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Design, synthesis, and evaluation of non-steroidal farnesoid X receptor (FXR) antagonist

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Abstract—A series of substituted-isoxazole derivatives was prepared as candidate farnesoid X receptor (FXR) antagonists, based on our previously proposed ligand superfamily concept. Structure–activity relationship studies indicated that the shape and the structural bulkiness of the substituent at the 5-position of the isoxazole ring affected FXR-antagonistic activity. Compounds **15g** (5-substituent: 2-naphthyl) and **15h** (5-substituent: 4-biphenyl) were identified as potent antagonists with higher selectivity for FXR over progesterone receptor than the naturally occurring FXR antagonist GS. The 5-substituent is also a critical determinant of the characteristic corepressor recruitment profile of this class of FXR antagonists, though distinct mechanisms appear to be involved: **15h** stabilizes the corepressor-nuclear receptor interaction, while **15g** inhibits coactivator recruitment.

1. Introduction

Nuclear receptors (NRs) are ligand-dependent transcription factors that control many biological functions, such as cell growth, differentiation, embryonic development, and metabolism. Upon activation by binding of small lipophilic molecules, such as steroids and thyroid hormones, retinoids, vitamin D, and dietary and endogenous lipids, NRs interact with coactivators to modulate directly the expression of responsive genes involved in development, reproduction, and metabolism.[1–3] Pharmaceutical control of the activity of NRs with synthetic ligands having agonistic or antagonistic activity is a powerful tool for the management of various clinical conditions, including several forms of cancer, type 2 diabetes, and metabolic syndrome.[4,5]

To date, 48 human nuclear receptors have been identified, but about a third of them have no characterized ligands. Recently, attention has been focused on the NR1H and NR1I subfamilies of the nuclear receptors, because of the increasing incidence of metabolic syndrome and the role of these receptors in the control of cholesterol and bile acid metabolism. These receptors include the farnesoid X receptor (FXR).

FXR is activated by cholesterol metabolism end-products, bile acid derivatives, such as primary bile acids and secondary bile acids, and synthetic ligands.[6,7] Primary bile acids include chenodeoxycholic acid (CDCA) and cholic acid (CA), while secondary bile acids include deoxycholic acid (DC) and lithocholic acid (LCA). FXR is mainly expressed in the liver, intestine, and kidney. It heterodimerizes with another nuclear receptor, retinoid X receptor (RXR), and the heterodimer regulates gene expression by binding to a specific consensus DNA sequence, termed farnesoid X responsive element (FXRE), which is an inverted repeat of the hexameric AGGTCA recognition motif separated by single nucleotide (IR-1), located in the promoter region of FXR target genes.[8]

FXR regulates the expression of genes encoding proteins involved in cholesterol homeostasis. It regulates genes for proteins involved in bile acid biosynthesis (CYP7A1[9] and CYP8B1,[10]) transport and disposition (BSEP,[11] IBABP,[12] and NTCP.[13]) That is, FXR regulates the expression of small heterodimer partner (SHP).[14] SHP attenuates the expression of CYP7A1 by inhibiting the activity of liver receptor homologue 1 (LRH-1), which is known to augment CYP7A1 expression.[14] FXR also

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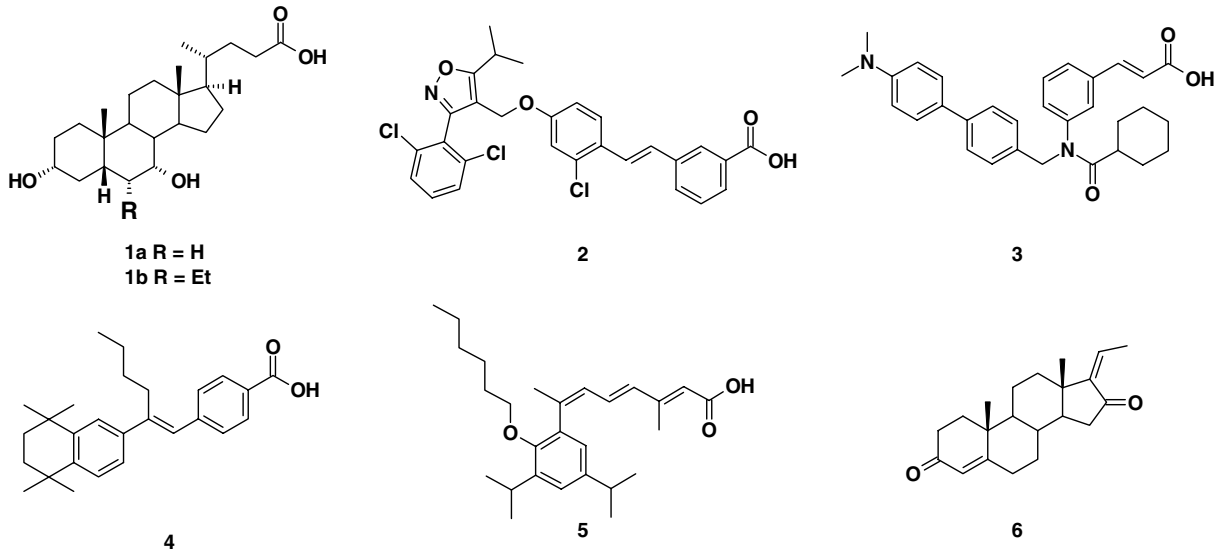


Figure 1. Structures of FXR agonists. CDCA (**1a**), 6-ECDCA (**1b**), GW-4064 (**2**), fexeramine (**3**), and AGN-31 (**4**), FXR antagonists AGN-34 (**5**), and guggulsterone (GS) (**6**).

decreases the expression of CYP8B1, which is the enzyme catalyzing hydroxylation of CDCA at the 12α-position to produce CA. FXR induces bile salt export pump (BSEP), which transports bile acids from hepatocytes to bile canaliculi, and induces the expression of the intestinal bile acid binding protein (IBABP), which shuttles bile acids from the apical to the basolateral side of the enterocytes during their absorption. It down-regulates the expression of Na^+ taurocholate cotransporting polypeptide (NCTP), which takes up bile salts into the liver after intestinal absorption.

After deorphanization of FXR in 1999,[15–17] extensive studies were directed to the creation of FXR ligands able to modulate FXR-mediated specific gene expression, and several steroidal- and non-steroidal FXR ligands have been reported (Fig. 1).[18–23] Most of the reports deal with FXR agonists (**1a**, **1b**, **2**, **3**, and **4**), and few FXR antagonists have been found so far (**5** and **6**).

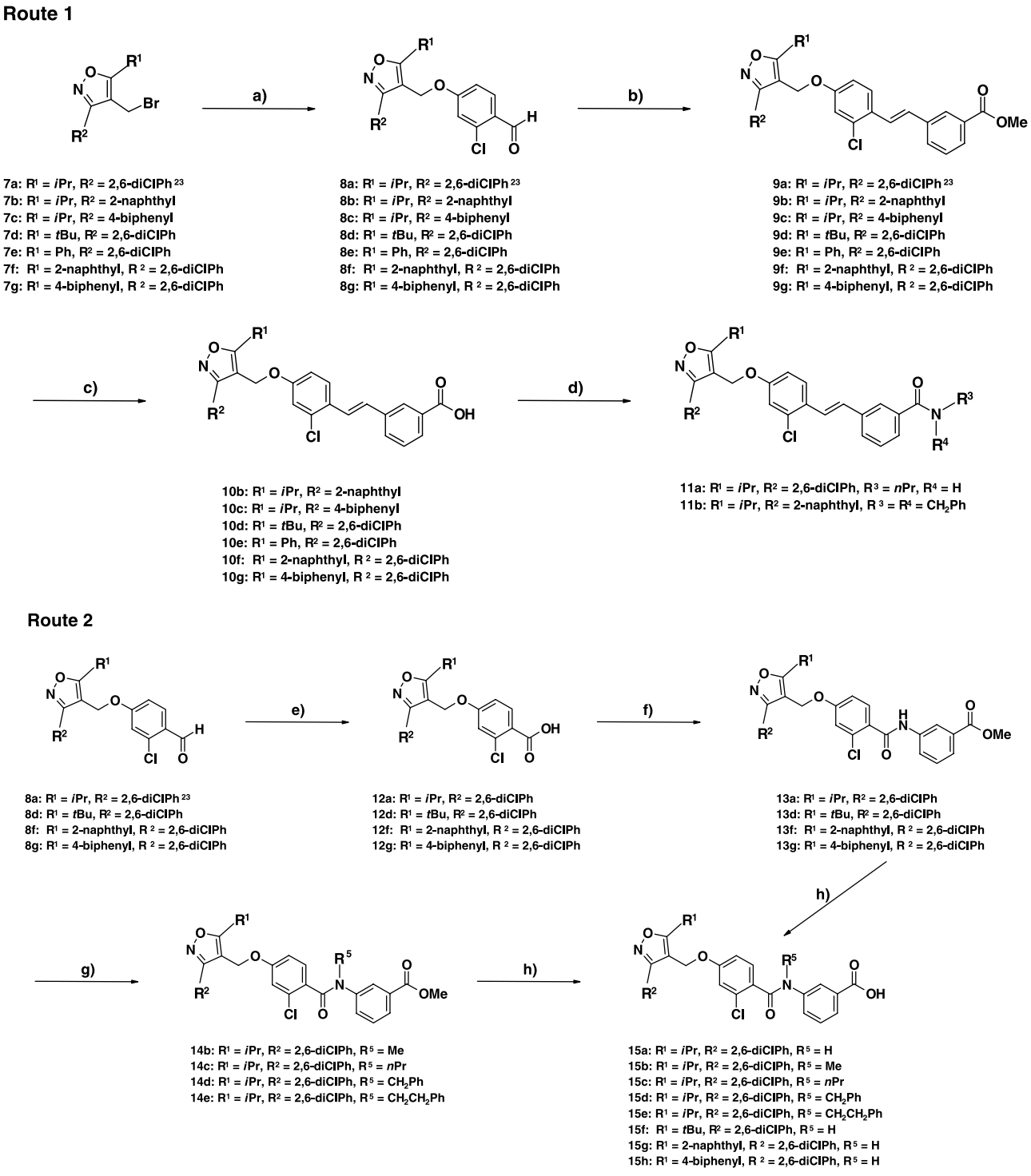
We have been engaged in structural development studies of NR ligands (agonists and antagonists), based on the NR ligand superfamily concept.[24] We hypothesize that the structural/functional features of NRs (48 NRs in humans) are broadly similar, that is, NRs generally consist of an N-terminal region with a ligand-independent transcriptional activation function (AF-1), a DNA-binding domain (DBD) with two zinc finger motifs that have a sequence-specific DNA-binding function, and a large C-terminal region (ligand-binding domain: LBD) with a specific ligand-binding function/dimerization function/ligand-dependent activation function (AF-2).[25–27] It is thought that NRs evolved from one ancestral protein to accommodate a variety of endogenous NR ligands. We speculate that a similar process has occurred in the case of NR ligands. That is, NR ligands may have evolved from an ancestral ligand, and therefore can be considered as a superfamily, even though their functions are diverse. Based on this working hypothesis, the structure of NR ligands can be divided into two portions. One is a common hydrophobic framework that fits into the ligand-binding pocket, and the other is a characteristic structural motif that provides NR selectivity. Therefore, we consider that the hydrophobic backbones of various NR ligands may be mutually exchangable. This working hypothesis also implies that the structural features of some NR antagonists can be adopted for the creation of other classes of NR antagonists.

As a part of our continuing research directed toward the creation of novel nuclear receptor antagonists based on the NR ligand superfamily concept, we report here novel FXR antagonists, developed by using GW-4064, the first reported potent FXR agonist with high NRs selectivity, as a lead template.

2. Chemistry

Synthetic routes to the present series of the compounds are outlined in Scheme 1. Substituted isoxazoles (**7a**–**7g**), which were prepared by the method described in the literature,[23] were reacted with 2-chloro-4-hydroxybenzaldehyde. The resulting aldehydes **8a**–**8g** were subjected to Horner–Emmons reaction to afford the stilbene derivatives **9a**–**9g**. Saponification of the ester yielded carboxylic acid derivatives **10b**–**10g** and subsequent amidation afforded the amide derivatives **11a**–**11b**. Compounds **8a**, **8d**, **8f**, and **8g** were also oxidized to the carboxylic acids **12a**, **12d**, **12f**, and **12g**, which were condensed with ethyl 3-aminobenzoate to afford the amide linker derivatives **13a**, **13d**, **13f**, and **13g**. *N*-Alkylation and saponification of the ester yielded carboxylic acid derivatives **15a**–**15h**.

Chenodeoxycholic acid (CDCA), guggulsterone (GS), and progesterone (PS) were commercial products, and GW-4064 was prepared according to the literature.[23]



Scheme 1. Synthetic routes to the present series of compounds. Reagents and conditions: (a) 2-chloro-4-hydroxybenzaldehyde, K_2CO_3, DMF, rt; (b) (3-methoxycarbonyl) benzyl phosphonate, NaH, THF, rt; (c) LiOH, H_2O, THF, rt; (d) (1) methanesulfonyl chloride, triethylamine, THF, rt; (2), rt; (e) 2-methyl-2-butene, $NaClO_2$, NaH_2PO_4, *t*-BuOH, H_2O, rt; (f) (1) methane sulfonyl chloride, triethylamine, THF, rt; (2) methyl 3-aminobenzoate, rt; (g) NaH, R^5I, DMF, rt; (h) LiOH, H_2O, EtOH, rt.

3. Biology

3.1. Plasmids

A fragment of human FXR was inserted into the pCMX-GAL4 vector to obtain pCMX-GAL4-hFXR (pCMX-flag vector to make pCMX-FXR). A full-length hFXR was inserted into the pCMX-VP16 vector to make pCMX-VP16-hFXR. Nuclear hormone receptor-interacting domains of steroid receptor coactivator-1 (SRC-1) (amino acids 595–771; GenBank Accession No. U90661) and nuclear receptor corepressor (N-CoR) (1990–2416; GenBank Accession No. U35312) were inserted into the pCMX-GAL4 vector to afford pCMX-GAL4-SRC-1 and pCMX-GAL4-N-CoR, respectively. GAL4-responsive MH100(UAS)x4-tk-LUC

reporters were used.[28] All plasmids were sequenced before use to verify the DNA sequence fidelity.

3.2. Cell culture and cotransfection assay

Human embryonic kidney (HEK) 293 cells were cultured in Dulbecco's modified Eagle's medium (DMEM) containing 5% fetal bovine serum and antibiotic–antimycotic (Nacalai) at 37 °C in a humidified atmosphere of 5% CO_2 in air. Transfections were performed by the calcium phosphate coprecipitation method. Test compounds were added 8 h after transfection, cells were harvested approximately 16–20 h after the treatment, and luciferase and β-galactosidase activities were assayed using a luminometer and a microplate reader. DNA cotransfection experiments were done with 50 ng of reporter plasmid, 15–20 ng pCMX-s-galactosidase, 10–15 ng of each receptor expression plasmid, and pGEM carrier DNA to make a total of 150 ng DNA per well in a 96-well plate. Luciferase data were normalized to an internal β-galactosidase control, and reported values are means of triplicate assays.

4. Results and discussion

Unfortunately, the co-crystal structure of GW-4064 complexed with the ligand-binding domain of FXR has not been disclosed. Therefore, we could not directly identify the structural feature of GW-4064 that interacts with the AF-2 motif of the FXR ligand-binding domain. Therefore, we planned to introduce bulky substituents at four points of GW-4064 to find a suitable position to generate antagonistic activity, that is, the carboxyl-terminal end, the center of the GW-4064 structure and the 3-position and the 5-position of the isoxazole moiety. First of all, we planned to introduce bulky substituents at the carboxyl-terminal end of GW-4064 as amide derivatives. In the case of other metabolic nuclear receptor ligands, such as peroxisome proliferator-activated receptor (PPAR) ligands, introduction of a bulky substituent at the carboxyl-terminal position has been effective. For example, naturally occurring unsaturated fatty acids are endogenous PPAR agonists, while their acyl-CoA derivatives exhibit PPAR antagonistic activity.[29] We prepared secondary and tertiary amide derivatives, **11a** and **11b**. However, these compounds did not exhibit any antagonistic activity, but retained FXR agonistic activity, although their activities were considerably weaker than that of GW-4064. Although only a few compounds were prepared, and the introduced substituents might not be optimum, we concluded that introduction of a bulky substituent at this position might not be appropriate to obtain potent FXR antagonists.

Then we turned our attention to the center of GW-4064 structure, and introduced secondary and tertiary amide linkers instead of the C–C double bond of GW-4064 (**15a**–**15e**). In our structural development studies of RAR antagonists using retinobenzoic acid Am-80, introduction of a bulky group at the amide linkage, followed by cyclization to fix the conformation, was effective for agonist–antagonist conversion.[30,31] We prepared secondary amide (**15a**), *N*-methyl amide (**15b**), *N*-*n*-propyl amide (**15c**), *N*-benzyl amide (**15d**), and *N*-phenethyl amide (**15e**) derivatives, but to our disappointment, none of these amide derivatives showed any antagonistic activity; they all retained comparable FXR agonistic activity. These might indicate that the binding pocket hosting the center of GW-4064 is sufficiently wide to accept larger substituents.

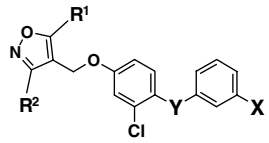
Then we turned our attention to the hydrophobic tail part of GW-4064, that is, the 3- and 5-positions of the distal isoxazole ring. In the case of GW-4064, a brief SAR report from GSK researchers disclosed that *para*-unsubstituted phenyl and benzyl groups are preferable at the 3-position, and an isopropyl group is preferable at the 5-position for FXR agonistic activity.[23]

We introduced a 2-naphthyl- or 4-biphenyl substituent as a bulky group at the isoxazole 3-position of GW-4064 (**10b** and **10c**). However, these compounds exhibited neither antagonistic activity nor agonistic activity, although the reason is unclear. We speculate that the region of the binding pocket hosting the 3-substituent of the isoxazole moiety of GW-4064 has limited capacity to accommodate a *para*-unsubstituted phenyl group.[23]

On the other hand, the steric bulkiness at the 5-position of the isoxazole ring of GW-4064 proved to be critical not only for agonistic activity, but also for antagonistic activity. We prepared *tert*-butyl (**10d**), phenyl (**10e**), 2-naphthyl (**10f**), and 4-biphenyl (**10g**) derivatives of GW-4064. The *tert*-butyl derivative exhibited decreased, though still significant, FXR-agonistic activity, while other bulky derivatives exhibited FXR-antagonistic activity, comparable to that of the naturally occurring FXR antagonist guggulsterone (GS). Based on the fact that the 5-methyl-substituted isoxazole derivative among the GSK compounds exhibited partial agonistic activity, while the 5-ethyl- and 5-isopropyl-substituted isoxazole derivatives exhibited full agonistic activity,[23] together with our results described above, we think it likely that the 5-position of the isoxazole ring in the present series of compounds interacts with the AF-2 helix of FXR to determine the nature of the FXR ligand activity.

Although compounds **10e**–**10g** exhibited FXR-antagonistic activity, these compounds tended to activate FXR to some extent at concentrations above 300 μM (data not shown), so they retain an FXR-agonistic nature. In order to exclude the partial agonistic activity (to obtain full antagonists), we prepared amide linker derivatives with a bulky substituent at the 5-position of the distal isoxazole ring (**15f**–**15h**); the activity of these compounds is also summarized in Table 1. The *tert*-butyl derivative (**15f**) exhibited FXR-agonistic activity, like **10c**, while the other bulky derivatives, **15g** and **15h**, exhibited FXR-antagonistic activity superior to that of **GS**, and none of these compounds exhibited FXR-agonistic activity at the concentrations tested. They were therefore considered to be full FXR antagonists (the dose dependencies of GS, **15g**, and **15f** are depicted in Fig. 2).

Table 1. In vitro functional FXR transactivation activity



Compound	R^1	R^2	X	Y	EC_{50}[a] (μM)	IC_{50}[b] (μM)
11a	*i*-Pr	2,6-Di-ClPh	CONH*n*Pr	CH=CH	9	IA[c]
11b	*i*-Pr	2,6-Di-ClPh	$CON(CH_2Ph)_2$	CH=CH	35.1	IA[c]
15a	*i*-Pr	2,6-Di-ClPh	COOH	CONH	3.0	IA[c]
15b	*i*-Pr	2,6-Di-ClPh	COOH	CON(Me)	3.1	IA[c]
15c	*i*-Pr	2,6-Di-ClPh	COOH	CON(*n*-Pr)	2.1	IA[c]
15d	*i*-Pr	2,6-Di-ClPh	COOH	$CON(CH_2Ph)$	2.5	IA[c]
15e	*i*-Pr	2,6-Di-ClPh	COOH	$CON(CH_2CH_2Ph)$	0.84	IA[c]
10b	*i*-Pr	2-Naphthyl	COOH	CH=CH	IA[c]	IA[c]
10c	*i*-Pr	4-Biphenyl	COOH	CH=CH	IA[c]	IA[c]
10d	*t*-Bu	2,6-Di-ClPh	COOH	CH=CH	1.3	IA[c]
10e	Ph	2,6-Di-ClPh	COOH	CH=CH	IA[c]	15.8
10f	2-Naphthyl	2,6-Di-ClPh	COOH	CH=CH	IA[c]	22.2
10g	4-Biphenyl	2,6-Di-ClPh	COOH	CH=CH	IA[c]	33.9
15f	*t*-Bu	2,6-Di-ClPh	COOH	CONH	1.3	IA[c]
15g	2-Naphthyl	2,6-Di-ClPh	COOH	CONH	IA[c]	4.0
15h	4-Biphenyl	2,6-Di-ClPh	COOH	CONH	IA[c]	3.7
CDCA[d]					27	IA[c]
GW-4064					0.07	IA[c]
Gs[e]					IA[c]	12

[a] Compounds were screened for agonist activity on FXR-GAL4 chimeric receptors in transiently transfected HEK-293 cells as described. The EC_{50} value is the molar concentration of the test compound that affords 50% of the maximal reporter activity.
[b] The IC_{50} value is the molar concentration of the test compound required to decrease the activity of 100 μM CDCA by 50%.
[c] 'IA' means inactive (no apparent activity) at the concentration of 100 μM.
[d] CDCA, chenodeoxycholic acid.
[e] GS, guggulsterone.

Although GS was proved to be a FXR antagonist, it also displayed high affinity for other steroid receptors, such as progesterone receptor (PR), so its nuclear receptor selectivity is not high.[32,33] In order to clarify the nuclear receptor selectivity of our synthetic FXR antagonists, **15g** and **15h**, their transactivation activity, as well as that of GS, against PR was investigated. As can be seen from Figure 3, 3 nM progesterone (PS) significantly transactivated PR. Similarly, 30 μM GS, which is only three times the IC_{50} value of FXR-antagonistic activity, exhibited significant PR transactivation activity. Thus, GS exhibited PR-agonistic activity at a comparable concentration to that exhibiting full FXR-antagonistic activity. In contrast, 30 μM **15g** and 30 μM **15h** (about ten times the IC_{50} values for FXR antagonistic activity) did not exhibit PR transactivation activity. Therefore, we conclude that **15g** and **15h** have a more distinct nuclear receptor selectivity profile than the naturally occurring FXR antagonist GS.

In the absence of agonists, or in some cases, in the presence of antagonists, nuclear receptors are complexed with corepressor proteins, such as nuclear receptor corepressor (NCoR)[34] and silencing mediator for retinoid and tyroid receptors (SMRT),[35] which repress transcription via an associated histone deacetylase activity. Agonists binding to NRs promote the dissociation of the corepressor proteins and the recruitment of coactivator proteins, such as steroid receptor coactivator-1 (SRC-1)[36] and vitamin D receptor-interacting protein (DRIP),[37] resulting in enhancement of the transcription of the specific gene(s). Therefore, we investigated the ligand-induced corepressor recruitment with a mammalian two-hybrid assay system, using GAL4-SMRT (and GAL4-NCoR) receptor-interacting domain, containing three LXXLL motifs, and VP16-FXR chimeric expression vectors. In the absence of ligand (DMSO control), basal luciferase activity was observed [Fig. 4a–c]. This means that both corepressors, SMRT and NcoR, were recruited to FXR to some extent. In the presence of the agonist CDCA, luciferase activity decreased considerably, indicating that corepressors were dissociated by the binding of the agonist to the FXR ligand-binding domain [Fig. 4a]. In the case of the presence of antagonists such as GS and **15g**, no enhancement of luciferase activity as compared with the control was observed [Fig. 4a–c], suggesting they do not affect the stability of the FXR-corepressor complex. In the presence of another antagonist **15h** at a high enough concentration to inhibit CDCA-induced activation of FXR, the luciferase activity was increased about threefold, with both SMRT and NCoR, indicating that **15h** can stabilize the FXR-corepressor complex or inhibit dissociation of corepressor(s) from FXR [Fig. 4a–c].

It was reported that the binding of corepressors to nuclear receptors occurs in the unliganded state, and can be stabilized by antagonists, by inducing a

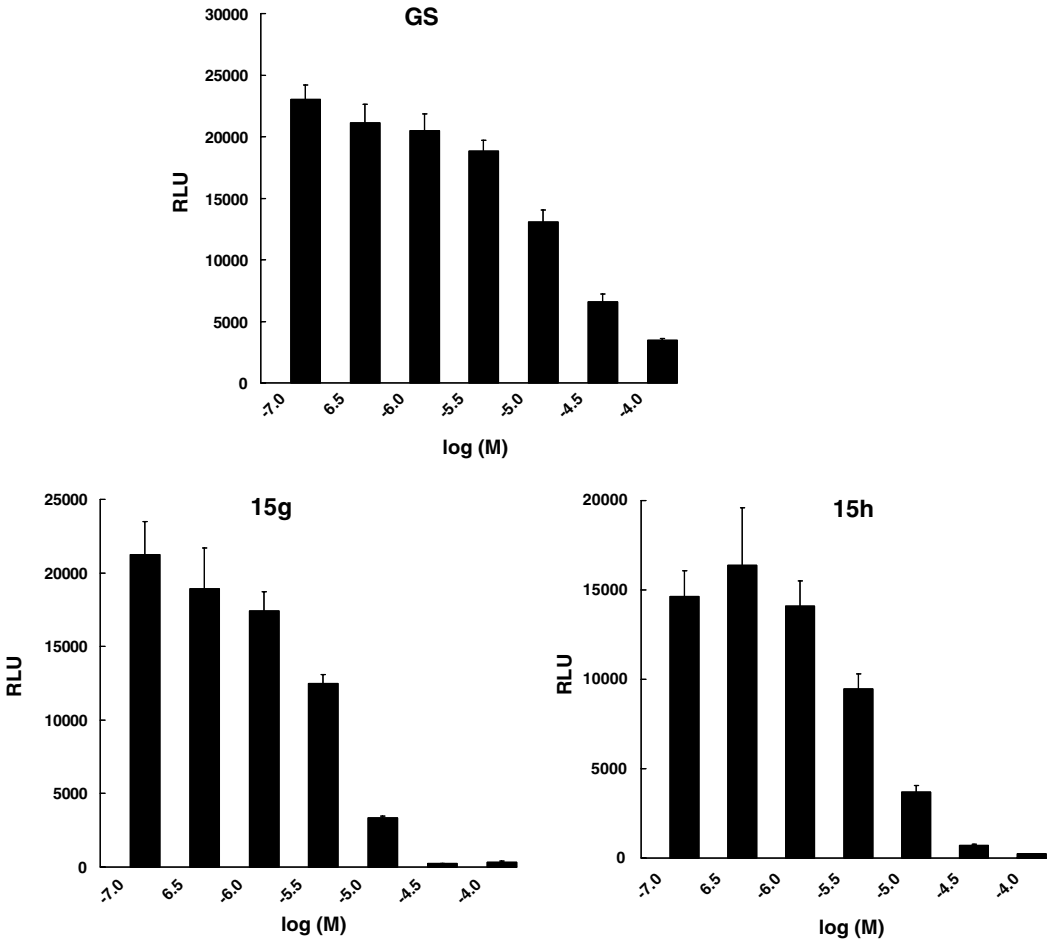


Figure 2. Dose dependency of the antagonistic activity of guggulsterone (GS), **15g**, and **15h** on CDCA ($1 \times 10^{-4.5}$ M)-mediated FXR transactivation.

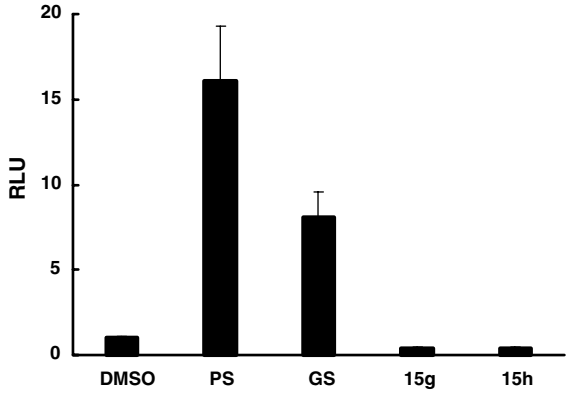


Figure 3. PR transactivation activity of progesterone (PS 3 nM), GS (30 μM), **15g** (30 μM), and **15h** (30 μM).

conformational change of the nuclear receptor–ligand-binding domain that allows it to interact efficiently with the corepressor.[38,39] But our present research indicated that there are two types of nuclear receptor antagonists as regards corepressor recruitment. One, that is, **15h**, stabilizes the corepressor-nuclear receptor interaction, and the other, that is, GS or **15g**, does not have the ability to stabilize the corepressor-nuclear receptor interaction, but inhibits coactivator recruitment. Although the exact molecular mechanisms involved remain unclear, we speculate that the steric bulkiness and/or hydrophobic nature of the 4-biphenyl group of the 5-position of the isoxazole moiety might be directly involved in stabilizing the interaction between corepressors and the FXR ligand-binding domain. A 2-naphthyl group is less able to stabilize the corepressor-FXR ligand-binding domain complex.

In summary, we have developed a series of non-steroidal FXR antagonists, with features superior to those of the steroidal FXR antagonist GS. We also found that nuclear receptor antagonists can be classified into two types based on the corepressor recruitment profile. Further pharmacological evaluation of the representative compounds is on-going.

5. Experimental

5.1. 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 JNM-GX500 (500 MHz) spectrometer. Chemical shifts are expressed in ppm relative to tetramethylsilane. Mass spectra were recorded on a JEOL JMS-DX303 spectrometer.

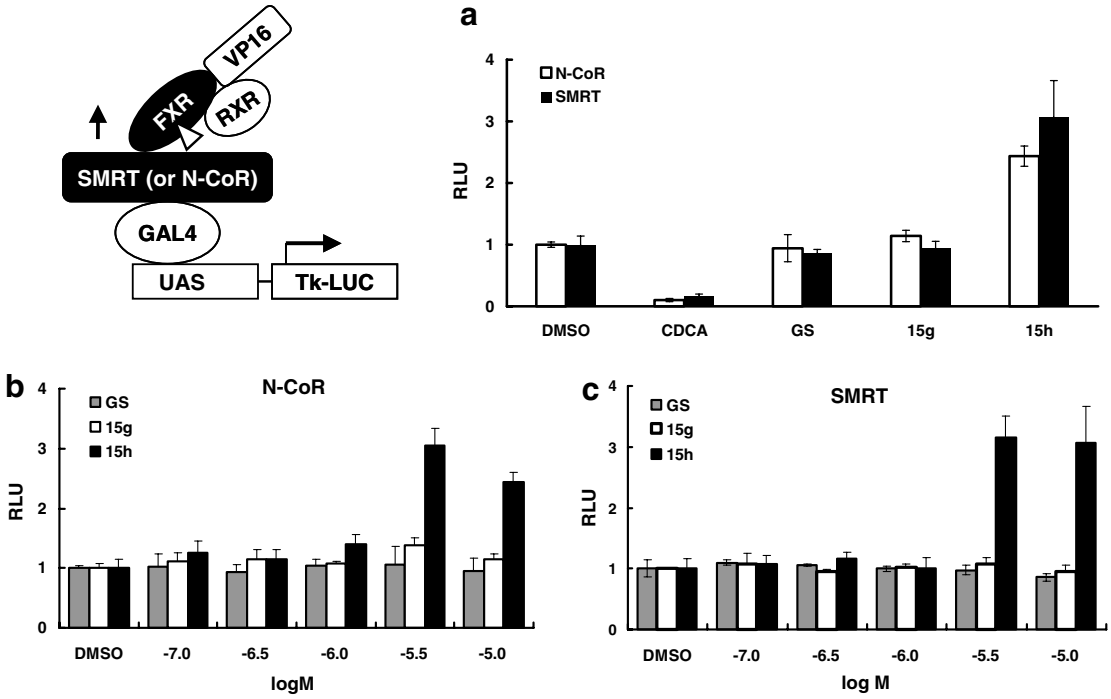


Figure 4. Functional analysis of FXR ligands with mammalian two-hybrid assay.

5.1.1. 3((*E*)-2-{2-Chloro-4-[3-(2,6-dichlorophenyl)-5-isopropylisoxazol-4-ylmethoxy]phenyl}vinyl)-*N*-*n*-propyl benzamide (11a). 3((*E*)-2-{2-Chloro-4-[3-(2,6-dichlorophenyl)-5-isopropylisoxazol-4-ylmethoxy]phenyl}vinyl)benzoic acid[23] (GW-4064; 217 mg, 0.40 mmol) was dissolved in 15 mL of dehydrated THF at 0 °C under an argon atmosphere. To this solution were added methanesulfonyl chloride (0.036 mL, 0.47 mmol) and triethylamine (0.15 mL, 1.1 mmol) and the whole was stirred for 30 min at 0 °C. *n*-Propylamine (0.05 mL, 0.6 mmol) in 15 mL of dehydrated THF was added to the solution and stirring was continued for further 30 min at ambient temperature. The reaction mixture was poured into 100 mL of water, and the whole was extracted with AcOEt. It was washed with aqueous sodium hydrogen carbonate, 1 mol/L HCl, and brine, then dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (eluant *n*-hexane/AcOEt = 9:1 to 4:1 v/v) to afford 583 mg of the target compound (yield 54%): mp 57–60 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53 (s, 1H), 8.26 (d, J = 9.1 Hz, 1H), 8.23 (d, J = 7.3 Hz, 1H), 8.19 (s, 1H), 8.10 (d, J = 7.3 Hz, 1H), 7.60 (t, J = 7.4 Hz, 1H), 7.41 (d, J = 8.5 Hz, 2H), 7.33 (t, J = 7.4 Hz, 1H), 6.87 (d, J = 2.4 Hz, 1H), 6.75 (dd, J = 3.0, 9.1 Hz, 1H), 4.73 (s, 2H), 3.96 (s, 3H), 3.36–3.30 (m, 1H), 1.43 (d, J = 6.7 Hz, 6H); FAB: MS *m*/*z* 583; HRMS (FAB, MH^+) calcd for $C_{31}H_{30}Cl_3N_2O_3$ 583.1322, found 583.1346.

5.1.2. *N*,*N*-Dibenzyl-3-((*E*)-2-{2-chloro-4-[3-(2,6-dichlorophenyl)-5-isopropylisoxazol-4-ylmethoxy]phenyl}vinyl)benzamide (11b). This compound was prepared from GW-4064[23] and dibenzylamine by means of a procedure similar to that used for **11a**: mp 49–52 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.53–7.49 (m, 2H), 7.41–7.30 (m, 17H), 6.90 (s, 1H), 6.87 (s, 1H), 6.79 (s, 1H), 6.69 (d, J = 6.1 Hz, 1H), 4.73 (s, 4H), 3.35–3.30 (m, 1H), 1.43 (d, J = 7.4 Hz, 6H); FAB: MS *m*/*z* 721; HRMS (FAB, MH^+) calcd for $C_{42}H_{36}Cl_3N_2O_3$ 721.1792, found 721.1802.

5.1.3. 2-Chloro-4-[3-(2,6-dichlorophenyl)-5-isopropylisoxazol-4-ylmethoxy]benzoic acid (12a). To a mixture of **8a** (249 mg, 0.59 mmol), sodium hydrogenphosphate dihydrate (92 mg, 0.59 mmol), *t*BuOH (4.7 mL), and water (1.3 mL) was added 2-methyl-2-butene (0.27 mL, 2.59 mmol) followed by sodium chlorite (213 mg, 2.36 mmol). The mixture was stirred for 3 h, and then 10 mL of 1 mol/L HCl was added under cooling. The whole was extracted with CH_2Cl_2, and the extract was dried over anhydrous $MgSO_4$ and evaporated. The residue was purified by silica gel column chromatography (eluant *n*-hexane/AcOEt = 1:1 v/v) to afford 235 mg of the target compound (yield 98%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, 1H, J = 8.5 Hz), 7.41 (d, 2H, J = 7.9 Hz), 7.33 (t, 1H, J = 8.2 Hz), 6.85 (s, 1H), 6.72 (d, 1H, J = 9.2 Hz), 4.78 (s, 2H), 3.33 (sept, 1H, J = 7.3 Hz), 1.44 (d, 6H, J = 6.7 Hz); FAB: MS *m*/*z* 440 $(M+H)^+$.

5.1.4. Methyl 3-{2-chloro-4-[3-(2,6-dichlorophenyl)-5-isopropylisoxazol-4-ylmethoxy]benzoylamino}-benzoate (13a). This compound was prepared from **12** and methyl 3-aminobenzoate by means of a procedure similar to that used for **11a**; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, 2H, J = 9.8 Hz), 8.03 (s, 1H), 7.83 (d, 1H, J = 7.9 Hz), 7.77 (d, 1H, J = 8.5), 7.47–7.41 (m, 2H), 7.33 (t, 1H, J = 8.0 Hz), 6.83 (s, 1H), 6.77 (d, 1H, J = 8.5 Hz), 4.78 (s, 2H), 3.93 (s, 3H) 3.34–3.32 (m, 1H), 1.44 (d, 6H, J = 6.7 Hz); FAB: MS *m*/*z* 573 $(M+H)^+$.

5.1.5. Methyl 3-({2-chloro-4-[3-(2,6-dichlorophenyl)-5-isopropylisoxazol-4-ylmethoxy]benzoyl}-*N*-methylamino)benzoate (14b). 60% Sodium hydride (2.2 mg, 0.055 mmol) was rinsed twice with *n*-hexane under an argon atmosphere to remove mineral oil, and 0.5 mL DMF was added to it. To the suspension was added **13** (28.6 mg, 0.05 mmol) in 0.5 mL DMF, and the whole was stirred for 30 min at 0 °C. Methyl iodide (0.0063 mL, 0.1 mmol) was added to the mixture and stirring was continued for 12 h at ambient temperature. Then 10 mL of water was added and the whole was extracted with AcOEt. The extract was washed with brine, dried over anhydrous $MgSO_4$, and evaporated. The residue was purified by silica gel column chromatography (eluant *n*-hexane/AcOEt = 3:1 to 2:1 v/v) to afford 28.9 mg of the target compound (yield 98%); ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 7.77–7.41 (m, 5H), 7.39 (t, J = 7.4 Hz, 1H), 7.18 (d, J = 8.5 Hz, 1H), 6.72 (s, 1H), 6.62 (d, J = 6.7 Hz, 1H), 4.81 (s, 2H), 3.84 (s, 3H), 3.42 (m, 1H), 3.31 (s, 3H), 1.31 (d, J = 6.7 Hz, 6H); FAB: MS m/z 587 $(M+H)^+$.

5.1.6. Methyl 3-({2-chloro-4-[3-(2,6-dichlorophenyl)-5-isopropylisoxazol-4-ylmethoxy]benzoyl}-*N*-*n*-propylamino)benzoate (14c). This compound was prepared from **13** and *n*-propyl iodide by means of a procedure similar to that used for **14b**; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (br, 2H), 7.37–7.22 (m, 5H), 6.94 (d, J = 8.5 Hz, 1H), 6.55 (s, 1H), 6.41 (d, J = 6.4 Hz, 1H), 4.61 (s, 2H), 3.89 (s, 5H), 3.24 (br, 1H), 1.63 (br, 2H), 1.36 (d, J = 6.7 Hz, 6H), 0.96 (br, 3H); FAB: MS m/z 615 $(M+H)^+$.

5.1.7. Methyl 3-({2-chloro-4-[3-(2,6-dichlorophenyl)-5-isopropylisoxazol-4-ylmethoxy]benzoyl}-*N*-phenylmethylamino)benzoate (14d). This compound was prepared from 12 and phenylmethylbromide by means of a procedure similar to that used for **14b**; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74–6.97 (m, 13H), 6.56 (s, 1H), 6.42 (d, J = 8.5 Hz, 1H), 5.12 (m, 2H), 4.62 (s, 2H), 3.87 (s, 3H), 3.27–3.21 (m, 1H), 1.36 (d, J = 6.7 Hz, 6H); FAB: MS m/z 663 $(M+H)^+$.

5.1.8. Methyl 3-({2-chloro-4-[3-(2,6-dichlorophenyl)-5-isopropylisoxazol-4-ylmethoxy]benzoyl}-*N*-phenylethylamino)benzoate (14e). This compound was prepared from **12** and methyl 3-phenylethylaminobenzoate by means of a procedure similar to that used for **11a**; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76–6.40 (m, 15H), 4.61 (s, 2H), 4.16 (s, 2H), 3.94 (s, 3H), 3.24 (br, 1H), 3.00 (s, 2H), 1.36 (d, J = 6.7 Hz, 6H); FAB: MS m/z 677 $(M+H)^+$.

5.1.9. 3-{2-Chloro-4-[3-(2,6-dichlorophenyl)-5-isopropylosoxazol-4-ylmethoxy]benzoylamino}benzoic acid (15a). A mixture of **14a** (124 mg, 0.216 mmol), 2.2 mL THF, and 1.3 mL of 1 mol/L LiOH was refluxed for 17 h, then allowed to cool to room temperature. Then 30 mL of water was added, and the whole was acidified with 2 mol/L HCl and the whole was extracted with AcOEt. The extract was washed with brine, dried over anhydrous $MgSO_4$, and evaporated. The residue was purified by silica gel column chromatography (eluant *n*-hexane/AcOEt = 1:1 v/v) to afford 104 mg of the target compound (yield 86%): mp 89–92 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (d, 2H, J = 14.6 Hz), 8.09 (d, 1H, J = 8.0 Hz), 7.89 (d, 1H, J = 8.0 Hz), 7.78 (d, 1H, J = 8.5 Hz), 7.50 (t, 1H, J = 8.0 Hz), 7.42 (d, 2H, J = 7.9 Hz), 7.35 (t, 1H, J = 7.9 Hz), 6.83 (s, 1H), 6.78 (d, 1H, J = 8.5 Hz), 4.79 (s, 2H), 3.35–3.32 (m, 1H), 1.44 (d, 6H, J = 6.7 Hz); FAB: MS m/z 559 $(M+H)^+$; HRMS (FAB, MH^+) calcd for $C_{27}H_{22}Cl_3N_2O_5$ 559.0594, found 559.0579.

5.1.10. 3-({2-Chloro-4-[3-(2,6-dichlorophenyl)-5-isopropylisoxazol-4-ylmethoxy]benzoyl}-*N*-methylamino)benzoic acid (15b). This compound was prepared from **14b** by means of a procedure similar to that used for **15a**: mp 86–89 °C; ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 7.76 (s, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.54–7.47 (m, 3H), 7.41 (d, J = 8.0 Hz, 1H), 7.36 (t, J = 7.5 Hz, 1H), 7.16 (d, J = 8.5 Hz, 1H), 6.72 (s, 1H), 6.61 (d, J = 8.0 Hz, 1H), 4.81 (s, 2H), 3.42–3.36 (m, 1H), 3.31 (s, 3H), 1.31 (d, J = 7.5 Hz, 6H); FAB: MS m/z 573 $(M+H)^+$, HRMS (FAB, MH^+) calcd for $C_{28}H_{24}Cl_3N_2O_5$ 573.0751, found 573.0720.

5.1.11. 3-({2-Chloro-4-[3-(2,6-dichlorophenyl)-5-isopropylisoxazol-4-ylmethoxy]benzoyl}-*N*-*n*-propylamino)benzoic acid (15c). This compound was prepared from **14c** by means of a procedure similar to that used for **15a**: mp 201–203 °C; ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 7.74–7.73 (m, 3H), 7.53–7.47 (m, 3H), 7.40–7.34 (m, 2H), 7.11 (d, J = 8.5 Hz, 1H), 6.69 (s, 1H), 6.57 (d, J = 8.5 Hz, 1H), 4.79 (s, 2H), 3.74 (br, 2H), 3.41–3.35 (m, 1H), 1.54–1.50 (m, 2H), 1.30 (d, J = 6.5 Hz, 6H), 0.87 (t, J = 7.0 Hz, 3H); FAB: MS m/z 601 $(M+H)^+$; HRMS (FAB, MH^+) calcd for $C_{30}H_{28}Cl_3N_2O_5$ 601.1064, found 601.1064.

5.1.12. 3-({2-Chloro-4-[3-(2,6-dichlorophenyl)-5-isopropylisoxazol-4-ylmethoxy]benzoyl}-*N*-phenylmethylamino)-benzoic acid (15d). This compound was prepared from **14d** by means of a procedure similar to that used for **15a**: mp 73–76 °C; ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 7.65–7.22 (m, 12H), 7.16 (d, J = 8.5 Hz, 1H), 6.69 (s, 1H), 6.56 (d, J = 8.5 Hz, 1H), 5.03 (s, 2H), 4.79 (s, 2H), 3.40–3.35 (m, 1H), 1.31 (d, J = 6.5 Hz, 6H); FAB: MS m/z 649 $(M+H)^+$; HRMS (FAB, MH^+) calcd for $C_{34}H_{28}Cl_3N_2O_5$ 649.1064, found 649.1072.

5.1.13. 3-({2-Chloro-4-[3-(2,6-dichlorophenyl)-5-isopropylisoxazol-4-ylmethoxy]benzoyl}-*N*-phenylethylamino)benzoate (15e). This compound was prepared from **14d** by means of a procedure similar to that used for **15a**: mp 52–55 °C; ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 7.84–6.42 (m, 15H), 4.62 (s, 2H), 4.18 (s, 2H), 3.23 (br, 1H), 3.02 (s, 2H), 1.36 (d, J = 6.7 Hz, 6H); FAB: MS m/z 663 $(M+H)^+$; HRMS (FAB, MH^+) calcd for $C_{35}H_{23}Cl_3N_2O_5$ 663.1220, found 663.1225.

5.1.14. Naphthalene-2-carbaldehyde oxime. To a solution of 2-naphthaldehyde (1.25 g, 8 mmol) and 10 mL ethanol was added a solution of hydroxylamine·HCl (0.61 g, 8.8 mmol) and sodium hydroxide (0.61 g, 8.8 mmol) in 10 mL of water, and the reaction mixture was heated to 90 °C for 2.5 h. The solvent was evaporated to afford 933 mg (68%) of the objective compound as a solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.31 (s, 1H), 8.28 (s, 1H),

8.00 (s, 1H), 7.92–7.89 (m, 3H), 7.81 (d, J = 7.3 Hz, 1H),7.55–7.51 (m, 2H); FAB: MS m/z 172 $(M+H)^+$.

5.1.15. 2-Naphthylhydroximic chloride. Naphthalene-2-carbaldehyde oxime (1.00 g, 5.89 mmol) was mixed with *N*-chlorosuccinimide (1.50 g, 11.8 mmol) in 15 mL DMF and the whole was stirred for 2 h at ambient temperature. To this solution was added 10 mL of water and the whole was extracted with ether. The extract was washed with water, brine, dried over anhydrous $MgSO_4$, and evaporated to afford 683 mg (56%) of the target compound; ^1H NMR (500 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.96–7.81 (m, 4H), 7.69–7.44 (m, 2H); FAB: MS m/z 206 $(M+H)^+$.

5.1.16. Methyl 5-isopropyl-3-naphthalen-2-yl-isoxazole-4-carboxylate. To a solution of sodium methoxide (35 mg, 0.65 mmol) and 5 mL of methanol was added a solution of methyl 4-methyl-3-oxopentanoate (0.071 mL, 0.5 mmol) in 2 mL of methanol and the mixture was stirred for 30 min at ambient temperature under argon atmosphere. Then a solution of 2-naphthylhydroximic chloride (103 mg, 0.50 mmol) in 2 mL of methanol was added during 2 h, and stirring was continued for a further 24 h. The solvent was evaporated, and the residue was taken up in 3 mL of water and extracted with AcOEt. The extract was washed with brine, dried over anhydrous $MgSO_4$, and evaporated. The residue was purified by silica gel column chromatography (eluant *n*-hexane: AcOEt = 5:1 v/v) to afford 55 mg of the target compound (yield 37%); ^1H NMR (500 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.91–7.51 (m, 6H), 3.88–3.82 (m, 1H), 3.75 (s, 3H), 1.43 (d, J = 7.3 Hz, 2H); FAB: MS m/z 296 $(M+H)^+$.

5.1.17. 5-Isopropyl-3-naphthalen-2-yl-isoxazole-4-methanol. To a solution of methyl 5-isopropyl-3-naphthalen-2-ylisoxazole-4-carboxylate (246 mg, 0.83 mmol) in 2 mL of dehydrated THF was added 2.5 mL of 1 mol/L diisobutylaluminum hydride in THF at 0 °C under an argon atmosphere. The mixture was stirred for 1 h at 0 °C, then for 4 h at ambient temperature. The whole was cooled and 0.3 mL of methanol was added dropwise, and stirring was continued for 10 min. Then 1.2 mL of 2 mol/L NaOH was added and the whole was filtered through Celite®, washed with AcOEt, and evaporated. The residue was taken up in 10 mL of water which was added to the residue and extracted with AcOEt. The extract was washed with brine, dried over anhydrous $MgSO_4$, and evaporated. The residue was purified by silica gel column chromatography (eluant *n*-hexane/AcOEt=3:1 v/v) to afford 152 mg of the target compound (yield 69%); ^1H NMR (500 MHz, $CDCl_3$) δ 8.32 (s, 1H), 7.96–7.87 (m, 4H), 7.56–7.51 (m, 2H), 4.65 (s, 2H), 3.35–3.30 (m, 1H), 1.42 (d, J = 7.3 Hz, 6H); FAB: MS m/z 268 $(M+H)^+$.

5.1.18. 4-Bromomethyl-5-isopropyl-3-(2-naphthyl)isoxazole (7b). To a solution of 5-isopropyl-3-naphthalen-2-ylisoxazole-4-methanol (152 mg, 0.57 mmol) and carbon tetrabromide (250 mg, 0.74 mmol) in 5 mL of dehydrated methylene chloride was added triphenylphosphine (325 mg, 0.74 mmol) in 10 mL of dehydrated methylene chloride at 0 °C under an argon atmosphere. The mixture was stirred for 1 h at 0 °C, then 5 mL of water was added and the whole was extracted with AcOEt. The extract was washed with brine, dried over anhydrous $MgSO_4$, and evaporated. The residue was purified by silica gel column chromatography (eluant *n*-hexane/AcOEt = 5:1 v/v) to afford 96 mg of the target compound (yield 51%); ^1H NMR (500 MHz, $CDCl_3$) δ 7.45–7.36 (m, 3H), 4.15 (s, 2H), 3.33–3.28 (m, 1H), 1.45 (d, J = 6.8 Hz, 6H); FAB: MS m/z 348 $(M+H)^+$.

5.1.19. 2-Chloro-4-(5-isopropyl-3-naphthalen-2-yl-isoxazol-4-ylmethoxy)benzaldehyde (8b). To a solution of **7b** (96 mg, 0.29 mmol) in 3 mL DMF were added 2-chloro-4-hydroxybenzaldehyde (45.4 mg, 0.29 mmol) in 5 mL DMF and anhydrous potassium carbonate (44.2 mg, 0.32 mmol) under an Ar atmosphere. The mixture was stirred for 10 h at ambient temperature. Water was added and the whole was extracted with AcOEt. The extract was washed with brine, dried over anhydrous $MgSO_4$, and evaporated. The residue was purified by silica gel column chromatography (eluant *n*-hexane/AcOEt = 5:1 v/v) to afford 76 mg of the target compound (yield 64%); ^1H NMR (500 MHz, $CDCl_3$) δ 10.36 (s, 1H), 8.10 (s, 1H), 7.93 (t, J = 8.0 Hz, 2H), 7.86 (d, J = 7.9 Hz, 1H), 7.75 (d, J = 8.5 Hz, 2H). 7.55–7.48 (m, 2H), 7.02–6.97 (m, 2H), 5.00 (s, 2H), 3.36–3.29 (m, 1H), 1.44 (d, J = 6.7 Hz, 6H); FAB: MS m/z 406 $(M+H)^+$.

5.1.20. Methyl 3-{(*E*)-2-[2-chloro-4(5-isopropyl-3-naphthalene-2-ylisoxazole-4-ylmethoxy)phenyl]vinyl}benzoate (9b). 60%, Sodium hydride (12 mg, 0.28 mmol) was rinsed twice with *n*-hexane under an argon atmosphere to remove mineral oil, and 4 mL THF was added to it. To the suspension was added methyl 3-(diethoxyphosphorylmethyl)benzoate (64 mg, 0.23 mmol) in 2 mL THF, and the mixture was stirred for 30 min at 0 °C. **8b** (76 mg, 0.19 mmol) was added to the mixture and stirring was continued for 5 h at ambient temperature. Then 10 mL of water was added to the mixture and the whole was extracted with AcOEt. The extract was washed with brine, dried over anhydrous $MgSO_4$, and evaporated. The residue was purified by silica gel column chromatography (eluant *n*-hexane/AcOEt = 5:1 v/v) to afford 69 mg of the target compound (yield 68%); ^1H NMR (500 MHz, $CDCl_3$) δ 8.19–8.17 (m, 2 H), 7.93–7.44 (m, 11H), 7.04–6.94 (m, 3H), 4.96 (s, 2H), 3.95 (s, 3H), 3.35–3.30 (m, 1H), 1.44 (d, J = 6.7 Hz, 6H); FAB: MS m/z 538 $(M+H)^+$.

5.1.21. 3-{(*E*)-2-Chloro-4(5-isopropyl-3-naphthalen-2-yl-isoxazol-4-ylmethoxy)phenyl}vinyl}benzoic acid (10b). This compound was prepared from **9b** by means of a procedure similar to that used for **15a**: mp 207–209 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.26 (s, 1H), 8.17 (s, 1H), 8.03–7.47 (m, 10H), 7.06–7.03 (m, 2H), 6.95–6.92 (m, 1H), 4.94 (s, 2H), 3.38–3.30 (m, 1H), 1.44 (d, J = 6.7 Hz, 6H); FAB: MS m/z 524 $(M+H)^+$; HRMS (FAB, MH^+) calcd for $C_{32}H_{27}ClNO_4$ 524.1629, found 524.1624.

5.1.22. Biphenyl-4-carbaldehyde oxime. This compound was prepared from 4-biphenylcarboxaldehyde and hydroxylamine·HCl by means of a procedure similar

to that used for naphthalene-2-carbaldehyde oxime; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.67–7.60 (m, 6H), 7.46 (t, J = 8.0 Hz, 2H), 7.38 (t, J = 8.0 Hz, 1H); FAB: MS m/z 198 $(M+H)^+$.

5.1.23. 4-Biphenylhydroximic chloride. This compound was prepared from biphenyl-4-carbaldehyde oxime and *N*-chlorosuccinimide by means of a procedure similar to that used for naphthalene-2-carbaldehyde oxime; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (d, J = 8.5 Hz, 2H), 7.77 (s, 1H), 7.65–761 (m, 4H), 7.47 (t, J = 8.0 Hz, 2H), 7.39 (t, J = 8.0 Hz, 1H); FAB: MS m/z 232 $(M+H)^+$.

5.1.24. Methyl 3-biphenyl-4-yl-5-isopropylisoxazole-4-carboxylate. This compound was prepared from 4-biphenylhydroximic chloride and methyl 4-methyl-3-oxopentanoate by means of a procedure similar to that used for methyl 5-isopropyl-3-naphthalen-2-ylisoxazole-4-carboxylate; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70–7.61 (m, 6H), 7.47 (t, J = 7.9 Hz, 2H) 7.38 (t, J = 7.9 Hz, 1H), 3.85–3.80 (m, 1H), 3.79 (s, 3H), 1.42 (d, J = 6.7 Hz, 6H); FAB: MS m/z 322 $(M+H)^+$.

5.1.25. 3-Biphenyl-4-yl-5-isopropylisoxazole-4-methanol. This compound was prepared from methyl 3-biphenyl-4-yl-5-isopropylisoxazole-4-carboxylate and DIBAL-H by means of a procedure similar to that used for 5-isopropyl-3-naphthalen-2-ylisoxazole-4-methanol; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70–7.61 (m, 6H), 7.47 (t, J = 7.9 Hz, 2H) 7.38 (t, J = 7.9 Hz, 1H), 3.85–3.80 (m, 1H), 3.79 (s, 3H), 1.42 (d, J = 6.7 Hz, 6H); FAB: MS m/z 322 $(M+H)^+$.

5.1.26. 3-Biphenyl-4-yl-4-bromomethyl-5-isopropylisoxazole (7c). This compound was prepared from 3-biphenyl-4-yl-5-isopropylisoxazole-4-methanol, carbon tetrabromide, and triphenylphosphine by means of a procedure similar to that used for 4-bromomethyl-5-isopropyl-3-(2-naphthyl)isoxazole; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, J = 8.0 Hz, 2H), 7.74 (d, J = 8.5 Hz, 2H), 7.65 (d, J = 8.0 Hz, 2H), 7.48 (t, J = 7.3 Hz, 2H), 7.39 (t, J = 7.3 Hz, 1H), 4.43 (s, 2H), 3.32–3.27 (m, 1H), 1.44 (d, J = 6.7 Hz, 6H); FAB: MS m/z 356 $(M+H)^+$.

5.1.27. 4-(3-Biphenyl-4-yl-5-isopropylisoxazol-4-ylmethoxy)-2-chlorobenzaldehyde (8c). This compound was prepared from **7c** and 3-chloro-4-formylphenol by means of a procedure similar to that used for 2-chloro-4-(5-isopropyl-3-naphthalen-2-ylisoxazol-4-ylmethoxy)benzaldehyde; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.36 (s, 1H), 7.94 (d, J = 9.1 Hz, 1H), 7.72–7.67 (m, 3H), 7.61 (d, J = 7.3 Hz, 2H), 7.45 (t, J = 7.3 Hz, 2H). 7.37 (t, J = 7.3 Hz, 1H). 7.01 (s, 1H), 6.95 (d, J = 8.5 Hz, 2H), 4.96 (s, 2H), 3.32–3.26 (m, 1H), 1.44 (d, J = 7.3 Hz, 6H); FAB: MS m/z 432 $(M+H)^+$.

5.1.28. Methyl 3-{(*E*)-2-(3-biphenyl-4-yl-5-isopropylisoxazol-4-ylmethoxy)-2-chlorophenyl}vinyl}benzoate (9c). This compound was prepared from **8c** and methyl 3-(diethoxyphosphorylmethyl)benzoate by means of a procedure similar to that used for methyl **9b**; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.94 (d, J = 7.3 Hz, 1H), 7.77–7.37 (m, 12H), 7.03 (s, 1H), 7.00 (s, 1H), 6.91 (d, J = 7.3 Hz, 2H), 4.90 (s, 2H), 3.95 (s, 3H), 3.33–3.27 (m, 1H), 1.42 (d, J = 6.7 Hz, 6H); FAB: MS m/z 564 $(M+H)^+$.

5.1.29. 3-{(*E*)-2-(3-Biphenyl-4-yl-5-isopropylisoxazol-4-ylmethoxy)-2-chlorophenyl}vinyl}benzoic acid (10c). This compound was prepared from **9c** by means of a procedure similar to that used for **15a**: mp 198–201 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (s, 1H), 8.01 (d, J = 7.7 Hz, 1H), 7.79–7.37 (m, 13H), 7.05–7.01 (m, 2H), 6.91 (s, 1H), 4.90 (s, 2H), 3.33–3.27 (m, 1H), 1.42 (d, J = 7.1 Hz, 6H); FAB: MS m/z 550 $(M+H)^+$; HRMS (FAB, MH^+) calcd for $C_{34}H_{29}ClNO_4$ 550.1785, found 550.1770.

5.1.30. Methyl 3-naphthalen-2-yl-3-oxo-propanoate. A solution of 2-paphthoic acid (11.0 g, 64.0 mmol) and 1,1′-carbonyldiimidazole (10.4 g, 64.0 mmol) in anhydrous tetrahydrofuran (60 mL) was stirred at room temperature overnight to form the active ester. To a suspension of potassium methyl malonate (20.0 g, 128 mmol) in anhydrous acetonitrile (200 mL), and triethyl amine (27 mL, 192 mmol) was added portionwise magnesium chloride (15.2 g, 160 mmol) while maintaining the temperature below 20 °C. The reaction mixture was stirred at room temperature for 4 h, then cooled in an ice bath. The solution of the active ester was added dropwise, and the suspension was stirred at room temperature overnight. The solvent was evaporated and the residue was cooled and the whole was acidified with aqueous HCl (12%, 240 mL). The whole was extracted with AcOEt. The extract was washed with brine, dried over anhydrous $MgSO_4$, and evaporated to afford 11.3 g (77%) of the target compound; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03–7.54 (m, 7H), 4.15 (s, 2H), 3.77 (s, 3H); FAB: MS m/z; 229 $(M+H)^+$.

5.1.31. Methyl 3-(2,6-dichlorophenyl)-5-naphthalene-2-yl-isoxazole-4-carboxylate. This compound was prepared from methyl 3-naphthalen-2-yl-3-oxo-propanoate and 2,6-dichlorophenylhydroximic chloride by means of a procedure similar to that used for methyl 5-isopropyl-3-naphthalen-2-ylisoxazole-4-carboxylate; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.70 (s, 1H), 8.11–8.09 (m, 1H), 7.99 (t, J = 7.3 Hz, 1H), 7.92–7.89 (m, 1H), 7.63–7.56 (m, 2H), 7.45 (d, J = 7.3 Hz, 2H), 7.38 (t, J = 7.3 Hz, 1H), 3.65 (s, 3H); FAB: MS m/z; 398 $(M+H)^+$.

5.1.32. 3-(2,6-Dichlorophenyl)-5-naphthalen-2-yl-isoxazole-4-methanol. This compound was prepared by DIBAL-H reduction of methyl 3-(2,6-dichlorophenyl)-5-naphthalen-2-ylisoxazole-4-carboxylate; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.51 (s, 1H), 8.07 (d, J = 8.5 Hz, 2H), 8.01–7.98 (m, 2H), 7.91 (d, J = 7.3 Hz, 1H),7.60–7.56 (m, 2H), 7.49 (d, J = 8.5 Hz, 2H), 7.44–7.40 (m, 1H), 4.57 (d, J = 6.1 Hz, 2H); FAB: MS m/z; 370 $(M+H)^+$.

5.1.33. 4-Bromomethyl-3-(2,6-dichlorophenyl)-5-naphthalen-2-ylisoxazole (7f). This compound was prepared by bromination of 3-(2,6-dichlorophenyl)-5-naphthalen-2-ylisoxazole-4-methanol by means of a procedure similar to that used for 4-bromomethyl-5-isopropyl-3-(2-naphthyl)isoxazole; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.43 (s, 1H), 8.05–7.98 (m, 3H), 7.92 (d, J = 6.7 Hz, 1H),

7.63–7.58 (m, 2H), 7.50 (d, J = 7.4 Hz, 2H), 7.44–7.42 (m, 1H), 4.41 (s, 2H); FAB: MS m/z; 434 $(M+H)^+$.

5.1.34. 2-Chloro-4-[3-(2,6-dichlorophenyl-)-5-naphthalen-2-ylisoxazol-4-ylmethoxy]benzaldehyde (8f). This compound was prepared from **7f** and 3-chloro-4-formylphenol by means of a procedure similar to that used for 2-chloro-4-(5-isopropyl-3-naphthalen-2-ylisoxazol-4-ylmethoxy)benzaldehyde;^{1}H NMR (500 MHz, $CDCl_3$) δ 10.31 (s, 1H), 8.31 (s, 1H), 8.00 (d, J = 8.5 Hz, 1H), 7.92–7.87 (m, 3H), 7.84 (d, J = 8.5 Hz, 1H), 7.62–7.55 (m, 2H), 7.46 (d, J = 7.3 Hz, 2H), 7.40–7.37 (m, 1H), 6.83–6.79 (m, 2H), 5.03 (s, 2H); FAB: MS m/z; 508 $(M+H)^+$.

5.1.35. Methyl 3-((*E*)-2-{2-chloro-4-[3-(2,6-dichlorophenyl)-5-naphthalen-2-ylisoxazol-4-yl methoxy]phenyl}vinyl)benzoate (9f). This compound was prepared from **8f** and methyl 3-(diethoxyphosphorylmethyl)benzoate by means of a procedure similar to that used for **9b**; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (s, 1H), 8.17 (s, 1H), 8.00 (d, J = 8.5 Hz, 1H), 7.95–7.88 (m, 4H), 7.70 (d, J = 7.9 Hz, 1H), 7.60–7.55 (m, 3H), 7.49–7.37 (m, 5H), 6.99 6.96 (s, 1H), 6.86 (s, 1H), 6.77 (d, J = 9.1 Hz, 1H), 4.96 (s, 2H), 3.94 (s, 3H); FAB: MS m/z; 640 $(M+H)^+$.

5.1.36. 3-((*E*)-2-{2-Chloro-4-[3-(2,6-dichlorophenyl)-5-naphthalen-2-ylisoxazol-4-yl methoxy]phenyl}vinyl)benzoic acid (10f). This compound was prepared from **9f** by means of a procedure similar to that used for **15a**: mp 260–263 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (s, 1H), 8.22 (s, 1H), 8.01–7.88 (m, 5H), 7.77–7.69 (m, 2H), 7.59–7.45 (m, 6H), 7.39 (t, J = 7.3 Hz, 1H), 7.00 6.97 (s, 1H), 6.86 (s, 1H), 6.77 (d, J = 8.5 Hz, 1H), 4.96 (s, 2H); FAB: MS m/z; 626 $(M+H)^+$; HRMS (FAB, MH^+) calcd for $C_{35}H_{23}Cl_3NO_4$ 626.0693, found 626.0685.

5.1.37. Methyl 3-biphenyl-4-yl-3-oxo-propanoate. The compound was prepared from 4-biphenylcarboxylic acid by means of a procedure similar to that used for methyl 3-naphthalen-2-yl-3-oxo-propanoate; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, J = 6.4 Hz, 2H), 7.71–7.39 (m, 7H), 4.05 (s, 2H), 3.77 (s, 3H); FAB: MS m/z; 255 $(M+H)^+$.

5.1.38. Methyl 5-biphenyl-4-yl-3-(2,6-dichlorophenyl)isoxazole-4-carboxylate. This compound was prepared from methyl 3-biphenyl-4-yl-3-oxo-propanoate and 2,6-dichlorophenylhydroximic chloride by means of a procedure similar to that used for methyl 5-isopropyl-3-naphthalen-2-ylisoxazole-4-carboxylate; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (d, J = 8.5 Hz, 1H), 7.77 (d, J = 8.5 Hz, 1H), 7.71–7.34 (m, 10H), 3.24 (s, 3H); FAB: MS m/z; 424 $(M+H)^+$.

5.1.39. 5-Biphenyl-4-yl-3-(2,6-dichlorophenyl)isoxazole-4-methanol. This compound was prepared by DIBAL-H reduction of methyl 5-biphenyl-4-yl-3-(2,6-dichlorophenyl)isoxazole-4-carboxylate; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, J = 8.5 Hz, 2H), 7.78 (d, J = 8.5 Hz, 2H), 7.66 (d, J = 7.9 Hz, 2H), 7.51–7.48 (m, 4H), 7.43–7.39 (m, 2H), 4.53 (d, J = 6.1 Hz, 2H); FAB: MS m/z; 396 $(M+H)^+$.

5.1.40. 5-Biphenyl-4-yl-4-bromomethyl-3-(2,6-dichlorophenyl)isoxazole (7g). This compound was prepared by bromination of 5-biphenyl-4-yl-3-(2,6-dichlorophenyl)isoxazole-4-methanol by means of a procedure similar to that used for 4-bromomethyl-5-isopropyl-3-(2-naphthyl)isoxazole; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, J = 8.5 Hz, 2H), 7.82 (d, J = 8.5 Hz, 2H), 7.67(d, J = 6.7 Hz, 2H), 7.51–7.48 (m, 4H), 7.45–7.42 (m, 2H), 4.36 (s, 2H); FAB: MS m/z; 460 $(M+H)^+$.

5.1.41. 4-[5-Biphenyl-4-yl-3-(2,6-dichlorophenyl)isoxazol-4-ylmethoxy]-2-chlorobenzaldehyde (8g). This compound was prepared from **7g** and 3-chloro-4-formylphenol by means of a procedure similar to that used for 2-chloro-4-(5-isopropyl-3-naphthalen-2-ylisoxazol-4-ylmethoxy)benzaldehyde; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.31 (s, 1H), 8.31 (s, 1H), 7.90 (d, J = 8.5 Hz, 2H), 7.83 (d, J = 8.5 Hz, 1H), 7.77 (d, J = 8.5 Hz, 2H), 7.65 (d, J = 6.7 Hz, 2H), 7.50–7.36 (m, 6H), 6.81 (s, 1H), 6.78 (d, J = 6.7 Hz, 1H), 4.98 (s, 2H); FAB: MS m/z; 534 $(M+H)^+$.

5.1.42. Methyl 3-((*E*)-2-{4-[5-biphenyl-4-yl-3-(2,6-dichlorophenyl)isoxazol-4-ylmethoxy]-2-chlorophenyl}vinyl)benzoate (9g). This compound was prepared from **8g** and methyl 3-(diethoxyphosphorylmethyl)benzoate by means of a procedure similar to that used for **9b**; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.94–7.92 (m, 3H), 7.77 (d, J = 7.9 Hz, 2H), 7.70 (d, J = 7.3 Hz, 1H), 7.66 (d, J = 7.3 Hz, 2H), 7.55 (d, J = 9.1 Hz, 1H), 7.55–7.36 (m, 8H), 6.99 6.95 (s, 1H), 6.84 (s, 1H), 6.76 (d, J = 8.5 Hz, 1H), 4.91 (s, 2H), 3.94 (s, 3H); FAB: MS m/z; 666 $(M+H)^+$.

5.1.43. 3-((*E*)-2-{4-[5-Biphenyl-4-yl-3-(2,6-dichlorophenyl)isoxazol-4-yl methoxy]-2-chlorophenyl}vinyl)benzoic acid (10g). This compound was prepared from **9g** by means of a procedure similar to that used for **15a**: mp 220–224 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (s, 1H), 8.00 (d, J = 7.7 Hz, 1H), 7.94 (d, J = 8.1 Hz, 2H), 7.78–7.75 (m, 3H), 7.66 (d, J = 6.8 Hz, 2H), 7.57 (d, J = 8.1 Hz, 1H), 7.51–7.37 (m, 8H), 7.00 6.97 (s, 1H), 6.85 (s, 1H), 6.77 (d, J = 8.5 Hz, 1H), 4.92 (s, 2H); FAB: MS m/z; 652 $(M+H)^+$; HRMS (FAB, MH^+) calcd for $C_{37}H_{25}Cl_3NO_4$ 652.0849, found 652.0848.

5.1.44. Methyl 5-*tert*-butyl-3-(2,6-dichlorophenyl)isoxazole-4-carboxylate. This compound was prepared from methyl pivaloylacetate and 2,6-dichlorophenylhydroximic chloride by means of a procedure similar to that used for methyl 5-isopropyl-3-naphthalen-2-ylisoxazole-4-carboxylate; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, J = 7.3 Hz, 2H), 7.32 (t, J = 6.7 Hz, 1H), 3.72 (s, 3H), 1.16 (s, 9H); FAB: MS m/z; 328 $(M+H)^+$.

5.1.45. 5-*tert*-Butyl-3-(2,6-dichlorophenyl)isoxazole-4-methanol. This compound was prepared by DIBAL-H reduction of methyl 5-*tert*-butyl-3-(2,6-dichlorophenyl)isoxazole-4-carboxylate; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, J = 6.7 Hz, 2H), 7.37 (t, J = 7.3 Hz, 1H), 4.36 (d, J = 7.3 Hz, 2H), 1.52 (s, 9H); FAB: MS m/z; 300 $(M+H)^+$.

5.1.46. 4-Bromomethyl-5-*tert*-butyl-3-(2,6-dichlorophenyl)-isoxazole (7d). This compound was prepared by bromination of 5-*tert*-butyl-3-(2,6-dichlorophenyl)isoxazole-4-methanol by means of a procedure similar to that used for

4-bromomethyl-5-isopropyl-3-(2-naphthyl)isoxazole; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45–7.44 (m, 2H), 7.40–7.36 (m, 1H), 4.22 (s, 2H), 1.53 (s, 9H); FAB: MS *m*/*z*; 362 $(M+H)^+$.

5.1.47. 4-[5-*tert*-Butyl-3-(2,6-dichlorophenyl)isoxazol-4-ylmethoxy]-2-chlorobenzaldehyde (8d). This compound was prepared from **7d** and 3-chloro-4-formylphenol by means of a procedure similar to that used for 2-chloro-4-(5-isopropyl-3-naphthalen-2-ylisoxazol-4-ylmethoxy)benzaldehyde; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.30 (s, 1H), 7.82 (d, J = 9.0 Hz, 1H), 7.40 (d, J = 7.7 Hz, 2H), 7.33 (t, J = 7.7 Hz, 1H), 6.79 (d, J = 6.8 Hz, 1H), 6.75 (d, J = 9.0 Hz, 1H), 4.79 (s, 2H),1.51 (s, 9H); FAB: MS *m*/*z*; 438 $(M+H)^+$.

5.1.48. Methyl 3-((*E*)-2-{4-[5-*tert*-butyl-3-(2,6-dichlorophenyl)isoxazol-4-ylmethoxy]-2-chlorophenyl}vinyl)benzoate (9d). This compound was prepared from **8d** and methyl 3-(diethoxyphosphorylmethyl)benzoate by means of a procedure similar to that used for **9b**; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.92 (d, J = 7.7 Hz, 1H), 7.70 (d, J = 7.7 Hz, 1H), 7.54 (d, J = 8.5 Hz, 1H), 7.47–7.39 (m, 4H), 7.33 (t, J = 8.5 Hz, 1H), 6.97 6.94 (s, 1H), 6.79 (s, 1H), 6.71 (d, J = 8.5 Hz, 1H), 4.73 (s, 2H), 3.94 (s, 3H), 1.51 (s, 9H); FAB: MS *m*/*z*; 570 $(M+H)^+$.

5.1.49. 3-((*E*)-2-{4-[5-*tert*-Butyl-3-(2,6-dichlorophenyl)isoxazol-4-ylmethoxy]-2-chlorophenyl}vinyl)benzoic acid (10d). This compound was prepared from **9d** by means of a procedure similar to that used for **15a**: mp 230–232 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 (s, 1H), 8.00 (d, J = 7.7 Hz, 1H), 7.76 (d, J = 7.7 Hz, 1H), 7.55 (d, J = 8.5 Hz, 1H), 7.49–7.45 (m, 2H), 7.40 (d, J = 7.7 Hz, 2H), 7.33 (t, J = 7.7 Hz, 1H), 6.96 (s, 1H), 6.80 (d, J = 2.5 Hz, 1H), 6.71 (d, J = 8.5 Hz, 1H), 4.73 (s, 2H), 1.51 (s, 9H); FAB: MS *m*/*z*; 556 $(M+H)^+$; HRMS (FAB, MH^+) calcd for $C_{29}H_{25}Cl_3NO_4$ 556.0849, found 556.0845.

5.1.50. Ethyl 3-(2,6-dichlorophenyl)-5-phenylisoxazole-4-carboxylate. This compound was prepared from ethyl benzoylacetate and 2,6-dichlorophenylhydroximic chloride by means of a procedure similar to that used for methyl 5-isopropyl-3-naphthalen-2-yl-isoxazole-4-carboxylate; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08–7.35 (m, 8H), 4.29–4.01 (m, 2H), 0.95–0.92 (s, 2H); FAB: MS *m*/*z*; 362 $(M+H)^+$.

5.1.51. 3-(2,6-Dichlorophenyl)-5-phenylisoxazole-4-methanol. This compound was prepared by DIBAL-H reduction of methyl ethyl 3-(2,6-dichlorophenyl)-5-phenylisoxazole-4-carboxylate; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07–7.98 (m, 2H), 7.56–7.38 (m, 6H), 4.49 (s, 2H); FAB: MS *m*/*z*; 320 $(M+H)^+$.

5.1.52. 4-Bromomethyl-3-(2,6-dichlorophenyl)-5-phenylisoxazole (7e). This compound was prepared by bromination of 3-(2,6-dichlorophenyl)-5-phenylisoxazole-4-methanol by means of a procedure similar to that used for 4-bromomethyl-5-isopropyl-3-(2-naphthyl)isoxazole; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93–7.91 (m, 2H), 7.60–7.53 (m, 3H), 7.49–7.48 (m, 2H), 7.44–7.41 (m, 1H), 4.33 (s, 2H); FAB: MS *m*/*z*; 384 $(M+H)^+$.

5.1.53. 4-[3-(2,6-Dichlorophenyl)-5-phenylisoxazol-4-ylmethoxy]-2-chlorobenzaldehyde (8e). This compound was prepared from **7e** and 3-chloro-4-formylphenol by means of a procedure similar to that used for 2-chloro-4-(5-isopropyl-3-naphthalen-2-ylisoxazol-4-ylmethoxy)benzaldehyde; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.31 (s, 1H), 7.83–7.80 (m, 3H), 7.55–7.54 (m, 3H), 7.44 (d, J = 8.9 Hz, 2H), 7.37 (t, J = 8.9 Hz, 1H), 6.78 (d, J = 2.5 Hz, 1H), 6.76 (d, J = 8.5 Hz, 1H), 4.95 (s, 2H); FAB: MS *m*/*z*; 459 $(M+H)^+$.

5.1.54. Methyl 3-((*E*)-2-{4-[3-(2,6-dichlorophenyl)-5-phenylisoxazol-4-ylmethoxy]-2-chlorophenyl}vinyl)benzoate (9e). This compound was prepared from **8e** and methyl 3-(diethoxyphosphorylmethyl)benzoate by means of a procedure similar to that used for **9b**; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.93 (d, J = 7.7 Hz, 1H), 7.87–7.85 (m, 3H), 7.70 (d, J = 7.7 Hz, 1H), 7.55–7.35 (m, 8H), 6.98 6.95 (s, 1H), 6.81 (d, J = 2.5 Hz, 1H), 6.73 (d, J = 8.5 Hz, 1H), 4.88 (s, 2H), 3.94 (s, 3H); FAB: MS *m*/*z*; 590 $(M+H)^+$.

5.1.55. 3-((*E*)-2-{4-[3-(2,6-Dichlorophenyl)-5-phenylisoxazol-4-ylmethoxy]-2-chlorophenyl}vinyl)benzoic acid (10e). This compound was prepared from **9e** by means of a procedure similar to that used for *15a*; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (s, 1H), 8.01 (d, J = 7.9 Hz, 1H), 7.87–7.85 (m, 3H), 7.76 (d, J = 7.9 Hz, 1H), 7.56–7.43 (m, 7H), 7.37 (t, J = 8.9 Hz, 1H), 7.00 6.97 (s, 1H), 6.82 (d, J = 2.5 Hz, 1H), 6.79 (d, J = 8.5 Hz, 1H), 4.89 (s, 2H); FAB: MS *m*/*z*; 576 $(M+H)^+$; HRMS (FAB, MH^+) calcd for $C_{31}H_{21}Cl_3NO_4$ 576.0536, found 576.0526.

5.1.56. 2-Chloro-4-[3-(2,6-dichlorophenyl-)-5-naphthalen-2-ylisoxazol-4-ylmethoxy]benzoic acid (12f). This compound was prepared from 2-chloro-4-[3-(2,6-dichlorophenyl-)-5-naphthalen-2-ylisoxazol-4-ylmethoxy]benzaldehyde by means of a procedure similar to that used for 2-chloro-4-[3-(2,6-dichlorophenyl)-5-isopropylosoxazol-4-ylmethoxy]benzoic acid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (s, 1H), 8.10–7.96 (m, 2H), 7.91–7.87 (m, 3H), 7.61–7.55 (m, 2H), 7.46 (d, J = 9.0 Hz, 2H), 7.39 (t, J = 9.0 Hz, 1H), 6.89 (d, J = 2.5 Hz, 1H), 6.77 (dd, J = 2.5, 8.5 Hz, 1H), 5.01 (s, 2H); FAB: MS *m*/*z*; 524 $(M+H)^+$.

5.1.57. Methyl 3-{2-chloro-4-[3-(2,6-dichlorophenyl)-5-naphthalen-2-ylisoxazol-4-ylmethoxy]benzoylamino}benzoate (13f). This compound was prepared from **12f** by means of a procedure similar to that used for 3((*E*)-2-{2-chloro-4-[3-(2,6-dichlorophenyl)-5-isopropylosoxazol-4-ylmethoxy]phenyl}vinyl)-*N*-*n*-propyl benzamide (**11a**); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (s, 1H), 8.11 (s, 1H), 8.03-8.00 (m, 2H), 7.93-7.89 (m, 3H), 7.83 (d, J = 8.5 Hz, 1H), 7.78 (d, J = 8.5 Hz, 1H), 7.62–7.56 (m, 2H), 7.47–7.44 (m, 3H), 7.40 (t, J = 9.4 Hz, 1H), 6.86 (d, J = 2.5 Hz, 1H), 6.83 (dd, J = 2.5, 8.5 Hz, 1H), 5.01 (s, 2H), 3.93 (s, 3H); FAB: MS *m*/*z*; 657 $(M+H)^+$.

5.1.58. 3-{2-Chloro-4-[3-(2,6-dichlorophenyl)-5-naphthalen-2-ylisoxazol-4-ylmethoxy]benzoylamino}benzoic acid (15g). This compound was prepared from **13f** by means of a procedure similar to that used for **15a**:

mp 112–115 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (s, 1H), 8.16 (d, J = 6.4 Hz, 2H), 8.11 (d, J = 8.4 Hz, 1H), 8.01 (d, J = 8.9 Hz, 1H), 7.93–7.89 (m, 4H), 7.79 (d, J = 8.9 Hz, 1H), 7.62–7.56 (m, 2H), 7.51–7.46 (m, 3H), 7.40 (t, J = 8.9 Hz, 1H), 6.87 (d, J = 2.5 Hz, 1H), 6.83 (dd, J = 2.5, 8.5 Hz, 1H), 5.02 (s, 2H); FAB: MS m/z; 643; HRMS (FAB, MH^+) calcd for $C_{34}H_{22}Cl_3N_2O_5$ 643.0594, found 643.0604.

5.1.59. 4-[5-Biphenyl-4-yl-3-(2,6-dichlorophenyl)isoxazol-4-ylmethoxy]-2-chlorobenzoic acid (12g). This compound was prepared from 4-[5-biphenyl-4-yl-3-(2,6-dichlorophenyl)isoxazol-4-ylmethoxy]-2-chlorobenzaldehyde by means of a procedure similar to that used for 2-chloro-4-[3-(2,6-dichlorophenyl)-5-isopropylisoxazol-4-ylmethoxy]benzoic acid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, J = 8.9 Hz, 1H), 7.90 (d, J = 8.5 Hz, 2H), 7.77 (d, J = 8.5 Hz, 2H), 7.65 (d, J = 7.7 Hz, 2H), 7.50–7.37 (m, 6H), 6.88 (d, J = 2.5 Hz, 1H), 6.75 (dd, J = 2.5, 8.9 Hz, 1H), 4.97 (s, 2H); FAB: MS m/z; 550 $(M+H)^+$.

5.1.60. Methyl 3-{4-biphenyl-4-yl-3-(2,6-dichlorophenyl)isoxazol-4-ylmethoxy]-2-chlorobenzoylamino}benzoate (13g). This compound was prepared from **12g** by means of a procedure similar to that used for **11a**; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (s, 2H), 8.02 (d, J = 7.7 Hz, 1H), 7.92 (d, J = 8.5 Hz, 2H), 7.83 (d, J = 8.5 Hz, 2H), 7.78 (d, J = 8.5 Hz, 1H), 7.66 (d, J = 7.3 Hz, 2H), 7.50–7.38 (m, 7H), 6.85 (d, J = 2.5 Hz, 1H), 6.81 (dd, J = 2.5, 8.5 Hz, 1H), 4.97 (s, 2H), 3.93 (s, 3H); FAB: MS m/z; 683 $(M+H)^+$.

5.1.61. 3-{4-Biphenyl-4-yl-3-(2,6-dichlorophenyl)-isoxazol-4-ylmethoxy]-2-chlorobenzoylamino}benzoate (15h). This compound was prepared from methyl 3-{2-chloro-4-[3-(2,6-dichlorophenyl)-5-naphthalen-2-ylisoxazol-4-ylmethoxy]benzoylamino}benzoate by means of a procedure similar to that used for**15a**: mp 115–117 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, J = 9.4 Hz, 2H), 8.10 (d, J = 8.7 Hz, 1H), 7.93–7.89 (m, 3H), 7.78 (d, J = 8.5 Hz, 2H), 7.66 (d, J = 8.5 Hz, 2H), 7.51–7.45 (m, 5H), 7.42–7.438 (m, 2H), 6.85 (d, J = 2.5 Hz, 1H), 6.81 (dd, J = 2.5, 8.5 Hz, 1H), 4.97 (s, 2H); FAB: MS m/z; 669 $(M+H)^+$; HRMS (FAB, MH^+) calcd for $C_{36}H_{24}Cl_3N_2O_5$ 669.0751, found 669.0759.

5.1.62. 4-[5-*tert*-Butyl-3-(2,6-dichlorophenyl)isoxazol-4-ylmethoxy]-2-chlorobenzoic acid (12d). This compound was prepared from 4-[5-*tert*-butyl-3-(2,6-dichlorophenyl)isoxazol-4-ylmethoxy]-2-chlorobenzaldehyde by means of a procedure similar to that used for 2-chloro-4-[3-(2,6-dichlorophenyl)-5-isopropylosoxazol-4-ylmethoxy]benzoic acid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, J = 9.0 Hz, 1H), 7.40 (d, J = 8.9 Hz, 2H), 7.32 (t, J = 8.9 Hz, 1H), 6.84 (d, J = 2.5 Hz, 1H), 6.71 (dd, J = 2.5, 9.0 Hz, 1H), 4.78 (s, 2H), 1.51 (s, 9H); FAB: MS m/z; 454 $(M+H)^+$.

5.1.63. Methyl 3-{5-*tert*-butyl-3-(2,6-dichlorophenyl)isoxazol-4-ylmethoxy]-2-chlorobenzoylamino}benzoate (13d). This compound was prepared from **12d** by means of a procedure similar to that used for **11a**; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, J = 15.3 Hz, 2H), 8.02 (d, J = 8.1 Hz, 1H), 7.84–7.76 (m, 1H), 7.45 (t, J = 8.1 Hz, 1H), 7.42–7.40 (m, 1H), 7.33 (t, J = 8.5 Hz, 1H), 6.82 (d, J = 2.5 Hz, 1H), 6.77 (dd, J = 2.5, 8.5 Hz, 1H), 4.78 (s, 2H), 3.92 (s, 3H), 1.52 (s, 9H); FAB: MS m/z; 587 $(M+H)^+$.

5.1.64. 3-{5-*tert*-Butyl-3-(2,6-dichlorophenyl)isoxazol-4-ylmethoxy]-2-chlorobenzoylamino}benzooic acid (15f). This compound was prepared from methyl 3-{5-*tert*-butyl-3-(2,6-dichlorophenyl)isoxazol-4-ylmethoxy]-2-chlorobenzoylamino}benzoate by means of a procedure similar to that used for **15a**: mp 100–104 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16–8.09 (m, 2H), 7.89 (d, J = 8.9 Hz, 1H), 7.79 (d, J = 8.5 Hz, 1H), 7.49 (t, J = 8.1 Hz, 1H), 7.42–7.40 (m, 2H), 7.34 (t, J = 8.9 Hz, 1H), 6.82 (d, J = 2.5 Hz, 1H), 6.78 (dd, J = 2.5, 8.9 Hz, 1H), 4.78 (s, 2H), 1.52 (s, 9H); MS (FAB, MH^+) m/z 573; HRMS (FAB, MH^+) calcd for $C_{28}H_{24}Cl_3N_2O_5$ 573.0751, found 573.0775.

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