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Aminomethylpyridines as DPP-IV inhibitors

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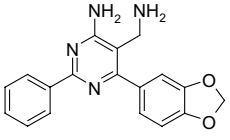
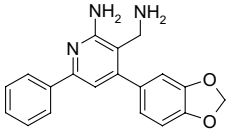
Abstract—In a novel series of DPP-IV inhibitors, a large increase of inhibitory activity was achieved by optimisation of aromatic substituents and conformational restriction.

Glucagon-like peptide 1 (GLP-1) has recently attracted attention as a new target for the treatment of type 2 diabetes.[1] GLP-1 is secreted by the gastrointestinal tract in response to food intake to stimulate insulin secretion.[2] Elevated levels of GLP-1 lead to an increased insulin release and an improved glycaemic control in type 2 diabetic patients.[3] The level of circulating GLP-1 can be increased by inhibition of dipeptidyl peptidase IV (DPP-IV),[4] which is responsible for the rapid degradation of this hormone.[5] Consequently, DPP-IV inhibitors have been explored as potential new medicines.[6]

In a search for novel DPP-IV inhibitors, we identified aminomethylpyrimidine **1** in a high-throughput screen. As part of an evaluation of this screening hit, we prepared **2a** as a pyridine analogue of **1**. Similar to **1**, **2a** was found to be a weak inhibitor of DPP-IV.[7]



1
HTS hit, IC_{50} = 10μM

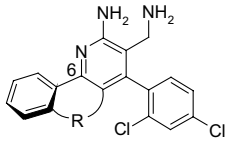


2a
IC_{50} = 47μM

To improve the weak inhibitory activity of **2a**, we prepared a number of derivatives **2b**–**k**. The replacement of the piperonyl substituent of **1** by a 2,4-dichlorophenyl substituent has led to a large activity increase in the pyrimidine series.[8] The structural similarity between the pyrimidine and the pyridine series prompted us to prepare the corresponding dichlorophenyl-pyridine **2b** (Table 1). As anticipated, **2b** was about 50-fold more active than **2a**.

Rotational restriction was explored as a possibility of further optimisation. The 6-phenyl–pyridine bond of **2b** can be locked by the introduction of an alkylidene tether R (Table 1, **2c**–**e**). The torsional minimum of the phenyl–pyridine bond, as calculated by the program Moloc (MAB force field),[9] depends on the length of the tether R, with shorter tethers leading to smaller angles. Locking the torsion to smaller angles led to increasingly active compounds, from **2c** over **2d** to **2e**, with indenopyridine **2e** being three orders of magnitude more active than **2a**.

Table 1. Effect of conformational restriction on the inhibitory activities of **2**



	R	Torsion[a]	IC_{50} (μM)
2b	H, H		0.92
2c	$(CH_2)_3$	32°	0.24
2d	$(CH_2)_2$	22°	0.045
2e	CH_2	0°	0.039

[a] 6-Ph–pyridine bond, calculated torsion.

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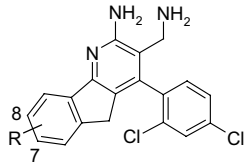
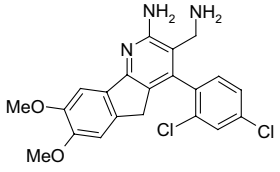
Table 2. Influence of single substituents on the inhibitory activities of indenopyridines



	R	IC_{50} (μM)
2f	7-MeO	0.082
2g	7-F	0.19
2h	7-Br	0.91
2i	8-MeO	0.13
2j	8-Me	0.28

Compound **2e** was further derivatised to investigate the influence of substitution on its inhibitory activity. The introduction of small single substituents into the 7- or 8-position gave generally less active compounds (**2f–j**, Table 2). For instance, a 7-MeO or a 8-MeO substituent caused a 2-fold (**2f** vs **2e**) or a 3-fold (**2i** vs **2e**) drop in activity, respectively. Surprisingly, a combination of the seemingly unfavourable 7-MeO and 8-MeO substituents in one molecule resulted in an improved, low nanomolar inhibitor, **2k**.



2k
IC_{50} = 0.007μM

Aminomethylpyridines **2** were accessed as outlined in Scheme 1: α-arylketones **3** were reacted with malononitriles **4** in the presence of ammonia to give 3-cyanopyridines **5**,[10] which were subsequently reduced to 3-aminomethylpyridines **2**.[11] Chiral analytical HPLC revealed that **2e** was obtained as a mixture of enantiomers. We assume that the chirality of **2e** arises from a restricted rotation of the dichlorophenyl–pyridine bond, caused by the steric bulk of adjacent substituents, leading to a chiral axis and atropisomerism. Compounds **2c**,**d**,**f–k** carry similar substituents and are therefore presumably also chiral. Compounds **2c–k** were tested as (putative) racemates.

In summary, a series of pyridine DPP-IV inhibitors **2** was derived from a weakly active pyrimidine screening hit **1**. A large activity increase was achieved by optimisation of aromatic substituents and conformational restriction, leading to a low nanomolar DPP-IV inhibitor, **2k**.

References and notes

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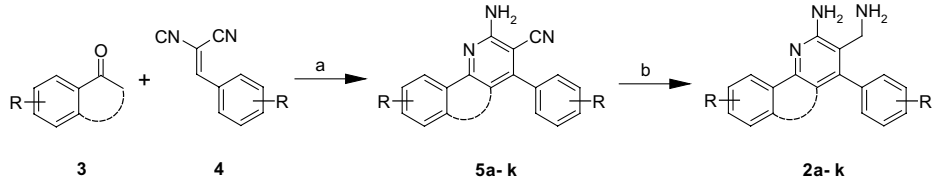

3 **4** **5a- k** **2a- k**

Scheme 1. Reagents and conditions: (a) NH_4OAc, toluene, 110 ° C, 4 h, representative yields: **5b** 35%, **5c** 38%, **5d** 42%, **5e** 18%; (b) $LiAlH_4$, THF, 40 °C, 3 h, representative yields: **2b** 6%, **2c** 25%, **2d** 26%, **2e** 67%.