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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-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 cornflower (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

![Image of Polyacetylenes and Alkamides]

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

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Fold activation of PPARγ³</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.2 ± 0.5 [3]</td>
</tr>
<tr>
<td>2</td>
<td>3.5 ± 1.5 [3]</td>
</tr>
<tr>
<td>3/4</td>
<td>12 ± 1.3 [4]</td>
</tr>
<tr>
<td>5</td>
<td>13 ± 2.4 [5]</td>
</tr>
</tbody>
</table>

*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.

![Image of Molecular Docking Studies]

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.

REFERENCES