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Polyacetylenes and alkamides as modulators of PPARγ 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 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.

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 indicate that 1–5 may represent scaffolds for the development of partial PPARγ agonists for the treatment of T2D.

Table 1. Transactivation of PPARγ by 1–5

<table>
<thead>
<tr>
<th>Compound</th>
<th>Fold activation of PPARγ</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.

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