

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

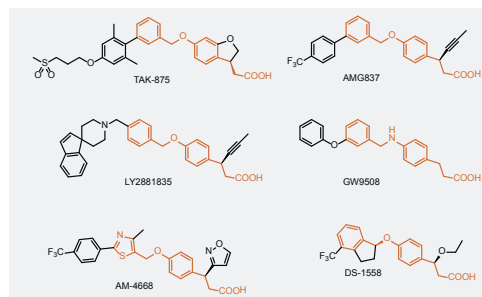
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## Introduction

• 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.

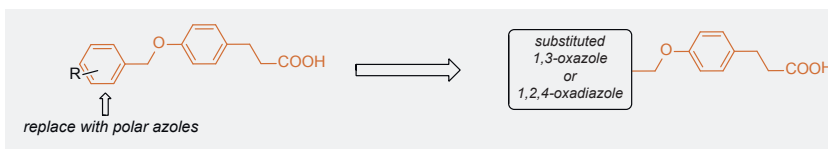
• Activation of free fatty acid receptor 1 (FFAR1 or GPR40) by endogenous free fatty acids was established in 2003 as a promising approach for T2DM treatment<sup>1</sup>.

• A majority of the reported GPR40 agonists (including the discontinued clinical candidates TAK-875,<sup>2</sup> AMG837,<sup>3</sup> 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

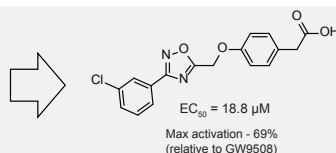
Identification of novel chemotypes for GPR40 agonist development, which would be more polar in comparison with the known advanced agents (e.g., GW9508 and AMG837)<sup>4</sup>.



## Results

### Design of library for primary screening

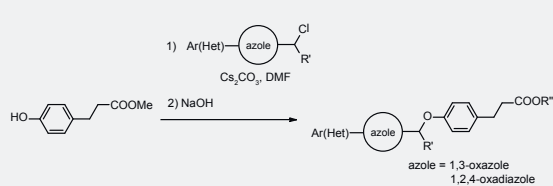
~6,000 screened compounds structurally related to the various known ligands of GPR40 were selected from Enamine's in-house 2,000,000+ compound collection.



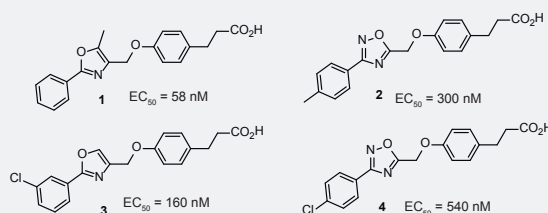
### Hit expansion (~80 cmpds)

- 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



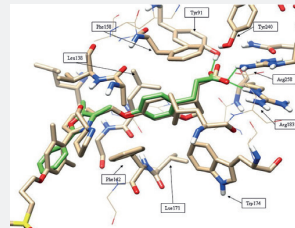
### ADME profile

	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, $\text{cm} \cdot \text{s}^{-1}$ ) <sup>5</sup>	$15.2 \cdot 10^{-6}$	$27.3 \cdot 10^{-6}$	$2.1 \cdot 10^{-6}$

### 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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4. Zahanich I. *at BMCL* 2015 in press