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Aminopiperidine-fused imidazoles as dipeptidyl peptidase-IV inhibitors

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ABSTRACT

A new series of DPP-4 inhibitors derived from piperidine-fused benzimidazoles and imidazopyridines is described. Optimization of this class of DPP-4 inhibitors led to the discovery of imidazopyridine **34**. The potency, selectivity, cross-species DMPK profiles, and in vivo efficacy of **34** is reported.

Since the approval of sitagliptin (**1**) by the US Food and Drug Administration in 2006, selective dipeptidyl peptidase IV (DPP-4) inhibitors have established themselves as an important new option for the treatment of type 2 diabetes.[1] In vivo, DPP-4 is responsible for the inactivation of glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), both of which enhance insulin secretion in a glucose-dependent manner. Additionally, GLP-1 stimulates insulin biosynthesis, inhibits glucagon secretion, slows gastric emptying, reduces appetite, and stimulates the regeneration and differentiation of islet β-cells.[2,3] DPP-4 inhibitors increase circulating GLP-1 and GIP levels in humans, which leads to decreased blood glucose levels, hemoglobin A_{1c} levels, and glucagon levels. DPP-4 inhibitors such as sitagliptin possess advantages over alternative diabetes therapies including a lowered risk of hypoglycemia, a potential for weight loss, and the potential for the regeneration and differentiation of pancreatic β-cells.[3,4]

Aminocyclohexane **2** was identified in an effort to restrict the rotation of sitagliptin (**1**) while maintaining excellent DPP-4 inhibition potency (Fig. 1).[5] The cyclohexane ring can be exchanged with an *N*-aryl aminopiperidine ring to afford a series of DPP-4 inhibitors that possess similar potency to cyclohexylamine analogs.[6] Although many of these aminopiperidines (e.g., **3**) exhibit excellent rat pharmacokinetic profiles, they also possess inferior off-target selectivity profiles. By fusing heterocycles to this piperidine ring to provide imidazole derivatives **4**, we sought to improve the off-target selectivity profile of compounds in this series while maintaining potent DPP-4 inhibition and excellent rat pharmacokinetic profiles.

The synthesis of fused aminopiperidines began by converting lactam **5**[6] to methyl imidate **6** using Meerwein's reagent (Scheme 1). Treatment of **6** with either 2-aminoacetophenone hydrochlo-

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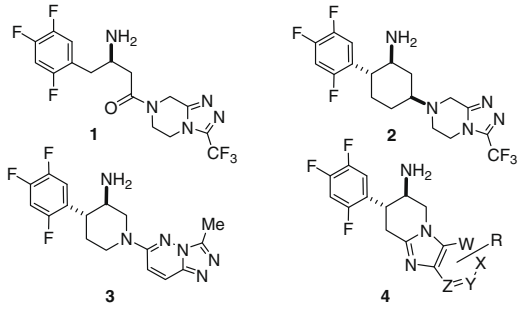
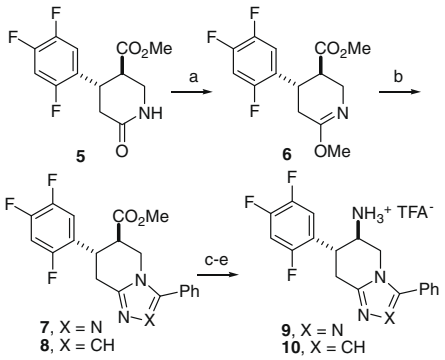


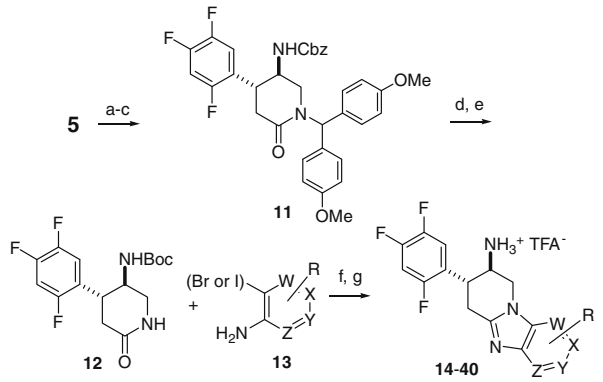
Figure 1. Potent and selective DPP-4 inhibitors, including sitagliptin (**1**), aminocyclohexane **2**, aminopiperidine **3**, and fused imidazole derivatives **4**.

ride or benzoic hydrazide in ethanol afforded the corresponding phenyl linked triazole and imidazole derivatives **7** and **8**, respectively. Hydrolysis of the ethyl ester, Curtius rearrangement, and Cbz deprotection then afforded the final DPP-4 inhibitors **9** and **10**.[7]

Benzimidazole and imidazopyridine derivatives were synthesized as shown in Scheme 2. Protection of the lactam **5** with 4,4′-dimethoxybenzhydrol was followed by ester hydrolysis and Curtius rearrangement to afford the carboxybenzyl (Cbz) protected amine **11**. Next, the Cbz group was exchanged with a Boc group and the secondary lactam was liberated using ceric ammonium nitrate (CAN). Exposure of the free lactam to *ortho* bromo or iodo aro-



Scheme 1. Synthesis of DPP-4 inhibitors **9** and **10**. Reagents and conditions: (a) Me_3OBF_3, CH_2Cl_2 (76% yield); (b) $PhCOYNH_2$, EtOH, Δ (Y = NH or CH_2); (c) $LiOH_{aq}$, MeOH, THF; (d) DPPA, TEA, tol; BnOH, Δ; (e) H_2, $Pd(OH)_2$, EtOAc, MeOH; then reverse phase purification with 1% TFA in H_2O/CH_3CN.



Scheme 2. Synthesis of DPP-4 inhibitors **14**–**40**. Reagents and conditions: (a) $(4\text{-MeOPh})_2CHOH$, H_2SO_4, HOAc (47% yield); (b) $LiOH_{(aq)}$, THF (80% yield); (c) DPPA, TEA, tol; BnOH, Δ; (65% yield); (d) $Pd(OH)_2$, H_2, MeOH, Boc_2O (73% yield); (e) CAN, CH_3CN, H_2O, 0 °C (75% yield of **12**); (f) CuI, $MeNHCH_2CH_2NHMe$, K_2CO_3, toluene, Δ; (g) TFA, CH_2Cl_2 (33–80% yield, two steps).

matic amines (i.e., **13**) under Buchwald's copper-catalyzed coupling conditions[8] then afforded the corresponding benzimidazoles and imidazopyridines in a single reaction. Importantly, this represents a new methodology for the synthesis of benzimidazoles or imidazopyridines. The same transformation could also be accomplished in a three step sequence (not pictured) by first using similar coupling conditions to attach *ortho* bromo-nitrobenzenes to lactam **12**, then reducing the nitro group to an amino group, and finally heating to induce the cyclocondensation that forms the corresponding benzimidazole. The brevity of the single step protocol described in Scheme 2 together with the increased availability of a variety of the starting aminoarenes **13**, however, allowed for a much more efficient method to synthesize analogs. Removal of the Boc group with strong acid then furnished analogs **14**–**40**.[7]

Compounds were tested for inhibition of DPP-4 and selectivity over DPP-4-like activity and/or structural homolog (DASH) proteins including quiescent cell proline peptidase (QPP, DPP-II), prolyl endopeptidase (PEP), aminopeptidase P (APP), prolidase, DPP-8, and DPP-9.[9,10] In general, all compounds possessed excellent selectivity (>1000-fold) over PEP, APP, and prolidase. Fused imidazoles displayed excellent selectivity for DPP-4 inhibition over all counter screens, including DPP-8 and DPP-9.[11] The improved DPP-4 potency of benzimidazole **14** compared to phenyl triazole **9** and phenyl imidazole **10** (Fig. 2) suggested that benzimidazole derivatives warranted further optimization.

In general, the addition of most substituents onto the benzimidazole improved DPP-4 inhibition potency (Table 1). Non-polar substituents (**15**–**24**) generally exhibited moderate improvements in potency over unsubstituted benzimidazole **14**, but many of these analogs exhibited sub-optimal selectivity over QPP (<1000-fold). The 6-fluoro derivative **17** and 5-trifluoromethyl derivative **23** exhibited the most promising profiles, with DPP-4 IC_{50}'s of 17 nM and 14 nM and QPP selectivities of 1400-fold and 2900-fold, respectively.

Introduction of polar substituents onto the 5-position of the benzimidazole ring typically resulted in enhancements in DPP-4 potency and QPP selectivity. Methyl sulfone **25** exhibits excellent DPP-4 potency (DPP-4 IC_{50} = 4.2 nM) and excellent selectivity over QPP, DPP-8 and DPP-9 (IC_{50}'s >100,000). Compared to **25**, the corresponding ethyl sulfone possessed a twofold decrease in DPP-4 intrinsic potency (**26**, DPP-4 IC_{50} = 8.0 nM) and shifting the methyl sulfone to the 6-position resulted in a 13-fold decrease in DPP-4 potency (**27**, DPP-4 IC_{50} = 56 nM). Replacement of the methyl sulfone with a carboxylic acid at the 5-position results in another potent and selective DPP-4 inhibitor (**28**, DPP-4 IC_{50} = 13 nM), but increasing steric bulk to a dimethyl carboxamide afforded a compound with diminished DPP-4 inhibition (**29**, DPP-4 IC_{50} = 52 nM) relative to the carboxylic acid. The placement of polar electron donating substituents onto the 5-position of the benzimidazole ring also afforded potent and selective DPP-4 inhibitors such as a methanesulfonamide **30** and acetamide **31** (DPP-4 IC_{50}'s = 7.1 nM and 8.6 nM, respectively).

The enhanced potency of polar electron donating and polar electron withdrawing substituents at the 5-position of the benz-

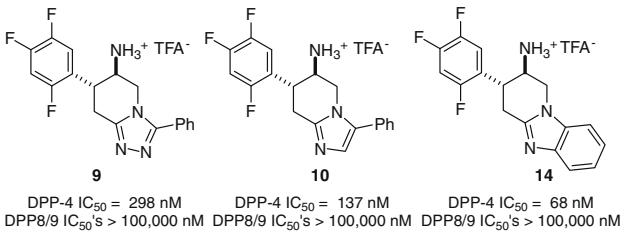


Figure 2. Aminopiperidine-fused heterocycle DPP-4 inhibitors.