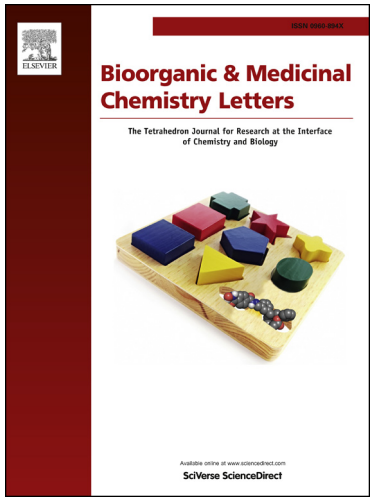

Novel tetrahydropyran analogs as dipeptidyl peptidase IV inhibitors: Profile of clinical candidate (2*R*,3*S*,5*R*)-2-(2,5-Difluorophenyl)-5-[2-(methylsulfonyl)-2,6-dihydropyrrolo[3,4-*c*]pyrazol-5(4*H*)-yl]tetrahydro-2*H*-pyran-3-amine (23)

Tesfaye Biftu, Xiaoxia Qian, Ping Chen, Dennis Feng, Giovanna Scapin, Ying-Duo Gao, Jason Cox, Ranabir Sinha Roy, George Eiermann, Huabing He, Kathy Lyons, Gino Salituro, Sangita Patel, Alexander Petrov, Feng Xu, Shiyao Sherrie Xu, Bei Zhang, Charles Caldwell, Joseph K. Wu, Kathy Lyons, Ann E. Weber

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Novel tetrahydropyran analogs as dipeptidyl peptidase 4 inhibitors: Profile of clinical candidate (2*R*,3*S*,5*R*)-2-(2,5-Difluorophenyl)-5-[2-(methylsulfonyl)-2,6-dihydropyrrolo[3,4-*c*]pyrazol-5(4*H*)-yl]tetrahydro-2*H*-pyran-3-amine (23)

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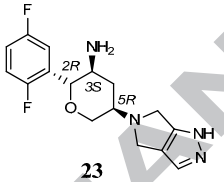

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Novel tetrahydropyran analogs as dipeptidyl peptidase IV inhibitors: Profile of clinical candidate (2*R*,3*S*,5*R*)-2-(2,5-Difluorophenyl)-5-[2-(methylsulfonyl)-2,6-dihydropyrrolo[3,4-*c*]pyrazol-5(4*H*)-yl]tetrahydro-2*H*-pyran-3-amine (23)

Tesfaye Biftu[a], Xiaoxia Qian[a], Ping Chen[a], Dennis Feng[a], Giovanna Scapin[b], Ying-Duo Gao[c], Jason Cox[a], Ranabir Sinha Roy[d],George Eiermann[d], Huabing He[e], Kathy Lyons[e], Gino Salituro[e], Sangita Patel[b], Alexander Petrov[d], Feng Xu[f], Shiyao Sherrie Xu[e], Bei Zhang[d], Charles Caldwell[a], Joseph K. Wu[d], Kathy Lyons[e], and Ann E. Weber[a]

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ABSTRACT

A series of novel *tri*-2,3,5-substituted tetrahydropyran analogs were synthesized and evaluated as inhibitors of dipeptidyl peptidase 4 (DPP-4) for the treatment of type 2 diabetes. Optimization of the series provided inhibitors with good DPP-4 potency and selectivity over other peptidases (QPP, DPP8, and FAP). Compound **23**, which is very potent, selective, efficacious in the diabetes PD model, and has an excellent pharmacokinetic profile, is selected as a clinical candidate.

Type 2 diabetes mellitus is a growing epidemic affecting approximately 220 million people worldwide.[1] Commercial proof of concept for DPP-4 inhibitors has been established with sitagliptin, Merck's lead DPP-4 inhibitor (**1**), which was the first DPP-4 inhibitor approved by the FDA in October 2006. Subsequently, additional DPP4i have entered the market. These include vildagliptin (**2**), saxagliptin (**3**), linagliptin (**4**) and alogliptin (**5**).

DPP-4 inhibitors prolong the circulating half-life of glucagon-like peptide 1 (GLP-1) and glucose-dependant insulinotropic polypeptide (GIP),[2] incretin hormones that stimulate insulin secretion in a glucose-dependent manner. Additionally, GLP-1 has been shown to inhibit glucagon release, decrease gastric emptying, and promote the regeneration and differentiation of islet β-cells.[3] By increasing the circulating concentration GLP-1 and GIP, DPP-4 inhibitors improve glucose control in patients with type 2 diabetes.

Given the clinical success of sitagliptin (**1**), our laboratories have been interested in generating structurally diverse, best-in-class DPP-4 inhibitors. Over the course of our studies, several lead classes have evolved. Critical to this work

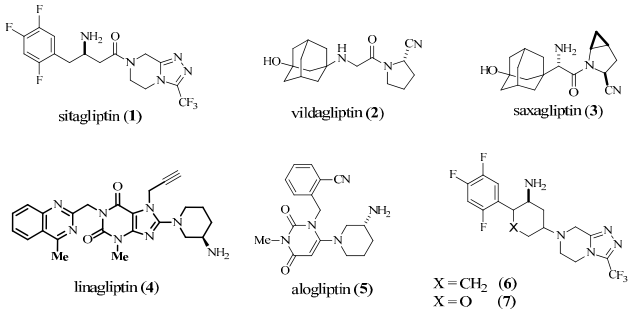


Figure 1. DPP-4 Inhibitors

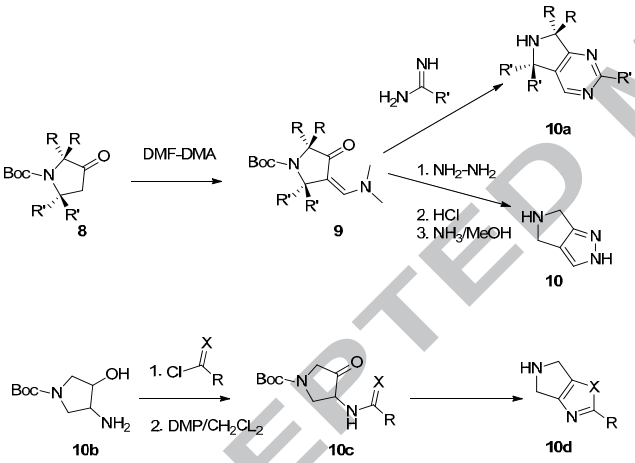
was the development of cyclohexylamine (**6**),[4] a structurally distinct rigid analog of sitagliptin (**1**). The cyclohexylamine analogs are potent and selective against other related proteases with excellent pharmacokinetic profiles; however, they block the human potassium channel hERG at low micromolar concentrations, resulting in QTc prolongation in a cardiovascular dog model (CV-dog).[5] The current tetrahydropyran (**23**) analogs have reduced basicity compared to the cyclohexylamines, and

thereby reduced hERG potency. In addition, they do not affect QTc (a measure of the time between the start of the **Q wave** and the end of the **T wave** in the heart's electrical cycle) prolongation in the cardiovascular (CV)-dog model**.** Following systematic Structure-activity-studies, tetrahydropyran (**23a**) was selected as a clinical candidate. In this paper, we describe the discovery, synthesis, SAR studies, and pharmacokinetic properties of the clinical candidate **23a**.

The synthesis of tetrahyrdopyran analogs (**23**) depicted in this manuscript is illustrated in Schemes 1-3.

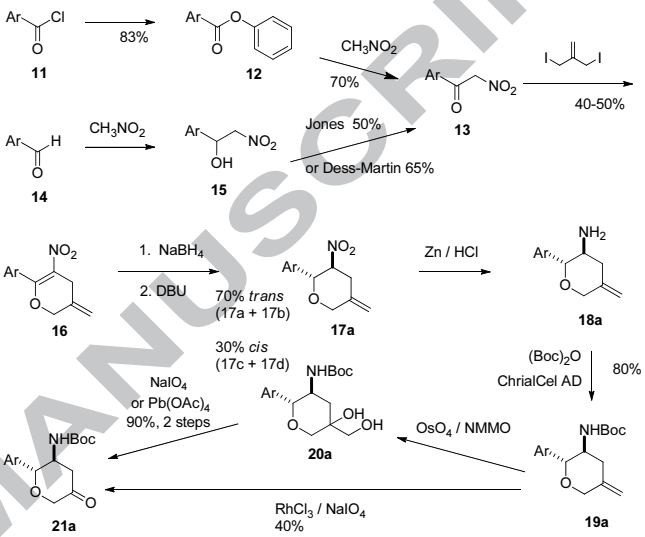
The pyrrolopyrazole intermediate **10** (Scheme 1) was made from the commercially available Boc-protected ketone **8**. Stirring a mixture of neat *N,N*-dimethylformamide dimethyl acetal (DMF-DMA) and ketone **8** gave the enamine **9.** Heating enamine **9** with hydrazine and ethanol under pressure followed by dehydration by treatment with hydrogen chloride in dry ethyl acetate gave the salt of the desired pyrrolopyrazole **10**. Upon neutralization with aqueous ammonium hydroxide, the free base pyrrolopyrazole **10** was obtained. The pyrrolopyrimidines **10a** were prepared from *gem*-dimethyl substituted **8** and substituted amidines in a similar manner. The other heterocycles **10d** used to prepare analogs **23** were prepared from pyrrolidine **10b**, by acylation to form intermediates **10c** and final cyclization to the desired heterocycle **10d.**

Scheme 1. Synthesis of pyrrolopyrazole



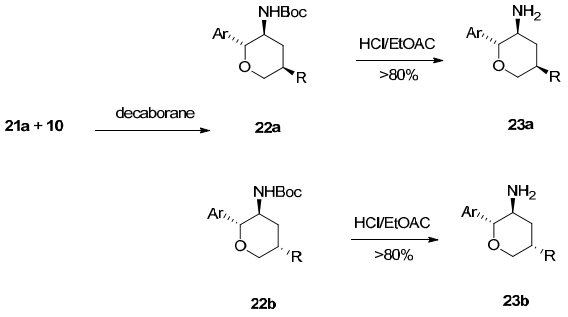
The synthesis of tetrahydropyranone intermediate **21a** is illustrated in Scheme 2. Substituted benzoyl halide **11** was treated with phenol in the presence of *N,N*-diisopropylethylamine to form the ester **12**. Treatment of **12** with the anion generated from nitromethane using sodium hydride gave the nitroketone **13**. Alternatively, the nitroketone **13** was made by reacting aldehyde **14** with nitromethane in the presence of catalytic amount of sodium hydroxide as a base and oxidizing the resulting nitroalcohol **15** with Jones or Dess-Martin reagent. Heating the nitroketone **13** with 3-iodo-2-(iodomethyl)prop-1-ene gave the pyran **16**, which was reduced with sodium borohydride to provide a mixture of *trans* and *cis* pyrans **17a/17b** and **17c/17d**, respectively. Separation of the *cis* and *trans* isomers was carried on a silica column by using gradient elution with ethyl acetate (0-36%) in hexane. The *trans* isomer is the less polar diastereoisomer. **17c/17d** could be isomerized to **17a/17b** by stirring a methanol solution in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). The enantiomers of **17a/17b** and **17c/17d** were separated by HPLC using a chiral column (Chiralpak 1A, hexane/ethanol 90:10). The nitro-substituted pyran **17a** was then reduced using zinc and hydrochloric acid, and the resulting amine **18a** was protected as its BOC derivative by treatment with di-*tert*-butyl dicarbonate to give **19a**. Treatment of **19a** with osmium tetroxide and *N*-methylmorpholine *N*-oxide gave the diol **20a,** which upon further treatment with sodium periodate or lead tetraacetate gave ketone **21a**. The desired ketone **21a** could alternatively be made directly from **19a** by treatment with ruthenium chloride and sodium periodate. All the other isomers **21b**, **21c** and **21d** were made from **17b**, **17c** and **17d** by a similar method.

Scheme 2. Synthetic of tetrahydropyranone



Reductive amination of tetrahydropyranone **21a** with pyrrolopyrazole **10** in the presence of decaborane in methanol gave intermediate **22a** as the major product and **22b** as the minor product**.** Separation of the two isomers was carried out on a silica column by eluting with ethanol (8.5% containing 10% ammonium hydroxide) in hexane. Deprotection with hydrogen chloride in dry ethyl acetate gave **23a** and its other diastereoisomer **23b**, respectively. The other six isomers of **23** were made from ketones **21b**, **21c** and **21d** by using a similar method. Other analogs of **23** were also made in a similar manner from their respective heterocyclic amines. The relative configurations of *trans*-isomers **21a/21b** and *cis*-isomers **21c/21d** were confirmed by NMR spectroscopy. The absolute configurations of each enantiomers **21a-d** were determined by Vibrational Circular Dichroism (VCD) spectroscopy and confirmed by x-ray crystallography of **23w**.

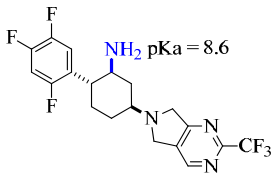
Scheme 3. Synthesis of tetrahydropyran DPP-4 Inhibitors



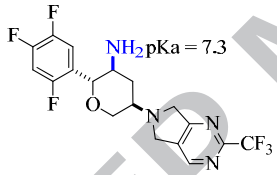
Compounds **23a-w** were examined for their *in vitro* inhibition of human DPP-4 and related enzymes[6] such as QPP,[7] DPP8,[8] and FAP.[9] Inhibition of DPP8 and DPP9[10] has been associated with toxicity in preclinical species.[11] While the relevance of this toxicity to humans is not known, it is of particular importance to avoid DPP8/9 off target activity. DPP9 inhibition typically tracks closely with DPP8 and thus was not reported for this series. The compounds were also evaluated in the hERG (human-Ether-a-go-go Related Gene) assay.

The cyclohexyamine analog **6a** reported in our earlier publications has excellent DPP-4 inhibition activity (IC_{50} = 0.5 nM). However selectivity against IKr (IC_{50} = 4.8 µM) was below the desired standard (IC_{50} > 30µM). In addition, in the CV-dog model, **6a** was found to prolong QTc (>5% at 3 mpk). Replacement of the cyclohexylamine with tetrahydropyran (e.g. **23i** and **23j**) reduced the pKa of the primary amine from 8.6 to 7.3 and the hERG selectivity improved accordingly (IC_{50} = 23µM and >30µM, respectively). In addition, pyrans **23i** and **23j** are devoid of any QTc prolongation in the CV dog at doses up to 30 mg/kg. However, we noticed **23j** was unstable and observed undesirable circulating **23k** upon dosing **23j** in both rats (~50%) and dogs (~30%). The metabolite **23k** has weaker potency in DPP4 (140 nM) and reduced selectivity against related proteases, QPP (IC_{50} = 160 nM).

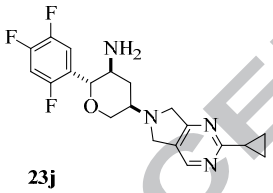
Figure 2. Attempts to reduce IKr activity and improve metabolic stability



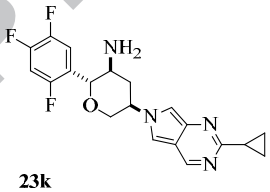
6a
DPP-4 IC_{50} = 0.5 nM
hERG IC_{50} = 4.8 µM



23i
DPP-4 IC_{50} = 1.3 nM
hERG IC_{50} = 23 µM



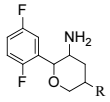
23j
DPP-4 IC_{50} = 0.66 nM
hERG IC_{50} > 30uM
QPP IC_{50} = 19,000 nM

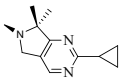
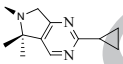
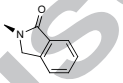
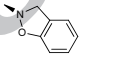


23k
DPP-4 IC50 = 140 nM
QPP IC_{50} = 160 nM

Several attempts were made to circumvent the metabolism on the right hand side amine. The tetrahydropyran analog **23l** has the same left hand heterocycle (triazolopiperazine) as sitagliptin. However, in the DPP-4 enzyme assay, its potency is lower (34 nM) than sitagliptin (18 nM). Attempts to block the oxidation sites with *gem*-dimethyl groups as shown for **23m** and **23n** gave compounds with much reduced potency. Introduction of lactam **23o** or other 5-member rings such as the iso-oxazole **23p** resulted in much reduced potency.

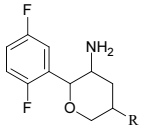
Table 1. Blocking the site of metabolism

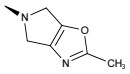
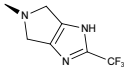
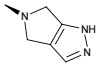


Compd	R	IC_{50} (nM) DPP-4	QPP	DPP8	FAP
23l		37	>100,000	>100,000	100,000
23m		27	15,000	>100,000	75,000
23n		12,600	3,900	>100,000	>100,000
23o		720	>100,000	>100,000	>100,000
23p		125	65,000	39,000	>100,000

We then considered evaluation of several 5,5-heterocycles. Pyrrolooxazole **23q** is less potent. Pyrroloimidazole **23r** has good potency, but selectivity against DPP-8 is poor. However, pyrrolopyrazole **23** gave compounds with good potency and selectivity. In addition, **23** was found to be stable and no oxidation product was observed when dosed to rats or dogs.

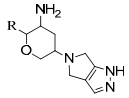
Table 2. Replacement of various heterocycles



Compd	R	IC_{50} (nM) DPP-4	QPP	DPP8	FAP
23q		11	>100,000	>100,000	>100000
23r		1.6	>100,000	220	>100,000
23		1.4	34,000	>100,000	22,000

Replacement of the left hand side diflurophenyl group of **23a** with other substituents **23s-23v** resulted in reduced potency. The trifluoro analog **23w** has comparable DPP-4i activity to **23a,** however, selectivity against FAP is lower.

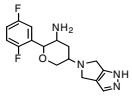
Table 4. Replacement of the Left-Hand-Side

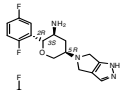
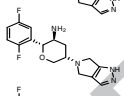
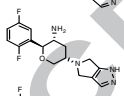
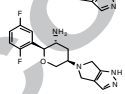
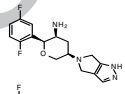
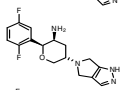
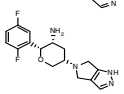
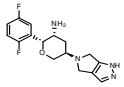


Compd	R	IC$_{50}$ (nM) DPP-4	QPP	DPP8	FAP
23s		64	>100,000	>100,000	>100000
23t		27	70,000	>100,000	>100,000
23u		48	11,000	>100,000	>100,000
23v		37	>100,000	50,000	>100,000
23w		1.0	38,0000	>100,000	6,400

Since the best analog in the series **23** has three chiral centers, all the possible eight stereoisomers were made and evaluated in the DPP-4 and counter assays. As shown in Table 5, the *2R, 3S, 5R* isomer is found to be the most potent isomer while the *2R, 3R, 5R* isomer is the least potent (>100,000 nM). In general, the order of potency is as follows: *3S>3R; 3,5 cis > 3,5 trans* and *2,3 trans > 2,3 cis.*

Table 5. Activities of Stereoisomers of 2,3,5-substituted Tetrahydropyrans



Compd	R	IC$_{50}$ (nM)* DPP-4	QPP	DPP8	FAP
23		1.4	42,000	>100,000	>100,000
23b		56	6,600	45,800	>100,000
23c		24,400	>100,000	>100,000	>100,000
23d		38,000	100,000	28,000	100,000
23e		2,800	>100,000	>100,000	>100,000
23f		26,600	>100,000	>100,000	>100000
23g		13,100	15,400	>100000	51000
23h		>100,000	>100000	>100000	>100000

*Purity of each isomer is >99.0%. Activity could be affected by minor impurity

The best analog in this series**, 23** was evaluated at Panlabs and in-house for off-target interactions including hERG potassium channel, Cav1.2 channel, and various P450 enzyme (Cyps) activities and found to be inactive.

The pharmacokinetic profile of DPP-4i **23** was determined in rat, dog and rhesus monkey (Table 6). This compound displayed a low clearance (2.7 to 9.7 mL/min/kg), long half-life (6.3 to 13 h), and excellent bioavailability (70 to 83%).

Table 6. Mean pharmacokinetic parameters of **23** in nonclinical species

Parameter[a]	**Rat**	**Dog**	**Rhesus**
Dose IV/P.O. (mg/kg)	1/2	1/2	1/2
Cl (mL/min/kg)[b]	9.7	2.7	5.2
Vd_{ss} (L/kg)	4.9	3.0	4.2
$T_{1/2}$ (hr)	6.3	13	9.7
C_{max} (μM)	0.800	1.92	1.48
T_{max} (hr)	0.5	3.5	1.1
F_{oral} (%)	70	83	72
nAUC (μM•hr/(mg/kg))	3.72	16.1	7.33

[a]*Blood clearance in the mouse, plasma clearance in the rat, dog and monkey.*

[b]*Cl, clearance; Vd_{ss}, volume of distribution at steady state; $T_{1/2}$, terminal half-life; C_{max}, maximum plasma concentration following oral dosing; T_{max}, time to maximum concentration; F_{oral}, oral bioavailability; nAUC, dose-normalized area under the plasma concentration vs. time curve following oral dosing. Pharmacokinetic parameters were obtained following administration of the free base in ethanol:water (5:95; v/v) to rats, and the di-hydrochloride salt in saline to mice, beagle dogs and rhesus monkeys.*

The lead candidate **23** was assessed for its ability to improve glucose tolerance in lean mice. In lean animals, **23**, orally administered 1 hour prior to dextrose challenge in an oral glucose tolerance test (OGTT), significantly reduced blood glucose excursion in a dose-dependent manner from 0.1 mg/kg (27% reduction in glucose AUC) to 3 mg/kg (47% reduction).

The efficacy of glucose lowering in this model was comparable to that achieved with sitagliptin. In the corresponding pharmacodynamic (PD) assay, **23**-mediated DPP-4 inhibition and plasma compound concentrations were dose-dependent 10 minutes following dextrose challenge. At the 0.3 mg/kg dosage, plasma DPP-4 activity was inhibited by >80%, the targeted inhibition associated with maximal glucose lowering efficacy, with a corresponding plasma concentration of 260 nM. The administration of **23** also dose-dependently increased plasma concentrations of active GLP-1 in this assay with the maximal increase observed at the 1 mg/kg dosage. The augmentation of active GLP-1 levels achieved at these dosages (up to 4-fold) was similar to the elevation in circulating hormone observed in DPP-4–deficient (*Dpp4*$^{-/-}$) mice[12] (3-8-fold) relative to wild type animals.

The effect of DPP-4i **23** on blood glucose during an OGTT was investigated in DPP-4 deficient and comparably aged wild type lean mice. **23** administered at 3 mg/kg, 1 hour prior to dextrose challenge, significantly inhibited blood glucose excursion by 53% in the control lean mice. In contrast, the administration of **23** at 3 mg/kg did not significantly inhibit blood glucose excursion compared to vehicle controls in the DPP-4 deficient mice.

In summary, we have discovered a series of structurally diverse tetrahydropyrans that are potent and selective DPP-4 inhibitors. The optimal side-chain for this series was determined to be a tetrahydropyrrolopyrazole. Compound **23** is a potent, selective DPP-4 inhibitor with an excellent pharmacokinetic profile, and efficacy in an oral glucose tolerance test in mice, and emerged as the lead clinical candidate.

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Novel tetrahydropyran analogs as dipeptidyl peptidase 4 inhibitors: Profile of clinical candidate (2*R*,3*S*,5*R*)-2-(2,5-Difluorophenyl)-5-[2-(methylsulfonyl)-2,6-dihydropyrrolo[3,4-*c*]pyrazol-5(4*H*)-yl]tetrahydro-2*H*-pyran-3-amine (23)

Tesfaye Biftu, Xiaoxia Qian, Ping Chen, Dennis Feng, Giovanni Scapin, Ping Liu, Ashvani Kamath, Sinha Roy, George Eiermann, Huabing He, Kathy Lyons, Gino Salituro, Sangita Patel, Alexander Petrov, Feng Xu, Shiyao Sherrie Xu, Bei Zhang, Charles Caldwell, Joseph K. Wu, and Ann E. Weber

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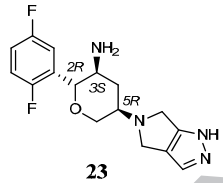

23

A series of novel *tri*-2,3,5-substituted tetrahydropyran analogs were synthesized and evaluated as inhibitors of dipeptidyl peptidase 4 (DPP-4) for the treatment of type 2 diabetes. Optimization of the series provided inhibitors with good DPP-4 potency and selectivity over other peptidases (QPP, DPP8, and FAP). Compound **23**, which is very potent, selective, efficacious in the diabetes PD model, and has an excellent pharmacokinetic profile, is selected as a clinical candidate.