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

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

Published in:
Planta Medica

DOI:
10.1055/s-0036-1596912

Publication date:
2016

Citation for published version (APA):

General rights
Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

• Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
• You may not further distribute the material or use it for any profit-making activity or commercial gain
• You may freely distribute the URL identifying the publication in the public portal?

Take down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.
Polyacetylenes and alkamides as modulators of PPARγ activity and promising candidates for the treatment of type 2 diabetes

Rime B. El-Houri1, Gerhard Wolber2, Lars P. Christensen1

1Department of Chemical Engineering, Biotechnology and Environmental Technology, University of Southern Denmark, Campusvej 55, 5230 Odense M, Denmark. 2Computer-Aided Drug Design, Institute of Pharmacy, Medical and Pharmaceutical Chemistry, Freie University Berlin, Königin-Luise Str. 2+4, 14195 Berlin, Germany. 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

Table 1. Transactivation of PPARγ by 1–5

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

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 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 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.

REFERENCES