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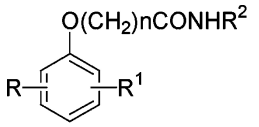

n = 5, 10, 15
R = H, OH
R^1 = H, nC_5H_{11}, nC_6H_{13}, $nC_{15}H_{31}$
R^2 = CH_2CH_2OH, cyclopropyl, p.hydroxyphenyl

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Design, Synthesis, and Binding Studies of New Potent Ligands of Cannabinoid Receptors

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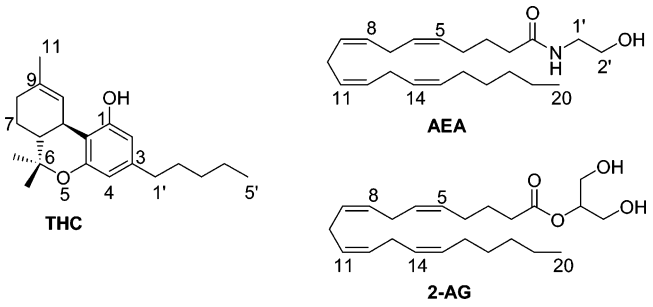
Despite their different chemical structures, Δ^9-tetrahydrocannabinol (THC) and anandamide (AEA) have common pharmacological properties. This study was aimed at finding new cannabinoid receptor ligands that overcome the instability of AEA and its analogues. To this end we planned the synthesis of a series of compounds which retained both a rigid structure, like that of plant cannabinoids, and a flexible portion similar to that of anandamide. Binding studies on CB_1 and CB_2 receptors, anandamide membrane transporter (AMT), and fatty acid amide hydrolase (FAAH) showed that some of the newly developed compounds have high affinity and specificity for cannabinoid CB_1 and CB_2 receptors. Compound **25** is a potent CB_1 and CB_2 ligand, with affinity constants significantly lower than AEA and similar to WIN 55-212, compound **52** is a potent CB_2 ligand, although not very selective over CB_1 receptors, and compound **43** is CB_2 ligand, with at least a 26-fold selectivity over CB_1 receptors. Compound **25** behaved as a inverse agonist at CB_1 receptors as assessed in the cyclic AMP functional assay.

Introduction

The great popularity of hashish and marihuana, both derived from the Indian hemp *Cannabis Sativa L.*, and of their major psychoactive component, (−)-*trans*-Δ^9-tetrahydrocannabinol (THC, Chart 1),[1] is due to their medicinal as well as their psychotomimetic effects. Cannabinoids have been shown to produce a wide range of pharmacological effects[2] mediated by two receptors: CB_1, very abundant in the brain[3] and cloned in 1990,[4] and CB_2, expressed predominantly in the periphery,[5] mainly in the spleen and in immune cells. The presence of these receptors in mammalian cells was indicative of the existence of an endogenous cannabinoid system. Several years ago the first natural ligand was isolated from porcine brain[6] and identified as an amide related to arachidonic acid, the *cis*-5,8,11,14-eicosatetraenoylethanolamide, or anandamide (AEA), showing properties similar to the plant-derived agonist THC. Three years later a well-known intermediate in phosphoglyceride metabolism, 2-arachidonoylglycerol (2-AG), was found to act also as a potential ligand at cannabinoid receptors.[7−9]

The molecular basis of the biological effects of these endogenous compounds were elucidated also thanks to the understanding of their metabolism, including biochemical pathways that lead to their synthesis and inactivation. Both AEA and 2-AG are produced from the metabolism of membrane phospholipids and immediately released into extracellular space. Inactivation occurs in two steps: cellular reuptake, facilitated by a putative transporter protein known as the anandamide membrane transporter (AMT)[10] and enzymatic hydrolysis by a fatty acid amide hydrolase (FAAH)[11] or by a monoacylglycerol lipase, in the case of 2-AG. The proteins of the endocannabinoid system, including CB_1, CB_2, AMT, and FAAH, represent excellent targets for the development of new therapeutic drugs to be employed in many pathologies, like pain, immunodepression, vascular perpherical disorders, increase or lowering of appetite, and motor disorders. The therapeutic value of these compounds as analgesic, anti-glaucoma, and antiinflammatory agents, and in the chemotherapy-induced nausea and vomiting and in appetite stimulation of patients with AIDS, is nowadays of great interest.[12]

Chart 1



Since these discoveries several groups have carried out the synthesis and biological evaluation of AEA analogues, obtained by modifications of the fatty acyl chain or/and of the ethanolamide "head".[13] Unfortunately, arachidonic acid and analogous polyunsaturated fatty acids are very expensive and/or easily oxidized. AEA itself is very unstable and in the body is rapidly metabolized by FAAH and/or oxidation. To prevent in part the degradation of AEA and of its synthetic

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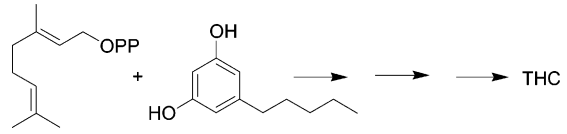


Figure 1.

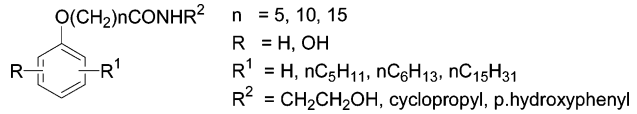
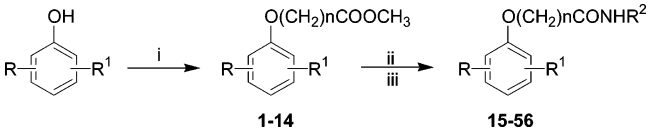


Figure 2.

Scheme 1[a]



[a] Reagents: (i) Br-(CH_2)nCOOCH$_3$, CH_3COCH_3, K_2CO_3, KF, reflux, 48−72 h; (ii) Method A: MeOH/NaOH, reflux, 3 h; amine, HOBt, CMC, r.t., overnight; (iii) Method B: $H_2NCH_2CH_2OH$, 120−130 °C, 5 h.

analogues their activity at cannabinoid receptors is often assessed by conducting receptor binding assays in the presence of a serine protease inhibitor, phenylmethanesulfonyl fluoride (PMSF).[14]

While AEA is a very flexible molecule, as demonstrated also by NMR studies,[15] and can assume both linear and nonlinear conformations, THC, and cannabinoid analogues, including tricyclic and bicyclic cannabinoids, are rigid compounds. Nevertheless, AEA and THC have been shown to share many, albeit not all, pharmacological properties. Bearing in mind the pharmacophore requirements[16] of both AEA and THC, necessary for the binding to cannabinoid CB_1 and CB_2 receptors, we have planned the synthesis of a series of stable compounds which consist of both a rigid aromatic portion, as in THC, and a flexible chain, as in AEA.

Olivetol, or 5-pentyl-benzene-1,3-diol (5-pentylresorcinol), is involved in the biogenesis of THC in Cannabis[17] (Figure 1), and it has been selected as the basic aromatic scaffold of the rigid part of our new derivatives; other modified phenols have also been considered in this work in order to define a structure−activity relationship. As flexible chains we have chosen saturated carboxylic acids with chain lengths of 6 or 11 or 16 carbon atoms, easily converted into the final amides. Finally, we have evaluated the influence of several factors such as substitutions of the aromatic backbone, the length of the chain carrying the amidic head, and nature of amide.

As a result, different series of new compounds were designed and synthesized, whose general structure is reported in Figure 2.

Chemistry. As shown in Scheme 1, the synthesis of the new compounds starts from a substituted phenol [3-pentadecylphenol, olivetol, resorcinol (or benzene-1,3-diol), and 4-hexylresorcinol] which is reacted with a bromoalkylmethyl ester (6-bromohexanoic acid methyl ester or 11-bromoundecanoic acid methyl ester or 16-bromo-hexadecanoic acid methyl ester) in dry acetone in the presence of anhydrous K_2CO_3 and KF, giving esters **1**−**14**. The final amides are obtained by either of two simple methods. Method A: esters were refluxed with methanolic/aqueous sodium hydroxide solution to give the corresponding acids, which were used as such and reacted with amines in the presence of 1-hydroxybenzotriazole (HOBt) and 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide methyl-*p*-toluenesulfonate (CMC) in dichloromethane or acetonitrile.[18] Method B: esters were warmed with ethanolamine as solvent.

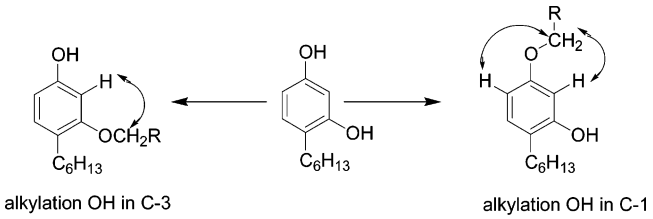


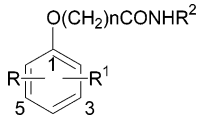
Figure 3.

The O-alkylation of phenols was carried out with or without KF; as expected, in both conditions the reaction afforded all possible alkylated products when the aromatic nucleus had two free hydroxyl groups, although addition of KF improved the yields and specifically increased those of monoalkylated over dialkylated products. Moreover, O-alkylation of 4-hexylresorcinol afforded two different monoalkylated regioisomers. The reaction occurred mainly on the hydroxyl in C-1 irrespectively of the bromomethyl ester used and independently from the length of its chain; in fact the C-1 position results less hindered when the hexyl chain is present as para substituent. The structure of two regioisomers has been definitively assigned by NOESY experiments which showed a NOE effect between the OCH_2 and both the ortho aromatic hydrogens (H-2 and H-6) in the isomer with the alkylated hydroxyl in C-1, and a NOE effect between the OCH_2 and the only ortho aromatic hydrogen (H-2) in the isomer with the alkylated hydroxyl in C-3 (Figure 3).

Pharmacological Evaluation. Binding Assays. For CB_1 and CB_2 receptor binding assays, the new compounds were first subjected to a preliminary screening carried out using three concentrations (5, 10, and 25 μM), membranes from rat brain and spleen, and [^{3}H]-*N*-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide hydrochloride (SR141716A, 2 nM) as the high affinity ligand.[19] Compounds which displaced [^{3}H]-SR141716A by more than 50% at 10 μM were further analyzed by using P_2 membranes from COS cells transfected with either the human CB_1 or CB_2 receptor and [^{3}H]-(−)-*cis*-3-[2-hydroxy-4-(1,1-dimethylheptyl)phenyl]-*trans*-4-(3-hydroxypropyl)cyclohexanol ([^{3}H]CP-55,940) (K_d = 690 pM) as the high affinity ligand as described by the manufacturer (Perkin-Elmer, Italy). Displacement curves were generated by incubating drugs with 0.5 nM of [^{3}H]CP-55,940. In all cases, K_i values were calculated by applying the Cheng−Prusoff equation to the IC_{50} values (obtained by GraphPad) for the displacement of the bound radioligand by increasing concentrations of the test compounds.

Fatty Acid Amide Hydrolase Assays. The effect of compounds on the enzymatic hydrolysis of [^{14}C]-anandamide (6 μM) was studied by using membranes prepared from rat brain incubated with increasing concentrations of compounds in 50 mM Tris-HCl, pH 9, for 30 min at 37 °C.[19] [^{14}C]Ethanolamine produced from [^{14}C]anandamide hydrolysis was measured by scintilla-

Table 1. Radioligand Binding Assays and Selectivity over Other Proteins of the Endocannabinoid System of the Synthesized Compounds[a]



compd	R	R_1	n	R_2	CB_1	CB_2	FAAH	AMT
15	H	3-$CH_2(CH_2)_{13}CH_3$	5	CH_2CH_2OH	n.t.	n.t.	n.a.	>25
16	H	3-$CH_2(CH_2)_{13}CH_3$	5	*c*.C_3H_5	n.t.	n.t.	n.a.	n.t.
17	H	3-$CH_2(CH_2)_{13}CH_3$	5	*p*.OH-C_6H_4	n.t.	n.t.	n.a.	>25
18	H	3-$CH_2(CH_2)_{13}CH_3$	10	CH_2CH_2OH	n.t.	n.t.	n.t.	n.t.
19	H	3-$CH_2(CH_2)_{13}CH_3$	10	*c*.C_3H_5	n.t.	n.t.	n.t.	n.t.
20	H	3-$CH_2(CH_2)_{13}CH_3$	10	*p*.OH-C_6H_4	n.t.	n.t.	n.t.	n.t.
21	3-OH	5-$CH_2(CH_2)_3CH_3$	5	CH_2CH_2OH	n.t.	n.a	n.a.	n.t.
22	3-OH	5-$CH_2(CH_2)_3CH_3$	5	*c*.C_3H_5	1.3	**0.96**	n.a	n.t.
23	3-OH	5-$CH_2(CH_2)_3CH_3$	5	*p*.OH-C_6H_4	n.t.	n.t.	n.a.	n.t.
24	3-OH	5-$CH_2(CH_2)_3CH_3$	10	CH_2CH_2OH	**0.8**	**0.16**	n.a	25
25	3-OH	5-$CH_2(CH_2)_3CH_3$	10	*c*.C_3H_5	**0.0052**	**0.013**	n.a	17
26	3-OH	5-$CH_2(CH_2)_3CH_3$	10	*p*.OH-C_6H_4	3	1.4	n.a.	n.a.
27	3-OH	5-$CH_2(CH_2)_3CH_3$	15	CH_2CH_2OH	12.5	n.a.	n.t.	n.t.
28	3-OH	5-$CH_2(CH_2)_3CH_3$	15	*c*.C_3H_5	>10	n.a.	n.t.	n.t.
29	3-OH	5-$CH_2(CH_2)_3CH_3$	15	*p*.OH-C_6H_4	>10	n.a.	n.t.	n.t.
30	3-OH	H	5	CH_2CH_2OH	n.t.	n.t.	n.a.	n.t.
31	3-OH	H	5	*c*.C_3H_5	n.t.	n.t.	n.a.	n.t.
32	3-OH	H	5	*p*.OH-C_6H_4	n.t.	n.t.	n.t.	n.t.
33	3-OH	H	10	CH_2CH_2OH	>10	n.a.	n.a.	n.t.
34	3-OH	H	10	*c*.C_3H_5	>10	5.4	n.a.	n.t.
35	3-OH	H	10	*p*.OH-C_6H_4	n.a.	>10	n.t.	n.t.
36	3-OH	H	15	CH_2CH_2OH	>10	n.a.	n.t.	n.t.
37	3-OH	H	15	*c*.C_3H_5	4.25	n.a.	n.t.	n.t.
38	3-OH	H	15	*p*.OH-C_6H_4	5	10	n.t.	n.t.
39	3-OH	4-$CH_2(CH_2)_4CH_3$	5	CH_2CH_2OH	n.t.	6.43	n.a.	n.t.
40	3-OH	4-$CH_2(CH_2)_4CH_3$	5	*c*.C_3H_5	**0.18**	**0.54**	n.a.	n.t.
41	3-OH	4-$CH_2(CH_2)_4CH_3$	5	*p*.OH-C_6H_4	n.t.	n.t.	n.t.	n.t.
42	3-OH	4-$CH_2(CH_2)_4CH_3$	10	CH_2CH_2OH	>10	2.7	n.a.	n.a.
43	3-OH	4-$CH_2(CH_2)_4CH_3$	10	*c*.C_3H_5	>10	**0.35**	n.a.	>25
44	3-OH	4-$CH_2(CH_2)_4CH_3$	10	*p*.OH-C_6H_4	n.a.	>10	50	>25
45	3-OH	4-$CH_2(CH_2)_4CH_3$	15	CH_2CH_2OH	n.a.	n.a.	n.t.	n.t.
46	3-OH	4-$CH_2(CH_2)_4CH_3$	15	*c*.C_3H_5	n.a.	n.a.	n.t.	n.t.
47	3-OH	4-$CH_2(CH_2)_4CH_3$	15	*p*.OH-C_6H_4	>10	n.a.	n.t.	n.t.
48	5-OH	2-$CH_2(CH_2)_4CH_3$	5	CH_2CH_2OH	n.t.	>10	n.a.	n.t.
49	5-OH	2-$CH_2(CH_2)_4CH_3$	5	*c*.C_3H_5	n.t.	3.57	n.a.	n.t.
50	5-OH	2-$CH_2(CH_2)_4CH_3$	5	*p*.OH-C_6H_4	n.t.	n.t.	n.t.	n.t.
51	5-OH	2-$CH_2(CH_2)_4CH_3$	10	CH_2CH_2OH	1.13	**0.42**	n.a.	>25
52	5-OH	2-$CH_2(CH_2)_4CH_3$	10	*c*.C_3H_5	**0.21**	**0.03**	>25	13
53	5-OH	2-$CH_2(CH_2)_4CH_3$	10	*p*.OH-C_6H_4	3.3	2.11	18.0	>25
54	5-OH	2-$CH_2(CH_2)_4CH_3$	15	CH_2CH_2OH	n.a	n.a.	n.t.	n.t.
55	5-OH	2-$CH_2(CH_2)_4CH_3$	15	*c*.C_3H_5	5.5	2.49	n.t.	n.t.
56	5-OH	2-$CH_2(CH_2)_4CH_3$	15	*p*.OH-C_6H_4	3	n.a.	n.t.	n.t.
anandamide					72 ± 3.1 n M	-		
WIN, 55−212					21 ± 1.1 nM	2.1 ± 0.1 nM		
HU-210					-	0.15 ± 0.03		

[a] Data are means ± SEM of $n = 3$ separate experiments and are expressed as K_i (μM), for CB_1 and CB_2 binding assays, and in IC_{50} (μM) for FAAH and AMT assays. Reference compounds were tested under the same conditions in this study. Anandamide was tested in the presence of PMSF (100 nM). n.a. = IC_{50} > 10 in the preliminary screening carried out with rat brain and spleen membranes; n.t. = not tested; insol. = insoluble in any of the solvents normally used in binding assays (DMSO, ethanol, or methanol). Binding affinity costants of the most potent compounds ($K_i \leq 1$ μM) are highlighted in bold.

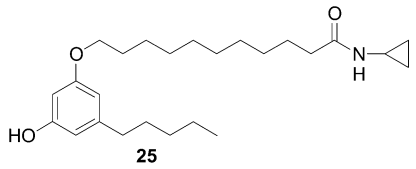
tion counting of the aqueous phase after extraction of the incubation mixture with 2 volumes of $CHCl_3/CH_3OH$ (2:1 by volume). In most cases, only the most potent compounds in the binding assays were subjected to this assay.

Anandamide Membrane Transporter (AMT) Assays. The effect of compounds on the uptake of anandamide by RBL-2H3 cells was studied as described previously.[19] Cells were incubated with [^{14}C]anandamide (4 μM) for 5 min at 37 °C, in the presence or absence of varying concentrations of the inhibitors. Residual [^{14}C]-anandamide in the incubation media after extraction with $CHCl_3/CH_3OH$ (2:1 by volume) was used as a measure of the anandamide that was taken up by cells. Data are expressed as the concentration exerting 50% inhibition of anandamide uptake (IC_{50}) calculated with GraphPad. In most cases, only the most potent compounds in the binding assays were subjected to this assay.

Cyclic AMP Assay. Cyclic AMP assays were performed on intact confluent N18TG2 cells plated in six-well dishes and stimulated for 10 min at 37 °C with forskolin 1 μM in 400 μL of serum-free Dulbecco's modified Eagle's Medium containing 20 mM HEPES, 0.1 mg/mL BSA, 0.1 mM 1-methyl-3-isobutylxanthine.[20] Cells were treated with vehicle (methanol, 0.1%) or compounds, or WIN55,212-2 at various concentrations, or with SR141716A (100 nM). After incubation, 800 μL of ethanol was added, cells were extracted and cyclic AMP was determined by means of a cyclic AMP assay kit (Amersham, UK), as advised by the manufacturer.

Results and Discussion

All the newly synthesized compounds that exibited $IC_{50} \leq 10$ μM in the preliminary screening for cannabinoid receptor binding activity were evaluated in radioligand binding assays for affinity at recombinant human CB_1, CB_2 overexpressed in COS cells, or for their inhibitory actions on FAAH and AMT, and the results are summarized in Table 1. Our preliminary goal was to evaluate the hypothesis that putting together in a



25

Figure 4.

single structure the chemical stability of THC with the flexibility of AEA might lead to compounds active on the endocannabinoid systhem. To this end we have introduced an aliphatic chain carrying an amidic "head" in the aromatic structure of 3-pentadecylphenol, olivetol, resorcinol, and 4-hexylresorcinol, achieving five series of O-alkylated derivatives from which we could get useful information on structure−activity relationships. In fact, the binding assay results of the compounds described here allow us to establish the effect of several factors on the affinity for CB_1 and CB_2 receptors, and the most important points can be summarized as follows: (a) the presence of a phenolic hydroxyl group seems to play an essential role, since without it the 3-pentadecyphenol derivatives **15**−**17** are unable to bind to cannabinoid receptors with high affinity; (b) the length of aliphatic chain on the aromatic ring has a crucial influence on the affinity of our compounds, since a chain of five or six carbon atoms, such as in olivetol and 4-hexylresorcinol, is required, while a longer chain, as in 3-pentadecylphenol, or its absence, as in resorcinol, leads respectively to insoluble (**18**−**20**) or inactive (**30**−**38**) compounds; (c) regarding the alkyloxy chain carrying the amidic "head", its length also turned out to be of great importance: in fact, the short, five-carbon atom derivatives (**15**−**17**, **21**−**23**, **30**−**32**, **39**−**41**, and **48**−**50**) or the long fifteen carbon atom derivatives (**27**−**29**, **36**−**38**, **45**−**47**, and **54**−**56**) are inactive independently of their aromatic structure. In support to this analysis one can observe that the most potent compounds are olivetol (**24**, **25**, and **26**) and 4-hexylresorcinol derivatives (**51** and **52**), all of them with a chain of 10 carbon atoms; one notable exception to this rule was compound **40** which was more potent than compound **43** at CB_1, and equipotent at CB_2, receptors; (d) in accordance with literature data,[13] cyclopropylamides (**25**, **43**, and **52**) are more potent than the respective ethanolamides (**24**, **42**, and **51**), and in particular special attention should be given to compound **25** (Figure 4), which exhibits the lowest K_i values and behaves as a very potent CB_1 (5.2 nM) and CB_2 ligand (13 nM), with affinities similar to WIN55-212-2 (CB_1 21 ± 1.1 nM and CB_2 2.1 ± 0.1 nM); (e) furthermore, it appears interesting to compare two isomers of 4-hexylresorcinol: while compound **52** is a potent CB_2 ligand (30 nM), although not very selective over CB_1 receptors (210 nM), its regioisomer **43**, even though less potent, resulted in a CB_2 selective ligand with at least a 26-fold selectivity over CB_1 receptors (CB_2 0.35 μM and CB_1 > 10 μM); (f) regarding the interaction of the most potent cannabinoid receptor ligands with FAAH and the AMT, the data obtained here show that all such compounds are essentially unable to bind to either the enzyme or the putative transporter.

To gain some insight into the possible use as a therapeutic agent of the most potent ligand described here, i.e., compound **25**, we carried out functional assays

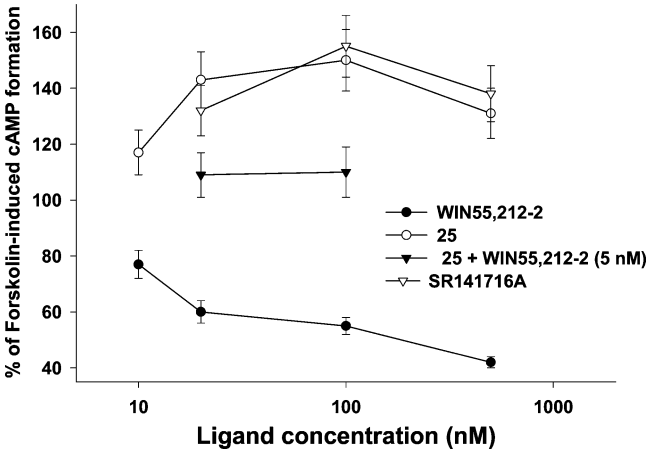


Figure 5.

for its activity at CB_1 receptors. We assessed the effect of this compound on forskolin-induced adenylate cyclase activity in mouse neuroblastoma N18TG2 cells, which constitutively and selectively express cannabinoid CB_1 receptors. As shown in Figure 5, similar to the well-known CB_1 inverse agonist/antagonist, SR141716A, compound **25** significantly stimulated forskolin-induced cyclic AMP formation (half-maximal effect observed at a concentration of 13 nM similar to the K_i for this compound at CB_1 receptors). As expected, WIN55,212-2 behaved as an agonist since it inhibited forskolin-induced cyclic AMP formation (half-maximal effect observed at a concentration of 15 nM). The effect of compound **25** at the doses of 20 and 100 nM was blocked by a per se inactive dose (5 nM) of WIN55,212 and hence was mediated by CB_1 receptors (Figure 5, higher doses of **25** could not be tested as they would have required non inactive doses of WIN55,212-2 to be counteracted). Therefore, this compound behaved as a inverse agonist/antagonist at CB_1 receptors. Also another compound that exhibited affinity for CB_1 receptors, albeit lower than compound **25**, i.e., compound **40**, also behaved as a inverse agonists/antagonist (half-maximal effect observed at a concentration of 150 nM, data not shown). We also attempted at performing functional assays for CB_2 receptors in cell lines constitutively expressing this receptor but could not get a response even with WIN55,-212-2 and, therefore, did not go further.

Conclusions

Our hypothesis that compounds active at cannabinoid receptors can be obtained by linking a stable and rigid structure typical of aromatic compounds, such THC, olivetol, and its analogues, to a flexible chain carrying an amidic "head", as in AEA, appeared to be correct and resulted in the synthesis of a new class of compounds. Some of the new compounds exhibited potent activity at CB_1 and CB_2 receptors and exhibited antagonist/inverse agonist activity. As a result of these studies we are currently pursuing new experiments in order to further evaluate the functional activity of these molecules, to elucidate the requirements involved in the recognition and binding of their biological targets, and to evaluate their pharmacological activity in vivo, to direct our research toward the design and synthesis of ever more potent and selective compounds.

Experimental Section

Melting points were determined on a Kofler hot stage apparatus (K) or using a Mettler FPI apparatus (2 °C/min) (M) and are uncorrected. Elemental analyses of all synthesized compounds were performed by our analytical laboratory in a Perkin-Elmer elemental apparatus Mod. 240 for C, H, N and the data are within ±0.4% of the theoretical values. ^{1}H NMR spectra were recorded at 25 °C on a Brucker AC200F employing TMS as internal standard, while NOESY experiments have been performed with a Varian VRX 300 MHz and chemical shifts are expressed as δ (ppm). Mass spectral data were determined by direct insertion at 70 eV with a VG70 spectrometer. All compounds were checked for purity by TLC on Merck 60 F_{254} silica plates. For column chromatography, Merck 60 silica gel, 230−400 mesh, was used. Final products were purified by a Biotage flash chromatography system with columns 12.25 mm, packed with KP−Sil, 60A, 32−63 μM. Reagents were purchased from Sigma Aldrich Srl (Italy) and used as received unless otherwise stated.

General Method for Esters. A mixture of phenolic compound (5.0 mmol), anhydrous potassium carbonate (2.5 mmol), and potassium fluoride (5.0 mmol) in dry acetone was refluxed under nitrogen atmosphere and continuously stirred for half hour, and then a solution of the corresponding bromoalkylmethyl ester (5.0 mmol) in dry acetone was added, refluxing for another 48−72 h and checking the reaction by TLC. Afterward the reaction mixture was concentrated, diluted with water, and extracted with chloroform. The extracts were collected, dried, and evaporated under reduced pressure, and the residue was purified by column chromatography on silica gel. Yields, melting points, and chemical and spectroscopic data of all esters are available in the Supporting Information.

General Methods for the Final Products. Method A. Each ester (1.0 mmol) was refluxed in a methanolic/aqueous sodium hydroxide solution (0.1 M, 3 equiv) for 3 h. Then the reaction mixture was allowed to get room temperature, made acidic (pH 3−4) by adding diluted HCl, and finally extracted with ethyl acetate. The organic layer was dried and the solvent evaporated to yield the crude acid, which was thoroughly dried under vacuum before being subjected to the successive reaction without further manipulation. To a mixture of the crude acid (1.0 mmol), the appropriate amine (1.5 mmol), and 1-hydroxybenzotriazole (HOBt, 1.2 mmol) in dry dichloromethane or in dry acetonitrile, kept in an ice bath, was added dropwise a solution, in the same solvent, of 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide methyl *p*-toluensulfonate (CMC, 1.5 mmol) under nitrogen atmosphere and continuous stirring. The reaction mixture was left to room temperature, and stirring was continued 24 h. The solvent was removed under reduced pressure, and the residue was diluted with chloroform. The organic layer was washed with 5% aqueous $NaHCO_3$ and then with 1 N HCl and dried. After drying and evaporation of the solvent, a crude residue was obtained and purified by column chromatography on silica gel.

Method B. Each ester (0.150 g) was dissolved, under nitrogen atmosphere and stirring, in ethanolamine (4 mL) and warmed at 120−130 °C for 4−6 h. The resulting mixture was diluted with water and extracted with chloroform, the extracts were washed with a solution of ammonium chloride, dried, evaporated, and the raw material was purified by column chromatography on silica gel.

6-(3-Pentadecylphenoxy)hexanoic Acid (2-Hydroxyethyl)amide (15).[21] White solid ($CHCl_3$/MeOH = 47/3) (80% yield): mp 62.7 °C (M). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.14−7.10 (m, 1H), 6.75−6.66 (m, 3H), 5.95 (s br, 1H), 3.93 (t, 2H, J = 6.3 Hz), 3.70 (t, 2H, J = 4.9 Hz), 3.44−3.36 (m, 2H), 2.65 (s br, 1H), 2.54 (t, 2H, J = 7.7 Hz), 2.22 (t, 2H, J = 7.3 Hz), 1.81−1.46 (mm, 8H), 1.44−1.24 (mm, 24H) 0.86 (t, 3H, J = 6.2 Hz). Anal. ($C_{29}H_{51}NO_3$) C, H, N.

6-(3-Pentadecylphenoxy)hexanoic Acid Cyclopropylamide (16). White solid ($CHCl_3$, recrystallized from acetone/ethyl ether) (50% yield): mp 67.8 °C (M). ^{1}H NMR ($CDCl_3$) δ (ppm): 6.65 (t, 1H, J = 7.7 Hz), 6.50 (s br, 1H), 6.26−6.17 (m, 3H), 3.46 (t, 2H, J = 6.3 Hz), 2.28−2.18 (m, 1H), 2.08 (t, 2H, J = 7.5 Hz), 1.69 (t, 2H, J = 7.3 Hz), 1.36−1.03 (mm, 8H), 1.0−0.79 (mm, 24H), 0.40 (t, 3H, J = 6.3 Hz), 0.24−0.15 (m, 2H), 0.11−0.02 (m, 2H). MS *m/z*: 458 $[M + 1]^+$ (100). Anal. ($C_{30}H_{51}NO_2$) C, H, N.

6-(3-Pentadecylphenoxy)hexanoic Acid (4-Hydroxyphenyl)amide (17). White solid ($CHCl_3$/MeOH = 47/3) (70% yield): mp 103.2 °C (M). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.31 (half of AB_q, 2H, J = 8.7 Hz), 7.20−7.12 (m, 2H), 7.00 (s br, 1H), 6.79−6.68 (m, 4H), 3.95 (t, 2H, J = 7.1 Hz), 3.92 (s br, 1H), 2.55 (t, 2H, J = 7.6 Hz), 2.36 (t, 2H, J = 7.0 Hz), 1.80−1.69 (m, 4H), 1.63−1.53 (m, 4H), 1.25−1.18 (mm, 24H), 0.87 (t, 3H, J = 6.6 Hz). MS *m/z*: 510 $[M + 1]^+$, 1019 $[2M + 1]^+$ (100). Anal. ($C_{33}H_{51}NO_3$) C, H, N.

11-(3-Pentadecylphenoxy)undecanoic Acid (2-Hydroxyethyl)amide (18). White solid ($CHCl_3$/MeOH = 47/3) (75% yield): mp 83−85 °C (K). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.18−7.11 (m, 1H), 6.74−6.67 (m, 3H), 5.85 (s br, 1H), 3.92 (t, 2H, J = 6.4 Hz), 3.71 (t, 2H, J = 4.7 Hz), 3.44−3.36 (m, 2H), 2.60 (s br, 1H), 2.55 (t, 2H, J = 7.5 Hz), 2.18 (t, 2H, J = 7.5 Hz), 1.78−1.51 (mm, 6H), 1.28−1.24 (mm, 36H), 0.86 (t, 3H, J = 6.3 Hz). Anal. ($C_{34}H_{61}NO_3$) C, H, N.

11-(3-Pentadecylphenoxy)undecanoic Acid Cyclopropylamide (19). White needles ($CHCl_3$, recrystallized from acetone) (91% yield): mp 82.0 °C (K). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.15 (t, 1H, J = 8.1 Hz), 6.75−6.67 (m, 3H), 5.46 (s br, 1H), 3.92 (t, 2H, J = 6.5 Hz), 2.71−2.64 (m, 1H), 2.55 (t, 2H, J = 7.6 Hz), 2.09 (t, 2H, J = 7.5 Hz), 1.78−1.41 (mm, 10H), 1.27−1.24 (mm, 32H), 0.86 (t, 3H, J = 6.2 Hz), 0.80−0.70 (m, 2H), 0.55−0.46 (m, 2H). MS *m/z*: 1077 $[2M + Na]^+$ (100). Anal. ($C_{35}H_{61}NO_2$) C, H, N.

11-(3-Pentadecylphenoxy)undecanoic Acid (4-Hydroxyphenyl)amide (20). White solid ($CHCl_3$/MeOH = 47/3) (86% yield): mp 107.0 °C (M). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.33 (half of AB_q, 2H, J = 7.5 Hz), 7.21−7.12 (m, 2H), 7.01 (s br, 1H), 6.97−6.54 (m, 4H), 3.93 (t, 2H, J = 6.5 Hz), 2.56 (t, 2H, J = 7.7 Hz), 2.35 (t, 2H, J = 7.4 Hz), 1.79−1.60 (m, 8H), 1.30−1.22 (mm, 34H), 0.87 (t, 3H, J = 6.6 Hz). MS: 579 $[M]^+$, 1159 $[2M + 1]^+$ (100). Anal. ($C_{38}H_{61}NO_3$) C, H, N.

6-(3-Hydroxy-5-pentylphenoxy)hexanoic Acid (2-Hydroxyethyl)amide (21). Pink oil (ethyl acetate/MeOH = 46/4) (65% yield). ^{1}H NMR (Acetone-d_6) δ (ppm): 8.43 (s, 1H), 7.33 (s br, 1H), 6.25−6.21 (m, 3H), 4.18 (s br, 1H), 3.86 (t, 2H, J = 6.3 Hz), 3.60−3.57 (m, 2H), 3.37−3.28 (m, 2H), 2.44 (t, 2H, J = 7.6 Hz), 2.22 (t, 2H, J = 7.3 Hz), 1.70−1.29 (mm, 12H), 0.85 (t, 3H, J = 6.5 Hz). Anal. ($C_{19}H_{31}NO_4$) C, H, N.

6-(3-Hydroxy-5-pentylphenoxy)hexanoic Acid Cyclopropylamide (22). Pale yellow oil ($CHCl_3$/MeOH = 48/2) (60%). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.04 (s br, 1H), 6.29−6.24 (m, 3H), 5.87 (s br, 1H), 3.86 (t, 2H, J = 6.2 Hz), 2.74−2.65 (m, 1H), 2.46 (t, 2H, J = 7.6 Hz), 2.14 (t, 2H, J = 7.3 Hz), 1.75−1.24 (mm, 12H), 0.86 (t, 3H, J = 6.5 Hz), 0.78−0.69 (m, 2H), 0.56−0.47 (m, 2H). Anal. ($C_{20}H_{31}NO_3$) C, H, N.

6-(3-Hydroxy-5-pentylphenoxy)hexanoic Acid (4-Hydroxyphenyl)amide (23). White solid ($CHCl_3$/MeOH = 45/5) (75% yield): mp 69.2 °C (M). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.33 (half of AB_q, 2H, J = 8.7 Hz), 7.02 (s br, 1H), 6.80 (half of AB_q, 2H, J = 8.7 Hz), 6.29−6.21 (m, 3H), 4.95 (s br, 1H), 3.92 (t, 2H, J = 6.2 Hz), 2.49 (t, 2H, J = 7.6 Hz), 2.36 (t, 2H, J = 7.2 Hz), 1.83−1.76 (m, 4H), 1.61−1.53 (m, 4H), 1.33−1.25 (mm, 4H), 0.88 (t, 3H, J = 6.5 Hz). MS *m/z*: 386 $[M + 1]^+$ (100), 771 $[2M + 1]^+$, 793 $[2M + Na]^+$. Anal. ($C_{23}H_{31}NO_4$) C, H, N.

11-(3-Hydroxy-5-pentylphenoxy)undecanoic Acid (2-Hydroxyethyl)amide (24). Pasty pink solid (ethyl acetate/MeOH = 44/6) (70% yield): mp 55−56 °C (K). ^{1}H NMR (DMSO) δ (ppm): 9.34 (s, 1H), 7.68 (s br, 1H), 6.13−6.09 (m, 3H), 4.57 (t, 1H, J = 5.3 Hz), 3.82 (t, 2H, J = 6.3 Hz), 3.39−3.30 (m, 2H), 3.11−3.03 (m, 2H), 2.39 (t, 2H, J = 7.5 Hz), 2.02 (t, 2H, J = 7.2 Hz), 1.63−1.45 (mm, 6H), 1.41−1.23 (mm, 16H), 0.83 (t, 3H, J = 6.4 Hz). Anal. ($C_{24}H_{41}NO_4$) C, H, N.

11-(3-Hydroxy-5-pentylphenoxy)undecanoic Acid Cyclopropylamide (25). White solid ($CHCl_3$/MeOH = 47/3) (61% yield): mp 70.7 °C (M). ^{1}H NMR ($CDCl_3$) δ (ppm): 6.98 (s br, 1H), 6.28−6.26 (m, 3H), 5.79 (s br, 1H), 3.88 (t, 2H, J = 6.3 Hz), 2.72−2.67 (m, 1H), 2.47 (t, 2H, J = 7.6 Hz), 2.12 (t, 2H,

J = 7.5 Hz), 1.75−1.49 (mm, 8H), 1.28−1.26 (mm, 14H), 0.87 (t, 3H, J = 6.4 Hz), 0.79−0.70 (m, 2H), 0.55−0.43 (m, 2H). Anal. ($C_{25}H_{41}NO_3$) C, H, N.

11-(3-Hydroxy-5-pentylphenoxy)undecanoic Acid (4-Hydroxyphenyl)amide (26). Pasty white solid ($CHCl_3$/MeOH = 47/3) (65% yield). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.28 (half of AB_q, 2H, J = 9.0 Hz), 7.15 (s br, 1H), 6.74 (half of AB_q, 2H, J = 8.8 Hz), 6.29−6.25 (m, 3H), 3.90 (t, 2H, J = 6.4 Hz), 2.50 (t, 2H, J = 7.6 Hz), 2.32 (t, 2H, J = 7.4 Hz), 1.73−1.53 (m, 8H), 1.33−1.29 (m, 14H), 0.87 (t, 3H, J = 6.6 Hz). MS *m/z*: 456 $[M + 1]^+$ (100), 911 $[2M + 1]^+$, 933 $[2M + Na]^+$. Anal. ($C_{28}H_{41}NO_4$) C, H, N.

16-(3-Hydroxy-5-pentylphenoxy)hexadecanoic Acid (2-Hydroxyethyl)amide (27). White solid (ethyl acetate/MeOH = 50/5; recrystallized from ethyl acetate) (57% yield): mp 84−85 °C (K). ^{1}H NMR (DMSO) δ (ppm): 9.17 (s, 1H), 7.72 (s br, 1H), 6.17−6.13 (m, 3H), 4.61 (t, 1H, J = 5.1 Hz), 3.86 (t, 2H, J = 6.1 Hz), 3.40−3.33 (m, 2H), 3.15−3.09 (m, 2H), 2.42 (t, 2H, J = 7.3 Hz), 2.06 (t, 2H, J = 7.2 Hz), 1.66−1.52 (mm, 8H), 1.48−1.25 (mm, 24H), 0.87 (t, 3H, J = 6.3 Hz). Anal. ($C_{29}H_{51}NO_4$) C, H, N.

16-(3-Hydroxy-5-pentylphenoxy)hexadecanoic Acid Cyclopropylamide (28). White solid ($CHCl_3$/MeOH = 48/2) (88.5% yield): mp 91.0 °C (M). ^{1}H NMR ($CDCl_3$) δ (ppm): 6.29−6.24 (m, 3H), 5.52 (s br, 1H), 3.89 (t, 2H, J = 6.4 Hz), 2.72−2.67 (m, 1H), 2.48 (t, 2H, J = 7.6 Hz), 2.11 (t, 2H, J = 7.5 Hz), 1.76−1.66 (mm, 8H), 1.57−1.24 (mm, 24H), 0.87 (t, 3H, J = 6.5 Hz), 0.80−0.71 (m, 2H), 0.55−0.42 (m, 2H). Anal. ($C_{30}H_{51}NO_3$) C, H, N.

16-(3-Hydroxy-5-pentylphenoxy)hexadecanoic Acid (4-Hydroxyphenyl)amide (29). White solid ($CHCl_3$/MeOH = 46/4) (83.0% yield): mp 89.5 °C (M). ^{1}H NMR (DMSO) δ (ppm): 9.50 (s, 1H), 9.30 (s, 1H), 9.12 (s br, 1H), 7.29 (half of AB_q, 2H, J = 8.4 Hz), 6.63 (half of AB_q, 2H, J = 8.6 Hz), 6.12−6.07 (m, 3H), 3.80 (t, 2H, J = 6.3 Hz), 2.37 (t, 2H, J = 7.4 Hz), 2.14 (t, 2H, J = 7.6 Hz), 1.70−1.15 (mm, 32H), 0.81 (t, 3H, J = 6.4 Hz). Anal. ($C_{33}H_{51}NO_4$) C, H, N.

6-(3-Hydroxyphenoxy)hexanoic Acid (2-Hydroxyethyl)-amide (30). Pale pink oil (ethyl acetate/MeOH = 50/2) (50.0% yield). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.70 (s br, 1H), 7.41 (s br, 1H), 7.02 (t, 1H, J = 8.3 Hz), 6.97−6.33 (m, 3H), 4.31 (s br, 1H), 3.87 (t, 2H, J = 6.3 Hz), 3.62−3.57 (m, 2H), 3.35−3.27 (m, 2H), 2.23 (t, 2H, J = 7.2 Hz), 1.74−1.58 (m, 4H), 1.50−1.43 (m, 2H). MS *m/z*: 268 $[M + 1]^+$ (100), 290 $[M + Na]^+$. Anal. ($C_{14}H_{21}NO_4$) C, H, N.

6-(3-Hydroxyphenoxy)hexanoic Acid Cyclopropylamide (31). White needles ($CHCl_3$/MeOH = 47/3) (86% yield): 102.5 °C (M). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.12−7.04 (m, 1H), 6.43−6.40 (m, 3H), 6.11 (s, 1H), 5.63 (s br, 1H), 3.90 (t, 2H, J = 6.1 Hz), 2.74−2.67 (m, 1H), 2.14 (t, 2H, J = 7.3 Hz), 1.82−1.62 (mm, 4H), 1.55−1.37 (m, 2H), 0.80−0.70 (m, 2H), 0.50−0.47 (m, 2H). MS: 264 $[M + 1]^+$, 527 $[2M + 1]^+$, 549 $[2M + Na]^+$ (100). Anal. ($C_{15}H_{21}NO_3$) C, H, N.

6-(3-Hydroxyphenoxy)hexanoic Acid (4-Hydroxyphenyl)amide (32). Pale pink solid ($CHCl_3$/MeOH = 45/5; recrystallized from ethyl acetate) (88.0% yield): 123.1 °C (M). ^{1}H NMR (DMSO) δ (ppm): 9.53 (s, 1H), 9.26 (s, 1H), 9.05 (s, 1H), 7.31 (half of AB_q, 2H, J = 8.8 Hz), 6.95 (t, 1H, J = 8.1 Hz), 6.64 (half of AB_q, 2H, J = 8.7 Hz), 6.31−6.27 (m, 3H), 3.85 (t, 2H, J = 6.3 Hz), 2.23 (t, 2H, J = 7.2 Hz), 1.74−1.53 (m, 4H), 1.46−1.36 (m, 2H). Anal. ($C_{18}H_{21}NO_4$) C, H, N.

11-(3-Hydroxyphenoxy)undecanoic Acid (2-Hydroxyethyl)amide (33). Cream solid (Ethyl acetate/MeOH = 50/4) (34% yield): mp 72.1 °C (M). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.10 (t, 1H, J = 8.0 Hz), 6.44−6.38 (m, 3H), 6.15 (s br, 1H), 5.96 (s br, 1H), 3.92 (t, 2H, J = 6.2 Hz), 3.74−3.70 (m, 2H), 3.46−3.38 (m, 2H), 2.58 (s br, 1H), 2.19 (t, 2H, J = 7.5 Hz), 2.02−1.56 (mm, 6H), 1.43−1.24 (mm, 10H). MS *m/z*: 338 $[M + 1]^+$, 360 $[M + Na]^+$, 697 $[2M + Na]^+$ (100). Anal. ($C_{19}H_{31}NO_4$) C, H, N.

11-(3-Hydroxyphenoxy)undecanoic Acid Cyclopropilamide (34). White solid (Ethyl acetate) (90% yield): mp 92.8 °C (M). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.08 (t, 1H, J = 8.2 Hz), 6.50 (s br, 1H), 6.47−6.39 (m, 3H), 5.60 (s br, 1H), 3.91 (t, 2H, J = 6.3 Hz), 2.76−2.66 (m, 1H), 2.11 (t, 2H, J = 7.2 Hz), 1.79−1.60 (mm, 4H), 1.46−1.27 (mm, 12H), 0.80−0.70 (m, 2H), 0.48−0.42 (m, 2H). MS *m/z*: 334 $[M + 1]^+$, 667 $[2M + 1]^+$ (100), 689 $[2M + Na]^+$. Anal. ($C_{20}H_{31}NO_3$) C, H, N.

11-(3-Hydroxyphenoxy)undecanoic Acid (4-Hydroxyphenyl)amide (35). White solid ($CHCl_3$/MeOH = 45/5) (79% yield): mp 121.2 °C (M). ^{1}H NMR (DMSO) δ (ppm): 9.50 (s, 1H), 9.26 (s, 1H), 9.05 (s, 1H), 7.30 (half of AB_q, 2H, J = 8.7 Hz), 6.98 (t, 1H, J = 8.0 Hz), 6.63 (half of AB_q, 2H, J = 8.6 Hz), 6.31−6.26 (m, 3H), 3.83 (t, 2H, J = 6.4 Hz), 2.19 (t, 2H, J = 7.3 Hz), 1.62−1.56 (m, 4H), 1.53−1.24 (mm, 12H). Anal. ($C_{23}H_{31}NO_4$) C, H, N.

16-(3-Hydroxyphenoxy)hexadecanoic Acid (2-Hydroxyethyl)amide (36). White solid (Ethyl acetate/MeOH = 50/1) (35% yield): mp 94.5 °C (M). ^{1}H NMR (DMSO) δ (ppm): 9.51 (s, 1H), 7.91 (s br, 1H), 7.44 (t, 1H, J = 8.2 Hz), 6.81−6.75 (m, 3H), 4.80 (t, 1H, J = 5.5 Hz), 4.33 (t, 2H, J = 6.4 Hz), 3.94−3.85 (m, 2H), 3.66−3.57 (m, 2H), 2.54 (t, 2H, J = 7.0 Hz), 2.18−2.10 (m, 4H), 2.00−1.70 (mm, 22H). Anal. ($C_{24}H_{41}NO_4$) C, H, N.

16-(3-Hydroxyphenoxy)hexadecanoic Acid Cyclopropylamide (37). White bright solid (Ethyl acetate/MeOH = 50/4; recrystallized Ethyl acetate) (78% yield): mp 105.6 °C (M). ^{1}H NMR (DMSO) δ (ppm): 9.25 (s, 1H), 7.73 (s br, 1H), 6.98 (t, 1H, J = 7.9 Hz), 6.31−6.26 (m, 3H), 3.83 (t, 2H, J = 6.4 Hz), 2.58−2.51 (m, 1H), 1.94 (t, 2H, J = 7.3 Hz), 1.64−1.59 (m, 2H), 1.41−1.20 (mm, 24H), 0.58−0.49 (m, 2H), 0.40−0.26 (m, 2H). Anal. ($C_{25}H_{41}NO_3$) C, H, N.

16-(3-Hydroxyphenoxy)hexadecanoic Acid (4-Hydroxyphenyl)amide (38). White solid ($CHCl_3$/MeOH = 50/5) (71.5% yield): 123.6 °C (M). ^{1}H NMR (DMSO) δ (ppm): 9.57 (s, 1H), 9.32 (s,1H), 9.05 (s, 1H), 7.36 (half of AB_q, 2H, J = 8.6 Hz), 7.04 (t, 1H, J = 7.9 Hz), 6.69 (half of AB_q, 2H, J = 8.6 Hz), 6.37−6.32 (m, 3H), 3.89 (t, 2H, J = 6.3 Hz), 2.24 (t, 2H, J = 7.3 Hz), 1.69−1.57 (m, 4H), 1.50−1.27 (mm, 22H). Anal. ($C_{28}H_{41}NO_4$) C, H, N.

6-(3-Hydroxy-4-hexylphenoxy)hexanoic Acid (2-Hydroxyethyl)amide (39). Pale yellow solid ($CHCl_3$/MeOH = 46/4) (55% yield): mp 71.2 °C (M). ^{1}H NMR (Acetone-d_6) δ (ppm): 8.42 (s, 1H), 7.42 (s br, 1H), 6.93 (d, 1H, J = 8.0 Hz), 6.45 (d, 1H, J = 2.0 Hz), 6.32 (dd, 1H, J = 2.0 Hz, J = 8.0 Hz), 4.30 (t, 1H, J = 5.2 Hz), 3.87 (t, 2H, J = 6.3 Hz), 3.67−3.59 (m, 2H), 3.40−3.31 (m, 2H), 2.54 (t, 2H, J = 7.5 Hz), 2.27 (t, 2H, J = 7.3 Hz), 1.76−1.65 (m, 4H), 1.61−1.42 (mm, 4H), 1.32−1.30 (m, 6H), 0.88 (t, 3H, J = 6.1 Hz). MS *m/z*: 352 $[M + 1]^+$, 374 $[M + Na]^+$ (100), 725 $[2M + Na]^+$. Anal. ($C_{20}H_{33}NO_4$) C, H, N.

6-(3-Hydroxy-4-hexylphenoxy)hexanoic Acid Cyclopropylamide (40). White bright solid (Ethyl acetate; recrystallized from *n*.hexane) (70% yield): mp 134.2 °C (M). ^{1}H NMR 300 MHz (DMSO) δ (ppm): 9.11 (s, 1H), 7.80 (d, 1H, J = 3.6 Hz)), 6.85 (d, 1H, J = 8.4 Hz), 6.31 (d, 1H, J = 2.4 Hz), 6.24 (dd, 1H, J = 2.4 Hz, J = 8.4 Hz), 3.80 (t, 2H, J = 6.6 Hz), 2.61−2.53 (m, 1H), 2.42 (t, 2H, J = 7.3 Hz), 2.00 (t, 2H, J = 7.1 Hz), 1.68−1.60 (m, 2H), 1.55−1.41 (m, 4H), 1.37−1.23 (mm, 8H), 0.83 (t, 3H, J = 6.6 Hz), 0.60−0.53 (m, 2H), 0.36−0.31 (m, 2H). MS *m/z*: 348 $[M + 1]^+$ (100), 695 $[2M + 1]^+$. Anal. ($C_{21}H_{33}NO_3$) C, H, N.

6-(3-Hydroxy-4-hexylphenoxy)hexanoic Acid (4-Hydroxyphenyl)amide (41). White solid ($CHCl_3$/MeOH = 47/3) (79.5% yield): mp 128.4 °C. ^{1}H NMR (Acetone-d_6) δ (ppm): 8.82 (s, 1H), 8.00 (s br, 1H), 7.43 (half of AB_q, 2H, J = 8.6 Hz), 6.92 (half of AB_q, 2H, J = 8.6 Hz), 6.73 (d, 1H, J = 8.8 Hz), 6.40 (d, 1H, J = 2.7 Hz), 6.31 (dd, 1H, J = 2.5 Hz, J = 8.7 Hz), 3.87 (t, 2H, J = 6.4 Hz), 2.51 (t, 2H, J = 7.4 Hz), 2.32 (t, 2H, J = 7.2 Hz), 1.77−1.64 (m, 6H), 1.55−1.44 (m, 4H), 1.40−1.27 (m, 4H), 0.85 (t, 3H, J = 6.6 Hz). Anal. ($C_{24}H_{33}NO_4$) C, H, N.

11-(3-Hydroxy-4-hexylphenoxy)undecanoic Acid (2-Hydroxyethyl)amide (42). White solid (Ethyl acetate/MeOH = 50/4) (43% yield): mp 85.3 °C (M). ^{1}H NMR ($CDCl_3$) δ (ppm): 6.96 (d, 1H, J = 9.0 Hz), 6.40−6.35 (m, 2H), 5.96 (s br, 1H), 3.89 (t, 2H, J = 6.2 Hz), 3.73 (t, 2H, J = 5.0 Hz), 3.46−3.39 (m, 2H), 2.51 (t, 2H, J = 7.6 Hz), 2.21 (t, 2H, J = 7.5 Hz), 1.76−1.52 (mm, 8H), 1.45−1.22 (mm, 16H), 0.87 (t, 3H, J =

6.4 Hz). MS *m/z*: 422 $[M + 1]^+$, 444 $[M + Na]^+$ (100). Anal. ($C_{25}H_{43}NO_4$) C, H, N.

11-(3-Hydroxy-4-hexylphenoxy)undecanoic Acid Cyclopropylamide (43). White bright solid (Ethyl acetate; recrystallized from ethyl acetate/*n*.hexane) (81% yield): 112.3 °C (M). ^{1}H NMR 300 MHz (DMSO) δ (ppm): 9.10 (s, 1H), 7.77 (s br, 1H), 6.85 (d, 1H, J = 8.4 Hz), 6.30 (d, 1H, J = 2.4 Hz), 6.24 (dd, 1H, J = 2.4 Hz, J = 8.0 Hz), 3.81 (t, 2H, J = 6.4 Hz), 2.59−2.53 (m, 1H), 2.39 (t, 2H, J = 7.4 Hz), 1.96 (t, 2H, J = 7.4 Hz), 1.65−1.58 (m, 2H), 1.46−1.38 (m, 4H), 1.34−1.23 (mm, 18H), 0.83 (t, 3H, J = 6.4 Hz), 0.57−0.53 (m, 2H), 0.34−0.31 (m, 2H). MS *m/z*: 418 $[M + 1]^+$, 440 $[M + Na]^+$ (100). Anal. ($C_{26}H_{43}NO_3$) C, H, N.

11-(3-Hydroxy-4-hexylphenoxy)undecanoic Acid (4-Hydroxyphenyl)amide (44). White solid ($CHCl_3$/MeOH = 48/2) (88.0% yield): mp 121.2 °C (M). ^{1}H NMR (DMSO) δ (ppm): 9.48 (s, 1H), 9.04 (s, 1H), 9.02 (s, 1H), 7.30 (half of AB_q, 2H, J = 8.8 Hz), 6.84 (d, 1H, J = 8.1 Hz), 6.63 (half of AB_q, 2H, J = 8.8 Hz), 6.29 (d, 1H, J = 2.1 Hz), 6.23 (dd, 1H, J = 2.3 Hz, J = 8.2 Hz), 3.80 (t, 2H, J = 6.4 Hz), 2.38 (t, 2H, J = 7.4 Hz), 2.20 (t, 2H, J = 7.4 Hz), 1.65−1.40 (mm, 10H), 1.37−1.22 (mm, 14H), 0.82 (t, 3H, CH_3, J = 6.4 Hz). Anal. ($C_{29}H_{43}NO_4$) C, H, N.

16-(3-Hydroxy-4-hexylphenoxy)hexadecanoic Acid (2-Hydroxyethyl)amide (45). White solid (Ethyl acetate/MeOH = 50/1) (50% yield): mp 96.4 °C. ^{1}H NMR (DMSO) δ (ppm): 9.14 (s, 1H), 7.73 (s br, 1H), 6.88 (d, 1H, J = 8.3 Hz), 6.34 (d, 1H, J = 1.7 Hz), 6.27 (dd, 1H, J = 8.3 Hz, J = 1.7 Hz), 4.63 (t, 1H, J = 5.2 Hz), 3.84 (t, 2H, J = 6.2 Hz), 3.57−3.40 (m, 2H), 3.15−3.06 (m, 2H), 2.43 (t, 2H, J = 7.2 Hz), 2.06 (t, 2H, J = 7.3 Hz), 1.70−1.48 (mm, 8H), 1.44−1.25 (mm, 26H), 0.87 (t, 3H, J = 5.8 Hz). Anal. ($C_{30}H_{53}NO_4$) C, H, N.

16-(3-Hydroxy-4-hexylphenoxy)hexadecanoic Acid Cyclopropylamide (46). White bright solid (Ethyl acetate/MeOH = 50/2; recrystallized from ethyl acetate) (94.5% yield): mp 114.3 °C (M). ^{1}H NMR (DMSO) δ (ppm): 9.15 (s, 1H), 7.80 (s br, 1H), 6.82 (d, 1H, J = 8.1 Hz), 6.34 (d, 1H, J = 2.6 Hz), 6.20 (dd, 1H, J = 2.4 Hz, J = 8.3 Hz), 3.79 (t, 2H, J = 6.3 Hz), 2.55−2.48 (m, 1H), 2.37 (t, 2H, J = 7.4 Hz), 1.94 (t, 2H, J = 7.3 Hz), 1.62−1.55 (m, 4H), 1.41−1.20 (mm, 30H), 0.82 (t, 3H, J = 6.0 Hz), 0.58−0.49 (m, 2H), 0.34−0.27 (m, 2H). Anal. ($C_{31}H_{53}NO_3$) C, H, N.

16-(3-Hydroxy-4-hexylphenoxy)hexadecanoic Acid (4-Hydroxyphenyl)amide (47). White solid ($CHCl_3$/MeOH = 45/5) (81% yield): mp 133.2 °C (M). ^{1}H NMR (DMSO) δ (ppm): 9.50 (s, 1H), 9.06 (s, 1H), 9.04 (s, 1H), 7.30 (half of AB_q, 2H, J = 8.5 Hz), 6.83 (d, 1H, J = 8.0 Hz), 6.62 (half of AB_q, 2H, J = 8.5 Hz), 6.28 (s, 1H), 6.22 (d, 1H, J = 8.1 Hz), 3.80 (t, 2H, J = 6.2 Hz), 2.38 (t, 2H, J = 7.3 Hz), 2.18 (t, 2H, J = 7.1 Hz), 1.61−1.21 (mm, 34H), 0.81 (t, 3H, J = 6.4 Hz). Anal. ($C_{34}H_{53}NO_4$) C, H, N.

6-(2-Hexyl-5-hydroxyphenoxy)hexanoic Acid (2-Hydroxyethyl)amide (48). Pale yellow thick oil ($CHCl_3$/MeOH = 46/4) (50% yield). ^{1}H NMR (Acetone-d_6) δ (ppm): 8.23 (s, 1H), 7.27 (s br, 1H), 6.88 (d, 1H, J = 8.0 Hz), 6.42 (d, 1H, J = 2.0 Hz), 6.35−6.31 (m, 1H), 4.08 (s br, 1H), 3.91 (t, 2H, J = 6.3 Hz), 3.61−3.58 (m, 2H), 3.36−3.28 (m, 2H), 2.50 (t, 2H, J = 7.4 Hz), 2.25 (t, 2H, J = 7.2 Hz), 1.85−1.67 (mm, 4H), 1.63−1.52 (m, 4H), 1.49−1.31 (mm, 6H), 0.88 (t, 3H, J = 6.4 Hz). MS *m/z*: 353 $[M + D]^+$, 374 $[M + Na]^+$, 725 $[2M + Na]^+$ (100). Anal. ($C_{20}H_{33}NO_4$) C, H, N.

6-(2-Hexyl-5-hydroxyphenoxy)hexanoic Acid Cyclopropylamide (49). Pale yellow thick oil (Ethyl acetate) (80% yield). ^{1}H NMR 300 MHz (DMSO) δ (ppm): 9.06 (s, 1H), 7.80 (d, 1H, J = 3.9 Hz)), 6.81 (d, 1H, J = 8.1 Hz), 6.30 (d, 1H, J = 2.3 Hz), 6.21 (dd, 1H, J = 2.2 Hz, J = 8.1 Hz), 3.82 (t, 2H, J = 6.2 Hz), 2.61−2.52 (m, 1H), 2.38 (t, 2H, J = 7.1 Hz), 2.00 (t, 2H, J = 7.1 Hz), 1.71−1.62 (m, 2H), 1.56−1.47 (m, 2H), 1.42−1.34 (m, 4H), 1.27−1.23 (mm, 6H), 0.82 (t, 3H, J = 6.6 Hz), 0.58−0.52 (m, 2H), 0.35−0.30 (m, 2H). MS *m/z*: 348 $[M + 1]^+$ (100), 695 $[2M + 1]^+$. Anal. ($C_{21}H_{33}NO_3$) C, H, N.

6-(2-Hexyl-5-hydroxyphenoxy)hexanoic Acid (4-Hydroxyphenyl)amide (50). White solid ($CHCl_3$/MeOH = 47/3) (63% yield): mp 106.0 °C (M). ^{1}H NMR (Acetone-d_6) δ (ppm): 9.52 (s, 1H), 9.04 (s, 1H), 9.02 (s, 1H), 7.30 (half of AB_q, 2H, J = 8.8 Hz), 6.80 (d, 1H, J = 8.1 Hz), 6.62 (half of AB_q, 2H, J = 8.7 Hz), 6.28 (s, 1H), 6.20 (d, 1H, J = 8.0 Hz), 3.83 (t, 2H, J = 6.0 Hz), 2.36 (t, 2H, J = 7.3 Hz), 2.23 (t, 2H, J = 7.1 Hz), 1.70−1.57 (mm, 10H), 1.53−1.20 (m, 4H), 0.81 (t, 3H, J = 6.7 Hz). Anal. ($C_{24}H_{33}NO_4$) C, H, N.

11-(2-Hexyl-5-hydroxyphenoxy)undecanoic Acid (2-Hydroxyethyl)amide (51). Pale yellow solid (Ethyl acetate/MeOH = 50/4) (25% yield): mp 75.4 °C (M). ^{1}H NMR ($CDCl_3$) δ (ppm): 6.90 (d, 1H, J = 7.9 Hz), 6.38−6.36 (d, 1H, J = 2.0 Hz), 6.31 (dd, 1H, J = 7.9 Hz, J = 2.0 Hz), 6.08 (s br, 1H), 3.87 (t, 2H, J = 6.3 Hz), 3.70 (t, 2H, J = 4.9 Hz), 3.43−3.36 (m, 2H), 2.48 (t, 2H, J = 7.5 Hz), 2.17 (t, 2H, J = 7.6 Hz), 1.81−1.68 (m, 2H), 1.63−1.43 (mm, 4H), 1.40−1.27 (mm, 18H), 0.86 (t, 3H, J = 6.3 Hz). MS *m/z*: 422 $[M + 1]^+$ (100), 444 $[M + Na]^+$, 843 $[2M + 1]^+$. Anal. ($C_{25}H_{43}NO_4$) C, H, N.

11-(2-Hexyl-5-hydroxyphenoxy)undecanoic Acid Cyclopropylamide (52). White solid ($CHCl_3$/MeOH = 47/3) (90% yield): mp 57.3 °C (M). ^{1}H NMR 300 MHz (DMSO) δ (ppm): 9.05 (s, 1H), 7.76 (s br, 1H), 6.81 (d, 1H, J = 7.7 Hz), 6.29 (s, 1H), 6.20 (d, 1H, J = 8.1 Hz), 3.83 (t, 2H, J = 5.5 Hz), 2.58−2.54 (m, 1H), 2.38 (t, 2H, J = 7.3 Hz), 1.95 (t, 2H, J = 6.9 Hz), 1.69−1.64 (m, 2H), 1.43−1.38 (m, 4H), 1.26−1.14 (mm, 18H), 0.82 (t, 3H, J = 6.1 Hz), 0.57−0.53 (m, 2H), 0.33−0.31 (m, 2H). MS *m/z*: 418 $[M + 1]^+$, 440 $[M + Na]^+$ (100). Anal. ($C_{26}H_{43}NO_3$) C, H, N.

11-(2-Hexyl-5-hydroxyphenoxy)undecanoic Acid (4-Hydroxyphenyl)amide (53). White solid ($CHCl_3$/MeOH = 47/3; recrystallized diethyl ether) (83% yield): mp 108.7 °C (M). ^{1}H NMR (Acetone-d_6) δ (ppm): 9.05 (s, 1H), 9.00 (s, 1H), 8.80 (s, 1H), 7.43 (half of AB_q, 2H, J = 8.8 Hz), 6.86 (d, 1H, J = 7.9 Hz), 6.73 (half of AB_q, 2H, J = 8.8 Hz), 6.40 (d, 1H, J = 2.5 Hz), 6.30 (dd, 1H, J = 2.5 Hz, J = 7.9 Hz), 3.90 (t, 2H, J = 6.1 Hz), 2.48 (t, 2H, J = 7.4 Hz), 2.28 (t, 2H, J = 7.2 Hz), 1.80−1.60 (mm, 14H), 1.50−1.32 (mm, 10H), 0.86 (t, 3H, J = 6.3 Hz). Anal. ($C_{29}H_{43}NO_4$) C, H, N.

16-(2-Hexyl-5-hydroxyphenoxy)hexadecanoic Acid (2-Hydroxyethyl)amide (54). White solid (Ethyl acetate/MeOH = 50/1) (60% yield): mp 77.2 °C (M). ^{1}H NMR (DMSO) δ (ppm): 9.00 (s, 1H), 7.64 (s br, 1H), 6.80 (d, 1H, J = 8.0 Hz), 6.28 (d, 1H, J = 1.7 Hz), 6.20 (dd, 1H, J = 8.0 Hz, J = 1.7 Hz), 4.53 (t, 1H, J = 5.2 Hz), 3.83 (t, 2H, J = 5.8 Hz), 3.40−3.33 (m, 2H), 3.10−3.05 (m, 2H), 2.38 (t, 2H, J = 7.3 Hz), 2.00 (t, 2H, J = 7.4 Hz), 1.66−1.63 (m, 2H), 1.41−1.15 (mm, 32H), 0.82 (t, 3H, J = 5.9 Hz). Anal. ($C_{30}H_{53}NO_4$) C, H, N.

16-(2-Hexyl-5-hydroxyphenoxy)hexadecanoic Acid Cyclopropylamide (55). White solid ($CHCl_3$/MeOH = 47/3) (80% yield): mp 72.8 °C (M). ^{1}H NMR 300 MHz (DMSO) δ (ppm): 9.05 (s, 1H), 7.75 (s br, 1H), 6.81 (d, 1H, J = 8.1 Hz), 6.29 (d, 1H, J = 2.4 Hz), 6.20 (dd, 1H, J = 2.4 Hz, J = 8.1 Hz), 3.83 (t, 2H, J = 6.3 Hz), 2.56−2.51 (m, 1H), 2.38 (t, 2H, J = 7.2 Hz), 1.95 (t, 2H, J = 7.2 Hz), 1.69−1.62 (m, 2H), 1.42−1.20 (mm, 32H), 0.82 (t, 3H, J = 6.3 Hz), 0.56−0.52 (m, 2H), 0.34−0.31 (m, 2H). Anal. ($C_{31}H_{53}NO_3$) C, H, N.

16-(2-Hexyl-5-hydroxyphenoxy)hexadecanoic Acid (4-Hydroxyphenyl)amide (56). White solid ($CHCl_3$/MeOH = 46/4) (70% yield): mp 82.4 °C (M). ^{1}H NMR (DMSO) δ (ppm): 9.45 (s, 1H), 9.05 (s, 1H), 9.02 (s, 1H), 7.30 (half of AB_q, 2H, J = 8.7 Hz), 6.91 (d, 1H, J = 8.0 Hz), 6.75 (half of AB_q, 2H, J = 8.7 Hz), 6.35 (d, 1H, J = 2.2 Hz), 6.29 (dd, 1H, J = 2.2 Hz, J = 8.0 Hz), 3.88 (t, 2H, J = 6.3 Hz), 2.40 (t, 2H, J = 7.5 Hz), 2.33 (t, 2H, J = 7.5 Hz), 1.80−1.62 (m, 4H), 1.58−1.25 (mm, 30H), 0.86 (t, 3H, J = 6.5 Hz). Anal. ($C_{34}H_{53}NO_4$) C, H, N.

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Supporting Information Available: Yields, melting points, and chemical and spectroscopic data of all synthe-

sized esters; elemental analysis data of final products. This material is available free of charge via the Internet at http://pubs.acs.org.

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