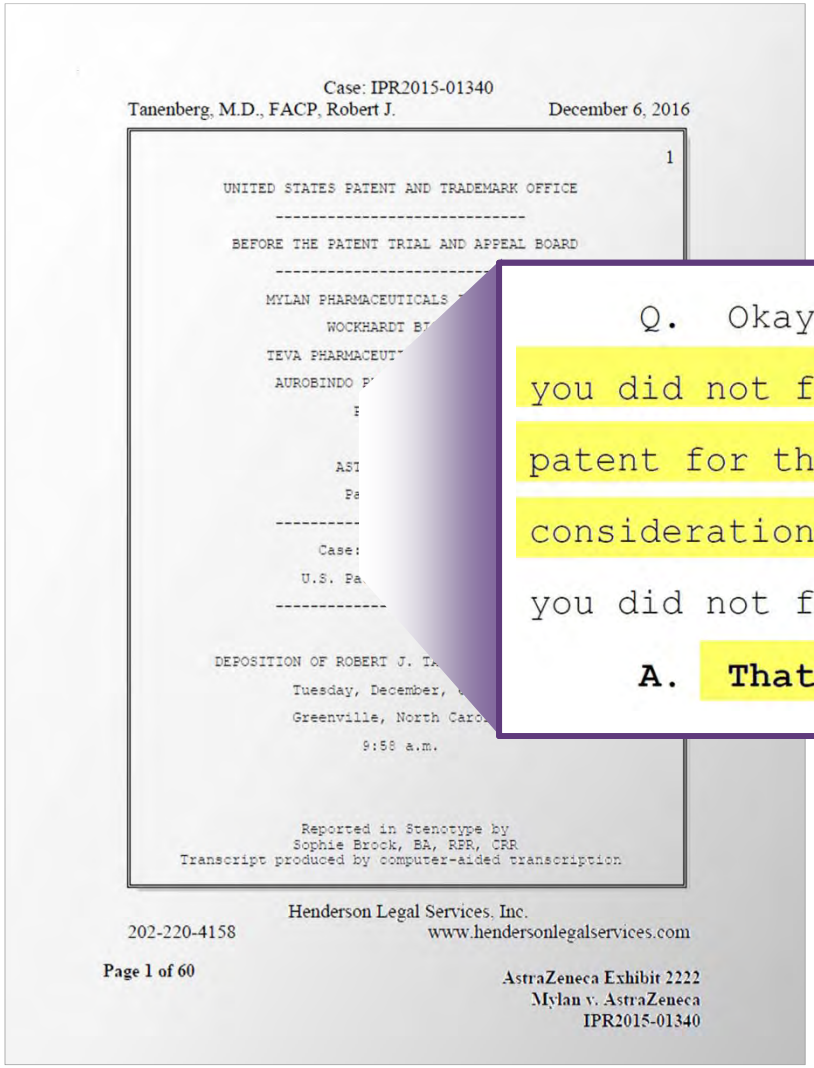
AstraZeneca Exhibit 2222
Mylan v. AstraZeneca
IPR2015-01340

Q. And you did not consider evidence of failures after the 2001 time frame in your analysis; correct?

A. That would be correct.

Paper 63 at Observation 4; Ex. 2222 at 35:22-24

Dr. Tanenberg



Case: IPR2015-01340
Tanenberg, M.D., FACP, Robert J. December 6, 2016

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS
WOCKHARDT BI
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AUROBINDO P
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Pa
Case:
U.S. Pa

DEPOSITION OF ROBERT J. TA
Tuesday, December,
Greenville, North Caro
9:58 a.m.

Reported in Stenotype by
Sophie Brock, BA, RPR, CRR
Transcript produced by computer-aided transcription

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AstraZeneca Exhibit 2222
Mylan v. AstraZeneca
IPR2015-01340

Q. Okay. So then the answer to my question that you did not focus on Claims 25 and 26 of the '186 patent for the purpose of your analysis of secondary considerations, the answer to that question is that you did not focus on those claims?

A. That's correct.

Paper 63 at Observation 1; Ex. 2222 at 23:3-8

October 30, 2000: Ex. 2189

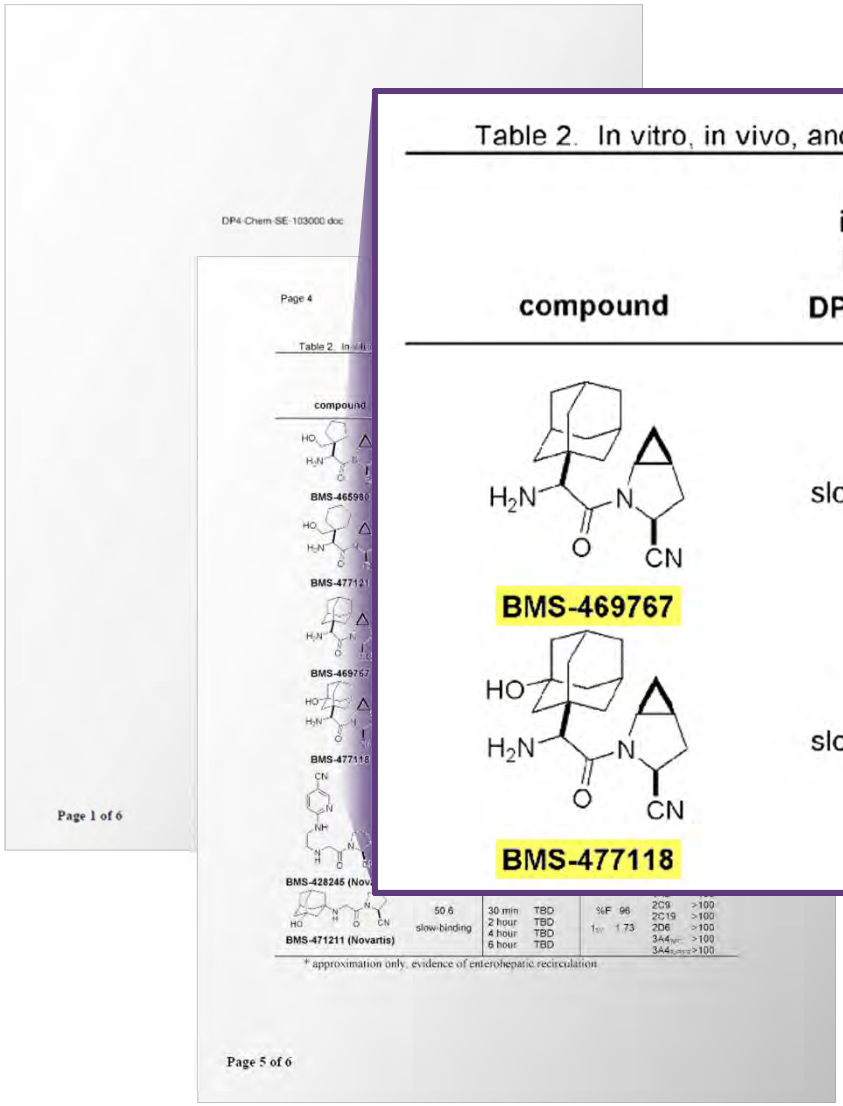
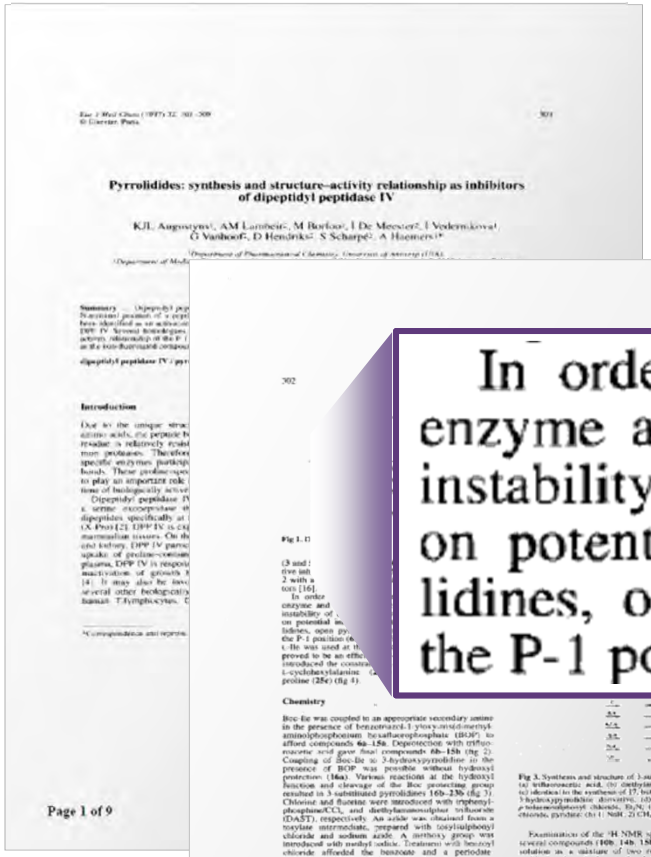


Table 2. In vitro, in vivo, and PK data for selected DP4 inhibitor compounds.

compound	isolated porcine DP4 K_{is} (nM)	rat *ex vivo* plasma DP4 inhibitory ED_{50} (μmol/kg, p.o.)	PK (rat)	CYP450 inhibition (μM)
BMS-469767	14.7 slow-binding	30 min 0.1 2 hour nd 4 hour 0.4 6 hour nd	%F 2.2 $t_{1/2}$ 1.35	1A2 >100 2C9 >100 2C19 >100 2D6 >100 $3A4_{BFC}$ 23 $3A4_{BzRES}$ 22
BMS-477118	18.9 slow-binding	30 min 0.12 2 hour 0.2 4 hour 0.3 6 hour 0.5	%F TBD $t_{1/2}$ TBD	1A2 >100 2C9 activ'n 2C19 >100 2D6 >100 $3A4_{BFC}$ >100 $3A4_{BzRES}$ activ'n

Paper 28 at 4; Ex. 2173 ¶ 13; Ex. 2189 at 5

Augustyns (1997): Ex. 2151



Pyrrolidides: synthesis and structure–activity relationship as inhibitors of dipeptidyl peptidase IV

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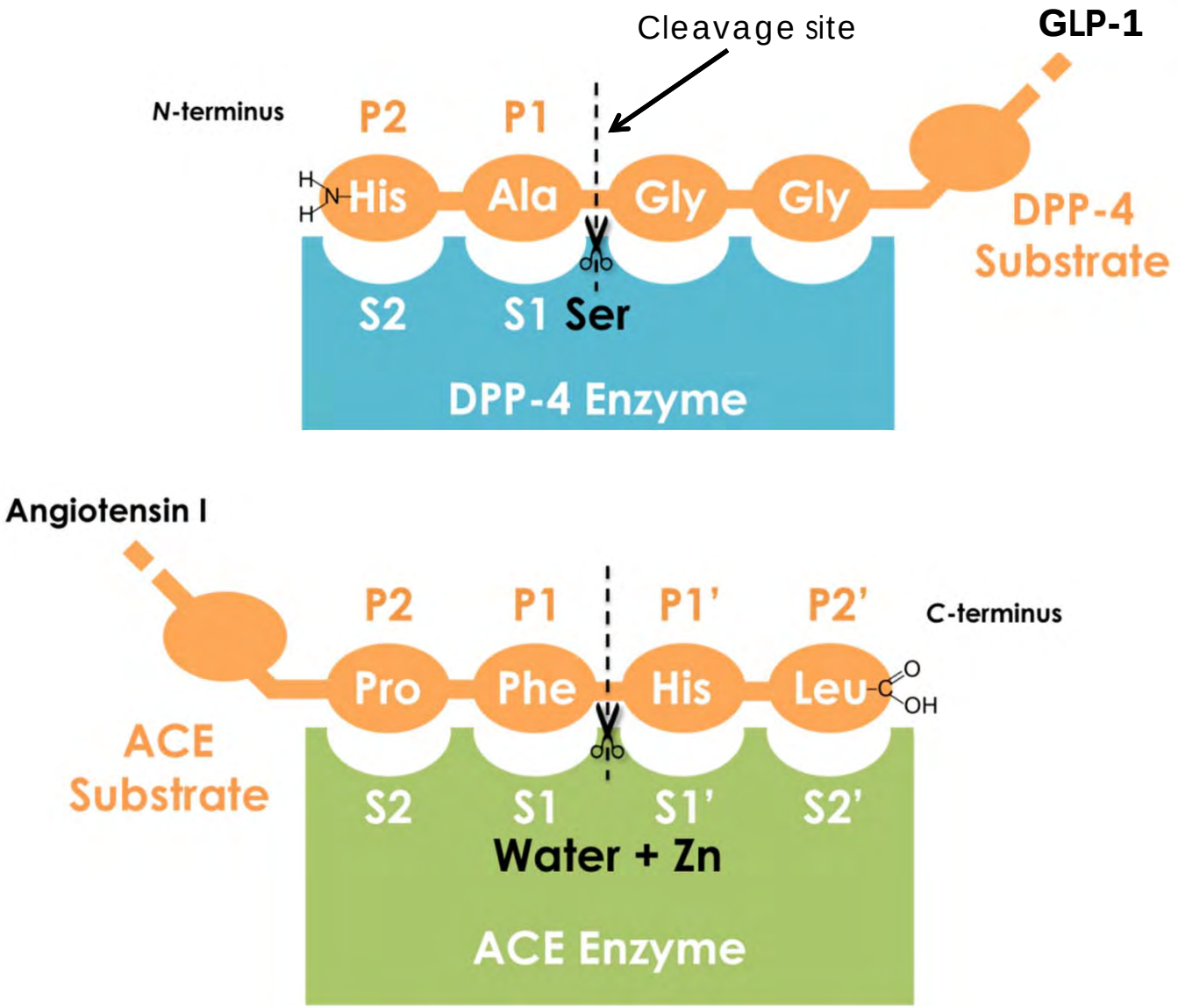
In order to fully explore the S-1 subsite of the enzyme and because of the chemical and biological instability of reactive electrophiles, we concentrated on potential inhibitors containing substituted pyrrolidines, open pyrrolidines or homologues thereof at the P-1 position (**6b–23b**) (figs 2 and 3). In this study,

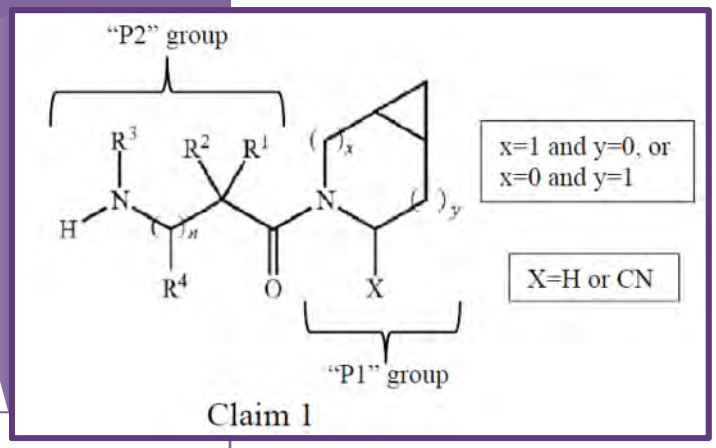
DPP-4 versus ACE



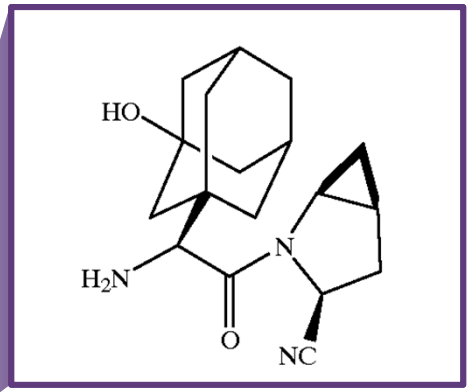
Ex. 2056 ¶¶ 82, 181

Challenged Claims

Claim(s)	Ground	Scope of Claim(s)
1	1	cyclopropyl-fused pyrrolidine and cyanopyrrolidine compounds
2	1	4,5-cyclopropyl pyrrolidine and cyanopyrrolidine compounds
4	1	*cis*-4,5-cyclopropyl cyanopyrrolidine compounds
6	1	"*C*-linked" compounds of claim 1
7	1	"up" cyclopropyl compounds of claim 1
8, 9	1	subgenera comprising eight *cis*-4,5-cyclopropyl cyanopyrrolidine compounds, each containing a quaternary β-carbon in the P2 group
10	1	*cis*-3,4 and *cis*-4,5-cyclopropyl cyanopyrrolidine compounds, each with a *C*-linked alkyl at P2
11	1	pharmaceutical compositions comprising a compound of claim 1 and a carrier
12-22	2-4	pharmaceutical combinations comprising a compound of claim 1 and another agent
25-28, 32-35, 39, 40	1	saxagliptin
29-30, 36-37, 41-42	2	pharmaceutical combinations comprising saxagliptin and another agent or methods of treating with such combinations



Claim 1



Paper 28 at 19-21; Ex. 2056 ¶¶ 19-38

CERTIFICATE OF SERVICE

In addition to the service via email on January 23, 2017 per the Order of Paper No. 69, the undersigned certifies that a copy of the foregoing **PATENT OWNER'S DEMONSTRATIVES** was served electronically via e-mail on January 24, 2017, pursuant to 37 C.F.R. 42.70(b), in its entirety to the following:

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