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Saxagliptin

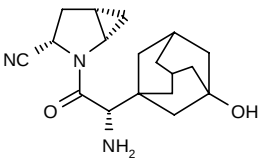
Dipeptidyl Peptidase IV Inhibitor
Antidiabetic Agent

Rec INN; USAN

BMS-477118
Onglyza™

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

InChI=1/C18H25N3O2/c19-8-13-2-12-3-14(12)21(13)16(22)15(20)17-4-10-1-11(5-17)7-18(23,6-10)9-17/h10-15,23H,1-7,9,20H2/t10?,11?,12-,13+,14+,15-,17?,18?/m1/s1



$C_{18}H_{25}N_3O_2$
Mol wt: 315.4101

CAS: 361442-04-8

CAS: 945667-22-1 (monohydrate)

EN: 310379

Abstract

Targeting glucagon-like peptide 1 (GLP-1) is an attractive strategy for the treatment of type 2 diabetes, as this incretin hormone enhances postprandial insulin secretion in a manner dependent on glycemia. Evidence also indicates that GLP-1 reduces glucagon secretion, induces satiety, delays gastric emptying and enhances β-cell function through stimulation of neogenesis and inhibition of apoptosis. One means of utilizing this target is by inhibiting its degradation, which is mediated by dipeptidyl peptidase IV (DPP IV). Saxagliptin is a DPP IV inhibitor that has displayed promising preclinical characteristics, such as dose-dependent clearance of glucose in animal models of diabetes. Data from clinical trials show significantly improved glycosylated hemoglobin (HbA1c) and fasting serum glucose in diabetes patients with saxagliptin alone and in combination with metformin, and the agent was well tolerated. Results from phase III studies are expected to soon provide a comprehensive view of saxagliptin's role in the expanding effort to improve the lives of diabetic patients. Just recently, Bristol-Myers Squibb and AstraZeneca submitted an NDA with the FDA and validation of an MAA to the EMEA for the use of saxagliptin in the treatment of type 2 diabetes.

Synthesis

Saxagliptin can be synthesized by several related methods:

After protection of (*S*)-adamantylglycine (I) as the *tert*-butyl carbamate (II) with Boc_2O and K_2CO_3, hydroxylation of the adamantane ring using $KMnO_4$ in hot aqueous KOH gives the alcohol (III) (1). Alternatively, the Boc-protected amino acid (III) can be prepared by treatment of (3-hydroxyadamantyl)glycine (IV) with Boc_2O and NaOH. Subsequent coupling of *N*-Boc-(*S*)-(3-hydroxyadamantyl)glycine (III) with (1*S*,3*S*,5*S*)-2-azabicyclo-[3.1.0]hexane-3-carboxamide (V) using either EDC/HOBt or methanesulfonyl chloride and Hunig's base produces amide (VI) (1-6). After protection of the hydroxyl group of (VI) with triethylsilyl triflate, the silylated carboxamide (VII) is dehydrated to the corresponding nitrile (VIII) by treatment with $POCl_3$ and imidazole in pyridine. Deprotection of (VIII) employing trifluoroacetic acid in CH_2Cl_2 then gives saxagliptin (1). Scheme 1.

Alternatively, direct dehydration of unsilylated carboxamide (VI) with trifluoroacetic anhydride in the presence of pyridine or NaOH produces nitrile (IX), which undergoes acidic Boc group cleavage to furnish saxagliptin (2-6). Scheme 1.

In a related strategy, (3-hydroxyadamantyl)glycine (IV) is protected with either ethyl trifluoroacetate and potassium methoxide or dodecyl trifluorothioacetate and NaOH to give the trifluoroacetamide (X), which is further esterified with trifluoroacetic anhydride in isopropyl acetate to yield the *N,O*-bis(trifluoroacetyl) derivative (XI). After conversion of (XI) to the corresponding acid chloride (XII) by means of Vilsmeier reagent, condensation with the bicyclic carbonitrile (XIII) leads to amide (XIV). Hydrolysis of the trifluoroacetate ester (XIV) with $NaHCO_3$ in MeOH provides (XV), from which the *N*-trifluoroacetyl group is reductively removed by means of $NaBH_4$ to yield saxagliptin.

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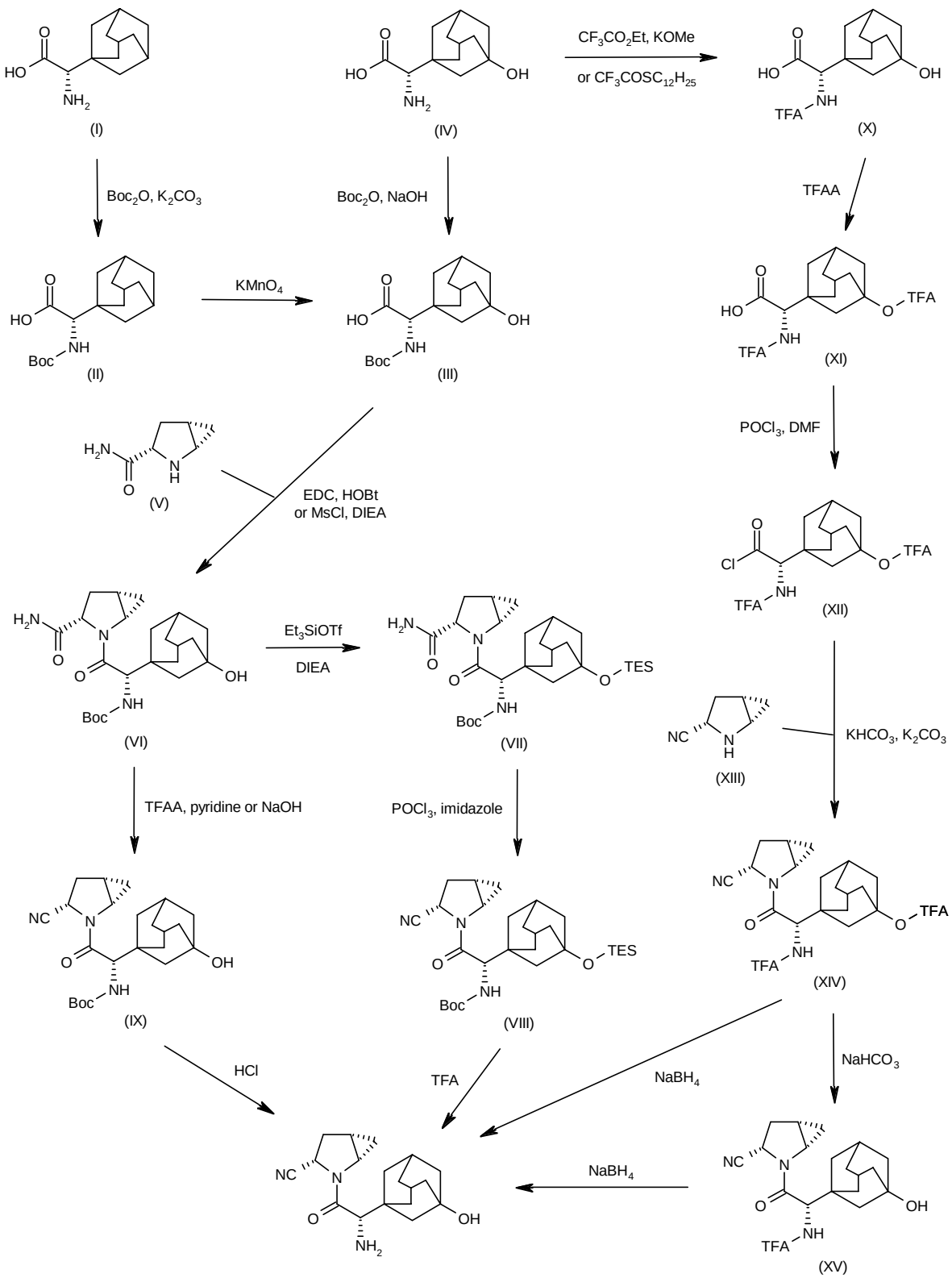
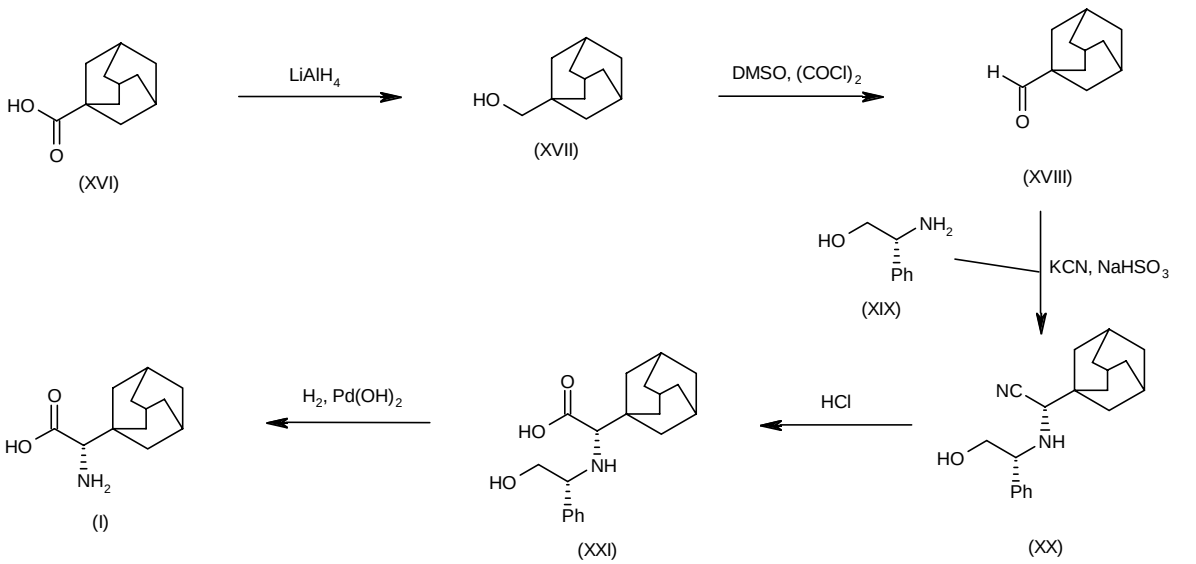
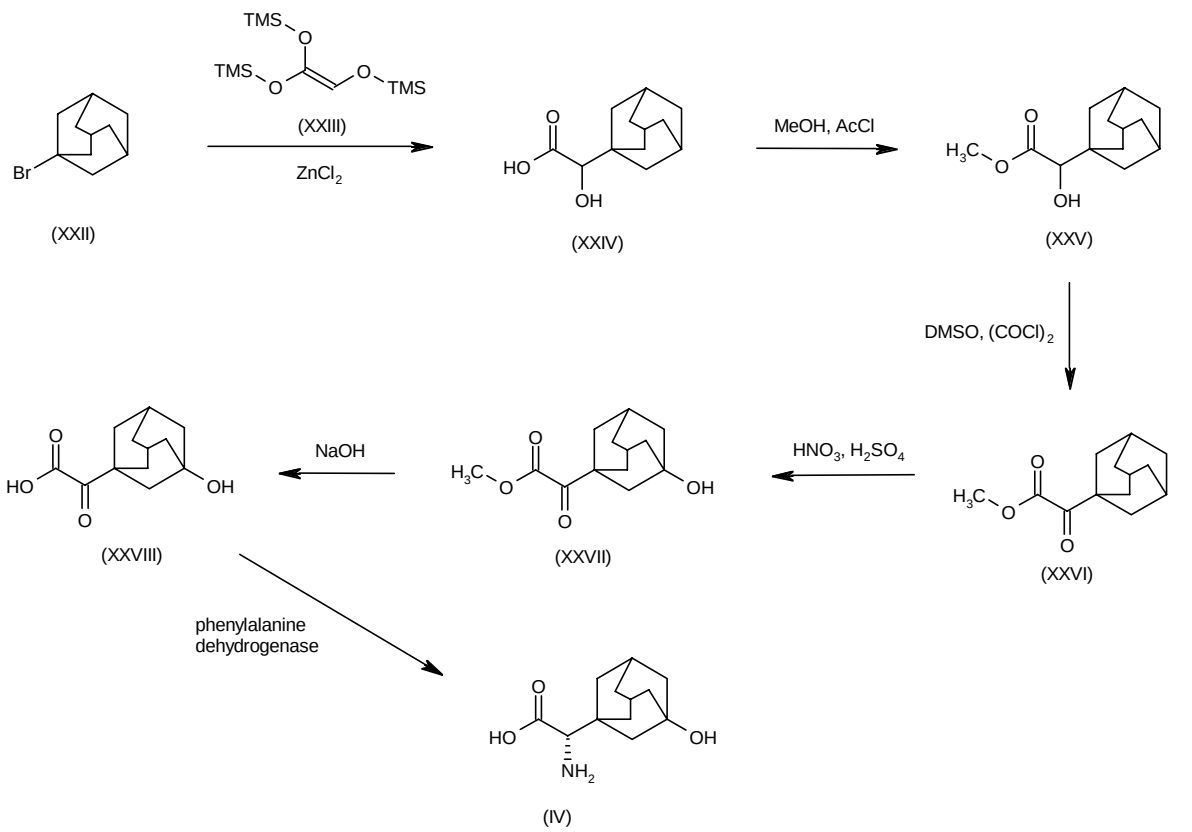
Scheme 1: Synthesis of Saxagliptin



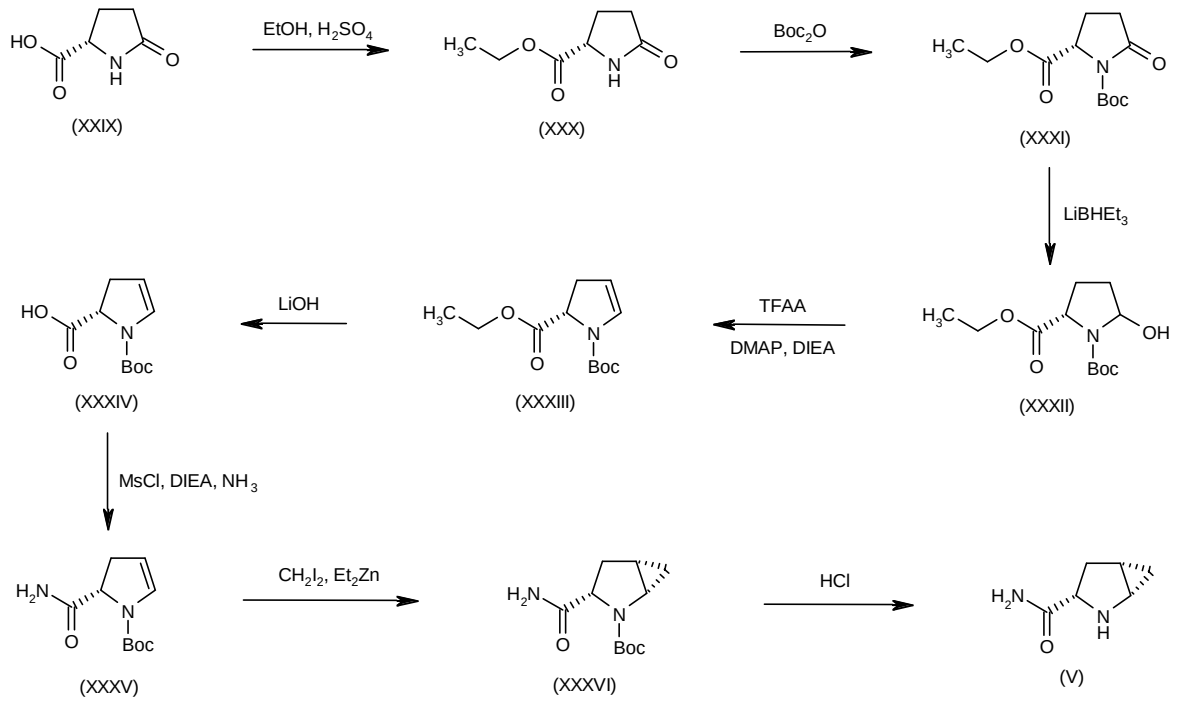
Scheme 2: Synthesis of Intermediate (I)



Scheme 3: Synthesis of Intermediate (IV)



Scheme 4: Synthesis Intermediate (V)



Alternatively, the title compound is directly produced by treatment of the bis(trifluoroacetyl)-protected precursor (XIV) with $NaBH_4$ in EtOH (7). Scheme 1.

The intermediate (*S*)-adamantylglycine (I) can be prepared as follows. Reduction of adamantane-1-carboxylic acid (XVI) using $LiAlH_4$ in THF gives the primary alcohol (XVII), which is oxidized to aldehyde (XVIII) under Swern conditions. Adamantane-1-carbaldehyde (XVIII) is then condensed with (*R*)-phenylglycinol (XIX) and KCN in the presence of $NaHSO_3$ to yield the chiral aminonitrile (XX). After acidic hydrolysis of nitrile (XX) to the corresponding amino acid (XXI), the chiral auxiliary group is removed by hydrogenolysis over Pearlman's catalyst to furnish intermediate (I) (1, 6). Scheme 2.

The preparation of the hydroxylated adamantane (IV) is shown in Scheme 3. 1-Adamantyl bromide (XXII) is condensed with 1,1,2-tris(trimethylsilyloxy)ethylene (XXIII) by means of $ZnCl_2$ in CH_2Cl_2 to afford the adamantylglycolic acid (XXIV), which is esterified to (XXV) utilizing a solution of acetyl chloride in MeOH. After Swern oxidation of (XXV) to the corresponding keto ester (XXVI), hydroxylation of the adamantane ring by means of HNO_3/H_2SO_4 provides (XXVII). Alkaline hydrolysis of ester (XXVII) leads to the oxoacetic acid (XXVIII), which is converted to the target (*S*)-amino acid (IV) by reductive amination with phenylalanine dehydrogenase (3).

The bicyclic carboxamide (V) can be obtained as follows. Esterification of L-pyroglutamic acid (XXIX) with ethanolic H_2SO_4 followed by protection with Boc_2O gives 1-Boc-5-oxoproline ethyl ester (XXXI). After reduction of (XXXI) with $LiBHEt_3$, the obtained hemiaminal (XXXII) is dehydrated to the dehydroproline derivative (XXXIII) employing trifluoroacetic anhydride, DMAP and DIEA. Subsequent hydrolysis of ethyl ester (XXXIII) by means of LiOH leads to the carboxylic acid (XXXIV), which is converted to the corresponding carboxamide (XXXV) via activation with methanesulfonyl chloride, followed by reaction with ammonia. Simmons-Smith cyclopropanation of (XXXV) using diiodomethane and diethylzinc gives the bicyclic derivative (XXXVI), which is then deprotected under acidic conditions to furnish (1*S*,3*S*,5*S*)-2-azabicyclo[3.1.0]hexane-3-carboxamide (V) (2, 3). Scheme 4.

Background

Anyone who has paid even scant attention to current events in recent years is aware that there is a worldwide obesity epidemic, and most would know that the prevalence of type 2 diabetes is on the rise and represents a major public health concern. The estimated figures are large enough to have a numbing effect: 170 million people with diabetes worldwide; a projected 370 million people affected in the next 25 years; 20.8 million Americans with diabetes in the year 2005, a figure expected to increase nearly 200% by the year 2050. There are other disturbing trends. The great majority of diabetes diag-

nosed are type 2, which is directly related not only to aging but to unhealthy diet, obesity and sedentary lifestyles. The rate of increase of diabetes is expected to be greater in developing countries than in the developed world: the age of diabetes onset is decreasing and its frequency among children is increasing, and in the near future most diabetes patients in the developing world will be younger than diabetes patients in the developed world. Moreover, the estimated diabetes-related costs in the United States alone in 2007 were $174 billion. Many treatments are available for diabetes, including sulfonylureas, thiazolidinediones, metformin and α-glycosidase inhibitors. However, the numbers above highlight the need for new treatments. Current treatment options are often effective over the short and medium term, but do not alter the underlying progression of the disease. Many patients given these treatments do not achieve their glycosylated hemoglobin (HbA1c) target of < 7%. In addition, weight gain, hypoglycemia, gastrointestinal events and peripheral edema are important adverse events associated with these agents which limit compliance. The need for new treatments is widely recognized and the search is on (8-13).

There are numerous targets for therapeutic intervention in diabetes, and one which reflects the increasing understanding of diabetes pathophysiology is glucagon-like peptide 1 (GLP-1). The rationale for this target is related to the incretin effect, whereby orally ingested glucose leads to an enhanced insulin response compared to intravenous glucose administration, resulting in identical postprandial plasma glucose excursions. The effect accounts for as much as 60% of postprandial insulin secretion and is reduced in patients with type 2 diabetes. The gastrointestinal hormone GLP-1 is an incretin, meaning that it promotes the incretin effect. GLP-1 stimulates insulin secretion under hyperglycemic conditions, normalizing blood glucose levels, but not at normal glucose levels. Therefore, it does not cause hypoglycemia. GLP-1 also inhibits glucagon secretion and delays gastric emptying. Preclinical studies have shown that GLP-1 increases β-cell mass by stimulating islet cell neogenesis and by inhibiting apoptosis of islets (14, 15).

Infusion of GLP-1 has been tried as a means of normalizing glycemia in diabetic patients, but such therapy is limited by the short half-life of GLP-1. This is due to rapid degradation by dipeptidyl peptidase IV (DPP IV). Therefore, to approach this target, investigators have sought GLP-1 analogues resistant to DPP IV-mediated degradation on the one hand and inhibitors of DPP IV on the other. The first strategy led to the identification of exenatide, which was approved by the FDA as a means of improving glycemic control in patients with type 2 diabetes. Liraglutide, another GLP-1 analogue, was filed for approval in the U.S. and the E.U. in 2008, and other GLP-1 mimetics are undergoing investigation. GLP-1 analogues are limited, however, by the need for subcutaneous or intravenous administration, their limited chemical stability, their potential for immunogenicity and side effects, notably nausea and vomiting (8, 16, 17).

The second approach, DPP IV inhibition, has also shown promise. DPP IV inhibitors extend the action of insulin while suppressing the release of glucagons, and by enabling the effects of GLP-1, they may also have the effects of inducing satiety, increasing β-cell production and inhibiting β-cell apoptosis (8, 17).

DPP IV inhibitors have demonstrated the ability to induce sustainable reductions in HbA1c in diabetic patients. While they do not appear to reduce glucose to a greater extent than other therapies, they do appear to be associated with advantages over other treatments, including a low risk of hypoglycemia, no effect on body weight, good tolerability and once-daily oral administration. These agents also appear to be effective as both monotherapy and in combination. One exciting possibility is that these agents could halt the decline in β-cell function seen in type 2 diabetes, perhaps even reversing the loss of insulin secretory capacity. It has been suggested that, compared to incretin mimetics which have only GLP-1-like effects, DPP IV inhibitors may have unwanted effects due to other possible roles of DPP IV. So far, however, this has not been seen in studies of such agents (17-19).

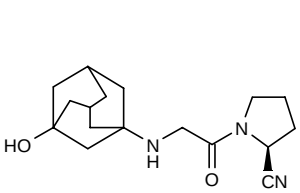
There are several classes of DPP IV inhibitors, among which the cyanopyrrolidines have been most thoroughly investigated, with research carried on since the mid-1990s (Table I). One agent in this class, vildagliptin, was launched last year as a once-daily treatment for type 2 diabetes. Saxagliptin, a compound under development at Bristol-Myers Squibb and AstraZeneca, is another member of this class which is in an advanced stage of clinical development (19). It was chosen from among a series of DPP IV inhibitors for clinical development due to its potency *in vivo* and superior duration of action. Saxagliptin has demonstrated significant efficacy in preclinical and clinical studies and has been well tolerated in humans. The long duration of action seen with saxagliptin in preclinical and clinical studies may be due to the formation of a reversible covalent enzyme–inhibitor complex, leading to slow inhibitor dissociation (6, 16, 20). With a good deal of preclinical and clinical data already available, a number of phase III studies completed but not yet reported and three phase III studies currently ongoing, a large pool of important data on the clinical utility of saxagliptin should soon be available. A more complete image of the drug's profile will be reflected in this pool, making a first comprehensive assessment of its place among DPP IV inhibitors, and more generally among the treatments for type 2 diabetes, possible.

Preclinical Pharmacology

The *in vitro* inhibition constant for human DPP IV for saxagliptin (K_i = 0.6 nM) was among the lowest of a series of newly developed DPP IV inhibitors, and the percentage of plasma DPP IV inhibition at 4 μmol/kg p.o. in normal rats (87% at 30 min and 4 h) was among the highest. Further studies showed saxagliptin to have a slow rat liver microsomal turnover rate, no cytochrome P-450 CYP3A4

Table I: Dipeptidyl peptidase IV (DPP IV) inhibitors approved or under clinical development for the treatment of diabetes.

Drug	Source	Phase
1. Vildagliptin (Galvus®)	Novartis	L-2007
2. Sitagliptin (Januvia™)	Merck & Co.	L-2006
3. Alogliptin benzoate	Takeda	Prereg.
4. Saxagliptin	AstraZeneca/Bristol-Myers Squibb	Prereg.
5. BI-1356	Boehringer Ingelheim	III
6. AMG-222*	Amgen/Servier	II
7. KRP-104*	ActivX/Kyorin	II
8. Melogliptin	Glenmark Pharmaceuticals	II
9. MP-513*	Mitsubishi Tanabe Pharma	II
10. PF-734200*	Pfizer	II
11. PHX-1149*	Phenomix Corp.	II
12. R-1579*	Roche	II
13. SK-0403*	Sanwa	II
14. SYR-472*	Takeda	II
15. ABT-279	Abbott	I
16. TA-6666*	Mitsubishi Tanabe Pharma	I
17. TAK-100*	Takeda	I



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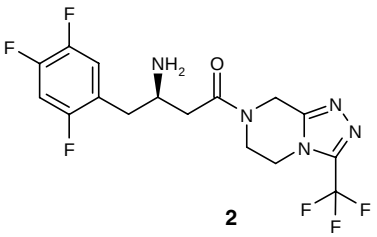

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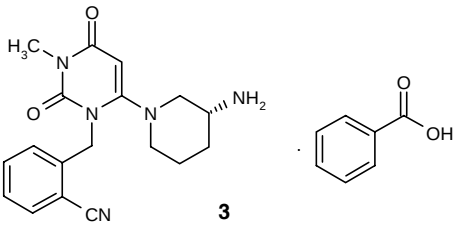

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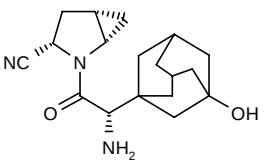

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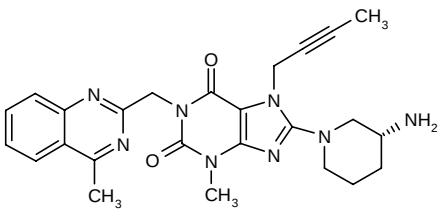

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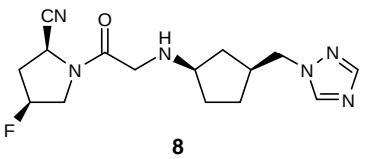

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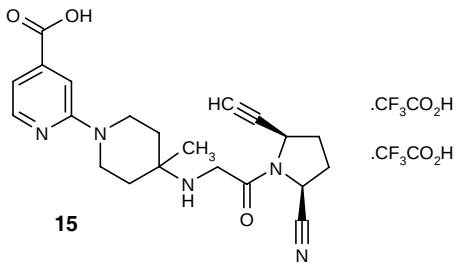

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*Structure not available.

inhibition up to 100 μM and good oral exposure (F = 75%, $t_{1/2}$ = 2.1 h). In an *ex vivo* rat plasma DPP IV inhibition model, the saxagliptin ED_{50} at 6 h was 0.5 μmol/kg. The long duration of action and the compound's potency led to its selection for further evaluation (6).

Saxagliptin was then studied in Zucker *fa/fa* rats, a model of obesity-induced insulin resistance, with the drug administered orally 0.5 h prior to an oral glucose tolerance test (OGTT). When a single dose was evaluated, maximal responses in glucose excursions were associated with plasma DPP IV inhibition of approximately 60% *versus* control, with no additional antihyperglycemic effects seen with greater inhibition. Further experiments in this model evaluated saxagliptin administration 4 h before the OGTT. Dose-dependent reductions in postprandial glucose excursions were seen with saxagliptin doses of 0.3-3 μmol/kg (6).

In experiments in the *ob/ob* mouse, the OGTT was performed 1 h after oral administration of saxagliptin 1, 3 or 10 μmol/kg. Dose-dependent elevations in plasma insulin were seen, with a significant effect noted at 15 min post-OGTT, along with improvement in glucose clearance

curves 60 min after the OGTT. These results support the role of potentiating GLP-1-induced insulin secretion in the antihyperglycemic activity of saxagliptin (6).

Safety

In a randomized, double-blind phase II trial in drug-naïve patients with type 2 diabetes, a low-dose cohort (n = 338) received saxagliptin 2.5, 5, 10, 20 or 40 mg once daily or placebo for 12 weeks, while a high-dose cohort (n = 85) received saxagliptin 100 mg once daily or placebo for 6 weeks. Adverse events occurred with similar frequency in all treatment groups. The most common events in the low-dose cohort were headache, upper respiratory tract infection and urinary tract infection, while the most common events in the high-dose cohort were headache, urinary tract infection and constipation. The agent had no effect on weight and there were no cases of confirmed hypoglycemia (21).

Clinical Studies

The results of four completed clinical trials of saxagliptin in healthy volunteers and patients with type 2 diabetes have been reported, and the results of several other completed studies are awaited. Three other trials are ongoing.

The safety, tolerability, pharmacokinetics and pharmacodynamics of a 2-week treatment course of saxagliptin were assessed in two randomized, double-blind studies, one in 40 patients with type 2 diabetes and another in 50 healthy subjects. In the latter study, volunteers received doses of 40, 100, 150, 200, 300 or 400 mg p.o. once daily or placebo, while in type 2 diabetes patients, doses of 2.5, 5, 15, 30 and 50 mg p.o. once daily were compared to placebo. In these studies, saxagliptin was not associated with dose-related adverse events or laboratory abnormalities, including hypoglycemia. There were also no dose- or concentration-dependent effects of saxagliptin on Q-T_c interval. Saxagliptin pharmacokinetics were similar in patients and healthy subjects, and systemic exposure was dose-proportional and similar on days 1 and 14. Plasma DPP IV activity was inhibited at all doses, and the effect was the same with doses of 150 mg and above. Plasma DPP IV was inhibited by 50% with saxagliptin 2.5 mg and by 79% with saxagliptin 400 mg 24 h after administration on day 1 compared to predose levels. After breakfast, lunch and dinner on day 13 in the type 2 diabetes study and on day 14 in the healthy subject study, all doses of saxagliptin were associated with elevations of 1.5-3-fold in postprandial plasma intact GLP-1 compared to placebo. The effects of saxagliptin on plasma intact GLP-1 levels did not appear to be dose-related (22).

In the phase II study including a low-dose and a high-dose cohort discussed above, significant reductions in HbA1c were seen at 12 weeks with all saxagliptin doses in the low-dose cohort (2.5-40 mg once daily) compared to placebo, with adjusted changes from baseline at week 12 ranging from –0.72% to –0.90% *versus* –0.27% with placebo. While 41-53% of saxagliptin-treated patients achieved HbA1c < 7.0%, only 20% of the placebo group did so. Fasting serum glucose declined 11-22 mg/dl with saxagliptin while it increased 3 mg/dl with placebo, and postprandial glucose 60 min after a liquid meal decreased 24-41 mg/dl with saxagliptin *versus* 1 mg/dl in the placebo group. In the high-dose group (saxagliptin 100 mg once daily), the adjusted change from baseline in HbA1c at week 6 was –1.09% with saxagliptin and –0.36% with placebo. Saxagliptin increased β-cell function in both dose cohorts (21).

Patients with type 2 diabetes and inadequate glycemic control while taking metformin (1500-2550 mg/day) were enrolled in a study in which they continued to receive metformin and were randomized to additional treatment with saxagliptin 2.5, 5 or 10 mg or placebo given once daily. The trial included 743 patients. After 24 weeks, adjusted mean placebo-subtracted decreases in HbA1c were 0.73%, 0.83% and 0.71%, respectively, with saxagliptin 2.5, 5 and 10 mg (all $P < 0.0001$). Adjusted mean placebo-subtracted differences in fasting plasma glucose were 16, 24 and 21 mg/day, respectively (all $P < 0.0001$). After standard oral glucose tolerance testing, saxagliptin-treated patients had significantly reduced glucose, decreased postprandial glucagon and increased postprandial insulin and C-peptide AUCs compared with placebo. Saxagliptin was well tolerated and not associated with an increased incidence of hypoglycemia compared with placebo or with significant weight changes (23).

The studies which have been completed but not reported are all multicenter, randomized, double-blind phase III trials and should provide great insight into the clinical utility of saxagliptin. Among them is a placebo-controlled study with a planned enrollment of 365 type 2 diabetes patients not controlled with diet and exercise evaluating saxagliptin monotherapy with titration. The primary outcome was the mean reduction in baseline HbA1c after 24 weeks (24). A similar placebo-controlled study of saxagliptin monotherapy in patients with inadequate glycemic control with diet and exercise has also been completed. Estimated enrollment was 460 patients, and the primary outcome measure was the change from baseline in HbA1c with each drug dose (25). Saxagliptin was combined with glyburide in a placebo-controlled trial in patients with uncontrolled type 2 diabetes receiving glyburide alone. Efficacy was again evaluated by the change in baseline HbA1c value after 24 weeks, and the study was intended to determine if the combination of saxagliptin and a sulfonylurea was safe and more effective than increasing sulfonylurea doses. The trial planned to enroll 780 patients (26). The combination of saxagliptin and immediate-release metformin (metformin IR) was assessed in a study comparing that treatment with saxagliptin alone and metformin IR alone. The reduction in HbA1c from baseline after 24 weeks was the primary outcome variable. Estimated enrollment was 1,396 (27). A study with an estimated enrollment of 555 patients lacking glycemic control while on thiazolidinedione therapy

alone evaluated, among other efficacy parameters, the change in HbA1c over 24 weeks with thiazolidinedione therapy alone and when combined with saxagliptin (28). In another recently completed phase III trial, measures of insulin secretion were taken over 12 weeks in patients with type 2 diabetes not controlled with diet and exercise. The randomized, double-blind study, with an estimated enrollment of 36 patients, compared saxagliptin treatment to placebo (29).

One of three ongoing phase III trials is currently recruiting patients with type 2 diabetes without glycemic control on metformin therapy and will compare saxagliptin in combination with metformin to sulfonylurea in combination with metformin. The randomized, double-blind study has an estimated enrollment of 838 and will last 52 weeks. The estimated conclusion date is September 2010 (30). A phase III study is recruiting patients with type 2 diabetes and renal impairment to compare the efficacy and safety of once-daily saxagliptin 2.5 mg p.o. with placebo. The multicenter, randomized, double-blind trial is expected to enroll 168 patients. After short-term 12-week treatment, a 40-week observation period will follow, and the primary outcome is the absolute change from baseline in HbA1c assessed after 12 and 52 weeks of treatment (31). A 24-week international trial is evaluating the efficacy and safety of saxagliptin in combination with metformin in adult patients with inadequate glycemic control on metformin in addition to diet and exercise. Again, the primary outcome measure is the absolute change from baseline in HbA1c after 24 weeks of administration. The study, enrolling an estimated 530 patients, began in May 2008 and is scheduled to be completed in November 2009 (32). Two other phase III trials, one in patients with type 2 diabetes with inadequate glycemic control on extended-release metformin (metformin XR) with diet and exercise evaluating add-on therapy with saxagliptin, and another in patients with inadequate glycemic control on diet and exercise (33, 34), are expected to begin enrolling patients soon.

Saxagliptin was just recently submitted for approval in the U.S. and the E.U. for the treatment of type 2 diabetes (35).

Drug Interactions

Pharmacokinetic studies have been conducted to assess the potential interactions between saxagliptin and diltiazem, ketoconazole, pioglitazone, glyburide, metformin and digoxin. A single study also evaluated the effect of magnesium and aluminum hydroxides plus simethicone, famotidine or omeprazole on the pharmacokinetics of saxagliptin.

Because saxagliptin is metabolized by CYP3A4/5 and diltiazem is an inhibitor of CYP3A4/5, their potential for interaction was investigated in an open study in 14 healthy volunteers aged 22-42 years. Study subjects received a single dose of saxagliptin 10 mg on day 1 and diltiazem 360 mg once daily was administered on days 2-8. On day 9, subjects received saxagliptin 10 mg and diltiazem 360 mg, and on day 10 a final dose of diltiazem 360 mg was given. Saxagliptin did not greatly affect diltiazem pharmacokinetics. As expected, an effect of diltiazem on saxagliptin was seen, with geometric means for saxagliptin C_{max} and $AUC_{(inf)}$ increased 63% and 109%, respectively, compared to saxagliptin alone. Coadministration with diltiazem was also associated with decreases in the geometric means for the C_{max} and $AUC_{(inf)}$ of the saxagliptin metabolite of 43% and 34%, respectively. Saxagliptin was well tolerated alone and when given with diltiazem (36).

Ketoconazole is also an inhibitor of CYP3A4/5, and a pharmacokinetic interaction with saxagliptin was expected in an open-label study including 16 healthy volunteers aged 22-43. A single 100-mg dose of saxagliptin was followed by a 48-h washout period, after which ketoconazole 200 mg p.o. was given every 12 h for 6 days. Subjects were then given a single dose of saxagliptin 100 mg and continued to receive ketoconazole 200 mg every 12 h for 3 days. Coadministration of saxagliptin and ketoconazole was associated with increases in geometric means for saxagliptin C_{max} and $AUC_{(inf)}$ of 62% and 145%, respectively, compared with saxagliptin alone. The corresponding values for the metabolite decreased by 95% and 88%, respectively. Saxagliptin did not have significant effects on the pharmacokinetics of ketoconazole (37).

The findings of an open-label evaluation of coadministration of saxagliptin and pioglitazone indicated that no dose adjustments are necessary for such combined treatment. Healthy male subjects (N = 30) were given saxagliptin 10 mg p.o. daily for 3 days, followed by pioglitazone 45 mg once daily for the next 5 days, and then both agents for another 5 days. For saxagliptin C_{max} and $AUC_{(tau)}$, prespecified criteria indicating an absence of an interaction between the drugs were met. The pharmacokinetics of the major active metabolite of saxagliptin, BMS-510849, were also unaffected by coadministration. An increase in the C_{max} of pioglitazone (14%) seen upon saxagliptin coadministration was not considered clinically significant. There were no episodes of hypoglycemia (38).

The results of a study of saxagliptin and glyburide coadministration were similar. This open, crossover study included 30 healthy males given three treatments in random order: a single oral dose of saxagliptin 10 mg, a single oral dose of glyburide 5 mg and a combination of the two drugs. Again, prespecified saxagliptin C_{max} and AUC criteria ruling out drug–drug interactions were met. The pharmacokinetics of BMS-510849 were also not altered by glyburide. The C_{max} of glyburide was increased 16% with saxagliptin coadministration, an effect considered most likely clinically inconsequential. Hypoglycemia was observed in a volunteer taking glyburide alone and in 3 subjects taking saxagliptin and glyburide, while there were no reports of hypoglycemia associated with saxagliptin alone (39).

The pharmacokinetic effects resulting from coadministration of saxagliptin and metformin are not sufficient to warrant dose adjustment for either agent according to the results of an interaction study. In this open-label, randomized, crossover study, 16 healthy males aged 19-42

received a single oral dose of saxagliptin 100 mg, a single oral dose of metformin 1000 mg and coadministration of both drugs. Metformin administration decreased the C_{max} of saxagliptin, with a point estimate for the ratio of population geometric means for saxagliptin C_{max} with and without metformin of 0.79. This decline was not considered to be of clinical significance. The overall exposure of saxagliptin and BMS-510849 was not affected by metformin, and the pharmacokinetics of metformin were not altered by saxagliptin. There were no cases of hypoglycemia, and the most common adverse events seen in subjects given saxagliptin alone or with metformin were headache, chills and upper respiratory tract infections (40).

Digoxin did not affect the pharmacokinetics of saxagliptin and saxagliptin did not affect the pharmacokinetics of digoxin in an open-label, randomized, crossover study in 14 healthy volunteers. In the first period, a single oral dose of saxagliptin 10 mg was administered. In the second period, loading doses of oral digoxin were given on days 1 and 2 and followed on days 3-7 by digoxin 0.25 mg daily alone or with saxagliptin 10 mg daily. In the third period, study subjects received the treatment they did not receive in the second period. For both digoxin and saxagliptin C_{max} and AUC values, prespecified criteria for a lack of an interaction were met with coadministration of the agents (41).

In the final study, oral saxagliptin 10 mg was administered alone and with oral doses of simethicone 30 ml, famotidine 40 mg (given 3 h earlier) and omeprazole 40 mg dosed to steady state (5 daily doses). The randomized, open-label, crossover study was completed by 15 healthy subjects. The coadministration of saxagliptin with simethicone and famotidine affected saxagliptin C_{max} values but in a manner not considered clinically meaningful. Simethicone and famotidine had no effect on saxagliptin exposure, and omeprazole had no effect on saxagliptin C_{max} or AUC. The pharmacokinetics of the saxagliptin metabolite were similarly affected by the agents tested (42).

Sources

Bristol-Myers Squibb (US); licensed to AstraZeneca (GB).

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