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(3R,4S)-4-(2,4,5-Trifluorophenyl)-pyrrolidin-3-ylamine inhibitors of dipeptidyl peptidase IV: Synthesis, in vitro, in vivo, and X-ray crystallographic characterization

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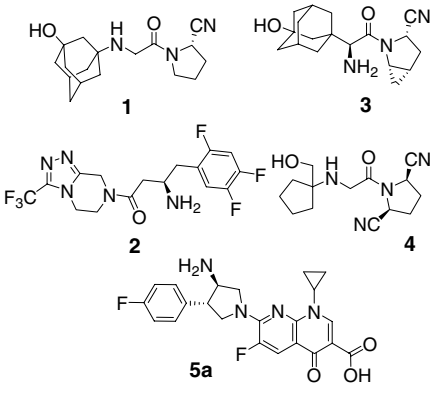
Abstract—A series of pyrrolidine based inhibitors of dipeptidyl peptidase IV were developed from a high throughput screening hit for the treatment of type 2 diabetes. Potency, selectivity, and pharmacokinetic properties were optimized resulting in the identification of a pre-clinical candidate for further profiling.

Type 2 diabetes is a severe and increasingly prevalent disease.[1] Diabetics may suffer debilitating cardiovascular, eye, kidney, and nerve damage and are at risk of premature handicap and death due to these and other diabetic complications, which are the result of glucose toxicity caused by their hyperglycemia. A progressive reduction in insulin sensitivity and insulin secretion are hallmarks of the disease, which eventually result in failure of the pancreatic islet cells and dependence on exogenous insulin. The incretin hormone glucagon-like peptide 1 (GLP-1) is a potent stimulator of endogenous insulin release. GLP-1 has beneficial effects on islet β-cell function and insulin sensitivity without induction of hypoglycemia.[2] Studies in rodents have indicated that GLP-1 may stop or reverse the loss of β-cell function.[3] Unfortunately, GLP-1 is rapidly degraded in vivo by the serine protease dipeptidyl peptidase IV (DPP4); therefore inhibition of DPP4 has emerged as a promising approach for the treatment of Type 2 diabetes.[4] This has been substantiated by the results of clinical trials of several inhibitors,[5] including vildagliptin **1** (LAF-237),[6] sitagliptin **2** (MK-0431),[7] and saxagliptin **3** (BMS-477118).[8]

We have previously reported our studies with the inhibitor **4** based on a *cis*-2,5-dicyanopyrrolidine template.[9] The quinolone **5a**, previously prepared as part of an antibacterial program, was identified in a high throughput screen of our corporate compound collection as an inhibitor of DPP4 (IC_{50} = 140 nM). We were intrigued by the unusual structure of **5a** and sought to determine whether it could be parlayed into a novel series of DPP4 inhibitors. This paper reports our discovery of a series of 3-amino-4-phenyl pyrrolidine inhibitors of DPP4.[10]



Keywords: DPPIV inhibitors; Diabetes; Structure-based design.
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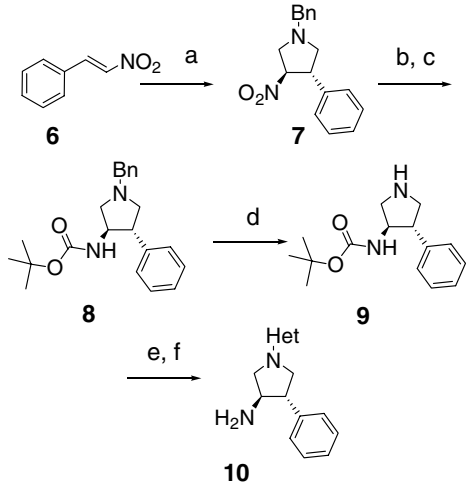
Substructure searching and screening quickly revealed key SAR information (Table 1): the *trans*-3,4-disubstituted pyrrolidine was more potent than the *cis* isomer, and enzyme inhibitory potency was critically dependent upon the substitution pattern of the phenyl ring.

We hypothesized that the *trans*-3-amino-4-phenyl pyrrolidine was the key pharmacophore, and docking experiments provided further support for this hypothesis. Recognizing that the quinolone fragment of **5** was undesirable,[11] we screened a variety of heterocycles as potential replacements for the quinolone fragment using the *trans*-3-amino-4-phenyl pyrrolidine scaffold. These compounds were prepared as racemates using the route shown in Scheme 1.

Nitrostyrene **6** was treated with the azomethine ylide generated from *N*-benzyl-*N*-(methoxy)methyl-*N*-trimethylsilylmethylamine to provide pyrrolidine (±)**7**.[12] Reduction of (±)**7** with hydrogen in the presence of Raney nickel was followed by protection with BOC anhydride to give (±)**8**. Subsequent debenzylation with hydrogen and Pd/C in acetic acid afforded (±)**9**, which was coupled with heteroaryl chlorides using parallel synthesis to provide (±)**10a**–**10m**. This effort identified the 6-phenylpyrimidine (±)**10a** as the best replacement for the quinolone, albeit with some loss of potency (Table 2).[13] Pharmacokinetic evaluation of (±)**10a** in the rat showed a correlation between clearance predicted from in vitro microsomal screens and in vivo clearance, and acceptable bioavailability (32%), suggesting that derivatives of (±)**10a** could be found that had acceptable pharmacokinetic properties.

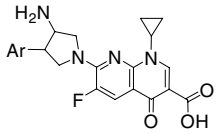


Scheme 1. Reagents and conditions: (a) *N*-benzyl-*N*-(methoxy)methyl-*N*-trimethylsilylmethylamine, TFA, CH_2Cl_2, 0 °C; (b) H_2, RaNi, MeOH–NH_3, 25 °C; (c) Boc_2O, Et_3N, THF, 25 °C; (d) H_2, Pd/C, EtOH, AcOH, 50 °C; (e) chloroheterocycle, *i*-Pr_2NEt, *t*-BuOH, 110 °C (microwave); (f) HCl, 1,4-dioxane, 25 °C.

Further improvement in potency was realized by the introduction of a 2,4,5-trifluorophenyl substitution pattern on the phenyl ring attached to the pyrrolidine 4-position.[14] The necessary 2,4,5-trifluorophenyl template ((±)**12**, Scheme 2) was prepared from **11** by the same sequence of reactions presented in Scheme 1.

Further SAR development was focused on the phenyl ring attached to the pyrimidine ring as shown in Scheme 3. Suzuki coupling of an appropriately substituted boronic acid with 4,6-dichloropyrimidine afforded the

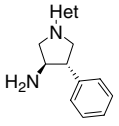
Table 1. Aryl substitution, pyrrolidine stereochemistry, and DPP4 enzyme inhibition assay results for compounds **5a**–**5k**



Compound	Ar	3-NH_2-4-Ar stereochemistry	DPP4 IC_{50}, nM[a]
5a	4-FC_6H_4	*trans*	140
5b	2-$CH_3OC_6H_4$	*cis*	2000
5c	2-$CH_3OC_6H_4$	*trans*	200
5d	C_6H_5	*trans*	150
5e	4-$H_2NC_6H_4$	*trans*	>3000
5f	4-*i*PrC_6H_4	*trans*	>3000
5g	4-$MeO_2CC_6H_4$	*trans*	>3000
5h	4-$CH_3OC_6H_4$	*trans*	>3000
5i	3,4-$Cl_2C_6H_4$	*trans*	1000
5j	4-Me_2NC6H_4	*trans*	>3000
5k	4-HOC_6H_4	*trans*	>3000

[a] Recombinant wild type human enzyme. Means of at least three experiments; standard deviations are ±15%. An IC_{50} of >3000 indicates that no curve was noted in the dose–response up to 3 μM; see Ref. 9.

Table 2. Heterocycle and DPP4 enzyme inhibition assay results for compounds **10a**–**10m**



Compound	Heterocycle	DPP4 IC_{50}, nM[a]
10a	6-Phenyl-pyrimidin-4-yl	790
10b	6-(3-Cyano)phenyl-pyrimidin-4-yl	1400
10c	6-(4-Methoxy)phenyl-pyrimidin-4-yl	2300
10d	6-(3-Chloro)phenyl-pyrimidin-4-yl	2900
10e	(3-Cyano)pyridin-2-yl	>3000
10f	6-(2-Chloro)phenyl-pyrimidin-4-yl	>3000
10g	6-Chloro-2-phenyl-pyrimidin-4-yl	>3000
10h	9-Methyl-9H-purin-6-yl	>3000
10i	6-(4-Hydroxy)phenyl-pyrimidin-4-yl	>3000
10j	6-(4-Chloro)phenyl-pyrimidin-4-yl	>3000
10k	(5-Acetyl)pyridin-2-yl	>3000
10l	1-Quinoxalin-2-yl	>3000
10m	1-Quinolin-2-yl	>3000

[a] Recombinant wild type human enzyme. Means of at least three experiments; standard deviations are ±15%. An IC_{50} of >3000 indicates that no curve was noted in the dose–response up to 3 μM; see Ref. 9.