Mylan Pharmaceuticals Inc.,
Wockhardt Bio AG, Teva Pharmaceuticals USA, Inc.,
Aurobindo Pharma U.S.A. Inc., and Sun Pharmaceutical
Industries, Ltd., Sun Pharma Global FZE and
Amneal Pharmaceuticals LLC,

Petitioners

v.

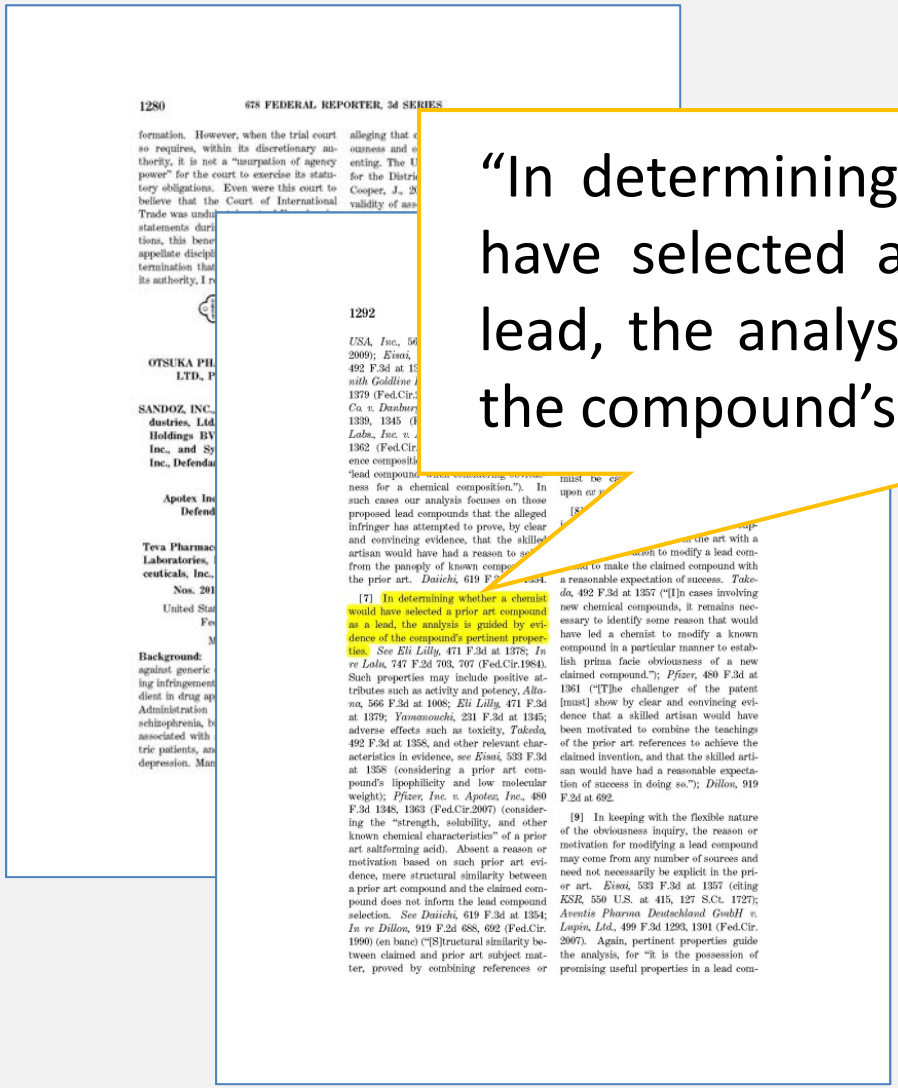
AstraZeneca AB,

Patent Owner

IPR2015-01340
US RE44,186 E

January 25, 2017

Otsuka v. Sandoz, 678 F.3d 1280, 1292 (Fed. Cir. 2012)



1280 678 FEDERAL REPORTER, 3d SERIES

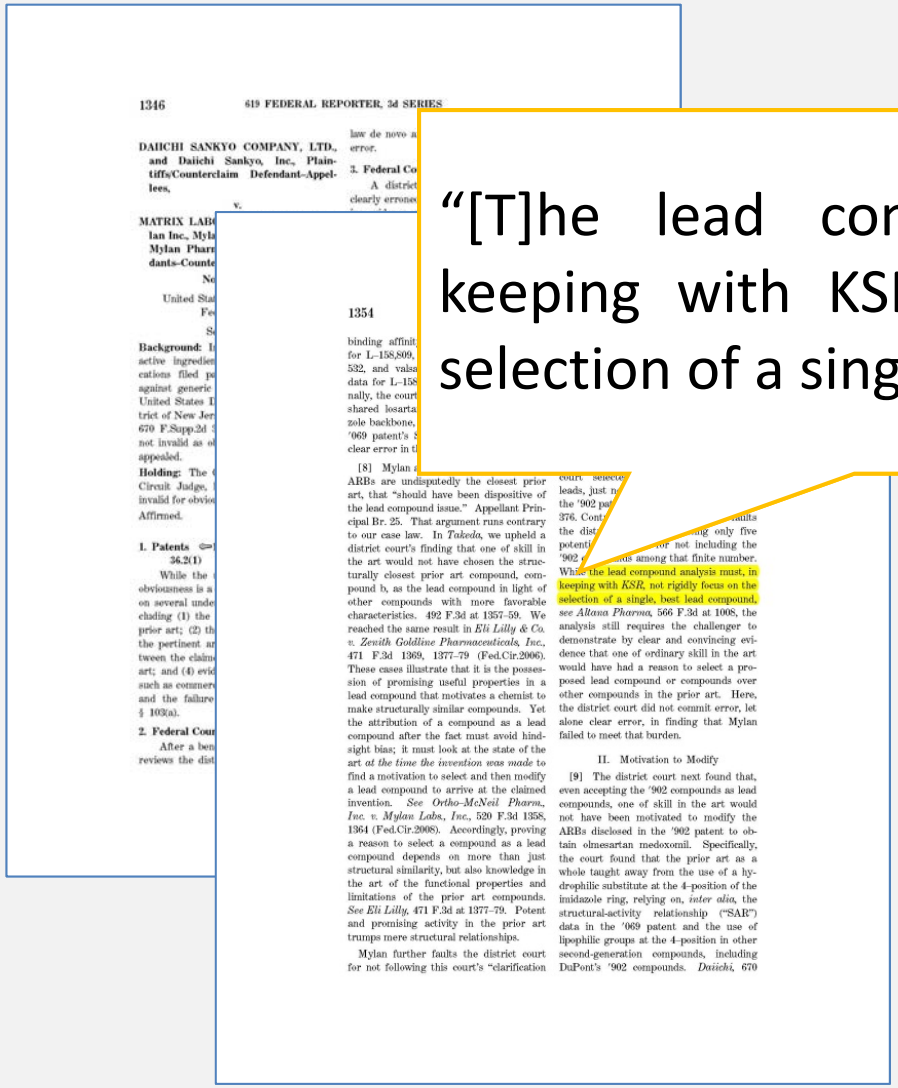
1292

[7] In determining whether a chemist would have selected a prior art compound as a lead, the analysis is guided by evidence of the compound's pertinent properties. *See Eli Lilly*, 471 F.3d at 1378; *In re Labs*, 747 F.2d 703, 707 (Fed.Cir.1984). Such properties may include positive attributes such as activity and potency, *Altana*, 566 F.3d at 1008; *Eli Lilly*, 471 F.3d at 1379; *Yamanouchi*, 231 F.3d at 1345; adverse effects such as toxicity, *Takeda*, 492 F.3d at 1358, and other relevant characteristics in evidence, *see Eisai*, 533 F.3d at 1358 (considering a prior art compound's lipophilicity and low molecular weight); *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1363 (Fed.Cir.2007) (considering the "strength, solubility, and other known chemical characteristics" of a prior art saltforming acid). Absent a reason or motivation based on such prior art evidence, mere structural similarity between a prior art compound and the claimed compound does not inform the lead compound selection. *See Daiichi*, 619 F.3d at 1354; *In re Dillon*, 919 F.2d 688, 692 (Fed.Cir. 1990) (en banc) ("[S]tructural similarity between claimed and prior art subject matter, proved by combining references or

"In determining whether a chemist would have selected a prior art compound as a lead, the analysis is guided by evidence of the compound's pertinent properties."

Source: Institution Dec. at 9.

Daiichi Sankyo v. Matrix Labs., 616 F.3d 1346, 1354 (Fed. Cir. 2010)



1346 619 FEDERAL REPORTER, 3d SERIES

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

v.

MATRIX LAB
Ian Inc., Myla
Mylan Pharr
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No

United Stat
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Background: I
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against generic
United States I
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670 F.Supp.2d
not invalid as o
appealed.

Holding: The
Circuit Judge,
invalid for obvio
Affirmed.

1. Patents
36.2(1)

While the
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prior art; (2) th
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art; and (4) evid
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§ 103(a).

2. Federal Cour

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3. Federal Co

A district
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data for L–158
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[8] Mylan
ARBs are undisputedly the closest prior art, that "should have been dispositive of the lead compound issue." Appellant Principal Br. 25. That argument runs contrary to our case law. In *Takeda*, we upheld a district court's finding that one of skill in the art would not have chosen the structurally closest prior art compound, compound b, as the lead compound in light of other compounds with more favorable characteristics. 492 F.3d at 1357–59. We reached the same result in *Eli Lilly & Co. v. Zenith Goldline Pharmaceuticals, Inc.*, 471 F.3d 1369, 1377–79 (Fed.Cir.2006). These cases illustrate that it is the possession of promising useful properties in a lead compound that motivates a chemist to make structurally similar compounds. Yet the attribution of a compound as a lead compound after the fact must avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to select and then modify a lead compound to arrive at the claimed invention. *See Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1364 (Fed.Cir.2008). 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.

Mylan further faults the district court for not following this court's "clarification

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376. Cont
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'902
While the lead compound analysis must, in keeping with *KSR*, not rigidly focus on the selection of a single, best lead compound, *see Altana Pharma*, 566 F.3d at 1008, the analysis still requires the challenger to demonstrate by clear and convincing evidence that one of ordinary skill in the art would have had a reason to select a proposed lead compound or compounds over other compounds in the prior art. Here, the district court did not commit error, let alone clear error, in finding that Mylan failed to meet that burden.

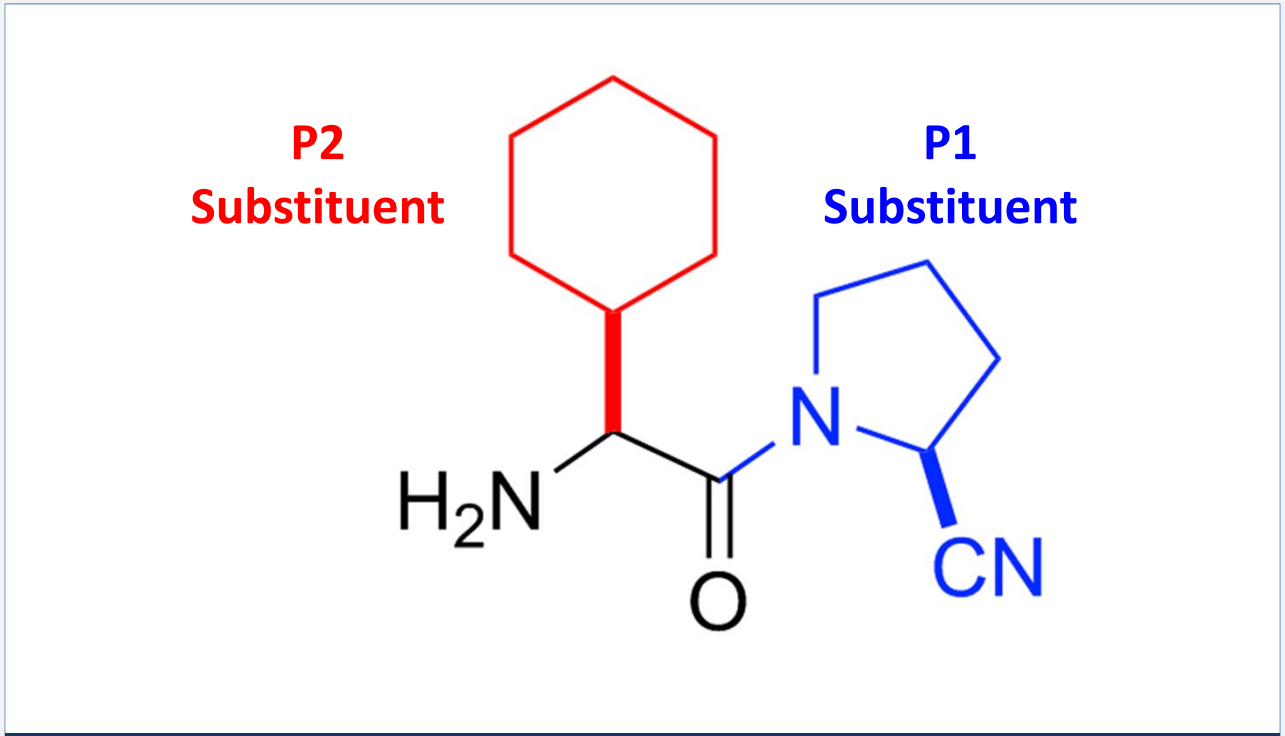
II. Motivation to Modify

[9] The district court next found that, even accepting the '902 compounds as lead compounds, one of skill in the art would not have been motivated to modify the ARBs disclosed in the '902 patent to obtain olmesartan medoxomil. Specifically, the court found that the prior art as a whole taught away from the use of a hydrophilic substitute at the 4–position of the imidazole ring, relying on, *inter alia*, the structural-activity relationship ("SAR") data in the '069 patent and the use of lipophilic groups at the 4–position in other second-generation compounds, including DuPont's '902 compounds. *Daiichi*, 670

"[T]he lead compound analysis must, in keeping with KSR, not rigidly focus on the selection of a single, best lead compound . . ."

Source: Institution Dec. at 10.

Ashworth 25 is a Pertinent Lead Compound

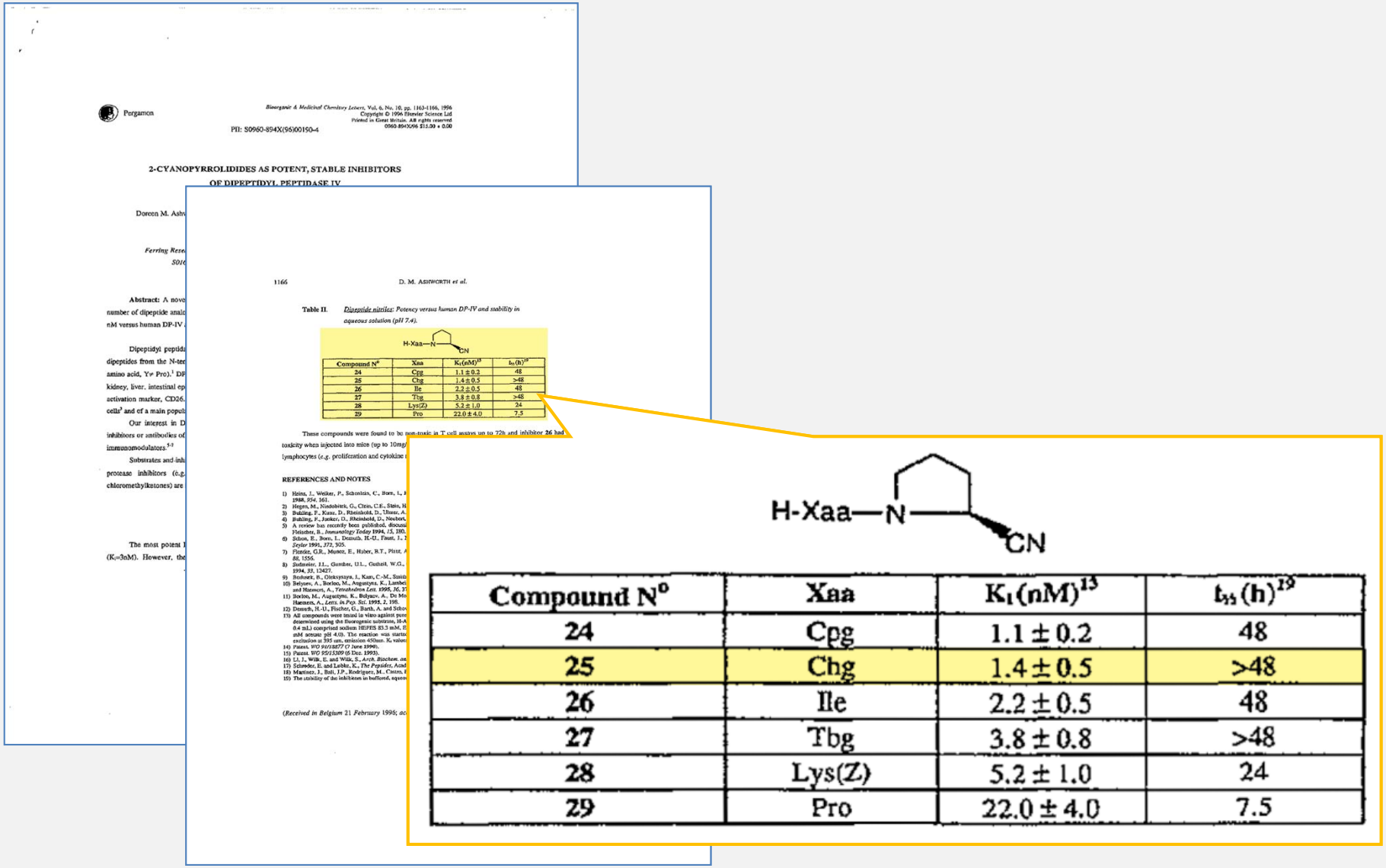


Ashworth 25

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

Source: EX1007 (Ashworth I) at 1166.

Ashworth 25 Has Good Potency and Stability



Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 6, No. 10, pp. 1163-1166, 1996
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PII: S0960-894X(96)00150-4 0960-894X/96 $15.00 + 0.00

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

Doreen M. Ashv

Ferring Rese

Abstract: A nove
number of dipeptide analo
nM versus human DP-IV

Dipeptidyl peptida
dipeptides from the N-ter
amino acid, Yaa Pro).[1] DP
kidney, liver, intestinal ep
activation marker, CD26,
cells[2] and of a main popul

Our interest in D
inhibitors or antibodies of
immunomodulators.[3-5]

Substrates and inh
protease inhibitors (e.g.
chloromethylketones) are

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

1166 D. M. ASHWORTH *et al.*

Table II. *Dipeptide nitriles: Potency versus human DP-IV and stability in aqueous solution (pH 7.4).*

H-Xaa—N(CN)

Compound N°	Xaa	K_i(nM)[13]	$t_{1/2}$(h)[19]
24	Cpg	1.1 ± 0.2	48
25	Chg	1.4 ± 0.5	>48
26	Ile	2.2 ± 0.5	48
27	Tbg	3.8 ± 0.8	>48
28	Lys(Z)	5.2 ± 1.0	24
29	Pro	22.0 ± 4.0	7.5

These compounds were found to be non-toxic in T cell assays up to 72h and inhibitor **26** had

toxicity when injected into mice (up to 10mg/

lymphocytes (e.g. proliferation and cytokine

REFERENCES AND NOTES

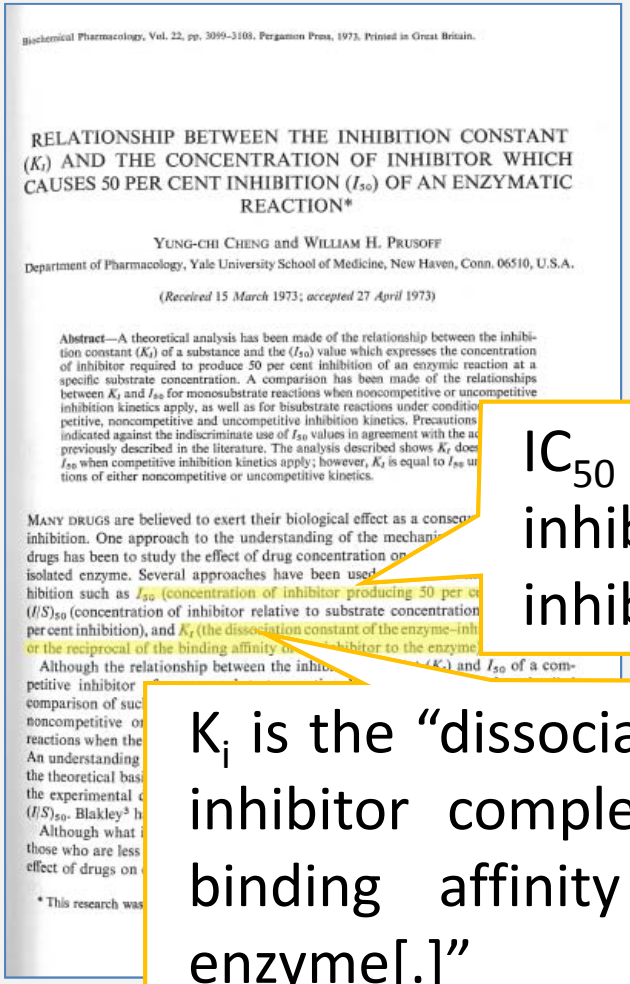
(*Received in Belgium* 21 *February* 1996; *ac*

H-Xaa—N(CN)

Compound N°	Xaa	K_i(nM)[13]	$t_{1/2}$(h)[19]
24	Cpg	1.1 ± 0.2	48
25	Chg	1.4 ± 0.5	>48
26	Ile	2.2 ± 0.5	48
27	Tbg	3.8 ± 0.8	>48
28	Lys(Z)	5.2 ± 1.0	24
29	Pro	22.0 ± 4.0	7.5

Source: EX1007 (Ashworth I) at 1165-66.

Measuring Potency by K_i and IC_{50} Values



Biochemical Pharmacology, Vol. 22, pp. 3099–3108. Pergamon Press, 1973. Printed in Great Britain.

RELATIONSHIP BETWEEN THE INHIBITION CONSTANT (K_I) AND THE CONCENTRATION OF INHIBITOR WHICH CAUSES 50 PER CENT INHIBITION (I_{50}) OF AN ENZYMATIC REACTION*

YUNG-CHI CHENG and WILLIAM H. PRUSOFF

Department of Pharmacology, Yale University School of Medicine, New Haven, Conn. 06510, U.S.A.

(*Received* 15 *March* 1973; *accepted* 27 *April* 1973)

Abstract—A theoretical analysis has been made of the relationship between the inhibition constant (K_I) of a substance and the (I_{50}) value which expresses the concentration of inhibitor required to produce 50 per cent inhibition of an enzymic reaction at a specific substrate concentration. A comparison has been made of the relationships between K_I and I_{50} for monosubstrate reactions when noncompetitive or uncompetitive inhibition kinetics apply, as well as for bisubstrate reactions under condition
petitive, noncompetitive and uncompetitive inhibition kinetics. Precautions
indicated against the indiscriminate use of I_{50} values in agreement with the a
previously described in the literature. The analysis described shows K_I does
I_{50} when competitive inhibition kinetics apply; however, K_I is equal to I_{50} u
tions of either noncompetitive or uncompetitive kinetics.

MANY DRUGS are believed to exert their biological effect as a conseq
inhibition. One approach to the understanding of the mechani
drugs has been to study the effect of drug concentration on
isolated enzyme. Several approaches have been used
hibition such as I_{50} (concentration of inhibitor producing 50 per c
$(I/S)_{50}$ (concentration of inhibitor relative to substrate concentration
per cent inhibition), and K_I (the dissociation constant of the enzyme–inh
or the reciprocal of the binding affinity of the inhibitor to the enzyme
Although the relationship between the inhib
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An understanding
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$(I/S)_{50}$. Blakley[3] h
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those who are less
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* This research was

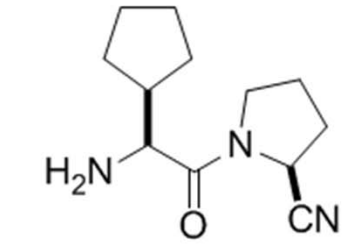
Smaller K_i and IC_{50} values represent greater potency

IC_{50} is the "concentration of inhibitor producing 50 per cent inhibition[.]"

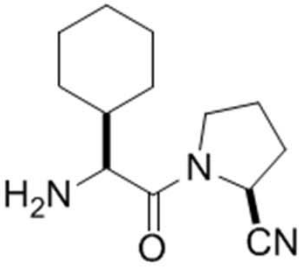
K_i is the "dissociation constant of the enzyme-inhibitor complex, or the reciprocal of the binding affinity of the inhibitor to the enzyme[.]"

Source: EX1025 (Cheng) at 3099; EX1003 (Rotella Decl.), ¶64.

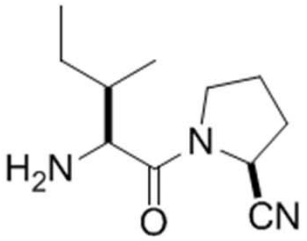
Ashworth I Table II Compounds



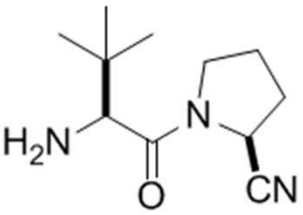
Cpg Analogue (Cyclopropylglycine) Compound 24



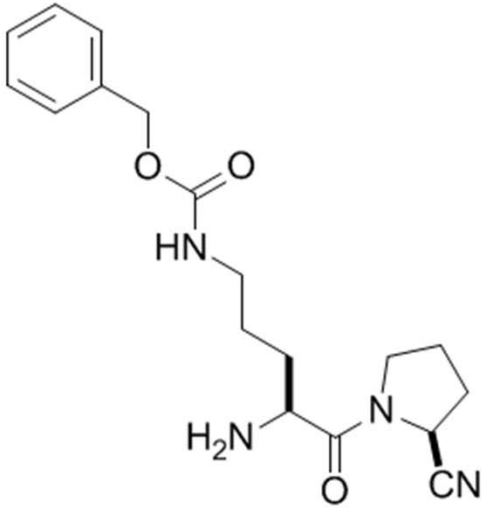
Chg Analogue (Cyclohexylglycine) Compound 25



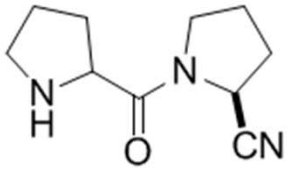
Ile Analogue (Isoleucine) Compound 26



Tbg Analogue (*Tert*-butylglycine) Compound 27



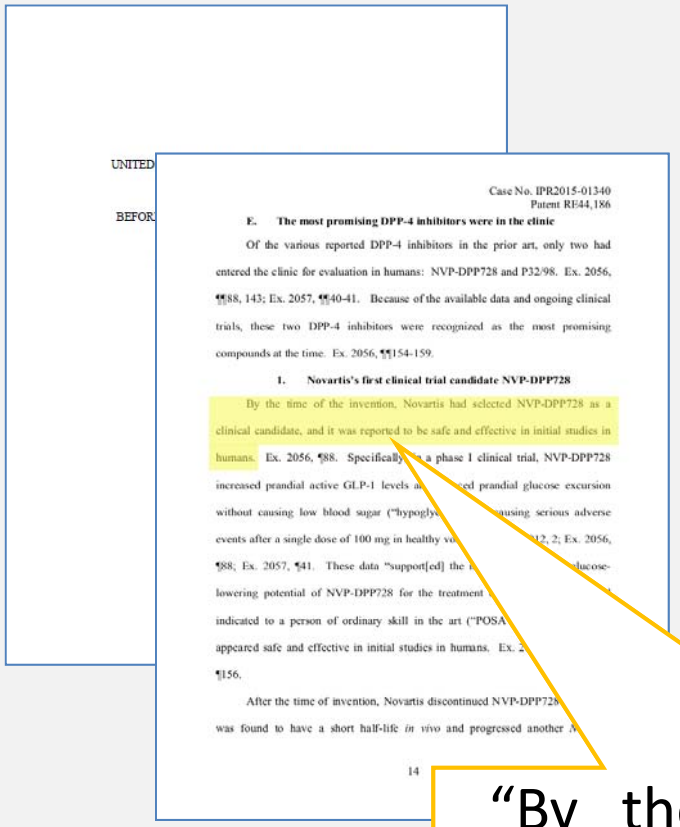
Lys(Z) Analogue (Carboxybenzyl-lysine) Compound 28



Pro Analogue (Proline) Compound 29

Source: EX1007 (Ashworth I) at 1166.

Cyanopyrrolidines Were of Interest



Case No. IPR2015-01340
Patent RE44,186

E. The most promising DPP-4 inhibitors were in the clinic

Of the various reported DPP-4 inhibitors in the prior art, only two had entered the clinic for evaluation in humans: NVP-DPP728 and P32/98. Ex. 2056, ¶¶88, 143; Ex. 2057, ¶¶40-41. Because of the available data and ongoing clinical trials, these two DPP-4 inhibitors were recognized as the most promising compounds at the time. Ex. 2056, ¶¶154-159.

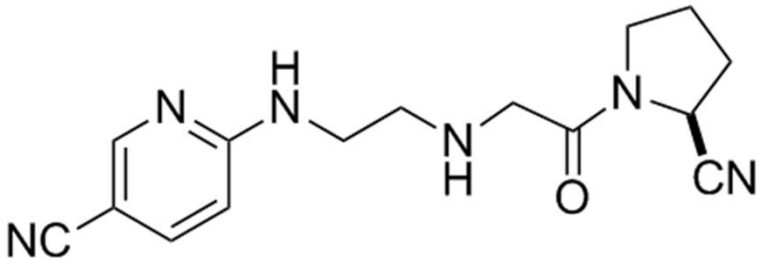
1. Novartis's first clinical trial candidate NVP-DPP728

By the time of the invention, Novartis had selected NVP-DPP728 as a clinical candidate, and it was reported to be safe and effective in initial studies in humans. Ex. 2056, ¶88. Specifically, in a phase 1 clinical trial, NVP-DPP728 increased prandial active GLP-1 levels and reduced prandial glucose excursion without causing low blood sugar ("hypoglycemia") or causing serious adverse events after a single dose of 100 mg in healthy volunteers. Ex. 2012, 2; Ex. 2056, ¶88; Ex. 2057, ¶41. These data "support[ed] the glucose-lowering potential of NVP-DPP728 for the treatment" of diabetes, indicated to a person of ordinary skill in the art ("POSA") that NVP-DPP728 appeared safe and effective in initial studies in humans. Ex. 2056, ¶156.

After the time of invention, Novartis discontinued NVP-DPP728 because it was found to have a short half-life *in vivo* and progressed another

14

NVP-DPP728, containing a cyanopyrrolidine, entered clinical trials in humans.

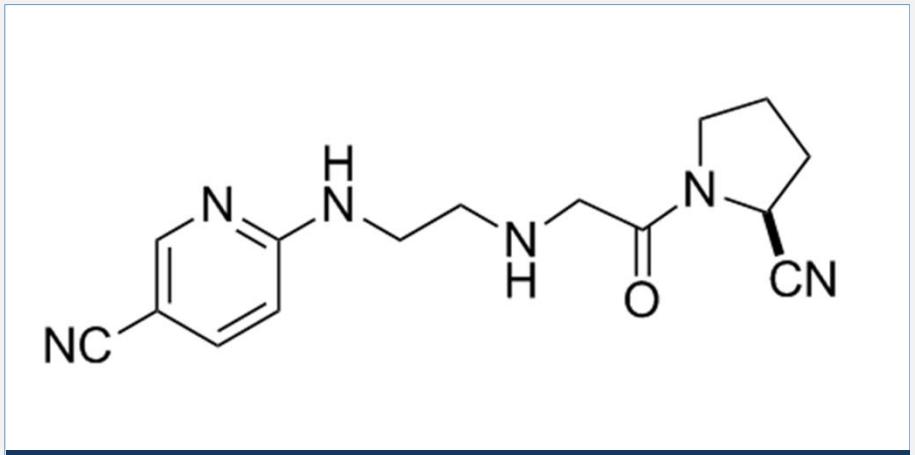


NVP-DPP728

"By the time of the invention, Novartis had selected NVP-DPP728 as a clinical candidate, and it was reported to be safe and effective in initial studies in humans."

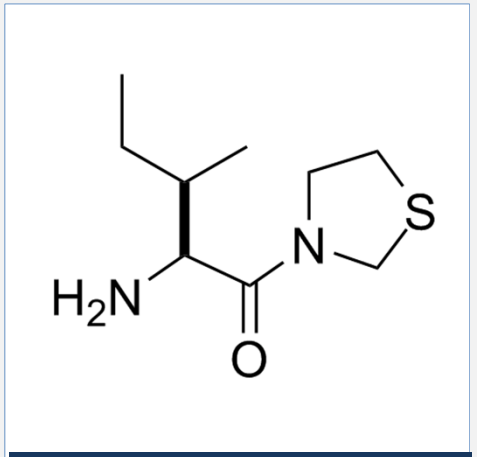
Source: PO Resp. at 12, 14; EX2012 (Rothenberg) at A39; EX1074 (Second Rotella Decl.), ¶15.

Ashworth 25 More Potent than Other Clinical Candidates



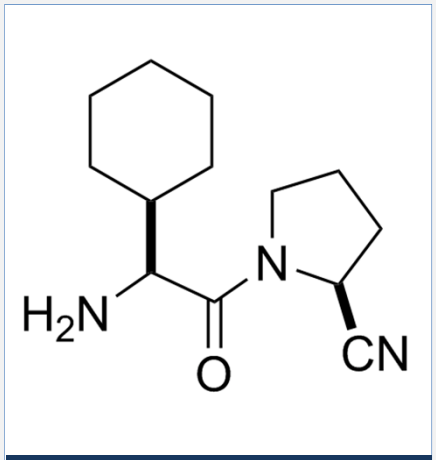
NVP-DPP728

K_i = 11 nM



P32/98

IC_{50} = 2800 nM



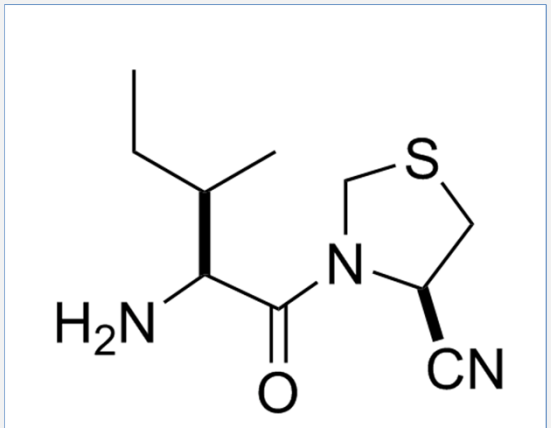
Ashworth 25

K_i = 1.4 nM

Dr. Weber concedes that "compound 25 of Ashworth-I [is] more potent than the clinical candidates NVP-DPP728 and P32/98[.]"

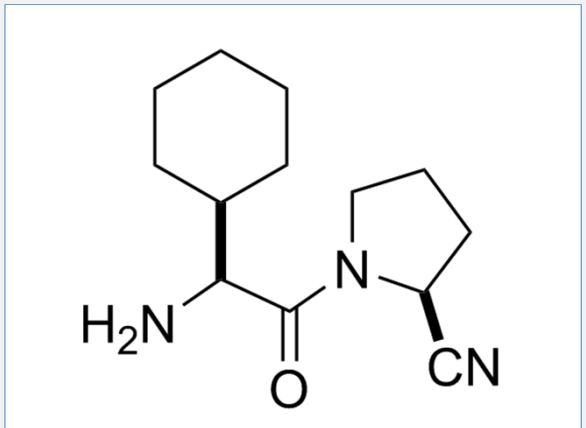
Source: EX1074 (Second Rotella Decl.), ¶11; EX2016 (Hughes) at 11600; EX1007 (Ashworth I) at Table 2, 1166; EX2078 (Schon) at 308; EX2056 (Weber Decl.), *¶172 .*

Superior Stability of Ashworth 25



Ashworth II compound 3

$t_{1/2}$ = 27 h



Ashworth I compound 25

$t_{1/2}$ = >48 h

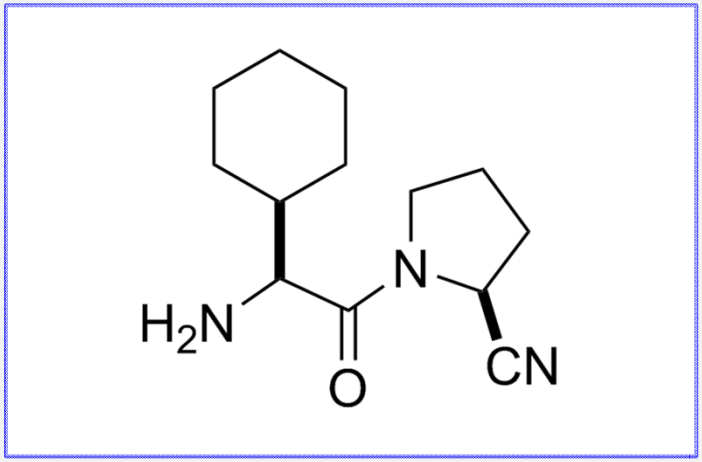
Ashworth 25 has greater *in vitro* stability (longer half-life, $t_{1/2}$) than compound 3 from Ashworth II.

Source: EX1074 (Second Rotella Decl.), ¶14; EX2001 (Ashworth II) at 2748.

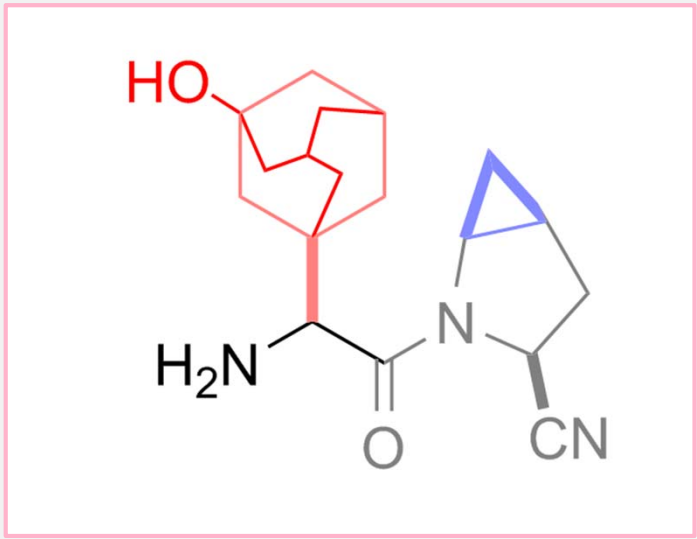
Summary of Structural Differences

- **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

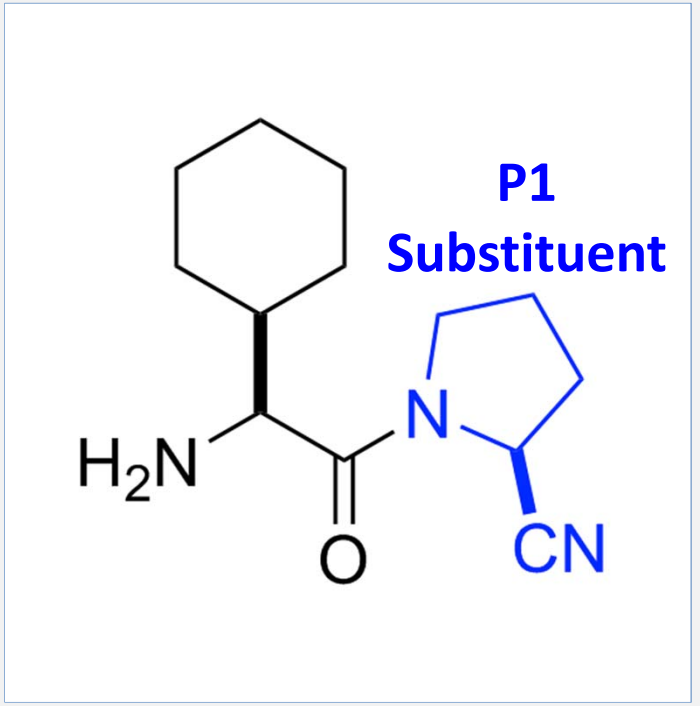


Saxagliptin



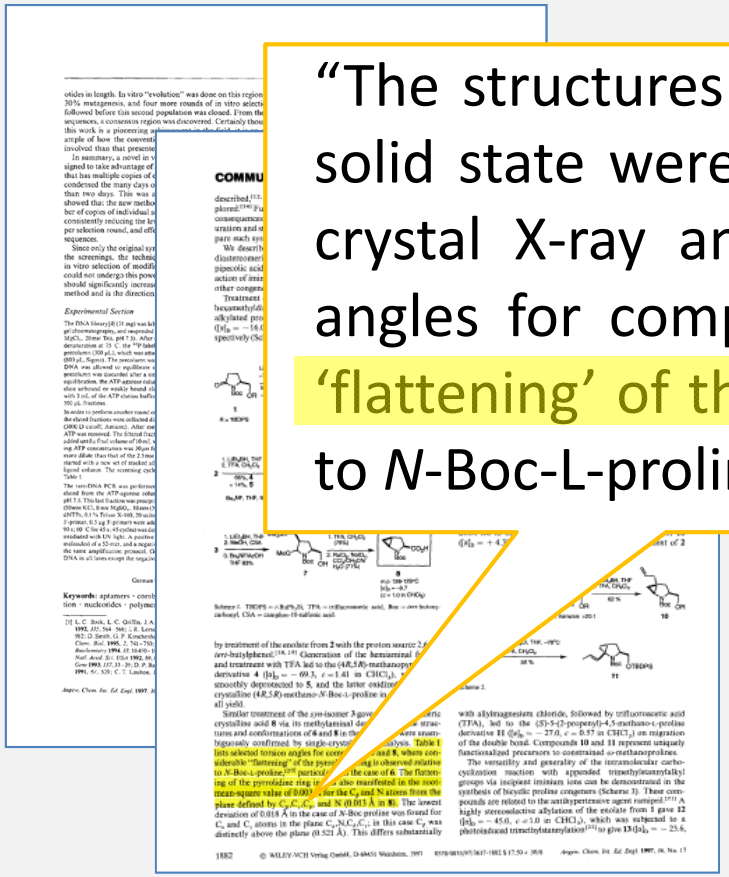
Petitioner's Motivation to Modify P1

- **Cyclopropanation**
  - flattens and rigidifies pyrrolidine ring
  - modulates cyano position
- **Optimizes interaction with DPP-4 enzyme to improve activity and stability**

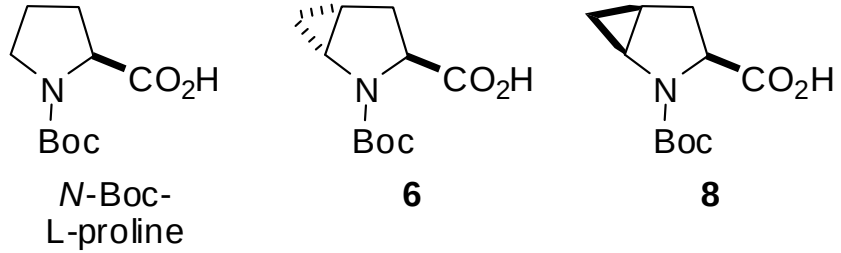


Source: Pet. at 29; EX1003 (First Rotella Decl.), ¶134; EX1010 (Hanessian).

Cyclopropanation Modulates Proline Conformation



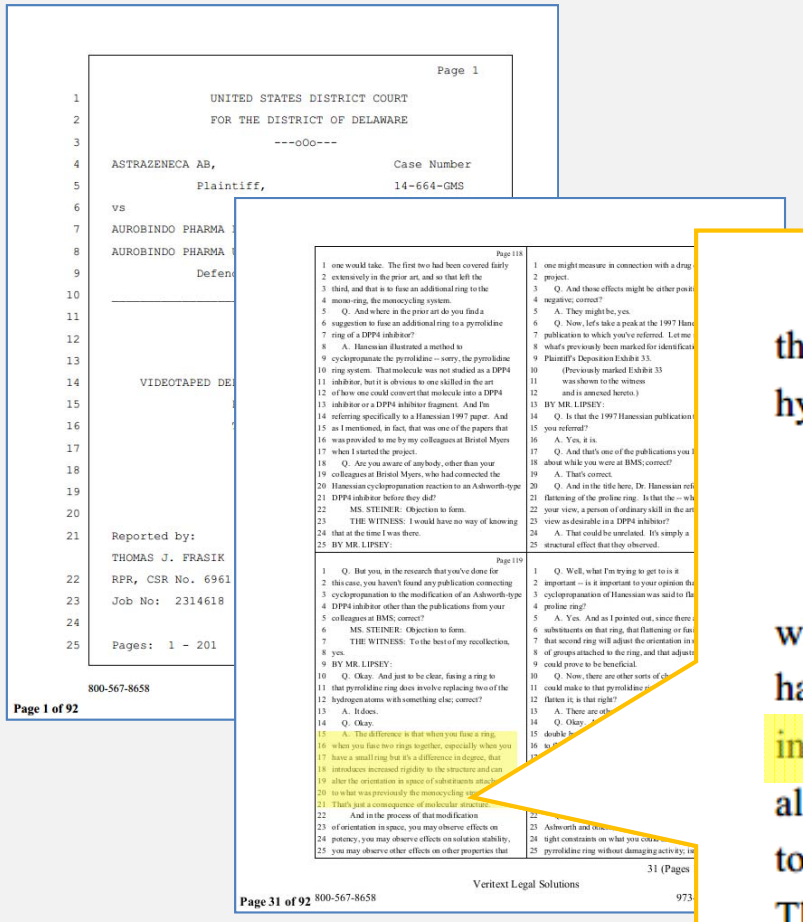
"The structures and conformations of **6** and **8** in the solid state were unambiguously confirmed by single-crystal X-ray analysis. Table 1 lists selected torsion angles for compounds **6** and **8**, where considerable 'flattening' of the pyrrolidine ring is observed relative to *N*-Boc-L-proline[.]"



N-Boc-L-proline **6** **8**

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

Cyclopropanation Confers Conformational Rigidity



Page 1

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

ASTRAZENECA AB, Plaintiff, vs AUROBINDO PHARMA … AUROBINDO PHARMA … Defen…

Case Number 14-664-GMS

VIDEOTAPED DE…

Reported by: THOMAS J. FRASIK
RPR, CSR No. 6961
Job No: 2314618
Pages: 1 - 201

800-567-8658

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Page 118

one would take. The first two had been covered fairly extensively in the prior art, and so that left the third, and that is to fuse an additional ring to the mono-ring, the monocycling system.

Q. And where in the prior art do you find a suggestion to fuse an additional ring to a pyrrolidine ring of a DPP4 inhibitor?

A. Hanessian illustrated a method to cyclopropanate the pyrrolidine -- sorry, the pyrrolidine ring system. That molecule was not studied as a DPP4 inhibitor, but it is obvious to one skilled in the art of how one could convert that molecule into a DPP4 inhibitor or a DPP4 inhibitor fragment. And I'm referring specifically to a Hanessian 1997 paper. And as I mentioned, in fact, that was one of the papers that was provided to me by my colleagues at Bristol Myers when I started the project.

Q. Are you aware of anybody, other than your colleagues at Bristol Myers, who had connected the Hanessian cyclopropanation reaction to an Ashworth-type DPP4 inhibitor before they did?

MS. STEINER: Objection to form.

THE WITNESS: I would have no way of knowing that at the time I was there.

BY MR. LIPSEY:

Page 119

Q. But you, in the research that you've done for this case, you haven't found any publication connecting cyclopropanation to the modification of an Ashworth-type DPP4 inhibitor other than the publications from your colleagues at BMS; correct?

MS. STEINER: Objection to form.

THE WITNESS: To the best of my recollection, yes.

BY MR. LIPSEY:

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.

Q. Okay.

A. The difference is that when you fuse a ring, when you fuse two rings together, especially when you have a small ring but it's a difference in degree, that introduces increased rigidity to the structure and can alter the orientation in space of substituents attached to what was previously the monocycling structure. That's just a consequence of molecular structure.

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

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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?

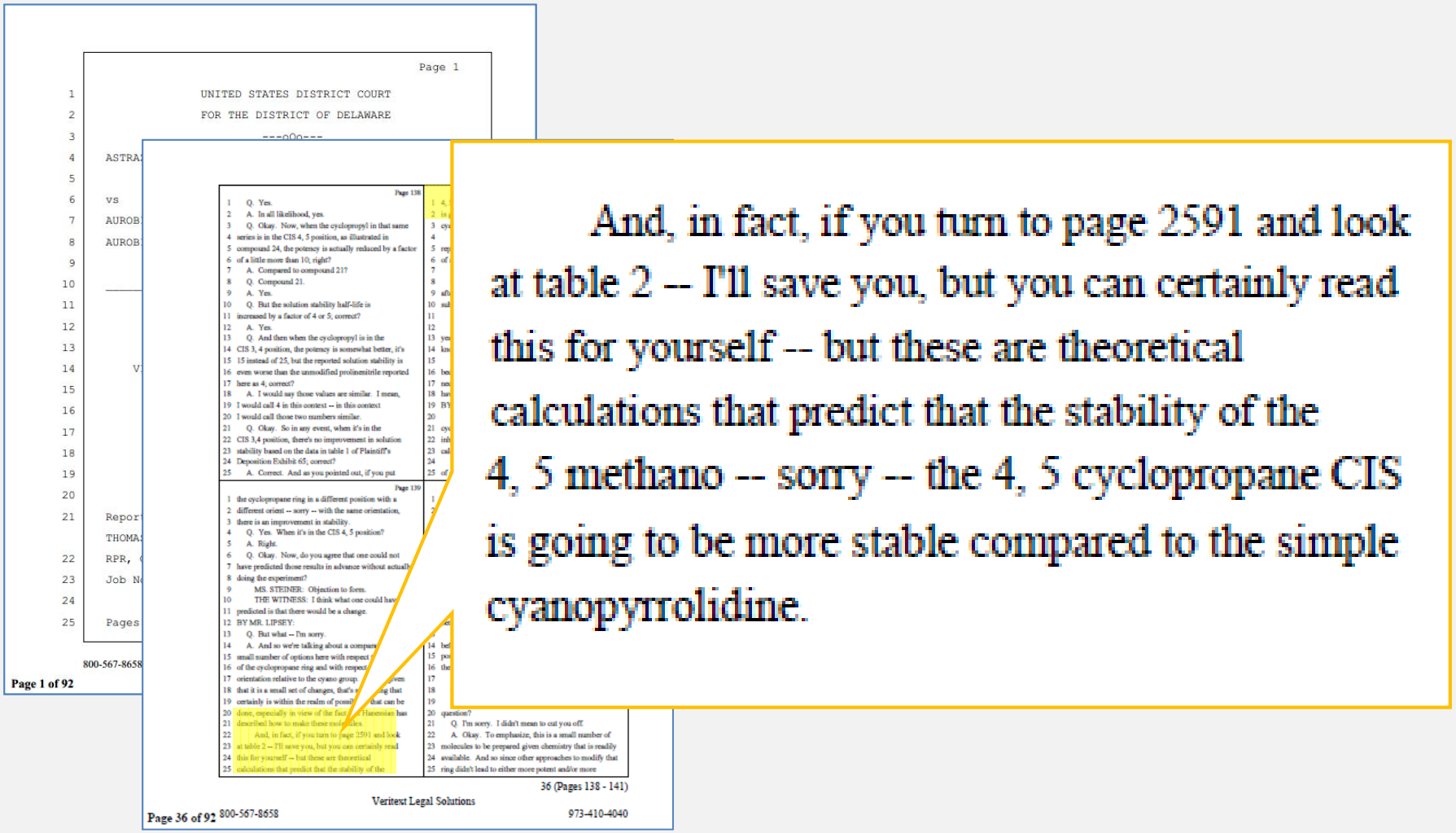
A. It does.

Q. Okay.

A. The difference is that when you fuse a ring, when you fuse two rings together, especially when you have a small ring but it's a difference in degree, that introduces increased rigidity to the structure and can alter the orientation in space of substituents attached to what was previously the monocycling structure. That's just a consequence of molecular structure.

Source: EX2174 (Rotella Depo. Trans.), 119:10-21.

Increase in Cyanopyrrolidine Stability Was Predictable



Page 1

UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

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ASTRA

vs

AUROB

AUROB

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Q. Yes.
A. In all likelihood, yes.
Q. Okay. Now, when the cyclopropyl in that same series is in the CIS 4, 5 position, as illustrated in compound 24, the potency is actually reduced by a factor of a little more than 10; right?
A. Compared to compound 21?
Q. Compound 21.
A. Yes.
Q. But the solution stability half-life is increased by a factor of 4 or 5; correct?
A. Yes.
Q. And then when the cyclopropyl is in the CIS 3, 4 position, the potency is somewhat better, it's 15 instead of 25, but the reported solution stability is even worse than the unmodified prolinenitrile reported here as 4; correct?
A. I would say those values are similar. I mean, I would call 4 in this context -- in this context I would call those two numbers similar.
Q. Okay. So in any event, when it's in the CIS 3,4 position, there's no improvement in solution stability based on the data in table 1 of Plaintiff's Deposition Exhibit 65; correct?
A. Correct. And as you pointed out, if you put

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the cyclopropane ring in a different position with a different orient -- sorry -- with the same orientation, there is an improvement in stability.
Q. Yes. When it's in the CIS 4, 5 position?
A. Right.
Q. Okay. Now, do you agree that one could not have predicted those results in advance without actually doing the experiment?
MS. STEINER: Objection to form.
THE WITNESS: I think what one could have predicted is that there would be a change.
BY MR. LIPSEY:
Q. But what -- I'm sorry.
A. And so we're talking about a compar... small number of options here with respect ... of the cyclopropane ring and with respect ... orientation relative to the cyano group ... that it is a small set of changes, that's ... certainly is within the realm of possib... done, especially in view of the fact ... described how to make these molecules.
And, in fact, if you turn to page 2591 and look at table 2 -- I'll save you, but you can certainly read this for yourself -- but these are theoretical calculations that predict that the stability of the

question?
Q. I'm sorry. I didn't mean to cut you off.
A. Okay. To emphasize, this is a small number of molecules to be prepared given chemistry that is readily available. And so since other approaches to modify that ring didn't lead to either more potent and/or more

36 (Pages 138 - 141)

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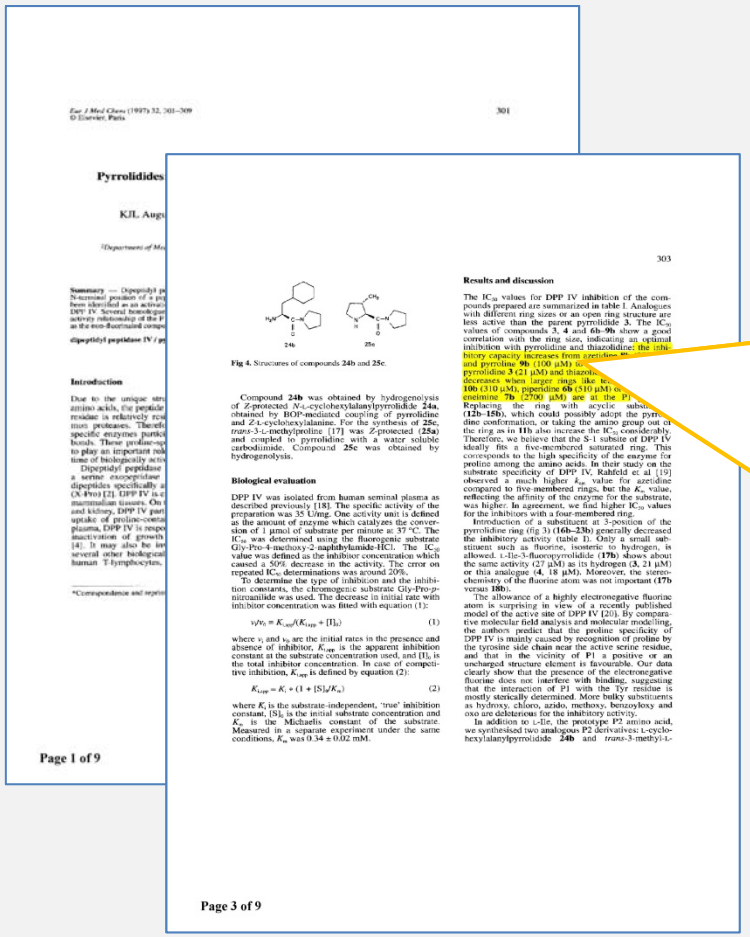
> And, in fact, if you turn to page 2591 and look at table 2 -- I'll save you, but you can certainly read this for yourself -- but these are theoretical calculations that predict that the stability of the 4, 5 methano -- sorry -- the 4, 5 cyclopropane CIS is going to be more stable compared to the simple cyanopyrrolidine.

Source: EX2174 (Rotella Depo. Trans.), 139:22-140:3; EX2002 (Magnin) at 2591.

Patent Owner Cites Augustyns 1997



Pyrrolidides

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Results and discussion

Fig 4. Structures of compounds 24b and 25e.

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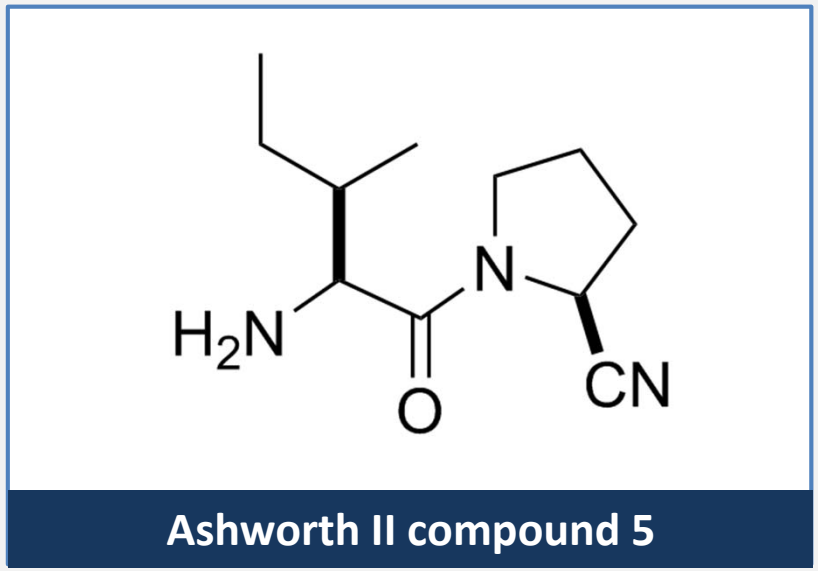
"[T]he inhibitory capacity increases from azetidine **8b** (270 µM) and pyrroline **9b** (100 µM) to the optimal five-rings pyrrolidine **3** (21 µM) and thiazolidine **4** (18 µM), and decreases when larger rings like tetrahydropyridine **10b** (310 µM), piperidine **6b** (510 µM) or hexamethyleneimine **7b** (2700 µM) are at the P1 position."

Patent Owner: "Increasing the pyrrolidine ring size to a 6- or 7-membered ring . . . was not well tolerated."

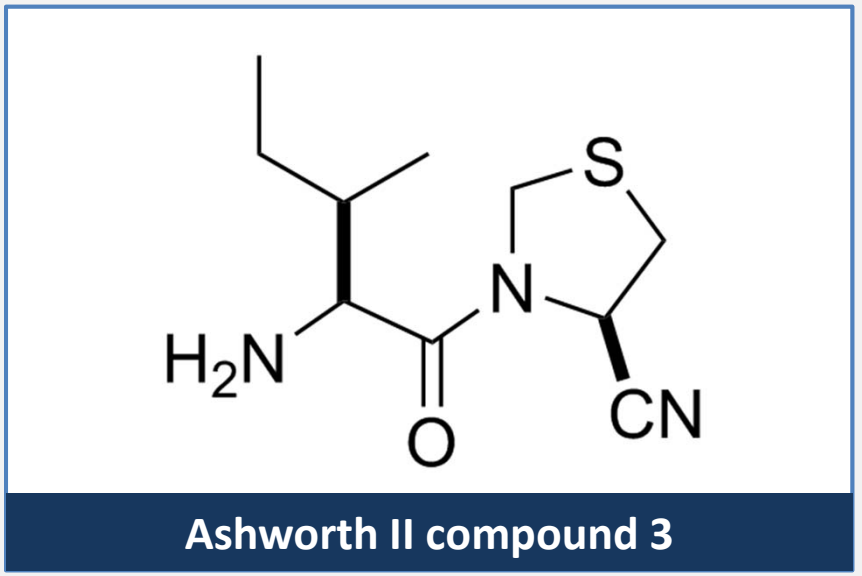
Source: Patent Owner Resp. at 10; EX2151 (Augustyns 1997) at 303.

Small Changes to P1 Ring Size Were Tolerated



Ashworth II compound 5

K_i = 2.2 nM

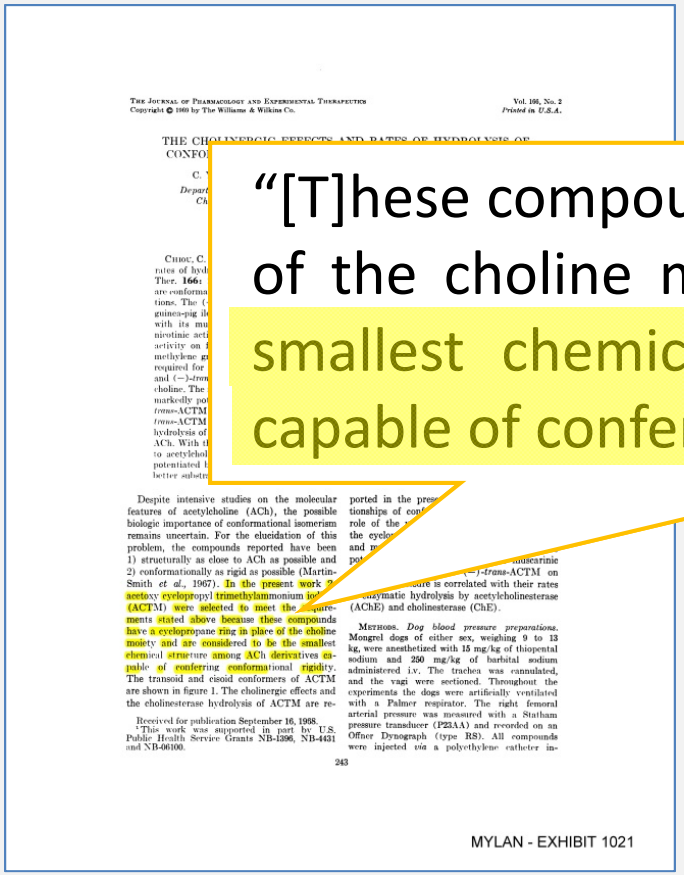


Ashworth II compound 3

K_i = 0.41 nM

Source: EX2001 (Ashworth II) at 2747; EX1074 (Second Rotella Decl.), ¶40.

Cyclopropanation Has Minimal Effect on Ring Size



THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS
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Despite intensive studies on the molecular features of acetylcholine (ACh), the possible biologic importance of conformational isomerism remains uncertain. For the elucidation of this problem, the compounds reported have been 1) structurally as close to ACh as possible and 2) conformationally as rigid as possible (Martin-Smith *et al.*, 1967). In the present work ... acetoxy cyclopropyl trimethylammonium ... (ACTM) were selected to meet the ... ments stated above because these 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. The transoid and cisoid conformers of ACTM are shown in figure 1. The cholinergic effects and the cholinesterase hydrolysis of ACTM are re-

Received for publication September 16, 1968.
This work was supported in part by U.S. Public Health Service Grants NB-1206, NB-8431 and NB-06100.

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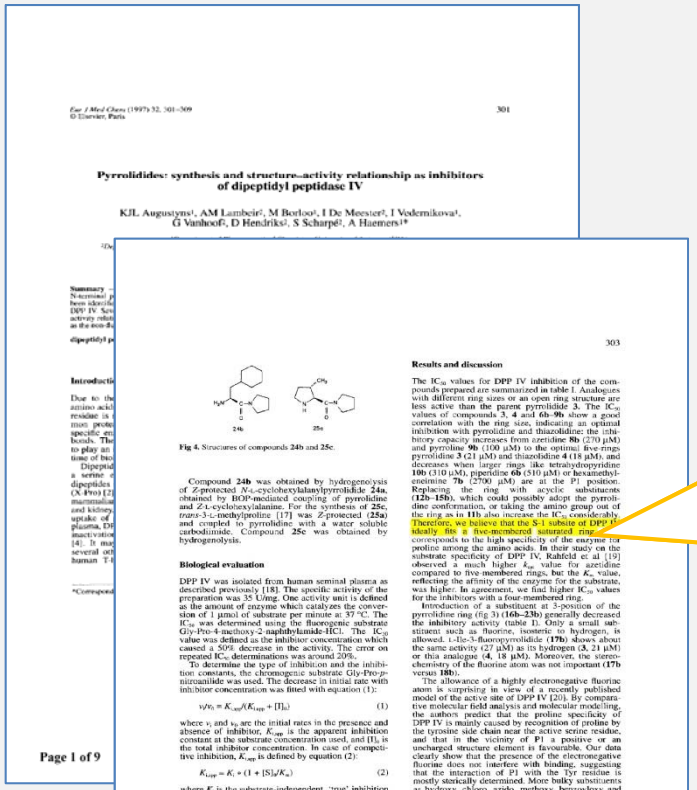
MYLAN - EXHIBIT 1021

"[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.

Cyclopropanation Fits with 5-Membered Ring Preference



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

KJL Augustyns[1], AM Lambeir[2], M Borloo[1], I De Meester[2], I Vedernikova[1], G Vanhoof[2], D Hendriks[2], S Scharpé[2], A Haemers[1]*

Page 1 of 9

Fig 4. Structures of compounds 24b and 25c.

Results and discussion

Biological evaluation

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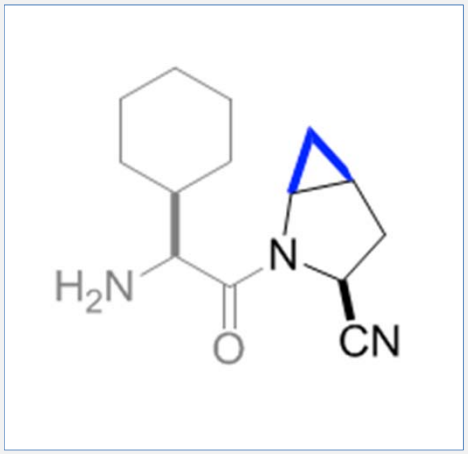
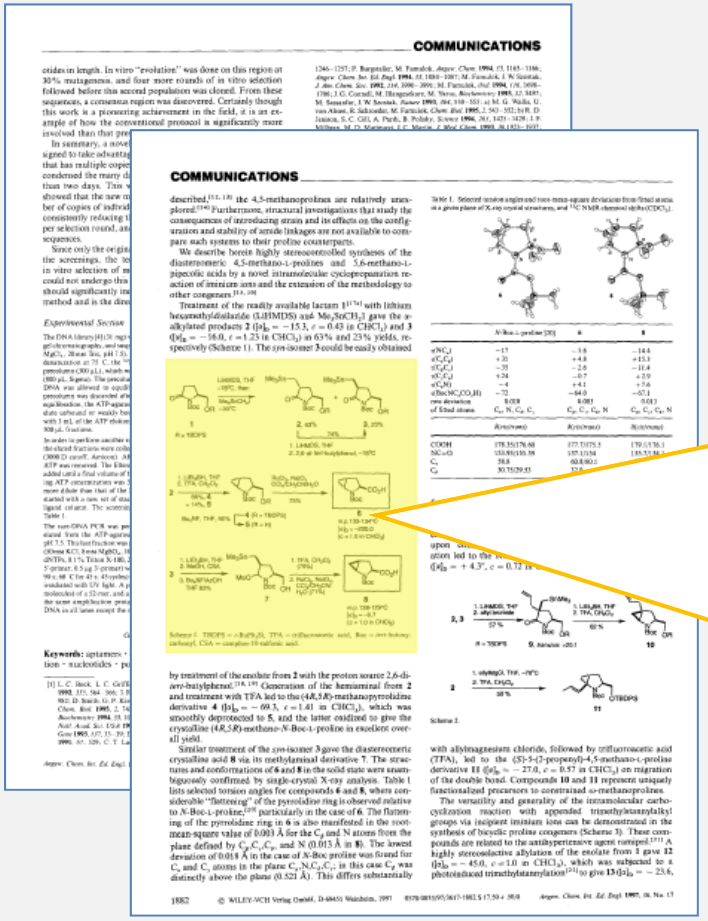
A POSA "would understand that cyclopropanation preserves the saturated five-membered ring, while also providing controlled modifications to the pyrrolidine conformation, as taught by Hanessian."

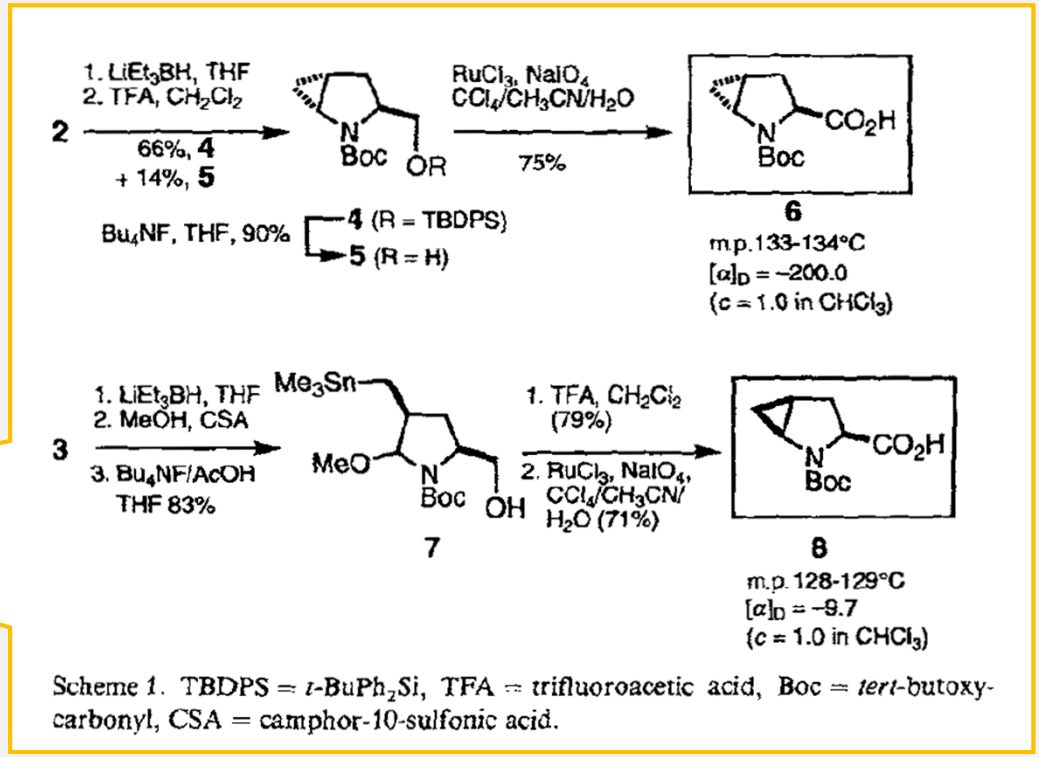
"Therefore, we believe that the S-1 subsite of DPP IV ideally fits a five-membered saturated ring."



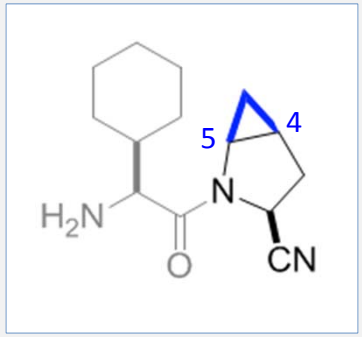
Source: EX2151 (Augustyns) at 303; EX1074 (Second Rotella Decl.), ¶40.

Methods For Cyclopropanating Pyrrolidine were Known





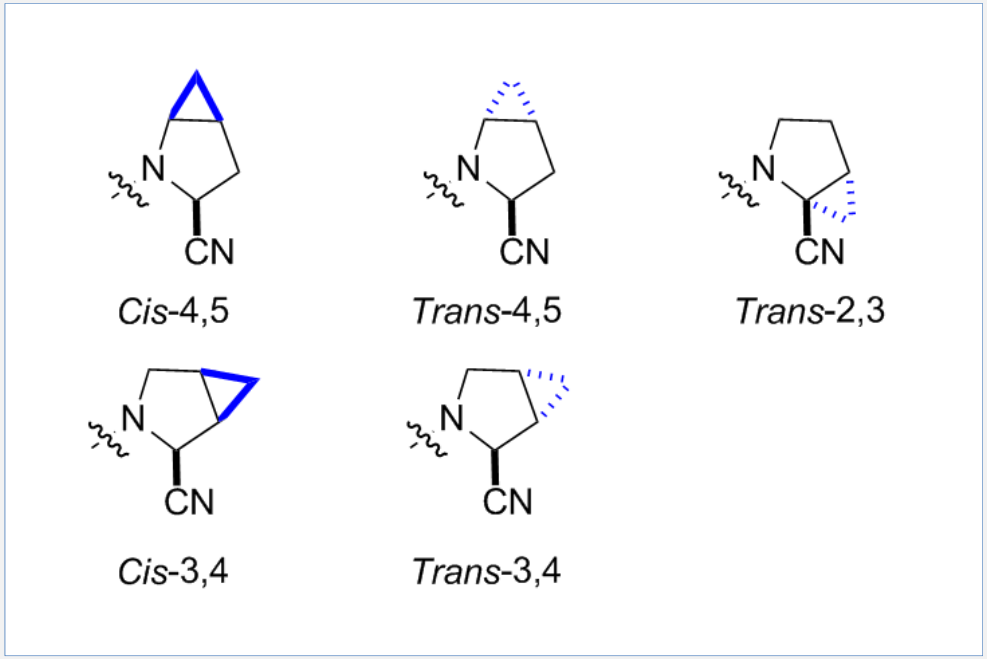
Scheme 1. TBDPS = *t*-BuPh$_2$Si, TFA = trifluoroacetic acid, Boc = *tert*-butoxycarbonyl, CSA = camphor-10-sulfonic acid.



Hanessian teaches synthesis of *cis*-4,5 and *trans*-4,5 cyclopropyl cyanopyrrolidine.

Source: EX1010 (Hanessian '97) at 1882; EX1074 (Second Rotella Decl.), ¶38.

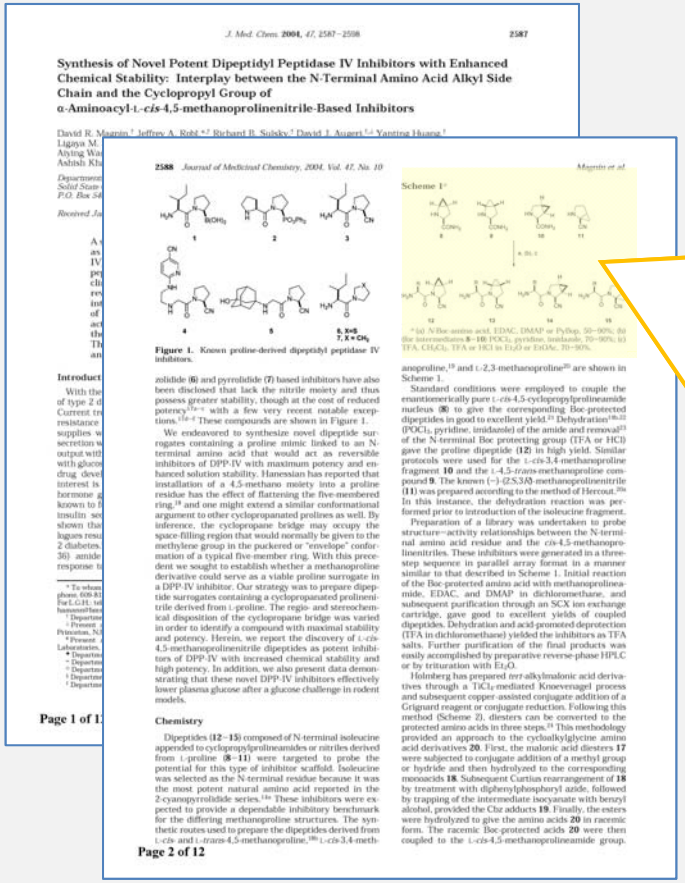
Limited Number of Positions to Cyclopropanate Pyrrolidine



Only 5 possible ways to cyclopropanate pyrrolidine ring (including *cis* and *trans* isomers).

Source: EX1010 (Hanessian '97) at 1882; EX1003 (Rotella Decl.), ¶¶139-40.

Magnin Confirms Ease of Evaluating Each Option



J. Med. Chem. 2004, 47, 2587–2598 2587

Synthesis of Novel Potent Dipeptidyl Peptidase IV Inhibitors with Enhanced Chemical Stability: Interplay between the N-Terminal Amino Acid Alkyl Side Chain and the Cyclopropyl Group of α-Aminoacyl-L-*cis*-4,5-methanoprolinenitrile-Based Inhibitors

2588 Journal of Medicinal Chemistry, 2004, Vol. 47, No. 10 Magnin et al.

Figure 1. Known proline-derived dipeptidyl peptidase IV inhibitors.

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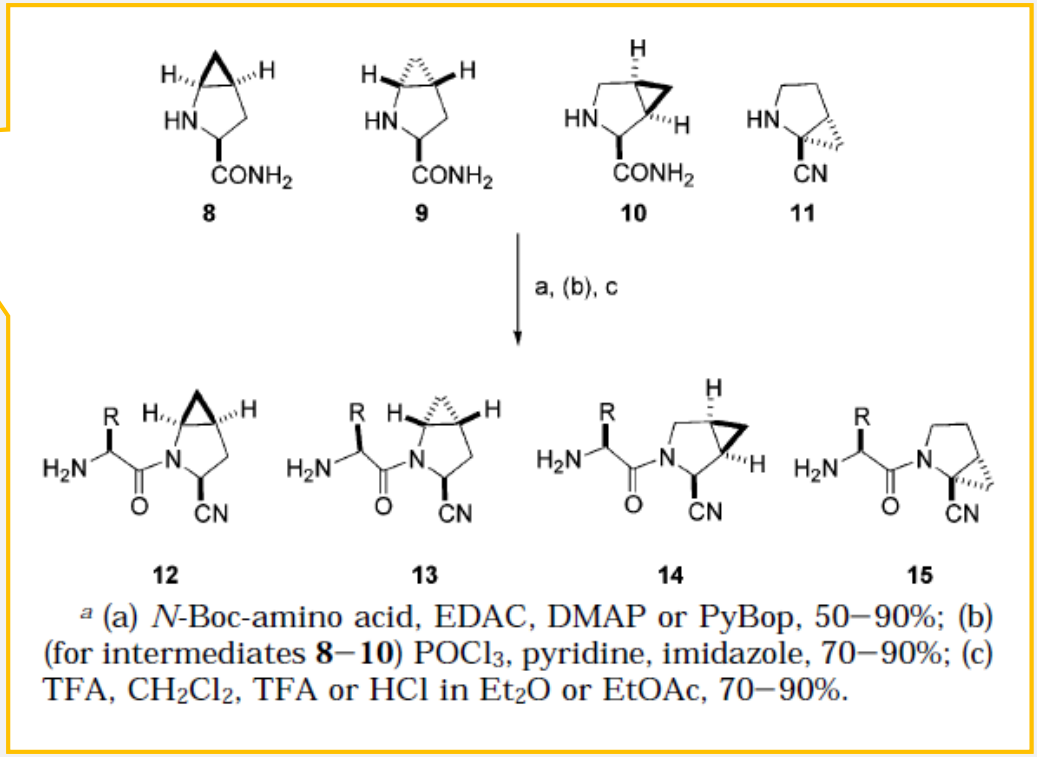


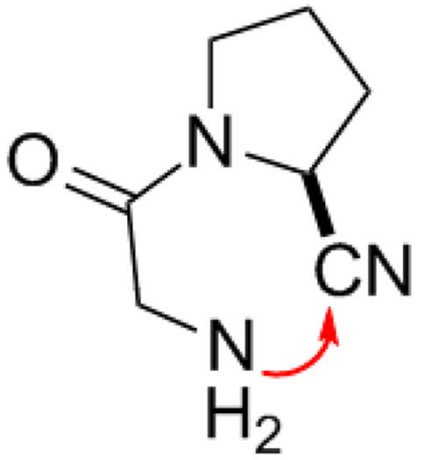
[a] (a) *N*-Boc-amino acid, EDAC, DMAP or PyBop, 50−90%; (b) (for intermediates **8**−**10**) $POCl_3$, pyridine, imidazole, 70−90%; (c) TFA, CH_2Cl_2, TFA or HCl in Et_2O or EtOAc, 70−90%.

Magnin confirms the straightforward task of screening cyclopropanation derivatives at each of the available cyanopyrrolidine positions.

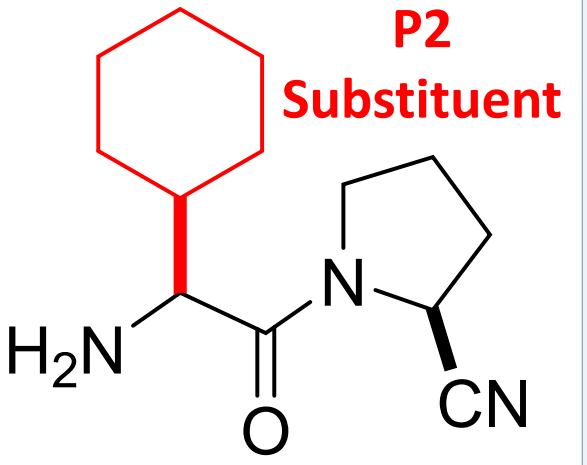
Source: EX2002 (Magnin) at 2588; EX1074 (Second Rotella Decl.), ¶50.

Motivation to Modify P2

- **Sterically bulky P2 substituents**
  - improve stability
  - improve potency
  - favor *trans* confirmation and reduce cyclization

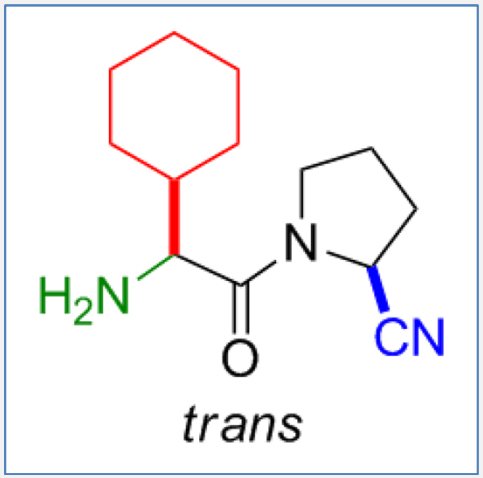


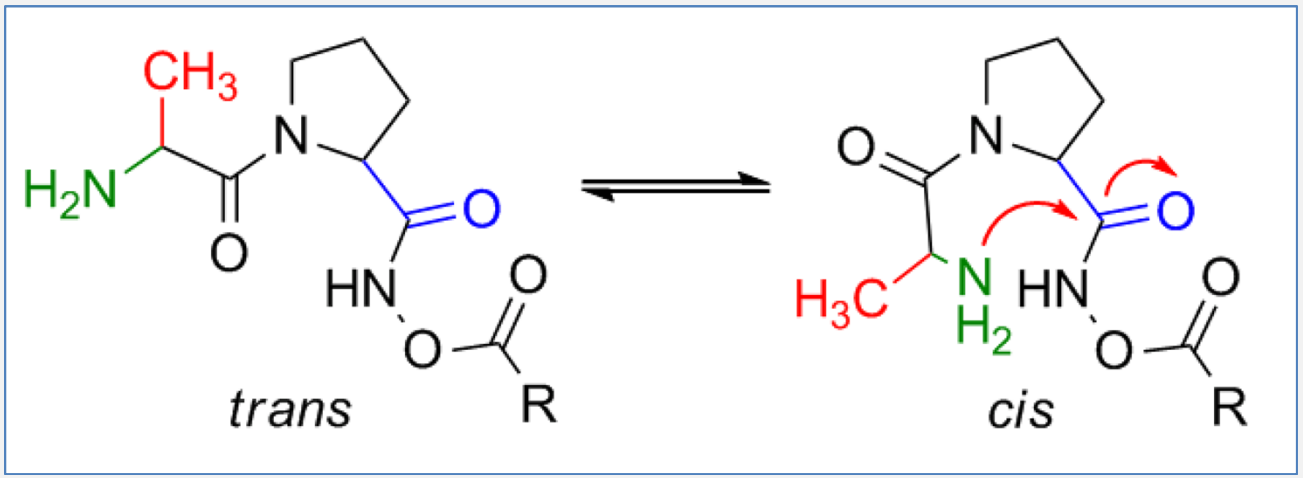
Cyclization



Source: Pet. at 7, 24; EX1003 (Rotella Decl.), ¶¶ 114-15; EX1007 at 1165-66.

Intramolecular Cyclization Favored in *Cis*-Conformation

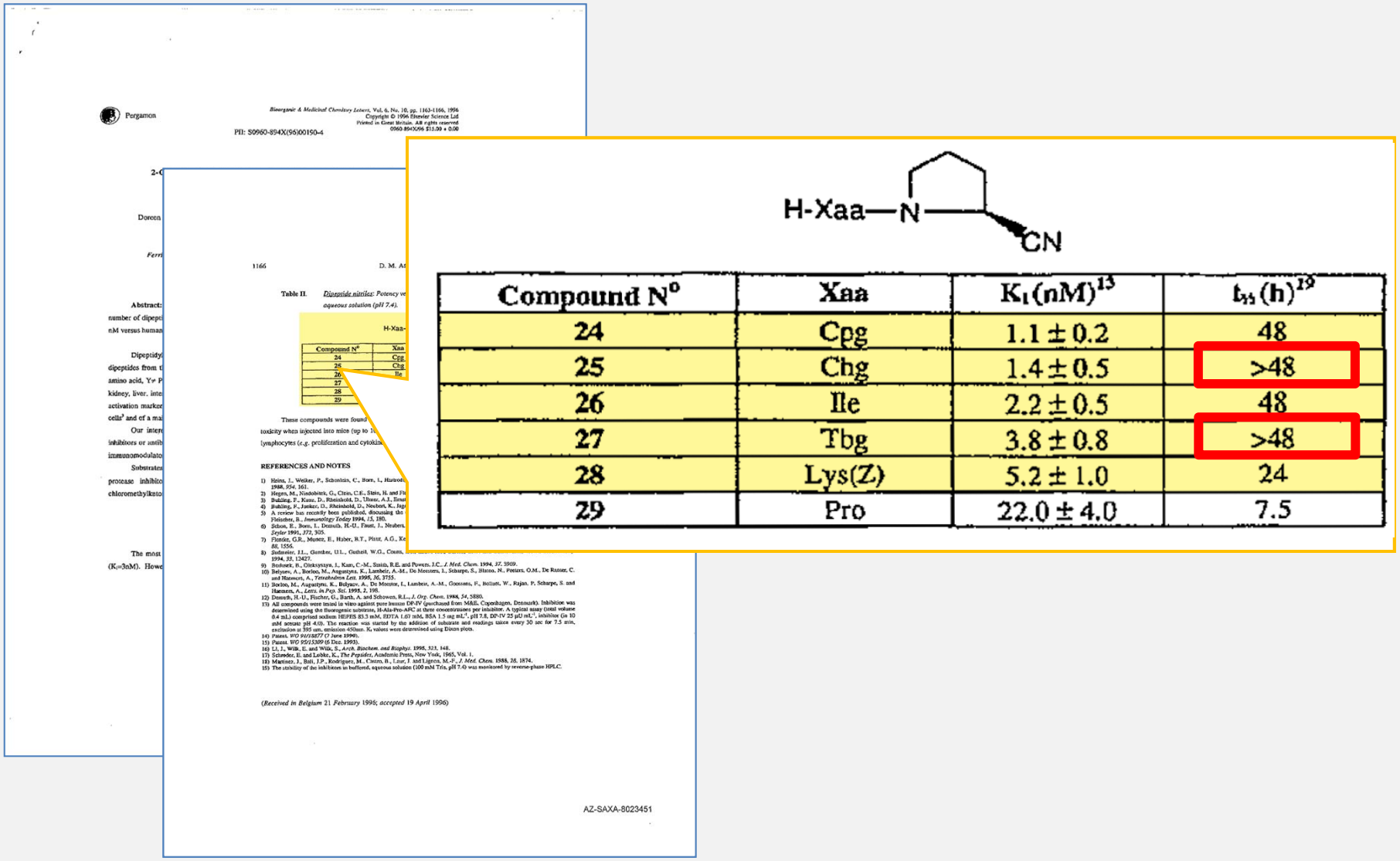




Intramolecular cyclization is minimized by favoring *trans*-conformation, instead of *cis*-conformation.

Source: EX1003 (Rotella Decl.), ¶¶46-47; EX1015 (Lin) at 14022; Pet. at 7.

Bulky P2 Groups Improve Stability

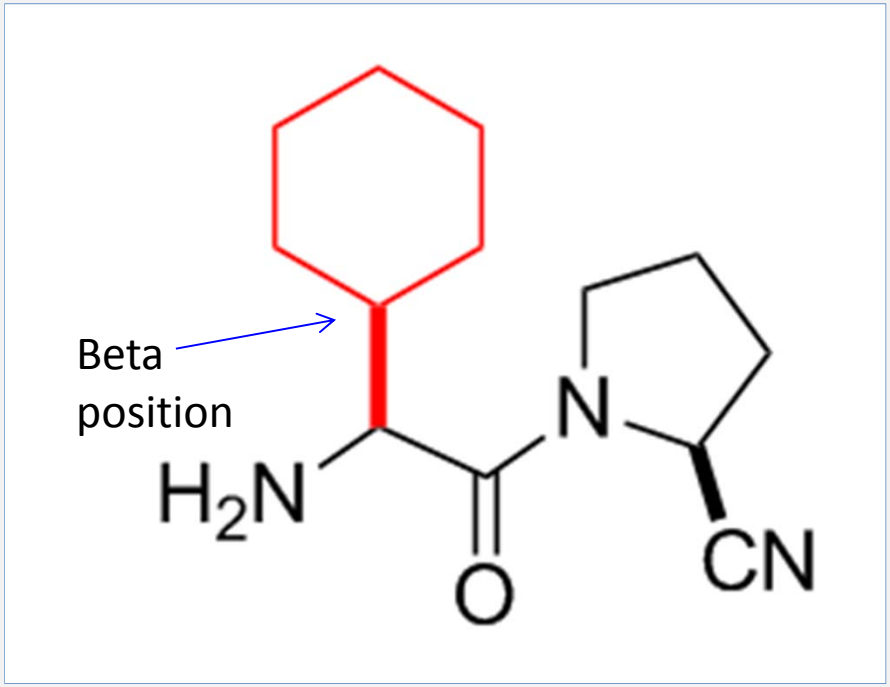


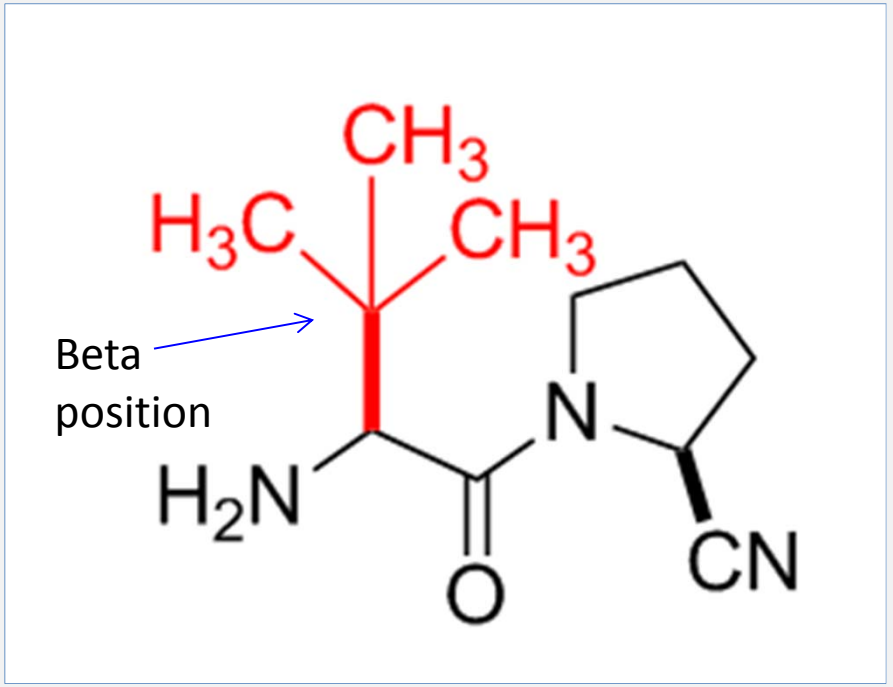
H-Xaa—N—CN

Compound N°	Xaa	K_i (nM)[13]	$t_{1/2}$ (h)[19]
24	Cpg	1.1 ± 0.2	48
25	Chg	1.4 ± 0.5	>48
26	Ile	2.2 ± 0.5	48
27	Tbg	3.8 ± 0.8	>48
28	Lys(Z)	5.2 ± 1.0	24
29	Pro	22.0 ± 4.0	7.5

Source: EX1007 (Ashworth I) at 1165-66; EX1074 (Second Rotella Decl.), ¶19.

Steric Bulk Localized at the Beta Position





Ashworth I Compound 25

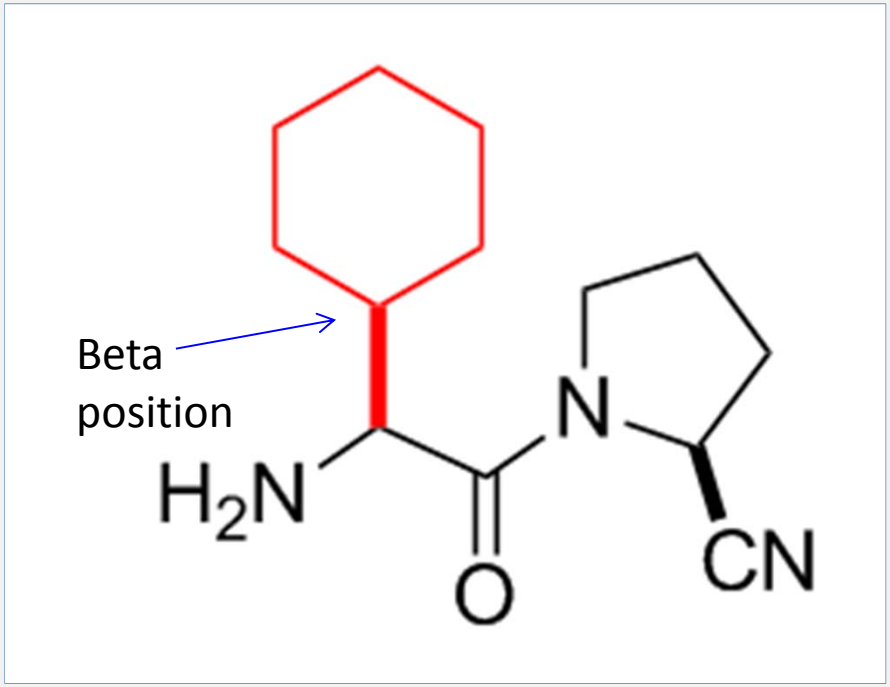
$t_{1/2}$= >48 h
K_i = 1.4 ± 0.5 nm

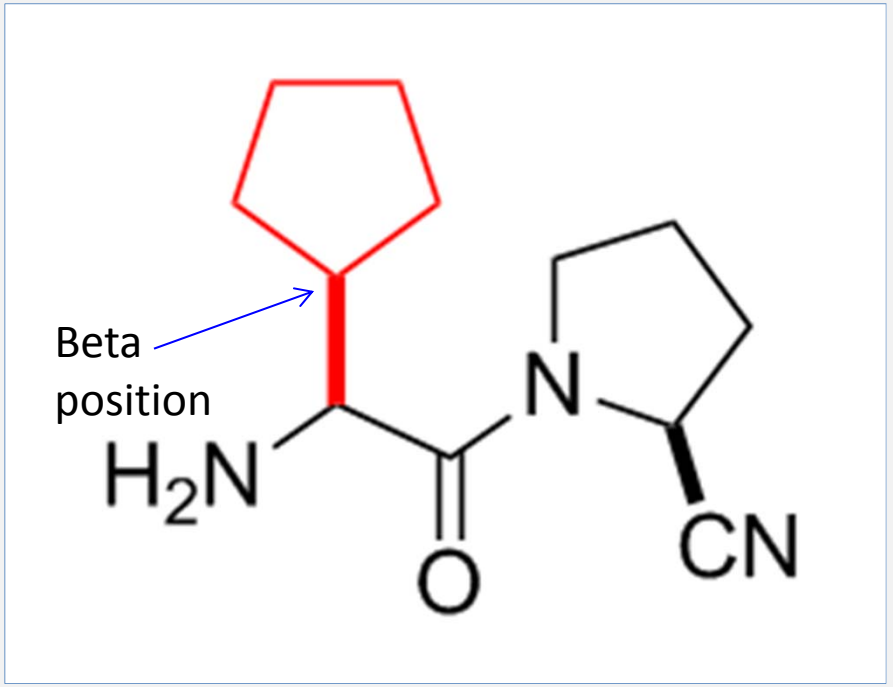
Ashworth I Compound 27

$t_{1/2}$= >48 h
K_i = 3.8 ± 0.8 nm

Source: EX1007 (Ashworth I) at Table 2; EX1074 (Second Rotella Decl.), ¶24.

Steric Bulk Localized at the Beta Position





Ashworth I Compound 25

$t_{1/2}$= >48 h
K_i = 1.4 ± 0.5 nm

Ashworth I Compound 24

$t_{1/2}$= 48 h
K_i = 1.1 ± 0.2 nm

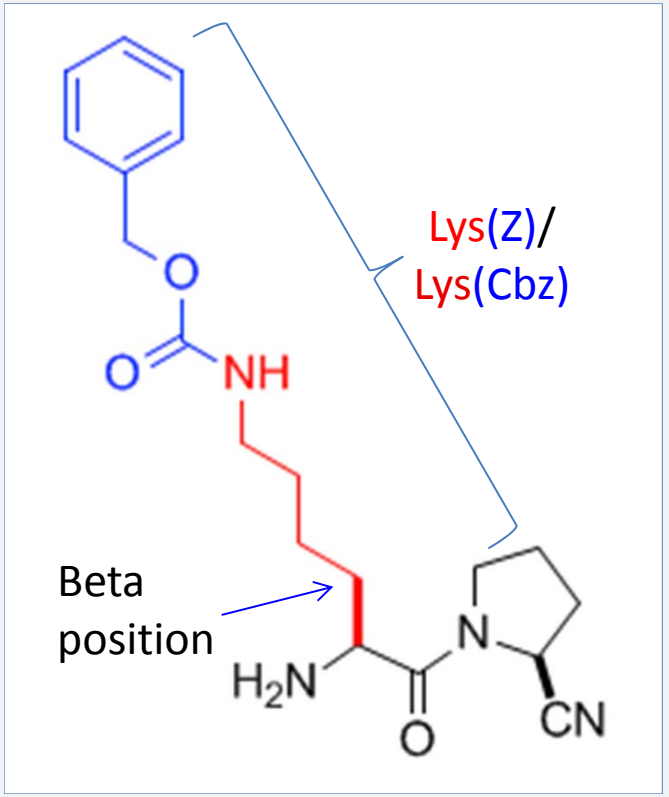
Source: EX1007 (Ashworth I) at Table 2; EX1074 (Second Rotella Decl.), ¶24.

More Atoms Alone ≠ Steric Bulk

Lys(Z) group is longer with more atoms.

Lys(Z) is less sterically bulky compared to a cyclohexyl group, with a smaller footprint at the β-position.

Lys(Z) has decreased stability compared to a cyclohexyl substituent.



Ashworth I Compound 28

$t_{1/2}$= 24 h

Source: EX1007 (Ashworth I) at Table 2; EX1074 (Second Rotella Decl.), ¶24; EX2261 (PO Demonstrative).

Use of Adamantyl at P2 was Known in DPP-4 Inhibitors

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION International Bureau

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(21) International Application Number: PCT/EP97/06125

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(30) Priority Data: 08/746,205 7 November 1996 (07.11.96) US

(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).

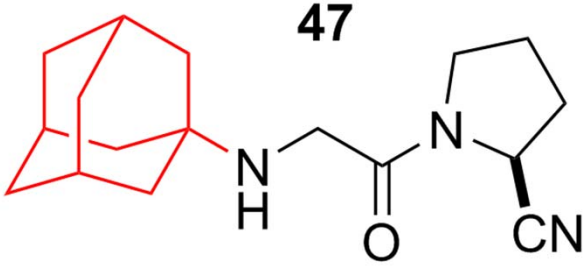
(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, 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



Example No.	R	Form	Analogously to Ex. No	
34	[S,S]-(1-hydroxymethyl)propyl	ch	1[11]	
35	[2-[(2-hydroxymethyl)phenyl]thio]phenylmethyl	ch	1[12]	
36	2-(2-methoxyphenyl)ethyl	ch	1	
37	5-hydroxypentyl	ch	1	
38	cyclobutyl	ch	1	off
39	2-(2,4-dichlorophenyl)ethyl	ch	1	
40	1-(S)-(+)-hydroxymethyl-3-methylbutyl	ch	1[13]	
41	[1R*,2S*]-2-hydroxy-2-phenylethyl	ch		
42	2-(2-fluorophenyl)ethyl	ch		
43	cyclopropyl			
44	[1S[1S,2S,3S,5R]]-2,6,6-trimethylbicyc[3.1.1]hept-3-yl		1[15]	
45	(2-phenoxy)ethyl	ch	1	
46	2-(3,5-dimethoxyphe...)ethyl	ch	1	
47	1-adamantyl	ch	1	white solid; m.p. 240-242°; ¹³C-NMR: 121.80 (ppm)
48	1,1,3,3-tetramethylbutyl	ch	1	white fluffy solid; m.p. 68-70°; ¹³C-NMR: 121.55 (ppm)
49	2-adamantyl	ch	1	off-white solid; m.p. 122-124°; ¹³C-NMR: 121.69 (ppm)
50	1,1-dimethylpropyl	ch	1	white fluffy solid; m.p. 62-64°; ¹³C-NMR: 121.53 (ppm)
51	benzyl	ch	1	white solid; m.p. 58-60°; ¹³C-NMR: 121.38 (ppm)
52	1,1-dimethylethyl	ch	1	white solid; m.p. 226-228°; ¹³C-NMR: 121.56 (ppm)
53	(2-adamantyl)methyl	ch	1	white solid; m.p. 158-160°; ¹³C-NMR: 121.53 (ppm)
54	2-phenylethyl	ch	1	white solid; m.p. 275-280° (dec.); ¹³C-NMR: 121.52 (ppm)
55	pentyl	ch	1	white solid; m.p. 176-178°; ¹³C-NMR: 121.67 (ppm)
56	butyl	ch	1	white solid; m.p. 180-182°; ¹³C-NMR: 121.53 (ppm)

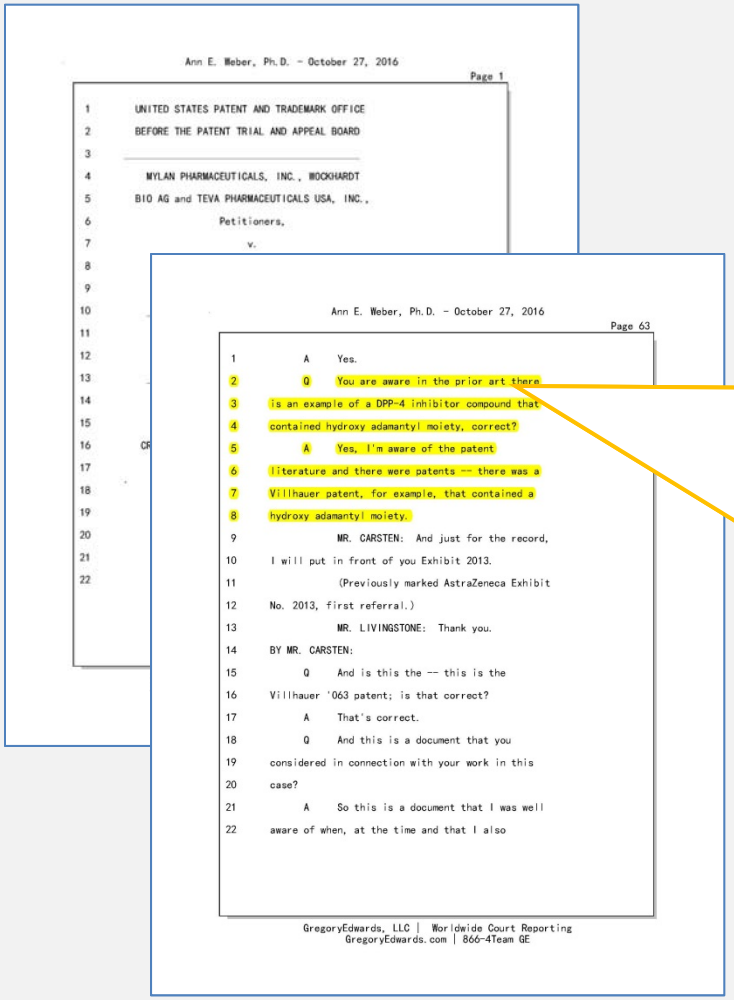
47 **1-adamantyl**

49 **2-adamantyl**

53 **(2-adamantyl)methyl**

Source: EX1008 (Villhauer WO '98) at 13; EX1074 (Second Rotella Decl.), ¶20.

Hydroxyadamantyl Was Known From Villhauer 2000



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.

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

Page 63

A Yes.
Q You are aware in the prior art there is an example of a DPP-4 inhibitor compound that contained hydroxy adamantyl moiety, correct?
A Yes, I'm aware of the patent literature and there were patents -- there was a Villhauer patent, for example, that contained a hydroxy adamantyl moiety.
MR. CARSTEN: And just for the record, I will put in front of you Exhibit 2013.
(Previously marked AstraZeneca Exhibit No. 2013, first referral.)
MR. LIVINGSTONE: Thank you.
BY MR. CARSTEN:
Q And is this the -- this is the Villhauer '063 patent; is that correct?
A That's correct.
Q And this is a document that you considered in connection with your work in this case?
A So this is a document that I was well aware of when, at the time and that I also

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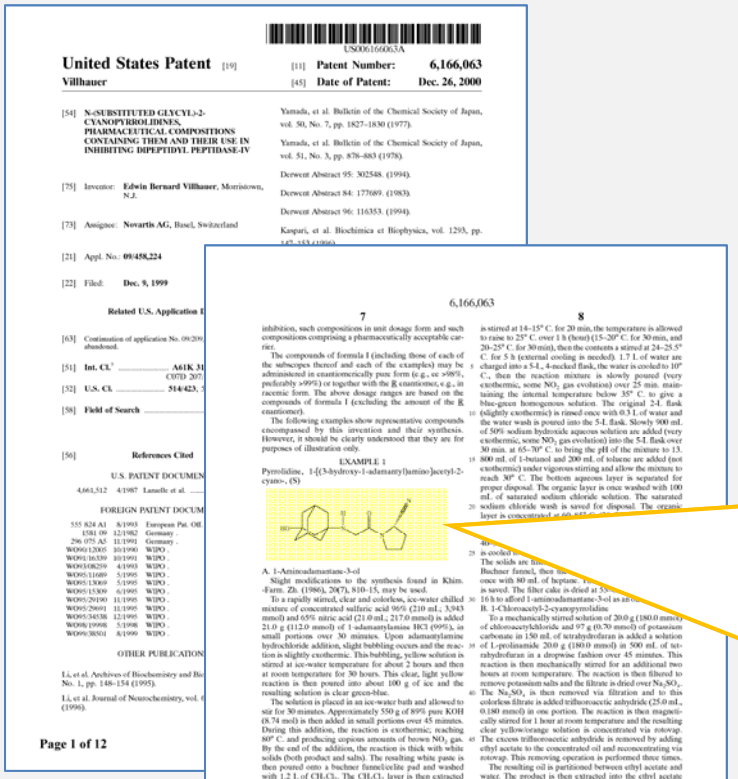
Q You are aware in the prior art there is an example of a DPP-4 inhibitor compound that contained hydroxy adamantyl moiety, correct?

A Yes, I'm aware of the patent literature and there were patents -- there was a Villhauer patent, for example, that contained a hydroxy adamantyl moiety.

Source: EX1073 (Weber Depo. Trans.), 63:2-8; EX1074 (Second Rotella Decl.), ¶33; EX2013 (Villhauer 2000), 7:15-27 .

Hydroxyadamantyl at P2 was Known in DPP-4 Inhibitors



United States Patent [19]
Villhauer

[11] Patent Number: 6,166,063
[45] Date of Patent: Dec. 26, 2000

[54] N-(SUBSTITUTED GLYCYL)-2-CYANOPYRROLIDINES, 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

[21] Appl. No.: 09/458,224

[22] Filed: Dec. 9, 1999

Related U.S. Application Data

[63] Continuation of application No. 09/20... abandoned.

[51] Int. Cl.[7] ..... A61K 31... C07D 207...

[52] U.S. Cl. ..... 514/423; ...

[58] Field of Search .....

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WO95/11689 5/1995 WIPO .
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WO95/34538 12/1995 WIPO .
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Yamada, et al. Bulletin of the Chemical Society of Japan, vol. 50, No. 7, pp. 1827–1830 (1977).

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Derwent Abstract 95: 302548. (1994).

Derwent Abstract 84: 177689. (1983).

Derwent Abstract 96: 116353. (1994).

Kaspari, et al. Biochimica et Biophysica, vol. 1293, pp. ...

Page 1 of 12

6,166,063

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inhibition, such compositions in unit dosage form and such compositions comprising a pharmaceutically acceptable carrier.

The compounds of formula I (including those of each of the subscopes thereof and each of the examples) may be administered in enantiomerically pure form (e.g., ee >98%, preferably >99%) or together with the R enantiomer, e.g., in racemic form. The above dosage ranges are based on the compounds of formula I (excluding the amount of the R enantiomer).

The following examples show representative compounds encompassed by this invention and their synthesis. However, it should be clearly understood that they are for purposes of illustration only.

EXAMPLE 1

Pyrrolidine, 1-[(3-hydroxy-1-adamanty)amino]acetyl-2-cyano-, (S)

A. 1-Aminoadamantane-3-ol

Slight modifications to the synthesis found in Khim.-Farm. Zh. (1986), 20(7), 810–15, may be used.

To a rapidly stirred, clear and colorless, ice-water chilled mixture of concentrated sulfuric acid 96% (210 mL; 3,943 mmol) and 65% nitric acid (21.0 mL, 217.0 mmol) is added 21.0 g (112.0 mmol) of 1-adamantylamine HCl (99%), in small portions over 30 minutes. Upon adamantylamine hydrochloride addition, slight bubbling occurs and the reaction is slightly exothermic. This bubbling, yellow solution is stirred at ice-water temperature for about 2 hours and then at room temperature for 30 hours. This clear, light yellow reaction is then poured into about 100 g of ice and the resulting solution is clear green-blue.

The solution is placed in an ice-water bath and allowed to stir for 30 minutes. Approximately 550 g of 89% pure KOH (8.74 mol) is then added in small portions over 45 minutes. During this addition, the reaction is exothermic, reaching 80° C. and producing copious amounts of brown NO_2 gas. By the end of the addition, the reaction is thick with white solids (both product and salts). The resulting white paste is then poured onto a buchner funnel/celite pad and washed with 1.2 L of CH_2Cl_2. The CH_2Cl_2 layer is then extracted from the water layer and dried over Na_2SO_4. The solution is then filtered and concentrated (rotovap pump) to provide 1-aminoadamantane-3-ol as a white solid.

Alternatively, the reaction may be carried out using n-butanol as solvent instead of methylene chloride.

Alternatively, 1-aminoadamantane-3-ol can be prepared e.g. as follows: A 2-L, 4-necked, round-bottomed flask is thoroughly flushed with nitrogen. The flask is charged under nitrogen with 420 mL of conc. sulfuric acid (98%). The contents are cooled to 8° C., then slowly (slightly exothermic & HCl gas evolution) 100.6 g of 1-aminoadamantane hydrochloride are added into the mixture in 8 portions at 9–10° C. over 20 min (minutes), then the hazy contents are stirred at 9–10° C. for 20 min to obtain a homogeneous mixture. 72 mL of conc. (concentrated) nitric acid (70%) are added (very exothermic) dropwise into the mixture maintaining inner temperature at 14–15° C. with efficient cooling (at this scale 20 min. needed for this addition). The mixture

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is stirred at 14–15° C. for 20 min, the temperature is allowed to raise to 25° C. over 1 h (hour) (15–20° C. for 30 min, and 20–25° C. for 30 min), then the contents a stirred at 24–25.5° C. for 5 h (external cooling is needed). 1.7 L of water are charged into a 5-L, 4-necked flask, the water is cooled to 10° C., then the reaction mixture is slowly poured (very exothermic, some NO_2 gas evolution) over 25 min. maintaining the internal temperature below 35° C. to give a blue-green homogeneous solution. The original 2-L flask (slightly exothermic) is rinsed once with 0.3 L of water and the water wash is poured into the 5-L flask. Slowly 900 mL of 50% sodium hydroxide aqueous solution are added (very exothermic, some NO_2 gas evolution) into the 5-L flask over 30 min. at 65–70° C. to bring the pH of the mixture to 13. 800 mL of 1-butanol and 200 mL of toluene are added (not exothermic) under vigorous stirring and allow the mixture to reach 30° C. The bottom aqueous layer is separated for proper disposal. The organic layer is once washed with 100 mL of saturated sodium chloride solution. The saturated sodium chloride wash is saved for disposal. The organic layer is concentrated

is cooled

The solids are filte... Buchner funnel, then ... once with 80 mL of heptane. ... is saved. The filter cake is dried at 5...

10 h to afford 1-aminoadamantane-3-ol as a...

B. 1-Chloroacetyl-2-cyanopyrrolidine

To a mechanically stirred solution of 20.0 g (180.0 mmol) of chloroacetylchloride and 97 g (0.70 mmol) of potassium carbonate in 150 mL of tetrahydrofuran is added a solution of L-prolinamide 20.0 g (180.0 mmol) in 500 mL of tetrahydrofuran in a dropwise fashion over 45 minutes. This reaction is then mechanically stirred for an additional two hours at room temperature. The reaction is then filtered to remove potassium salts and the filtrate is dried over Na_2SO_4. The Na_2SO_4 is then removed via filtration and to this colorless filtrate is added trifluoroacetic anhydride (25.0 mL, 0.180 mmol) in one portion. The reaction is then magnetically stirred for 1 hour at room temperature and the resulting clear yellow/orange solution is concentrated via rotovap. The excess trifluoroacetic anhydride is removed by adding ethyl acetate to the concentrated oil and reconcentrating via rotovap. This removing operation is performed three times.

The resulting oil is partitioned between ethyl acetate and water. The product is then extracted into the ethyl acetate and the aqueous layer is then washed twice with ethyl acetate. The combined organic layers are then washed successively with water and brine dried over magnesium sulfate, filtered and concentrated to obtain 1-chloroacetyl-2-cyanopyrrolidine as a yellow solid.

Alternatively, the reaction may be carried out by using, as base, a mixture, e.g. 2-ethyl-hexanoic acid/sodium hydrate.

C. Pyrrolidine, 1-[(3-hydroxy-1-adamanty)amino]acetyl-2-cyano-, (S)

To a heterogeneous solution of the title A compound (1-aminoadamantane-3-ol (5.80 g, 34.7 mmol) in CH_2Cl_2 (68.0 mL) is added 9.6 g (69 mmol) of K_2CO_3. This heterogeneous mixture is then cooled in an ice-water bath and a solution of 7.0 g (17 mmol) of the title B compound (1-chloroacetyl-2-cyanopyrrolidine) dissolved in 23.0 mL of CH_2Cl_2 is added dropwise over a period of 30 minutes. The resulting mixture is stirred for 2 hours at 0° C. and at room temperature for 6 days. The reaction is then concentrated to

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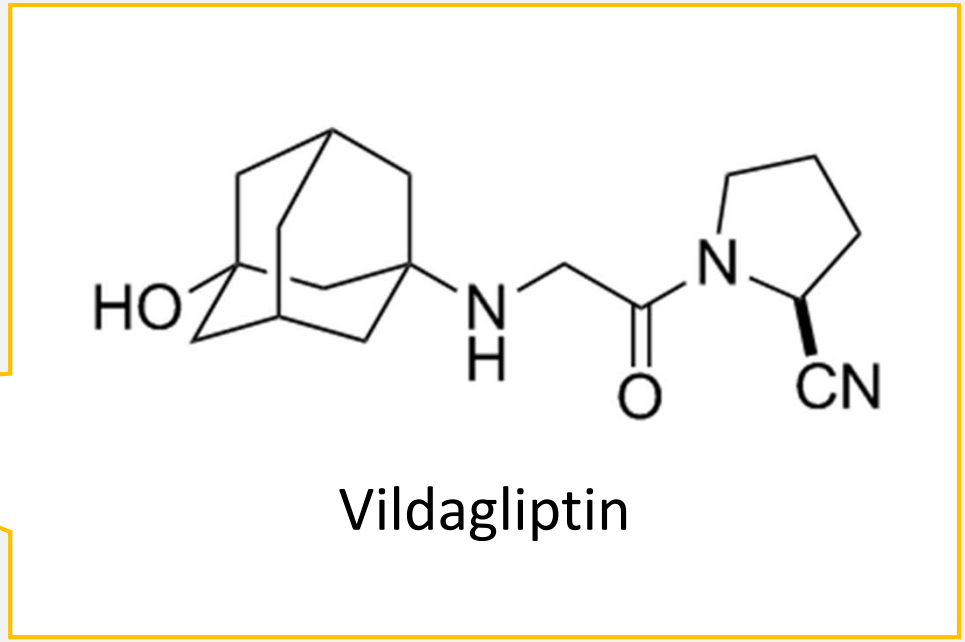
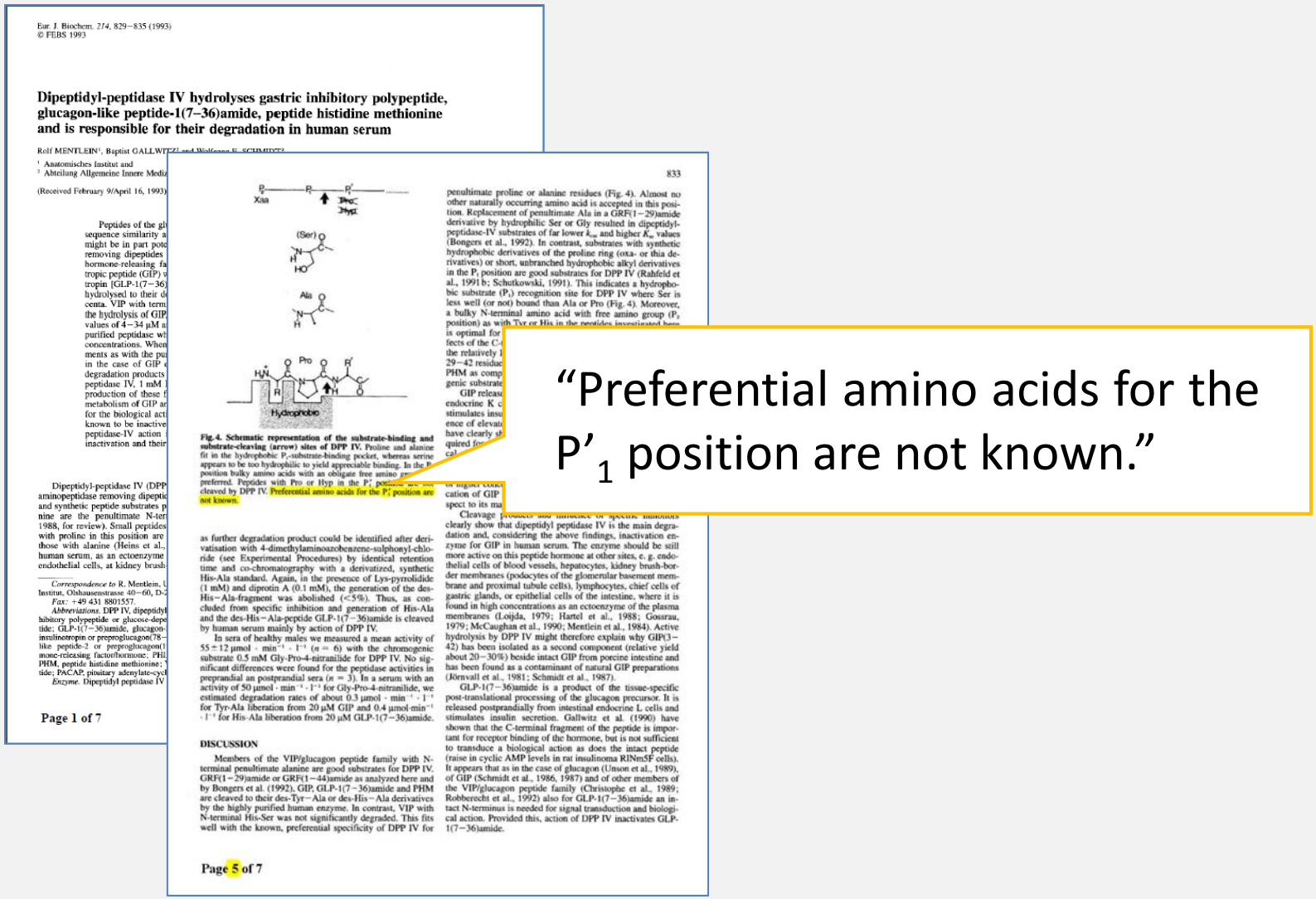


Vildagliptin

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

Patent Owner Cites Mentlein 1993



Eur. J. Biochem. 214, 829–835 (1993)
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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

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

[1] Anatomisches Institut and
[2] Abteilung Allgemeine Innere Mediz

(Received February 9/April 16, 1993)

Page 1 of 7

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Fig. 4. Schematic representation of the substrate-binding and substrate-cleaving (arrow) sites of DPP IV. Proline and alanine fit in the hydrophobic P_1-substrate-binding pocket, whereas serine appears to be too hydrophilic to yield appreciable binding. In the P_2 position bulky amino acids with an obligate free amino g… preferred. Peptides with Pro or Hyp in the P_1 position are … cleaved by DPP IV. Preferential amino acids for the P'_1 position are not known.

DISCUSSION

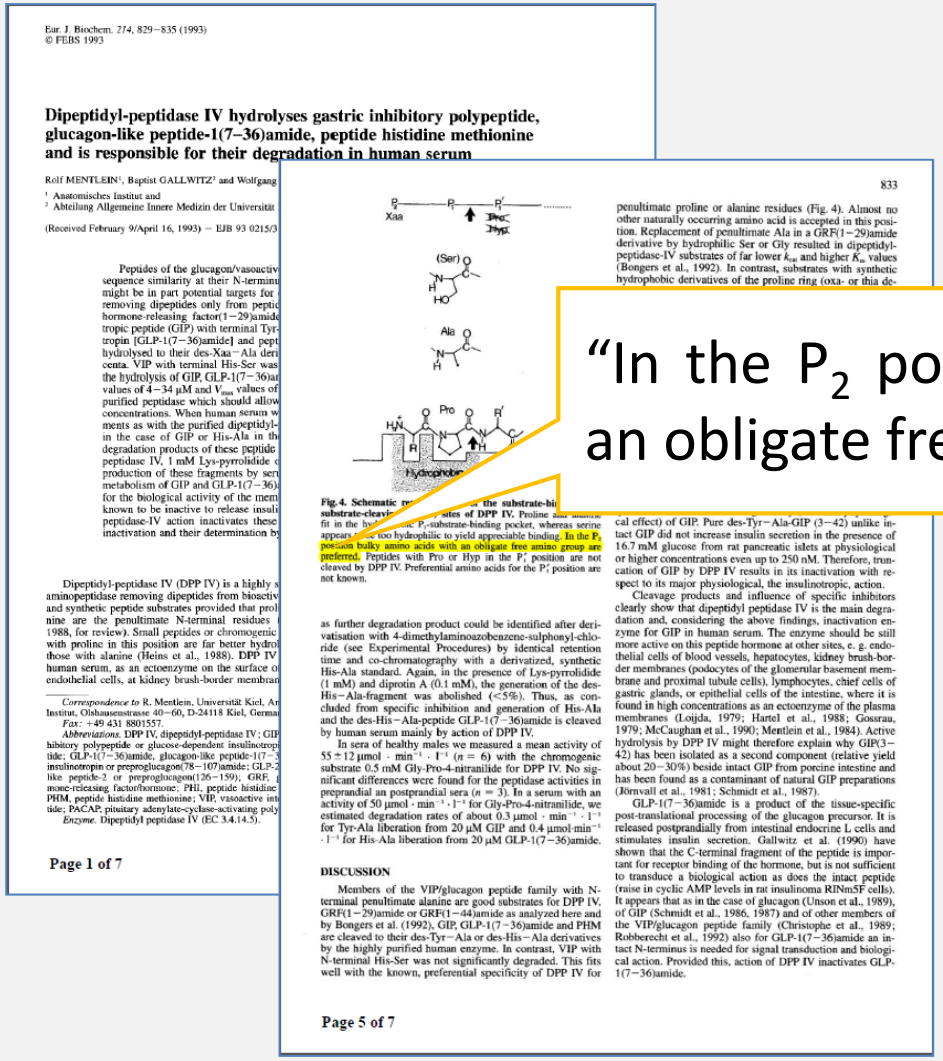
Members of the VIP/glucagon peptide family with N-terminal penultimate alanine are good substrates for DPP IV. GRF(1–29)amide or GRF(1–44)amide as analyzed here and by Bongers et al. (1992), GIP, GLP-1(7–36)amide and PHM are cleaved to their des-Tyr–Ala or des-His–Ala derivatives by the highly purified human enzyme. In contrast, VIP with N-terminal His-Ser was not significantly degraded. This fits well with the known, preferential specificity of DPP IV for

Page 5 of 7

"Preferential amino acids for the P'_1 position are not known."

Source: EX2056 (Weber Decl.), ¶91; EX2096 (Mentlein) at 833.

Mentlein: Bulky Groups are Preferred at P2



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[2] Abteilung Allgemeine Innere Medizin der Universität

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

Peptides of the glucagon/vasoactiv
sequence similarity at their N-terminu
might be in part potential targets for
removing dipeptides only from peptic
hormone-releasing factor(1–29)amide
tropic peptide (GIP) with terminal Tyr-
tropin [GLP-1(7–36)amide] and pept
hydrolysed to their des-Xaa–Ala deri
centa. VIP with terminal His-Ser was
the hydrolysis of GIP, GLP-1(7–36)ar
values of 4–34 μM and V_{max} values of
purified peptidase which should allow
concentrations. When human serum w
ments as with the purified dipeptidyl-
in the case of GIP or His-Ala in th
degradation products of these peptide
peptidase IV, 1 mM Lys-pyrrolidide
production of these fragments by seri
metabolism of GIP and GLP-1(7–36)
for the biological activity of the mem
known to be inactive to release insuli
peptidase-IV action inactivates these
inactivation and their determination by

Dipeptidyl-peptidase IV (DPP IV) is a highly
aminopeptidase removing dipeptides from bioactiv
and synthetic peptide substrates provided that prol
nine are the penultimate N-terminal residues
1988, for review). Small peptides or chromogenic
with proline in this position are far better hydrol
those with alanine (Heins et al., 1988). DPP IV
human serum, as an ectoenzyme on the surface o
endothelial cells, at kidney brush-border membran

Correspondence to R. Mentlein, Universität Kiel, An
Institut, Olshausenstrasse 40–60, D-24118 Kiel, Germa
Fax: +49 431 8801557.
Abbreviations. DPP IV, dipeptidyl-peptidase IV; GIP
hibitory polypeptide or glucose-dependent insulinotrop
tide; GLP-1(7–36)amide, glucagon-like peptide-1(7–3
insulinotropin or preproglucagon(78–107)amide; GLP-2
like peptide-2 or preproglucagon(126–159); GRF,
mone-releasing factor/hormone; PHI, peptide histidine
PHM, peptide histidine methionine; VIP, vasoactive int
tide; PACAP, pituitary adenylate-cyclase-activating poly
Enzyme. Dipeptidyl peptidase IV (EC 3.4.14.5).

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penultimate proline or alanine residues (Fig. 4). Almost no other naturally occurring amino acid is accepted in this position. Replacement of penultimate Ala in a GRF(1–29)amide derivative by hydrophilic Ser or Gly resulted in dipeptidyl-peptidase-IV substrates of far lower k_{cat} and higher K_m values (Bongers et al., 1992). In contrast, substrates with synthetic hydrophobic derivatives of the proline ring (oxa- or thia de-

Fig. 4. Schematic r… the substrate-bi…
substrate-cleavi… sites of DPP IV. Proline …
fit in the hy… P₁-substrate-binding pocket, whereas serine
appears … too hydrophilic to yield appreciable binding. In the P_2 position bulky amino acids with an obligate free amino group are preferred. Peptides with Pro or Hyp in the P'_1 position are not cleaved by DPP IV. Preferential amino acids for the P'_1 position are not known.

cal effect) of GIP. Pure des-Tyr–Ala-GIP (3–42) unlike intact GIP did not increase insulin secretion in the presence of 16.7 mM glucose from rat pancreatic islets at physiological or higher concentrations even up to 250 nM. Therefore, truncation of GIP by DPP IV results in its inactivation with respect to its major physiological, the insulinotropic, action.

Cleavage products and influence of specific inhibitors clearly show that dipeptidyl peptidase IV is the main degradation and, considering the above findings, inactivation enzyme for GIP in human serum. The enzyme should be still more active on this peptide hormone at other sites, e. g. endothelial cells of blood vessels, hepatocytes, kidney brush-border membranes (podocytes of the glomerular basement membrane and proximal tubule cells), lymphocytes, chief cells of gastric glands, or epithelial cells of the intestine, where it is found in high concentrations as an ectoenzyme of the plasma membranes (Loijda, 1979; Hartel et al., 1988; Gossrau, 1979; McCaughan et al., 1990; Mentlein et al., 1984). Active hydrolysis by DPP IV might therefore explain why GIP(3–42) has been isolated as a second component (relative yield about 20–30%) beside intact GIP from porcine intestine and has been found as a contaminant of natural GIP preparations (Jörnvall et al., 1981; Schmidt et al., 1987).

GLP-1(7–36)amide is a product of the tissue-specific post-translational processing of the glucagon precursor. It is released postprandially from intestinal endocrine L cells and stimulates insulin secretion. Gallwitz et al. (1990) have shown that the C-terminal fragment of the peptide is important for receptor binding of the hormone, but is not sufficient to transduce a biological action as does the intact peptide (raise in cyclic AMP levels in rat insulinoma RINm5F cells). It appears that as in the case of glucagon (Unson et al., 1989), of GIP (Schmidt et al., 1986, 1987) and of other members of the VIP/glucagon peptide family (Christophe et al., 1989; Robberecht et al., 1992) also for GLP-1(7–36)amide an intact N-terminus is needed for signal transduction and biological action. Provided this, action of DPP IV inactivates GLP-1(7–36)amide.

as further degradation product could be identified after derivatisation with 4-dimethylaminoazobenzene-sulphonyl-chloride (see Experimental Procedures) by identical retention time and co-chromatography with a derivatized, synthetic His-Ala standard. Again, in the presence of Lys-pyrrolidide (1 mM) and diprotin A (0.1 mM), the generation of the des-His–Ala-fragment was abolished (<5%). Thus, as concluded from specific inhibition and generation of His-Ala and the des-His–Ala-peptide GLP-1(7–36)amide is cleaved by human serum mainly by action of DPP IV.

In sera of healthy males we measured a mean activity of 55 ± 12 μmol · min^{-1} · l^{-1} (n = 6) with the chromogenic substrate 0.5 mM Gly-Pro-4-nitranilide for DPP IV. No significant differences were found for the peptidase activities in preprandial an postprandial sera (n = 3). In a serum with an activity of 50 μmol · min^{-1} · l^{-1} for Gly-Pro-4-nitranilide, we estimated degradation rates of about 0.3 μmol · min^{-1} · l^{-1} for Tyr-Ala liberation from 20 μM GIP and 0.4 μmol·min^{-1} · l^{-1} for His-Ala liberation from 20 μM GLP-1(7–36)amide.

DISCUSSION

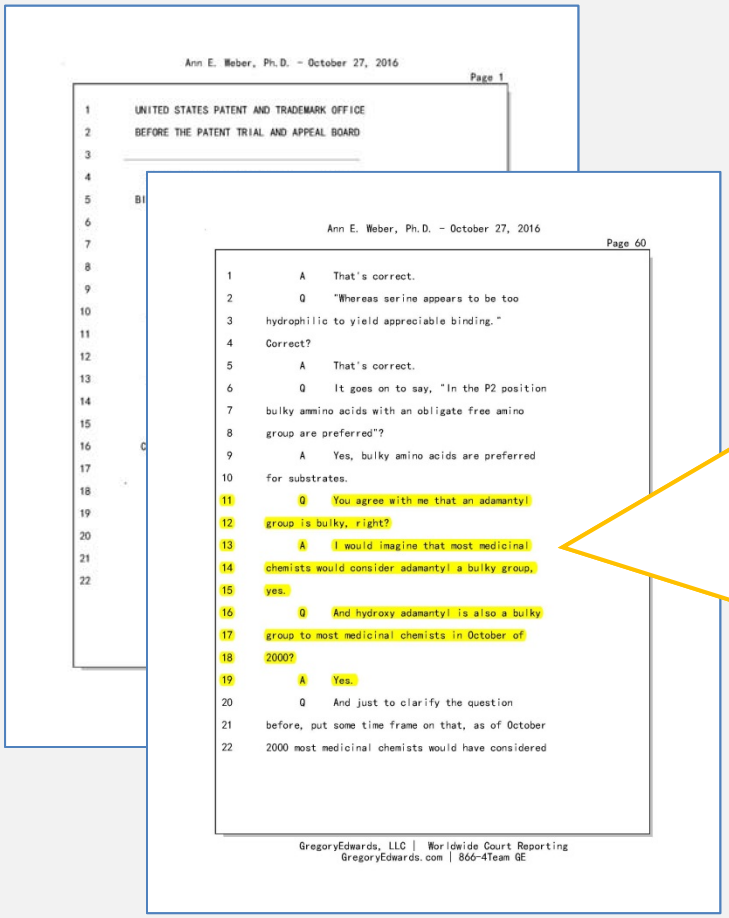
Members of the VIP/glucagon peptide family with N-terminal penultimate alanine are good substrates for DPP IV. GRF(1–29)amide or GRF(1–44)amide as analyzed here and by Bongers et al. (1992), GIP, GLP-1(7–36)amide and PHM are cleaved to their des-Tyr–Ala or des-His–Ala derivatives by the highly purified human enzyme. In contrast, VIP with N-terminal His-Ser was not significantly degraded. This fits well with the known, preferential specificity of DPP IV for

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.

Hydroxyadamantyl is a Bulky Group



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

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

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

Page 60

A That's correct.
Q "Whereas serine appears to be too hydrophilic to yield appreciable binding." Correct?
A That's correct.
Q It goes on to say, "In the P2 position bulky ammino acids with an obligate free amino group are preferred"?
A Yes, bulky amino acids are preferred for substrates.
Q You agree with me that an adamantyl group is bulky, right?
A I would imagine that most medicinal chemists would consider adamantyl a bulky group, yes.
Q And hydroxy adamantyl is also a bulky group to most medicinal chemists in October of 2000?
A Yes.
Q And just to clarify the question before, put some time frame on that, as of October 2000 most medicinal chemists would have considered

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Q You agree with me that an adamantyl group is bulky, right?

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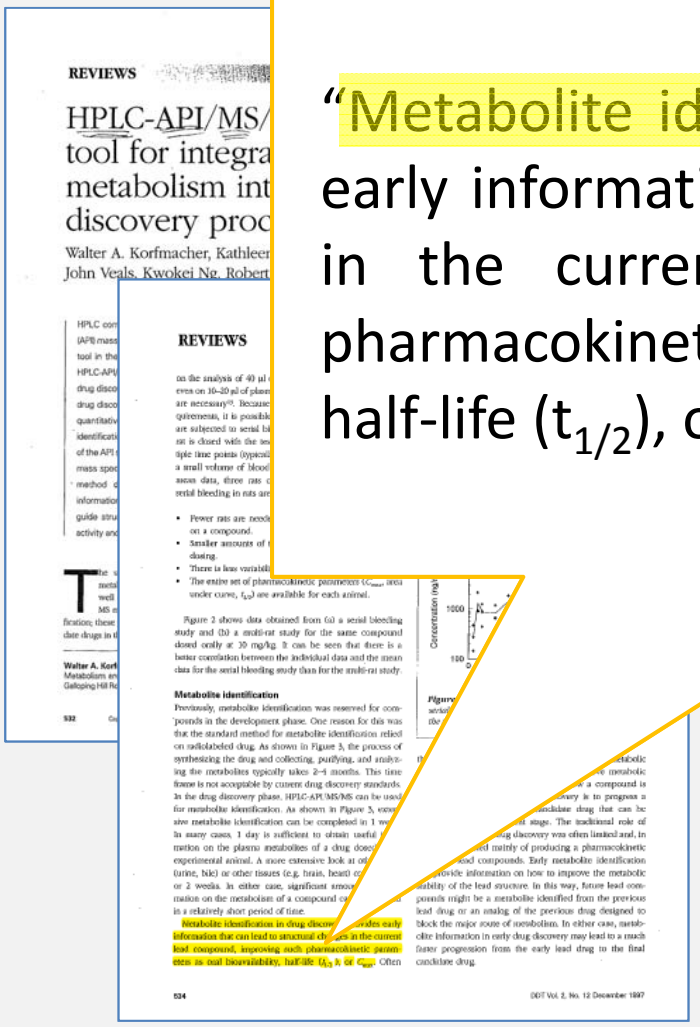
A Yes.

Source: Pet. Reply at 13; EX1073 (Weber Depo. Trans.), 60:11-19.

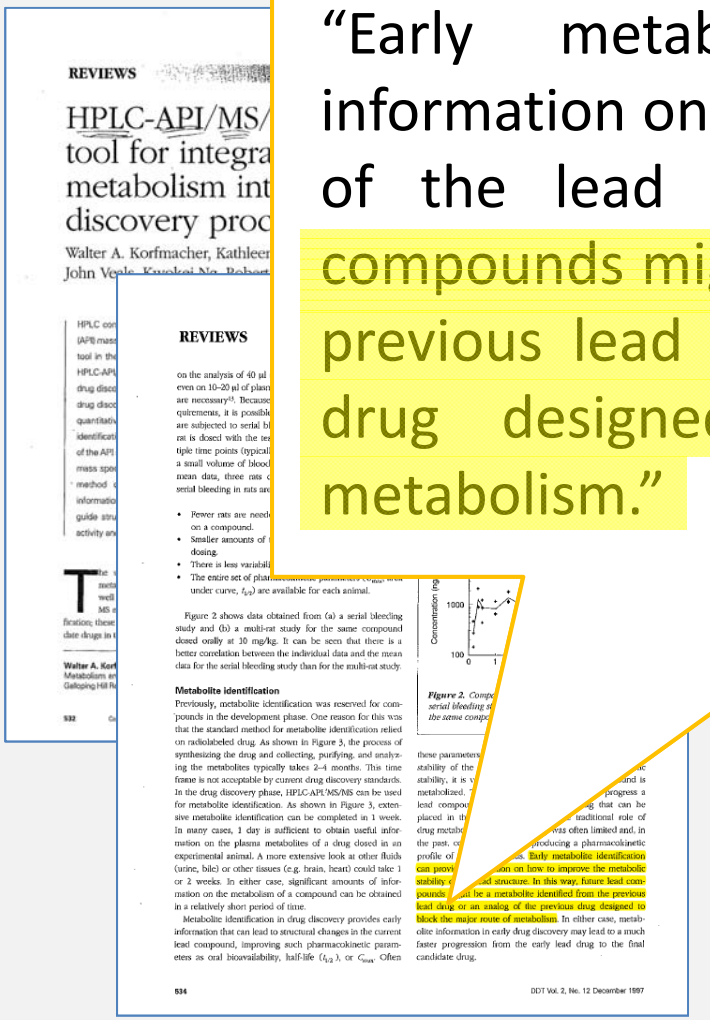
Metabolites Guide Modification of Drug Candidates



"Metabolite identification in drug discovery provides early information that can lead to structural changes in the current lead compound, improving such pharmacokinetic parameters as oral bioavailability, half-life ($t_{1/2}$), or C_{max}."

Source: EX1020 (Korfmacher) at 534; EX1003 (Rotella Decl.), ¶53.

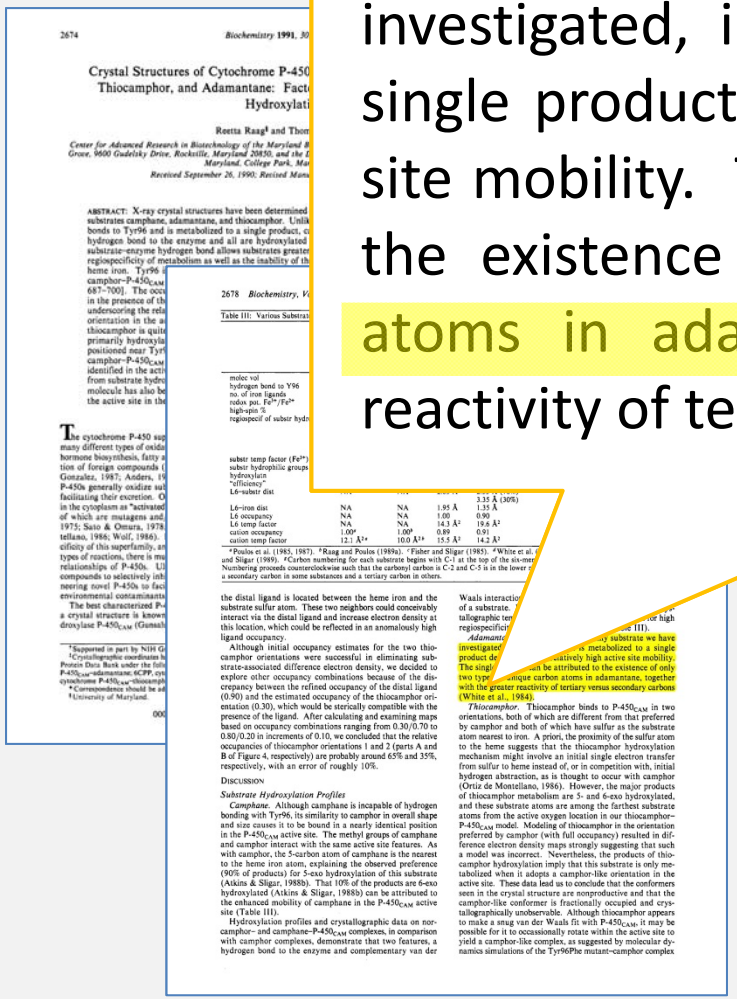
Metabolites Guide Modification of Drug Candidates



"Early metabolite identification can provide information on how to improve the metabolic stability of the lead structure. In this way, future lead compounds might be a metabolite identified from the previous lead drug or an analogue of the previous drug designed to block the major route of metabolism."

Source: EX1020 (Korfmacher) at 534; EX1003 (Rotella Decl.), ¶53.

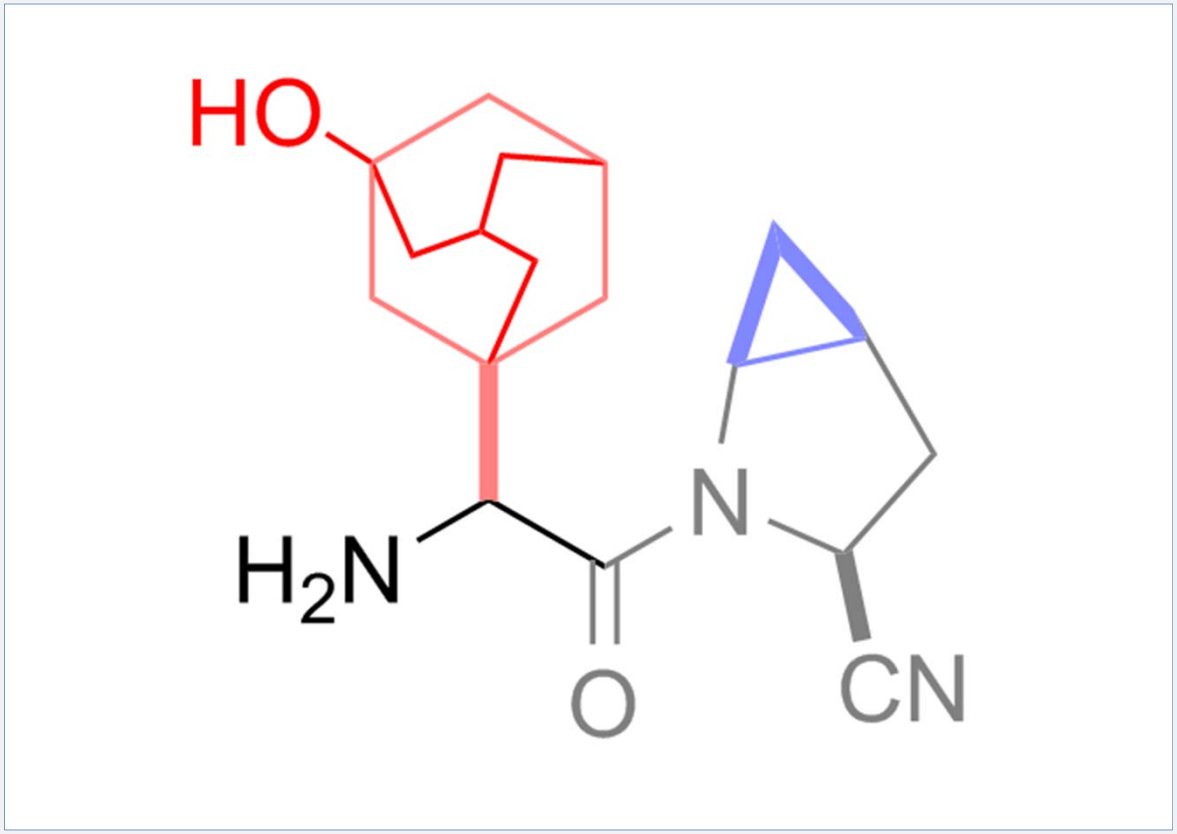
Adamantane is Metabolized at Tertiary Carbons



"Adamantane is the only substrate we have investigated, in this study, that is metabolized to a single product despite having a relatively high active site mobility. The single product can be attributed to the existence of only two types of unique carbon atoms in adamantane, together with the greater reactivity of tertiary versus secondary carbons."

Source: EX1009 (Raag) at 2678; EX1003 (Rotella Decl.), ¶¶ 80, 126.

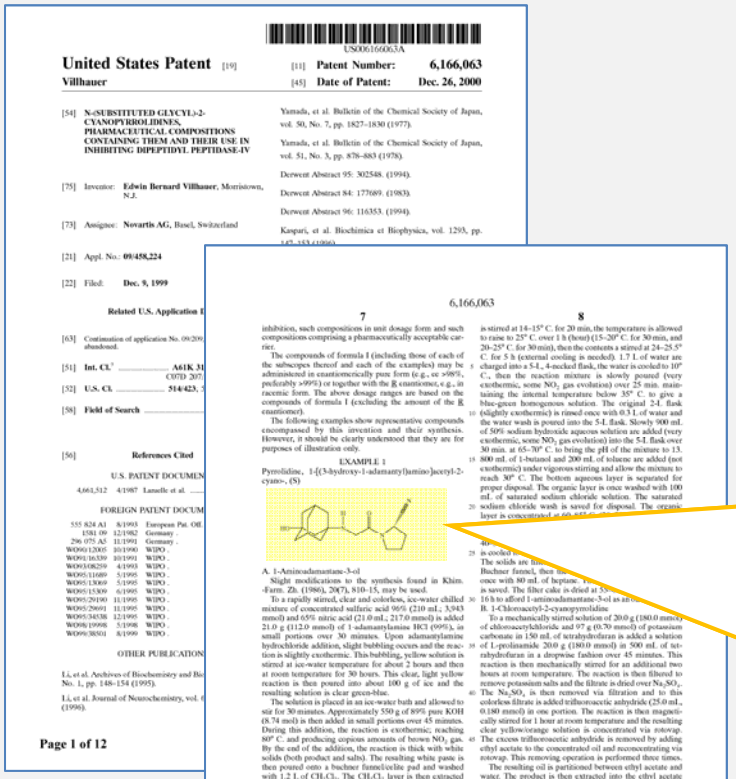
Hydroxylated Adamantane Can Impede Metabolism



"Blocking metabolism at the 3-position would result in greater metabolic stability."

Source: EX1003 (Rotella Decl.), ¶¶ 53, 127; EX1020 (Korfmacher) at 534.

Hydroxyadamantyl at P2 was Known in DPP-4 Inhibitors



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[73] Assignee: Novartis AG, Basel, Switzerland

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Kasparí, et al. Biochimica et Biophysica, vol. 1293, pp. ...

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inhibition, such compositions in unit dosage form and such compositions comprising a pharmaceutically acceptable carrier.

The compounds of formula I (including those of each of the subscopes thereof and each of the examples) may be administered in enantiomerically pure form (e.g., or >98%), preferably >99%) or together with the R enantiomer, e.g., in racemic form. The above dosage ranges are based on the compounds of formula I (excluding the amount of the R enantiomer).

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A. 1-Aminoadamantane-3-ol

Slight modifications to the synthesis found in Khim.-Farm. Zh. (1986), 20(7), 810–15, may be used.

To a rapidly stirred, clear and colorless, ice-water chilled mixture of concentrated sulfuric acid 96% (210 mL; 3,943 mmol) and 65% nitric acid (21.0 mL, 217.0 mmol) is added 21.0 g (112.0 mmol) of 1-adamantylamine HCl (99%), in small portions over 30 minutes. Upon adamantylamine hydrochloride addition, slight bubbling occurs and the reaction is slightly exothermic. This bubbling, yellow solution is stirred at ice-water temperature for about 2 hours and then at room temperature for 30 hours. This clear, light yellow reaction is then poured into about 100 g of ice and the resulting solution is clear green-blue.

The solution is placed in an ice-water bath and allowed to stir for 30 minutes. Approximately 550 g of 80% pure KOH (8.74 mol) is then added in small portions over 45 minutes. During this addition, the reaction is exothermic, reaching 80° C. and producing copious amounts of brown NO_2 gas. By the end of the addition, the reaction is thick with white solids (both product and salts). The resulting white paste is then poured onto a buchner funnel/celite pad and washed with 1.2 L of CH_2Cl_2. The CH_2Cl_2 layer is then extracted from the water layer and dried over Na_2SO_4. The solution is then filtered and concentrated (rotovap pump) to provide 1-aminoadamantane-3-ol as a white solid.

Alternatively, the reaction may be carried out using n-butanol as solvent instead of methylene chloride.

Alternatively, 1-aminoadamantane-3-ol can be prepared e.g. as follows: A 2-L, 4-necked, round-bottomed flask is thoroughly flushed with nitrogen. The flask is charged under nitrogen with 420 mL of conc. sulfuric acid (98%). The contents are cooled to 8° C., then slowly (slightly exothermic & HCl gas evolution) 100.6 g of 1-aminoadamantane hydrochloride are added into the mixture in 8 portions at 9–10° C. over 20 min (minutes), then the hazy contents are stirred at 9–10° C. for 20 min to obtain a homogenous mixture. 72 mL of conc. (concentrated) nitric acid (70%) are added (very exothermic) dropwise into the mixture maintaining inner temperature at 14–15° C. with efficient cooling (at this scale 20 min. needed for this addition). The mixture is stirred at 14–15° C. for 20 min, the temperature is allowed to raise to 25° C. over 1 h (hour) (15–20° C. for 30 min, and 20–25° C. for 30 min), then the contents a stirred at 24–25.5° C. for 5 h (external cooling is needed). 1.7 L of water are charged into a 5-L, 4-necked flask, the water is cooled to 10° C., then the reaction mixture is slowly poured (very exothermic, some NO_2 gas evolution) over 25 min. maintaining the internal temperature below 35° C. to give a blue-green homogeneous solution. The original 2-L flask (slightly exothermic) is rinsed once with 0.3 L of water and the water wash is poured into the 5-L flask. Slowly 900 mL of 50% sodium hydroxide aqueous solution are added (very exothermic, some NO_2 gas evolution) into the 5-L flask over 30 min. at 65–70° C. to bring the pH of the mixture to 13. 800 mL of 1-butanol and 200 mL of toluene are added (not exothermic) under vigorous stirring and allow the mixture to reach 30° C. The bottom aqueous layer is separated for proper disposal. The organic layer is once washed with 100 mL of saturated sodium chloride solution. The saturated sodium chloride wash is saved for disposal. The organic layer is concentrated at 60–65° C. ...

Buchner funnel, then ... once with 80 mL of heptane. ... is saved. The filter cake is dried at 55 ... 16 h to afford 1-aminoadamantane-3-ol as a ...

B. 1-Chloroacetyl-2-cyanopyrrolidine

To a mechanically stirred solution of 20.0 g (180.0 mmol) of chloroacetylchloride and 97 g (0.70 mmol) of potassium carbonate in 150 mL of tetrahydrofuran is added a solution of L-prolinamide 20.0 g (180.0 mmol) in 500 mL of tetrahydrofuran in a dropwise fashion over 45 minutes. This reaction is then mechanically stirred for an additional two hours at room temperature. The reaction is then filtered to remove potassium salts and the filtrate is dried over Na_2SO_4. The Na_2SO_4 is then removed via filtration and to this colorless filtrate is added trifluoroacetic anhydride (25.0 mL, 0.180 mmol) in one portion. The reaction is then magnetically stirred for 1 hour at room temperature and the resulting clear yellow/orange solution is concentrated via rotovap. The excess trifluoroacetic anhydride is removed by adding ethyl acetate to the concentrated oil and reconcentrating via rotovap. This removing operation is performed three times.

The resulting oil is partitioned between ethyl acetate and water. The product is then extracted into the ethyl acetate and the aqueous layer is then washed twice with ethyl acetate. The combined organic layers are then washed successively with water and brine dried over magnesium sulfate, filtered and concentrated to obtain 1-chloroacetyl-2-cyanopyrrolidine as a yellow solid.

Alternatively, the reaction may be carried out by using, as base, a mixture, e.g. 2-ethyl-hexanoic acid/sodium hydrate.

C. Pyrrolidine, 1-[(3-hydroxy-1-adamanty)amino]acetyl-2-cyano-, (S)

To a heterogeneous solution of the title A compound (1-aminoadamantane-3-ol (5.80 g, 34.7 mmol) in CH_2Cl_2 (68.0 mL) is added 9.6 g (69 mmol) of K_2CO_3. This heterogeneous mixture is then cooled in an ice-water bath and a solution of 7.0 g (17 mmol) of the title B compound (1-chloroacetyl-2-cyanopyrrolidine) dissolved in 23.0 mL of CH_2Cl_2 is added dropwise over a period of 30 minutes. The resulting mixture is stirred for 2 hours at 0° C. and at room temperature for 6 days. The reaction is then concentrated to ...

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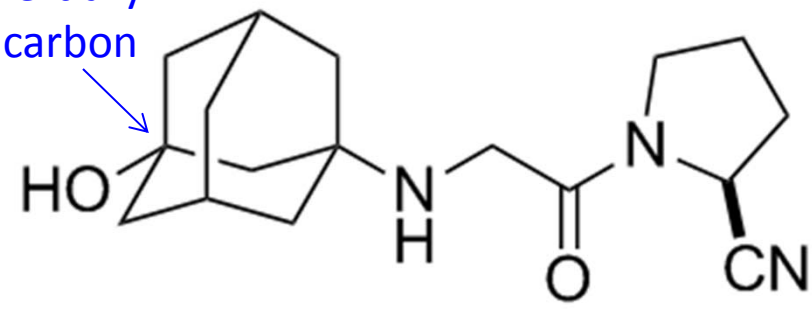
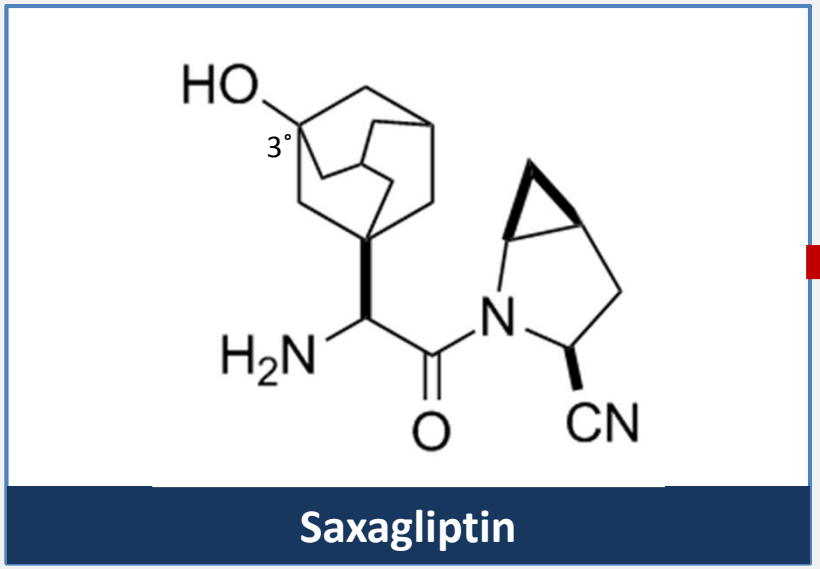
Tertiary carbon



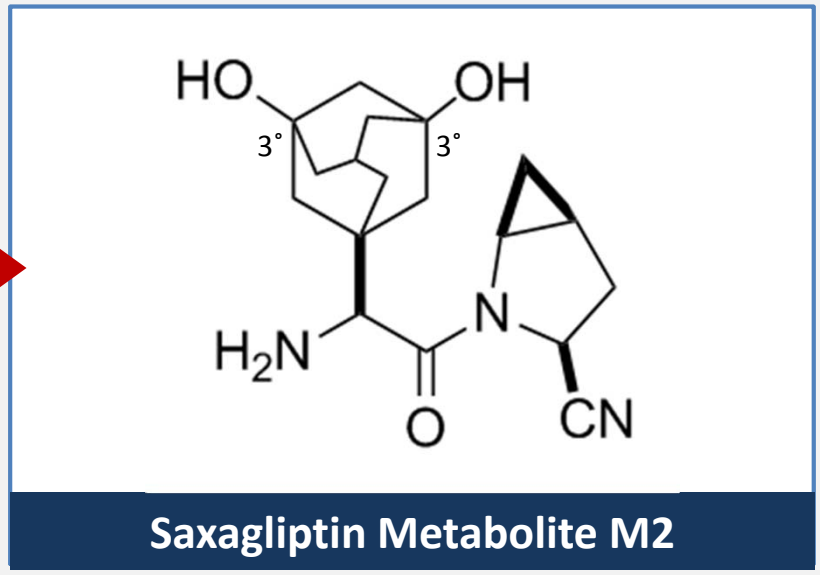
Vildagliptin

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

Saxagliptin is also Metabolized at a 3˚ Carbon



Saxagliptin



Saxagliptin Metabolite M2

M2 metabolite predictably results from a second oxidation at one of only two remaining tertiary adamantyl carbons.

Source: EX2045 (Su) at 1346; EX1074 (Second Rotella Decl.), ¶32.

Summary of Structural Modifications

- Cyclopropanate the pyrrolidine ring
  - Smallest possible fusion confers conformational rigidity and modulate position of cyano group

    Source: EX1007 (Ashworth I) at 1163

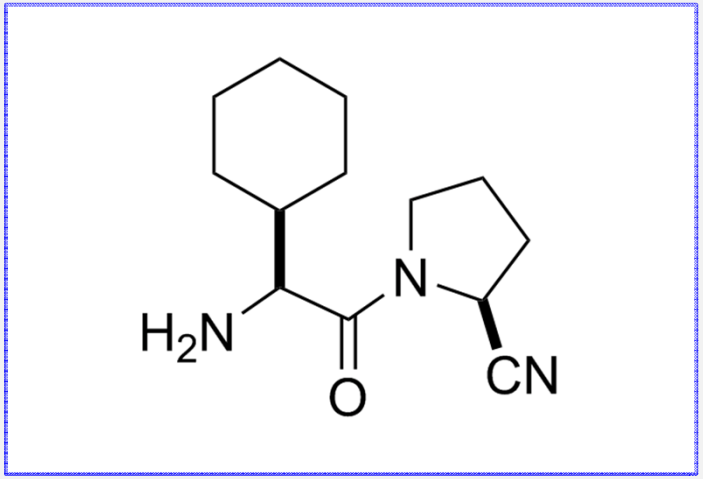
    EX1010 (Hanessian) at 1882
- Replace cyclohexyl ring with hydroxyadamantyl
  - Sterically bulky substituent favors *trans* conformation to maintain or improve stability and prevent intramolecular cyclization; potential to improve potency

    Source: EX1007 (Ashworth I) at 1163

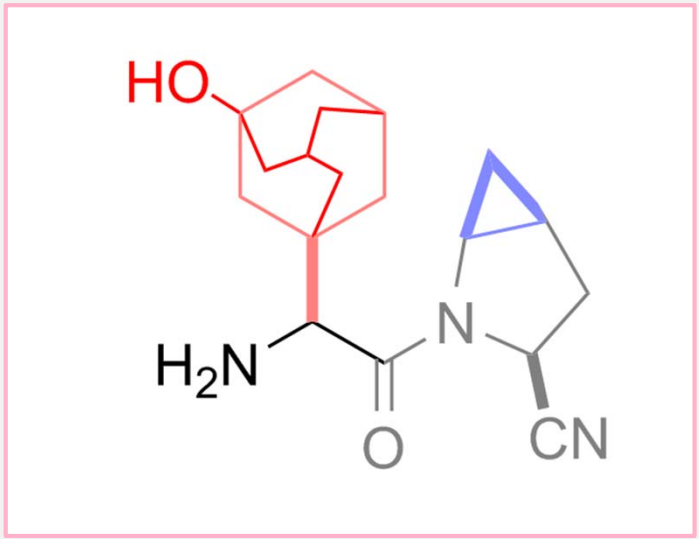
    EX1008 (Villhauer) at 13
  - Routine evaluation of metabolites

    Source: EX1009 (Raag)

Ashworth 25



Saxagliptin



Secondary Considerations Don't Overcome *Prima Facie* Case

- Did not meet a long-felt need
- No commercial success
- No evidence of failure of others
- No unexpected results

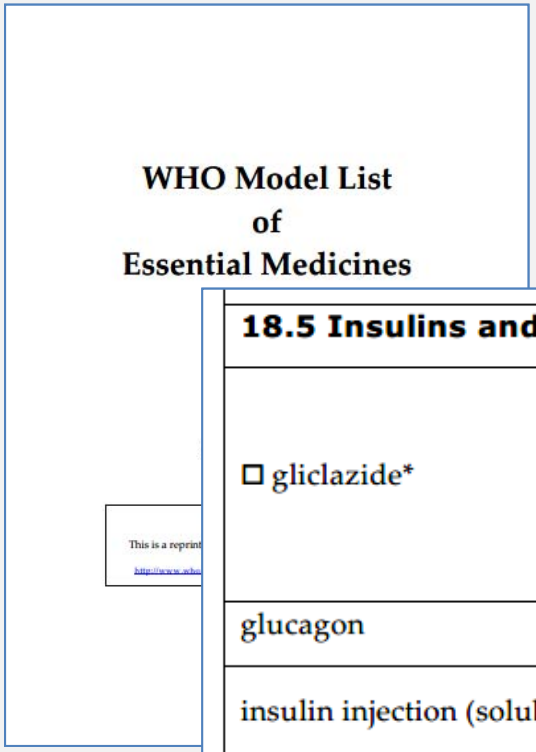
Metformin is Still the Most Preferred Anti-Diabetic Drug

"Metformin has the strongest evidence base and demonstrated long-term safety as pharmacological therapy for diabetes prevention."

"In my opinion, there is no drug (including saxagliptin) that stands out above the others as the second best choice alternative to metformin."

Source: EX2065 (American Diabetes) at 44; EX1041 (Tanenberg Decl.), ¶¶20-21; Pet. Reply at 4.

Metformin is Essential Medicine for Type 2 Diabetes

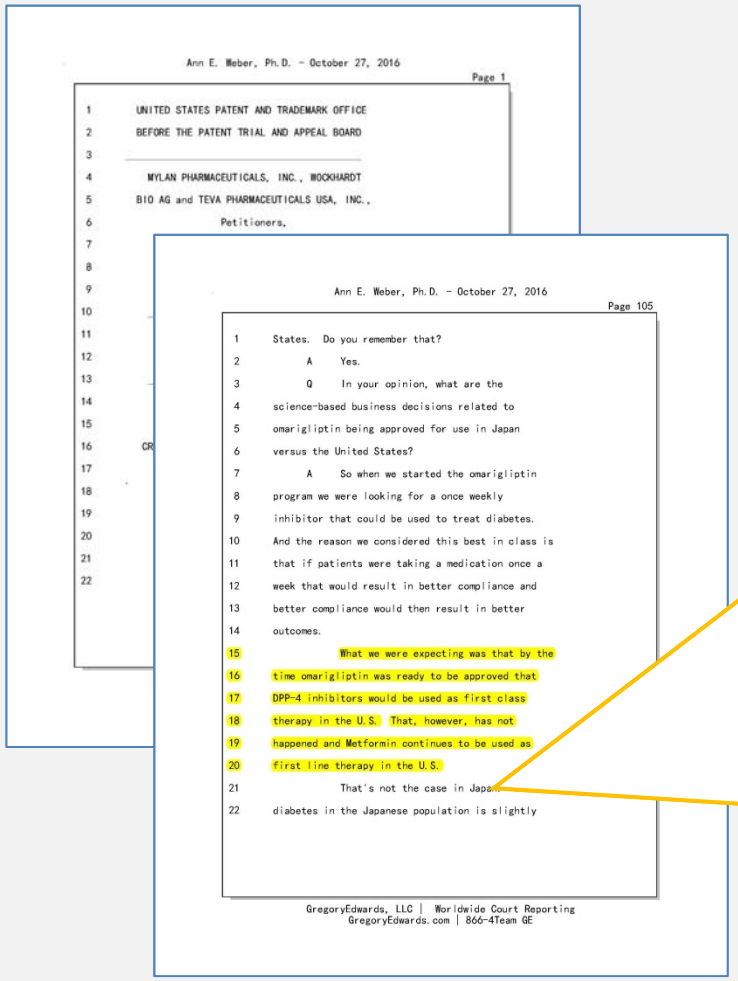


The World Health Organization DOES NOT list saxagliptin as an essential medicine in the treatment of Type 2 Diabetes.

18.5 Insulins and other medicines used for diabetes	
☐ gliclazide*	**Solid oral dosage form:** (controlled-release tablets) 30 mg; 60 mg; 80 mg. * glibenclamide not suitable above 60 years.
glucagon	**Injection:** 1 mg/ mL.
insulin injection (soluble)	**Injection:** 40 IU/ mL in 10- mL vial; 100 IU/ mL in 10- mL vial.
intermediate-acting insulin	**Injection:** 40 IU/ mL in 10- mL vial; 100 IU/ mL in 10- mL vial (as compound insulin zinc suspension **or** isophane insulin).
metformin	**Tablet:** 500 mg (hydrochloride).
Complementary List [c]	
metformin	***Tablet:*** *500 mg (hydrochloride).*

Source: EX1043 (WHO) at 34; EX1041 (Tanenberg Decl.), ¶¶19, 21.

Metformin is Still the Most Preferred Anti-Diabetic Drug



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

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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,

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States. Do you remember that?
A Yes.
Q In your opinion, what are the science-based business decisions related to omarigliptin being approved for use in Japan versus the United States?
A So when we started the omarigliptin program we were looking for a once weekly inhibitor that could be used to treat diabetes. And the reason we considered this best in class is that if patients were taking a medication once a week that would result in better compliance and better compliance would then result in better outcomes.
What we were expecting was that by the time omarigliptin was ready to be approved that DPP-4 inhibitors would be used as first class therapy in the U.S. That, however, has not happened and Metformin continues to be used as first line therapy in the U.S.
That's not the case in Japa
diabetes in the Japanese population is slightly

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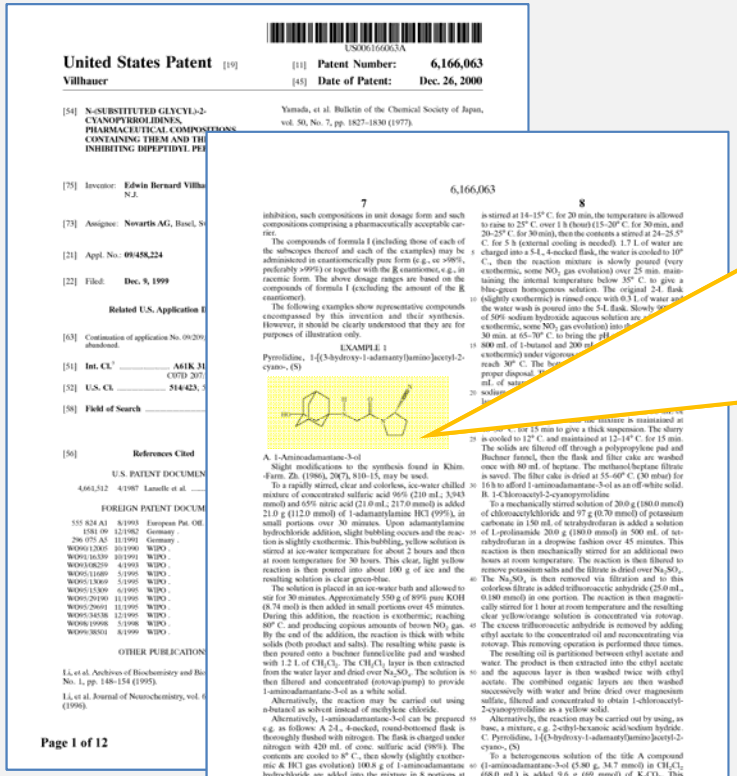
"What we were expecting was that by the time omarigliptin was ready to be approved that DPP-4 inhibitors would be used as first class therapy in the U.S. That, however, has not happened and Metformin continues to be used as first line therapy in the U.S."

Source: EX1073 (Weber Depo. Trans.), 105:15-20; EX1041 (Tanenberg Decl.), ¶¶20-21; Pet. Reply at 23.

Vildagliptin was Invented Before Saxagliptin



United States Patent [19]
Villhauer

[11] Patent Number: 6,166,063
[45] Date of Patent: Dec. 26, 2000

[54] N-(SUBSTITUTED GLYCYL)-2-CYANOPYRROLIDINES, PHARMACEUTICAL COMPOSITIONS CONTAINING THEM AND THEIR USE AS INHIBITING DIPEPTIDYL PEPTIDASE

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

[73] Assignee: Novartis AG, Basel, Switzerland

[21] Appl. No.: 09/458,224

[22] Filed: Dec. 9, 1999

Related U.S. Application Data

[63] Continuation of application No. 09/200,... abandoned.

[51] Int. Cl.[7] ..... A61K 31/... C07D 207...

[52] U.S. Cl. ..... 514/423, ...

[58] Field of Search ...

[56] References Cited

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Yamada, et al. Bulletin of the Chemical Society of Japan, vol. 50, No. 7, pp. 1827–1830 (1977).

6,166,063

7 8

inhibition, such compositions in unit dosage form and such compositions comprising a pharmaceutically acceptable carrier.

The compounds of formula I (including those of each of the subscopes thereof and each of the examples) may be administered in enantiomerically pure form (e.g., ee >98%, preferably >99%) or together with the R enantiomer, e.g., in racemic form. The above dosage ranges are based on the compounds of formula I (excluding the amount of the R enantiomer).

The following examples show representative compounds encompassed by this invention and their synthesis. However, it should be clearly understood that they are for purposes of illustration only.

EXAMPLE 1

Pyrrolidine, 1-[(3-hydroxy-1-adamantyl)amino]acetyl-2-cyano-, (S)

A. 1-Aminoadamantane-3-ol

Slight modifications to the synthesis found in Khim.-Farm. Zh. (1986), 20(7), 810-15, may be used.

To a rapidly stirred, clear and colorless, ice-water chilled mixture of concentrated sulfuric acid 96% (210 mL; 3,943 mmol) and 65% nitric acid (21.0 mL; 217.0 mmol) is added 21.0 g (112.0 mmol) of 1-adamantylamine HCl (99%), in small portions over 30 minutes. Upon adamantylamine hydrochloride addition, slight bubbling occurs and the reaction is slightly exothermic. This bubbling, yellow solution is stirred at ice-water temperature for about 2 hours and then at room temperature for 30 hours. This clear, light yellow reaction is then poured into about 100 g of ice and the resulting solution is clear green-blue.

The solution is placed in an ice-water bath and allowed to stir for 30 minutes. Approximately 550 g of 89% pure KOH (8.74 mol) is then added in small portions over 45 minutes. During this addition, the reaction is exothermic; reaching 80° C. and producing copious amounts of brown NO_2 gas. By the end of the addition, the reaction is thick with white solids (both product and salts). The resulting white paste is then poured onto a buchner funnel/celite pad and washed with 1.2 L of CH_2Cl_2. The CH_2Cl_2 layer is then extracted from the water layer and dried over Na_2SO_4. The solution is then filtered and concentrated (rotovap/pump) to provide 1-aminoadamantane-3-ol as a white solid.

Alternatively, the reaction may be carried out using n-butanol as solvent instead of methylene chloride.

Alternatively, 1-aminoadamantane-3-ol can be prepared e.g. as follows: A 2-L, 4-necked, round-bottomed flask is thoroughly flushed with nitrogen. The flask is charged under nitrogen with 420 mL of conc. sulfuric acid (98%). The contents are cooled to 8° C., then slowly (slightly exothermic & HCl gas evolution) 100.8 g of 1-aminoadamantane hydrochloride are added into the mixture in 8 portions at 9–10° C. over 20 min (minutes), then the hazy contents are stirred at 9–10° C. for 20 min to obtain a homogenous mixture. 72 mL of conc. (concentrated) nitric acid (70%) are added (very exothermic) dropwise into the mixture maintaining inner temperature at 14–15° C. with efficient cooling (at this scale 20 min. needed for this addition). The mixture is stirred at 14–15° C. for 20 min, the temperature is allowed to raise to 25° C. over 1 h (hour) (15–20° C. for 30 min, and 20–25° C. for 30 min), then the contents a stirred at 24–25.5° C. for 5 h (external cooling is needed). 1.7 L of water are charged into a 5-L, 4-necked flask, the water is cooled to 10° C., then the reaction mixture is slowly poured (very exothermic, some NO_2 gas evolution) over 25 min. maintaining the internal temperature below 35° C. to give a blue-green homogenous solution. The original 2-L flask (slightly exothermic) is rinsed once with 0.3 L of water and the water wash is poured into the 5-L flask. Slowly 9... of 50% sodium hydroxide aqueous solution are ... exothermic, some NO_2 gas evolution) into t... 30 min. at 65–70° C. to bring the pH ... 800 mL of 1-butanol and 200 mL ... exothermic) under vigorous ... reach 30° C. The ... proper disposal. ... mL of satu... solids ... mixture is maintained at ... C. for 15 min to give a thick suspension. The slurry is cooled to 12° C. and maintained at 12–14° C. for 15 min. The solids are filtered-off through a polypropylene pad and Buchner funnel, then the flask and filter cake are washed once with 80 mL of heptane. The methanol/heptane filtrate is saved. The filter cake is dried at 55–60° C. (30 mbar) for 16 h to afford 1-aminoadamantane-3-ol as an off-white solid.

B. 1-Chloroacetyl-2-cyanopyrrolidine

To a mechanically stirred solution of 20.0 g (180.0 mmol) of chloroacetylchloride and 97 g (0.70 mmol) of potassium carbonate in 150 mL of tetrahydrofuran is added a solution of L-prolinamide 20.0 g (180.0 mmol) in 500 mL of tetrahydrofuran in a dropwise fashion over 45 minutes. This reaction is then mechanically stirred for an additional two hours at room temperature. The reaction is then filtered to remove potassium salts and the filtrate is dried over Na_2SO_4. The Na_2SO_4 is then removed via filtration and to this colorless filtrate is added trifluoroacetic anhydride (25.0 mL, 0.180 mmol) in one portion. The reaction is then magnetically stirred for 1 hour at room temperature and the resulting clear yellow/orange solution is concentrated via rotovap. The excess trifluoroacetic anhydride is removed by adding ethyl acetate to the concentrated oil and reconcentrating via rotovap. This removing operation is performed three times.

The resulting oil is partitioned between ethyl acetate and water. The product is then extracted into the ethyl acetate and the aqueous layer is then washed twice with ethyl acetate. The combined organic layers are then washed successively with water and brine dried over magnesium sulfate, filtered and concentrated to obtain 1-chloroacetyl-2-cyanopyrrolidine as a yellow solid.

Alternatively, the reaction may be carried out by using, as base, a mixture, e.g. 2-ethyl-hexanoic acid/sodium hydride.

C. Pyrrolidine, 1-[(3-hydroxy-1-adamantyl)amino]acetyl-2-cyano-, (S)

To a heterogeneous solution of the title A compound (1-aminoadamantane-3-ol (5.80 g, 34.7 mmol) in CH_2Cl_2 (68.0 mL) is added 9.6 g (69 mmol) of K_2CO_3. This heterogeneous mixture is then cooled in an ice-water bath and a solution of 3.0 g (17 mmol) of the title B compound (1-chloroacetyl-2-cyanopyrrolidine) dissolved in 25.0 mL of CH_2Cl_2 is added dropwise over a period of 30 minutes. The resulting mixture is stirred for 2 hours at 0° C. and at room temperature for 6 days. The reaction is then concentrated to

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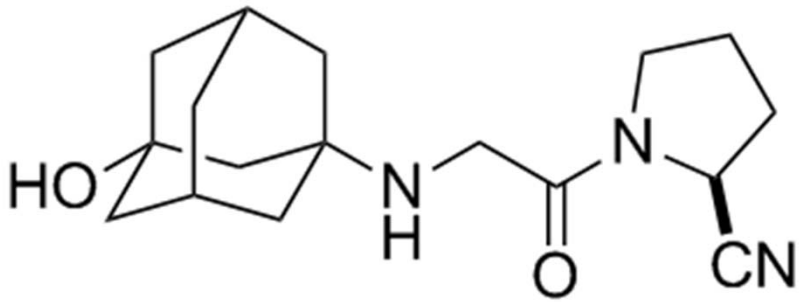
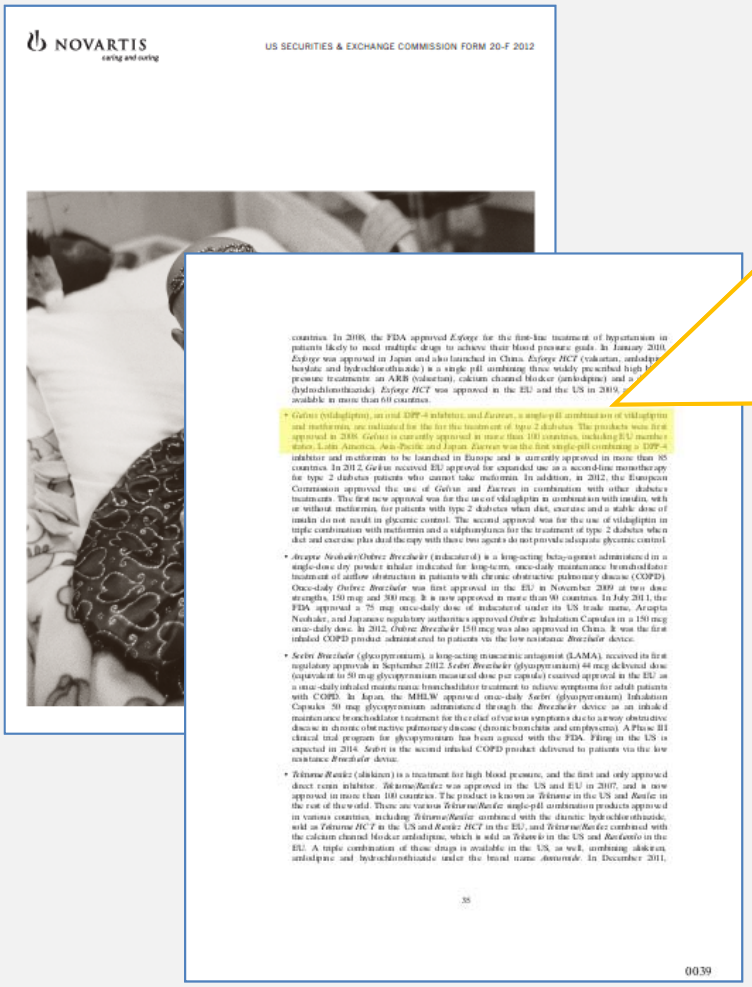


Vildagliptin

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

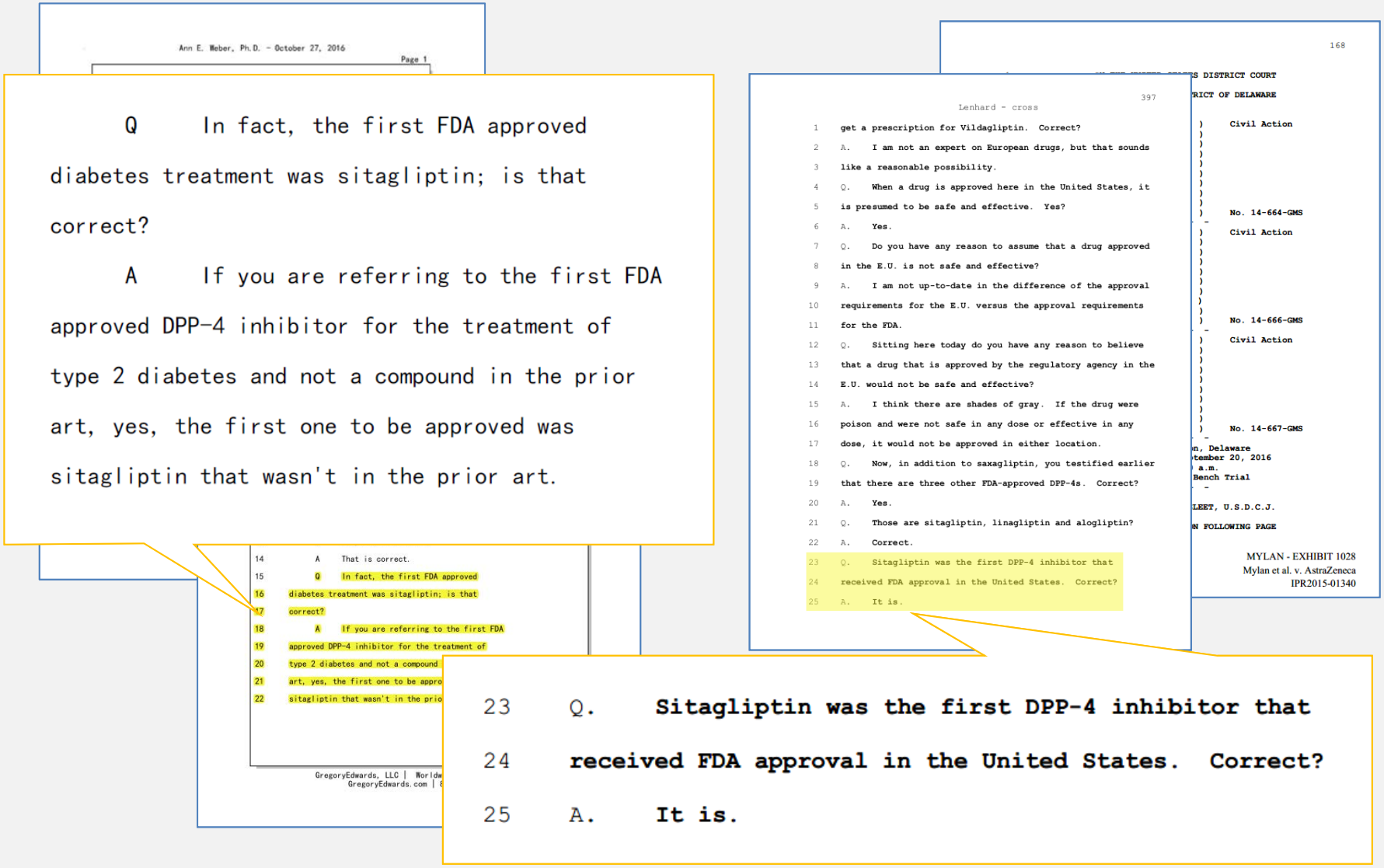
Vildagliptin Received Regulatory Approval Before Saxagliptin



"Galvus (vildagliptin) , an oral DPP-4 inhibitor, and Eucreas, a single-pill combination of vildagliptin and metformin, are indicated for the treatment of type 2 diabetes. The products were first approved in 2008. Galvus is currently approved in more than 100 countries[.]"

Source: EX1048 (2012 Novartis Annual Report) at 0039; Pet. Reply at 23.

Sitagliptin was FDA-Approved Before Saxagliptin



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Q In fact, the first FDA approved diabetes treatment was sitagliptin; is that correct?

A If you are referring to the first FDA approved DPP-4 inhibitor for the treatment of type 2 diabetes and not a compound in the prior art, yes, the first one to be approved was sitagliptin that wasn't in the prior art.

14 A That is correct.
15 Q In fact, the first FDA approved
16 diabetes treatment was sitagliptin; is that
17 correct?
18 A If you are referring to the first FDA
19 approved DPP-4 inhibitor for the treatment of
20 type 2 diabetes and not a compound
21 art, yes, the first one to be appro
22 sitagliptin that wasn't in the prio

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Lenhard - cross

1 get a prescription for Vildagliptin. Correct?
2 A. I am not an expert on European drugs, but that sounds
3 like a reasonable possibility.
4 Q. When a drug is approved here in the United States, it
5 is presumed to be safe and effective. Yes?
6 A. Yes.
7 Q. Do you have any reason to assume that a drug approved
8 in the E.U. is not safe and effective?
9 A. I am not up-to-date in the difference of the approval
10 requirements for the E.U. versus the approval requirements
11 for the FDA.
12 Q. Sitting here today do you have any reason to believe
13 that a drug that is approved by the regulatory agency in the
14 E.U. would not be safe and effective?
15 A. I think there are shades of gray. If the drug were
16 poison and were not safe in any dose or effective in any
17 dose, it would not be approved in either location.
18 Q. Now, in addition to saxagliptin, you testified earlier
19 that there are three other FDA-approved DPP-4s. Correct?
20 A. Yes.
21 Q. Those are sitagliptin, linagliptin and alogliptin?
22 A. Correct.
23 Q. Sitagliptin was the first DPP-4 inhibitor that
24 received FDA approval in the United States. Correct?
25 A. It is.

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S DISTRICT COURT
TRICT OF DELAWARE

) Civil Action
) No. 14-664-GMS
) Civil Action
) No. 14-666-GMS
) Civil Action
) No. 14-667-GMS

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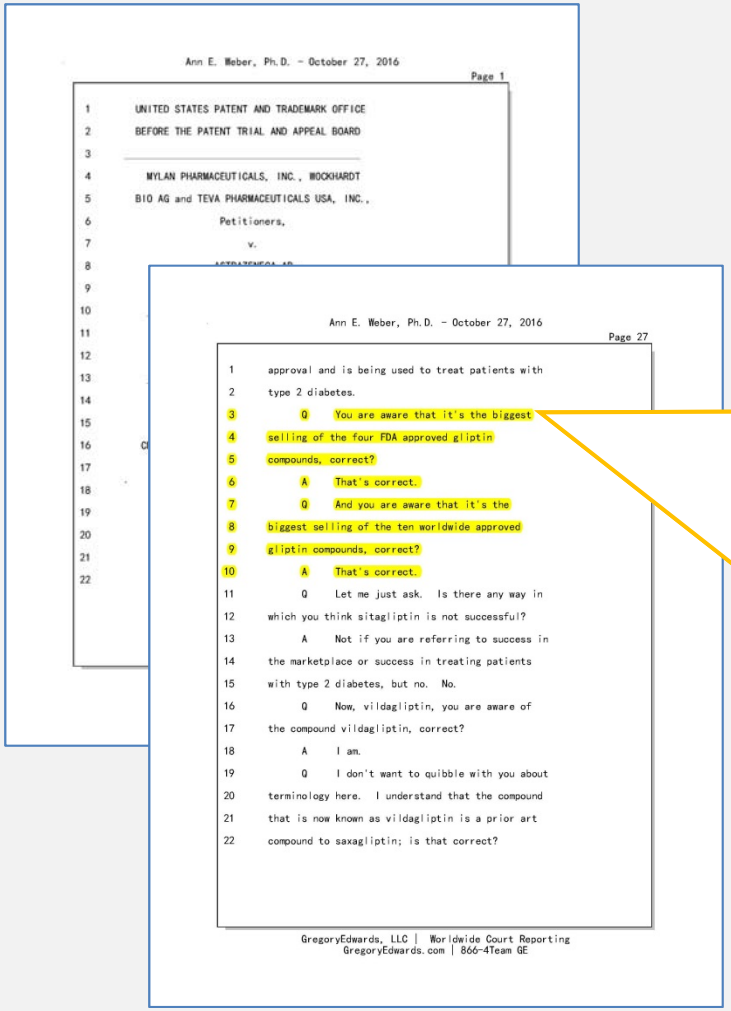
N FOLLOWING PAGE

MYLAN - EXHIBIT 1028
Mylan et al. v. AstraZeneca
IPR2015-01340

23 Q. **Sitagliptin was the first DPP-4 inhibitor that**
24 **received FDA approval in the United States. Correct?**
25 A. **It is.**

Source: EX1073 (Weber Depo. Trans.), 25:15-22; EX1028 (Lenhard Depo. Trans.), 397:23-25.

Sitagliptin is the Highest Selling Gliptin



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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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

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

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approval and is being used to treat patients with type 2 diabetes.

Q You are aware that it's the biggest selling of the four FDA approved gliptin compounds, correct?

A That's correct.

Q And you are aware that it's the biggest selling of the ten worldwide approved gliptin compounds, correct?

A That's correct.

Q Let me just ask. Is there any way in which you think sitagliptin is not successful?

A Not if you are referring to success in the marketplace or success in treating patients with type 2 diabetes, but no. No.

Q Now, vildagliptin, you are aware of the compound vildagliptin, correct?

A I am.

Q I don't want to quibble with you about terminology here. I understand that the compound that is now known as vildagliptin is a prior art compound to saxagliptin; is that correct?

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Q You are aware that it's the biggest selling of the four FDA approved gliptin compounds, correct?

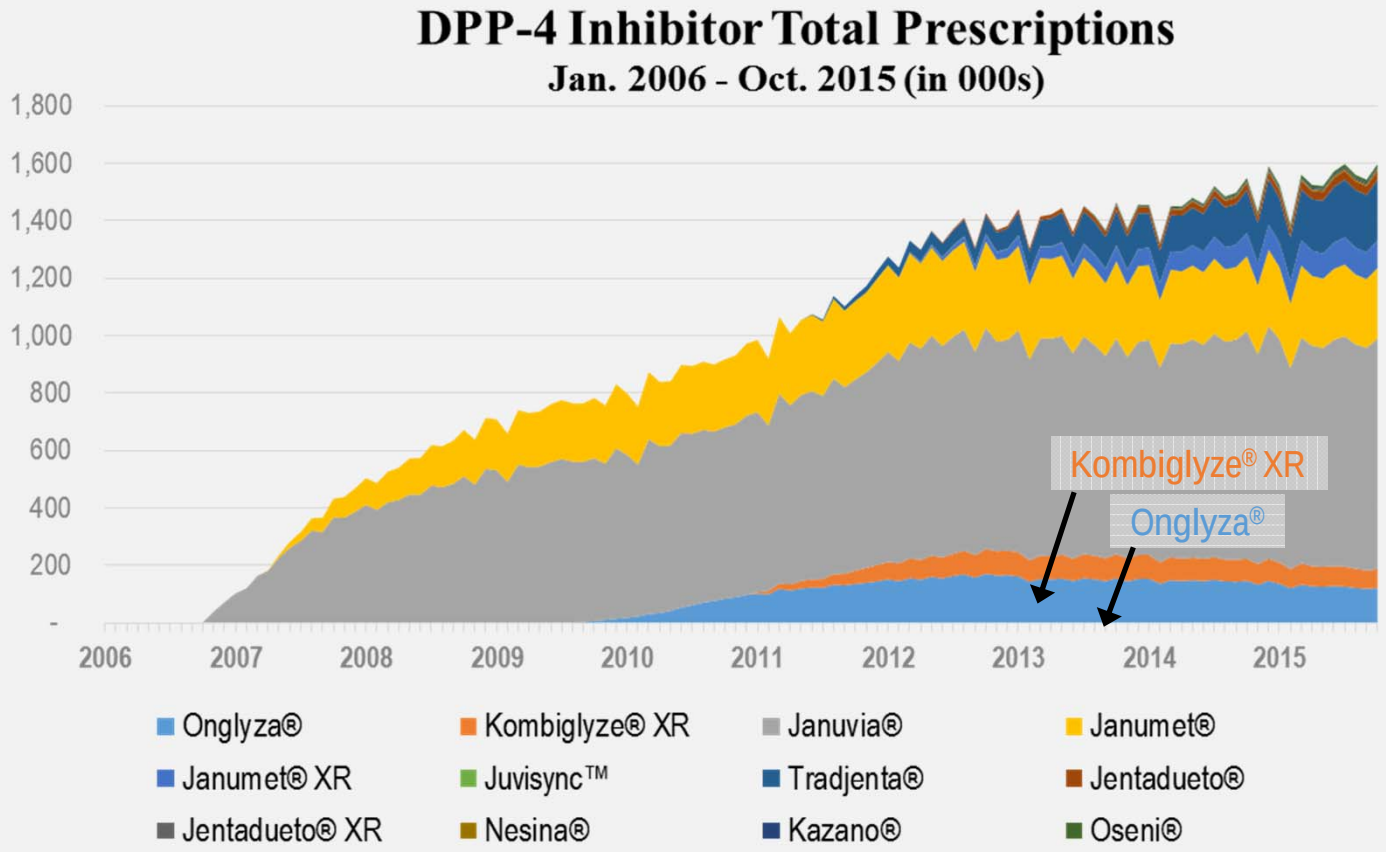
A That's correct.

Q And you are aware that it's the biggest selling of the ten worldwide approved gliptin compounds, correct?

A That's correct.

Source: EX1073 (Weber Depo. Trans.), 27:3-10.

Saxagliptin Under-Performs Sitagliptin (Januvia®)



Saxagliptin products failed to capture a substantial share of the U.S. DPP-4 inhibitor market.

Source: EX1060B (McDuff Decl.), ¶20; EX1062B (McDuff Attachments) at B-3; EX1035, ¶36; EX2117 (IMS Health Audit); EX1029 (Meyer Depo. Trans.), 422:4-13.

Large and Increasing Rebates for Saxagliptin

Onglyza®							
	2009	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**
Net Sales Adjustments as a % of Gross Sales	11%	32%	33%	37%	35%	54%	66%

Kombiglyze® XR						
	2010	**2011**	**2012**	**2013**	**2014**	**2015**
Net Sales Adjustments as a % of Gross Sales	26%	33%	37%	38%	53%	57%

Net sales adjustments are a large percentage of gross sales and have increased continuously and significantly from launch through 2015.

Source: EX1060B (McDuff Decl.), ¶41; EX1062B (McDuff Attachments) at B-8a; EX1035, ¶63.

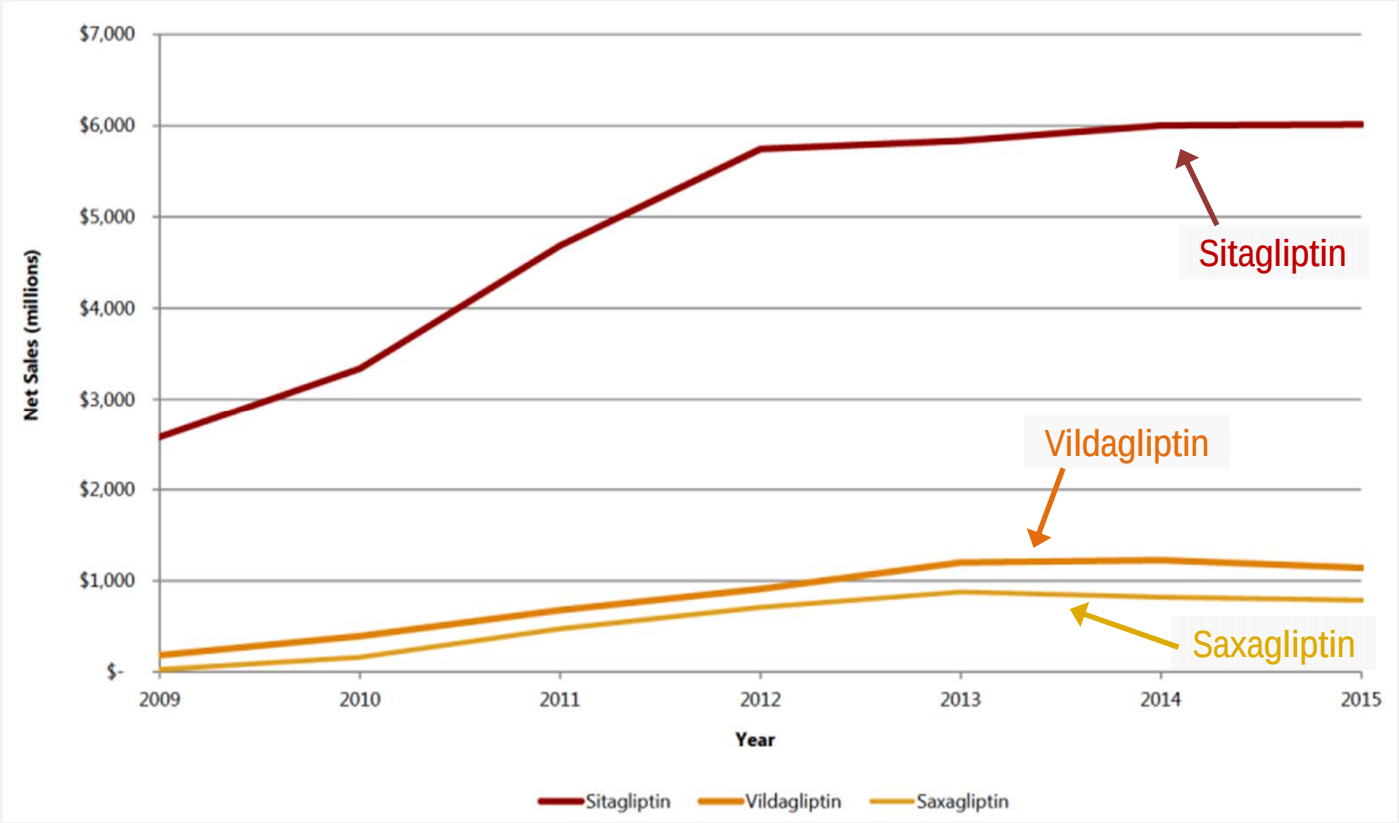
Large Marketing Expenditure on Saxagliptin

Product	Measure	2009 (Jul - Dec)	2010	2011	2012	2013	2014	2015 (Jan - Jul)	Total (2009-2015)	Total (2011-2015)
Promotional Spending (millions)	Onglyza	$ 44.1	$ 128.6	$ 85.5	$ 65.8	$ 55.0	$ 35.7	$ 14.6	$ 429.3	$ 256.7
	Kombiglyze XR	$ -	$ 0.5	$ 54.1	$ 38.2	$ 33.1	$ 11.1	$ 5.0	$ 141.9	$ 141.4
	Total	$ 44.1	$ 129.1	$ 139.5	$ 104.0	$ 88.1	$ 46.8	$ 19.6	$ 571.3	$ 398.1
US Sales (millions)	Onglyza	$ 13.3	$ 150.5	$ 361.1	$ 481.8	$ 524.8	$ 579.0	$ 338.5	$ 2,449.0	$ 2,285.2
	Kombiglyze XR	$ -	$ 0.3	$ 73.0	$ 200.0	$ 253.1	$ 288.1	$ 180.0	$ 994.5	$ 994.2
	Total gross sales	$ 13.3	$ 150.8	$ 434.1	$ 681.8	$ 778.0	$ 867.1	$ 518.5	$ 3,443.5	$ 3,279.4
	Total net sales	$ 22.0	$ 119.0	$ 339.0	$ 516.0	$ 591.0	$ 481.0	$ 420.0	$ 2,488.0	$ 2,347.0
Marketing Share Sales	Onglyza	330.7%	85.5%	23.7%	13.7%	10.5%	6.2%	4.3%	17.5%	11.2%
	Kombiglyze XR	n/a	163.3%	74.1%	19.1%	13.1%	3.8%	2.8%	14.3%	14.2%
	Total gross sales	330.7%	85.6%	32.1%	15.3%	11.3%	5.4%	3.8%	16.6%	12.1%
	Total net sales	200.4%	108.5%	41.2%	20.2%	14.9%	9.7%	4.7%	23.0%	17.0%

$571 million in promotional expenditures on Onglyza and Kombiglyze XR in the U.S. from 2009 to 2015, which is 23.0% of total U.S. sales over the same time period.

Source: EX1060B (McDuff Decl.), ¶25; EX1062B (McDuff Attachments) at B-4.

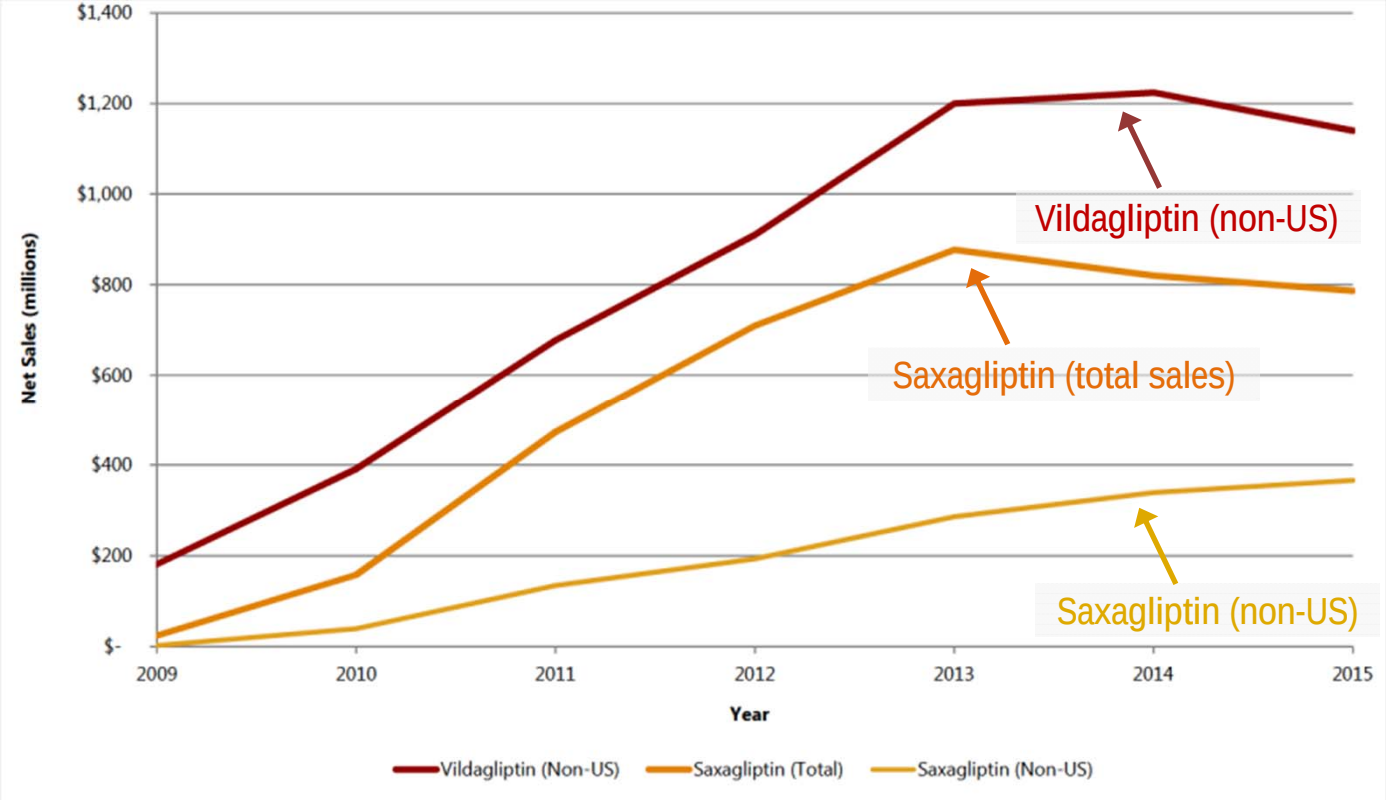
Saxagliptin Also Underperforms Vildagliptin (Galvus)



Worldwide sales of vildagliptin beat worldwide sales of saxagliptin.

Source: EX1060B (McDuff Decl.), ¶18; EX1062B (McDuff Attachments) at B-1b.

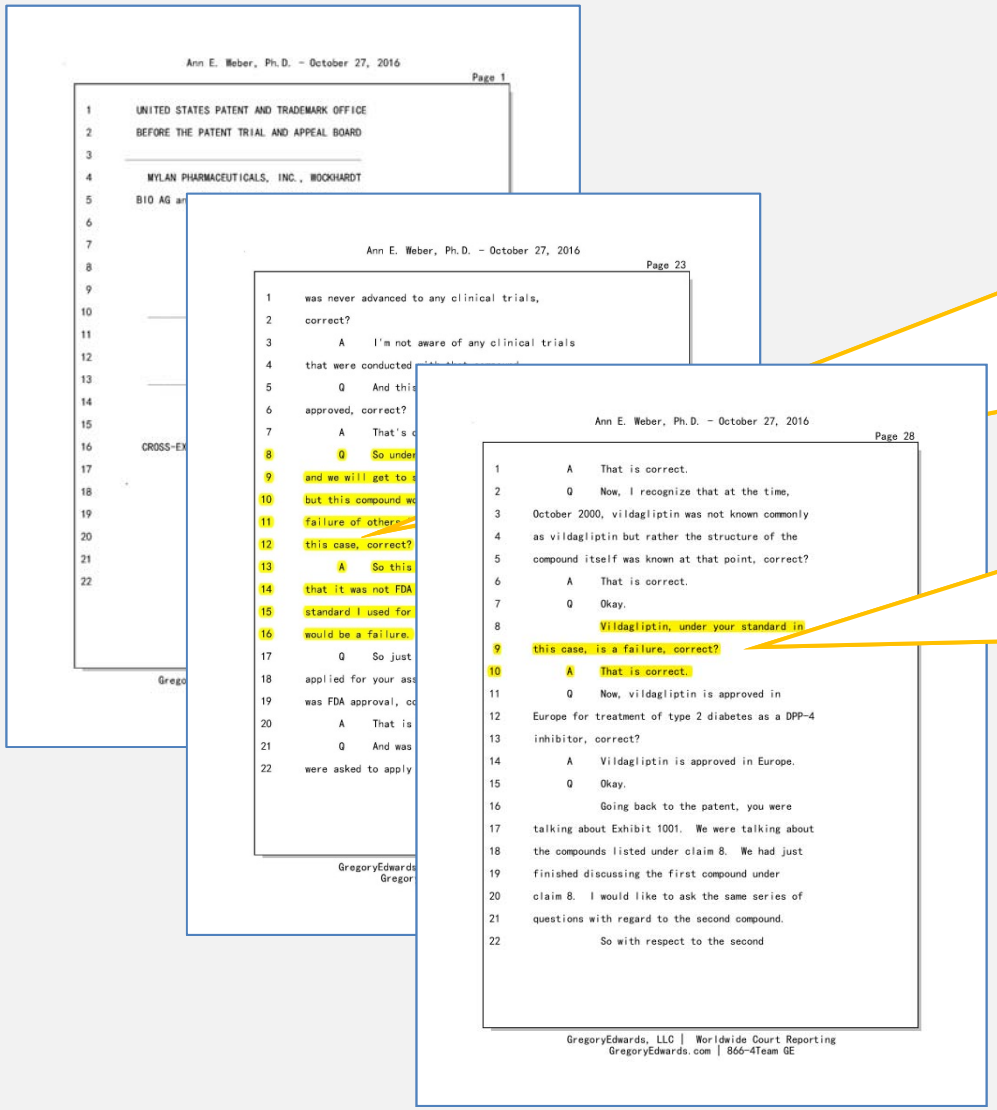
Saxagliptin Also Underperforms Vildagliptin (Galvus)



Even without U.S. sales, worldwide sales of vildagliptin beat worldwide sales of saxagliptin.

Source: EX1060B (McDuff Decl.), ¶18; EX1062B (McDuff Attachments) at B-1c.

They Call Vildagliptin a "Failure"



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 ar

CROSS-EX

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

Page 23

was never advanced to any clinical trials, correct?
A I'm not aware of any clinical trials that were conducted
Q And this approved, correct?
A That's
Q So under
and we will get to
but this compound w
failure of others
this case, correct?
A So this
that it was not FDA
standard I used for
would be a failure.
Q So just
applied for your as
was FDA approval, c
A That is
Q And was
were asked to apply

GregoryEdwards
Gregor

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

Page 28

A That is correct.
Q Now, I recognize that at the time, October 2000, vildagliptin was not known commonly as vildagliptin but rather the structure of the compound itself was known at that point, correct?
A That is correct.
Q Okay.
Vildagliptin, under your standard in this case, is a failure, correct?
A That is correct.
Q Now, vildagliptin is approved in Europe for treatment of type 2 diabetes as a DPP-4 inhibitor, correct?
A Vildagliptin is approved in Europe.
Q Okay.
Going back to the patent, you were talking about Exhibit 1001. We were talking about the compounds listed under claim 8. We had just finished discussing the first compound under claim 8. I would like to ask the same series of questions with regard to the second compound.
So with respect to the second

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Q So under your analysis in this case, and we will get to some of this a little later, but this compound would be a failure, exhibit a failure of others in connection with your work in this case, correct?

A So this compound by virtue of the fact that it was not FDA approved, and that was the standard I used for failure of others, yes, this would be a failure.

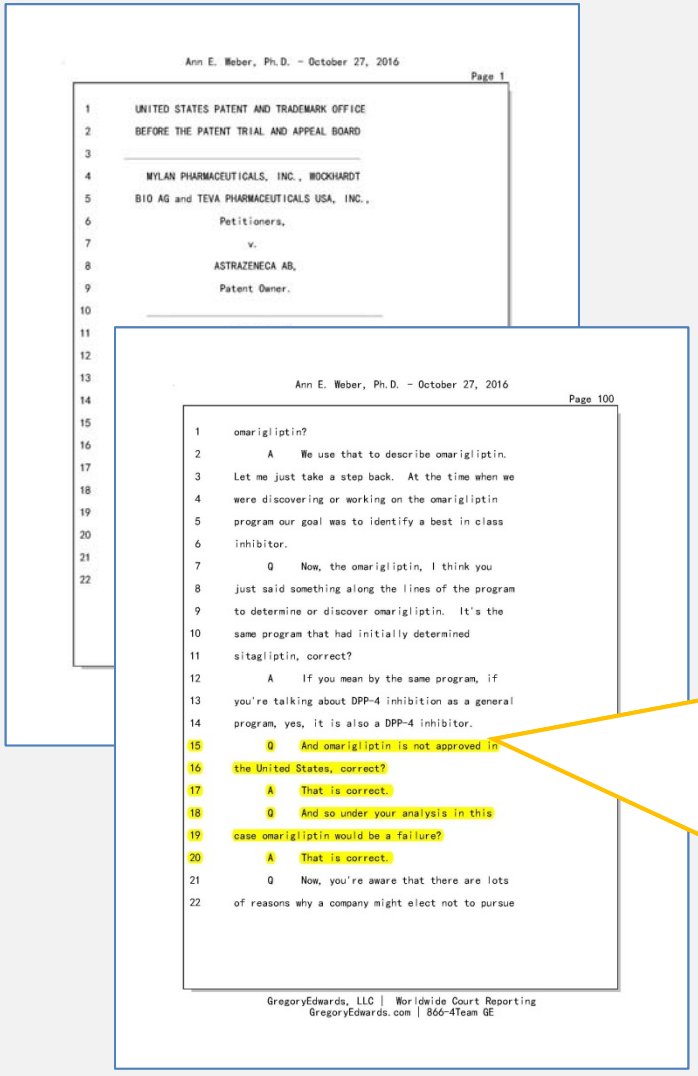
Q Okay.

Vildagliptin, under your standard in this case, is a failure, correct?

A That is correct.

Source: EX1073 (Weber Depo. Trans.), 23:8-16, 28:7-10; EX2057 (Lenhard Decl.), ¶76.

Best-in-class Glyptin "a Failure"



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.

Ann E. Weber, Ph.D. - October 27, 2016
Page 100

omarigliptin?
A We use that to describe omarigliptin. Let me just take a step back. At the time when we were discovering or working on the omarigliptin program our goal was to identify a best in class inhibitor.
Q Now, the omarigliptin, I think you just said something along the lines of the program to determine or discover omarigliptin. It's the same program that had initially determined sitagliptin, correct?
A If you mean by the same program, if you're talking about DPP-4 inhibition as a general program, yes, it is also a DPP-4 inhibitor.
Q And omarigliptin is not approved in the United States, correct?
A That is correct.
Q And so under your analysis in this case omarigliptin would be a failure?
A That is correct.
Q Now, you're aware that there are lots of reasons why a company might elect not to pursue

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Dr. Weber's own "best in class of the gliptins" omarigliptin qualifies as an FDA-approval "failure."

Q And omarigliptin is not approved in the United States, correct?

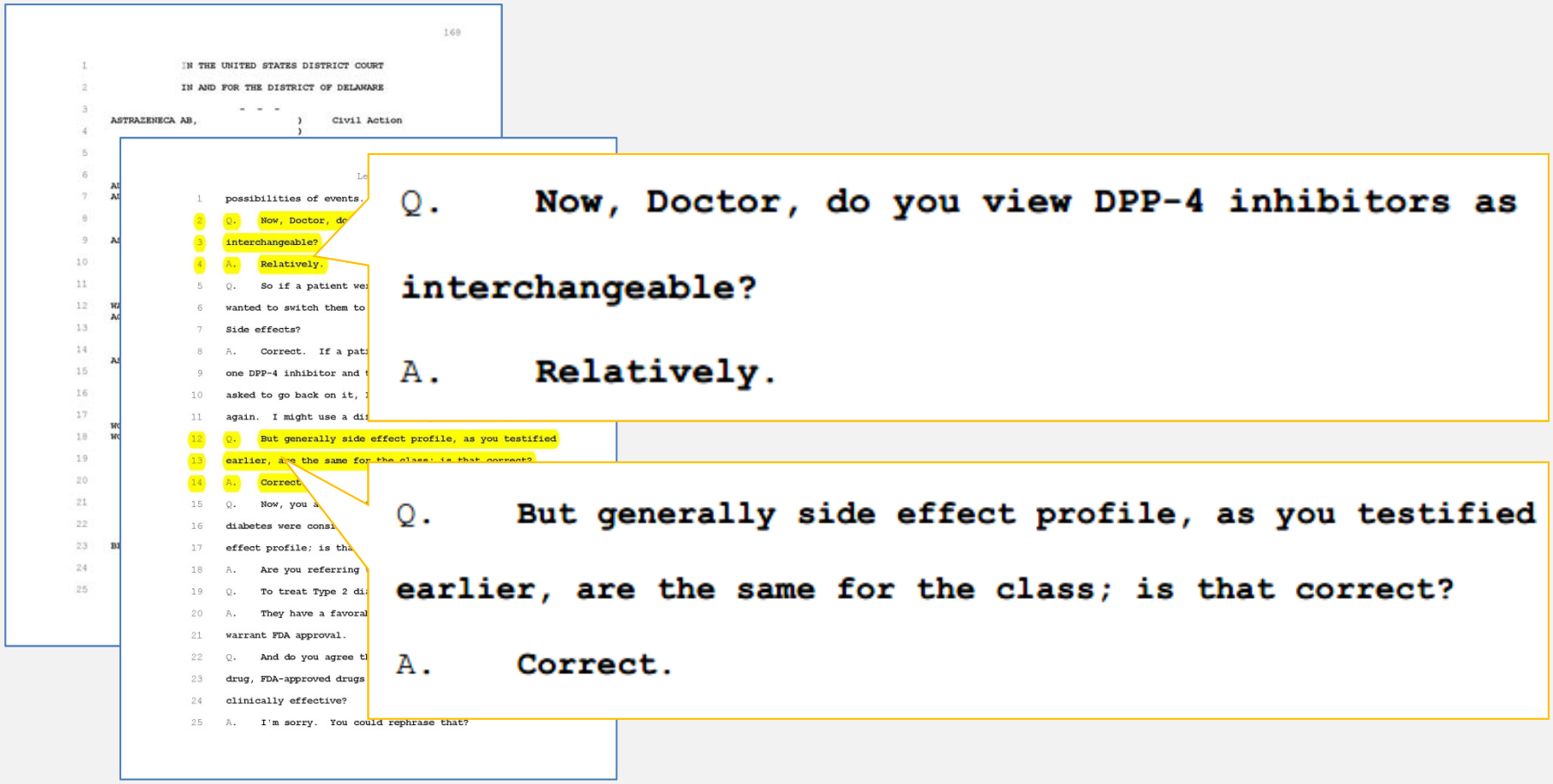
A That is correct.

Q And so under your analysis in this case omarigliptin would be a failure?

A That is correct.

Source: EX1073 (Weber Depo. Trans.), 99:9-100:20.

FDA-Approved DPP-4 Inhibitors are Interchangeable



IN THE UNITED STATES DISTRICT COURT
IN AND FOR THE DISTRICT OF DELAWARE

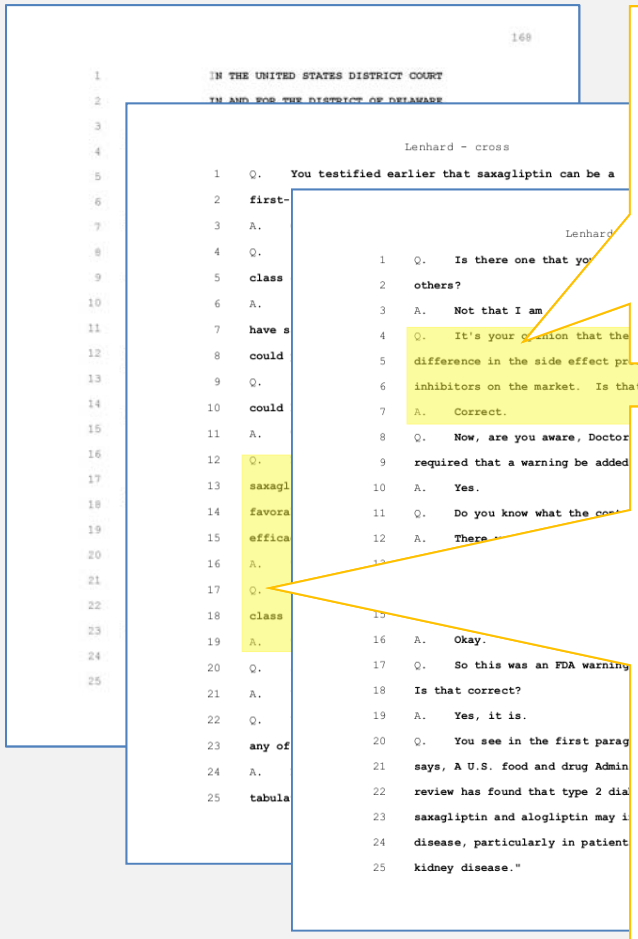
ASTRAZENECA AB,) Civil Action

Q. Now, Doctor, do you view DPP-4 inhibitors as interchangeable?
A. Relatively.

Q. But generally side effect profile, as you testified earlier, are the same for the class; is that correct?
A. Correct.

Source: EX1028 (Lenhard Depo. Trans.), 402:2-14; EX1041 (Tanenberg Decl.), ¶¶24-25; Pet. Reply at 21.

FDA-Approved DPP-4 Inhibitors are Interchangeable



Q. It's your opinion that there is no meaningful difference in the side effect profile of the DPP-4 inhibitors on the market. Is that correct?

A. Correct.

Q. Now, Doctor, you also testified earlier that saxagliptin demonstrated unexpected results because of its favorable side effect profile of once-daily dosing and efficacy. Correct?

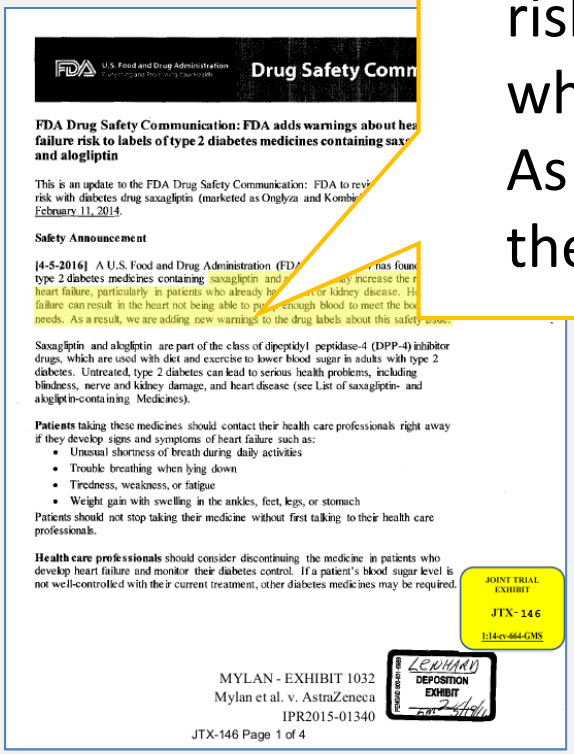
A. That's correct.

Q. That would apply to the other members of the DPP-4 class that have been FDA-approved. Correct?

A. That would.

Source: EX1028 (Lenhard Depo. Trans.), 398:12-19, 399:4-7; EX1041 (Tanenberg Decl.) , ¶¶ 25-29.

FDA Requires Safety Warning on Saxagliptin Product Label



U.S. Food and Drug Administration — Drug Safety Comm

FDA Drug Safety Communication: FDA adds warnings about hea failure risk to labels of type 2 diabetes medicines containing sax and alogliptin

This is an update to the FDA Drug Safety Communication: FDA to revi risk with diabetes drug saxagliptin (marketed as Onglyza and Kombi February 11, 2014.

Safety Announcement

[4-5-2016] A U.S. Food and Drug Administration (FDA ... has found type 2 diabetes medicines containing saxagliptin and ... may increase the r heart failure, particularly in patients who already he ... or kidney disease. H failure can result in the heart not being able to pu... enough blood to meet the bo needs. As a result, we are adding new warnings to the drug labels about this safety issue.

Saxagliptin and alogliptin are part of the class of dipeptidyl peptidase-4 (DPP-4) inhibitor drugs, which are used with diet and exercise to lower blood sugar in adults with type 2 diabetes. Untreated, type 2 diabetes can lead to serious health problems, including blindness, nerve and kidney damage, and heart disease (see List of saxagliptin- and alogliptin-containing Medicines).

Patients taking these medicines should contact their health care professionals right away if they develop signs and symptoms of heart failure such as:

- Unusual shortness of breath during daily activities
- Trouble breathing when lying down
- Tiredness, weakness, or fatigue
- Weight gain with swelling in the ankles, feet, legs, or stomach

Patients should not stop taking their medicine without first talking to their health care professionals.

Health care professionals should consider discontinuing the medicine in patients who develop heart failure and monitor their diabetes control. If a patient's blood sugar level is not well-controlled with their current treatment, other diabetes medicines may be required.

JOINT TRIAL EXHIBIT JTX-146 1:14-cv-464-GMS

MYLAN - EXHIBIT 1032
Mylan et al. v. AstraZeneca
IPR2015-01340

LENHARD DEPOSITION EXHIBIT

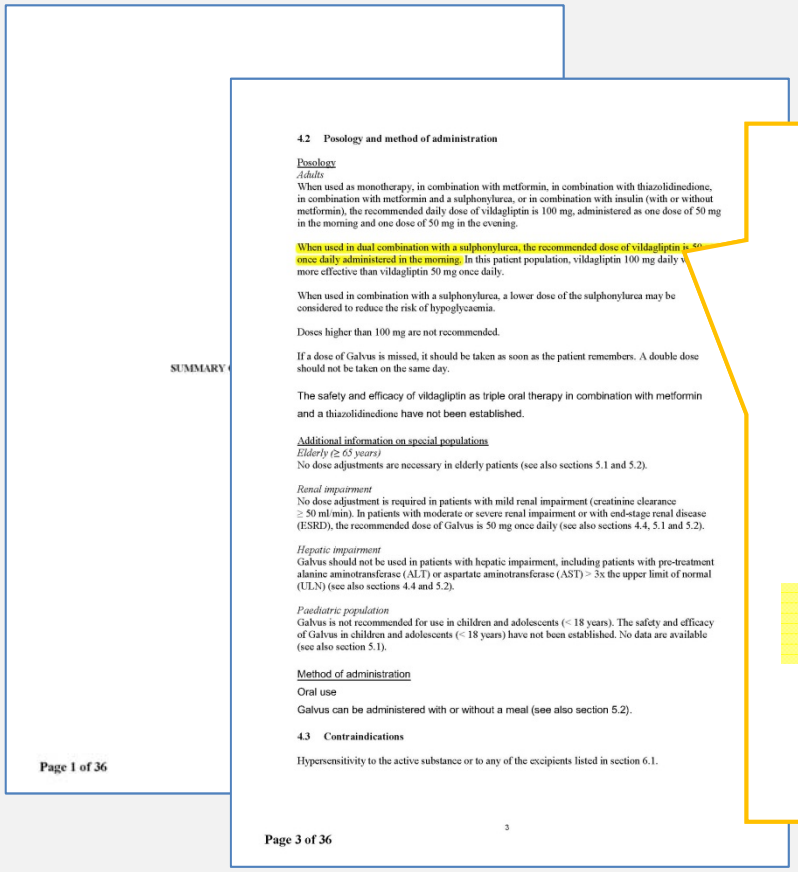
JTX-146 Page 1 of 4

"Saxagliptin and alogliptin may increase the risk of heart failure, particularly in patients who already have heart or kidney disease. . . . As a result, we are adding new warnings to the drug labels about this safety issue."

Sitagliptin does not have a heart failure warning.

Source: EX1032 (FDA Drug Safety Communication); EX1041 (Tanenberg Decl.), ¶26; EX1060 (McDuff Decl.), ¶35.

Vildagliptin Also Has a Once-Daily Combination Form



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4.2 Posology and method of administration

Posology

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 once daily administered in the morning. In this patient population, vildagliptin 100 mg daily w more effective than vildagliptin 50 mg once daily.

When used in combination with a sulphonylurea, a lower dose of the sulphonylurea may be considered to reduce the risk of hypoglycaemia.

Doses higher than 100 mg are not recommended.

If a dose of Galvus is missed, it should be taken as soon as the patient remembers. A double dose should not be taken on the same day.

The safety and efficacy of vildagliptin as triple oral therapy in combination with metformin and a thiazolidinedione have not been established.

Additional information on special populations

Elderly (≥ 65 years)

No dose adjustments are necessary in elderly patients (see also sections 5.1 and 5.2).

Renal impairment

No dose adjustment is required in patients with mild renal impairment (creatinine clearance ≥ 50 ml/min). In patients with moderate or severe renal impairment or with end-stage renal disease (ESRD), the recommended dose of Galvus is 50 mg once daily (see also sections 4.4, 5.1 and 5.2).

Hepatic impairment

Galvus should not be used in patients with hepatic impairment, including patients with pre-treatment alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3x the upper limit of normal (ULN) (see also sections 4.4 and 5.2).

Paediatric population

Galvus is not recommended for use in children and adolescents (< 18 years). The safety and efficacy of Galvus in children and adolescents (< 18 years) have not been established. No data are available (see also section 5.1).

Method of administration

Oral use

Galvus can be administered with or without a meal (see also section 5.2).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

3

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"When used in dual combination with a sulphonylurea, the recommended dose of vildagliptin is 50 mg once daily administered in the morning."

Source: EX2080 (Galvus Summary of Product Characteristics) at 3; Pet. Reply at 22.

Additional Slides

Patent Owner's Cyanopyrrolidine Arguments

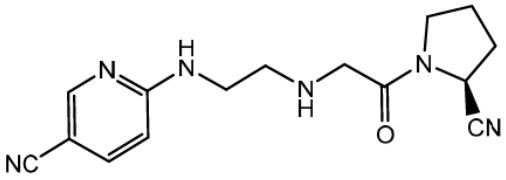


Figure 3: NVP-DPP728

1. NVP-DPP728 and P32/98 were more plausible leads

compound, vildagliptin, into the clinic. Ex. 2056, ¶¶146, 252; Ex. 2098, 4138. Vildagliptin, described in the prior art U.S. Patent No. 6,166,063 (Ex. 2013), also had the stabilizing *N*-linkage but ultimately failed to obtain FDA approval. It is approved in Europe but only for administration twice-daily and with a requirement for liver toxicity screening. Ex. 2056, ¶248; Ex. 2057, ¶¶67-70; Ex. 2050, 3-4. The structure of vildagliptin is shown in **Figure 5** below. *See* Ex. 2013, 5.

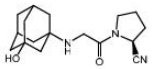


Figure 5: Vildagliptin

2. Merck's first clinical trial candidate P32/98

When Merck began medicinal chemistry on DPP-4 inhibitors, it performed a real-world lead compound analysis. Ex. 2056, ¶¶116-118. Merck scientists were concerned by the presence of a cyano group in the P1 position of Ashworth-I-type compounds because of the potential for cyclization and for toxic cyanide release should amide bond cleavage occur *in vivo*. Ex. 2056, ¶¶116-117; **Figure 6** below.

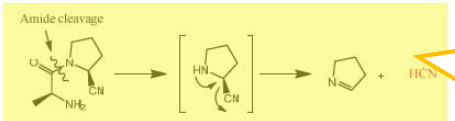


Figure 6: Avoidance of the cyano for risk of toxic cyanide release

"But there were additional reasons to dismiss Compound 25 as a lead. For instance, the cyano group introduced the concern of toxic cyanide release *in vivo* (Ex. 2056, ¶162), leading Merck to dismiss cyanopyrrolidine compounds[.]"

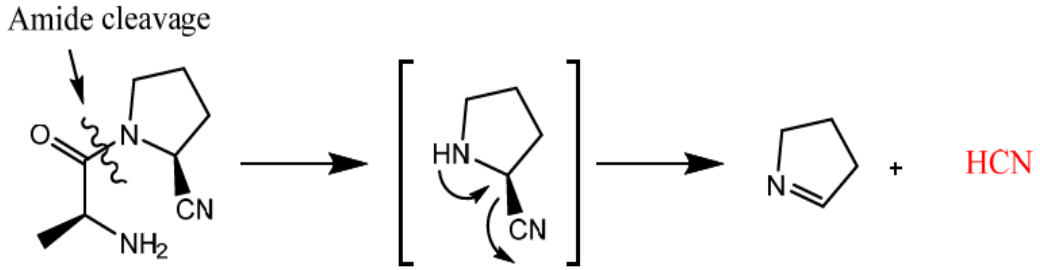
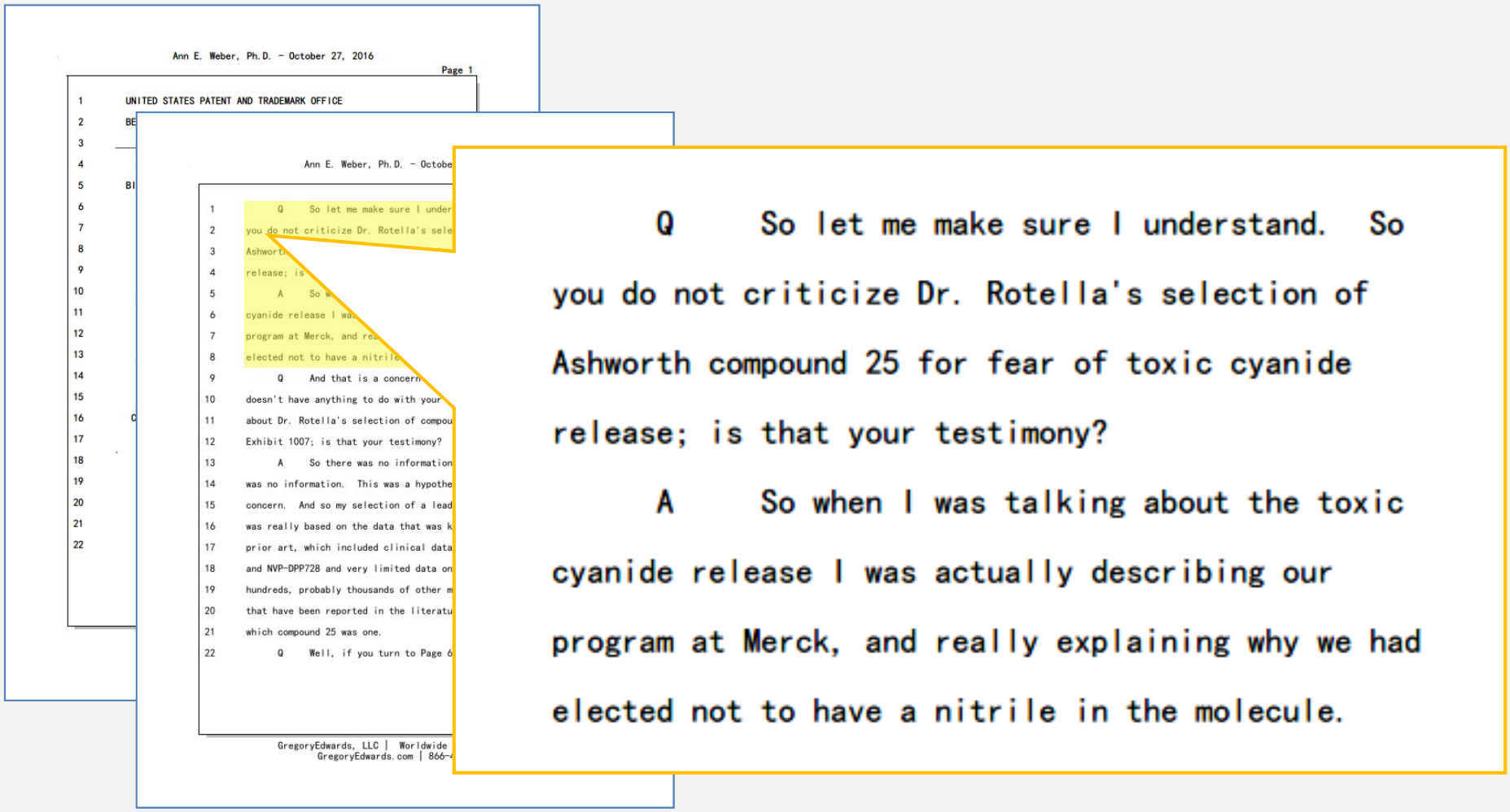


Figure 6: Avoidance of the cyano for risk of toxic cyanide release

Source: Patent Owner Resp. at 15, 23-25.

Cyanopyrrolidines Do Not Release HCN



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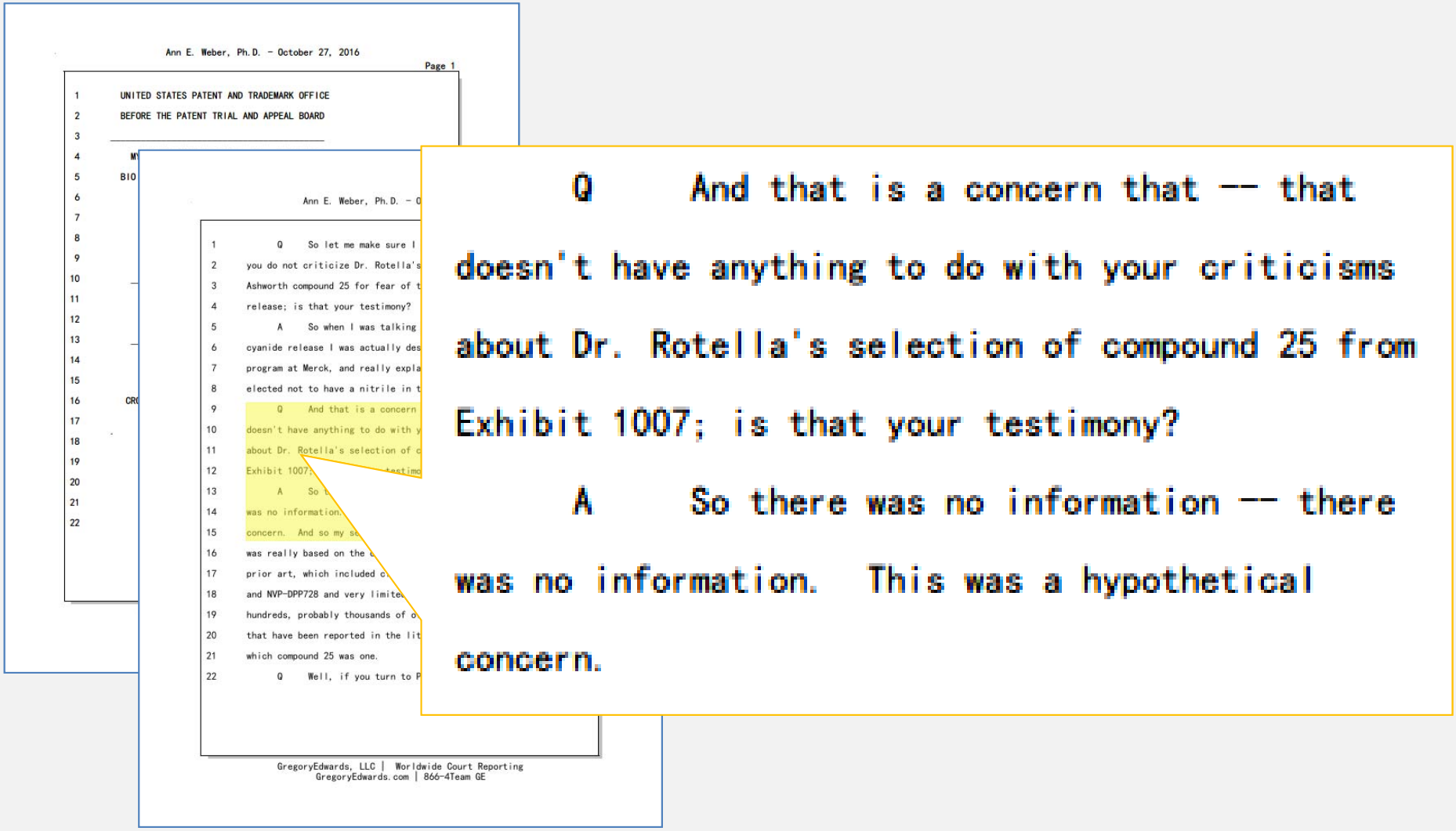
UNITED STATES PATENT AND TRADEMARK OFFICE

Q So let me make sure I understand. So you do not criticize Dr. Rotella's selection of Ashworth compound 25 for fear of toxic cyanide release; is that your testimony?

A So when I was talking about the toxic cyanide release I was actually describing our program at Merck, and really explaining why we had elected not to have a nitrile in the molecule.

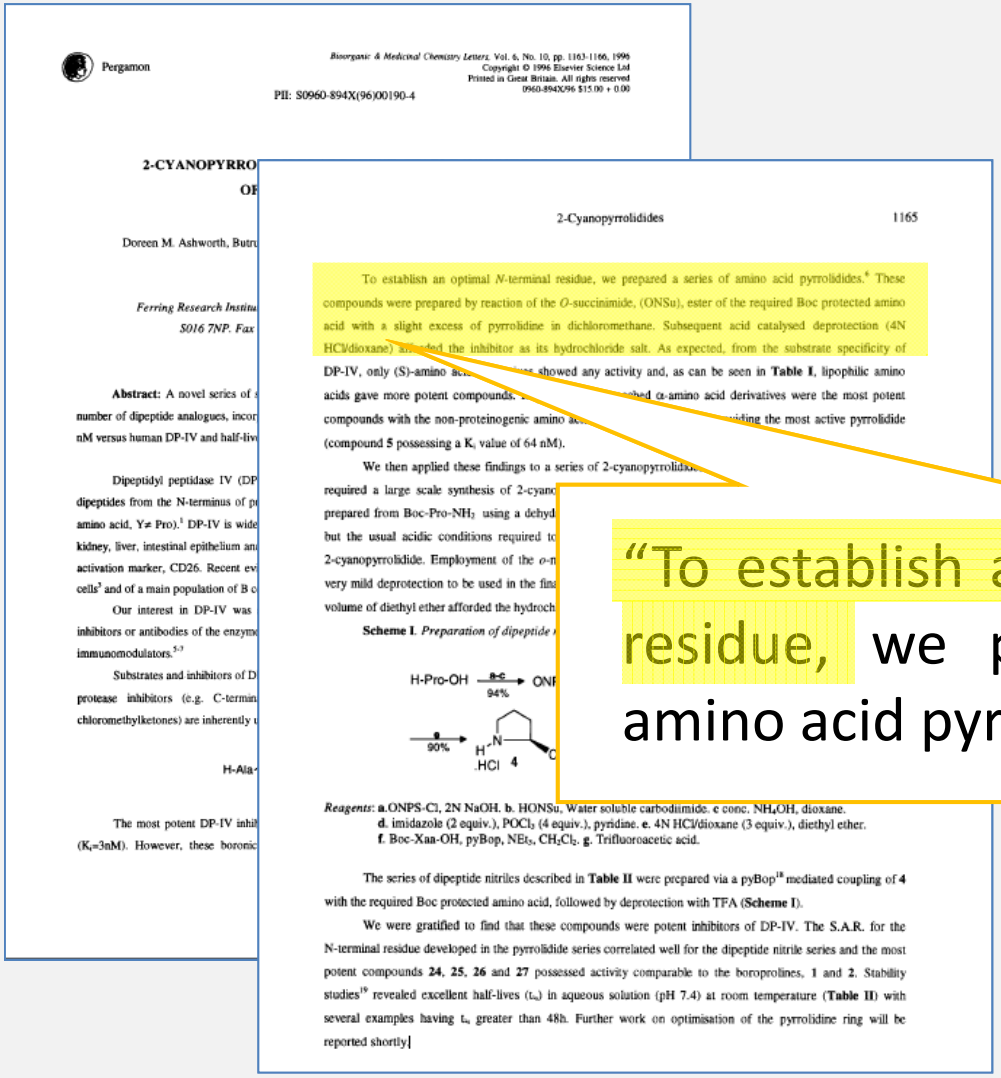
Source: EX1073 (Weber Cross-Examination), 52:1-8.

Cyanopyrrolidines Do Not Release HCN



Source: EX1073 (Weber Depo. Trans.), 52:9-15.

Ashworth I Table I Explores Optimal *N*-Terminal Residues



Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 6, No. 10, pp. 1163-1166, 1996
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PII: S0960-894X(96)00190-4

2-CYANOPYRRO
OF

Doreen M. Ashworth, Butru

Ferring Research Institu
S016 7NP. Fax

Abstract: A novel series of
number of dipeptide analogues, incor
nM versus human DP-IV and half-liv

Dipeptidyl peptidase IV (DP
dipeptides from the N-terminus of p
amino acid, Y≠ Pro).[1] DP-IV is wide
kidney, liver, intestinal epithelium an
activation marker, CD26. Recent ev
cells[2] and of a main population of B c
Our interest in DP-IV was
inhibitors or antibodies of the enzym
immunomodulators.[3-7]
Substrates and inhibitors of D
protease inhibitors (e.g. C-termin
chloromethylketones) are inherently

H-Ala-

The most potent DP-IV inhib
(K_i=3nM). However, these boronic

2-Cyanopyrrolidides 1165

To establish an optimal *N*-terminal residue, we prepared a series of amino acid pyrrolidides.[6] 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 ac showed any activity and, as can be seen in **Table I**, lipophilic amino acids gave more potent compounds. bed α-amino acid derivatives were the most potent compounds with the non-proteinogenic amino ac viding the most active pyrrolidide (compound **5** possessing a K_i value of 64 nM).

We then applied these findings to a series of 2-cyanopyrrolidi required a large scale synthesis of 2-cyanc prepared from Boc-Pro-NH_2 using a dehyd but the usual acidic conditions required t 2-cyanopyrrolidide. Employment of the *o*-n very mild deprotection to be used in the fin volume of diethyl ether afforded the hydroch

Scheme I. *Preparation of dipeptide*

H-Pro-OH —a-c, 94%→ ONP
—e, 90%→ H-N .HCl 4

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.

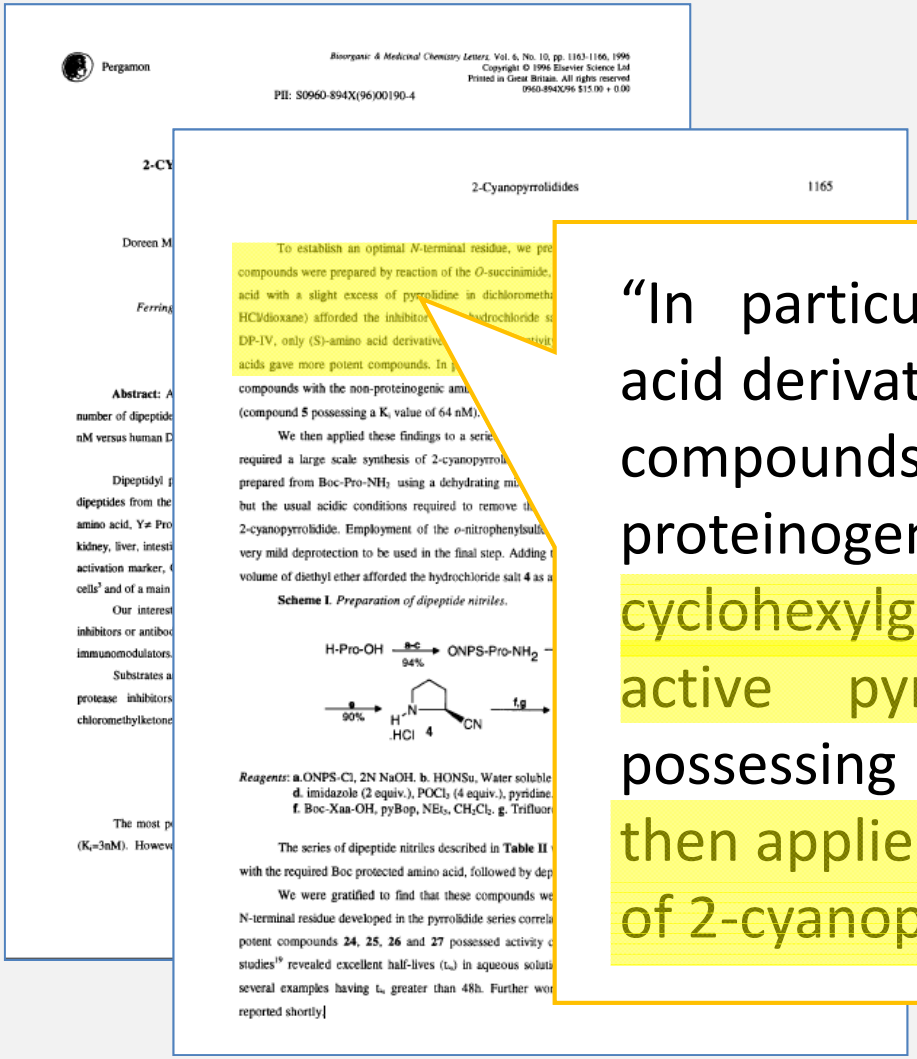
The series of dipeptide nitriles described in **Table II** were prepared via a pyBop[18] mediated coupling of **4** with the required Boc protected amino acid, followed by deprotection with TFA (**Scheme I**).

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 ($t_{\frac{1}{2}}$) in aqueous solution (pH 7.4) at room temperature (**Table II**) with several examples having $t_{\frac{1}{2}}$ greater than 48h. Further work on optimisation of the pyrrolidine ring will be reported shortly.

"To establish an optimal N-terminal residue, we prepared a series of amino acid pyrrolidides[.]"

Source: EX1007 (Ashworth I) at 1165.

Bulky Cylcohexyl at P2 Was Most Potent



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

2-Cyanopyrrolidides 1165

Doreen M

Ferring

Abstract: A

number of dipeptide

nM versus human D

Dipeptidyl p

dipeptides from the

amino acid, Y≠ Pro

kidney, liver, intest

activation marker,

cells[3] and of a main

Our interest

inhibitors or antiboc

immunomodulators.

Substrates a

protease inhibitors

chloromethylketone

The most p

(K_i=3nM). Howev

To establish an optimal *N*-terminal residue, we pre

compounds were prepared by reaction of the *O*-succinimide,

acid with a slight excess of pyrrolidine in dichlorometh

HCl/dioxane) afforded the inhibitor

DP-IV, only (S)-amino acid derivative

acids gave more potent compounds. In

compounds with the non-proteinogenic ami

(compound **5** possessing a K_i value of 64 nM).

We then applied these findings to a serie

required a large scale synthesis of 2-cyanopyrrol

prepared from Boc-Pro-NH_2 using a dehydrating m

but the usual acidic conditions required to remove t

2-cyanopyrrolidide. Employment of the *o*-nitrophenylsulf

very mild deprotection to be used in the final step. Adding

volume of diethyl ether afforded the hydrochloride salt **4** as a

Scheme I. *Preparation of dipeptide nitriles.*

H-Pro-OH —a-c, 94%→ ONPS-Pro-NH_2 —

—a, 90%→ H-Pro-CN .HCl **4** —f,g→

Reagents: **a**. ONPS-Cl, 2N NaOH. **b**. HONSu, Water soluble

d. imidazole (2 equiv.), $POCl_3$ (4 equiv.), pyridine.

f. Boc-Xaa-OH, pyBop, NEt_3, CH_2Cl_2. **g**. Trifluor

The series of dipeptide nitriles described in **Table II**

with the required Boc protected amino acid, followed by dep

We were gratified to find that these compounds we

N-terminal residue developed in the pyrrolidide series correla

potent compounds **24**, **25**, **26** and **27** possessed activity

studies[19] revealed excellent half-lives ($t_{1/2}$) in aqueous soluti

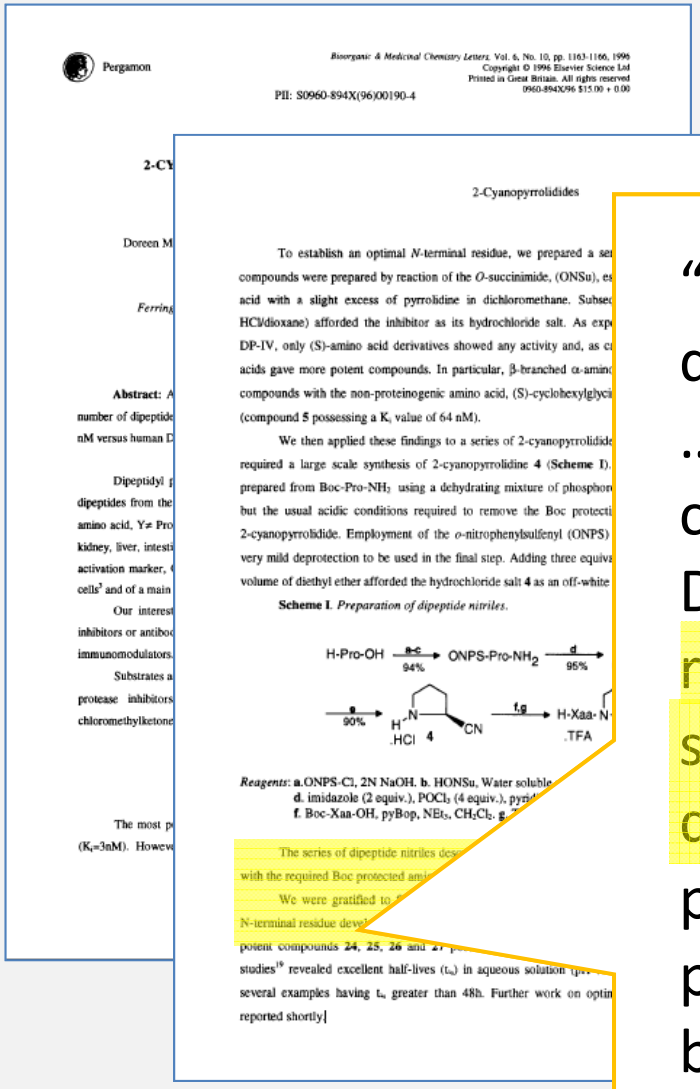
several examples having $t_{1/2}$ greater than 48h. Further wo

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 Ki value of 64 nM). We then applied these findings to a series of 2-cyanopyrrolidides."

Source: EX1007 (Ashworth I) at 1165.

Ashworth I Table I SAR Applied to Table II



2-Cyanopyrrolidides

To establish an optimal *N*-terminal residue, we prepared a ser
compounds were prepared by reaction of the *O*-succinimide, (ONSu), es
acid with a slight excess of pyrrolidine in dichloromethane. Subsec
HCl/dioxane) afforded the inhibitor as its hydrochloride salt. As exp
DP-IV, only (S)-amino acid derivatives showed any activity and, as c
acids gave more potent compounds. In particular, β-branched α-amino
compounds with the non-proteinogenic amino acid, (S)-cyclohexylglyci
(compound **5** possessing a K_i value of 64 nM).

We then applied these findings to a series of 2-cyanopyrrolidide
required a large scale synthesis of 2-cyanopyrrolidine **4** (**Scheme I**).
prepared from Boc-Pro-NH_2 using a dehydrating mixture of phosphon
but the usual acidic conditions required to remove the Boc protecti
2-cyanopyrrolidide. Employment of the *o*-nitrophenylsulfenyl (ONPS)
very mild deprotection to be used in the final step. Adding three equiva
volume of diethyl ether afforded the hydrochloride salt **4** as an off-white

Scheme I. *Preparation of dipeptide nitriles.*

H-Pro-OH —a-c, 94%→ ONPS-Pro-NH_2 —d, 95%→ —e, 90%→ H-Pro-CN .HCl **4** —f,g→ H-Xaa-N- .TFA

Reagents: **a**. ONPS-Cl, 2N NaOH. **b**. HONSu, Water soluble
d. imidazole (2 equiv.), $POCl_3$ (4 equiv.), pyri
f. Boc-Xaa-OH, pyBop, NEt_3, CH_2Cl_2. **g**.

The series of dipeptide nitriles des
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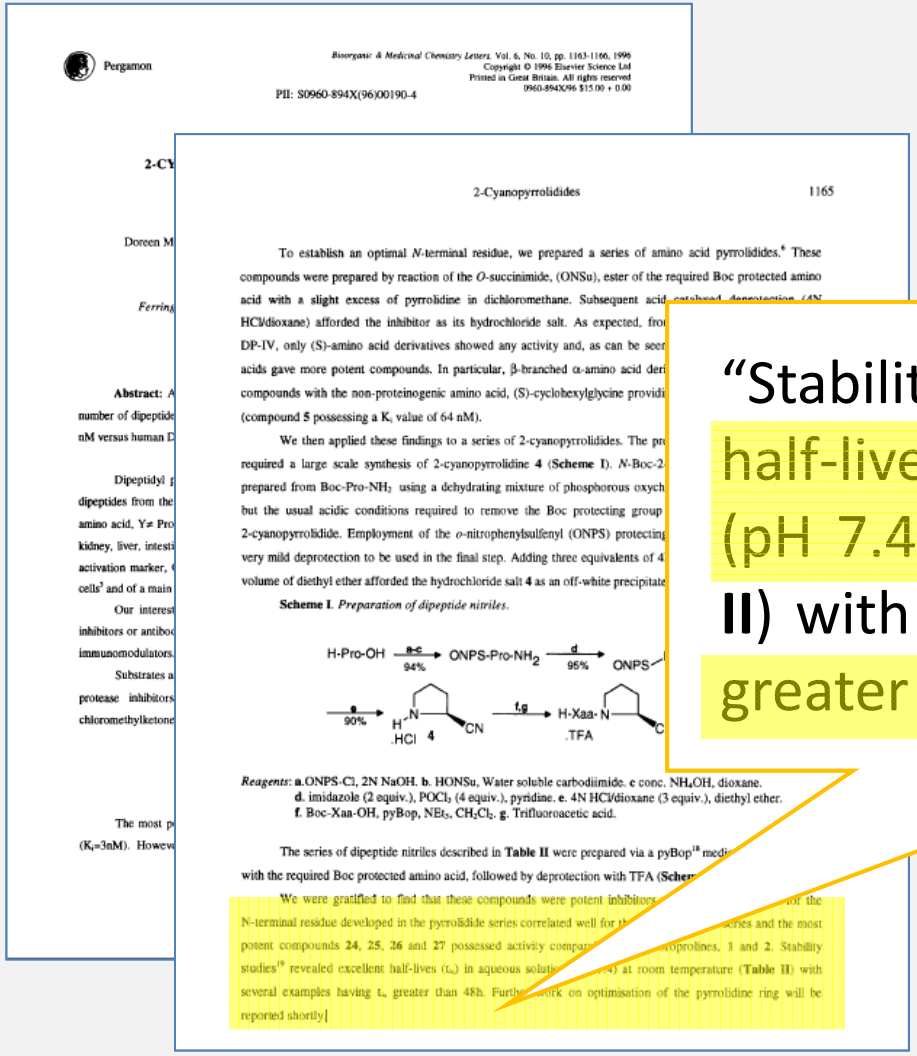
studies[19] revealed excellent half-lives ($t_{1/2}$) in aqueous solution
several examples having $t_{1/2}$ greater than 48h. Further work on optin
reported shortly.

"The series of dipeptide nitriles described in Table II were prepared ….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."

Source: EX1007 (Ashworth I) at 1165.

Ashworth I Finds Excellent Stability Greater Than 48 Hours



2-Cyanopyrrolidides 1165

To establish an optimal *N*-terminal residue, we prepared a series of amino acid pyrrolidides.[6] 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

HCl/dioxane) afforded the inhibitor as its hydrochloride salt. As expected, fro

DP-IV, only (S)-amino acid derivatives showed any activity and, as can be seer

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required a large scale synthesis of 2-cyanopyrrolidine **4** (**Scheme I**). *N*-Boc-2

prepared from Boc-Pro-NH_2 using a dehydrating mixture of phosphorous oxych

but the usual acidic conditions required to remove the Boc protecting group

2-cyanopyrrolidide. Employment of the *o*-nitrophenylsulfenyl (ONPS) protecting

very mild deprotection to be used in the final step. Adding three equivalents of 4

volume of diethyl ether afforded the hydrochloride salt **4** as an off-white precipitate

Scheme I. *Preparation of dipeptide nitriles.*

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] medi

with the required Boc protected amino acid, followed by deprotection with TFA (**Scher**

We were gratified to find that these compounds were potent inhibitors

N-terminal residue developed in the pyrrolidide series correlated well for t

potent compounds **24**, **25**, **26** and **27** possessed activity compar

studies[19] revealed excellent half-lives ($t_{1/2}$) in aqueous solut

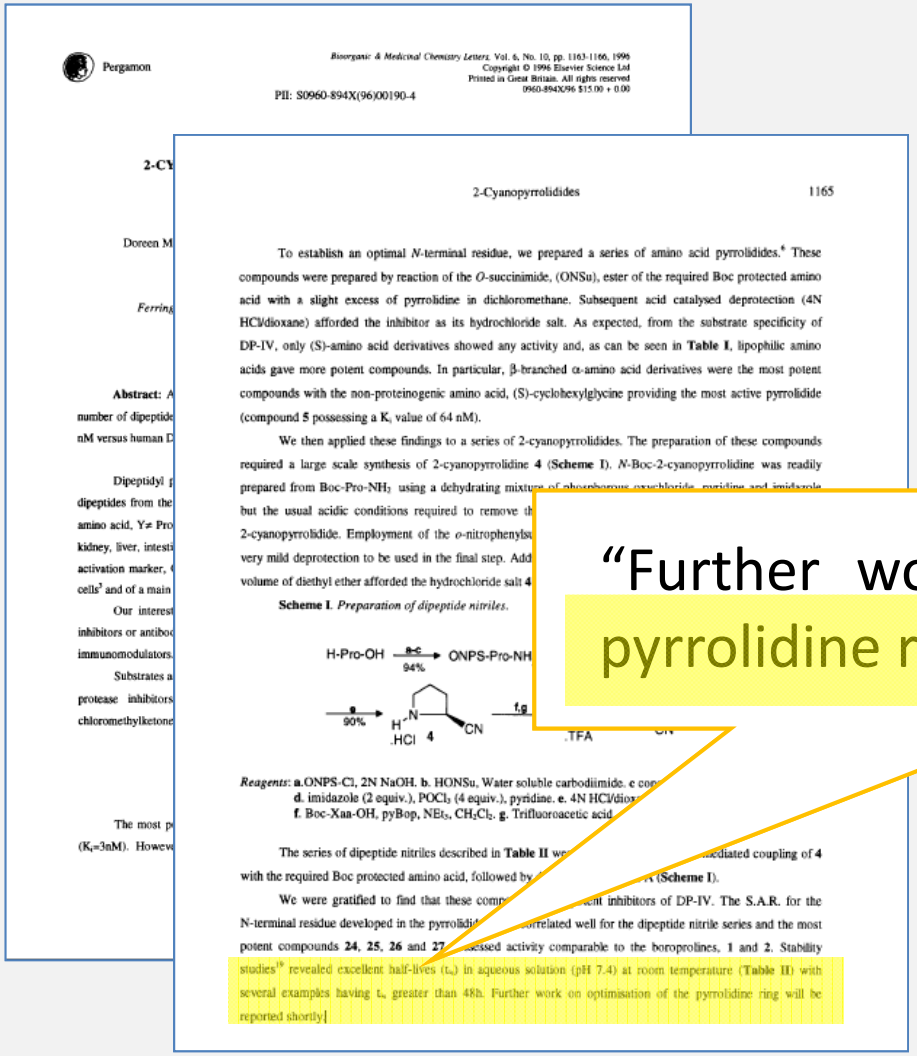
several examples having $t_{1/2}$ greater than 48h. Furth

reported shortly.

"Stability studies 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."

Source: EX1007 (Ashworth I) at 1165.

Ashworth Promises Further Investigation at P1



Pergamon

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PII: S0960-894X(96)00190-4 0960-894X/96 $15.00 + 0.00

2-Cyanopyrrolidides 1165

To establish an optimal *N*-terminal residue, we prepared a series of amino acid pyrrolidides.[6] 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).

We then applied these findings to a series of 2-cyanopyrrolidides. The preparation of these compounds required a large scale synthesis of 2-cyanopyrrolidine **4** (**Scheme I**). *N*-Boc-2-cyanopyrrolidine was readily prepared from Boc-Pro-NH_2 using a dehydrating mixture of phosphorous oxychloride, pyridine and imidazole but the usual acidic conditions required to remove th 2-cyanopyrrolidide. Employment of the *o*-nitrophenyls very mild deprotection to be used in the final step. Add volume of diethyl ether afforded the hydrochloride salt **4**

Scheme I. *Preparation of dipeptide nitriles.*

H-Pro-OH —a–c, 94%→ ONPS-Pro-NH

—g, 90%→ H-N(·HCl)-CN **4** —f,g→ ·TFA

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

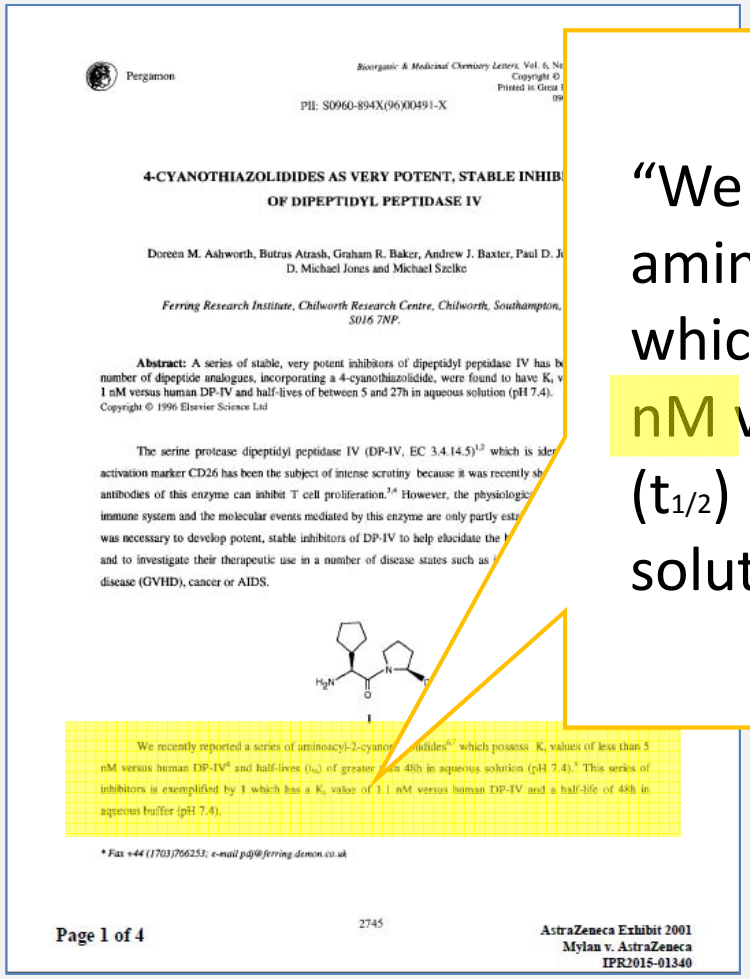
The series of dipeptide nitriles described in **Table II** w ediated coupling of **4** with the required Boc protected amino acid, followed by (**Scheme I**).

We were gratified to find that these comp ent inhibitors of DP-IV. The S.A.R. for the N-terminal residue developed in the pyrrolidi related well for the dipeptide nitrile series and the most potent compounds **24**, **25**, **26** and **27** essed 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.

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

Source: EX1007 (Ashworth I) at 1165.

Ashworth II Supports Selection of Compound 25



Pergamon

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096

PII: S0960-894X(96)00491-X

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

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

Ferring Research Institute, Chilworth Research Centre, Chilworth, Southampton,
S016 7NP.

Abstract: A series of stable, very potent inhibitors of dipeptidyl peptidase IV has b
number of dipeptide analogues, incorporating a 4-cyanothiazolidide, were found to have K_i v
1 nM versus human DP-IV and half-lives of between 5 and 27h in aqueous solution (pH 7.4).

The serine protease dipeptidyl peptidase IV (DP-IV, EC 3.4.14.5)[1,2] which is ide
activation marker CD26 has been the subject of intense scrutiny because it was recently sh
antibodies of this enzyme can inhibit T cell proliferation.[3,4] However, the physiologic
immune system and the molecular events mediated by this enzyme are only partly est
was necessary to develop potent, stable inhibitors of DP-IV to help elucidate the
and to investigate their therapeutic use in a number of disease states such as
disease (GVHD), cancer or AIDS.

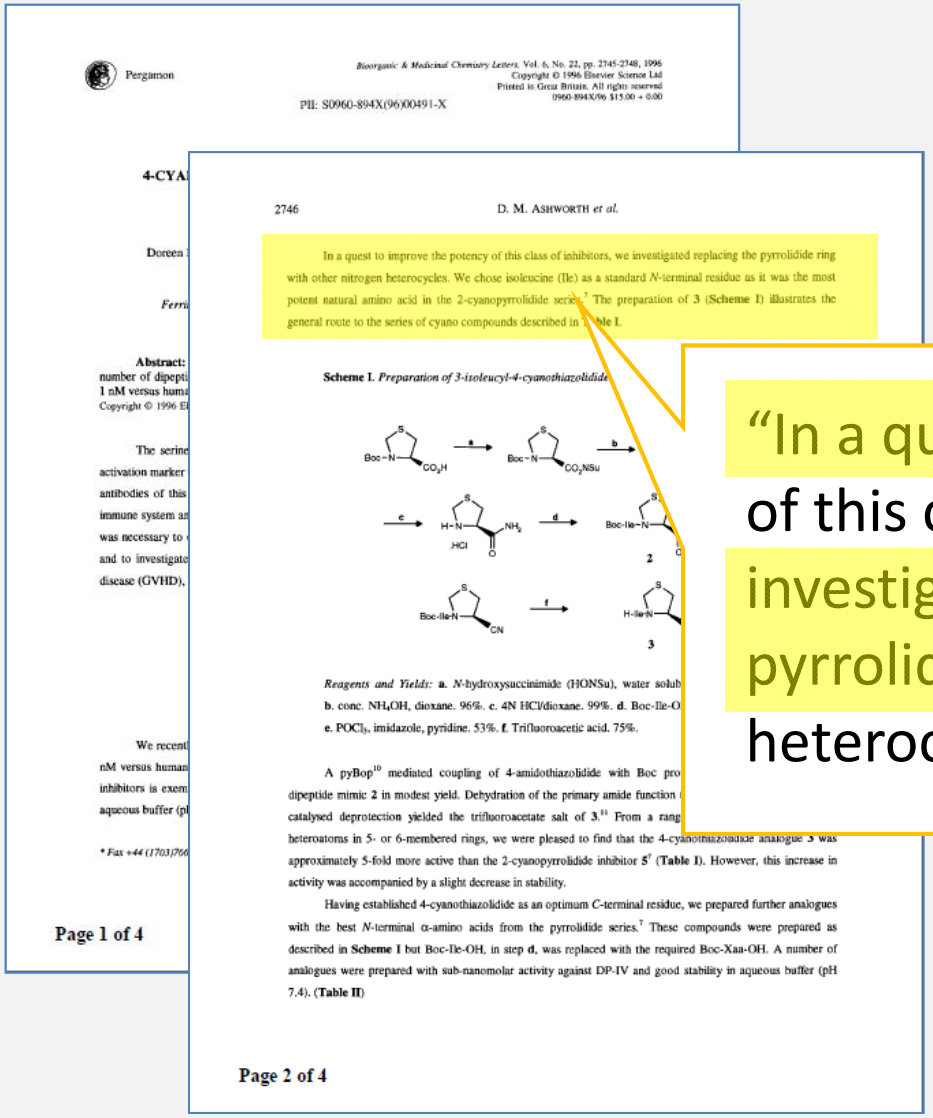
We recently reported a series of aminoacyl-2-cyano idides[6,7] which possess K_i values of less than 5 nM versus human DP-IV[5] and half-lives ($t_{1/2}$) of greater than 48h in aqueous solution (pH 7.4).[5] This series of inhibitors is exemplified by 1 which has a K_i value of 1.1 nM versus human DP-IV and a half-life of 48h in aqueous buffer (pH 7.4).

* Fax +44 (1703)756253; e-mail pdj@ferring.demon.co.uk

"We recently reported a series of aminoacyl-2-cyanopyrrolidides[6,7] which possess Ki values of less than 5 nM versus human DP-IV and half-lives ($t_{1/2}$) of greater than 48h in aqueous solution (pH 7.4)."

Source: EX2001 (Ashworth II) at 2745.

Ashworth II Seeks Even Greater Potency



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PII: S0960-894X(96)00491-X
0960-894X/96 $15.00 + 0.00

4-CYA

Doreen

Ferri

Abstract:
number of dipepti
1 nM versus huma
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The serine
activation marker
antibodies of this
immune system a
was necessary to
and to investigate
disease (GVHD),

We recent
nM versus human
inhibitors is exem
aqueous buffer (p

* Fax +44 (1703)76

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 I**) illustrates the general route to the series of cyano compounds described in Table I.

Scheme I. *Preparation of 3-isoleucyl-4-cyanothiazolidide*

Reagents and Yields: **a.** *N*-hydroxysuccinimide (HONSu), water solub
b. conc. NH_4OH, dioxane. 96%. **c.** 4N HCl/dioxane. 99%. **d.** Boc-Ile-O
e. $POCl_3$, imidazole, pyridine. 53%. **f.** Trifluoroacetic acid. 75%.

A pyBop[10] mediated coupling of 4-amidothiazolidide with Boc pro
dipeptide mimic **2** in modest yield. Dehydration of the primary amide function
catalysed deprotection yielded the trifluoroacetate salt of **3**.[11] From a rang
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.

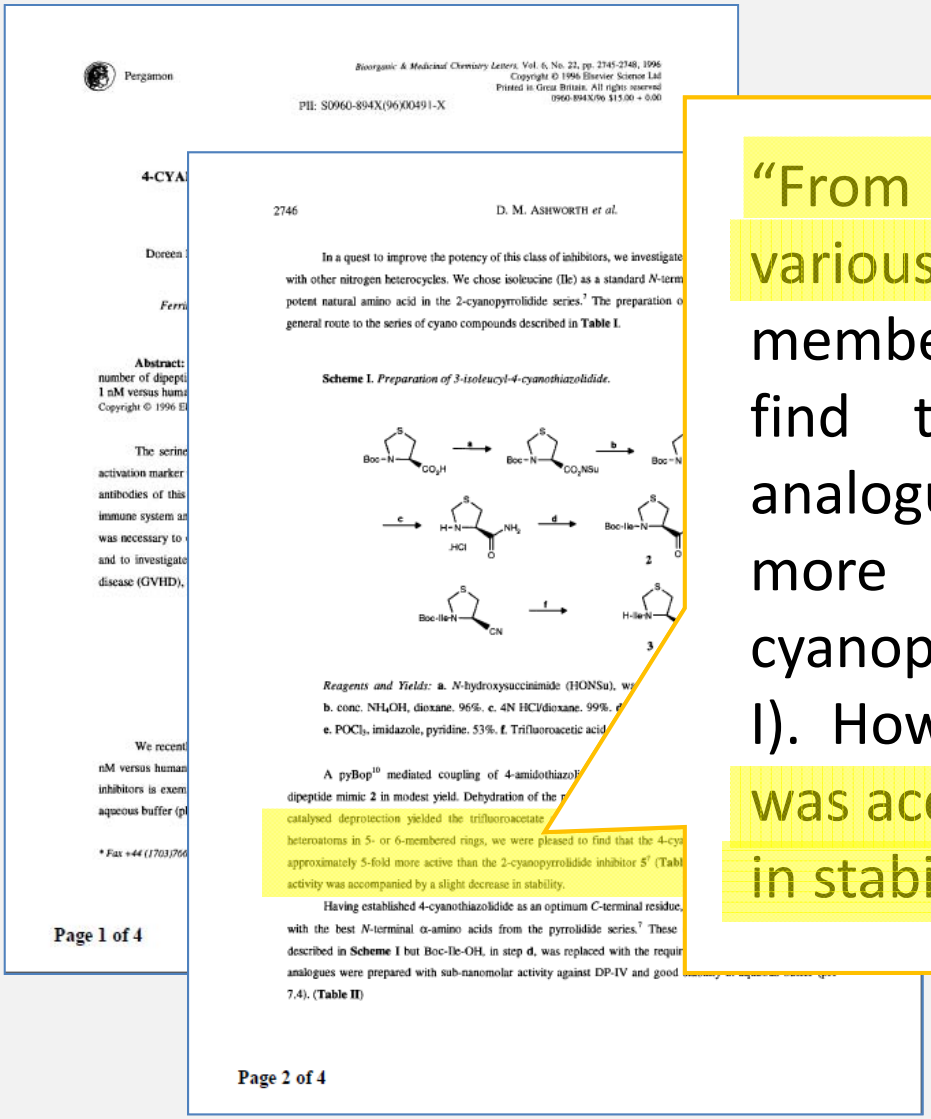
Having established 4-cyanothiazolidide as an optimum *C*-terminal residue, we prepared further analogues with the best *N*-terminal α-amino acids from the pyrrolidide series.[7] These compounds were prepared as described in **Scheme I** but Boc-Ile-OH, in step **d**, was replaced with the required Boc-Xaa-OH.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

Page 2 of 4

"In a quest to improve the potency of this class of inhibitors, we investigated replacing the pyrrolidide ring with other nitrogen heterocycles."

Source: EX2001 (Ashworth II) at 2746.

Ashworth II Supports Selection of Compound 25



Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 6, No. 22, pp. 2745-2748, 1996
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PII: S0960-894X(96)00491-X

4-CYA

Doreen

Ferri

Abstract:
number of dipepti
1 nM versus huma
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The serine
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* Fax +44 (1703)76

Page 1 of 4

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Reagents and Yields: **a.** *N*-hydroxysuccinimide (HONSu), w
b. conc. NH_4OH, dioxane. 96%. **c.** 4N HCl/dioxane. 99%.
e. $POCl_3$, imidazole, pyridine. 53%. **f.** Trifluoroacetic acid

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analogues were prepared with sub-nanomolar activity against DP-IV and good
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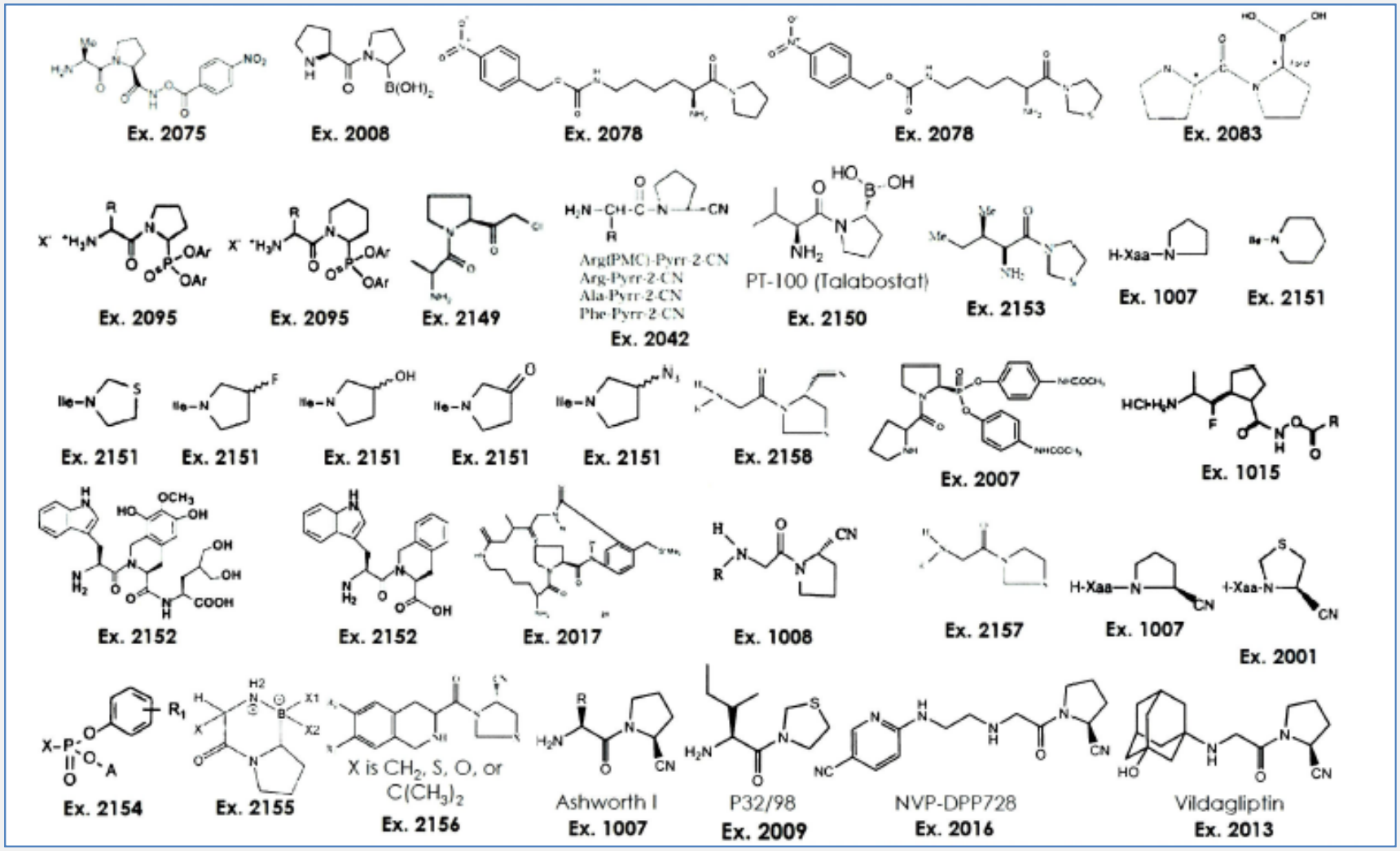
Page 2 of 4

"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 57 (Table I). However, this increase in activity was accompanied by a slight decrease in stability."

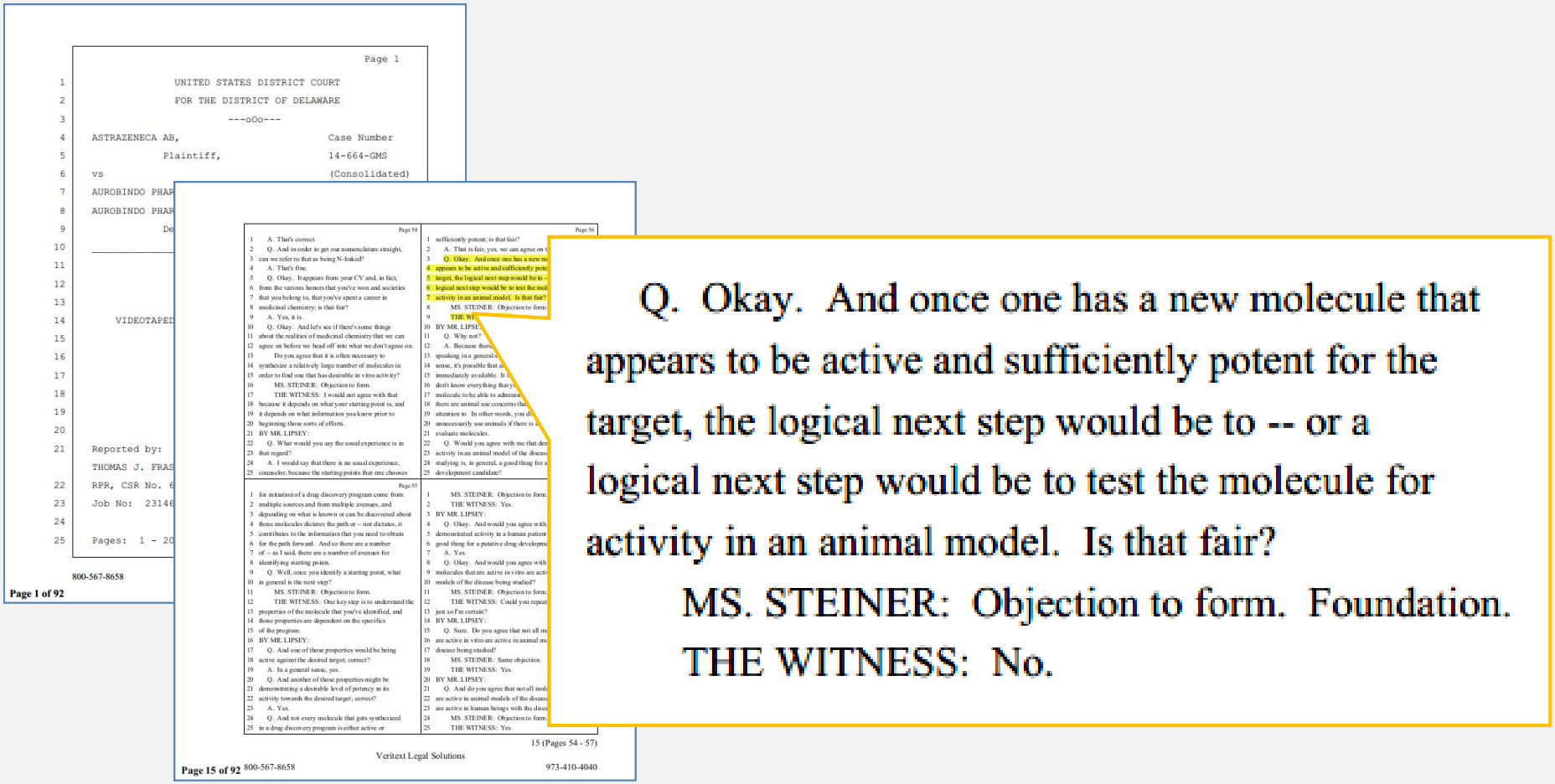
Source: EX2001 (Ashworth II) at 2746.

Many Structures Successfully Inhibit DPP-4



Source: EX2246 (AstraZeneca Demonstrative Exhibit).

In Vivo Toxicity Testing Not Required



Page 1

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

ASTRAZENECA AB, Plaintiff, vs AUROBINDO PHAR... AUROBINDO PHAR... De...

Case Number 14-664-GMS (Consolidated)

VIDEOTAPED...

Reported by: THOMAS J. FRAS...
RPR, CSR No. 6...
Job No: 23146...
Pages: 1 - 20...

800-567-8658

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Page 54

A. That's correct.
Q. And in order to get our nomenclature straight, can we refer to that as being N-linked?
A. That's fine.
Q. Okay. It appears from your CV and, in fact, from the various honors that you've won and societies that you belong to, that you've spent a career in medicinal chemistry; is that fair?
A. Yes, it is.
Q. Okay. And let's see if there's some things about the realities of medicinal chemistry that we can agree on before we head off into what we don't agree on. Do you agree that it is often necessary to synthesize a relatively large number of molecules in order to find one that has desirable in vitro activity?
MS. STEINER: Objection to form.
THE WITNESS: I would not agree with that because it depends on what your starting point is, and it depends on what information you know prior to beginning those sorts of efforts.
BY MR. LIPSEY:
Q. What would you say the usual experience is in that regard?
A. I would say that there is no usual experience, counselor, because the starting points that one chooses

Page 55

for initiation of a drug discovery program come from multiple sources and from multiple avenues, and depending on what is known or can be discovered about those molecules dictates the path or -- not dictates, it contributes to the information that you need to obtain for the path forward. And so there are a number of -- as I said, there are a number of avenues for identifying starting points.
Q. Well, once you identify a starting point, what in general is the next step?
MS. STEINER: Objection to form.
THE WITNESS: One key step is to understand the properties of the molecule that you've identified, and those properties are dependent on the specifics of the program.
BY MR. LIPSEY:
Q. And one of those properties would be being active against the desired target; correct?
A. In a general sense, yes.
Q. And another of those properties might be demonstrating a desirable level of potency in its activity towards the desired target; correct?
A. Yes.
Q. And not every molecule that gets synthesized in a drug discovery program is either active or

Page 56

sufficiently potent; is that fair?
A. That is fair, yes, we can agree on t...
Q. Okay. And once one has a new mo...
appears to be active and sufficiently pote...
target, the logical next step would be to -...
logical next step would be to test the mol...
activity in an animal model. Is that fair?
MS. STEINER: Objection to form.
THE WI...
BY MR. LIPSEY:
Q. Why not?
A. Because there...
speaking in a general s...
sense, it's possible that a...
immediately available. It ...
don't know everything that y...
molecule to be able to administ...
there are animal use concerns tha...
attention to. In other words, you d...
unnecessarily use animals if there is a...
evaluate molecules.
Q. Would you agree with me that den...
activity in an animal model of the disease...
studying is, in general, a good thing for a...
development candidate?

MS. STEINER: Objection to form.
THE WITNESS: Yes.
BY MR. LIPSEY:
Q. Okay. And would you agree with...
demonstrated activity in a human patient...
good thing for a putative drug developme...
A. Yes.
Q. Okay. And would you agree with...
molecules that are active in vitro are acti...
models of the disease being studied?
MS. STEINER: Objection to form.
THE WITNESS: Could you repeat...
just so I'm certain?
BY MR. LIPSEY:
Q. Sure. Do you agree that not all m...
are active in vitro are active in animal m...
disease being studied?
MS. STEINER: Same objection.
THE WITNESS: Yes.
BY MR. LIPSEY:
Q. And do you agree that not all mole...
are active in animal models of the disease...
are active in human beings with the disea...
MS. STEINER: Objection to form.
THE WITNESS: Yes.

15 (Pages 54 - 57)

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Page 15 of 92 800-567-8658 973-410-4040

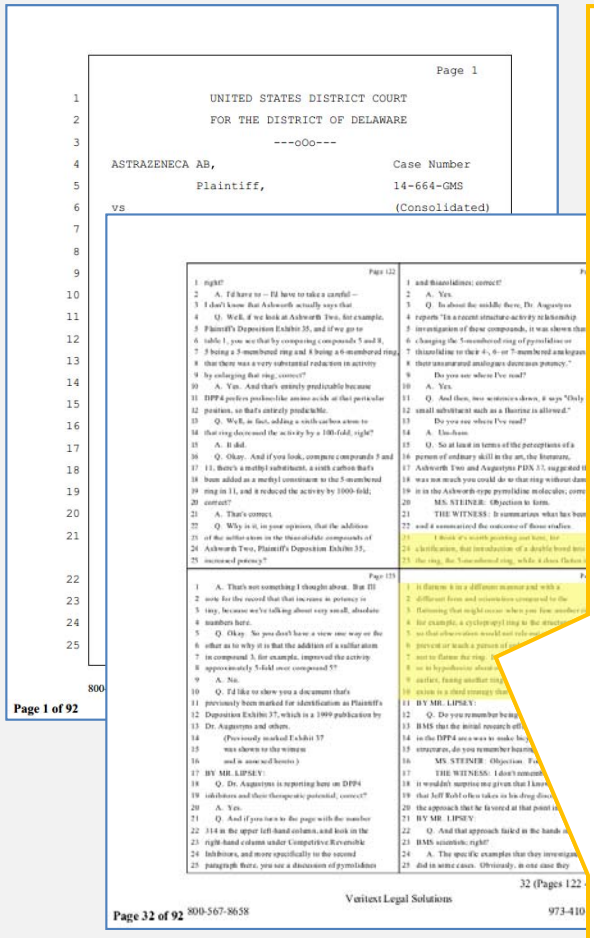
Q. Okay. And once one has a new molecule that appears to be active and sufficiently potent for the target, the logical next step would be to -- or a logical next step would be to test the molecule for activity in an animal model. Is that fair?

MS. STEINER: Objection to form. Foundation.

THE WITNESS: No.

Source: EX2174 (Rotella Depo. Trans.), 56:3-9; Institution Dec. at 11.

Double Bonds Affect Pyrrolidine Conformation Differently



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

ASTRAZENECA AB, Plaintiff, vs

Case Number 14-664-GMS (Consolidated)

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Veritext Legal Solutions

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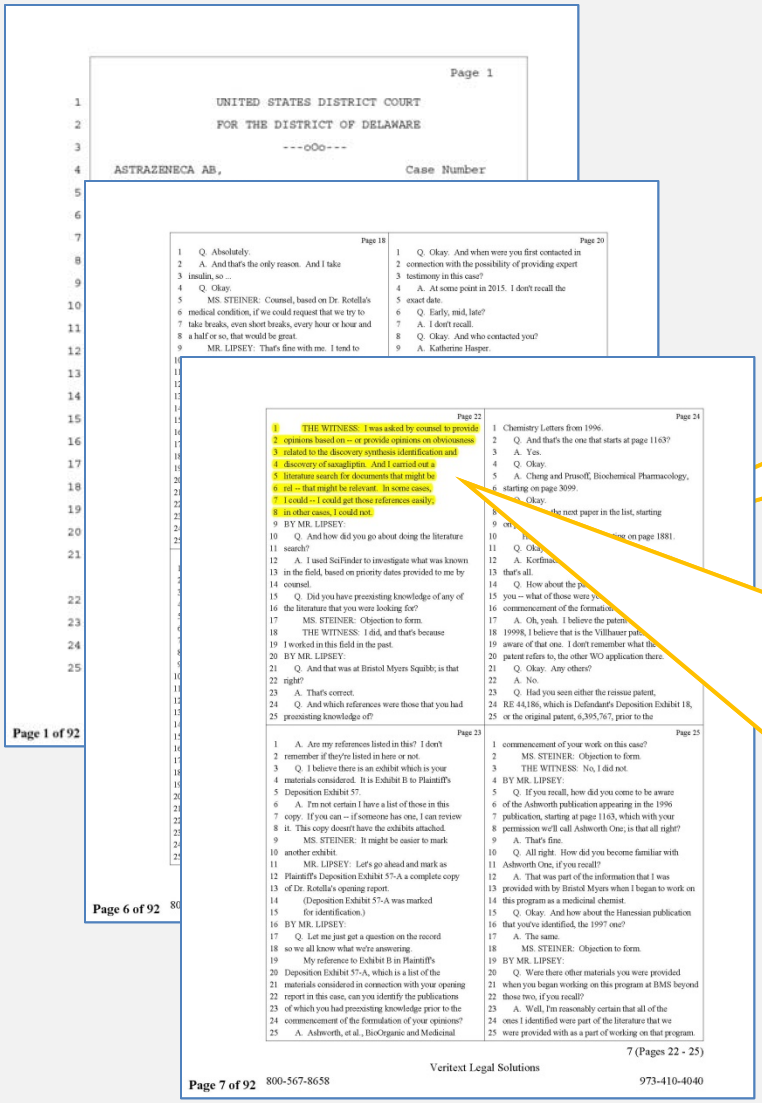
I think it's worth pointing out here, for clarification, that introduction of a double bond into the ring, the 5-membered ring, while it does flatten it, it flattens it in a different manner and with a different form and orientation compared to the flattening that might occur when you fuse another ring, for example, a cyclopropyl ring to the structure. And so that observation would not rule out or would not prevent or teach a person of ordinary skill in the art not to flatten the ring. It might lead them to suggest or to hypothesize about other ways, and as I outlined earlier, fusing another ring system to the one that exists is a third strategy that is commonly employed.

Source: EX2174 (Rotella Depo. Trans.), 124:23-125:10.

Dr. Rotella's Prior Art Search



Page 1

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE
---oOo---
ASTRAZENECA AB, Case Number

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Page 18

Q. Absolutely.
A. And that's the only reason. And I take insulin, so ...
Q. Okay.
MS. STEINER: Counsel, based on Dr. Rotella's medical condition, if we could request that we try to take breaks, even short breaks, every hour or hour and a half or so, that would be great.
MR. LIPSEY: That's fine with me. I tend to

Page 20

Q. Okay. And when were you first contacted in connection with the possibility of providing expert testimony in this case?
A. At some point in 2015. I don't recall the exact date.
Q. Early, mid, late?
A. I don't recall.
Q. Okay. And who contacted you?
A. Katherine Hasper.

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Page 22

THE WITNESS: I was asked by counsel to provide opinions based on -- or provide opinions on obviousness related to the discovery synthesis identification and discovery of saxagliptin. And I carried out a literature search for documents that might be rel -- that might be relevant. In some cases, I could -- I could get those references easily; in other cases, I could not.
BY MR. LIPSEY:
Q. And how did you go about doing the literature search?
A. I used SciFinder to investigate what was known in the field, based on priority dates provided to me by counsel.
Q. Did you have preexisting knowledge of any of the literature that you were looking for?
MS. STEINER: Objection to form.
THE WITNESS: I did, and that's because I worked in this field in the past.
BY MR. LIPSEY:
Q. And that was at Bristol Myers Squibb; is that right?
A. That's correct.
Q. And which references were those that you had preexisting knowledge of?

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Chemistry Letters from 1996.
Q. And that's the one that starts at page 1163?
A. Yes.
Q. Okay.
A. Cheng and Prusoff, Biochemical Pharmacology, starting on page 3099.
Q. Okay.
A. [illegible] the next paper in the list, starting on page 1881.
Q. Okay.
A. Korfmacher, that's all.
Q. How about the patent [illegible] you -- what of those were you [illegible] commencement of the formation [illegible]
A. Oh, yeah. I believe the patent [illegible] 19998, I believe that is the Villhauer patent [illegible] aware of that one. I don't remember what the patent refers to, the other WO application there.
Q. Okay. Any others?
A. No.
Q. Had you seen either the reissue patent, RE 44,186, which is Defendant's Deposition Exhibit 18, or the original patent, 6,305,767, prior to the

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A. Are my references listed in this? I don't remember if they're listed in here or not.
Q. I believe there is an exhibit which is your materials considered. It is Exhibit B to Plaintiff's Deposition Exhibit 57.
A. I'm not certain I have a list of those in this copy. If you can -- if someone has one, I can review it. This copy doesn't have the exhibits attached.
MS. STEINER: It might be easier to mark another exhibit.
MR. LIPSEY: Let's go ahead and mark as Plaintiff's Deposition Exhibit 57-A a complete copy of Dr. Rotella's opening report.
(Deposition Exhibit 57-A was marked for identification.)
BY MR. LIPSEY:
Q. Let me just get a question on the record so we all know what we're answering.
My reference to Exhibit B in Plaintiff's Deposition Exhibit 57-A, which is a list of the materials considered in connection with your opening report in this case, can you identify the publications of which you had preexisting knowledge prior to the commencement of the formulation of your opinions?
A. Ashworth, et al., BioOrganic and Medicinal

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commencement of your work on this case?
MS. STEINER: Objection to form.
THE WITNESS: No, I did not.
BY MR. LIPSEY:
Q. If you recall, how did you come to be aware of the Ashworth publication appearing in the 1996 publication, starting at page 1163, which with your permission we'll call Ashworth One; is that all right?
A. That's fine.
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.
MS. STEINER: Objection to form.
BY MR. LIPSEY:
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.

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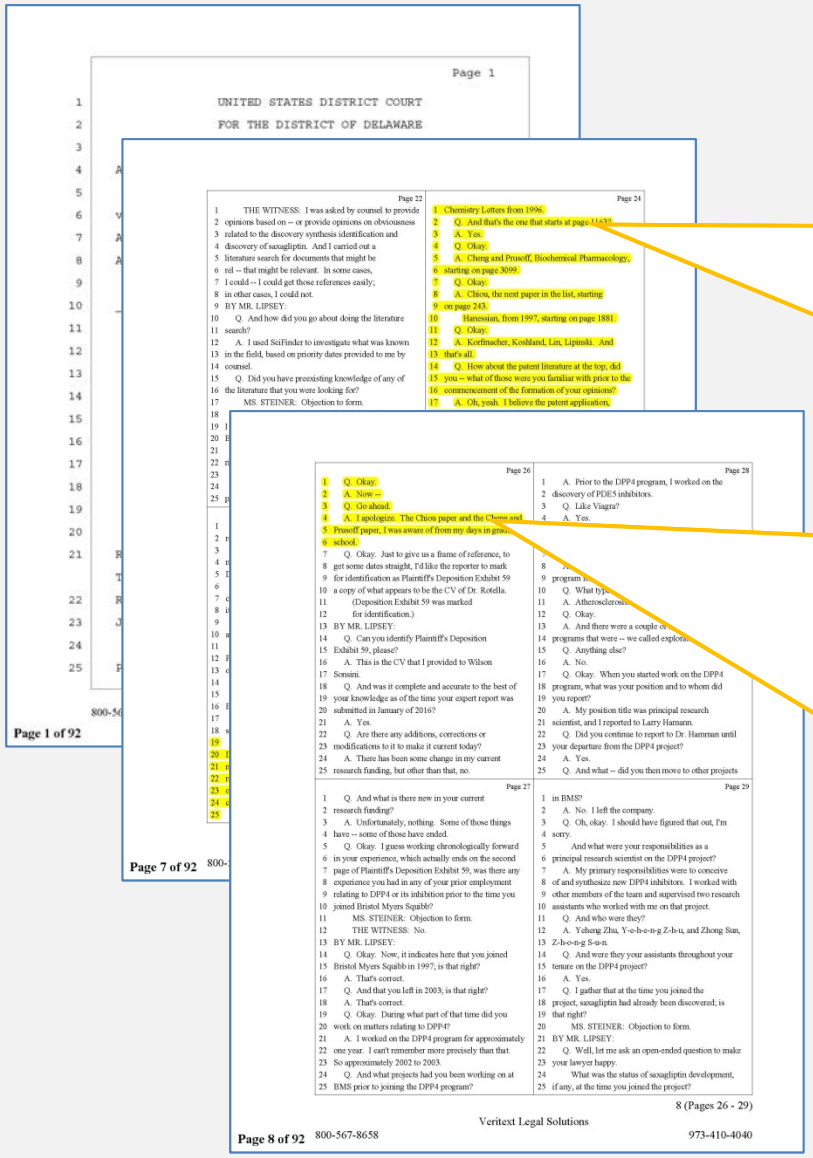
"Q. What I'm trying to get at is how you came to know of the existence of the materials that you principally rely upon in your report."

"THE WITNESS: I was asked by counsel to provide…opinions on obviousness related to the discovery[,] synthesis[,] identification[,] and discovery of saxagliptin. And I carried out a literature search for documents that might be rel[evant]…. In some cases, I could -- I could get those references easily; in other cases, I could not."

Source: EX2174 (Rotella Depo.), 22:15-26:4.

Dr. Rotella's Prior Art Search



"[C]an you identify the publications of which you had preexisting knowledge prior to the commencement of the formulation of your opinions?

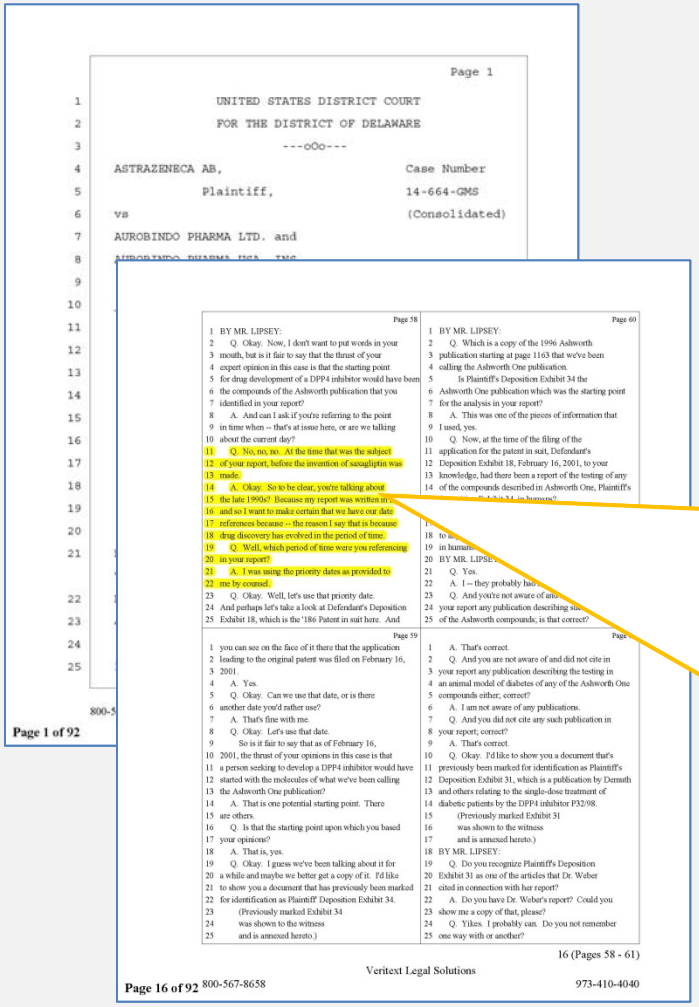
A. Ashworth[I]…, Cheng,… Chiou,… Hanessian, Korfmacher,… the Villhauer patent…."

"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…. I apologize. The Chiou paper and the Cheng and Prusoff paper, I was aware of from my days in graduate school."

Source: EX2174 (Rotella Depo.), 23:25-24:22, 25:20-26:6 .

Dr. Rotella's Prior Art Search



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

ASTRAZENECA AB, Plaintiff, vs AUROBINDO PHARMA LTD. and

Case Number 14-664-GMS (Consolidated)

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BY MR. LIPSEY:
Q. Okay. Now, I don't want to put words in your mouth, but is it fair to say that the thrust of your expert opinion in this case is that the starting point for drug development of a DPP4 inhibitor would have been the compounds of the Ashworth publication that you identified in your report?
A. And can I ask if you're referring to the point in time when -- that's at issue here, or are we talking about the current day?
Q. No, no, no. At the time that was the subject of your report, before the invention of saxagliptin was made.
A. Okay. So to be clear, you're talking about the late 1990s? Because my report was written in 2016, and so I want to make certain that we have our date references because -- the reason I say that is because drug discovery has evolved in the period of time.
Q. Well, which period of time were you referencing in your report?
A. I was using the priority dates as provided to me by counsel.
Q. Okay. Well, let's use that priority date.
And perhaps let's take a look at Defendant's Deposition Exhibit 18, which is the '186 Patent in suit here. And

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you can see on the face of it there that the application leading to the original patent was filed on February 16, 2001.
A. Yes.
Q. Okay. Can we use that date, or is there another date you'd rather use?
A. That's fine with me.
Q. Okay. Let's use that date.
So is it fair to say that as of February 16, 2001, the thrust of your opinions in this case is that a person seeking to develop a DPP4 inhibitor would have started with the molecules of what we've been calling the Ashworth One publication?
A. That is one potential starting point. There are others.
Q. Is that the starting point upon which you based your opinions?
A. That is, yes.
Q. Okay. I guess we've been talking about it for a while and maybe we better get a copy of it. I'd like to show you a document that has previously been marked for identification as Plaintiff' Deposition Exhibit 34.
(Previously marked Exhibit 34 was shown to the witness and is annexed hereto.)

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BY MR. LIPSEY:
Q. Which is a copy of the 1996 Ashworth publication starting at page 1163 that we've been calling the Ashworth One publication.
Is Plaintiff's Deposition Exhibit 34 the Ashworth One publication which was the starting point for the analysis in your report?
A. This was one of the pieces of information that I used, yes.
Q. Now, at the time of the filing of the application for the patent in suit, Defendant's Deposition Exhibit 18, February 16, 2001, to your knowledge, had there been a report of the testing of any of the compounds described in Ashworth One, Plaintiff's

Q. Yes.
A. I -- they probably ha
Q. And you're not aware of an
your report any publication describing
of the Ashworth compounds; is that correct?

A. That's correct.
Q. And you are not aware of and did not cite in your report any publication describing the testing in an animal model of diabetes of any of the Ashworth One compounds either; correct?
A. I am not aware of any publications.
Q. And you did not cite any such publication in your report; correct?
A. That's correct.
Q. Okay. I'd like to show you a document that's previously been marked for identification as Plaintiff's Deposition Exhibit 31, which is a publication by Demuth and others relating to the single-dose treatment of diabetic patients by the DPP4 inhibitor P32/98.
(Previously marked Exhibit 31 was shown to the witness and is annexed hereto.)
BY MR. LIPSEY:
Q. Do you recognize Plaintiff's Deposition Exhibit 31 as one of the articles that Dr. Weber cited in connection with her report?
A. Do you have Dr. Weber's report? Could you show me a copy of that, please?
Q. Yikes. I probably can. Do you not remember one way with or another?

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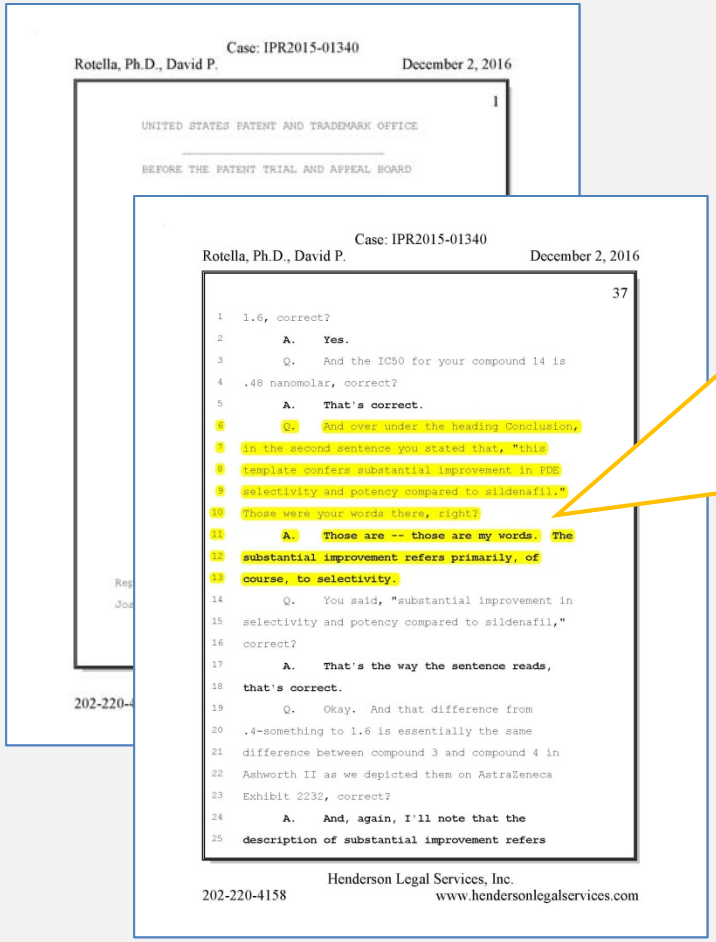
"Q. No, no, no. At the time that was the subject of your report, before the invention of saxagliptin was made.
A. Okay. So to be clear, you're talking about the late 1990s? Because my report was written in 2016, and so I want to make certain that we have our date references because -- the reason I say that is because drug discovery has evolved in the period of time.
Q. Well, which period of time were you referencing in your report?
A. I was using the priority dates as provided to me by counsel."

Source: EX2174 (Rotella Depo.), 58:2-22.

Dr. Rotella



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1.6, correct?
A. Yes.
Q. And the IC50 for your compound 14 is .48 nanomolar, correct?
A. That's correct.
Q. And over under the heading Conclusion, in the second sentence you stated that, "this template confers substantial improvement in PDE selectivity and potency compared to sildenafil." Those were your words there, right?
A. Those are -- those are my words. The substantial improvement refers primarily, of course, to selectivity.
Q. You said, "substantial improvement in selectivity and potency compared to sildenafil," correct?
A. That's the way the sentence reads, that's correct.
Q. Okay. And that difference from .4-something to 1.6 is essentially the same difference between compound 3 and compound 4 in Ashworth II as we depicted them on AstraZeneca Exhibit 2232, correct?
A. And, again, I'll note that the description of substantial improvement refers

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"Q. And over under the heading Conclusion, in the second sentence you stated that, 'this template confers substantial improvement in PDE selectivity and potency compared to sildenafil.' Those were your words there, right?

A. Those are – those are my words. The substantial improvement refers primarily, of course, to selectivity."

Source: EX2221 (Rotella Depo. Transcript), 37:6-13.

CERTIFICATE OF SERVICE

On 23 January 2017, Mylan served a copy of its demonstrative exhibits on counsel for Patent Owner AstraZeneca AB at the following electronic service addresses:

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Respectfully submitted,

Dated: 23 January 2017

By: /Richard Torczon /
Richard Torczon, Backup Counsel
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