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Discovery of conformationally rigid 3-azabicyclo[3.1.0]hexane-derived dipeptidyl peptidase-IV inhibitors

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ABSTRACT

The induction of conformationally restricted *N*-(aryl or heteroaryl)-3-azabicyclo[3.1.0]hexane derivatives at P_2 region of compounds of 2-cyanopyrrolidine class was explored to develop novel DPP-IV inhibitors. The synthesis, structure–activity relationship, and selectivity against related proteases are delineated.

Recently, inhibition of dipeptidyl peptidase-IV (DPP-IV, CD26, EC 3.4.14.5) has turned out to be a promising approach for treatment of type 2 diabetes.[1] While the DPP-IV inhibitor, Sitagliptin (Januvia®), was approved worldwide in 2006 as a first-in-class drug, Vildagliptin (Galvus®) was recently approved for the European market (Fig. 1). Several other potential gliptins are under various phases of development.[2] DPP-IV diminishes the physiological level of incretin (insulin-secreting) hormone, glucagon-like peptide-1 (GLP-1) {$t_{1/2}$: ~2 min}, by proteolytic deactivation. The inhibition of DPP-IV elevates the level of GLP-1 by 2- to 3-fold. GLP-1 targets multiple pathways of glucose regulation. It augments insulin secretion in a glucose-dependent manner, thereby avoiding hypoglycemic episodes. Importantly, GLP-1 increases β-cell mass in animal models, which offers the potential to prevent or reverse the progression of the disease. DPP-IV is an ubiquitous serine protease, which exists in both the soluble and membrane-bound forms with identical structure and function. It is clinically proven that DPP-IV inhibition leads to an increase of GLP-1 to therapeutically beneficial levels and consequent enhancement of body's own normal glucose homeostatic mechanism.

The cyanopyrrolidine class of DPP-IV ligands incorporating an N-(substituted)piperidine at the P_2 position has recently been disclosed as potent DPP-IV inhibitors in a number of publications (Fig. 2).[3] We sought to explore the replacement of the piperidine ring with a 3-azabicyclo[3.1.0]hexane {ABH} ring, as the ABH fragment has frequently been employed by medicinal chemists in the construction of novel chemical entities.[4] This structural modification

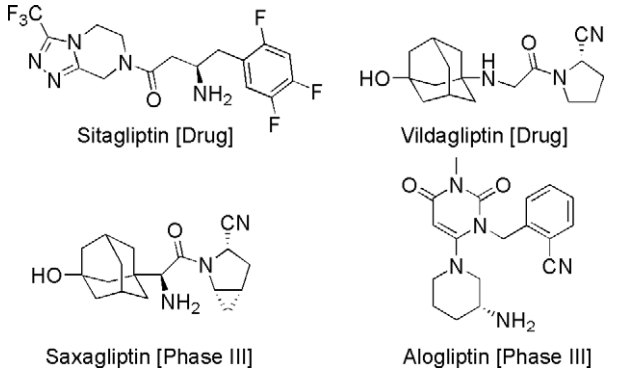

Figure 1. DPP-IV inhibitors with diverse chemotypes.

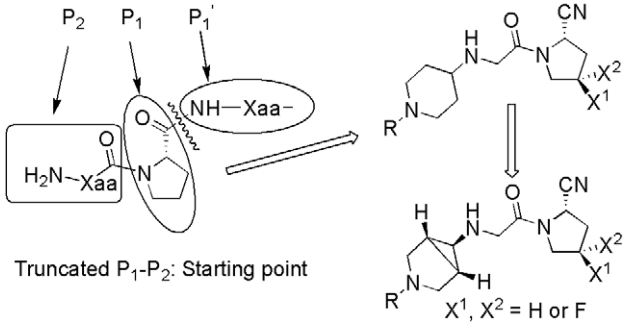

Figure 2. Design of DPP-IV ligands bearing ABH motif.

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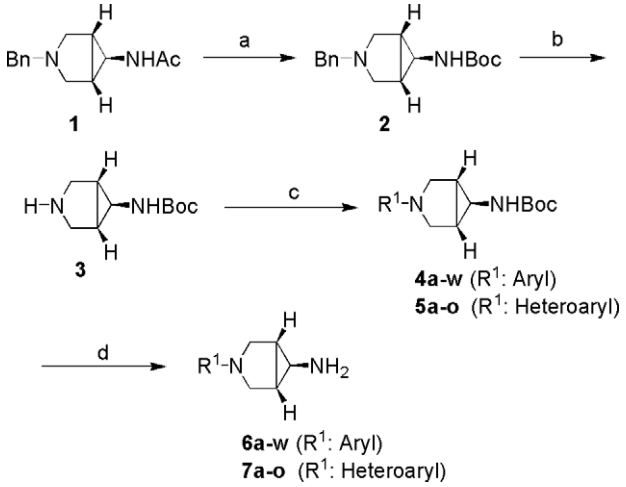
involves the introduction of a bridge in the piperidine ring leading to a puckered shape and a restriction in conformational flexibility (Fig. 2). Herein, we report preliminary results of the synthesis and evaluation of *N*-aryl and *N*-heteroaryl ABH derivatives as DPP-IV inhibitors.

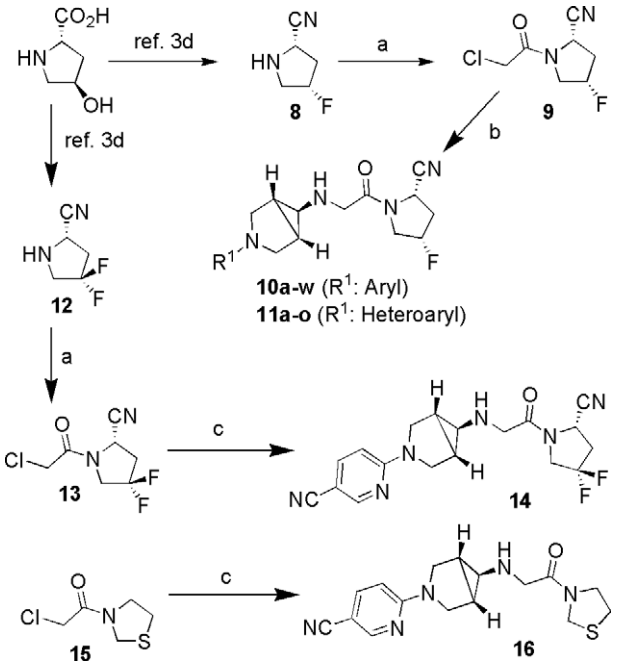
The requisite *N*-aryl and *N*-heteroaryl 3-azabicyclo [3.1.0]hexane-6-amine intermediates were synthesized starting from the known intermediate **1** (Scheme 1).[5] Alkaline hydrolysis of the amide **1** followed by protection of the resultant amine provided the carbamate derivative **2**. The removal of the *N*-benzyl group was accomplished by catalytic hydrogenolysis. The ensuing amine **3** was coupled, in parallel, to a series of activated aryl and heteroaryl halides to afford the corresponding 3-(*N*-substituted)azabicyclo[3.1.0]hexan-6-amine derivatives (**4a**–**w** and **5a**–**o**), which were subsequently deprotected on treatment with TFA or *p*TSA to obtain the corresponding amines (**6a**–**w** and **7a**–**o**) in free or salt forms.

The chiral *N*-chloroacetyl-2-cyanopyrrolidine intermediate **9** was acquired following a one-step procedure from the known intermediate **8** (Scheme 2).[3d] The compound **9** was subjected to amination with various amine partners, **6a**–**w** and **7a**–**o**, to provide the final compounds **10a**–**w** and **11a**–**o** (Tables 1 and 2).[6] Two P_1-modified analogs (**14** and **16**) of the compound **11l** were also prepared from the respective known intermediates (**13** and **15**) to explore additional SAR, as depicted in the Scheme 2.[3a,d,6] Recently, highly potent DPP-IV inhibitors with a des-cyanothiazolidine at the P_1 position have been identified.[7]

All compounds were tested in vitro for inhibitory activity against soluble DPP-IV isolated from citrated human plasma.[8] The DPP-IV inhibitors, which are non-selective against DASH (DPP-IV activity and/or structural homolog) members, viz, DPP-2, DPP-8 and DPP-9, have been implicated in species- and tissue-specific toxicities in preclinical studies.[1a,9] Hence, selectivity against DPP-2, DPP-8, and DPP-9 appears to be essential. The attenuation of T-cell activation *in vitro* has been observed with DPP-8 and DPP-9 inhibitors.[9] Compounds with DPP-IV $IC_{50} < 1000$ nM were assessed for selectivity against DPP-2, DPP-8, DPP-9, and PPCE.[8] Furthermore, selected compounds were screened against other DASH [APP and Prolidase] and related [APN and NEP] peptidases and examined for effects on T-cell proliferation.[8] NEP was included in the selectivity panel because of safety concerns, as inhibition of NEP enhances the incidence of life-threatening angioedema.[10] NEP like DPP-IV also degrades GLP-1.



Scheme 1. Reagents and conditions: (a) i—NaOH, H_2O-EtOH, 100 °C; ii—di-*tert*-butyl dicarbonate, $NaHCO_3$, H_2O-dioxane; (b) H_2 [50 psi], Pearlman's catalyst, MeOH-THF; (c) aryl or heteroaryl halide (-F/-Cl/-Br), K_2CO_3, DMF, 100–140 °C; (d) TFA, DCM or *p*TSA,MeCN.

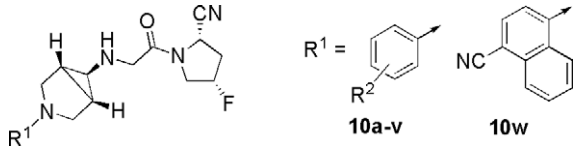


Scheme 2. Reagents and conditions: (a) $ClCH_2COCl$, TEA, DCM; (b) **6a**–**w** and **7a**–**o**, K_2CO_3, DMF (or TEA, DCM), RT; (c) **7l**, K_2CO_3, DMF.

The DPP-IV inhibitory activities of *N*-aryl (**10a**–**w**) and *N*-heteroaryl (**11a**–**o**, **14** and **16**) ABH derivatives are listed in Tables 1 and 2. Since *N*-(4-cyanophenyl) piperidine derivatives have been reported to be highly potent (Table 3),[3f] we investigated foremost the activity of similar compounds by replacing the piperidine with an ABH ring (**10a**–**h**). The 4-cyanophenyl derivative (**10a**) exhibited moderate activity (165 nM). Further substitution with mixed halides (–F and –Cl) at the 2- or 3-position was explored (**10b**–**f**). While the 2-F group (**10b**) did not improve the activity (153 nM), its 3-F isomer (**10c**) exhibited an improved activity (110 nM). The 3,5-difluoro substitution (**10d**) demonstrated an additive effect and enhanced the activity by about 4-fold (38 nM) compared to 3-fluoro substitution (**10c**) alone (110 nM). Contrary to the fluoro group, the chloro substitution had a reverse effect on activity. Thus, while the –Cl group at the 2-position (**10e**) improved the activity (95 nM), no significant improvement was noted at the 3-position (**10f**). While the $-CF_3$ group (**10g**) at the 2-position improved activity by ~3-fold, it (**10h**) caused severe loss of activity at the 3-position (42-fold). The replacement of nitrile in 4-cyanophenyl with other electron withdrawing groups was also investigated. While $-COCH_3$ (**10i**) and $-CONH_2$ (**10k**) groups imparted improvements in activity, the $-CO_2Et$ (**10j**) group lowered the potency. The replacement of $-CONH_2$ (**10k**) with secondary amides –CONHMe and –CONHCyPr (**10l**–**m**) was found to be detrimental to activity.

Activity could be optimized (2-fold) by relocating the –CN group on the *N*-phenyl from the 4- to the 2-position (**10a** and **10n**). Further substitution with a 3-Cl group (**10o**) enhanced the activity resulting in the most potent compound (31 nM) in the *N*-aryl series. While the 3-fluoro substitution (**10r**) depreciated the activity by ~2-fold, the 3,5-difluoro substitution (**10u**) resulted in a further erosion of activity (~12-fold). The 2-cyanophenyl derivative (**10n**) had higher affinity than the 4-cyanophenyl derivative (**10a**) and this effect was mirrored in compounds containing either 3-F, 3-Cl, or 3-CF_3 group as additional substituents (*cf.* **10r**, **10o**, **10p** *vs* **10c**, **10f**, **10h**). However, the trend was reversed in the case of isomeric pair with 3,5-difluoro substitution (**10u** and **10d**). No activity enhancement was realized by repositioning the –CN group to 3-position (*cf.* **10v** *vs.* **10c**, **10r**).

Table 1
Activity of (2*S*, 4*S*)-*N*-{3-(aryl)azabicyclo[3.1.0]hex-6-yl}glycyl-2-cyano-4-fluoropyrrolidine derivatives[a,b]



10a-v **10w**

Compound	R^2	IC_{50} (nM)				
		DPP-IV	DPP-2	DPP-8	DPP-9	PPCE
10a	R^2 = 4-CN	165	18,100	2210	421	12,300
10b	R^2 = 4-CN, 2-F	153	2760	637	131	>10,000
10c	R^2 = 4-CN, 3-F	110	1200	3030	1660	9940
10d	R^2 = 4-CN, 3,5-F_2	38	10,900	1675	343	9700
10e	R^2 = 4-CN, 2-Cl,	95	1000	399	66	392
10f	R^2 = 4-CN, 3-Cl	152	907	3020	807	26,800
10g	R^2 = 4-CN, 2-CF_3	59	1000	652	130	2100
10h	R^2 = 4-CN, 3-CF_3	2540	n.d.	n.d.	n.d.	n.d.
10i	R^2 = 4-$COCH_3$	109	9000	500	771	492
10j	R^2 = 4-CO_2Et	229	9880	2080	640	62,200
10k	R^2 = 4-$CONH_2$	95	21,800	2130	3030	18,300
10l	R^2 = 4-CONHMe	3430	n.d.	n.d.	n.d.	n.d.
10m	R^2 = 4-CONHCyPr[c]	3740	n.d.	n.d.	n.d.	n.d.
10n	R^2 = 2-CN	51	406	2400	729	>10,000
10o	R^2 = 2-CN, 3-Cl	31	96	>10,000	119	417
10p	R^2 = 2-CN, 3-CF_3	42	1300	6500	1910	>10,000
10q	R^2 = 2-CN, 6-F	63	1300	366	169	>10,000
10r	R^2 = 2-CN, 3-F	92	>10,000	>10,000	1910	>10,000
10s	R^2 = 2-CN, 4-CF_3	141	4330	28,600	3680	>100,000
10t	R^2 = 2-CN, 4-F	422	>10,000	3090	4850	>10,000
10u	R^2 = 2-CN, 3,5-F_2	630	3900	2050	1960	8700
10v	R^2 = 5-CN, 3-F	118	1800	3270	1200	9150
10w	-	1715	n.d.	n.d.	n.d.	n.d.
A[d]	—	—	163	—	—	—
B[e]	—	—	—	147	168	—
C[f]	—	—	—	—	—	3870

[a] Values are the mean of three experiments; standard deviations are ± 15%.
[b] n.d.: not determined.
[c] CyPr: cyclopropyl.
[d] A: Dab-Pip (reference).[3a]
[e] B: Lys[Z(NO_2)] pyrrolidide (reference).[9]
[f] C: *Z*-Pro-Pro aldehyde dimethyl acetal (reference).[3a]

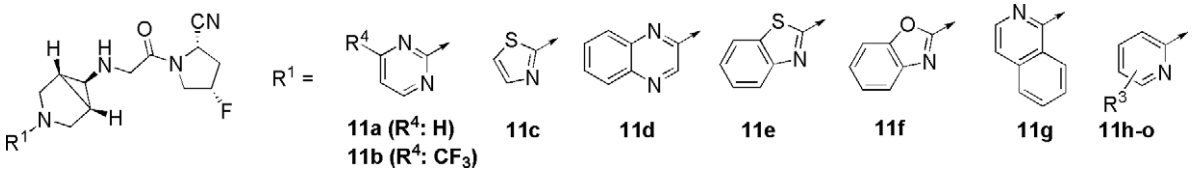
We next investigated the impact of different *N*-heteroaryl rings on activity (**11a–h**). The monocyclic heteroaryl compounds (**11a**, **11c** and **11h**) gave higher activity than the bicyclic heteroaryl groups (**11d–g**), indicating presumably steric inhibition to binding. This also happened to be true in the *N*-aryl series, where the monocyclic 4-cyanophenyl derivative (**10a**) displayed better activity (23-fold) than the bicyclic 4-cyanonaphthyl derivative (**10w**). Within the monocyclic heteroaryl groups, the pyridin-2-yl group gave the best activity, which was higher than the phenyl analog **10o**. The thiazol-2-yl group (**11c**) was 5-fold less potent compared to the pyridin-2-yl group, albeit being the bioisostere of pyridin-2-yl group. The appendage of aromatic ring on thiazolyl nucleus (**11e**) led to decreased affinity.

Having identified the pyridin-2-yl group as the optimal heteroaryl group, we subsequently examined the influence of electron-withdrawing substitutents (–CF_3, –Cl, –NO_2, and -CN) at either the C-3 or C-5 position of the pyridine ring (**11i–o**). In all cases, the compounds were found to be less potent than the parent compound (**11h**). The strong electron-accepting group, –NO_2, was equally accommodated at the 3- and 5-position (**11m** and **11j**). The –CN group was better tolerated at the C-3 (**11n**) than the C-5 position (**11l**). The 3-chloro analog (**11o**) was several fold less potent than its 5-chloro counterpart (**11i**). The P_1 modification of the pyridyl derivative **11l** with C-4 *gem*-difluoro substitution on the pyrrolidine (**14**), which occupies the tight-binding S_1 pocket, caused an improvement in activity. However, the replacement of 5-fluoro-2-cyanopyrrolidine (**14**) with thiazolidine (**16**) was met with a dramatic loss of affinity. This demonstrates that the P_1 nitrile, which interacts with S630 in the S_1 pocket, is an indispensable requisite for any meaningful inhibition.[3a]

The activities of corresponding ABH and piperidine derivatives[3f] were compared to examine the influence of the bridge (Table 3). The bridged piperidine derivatives (**10a, 10d, 10g** and **11k–l**) were uniformly less active than their piperidine counterparts. The disparity in activity may be attributed to the difference in the conformational preferences of the piperidine and ABH rings. The chair-like conformation of piperidine, in contrast to the puckered conformation of ABH, may be vital for maximal interaction of the ring and peripheral N-1 substituent with the largely lipophilic S_2 backbone.

None of the compounds from the *N*-aryl and *N*-heteroaryl series qualified for '$\geqslant$1000-fold selectivity' against all four DASH members, DPP-2, DPP-8, DPP-9 and PPCE (Tables 1 and 2). The compounds from both the series were more potent against DPP-9 over DPP-8, though there were a few exceptions. Interestingly, the representative compounds tested against other proline-specific enzymes, Prolidase and APP, were found to be highly selective (>1000-fold) (Table 4). These compounds were also selective against T-cell proliferation, though they were less selective against DPP8/9.[9]

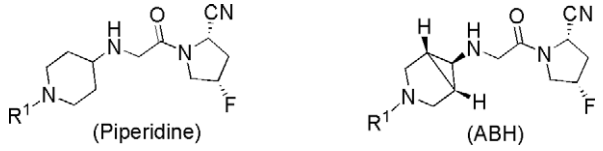
Table 2
Activity of (2*S*, 4*S*)-*N*-{3-(heteroaryl)azabicyclo[3.1.0]hex-6-yl}glycyl-2-cyano-4-fluoropyrrolidine derivatives[a,b]



Compound	R^3	IC_{50} (nM)				
		DPP-IV	DPP-2	DPP-8	DPP-9	PPCE
11a	—	84	16,500	4030	>100,000	46
11b	—	181	2200	11,100	5420	>100,000
11c	—	146	11,000	11,499	448	>100,000
11d	—	186	226	7270	7810	>10,000
11e	—	186	5100	14,900	547	>10,000
11f	—	221	5100	13,100	5990	>100,000
11g	—	3670	n.d.	n.d.	n.d.	n.d.
11h	R^3 = H	27	10,800	837	n.d.	1420
11i	R^3 = 5-Cl	49	8750	2375	n.d.	9044
11j	R^3 = 5-NO_2	85	13,050	1667	n.d.	8500
11k	R^3 = 5-CF_3	123	4000	35,500	63,200	>100,000
11l	R^3 = 5-CN	147	11,000	2180	350	>100,000
11m	R^3 = 3-NO_2	78	6420	3400	525	>10,000
11n	R^3 = 3-CN	91	1340	16,100	7300	11,790
11o	R^3 = 3-Cl	1300	n.d.	n.d.	n.d.	n.d.
14	—	93	2800	10,100	2410	14100
16	—	>10,000	n.d.	n.d.	n.d.	n.d.

[a] Values are the mean of three experiments; standard deviations are ±15%.
[b] n.d.: not determined.

Table 3
Effect of piperidine bridge on DPP-IV activity



R^1	DPP-IV (K_i, nM)	
	Piperidine[a]	ABH (compound)[b]
4-CN, 3,5-F_2-Phenyl	1	38 (**10d**)
4-CN, 2-CF_3-Phenyl	5	59 (**10g**)
5-CF_3-Pyridin-2-yl	12	122 (**11k**)
5-CN-Pyridin-2-yl	31	147 (**11l**)
4-CN-Phenyl	79	165 (**10a**)

[a] See Ref. 3f.
[b] Values are the mean of three experiments; standard deviations are ±15%.

Table 4
Selectivity (×fold) against other DASH and related peptidases, and T-cell proliferation activity[a]

Compound	Selectivity (×fold)				T-Cell[b] (IC_{50}, nM)
	Prolidase	APP	APN	NEP	
10c	>3194	>3194	>3194	>3194	>10,000
10i	>1086	>1086	>1086	>1086	>10,000
10k	>2369	>2369	>2369	>2369	>10,000
10l	>1052	>1052	>1052	>1052	>10,000
10m	>1694	>1694	>1694	>1694	>10,000
10o	>1960	>1960	>1960	>1960	>10,000
11h	>3773	>3773	n.d.	>3773	>10,000
11i	>2040	>2040	n.d.	>2040	>10,000
11n	>1179	>1179	n.d.	>1179	>10,000
B	–	–	–	–	839
D[c]	–	–	–	–	>10,000

[a] n.d.: not determined.
[b] Values are the mean of three experiments; standard deviations are ± 15%.
[c] D:LAF-237.[3a]

In summary, we have identified potent DPP-IV inhibitors using the conformationally constrained 3-(*N*-substituted)azabicyclo[3.1.0]hexane. The ABH bridge resulted in a slight attenuation of activity, as evident from the SAR between the corresponding piperidine and ABH analogs. The most potent compounds displayed off-target activity against DPP-2, DPP-8 or DPP-9, which precluded further profiling. However, none of the compounds profiled against Prolidase, APP, APN, NEP and T-cell proliferation exhibited any significant activity. After realizing DASH liabilities, we undertook optimization of the N-1-substitution of the ABH ring, which culminated in a preclinical candidate with remarkable DASH selectivity. This modification will remain as the subject of our forthcoming publication.

Acknowledgments

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References and notes

1. (a) Drucker, D. J. *Diabetes Care* **2007**, *30*, 1335; (b) Sebokova, E.; Christ, A. D.; Boehringer, M.; Mizrahi, J. *Curr. Top. Med. Chem.* **2007**, *7*, 547; (c) Thornberry, N. A.; Weber, A. E. *Curr. Top. Med. Chem.* **2007**, *7*, 557; (d) Szczepankiewicz, B. G.; Kurukulasuria, R. *Curr. Top. Med. Chem.* **2007**, *7*, 569; (e) Peters, J.-U. *Curr. Top. Med. Chem.* **2007**, *7*, 579; (f) Ferraris, D.; Belyakov, S.; Li, W.; Oliver, E.; Ko, Y.-S.; Calvin, D.; Lautar, S.; Thomas, B.; Rojas, C. *Curr. Top. Med. Chem.* **2007**, *7*, 597; (g) Kuhn, B.; Henning, M.; Mattei, P. *Curr. Top. Med. Chem.* **2007**, *7*, 609; Van der (h) Veken, P.; Haemers, A.; Augustyns, K. *Curr. Top. Med. Chem.* **2007**, *7*, 621.
2. At least 13 DPP-IV inhibitors are said to be in clinical development with eight in advanced phase [II or III stage] (source: www.PipelineReview.com).
3. For select references, see: (a) Villhauer, E. B.; Brinkman, J. A.; Naderi, G. B.; Burkey, B. F.; Dunning, B. E.; Prasad, K.; Mangold, B. L.; Russell, M. E.; Hughes, T. E. *J. Med. Chem.* **2003**, *46*, 2774; (b) Yasuda, K.; Morimoto, H.; Kawanami, S.; Hikota, M.; Matsumoto, T.; Arakawa, K. World Patent 2002030890, 2002.; (c) Matsuno, K.; Ueno, K.; Iwata, Y.; Matsumoto, Y.; Nakanishi, S.; Takasaki, K.; Kusaka, H.; Nomoto, Y.; Ogawa, A. World Patent 2002051836, 2002.; (d) Haffner, C.D.; McDougald, D.L.; Lenhard, J.M. World Patent 2003002553, 2003.; (e) Hayakawa, M.; Nakano, R.; Furutani, M. World Patent 2005116012, 2005.;

(f) Caldwell, R.; Haffner, C.D.; McDougald, D.L.; Reister, S.M.; Dwornik, K; Randhawy, S.; Thompson, B.; Cowan, D.; Henke, B.; Kaldor, I.; Lenhard, J.M.; Croom, D.; Clancy, D.; McConn, D.; Hedeen, K.M.; Wells-Kencht, K.J.; Secosky, M.; Zhang, W. Abstracts of Papers, 29th National Medicinal Chemistry Symposium, University of Wisconsin, June 27–July 1, 2004, USA.

4. The substructure search on ABH ring in SciFinder brings >500 references inclusive of about 250 patents.
5. Chiu, C. K-F.A.; Wint L.T. European Patent 090330297, 1999.
6. Compounds were purified by flash column chromatography [silica gel: 100–200 mesh; eluent: a gradient of EtOAc and hexane] and characterized by NMR and mass spectrometry.
7. Yoshida, T.; Sakashita, H.; Akahoshi, F.; Hayashi, Y.; Ishii, S. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2618. and the references cited therein.
8. For assay conditions, see: DPP-IV, DPP-2 and PPCE [Post-proline cleaving enzyme; EC 3.4.21.26]: (a) Ref. 3a; DPP-8: (b) Abbot, C. A.; Yu, D. M.; Woollatt, E.; Sutherland, G. R.; McCaughan, G. W.; Gorrell, M. D. *Eur. J. Biochem.* **2000**, *267*, 6140; DPP-9: (c) Olsen, C.; Wagtmann, N. *Gene* **2002**, *299*, 185; Prolidase: (d) Hu, M.; Cheng, Z.; Zheng, L. *Pediatr. Res.* **2003**, *53*, 905; APP [Aminopeptidase P; EC 3.4.11.9] and APN [Aminopeptidase N; EC 3.4.11.2]: (e) Brandt, I.; Joossens, J.; Chen, X.; Maes, M.-B.; Scharpé, S.; De Meester, I.; Lambeir, A.-M. *Biochem. Pharmacol.* **2005**, *70*, 134; NEP [neutral endopeptidase; EC 3.4.24.11]: (f) Medeiros, M. A. S.; Franca, M. S. F.; Boileau, G.; Juliano, L.; Carvalho, K. M. *Braz. J. Med. Biol. Res.* **1997**, *30*, 1157; T-cell: (g) Weichert, H.; Blechschmidt, I.; Schroder, S.; Ambrisius, H. *Allerg. Immunol.* **1991**, *37*, 139.
9. Lankas, G. R.; Leiting, B.; Sinha Roy, R.; Eiermann, G. J.; Beconi, M. G.; Biftu, T.; Chan, C.-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.; Pryor, 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.
10. (a) Plamboeck, A.; Holst, J. J.; Carr, R. D.; Deacon, C. F. *Diabeteologia* **2005**, *48*, 1882; (b) Jandeleit-Dahm, K. A. M. *J. Hum. Hypertens.* **2006**, *20*, 478.