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Polyacetylenes and alkamides as modulators of PPAR γ activity and promising candidates for the treatment of type 2 diabetes

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INTRODUCTION

Screening of food and medicinal plants for antidiabetic effects revealed that in particular extracts of carrot (*Daucus carota*) and purple coneflower (*Echinacea purpurea*) contain compounds with promising effects on type 2 diabetes (T2D) [1, 2]. A bioassay-guided fractionation approach resulted in the isolation of the polyacetylenes **1** and **2** from carrots [3] and the alkamides **3–5** from *E. purpurea* extracts (Fig. 1) [4, 5]. All compounds are able to stimulate insulin-dependent glucose uptake (GU) and transactivate the nuclear receptor PPAR γ in adipocytes in a dose-dependent manner, but to a different extent and show the characteristics of PPAR γ partial agonists [3, 5].

IN VITRO TRANSACTIVATION OF PPAR γ

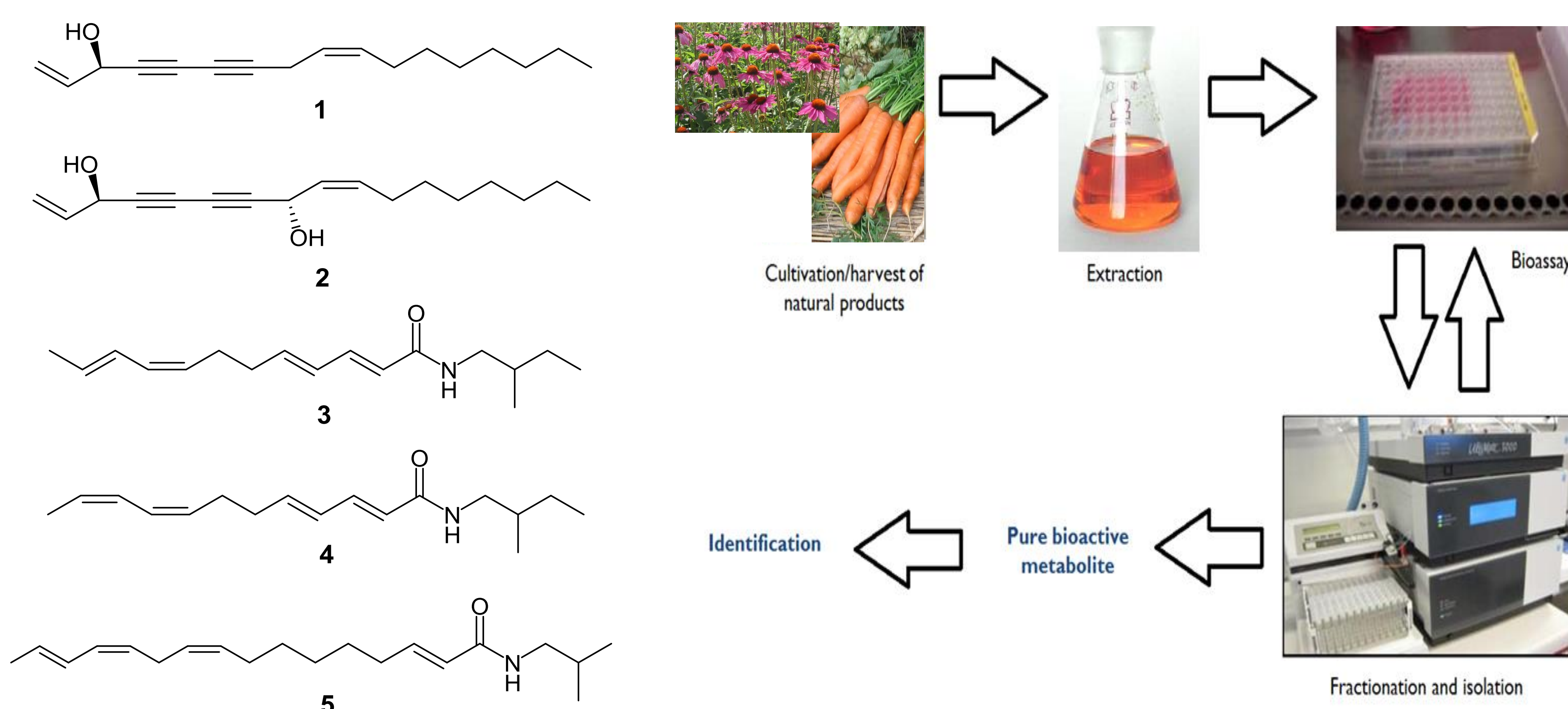


Fig. 1. Polyacetylenes (**1** and **2**) and alkamides (**3–5**) isolated by a bioassay-guided fractionation approach have demonstrated promising antidiabetic effects.

Table 1. Transactivation of PPAR γ by **1–5**

Compound	Fold activation of PPAR γ ^a
1	1.2 ± 0.5 [3]
2	3.5 ± 1.5 [3]
3/4	12 ± 1.3 [4]
5	13 ± 2.4 [5]

^aTransactivation of PPAR γ by **1–5** (30 μ M) relative to DMSO (vehicle). DMSO was set to 1 and the results normalized to this. Rosi (1 μ M) was the positive control. All values are expressed as mean ± SD of three independent experiments in triplicates.

IN SILICO DOCKING STUDIES

Molecular docking studies of **1–5** revealed the characteristic binding modes of partial PPAR γ agonists with a hydrogen bond to Ser342 (Fig. 2). Compounds **1–5** also showed hydrophobic contacts but to different amino acids in the ligand binding domain of PPAR γ , which can explain the differences in insulin-dependent GU and PPAR γ activity observed for **1–5** (Table 1) [3–5]. The present results indicate that **1–5** may represent scaffolds for the development of partial PPAR γ agonists for the treatment of T2D.

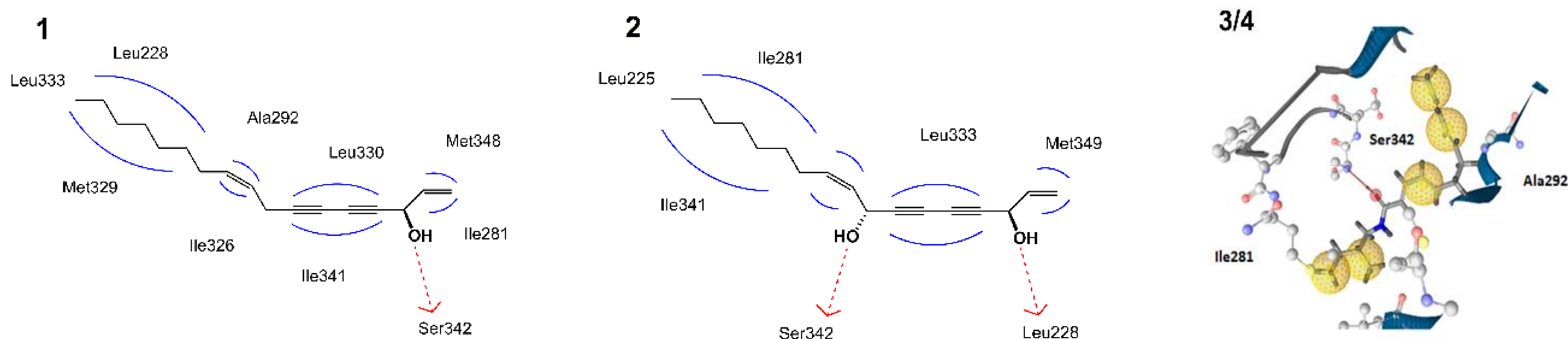


Fig. 2. Potential binding conformation of **1** and **2** in PPAR γ (PDB code 2Q5S) in 2D and **3/4** in 3D. Blue brace/yellow spheres indicate lipophilic areas and red arrows indicate hydrogen bonds.

REFERENCES

- [1] El-Houri RB, Kotowska D, Olsen LCB, Bhattacharya S, Christensen LP, Grevsen K, Oksbjerg K, Færgeman N, Kristiansen K, Christensen KB. Evid Based Complement Alternat Med 2014; Article ID 156398
- [2] Christensen KB, Minet A, Svenstrup H, Grevsen K, Zhang H, Scharder E, Rimbach G, Wein S, Wolfram S, Kristiansen K, Christensen LP. Phytother Res 2009; 23: 1316–1325
- [3] El-Houri RB, Kotowska D, Christensen KB, Bhattacharya S, Oksbjerg N, Wolber G, Kristiansen K, Christensen LP. Food Funct 2015; 6: 2135–2144
- [4] Kotowska D, El-Houri RB, Borkowski K, Petersen RK, Fretté X, Wolber G, Grevsen K, Christensen KB, Christensen LP, Kristiansen K. Planta Med 2014; 80: 1712–1720
- [5] Christensen KB, Petersen RK, Petersen S, Kristiansen K, Christensen LP. J Nat Prod 2009; 72: 933–937

