Discovery and Structure−Activity Relationships of Piperidinone- and Piperidine-Constrained Phenethylamines as Novel, Potent, and Selective Dipeptidyl Peptidase IV Inhibitors

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Dipeptidyl peptidase IV (DPP4) inhibitors are emerging as a new class of therapeutic agents for the treatment of type 2 diabetes. They exert their beneficial effects by increasing the levels of active glucagon-like peptide-1 and glucose-dependent insulinotropic peptide, which are two important incretins for glucose homeostasis. Starting from a high-throughput screening hit, we were able to identify a series of piperidinone- and piperidine-constrained phenethylamines as novel DPP4 inhibitors. Optimized compounds are potent, selective, and have good pharmacokinetic profiles.

Type 2 diabetes is a rapidly growing disease that affects millions of people worldwide. For instance, 20.8 million children and adults in the United States alone, or 7% of the population, have diabetes. The death toll and economic costs associated with diabetes and its complications are enormously high.[1] Recently dipeptidyl peptidase IV (DPP4,[a] EC 3.4.14.5) inhibitors have emerged as a new class of therapeutic agents for treating diabetes, as evidenced by the FDA approval of **1** (sitagliptin, Chart 1) as a monotherapy or in combination with other antidiabetic agents.[2,3] Several other DPP4 inhibitors such as **2** (vildagliptin),[4] **3** (saxagliptin),[5] **4** (SYR-322),[6] and **5** (ABT-279)[7] are either awaiting regulatory approval or are in human clinical trials (Chart 1). Compared to other existing antidiabetic agents, DPP4 inhibitors have the advantage of (1) not causing hypoglycemic episodes; (2) not causing body-weight gain; and (3) potentially altering disease progression by restoring β-cell function of the pancreas.[8]

It is generally accepted that DPP4 inhibitors exert their beneficial effects by increasing the levels of active glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP). After ingestion of nutrients, GLP-1 and GIP are released (from *L*-cells and *K*-cells, respectively) and then function through their respective receptors. Specifically, GLP-1 stimulates insulin secretion,[9] inhibits glucagon secretion,[9c,10] and delays gastric emptying,[11] each a benefit in controlling blood glucose. GIP has a similar insulinotropic effect but does not inhibit glucagon secretion or influence gastric emptying in humans.[12,13] However, active GLP-1 (7−36) and GIP (1−42) are inactivated by DPP4 rapidly by cleavage of two amino acid residues from the N-terminus.[14] Inhibition of DPP4 restores active GLP-1 and GIP levels and improves glycemic control for diabetics.

After the successful identification of our first DPP4 inhibitor, clinical candidate **5** at Abbott,[7] our attention focused on the discovery of noncyanopyrrolidine DPP4 inhibitors. Starting with the high-throughput screening (HTS) hit **6** (Chart 2), we were able to identify cyclohexene-constrained phenethylamine **7** (ABT-341) as a backup clinical development candidate.[15] Lead-hopping efforts from the same HTS lead led to a series of pyrrolidine-constrained phenethylamines as novel and potent DPP4 inhibitors.[16] Herein we report the discovery and structure−activity relationship (SAR) of a series of piperidinone- and piperidine-constrained phenethylamines as novel and potent DPP4 inhibitors.

Chart 1. DPP4 Inhibitors

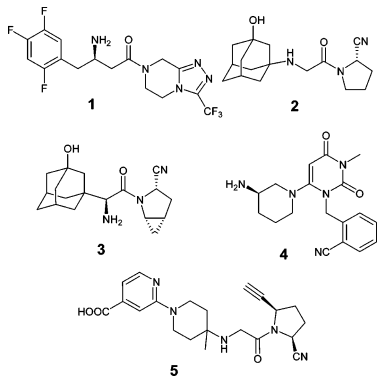
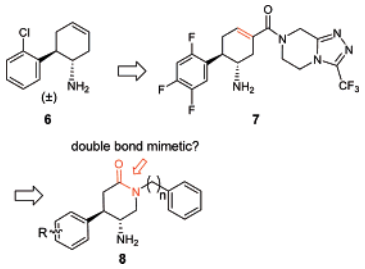


Chart 2



During the optimization of the cyclohexene-constrained phenethylamine series, we envisioned that a lactam such as **8** might be a good target to pursue. This core motif offers several attributes compared to cyclohexene: (1) the amide moiety might be a good mimetic of the double bond to provide similar rigidity and trajectory for the required appendages off the central ring; (2) the nitrogen atom would provide a position for easier introduction of different substituents *para* to the aromatic ring.

The synthesis of racemic piperidinone-constrained phenethylamines is outlined in Scheme 1. α,β-Unsaturated esters **9** or **10** underwent Michael addition with nitromethane to give γ-nitro esters **11** or **12** under basic conditions. A three-component cyclization[17] involving nitro ester **11** or **12**, paraformaldehyde, and amines afforded lactams **13** or **14** as the major isomers,

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[a] Abbreviations: DPP4, dipeptidyl peptidase IV; GLP-1, glucagon-like peptide-1; GIP, glucose-dependent insulinotropic polypeptide; HTS, high-throughput screening.

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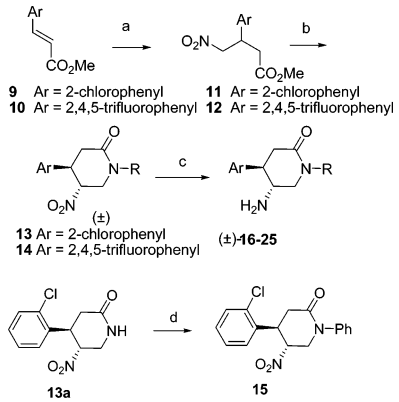
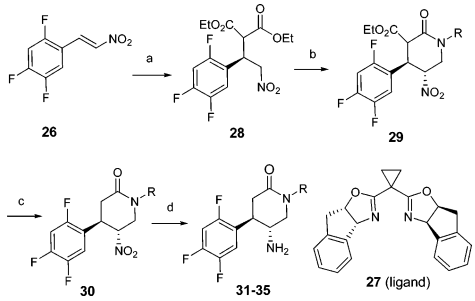
Scheme 1[a]



[a] Reagents and conditions: (a) CH_3NO_2, DBU; (b) paraformaldehyde, RNH_2, ethanol, 90 °C; (c) Zn, HOAc, MeOH, 75 °C; (d) cat. CuI, *N*,*N*'-dimethylethylenediamine, iodobenzene, toluene, 110 °C.

Scheme 2[a]



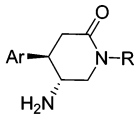
[a] Reagents and conditions: (a) diethyl malonate, *N*-methylmorpholine, cat. $Mg(OTf)_2$, ligand **27**, 4 Å mol. sieves, $CHCl_3$; (b) paraformaldehyde, RNH_2, ethanol, 85 °C; (c) NaCl, DMSO/H_2O, 140 °C; (d) Zn, HOAc, MeOH, 75 °C.

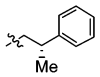
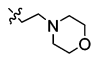
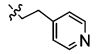
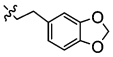
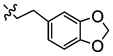
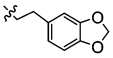
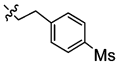
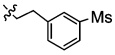
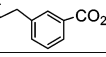
wherein with the nitro and aromatic groups *trans* to each other. This cyclization failed when aniline was used (R = Ph) presumably due to insufficient nucleophilicity of the anilinic nitrogen. The phenyl group was introduced by using a Buchwald condition of Goldberg coupling between iodobenzene and **13a** to give **15** in low yield.[18] Reduction of the nitro group of **13**−**15** provided aminolactams **16**−**25**.

Synthesis of optically pure piperidinone-constrained phenethylamines was accomplished by a methodology developed in these laboratories (Scheme 2).[19] Asymmetric Michael addition[20] of the malonate anion to nitrostyrene **26** catalyzed by the complex of magnesium triflate and the C2-symmetric bisoxazoline ligand **27** provided 1,3-diester **28** in *R*-configuration as shown in >95% ee, as determined by chiral HPLC.[21] The critical three-component cyclization of dicarbonyl **28**, paraformaldehyde, and amines efficiently yielded lactams **29**. Decarboxylation was achieved under neutral conditions at 140 °C[22] to give lactams **30**, which were converted to amines **31**−**35** by reduction of the nitro group with zinc.

Inhibitory potency of the synthesized compounds was measured by monitoring the hydrolytic reaction of Gly-Pro-7-amidomethylcoumarin (Gly-Pro-AMC) by human DPP4, and the results are reported as inhibitory constants (K_i).[23] Piperidinone **16** with a phenyl group directly attached to the ring nitrogen atom was a weak inhibitor with a K_i of 1.6 μM (Table 1). Replacement of the phenyl with a benzyl group led to **17** with K_i of 1.4 μM. Analogue **18**, with a saturated cyclohexyl ring, did not possess significantly improved potency (K_i = 0.93 μM). When the aromatic group was switched from 2-chlorophenyl to 2,4,5-trifluorophenyl, a group that was used by others[2] and us in other series,[15,16] the resulting amine **19** was about 3-fold more potent (K_i = 0.44 μM) than **17**. A dramatic improvement came when the *N*-benzyl was extended to a phenethyl. The resulting analogue **20** showed a 25-fold improved potency over **19**, achieving a K_i of 17 nM. When the linker was extended further to three carbons, the potency of the resulting analog **21** suffered (K_i = 270 nM). Within the two-carbon linker series, a methyl group on the linker (**22**) caused an approximate 5-fold loss of potency compared to that of **20**. When the phenyl ring was replaced with a morpholinyl ring, the potency (**23**) decreased significantly (K_i = 590 nM). When the phenyl group was replaced with a pyridinyl group, the corresponding analogue **24** showed approximately the same potency (24 nM) as the phenyl analogue. Introduction of the methylenedioxyphenyl group provided racemic **25** with an improved K_i of 7.1 nM. When this analogue was prepared in optically pure form, the corresponding amine **31** had a K_i of roughly half of that of **25**, 3.2 nM. The corresponding enantiomer **32** was much less potent, with a K_i of 105 nM, demonstrating the importance of the absolute stereochemistry. Analogue **33**, with a methylsulfonyl group at the *para*-position, had a K_i of 12 nM. When the methylsulfonyl group was moved to the *meta*-position, the resulting analogue **34** exhibited improved potency (4 nM) and good PK (vide infra). Analogue **35**, with an ionizable carboxylate group, was also very potent (3.8 nM).

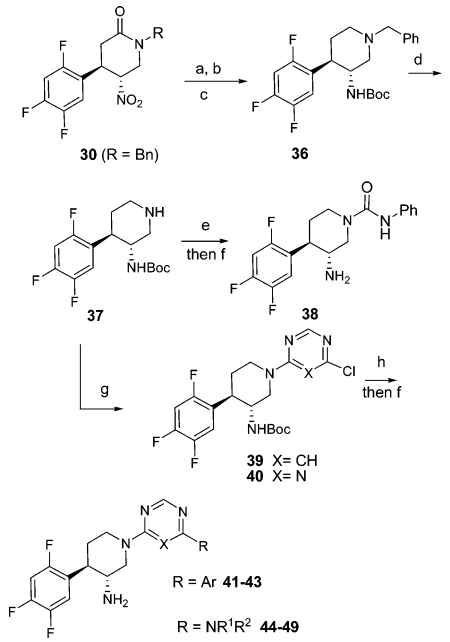
Table 1. Inhibition Constant (K_i) of Piperidinone-Constrained Phenethylamines[a]



compd	Ar[b]	R	K_i (nM) DPP4
16[c]	A	Ph	1,600
17[c]	A	-CH_2Ph	1,400
18[c]	A	-CH_2(c-Hex)	930
19[c]	B	-CH_2Ph	440
20[c]	B	-$(CH_2)_2$Ph	17
21[c]	B	-$(CH_2)_3$Ph	270
22[d]	B		83
23[c]	B		590
24[c]	B		24
25[c]	B		7.1
31[e]	B		3.2
32[f]	B		105
33[e]	B		12
34[e]	B		4.0
35[e]	B		3.8

[a] Values reported are the mean of at least two runs using human DPP4. [b] A = 2-chlorophenyl; B = 2,4,5-trifluorophenyl. [c] Racemic. [d] Diastereomeric mixture of racemic core and (*S*)-2-phenylpropan-1-amine. [e] Enantiomerically pure. [f] The enantiomer of compound **31**.

Scheme 3[a]

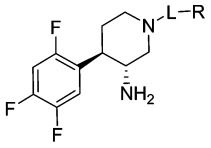


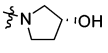
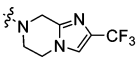
[a] Reagents and conditions: (a) BH_3, THF (b) Zn, HOAc, MeOH, Δ; (c) Boc_2O, CH_2Cl_2/THF; (d) Pd/C, HCO_2NH_4, MeOH, Δ; (e) PhNCO, TEA, CH_2Cl_2; (f) TFA, CH_2Cl_2; (g) 4,6-dichloropyrimidine, 100 °C or 2,4-dichloro-1,3,5-triazine, *i*-Pr_2NEt, −40 to −5 °C; (h) $ArB(OH)_2$, cat. $Pd(PPh_3)_4$, Na_2CO_3, toluene/EtOH/H_2O, 90 °C for **41**−**43**; or NHR^1R^2, 145−160 °C, microwave for **44**−**49**.

Because it was unclear whether the lactam carbonyl group interacts with DPP4, piperidine-constrained phenethylamines were prepared (Scheme 3). A series of structurally related aminopiperidines, which were synthesized via a different route, were recently patented.[24] After the carbonyl group of optically pure lactam **30** (R = Bn) was selectively reduced by borane, the nitro group was reduced to the corresponding amine group, which was then protected by a *tert*-butoxycarbonyl (Boc) group to provide **36**. Removal of the *N*-benzyl group by catalytic hydrogen transfer provided the key intermediate, piperidine **37**. Reaction of piperidine **37** with phenylisocyanate and subsequent removal of the Boc group gave urea **38**. Alternatively, a nucleophilic substitution reaction between piperidine **37** and 4,6-dichloropyrimidine or 2,6-dichlorotriazine gave chlorides **39** or **40**. A Suzuki coupling between chloride **39** or **40** and boronic acids followed by removal of the Boc group gave amines **41**−**43**. A nucleophilic substitution reaction between chloride **39** and different amines at elevated temperatures and subsequent removal of the Boc group gave amines **44**−**49**.

Structure−activity relationships of the piperidine-constrained phenethylamines are summarized in Table 2. Piperidine **38**, with a urea linker between the phenyl group and the core lactam, was reasonably potent, with a K_i of 140 nM. Replacement of the open-chain linker with a more rigid pyrimidine dramatically improved the potency of the resulting analogue **41** (K_i = 6.1 nM). Unlike the pyrrolidine-constrained phenethylamine series, where the introduction of a methylsulfonyl group improved potency significantly,[16] introduction of a methylsulfonyl group here (**42**) changed the potency very little (K_i = 4 nM). Again unlike the pyrrolidine-constrained phenethylamine series, where the triazine analogues are more potent than the corresponding pyridimine agalogues, triazine sulfone **43** was *less* potent than the corresponding pyrimidine sulfone **42**, demonstrating the subtle difference between these two series. When the aromatic group was replaced with a nonaromatic pyrrolidinyl group, the resulting analogue **44** had a K_i of 2.3 nM. When the five-membered pyrrolidinyl group was replaced with a six-membered

Table 2. Inhibition Constant (K_i) of Piperidine-Constrained Phenethylamines[a]



compd	L	R	K_i (nM)
38	-C(O)NH-	Ph	140
41		Ph	6.1
42			4.0
43			13
44			2.3
45			11
46			23
47			1.6
48			2.3
49			3.0

[a] Values reported are the mean of at least two runs using human DPP4.

Table 3. Selectivity of Selected Inhibitors[a]

compd	DPP4	DPP8	DPP9
31	3.2	>3000	>3000
34	4.0	>3000	>3000
35	3.8	>3000	>3000
42	4.0	>30 000	>30 000
47	1.6	19 100	18 300
48	2.3	>30 000	19 700

[a] All are K_i values in nM. For structures, see Tables 1 and 2.

piperdinyl group (**45**), the potency decreased (K_i = 11 nM). When the pyrrolidine ring was replaced by an open-chain diethylamine group, the resulting analogue **46** was 10-fold less potent than **44**. Difluoro substitution on the pyrrolidinyl ring provided the most potent analogue **47**, with a K_i of 1.6 nM. Both a polar hydroxyl group on the pyrrolidinyl ring (**48**) and a bicyclic heteroaromatic ring (**49**) were well tolerated, providing very potent inhibitors.

Potent inhibitors were tested against a panel of related peptidases, including FAPα, POP, DPP7, DPP8, and DPP9. Selectivity against DPP8/9 is of particular importance because inhibition of DPP8/9 has been associated with toxicity in animal studies.[25] Our piperidinone- and piperidine-constrained phenethylamines are generally highly selective for DPP4 over the related dipeptidyl peptidases FAPα, POP, DPP7 (data not shown), DPP8, and DPP9 (data shown in Table 3). As can be seen, all the compounds show at least ~1000-fold selectivity over these two enzymes.

X-ray crystal structures of the complexes of inhibitors **31** and **42** bound to human DPP4 reveal several interesting features (Figure 1).[26] The general orientation of the two inhibitors is very similar. The trifluorophenyl group occupies the S1 pocket

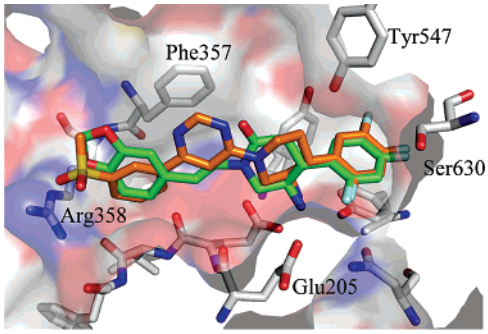


Figure 1. X-ray crystal structures of inhibitors **31** (green) and **42** (brown) complexed to huDPP4. Color-coding: all nitrogen atoms are in blue, oxygen atoms are in red, and fluorine atoms are in cyan. The carbon atoms of DPP4 are in gray.

Table 4. Pharmacokinetic Properties of Selected Compounds[a]

compd	CL_p (L/hr·kg)	V_{ss} (L/kg)	C_{max} (ng/mL)	$t_{1/2}$ (h)	AUC (ng·hr/kg)	F (%)
	iv		po			
31	2.18	1.04	192	0.42	223	9.0
34	1.81	1.24	710	1.8	771	27.6
42	0.19	1.28	1997	7.8	24 350	90.3

[a] All PK was measured in rats ($n = 6$) at 5 mg/kg dose. CL_p, plasma clearance; V_{ss}, volume of distribution at steady state; C_{max}, maximal concentration when dosed orally; $t_{1/2}$, terminal half-life when dosed orally; AUC, area under curve; *F*, oral bioavailability. For structures, see Tables 1 and 2.

of the enzyme, and the amine group forms an electrostatic interaction with the side chains of Glu205 and Glu206 in both complexes. In the case of the **31**/DPP4 complex, while the lactam carbonyl of **31** does not form any specific interaction with the enzyme, the methylenedioxyphenyl group forms a hydrophobic interaction with the side chain of Phe357. This binding mode explains why analog **21** with a three-carbon linker is much less potent: the chain is too long to maintain the same hydrophobic interaction without suffering an entropic penalty. One of the oxygen atoms of the methylenedioxyphenyl group may form a hydrogen bond with the NH of Arg358 side chain (3.2 Å). In the case of the **42**/DPP4 complex, the trajectory of the nitrogen is different from that of the **31**/DPP4 complex such that a $\pi-\pi$ interaction is formed between the pyrimidine ring of the ligand and the phenyl ring of Phe357.

Pharmacokinetic (PK) parameters of selected inhibitors are shown in Table 4. While methylenedioxy piperidinone **31** has a very high clearance (2.18 L/hr·Kg) and low oral bioavailability (9.0%), sulfone **34**, where the methylenedioxy was replaced with methylsulfonyl, has a reduced clearance (1.81 L/hr·Kg) and improved oral bioavailability (27.6%). Further PK improvement was achieved in **42**, where the flexible linker was replaced with a more rigid and more polar pyrimidine ring. Thus, sulfone **42** has a very low clearance (0.19 L/hr·Kg), a long half-life (7.8 h), and high oral bioavailability (90%). All three compounds show very similar volumes of distribution (1.04 to 1.28 L/Kg).

In summary, starting from a HTS hit, we were able to identify a series of piperidinone- and piperidine-constrained phenethylamines as novel DPP4 inhibitors. A new asymmetric synthetic methodology was applied to synthesize these analogs in optically pure form. X-ray crystallographic data show that halogenated phenyl rings occupy the S1 pocket. The middle piperidinone and piperidine rings act to orient the exocyclic primary amino group and the appendages off the endocyclic nitrogen atom in the correct directions. Optimized compounds are potent, selective, and exhibit good to excellent PK.

Experimental Section

The synthesis of **42** (last three steps) is illustrated below. For complete experimental details of the synthesis of all intermediates and final products, see Supporting Information.

***tert*-Butyl (3*R*,4*R*)-1-(6-Chloropyrimidin-4-yl)-4-(2,4,5-trifluorophenyl)piperidin-3-ylcarbamate (39).** Piperidine **37** (1.21 g, 3.66 mmol, 1 equiv), 4,6-dichloropyrimidine (0.655 g, 1.2 equiv), and *i*-$PrNEt_2$ (0.96 mL, 1.5 equiv) were mixed in *i*-PrOH (12 mL). The mixture was heated to 100 °C and stirred for 1.3 h. After the reaction was cooled to rt, saturated aq $NaHCO_3$ solution was added, and the mixture was extracted with EtOAc (3 × 30 mL). The combined organic extract was dried (Na_2SO_4) and concentrated. The resulting residue was purified using an Analogix flash chromatographer (13% then 22% EtOAc/Hex) to give the desired product as a white solid (1.5 g, 86%). ^1H NMR (300 MHz, $CDCl_3$) δ ppm 8.42 (s, 1H), 6.99−7.15 (m, 1H), 6.86−7.00 (m, 1H), 6.63 (s, 1H), 4.50−4.75 (m, 1H), 4.29−4.46 (m, 1H), 3.62−3.82 (m, 1H), 2.87−3.11 (m, 2H), 2.81 (t, $J = 11.9$ Hz, 1H), 1.98 (d, $J = 10.8$ Hz, 1H), 1.61−1.85 (m, 2H), 1.35 (s, 9H). MS (ESI) *m*/*z* 443 and 445 $(M + H)^+$.

(3*R*,4*R*)-1-(6-(3-(Methylsulfonyl)phenyl)pyrimidin-4-yl)-4-(2,4,5-trifluorophenyl)piperidin-3-amine (42). Chloride **39** (1.10 g, 2.48 mmol, 1 equiv), 3-methylsulfonylphenyl boronic acid (0.62 g, 6.20 mmol, 1.25 equiv), $Pd(PPh_3)_4$ (0.287 g, 0.248 mmol, 0.1 equiv), and Na_2CO_3 (0.657 g, 6.2 mmol, 2.5 equiv) were mixed in toluene/EtOH/H_2O (3.2:3.2:1.0 mL). The mixture was then heated to 90 °C under argon. After 2 h, additional $Pd(PPh_3)_4$ (100 mg) and dioxane (4 mL) were added. After about 3 h, the reaction was cooled to rt and water was added. The mixture was extracted with Et_2O/EtOAc (3×). The combined organic extract was dried (Na_2SO_4) and concentrated. The resulting residue was purified using an Analogix flash chromatographer (40% then 65% EtOAc/hexane) to give the desired product as a yellow solid (1.29 g, 93%).

The above sulfone (1.27 g, 2.26 mmol) was treated with precooled (0 °C) 4 N HCl in dioxane (6 mL). The mixture was stirred at rt for 2 h, and then MeOH (7 mL) was added to dissolve the precipitate. This homogeneous solution was then added slowly to stirred ether (220 mL) in a separate flask. The resulting precipitate was collected by filtration and dried in vacuo to give the desired product as a HCl salt (1.02 g, 95%). ^1H NMR (300 MHz, MeOH-d_4) δ ppm 8.87 (s, 1H), 8.52 (t, $J = 1.7$ Hz, 1H), 8.29 (d, $J = 1.7$ Hz, 1H), 8.27 (d, $J = 2.0$ Hz, 1H), 7.93 (t, $J = 7.6$ Hz, 1H), 7.66 (d, $J = 0.68$ Hz, 1H), 7.44−7.56 (m, 1H), 7.23−7.34 (m, 1H), 5.41 (br s, 1H), 4.79 (br s, 1H), 3.70−3.82 (m, 1H), 3.35−3.53 (m, 3H), 3.25 (s, 3H), 2.02−2.20 (m, 2H). MS (ESI) *m*/*z* 463 $(M + H)^+$. Anal. ($C_{22}H_{21}F_3N_4O_2S·2HCl·H_2O$) C, H, N, Cl.

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Supporting Information Available: Experimental procedures, including characterization data for intermediates and final products, X-ray data, and refinement of crystal structures of human DPP4 complexed with inhibitors. This material is available free of charge via the Internet at http://pubs.acs.org.

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