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Peroxisome proliferator-activated receptor agonists with phenethylphenylphthalimide skeleton derived from thalidomide-related liver X receptor antagonists: Relationship between absolute configuration and subtype selectivity

Kazunori Motoshima, Minoru Ishikawa, Yuichi Hashimoto, Kazuyuki Sugita *

Institute of Molecular & Cellular Bioscience, The University of Tokyo, 1-1-1 Yayoi, Bunkyo-ku, Tokyo 113-0032, Japan

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ABSTRACT

Introduction of an alkylcarboxylic acid unit, which is a partial structure of endogenous peroxisome proliferator-activated receptor (PPAR) ligands, into a phenethylphenylphthalimide skeleton, which possesses liver X receptor (LXR) antagonistic activity, afforded novel PPAR ligands. The results of structure–activity relationship analysis and docking studies led us to the potent PPAR agonists **13c–e**. The absolute configuration of **13c–e** affects the PPAR subtype selectivity.

1. Introduction

Peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors belonging to the nuclear hormone receptor superfamily. There are three subtypes, PPARα, PPARδ, and PPARγ.[1] Lipids, such as linoleic acid (**1**), α-linolenic acid (**2**), and arachidonic acid (**3**), and eicosanoids, such as prostaglandin and leukotriene, are endogenous ligands for all PPARs.[2,3] Each PPAR isotype displays a distinct pattern of tissue distribution and a distinct pharmacological profile.[4] PPARα is mainly expressed in the liver, where it regulates free fatty acid oxidation, and is also expressed to a lesser extent in the heart, skeletal muscle, small intestine and kidney.[5] A PPARα-selective agonist, fenofibrate (**4**), has been used for many years to treat hyperlipidemia and to decrease serum levels of triglyceride, which is one of the risk factors for metabolic syndrome.[6] PPARδ is expressed in a variety of tissues, including skin, skeletal muscle, adipose tissue, and heart.[7] A specific agonist, GW501516 (**5**),[8] increased circulating HDL cholesterol levels and lowered triglyceride.[9,10] Consequently, PPARδ activation is thought to be a novel approach for the treatment of metabolic syndrome. PPARγ is expressed in white and brown adipose tissue, the gut, and immune cells. It regulates adipocyte differentiation and lipid storage in white adipose tissue. Moreover, PPARγ coordinates glucose metabolism to improve insulin sensitivity. Thiazolidinediones such as pioglitazone (**6**) are in clinical use for the treatment of type 2 diabetes.[11,12] As mentioned above, PPARs play an important role in regulating lipid, lipoprotein and glucose homeostasis.[4] Therefore PPARs have emerged as a novel therapeutic target for treatment of various components of metabolic syndrome. Some endogenous and synthetic ligands of PPARs are illustrated in Fig. 1.

We have been engaged in the creation of bioactive compounds based on the multi-template approach utilizing thalidomide.[13–18] The basis of the multi-template approach is that the number of three-dimensional spatial structures (fold structures) of human proteins is only approximately 1000, which is much smaller than the number of human proteins, estimated to be 50,000–70,000.[19–21] Therefore, ignoring physical/chemical interactions, a template/scaffold structure which is spatially complementary to onefold structure might serve as a multi-template for structural development of ligands that would interact specifically with more than 50–70 different human proteins. We have focused on thalidomide as a candidate multi-template structure. Thalidomide is a hypnotic/sedative drug, which was launched in the 1950's, but was withdrawn from the market in the 1960's because of severe teratogenicity. In spite of this, thalidomide has been established to be useful for the treatment of Hansen's disease and multiple myeloma. Additionally, many reports have appeared on its therapeutic potential for the treatment of a range of diseases, including cancers, rheumatoid arthritis, and diabetes.[13–18,22] We have created many thalidomide analogues with a range of biological activities, including tumor necrosis factor-α (TNF-α) production regulators,[23,24] nitric oxide synthase (NOS) inhibitors,[25,26] cyclooxygenase (COX) inhibitors,[27–29] liver X receptor (LXR) antagonists,[30–33] α-glucosidase inhibitors,[33–36] and glycogen phosphorylase inhibitors.[37] Recently, we have created phenethylphenylphthalimide derivatives such as **9**, which exhibit

* Corresponding author.
E-mail address: sugitakazu@iam.u-tokyo.ac.jp (K. Sugita).

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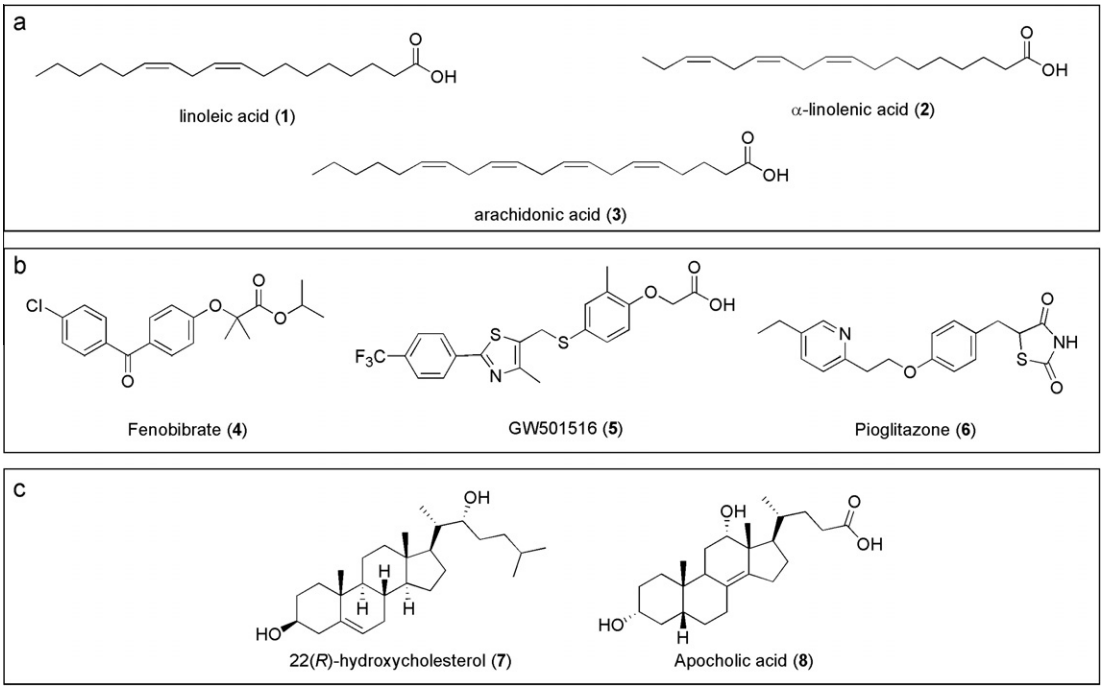


Figure 1. (a) Chemical structures of representative endogenous PPAR ligands. (b) Synthetic PPAR agonists. (c) Chemical structures of 22(*R*)-hydroxycholesterol (**7**) and apocholic acid (**8**).

LXRα-selective antagonist activity (Fig. 2).[33] Here, we describe the design, synthesis, and evaluation of the structure–activity relationship of phenethylphenylphthalimide derivatives, aimed at generating novel PPARs agonists.

2. Results and discussion

2.1. Introduction of alkyl carboxyl group into phenethylphenylphthalimide skeleton

PPARs and LXRs all belong to the nuclear hormone receptor superfamily and PPARs are similar to LXR in fold structure (Fig. 2a).[1] Therefore, we speculated that phenethylphenylphthalimides possessing LXR-antagonistic activity might be a suitable scaffold for creation of PPAR ligands. Next, we focused on the difference of endogenous ligands between PPAR and LXR. The endogenous ligands of PPAR and LXR are oxysterols such as 22(*R*)-hydroxycholesterol (**7**) and unsaturated long-chain fatty acids such as linoleic acid (**1**), respectively (Fig. 1a and c).[2,3,38] Although these ligands appear to have diverse structures, they possess a common feature, that is, hydrophobic partial structure. Thus, we thought that introduction of an alkyl carboxyl group, which is a partial structure of endogenous PPAR ligands, into LXRα antagonist **9** might generate PPAR ligands. On the other hand, apocholic acid (**8**), which is an oxysterol, has no LXR-agonistic activity (Fig. 1c),[38] so we speculated that it would be possible to separate PPAR and LXR activities. Therefore, we designed and synthesized a series of compounds possessing an alkyl carboxyl group (Fig. 2b).

Our designed compounds were prepared as shown in Schemes 1–3. Introduction of a *t*-butyl group into *p*-toluic acid gave compound **14**, and subsequent bromination of **14** with AIBN and NBS gave **15**. Compound **15** was reacted with triphenylphosphine to generate triphenylphosphonium salt **16**. A diphenylethene derivative **17** was prepared as an *E*/*Z* mixture by means of Wittig reaction of 4-nitrobenzaldehyde with **16**. After simultaneous reduction of the nitro group and olefin moiety of compound **17**, phenethylphenylphthalimide **19** was obtained by condensation with phthalic anhydride, followed by alkaline hydrolysis to afford compound **10**. 4-(Bromomethyl)benzoic acid methyl ester was reacted with triphenylphosphine to generate triphenylphosphonium salt **20**. Compound **22** was prepared by Wittig reaction of *p*-acetaminobenzaldehyde with **20**. After reduction of the olefin moiety of compound **22**, compound **23** was reduced with BH_3, followed by oxidation by MnO_2 to afford the aldehyde intermediate **25**. Compound **25** was treated with Wittig reagents **21a–c**, followed by reduction by Pd/C, hydrolysis, condensation with phthalic anhydride, and alkaline hydrolysis to afford the desired products **11a–c**. Introduction of an alkyl carboxyl group into compound **29** gave compounds **30a–c**, followed by hydrolysis to afford target compounds **12a–c**.

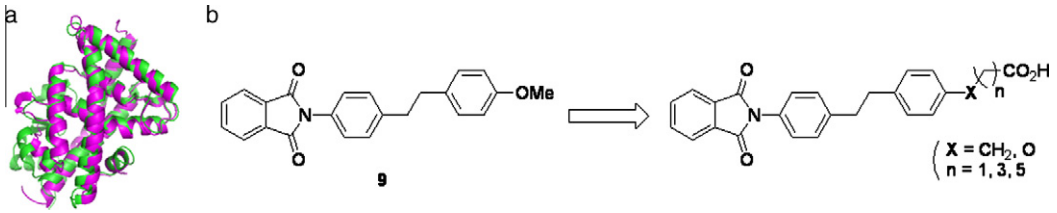
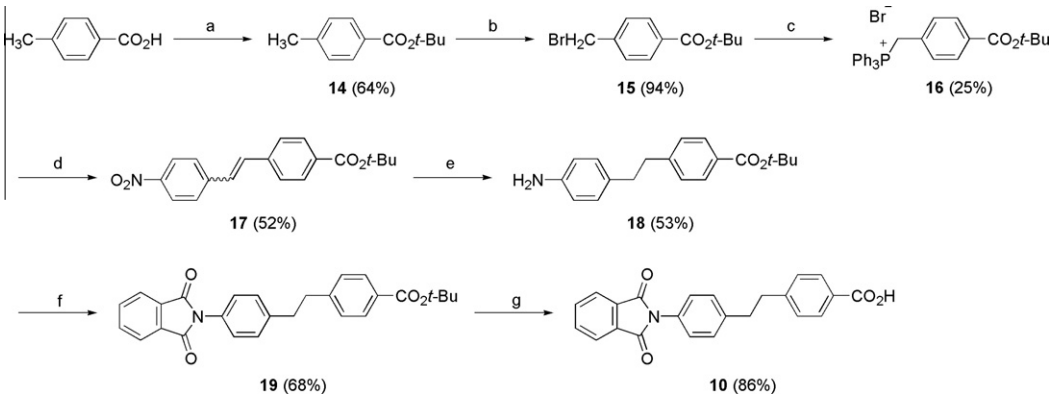
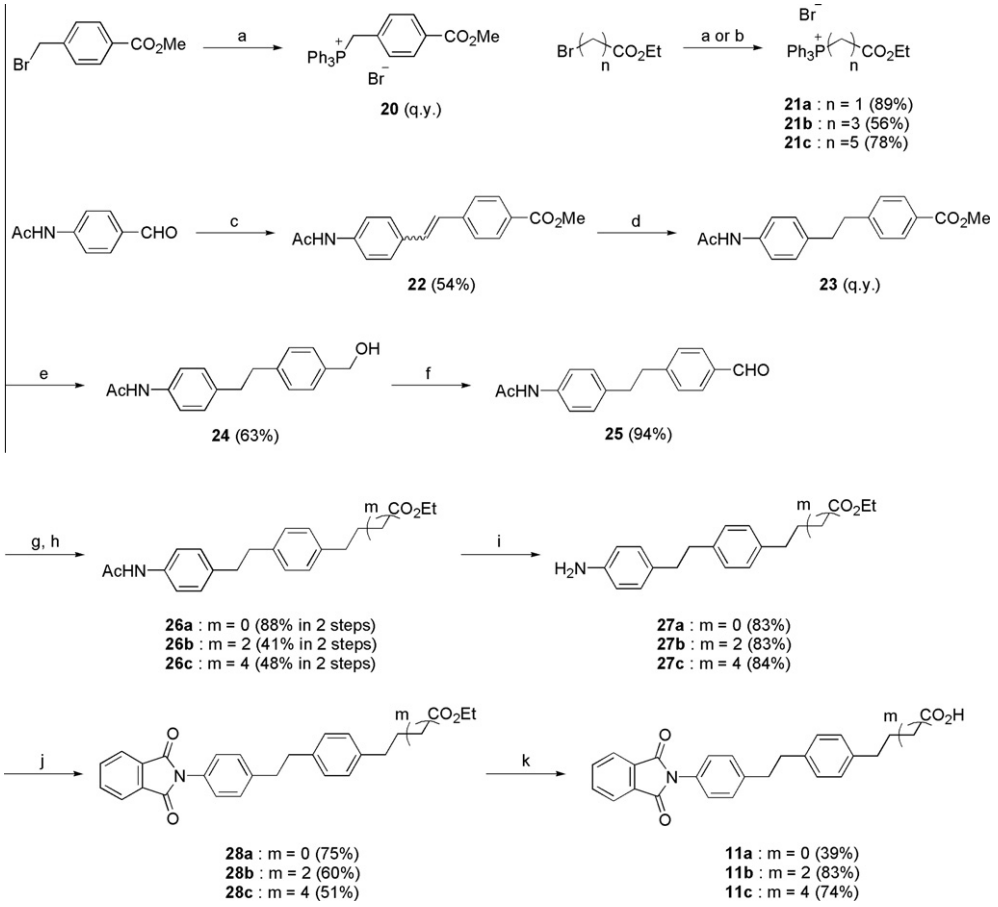


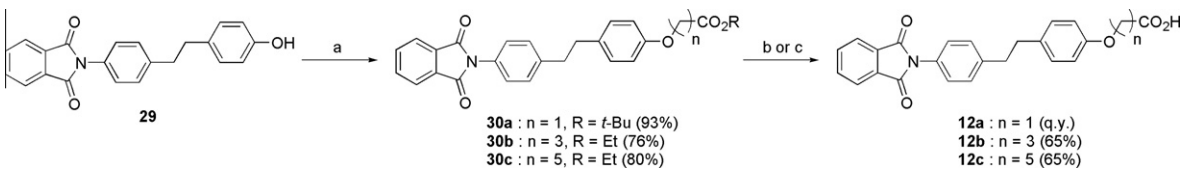
Figure 2. (a) Superposition of X-ray crystal structures of PPARα (green, PDB ID: 2ZNN) and LXRα (magenta, PDB ID: 3IPU). (b) Molecular design of PPAR ligands bearing an aliphatic carboxyl group.



Scheme 1. Synthesis of **10**. Reagents and conditions: (a) *t*-BuOH, EDC, DMAP, reflux; (b) AIBN, NBS, CCl_4, reflux; (c) PPh_3, MeCN, reflux; (d) 4-nitrobenzaldehyde, K_2CO_3, 18-crown-6, CH_2Cl_2, reflux; (e) H_2, 10% Pd/C, EtOAc, rt; (f) phthalic anhydride, neat, 200 °C; (g) TFA, CH_2Cl_2, rt.



Scheme 2. Synthesis of **11a–c**. Reagents and conditions: (a) PPh_3, MeCN, reflux; (b) PPh_3, EtOAc, rt; (c) **20**, K_2CO_3, 18-crown-6, CH_2Cl_2, reflux; (d) H_2 (0.2 MPa), 10% Pd/C, EtOAc, MeOH, rt; (e) $LiBH_4$, THF, rt; (f) MnO_2, CH_2Cl_2, rt; (g) **21a–c**, K_2CO_3, 18-crown-6, CH_2Cl_2, reflux; (h) H_2, 10% Pd/C, EtOAc, rt; (i) concd HCl, EtOH, 100 °C; (j) phthalic anhydride, neat, 200 °C; (k) AcOH, 6 N HCl, 70 °C.



Scheme 3. Synthesis of **12a–c**. Reagents and conditions: (a) ω-bromoalkyl carboxylic acid ester, K_2CO_3, DMF, 50 °C; (b) TFA, CH_2Cl_2, rt; (c) AcOH, 6 N HCl, 70 °C.

To investigate the cell-level PPAR-agonistic activity, we utilized a PPAR-responsive reporter gene assay with CMX-GAL4N-hPPAR LBD as the recombinant receptor gene, TK-MH100x4-LUC as the reporter gene, and the CMX β-galactosidase gene for normalization, as previously reported.[39] After incubation, cells were assayed for luciferase reporter gene and β-galactosidase activities. None of the compounds evaluated in our experiments reduced β-galactosidase activity in the concentration range investigated. Percent efficacy (E_{max}) of PPARα, PPARδ, and PPARγ agonists was estimated at the maximal stimulatory response, in relation to the activity of 10 μM fenofibric acid, 100 nM GW501516, and 10 μM ciglitazone, respectively.

The PPAR-agonistic activities of the synthesized compounds are shown in Table 1. Compound **11a** showed PPARαδ dual agonistic activity (PPARα: E_{max} = 53%, EC_{50} = 11 μM; PPARδ: E_{max} = 27%, EC_{50} = 13 μM) (Table 1). Compounds **12a** and **12b** also showed weak PPARαδ dual agonistic activity and PPARγ-selective agonistic activity, respectively. As a result of docking study using the AUTODOCK 4.2 docking program,[40] **12a** was suggested to bind to PPARα and PPARδ in ways similar to **11a** (Fig. S1). Therefore the reason why compound **12a** showed weak PPARα and PPARδ agonistic activities compared with those of compound **11a** might be an unfavorable interaction between oxygen of **12a** and Cys276 and Ser280 in PPARα and Cys285 and Thr289 in PPARδ. None of the compounds tested showed LXR-agonistic or antagonistic activity (data not shown).

2.2. Introduction of alkyl chains into phenethylphenylphthalimide skeleton: structure-based drug design

To generate more potent PPAR agonists, we performed a docking study using the AUTODOCK 4.2 docking program.[40] Docking of **11a**, which shows PPARα/δ dual agonistic activity, to PPARα, δ, and γ indicated that there are two unoccupied spaces in all of the PPAR subtypes, shown by red and yellow circles in Figure 3. Based on these results, analogs of **11a** which possess alkyl chains directed toward those spaces were designed (Fig. 4). Docking study indicated that the designed compounds would possess stronger affinity for both PPAR subtypes, as compared with compound **11a** (Table S1).

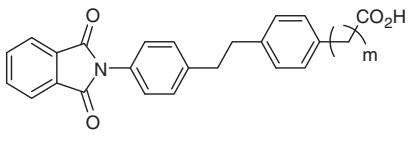
The designed compounds were prepared as shown in Scheme 4. Protection of one of the two primary alcohols of *p*-xylene-α,α′-diol with a *t*-butyldimethylsilyl (TBS) group and subsequent oxidation of the primary alcohol gave **32**. Compound **32** was treated with Horner-Emmons reagents, followed by reduction, deprotection of TBS with TBAF, and oxidation to afford the intermediate **36**. Diphenylethene derivatives **39** were prepared by Wittig reaction of **36** with ylides **38**. After hydrolysis with LiOH, *t*-butyl esters **41** were obtained by esterification of **40**. Simultaneous Pd/C reduction of the nitro group and olefin moiety of compounds **41** and subsequent condensation with phthalic anhydride gave compounds **43**. Compounds **43** were hydrolyzed to afford compounds **13**. Compound **13c** was treated with BBr_3 to give compound **13b**.

As expected, introduction of alkyl chains into **11a** enhanced the PPAR-agonistic activities (Table 2). There is a tendency for PPAR-agonistic activities to increase with increase of alkyl chain length at the alkoxy group. Compounds **13d**, **13e**, and **13c** showed the most potent agonistic activities toward PPARα, PPARδ and PPARγ, respectively. Compound **13a**, which possesses an ethyl group at the α position of carboxylic acid, showed more potent or similar agonistic activity, as compared with **11a**, and compounds **13c–f**, bearing ethyl and alkoxy groups, showed more potent PPAR-agonistic activities than **13a**. Docking study suggested that the alkyl chains of **13d**, **13e**, and **13c** occupy the spaces indicated by red and yellow circles in Figure 3 (Fig. S2).

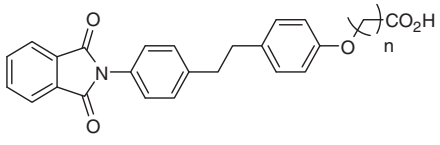
2.3. Effects of absolute configuration on the subtype selectivity

To investigate the effect of absolute configuration on PPAR activity, racemic **13c–e** were separated into their enantiomers by means of chiral chromatography. The PGME (phenylglycine methyl ester) method was used to determine the absolute configuration. The PGME method is a NMR methodology using (*S*)- and (*R*)-phenylglycine methyl ester, which enables the determination of the absolute configurations of chiral carboxylic acids.[41–43] The enantiomers were separated by chiral chromatography, and the one whose retention time was shorter was defined as 'former' and the one whose retention time was longer was defined as 'latter'. Each enantiomer was condensed with (*S*)-PGME to afford the PGME amides (scheme 5). By comparing the ^{1}H NMR spectra of the former and latter amides, the absolute configurations of these compounds could be estimated (Figs. S3–5). The PPAR-agonistic activities of the enantiomers **(*S*)-13c–e** and **(*R*)-13c–e** were evaluated.

Table 1
PPAR-agonistic activities of phenethylphenylphthalimides with an aliphatic carboxyl group (**10**, **11a–c**, and **12a–c**)



10, 11a-c



12a-c

Compound	m or n	PPARα		PPARδ		PPARγ	
		E_{max}[a] (%)	EC_{50} [μM]	E_{max}[a] (%)	EC_{50} [μM]	E_{max}[a] (%)	EC_{50} [μM]
10	0	14	33	0	N.D.	2	N.D.
11a	2	53	11	27	13	7	N.D.
11b	4	4	N.D.	4	N.D.	7	N.D.
11c	6	8	N.D.	4	N.D.	5	N.D.
12a	1	29	29	10	62	6	N.D.
12b	3	0	N.D.	1	N.D.	31	12
12c	5	0	N.D.	0	N.D.	6	N.D.

[a] % Efficacy relative to the positive control, fenofibric acid for PPARα, GW501516 for PPARδ, ciglitazone for PPARγ.

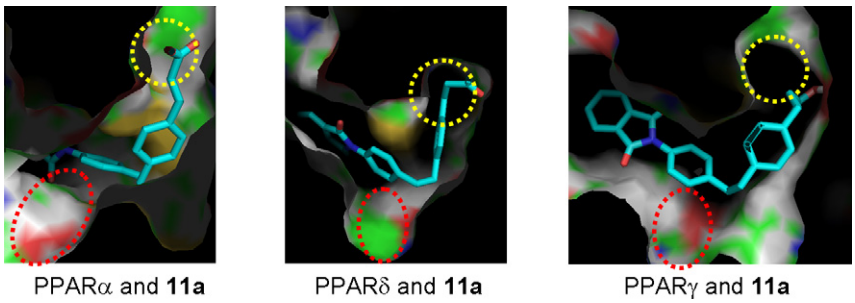


Figure 3. Compound **11a** docked into the X-ray crystal structure of PPARα (PDB ID: 2ZNN), PPARδ (PDB ID: 2ZNP) and PPARγ (PDB ID: 2ZNO) using the AUTODOCK 4.2 docking program.

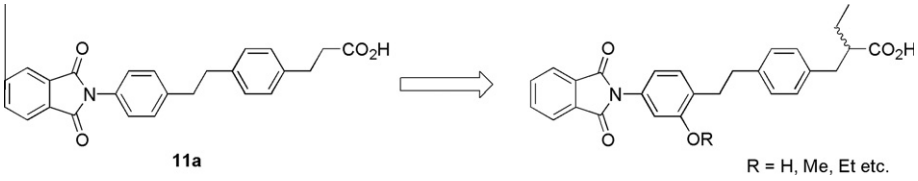


Figure 4. Molecular design based on the docking study.

In the case of **13c** and **13d**, the (*R*)-derivatives showed more potent PPARα-agonistic activities than the (*S*)-derivatives, and the (*S*)-derivatives showed more potent PPARδ and PPARγ agonistic activities than the (*R*)-derivatives (Table 3). On the other hand, **(*S*)-13e** showed more potent agonistic activities against all of the PPAR subtypes, as compared with **(*R*)-13e**. These results suggest that absolute configuration of these compounds affects the subtype selectivity. The results of docking studies did not seem to account for these selectivities (Table S1).

2.4. Selectivity for FXR

Farnesoid X receptor (FXR) is ligand-activated transcription factor belonging to the nuclear hormone receptor superfamily. The physiological ligands are considered to be bile acids, including CDCA (**44**) (Fig. 5).[44] CDCA (**44**) has partial structures of 22(*R*)-hydroxycholesterol (steroid skeleton) and fatty acid (alkyl carboxyl group) (Fig. 5). Therefore, we speculated that our PPAR agonists might possess FXR-agonistic activity. Thus, we examined the selectivity of our derivatives for FXR.

The FXR receptor agonist assay system is similar to that of PPAR. None of the compounds examined showed FXR-agonistic or antagonistic activity (Fig. 6 and data not shown, respectively). The lack of FXR-agonistic activity might be explained in terms of structural differences, compared with endogenous ligands, in the absolute configuration of the 3-hydroxyl group in the steroid skeleton and the absence or presence of a double bond in the steroid skeleton.

3. Conclusion

Introduction of an alkyl carboxyl group, which is a partial structure of PPAR endogenous ligands, into the phenethylphenylphthalimide skeleton, which possesses LXR-antagonistic activity, yielded novel PPAR ligands. Among them, compound **11a** possesses PPARα/δ dual agonistic activity. To generate more potent PPAR agonists, we performed a docking study, and structure-based drug design afforded more potent PPAR agonists **13c–e**. The absolute configuration of these compounds affected the subtype selectivity. Thus, our multi-template approach was adaptable to obtain PPAR subtype-selective agonists.

4. Experimental

4.1. Reporter gene assay

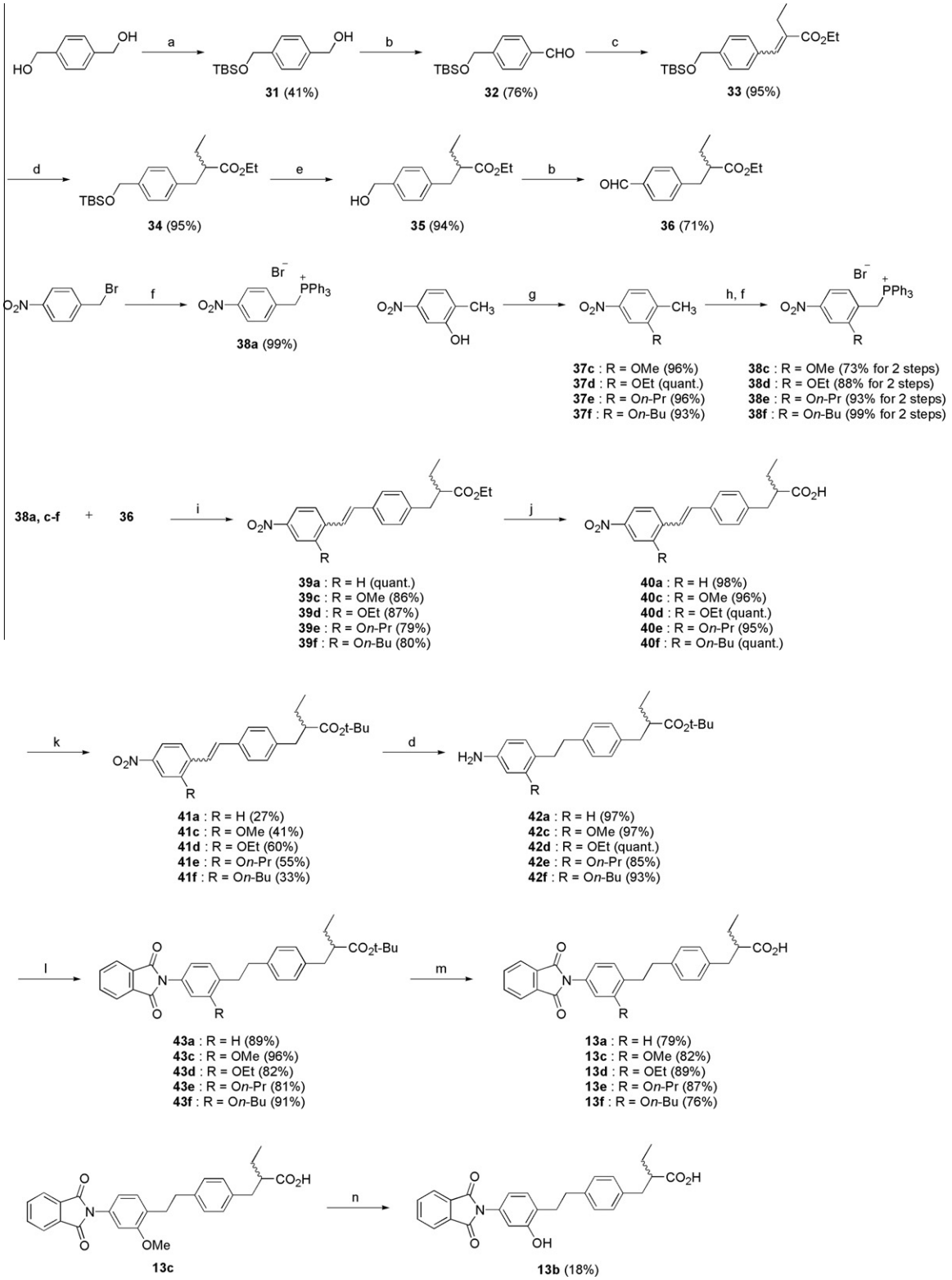
Human embryonic kidney (HEK) 293 cells were cultured in Dulbecco's modified Eagle's medium containing 5% fetal bovine serum at 37 °C in a humidified atmosphere of 5% CO_2 in air. Transfections were performed by the calcium phosphate coprecipitation method. Test compounds with or without each positive control were added 8 h after the transfection, and luciferase and β-galactosidase activities were assayed using a luminometer and microplate reader, respectively. Each experiment was performed in triplicate and repeated at least twice, and the normalized average values are presented. The EC_{50} values were reproducible.

4.2. General

Melting points were determined by using a Yanagimoto hot-stage melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a JEOL ALPHA500 (500 MHz) spectrometer. Chemical shifts (δ) are expressed in parts per million (ppm) relative to deuteriochloroform or tetramethylsilane as an internal reference with coupling constants in Hertz. The abbreviations s, d, t, dt, q, quin, sex, and m signify singlet, doublet, triplet, doublet triplet quartet, quintet, sextet and multiplet, respectively. Fast atom bombardment mass spectra (FAB-MS) and high resolution mass spectra (HRMS) were recorded on a JEOL JMS-HX110 spectrometer with m-nitrobenzyl alcohol. Elemental analyses were carried out in the Microanalytical Laboratory, Faculty of Pharmaceutical Sciences, University of Tokyo, and were within ±0.4% of theoretical values.

4.2.1. General procedure A (GP-A)

To a solution of alkanoic acid in *tert*-butanol were added DMAP (3.0 equiv) and EDC (2.0 equiv). The reaction mixture was refluxed for 1–4 h, then poured into water and extracted with EtOAc. The organic layer was washed with H_2O and brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography to give the target compound.



Scheme 4. Synthesis of **13a**–**f**. Reagents and conditions: (a) TBSCl, imidazole, DMF, rt; (b) PDC, CH_2Cl_2, rt; (c) triethyl 2-phosphonobutyrate, *t*-BuOK, THF, rt; (d) H_2, 10% Pd/C, EtOAc, rt; (e) TBAF, THF, 0 °C; (f) PPh_3, toluene, reflux; (g) alkyl halide, K_2CO_3, DMF, 40 °C; (h) AIBN, NBS, CCl_4, reflux; (i) K_2CO_3, 18-crown-6, CH_2Cl_2, reflux; (j) EtOH, 1 M LiOH, 75 °C; (k) *t*-BuOH, DMAP, EDC, reflux; (l) phthalic anhydride, neat, 160 °C; (m) TFA, CH_2Cl_2, rt; (n) BBr_3, CH_2Cl_2, 0 °C.

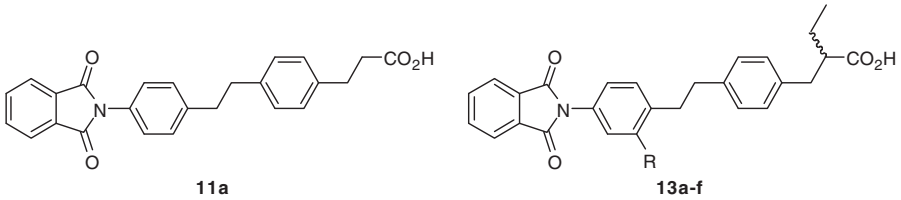
4.2.2. General procedure B (GP-B)

To a solution of substituted toluene in carbon tetrachloride were added N-bromosuccinimide (1.1 equiv) and 2,2′-azobis-(isobutyronitrile) (0.15 equiv). The mixture was refluxed, then filtered and concentrated. The residue was purified by silica gel column chromatography to give the target compound.

4.2.3. General procedure C-1 (GP-C-1)

To a solution of substituted benzyl halide in acetonitrile was added triphenylphosphine (1.5 equiv), and the mixture was refluxed. The reaction mixture was concentrated and the residue was mixed with toluene. The whole was filtered to give the target compound.

Table 2
PPAR-agonistic activities of compounds **11a** and **13a–f**



11a **13a-f**

Compound	R	PPARα		PPARδ		PPARγ	
		E_{max}[a] (%)	EC_{50} [μM]	E_{max}[a] (%)	EC_{50} [μM]	E_{max}[a] (%)	EC_{50} [μM]
11a	—	53	11	27	13	7	23
13a	H	72	6.6	22	14	42	11
13b	OH	20	14	7	25	21	17
13c	OMe	73	3.4	24	11	78	8.5
13d	OEt	102	1.4	33	4.8	49	9.3
13e	O*n*-Pr	70	1.7	40	2.9	26	6.9
13f	O*n*-Bu	63	1.8	32	3.2	36	7.9

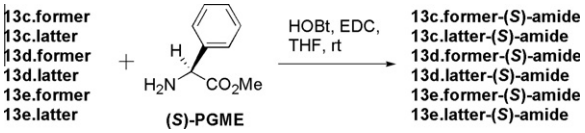
[a] % Efficacy relative to the positive control, fenofibric acid for PPARα, GW501516 for PPARδ, ciglitazone for PPARγ.

4.2.4. General procedure C-2 (GP-C-2)

To a solution of substituted benzyl halide in toluene was added triphenylphosphine (1.5 equiv) and the mixture was refluxed. After cooling, the precipitate was collected by filtration to give the target compound.

4.2.5. General procedure D (GP-D)

To a solution of nitrobenzaldehyde in dehydrated CH_2Cl_2 were added benzyltriphenylphosphonium salt (1.0 equiv), potassium carbonate (1.1 equiv) and 18-crown-6 (0.18 equiv), and the mixture was refluxed, then filtered and the filtrate was concentrated. The residue was purified by silica gel column chromatography to give the target compound as an *EZ* mixture.



Scheme 5. Synthesis of the PGME amides.

4.2.6. General procedure E (GP-E)

Substituted nitrobenzene was dissolved in EtOAc and hydrogenated with 10% Pd/C (catalytic amount). The mixture was filtered through a pad of Celite, and the filtrate was evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give the target compound.

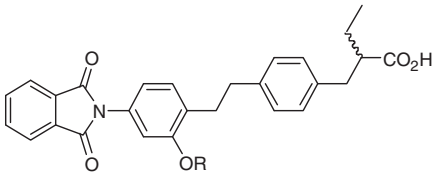
4.2.7. General procedure F (GP-F)

A mixture of phthalic anhydride and substituted aniline (1.0 equiv) was heated at 160 or 200 °C for 1 h. After the reaction was completed, the residue was purified by silica gel column chromatography to give the target compound.

4.2.8. General procedure G (GP-G)

To a solution of the *t*-Bu ester in CH_2Cl_2 was added TFA (the same amount as that of CH_2Cl_2). The mixture was stirred at rt for overnight. The solvent was removed under reduced pressure. The

Table 3
PPAR-agonistic activities of (***S***)- and (***R***)-**13c–e**



13c-e

Compound	R	PPARα		PPARδ		PPARγ	
		E_{max}[a] (%)	EC_{50} [μM]	E_{max}[a] (%)	EC_{50} [μM]	E_{max}[a] (%)	EC_{50} [μM]
(***S***)-**13c**	Me	66	8.9	41	7.3	102	7.1
(***R***)-**13c**	Me	103	4.5	8	N.D.	40	12
(***S***)-**13d**	Et	69	1.7	29	1.9	62	3.2
(***R***)-**13d**	Et	126	1.1	12	9.7	23	6.9
(***S***)-**13e**	*n*-Pr	87	1.7	54	1.8	36	5.2
(***R***)-**13e**	*n*-Pr	70	2.5	8	N.D.	7	N.D.

[a] % Efficacy relative to the positive control, fenofibric acid for PPARα, GW501516 for PPARδ, ciglitazone for PPARγ.

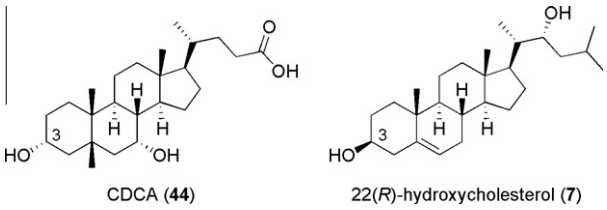


Figure 5. Chemical structures of CDCA (**44**) and 22(*R*)-hydroxycholesterol (**7**).

residue was purified by silica gel column chromatography to give the target compound.

4.2.9. General procedure H (GP-H)

To a solution of ethyl ester in EtOH was added concd HCl (1/10 amount of EtOH). The mixture was heated at 100 °C for 4–6 h, then poured into sat. $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with H_2O and brine, then dried over $MgSO_4$. The solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography to give the target compound.

4.2.10. General procedure I (GP-I)

To a solution of ethyl ester in AcOH was added dropwise 6 N HCl (1/5 amount of AcOH) at 0 °C. The mixture was heated at 70 °C for 2.5–5 h, then poured into water and extracted with EtOAc. The organic layer was washed with H_2O and brine, then dried over $MgSO_4$. The solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography to give the target compound.

4.2.11. General procedure J (GP-J)

To a solution of 2-methyl-5-nitrophenol (613 mg, 4.0 mmol) in dehydrated DMF (7 mL) were added potassium carbonate (608 mg, 4.4 mmol) and iodoalkane (12.0 mmol) under an argon atmosphere. The mixture was heated at 40 °C for 2–3 h, then poured into water and extracted with EtOAc. The organic layer was washed with H_2O and brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography to give the target compound.

4.2.12. General procedure K (GP-K)

To a solution of ethyl ester in EtOH was added 1 M LiOH (the same amount as that of EtOH). The mixture was heated at 75 °C for 3.5–7.5 h, then poured into 2 N HCl and extracted with EtOAc. The organic layer was washed with H_2O and brine, then dried over $MgSO_4$. The solvent was removed under reduced pressure to give the target compound.

4.2.13. 4-Methylbenzoic acid *t*-butyl ester (14)

This compound was prepared from *p*-toluic aicd by means of GP-A. Compound **14** was obtained in 64% yield as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.87 (d, 2H, J = 8.2 Hz), 7.21 (d, 2H, J = 8.2 Hz), 1.67 (s, 3H), 1.59 (s, 9H). FAB-MS m/z: not detected.

4.2.14. 4-(Bromomethyl)benzoic acid *t*-butyl ester (15)

This compound was prepared from **14** by means of GP-B. Compound **15** was obtained in 94% yield as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.96 (d, 2H, J = 8.5 Hz), 7.43 (d, 2H, J = 8.5 Hz), 4.50 (s, 2H), 1.59 (s, 9H). FAB-MS m/z: 269, 271 $[M]^+$.

4.2.15. {[4-(*t*-Butoxyoxycarbonyl)phenyl]methyl}triphenyl phosphonium bromide (16)

This compound was prepared from **15** by means of GP-C-1. Compound **16** was obtained in 25% yield as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.84–7.73 (m, 9H), 7.67–7.58 (m, 6H), 7.19 (dd, 2H, J = 8.5, 2.4 Hz), 7.13 (dd, 2H, J = 8.5, 2.4 Hz), 5.56 (d, 2H, J = 14.6 Hz), 1.56 (s, 9H). FAB-MS m/z: 453 $[M-Br]^+$.

4.2.16. 4-[2-(4-Nitrophenyl)ethenyl]benzoic acid *t*-butyl ester (17)

This compound was prepared from 4-nitrobenzaldehyde and **16** by means of GP-D. Compound **17** was obtained in 52% yield as a pale yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) **17*Z*** δ: 8.08 (d, 2H, J = 8.5 Hz), 7.87 (d, 2H, J = 8.5 Hz), 7.35 (d, 2H, J = 9.2 Hz), 7.23 (d, 2H, J = 7.9 Hz), 6.83 (d, 1H, J = 12.2 Hz), 6.71 (d, 1H, J = 12.2 Hz), 1.59 (s, 9H). **17*E*** δ: 8.24 (d, 2H, J = 8.5 Hz), 8.01 (d, 2H, J = 7.9 Hz), 7.67 (d, 2H, J = 8.5 Hz), 7.59 (d, 2H, J = 8.5 Hz), 7.29 (d, 1H, J = 16.5 Hz), 7.23 (d, 1H, J = 16.5 Hz), 1.61 (s, 9H). FAB-MS m/z: 325 $[M]^+$, 326 $[M+H]^+$.

4.2.17. 4-[2-(4-Aminophenyl)ethyl]benzoic acid *t*-butyl ester (18)

This compound was prepared from **17** by means of GP-E. Compound **18** was obtained in 90% yield as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.88 (d, 2H, J = 7.9 Hz), 7.18 (d, 2H, J = 7.9 Hz), 6.93 (d, 2H, J = 7.9 Hz), 6.61 (d, 2H, J = 8.5 Hz), 3.57 (br s, 2H), 2.92–2.89 (m, 2H), 2.83–2.79 (m, 2H), 1.59 (s, 9H). FAB-MS m/z: 297 $[M]^+$, 298 $[M+H]^+$.

4.2.18. 4-{2-[4-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)phenyl] ethyl}benzoic acid *t*-butyl ester (19)

This compound was prepared from phthalic anhydride and **18** by means of GP-F. Compound **19** was obtained in 68% yield as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.96 (dd, 2H, J = 5.5, 3.1 Hz), 7.92 (d, 2H, J = 8.5 Hz), 7.79 (dd, 2H, J = 5.5, 3.1 Hz), 7.36 (d, 2H, J = 7.9 Hz), 7.31 (d, 2H, J = 7.9 Hz), 7.25 (d, 2H, J = 8.5 Hz), 3.00–2.98 (m, 4H), 1.59 (s, 9H). FAB-MS m/z: 427 $[M]^+$, 428 $[M+H]^+$.

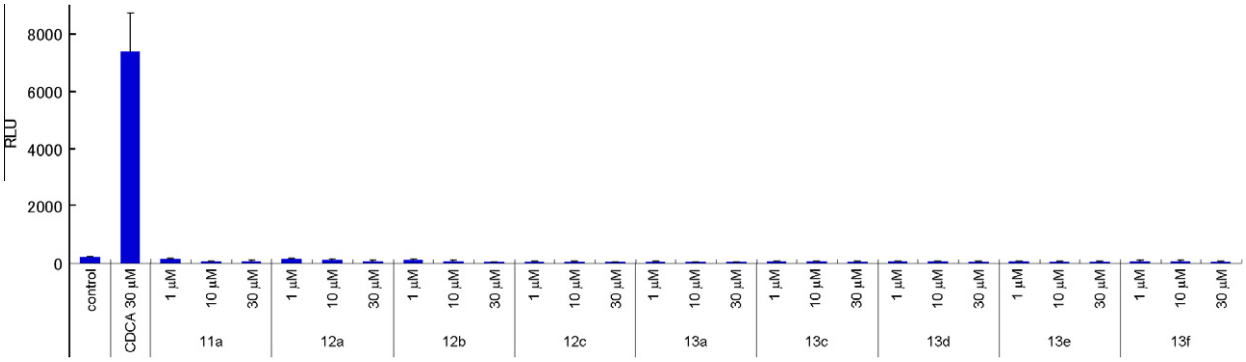


Figure 6. Selectivity of PPAR ligands for FXR.

4.2.19. 4-{2-[4-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)phenyl]-ethyl}benzoic acid (10)

This compound was prepared from **19** by means of GP-G. Compound **10** was obtained in 86% yield as a white solid.

^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.96 (dd, 2H, J = 5.5, 3.1 Hz), 7.91 (dd, 2H, J = 5.5, 3.1 Hz), 7.87 (d, 2H, J = 8.5 Hz), 7.40–7.38 (m, 2H), 7.39 (d, 2H, J = 8.5 Hz), 7.34 (d, 2H, J = 8.5 Hz), 3.02–3.00 (m, 2H), 2.99–2.96 (m, 2H). FAB-MS m/z: 371 $[M]^+$, 372 $[M+H]^+$. Anal. Calcd for $C_{23}H_{17}NO_4 \cdot 1/3H_2O$: C, 73.49; H, 4.69; N, 3.73. Found: C, 73.28; H, 4.77; N, 3.61.

4.2.20. {[4-(Methoxycarbonyl)phenyl]methyl}triphenyl phosphonium bromide (20)

This compound was prepared from 4-(bromomethyl)benzoic acid methyl ester by means of GP-C-1. Compound **20** was obtained in 100% yield as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.80–7.75 (m, 11H), 7.65–7.61 (m, 6H), 7.23 (dd, 2H, J = 8.5, 2.4 Hz), 5.66 (d, 2H, J = 15.3 Hz), 3.88 (s, 3H). FAB-MS m/z: 490 $[M-Br]^+$.

4.2.21. Ethoxycarbonylmethyl-triphenyl-phosphonium bromide (21a)

To a solution of triphenylphosphine (787 mg, 3.0 mmol) in EtOAc (10 mL) was added dropwise ethyl bromoacetate (388 μL, 3.5 mmol). The mixture was stirred at rt for overnight. The whole was filtered to give the target compound (1.15 g, 89%) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.94–7.89 (m, 6H), 7.81–7.78 (m, 3H), 7.70–7.66 (m, 6H), 5.60 (d, 2H, J = 13.4 Hz), 4.05 (q, 2H, J = 7.3 Hz), 1.08 (t, 3H, J = 7.3 Hz). FAB-MS m/z: 349 $[M-Br]^+$.

4.2.22. Ethoxycarbonylpropyl-triphenyl-phosphonium bromide (21b)

To a solution of triphenylphosphine (918 mg, 3.5 mmol) in MeCN (5 mL) was added ethyl 4-bromobutyrate (429 μL, 3.0 mmol). The mixture was refluxed for 6 h and concentrated. The residue was purified by silica gel column chromatography to give the target compound (764 mg, 56%) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.92–7.87 (m, 6H), 7.80–7.77 (m, 3H), 7.72–7.68 (m, 6H), 4.12–4.08 (m, 4H), 2.91 (d, 2H, J = 6.7 Hz), 1.96–1.89 (m, 2H), 1.24 (t, 3H, J = 7.3 Hz). FAB-MS m/z: 377 $[M-Br]^+$.

4.2.23. Ethoxycarbonylpentyl-triphenyl-phosphonium bromide (21c)

To a solution of triphenylphosphine (918 mg, 3.5 mmol) in MeCN (5 mL) was added 6-bromohexanoic acid ethyl ester (669 μL, 3.0 mmol). The mixture was refluxed for 7 h and concentrated. The residue was purified by silica gel column chromatography to give the target compound (1.14 g, 78%) as a white foam.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.89–7.85 (m, 6H), 7.81–7.78 (m, 3H), 7.72–7.68 (m, 6H), 4.07 (q, 2H, J = 7.3 Hz), 3.95–3.89 (m, 2H), 2.27 (t, 2H, J = 7.3 Hz), 1.76–1.72 (m, 2H), 1.66–1.58 (m, 4H), 1.22 (t, 3H, J = 7.3 Hz). FAB-MS m/z: 405 $[M-Br]^+$.

4.2.24. 4-[2-(4-Acetylaminophenyl)vinyl]benzoic acid methyl ester (22)

This compound was prepared from *p*-acetaminobenzaldehyde and **20** by means of GP-D. Compound **22** was obtained in 54% yield as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) **22*Z*** δ: 7.89 (d, 2H, J = 8.5 Hz), 7.36 (d, 2H, J = 8.5 Hz), 7.30 (d, 2H, J = 8.5 Hz), 7.17 (d, 2H, J = 8.5 Hz), 7.16 (br s, 1H), 6.64 (d, 1H, J = 12.2 Hz), 6.57 (d, 1H, J = 12.2 Hz), 3.90 (s, 3H), 2.17 (s, 3H). FAB-MS m/z: 295 $[M]^+$, 296 $[M+H]^+$.

4.2.25. 4-[2-(4-Acetylaminophenyl)ethyl]benzoic acid methyl ester (23)

Compound **22** (1.13 g, 3.83 mmol) was dissolved in EtOAc (20 mL) and MeOH (20 mL), and hydrogenated with 10% Pd/C (catalytic amount). The mixture was filtered through a pad of Celite, and the filtrate was evaporated under reduced pressure to give the target compound (1.21 g, q.y.) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.93 (d, 2H, J = 7.9 Hz), 7.39 (d, 2H, J = 7.9 Hz), 7.20 (d, 2H, J = 7.9 Hz), 7.11 (br s, 1H), 7.08 (d, 2H, J = 7.9 Hz), 3.90 (s, 3H), 2.96–2.93 (m, 2H), 2.91–2.88 (m, 2H), 2.17 (s, 3H). FAB-MS m/z: 297 $[M]^+$, 298 $[M+H]^+$.

4.2.26. *N*-{4-[2-(4-Hydroxymethylphenyl)ethyl]phenyl} acetamide (24)

To a solution of **23** (29 mg, 0.1 mmol) in dehydrated THF (1 mL) was added dropwise $LiBH_4$ (4.4 mg, 0.2 mmol) at 0 °C under an argon atmosphere. The mixture was stirred at rt for 4 h, then poured into MeOH (1 mL) and sat. NH_4Cl aq (10 mL), and extracted with EtOAc (10 mL × 3). The organic layer was washed with H_2O (10 mL) and brine (10 mL), then dried over $MgSO_4$. The solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography to give the target compound (17 mg, 63%) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.39 (d, 2H, J = 7.9 Hz), 7.27 (d, 2H, J = 7.9 Hz), 7.16 (d, 2H, J = 7.9 Hz), 7.11 (d, 2H, J = 7.9 Hz), 7.10 (br s, 1H), 4.66 (s, 2H), 2.92–2.86 (m, 4H), 2.17 (s, 3H). FAB-MS m/z: 269 $[M]^+$, 270 $[M+H]^+$.

4.2.27. *N*-{4-[2-(4-Formylphenyl)ethyl]phenyl}acetamide (25)

To a solution of **24** (17 mg, 0.063 mmol) in CH_2Cl_2 (10 mL) was added MnO_2 (55 mg, 0.63 mmol). The mixture was stirred at rt overnight. The solvent was removed under reduced pressure to give the target compound (16 mg, 94%) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.97 (s, 1H), 7.78 (d, 2H, J = 7.9 Hz), 7.40 (d, 2H, J = 8.5 Hz), 7.29 (d, 2H, J = 7.9 Hz), 7.21 (br s, 1H), 7.08 (d, 2H, J = 7.9 Hz), 2.99–2.96 (m, 2H), 2.93–2.89 (m, 2H), 2.17 (s, 3H). FAB-MS m/z: 267 $[M]^+$, 268 $[M+H]^+$.

4.2.28. 3-{4-[2-(4-Acetylaminophenyl)ethyl]phenyl}propionic acid ethyl ester (26a)

This compound was prepared from **25** and **21a** by means of GP-D and GP-E. Compound **26a** was obtained in 88% yield in two steps as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.39 (d, 2H, J = 8.5 Hz), 7.13–7.08 (m, 7H), 4.13 (q, 2H, J = 7.3 Hz), 2.92 (t, 2H, J = 7.9 Hz), 2.87–2.85 (m, 4H), 2.60 (t, 2H, J = 7.3 Hz), 2.17 (s, 3H), 1.24 (t, 3H, J = 7.3 Hz). FAB-MS m/z: 339 $[M]^+$, 340 $[M+H]^+$.

4.2.29. 5-{4-[2-(4-Acetylamino-phenyl)ethyl]phenyl}pentanoic acid ethyl ester (26b)

This compound was prepared from **25** and **21b** by means of GP-D and GP-E. Compound **26b** was obtained in 41% yield in two steps as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.38 (d, 2H, J = 7.9 Hz), 7.12 (br s, 1H), 7.11 (d, 2H, J = 7.9 Hz), 7.07 (s, 4H), 4.12 (q, 2H, J = 7.3 Hz), 2.86 (s, 4H), 2.59 (t, 2H, J = 7.3 Hz), 2.31 (t, 2H, J = 7.3 Hz), 2.16 (s, 3H), 1.65–1.64 (m, 4H), 1.25 (t, 3H, J = 7.3 Hz). FAB-MS m/z: 367 $[M]^+$, 368 $[M+H]^+$.

4.2.30. 7-{4-[2-(4-Acetylaminophenyl)ethyl]phenyl}heptanoic acid ethyl ester (26c)

This compound was prepared from **25** and **21c** by means of GP-D and GP-E. Compound **26c** was obtained in 48% yield in two steps as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.39 (d, 2H, J = 8.5 Hz), 7.18 (br s, 1H), 7.10 (d, 2H, J = 7.9 Hz), 7.06 (s, 4H), 4.12 (q, 2H, J = 7.3 Hz),

2.86 (s, 4H), 2.56 (t, 2H, J = 7.3 Hz), 2.28 (t, 2H, J = 7.3 Hz), 2.17 (s, 3H), 1.63–1.58 (m, 4H), 1.34–1.32 (m, 4H), 1.25 (t, 3H, J = 7.3 Hz). FAB-MS m/z: 395 $[M]^+$, 396 $[M+H]^+$.

4.2.31. 3-{4-[2-(4-Aminophenyl)ethyl]phenyl}propionic acid ethyl ester (27a)

This compound was prepared from **26a** by means of GP-H. Compound **47a** was obtained in 83% yield as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.11 (d, 2H, J = 8.5 Hz), 7.10 (d, 2H, J = 9.2 Hz), 6.97 (d, 2H, J = 8.5 Hz), 6.62 (d, 2H, J = 7.9 Hz), 4.13 (q, 2H, J = 7.3 Hz), 3.57 (br s, 2H), 2.92 (t, 2H, J = 7.3 Hz), 2.85–2.82 (m, 2H), 2.80–2.77 (m, 2H), 2.60 (t, 2H, J = 7.9 Hz), 1.24 (t, 3H, J = 7.3 Hz). FAB-MS m/z: 297 $[M]^+$, 298 $[M+H]^+$.

4.2.32. 5-{4-[2-(4-Aminophenyl)ethyl]phenyl}pentanoic acid ethyl ester (27b)

This compound was prepared from **26b** by means of GP-H. Compound **27b** was obtained in 83% yield as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.10 (d, 2H, J = 8.5 Hz), 7.08 (d, 2H, J = 8.5 Hz), 6.98 (d, 2H, J = 7.9 Hz), 6.63 (d, 2H, J = 7.9 Hz), 4.12 (q, 2H, J = 7.3 Hz), 3.56 (br s, 2H), 2.84–2.81 (m, 2H), 2.80–2.77 (m, 2H), 2.60 (t, 2H, J = 7.3 Hz), 2.32 (t, 2H, J = 7.3 Hz), 1.67–1.61 (m, 4H), 1.25 (t, 3H, J = 7.3 Hz). FAB-MS m/z: 325 $[M]^+$, 326 $[M+H]^+$.

4.2.33. 7-{4-[2-(4-Aminophenyl)ethyl]phenyl}heptanoic acid ethyl ester (27c)

This compound was prepared from **26c** by means of GP-H. Compound **27c** was obtained in 84% yield as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.09 (d, 2H, J = 7.9 Hz), 7.07 (d, 2H, J = 8.5 Hz), 6.98 (d, 2H, J = 7.9 Hz), 6.63 (d, 2H, J = 7.9 Hz), 4.12 (q, 2H, J = 7.3 Hz), 3.56 (br s, 2H), 2.85–2.81 (m, 2H), 2.80–2.77 (m, 2H), 2.57 (t, 2H, J = 7.3 Hz), 2.28 (t, 2H, J = 7.3 Hz), 1.65–1.58 (m, 6H), 1.36–1.33 (m, 2H), 1.25 (t, 3H, J = 7.3 Hz). FAB-MS m/z: 353 $[M]^+$, 354 $[M+H]^+$.

4.2.34. 3-(4-{2-[4-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl) phenyl]ethyl}phenyl)propionic acid ethyl ester (28a)

This compound was prepared from phthalic anhydride and **27a** by means of GP-F. Compound **28a** was obtained in 75% yield as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.96 (dd, 2H, J = 5.5, 3.1 Hz), 7.79 (dd, 2H, J = 5.5, 3.1 Hz), 7.35 (d, 2H, J = 8.5 Hz), 7.33 (d, 2H, J = 7.9 Hz), 7.14 (s, 4H), 4.13 (q, 2H, J = 7.3 Hz), 2.98–2.95 (m, 2H), 2.96–2.91 (m, 2H), 2.93–2.90 (m, 2H), 2.62 (t, 2H, J = 7.3 Hz), 1.24 (t, 3H, J = 7.3 Hz). FAB-MS m/z: 427 $[M]^+$, 428 $[M+H]^+$.

4.2.35. 5-(4-{2-[4-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl) phenyl]ethyl}phenyl)pentanoic acid ethyl ester (28b)

This compound was prepared from phthalic anhydride and **27b** by means of GP-F. Compound **28b** was obtained in 60% yield as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.96 (dd, 2H, J = 5.5, 3.1 Hz), 7.79 (dd, 2H, J = 5.5, 3.1 Hz), 7.34 (s, 4H), 7.12 (q, 4H, J = 7.3 Hz), 4.12 (q, 2H, J = 7.3 Hz), 2.98–2.95 (m, 2H), 2.93–2.92 (m, 2H), 2.61 (t, 2H, J = 7.3 Hz), 2.32 (t, 2H, J = 7.3 Hz), 1.70–1.63 (m, 4H), 1.25 (t, 3H, J = 7.3 Hz). FAB-MS m/z: 455 $[M]^+$, 456 $[M+H]^+$.

4.2.36. 7-(4-{2-[4-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl) phenyl]ethyl}phenyl)heptanoic acid ethyl ester (28c)

This compound was prepared from phthalic anhydride and **27c** by means of GP-F. Compound **28c** was obtained in 51% yield as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.96 (dd, 2H, J = 5.5, 3.1 Hz), 7.79 (dd, 2H, J = 5.5, 3.1 Hz), 7.36–7.33 (m, 4H), 7.12 (q, 4H, J = 7.3 Hz), 4.12 (q, 2H, J = 7.3 Hz), 2.99–2.95 (m, 2H), 2.94–2.90 (m, 2H), 2.58 (t, 2H, J = 7.3 Hz), 2.29 (t, 2H, J = 7.3 Hz), 1.65–1.58 (m, 6H), 1.37–1.34 (m, 2H), 1.25 (t, 3H, J = 7.3 Hz).

4.2.37. 3-(4-{2-[4-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl) phenyl]ethyl}phenyl)propionic acid (11a)

This compound was prepared from **28a** by means of GP-I. Compound **11a** was obtained in 39% yield as colorless needles after recrystallization from EtOAc/n-hexane.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.96 (dd, 2H, J = 5.5, 3.1 Hz), 7.79 (dd, 2H, J = 5.5, 3.1 Hz), 7.33 (d, 2H, J = 7.9 Hz), 7.28 (d, 2H, J = 8.5 Hz), 7.14 (d, 2H, J = 8.5 Hz), 7.11 (d, 2H, J = 8.5 Hz), 2.98–2.95 (m, 2H), 2.96–2.93 (m, 2H), 2.95–2.92 (m, 2H), 2.68 (t, 2H, J = 7.3 Hz). FAB-MS m/z: 399 $[M]^+$, 400 $[M+H]^+$. Anal. Calcd for $C_{25}H_{21}NO_4$: C, 75.17; H, 5.30; N, 3.51. Found: C, 74.87; H, 5.38; N, 3.56.

4.2.38. 5-(4-{2-[4-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl) phenyl]ethyl}phenyl)pentanoic acid (11b)

This compound was prepared from **28b** by means of GP-I. Compound **11b** was obtained in 83% yield as a white powder after recrystallization from CH_2Cl_2/n-hexane.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.96 (dd, 2H, J = 5.5, 3.1 Hz), 7.79 (dd, 2H, J = 5.5, 3.1 Hz), 7.34 (d, 2H, J = 9.2 Hz), 7.32 (d, 2H, J = 8.5 Hz), 7.13 (d, 2H, J = 8.5 Hz), 7.11 (d, 2H, J = 8.5 Hz), 2.98–2.95 (m, 2H), 2.94–2.91 (m, 2H), 2.62 (t, 2H, J = 7.3 Hz), 2.38 (t, 2H, J = 7.3 Hz), 1.69–1.67 (m, 4H). FAB-MS m/z: 427 $[M]^+$, 428 $[M+H]^+$. Anal. Calcd for $C_{27}H_{25}NO_4 \cdot 1/4H_2O$: C, 75.22; H, 5.94; N, 3.25. Found: C, 75.12; H, 5.89; N, 3.18.

4.2.39. 7-(4-{2-[4-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl) phenyl]ethyl}phenyl)heptanoic acid (11c)

This compound was prepared from **28c** by means of GP-I. Compound **11c** was obtained in 74% yield as a white powder after recrystallization from CH_2Cl_2/n-hexane.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.96 (dd, 2H, J = 5.5, 3.1 Hz), 7.79 (dd, 2H, J = 5.5, 3.1 Hz), 7.36–7.32 (m, 4H), 7.13 (d, 2H, J = 8.5 Hz), 7.10 (d, 2H, J = 8.5 Hz), 2.99–2.95 (m, 2H), 2.94–2.90 (m, 2H), 2.58 (t, 2H, J = 7.3 Hz), 2.35 (t, 2H, J = 7.3 Hz), 1.63 (quin, 2H, J = 7.3 Hz), 1.38–1.36 (m, 6H). FAB-MS m/z: 455 $[M]^+$, 456 $[M+H]^+$. Anal. Calcd for $C_{29}H_{29}NO_4 \cdot 1/3H_2O$: C, 75.71; H, 6.46; N, 3.04. Found: C, 75.76; H, 6.43; N, 2.87.

4.2.40. (4-{2-[4-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl) phenyl]ethyl}phenoxy)-acetic acid *t*-butyl ester (30a)

To a solution of **29** (62 mg, 0.18 mmol) in dehydrated DMF (7 mL) were added potassium carbonate (75 mg, 0.54 mmol) and bromoacetic acid *tert*-butyl ester (80 μL, 0.54 mmol) under an argon atmosphere. The mixture was heated at 50 °C for 4 h, then poured into water (60 mL) and extracted with EtOAc (20 mL × 4). The organic layer was washed with H_2O (20 mL × 2) and brine (20 mL), and dried over $MgSO_4$. The solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography to give the target compound (76 mg, 93%) as a pale yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.96 (dd, 2H, J = 5.5, 3.1 Hz), 7.79 (dd, 2H, J = 5.5, 3.1 Hz), 7.34 (d, 2H, J = 8.5 Hz), 7.31 (d, 2H, J = 8.5 Hz), 7.12 (d, 2H, J = 8.5 Hz), 6.83 (d, 2H, J = 8.5 Hz), 4.50 (s, 2H), 2.96–2.93 (m, 2H), 2.91–2.88 (m, 2H), 1.49 (s, 9H). FAB-MS m/z: 457 $[M]^+$, 458 $[M+H]^+$.

4.2.41. 4-(4-{2-[4-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl) phenyl]ethyl}phenoxy)butyric acid ethyl ester (30b)

To a solution of **29** (34 mg, 0.1 mmol) in dehydrated DMF (4 mL) were added potassium carbonate (81 mg, 0.59 mmol) and ethyl 4-bromobutyrate (68 μL, 0.48 mmol) under an argon atmosphere. The mixture was heated overnight at 60 °C, then poured into water

(30 mL) and extracted with EtOAc (15 mL × 3). The organic layer was washed with H_2O (10 mL × 2) and brine (10 mL), and dried over $MgSO_4$. The solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography to give the target compound (35 mg, 76%) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.96 (dd, 2H, J = 5.5, 3.1 Hz), 7.79 (dd, 2H, J = 4.9, 3.1 Hz), 7.34 (d, 2H, J = 7.9 Hz), 7.31 (d, 2H, J = 8.5 Hz), 7.11 (d, 2H, J = 8.5 Hz), 6.82 (d, 2H, J = 8.5 Hz), 4.15 (q, 2H, J = 7.3 Hz), 3.99 (t, 2H, J = 6.1 Hz), 2.96–2.92 (m, 2H), 2.90–2.87 (m, 2H), 2.52 (t, 2H, J = 7.3 Hz), 2.11 (quin, 2H, J = 6.7 Hz), 1.26 (t, 3H, J = 7.3 Hz). FAB-MS m/z: 457 $[M]^+$, 458 $[M+H]^+$.

4.2.42. 6-(4-{2-[4-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl) phenyl]ethyl}phenoxy)hexanoic acid ethyl ester (30c)

To a solution of **29** (172 mg, 0.5 mmol) in dehydrated DMF (4 mL) were added potassium carbonate (138 mg, 1.0 mmol) and 6-bromohexanoic acid ethyl ester (712 μL, 4.0 mmol) under an argon atmosphere. The mixture was heated for 6 h at 70 °C, then poured into water (20 mL) and extracted with EtOAc (15 mL × 3). The organic layer was washed with H_2O (10 mL × 2) and brine (10 mL), and dried over $MgSO_4$. The solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography to give the target compound (194 mg, 80%) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.96 (dd, 2H, J = 4.9, 3.1 Hz), 7.79 (dd, 2H, J = 5.5, 3.1 Hz), 7.34 (d, 2H, J = 8.5 Hz), 7.31 (d, 2H, J = 8.5 Hz), 7.11 (d, 2H, J = 8.5 Hz), 6.82 (d, 2H, J = 8.5 Hz), 4.13 (q, 2H, J = 6.7 Hz), 3.95 (t, 2H, J = 6.7 Hz), 2.96–2.93 (m, 2H), 2.90–2.88 (m, 2H), 2.34 (t, 2H, J = 7.9 Hz), 1.80 (quin, 2H, J = 7.9 Hz), 1.71 (quin, 2H, J = 7.9 Hz), 1.54–1.48 (m, 2H), 1.26 (t, 3H, J = 6.7 Hz). FAB-MS m/z: 485 $[M]^+$, 486 $[M+H]^+$.

4.2.43. (4-{2-[4-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl) phenyl]ethyl}phenoxy)acetic acid (12a)

This compound was prepared from **30a** by means of GP-G. Compound **12a** was obtained in 100% yield as a white powder after recrystallization from EtOAc/*n*-hexane.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.96 (dd, 2H, J = 5.5, 3.1 Hz), 7.79 (dd, 2H, J = 5.5, 3.1 Hz), 7.34 (d, 2H, J = 8.5 Hz), 7.29 (d, 2H, J = 8.5 Hz), 7.13 (d, 2H, J = 8.5 Hz), 6.87 (d, 2H, J = 9.2 Hz), 4.66 (s, 2H), 2.97–2.94 (m, 2H), 2.93–2.90 (m, 2H). FAB-MS m/z: 401 $[M]^+$, 402 $[M+H]^+$. Anal. Calcd for $C_{24}H_{19}NO_5 \cdot 1/4H_2O$: C, 71.01; H, 4.84; N, 3.45. Found: C, 71.43; H, 4.96; N, 3.46.

4.2.44. 4-(4-{2-[4-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl) phenyl]ethyl}phenoxy)butyric acid (12b)

This compound was prepared from **30b** by means of GP-I. Compound **12b** was obtained in 65% yield as a white powder after recrystallization from CH_2Cl_2/*n*-hexane.

^{1}H NMR (500 MHz, DMSO-d_6) δ: 12.12 (br s, 1H), 7.95 (dd, 2H, J = 5.5, 3.1 Hz), 7.89 (dd, 2H, J = 5.5, 3.1 Hz), 7.36 (d, 2H, J = 8.5 Hz), 7.32 (d, 2H, J = 8.5 Hz), 7.16 (d, 2H, J = 8.5 Hz), 6.83 (d, 2H, J = 7.9 Hz), 3.93 (t, 2H, J = 6.7 Hz), 2.92–2.88 (m, 2H), 2.86–2.83 (m, 2H), 2.36 (t, 2H, J = 7.3 Hz), 1.91 (quin, 2H, J = 6.7 Hz). FAB-MS m/z: 429 $[M]^+$, 430 $[M+H]^+$. Anal. Calcd for $C_{26}H_{23}NO_5 \cdot 1/5H_2O$: C, 72.21; H, 5.44; N, 3.24. Found: C, 72.31; H, 5.28; N, 3.19.

4.2.45. 6-(4-{2-[4-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl) phenyl]ethyl}phenoxy)hexanoic acid (12c)

This compound was prepared from **30c** by means of GP-I. Compound **12c** was obtained in 65% yield as a white powder after recrystallization from CH_2Cl_2/*n*-hexane.

^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.95 (dd, 2H, J = 5.5, 3.1 Hz), 7.89 (dd, 2H, J = 5.5, 3.1 Hz), 7.36 (d, 2H, J = 8.5 Hz), 7.32 (d, 2H, J = 8.5 Hz), 7.15 (d, 2H, J = 8.5 Hz), 6.82 (d, 2H, J = 8.5 Hz), 3.90 (t, 2H, J = 6.7 Hz), 2.92–2.88 (m, 2H), 2.86–2.84 (m, 2H), 2.22 (t, 2H, J = 7.3 Hz), 1.68 (quin, 2H, J = 7.3 Hz), 1.55 (quin, 2H, J = 7.3 Hz), 1.40 (quin, 2H, J = 7.3 Hz). FAB-MS m/z: 457 $[M]^+$, 458 $[M+H]^+$. Anal. Calcd for $C_{28}H_{27}NO_5 \cdot 1/4H_2O$: C, 72.79; H, 6.00; N, 3.03. Found: C, 72.98; H, 5.90; N, 2.91.

4.2.46. [4-(*tert*-Butyl-dimethyl-silanyloxymethyl)phenyl] methanol (31)

To a solution of TBSCl (11.4 g, 76 mmol) in dehydrated DMF (190 mL) were added *p*-xylene-α,α′-diol (10.36 g, 75 mmol) and imidazole (10.21 g, 150 mmol) under an argon atmosphere. The mixture was stirred at rt overnight, then poured into water (500 mL) and extracted with EtOAc (150 mL × 3). The organic layer was washed with H_2O (100 mL × 2) and brine (100 mL), and dried over $MgSO_4$. The solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography to give the target compound (4.97 g, 26%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.34 (d, 2H, J = 9.2 Hz), 7.32 (d, 2H, J = 8.5 Hz), 4.74 (s, 2H), 4.68 (d, 2H, J = 6.1 Hz), 0.94 (s, 9H), 0.10 (s, 6H). FAB-MS m/z: 252 $[M]^+$, 253 $[M+H]^+$.

4.2.47. 4-(*tert*-Butyl-dimethyl-silanyloxymethyl)benzaldehyde (32)

To a solution of **31** (2.57 g, 10.18 mmol) in dehydrated CH_2Cl_2 (20 mL) was added PDC (7.66 g, 20.36 mmol), and the mixture was stirred at rt overnight. The mixture was filtered through a pad of Celite, and the filtrate was evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give the target compound (1.95 g, 76%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 10.00 (s, 1H), 7.85 (d, 2H, J = 7.9 Hz), 7.49 (d, 2H, J = 7.9 Hz), 4.82 (s, 2H), 0.96 (s, 9H), 0.12 (s, 6H). FAB-MS m/z: 250 $[M]^+$, 251 $[M+H]^+$.

4.2.48. 2-[4-(*tert*-Butyl-dimethyl-silanyloxymethyl) benzylidene]butyric acid ethyl ester (33)

Potassium *t*-butoxide (1.63 g, 14.5 mmol) was suspended in dehydrated THF (5 mL) under Ar and cooled with ice. Trimethyl 2-phosphonobutyrate (3.44 mL, 14.5 mmol) was added dropwise. When the addition was completed, the mixture was stirred for 5 min, then compound **32** (3.52 g, 14.06 mmol) dissolved in dehydrated THF (20 mL) was added dropwise at 0 °C. The mixture was stirred for 15 min at rt, then poured into water (40 mL) and extracted with EtOAc (45 mL × 3). The organic layer was washed with H_2O (20 mL × 2) and brine (20 mL), and dried over $MgSO_4$. The solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography to give the target compound (4.67 g, 95%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) *major*δ: 7.34 (s, 4H), 4.76 (s, 2H), 4.28 (q, 2H, J = 7.3 Hz), 2.55 (q, 2H, J = 7.3 Hz), 1.35 (t, 3H, J = 7.3 Hz), 1.18 (t, 3H, J = 7.3 Hz), 0.95 (s, 9H), 0.11 (s, 6H). *minor* δ: 7.23 (s, 2H), 7.21 (s, 2H), 4.72 (s, 2H), 4.14 (q, 2H, J = 7.9 Hz), 2.44 (q, 2H, J = 7.9 Hz), 1.13 (t, 3H, J = 7.3 Hz), 0.93 (s, 9H), 0.09 (s, 6H). FAB-MS m/z: 348 $[M]^+$, 349 $[M+H]^+$.

4.2.49. 2-[4-(*tert*-Butyl-dimethyl-silanyloxymethyl)benzyl] butyric acid ethyl ester (34)

This compound was prepared from **33** by means of GP-E. Compound **34** was obtained in 95% yield as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.22 (d, 2H, J = 7.9 Hz), 7.12 (d, 2H, J = 8.5 Hz), 4.70 (s, 2H), 4.06 (m, 2H), 2.91 (dd, 1H, J = 14.0, 8.5 Hz), 2.72 (dd, 1H, J = 13.4, 6.7 Hz), 2.59–2.53 (m, 1H), 1.67–1.61 (m, 1H), 1.58–1.52 (m, 1H), 1.16 (t, 3H, J = 7.3 Hz), 0.93 (s, 9H), 0.91 (t, 3H, J = 7.3 Hz), 0.08 (s, 6H). FAB-MS m/z: 350 $[M]^+$, 351 $[M+H]^+$.

4.2.50. 2-(4-Hydroxymethylbenzyl)butyric acid ethyl ester (35)

To a solution of **34** (4.48 g, 12.78 mmol) in dehydrated THF was added TBAF (1.0 M solution in THF) (14.06 mL, 14.06 mmol) at 0 °C

under an argon atmosphere. The mixture was stirred for 20 min, then poured into water (50 mL) and extracted with EtOAc (40 mL × 3). The organic layer was washed with H_2O (20 mL × 2) and brine (10 mL), and dried over $MgSO_4$. The solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography to give the target compound (2.84 g, 94%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.27 (d, 2H, J = 7.9 Hz), 7.16 (d, 2H, J = 7.9 Hz), 4.66 (d, 2H, J = 6.1 Hz), 4.11–4.04 (m, 4H), 2.93 (dd, 1H, J = 13.4, 8.5 Hz), 2.74 (dd, 1H, J = 14.0, 6.7 Hz), 2.60–2.54 (m, 1H), 1.68–1.62 (m, 1H), 1.58–1.52 (m, 1H), 1.17 (t, 3H, J = 7.3 Hz), 0.92 (t, 3H, J = 7.3 Hz). FAB-MS m/z: 236 $[M]^+$.

4.2.51. 2-(4-Formylbenzyl)butyric acid ethyl ester (36)

To a solution of **35** (2.83 g, 11.98 mmol) in dehydrated CH_2Cl_2 (30 mL) was added PDC (6.76 g, 17.97 mmol), and the mixture was stirred at rt overnight. The mixture was filtered through a pad of Celite, and the filtrate was evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give the target compound (1.99 g, 71%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.97 (s, 1H), 7.80 (d, 2H, J = 8.5 Hz), 7.34 (d, 2H, J = 7.9 Hz), 4.10–4.03 (m, 2H), 3.01 (dd, 1H, J = 13.4, 9.2 Hz), 2.84 (dd, 1H, J = 13.4, 6.1 Hz), 2.65–2.59 (m, 1H), 1.72–1.66 (m, 1H), 1.62–1.54 (m, 1H), 1.14 (t, 3H, J = 7.3 Hz), 0.94 (t, 3H, J = 7.3 Hz). FAB-MS m/z: 235 $[M+H]^+$.

4.2.52. 2-Methoxy-1-methyl-4-nitrobenzene (37c)

This compound was prepared from 2-methyl-5-nitrophenol and iodomethane by means of GP-J. Compound **37c** was obtained in 96% yield as a brown solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.77 (dd, 1H, J = 7.9, 2.4 Hz), 7.66 (d, 1H, J = 2.4 Hz), 7.26 (d, 1H, J = 7.9 Hz), 3.92 (s, 3H), 2.30 (s, 3H). FAB-MS m/z: 167 $[M]^+$, 168 $[M+H]^+$.

4.2.53. 2-Ethoxy-1-methyl-4-nitrobenzene (37d)

This compound was prepared from 2-methyl-5-nitrophenol and iodoethane by means of GP-J. Compound **37d** was obtained in 100% yield as a brown solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.74 (dd, 1H, J = 8.5, 2.4 Hz), 7.64 (d, 1H, J = 2.4 Hz), 7.25 (d, 1H, J = 8.5 Hz), 4.12 (q, 2H, J = 7.3 Hz), 2.30 (s, 3H), 1.48 (t, 3H, J = 7.3 Hz). FAB-MS m/z: 181 $[M]^+$, 182 $[M+H]^+$.

4.2.54. 1-Methyl-4-nitro-2-*n*-propoxybenzene (37e)

This compound was prepared from 2-methyl-5-nitrophenol and 1-iodopropane by means of GP-J. Compound **37e** was obtained in 96% yield as a brown solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.74 (dd, 1H, J = 7.9, 2.4 Hz), 7.64 (d, 1H, J = 1.8 Hz), 7.25 (d, 1H, J = 8.5 Hz), 4.01 (t, 2H, J = 6.7 Hz), 2.31 (s, 3H), 1.88 (sex, 2H, J = 6.7 Hz), 1.08 (t, 3H, J = 7.3 Hz). FAB-MS m/z: 195 $[M]^+$, 196 $[M+H]^+$.

4.2.55. 2-Butoxy-1-methyl-4-nitrobenzene (37f)

This compound was prepared from 2-methyl-5-nitrophenol and 1-iodobutane by means of GP-J. Compound **37f** was obtained in 93% yield as a brown solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.74 (dd, 1H, J = 7.9, 1.8 Hz), 7.64 (d, 1H, J = 1.8 Hz), 7.25 (d, 1H, J = 7.9 Hz), 4.05 (t, 2H, J = 6.7 Hz), 2.30 (s, 3H), 1.86–1.81 (m, 2H), 1.57–1.51 (m, 2H), 1.00 (t, 3H, J = 7.3 Hz). FAB-MS m/z: 209 $[M]^+$, 210 $[M+H]^+$.

4.2.56. (4-Nitrobenzyl)triphenylphosphonium bromide (38a)

This compound was prepared from 4-nitrobenzyl bromide by means of GP-C-2. Compound **38a** was obtained in 99% yield as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.91 (d, 2H, J = 9.2 Hz), 7.84–7.77 (m, 9H), 7.66–7.62 (m, 6H), 7.45 (dd, 2H, J = 9.2, 2.4 Hz), 5.91 (dd, 2H, J = 15.3 Hz). FAB-MS m/z: 398 $[M-Br]^+$

4.2.57. (2-Methoxy-4-nitrobenzyl)triphenylphosphonium bromide (38c)

This compound was prepared from **37c** by means of GP-B and GP-C-2. Compound **38c** was obtained in 73% yield as a brown solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.85 (dd, 1H, J = 8.5, 2.4 Hz), 7.81–7.76 (m, 9H), 7.71 (d, 1H, J = 8.5 Hz), 7.68–7.64 (m, 6H), 7.43 (d, 1H, J = 1.8 Hz), 5.64 (d, 2H, J = 15.3 Hz), 3.34 (s, 3H). FAB-MS m/z: 428 $[M-Br]^+$.

4.2.58. (2-Ethoxy-4-nitrobenzyl)triphenylphosphonium bromide (38d)

This compound was prepared from **37d** by means of GP-B and GP-C-2. Compound **38d** was obtained in 88% yield as a brown solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.81–7.74 (m, 10H), 7.71 (dd, 1H, J = 8.5, 2.4 Hz), 7.67–7.63 (m, 6H), 7.43 (d, 1H, J = 1.8 Hz), 5.70 (d, 2H, J = 14.6 Hz), 3.59 (q, 2H, J = 7.3 Hz), 1.09 (t, 3H, J = 7.3 Hz). FAB-MS m/z: 442 $[M-Br]^+$.

4.2.59. (4-Nitro-2-*n*-propoxybenzyl)triphenylphosphonium bromide (38e)

This compound was prepared from **37e** by means of GP-B and GP-C-2. Compound **38e** was obtained in 93% yield as a brown solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.81–7.73 (m, 10H), 7.70 (dd, 1H, J = 8.5, 1.2 Hz), 7.67–7.63 (m, 6H), 7.44 (d, 1H, J = 1.8 Hz), 5.71 (d, 2H, J = 15.3 Hz), 3.47 (t, 2H, J = 6.7 Hz), 1.46 (sex, 2H, J = 7.3 Hz), 0.86 (t, 3H, J = 7.3 Hz). FAB-MS m/z: 456 $[M-Br]^+$.

4.2.60. (2-*n*-Butoxy-4-nitrobenzyl)triphenylphosphonium bromide (38f)

This compound was prepared from **37f** by means of GP-B and GP-C-2. Compound **38f** was obtained in 99% yield as a brown solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.81–7.73 (m, 10H), 7.70 (dd, 1H, J = 8.5, 1.2 Hz), 7.67–7.63 (m, 6H), 7.44 (d, 1H, J = 1.8 Hz), 5.70 (d, 2H, J = 15.3 Hz), 3.52 (t, 2H, J = 6.7 Hz), 1.40 (quin, 2H, J = 6.7 Hz), 1.27 (sex, 2H, J = 7.3 Hz), 0.90 (t, 3H, J = 7.3 Hz). FAB-MS m/z: 470 $[M-Br]^+$.

4.2.61. 2-{4-[2-(4-Nitrophenyl)vinyl]benzyl}butyric acid ethyl ester (39a)

This compound was prepared from **36** and **38a** by means of GP-D. Compound **39a** was obtained in 100% yield as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) **39a*Z*** δ: 8.07 (d, 2H, J = 9.2 Hz), 7.37 (d, 2H, J = 9.2 Hz), 7.10 (d, 2H, J = 7.9 Hz), 7.05 (d, 2H, J = 8.5 Hz), 6.77 (d, 1H, J = 12.2 Hz), 6.57 (d, 1H, J = 12.2 Hz), 4.11–4.05 (m, 2H), 2.90 (dd, 1H, J = 14.0, 9.2 Hz), 2.73 (dd, 1H, J = 14.0, 6.7 Hz), 2.60–2.55 (m, 1H), 1.71–1.63 (m, 1H), 1.61–1.52 (m, 1H), 1.17 (t, 3H, J = 7.3 Hz), 0.92 (t, 3H, J = 7.3 Hz). Compound **39a*E*** δ: 8.22 (d, 2H, J = 8.5 Hz), 7.62 (d, 2H, J = 9.2 Hz), 7.46 (d, 2H, J = 8.5 Hz), 7.25 (d, 1H, J = 16.5 Hz), 7.20 (d, 2H, J = 8.5 Hz), 7.10 (d, 1H, J = 16.5 Hz), 4.11–4.05 (m, 2H), 2.95 (dd, 1H, J = 14.0, 9.2 Hz), 2.78 (dd, 1H, J = 14.0, 6.7 Hz), 2.63–2.56 (m, 1H), 1.71–1.64 (m, 1H), 1.62–1.54 (m, 1H), 1.17 (t, 3H, J = 7.3 Hz), 0.92 (t, 3H, J = 7.3 Hz). FAB-MS m/z: 353 $[M]^+$, 354 $[M+H]^+$.

4.2.62. 2-{4-[2-(2-Methoxy-4-nitrophenyl)vinyl]benzyl}butyric acid ethyl ester (39c)

This compound was prepared from **36** and **38c** by means of GP-D. Compound **39c** was obtained in 86% yield as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) **39c*Z*** δ: 7.73 (d, 1H, J = 2.4 Hz), 7.62 (dd, 1H, J = 8.5, 2.4 Hz), 7.28–7.24 (m, 1H), 7.08 (d, 2H, J = 7.9 Hz), 7.01 (d, 2H, J = 7.9 Hz), 6.76 (d, 1H, J = 12.2 Hz), 6.61 (d, 1H, J = 12.2 Hz), 4.11–4.04 (m, 2H), 3.92 (s, 3H), 2.88 (dd, 1H, J = 14.0,

8.5 Hz), 2.70 (dd, 1H, *J* = 14.0, 6.7 Hz), 2.56–2.52 (m, 1H), 1.70–1.52 (m, 2H), 1.16 (t, 3H, *J* = 6.7 Hz), 0.91 (t, 3H, *J* = 7.9 Hz). Compound **39c*E*** δ: 7.86 (dd, 1H, *J* = 8.5, 2.4 Hz), 7.75 (d, 1H, *J* = 2.4 Hz), 7.69 (d, 1H, *J* = 8.5 Hz), 7.47 (d, 2H, *J* = 7.9 Hz), 7.42 (d, 1H, *J* = 16.5 Hz), 7.23 (d, 2H, *J* = 16.5 Hz), 7.19 (d, 2H, *J* = 8.5 Hz), 4.11–4.04 (m, 2H), 3.99 (s, 3H), 2.95 (dd, 1H, *J* = 13.4, 8.5 Hz), 2.77 (dd, 1H, *J* = 14.0, 6.7 Hz), 2.62–2.58 (m, 1H), 1.70–1.52 (m, 2H), 1.17 (t, 3H, *J* = 7.3 Hz), 0.93 (t, 3H, *J* = 7.3 Hz). FAB-MS *m*/*z*: 383 $[M]^+$, 384 $[M+H]^+$.

4.2.63. 2-{4-[2-(2-Ethoxy-4-nitrophenyl)vinyl]benzyl}butyric acid ethyl ester (39d)

This compound was prepared from **36** and **38d** by means of GP-D. Compound **39d** was obtained in 87% yield as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) **39d*Z*** δ: 7.70 (d, 1H, *J* = 1.8 Hz), 7.60 (dd, 1H, *J* = 8.5, 1.8 Hz), 7.27–7.24 (m, 1H), 7.09 (d, 2H, *J* = 8.5 Hz), 7.02 (d, 2H, *J* = 8.5 Hz), 6.74 (d, 1H, *J* = 12.2 Hz), 6.62 (d, 1H, *J* = 12.2 Hz), 4.12–4.04 (m, 4H), 2.88 (dd, 1H, *J* = 13.4, 9.2 Hz), 2.70 (dd, 1H, *J* = 13.4, 6.7 Hz), 2.62–2.57 (m, 1H), 1.70–1.52 (m, 2H), 1.17 (t, 3H, *J* = 6.7 Hz), 0.91 (t, 3H, *J* = 7.3 Hz). Compound **39d*E*** δ: 7.84 (dd, 1H, *J* = 8.5, 2.4 Hz), 7.73 (d, 1H, *J* = 2.4 Hz), 7.68 (d, 1H, *J* = 8.5 Hz), 7.46 (d, 2H, *J* = 8.5 Hz), 7.43 (d, 1H, *J* = 16.5 Hz), 7.27–7.24 (m, 1H), 7.19 (d, 2H, *J* = 7.9 Hz), 4.12–4.04 (m, 2H), 2.95 (dd, 1H, *J* = 13.4, 9.2 Hz), 2.77 (dd, 1H, *J* = 13.4, 6.7 Hz), 2.62–2.56 (m, 1H), 1.70–1.52 (m, 2H), 1.17 (t, 3H, *J* = 7.3 Hz), 0.93 (t, 3H, *J* = 7.9 Hz). FAB-MS *m*/*z*: 397 $[M]^+$, 398 $[M+H]^+$.

4.2.64. 2-{4-[2-(4-Nitro-2-*n*-propoxyphenyl)vinyl]benzyl} butyric acid ethyl ester (39e)

This compound was prepared from **36** and **38e** by means of GP-D. Compound **39e** was obtained in 79% yield as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) **39e*Z*** δ: 7.71 (d, 1H, *J* = 2.4 Hz), 7.59 (dd, 1H, *J* = 8.5, 1.8 Hz), 7.29 (d, 1H, *J* = 1.8 Hz), 7.10 (d, 2H, *J* = 7.9 Hz), 7.02 (d, 2H, *J* = 7.9 Hz), 6.74 (d, 1H, *J* = 12.2 Hz), 6.62 (d, 1H, *J* = 12.8 Hz), 4.11–4.01 (m, 4H), 2.88 (dd, 1H, *J* = 14.0, 8.5 Hz), 2.70 (dd, 1H, *J* = 13.4, 6.7 Hz), 2.55–2.53 (m, 1H), 1.82 (sex, 2H, *J* = 7.3 Hz), 1.68–1.53 (m, 2H), 1.13 (t, 3H, *J* = 7.9 Hz), 1.05 (t, 3H, *J* = 7.3 Hz), 0.91 (t, 3H, *J* = 7.3 Hz). Compound **39e*E*** δ: 7.84 (dd, 1H, *J* = 8.5, 1.8 Hz), 7.73 (d, 1H, *J* = 1.8 Hz), 7.68 (d, 1H, *J* = 8.5 Hz), 7.46 (d, 2H, *J* = 7.9 Hz), 7.43 (d, 1H, *J* = 16.5 Hz), 7.27–7.25 (m, 1H), 7.19 (d, 2H, *J* = 7.9 Hz), 4.11–4.04 (m, 4H), 2.95 (dd, 1H, *J* = 14.0, 8.5 Hz), 2.77 (dd, 1H, *J* = 13.4, 6.7 Hz), 2.62–2.58 (m, 1H), 1.68–1.53 (m, 2H), 1.17 (t, 3H, *J* = 6.7 Hz), 1.16 (t, 3H, *J* = 7.3 Hz), 0.93 (t, 3H, *J* = 7.3 Hz). FAB-MS *m*/*z*: 411 $[M]^+$, 412 $[M+H]^+$.

4.2.65. 2-{4-[2-(2-*n*-Butoxy-4-nitrophenyl)vinyl]benzyl}butyric acid ethyl ester (39f)

This compound was prepared from **36** and **38f** by means of GP-D. Compound **39f** was obtained in 80% yield as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) **39f*Z*** δ: 7.71 (d, 1H, *J* = 2.4 Hz), 7.59 (dd, 1H, *J* = 8.5, 2.4 Hz), 7.28–7.25 (m, 1H), 7.09 (d, 2H, *J* = 7.9 Hz), 7.02 (d, 2H, *J* = 7.9 Hz), 6.73 (d, 1H, *J* = 12.2 Hz), 6.61 (d, 1H, *J* = 12.2 Hz), 4.11–4.03 (m, 4H), 2.88 (dd, 1H, *J* = 14.0, 8.5 Hz), 2.70 (dd, 1H, *J* = 14.0, 6.7 Hz), 2.57–2.53 (m, 1H), 1.78 (quin, 2H, *J* = 6.7 Hz), 1.70–1.49 (m, 4H), 1.16 (t, 3H, *J* = 6.7 Hz), 0.98 (t, 3H, *J* = 7.3 Hz), 0.91 (t, 3H, *J* = 7.3 Hz). Compound **39f*E*** δ: 7.84 (dd, 1H, *J* = 8.5, 1.8 Hz), 7.73 (d, 1H, *J* = 1.8 Hz), 7.67 (d, 1H, *J* = 8.5 Hz), 7.45 (d, 2H, *J* = 8.5 Hz), 7.42 (d, 1H, *J* = 16.5 Hz), 7.28–7.25 (m, 1H), 7.19 (d, 2H, *J* = 8.5 Hz), 4.13 (t, 2H, *J* = 6.1 Hz), 4.06 (t, 2H, *J* = 7.3 Hz), 2.95 (dd, 1H, *J* = 13.4, 8.5 Hz), 2.78 (dd, 1H, *J* = 14.0, 6.7 Hz), 2.63–2.58 (m, 1H), 1.90 (quin, 2H, *J* = 6.7 Hz), 1.70–1.54 (m, 4H), 1.17 (t, 3H, *J* = 7.3 Hz), 1.04 (t, 3H, *J* = 7.3 Hz), 0.93 (t, 3H, *J* = 7.9 Hz). FAB-MS *m*/*z*: 425 $[M]^+$, 426 $[M+H]^+$.

4.2.66. 2-{4-[2-(4-Nitrophenyl)vinyl]benzyl}butyric acid (40a)

This compound was prepared from **39a** by means of GP-K. Compound **40a** was obtained in 98% yield as a yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) **40a*Z*** δ: 8.07 (d, 2H, *J* = 8.5 Hz), 7.36 (d, 2H, *J* = 8.5 Hz), 7.11 (d, 2H, *J* = 6.7 Hz), 7.07 (d, 2H, *J* = 8.5 Hz), 6.77 (d, 1H, *J* = 12.2 Hz), 6.57 (d, 1H, *J* = 12.2 Hz), 2.94 (dd, 1H, *J* = 14.0, 8.5 Hz), 2.76 (dd, 1H, *J* = 14.0, 6.7 Hz), 2.66–2.58 (m, 1H), 1.73–1.58 (m, 2H), 0.97 (t, 3H, *J* = 7.3 Hz). Compound **40a*E*** δ: 8.21 (d, 2H, *J* = 8.5 Hz), 7.61 (d, 2H, *J* = 8.5 Hz), 7.47 (d, 2H, *J* = 8.5 Hz), 7.24 (d, 1H, *J* = 16.5 Hz), 7.22 (d, 2H, *J* = 7.9 Hz), 7.10 (d, 1H, *J* = 16.5 Hz), 3.00 (dd, 1H, *J* = 14.0, 7.9 Hz), 2.80 (dd, 1H, *J* = 14.0, 6.7 Hz), 2.68–2.61 (m, 1H), 1.73–1.58 (m, 2H), 0.98 (t, 3H, *J* = 7.3 Hz). FAB-MS *m*/*z*: 325 $[M]^+$, 326 $[M+H]^+$.

4.2.67. 2-{4-[2-(2-Methoxy-4-nitrophenyl)vinyl]benzyl}butyric acid (40c)

This compound was prepared from **39c** by means of GP-K. Compound **40c** was obtained in 96% yield as a yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) **40c*Z*** δ: 7.72 (d, 1H, *J* = 2.4 Hz), 7.63 (dd, 1H, *J* = 8.5, 2.4 Hz), 7.28–7.24 (m, 1H), 7.09 (d, 1H, *J* = 8.5 Hz), 7.04 (d, 2H, *J* = 7.9 Hz), 6.76 (d, 1H, *J* = 12.2 Hz), 6.61 (d, 1H, *J* = 12.2 Hz), 3.90 (s, 3H), 2.92 (dd, 1H, *J* = 14.0, 8.5 Hz), 2.74 (dd, 1H, *J* = 14.0, 6.7 Hz), 2.65–2.58 (m, 1H), 1.73–1.55 (m, 2H), 0.96 (t, 3H, *J* = 7.3 Hz). Compound **40c*E*** δ: 7.86 (dd, 1H, *J* = 8.5, 2.4 Hz), 7.74 (d, 1H, *J* = 1.8 Hz), 7.68 (d, 1H, *J* = 8.5 Hz), 7.48 (d, 2H, *J* = 7.9 Hz), 7.43 (d, 1H, *J* = 16.5 Hz), 7.23 (d, 2H, *J* = 16.5 Hz), 7.21 (dd, 2H, *J* = 8.5 Hz), 3.98 (s, 3H), 2.99 (dd, 1H, *J* = 14.0, 8.5 Hz), 2.80 (dd, 1H, *J* = 13.4, 6.7 Hz), 2.69–2.63 (m, 1H), 1.73–1.55 (m, 2H), 0.98 (t, 3H, *J* = 7.9 Hz). FAB-MS *m*/*z*: 355 $[M]^+$, 356 $[M+H]^+$.

4.2.68. 2-{4-[2-(2-Ethoxy-4-nitrophenyl)vinyl]benzyl}butyric acid (40d)

This compound was prepared from **39d** by means of GP-K. Compound **40d** was obtained in 100% yield as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) **40d*Z*** δ: 7.69 (d, 1H, *J* = 2.4 Hz), 7.61 (dd, 1H, *J* = 8.5, 2.4 Hz), 7.29–7.21 (m, 1H), 7.10 (d, 2H, *J* = 7.9 Hz), 7.04 (d, 2H, *J* = 7.9 Hz), 6.74 (d, 1H, *J* = 12.2 Hz), 6.62 (d, 1H, *J* = 12.2 Hz), 4.15 (q, 2H, *J* = 6.7 Hz), 2.92 (dd, 1H, *J* = 14.0, 8.5 Hz), 2.73 (dd, 1H, *J* = 14.0, 6.7 Hz), 2.65–2.58 (m, 1H), 1.73–1.52 (m, 2H), 1.39 (t, 3H, *J* = 6.7 Hz), 0.96 (t, 3H, *J* = 7.3 Hz). Compound **40d*E*** δ: 7.83 (dd, 1H, *J* = 8.5, 1.8 Hz), 7.72 (d, 1H, *J* = 2.4 Hz), 7.67 (d, 1H, *J* = 8.5 Hz), 7.48 (d, 2H, *J* = 7.9 Hz), 7.43 (d, 1H, *J* = 16.5 Hz), 7.29–7.21 (m, 3H), 4.20 (q, 2H, *J* = 6.7 Hz), 2.99 (dd, 1H, *J* = 14.0, 8.5 Hz), 2.80 (dd, 1H, *J* = 13.4, 6.7 Hz), 2.70–2.63 (m, 1H), 1.73–1.52 (m, 2H), 1.54 (t, 3H, *J* = 6.7 Hz), 0.98 (t, 3H, *J* = 7.3 Hz). FAB-MS *m*/*z*: 369 $[M]^+$, 370 $[M+H]^+$.

4.2.69. 2-{4-[2-(4-Nitro-2-*n*-propoxyphenyl)vinyl]benzyl} butyric acid (40e)

This compound was prepared from **39e** by means of GP-K. Compound **40e** was obtained in 95% yield as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) **40e*Z*** δ: 7.70 (d, 1H, *J* = 1.8 Hz), 7.60 (dd, 1H, *J* = 7.9, 1.8 Hz), 7.28–7.22 (m, 1H), 7.11 (d, 2H, *J* = 7.9 Hz), 7.04 (d, 2H, *J* = 7.9 Hz), 6.74 (d, 1H, *J* = 12.2 Hz), 6.63 (d, 1H, *J* = 12.8 Hz), 4.01 (t, 2H, *J* = 6.7 Hz), 2.93 (dd, 1H, *J* = 14.0, 7.9 Hz), 2.73 (dd, 1H, *J* = 14.0, 6.7 Hz), 2.63–2.59 (m, 1H), 1.81 (sex, 2H, *J* = 7.3 Hz), 1.73–1.56 (m, 2H), 1.04 (t, 3H, *J* = 7.3 Hz), 0.96 (t, 3H, *J* = 7.3 Hz). Compound **40e*E*** δ: 7.84 (dd, 1H, *J* = 8.5, 1.8 Hz), 7.73 (d, 1H, *J* = 2.4 Hz), 7.67 (d, 1H, *J* = 8.5 Hz), 7.47 (d, 2H, *J* = 8.5 Hz), 7.43 (d, 1H, *J* = 16.5 Hz), 7.28–7.22 (m, 1H), 7.22 (d, 2H, *J* = 7.9 Hz), 4.09 (t, 2H, *J* = 6.7 Hz), 2.99 (dd, 1H, *J* = 14.0, 7.9 Hz), 2.80 (dd, 1H, *J* = 14.0, 6.7 Hz), 2.70–2.65 (m, 1H), 1.94 (sex, 2H, *J* = 7.3 Hz), 1.73–1.56 (m, 2H), 1.13 (t, 3H, *J* = 7.3 Hz), 0.98 (t, 3H, *J* = 7.3 Hz). FAB-MS *m*/*z*: 383 $[M]^+$, 384 $[M+H]^+$.

4.2.70. 2-{4-[2-(2-*n*-Butoxy-4-nitrophenyl)vinyl]benzyl}butyric acid (40f)

This compound was prepared from **39f** by means of GP-K. Compound **40f** was obtained in 100% yield as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) **40f*Z*** δ: 7.70 (d, 1H, J = 1.8 Hz), 7.60 (dd, 1H, J = 8.5, 2.4 Hz), 7.28–7.23 (m, 1H), 7.11 (d, 2H, J = 8.5 Hz), 7.04 (d, 2H, J = 7.9 Hz), 6.73 (d, 1H, J = 12.2 Hz), 6.62 (d, 1H, J = 12.2 Hz), 4.05 (t, 2H, J = 6.7 Hz), 2.93 (dd, 1H, J = 14.0, 8.5 Hz), 2.74 (dd, 1H, J = 13.4, 7.3 Hz), 2.62–2.59 (m, 1H), 1.79–1.73 (m, 2H), 1.72–1.43 (m, 4H), 0.98 (t, 3H, J = 7.9 Hz), 0.96 (t, 3H, J = 6.7 Hz). Compound **40f*E*** δ: 7.83 (dd, 1H, J = 8.5, 1.8 Hz), 7.73 (d, 1H, J = 1.8 Hz), 7.67 (d, 1H, J = 8.5 Hz), 7.47 (d, 2H, J = 8.5 Hz), 7.42 (d, 1H, J = 16.5 Hz), 7.28–7.23 (m, 1H), 7.21 (d, 2H, J = 7.9 Hz), 4.13 (t, 2H, J = 6.7 Hz), 2.99 (dd, 1H, J = 13.4, 8.5 Hz), 2.81 (dd, 1H, J = 14.0, 7.3 Hz), 2.68–2.65 (m, 1H), 1.93–1.87 (m, 2H), 1.72–1.43 (m, 4H), 1.03 (t, 3H, J = 7.3 Hz), 0.98 (t, 3H, J = 7.3 Hz). FAB-MS m/z: 397 $[M]^+$, 398 $[M+H]^+$.

4.2.71. 2-{4-[2-(4-Nitrophenyl)vinyl]benzyl}butyric acid *t*-butyl ester (41a)

This compound was prepared from **40a** by means of GP-A. Compound **41a** was obtained in 27% yield as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) **41a*Z*** δ: 8.06 (d, 2H, J = 9.2 Hz), 7.37 (d, 2H, J = 8.5 Hz), 7.10 (d, 2H, J = 8.5 Hz), 7.07 (d, 2H, J = 7.9 Hz), 6.77 (d, 1H, J = 12.2 Hz), 6.57 (d, 1H, J = 12.2 Hz), 2.83 (dd, 1H, J = 14.0, 9.2 Hz), 2.69 (dd, 1H, J = 13.4, 6.1 Hz), 2.53–2.45 (m, 1H), 1.68–1.48 (m, 2H), 1.35 (s, 9H), 0.93 (t, 3H, J = 7.9 Hz). Compound **41a*E*** δ: 8.21 (d, 2H, J = 9.2 Hz), 7.62 (d, 2H, J = 9.2 Hz), 7.46 (d, 2H, J = 7.9 Hz), 7.24 (d, 1H, J = 16.5 Hz), 7.21 (d, 2H, J = 7.9 Hz), 7.11 (d, 1H, J = 16.5 Hz), 2.90 (dd, 1H, J = 14.0, 9.2 Hz), 2.73 (dd, 1H, J = 14.0, 6.7 Hz), 2.53–2.45 (m, 1H), 1.68–1.48 (m, 2H), 1.36 (s, 9H), 0.94 (t, 3H, J = 7.3 Hz). FAB-MS m/z: 381 $[M]^+$, 382 $[M+H]^+$.

4.2.72. 2-{4-[2-(2-Methoxy-4-nitrophenyl)vinyl]benzyl}butyric acid *t*-butyl ester (41c)

This compound was prepared from **40c** by means of GP-A. Compound **41c** was obtained in 41% yield as a brown oil.

^{1}H NMR (500 MHz, $CDCl_3$) **41c*Z*** δ: 7.73 (d, 1H, J = 1.8 Hz), 7.61 (dd, 1H, J = 8.5, 1.8 Hz), 7.29–7.22 (m, 1H), 7.08 (d, 1H, J = 7.9 Hz), 7.03 (d, 2H, J = 7.9 Hz), 6.76 (d, 1H, J = 12.2 Hz), 6.60 (d, 1H, J = 12.2 Hz), 3.92 (s, 3H), 2.81 (dd, 1H, J = 14.0, 9.2 Hz), 2.67 (dd, 1H, J = 14.0, 7.9 Hz), 2.49–2.42 (m, 1H), 1.67–1.52 (m, 2H), 1.34 (s, 9H), 0.92 (t, 3H, J = 7.3 Hz). Compound **41c*E*** δ: 7.86 (dd, 1H, J = 8.5, 1.2 Hz), 7.75 (d, 1H, J = 1.2 Hz), 7.70 (d, 1H, J = 8.5 Hz), 7.47 (d, 2H, J = 7.9 Hz), 7.43 (d, 1H, J = 16.5 Hz), 7.29–7.22 (m, 1H), 7.20 (d, 2H, J = 7.9 Hz), 3.99 (s, 3H), 2.89 (dd, 1H, J = 13.4, 8.5 Hz), 2.73 (dd, 1H, J = 14.0, 6.7 Hz), 2.52–2.46 (m, 1H), 1.67–1.52 (m, 2H), 1.36 (s, 9H), 0.94 (t, 3H, J = 7.9 Hz). FAB-MS m/z: 411 $[M]^+$, 412 $[M+H]^+$.

4.2.73. 2-{4-[2-(2-Ethoxy-4-nitrophenyl)vinyl]benzyl}butyric acid *t*-butyl ester (41d)

This compound was prepared from **40d** by means of GP-A. Compound **41d** was obtained in 60% yield as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) **41d*E*** δ: 7.84 (dd, 1H, J = 8.5, 1.8 Hz), 7.73 (d, 1H, J = 2.4 Hz), 7.69 (d, 1H, J = 8.5 Hz), 7.46 (d, 2H, J = 7.9 Hz), 7.43 (d, 1H, J = 16.5 Hz), 7.28–7.25 (m, 1H), 7.20 (d, 2H, J = 7.9 Hz), 4.20 (q, 2H, J = 7.3 Hz), 2.90 (dd, 1H, J = 14.0, 8.5 Hz), 2.73 (dd, 1H, J = 14.0, 6.7 Hz), 2.51–2.47 (m, 1H), 1.67–1.52 (m, 5H), 1.36 (s, 9H), 0.94 (t, 3H, J = 7.3 Hz). FAB-MS m/z: 425 $[M]^+$, 426 $[M+H]^+$.

4.2.74. 2-{4-[2-(4-Nitro-2-*n*-propoxyphenyl)vinyl]benzyl} butyric acid *t*-butyl ester (41e)

This compound was prepared from **40e** by means of GP-A. Compound **41e** was obtained in 55% yield as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) **41e*Z*** δ: 7.71 (d, 1H, J = 2.4 Hz), 7.58 (dd, 1H, J = 8.5, 2.4 Hz), 7.29–7.27 (m, 1H), 7.09 (d, 2H, J = 7.9 Hz), 7.03 (d, 2H, J = 7.9 Hz), 6.74 (d, 1H, J = 12.2 Hz), 6.62 (d, 1H, J = 12.2 Hz), 4.03 (t, 2H, J = 6.7 Hz), 2.82 (dd, 1H, J = 14.0, 9.2 Hz), 2.67 (dd, 1H, J = 13.4, 6.1 Hz), 2.46–2.43 (m, 1H), 1.83 (sex, 2H, J = 7.3 Hz), 1.67–1.49 (m, 2H), 1.35 (s, 9H), 1.05 (t, 3H, J = 7.3 Hz), 0.92 (t, 3H, J = 7.9 Hz). Compound **41e*E*** δ: 7.84 (dd, 1H, J = 8.5, 2.4 Hz), 7.73 (d, 1H, J = 1.8 Hz), 7.68 (d, 1H, J = 8.5 Hz), 7.45 (d, 2H, J = 7.9 Hz), 7.43 (d, 1H, J = 17.1 Hz), 7.29–7.27 (m, 1H), 7.20 (d, 2H, J = 8.5 Hz), 4.09 (t, 2H, J = 6.7 Hz), 2.90 (dd, 1H, J = 14.0, 9.2 Hz), 2.73 (dd, 1H, J = 13.4, 6.1 Hz), 2.52–2.47 (m, 1H), 1.95 (sex, 2H, J = 7.3 Hz), 1.67–1.49 (m, 2H), 1.36 (s, 9H), 1.13 (t, 3H, J = 7.3 Hz), 0.94 (t, 3H, J = 7.3 Hz). FAB-MS m/z: 439 $[M]^+$, 440 $[M+H]^+$.

4.2.75. 2-{4-[2-(2-*n*-Butoxy-4-nitrophenyl)vinyl]benzyl}butyric acid *t*-butyl ester (41f)

This compound was prepared from **40f** by means of GP-A. Compound **41f** was obtained in 33% yield as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) **41f*Z*** δ: 7.71 (d, 1H, J = 1.8 Hz), 7.57 (dd, 1H, J = 8.5, 2.4 Hz), 7.29–7.26 (m, 1H), 7.09 (d, 2H, J = 7.9 Hz), 7.03 (d, 2H, J = 7.9 Hz), 6.74 (d, 1H, J = 12.2 Hz), 6.61 (d, 1H, J = 12.2 Hz), 4.07 (t, 2H, J = 6.7 Hz), 2.82 (dd, 1H, J = 14.0, 9.2 Hz), 2.67 (dd, 1H, J = 14.0, 6.7 Hz), 2.48–2.43 (m, 1H), 1.79 (quin, 2H, J = 6.7 Hz), 1.67–1.48 (m, 4H), 1.35 (s, 9H), 0.98 (t, 3H, J = 7.3 Hz), 0.92 (t, 3H, J = 7.3 Hz). Compound **41f*E*** δ: 7.83 (dd, 1H, J = 8.5, 2.4 Hz), 7.73 (d, 1H, J = 1.8 Hz), 7.67 (d, 1H, J = 8.5 Hz), 7.45 (d, 2H, J = 7.9 Hz), 7.42 (d, 1H, J = 16.5 Hz), 7.29–7.26 (m, 1H), 7.20 (d, 2H, J = 7.9 Hz), 4.13 (t, 2H, J = 6.7 Hz), 2.90 (dd, 1H, J = 14.0, 9.2 Hz), 2.73 (dd, 1H, J = 14.0, 6.7 Hz), 2.52–2.47 (m, 1H), 1.90 (quin, 2H, J = 6.7 Hz), 1.67–1.48 (m, 4H), 1.36 (s, 9H), 1.03 (t, 3H, J = 7.3 Hz), 0.94 (t, 3H, J = 7.3 Hz). FAB-MS m/z: 453 $[M]^+$, 454 $[M+H]^+$.

4.2.76. 2-{4-[2-(4-Aminophenyl)ethyl]benzyl}butyric acid *t*-butyl ester (42a)

This compound was prepared from **41a** by means of GP-E. Compound **42a** was obtained in 97% yield as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.07 (s, 4H), 6.96 (d, 2H, J = 7.9 Hz), 6.62 (d, 2H, J = 8.5 Hz), 3.55 (br s, 2H), 2.86–2.77 (m, 5H), 2.67 (dd, 1H, J = 14.0, 6.7 Hz), 2.48–2.42 (m, 1H), 1.62–1.50 (m, 2H), 1.35 (s, 9H), 0.92 (t, 3H, J = 7.3 Hz). FAB-MS m/z: 353 $[M]^+$, 354 $[M+H]^+$.

4.2.77. 2-{4-[2-(4-Amino-2-methoxyphenyl)ethyl]benzyl} butyric acid *t*-butyl ester (42c)

This compound was prepared from **41c** by means of GP-E. Compound **42c** was obtained in 97% yield as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.10 (d, 2H, J = 7.9 Hz), 7.07 (d, 2H, J = 7.9 Hz), 6.85 (d, 1H, J = 7.9 Hz), 6.24 (d, 1H, J = 2.4 Hz), 6.21 (dd, 1H, J = 8.9, 2.4 Hz), 3.77 (s, 3H), 3.59 (br s, 2H), 2.85 (dd, 1H, J = 14.0, 8.5 Hz), 2.79–2.74 (m, 4H), 2.66 (dd, 1H, J = 14.0, 7.3 Hz), 2.48–2.42 (m, 1H), 1.63–1.48 (m, 2H), 1.36 (s, 9H), 0.91 (t, 3H, J = 7.3 Hz). FAB-MS m/z: 383 $[M]^+$, 384 $[M+H]^+$.

4.2.78. 2-{4-[2-(4-Amino-2-ethoxyphenyl)ethyl]benzyl}butyric acid *t*-butyl ester (42d)

This compound was prepared from **41d** by means of GP-E. Compound **42d** was obtained in 100% yield as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.10 (d, 2H, J = 8.5 Hz), 7.07 (d, 2H, J = 8.5 Hz), 6.86 (d, 1H, J = 7.9 Hz), 6.23 (d, 1H, J = 1.8 Hz), 6.20 (dd, 1H, J = 7.9, 2.4 Hz), 3.98 (q, 2H, J = 6.7 Hz), 3.56 (br s, 2H), 2.85 (dd, 1H, J = 14.0, 8.5 Hz), 2.80–2.74 (m, 4H), 2.67 (dd, 1H, J = 14.0, 6.7 Hz), 2.48–2.42 (m, 1H), 1.63–1.48 (m, 2H), 1.41 (t, 3H, J = 7.3 Hz), 1.36 (s, 9H), 0.91 (t, 3H, J = 7.3 Hz). FAB-MS m/z: 397 $[M]^+$, 398 $[M+H]^+$.

4.2.79. 2-{4-[2-(4-Amino-2-propoxyphenyl)ethyl]benzyl} butyric acid *t*-butyl ester (42e)

This compound was prepared from **41e** by means of GP-E. Compound **42e** was obtained in 80% yield as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.10 (d, 2H, J = 8.5 Hz), 7.08 (d, 2H, J = 7.9 Hz), 6.86 (d, 1H, J = 7.9 Hz), 6.24 (d, 1H, J = 1.8 Hz), 6.20 (dd, 1H, J = 7.9, 1.8 Hz), 3.88 (t, 2H, J = 6.1 Hz), 3.56 (br s, 2H), 2.84 (dd, 1H, J = 13.4, 8.5 Hz), 2.80–2.75 (m, 4H), 2.67 (dd, 1H, J = 14.0, 6.7 Hz), 2.48–2.43 (m, 1H), 1.83 (sex, 2H, J = 6.7 Hz), 1.63–1.48 (m, 2H), 1.35 (s, 9H), 1.07 (t, 3H, J = 7.3 Hz), 0.92 (t, 3H, J = 7.3 Hz). FAB-MS m/z: 411 $[M]^+$, 412 $[M+H]^+$.

4.2.80. 2-{4-[2-(4-Amino-2-butoxyphenyl)ethyl]benzyl}butyric acid *t*-butyl ester (42f)

This compound was prepared from **41f** by means of GP-E. Compound **42f** was obtained in 93% yield as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.10 (d, 2H, J = 7.9 Hz), 7.08 (d, 2H, J = 7.9 Hz), 6.86 (d, 1H, J = 7.9 Hz), 6.24 (d, 1H, J = 2.4 Hz), 6.20 (dd, 1H, J = 7.9, 2.4 Hz), 3.92 (t, 2H, J = 6.7 Hz), 3.56 (br s, 2H), 2.84 (dd, 1H, J = 14.0, 8.5 Hz), 2.79–2.74 (m, 4H), 2.67 (dd, 1H, J = 14.0, 6.7 Hz), 2.48–2.43 (m, 1H), 1.81–1.76 (m, 2H), 1.63–1.50 (m, 4H), 1.35 (s, 9H), 0.98 (t, 3H, J = 7.3 Hz), 0.92 (t, 3H, J = 7.3 Hz). FAB-MS m/z: 425 $[M]^+$, 426 $[M+H]^+$.

4.2.81. 2-(4-{2-[4-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)phenyl]ethyl}benzyl)butyric acid *t*-butyl ester (43a)

This compound was prepared from phthalic anhydride and **42a** by means of GP-F. Compound **43a** was obtained in 89% yield as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.96 (dd, 2H, J = 5.5, 3.1 Hz), 7.79 (dd, 2H, J = 5.5, 3.1 Hz), 7.35 (d, 2H, J = 6.1 Hz), 7.32 (d, 2H, J = 8.5 Hz), 7.12 (d, 2H, J = 9.2 Hz), 7.11 (d, 2H, J = 8.5 Hz), 2.95–2.92 (m, 4H), 2.86 (dd, 1H, J = 13.4, 8.5 Hz), 2.69 (dd, 1H, J = 13.4, 6.7 Hz), 2.50–2.44 (m, 1H), 1.62–1.48 (m, 2H), 1.36 (s, 9H), 0.92 (t, 3H, J = 7.3 Hz). FAB-MS m/z: 484 $[M+H]^+$.

4.2.82. 2-(4-{2-[4-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-2-methoxyphenyl]ethyl}benzyl)butyric acid *t*-butyl ester (43c)

This compound was prepared from phthalic anhydride and **42c** by means of GP-F. Compound **43c** was obtained in 96% yield as a pale brown solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.96 (dd, 2H, J = 5.5, 3.1 Hz), 7.80 (dd, 2H, J = 5.5, 3.1 Hz), 7.23 (d, 1H, J = 7.9 Hz), 7.14 (d, 2H, J = 7.9 Hz), 7.11 (d, 2H, J = 7.9 Hz), 6.94 (dd, 1H, J = 7.9, 1.8 Hz), 6.91 (d, 1H, J = 1.8 Hz), 3.85 (s, 3H), 2.93–2.84 (m, 5H), 2.68 (dd, 1H, J = 12.8, 6.1 Hz), 2.48–2.44 (m, 1H), 1.62–1.51 (m, 2H), 1.36 (s, 9H), 0.92 (t, 3H, J = 7.3 Hz). FAB-MS m/z: 513 $[M]^+$, 514 $[M+H]^+$.

4.2.83. 2-(4-{2-[4-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-2-ethoxyphenyl]ethyl}benzyl)butyric acid *t*-butyl ester (43d)

This compound was prepared from phthalic anhydride and **42d** by means of GP-F. Compound **43d** was obtained in 82% yield as a pale brown solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.96 (dd, 2H, J = 5.5, 3.1 Hz), 7.79 (dd, 2H, J = 5.5, 3.1 Hz), 7.23 (d, 1H, J = 7.9 Hz), 7.15 (d, 2H, J = 7.9 Hz), 7.11 (d, 2H, J = 7.9 Hz), 6.93 (dd, 1H, J = 7.9, 1.8 Hz), 6.89 (d, 1H, J = 1.8 Hz), 4.06 (q, 2H, J = 14.0, 7.3 Hz), 2.93–2.84 (m, 5H), 2.68 (dd, 1H, J = 13.4, 6.7 Hz), 2.50–2.44 (m, 1H), 1.64–1.49 (m, 2H), 1.45 (t, 3H, J = 7.3 Hz), 1.36 (s, 9H), 0.92 (t, 3H, J = 7.3 Hz). FAB-MS m/z: 527 $[M]^+$, 528 $[M+H]^+$.

4.2.84. 2-(4-{2-[4-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-2-*n*-propoxy-phenyl]ethyl}benzyl)butyric acid *t*-butyl ester (43e)

This compound was prepared from phthalic anhydride and **42e** by means of GP-F. Compound **43e** was obtained in 81% yield as a pale brown solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.96 (dd, 2H, J = 5.5, 3.1 Hz), 7.79 (dd, 2H, J = 5.5, 3.1 Hz), 7.24 (d, 1H, J = 7.3 Hz), 7.15 (d, 2H, J = 7.9 Hz), 7.11 (d, 2H, J = 8.5 Hz), 6.92 (dd, 1H, J = 7.9, 1.8 Hz), 6.89 (d, 1H, J = 1.8 Hz), 3.96 (t, 2H, J = 6.7 Hz), 2.93–2.84 (m, 4H), 2.88–2.84 (m, 1H), 2.69 (dd, 1H, J = 13.4, 6.7 Hz), 2.50–2.44 (m, 1H), 1.86 (sex, 2H, J = 13.4, 6.7 Hz), 1.65–1.52 (m, 2H), 1.36 (s, 9H), 1.08 (t, 3H, J = 7.3 Hz), 0.92 (t, 3H, J = 7.3 Hz). FAB-MS m/z: 541 $[M]^+$, 542 $[M+H]^+$.

4.2.85. 2-(4-{2-[2-*n*-Butoxy-4-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)phenyl]ethyl}benzyl)butyric acid *t*-butyl ester (43f)

This compound was prepared from phthalic anhydride and **42f** by means of GP-F. Compound **43f** was obtained in 91% yield as a pale brown solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.96 (dd, 2H, J = 5.5, 3.1 Hz), 7.79 (dd, 2H, J = 5.5, 3.1 Hz), 7.23 (d, 1H, J = 7.9 Hz), 7.15 (d, 2H, J = 7.9 Hz), 7.11 (d, 2H, J = 7.9 Hz), 6.92 (dd, 1H, J = 7.3, 1.8 Hz), 6.89 (d, 1H, J = 1.8 Hz), 4.00 (t, 2H, J = 6.7 Hz), 2.93–2.84 (m, 5H), 2.69 (dd, 1H, J = 13.4, 6.7 Hz), 2.50–2.44 (m, 1H), 1.85–1.79 (m, 2H), 1.65–1.52 (m, 4H), 1.36 (s, 9H), 0.99 (t, 3H, J = 7.3 Hz), 0.92 (t, 3H, J = 7.3 Hz). FAB-MS m/z: 555 $[M]^+$, 556 $[M+H]^+$.

4.2.86. 2-(4-{2-[4-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl) phenyl]ethyl}benzyl)butyric acid (13a)

This compound was prepared from **43a** by means of GP-G. Compound **13a** was obtained in 79% yield as a white powder after recrystallization from CH_2Cl_2/*n*-hexane.

Mp 180.5–182.0 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.95 (dd, 2H, J = 5.5, 3.1 Hz), 7.79 (dd, 2H, J = 5.5, 3.1 Hz), 7.29 (d, 2H, J = 8.5 Hz), 7.22 (d, 2H, J = 8.5 Hz), 7.09 (d, 2H, J = 7.9 Hz), 7.05 (d, 2H, J = 7.9 Hz), 3.00–2.86 (m, 5H), 2.78 (dd, 1H, J = 13.4, 6.1 Hz), 2.64–2.60 (m, 1H), 1.73–1.56 (m, 2H), 0.99 (t, 3H, J = 7.3 Hz). FAB-MS m/z: 427 $[M]^+$, 428 $[M+H]^+$. HRMS (FAB) calcd for $C_{27}H_{25}NO_4$ 427.1784; found: 427.1785 $(M)^+$.

4.2.87. 2-(4-{2-[4-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-2-hydroxyphenyl]ethyl}benzyl)butyric acid (13b)

To a solution of **13c** (25 mg, 0.055 mmol) in dichloromethane (3 mL) was added dropwise boron tribromide (1.0 M solution in dichloromethane) (550 μL, 0.55 mmol) at 0 °C. The mixture was stirred for 15 min, then poured into ice water (10 mL) and CH_2Cl_2 was removed under reduced pressure. EtOAc (30 mL) was added to the residue. The organic layer was washed with H_2O (10 mL) and brine (10 mL), then dried over $MgSO_4$. The solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography to give the target compound (4.2 mg, 18%) as a white powder after recrystallization from EtOAc/*n*-hexane.

Mp 197.0–199.0 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 12.05 (br s, 1H), 9.71 (s, 1H), 7.94 (dd, 2H, J = 5.5, 3.1 Hz), 7.89 (dd, 2H, J = 5.5, 3.1 Hz), 7.18 (d, 1H, J = 7.9 Hz), 7.16 (d, 2H, J = 7.9 Hz), 7.10 (d, 2H, J = 7.9 Hz), 6.87 (d, 1H, J = 1.8 Hz), 6.77 (dd, 1H, J = 7.9, 2.4 Hz), 2.82 (s, 4H), 2.79 (dd, 1H, J = 13.4, 8.5 Hz), 2.64 (dd, 1H, J = 14.0, 6.7 Hz), 2.51–2.47 (m, 1H), 1.50–1.46 (m, 2H), 0.86 (t, 3H, J = 7.3 Hz). FAB-MS m/z: 443 $[M]^+$, 444 $[M+H]^+$. HRMS (FAB) calcd for $C_{27}H_{25}NO_5$ 443.1733; found: 443.1713 $(M)^+$.

4.2.88. 2-(4-{2-[4-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-2-methoxyphenyl]ethyl}benzyl)butyric acid (13c)

This compound was prepared from **43c** by means of GP-G. Compound **13c** was obtained in 82% yield as a white solid. Chiral separation and enantiomeric excess (ee) determination were performed on CHIRALPAK IA.

Compound (***S***)**-13c:** White powder from CH_2Cl_2/*n*-hexane. Ee >99%. Mp 168.0–169.5 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.95 (dd, 2H, J = 5.5, 3.1 Hz), 7.79 (dd, 2H, J = 5.5, 3.1 Hz), 7.13 (d, 1H,

J = 7.9 Hz), 7.10 (d, 2H, J = 8.5 Hz), 7.09 (d, 2H, J = 8.5 Hz), 6.89 (dd, 1H, J = 7.9, 1.8 Hz), 6.87 (d, 1H, J = 1.8 Hz), 3.83 (s, 3H), 2.98–2.86 (m, 5H), 2.76 (dd, 1H, J = 10.4, 6.1 Hz), 2.61 (quin, 1H, J = 6.1 Hz), 1.72–1.58 (m, 2H), 0.98 (t, 3H, J = 7.3 Hz). FAB-MS m/z: 457 $[M]^+$, 458 $[M+H]^+$. HRMS (FAB) calcd for $C_{28}H_{27}NO_5$ 457.1889; found: 457.1918 $(M)^+$. $[\alpha]_D$ −6.9 (23.2 °C, c 0.409, $CHCl_3$).

Compound **(*R*)-13c:** White powder from CH_2Cl_2/*n*-hexane. Ee >99%. Mp 172.0–173.5 °C. ^1H NMR (500 MHz, $CDCl_3$) δ: 7.95 (dd, 2H, J = 5.5, 3.1 Hz), 7.79 (dd, 2H, J = 5.5, 3.1 Hz), 7.12 (d, 1H, J = 7.9 Hz), 7.09 (s, 4H), 6.88 (dd, 1H, J = 7.9, 1.8 Hz), 6.86 (d, 1H, J = 1.8 Hz), 3.83 (s, 3H), 2.97–2.95 (m, 1H), 2.92–2.87 (m, 4H), 2.76 (dd, 1H, J = 10.4, 6.1 Hz), 2.61 (quin, 1H, J = 6.1 Hz), 1.72–1.67 (m, 1H), 1.67–1.60 (m, 1H), 0.98 (t, 3H, J = 7.3 Hz). FAB-MS m/z: 457 $[M]^+$, 458 $[M+H]^+$. HRMS (FAB) calcd for $C_{28}H_{27}NO_5$ 457.1889; found: 457.1901 $(M)^+$. $[\alpha]_D$ +6.1 (23.2 °C, c 0.397, $CHCl_3$).

4.2.89. 2-(4-{2-[4-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-2-ethoxyphenyl]ethyl}benzyl)butyric acid (13d)

This compound was prepared from **43d** by means of GP-G. Compound **13d** was obtained in 89% yield as a white solid. Chiral separation and enantiomeric excess (ee) determination were performed on CHIRALPAK IA.

Compound **(*S*)-13d**: White powder from CH_2Cl_2/*n*-hexane. Ee >99%. Mp 160.0–162.0 °C. ^1H NMR (500 MHz, $CDCl_3$) δ: 7.95 (dd, 2H, J = 5.5, 3.1 Hz), 7.79 (dd, 2H, J = 5.5, 3.1 Hz), 7.12 (d, 1H, J = 7.9 Hz), 7.09 (s, 4H), 6.87 (dd, 1H, J = 7.9, 1.8 Hz), 6.85 (d, 1H, J = 1.8 Hz), 4.04 (q, 2H, J = 7.3 Hz), 2.97–2.88 (m, 5H), 2.76 (dd, 1H, J = 13.4, 6.1 Hz), 2.61 (quin, 1H, J = 6.1 Hz), 1.73–1.57 (m, 2H), 1.45 (t, 3H, J = 7.3 Hz), 0.98 (t, 3H, J = 7.3 Hz). FAB-MS m/z: 471 $[M]^+$, 472 $[M+H]^+$. HRMS (FAB) calcd for $C_{29}H_{29}NO_5$ 471.2046; found: 471.2032 $(M)^+$. $[\alpha]_D$ −6.7 (23.2 °C, c0.178, $CHCl_3$).

Compound **(*R*)-13d**: White powder from CH_2Cl_2/*n*-hexane. Ee > 99%. Mp 156.5–159.5 °C. ^1H NMR (500 MHz, $CDCl_3$) δ: 7.95 (dd, 2H, J = 5.5, 3.1 Hz), 7.79 (dd, 2H, J = 5.5, 3.1 Hz), 7.12 (d, 1H, J = 7.9 Hz), 7.09 (s, 4H), 6.87 (dd, 1H, J = 7.9, 1.8 Hz), 6.85 (d, 1H, J = 1.8 Hz), 4.04 (q, 2H, J = 6.7 Hz), 2.97–2.88 (m, 5H), 2.76 (dd, 1H, J = 13.4, 6.7 Hz), 2.61 (quin, 1H, J = 6.1 Hz), 1.72–1.59 (m, 2H), 1.45 (t, 3H, J = 6.7 Hz), 0.98 (t, 3H, J = 7.3 Hz). FAB-MS m/z: 471 $[M]^+$, 472 $[M+H]^+$. HRMS (FAB) calcd for $C_{29}H_{29}NO_5$ 471.2046; found: 471.2032 $(M)^+$. $[\alpha]_D$ +6.5 (23.2 °C, c 0.173, $CHCl_3$).

4.2.90. 2-(4-{2-[4-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-2-propoxyphenyl]ethyl}benzyl)butyric acid (13e)

This compound was prepared from **43e** by means of GP-G. Compound **13e** was obtained in 87% yield as a white solid. Chiral separation and enantiomeric excess (ee) determination were performed on CHIRALPAK IA.

Compound **(*S*)-13e:** White powder from CH_2Cl_2/*n*-hexane. Ee >99%. Mp 161.0–164.0 °C. ^1H NMR (500 MHz, $CDCl_3$) δ: 7.95 (dd, 2H, J = 5.5, 3.1 Hz), 7.79 (dd, 2H, J = 5.5, 3.1 Hz), 7.13 (d, 1H, J = 7.9 Hz), 7.10 (s, 4H), 6.87 (dd, 1H, J = 8.5, 1.8 Hz), 6.85 (d, 1H, J = 1.8 Hz), 3.93 (t, 2H, J = 6.7 Hz), 2.97–2.88 (m, 5H), 2.76 (dd, 1H, J = 13.4, 6.1 Hz), 2.64–2.59 (m, 1H), 1.86 (sex, 2H, J = 6.7 Hz), 1.72–1.59 (m, 2H), 1.08 (t, 3H, J = 7.3 Hz), 0.98 (t, 3H, J = 6.7 Hz). FAB-MS m/z: 485 $[M]^+$, 486 $[M+H]^+$. HRMS (FAB) calcd for $C_{30}H_{31}NO_5$ 485.2202; found: 485.2248 $(M)^+$. $[\alpha]_D$ −3.6 (23.2 °C, c 0.283, $CHCl_3$).

Compound **(*R*)-13e:** White powder from CH_2Cl_2/*n*-hexane. Ee >99%. Mp 158.0–161.0 °C. ^1H NMR (500 MHz, $CDCl_3$) δ: 7.95 (dd, 2H, J = 5.5, 3.1 Hz), 7.79 (dd, 2H, J = 5.5, 3.1 Hz), 7.12 (d, 1H, J = 7.3 Hz), 7.10 (s, 4H), 6.87 (dd, 1H, J = 8.5, 1.8 Hz), 6.85 (d, 1H, J = 1.8 Hz), 3.94 (t, 2H, J = 6.7 Hz), 2.97–2.88 (m, 5H), 2.76 (dd, 1H, J = 14.0, 6.7 Hz), 2.64–2.59 (m, 1H), 1.86 (sex, 2H, J = 6.7 Hz), 1.72–1.59 (m, 2H), 1.08 (t, 3H, J = 7.3 Hz), 0.98 (t, 3H, J = 7.3 Hz). FAB-MS m/z: 485 $[M]^+$, 486 $[M+H]^+$. HRMS (FAB) calcd for $C_{30}H_{31}NO_5$ 485.2202; found: 485.2244 $(M)^+$. $[\alpha]_D$ +3.4 (23.2 °C, c 0.291, $CHCl_3$).

4.2.91. 2-(4-{2-[2-Butoxy-4-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)phenyl]ethyl}benzyl)butyric acid (13f)

This compound was prepared from **43f** by means of GP-G. Compound **13f** was obtained in 76% yield as a white solid.

Mp 132.0–133.0 °C. ^1H NMR (500 MHz, $CDCl_3$) δ: 7.95 (dd, 2H, J = 5.5, 3.1 Hz), 7.79 (dd, 2H, J = 5.5, 3.1 Hz), 7.10 (d, 1H, J = 8.5 Hz), 6.86 (dd, 1H, J = 6.1, 1.8 Hz), 6.85 (d, 1H, J = 2.4 Hz), 3.98 (t, 2H, J = 6.7 Hz), 2.97–2.86 (m, 5H), 2.77 (dd, 1H, J = 14.0, 6.7 Hz), 2.65–2.59 (m, 1H), 1.85–1.79 (m, 2H), 1.72–1.66 (m, 1H), 1.66–1.58 (m, 1H), 1.59–1.51 (m, 2H), 1.00 (t, 3H, J = 7.3 Hz), 0.98 (t, 3H, J = 7.3 Hz). FAB-MS m/z: 499 $[M]^+$, 500 $[M+H]^+$. HRMS (FAB) calcd for $C_{31}H_{33}NO_5$ 499.2359; found: 499.2311 $(M)^+$.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2011.03.065.

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