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El-Houri, Rime Bahij; Wolber, Gerhard; Christensen, Lars Porskjær

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

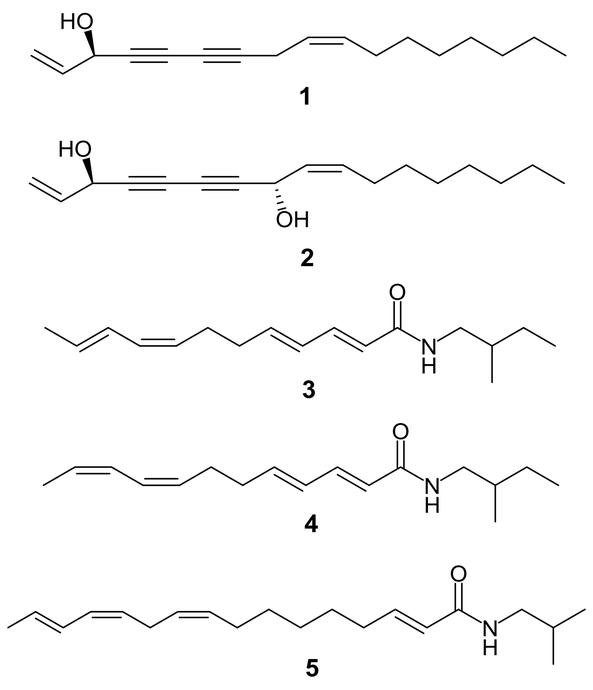
Rime B. El-Houri[1], Gerhard Wolber[2], Lars P. Christensen[1]

[1]Department of Chemical Engineering, Biotechnology and Enviromental Technology, University of Southern Denmark, Campusvej 55, 5230 Odense M, Denmark. [2]Computer-Aided Drug Design, Institute of Pharmacy, Medical and Pharmaceutical Chemistry, Freie University Berlin, Königin-Luise Str. 2+4, 14195 Berlin, Gemany. rbeh@kbm.sdu.dk

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 PPARγ in adipocytes in a dose-dependent manner, but to a different extent and show the characteristics of PPARγ partial agonists [3, 5].

IN VITRO TRANSACTIVATION OF PPARγ



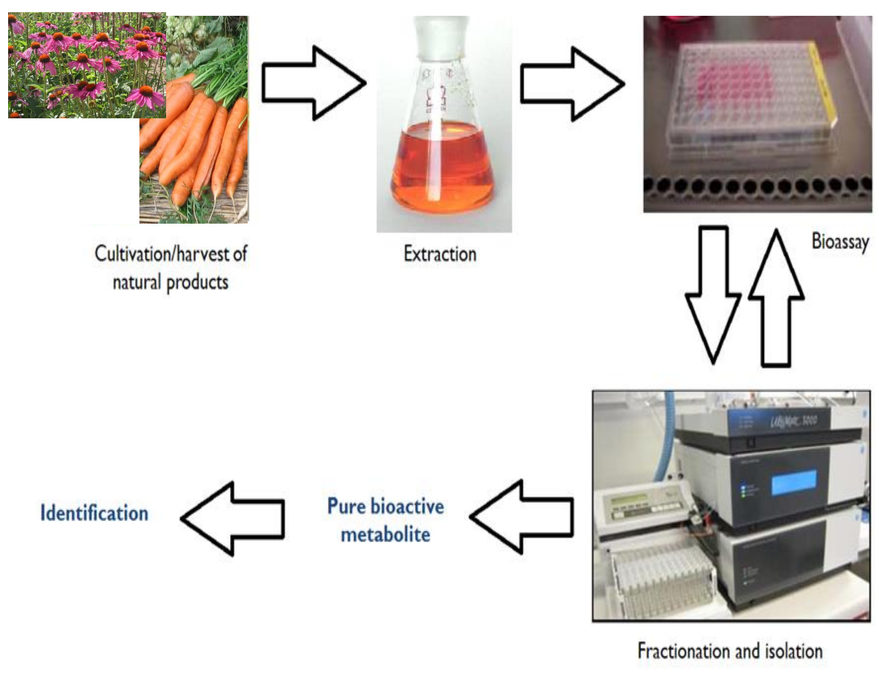


Fig. 1. Polyacetylenes (**1** and **2**) and alkamides (**3**–**5**) isolated by a bioassay-guided fractionation approach have demonstrated promising antidiabetic effects.

Table 1. Transactivation of PPARγ by **1**–**5**

Compoud	Fold activation of PPARγ[a]
1	1.2 ± 0.5 [3]
2	3.5 ± 1.5 [3]
3/4	12 ± 1.3 [4]
5	13 ± 2.4 [5]

[a]Transactivation of PPARγ by **1**–**5** (30 μM) relative to DMSO (vehicle). DMSO was set to 1 and the results normalized to this. Rosi (1 μM) was the positive control. All values re 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 PPARγ 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 PPARγ, which can explain the differences in insulin-dependent GU and PPARγ activity observed for **1**–**5** (Table 1) [3–5]. The present results indicates that **1**–**5** may represent scaffolds for the development of partial PPARγ agonists for the treatment of T2D.

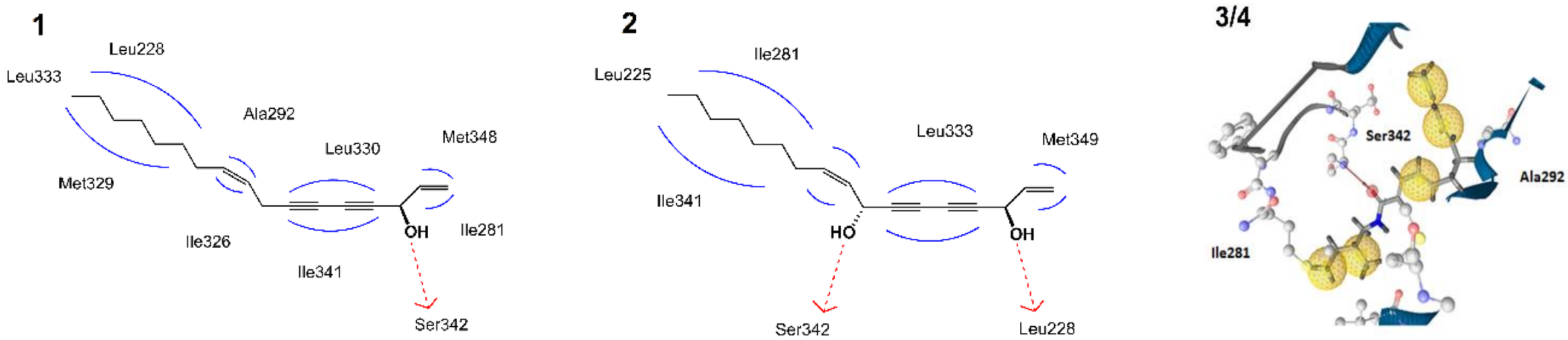


Fig. 2. Potential binding conformation of **1** and **2** in PPARγ (PDB code 2Q5S) in 2D and **3/4** in 3D. Blue brace/yellow spheres indicate lipophilic areas and red arrows indicate hydrogen bonds.

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