Naphthalen-1-yl-(4-pentyloxynaphthalen-1-yl)methanone: A Potent, Orally Bioavailable Human CB_1/CB_2 Dual Agonist with Antihyperalgesic Properties and Restricted Central Nervous System Penetration

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Selective activation of peripheral cannabinoid CB_1 receptors has the potential to become a valuable therapy for chronic pain conditions as long as central nervous system effects are attenuated. A new class of cannabinoid ligands was rationally designed from known aminoalkylindole agonists and showed good binding and functional activities at human CB_1 and CB_2 receptors. This has led to the discovery of a novel CB_1/CB_2 dual agonist, naphthalen-1-yl-(4-pentyloxynaphthalen-1-yl)methanone (**13**), which displays good oral bioavailability, potent antihyperalgesic activity in animal models, and limited brain penetration.

Introduction

There is evidence that the predominant active constituent of marijuana (*Cannabis sativa* L.), Δ^9-tetrahydrocannabinol (Δ^9-THC, **1**), is effective in a variety of important medical conditions such as pain, anxiety, emesis, glaucoma, feeding disorders, and movement disorders.[1,2] However, therapeutic advances in this area will continue to be limited unless the potential medical benefits of cannabinoids can be dissociated from the undesirable psychotropic side effects.[3] In spite of this obstacle, there is a considerable research effort being directed at seeking novel opportunities to develop cannabinoid-based medicines for these indications.[4] In the past decade or so, this endeavor has been greatly facilitated inter alia by the cloning[5,6] and pharmacological characterization[7] of two mammalian G-protein-coupled cannabinoid receptors, CB_1 and CB_2. The CB_1 subtype is widely distributed in the brain and spinal cord but is also expressed in several peripheral tissues.[4] CB_2 receptors, on the other hand, are found mainly in the spleen and cells of the immune system,[6a] though they have also been detected in the brain.[6b,c] Both receptors are negatively coupled to adenylate cyclase, and their activation has the net effect of inhibiting neuronal activity and downregulating inflammatory cell function.

Among the pharmacological effects elicited by cannabinoids, analgesia is one of the important properties with therapeutic prospects.[8−10] If realized, this would address a major unmet medical need, as some chronic pain syndromes do not respond to current therapy.[11] In a study published in 2001, we showed that cannabinoids produce pronounced inhibition of hyperalgesia (abnormally increased reactivity to pain) and allodynia (pain elicited by stimuli that are normally innocuous) in a rat model of neuropathic pain.[12] Together with evidence from other studies, this work suggested that at least part of the effect is mediated via peripheral CB_1 receptors.[13,14] These important results defined a strategy for the development of a new class of analgesic drug with reduced side effects: agonists that bind to and activate peripheral CB_1 receptors and that do not cross the blood−brain barrier into the central nervous system (CNS).[14] Furthermore, it may not be necessary (or desirable) to achieve complete receptor subtype selectivity. Recent studies have demonstrated that activation of peripheral CB_2 receptors also produces antinociceptive effects.[15] Inherent CB_2 agonism in any new compound class might therefore be expected to enhance the peripheral analgesic effect. Indeed, it was noted in 1998 that the cannabinoid receptor subtypes appear to act synergistically.[16]

Apart from analogues of the classical cannabinoid **1**,[17] there are a number of nonclassical cannabinoid classes reported in the literature that could be considered as starting points for de novo lead generation (Figure 1).[18] These include the 3-arylcyclohexanols (e.g., CP 55,940, **2**),[19] the aminoalkylindoles (AAIs; e.g., WIN 55,212-2, **3**),[20] the pyrazoles (e.g., SR141716A, **4**),[21] and amides of long-chain fatty acids, particularly arachidonic acid.[22] The latter compounds resemble anandamide (**5**), the first endogenous cannabinoid, which was isolated from porcine brain tissue.[23] From a medicinal chemistry perspective, the AAIs are the most druglike of the nonclassical cannabinoid agonists, and rational design of a proprietary compound series was therefore based on the simplified prototype WIN 53,365 (**6**); the pyrazoles, though druglike, behave as inverse agonists.

Compound Design. Compound **6** was structurally modified in several ways (Figure 2). First, we replaced the indole ring system with a naphthalene one, as previous work in the melatonin and serotonin areas had demonstrated a bioisosteric equivalency between indole and naphthalene.[24] As a consequence of expanding to a 6,6-bicyclic core, the aminoalkyl and aroyl side chains of compound **6** were redeployed to the peri positions of one of the fused rings. Second, with an increase in the angle between the substituents (broken lines, Figure 2), we introduced an ether oxygen link so that the longer morpholinoethoxy side chain could still be suitably located in the lower right quadrant (**7**), this being the apparent optimum location of the amine in three-dimensional space.[25a] Parenthetically, linking

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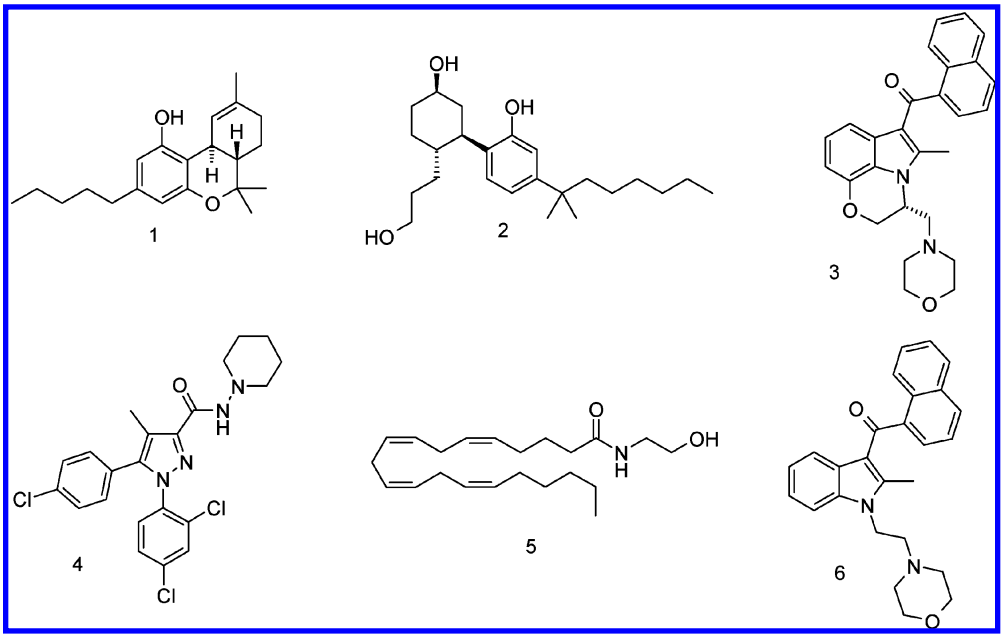


Figure 1. Structures of cannabinoid agonists and antagonists.

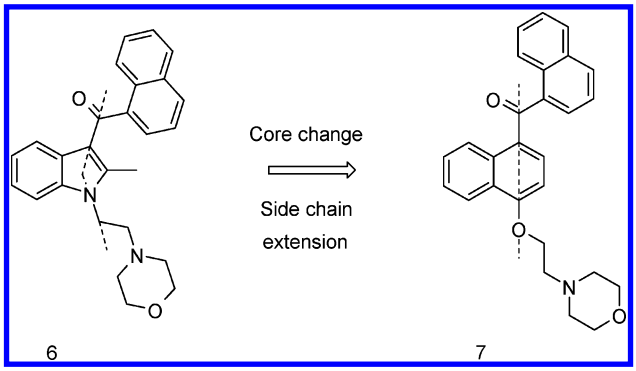


Figure 2. Rational design of a proprietary series of CB_1/CB_2 receptor agonists. The broken lines indicate the initial side-chain trajectories.

through oxygen[25b] facilitated construction of the congeneric series (vide infra). Finally, a number of side chains, previously investigated by Bell et al.[26] and Huffman et al.,[27] were introduced at the ether oxygen atom. Intensive evaluation of this class led to the selection of naphthalen-1-yl-(4-pentyloxynaphthalen-1-yl)methanone, compound **13**,[28] as a clinical development candidate for chronic pain. In this paper, we describe a method of synthesis for **13** and summarize the key pharmacological attributes of this CB_1/CB_2 mixed agonist, which displays good potency, oral bioavailability, and restriction to the peripheral nervous system.

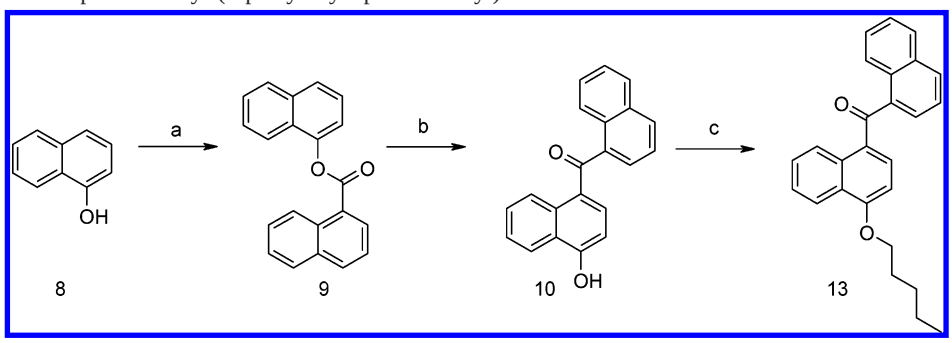
Synthesis. The synthesis of **13** proceeds in three chemical steps from commercially available and inexpensive starting materials (Scheme 1).[28] Esterification of 1-naphthol (**8**) with 1-naphthoyl chloride, followed by Fries rearrangement of the resulting ester (**9**) with $AlCl_3$ in toluene, afforded the bis-aryl ketone **10** in 62% yield over two steps. The Fries rearrangement of ester **9** yields a mixture of 1,4- and 1,2-regioisomers in a 66:34 ratio, but the desired 1,4-product can be separated by crystallization from toluene. The unmasked hydroxy group was then alkylated with 1-bromopentane in acetone to give **13** in 59% overall yield. Although this approach is suited for provision of multikilogram quantities of **13**, a more efficient route has been identified (Scheme 2). This latter approach is based on a regioselective Friedel−Crafts reaction and omits a chemical step by reversing the order in which the substituents are introduced. The overall yield of **13** from this route is increased to 76%. Compound **13** was purified by crystallization from propan-2-ol, and single-crystal X-ray analysis shows a pronounced nonplanar conformation and a more or less fully extended side chain (see Supporting Information).

Results and Discussion

The compounds reported in this paper were evaluated in vitro for their ability to displace [^{3}H]-**2** from cloned human CB_1 and CB_2 receptors stably expressed in human embryonic kidney (HEK293) and Chinese hamster ovary (CHO-K1) cell lines, respectively (Table 1). The functional activities of selected compounds were assessed by measuring their maximal effects in reversing the forskolin-evoked accumulation of cAMP in HEK293 and CHO cells expressing human CB_1 and CB_2 receptors, respectively. Agonist efficacies (E_{max}) were expressed relative to that of **2**, taken as 100%. Selection of compounds for the cAMP functional assay (only compound **13** is illustrated) was based on a preliminary evaluation in agonist-stimulated [^{35}S]-GTP-γ-S binding assays, in which most of the compounds described herein exhibited full agonism (data not shown).

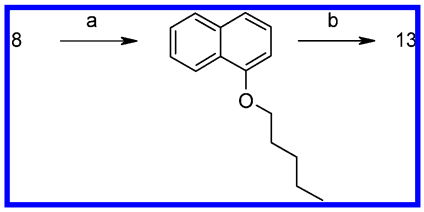
There was a marked preference for lipophilic side chains with the current compound series since the butoxy analogue (**12**) was 23-fold more potent at CB_1 than the initial lead (**7**). Shortening the alkoxy side chain of **12** caused a 6-fold drop in affinity (**11**), while extending it by one carbon resulted in a 3-fold increase in binding (**13**). The CB_2 affinities of compounds **11**−**13** remain constant at ca. 100 nM, so that CB_1 selectivity increases with increasing alkoxy chain length. Further lengthening of the chain (**14**) or introduction of a terminal phenyl group (**15**) caused a drop in affinity at both receptor subtypes, reflecting the size constraints of the hydrophobic pocket in which the side chain presumably resides. Incorporation of heteroatoms elsewhere in the chain was equally detrimental.[29] The ether oxygen atom of compound **13** could be replaced by NH (**16**) or NMe (data not shown) without affecting either CB_1 or CB_2 binding affinities,[30] and is therefore not thought to be involved in hydrogen bonding. Extensive studies with a variety of nonclassical carbonyl bioisosteres and other spacer groups confirmed that a carbonyl moiety separating the two naphthalene rings is essential for high potency,[29] suggesting that this group is interacting as a very specific hydrogen-bond acceptor. Finally,

Scheme 1. Synthesis of Naphthalen-1-yl-(4-pentyloxynaphthalen-1-yl)methanone[a]



[a] Reagents and conditions: (a) 1-Naphthoyl chloride, Et_3N, cyclohexane/CH_2Cl_2, rt, 1.5 h (99%). (b) (i) $AlCl_3$, toluene, 25 °C, 16 h; (ii) butan-2-one, 2 M HCl, H_2O; (iii) toluene (crystallization) (63%). (c) (i) 1-Bromopentane, K_2CO_3, acetone, 60 °C, 16 h; (ii) propan-2-ol, H_2O (crystallization) (95%).

Scheme 2. Regioselective Synthesis of Naphthalen-1-yl-(4-pentyloxynaphthalen-1-yl)methanone[a]



[a] Reagents and conditions: (a) 1-Bromopentane, K_2CO_3, butan-2-one, 80 °C (94%). (b) (i) $AlCl_3$, toluene, 1-naphthoyl chloride, 20 °C; (ii) 2 M HCl, H_2O; (iii) propan-2-ol, H_2O (crystallization) (81%).

use of monocyclic aroyl substituents, or a benzene core instead of a naphthalene one, dramatically reduced potency.[29] From this group, compound **13** was selected for in vivo evaluation in rat (rCB_1 $IC_{50} = 22 \pm 5.1$ nM). The in vitro selectivity of **13** was also investigated in 60 receptor and ion channel assays, and no significant binding was observed up to a concentration of 10 μM.

In vivo, the antihyperalgesic activity of **13** was compared with its ability to elicit behavioral effects characteristic of CNS penetration by cannabimimetic agents (catalepsy, motor dysfunction, antinociception in acute models, and hypothermia). In a model of neuropathic mechanical hyperalgesia,[12] oral administration of **13** (3 mg/kg; 8.1 μmol/kg) produced up to 90% reversal of hyperalgesia, with an effect that was rapid in onset (1 h) and of long duration (Figure 3A). In separate experiments, the antihyperalgesic effect of **13** was inhibited by the CB_1-selective antagonist/inverse agonist **4** (0.3 mg/kg sc) but not by a CB_2-selective antagonist SR 144528 (10 mg/kg sc, structure not shown[31]) when the latter were administered 30 min prior to the oral dose of **13**. This finding demonstrates that CB_1 receptors are implicated in neuropathic pain but casts doubt on the involvement of CB_2 receptors in this particular assay.[32]

The D_{50} calculated 3 h after administration was 0.17 mg/kg (0.46 μmol/kg) and compares well with those of the reference compounds **2** (0.08 mg/kg sc) and **3** (0.52 mg/kg sc), which are also efficacious in the same model. However, unlike compounds **2** and **3**, which are highly active in the CNS tests,[12] compound **13** showed little activity in these tests, producing effects only at doses ca. 170-fold greater than that required to produce reversal of hyperalgesia (Figure 3B: catalepsy is used as the representative CNS test). Although there was a small effect at 10 mg/kg po (27 μmol/kg po) in the catalepsy assay, these data indicate that the antihyperalgesic activity of **13** results from a peripheral mechanism of action. The peak effect in the CNS tests occurred 6−9 h after administration, whereas pronounced antihyperalgesic activity was evident at 1 h, indicating a poor and slow penetration into the CNS. Furthermore, CNS-mediated side effects were not observed at 0.2 mg/kg po (the analgesic dose) and 2 mg/kg po when **13** was administered twice daily over the course of 5 days, indicating the lack of accumulation in the CNS.[32]

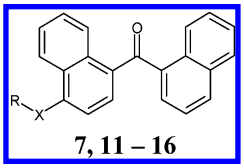
The pharmacokinetic profile of **13** after oral and intravenous administration to Wistar rats is shown in Table 2. Absolute bioavailability was good (43%), indicating that presystemic first-pass metabolism is limited. The large steady-state volume of distribution (9.6 L/kg) and long terminal half-life (>60 h) after iv administration were likely due to the moderate total clearance (8 mL min^{-1} kg^{-1}) coupled with the high tissue affinity expected for a neutral, lipophilic compound (log $P = 6.85$). Compound **13** also exhibits a high affinity for plasma protein (>99%), which restricts movement out of the blood compartment and may account for the limited activity in the CNS tetrad tests. Following oral administration of 3 mg/kg, a C_{max} of 1.13 μM was observed at 1 h postdose, whereas a maximal brain concentration of 0.24 μmol/kg was reached only at 4 h postdose. The pharmacokinetic studies were therefore in agreement with the behavioral pharmacology observations in demonstrating a slow and time-dependent penetration of **13** into the CNS.

The metabolic stability of **13** in rat and human liver microsomes was high: the low intrinsic metabolic clearance values [<5 μL min^{-1} (mg of microsomal protein)$^{-1}$] are consistent with our expectation of an acceptable bioavailability in man. The cytochrome P_{450} inhibitory potential of **13** was determined in human liver microsomes by use of the major isoforms CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4, in order to assess the potential likelihood of drug interactions. Compound **13** exhibited only low inhibition against CYP2C9 ($IC_{50} = 80.8 \pm 13.1$ μM) and was inactive (>200 μM) against the other isoforms. Interaction with coadministered drugs eliminated by these routes was therefore deemed unlikely.

Compound **13** does not possess genotoxic potential, as evidenced by the negative results obtained in the in vitro chromosome aberration test (V79 Chinese hamster cells) and the reverse mutation assay (Ames test).

In conclusion, we investigated the bioisosteric replacement of the indole core in potent AAI CB agonists with the naphthalene moiety and evaluated this novel series for affinity to hCB_1 and hCB_2. In vitro, compound **13** was a potent and full CB_1/CB_2 mixed agonist. In vivo, it exhibited good oral bioavailability, produced an excellent antihyperalgesic effect in a rat model of neuropathic pain, and displayed no CNS effects at the maximally effective analgesic dose of 3 mg/kg po.[32] These findings demonstrate the potential utility of selectively targeting peripheral CB receptors as a means of harnessing the known

Table 1. hCB_1 and hCB_2 Receptor Binding Affinities (IC_{50}) of Compounds **7** and **11**−**16** and Functional Activities (EC_{50}) of Compound **13**



			IC_{50}[a] (nM)		EC_{50}[b] (nM), cAMP [E_{max} (%)]	
compd[c]	R	X	hCB_1, HEK cells	hCB_2, CHO cells	hCB_1, HEK cells	hCB_2, CHO cells
7	morph$(CH_2)_2$[d]	O	1100 ± 360	11000 ± 5700	ND[e]	ND
11	$CH_3(CH_2)_2$	O	300 ± 96	90 ± 20	ND	ND
12	$CH_3(CH_2)_3$	O	48 ± 14	85 ± 20	ND	ND
13	$CH_3(CH_2)_4$	O	15 ± 5	98 ± 7.6	6.1 ± 1.1 [104.7 ± 7]	27.9 ± 14.8 [88.4 ± 6.8]
14	$CH_3(CH_2)_5$	O	160 ± 5.5	660 ± 85	ND	ND
15	$Ph(CH_2)_2$	O	930 ± 130	2000 ± 670	ND	ND
16	$CH_3(CH_2)_4$	NH	25 ± 5	120 ± 22	ND	ND
2			0.77 ± 0.12	1.3 ± 0.27	0.28 ± 0.04 [100]	0.35 ± 0.12 [100]
3			140 ± 6.4	8.9 ± 0.76	12.3 ± 7.8 [98.3 ± 3.2]	0.47 ± 0.15 [96.9 ± 2.4]

[a] Receptor binding affinities: concentration required to inhibit specific binding of [^{3}H]-**2** to hCB_1 and hCB_2 receptors by 50% in HEK293 and CHO-K1 cell membranes, respectively. The results are expressed as the mean of at least three determinations ± SEM and were calculated in ORIGIN by use of a logistic fit. [b] Agonist potencies are expressed as the means ± SEM for $n = 3-13$ independent measurements. E_{max} in brackets is the maximal effect of the test compound in reversing the forskolin-evoked accumulation of cyclic AMP in HEK293 or CHO cells expressing either hCB1 or hCB2, respectively, and is expressed as a percentage of that value obtained with **2**. [c] All of the compounds gave satisfactory ^{1}H NMR, HRMS, and HPLC analyses (see Supporting Information). [d] Abbreviation: morph = 4-morpholinyl. [e] ND, not determined.

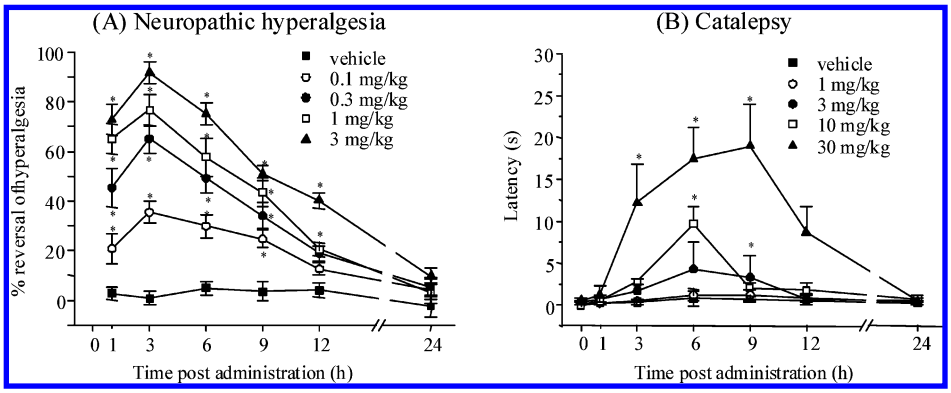


Figure 3. (A) Reversal of neuropathic mechanical hyperalgesia in the rat following oral administration of compound **13** in 20% cremophor/water. Each point represents mean ± SEM paw withdrawal threshold from the ipsilateral paw from 12 animals/treatment group. *$P < 0.05$ compared to vehicle by ANOVA followed by Tukey's HSD test. See ref 12 for experimental procedure. (B) Activity of compound **13** in the catalepsy test. Animals were tested prior to (0 h) and up to 24 h after oral administration of **13** in 20% cremophor/water. Each point represents mean ± SEM from six animals per treatment group. *$P < 0.05$ compared to vehicle by ANOVA plus Tukey's HSD test. See ref 12 for experimental procedure.

Table 2. Pharmacokinetic Parameters of **13** in Wistar Rats[a]

13 Administered iv (1 mg/kg)	
$t_{1/2}$[b]	64.6 h[c]
Vd_{ss}	9.6 L kg^{-1}
CL_{tot}	8.0 mL min^{-1} kg^{-1}
$AUC_{0-\infty}$	5718 nM h
13 Administered po (3.4 mg/kg)	
T_{max}	1 h
C_{max}	1.6 μM
$AUC_{0-\infty}$	8392 nM h
F (%)	43%

[a] Values represent the means only for $n = 4$. [b] Terminal half-life. [c] This value represents only ca. 30% of the AUC.

analgesic properties of cannabinoids but reducing the inherent risk of CNS side effects.

Experimental Section

1-Pentyloxynaphthalene. A stirred suspension of potassium carbonate (4.98 g, 36.03 mmol) and 1-naphthol (4.33 g, 30.03 mmol) in 2-butanone (120 mL) was heated to 80 °C and stirred under reflux for a further 30 min. 1-Bromopentane (6.79 g, 5.6 mL, 44.97 mmol) was then added over a 30 min period and the mixture was heated at reflux for 24 h. Potassium carbonate (2.08 g, 15.05 mmol) and 1-bromopentane (2.3 g, 1.9 mL, 15.25 mmol) were added, and the mixture was stirred for an additional 22 h. The mixture was allowed to cool to 20 °C and stirred for 30 min. The potassium salts were removed by filtration and washed with 2-butanone (20 mL). The combined filtrate was concentrated at 50−60 °C and degassed at <10 mbar for 30 min to afford 1-pentyloxynaphthalene (6.42 g, 29.96 mmol, 99.8%) which was 93.8% pure by HPLC analysis and used in the next step without characterization [**CAUTION:** the product is sensitive to light].

Naphthalen-1-yl-(4-pentyloxynaphthalen-1-yl)methanone (13). Aluminum chloride (0.733 g, 5.5 mmol) was added portionwise to a stirred mixture of 1-pentyloxynaphthalene (1.18 g, 5.5 mmol) in toluene (12 mL) at 18−22 °C. The resulting black solution was treated with 1-naphthoyl chloride (1.05 g, 0.83 mL, 5.5 mmol) over a 30 min period. After the brown reaction mixture was stirred for an additional 30 min, 2 M HCl solution (24 mL) was added over a 30 min period [**CAUTION:** initially strongly exothermic]. After a further 15 min of stirring, the solution was allowed to stand in

order to facilitate a separation of the layers. The lower, turbid aqueous layer was separated and extracted with toluene (5 mL). The combined organic phase was washed with water (5 mL), dried (Na_2SO_4), concentrated at 90 °C, and degassed at ca. 20 mbar for 20 min to afford crude **13** (2.18 g) as a brown oil. The crude product was dissolved in propan-2-ol (10 mL) at 70 °C and allowed to cool to 20 °C, whereupon a sandy suspension was obtained (may need seeding with sample obtained chromatographically). The precipitated solid was filtered, washed successively with propan-2-ol/water (6 mL, 9:1) and water (8 mL), and dried at 60 °C/4−10 mbar to constant weight to afford **13** as a beige powder (1.65 g, 4.48 mmol, 81%). Mp 71.7−72.6 °C (propan-2-ol). IR (KBr) ν_{max} 3100−3000 (aromatic CH), 2931, 2872, 2857 (aliphatic CH), 1633 (C═O), 1617, 1575, 1511, 1430, 1269, 1242, 1091, 998, 830, 794, 781, 768 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 9.02 (1H, d, J = 8.4 Hz), 8.43 (1H, br d, J = 7.7 Hz), 8.25 (1H, d, J = 8.4 Hz), 7.99 (1H, d, J = 8.2 Hz), 7.93 (1H, br d, J = 7.9 Hz), 7.69 (1H, dt, J = 5.4, 1.5 Hz), 7.61−7.58 (3H, m), 7.54 (1H, tm), 7.50 (1H, tm), 7.48 (1H, dd, J = 8.2, 7.0 Hz), 6.64 (1H, d, J = 8.2 Hz), 4.16 (2H, t, J = 6.4 Hz), 1.95 (2H, m), 1.56 (2H, m), 1.45 (2H, sext), 0.98 (3H, t, J = 7.2 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.0, 159.1, 138.9, 135.3, 133.9, 133.0, 131.4, 131.2, 128.9, 128.5, 128.4, 128.3, 127.3, 126.5, 126.2, 126.1, 126.0, 124.6, 122.5, 102.9, 68.7, 28.9, 28.5, 22.6, 14.2. Calcd for $C_{26}H_{24}O_2 \cdot 0.25H_2O$: C 83.73, H 6.62. Found: C 83.91,, H 6.89. MS (ESI+) m/z 369 ($M + H^+$; 100%). HRMS (ESI+) calcd for $C_{26}H_{25}O_2$ ($M + H^+$), 369.1855; found, 369.1857.

An alternative synthesis of **13** via naphthalene-1-carboxylic acid naphthalen-1-yl ester (**9**) and (4-hydroxynaphthalen-1-yl)-naphthalen-1-ylmethanone (**10**) is described in ref 28.

[4-(2-Morpholin-4-ylethoxy)naphthalen-1-yl]naphthalene-1-ylmethanone (7). To a solution of 4-(2-hydroxyethyl)morpholine (0.66 g, 5.03 mmol) and triphenylphosphine (1.32 g, 5.03 mmol) in dry THF (30 mL) at room temperature was added a solution of **10** (1.5 g, 5.03 mmol) and diisopropylazodicarboxylate (1.09 mL, 5.03 mmol) in dry THF (30 mL) dropwise over 15 min. When the addition was complete, the mixture was stirred at room temperature for 18 h. The mixture was diluted with water (200 mL) and extracted with ethyl acetate (3 × 100 mL). The ethyl acetate extracts were combined, washed with saturated brine, dried ($MgSO_4$), filtered, and absorbed directly onto silica gel. Chromatography on silica gel with ethyl acetate as the eluant gave the title compound, 0.69 g, 33%. Mp 159−161 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 8.88 (1H, d, J = 8.4 Hz), 8.33 (1H, d, J = 8.4 Hz), 8.17 (1H, m), 8.08 (1H, d, J = 8.4 Hz), 8.04 (1H, d, J = 8.4 Hz), 7.74 (1H, t, J = 8.1 Hz), 7.7−7.5 (6H, m), 6.99 (1H, d, J = 8.4 Hz), 4.35 (2H, t, J = 7.2 Hz), 3.63−3.54 (4H, m), 2.89 (2H, t, J = 7.2 Hz), 2.6−2.5 (4H, m). IR (KBr) ν_{max} 3050−2800, 1639 (C═O), 1573, 1511, 1428, 1328, 1272, 1264, 1251, 1217, 1116, 1085, 1005, 793, 782, 771 cm^{-1}. MS (ESI+) m/z 412 ($M + H^+$; 100%). HRMS (ESI+) calcd for $C_{27}H_{26}NO_3$ ($M + H^+$), 412.1913; found, 412.1912.

Naphthalen-1-yl-(4-propoxynaphthalen-1-yl)methanone (11). Prepared as described for compound **7** with 1-propanol (0.031 g, 0.52 mmol) to give the title compound, 0.078 g, 45% yield, following chromatography on silica gel with 2% diethyl ether/cyclohexane as eluant. ^1H NMR (200 MHz, $CDCl_3$) δ 9.01 (1H, d, J = 8.9 Hz), 8.43 (1H, d, J = 8.4 Hz), 8.25 (1H, d, J = 8.3 Hz), 8.06−7.88 (2H, m), 7.78−7.41 (7H, m), 6.67 (1H, d, J = 8.3 Hz), 4.13 (2H, t, J = 6.7 Hz), 2.09−1.88 (2H, sext, J = 7.3 Hz), 1.14 (3H, t, J = 7.8 Hz). MS (ESI+) m/z 341 ($M + H^+$; 100%). HRMS (ESI+) calcd for $C_{24}H_{21}O_2$ ($M + H^+$), 341.1542; found, 341.1541.

Naphthalen-1-yl-(4-butoxynaphthalen-1-yl)methanone (12). Prepared as described for compound **7** with 1-butanol (0.46 g, 6.22 mmol) to give the title compound, 1.84 g, 84% yield, following chromatography on silica gel with 10% ethyl acetate in cyclohexane as eluant. ^1H NMR (400 MHz, DMSO-d_6) δ 8.89 (1H, d, J = 8.5 Hz), 8.34 (1H, d, J = 8.5 Hz), 8.16 (1H, m), 8.08 (1H, d, J = 8.5 Hz), 8.04 (1H, d, J = 8.5 Hz), 7.74 (1H, t, J = 7.8 Hz), 7.7−7.5 (6H, m), 6.97 (1H, d, J = 8.5 Hz), 4.24 (2H, t, J = 6.9 Hz), 1.93−1.81 (2H, quint, J = 7 Hz), 1.62−1.5 (2H, sext, J = 7 Hz), 1.0 (3H, t, J = 7.2 Hz). IR (film) ν_{max} 3050, 2958, 2932, 1647 (C═O), 1576, 1511, 1460, 1428, 1327, 1271, 1243, 1215, 1158, 1088, 792, 780 cm^{-1}. MS (ESI+) m/z 355 ($M + H^+$; 100%). HRMS (ESI+) calcd for $C_{25}H_{23}O_2$ ($M + H^+$), 355.1698; found, 355.1697.

(4-Hexyloxynaphthalen-1-yl)naphthalen-1-ylmethanone (14). Prepared as described for compound **7** with 1-hexanol (0.046 mL, 0.37 mmol) to give the title compound, 0.1 g, 77% yield, following chromatography on silica gel with 5% diethyl ether in cyclohexane as eluant. ^1H NMR (400 MHz, $CDCl_3$) δ 8.99 (1H, d, J = 8.5 Hz), 8.40 (1H, d, J = 8.4 Hz), 8.22 (1H, d, J = 8.5 Hz), 7.99 (1H, d, J = 8.2 Hz), 7.93 (1H, d, J = 8.5 Hz), 7.67 (1H, m), 7.6−7.47 (6H, m), 6.66 (1H, d, J = 8.2 Hz), 4.17 (2H, t, J = 6.4 Hz), 1.96−1.92 (2H, m), 1.6−1.3 (6H, m), 0.92 (3H, t, J = 6.2 Hz). MS (ESI+) m/z 383 ($M + H^+$; 100%). HRMS (ESI+) calcd for $C_{27}H_{27}O_2$ ($M + H^+$), 383.2011; found, 383.2013.

Naphthalen-1-yl-(4-phenethyloxynaphthalen-1-yl)methanone (15). Prepared as described for compound **7** with 2-phenylethanol (0.047 mL, 0.38 mmol) to give the title compound, 0.141 g, 90% yield, following chromatography on silica gel with 5% diethyl ether in cyclohexane as eluant. ^1H NMR (200 MHz, $CDCl_3$) δ 8.96 (1H, d, J = 8.4 Hz), 8.37 (1H, d, J = 8.4 Hz), 8.22 (1H, d, J = 8.4 Hz), 8.02−7.83 (2H, m), 7.75−7.18 (12H, m), 6.61 (1H, d, J = 8.4 Hz), 4.35 (2H, t, J = 7.9 Hz), 3.23 (2H, t, J = 7.4 Hz). MS (ESI+) m/z 403 ($M + H^+$; 100%). HRMS (ESI+) calcd for $C_{29}H_{23}O_2$ ($M + H^+$), 403.1698; found, 403.1699.

Naphthalen-1-yl-(4-pentylaminonaphthalen-1-yl)methanone (16). To a solution of **10** (5 g, 16.78 mmol) in dry pyridine (15 mL) at 0 °C was added, dropwise, trifluoromethanesulfonic anhydride (3.11 mL, 18.66 mmol). The mixture was stirred at room temperature for 30 min and then allowed to warm to room temperature over 18 h. Volatiles were removed under reduced pressure and the crude product was dissolved in ethyl acetate (100 mL) and washed successively with water and saturated brine, dried ($MgSO_4$), filtered, and evaporated to give trifluoromethanesulfonic acid 4-(naphthalene-1-carbonyl)naphthalen-1-yl ester as a yellow oil that was used directly in the next step. A solution of the crude triflate so prepared (0.34 g, 0.792 mmol) and 1-aminopentane (0.11 mL, 0.95 mmol) in dry toluene (4 mL) was added to a flame-dried flask containing sodium *t*-butoxide (0.106 g, 1.11 mmol), palladium-(II) acetate (0.01 g, 0.045 mmol), and *rac*-BINAP (0.011 g, 0.038 mmol) under argon atmosphere. The mixture was heated at 80 °C with stirring for 4 h and then cooled to room temperature. The crude mixture was taken up in EtOAc (25 mL) and washed successively with water and saturated brine, dried ($MgSO_4$), filtered, and evaporated to give a brown oil. This was purified by chromatography on silica gel with 5% diethyl ether in cyclohexane as eluant to give the title compound, 89 mg, 31% (uncorrected for unreacted triflate). ^1H NMR (400 MHz, $CDCl_3$) δ 9.32 (1H, d, J = 8.6 Hz), 8.04 (1H, d, J = 8.4 Hz), 7.87 (1H, d, J = 8.1 Hz), 7.83 (1H, d, J = 8.1 Hz), 7.75 (1H, d, J = 8.2 Hz), 7.62 (1H, m), 7.5−7.3 (6H, m), 6.28 (1H, d, J = 8.4 Hz), 4.99 (1H, br s), 3.22 (2H, br s), 1.74−1.64 (2H, m), 1.4−1.2 (4H, m), 0.86 (3H, t, J = 7 Hz). MS (ESI+) m/z 368 ($M + H^+$; 100%). HRMS (ESI+) calcd for $C_{26}H_{26}NO$ ($M + H^+$), 368.2014; found, 368.2017.

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Supporting Information Available: General experimental details and further characterization data (HPLC) for all novel compounds, details of in vivo and in vitro pharmacological assays, and crystallographic data for compound **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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