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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Aryloxyacetic esters structurally related to α-Asarone as potential antifungal agents

Fabiola Jiménez · María del Carmen Cruz · Clara Zúñiga · María A. Martínez · Germán Chamorro · Francisco Díaz · Joaquín Tamariz

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Abstract A series of aryloxyacetic ester analogues **8–13** was synthesized based on the potential pharmacophores of the antifungal agents α-Asarone (**1**) and **2–5**. Their antifungal activity was tested in vitro for their growth inhibitory activities against pathogenic fungi. The in vitro antifungal evaluation of these alkyl and aryl esters shows that derivatives **10** displayed the highest antifungal and fungicidal activities against *Cryptococcus neoformans* and *C. gattii*. These results support the idea that the phenoxyacetic frame is a potent pharmacophore for the design of potential antifungal drugs.

Keywords α-Asarone · Antifungal activity · *Cryptococcus neoformans* var. *neoformans* · *Cryptococcus gattii* · Phenoxyacetic frame

F. Jiménez · M. Cruz · C. Zúñiga · F. Díaz · J. Tamariz (✉)
Departamento de Química Orgánica, Escuela Nacional de Ciencias Biológicas, Instituto Politécnico Nacional, Prol. Carpio y Plan de Ayala, 11340 México, DF, Mexico
e-mail: jtamariz@woodward.encb.ipn.mx

M. Cruz
Centro de Investigación en Biotecnología Aplicada, Instituto Politécnico Nacional, Km 15 Carretera Sta. Inés Tecuexcomac, Tepetitla 90700, Tlaxcala, Mexico

C. Zúñiga · G. Chamorro
Laboratorio de Toxicología Preclínica, Escuela Nacional de Ciencias Biológicas, Instituto Politécnico Nacional, Prol. Carpio y Plan de Ayala, 11340 México, DF, Mexico

M. A. Martínez
Departamento de Microbiología, Escuela Nacional de Ciencias Biológicas, Instituto Politécnico Nacional, Prol. Carpio y Plan de Ayala, 11340 México, DF, Mexico

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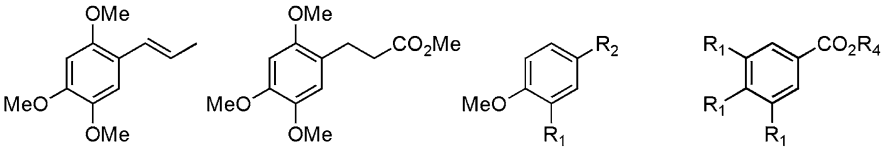
Introduction

Since in the last two decades the incidence of invasive fungal infections has risen sharply, it has become imperative to enlarge the number of antifungal drugs with more potent activity and less toxicity (Maertens and Boogaerts, 2005; Datry and Bart-Delabesse, 2006). Until recently, such treatment was composed of amphotericin B and azoles (Vazquez and Sobel, 2006). However, fungal pathogens acquire resistance, which hampers effective treatment strategies (Prasad *et al.*, 2002). These mainly opportunistic fungi acquire resistance during prophylaxis, intermittent or monotherapy, for instance, in the case of the resistance of *Candida* species, *Cryptococcus neoformans* and the recently accepted species (Kwon-Chung *et al.*, 2002) *C. gattii* to flucytosine, amphotericin B, and azoles (Kwon-Chung *et al.*, 2002; White *et al.*, 1998; Sterling and Merz, 1998; Vanden Bossche *et al.*, 1998; Pfaller *et al.*, 2004).

α-Asarone (**1**) has been isolated from multiple natural sources, such as *Acorus* family and *Guatteria gaumeri* (Martínez, 1992), and it displays a broad spectrum of biological activity. It has powerful hypolipidemic activity (Chamorro *et al.*, 1993; Garduño *et al.*, 1997), showing high binding affinity to hepatic 3-hydroxy-3-methylglutaryl-CoA reductase (HMGR) (Rodríguez-Páez *et al.*, 2003). It has also been isolated from the seed extracts of *Daucus carota*, and was active in antilarvaric assays of the yellow-fever- and dengue-transmitting mosquito *Aedes aegyptii*, as well as in nematicidal (*Caenorhabditis elegans* and *Panagrellus redivivus*) and antifeedant (*Helicovarpa zea, Heliothis virescens*, and *Manduca sexta*) activity evaluations (Momin and Nair, 2002). In particular, α-Asarone (**1**) has exhibited activity against the yeasts *Candida albicans*, *Candida parapsilasis*, and *Candida krusei* (Momin and Nair, 2002).

β-Asarone and the trimethoxyphenyl compound **2**, whose structure is closely related to **1**, have shown marked activity against larvae of *Aedes aegyptii*, as well as antifungal activity (Lee *et al.*, 2004; Ioset *et al.*, 2000). Some other analogues such as anethole (**3**) and methyleugenol (**4**) enhance the fungicidal action of the bicyclic sesquiterpene called polygodial upon combined administration (Kubo *et al.*, 2001), and alkyl gallates **5** exhibit antifungal activity against *S. cerevisiae* at any growth stage (Kubo *et al.*, 2002).

We have reported that phenoxyacetic acids and esters **6**, which take advantage of some structural pharmacophoric features of both α-Asarone (**1**) (Chamorro *et al.*, 1998; Díaz *et al.*, 1993) and fibrates, displayed a significant hypocholesterolemic activity (Labarrios *et al.*, 1999; Cruz *et al.*, 2003; Zúñiga *et al.*, 2005). Recently, a number of fibrate mimetic amides, which were prepared and evaluated biologically, showed a decrease of serum cholesterol and a lowering of low-density lipoprotein (LDL) cholesterol (Hernández *et al.*, 2004). Phenoxyacetic acids **7** have been reported to exhibit antimicrobial, herbicidal, and low and moderate fungicidal activities (Nair and Burke, 1988; Zawadowska, 1962, 1963; Suyama and Kato, 1989; Purohit and Shah, 1999; Arcamone *et al.*, 1957). The latter reports together with our results suggest that the phenoxyacetic moiety has a high pharmacophore value, independently of other groups present in the benzene ring.



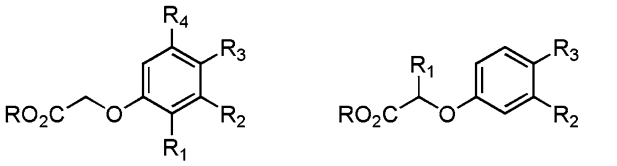
1 **2**

3, R_1 = H, R_2 = (*E*)-CH=CHMe
4, R_1 = OMe, R_2 = $CH_2CH=CH_2$

5, R_1= H, OH, OMe
R_2= H, OH, OMe
R_3 = H, OH, OMe
R_4 = H, alkyl

Structure 1-5

Owing to the significant antifungal activity of **1**–**5**, in this report we address the evaluation of the series of analogues **8**–**13** as potential antifungal agents that contain a combination of pharmacophores of the former compounds and those related to the phenoxyacetic acid compounds **7**.



6, R = H, Me, Et
R_1 = H, Me, Et, MeO, NO_2
R_2 = H, Me, Et, MeO
R_3 = H, Me, Et, $CH_2CH=CH_2$, MeO, NO_2
R_4 = H, NO_2

7, R = H, Me, Et, Cy, aryl, Bn
R_1 = H, Me, Py
R_2 = H, NO_2
R_3 = H, Me, Ac, $CH(CCl_3)Ar$, Cl, NO_2, NH_2

Structure 6-7

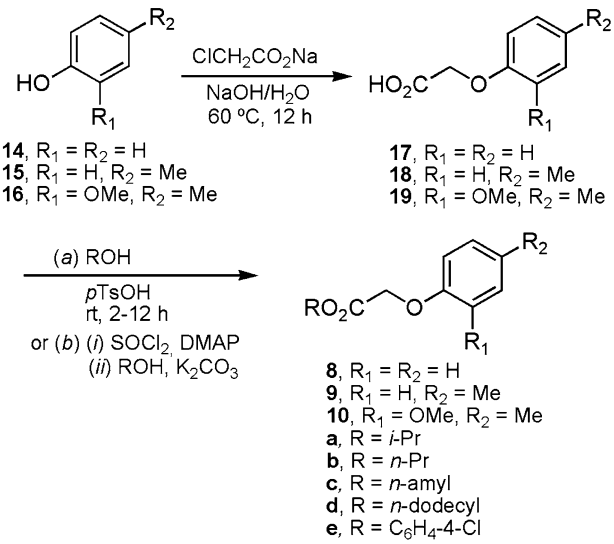
Results

Synthesis

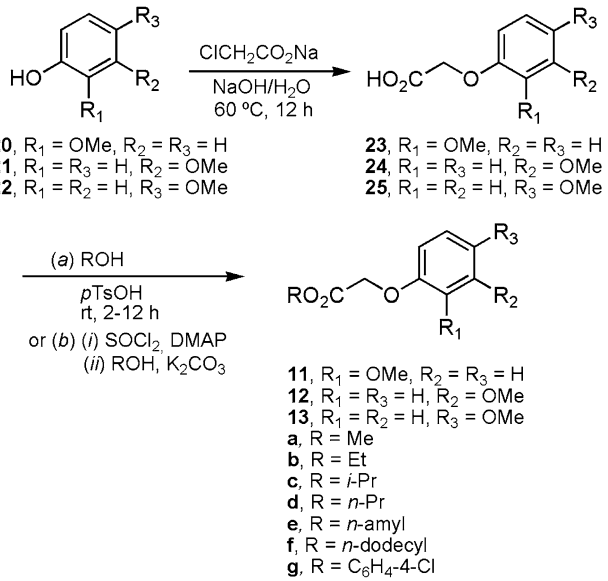
Esters **8a**–**e** were prepared by a two-step reaction synthesis, starting from the reaction of phenol **14** with sodium chloroacetate under basic conditions to furnish phenoxyacetic acid **17**, in good yield (75%). The latter was treated with a series of alcohols (*i*-PrOH, *n*-PrOH, *n*-amylOH, *n*-dodecylOH, or ClC_6H_4OH) to give the series **8a**–**e**, respectively, e.g., **8a** with R = *i*-Pr, $R_1 = R_2 = H$ (Scheme 1). Unlike derivatives **8a–c**, which were obtained in high yields (81–86%) after treating the phenoxyacetic acid **17** with the desired alcohol in the presence of *p*TsOH at r.t., derivatives **8d** and **8e** were more efficiently prepared (71–80%) with in situ formation of the respective acid chloride, by treating the same phenoxyacetic acid

with thionyl chloride, then adding the corresponding alcohol (*i*-PrOH, *n*-PrOH, *n*-amylOH, *n*-dodecylOH, or ClC_6H_4OH). Series of esters **9a–e**, which has a methyl group at the *para* position with respect to the acetic ester moiety, was prepared from phenol **15** through an analogous synthetic route to that for the series **8**, and conserving the same series of alcohols, *e.g.,* **9c** with R = *n*-amyl, R_1 = H, R_2 = Me (Scheme 1). The overall yields of esters **9a–e** were satisfactory (68–85%). Concerning the series of derivatives **10a–e**, the reactions proceeded efficiently from phenol **16** via the aryloxyacetic acid **19** to give the desired products, e.g., **10e** with R = C_6H_4–4–Cl, R_1 = OMe, R_2 = Me (Scheme 1), in good yields (64–86%).

Preparation of the isomeric phenoxyacetic esters **11–13** followed a similar synthetic route to that of the previous series (Scheme 2). Thus, the 2-, 3-, and 4-methoxyphenols **20–22** were treated with sodium chloroacetate to give the phenoxyacetic acids **23–25** (80–85%), respectively. Through an analogous esterification to that of the series shown in Scheme 1, we obtained the three series of esters **11a–g**, **12a–g**, and **13a–g**, respectively, e.g., **11a** with R = Me, R_1 = OMe, R_2 = R_3 = Me; **12e** with R = *n*-amyl, R_1 = R_3 = H, R_2 = OMe; and **13g** with R = C_6H_4–4–Cl, R_1 = R_2 = H, R_3 = Me (Scheme 2). In general, the yields were rather high (79–95%), except for derivative **12g**, which was isolated in 60% yield. In these series, the methyl and ethyl esters were also included (i.e., **11a**,**b**, **12a**,**b**, and **13a**,**b**), considering that similar esters were biologically active in compounds **7**.



Scheme 1 Preparation of the series **8–10**



Scheme 2 Preparation of the series **11–13**

Table 1 In vitro antifungal activities (MIC_{50}, μg/ml) of aryloxyacetic esters **8–12**[a]

Compound	*C. neoformans* var. *neoformans*[b]	*C. gattii*[b]
Ketoconazole	0.12	0.06
Itraconazole	0.03	0.03
Fluconazole	4	4
Amphotericin B	0.12	0.12
Caspofungine	8	16
8c	16	2
9a	8	128
10a	64	0.25
10b	2	0.25
10c	32	0.5
10e	0.25	0.5
11a	0.5	128
11e	16	64
12d	0.5	64

[a] All the prepared series, **8–13**, were tested, but only the derivatives exhibiting MIC_{50} <32 μg/ml in any of the *Cryptococcus* species are included

[b] MIC_{50} was evaluated by the modified CLSI M27-A2 broth microdilution method

Antifungal activity

All the prepared series, **8–13**, were evaluated in the in vitro antifungal activity tests. Table 1 summarizes the minimal inhibitory concentration 50% (MIC_{50}) required for the 50% inhibition of fungal growth only for those analogues that showed antifungal activity <32 μg/ml, in which ketoconazole, itraconazole, fluconazole, amphotericin

Table 2 In vitro fungicide activities (MFC, μg/ml) of aryloxyacetic esters **8–12**[a]

Compound	*C. neoformans* var. *neoformans*[b]	*C. gattii*[b]
8c	64	2
9a	>64	[c]
10a	[c]	0.25
10b	[d]	[d]
10c	[c]	0.5
10e	0.25	0.5
11a	>64	[c]
11e	>64	[c]
12d	>64	[c]

[a] Only the derivatives exhibiting $IC_{50\%}$ <32 μg/ml against any of the *Cryptococcus* strains are included

[b] MFC (μg/ml) estimations were determined by directly plating dilutions of culture medium from wells with no growth onto potato dextrose agar and incubating the plates at 35°C for 48 h

[c] Not tested

[d] Decreased growth rate in the Petri dish

B, and caspofungine are listed as the reference compounds. Except for caspofungine, the remainder of the latter compounds were susceptible to both strains.

Fungicidal activity

The minimal fungicidal concentrations (MFCs) were examined only for those compounds showing a significant MIC_{50} activity (<32 μg/ml), and the results are summarized in Table 2.

Discussion

To establish the minimal pharmacophore features associated with the antifungal activity of these compounds, we prepared a series of homologous esters **8a–e** with no substituents at the benzene ring (Scheme 1). The fact that the lipophilic effect might play a role in facilitating the transport of the drugs through the lipophilic membranes of the yeasts (White *et al*., 1998) prompted us to choose a series of long and lineal hydrocarbon chains for the partnership alcohols, as well as an aromatic ring substituted by a chlorine atom. In the series of esters **9a–e**, a methyl group was introduced at the *para* position with respect to the acetic ester moiety, conserving the same series of alcohols (Scheme 1). An additional methoxy group, which was introduced in the series **9a–e** to be evaluated as the series of derivatives **10a–e**, was attached to the C-2 carbon atom of the benzene ring with the aim of mimicking the structure of compounds **6**. The structural simplicity of these analogues was also a characteristic in the series of *ortho*, *meta*, and *para* isomeric phenoxyacetic esters **11–13** (Scheme 2).

For series **8** and **9**, only compounds **8c** and **9a** exhibited antifungal activity, though the latter was not active against *Cryptococcus gattii*. In contrast, series **10**

was largely the most active among all those tested. Thus, derivatives **10a** and **10c** exhibited high antifungal activity against *C. gattii*, but **10b** and **10e** were even more active against both *Cryptococcus* species. It is worth noting that this series, which bears the methoxy group at the C-2 carbon atom of the benzene ring, displayed more potency than its demethoxylated analogues **9a–e**.

Considering these results, we prepared (Scheme 2) and tested the isomeric series **11–13**, in order to evaluate the role of the methoxy group in a benzene ring without the methyl group. However, only derivatives **11a**, **11e**, and **12d** showed antifungal activity. Actually, their activity was limited against the two *Cryptococcus* species, in which compounds **11a** and **12d** were highly active. Acid precursors **23–25** were also tested but no activity was shown at all.

As these results suggest that the ester function is necessary for exhibiting antifungal activity, the lipophilic effect provided by the hydrocarbon ester chain would contribute to such activity. However, there was not a lineal correlation between the length of the ester chain and the antifungal activity, since the ester analogues with the longest chain (*n*-dodecyl) did not show any significant activity. Conformational and steric factors might counterbalance the potential lipophilic effect, thus inhibiting the approach to the receptor.

Although not all compounds demonstrated fungicidal activity, some of the most active antifungal ones did. In particular, compound **10e** was the most active agent against both *Cryptococcus* species. In contrast, its analogue **10b** was only fungistatic, and analogues **10a** and **10c** maintained fungicidal activity only against the *C. gattii* strain. It is interesting to note that the fungicidal activity of these aryloxyacetic esters was reached at a similar potency to that of the antifungal activity.

In summary, the above results agree with our hypothesis, suggesting that the aryloxyacetic moiety has a pharmacophore value for the antifungal activity. Derivatives bearing both the methyl and the methoxy groups (**10**), related to α-Asarone (**1**) and aryloxyacetic compounds **7**, proved to be the most potent antifungal agents. Moreover, some of them also exhibited a high fungicidal activity. It is likely that the hydrophobicity introduced by the ester group can explain the differences in activity of the tested esters with respect to the corresponding inactive aryloxyacetic acids. Therefore, the most active analogues described in this report, which were designed considering some of the possible combinations of the pharmacophores present in the structures of compounds **1–7**, proved to be highly promising fungicidal agents. In addition, the series **8–13** exhibits high economy in terms of the number of pharmacophores present and, as a consequence, in the synthetic methodology leading to its preparation.

Experimental

Chemistry

Melting points were determined with an Electrothermal capillary melting point apparatus and are reported uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer 1600 spectrophotometer (Perkin-Elmer Corp., Norwalk, CT, USA).

^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a Varian Mercury-300 (300 MHz and 75.4 MHz) (Varian, Palo Alto, CA, USA) instrument, with $CDCl_3$ as solvent and trimethylsilane (TMS) (Aldrich Chemical Co., Milwaukee, WI, USA) as internal standard. Mass spectra (MS) spectrometry were taken, in electron impact (70 eV) mode, on a Hewlett-Packard 5971A (Hewlett-Packard Co., Palo Alto, CA, USA) spectrometer. Microanalyses were performed by M-H-W Laboratories (Phoenix, AZ, USA). Starting materials and reagents were purchased from Aldrich Chemical Co. (Milwaukee, WI, USA), and were used without any further purification. Analytical thin-layer chromatography (TLC) was performed on precoated TLC sheets of silica gel 60 F_{254} (Merck, Darmstadt, Germany), visualizing by long- and short-wavelength ultraviolet (UV) lamps. Flash column chromatography was performed on silica gel (230–400 mesh, Natland Int., USA). All air moisture sensitive reactions were carried out under nitrogen using oven-dried glassware.

General procedure for the preparation of phenoxyacetic acids

Solutions of NaOH (4.4 g, 0.11 mol) in 20 ml H_2O and of sodium chloroacetate (12.8 g, 0.11 mol) in 20 ml H_2O were successively added dropwise at room temperature to the corresponding phenol **14**–**17** or **20**, **21** (0.1 mol). The mixture was stirred and heated to 60°C for 12 h. HCl (36%) was added until pH 2, and a precipitate was formed, which was filtered and purified by recrystallization (hexane/EtOAc, 2:8).

Phenoxyacetic acid (**17**)

Following the general procedure with 9.4 g of **14**, gave 11.4 g (75%) of **17** as a white solid: R_f 0.44 (hexane/EtOAc/AcOH, 1:1:0.1); mp 98–100°C [lit. (Guha, 1950) 96–97°C]; IR (KBr) 3350–2393, 1732, 1703, 1598, 1584, 1498, 1437, 1310, 1288, 1231, 1094, 754 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.69 (s, 2H, OCH_2), 6.88–6.95 (m, 2H, H-2), 6.98–7.50 (m, 1H, H-4), 7.26–7.35 (m, 2H, H-3), 10.75 (br s, 1H, CO_2H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 64.6 (OCH_2), 114.5 (C-2), 122.0 (C-4), 129.6 (C-3), 157.3 (C-1), 175.0 (CO).

4-Methylphenoxyacetic acid (**18**)

Following the general procedure with 10.8 g (0.1 mol) of **15**, gave 13.3 g (80%) of **18** as a white solid: R_f 0.43 (hexane/EtOAc/AcOH, 2:3:0.1); mp 138–139°C [lit. (Guha, 1950) 134–135°C]; IR (KBr) 3260–2360, 1735, 1705, 1511, 1436, 1289, 1236, 1089, 814 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.29 (s, 3H, CH_3), 4.65 (s, 2H, OCH_2), 6.79–6.86 (m, 2H, H-2, H-6), 7.06–7.13 (m, 2H, H-3, H-5), 7.75–8.30 (br s, 1H, CO_2H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 21.0 (CH_3), 64.9 (OCH_2), 114.4 (C-2, C-6), 130.1 (C-3, C-5), 131.5 (C-4), 155.2 (C-1), 174.4 (CO).

2-Methoxy-4-methylphenoxyacetic acid (**19**)

Following the general procedure with 13.8 g (0.1 mol) of **16**, gave 15.7 g (80%) of **19** as a white solid: R_f 0.35 (hexane/EtOAc/AcOH, 1:1:0.1); mp 121–122°C [lit. (Guha, 1950) 121–122°C]; IR (KBr) 3550–2490, 1771, 1740, 1511, 1466, 1269, 1146, 1037, 816 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.28 (s, 3H, CH_3), 3.84 (s, 3H, OCH_3), 4.64 (s, 2H, OCH_2), 6.67 (br d, J = 8.1 Hz, 1H, H-5), 6.71 (br s, 1H, H-3), 6.77 (d, J = 8.1 Hz, 1H, H-6), 10.58 (br s, 1H, CO_2H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 21.0 (CH_3), 55.7 (OCH_3), 67.3 (OCH_2), 113.0 (C-6), 115.8 (C-3), 121.0 (C-5), 133.2 (C-4), 144.7 (C-1), 149.3 (C-2), 173.8 (CO); MS (70 eV) m/z 196 (M^+, 100), 137 (82), 109 (35), 91 (23), 77 (13).

2-Methoxyphenoxyacetic acid (**23**)

Following the general procedure with 12.4 g (0.1 mol) of **20**, gave 15.5 g (85%) of **23** as a white solid: R_f 0.65 (EtOAc/AcOH, 10:0.1); mp 120–122°C [lit. (Csiba *et al*., 1968) 128°C]; IR (KBr) 3280–2340, 1741, 1710, 1589, 1509, 1457, 1425, 1332, 1254, 1233, 1130, 1025, 753 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 3.81 (s, 3H, OCH_3), 4.69 (s, 2H, OCH_2), 6.83–7.00 (m, 4H, ArH), 7.83 (br, 1H, CO_2H); ^{13}C NMR (75.4 MHz, acetone-d_6) δ 55.2 (OCH_3), 65.6 (OCH_2), 112.5 (ArH), 114.5 (ArH), 120.6 (ArH), 122.1 (ArH), 147.7 (Ar), 149.8 (Ar), 169.8 (CO); MS (70 eV) m/z 182 (M^+, 3), 138 (7), 123 (20), 109 (7), 95 (42), 77 (100), 65 (27), 63 (17).

3-Methoxyphenoxyacetic acid (**24**)

Following the general procedure with 12.4 g (0.1 mol) of **21**, gave 14.56 g (80%) of **24** as a white solid: R_f 0.51 (hexane/EtOAc/AcOH, 1:1:0.1); mp 117–119°C [lit. (Csiba *et al*., 1968) 114–115°C]; IR (KBr) 3292–2380, 1744, 1712, 1598, 1494, 1466, 1430, 1270, 1247, 1208, 1183, 1158, 1047, 923, 842, 765 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.79 (s, 3H, OCH_3), 4.67 (s, 2H, OCH_2), 6.48–6.61 (m, 3H, H-2, H-4, H-6), 7.17–7.24 (m, 1H, H-5), 8.92 (br s, 1H, CO_2H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 55.3 (OCH_3), 64.7 (OCH_2), 101.3 (C-2), 106.3 (ArH), 107.8 (ArH), 130.1 (ArH), 158.5 (Ar), 160.9 (Ar), 174.0 (CO); MS (70 eV) m/z 182 (M^+, 7), 137 (14), 125 (26), 109 (36), 107 (22), 94 (20), 77 (100), 65 (30), 63 (42).

4-Methoxyphenoxyacetic acid (**25**)

Following the general procedure with 12.4 g (0.1 mol) of **22**, gave 15.47 g (85%) of **25** as a white solid: R_f 0.51 (hexane/EtOAc/AcOH, 1:1:0.2); mp 110-112°C [lit. (Csiba *et al*., 1968) 110–112°C]; IR (KBr) 3270–2430, 1735, 1508, 1461, 1426, 1291, 1271, 1226, 1089, 1037, 905, 825, 754 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.76 (s, 3H, OCH_3), 4.62 (s, 2H, OCH_2), 6.80–6.90 (m, 4H, ArH), 9.70 (br s, 1H, CO_2H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 55.7 (OCH_3), 65.7 (OCH_2), 114.8 (ArH), 115.9 (ArH), 151.6 (Ar), 154.7 (Ar), 174.7 (CO); MS (70 eV) m/z 182 (M^+, 4), 123 (100), 109 (15), 95 (79), 81 (19), 77 (35), 65 (54), 63 (34).

General procedure for the preparation of esters

Method A

A mixture of the corresponding phenoxyacetic acid **17–19** and **23–25** (1 mol equiv.), *p*-TsOH (0.1 mol equiv.), and the corresponding alcohol (20 mol equiv.) was stirred at room temperature for 2–12 h. The remained alcohol was removed under vacuum, the oily residue was dissolved in EtOAc (20 ml), and was washed with aqueous saturated solution of $NaHCO_3$ until neutral. The organic layer was dried (Na_2SO_4) and the solvent was removed under vacuum. The residue was purified by column chromatography over silica gel (hexane/EtOAc, 9:1).

Method B

A mixture of the corresponding phenoxyacetic acid, **17–19** and **23–25** (1.0 mol equiv.) and *N*,*N*-dimethylaminopyridine (DMAP) (0.1 mol equiv.) in dry CH_2Cl_2 (10 ml) was heated to reflux, then $SOCl_2$ (1.5 mol equiv.) was added dropwise, and maintained for 2 h. After evaporating under vacuum, the residue was added at 5°C to a stirring mixture of dry K_2CO_3 (1.1 mol equiv) and the corresponding alcohol in dry toluene (30 ml). The mixture was stirred at room temperature for 24 h, then icy H_2O (10 ml) was added, and extracted with toluene (3 × 20 ml). The organic layer was washed with brine (3 × 10 ml), dried (Na_2SO_4), and the solvent was removed under vacuum. The residue was purified by column chromatography over silica gel (hexane/EtOAc, 9:1).

Isopropyl phenoxyacetate (**8a**) (Rivalle and Bisagni, 1972)

Following method A, with a mixture of 1.0 g (6.6 mmol) of **17**, 0.11 g (0.66 mmol) of *p*-TsOH, and 7.92 g (132 mmol) of *i*-PrOH, gave 1.1 g (86%) of **8a** as a colorless oil: *Rf* 0.40 (hexane/EtOAc, 9:1); IR (film) 2981, 1780, 1753, 1599, 1494, 1377, 1287, 1200, 1100, 1086, 754, 691 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.26 (d, $J = 6.3$ Hz, 3H, $(CH_3)_2CHOCO$), 4.58 (s, 2H, OCH_2), 5.14 (sep, $J = 6.3$ Hz, 1H, $(CH_3)_2CHO$), 6.87–6.93 (m, 2H, H-2, H-6), 6.95–7.02 (m, 1H, H-4), 7.24–7.32 (m, 2H, H-3, H-5); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 21.6 ($OCH(CH_3)_2$), 65.4 (OCH_2), 69.0 ($OCH(CH_3)_2$), 114.5 (C-2, C-6), 121.5 (C-4), 129.4 (C-3, C-5), 157.7 (C-1) 168.4 (CO_2); MS (70 eV) m/z 194 (M^+, 64), 152 (3), 107 (100), 94 (19), 77 (65), 65 (5), 51 (17), 43 (44). Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.26. Found: C, 68.30; H, 7.14.

n-Propyl phenoxyacetate (**8b**) (Tolstikov *et al.*, 1983)

Following method A, with a mixture of 1.0 g (6.6 mmol) of **17**, 0.11 g (0.66 mmol) of *p*-TsOH, and 7.92 g (132 mmol) of *n*-PrOH, gave 1.07 g (84%) of **8b** as a colorless oil: *Rf* 0.50 (hexane/EtOAc, 9:1); IR (film) 2967, 1758, 1734, 1599, 1495, 1288, 1193, 1087, 754, 691 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, $J = 7.3$ Hz, 3H, $CH_3CH_2CH_2O$), 1.58–1.71 (m, 2H, $CH_3CH_2CH_2O$), 4.13

(t, $J = 6.6$ Hz, 2H, $CH_3CH_2CH_2O$), 4.59 (s, 2H, OCH_2), 6.86–6.91 (m, 2H, ArH), 6.93–6.99 (m, 1H, ArH), 7.22–7.30 (m, 2H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 10.0 ($CH_3CH_2CH_2O$), 21.7 ($CH_3CH_2CH_2O$), 65.0 ($CH_3CH_2CH_2O$), 65.5 (OCH_2), 114.4 (ArH), 121.4 (ArH), 129.3 (ArH), 157.6 (Ar), 168.8 (CO_2); MS (70 eV) m/z 194 (M^+, 76), 152 (13), 107 (100), 94 (22), 79 (26), 77 (74), 65 (10), 51 (19), 43 (32). Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.26. Found: C, 67.96; H, 7.13.

n-Amyl phenoxyacetate (**8c**)

Following method A, with a mixture of 1.0 g (6.6 mmol) of **17**, 0.11 g (0.66 mmol) of *p*-TsOH, and 11.6 g (130 mmol) of *n*-amylOH, gave 1.19 g (81%) of **8c** as a colorless oil: *Rf* 0.44 (hexane/EtOAc, 9:1); IR (film) 2956, 2932, 1759, 1735, 1596, 1495, 1286, 1192, 1086, 754, 690 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, $J = 6.9$ Hz, 3H, $CH_3(CH_2)_3CH_2O$), 1.22–1.36 (m, 4H, $2CH_2$), 1.58–1.70 (m, 2H, CH_2), 4.19 (t, $J = 6.7$ Hz, 2H, $CH_3(CH_2)_3CH_2O$), 4.61 (s, 2H, OCH_2), 6.86–6.93 (m, 2H, ArH), 6.94–7.10 (m, 1H, ArH), 7.23–7.32 (m, 2H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 13.8 ($CH_3(CH_2)_3CH_2O$), 22.1 ($CH_3CH_2(CH_2)_2CH_2O$), 27.8 ($EtCH_2CH_2CH_2O$), 28.1 ($PrCH_2CH_2O$), 65.2 (OCH_2 or $BuCH_2O$), 65.3 ($BuCH_2O$ or OCH_2), 114.5 (ArH), 121.6 (ArH), 129.4 (ArH), 157.7 (Ar), 169.0 (CO_2); MS (70 eV) m/z 222 (M^+, 64), 152 (76), 107 (100), 94 (29), 79 (26), 77 (85), 65 (11), 51 (19), 43 (81). Anal. Calcd. for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.10; H, 7.97.

n-Dodecyl phenoxyacetate (**8d**)

Following method B, with 1.0 g (6.6 mmol) of **17**, 0.079 g (0.65 mmol) of DMAP in CH_2Cl_2 (20 ml), 1.18 g (9.9 mmol) of $SOCl_2$, 0.99 g (7.2 mmol) of K_2CO_3, and 1.34 g (7.2 mmol) of *n*-dodecyl alcohol in toluene (30 ml), gave 1.68 g (80%) of **8d** as a colorless oil: *Rf* 0.51 (hexane/EtOAc, 9:1); IR (film) 2924, 2854, 1762, 1735, 1597, 1496, 1286, 1192, 1087, 753, 690 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, $J = 6.7$ Hz, 3H, $CH_3(CH_2)_{10}CH_2O$), 1.25 (br s, 18H, $9CH_2$), 1.58–1.67 (m, 2H, CH_2), 4.18 (t, $J = 6.7$ Hz, 2H, $CH_3(CH_2)_{10}CH_2O$), 4.62 (s, 2H, OCH_2), 6.85–6.93 (m, 2H, ArH), 6.95–7.01 (m, 1H, ArH), 7.24–7.32 (m, 2H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 14.1 (CH_3), 22.7 (CH_2), 25.7 (CH_2), 28.5 (CH_2), 29.1 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 29.59 (CH_2), 29.61 (CH_2), 31.9 (CH_2), 65.3 ($ArOCH_2$ or $CH_3(CH_2)_{10}CH_2O$), 65.4 ($CH_3(CH_2)_{10}CH_2O$ or $ArOCH_2$), 114.6 (ArH), 121.6 (ArH), 129.5 (ArH), 157.8 (Ar), 169.1 (CO_2); MS (70 eV) m/z 320 (M^+, 90), 213 (4), 152 (100), 107 (65), 77 (41), 57 (19), 43 (26). Anal. Calcd. for $C_{20}H_{32}O_3$: C, 74.95; H, 10.06. Found: C, 74.69; H, 9.99.

4-Chlorophenyl phenoxyacetate (**8e**)

Following method B, with 1.0 g (6.6 mmol) of **17**, 0.079 g (0.65 mmol) of DMAP in CH_2Cl_2 (20 ml), 1.18 g (9.9 mmol) of $SOCl_2$, 0.99 g (7.2 mmol) of K_2CO_3, and 0.92 g (7.2 mmol) of 4-chlorophenol in toluene (30 ml), gave 1.22 g (71%) of **8e** as a white solid: *Rf* 0.37 (hexane/EtOAc, 9:1); mp 100–101°C [lit. (Khan and Bahel,

1976) 82°C]; IR (KBr) 3093, 3059, 1775, 1591, 1493, 1436, 1229, 1174, 1088, 849, 751, 692 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.86 (s, 2H, OCH_2), 6.94–7.01 (m, 2H, ArH), 7.02–7.09 (m, 3H, ArH), 7.28–7.38 (m, 4H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 65.3 (OCH_2), 114.7 (PhH), 122.1 (PhH), 122.6 (ArH), 129.6 (PhH or ArH), 129.7 (ArH or PhH), 131.6 (Ar), 148.5 (Ar), 157.6 (Ph), 169.3 (CO_2); MS (70 eV) m/z 264 ($M^+ + 2$, 8), 262 (M^+, 19), 236 (5), 234 (13), 141 (8), 128 (9), 107 (100), 99 (17), 79 (19), 77 (55), 63 (9), 51 (15). Anal. Calcd. for $C_{14}H_{11}ClO_3$: C, 64.01; H, 4.22. Found: C, 63.85; H, 4.10.

Isopropyl 4-methylphenoxyacetate (**9a**) (Rivalle and Bisagni, 1972)

Following method A, with a mixture of 1.0 g (6.0 mmol) of **18**, 0.1 g (0.6 mmol) of *p*-TsOH, and 7.2 g (120 mmol) of *i*-PrOH, gave 1.01 g (81%) of **9a** as a colorless oil: *Rf* 0.43 (hexane/EtOAc, 9:1); IR (film) 2981, 2925, 1756, 1730, 1511, 1288, 1200, 1178, 1107, 1081, 817 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (d, $J = 6.3$ Hz, 6H, $OCH(CH_3)_2$), 2.26 (s, 3H, CH_3), 4.53 (s, 2H, OCH_2), 5.12 (m, $J = 6.3$ Hz, 1H, $OCH(CH_3)_2$), 6.74–6.82 (m, 2H, ArH), 7.03–7.09 (m, 2H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 20.2 (CH_3Ar), 21.5 (($OCH(CH_3)_2$)), 65.5 (OCH_2), 68.7 ($OCH(CH_3)_2$), 114.3 (ArH), 129.7 (ArH), 130.6 (Ar), 155.6 (Ar), 168.4 (CO_2); MS (70 eV) m/z 208 (M^+, 85), 166 (40), 121 (100), 108 (22), 91 (64), 77 (14), 65 (24), 43 (42).

n-Propyl 4-methylphenoxyacetate (**9b**) (Voronkov *et al.*, 1990)

Following method A, with a mixture of 1.0 g (6.0 mmol) of **18**, 0.1 g (0.6 mmol) of *p*-TsOH, and 7.2 g (120 mmol) of *n*-PrOH, gave 1.0 g (80%) of **9b** as a colorless oil: *Rf* 0.45 (hexane/EtOAc, 9:1); IR (film) 2967, 2927, 1759, 1734, 1511, 1289, 1193, 1084, 817 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, $J = 7.3$ Hz, 3H, $OCH_2CH_2CH_3$), 1.61–1.73 (m, 2H, $OCH_2CH_2CH_3$), 2.27 (s, 3H, CH_3Ar), 4.14 (t, $J = 6.7$ Hz, 2H, $OCH_2CH_2CH_3$), 4.57 (s, 2H, OCH_2), 6.77–6.83 (m, 2H, ArH), 7.02–7.08 (m, 2H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 10.0 ($CH_3CH_2CH_2OCO$), 20.2 (CH_3Ar), 21.7 ($CH_3CH_2CH_2OCO$), 65.3 (OCH_2), 66.5 ($CH_3CH_2CH_2OCO$), 114.3 (ArH), 129.7 (ArH), 130.6 (Ar), 155.6 (Ar), 169.0 (CO_2); MS (70 eV) m/z 208 (M^+, 100), 166 (9), 121 (81), 108 (17), 107 (16), 91 (59), 77 (15), 65 (17).

n-Amyl 4-methylphenoxyacetate (**9c**)

Following method A, with a mixture of 1.0 g (6.0 mmol) of **18**, 0.1 g (0.6 mmol) of *p*-TsOH, and 10.6 g (120 mmol) of *n*-amyl alcohol, gave 1.2 g (85%) of **9c** as a colorless oil: *Rf* 0.55 (hexane/EtOAc, 9:1); IR (film) 2957, 2928, 1760, 1734, 1511, 1288, 1192, 1084, 817 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, $J = 6.9$ Hz, 3H, $OCH_2(CH_2)_3CH_3$), 1.22–1.36 (m, 4H, $2CH_2$), 1.54–1.67 (m, 2H, CH_2), 2.25 (s, 3H, CH_3Ar), 4.15 (t, $J = 6.9$ Hz, 2H, $OCH_2(CH_2)_3CH_3$), 4.55 (s, 2H, OCH_2), 6.73–6.82 (m, 2H, ArH), 6.98–7.08 (m, 2H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 13.8 ($CH_3(CH_2)_3CH_2O$), 20.3 (CH_3Ar), 22.1 ($CH_3CH_2(CH_2)_2CH_2O$), 27.7 ($EtCH_2CH_2CH_2O$), 28.1 ($PrCH_2CH_2O$), 65.2 (OCH_2 or $BuCH_2O$), 65.3 ($BuCH_2O$

or OCH_2), 114.3 (ArH), 129.8 (ArH), 130.7 (Ar), 155.6 (Ar), 169.1 (CO_2); MS (70 eV) m/z 236 (M^+, 100), 166 (58), 121 (89), 108 (28), 91 (66), 77 (14), 65 (14). Anal. Calcd. for $C_{14}H_{20}O_3$: C, 71.15; H, 8.53. Found: C, 71.21; H, 8.36.

n-Dodecyl 4-methylphenoxyacetate (**9d**)

Following method B, with 1.0 g (6.0 mmol) of **18**, 0.073 g (0.6 mmol) of DMAP in CH_2Cl_2 (20 ml), 1.07 g (9.0 mmol) of $SOCl_2$, 0.91 g (6.6 mmol) of K_2CO_3, and 1.22 g (6.6 mmol) of *n*-dodecyl alcohol in toluene (30 ml), gave 1.67 g (83%) of **9d** as a colorless oil: *Rf* 0.62 (hexane/EtOAc, 9:1); IR (film) 2922, 2853, 1761, 1737, 1512, 1461, 1288, 1187, 1083, 817 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, $J = 6.7$ Hz, 3H, $OCH_2CH_2(CH_2)_9CH_3$), 1.27 (sa, 18H, $9CH_2$), 1.58–1.68 (m, 2H, $OCH_2CH_2(CH_2)_9CH_3$), 2.27 (s, 3H, CH_3Ar), 4.18 (t, $J = 6.7$ Hz, 2H, $OCH_2(CH_2)_{10}CH_3$), 4.57 (s, 2H, OCH_2), 6.76–6.83 (m, 2H, ArH), 7.03–7.10 (m, 2H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 14.0 (CH_3), 20.3 (CH_3Ar), 22.6 (CH_2), 25.7 (CH_2), 28.4 (CH_2), 29.1 (CH_2), 29.2 (CH_2), 29.4 (CH_2), 29.45 (CH_2), 29.53 (CH_2), 29.54 (CH_2), 31.8 (CH_2), 65.2 ($CH_3(CH_2)_{10}CH_2O$ or OCH_2), 65.4 (OCH_2 or $CH_3(CH_2)_{10}CH_2O$), 114.4 (ArH), 129.8 (ArH), 130.7 (Ar), 155.7 (Ar), 169.0 (CO_2); MS (70 eV) m/z 334 (M^+, 52), 166 (90), 121 (100), 108 (33), 91 (73), 69 (20), 57 (40), 55 (35), 43 (53). Anal. Calcd. for $C_{21}H_{34}O_3$: C, 74.04; H, 10.25. Found: C, 75.61; H, 10.12.

4-Chlorophenyl 4-methylphenoxyacetate (**9e**)

Following method B, with 1.0 g (6.0 mmol) of **18**, 0.073 g (0.6 mmol) of DMAP in CH_2Cl_2 (20 ml), 1.07 g (9.0 mmol) of $SOCl_2$, 0.91 g (6.6 mmol) of K_2CO_3, and 0.85 g (6.6 mmol) of 4-chlorophenol in toluene (30 ml), gave 1.13 g (68%) of **8e** as a white solid: *Rf* 0.55 (hexane/ EtOAc, 9:1); mp 105–106°C [lit. (Khan and Bahel, 1976) 83°C]; IR (KBr) 1767, 1513, 1488, 1252, 1206, 1084, 848, 811 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.29 (s, 3H, CH_3Ar), 4.82 (s, 2H, OCH_2), 6.83–6.90 (m, 2H, ArH), 7.02–7.08 (m, 2H, Ar′H), 7.08–7.14 (m, 2H, ArH), 7.30–7.36 (m, 2H, Ar′H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 20.5 (CH_3Ar), 65.6 (OCH_2), 114.3 (ArH), 122.6 (Ar′H), 129.6 (ArH or Ar′H), 130.1 (Ar′H or ArH), 131.4 (Ar), 131.6 (Ar′), 148.5 (Ar′), 155.7 (Ar), 167.5 (CO_2); MS (70 eV) m/z 278 (M^++2, 11), 276 (M^+, 26), 248 (6), 141 (6), 121 (100), 99 (20), 91 (62), 65 (23).

Isopropyl 2-(2-methoxy-4-methylphenoxy)acetate (**10a**)

Following method A, with a mixture of 1.0 g (5.1 mmol) of **19**, 0.088 g (0.51 mmol) of *p*-TsOH, and 6.12 g (102 mmol) of *i*-PrOH, gave 1.03 g (85%) of **10a** as a pale yellow oil: *Rf* 0.43 (hexane/EtOAc, 8:2); IR (film) 2980, 2936, 1754, 1729, 1512, 1465, 1267, 1200, 1146, 1107, 1069, 1036, 800 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (d, $J = 6.3$ Hz, 6H, $OCH(CH_3)_2$), 2.29 (s, 3H, CH_3Ar), 3.86 (s, 3H, OCH_3), 4.61 (s, 2H, OCH_2), 5.12 (m, 2H, $OCH(CH_3)_2$), 6.63–6.75 (m, 3H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 20.9 (CH_3Ar), 21.6 ($OCH(CH_3)_2$), 55.6 (OCH_3), 66.8 (OCH_2), 68.7 ($OCH(CH_3)_2$), 112.9 (C-6), 114.4 (C-3), 120.6 (C-5), 132.0 (C-4), 145.0 (C-1), 149.2 (C-2), 168.6 (CO_2); MS (70 eV) m/z 238 (M^+, 68),

196 (32), 151 (39), 137 (100), 123 (14), 109 (17), 91 (29), 77 (10). Anal. Calcd. for $C_{13}H_{18}O_4$: C, 65.52; H, 7.61. Found: C, 65.32; H, 7.50.

n-Propyl 2-(2-methoxy-4-methylphenoxy)acetate (**10b**)

Following method A, with a mixture of 1.0 g (5.1 mmol) of **19**, 0.088 g (0.51 mmol) of *p*-TsOH, and 6.12 g (102 mmol) of *n*-PrOH, gave 1.04 g (86%) of **10b** as a colorless oil: *Rf* 0.40 (hexane/EtOAc, 8:2); IR (film) 2966, 2937, 1758, 1732, 1511, 1464, 1266, 1192, 1145, 1073, 1036, 799 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, $J = 7.2$ Hz, 3H, $OCH_2CH_2CH_3$), 1.57–1.70 (m, 2H, $OCH_2CH_2CH_3$), 2.27 (s, 3H, CH_3Ar), 3.83 (s, 3H, OCH_3), 4.11 (t, $J = 6.7$ Hz, 2H, $OCH_2CH_2CH_3$), 4.63 (s, 2H, OCH_2), 6.61–6.73 (m, 3H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 10.1 ($OCH_2CH_2CH_3$), 20.9 (CH_3Ar), 21.8 ($OCH_2CH_2CH_3$), 55.6 (OCH_3), 66.58 (OCH_2 or $OCH_2CH_2CH_3$), 66.60 ($OCH_2CH_2CH_3$ or OCH_2), 112.9 (C-6), 114.4 (C-3), 120.6 (C-5), 132.1 (C-4), 145.0 (C-1), 149.2 (C-2), 169.2 (CO_2); MS (70 eV) m/z 238 (M^+, 100), 196 (2), 151 (18), 137 (83), 123 (12), 109 (31), 91 (30), 77 (14). Anal. Calcd. for $C_{13}H_{18}O_4$: C, 65.52; H, 7.61. Found: C, 65.38; H, 7.72.

n-Amyl 2-(2-methoxy-4-methylphenoxy)acetate (**10c**)

Following method A, with a mixture of 1.0 g (5.1 mmol) of **19**, 0.088 g (0.51 mmol) of *p*-TsOH, and 8.98 g (102 mmol) of *n*-amylOH, gave 1.15 g (85%) of **10c** as a colorless oil: *Rf* 0.48 (hexane/EtOAc, 8:2); IR (film) 2957, 2932, 1759, 1734, 1512, 1464, 1267, 1192, 1147, 1073, 1037, 799 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.86 (t, $J = 6.7$ Hz, 3H, $OCH_2(CH_2)_3CH_3$), 1.20–1.32 (m, 4H, $OCH_2(CH_2)_3CH_3$), 1.55–1.66 (m, 2H, $OCH_2(CH_2)_3CH_3$), 2.27 (s, 3H, CH_3Ar), 3.83 (s, 3H, OCH_3), 4.15 (t, $J = 6.7$ Hz, 2H, $OCH_2(CH_2)_3CH_3$), 4.63 (s, 2H, OCH_2), 6.61–6.73 (m, 3H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 13.8 ($OCH_2(CH_2)_3CH_3$), 20.9 (CH_3Ar), 22.1 ($OCH_2(CH_2)_2CH_2CH_3$), 27.8 ($O(CH_2)_2CH_2CH_2CH_3$), 28.1 ($OCH_2CH_2(CH_2)_2CH_3$), 55.6 (OCH_3), 65.1 ($OCH_2(CH_2)_3CH_3$), 66.7 (OCH_2), 113.0 (C-6), 114.5 (C-3), 120.7 (C-5), 132.1 (C-4), 145.0 (C-1), 149.3 (C-2), 169.2 (CO_2); MS (70 eV) m/z 266 (M^+, 49), 196 (4), 151 (13), 137 (100), 123 (11), 109 (24), 91 (33), 77 (14). Anal. Calcd. for $C_{15}H_{22}O_4$: C, 67.64; H, 8.32. Found: C, 67.74; H, 8.16.

n-Dodecyl 2-(2-methoxy-4-methylphenoxy)acetate (**10d**)

Following method B, with 1.0 g (5.1 mmol) of **19**, 0.062 g (0.51 mmol) of DMAP in CH_2Cl_2 (20 ml), 0.91 g (7.6 mmol) of $SOCl_2$, 0.77 g (5.6 mmol) of K_2CO_3, and 1.04 g (5.6 mmol) of *n*-dodecyl alcohol in toluene (30 ml), gave 1.41 g (76%) of **10d** as a colorless oil: *Rf* 0.54 (hexane/EtOAc, 8:2); IR (film) 2923, 2853, 1760, 1737, 1512, 1462, 1268, 1192, 1152, 1073, 1037, 799 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.85 (t, $J = 6.9$ Hz, 3H, $OCH_2CH_2(CH_2)_9CH_3$), 1.23 (br s, 18H, $9CH_2$), 1.56–1.63 (m, 2H, $OCH_2CH_2(CH_2)_9CH_3$), 2.27 (s, 3H, CH_3Ar), 3.83 (s, 3H, OCH_3), 4.15 (t, $J = 6.9$ Hz, 2H, $OCH_2(CH_2)_{10}CH_3$), 4.63 (s, 2H, OCH_2), 6.61–6.73 (m, 3H,

ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 14.0 (CH_3), 20.9 (CH_3Ar), 22.6 (CH_2), 25.7 (CH_2), 28.4 (CH_2), 29.1 (CH_2), 29.2 (CH_2), 29.41 (CH_2), 29.46 (CH_2), 29.53 (CH_2), 29.55 (CH_2), 31.8 (CH_2), 55.7 (OCH_3), 65.2 ($CH_3(CH_2)_{10}CH_2O$), 66.6 (OCH_2), 113.0 (C-6), 114.4 (C-3), 120.7 (C-5), 132.1 (C-4), 145.0 (C-1), 149.3 (C-2), 169.2 (CO_2); MS (70 eV) m/z 364 (M^+, 100), 320 (45), 196 (7), 152 (59), 137 (42), 107 (34), 77 (26), 43 (30). Anal. Calcd. for $C_{22}H_{36}O_4$: C, 72.42; H, 9.95. Found: C, 72.21; H, 9.82.

4-Chlorophenyl 2-(2-methoxy-4-methylphenoxy)acetate (**10e**)

Following method B, with 1.0 g (5.1 mmol) of **19**, 0.062 g (0.51 mmol) of DMAP in CH_2Cl_2 (20 ml), 0.91 g (7.6 mmol) of $SOCl_2$, 0.77 g (5.6 mmol) of K_2CO_3, and 0.72 g (5.6 mmol) of 4-chlorophenol in toluene (30 ml), gave 1.0 g (64%) of **10e** as a white solid: *Rf* 0.4 (hexane/EtOAc, 8:2); mp 90–91°C (hexane/EtOAc, 8:2); IR (KBr) 1780, 1512, 1487, 1264, 1200, 1141, 1085, 1038, 841 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.31 (s, 3H, CH_3Ar), 3.86 (s, 3H, OCH_3), 4.88 (s, 2H, OCH_2), 6.69 (dm, $J = 8.1$ Hz, 1H, H-5), 6.74 (d, $J = 1.8$ Hz, 1H, H-3), 6.85 (d, $J = 8.1$ Hz, 1H, H-6), 7.02–7.07 (m, 2H, Ar′H), 7.29–7.34 (m, 2H, Ar′H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 21.0 (CH_3Ar), 55.7 (OCH_3), 67.0 (OCH_2), 113.2 (C-6), 115.5 (C-3), 120.8 (C-5), 122.6 (C-2′, C-6′), 129.4 (C-3′, C-5’), 131.4 (C-4′), 132.9 (C-4), 144.8 (C-1), 148.5 (C-1′), 149.6 (C-2), 167.6 (CO_2); MS (70 eV) m/z 308 (M^++2, 14), 306 (M^+, 41), 151 (100), 136 (97), 123 (8), 91 (30), 77 (13). Anal. Calcd. for $C_{16}H_{15}ClO_4$: C, 62.65; H, 4.93. Found: C, 62.63; H, 5.05.

Methyl 2-(2-methoxyphenoxy)acetate (**11a**)

Following method A, with a mixture of 1.0 g (5.5 mmol) of **23**, 0.095 g (0.55 mmol) of *p*-TsOH, and 3.5 g (110 mmol) of MeOH, gave 0.97 g (90%) of **11a** as a white solid: *Rf* 0.43 (2× hexane/EtOAc, 8:2); mp 48–50°C (hexane/EtOAc, 8:2) [lit. (Ahvonen *et al*., 1983) 47°C]; IR (film) 2953, 1759, 1504, 1444, 1252, 1206, 1178, 1128, 1027, 747 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.77 (s, 3H, CH_3OCO), 3.86 (s, 3H, OCH_3), 4.68 (s, 2H, OCH_2), 6.79–7.00 (m, 4H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 52.2 (CH_3OCO), 55.8 (OCH_3), 66.3 (OCH_2), 111.9 (ArH), 114.1 (ArH), 120.6 (ArH), 122.5 (ArH), 147.1 (Ar), 149.5 (Ar), 169.5 (CO_2); MS (70 eV) m/z 196 (M^+, 100), 137 (25), 123 (40), 122 (40), 95 (31), 77 (46), 65 (10).

Ethyl 2-(2-methoxyphenoxy)acetate (**11b**) (Myska *et al*., 1961)

Following method A, with a mixture of 1.0 g (5.5 mmol) of **23**, 0.095 g (0.55 mmol) of *p*-TsOH, and 5.1 g (110 mmol) of EtOH, gave 1.06 g (92%) of **11b** as a colorless oil: *Rf* 0.52 (2× hexane/EtOAc, 8:2); IR (film) 2980, 1756, 1734, 1593, 1502, 1458, 1252, 1196, 1178, 1128, 1073, 1027, 746 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (t, $J = 7.2$ Hz, 3H, OCH_2CH_3), 3.84 (s, 3H, OCH_3), 4.21 (q, $J = 7.2$ Hz, 2H, OCH_2CH_3), 4.65 (s, 2H, OCH_2), 6.78–6.97 (m, 4H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 14.0 (OCH_2CH_3), 55.7 (OCH_3), 61.1 (OCH_2CH_3), 66.3

(OCH_2), 111.9 (ArH), 114.1 (ArH), 120.5 (ArH), 122.3 (ArH), 147.1 (Ar), 149.4 (Ar), 168.9 (CO_2); MS (70 eV) m/z 210 (M^+, 100), 137 (35), 123 (37), 122 (55), 109 (14), 95 (25), 77 (41).

Isopropyl 2-(2-methoxyphenoxy)acetate (**11c**) (Myska *et al*., 1961)

Following method A, with a mixture of 1.0 g (5.5 mmol) of **23**, 0.095 g (0.55 mmol) of *p*-TsOH, and 6.6 g (110 mmol) of *n*-PrOH, which was heated to 60°C for 12 h to give 1.08 g (88%) of **11c** as a colorless oil: *Rf* 0.41 (hexane/EtOAc, 8:2); IR (film) 2980, 2937, 1753, 1729, 1593, 1502, 1457, 1376, 1285, 1199, 1177, 1128, 1106, 1070, 1027, 743 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.22 (d, $J = 6.3$ Hz, 6H, $OCH(CH_3)_2$), 3.85 (s, 3H, OCH_3), 4.62 (s, 2H, OCH_2), 5.10 (sep, $J = 6.3$ Hz, 1H, $OCH(CH_3)_2$), 6.77–6.98 (m, 4H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 21.7 ($OCH(CH_3)_2$), 55.8 (OCH_3), 66.5 (OCH_2), 68.9 ($OCH(CH_3)_2$), 112.0 (ArH), 114.2 (ArH), 120.6 (ArH), 122.3 (ArH), 147.3 (Ar), 149.5 (Ar), 168.5 (CO_2); MS (70 eV) m/z 224 (M^+, 100), 182 (34), 137 (68), 123 (50), 122 (85), 109 (22), 95 (20), 92 (24), 77 (61), 65 (11), 51 (11), 43 (56).

n-Propyl 2-(2-Methoxyphenoxy)acetate (**11d**) (Myska *et al*., 1961)

Following method A, with a mixture of 1.0 g (5.5 mmol) of **23**, 0.095 g (0.55 mmol) of *p*-TsOH, and 6.6 g (110 mmol) of *n*-PrOH, gave 1.06 g (86%) of **11d** as a colorless oil: *Rf* 0.59 (2× hexane/EtOAc, 8:2); IR (film) 2965, 2837, 1756, 1733, 1593, 1501, 1458, 1250, 1192, 1176, 1126, 1072, 1027, 970, 744 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, $J = 7.3$ Hz, 3H, $OCH_2CH_2CH_3$), 1.57–1.70 (m, 2H, $OCH_2CH_2CH_3$), 3.85 (s, 3H, OCH_3), 4.12 (t, $J = 6.7$ Hz, 2H, $OCH_2CH_2CH_3$), 4.67 (s, 2H, OCH_2), 6.77–6.99 (m, 4H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 10.1 ($OCH_2CH_2CH_3$), 21.8 ($OCH_2CH_2CH_3$), 55.7 (OCH_3), 66.3 (OCH_2), 66.6 ($OCH_2CH_2CH_3$), 111.9 (ArH), 114.0 (ArH), 120.5 (ArH), 122.3 (ArH), 147.1 (Ar), 149.4 (Ar), 169.0 (CO_2); MS (70 eV) m/z 224 (M^+, 99), 182 (4), 137 (65), 123 (84), 122 (100), 109 (33), 95 (42), 93 (30), 77 (84), 65 (18), 52 (19), 52 (19), 43 (24).

n-Amyl 2-(2-methoxyphenoxy)acetate (**11e**)

Following method A, with a mixture of 1.0 g (5.5 mmol) of **23**, 0.095 g (0.55 mmol) of *p*-TsOH, and 9.7 g (110 mmol) of *n*-amylOH, gave 1.24 g (90%) of **11e** as a colorless oil: *Rf* 0.45 (hexane/EtOAc, 8:2); IR (film) 2965, 2932, 2870, 1758, 1733, 1593, 1502, 1459, 1250, 1192, 1176, 1127, 1073, 1027, 975, 743 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.82 (t, $J = 6.9$ Hz, 3H, $OCH_2(CH_2)_3CH_3$), 1.18–1.28 (m, 4H, $OCH_2(CH_2)_3CH_3$), 1.53–1.62 (m, 2H, $OCH_2(CH_2)_3CH_3$), 3.80 (s, 3H, OCH_3), 4.12 (t, $J = 6.7$ Hz, 2H, $OCH_2(CH_2)_3CH_3$), 4.63 (s, 2H, OCH_2), 6.75–6.94 (m, 4H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 13.7 ($OCH_2(CH_2)_3CH_3$), 22.0 ($OCH_2(CH_2)_2CH_2CH_3$), 27.6 ($O(CH_2)_2CH_2CH_2CH_3$), 28.0 ($OCH_2CH_2(CH_2)_2CH_3$), 55.6 (OCH_3), 65.0 ($OCH_2(CH_2)_3CH_3$), 66.2 (OCH_2), 111.9 (ArH), 114.1 (ArH), 120.4 (ArH), 122.2 (ArH), 147.1 (Ar), 149.4 (Ar), 168.9 (CO_2); MS (70 eV) m/z

252 (M^+, 89), 182 (14), 137 (62), 123 (88), 122 (100), 109 (29), 95 (34), 93 (27), 77 (80), 65 (15), 43 (34). Anal. Calcd. for $C_{14}H_{20}O_4$: C, 66.64; H, 7.94. Found: C, 66.83; H, 7.95.

n-Dodecyl 2-(2-Methoxyphenoxy)acetate (**11f**)

Following method B, with a mixture of 1.0 g (5.5 mmol) of **23**, 0.067 g (0.55 mmol) of DMAP in CH_2Cl_2 (20 ml), 0.98 g (8.25 mmol) of $SOCl_2$, 0.835 g (6.05 mmol) of K_2CO_3, and 1.12 g (6.05 mmol) of *n*-dodecyl alcohol in toluene (30 ml), gave 1.63 g (85%) of **11f** as a colorless oil: *Rf* 0.55 (hexane/EtOAc, 8:2); IR (film) 2928, 2853, 1760, 1593, 1503, 1460, 1252, 1177, 1128, 1073, 1029, 742 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.85 (t, $J = 6.7$ Hz, 3H, $OCH_2CH_2(CH_2)_9CH_3$), 1.27 (br s, 18H, $9CH_2$), 1.54–1.64 (m, 2H, $OCH_2CH_2(CH_2)_9CH_3$), 3.86 (s, 3H, OCH_3), 4.16 (t, $J = 6.7$ Hz, 2H, $OCH_2(CH_2)_{10}CH_3$), 4.67 (s, 2H, OCH_2), 6.78–6.99 (m, 4H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 14.1 (CH_3), 22.6 (CH_2), 25.7 (CH_2), 28.5 (CH_2), 29.1 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 29.50 (CH_2), 29.57 (CH_2), 29.59 (CH_2), 31.9 (CH_2), 55.8 (OCH_3), 65.3 ($CH_3(CH_2)_{10}CH_2O$), 66.4 (OCH_2), 112.0 (ArH), 114.2 (ArH), 120.7 (ArH), 122.4 (ArH), 147.3 (Ar), 149.6 (Ar), 169.1 (CO_2); MS (70 eV) m/z 350 (M^+, 100), 182 (29), 137 (72), 123 (51), 122 (77), 109 (16), 95 (24), 77 (53), 55 (45), 43 (64).

4-Chlorophenyl 2-(2-methoxyphenoxy)acetate (**11g**)

Following method B, with a mixture of 1.0 g (5.5 mmol) of **23**, 0.067 g (0.55 mmol) of DMAP in CH_2Cl_2 (20 ml), 0.98 g (8.25 mmol) of $SOCl_2$, 0.835 g (6.05 mmol) of K_2CO_3, and 0.72 g (5.6 mmol) of 4-chlorophenol in toluene (30 ml), gave 1.28 g (80%) of **11g** as a white solid: *Rf* 0.52 (2× hexane/EtOAc, 8:2); mp 93–94°C (hexane/EtOAc, 8:2); IR (KBr) 2924, 1780, 1592, 1502, 1486, 1457, 1252, 1198, 1165, 1127, 1086, 1014, 742 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.88 (s, 3H, OCH_3), 4.91 (s, 2H, OCH_2), 6.87–7.06 (m, 6H, H-5), 7.29–7.35 (m, 2H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 55.8 (OCH_3), 66.6 (OCH_2), 112.2 (ArH), 115.1 (ArH), 120.7 (ArH), 122.6 (ArH), 123.0 (ArH), 129.5 (ArH), 131.4 (Ar), 147.0 (Ar), 148.5 (Ar), 149.8 (Ar), 167.5 (CO_2); MS (70 eV) m/z 294 (M^++2, 3), 292 (M^+, 14), 137 (100), 122 (78), 92 (22), 77 (44). Anal. Calcd. for $C_{15}H_{13}ClO_4$: C, 61.54; H, 4.47. Found: C, 61.70; H, 4.63.

Methyl 2-(3-methoxyphenoxy)acetate (**12a**) (Myska *et al.*, 1961)

Following method A, with a mixture of 1.0 g (5.5 mmol) of **24**, 0.095 g (0.55 mmol) of *p*-TsOH, and 3.5 g (110 mmol) of MeOH, gave 0.99 g (92%) of **12a** as a colorless oil: *Rf* 0.30 (hexane/EtOAc, 8:2); IR (film) 1759, 1592, 1492, 1456, 1436, 1265, 1195, 1152, 1086, 1036, 835, 760, 685 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.72 (s, 3H, CH_3OCO), 3.75 (s, 3H, OCH_3), 4.57 (s, 2H, OCH_2), 6.41–6.54 (m, 3H, ArH), 7.14 (t, $J = 8.1$ Hz, 1H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 52.0 (CH_3OCO), 55.0 (OCH_3), 64.9 (OCH_2), 101.0 (ArH), 106.0 (ArH), 107.2 (ArH), 129.8 (ArH), 158.7 (Ar), 160.6 (Ar), 169.1 (CO_2); MS

(70 eV) m/z 196 (M^+, 100), 137 (53), 109 (20), 107 (50), 92 (23), 77 (31), 64 (15), 63 (13).

Ethyl 2-(3-methoxyphenoxy)acetate (**12b**) (Myska *et al*., 1961)

Following method A, with a mixture of 1.0 g (5.5 mmol) of **24**, 0.095 g (0.55 mmol) of *p*-TsOH, and 5.1 g (110 mmol) of EtOH, gave 1.0 g (88%) of **12b** as a colorless oil: *Rf* 0.40 (hexane/EtOAc, 8:2); IR (film) 1756, 1730, 1594, 1492, 1457, 1266, 1193, 1152, 1086, 1032, 835, 761, 685 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.27 (t, $J = 7.2$ Hz, 3H, OCH_2CH_3), 3.75 (s, 3H, OCH_3), 4.24 (q, $J = 7.2$ Hz, 2H, OCH_2CH_3), 4.57 (s, 2H, OCH_2), 6.44–6.56 (m, 3H, ArH), 7.16 (t, $J = 8.1$ Hz, 1H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 14.0 (OCH_2CH_3), 55.0 (OCH_3), 61.1 (OCH_2CH_3), 65.1 (OCH_2), 101.1 (ArH), 106.2 (ArH), 107.3 (ArH), 129.8 (ArH), 158.8 (Ar), 160.7 (Ar), 168.7 (CO_2); MS (70 eV) m/z 210 (M^+, 100), 182 (5), 137 (60), 124 (11), 109 (23), 107 (58), 92 (27), 77 (34).

Isopropyl 2-(3-methoxyphenoxy)acetate (**12c**) (Myska *et al*., 1961)

Following method A, with a mixture of 1.0 g (5.5 mmol) of **24**, 0.095 g (0.55 mmol) of *p*-TsOH, and 6.6 g (110 mmol) of *n*-PrOH, which was heated to 60°C for 12 h to give 1.05 g (85%) of **12c** as a colorless oil: *Rf* 0.45 (hexane/EtOAc, 8:2); IR (film) 1753, 1730, 1593, 1492, 1456, 1284, 1266, 1194, 1154, 1105, 1087, 1039, 834, 762, 686 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.23 (d, $J = 6.3$ Hz, 6H, $OCH(CH_3)_2$), 3.73 (s, 3H, OCH_3), 4.52 (s, 2H, OCH_2), 5.10 (m, 1H, $OCH(CH_3)_2$), 6.41–6.54 (m, 3H, ArH), 7.13 (t, $J = 8.1$ Hz, 1H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 21.5 ($OCH(CH_3)_2$), 55.0 (OCH_3), 65.3 (OCH_2), 68.9 ($OCH(CH_3)_2$), 101.1 (ArH), 106.1 (ArH), 107.2 (ArH), 129.7 (ArH), 158.9 (Ar), 160.6 (Ar), 168.2 (CO_2); MS (70 eV) m/z 224 (M^+, 100), 182 (43), 165 (8), 137 (89), 124 (17), 109 (20), 107 (54), 92 (28), 77 (30), 64 (13), 43 (42).

n-Propyl 2-(3-Methoxyphenoxy)acetate (**12d**) (Myska *et al*., 1961)

Following method A, with a mixture of 1.0 g (5.5 mmol) of **24**, 0.095 g (0.55 mmol) of *p*-TsOH, and 6.6 g (110 mmol) of *n*-PrOH, which was heated to 60°C for 12 h to give 1.06 g (86%) of **12d** as a colorless oil: *Rf* 0.48 (hexane/EtOAc, 8:2); IR (film) 1757, 1597, 1491, 1460, 1269, 1194, 1153, 1085, 1044, 836, 736, 686 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, $J = 7.5$ Hz, 3H, $OCH_2CH_2CH_3$), 1.58–1.71 (m, 2H, $OCH_2CH_2CH_3$), 3.74 (s, 3H, OCH_3), 4.13 (t, $J = 6.6$ Hz, 2H, $OCH_2CH_2CH_3$), 4.57 (s, 2H, OCH_2), 6.43–6.54 (m, 3H, ArH), 7.14 (t, $J = 8.1$ Hz, 1H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 10.1 ($OCH_2CH_2CH_3$), 21.7 ($OCH_2CH_2CH_3$), 55.0 (OCH_3), 65.1 (OCH_2), 66.6 ($OCH_2CH_2CH_3$), 101.1 (ArH), 106.2 (ArH), 107.2 (ArH), 129.8 (ArH), 158.9 (Ar), 160.7 (Ar), 168.8 (CO_2); MS (70 eV) m/z 224 (M^+, 100), 182 (37), 165 (8), 137 (78), 124 (19), 109 (38), 107 (65), 92 (44), 77 (42), 64 (20), 63 (17).

n-Amyl 2-(3-methoxyphenoxy)acetate (**12e**)

Following method A, with a mixture of 1.0 g (5.5 mmol) of **24**, 0.095 g (0.55 mmol) of *p*-TsOH, and 9.7 g (110 mmol) of *n*-amylOH, gave 1.1 g (80%) of **12e** as a colorless oil: *Rf* 0.53 (hexane/EtOAc, 8:2); IR (film) 2958, 1759, 1736, 1596, 1492, 1460, 1267, 1193, 1154, 1087, 1042, 762, 686 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, $J = 6.9$ Hz, 3H, $OCH_2(CH_2)_3CH_3$), 1.22–1.38 (m, 4H, $OCH_2(CH_2)_3CH_3$), 1.58–1.68 (m, 2H, $OCH_2(CH_2)_3CH_3$), 3.75 (s, 3H, OCH_3), 4.18 (t, $J = 6.6$ Hz, 2H, $OCH_2(CH_2)_3CH_3$), 4.59 (s, 2H, OCH_2), 6.44–6.55 (m, 3H, ArH), 7.16 (t, $J = 8.0$ Hz, 1H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 13.8 ($OCH_2(CH_2)_3CH_3$), 22.1 ($OCH_2(CH_2)_2CH_2CH_3$), 27.8 ($O(CH_2)_2CH_2CH_2CH_3$), 28.1 ($OCH_2CH_2(CH_2)_2CH_3$), 55.1 (OCH_3), 65.2 ($OCH_2(CH_2)_3CH_3$ or OCH_2), 65.3 (OCH_2 or $OCH_2(CH_2)_3CH_3$), 101.2 (ArH), 106.2 (ArH), 107.3 (ArH), 129.8 (ArH), 158.9 (Ar), 160.7 (Ar), 168.8 (CO_2); MS (70 eV) m/z 252 (M^+, 87), 182 (13), 137 (17), 123 (100), 109 (15), 107 (13), 92 (14), 77 (17). Anal. Calcd. for $C_{14}H_{20}O_4$: C, 66.64; H, 7.94. Found: C, 66.51; H, 7.96.

n-Dodecyl 2-(3-methoxyphenoxy)acetate (**12f**)

Following method B, with a mixture of 1.0 g (5.5 mmol) of **24**, 0.067 g (0.55 mmol) of DMAP in CH_2Cl_2 (20 ml), 0.98 g (8.25 mmol) of $SOCl_2$, 0.835 g (6.05 mmol) of K_2CO_3, and 1.12 g (6.05 mmol) of *n*-dodecyl alcohol in toluene (30 ml), gave 1.57 g (82%) of **12f** as a colorless oil: *Rf* 0.63 (hexane/EtOAc, 8:2); IR (film) 2922, 2853, 1760, 1597, 1491, 1461, 1269, 1193, 1154, 1086, 1043, 835, 761, 685 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, $J = 6.6$ Hz, 3H, $OCH_2CH_2(CH_2)_9CH_3$), 1.24 (br s, 18H, $9CH_2$), 1.56–1.69 (m, 2H, $OCH_2CH_2(CH_2)_9CH_3$), 3.75 (s, 3H, OCH_3), 4.18 (t, $J = 6.6$ Hz, 2H, $OCH_2(CH_2)_{10}CH_3$), 4.58 (s, 2H, OCH_2), 6.43–6.55 (m, 3H, ArH), 7.12–7.19 (m, 1H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 14.0 (CH_3), 22.6 (CH_2), 25.7 (CH_2), 28.5 (CH_2), 29.1 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 29.50 (CH_2), 29.55 (CH_2), 29.57 (CH_2), 31.8 (CH_2), 55.1 (OCH_3), 65.3 ($CH_3(CH_2)_{10}CH_2O$ or OCH_2), 65.4 (OCH_2 or $CH_3(CH_2)_{10}CH_2O$), 101.2 (ArH), 106.3 (ArH), 107.3 (ArH), 129.9 (ArH), 159.0 (Ar), 160.8 (Ar), 168.9 (CO_2); MS (70 eV) m/z 350 (M^+, 100), 184 (52), 182 (91), 138 (15), 137 (20), 125 (9), 109 (8), 77 (6). Anal. Calcd. for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78. Found: C, 72.04; H, 9.76.

4-Chlorophenyl 2-(3-methoxyphenoxy)acetate (**12g**)

Following method B, with a mixture of 1.0 g (5.5 mmol) of **24**, 0.067 g (0.55 mmol) of DMAP in CH_2Cl_2 (20 ml), 0.98 g (8.25 mmol) of $SOCl_2$, 0.835 g (6.05 mmol) of K_2CO_3, and 0.78 g (6.05 mmol) of 4-chlorophenol in toluene (30 ml), gave 0.96 g (60%) of **12g** as a white solid: *Rf* 0.46 (hexane/EtOAc, 8:2); mp 67–68°C (hexane/EtOAc, 8:2); IR (KBr) 1780, 1598, 1488, 1266, 1198, 1146, 1086, 836, 742, 685 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.77 (s, 3H, OCH_3), 4.82 (s, 2H, OCH_2), 6.51–6.60 (m, 3H, ArH), 7.02–7.08 (m, 2H, ArH), 7.17–7.24 (m, 1H, ArH), 7.29–7.36 (m, 2H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 55.2 (OCH_3), 65.2 (OCH_2), 101.4 (ArH), 106.3 (ArH), 107.7 (ArH), 122.6 (ArH), 129.5 (ArH), 130.0

(ArH), 131.5 (Ar), 148.4 (Ar), 158.7 (Ar), 160.9 (Ar), 167.1 (CO_2); MS (70 eV) m/z 294 (M^++2, 9), 292 (M^+, 29), 165 (10), 137 (100), 109 (12),107 (45), 92 (21), 77 (25). Anal. Calcd. for $C_{15}H_{13}ClO_4$: C, 61.54; H, 4.47. Found: C, 61.51; H, 4.41.

Methyl 2-(4-Methoxyphenoxy)acetate (**13a**)

Following method A, with a mixture of 1.0 g (5.5 mmol) of **25**, 0.095 g (0.55 mmol) of *p*-TsOH, and 3.5 g (110 mmol) of MeOH, gave 1.01 g (94%) of **13a** as a white solid: *Rf* 0.49 (hexane/EtOAc, 8:2); mp 49–50°C [lit. (Hayashi *et al.*, 1983) 44–46°C] (hexane/EtOAc, 8:2); IR (film) 1759, 1507, 1438, 1201, 1178, 1083, 1031, 825 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.66 (s, 3H, CH_3OCO), 3.69 (s, 3H, OCH_3), 4.94 (s, 2H, OCH_2), 6.73–6.81 (m, 4H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 51.7 (CH_3OCO), 55.2 (OCH_3), 65.7 (OCH_2), 114.3 (ArH), 115.4 (ArH), 151.6 (Ar), 154.2 (Ar), 169.3 (CO_2); MS (70 eV) m/z 196 (M^+, 52), 137 (10), 123 (100), 107 (8), 95 (16), 77 (10).

Ethyl 2-(4-methoxyphenoxy)acetate (**13b**) (Benjamin *et al.*, 1998)

Following method A, with a mixture of 1.0 g (5.5 mmol) of **25**, 0.095 g (0.55 mmol) of *p*-TsOH, and 5.1 g (110 mmol) of EtOH, gave 1.09 g (95%) of **13b** as a colorless oil: *Rf* 0.46 (hexane/EtOAc, 8:2); IR (film) 1756, 1730, 1506, 1441, 1193, 1081, 1031, 825 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.23 (t, $J = 7.2$ Hz, 3H, OCH_2CH_3), 3.69 (s, 3H, OCH_3), 4.19 (q, $J = 7.2$ Hz, 2H, OCH_2CH_3), 4.50 (s, 2H, OCH_2), 6.73–6.83 (m, 4H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 13.9 (OCH_2CH_3), 55.3 (OCH_3), 61.0 (OCH_2CH_3), 66.0 (OCH_2), 114.3 (ArH), 115.5 (ArH), 151.7 (Ar), 154.2 (Ar), 168.9 (CO_2); MS (70 eV) m/z 210 (M^+, 57), 137 (16), 123 (100), 107 (12), 95 (10), 77 (12).

Isopropyl 2-(4-methoxyphenoxy)acetate (**13c**) (Myska *et al.*, 1961)

Following method A, with a mixture of 1.0 g (5.5 mmol) of **25**, 0.095 g (0.55 mmol) of *p*-TsOH, and 6.6 g (110 mmol) of *n*-PrOH, which was heated to 60°C for 12 h to give 1.13 g (92%) of **13c** as a colorless oil: *Rf* 0.40 (hexane/EtOAc, 8:2); IR (film) 2981, 2936, 1752, 1729, 1506, 1456, 1442, 1376, 1287, 1197, 1106, 1080, 1034, 825 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.22 (d, $J = 6.3$ Hz, 6H, $OCH(CH_3)_2$), 3.71 (s, 3H, OCH_3), 4.49 (s, 2H, OCH_2), 5.09 (sep, $J = 6.3$ Hz, 1H, $OCH(CH_3)_2$), 6.76–6.84 (m, 4H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 21.5 ($OCH(CH_3)_2$), 55.4 (OCH_3), 66.2 ($OCH(CH_3)_2$), 68.8 (OCH_2), 114.4 (ArH), 115.6 (ArH), 151.8 (Ar), 154.2 (Ar), 168.6 (CO_2); MS (70 eV) m/z 224 (M^+, 74), 182 (57), 137 (39), 123 (100), 109 (21), 107 (17), 92 (18), 77 (18).

n-Propyl 2-(4-methoxyphenoxy)acetate (**13d**) (Myska *et al.*, 1961)

Following method A, with a mixture of 1.0 g (5.5 mmol) of **25**, 0.095 g (0.55 mmol) of *p*-TsOH, and 6.6 g (110 mmol) of *n*-PrOH, gave 1.16 g (95%) of **13d** as a colorless oil: *Rf* 0.49 (hexane/EtOAc, 8:2); IR (film) 2965, 1757, 1733,

1507, 1463, 1441, 1270, 1238, 1191, 1083, 1034, 825 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, $J = 7.5$ Hz, 3H, $OCH_2CH_2CH_3$), 1.56–1.72 (m, 2H, $OCH_2CH_2CH_3$), 3.69 (s, 3H, OCH_3), 4.10 (t, $J = 6.7$ Hz, 2H, $OCH_2CH_2CH_3$), 4.52 (s, 2H, OCH_2), 6.73–6.86 (m, 4H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 10.0 ($OCH_2CH_2CH_3$), 21.6 ($OCH_2CH_2CH_3$), 55.3 (OCH_3), 65.9 ($OCH_2CH_2CH_3$), 66.4 (OCH_2), 114.3 (ArH), 115.5 (ArH), 151.7 (Ar), 155.2 (Ar), 169.0 (CO_2); MS (70 eV) m/z 224 (M^+, 66), 182 (4), 137 (18), 123 (100), 109 (12), 92 (10), 77 (11).

n-Amyl 2-(4-Methoxyphenoxy)acetate (**13e**)

Following method A, with a mixture of 1.0 g (5.5 mmol) of **25**, 0.095 g (0.55 mmol) of *p*-TsOH, and 9.7 g (110 mmol) of *n*-amylOH, gave 1.27 g (92%) of **13e** as a colorless oil: *Rf* 0.56 (hexane/EtOAc, 8:2); IR (film) 2954, 1757, 1507, 1462, 1283, 1183, 1083, 1036, 826, 721 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.83 (t, $J = 6.9$ Hz, 3H, $OCH_2(CH_2)_3CH_3$), 1.16–1.33 (m, 4H, $OCH_2(CH_2)_3CH_3$), 1.52–1.64 (m, 2H, $OCH_2(CH_2)_3CH_3$), 3.67 (s, 3H, OCH_3), 4.11 (t, $J = 6.6$ Hz, 2H, $OCH_2(CH_2)_3CH_3$), 4.50 (s, 2H, OCH_2), 6.73–6.82 (m, 4H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 13.6 ($OCH_2(CH_2)_3CH_3$), 22.0 ($OCH_2(CH_2)_2CH_2CH_3$), 27.6 ($O(CH_2)_2CH_2CH_2CH_3$), 27.9 ($OCH_2CH_2(CH_2)_2CH_3$), 55.2 (OCH_3), 64.9 ($OCH_2(CH_2)_3CH_3$ or OCH_2), 65.9 (OCH_2 or $OCH_2(CH_2)_3CH_3$), 114.3 (ArH), 115.5 (ArH), 151.8 (Ar), 154.2 (Ar), 168.9 (CO_2); MS (70 eV) m/z 252 (M^+, 70), 182 (24), 137 (21), 123 (100), 109 (12), 107 (11), 92 (9), 77 (21). Anal. Calcd. for $C_{14}H_{20}O_4$: C, 66.64; H, 7.94. Found: C, 66.54; H, 7.92.

n-Dodecyl 2-(4-methoxyphenoxy)acetate (**13f**)

Following method B, with a mixture of 1.0 g (5.5 mmol) of **25**, 0.067 g (0.55 mmol) of DMAP in CH_2Cl_2 (20 ml), 0.98 g (8.25 mmol) of $SOCl_2$, 0.835 g (6.05 mmol) of K_2CO_3, and 1.12 g (6.05 mmol) of *n*-dodecyl alcohol in toluene (30 ml), gave 1.59 g (83%) of **13f** as a colorless oil: *Rf* 0.61 (hexane/EtOAc, 8:2); IR (film) 2924, 2853, 1760, 1508, 1462, 1284, 1191, 1084, 1038, 826, 721 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, $J = 6.7$ Hz, 3H, $OCH_2CH_2(CH_2)_9CH_3$), 1.24 (br s, 18H, $9CH_2$), 1.56–1.70 (m, 2H, $OCH_2CH_2(CH_2)_9CH_3$), 3.74 (s, 3H, OCH_3), 4.17 (t, $J = 6.7$ Hz, 2H, $OCH_2(CH_2)_{10}CH_3$), 4.56 (s, 2H, OCH_2), 6.78–6.87 (m, 4H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 14.0 (CH_3), 22.6 (CH_2), 25.7 (CH_2), 28.5 (CH_2), 29.1 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 29.50 (CH_2), 29.57 (CH_2), 29.59 (CH_2), 31.8 (CH_2), 55.5 (OCH_3), 65.3 ($CH_3(CH_2)_{10}CH_2O$ or OCH_2), 66.2 (OCH_2 or $CH_3(CH_2)_{10}CH_2O$), 114.6 (ArH), 115.7 (ArH), 152.0 (Ar), 154.4 (Ar), 169.3 (CO_2); MS (70 eV) m/z 350 (M^+, 100), 182 (9), 137 (11), 123 (38), 107 (6), 77 (5). Anal. Calcd. for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78. Found: C, 72.02; H, 9.78.

4-Chlorophenyl 2-(4-methoxyphenoxy)acetate (**13g**)

Following method B, with a mixture of 1.0 g (5.5 mmol) of **25**, 0.067 g (0.55 mmol) of DMAP in CH_2Cl_2 (20 ml), 0.98 g (8.25 mmol) of $SOCl_2$, 0.835 g (6.05 mmol) of K_2CO_3, and 0.78 g (6.05 mmol) of 4-chlorophenol in toluene

(30 ml), gave 1.27 g (79%) of **13g** as a white solid: *Rf* 0.31 (hexane/EtOAc, 8:2); mp 103–104°C (hexane/EtOAc, 8:2); IR (KBr) 1773, 1512, 1437, 1237, 1182, 1086, 1026, 830 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.77 (s, 3H, OCH_3), 4.80 (s, 2H, OCH_2), 6.83–6.96 (m, 4H, ArH), 7.02–7.08 (m, 2H, ArH), 7.30–7.38 (m, 2H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 55.5 (OCH_3), 66.3 (OCH_2), 114.7 (ArH), 116.0 (ArH), 122.6 (ArH), 129.6 (ArH), 131.6 (ArH), 131.6 (Ar), 148.5 (Ar), 151.8 (Ar), 154.8 (Ar), 167.6 (CO_2); MS (70 eV) m/z 294 (M^++2, 15), 292 (M^+, 43), 164 (5), 137 (100), 109 (29),107 (28), 92 (24), 77 (28). Anal. Calcd. for $C_{15}H_{13}ClO_4$: C, 61.54; H, 4.47. Found: C, 61.71; H, 4.57.

Pharmacology

All synthesized compounds were assessed in vitro for fungal activity. This activity was performed by minimal inhibitory concentration 50% (MIC_{50}) against two strains of *Candida* from American Type Culture Collection (ATCC): *C. parapsilosis* ATCC 22019, susceptible to fluconazole (Quemical Iberica; Madrid, Spain), and *C. krusei* ATCC 6258, resistant to fluconazole, as well as against two clinical isolated of *Cryptococcus*, *C. neoformans* and *C. gattii*, both of which have been isolated from Mexican patients and identified at the Medical Mycology Laboratory, Escuela Nacional de Ciencias Biológicas, Instituto Politecnico Nacional, in Mexico City. The isolates were identified presumptively as *C. neoformans* by capsule production and positive urea test. To distinguish the species of *Cryptococcus*, isolates were streaked on Niger agar for the presence of laccases, and canavanine–glycine–bromothymol blue (CGB) agar plates for resistance to L-canavanine culture. To ensure viability and purity, the strains were grown onto potato dextrose agar (DIBICO; Mexico City, Mexico). Stock solutions for ketoconazole (Sigma), itraconazole (European Pharmacopoeiae; Strasbourg, France), fluconazole (Chemical Iberica; Madrid, Spain), amphotericin B (Sigma; St. Louis MO, USA), and caspofungine (Merck, Mexico) were serially diluted in dimethyl sulfoxide at 100×, and dilutions of antifungal drugs were prepared (amphotericin B, ketoconazole, and itraconazole, range 16–0.03 μg/mL; fluconazole and phenoxyacetic derivates, range 128–0.25 μg/mL).

In vitro susceptibility testing was performed by Clinical and Laboratory Standards Institute (CLSI) M27-A2 standardized method for yeast (National Committee for Clinical Laboratory Standards, 2002). Yeasts cells were suspended in sterile normal saline and adjusted to 0.5 McFarland standard. Roswell Park Memorial Institute (RPMI) 1640 culture medium containing l-glutamine and 0.165 M 3-(*N*-morpholine)propansulfonic acid (MOPS, Sigma) at pH 7.0 was used. CLSI M27-A was modified for the *Cryptococcus* strains, in which during incubation agitation was included (125 rpm/min) (Orbital Shaker, New Bronswick Scientific Co., USA). Assays were performed four times with each strain, obtaining reproducible results. The MIC_{50} value was defined as the minimal concentration of a drug at which $\leq$50% growth inhibition occurred in comparison with nondrug control. Growth evaluation was determined at 24 h for *Candida* strains and at 48 h for *Cryptococcus* species by optical density (Labsystems Multiskan Plus, serial RS

232C; Helsinki, Finland) at 405 nm. Clinical and Laboratory Standard Index (CLSI) M27-A2 micromethod-established cutoff points for strain sensitivity and resistance to the drugs employed were as follows: amphotericin B (≤2 μg/mL, sensitive; >3 μg/mL, resistant); ketoconazole and itraconazole (≤0.125 μg/mL, sensitive; ≥1.0 μg/mL, resistant), and fluconazole (≤8 μg/mL, sensitive; ≥64 μg/mL, resistant). None of the synthesized compounds (α-Asarone analogues) inhibited the growth of both strains of *Candida* when tested at a concentration range of 0.25–128 μg/mL after 48 h of incubation. However, several derivatives showed evidence of modest to strong activity against both *Cryptococcus* yeasts.

MFC was defined as the minimal concentration at which no visible growth was observed, and represents killing of ≥99% of the original inoculum [≤3 colony forming units (CFU)/Petri dish]. MFC determination was performed similarly to that for MIC_{50}; the MFC were determined in microplates with inoculum size of $1.0–2.5 \times 10^4$ yeast cells/mL, on RPMI 1640 medium (MOPS, Sigma) and incubated with agitation at 35°C for 48 h. MFC estimations were determined by directly plating dilutions of culture medium from wells with no growth onto potato dextrose agar (DIBICO; Mexico City, Mexico) and incubating the plates at 35°C for 48 h.

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