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Structure–activity-relationship of amide and sulfonamide analogs of omarigliptin

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ABSTRACT

A series of novel substituted-[(3*R*)-amino-2-(2,5-difluorophenyl)]tetrahydro-2*H*-pyran analogs have been prepared and evaluated as potent, selective and orally active DPP-4 inhibitors. These efforts lead to the discovery of a long acting DPP-4 inhibitor, omarigliptin (MK-3102), which recently completed phase III clinical development and has been approved in Japan.

Type 2 diabetes mellitus (T2DM) is a fast growing epidemic, affecting nearly 387 million people worldwide in 2014.[1] Among a wide range of therapeutic targets, dipeptidyl peptidase IV (DPP-4) inhibition with small molecules has become a clinically proven therapeutic approach for the treatment of Type 2 diabetes mellitus (T2DM).[2,3] Glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are incretin hormones which stimulate glucose dependent insulin secretion and slow gastric emptying.[4a,b] In addition, GLP-1 has been shown to inhibit glucagon secretion, reduce appetite, and stimulate the regeneration and differentiation of islet β-cells in rodent models. However, both hormones are rapidly cleaved to their inactive forms by the enzyme DPP-4.[4c,d] Therefore, inhibition of DPP-4 can increase levels of endogenous incretin hormones GLP-1and GIP. The DPP-4 inhibitor program culminated in the discovery of JANUVIA® (sitagliptin phosphate) as the first FDA approved DPP-4 inhibitor for the treatment of patients with T2DM. Subsequently, additional DPP-4 inhibitors such as vildagliptin (Novartis), saxagliptin (BMS), linagliptin (Lilly) and alogliptin (Takeda) have entered market.

A conceptual cyclization of the sitagliptin core provided the rationale to prepare structurally rigid tetrahydropyran (THP) analogs (Fig. 1) and led to the identification of the dihydropyrrolopyrazole clinical candidate **2**.[5] Extensive structure–activity relationship (SAR) studies on the pyrazole ring identified several series including amide, sulfonamide and sulfone analogs. These efforts culminated in the discovery of the potent and selective DPP-4 inhibitor **20**, omarigliptin (MK-3102),[6] which has a pharmacokinetic profile amenable to once weekly dosing. Omarigliptin has completed phase III clinical development in Japan and is filed for registration in that country. In this manuscript, we describe our broader efforts at the optimization of the pyrazolopyrolidine series of DPP-4 inhibitors by making several amide and sulfonamide analogs.

Several approaches for the variation of the substituents on the dihydropyrrolopyrazole side chain are described in Scheme 1. Reaction of the Boc protected ketone **3** with *N*,*N*-dimethylformamide dimethylacetal (DMF-DMA) in THF generated enamine

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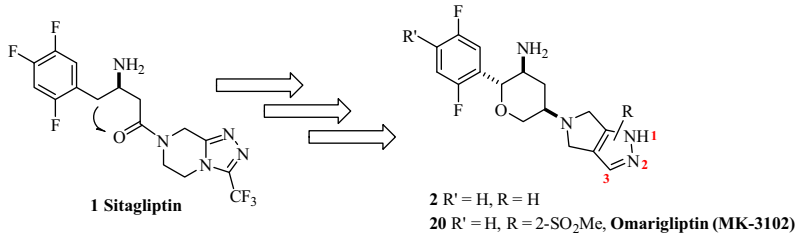
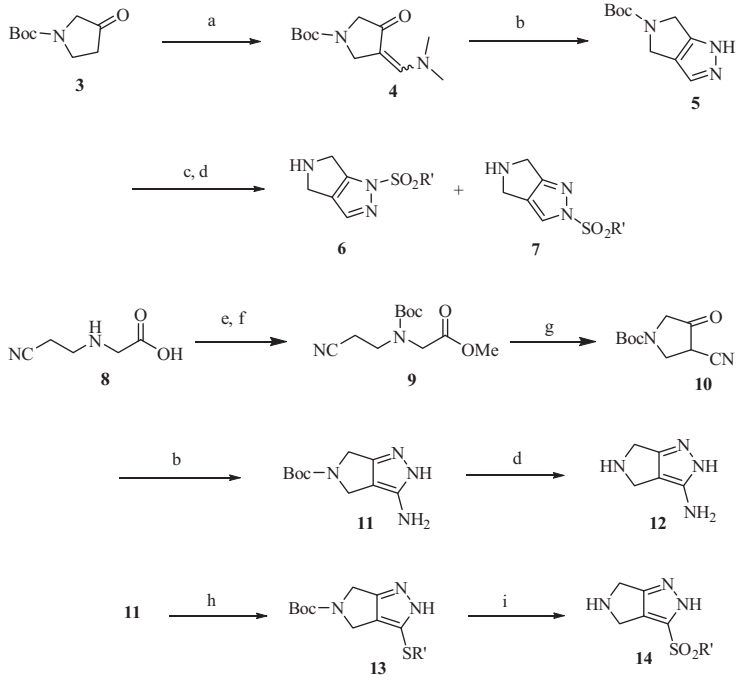


Figure 1. Rational design of DPP-4 inhibitors.

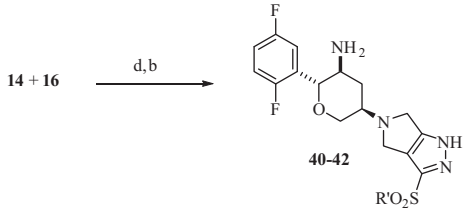


Scheme 1. Preparation of substituted dihydropyrrolopyrazole intermediates. Reagents and conditions: (a) DMF-DMA, THF, 60 °C; (b) NH_2NH_2 (35% aq), EtOH, reflux; (c) $R'SO_2Cl$, NaH, acetonitrile, 60 °C; (d) TFA, CH_2Cl_2, rt; (e) Boc_2O, DIPEA, CH_2Cl_2, rt; (f) CH_3I, K_2CO_3, acetonitrile, 80 °C; (g) $NaOCH_3$, toluene, 80 °C; (h) R'S-SR', ^tBuONO, CCl_4, 70 °C; (i) *m*CPBA, TFA, CH_2Cl_2, rt.

intermediate **4**, which was subsequently reacted with hydrazine to yield Boc-protected dihydropyrrolopyrazole **5**. Reaction of **5** with variety of sulfonyl chlorides in the presence of sodium hydride afforded chromatographically separable 1- and 2-substituted dihydropyrrolopyrazoles which were then treated with TFA to give key intermediates **6** and **7**. The structures of the two isomeric compounds **6** and **7** were confirmed by NMR. It was observed that under Boc deprotection conditions (TFA/CH_2Cl_2), only three dihydropyrrolopyrazoles substituted by cyclopropyl, cyclopentyl and *N*-methylimidazolyl groups at the 1-position (isomer A) were stable. These intermediates were isolated and converted into the corresponding DPP-4 inhibitors (**25a**, **26a** and **27a**).

3-Aminodihydropyrrolopyrazole intermediate **12** was prepared through the route also described in Scheme 1. Reaction of 2-((2-cyanoethyl)amino) acetic acid (**8**) with Boc anhydride was followed by esterification with iodomethane to afford ester **9**. Cyclization of **9** in the presence of sodium methoxide yielded α-cyano ketone **10**. Refluxing **10** with hydrazine in ethanol followed by TFA deprotection of the Boc group provided 3-amino pyrazole intermediate **12**. Attempts to halogenate the 3-position of **5** were unsuccessful under a variety of reaction conditions. Functionalization at the 3-position was accomplished by diazotization of the aminopyrazole **11** and trapping of the intermediate carbonium ion with an alkyl disulfide to give **13**. The thiol **13** was oxidized to the sulfone **14** using *m*CPBA.

Pyranone key intermediate 1**6** was prepared from aldehyde **15** as described previously by our group.[6] Reductive amination of pyranone **16** with 1- or 2-substituted dihydropyrrolopyrazoles **6** and **7**, employing decaborane in methanol, followed by removing the Boc protecting group yielded the desired tetrahydropyran products **17** and **18** (Scheme 2). Utilizing the same reductive amination conditions, the 3-amino pyrazole product **19** was made from pyranone **16** and 3-amino dihydropyrrolopyrazole **12**.



Scheme 2. Preparation of tetrahydropyran DPP-4 inhibitors. Reagents and conditions: (a) **6** or **7**, $B_{10}H_{14}$, MeOH, rt; (b) TFA, CH_2Cl_2, rt; (c) $R'SO_2Cl$ or $(R'CO)_2O$, Et_3N, CH_2Cl_2, rt; (d) $NaBH_3CN$, Et_3N, HOAc, DMA, rt.

Sulfonylation or acylation of the amino group with several sulfonyl chlorides and anhydrides proceeded smoothly to give the desired 3-substituted pyrazole analogs **30**–**39** after deprotection. Reductive amination of **16** with **14** provided the 3-methylsulfonyl, 3-isopropylsulfonyl and 3-phenysulfonyl pyrazole derivatives **40**–**42**.

Compounds were evaluated in vitro for their inhibition of DPP-4.[7a] The inhibitors were also tested against DPP-4 structural homologs of the DPP-4 gene family, including FAP,[7b,8] DPP-8,[9] DPP-9,[10] and QPP.[7] Inhibition of DPP-8 and DPP-9 has been associated with profound toxicity in animal studies.[11] While the significance of this adverse effect in humans has not been demonstrated, treatment-related dermatological toxicity in monkeys was observed with non-selective DPP-4, DPP-8, and DPP-9 inhibitors.[12] Further in recent cardiovascular safety studies among diabetic patients using a selective DPP-4 inhibitor, Januvia (sitagliptin), no increased hospitalization for heart failure was reported.[13] Therefore, selectivity profiles against DPP-8 and DPP-9 is highly desirable (>30 μM) for safety reasons. DPP-9 inhibition typically tracks closely with DPP8 and thus is not reported in this manuscript.

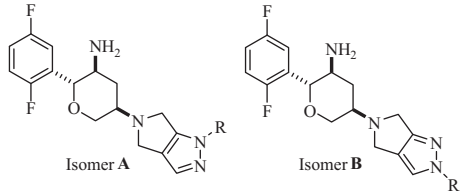
Results for a series of 1- and 2-substituted pyrazole sulfonamide analogs are listed in Table 1. In general, installation of a sulfonyl group at the 1- or 2-position of the pyrazole provided potent DPP-4 inhibitory activity (DPP-4 IC_{50} = 0.7–7.5 nM) and desirable off target selectivities (>4000 fold) comparable to the unsubstituted parent compound **2**.[5] In the case of alkylsulfonamide analogs **20**–**26**, isopropylsulfonamide **24** was found to be the most potent DPP-4 inhibitor (DPP-4 IC_{50} = 0.7 nM) while *n*-propylsulfonamide **23** was the least potent DPP-4 inhibitor (DPP-4 IC_{50} = 5.7 nM). Two isomeric cyclopropylsulfonamides **25a** and **25b** were equally potent DPP-4 inhibitors (DPP-4 IC_{50} = 1.6 nM) with excellent selectivity against off targets although a slightly reduction of FAP selectivity was seen in the isomer **25a**. Increasing steric bulk to cyclopentylsulfonyl, imidazolosulfonyl and phenyl-sulfonyl groups (compounds **26**–**29**) afforded compounds with the similar DPP-4 inhibition and a varying degree of selectivity reduction over QPP, DPP-8 and FAP enzymes relative to the methylsulfonamide **20**. The 1-substituted compounds **26a** and **27a** were slightly less potent DPP-4 inhibitors than the corresponding 2-substituted analogs **26b** and **27b**.

Analogs bearing an amide, sulfonamide or sulfone side chain at the 3-position of the pyrazole moiety are summarized in Table 2. In general, analogs **30**–**42** were comparable to parent compound **2** in terms of DPP-4 potencies, although slightly reduction of selectivity against FAP and, in certain cases, QPP and DPP-8 were observed. In the case of amide derivatives **30**–**33**, an increase in the size and polarity of the amide substituents resulted in only 2- to 3-fold decline in DPP-4 potency, as seen in **30** versus **32** and **33**. However, this trend was not observed in the sulfonamide series **34**–**39**, specially the imidazole sulfonamide **39** which was ten times more potent than the methylsulfonamide **34** in DPP-4 inhibition. The attachment of electron deficient sulfonyl groups at the 3-position of pyrazole ring **40**–**42** maintained excellent DPP-4 inhibitory activities. The retention of DPP-4 in vitro potencies of analogs in Tables 1 and 2 relative to the parent compound **2** strongly suggests that substitution around the pyrazole ring is well tolerated.

Several representative DPP-4 inhibitors were selected for in vivo pharmacokinetic studies in rat. PK experiments were conducted using the procedure described in our previous manuscript[6] and results are listed in Table 3. In general, 1- and 3-substituted pyrazole analogs **25a**, **26a**, **30** and **31** gave sub-optimal PK profiles with high clearance rates, shorter half-life and lower oral exposure when compared to the non-substituted analog **2**. However, the cyclopropyl sulfonamide analog **25a**, when administered to rats orally, gave 79% oral bioavailability. The majority of 2-substituted pyrazole analogs **20**–**26b** displayed equivalent or superior PK profiles compared to the non-substituted analog **2**.

Based on the superior in vitro DPP-4 potency, off-target selectivity, and rat pharmacokinetics profile, the methylsulfonamide **20**, ethylsulfonamide **22** and cyclopropylsulfonamide **25b** were

Table 1
1- and 2-Substituted DPP-4 inhibitors



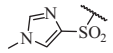
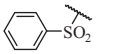
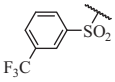
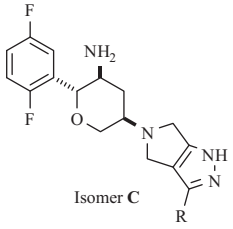
Compd	R	A/B	DPP-IV IC_{50} (nM)	QPP IC_{50} (nM)	DPP-8 IC_{50} (nM)	FAP IC_{50} (nM)
2	H	—	1.4	42,000	>100,000	>100,000
20	CH_3SO_2	**B**	2.6	>100,000	>100,000	>100,000
21	CF_3SO_2	**B**	2.3	>100,000	>100,000	>100,000
22	$CH_3CH_2SO_2$	**B**	1.8	>100,000	>100,000	69,000
23	*n*-$PrSO_2$	**B**	5.7	>100,000	>100,000	>100,000
24	*i*-$PrSO_2$	**B**	0.7	>100,000	>100,000	>100,000
25a	*c*-$PrSO_2$	**A**	1.6	88,000	>100,000	54,000
25b		**B**	1.6	87,000	>100,000	>100,000
26a	*c*-$PentSO_2$	**A**	2.6	>100,000	>100,000	26,000
26b		**B**	1.6	56,000	60,000	50,000
27a		**A**	4.9	33,000	44,000	45,000
27b		**B**	1.9	61,000	41,000	95,000
28		**B**	2.3	95,000	25,000	>100,000
29		**B**	1.9	>100,000	27,000	>100,000

Table 2
3-Substituted DPP-4 inhibitors



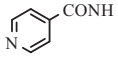
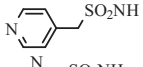
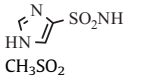
Compd	R	DPP-IV IC_{50} (nM)	QPP IC_{50} (nM)	DPP-8 IC_{50} (nM)	FAP IC_{50} (nM)
30	CH_3CH_2CONH	1.4	>100,000	>100,000	47,000
31	*c*-PrCONH	1.6	>100,000	>100,000	22,000
32		4.3	70,000	55,000	40,000
33		3.7	>100,000	47,000	27,000
34	CH_3SO_2NH	3.2	>100,000	>100,000	8800
35	$CH_3CH_2SO_2NH$	1.1	57,000	89,000	32,000
36	$CF_3CH_2SO_2NH$	1.3	>100,000	>100,000	32,000
37	*c*-$PrSO_2NH$	1.8	>100,000	91,000	3,800
38		1.8	88,000	>100,000	60,000
39		0.3	44,000	62,000	6,300
40	CH_3SO_2	1.7	>100,000	60,000	20,000
41	*i*-$PrSO_2$	1.7	>100,000	>100,000	16,000
42	$C_6H_5SO_2$	0.4	27,000	41,000	14,000

Table 3
Pharmacokinetic properties of selected inhibitors in rat (1 mg/kg iv and 2 mg/kg po or 0.4 mg/kg iv only)

Compd	R	Isomer	Clp (ml/min/kg)	$t_{1/2}$ (h)	AUC_{norm} (μM h/mg/kg)	F (%)
2[5]	H	—	10	6.3	3.7	70
25a	*c*-$PrSO_2$	A	24	1.6	1.7	79
26a	*c*-$PentSO_2$	A	96	0.5	0.4	nd*
20	CH_3SO_2	B	1.1	11	48	~100
22	$CH_3CH_2SO_2$	B	1.6	5.2	22	84
24	*i*-$PrSO_2$	B	7.0	1.3	5.6	93
25b	*c*-$PrSO_2$	B	0.9	6.2	47	~100
26b	*c*-$PentSO_2$	B	41	1.5	0.9	nd*
30	CH_3CH_2CONH	C	60	2.2	0.7	nd*
31	*c*-PrCONH	C	64	5.5	0.6	nd*
34	CH_3SO_2NH	C	16	2.0	2.5	nd*
35	$CH_3CH_2SO_2NH$	C	12	2.1	3.4	nd*
37	*c*-$PrSO_2NH$	C	24	1.5	1.6	nd*

* Compounds were tested in mixture PK studies, no *F* % was measured.

selected for further PK profiling in dog. The results of these studies are shown in Table 4. Overall, these three analogs displayed excellent pharmacokinetic profiles compared to the non-substituted analog **2** in rats and dogs.[5] The methylsulfonamide **20** exhibited the longest half-life in rats (11 h) and dogs (22 h). In addition, this compound was found to be clean of ion channel activity (IC_{50} >30 μM at IKr and Cav1.2).[5] In a glucose tolerance test (OGTT) in lean mice, compound **20** displayed comparable glucose lowering efficacy to sitagliptin and inhibited 85% DPP-4 activity at 0.3 mg/kg dose in a pharmacodynamic (PD) assay.[6]

The retention of potency with structurally diverse side-chains prompted us to examine the X-ray of this class of compounds. The 2-cyclopropylsulfonamide analog **25b** was co-crystallized with DPP-4 enzyme to obtain an X-ray crystal structure of the ligand–enzyme complex. 1- and 3-Cyclopropyl sulfonamides **25a** and **37** were then selected to model in the DPP-4 enzyme to better understand the binding mode of the three cyclopropysulfonamide regioisomers. As shown in the top image of Figure 2, the major binding interactions of sitagliptin **1** (yellow) and the compound **25b** (green) with DPP-4 are conserved. The 2-F atom of the difluorophenyl group interacts with the side chain of R125 via a hydrogen bonding. Two additional hydrogen bonds are formed between the basic amine and E205 and E206.[6] The cyclopropylsulfonyl side chain extends further into the binding cavity than sitagliptin but is located in an area opened up by the flexible side chain of R358.

The middle image of Figure 2 displays the model analysis of compound **25a** (green) and is superpostitioned with the sitagliptin **1** (yellow) bounded to the DPP-4 enzyme. Similar to **25b**, the compound **25a** shares the key binding interactions with sitagliptin **1**. The cyclopropylsulfonyl group now faces the solvent cavity and is easily accommodated in this location.

The modeling of 3-cyclopropylsulfonamide compound **37** (green) and overlay with sitagliptin **1** (yellow) are shown in the

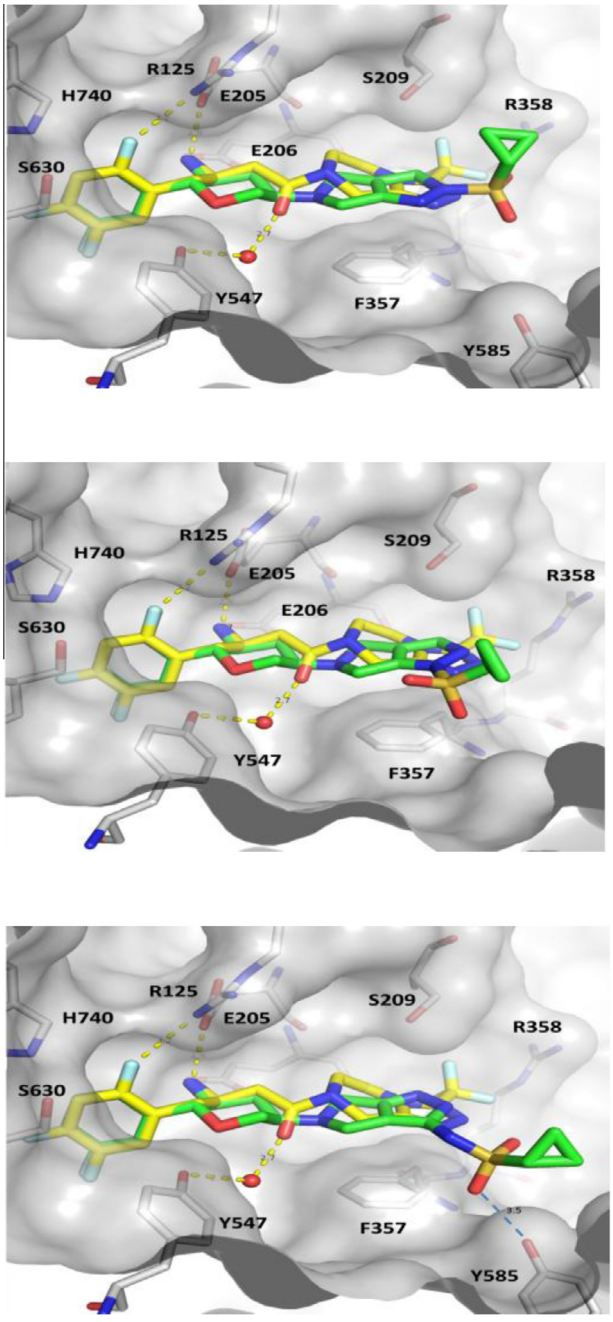


Figure 2. Top: superposition of sitagliptin **1** and compound **25b** bounded in the DPP-4 enzyme using their X-ray structures (PDB code: 4PNZ). Middle: X-ray crystal structure of sitagliptin **1** and modeling of compound **25a**. Bottom: X-ray crystal structure of sitagliptin **1** and modeling of compound **37**. The images were generated using Pymol.

Table 4
Pharmacokinetic properties of long acting DPP-4 inhibitors in preclinical spices (1 mg/kg iv and 2 mg/kg po)

Compd	R	Species	Clp (ml/min/kg)	$t_{1/2}$ (h)	AUC (μM h/mg/kg)	F (%)	IKr IC_{50} (nM)	Cavl.2 IC_{50} (nM)
2	H	Rat	10	6.3	3.7	70	>30,000	>30,000
		Dog	2.7	13	16	83		
20	CH_3SO_2	Rat	1.1	11	48	~100	39,000	>30,000
		Dog	0.9	22	54	~100		
22	$C_2H_5SO_2$	Rat	1.6	5.2	22	84	>60,000	>30,000
		Dog	3.3	13	25	~100		
25b	*c*-$PrSO_2$	Rat	0.9	6.2	47	~100	21,000	>30,000
		Dog	1.6	17	25	90		

bottom image of Figure 2. A direct overlay of **37** would cause the 3-cyclopropyl sulfonamide group to bump into the enzyme back wall. Rotation of **37** would then move the cyclopropyl sulfonamide group into the open area of the solvent cavity with minimal energetic cost. In addition to the similar hydrogen bonding interactions as compound **1**, the sulfonamide group would be further stabilized by an additional hydrogen bond formed with the side chain of Y585.

In conclusion, we have prepared a series of novel substituted dihydropyrrolopyrazole DPP-4 inhibitors. In most cases, they are potent and highly selective DPP-4 inhibitors with excellent pharmacokinetic properties and safety profiles. X-ray and modeling analysis demonstrate that selected analogs retain the key interactions that sitagliptin expresses with the DPP-4 binding pocket.

Among all the amide and sulfonamide analogs made in this study, the methylsulfonamide analog **20** (MK-3102, omarigliptin)[6] has the longest half-life and been chosen for clinical development suitable for once weekly dosing. Currently, the phase III study was completed and a new drug application has been approved in Japan.

References and notes

1. *IDF Diabetes Atlas*, 3rd ed.; International Diabetes Federation: Brussels, Belgium, 2013. http://www.idf.org/diabetesatlas/5e/the-global-burden.
2. (a) Karagiannis, J.; Pascho, P.; Paletas, K.; Matthews, D.; Tsapas, A. *Br. Med. J.* **2012**, *344*, e1369; (b) Dicker, D. *Diabetes Care* **2011**, *34*, s276; (c) Deacon, C.; Mannucci, E.; Ahren, B. *Diabetes Obes.* **2012**, *14*, 762; (d) Aroda, V.; Henry, R.; Han, J.; Huang, W.; Deyoung, M.; Darsow, T., et al. *Clin. Ther.* **2012**, *34*, 1247.
3. (a) Weber, A. E. *J. Med. Chem.* **2004**, *47*, 4135; (b) Havale, S. H.; Pal, M. *Bioorg. Med. Chem. Lett.* **2009**, *17*, 1783; (c) Gerich, J. *Diabetes Res. Clin. Pract.* **2010**, *90*, 131.
4. (a) Holst, J. J. *Diabetologia* **2006**, *49*, 253; (b) Baggio, L. L.; Drucker, D. J. *Gastroenterology* **2007**, *132*, 2131; (c) Holst, J. J.; Vilsboll, T.; Deacon, C. F. *Mol. Cell. Endocrinol.* **2009**, *297*, 127; (d) Brubaker, P. L. *Endocrinology* **2010**, *151*, 1984.
5. Biftu, T.; Qian, X.; Chen, P.; Feng, D.; Scapin, G.; Gao, Y. D.; Cox, J.; Roy, R. S.; Eiermann, G.; He, H.; Lyons, K.; Salituro, G.; Patel, S.; Petrov, A.; Xu, F.; Xu, S. S.; Zhang, B.; Caldwell, C.; Wu, J. K.; Lyons, K.; Weber, A. E. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 5361.
6. Biftu, T.; Roy, R. S.; Chen, P.; Qian, X.; Feng, D.; Kuethe, J. T.; Scapin, G.; Gao, Y. D.; Yan, Y.; Krueger, D.; Bak, A.; Eiermann, G.; He, J.; Cox, J.; Hicks, J.; Lyons, K.; He, H.; Salituro, G.; Tong, S.; Patel, S.; Doss, G.; Petrov, A.; Wu, J.; Xu, S. S.; Sewall, C.; Zhang, X.; Zhang, B.; Thornberry, N. A.; Weber, A. E. *J. Med. Chem.* **2014**, *57*, 3205.
7. (a) Leiting, B.; Pryor, K. D.; Wu, J. K.; Marsilio, F.; Patel, R. A.; Craik, C. S.; Ellman, J. A.; Cummings, R. T.; Thornberry, N. A. *Biochem. J.* **2003**, *371*, 525; (b) Rosenblum, J. S.; Kozarich, J. W. *Curr. Opin. Chem. Biol.* **2003**, *7*, 496; (c) Collins, P. J.; McMahon, G.; O'Brien, P.; O'Connor, B. *Int. J. Biochem. Cell Biol.* **2004**, *36*, 2320.
8. Scanlan, M. J.; Raj, B. K. M.; Calvo, B.; Garin-Chesa, P.; Sanz-Moncasi, M. P.; Healey, J. H.; Old, L. J.; Retting, W. J. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 5657.
9. Abbott, C. A.; Yu, D. M.; Woollatt, E.; Sutherland, G. R.; McCaughan, G. W.; Gorrell, M. D. *Eur. J. Biochem.* **2000**, *267*, 6140.
10. Olsen, C.; Wagtmann, N. *Gene* **2002**, *299*, 185.
11. (a) Lankas, G. R.; Leiting, B.; Roy, R. S.; Wiermann, G. J.; Beconi, M. G.; Biftu, T.; Chan, C.; Edmondson, S.; Feeney, W. P.; He, H.; Ippolito, D. E.; Kim, D.; Lyons, K. A.; Ok, H. O.; Patel, R. A.; Petrov, A. N.; Pryon, K. A.; Qian, X.; Reigle, L.; Woods, A.; Wu, J. K.; Zaller, D.; Zhang, X.; Zhu, L.; Weber, A. E.; Thornberry, N. A. *Diabetes* **2005**, *54*, 2988; (b) Burkey, B. F.; Hoffman, P. K.; Hassiepen, U.; Trappe, J.; Juedes, M.; Foley, J. E. *Diabetes Obes. Metab.* **2008**, *10*, 1057.
12. Barnett, A. *Int. J. Clin. Pract.* **2006**, *60*, 1454.
13. Green, J. B.; Bethel, M. A.; Armstrong, P. W.; Buse, J. B.; Engel, S. S.; Garg, J.; Joss, R.; Kaufman, K. D.; Koglin, J.; Korn, S.; Lachin, J. M.; McGuire, D. K.; Pencina, M. J.; Standl, E.; Stein, P. P.; Suryawanshi, S.; Van de Werf, F. V.; Peterson, E. D.; Holman, R. R. *N. Engl. J. Med.* **2015**, *373*, 232.

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