8-(3-(*R*)-Aminopiperidin-1-yl)-7-but-2-ynyl-3-methyl-1-(4-methyl-quinazolin-2-ylmethyl)-3,7-dihydropurine-2,6-dione (BI 1356), a Highly Potent, Selective, Long-Acting, and Orally Bioavailable DPP-4 Inhibitor for the Treatment of Type 2 Diabetes†

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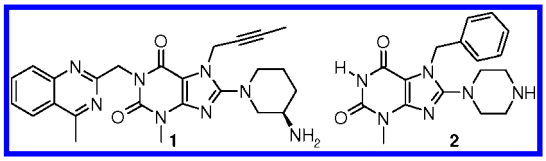
Abstract: A new chemical class of potent DPP-4 inhibitors structurally derived from the xanthine scaffold for the treatment of type 2 diabetes has been discovered and evaluated. Systematic structural variations have led to **1** (BI 1356), a highly potent, selective, long-acting, and orally active DPP-4 inhibitor that shows considerable blood glucose lowering in different animal species. **1** is currently undergoing clinical phase IIb trials and holds the potential for once-daily treatment of type 2 diabetics.

Type 2 diabetes is establishing itself as an epidemic of the 21st century with an estimated 5% of the adult world population suffering from the disease.[1] The number of deaths attributable to diabetes is steadily growing, currently estimated at 3.8 million cases each year, reflecting the insufficient glycemic control achieved with currently available treatments. Therefore, more effective therapeutics for glycemic control are badly needed. DPP-4[a] is a protease that specifically cleaves dipeptides from proteins and oligopeptides after a penultimate N-terminal proline or alanine.[2] DPP-4 is involved in the degradation of a number of neuropeptides, peptide hormones, and cytokines, including the incretins GLP-1 and GIP.[3] GLP-1 and GIP are released from the gut in response to food intake and exert a potent glucose-dependent insulinotropic action and thereby contribute to the maintenance of postmeal glycemic control.[4] In addition, they exhibit beneficial effects on pancreatic β cells.[5] Other effects that have been described for GLP-1 are an inhibition of glucagon release from pancreatic α cells, a reduction of food intake, and a retardation of gastric emptying.[6] Consequently, inhibiting DPP-4 prolongs the action of GLP-1 and GIP, which in turn improves glucose homeostasis with a low risk of hypoglycemia and potential for disease modification. Indeed, clinical trials involving diabetic patients have shown improved glucose control by administering DPP-4 inhibitors, thus demonstrating the benefit of this promising new class of antidiabetics.[7] Intense research in the DPP-4 field has resulted in the launch of one inhibitor and the advancement of others into preregistration/phase III.[8]

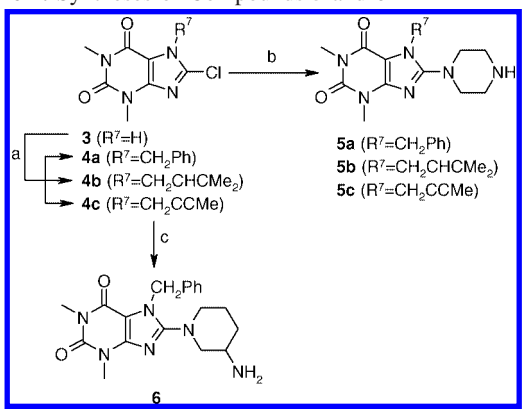
Herein, we report the discovery of the novel, potent, and selective DPP-4 inhibitor **1** (BI 1356)[9] originating from the class of xanthines (Chart 1).

Compound **2**, discovered through a high-throughput screening campaign that involved about 500 000 compounds and showing promising inhibitory activity in the low micromolar range, was our starting point in the search for an effective DPP-4 inhibitor.[10] Systematic structural modifications on the xanthine scaffold were carried out to study the structure–activity relationship and optimize inhibition of DPP-4. Various substituents on the xanthine core were scrutinized in a broad manner while a stronger emphasis was put on the residues at N-1, N-7, and C-8 because of their higher impact on activity. Common synthetic starting materials for the study were 8-chlorotheophylline **3** and 8-bromoxanthine **7** (Schemes 1 and 2). Derivative syntheses starting from theophylline **3** were routinely carried out first with alkylation of N-7 followed by nucleophilic displacement of the chlorine at C-8 by a diamine. The alkylations were conducted using an appropriate alkyl halide in the presence of a base. Displacement of the chlorine was performed employing an excess of the diamine to be introduced or the diamine in combination with potassium carbonate. In the case of an asymmetric diamine, the nitrogen not to be reacted was preferentially embedded in *tert*-butyl carbamate, with subsequent release by treatment with acid. Employing **7** as the starting material followed a similar reaction sequence to

Chart 1



Scheme 1. Syntheses of Compounds **5** and **6** [a]



[a] Reagents: (a) $PhCH_2Cl$, Me_2CCHCH_2Br, or $MeCCCH_2Br$, $^iPr_2NEt$, DMF, room temp, **4a** 75%, **4b** 91%, **4c** 84%; (b) piperazine (excess), THF or MeCN, reflux, **5a** 64%, **5b** 39%, **5c** 98%; (c) 3-aminopiperidine·2HCl, K_2CO_3, MeCN, 70 °C, 58%.

† Compound **1** has been deposited into the Protein Data Bank: PDB code 2RGU.

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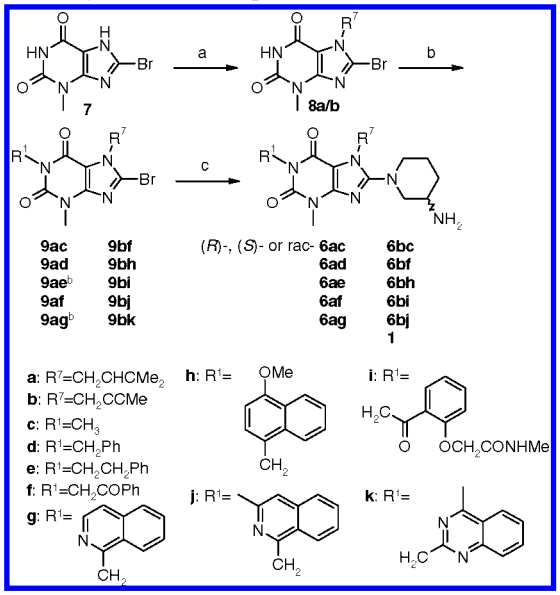
[a] Abbreviations: DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide 1; GIP, glucose-dependent insulinotropic peptide.

Scheme 2. Syntheses of Compounds **6** and **1** [a]



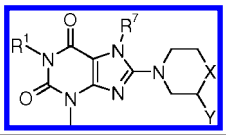
[a] Reagents: (a) Me_2CCHCH_2Br or $MeCCCH_2Br$, $^iPr_2NEt$, DMF, room temp, **8a** 86%, **8b** 86%; (b) R^1-Hal, K_2CO_3, DMF, room temp, 77–98%; (c) (I) racemic, (*R*)- or (*S*)-3-Boc-aminopiperidine, K_2CO_3, DMF, 75 °C, 67–96%; (II) TFA, DCM or HCl, ^{i}PrOH, 69–98%. [b] Compound bears chlorine instead of bromine at C-8.

assemble the fully substituted xanthines. The preferred order of attachment of the three substituents was N-7 followed by N-1 and C-8, though the order of introduction of the last two substituents could be reversed to streamline the examination of the residue on N-1. Accordingly, treatment of xanthine **7** with different alkyl halides was conducted in the presence of a mild base, such as triethylamine or ethyldiisopropylamine, furnishing the N-7 derivatized xanthine **8** selectively; competing N-1 alkylation was usually not observed. The next step, alkylation at N-1, was regularly performed using the stronger base potassium carbonate leading to **9**. The ensuing nucleophilic substitution of the bromine at C-8 in xanthine **9** for the diamine, 3-aminopiperidine, was preferably carried out using the N-*tert*-butyloxycarbonyl protected 3-aminopiperidine in the presence of potassium carbonate. The synthesis was concluded by the release of the amino functionality from its protection by treatment with acid. The enantiomerically pure compounds were obtained by reaction with the commercial enantiopure N-*tert*-butyloxycarbonyl protected 3-aminopiperidines.

The DPP-4 inhibitory activity of the compounds was tested using a preparation of human DPP-4 derived from Caco-2 cells. The results obtained for the racemic xanthine derivatives in Schemes 1 and 2 are compiled in Table 1. Variations at N-7 or C-8 of **5a** yielded **5b**, **5c**, and **6**, all showing significantly increased DPP-4 inhibition. In particular, replacement of the piperazine at C-8 for the 3-aminopiperidine in **5a** resulted in a tremendous increase in potency. Combining the structural features of these more potent compounds led to compounds **6ac** and **6bc**, which exhibited approximately a 100-fold and 50-fold higher inhibitory activity, respectively, than the original **2**. Further optimization at N-1 based on the structure of **6ac** resulted in an additional increase of potency when attaching the phenacyl group (**6af**), while the benzylated and the phenethylated **6ad** and **6ae** showed inferior activity.

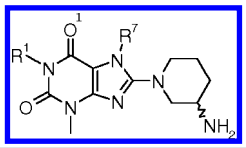
Further profiling was conducted using the pure enantiomers (*R*)-**6af** and (*S*)-**6af** (Table 2). DPP-4 inhibition of the (*S*)-

Table 1. DPP-4 Inhibitory Activity of Xanthines



compd	R^7	R^1	X/Y	DPP-4 IC_{50} (nM)
2	CH_2Ph	H	NH/H	3900
5a	CH_2Ph	Me	NH/H	2800
5b	CH_2CHCMe_2	Me	NH/H	580
5c	CH_2CCMe	Me	NH/H	200
6	CH_2Ph	Me	CH_2/NH_2	82
6ac	CH_2CHCMe_2	Me	CH_2/NH_2	35
6bc	CH_2CCMe	Me	CH_2/NH_2	88
6ad	CH_2CHCMe_2	CH_2Ph	CH_2/NH_2	284
6ae	CH_2CHCMe_2	$(CH_2)_2Ph$	CH_2/NH_2	56
6af	CH_2CHCMe_2	CH_2COPh	CH_2/NH_2	5

Table 2. Effects of 8-(3-Aminopiperidin-1-yl)xanthines on DPP-4, hERG, and M_1



compd	R^7	R^1	DPP-4 IC_{50} (nM)	hERG (%)[a]	M_1 IC_{50} (nM)
(*R*)-**6af**	CH_2CHCMe_2	**f**	6	31	25
(*S*)-**6af**	CH_2CHCMe_2	**f**	3	23	50
(*R*)-**6ag**	CH_2CHCMe_2	**g**	4	51	5
(*S*)-**6ag**	CH_2CHCMe_2	**g**	2	51	26
(*R*)-**6bf**	CH_2CCMe	**f**	4	88[b]	6161
(*S*)-**6bf**	CH_2CCMe	**f**	9	88[b]	1129
(*R*)-**6bh**	CH_2CCMe	**h**	8	51	518
(*R*)-**6bi**	CH_2CCMe	**i**	1	88	1174
(*R*)-**6bj**	CH_2CCMe	**j**	3	78	430
1 [(*R*)]	CH_2CCMe	**k**	1	97	295

[a] hERG current remaining at a test concentration of 1 μM. [b] Value of the racemic compound.

Table 3. Selected Basic PK Data of Compound **1** in Rat and Cynomolgus Monkey

species	CL ((mL/min)/kg)	V_{ss} (L/kg)	$MRT_{tot,oral}$ (h)	$t_{1/2,oral}$ (h)	F_{oral} (%)
rat[a]	37.3	5.4	14.3	35.9	50.7
monkey[b]	15.8	15.8	17.4	41.4	50.1

[a] 5 mg/kg oral and intravenous dose. [b] 5 mg/kg oral and 1.5 mg/kg intravenous dose.

enantiopure compounds bearing a dimethylallyl group on N-7. Unfortunately, both compounds show an unacceptably high inhibition of the hERG channel and affinity for the muscarinic receptor M_1. By variation of the residue on N-1 based on the dimethylallylated xanthine, both side effects could not concomitantly be reduced sufficiently while retaining the desired high inhibitory activity. These shortcomings also extended to compounds with bicyclic aryl- or heteroarylmethyl residues attached to N-1 such as in **6ag** that were otherwise highly potent DPP-4 inhibitors. Switching to the 7-butynyl derivatized scaffold proved to be a very effective measure to essentially abolish hERG channel inhibition and reduce interaction with receptor M_1 to a high degree. Various phenacyl and bicyclic aryl- and heteroarylmethyl residues attached to N-1 of this scaffold exhibited high DPP-4 inhibition with no perturbing interactions with the hERG channel or M_1 receptor. Curiously, in the 7-butynyl series the (*R*)-configured compounds were signifi-

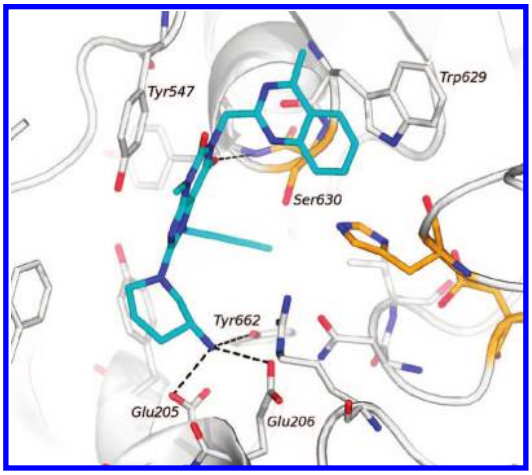


Figure 1. Compound **1** (light-blue carbon atoms) bound to DPP-4. Active site residues Ser630, His740, and Asp708 are shown in orange. Three hydrogen bonds (shown by black dashes) are formed by the amino function on the piperidine ring with acceptor groups on the protein Glu205, Glu206, and Tyr662. A fourth hydrogen bond is formed between the C-6 carbonyl of the xanthine scaffold and the backbone amide of residue Tyr631. Aromatic stacking interactions are formed between the xanthine ring system and Tyr547 as well as between the quinazoline ring and Trp629.

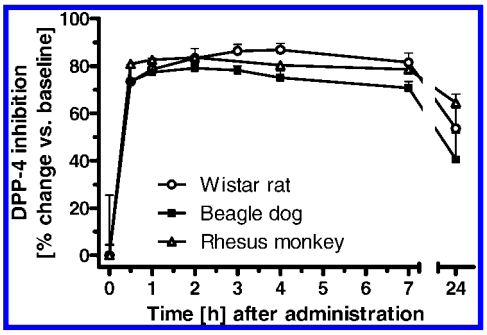


Figure 2. Inhibition of plasma DPP-4 activity after oral administration of **1** at 1 mg/kg in Wistar rats, Beagle dogs, and Rhesus monkeys. Data are represented as the mean ± SEM (n = 5 for rats, n = 3 for dogs and monkeys).

Compound **1**, showing potent DPP-4 inhibition in vitro and a low affinity for hERG channel and M_1 receptor, has been further examined. A favorable crystalline modification of the free base of **1** has been produced that is characterized by a high melting point (202 °C) and high aqueous solubility at physiological pH value (pH 7.4, >5 g/L). Compound **1** displays a log D of 0.4 at pH 7.4 and pK_a of 1.9 and 8.6 corresponding to the protonation of the quinazoline and the primary amino group, respectively.

The X-ray crystal structure of **1** in complex with human DPP-4 allows one to depict the main interactions of the inhibitor within the enzyme active site and to rationalize the observed SAR (Figure 1). The aminopiperidine substituent at C-8 of the xanthine scaffold occupies the S2 subsite. Its primary amine forms a network of charge-reinforced hydrogen bonds to Glu205, Glu206, and Tyr662, amino acid residues that constitute the recognition site for the amino terminus of peptide substrates of DPP-4. The butynyl substituent at N-7 occupies the hydrophobic S1 pocket of the enzyme. The xanthine moiety is positioned such that its uracil moiety lies on top of Tyr547, forming aromatic π-stacking interactions with the phenol of

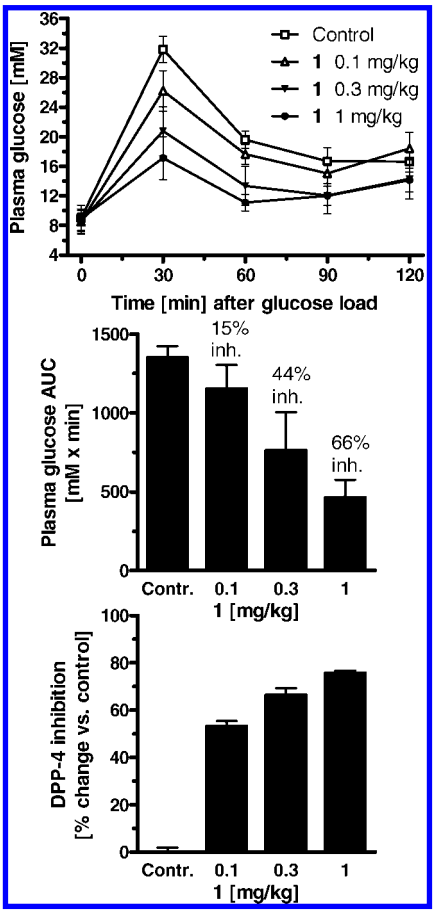


Figure 3. Effect of **1** on plasma glucose levels in an oral glucose tolerance test in db/db mice (top). Compound or vehicle was administered 45 min before an oral glucose load. Reactive plasma glucose AUC was calculated from 0 to 120 min (middle). Inhibition of plasma DPP-4 activity was measured 30 min after the glucose load at the peak of the glucose excursion. Data are represented as the mean ± SEM (n = 7/group).

conformational change has been reported for related xanthine based inhibitors and for inhibitors from other structural classes.[12–14] The C-6 carbonyl function of the xanthine scaffold forms a hydrogen bond to the backbone NH of Tyr631. Finally, the quinazoline subsituent at N-1 is placed on a hydrophobic surface patch of the protein and interacts with Trp629 by π-stacking its phenyl ring with the pyrrol ring of the amino acid side chain.

The observed boost in affinity upon the introduction of the aminopiperidine group at C-8 is due to the very intimate interaction of the positively charged terminal ammonium that can form three strong hydrogen bonds with the protein. Further, the observed bound chair conformation of the piperidine ring is a low-energy conformation. The original piperazine derivative **2** can only form two hydrogen bonds and needs to adopt an unfavorable conformation upon binding.[12]

The strong DPP-4 inhibition of **1** has been confirmed in various species in vitro and in vivo. In male Wistar rats, Beagle dogs, and Rhesus monkeys, xanthine **1** proved to be a highly efficacious, long-lasting, and potent DPP-4 inhibitor providing >70% inhibition for >7 h for all three species after oral administration of 1 mg/kg (Figure 2).

Pharmacokinetic parameters including oral bioavailability, clearance, mean residence time, and volume of distribution of

key characteristics of **1** and, in combination with its high potency and good oral bioavailability, are thought to contribute to the strong and long-lasting inhibitory effect on DPP-4 observed in vivo.

Compound **1** was further characterized in vivo in diabetic mice (Figure 3). Single oral administration of **1** to db/db mice 45 min prior to an oral glucose tolerance test reduced plasma glucose excursion in a dose-dependent manner from 0.1 mg/kg (15% inhibition) to 1 mg/kg (66% inhibition). The improvement of oral glucose tolerance correlated with the DPP-4 activity in plasma, which was inhibited by 76% with the 1 mg/kg dose 30 min after the glucose load was administered.

Compound **1** exhibits no interaction with CYP-450 enzymes up to 50 μM. Because inhibition of DPP-8 and DPP-9, which are closely related to DPP-4, has been associated with toxicities in animals, it is important to note that **1** displays a more than 10000-fold selectivity against both of these enzymes.[15]

In summary, a new chemical class of highly potent DPP-4 inhibitors structurally based on the xanthine scaffold has been discovered. The 3-aminopiperidine attached to C-8 proved to be a crucial constituent for high inhibitory activity, and but-2-ynyl on N-7 was essential to eliminate interaction with the hERG channel and M_1 receptor. Further optimization led to **1** bearing a quinazolin-2-ylmethyl at N-1. **1** represents a highly potent, selective, and long-acting DPP-4 inhibitor of a novel chemotype that shows promise for once-daily treatment of type 2 diabetic patients. Compound **1** is currently undergoing clinical phase IIb trials.

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Supporting Information Available: Experimental details, analytical data of the compounds, and X-ray crystallograpic data of **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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