1,3-Oxazoles and 1,2,4-oxadiazoles as selective agonists of GPR40 receptor

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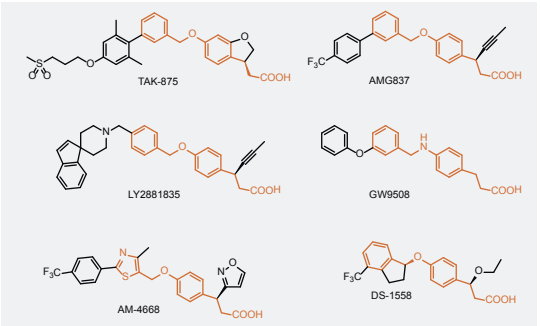
Introduction

• Type 2 diabetes mellitus (T2DM) is a debilitating metabolic disease in which glucose levels are persistently elevated, which leads, in long term, to cardiovascular complications, renal failure and affected eyesight.

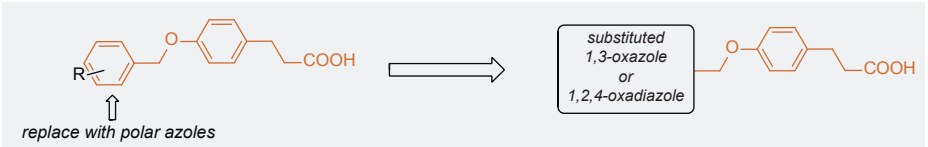
• Activation of free fatty acid receptor 1 (FFAR1 or GPR40) by endogenous free fatty acids was established in 2003 as a promising approach for T2DM treatment[1].

• A majority of the reported GPR40 agonists (including the discontinued clinical candidates TAK-875,[2] AMG837,[3] LY2881835 and a pioneering preclinical lead GW9508) are 3-phenyl propionic acids carrying an appropriately substituted benzyloxy (or benzylamino) substituent in position 4 of the phenyl ring.



Aim

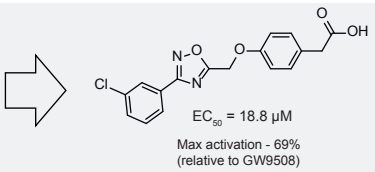
Identification of novel chemotypes for GPR40 agonist development, which would be more polar in comparison with the known advanced agents (*e.g.*, GW9508 and AMG837)[4].



Results

Design of library for primary screening

~6,000 screened compounds structurally related to the various known ligands of GPR40 were selected from Enamine's in-house 2,000,000+ compound collection.

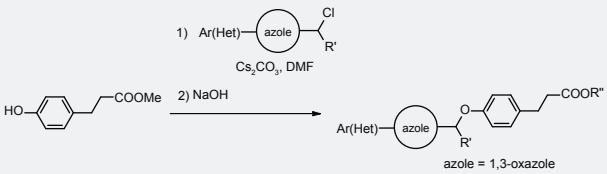


Hit expansion (~80 cmpds)

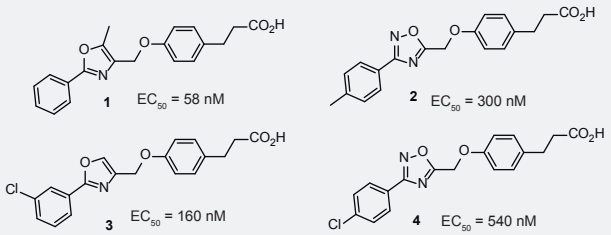
• Based on numerous azole-containing building blocks in the commercial stock of Enamine

• Structures from Enamine database of feasible screening compounds (REAL Database)

Synthesis



Representative new GPR40-agonists



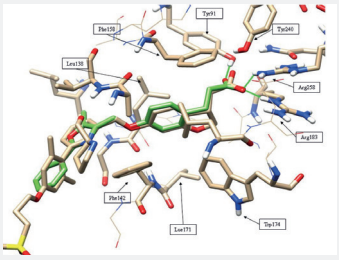
ADME profile

	1	2	4
Plasma protein binding (human)	98.6%	98.5%	99.9%
Aqueous solubility (PBS, pH 7.4)	404 mM	334 mM	214 mM
Metabolic stability (mouse, $t_{1/2}$)	434 min	373 min	724 min
A-B permeability (Caco-2, cm·s^{-1})[d]	15.2 · 10^{-6}	27.3 · 10^{-6}	2,1 · 10^{-6}

Cytochrome P450 % inhibition data at 5 μM

	1	2	4
1A2	8.90	13.58	25.92
2C9	10.78	4.26	16.22
2C19	23.56	20.56	31.56
2D6	17.71	-8.30	-5.80
3A4	36.24	29.18	50.10

Docking (compound 1 and TAK-875)



Conclusions

• Two new chemotypes of GPR40 agonists are established and promising lead compounds with good ADME-profiles are identified and represent new starting points for further development

• Rapid hit-expansion was effectively carried out applying Enamine off-the-shelf building-block collection

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References

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