Discovery and Preclinical Profile of Saxagliptin (BMS-477118): A Highly Potent, Long-Acting, Orally Active Dipeptidyl Peptidase IV Inhibitor for the Treatment of Type 2 Diabetes

David J. Augeri,*[,†,‡] Jeffrey A. Robl,[†] David A. Betebenner,[†,§] David R. Magnin,[†] Ashish Khanna,[∥] James G. Robertson,[⊥] Aiying Wang,[⊥] Ligaya M. Simpkins,[†] Prakash Taunk,[†] Qi Huang,[⊥] Song-Ping Han,[⊥] Benoni Abboa-Offei,[⊥] Michael Cap,[⊥] Li Xin,[⊥] Li Tao,[#] Effie Tozzo,[⊥] Gustav E. Welzel,[⊥] Donald M. Egan,[⊥] Jovita Marcinkeviciene,[⊗] Shu Y. Chang,[∥] Scott A. Biller,[†,∞] Mark S. Kirby,[⊥] Rex A. Parker,[⊥] and Lawrence G. Hamann*[,▽]

Departments of Discovery Chemistry, Metabolic Diseases, Pharmaceutical Candidate Optimization, Exploratory Pharmaceutics, Chemical Enzymology, Bristol-Myers Squibb, Pharmaceutical Research Institute, P.O. Box 5400, Princeton, New Jersey 08543-5400

Received March 22, 2005

Efforts to further elucidate structure−activity relationships (SAR) within our previously disclosed series of β-quaternary amino acid linked L-*cis*-4,5-methanoprolinenitrile dipeptidyl peptidase IV (DPP-IV) inhibitors led to the investigation of vinyl substitution at the β-position of α-cycloalkyl-substituted glycines. Despite poor systemic exposure, vinyl-substituted compounds showed extended duration of action in acute rat ex vivo plasma DPP-IV inhibition models. Oxygenated putative metabolites were prepared and were shown to exhibit the potency and extended duration of action of their precursors in efficacy models measuring glucose clearance in Zucker$^{fa/fa}$ rats. Extension of this approach to adamantylglycine-derived inhibitors led to the discovery of highly potent inhibitors, including hydroxyadamantyl compound BMS-477118 (saxagliptin), a highly efficacious, stable, and long-acting DPP-IV inhibitor, which is currently undergoing clinical trials for treatment of type 2 diabetes.

Introduction

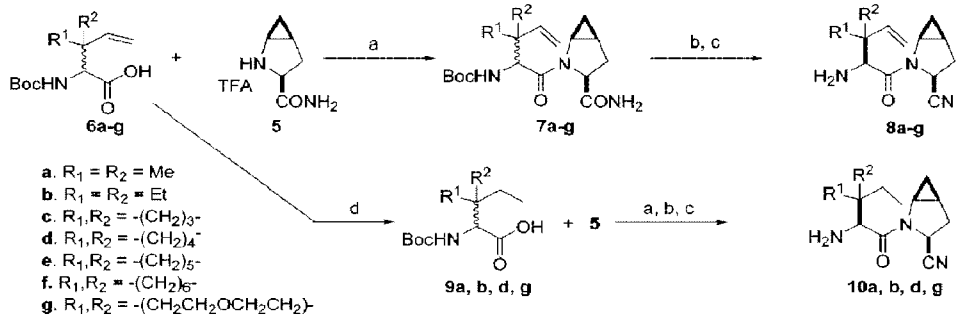
Primary defects in insulin secretion, along with development of insulin resistance, contribute to the etiology of type 2 diabetes mellitus. Diminished postprandial insulin secretion resulting from both functional defects and loss of survival of pancreatic β-cells progresses into hyperglycemia and declining insulin sensitivity. As lifestyle trends and dietary factors have contributed to an alarming rise in the incidence of type 2 diabetes,[1] the search for novel mechanistic approaches to control this chronic metabolic disease has intensified in parallel. To complement the currently available diabetes treatments,[2] approaches operating within the enteroinsular axis through the incretin hormone glucagon-like peptide 1 (GLP-1), alone or in combination with other agents, are beginning to show promise in the treatment of diabetes.[3] GLP-1 is a major component of the prandial nutrient-sensing mechanism regulating insulin secretion following meals.[4] Intact, active GLP-1(7−36) amide is secreted into the circulation from intestinal L-cells in response to dietary signals. Concentrations of GLP-1(7−36) amide sufficient to activate the GLP-1 receptor expressed on pancreatic β-cells result in increased insulin secretion, delayed glucose absorption, and reduced hepatic glucose production. All of these components work in concert to modulate blood glucose levels. Because GLP-1 release is nutrient stimulated, this mechanism promotes insulin secretion under prandial glycemia conditions, minimizing the potential for hypoglycemia. Recent reports have further demonstrated a beneficial effect of agents acting through the GLP-1 axis on the preservation and/or restoration of β-cell function in animals,[5] suggesting the exciting possibility that emerging drugs acting in this pathway may lead to improvement of the diabetic condition.

GLP-1 is rapidly truncated during its secretion in the ileum by the dipeptidyl peptidase IV (DPP-IV, EC 3.4.14.5) located on the capillary endothelium proximal to the L-cells where GLP-1 is secreted. The efficient cleavage by DPP-IV of the N-terminal dipeptide His-Ala from GLP-1(7−36) amide yields GLP-1(9−36) amide, a weak antagonist of the receptor,[6] and this cleavage has been demonstrated to be the primary physiological route of degradation of GLP-1(7−36) amide in both humans and animals.[7] The rapid cleavage by DPP-IV results in an apparent elimination half-life of only 60−90 s for GLP-1(7−36) amide, and peak circulating levels of intact GLP-1(7−36) amide typically do not exceed 5−10 pM, a range bracketing its K_a as GLP-1 receptor agonist. Inhibition of DPP-IV prevents the degradation of the incretin hormones GLP-1 and glucose-dependent insulinotropic peptide (GIP) and has been demonstrated to potentiate the levels of these peptides in multiple species.[8]

* Corresponding author. Telephone: 609-818-5526. fax: 609-818-3550. E-mail: lawrence.hamann@bms.com.
† Discovery Chemistry.
‡ Present address: Lexicon Pharmaceuticals, 350 Carter Road, Princeton, NJ 08540.
§ Present address: Pharmaceutical Discovery Division, Abbott Laboratories, Abbott Park, IL 60064.
∥ Pharmaceutical Candidate Optimization.
⊥ Metabolic Diseases.
Exploratory Pharmaceutics.
⊗ Chemical Enzymology.
∞ Present address: Novartis Institute for BioMedical Research, 250 Massachusetts Avenue, Cambridge, MA 02139.

10.1021/jm050261p CCC: $30.25
Published on Web 06/24/2005

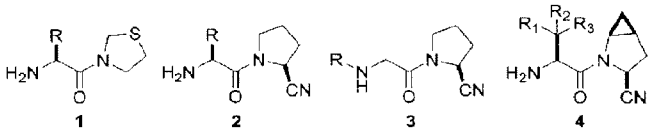
Scheme 1[a]



[a] (a) EDAC, HOBT, DMF; (b) $POCl_3$, pyridine, imidazole, −20 °C; (c) TFA, CH_2Cl_2, rt; (d) 5% Pd/C, H_2 1 atm, MeOH.

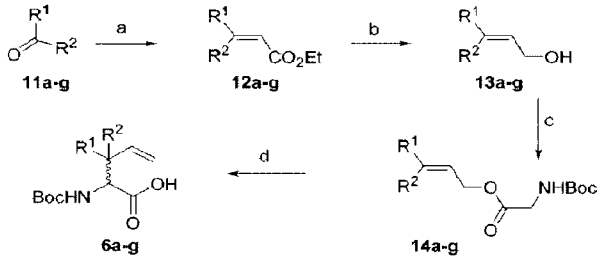
DPP-IV is a 240 kDa, 766 residue N-terminal dipeptidyl exopeptidase that is composed of two 110 kDa subunits[9] and exists as both a membrane-bound protein and as a soluble protein in plasma. It is a nonclassical serine protease that exhibits high specificity for peptides with proline or alanine in the P1 position. Any amino acid can occupy the P2 position so long as the P2−P1 peptide bond can adopt a trans configuration.[10] The membrane-bound form of DPP-IV is expressed in several tissues, including kidney, liver, the brush border membranes of intestinal enterocytes, on the pancreatic duct epithelia, and in vascular endothelial cells. In these tissues DPP-IV is N-terminally bound to the membrane with its catalytic activity located in the extracellular domain. The soluble, circulating form of DPP-IV is shed from cell surfaces by proteolytic cleavage releasing a fully active soluble form minus the 29 amino acids of the N-terminus.

Clinical evidence has shown that small molecule inhibitors of DPP-IV lower blood glucose levels, increase glucose tolerance, and improve insulin response to oral glucose in patients with type 2 diabetes.[11] Reversible small-molecule inhibitors of DPP-IV have been studied for the past several years, and a large body of structure−activity relationship (SAR) data has been generated.[3b,12] Until the very recent disclosures of several nonpeptidic chemotypes,[13,14] the known inhibitors had all been dipeptidomimetic in nature, bearing structural resemblance to the N-terminal dipeptide of the enzyme substrates. For this class of inhibitors, the penultimate N-terminal proline or proline mimetic, generally a thiazolidine (**1**),[15] a C-substituted or N-substituted



cyanopyrrolidine (**2**, **3**),[16,17] or a cyclopropanated cyanopyrrolidine (**4**),[18] is appended to an amino acid or an amino acid surrogate. Many inhibitors in this cyanopyrrolidine structural class have suffered from varying degrees of chemical instability which have hampered formulation efforts. In addition, many examples of this class exhibit limited pharmacodynamic duration of action. We report herein the discovery of highly efficacious long-acting inhibitors of DPP-IV that have led to the identification of compound **26** (BMS-477118, saxagliptin), which is currently undergoing clinical evaluation for the treatment of type 2 diabetes.

Scheme 2[a]



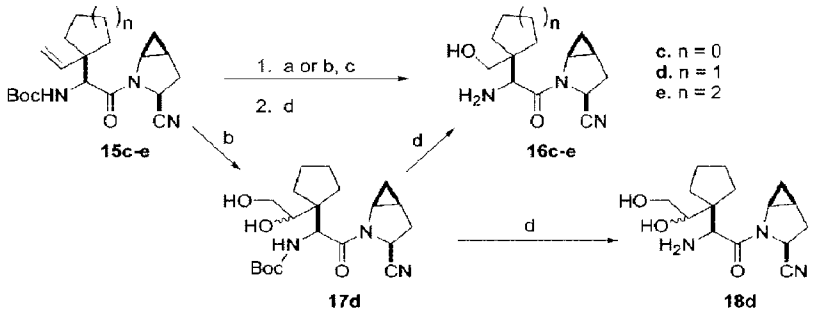
[a] (a) triethylphosphonoacetate, NaH, THF 0 °C to rt; (b) DIBAL-H, toluene, −78 °C to rt; (c) N−Boc glycine, DCC, DMAP, CH_2Cl_2, rt; (d) $ZnCl_2$, THF, LDA, −78 °C to rt.

Chemistry

To further our understanding of the SAR surrounding β-quaternary N-terminal amino acid-containing inhibitors, we focused on elaboration of our previously disclosed cyanomethanopyrrolidine-based scaffold[18] to produce long-acting inhibitors structurally related to the prototype scaffold **4**. A general synthesis route was chosen that incorporated at the β-position a vinyl substituent amenable to functionalization for further elucidation of SAR. Standard peptide coupling conditions[19] were employed to link enantiomerically pure L-methanoprolinamide core fragment **5** with various racemic vinyl-substituted amino acids **6a**−**g** to give dipeptides **7a**−**g** in yields of 85−95% (Scheme 1). Dehydration of the resultant amides using TFAA or $POCl_3$ gave the corresponding nitriles.[20] Chromatographic isolation of the bioactive L-isomer was generally carried out at the stage of the Boc-protected nitrile.[21] Finally, removal of the N-terminal Boc using TFA gave inhibitors **8a**−**g** in high yield. The vinyl groups of **6a**−**f** could be reduced (Pd/C, H_2) to afford the corresponding ethyl compounds, which were similarly elaborated to dipeptides **10a,b,d,g**.

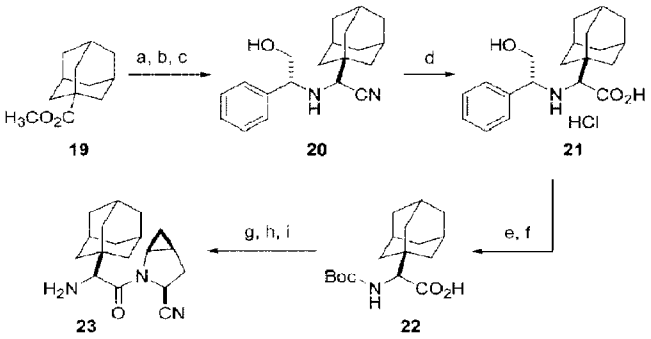
Amino acids possessing a β-quaternary vinyl group were prepared in a manner complementary to the malonate Knoevenagel/Michael addition sequence used previously.[18] Lewis acid-mediated ester enolate Claisen rearrangement of substituted glycinyl allylic esters[22] led directly to β-vinyl amino acids **6a**−**g** in 58−85% overall yields (Scheme 2). The requisite Claisen precursors were readily prepared in three steps from the appropriate ketones **11a**−**g**. Horner−Emmons olefination of ketones

Scheme 3[a]



[a] (a) O_3, MeOH/CH_2Cl_2 10:4, −78 °C; then $NaBH_4$, −78 to 0 °C, 60−79%; (b) OsO_4, NMNO, THF/H_2O 1:1, rt, 47−63%; (c) $NaIO_4$; workup, then $NaBH_4$, MeOH, rt, 56%; (d) TFA/CH_2Cl_2 1:2, 0 °C to rt.

Scheme 4[a]



[a] (a) LAH, THF, 0 °C to rt, 96%; (b) $(ClCO)_2$, DMSO, CH_2Cl_2, −78 °C, 98%; (c) (*R*)-(−)-2-phenylglycinol, $NaHSO_3$, KCN, 65%; (d) 12 M HCl, HOAc, 80 °C, 16 h, 78%; (e) 20% $Pd(OH)_2$, 50 psi H_2, MeOH/HOAc 5:1; (f) $(Boc)_2O$, K_2CO_3, DMF, 92%, two steps; (g) **5**, EDAC, HOBT, DMF, 92%; (h) $POCl_3$, pyridine, imidazole, −20 °C; (i) TFA, CH_2Cl_2, rt, quant.

11a−g with the ylide generated from triethylphosphonoacetate gave the α,β-unsaturated esters **12a−g** in 92−98% yield. Esters **12a−g** were then reduced with DIBAL to the corresponding allylic alcohols **13a−g** and condensed with *N*-Boc glycine using DCC/DMAP to give esters **14a−g** in 79−87% yield over two steps. $ZnCl_2$-mediated Claisen rearrangement of the LDA-generated enolate of glycine esters **14a−g** proceeded at low temperature to give the desired β-vinyl amino acids **6a−g** in 65−90% yield.

Further elaboration of vinyl-containing dipeptides **7c−e** was accomplished at the stage of the dehydrated cyano-containing compounds **15c−e** (Scheme 3). Oxidative cleavage of the vinyl substituent to prepare hydroxymethyl compounds **16c−e** was achieved either by ozonolysis/$NaBH_4$ reduction or by catalytic OsO_4−NMNO/$NaIO_4$/$NaBH_4$ conditions, followed by acidic deprotection of the Boc group. Additionally, **15d** was converted to the corresponding diol and deprotected to give **18d**.

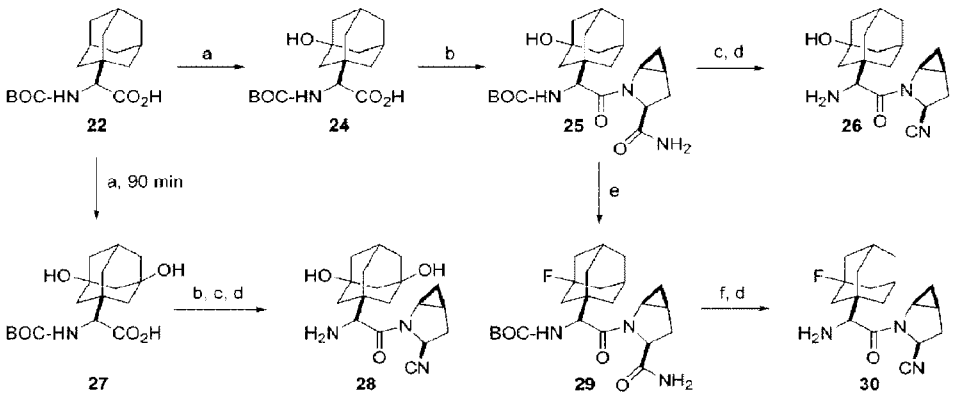
A logical extension of our previously observed SAR trends favoring β-branched P2 units led us to explore rigidly bridged polycyclic systems such as adamantyl. Analogues bearing an adamantyl ring at the *N*-terminal α-carbon were synthetically derived from a common homochiral adamantylglycine intermediate prepared using asymmetric Strecker chemistry (Scheme 4).[23] Reduction of commercially available adamantane carboxylic acid methyl ester **19** by LAH, followed by Swern oxidation, afforded the requisite aldehyde, which was then subjected to asymmetric Strecker conditions (condensation with (*R*)-(−)-2-phenylglycinol with addition of KCN) to give the desired homochiral *R,S* diastereomer **20** in 65% yield. Hydrolysis of the nitrile group to give acid **21**, followed by hydrogenolysis of the chiral auxiliary, afforded the enantiomerically pure amino acid **22**. Boc protection of the resulting primary amine, followed by coupling to methanoprolinamide core **5**, dehydration of the amide to nitrile, and deprotection, afforded the adamantylglycine containing inhibitor **23** in good overall yield.

Hydroxylation of *N*-Boc-adamantylglycine **22** at the bridgehead was accomplished using $KMnO_4$ in 2% aqueous KOH at elevated temperature to give *N*-Boc hydroxyadamantyl glycine **24** in 51% yield (Scheme 5).[24] Standard acylation conditions were used to couple **24** to methanoprolinamide core **5**, furnishing amide **25** in high yield. Amide **25** was subsequently elaborated to provide two additional analogues. Dehydration of amide **25** with TFAA, followed by in situ basic hydrolysis of the resulting trifluoroacetate and deprotection of the N-terminus, gave hydroxy derivative **26** in 87% yield over three steps. The hydroxy group of **25** was subjected to fluoride substitution using DAST,[24] and subsequent dehydration using $POCl_3$ in pyridine, followed by deprotection of the terminal nitrogen, provided fluoroadamantylglycine analogue **30** in 73% overall yield for three steps. Prolonged exposure of protected adamantylglycine **22** to $KMnO_4$ in 2% aqueous KOH provided the dihydroxyadamantylglycine derivative **27**. Coupling of **27** to **5**, followed by dehydration of the resultant prolineamide with TFAA, in situ basic hydrolysis of the bis-trifluoroacetate, and removal of the terminal Boc group using TFA, afforded dihydroxyadamantyl analogue **28** in 74% overall yield.

In Vitro and in Vivo Biological Activity. DPP-IV Inhibitory Activity in Vitro and ex Vivo. The DPP-IV inhibitory activity of analogues in the present series was measured against human DPP-IV using standard assays as described in the Experimental Section (Table 1). Many of the compounds in this series were potent inhibitors of DPP-IV in vitro, several with K_i's in the sub-nanomolar range. Additionally, several inhibitors in this series exhibited significant slow, tight-binding kinetics.[25]

A finer discrimination between the most potent compounds within this structurally related series of inhibitors with respect to pharmacodynamic effects and

Scheme 5[a]



[a] (a) $KMnO_4$, 2% aq KOH, **60** to 90 °C, 60 min, 51%; (b) **5**, EDAC, HOBT, DMF, 77−85%; (c) $(CF_3CO)_2O$, pyridine, THF 0 °C to rt, then 10% aq K_2CO_3 in MeOH, 89−92%; (d) **TFA**, CH_2Cl_2, rt, 89−95%; (e) **DAST**, CH_2Cl_2, −78 °C, 94%; (f) $POCl_3$, pyridine, imidazole, 82%.

Table 1. In Vitro Inhibition Constants for Human DPP-IV and ex Vivo Plasma DPP-IV Inhibition in Normal Rats

		% plasma DPP-IV inhibn at 4 μmol/kg po, normal rats	
compd	human DPP-IV K_i (nM)[a]	30 min	4 h
8a	57 + 8	13	10
8b	25 ± 4	39	20
8c	12 ± 0.9	42	32
8d	3.9 ± 0.6	71	64
8e	1.4 ± 0.06	76	60
8f	10 ± 3	77	66
8g	10 ± 2	nd[b]	nd
10a	7.1 ± 0.7	0	0
10b	31 ± 2	nd	nd
10d	5.5 ± 0.7	40	44
10g	21 ± 0.6	nd	nd
16c	42 ± 4	36	17
16d	7.4 ± 1.1	69	56
16e	8.0 ± 0.4	17	8
18d	143 ± 15	nd	nd
23	0.9 ± 0.32	84	83
26	0.6 ± 0.06[c]	87	87
28	2.1 ± 0.3	62	57
30	1.8 ± 0.5	80	61

[a] Values represent the mean ± SEM and are at least triplicate determinations. [b] nd = not determined. [c] Compound **26** did not show any significant inhibition of dipeptidyl peptidase II (DPP-II) at concentrations up to 30 μM.

Table 2. Potency and Duration of Effect of Compounds **16d** and **26** in the ex Vivo Rat Plasma DPP-IV Inhibition Model

	ED_{50}, μmol/kg at time postdose[a]			
compd	0.5 h	2 h	4 h	6 h
16d	0.4 ± 0.15	3.2 ± 1.2	5.0 ± 1.9	11 ± 4.2
26	0.12 ± 0.04	0.2 ± 0.07	0.3 ± 0.10	0.5 ± 0.15

[a] Compounds dosed po to fasted normal SD rats at the indicated times postdose, plasma aliquots were isolated, and DPP-IV inhibition was assayed using the fluorogenic peptide assay. ED_{50} is the 50% inhibitory dose calculated from the plots of percent inhibition vs dose at each time point.

duration of action required utilization of a medium-throughput acute efficacy model measuring a surrogate biomarker expected to be predictive of downstream antihyperglycemic effects. As DPP-IV is found in plasma and on the surfaces of blood and tissue cells, it was reasoned that measurement of inhibition of the circulating enzyme in plasma might provide a convenient biomarker for the degree of preservation of plasma incretin hormone levels. Though the relative contribution of these enzyme loci to the physiological degradation of GLP-1(7−36) amide important for antihyperglycemic effects is not fully understood, it was further envisioned that plasma enzyme inhibition measured ex vivo after an oral dose of test compound might be used to develop pharmacokinetic−pharmacodynamic relationships and provide information regarding duration of action. Compounds were administered orally in water vehicle at 4 μmol/kg to normal Sprague−Dawley rats, and blood samples were taken at 30 min and 4 h postdose to assay plasma (prepared with EDTA) DPP-IV activity in vitro using the fluorogenic DPP-IV-specific substrate Ala-Pro-AFC. Plasma DPP-IV activity determinations were calculated by linear regression from plots of product vs time (initial 20 min). Data were calculated as mean percent inhibition vs controls receiving water vehicle. Maximal inhibition of plasma DPP-IV under the conditions of this assay reached 85−90% (Table 1). In a dose−relationship mode, ED_{50}'s were determined for select compounds at multiple time points of 0.5, 2, 4, and 6 h postdose (Table 2).

Results and Discussion

The SAR described in our previous account culminating in 4,5-methanoprolinenitrile analogues **4** revealed a strong preference for compounds with lipophilic N-terminal β-quaternary amino acids.[18] In the course of further studies exploring SAR around β-quaternary cycloalkylglycine-based inhibitors, we encountered unexpectedly potent activity and extended duration of action in ex vivo DPP-IV inhibition studies with compound **8d**, which contains a (vinylcyclopentyl)glycine amino acid fragment. However, metabolism and pharmacokinetic studies with **8d** revealed uncharacteristically poor oral bioavailability (F = 5.3%) and high rat liver microsomal turnover rate [0.55 nmol/min/mg protein for **8d** vs 0.32 for compound **4** (where R_1 and R_2 taken together = cyclopentyl, and R_3 = Me)]. Similar observations were made for other vinyl-containing analogues **8c,e,g**, and these results suggested conversion to an active metabolite in vivo. As the vinyl substituent seemed a likely site of metabolism, synthesis of oxygenated analogues (**16d** and **18d**) derived from chemical modification of the olefin moiety was under-

taken. Diol **18d** showed only weak inhibitory activity; however, hydroxymethyl analogue **16d** exhibited potency similar to that of the vinyl analogue in both in vitro and ex vivo assays, restored rat liver microsomal turnover rate to a more moderate level (0.16 nmol/min/mg protein), and restored oral bioavailability to within the range characteristic for other structurally related analogues in the series (F = 59%). Unequivocal characterization of **16d** as the active metabolite of **8d** was never established, though the behavior of **16d** mirrored that achieved upon administration of **8d**. Accordingly, DPP-IV inhibitors **16c** and **16e** were prepared. A similar trend toward reconnection of pharmacokinetic properties with pharmacodynamic measurements was observed for the homologous pairs of inhibitors **8c/16c** and **8e/16e**. Despite this latter observation, the five-membered ring compound **16d** stood out as significantly more effective in the rat ex vivo plasma DPP-IV inhibition assay.

A more striking observation of metabolic conversion was seen with the highly potent adamantylglycine-containing analogue **23** (K_i = 0.9 nM). Although this compound afforded potent plasma DPP-IV inhibition after oral administration to rats (84% at 0.5 h, 83% at 4 h), it exhibited poor absolute bioavailability (F = 2%) after oral dosing and rapid turnover in rat liver microsomes. Interestingly, compound **23** also weakly inhibited CYP3A4 with an IC_{50} of 20 μM, where previous closely related analogues were devoid of any CYP inhibitory activity. Preparation of the bridgehead-hydroxylated analogue **26** gave a compound with a virtually identical in vitro (K_i = 0.6 nM) and ex vivo (87% inhibition of plasma DPP-IV at 0.5 and 4 h) profile, a slow rat liver microsomal turnover rate, no CYP3A4 inhibition up to 100 μM, and good oral exposure (F = 75%, $t_{1/2}$ = 2.1 h). Two other substituted adamantyl-derived compounds were also synthesized and investigated. Dihydroxyadamantyl compound **28**, while still reasonably active in the ex vivo assay, exhibited extremely high aqueous solubility but exhibited low oral exposure in rats, presumably resulting from very poor absorption. Though fluoroadamantyl compound **30** was also effective ex vivo, it exhibited very low oral exposure and had a rat liver microsomal turnover rate indicative of extensive metabolism, similar to that of compound **23**. Due to its exceptional plasma inhibitory potency and pharmacodynamic duration of action in this preliminary ex vivo assay (ED_{50} for **26** at 6 h = 0.5 μmol/kg vs ED_{50} for **16d** at 6 h = 11 μmol/kg, Table 2), compound **26** was chosen for further study in acute efficacy models.

Oral Glucose Tolerance in Zucker$^{fa/fa}$ Rats. Zucker$^{fa/fa}$ rats are a well-established genetically modified rodent model of obesity-induced insulin resistance[26] and provide a background to measure the effects of DPP-IV inhibitors in a prediabetic animal.[27] The nutrient-induced incretin secretion component of the GLP-1-dependent mechanism makes this a suitable model with which to study postprandial glucose excursions after administration of an oral glucose tolerance test (oGTT). DPP-IV inhibitor **26** was chosen for further study in this animal model by virtue of its highly potent effects in vitro and ex vivo. Compound **26** was administered orally to Zucker$^{fa/fa}$ rats at 0.5 h prior to oGTT, consisting of a glucose challenge (2.0 g/kg), followed by blood sampling at intervals over the next 2 h for plasma glucose measurements (data not shown). Maximal responses in glucose excursion in this model were associated with plasma DPP-IV inhibition of approximately 60% vs control, and no additional antihyperglycemic effects were seen at higher percent inhibition. On the basis of these preliminary findings at a single dose, compound **26** was further evaluated in the Zucker$^{fa/fa}$ rat model with an oGTT performed 4 h after oral administration of test compound in a dose−response format. Postprandial plasma glucose and insulin levels were again measured at intervals over 2 h following the glucose challenge. Compound **26** was highly effective at eliciting marked dose-dependent enhancements in glucose clearance in the dose range 0.3−3 μmol/kg (0.13−1.3 mg/kg) in this model relative to controls (Figure 1).

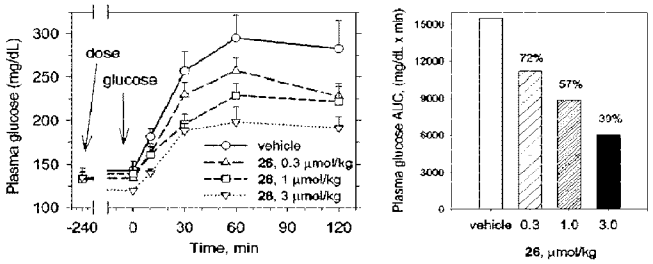


Figure 1. Effects of inhibitor **26** dosed at 0.3, 1, and 3 μmol/kg po versus vehicle control on plasma glucose clearance after an oGTT given 4 h postdose in Zucker$^{fa/fa}$ rats.

Oral Glucose Tolerance in *ob/ob* Mice. Evidence from both inhibitor studies and knock-out animals support that the mouse is also a suitable species in which to study the effects of DPP-IV inhibition on glucose clearance and insulin potentiation.[28] To this end, the effects of compound **26** on glucose clearance and enhancement of insulin secretion was studied in the *ob/ob* mouse. In this model the oGTT was performed at 1 h after oral administration of **26** at 1, 3, or 10 μmol/kg (Figure 2). The data show that compound **26** dose-dependently elevated plasma insulin significantly at 15 min post-oGTT, with concomitant improvement in the glucose clearance curves at 60 min post-oGTT.

Compound **26** exhibited robust glucose-lowering effects in a dose-relational manner in the Zucker$^{fa/fa}$ rat oGTT model, even when the glucose challenge was administered 4 h postdose of compound. Similarly outstanding efficacy was observed in reducing postprandial glucose AUC in *ob/ob* mice. This compound also proved quite effective in elevating insulin levels after an oGTT in *ob/ob* mice, further demonstrating the effectiveness of potentiating GLP-1-induced insulin secretion as a key component mediating the antihyperglycemic actions of this potent DPP-IV inhibitor. It is anticipated that compound **26**, given its extended pharmacodynamic response, will be amenable to once daily dosing in humans.

Conclusion

A series of β-quaternary cycloalkylglycine amino acid residues were incorporated into our previously disclosed 4,5-methanoprolinenitrile scaffold, and many of these compounds showed potent DPP-IV inhibitory activity. Several compounds containing a vinyl functionality also

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.