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Separation of α-glucosidase-inhibitory and liver X receptor-antagonistic activities of phenethylphenyl phthalimide analogs and generation of LXRα-selective antagonists

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ABSTRACT

Liver X receptor (LXR) α/β dual agonists are candidate medicaments for the treatment of metabolic syndrome, because their biological actions include increasing cholesterol efflux mediated by LXRβ. However, their clinical application is currently limited by their enhancing effect on triglyceride (TG) synthesis mediated by LXRα. Combination of an LXRα-selective antagonist with an LXRα/β dual agonist may overcome this disadvantage. In the present work, structural development studies of phenethylphenyl phthalimide **9**, which possesses LXRα/β dual-antagonistic activity and α-glucosidase-inhibitory activity, led to the LXRα-selective antagonist **23f**. Specific α-glucosidase inhibitors were also obtained.

1. Introduction

Liver X receptors (LXRα and LXRβ) are members of the nuclear receptor superfamily.[1] LXRα is most highly expressed in liver and is abundant in other tissues involved in lipid metabolism. LXRβ has a more widespread pattern of expression, being almost ubiquitous. Their physiological ligands are considered to be oxysterols, including 24(*S*),25-epoxycholesterol and 22(*R*)-hydroxycholesterol. Upon ligand binding, LXRs form heterodimers with the retinoid X receptor (RXR). The LXR/RXR heterodimer binds to LXR response elements in promoter regions of specific genes,[2,3] modulating gene transcription by recruiting coactivators.[4,5] LXRs are considered to function as cholesterol sensors, and to regulate the expression of genes associated with cholesterol efflux, absorption and transport.[6,7] The activation of LXRs leads to an increase in plasma HDL levels and net cholesterol efflux via up-regulation of gene expression of ATP-binding cassette (ABC) membrane transporters, including ABCA1,[8,9] ABCG5, ABCG8[10] and ABCG1.[11,12] ABCA1 functions in transporting cholesterol and phospholipids to ApoA-I, which is a critical step in cholesterol efflux via HDL. In animal studies, the activation of LXR led to an increase of HDL level and a decrease of atherosclerotic lesions through the induction of peripheral cholesterol efflux.[9,13] There is increasing evidence suggesting that the therapeutic effects of LXR activation on atherosclerosis are associated with stimulation of cholesterol efflux, rather than simply an increase of serum HDL.[13,14]

Currently available typical synthetic LXR agonists T0901317 (**1**)[15] and GW3965 (**2**)[16] (Fig. 1) non-selectively activate both LXRα and LXRβ. They also activate triglyceride (TG) synthesis in the liver by the up-regulation of sterol regulatory element binding protein 1c (SREBP1c) and fatty acid synthase (FAS), and this activity limits the clinical utility of these LXR agonists.[15,17] There is increasing evidence that the undesirable stimulation of lipogenesis by LXR ligands is largely attributable to LXRα. It has been demonstrated that administration of an LXRα/β dual agonist to LXRα-null mice results in increased HDL levels without significant hepatic TG accumulation.[18] In these genetically modified mice, hepatic mRNA levels of many lipogenic genes, including SREBP1c, FAS, and lipoprotein lipase genes, were markedly reduced by LXR agonists, as compared to wild-type mice. More importantly, LXRα-deficient macrophages from LXRα-null mice retained the ability to increase ABCA1,[9,19] implying that LXRβ is capable of inducing cholesterol efflux in macrophages without inducing significant hepatic fatty acid synthesis.

These considerations led researchers to focus on LXRβ-selective ligands. LXRα and LXRβ are highly related and share 77% amino acid sequence identity in both the DNA-binding and ligand-binding domains (LBD).[1] Therefore, the design of LXR subtype-selective ligands is challenging. To date, only one series of ligands, including **3**, appear to be LXRβ-selective agonists based on binding assay, although they act as LXRα/β dual agonists in reporter gene assay.[20] As an alternative approach, it seems plausible to speculate that usage of an LXRα-selective antagonist in conjunction with an LXR α/β dual agonist may circumvent the undesirable effect of increased lipogenesis mediated by LXRα while maintaining the

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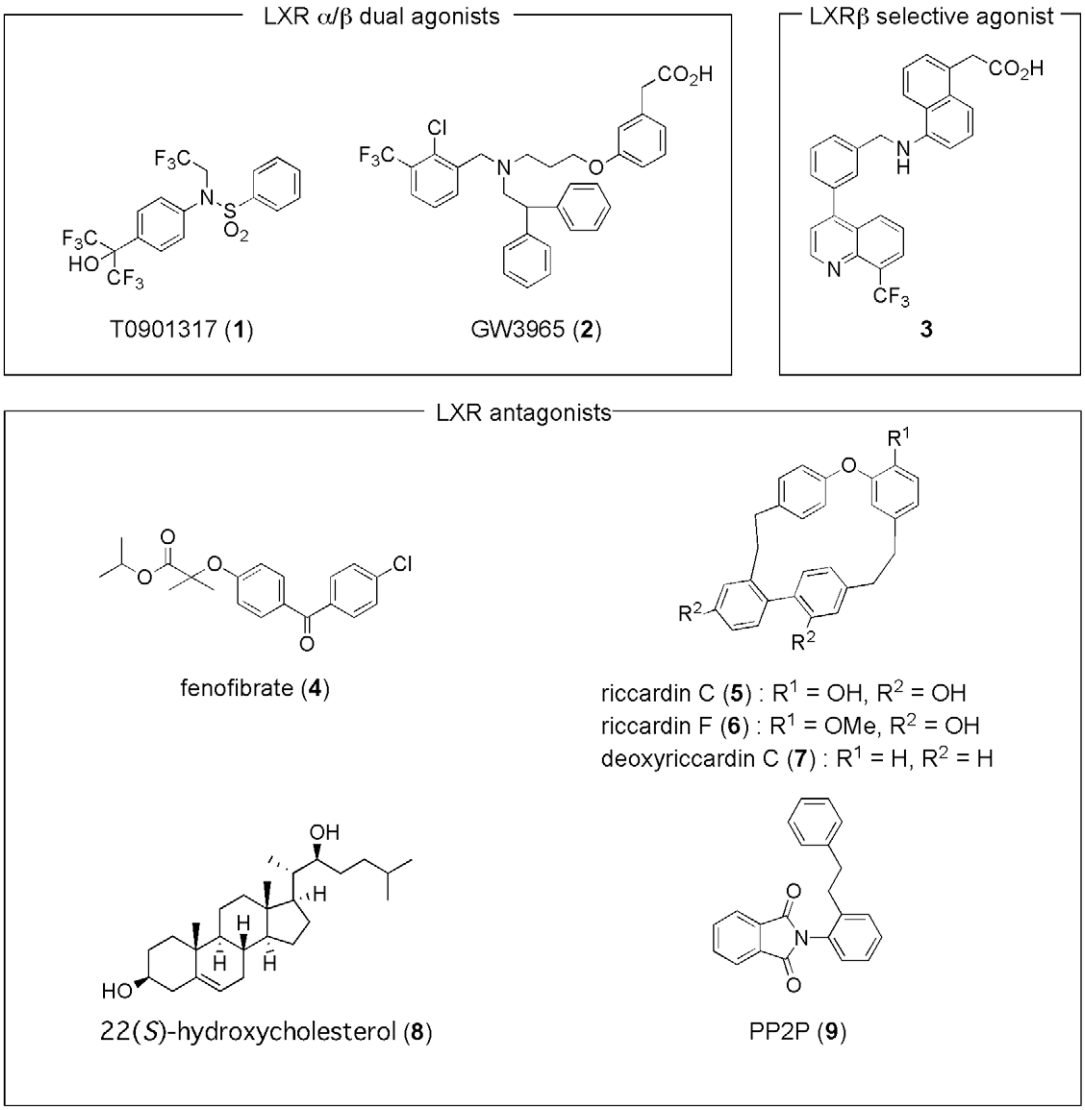


Figure 1. Chemical structures of LXR ligands.

enhanced cholesterol efflux mediated by LXRβ. There is some evidence in support of this idea. Herbal extracts, which have LXRα-selective antagonistic activity, have been reported to suppress the expression of LXRα-responsive genes, such as FAS and SREBP1c.[21] These extracts also significantly reduce lipogenesis and adipocyte differentiation. However, the active ingredients have not been identified. As another example, an LXR α/β dual antagonist, fenofibrate (**4**), was reported to repress LXR agonist-induced transcription of hepatic lipogenic genes.[22] Surprisingly, however, fenofibrate (**4**) did not repress LXR-induced transcription of ABCA1 in liver or in macrophages. Concerning LXR antagonists, those reported so far include riccardin C (**5**)[23] (LXRα partial agonist/LXRβ antagonist), riccardin F (**6**)[23] (LXRα antagonist), riccardin C analogs[24] [LXRα/β dual antagonists and an antagonist with slight LXRα selectivity (**7**)], and 22(*S*)-hydroxycholesterol (**8**)[25] (LXRα/β dual antagonists) (Fig. 1).

We have focused on the creation of LXR antagonists using a multi-template approach based on thalidomide. The multi-template approach is based on the reports that the number of three-dimensional spatial structures (fold structures) of human proteins is much smaller (more than 50 times smaller) than the number of human proteins (50,000–70,000).[26–29] Therefore, ignoring physical/chemical interactions, a template/scaffold structure which is spatially complementary to one fold structure might serve as a multi-template for structural development of ligands that would interact specifically with more than 50 different human proteins. In other words, the structures of ligands that bind to a protein having a certain fold structure may be useful for the development of novel ligands for other proteins possessing the same fold structure. One of the multi-templates that we have adopted is thalidomide, which is a drug first launched as a sedative/hypnotic agent, but withdrawn from the market because of its severe teratogenicity. Focusing on the potential of the thalidomide template for the treatment of a wide range of diseases, including cancers, diabetes, and rheumatoid arthritis, we have created compounds thalidomide analogs with a range of biological activities.[30–33] During our studies, we found that several thalidomide-related phthalimide derivatives, including PP2P (**9**) (Fig. 1), possess LXR-antagonistic activity as well as α-glucosidase-inhibitory activity.[24,34,35] The co-existence of LXR-modulating activity and α-glucosidase-inhibitory activity may be general, because typical LXR ligands, including T0901317 (**1**), GW3965 (**2**), 22-(*R*)-hydroxycholesterol and riccardin C (**5**) were found to possess potent α-glucosidase-inhibitory activity.[24] These results suggested that our previously reported thalidomide-related α-glucosidase inhibitors[24,34–38] might represent a superior scaffold structure for the development of LXR antagonists.

The issues to be addressed were therefore the separation of α-glucosidase-inhibitory and LXR-antagonistic activities and the creation of LXRα-selective antagonists. Here, we describe the design, synthesis, and structure–activity relationship studies of phenethylphenyl phthalimide derivatives to generate an LXRα-selective antagonist.

2. Results and discussion

2.1. Choice of the phenethylphthalimide skeleton as a scaffold

Initially, we selected our previously reported PP2P (**9**) as a prototype.[24,34,35] We also noted the similarity of the biological activities (i.e., LXR-antagonistic activity and α-glucosidase-inhibitory activity) elicited by PP2P (**9**) and riccardin C (**5**).[24] Although the binding site of PP2P (**9**)/riccardin C (**5**) on α-glucosidase, the crystal structure of α-glucosidase, and the precise binding mode of PP2P (**9**)/riccardin C (**5**) to LXR are all unknown, we expected that PP2P (**9**) and riccardin C (**5**) would bind to the same, or at least similar, sites in both LXR and α-glucosidase. If this were the case, the common structure of PP2P (**9**) and riccardin C (**5**), represented by bold lines/letters in Figure 2 might be critical. This speculation, as well as the results of our previous structural development studies of riccardin C (**5**), which afforded novel LXR antagonists lacking α-glucosidase-inhibitory activity,[24] prompted us to prepare regioisomers of the phenethyl group and cinnamyl analogs of PP2P (**9**), focusing on differences in the position or rigidity of the phenethyl moiety in PP2P (**9**) and riccardin C (**5**). In addition, based on the structure of riccardins and the critical role of hydroxyl and/or methoxy group(s) for their biological activities,[24] substituent

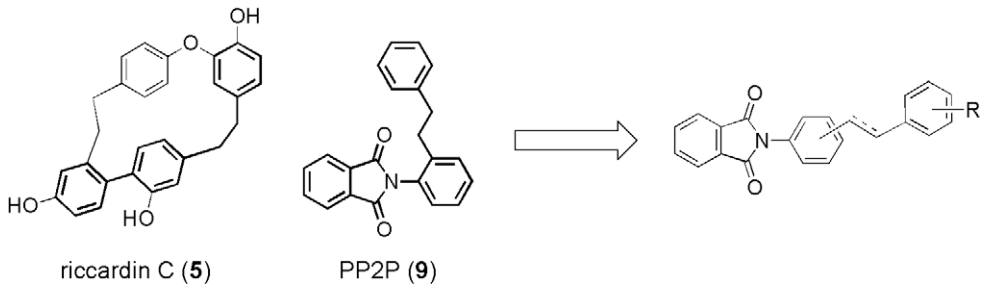
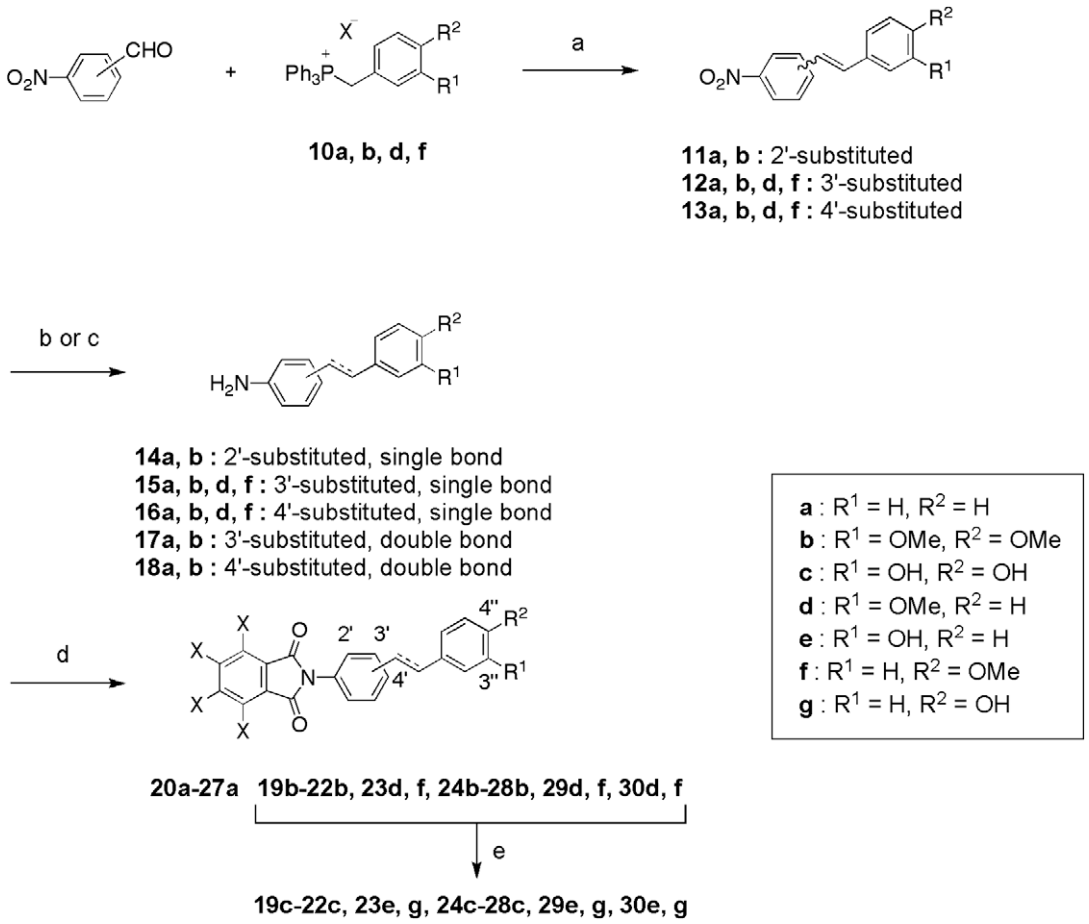


Figure 2. Common structure of riccardin C (**5**) and PP2P (**9**), and molecular design of phenethylphenyl phthalimide.



Scheme 1. Synthesis of phenethylphenyl phthalimide analogs. *Reagents and conditions*: (a) K_2CO_3, 18-crown-6, CH_2Cl_2, reflux; (b) H_2 10% Pd/C, EtOAc, rt; (c) $SnCl_2{\cdot}2H_2O$, EtOAc, reflux; (d) phthalic anhydride or tetrachlorophthalic anhydride, neat, 200 °C; (e) BBr_3, CH_2Cl_2, 0 °C.

effects involving one or two hydroxyl or methoxy group(s) were investigated. We also aimed to generate specific α-glucosidase inhibitors lacking LXRs-antagonistic activity, in order to extend the multi-template approach. Thus, tetrachlorophthalimide analogs were also designed based on our previous structure–activity relationship studies indicating that tetrachlorophthalimide analogs possess more potent α-glucosidase-inhibitory activity than the corresponding phthalimide analogs.[36–38]

Phenylphthalimide analogs were synthesized as shown in Scheme 1. Briefly, diphenylethene derivatives **11**–**13** were prepared as *E*/*Z* mixtures by Wittig reaction of nitrobenzaldehyde with ylide **10**. For the synthesis of cinnamyl analogs, *E* derivatives (**12*E***, **13*E***) were separated by the use of silica gel column chromatography. After reduction of the nitro group and/or olefin moiety of compounds **11**–**13**, phenylphthalimide series **19**–**30** were obtained by condensation with phthalic anhydride.

2.2. Structure–activity relationship for α-glucosidase-inhibitory activity

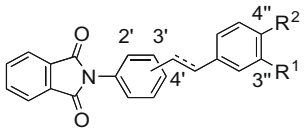
Antagonistic activities for LXRs were evaluated using a reporter gene assay method with CMX-GAL4 N-hLXR as the recombinant receptor gene, TK-MH100x4-LUC as the reporter gene, and the CMX β-galactosidase gene for normalization, as previously reported.[39–41] All compounds did not reduce β-galactosidase activity at evaluated concentrations unless otherwise noted in Tables 1–3. None of the compounds tested show agonistic activity under the experimental conditions used (data not shown).

First, the activities of PP2P (**9**) were compared with those of its regio-isomers, **20a** and **21a** (Table 1). Positional shift of the phenethyl moiety of PP2P (**9**) from the 2′-position to the 3′- or 4′-position resulted in disappearance of α-glucosidase-inhibitory activity. Introduction of two methoxy or hydroxyl groups into the terminal phenyl moiety of PP2P (**9**), that is, compounds **19b** and **19c**, also resulted in disappearance of α-glucosidase-inhibitory activity (Table 1). However, introduction of two hydroxyl groups into the corresponding positions of the 3′-isomer **20a**, that is, compound **20c**, resulted in re-appearance of the activity, though it was weaker than that of PP2P (**9**). Cinnamyl analog **22a** showed very weak activity. Among the compounds listed in Table 1, only PP2P (**9**), **20c** and **22a** were found to elicit α-glucosidase-inhibitory activity under the experimental conditions used. Broadly speaking, 4′-phenethyl derivatives are all inactive toward α-glucosidase regardless of the presence of one (Table 2) or two (Table 1) methoxy or hydroxyl group(s).

Next, based on our previous finding that tetrachlorophthalimide derivatives tend to possess α-glucosidase-inhibitory activity, tetrachlorophthalimide analogs **24**–**30** were prepared and their activities were evaluated (Table 3). Although tetrachlorination of PP2P (**9**), that is, compound **24a**, resulted in disappearance of the activity, this seemed to be exceptional. Concerning other derivatives, almost all of the tetrachlorophthalimide derivatives showed more potent α-glucosidase-inhibitory activity (Table 3) than that of the corresponding phthalimide derivatives (Tables 1 and 2), that is, the orders of the potency of the activity are: **24c** > **19c**, **25b** > **20b**, **25c** > **20c**, **26a** > **21a**, **26b** > **21b**, **28a** > **22a**, **28b** > **22b**, **30d** > **23d**, **30e** > **23e**, and **30g** > **23g**. Concerning the substituent effects of methoxy and hydroxyl groups, the case observed in 2′-phenethyl isomers seem exceptional, as mentioned above. In the case of 3′-phenethyl [**20a–c** (Table 1) and **25a–c** (Table 3)] and 3′-cinnamyl derivatives [**27a–c** (Table 3)], the potency of α-glucosidase-inhibitory activity decreased in the order of: dihydroxyl > dimethoxy > non-substituted derivatives [**20c** > **20b** (inactive) = **20a** (inactive), **25c** > **25b** > **25a** (inactive), and **27c** > **27b** > **27a**]. Concerning the substituent effect elicited by hydroxyl groups, the 3″-position seems to be critical, because **29e** showed moderate activity, while its regio-isomer **29g** was inactive (Table 3). On the other hand, in the case of 4′-phenethyl [**26a–c** (Table 3)] and 4′-cinnamyl derivatives [**22a–c** (Table 1) and **28a–c** (Table 3)], the order of the potency seems just reversed, that is, non-substituted > dimethoxy > dihydroxyl derivatives [**22a** > **22b** (inactive) = **22c** (inactive), **26a** ≥ **26b** > **26c** (inactive), **28a** > **28b** > **28c** (inactive)]. Concerning the substituent effect elicited by methoxy groups, the 3″-position seems to be critical, as is the case for hydroxyl groups (vide supra), because **30d** showed moderate activity while its regio-isomer **30f** was inactive (Table 3).

Overall, the structure–activity relationships for α-glucosidase-inhibitory activity mentioned above are quite complex, though some trends are apparent. Among the compounds prepared, **24c**, **26a**, **26b**, and **27c** showed rather potent α-glucosidase-inhibitory activities, which are comparable to that of PP2P (**9**), with IC_{50} values of lower than 20 μM. Especially, **26a** and **26b** showed only very

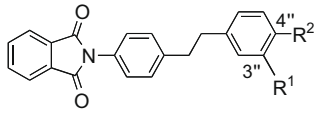
Table 1
α-Glucosidase-inhibitory and LXR-antagonistic activities of phenethylphenyl phthalimides (**9**, **19**–**22**)



Compound	Position	Single (s) or double bond (d)	R^1, R^2	α-Glucosidase IC_{50} (μM)	LXRα		LXRβ	
					% inhibition at 10 μM	IC_{50} (μM)	% inhibition at 10 μM	IC_{50} (μM)
9	2′	s	H	16.2	40	9.8	24	>30
19b	2′	s	OMe	>100	56	7.4	13	>30
19c	2′	s	OH	>100	50	9.8	6	>30
20a	3′	s	H	>100	34	>30	40	>30
20b	3′	s	OMe	>100	33	>30	41	>30
20c	3′	s	OH	38	68	6.1	61	7.6
21a	4′	s	H	>100	23	>30	7	>30
21b	4′	s	OMe	>100	65	4.8	62	4.3
21c	4′	s	OH	>100	Toxic[a]	1.7	Toxic[a]	>3[b]
22a	4′	d	H	90	30	>30	10	>30
22b	4′	d	OMe	>100	66	3.8	10	>30
22c	4′	d	OH	>100	Toxic[a]	1.6	Toxic[a]	>1[b]

[a] The cytotoxicity was observed when the assay was performed at 10 μM.
[b] IC_{50} values could not be calculated because the cytotoxicity of this compound was observed at this concentration.

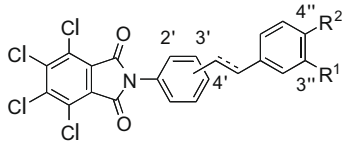
Table 2
α-Glucosidase-inhibitory and LXR-antagonistic activities of 3″- or 4″-substituted analogues of phenethylphenyl phthalimides (**21b**, **21c**, **23**)



Compound	R^1	R^2	α-Glucosidase IC_{50} (μM)	LXRα		LXRβ	
				% inhibition at 10 μM	IC_{50} (μM)	% inhibition at 10 μM	IC_{50} (μM)
21c	OH	OH	>100	Toxic[a]	1.7	Toxic[a]	>3[b]
23e	OH	H	>100	54	7.5	23	>30
23g	H	OH	>100	72	2.9	45	>30
21b	OMe	OMe	>100	65	4.8	62	4.3
23d	OMe	H	>100	72	2.4	75	3.5
23f	H	OMe	>100	95	0.2	43	>30

[a] The cytotoxicity was observed when the assay was performed at 10 μM.
[b] IC_{50} values could not be calculated because the cytotoxicity of this compound was observed at this concentration.

Table 3
α-Glucosidase-inhibitory and LXR-antagonistic activities of 4,5,6,7-tetrachlorophenethylphenyl phthalimides (**24**–**30**)



Compound	Position	Single (s) or double bond (d)	R^1	R^2	α-Glucosidase IC_{50} (μM)	LXRα		LXRβ	
						% inhibition at 10 μM	IC_{50} (μM)	% inhibition at 10 μM	IC_{50} (μM)
24a	2′	s	H	H	>100	Toxic[a]	>3[b]	Toxic[a]	>3[b]
24b	2′	s	OMe	OMe	>100	64	6.1	57	7.7
24c	2′	s	OH	OH	20	32	15	26	17
25a	3′	s	H	H	>100	6	>30	0	>30
25b	3′	s	OMe	OMe	83	23	>30	11	>30
25c	3′	s	OH	OH	23	66	6.3	21	21
26a	4′	s	H	H	17	24	>30	18	>30
26b	4′	s	OMe	OMe	18	26	>30	6	>30
26c	4′	s	OH	OH	>100	62	5.1	22	>30
27a	3′	d	H	H	31	28	>30	9	>30
27b	3′	d	OMe	OMe	27	31	>30	8	>30
27c	3′	d	OH	OH	13	65	6.6	24	>30
28a	4′	d	H	H	21	7	>30	12	>30
28b	4′	d	OMe	OMe	40	19	>20	8	14
28c	4′	d	OH	OH	>100	56	2.7	26	>30
29d	3′	s	OMe	H	69	60	4.2	17	>30
29f	3′	s	H	OMe	49	62	5.5	18	>30
29e	3′	s	OH	H	50	70	2.6	9	>30
29g	3′	s	H	OH	>100	72	3.7	21	>30
30d	4′	s	OMe	H	65	55	6.9	30	>30
30f	4′	s	H	OMe	>100	53	8.8	12	>30
30e	4′	s	OH	H	21	60	3.9	18	>30
30g	4′	s	H	OH	23	36	>30	36	>30

[a] Cytotoxicity was observed when the assay was performed at 10 μM.
[b] IC_{50} values could not be calculated because the compound was cytotoxic at this concentration.

weak LXR-antagonistic activities (Table 3, vide infra). To examine the mode of α-glucosidase inhibition elicited by **26b**, Lineweaver–Burk plot analysis was performed for **26b**, riccardin C (**5**) and the typical α-glucosidase inhibitor deoxynojirimycin (Fig. 3). Compound **26b** was found to be a non-competitive inhibitor. We confirmed that deoxynojirimycin[42] and riccardin C (**5**)[24] showed competitive inhibition and non-competitive inhibition, respectively, as reported.

2.3. Structure–activity relationship for LXR-antagonistic activity

As previously reported, PP2P (**9**) showed slightly LXRα-selective antagonistic activity.[24,34,35] Its regio-isomers (**20a**, **21a** and **22a**), were less potent than PP2P (**9**), with almost no LXRα/β-selectivity (Table 1). Introduction of two methoxy or hydroxyl groups into PP2P (**9**) had no apparent effect on the activity. However, introduction of two hydroxyl groups into **20a** and **21a**, that is, compounds **20c** and **21c**, respectively, resulted in a dramatic increase of the activity for both LXRα and LXRβ (Table 1). Introduction of two methoxy groups into **21a**, that is, compound **21b**, also resulted in increased activity, though the effects were less potent than those of hydroxyl groups. On the contrary, introduction of two methoxy groups into **20a**, that is, **20b**, had no apparent effect on the activity. Among these dimethoxy and dihydroxyl derivatives, 4′-substituted analogs were more potent towards LXRs than 3′-substituted analogs (**21b** > **20b**, and **21c** > **20c**). In the case of cinnamyl analogs **22a–c**, substituent effects are much more apparent, especially for

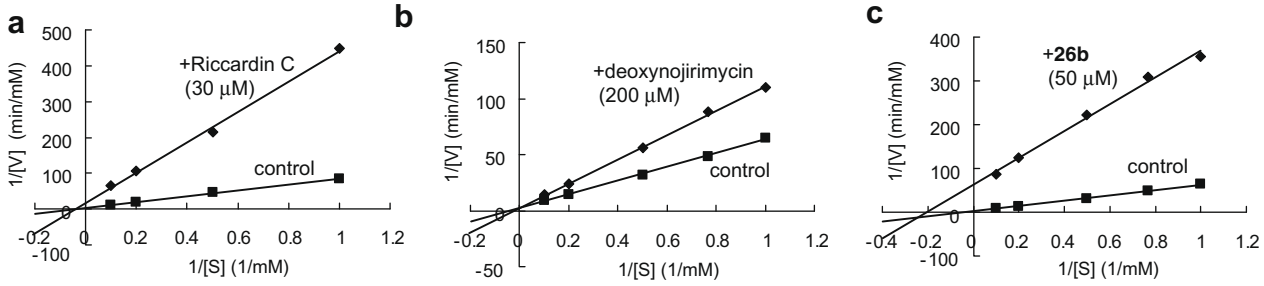


Figure 3. Lineweaver–Burk plot analysis of the inhibition of α-glucosidase by (a) riccardin C (**5**), (b) deoxynojirimycin and (c) **26b**.

LXRα-antagonistic activity, with hydroxyl groups being more effective. Although cytotoxicity appeared in dihydroxyl derivatives **21c** and **22c**, these compounds were found to be potent LXRα-selective antagonists with IC_{50} values of 1.6–1.7 μM, with almost no LXRβ-antagonistic or α-glucosidase-inhibitory activity (Table 1).

Based on the results shown in Table 1, the 4′-phenethyl series of compounds, which lack α-glucosidase-inhibitory activity, were selected for further study (Table 2). Because deoxyriccardin C (**7**, Fig. 1) showed 11-fold selective antagonistic activity for LXRα over LXRβ,[24] mono-deoxy or mono-demethoxy analogs of **21b**/**21c** were investigated. The mono-hydroxyl derivatives, **23e** and **23g**, were less potent LXRα antagonists than the corresponding dihydroxyl derivative **21c**, but they retained selectivity for LXRα over LXRβ. On the other hand, removal of one methoxy group from **21b** resulted in an increase of LXRα-antagonistic activity, with removal of the 3″-methoxy group, that is, compound **23f**, being more effective. Concerning LXRβ-antagonistic activity, the effect of removal of one methoxy group from **21b** seems to be position-dependent: removal of the 4″-methoxy group (i.e., compound **23d**) resulted in slight increase in LXRβ-antagonistic activity, while that of the 3″-methoxy group (i.e., compound **23f**) resulted in a decrease of LXRβ-antagonistic activity. Finally, the 4″-methoxy analog **23f** possessed very potent LXRα-selective antagonistic activity (IC_{50} value of 0.2 μM for LXRα) with more than 150-fold selectivity over LXRβ. Thus, substitution of the 3″-methoxy group of the LXRα/β dual antagonist **21b** with hydrogen led to a potent LXRα-selective antagonist, **23f**. Its regio-isomer, the 3″-methoxy analog **23d**, was found to be a rather potent non-selective LXRs dual antagonist with IC_{50} values of 2.4–3.5 μM.

Concerning tetrachlorophthalimide derivatives (**24**–**30**, Table 3), the effects of tetrachlorination are not so clear as in the case of α-glucosidase-inhibitory activity. Broadly speaking, tetrachlorophthalimide derivatives show slightly LXRα-selective antagonistic activity (their LXRβ-antagonistic activities were not so potent, or were absent, except for **24b**). The substituent effects of dimethoxy and dihydroxyl groups (compounds **24**–**28**, Table 3) are complex, as was found in the case of α-glucosidase-inhibitory activity. Concerning the LXRα-antagonistic activity of the 3′-(**25a**–**c** and **27a**–**c**) and 4′-phenethyl/cinnamyl (**26a**–**c** and **28a**–**c**) derivatives, the potency decreased in the order of: dihydroxyl > dimethoxy > non-substituted derivatives [**25c** > **25b** > **25a**, **26c** > **26b** ≥ **26a**, **27c** > **27b** ≥ **27a**, and **28c** > **28b** > **28a** (Table 3)]. Concerning the substituent effect elicited by hydroxyl groups, that introduced at the 3″-position seems to be more effective than that at the 4″-position (**29e** and **30e** are more potent than **29g** and **30g**, respectively), as was the case for α-glucosidase-inhibitory activity (vide supra). In the case of LXRβ-antagonistic activity, the orders of potency of 3′-phenethyl/cinnamyl derivatives (**25a**–**c** and **27a**–**c**) are the same as those for LXRα-antagonistic activity. However, those of the 4′-phenethyl/cinnamyl derivatives (**26a**–**c** and **28a**–**c**) are different, that is, the order of potency decreased in the order of: dihydroxyl > non-substituted > dimethoxy derivatives [**26c** > **26a** > **26b**, and **28c** > **28a** > **28b** (Table 3)]. Concerning the substituent effect elicited by hydroxyl groups, the 4″-position seems to be more effective than the 3″-position (**29g** and **30g** are more potent than **29e** and **30e**, respectively), which is the reverse of the order found for LXRα-antagonistic and α-glucosidase-inhibitory activities (vide supra). Finally, **28c** and **29g** are LXRα-selective antagonists with IC_{50} values of 2.7 and 3.7 μM for LXRα, IC_{50} values of >30 μM for LXRβ, and no apparent α-glucosidase inhibitory activity. Compounds **29d**, **29e**, **29f**, **30d**, **30e** and **30f** are also LXRα-selective antagonists (IC_{50} values of 2.6–8.8 μM), but they also possess α-glucosidase-inhibitory activity (Table 3).

3. Conclusion

Structural development studies of PP2P (**9**), which had been derived from thalidomide and found to possess LXRα/β-antagonistic and α-glucosidase-inhibitory activities, were performed. We were able to separate the LXR-antagonistic and α-glucosidase-inhibitory activities, at least under the experimental conditions used here. A potent LXRα-selective antagonist **23f** with very low LXRβ-antagonistic activity (IC_{50} values of 0.2 μM for LXRα and >30 μM for LXRβ) and no α-glucosidase-inhibitory activity was obtained. The reason why **23f** selectively antagonizes LXRα is not clear, but it is interesting that both riccardin F (**6**) and compound **23f**, each possessing a 4-methoxyphenethyl group, showed LXRα-selective antagonistic activity. There is no difference in amino acid sequences between LXRα and LXRβ in the region of the ligand binding pocket;[43,44] all amino acid residues that are in close contact with known ligands (i.e., within 5 Å distance from the molecular surface of the ligands) are reported to be identical. However, there is one amino acid difference within helix-3 of the LBD (i.e., LXRβ Ile277/LXRαVal263).[20] One possible interpretation of the LXRα-selectivity of **23f** might be an interaction of the 4-methoxyphenethyl moiety of **23f** with helix-3. X-ray structural investigation of LXRs complexed with **23f** seems to be needed for a further consideration of the basis of the selectivity.

4. Experimental

4.1. Biology

4.1.1. α-Glucosidase inhibition assay

α-Glucosidase (*Saccharomyces* sp., Wako) 0.2 mU/mL in 10 mM phosphate buffer (pH 7.0) was treated with DMSO solution of various compounds (final DMSO concentration 1% v/v) in a 96-well plate (final volume 90 μL). After 10 min incubation at 37 °C, 10 μL pNPG solution (final concentration 0.2 mM) was added. The mixture was incubated at 37 °C for 10 min, then basified by adding 100 μL of 0.5 M Na_2CO_3 solution. The amount of released *p*-nitrophenol was measured based on the absorbance at 405 nm. The experiment was performed in triplicate and repeated at least twice, and the normalized average values are presented. The IC_{50} values were reproducible.

4.1.2. Reporter gene assay

Human embryonic kidney (HEK) 293 cells were cultured in Dulbecco's modified Eagle's medium containing 5% fetal bovine serum at 37 °C in a humidified atmosphere of 5% CO_2 in air. Transfections were performed by the calcium phosphate coprecipitation method. Test compounds with or without 0.1 μM **1** were added 8 h after the transfection, and luciferase and β-galactosidase activities were assayed using a luminometer and microplate reader. The experiment was performed in triplicate and repeated at least twice, and the normalized average values are presented. The IC_{50} values were reproducible.

4.2. General

Melting points were determined by using a Yanagimoto hot-stage melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a JEOL JNMGX500 (500 MHz) spectrometer. Chemical shifts are expressed in parts per million relative to tetramethylsilane. Mass spectra were recorded on a JEOL JMS-DX303 spectrometer.

4.2.1. 3,4-Dimethoxybenzyltriphenylphosphonium bromide (10b)

To a solution of 3,4-dimethoxytoluene (2.90 mL, 20 mmol) in carbon tetrachloride (40 mL) were added *N*-bromosuccinimide (3.92 g, 22 mmol) and 2,2′-azobis(isobutyronitrile) (476 mg, 2.9 mmol). The mixture was refluxed for 1 h. The mixture was filtered and concentrated. The residue was purified by silica gel column chromatography to give an intermediate. To a solution of the intermediate (5.89 g, 25.4 mmol) in acetonitrile (40 mL) was added triphenylphosphine (9.99 g, 38.1 mmol). The mixture was refluxed for 45 min. The reaction mixture was concentrated and mixed with toluene. The whole was filtered to give the target compound (8.07 g, 82%) as a pale yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.79–7.73 (m, 9H), 7.66–7.62 (m, 6H), 6.85 (s, 1H), 6.62 (s, 2H), 5.36 (d, 2H, J = 14.0 Hz), 3.81 (s, 3H), 3.55 (s, 3H). FAB-MS m/z: 413 $[M-Br]^+$.

4.2.2. 3-Methoxybenzyltriphenylphosphonium bromide (10d)

To a solution of 3-methoxybenzyl bromide (700 μL, 5.0 mmol) in acetonitrile (20 mL) was added triphenylphosphine (3.72 g, 14.2 mmol). The mixture was refluxed for 45 min. The reaction mixture was concentrated and mixed with toluene. The whole was filtered to give the target compound (2.19 g, 94%) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.79–7.73 (m, 9H), 7.66–7.62 (m, 6H), 7.03 (t, 1H, J = 7.9 Hz), 6.82–6.80 (m, 1H), 6.77 (dt, 1H, J = 8.5, 2.4 Hz), 6.63 (d, 1H, J = 7.3 Hz), 5.38 (d, 2H, J = 14.6 Hz), 3.55 (s, 3H). FAB-MS m/z: 383 $[M-Br]^+$.

4.2.3. 4-Methoxybenzyltriphenylphosphonium bromide (10f)

This compound was prepared from 4-methoxybenzyl bromide by means of a procedure similar to that used for **10d**. Compound **10f** was obtained in 91% yield as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.79–7.72 (m, 9H), 7.66–7.62 (m, 6H), 7.03 (dd, 2H, J = 8.5, 2.4 Hz), 6.66 (d, 2H, J = 8.5 Hz), 5.33 (d, 2H, J = 14.0 Hz), 3.73 (s, 3H). FAB-MS m/z: 383 $[M-Br]^+$.

4.2.4. 1-Nitro-2-(2-phenylethenyl)benzene (11a)

To a solution of 2-nitrobenzaldehyde (302 mg, 2.0 mmol) in dehydrated dichloromethane (12 mL) were added benzyltriphenylphosphonium chloride (778 mg, 2.0 mmol), potassium carbonate (304 mg, 2.2 mmol) and 18-crown-6 (95 mg, 0.36 mmol). The mixture was refluxed for 9 h, then filtered and concentrated. The residue was purified by silica gel column chromatography to give the target compound (410 mg, 91%) as a yellow oil. Additionally, the *EZ* mixture was purified by silica gel column chromatography to provide a sample for instrumental analysis.

^{1}H NMR (500 MHz, $CDCl_3$) **11a*Z*** δ: 8.08–8.06 (m, 1H), 7.38–7.36 (m, 2H), 7.26–7.24 (m, 1H), 7.15–7.14 (m, 3H), 7.05–7.02 (m, 2H), 6.88 (d, 1H, J = 12.2 Hz), 6.75 (d, 1H, J = 12.2 Hz). Compound **11a*E*** δ: 7.95 (dd, 1H, J = 7.9, 1.2 Hz), 7.75 (d, 1H, J = 7.9 Hz), 7.59 (d, 1H, J = 6.1 Hz), 7.57 (s, 1H), 7.53 (d, 2H, J = 7.3 Hz), 7.40–7.35 (m, 3H), 7.30 (t, 1H, J = 7.3 Hz), 7.07 (d, 1H, J = 16.5 Hz). FAB-MS m/z: 225 $[M]^+$, 226 $[M+H]^+$.

4.2.5. 1,2-Dimethoxy-4-[2-(2-nitrophenyl)ethenyl]benzene (11b)

This compound was prepared from 2-nitrobenzaldehyde and **10b** by means of a procedure similar to that used for **11a**. Compound **11b** was obtained in 95% yield as a brown oil.

^{1}H NMR (500 MHz, $CDCl_3$) **11b*Z*** δ: 8.08 (dd, 1H, J = 7.9, 1.2 Hz), 7.45–7.42 (td, 1H, J = 7.3, 1.2 Hz), 7.41–7.37 (td, 1H, J = 7.9, 1.8 Hz), 7.35 (d, 1H, J = 7.3 Hz), 6.81 (d, 1H, J = 12.2 Hz), 6.70–6.66 (m, 3H), 6.50 (d, 1H, J = 1.8 Hz), 3.83 (s, 3H), 3.55 (s, 3H). FAB-MS m/z: 285 $[M]^+$, 286 $[M+H]^+$.

4.2.6. 1-Nitro-3-(2-phenylethenyl)benzene (12a)

To a solution of 3-nitrobenzaldehyde (680 mg, 4.5 mmol) in dehydrated dichloromethane (20 mL) were added benzyltriphenylphosphonium chloride (1.75 g, 4.5 mmol), potassium carbonate (691 mg, 5.0 mmol) and 18-crown-6 (211 mg, 0.8 mmol). The mixture was refluxed for 5 h, then filtered and concentrated. The residue was purified by silica gel column chromatography to give the target compound (994 mg, 98%) as a pale yellow solid. Additionally, the *EZ* mixture was purified by silica gel column chromatography to afford **12a*E*** (32%) as a pale yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) **12a*Z*** δ: 8.08 (t, 1H, J = 1.8 Hz), 8.03 (dd, 1H, J = 8.5, 1.8 Hz), 7.52 (d, 1H, J = 7.9 Hz), 7.35 (t, 1H, J = 7.9 Hz), 7.25-7.23 (m, 3H), 7.20-7.18 (m, 2H), 6.78 (d, 1H, J = 12.2 Hz), 6.61 (d, 1H, J = 12.2 Hz). Compound **12a*E*** δ: 8.35 (t, 1H, J = 1.8 Hz), 8.09–8.07 (m, 1H), 7.78 (d, 1H, J = 7.9 Hz), 7.53 (m, 1H), 7.52–7.49 (m, 2H), 7.38 (t, 2H, J = 7.3 Hz), 7.30 (tt, 1H, J = 7.3, 1.8 Hz), 7.22 (d, 1H, J = 15.9 Hz), 7.12 (d, 1H, J = 15.9 Hz). FAB-MS m/z: 225 $[M]^+$, 226 $[M+H]^+$.

4.2.7. 1,2-Dimethoxy-4-[2-(3-nitrophenyl)ethenyl]benzene (12b)

This compound was prepared from 3-nitrobenzaldehyde and **10b** by means of a procedure similar to that used for **12a**. Compound **12b** was obtained in 95% yield as a brown oil. Compound **12b*E*** was obtained in 40% yield as a yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) **12b*Z*** δ: 8.15 (t, 1H, J = 1.8 Hz), 8.04 (dd, 1H, J = 7.3, 2.4 Hz), 7.59 (d, 1H, J = 7.3 Hz), 7.39 (t, 1H, J = 7.9 Hz), 6.80-6.75 (m, 2H), 6.71 (s, 1H), 6.70 (d, 1H, J = 12.2 Hz), 6.53 (d, 1H, J = 12.2 Hz), 3.87 (s, 3H), 3.65 (s, 3H). Compound **12b*E*** δ: 8.35 (t, 1H, J = 1.8 Hz), 8.08–8.06 (m, 1H), 7.78 (d, 1H, J = 7.9 Hz), 7.51 (t, 1H, J = 7.9 Hz), 7.19 (d, 1H, J = 15.9 Hz), 7.10 (dd, 1H, J = 7.3, 1.8 Hz), 7.09 (s, 1H), 7.01 (d, 1H, J = 15.9 Hz), 6.89 (d, 1H, J = 9.2 Hz), 3.96 (s, 3H), 3.92 (s, 3H). FAB-MS m/z: 285 $[M]^+$, 286 $[M+H]^+$.

4.2.8. 1-Methoxy-3-[2-(3-nitrophenyl)ethenyl]benzene (12d)

This compound was prepared from 3-nitrobenzaldehyde and **10d** by means of a procedure similar to that used for **11a**. Compound **12d** was obtained in 93% yield as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) **12d*Z*** δ: 8.09 (t, 1H, J = 1.8 Hz), 8.02 (dd, 1H, J = 7.9, 1.2 Hz), 7.54 (d, 1H, J = 7.9 Hz), 7.35 (t, 1H, J = 7.9 Hz), 7.16 (t, 1H, J = 7.9 Hz), 6.79–6.73 (m, 3H), 6.74 (d, 1H, J = 12.2 Hz), 6.59 (d, 1H, J = 12.2 Hz), 3.68 (s, 3H). Compound **12d*E*** δ: 8.37 (t, 1H, J = 1.8 Hz), 8.10 (dd, 1H, J = 8.5, 1.8 Hz), 7.80 (d, 1H, J = 7.9 Hz), 7.53 (t, 1H, J = 7.9 Hz), 7.31 (t, 1H, J = 7.9 Hz), 7.21 (d, 1H, J = 16.5 Hz), 7.14 (d, 1H, J = 7.3 Hz), 7.13 (d, 1H, J = 16.5 Hz), 7.07 (t, 1H, J = 1.8 Hz), 6.89 (dd, 1H, J = 8.5, 2.4 Hz), 3.87 (s, 3H). FAB-MS m/z: 255 $[M]^+$, 256 $[M+H]^+$.

4.2.9. 1-Methoxy-4-[2-(3-nitrophenyl)ethenyl]benzene (12f)

This compound was prepared from 3-nitrobenzaldehyde and **10f** by means of a procedure similar to that used for **11a**. Compound **12f** was obtained in 92% yield as a yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) **12f*Z*** δ: 8.12 (t, 1H, J = 1.8 Hz), 8.04–8.02 (m, 1H), 7.56 (d, 1H, J = 7.9 Hz), 7.37 (t, 1H, J = 7.9 Hz), 7.13 (d, 2H, J = 8.5 Hz), 6.77 (d, 2H, J = 8.5 Hz), 6.70 (d, 1H, J = 12.2 Hz), 6.51 (d, 1H, J = 12.2 Hz), 3.79 (s, 3H). Compound **12f*E*** δ: 8.34 (t, 1H, J = 1.8 Hz), 8.08–8.06 (m, 1H), 7.76 (d, 1H, J = 7.3 Hz), 7.50 (t, 1H, J = 7.9 Hz), 7.49 (d, 2H, J = 8.5 Hz), 7.19 (d, 1H, J = 16.2 Hz), 7.00 (d, 1H, J = 16.2 Hz), 6.93 (d, 2H, J = 8.5 Hz), 3.85 (s, 3H). FAB-MS m/z: 255 $[M]^+$, 256 $[M+H]^+$.

4.2.10. 1-Nitro-4-(2-phenylethenyl)benzene (13a)

This compound was prepared from 4-nitrobenzaldehyde and **10a** by means of a procedure similar to that used for **12a**. Compound **13a** was obtained in 86% yield as yellow solid. Compound **13a*E*** was obtained in 23% yield as a yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) **13a*Z*** δ: 8.07 (d, 2H, J = 8.9 Hz), 7.37 (d, 2H, J = 8.9 Hz), 7.27–7.25 (m, 3H), 7.21–7.19 (m, 2H), 6.82 (d, 1H, J = 12.2 Hz), 6.62 (d, 1H, J = 12.2 Hz). Compound **13a*E*** δ: 8.23 (dt, 2H, J = 9.2, 2.4 Hz), 7.64 (dt, 2H, J = 9.2, 2.4 Hz), 7.56 (d, 2H, J = 7.3 Hz), 7.40 (d, 2H, J = 7.3 Hz), 7.34 (tt, 1H, J = 7.3, 2.4 Hz), 7.28 (d, 1H, J = 16.5 Hz), 7.15 (d, 1H, J = 16.5 Hz). FAB-MS m/z: 225 $[M]^+$, 226 $[M+H]^+$.

4.2.11. 1,2-Dimethoxy-4-[2-(4-nitrophenyl)ethenyl]benzene (13b)

This compound was prepared from 4-nitrobenzaldehyde and **10b** by means of a procedure similar to that used for **12a**. Compound **13b** was obtained in 98% yield as a yellow solid. Compound **13b*E*** was obtained in 46% yield as a yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) **13b*Z*** δ: 8.09 (d, 2H, J = 8.9 Hz), 7.43 (d, 2H, J = 8.9 Hz), 6.80–6.71 (m, 4H), 6.53 (d, 1H, J = 12.2 Hz), 3.88 (s, 3H), 3.67 (s, 3H). Compound **13b*E*** δ: 8.21 (d, 2H, J = 8.5 Hz), 7.61 (d, 2H, J = 8.5 Hz), 7.22 (d, 2H, J = 16.5 Hz), 7.11 (dd, 1H, J = 7.9, 1.8 Hz), 7.10 (d, 1H, J = 1.8 Hz), 7.01 (d, 1H, J = 16.5 Hz), 6.90 (d, 1H, J = 7.9 Hz), 3.96 (s, 3H), 3.92 (s, 3H). FAB-MS m/z: 285 $[M]^+$, 286 $[M+H]^+$.

4.2.12. 1-Methoxy-3-[2-(4-nitrophenyl)ethenyl]benzene (13d)

This compound was prepared from 4-nitrobenzaldehyde and **10d** by means of a procedure similar to that used for **11a**. Compound **13d** was obtained in 100% yield as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) **13d*Z*** δ: 8.08 (d, 2H, J = 8.5 Hz), 7.39 (d, 2H, J = 8.5 Hz), 7.18 (t, 1H, J = 7.9 Hz), 6.81–6.74 (m, 4H), 6.61 (d, 1H, J = 12.2 Hz), 3.70 (s, 3H). Compound **13d*E*** δ: 8.22 (d, 2H, J = 8.5 Hz), 7.64 (d, 2H, J = 8.5 Hz), 7.32 (t, 1H, J = 7.9 Hz), 7.24 (d, 1H, J = 16.5 Hz), 7.14 (d, 1H, J = 16.5 Hz), 7.08 (t, 1H, J = 1.8 Hz), 6.89 (dd, 1H, J = 7.9, 2.4 Hz), 3.86 (s, 3H). FAB-MS m/z: 255 $[M]^+$, 256 $[M+H]^+$.

4.2.13. 1-Methoxy-4-[2-(4-nitrophenyl)ethenyl]benzene (13f)

This compound was prepared from 4-nitrobenzaldehyde and **10f** by means of a procedure similar to that used for **11a**. Compound **13f** was obtained in 94% yield as a yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) **13f*Z*** δ: 8.08 (d, 2H, J = 9.2 Hz), 7.40 (d, 2H, J = 8.5 Hz), 7.14 (d, 2H, J = 8.5 Hz), 6.78 (d, 2H, J = 9.8 Hz), 6.73 (d, 1H, J = 12.2 Hz), 6.51 (d, 1H, J = 12.2 Hz), 3.80 (s, 3H). Compound **13f*E*** δ: 8.20 (d, 2H, J = 8.5 Hz), 7.60 (d, 2H, J = 8.5 Hz), 7.50 (d, 2H, J = 8.5 Hz), 7.23 (d, 1H, J = 16.5 Hz), 7.01 (d, 1H, J = 16.5 Hz), 6.93 (d, 2H, J = 8.5 Hz), 3.85 (s, 3H). FAB-MS m/z: 255 $[M]^+$, 256 $[M+H]^+$.

4.2.14. 2-(2-Phenylethyl)aniline (14a)

Compound **11a** (410 mg, 1.82 mmol) was dissolved in EtOAc (20 mL) and hydrogenated with 10% Pd/C (catalytic amount). The mixture was filtered through a pad of Celite, and the filtrate was evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give the target compound (366 mg, 100%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.31–7.28 (m, 2H), 7.23–7.20 (m, 3H), 7.07–7.04 (m, 2H), 6.75 (td, 1H, J = 7.3, 1.2 Hz), 6.68 (dd, 1H, J = 7.3, 1.2 Hz), 3.50 (br s, 2H), 2.96–2.92 (m, 2H), 2.81–2.78 (m, 2H). FAB-MS m/z: 197 $[M]^+$, 198 $[M+H]^+$.

4.2.15. 2-[2-(3,4-Dimethoxyphenyl)ethyl]aniline (14b)

This compound was prepared from **11b** by means of a procedure similar to that used for **14a**. Compound **14b** was obtained in 92% yield as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.06–7.02 (m, 2H), 6.80 (d, 1H, J = 7.9 Hz), 6.76–6.73 (m, 2H), 6.67 (d, 1H, J = 7.9 Hz), 6.63 (d, 1H, J = 1.8 Hz), 3.86 (s, 3H), 3.81 (s, 3H), 3.47 (br s, 2H), 2.90–2.86 (m, 2H), 2.79–2.76 (m, 2H). FAB-MS m/z: 257 $[M]^+$, 258 $[M+H]^+$.

4.2.16. 3-(2-Phenylethyl)aniline (15a)

This compound was prepared from **12a** by means of a procedure similar to that used for **14a**. Compound **15a** was obtained in 96% yield as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.28 (s, 1H), 7.26 (d, 1H, J = 7.9 Hz), 7.20–7.18 (m, 3H), 7.09–7.06 (m, 1H), 6.61 (d, 1H, J = 7.9 Hz), 6.54–6.53 (m, 2H), 3.57 (br s, 2H), 2.92–2.88 (m, 2H), 2.85–2.81 (m, 2H). FAB-MS m/z: 197 $[M]^+$, 198 $[M+H]^+$.

4.2.17. 3-[2-(3,4-Dimethoxyphenyl)ethyl]aniline (15b)

This compound was prepared from **12b** by means of a procedure similar to that used for **14a**. Compound **15b** was obtained in 74% yield as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.07 (td, 1H, J = 7.3, 1.2 Hz), 6.79 (d, 1H, J = 7.9 Hz), 6.73 (dd, 1H, J = 7.9, 1.8 Hz), 6.67 (d, 1H, J = 1.8 Hz), 6.60 (d, 1H, J = 7.9 Hz), 6.54–6.52 (m, 1H), 6.52 (d, 1H, J = 1.2 Hz), 3.86 (s, 3H), 3.84 (s, 3H), 2.87–2.83 (m, 2H), 2.82–2.79 (m, 2H). FAB-MS m/z: 257 $[M]^+$, 258 $[M+H]^+$.

4.2.18. 3-[2-(3-Methoxyphenyl)ethyl]aniline (15d)

This compound was prepared from **12d** by means of a procedure similar to that used for **14a**. Compound **15d** was obtained in 74% yield as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.22–7.18 (m, 1H), 7.09–7.06 (m, 1H), 6.79 (d, 1H, J = 7.9 Hz), 6.75–6.73 (m, 2H), 6.62–6.60 (d, 1H, J = 7.3 Hz), 6.53 (s, 1H), 6.53–6.52 (m, 1H), 3.78 (s, 3H), 3.59 (br s, 2H), 2.89–2.85 (m, 2H), 2.83–2.80 (m, 2H). FAB-MS m/z: 227 $[M]^+$, 228 $[M+H]^+$.

4.2.19. 3-[2-(4-Methoxyphenyl)ethyl]aniline (15f)

This compound was prepared from **12f** by means of a procedure similar to that used for **14a**. Compound **15f** was obtained in 91% yield as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.10 (d, 2H, J = 8.5 Hz), 7.09–7.05 (m, 1H), 6.83 (d, 2H, J = 8.5 Hz), 6.60 (d, 1H, J = 7.9 Hz), 6.54–6.53 (m, 2H), 3.79 (s, 3H), 3.60 (br s, 2H), 2.86–2.82 (m, 2H), 2.81–2.77 (m, 2H). FAB-MS m/z: 227 $[M]^+$, 228 $[M+H]^+$.

4.2.20. 4-(2-Phenylethyl)aniline (16a)

This compound was prepared from **13a** by means of a procedure similar to that used for **14a**. Compound **16a** was obtained in 95% yield as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.29–7.26 (m, 2H), 7.20–7.17 (m, 3H), 6.97 (d, 2H, J = 8.0 Hz), 6.63 (d, 2H, J = 8.0 Hz), 3.55 (br s, 2H), 2.88–2.86 (m, 2H), 2.83–2.79 (m, 2H). FAB-MS m/z: 197 $[M]^+$, 198 $[M+H]^+$.

4.2.21. 4-[2-(3,4-Dimethoxyphenyl)ethyl]aniline (16b)

This compound was prepared from **13b** by means of a procedure similar to that used for **14a**. Compound **16b** was obtained in 100% yield as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.96 (d, 2H, J = 8.5 Hz), 6.78 (d, 1H, J = 7.9 Hz), 6.71 (dd, 1H, J = 7.9, 1.8 Hz), 6.65 (d, 1H, J = 1.8 Hz), 6.62 (d, 2H, J = 8.5 Hz), 3.86 (s, 3H), 3.84 (s, 3H), 3.57 (br s, 2H), 2.82–2.78 (m, 4H). FAB-MS m/z: 257 $[M]^+$, 258 $[M+H]^+$.

4.2.22. 4-[2-(3-Methoxyphenyl)ethyl]aniline (16d)

This compound was prepared from **13d** by means of a procedure similar to that used for **14a**. Compound **16d** was obtained in 93% yield as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.19 (td, 1H, J = 7.6, 1.2 Hz), 6.98 (d, 2H, J = 8.5 Hz), 6.78 (d, 1H, J = 7.3 Hz), 6.73 (dd, 1H, J = 7.3, 1.8 Hz), 6.73 (s, 1H), 6.63 (d, 2H, J = 7.9 Hz), 3.78 (s, 3H), 3.55 (br s, 2H), 2.86–2.82 (m, 2H), 2.82–2.78 (m, 2H). FAB-MS m/z: 227 $[M]^+$, 228 $[M+H]^+$.

4.2.23. 4-[2-(4-Methoxyphenyl)ethyl]aniline (16f)

This compound was prepared from **16f** by means of a procedure similar to that used for **14a**. Compound **16f** was obtained in 91% yield as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.08 (d, 2H, J = 8.5 Hz), 6.96 (d, 2H, J = 7.9 Hz), 6.82 (d, 2H, J = 8.5 Hz), 6.62 (d, 2H, J = 7.9 Hz), 3.79 (s, 3H), 3.55 (br s, 2H), 2.83–2.79 (m, 2H), 2.78–2.75 (m, 2H). FAB-MS m/z: 227 $[M]^+$, 228 $[M+H]^+$.

4.2.24. 3-[(1*E*)-2-Phenylethenyl]aniline (17a)

To a solution of **12a*E*** (73 mg, 0.32 mmol) in EtOAc (10 mL) was added tin (II) chloride dihydrate (361 mg, 1.60 mmol) and the mixture was refluxed for 5 h. The reaction was then terminated by the addition of satd $NaHCO_3$ aq. The resulting mixture was filtered through a pad of Celite and extracted with EtOAc (100 mL × 2). The organic layer was washed with H_2O (30 mL) and brine (20 mL) and then dried over $MgSO_4$. The solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography to give the target compound (50 mg, 81%) as a pale yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.50 (d, 2H, J = 7.3 Hz), 7.35 (t, 2H, J = 7.3 Hz), 7.24 (d, 1H, J = 7.3 Hz), 7.15 (t, 1H, J = 7.9 Hz), 7.07 (d, 1H, J = 16.5 Hz), 7.02 (d, 1H, J = 16.5 Hz), 6.94 (d, 1H, J = 7.9 Hz), 6.85 (t, 1H, J = 1.8 Hz), 6.61 (dd, 1H, J = 7.9, 2.4 Hz), 3.68 (br s, 2H). FAB-MS m/z: 195 $[M]^+$, 196 $[M+H]^+$.

4.2.25. 3-[(1*E*)-2-(3,4-Dimethoxyphenyl)ethenyl]aniline (17b)

This compound was prepared from **12b*E*** by means of a procedure similar to that used for **17a**. Compound **17b** was obtained in 76% yield as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.14 (t, 1H, J = 7.9 Hz), 7.06 (d, 1H, J = 1.8 Hz), 7.04 (dd, 1H, J = 7.9, 1.8 Hz), 7.01 (d, 1H, J = 16.8 Hz), 6.92 (d, 1H, J = 7.9 Hz), 6.89 (d, 1H, J = 16.8 Hz), 6.86 (d, 1H, J = 8.5 Hz), 6.84 (m, 1H), 6.59 (dd, 1H, J = 7.9, 2.4 Hz), 3.95 (s, 3H), 3.90 (s, 3H), 3.67 (br s, 2H). FAB-MS m/z: 255 $[M]^+$, 256 $[M+H]^+$.

4.2.26. 4-[(1*E*)-2-Phenylethenyl]aniline (18a)

This compound was prepared from **13a*E*** by means of a procedure similar to that used for **17a**. Compound **18a** was obtained in 83% yield as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.47 (d, 2H, J = 7.3 Hz), 7.35–7.31 (m, 4H), 7.21 (t, 1H, J = 7.3 Hz), 7.03 (d, 1H, J = 16.2 Hz), 6.92 (d, 1H, J = 16.2 Hz), 6.68 (d, 2H, J = 8.5 Hz), 3.74 (br s, 2H). FAB-MS m/z: 195 $[M]^+$, 196 $[M+H]^+$.

4.2.27. 4-[(1*E*)-2-(3,4-Dimethoxyphenyl)ethenyl]aniline (18b)

This compound was prepared from **13b*E*** by means of a procedure similar to that used for **17a**. Compound **18b** was obtained in 88% yield as a yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.32 (d, 2H, J = 8.5 Hz), 7.04 (d, 1H, J = 1.8 Hz), 7.00 (dd, 1H, J = 7.9, 1.8 Hz), 6.88 (m, 1H), 6.88 (m, 1H), 6.84 (d, 1H, J = 7.9 Hz), 6.68 (d, 2H, J = 8.5 Hz), 3.94 (s, 3H), 3.90 (s, 3H), 3.73 (br s, 2H). FAB-MS m/z: 255 $[M]^+$, 256 $[M+H]^+$.

4.2.28. *N*-{2-[2-(3,4-Dimethoxyphenyl)ethyl]phenyl}phthalimide (19b)

A mixture of phthalic anhydride (87 mg, 0.59 mmol) and **14b** (151 mg, 0.59 mmol) was heated at 200 °C for 1 h. After the reaction was completed, the residue was purified by silica gel column chromatography to give the target compound (201 mg, 88%) as a white solid.

Colorless needles from CH_2Cl_2/*n*-hexane. Mp 103.0–105.0 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.95 (dd, 2H, J = 5.5, 3.1 Hz), 7.80 (dd, 2H, J = 5.5, 3.1 Hz), 7.41–7.37 (m, 1H), 7.37–7.33 (m, 1H), 7.31 (dd, 1H, J = 7.3, 1.8 Hz), 7.20 (dd, 1H, J = 7.3, 1.8 Hz), 6.69 (d, 1H, J = 7.9 Hz), 6.59 (dd, 1H, J = 7.9, 1.8 Hz), 6.50 (d, 1H, J = 1.8 Hz), 3.80 (s, 3H), 3.68 (s, 3H), 2.79 (s, 4H). FAB-MS m/z: 387 $[M]^+$, 388 $[M+H]^+$. Anal. Calcd for $C_{24}H_{21}NO_4$: C, 74.40; H, 5.46; N, 3.62. Found: C, 74.34; H, 5.59; N, 3.55.

4.2.29. *N*-{2-[2-(3,4-Dihydroxyphenyl)ethyl]phenyl}phthalimide (19c)

To a solution of **19b** (88 mg, 0.23 mmol) in dehydrated dichloromethane (2 mL) was added dropwise boron tribromide (1.0 M solution in dichloromethane) (2.3 mL, 2.30 mmol) at 0 °C under an argon atmosphere. The mixture was stirred for 30 min, then poured into water (20 mL) and extracted with CH_2Cl_2 (20 mL × 3). The organic layer was washed with H_2O (20 mL) and then dried over $MgSO_4$. The solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography to give the target compound (75 mg, 90%) as a white solid.

Mp 63.0–65.0 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.95 (dd, 2H, J = 5.5, 2.4 Hz), 7.81 (dd, 2H, J = 5.5, 2.4 Hz), 7.41–7.38 (m, 1H), 7.36–7.31 (m, 2H), 7.18 (dd, 1H, J = 7.9, 1.2 Hz), 6.66 (d, 1H, J = 7.9 Hz), 6.52 (d, 1H, J = 1.8 Hz), 6.49 (dd, 1H, J = 7.9, 1.8 Hz), 5.16 (s, 1H), 5.00 (s, 1H), 2.76 (m, 4H). FAB-MS m/z: 359 $[M]^+$, 360 $[M+H]^+$. HRMS (FAB) calcd for $C_{22}H_{17}NO_4$ 359.1158; found: 359.1127 $(M)^+$.

4.2.30. *N*-[3-(2-Phenylethyl)phenyl]phthalimide (20a)

This compound was prepared from **15a** by means of a procedure similar to that used for **19b**. Compound **20a** was obtained in 83% yield as colorless needles after recrystallization from CH_2Cl_2/*n*-hexane.

Mp 98.0–98.5 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.96 (dd, 2H, J = 5.5, 2.4 Hz), 7.80 (dd, 2H, J = 5.5, 2.4 Hz), 7.42 (t, 1H, J = 7.9 Hz), 7.31–7.28 (m, 4H), 7.23–7.20 (m, 4H), 3.02–2.94 (m, 4H). FAB-MS m/z: 327 $[M]^+$, 328 $[M+H]^+$. Anal. Calcd for $C_{22}H_{17}NO_2 \cdot 1/4H_2O$: C, 79.62; H, 5.31; N, 4.22. Found: C, 79.50; H, 5.34; N, 4.19.

4.2.31. *N*-{3-[2-(3,4-Dimethoxyphenyl)ethyl]phenyl}phthalimide (20b)

This compound was prepared from **15b** by means of a procedure similar to that used for **19b**. Compound **20b** was obtained in 71% yield as colorless needles after recrystallization from CH_2Cl_2/*n*-hexane.

Mp 132.5–133.5 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.96 (dd, 2H, J = 5.5, 3.1 Hz), 7.80 (dd, 2H, J = 5.5, 3.1 Hz), 7.43–7.39 (m, 1H), 7.28–7.26 (m, 2H), 7.19 (d, 1H, J = 7.3 Hz), 6.80 (d, 1H, J = 7.9 Hz), 6.73 (dd, 1H, J = 7.9, 1.8 Hz), 6.65 (d, 1H, J = 1.8 Hz), 3.85 (s, 3H), 3.83 (s, 3H), 2.99–2.95 (m, 2H), 2.93–2.89 (m, 2H). FAB-MS m/z: 387 $[M]^+$, 388 $[M+H]^+$. Anal. Calcd for $C_{24}H_{21}NO_4$: C, 74.40; H, 5.46; N, 3.62. Found: C, 74.33; H, 5.49; N, 3.54.

4.2.32. *N*-{3-[2-(3,4-Dihydroxyphenyl)ethyl]phenyl}phthalimide (20c)

This compound was prepared from **20b** by means of a procedure similar to that used for **19c**. Compound **20c** was obtained in 70% yield as yellow needles after recrystallization from EtOAc/*n*-hexane.

Mp 171.5–172.0 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.96 (dd, 2H, J = 5.5, 2.4 Hz), 7.81 (dd, 2H, J = 5.5, 2.4 Hz), 7.42 (t, 1H, J = 7.9 Hz), 7.23 (dd, 1H, J = 7.9, 2.4 Hz), 7.22 (dd, 1H, J = 7.9, 1.8 Hz), 7.13 (m, 1H), 6.78 (d, 1H, J = 7.9 Hz), 6.63 (dd, 1H, J = 7.9, 1.8 Hz), 6.56 (d, 1H, J = 1.8 Hz), 5.66 (s, 1H), 5.16 (s, 1H), 2.94–2.90 (m, 2H), 2.86–2.83 (m, 2H). FAB-MS m/z: 359 $[M]^+$, 360 $[M+H]^+$. Anal. Calcd for $C_{22}H_{17}NO_4$: C, 73.53; H, 4.77; N, 3.90. Found: C, 73.24; H, 4.84; N, 3.83.

4.2.33. *N*-(4-(2-Phenylethyl)phenyl)phthalimide (21a)

This compound was prepared from **16a** by means of a procedure similar to that used for **19b**. Compound **21a** was obtained in 89% yield as colorless needles after recrystallization from CH_2Cl_2/*n*-hexane.

Mp 216.5–218.0 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.96 (dd, 2H, J = 5.5, 3.1 Hz), 7.79 (dd, 2H, J = 5.5, 3.1 Hz), 7.36–7.29 (m, 6H), 7.23–7.19 (m, 3H), 3.01–2.94 (m, 4H). FAB-MS m/z: 327 $[M]^+$, 328 $[M+H]^+$. Anal. Calcd for $C_{22}H_{17}NO_2$: C, 80.71; H, 5.23; N, 4.28. Found: C, 80.71; H, 5.53; N, 4.27.

4.2.34. *N*-{4-[2-(3,4-Dimethoxyphenyl)ethyl]phenyl}phthalimide (21b)

This compound was prepared from **16b** by means of a procedure similar to that used for **19b**. Compound **21b** was obtained in 79% yield as yellow plates after recrystallization from CH_2Cl_2/*n*-hexane.

Mp 180.0–181.0 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.94 (dd, 2H, J = 5.5, 3.1 Hz), 7.77 (dd, 2H, J = 5.5, 3.1 Hz), 7.33–7.28 (m, 4H), 6.79 (d, 1H, J = 7.9 Hz), 6.73 (dd, 1H, J = 7.9, 1.8 Hz), 6.63 (d, 1H, J = 1.8 Hz), 3.85 (s, 3H), 3.82 (s, 3H), 2.95–2.92 (m, 2H), 2.90–2.87 (m, 2H). FAB-MS m/z: 387 $[M]^+$, 388 $[M+H]^+$. Anal. Calcd for $C_{24}H_{21}NO_4 \cdot 1/5H_2O$: C, 73.72; H, 5.52; N, 3.58. Found: C, 73.98; H, 5.44; N, 3.64.

4.2.35. *N*-{4-[2-(3,4-Dihydroxyphenyl)ethyl]phenyl}phthalimide (21c)

This compound was prepared from **21b** by means of a procedure similar to that used for **19c**. Compound **21c** was obtained in 27% yield as yellow needles after recrystallization from CH_2Cl_2/*n*-hexane.

Mp 205.0–206.0 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.73 (br s, 1H), 8.65 (br s, 1H), 7.95 (dd, 2H, J = 5.5, 3.1 Hz), 7.90 (dd, 2H, J = 5.5, 3.1 Hz), 7.36–7.31 (m, 4H), 6.64 (d, 1H, J = 1.8 Hz), 6.62 (d, 1H, J = 7.9 Hz), 6.49 (dd, 1H, J = 7.9, 1.8 Hz), 2.87–2.84 (m, 2H), 2.75–2.71 (m, 2H). FAB-MS m/z: 359 $[M]^+$, 360 $[M+H]^+$. HRMS (FAB) calcd for $C_{22}H_{17}NO_4$ 359.1158; found: 359.1179 $(M)^+$.

4.2.36. *N*-{4-[(1*E*)-2-Phenylethenyl]phenyl}phthalimide (22a)

This compound was prepared from **18a** by means of a procedure similar to that used for **19b**. Compound **22a** was obtained in 88% yield as a white powder after recrystallization from CH_2Cl_2/*n*-hexane.

Mp 297.0–299.0 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.97 (dd, 2H, J = 5.5, 3.1 Hz), 7.81 (dd, 2H, J = 5.5, 3.1 Hz), 7.65 (d, 2H, J = 8.5 Hz), 7.54 (d, 2H, J = 7.9 Hz), 7.46 (d, 2H, J = 8.5 Hz), 7.38 (t, 2H, J = 7.9 Hz), 7.28 (tt, 1H, J = 7.9, 1.2 Hz), 7.15 (s, 2H). FAB-MS m/z: 325 $[M]^+$, 326 $[M+H]^+$. Anal. Calcd for $C_{22}H_{15}NO_2 \cdot 1/3H_2O$: C, 79.74; H, 4.77; N, 4.23. Found: C, 79.50; H, 4.69; N, 4.19.

4.2.37. *N*-{4-[(1*E*)-2-(3,4-Dimethoxyphenyl)ethenyl]phenyl}phthalimide (22b)

This compound was prepared from **18a** by means of a procedure similar to that used for **19b**. Compound **22b** was obtained in 64% yield as yellow needles after recrystallization from CH_2Cl_2/*n*-hexane.

Mp 224.0–226.0 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.97 (dd, 2H, J = 5.5, 3.1 Hz), 7.81 (dd, 2H, J = 5.5, 3.1 Hz), 7.63 (d, 2H, J = 8.5 Hz), 7.45 (d, 2H, J = 8.5 Hz), 7.10 (d, 1H, J = 16.2 Hz), 7.09–7.05 (m, 2H), 7.01 (d, 1H, J = 16.2 Hz), 6.88 (d, 1H, J = 7.9 Hz), 3.97 (s, 3H), 3.92 (s, 3H). FAB-MS m/z: 385 $[M]^+$, 386 $[M+H]^+$. Anal. Calcd for $C_{24}H_{19}NO_4 \cdot 1/3H_2O$: C, 73.64; H, 5.06; N, 3.58. Found: C, 73.83; H, 5.01; N, 3.30.

4.2.38. *N*-{4-[(1*E*)-2-(3,4-Dihydroxyphenyl)ethenyl]phenyl}phthalimide (22c)

This compound was prepared from **22b** by means of a procedure similar to that used for **19c**. Compound **22c** was obtained in 44% yield as yellow needles after recrystallization from EtOAc/*n*-hexane.

Mp 278.0–281.0 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.97 (dd, 2H, J = 5.5, 3.1 Hz), 7.90 (dd, 2H, J = 5.5, 3.1 Hz), 7.67 (d, 2H, J = 8.5 Hz), 7.40 (d, 2H, J = 8.5 Hz), 7.14 (d, 1H, J = 16.2 Hz), 7.01 (d, 1H, J = 2.4 Hz), 6.97 (d, 1H, J = 16.2 Hz), 6.89 (dd, 1H, J = 8.5, 1.8 Hz), 6.73 (d, 1H, J = 7.9 Hz). FAB-MS m/z: 357 $[M]^+$, 358 $[M+H]^+$. Anal. Calcd for $C_{22}H_{15}NO_4 \cdot 1/4H_2O$: C, 73.02; H, 4.32; N, 3.87. Found: C, 73.21; H, 4.36; N, 3.91.

4.2.39. *N*-{4-[2-(3-Methoxyphenyl)ethyl]phenyl}phthalimide (23d)

This compound was prepared from **16d** by means of a procedure similar to that used for **19b**. Compound **23d** was obtained in 78% yield as colorless needles after recrystallization from CH_2Cl_2/*n*-hexane.

Mp 127.0–127.5 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.96 (dd, 2H, J = 5.5, 3.1 Hz), 7.79 (dd, 2H, J = 5.5, 3.1 Hz), 7.36–7.32 (m, 4H), 7.22 (t, 1H, J = 7.9 Hz), 6.82 (d, 1H, J = 7.3 Hz), 6.76 (dd, 1H, J = 7.3, 1.8 Hz), 6.74 (d, 1H, J = 1.8 Hz), 3.79 (s, 3H), 3.00–2.96 (m, 2H), 2.95–2.91 (m, 2H). FAB-MS m/z: 357 $[M]^+$, 358 $[M+H]^+$. Anal. Calcd for $C_{23}H_{19}NO_3 \cdot 1/4H_2O$: C, 76.33; H, 5.43; N, 3.87. Found: C, 76.34; H, 5.40; N, 3.87.

4.2.40. *N*-{4-[2-(3-Hydroxyphenyl)ethyl]phenyl}phthalimide (23e)

This compound was prepared from **23d** by means of a procedure similar to that used for **19c**. Compound **23e** was obtained in 68% yield as colorless needles after recrystallization from EtOAc/*n*-hexane.

Mp 229.0–232.0 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.96 (dd, 2H, J = 5.5, 3.1 Hz), 7.80 (dd, 2H, J = 5.5, 3.1 Hz), 7.35–7.30 (m, 4H), 7.17 (t, 1H, J = 7.9 Hz), 6.80 (d, 1H, J = 7.3 Hz), 6.68 (dd, 1H, J = 7.9, 2.4 Hz), 6.60 (s, 1H), 2.98–2.95 (m, 2H), 2.92–2.89 (m, 2H). FAB-MS m/z: 343 $[M]^+$, 344 $[M+H]^+$. Anal. Calcd for $C_{22}H_{17}NO_3 \cdot 1/5H_2O$: C, 76.15; H, 5.05; N, 4.04. Found: C, 76.38; H, 5.24; N, 4.05.

4.2.41. *N*-{4-[2-(4-Methoxyphenyl)ethyl]phenyl}phthalimide (23f)

This compound was prepared from **16f** by means of a procedure similar to that used for **19b**. Compound **23f** was obtained in 93% yield as colorless needles after recrystallization from CH_2Cl_2/*n*-hexane.

Mp 196.5–199.0 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.96 (dd, 2H, J = 5.5, 3.1 Hz), 7.79 (dd, 2H, J = 5.5, 3.1 Hz), 7.36–7.31 (m, 4H), 7.13 (d, 2H, J = 8.5 Hz), 6.85 (d, 2H, J = 9.2 Hz), 3.80 (s, 3H). FAB-MS m/z: 357 $[M]^+$, 358 $[M+H]^+$. Anal. Calcd for $C_{23}H_{19}NO_3$: C, 77.29; H, 5.36; N, 3.92. Found: C, 77.21; H, 5.51; N, 3.83.

4.2.42. *N*-{4-[2-(4-Hydroxyphenyl)ethyl]phenyl}phthalimide (23g)

This compound was prepared from **23f** by means of a procedure similar to that used for **19c**. Compound **23g** was obtained in 29% yield as a brown powder after recrystallization from EtOAc/*n*-hexane.

Mp 285.0–288.0 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.96 (dd, 2H, J = 5.5, 3.1 Hz), 7.80 (dd, 2H, J = 5.5, 3.1 Hz), 7.35–7.30 (m, 4H), 7.08 (d, 2H, J = 7.9 Hz), 6.77 (d, 2H, J = 8.5 Hz), 2.94–2.92 (m, 2H), 2.90–2.88 (m, 2H). FAB-MS m/z: 343 $[M]^+$, 344 $[M+H]^+$. Anal. Calcd for $C_{22}H_{17}NO_3 \cdot 1/2H_2O$: C, 74.99; H, 5.15; N, 3.97. Found: C, 74.97; H, 5.20; N, 3.89.

4.2.43. 4,5,6,7-Tetrachloro-*N*-[2-(2-phenylethyl)phenyl]phthalimide (24a)

This compound was prepared from **14a** by means of a procedure similar to that used for **19b**. Compound **24a** was obtained in 82% yield as colorless plates after recrystallization from CH_2Cl_2/*n*-hexane.

Mp 148.0–149.0 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.42–7.39 (m, 1H), 7.35–7.32 (m, 2H), 7.19–7.16 (m, 2H), 7.14–7.09 (m, 2H), 7.06 (d, 2H, J = 6.7 Hz), 2.87–2.84 (m, 2H), 2.78–2.75 (m, 2H). FAB-MS m/z: 463 $[M]^+$, 464 $[M+H]^+$, 465 $[M+2]^+$, 466 $[M+3]^+$, 467 $[M+4]^+$, 468 $[M+5]^+$. Anal. Calcd for $C_{22}H_{13}Cl_4NO_2$: C, 56.81; H, 2.82; N, 3.01. Found: C, 56.67; H, 2.92; N, 2.94.

4.2.44. 4,5,6,7-Tetrachloro-*N*-{2-[2-(3,4-dimethoxyphenyl)ethyl]phenyl}phthalimide (24b)

This compound was prepared from **14b** by means of a procedure similar to that used for **19b**. Compound **24b** was obtained in 92% yield as a yellow powder after recrystallization from CH_2Cl_2/*n*-hexane.

Mp 157.0–158.0 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.41 (td, 1H, J = 7.9, 1.8 Hz), 7.35 (td, 1H, J = 7.9, 1.8 Hz), 7.32 (dd, 1H, J = 7.3, 1.8 Hz), 7.15 (dd, 1H, J = 7.9, 1.8 Hz), 6.68 (d, 1H, J = 7.9 Hz), 6.61 (dd, 1H, J = 7.9, 1.8 Hz), 6.53 (d, 1H, J = 1.8 Hz), 3.81 (s, 3H), 3.75 (s, 3H), 2.80 (s, 4H). FAB-MS m/z: 523 $[M]^+$, 524 $[M+H]^+$, 525 $[M+2]^+$, 526 $[M+3]^+$, 527 $[M+4]^+$, 528 $[M+5]^+$. Anal. Calcd for $C_{24}H_{17}Cl_4NO_4$: C, 54.88; H, 3.26; N, 2.67. Found: C, 54.63; H, 3.37; N, 2.54.

4.2.45. 4,5,6,7-Tetrachloro-*N*-{2-[2-(3,4-dihydroxyphenyl)ethyl]phenyl}phthalimide (24c)

This compound was prepared from **24b** by means of a procedure similar to that used for **19c**. Compound **24c** was obtained in 90% yield as colorless plates after recrystallization from EtOAc/*n*-hexane.

Mp 227.0–229.5 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.41 (m, 1H), 7.36–7.32 (m, 2H), 7.14–7.13 (m, 1H), 6.66 (d, 1H, J = 7.9 Hz), 6.53 (d, 1H, J = 2.4 Hz), 6.49 (dd, 1H, J = 7.9, 1.8 Hz), 5.09 (s, 1H), 4.94 (s, 1H), 2.76 (s, 4H). FAB-MS m/z: 495 $[M]^+$, 496 $[M+H]^+$, 497 $[M+2]^+$, 498 $[M+3]^+$, 499 $[M+4]^+$, 500 $[M+5]^+$. Anal. Calcd for $C_{22}H_{13}Cl_4NO_4$: C, 53.15; H, 2.64; N, 2.82. Found: C, 53.03; H, 2.88; N, 2.62.

4.2.46. 4,5,6,7-Tetrachloro-*N*-[3-(2-phenylethyl)phenyl]phthalimide (25a)

This compound was prepared from **15a** by means of a procedure similar to that used for **19b**. Compound **25a** was obtained in 89% yield as colorless needles after recrystallization from CH_2Cl_2/*n*-hexane.

Mp 187.0–187.5 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.42 (t, 1H, J = 7.9 Hz), 7.29 (t, 2H, J = 7.9 Hz), 7.26–7.25 (m, 1H), 7.24 (dd, 2H, J = 7.9, 1.8 Hz), 7.20 (dd, 1H, J = 7.9, 1.2 Hz), 7.19 (d, 2H, J = 7.9 Hz), 3.00–2.97 (m, 2H), 2.96–2.94 (m, 2H). FAB-MS m/z: 463 $[M]^+$, 464 $[M+H]^+$, 465 $[M+2]^+$, 466 $[M+3]^+$, 467 $[M+4]^+$, 468 $[M+5]^+$. Anal. Calcd for $C_{22}H_{13}Cl_4NO_2$: C, 56.81; H, 2.82; N, 3.01. Found: C, 56.66; H, 2.91; N, 2.95.

4.2.47. 4,5,6,7-Tetrachloro-*N*-{3-[2-(3,4-dimethoxyphenyl)ethyl]phenyl}phthalimide (25b)

This compound was prepared from **15b** by means of a procedure similar to that used for **19b**. Compound **25b** was obtained in 90% yield as yellow needles after recrystallization from CH_2Cl_2/*n*-hexane.

Mp 166.0–167.0 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.43–7.39 (m, 1H), 7.24–7.20 (m, 3H), 6.79 (d, 1H, J = 7.9 Hz), 6.71 (dd, 1H, J = 7.9, 1.8 Hz), 6.64 (d, 1H, J = 1.8 Hz), 3.86 (s, 3H), 3.83 (s, 3H), 2.97–2.94 (m, 2H), 2.91–2.88 (m, 2H). FAB-MS m/z: 523 $[M]^+$, 524 $[M+H]^+$, 525 $[M+2]^+$, 526 $[M+3]^+$, 527 $[M+4]^+$, 528 $[M+5]^+$. Anal. Calcd for $C_{24}H_{17}Cl_4NO_4 \cdot 1/4H_2O$: C, 54.42; H, 3.33; N, 2.64. Found: C, 54.49; H, 3.36; N, 2.61.

4.2.48. 4,5,6,7-Tetrachloro-*N*-{3-[2-(3,4-dihydroxyphenyl)ethyl]phenyl}phthalimide (25c)

This compound was prepared from **25b** by means of a procedure similar to that used for **19c**. Compound **25c** was obtained in 70% yield as a pale yellow powder after recrystallization from EtOAc/*n*-hexane.

Mp 208.0–210.0 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.43 (t, 1H, J = 7.9 Hz), 7.24 (d, 1H, J = 7.3 Hz), 7.20 (m, 1H), 7.10 (s, 1H), 6.78 (d, 1H, J = 7.9 Hz), 6.63 (dd, 1H, J = 7.9, 1.8 Hz), 6.58 (d, 1H, J = 1.8 Hz), 5.53 (s, 1H), 5.15 (s, 1H), 2.93–2.91 (m, 2H), 2.85–2.82 (m, 2H). FAB-MS m/z: 495 $[M]^+$, 496 $[M+H]^+$, 497 $[M+2]^+$, 498 $[M+3]^+$, 499 $[M+4]^+$, 500 $[M+5]^+$. Anal. Calcd for $C_{22}H_{13}Cl_4NO_4 \cdot 2/3H_2O$: C, 51.90; H, 2.84; N, 2.75. Found: C, 51.70; H, 3.03; N, 2.60.

4.2.49. 4,5,6,7-Tetrachloro-*N*-[4-(2-phenylethyl)phenyl]phthalimide (26a)

This compound was prepared from **16a** by means of a procedure similar to that used for **19b**. Compound **26a** was obtained in 96% yield as colorless needles after recrystallization from CH_2Cl_2/*n*-hexane.

Mp 222.0–223.0 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.33–7.28 (m, 6H), 7.22–7.19 (m, 3H), 3.00–2.98 (m, 2H), 2.97–2.94 (m, 2H). FAB-MS m/z: 463 $[M]^+$, 464 $[M+H]^+$, 465 $[M+2]^+$, 466 $[M+3]^+$, 467 $[M+4]^+$, 468 $[M+5]^+$. Anal. Calcd for $C_{22}H_{13}Cl_4NO_2$: C, 56.81; H, 2.82; N, 3.01. Found: C, 56.85; H, 3.02; N, 2.94.

4.2.50. 4,5,6,7-Tetrachloro-*N*-{4-[2-(3,4-dimethoxyphenyl)ethyl]phenyl}phthalimide (26b)

This compound was prepared from **16b** by means of a procedure similar to that used for **19b**. Compound **26b** was obtained in 99% yield as a yellow powder after recrystallization from CH_2Cl_2/*n*-hexane.

Mp 220.0–221.5 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.28 (s, 4H), 6.78 (d, 1H, J = 8.5 Hz), 6.71 (dd, 1H, J = 8.5, 1.8 Hz), 6.62 (d, 1H, J = 1.8 Hz), 3.85 (s, 3H), 3.82 (s, 3H), 2.96–2.93 (m, 2H), 2.90–2.87 (m, 2H). FAB-MS m/z: 523 $[M]^+$, 524 $[M+H]^+$, 525 $[M+2]^+$, 526 $[M+3]^+$, 527 $[M+4]^+$, 528 $[M+5]^+$. HRMS (FAB) calcd for $C_{24}H_{17}Cl_4NO_4$ 522.9912; found: 522.9929 $(M)^+$.

4.2.51. 4,5,6,7-Tetrachloro-*N*-{4-[2-(3,4-dihydroxyphenyl)ethyl]phenyl}phthalimide (26c)

This compound was prepared from **26b** by means of a procedure similar to that used for **19c**. Compound **26c** was obtained in 64% yield as a yellow powder after recrystallization from EtOAc/*n*-hexane.

Mp 260.0–263.0 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.70 (s, 1H), 8.62 (s, 1H), 7.38 (d, 2H, J = 8.5 Hz), 7.30 (d, 2H, J = 8.5 Hz), 6.64 (d, 1H, J = 2.1 Hz), 6.62 (d, 1H, J = 7.9 Hz), 6.47 (dd, 1H, J = 7.9, 2.1 Hz), 2.88–2.85 (m, 2H), 2.75–2.72 (m, 2H). FAB-MS $m/$

z: 495 $[M]^+$, 496 $[M+H]^+$, 497 $[M+2]^+$, 498 $[M+3]^+$, 499 $[M+4]^+$, 500 $[M+5]^+$. Anal. Calcd for $C_{22}H_{13}Cl_4NO_4 \cdot 1/3H_2O$: C, 52.52; H, 2.74; N, 2.78. Found: C, 52.47; H, 2.85; N, 2.51.

4.2.52. 4,5,6,7-Tetrachloro-*N*-{3-[(1*E*)-2-phenylethenyl]phenyl} phthalimide (27a)

This compound was prepared from **17a** by means of a procedure similar to that used for **19b**. Compound **27a** was obtained in 77% yield as a white powder after recrystallization from CH_2Cl_2/*n*-hexane.

Mp 259.5–261.5 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.58–7.56 (m, 2H), 7.52–7.49 (m, 3H), 7.37 (t, 2H, *J* = 7.9 Hz), 7.31–7.28 (m, 2H), 7.15 (d, 1H, *J* = 16.8 Hz), 7.12 (d, 1H, *J* = 16.8 Hz). FAB-MS *m*/*z*: 461 $[M]^+$, 462 $[M+H]^+$, 463 $[M+2]^+$, 464 $[M+3]^+$, 465 $[M+4]^+$, 466 $[M+5]^+$. Anal. Calcd for $C_{22}H_{11}Cl_4NO_2 \cdot 1/3H_2O$: C, 56.32; H, 2.51; N, 2.99. Found: C, 56.55; H, 2.56; N, 2.98.

4.2.53. 4,5,6,7-Tetrachloro-*N*-{3-[(1*E*)-2-(3,4-dimethoxyphenyl) ethenyl]phenyl}phthalimide (27b)

This compound was prepared from **17b** by means of a procedure similar to that used for **19b**. Compound **27b** was obtained in 73% yield as a yellow powder after recrystallization from CH_2Cl_2/*n*-hexane.

Mp 248.0–249.0 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.56–7.54 (m, 2H), 7.49 (t, 1H, *J* = 7.9 Hz), 7.29–7.27 (m, 1H), 7.09 (d, 1H, *J* = 16.2 Hz), 7.07–7.05 (m, 2H), 6.99 (d, 1H, *J* = 16.2 Hz), 6.87 (d, 1H, *J* = 7.9 Hz), 3.95 (s, 3H), 3.91 (s, 3H). FAB-MS *m*/*z*: 521 $[M]^+$, 522 $[M+H]^+$, 523 $[M+2]^+$, 524 $[M+3]^+$, 525 $[M+4]^+$, 526 $[M+5]^+$. Anal. Calcd for $C_{24}H_{15}Cl_4NO_4 \cdot 1/2H_2O$: C, 54.16; H, 3.03; N, 2.63. Found: C, 53.98; H, 3.03; N, 2.49.

4.2.54. 4,5,6,7-Tetrachloro-*N*-{3-[(1*E*)-2-(3,4-dihydroxyphenyl) ethenyl]phenyl}phthalimide (27c)

This compound was prepared from **27b** by means of a procedure similar to that used for **19c**. Compound **27c** was obtained in 92% yield as orange needles after recrystallization from EtOAc/*n*-hexane.

Mp 257.0–260.0 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.51 (dt, 1H, *J* = 7.9, 1.2 Hz), 7.50 (m, 1H), 7.47 (t, 1H, *J* = 7.9 Hz), 7.26–7.25 (m, 1H), 7.05 (d, 1H, *J* = 1.8 Hz), 7.00 (d, 1H, *J* = 16.5 Hz), 6.95 (dd, 1H, *J* = 8.5, 1.8 Hz), 6.91 (d, 1H, *J* = 16.5 Hz), 6.85 (d, 1H, *J* = 8.5 Hz), 5.59 (br s, 1H), 5.54 (br s, 1H). FAB-MS *m*/*z*: 493 $[M]^+$, 494 $[M+H]^+$, 495 $[M+2]^+$, 496 $[M+3]^+$, 497 $[M+4]^+$, 498 $[M+5]^+$. HRMS (FAB) calcd for $C_{22}H_{11}Cl_4NO_4$ 492.9442; found: 492.9467 $(M)^+$.

4.2.55. 4,5,6,7-Tetrachloro-*N*-{4-[(1*E*)-2-phenylethenyl]phenyl} phthalimide (28a)

This compound was prepared from **18a** by means of a procedure similar to that used for **19b**. Compound **28a** was obtained in 73% yield as yellow needles after recrystallization from CH_2Cl_2/*n*-hexane.

Mp 296.0–296.5 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.65 (d, 2H, *J* = 8.5 Hz), 7.54 (d, 2H, *J* = 7.3 Hz), 7.42 (d, 2H, *J* = 8.5 Hz), 7.38 (t, 2H, *J* = 7.3 Hz), 7.29 (tt, 1H, *J* = 7.3, 1.2 Hz), 7.17 (d, 1H, *J* = 16.5 Hz), 7.13 (d, 1H, *J* = 16.5 Hz). FAB-MS *m*/*z*: 461 $[M]^+$, 462 $[M+H]^+$, 463 $[M+2]^+$, 464 $[M+3]^+$, 465 $[M+4]^+$, 466 $[M+5]^+$. Anal. Calcd for $C_{22}H_{11}Cl_4NO_2$: C, 57.05; H, 2.39; N, 3.02. Found: C, 56.83; H, 2.69; N, 3.09.

4.2.56. 4,5,6,7-Tetrachloro-*N*-{4-[(1*E*)-2-(3,4-dimethoxyphenyl) ethenyl]phenyl}phthalimide (28b)

This compound was prepared from **18b** by means of a procedure similar to that used for **19b**. Compound **28b** was obtained in 68% yield as an orange powder after recrystallization from CH_2Cl_2/*n*-hexane.

Mp 281.0–284.0 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.62 (d, 2H, *J* = 8.5 Hz), 7.40 (d, 2H, *J* = 8.5 Hz), 7.11 (d, 1H, *J* = 16.2 Hz), 7.09–7.05 (m, 2H), 7.00 (d, 1H, *J* = 16.2 Hz), 6.88 (d, 1H, *J* = 8.5 Hz), 3.96 (s, 3H), 3.91 (s, 3H). FAB-MS *m*/*z*: 521 $[M]^+$, 522 $[M+H]^+$, 523 $[M+2]^+$, 524 $[M+3]^+$, 525 $[M+4]^+$, 526 $[M+5]^+$. Anal. Calcd for $C_{24}H_{15}Cl_4NO_4 \cdot 1/2H_2O$: C, 54.16; H, 3.03; N, 2.63. Found: C, 54.24; H, 2.97; N, 2.55.

4.2.57. 4,5,6,7-Tetrachloro-*N*-{4-[(1*E*)-2-(3,4-dihydroxyphenyl) ethenyl]phenyl}phthalimide (28c)

This compound was prepared from **28b** by means of a procedure similar to that used for **19c**. Compound **28c** was obtained in 52% yield as red plates after recrystallization from EtOAc/*n*-hexane.

Mp >300 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.69 (d, 2H, *J* = 8.5 Hz), 7.38 (d, 2H, *J* = 8.5 Hz), 7.16 (d, 1H, *J* = 16.5 Hz), 7.02 (d, 1H, *J* = 1.8 Hz), 6.98 (d, 1H, *J* = 16.5 Hz), 6.89 (dd, 1H, *J* = 8.5, 1.8 Hz), 6.73 (d, 1H, *J* = 7.9 Hz). FAB-MS *m*/*z*: 493 $[M]^+$, 494 $[M+H]^+$, 495 $[M+2]^+$, 496 $[M+3]^+$, 497 $[M+4]^+$, 498 $[M+5]^+$. Anal. Calcd for $C_{22}H_{11}Cl_4NO_4 \cdot 1/5H_2O$: C, 52.98; H, 2.30; N, 2.81. Found: C, 53.31; H, 2.64; N, 2.64.

4.2.58. 4,5,6,7-Tetrachloro-*N*-{3-[2-(3-methoxyphenyl)ethyl] phenyl}phthalimide (29d)

This compound was prepared from **15d** by means of a procedure similar to that used for **19b**. Compound **29d** was obtained in 83% yield as colorless needles after recrystallization from CH_2Cl_2/*n*-hexane.

Mp 150.0–151.0 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.42 (t, 1H, *J* = 7.9 Hz), 7.26–7.25 (m, 2H), 7.23 (m, 1H), 7.20 (t, 1H, *J* = 7.9 Hz), 6.78 (d, 1H, *J* = 7.3 Hz), 6.75 (dd, 1H, *J* = 7.9, 1.8 Hz), 6.72–6.72 (m, 1H), 3.78 (s, 3H), 3.00–2.96 (m, 2H), 2.94–2.91 (m, 2H). FAB-MS *m*/*z*: 493 $[M]^+$, 494 $[M+H]^+$, 495 $[M+2]^+$, 496 $[M+3]^+$, 497 $[M+4]^+$, 498 $[M+5]^+$. Anal. Calcd for $C_{23}H_{15}Cl_4NO_3 \cdot 1/4H_2O$: C, 55.28; H, 3.13; N, 2.80. Found: C, 55.43; H, 3.11; N, 2.82.

4.2.59. 4,5,6,7-Tetrachloro-*N*-{3-[2-(3-hydroxyphenyl)ethyl] phenyl}phthalimide (29e)

This compound was prepared from **29d** by means of a procedure similar to that used for **19c**. Compound **29e** was obtained in 60% yield as colorless needles after recrystallization from EtOAc/*n*-hexane.

Mp 213.0–215.0 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.42 (t, 1H, *J* = 7.9 Hz), 7.25–7.20 (m, 3H), 7.15 (t, 1H, *J* = 7.9 Hz), 6.76 (d, 1H, *J* = 7.9 Hz), 6.68 (dd, 1H, *J* = 7.9, 2.4 Hz), 6.62 (t, 1H, *J* = 1.8 Hz), 2.98–2.95 (m, 2H), 2.92–2.88 (m, 2H). FAB-MS *m*/*z*: 479 $[M]^+$, 480 $[M+H]^+$, 481 $[M+2]^+$, 482 $[M+3]^+$, 483 $[M+4]^+$, 484 $[M+5]^+$. Anal. Calcd for $C_{22}H_{13}Cl_4NO_3$: C, 54.92; H, 2.72; N, 2.91. Found: C, 54.68; H, 2.99; N, 2.77.

4.2.60. 4,5,6,7-Tetrachloro-*N*-{3-[2-(4-methoxyphenyl)ethyl] phenyl}phthalimide (29f)

This compound was prepared from **15f** by means of a procedure similar to that used for **19b**. Compound **29f** was obtained in 74% yield as pale yellow plates after recrystallization from CH_2Cl_2/*n*-hexane.

Mp 169.0–170.0 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.41 (t, 1H, *J* = 8.5 Hz), 7.23–7.22 (m, 2H), 7.09 (d, 2H, *J* = 8.5 Hz), 6.83 (d, 2H, *J* = 8.5 Hz), 3.79 (s, 3H), 2.96–2.93 (m, 2H), 2.91–2.87 (m, 2H). FAB-MS *m*/*z*: 494 $[M+H]^+$, 495 $[M+2]^+$, 496 $[M+3]^+$, 497 $[M+4]^+$, 498 $[M+5]^+$. Anal. Calcd for $C_{23}H_{15}Cl_4NO_3 \cdot 1/4H_2O$: C, 55.28; H, 3.13; N, 2.80. Found: C, 55.28; H, 3.09; N, 2.78.

4.2.61. 4,5,6,7-Tetrachloro-*N*-{3-[2-(4-hydroxyphenyl)ethyl] phenyl}phthalimide (29g)

This compound was prepared from **29f** by means of a procedure similar to that used for **19c**. Compound **29g** was obtained in 67%

yield as a white powder after recrystallization from EtOAc/*n*-hexane.

Mp 210.0–212.0 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.41 (t, 1H, J = 7.3 Hz), 7.24–7.20 (m, 3H), 7.03 (d, 2H, J = 8.5 Hz), 6.75 (d, 2H, J = 8.5 Hz), 4.60 (br s, 1H), 2.95–2.92 (m, 2H), 2.89–2.86 (m, 2H). FAB-MS m/z: 479 $[M]^+$, 480 $[M+H]^+$, 481 $[M+2]^+$, 482 $[M+3]^+$, 483 $[M+4]^+$, 484 $[M+5]^+$. Anal. Calcd for $C_{22}H_{13}Cl_4NO_3$: C, 54.92; H, 2.72; N, 2.91. Found: C, 54.68; H, 2.82; N, 2.83.

4.2.62. 4,5,6,7-Tetrachloro-*N*-{4-[2-(3-methoxyphenyl)ethyl] phenyl}phthalimide (30d)

This compound was prepared from **16d** by means of a procedure similar to that used for **19b**. Compound **30d** was obtained in 95% yield as colorless plates after recrystallization from CH_2Cl_2/*n*-hexane.

Mp 170.5–172.0 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.34–7.29 (m, 4H), 7.22 (t, 1H, J = 7.9 Hz), 6.80 (d, 1H, J = 7.3 Hz), 6.76 (dd, 1H, J = 7.9, 1.8 Hz), 6.73 (s, 1H), 3.79 (s, 3H), 3.00–2.97 (m, 2H), 2.95–2.91 (m, 2H). FAB-MS m/z: 493 $[M]^+$, 494 $[M+H]^+$, 495 $[M+2]^+$, 496 $[M+3]^+$, 497 $[M+4]^+$, 498 $[M+5]^+$. HRMS (FAB) calcd for $C_{23}H_{15}Cl_4NO_3$ 492.9806; found: 492.9834 $(M)^+$.

4.2.63. 4,5,6,7-Tetrachloro-*N*-{4-[2-(3-hydroxyphenyl)ethyl] phenyl}phthalimide (30e)

This compound was prepared from **30d** by means of a procedure similar to that used for **19c**. Compound **30e** was obtained in 66% yield as a pale brown powder after recrystallization from EtOAc/*n*-hexane.

Mp 267.0–268.0 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 9.25 (br s, 1H), 7.40 (d, 2H, J = 7.9 Hz), 7.31 (d, 2H, J = 7.9 Hz), 7.06 (t, 1H, J = 7.3 Hz), 6.67 (d, 1H, J = 7.3 Hz), 6.66 (s, 1H), 6.58 (d, 1H, J = 7.3 Hz), 2.92–2.90 (m, 2H), 2.84–2.81 (m, 2H). FAB-MS m/z: 479 $[M]^+$, 480 $[M+H]^+$, 481 $[M+2]^+$, 482 $[M+3]^+$, 483 $[M+4]^+$, 484 $[M+5]^+$. HRMS (FAB) calcd for $C_{22}H_{13}Cl_4NO_3$ 478.9650; found: 478.9694 $(M)^+$.

4.2.64. 4,5,6,7-Tetrachloro-*N*-{4-[2-(4-methoxyphenyl)ethyl] phenyl}phthalimide (30f)

This compound was prepared from **16f** by means of a procedure similar to that used for **19b**. Compound **30f** was obtained in 70% yield as a white powder after recrystallization from CH_2Cl_2/*n*-hexane.

Mp 209.5–211.5 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.30 (s, 4H), 7.10 (d, 2H, J = 8.5 Hz), 6.84 (d, 2H, J = 8.5 Hz), 3.80 (s, 3H), 2.96–2.93 (m, 2H), 2.91–2.90 (m, 2H). FAB-MS m/z: 494 $[M+H]^+$, 495 $[M+2]^+$, 496 $[M+3]^+$, 497 $[M+4]^+$, 498 $[M+5]^+$. Anal. Calcd for $C_{23}H_{15}Cl_4NO_3$: C, 55.79; H, 3.05; N, 2.83. Found: C, 55.43; H, 3.20; N, 2.76.

4.2.65. 4,5,6,7-Tetrachloro-*N*-{4-[2-(4-hydroxyphenyl)ethyl] phenyl}phthalimide (30g)

This compound was prepared from **30f** by means of a procedure similar to that used for **19c**. Compound **30g** was obtained in 88% yield as a pale brown powder after recrystallization from EtOAc/*n*-hexane.

Mp 266.0–268.0 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 9.15 (br s, 1H), 7.37 (d, 2H, J = 8.5 Hz), 7.30 (d, 2H, J = 8.5 Hz), 7.03 (d, 2H, J = 8.5 Hz), 6.66 (d, 2H, J = 8.5 Hz), 2.89–2.86 (m, 2H), 2.81–2.78 (m, 2H). FAB-MS m/z: 479 $[M]^+$, 480 $[M+H]^+$, 481 $[M+2]^+$, 482 $[M+3]^+$, 483 $[M+4]^+$, 484 $[M+5]^+$. Anal. Calcd for $C_{22}H_{13}Cl_4NO_3$: C, 54.92; H, 2.72; N, 2.91. Found: C, 54.60; H, 3.00; N, 2.82.

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