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Novel Oxazolidinone-Based Peroxisome Proliferator Activated Receptor Agonists: Molecular Modeling, Synthesis, and Biological Evaluation

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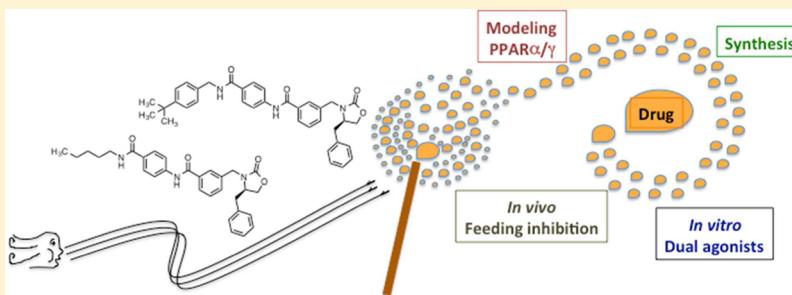
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Supporting Information



ABSTRACT: A series of new peroxisome proliferator activated receptors (PPARs) chiral ligands have been designed following the accepted three-module structure comprising a polar head, linker, and hydrophobic tail. The majority of the ligands incorporate the oxazolidinone moiety as a novel polar head, and the nature of the hydrophobic tail has also been varied. Docking studies using the crystal structure of an agonist bound to the ligand binding domain of the PPAR α receptor have been performed as a tool for their design. Suitable synthetic procedures have been developed, and compounds with different stereochemistries have been prepared. Evaluation of basal and ligand-induced activity proved that several compounds showed agonist activity at the PPAR α receptor, thus validating the oxazolidinone template for PPAR activity. In addition, two compounds, 2 and 4, showed dual PPAR α /PPAR γ agonism and interesting food intake reduction in rats.

INTRODUCTION

The peroxisome proliferator activated receptors (PPARs) are nuclear receptors activated by the binding of small lipophilic ligands, either natural or synthetic. They can induce or repress genes modulating different biochemical processes such as adipogenesis, lipid and glucose metabolism, energy balance, and inflammation, among others. Considered an important target in medicinal chemistry, significant efforts have been devoted to search new ligands capable of treating chronic disorders such as high levels of triglycerides, diabetes, metabolic syndrome, and chronic inflammatory bowel disease.

There are three known subtypes of PPAR receptors: α , γ , and β/δ . Whereas PPAR α is expressed in tissues with a high rate of fatty acid catabolism and modulates lipid metabolism and inflammation, PPAR γ is predominant in adipose tissue and

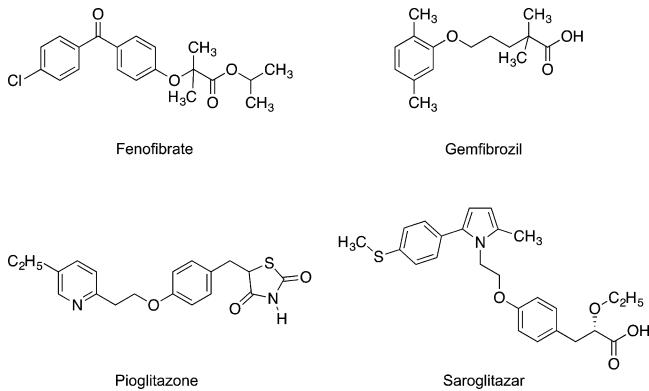
regulates glucose and lipid metabolism. Finally, the β/δ type is the most ubiquitous and has been less investigated.¹

Despite intense research in developing PPAR ligands,^{2,3} there are only a few marketed drugs targeting PPAR α and PPAR γ , and several promising candidates have failed in clinical trials (Figure 1). The α agonists, represented by fibrates (e.g., fenofibrate and gemfibrozil), are clinically used for the treatment of dyslipidemia. The thiazolidindiones (TZDs) or glitazones (e.g., pioglitazone) are considered as specific ligands for the γ receptor. They are being used for treating hyperglycemia in patients with type 2 diabetes. Due to the considerable structural homology between these PPAR isoforms, there are other kinds of dual ligands that bind to two or

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Figure 1. PPAR α and PPAR γ marketed drugs.

more isoforms. The most studied compounds under this description are the glitazars from which the saroglitazar (*S* enantiomer) has been recently approved and marketed under the trade name Lipaglyn as a novel antidiabetic agent.⁴ Nowadays, there is a growing interest in developing dual PPAR α and PPAR γ agonists, since they may have fewer secondary effects compared to selective α and γ ligands.

The LBD (ligand binding domain) is responsible for ligand specificity and PPAR activation. The core of the Y-shaped LBD consists of a set of 12 antiparallel α -helices (helices 1–12) and a three-stranded antiparallel β -sheet. The activation function 2 (AF-2) domain located at the end of C-terminal helix 12 plays a critical role after ligand binding, reducing the LBD flexibility and providing an appropriate interface for the cofactor recruitment. A large number of crystal structures of the PPAR-LBD with different ligands have been reported in the

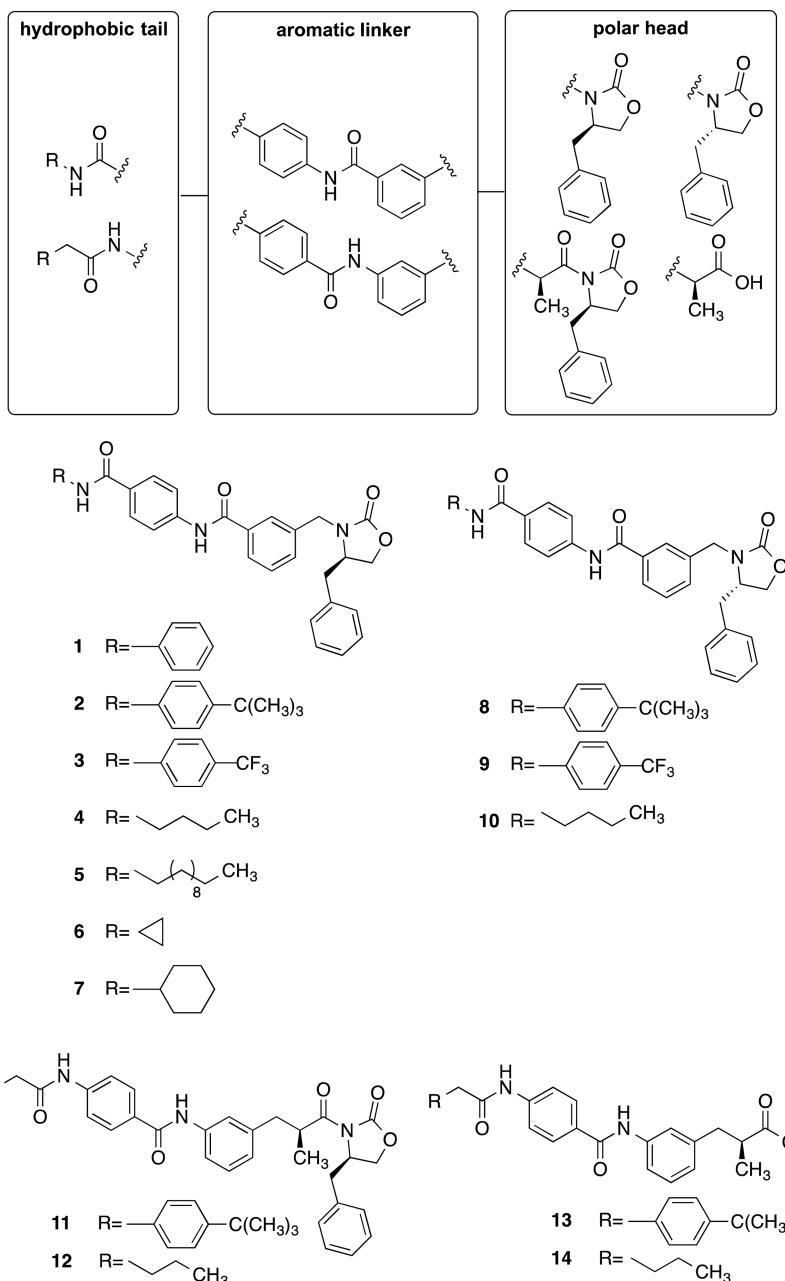


Figure 2. General scheme and formulas for PPAR chiral ligands.

Table 1. Docking of Compounds in the LBD of PPAR α and PPAR γ

compd	docking energy (kcal/mol)	Tyr464 HB percentage	polar interaction (PPAR α)	docking energy (kcal/mol)	Tyr473 HB percentage	polar interaction (PPAR γ)
GW409544	-18.25	31	Ser280 Tyr314 Tyr464 His440	-14.45	23	Ser289 His323 Tyr473 His449
WY-14643	-8.99	63	Ser280 Tyr314 Tyr464 His440			
2	-10.68	4	Tyr314 Tyr464 His-40	-13.55	4	Tyr473 His449
3	-11.93	4	Tyr464 His440			
4	-11.54	12	Tyr464 His440	-11.1	3	Tyr473 His449
7	-12.24	3	Tyr314 Tyr-64 His440			
8	-13.33	13	Ser280 Tyr464 His440	-13.36	7	Ser289 His323 Tyr473
9	-10.85	2	Tyr464 His440			
10	-11.24	4	Tyr464 His440	-11.21	4	Tyr473 His449
13	-11.61	15	Ser280 Tyr314 Tyr464 His440	-11.08	7	Ser289 His323 Tyr473 His449
14	-9.99	22	Ser280 Tyr314 Tyr464 His440	-9.76	19	Ser289 His323 Tyr473 His449

literature, enlightening a well-defined view of the agonist binding mode.⁵ In some cases, chirality is a crucial point determining the PPAR binding mode, and synthetic strategies to deal with these stereoselectivity issues have been recently reviewed.⁶ Laghezza et al. reported the 2-(aryloxy)-3-phenylpropanoic acid family with PPAR α/γ dual agonist activity. The S and R enantiomers of the isopropyl derivative were crystallized bound to the LBD of the receptor. The S stereoisomer behaved as a full and partial agonist of PPAR α and PPAR γ , respectively.⁷ In 2002, α -substituted phenylpropanoic acid-type PPAR agonists were reported to bind to the LBD in different conformations, indicating multiple binding points inside the binding pocket.⁸ New PPAR γ scaffolds have also been reported following a virtual screening approach to identify PPAR chemotypes; however, further biological studies need to be performed.⁹

The oxazolidinone is a five-membered heterocyclic ring with several applications as an organocatalyst and a chiral auxiliary (e.g., asymmetric aldol reactions).¹⁰ It is considered a valuable structural motif in medicinal chemistry.^{11–13} Oxazolidinones as chiral auxiliaries have been used by Miyachi and co-workers for the asymmetric synthesis of chiral α -acid derivatives as PPAR γ and PPAR α/γ ligands.^{14–16} On the other hand, in vitro metabolism studies of a PPAR γ ligand structurally similar to the oxazolidinone ring was reported by Agrawal et al.¹⁷

In this paper we describe 14 new PPAR chiral ligands¹⁸ mainly based on an oxazolidinone motif following the three-module structure described by Pirat et al.⁵ A structure–activity relationship study was conducted by varying the hydrophobic tail and polar head. Moreover, compounds with different stereochemistries were synthesized to understand the PPAR binding mode. Docking studies were used as a tool to design these ligands. Some of these ligands showed interesting in vitro and in vivo pharmacological activities.

RESULTS AND DISCUSSION

According to the accepted model, the ligands bind through three chemical features: a polar head, a linker region, and a hydrophobic tail (Figure 2). In our case, the choice of the hydrophobic tail group was determined by the docking studies going from alkyl chains (acyclic and cyclic) to aromatic rings trying to occupy the large hydrophobic cavity of the binding site. In addition, a hydrophobic aromatic linker with the appropriate length was introduced. Finally, a polar head such as an oxazolidinone ring or a carboxylic acid should enable the hydrogen bonds in front of the AF-2 helix to stabilize its conformation. The chirality in our ligands has been introduced either on the oxazolidinone ring (substituent in position 4, compounds 1–10) or in the optically active (S)- α -acid (compounds 13 and 14) or in both of them (11 and 12).

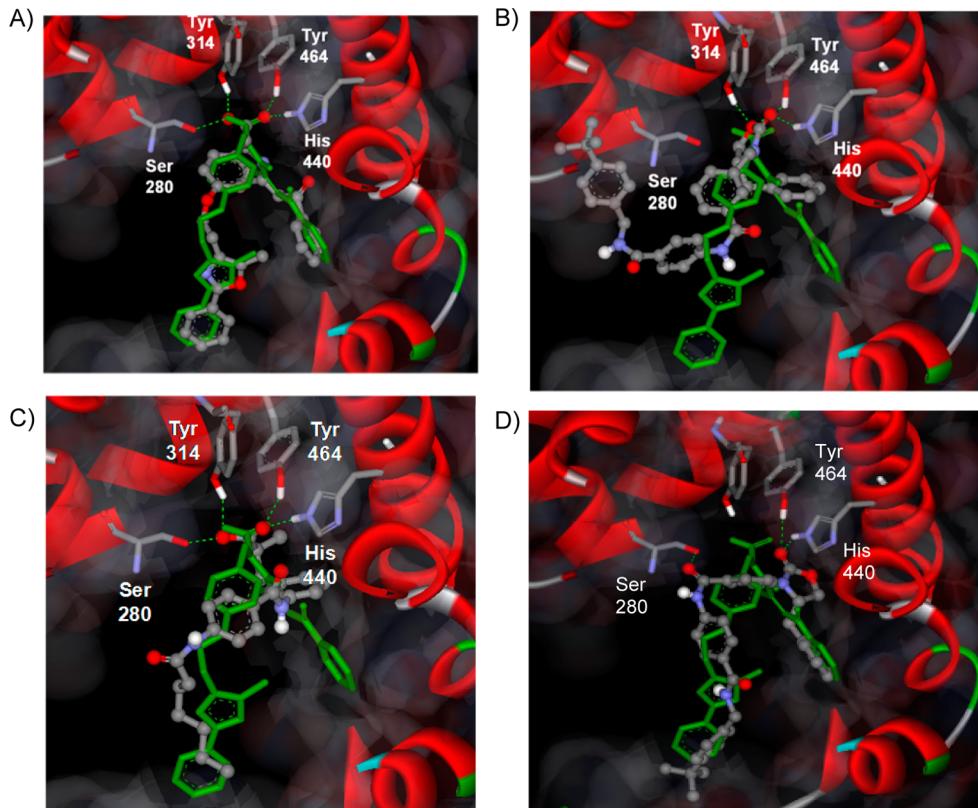


Figure 3. Docking representation of the best location/orientation binding modes of GW409544 pose 55 (A), 2 pose 62 (B), 14 pose 3 (C), and 8 pose 4 (D) in balls and sticks colored by atom type. The cocrystallized conformation of GW409544 is shown in green and the protein backbone by ribbons (blue). The most important polar interactions (dashed green lines) and residues involved are shown (Ser280, Tyr314, His440, and Tyr464). All agonist compounds form a hydrogen bond with Tyr464.

Docking Studies. Docking studies of two known PPAR agonists (GW409544, WY-1463) and compounds **2**, **3**, **4**, **7**, **8**, **9**, **10**, **13**, and **14** were carried out by means of the AutoDock v4 package. Table 1 summarizes the most stable conformations, the percentage of hydrogen bonds with the hydroxyl group of Try464 (PPAR α) and Tyr473 (PPAR γ) of the 100 best docked conformations, the main polar interactions inside the LBD, and the docking energy for the selected pose of each compound.

The validation of the in silico model was performed comparing the X-ray data of commercial compound GW409544 bound to the ligand domain of PPAR α (PDB entry 1K71) and to PPAR γ (PDB entry 1K74).¹⁹ According to the crystal structure, the aromatic rings of GW409544 established several interactions with nonpolar amino acids of the PPAR α -LBD and PPAR γ -LBD. Additionally, GW409544 adopted a conformation within the receptor that allowed the carboxylate group to form hydrogen bonds with Ser280, Tyr314, His440, and Tyr464 of PPAR α and Ser289, His323, His449, and Tyr473 of PPAR γ . These polar interactions and specifically the formation of hydrogen bonds with Tyr464 (PPAR α) and Tyr473 (PPAR γ) typically trigger a conformational change, notably in the AF-2 helix, which aids in the recruitment of coregulatory factors to regulate gene transcription.

For the PPAR α ligand binding domain, the AutoDock suite successfully reproduced the binding mode for GW409544, showing a root-mean-square deviation (RMSD) of one of the most stable binding conformations (pose 55) of 0.7 Å in comparison with the experimental geometry, and the same hydrogen bond patterns (Figure 3A).²⁰ An additional reference,

the ligand WY-1463, which is the control ligand used in the in vivo tests, has also been included in the docking studies (Table 1).

The most stable docking solutions for the different ligands were analyzed, and the results suggest the existence of different potential binding modes of each compound onto the structure of the PPAR α -LBD. The hydrophobic tails of each compound were assigned to the same hydrophobic region occupied by the synthetic agonist GW409544 in the crystal structure of the PPAR α -LBD (Figure 3).¹⁷ For these solutions, the oxazolidinone (CO) and carboxylic acid polar groups were close to the hydroxyl group of the lateral chain of Tyr464, which donated a hydrogen bond. The binding modes were stabilized by the hydrogen bond network with Tyr314, Tyr464, and His440 (**2** and **7**), Tyr464 and His440 (**3**, **4**, **9**, and **10**), and Ser280, Tyr464, and His440 (**8**), and with the four residues for just compounds **13** and **14**. The chirality induced by the substituent attached to the oxazolidinone ring in position 4 is responsible for the orientation of the CO group toward the polar residues. For instance, enantiomers **2** and **8** showed some differences in the percentage of hydrogen bonds with the hydroxyl group of Tyr464 and in the polar residue interactions. However, at this point, in the absence of crystallization data, these results must be considered as a theoretical approximation.

In the case of the PPAR γ -LBD, docking studies were carried out with **2**, **4**, **8**, **10**, **13**, and **14**. The hydrophobic tails of these compounds were assigned to the same hydrophobic region occupied by the synthetic agonist GW409544 in the crystal structure of the PPAR γ -LBD, whereas the polar heads of the compounds were involved in a hydrogen bond network with

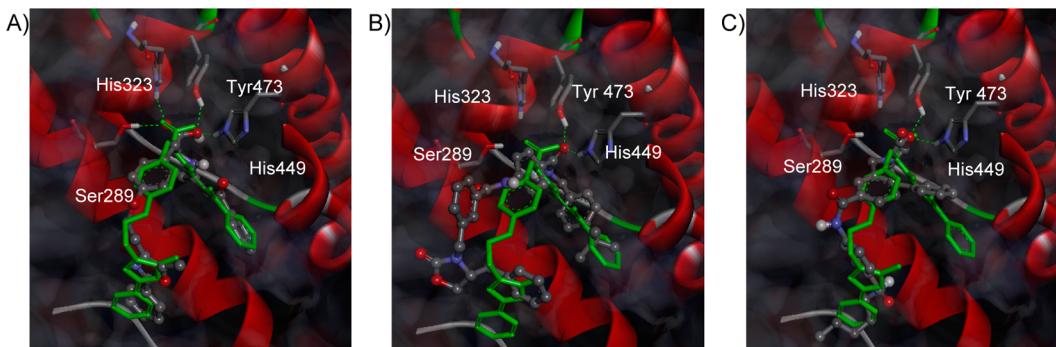
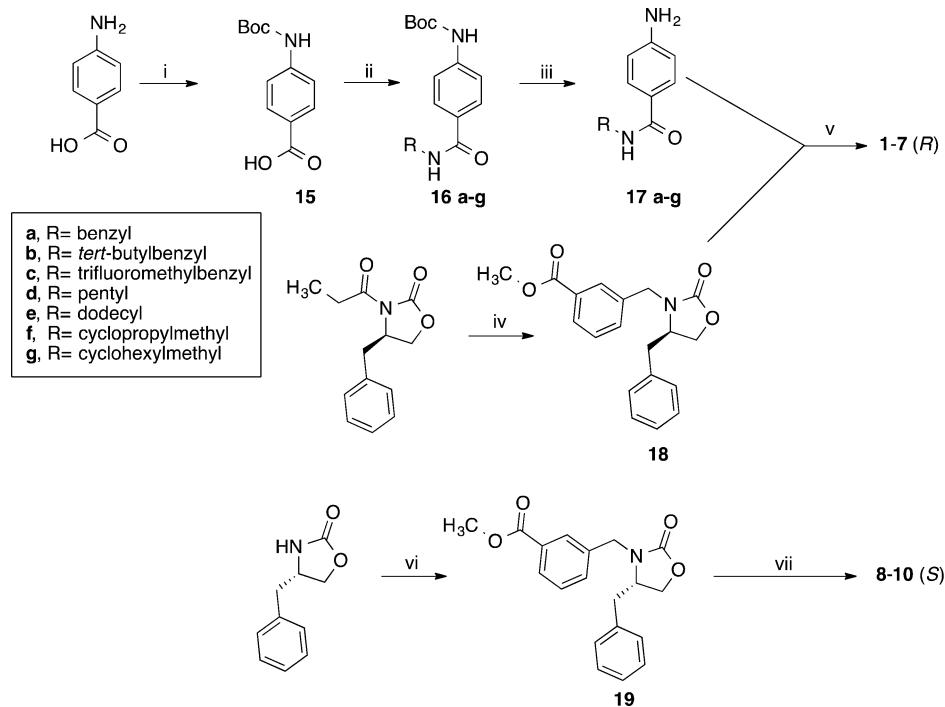


Figure 4. Docking representation of the best location/orientation binding modes to the PPAR γ -LBD of GW409544 pose 3 (A), 2 pose 4 (B), and 4 pose 31 (C) in balls and sticks colored by atom type. The cocrystallized conformation of GW409544 is shown in green and the protein backbone by ribbons (blue). The most important polar interactions (dashed green lines) and residues involved are shown (Ser289, His323, Tyr473, and His449). All agonist compounds form a hydrogen bond with Tyr473.

Scheme 1. Synthesis of Compounds 1–10^a



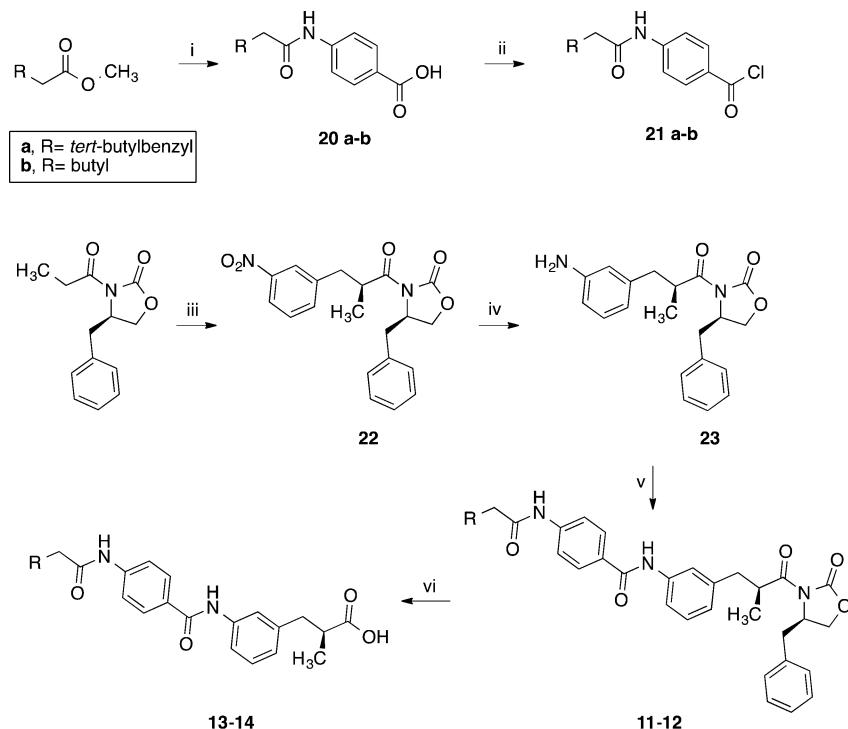
^aReagents and conditions: (i) Boc₂O, Et₃N, dioxane/H₂O (2:1), rt, 24 h (89%); (ii) coupling agent, HOBr, Et₃N, R-NH₂, solvent, rt, 12 h (31–84%); (iii) CH₂Cl₂/TFA (1:1), rt, 12 h (80–92%); (iv) ⁱBuOK, methyl 3-(bromomethyl)benzoate, THF(anhyd), rt, 7 h (62%); (v) Al(CH₃)₃, THF, microwave, 125 °C, 20 min (40–50%); (vi) methyl 3-(bromomethyl)benzoate, Cs₂CO₃, THF(anhyd)/CH₃CN(anhyd) (1:1), rt 6 h (66%); (vii) 17, Al(CH₃)₃, THF, microwave, 125 °C, 20 min (80–89%).

the following residues (i.e., Ser289, His323, His449, and Tyr473). Docking representations of the structures of compounds 2 and 4 onto the PPAR γ -LBD are represented in Figure 4.

Chemistry. For the preparation of compounds 1–10, we followed the synthetic strategy depicted in Scheme 1. The key intermediate 17 was synthesized in three steps. Starting from commercially available 4-aminobenzoic acid, protection of the amine with Boc anhydride provided 15. Amide bond formation between the carboxylic group of 15 with several amines (Figure 1) using EDCI or PyBOP gave intermediate 16 in moderate yields. The *tert*-butyl carbamate 16 was cleaved under anhydrous acidic conditions, giving 17 in good yields. The oxazolidinone motif was incorporated after a two-step synthesis starting from the commercially available (*R*)-4-benzyl-3-

propionyl-2-oxazolidinone in the case of compounds 1–7 and from the (*S*)-4-benzylloxazolidinone for compounds 8–10. In the first case, the use of ⁱBuOK at room temperature triggered a cross-alkylation reaction in which the oxazolidinone anion attacked the benzyl bromide derivative as we have recently reported, providing the oxazolidinone derivative 18 in moderate yields.²¹ In the second case, the alkyl halide underwent a nucleophilic substitution under basic conditions, giving the (*S*)-4-benzylloxazolidinone derivative 19. The final step to obtain compounds 1–10 involved a microwave-assisted amide bond formation between an ester (18 or 19) and various amine derivatives (17) mediated by a trimethylaluminum complex.

The synthesis of compounds 11–14 is summarized in Scheme 2. For these compounds, two different hydrophobic

Scheme 2. Synthesis of Compounds 11–14^a

^aReagents and conditions: (i) 4-aminobenzoic acid, Al(CH₃)₃, THF, microwave, 125 °C, 20 min (65–70%); (ii) SOCl₂, THF, 80 °C, 6 h; (iii) NaHMDS, THF(anhyd), 3-nitrobenzyl bromide, −78 °C, 6 h (70%); (iv) H₂/Pd–C, THF/EtOAc (1:2), 21 psi, rt, 12 h (90%); (v) 21, THF, rt, 12 h (34–68%); (vi) LiOH, H₂O₂, 0 °C to rt, 6 h (62–70%).

tails were selected: a *p*-*tert*-butylbenzyl tail and a butyl tail. Intermediate 21 was synthesized in two steps starting from commercially available methyl *p*-*tert*-butylphenylacetate or methyl hexanoate. An amide bond formation with the two different amines followed by the acid conversion to acyl chloride gave 21 in moderate yield. The second fragment of this synthesis (compound 23) is obtained in two steps. First, an Evans asymmetric alkylation in which the (*R*)-4-benzyl-3-propionyl-2-oxazolidinone was treated with 3-nitrobenzyl bromide under the Evans protocol (NaHMDS at −78 °C) provided 22. Second, a palladium-catalyzed reduction of the aromatic nitro group to amine gave 23 in good yield. Compounds 11 and 12 resulted from the amide bond formation between the acyl chloride 21 and the amine derivative 23. Then a hydrogenolysis of the oxazolidinone ring using LiOH/H₂O₂ gave the chiral acid derivatives in the α position, compounds 13 and 14.

Pharmacology. Luciferase reporter gene assays were performed with extracts from MCF-7 cells that were transiently transfected with a reporter construct containing four copies of the human CPTI DR1-type response element (RE) (for PPARs) and the indicated expression vectors for PPAR α , RXR α , and NCoR (CoR). Cells were treated for 16 h with a 10 μ M concentration of different compounds: DMSO (solvent), the reference PPAR α agonist GW7647, the endogenous PPAR α agonist OEA, the reference PPAR γ rosiglitazone, and compounds 1–14. MD simulation of luciferase activity was normalized to the basal activity of PPAR α -RXR α -SRC1 in the presence of the solvent (DMSO). Details on the methodology have been published previously.^{22–26} For the pharmacological properties of compounds 1–14, see Table 2.

Table 2. Pharmacological Properties of Compounds 1–14^a

compd	PPAR α activation EC ₅₀ (nM)	PPAR γ activation EC ₅₀ (nM)
OEA	152 ± 31	
GW7647	6.5 ± 1	
rosiglitazone		87.0 ± 11
1	>10 ^{−4} M	>10 ^{−4} M
2	670 ± 157	1298 ± 261
3	>10 ^{−4} M	>10 ^{−4} M
4	821 ± 139	1622 ± 388
5	6623 ± 1232	>10 ^{−4} M
6	1978 ± 213	
7	>10 ^{−4} M	>10 ^{−4} M
8	756 ± 125	
9	> 10 ^{−4} M	
10	> 10 ^{−4} M	
11	966 ± 233	
12	1922 ± 408	
13	866 ± 188	
14	981 ± 476	

^aEC₅₀ values calculated in the presence of the different compounds by GraphPad Prism 4. Results are the mean ± SEM of three experiments.

Compounds 2, 4, 5, 6, 8, 11, 12, 13, and 14 showed agonist activity at the PPAR α receptor. Among them, compounds 2 and 4 displayed moderate agonism at the PPAR γ receptor so they may be considered as interesting dual PPAR α/γ agonists. These compounds also showed key important interactions in the docking studies with both PPAR isoforms. Flexibility in the hydrophobic tail is desired (4) over rigid hydrogenated rings (7) in accordance with the performed docking studies. The *R* stereochemistry at the oxazolidinone ring is preferred over the *S* stereochemistry, and the oxazolidinone ring choice as polar

head with a shorter linker resulted to be slightly better than the existing one in compounds **11** and **12**. On the other hand, a difference of 1 order of magnitude in activity was observed between the carboxylate polar head of **14** and the oxazolidinone ring in **12** with the same hydrophobic tail and linker. This fact correlates perfectly with the docking studies where the (*S*)- α -acid derivative showed interactions with all the key residues at the LBD and a high HB percentage with Tyr464. As we can observe from the *in vitro* and docking results, interactions with the polar residues are important, but in some cases flexibility and the length of the ligand compensate for the loss of HBs with the polar residues in the LBD. This could explain why smaller ligands such as (*R*)-oxazolidinone **2** show *in vitro* results similar to those of (*S*)- α -acid **13**.

Considering the EC₅₀ values obtained at PPAR α receptors, the data suggest an intermediate position between fibrates and the natural ligand OEA. However, the efficacy at the receptor is not strictly related to *in vivo* efficacy. The most successful PPAR α agonists used in human therapy, the fibrates (i.e., fenofibrate, gemfibrozil), have reported EC₅₀ values at the PPAR α receptor in the micromolar range, more than 2-fold greater than those of compounds **2** and **4**.²⁷

On the basis of this assumption, for the *in vivo* studies, we selected compounds **2** and **4** since they behaved as dual agonists with interesting PPAR α EC₅₀ values and moderate affinity for the PPAR γ isoform.^{20,28} In *in vivo* pharmacology was tested using the model of feeding behavior in food-deprived animals, which provides a good screening test for PPAR α agonists with efficacy in animal models of obesity and metabolic disorders.^{29,30} Long-term effects such as reductions in plasma lipids will be analyzed in future studies.

In Vivo Food Intake Studies. The acute administration of compound **2** induced a dose-dependent reduction of food intake in adult obese male rats that had been deprived of food for 24 h. Compound **2** at the effective dose of 3.0 mg/kg is able to reduce food intake by around 50%, being active for up to 120 min. This effect disappears after 240 min (Figure 5).

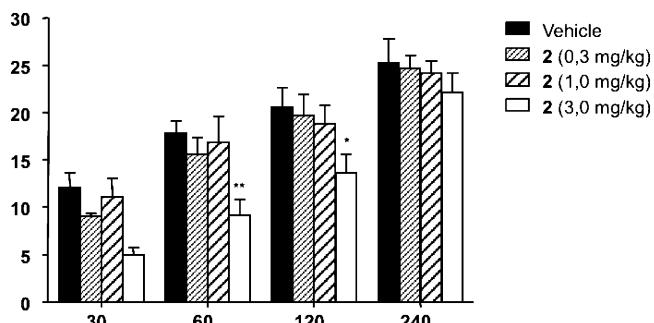


Figure 5. Feeding inhibition induced by acute administration of compound **2**. Time course of the inhibition of food intake induced by **2** at doses of 0.3, 1.0, and 3.0 mg/kg. The compound is active for up to 120 min after administration at 3.0 mg/kg (0–60 min, $P < 0.01**$; 60–120 min, $P < 0.05^*$). The abscissa represents time (min), while the ordinate axis represents the cumulative food intake (mg/kg).

The acute administration of compound **4** induced a dose-dependent reduction of food intake at the effective doses of 1.0 and 3.0 mg/kg (Figure 6). This compound remained active 240 min after dosing, and surprisingly, it continued exerting its effect 24 h later, an effect only observed before in nano-formulated oral oleoylethanolamide.³¹ Therefore, compound **4**

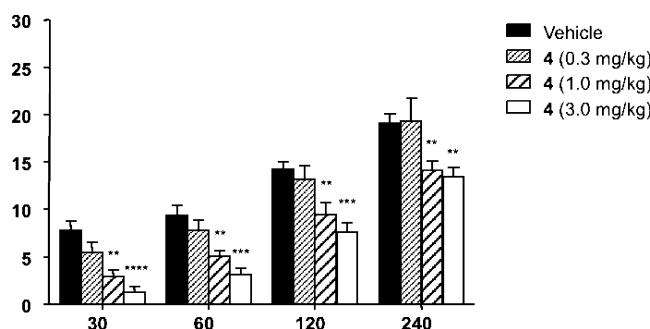


Figure 6. Feeding inhibition induced by acute administration of compound **4**. Time course of the inhibition of food intake induced by **4** at doses of 0.3, 1.0, and 3.0 mg/kg. The compound is active for up to 240 min after administration at 1.0 mg/kg (0–240 min, $P < 0.01^{**}$) and at 3.0 mg/kg (0–30 min, $P < 0.0001^{****}$; 30–120 min, $P < 0.001^{***}$; 120–240 min, $P < 0.01^{**}$). The abscissa represents time (min), while the ordinate axis represents the cumulative food intake (mg/kg).

is an interesting candidate for chronic administration studies (Figure 7).

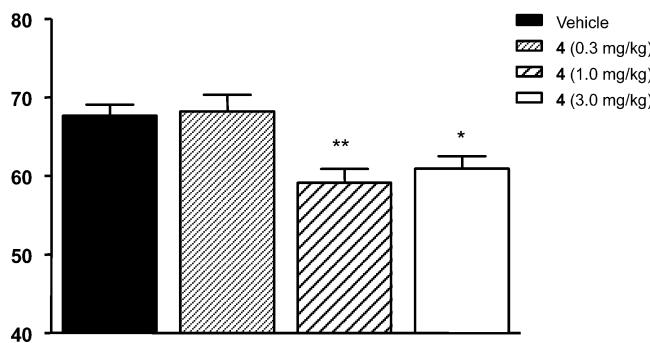


Figure 7. Feeding inhibition results 24 h after compound **4** administration. Compound **4** at 1.0 mg/kg ($P < 0.01^{**}$) remained active over 24 h after dosing in a dose-dependent manner. The abscissa represents time (24 h), while the ordinate axis represents the cumulative food intake (mg/kg).

In summary, on the basis of molecular modeling and docking studies, we have prepared novel PPAR ligands incorporating an oxazolidinone ring. Pharmacological assays, both *in vitro* and *in vivo*, of these chiral PPAR ligands have shown that the oxazolidinone motif is an interesting structural feature for PPAR activity. The ease of synthetically reaching these compounds and performing structural modifications makes them interesting leads for further development. Two of them (compounds **2** and **4**) can be considered as dual well-balanced PPAR α/γ ligands. Furthermore, they have shown interesting *in vivo* properties that make them attractive candidates for further research in the treatment of metabolic syndrome.

EXPERIMENTAL SECTION

General Chemistry Methods. All chemicals were purchased from commercial suppliers and used without further purification. For TLC, precoated silica gel 60 254 plates (Merck) were used, with detection by UV light (254 nm). For flash column chromatography (FC), Kieselgel 60 (230–400 mesh, Merck) was used. Melting points (mp's) were determined in open capillaries with a Gallenkamp capillary melting point apparatus. ¹H and ¹³C NMR spectra were recorded on a Bruker Advance 300 spectrometer operating at 300.13 and 75.47 MHz, respectively, in CDCl₃ or DMSO-d₆ as the solvent. Chemical shifts are

reported in parts per million on the δ scale. In the case of multiplets, the signals are reported as intervals. Signals are abbreviated as s for singlet, d for doublet, t for triplet, q for quartet, and m for multiplet. Coupling constants are expressed in hertz. Hydrogenation reactions were carried out in a Shaker-type hydrogenation apparatus (Parr). Elemental analysis was determined with a LECO CHNS-932 elemental analyzer. LC-MS analyses were performed using an Alliance 2695 (Waters) with a Waters 2996 diode array UV-vis detector, and the Alliance 2695 was interfaced to a Micromass ZQ mass spectrometer. Analyses were performed using reversed-phase HPLC silica-based columns: column bridge C18, 3.5 mm (2.1×100 mm). An injection volume of 3 mL, a flow rate of 0.25 mL/min, and gradient elution (15–95% over 10 min) of acetonitrile in water were used. The acetonitrile solution contained 0.08% (v/v) formic acid, and the water solution contained 0.1% (v/v) formic acid. Analyses were monitored at a 254 nm wavelength. Flash chromatography was performed using a Biotage Isolera flash purification system.

General Procedure for the Synthesis of 1–10. To a solution of 18 or 19 (1 equiv) and the corresponding amines (2 equiv) in dry THF was added Al(CH₃)₃ in heptane (2.0 M) (2 equiv). The mixture was heated at 125 °C for 35 min in a microwave reactor. The reaction mixture was poured into an Erlenmeyer flask and cooled in an ice bath, and 1 N HCl aqueous solution was slowly added until the effervescence ended. The mixture was taken to an extraction funnel, and Et₂O was added. The residue was purified by flash chromatography.

(*R*)-3-[(4-Benzyl-2-oxooxazolidin-3-yl)methyl]-N-[4-(benzylcarbamoyl)phenyl]benzamide (1). Compound 18 (0.06 g, 0.18 mmol), compound 17a (0.08 g, 0.36 mmol), and Al₃(CH₃)₃ in heptane (2.0 M) (0.2 mL, 0.36 mmol) in THF (10 mL) were heated at 125 °C for 35 min in a microwave reactor. The residue was purified (Biotage KP-Sil, 25 g; EtOAc/hexane from 5:95 to 10:90), yielding a white solid (0.04 g, 40%). Mp: 120 °C. ¹H NMR (300 MHz, DMSO-*d*₆): δ (ppm) 10.47 (s, 1H, NH), 8.95 (t, *J* = 6.0 Hz, 1H, NHCH₂), 8.04–7.78 (m, 6H, H-Ar), 7.64–7.48 (m, 4H, H-Ar), 7.45–7.13 (m, 8H, H-Ar), 4.68 (m, 1H), 4.47 (d, *J* = 6.0 Hz, 2H, NHCH₂), 4.41–4.31 (m, 1H), 4.22 (m, 1H), 4.08–3.99 (m, 1H), 4.03–3.83 (m, 1H), 3.05 (dd, *J*_{ab} = 13.5, *J*_{a4} = 4.2 Hz, 1H), 2.75 (dd, *J*_{ba} = 13.5, *J*_{b4} = 8.2 Hz, 1H). ¹³C NMR (75 MHz, DMSO-*d*₆): δ (ppm) 165.6 (CO), 165.5 (CO), 158.6 (C), 139.8, 137.3, 136.1, 135.1, 135.5, 131.0, 129.2 (2C), 128.7, 128.5 (2C), 128.2 (3C), 127.9 (2C), 127.2 (3C), 126.8, 126.7 (2C), 119.5 (2C), 66.3 (C), 55.3 (C), 45.1 (C), 42.5 (CH₂), 37.2 (C). HPLC-MS: gradient elution (40–95% over 10 min) of acetonitrile in water, retention time 4.61 min, [M + H]⁺ = 520. Anal. Calcd for C₃₂H₂₉N₃O₄: C, 73.97; H, 5.63; N, 8.09. Found: C, 73.88; H, 5.66; N, 8.08.

(*R*)-3-[(4-Benzyl-2-oxooxazolidin-3-yl)methyl]-N-[4-((4-(tert-butyl)benzyl)carbamoyl)phenyl]benzamide (2). Compound 18 (0.06 g, 0.18 mmol), compound 17b (0.08 g, 0.36 mmol), and Al(CH₃)₃ in heptane (2.0 M) (0.2 mL, 0.36 mmol) in THF (10 mL) were heated at 125 °C for 35 min in a microwave reactor. The residue was purified (Biotage KP-Sil, 25 g; EtOAc/hexane from 5:95 to 10:90), yielding a white solid (0.05 g, 44%). Mp: 110 °C. ¹H NMR (300 MHz, CDCl₃): δ (ppm) 8.91 (s, 1H, NH), 7.83–7.80 (m, 1H, H-Ar), 7.78–7.63 (m, SH, H-Ar), 7.44–7.15 (m, 9H, H-Ar), 7.07–6.96 (m, 2H, H-Ar), 6.66 (t, *J* = 5.7 Hz, 1H, NHCH₂), 4.74–4.65 (m, 1H), 4.57 (d, *J* = 5.4 Hz, 2H, NHCH₂), 4.21–4.07 (m, 2H), 4.00–3.90 (m, 1H), 3.87–3.76 (m, 1H), 3.04 (dd, *J*_{ab} = 13.6, *J*_{a4} = 4.8 Hz, 1H), 2.63 (dd, *J*_{ba} = 13.6, *J*_{b4} = 8.5 Hz, 1H), 1.30 (s, 9H, 3CH₃). ¹³C NMR (75 MHz, CDCl₃): δ (ppm) 166.8 (CO), 165.8 (CO), 158.6, 150.5, 141.2, 139.7, 136.5, 135.2, 131.2, 129.8, 129.2, 128.9 (2C), 128.9 (2C), 127.9 (2C), 127.7 (2C), 127.2, 127.1, 126.6, 125.6 (2C), 119.9 (2C), 67.1 (C), 55.8 (C), 46.0 (C), 43.8 (CH₂), 38.6 (C), 34.5 (C(CH₃)₃), 31.3 (3CH₃). HPLC-MS: gradient elution (40–95% over 10.0 min) of acetonitrile in water, retention time 8.83 min, [M + H]⁺ = 576. Anal. Calcd for C₃₆H₃₇N₃O₄: C, 75.11; H, 6.48; N, 7.30. Found: C, 75.00; H, 6.75; N, 7.70.

(*R*)-3-[(4-Benzyl-2-oxooxazolidin-3-yl)methyl]-N-[4-((4-(trifluoromethyl)benzyl)carbamoyl)phenyl]benzamide (3). Compound 18 (0.1 g, 0.31 mmol), compound 17c (0.18 g, 0.61 mmol),

and Al(CH₃)₃ in heptane (2.0 M) (0.3 mL, 0.61 mmol) in THF (10 mL) were heated at 125 °C for 35 min in a microwave reactor. The residue was purified (Biotage KP-Sil, 25 g; EtOAc/hexane from 5:95 to 10:90), yielding a white solid (0.09 g, 50%). Mp: 114 °C. ¹H NMR (300 MHz, DMSO-*d*₆): δ (ppm) 10.49 (s, 1H, NH), 9.07 (t, *J* = 6.1 Hz, 1H, CH₂NH), 7.98–7.77 (m, 6H, H-Ar), 7.69 (m, 2H, H-Ar), 7.53 (m, SH, H-Ar), 7.35–7.10 (m, 4H, H-Ar), 4.68 (d, *J* = 15.6 Hz, 1H) 4.55 (d, *J* = 5.8 Hz, 2H, CH₂NH), 4.41 (m, 1H), 4.22 (m, 1H), 4.04 (m, 1H), 3.92 (m, 1H), 3.05 (dd, *J*_{ab} = 13.5, *J*_{a4} = 4.2 Hz, 1H), 2.75 (dd, *J*_{ba} = 13.6, *J*_{b4} = 8.1 Hz, 1H). ¹³C NMR (75 MHz, DMSO): δ (ppm) 165.8 (CO), 165.7 (CO), 157.7 (C), 144.7, 141.9, 139.2, 137.3, 136.1, 135.1, 131.0, 129.2 (2C), 129.0, 128.7, 128.5 (3C), 128.0 (2C), 127.9 (3C), 127.85, 127.6, 126.8, 126.7, 125.2, 119.5, 66.3 (C), 55.3 (C), 45.1 (C), 42.3 (NHCH₂), 37.2 (C). HPLC-MS: gradient elution (40–95% over 10.0 min) of acetonitrile in water, retention time 10.2 min, [M + H]⁺ = 588. Anal. Calcd for C₃₃H₂₈F₃N₃O₄: C, 67.45; H, 6.79; N, 7.15. Found: C, 67.69; H, 5.00; N, 7.14.

(*R*)-3-[(4-Benzyl-2-oxooxazolidin-3-yl)methyl]-N-[4-(pentylcarbamoyl)phenyl]benzamide (4). Compound 18 (0.10 g, 0.31 mmol), compound 17d (0.13 g, 0.61 mmol), and Al(CH₃)₃ in heptane (2.0 M) (0.31 mL, 0.61 mmol) in THF (10 mL) were heated at 125 °C for 35 min in a microwave reactor. The crude was purified (Biotage KP-Sil, 25 g; EtOAc/hexane from 5:95 to 10:90), yielding a white solid (0.07 g, 45%). Mp: 140 °C. ¹H NMR (300 MHz, DMSO-*d*₆): δ (ppm) 10.46 (s, 1H, NH), 8.35 (t, *J* = 5.6 Hz, 1H, CH₂NH), 7.91 (m, 1H, H-Ar), 7.86 (br s, SH-Ar), 7.58–7.51 (m, 2H, H-Ar), 7.32–7.17 (m, SH, H-Ar), 4.69 (m, 1H), 4.42 (m, 1H), 4.23 (m, 1H), 4.06 (m, 1H), 4.00–3.89 (m, 1H), 3.25 (m, 2H, NHCH₂), 3.06 (dd, *J*_{ab} = 13.6, *J*_{a4} = 4.2 Hz, 1H), 2.77 (dd, *J*_{ba} = 13.6, *J*_{b4} = 8.1 Hz, 1H), 1.52 (m, 2H), 1.42–1.18 (m, 4H), 0.85 (t, *J* = 6.8 Hz, 3H, CH₃). ¹³C NMR (75 MHz, DMSO-*d*₆): δ (ppm) 166.0 (CO), 165.9 (CO), 158.1, 141.9, 137.6, 136.5, 135.5, 131.4, 130.1, 129.6 (2C), 129.1, 128.9 (2C), 128.2 (2C), 127.6, 127.2, 127.1, 119.8 (2C), 66.7 (C), 55.7 (C), 45.5 (C), 40.7 (CH₂), 37.6 (C), 29.2 (CH₂), 29.1 (CH₂), 22.3 (CH₂), 14.3 (CH₃). HPLC-MS: gradient elution (40–95% over 10.0 min) of acetonitrile in water, retention time 5.09 min, [M + H]⁺ = 500. Anal. Calcd for C₃₀H₃₃N₃O₄: C, 72.12; H, 6.66; N, 8.41. Found: C, 72.40; H, 6.83; N, 8.68.

(*R*)-3-[(4-Benzyl-2-oxooxazolidin-3-yl)methyl]-N-[4-(dodecylcarbamoyl)phenyl]benzamide (5). Compound 18 (0.06 g, 0.18 mmol), compound 17e (0.11 g, 0.36 mmol), and Al(CH₃)₃ in heptane (2.0 M) (0.18 mL, 0.36 mmol) in THF (10 mL) were heated at 125 °C for 35 min in a microwave reactor. The organic layers were dried, the solvent was evaporated under reduced pressure, and the crude was purified (Biotage KP-Sil, 25 g; EtOAc/hexane from 5:95 to 10:90), yielding a white solid (0.05 g, 45%). Mp: 115 °C. ¹H NMR (300 MHz, CDCl₃): δ (ppm) 8.69–8.56 (m, 1H, NH), 7.94–7.64 (m, SH, H-Ar), 7.53–7.19 (m, 4H, H-Ar), 7.13–7.00 (m, 3H, H-Ar), 6.34–6.14 (m, 1H, H-Ar), 4.81 (m, 1H), 4.30–4.13 (m, 1H), 4.02 (m, 1H), 3.94–3.79 (m, 1H), 3.45–3.30 (m, 1H), 3.06 (dd, *J*_{ab} = 13.6, *J*_{a4} = 4.8 Hz, 1H), 2.66 (dd, *J*_{ba} = 13.6, *J*_{b4} = 8.6 Hz, 1H), 1.60–1.55 (m, 2H, CH₂), 1.46–1.15 (m, 18H, 9CH₂), 0.87 (t, *J* = 6.7 Hz, 3H, CH₃). ¹³C NMR (75 MHz, CDCl₃): δ (ppm) 166.9 (CO), 165.6 (CO), 158.6 (C), 140.7, 139.7, 136.7, 135.4, 135.3, 131.4, 130.5, 129.3, 129.0 (2C), 127.8 (2C), 127.3, 127.0, 126.6, 119.9 (2C), 116.7, 67.2 (C), 55.7 (C), 46.1 (C), 40.2 (CH₂), 38.7 (C), 31.9 (CH₂), 29.6 (4CH₂), 29.3 (3CH₂), 27.0 (CH₂), 22.7 (CH₂), 14.1 (CH₃). HPLC-MS: gradient elution (40–95% over 10.0 min) of acetonitrile in water, retention time 9.93 min, [M + H]⁺ = 599. Anal. Calcd for C₃₇H₄₇N₃O₄: C, 74.34; H, 7.93; N, 7.03. Found: C, 74.20; H, 7.50; N, 7.04.

(*R*)-3-[(4-Benzyl-2-oxooxazolidin-3-yl)methyl]-N-[4-(cyclopropylcarbamoyl)phenyl]benzamide (6). Compound 18 (0.18 g, 0.56 mmol), compound 17f (0.18 g, 0.67 mmol), and Al(CH₃)₃ in heptane (2.0 M) (1.11 mL, 2.24 mmol) in THF (10 mL) were heated at 125 °C for 35 min in a microwave reactor. The residue was purified (Biotage KP-Sil, 25 g; EtOAc/hexane (4:6)), yielding a white solid (0.05 g, 2%). ¹H NMR (300 MHz, MeOD): δ (ppm) 7.90–7.88 (m, 1H), 7.84 (br s, 2H), 7.79–7.77 (m, 2H), 7.55–7.51 (m, 4H), 7.30–7.26 (m, 2H), 7.18–7.16 (m, 2H), 4.81 (d, *J* = 4.8 Hz, 1H), 4.36 (d, *J* = 4.4 Hz 1H), 4.30–4.26 (m, 1H), 4.15–4.12 (m,

1H), 4.06–4.02 (m, 1H), 3.11 (dd, J = 13.7, 5.1 Hz, 1H), 2.87–2.80 (m, 2H), 0.83–0.79 (m, 2H), 0.66–0.63 (m, 2H). ^{13}C NMR (75 MHz, MeOD): δ 169.7 (C), 167.2 (C), 159.5 (C), 141.7 (C), 137 (C), 135.9 (C), 135.3 (C), 131.1 (2CH), 129.5 (C), 128.9 (2CH), 128.8 (2CH), 128.4 (2CH), 126.9 (2CH), 126.7 (CH), 119.8 (2CH), 67.2 (CH₂), 55.9 (CH), 45.5 (CH₂), 37.8 (CH₂), 22.6 (CH), 5.14 (2CH₂).

(R)-3-[(4-Benzyl-2-oxooxazolidin-3-yl)methyl]-N-[4-((cyclohexylmethyl)carbamoyl)phenyl]benzamide (7). Compound 18 (0.06 g, 0.18 mmol), compound 17g (0.08 g, 0.36 mmol), and Al(CH₃)₃ in heptane (2.0 M) (0.18 mL, 0.36 mmol) in THF (10 mL) were heated at 125 °C for 35 min in a microwave reactor. The residue was purified (Biotage KP-Sil, 25 g; EtOAc/hexane from 5:95 to 10:90), yielding a white solid (0.04 g, 42%). Mp: 130 °C. ^1H NMR (300 MHz, CDCl₃): δ (ppm) 9.08 (s, 1H, NH), 7.85 (m, 1H, H-Ar), 7.78–7.61 (m, 5H, H-Ar), 7.45–7.16 (m, 5H, H-Ar), 7.09–6.96 (m, 2H, H-Ar), 6.50 (t, J = 6.0 Hz, 1H, CH₂NH), 4.73 (m, 1H), 4.21–4.06 (m, 2H), 4.00 (m, 1H), 3.93–3.79 (m, 1H), 3.25 (m, 2H, CH₂NH), 3.03 (dd, J_{ab} = 13.6, J_{a4} = 4.9 Hz, 1H), 2.63 (dd, J_{ba} = 13.6, J_{b4} = 8.6 Hz, 1H), 1.82–1.52 (m, 6H), 1.32–1.10 (m, 4H), 0.93 (m, 1H). ^{13}C NMR (75 MHz, CDCl₃): δ (ppm) 166.9 (CO), 165.5 (CO), 158.5 (C), 140.8, 136.8, 135.4, 135.3, 131.4, 130.5, 129.3, 129.0, 127.9 (3C), 127.3 (2C), 127.0, 126.6, 119.8, 119.7 (2C), 67.2 (C), 55.7 (C), 46.3 (CH₂NH), 46.1, 38.8 (C), 38.0 (CH), 30.9 (2CH₂), 26.4 (CH₂), 25.8 (2CH₂). HPLC–MS: gradient elution (40–95% over 10.0 min) of acetonitrile in water, retention time 5.71 min, [M + H]⁺ = 527. Anal. Calcd for C₃₂H₃₅N₃O₄: C, 73.12; H, 6.71; N, 7.99. Found: C, 73.44; H, 6.58; N, 7.52.

(S)-3-[(4-Benzyl-2-oxooxazolidin-3-yl)methyl]-N-[4-((4-(tert-butyl)benzyl)carbamoyl)phenyl]benzamide (8). Compound 19 (0.20 g, 0.62 mmol), compound 17b (0.21 g, 0.74 mmol), and Al(CH₃)₃ in heptane (2.0 M) (1.24 mL, 2.48 mmol) in THF (10 mL) were heated at 125 °C for 20 min in a microwave reactor. The residue was purified (Biotage KP-Sil, 25 g; EtOAc/hexane (8:2)), yielding a white solid (0.02 g, 4%). Mp: 171 °C. ^1H NMR (300 MHz, CDCl₃): δ (ppm) 8.32 (s, 1H, H), 7.89–7.71 (m, 6H), 7.48–7.22 (m, 9H, H), 7.06 (d, J = 7.53 Hz, 2H), 6.44 (s, 1H), 4.81 (d, J = 15.28 Hz, 1H), 4.61 (s, 2H), 4.23–4.15 (m, 2H, H), 4.04 (dd, J = 5.78, 8.91 Hz, 1H), 3.89 (m, 1H), 3.08 (dd, J = 4.69, 13.47 Hz, 1H), 2.68 (dd, J = 8.42, 13.47 Hz, 1H), 2.17 (s, 9H). ^{13}C NMR (MHz, CDCl₃): δ 166.7, 165.4, 158.5, 150.7, 140.9, 136.8, 135.3, 135.0, 131.5, 129.4, 129.0, 128.1, 127.8, 127.3, 127.0, 126.6, 125.7, 119.8, 67.2, 55.7, 46.1, 43.9, 38.8, 34.5, 31.3. HPLC–MS: gradient elution (30–95% in 10 min), retention time 7.66 min, [M + H]⁺ = 576. Anal. Calcd for C₃₆H₄₁N₃O₄: C, 75.11; H, 6.48; N, 7.30. Found: C, 75.10; H, 6.29; N, 7.18.

(S)-3-[(4-Benzyl-2-oxooxazolidin-3-yl)methyl]-N-[4-((4-(trifluoromethyl)benzyl)carbamoyl)phenyl]benzamide (9). Compound 19 (0.20 g, 0.62 mmol), compound 17c (0.22 g, 0.74 mmol), and Al(CH₃)₃ in heptane (2.0 M) (1.24 mL, 2.48 mmol) in THF (10 mL) were heated at 125 °C for 35 min in a microwave reactor. The residue was purified (Biotage KP-Sil, 25 g; EtOAc/hexane from 5:95 to 10:90), yielding a white solid (0.32 g, 87%). Mp: 176 °C. ^1H NMR (300 MHz, MeOD): δ (ppm) 7.93–7.78 (m, 4H), 7.65–7.50 (m, 7H), 7.27–7.15 (m, 6H), 4.75 (d, J = 15.32 Hz, 1H), 4.61 (d, J = 5.84 Hz, 2H), 4.57–4.50 (m, 1H), 4.48–4.32 (m, 1H), 4.26–4.15 (m, 1H), 4.10–4.02 (m, 1H), 3.08 (dd, J = 4.88, 13.53 Hz, 1H), 2.81 (dd, J = 7.78, 13.35 Hz, 1H). ^{13}C NMR (75 MHz, MeOD): δ (ppm) 169.6 (CO), 168.6 (CO), 160.9, 145.0, 143.3, 138.4, 137.3, 136.6, 133.7, 132.5, 130.8, 130.3, 130.2, 129.8, 129.2, 127.1 (c, J = 30.31 Hz), 126.8, 126.4 (c, J = 9.17 Hz), 126.1 (d, J = 214.1 Hz), 124.7, 121.3, 68.6, 57.3, 46.8, 44.0, 39.2. HPLC–MS: gradient elution (30–95% over 10 min), retention time 6.84 min, [M + H]⁺ = 588.

(S)-3-[(4-Benzyl-2-oxooxazolidin-3-yl)methyl]-N-[4-(pentylcarbamoyl)phenyl]benzamide (10). Compound 19 (0.20 g, 0.62 mmol), compound 17d (0.15 g, 0.74 mmol), and Al(CH₃)₃ in heptane (2.0 M) (1.24 mL, 2.48 mmol) in THF (10 mL) were heated at 125 °C for 10 min in a microwave reactor. The crude was purified (Biotage KP-Sil, 25 g; EtOAc/hexane from 5:95 to 10:90), yielding a white solid (0.25 g, 80%). Mp: 267 °C. ^1H NMR (300 MHz, DMSO-d₆): δ (ppm) 8.36 (br s, 1H, NH), 7.92–7.82 (m, 3H), 7.57–7.53 (m,

4H), 7.31–7.19 (m, 6H), 4.69 (d, J = 15.61 Hz, 1H), 4.42 (d, J = 15.54 Hz, 1H), 4.26–4.20 (m, 1H), 4.08–4.03 (m, 1H), 3.98–3.89 (m, 1H), 3.36–3.32 (m, 2H), 3.05 (dd, J = 3.78, 13.32 Hz, 1H), 2.75 (dd, J = 8.12, 13.43 Hz, 1H), 1.56–1.47 (m, 2H), 1.32–1.26 (m, 4H), 0.87 (t, J = 6.46 Hz, 3H). ^{13}C NMR (75 MHz, DMSO-d₆): δ (ppm) 165.6 (CO), 165.5 (CO), 157.7, 141.5, 137.3, 136.1, 135.1, 131.0, 129.7, 129.3, 128.7, 128.5, 127.8, 126.8, 126.7, 119.5, 66.3, 55.3, 45.1, 38.7, 37.2, 28.9, 28.7, 21.9, 13.9. HPLC–MS: gradient elution (30–95% over 10 min), retention time 6.30 min, [M + H]⁺ = 500.

N-[3-((S)-3-((R)-4-Benzyl-2-oxooxazolidin-3-yl)-2-methyl-3-oxopropyl)phenyl]-4-(2-(4-(tert-butyl)phenyl)acetamido)benzamide (11). To a solution of 23 (0.16 g, 0.56 mmol) in dry THF was added 21a in dry THF (10 mL) under a nitrogen atmosphere, and the resulting solution was stirred for 12 h. The reaction mixture was treated with a 1 N HCl aqueous solution (10 mL) and extracted with AcOEt (20 mL). The organic layer was washed with saturated aqueous NH₄Cl and dried over MgSO₄. The residue was purified (Biotage KP-Sil, 25 g; EtOAc/hexane from 5:95 to 10:90), yielding a white solid (0.24 g, 68%). Mp: 130 °C. $[\alpha]_D^{20} = -16.9$. ^1H NMR (300 MHz, CDCl₃): δ (ppm) 7.75 (m, 2H, H-Ar), 7.68–7.60 (m, 1H, H-Ar), 7.54 (m, 2H, H-Ar), 7.44 (m, 3H, H-Ar), 7.32–7.20 (m, 6H, H-Ar), 7.13–7.00 (m, 3H, H-Ar), 4.66 (m, 1H, CH), 4.23–4.00 (m, 3H, CH₂/CH), 3.74 (s, 2H, CH₂CO), 3.25–3.06 (m, 2H), 2.63 (m, 2H), 1.34 (s, 9H, 3CH₃), 1.18 (d, J = 6.6 Hz, 3H, CH₃). ^{13}C NMR (75 MHz, CDCl₃): δ (ppm) 176.4 (CO), 176.3 (CO), 169.5 (CO), 153.1 (C-2), 150.9, 140.8, 140.2, 138.0, 135.1, 130.8, 129.4 (2C), 129.2 (2C), 129.1, 128.9 (2C), 128.1 (2C), 127.3, 126.3 (2C), 125.5, 120.8, 119.3 (2C), 118.4, 66.0 (C), 55.2 (C), 44.5 (CH₂), 39.7 (C), 39.6 (C), 37.8 (C), 34.6 (C(CH₃)), 31.3 (3CH₃), 16.5 (CH₃). HPLC–MS: retention time 8.78 min, [M + H]⁺ = 632. Anal. Calcd for C₃₉H₄₁N₃O₅: C, 74.14; H, 6.54; N, 6.65. Found: C, 73.89; H, 6.82; N, 6.41.

N-[3-((S)-3-((R)-4-Benzyl-2-oxooxazolidin-3-yl)-2-methyl-3-oxopropyl)phenyl]-4-hexamidobenzamide (12). To a solution of 23 (0.39 g, 1.65 mmol) in dry THF was added 21b in dry THF (10 mL) under a nitrogen atmosphere, and the resulting solution was stirred for 12 h. The reaction mixture was treated with a 1 N HCl aqueous solution (10 mL) and extracted with AcOEt (20 mL). The organic layer was washed with saturated aqueous NH₄Cl and dried over MgSO₄. The residue was purified (Biotage KP-Sil, 25 g; EtOAc/hexane from 5:95 to 10:90), yielding a white solid (0.21 g, 34%). Mp: 141 °C. $[\alpha]_D^{20} = -32.2$. ^1H NMR (300 MHz, CDCl₃): δ (ppm) 8.13–8.10 (br s, 1H, NH), 7.86–7.81 (br s, 1H, NH), 7.76–7.70 (m, 2H, H-Ar), 7.67–7.54 (m, 3H, H-Ar), 7.47–7.37 (m, 2H, H-Ar), 7.24–7.15 (m, 4H, H-Ar), 7.11–7.00 (m, 2H, H-Ar), 4.67–4.57 (m, 1H), 4.22–4.01 (m, 3H), 3.14–3.06 (m, 2H), 2.62–2.50 (m, 2H), 2.36 (t, J = 7.6 Hz, 2H, CH₂CO), 1.70–1.59 (m, 2H), 1.37–1.23 (m, 4H), 1.16 (d, J = 6.7 Hz, 3H, CH₃CH), 0.97–0.79 (t, J = 6.6 Hz, 3H, CH₃). ^{13}C NMR (75 MHz, CDCl₃): δ (ppm) 176.3 (CO), 172.1 (CO), 165.3 (CO), 153.2, 141.3, 140.1, 138.1, 135.1, 129.9, 129.3 (2C), 129.0, 128.9 (2C), 128.2 (2C), 127.3 (2C), 125.5, 121.0, 119.3, 118.6, 66.0, 55.2, 39.7, 39.6, 37.8, 37.7 (CH₂CO), 31.4 (CH₂), 25.2 (CH₂), 22.4 (CH₂), 16.5 (CH₃CH), 13.9 (CH₃). HPLC–MS: retention time 7.70 min, [M + H]⁺ = 556. Anal. Calcd for C₃₃H₃₇N₃O₅: C, 71.33; H, 6.71; N, 7.56. Found: C, 71.18 ; H, 6.42 ; N, 7.31.

(S)-3-[3-(4-(2-(4-(tert-Butyl)phenyl)acetamido)benzamido)-2-methylpropanoic Acid (13). To a solution of 11 (0.14 g, 0.22 mmol) in THF/H₂O (3:1) (30 mL) at 0 °C were added a 30% H₂O₂ aqueous solution (0.1 mL, 0.88 mmol) and LiOH (0.01 g, 0.44 mmol) in H₂O (2 mL). The resulting solution was stirred for 2 h at rt. The reaction mixture was treated with a 1 N HCl aqueous solution (1 mL) and extracted with AcOEt (2x 20 mL). The organic layers were washed with brine and dried over MgSO₄. The residue was purified (Biotage KP-Sil, 25 g; ethanol/CH₂Cl₂ (0–6%)), yielding a white solid (0.07 g, 70%). Mp: 180.9 °C. $[\alpha]_D^{20} = 11.1$. ^1H NMR (300 MHz, DMSO-d₆): δ (ppm) 12.16 (s, 1H, COOH), 10.40 (s, 1H, NH), 10.04 (s, 1H, NH), 7.92 (d, J = 8.7 Hz, 2H), 7.72 (d, J = 8.7 Hz, 2H), 7.64–7.57 (m, 2H, H-Ar), 7.34 (m, 2H, H-Ar), 7.26 (m, 3H, H-Ar), 6.91 (m, 1H, H-Ar), 3.62 (s, 2H, CH₂CO), 2.89 (m, 1H), 2.66–2.54 (m, 2H), 1.26 (s, 9H, 3CH₃), 1.05 (d, J = 6.5 Hz, 3H, CH₃). ^{13}C NMR (75

MHz, DMSO-*d*₆): δ (ppm) 176.7 (CO), 169.7 (CO), 164.7 (CO), 148.9, 142.1, 139.9, 139.1, 132.6, 130.3, 129.1, 128.8 (2C), 128.5 (2C), 128.3, 125.1 (2C), 123.9, 120.8, 118.2 (2C), 42.9 (CH₂CO), 40.6, 38.7, 34.1 (C(CH₃)₃), 31.1 (3CH₃), 16.7 (CH₃). HPLC-MS: gradient elution (40–95% over 10.0 min) of acetonitrile in water, retention time 6.72 min, [M + H]⁺ = 473. Anal. Calcd for C₂₉H₃₂N₂O₄: C, 73.7; H, 6.83; N, 5.93. Found: C, 74.00; H, 7.00; N, 5.70.

(S)-3-[3-(4-Hexanamidobenzamido)phenyl]-2-methylpropanoic Acid (14). To a solution of **12** (0.10 g, 0.18 mmol) in THF/H₂O (3:1) (30 mL) at 0 °C were added a 30% H₂O₂ aqueous solution (0.1 mL, 0.72 mmol) and LiOH (0.008 g, 0.36 mmol) in H₂O (2 mL). The resulting solution was stirred for 2 h at rt. The reaction mixture was treated with a 1 N HCl aqueous solution (1 mL) and extracted with AcOEt (2 × 20 mL). The organic layers were washed with brine and dried over MgSO₄. The residue was purified (Biotage KP-Sil, 25 g; CH₃OH/CH₂Cl₂ (0–6%)), yielding a white solid (0.09 g, 62%). Mp: 200 °C. $[\alpha]_{D}^{20}$ = 12.9. ¹H NMR (300 MHz, DMSO-*d*₆): δ (ppm) 12.18 (s, 1H, COOH), 10.13 (s, 1H, NHCO), 10.03 (s, 1H, NHCO), 7.91 (d, *J* = 8.7 Hz, 2H), 7.71 (d, *J* = 8.5 Hz, 2H), 7.68–7.53 (m, 2H), 7.23 (m, 1H), 6.91 (m, 1H), 2.90 (m, 1H), 2.61 (m, 3H), 2.33 (t, *J* = 7.4 Hz, 2H, CH₂CO), 1.58 (m, 2H, CH₂), 1.28 (m, 4H, 2CH₂), 1.05 (d, *J* = 6.2 Hz, 3H, CH₃CH), 0.87 (t, *J* = 6.6 Hz, 3H, CH₃). ¹³C NMR (75 MHz, DMSO-*d*₆): δ (ppm) 176.7 (CO), 171.7 (CO), 164.7 (CO), 142.2, 139.9, 139.1, 128.7, 128.5 (2C), 128.2, 124.0, 120.7, 118.2, 118.1 (2C), 40.6 (CH), 38.6, 36.4 (CH₂CO), 30.9 (CH₂), 24.6 (CH₂), 21.9 (CH₂), 16.7 (CH₃CH), 13.8 (CH₃). HPLC-MS: retention time 7.93 min, [M + H]⁺ = 236. Anal. Calcd for C₂₃H₂₈N₂O₄: C, 69.68; H, 7.12; N, 7.07. Found: C, 70.21; H, 7.08; N, 6.95.

4-[(tert-Butoxycarbonyl)amino]benzoic Acid (15). To a solution of 4-aminobenzoic acid (0.2 g, 1.5 mmol) in water/dioxane (1:2, 6 mL) were added Et₃N (0.4 mL, 3.0 mmol) and di-*tert*-butyl dicarbonate (0.6 g, 3.0 mmol). The resulting solution was stirred at room temperature for 24 h. The solvent was evaporated, and the residue was acidified with a 1 N HCl aqueous solution. The obtained precipitate was washed with water, yielding **15** as a white solid (0.47 g, 89%). Mp: 181 °C. ¹H NMR (300 MHz, DMSO-*d*₆): δ (ppm) 12.21 (s, 1H, COOH), 9.71 (s, 1H, NH), 7.82 (d, *J* = 8.7 Hz, 2H), 7.54 (d, *J* = 8.7 Hz, 2H), 1.44 (s, 9H, 3CH₃). ¹³C NMR (75 MHz, DMSO-*d*₆): δ 167.4 (CO₂H), 152.9 (CONH), 144.1, 130.3 (C), 124.4, 117.6 (C), 80.0 (C(CH₃)₃), 28.4 (3CH₃). HPLC-MS: retention time 4.25 min, [M + H]⁺ = 237. Anal. Calcd for C₁₂H₁₅NO₄: C, 60.75; H, 6.37; N, 5.90. Found: C, 60.84; H, 6.09; N, 5.95.

General Procedure for the Synthesis of 16a–g. To a cooled mixture of **15** (1 equiv) in THF or DMF were added Et₃N (1.2 equiv), HOBr (1.2 equiv), and corresponding coupling reagents (1.2 equiv). Then the corresponding amines were added, and the mixture was stirred for 12 h at rt. The reaction mixture was treated with a 1 N HCl aqueous solution and extracted with AcOEt. The organic layers were washed with brine, dried over MgSO₄, and concentrated in vacuo. The residue was purified by flash chromatography.

4-[N-(tert-Butoxycarbamoyl)amino]benzylamine (16a). To a solution of **15** (0.20 g, 0.84 mmol) in THF at 0 °C were added PyBOP (0.53 g, 1.01 mmol), HOBr (0.14 g, 1.01 mmol), Et₃N (0.14 mL, 1.01 mmol), and benzylamine (0.11 mL, 1.01 mmol). The residue was purified (Biotage KP-Sil, 25 g; EtOAc/hexane from 5:95 to 10:90), yielding a white solid (0.19 g, 80%). Mp: 150 °C. ¹H NMR (300 MHz, DMSO-*d*₆): δ 9.60 (s, 1H, NH), 8.86 (t, *J* = 6.0 Hz, 1H, NHCH₂), 7.80 (d, *J* = 8.7 Hz, 2H), 7.52 (d, *J* = 8.7 Hz, 2H), 7.38–7.18 (m, 5H), 4.45 (d, *J* = 5.9 Hz, 2H, NHCH₂), 1.47 (s, 9H, 3CH₃). ¹³C NMR (75 MHz, DMSO-*d*₆): δ 165.7 (CO), 152.5 (CO), 142.3, 139.8, 128.2 (C), 128.0 (C), 127.6, 127.1, 126.1, 117.1, 79.4 (C(CH₃)₃), 42.5 (NHCH₂), 28.0 (3CH₃). HPLC-MS: retention time 9.05 min, [M + H]⁺ = 327. Anal. Calcd for C₁₉H₂₂N₂O₃: C, 69.92; H, 6.79; N, 8.58. Found: C, 70.16; H, 6.49; N, 8.58.

4-[N-(tert-Butoxycarbamoyl)amino]-N-(*tert*-butyl)benzylamine (16b). To a solution of **15** (0.30 g, 1.26 mmol) in THF (20 mL) at 0 °C were added PyBOP (0.79 g, 1.52 mmol), HOBr (0.21 g, 1.52 mmol), Et₃N (0.21 mL, 1.52 mmol), and 4-(*tert*-butyl)benzylamine (0.08 g, 1.52 mmol). The residue was purified (Biotage KP-Sil, 25 g; EtOAc/hexane from 5:95 to 10:90), yielding a white solid (0.3 g,

60%). Mp: 112 °C. ¹H NMR (300 MHz, CDCl₃): δ (ppm) 7.72 (d, *J* = 8.6 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.38 (d, *J* = 8.4 Hz, 2H), 7.29 (d, *J* = 8.6 Hz, 2H), 6.77 (s, 1H, NH), 6.37 (t, *J* = 5.7 Hz, 1H, NHCH₂), 4.59 (d, *J* = 5.4 Hz, 2H, NHCH₂), 1.51 (s, 9H, 3CH₃), 1.31 (s, 9H, 3CH₃). ¹³C NMR (75 MHz, CDCl₃): δ (ppm) 166.7 (CO), 152.3 (CO), 150.6, 141.5, 135.2, 128.5, 128.0 (C), 127.8 (C), 125.7 (C), 117.7 (C), 81.0 (OC(CH₃)₃), 43.8 (CH₂), 34.5 (C(CH₃)₃), 31.3 (3CH₃), 28.3 (3CH₃). HPLC-MS: gradient elution (15–95% over 5 min) of acetonitrile in water, retention time 5.71 min, [M + H]⁺ = 383. Anal. Calcd for C₂₃H₃₀N₂O₃: C, 72.22; H, 7.91; N, 7.32. Found: C, 72.51; H, 7.95; N, 7.20.

4-[N-(*tert*-Butoxycarbamoyl)amino]-N-(4-trifluoromethyl)benzylamine (16c). To a solution of **15** (0.10 g, 0.42 mmol) in THF (20 mL) at 0 °C were added PyBOP (0.26 g, 0.51 mmol), HOBr (0.07 g, 0.51 mmol), Et₃N (0.07 mL, 0.51 mmol), and 4-(trifluoromethyl)benzylamine (0.07 mL, 0.51 mmol). The residue was purified (Biotage KP-Sil, 25 g; AcOEt/hexane from 5:95 to 10:90) gave **16c** as a white solid (0.14 g, 84%). Mp: 141 °C. ¹H NMR (300 MHz, DMSO-*d*₆): δ (ppm) 9.61 (s, 1H, NH), 8.96 (t, *J* = 6.0 Hz, 1H, NHCH₂), 7.81 (d, *J* = 8.8 Hz, 2H, CH-Ar), 7.68 (d, *J* = 8.8 Hz, 2H, CH-Ar), 7.56–7.47 (m, 4H, CH-Ar), 4.52 (d, *J* = 5.8 Hz, 2H, NHCH₂), 1.47 (s, 9H, 3CH₃). ¹³C NMR (75 MHz, DMSO-*d*₆): δ (ppm) 165.8 (CO), 152.5 (CO), 144.7, 142.4, 128.0, 127.8 (C), 127.3 (C), 125.9 (C), 125.1 (q, *J* = 268 Hz, CF₃), 117.1 (C), 79.4 (OC(CH₃)₃), 42.2 (CH₂), 28.0 (3CH₃). HPLC-MS: retention time 5.24 min, [M + H]⁺ = 395. Anal. Calcd for C₂₀H₂₁F₃N₂O₃: C, 60.91; H, 5.37; N, 7.10. Found: C, 61.10; H, 5.25; N, 6.88.

tert-Butyl (4-(Pentylcarbamoyl)phenyl)carbamate (16d). To a solution of **15** (0.3 g, 1.26 mmol) in THF (20 mL) at 0 °C were added PyBOP (0.78 g, 1.52 mmol), HOBr (0.21 g, 1.52 mmol), Et₃N (0.21 mL, 1.52 mmol), and 1-pentylamine (0.17 mL, 1.52 mmol). The residue was purified (Biotage KP-Sil, 25 g; 2% CH₃OH in CH₂Cl₂), yielding an orange solid (0.12 g, 33%). Mp: 99 °C. ¹H NMR (300 MHz, CDCl₃): δ (ppm) 7.70 (d, *J* = 8.6 Hz, 2H), 7.42 (d, *J* = 8.6 Hz, 2H), 6.70 (br s, 1H, NHCH₂), 6.08 (s, 1H, NH), 3.41–3.38 (m, 2H, NHCH₂CH₂), 1.52 (s, 9H, 3CH₃), 1.40–1.29 (m, 6H, 3CH₂), 0.91 (t, *J* = 6.8 Hz, 3H, CH₃). ¹³C NMR (75 MHz, CDCl₃): δ (ppm) 166.8 (CO), 152.3 (CO), 141.2, 129.0, 127.9 (C), 117.7 (C), 81.0 (OC(CH₃)₃), 40.0 (CH₂), 29.4 (CH₂), 29.1 (CH₂), 28.2 (3CH₃), 22.4 (CH₂), 13.9 (CH₃). HPLC-MS: retention time 5.03 min, [M + H]⁺ = 307. Anal. Calcd for C₁₇H₂₆N₂O₃: C, 66.64; H, 8.55; N, 9.14. Found: C, 66.20; H, 8.30; N, 9.11.

tert-Butyl (4-(Dodecylcarbamoyl)phenyl)carbamate (16e). To a solution of **15** (0.20 g, 0.84 mmol) in THF (20 mL) at 0 °C were added PyBOP (0.19 g, 1.01 mmol), HOBr (0.19 g, 1.01 mmol), Et₃N (0.14 mL, 1.01 mmol), and 1-dodecylamine (0.23 mL, 1.01 mmol). The residue was purified (Biotage KP-Sil, 25 g; EtOAc/hexane from 5:95 to 10:90), yielding a white solid (0.22 g, 65%). Mp: 110 °C. ¹H NMR (300 MHz, CDCl₃): δ (ppm) 7.69 (d, *J* = 8.6 Hz, 2H), 7.42 (d, *J* = 8.6 Hz, 2H), 6.70 (s, 1H, NHCOO), 6.12 (br s, 1H, NHCH₂), 3.42 (m, 2H, CH₂NH), 1.61 (m, 2H, CH₂), 1.52 (s, 9H, 3CH₃), 1.42–1.17 (m, 18H, 9CH₂), 0.86 (t, *J* = 7.1, 3H, CH₃). ¹³C NMR (75 MHz, CDCl₃): δ (ppm) 166.8 (CO), 152.3 (CO), 141.3, 128.9, 127.9, 117.7, 81.0 (OC(CH₃)₃), 40.1 (CH₂N), 31.9 (CH₂), 29.7 (CH₂), 29.6 (CH₂), 29.54 (CH₂), 29.50 (CH₂), 29.3 (3CH₂), 28.3 (3CH₃), 27.0 (CH₂), 22.6 (CH₂), 14.1 (CH₃). HPLC-MS: retention time 6.0 min, [M + H]⁺ = 405. Anal. Calcd for C₂₄H₄₀N₂O₃: C, 71.25; H, 9.97; N, 6.92. Found: C, 71.08; H, 10.12; N, 6.63.

tert-Butyl (4-(Cyclopropyl)carbamoyl)phenyl)carbamate (16f). To a solution of **15** (0.50 g, 2.11 mmol) in DMF (25 mL) at 0 °C were added EDCI (0.61 g, 3.17 mmol), HOBr (0.43 g, 3.17 mmol), Et₃N (0.88 mL, 6.33 mmol), and cyclopropylamine (0.22 mL, 3.17 mmol). The residue was purified (Biotage KP-Sil, 25 g; EtOAc/hexane from 5:95 to 10:90), yielding a white solid (0.28 g, 48%). Mp: 184 °C. ¹H NMR (300 MHz, MeOD): δ (ppm) 7.72 (d, *J* = 8.8 Hz, 2H), 7.48 (d, *J* = 8.8 Hz, 2H), 2.82 (dq, *J* = 7.4, 3.9 Hz, 1H), 1.52 (s, 9H), 0.93–0.73 (m, 2H), 0.69–0.50 (m, 2H). ¹³C NMR (75 MHz, MeOD): δ 164.6 (CO), 155.2 (CO), 144.5 (C), 139.15 (C), 129.6 (2CH), 119.1 (2CH), 81.6 (C), 29.0 (3CH₃), 24.3 (CH), 6.95 (2CH₂). HPLC-MS: retention time 7.84 min, [M + H]⁺ = 277. Anal. Calcd for

$C_{15}H_{20}N_2O_3$: C, 65.2; H, 7.3; N, 10.14. Found: C, 68.18; H, 6.94; N, 10.08.

tert-Butyl (4-((Cyclohexylmethyl)carbamoyl)phenyl)carbamate (16g). To a solution of **15** (0.14 g, 0.57 mmol) in THF (20 mL) at 0 °C were added EDCI (0.17 g, 0.88 mmol), HOEt (0.12 g, 0.88 mmol), Et₃N (0.12 mL, 0.88 mmol), and cyclohexylamine (0.11 mL, 0.88 mmol). The residue was purified (Biotage KP-Sil, 25 g; EtOAc/hexane from 5:95 to 10:90), yielding a white solid (0.06 g, 31%). Mp: 114 °C. ¹H NMR (300 MHz, DMSO-*d*₆): δ (ppm) 9.56 (s, 1H, NH), 8.24 (t, *J* = 5.8 Hz, 1H, NHCH₂), 7.74 (d, *J* = 8.7 Hz, 2H), 7.49 (d, *J* = 8.7 Hz, 2H), 3.05 (m, 2H, NHCH₂), 1.67 (m, 5H), 1.47 (s, 9H, 3CH₃), 1.24–1.01 (m, 4H), 0.90 (m, 2H). ¹³C NMR (75 MHz, DMSO-*d*₆): δ (ppm) 165.7 (CO), 152.6 (CO), 142.0, 128.06, 127.9 (C), 117.0 (C), 79.4 (OC(CH₃)₃), 45.3 (NHCH₂), 37.5 (C), 30.5 (C), 28.0 (3CH₃), 26.1 (C), 25.4 (C). HPLC–MS: retention time 6.02 min, [M + H]⁺ = 333. Anal. Calcd for $C_{19}H_{28}N_2O_3$: C, 68.65; H, 8.49; N, 8.43. Found: C, 68.40; H, 8.70; N, 8.20.

General Procedure for the Synthesis of 17a–g. The corresponding N-Boc amino acid (**16a–g**) was treated with a mixture of TFA and dichloromethane (1:1, 40 mL) at room temperature for 12 h. The reaction mixture was quenched with aqueous 1 N NaOH (15 mL). The organic layer separated, washed with water, and dried over anhydrous MgSO₄. The solvent was evaporated under reduced pressure, obtaining the desired compounds.

4-Amino-N-benzylbenzamide (17a). The general method was used with compound **16a** (0.35 g, 1.07 mmol). White solid (0.22 g, 92%). Mp: 150 °C. ¹H NMR (300 MHz, DMSO-*d*₆): δ (ppm) 8.55 (t, *J* = 6.1 Hz, 1H, NHCH₂), 7.62 (d, *J* = 8.6 Hz, 2H), 7.40–7.17 (m, 5H, H-Ar), 6.54 (d, *J* = 8.6 Hz, 2H), 5.60 (br s, 2H, NH₂), 4.42 (d, *J* = 5.9 Hz, 2H, NHCH₂). ¹³C NMR (75 MHz, DMSO-*d*₆): δ (ppm) 166.2 (CO), 151.6, 140.3, 128.7 (C), 128.1, 127.1, 126.5, 125.3, 124.2, 121.0, 112.5 (C), 42.3 (CH₂). HPLC–MS: retention time 8.5 min, [M + H]⁺ = 227. Anal. Calcd for $C_{14}H_{20}N_2O$: C, 74.31; H, 6.24; N, 12.38. Found: C, 74.39; H, 6.43; N, 12.55.

4-Amino-N-(4-(*tert*-butyl)benzyl)benzamide (17b). The general method was used with compound **16b** (0.20 g, 0.52 mol). White solid (0.13 g, 90%). Mp: 113 °C. ¹H NMR (300 MHz, CDCl₃): δ (ppm) 7.62 (d, *J* = 8.3 Hz, 2H), 7.37 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.2 Hz, 2H), 6.64 (d, *J* = 8.3 Hz, 2H), 4.59 (d, *J* = 5.4 Hz, 2H, NHCH₂), 1.32 (s, 9H, 3CH₃). ¹³C NMR (75 MHz, CDCl₃): δ (ppm) 167.0 (CO), 150.5, 149.5, 135.5, 128.7 (C), 127.7 (C), 125.6 (C), 124.0, 114.1 (C), 43.7 (CH₂), 34.5 (C(CH₃)₃), 31.3 (3CH₃). HPLC–MS: retention time 4.67 min, [M + H]⁺ = 283. Anal. Calcd for $C_{18}H_{22}N_2O$: C, 76.56; H, 7.85; N, 9.92. Found: C, 76.71; H, 8.10; N, 9.94.

4-Amino-N-(4-(trifluoromethyl)benzyl)benzamide (17c). The general method was used with compound **16c** (0.20 g, 0.51 mol). White solid (0.14 g, 92%). Mp: 113 °C. ¹H NMR (300 MHz, CDCl₃): δ (ppm) 7.63 (d, *J* = 8.0 Hz, 2H), 7.58 (d, *J* = 7.8 Hz, 2H), 7.44 (d, *J* = 7.8 Hz, 2H), 6.65 (d, *J* = 8.0 Hz, 2H), 6.42 (br s, 1H, NHCH₂), 4.67 (d, *J* = 5.8 Hz, 2H, NHCH₂), 4.34–3.49 (br s, 2H, NH₂). ¹³C NMR (75 MHz, CDCl₃): δ (ppm) 167.2 (CO), 149.8, 142.8, 131.1, 128.8 (C), 127.9 (C), 125.7 (C), 125.6, 124.9 (q, *J* = 268 Hz, CF₃), 114.1 (C), 43.4 (CH₂). HPLC–MS: retention time 4.21 min, [M + H]⁺ = 295. Anal. Calcd for $C_{15}H_{13}F_3N_2O$: C, 61.22; H, 4.45; N, 9.52. Found: C, 61.23; H, 4.60; N, 9.60.

4-Amino-N-pentylbenzamide (17d). The general method was used with compound **16d** (0.76 g, 3.68 mmol). White solid (0.44 g, 85%). Mp: 100 °C. ¹H NMR (300 MHz, CDCl₃): δ (ppm) 7.58 (d, *J* = 8.6 Hz, 2H), 6.64 (d, *J* = 8.6 Hz, 2H), 6.01 (br s, 1H, NHCH₂), 3.40–3.37 (m, 2H, NHCH₂CH₂), 1.57–1.51 (m, 2H, NHCH₂CH₂), 1.43–1.24 (m, 4H, 2CH₂), 0.99–0.79 (t, *J* = 6.8 Hz, 3H, CH₃). ¹³C NMR (75 MHz, CDCl₃): δ (ppm) 167.2 (CO), 149.4, 128.5 (C), 124.4, 114.1 (C), 40.0 (CH₂), 29.5 (CH₂), 29.1 (CH₂), 22.4 (CH₂), 14.0 (CH₃). HPLC–MS: retention time 3.7 min, [M + H]⁺ = 207. Anal. Calcd for $C_{12}H_{18}N_2O$: C, 69.87; H, 8.80; N, 13.58. Found: C, 69.23; H, 8.60; N, 13.60.

4-Amino-N-dodecylbenzamide (17e). The general method was used with compound **16e** (0.20 g, 0.49 mmol). White solid (0.14 g, 92%). Mp: 112 °C. ¹H NMR (300 MHz, CDCl₃): δ (ppm) 7.59 (d, *J* = 8.6 Hz, 2H), 6.65 (d, *J* = 8.6 Hz, 2H), 6.05–5.91 (br s, 1H, NH,

NHCH₂), 3.40 (m, 2H, NHCH₂), 1.65–1.50 (m, 2H, NHCH₂CH₂), 1.45–1.16 (m, 18H, 9CH₂), 0.87 (t, *J* = 7.1, 3H, CH₃). ¹³C NMR (75 MHz, CDCl₃): δ (ppm) 167.2 (CO), 149.3, 128.9, 127.8, 114.1, 39.9 (NHCH₂), 31.9 (CH₂), 29.8 (CH₂), 29.6 (3CH₂), 29.3 (3CH₂), 27.0 (CH₂), 22.7 (CH₂), 14.1 (CH₃). HPLC–MS: retention time 11.0 min, [M + H]⁺ = 305. Anal. Calcd for $C_{19}H_{32}N_2O$: C, 74.95; H, 10.59; N, 9.20. Found: C, 74.60; H, 10.55; N, 9.16.

4-Amino-N-cyclopropylbenzamide (17f). The general method was used with compound **16f** (0.55 g, 1.99 mmol). White solid (0.22 g, 63%). Mp: 142 °C. ¹H NMR (300 MHz, MeOD): δ 7.57 (d, *J* = 8.7 Hz, 2H), 6.64 (d, *J* = 8.7 Hz, 2H), 4.86 (s, 4H), 2.85–2.71 (m, 1H), 0.83–0.70 (m, 2H), 0.65–0.53 (m, 2H). ¹³C NMR (75 MHz, MeOD): δ 172.1 (CO), 153.2 (C), 129.9 (C), 123.1 (2CH), 114.6 (2CH), 23.8 (CH), 6.6 (2CH₂). HPLC–MS: retention time 1.2 min, [M + H]⁺ = 177. Anal. Calcd for $C_{10}H_{12}N_2O$: C, 68.16; H, 6.86; N, 15.90. Found: C, 67.97; H, 6.80; N, 15.75.

4-Amino-N-(cyclohexylmethyl)benzamide (17g). The general method was used with compound **16g** (0.20 g, 0.60 mmol). White solid (0.11 g, 80%). Mp: 150 °C. ¹H NMR (300 MHz, DMSO-*d*₆): δ 7.92 (t, *J* = 5.8 Hz, 1H, CH₂NH), 7.54 (d, *J* = 8.6 Hz, 2H), 6.50 (d, *J* = 8.6 Hz, 2H), 5.60–5.48 (m, 2H, NH₂), 3.08–2.92 (m, 2H, CH₂NH), 1.66–1.62 (m, 5H), 1.47–1.41 (m, 1H), 1.13–1.11 (m, 3H), 0.95–0.77 (m, 2H). ¹³C NMR (75 MHz, DMSO-*d*₆): δ (ppm) 165.7 (CO), 142.0, 128.1, 127.6 (C), 116.0 (C), 45.3 (NHCH₂), 37.5 (C), 30.5 (C), 26.1 (C), 25.4 (C). HPLC–MS: retention time 5.34 min, [M + H]⁺ = 333. Anal. Calcd for $C_{14}H_{20}N_2O$: C, 72.38; H, 8.68; N, 12.06. Found: C, 72.60; H, 8.55; N, 12.16.

(R)-Methyl 3-[(4-Benzyl-2-oxooxazolidin-3-yl)methyl]benzoate (18). To a solution of (R)-4-benzyl-3-propionyl-2-oxazolidinone (1.2 g, 5.24 mmol) in anhydrous THF (13 mL) was added potassium *tert*-butoxide (0.6 g, 5.24 mmol), and the resulting solution was stirred for 45 min under a nitrogen atmosphere at room temperature. Then methyl 3-(bromomethyl)benzoate (1.0 g, 4.36 mmol) was added to the stirred solution. The reaction mixture was stirred for 6 h. A saturated solution of NH₄Cl (15 mL) was added and the reaction extracted with ethyl acetate (30 mL). The combined organic extracts were washed successively with H₂O (30 mL) and brine (30 mL) and dried over Na₂SO₄. The solvent was evaporated and the crude purified (Biotage KP-Sil, 25 g; EtOAc/hexane from 5:95 to 10:90), yielding a white solid (0.43 g, 62%). Mp: 62 °C. ¹H NMR (300 MHz, CDCl₃): δ (ppm) 8.06–7.95 (m, 1H, H-Ar), 7.90–7.88 (m, 1H, H-Ar), 7.54–7.40 (m, 2H, H-Ar), 7.36–7.22 (m, 3H, H-Ar), 7.12–7.02 (m, 2H, H-Ar), 4.86 (d, *J* = 15.4 Hz, 1H), 4.18 (m, 2H), 4.10–4.02 (m, 1H), 3.93 (s, 3H, CH₃), 3.89–3.77 (m, 1H), 3.09 (dd, *J*_{ab} = 13.6, *J*_{a4} = 4.7 Hz, 1H), 2.66 (dd, *J*_{ba} = 13.6, *J*_{b4} = 8.9 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃): δ (ppm) 166.5 (CO), 157.9, 136.4, 135.4, 132.4, 130.8, 129.3, 129.1, 129.0, 128.9, 127.1, 67.0, 55.5, 51.9 (OCH₃), 45.9, 38.3. HPLC–MS: retention time 4.8 min, [M + H]⁺ = 326. Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.31. Found: C, 70.31; H, 5.67; N, 4.60.

(S)-Methyl 3-[(4-Benzyl-2-oxooxazolidin-3-yl)methyl]benzoate (19). To a solution of (S)-4-benzyl-3-propionyl-2-oxazolidinone (0.5 g, 2.82 mmol) in anhydrous THF/CH₃CN (20 mL, 1:1) was added Cs₂CO₃ (2.76 g, 8.46 mmol), and the resulting solution was stirred for 45 min under a nitrogen atmosphere at room temperature. Then methyl 3-(bromomethyl)benzoate (1.3 g, 5.64 mmol) was added to the stirred solution. The reaction mixture was stirred for 6 h. A saturated solution of NH₄Cl (25 mL) was added and the reaction extracted with ethyl acetate (2 × 30 mL). The combined organic extracts were washed successively with water (30 mL) and brine (30 mL) and dried over Na₂SO₄. The solvent was evaporated, and the crude was purified (Biotage KP-Sil, 25 g; EtOAc/hexane from 5:95 to 10:90), yielding a white solid (0.60 g, 66%). Mp: 61.1 °C. ¹H NMR (300 MHz, CDCl₃): δ (ppm) 8.00 (d, *J* = 6.5 Hz, 1H), 7.90 (s, 1H), 7.52–7.40 (m, 2H), 7.35–7.17 (m, 3H), 7.10–6.99 (m, 2H), 4.86 (d, *J* = 15.4 Hz, 1H), 4.24–4.10 (m, 2H), 4.08–3.98 (m, 1H), 3.93 (s, 3H), 3.88–3.73 (m, 1H), 3.09 (dd, *J* = 13.6, 4.8 Hz, 1H), 2.66 (dd, *J* = 13.6, 8.9 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃): δ (ppm) 166.6, 158.3, 136.3, 135.3, 132.6, 130.7, 129.3, 129.1, 129.0, 128.9, 127.2, 67.0, 55.5, 52.2, 46.1, 38.6. HPLC–MS: retention time 9.06 min, [M +

$[H]^+ = 326$. Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.31. Found: C, 70.42; H, 5.62; N, 4.13.

4-[2-(4-(*tert*-Butyl)phenyl)acetamido]benzoic Acid (20a). 4-Aminobenzoic acid (0.20 g, 1.46 mmol), methyl *p*-*tert*-butylphenylacetate (0.45 mL, 2.19 mmol), and Al(CH₃)₃ in heptane (2.0 M) (1.10 mL, 2.19 mmol) in THF (10 mL) were heated at 125 °C for 40 min in a microwave reactor. The reaction mixture was poured into an Erlenmeyer flask and cooled in an ice bath, and a 1 N HCl aqueous solution was slowly added until the effervescence ended. The mixture was extracted with AcOEt (2 × 20 mL), and the organic layer was washed with saturated aqueous NH₄Cl and dried over MgSO₄. The residue was purified (Biotage KP-Sil, 25 g; EtOH/CH₂Cl₂ (0–6%)), yielding a white solid (0.30 g, 65%). Mp: 155 °C. ¹H NMR (300 MHz, DMSO-*d*₆): δ (ppm) 12.66 (s, 1H, CO₂H), 10.43 (s, 1H, NH), 7.86 (d, *J* = 8.8 Hz, 2H), 7.69 (d, *J* = 8.8 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 3.61 (s, 2H, CH₂CO), 1.34 (s, 9H, 3CH₃). ¹³C NMR (75 MHz, DMSO-*d*₆): δ (ppm) 169.8(CO), 166.8 (CO), 148.9, 143.2, 132.6, 130.3, 128.7, 125.1, 118.3, 49.2 (CH₂CO), 34.1 (C(CH₃)₃), 31.1 (3CH₃). HPLC–MS: retention time 5.25 min, [M + H]⁺ = 312. Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.10; H, 6.78; N, 4.52.

4-Hexanamidobenzoic Acid (20b). 4-Aminobenzoic acid (0.25 g, 1.81 mmol), ethyl hexanoate (0.6 g, 3.64 mmol), and Al(CH₃)₃ in heptane 2.0 M (1.82 mL, 3.64 mmol) in THF (20 mL) were heated at 125 °C for 20 min in a microwave reactor. The reaction mixture was poured into an Erlenmeyer flask and cooled in an ice bath, and a 1 N HCl aqueous solution was slowly added until the effervescence ended. The precipitate obtained was washed with H₂O (2 × 10 mL), yielding a white solid (0.30 g, 70%). Mp: 245 °C. ¹H NMR (300 MHz, DMSO-*d*₆): δ (ppm) 12.65 (s, 1H, CO₂H), 10.15 (s, 1H, NH), 7.86 (d, *J* = 8.7 Hz, 2H), 7.69 (d, *J* = 8.7 Hz, 2H), 2.32 (t, *J* = 7.4 Hz, 2H, CH₂CO), 1.65–1.46 (m, 2H, CH₂), 1.40–1.18 (m, 4H, 2CH₂), 0.95–0.75 (t, *J* = 6.7 Hz, 3H, CH₃). ¹³C NMR (75 MHz, DMSO-*d*₆): δ (ppm) 171.8 (CO), 166.9 (CO), 143.3, 130.3, 124.7, 118.2, 36.4 (CH₂CO), 30.8 (CH₂), 24.6 (CH₂), 21.9 (CH₂), 13.8 (CH₃). HPLC–MS: retention time 7.93 min, [M + H]⁺ = 236. Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.50; H, 7.50; N, 5.84.

4-[2-(4-(*tert*-Butyl)phenyl)acetamido]benzoyl Chloride (21a). To a solution of 20a (0.10 g, 0.32 mmol) in dry THF was added thionyl chloride (2 mL). The solution was stirred under reflux for 2 h. The solvent was removed under reduced pressure, yielding 0.11 g of 21a.

4-Hexanamidobenzoyl Chloride (21b). To a solution of 20b (0.10 g, 0.43 mmol) in dry THF was added thionyl chloride (2 mL). The solution was stirred under reflux for 2 h. The solvent was removed under reduced pressure, yielding 0.11 g of 21b.

(R)-4-Benzyl-3-[(S)-2-methyl-3-(3-nitrophenyl)propanoyl]oxazolidin-2-one (22). A solution of (R)-(-)-4-benzyl-3-propionyl-2-oxazolidinone (0.60 g, 2.58 mmol) in anhydrous THF (11 mL) was stirred for 15 min under a nitrogen atmosphere at –78 °C. Then sodium bis(trimethylsilyl)amide (1.0 M) in THF (2.84 mL, 2.84 mmol) was added dropwise with a syringe to the stirred solution. The reaction mixture was allowed to stir for 1 h at –78 °C. 1-(Bromomethyl)-3-nitrobenzene (0.61 g, 2.84 mmol) was added and the reaction stirred at this temperature for 6 h. After the reaction reached room temperature, a saturated solution of NH₄Cl (15 mL) was added and the reaction extracted with ethyl acetate (30 mL). The combined organic extracts were washed successively with water (30 mL) and brine (30 mL) and dried over Na₂SO₄. The residue was purified (Biotage KP-Sil, 25 g; EtOAc/hexane from 5:95 to 10:90), yielding an oil (0.67 g, 70%). $[\alpha]_D^{20} = -56.0$. ¹H NMR (300 MHz, CDCl₃): δ (ppm) 8.22–8.04 (m, 2H, H-Ar), 7.66 (dt, *J* = 7.7, 1.3 Hz, 1H, H-Ar), 7.48 (t, *J* = 7.9 Hz, 1H, H-Ar), 7.34–7.20 (m, 3H, H-Ar), 7.16–6.99 (m, 2H, H-Ar), 4.68 (m, 1H, CH), 4.15–3.90 (m, 3H), 3.28 (dd, *J*_{ab} = 13.5, *J*_{a14} = 7.0 Hz, 1H), 3.14 (dd, *J*_{ab} = 13.4, *J*_{a4} = 3.4 Hz, 1H), 2.76 (dd, *J*_{ba} = 13.5, *J*_{b14} = 7.6 Hz, 1H), 2.62 (dd, *J*_{ba} = 13.4, *J*_{b4} = 9.4 Hz, 1H), 1.21 (d, *J* = 6.7 Hz, 2H, CH₃). ¹³C NMR (75 MHz, CDCl₃): δ (ppm) 175.6 (CO), 153.0, 148.3, 141.3, 139.6, 135.5, 134.9, 129.3 (2C), 128.9 (2C), 127.4, 124.1, 121.6, 66.1, 55.2, 39.5, 39.2,

37.8, 16.6 (CH₃). HPLC–MS: retention time 10.04 min, [M + H]⁺ = 368. Anal. Calcd for $C_{20}H_{20}N_2O_5$: C, 65.21; H, 5.47; N, 7.60. Found: C, 65.50; H, 5.71; N, 7.83.

(R)-3-[(S)-3-(3-Aminophenyl)-2-methylpropanoyl]-4-benzyl-oxazolidin-2-one (23). The catalytic hydrogenation of 22 (0.25 g, 0.68 mmol) in THF/AcOEt (1:2, 20 mL), with addition of Pd–C (10%) catalyst was carried out in mild conditions (21 psi, rt) in a PAR reactor over 12 h. Finally, the reaction mixture was filtered through a hydrophilic PVDF filter (30 mm, 0.45 μ) and the solvent removed under reduced pressure, yielding 23 as an oil (0.21 g, 90%). $[\alpha]_D^{20} = -14.8$. ¹H NMR (300 MHz, CDCl₃): δ (ppm) 7.30–7.24 (m, 2H, H-Ar), 7.20 (m, 3H, H-Ar), 7.15–7.06 (m, 2H, H-Ar), 7.00 (m, 2H, H-Ar), 4.65 (m, 1H), 4.20–4.01 (m, 3H), 3.17–2.98 (m, 2H), 2.62 (m, 2H), 1.16 (d, *J* = 6.8 Hz, 3H, CH₃). ¹³C NMR (75 MHz, CDCl₃): δ (ppm) 176.4 (CO), 153.1 (CO), 140.8, 135.2, 135.2 (2C), 129.2 (2C), 128.9, 127.1, 120.5 (2C), 117.8, 66.0, 55.2, 39.6, 39.2, 37.5, 16.5 (CH₃). HPLC–MS: retention time 6.94 min, [M + H]⁺ = 338. Anal. Calcd for $C_{20}H_{22}N_2O_5$: C, 70.99; H, 6.55; N, 8.28. Found: C, 71.04; H, 6.78; N, 8.19.

Pharmacological Evaluation: In Vivo Food Intake Studies.

To facilitate the rapid screening of PPAR α -related activity, we selected the inhibition of food intake in food-deprived animals. Although the gold standard in PPAR α activity has been considered the reduction of triglycerides after chronic administration, the reduction of forced food intake has been identified as a reliable action of PPAR α agonists. The acute effects of drugs on feeding behavior were analyzed in 24 h food-deprived male Wistar rats weighing 300–350 g from Charles Rivers Laboratories España, S.A. (Barcelona, Spain). Animals were housed individually in cages in a temperature- and humidity-controlled room (22 °C and 55% relative humidity) with a 12 h/12 h yellow light/dark cycle.

Water and food were available ad libitum. Animals were handled daily for a week before the experiments were started. The drugs were administered intraperitoneally (ip) at doses of 0.3, 1, and 3 mg/kg suspended in Tween 80 and saline as the vehicle. After a period of 15 min after drug administration, the animals were returned to their home cage and food intake was monitored 30, 60, 120, and 240 min after the test was started. In some cases the food intake was monitored after 24 h. At the end of the test, the amount of water consumed was also measured. All animal procedures met the National Institutes of Health guidelines for the care and use of laboratory animals and the European Communities Directive 86/609/EEC regulating animal research.

Computational Details. Theoretical Calculations. All calculations were performed on an Intel Core2 Quad Workstation using Linux Ubuntu kernel 3.4.0.

Preparation of Ligands and Target Macromolecules. The ChemAxon Marvin 5.4.1 software package (2013) (<http://www.chemaxon.com>), accessed Oct 9, 2012) was used to build the structure of the ligands. Energy minimization and partial charges were calculated using the PM6 method available in MOPAC 2012.³²

The three-dimensional structures of the PPAR α -LBD (PDB entry 1K7L, chain A) and PPAR γ -LBD (PDB entry 1K74, chain A) were retrieved from the RCSB Protein Data Bank.³³ Ligands, salts, and water molecules were removed, and the tautomeric forms were checked. To optimize hydrogen bond networks, the MolProbity server was used to add hydrogen atoms.³⁴ Finally, Kollman charges were computed through ADT.

To prepare the appropriate file needed for the docking study, nonpolar hydrogen atoms were merged, and rotatable bonds within the ligands were defined through the AutoDockTools v1.5 (ADT) program (The Scripps Research Institute, La Jolla, CA, <http://mgmtools.scripps.edu/>), accessed June 22, 2012).

Protocol for the Docking Study. Docking experiments of the compounds were carried out by means of the AutoDock v4 package.³⁵ For the calculations, a grid box with the dimensions 60 × 60 × 60 points was constructed around the binding site on the basis of the location of the cocrystallized ligand GW409544 (PDB entry 1K7L, chain A; PDB entry 1K74, chain B). The dimension of the axis was 22.5 Å, and the spacing of the grid points was 0.375 Å. The Lamarckian genetic algorithm (LGA) procedure was employed, and

the docking runs were set to 100, the maximum number of generations to 27 000, and the maximum number of energy evaluations to 25 000 000. The rest of the parameters were taken as default.

Analysis of the Binding Mode. To select the binding mode of each compound, we applied a qualitative analysis based on the location/orientation of the best 100 docked conformations given by AutoDock in relation to the cocrystallized ligand GW409544.³⁶ Hydrogen bonds and properties in the ligand–receptor interaction of the binding mode of each compound were evaluated by using Accelrys Discovery Studio v2.0 (Accelrys, Inc., San Diego, CA). Measurements of docked conformation RMSDs were carried out through ADT.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: [10.1021/acs.jmedchem.Sb00849](https://doi.org/10.1021/acs.jmedchem.Sb00849).

Molecular formula strings and the associated biological data ([CSV](#))

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS USED

PPAR, peroxisome proliferator activated receptor; LBD, ligand binding domain; AF, activation function; HB, hydrogen bond; NCoR, nuclear receptor corepressor; RXR, retinoid X receptor; CPT1-DR1, carnitine palmitoyltransferase I response element direct repeat 1

■ REFERENCES

- Wright, M. B.; Bortolini, M.; Tadayyon, M.; Bopst, M. Challenges and Opportunities in Development of PPAR Ligands. *Mol. Endocrinol.* **2014**, *28*, 1756–1758.
- Feldman, P. L.; Lambert, M. H.; Henke, B. R. PPAR Modulators and PPAR Pan Agonists for Metabolic Diseases: the Next Generation of Drugs Targeting Peroxisome Proliferator-Activated Receptors? *Curr. Top. Med. Chem.* **2008**, *8*, 728–749.
- Liu, Z.-M.; Hu, M.; Chan, P.; Tomlinson, B. Early Investigational Drugs Targeting PPAR α for the Treatment of Metabolic Disease. *Expert Opin. Invest. Drugs* **2015**, *24*, 611–621.
- Agrawal, R. The First Approved Agent in the Glitazars’ Class: Saroglitazar. *Curr. Drug Targets* **2014**, *15*, 151–155.
- Pirat, C.; Farce, A.; Lebègue, N.; Renault, N.; Furman, C.; Millet, R.; Yous, S.; Specia, S.; Berthelot, P.; Desreumaux, P.; Chavatte, P. Targeting PPARs: Development of Modulators. *J. Med. Chem.* **2012**, *55*, 4027–4061.

(6) Goya, P.; Pérez-Fernández, R.; González-Muñiz, R.; Elguero, J. Enantioselective Synthesis of PPAR Agonists and Antagonists. *Curr. Top. Med. Chem.* **2014**, *14*, 1283–1293 and references herein.

(7) Laghezza, A.; Pochetti, G.; Lavecchia, A.; Fracchiolla, G.; Faliti, S.; Piemontese, L.; Di Giovanni, C.; Iacobazzi, V.; Infantino, V.; Montanari, R.; Capelli, D.; Tortorella, P.; Loiodice, F. s New 2-(Aryloxy)-3-phenylpropanoic Acids as Peroxisome Proliferator-Activated Receptor α/γ Dual Agonists Able to Upregulate Mitochondrial Carnitine Shuttle System Gene Expression. *J. Med. Chem.* **2013**, *56*, 60–72.

(8) Kuwabara, N.; Oyama, T.; Tomioka, D.; Ohashi, M.; Yanagisawa, J.; Shimizu, T.; Miyachi, H. PPARs Have Multiple Binding Points that Accommodate Ligands in Various Conformations: Phenylpropanoic Acid-type PPAR Ligands Bind to PPAR in Different Conformations, Depending on the Subtype. *J. Med. Chem.* **2012**, *55*, 893–902.

(9) Nevin, D. K.; Peters, M. B.; Carta, G.; Fayne, D.; Lloyd, D. G. Integrated Virtual Screening for the Identification of Novel and Selective PPAR Scaffolds. *J. Med. Chem.* **2012**, *55*, 4978–4989.

(10) Heravi, M. M.; Zadsirjan, V. Oxazolidinones as Chiral Auxiliaries in Asymmetric Aldol Reactions Applied to Total Synthesis. *Tetrahedron: Asymmetry* **2013**, *24*, 1149–1188.

(11) Pandit, N.; Singla, R. K.; Shrivastava, B. Current Updates on Oxazolidinone and its Significance. *Int. J. Med. Chem.* **2012**, *2012*, 159285.

(12) Suzuki, H.; Utsunomiya, I.; Shudo, K.; Fujimura, T.; Tsuji, M.; Kato, I.; Aoki, T.; Ino, A.; Iwaki, T. Potent Oxazolidinone Antibacterials with Heteroaromatic C-ring Substructure. *ACS Med. Chem. Lett.* **2013**, *4*, 1074–1078.

(13) Reddy, G. S. K. K.; Ali, A.; Nalam, M. N. L.; Anjum, S. G.; Cao, H.; Nathans, R. S.; Schiffer, C. A.; Rana, T. M. Design and Synthesis of HIV-1 Protease Inhibitors Incorporating Oxazolidinones as P2/P2' Ligands in Pseudosymmetric Dipeptide Isosteres. *J. Med. Chem.* **2007**, *50*, 4316–4328.

(14) Ohashi, M.; Nakagome, I.; Kasuga, J.-I.; Nobusada, H.; Matsuno, K.; Makishima, M.; Hirose, S.; Hashimoto, Y.; Miyachi, H. Design, Synthesis and in Vitro Evaluation of a Series of α -Substituted Phenylpropanoic Acid PPAR γ Agonists to Further Investigate the Stereochemistry-Activity Relationship. *Bioorg. Med. Chem.* **2012**, *20*, 6375–6383.

(15) Nomura, M.; Tanase, T.; Miyachi, H. Efficient Asymmetric Synthesis of (S)-2-Ethylphenylpropanoic Acid Derivative, a Selective Agonist for Human PPAR α . *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2101–2104.

(16) Kasuga, J.-I.; Hashimoto, Y.; Miyachi, H. Concise and Efficient Asymmetric Synthesis of (S)-2-Ethylphenylpropanoic Acid Derivatives: Dual Agonists for Human PPAR α and γ . *Bioorg. Med. Chem. Lett.* **2006**, *16*, 771–774.

(17) Agrawal, A. K.; Hop, C. E. C. A.; Pang, J.; Silva Elipe, M. V.; Desai, R. C.; Leung, K. H.; Franklin, R. B. In Vitro Metabolism of a New Oxazolidinedione Hypoglycemic Agent Utilizing Liver Microsomes and Recombinant Human Cytochrome P450 Enzymes. *J. Pharm. Biomed. Anal.* **2005**, *37*, 351–358.

(18) Pérez-Fernández, R.; Fresno López, M. N.; Elguero Bertolini, J.; Goya Laza, P.; Torres Zaguirre, A. B.; Rodríguez de Fonseca, F.; Pavón Morón, F. J.; Macías González, M.; Romero Cuevas, M. Oxazolidinone Derivatives as PPAR Ligands. Patent WO2015004306.

(19) Xu, H. E.; Lambert, M. H.; Montana, V. G.; Plunkett, K. D.; Moore, L. B.; Collins, J. L.; Oplinger, J. A.; Kliewer, S. A.; Gampe, R. T., Jr.; McKee, D. D.; Moore, J. T.; Willson, T. M. Structural Determinants of Ligand Binding Selectivity Between the PPARs. *Proc. Natl. Acad. Sci. U. S. A.* **2001**, *98*, 13919.

(20) Decara, J. M.; Romero-Cuevas, M.; Rivera, P.; Macias-González, M.; Vida, M.; Pavón, F. J.; Serrano, A.; Cano, C.; Fresno, N.; Pérez-Fernández, R.; Rodriguez de Fonseca, F.; Suárez, J. Elaidyl-sulfamide, an Oleoylethanolamide-modelled PPAR α Agonist, Reduces Body Weight Gain and Plasma Cholesterol in Rats. *Dis. Models & Mech.* **2012**, *5*, 660–670.

(21) Fresno, N.; Pérez-Fernández, R.; Goya, P.; Jimeno, M. L.; Alkorta, I.; Elguero, J.; Menéndez-Taboada, L.; García-Granda, S.

- Oxazolidinone Cross-Alkylation during Evans' Asymmetric Alkylation Reaction. *Tetrahedron* **2011**, *67*, 9104–9111.
- (22) Cano, C.; Pavón, J.; Serrano, A.; Goya, P.; Páez, J. A.; Rodríguez de Fonseca, F.; Macías-González, M. Novel Sulfamide Analogs of Oleylethanolamide Showing in Vivo Satiety Inducing Actions and PPAR α Activation. *J. Med. Chem.* **2007**, *50*, 389–393.
- (23) Cardona, F.; Morcillo, S.; Gonzalo-Marín, M.; Garrido-Sánchez, L.; Macías-González, M.; Tinahones, F. J. Pro12Ala Sequence Variant of the PPAR γ gene Is Associated with Postprandial Hypertriglyceridemia in Non-E3/E3 Patients with Metabolic Syndrome. *Clin. Chem.* **2006**, *52*, 1920–1925.
- (24) Macías-González, M.; Cardona, F.; Queipo-Ortuño, M.; Bernal, R.; Martín, M.; Tinahones, F. J. PPAR γ mRNA Expression Is Reduced in Peripheral Blood Mononuclear Cells after Fat Overload in Patients with Metabolic Syndrome. *J. Nutr.* **2008**, *138*, 903–907.
- (25) Pérez-Fernández, R.; Fresno, N.; Macías-González, M.; Elguero, J.; Decara, J.; Girón, R.; Rodríguez-Alvarez, A.; Martín, M. I.; Rodríguez de Fonseca, F.; Goya, P. Discovery of Potent Dual PPAR α Agonists/CB1 Ligands. *ACS Med. Chem. Lett.* **2011**, *2*, 793–797.
- (26) Alvarado, M.; Goya, P.; Macías-González, M.; Pavón, F. J.; Serrano, A.; Jagerovic, N.; Elguero, J.; Gutiérrez-Rodríguez, A.; García-Granda, S.; Suárez, M.; Rodríguez de Fonseca, F. Antibesity Designed Multiple Ligands: Synthesis of Pyrazole Fatty Acid Amides and Evaluation as Hypophagic Agents. *Bioorg. Med. Chem.* **2008**, *16*, 10098.
- (27) Duez, H.; Lefebvre, B.; Poulin, P.; Torra, I. P.; Percevault, F.; Luc, G.; Peters, J. M.; Gonzalez, F. J.; Gineste, R.; Helleboid, S.; Dzavik, V.; Fruchart, J. C.; Fiévet, C.; Lefebvre, P.; Staels, B. Regulation of Human ApoA-I by Gemfibrozil and Fenofibrate through Selective Peroxisome Proliferator-Activated Receptor Alpha Modulation. *Arterioscler., Thromb., Vasc. Biol.* **2005**, *25*, 585–591.
- (28) Serrano, A.; del Arco, I.; Pavón, F. J.; Macías, M.; Pérez-Valero, V.; Rodríguez de Fonseca, F. The Cannabinoid CB1 Receptor Antagonist SR141716A (Rimonabant) Enhances the Metabolic Benefits of Long-term Treatment with Oleylethanolamide in Zucker Rats. *Neuropharmacology* **2008**, *54*, 226–234.
- (29) Rodríguez de Fonseca, F.; Navarro, M.; Gómez, R.; Escuredo, L.; Nava, F.; Fu, J.; Murillo-Rodríguez, E.; Giuffrida, A.; LoVerme, J.; Gaetani, S.; Kathuria, S.; Gall, C.; Piomelli, D. An Anorexic Lipid Mediator Regulated by Feeding. *Nature* **2001**, *414*, 209–212.
- (30) Fu, J.; Gaetani, S.; Oveisi, F.; Lo Verme, J.; Serrano, A.; Rodríguez De Fonseca, F.; Rosengarth, A.; Luecke, H.; Di Giacomo, B.; Tarzia, G.; Piomelli, D. Oleylethanolamide Regulates Feeding and Body Weight through Activation of the Nuclear Receptor PPAR-alpha. *Nature* **2003**, *425*, 90–93.
- (31) Wulff-Pérez, M.; Pavón, F. J.; Martín-Rodríguez, A.; de Vicente, J.; Alen, F.; de Fonseca, F. R.; Gálvez-Ruiz, M. J.; Serrano, A. Preparation, Characterization and In Vivo Evaluation of Nanoemulsions for the Controlled Delivery of the Antibesity Agent N-oleylethanolamine. *Nanomedicine* **2014**, *9*, 2761–2772.
- (32) Stewart, J. P. MOPAC 2012; Stewart Computational Chemistry: Colorado Springs, CO, 2012; <http://OpenMOPAC.net/>.
- (33) Berman, H.M.; Westbrook, J.; Feng, Z.; Gilliland, G.; Bhat, T.N.; Weissig, H.; Shindyalov, I.N.; Bourne, P. E. The Protein Data Bank. *Nucleic Acids Res.* **2000**, *28*, 235–242.
- (34) Chen, V. B.; Bryan Arendall, W., III; Headd, J. J.; Keedy, D. A.; Immormino, R. M.; Kapral, G. J.; Murray, L. W.; Richardson, J. S.; Richardson, D. C. (2010) MolProbity: All-atom Structure Validation for Macromolecular Crystallography. *Acta Crystallogr., Sect. D: Biol. Crystallogr.* **2010**, *D66*, 12–21.
- (35) Morris, G. M.; Goodsell, D. S.; Halliday, R. S.; Huey, R.; Hart, W. E.; Belew, R. K.; Olson, A. J. Automated Docking Using a Lamarckian Genetic Algorithm and Empirical Binding Free Energy Function. *J. Comput. Chem.* **1998**, *19*, 1639–1662.
- (36) Ali, H. I.; Tomita, K.; Akaho, E.; Kunishima, M.; Kawashima, Y.; Yamagishi, T.; Ikeya, H.; Nagamatsu, T. Antitumor Studies – part 2, Structure-Activity Relationship Study for Flavin Analogs Including Investigations on their In Vitro Antitumor Assay and Docking Simulation into Protein Tyrosine Kinase. *Eur. J. Med. Chem.* **2008**, *43*, 1376–1389.