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Effect of Oxime Ether Incorporation in Acyl Indole Derivatives on PPAR Subtype Selectivity

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Compounds that simultaneously activate peroxisome proliferator-activated receptor (PPAR) subtypes α and γ have the potential to effectively treat dyslipidemia and type 2 diabetes (T2D) in a single pharmaceutically active molecule. The frequently observed side effects of selective PPARγ agonists, such as edema and weight gain, were expected to be overcome by using additive PPARα activity, leading to dual PPARα/γ agonists with balanced activity for both subtypes. Herein we report the discovery, synthesis, and optimization of a new series of α-ethoxyphenylpropionic acid bearing 5- or 6-substituted indoles. The incorporation of oxime ethers on the carbonyl portion of the benzoyl group can bring the PPARα/γ potency ratio equal to or slightly greater than one, as is the case for compounds **20c** and **21a**. Compound **20c** shows high efficacy in an *ob/ob* mouse model of T2D and dyslipidemia, similar to that of rosiglitazone and tesaglitazar, but with a significant increase in body weight gain. In contrast, compound **21a**, less potent as a dual PPARα/γ activator than **20c**, showed an interesting pharmacological profile, as it elicits a decrease in body weight relative to reference compounds.

Introduction

Metabolic syndrome remains one of the leading causes of mortality in Western society and has become a major public health challenge worldwide. The term *metabolic syndrome* refers to a cluster of risk factors of metabolic origin that promote the development of cardiovascular diseases and type 2 diabetes mellitus. Metabolic syndrome includes such pathological factors as insulin resistance, hyperinsulinemia, abdominal obesity, impaired glucose tolerance, type 2 diabetes, microalbuminuria, high triglyceride levels, low HDL cholesterol levels, elevated blood pressure, and pro-inflammatory and pro-thrombic states.[1]

The peroxisome proliferator-activated receptors (PPARs) were cloned in 1990[2] as orphan members of the nuclear receptor family, which includes receptors for steroid, retinoid and thyroid hormones,[3] and vitamin D.[4] PPARs are transcription factors that are activated by the binding of small lipophilic ligands. They induce or repress the transcription of a large number of various genes, thereby influencing cellular function.[5] Among these functions, PPARs contribute to the regulation of glucose, lipid, and cholesterol metabolism, apparently making them ideal targets for the development of oral agents for the treatment of metabolic syndrome.[6] Consequently, for years, PPAR agonists have represented a promising approach to treat type 2 diabetes (T2D) and the associated metabolic diseases, including obesity, hypertension, and dyslipidemia. There are three known PPAR receptor subtypes, designated as PPARα, γ, and β/δ. Although the PPAR subtypes share a high degree of sequence and structural similarity, each PPAR subtype exhibits a unique tissue expression profile.[7]

Given the importance of controlling both glucose and lipid levels in T2D, the concept of identifying ligands that bind to and activate both PPARα and γ represent a logical continuation in the field of PPAR research. PPARγ agonists have been associated with improved insulin sensitivity and glucose tolerance, but at the cost of increased weight gain and other side effects such as liver dysfunction[8] and bone loss.[9] The fibrates have shown specific efficacy in decreasing the angiographic progression of coronary heart disease in T2D, and the effect is

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most likely related to the correction of atherogenic dyslipidemia. In addition to their benefit on lipids, there are reports that fibrates decrease body weight gain in rodents without affecting food intake.[10] Thus, activation of PPARα may mitigate the weight gain induced by PPARγ activation observed in humans. The hypothesis that dual PPARα/γ agonism should provide additive—and possibly synergistic—pharmacology has resulted in an intense effort within the pharmaceutical industry to develop and evaluate these agents. Dual activation of PPARα and γ could, in theory, also limit the occurrence of side effects associated with thiazolidinedione (TZD) therapy.[11] Thus, combined PPARα/γ activation has emerged as an interesting concept and has spawned the development of various co-agonists. A number of dual PPARα/γ agonists have been reported in this class of compounds and have shown robust insulin-sensitizing and hypolipidemic activities in clinical trials.[12]

In our continued search for PPAR ligands, we synthesized a large series of α-ethoxyphenylpropionic acid bearing an acylheteroaryl core and found that many of them are full PPARγ agonists.[13] Pharmacophore modulations performed within this class of compounds led to the discovery of the potent compound S73362, which exhibits better in vitro PPAR activity than the dual PPARα/γ agonist tesaglitazar, with higher selectivity for the PPARγ receptor.

Molecular modeling studies were conducted to understand the PPARγ selectivity of S73362, by docking S73362 into the PPARα and γ ligand binding domains (LBDs). The binding poses of S73362 with the LBDs of PPARα and γ are shown in Figure 1; further details of the molecular modeling studies will be reported in due course. From the results, it was apparent that the benzoyl moiety and the indole core of S73362 are buried in a binding cavity of PPARα LBD composed of a cluster of hydrophobic residues (Ile241, Leu247, Ile272, Met330, Val332, Ile339, and Leu344), closed on its lower part by Met355. In the case of PPARγ, the narrower pocket is spread more in depth, and the carbonyl portion of the benzoyl group is directed toward Phe264 and His266, while position 3 of the indole is oriented toward Leu228 and Leu333. The overall picture suggests that the introduction of small hydrophobic substituents on the ketone tail portion of the acyl group or at the 3-position of the indole group would increase the contact surface with the receptors and thus benefit binding at both PPAR subtypes.

Herein we report the effect of linking oxime ethers to the ketone tail of 5- or 6-acylindole and/or at position 3 of the indole ring, on the selectivity between PPARα and γ, while retaining the α-ethoxypropionic acid moiety of tesaglitazar as an acidic head group (Figure 2). The binding affinity to human PPARγ was characterized by using a competitive binding assay with [^{3}H]rosiglitazone, and the in vitro PPAR agonist activity and subtype selectivity of all test compounds were assessed with in vitro pGal4–hPPAR transactivation assays. Furthermore, several selected compounds with a PPARα:PPARγ potency ratio equal to or slightly greater than one, were subjected to in vivo studies to assess their anti-hyperlipidemic, anti-hyperglycemic, and body weight effects in experimental animal models.

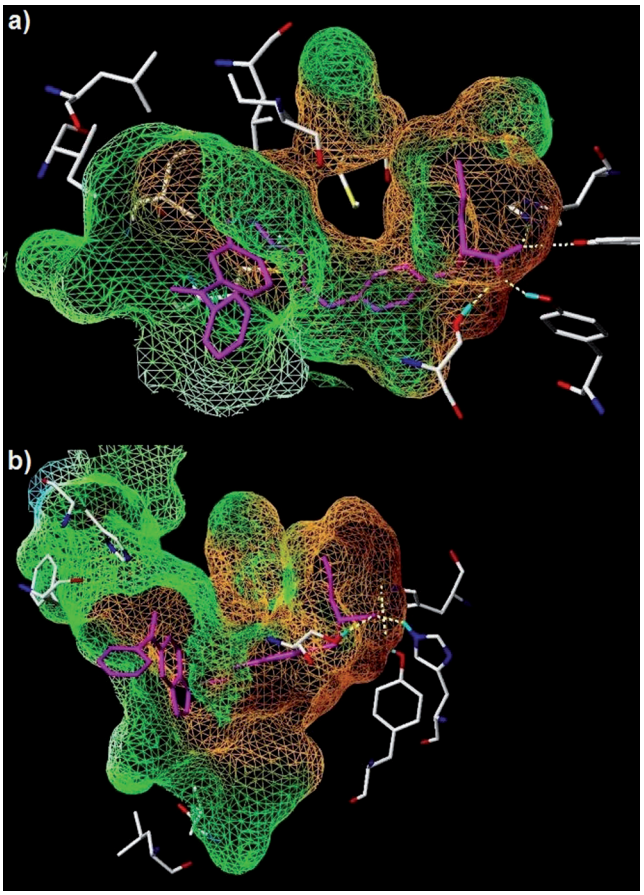


Figure 1. Molecular modeling results of S73362 (pink) docked into the LBD of PPARα and PPARγ: shown are the molecular surface maps and key residues (in white) showing the binding pose of S73362 in complex with a) PPARα (PDB code: 3FEI) and b) PPARγ (PDB code: 1KNU).

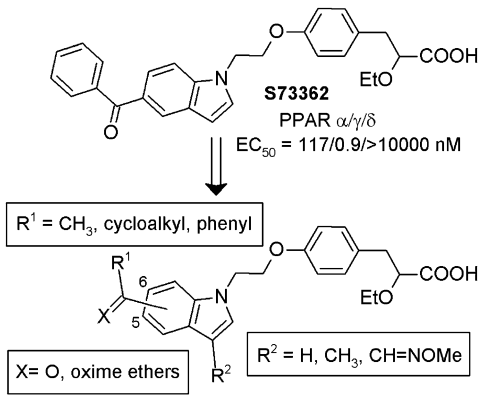
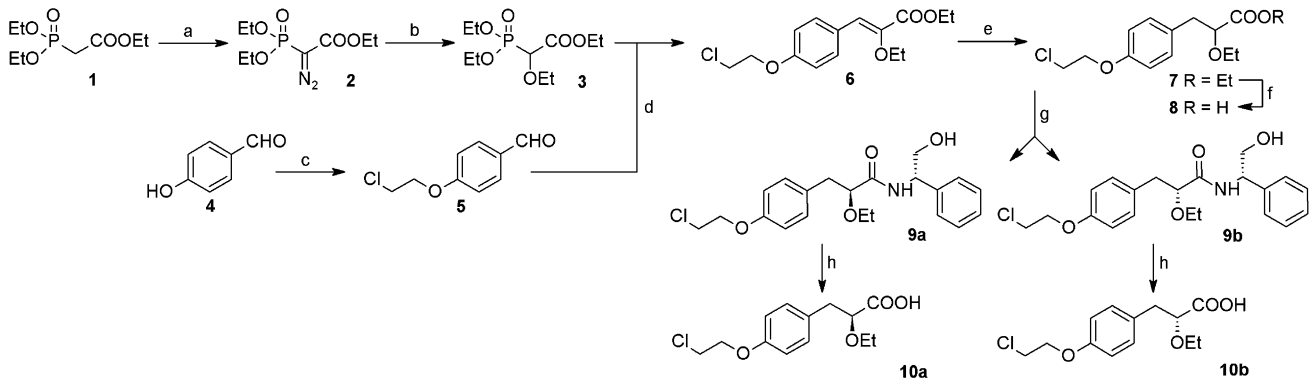


Figure 2. Design of dual PPARα/γ agonists.

Results and Discussion

Chemistry

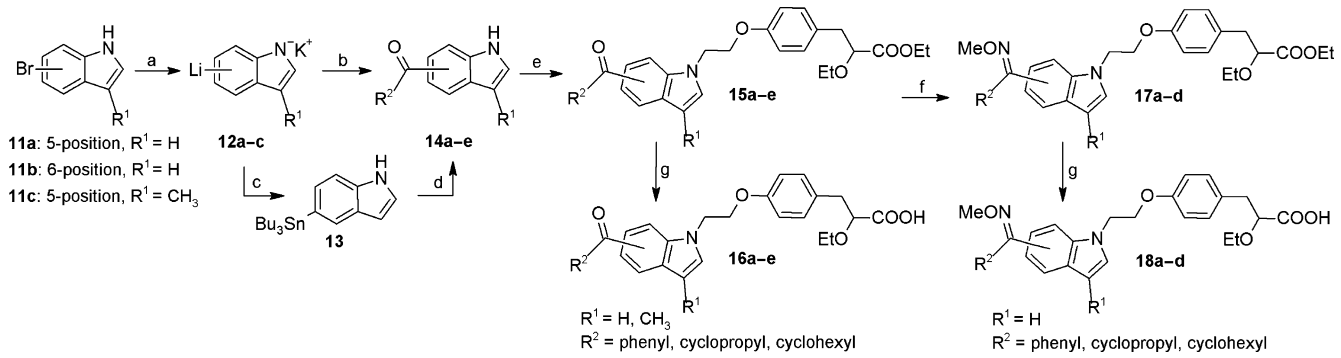
The key α-ethoxypropionic acid ester intermediate was synthesized as illustrated in Scheme 1. For the synthesis of the ethoxy phosphonoacetate **3**, benzenesulfonyl azide was prepared by coupling sodium azide with benzenesulfonyl chlo-



Scheme 1. *Reagents and conditions:* a) benzenesulfonyl azide, NaH, dry THF, 0 °C, 16 h, 87%; b) EtOH, $[Rh(OAc)_2]_2$, toluene, reflux, 4 h, 80%; c) 1-bromo-2-chloroethane, K_2CO_3, CH_3CN, reflux, 15 h, 92%; d) NaH, dry THF, 0 °C→RT, 5 h, 86%; e) H_2, Pd/C, EtOH, RT, 20 h, 93%; f) LiOH, THF/H_2O, RT, 20 h, 85%; g) 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, Et_3N, HOBT, (*S*)-(−)-2-phenylglycinol, CH_2Cl_2, 0 °C→RT, 12 h, 33–37%; h) 5 M H_2SO_4, dioxane/H_2O, reflux, 8 h, 78–81%.

ride.[14] This azide was sufficiently stable for handling and was used to synthesize diazo intermediate **2** from phosphonoacetate **1** using sodium hydride in dry THF as described by Moody et al.[15] and Regitz et al.[16] Diazo intermediate **2** proved stable to silica chromatography. Thereafter, the rhodium(II) acetate dimer was used to generate a carbenoid from the diazo compound which was inserted into the O–H bond of ethanol, as per Haigh et al.[17] (Scheme 1). A Horner–Wadsworth–Emmons (HWE) coupling[18] was carried out between ethoxy phosphonoacetate **3** and benzaldehyde **5** to give compound **6** as a mixture of *E*/*Z* isomers, which were not separated, but used directly in the next step. Reduction of the double bond was realized by catalytic hydrogenation with 10% Pd/C, leading to the racemic α-ethoxypropionic acid ester **7**. Ester **7** could be saponified to the racemic acid **8**, which was transformed into the optically pure amides **9a** and **9b** via (*S*)-2-phenylglycinol coupling.[19] Separation of the resulting two diastereomers and amide hydrolysis afforded the optically pure carboxylic acids **10a** and **10b**. Chiral liquid chromatography was used to determine enantiomeric purity, estimated to be 98% *ee*.

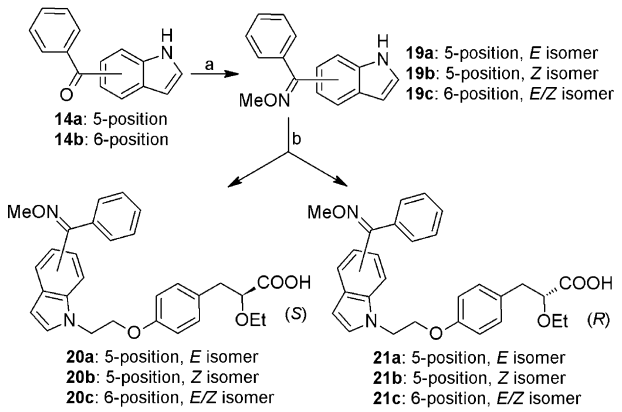
The general procedure for the synthesis of indole derivatives **16a**–**e** and **18a**–**d** is represented in Scheme 2. Reaction of 5- or 6-bromoindole or 5-bromo-3-methylindole with potassium hydride in THF at −78 °C allowed abstraction of the indole NH to afford a homogeneous solution of the potassium salt, which upon treatment with *tert*-butyllithium, underwent rapid and efficient lithium–halogen exchange.[20] The metalated species **12a**–**c** were then treated with the appropriate methyl or phenyl Weinreb amide to prepare 5- and 6-benzoylindole derivatives **14a**–**c**. This method cannot be used for the introduction of cycloalkylcarbonyl groups, and we recently developed an effective procedure for the synthesis of acylindoles under Stille conditions.[21] Compound **12a** was then treated with tributyltin chloride as electrophile to afford 5-tributylstannylindole **13** in 78% yield. Stannane **13** was then treated with cyclopropanoyl or cyclohexanoyl chloride under the Stille-type cross-coupling conditions, leading to the corresponding acylindoles **14d**,**e** in 70% yield. Condensation of acylindoles **14a**–**e** with intermediates **7** was carried out in the presence of potassium carbonate in DMF at reflux, and the desired acids **16a**–**e** were obtained after lithium hydroxide mediated saponification. Esters **15a**,**b**,**d**,**e** were further functionalized into the required oxime ethers **17a**–**d** by treatment with *O*-methylhydroxylamine hydrochloride in pyridine followed by alkaline hydrolysis



Scheme 2. *Reagents and conditions:* a) 1. KH, dry THF, 0 °C, 2. *t*BuLi, −78 °C; b) *N*-methoxy-*N*-methylbenzamide, dry THF, −78 °C→RT, 12 h, 48–64%; c) 1. Bu_3SnCl, dry THF, −78 °C→RT, 2. H_2O, 0 °C, 78%; d) cyclopropyl- or cyclohexylcarbonyl chloride, $PdCl_2(PPh_3)_2$, dry toluene, reflux, 16 h, 70–71%; e) **7**, K_2CO_3, DMF, reflux, 15 h, 55–65%; f) *O*-methylhydroxylamine hydrochloride, pyridine, 100 °C, 4 h, 75–81%; g) LiOH, THF/H_2O, RT, 15 h, 78–85%.

to provide the corresponding carboxylic acids **18a–d** in yields.

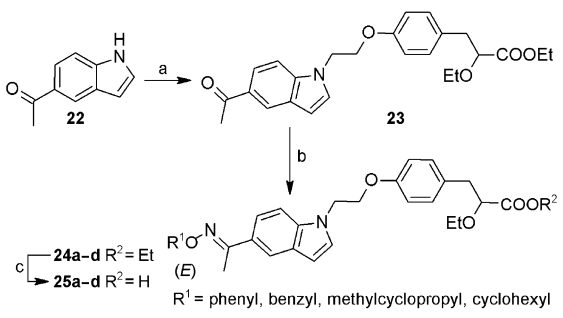
Synthesis of enantiomerically pure **20a–c** and **21a–c** is outlined in Scheme 3. Treatment of 5- or 6-benzoylindole with *O*-methylhydroxylamine hydrochloride led to the corresponding oxime ethers, the *E* and *Z* isomers of which, respectively **19a** and **19b**, could be separated by liquid chromatography for the 5-benzoyl derivative, and the stereochemistry of each isomer was assigned by NOE experiments. Condensation with the optically pure carboxylic acids **10a** and **10b** under alkaline conditions followed by acid hydrolysis provided the desired products **20a–c** and **21a–c** in >95% *ee* and 47–63% yield.



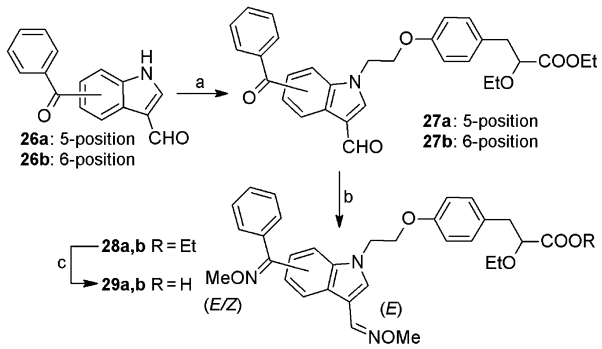
Scheme 3. *Reagents and conditions:* a) *O*-methylhydroxylamine hydrochloride, pyridine, MeOH, RT, 24 h, 38–79%; b) NaH, **10a** or **10b**, HMPA, RT, 24 h, 47–63%.

Synthesis of the target compounds **25a–d** was realized from 5-acetylindole[22] **22** by using the same chemical pathway as **18a–d** (Scheme 4). Condensation with intermediate **7** was followed by introduction of various oxime ethers to provide the *E* isomers exclusively, which were finally saponified to the corresponding racemic acids.

Introduction of oxime ethers at position 3 of the indole ring was carried out as depicted in Scheme 5. Formylation at the indole 3-position was carried out by a Vilsmeier–Haack reaction with oxalyl chloride and DMF followed by acylation with benzoyl chloride and excess aluminum chloride to provide the 5- and 6-benzoyl-3-formylindoles **26a,b** in a one-pot procedure in 60 and 20% yields, respectively.[23] Condensation with intermediate **7** followed by reaction with *O*-methylhydroxylamine hydrochloride led to the formation of a racemic mixture of *E* and *Z* isomers in the benzoyl group, whereas the *E* isomer was exclusively obtained at the indole 3-position. Compounds **28a,b** were finally saponified to afford the desired carboxylic acids **29a,b**.



Scheme 4. *Reagents and conditions:* a) **7**, K_2CO_3, DMF, reflux, 15 h, 56%; b) *O*-substituted hydroxylamine hydrochloride, pyridine, MeOH, reflux, 4 h, 87–93%; c) LiOH, THF/H_2O, RT, 15 h, 76–81%.



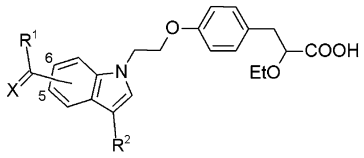
Scheme 5. *Reagents and conditions:* a) **7**, K_2CO_3, DMF, reflux, 15 h, 56–62%; b) *O*-methylhydroxylamine hydrochloride, pyridine, reflux, 4 h, 88%; c) LiOH, THF/H_2O, RT, 15 h, 83–85%.

In vitro biological evaluation

Compounds were characterized by determining the binding affinity to human PPARγ using a competitive binding assay with [^{3}H]rosiglitazone, an appropriate radioligand for PPARγ. The binding profiles of test compounds were compared with those of two references: rosiglitazone and tesaglitazar. Functional activity was measured in a transient transfection assay using human pGal4–hPPARα and pGal4–hPPARγ constructs, and the results are listed in Table 1. All tested compounds were functionally inactive at 10 μM against human PPARδ. As described above, **16a** (S73362) is a full dual PPARα/γ agonist, with higher selectivity for the PPARγ receptor. Its 6-benzoyl regioisomer **16b** shows increased α functional potency (EC_{50} ratio: 3.8) while maintaining the same in vitro PPARγ pharmacological profile as S73362. Replacement of the 5-benzoyl substituent by cycloalkylcarbonyl to give compounds **16d** and **16e** provided the desired α/γ potency ratio of approximately one or greater (i.e., **16d** EC_{50} ratio: 0.8; **16e** EC_{50} ratio: 7). The weak α selectivity of **16d** is not due to enhanced PPARα potency, but by decreased PPARγ functional activity, while the γ affinity is maintained. Acyl substitution with cyclohexyl or phenyl groups seemed to be most tolerated among the steric bulk of substituents for PPARγ activity.

The incorporation of small hydrophobic substituents such as methyl oxime ethers on the ketone tail portion of the acyl group led to compounds **18a–d**. In agreement with docking studies, these compounds exhibited better α functional activity than their carbonyl counterparts and proved to interact better with the PPARα LBD, with an appropriate α/γ ratio (com-

Table 1. In vitro profile of compounds **16a–e**, **18a–d**, **20a–c**, **21a–c**, **25a–d**, and **29a–b** as PPAR agonists.



Compd	Pos[a]	R^1	X	R^2	Stereo	hPPAR gene reporter				K_i [nM][b]	α/γ[c]
						αGal4 [%][d]	αEC_{50} [nM][e]	γGal4 [%][d]	γEC_{50} [nM][e]		
16a[f]	5	Ph	O	H	*Rac*	105	117	90	0.9	0.9	130
16b	6	Ph	O	H	*Rac*	96	19	92	5	1.2	3.8
16c	5	Ph	O	Me	*Rac*	117	22	108	6.5	1.4	3.4
16d	5	*c*Pr	O	H	*Rac*	74	123	138	151	1.2	0.8
16e	5	*c*Hex	O	H	*Rac*	332	112	99	16	0.7	7
18a	5	Ph	NOMe (*E/Z*)	H	*Rac*	165	13	170	7.6	2.8	1.7
18b	6	Ph	NOMe (*E/Z*)	H	*Rac*	94	8.2	115	5.5	14.4	1.5
18c	5	*c*Pr	NOMe (*E/Z*)	H	*Rac*	302	9	92	102	2.4	0.08
18d	5	*c*Hex	NOMe (*E/Z*)	H	*Rac*	79	15	90	5	2.7	3
20a	5	Ph	NOMe (*E*)	H	*S*	109	3	107	0.3	2	10
21a	5	Ph	NOMe (*E*)	H	*R*	78	1000	72	700	157	1.4
20b	5	Ph	NOMe (*Z*)	H	*S*	107	250	129	8	3.1	31.2
21b	5	Ph	NOMe (*Z*)	H	*R*	77	10000	71	1100	183	9.1
20c	6	Ph	NOMe (*E/Z*)	H	*S*	78	50	66	46	4.8	1.1
21c	6	Ph	NOMe (*E/Z*)	H	*R*	80	212	48	10000	841	0.02
25a	5	Me	NOPh (*E*)	H	*Rac*	60	200	73	3	5.5	66.6
25b	5	Me	NOBn (*E*)	H	*Rac*	64	2000	75	10	2.7	200
25c	5	Me	$NOCH_2$*c*Pr (*E*)	H	*Rac*	97	200	97	10	3.4	20
25d	5	Me	NOcHex (*E*)	H	*Rac*	115	129	135	0.3	17	430
29a	5	Ph	NOMe (*E/Z*)	CH=NOMe (*E*)	*Rac*	129	59	113	14	25	4.2
29b	6	Ph	NOMe (*E/Z*)	CH=NOMe (*E*)	*Rac*	88	24	98	12	65	2
rosi[g]	–	–	–	–	–	28	10000	100	4	8	>100
tesa[h]	–	–	–	–	–	89	414	76	37	18	11.2

[a] Indole position. [b] hPPARγ binding affinity: K_i is the test compound concentration required to achieve an apparent concentration value according to the equation $K_i = IC_{50}/(1+[L]/K_d)$, for which IC_{50} is the test compound concentration required to inhibit 50% of specific binding of the radioligand, [L] is the radioligand concentration used, and K_d is the dissociation constant for the radioligand at the receptor. [c] PPAR α/γ selectivity ratio. [d] Potency. [e] Compound concentration required to induce 50% maximum activity of WY 14,643 (10 μM) for PPARα and rosiglitazone (1 μM) for PPARγ; fold activation relative to maximum activation obtained with WY 14,643 (10 μM) and rosiglitazone (1 μM) corresponded to 100% in Gal4 chimeric PPARα and PPARγ systems. [f] S73362. [g] Rosiglitazone. [h] Tesaglitazar.

pounds **18a**, **18b**, and **18d** have respective EC_{50} ratios of 1.7, 1.5, and 3). As for cyclopropyl carbonyl derivative **16d**, which has weak PPARα selectivity, its functionalization with *O*-methyl oxime ether (giving compound **18c**) enhanced α selectivity to afford 10-fold more potent activity at the α receptor than the PPARγ subtype, and displaying threefold more activation than the reference compound WY 14,643. These results confirm that the incorporation of small lipophilic substituents such as methyl oxime ether strengthens the ligand–PPARα interaction and likely increases activity while maintaining good PPARγ potency.

We were also interested in synthesizing 5-acetylindoles, in which bulkier oxime ethers such as phenyl (compound **25a**), benzyl (**25b**), methylcyclopropyl (**25c**), or cyclohexyl (**25d**) substituents are introduced. Although these compounds displayed PPARγ activities and affinities similar to those of their parent *O*-methyl oxime ether derivatives **18a** and **18d**, these modifications led to a significant decrease in PPARα potency and so improved PPARγ selectivity. Regarding PPARα, the introduction of a short-chain oxime ether group on bulky acyl substituents was found to be favorable for transactivation activity, and might be better at filling the PPARα hydrophobic cavity. In contrast, a longer oxime ether group introduced on the acetyl derivative was not preferable and led to less potent PPARα agonists. These results are consistent with the working hypothesis that the shape and environment of the hydrophobic cavity that hosts the acyl group substituted by oxime ethers differs somewhat between the PPARα and γ subtypes.

Further chemical modifications that may improve the potency and selectivity for the PPARα subtype were performed at the 3-position of the indole ring by introducing small hydrophobic substituents such as methyl (compound **16c**) or *O*-methyl oxime ethers (compounds **29a**,**b**). Altogether, compounds **16c** and **29a**,**b** displayed higher PPARα activity and lower PPARγ activity than the unsubstituted indole analogue **16a**, providing the desired α/γ ratio of approximately one or higher (i.e., **16c** EC_{50} ratio: 3.4; **29a** EC_{50} ratio: 4.2; **29b** EC_{50} ratio: 2). These small substituents appear to lie closer to Ile272, Ile339, and Leu344 of the PPARα LDB, thereby forming stronger hydrophobic interactions than **16a**. In the γ receptor, higher affinity was observed with a methyl substitution, whereas an oxime ether group led to decreased affinity. The larger

the size of the substituent, the greater the loss in PPARγ binding affinity. From all the compounds synthesized, adjustment of the PPARα/γ potency ratio to an equal balance was observed for racemates **18a** and **18b**, which were then resolved into their pure enantiomers following the synthetic procedure of Scheme 3. As described for other PPAR agonists,[24] analogues containing (*S*)-ethoxypropanoic acid had higher activities than analogues containing (*R*)-ethoxypropanoic acid at both PPARα and PPARγ (**20a** vs. **21a**, **20b** vs. **21b**, and **20c** vs. **21c**). Regarding the 5-substituted indole derivatives, *E* isomers **20a** and **21a** displayed better functional activities and affinities than their *Z* isomer counterparts **20b** and **21b**. The optically pure *S*-configured derivative **20a** represents the most potent dual PPARα/γ full agonist, but with a lower α/γ ratio of 10, whereas its *R*-configured analogue provides the appropriate ratio, slightly greater than one, with partial activity in the micromolar range at both receptors. The resolution of racemate **18b** into its optical antipodes first led to compound **20c**, which corresponds to the *S* enantiomer of the racemic mixture of *E*/*Z* oxime ether isomers, and possesses the desired equal potency ratio (i.e., **20c** EC_{50} ratio: 1.1) with dual PPARα/γ partial agonist activity. In contrast, its *R*-configured counterpart **21c** was found to be a selective PPARα partial agonist with no activity and affinity for the PPARγ subtype.

In vivo biological evaluation

The in vivo effects of test compounds were determined by measuring glycemia, triglyceridemia, insulinemia, and body weight in *ob*/*ob* mice, which are obese, insulin resistant with hypertriglyceridemia and hyperglycemia, and have been used as a rodent model of obesity-induced insulin resistance. In this model, mice were dosed orally with either compounds **20a–c** and **21a–c** or standard reference compounds (rosiglitazone and tesaglitazar) at 3 mg kg^{-1} for four days. As listed in Table 2,

Table 2. In vivo efficacy of compounds **20a–c** and **21a–c** in *ob*/*ob* mice.

Compound	Change [%][a] TG[b]	Gly[c]	Ins[d]	ΔBW[e]
20a	−57	−47	−86	490
20b	−46	−41	−37	370
20c	−40	−52	−49	305
21a	−17	−32	−3	66
21b	6	−5	5	54
21c	−19	−22	−26	42
rosiglitazone	−61	−59	−54	100
tesaglitazar	−60	−51	−94	93

[a] Percent change versus control for *ob*/*ob* mice at day 4 (dose: 3 mg kg^{-1} p.o.). [b] Triglycerides. [c] Glycemia. [d] Insulin. [e] Body weight variation between day 0 and day 4.

S-enantiomer derivatives **20a–c** elicited significant decreases in serum triglyceride, glucose, and insulin levels and were found to be similar to the two reference compounds. The good in vivo efficacy of compounds **20a–c** observed in the mouse model is consistent with the good potency displayed in the PPARα and γ gene reporter assays. Body weight was also measured daily, and body weight variation was calculated as a percentage of the difference in body weight between days 4 and 0. Thus, at the end of treatment, body weight gain was three- to fivefold higher for compounds **20a–c** than for rosiglitazone and tesaglitazar. PPARγ activation is well known to enhance body weight gain through two major mechanisms: increase in fat mass by pre-adipocyte recruitment from bone marrow, and adipocyte differentiation and fluid retention.[25] Whereas they are highly potent agonists of both human PPARα and γ in cellular assays, compounds **20a–c** appeared to be predominantly PPARγ activators in the *ob*/*ob* mice model. The functional activity of **20c**, the best equally balanced PPARα/γ ligand, was then measured in a murine PPARα transient transfection assay and was found to be 20-fold less potent toward the human receptor, as observed for tesaglitazar (i.e., **20c** and tesaglitazar murine PPARα EC_{50} values of 1 and 10 μM, respectively). These results are in accord with those of previous studies, which describe the beneficial effect of PPARα activity on body weight as being dependent on the animal model used.[10b] The profile of in vivo efficacy on both insulin sensitivity and energy homeostasis of compounds **21a–c** showed lower pharmacological action in *ob*/*ob* mice than their *S* enantiomers, but without promoting body weight gain relative to rosiglitazone and tesaglitazar. The triglyceride- and glucose-lowering activity of **21a** could be associated with its weak dual PPARα/γ potency, which down-regulated the adipocyte differentiation gene expression mediated by PPARγ and decreased fluid retention and body weight gain. The pharmacological profile of compound **21c** could be partially due to the selective activation of PPARα which decreased serum triglyceride levels and exerted its glucose-lowering activity through insulin-sensitizing effects.

Conclusions

In summary, a molecular docking design approach has led to a novel series of α-ethoxyphenylpropionic acids bearing 5- or -6-substituted indoles displaying highly potent activities toward both PPARα and PPARγ. Oxime ether introduction on the carbonyl portion of the benzoyl group within this series provided compounds **18a** and **18b**, and allowed adjustment of the PPARα/γ potency ratio to be equal to or slightly greater than one. Enantiomeric resolution led to the best equally balanced PPARα/γ ligands **20c** and **21a**, with respective α/γ potency ratios of 1.1 and 1.4. Compound **20c** shows high efficacy in an *ob*/*ob* mice model of T2D and dyslipidemia, similar to rosiglitazone and tesaglitazar, but with a significant increase in body weight gain. Our primary hypothesis, that equally balanced dual PPARα/γ agonists might overcome or diminish the side effects of the glitazones as PPARγ agonists, such as weight gain, is not supported by our in vivo results. Compound **20c** seems to be a predominant PPARγ activator in the *ob*/*ob* mice model, as it was found to be 20-fold less potent in the murine PPARα transactivation assay than on the human receptor. The beneficial effect of PPARα activity on body weight could not be monitored by our in vivo study, as this depends on the animal model employed. In contrast, compound **21a**,

a less potent dual PPARα/γ activator than **20c**, shows an interesting pharmacological profile, with a decrease in body weight gain relative to rosiglitazone and tesaglitazar; this could be due to a down-regulation of adipocyte differentiation gene expression mediated by PPARγ. Further in vivo studies are needed to evaluate the efficacy of these equally balanced dual PPARα/γ agonists in order to provide insight into the properties of these molecules and their biological actions. Further studies might also be useful in determining whether these compounds exhibit an improved benefit–risk ratio for the treatment of diabetes.

Experimental Section

Chemistry

General methods: All commercially available reagents and solvents were used without further purification. Melting points were determined on a Büchi B-540 apparatus and are uncorrected. NMR spectra were acquired with NMR spectrometers operating at 300 (^{1}H) or 75 MHz (^{13}C); chemical shifts (δ) are given in ppm. The following abbreviations are used: singlet (s), broad singlet (brs), doublet (d), double doublet (dd), triplet (t). HPLC–MS analyses were performed with an HPLC instrument combined with a Surveyor MSQ (Thermo Electron) equipped with an APCI source (ODS-30 column, mobile phase of $H_2O/CH_3CN/HCO_2H$ (gradient mode). Elemental analyses were performed by CNRS–Vernaison, and data are in agreement with calculated values within $\pm$0.4%. Reference compounds rosiglitazone[26] and tesaglitazar[27] were synthesized by previously described procedures.

Chiral HPLC method: A Waters HPLC system was equipped with an HPLC 600 pump and a 2996 photodiode array detector. The column used was a Daicel Chiralpak AD (250×4.6 mm) at a flow rate of 1 mL min^{-1} and 20 °C. The eluents were: A) IPA + 0.1% TFA, B) petroleum ether (PE), C) EtOH + 0.2% TFA, and D) MeOH. Isocratic elution conditions involved a flow rate of 0.8 or 1 mL min^{-1} at 20 °C with a total run time of 25 min.

Ethyl 2-diazo-2-(diethoxyphosphoryl)acetate 2: The formation of benzenesulfonyl azide was carried out according to published procedures.[16] In brief, benzenesulfonyl chloride (10 g, 56.6 mmol, 1.0 equiv) in acetone (100 mL) and NaN_3 (5.52 g, 84.9 mmol, 1.5 equiv) in H_2O (20 mL) were combined to yield 9.6 g of the desired reagent as a colorless liquid (93%); ^{1}H NMR ($CDCl_3$): δ = 7.63 (dd, 2H, ^3J = 7.2 and 8.3 Hz), 7.75 (dd, 1H, ^3J = 7.2 Hz, ^4J = 1.5 Hz), 7.97 ppm (dd, 2H, ^3J = 8.3 Hz, ^4J = 1.5 Hz); MS *m/z* 184 $[M+H]^+$. The next stage was carried out according to the procedure of Regitz et al.[16] Triethyl phosphonoacetate **1** (10.4 mL, 52.4 mmol, 1.0 equiv) in dry THF (50 mL) was added dropwise to an ice-cold suspension of 60% NaH (3.14 g, 78.6 mmol, 1.5 equiv) in dry THF (50 mL). The reaction mixture was stirred at 0 °C for 1 h, after which time benzenesulfonyl azide (9.6 g, 52.4 mmol, 1.00 equiv) in dry THF (100 mL) was added under a constant flow of N_2. The reaction mixture was further stirred for 16 h at 0 °C, then quenched by the addition of a 5% aqueous solution of $NaHCO_3$ (200 mL). Thereafter, the aqueous phase was extracted with EtOAc and washed with H_2O and brine. The organic extract was then dried over $MgSO_4$, filtered off and concentrated in vacuo. The residue was purified by flash column chromatography (cyclohexane/EtOAc 5:5) to yield **2** as a pale-yellow liquid (11.4 g, 87%); ^{1}H NMR ($CDCl_3$): δ = 1.19 (t, 3H, ^3J = 7.2 Hz), 1.36 (t, 6H, ^3J = 7.2 Hz), 4.18–4.23 ppm (m, 6H); MS *m/z* 251.1 $[M+H]^+$.

Ethyl 2-(diethoxyphosphoryl)-2-(ethoxy)acetate 3: This conversion was performed according to the method of Haigh et al.[17] A mixture of diazo ester **2** (10 g, 40 mmol, 1.0 equiv), EtOH (23.0 mL, 400 mmol, 10 equiv), and $[Rh(OAc)_2]_2$ (176.8 mg, 0.4 mmol, 0.01 equiv) in toluene (60 mL) was heated with stirring at reflux for 4 h. Thereafter, the solution was concentrated in vacuo, hydrolyzed and extracted three times with EtOAc. The combined organic extracts were washed with H_2O, brine, dried over $MgSO_4$, filtered off, and concentrated under reduced pressure. The resulting colorless liquid (8.6 g, 80%) was used in the next step without further purification; ^{1}H NMR ($CDCl_3$): δ = 1.24–1.35 (m, 12H), 3.55 (m, 1H), 3.70 (m, 1H), 4.23–4.28 (m, 6H), 4.35 ppm (s, 1H); MS *m/z* 269.2 $[M+H]^+$.

4-(2-Chloroethoxy)benzaldehyde 5: A mixture of 4-hydroxybenzaldehyde (10 g, 80 mmol, 1.0 equiv), K_2CO_3 (22 g, 160 mmol, 2.0 equiv), and 1-bromo-2-chloroethane (30 mL, 320 mmol, 4.0 equiv) was held at reflux in CH_3CN (80 mL) for 15 h. The reaction mixture was filtered, and the filtrate was evaporated under reduced pressure. The residue was purified by flash column chromatography (cyclohexane/EtOAc 7:3) to yield **4** as a white powder (13.6 g, 92%); mp: 29–32 °C; ^{1}H NMR ($CDCl_3$): δ = 3.86 (t, 2H, ^3J = 6.1 Hz), 4.32 (t, 2H, ^3J = 6.1 Hz), 7.03 (d, 2H, ^3J = 8.9 Hz), 7.86 (d, 2H, ^3J = 8.9 Hz), 9.90 ppm (s, 1H); MS *m/z* 185 $[M+H^{35}Cl]^+$, 187 $[M+H^{37}Cl]^+$.

Ethyl 3-[4-(2-chloroethoxy)phenyl]-2-ethoxypropionate 7: Phosphonoacetate **3** (5 g, 18.6 mmol, 1.2 equiv) in THF (50 mL) was added dropwise to a suspension of 60% NaH (0.93 g, 23.2 mmol, 1.5 equiv) in anhydrous THF (100 mL) at 0 °C under a constant flow of N_2, and the reaction mixture was stirred at 0 °C for 1 h. Benzaldehyde **5** (2.85 g, 15.5 mmol, 1.0 equiv) was then added in dry THF (50 mL). After stirring for a further 4 h at room temperature, the solution was concentrated in vacuo, and the residue was dissolved in EtOAc for washing with H_2O and brine. Combined organic extracts were dried over $MgSO_4$, filtered off, and concentrated in vacuo to give a residue that was purified by flash column (cyclohexane/EtOAc 8:2) to yield **6** (3.95 g, 86%) as two isomers (*Z*/*E* = 59:41) which were not separated, but used directly in the next catalytic hydrogenation step. A solution of **6** (3.95 g, 13.2 mmol) in EtOH (150 mL) was stirred with 10% Pd/C catalyst at room temperature under H_2 (1 atm) for 20 h. The catalyst was separated by filtration, and the solvent evaporated under reduced pressure. The crude product was purified by flash column chromatography (cyclohexane/EtOAc 7:3) to yield **7** as a colorless liquid (3.68 g, 93%); ^{1}H NMR ($CDCl_3$): δ = 1.17 (t, 3H, ^3J = 7.1 Hz), 1.24 (t, 3H, ^3J = 7.1 Hz), 2.97 (d, 2H, ^3J = 5.6 Hz), 3.33 (m, 1H), 3.59 (m, 1H), 3.81 (t, 2H, ^3J = 5.9 Hz), 3.98 (t, 1H, ^3J = 5.6 Hz), 4.12–4.25 (m, 4H), 6.85 (d, 2H, ^3J = 8.6 Hz), 7.17 ppm (d, 2H, ^3J = 8.6 Hz); MS *m/z* 300.1 $[M+H^{35}Cl]^+$, 302.2 $[M+H^{37}Cl]^+$; Anal. calcd for $C_{15}H_{21}ClO_4$: C 59.90, H 7.04, found: C 60.02, H 6.98.

3-[4-(2-Chloroethoxy)phenyl]-2-ethoxypropionic acid 8: LiOH (0.49 g, 20.4 mmol, 3.0 equiv) was added to a solution of **7** (2 g, 6.6 mmol, 1.0 equiv) dissolved in a 1:1 mixture of THF (30 mL) and H_2O (30 mL), and the mixture was then stirred at room temperature for 20 h. Thereafter, the whole was concentrated in vacuo, and the concentrate was subjected to vigorous stirring at 0 °C as the solution was adjusted to pH 1 with 1 N $HCl_{(aq)}$. The resulting precipitate was filtered, washed with H_2O and pentane, and dried under reduced pressure to give **8** as a white solid (1.71 g, 85%); mp: 49–51 °C; ^{1}H NMR ($CDCl_3$): δ = 1.19 (t, 3H, ^3J = 7.0 Hz), 2.95 (m, 2H), 3.45 (m, 1H), 3.63 (m, 1H), 3.82 (t, 2H, ^3J = 6.1 Hz), 4.06 (dd, 1H, ^3J = 7.9 Hz, ^3J = 4.4 Hz), 4.22 (t, 2H, ^3J = 6.1 Hz), 6.87 (d, 2H, ^3J = 8.7 Hz), 7.20 (d, 2H, ^3J = 8.7 Hz), 10.3 ppm (brs, 1H); MS *m/z* 273.2

$[M+H^{35}Cl]^+$, 275.3 $[M+H^{37}Cl]^+$; Anal. calcd for $C_{13}H_{17}ClO_4$: C 57.25, H 6.28, O 23.47, found: C 57.41, H 6.19, O 23.52.

2-(*S*)-3-[4-(2-Chloroethoxy)phenyl]-2-ethoxy-*N*-((*S*)-2-hydroxy-1-phenylethyl)propanamide 9a and 2-(*R*)-3-[4-(2-chloroethoxy)-phenyl]-2-ethoxy-*N*-((*S*)-2-hydroxy-1-phenylethyl)propanamide 9b: EDCI (2.87 g, 15.0 mmol, 1.2 equiv), (*S*)-(−)-2-phenylgycinol (1.74 g, 12.5 mmol, 1.0 equiv), and HOBT (2.0 g, 15.0 mmol, 1.2 equiv) were added to a solution of **8** (3.4 g, 12.5 mmol, 1.0 equiv) in CH_2Cl_2 (150 mL) at 0 °C. Finally, Et_3N (2.1 mL, 15.0 mmol, 1.2 equiv) was added dropwise at 0 °C. The reaction mixture was then stirred for 12 h at room temperature, quenched with saturated $NH_4Cl_{(aq)}$, and diluted with CH_2Cl_2. The organic layer so obtained was washed with H_2O, dried over $MgSO_4$, filtered off and concentrated in vacuo. Purification of the residue by flash column chromatography (PE/EtOAc 45:55) afforded **9a** (1.8 g, 37%) as an off-white solid, and **9b** (1.6 g, 33%) as a white solid.

9a: mp: 135–137 °C; ^{1}H NMR ($CDCl_3$): $\delta=1.21$ (t, 3H, $^3J=7.0$ Hz), 2.91 (dd, 1H, $^2J=14.3$ Hz, $^3J=8.5$ Hz), 3.09 (dd, 1H, $^2J=14.3$ Hz, $^3J=8.5$ Hz), 3.58 (m, 2H), 3.85 (m, 4H), 4.02 (dd, 1H, $^3J=6.4$ Hz, $^3J=3.8$ Hz), 4.19 (t, 2H, $^3J=5.8$ Hz), 5.01 (m, 1H), 6.78 (d, 2H, $^3J=8.7$ Hz), 7.07 (dd, 2H, $^3J=7.6$ Hz, $^4J=2.0$ Hz), 7.13 (m, 3H), 7.33 ppm (m, 3H); MS *m/z* 393.0 $[M+H^{35}Cl]^+$, 395.1 $[M+H^{37}Cl]^+$; Anal. calcd for $C_{21}H_{26}ClNO_4$: C 64.36, H 6.69, N 3.57, found: C 64.45, H 6.57, N 3.61.

9b: mp: 127–128 °C; ^{1}H NMR ($CDCl_3$): $\delta=1.16$ (t, 3H, $^3J=7.0$ Hz), 2.96 (dd, 1H, $^2J=14.3$ Hz, $^3J=6.4$ Hz), 3.15 (dd, 1H, $^2J=14.3$ Hz, $^3J=6.4$ Hz), 3.52 (m, 2H), 3.71 (m, 2H), 3.83 (t, 2H, $^3J=5.8$ Hz), 4.00 (dd, 1H, $^3J=6.7$ Hz, $^3J=3.9$ Hz), 4.24 (t, 2H, $^3J=5.8$ Hz), 4.99 (m, 1H), 6.88 (d, 2H, $^3J=8.7$ Hz), 7.03 (d, 1H, $^3J=7.3$ Hz), 7.20 (m, 4H), 7.34 ppm (m, 3H); MS *m/z* 393.0 $[M+H^{35}Cl]^+$, 395.1 $[M+H^{37}Cl]^+$; Anal. calcd for $C_{21}H_{26}ClNO_4$: C 64.36, H 6.69, N 3.57, found: C 64.44, H 6.61, N 3.60.

2-(*S*)-3-[4-(2-Chloroethoxy)phenyl]-2-ethoxypropionic acid 10a and 2-(*R*)-3-[4-(2-chloroethoxy)phenyl]-2-ethoxypropionic acid 10b: 5 M H_2SO_4 (82 mL, 408 mmol, 100 equiv) was added to a solution of **9a** or **9b** (1.6 g, 4.08 mmol, 1 equiv) in a 1:1 mixture of 1,4-dioxane (80 mL) and H_2O (80 mL). The reaction mixture was held at reflux for 8 h, cooled to room temperature, diluted with EtOAc, and the organic layer so obtained was washed with H_2O, dried over $MgSO_4$, filtered off and concentrated in vacuo. The brown residue was purified by flash column chromatography (CH_2Cl_2/MeOH/Et_3N 96:2:2) to afford the corresponding carboxylic acid **10a** (0.90 g, 81%) or **10b** (0.87 g, 78%) as white solids.

10a: mp: 49–51 °C; ^{1}H NMR (DMSO): $\delta=1.04$ (t, 3H, $^3J=7.0$ Hz), 2.83 (m, 2H), 3.29 (m, 1H), 3.52 (m, 1H), 3.92 (t, 2H, $^3J=5.5$ Hz), 4.21 (t, 2H, $^3J=5.5$ Hz), 6.87 (d, 2H, $^3J=8.5$ Hz), 7.14 ppm (d, 2H, $^3J=8.5$ Hz); MS *m/z* 273.1 $[M+H^{35}Cl]^+$, 275.0 $[M+H^{37}Cl]^+$; Anal. calcd for $C_{13}H_{17}ClO_4$: C 57.25, H 6.28, found: C 57.32, H 6.24; chiral HPLC method: flow rate = 1.0 mL min^{-1}, eluents = A/B 5:95, t_R = 16.62 min.

10b: mp: 49–51 °C; ^{1}H NMR (DMSO): $\delta=1.04$ (t, 3H, $^3J=7.0$ Hz), 2.83 (m, 2H), 3.29 (m, 1H), 3.52 (m, 1H), 3.92 (t, 2H, $^3J=5.5$ Hz), 4.21 (t, 2H, $^3J=5.5$ Hz), 6.87 (d, 2H, $^3J=8.5$ Hz), 7.14 ppm (d, 2H, $^3J=8.5$ Hz); MS *m/z* 273.1 $[M+H^{35}Cl]^+$, 275.0 $[M+H^{37}Cl]^+$; Anal. calcd for $C_{13}H_{17}ClO_4$: C 57.25, H 6.28, found: C 57.37, H 6.21; chiral HPLC method: flow rate = 1.0 mL min^{-1}, eluents = A/B 5:95, t_R = 12.48 min.

5-Bromo-3-methyl-1*H*-indole 11c: Phosphorus oxychloride (4.3 g, 30 mmol, 1.15 equiv) was added dropwise to DMF (8.6 mL) with ice-bath cooling. The mixture was stirred for 5 min, then 5-bromo-1*H*-indole (5 g, 25.5 mmol, 1 equiv) was added as a DMF solution (10 mL). The mixture was then allowed to warm to room temperature and stirred for 1 h. The reaction became a heavy suspension that required vigorous stirring. $NaOH_{(aq)}$ (9.3 M, 30 mL, 11 equiv) was added dropwise, and the mixture was heated at reflux overnight. After cooling to room temperature, the precipitate was collected by filtration, washed with H_2O, and recrystallized from EtOH to afford 5-bromo-3-formyl-1*H*-indole as a light-yellow solid (5.3 g, 93%); mp: 205–207 °C; ^{1}H NMR (DMSO): $\delta=7.38$ (dd, 1H, $^3J=8.7$ Hz, $^4J=2.0$ Hz), 7.50 (d, 1H, $^3J=8.7$ Hz), 8.22 (d, 1H, $^4J=2.0$ Hz), 8.36 (s, 1H), 9.93 (s, 1H), 12.32 ppm (s, 1H). A solution of formylindole (5.3 g, 23.6 mmol, 1 equiv) in dry THF (35 mL) was added dropwise to a suspension of $LiAlH_4$ (1.85 g, 47.2 mmol, 2 equiv) in dry THF (10 mL) at 0 °C and then heated at 65–70 °C for 4 h under N_2. After cooling, the suspension was quenched with H_2O, extracted twice with EtOAc, and the combined organic extracts were dried over $MgSO_4$, filtered off and concentrated in vacuo. The residue was purified by flash column chromatography (toluene/PE 75:25) to yield 3.4 g (68%) of **11b** as a pale-brown solid; mp: 80–81 °C; ^{1}H NMR ($CDCl_3$): $\delta=2.32$ (s, 3H), 6.69 (s, 1H), 7.18–7.32 (m, 2H), 7.72 (s, 1H), 7.93 ppm (br s, 1H); MS *m/z* 211.2 $[M+H]^+$.

5-Tributylstannylindole 13: A solution of 5-bromoindole **11a** (3.98 g, 20 mmol, 1 equiv) in dry THF (40 mL) was added to a 35% KH dispersion in mineral oil (2.29 g, 20 mmol, 1 equiv) in dry THF (40 mL) at 0 °C. After 15 min the solution was cooled to −78 °C and a solution of *t*BuLi in pentane (1.5 M, 26.6 mL, 40 mmol, 2 equiv) precooled to −78 °C was added via cannula. A white precipitate immediately formed and after 10 min, tributyltin chloride (13 g, 40 mmol, 2 equiv) dissolved in dry THF (10 mL) was added. The reaction mixture was allowed to slowly warm to room temperature, and the suspension was poured into 150 mL ice-cold H_2O. The organic layer was separated, and the aqueous layer was extracted twice with Et_2O. The ether extracts were combined, dried over $MgSO_4$, filtered off and evaporated under reduced pressure. The residue was purified by flash column chromatography (PE/EtOAc/Et_3N 90:9:1) previously neutralized with Et_3N to yield **13** as a colorless oil (6.3 g, 78%); ^{1}H NMR ($CDCl_3$): $\delta=0.89$ (t, 9H, $^3J=7.3$ Hz), 1.07 (m, 6H), 1.34 (m, 6H), 1.55 (m, 6H), 6.55 (m, 1H), 7.17 (m, 1H), 7.27 (d, 1H, $^3J=8.4$ Hz), 7.40 (d, 1H, $^3J=8.4$ Hz), 7.76 (t, 1H, $^3J=22$ Hz), 8.16 ppm (br s, 1H); MS *m/z* 407.2 $[M+H]^+$; Anal. calcd for $C_{20}H_{33}NSn$: C 59.14, H 8.19, N 3.45, found: C 59.48, H 8.11, N 3.51.

General procedure for the synthesis of 5- and 6-acylindole derivatives 14a–c: A solution of bromoindole **11a–c** (3.98 g, 20 mmol, 1 equiv) in dry THF (40 mL) was added to a 35% KH dispersion in mineral oil (2.29 g, 20 mmol, 1 equiv) in dry THF (40 mL) at 0 °C. After 15 min the solution was cooled to −78 °C, and a solution of *t*BuLi in pentane (1.5 M, 26.6 mL, 40 mmol, 2 equiv) precooled to −78 °C was added via cannula, and the solution was stirred for 20 min. *N*-methoxy-*N*-methylbenzamide (3.96 g, 24 mmol, 1.2 equiv) in dry THF (40 mL) was added at −78 °C, and the mixture was then allowed to warm to room temperature and stirred for 12 h. The reaction mixture was hydrolyzed with an aqueous solution of H_3PO_4 (1 M, 300 mL) and extracted twice with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered off and concentrated in vacuo, and the residue was purified by flash column chromatography (toluene/EtOAc 9:1) to afford the corresponding benzoyl indole derivative.

5-Benzoyl-1*H*-indole 14a: Off-white solid (2.83 g, 64%); mp: 152–153 °C (PE); ^{1}H NMR ($CDCl_3$): $\delta=6.67$ (m, 1H), 7.32 (t, 1H, $^3J=3.1$ Hz), 7.45–7.54 (m, 3H), 7.59 (t, 1H, $^3J=7.5$ Hz), 7.79–7.87 (m, 3H), 8.6 (s, 1H), 8.60 ppm (br s, 1H); MS *m/z* 222.2 $[M+H]^+$; Anal.

calcd for $C_{15}H_{11}NO$: C 81.43, H 5.01, N 6.33, found: C 81.52, H 4.96, N 6.40.

6-Benzoyl-1*H*-indole 14b: Off-white solid (2.12 g, 48%); mp: 149–151 °C (PE); ^{1}H NMR ($CDCl_3$): δ = 6.67 (m, 1H), 7.44 (t, 1H, ^3J = 2.9 Hz), 7.51 (t, 2H, ^3J = 6.1 Hz), 7.60 (t, 1H, ^3J = 7.6 Hz), 7.65 (dd, 1H, ^3J = 8.2 Hz, ^4J = 1.5 Hz), 7.73 (d, 1H, ^3J = 8.2 Hz), 7.84 (d, 2H, ^3J = 6.7 Hz), 7.97 (m, 1H), 8.46 ppm (br s, 1H); MS *m/z* 222.2 [*M*+H]$^+$; Anal. calcd for $C_{15}H_{11}NO$: C 81.43, H 5.01, N 6.33, found: C 81.49, H 4.95, N 6.38.

5-Benzoyl-3-methyl-1*H*-indole 14c: Light-brown solid (2.06 g, 49%); mp: 148–150 °C (PE); ^{1}H NMR ($CDCl_3$): δ = 2.72 (s, 3H), 7.09 (m, 1H), 7.42 (d, 1H, ^3J = 8.5 Hz), 7.51 (t, 2H, ^3J = 6.3 Hz), 7.60 (t, 1H, ^3J = 7.6 Hz), 7.77 (dd, 1H, ^3J = 8.5 Hz, ^4J = 1.75 Hz), 7.84 (d, 2H, ^3J = 6.6 Hz), 8.13 (d, 1H, ^4J = 1.75 Hz), 8.17 (br s, 1H); MS *m/z* 236.3 [*M*+H]$^+$; Anal. calcd for $C_{16}H_{13}NO$: C 81.68, H 5.57, N 5.95, found: C 81.77, H 5.47, N 6.01.

General procedure for the synthesis of 5-cycloalkylcarbonyl indole derivatives 14d,e: $PdCl_2(PPh_3)_2$ (140.4 mg, 0.2 mmol, 0.02 equiv) was added to a solution of cyclopropylcarbonyl chloride (1.04 g, 10 mmol, 1 equiv) or cyclohexylcarbonyl chloride (1.46 g, 10 mmol, 1 equiv) in anhydrous toluene (40 mL) under Ar. The mixture was stirred at room temperature for 10 min, and 5-tributylstannylindole **13** (5.3 g, 13 mmol, 1.3 equiv) in toluene (10 mL) was added. The reaction mixture was stirred and heated at 110 °C for 16 h. After conversion was complete (checked by TLC), the solvent was evaporated under reduced pressure, and the oily mixture was treated with EtOAc and a solution of KF (1 M) at room temperature for 30 min to precipitate the formed tributyltin fluoride. The resulting solution was filtered through a Celite pad and extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered off and evaporated under reduced pressure. The crude product was purified by flash column chromatography (PE/EtOAc 75:25) to afford the corresponding 5-cycloalkylcarbonyl indole derivative.

5-cyclopropylcarbonyl-1*H*-indole 14d: Off-white solid (1.64 g, 70%); mp: 114–116 °C; ^{1}H NMR ($CDCl_3$): δ = 1.05 (m, 2H), 1.27 (m, 2H), 2.82 (m, 1H), 6.69 (m, 1H), 7.30 (m, 1H), 7.44 (d, 1H, ^3J = 8.8 Hz), 7.93 (dd, 1H, ^3J = 8.8 Hz, ^4J = 1.7 Hz), 8.44 (d, 1H, ^4J = 1.7 Hz), 8.51 (br s, 1H); MS *m/z* 236.2 [*M*+H]$^+$; Anal. calcd for $C_{12}H_{11}NO$: C 77.81, H 5.99, N 7.56, found: C 78.03, H 6.04, N 7.47.

5-cyclohexylcarbonyl-1*H*-indole 14e: Off-white solid (1.61 g, 71%); mp: 119–121 °C; ^{1}H NMR ($CDCl_3$): δ = 1.24–1.96 (m, 10H), 3.43 (m, 1H), 6.68 (m, 1H), 7.30 (t, 1H, ^3J = 2.9 Hz), 7.44 (d, 1H, ^3J = 8.7 Hz), 7.88 (dd, 1H, ^3J = 8.7 Hz, ^4J = 1.65 Hz), 8.33 (d, 1H, ^3J = 1.7 Hz), 8.48 ppm (br s, 1H); MS *m/z* 228.2 [*M*+H]$^+$; Anal. calcd for $C_{15}H_{17}NO$: C 79.26, H 7.54, N 6.16, found: C 79.34, H 7.48, N 6.22.

General procedure for the synthesis of compounds 15a–e and 23: To a solution of 5- or 6-substituted indole derivative **14a–e** or **22** (5 mmol, 1.0 equiv) in DMF (50 mL) was added K_2CO_3 (15 mmol, 3 equiv), and the mixture was stirred for 1 h at 100 °C. A solution of **7** (6 mmol, 1.2 equiv) in DMF (10 mL) was added dropwise, and the mixture was stirred at reflux for 15 h. After cooling, the reaction mixture was filtered, hydrolyzed, and extracted twice with EtOAc. The combined organic extracts were washed with H_2O, dried over $MgSO_4$, filtered off and concentrated in vacuo. The crude product was purified by flash column chromatography (toluene/EtOAc 95:5) to afford the corresponding *N*-alkylated indole derivative.

Ethyl 3-{4-[2-(5-benzoylindol-1-yl)ethoxy]phenyl}-2-ethoxypropionate 15a: Colorless oil (1.48 g, 61%); ^{1}H NMR ($CDCl_3$): δ = 1.15 (t, 3H, ^3J = 6.8 Hz), 1.23 (t, 3H, ^3J = 7.3 Hz), 2.92 (m, 2H), 3.33 (m, 1H), 3.59 (m, 1H), 3.95 (t, 1H, ^3J = 6.3 Hz), 4.17 (q, 2H, ^3J = 6.8 Hz), 4.30 (t, 2H, ^3J = 5.7 Hz), 4.58 (t, 2H, ^3J = 5.7 Hz), 6.62 (d, 1H, ^3J = 3.1 Hz), 6.78 (d, 2H, ^3J = 8.9 Hz), 7.17 (m, 3H), 7.32 (d, 1H, ^3J = 3.1 Hz), 7.50 (m, 3H), 7.58 (t, 1H, ^3J = 7.3 Hz), 7.82 (d, 2H, ^3J = 7.5 Hz), 8.12 ppm (d, 1H, ^3J = 1.5 Hz); MS *m/z* 486.3 [*M*+H]$^+$; Anal. calcd for $C_{30}H_{31}NO_5$: C 74.21, H 6.43, N 2.88, found: C 74.30, H 6.38, N 2.94.

Ethyl 3-{4-[2-(6-benzoylindol-1-yl)ethoxy]phenyl}-2-ethoxypropionate 15b: Colorless oil (1.43 g, 59%); ^{1}H NMR ($CDCl_3$): δ = 1.15 (t, 3H, ^3J = 7.0 Hz), 1.22 (t, 3H, ^3J = 7.2 Hz), 2.92 (m, 2H), 3.32 (m, 1H), 3.60 (m, 1H), 3.93 (t, 1H, ^3J = 6.4 Hz), 4.19 (q, 2H, ^3J = 6.9 Hz), 4.28 (t, 2H, ^3J = 5.5 Hz), 4.60 (t, 2H, ^3J = 5.5 Hz), 6.61 (d, 1H, ^3J = 3.1 Hz), 6.74 (d, 2H, ^3J = 8.5 Hz), 7.12 (d, 2H, ^3J = 8.5 Hz), 7.42–7.61 (m, 5H), 7.68 (d, 1H, ^3J = 8.2 Hz), 7.83 (d, 2H, ^3J = 7.5 Hz), 8.05 ppm (d, 1H, ^3J = 1.7 Hz); MS *m/z* 486.1 [*M*+H]$^+$; Anal. calcd for $C_{30}H_{31}NO_5$: C 74.21, H 6.43, N 2.88, found: C 74.28, H 6.36, N 2.95.

Ethyl 3-{4-[2-(5-benzoyl-3-methylindol-1-yl)ethoxy]phenyl}-2-ethoxypropionate 15c: Colorless oil (1.55 g, 62%); ^{1}H NMR ($CDCl_3$): δ = 1.16 (t, 3H, ^3J = 7.1 Hz), 1.24 (t, 3H, ^3J = 6.6 Hz), 2.33 (s, 3H), 2.93 (m, 2H), 3.33 (m, 1H), 3.60 (m, 1H), 3.95 (t, 1H, ^3J = 5.9 Hz), 4.19 (q, 2H, ^3J = 6.6 Hz), 4.28 (t, 2H, ^3J = 5.6 Hz), 4.60 (t, 2H, ^3J = 5.6 Hz), 6.78 (d, 2H, ^3J = 8.3 Hz), 7.07 (s, 1H), 7.14 (d, 2H, ^3J = 8.3 Hz), 7.41–7.61 (m, 4H), 7.75–7.87 (m, 3H), 8.10 ppm (d, 1H, ^4J = 1.5 Hz); MS *m/z* 500.4 [*M*+H]$^+$; Anal. calcd for $C_{31}H_{33}NO_5$: C 74.53, H 6.66, N 2.80, found: C 74.62, H 6.59, N 2.84.

Ethyl 3-{4-[2-(5-cyclopropanoylindol-1-yl)ethoxy]phenyl}-2-ethoxypropionate 15d: Colorless oil (1.46 g, 65%); ^{1}H NMR ($CDCl_3$): δ = 1.03 (m, 2H), 1.15 (t, 3H, ^3J = 7.0 Hz), 1.26 (m, 5H), 2.81 (m, 1H), 2.93 (m, 2H), 3.33 (m, 1H), 3.60 (m, 1H), 3.95 (t, 1H, ^3J = 5.8 Hz), 4.17 (q, 2H, ^3J = 6.6 Hz), 4.28 (t, 2H, ^3J = 5.6 Hz), 4.57 (t, 2H, ^3J = 5.6 Hz), 6.67 (d, 1H, ^3J = 3.2 Hz), 6.78 (d, 2H, ^3J = 8.2 Hz), 7.14 (d, 2H, ^3J = 8.2 Hz), 7.31 (d, 1H, ^3J = 3.2 Hz), 7.46 (d, 1H, ^3J = 8.5 Hz), 7.98 (dd, 1H, ^3J = 8.5 Hz, ^4J = 1.5 Hz), 8.42 (d, 1H, ^4J = 1.5 Hz); MS *m/z* 450.3 [*M*+H]$^+$; Anal. calcd for $C_{27}H_{31}NO_5$: C 72.14, H 6.95, N 3.12, found: C 72.25, H 6.89, N 3.21.

Ethyl 3-{4-[2-(5-cyclohexanoylindol-1-yl)ethoxy]phenyl}-2-ethoxypropionate 15e: Colorless oil (1.35 g, 55%); ^{1}H NMR ($CDCl_3$): δ = 1.16 (t, 3H, ^3J = 7.0 Hz), 1.23 (t, 3H, ^3J = 7.0 Hz), 1.32–1.66 (m, 6H), 1.72–2.0 (m, 4H), 2.93 (m, 2H), 3.38 (m, 2H), 3.59 (m, 1H), 3.95 (t, 1H, ^3J = 5.8 Hz), 4.19 (q, 2H, ^3J = 6.7 Hz), 4.28 (t, 2H, ^3J = 5.6 Hz), 4.55 (t, 2H, ^3J = 5.6 Hz), 6.62 (d, 1H, ^3J = 3.1 Hz), 6.75 (d, 2H, ^3J = 8.4 Hz), 7.14 (d, 2H, ^3J = 8.4 Hz), 7.29 (d, 1H, ^3J = 3.1 Hz), 7.47 (d, 1H, ^3J = 8.3 Hz), 7.92 (dd, 1H, ^3J = 8.3 Hz, ^4J = 1.6 Hz), 8.32 (d, 1H, ^4J = 1.6 Hz); MS *m/z* 492.4 [*M*+H]$^+$; Anal. calcd for $C_{30}H_{37}NO_5$: C 73.29, H 7.59, N 2.85, found: C 73.36, H 7.48, N 2.94.

Ethyl 3-{4-[2-(5-acetylindol-1-yl)ethoxy]phenyl}-2-ethoxypropionate 23: Pasty solid (1.18 g, 56%); ^{1}H NMR ($CDCl_3$): δ = 1.16 (t, 3H, ^3J = 7.0 Hz), 1.24 (t, 3H, ^3J = 7.0 Hz), 2.69 (s, 3H), 2.93 (m, 2H), 3.33 (m, 1H), 3.60 (m, 1H), 3.95 (t, 1H, ^3J = 6.4 Hz), 4.18 (q, 2H, ^3J = 7.0 Hz), 4.29 (t, 2H, ^3J = 5.5 Hz), 4.57 (t, 2H, ^3J = 5.5 Hz), 6.65 (d, 1H, ^3J = 3.2 Hz), 6.78 (d, 2H, ^3J = 8.2 Hz), 7.13 (d, 2H, ^3J = 8.2 Hz), 7.32 (d, 1H, ^3J = 3.2 Hz), 7.47 (d, 1H, ^3J = 8.5 Hz), 7.93 (d, 1H, ^3J = 8.5 Hz), 8.32 ppm (s, 1H); MS *m/z* 424.1 [*M*+H]$^+$; Anal. calcd for $C_{25}H_{29}NO_5$: C 70.90, H 6.90, N 3.31, found: C 70.81, H 6.97, N 3.42.

General procedure for the synthesis of oxime ethers 17a–d: *O*-Methylhydroxylamine hydrochloride (10 mmol, 4 equiv) was added to a solution of **15a,b,d,e** (2.5 mmol, 1 equiv) in pyridine (20 mL), and the mixture was stirred at 100 °C for 4 h. The reaction mixture was concentrated in vacuo, hydrolyzed with 1 N $HCl_{(aq)}$, and extracted twice with CH_2Cl_2. The combined organic extracts were dried

over $MgSO_4$, filtered off, evaporated under reduced pressure, and the resulting residue was purified by flash column chromatography (toluene/EtOAc 97:3) to afford the corresponding oxime ether as a racemic mixture of *E* and *Z* isomers.

Ethyl 2-ethoxy-3-{4-[2-(5-{[*Z*/*E*]-methoxyimino]phenylmethyl}indol-1-yl)ethoxy]phenyl}propionate 17a: Colorless oil (0.97 g, 76%); ^{1}H NMR ($CDCl_3$): δ = 1.16 (m, 3H), 1.24 (m, 3H), 2.93 (m, 2H), 3.33 (m, 1H), 3.60 (m, 1H), 3.96 (m, 4H), 4.18 (m, 2H), 4.27 (m, 2H), 4.52 (m, 2H), 6.50 (m, 1H), 6.75 (m, 2H), 7.10–7.21 (m, 4H), 7.24–7.45 (m, 4H), 7.51–7.67 ppm (m, 3H); MS *m/z* 515.1 $[M+H]^+$; Anal. calcd for $C_{31}H_{34}N_2O_5$: C 72.35, H 6.66, N 5.44, found: C 72.46, H 6.57, N 5.50.

Ethyl 2-ethoxy-3-{4-[2-(6-{[*Z*/*E*]-methoxyimino]phenylmethyl}indol-1-yl)ethoxy]phenyl}propionate 17b: Colorless oil (1.01 g, 79%); ^{1}H NMR ($CDCl_3$): δ = 1.18 (m, 3H), 1.23 (m, 3H), 2.96 (m, 2H), 3.35 (m, 1H), 3.61 (m, 1H), 3.96 (m, 1H), 4.03 (s, 3H), 4.21 (m, 4H), 4.50 (m, 2H), 6.54 (m, 1H), 6.75 (m, 2H), 7.10–7.21 (m, 4H), 7.23–7.50 (m, 4H), 7.52–7.72 ppm (m, 3H); MS *m/z* 515.1 $[M+H]^+$; Anal. calcd for $C_{31}H_{34}N_2O_5$: C 72.35, H 6.66, N 5.44, found: C 72.42, H 6.60, N 5.49.

Ethyl 2-ethoxy-3-{4-[2-(5-{cyclopropyl-[*Z*/*E*]-methoxyimino]methyl}indol-1-yl)ethoxy]phenyl}propionate 17c: Colorless oil (0.97 g, 81%); ^{1}H NMR ($CDCl_3$): δ = 0.62–0.96 (m, 4H), 1.16 (m, 3H), 1.22 (m, 3H), 2.35 (m, 1H), 2.94 (m, 2H), 3.34 (m, 1H), 3.61 (m, 1H), 3.96 (m, 1H), 4.02 (s, 3H), 4.18 (m, 2H), 4.25 (m, 2H), 4.52 (m, 2H), 6.53 (m, 1H), 6.78 (m, 2H), 7.17 (m, 2H), 7.21–7.42 (m, 3H), 7.68 ppm (m, 1H); MS *m/z* 479.4 $[M+H]^+$; Anal. calcd for $C_{28}H_{34}N_2O_5$: C 70.27, H 7.16, N 5.85, found: C 70.35, H 7.08, N 5.92.

Ethyl 2-ethoxy-3-{4-[2-(5-{cyclohexyl-[*Z*/*E*]-methoxyimino]methyl}indol-1-yl)ethoxy]phenyl}propionate 17d: Colorless oil (0.97 g, 75%); ^{1}H NMR ($CDCl_3$): δ = 1.15 (m, 3H), 1.22–1.38 (m, 7H), 1.43–1.92 (m, 6H), 2.95 (m, 2H), 3.34 (m, 2H), 3.60 (m, 1H), 3.80–3.95 (m, 4H), 4.18 (m, 2H), 4.24 (m, 2H), 4.52 (m, 2H), 6.57 (m, 1H), 6.73 (m, 2H), 7.13 (m, 2H), 7.26 (m, 2H), 7.39 (m, 2H), 7.48 (s, 0.5H), 7.63 ppm (s, 0.5H); MS *m/z* 521.2 $[M+H]^+$; Anal. calcd for $C_{31}H_{40}N_2O_5$: C 71.51, H 7.74, N 5.38, found: C 71.64, H 7.67, N 5.42.

General procedure for the synthesis of carboxylic acids 16a–e, 18a–d: LiOH (0.15 g, 6.0 mmol, 3.0 equiv) was added to a solution of ester **15a–e** or **17a–d** (2.0 mmol, 1.0 equiv) dissolved in a 2:1 mixture of THF (20 mL) and H_2O (10 mL), and the mixture was then stirred at room temperature for 12 h. Thereafter, the whole was concentrated in vacuo, and the concentrate was hydrolyzed with 1 M $HCl_{(aq)}$, then extracted twice with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, filtered off, evaporated under reduced pressure, and the resulting residue was purified by flash column chromatography (CH_2Cl_2/MeOH 95:5) to afford the corresponding carboxylic acids.

3-{4-[2-(5-Benzoylindol-1-yl)ethoxy]phenyl}-2-ethoxypropionic acid 16a: White solid (0.77 g, 84%); mp: 49–52 °C; ^{1}H NMR (DMSO): δ = 1.03 (t, 3H, ^3J = 6.8 Hz), 2.82 (m, 2H), 3.27 (m, 1H), 3.48 (m, 1H), 3.91 (t, 1H, ^3J = 6.3 Hz), 4.30 (t, 2H, ^3J = 5.9 Hz), 4.66 (t, 2H, ^3J = 5.9 Hz), 6.66 (d, 1H, ^3J = 3.1 Hz), 6.80 (d, 2H, ^3J = 8.6 Hz), 7.12 (d, 2H, ^3J = 8.6 Hz), 7.57 (m, 3H), 7.67 (m, 2H), 7.73 (m, 3H), 7.99 ppm (s, 1H); LC–MS: t_R = 4.19 min (98%), *m/z* 458.1 $[M+H]^+$; Anal. calcd for $C_{28}H_{27}NO_5$: C 73.51, H 5.95, N 3.06, found: C 73.59, H 5.88, N 3.10.

3-{4-[2-(6-Benzoylindol-1-yl)ethoxy]phenyl}-2-ethoxypropionic acid 16b: White solid (0.74 g, 81%); mp: 131–132 °C; ^{1}H NMR (DMSO): δ = 1.01 (t, 3H, ^3J = 6.7 Hz), 2.80 (m, 2H), 3.28 (m, 1H), 3.49 (m, 1H), 3.90 (t, 1H, ^3J = 6.1 Hz), 4.27 (t, 2H, ^3J = 5.7 Hz), 4.65 (t, 2H, ^3J = 5.7 Hz), 6.60 (d, 1H, ^3J = 2.6 Hz), 6.74 (d, 2H, ^3J = 8.5 Hz), 7.09 (d, 2H, ^3J = 8.5 Hz), 7.46 (d, 1H, ^3J = 8.2 Hz), 7.56 (t, 2H, ^3J = 7.3 Hz), 7.62–7.80 (m, 5H), 8.07 ppm (s, 1H); LC–MS: t_R = 4.12 min (96%), *m/z* 458.0 $[M+H]^+$; Anal. calcd for $C_{28}H_{27}NO_5$: C 73.51, H 5.95, N 3.06, found: C 73.35, H 6.10, N 3.02.

3-{4-[2-(5-Benzoyl-3-methylindol-1-yl)ethoxy]phenyl}-2-ethoxypropionic acid 16c: White solid (0.79 g, 84%); mp: 54–58 °C; ^{1}H NMR ($CDCl_3$): δ = 1.13 (t, 3H, ^3J = 7.3 Hz), 2.31 (s, 3H), 2.98 (m, 2H), 3.43 (m, 1H), 3.57 (m, 1H), 4.02 (t, 1H, ^3J = 5.7 Hz), 4.21 (t, 2H, ^3J = 6.9 Hz), 4.47 (t, 2H, ^3J = 6.9 Hz), 6.75 (d, 2H, ^3J = 8.1 Hz), 7.05 (s, 1H), 7.11 (d, 2H, ^3J = 8.1 Hz), 7.39–7.62 (m, 4H), 7.72–7.82 (m, 3H), 8.09 ppm (d, 1H, ^4J = 1.5 Hz); LC–MS: t_R = 4.15 min (99%), *m/z* 472.2 $[M+H]^+$; Anal. calcd for $C_{29}H_{29}NO_5$: C 73.87, H 6.20, N 2.97, found: C 73.76, H 6.24, N 3.01.

3-{4-[2-(5-Cyclopropanoylindol-1-yl)ethoxy]phenyl}-2-ethoxypropionic acid 16d: Pasty solid (0.66 g, 79%); ^{1}H NMR ($CDCl_3$): δ = 1.04 (m, 2H), 1.17 (t, 3H, ^3J = 6.7 Hz), 1.27 (m, 2H), 2.82 (m, 1H), 2.93 (dd, 1H, ^3J = 14.0 Hz, ^3J = 7.6 Hz), 3.06 (dd, 1H, ^3J = 14.0 Hz, ^3J = 7.6 Hz), 3.41 (m, 1H), 3.62 (m, 1H), 4.02 (t, 1H, ^3J = 5.8 Hz), 4.28 (t, 2H, ^3J = 5.9 Hz), 4.55 (t, 2H, ^3J = 5.9 Hz), 6.67 (d, 1H, ^3J = 3.2 Hz), 6.77 (d, 2H, ^3J = 8.5 Hz), 7.16 (d, 2H, ^3J = 8.5 Hz), 7.30 (d, 1H, ^3J = 3.2 Hz), 7.46 (d, 1H, ^3J = 8.8 Hz), 7.97 (dd, 1H, ^3J = 8.8 Hz, ^4J = 1.8 Hz), 8.42 ppm (d, 1H, ^4J = 1.8 Hz); LC–MS: t_R = 3.84 min (95%), *m/z* 422.3 $[M+H]^+$; Anal. calcd for $C_{25}H_{27}NO_5$: C 71.24, H 6.46, N 3.32, found: C 71.31, H 6.40, N 3.38.

3-{4-[2-(5-Cyclohexanoylindol-1-yl)ethoxy]phenyl}-2-ethoxypropionic acid 16e: White solid (0.78 g, 85%); mp: 72–76 °C; ^{1}H NMR ($CDCl_3$): δ = 1.16 (t, 3H, ^3J = 7.0 Hz), 1.20–1.62 (m, 6H), 1.72–1.98 (m, 4H), 2.92 (m, 1H), 3.08 (m, 1H), 3.42 (m, 2H), 3.58 (m, 1H), 4.01 (t, 1H, ^3J = 5.9 Hz), 4.26 (t, 2H, ^3J = 6.2 Hz), 4.52 (t, 2H, ^3J = 6.2 Hz), 6.64 (d, 1H, ^3J = 2.9 Hz), 6.74 (d, 2H, ^3J = 7.9 Hz), 7.12 (d, 2H, ^3J = 7.9 Hz), 7.27 (d, 1H, ^3J = 2.9 Hz), 7.43 (d, 1H, ^3J = 8.8 Hz), 7.92 (d, 1H, ^3J = 8.8 Hz), 8.31 ppm (s, 1H); LC–MS: t_R = 4.33 min (94%), *m/z* 464.2 $[M+H]^+$; Anal. calcd for $C_{28}H_{33}NO_5$: C 72.55, H 7.18, N 3.02, found: C 72.46, H 7.25, N 2.94.

2-Ethoxy-3-{4-[2-(5-{[*Z*/*E*]-methoxyimino]phenylmethyl}indol-1-yl)ethoxy]phenyl}propionic acid 18a: White solid (0.79 g, 82%); mp: 47–50 °C; ^{1}H NMR ($CDCl_3$): δ = 1.18 (m, 3H), 2.95 (m, 1H), 3.08 (m, 1H), 3.44 (m, 1H), 3.60 (m, 1H), 4.01 (m, 4H), 4.28 (m, 2H), 4.52 (m, 2H), 6.50 (m, 1H), 6.78 (m, 2H), 7.10–7.69 ppm (m, 11H); LC–MS: t_R = 4.22 and 4.27 min (52 and 45%), *m/z* 487.1 $[M+H]^+$; Anal. calcd for $C_{29}H_{30}N_2O_5$: C 71.59, H 6.21, N 5.76, found: C 71.64, H 6.32, N 5.81.

2-Ethoxy-3-{4-[2-(6-{[*Z*/*E*]-methoxyimino]phenylmethyl}indol-1-yl)ethoxy]phenyl}propionic acid 18b: White solid (0.81 g, 83%); mp: 104–105 °C; ^{1}H NMR (DMSO): δ = 1.02 (m, 3H), 2.81 (m, 2H), 3.28 (m, 1H), 3.49 (m, 1H), 3.90 (m, 4H), 4.21 (m, 2H), 4.51 (m, 2H), 6.59 (m, 1H), 6.71 (m, 2H), 6.92 (m, 0.5H), 7.09 (m, 2.5H), 7.28–7.63 ppm (m, 8H); LC–MS: t_R = 4.44 and 4.46 min (50 and 48%), MS *m/z* 487.2 $[M+H]^+$; Anal. calcd for $C_{29}H_{30}N_2O_5$: C 71.59, H 6.21, N 5.76, found: C 71.50, H 6.30, N 5.58.

2-Ethoxy-3-{4-[2-(5-{cyclopropyl-[*Z*/*E*]-methoxyimino]methyl}indol-1-yl)ethoxy]phenyl}propionic acid 18c: Colorless oil (0.73 g, 81%); ^{1}H NMR ($CDCl_3$): δ = 0.62–0.96 (m, 4H), 1.18 (m, 3H), 1.82 (m, 0.5H), 2.36 (m, 0.5H), 2.92 (m, 1H), 3.07 (m, 1H), 3.47 (m, 1H), 3.58 (m, 1H), 3.82 (s, 1.5H), 4.01 (m, 2.5H), 4.25 (m, 2H), 4.51 (m, 2H), 6.52 (m, 1H), 6.73 (m, 2H), 7.05–7.44 (m, 5H), 7.60 (m, 0.5H), 7.62 ppm (m, 0.5H); LC–MS: t_R = 4.83 and 4.09 min (30 and 67%), *m/z* 451.2 $[M+H]^+$; Anal. calcd for $C_{26}H_{30}N_2O_5$: C 69.31, H 6.71, N 6.22, found: C 69.42, H 6.65, N 6.27.

2-Ethoxy-3-{4-[2-(5-{cyclohexyl-[*Z*/*E*]-methoxyimino]methyl}indol-1-yl)ethoxy]phenyl}propionic acid 18 d: Pasty solid (0.77 g, 78%); ^{1}H NMR ($CDCl_3$): δ = 1.18 (m, 3H), 1.22–1.40 (m, 4H), 1.42–1.92 (m, 6H), 2.53 (m, 0.5H), 2.95 (m, 1H), 3.08 (m, 1H), 3.28 (m, 0.5H), 3.47 (m, 1H), 3.59 (m, 1H), 3.80 (s, 1.5H), 3.95 (s, 1.5H), 4.05 (m, 1H), 4.28 (m, 2H), 4.52 (m, 2H), 6.54 (m, 1H), 6.77 (m, 2H), 7.12 (m, 2H), 7.23 (m, 1.5H), 7.39 (m, 1.5H), 7.49 (s, 0.5H), 7.62 ppm (s, 0.5H); LC–MS: t_R = 4.28 and 4.56 min (41 and 57%), *m/z* 493.2 $[M+H]^+$; Anal. calcd for $C_{29}H_{36}N_2O_5$: C 70.71, H 7.37, N 5.69, found: C 70.62, H 7.46, N 5.61.

General procedure for the synthesis of oxime ethers 19 a–c: *O*-Methylhydroxylamine hydrochloride (3.34 g, 40 mmol, 4 equiv) was added to a solution of 5- or 6-benzoylindole **14 a,b** (2.22 g, 10 mmol, 1 equiv) in pyridine (40 mL), and the mixture was stirred at 100 °C for 4 h. The reaction mixture was concentrated in vacuo, hydrolyzed with 1 N $HCl_{(aq)}$, and extracted twice with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, filtered off, evaporated under reduced pressure, and the resulting residue was purified by flash column chromatography (PE/CH_2Cl_2/EtOAc 75:24:1) to afford the corresponding oxime ethers **19 a–c**.

5-{[(*E*)-Methoxyimino]phenylmethyl}-1*H*-indole 19 a: Brown solid (1.10 g, 44%); mp: 101–103 °C; ^{1}H NMR ($CDCl_3$): δ = 4.01 (s, 3H), 6.53 (m, 1H), 7.21 (t, 1H, ^3J = 3.2 Hz), 7.35–7.48 (m, 6H), 7.54 (dd, 1H, ^3J = 8.2 Hz, ^4J = 1.8 Hz), 7.62 (s, 1H), 8.23 ppm (br s, 1H); MS *m/z* 251.2 $[M+H]^+$; Anal. calcd for $C_{16}H_{14}N_2O$: C 76.78, H 5.64, N 11.19, found: C 76.65, H 5.71, N 11.25.

5-{[(*Z*)-Methoxyimino]phenylmethyl}-1*H*-indole 19 b: Brown solid (0.95 g, 38%); mp: 113–115 °C; ^{1}H NMR ($CDCl_3$): δ = 4.03 (s, 3H), 6.59 (m, 1H), 7.25 (m, 2H), 7.35 (m, 3H), 7.46 (d, 1H, ^3J = 8.5 Hz), 7.54 (m, 2H), 7.68 (d, 1H, ^4J = 1.5 Hz), 8.28 ppm (br s, 1H); MS *m/z* 251.2 $[M+H]^+$; Anal. calcd for $C_{16}H_{14}N_2O$: C 76.78, H 5.64, N 11.19, found: C 76.67, H 5.54, N 11.31.

6-{[(*Z*/*E*)-Methoxyimino]phenylmethyl}-1*H*-indole 19 c: Brown solid (1.97 g, 79%); mp: 168–170 °C; ^{1}H NMR (DMSO): δ = 3.93 (m, 3H), 6.57 (m, 1H), 6.90 (m, 0.5H), 7.11 (m, 0.5H), 7.30–7.65 ppm (m, 8H); MS *m/z* 251.2 $[M+H]^+$; Anal. calcd for $C_{16}H_{14}N_2O$: C 76.78, H 5.64, N 11.19, found: C 76.71, H 5.70, N 11.12.

General procedure for the synthesis of optically pure carboxylic acids 20 a–c, 21 a–c: A solution of **19 a–c** (0.5 g, 2 mmol, 1 equiv) in HMPA (5 mL) was added dropwise to a 60% NaH dispersion in mineral oil (0.12 g, 3 mmol, 1.5 equiv) in HMPA (5 mL) at 0 °C under N_2, and the solution was stirred for 30 min at room temperature. A solution of **10 a** or **10 b** (0.66 g, 2.4 mmol, 1.2 equiv) in HMPA (5 mL) was then added, and the mixture was stirred at room temperature for 12 h under N_2. The reaction mixture was hydrolyzed with 1 M $HCl_{(aq)}$, and the precipitate was filtered off, dried and purified by flash column chromatography (CH_2Cl_2/MeOH 95:5) to afford the corresponding optically pure carboxylic acids **20 a–c** and **21 a–c**.

(*S*)-2-Ethoxy-3-{4-[2-(5-{[*E*]-methoxyimino]phenylmethyl}indol-1-yl)ethoxy]phenyl}propionic acid 20 a: White solid (0.46 g, 47%); mp: 43–46 °C; ^{1}H NMR ($CDCl_3$): δ = 1.19 (t, 3H, ^3J = 7.0 Hz), 2.95 (dd, 1H, ^3J = 14.0 Hz, ^3J = 7.0 Hz), 3.08 (dd, 1H, ^3J = 14.0 Hz, ^3J = 7.0 Hz), 3.48 (m, 1H), 3.58 (m, 1H), 4.01 (s, 3H), 4.05 (dd, 1H, ^3J = 7.0 Hz), 4.28 (t, 2H, ^3J = 5.6 Hz), 4.52 (t, 2H, ^3J = 5.6 Hz), 6.48 (d, 1H, ^3J = 3.2 Hz), 6.76 (d, 2H, ^3J = 8.8 Hz), 7.13 (d, 2H, ^3J = 8.8 Hz), 7.22 (d, 1H, ^3J = 3.2 Hz), 7.34–7.47 (m, 6H), 7.56 ppm (m, 2H); LC–MS: t_R = 4.36 min (95%), *m/z* 487.1 $[M+H]^+$; Anal. calcd for $C_{29}H_{30}N_2O_5$: C 71.59, H 6.21, N 5.76, found: C 71.45, H 6.30, N 5.69; Chiral HPLC method: flow rate = 0.8 mL min^{-1}, eluents = C/D 50:50, t_R = 8.92 min.

(*S*)-2-Ethoxy-3-{4-[2-(5-{[*Z*]-methoxyimino]phenylmethyl}indol-1-yl)ethoxy]phenyl}propionic acid 20 b: White solid (0.52 g, 54%); mp: 50–52 °C; ^{1}H NMR ($CDCl_3$): δ = 1.18 (t, 3H, ^3J = 7.0 Hz), 2.95 (dd, 1H, ^3J = 14.0 Hz, ^3J = 7.0 Hz), 3.08 (dd, 1H, ^3J = 14.0 Hz, ^3J = 7.0 Hz), 3.46 (m, 1H), 3.62 (m, 1H), 4.04 (m, 4H), 4.29 (t, 2H, ^3J = 5.3 Hz), 4.54 (t, 2H, ^3J = 5.3 Hz), 6.55 (d, 1H, ^3J = 2.9 Hz), 6.81 (d, 2H, ^3J = 8.8 Hz), 7.17 (d, 2H, ^3J = 8.8 Hz), 7.25–7.38 (m, 5H), 7.46 (d, 1H, ^3J = 8.8 Hz), 7.54 (dd, 2H, ^3J = 7.9 Hz, ^4J = 1.75 Hz), 7.68 ppm (s, 1H); LC–MS: t_R = 4.43 min (97%), *m/z* 487.2 $[M+H]^+$; Anal. calcd for $C_{29}H_{30}N_2O_5$: C 71.59, H 6.21, N 5.76, found: C 71.51, H 6.36, N 5.67; Chiral HPLC method: flow rate = 0.8 mL min^{-1}, eluents = C/D 50:50, t_R = 6.63 min.

(*S*)-2-Ethoxy-3-{4-[2-(6-{[*Z*/*E*]-methoxyimino]phenylmethyl}indol-1-yl)ethoxy]phenyl}propionic acid 20 c: White solid (0.61 g, 63%); mp: 104–105 °C; ^{1}H NMR (DMSO): δ = 1.02 (m, 3H), 2.81 (m, 2H), 3.28 (m, 1H), 3.49 (m, 1H), 3.90 (m, 4H), 4.21 (m, 2H), 4.51 (m, 2H), 6.59 (m, 1H), 6.71 (m, 2H), 6.92 (m, 0.4H), 7.09 (m, 2.6H), 7.28–7.63 ppm (m, 8H); LC–MS: t_R = 4.30 and 4.33 min (59 and 38%), *m/z* 487.2 $[M+H]^+$; Anal. calcd for $C_{29}H_{30}N_2O_5$: C 71.59, H 6.21, N 5.76, found: C 71.47, H 6.15, N 5.82; Chiral HPLC method: flow rate = 1.0 mL min^{-1}, eluents = A/B 10:90, t_R = 16.21 min (40%) and 22.32 min (60%).

(*R*)-2-Ethoxy-3-{4-[2-(5-{[*E*]-methoxyimino]phenylmethyl}indol-1-yl)ethoxy]phenyl}propionic acid 21 a: White solid (0.59 g, 61%); mp: 43–46 °C; ^{1}H NMR ($CDCl_3$): δ = 1.19 (t, 3H, ^3J = 7.0 Hz), 2.95 (dd, 1H, ^3J = 14.0 Hz, ^3J = 7.0 Hz), 3.08 (dd, 1H, ^3J = 14.0 Hz, ^3J = 7.0 Hz), 3.48 (m, 1H), 3.58 (m, 1H), 4.01 (s, 3H), 4.05 (dd, 1H, ^3J = 7.0 Hz), 4.28 (t, 2H, ^3J = 5.6 Hz), 4.52 (t, 2H, ^3J = 5.6 Hz), 6.48 (d, 1H, = 3.2 Hz), 6.76 (d, 2H, ^3J = 8.8 Hz), 7.13 (d, 2H, ^3J = 8.8 Hz), 7.22 (d, ^3J 1H, ^3J = 3.2 Hz), 7.34–7.47 (m, 6H), 7.56 ppm (m, 2H); LC–MS: t_R = 4.36 min (96%), *m/z* 487.1 $[M+H]^+$; Anal. calcd for $C_{29}H_{30}N_2O_5$: C 71.59, H 6.21, N 5.76, found: C 71.52, H 6.15, N 5.69; Chiral HPLC method: flow rate = 0.8 mL min^{-1}, eluents = C/D 50:50, t_R = 11.22 min.

(*R*)-2-Ethoxy-3-{4-[2-(5-{[*Z*]-methoxyimino]phenylmethyl}indol-1-yl)ethoxy]phenyl}propionic acid 21 b: White solid (0.57 g, 59%); mp: 50–52 °C; ^{1}H NMR ($CDCl_3$): δ = 1.18 (t, 3H, ^3J = 7.0 Hz), 2.95 (dd, 1H, ^3J = 14.0 Hz, ^3J = 7.0 Hz), 3.08 (dd, 1H, ^3J = 14.0 Hz, ^3J = 7.0 Hz), 3.46 (m, 1H), 3.62 (m, 1H), 4.04 (m, 4H), 4.29 (t, 2H, ^3J = 5.3 Hz), 4.54 (t, 2H, ^3J = 5.3 Hz), 6.55 (d, 1H, ^3J = 2.9 Hz), 6.81 (d, 2H, ^3J = 8.8 Hz), 7.17 (d, 2H, ^3J = 8.8 Hz), 7.25–7.38 (m, 5H), 7.46 (d, 1H, ^3J = 8.8 Hz), 7.54 (dd, 2H, ^3J = 7.9 Hz, ^4J = 1.75 Hz), 7.68 ppm (s, 1H); LC–MS: t_R = 4.43 min (94%), *m/z* 487.1 $[M+H]^+$; Anal. calcd for $C_{29}H_{30}N_2O_5$: C 71.59, H 6.21, N 5.76, found: C 71.70, H 6.14, N 5.70; Chiral HPLC method: flow rate = 0.8 mL min^{-1}, eluents = C/D 50:50, t_R = 6.94 min.

(*R*)-2-Ethoxy-3-{4-[2-(6-{[*Z*/*E*]-methoxyimino]phenylmethyl}indol-1-yl)ethoxy]phenyl}propionic acid 21 c: White solid (0.52 g, 54%); mp: 104–105 °C; ^{1}H NMR (DMSO): δ = 1.02 (m, 3H), 2.81 (m, 2H), 3.28 (m, 1H), 3.49 (m, 1H), 3.90 (m, 4H), 4.21 (m, 2H), 4.51 (m, 2H), 6.59 (m, 1H), 6.71 (m, 2H), 6.92 (m, 0.4H), 7.09 (m, 2.6H), 7.28–7.63 ppm (m, 8H); LC–MS: t_R = 4.30 and 4.33 min (60 and 37%), *m/z* 487.2 $[M+H]^+$; Anal. calcd for $C_{29}H_{30}N_2O_5$: C 71.59, H 6.21, N 5.76, found: C 71.47, H 6.15, N 5.82; Chiral HPLC method: flow rate = 1.0 mL min^{-1}, eluents = A/B 20:80, t_R = 7.09 min (40%) and 8.43 min (60%).

General procedure for the synthesis of oxime ethers 24 a–d: *O*-Substituted hydroxylamine hydrochloride (10 mmol, 2 equiv) and

pyridine (0.60 mL, 15 mmol, 3 equiv) were added to a solution of **23** (2.11 g, 5 mmol, 1 equiv) in MeOH (60 mL), and the mixture was stirred at reflux for 4 h. The reaction mixture was concentrated in vacuo, hydrolyzed with 1 N $HCl_{(aq)}$, and extracted twice with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered off, evaporated under reduced pressure, and the resulting residue was purified by flash column chromatography (cyclohexane/EtOAc 80:20) to afford the corresponding *E* isomers of oxime ethers **24a–d**.

Ethyl 2-ethoxy-3-{4-[2-(5-{1-[*E*]-phenoxyimino]ethyl}indol-1-yl)ethoxy]phenyl}propionate 24a: Colorless oil (2.39 g, 93%); ^{1}H NMR ($CDCl_3$): δ = 1.18 (t, 3H, ^3J = 7.0 Hz), 1.24 (t, 3H, ^3J = 7.0 Hz), 2.56 (s, 3H), 2.96 (m, 2H), 3.33 (m, 1H), 3.60 (m, 1H), 3.96 (t, 1H, ^3J = 6.3 Hz), 4.18 (q, 2H, ^3J = 7.0 Hz), 4.29 (t, 2H, ^3J = 5.7 Hz), 4.55 (t, 2H, ^3J = 5.7 Hz), 6.59 (d, 1H, ^3J = 3.1 Hz), 6.78 (d, 2H, ^3J = 8.3 Hz), 7.05 (m, 2H), 7.15 (m, 3H), 7.31 (m, 3H), 7.45 (d, 1H, ^3J = 8.7 Hz), 7.81 (d, 1H, ^3J = 8.7 Hz), 8.02 ppm (s, 1H); MS *m/z* 515.2 $[M+H]^+$; Anal. calcd for $C_{31}H_{34}N_2O_5$: C 72.35, H 6.66, N 5.44, found: C 72.19, H 6.75, N 5.39.

Ethyl 2-ethoxy-3-{4-[2-(5-{1-[*E*]-benzyloxyimino]ethyl}indol-1-yl)ethoxy]phenyl}propionate 24b: Colorless oil (2.33 g, 91%); ^{1}H NMR ($CDCl_3$): δ = 1.17 (t, 3H, ^3J = 7.0 Hz), 1.24 (t, 3H, ^3J = 7.0 Hz), 2.38 (s, 3H), 2.95 (m, 2H), 3.35 (m, 1H), 3.60 (m, 1H), 3.96 (t, 1H, ^3J = 5.8 Hz), 4.18 (q, 2H, ^3J = 7.0 Hz), 4.27 (t, 2H, ^3J = 5.7 Hz), 4.52 (t, 2H, ^3J = 5.7 Hz), 5.29 (s, 2H), 6.55 (d, 1H, ^3J = 2.9 Hz), 6.78 (d, 2H, ^3J = 8.1 Hz), 7.14 (d, 2H, ^3J = 8.1 Hz), 7.24 (d, 1H, ^3J = 2.9 Hz), 7.31–7.44 (m, 4H), 7.47 (d, 2H, ^3J = 7.3 Hz), 7.66 (dd, 1H, ^3J = 8.7 Hz, ^4J = 1.75 Hz), 7.88 ppm (d, 1H, ^4J = 1.75 Hz); MS *m/z* 515.2 $[M+H]^+$; Anal. calcd for $C_{32}H_{36}N_2O_5$: C 72.70, H 6.86, N 5.30, found: C 72.61, H 6.75, N 5.41.

Ethyl 2-ethoxy-3-{4-[2-(5-{1-[*E*]-cyclopropylmethoxyimino]ethyl}indol-1-yl)ethoxy]phenyl}propionate 24c: Colorless oil (2.14 g, 87%); ^{1}H NMR ($CDCl_3$): δ = 0.36 (m, 2H), 0.60 (m, 2H), 1.17 (t, 3H, ^3J = 7.0 Hz), 1.23 (m, 4H), 2.38 (s, 3H), 2.95 (m, 2H), 3.35 (m, 1H), 3.60 (m, 1H), 3.95 (t, 1H, ^3J = 7.3 Hz), 4.06 (d, 2H, ^3J = 7.0 Hz), 4.18 (q, 2H, ^3J = 7.0 Hz), 4.27 (t, 2H, ^3J = 5.3 Hz), 4.52 (t, 2H, ^3J = 5.3 Hz), 6.54 (d, 1H, ^3J = 3.1 Hz), 6.78 (d, 2H, ^3J = 8.4 Hz), 7.13 (d, 2H, ^3J = 8.4 Hz), 7.22 (d, 1H, ^3J = 3.1 Hz), 7.39 (d, 2H, ^3J = 8.8 Hz), 7.67 (d, 1H, ^3J = 8.8 Hz), 7.88 ppm (s, 1H); MS *m/z* 493.1 $[M+H]^+$; Anal. calcd for $C_{29}H_{36}N_2O_5$: C 70.71, H 7.37, N 5.69, found: C 70.62, H 7.48, N 5.60.

Ethyl 2-ethoxy-3-{4-[2-(5-{1-[*E*]-cyclohexyloxyimino]ethyl}indol-1-yl)ethoxy]phenyl}propionate 24d: Colorless oil (2.36 g, 91%); ^{1}H NMR ($CDCl_3$): δ = 1.18 (t, 3H, ^3J = 7.0 Hz), 1.21–1.62 (m, 9H), 1.80 (m, 4H), 2.35 (s, 3H), 2.93 (m, 2H), 3.32 (m, 1H), 3.60 (m, 1H), 3.95 (t, 1H, ^3J = 6.9 Hz), 4.18 (m, 3H), 4.27 (t, 2H, ^3J = 5.5 Hz), 4.52 (t, 2H, ^3J = 5.5 Hz), 6.54 (d, 1H, ^3J = 3.2 Hz), 6.76 (d, 2H, ^3J = 8.2 Hz), 7.14 (d, 2H, ^3J = 8.2 Hz), 7.22 (d, 1H, ^3J = 3.2 Hz), 7.39 (d, 2H, ^3J = 8.6 Hz), 7.66 (d, 1H, ^3J = 8.6 Hz), 7.88 ppm (s, 1H); MS *m/z* 521.3 $[M+H]^+$; Anal. calcd for $C_{31}H_{40}N_2O_5$: C 71.51, H 7.74, N 5.38, found: C 71.63, H 7.68, N 5.47.

General procedure for the synthesis of carboxylic acids 25a–d: Compounds **24a–d** were treated according to the same procedure described for the preparation of **16a–e** and **18a–d**.

2-Ethoxy-3-{4-[2-(5-{1-[*E*]-phenoxyimino]ethyl}indol-1-yl)ethoxy]phenyl}propionic acid 25a: Off-white solid (0.74 g, 76%); mp: 87–89 °C; ^{1}H NMR (DMSO): δ = 1.02 (t, 3H, ^3J = 7.0 Hz), 2.50 (s, 3H), 2.81 (m, 2H), 3.26 (m, 1H), 3.48 (m, 1H), 3.92 (t, 1H, ^3J = 5.3 Hz), 4.28 (t, 2H, ^3J = 5.9 Hz), 4.59 (t, 2H, ^3J = 5.9 Hz), 6.55 (d, 1H, ^3J = 3.3 Hz), 6.79 (d, 2H, ^3J = 8.1 Hz), 7.03 (t, 1H, ^3J = 7.3 Hz), 7.11 (d, 1H, ^3J = 8.1 Hz), 7.28 (m, 2H), 7.36 (t, 2H, ^3J = 7.3 Hz), 7.50 (d, 1H, ^3J = 3.3 Hz), 7.63 (d, 1H, ^3J = 8.6 Hz), 7.70 (d, 1H, ^3J = 8.6 Hz), 8.01 ppm (s, 1H); LC–MS: t_R = 4.55 min (98%), *m/z* 487.1 $[M+H]^+$; Anal. calcd for $C_{29}H_{30}N_2O_5$: C 71.59, H 6.21, N 5.76, found: C 71.74, H 6.18, N 5.69.

2-Ethoxy-3-{4-[2-(5-{1-[*E*]-benzyloxyimino]ethyl}indol-1-yl)ethoxy]phenyl}propionic acid 25b: Off-white solid (0.79 g, 79%); mp: 72–74 °C; ^{1}H NMR (DMSO): δ = 1.02 (t, 3H, ^3J = 7.0 Hz), 2.29 (s, 3H), 2.81 (m, 2H), 3.27 (m, 1H), 3.49 (m, 1H), 3.92 (t, 1H, ^3J = 5.7 Hz), 4.27 (t, 2H, ^3J = 5.9 Hz), 4.59 (t, 2H, ^3J = 5.9 Hz), 5.20 (s, 2H), 6.51 (d, 1H, ^3J = 3.1 Hz), 6.78 (d, 2H, ^3J = 8.3 Hz), 7.10 (d, 1H, ^3J = 8.3 Hz), 7.27–7.49 (m, 6H), 7.54 (m, 2H), 7.82 ppm (s, 1H); LC–MS: t_R = 4.50 min (98%), *m/z* 501.2 $[M+H]^+$; Anal. calcd for $C_{30}H_{32}N_2O_5$: C 71.98, H 6.44, N 5.60, found: C 71.91, H 6.52, N 5.71.

2-Ethoxy-3-{4-[2-(5-{1-[*E*]-cyclopropylmethoxyimino]ethyl}indol-1-yl)ethoxy]phenyl}propionic acid 25c: Pasty solid (0.75 g, 81%); ^{1}H NMR ($CDCl_3$): δ = 0.38 (m, 2H), 0.60 (m, 2H), 1.27 (m, 4H), 2.39 (s, 3H), 3.0 (m, 2H), 3.51 (m, 2H), 4.05 (m, 3H), 4.25 (t, 2H, ^3J = 5.8 Hz), 4.52 (t, 2H, ^3J = 5.8 Hz), 6.55 (d, 1H, ^3J = 3.0 Hz), 6.76 (d, 2H, ^3J = 8.4 Hz), 7.13 (d, 2H, ^3J = 8.4 Hz), 7.22 (d, 1H, ^3J = 3.0 Hz), 7.35 (d, 2H, ^3J = 8.5 Hz), 7.64 (d, 1H, ^3J = 8.5 Hz), 7.86 ppm (s, 1H); LC–MS: t_R = 4.49 min (95%), *m/z* 465.2 $[M+H]^+$; Anal. calcd for $C_{27}H_{32}N_2O_5$: C 69.81, H 6.94, N 6.03, found: C 69.94, H 6.88, N 6.12.

2-Ethoxy-3-{4-[2-(5-{1-[*E*]-cyclohexyloxyimino]ethyl}indol-1-yl)ethoxy]phenyl}propionic acid 25d: Pasty solid (0.75 g, 76%); ^{1}H NMR ($CDCl_3$): δ = 1.18 (t, 3H, ^3J = 7.0 Hz), 1.25–1.62 (m, 6H), 1.78 (m, 2H), 2.04 (m, 2H), 2.32 (s, 3H), 2.93 (m, 1H), 3.05 (m, 1H), 3.41 (m, 1H), 3.59 (m, 1H), 4.01 (t, 1H, ^3J = 7.1 Hz), 4.22 (m, 3H), 4.50 (t, 2H, ^3J = 5.8 Hz), 6.53 (d, 1H, ^3J = 2.9 Hz), 6.76 (d, 2H, ^3J = 8.1 Hz), 7.13 (d, 2H, ^3J = 8.1 Hz), 7.22 (d, 1H, ^3J = 2.9 Hz), 7.36 (d, 2H, ^3J = 8.8 Hz), 7.63 (dd, 1H, ^3J = 8.8 Hz, ^4J = 1.75 Hz), 7.85 ppm (d, 1H, ^4J = 1.75 Hz); LC–MS: t_R = 4.46 min (94%), *m/z* 493.2 $[M+H]^+$; Anal. calcd for $C_{29}H_{36}N_2O_5$: C 70.71, H 7.37, N 5.69, found: C 70.59, H 7.45, N 5.62.

Synthesis of compounds 26a,b: Oxalyl chloride (8.2 mL, 93.4 mmol, 1.1 equiv) in 1,2-dichloroethane (170 mL) was added dropwise over a period of 15 min into a stirred, ice-cold solution of DMF (7.35 mL, 100.7 mmol, 1.15 equiv) in 1,2-dichloroethane (170 mL) under a N_2 atmosphere, and then the mixture was allowed to warm to room temperature for 15 min. The mixture was cooled to 0 °C, and a solution of indole (10 g, 85.4 mmol, 1.0 equiv) in 1,2-dichloroethane (170 mL) was added rapidly. The resulting mixture was warmed to room temperature for 15 min and then cooled. $AlCl_3$ (42 g, 315 mmol, 3.7 equiv) was added rapidly, and the mixture was allowed to warm to room temperature for 15 min. The mixture was cooled, and a solution of benzoyl chloride (13.32 g, 93.4 mmol, 1.1 equiv) in 1,2-dicloroethane (84 mL) was added rapidly, and the reaction was allowed to proceed overnight at room temperature. The reaction mixture was poured into ice/H_2O, alkalinized to pH 8 with solid NaOH and stirred vigorously for 4 h. Concentrated HCl was added (100 mL), and the resulting mixture was extracted twice with CH_2Cl_2. The combined extracts were washed with brine, dried over $MgSO_4$, filtered off and evaporated under reduced pressure. The residue was purified by flash column chromatography (PE/EtOAc 65:35) to afford the two regioisomers **26a,b**.

5-Benzoyl-1*H*-indole-3-carboxaldehyde 26a: Pale-brown solid (11.91 g, 56%); mp: 198–200 °C; ^{1}H NMR (DMSO): δ = 7.58 (t, 2H, ^3J = 7.6 Hz), 7.63–7.78 (m, 5H), 8.49 (d, 2H, ^3J = 7.6 Hz), 9.98 (s, 1H), 12.50 ppm (br s, 1H); MS *m/z* 250.2 $[M+H]^+$.

6-Benzoyl-1*H*-indole-3-carboxaldehyde 26b: White needles (4.89 g, 23%); mp: 166–168 °C; ^{1}H NMR (DMSO): δ = 7.58 (t, 2H, ^3J = 7.3 Hz), 7.62–7.80 (m, 4H), 7.91 (s, 1H), 8.23 (d, 1H, ^3J = 8.2 Hz), 8.53 (d, 1H, ^4J = 2.6 Hz), 10.01 (s, 1H), 12.42 ppm (br s, 1H); MS *m/z* 250.2 $[M+H]^+$.

Synthesis of compounds 27a,b: Compounds **26a,b** were treated according to the same procedure described for the preparation of **15a–e** and **23**. The crude products were purified by flash column chromatography (toluene/EtOAc 75:25) to afford the corresponding N-alkylated indole derivatives.

Ethyl 3-{4-[2-(5-benzoyl-3-formylindol-1-yl)ethoxy]phenyl}-2-ethoxypropionate 27a: Colorless oil (1.95 g, 76%); ^{1}H NMR ($CDCl_3$): δ = 1.15 (t, 3H, ^3J = 6.8 Hz), 1.23 (t, 3H, ^3J = 7.3 Hz), 2.96 (m, 2H), 3.34 (m, 1H), 3.60 (m, 1H), 3.96 (t, 1H, ^3J = 6.5 Hz), 4.18 (q, 2H, ^3J = 6.8 Hz), 4.36 (t, 2H, ^3J = 6.2 Hz), 4.65 (t, 2H, ^3J = 6.2 Hz), 6.77 (d, 2H, ^3J = 8.4 Hz), 7.17 (d, 2H, ^3J = 8.4 Hz), 7.47–7.63 (m, 4H), 7.84 (d, 2H, ^3J = 7.5 Hz), 7.97 (m, 2H), 8.72 (s, 1H), 10.05 ppm (s, 1H); MS *m/z* 514.3 $[M+H]^+$; Anal. calcd for $C_{31}H_{31}NO_6$: C 72.50, H 6.08, N 2.73, found: C 72.41, H 6.17, N 2.79.

Ethyl 3-{4-[2-(6-benzoyl-3-formylindol-1-yl)ethoxy]phenyl}-2-ethoxypropionate 27b: Colorless oil (1.72 g, 67%); ^{1}H NMR ($CDCl_3$): δ = 1.16 (t, 3H, ^3J = 7.2 Hz), 1.23 (t, 3H, ^3J = 7.3 Hz), 2.95 (m, 2H), 3.33 (m, 1H), 3.59 (m, 1H), 3.95 (t, 1H, ^3J = 6.2 Hz), 4.18 (q, 2H, ^3J = 7.2 Hz), 4.35 (t, 2H, ^3J = 6.5 Hz), 4.65 (t, 2H, ^3J = 6.5 Hz), 6.78 (d, 2H, ^3J = 8.3 Hz), 7.16 (d, 2H, ^3J = 8.3 Hz), 7.52 (t, 2H, ^3J = 7.6 Hz), 7.62 (t, 1H, ^3J = 7.6 Hz), 7.74 (d, 1H, ^3J = 8.5 Hz), 7.82 (d, 2H, ^3J = 7.6 Hz), 8.08 (m, 2H), 8.38 (d, 1H, ^3J = 8.5 Hz), 10.08 ppm (s, 1H); MS *m/z* 514.2 $[M+H]^+$; Anal. calcd for $C_{31}H_{31}NO_6$: C 72.50, H 6.08, N 2.73, found: C 72.64, H 6.16, N 2.62.

Synthesis of compounds 28a,b: Compounds **27a,b** were treated according to the same procedure described for the preparation of **24a–d**. The crude products were purified by flash column chromatography (PE/EtOAc 70:30) to afford the corresponding oxime derivatives.

Ethyl 2-ethoxy-3-{4-[2-(3-[*E*]-methoxyiminomethyl-5-{[*Z*/*E*]-methoxyimino]phenylmethyl}indol-1-yl)ethoxy]phenyl}propionate 28a: Colorless oil (2.37 g, 83%); ^{1}H NMR ($CDCl_3$): δ = 1.18 (m, 3H), 1.24 (m, 3H), 2.94 (m, 2H), 3.32 (m, 1H), 3.60 (m, 1H), 3.82–3.99 (m, 4H), 4.01–4.12 (m,3H), 4.18 (m, 2H), 4.28 (m, 2H), 4.54 (m, 2H), 6.78 (m, 2H), 7.15 (m, 2H), 7.31–7.68 (m, 9H), 8.22 ppm (m, 1H); MS *m/z* 572.2 $[M+H]^+$; Anal. calcd for $C_{33}H_{37}N_3O_6$: C 69.33, H 6.52, N 7.35, found: C 69.21, H 6.62, N 7.40.

Ethyl 2-ethoxy-3-{4-[2-(3-[*E*]-methoxyiminomethyl-6-{[*Z*/*E*]-methoxyimino]phenylmethyl}indol-1-yl)ethoxy]phenyl}propionate 28b: Colorless oil (2.22 g, 78%); ^{1}H NMR ($CDCl_3$): δ = 1.17 (m, 3H), 1.25 (m, 3H), 2.94 (m, 2H), 3.33 (m, 1H), 3.61 (m, 1H), 3.92–4.04 (m, 7H), 4.15 (m, 2H), 4.25 (m, 2H), 4.49 (m, 2H), 6.74 (m, 2H), 7.13 (m, 2H), 7.20–7.62 (m, 8H), 8.09 (d, 0.5H, ^3J = 8.1 Hz) 8.27 ppm (m, 1.5H); MS *m/z* 572.3 $[M+H]^+$; Anal. calcd for $C_{33}H_{37}N_3O_6$: C 69.33, H 6.52, N 7.35, found: C 69.18, H 6.58, N 7.24.

Synthesis of compounds 29a,b: Compounds **28a,b** were treated according to the same procedure described for the preparation of **16a–e** and **18a–d**.

2-Ethoxy-3-{4-[2-(3-[*E*]-methoxyiminomethyl-5-{[*Z*/*E*]-methoxyimino]phenylmethyl}indol-1-yl)ethoxy]phenyl}propionic acid 29a: White foam (0.74 g, 69%); mp: 68–70 °C; ^{1}H NMR (DMSO): δ = 1.02 (m, 3H), 2.82 (m, 2H), 3.29 (m, 1H), 3.51 (m, 1H), 3.72 (m, 3H), 3.91 (m, 4H), 4.31 (m, 2H), 4.62 (m, 2H), 6.81 (m, 2H), 7.15 (m, 2H), 7.28–7.52 (m, 6H), 7.69 (m, 1H), 7.90 (m, 2H), 8.32 (m, 1H), 12.65 (br s, 1H); LC–MS: t_R = 4.27 and 4.37 min (47 and 49%), *m/z* 544.1 $[M+H]^+$; Anal. calcd for $C_{31}H_{33}N_3O_6$: C 68.49, H 6.12, N 7.73, found: C 68.56, H 6.01, N 7.62.

2-Ethoxy-3-{4-[2-(3-[*E*]-methoxyiminomethyl-6-{[*Z*/*E*]-methoxyimino]phenylmethyl}indol-1-yl)ethoxy]phenyl}propionic acid 29b: Pale-yellow foam (0.80 g, 74%); mp: 53–56 °C; ^{1}H NMR (DMSO): δ = 1.01 (m, 3H), 2.79 (m, 2H), 3.24 (m, 1H), 3.47 (m, 1H), 3.80–4.01 (7H), 4.22 (m, 2H), 4.60 (m, 2H), 6.69 (m, 2H), 7.08 (m, 2H), 7.30–7.50 (m, 6H), 7.59 (m, 1H), 7.84 (m, 1H), 7.95 (m, 0.5H), 8.05 (m, 0.5H), 8.36 (m, 1H), 12.54 (br s, 1H); LC–MS: t_R = 4.17 and 4.31 min (48 and 49%), MS *m/z* 544.2 $[M+H]^+$; Anal. calcd for $C_{31}H_{33}N_3O_6$: C 68.49, H 6.12, N 7.73, found: C 68.36, H 6.22, N 7.60.

Docking

Molecular modeling studies were performed with SYBYL 6.9.1 running on SGI Octane 2 workstations. The geometry of S73362 was subsequently optimized using the Tripos force field[28] including the electrostatic term calculated from Gasteiger–Hückel atomic charges. The method of Powell, available in the Maximin2 procedure, was used for energy minimization until the gradient value was < 0.001 kcal mol^{-1} Å^{-1}. The crystallographic data for PPARα and γ were retrieved from the RCSB Protein Data Bank (PDB) with particular concern for the structural proximity of the co-crystallized ligand and S73362. We therefore chose PDB codes 3FEI[29] for PPARα and 1KNU[30] for PPARγ. S73362 was docked using GOLD 3.2[31] in both receptors, and the consistency of the 30 solutions generated was assessed before selecting the most representative.

In vitro assays

Membrane-bound PPARγ binding assay: Binding assays were performed in 96-well plate format using a classical filtration assay with a human full-length PPARγ construct [GST–PPAR LBD (25 μg mL^{-1})] expressed in bacteria with some modifications regarding the conditions of the experiments. Membrane-associated PPARγ was used as the biological source as previously described. Binding buffer consisted of 10 mM Tris·HCl (pH 8.2) containing 50 mM KCl and 1 mM dithiothreitol. Membrane preparations (5 μg mL^{-1}) were incubated for 180 min at 4 °C in the presence of [^{3}H]rosiglitazone [BRL49653, Amersham] (4 nM) and the tested compounds. Nonspecific binding was defined by using excess unlabeled rosiglitazone (10 μM). Incubation was terminated by the addition of ice-cold 50 mM Tris·HCl buffer (pH 7.4) followed by rapid filtration under reduced pressure through Whatman GF/C filter plates presoaked with ice-cold buffer, followed by three successive washes with the same buffer. Radioactivity was measured in a TopCount apparatus (Packard). The receptor preparation used during these experiments gave a B_{max} value of 49 pmol (mg protein)$^{-1}$ and a K_d value of 5.58 nM for [^{3}H]rosiglitazone. The compounds were solubilized in pure DMSO and diluted to the appropriate working concentrations (100 μM to 0.1 nM). For each compound tested, plots of ligand concentration versus DPM of radioligand bound were constructed, and apparent K_i values were estimated from nonlinear least-squares fit of the data, assuming simple competitive binding. The details of this assay have been reported previously.[32]

Gene reporter assays: cell culture and transfection: Cos-7 cells were transiently transfected with luciferase reporter plasmid (pG5-TK-pGL3) in the presence of pGal4–hPPARγ expression vector; this vector expresses chimeric proteins containing the Gal4 DNA binding domain fused to the human PPARγ LBD coding sequence. Plas-

mids pGal4–hPPARγ and pG5-TK-pGL3 were constructed as described previously.[33] Cells were seeded in ∅ = 60 mm dishes at a density of 5.5×10^5 cells per dish in DMEM supplemented with 10% FCS and incubated at 37 °C for 24 h prior to transfection. Cells were transfected in OptiMEM without FCS for 3 h at 37 °C using polyethylenimine (PEI) with reporter and expression plasmids. The plasmid pBluescript (Stratagene, La Jolla, CA, USA) was used as carrier DNA to set the final amount of DNA to 5.5 μg per dish. The pCMV-β-galactosidase expression plasmid was co-transfected as a control for transfection efficiency. Transfection was stopped by the addition of DMEM supplemented with 10% FCS, and cells were then incubated at 37 °C. After 16 h, cells were trypsinized and seeded in 96-well plates at a density of 2×10^4 cells per well and incubated for 6 h in DMEM containing 10% FCS. Cells were then incubated for 24 h in DMEM containing 0.2% FCS and various concentrations of test compound or vehicle (DMSO). At the end of the experiment, cells were washed once with ice-cold PBS, and luciferase and β-galactosidase assays were performed as described previously.[34] Cells were incubated for 24 h in the presence of indicated concentrations of compound. Luciferase activity was measured and normalized to internal control β-galactosidase activity. Compounds that elicited, on average, at least 80% activation of PPARα or PPARγ versus WY 14,643 or rosiglitazone, respectively, (positive controls) were considered full agonists. EC_{50} values were estimated using GraphPad Prism software. All transfection experiments were performed at least three times.

In vivo models

The glucose- and triglyceride-lowering activities of the compounds prepared were then tested using 10–12-week-old male *ob*/*ob* mice. The mice were housed in a temperature-controlled room (21.8–24.0 °C) at a relative humidity of 45–65%, and a 12 h light–dark cycle (light period 5:30–17:30). Mice had access to filtered (0.22 μm) tap water ad libitum and irradiated pelleted laboratory chow (transbreed, Special Diet Services, England) throughout the study. Compounds were prepared as a suspension in 1% hydroxyethylcellulose (HEC) for oral administration (10 mL kg^{-1}). The mice (n = 8–12 per group) were dosed by gavage daily between 15:00 and 17:00 for four days. Randomization was performed based on glycemia values. The body weight gain (ΔBW in grams) of the animals was determined by measuring the difference between body weight at the beginning and end of the study for each mouse. At day 5 between 9:00 and 11:00 the mice were weighed, and blood samples were collected into heparin-containing tubes by retro-orbital puncture (500 μL per mouse). All procedures complied with International European Ethical Standards (86/609-EEC), the French National Committee (décret 87/848) for the care and use of laboratory animals and were approved by our institutional ethical committee. Plasma samples were prepared by centrifugation (2000 *g* for 10 min), and stored at −20 °C. For triglycerides and insulin determination, the percent change in plasma level in the treated group was calculated relative to the mean plasma level in the vehicle-treated group. ANOVA, followed by Dunnett's comparison test (one-tailed) was used to estimate significant differences between the plasma glycemia, triglycerides, insulin, and ΔBW values between the control group and the individual compound-treated groups. The compound is considered active at the specific dosage administered if the difference in plasma levels has $p < 0.05$; all compounds with $p > 0.05$ were reported as inactive.

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Keywords: 2-ethoxypropionic acid · diabetes · docking · drug design · PPAR

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