Design and Synthesis of Selective Dipeptidyl Peptidase IV Inhibitors, A New Approach to the Treatment of Type 2 Diabetes

Ischia Advanced School of Organic Chemistry
Ischia Porto, Napoli (Italy)
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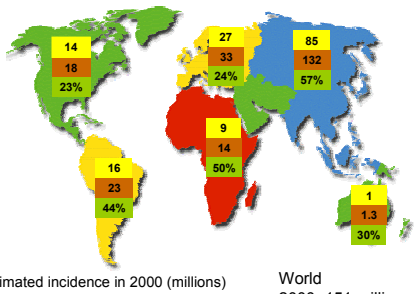
Merck Research Laboratories

Diabetes Is a Growing Worldwide Epidemic



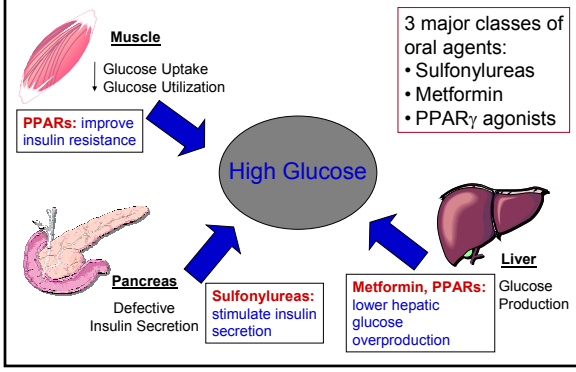
- Estimated incidence in 2000 (millions)
- Estimated incidence in 2010 (millions)
- **% increase from 2000 to 2010**

World
2000: 151 million
2010: 221 million (+46%)

Adapted from Amos AF et al *Diabet Med* 1997;14:S7–S85.

Elevated Blood Glucose in Diabetes

Causes and Consequences



Liabilities of 3 Major Classes of Oral Agents

	Metformin	Sulfonylurea	PPARγ
Increased Risk of Hypoglycemia		●	
Drug Interactions		●	
GI Side Effects	●		
Risk of Lactic Acidosis	●		
Risk of β cell Exhaustion		●	
Weight Gain		●	●
Edema			●
Inadequate long-term efficacy	●	●	?

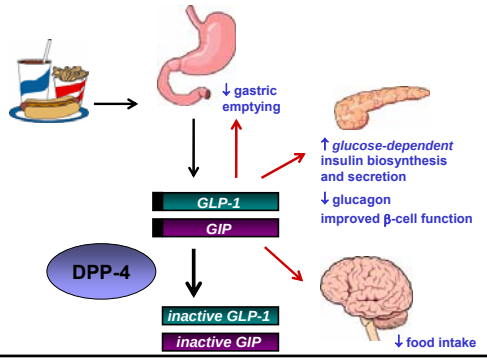
Dipeptidyl Peptidase IV (DPP-4)

- Cell surface serine dipeptidase belonging to the prolyl oligopeptidase family
- Specificity for P_1 Pro >>> Ala
- Widely expressed
- Identical to CD26, a marker for activated T cells

Rasmussen et al., *Nat. Struct. Biol.* 10, 19 -25 (2003)

Role of Dipeptidyl Peptidase IV in Metabolic Control

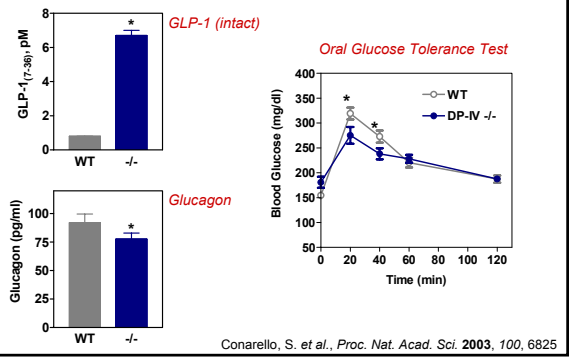
Established Mechanism through GLP-1 and GIP



DPP-4 Inhibition: Proof of Concept

- DPP-4 deficient mice
  - healthy and fertile
  - improved metabolic profile
- DPP-4 inhibitors stabilize GLP-1 & GIP and lower prandial and fasting glucose in humans (e.g., DPP728, LAF237, Ile thiazolidide)

DPP-4 $^{-/-}$ Mice: Improved Glucose Tolerance



Conarello, S. *et al.*, *Proc. Nat. Acad. Sci.* **2003**, *100*, 6825

DPP-4 Inhibition: Proof of Concept

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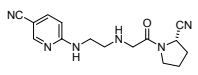
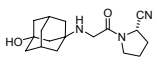
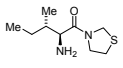


DPP728



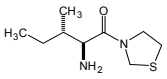
LAF237



Ile-Thia

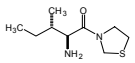
Isoleucyl Thiazolidide: Early Indication of "Off-Target" Activity

- Moderately potent, reversible DPP-4 inhibitor in Phase I
- Preclinical toxicology study findings in dogs:
  - Acute gastrointestinal toxicity
  - Anemia, thrombocytopenia
  - Mortality
- Development discontinued
  - Basic Research and Preclinical studies designed to elucidate mechanism of toxicity

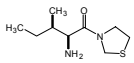


threo isoleucyl thiazolidide

Preclinical Profiles of *Threo* and *Allo* Isomers of Isoleucyl Thiazolidide

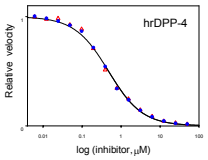


threo isomer



allo isomer

- Mechanism: Competitive, reversible
- Identical K_i values (~ 195 nM)
- Clean in Panlabs at 100 μM
- Same efficacy in OGTT (3 mpk)
- Similar PK and metabolic profile
- Toxic in rats and dogs
  - allo is toxic at ~ 10-fold lower dosage



Selectivity of *Threo* and *Allo* Isomers of Isoleucyl Thiazolidide

		IC_{50}, threo (nM)	IC_{50}, allo (nM)
DPP-4 Gene Family	DPP-9	1600	320
	DPP-8	2170	220
	FAP	ND	ND
	DPP-4	420	460
	DPP-6	not catalytically active	
Other Proline Specific Enzymes	PEP	> 100000	> 100000
	QPP/DPP-2	14,000	18,000
	APP	> 100000	> 100000
	prolidase	> 100000	> 100000

Toxicity of Isoleucinyl Thiazolidide Inhibitors

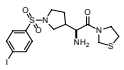
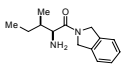
Hypothesis

Toxicity due to off-target activity (DPP-8, DPP-9 or QPP)

Strategy

- Identify selective inhibitors of DPP-4, DPP-8, DPP-9 and QPP
- Test in comparative toxicity studies
  - 2 week rat toxicity study (10, 30, 100 mg/kg PO)
  - single dose dog tolerability study (10 mg/kg PO)

Identification of Selective Inhibitors

	Sitagliptin Analog		
	DPP-4 Selective	QPP Selective	DPP-8/9 Selective

Enzyme	IC_{50}, nM		
DPP-9	> 100,000	11,000	**55**
DPP-8	69,000	22,000	**38**
FAP	> 100,000	> 100,000	> 100,000
DPP-4	**27**	1900	30,000
PEP	> 100,000	> 100,000	> 100,000
QPP/DPP-2	> 100,000	**19**	14,000
APP	> 100,000	> 100,000	> 100,000
prolidase	> 100,000	> 100,000	> 100,000

Comparative Toxicity Study

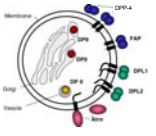
2 wk. Rat Toxicity	*allo*	*threo*	QPP Selective	DPP-8/9 Selective	DPP-4 Selective
alopecia	✓			✓	
thrombocytopenia	✓	✓		✓	
anemia	✓				
reticulocytopenia	n.d.	n.d.	✓	✓	
enlarged spleen	✓			✓	
mortality	✓			✓	
Acute Dog Toxicity					
Bloody diarrhea	✓			✓	

n.d. = not detemined

G. Lankas, *et al.*, *Diabetes* **2005**, *54*, 2988

Potential Importance of Selective Inhibition for the Treatment of Type 2 Diabetes

- Conclusion
  - "Off-target" peptidase inhibition (i.e. inhibition of other DPP family peptidases such as DPP-8/9) can produce severe toxicity in preclinical species
- Variables that may determine degree of toxicity
  - Cell penetration
    - Unlike DPP-4, DPP-8/9 are intracellular proteins
  - Extent of inhibition of DPP-8 and/or DPP-9
    - Not known if inhibition of both enzymes (or how much) is required to produce toxicities
  - Intra-species differences in inhibition of DPP-8/9

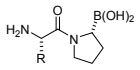


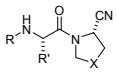
from Demuth *et al. Biochim. Biophys. Acta* **2005**, *1751*, 33

DPP-4 Inhibitor Program - Objective

Identify a potent and selective DPP-4 inhibitor for the treatment of type 2 diabetes mellitus with the following characteristics:

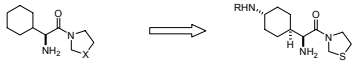
- >1000-fold selectivity over other proline peptidases, especially DPP-8 and DPP-9
- Half-life suitable for BID or preferably QD dosing
- Structure lacking reactive electrophile as a serine trap, e.g.,





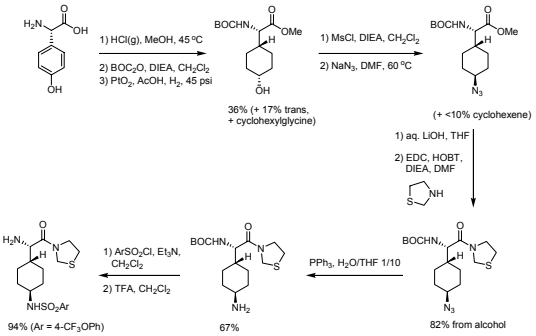
DPP-4 Lead Series

- Screening leads
  - β-Amino acid proline amides
  - β-Amino piperazines
- α-Amino acid thiazolidines

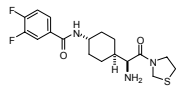
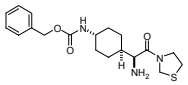
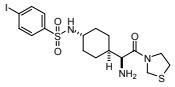


X	IC_{50} (nM)
CH_2	320
S	89

Synthesis of 4-Aminocyclohexylglycine Analogs



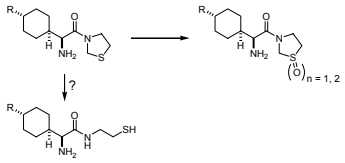
Substituted cHexylglycine Analogs

	DPP-4 IC_{50} (nM)	F(rat)
	54	81%
	25	76%
	24	46%

E. Parmee, *et al.*, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 43

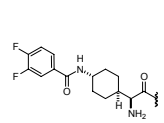
Thiazolidide DPP-4 Inhibitors

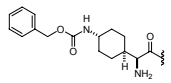
- Thiazolidine:
  - potential site of in vivo metabolism
  - potential for ring opening?

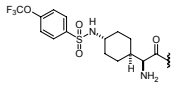


- Focus on analogs lacking thiazolidine ring

Thiazolidines vs. Pyrrolidines



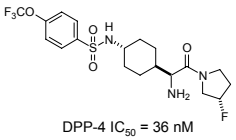




	DPP-4 IC_{50} (nM)		
			
	54	190	54
	25	94	56
	22	89	36

C. Caldwell *et al.*, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1265

A Potential Development Candidate



DPP-4 IC_{50} = 36 nM

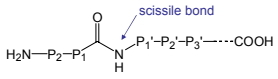
species	Clp (mL/min/kg)	$t_{½}$ (h)	F (%)
rat	18	3.7	37
dog	2.8	12	89
rhesus	12	4.6	64

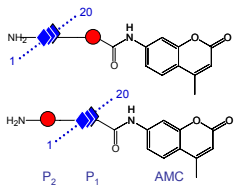
Discontinued due to off-target activity

Enzyme	IC_{50} (nM)
DPP-8	1400
DPP-9	1700
QPP	8300

Positional Scanning Combinatorial Library

Tool for the Analysis of Protease Specificity





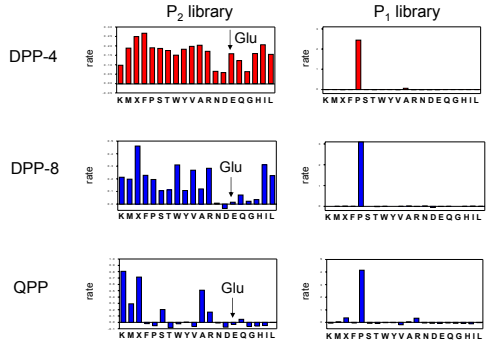
= isokinetic mixture of AAs

= spatially addressed AAs

C. Craik, UCSF
J. Ellman, Berkeley

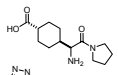
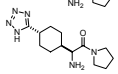
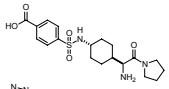
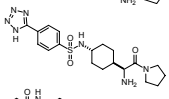
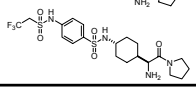
B. Leiting *et al.*, *Biochem. J.* **2003**, *371*, 525

Specificity of Proline Peptidases



X = Nle

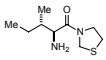
P_2-Acidic DPP-4 Inhibitors

	DPP-4 (nM)	QPP (nM)	DPP-8 (nM)	F(rat)
	61	>100,000	6100	8
	14	66,000	870	<1%
	15	26,000	2800	<1%
	8.4	11,000	220	8%
	2.6	15,000	1000	<1%

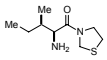
α-Amino Acid Series

- MRL proprietary derivatives identified
- Good pharmacokinetic properties
  - Potent, but < 30-fold selective over DPP-8 and DPP-9
- More selective derivatives lack oral bioavailability

α-Amino acid series revisited:



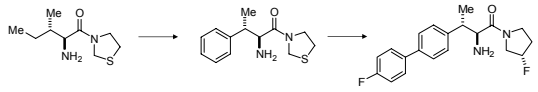
threo Ile-thiazolidide



allo Ile-thiazoldide

- *Allo* isomer is ~10-fold more toxic than *threo*
- Incorporate “threo” bias into α-amino acid series?

α-Amino Acid Series Revisited: β-Methyl Phenylalanine Derivatives



Enzyme	IC_{50} (nM)
DPP-4	420
QPP	14,000
DPP-8	2,200
DPP-9	1,600

Enzyme	IC_{50} (nM)
DPP-4	970
QPP	12,000
DPP-8	>100,000
DPP-9	>100,000

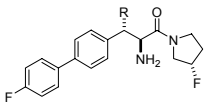
Enzyme	IC_{50} (nM)
DPP-4	64
QPP	2,700
DPP-8	88,000
DPP-9	86,000

Rat PK	
Cl_p	8.6
$t_{1/2}$ (h)	2.2
F (%)	85

hERG IC_{50} = 1100 nM

J. Xu *et al. Bioorg. Chem. Med. Lett.* **2005**, *15*, 2533

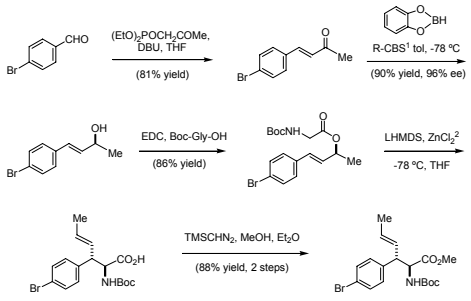
β-Substituted Biphenyl Derivatives: Dimethyl Amides are Optimal



R =	DPP-4 (nM)	QPP (nM)	DPP-8 (nM)	hERG (nM)	Rat PK Clp	Rat PK $t_{1/2}$ (h)	Rat PK F (%)
H	980	6,700	75,000				
Me	64	2,700	88,000	1,100	8.6	2.2	85
COOH	6.6	>100,000	>100,000	76,000	0.25	3.1	16
$CONMe_2$	12	45,000	>100,000	4,600	4.8	3.5	67

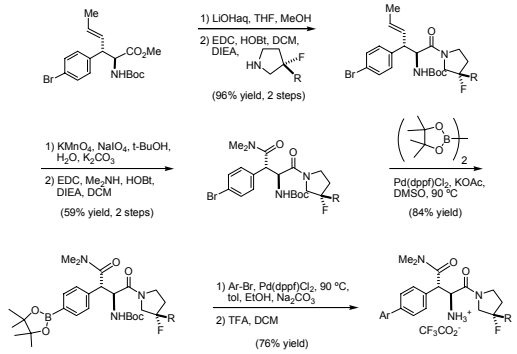
S. D. Edmondson *et al., Bioorg. Med. Chem. Lett.* **2005**, *15*, 3048

Synthesis of β-Substituted Phenylalanines

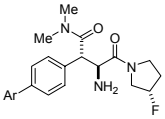


[1] Corey, E. J.; Helal, C. J. *Tetrahedron Lett.* **1995**, *36*, 9153.
[2] Kazmaier, U. *Liebigs Ann. Recl.* **1997**, 285.

Synthesis of β-Substituted Phenylalanines



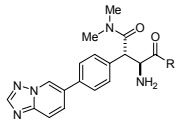
Biaryl β-Dimethylamide α-Amino Acids



Ar =	DPP-4 (nM)	QPP (nM)	DPP-8/9 (nM)	hERG (nM)	Rat PK Clp	$t_{1/2}$ (h)	F (%)
	8.0	>100,000	>100,000	83,000	15	1.2	1.8
	13	>100,000	>100,000	>100,000	15	2.3	10
	4.1	>100,000	>100,000	>100,000	34	1.1	0.8
	4.3	>100,000	>100,000	86,000	7.0	2.0	43

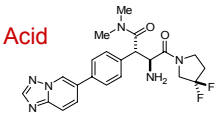
S. D. Edmondson *et al.*, *J. Med. Chem.* **2006**, *49*, 3614

Fluoropyrrolidine Replacements



Ar =	DPP-4 (nM)	QPP (nM)	DPP-8/9 (nM)	hERG (nM)	Rat PK Clp	$t_{1/2}$ (h)	F (%)
	4.3	>100,000	>100,000	86,000	7.0	2.0	43
	2.3	>100,000	>100,000	>100,000	7.4	2.1	38
	3.7	47,000	>82,000	15,000	7.7	1.6	46
	8.8	100,000	>100,000	>100,000	2.8	1.6	100

A Highly Selective α-Amino Acid Derived DPP-4 Inhibitor



Potency and selectivity:

Enzyme	IC_{50} (nM)
DPP-4	8.8
QPP	~100,000
DPP-8	>100,000
DPP-9	>100,000
PEP	>100,000
APP	>100,000
Prolidase	>100,000
FAP	>100,000

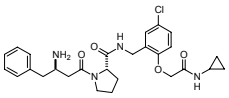
Off-target Activities:

Target	IC_{50} (nM)
hERG	>100,000
Ca	>100,000
Na	>100,000
Cyp3A4	>100,000
Cyp2D6	>100,000
Cyp2C9	>100,000
Cyp2C19	>100,000
Cyp1A2	>100,000

Screening Leads

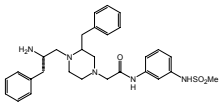
- β-Amino acid proline amides

IC_{50} = 1.9 μM
thrombin IC_{50} = 52 nM

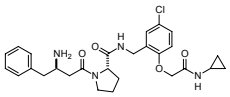
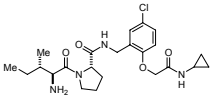
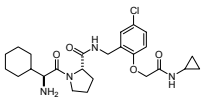


- β-Amino piperazines

IC_{50} = 11 μM

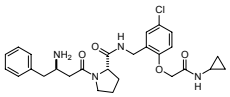


Proline Amide Lead SAR

	DPP-4 IC_{50} (nM)
	1900
	4300
	7000

Proline Amide Lead SAR

DPP-4 IC_{50} (nM)



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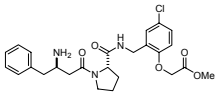

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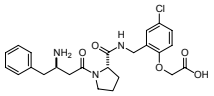


1000

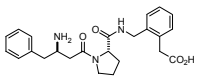
Glucagon Family: Potential Substrates

Preference for P_1' Acid

	cleavage sequence
glucagon-like peptide-1 (GLP-1)	HA$^{\downarrow}$**E**GTFTS...
glucagon-like peptide -2 (GLP-2)	HA$^{\downarrow}$**D**GSFSD...
peptide histidine methionine (PHM)	HA$^{\downarrow}$**D**GVFTSD…
glucose-dependent insulinotropic peptide (GIP)	YA$^{\downarrow}$**E**GTFISD…
growth hormone-releasing factor (GRF)	YA$^{\downarrow}$**D**AIFTNS…
secretin	HS$^{\downarrow}$**D**GTFTS...
glucagon	HS$^{\downarrow}$QGTFTS...
vasoactive intestinal peptide (VIP)	HS$^{\downarrow}$**D**AVFTD...
pituitary adenylate cyclase activating polypeptide (PACAP)	HS$^{\downarrow}$**D**GIFTDS…

Proline Amide Lead SAR

DPP-4 IC_{50} (nM)



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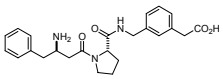

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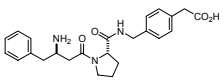
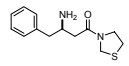
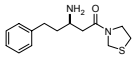
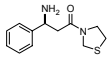
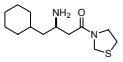


510

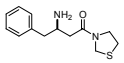
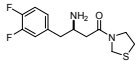
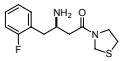
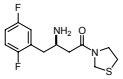
Thrombin IC_{50} > 500 µM

β-Aminoacid Thiazolidines

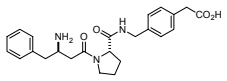
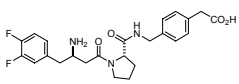
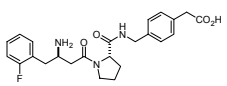
	DPP-4 IC_{50} (nM)
	3000
	16,000
	>100,000
	33,000

J. Xu, *et al.*, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4759

β-Aminoacid Thiazolidines

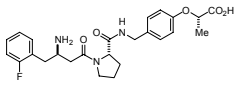
	DPP-4 IC_{50} (nM)
	3000
	1700
	930
	270

Proline Amide – Fluorinated Phenyl Analogs

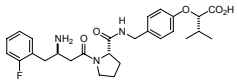
	DPP-4 IC_{50} (nM)
	510
	75
	54

S. Edmondson, *et al.*, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5155

Proline Amide – Lactic Acid Derivatives



DPP-4 IC_{50} (nM): 12



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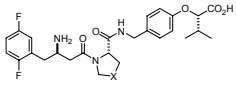
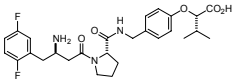


X = CH_2 0.48

X = S 0.30

Subnanomolar Proline Amide Lead

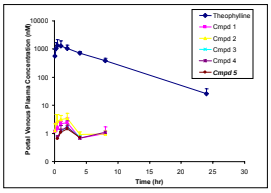
≫Unique Structural Class



≫Excellent Selectivity

	IC_{50} (nM)
DPP-4	0.48
QPP	>100,000
DPP-8	>100,000
DPP-9	>100,000

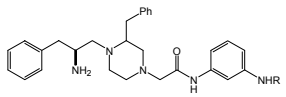
≫Poor Oral Absorption in Rats



Pharmacokinetics in Rats:

Cl_p = 150 mL/min/kg
$t_{1/2}$ = 4.1 h
F = 1%

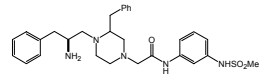
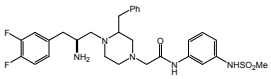
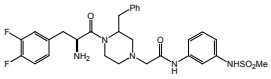
Piperazine Lead: Sulfonamide SAR



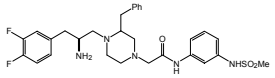
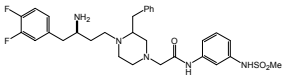
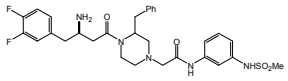
R	DPP-4 IC_{50} (nM)
$-SO_2Me$	11,000
$-SO_2CH_2CF_3$	4700
$-SO_2CF_3$	3200
-CONH-(3-F-Ph)	3600

L. Brockunier, *et al.*, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4763

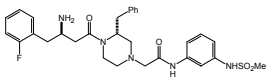
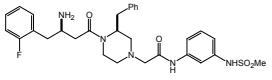
Piperazine Lead: Left Hand Side SAR

	DPP-4 IC_{50} (nM)
	11,000
	4100
	>100,000

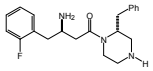
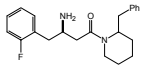
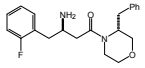
Piperazine Lead: Left Hand Side SAR

	DPP-4 IC_{50} (nM)
	4100
	6300
	44

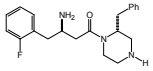
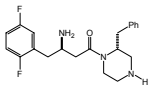
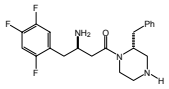
Piperazine Lead: Benzyl Diastereomers

	DPP-4 IC_{50} (nM)
	14
	690

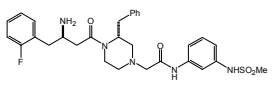
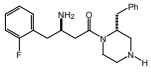
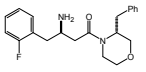
Piperazine Lead: Truncated Analogs

	DPP-4 IC_{50} (nM)
	140
	1040
	110

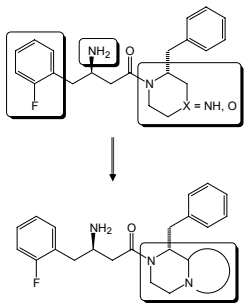
Piperazine Lead: Truncated Analogs

	DPP-4 IC_{50} (nM)
	140
	51
	19

Piperazine Lead: PK in Rats

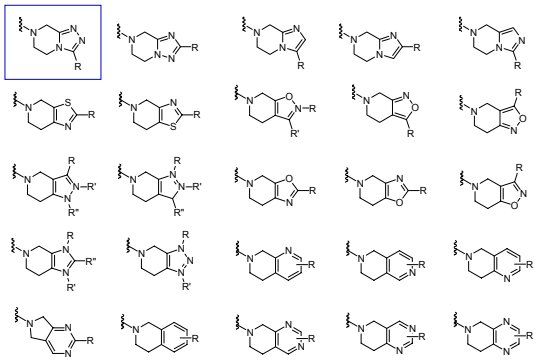
	DPP-4 IC_{50} (nM)	%F(rat)
	14	<1
	140	<20
	110	2

Piperazine Lead: Metabolism Issues

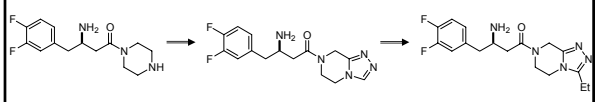


Stabilize through cyclization?

Bicyclic Piperazine Replacements



Bicyclic Piperazine Replacements: Ethyl Triazolopiperazine



Enzyme	IC_{50} (nM)
DPP-4	3,100
DPP-8	>10,000
DPP-9	>100,000

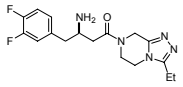
Enzyme	IC_{50} (nM)
DPP-4	460
DPP-8	38,000
DPP-9	>100,000

Enzyme	IC_{50} (nM)
DPP-4	230
DPP-8	45,000
DPP-9	>100,000

- Stable in rat hepatocytes

Pharmacokinetics of Ethyl Triazolopiperazine Derivative

1 mg/kg IV, 2 mg/kg PO

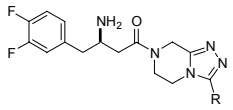


species	Clp (mL/min/kg)	Vd (mL/kg)	$t_{½}$ (h)	PO C_{max} (μM)	F (%)
rat	45	5.6	2.7	0.01	2
dog	13	2.1	2.3	0.73	33
rhesus	26	2.2	1.3	0.012	1

In rats:

- Low, variable absorption (intestinal loop, *in vitro* permeability, PV rat)
- Low hepatic extraction (E_h = 10-20%)

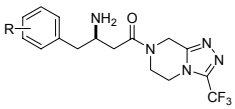
Triazolopiperazine SAR



R	DPP-4 IC_{50} (nM)	DPP-8 IC_{50} (nM)	DPP-9 IC_{50} (nM)	Rat PK Clp (mL/min/kg)	Rat PK $t_{½}$ (h)	Rat PK F_{rat} (%)
Et	230	45,000	>100,000	45	2.7	1.8
Me	230	75,000	>100,000	33	2.1	2.1
CF_3	130	46,000	>100,000	51	1.8	44

D. Kim, *et al.*, *J. Med. Chem.* **2005**, *48*, 141

Left Hand Side SAR

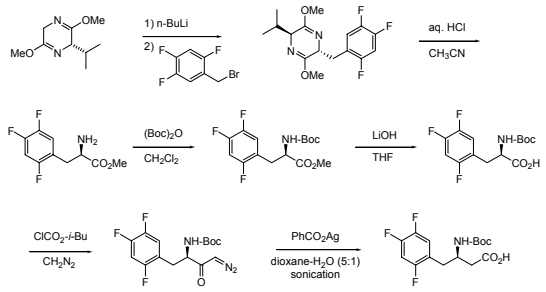


R	DPP-4 IC_{50} (nM)	Rat PK Clp (mL/min/kg)	Rat PK $t_{½}$ (h)	Rat PK F_{rat} (%)
3,4-diF	130	51	1.8	44
2,5-diF	27	43	1.6	50
2,4,5-triF	18	60	1.7	76

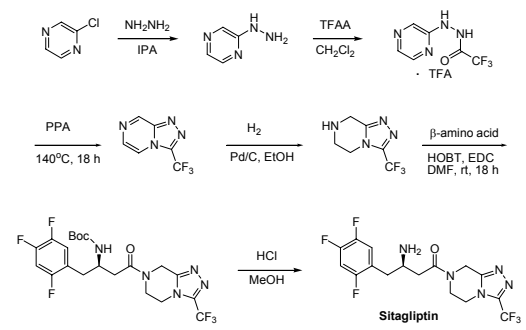
MK-0431 = JANUVIA™ (sitagliptin)

D. Kim, *et al.*, *J. Med. Chem.* **2005**, *48*, 141

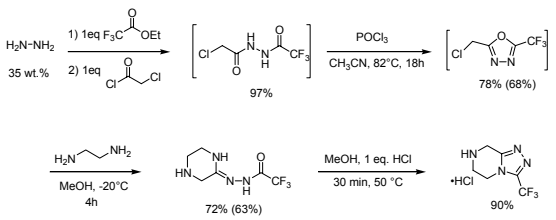
Med Chem Synthesis of Sitagliptin



Med Chem Synthesis, continued



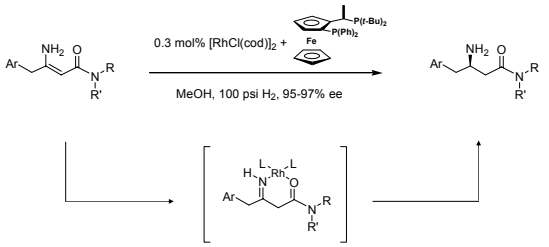
Process Chemistry Route to Heterocyle



- 49% overall yield
- No safety issues
- Inexpensive raw materials
- >1 MT prepared within 1 year

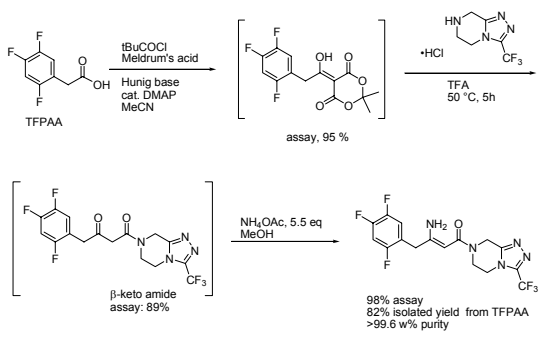
J. Balsells *et al.*, *Org. Lett.* **2005**, 7, 1039

Process Route to β-Amino Acid DPP-IV Inhibitors



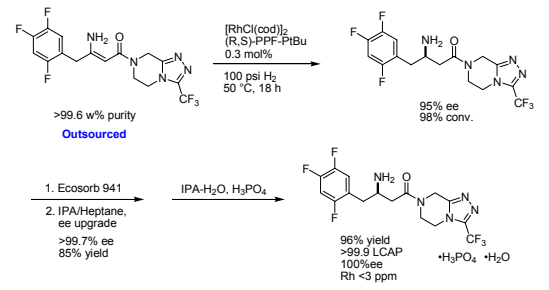
Y. Hsiao *et al.*, *J. Am. Chem. Soc.* **2004**, *126*, 9918

Process Route to Enamine Amide Intermediate

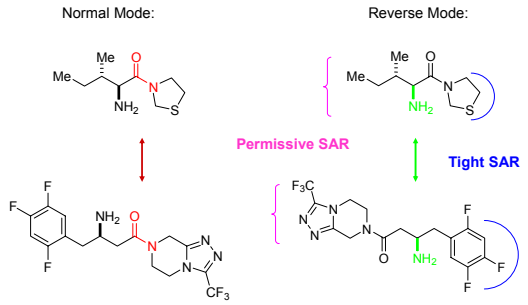


Ultimate Synthesis of Sitagliptin

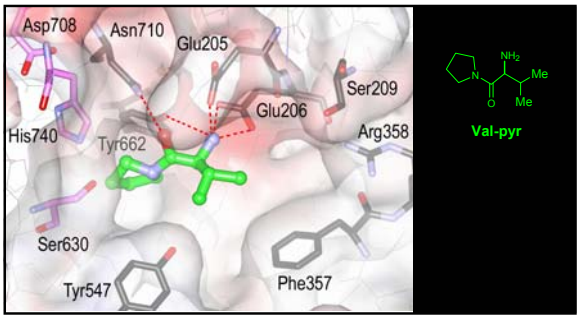
Manufacturing Route



Sitagliptin Binding Mode: "Normal" or "Reverse"?

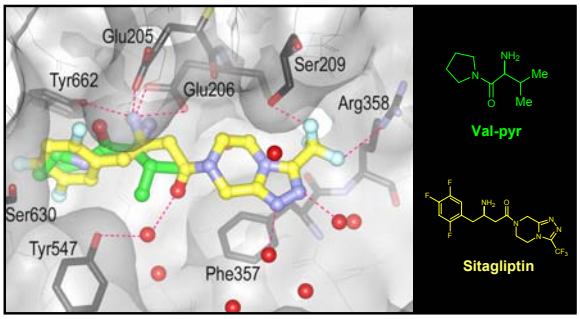


Structure of DPP-4 Complex with Val-Pyr

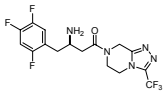


H. Rasmussen *et al.*, *Nat. Struct. Biol.* **2003**, *10*, 19

Structure of DPP-4 Complex with Sitagliptin



Sitagliptin: *In Vitro* Potency and Selectivity



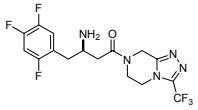
	IC_{50}, (nM)	-fold selectivity
DPP-9	> 100000	> 5000
DPP-8	48000	2700
FAP	> 100000	> 5000
DPP-4	**18**	**1**
DPP-6	not active	not active
PEP	> 100000	> 5000
QPP/DPP-2	> 100000	> 5000
APP	> 100000	> 5000
prolidase	> 100000	> 5000

DPP-4 Gene Family

Other Proline Specific Enzymes

PK Properties of Sitagliptin

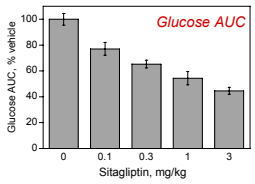
1 mg/kg IV, 2 mg/kg PO

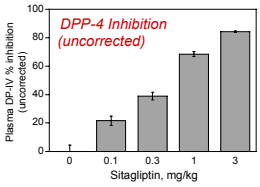


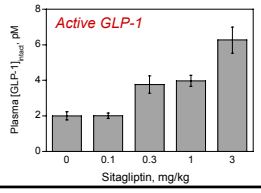
species	Clp (mL/min/kg)	Vd (mL/kg)	$t_{½}$ (h)	PO AUC_{norm} (μM·h/mpk)	PO C_{max} (μM)	F (%)
Mouse	64	3.8	0.8	0.41	0.51	61
Rat	60	6.4	1.7	0.52	0.33	76
Dog	6.0	9.0	4.9	8.3	2.2	100
Monkey	28	2.3	3.7	1.0	0.33	68

Pharmacodynamics of Sitagliptin: OGTT in Lean Mice

20 min post Glucose, 80 min post Compound





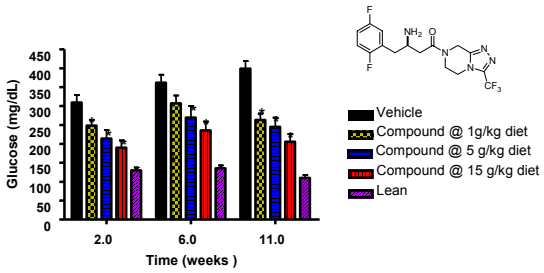


Dose, mg/kg	[sitagliptin], nM
0.1	19
0.3	52
1	190
3	600

Mouse DPP-4: IC_{50} = 69 nM

Chronic Efficacy with a Sitagliptin Analog

Improved fasting glucose in HFD/STZ diabetic mice

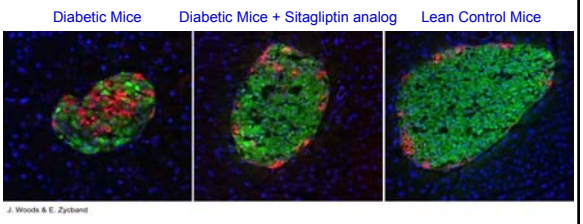


B. Zhang *et al. Diabetes* **2006**, *55*, 1695

Chronic Efficacy with a Sitagliptin Analog in Mice

Restoration of Pancreatic Islet β Cells

Islets from HFD/STZ mice +/- 10 weeks of treatment with sitagliptin analog



Green: Insulin-producing β cell
Red: Glucagon-producing α cell

Conclusions

- Selective inhibition of DPP-4, in particular with respect to DPP-8 and/or DPP-9, provides an improved safety profile in preclinical species.
- Sitagliptin is a potent and selective DPP-4 inhibitor, very well tolerated in pre-clinical toxicity studies and in human clinical trials.
- Sitagliptin displays a good pharmacokinetic profile in preclinical species, with excellent oral bioavailability, and is suitable for QD dosing in patients with type 2 diabetes.
- In patients with type 2 diabetes, sitagliptin reduces glucose excursion, enhances insulin levels, suppresses glucagon levels, and improves glycemic control in a dose-dependent fashion.
- JANUVIA™ (sitagliptin) is approved in Mexico and currently under review by the FDA and other regulatory agencies as a potential new treatment for type 2 diabetes.