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2-Cyano-4-fluoro-1-thiovalylpyrrolidine analogues as potent inhibitors of DPP-IV

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Abstract—We report the synthesis and biological activity of a series of 2-cyano-4-fluoro-1-thiovalylpyrrolidine inhibitors of DPP-IV. Within this series, compound **19** provided a potent, selective, and orally active DPP-IV inhibitor which demonstrated a very long duration of action in both rat and dog.

Dipeptidyl peptidase IV (DPP-IV), also known as T-cell antigen CD26, first identified in 1966,[1] is a widely expressed serine exopeptidase. It has been shown to have several functions in humans. First, it contributes to extracellular matrix binding.[2] Second, it functions as an adenosine deaminase (ADA)-binding protein[3] and third, it exhibits post-proline or alanine cleaving properties from oligo or polypeptides at the N-terminus.[4] It has also been shown to inactivate two important incretins, glucagon-like peptide 1 (GLP-1) and glucose-dependent inhibitory polypeptide (GIP).[5] Both of these incretins act as glucose-dependent secretagogues upon meal ingestion. However, in the presence of DPP-IV both of them are rapidly inactivated.[5] Previous studies have shown that in patients with type 2 diabetes, GLP-1 remains strongly insulinotropic even though its secretion levels are reduced relative to non-diabetic subjects.[6] However, GIP's insulinotropic effect is less if not absent even though its secretion levels are normal or slightly below normal.[7] GLP-1's strong insulinotropic effect, but poor pharmacokinetic profile, has led several companies to identify GLP-1 agonists that are resistant to degradation by DPP-IV. Several of these have now been shown to be clinically efficacious.[8] However, all of these agonists need to be dosed either s.c. or i.v. Some adverse events have also been noted (e.g., nausea).

An indirect approach to harnessing the antihyperglycemic properties of GLP-1 is to inhibit DPP-IV, thus increasing the $t_{1/2}$ of native protein in vivo. Indeed, numerous small molecule DPP-IV inhibitors have now been reported[9] and more importantly several of them have achieved a positive proof-of-concept within a

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clinical setting. Among these are P32/98 from Probiodrug,[10] LAF-237 from Novartis,[11] BMS-477118 from Bristol-Myers Squibb,[12] and MK-0431 from Merck & Co. (Fig. 1).[13]

The C2 nitrile moiety found on the P1 pyrrolidine ring on a number of reported DPP-IV inhibitors not only forms a key interaction with the catalytic serine 630, but also in combination with the P2 basic amine can undergo an intramolecular cyclization reaction to form a cyclic amidine which can subsequently get hydrolyzed to form a diketopiperazine.[14] In this same report, it was shown that steric bulk appropriately placed on the P2 fragment can slow this cyclization. Another report has shown that a cyclopropyl ring fused on the P1 pyrrolidine ring can also slow this cyclization.[15] An obvious solution to this problem would be to remove the nitrile moiety. Unfortunately in so doing one usually loses a significant amount of potency versus DPP-IV,[16] although there have been several reports recently of P1 pyrrolidine containing DPP-IV inhibitors that lack the nitrile yet retain good potency versus DPP-IV.[17] We report herein a series of 2-cyano-4-fluoro-1-thiovalylpyrrolidine inhibitors of DPP-IV. The main focus of this work centered on the P2 fragment and blocking groups to slow the cyclization as noted above. However, some interesting properties were also noted by incorporation of a C4 fluoro substituent on the pyrrolidine ring (see Table 3 for additional information).

The synthesis into these compounds started with either the known 4-fluoropyrrolidine carboxylate **2**[18] or a modified procedure to make the known 2-cyanopyrrolidine **5**.[16] Hydrolysis of esters **1** and **2** generated the corresponding acids, which were then converted to the primary carboxamides **3** and **4** by first generating the mixed anhydride via di-*t*-butyldicarbonate (BOC_2O) and then reacting with ammonium bicarbonate. The carboxamides **3** and **4** were then dehydrated with $POCl_3$ followed by removal of the BOC-protecting group with *p*-toluenesulfonic acid to give amines **5** and **6** (Scheme 1).

The amino acid portion of the molecule was generated by starting with the commercially available D-penicillamine **7**. A general synthetic route to afford the final desired compounds is described in Scheme 2. Initially the

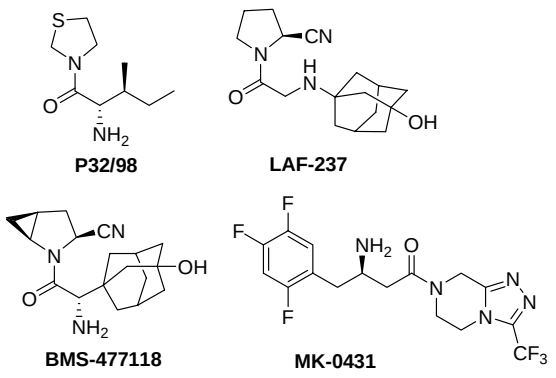
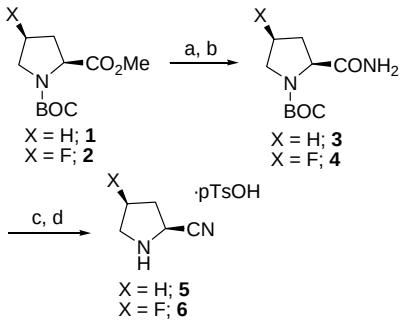
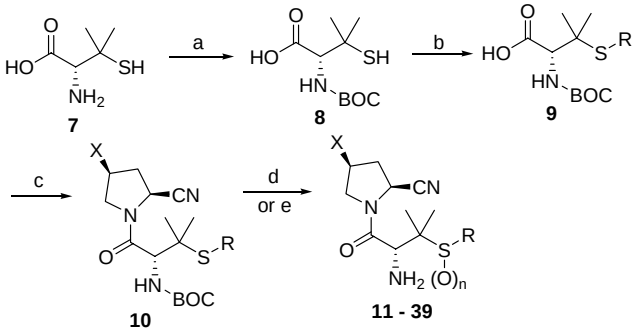


Figure 1.



Scheme 1. Reagents and conditions: (a) dioxane, H_2O, $LiOHH_2O$; (b) CH_3CN, BOC_2O, NH_4HCO_3; (c) pyridine, imidazole, $POCl_3$, 0 °C; (d) CH_3CN, pTsOH.

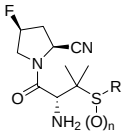


Scheme 2. Reagents and conditions: (a) THF, KOH, BOC_2O; (b) 1 N NaOH, H_2O, RBr or RCl; (c) DMF, HATU, *i*-Pr_2NEt, **5** or **6**; (d) CH_2Cl_2, TFA or HCl, dioxane; (e) MeOH, $NaIO_4$ or mCPBA, CH_2Cl_2; step d.

amino acid was protected as the *t*-butyl carbamate with BOC_2O under basic conditions to generate acid **8**. The acid was then alkylated again under basic conditions with either the requisite alkyl bromide or chloride to give sulfide **9**. The acid was then coupled to either amine **5** or **6** utilizing HATU as the coupling agent in DMF to afford the amide **10**. The sulfide was then directly deprotected with TFA or HCl to yield final amine or alternatively, the sulfur was oxidized to give either the sulfoxide (sodium periodate, MeOH) or the sulfone (mCPBA, CH_2Cl_2) followed by deprotection as before, yielding final products **11**–**39** (Scheme 2).

The data shown in Table 1 compare the in vitro selectivity of these inhibitors versus DPP-IV, DPP-II, and seprase.[19] Most of the compounds showed very weak inhibitory activity against both DPP-II and seprase. The selectivity versus seprase is especially noteworthy, given the fact that seprase has been shown to have the highest degree of identity to DPP-IV.[20] Initially benzyl derivatives at either the sulfide or sulfone oxidation state in the P2 moiety were examined. In general, the functionality placed on the phenyl ring produced very little variation in the potency against DPP-IV. However, compounds **13**, **18**–**19**, **24**, and **26** did demonstrate sub 100 nM potency versus DPP-IV. Comparison of compounds **17**, **19**, and **23** to **34**, **30**, and **27**, respectively, demonstrated a drop in potency against DPP-IV upon oxidation of the sulfide to the sulfone. Extending the

Table 1. Inhibition and selectivity properties for compounds **11–39**



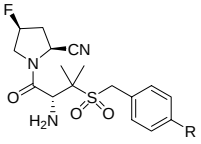
Compound	*n*	R	K_i (nM)[a]		
			DPP-IV	DPP-II	Seprase
11	2	CH_2Ph	324	>22385	>23440
12	2	CH_2-4-F-Ph	281	>22385	>23440
13	2	CH_2-4-CN-Ph	68	>22385	9450
14	2	CH_2-4-Me-Ph	530	>22385	>23440
15	2	CH_2-4-Ph-Ph	579	>22385	9660
16	2	CH_2-4-OBn-Ph	428	>22385	20395
17	2	CH_2-3-OPh-Ph	310	>22385	6863
18	2	CH_2-4-SO_2Me-Ph	76	17258	>23440
19	2	CH_2-4-OMe-Ph	53	>22385	>23440
20	2	CH_2-3-OMe-Ph	316	>22385	16980
21	2	CH_2-2-OMe-Ph	309	>22385	12380
22	2	CH_2-4-NHCOMe-Ph	225	>22385	7925
23	2	CH_2-4-Pyridyl	1278	>22385	>23440
24	2	CH_2-4-Thiadiazole-Ph	74	>22385	3656
25	2	OH	154	>22385	14639
26	2	CH_2-5-Cl-3-Benzothiophenesulfone	40	>22385	5158
27	0	CH_2-4-Pyridyl	33	>22385	9660
28	0	CH_2-2-Pyridyl	12	>22385	19076
29	0	CH_2-3-Pyridyl	18	>22385	>23440
30	0	CH_2-4-OMe-Ph	29	3949	>23440
31	1	CH_2-4-OMe-Ph[b]	112	>22385	>23440
32	0	CH_2-4-CF_3-Ph	63	1127	>23440
33	0	CH_2NHCOMe[c]	46	>22385	1276
34	0	CH_2-3-OPh-Ph	65	1066	12845
35	0	CH_2-2,3-Benzoxadiazole	40	>22385	>23440
36	0	$(CH_2)_2$Ph	56	14421	>23440
37	0	$(CH_2)_3$Ph	24	523	12176
38	0	$(CH_2)_3$-4-F-Ph	45	701	15776
39	2	$(CH_2)_3$Ph	302	>22385	>23440

[a] The K_i was calculated from the equation $K_i = IC_{50}/(1+S/K_m)$, where S is the substrate concentration.
[b] Mixture of diastereomers.
[c] The BOC protected amino acid used to synthesize this compound was commercially available.

chain length resulted in no change in DPP-IV potency (**11** vs. **39**). However, as was noted with other compounds, oxidation of the chain extended analogue **37** to give **39** lowered potency by approximately 12-fold against DPP-IV. Most of the sulfone analogues showed very poor or no inhibition versus DPP-II. However, DPP-II activity was noted for some, but not all, of the sulfide compounds (e.g., **30**, **32**, and **34**).

The sulfonic acid **25** was also made and showed moderate potency versus DPP-IV, but good to moderate selectivity, respectively, against both DPP-II and seprase. In vivo pharmacokinetic experiments revealed that the compounds containing the sulfide moiety were rapidly oxidized to a mixture of sulfoxide and sulfone (data not shown). Therefore, further compound progression focused on several of the sulfone compounds. Compounds **13**, **18**, and **19** were orally dosed in both rat and dog to determine their duration of action. As seen in Table 2, compound **19** turned out to have the longest duration in both rat and dog (84% DPP-IV inhibition at 1 mpk in rat at 6 h and >12 h above the IC_{50} at 0.2 mpk in dog). Interestingly, we also found that incorporation of a fluorine atom at C4 on the pyrrolidine ring imparted unexpected differences in the pharmacological

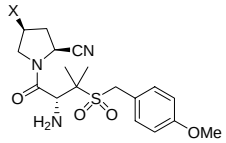
Table 2. In vivo properties for select compounds



Compound	R	% *I* in rat at 6 h at 1 mpk	Hours above IC_{50} at 0.2 mpk p.o. dog
13	CN	69	10[a]
18	SO_2Me	68[b]	7.8
19	OMe	84	>12

[a] GI toxicity was seen in the dog when orally dosed at 10 mpk.
[b] Poor %*F* (<5%) was seen upon oral dosing in the rat.

Table 3. Pharmacological differences between compounds **19** and **40**



19, X = F
40, X = H

	Compound **19**	Compound **40**
K_i (nM)	53	115
DPP-IV inhibition at 6 h 1 mpk rat	84%	62%
Hours above IC_{50} at 0.2 mpk dog	>12	7
IC_{50} vs P450's	>15 μM	>15 μM
Selectivity ratio versus DPP-II	>422	>195
Selectivity ratio versus seprase	>442	>204
$t_{1/2}$ (h)	2.3 (r), 3.9 (d)	4.2 (r), 3.0 (d)
% *F*	32 (r), 80 (d)	4.0 (r), 100 (d)
$t_{1/2}$ offset	87 min	41 min
$t_{1/2}$ cyclization at 37 °C pH 7.2	1733 h	360 h

properties of compound **19**. A recent report has also noted differences in potency and in vivo drug levels when comparing a 2-cyano-4-fluoropyrrolidine derivative to its des-fluoro counterpart. However, no other differences were noted in this report.[21] Table 3 demonstrates some of the observed differences in compound **19** versus the des-fluoro analogue, compound **40**.

As can be seen in Table 3, compound **19** was more potent than compound **40**. It had a longer duration of action in both rat and dog, which in part might be a result of the differences seen in the $t_{1/2}$ offset values (87 min vs. 41 min). Its pharmacokinetic properties were better, as was its stability toward intramolecular cyclization. Both compounds were very selective against DPP-II, seprase, and P450's. Addition of the *gem*-dimethyl group significantly added to the stability of compound **19** toward cyclization as the compound lacking this moiety had a $t_{1/2}$ cyclization of 80 h (compound not shown). In conclusion, we have identified a series of 2-cyano-4-fluoro-1-thiovalylpyrrolidine inhibitors of DPP-IV. The most promising compound within this series was compound **19** which demonstrated a good inhibitory, selectivity, and pharmacokinetic profile toward DPP-IV.

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