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New *N*-(phenoxydecyl)phthalimide derivatives displaying potent inhibition activity towards α-glucosidase

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ABSTRACT

Several members of a new family of non-sugar-type α-glucosidase inhibitors, bearing a phthalimide moiety connected to a variously substituted phenoxy ring by an alkyl chain, were synthesized and their activities were investigated. The efficacy of the inhibition activity appeared to be governed by the chain length of the substrate. Substrates possessing 10 carbons afforded the highest levels of activity, which were one to two orders of magnitude more potent than the known inhibitor 1-deoxynojirimycin (dNM). Furthermore, structure–activity relationship studies indicated a critical role of electron-withdrawing substituents at the phenoxy group for the activity. Derivatives bearing a chlorine atom along with a strong electron-withdrawing group, such as a nitro group, were the most potent of the series.

1. Introduction

α-Glucosidase (EC 3.2.1.20, α-D-glucoside glucohydrolase) is the key enzyme which catalyzes the final step in the digestive process of carbohydrates in mammalians. Hence, α-glucosidase inhibitors can retard the liberation of D-glucose of oligosaccharides and disaccharides from dietary complex carbohydrates and delay glucose absorption, resulting in reduced post-prandial plasma glucose levels and suppressed post-prandial hyperglycaemia.[1] Consequently, α-glucosidase inhibitors such as acarbose[2] and miglitol[3] (Fig. 1) have been approved for clinical use in the management of type 2 diabetes, as well as the treatment of obesity. Glucosidase inhibition may also retard cancer growth since the spread of cancer as well as the structural changes of cell surface glycoconjugates within neoplasmic cells is proliferated by glycosidases.[4] α-Glucosidase inhibitors have also been observed to block viral infections[5] and proliferation in HIV-infections.[6] In fact, the well established α-glucosidase inhibitor 1-deoxynojirimycin (dNM, Fig. 1) exhibits potential anti-human HIV activity.[7] As a consequence, many efforts have been made to develop new α-glucosidase inhibitors, as recently reviewed in an extensive fashion.[8] These include transition state analogues,[9] newly identified synthetic compounds,[10–13] and natural products isolated from a variety of species.[14–16] However, most of developed glycosidase inhibitors are sugar mimics which require tedious multi-steps chemical procedures.[17–19] Amongst the various types of glucosidase inhibitors, also non-sugar derivatives have drawn considerable attention. Indeed, there is great structural diversity amongst glucosidase inhibitors, which are not based on a sugar scaffold. In particular, basing on pharmacological studies involving thalidomide, it was found that phenylalkyl tetrachlorophthalimide derivatives exhibited potent α-glucosidase inhibition.[20,21] The structure–activity relationship

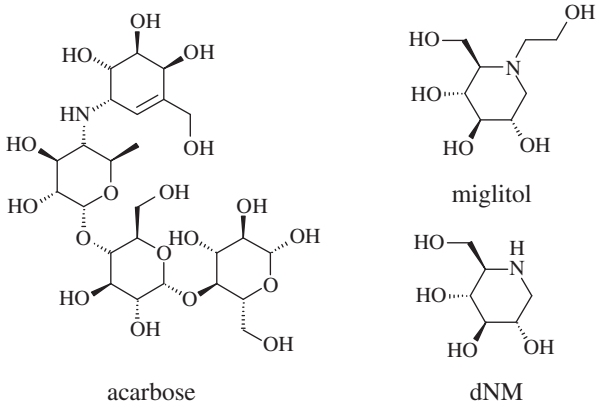

Figure 1. Structures of acarbose, miglitol and dNM.

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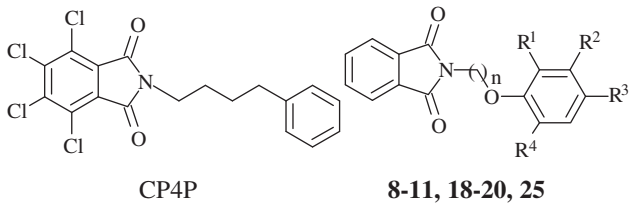
studies revealed the importance of the distance between the phthalimide ring and the phenyl moiety and the positive influence of electron-withdrawing groups attached to the phthalimide moiety. The authors suggested that the length of four methylene units was the optimum for the fitting/binding of the compound to α-glucosidase as exemplified by 4,5,6,7-tetrachloro-2-(4-phenylbutyl)-1*H*-isoindole-1,3(2*H*)-dione (CP4P, Fig. 2) which possesses activity one order of magnitude higher than that of dNM.[20] Although the tetrachlorophthalimide skeleton is a useful non-sugar-type sugar mimic pharmacophore, the above mentioned compounds are characterized by high lipophilicity which could influence their pharmacokinetic properties and biological activity. In the present study, with the ultimate aim of developing more potent and selective α-glucosidase inhibitors, a large series of phenoxyalkyl derivatives, bearing a non-substituted phthalimide moiety, were prepared in order to investigate structure–activity relationships and improve druglikeness. In particular, the effects of substitutions at the aryloxy moiety and the length of the methylene spacer between the phthalimide group and the phenoxy moiety were investigated.

2. Chemistry

Compounds **8a,b,e,f**, **9a–f**, **10a** and **11a** were prepared via the synthetic route shown in Scheme 1. It starts from the efficient protection of aminoalcohols **1–3** with phthalic anhydride. The phthalimido alcohols obtained (**5–7**) or commercial **4** were submitted to condensation with the appropriate phenol under Mitsunobu conditions[22] to give the desired compounds. Compounds **18a**, **19a**, **20a,b,d,f,g** (Scheme 2) were prepared by submitting commercial bromo propanols **12–14** to Williamson reaction with the appropriate phenol. The alcohols obtained underwent Mitsunobu oxidoreductive condensation with phthalimide to give the final compounds. Compounds **20h–o** were obtained by submitting decane-1,10-diol (**21**) to two successive Mitsunobu reactions with phthalimide, the former, and the appropriate phenol, the latter, via the intermediate **22** as shown in Scheme 3. For the synthesis of compound **20p** (Scheme 4) the replacement of hydroxy group of **22** with iodine in the presence of triphenylphosphine was needed before reaction of iodo derivative **23** with 4-(trifluoromethyl)phenol. Compounds **20j,q–x** were obtained by nitration of the appropriate phthalimidoalkyl aryl ether with sodium nitrite (Scheme 5). For the preparation of compound **25a**, (4-bromobutoxy)benzene (**24**) was reacted with potassium phthalimide according to the Scheme 6.

3. Results and discussion

On the basis of the studies of Takahashi et al.,[20,21] starting from CP4P as lead compound, a large series of new phthalimide derivatives (Fig. 2) were prepared. All the developed compounds are characterized by an unsubstituted phthalimide moiety connected to a variously decorated phenoxy group by an alkyl chain. The α-glucosidase inhibitory activity of the compounds is reported in Tables 1–3 and was performed as described in Section 5; as a positive control, dNM was adopted. At first, the effect of the distance between the phthalimide ring and a phenoxy moiety was considered. The compounds listed in Table 1 have a methylene spacer of different length inserted between the phthalimide moiety and the phenoxy group. As expected, the length of the methylene spacer seems to be critical for enzyme inhibition. Amongst this series (n = 2–10), the potency of the α-glucosidase inhibitory activity increased as the length of the methylene spacer increased to n = 10, being compound **20a** the most potent of the series. Next, we investigated the effects of substitution at the phenoxy ring starting from compounds **8a** (n = 2) and **9a** (n = 3) as scaffolds (Table 2). Introduction of a chlorine atom at the *para*-position (R_3), that is, compounds **8b** and **9b**, caused the enhancement of the activity, which seemed to be further increased by the introduction of one or two additional methyl groups at the *ortho*-positions (R_1, R_4) (**8e,f** and **9e,f**). Dichlorination of compound **9a** clearly enhanced α-glucosidase inhibitory activity (**9c,d**). Thus, the very potent activity of **20a** (Table 1) and the results shown in Table 2 led us to develop new decamethylene derivatives, variously substituted at the phenoxy moiety (Table 3). Notably, all the compounds of the **20** series showed IC_{50} values ranging from 0.5 to 3.5 μM which are one to two orders of magnitude more potent than the dNM. Interestingly, compounds **20b,d,f** showed an activity higher than **20a**, with only slight differences between each others. The results obtained with these compounds revealed the importance of the presence of an electron-withdrawing group at the 4-position (R_3); in fact, compounds **20b,j,p** were more potent than the corresponding 4-methyl derivative **20i** [the order of potency is: **20p** > **20j** > **20b** > **20i**]. Introduction of a nitro group at the *ortho*-position (R_1) of **20b** markedly enhanced the activity giving the most potent compound of the series (**20q**, IC_{50} = 0.475 μM). However, the same substitution run on compounds **20j,p**, that is, compounds **20t,u**, respectively, did not increase the activity; conceivably, this behaviour could be ascribed to the presence of two strong electron-withdrawing group at the phenoxy ring simultaneously. An additional chlorine atom on **20q** at *meta*-position (**20r**) or at the other *ortho*-position (**20s**) did not substantially affect the activity. Concerning the effect of *o,o′*-methyl substituents, the activity decreased in the order of **20w** > **20f** > **20m** > **20v**. Finally, it is noteworthy that compound **20x** showed an activity comparable to that of the best compounds of the series (**20q,r,s**), outlying the importance of the simultaneous presence of at least a chlorine atom and a strong electron-withdrawing group, such as a nitro group, at the phenoxy moiety. Notably, these results are in agreement with those recently reported in the literature by Rawlings et al.[23] which identified a dNM derivative, bearing a nitro substituted phenyl moiety, as the best α-glucosidase inhibitor reported to date. The most potent compounds of the series (**20q,r,s,x**) concerned for β-glucosidase, α-mannosidase, and α-galactosidase showed no inhibition activity at the maximal tested concentration of 25 μM (i.e., two orders of magnitude higher than IC_{50} values observed for α-glucosidase). The results obtained from the MTT assay on SH-SY5Y human neuroblastoma cells indicate that these compounds show no cytotoxicity.

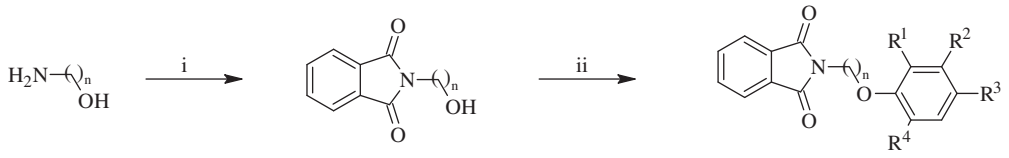


CP4P **8-11, 18-20, 25**

Figure 2. Structures of CP4P and newly synthesized *N*-(phenoxyalkyl) phthalimide derivatives.

4. Conclusions

Application of simple chemical transformations to easily available starting materials has generated several members of a new family of non-sugar-type sugar mimic α-glucosidase inhibitors bearing a phthalimide skeleton connected to a variously substituted phenoxy ring by an alkyl chain. All the compounds (Tables 1–3) were screened for α-glucosidase inhibitory activity, and structure–activity relationship studies were carried out. As a result, we



1-3 **4-7** **8a,b,e,f, 9a-f, 10a, 11a**

4, 8: n = 2

1, 5, 9: n = 3

2, 6, 10: n = 5

3, 7, 11: n = 6

a: $R^1 = R^2 = R^3 = R^4 = H$

b: $R^1 = R^2 = R^4 = H$, $R^3 = Cl$

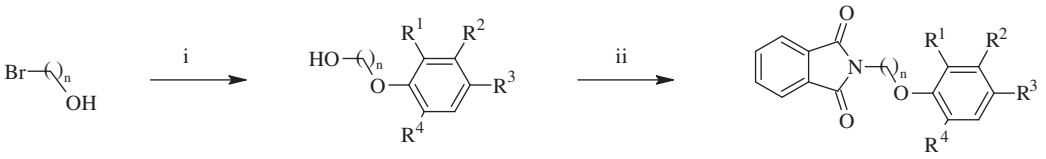
c: $R^1 = R^2 = Cl$, $R^3 = R^4 = H$

d: $R^1 = R^4 = H$, $R^2 = R^3 = Cl$

e: $R^1 = CH_3$, $R^2 = R^4 = H$, $R^3 = Cl$

f: $R^1 = R^4 = CH_3$, $R^2 = H$, $R^3 = Cl$

Scheme 1. Reagents and conditions: (i) phthalic anhydride, Et_3N, toluene, reflux; (ii) substituted phenol, TPP, DEAD or DIAD, anhyd THF, rt.



12-14 **15a, 16a, 17a,b,d,f,g** **18a, 19a, 20a,b,d,f,g**

12, 15, 18: n = 8

13, 16, 19: n = 9

14, 17, 20: n = 10

a: $R^1 = R^2 = R^3 = R^4 = H$

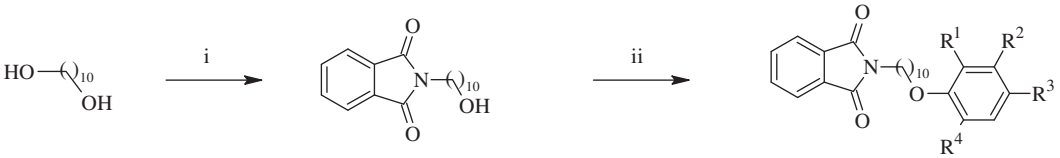
b: $R^1 = R^2 = R^4 = H$, $R^3 = Cl$

d: $R^1 = R^4 = H$, $R^2 = R^3 = Cl$

f: $R^1 = R^4 = CH_3$, $R^2 = H$, $R^3 = Cl$

g: $R^1 = R^3 = Cl$, $R^2 = R^4 = H$

Scheme 2. Reagents and conditions: (i) substituted phenol, K_2CO_3, anhyd DMF, 130 °C; (ii) phthalimide, TPP, DEAD or DIAD, anhyd THF, rt.



21 **22** **20h-o**

h: $R^1 = R^4 = H$, $R^2 = CF_3$, $R^3 = NO_2$

i: $R^1 = R^2 = R^4 = H$, $R^3 = CH_3$

j: $R^1 = R^2 = R^4 = H$, $R^3 = NO_2$

k: $R^1 = NO_2$, $R^2 = R^3 = R^4 = H$

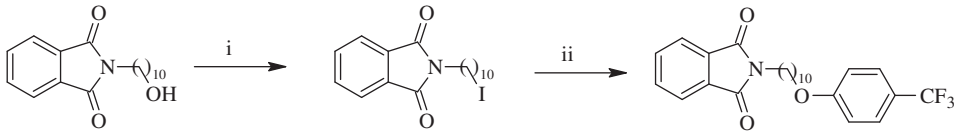
l: $R^1 = R^3 = R^4 = H$, $R^2 = NO_2$

m: $R^1 = R^4 = CH_3$, $R^2 = R^3 = H$

n: $R^1 = R^3 = R^4 = H$, $R^2 = Cl$

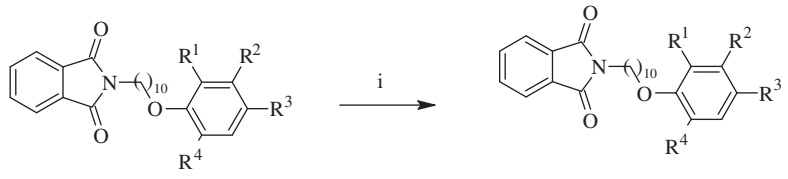
o: $R^1 = R^3 = H$, $R^2 = Cl$, $R^4 = CH_3$

Scheme 3. Reagents and conditions: (i) phthalimide, TPP, DBAD, anhyd THF, rt; (ii) substituted phenol, TPP, DIAD, anhyd THF, rt.



22 **23** **20p**

Scheme 4. Reagents and conditions: (i) TPP, I_2, anhyd toluene, reflux; (ii) 4-(trifluoromethyl)phenol, NaH, anhyd DMF, 0 °C then 75 °C.



20a,b,d,f,g,m,o,p **20j,q-x**

a: $R^1 = R^2 = R^3 = R^4 = H$

b: $R^1 = R^2 = R^4 = H$, $R^3 = Cl$

d: $R^1 = R^4 = H$, $R^2 = R^3 = Cl$

f: $R^1 = R^4 = CH_3$, $R^2 = H$, $R^3 = Cl$

g: $R^1 = R^3 = Cl$, $R^2 = R^4 = H$

m: $R^1 = R^4 = CH_3$, $R^2 = R^3 = H$

o: $R^1 = R^3 = H$, $R^2 = Cl$, $R^4 = CH_3$

p: $R^1 = R^2 = R^4 = H$, $R^3 = CF_3$

j: $R^1 = R^2 = R^4 = H$, $R^3 = NO_2$

q: $R^1 = NO_2$, $R^2 = R^4 = H$, $R^3 = Cl$

r: $R^1 = H$, $R^2 = R^3 = Cl$, $R^4 = NO_2$

s: $R^1 = R^3 = Cl$, $R^2 = H$, $R^4 = NO_2$

t: $R^1 = R^3 = NO_2$, $R^2 = R^4 = H$,

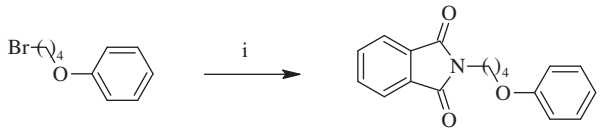
u: $R^1 = NO_2$, $R^2 = R^4 = H$, $R^3 = CF_3$

v: $R^1 = R^4 = CH_3$, $R^2 = NO_2$, $R^3 = Cl$

w: $R^1 = R^4 = CH_3$, $R^2 = H$, $R^3 = NO_2$

x: $R^1 = H$, $R^2 = Cl$, $R^3 = NO_2$, $R^4 = CH_3$

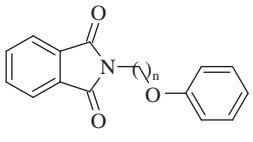
Scheme 5. Reagents and conditions: (i) $NaNO_2$, trifluoroacetic acid, rt.



24 **25a**

Scheme 6. Reagents and conditions: (i) potassium phthalimide, anhyd DMF, 80 °C.

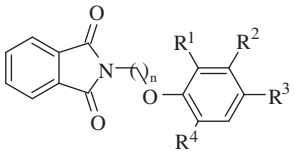
Table 1
α-Glucosidase inhibitory activity of *N*-(phenoxyalkyl)phthalimide derivatives



Compd	*n*	IC_{50} (μM)
dNM	—	52 ± 2[a]
8a	2	296 ± 4
9a	3	240 ± 40
25a	4	33 ± 3
10a	5	20.2 ± 0.2
11a	6	10.3 ± 0.1
18a	8	6.5 ± 0.2
19a	9	3.04 ± 0.01
20a	10	2.5 ± 0.2

[a] 34 ± 4 (Ref. 20).

Table 2
α-Glucosidase inhibitory activity of substituted *N*-(phenoxyalkyl)phthalimide derivatives

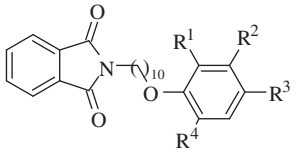


Compd	*n*	R^1	R^2	R^3	R^4	IC_{50} (μM)
dNM	—					52 ± 2[a]
8a	2	H	H	H	H	296 ± 4
8b	2	H	H	Cl	H	94 ± 4
8e	2	CH_3	H	Cl	H	14.8 ± 0.8
8f	2	CH_3	H	Cl	CH_3	13.0 ± 0.1
9a	3	H	H	H	H	240 ± 40
9b	3	H	H	Cl	H	59.0 ± 0.5
9c	3	Cl	Cl	H	H	15.0 ± 0.8
9d	3	H	Cl	Cl	H	7.55 ± 0.25
9e	3	CH_3	H	Cl	H	8.9 ± 0.4
9f	3	CH_3	H	Cl	CH_3	9.5 ± 0.3

[a] 34 ± 4 (Ref. 20).

identified potent α-glucosidase inhibitors (**20** series, Table 3) which possess activity one to two orders of magnitude higher than dNM, with IC_{50} values of 0.5–3.6 μM in our assay system. These biological results clearly demonstrated that the length of 10 methylene units and the simultaneous presence of a chlorine atom and a strong electron-withdrawing group, such as a nitro group, at the phenoxy moiety, are the optimum for the binding to α-glucosidase (see **20q,r,s**).

Table 3
α-Glucosidase inhibitory activity of *N*-(phenoxydecyl)phthalimide derivatives



Compd	R^1	R^2	R^3	R^4	IC_{50} (μM)
dNM					52 ± 2[a]
20a	H	H	H	H	2.5 ± 0.2
20b	H	H	Cl	H	1.2 ± 0.2
20d	H	Cl	Cl	H	1.00 ± 0.01
20f	CH_3	H	Cl	CH_3	1.34 ± 0.04
20g	Cl	H	Cl	H	1.19 ± 0.11
20h	H	CF_3	NO_2	H	0.83 ± 0.05
20i	H	H	CH_3	H	2.10 ± 0.01
20j	H	H	NO_2	H	0.86 ± 0.03
20k	NO_2	H	H	H	1.78 ± 0.01
20l	H	NO_2	H	H	1.075 ± 0.005
20m	CH_3	H	H	CH_3	3.25 ± 0.02
20n	H	Cl	H	H	1.09 ± 0.08
20o	H	Cl	H	CH_3	0.91 ± 0.05
20p	H	H	CF_3	H	0.83 ± 0.12
20q	NO_2	H	Cl	H	0.475 ± 0.05
20r	H	Cl	Cl	NO_2	0.52 ± 0.02
20s	Cl	H	Cl	NO_2	0.75 ± 0.01
20t	NO_2	H	NO_2	H	0.97 ± 0.04
20u	NO_2	H	CF_3	H	1.31 ± 0.01
20v	CH_3	NO_2	Cl	CH_3	3.6 ± 1.5
20w	CH_3	H	NO_2	CH_3	1.32 ± 0.12
20x	H	Cl	NO_2	CH_3	0.65 ± 0.01

[a] 34 ± 4 (Ref. 20).

The results obtained strongly suggest that the phenoxy moiety, appropriately substituted, is an important core for α-glucosidase inhibitory activity. It is interesting to note that all of the most potent compounds of the series (**20q,r,s,x**) did not inhibit other glycosidases, such as β-glucosidase, α-mannosidase, and α-galactosidase, neither did they show cytotoxicity on SH-SY5Y human neuroblastoma cells.

5. Experimental section

5.1. General methods and materials

All chemicals were purchased from Sigma–Aldrich or Lancaster. Yields refer to purified products and were not optimized. The structures of the compounds were confirmed by routine spectrometric analyses. Only spectra for compounds not previously described are given. Melting points were determined on a Gallenkamp melting point apparatus in open glass capillary tubes and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer (Norwalk, CT) Spectrum One FT spectrophotometer and band positions are given in reciprocal centimetres (cm^{-1}). ^1H NMR and ^{13}C NMR spectra were recorded on a Varian VX Mercury spectrometer operating at 300 and 75 MHz for ^1H and ^{13}C, respectively, using $CDCl_3$ as solvent. Chemical shifts are reported in parts per million (ppm) relative to solvent resonance: $CDCl_3$, δ 7.26 (^1H NMR) and δ 77.3 (^{13}C NMR). *J* values are given in Hz. EIMS spectra were recorded on a Hewlett–Packard 6890-5973 MSD gas chromatograph/mass spectrometer at low resolution. GC was performed on a Varian 3800 gas chromatograph equipped with a flame ionization detector and a Jew Scientific DB-5 capillary column (30 m, 0.25 mm i.d., 0.25 μm film thickness). Chromatographic separations were performed on silica gel columns by flash chromatography (Kieselgel 60, 0.040–0.063 mm, Merck, Darmstadt, Germany) as described by Still et al.[24] TLC analyses were performed on precoated silica gel on aluminium sheets (Kieselgel 60 F_{254}, Merck).

5.2. General procedure for the preparation of phthalimido alcohols (5–7)

The method adopted for the synthesis of 2-(3-hydroxypropyl)-1*H*-isoindole-1,3(2*H*)-dione (**5**) is described. A mixture of 3-amino-propan-1-ol (**1**) (2.0 g, 26.6 mmol), phthalic anhydride (3.9 g, 26.6 mmol), Et_3N (0.27 g, 2.66 mmol) and toluene (40 mL) was heated under reflux in a flask fitted with a Dean–Stark tube for 3 h. During this period, the temperature of the oil bath was maintained at about 130 °C and water separates. All volatile matter was then evaporated under vacuum and the solid residue was taken up with EtOAc and washed with 2 N HCl, $NaHCO_3$ saturated solution, and H_2O. The organic phase was dried (Na_2SO_4) and concentrated under vacuum. The crude solid was recrystallized (EtOAc/hexane) to give 5.2 g (95%) of **5** as white crystals: mp 79–80 °C, lit. mp 74–75 °C (MeOH);[25] IR (KBr): 3450 (OH), 1775, 1715 (C=O) cm^{-1}; MS (70 eV) *m/z* (%) 205 (M^+, 22), 160 (100). Anal. Calcd for $C_{11}H_{11}NO_3$ (205.21): C, 64.38; H, 5.40; N, 6.83. Found: C, 64.66; H, 5.44; N, 6.90. ^1H NMR and ^{13}C NMR are in agreement with those reported in the literature.[25]

5.2.1. 2-(5-Hydroxypentyl)-1*H*-isoindole-1,3(2*H*)-dione (6)

Prepared as reported above for **5** starting from **2**. Yield: 48%; slightly yellowish oil. Spectroscopic data were in agreement with those reported in the literature.[26]

5.2.2. 2-(6-Hydroxyhexyl)-1*H*-isoindole-1,3(2*H*)-dione (7)

Prepared as reported above for **5** starting from **3**. Yield: 65%; white solid: mp 55–57 °C ($CHCl_3$/hexane), lit. mp 49–50 °C;[27] IR (KBr): 3461 (OH), 1771, 1708 (C=O) cm^{-1}. Anal. Calcd for $C_{14}H_{17}NO_3$ (247.29): C, 68.00; H, 6.93; N, 5.66. Found: C, 67.99; H, 6.96; N, 5.69. Other spectroscopic data were in agreement with those reported in the literature.[27]

5.3. General procedure for the preparation of phthalimidoalkyl aryl ethers (8a,b,e,f)

The method adopted for the synthesis of 2-[2-(4-chloro-2,6-dimethylphenoxy)ethyl]-1*H*-isoindole-1,3(2*H*)-dione (**8f**) is described. A solution of diethyl azodicarboxylate (DEAD, 0.96 g, 5.50 mmol) in dry THF (30 mL) was added dropwise to a solution of commercial 2-(2-hydroxyethyl)-1*H*-isoindole-1,3(2*H*)-dione (**4**) (0.70 g, 3.66 mmol), 4-chloro-2,6-dimethylphenol (0.86 g, 5.50 mmol), and triphenylphosphine (1.44 g, 5.50 mmol) in dry THF (60 mL) under N_2 atmosphere at room temperature. The reaction mixture was stirred overnight and then concentrated in vacuo. Et_2O was added to the residue and the solid filtered off. The filtrate was evaporated and the residue was purified by flash chromatography (EtOAc/petroleum ether 0.5:9.5) to give 0.39 g of a white solid (32%): IR (KBr): 1773, 1713 (C=O) cm^{-1}; ^1H NMR δ 2.14 (s, 6H, $2CH_3$), 3.95–4.02 (m, 2H, CH_2), 4.07–4.15 (m, 2H, CH_2), 6.92 (s, 2H, ArO), 7.70–7.78 (m, 2H, Ar), 7.84–7.92 ppm (m, 2H, Ar); ^{13}C NMR δ 16.3 (2C), 38.2 (1C), 68.6 (1C), 123.6 (2C), 128.7 (2C), 128.9 (1C), 132.2 (2C), 132.7 (2C), 134.4 (2C), 154.1 (1C), 168.5 ppm (2C); MS (70 eV) *m/z* (%) 329 (M^+, 6), 174 (100). A small amount of **8f** was recrystallized from *i*-Pr_2O/petroleum ether to give white crystals: mp 94–95 °C. Anal. Calcd for $C_{18}H_{16}ClNO_3$ (329.78): C, 65.56; H, 4.89; N, 4.25. Found: C, 65.29; H, 4.88; N, 4.27.

5.3.1. 2-(2-Phenoxyethyl)-1*H*-isoindole-1,3(2*H*)-dione (8a)

Prepared as reported above for **8f** starting from **4** and phenol. Yield: 59%; white solid: mp 130–132 °C; IR (KBr): 1771, 1716 (C=O) cm^{-1}; ^1H NMR δ 4.11 (t, *J* = 5.8 Hz, 2H, CH_2N), 4.22 (t, *J* = 5.6 Hz, 2H, CH_2O), 6.85–6.97 (m, 3H, ArO), 7.18–7.30 (m, 2H, ArO), 7.67–7.78 (m, 2H, Ar), 7.82–7.90 (m, 2H, Ar); ^{13}C NMR δ 37.6 (1C), 64.8 (1C), 114.8 (2C), 121.3 (1C), 123.6 (2C), 129.7 (2C), 132.3

(2C), 134.3 (2C), 158.5 (1C), 168.4 (2C); MS (70 eV) *m/z* (%) 267 (M^+, 17), 174 (100). Anal. Calcd for $C_{16}H_{13}NO_3 \cdot 0.33H_2O$ (273.28): C, 70.32, H, 5.04, N, 5.13. Found: C, 70.18, H, 4.85, N, 5.22.

5.3.2. 2-[2-(4-Chlorophenoxy)ethyl]-1*H*-isoindole-1,3(2*H*)-dione (8b)

Prepared as reported above for **8f** starting from **4** and 4-chlorophenol. Yield: 88%; white solid: mp 146–147 °C; IR (KBr): 1770, 1714 (C=O) cm^{-1}; ^1H NMR δ 4.04–4.14 (m, 2H, CH_2), 4.16–4.24 (m, 2H, CH_2), 6.75–6.84 (m, 2H, ArO), 7.14–7.24 (m, 2H, ArO), 7.68–7.78 (m, 2H, Ar), 7.82–7.90 ppm (m, 2H, Ar); ^{13}C NMR δ 34.4 (1C), 65.3 (1C), 116.2 (2C), 123.6 (2C), 126.3 (1C), 129.5 (2C), 132.2 (2C), 134.3 (2C), 157.1 (1C), 168.3 ppm (2C); MS (70 eV) *m/z* (%) 301 (M^+, 10), 174 (100). Anal. Calcd for $C_{16}H_{12}ClNO_3$ (301.72): C, 63.69; H, 4.01; N, 4.64. Found: C, 63.70; H, 4.02; N, 4.68.

5.3.3. 2-[2-(4-Chloro-2-methylphenoxy)ethyl]-1*H*-isoindole-1,3(2*H*)-dione (8e)

Prepared as reported above for **8f** starting from **4** and 4-chloro-2-methylphenol. Yield: 54% (after recrystallization); white solid: mp 127–128 °C (THF/petroleum ether); IR (KBr): 1779, 1721 (C=O) cm^{-1}; ^1H NMR δ 2.08 (s, 3H, CH_3), 4.08–4.22 (m, 4H, 2CH_2), 6.64–6.72 (m, 1H, ArO), 7.00–7.08 (m, 2H, ArO), 7.68–7.76 (m, 2H, Ar), 7.82–7.90 ppm (m, 2H, Ar); ^{13}C NMR δ 16.2 (1C), 37.5 (1C), 65.2 (1C), 111.9 (1C), 123.6 (2C), 125.6 (1C), 126.5 (1C), 129.0 (1C), 130.7 (1C), 132.2 (2C), 134.3 (2C), 155.3 (1C), 168.4 ppm (2C); MS (70 eV) *m/z* (%) 315 (M^+, 7), 174 (100). Anal. Calcd for $C_{17}H_{14}ClNO_3$ (315.75): C, 64.67; H, 4.47; N, 4.44. Found: C, 64.68; H, 4.75; N, 4.54.

5.3.4. 2-(3-Phenoxypropyl)-1*H*-isoindole-1,3(2*H*)-dione (9a)

Prepared as reported above for **8f** starting from **5** and phenol. Yield: 61% (after recrystallization); white solid: mp 94–95 °C (EtOAc/petroleum ether); IR (KBr): 1770, 1718 (C=O) cm^{-1}; ^1H NMR δ 2.10–2.30 (m, 2H, CH_2), 3.91 (t, *J* = 6.9 Hz, 2H, CH_2), 4.03 (t, *J* = 6.1 Hz, 2H, CH_2), 6.76–6.96 (m, 3H, ArO), 7.12–7.35 (m, 2H, ArO), 7.68–7.94 ppm (m, 4H, Ar); ^{13}C NMR δ 28.6 (1C), 35.7 (1C), 65.8 (1C), 114.7 (2C), 121.0 (1C), 123.4 (1C), 123.6 (1C), 129.5 (1C), 129.7 (1C), 132.4 (2C), 134.0 (1C), 134.3 (1C), 158.9 (1C), 168.6 (2C); MS (70 eV) *m/z* (%) 281 (M^+, 6), 188 (100). Anal. Calcd for $C_{17}H_{15}NO_3$ (281.31): C, 72.58; H, 5.37; N, 4.98. Found: C, 72.36; H, 5.39; N, 5.04.

5.3.5. 2-[3-(4-Chlorophenoxy)propyl]-1*H*-isoindole-1,3(2*H*)-dione (9b)

Prepared as reported above for **8f** starting from **5** and 4-chlorophenol. Yield: 64% (after recrystallization); white solid: mp 114–115 °C (EtOAc/petroleum ether); IR (KBr): 1772, 1705 (C=O) cm^{-1}; ^1H NMR δ 2.17 (apparent quintet, 2H, CH_2), 3.90 (t, *J* = 6.9 Hz, 2H, CH_2), 3.99 (t, *J* = 6.1 Hz, 2H, CH_2), 6.68–6.76 (m, 2H, ArO), 7.14–7.22 (m, 2H, ArO), 7.68–7.76 (m, 2H, Ar), 7.80–7.88 ppm (m, 2H, Ar); ^{13}C NMR δ 28.5 (1C), 35.6 (1C), 66.2 (1C), 115.9 (2C), 123.5 (2C), 125.9 (1C), 129.5 (2C), 132.4 (2C), 134.2 (2C), 157.5 (1C), 168.6 ppm (2C); MS (70 eV) *m/z* (%) 315 (M^+, 7), 188 (100). Anal. Calcd for $C_{17}H_{14}ClNO_3$ (315.75): C, 64.67; H, 4.47; N, 4.44. Found: C, 64.33; H, 4.44; N, 4.45.

5.3.6. 2-[3-(2,3-Dichlorophenoxy)propyl]-1*H*-isoindole-1,3(2*H*)-dione (9c)

Prepared as reported above for **8f** starting from **5** and 2,3-dichlorophenol. Yield: 72% (after recrystallization); white solid: mp 169–170 °C (EtOAc/hexane); IR (KBr): 1770, 1715 (C=O) cm^{-1}; ^1H NMR δ 2.25 (apparent quintet, 2H, CH_2), 3.94 (t, *J* = 6.6 Hz, 2H, CH_2), 4.09 (t, *J* = 6.1 Hz, 2H, CH_2), 6.79 (dd, *J* = 8.0, 1.7 Hz, 1H, ArO), 7.03 (dd, *J* = 8.1, 1.5 Hz, 1H, ArO), 7.10 (apparent t, 1H, ArO), 7.66–7.74 (m, 2H, Ar), 7.78–7.86 ppm (m, 2H, Ar); ^{13}C NMR δ 28.6 (1C), 35.7 (1C), 67.6 (1C), 111.4 (1C), 122.2 (1C), 122.6 (1C), 123.4 (2C), 127.4 (1C), 132.4 (2C), 134.0 (1C), 134.2 (2C), 155.9 (1C), 168.6 ppm (2C); MS (70 eV) *m/z* (%) 349 (M^+, 3), 188 (100). Anal. Calcd for $C_{17}H_{13}Cl_2NO_3$ (350.20): C, 58.31; H, 3.74; N, 4.00. Found: C, 58.16; H, 3.74; N, 4.05.

5.3.7. 2-[3-(3,4-Dichlorophenoxy)propyl]-1*H*-isoindole-1,3(2*H*)-dione (9d)

Prepared as reported above for **8f** starting from **5** and 3,4-dichlorophenol. Yield: 51% (after recrystallization); white solid: mp 143–144 °C (THF/petroleum ether); IR (KBr): 1771, 1706 (C=O) cm^{-1}; ^1H NMR δ 2.17 (quintet, *J* = 6.3 Hz, 2H, CH_2), 3.89 (t, *J* = 6.6 Hz, 2H, CH_2), 3.98 (t, *J* = 5.8 Hz, 2H, CH_2), 6.63 (dd, *J* = 8.8, 2.8 Hz, 1H, ArO), 6.85 (d, *J* = 3.0 Hz, 1H, ArO), 7.26 (d, *J* = 9.1 Hz, 1H, ArO), 7.68–7.76 (m, 2H Ar), 7.80–7.88 ppm (m, 2H, Ar); ^{13}C NMR δ 28.3 (1C), 35.5 (1C), 66.5 (1C), 114.6 (1C), 116.5 (1C), 123.5 (2C), 124.2 (1C), 130.8 (1C), 132.3 (1C), 133.0 (2C), 134.3 (2C), 157.9 (1C), 168.6 ppm (2C); MS (70 eV) *m/z* (%) 349 (M^+, 4), 188 (100). Anal. Calcd for $C_{17}H_{13}Cl_2NO_3$ (350.20): C, 58.31; H, 3.74; N, 4.00. Found: C, 58.35; H, 3.77; N, 3.99.

5.3.8. 2-[3-(4-Chloro-2-methylphenoxy)propyl]-1*H*-isoindole-1,3(2*H*)-dione (9e)

Prepared as reported above for **8f** starting from **5** and 4-chloro-2-methylphenol, using diisopropyl azodicarboxylate (DIAD) instead of DEAD. Yield: 30% (after recrystallization); white solid: mp 122–123 °C (THF/petroleum ether); IR (KBr): 1766, 1716 (C=O) cm^{-1}; ^1H NMR δ 2.12 (s, 3H, CH_3), 2.20 (quintet, *J* = 6.5 Hz, 2H, CH_2), 3.92 (t, *J* = 6.9 Hz, 2H, CH_2), 3.99 (t, *J* = 6.1 Hz, 2H, CH_2), 6.65–6.72 (m, 1H, ArO), 7.02–7.10 (m, 2H, ArO), 7.68–7.76 (m, 2H Ar), 7.78–7.88 ppm (m, 2H, Ar); ^{13}C NMR δ 16.2 (1C), 28.7 (1C), 35.6 (1C), 66.0 (1C), 112.1 (1C), 123.5 (2C), 125.3 (1C), 126.5 (1C), 129.0 (1C), 130.6 (1C), 132.3 (2C), 134.2 (2C), 155.7 (1C), 168.6 ppm (2C); MS (70 eV) *m/z* (%) 329 (M^+, 7), 188 (100). Anal. Calcd for $C_{18}H_{16}ClNO_3 \cdot 0.33H_2O$ (335.78): C, 64.38; H, 5.00; N, 4.17. Found: C, 64.21; H, 4.83; N, 4.20.

5.3.9. 2-[3-(4-Chloro-2,6-dimethylphenoxy)propyl]-1*H*-isoindole-1,3(2*H*)-dione (9f)

Prepared as reported above for **8f** starting from **5** and 4-chloro-2,6-dimethylphenol, using DIAD instead of DEAD. Yield: 56% (after recrystallization); white solid: mp 136–137 °C (THF/petroleum ether); IR (KBr): 1773, 1716 (C=O) cm^{-1}; ^1H NMR δ 2.12–2.27 (m overlapping s at 2.22, 2H, CH_2), 2.22 (s overlapping m at 2.12–2.27, 6H, 2CH_3), 3.81 (t, *J* = 6.2 Hz, 2H, CH_2), 3.94 (t, *J* = 7.3 Hz, 2H, CH_2), 6.95 (s, 2H, ArO), 7.66–7.76 (m, 2H, Ar), 7.80–7.90 ppm (m, 2H, Ar); ^{13}C NMR δ 16.5 (2C), 29.7 (1C), 35.7 (1C), 70.1 (1C), 123.5 (2C), 128.6 (3C), 132.3 (2C), 132.8 (2C), 134.2 (2C), 154.7 (1C), 168.6 ppm (2C); MS (70 eV) *m/z* (%) 343 (M^+, 1), 188 (100). Anal. Calcd for $C_{19}H_{18}ClNO_3$ (343.80): C, 66.38; H, 5.28; N, 4.07. Found: C, 66.75; H, 5.30; N, 4.11.

5.3.10. 2-(5-Phenoxypentyl)-1*H*-isoindole-1,3(2*H*)-dione (10a)

Prepared as reported above for **8f** starting from **6** and phenol. Yield: 61% (after recrystallization); white solid: mp 76–77 °C (EtOAc/hexane); IR (KBr): 1771, 1704 (C=O) cm^{-1}; ^1H NMR δ 1.45–1.60 (m, 2H, CH_2), 1.68–1.90 (m, 4H, 2CH_2), 3.72 (t, *J* = 7.1 Hz, 2H, CH_2), 3.95 (t, *J* = 6.5 Hz, 2H, CH_2), 6.80–6.96 (m, 3H, ArO), 7.18–7.32 (m, 2H, ArO), 7.65–7.75 (m, 2H, Ar), 7.76–7.88 ppm (m, 2H, Ar); ^{13}C NMR δ 23.7 (1C), 28.6 (1C), 29.1 (1C), 38.1 (1C), 67.7 (1C), 114.7 (2C), 120.7 (1C), 123.4 (2C), 129.6 (2C), 132.4 (2C), 134.1 (2C), 159.2 (1C), 168.7 ppm (2C); MS (70 eV) *m/z* (%) 309 (M^+, 13), 160 (100). Anal. Calcd for $C_{19}H_{19}NO_3 \cdot 0.25H_2O$ (313.86): C, 72.71; H, 6.26; N, 4.46. Found: C, 72.85; H, 6.10; N, 4.51.

5.3.11. 2-(6-Phenoxyhexyl)-1*H*-isoindole-1,3(2*H*)-dione (11a)

Prepared as reported above for **8f** starting from **7** and phenol. Yield: 53% (after recrystallization); white solid: mp 66–68 °C (EtOAc/petroleum ether); IR (KBr): 1773, 1704 (C=O) cm^{-1}; ^1H NMR δ 1.35–1.60 (m, 4H, 2CH_2), 1.60–1.85 (m, 4H, 2CH_2), 3.69 (t, J = 7.1 Hz, 2H, CH_2), 3.94 (t, J = 6.5 Hz, 2H, CH_2), 6.82–6.97 (m, 3H, ArO), 7.20–7.32 (m, 2H, ArO), 7.65–7.75 (m, 2H, Ar), 7.78–7.88 ppm (m, 2H, Ar); ^{13}C NMR δ 25.9 (1C), 26.8 (1C), 28.7 (1C), 29.4 (1C), 38.1 (1C), 67.9 (1C), 114.8 (2C), 120.7 (1C), 123.3 (2C), 129.6 (2C), 132.5 (2C), 134.0 (2C), 159.3 (1C), 168.6 ppm (2C); MS (70 eV) *m/z* (%) 323 (M^+, 17), 160 (100). Anal. Calcd for $C_{20}H_{21}NO_3$ (323.39): C, 74.28; H, 6.55; N, 4.33. Found: C, 74.61; H, 6.59; N, 4.43.

5.4. General procedure for the preparation of phenoxy alcohols (15a, 16a, 17a,b,d,f,g)

The method adopted for the synthesis of 10-phenoxydecan-1-ol (**17a**) is described. K_2CO_3 (0.32 g, 2.32 mmol) was added to a solution of 10-bromodecan-1-ol (**14**) (0.50 g, 2.11 mmol) in dry DMF (30 mL) under N_2 atmosphere. The reaction mixture was heated at 130 °C and then a solution of phenol (0.22 g, 2.32 mmol) in 20 mL of dry DMF was added dropwise during a period of 3 h. The mixture was stirred at this temperature for 24 h. After evaporation of the solvent, the residue was taken up with EtOAc, washed with 2 N NaOH, and then with brine. The organic phase was dried (Na_2SO_4) and concentrated under vacuum. The residue was purified by column chromatography on silica gel (EtOAc/petroleum ether 1.5:8.5) to give 0.12 g (23%) of **17a** as a white solid: mp 52–54 °C; IR (KBr): 3304 (OH) cm^{-1}; ^1H NMR δ 1.20–1.50 (m, 12H, 6CH_2), 1.50–1.62 (m, 2H, CH_2), 1.67 (br s, 1H, OH), 1.78 (apparent quintet, 2H, CH_2), 3.63 (t, J = 6.6 Hz, 2H, CH_2), 3.95 (t, J = 6.6 Hz, 2H, CH_2), 6.85–6.98 (m, 3H, Ar), 7.22–7.32 ppm (m, 2H, Ar); ^{13}C NMR δ 25.9 (1C), 26.3 (1C), 29.5 (1C), 29.6 (2C), 29.7 (2C), 33.0 (1C), 63.3 (1C), 68.1 (1C), 114.8 (2C), 120.7 (1C), 129.6 (2C), 159.4 ppm (1C); MS (70 eV) *m/z* (%) 250 (M^+, 15), 94 (100).

5.4.1. 8-Phenoxyoctan-1-ol (15a)

Prepared as reported above for **17a** starting from **12** and phenol. Yield: 20%; white solid: mp 37–39 °C; IR (KBr): 3305 (OH) cm^{-1}; ^1H NMR δ 1.25–1.63 (m, 11H, 5CH_2 + OH), 1.78 (apparent quintet, 2H, CH_2), 3.63 (t, J = 6.6 Hz, 2H, CH_2), 3.95 (t, J = 6.6 Hz, 2H, CH_2), 6.86–6.97 (m, 3H, Ar), 7.23–7.32 ppm (m, 2H, Ar); ^{13}C NMR δ 25.9 (1C), 26.3 (1C), 29.5 (2C), 29.7 (1C), 33.0 (1C), 63.3 (1C), 68.1 (1C), 114.7 (2C), 120.7 (1C), 129.6 (2C), 159.3 ppm (1C); MS (70 eV) *m/z* (%) 222 (M^+, 15), 94 (100).

5.4.2. 9-Phenoxynonan-1-ol (16a)

Prepared as reported above for **17a** starting from **13** and phenol. Yield: 28% (after recrystallization); white crystals: mp 49–51 °C (EtOAc/petroleum ether); IR (KBr): 3307 (OH) cm^{-1}; ^1H NMR δ 1.18–1.50 (m, 10H, 5CH_2), 1.50–1.64 (m, 3H, CH_2 + OH), 1.78 (apparent quintet, 2H, CH_2), 3.64 (t, J = 6.5 Hz, 2H, CH_2), 3.95 (t, J = 6.6 Hz, 2H, CH_2), 6.86–6.97 (m, 3H, Ar), 7.23–7.32 ppm (m, 2H, Ar); ^{13}C NMR δ 25.9 (1C), 26.2 (1C), 29.5 (2C), 29.6 (1C), 29.7 (1C), 33.0 (1C), 63.3 (1C), 68.1 (1C), 114.8 (2C), 120.7 (1C), 129.6 (2C), 159.3 ppm (1C); MS (70 eV) *m/z* (%) 236 (M^+, 25), 94 (100).

5.4.3. 10-(4-Chlorophenoxy)decan-1-ol (17b)

Prepared as reported above for **17a** starting from **14** and 4-chlorophenol. Yield: 36%; slightly yellow solid: mp 44–45 °C; IR (KBr): 3370 (OH) cm^{-1}; ^1H NMR δ 1.20–1.50 (m, 12H, 6CH_2), 1.50–1.64 (m, 3H, CH_2 + OH), 1.76 (apparent quintet, 2H, CH_2), 3.64 (t, J = 6.6 Hz, 2H, CH_2), 3.91 (t, J = 6.6 Hz, 2H, CH_2), 6.75–6.86 (m, 2H, Ar), 7.14–7.26 ppm (m, 2H, Ar); ^{13}C NMR δ 25.9 (1C), 26.2 (1C), 29.4 (1C), 29.6 (2C), 29.7 (2C), 33.0 (1C), 63.3 (1C), 68.5 (1C), 116.0 (2C), 125.5 (1C), 129.5 (2C), 158.0 ppm (1C); MS (70 eV) *m/z* (%) 284 (M^+, 19), 128 (100).

5.4.4. 10-(3,4-Dichlorophenoxy)decan-1-ol (17d)

Prepared as reported above for **17a** starting from **14** and 3,4-dichlorophenol. Yield: 47%; slightly yellowish oil: IR (neat): 3340 (OH) cm^{-1}; ^1H NMR δ 1.20–1.62 (m, 15H, 7CH_2 + OH), 1.76 (apparent quintet, 2H, CH_2), 3.64 (t, J = 6.6 Hz, 2H, CH_2), 3.90 (t, J = 6.5 Hz, 2H, CH_2), 6.74 (dd, J = 8.9, 2.9 Hz, 1H, Ar), 6.97 (d, J = 2.8 Hz, 1H, Ar), 7.30 ppm (d, J = 8.8 Hz, 1H, Ar); ^{13}C NMR δ 25.9 (1C), 26.1 (1C), 29.3 (1C), 29.5 (1C), 29.6 (2C), 29.7 (1C), 33.0 (1C), 63.3 (1C), 68.9 (1C), 114.8 (1C), 116.6 (1C), 123.9 (1C), 130.8 (1C), 133.0 (1C), 158.5 ppm (1C); MS (70 eV) *m/z* (%) 318 (M^+, 20), 162 (100).

5.4.5. 10-(4-Chloro-2,6-dimethylphenoxy)decan-1-ol (17f)

Prepared as reported above for **17a** starting from **14** and 4-chloro-2,6-dimethylphenol. Yield: 29%; slightly yellowish oil: IR (neat): 3343 (OH) cm^{-1}; ^1H NMR δ 1.26–1.42 (m, 10H, 5CH_2), 1.42–1.62 (m overlapping br s at 1.50, 4H, 2CH_2), 1.50 (br s overlapping m at 1.42–1.62, 1H, OH), 1.78 (apparent quintet, 2H, CH_2), 2.23 (s, 6H, 2CH_3), 3.64 (t, J = 6.6 Hz, 2H, CH_2), 3.71 (t, J = 6.6 Hz, 2H, CH_2), 6.97 ppm (s, 2H, Ar); ^{13}C NMR δ 16.4 (2C), 25.9 (1C), 26.3 (1C), 29.6 (1C), 29.7 (2C), 29.8 (1C), 30.6 (1C), 33.0 (1C), 63.3 (1C), 72.7 (1C), 128.4 (1C), 128.6 (2C), 132.9 (2C), 154.9 ppm (1C); MS (70 eV) *m/z* (%) 312 (M^+, 9), 156 (100).

5.4.6. 10-(2,4-Dichlorophenoxy)decan-1-ol (17g)

Prepared as reported above for **17a** starting from **14** and 2,4-dichlorophenol. Yield: 65%; slightly yellowish oil: IR (neat): 3369 (OH) cm^{-1}; ^1H NMR δ 1.20–1.40 (m, 11H, 5CH_2 + OH), 1.40–1.70 (m, 4H, 2CH_2), 1.82 (apparent quintet, 2H, CH_2), 3.64 (t, J = 6.6 Hz, 2H, CH_2), 3.98 (t, J = 6.5 Hz, 2H, CH_2), 6.82 (d, J = 8.8 Hz, 1H, Ar), 7.15 (dd, J = 8.8, 2.5 Hz, 1H, Ar), 7.35 ppm (d, J = 2.8 Hz, 1H, Ar); ^{13}C NMR δ 25.9 (1C), 26.1 (1C), 29.2 (1C), 29.5 (1C), 29.6 (2C), 29.7 (1C), 33.0 (1C), 63.3 (1C), 69.8 (1C), 114.3 (1C), 124.0 (1C), 125.7 (1C), 127.7 (1C), 130.1 (1C), 153.8 ppm (1C); MS (70 eV) *m/z* (%) 318 (M^+, 15), 162 (100).

5.4.7. 2-(8-Phenoxyoctyl)-1*H*-isoindole-1,3(2*H*)-dione (18a)

Prepared as reported above for **8f** starting from **15a** and phthalimide. Yield: 20% (after recrystallization); white crystals: mp 76–77 °C (THF/petroleum ether + hexane); IR (KBr): 1765, 1714 (C=O) cm^{-1}; ^1H NMR δ 1.28–1.51 (m, 8H, 4CH_2), 1.67 (apparent br t overlapping apparent quintet at 1.76, 2H, CH_2), 1.76 (apparent quintet overlapping apparent br t at 1.67, 2H, CH_2), 3.68 (t, J = 7.3 Hz, 2H, CH_2), 3.93 (t, J = 6.6 Hz, 2H, CH_2), 6.82–6.96 (m, 3H, ArO), 7.22–7.32 (m, 2H, ArO), 7.66–7.74 (m, 2H, Ar), 7.80–7.88 ppm (m, 2H, Ar); ^{13}C NMR δ 26.2 (1C), 27.0 (1C), 28.8 (1C), 29.3 (1C), 29.5 (2C), 38.3 (1C), 68.0 (1C), 114.7 (2C), 120.7 (1C), 123.4 (2C), 129.6 (2C), 132.4 (2C), 134.1 (2C), 159.3 (1C), 168.7 ppm (2C); MS (70 eV) *m/z* (%) 351 (M^+, 24), 160 (100). Anal. Calcd for $C_{22}H_{25}NO_3$ (351.44): C, 75.19; H, 7.17; N, 3.99. Found: C, 75.19; H, 7.18; N, 4.13.

5.4.8. 2-(9-Phenoxynonyl)-1*H*-isoindole-1,3(2*H*)-dione (19a)

Prepared as reported above for **8f** starting from **16a** and phthalimide, using DIAD instead of DEAD. Yield: 60% (after recrystallization); white crystals: mp 69–71 °C (EtOAc/hexane); IR (KBr): 1773, 1705 (C=O) cm^{-1}; ^1H NMR δ 1.25–1.52 (m, 10H, 5CH_2), 1.67 (apparent br t overlapping apparent quintet at 1.76, 2H, CH_2), 1.76 (apparent quintet overlapping apparent br t at 1.67, 2H, CH_2), 3.67 (t, J = 7.3 Hz, 2H, CH_2), 3.93 (t, J = 6.5 Hz, 2H, CH_2), 6.84–6.96 (m, 3H, ArO), 7.22–7.32 (m, 2H, ArO), 7.66–7.74 (m, 2H, Ar), 7.80–7.88 ppm (m, 2H, Ar); ^{13}C NMR δ 26.2 (1C), 27.0 (1C), 28.8 (1C), 29.3 (1C), 29.5 (2C), 29.6 (1C), 38.3 (1C), 68.1

(1C), 114.7 (2C), 120.6 (1C), 123.4 (2C), 129.6 (2C), 132.4 (2C), 134.1 (2C), 159.3 (1C), 168.7 ppm (2C); MS (70 eV) *m/z* (%) 365 (M^+, 25), 160 (100). Anal. Calcd for $C_{23}H_{27}NO_3 \cdot 0.20H_2O$ (369.06): C, 74.85; H, 7.48; N, 3.80. Found: C, 75.13; H, 7.39; N, 3.86.

5.4.9. 2-(10-Phenoxydecyl)-1*H*-isoindole-1,3(2*H*)-dione (20a)

Prepared as reported above for **8f** starting from **17a** and phthalimide. Yield: 50% (after recrystallization); white crystals: mp 73–74 °C (EtOAc); IR (KBr): 1771, 1715 (C=O) cm^{-1}; ^1H NMR δ 1.22–1.50 (m, 12H, 6CH_2), 1.66 (apparent br t overlapping apparent quintet at 1.76, 2H, CH_2), 1.76 (apparent quintet overlapping apparent br t at 1.66, 2H, CH_2), 3.67 (t, J = 7.4 Hz, 2H, CH_2), 3.94 (t, J = 6.6 Hz, 2H, CH_2), 6.84–6.96 (m, 3H, ArO), 7.22–7.32 (m, 2H, ArO), 7.66–7.74 (m, 2H, Ar), 7.78–7.88 ppm (m, 2H, Ar); ^{13}C NMR δ 26.3 (1C), 27.1 (1C), 28.8 (1C), 29.4 (1C), 29.5 (1C), 29.6 (2C), 29.7 (1C), 38.3 (1C), 68.1 (1C), 114.7 (2C), 120.6 (1C), 123.4 (2C), 129.6 (2C), 132.4 (2C), 134.1 (2C), 159.3 (1C), 168.7 ppm (2C); MS (70 eV) *m/z* (%) 379 (M^+, 18), 160 (100). Anal. Calcd for $C_{24}H_{29}NO_3$ (379.49): C, 75.96; H, 7.70; N, 3.69. Found: C, 76.30; H, 7.75; N, 3.71.

5.4.10. 2-[10-(4-Chlorophenoxy)decyl]-1*H*-isoindole-1,3(2*H*)-dione (20b)

Prepared as reported above for **8f** starting from **17b** and phthalimide, using DIAD instead of DEAD. Yield: 75% (after recrystallization); white crystals: mp 72–73 °C (THF/petroleum ether); IR (KBr): 1768, 1695 (C=O) cm^{-1}; ^1H NMR δ 1.20–1.48 (m, 12H, 6CH_2), 1.66 (apparent br t overlapping apparent quintet at 1.75, 2H, CH_2), 1.75 (apparent quintet overlapping apparent br t at 1.66, 2H, CH_2), 3.67 (t, J = 7.3 Hz, 2H, CH_2), 3.90 (t, J = 6.6 Hz, 2H, CH_2), 6.76–6.84 (m, 2H, ArO), 7.16–7.24 (m, 2H, ArO), 7.66–7.74 (m, 2H, Ar), 7.80–7.88 ppm (m, 2H, Ar); ^{13}C NMR δ 26.2 (1C), 27.1 (1C), 28.8 (1C), 29.4 (2C), 29.5 (1C), 29.6 (2C), 38.3 (1C), 68.5 (1C), 116.0 (2C), 123.4 (2C), 125.5 (1C), 129.4 (2C), 132.4 (2C), 134.1 (2C), 158.0 (1C), 168.7 ppm (2C); MS (70 eV) *m/z* (%) 413 (M^+, 13), 160 (100). Anal. Calcd for $C_{24}H_{28}ClNO_3 \cdot 033H_2O$ (419.94): C, 68.64; H, 6.88; N, 3.34. Found: C, 68.68; H, 6.73; N, 3.44.

5.4.11. 2-[10-(3,4-Dichlorophenoxy)decyl]-1*H*-isoindole-1,3(2*H*)-dione (20d)

Prepared as reported above for **8f** starting from **17d** and phthalimide, using DIAD instead of DEAD. Yield: 57% (after recrystallization); white crystals: mp 82–83 °C (THF/petroleum ether); IR (KBr): 1771, 1720 (C=O) cm^{-1}; ^1H NMR δ 1.20–1.48 (m, 12H, 6CH_2), 1.66 (apparent br t overlapping apparent quintet at 1.74, 2H, CH_2), 1.74 (apparent quintet overlapping apparent br t at 1.66, 2H, CH_2), 3.67 (t, J = 7.3 Hz, 2H, CH_2), 3.89 (t, J = 6.5 Hz, 2H, CH_2), 6.73 (dd, J = 8.8, 3.0 Hz, 1H, ArO), 6.97 (d, J = 2.8 Hz, 1H, ArO), 7.29 (d, J = 9.1 Hz, 1H, ArO), 7.66–7.76 (m, 2H, Ar), 7.78–7.88 ppm (m, 2H, Ar); ^{13}C NMR δ 26.1 (1C), 27.0 (1C), 28.8 (1C), 29.3 (2C), 29.5 (1C), 29.6 (2C), 38.3 (1C), 68.8 (1C), 114.8 (1C), 116.5 (1C), 123.4 (2C), 123.8 (1C), 130.8 (1C), 132.4 (1C), 133.0 (2C), 134.1 (2C), 158.4 (1C), 168.7 ppm (2C); MS (70 eV) *m/z* (%) 447 (M^+, 8), 160 (100). Anal. Calcd for $C_{24}H_{27}Cl_2NO_3 \cdot 0.25H_2O$ (452.88): C, 63.65; H, 6.12; N, 3.09. Found: C, 63.74; H, 6.06; N, 3.20.

5.4.12. 2-[10-(4-Chloro-2,6-dimethylphenoxy)decyl]-1*H*-isoindole-1,3(2*H*)-dione (20f)

Prepared as reported above for **8f** starting from **17f** and phthalimide, using DIAD instead of DEAD. Yield: 87% (after recrystallization); white crystals: mp 56–58 °C (EtOAc/petroleum ether); IR (KBr): 1770, 1706 (C=O) cm^{-1}; ^1H NMR δ 1.22–1.40 (m, 10H, 5CH_2), 1.40–1.54 (m, 2H, CH_2), 1.62–1.70 (m, 2H, CH_2), 1.77 (apparent quintet, 2H, CH_2), 2.22 (s, 6H, 2CH_3), 3.67 (t overlapping t at 3.70, J = 7.4 Hz, 2H, CH_2), 3.70 (t overlapping t at 3.67, J = 6.6 Hz, 2H, CH_2), 6.97 (d, J = 0.6 Hz, 2H, ArO), 7.66–7.74 (m, 2H, Ar), 7.78–7.88 ppm (m, 2H, Ar); ^{13}C NMR δ 16.4 (2C), 26.3 (1C), 27.1 (1C), 28.8 (1C), 29.4 (1C), 29.6 (1C), 29.7 (2C), 30.6 (1C), 38.3 (1C), 72.7 (1C), 123.4 (2C), 128.4 (1C), 128.6 (2C), 132.4 (2C), 132.9 (2C), 134.1 (2C), 154.9 (1C), 168.7 ppm (2C); MS (70 eV) *m/z* (%) 441 (M^+, 5), 156 (100). Anal. Calcd for $C_{26}H_{32}ClNO_3 \cdot 0.25H_2O$ (441.99): C, 69.94; H, 7.34; N, 3.14. Found: C, 70.24; H, 7.75; N, 3.17.

5.4.13. 2-[10-(2,4-Dichlorophenoxy)decyl]-1*H*-isoindole-1,3(2*H*)-dione (20g)

Prepared as reported above for **8f** starting from **17g** and phthalimide, using DIAD instead of DEAD. Yield: 40% (after recrystallization); white crystals: mp 82–83 °C (EtOAc/petroleum ether); IR (KBr): 1766, 1711 (C=O) cm^{-1}; ^1H NMR δ 1.20–1.40 (m overlapping m at 1.38–1.52, 10H, 5CH_2), 1.38–1.52 (m overlapping m at 1.20–1.40, 2H, CH_2), 1.58–1.73 (m, 2H, CH_2), 1.81 (apparent quintet, 2H, CH_2), 3.67 (t, J = 7.4 Hz, 2H, CH_2), 3.98 (t, J = 6.5 Hz, 2H, CH_2), 6.81 (d, J = 8.8 Hz, 1H, ArO), 7.15 (dd, J = 8.8, 2.8 Hz, 1H, ArO), 7.34 (d, J = 2.5 Hz, 1H, ArO), 7.66–7.74 (m, 2H, Ar), 7.78–7.88 ppm (m, 2H, Ar); ^{13}C NMR δ 26.1 (1C), 27.1 (1C), 28.8 (1C), 29.2 (1C), 29.4 (2C), 29.6 (2C), 38.3 (1C), 69.7 (1C), 114.2 (1C), 123.4 (2C), 123.9 (1C), 125.6 (1C), 127.7 (1C), 130.1 (1C), 132.4 (2C), 134.1 (2C), 153.7 (1C), 168.7 ppm (2C); MS (70 eV) *m/z* (%) 447 (M^+, 2), 160 (100). Anal. Calcd for $C_{24}H_{27}Cl_2NO_3 \cdot 0.33H_2O$ (454.38): C, 63.44; H, 6.14; N, 3.08. Found: C, 63.63; H, 6.00; N, 3.27.

5.4.14. 2-{10-[4-Nitro-3-(trifluoromethyl)phenoxy]decyl}-1*H*-isoindole-1,3(2*H*)-dione (20h)

Prepared as reported above for **8f** starting from **22** and 4-nitro-3-(trifluoromethyl)phenol, using DIAD instead of DEAD. Yield: 61% (after recrystallization); white crystals: mp 89–91 °C (EtOAc/hexane); IR (KBr): 1774, 1712 (C=O), 1532, 1355 (NO_2) cm^{-1}; ^1H NMR δ 1.20–1.52 (m, 12H, 6CH_2), 1.54–1.74 (m, 2H, CH_2), 1.82 (apparent quintet, 2H, CH_2), 3.67 (t, J = 7.4 Hz, 2H, CH_2), 4.06 (t, J = 6.5 Hz, 2H, CH_2), 7.08 (dd, J = 8.9, 2.6 Hz, 1H, ArO), 7.28 (d, J = 2.5 Hz, 1H, ArO), 7.66–7.75 (m, 2H, Ar), 7.78–7.88 (m, 2H, Ar), 8.00 ppm (d, J = 9.1 Hz, 1H, ArO); ^{13}C NMR δ 26.0 (1C), 27.0 (1C), 28.8 (1C), 29.0 (1C), 29.3 (1C), 29.4 (1C), 29.5 (1C), 29.6 (1C), 38.2 (1C), 69.5 (1C), 115.0 (q, J_{CF} = 5.9 Hz, 1C), 116.7 (1C), 122.1 (br q, J_{CF} = 273.5 Hz, 1C), 123.4 (2C), 126.3 (q, J_{CF} = 34.0 Hz, 1C), 128.4 (1C), 132.4 (2C), 134.1 (2C), 140.8 (1C), 162.5 (1C), 168.7 ppm (2C). Anal. Calcd for $C_{25}H_{27}F_3N_2O_5$ (492.49): C, 60.97; H, 5.53; N, 5.69. Found: C, 61.21; H, 5.58; N, 5.79.

5.4.15. 2-[10-(4-Methylphenoxy)decyl]-1*H*-isoindole-1,3(2*H*)-dione (20i)

Prepared as reported above for **8f** starting from **22** and 4-methylphenol, using DIAD instead of DEAD. Yield: 90% (after recrystallization); white crystals: mp 77–79 °C (THF/petroleum ether); IR (KBr): 1770, 1703 (C=O), cm^{-1}; ^1H NMR δ 1.20–1.50 (m, 12H, 6CH_2), 1.55–1.82 (m, 4H, 2CH_2), 2.27 (s, 3H, CH_3), 3.67 (t, J = 7.3 Hz, 2H, CH_2), 3.91 (t, J = 6.6 Hz, 2H, CH_2), 6.72–6.82 (m, 2H, ArO), 7.02–7.10 (m, 2H, ArO), 7.65–7.74 (m, 2H, Ar), 7.78–7.88 ppm (m, 2H, Ar); ^{13}C NMR δ 20.7 (1C), 26.2 (1C), 27.1 (1C), 28.8 (1C), 29.4 (1C), 29.5 (2C), 29.6 (1C), 29.7 (1C), 38.3 (1C), 68.3 (1C), 114.6 (2C), 123.4 (2C), 129.8 (1C), 130.0 (2C), 132.4 (2C), 134.0 (2C), 157.2 (1C), 168.7 ppm (2C); MS (70 eV) *m/z* (%) 393 (M^+, 15), 108 (100). Anal. Calcd for $C_{25}H_{31}NO_3 \cdot 0.25H_2O$ (398.02): C, 75.44; H, 7.98; N, 3.52. Found: C, 75.70; H, 7.87; N, 3.61.

5.4.16. 2-[10-(4-Nitrophenoxy)decyl]-1*H*-isoindole-1,3(2*H*)-dione (20j)

Prepared as reported above for **8f** starting from **22** and 4-nitrophenol and DIAD. Yield: 52%; white solid: mp 100–102 °C; IR

(KBr): 1772, 1718 (C=O), 1501, 1345 (NO_2) cm^{-1}; ^1H NMR δ 1.22–1.50 (m, 12H, 6CH_2), 1.54–1.70 (m, 2H, CH_2), 1.80 (apparent quintet, 2H, CH_2), 3.67 (t, J = 7.3 Hz, 2H, CH_2), 4.03 (t, J = 6.5 Hz, 2H, CH_2), 6.86–6.96 (m, 2H, ArO), 7.66–7.74 (m, 2H, Ar), 7.78–7.88 (m, 2H, Ar), 8.14–8.22 ppm (m, 2H, ArO); ^{13}C NMR δ 26.1 (1C), 27.0 (1C), 28.8 (1C), 29.2 (1C), 29.3 (1C), 29.4 (1C), 29.5 (1C), 29.6 (1C), 38.3 (1C), 69.1 (1C), 114.6 (2C), 123.4 (2C), 126.1 (2C), 132.4 (2C), 134.1 (2C), 141.5 (1C), 164.5 (1C), 168.7 ppm (2C); MS (70 eV) m/z (%) 407 ($M^+ - 17$, <1), 160 (100). Anal. Calcd for $C_{24}H_{28}N_2O_5$ (424.49): C, 67.91; H, 6.65; N, 6.60. Found: C, 68.14; H, 6.83; N, 6.43.

5.4.17. 2-[10-(2-Nitrophenoxy)decyl]-1*H*-isoindole-1,3(2*H*)-dione (20k)

Prepared as reported above for **8f** starting from **22** and 2-nitrophenol, using DIAD instead of DEAD. Yield: 88% (after recrystallization); white crystals: mp 101–103 °C (EtOAc/hexane); IR (KBr): 1766, 1714 (C=O), 1518, 1337 (NO_2) cm^{-1}; ^1H NMR δ 1.21–1.40 (m overlapping m at 1.38–1.52, 10H, 5CH_2), 1.38–1.52 (m overlapping m at 1.21–1.40, 2H, CH_2), 1.58–1.72 (m, 2H, CH_2), 1.81 (apparent quintet, 2H, CH_2), 3.67 (t, J = 7.3 Hz, 2H, CH_2), 4.03 (t, J = 6.5 Hz, 2H, CH_2), 6.99 (t, J = 7.8 Hz, 1H, ArO), 7.05 (d, J = 8.5 Hz, 1H, ArO), 7.45–7.54 (m, 1H, ArO), 7.66–7.74 (m, 2H, Ar), 7.78–7.88 (m overlapping d at 7.79, 2H, Ar), 7.79 ppm (d overlapping m at 7.78–7.88, J = 1.6 Hz, 1H, ArO); ^{13}C NMR δ 26.0 (1C), 27.0 (1C), 28.8 (1C), 29.1 (1C), 29.3 (1C), 29.4 (1C), 29.6 (2C), 38.3 (1C), 69.8 (1C), 114.7 (1C), 120.2 (1C), 123.4 (2C), 125.7 (1C), 132.4 (2C), 134.0 (2C), 134.1 (1C), 140.3 (1C), 152.7 (1C), 168.7 ppm (2C). Anal. Calcd for $C_{24}H_{28}N_2O_5$ (424.49): C, 67.91; H, 6.65; N, 6.60. Found: C, 68.33; H, 6.65; N, 6.63.

5.4.18. 2-[10-(3-Nitrophenoxy)decyl]-1*H*-isoindole-1,3(2*H*)-dione (20l)

Prepared as reported above for **8f** starting from **22** and 3-nitrophenol, using DIAD instead of DEAD. Yield: 78% (after recrystallization); white crystals: mp 68–71 °C (EtOAc/hexane); IR (KBr): 1775, 1720 (C=O), 1517, 1353 (NO_2) cm^{-1}; ^1H NMR δ 1.22–1.52 (m, 12H, 6CH_2), 1.58–1.72 (m, 2H, CH_2), 1.80 (apparent quintet, 2H, CH_2), 3.67 (t, J = 7.4 Hz, 2H, CH_2), 4.01 (t, J = 6.5 Hz, 2H, CH_2), 7.20 (dd, J = 8.5, 2.5 Hz, 1H, ArO), 7.40 (t, J = 8.3 Hz, 1H, ArO), 7.66–7.74 (m, 2H, Ar + 1H, ArO), 7.76–7.88 ppm (m, 2H, Ar + 1H, ArO); ^{13}C NMR δ 26.1 (1C), 27.0 (1C), 28.7 (1C), 29.2 (1C), 29.3 (1C), 29.4 (1C), 29.5 (1C), 29.6 (1C), 38.3 (1C), 69.0 (1C), 109.0 (1C), 115.7 (1C), 121.8 (1C), 123.3 (2C), 130.0 (1C), 132.5 (2C), 134.0 (2C), 149.5 (1C), 160.0 (1C), 168.6 ppm (2C). Anal. Calcd for $C_{24}H_{28}N_2O_5 \cdot 0.33H_2O$ (424.49): C, 66.96; H, 6.71; N, 6.51. Found: C, 67.08; H, 6.53; N, 6.37.

5.4.19. 2-[10-(2,6-Dimethylphenoxy)decyl]-1*H*-isoindole-1,3(2*H*)-dione (20m)

Prepared as reported above for **8f** starting from **22** and 2,6-dimethylphenol, using DIAD instead of DEAD. Yield: 56% (after recrystallization); white crystals: mp 41–42 °C (i-Pr_2O/petroleum ether); IR (KBr): 1772, 1713 (C=O) cm^{-1}; ^1H NMR δ 1.24–1.40 (m, 10H, 5CH_2), 1.41–1.53 (m, 2H, CH_2), 1.62–1.74 (m overlapping apparent quintet at 1.78, 2H, CH_2), 1.78 (apparent quintet overlapping m at 1.62–1.74, 2H, CH_2), 2.26 (s, 6H, 2CH_3), 3.67 (t, J = 7.3 Hz, 2H, CH_2), 3.73 (t, J = 6.6 Hz, 2H, CH_2), 6.88 (dd, J = 8.3, 6.6 Hz, 1H, ArO), 6.98 (d, J = 7.4 Hz, 2H, ArO), 7.66–7.74 (m, 2H, Ar), 7.78–7.88 ppm (m, 2H, Ar); ^{13}C NMR δ 16.5 (2C), 26.3 (1C), 27.1 (1C), 28.8 (1C), 29.4 (1C), 29.6 (1C), 29.7 (1C), 30.6 (1C), 31.1 (1C), 38.3 (1C), 72.5 (1C), 123.3 (2C), 123.8 (1C), 128.9 (2C), 131.2 (2C), 132.4 (2C), 134.0 (2C), 156.3 (1C), 168.7 ppm (2C); MS (70 eV) m/z (%) 407 (M^+, 9), 122 (100). Anal. Calcd for $C_{26}H_{33}NO_3$ (407.54): C, 76.62; H, 8.16; N, 3.44. Found: C, 77.05; H, 8.16; N, 3.55.

5.4.20. 2-[10-(3-Chlorophenoxy)decyl]-1*H*-isoindole-1,3(2*H*)-dione (20n)

Prepared as reported above for **8f** starting from **22** and 3-chlorophenol, using DIAD instead of DEAD. Yield: 95% (after recrystallization); white crystals: mp 70–71 °C (EtOAc/hexane); IR (KBr): 1768, 1715 (C=O) cm^{-1}; ^1H NMR δ 1.22–1.50 (m, 12H, 6CH_2), 1.55–1.72 (m, 2H, CH_2), 1.75 (apparent quintet, 2H, CH_2), 3.67 (t, J = 7.4 Hz, 2H, CH_2), 3.92 (t, J = 6.6 Hz, 2H, CH_2), 6.77 (ddd, J = 8.3, 2.3, 1.0 Hz, 1H, ArO), 6.88 (d overlapping ddd at 6.89, J = 1.4 Hz, 1H, ArO), 6.89 (ddd overlapping d at 6.88, J = 10.2, 1.9, 0.8 Hz, 1H, ArO), 7.17 (apparent t, 1H, ArO), 7.66–7.74 (m, 2H, Ar), 7.80–7.88 ppm (m, 2H, Ar); ^{13}C NMR δ 26.2 (1C), 27.0 (1C), 28.8 (1C), 29.3 (2C), 29.5 (1C), 29.6 (2C), 38.3 (1C), 68.4 (1C), 113.3 (1C), 115.1 (1C), 120.8 (1C), 123.4 (2C), 130.3 (1C), 132.4 (2C), 134.1 (2C), 135.0 (1C), 160.1 (1C), 168.7 ppm (2C); MS (70 eV) m/z (%) 413 (M^+, 12), 160 (100). Anal. Calcd for $C_{24}H_{28}ClNO_3$ (413.94): C, 69.64; H, 6.82; N, 3.38. Found: C, 69.46; H, 6.80; N, 3.41.

5.4.21. 2-[10-(5-Chloro-2-methylphenoxy)decyl]-1*H*-isoindole-1,3(2*H*)-dione (20o)

Prepared as reported above for **8f** starting from **22** and 5-chloro-2-methylphenol, using DIAD instead of DEAD. Yield: 94% (after recrystallization); white crystals: mp 63–64 °C (THF + i-Pr_2O/petroleum ether); IR (KBr): 1772, 1721 (C=O), cm^{-1}; ^1H NMR δ 1.24–1.40 (m overlapping m at 1.38–1.50, 10H, 5CH_2), 1.38–1.50 (m overlapping m at 1.24–1.40, 2H, CH_2), 1.58–1.72 (m, 2H, CH_2), 1.78 (apparent quintet, 2H, CH_2), 2.15 (s, 3H, CH_3), 3.67 (t, J = 7.4 Hz, 2H, CH_2), 3.91 (t, J = 6.5 Hz, 2H, CH_2), 6.78 (dd, J = 6.1, 1.9 Hz, 1H, ArO), 6.81 (d, J = 1.9 Hz, 1H, ArO), 7.02 (dd, J = 7.8, 0.7 Hz, 1H, ArO), 7.66–7.74 (m, 2H, Ar), 7.79–7.87 ppm (m, 2H, Ar); ^{13}C NMR δ 16.0 (1C), 26.3 (1C), 27.1 (1C), 28.8 (1C), 29.4 (2C), 29.5 (1C), 29.6 (1C), 29.7 (1C), 38.3 (1C), 68.4 (1C), 111.7 (1C), 120.0 (1C), 123.4 (2C), 125.5 (1C), 131.2 (1C), 131.9 (1C), 132.4 (2C), 134.1 (2C), 160.0 (1C), 168.7 (2C); MS (70 eV) m/z (%) 427 (M^+, 15), 160 ppm (100). Anal. Calcd for $C_{25}H_{30}ClNO_3 \cdot 0.50H_2O$ (436.96): C, 68.72; H, 7.15; N, 3.21. Found: C, 68.96; H, 6.99; N, 3.28.

5.4.22. 2-{10-[4-(Trifluoromethyl)phenoxy]decyl}-1*H*-isoindole-1,3(2*H*)-dione (20p)

NaH (0.100 g, 0.24 mmol) was added to a solution of 4-(trifluoromethyl)phenol (0.044 g, 0.27 mmol) in dry DMF (10 mL) under N_2 atmosphere. The suspension was kept under stirring at 0 °C for 1 h, and then a solution of 2-(10-iododecyl)-1*H*-isoindole-1,3(2*H*)-dione (**23**) (0.100 g, 0.24 mmol) in dry DMF (10 mL) was added dropwise. The reaction mixture was heated at 75 °C and stirred at this temperature for 1 h. After evaporation of the solvent, the residue was taken up with EtOAc and washed with water. The organic phase was dried (Na_2SO_4) and concentrated under vacuum. The crude solid was recrystallized (THF/petroleum ether) to give 0.095 g (89%) of **20p**: mp 77–79 °C; IR (KBr): 1770, 1715 (C=O), 1333 (CF_3) cm^{-1}; ^1H NMR δ 1.20–1.42 (m overlapping m at 1.38–1.50, 10H, 5CH_2), 1.38–1.50 (m overlapping m at 1.20–1.42, 2H, CH_2), 1.60–1.72 (m, 2H, CH_2), 1.78 (apparent quintet, 2H, CH_2), 3.67 (t, J = 7.3 Hz, 2H, CH_2), 3.97 (t, J = 6.6 Hz, 2H, CH_2), 6.93 (d, J = 8.5 Hz, 2H, ArO), 7.51 (d, J = 8.5 Hz, 2H, ArO), 7.66–7.74 (m, 2H, Ar), 7.78–7.88 ppm (m, 2H, Ar); ^{13}C NMR δ 26.1 (1C), 27.0 (1C), 28.8 (1C), 29.4 (2C), 29.5 (1C), 29.6 (2C), 38.3 (1C), 68.4 (1C), 114.6 (2C), 122.7 (q, J_{CF} 30.1 Hz, 1C), 123.4 (2C), 124.7 (br q, J_{CF} 271.5 Hz, 1C), 127.0 (q, J_{CF} 3.9 Hz, 2C), 132.4 (2C), 134.0 (2C), 161.8 (1C), 168.7 ppm (2C); MS (70 eV) m/z (%) 447 (M^+, 6), 160 (100). Anal. Calcd for $C_{25}H_{28}F_3NO_3$ (447.49): C, 67.10; H, 6.31; N, 3.13. Found: C, 66.69; H, 6.35; N, 3.21.

5.5. General procedure for the aromatic nitration (20j,q–x)

The method adopted for the synthesis of 2-[10-(4-chloro-2-nitrophenoxy)decyl]-1*H*-isoindole-1,3(2*H*)-dione (**20q**) is described. To

a solution of 2-[10-(4-chlorophenoxy)decyl]-1*H*-isoindole-1,3(2*H*)-dione (**20b**) (0.032 g, 0.08 mmol) in TFA (2 mL), $NaNO_2$ (0.016 g, 0.23 mmol) was added. The resulted dark brown mixture was stirred for 8 h at room temperature, and, during this period, the mixture turned to orange. Water (120 mL) was then added and the solution was extracted with EtOAc. The combined organic phases were washed with water and with saturated $NaHCO_3$ aqueous solution, dried (Na_2SO_4) and then the solvent evaporated. The yellow solid obtained was purified by column chromatography on silica gel (EtOAc/petroleum ether 2:8) and then recrystallized from EtOAc/hexane to give 0.026 g of **20q** as yellow crystals (71%): mp 97–98 °C; IR (KBr): 1769, 1713 (C=O), 1519, 1340 (NO_2) cm^{-1}; ^1H NMR δ 1.22–1.40 (m overlapping m at 1.38–1.52, 10H, 5CH_2), 1.38–1.52 (m overlapping m at 1.22–1.40, 2H, CH_2), 1.60–1.72 (m, 2H, CH_2), 1.81 (apparent quintet, 2H, CH_2), 3.67 (t, J = 7.3 Hz, 2H, CH_2), 4.07 (t, J = 6.5 Hz, 2H, CH_2), 7.01 (d, J = 9.1 Hz, 1H, ArO), 7.46 (dd, J = 9.1, 2.5 Hz, 1H, ArO), 7.66–7.74 (m, 2H, Ar), 7.79–7.86 ppm (m, 2H, Ar + 1H, ArO); ^{13}C NMR δ 25.9 (1C), 27.0 (1C), 28.8 (1C), 29.0 (1C), 29.3 (2C), 29.5 (2C), 38.3 (1C), 70.3 (1C), 115.9 (1C), 123.4 (2C), 125.2 (1C), 125.6 (1C), 132.4 (2C), 134.0 (2C), 134.1 (1C), 140.3 (1C), 151.4 (1C), 168.7 ppm (2C). Anal. Calcd for $C_{24}H_{27}N_2O_5$ (458.93): C, 62.81; H, 5.93; N, 6.10. Found: C, 63.13; H, 6.00; N, 6.14.

5.5.1. 2-[10-(4,5-Dichloro-2-nitrophenoxy)decyl]-1*H*-isoindole-1,3(2*H*)-dione (20r)

Prepared as reported above for **20q** starting from **20d**. Yield: 46% (after recrystallization); white crystals: mp 100–102 °C (THF/petroleum ether); IR (KBr): 1771, 1710 (C=O), 1512, 1337 (NO_2) cm^{-1}; ^1H NMR δ 1.20–1.42 (m overlapping m at 1.38–1.52, 10H, 5CH_2), 1.38–1.52 (m overlapping m at 1.20–1.42, 2H, CH_2), 1.53–1.72 (m, 2H, CH_2), 1.82 (apparent quintet, 2H, CH_2), 3.67 (t, J = 7.3 Hz, 2H, CH_2), 4.07 (t, J = 6.5 Hz, 2H, CH_2), 7.17 (s, 1H, ArO), 7.66–7.74 (m, 2H, Ar), 7.78–7.88 (m, 2H, Ar), 7.97 ppm (s, 1H, ArO); ^{13}C NMR δ 25.9 (1C), 27.0 (1C), 28.8 (1C), 28.9 (1C), 29.3 (2C), 29.5 (2C), 38.3 (1C), 70.7 (1C), 116.6 (1C), 123.4 (2C), 123.8 (1C), 127.2 (1C), 132.4 (2C), 134.1 (2C), 138.4 (1C), 138.6 (1C), 151.7 (1C), 168.7 ppm (2C). Anal. Calcd for $C_{24}H_{26}Cl_2N_2O_5 \cdot H_2O$ (511.39): C, 56.37; H, 5.52; N, 5.48. Found: C, 56.14; H, 5.20; N, 5.73.

5.5.2. 2-[10-(4,6-Dichloro-2-nitrophenoxy)decyl]-1*H*-isoindole-1,3(2*H*)-dione (20s)

Prepared as reported above for **20q** starting from **20g**. Yield: 90% (after recrystallization); pale yellow crystals: mp 46–48 °C (*i*-Pr_2O/hexane); IR (KBr): 1772, 1714 (C=O), 1538, 1356 (NO_2) cm^{-1}; ^1H NMR δ 1.22–1.40 (m overlapping m at 1.38–1.50, 10H, 5CH_2), 1.38–1.50 (m overlapping m at 1.22–1.40, 2H, CH_2), 1.52–1.74 (m, 2H, CH_2), 1.81 (apparent quintet, 2H, CH_2), 3.67 (t, J = 7.4 Hz, 2H, CH_2), 4.10 (t, J = 6.6 Hz, 2H, CH_2), 7.60 (d, J = 2.8 Hz, 1H, ArO), 7.66–7.74 (m, 2H, Ar + 1H, ArO), 7.80–7.88 ppm (m, 2H, Ar); ^{13}C NMR δ 25.7 (1C), 27.1 (1C), 28.8 (1C), 29.4 (1C), 29.5 (1C), 29.6 (2C), 30.0 (1C), 38.3 (1C), 76.2 (1C), 123.4 (2C), 123.8 (1C), 129.3 (1C), 129.3 (1C), 131.9 (1C), 132.4 (2C), 134.1 (1C), 134.5 (1C), 145.7 (1C), 148.3 (1C), 168.7 ppm (2C); MS (70 eV) *m/z* (%) 476 ($M^+ - 16$, <1), 160 (100). Anal. Calcd for $C_{24}H_{26}Cl_2N_2O_5$ (493.38): C, 58.42; H, 5.31; N, 5.68. Found: C, 58.22, H, 5.44; N, 5.57.

5.5.3. 2-[10-(2,4-Dinitrophenoxy)decyl]-1*H*-isoindole-1,3(2*H*)-dione (20t)

Prepared as reported above for **20q** starting from **20a**. It was obtained in 50% yield along with **20j**. The mixture of **20t** and **20j** was purified by flash chromatography (EtOAc/petroleum ether 2:8) to give **20t** as a yellow solid which was recrystallized from EtOAc/petroleum ether. Yield: 18%; pale yellow crystals: mp 111–113 °C; IR (KBr): 1766, 1712 (C=O), 1526, 1345 (NO_2) cm^{-1}; ^1H NMR δ 1.20–1.40 (m, 10H, 5CH_2), 1.40–1.50 (m, 2H, CH_2), 1.50–1.72 (m, 2H, CH_2), 1.82–1.94 (m, 2H, CH_2), 3.67 (t, J = 7.3 Hz, 2H, CH_2), 4.22 (t, J = 6.3 Hz, 2H, CH_2), 7.18 (d, J = 9.1 Hz, 1H, ArO), 7.66–7.74 (m, 2H, Ar), 7.78–7.88 (m, 2H, Ar), 8.41 (dd, J = 9.4, 2.8 Hz, 1H, ArO), 8.73 ppm (d, J = 2.8 Hz, 1H, ArO); ^{13}C NMR δ 25.8 (1C), 27.0 (1C), 28.8 (2C), 29.2 (2C), 29.5 (2C), 38.3 (1C), 71.1 (1C), 114.4 (1C), 122.1 (1C), 123.4 (2C), 129.2 (1C), 132.4 (2C), 134.1 (2C), 139.2 (1C), 140.1 (1C), 157.1 (1C), 168.7 ppm (2C). Anal. Calcd for $C_{24}H_{27}N_3O_7$ (469.49): C, 61.40; H, 5.80; N, 8.95. Found: C, 61.42; H, 5.88; N, 8.74.

5.5.4. 2-{10-[2-Nitro-4-(trifluoromethyl)phenoxy]decyl}-1*H*-isoindole-1,3(2*H*)-dione (20u)

Prepared as reported above for **20q** starting from **20p**. Yield: 94% (after recrystallization); yellow crystals: mp 84–86 °C (EtOAc/hexane); IR (KBr): 1770, 1713 (C=O), 1540, 1332 (NO_2), 1332 (CF_3) cm^{-1}; ^1H NMR δ 1.20–1.40 (m, 10H, 5CH_2), 1.40–1.54 (m, 2H, CH_2), 1.54–1.72 (m, 2H, CH_2), 1.84 (apparent quintet, 2H, CH_2), 3.67 (t, J = 7.3 Hz, 2H, CH_2), 4.15 (t, J = 6.5 Hz, 2H, CH_2), 7.16 (d, J = 8.8 Hz, 1H, ArO), 7.66–7.79 (m, 2H, Ar + 1H, ArO), 7.80–7.88 (m, 2H, Ar), 8.09 ppm (d, J = 2.2 Hz, 1H, ArO); ^{13}C NMR δ 25.9 (1C), 27.0 (1C), 28.8 (1C), 28.9 (1C), 29.3 (2C), 29.5 (2C), 38.3 (1C), 70.4 (1C), 114.8 (1C), 122.7 (q, J_{CF} = 34.5 Hz, 1C), 123.3 (s overlapping q at 123.4, 2C), 123.3 (br q, J_{CF} = 271.4 Hz, 1C), 123.4 (q overlapping s at 123.3, J_{CF} = 4.1 Hz, 1C), 130.9 (q, J_{CF} = 3.3 Hz, 1C), 132.4 (2C), 134.0 (2C), 140.0 (1C), 155.0 (1C), 168.7 ppm (2C). Anal. Calcd for $C_{25}H_{27}F_3N_2O_5 \cdot 0.50C_6H_{14}$ (535.58): C, 62.79; H, 6.40; N, 5.23. Found: C, 62.86; H, 6.08; N, 5.11.

5.5.5. 2-[10-(4-Chloro-2,6-dimethyl-3-nitrophenoxy)decyl]-1*H*-isoindole-1,3(2*H*)-dione (20v)

Prepared as reported above for **20q** starting from **20f**. Yield: 67% (after recrystallization); white crystals: mp 50–52 °C (EtOAc/petroleum ether); IR (KBr): 1766, 1717 (C=O), 1528, 1364 (NO_2) cm^{-1}; ^1H NMR δ 1.25–1.40 (m, 10H, 5CH_2), 1.40–1.53 (m, 2H, CH_2), 1.55–1.72 (m, 2H, CH_2), 1.78 (apparent quintet, 2H, CH_2), 2.21 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 3.67 (t, J = 7.3 Hz, 2H, CH_2), 3.73 (t, J = 6.6 Hz, 2H, CH_2), 7.14 (s, 1H, ArO), 7.65–7.75 (m, 2H, Ar), 7.80–7.87 ppm (m, 2H, Ar); ^{13}C NMR δ 11.8 (1C), 16.6 (1C), 26.2 (1C), 27.0 (1C), 28.8 (1C), 29.3 (1C), 29.6 (2C), 29.9 (1C), 30.4 (1C), 38.3 (1C), 73.6 (1C), 119.2 (1C), 123.4 (2C), 125.5 (1C), 129.8 (1C), 132.4 (2C), 134.1 (2C), 135.3 (1C), 149.0 (1C), 155.4 (1C), 168.7 ppm (2C); MS (70 eV) *m/z* (%) 586 ($M^+ - 200$, 16), 160 (100). Anal. Calcd for $C_{26}H_{31}ClN_2O_5 \cdot 0.50H_2O$ (495.99): C, 62.96; H, 6.50; N, 5.65. Found: C, 63.02; H, 6.33; N, 5.77.

5.5.6. 2-[10-(2,6-Dimethyl-4-nitrophenoxy)decyl]-1*H*-isoindole-1,3(2*H*)-dione (20w)

Prepared as reported above for **20q** starting from **20m**. Yield: 21% (after recrystallization); white solid: mp 68–70 °C (EtOAc/hexane); IR (KBr): 1773, 1720 (C=O), 1513, 1343 (NO_2) cm^{-1}; ^1H NMR δ 1.20–1.42 (m, 10H, 5CH_2), 1.42–1.52 (m, 2H, CH_2), 1.60–1.74 (m, 2H, CH_2), 1.81 (apparent quintet, 2H, CH_2), 2.33 (s, 6H, 2CH_3), 3.67 (t, J = 7.3 Hz, 2H, CH_2), 3.80 (t, J = 6.5 Hz, 2H, CH_2), 7.67–7.75 (m, 2H, Ar), 7.80–7.88 (m, 2H, Ar), 7.91 ppm (s, 2H, ArO); ^{13}C NMR δ 16.8 (2C), 26.2 (1C), 27.0 (1C), 28.8 (1C), 29.3 (1C), 29.6 (2C), 29.9 (1C), 30.5 (1C), 38.3 (1C), 73.0 (1C), 123.4 (2C), 124.4 (2C), 132.4 (2C), 132.6 (2C), 134.1 (2C), 143.6 (1C), 161.9 (1C), 168.7 ppm (2C). Anal. Calcd for $C_{26}H_{32}N_2O_5 \cdot 0.5C_6H_{14}$ (495.63): C, 70.28; H, 7.93; N, 5.65. Found: C, 70.10; H, 7.61; N, 5.72.

5.5.7. 2-[10-(5-Chloro-2-methyl-4-nitrophenoxy)decyl]-1*H*-isoindole-1,3(2*H*)-dione (20x)

Prepared as reported above for **20q** starting from **20o**. Yield: 14% (after recrystallization); pale yellow crystals: mp 106–107 °C (THF/

petroleum ether); IR (KBr): 1772, 1717 (C=O), 1519, 1334 (NO_2) cm^{-1}; ^{1}H NMR δ 1.20–1.40 (m, 10H, 5CH_2), 1.40–1.54 (m, 2H, CH_2), 1.60–1.73 (m, 2H, CH_2), 1.75–1.88 (m, 2H, CH_2), 2.22 (s, 3H, CH_3), 3.67 (t, J = 7.4 Hz, 2H, CH_2), 4.01 (t, J = 6.5 Hz, 2H, CH_2), 6.86 (s, 1H, ArO), 7.26 (s, 1H, ArO), 7.68–7.74 (m, 2H, Ar), 7.80–7.88 ppm (m, 2H, Ar); ^{13}C NMR δ 16.0 (1C), 26.1 (1C), 27.0 (1C), 28.8 (1C), 29.1 (1C), 29.3 (1C), 29.5 (1C), 29.9 (1C), 31.1 (1C), 38.3 (1C), 69.4 (1C), 113.5 (1C), 123.4 (2C), 127.0 (1C), 127.2 (1C), 128.2 (1C), 132.4 (2C), 134.1 (2C), 139.9 (1C), 161.0 (1C), 168.7 ppm (2C). Anal. Calcd for $C_{25}H_{29}ClN_2O_5 \cdot 0.33H_2O$ (478.96): C, 62.69; H, 6.24; N, 5.85. Found: C, 62.77; H, 6.58; N, 5.50.

5.5.8. 2-(10-Hydroxydecyl)-1*H*-isoindole-1,3(2*H*)-dione (22)

Prepared as reported above for **8f** starting from **21**, phthalimide and di-*tert*-butyl azodicarboxylate (DBAD). Yield: 55% (after recrystallization); white crystals: mp 76–78 °C (EtOAc/petroleum ether); IR (KBr): 3510 (OH), 1774, 1700 (C=O) cm^{-1}; ^{1}H NMR δ 1.15–1.40 (m, 12H, 6CH_2), 1.42–1.62 (m overlapping m at 1.58–1.72, 2H, CH_2 + 1H, OH), 1.58–1.72 (m overlapping m at 1.42–1.62, 2H, CH_2), 3.63 (t overlapping t at 3.67, J = 6.6 Hz, 2H, CH_2), 3.67 (t overlapping t at 3.63, J = 7.3 Hz, 2H, CH_2), 7.65–7.73 (m, 2H, Ar), 7.75–7.88 ppm (m, 2H, Ar); ^{13}C NMR δ 25.9 (1C), 27.0 (1C), 28.8 (1C), 29.3 (1C), 29.5 (2C), 29.6 (1C), 33.0 (1C), 38.3 (1C), 63.3 (1C), 123.4 (2C), 132.4 (2C), 134.1 (2C), 168.7 ppm (2C); MS (70 eV) m/z (%) 303 (M$^+$, 14), 160 (100). Anal. Calcd for $C_{18}H_{25}NO_3$ (303.40): C, 71.26; H, 8.31; N, 4.62. Found: C, 71.20; H, 8.31; N, 4.74.

5.5.9. 2-(10-Iododecyl)-1*H*-isoindole-1,3(2*H*)-dione (23)

To a refluxing solution of 2-(10-hydroxydecyl)-1*H*-isoindole-1,3(2*H*)-dione (**22**) (0.150 g, 0.49 mmol) and triphenylphosphine (0.170 g, 0.65 mmol) in dry toluene (16 mL), iodine (0.165 g, 0.65 mmol) was added portionwise. The mixture was heated at reflux for 1 h, and then absolute ethanol (1 mL) was added in two portions at ca. 30 min. intervals. After evaporation of the solvent, the residue was taken up with EtOAc, washed twice with saturated $Na_2S_2O_3$ aqueous solution and then with water. The organic phase was dried and the solvent evaporated. The white solid obtained was purified by column chromatography on silica gel (EtOAc/petroleum ether 1:9) giving 0.104 g (51%) of **23** as a white solid: mp 68–70 °C; IR (KBr): 1764, 1700 (C=O) cm^{-1}; ^{1}H NMR δ 1.22–1.42 (m, 12H, 6CH_2), 1.60–1.72 (m, 2H, CH_2), 1.81 (apparent quintet, 2H, CH_2), 3.18 (t, J = 7.0 Hz, 2H, CH_2), 3.67 (t, J = 7.3 Hz, 2H, CH_2), 7.66–7.74 (m, 2H, Ar), 7.80–7.88 ppm (m, 2H, Ar); ^{13}C NMR δ 7.1 (1C), 26.8 (1C), 28.4 (1C), 28.5 (1C), 29.1 (1C), 29.3 (2C), 30.4 (1C), 33.6 (1C), 38.0 (1C), 123.1 (2C), 132.2 (2C), 133.8 (2C), 168.4 ppm (2C); MS (70 eV) m/z (%) 413 (M$^+$, <1), 160 (100).

5.5.10. 2-(4-Phenoxybutyl)-1*H*-isoindole-1,3(2*H*)-dione (25a)

Potassium phthalimide (0.50 g, 2.69 mmol) was added to a solution of (4-bromobutoxy)benzene (**24**) (0.550 g, 2.40 mmol) in dry DMF (10 mL) under N_2 atmosphere. The reaction mixture was heated to 80 °C and stirred at this temperature for 5 h. The solid residue was filtered off. After evaporation of the solvent, the residue was taken up with EtOAc and washed with water. The organic phase was dried (Na_2SO_4) and concentrated under vacuum. The residue was purified by crystallization (EtOAc/hexane) to give 0.50 g (71%) of **25a** as white crystals: mp 103–104 °C; IR (KBr): 1775, 1712 (C=O) cm^{-1}; ^{1}H NMR δ 1.75–1.96 (m, 4H, 2CH_2), 3.77 (t, J = 6.7 Hz, 2H, CH_2), 3.99 (t, J = 5.8 Hz, 2H, CH_2), 6.82–6.96 (m, 3H, ArO), 7.20–7.32 (m, 2H, ArO), 7.66–7.76 (m, 2H, Ar), 7.80–7.88 ppm (m, 2H, Ar); ^{13}C NMR δ 25.6 (1C), 26.9 (1C), 37.9 (1C), 67.2 (1C), 114.7 (2C), 120.8 (1C), 123.4 (2C), 129.6 (2C), 132.3 (2C), 134.1 (2C), 159.1 (1C), 168.7 ppm (2C); MS (70 eV) m/z (%) 295 (M$^+$, 9), 160 (100). Anal. Calcd for $C_{18}H_{17}NO_3$ (295.33): C, 73.20; H, 5.80; N, 4.74. Found: C, 72.77; H, 5.82; N, 4.75.

5.6. Biology

5.6.1. α-Glucosidase inhibitory activity determination

The α-glucosidase inhibitory activity of the newly synthesized compounds (Tables 1–3) was determined as described in the literature[20] and was expressed as the inhibitor concentration required for 50% inhibition of the α-glucosidase activity (IC_{50}). Briefly, α-glucosidase from *Saccharomyces cerevisiae* (Sigma, G-0660 Lot 015K0869) was dissolved in 445 μL of 10 mM phosphate buffer (pH 7.28) at a final concentration of 25 mU/mL and incubated in the presence of 5 μL of test compound in DMSO at 37 °C for 5 min. The reaction was started by the addition of 50 μL of 4-nitrophenyl α-D-glucopyranoside (*p*-NPG, final concentration 80 μM) and stopped after 10 min with 500 μL of 0.5 M Na_2CO_3. The amount of released 4-nitrophenol from *p*-NPG was measured as the absorbance at 400 nm. The assay was performed with eight different concentrations around the IC_{50} values, approximately estimated in previous experiments. In each set of experiments the assay was performed in triplicate and at least two times. The increased absorbance was compared with that of the control containing 5 μL of DMSO in the place of the test solution. The IC_{50} values were measured graphically by a plot of percent activity versus log of the test compound concentration.

5.6.2. β-Glucosidase, α-mannosidase, and α-galactosidase inhibitory activity determination

The inhibitory activity of β-glucosidase from almonds (Sigma, G-0395 Lot 109K4039), α-mannosidase from *Canavalia ensiformis* (Sigma, M-7257 Lot 039K7695), and α-galactosidase from green coffee beans (Sigma, G-8507 Lot 068K1400) was determined as for α-glucosidase. The enzymatic hydrolysis of substrates was monitored by measuring the amount of *p*-nitrophenol released from 4-nitrophenyl β-D-glucopyranoside, 4-nitrophenyl α-D-mannopyranoside, and 4-nitrophenyl α-D-galactopyranoside, respectively. The enzymes (12.5 mU per sample test) were dissolved in 445 μL of buffer: β-glucosidase in 50 mM sodium citrate (pH 5.0), α-mannosidase in 10 mM sodium acetate (pH 4.5) and α-galactosidase in 50 mM potassium phosphate (pH 6.5). Five microlitres of test compound in DMSO, at the concentration of 25 μM, were incubated at 37 °C for 5 min and the reaction was started by the addition of 50 μL of the substrate (final concentration 80 μM). The reaction was stopped after 10 min of incubation with 500 μL of 1 M Na_2CO_3. The absorbance in the presence of the test compound was compared to that of the control (5 μL of DMSO). All the experiments were carried out in triplicate.

5.6.3. MTT assay

The cytotoxicity of compounds on SH-SY5Y human neuroblastoma cells was evaluated by slightly modifying the MTT cell proliferation assay.[28] Briefly, the cell were seeded in a 96-well plate and the test compounds were added at both the concentration of 5 μM and the one corresponding to IC_{50} value, and after 2 h exposure, 12 μL of a solution of MTT (5 mg/mL) dissolved in DMEM + 10% FBS were added to each well and each plate was incubated at 37 °C for 4 h. The supernatants were then aspirated and 100 microlitres of DMSO were added to each well. The absorbance at 540 nm was measured using a Wallac Victor 3 1421 Multilabel Counter. All experiments were carried out in sextuplicate and were repeated twice.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2010.06.088. These data include MOL files and InChiKeys of the most important compounds described in this article.

References and notes

1. Gao, H.; Huang, Y. N.; Gao, B.; Lee, P.; Inagaki, C.; Kawabata, J. *Nees. Food Chem.* **2008**, *108*, 965.
2. Balfour, J. A.; McTavish, D. *Drugs* **1993**, *46*, 1025.
3. Pogano, G.; Marena, S.; Corgiat-Mansin, L.; Cravero, F.; Giorda, C.; Bozza, M. *Diabetes Metab.* **1995**, *21*, 162.
4. Bernaeki, R. J.; Niedbala, M. J.; Korytryk, W. *Cancer Metastasis Rev.* **1985**, *4*, 81.
5. Metha, A.; Zitzmann, N.; Rudd, P. M.; Block, T. M.; Dwek, R. A. *FEBS Lett.* **1998**, *430*, 17.
6. Gruters, R. A.; Neefjes, J. J.; Tersmetti, M.; De Goede, R. E. W.; Tulp, A.; Huisman, H. G.; Miedeme, F.; Ploegh, H. C. *Nature* **1987**, *330*, 74.
7. Ratner, L.; Wander Heyden, N. *AIDS Res. Hum. Retroviruses* **1993**, *9*, 291.
8. de Melo, E. B.; Gomes, A. S.; Carvalho, I. *Tetrahedron* **2006**, *62*, 10277.
9. Lillelund, V. H.; Gensen, H. H.; Liang, X.; Bols, M. *Chem. Rev.* **2002**, *102*, 515.
10. Xu, H.-W.; Dai, G.-F.; Liu, G.-Z.; Wang, J.-F.; Liu, H.-M. *Bioorg. Med. Chem.* **2007**, *15*, 4247.
11. Seo, W. D.; Kim, J. H.; Kang, J. E.; Rwu, H. W.; Curtis-Long, M. J.; Lee, H. S.; Jang, M. S.; Park, K. H. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5514.
12. Hakamata, W.; Nakanishi, I.; Masuda, Y.; Shimizu, T.; Higuchi, H.; Nakamura, Y.; Saito, S.; Urano, S.; Oku, T.; Ozawa, T.; Ikota, N.; Miyata, N.; Okuda, H.; Fukuhara, K. *J. Am. Chem. Soc.* **2006**, *128*, 6524.
13. Liu, H.; Sim, L.; Rose, D. R.; Pinto, B. M. *J. Org. Chem.* **2006**, *71*, 3007.
14. Luo, J.-G.; Wang, X.-B.; Ma, L.; Kong, L.-Y. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4460.
15. Saludes, J. P.; Lievens, S. C.; Molinski, T. F. *J. Nat. Prod.* **2007**, *70*, 436.
16. Du, Z.-Y.; Liu, R.-R.; Shao, W.-Y.; Mao, X.-P.; Ma, L.; Gu, L.-Q.; Huang, Z.-S.; Chan, A. S. C. *Eur. J. Med. Chem.* **2006**, *41*, 213.
17. Atsushi, K.; Noriko, K.; Erika, K.; Isao, A.; Kyoko, I.; Liang, Y.; Tadashi, O.; Yasunori, B.; Hidekazu, O.; Hiroki, T.; Naoki, A. *J. Med. Chem.* **2005**, *48*, 2036.
18. Schaller, C.; Demange, R.; Picasso, S.; Vogel, P. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 277.
19. Chen, X.; Fan, Y.; Zhen, Y.; Shen, Y. *Chem. Rev.* **2003**, *103*, 1955.
20. Takahashi, H.; Sou, S.; Yamasaki, R.; Sodeoka, M.; Hashimoto, Y. *Chem. Pharm. Bull.* **2000**, *48*, 1494.
21. Sou, S.; Mayumi, S.; Takahashi, H.; Yamasaki, R.; Kadoya, S.; Sodeoka, M.; Hashimoto, Y. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1081.
22. Mitsunobu, O. *Synthesis* **1981**, 1.
23. Rawlings, A. J.; Lomas, H.; Illing, A. V.; Lee, M. J.-R.; Alonzi, D. S.; Rountree, J. S. S.; Jenkinson, S. F.; Fleet, G. W. J.; Dwek, R. A.; Jones, J. H.; Butters, T. D. *ChemBioChem* **2009**, *10*, 1101.
24. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
25. Pierwocha, A. W.; Walczak, K. *Carbohydr. Res.* **2008**, *343*, 2680.
26. Xiao, X.; Antony, S.; Kohlhagen, G.; Pommier, Y.; Cushman, M. *Bioorg. Med. Chem.* **2004**, *12*, 5147.
27. Neelakantan, S.; Surjawan, I.; Karacelik, H.; Hicks, C. L.; Crooks, P. A. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5722.
28. Polimeno, L.; Pesetti, B.; Lisowsky, T.; Iannone, F.; Resta, L.; Giorgio, F.; Mallamaci, R.; Buttiglione, M.; Santovito, D.; Vitiello, F.; Mancini, M. E.; Francavilla, A. *Free Radical Res.* **2009**, *43*, 865.