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PATENT HIGHLIGHT

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Diphenylpropane Derivatives as Agonist of PPAR Nuclear Receptors

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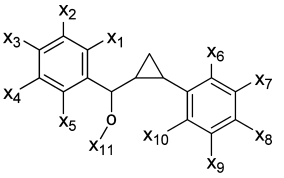
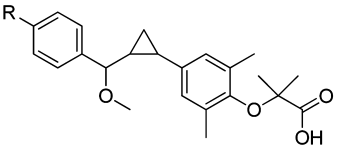
Title:	Diphenylpropane Derivatives as Agonist of PPAR Nuclear Receptors		
Patent/Patent Application Number:	WO 2013098374 A1	**Publication date:**	July 04, 2013
Priority Application:	EP 2011-306790	**Priority date:**	December 28, 2011
Inventors:	Dubernet, M.; Delhomel, J.-F.; Bertrand, K.		
Assignee Company:	Genfit, France		
Disease Area:	Metabolic, inflammatory, neurodegenerative diseases	**Biological Target:**	PPAR nuclear receptors

Summary: This application claims derivatives of diphenylpropane as agonists of PPAR receptors for the treatment of a wide variety of diseases including metabolic, inflammatory, and neurodegenerative diseases such as Alzheimer's and Parkinson's diseases.

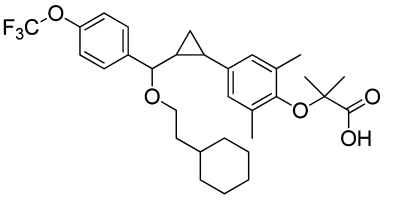
Important Compound Classes:



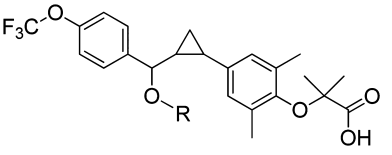
Key Structures:



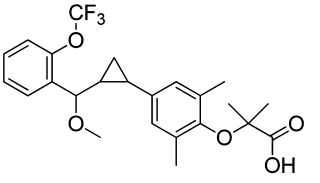
Compound 1-1, R=Br, diastereoisomer 1
Compound 1-2, R=Br, diastereoisomer 2
Compound 2-1, R=Me, diastereoisomer 1
Compound 4-1, R=CF3, diastereoisomer 1



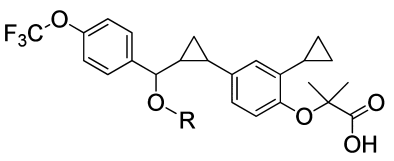
Compound 6-2, diastereoisomer 2



Compound 10-1, R=Et, diastereoisomer 1
Compound 10-2, R=Et, diastereoisomer 2
Compound 11-1, R=Bz, diastereoisomer 1
Compound 11-2, R=Bz, diastereoisomer 2
Compound 14-1, R=Me, diastereoisomer 1
Compound 14-2, R=Me, diastereoisomer 2
Compound 14-2-1, R=Me, enantiopure, obtained from diastereoisomer 2
Compound 14-2-2, R=Me, enantiopure, obtained from diastereoisomer 2



Compound 13-1, diastereoisomer 1



Compound 21-1, diastereoisomer 1

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Biological Assay: The agonist activity of the compounds against the PPAR receptors was evaluated in a recombinant assay using monkey kidney COS-7 cells. The in vivo efficacy of one (1) compound was tested in an Alzheimer's disease model using APPPS1 mice.

Pharmacological Data: Thirty-seven compounds were tested against PPAR receptors. The agonist activity of selected compounds is shown below.

Compound	Gal4-hPPARα(LBD) EC_{50} (μM)	HCV replicon Gal4-hPPARγ(LBD) EC_{50} (μM)	Gal4-hPPARδ(LBD) EC_{50} (μM)
1-1	0.239	0.044	0.040
1-2	0.186	0.019	0.054
2-1	0.635	0.110	0.152
4-1	0.064	0.020	0.016
6-2	0.026	0.034	0.131
10-1	0.038	0.095	0.014
10-2	0.030	0.039	0.024
11-1	0.021	0.116	0.079
11-2	0.100	0.023	0.122
13-1	0.652	0.072	0.328
14-1	0.032	0.025	0.007
14-2	0.041	0.017	0.030
14-2-1	0.050	0.016	0.019
14-2-2	0.017	0.016	0.059
21-1	3.650	0.828	3.271

Compound 14-2-1 had an estimated bioavailability of 92.9% and a brain/plasma ratio of 0.37.

Compound 14-2-1 was tested in vivo using APPPS1 mice. Compound 14-2-1 showed efficacy in the Morris−Water maze assay and also decreased beta-amyloid accumulation in the brain at 1 and 10 mg/kg. The route of administration was not described.

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Notes

The authors declare no competing financial interest.