New *N*-Arachidonoylserotonin Analogues with Potential "Dual" Mechanism of Action against Pain

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N-Arachidonoylserotonin (AA-5-HT, **1a**) is an inhibitor of fatty acid amide hydrolase (FAAH) that acts also as an antagonist of transient receptor potential vanilloid-type 1 (TRPV1) channels and is analgesic in rodents. We modified the chemical structure of **1a** with the aim of developing "hybrid" FAAH/TRPV1 blockers more potent than the parent compound or obtaining analogues with single activity at either of the two targets to study the mechanism of the analgesic action of **1a**. Thirty-eight AA-5-HT analogues, containing a serotonin "head" bound to a variety of lipophilic moieties via amide, urea, or carbamate functionalities, were synthesized. Unlike **1a**, most of the new compounds possessed activity at only one of the two considered targets. The amides **1b** and **1c** of α- and γ-linolenic acid, however, showed "hybrid" activity similar to **1a**. The carbamate **3f** (OMDM106), although unable to antagonize TRPV1 receptors, was the most potent FAAH inhibitor in this study (IC_{50} = 0.5 μM). Compounds **3f** and **1m** (OMDM129), which exhibited activity at only FAAH or TRPV1, respectively, were 10-fold less potent than **1a** at preventing formalin-induced hyperalgesia in mice.

Introduction

The proteins of the endocannabinoid system, including CB_1 and CB_2 cannabinoid receptors, a putative and still elusive endocannabinoid membrane transporter, and fatty acid amide hydrolase (FAAH[a]), represent excellent targets for the development of new therapeutic drugs to be employed in many pathologies, including pain, inflammation, cancer, neuronal excitotoxicity and eating and motor disorders.[1] In particular, FAAH, first identified and cloned from several mammalian species in the mid- to late 1990s,[2–5] might be considered a promising target for the treatment of chronic pain conditions. It catalyzes the hydrolysis of several bioactive fatty acid amides and esters,[6] including (1) the endogenous ligands of cannabinoid receptors, anandamide (AEA) and 2-arachidonoylglycerol (2-AG),[7–9] (2) the anandamide congeners, *N*-palmitoylethanolamide (PEA) and *N*-oleoylethanolamide, which do not bind to cannabinoid receptors,[10–13] and (3) the sleep-inducing factor, *cis*-9-octadecenamide[14] (oleamide) and its congeners (Figure 1). Since FAAH null mice[15] exhibit less sensitivity to several pain stimuli,[16,17] this enzyme has been suggested to control tonically the levels of endogenous analgesic fatty acid amides, such as AEA and PEA, and this indicates that synthetic compounds with strong inhibitory action on FAAH may act as analgesic and anti-inflammatory agents.

The transient receptor potential vanilloid-type 1 (TRPV1) channel is another potential new target for the development of analgesic and anti-inflammatory drugs. It has been described as a molecular integrator, expressed mostly in unmyelinated sensory fiber afferents of the C-type, of various nociceptive stimuli, and of both a physical (high temperature and low pH) and chemical (plant toxins and endogenous fatty acid derivatives) nature.[18] Several studies using animal models have shown altered levels of expression of TRPV1 in pain states. In particular, in models of neuropathic pain,[19–22] there is evidence that TRPV1 expression is decreased in the injured nerve fibers but increased in those proximal to the site damage. Both agonists, through desensitization of TRPV1 receptors[23,24] or inhibition of voltage-activated Ca^{2+} channels,[25] and antagonists[26] have been proposed as new therapies for the treatment of chronic and inflammatory pain.

In view of this background, a possible strategy for the development of new analgesic drugs might be to design molecules with the capability of both (1) inhibiting FAAH in order to elevate the levels of the endogenous analgesic and anti-inflammatory substrates of this enzyme (i.e., fatty acid amides such as AEA and PEA, and the endocannabinoid 2-AG)[27,28] and (2) inactivating TRPV1 receptors, e.g., through pharmacological antagonism. *N*-Arachidonoylserotonin (AA-5-HT, **1a**, Table 1) is a well-known FAAH inhibitor (IC_{50} = 1–12 μM),[29–31] and it was also recently reported to act as a potent antagonist of both human and rat recombinant TRPV1 receptors (IC_{50} = 70–100 nM vs capsaicin 10^{-7} M).[32] This prototypical "hybrid" FAAH/TRPV1 blocker has been selected in the present study as the lead compound for the synthesis of new analogues with potential "dual" effects (FAAH inhibitors/TRPV1 antagonists). Our present aim was to investigate the structure−activity

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[a] Abbreviations: AA-5-HT, *N*-arachidonoylserotonin; AEA, anandamide; 2-AG, 2-arachidonoylglycerol; EDC, *N*-ethyl-*N*′-(3-dimethylaminopropyl)-carbodiimide hydrochloride; HEK293, human embryonic kidney cells; HOBt, 1-hydroxybenzotriazole; PEA, *N*-palmitoylethanolamide; FAAH, fatty acid amide hydrolase; I-RTX, iodoresiniferatoxin; TRPV1, transient receptor potential vanilloid-type 1.

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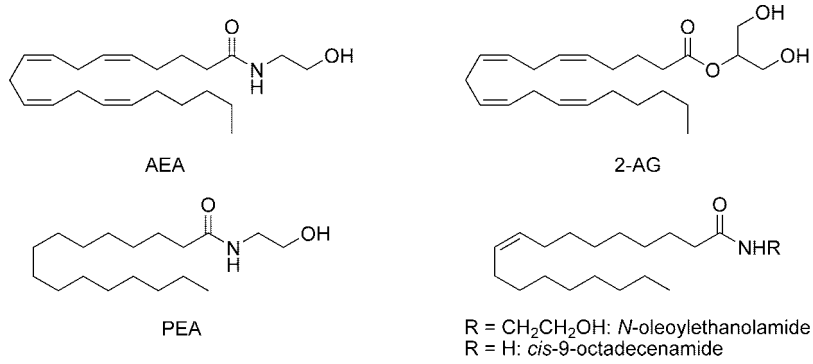


Figure 1. Substrates of fatty acid amide hydrolase (FAAH).

relationships for the interaction of **1a** with FAAH and TRPV1 in order to either develop "hybrid" FAAH/TRPV1 blockers more potent than the parent compound or obtain analogues with single activity at either of the two targets, to be used as leads for the design of new therapeutic drugs. Thirty-eight structural analogues of **1a** containing the unmodified serotonin moiety bound to a variety of lipophilic side chains were synthesized, thereby systematically modulating two of three pharmacophoric regions of **1a**, i.e., the hydrophobic region and the amide template. In fact, we have also evaluated the influence of the nature of the link between serotonin and the side chain, by synthesizing urea, amide, and carbamate derivatives. The structures of the new compounds are reported in Table 1.

Chemistry. The analogues of **1a** in Table 1 were prepared as detailed below and as summarized in Schemes 1–3. The synthesis of amides **1b**−**o** has been carried out by condensation between the appropriate carboxylic acids **4b**−**o** and serotonin using 1-hydroxybenzotriazole (HOBt)/*N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC) as the carboxylate activator (Scheme 1). Ureas **2a**−**g** were synthesized by treatment of the appropriate primary amines **5a**−**g** with bis(trichloromethyl)carbonate, followed by coupling of the resulting isocyanates with serotonin (Scheme 2). Finally, the preparation of carbamates **3a**−**q** involved conversion of the appropriate alcohols or phenols **6a**−**q** with phosgene to the corresponding chloroformates and subsequent reaction with serotonin (Scheme 3).

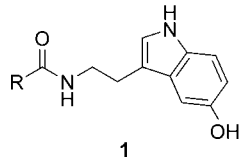
The preparation of the noncommercial reagents has been carried out as follows. 9-Phenylnonanoic acid (**4k**)[33] was obtained by oxidation of 9-phenyl-1-nonanol with pyridinium dichromate. (3-Pentylphenyl)acetic acid (**4l**) was synthesized by the Sonogashira reaction of methyl (3-iodophenyl)acetate (**7**) with 1-pentyne followed by catalytic reduction of arylalkyne **8** and alkaline hydrolysis (Scheme 4). [1,1′-Biphenyl]-3-acetic acid (**4m**)[34] was prepared by Suzuki cross-coupling of **7** with phenylboronic acid followed by alkaline hydrolysis (Scheme 5). The synthesis of [3′-pentyl-1,1′-biphenyl]-4-butanoic acid (**4n**) was carried out in six steps from 3-pentylphenol (**9**).[35] After triflation of **9**, the triflate **10** was subjected to a Suzuki cross-coupling with 3-hydroxyphenylboronic acid to give [3′-pentyl-1,1′-biphenyl]-3-ol (**11**). Triflation of **11** followed by a Sonogashira reaction of the triflate **12** with 3-butyn-1-ol afforded the alkynol **13**. Catalytic reduction of **13** to give **14** followed by oxidation of the alcoholic group with pyridinium dichromate provided eventually the acid **4n** (Scheme 6). For the preparation of 7-pentyl-2-naphthalenebutanoic acid (**4o**), 7-hydroxy-2-naphthalenyl triflate (**15**)[36] was employed as the starting material. Protection of the phenol function followed by Ni(0)-catalyzed cross-coupling of triflate **16** with pentylmagnesium chloride[37] and deprotection of the MOM protecting group[38] gave 7-pentyl-2-naphthalenol (**18**). Repetition of steps c−f of Scheme 6 on **18** afforded acid **4o** (Scheme 7). Primary amines **5f**,**g** were obtained by catalytic reduction of the appropriate nitriles. 3-Pentylaniline **5b** was prepared by Sonogashira coupling between 3-iodonitrobenzene (**22**) and 1-pentyne followed by catalytic reduction of the resulting arylalkyne **23** according to Gaudreault and co-workers[39] (Scheme 8). Alcohols **6a**−**d** were eventually obtained by reduction of the corresponding acids **4a**−**d**, activated as mixed anhydrides, with $NaBH_4$.

Biological Evaluation. In vitro assays were aimed at examining the effect of the new compounds on rat brain FAAH activity and on TRPV1 by measuring the effect on [^{14}C]anandamide hydrolysis by rat brain membranes and on capsaicin-induced intracellular Ca^{2+} elevation in HEK293 cells overexpressing the human recombinant TRPV1 receptor, respectively. We also evaluated the effect of different doses of **3f** (OMDM106) and **1m** (OMDM129), two structurally related serotonin derivatives with high activity at only either FAAH or TRPV1, respectively, compared to **1a**, on the biphasic nociceptive response induced by an intrapaw injection of a formalin-containing aqueous solution in mice in vivo. This test was used for three reasons: (1) it allows the determination of the effect of administered compounds on both acute peripheral pain (especially during the first phase of the nocifensive response to formalin) and inflammatory-like pain (especially during the second phase of the nocifensive response to formalin);[32] (2) it has been previously used to study the analgesic effects of both FAAH and TRPV1 blockers;[46,47] (3) it was originally employed to establish the analgesic effect of **1a**.[32] It is noteworthy that all pharmacological tools used in the present study to evaluate the mechanism of the in vivo antinociceptive effects of compounds **1a**, **3f**, and **1m**, i.e., AM251, AM639, and iodoresiniferatoxin (I-RTX) were inactive at inhibiting [^{14}C]anandamide hydrolysis (less than 10% inhibition) up to 50 μM; AM251 and AM639 were also inactive on TRPV1 (less than 15% stimulation or inhibition of capsaicin response) up to 10 μM (data not shown).

Results and Discussion

All newly synthesized compounds were evaluated in both TRPV1 and FAAH assays, and the results are summarized in Table 1. The most important points are as following. The urea derivatives (**2a**−**g**) are generally inactive ($IC_{50} \geq 50$ μM) FAAH inhibitors, while their TRPV1 antagonistic effects appear to be highly dependent on the length of the linker between the urea functionality and the aromatic portion and on the proper choice of the lipophilic substituents on the phenyl ring, according to structure–activity relationships developed for small-molecule TRPV1 antagonists whose structural features can be traced back to the prototypical TRPV1 antagonist capsazepine.[40] Amide

Table 1. Structures and Results of FAAH (IC_{50}) and TRPV1 (IC_{50}) Assays on **1a** and **1a** Analogues[a]



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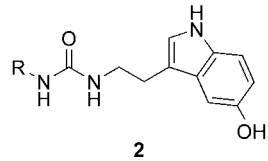

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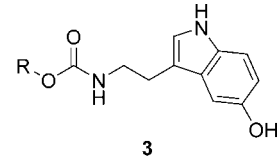


3

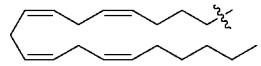
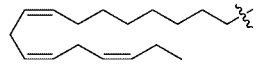
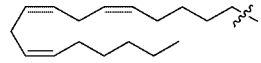
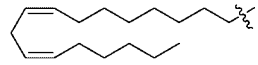
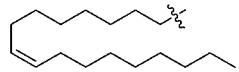
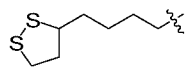
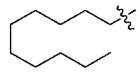
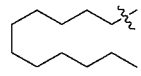
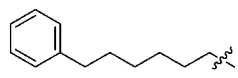
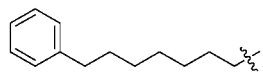
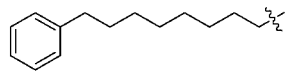
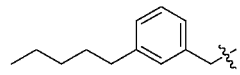
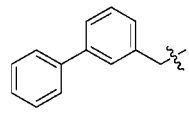
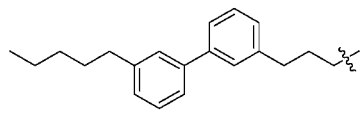
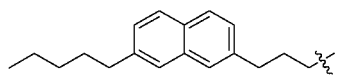
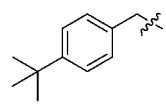
Compd	R	AEA hydrolysis IC_{50}	Human TRPV1 IC_{50}
1a		8 ± 0.6	0.27 ± 0.07
1b		10 ± 1	0.47 ± 0.16
1c		10 ± 1	0.95 ± 0.33
1d		30 ± 2	1.82 ± 0.82
1e		> 50	2.57 ± 1.31
1f		> 50	> 10
1g		> 50	0.76 ± 0.13
1h		> 50	0.74 ± 0.09
1i		> 50	9.12 ± 2.04
1j		34 ± 3	2.13 ± 1.06
1k		30 ± 2	0.68 ± 0.15
1l		> 50	0.24 ± 0.16
1m		> 50	0.43 ± 0.18
1n		50 ± 4	> 10
1o		50 ± 1	> 10
2a		50 ± 4	3.80 ± 2.29

Table 1. Continued

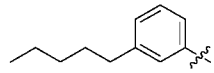
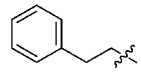
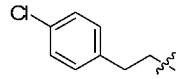
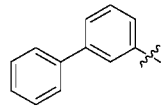
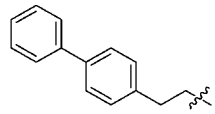
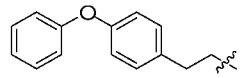
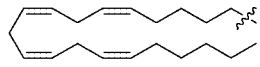
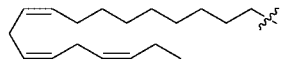
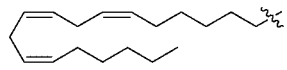
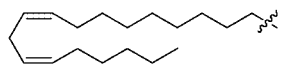
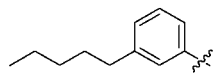
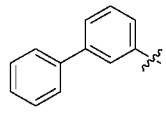
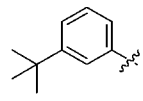
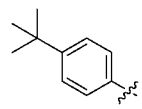
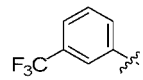
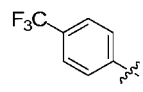
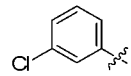
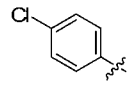
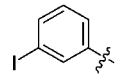
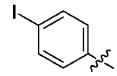
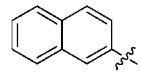
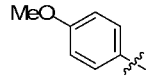
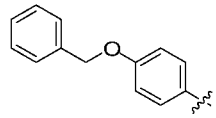
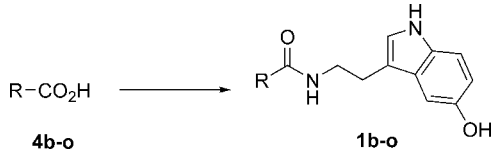
Compd	R	AEA hydrolysis IC_{50}	Human TRPV1 IC_{50}
2b		> 50	2.63 ±1.40
2c		> 50	> 10
2d		> 50	> 10
2e		> 50	0.72 ± 0.23
2f		> 50	> 10
2g		> 50	> 10
3a		> 50	2.82 ± 1.90
3b		> 50	> 10
3c		> 50	> 10
3d		> 50	> 10
3e		3.6 ± 0.2	2.40 ± 0.91
3f		0.5 ± 0.06	> 10
3g		3.7 ± 0.3	> 10
3h		> 10	5.25 ± 0.78
3i		2.2 ± 0.2	> 10
3j		6.4 ± 0.5	> 10

Table 1. Continued

Compd	R	AEA hydrolysis IC_{50}	Human TRPV1 IC_{50}
3k		1.9 ± 0.1	> 10
3l		6.8 ± 0.5	> 10
3m		1.8 ± 0.1	> 10
3n		5.0 ± 0.5	> 10
3o		10 ± 1	> 10
3p		10 ± 2	> 10
3q		1.17 ± 0.1	> 10

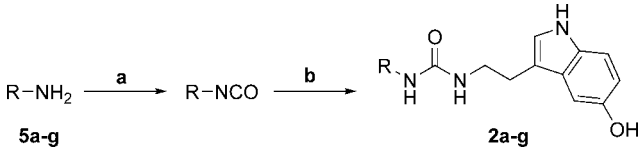
[a] Data represent mean values ± SD for at least three separate experiments performed in duplicate and are expressed as IC_{50} (μM) for FAAH and for TRPV1 assays.

Scheme 1[a]



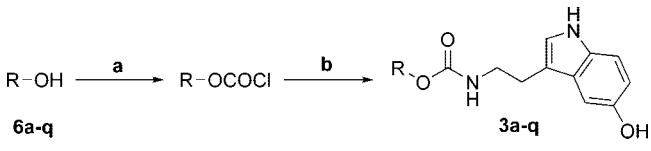
[a] Reagents and conditions: HOBt/EDC, room temp, 1 h, then serotonin·HCl, Et_3N, DMF, room temp, 16 h.

Scheme 2[a]



[a] Reagents and conditions: (a) $Cl_3COCOOCCl_3$, Et_3N, dry CH_2Cl_2, reflux, 5 h; (b) serotonin·HCl, Et_3N, dry CH_2Cl_2−pyridine, room temp, 16 h.

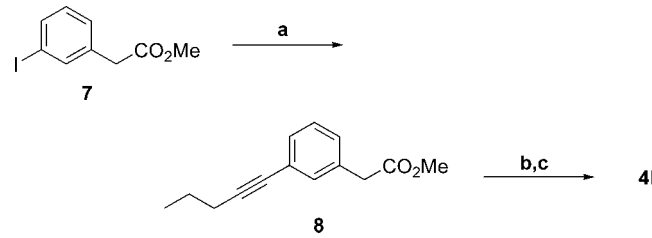
Scheme 3[a]



[a] Reagents and conditions: (a) $COCl_2$, Et_3N, dry toluene, room temp, 2 h; (b) serotonin·HCl, Et_3N, dry DMF, room temp, 16 h.

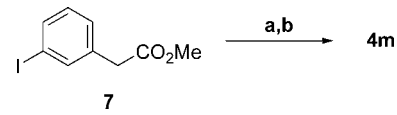
compounds with saturated aliphatic or arylaliphatic chains (**1f**−**o**) are essentially inactive as FAAH inhibitors, although the activity exhibits a modest increase with increasing alkyl chain length in the case of ω-phenylalkylamides (**1i**, **1j**, and **1k** IC_{50} >50, 34 ± 3, and 30 ± 2 μM, respectively). Remarkably, in the acyl heterocycle series of competitive FAAH inhibitors described by Boger and co-workers, the introduction of ω-phenylalkyl moieties led to the most potent inhibitors.[41] FAAH inhibitory activity of aliphatic amides increases significantly with increasing number of double bonds in the chain (**1a**−**e**). Most amides are able to antagonize TRPV1 receptors (9.12 > IC_{50} > 0.24), and in particular, **1b**,**l**,**m** exhibit equipotent antagonistic activities compared to **1a**. The nature of the lipophilic portion does not seem to influence critically the

Scheme 4[a]



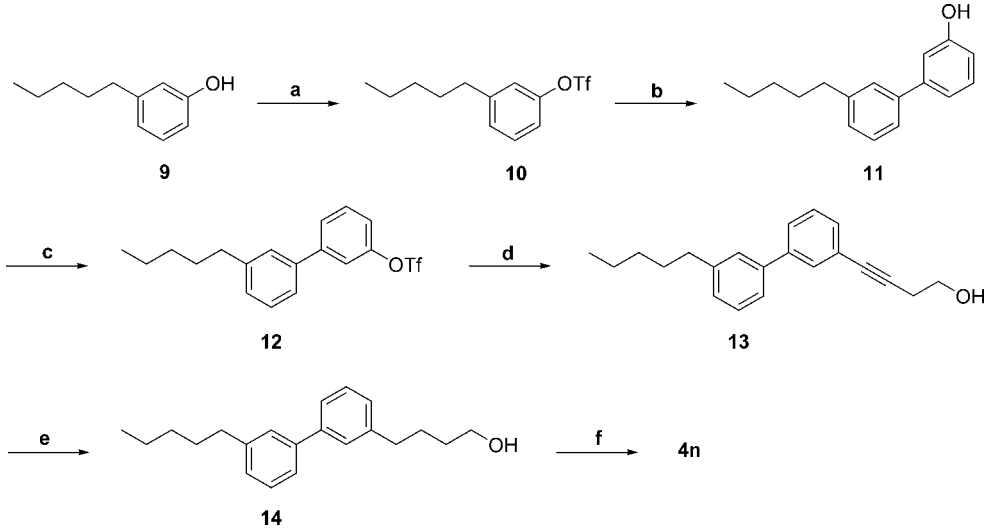
[a] Reagents and conditions: (a) 1-pentyne, $Pd(OAc)_2/2PPh_3$, CuI, DMSO−$^i Pr_2NH$, room temp, 4 h; (b) H_2, Pd/C, 12 N HCl, AcOEt, room temp, 4 h; (c) 1 N LiOH, THF−H_2O, room temp, 16 h.

Scheme 5[a]



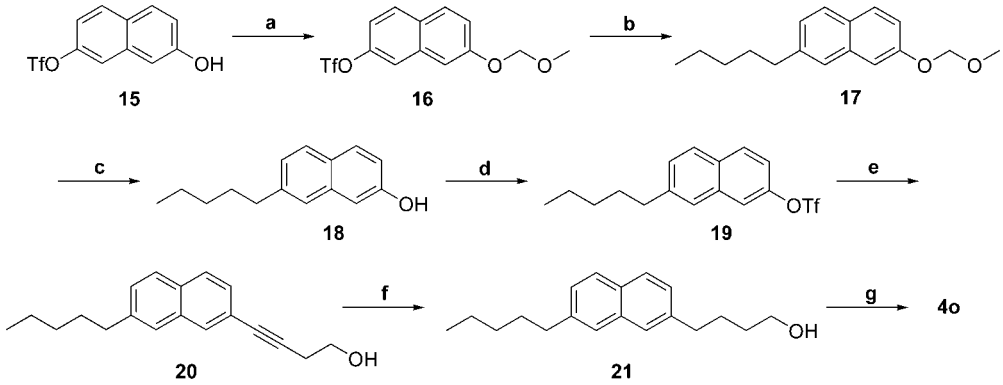
[a] Reagents and conditions: (a) phenylboronic acid, $Pd(PPh_3)_4$, K_3PO_4, DMF, 90 °C, 16 h; (b) 1 N LiOH, THF−H_2O, 16 h.

Scheme 6[a]



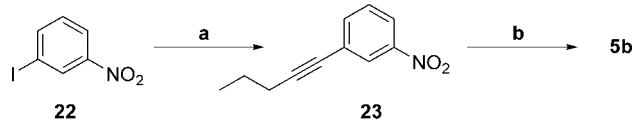
[a] Reagents and conditions: (a) $(CF_3SO_2)_2O$, 2,6-di-*tert*-butyl-4-methylpyridine, dry CH_2Cl_2, room temp, 3.5 h; (b) 3-hydroxyphenylboronic acid, $Pd(PPh_3)_4$, K_3PO_4, KBr, dioxane, 85 °C, 5 h; (c) $(CF_3SO_2)_2O$, 2,6-di-*tert*-butyl-4-methylpyridine, dry CH_2Cl_2, room temp, 16 h; (d) 3-butynol, $Pd(OAc)_2/2PPh_3$, CuI, DMSO−^{i}Pr$_2$NH, room temp, 48 h; (e) H_2, Pd/C, AcOEt, room temp, 3 h; (f) PDC, DMF, room temp, 16 h.

Scheme 7[a]



[a] Reagents and conditions: (a) $MeOCH_2Cl$, Et_3N, dry THF, room temp, 16 h; (b) 2 M $C_5H_{11}MgCl$, $NiCl_2$(dppp), dry THF, room temp, 1 h; (c) CBr_4, dry ^{i}PrOH, reflux, 1.5 h; (d) $(CF_3SO_2)_2O$, 2,6-di-*tert*-butyl-4-methylpyridine, dry CH_2Cl_2, room temp, 2.5 h; (e) 3-butynol, $Pd(OAc)_2/2PPh_3$, CuI, DMSO−^{i}Pr$_2$NH, room temp, 4 h; (f) H_2, Pd/C, AcOEt, room temp, 1.5 h; (g) PDC, dry DMF, room temp, 16 h.

Scheme 8[a]



[a] Reagents and conditions: (a) 1-pentyne, $Pd(OAc)_2/2PPh_3$, CuI, DMSO−^{i}Pr$_2$NH, room temp, 4 h; (b) H_2, Pd/C, EtOH, 60 °C, 6 h.

activity of amides on TRPV1. Special attention should be paid to compounds **1b** and **1c**, which behave as the lead compound **1a** as both FAAH inhibitors (IC_{50} = 10 vs 8 μM for **1a**) and TRPV1 antagonists (IC_{50} = 0.47 ± 0.16 and 0.95 ± 0.33 vs 0.27 ± 0.07 for **1a**). All carbamates with aromatic O-substituents show good FAAH inhibitory activities, while the presence of an unsaturated alkyl chain is detrimental to the inhibitory activity, according to the notion that the O-substituted moiety of carbamates acts as the leaving group in the reaction leading to enzyme carbamoylation.[42] Compounds with meta substituted aromatic rings are invariably more potent as FAAH inhibitors than the para substituted ones, independent of the nature of the substituent. The strongest FAAH inhibition is observed with the *m*-biphenyl derivative **3f**, a result similar to that previously described by Mor and co-workers for their alkylcarbamic acid aryl ester series of FAAH inhibitors.[43] Carbamates are generally unable to antagonize TRPV1 receptors, with the exception of **3a**, **3e**, and **3h** (5.25 > IC_{50} > 2.40). Some of the compounds of this series (**3e**, **3o**, **3f**, and **3q**) were also evaluated as inhibitors of anandamide cellular uptake, but they were inactive up to 25 μM (data not shown). A comparison between amides and carbamates with analogous lipophilic moieties (e.g., **1a**−**3a**, **1b**−**3b**, **1c**−**3c, 1d**−**3d**, and **1l**−**3e**) indicates a 10-fold difference of the TRPV1 antagonistic effects between the two classes of compounds. In summary, (a) the urea motif might be suitable for the interaction with TRPV1 as a central hydrogen bond acceptor/donor motif, but none of our ureidic compounds were able to efficaciously inhibit FAAH. (b) The amide functionality seems to serve as a better template for the "dual" action than the carbamate functionality in compounds with unsaturated aliphatic chains (see compounds **1a**−**d** and **3a**−**d**). (c) The carbamate moiety appears to be superior to the other two templates for FAAH inhibitory activity, provided that O-aromatic substituents are present, as suggested by the comparison between compounds **1l** and **3e**, **1m** and **3f**, **2b** and **3e**, and **2e** and **3f**. In contrast, O-alkyl substituted carbamates are worse than the corresponding amides as FAAH inhibitors (see compounds **1a**−**d** and **3a**−**d**). Some compounds of the series

3 are also TRPV1 antagonists. (d) The serotonin template may afford compounds endowed with dual activity against FAAH and TRPV1.

In order to support the hypothesis that the previously described high efficacy of **1a** as an analgesic compound was due to its unique capability of inhibiting both FAAH and TRPV1, we compared the potency of this compound to two of its analogues with "single" activity as either FAAH inhibitors or TRPV1 antagonists. We selected two structurally related analogues, **3f** and **1m**, which were among the most potent FAAH or TRPV1 blockers, respectively, out of the 38 new compounds synthesized here (Table 1). These compounds were also selected because, among those belonging to the amide/carbamate "couples" synthesized here, they were the only ones to be active at inhibiting only either FAAH or TRPV1. Therefore, **3f** and **1m**, by being as structurally similar as possible for two compounds belonging to the **1** and **3** series, represented ideal candidates to test the role of FAAH and TRPV1 in the analgesic effects of **1a** analogues in vivo. These compounds are also likely to have pharmacokinetic profiles similar to each other and to most of the other serotonin derivatives studied here, including **1a**. The biphasic nocifensive response of mice treated with formalin was selected as the in vivo assay to compare the analgesic activity of the three compounds (Figures 2 and 3). In fact, it has been reported that formalin injection in mice causes a late phase (15–60 min after injection) of hyperalgesia, probably through activation of the PKA/PKC pathway and sensitization of the TRPV1 receptors,[44,45] and this late response is blocked by TRPV1 antagonists[46] and also by FAAH inhibitors.[47,48] As shown in Figure 2 (upper panel), we found that the systemic administration of **1a** (0.3, 1, 2.5, and 5 mg/kg) dose-dependently inhibited the late phase of formalin-induced hyperalgesia, with $IC_{50} = 0.5$ mg/kg (estimated at 40 min from formalin injection). The effect of **1a** (5 mg/kg) was antagonized by the CB_1 antagonist AM251 (but not by the CB_2 antagonist AM630), in agreement with FAAH inhibition by **1a** and subsequent elevation of endocannabinoid levels and activation of CB_1 receptors (Figure 2, upper middle panel). The TRPV1 antagonist, I-RTX, exerted a strong antihyperalgesic effect per se (Figure 2, lower middle panel) and did not antagonize the effect of **1a** (Figure 2, lower panel). Therefore, although this experiment confirms that TRPV1 antagonists are antihyperlgesic in the second phase of the formalin test, it cannot be used to demonstrate that compound **1a** acts in this assay by also blocking TRPV1 receptors. The administration of compounds **3f** (FAAH inhibitor) and **1m** (TRPV1 antagonist) also prevented the second phase of formalin-induced hyperalgesia, although with significantly less potency than **1a**, with IC_{50} values of 4 and 5 mg/kg, respectively (estimated at 40 min from formalin injection) (Figure 3). Furthermore, the antihyperalgesic effect of **3f** was prevented only by the CB_1 antagonist AM251, as one would expect from a compound with inhibitory action at FAAH. By contrast, the antihyperalgesic effect of **1m** was not significantly attenuated by AM251 (except for a small reduction observed only at two time-points, which might have been due to some nonspecific activity of **1m** at FAAH or cannabinoid receptor at the high systemic dose tested), in agreement with the present finding that this compound is not a FAAH inhibitor, nor, as expected, by I-RTX (Figure 3). The relative potencies of **1m**, **3f**, and **1a** in the formalin assay do not disagree with our hypothesis that **1a** might exert its antihyperalgesic effects by inhibiting both FAAH and TRPV1 receptors. In fact, if only FAAH had been involved in these effects of **1a**, **3f**, which is >10-fold more potent than **1a** as a FAAH inhibitor and is likely

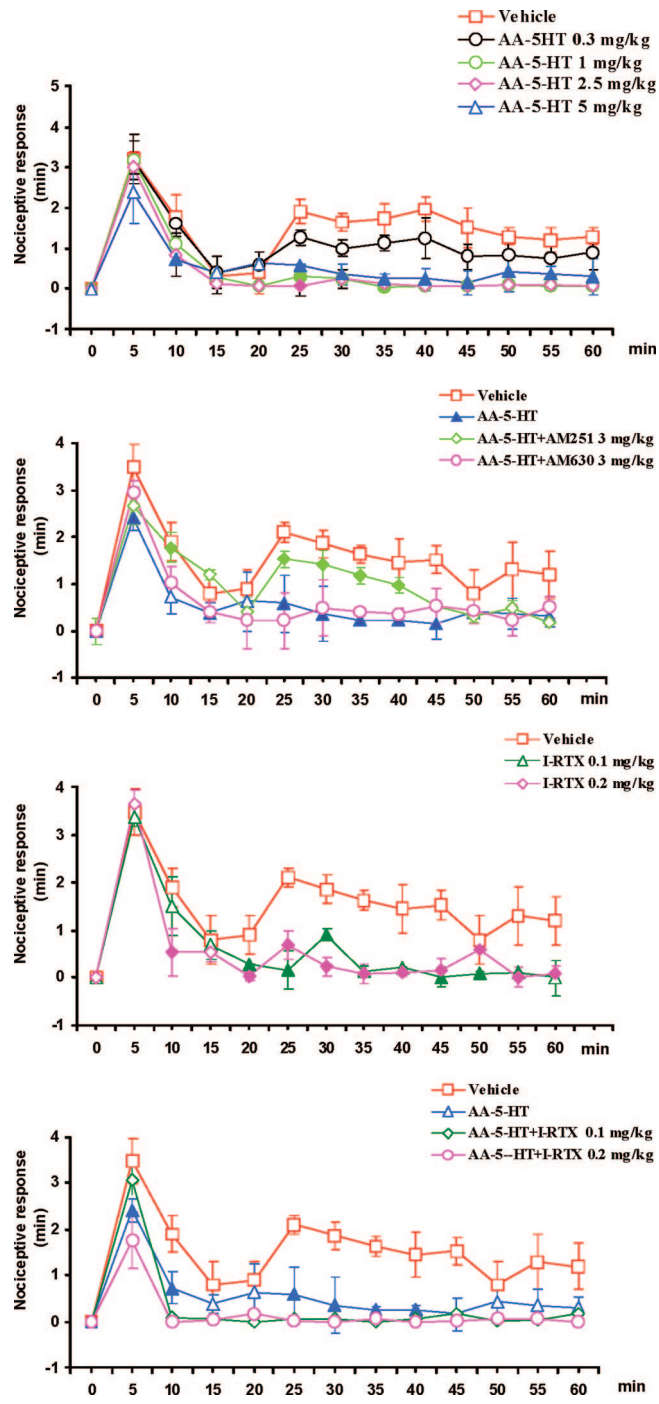


Figure 2. Analgesic effect of **1a** in the formalin test in mice. Each point represents the mean ± standard error of the mean (SEM) of 8–10 animals per group. Full symbols denote effects that are significantly different from the respective control as assessed using two-way ANOVA followed by the Bonferroni's test. For the lower two panels, the **1a** dose was 5 mg/kg.

to have similar pharmacokinetics (and, by being a carbamate and not an amide, should possess even higher metabolic stability to enzymatic hydrolysis), should have also been more potent in vivo. On the other hand, if only TRPV1 had been involved in the actions of **1a**, its effects in the formalin test should not have been blocked by the CB_1 antagonist and **1m** should have been equipotent at inhibiting formalin-induced nociception. However, only specific experiments, analyzing the activity in vivo of all the new serotonin derivatives synthesized in this study

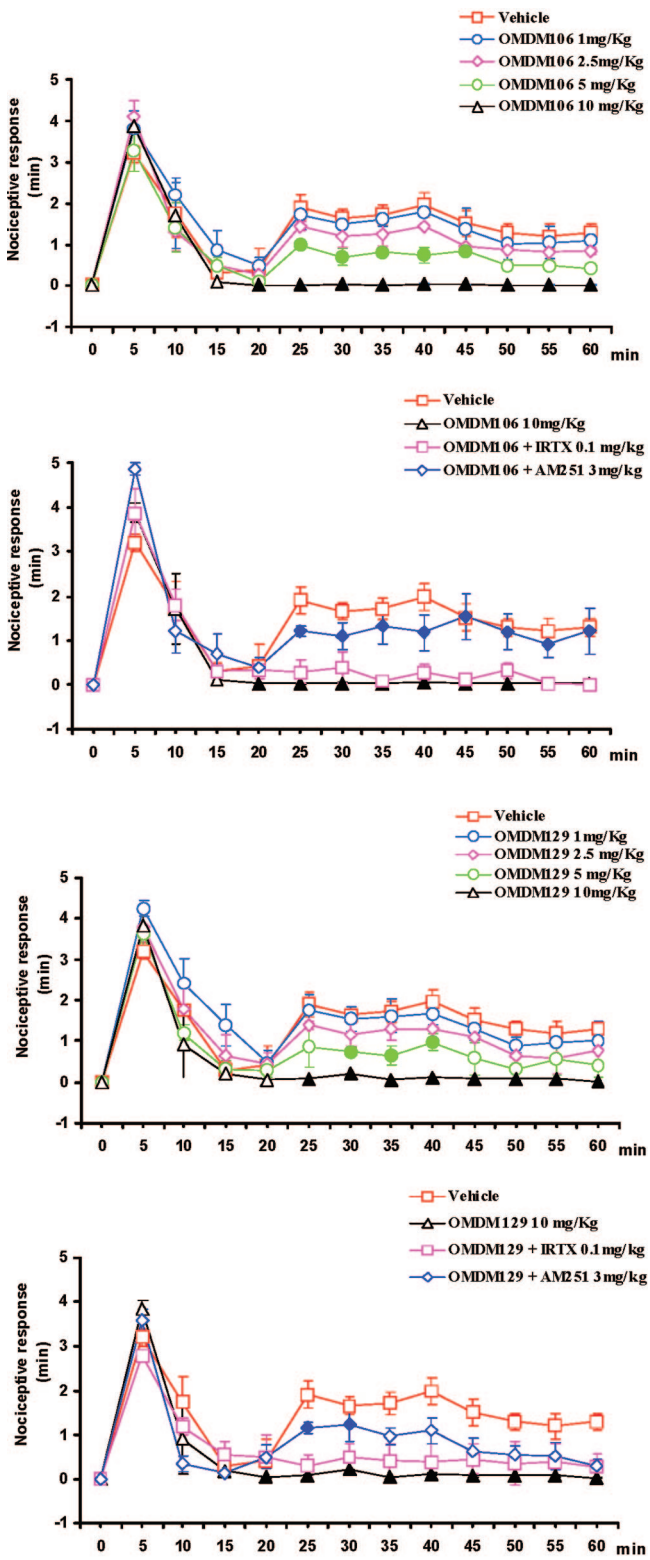


Figure 3. Analgesic effect of **3f** (OMDM106) and **1m** (OMDM129) in the formalin test in mice. Each point represents the mean ± standard error of the mean (SEM) of 8–10 animals per group. Full symbols denote effects that are significantly different from the respective control as assessed using two-way ANOVA followed by the Bonferroni's test.

and using also FAAH and TRPV1 null mice in these tests, need to be carried out in order to demonstrate the mechanism of action in vivo of **1a**. It is emphasized that **1a**, **3f**, and **1m** have little, if any, affinity ($K_i > 5\ \mu M$) for CB_1 receptors in binding assays previously carried out in our laboratory (refs 29 and 32 and Cascio and Di Marzo, unpublished data) and hence are unlikely to act as "direct" CB_1 agonists in vivo. Independent of their circulating concentrations after systemic administration, it has been suggested[16] that compounds that exhibit affinity constants higher than 5 μM in binding assays are very unlikely to exert any direct CB_1-mediated effect in vivo, whereas FAAH inhibitors with $IC_{50} \approx 5\ \mu M$ can still exert pharmacological actions in vivo via FAAH blockade, enhancement of AEA levels, and indirect activation of CB_1 receptors. This is possibly due to the fact that AEA has micromolar affinity for FAAH and nanomolar affinity for CB_1 receptors, and hence, compounds that inhibit FAAH with $IC_{50} \approx 5\ \mu M$ can still efficaciously reduce AEA degradation, whereas those that bind to CB_1 with micromolar affinity cannot compete with, or add to, endogenous AEA activity at this receptor.

Conclusions

In the present study, we have described the synthesis and the pharmacological evaluation of the new structural analogues of **1a**. Our goal was to obtain new molecules able, like the starting compound, to target simultaneously both FAAH and TRPV1 receptors in order to have new analgesic drugs. Of the new compounds, **1b** and **1c**, i.e., the α- and γ-linolenic acid amides of serotonin, showed high dual efficacy as inhibitors for the two considered targets, a result that could have been expected from the chemical similarity of these two compounds with **1a**. Also, compound **3e** exhibited the capability of inhibiting both FAAH and TRPV1, although it was relatively less potent than **1a** at the latter target. However, we identified several compounds with potent "single" activity at either FAAH or TRPV1, which might be used as templates for the future development of novel FAAH and TRPV1 blockers. Furthermore, compounds **3f** and **1m**, two analogues of **1a** with activity at only FAAH and TRPV1, respectively, were found here to be ~10-fold less potent than **1a** at preventing the second phase of formalin-induced hyperalgesia. New studies are now necessary to understand the structural requirements involved in the simultaneous recognition of the two targets, FAAH and TRPV1, in order to direct our future research toward the design and the synthesis of new and ever more potent analgesic drugs.

Experimental Section

Chemistry. All chemical reagents were commercially available unless otherwise indicated. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 1000 FT-IR spectrophotometer as KBr disks unless otherwise indicated. ^1H and ^{13}C NMR spectra were obtained on a Varian Mercury 300 spectrometer using $CDCl_3$ as solvent unless otherwise indicated and using TMS as the internal standard. Satisfactory elemental analysis results were obtained for the newly synthesized compounds (C, H, N, ±0.4%).

***N*-[2-(5-Hydroxy-1*H*-indol-3-yl)ethyl]-α-linolenamide (1b).** To a stirred solution of **4b** (160 mg, 0.58 mmol) in DMF (3 mL) were added at 0 °C HOBT (102 mg, 0.60 mmol) and EDC (116 mg, 0.60 mmol). The mixture was stirred for 15 min at 0 °C and for 1 h at room temperature. Then serotonin hydrochloride (146 mg, 0.68 mmol) and Et_3N (0.080 mL, 0.68 mmol) were added, and the mixture was stirred overnight at room temperature. The mixture was diluted with brine and extracted with AcOEt. The organic phase was washed with 2 N HCl solution, saturated $NaHCO_3$, and brine, dried (Na_2SO_4), and evaporated under vacuum. The residue (265 mg) was chromatographed on silica gel (14 g) using CH_2Cl_2/AcOEt = 85/15 as eluent to give 220 mg (88%) of **1b** as an oil. IR ($CHCl_3$) 3481, 3009, 2931, 2856, 1657, 1518, 1465, 1234, 1170, 1088 cm^{-1}; ^1H NMR (300 MHz) δ 0.96 (3H, t, J = 7.4 Hz), 1.26 (8H, m), 1.54 (2H, m), 1.98–2.10 (6H, m), 2.77 (6H, m), 3.46 (2H, m), 5.35

(6H, m), 5.85 (1H, t, $J = 5.8$ Hz), 6.77–7.12 (4H, m), 7.24 (1H, br s), 8.24 (1H, m); ^{13}C NMR (75 MHz) δ 14.27, 20.56, 25.34, 25.55, 25.64, 25.78, 27.23, 29.16, 29.25, 29.61, 36.78, 39.80, 103.18, 111.96, 112.28, 123.06, 127.13, 127.71, 128.02, 128.28, 128.34, 130.33, 131.47, 132.01, 150.11, 174.08. Anal. ($C_{28}H_{40}N_2O_2$) C, H, N.

***N*-[2-(5-Hydroxy-1*H*-indol-3-yl)ethyl]-γ-linolenamide (1c).** The title compound was prepared from **4c** following the same procedure that was used for the synthesis of **1b** and using CH_2Cl_2/AcOEt =85/15 as eluent for the chromatographic purification. Yield 81%; oil; IR ($CHCl_3$) 3481, 3009, 2930, 2858, 1659, 1518, 1466, 1231, 1170, 1088 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.87 (3H, t, $J =$ 7.4 Hz), 1.28 (8H, m), 1.58 (2H, m), 2.01–2.12 (6H, m), 2.80 (6H, m), 3.51 (2H, m), 5.36 (6H, m), 5.73 (1H, t, $J = 5.6$ Hz), 6.73–7.26 (5H, m), 8.12 (1H, m); ^{13}C NMR (75 MHz) δ 14.08, 22.57, 25.37, 25.61, 25.64, 26.90, 27.22, 29.20, 29.32, 31.51, 36.70, 39.73, 103.17, 111.92, 112.09, 112.28, 123.02, 127.58, 128.01, 128.13, 128.15, 128.44, 129.69, 130.52, 131.45, 150.09, 173.65. Anal. ($C_{28}H_{40}N_2O_2$) C, H, N.

***N*-[2-(5-Hydroxy-1*H*-indol-3-yl)ethyl]linoleamide (1d).** The title compound was prepared from **4d** following the same procedure that was used for the synthesis of **1b** and using CH_2Cl_2/AcOEt = 85/15 as eluent for the chromatographic purification. Yield 85%; mp 65–66 °C; IR ($CHCl_3$) 3687, 3481, 3009, 2929, 2857, 1657, 1602, 1518, 1466, 1234, 1170, 1088 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.88 (3H, t, $J = 6.6$ Hz), 1.22–1.36 (14H, m), 1.55 (2H, m), 1.99–2.10 (6H, m), 2.78 (4H, m), 3.47 (2H, m), 5.33 (4H, m), 5.79 (1H, t, $J = 5.5$ Hz), 6.78–7.15 (5H, m), 8.20 (1H, m); ^{13}C NMR (75 MHz) δ 14.09, 22.58, 25.35, 25.64, 25.77, 27.21, 29.17, 29.27, 29.34, 29.63, 31.52, 36.80, 39.75, 103.16, 111.94, 112.00, 112.28, 123.03, 127.92, 128.02, 130.11, 130.28, 131.44, 150.10, 174.00. Anal. ($C_{28}H_{42}N_2O_2$) C, H, N.

(*Z*)-*N*-[2-(5-Hydroxy-1*H*-indol-3-yl)ethyl]-9-octadecenamide (1e). The title compound was prepared from **4e** following the same procedure that was used for the synthesis of **1b** and using hexane/AcOEt = 1/1 as eluent for the chromatographic purification. Yield 82%; mp 67–68 °C; IR ($CHCl_3$) 3480, 3011, 2928, 2855, 1657, 1518, 1466, 1234, 1170, 1088 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.87 (3H, t, $J = 6.8$ Hz), 1.26 (20H, m), 1.54 (2H, m), 1.98 (4H, m), 2.08 (2H, t, $J = 7.6$ Hz), 2.79 (2H, t, $J = 6.8$ Hz), 3.46 (2H, m), 5.33 (2H, m), 5.81 (1H, t, $J = 5.7$ Hz), 6.78–7.25 (5H, m), 8.20 (1H, m); ^{13}C NMR (75 MHz) δ 14.13, 22.69, 25.34, 25.79, 27.21, 27.24, 29.19, 29.28, 29.34, 29.55, 29.74, 29.79, 31.91, 36.80, 39.75, 103.16, 111.95, 112.00, 112.29, 123.04, 127.99, 129.80, 129.99, 131.44, 150.11, 174.03. Anal. ($C_{28}H_{44}N_2O_2$) C, H, N.

(±)-*N*-[2-(5-Hydroxy-1*H*-indol-3-yl)ethyl]-5-(1,2-dithiolan-3-yl)pentanamide (1f). The title compound was prepared from **4f** following the same procedure that was used for the synthesis of **1b** and using CH_2Cl_2/AcOEt = 3/7 as eluent for the chromatographic purification. Yield 86%; oil; IR ($CHCl_3$) 3301, 2923, 1624, 1456, 1362, 1188 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3/CD_3OD$ = 5/1) δ 1.33 (2H, m), 1.58 (4H, m), 1.84 (1H, m), 2.07 (2H, m), 2.38 (1H, m), 2.84 (2H, t, $J = 6.9$ Hz), 3.11 (2H, m), 3.46 (3H, m), 6.49 (1H, t, $J = 5.6$ Hz), 6.74–7.19 (4H, m), 9.01 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3/CD_3OD$ = 5/1) δ 25.33, 25.50, 28.83, 34.57, 36.40, 38.49, 40.07, 40.31, 56.53, 102.78, 111.65, 111.96, 112.07, 123.35, 128.14, 131.59, 150.08, 174.20. Anal. ($C_{18}H_{24}N_2O_2S_2$) C, H, N.

***N*-[2-(5-Hydroxy-1*H*-indol-3-yl)ethyl]undecanamide (1g).** The title compound was prepared from **4g** following the same procedure that was used for the synthesis of **1b** and using hexane/AcOEt = 45/55 as eluent for the chromatographic purification. Yield 85%; mp 95 °C; IR ($CHCl_3$) 3480, 3017, 2928, 2855, 1657, 1518, 1467, 1200, 1170, 1088 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3/CD_3OD$ = 5/1) δ 0.88 (3H, t, $J = 6.3$ Hz), 1.24 (14H, m), 1.57 (2H, m), 2.11 (2H, t, $J = 7.6$), 2.86 (2H, t, $J = 7.0$ Hz), 3.48 (2H, t, $J = 7.0$ Hz), 6.74–7.21 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3/CD_3OD$ = 5/1) δ 14.12, 22.75, 25.45, 25.87, 29.35, 29.42, 29.58, 29.70, 31.99, 36.77, 39.95, 102.82, 111.72, 111.96, 112.06, 123.06, 128.11, 131.47, 150.21, 174.48. Anal. ($C_{21}H_{32}N_2O_2$) C, H, N.

***N*-[2-(5-Hydroxy-1*H*-indol-3-yl)ethyl]lauramide (1h).** The title compound was prepared from **4h** following the same procedure that was used for the synthesis of **1b** and using hexane/AcOEt = 1/1 as eluent for the chromatographic purification. Yield 87%; mp 103–105 °C; IR 3499, 3415, 3307, 2918, 2849, 1635, 1542, 1487, 1469, 1417, 1247, 1218, 1193, 1093 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3/CD_3OD$ = 5/1) δ 0.87 (3H, t, $J = 6.2$ Hz), 1.24 (16H, m), 1.58 (2H, m), 2.10 (2H, t, $J = 7.6$ Hz), 2.84 (2H, t, $J = 7.0$ Hz), 3.49 (2H, m), 6.75–7.20 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3/CD_3OD$ = 5/1) δ 14.11, 22.73, 25.45, 25.85, 29.37, 29.56, 29.64, 31.96, 36.77, 36.82, 39.93, 40.05, 102.87, 111.77, 111.84, 111.95, 111.99, 112.11, 123.02, 123.18, 128.12, 131.43, 131.57, 150.24, 174.40, 174.48. Anal. ($C_{22}H_{34}N_2O_2$) C, H, N.

***N*-[2-(5-Hydroxy-1*H*-indol-3-yl)ethyl]-7-phenylheptanamide (1i).** The title compound was prepared from **4i** following the same procedure that was used for the synthesis of **1b** and using hexane/AcOEt = 4/6 as eluent for the chromatographic purification. Yield 92%; oil; IR ($CHCl_3$) 3480, 3336, 3029, 2933, 2858, 1657, 1519, 1495, 1454, 1356, 1234, 1170, 1088 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.16 (4H, m), 1.45 (4H, m), 1.96 (2H, t, $J = 7.4$ Hz), 2.46 (2H, t, $J = 7.5$ Hz), 2.66 (2H, m), 3.34 (2H, m), 5.81 (1H, t, $J = 5.5$ Hz), 6.71–7.24 (9H, m), 7.89 (1H, br s), 8.28 (1H, s); ^{13}C NMR (75 MHz) δ 25.17, 25.65, 28.88, 29.00, 31.22, 35.79, 36.55, 39.81, 103.07, 111.65, 112.02, 112.12, 123.13, 125.57, 127.92, 128.22, 128.39, 131.36, 142.74, 149.96, 174.30. Anal. ($C_{23}H_{28}N_2O_2$) C, H, N.

***N*-[2-(5-Hydroxy-1*H*-indol-3-yl)ethyl]-8-phenyloctanamide (1j).** The title compound was prepared from **4j** following the same procedure that was used for the synthesis of **1b** and using hexane/AcOEt = 4/6 as eluent for the chromatographic purification. Yield 92%; oil; IR ($CHCl_3$) 3480, 3011, 2932, 2857, 1657, 1519, 1454, 1209, 1170, 1088 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.18 (6H, m), 1.50 (4H, m), 2.01 (2H, t, $J = 7.8$ Hz), 2.51 (2H, t, $J = 7.6$ Hz), 2.72 (2H, t, $J = 6.7$ Hz), 3.41 (2H, m), 5.81 (2H, m), 5.81 (1H, t, $J = 5.8$ Hz), 6.75–7.26 (9H, m), 7.43 (1H, br s), 8.16 (1H, m); ^{13}C NMR (75 MHz) δ 25.27, 25.74, 29.09, 29.14, 29.16, 31.39, 35.89, 36.71, 39.78, 103.13, 111.87, 111.98, 112.23, 123.08, 125.58, 127.98, 128.24, 128.42, 131.41, 142.88, 150.07, 174.10. Anal. ($C_{24}H_{30}N_2O_2$) C, H, N.

9-Phenylnonanoic Acid (4k).[33] A suspension of 9-phenylnonan-1-ol (500 mg, 2.27 mmol) and pyridinium dichromate (5.124 g, 13.67 mmol) in DMF (20 mL) was stirred at room temperature for 20 h. The mixture was then diluted with water and extracted with AcOEt. The organic phase was washed twice with brine, dried (Na_2SO_4), and evaporated under vacuum. The residue (652 mg) was chromatographed on silica gel (20 g) using CH_2Cl_2/AcOEt = 94/6 as eluent to give pure **4k** (420 mg, 79%).

***N*-[2-(5-Hydroxy-1*H*-indol-3-yl)ethyl]-9-phenylnonanamide (1k).** The title compound was prepared from **4k** following the same procedure that was used for the synthesis of **1b** and using CH_2Cl_2/AcOEt = 65/35 as eluent for the chromatographic purification. Yield 94%; oil; IR ($CHCl_3$) 3480, 3009, 2931, 2856, 1657, 1519, 1466, 1234, 1199, 1089 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.16 (8H, m), 1.51 (4H, m), 2.02 (2H, t, $J = 6.8$ Hz), 2.54 (2H, t, $J = 7.6$ Hz), 2.72 (2H, t, $J = 6.8$ Hz), 3.40 (2H, m), 5.84 (1H, t, $J = 5.4$ Hz), 6.77–7.27 (9H, m), 7.53 (1H, br s), 8.19 (1H, m); ^{13}C NMR (75 MHz) δ 25.26, 25.73, 29.23, 29.31, 31.44, 35.92, 36.69, 39.78, 103.11, 111.82, 111.96, 112.20, 123.06, 125.55, 127.95, 128.22, 128.40, 131.39, 142.90, 150.04, 174.17. Anal. ($C_{25}H_{32}N_2O_2$) C, H, N.

Methyl [3-(1-Pentynyl)phenyl]acetate (8). A stirred suspension of methyl (3-iodophenyl)acetate (**7**) (276 mg, 1 mmol), $Pd(OAc)_2$ (11 mg, 0.05 mmol), PPh_3 (26 mg, 0.1 mmol), and CuI (5 mg, 0.025 mmol) in DMSO/^{i}Pr$_2$NH = 1/1 (2.8 mL) was purged with N_2 for 15 min at room temperature. 1-Pentyne (0.40 mL, 4 mmol) was then added, and the mixture was then stirred at room temperature for 2 h under N_2. The mixture was diluted with water and extracted with AcOEt. The organic phase was washed with 2 N HCl solution, saturated $NaHCO_3$, and brine, dried (Na_2SO_4), and evaporated under vacuum. The residue (324 mg) was chromatographed on silica gel (10 g) using hexane/AcOEt = 95/5 as eluent

to give 204 mg (94%) of **8** as an oil. IR ($CHCl_3$) 3025, 2966, 2228, 1735, 1580, 1484, 1437, 1339, 1159, 1017 cm^{-1}; ^1H NMR (300 MHz) δ 1.04 (3H, t, $J = 7.2$ Hz), 1.62 (2H, m), 2.37 (2H, t, $J = 6.9$ Hz), 3.57 (2H, s), 3.67 (3H, s), 7.16–7.35 (4H, m); ^{13}C NMR (75 MHz) δ 13.56, 21.39, 22.22, 40.93, 52.06, 80.48, 90.52, 124.44, 128.45, 128.47, 130.30, 132.41, 134.00, 171.71. Anal. ($C_{14}H_{16}O_2$) C, H.

Methyl (3-Pentylphenyl)acetate. A stirred solution of **8** (100 mg, 0.46 mmol) in AcOEt (2 mL) was hydrogenated in the presence of 10% Pd/C (11 mg) at room temperature and atmospheric pressure for 4 h. The suspension was filtered through a short pad of silica gel, and the filtrate was evaporated under vacuum to leave the title compound (108 mg, 99%) as an oil; IR ($CHCl_3$) 3031, 2956, 2931, 2858, 1733, 1607, 1488, 1437, 1266, 1153, 1016 cm^{-1}; ^1H NMR (300 MHz) δ 0.95 (3H, t, $J = 7.0$ Hz), 1.30 (4H, m), 1.58 (2H, m), 2.54 (2H, t, $J = 7.6$ Hz), 3.60 (2H, s), 3.70 (3H, s), 7.07–7.27 (4H, m); ^{13}C NMR (75 MHz) δ 14.01, 22.54, 31.10, 31.58, 35.87, 41.24, 51.94, 126.47, 127.19, 128.45, 129.36, 133.87, 143.32, 172.10. Anal. ($C_{14}H_{20}O_2$) C, H.

(3-Pentylphenyl)acetic Acid (4l). Aqueous LiOH (1 N, 0.65 mL) was added to a stirred solution of methyl (3-pentylphenyl)acetate (101 mg, 0.43 mmol) in THF/H_2O = 5/1 (7 mL), and the solution was stirred at room temperature overnight. After acidification to pH 4 with 2 N HCl, the mixture was concentrated under vacuum and extracted with AcOEt. The organic phase was washed with brine until neutral, dried (Na_2SO_4), and evaporated under vacuum to give the title compound (89 mg, 100%), which was used in the next step without further purification.

***N*-[2-(5-Hydroxy-1*H*-indol-3-yl)ethyl]-2-(3-pentylphenyl)-acetamide (1l).** The title compound was prepared from **4l** following the same procedure that was used for the synthesis of **1b** and using CH_2Cl_2/AcOEt = 75/25 as eluent for the chromatographic purification. Yield 77%; oil; IR ($CHCl_3$) 3481, 3424, 3029, 2931, 2858, 1655, 1522, 1487, 1467, 1234, 1170, 1088 cm^{-1}; ^1H NMR (300 MHz) δ 0.85 (3H, t, $J = 6.7$ Hz), 1.24 (4H, m), 1.51 (2H, m), 2.47 (2H, t, $J = 7.7$ Hz), 2.70 (2H, t, $J = 6.7$ Hz), 3.38 (2H, m), 3.45 (2H, s), 5.72 (1H, t, $J = 5.8$ Hz), 6.62–7.17 (8H, m), 7.26 (1H, br s), 8.12 (1H, m); ^{13}C NMR (75 MHz) δ 14.02, 22.50, 25.05, 31.06, 31.56, 35.76, 40.02, 43.74, 103.21, 111.85, 111.90, 112.28, 123.01, 126.66, 127.28, 128.02, 128.78, 129.58, 131.48, 134.64, 143.75, 150.11, 171.96. Anal. ($C_{23}H_{28}N_2O_2$) C, H, N.

Methyl [1,1′-Biphenyl]-3-acetate. A suspension of methyl (3-iodophenyl)acetate (**7**) (138 mg, 0.50 mmol), phenylboronic acid (67 mg, 0.55 mmol), K_3PO_4 (265 mg, 1.25 mmol), and $Pd(PPh_3)_4$ (17 mg, 0.015 mmol) in dry DMF (2.0 mL) was stirred at 90 °C for 16 h under N_2. The mixture was cooled, diluted with water, and extracted with AcOEt. The organic phase was washed twice with brine until neutral, dried (Na_2SO_4), and evaporated under vacuum. The residue (123 mg) was chromatographed on silica gel (4 g) using hexane/CH_2Cl_2 = 2/1 as eluent to give 56 mg (50%) of the title compound as an oil.[34] IR ($CHCl_3$) 3025, 2954, 1735, 1600, 1479, 1437, 1342, 1260, 1217, 1160, 1014 cm^{-1}; ^1H NMR (300 MHz) δ 3.70 (5H, br s), 7.25–7.61 (9H, m); ^{13}C NMR (75 MHz) δ 41.28, 52.04, 125.99, 127.21, 127.37, 128.16, 128.74, 128.99, 134.49, 140.96, 141.66, 171.91.

[1,1′-Biphenyl]-3-acetic Acid (4m). Aqueous LiOH (1 N, 2.1 mL) was added to a stirred solution of methyl [1,1′-biphenyl]-3-acetate (312 mg, 1.38 mmol) in THF/H_2O = 5/1 (23 mL), and the solution was stirred at room temperature overnight. After acidification to pH 4 with 2 N HCl, the mixture was concentrated under vacuum and extracted with AcOEt. The organic phase was washed with brine until neutral, dried (Na_2SO_4), and evaporated under vacuum to give the title compound[34] (289 mg, 99%), which was used in the next step without further purification.

***N*-[2-(5-Hydroxy-1*H*-indol-3-yl)ethyl]-[1,1′-biphenyl]-3-acetamide (1m).** The title compound was prepared from **4m** following the same procedure that was used for the synthesis of **1b** and using CH_2Cl_2/AcOEt = 6/4 as eluent for the chromatographic purification. Yield 93%; mp 67–70 °C; IR 3406, 3300, 2919, 2850, 1638, 1528, 1455, 1365, 1213, 1187, 1093 cm^{-1}; ^1H NMR (300 MHz) δ 2.66 (2H, t, $J = 6.2$ Hz), 3.36 (2H, m), 3.46 (2H, s), 5.72 (1H, t, $J = 5.1$ Hz), 6.52–7.79 (14H, m), 7.79 (1H, m); ^{13}C NMR (75 MHz) δ 24.93, 39.82, 43.74, 103.18, 111.71, 111.94, 112.28, 123.11, 125.95, 127.14, 127.51, 127.89, 128.16, 128.36, 128.83, 129.35, 131.46, 135.31, 140.65, 141.71, 150.02, 171.59. Anal. ($C_{24}H_{22}N_2O_2$) C, H, N.

3-Pentylphenyl Trifluoromethanesulfonate (10). A stirred solution of 3-pentylphenol (**9**)[35] (1.376 g, 8.4 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (2.414 g, 11.8 mmol) in dry CH_2Cl_2 (42 mL) was treated with triflic anhydride (1.65 mL, 10.1 mmol) at 0 °C, and the mixture was stirred at room temperature for 3.5 h. The resulting suspension was filtered, and the filtrate was diluted with AcOEt, washed with 2 N HCl solution, saturated $NaHCO_3$ and brine, dried (Na_2SO_4), and evaporated under vacuum. The residue (3.10 g) was chromatographed on silica gel (100 g) using hexane as eluent to give 2.205 g (89%) of **10** as an oil. IR ($CHCl_3$) 3038, 2932, 2860, 1614, 1580, 1486, 1423, 1249, 1223, 1142, 939 cm^{-1}; ^1H NMR (300 MHz) δ 0.90 (3H, t, $J = 6.9$ Hz), 1.32 (4H, m), 1.62 (2H, m), 2.64 (2H, t, $J = 7.8$ Hz), 7.07–7.36 (4H, m); ^{13}C NMR (75 MHz) δ 13.94, 22.42, 30.71, 31.25, 35.53, 118.18, 118.58 (q, $J = 318$ Hz), 120.91, 128.23, 129.67, 145.74, 149.41. Anal. ($C_{12}H_{15}F_3O_3S$) C, H.

[3′-Pentyl-1,1′-biphenyl]-3-ol (11). A suspension of **10** (1.464 g, 4.94 mmol), 3-hydroxyphenylboronic acid (954 mg, 6.92 mmol), K_3PO_4 (1.573 g, 7.41 mmol), KBr (647 mg, 5.43 mmol), and $Pd(PPh_3)_4$ (173 mg, 0.15 mmol) in dioxane (25 mL) was stirred at 85 °C for 5 h under N_2. The mixture was cooled, diluted with water, and extracted with AcOEt. The organic phase was washed with brine until neutral, dried (Na_2SO_4), and evaporated under vacuum. The residue (2.204 g) was chromatographed on silica gel (110 g) using hexane/CH_2Cl_2 = 88/12 as eluent to give 834 mg (70%) of the title compound as an oil. IR ($CHCl_3$) 3596, 3320, 2959, 2931, 2859, 1596, 1578, 1471, 1309, 1205, 1176, 1038 cm^{-1}; ^1H NMR (300 MHz) δ 0.88 (3H, t, $J = 6.9$ Hz), 1.32 (4H, m), 1.63 (2H, m), 2.62 (2H, t, $J = 7.8$ Hz), 5.60 (1H, br s), 6.77–7.36 (8H, m); ^{13}C NMR (75 MHz) δ 13.99, 22.53, 31.17, 31.55, 36.01, 114.14, 114.18, 119.86, 124.44, 127.25, 127.61, 128.63, 129.92, 140.66, 143.27, 143.44, 155.70. Anal. ($C_{17}H_{20}O$) C, H.

3′-Pentyl-[1,1′-biphenyl]-3-yl Trifluoromethanesulfonate (12). A stirred solution of **11** (1.002 g, 4.17 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (1.191 g, 5.8 mmol) in dry CH_2Cl_2 (21 mL) was treated with triflic anhydride (0.82 mL, 5.0 mmol) at 0 °C, and the mixture was stirred at room temperature overnight. The resulting suspension was filtered, and the filtrate was diluted with AcOEt, washed with 2 N HCl solution, saturated $NaHCO_3$ and brine, dried (Na_2SO_4), and evaporated under vacuum. The residue (1.64 g) was chromatographed on silica gel (60 g) using hexane as eluent to give 1.343 g (86%) of **12** as an oil. IR ($CHCl_3$) 3008, 2932, 2859, 1607, 1573, 1474, 1424, 1248, 1141, 932 cm^{-1}; ^1H NMR (300 MHz) δ 0.90 (3H, t, $J = 6.5$ Hz), 1.37 (4H, m), 1.70 (2H, m), 2.68 (2H, t, $J = 7.7$ Hz), 7.22–7.62 (8H, m); ^{13}C NMR (75 MHz) δ 14.01, 22.56, 31.22, 31.59, 36.04, 118.58 (q, $J = 318$ Hz), 119.66, 120.04, 124.56, 127.11, 127.30, 128.50, 128.98, 130.40, 139.07, 143.92, 144.36, 150.06. Anal. ($C_{18}H_{19}F_3O_3S$) C, H.

4-(3′-Pentyl[1,1′-biphenyl]-3-yl)-3-butyn-1-ol (13). A stirred suspension of **12** (559 mg, 1.5 mmol), $Pd(OAc)_2$ (17 mg, 0.075 mmol), PPh_3 (39 mg, 0.15 mmol), and CuI (7 mg, 0.038 mmol) in DMSO/^{i}Pr$_2$NH = 1/1 (8.4 mL) was purged with N_2 for 15 min at room temperature. 3-Butyn-1-ol (0.23 mL, 3 mmol) was then added, and the mixture was stirred at room temperature for 48 h under N_2. The mixture was diluted with water and extracted with AcOEt. The organic phase was washed with 2 N HCl solution, saturated $NaHCO_3$ and brine, dried (Na_2SO_4), and evaporated under vacuum. The residue (714 mg) was chromatographed on silica gel (22 g) using hexane/AcOEt = 9/1 as eluent to give 272 mg (62%) of **13** as an oil. IR ($CHCl_3$) 3591, 3030, 2931, 2859, 1597, 1472, 1220, 1051 cm^{-1}; ^1H NMR (300 MHz) δ 0.89 (3H, m), 1.33 (4H, m), 1.65 (2H, m), 2.23 (1H, br s), 2.67 (4H, m), 3.81 (2H, t, $J = 6.3$ Hz), 7.14–7.65 (8H, m); ^{13}C NMR (75 MHz) δ 14.01, 22.52, 23.78, 31.20, 31.51, 35.97, 61.04, 82.32, 86.34, 123.49, 124.17, 126.60, 126.97, 127.45, 128.41, 128.45, 130.06, 130.18, 140.03, 141.28, 143.24, 162.40. Anal. ($C_{21}H_{24}O$) C, H.

4-(3′-Pentyl[1,1′-biphenyl]-3-yl)butan-1-ol (14). A stirred solution of **13** (272 mg, 0.93 mmol) in AcOEt (2 mL) was hydrogenated in presence of 10% Pd/C (27 mg) at room temperature and atmospheric pressure for 3 h. The suspension was filtered through a short pad of silica gel, and the filtrate was evaporated under vacuum to leave the title compound (273 mg, 99%) as an oil. IR ($CHCl_3$) 3588, 3032, 2931, 2859, 1602, 1472, 1410, 1230, 1058 cm^{-1}; ^1H NMR (300 MHz) δ 0.91 (3H, m), 1.32 (4H, m), 1.66 (6H, m), 2.68 (4H, m), 3.62 (2H, t, J = 6.5 Hz), 7.12–7.41 (8H, m); ^{13}C NMR (75 MHz) δ 14.02, 22.26, 27.57, 31.23, 31.52, 32.27, 35.68, 36.00, 62.60, 124.28, 124.48, 126.99, 127.06, 127.09, 128.34, 128.40, 141.04, 141.24, 142.47, 143.10. Anal. ($C_{21}H_{28}O$) C, H.

4-(3′-Pentyl[1,1′-biphenyl]-3-yl)butanoic Acid (4n). To a stirred solution of **14** (273 mg, 0.92 mmol) in DMF (18 mL) was added portionwise pyridinium dichromate (2.077 g, 5.52 mmol). The mixture was stirred overnight at room temperature and then was diluted with brine and extracted with AcOEt. The organic phase was washed twice with brine, dried (Na_2SO_4), and evaporated under vacuum. The residue (308 mg) was chromatographed on silica gel (10 g) using hexane/AcOEt = 8/2 as eluent to give 226 mg (79%) of **4n**. Mp 50–51 °C; IR ($CHCl_3$) 3035, 2931, 2859, 1709, 1601, 1474, 1408, 1270, 1223, 1127 cm^{-1}; ^1H NMR (300 MHz) δ 0.90 (3H, m), 1.34 (4H, m), 1.66 (2H, m), 2.01 (2H, m), 2.40 (2H, t, J = 7.5 Hz), 2.66 (2H, t, J = 7.8 Hz), 2.73 (2H, t, J = 7.5 Hz), 7.16–7.41 (8H, m); ^{13}C NMR (75 MHz) δ 14.02, 22.53, 26.20, 31.23, 31.54, 33.35, 35.04, 36.01, 124.30, 124.80, 127.06, 127.11, 127.12, 127.17, 128.36, 128.54, 140.94, 141.34, 141.42, 143.14, 179.72. Anal. ($C_{21}H_{26}O_2$) C, H, N.

***N*-[2-(5-Hydroxy-1*H*-indol-3-yl)ethyl]-4-(3′-pentyl[1,1′-biphenyl]-3-yl)butanamide (1n).** The title compound was prepared from **4n** following the same procedure that was used for the synthesis of **1b** and using hexane/AcOEt = 1/1 as eluent for the chromatographic purification. Yield 80%; oil; IR ($CHCl_3$) 3405, 2925, 2853, 1645, 1529, 1456, 1365, 1213, 1186, 1093 cm^{-1}; ^1H NMR (300 MHz) δ 0.87 (3H, m), 1.26 (4H, m), 1.61 (2H, m), 2.02 (4H, m), 2.58 (6H, m), 3.36 (2H, m), 5.73 (1H, m), 6.72–7.36 (13H, m), 8.10 (1H, br s); ^{13}C NMR (75 MHz) δ 14.13, 14.16, 22.53, 25.24, 27.11, 29.69, 31.25, 31.57, 35.19, 35.88, 36.04, 39.79, 103.16, 111.87, 111.98, 112.25, 123.09, 124.50, 124.83, 127.29, 127.99, 128.64, 128.74, 131.43, 141.16, 141.45, 141.96, 143.46, 150.06. Anal. ($C_{31}H_{36}N_2O_2$) C, H, N.

7-(Methoxymethoxy)-2-naphthalenyl Trifluoromethanesulfonate (16). To a stirred solution of 7-hydroxy-2-naphthalenyl trifluoromethanesulfonate (**15**)[36] (3.17 g, 10.85 mmol) and Et_3N (9.1 mL, 65.1 mmol) in dry THF (40 mL) was added dropwise at 0 °C chloromethyl methyl ether (3.3 mL, 43 mmol). After being stirred at room temperature overnight, the solution was concentrated under reduced pressure, diluted with water, and extracted with AcOEt. The organic phase was washed with 2 N HCl solution, saturated $NaHCO_3$ and brine, dried (Na_2SO_4), and evaporated under vacuum. The residue (3.19 g) was chromatographed on silica gel (100 g) using hexane/AcOEt = 92/8 as eluent hexane to give 1.94 g (53%) of **16** as an oil. IR ($CHCl_3$) 3052, 2962, 2931, 2859, 1634, 1606, 1511, 1421, 1385, 1250, 1141, 1110 cm^{-1}; ^1H NMR (300 MHz) δ 3.51 (3H, s), 5.29 (3H, s), 7.20–7.82 (6H, m); ^{13}C NMR (75 MHz) δ 56.09, 94.31, 109.72, 117.31, 118.12, 118.66 (q, J = 318 Hz), 120.23, 128.13, 129.24, 130.02, 134.53, 147.52, 156.12. Anal. ($C_{13}H_{11}F_3O_5S$) C, H.

2-(Methoxymethoxy)-7-pentylnaphthalene (17). To a stirred solution of **16** (1.100 g, 3.27 mmol) and $NiCl_2$(dppp)[49] (89 mg, 0.16 mmol) in dry THF (6.5 mL) was added dropwise at 0 °C a 2 M solution of pentylmagnesium chloride in dry THF (3.3 mL). The mixture was stirred at room temperature for 1 h under N_2 and then diluted with water and extracted with AcOEt. The organic phase was washed with brine, dried (Na_2SO_4), and evaporated under vacuum. The residue (996 mg) was chromatographed on silica gel (30 g) using hexane/AcOEt = 98/2 as eluent to give 628 mg (70%) of **17** as an oil. IR ($CHCl_3$) 3009, 2962, 2931, 1633, 1607, 1513, 1463, 1385, 1250, 1152, 1125 cm^{-1}; ^1H NMR (300 MHz) δ 0.89 (3H, m), 1.33 (4H, m), 1.68 (2H, m), 2.72 (2H, t, J = 7.6 Hz), 3.50 (3H, s), 5.27 (3H, s), 7.12–7.71 (6H, m); ^{13}C NMR (75 MHz) δ 13.72, 22.25, 30.68, 31.18, 35.73, 55.59, 94.05, 109.14, 117.49, 125.04, 125.14, 126.90, 127.44, 128.56, 134.11, 140.48, 154.52. Anal. ($C_{17}H_{22}O_2$) C, H.

7-Pentyl-2-naphthalenol (18). A solution of **17** (628 mg, 2.3 mmol) and CBr_4 (76 mg, 0.23 mmol) in dry ^{i}PrOH (11.5 mL) was refluxed for 1.5 h.[38] The solution was cooled to room temperature, and the organic solvent was removed under reduced pressure. The residue (553 mg) was chromatographed on silica gel (17 g) using hexane/AcOEt = 8/2 as eluent to give 468 mg (95%) of **18** as an oil. IR ($CHCl_3$) 3284, 3052, 2960, 2931, 2859, 1632, 1605, 1510, 1450, 1239, 1141, 1047 cm^{-1}; ^1H NMR (300 MHz) δ 0.88 (3H, t, J = 6.8 Hz), 1.32 (4H, m), 1.66 (2H, m), 2.69 (2H, t, J = 7.8 Hz), 6.97–7.66 (6H, m); ^{13}C NMR (75 MHz) δ 14.02, 22.53, 30.96, 31.50, 35.98, 109.00, 116.60, 124.65, 125.03, 127.17, 127.33, 129.28, 134.56, 140.98, 153.03. Anal. ($C_{15}H_{18}O$) C, H.

7-Pentyl-2-naphthalenyl Trifluoromethanesulfonate (19). A stirred solution of **18** (705 mg, 3.3 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (950 mg, 4.62 mmol) in dry CH_2Cl_2 (16.5 mL) was treated with triflic anhydride (0.65 mL, 4.0 mmol) at 0 °C, and the mixture was stirred at room temperature for 2.5 h. The resulting suspension was filtered, and the filtrate was diluted with AcOEt, washed with 2 N HCl solution, saturated $NaHCO_3$, and brine, dried (Na_2SO_4), and evaporated under vacuum. The residue (1.17 g) was chromatographed on silica gel (35 g) using hexane as eluent to give 873 mg (76%) of **19** as an oil. IR ($CHCl_3$) 3052, 2959, 2931, 2859, 1635, 1604, 1509, 1422, 1239, 1141, 1110, 955 cm^{-1}; ^1H NMR (300 MHz) δ 0.91 (3H, m), 1.34 (4H, m), 1.70 (2H, m), 2.77 (2H, t, J = 7.8 Hz), 7.27–7.86 (6H, m); ^{13}C NMR (75 MHz) δ 14.00, 22.53, 30.84, 31.46, 35.98, 118.40, 118.52, 118.66 (q, J = 320 Hz), 126.21, 127.53, 128.67, 130.03, 130.65, 133.42, 142.34, 147.01. Anal. ($C_{16}H_{17}F_3O_3S$) C, H.

4-(7-Pentyl-2-naphthalenyl)-3-butyn-1-ol (20). A stirred suspension of **19** (522 mg, 1.5 mmol), $Pd(OAc)_2$ (17 mg, 0.075 mmol), PPh_3 (39 mg, 0.15 mmol), and CuI (7 mg, 0.038 mmol) in DMSO/^{i}Pr$_2$NH = 1/1 (8.4 mL) was purged with N_2 for 15 min at room temperature. 3-Butyn-1-ol (0.158 mg, 2.25 mmol) was then added, and the mixture was stirred at room temperature for 4 h under N_2. The mixture was diluted with water and extracted with AcOEt. The organic phase was washed with 2 N HCl solution, saturated $NaHCO_3$, and brine, dried (Na_2SO_4), and evaporated under vacuum. The residue (500 mg) was chromatographed on silica gel (20 g) using CH_2Cl_2/AcOEt = 98/2 as eluent to give 333 mg (83%) of **20**. Mp 103–104.5 °C; IR ($CHCl_3$) 3587, 3028, 2931, 2859, 1603, 1510, 1468, 1228, 1058 cm^{-1}; ^1H NMR (300 MHz) δ 0.89 (3H, m), 1.33 (4H, m), 1.65 (2H, m), 2.23 (1H, br s), 2.67 (4H, m), 3.81 (2H, t, J = 6.3 Hz), 7.14–7.65 (8H, m); ^{13}C NMR (75 MHz) δ 14.01, 22.52, 23.78, 31.20, 31.51, 35.97, 61.04, 82.32, 86.34, 123.49, 124.17, 126.60, 126.97, 127.45, 128.41, 128.45, 130.06, 130.18, 140.03, 141.28, 143.24, 162.40. Anal. ($C_{19}H_{22}O$) C, H.

4-(7-Pentyl-2-naphthalenyl)butan-1-ol (21). A stirred solution of **20** (390 mg, 1.46 mmol) in AcOEt (3 mL) was hydrogenated in the presence of 10% Pd/C (40 mg) at room temperature and atmospheric pressure for 1.5 h. The suspension was filtered through a short pad of silica gel, and the filtrate was evaporated under vacuum to leave the title compound (391 mg, 99%). Mp 43.5–46 °C; IR ($CHCl_3$) 3627, 3050, 3007, 2933, 2859, 1636, 1605, 1512, 1458, 1237, 1199, 1061, 1020 cm^{-1}; ^1H NMR (300 MHz) δ 0.89 (3H, m), 1.34 (4H, m), 1.68 (2H, m), 2.52 (1H, br s), 2.70 (4H, m), 3.83 (2H, t, J = 6.3 Hz), 7.28–7.85 (6H, m); ^{13}C NMR (75 MHz) δ 13.99, 22.50, 23.85, 30.88, 31.43, 35.95, 61.06, 82.74, 86.43, 120.36, 125.76, 127.30, 127.34, 127.53, 127.86, 130.67, 130.87, 132.94, 140.91. Anal. ($C_{19}H_{26}O$) C, H.

4-(7-Pentyl-2-naphthalenyl)butanoic Acid (4o). To a stirred solution of **21** (391 mg, 1.44 mmol) in dry DMF (30 mL) was added portionwise pyridinium dichromate (3.250 g, 8.64 mmol). The mixture was stirred overnight at room temperature and then was diluted with brine and extracted with AcOEt. The organic phase was washed with brine, dried (Na_2SO_4), and evaporated under vacuum. The residue (556 mg) was chromatographed on silica gel (23 g) using hexane/AcOEt = 8/2 as eluent to give 250 mg (61%) of **4o**. Mp 85–87 °C; IR 3048, 2927, 2854, 1690, 1511, 1459, 1436,

1408, 1283, 1213, 904 cm^{-1}; ^1H NMR (300 MHz) δ 0.89 (3H, t, $J = 6.3$ Hz), 1.34 (4H, m), 1.69 (2H, m), 2.04 (2H, m), 2.39 (2H, t, $J = 7.5$ Hz), 2.74 (2H, t, $J = 7.5$ Hz), 2.81 (2H, t, $J = 7.5$ Hz), 7.23–7.73 (6H, m); ^{13}C NMR (75 MHz) δ 14.00, 22.53, 26.03, 30.99, 31.47, 33.25, 35.08, 36.03, 125.65, 125.96, 126.08, 126.65, 127.20, 127.51, 130.34, 133.55, 138.34, 140.36, 179.52. Anal. ($C_{19}H_{24}O_2$) C, H, N.

***N*-[2-(5-Hydroxy-1*H*-indol-3-yl)ethyl]-4-(7-pentyl-2-naphthalenyl)butanamide (1o).** The title compound was prepared from **4o** following the same procedure that was used for the synthesis of **1b** and using hexane/AcOEt = 1/1 as eluent for the chromatographic purification. Yield 97%; mp 141–142 °C; IR 3522, 3386, 2925, 1630, 1567, 1485, 1463, 1312, 1202, 1157, 1056 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3/CD_3OD$ = 5/1) δ 0.89 (3H, m), 1.34 (4H, m), 1.68 (2H, m), 1.97 (2H, m), 2.10 (2H, m), 2.78 (4H, m), 2.96 (2H, m), 3.46 (2H, m), 6.06 (1H, t, $J = 5.2$ Hz), 6.64–7.71 (10H, m); ^{13}C NMR (75 MHz, $CDCl_3/CD_3OD$ = 5/1) δ 14.06, 22.61, 25.39, 26.99, 31.14, 31.57, 35.25, 35.86, 36.12, 39.96, 102.81, 111.70, 112.11, 123.09, 125.98, 126.13, 126.39, 126.91, 127.08, 127.46, 127.70, 128.04, 130.53, 131.29, 133.78, 138.94, 140.71, 150.22, 173.86. Anal. ($C_{29}H_{34}N_2O_2$) C, H, N.

***N*-(4-*tert*-Butylbenzyl)-*N*′-[2-(5-hydroxy-1*H*-indol-3-yl)ethyl]urea (2a).** To a stirred solution of 4-*tert*-butylbenzylamine (49 mg, 0.30 mmol) and Et_3N (0.084 mL, 0.60 mmol) in dry CH_2Cl_2 (2 mL) was added at 0 °C under N_2 bis(trichloromethyl) carbonate (89 mg, 0.30 mmol), and the reaction mixture was then gradually brought to reflux. After 5 h at reflux, the reaction mixture was cooled and filtered through a short pad of silica, and the filtrate was evaporated under vacuum to leave the crude isocyanate intermediate (55 mg), monitored by IR analysis for the strong NCO stretching band (2269 cm^{-1}). A solution of serotonin hydrochloride (64 mg, 0.30 mmol) and Et_3N (0.126 mL, 0.90 mmol) in dry pyridine (0.5 mL) was added to a cooled solution of the crude isocyanate in dry CH_2Cl_2 (2 mL). The reaction mixture was stirred at room temperature for 18 h and then diluted with water and extracted with AcOEt. The organic phase was washed with water until neutral, dried (Na_2SO_4), and evaporated under vacuum to leave a residue (101 mg), which was chromatographed on silica gel using CH_2Cl_2/AcOEt = 1/1 as eluant to give 47 mg of pure **2a** (44%). Mp 136–138 °C; IR 3379, 2965, 2870, 1609, 1564, 1478, 1435, 1362, 1270, 1185 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 1.28 (9H, s), 2.84 (2H, t, $J = 7.0$ Hz), 3.30 (1H, s), 3.42 (2H, t, $J = 7.0$ Hz), 4.24 (2H, s), 6.65–7.33 (8H, m); ^{13}C NMR (75 MHz, CD_3OD) δ 27.23, 31.86, 35.30, 41.81, 44.48, 103.63, 112.41, 112.66, 112.68, 124.39, 126.35, 127.96, 129.54, 133.20, 138.21, 151.00, 151.16, 161.24. Anal. ($C_{22}H_{27}N_3O_2$) C, H, N.

1-Nitro-3-(1-pentynyl)benzene (23).[39] A stirred suspension of 3-iodonitrobenzene (**22**) (996 mg, 4 mmol), $Pd(OAc)_2$ (45 mg, 0.2 mmol), PPh_3 (105 mg, 0.4 mmol), and CuI (19 mg, 0.1 mmol) in DMSO/^{i}Pr$_2$NH = 1/1 (22 mL) was purged with N_2 for 15 min at room temperature. 1-Pentyne (0.79 mL, 8 mmol) was then added, and the mixture was stirred at room temperature for 4 h under N_2. The mixture was diluted with water and extracted with AcOEt. The organic phase was washed with 2 N HCl solution, saturated $NaHCO_3$, and brine, dried (Na_2SO_4), and evaporated under vacuum. The residue (976 mg) was chromatographed on silica gel (30 g) using hexane as eluent to give 695 mg (92%) of **23**[39] as an oil. IR ($CHCl_3$) 3085, 2967, 2242, 1531, 1352, 1215, 1096 cm^{-1}; ^1H NMR (300 MHz) δ 1.06 (3H, t, $J = 7.0$ Hz), 1.64 (2H, m), 2.41(2H, t, $J = 7.2$ Hz) 7.43–8.27 (4H, m); ^{13}C NMR (75 MHz) δ 13.56, 21.35, 21.97, 78.67, 93.43, 122.23, 125.96, 126.40, 129.14, 137.32, 148.09.

3-Pentylaniline (5b).[39] A stirred solution of **23** (673 mg, 3.56 mmol) in EtOH (10 mL) was hydrogenated in the presence of 10% Pd/C (182 mg) at 60 °C and atmospheric pressure for 4 h. The suspension was filtered through a short pad of silica gel and the filtrate was evaporated under vacuum to leave a residue (563 mg), which was chromatographed on silica gel (30 g) using hexane/AcOEt = 85/15 as eluent to give 523 mg (90%) of **5b**[39] as an oil. IR ($CHCl_3$) 3451, 3375, 3038, 3009, 2959, 2931, 2859, 1619, 1493, 1460, 1288, 1167 cm^{-1}; ^1H NMR (300 MHz) δ 0.89 (3H, t, $J =$ 6.8 Hz), 1.31 (4H, m), 1.58 (2H, m), 2.50 (2H, t, $J = 7.6$ Hz), 3.43 (2H, br s), 6.49–7.07 (4H, m); ^{13}C NMR (75 MHz) δ 14.04, 22.58, 31.07, 31.58, 35.96, 112.52, 115.29, 118.86, 129.10, 144.25, 146.29.

***N*-[2-(5-Hydroxy-1*H*-indol-3-yl)ethyl]-*N*′-(3-pentylphenyl)urea (2b).** The title compound was prepared from **5b** following the same procedure that was used for the synthesis of **2a** and using CH_2Cl_2/AcOEt = 7/3 as eluent for the chromatographic purification. Yield 76%; mp 172–174 °C; IR 3425, 3331, 2928, 2855, 1643, 1611, 1596, 1489, 1457, 1366, 1315, 1268, 1245, 1208, 1187, 1092, 1037 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 0.89 (3H, t, $J = 6.8$ Hz), 1.31 (4H, m), 1.57 (2H, m), 2.51 (2H, t, $J = 7.6$ Hz), 2.88 (2H, t, $J = 7.0$ Hz), 3.48 (2H, t, $J = 7.0$ Hz), 6.68–7.17 (8H, m); ^{13}C NMR (75 MHz, CD_3OD) δ 14.41, 23.58, 27.07, 32.30, 32.62, 36.96, 41.45, 103.60, 112.44, 112.49, 112.71, 117.73, 120.37, 123.63, 124.42, 129.44, 129.61, 133.19, 140.78, 144.78, 151.13, 158.47. Anal. ($C_{22}H_{27}N_3O_2$) C, H, N.

***N*-[2-(5-Hydroxy-1*H*-indol-3-yl)ethyl]-*N*′-(2-phenylethyl)urea (2c).** The title compound was prepared from **5c** following the same procedure that was used for the synthesis of **2a** and using preparative layer chromatography (silica gel, 0.5 cm thick) and CH_2Cl_2/AcOEt = 3/7 as eluent for the purification of **2c**. Yield 32%; mp 148–150 °C; IR 3361, 3317, 2936, 2870, 1607, 1588, 1520, 1495, 1458, 1384, 1258, 1235, 1209, 1192, 1072 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 2.71 (2H, t, $J = 7.1$ Hz), 2.82 (2H, t, $J = 7.1$ Hz), 3.31 (2H, t, $J = 7.1$ Hz), 3.38 (2H, t, $J = 7.1$ Hz), 6.65–7.26 (9H, m); ^{13}C NMR (75 MHz, CD_3OD) δ 27.19, 37.54, 41.70, 42.63, 103.62, 112.40, 112.67, 124.35, 127.22, 129.46, 129.86, 133.16, 140.80, 151.13, 161.19. Anal. ($C_{19}H_{21}N_3O_2$) C, H, N.

***N*-[2-(4-Chlorophenyl)ethyl]-*N*′-[2-(5-hydroxy-1*H*-indol-3-yl)ethyl]urea (2d).** The title compound was prepared from **5d** following the same procedure that was used for the synthesis of **2a** and using CH_2Cl_2/AcOEt = 4/6 as eluent for the chromatographic purification. Yield 38%; mp 114–116 °C; IR 3424, 3322, 2927, 1626, 1581, 1459, 1367, 1273, 1132, 1054 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 2.85 (4H, m), 3.36 (4H, m), 6.65–7.31 (8H, m); ^{13}C NMR (75 MHz, CD_3OD) δ 27.19, 35.22, 40.80, 41.69, 103.63, 112.41, 112.65, 124.36, 128.11, 129.01, 129.51, 130.46, 132.35, 133.18, 135.12, 138.29, 151.13. Anal. ($C_{19}H_{20}ClN_3O_2$) C, H, N.

***N*-[1,1′-Biphenyl]-3-yl-*N*′-[2-(5-hydroxy-1*H*-indol-3-yl)ethyl]urea (2e).** The title compound was prepared from **5e** following the same procedure that was used for the synthesis of **2a** and using CH_2Cl_2/AcOEt = 6/4 as eluent for the chromatographic purification. Yield 68%; mp 191–193 °C; IR 3423, 3313, 2923, 1636, 1560, 1480, 1457, 1365, 1207, 1181, 1091, 1075 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 2.89 (2H, t, $J = 7.1$ Hz), 3.50 (2H, t, $J = 7.1$ Hz), 6.69–7.64 (13H, m); ^{13}C NMR (75 MHz, CD_3OD) δ 27.02, 41.46, 103.62, 112.45, 112.76, 118.79, 119.08, 122.06, 124.44, 124.61, 127.95, 128.32, 129.43, 129.74, 130.24, 133.16, 141.36, 143.32, 143.12, 151.10, 158.38. Anal. ($C_{23}H_{21}N_3O_2$) C, H, N.

2-[1,1′-Biphenyl]-4-ethanamine Hydrochloride (5f). A stirred solution of 4-biphenylacetonitrile (500 mg, 2.6 mmol) in MeOH (20 mL) containing a few drops of concentrated hydrochloric acid was hydrogenated in the presence of 10% Pd/Cl (370 mg) at room temperature and atmospheric pressure for 16 h. The suspension was filtered through a short pad of Celite, and the filtrate was evaporated under vacuum to leave the crude title compound (600 mg, 99%). Mp 243–245 °C (lit.[50] 245 °C); IR 3422, 3026, 1582, 1511, 1487, 1409, 1125, 1075, 1006 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 3.03 (2H, m), 3.08 (2H, m), 7.35–7.66 (9H, m), 8.37 (3H, br s); ^{13}C NMR (75 MHz, DMSO-d_6) δ 32.49, 39.82, 126.54, 126.87, 127.36, 128.95, 129.28, 136.81, 138.57, 139.87.

***N*-(2-[1,1′-Biphenyl]-4-ylethyl)-*N*′-[2-(5-hydroxy-1*H*-indol-3-yl)ethyl]urea (2f).** The title compound was prepared from **5f** following the same procedure that was used for the synthesis of **2a** and using CH_2Cl_2/AcOEt = 4/6 as eluent for the chromatographic purification. Yield 40%; mp 159–161 °C; IR 3436, 3395, 3311, 1629, 1557, 1488, 1250, 1218, 1189 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 2.75 (2H, t, $J = 6.9$ Hz), 2.83 (2H, t, $J = 6.9$ Hz), 3.33 (2H, t, $J = 7.2$ Hz), 3.39 (2H, t, $J = 7.2$ Hz), 6.96–7.55

(13H, m); ^{13}C NMR (75 MHz, CD_3OD) δ 27.17, 37.11, 41.68, 42.55, 103.63, 112.41, 112.66, 124.35, 127.82, 128.02, 128.11, 129.54, 129.80, 130.39, 133.16, 139.94, 140.40, 142.27, 151.14, 161.19. Anal. ($C_{25}H_{25}N_3O_2$) C, H, N.

2-(4-Phenoxyphenyl)ethanamine Hydrochloride (5g). A stirred solution of (4-phenoxyphenyl)acetonitrile (209 mg, 1 mmol) in MeOH (10 mL) containing a few drops of concentrated hydrochloric acid was hydrogenated in the presence of 10% Pd/C (140 mg) at room temperature and atmospheric pressure for 16 h. The suspension was filtered through a short pad of Celite, and the filtrate was evaporated under vacuum to leave the crude title compound (245 mg, 98%). Mp 195–197 °C (lit.[51] 209–210 °C); IR 3423, 3001, 1592, 1507, 1489, 1251, 1113, 1068, 1017 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.89 (2H, m), 3.03 (2H, m), 6.99–7.43 (9H, m), 8.00 (3H, br s); ^{13}C NMR (75 MHz, DMSO-d_6) δ 32.12, 40.01, 118.39, 118.95, 123.32, 130.03, 130.30, 132.62, 155.28, 156.88.

***N*-[2-(5-Hydroxy-1*H*-indol-3-yl)ethyl]-*N*′-[2-(4-phenoxyphenyl)ethyl]urea (2g).** The title compound was prepared from **5g** following the same procedure that was used for the synthesis of **2a** and using CH_2Cl_2/AcOEt = 4/6 as eluent for the chromatographic purification. Yield 41%; mp 164–166 °C; IR 3394, 3293, 2920, 1622, 1573, 1505, 1489, 1250, 1194 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ 2.68 (2H, t, J = 7.0 Hz), 2.82 (2H, t, J = 7.0 Hz), 3.30 (2H, t, J = 7.1 Hz), 3.39 (2H, t, J = 7.1 Hz), 6.65–7.05 (13H, m); ^{13}C NMR (75 MHz, CD_3OD) δ 27.17, 36.77, 41.71, 42.64, 103.61, 112.39, 112.68, 119.53, 120.01, 124.10, 124.35, 129.51, 130.72, 131.23, 133.14, 135.88, 151.11, 156.97, 159.00, 161.16. Anal. ($C_{25}H_{25}N_3O_3$) C, H, N.

(*all-Z*)-Eicosan-5,8,11,14-tetraenol (6a). To a stirred solution of arachidonic acid (**4a**) (82 mg, 0.27 mmol) and *N*-methylmorpholine (0.025 mL, 0.27 mmol) in dry THF (0.5 mL) was added dropwise at −15 °C isobutyl chloroformate (0.035 mL, 0.27 mmol), and the mixture was stirred at −15 °C for 15 min. The suspension was filtered, and $NaBH_4$ (15 mg, 0.40 mmol) was added at 0 °C to the filtrate, followed by 0.020 mL of water. The reaction mixture was stirred in an ice bath for 1 h and then diluted with water and extracted with AcOEt. The organic phase was washed with water until neutral, dried (Na_2SO_4), and evaporated under vacuum to leave the title alcohol (78 mg), pure from TLC, which was used in the next step without further purification.

(*all-Z*)-Octadeca-9,12,15-trienol (6b). Prepared as above from α-linolenic acid.

(*all-Z*)-Octadeca-6,9,12-trienol (6c). Prepared as above from γ-linolenic acid.

(*all-Z*)-Octadeca-9,12-dienol (6d). Prepared as above from linoleic acid.

(*all-Z*)-Eicosan-5,8,11,14-tetraenyl [2-(5-Hydroxy-1*H*-indol-3-yl)ethyl]carbamate (3a). To a stirred solution of **6a** (78 mg, 0.27 mmol) and Et_3N (0.045 mL, 0.32 mmol) in dry toluene (2.7 mL) was added dropwise at 0 °C a 20% phosgene solution in toluene (0.56 mL, 1.08 mmol). After being stirred at room temperature for 2 h, the solution was evaporated under reduced pressure to give the crude chloroformate, which was dissolved in dry CH_2Cl_2 (1.4 mL) and to which was added dropwise a solution of serotonin hydrochloride (63 mg, 0.30 mmol) and Et_3N (0.083 mL, 0.59 mmol) in dry DMF (1.3 mL). The mixture was stirred at room temperature overnight and then diluted with water, neutralized with 2 N HCl, and extracted with AcOEt. The organic phase was washed with water, dried (Na_2SO_4), and evaporated under vacuum to leave a residue (141 mg), which was chromatographed on silica gel (7 g) using CH_2Cl_2/AcOEt = 85/15 as eluent to give the title compound (73 mg, 55% yield) as an oil. IR ($CHCl_3$) 3481, 3349, 2930, 2858, 1706, 1627, 1586, 1516, 1467, 1340, 1236, 1170, 1140, 1088, 1042 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.88 (3H, t, J = 6.6 Hz), 1.29 (8H, m), 1.60 (2H, m), 2.06 (4H, m), 2.81 (8H, m), 3.43 (2H, m), 4.07 (2H, t, J = 6.4 Hz), 4.83 (1H, m), 5.36 (8H, m), 6.15 (1H, br s), 6.76–7.25 (4H, m) 8.06 (1H, m); ^{13}C NMR (75 MHz) δ 14.05, 22.56, 25.67, 25.92, 26.85, 27.24, 28.68, 29.32, 31.52, 41.10, 41.13, 41.17, 51.50, 65.09, 103.28, 111.86, 112.10, 112.18, 123.14, 127.58, 127.93, 128.02, 128.17, 128.23, 128.32, 128.60, 129.73, 130.51, 131.62, 149.82, 157.13. Anal. ($C_{31}H_{44}N_2O_3$) C, H, N.

(*all-Z*)-Octadeca-9,12,15-trienyl [2-(5-Hydroxy-1*H*-indol-3-yl)ethyl]carbamate (3b). The title compound was prepared from **6b** following the same procedure that was used for the synthesis of **3a** and using CH_2Cl_2/AcOEt = 85/15 as eluent for the chromatographic purification. Yield 61%; oil; IR ($CHCl_3$) 3481, 3344, 2931, 2856, 1704, 1628, 1586, 1516, 1465, 1340, 1236, 1203, 1170, 1072 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.97 (3H, t, J = 7.3 Hz), 1.26 (10H, m), 1.56 (2H, m), 2.06 (4H, m), 2.80 (6H, m), 3.36 (2H, m), 4.04 (2H, m), 4.93 (1H, m), 5.36 (6H, m), 6.77–7.11 (5H, m), 8.19 (1H, br s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.27, 20.55, 25.53, 25.62, 25.85, 27.23, 29.00, 29.24, 29.27, 29.44, 29.62, 41.02, 65.27, 103.20, 111.84, 111.92, 112.13, 123.16, 127.13, 127.68, 127.92, 128.28, 130.34, 131.53, 131.97, 149.77, 157.29. Anal. ($C_{29}H_{42}N_2O_3$) C, H, N.

(*all-Z*)-Octadeca-6,9,12-trienyl [2-(5-Hydroxy-1*H*-indol-3-yl)ethyl]carbamate (3c). The title compound was prepared from **6c** following the same procedure that was used for the synthesis of **3a** and using CH_2Cl_2/AcOEt = 8/2 as eluent for the chromatographic purification. Yield 59%; oil; IR ($CHCl_3$) 3481, 3349, 2931, 2858, 1705, 1627, 1588, 1515, 1466, 1340, 1236, 1206, 1170, 1088, 1073 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.88 (3H, t, J = 7.3 Hz), 1.33 (10H, m), 1.58 (2H, m), 2.04 (4H, m), 2.79 (6H, m), 3.39 (2H, m), 4.05 (2H, m), 4.89 (1H, m), 5.38 (6H, m), 6.60 (1H, br s), 6.77–7.13 (4H, m), 8.15 (1H, br s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.07, 22.57, 25.41, 25.53, 25.64, 25.81, 27.10, 27.22, 28.94, 29.28, 29.32, 31.51, 41.04, 65.16, 103.23, 111.91, 112.15, 123.14, 127.62, 127.95, 127.98, 128.18, 128.39, 129.97, 130.47, 131.55, 149.80, 157.21. Anal. ($C_{29}H_{42}N_2O_3$) C, H, N.

(*all-Z*)-Octadeca-9,12-dienyl [2-(5-Hydroxy-1*H*-indol-3-yl)ethyl]carbamate (3d). The title compound was prepared from **6b** following the same procedure that was used for the synthesis of **3a** and using CH_2Cl_2/AcOEt =85/15 as eluent for the chromatographic purification. Yield 40%; oil; IR ($CHCl_3$) 3481, 3349, 2929, 2856, 1705, 1627, 1586, 1517, 1466, 1340, 1236, 1200, 1170, 1087, 1074 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.88 (3H, t, J = 6.7 Hz), 1.28 (16H, m), 1.58 (2H, m), 2.04 (4H, m), 2.80 (4H, m), 3.43 (2H, m), 4.05 (2H, t, J = 6.6 Hz), 4.86 (1H, t, J = 5.2 Hz), 5.34 (4H, m), 6.25 (1H, br s), 6.76–7.18 (4H, m), 8.08 (1H, m); ^{13}C NMR (75 MHz) δ 14.05, 22.57, 25.68, 25.89, 27.24, 29.06, 29.26, 29.36, 29.45, 29.67, 31.54, 41.15, 41.19, 65.27, 103.31, 111.86, 112.08, 112.18, 123.13, 127.97, 128.05, 130.14, 130.25, 131.64, 149.83, 157.17. Anal. ($C_{29}H_{44}N_2O_3$) C, H, N.

3-Pentylphenyl [2-(5-Hydroxy-1*H*-indol-3-yl)ethyl]carbamate (3e). The title compound was prepared from **6e** following the same procedure that was used for the synthesis of **3a** and using CH_2Cl_2/AcOEt = 87/13 as eluent for the chromatographic purification. Yield 58%; oil; IR ($CHCl_3$) 3480, 3009, 2931, 2859, 1729, 1588, 1509, 1484, 1376, 1238, 1156, 1090, 1041 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.85 (3H, t, J = 6.5 Hz), 1.26 (4H, m), 1.56 (2H, m), 2.53 (2H, t, J = 7.7 Hz), 2.82 (2H, t, J = 6.7 Hz), 3.43 (2H, m), 5.22 (1H, t, J = 5.8 Hz), 6.29 (1H, br s), 6.68–7.24 (8H, m), 8.08 (1H, m); ^{13}C NMR (75 MHz) δ 13.99, 22.48, 25.59, 30.85, 31.49, 35.69, 41.39, 103.24, 111.79, 111.95, 112.14, 118.79, 121.54, 123.23, 125.47, 127.98, 129.00, 131.62, 144.62, 149.69, 150.97, 155.17. Anal. ($C_{22}H_{26}N_2O_3$) C, H, N.

[1,1′-Biphenyl]-3-yl [2-(5-Hydroxy-1*H*-indol-3-yl)ethyl]carbamate (3f). The title compound was prepared from **6f** following the same procedure that was used for the synthesis of **3a** and using CH_2Cl_2/AcOEt = 85/15 as eluent for the chromatographic purification. Yield 63%; oil; IR ($CHCl_3$) 3480, 3014, 1731, 1598, 1506, 1477, 1420, 1236, 1189, 1089, 1045 cm^{-1}; ^{1}H NMR (300 MHz) δ 2.81 (2H, t, J = 6.6 Hz), 3.42 (2H, m), 5.23 (1H, t, J = 5.9 Hz), 6.13 (1H, br s), 6.67–7.51 (13H, m), 8.02 (1H, m); ^{13}C NMR (75 MHz) δ 25.57, 41.43, 103.26, 111.83, 111.96, 112.16, 120.38, 120.45, 123.24, 124.10, 127.17, 127.58, 128.01, 128.76, 129.59, 131.63, 140.24, 142.67, 149.68, 151.41, 154.99. Anal. ($C_{23}H_{20}N_2O_3$) C, H, N.

3-*tert*-Butylphenyl [2-(5-Hydroxy-1*H*-indol-3-yl)ethyl]carbamate (3g). The title compound was prepared from **6g** following the same procedure that was used for the synthesis of **3a** and using CH_2Cl_2/AcOEt = 9/1 as eluent for the chromatographic purification.

Yield 41%; oil; IR ($CHCl_3$) 3480, 3029, 2967, 1731, 1606, 1509, 1487, 1374, 1236, 1197, 1044 cm^{-1}; ^1H NMR (300 MHz) δ 1.26 (9H, s), 2.86 (2H, t, J = 6.8 Hz), 3.47 (2H, m), 5.21 (1H, t, J = 5.7 Hz), 5.99 (1H, br s), 6.69–7.30 (8H, m), 8.05 (1H, br s); ^{13}C NMR (75 MHz) δ 25.63, 31.24, 34.74, 41.38, 103.26, 111.88, 111.94, 112.15, 118.69, 122.40, 123.22, 127.99, 128.80, 131.64, 149.68, 150.88, 152.97, 155.15, 155.19. Anal. ($C_{21}H_{24}N_2O_3$) C, H, N.

4-*tert*-Butylphenyl [2-(5-Hydroxy-1*H*-indol-3-yl)ethyl]carbamate (3h). The title compound was prepared from **6h** following the same procedure that was used for the synthesis of **3a** and using CH_2Cl_2/AcOEt = 9/1 as eluent for the chromatographic purification. Yield 24%; mp 159–160 °C; IR 3421, 3320, 2961, 1708, 1582, 1540, 1508, 1460, 1394, 1275, 1225, 1178, 1029 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3/CD_3OD$ = 3/1) δ 1.29 (9H, s), 2.91 (2H, t, J = 7.0 Hz), 3.48 (2H, m), 5.54 (1H, t, J = 5.8 Hz), 6.75–7.38 (8H, m), 8.52 (1H, br s); ^{13}C NMR (75 MHz, $CDCl_3/CD_3OD$ = 3/1) δ 25.78, 31.45, 34.48, 41.63, 102.98, 111.73, 112.00, 112.16, 121.09, 123.23, 126.23, 128.14, 131.60, 148.32, 148.70, 150.17, 155.52. Anal. ($C_{21}H_{24}N_2O_3$) C, H, N.

3-(Trifluoromethyl)phenyl [2-(5-Hydroxy-1*H*-indol-3-yl)ethyl]carbamate (3i). The title compound was prepared from **6i** following the same procedure that was used for the synthesis of **3a** and using CH_2Cl_2/AcOEt = 8/2 as eluent for the chromatographic purification. Yield 68%; mp 91–93 °C; IR 3419, 2927, 1709, 1528, 1452, 1338, 1328, 1253, 1208, 1173, 1117, 1066, 1030 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3/CD_3OD$ = 2/1) δ 2.98 (2H, t, J = 7.2 Hz), 3.52 (2H, t, J = 7.2 Hz), 6.74–7.46 (8H, m); ^{13}C NMR (75 MHz, $CDCl_3$/CD_3OD = 2/1) δ 25.97, 42.09, 102.95, 111.48, 111.97, 112.27, 119.25, 122.29, 123.70, 125.80, 128.44, 130.29, 132.04, 150.25, 151.75, 155.42. Anal. ($C_{18}H_{15}F_3N_2O_3$) C, H, N.

4-(Trifluoromethyl)phenyl [2-(5-Hydroxy-1*H*-indol-3-yl)ethyl]carbamate (3j). The title compound was prepared from **6j** following the same procedure that was used for the synthesis of **3a** and using CH_2Cl_2/AcOEt = 8/2 as eluent for the chromatographic purification. Yield 30%; mp 130–133 °C; IR ($CHCl_3$) 3480, 3029, 2944, 1735, 1615, 1484, 1415, 1325, 1238, 1170, 1130, 1065 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3/CD_3OD$ = 1/1) δ 2.97 (2H, t, J = 7.0 Hz), 3.51 (2H, t, J = 7.0 Hz), 6.75–7.62 (8H, m); ^{13}C NMR (75 MHz, $CDCl_3/CD_3OD$ = 1/1) δ 25.86, 42.00, 102.93, 111.45, 111.98, 112.25, 122.43, 123.65, 126.82, 126.86, 128.40, 131.96, 150.22, 154.16, 155.14. Anal. ($C_{18}H_{15}F_3N_2O_3$) C, H, N.

3-Chlorophenyl [2-(5-Hydroxy-1*H*-indol-3-yl)ethyl]carbamate (3k). The title compound was prepared from **6k** following the same procedure that was used for the synthesis of **3a** and using CH_2Cl_2/AcOEt = 8/2 as eluent for the chromatographic purification. Yield 37%; mp 120–123 °C; IR 3395, 3286, 2913, 2863, 1706, 1589, 1549, 1470, 1255, 1211, 1068 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3/CD_3OD$ = 1/1) δ 2.96 (2H, t, J = 7.4 Hz), 3.48 (2H, t, J = 7.4 Hz), 6.71–7.67 (8H, m); ^{13}C NMR (75 MHz, $CDCl_3/CD_3OD$ = 1/1) δ 26.22, 42.42, 103.16, 111.78, 112.08, 112.43, 120.83, 122.92, 123.92, 125.97, 128.81, 130.69, 132.42, 134.97, 150.50, 152.58. Anal. ($C_{17}H_{15}ClN_2O_3$) C, H, N.

4-Chlorophenyl [2-(5-Hydroxy-1*H*-indol-3-yl)ethyl]carbamate (3l). The title compound was prepared from **6l** following the same procedure that was used for the synthesis of **3a** and using CH_2Cl_2/AcOEt = 8/2 as eluent for the chromatographic purification. Yield 36%; mp 130–133 °C; IR 3524, 3410, 3319, 2927, 1701, 1487, 1365, 1216, 1166, 1088 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$/CD_3OD = 1/1) δ 2.95 (2H, t, J = 7.2 Hz), 3.48 (2H, t, J = 7.2 Hz), 6.74–7.51 (8H, m); ^{13}C NMR (75 MHz, $CDCl_3/CD_3OD$ = 1/1) δ 25.95, 42.08, 102.99, 111.54, 111.98, 112.30, 123.56, 123.71, 128.50, 129.58, 130.89, 132.06, 150.15, 150.24, 155.77. Anal. ($C_{17}H_{15}ClN_2O_3$) C, H, N.

3-Iodophenyl [2-(5-Hydroxy-1*H*-indol-3-yl)ethyl]carbamate (3m). The title compound was prepared from **6m** following the same procedure that was used for the synthesis of **3a** and using CH_2Cl_2/AcOEt = 87/13 as eluent for the chromatographic purification. Yield 37%; mp 130–131 °C; IR ($CHCl_3$) 3480, 3025, 3009, 2929, 1734, 1578, 1506, 1466, 1234, 1197, 1089, 1043 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3/CD_3OD$ = 2/1) δ 2.93 (2H, t, J = 7.0 Hz), 3.49 (2H, m), 5.68 (1H, br s), 6.76–7.55 (8H, m), 8.59 (1H, br s); ^{13}C NMR (75 MHz, $CDCl_3/CD_3OD$ = 2/1) δ 25.72, 41.67, 93.33, 102.94, 111.55, 112.01, 112.20, 121.29, 123.26, 128.12, 130.60, 130.91, 131.60, 134.50, 150.20, 151.37, 154.66. Anal. ($C_{17}H_{15}IN_2O_3$) C, H, N.

4-Iodophenyl [2-(5-Hydroxy-1*H*-indol-3-yl)ethyl]carbamate (3n). The title compound was prepared from **6n** following the same procedure that was used for the synthesis of **3a** and using CH_2Cl_2/AcOEt = 87/13 as eluent for the chromatographic purification. Yield 43%; mp 146–149 °C; IR 3383, 2922, 2848, 1717, 1579, 1478, 1208, 1007 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3/CD_3OD$ = 2/1) δ 2.94 (2H, t, J = 7.1 Hz), 3.49 (2H, t, J = 7.1 Hz), 6.69–7.67 (8H, m); ^{13}C NMR (75 MHz, $CDCl_3/CD_3OD$ = 2/1) δ 25.72, 41.74, 89.09, 102.87, 111.42, 112.03, 112.09, 123.41, 124.07, 128.23, 131.73, 138.44, 150.19, 151.20, 155.15. Anal. ($C_{17}H_{15}IN_2O_3$) C, H, N.

2-Naphthalenyl [2-(5-Hydroxy-1*H*-indol-3-yl)ethyl]carbamate (3o). The title compound was prepared from **6o** following the same procedure that was used for the synthesis of **3a** and using CH_2Cl_2/AcOEt = 9/1 as eluent for the chromatographic purification. Yield 58%. Mp 158–159 °C; IR 3392, 3265, 3050, 2911, 1702, 1557, 1508, 1462, 1360, 1279, 1240, 1210, 1068 cm^{-1}; ^1H NMR (300 MHz) δ 2.96 (2H, t, J = 7.0 Hz), 3.52 (2H, m), 6.76–7.82 (11H, m); ^{13}C NMR (75 MHz) δ 25.76, 41.69, 102.82, 111.38, 111.96, 112.09, 118.58, 121.59, 123.38, 123.54, 125.64, 126.62, 127.65, 127.82, 128.18, 129.34, 131.38, 133.94, 148.78, 150.12, 155.77. Anal. ($C_{21}H_{18}N_2O_3$) C, H, N.

4-Methoxyphenyl [2-(5-Hydroxy-1*H*-indol-3-yl)ethyl]carbamate (3p). The title compound was prepared from **6p** following the same procedure that was used for the synthesis of **3a** and using CH_2Cl_2/AcOEt = 8/2 as eluent for the chromatographic purification. Yield 39%; mp 151–153 °C; IR ($CHCl_3$) 3480, 3031, 2938, 2838, 1731, 1601, 1496, 1374, 1249, 1197, 1180, 1042 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 2.84 (2H, t, J = 7.4 Hz), 3.34 (2H, m), 3.74 (3H, s), 6.64–7.21 (8H, m), 7.70 (1H, t, J = 5.4 Hz), 8.90 (1H, s), 10.47 (1H, s); ^{13}C NMR (75 MHz, DMSO-d_6) δ 25.71, 41.77, 55.80, 102.76, 111.18, 111.79, 112.30, 114.67, 123.20, 123.76, 128.42, 131.32, 144.88, 150.44, 155.52, 156.76. Anal. ($C_{18}H_{18}N_2O_4$) C, H, N.

4-(Benzyloxy)phenyl [2-(5-Hydroxy-1*H*-indol-3-yl)ethyl]carbamate (3q). The title compound was prepared from **6q** following the same procedure that was used for the synthesis of **3a** and using CH_2Cl_2/AcOEt = 85/15 as eluent for the chromatographic purification. Yield 39%; mp 120–121 °C; IR 3394, 3287, 2916, 2865, 1702, 1552, 1507, 1453, 1382, 1267, 1246, 1215, 1101, 1069, 1042, 1028 cm^{-1}; ^1H NMR (300 MHz) δ 2.90 (2H, t, J = 6.9 Hz), 3.46 (2H, m), 4.99 (2H, s), 5.63 (1H, t, J = 5.6 Hz), 6.74–7.42 (13H, m); ^{13}C NMR (75 MHz) δ 25.73, 41.67, 70.58, 102.95, 111.64, 112.01, 112.12, 115.51, 122.61, 123.29, 127.54, 128.06, 128.16, 128.64, 131.64, 136.99, 144.87, 150.17, 155.74, 156.26. Anal. ($C_{24}H_{22}N_2O_4$) C, H, N.

FAAH Assays. The effect of increasing concentrations of the new synthetic compounds on the enzymatic hydrolysis of [^{14}C]anandamide was studied as described previously[52] by using membranes prepared from rat brain. In brief, the entire rat brain was homogenized at 4 °C in 50 mM Tris-HCl buffer, pH 7.0, by using an Ultraturrax and a Dounce homogenizer. Homogenates were first centrifuged at 800g to rid the debris, and the supernatant was centrifuged at 10000g. The pellet from this latter centrifugation was used for the assay. Membranes (70–100 μg) were incubated with increasing concentrations (up to 50 μM) of the test compounds and [^{14}C]AEA (10 000 cpm, 1.8 μM) in 50 mM Tris-HCl, pH 9, for 30 min at 37 °C. [^{14}C]Ethanolamine produced from [^{14}C]AEA hydrolysis was used to calculate FAAH activity and was measured by scintillation counting of the aqueous phase after extraction of the incubation mixture with 2 volumes of $CHCl_3/CH_3OH$ (1:1 by volume). Data are expressed as the concentration exerting a half-maximal inhibition (IC_{50}). The effect of the compounds on the uptake of anandamide by RBL-2H3 cells was studied as described previously.[53]

Assays for Activity at Human Recombinant TRPV1. Human embryonic kidney (HEK) 293 cells stably overexpressing human recombinant TRPV1 cDNA were grown as monolayers in minimum essential medium supplemented with nonessential amino acids, 10% fetal calf serum, and 0.2 mM glutamine and maintained under 95%/5% O_2/CO_2 at 37 °C. The effect of the new compounds on $[Ca^{2+}]_I$ was determined by using Fluo-3, a selective intracellular fluorescent probe for Ca^{2+}. One day prior to experiments, cells were transferred into six-well dishes coated with poly-L-lysine (Sigma) and grown in the culture medium mentioned above. On the day of the experiment, the cells (50000–60000 per well) were loaded for 2 h at 25 °C with 4 μM Fluo-3 methyl ester (Molecular Probes) in DMSO. After the loading, cells were washed with Tyrode, pH 7.4, trypsinized, resuspended in Tyrode, and transferred into the cuvette of the fluorescence detector (Perkin-Elmer LS50B) under continuous stirring. Experiments were carried out by measuring cell fluorescence at 25 °C (λ_{EX} = 488 nm, λ_{EM} = 540 nm) before and after the addition of the test compounds at various concentrations. Potency data are expressed as the concentrations exerting a half-maximal inhibition (IC_{50}).

Test of Antinociceptive Activity in Mice Treated with Formalin. Formalin injection induces a biphasic stereotypical nocifensive behavior. Nociceptive responses are divided into an early, short-lasting first phase (0–7 min) caused by a primary afferent discharge produced by the stimulus, followed by a quiescent period and then a second, prolonged phase (15–60 min) of tonic pain. Mice received formalin (1.25%) in the dorsal surface of one side of the hind paw. Each mouse was randomly assigned to one of the experimental groups (n = 8–10) and placed in a Plexiglas cage and allowed to move freely for 15–20 min. A mirror was placed at a 45° angle under the cage to allow full view of the hind paws. Lifting, favoring, licking, shaking, and flinching of the injected paw were recorded as nociceptive responses. Mice received intraperitoneal administration of **1a** (0.3–5 mg/kg, ip), **3f** (1–10 mg/kg, ip), or **1m** (1–10 mg/kg, ip), alone or in combination with the selective cannabinoid CB_1 receptor antagonist AM251 (3 mg/kg, ip), the selective cannabinoid CB_2 receptor antagonist AM630 (3 mg/kg, ip), or the selective TRPV1 receptor antagonist iodoresiniferatoxin (I-RTX, 0.1–0.2 mg/kg, ip). **1a**, **3f**, or **1m** were administered 15 min before peripheral injection of formalin. The CB_1 or TRPV1 antagonists were administered 5 min before **1a**, **3f**, or **1m**. The total time of the nociceptive response was measured every 5 min and expressed as the total time of the nociceptive responses in min (mean ± SEM). Recording of nociceptive behavior commenced immediately after formalin injection and was continued for 60 min.

Supporting Information Available: Elemental analysis data. This material is available free of charge via the Internet at http://pubs.acs.org.

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