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Discovery of Imigliptin, a Novel Selective DPP-4 Inhibitor for the Treatment of Type 2 Diabetes

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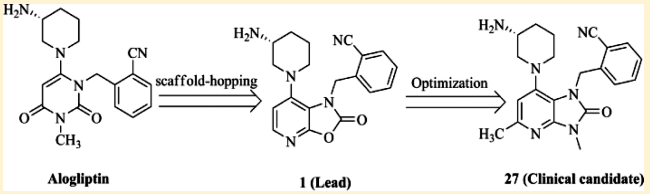
Supporting Information

ABSTRACT: We report our discovery of a novel series of potent and selective dipeptidyl peptidase IV (DPP-4) inhibitors. Starting from a lead identified by scaffold-hopping approach, our discovery and development efforts were focused on exploring structure−activity relationships, optimizing pharmacokinetic profile, improving *in vitro* and *in vivo* efficacy, and evaluating safety profile. The selected candidate, Imigliptin, is now undergoing clinical trial.



KEYWORDS: *Diabetes, dipeptidyl peptidase IV (DPP-4), inhibitor, scaffold-hopping, imigliptin, OGTT, pyridinylimidazolone*

The prevalence of Type 2 diabetes mellitus (T2DM) is increasing at an alarming rate, affecting 382 million people worldwide in 2013, and China now has the largest patient population.[1,2] Dipeptidyl peptidase IV (DPP-4) is a widely distributed physiological enzyme that can be found solubilized in blood or membrane-anchored in tissues. The rationale for inhibiting DPP IV activity in type 2 diabetes is that it decreases peptide cleavage and thereby enhances endogenous incretin hormone activity.[3]

Since the first approval of Sitagliptin in 2006, there are several DPP-4 inhibitors in clinical use today (Figure 1).[4] However, the need for more therapeutic options is still unmet as a significant number of patients fail to control blood sugar, experience hypoglycemic conditions, and remain at risk from complications such as cardiovascular and chronic kidney diseases. We believe a novel chemical structure of inhibitor differentiating from existing DPP-4 compounds may provide a unique therapeutic profile in terms of safety and efficacy. Here, we wish to report our discovery of Imigliptin, a novel class of DPP-4 inhibitor currently undergoing clinical trial in China.

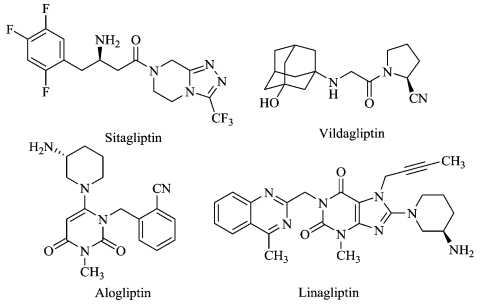


Figure 1. Marketed DPP-4 inhibitors.

Our discovery started with a lead compound **1**, identified via scaffold-hopping from Alogliptin structure assisted by molecular modeling (Figure 2).

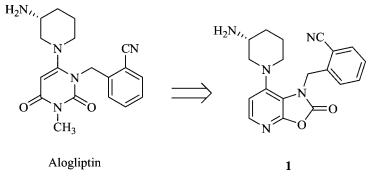


Figure 2. Scaffold-hopping leads to novel structure.

Our first tier assays were using DPP-4 enzyme with counter screening enzymes DPP-8 and DPP-9. Compound **1** has DPP-4 potency of 100 nM with excellent selectivity against DPP-8 and DPP-9 (both >100,000 nM). This is a good starting point for our initial structure−activity relationship (SAR) studies, which focused on pyridinyloxazolone core, and the results are summarized in Table 1. Converting pyridinyloxazolone oxygen of **1** with dimethylmethelene group resulted in compound **2** with a significant loss of activity, while replacing oxygen with NH yielded a pyridinylimidazolone compound **3** with a

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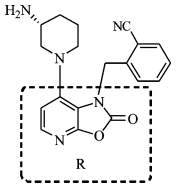
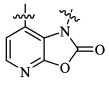
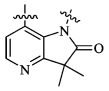
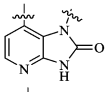
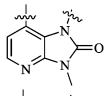
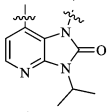
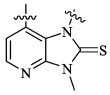
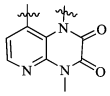
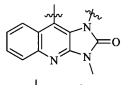
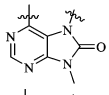
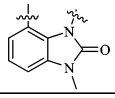
Table 1. SARs of Pyridinyloxazolone Core R

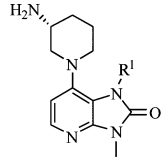


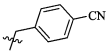
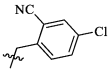
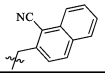
Compound	R	IC50 (nM)		
		DPP-4	DPP-8	DPP-9
Sitagliptin	-	29	32,000	88,000
Alogliptin	-	7	>100,000	>100,000
1		100	>100,000	>100,000
2		3,400	>100,000	>100,000
3		45	>100,000	>100,000
4		13	>100,000	>100,000
5		480	>100,000	>100,000
6		38,000	>100,000	>100,000
7		55,000	>100,000	>100,000
8		1,100	>100,000	>100,000
9		10	>100,000	>100,000
10		45	>100,000	>100,000

moderate 2-fold increase of activity without any loss of selectivity. Methylation of nitrogen on pyridinylimidazolone (compound **4**) boosted 3-fold potency, but substituting with an isobutyl group appeared to be unfavorable (compound **5**). These results may suggest there exists a greasy but small cavity in the enzyme pocket, and the moderate 3-fold potency increase of **4** is a typical methyl desolvation effect.[5] Because of its good potency, compound **4** becomes a central point for the rest of the SARs in this report. Interestingly, replacing pyridinylimidazolone carbonyl oxygen of **4** with sulfur (compound **6**) was detrimental, implying an oxygen atom likely involves a specific H-bond interaction with enzyme backbone. This notion is further supported by the fact that compound **7** has very weak potency. The carbonyl oxygen of compound **7** appears to have different topology as its structure was modified by a ring expansion from compound **4**. Fusing an extra aromatic group onto compound **4** provided compound **8** with a significant loss of activity, conceivably due to the steric hindrance. Modulation of nitrogen on pyridinyl portion (compound **9** and **10**) does not appear to perturb significant changes of inhibitory activity nor selectivity.

We next studied SARs of the cyanobenzyl portion of the molecule. Table 2 summarizes the results. Apparently, there is a

Table 2. SAR of Cyanobenzyl Group R^1



Compound	R^1	IC50 (nM)		
		DPP-4	DPP-8	DPP-9
4		13	>100,000	>100,000
11		88,000	>100,000	>100,000
12		>100,000	>100,000	>100,000
13		110	>100,000	>100,000
14		2,500	>100,000	>100,000
15		16,000	>100,000	>100,000
16		20,000	>100,000	>100,000

strong regio-requirement for cyano substitution at ortho-position, as meta- or para-substitution had several orders of magnitude loss of activity (**4** vs **11** and **12**). This may imply strongly a role of cyano group participating a critical interaction with enzyme in a regio-specific fashion. Chlorine replacing cyano group, compound **13**, was somewhat acceptable with a loss of 10-fold, but replacement with fluorine group saw 2 orders of magnitude loss of activity (compound **14**). Other modifications included chlorine substituting at the para-position on the phenyl ring (compound **15**) or fusing an extra ring on the phenyl ring (compound **16**) of compound **4**, which all resulted in a large loss of potency. In general, this portion of the molecule has a steep SAR and appears to lack much room for chemistry and optimization.

DPP-4 enzyme is an exopetidase and recognizes substrates with uncapped, protonated amino group at its N-terminal.[6] The aminopiperidine portion of the molecule appears to occupy substrate N-terminal site. A summary of aminopiperidine ring SAR is presented in Table 3. Studies of piperidine with analogues of various ring sizes, where an amino group is attached, suggested a five-membered pyrrolidine and six-membered piperidine are optimal for potency (**18** and **4** vs **17** and **19**). It is worthy to notice azitidine analogue has no activity at all at a concentration of 100 μM, and it is likely due to the dramatic changes between the trajectory of amino group on azetidine and that of piperidine. When aminopiperidine group of compound **4** was replaced by a number of heterocycles containing protonable endoamine, such as compounds **20**−**22**, these analogues have weak or no appreciable potency. N-methylation of the amino group significantly decreased potency (**4** vs **23**), while N-acetylation

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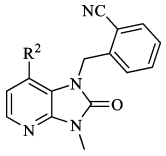
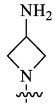
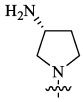
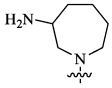
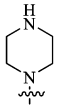
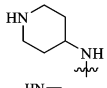
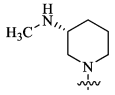
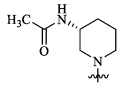
Table 3. SAR of Aminopyperidine R^2



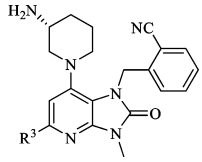
Compound	R^2	IC50 (nM)		
		DPP-4	DPP-8	DPP-9
17		>100,000	>100,000	>100,000
18		22	>100,000	>100,000
4		13	>100,000	>100,000
19		530	>100,000	>100,000
20		23,000	>100,000	>100,000
21		>100,000	>100,000	>100,000
22		5,200	>100,000	>100,000
23		430	>100,000	>100,000
24		>100,000	>100,000	>100,000
25		>100,000	>100,000	>100,000

was detrimental (**4** vs **24**). Further SARs indicate the amino group on piperidine is stereospecific, as R configuration is strongly preferable to S configuration (**4** vs **25**). Combining the above observations implies that there exists an important interaction between protein backbone residue(s) with inhibitor amino group, and such interaction requires a proper and strict spatial orientation.

Finally, we explored the SAR at position 7 of the pyridinyl-imidazolone core with a large number of diversified substituents (compounds **26**–**34**). The results are summarized in Table 4. Interestingly, the SAR in the region is fairly flat, and all analogues made have reasonably good potency despite their large diversity in physical–chemical properties (pK_a, logD, bulkiness, etc.). It hints that this portion of the molecule is out of enzyme active site and likely exposes to solvent region. This is the "sweet spot" on a molecule where it is ideal to modulate physicochemical properties for drug-like optimization.

It should further be noted that throughout the SARs around the molecule, none of the analogues have any appreciable activity against DPP-8 and DPP-9. The high selectivity profile is known to be very important to avoid potential off-target side effects.[7]

Table 4. SAR of Substituents R^3



Compound	R^3	IC50 (nM)		
		DPP-4	DPP-8	DPP-9
4		13	>100,000	>100,000
26		32	>100,000	>100,000
27		9	>100,000	>100,000
28		19	>100,000	>100,000
29		13	>100,000	>100,000
30		16	>100,000	>100,000
31		10	>100,000	>100,000
32		8	>100,000	>100,000
33		37	>100,000	>100,000
34		19	>100,000	>100,000

Molecular modeling was instrumental in obtaining initial leads and guiding our SAR work. We used the molecular docking program GLIDE[8] to dock compounds into a DPP-4 crystal structure, which is available from the RCSB Protein Data Bank (PDB ID: 2ONC). Shown in Figure 3 is a docking pose

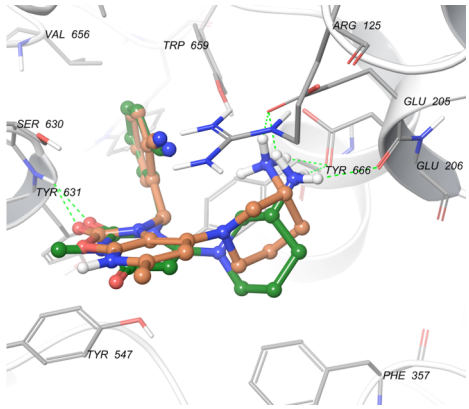


Figure 3. Superposed binding conformations of compound **27** (brown) and Alogliptin (dark green).

of compound **27** at the enzyme active site. This model highlights key interactions of our novel structure, reconfirming the SAR we discussed above. Compound **27** fits in the enzyme pocket very well topologically. The overlay of **27** against Alogliptin shows two molecules interact with DPP-4 in a similar fashion. The pyridinylimidazolone core of **27** lays flat in the enzyme cavity, "sandwiched" by some hydrophobic residues, most noticeably residues Phe357 and Tyr574. These hydrophobic residues may provide π–π interactions with the core.

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Table 5. Pharmacokinetics in Rat

		IV			PO			
compd	cLogP	Cl (L/h/kg)	Vss (L/kg)	$T_{1/2}$ (h)	C_{max} (ng/mL)	AUC_{last} (ng/mL·h)	$T_{1/2}$ (h)	F (%)
4[a]	2.24	3.9	5.42	2.4	175	880	2.8	35
9[b]	1.90	3.67	2.78	0.8	86	249	1.5	12
10[a]	2.40	5.44	5.89	1.2	198	896	3.3	48
18[a]	1.68	5.04	4.55	1.1	291	541	1.6	28
27[c]	2.48	2.40	6.17	1.83	1250	3980	2.4	97
29[d]	3.26	2.16	12.2	4.72	256	1610	4.4	89
30[d]	0.2	1.65	1.02	2.48	3.52	19.5	1.9	<1
31[a]	1.11	4.39	4.22	0.8	103	209	3.7	9

[a]Dose: po at 10 mg/kg; iv at 5 mg/kg (n = 3). [b]Dose: po at 8 mg/kg; iv at 4 mg/kg (n = 3). [c]Dose: po at 10 mg/kg; iv at 10 mg/kg (n = 3). [d]Dose: po at 4 mg/kg; iv at 2 mg/kg (n = 3).

Carbonyl oxygen of imidazolone serves as a H-bond acceptor and forms a specific H-bond with the backbone NH of Tyr631. The flat pyridinylimidazolone core also anchors two side moieties into their corresponding pockets well. Benzyl side moiety fits nicely in a tight hydrophobic groove, where it forms $\pi-\pi$ interactions with its surrounding residues Trp659 and Tyr666. Nitrogen atom of benzyl cyano group functions as an H-bond acceptor to Arg125. However, the amino group from piperidine site moiety is protonated under physiological pH and forms an essential salt bridge with the backbone carboxylate of Glu205 and Glu206. It should be mentioned that this type of salt bridge interaction between enzyme and ligand is a key feature of exopeptidase such as DPP-4. Naturally, all marketed DPP-4 inhibitors contain such a protonable amino group.

A large number of compounds identified with good potency were selected for rat pharmacokinetics (PK) evaluation in our lead optimization. Table 5 summarizes key parameters of some examples. We had initial difficulty achieving good oral exposure and bioavailability. As we built up a larger data set, we noticed a reasonable connection between lipophilicity and PK properties. Good oral compounds in this class of molecules starts to populate around cLogP greater than 2, regardless of structural diversity (Figure 4). We then utilized the SAR knowledge of

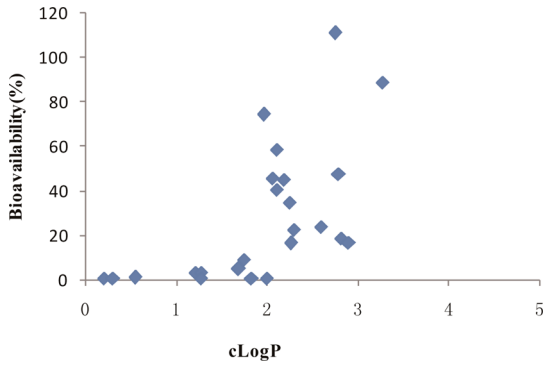

Figure 4. Bioavailability and cLogP.

the above-mentioned "sweet spot", tuned in preferable lipophilicity, and quickly identified good oral compound such as **27** and **29**. Of particular interest, compound **27** demonstrated a superior PK profile with a moderate clearance, a high plasma exposure, and near 100% rat oral bioavailability. These good PK attributes were translated into nonrodent species of dog and monkey in our further characterizations (Table 6).

On the basis of its attractive *in vitro* and *ex vivo* potency (data not shown), high selectivity over other subfamily enzymes, and favorable pharmacokinetic profile, compound **27** was advanced into *in vivo* efficacy studies. Compound **27** was first evaluated in a proof-of-concept pharmacodynamics model, assessing its ability to improve glucose tolerance in mice (OGTT, oral glucose tolerance test). In the studies, a single dose of compound **27** (0.1, 0.3, 1.0, and 3.0 mg/kg) was given orally to C57BL/6 mice 30 min prior to the glucose challenge (3.0 g/kg). The plasma glucose was then measured at 20, 40, 60, and 120 min after the glucose challenge, while DPP-4 activity, GLP-1 level, and plasma drug concentration were monitored at 20 min. As shown in Table 7, compound **27** was able to reduce plasma glucose excursion in a dose-dependent manner with a minimum effective dose at 0.3 mg/kg (48% inhibition). The observed glucose reduction tracked very well with drug exposure, DPP-4 inhibition, and augmented GLP-1 level. With regard to the comparison of Sitagliptin in the head-to-head experiment, compound **27** showed better inhibition of DPP-4 enzyme and comparable glucose reduction effects.[9]

To further characterize the effects in long-term treatment of **27** in rodent diabetic model, db/db mice were fed continuously with food formulated-**27** for 28 days. The random glucose level, lipids, oral glucose tolerance test, GLP-1, DPP-4, and insulin level were measured over the course of the study. Compound **27** has shown strong effects on all treated db/db mice in lowing glucose level, reducing AUC of oral glucose tolerance test, decreasing TG and HbA1c levels, and protecting beta-cell. These effects correlated well with the inhibition of DPP-4 and elevated the plasma GLP-1 level. In addition, no effects on the body weights in db/db mice were observed under the test conditions (data are not shown and will be published elsewhere separately).

In order to assess the key areas for further development, compound **27** was profiled extensively in a battery of target independent drug-like properties and safety assays. Shown in Table 8 are examples of these assays that include solubility, permeability, protein binding, CYP450 inhibitions, hERG channel inhibition/dog QT prolongation, Ames test, and *in vivo* tox. These data demonstrate remarkable physicochemical properties and good safety profile of **27** and strongly support its developability.

The synthesis of **27** is illustrated in Scheme 1. The process was well developed and validated at kiloscale to support early development activities. The linear synthesis began from a commercially available hydroxypyridone starting material **27−01**. Conversion of **27−01** under the treatment of $POCl_3$ yielded dichloropyridine intermediate **27−02**. Subsequently,

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Table 6. Pharmacokinetics of Compound 27 in Rat, Dog, and Monkey

	IV			PO			
species	Cl (L/h/kg)	Vss (L/kg)	$T_{1/2}$ (h)	C_{max} (ng/mL)	AUC_{last} (ng/mL·h)	$T_{1/2}$ (h)	F (%)
rat[a]	2.40	6.17	1.83	1250	3980	2.4	97
dog[b]	2.12	2.46	1.12	1355	3630	1.3	89
monkey[c]	0.67	2.44	3.68	3030	12900	4.8	86

[a]Dose: po at 10 mg/kg; iv at 10 mg/kg (n = 3). [b]Dose: po at 5 mg/kg; iv at 6.25 mg/kg (n = 3). [c]Dose: po at 10 mg/kg; iv at 5 mg/kg (n = 3).

Table 7. OGTT Results of 27 and Sitagliptin in C57BL/6 Mice

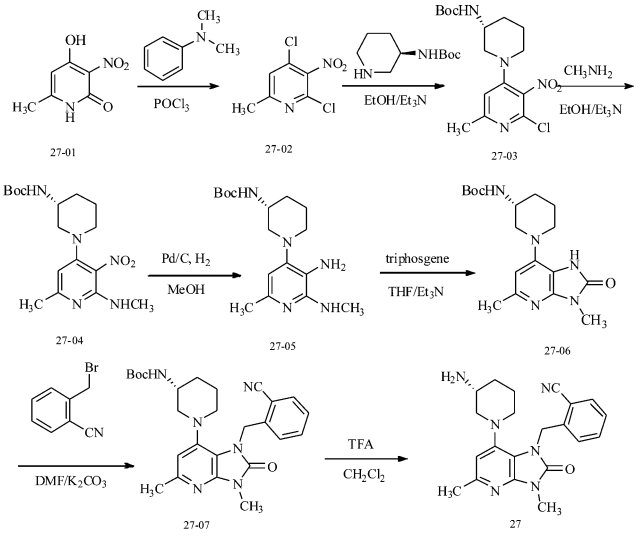
		20 min after glucose challenge				
group	N	plasma glucose (mM)	DPP-4 inhibition (%)	plasma GLP-1 (pM)	drug plasma concentration (ng/mL)	inhibition[a] (%)
control	20	15.6	0	4.0		
Sitagliptin (3.0 mg/kg)	20	11.7[c]	59.5	10.7[c]	179	59
27 (0.1 mg/kg)	20	14.1[b]	23.8	5.7	3.90	3
27 (0.3 mg/kg)	20	12.4[c]	43.8	5.7	10.3	40
27 (1 mg/kg)	20	11.4[c]	71.2	6.9	36.1	57
27 (3.0 mg/kg)	20	10.1[c,d]	82.1[d]	10.4[c]	129	65

[a]Inhibition reflects the % decrease of plasma glucose $AUC_{0-120min}$. [b]$p < 0.05$ (vs vehicle control using t test). [c]$p < 0.01$ (vs vehicle control using t test). [d]$p < 0.01$ (vs Sitagliptin using t test).

Table 8. Additional Profile of Compound 27

Compound	**27**
solubility pH (1.2/4.5/6.8)	560/560/551 mg/mL
Caco2 (ab/ba)	9/28 × 10^{-6} cm/sec
PB% (rat/dog/human)	42/74/62
CYP450 inhibition (3A4, 2D6, 2C9, 2C19)	>30 μM
hERG inhibition	>25 μM
QT prolongation	not observed at 20 mg/kg in conscious dog
AMES	negative at maximal dose of 5000 μg/plate
tox (28 days, rat)	NOAEL 150 mg/kg

Scheme 1. Synthetic Route of Compound 27



dichloropyridine **27−02** was reacted with another readily available intermediate Boc-protected aminopiperidine in the presence of triethylamine under the room temperature. The nucleophilic reaction was highly regioselective, and the resulting **27−03** anchored aminopiperidine moiety at para-position on pyridine ring, leaving *ortho*-chloro group untouched. Further functioning at ortho-position with methylamine was achieved under elevated temperature. The nitro group of the resulting **27−04** was then reduced to amino group. The diamino moieties of **27−05** were subsequently treated with phosgene to give a ring closure intermediate **27−06**. Introducing cyano substituted benzyl side moiety was completed by reacting **27−06** with the third commercially available cyanobenzyl bromide in basic conditions in DMF. Deprotection of Boc-group finally gave target compound **27**. The synthesis steps and conditions were optimized, and currently, the yields for key intermediates in the illustrated procedure are above 90%.

In summary, our fast follow-up program utilizing "scaffold−hopping" technique identified a novel series of highly potent and selective DPP-4 inhibitors. SARs and optimization in terms of DMPK properties, *in vivo* efficacy, safety characterization, and Chemistry Manufacturing and Controls evaluation led to the discovery of compound **27** (common name known as Imigliptin) as a clinical candidate. Currently, Imigliptin is under clinical development in China after it got CFDA regulatory approval. The profiles of Imigliptin's *in vivo* evaluation, PK/metabolism, and clinical pharmacology will be published in due course.

■ ASSOCIATED CONTENT

Supporting Information

Synthetic procedures, characterization data of representative compounds, description of *in vitro* DPP-4 enzyme assay and *in vivo* OGTT studies. This material is available free of charge via the Internet at http://pubs.acs.org.

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The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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