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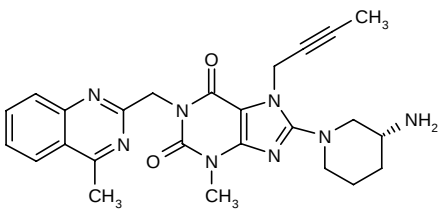
BI-1356

Dipeptidyl-Peptidase IV Inhibitor
Antidiabetic Agent

BI-1356-BS
Ondero™

8-[3(*R*)-Aminopiperidin-1-yl]-7-(2-butynyl)-3-methyl-1-(4-methylquinazolin-2-ylmethyl)xanthine

InChI=1/C25H28N8O2/c1-4-5-13-32-21-22(29-24(32)31-12-8-9-17(26)14-31)30(3)25(35)33(23(21)34)15-20-27-16(2)18-10-6-7-11-19(18)28-20/h6-7,10-11,17H,8-9,12-15,26H2,1-3H3/t17-/m1/s1



$C_{25}H_{28}N_8O_2$
Mol wt: 472.5422

CAS: 668270-12-0

EN: 365734

Abstract

BI-1356 is a dipeptidyl-peptidase IV (DPP IV, or CD26) inhibitor developed at Boehringer Ingelheim for the treatment of type 2 diabetes. BI-1356 demonstrated long-lasting DPP IV inhibition both *in vitro* and *in vivo*. *In vitro*, BI-1356 was at least 10,000-fold more selective for DPP IV than for DPP-8 and DPP-9. High potency and long-lasting inhibitory effects were also observed *in vivo* in mice and rats, the inhibition induced by BI-1356 being longer lasting than that induced by any other DPP IV inhibitor tested. BI-1356 exhibited nonlinear pharmacokinetics in healthy volunteers and patients with type 2 diabetes. Oral BI-1356 administered once daily proved to be well tolerated in healthy volunteers and patients with type 2 diabetes. Treatment with BI-1356 increased concentrations of GLP-1 and reduced concentrations of glucose in patients with type 2 diabetes, and it also significantly reduced Hb1Ac in diabetic patients. Phase III clinical trials are under way.

Synthesis*

BI-1356 can be synthesized as follows. Cyclization of 2-aminoacetophenone (I) with chloroacetonitrile (II) in the presence of HCl in dioxane gives 2-(chloromethyl)-4-methylquinazoline (III) (1), which can also be prepared by reaction of 2-(chloromethyl)-4-methylquinazoline-3-oxide (IV) with PCl_3 in refluxing chloroform (2). Coupling of the quinazoline derivative (III) with 3-methyl-7-(2-butyn-1-yl)-8-bromoxanthine (V) –prepared by treatment of 8-bromo-3-methylxanthine (VI) with butyn-2-yl bromide (VII) in the presence of TEA or DIEA in DMF (3)–, in the presence of Na_2CO_3 or K_2CO_3 provides 1-(4-methylquinazolin-2-ylmethyl)-3-methyl-7-(2-butyn-1-yl)-8-bromoxanthine (VIII). Condensation of bromoxanthine (VIII) with (*R*)-3-(phthalimido)piperidine D-tartrate (IX) affords the adduct (X), which is deprotected by heating with 2-aminoethanol in either toluene at 85 ºC or in THF at 65 ºC (1). Scheme 1.

The title compound can also be prepared by coupling of the bromoxanthine (VIII) with 3(*R*)-(*tert*-butoxycarbonylamino)piperidine (XI) by means of K_2CO_3 in DMF to give the *N*-protected piperidine derivative (XII), which is deprotected with TFA in CH_2Cl_2 (2, 3). Scheme 1.

Background

Diabetes is rapidly becoming a worldwide health concern. According to the International Diabetes Federation, approximately 245 million people around the world have diabetes and type 2 diabetes accounts for approximately 90% of all cases (4). Characterized by insulin resistance and impaired insulin secretion, type 2 diabetes causes considerable morbidity and mortality, and the cost and healthcare burden associated with the condition are substantial. Because of the progressive nature of the disease and limited long-term efficacy and tolerability of traditional antidiabetic therapies, type 2 diabetes is often inadequately controlled (5-7).

Dipeptidyl-peptidase IV (DPP IV, CD26) is a membrane glycoprotein that is involved in the degradation of glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), two incretin hormones that

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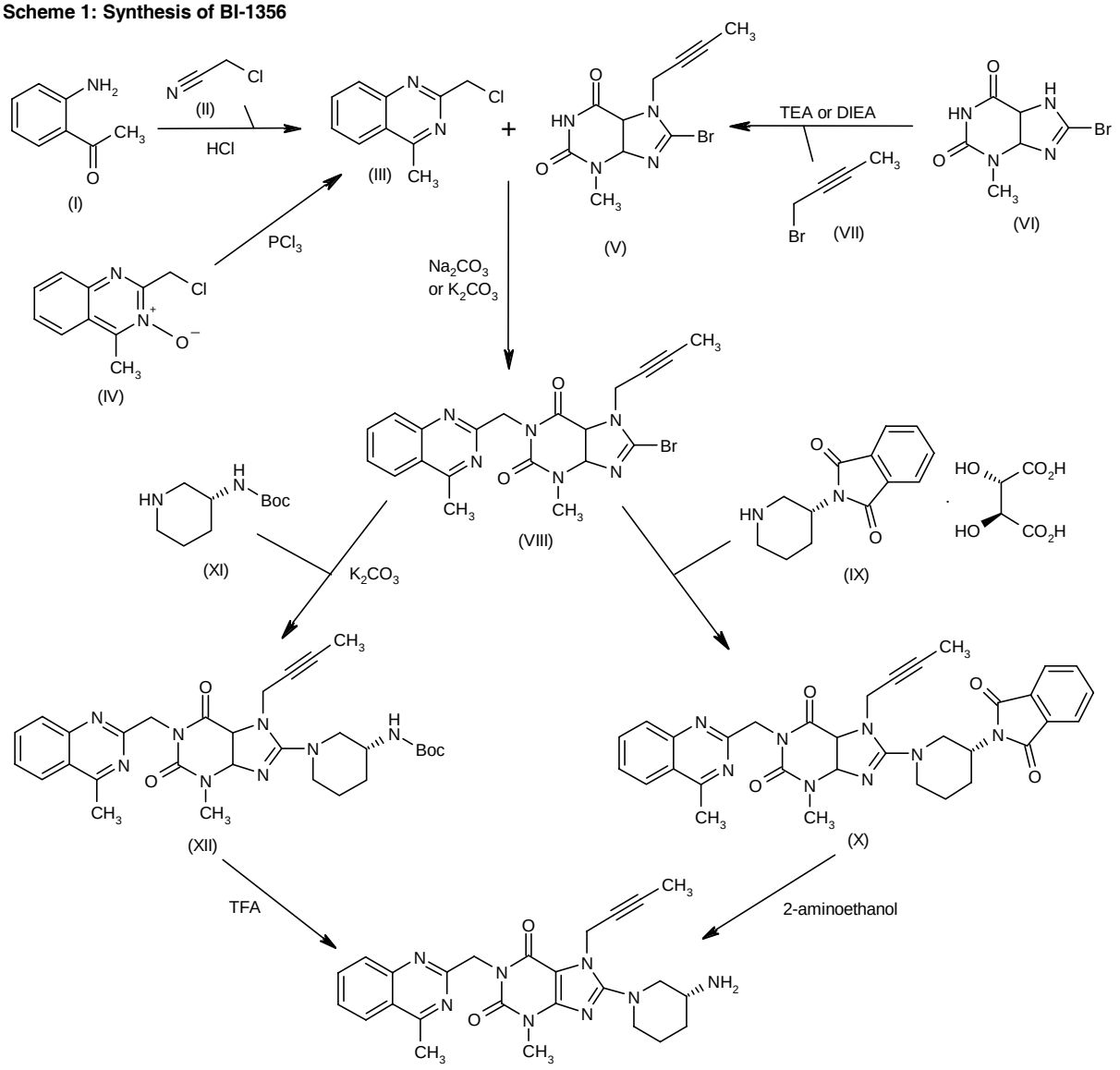
Scheme 1: Synthesis of BI-1356



play important roles in maintaining glucose homeostasis. As a new class of antidiabetic agents, DPP IV inhibitors have demonstrated comparable efficacy to traditional antidiabetic therapies with a low risk of hypoglycemia and no effect on body weight (8-11). To date, two DPP IV inhibitors, vildagliptin (Novartis) and sitagliptin (Merck & Co.), have gained approval from regulatory authorities for their use as oral antidiabetic drugs; in early 2007, the European Medicines Agency (EMEA) approved the use of vildagliptin (Galvus™, LAF-237) in combination with other antidiabetic medications such as metformin, sulfonylureas and thiazolidinediones for the treatment of type 2 diabetes, and the United States Food and Drug Administration (FDA) approved sitagliptin (Januvia™, MK-0431) in 2006 and the combination (Janumet™) of sitagliptin and metformin in 2007 for the treatment of type 2 diabetes. Both vildagliptin and sitagliptin proved effective and well tolerated in clinical studies conducted in patients with type 2 diabetes. Compared with traditional therapies, these DPP IV inhibitors induced sustainable reductions in glycosylated hemoglobin (HbA1c), with a low risk for developing hypoglycemia and no weight gain (9-11).

Three DPP IV inhibitors, saxagliptin (BMS-477118; Bristol-Myers Squibb, AstraZeneca), alogliptin (SYR-322; Takeda) and BI-1356 (Boehringer Ingelheim), are currently in late-stage clinical development (3, 8, 10-12). Compared with metformin alone, combination therapy

with saxagliptin and metformin significantly ($p < 0.0001$) improved glycemic control in patients with type 2 diabetes in a phase III study (13). Alogliptin demonstrated encouraging efficacy in reducing glucose and increasing insulin concentrations in preclinical and early clinical studies, and the agent proved to be well tolerated in healthy subjects and patients with type 2 diabetes. Phase III clinical trials involving over 2,000 patients demonstrated that alogliptin significantly reduced HbA1c, with a good safety profile. Supported by these phase III trials, Takeda submitted a New Drug Application (NDA) to the U.S. FDA for alogliptin for the treatment of type 2 diabetes in early 2008 (12, 14).

Structurally derived from the xanthine scaffold, BI-1356 (Ondero™) is a DPP IV inhibitor developed at Boehringer Ingelheim using systematic structural variations. The compound is structurally different from other DPP IV inhibitors (3, 8). BI-1356 is currently undergoing phase III clinical development for the treatment of type 2 diabetes.

Preclinical Pharmacology

BI-1356 inhibited human DPP IV activity *in vitro* with a mean IC_{50} of approximately 1 nM, which is markedly lower than the mean IC_{50} of sitagliptin (19 nM), alogliptin (24 nM), saxagliptin (50 nM) and vildagliptin (approximately 62 nM), indicating that BI-1356 may have greater potency than the other DPP IV inhibitors, which was confirmed by K_i values of 1 and 10 nM, respectively, for BI-1356 and vildagliptin; the effect of BI-1356 was also longer lasting. *In vitro*, BI-1356 was at least 10,000-fold more selective for DPP IV than for DPP-8, DPP-9, aminopeptidases N and P, prolyloligopeptidase, trypsin, plasmin and thrombin, and it was approximately 90-fold more selective for DPP IV than for fibroblast activation protein (FAP) and the hERG channel. Because inhibition of DPP-8 and DPP-9 has been associated with toxicity in animals, the high selectivity of BI-1356 for DPP IV suggested that it may have less toxicity (3, 15-17).

BI-1356 also demonstrated strong and long-lasting DPP IV inhibition *in vivo*. In male Wistar rats, beagle dogs and rhesus monkeys, an oral dose of 1 mg/kg of BI-1356 induced > 70% inhibition of the enzyme for > 7 h (3).

In rats, BI-1356 inhibited DPP IV in plasma in a dose-dependent manner within 30 min after oral administration. At doses of 3 and 10 mg/kg, it provided approximately 90% inhibition over a 7-h period, and the inhibition persisted over 24 h. The ED_{50} for plasma DPP IV was approximately 0.3 mg/kg 7 h after administration and 0.9 mg/kg 24 h after administration. The DPP IV inhibition 24 h after administration of BI-1356 was more profound than that induced by any of the other DPP IV inhibitors tested (15, 16).

In C57BL/6J mice, BI-1356 showed a long-lasting effect on glucose tolerance. Following an oral dose of 1 mg/kg of BI-1356 45 min before an oral glucose tolerance test (OGTT), glucose excursion was reduced by 50%, which was similar to the reduction induced by vildagliptin, sitagliptin and saxagliptin at the same dose level. The reduction induced by BI-1356 was sustained, being 20-30% at 16 h, whereas other DPP IV inhibitors did not yield any improvement in glucose tolerance 16 h after administration of the same dose. In C57BL/6J mice and Zucker fatty (*fa/fa*) rats, the duration of action on glucose tolerance was longer for BI-1356 than for sitagliptin, saxagliptin and vildagliptin. In Zucker rats, BI-1356 reduced total glucose excursion by 29% during an OGTT 30 min after administration. The suppression of glucose excursion was associated with increases in plasma concentrations of GLP-1 and insulin (15, 16).

In diabetic *db/db* mice, BI-1356 dose-dependently reduced plasma glucose excursion at oral doses of 0.1 mg/kg (15% inhibition) to 1 mg/kg (66% inhibition) administered 45 min before an OGTT. BI-1356 at a dose of 1 mg/kg inhibited the plasma activity of DPP IV by 76% 30 min after the glucose load. Reduced plasma DPP IV activity was correlated with the improvement in oral glucose tolerance (3).

Pharmacokinetics and Metabolism

Pharmacokinetic parameters, including oral bioavailability, elimination half-life ($t_{1/2}$) and steady-state volume of distribution (V_{ss}) of BI-1356 were evaluated in rats and cynomolgus monkeys. BI-1356 exhibited good oral bioavailability (50%), a long $t_{1/2}$ (35.9 and 41.4 h in rats and monkeys, respectively) and a high V_{ss} (5.4 and 15.8 l/kg in rats and monkeys, respectively). This was suggested to account for the strong and long-lasting inhibitory effect on DPP IV observed *in vivo*. BI-1356 exhibited no interaction with cytochrome P-450 (CYP) enzymes (3).

The pharmacokinetics and pharmacodynamics of BI-1356 were evaluated in a randomized, double-blind, placebo-controlled trial of single rising doses (2.5-600 mg) in healthy male subjects (aged 21-65 years) who received BI-1356 or placebo once daily for 12 days. The pharmacokinetics of BI-1356 fit a 3-compartment model: exposure increased less than proportionally in the dose range 1-10 mg, more than proportionally in the dose range 25-100 mg, and approximately proportionally in the dose range 100-600 mg. Renal excretion of BI-1356 was low and was not the major pathway of elimination. Plasma concentrations of BI-1356 were directly correlated to plasma DPP IV-inhibitory activity (18-20).

Dittberner *et al*. determined the absolute bioavailability of BI-1356 using a population pharmacokinetic modeling approach. In this study, 862 plasma and 304 urine samples obtained from 28 healthy volunteers receiving 0.5, 2.5 or 10 mg BI-1356 i.v. or 5 mg BI-1356 i.v. plus 10 mg BI-1356 orally were included in the analysis. The FOCE INTERACTION estimation method implemented in NONMEM V was used to perform the modeling. According to the study, the plasma concentration-time profile of BI-1356 in healthy volunteers fit a 3-compartment model. The absolute bioavailability of BI-1356 was estimated to be approximately 30%. It was suggested that concentration-dependent protein binding in the cen-

tral and peripheral compartments indicated that BI-1356 might bind to DPP IV in both plasma and tissues, including kidney, liver and lung. The parameters obtained from modeling using urine data were nearly identical to those obtained from modeling using only the plasma data. The findings indicated that concentration-dependent target protein binding accounted for the nonlinear pharmacokinetics of BI-1356 (21).

The pharmacokinetics and pharmacodynamics of BI-1356 were analyzed in 47 male patients with type 2 diabetes in a randomized, double-blind, placebo-controlled study (BI-1356, n=35; placebo, n=12; aged 21-65 years; body mass index [BMI] 18-35 kg/m^2]. The patients received either BI-1356 (1, 2.5, 5 or 10 mg) or placebo once daily for 12 days. BI-1356 exhibited nonlinear pharmacokinetics. The plasma concentrations and exposure of BI-1356 increased less than proportionally with dose. The C_{max} of BI-1356 at steady state ranged from 4.5 nmol/l for the 1-mg dose to 13.6 nmol/l for the 10-mg dose. The median t_{max} was 1.5 h. Data from this study showed that reductions in plasma DPP IV activity were correlated with plasma concentrations of BI-1356 (22, 23).

Safety

Single or multiple oral doses of BI-1356 ranging from 2.5 to 600 mg proved to be well tolerated in healthy male volunteers. The incidence of any adverse events (AEs) (28% for BI-1356, 38% for placebo) or drug-related AEs (19% for BI-1356, 31% for placebo) for BI-1356 was not higher than for placebo. No serious AEs and no hypoglycemia were reported. The most frequent AEs were nausea and headache. No clinically relevant deviations in ECGs and other laboratory parameters, including hematology, coagulation, clinical chemistry and urinalysis, were reported. A similar safety profile was also seen in men with type 2 diabetes who were randomized to receive 1-10 mg BI-1356 once daily (18-20).

The safety and tolerability of oral BI-1356 (1, 2.5, 5 or 10 mg) administered once daily for 12 days were evaluated in male patients with type 2 diabetes. Treatment with BI-1356 was well tolerated. No signs of hypoglycemia were observed and no serious AEs or clinically relevant changes in ECG were reported. The overall incidence of AEs in the BI-1356 group was not higher than in the placebo group (54% *vs.* 75%) (22, 23).

Further evaluation of the safety and tolerability of oral BI-1356 (2.5, 5 and 10 mg) administered once daily for 28 days after a 14-day washout period was performed in a randomized, double-blind, placebo-controlled, multiple-dose study conducted in 77 male and female patients with type 2 diabetes (aged 40-69 years). BI-1356 was well tolerated. A total of 5 patients (31%) treated with placebo and 21 patients (34%) treated with BI-1356 experienced at least one AE, with nasopharyngitis (5 patients), back pain (5 patients), upper abdominal pain (3 patients) and headache (3 patients) being the most common AEs. None of the patients experienced symptoms of hypoglycemia. Most AEs were mild in intensity (24).

Clinical Studies

In the study in healthy volunteers, DPP IV activity was inhibited by > 80% at doses of 5 mg and above within 3 h, an effect which was sustained at 24 h at doses of 25-600 mg (18-20).

The efficacy of BI-1356 was also evaluated in the multiple-dose trial in patients with type 2 diabetes. Forty-seven male patients received BI-1356 (1, 2.5, 5 or 10 mg) once daily or placebo for 12 days. Enzyme activity and plasma concentrations of BI-1356 were measured at regular intervals. An OGTT was performed on days 1 and 13. BI-1356 (2.5 mg and higher) dose-dependently inhibited plasma DPP IV activity by approximately 80% at 24 h after the last dose. Compared with baseline and placebo, a statistically significant ($p < 0.05$) reduction in postprandial glucose excursion 24 h after the last dose was observed for doses of 2.5 mg (–106 mg.h/dl), 5 mg (–82 mg.h/dl) and 10 mg (–111 mg.h/dl). Levels of GLP-1 were increased by > 2-fold (18, 22, 23).

The efficacy of oral BI-1356 was further evaluated in the 77 patients with type 2 diabetes who received BI-1356 (2.5, 5 and 10 mg; n=16) or placebo (n=26) once daily for 28 days. After 4 weeks, treatment with BI-1356 increased concentrations of GLP-1 by up to 4-fold and concentrations of glucagon by up to 24%. Reductions in glucose concentrations from baseline were up to 105 mg.h/dl. A significant placebo-corrected mean change in HbA1c of –0.31%, –0.37% and –0.28%, respectively, from baseline (7.0%) was observed for doses of 2.5, 5 and 10 mg (24).

Several phase III clinical studies of BI-1356 are currently recruiting participants (25-30).

Source

Boehringer Ingelheim GmbH (DE).

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