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Diaryldiamines with Dual Inhibition of the Histamine H_3 Receptor and the Norepinephrine Transporter and the Efficacy of 4-(3-(Methylamino)-1-phenylpropyl)-6-(2-(pyrrolidin-1-yl)ethoxy)naphthalen-1-ol in Pain

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A series of compounds was designed as dual inhibitors of the H_3 receptor and the norepinephrine transporter. Compound **5** (rNET K_i = 14 nM; rH_3R K_i = 37 nM) was found to be efficacious in a rat model of osteoarthritic pain.

Introduction

The histamine 3 receptor (H_3R[a]) is primarily located in the central nervous system and is one of four histamine receptors known.[1] Histamine H_3 receptors are localized on presynaptic terminals, and H_3 antagonists have been widely reported to increase the levels of several neurotransmitters, including histamine, acetylcholine, norepinephrine (NE), and others.[2,3] H_3R antagonists are currently being evaluated clinically for the treatment of conditions such as attention deficit hyperactivity disorder, Alzheimer's disease, narcolepsy, and pain.[4]

H_3 antagonists such as thioperamide have been reported to be active in models of pain.[5] More recently, the H_3R antagonist GSK-189254 (**1**) was reported to be efficacious in preclinical models of neuropathic pain and was examined in a phase I electrical hyperalgesia model.[6,7] The efficacy of histamine H_3 antagonists can be rationalized as likely due to increases in levels of monoamines that are recognized to modulate pain sensation, such as NE. Norepinephrine is thought to be involved in the descending inhibitory pain pathways and to act through sites in the dorsal horn of the spinal cord via presynaptic α_2 (particularly α_{2A}) adrenoceptors in primary nociceptive terminals.[8] Agents that activate α_2 adrenergic receptors, such as clonidine,[9] are effective in pain.

The norepinephrine transporter (NET) is located presynaptically on noradrenergic neurons and, in addition to enzymatic degradation and diffusion, is a primary mechanism for terminating the actions of NE by removing NE from the nerve synapse.[10] Blockade of NET results in an increase in the levels of NE, as has been shown by microdialysis studies.[11] The nonselective serotonin–norepinephrine reuptake inhibitor (SNRI) duloxetine (**2**) is used clinically for the treatment of neuropathic pain.[12] Inhibition of NE uptake is requisite for the pain efficacy of **2**, since NET selective inhibitors such as reboxetine have been shown to be effective in pain models,[13] whereas, serotonin-selective reuptake inhibitors (SSRIs) have been shown clinically to have only limited analgesic effects.[14]

We hypothesized that since H_3 and NET blockers have pain efficacy and can increase NE levels, an agent combining both activities would be highly effective. We therefore targeted compounds with dual activity of H_3R antagonism and NET inhibition. One of our strategies to design such molecules was to combine pharmacophores of NET inhibition and H_3 antagonism into one molecule. This approach has been used by others to provide H_3 antagonists with dual pharmacology.[15]

Compound **3**,[16] a synthetically more accessible phenyl analogue of **2** with similar affinity for NET, was selected as the NET pharmacophore (see Figure 1). Our initial target, **4**, was chosen with the anticipation that appending an H_3R pharmacophore on the naphthalene ring of **3** would maintain the NET activity. Our results are discussed herein.

Chemistry

The synthesis of **4** is shown in Scheme 1. Alkylation of **11**[17] with *N*-(2-chloroethyl)pyrrolidine followed by debenzylation provided naphthol **12**. Under Mitsunobu conditions, reaction between **12** and Boc-protected amino alcohol **13**,[18] followed by deprotection with TFA, provided the desired product **4** and an unexpected product, **5**. An improved yield of **5** was obtained by the reaction of **12** with 3-(methylamino)-1-phenylpropan-1-ol (**20**) in TFA (see Supporting Information).

Diphenylamine **15** was alkylated with the 2-carbon or the 3-carbon-linked chloroalkylamines (**16**[19] or **17**[20]) to provide intermediates **18** and **19**, respectively (see Scheme 2). These intermediates were deprotected catalytically to provide **6** and **7**.

As shown in Scheme 3, phenol was reacted with amino alcohol **20** or **21** in the presence of acid (TFA) to provide, after Boc protection, **22** and **23**, respectively. The initial reaction

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[a] Abbreviations: H_3R, histamine 3 receptor; PK, pharmacokinetic; NE, norepinephrine; NET, norepinephrine transporter; NRI, norepinephrine reuptake inhibitor; OA, osteoarthritis; SERT, serotonin transporter; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

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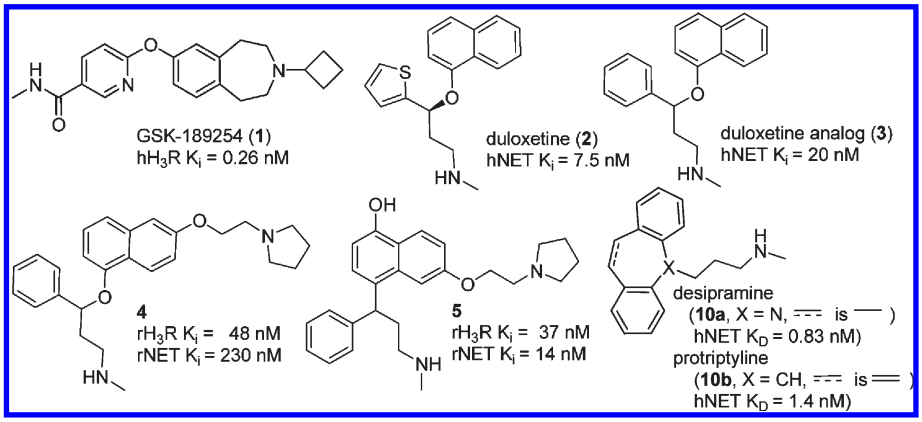
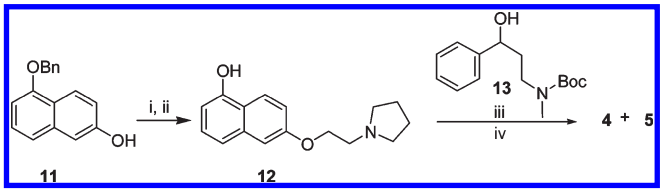


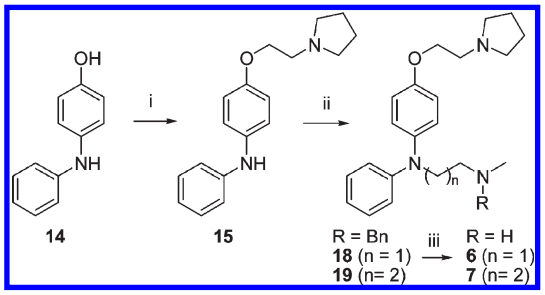
Figure 1. H_3R antagonist **1**, SNRIs **2** and **3**, dual H_3R-antagonists-NET inhibitors **4** and **5**, and NET inhibitors **10a** and **10b**.

Scheme 1[a]



[a] (i) *N*-(2-chloroethyl)pyrrolidine·HCl, NaH, DMF, 70 °C; (ii) H_2, 10% Pd/C, MeOH; (iii) **13**, DEAD, Ph_3P, THF; (iv) TFA.

Scheme 2[a]



[a] (i) *N*-(2-Chloroethyl)pyrrolidine·HCl, NaH, DMF, 70 °C. (ii) **18**: $Cl(CH_2)_2NMeBn$·HCl (**16**), NaH, DMF, 70 °C. **19**: $Cl(CH_2)_3NMeBn$·HCl (**17**), NaH, DMF, 70 °C. (iii) H_2, 20% $Pd(OH)_2$/C, IPA, 80 °C.

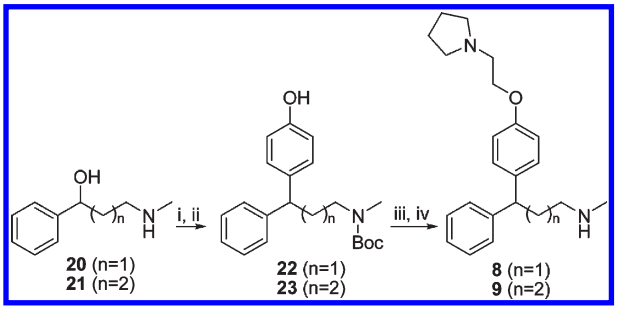
proceeded in low yield due to the major product being alkylation of phenol ortho to the hydroxy group. Intermediates **22** and **23** were converted to **8** and **9** via O-alkylation and Boc deprotection.

Results

Our first target was **4**, wherein an ethoxypyrrolidine H_3R moiety was appended to the naphthyl group of **3**. Structure **3** was selected as supportive of facile SAR studies, as **3** is synthetically more accessible than **2**, yet retains similar affinity for the human NET.[16] The design hypothesis was supported in that the targeted structure (**4**) was active at H_3 and NET (Table 1). Though ~10-fold less potent than **3** at the rat NET (K_i = 230 nM), **4** had a binding affinity of 48 nM for the rat H_3R. Surprisingly, **5**, which was formed as an unexpected synthetic byproduct in the synthesis of **4**, was very potent at NET (K_i = 14 nM) and H_3R (rat K_i = 37 nM, human K_i = 7.4 nM). Compounds **4** and **5** were shown to be antagonists of the H_3R in GTPγS binding studies.[21] Thus, the accidental byproduct **5** was found to be > 10-fold more potent than **4** in its affinity for NET. A limited number of other derivatives structurally similar to **4** and **5** were synthesized, but a superior naphthyl containing analogue was not found.[22]

The structure of **5**,[24] in which a diarylmethane is linked to a methylamino group through a two-carbon chain, was noted to have similarity to the structures of known potent NET inhibitors desipramine (**10a**) and protriptyline (**10b**) (wherein a diphenylamino or diphenylmethyl core is linked to a methylamino group though a three-carbon chain; see Figure 1). We further investigated the potential of the diarylmethane moiety in **5** to induce dual potency at NET and H_3R in additional analogues. To explore the importance of carbon versus nitrogen at the diphenyl junction and a two-carbon versus three-carbon linker, **6**−**9** were synthesized.

Scheme 3[a]



[a] (i) Phenol, TFA; (ii) Boc_2O, CH_3CN, Δ; (iii) *N*-(2-chloroethyl)pyrrolidine·HCl, NaH, DMF, 70 °C; (iv) TFA.

Table 1. Binding Affinity for the Rat NET, Rat H_3R, and Human H_3R[a]

	rat NET[b] K_i (nM)		rat H_3R[c] K_i (nM)		human H_3R[c] K_i (nM)	
compd						
2	3.0	(2.3, 3.8)[d]	> 5000		> 5000	
4	230	(200, 260)[d]	48	(47, 48)[d]	ND[e]	
5	14	(11, 19)	37	(32, 43)	7.4	(6.2, 8.9)
6	89	(50, 150)[d]	5.4	(4.8, 6.0)[d]	1.6	(1.6, 1.6)[d]
7	110	(85, 150)[d]	0.72	(0.58, 0.91)[d]	0.28	(0.26, 0.30)[d]
8	4.3	(3.3, 5.5)	5.2	(4.4, 6.0)	1.4	(0.9, 2.0)
9	14	(12, 17)	2.9	(2.2, 3.7)	0.89	(0.73, 1.08)
10a	0.78	(0.43, 1.41)	> 5000		> 5000	

[a] $n \geq 3$. Values in parentheses are the upper and lower limits derived as a result of the standard deviation. [b] Assessed by displacement of [^{3}H]nisoxetine from cell membranes isolated from rat cerebral cortex.[31] [c] Assessed by displacement of [^{3}H]*N*-*R*-methyl histamine from cell membranes isolated from C6 cells expressing cloned rat or human H_3R.[23] [d] n = 2 [e] ND = not determined.

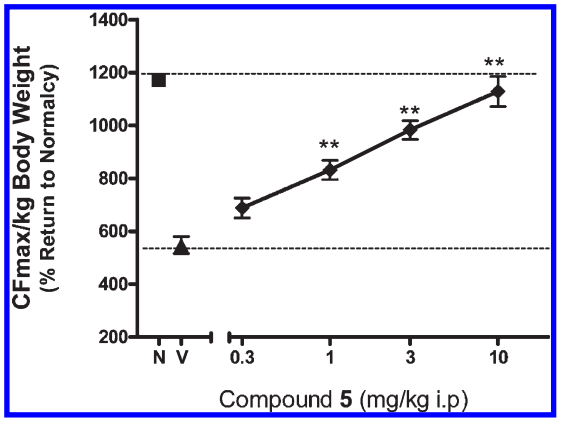


Figure 2. Efficacy of **5** in OA model of inflammatory pain ($n = 12$) in rats (Sprague−Dawley). Rats were administered **5** at 0.3, 1, and 3 mg/kg ip, 2 mL/kg 30 min before testing. Data are expressed as maximum hindlimb compressive force (CF_{max}) (gram force) per kg body weight for each dose group: (**) $p < 0.05$ vs vehicle (One-way analysis of variance (ANOVA), followed by Bonferroni's post-hoc analysis). Positive control is diclofenac 30 mg/kg in water (ip) 30 min before testing. N is naive rat. V is vehicle treated rat.

As can be seen from Table 1, the H_3R potency of **6**−**9** increased 7- to 50-fold relative to **5**, with **7** being the most potent of these analogs at rat H_3R. Compound **7**, the analogue most structurally similar to **10a**, was the least potent for the NET site. The fused dihydrodibenzo[*b*,*f*]azepine of **10a** apparently is critical for potent NET activity. Compound **8** was potent at NET ($K_i = 4$ nM) and had similar high affinity for rat H_3R ($K_i = 5$ nM). The 3-fold higher potency of **8** over **9** at the NET may indicate a slight preference for a two-carbon versus three-carbon linker in the presence of a diphenylmethane moiety. In a limited exploration of the SAR surrounding **8**, the phenyl group not containing the H_3R moiety was replaced with more polar heteroaromatic derivatives, all of which resulted in a reduction in NET activity.[22]

Compound **5** was evaluated in detail in vitro and found to also possess significant affinity for the serotonin transporter, with a potency of 7.6 nM. Examination of the profile of **5** in an in vitro microsomal turnover assay revealed that 56% of the compound remained after 0.5 h exposure, indicating that **5** is sufficiently stable to justify a PK study in rodent. The animal pain models were targeted for ip dosing of compounds, so the PK was examined by this route. A dose of 1 mg/kg (ip) achieved a peak concentration (C_{max}) of 0.21 μg/mL, reached at 0.25 h (T_{max}), with good bioavailability ($F_{ip/iv} = 43\%$) and $t_{1/2}$ of 12 h. Dosed iv (1 mg/kg), the compound demonstrated a very high volume of distribution ($V_\beta = 8.2$ L/kg), with low clearance (Cl = 0.46 (L/h)/kg), inducing a very long half-life ($t_{1/2} = 12$ h). The rat plasma protein binding of **5** was found to be 67%, indicating that a significant fraction (33%) of the compound in circulation would be free unbound drug. Overall, **5** was thus found to have a very good PK profile to enable testing in rodent pain models.

We have previously reported that the H_3R antagonist **1** is effective in an osteoarthritis (OA) pain model in rats.[25] Compound **2** was also found efficacious in the same rat model,[26] a result that is consistent with its reported clinical efficacy[27] in OA in the clinic. The dual potency inhibitor **5** was also tested in this rat OA model.[26a] Compound **5** was dosed ip 20 days after injection of monoiodoacetate into the knee joint and was found to be potent and effective, with 70% efficacy at a dose 3 mg/kg and 93% efficacy at a dose of 10 mg/kg (Figure 2). From this, an ED_{50} level was calculated to be 1.2 mg/kg. Plasma samples were taken immediately after completion of the pain testing (45 min postdose) to determine drug levels, the 1 mg/kg dose giving 129 ng/mL, the 3 mg/kg dose giving 382 ng/mL, and the 10 mg/kg dose giving 1239 ng/mL, from which an ED_{50} of 150 ng/mL (370 nM) was calculated. To calculate the free drug level required for efficacy, the plasma ED_{50} was multiplied by the free unbound fraction (33%) to give 120 nM. The observed analgesic efficacy is consistent with a mechanism involving inhibition of the H_3 and NET sites, since the ED_{50} free levels were found to be greater than the in vitro potency of **5** at these sites (14 and 37 nM, respectively).

Compound **5** was brain permeable, as determined by evaluation of a 3 mg/kg dose. On the basis of the free drug principle,[28] equilibrium free drug concentrations are equal in all compartments. Thus, receptor occupancy for **5** can be calculated. At the 1, 3, and 10 mg/kg doses, the estimated receptor occupancies are 74%, 89%, and 97% for the rat H_3R and 88%, 96%, and 99% for the NET, respectivly.[29] This predicts that the compound should have substantial occupancy at the H_3 and NET sites at the pain-effective concentrations.

Although we cannot entirely rule out a role for a contribution to efficacy in the OA model from inhibition of the serotonin transporter by **5** ($K_i = 7$ nM),[13a] pure selective serotonin reuptake inhibitors have been reported to not be clinically effective in pain.[14] Compound **5** had SERT affinity comparable to that reported for **3** ($K_i = 2.4$ nM).[16] In contrast, **6**−**9** had reduced affinity for SERT (all $K_i > 70$ nM), which is more aligned with the SERT potency of diphenylamino analogue **10a** ($K_i = 20$ nM).

Compounds **8** and **9**, due to high affinity at NET and H_3R and reduced affinity at SERT, had improved in vitro selectivity (> 10-fold) for NET and H_3 over SERT. Compound **8** is a potential tool for further probing contributions of SERT to in vivo pharmacology and will be analyzed in more detail in an upcoming publication, with the aim of testing in additional pain models and understanding potential liabilities in comparison to a clinically used SNRI (i.e., **2**).

In summary, we were able to design compounds with nanomolar potency and dual affinity for the H_3R and the NET. Biphenylmethyl analogue **5** displayed a balanced affinity for H_3R and NET, combined with excellent PK properties. This compound was found to be potent and effective in an osteoarthritis pain model in rat.

Experimental Section

General. Proton NMR spectra were obtained on a Varian Mercury plus 300 or Varian UNITY plus 300 MHz instrument with chemical shifts (δ) reported relative to tetramethylsilane as an internal standard. Target compounds possess a purity of at least 95% based on combustion analysis (< ±0.4), performed by QTI (Quantitative Technologies, Inc.). Column chromatography was carried out with an Analogix IntelliFlash 280 chromatography apparatus using SuperFlash compound purification columns or on silica gel 60 (230−400 mesh). Thin-layer chromatography was performed using 250 mm silica gel 60 glass-backed plates with F254 as indicator.

***N*-Methyl-3-phenyl-3-(6-(2-(pyrrolidin-1-yl)ethoxy)naphthalen-1-yloxy)propan-1-amine (4) and 4-(3-(Methylamino)-1-phenylpropyl)-6-(2-(pyrrolidin-1-yl)ethoxy)naphthalen-1-ol (5). Step 1.** A solution of **12** (127 mg, 0.49 mmol), *tert*-butyl 3-hydroxy-3-phenylpropyl(methyl)carbamate (**13**)[18] (170 mg, 0.64 mmol), and Ph_3P (170 mg, 0.64 mmol) in THF (2 mL) under N_2 at 0 °C was treated in portions over 45 min with DEAD (100 μL, 0.64 mmol) in THF (2 mL).

The mixture was stirred at room temperature overnight, concentrated, and chromatographed, eluting with 2−10% (9:1 MeOH/NH_4OH) in CH_2Cl_2 to provide the desired Boc-protected intermediates.

Step 2. This residue was treated with TFA (2 mL), heated to 60 °C for 2 min, concentrated, and directly chromatographed, eluting with 2−10% (9:1 MeOH.NH_4OH) in CH_2Cl_2 to provide **5** (5 mg, 12%) as the less polar isomer (^{1}H NMR ($CDCl_3$) δ 1.85 (m, 5H), 2.13−2.28 (m, 1H), 2.37−2.48 (m, 2H), 2.49 (s, 3H), 2.69−2.83 (m, 5H), 3.01 (t, J = 5.9 Hz, 2H), 4.24 (t, J = 5.9 Hz, 2H), 4.79 (dd, J = 13.1, 2.9 Hz, 1H), 6.74 (d, J = 8.5 Hz, 1H), 7.01 (d, J = 2.4 Hz, 1H), 7.07 (d, J = 8.5 Hz, 1H), 7.13 (dd, J = 9.2, 2.7 Hz, 1H), 7.18−7.25 (m, 1H), 7.28−7.33 (m, 4H), 8.30 (d, J = 9.2 Hz, 1H); MS (DCI/NH_3) m/z 405 (M + H)$^+$) and **4** as the more polar isomer (20 mg, 48%) (^{1}H NMR ($CDCl_3$) δ 1.83 (m, 4H), 2.04−2.20 (m, 1H), 2.25−2.39 (m, 1H), 2.43 (s, 3H), 2.66 (m, 4H), 2.78−2.89 (m, 2H), 2.97 (t, J = 5.9 Hz, 2H), 4.23 (t, J = 6.1 Hz, 2H), 5.44 (dd, J = 8.3, 4.8 Hz, 1H), 6.48 (d, J = 7.5 Hz, 1H), 7.07−7.43 (m, 9H), 8.32 (d, J = 9.5 Hz, 1H); MS (DCI/NH_3) m/z 405 (M + H)$^+$. Anal. ($C_{26}H_{32}N_2O_2 \cdot 0.1H_2O$) C, H, N).

***N*^{1}-Methyl-*N*^{2}-phenyl-*N*^{2}-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)-ethane-1,2-diamine (6).** A solution of **18** (245 mg, 0.570 mmol) and Pearlman's catalyst (145 mg) in IPA (3 mL) under H_2 was heated to 80 °C for 4 h, stirred at room temperature overnight, diluted with CH_2Cl_2 (50 mL), stirred for 5 min under N_2, and filtered. The filtrate was concentrated and chromatographed, eluting with 4−20% (9:1 MeOH/NH_4OH) in CH_2Cl_2 to provide **6** (111 mg, 57%). ^{1}H NMR ($CDCl_3$) δ 1.81 (m, 4H), 2.43 (s, 3H), 2.63 (m, 4H), 2.82 (t, J = 6.6 Hz, 2H), 2.90 (t, J = 5.9 Hz, 2H), 3.78 (t, J = 6.6 Hz, 2H), 4.10 (t, J = 5.9 Hz, 2H), 6.72−6.81 (m, 3H), 6.87−6.94 (m, 2H), 7.04−7.10 (m, 2H), 7.13−7.20 (m, 2H); MS (DCI/NH_3) m/z 340 (M + H)$^+$. Anal. ($C_{21}H_{29}N_3O \cdot 0.3H_2O$) C, H, N.

***N*^{1}-Methyl-*N*^{3}-phenyl-*N*3-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)-propane-1,3-diamine (7).** Compound **19** (100 mg, 0.225 mmol) via the procedure for **6** provided **7** (49 mg, 61%). ^{1}H NMR ($CDCl_3$) δ 1.75−1.87 (m, 6H), 2.41 (s, 3H), 2.63 (m, 6H), 2.90 (t, J = 6.1 Hz, 2H), 3.69 (t, J = 7.5 Hz, 2H), 4.10 (t, J = 5.9 Hz, 2H), 6.70−6.77 (m, 3H), 6.86−6.94 (m, 2H), 7.02−7.09 (m, 2H), 7.12−7.20 (m, 2H); MS (DCI/NH_3) m/z 354 (M + H)$^+$. Anal. ($C_{22}H_{31}N_3O \cdot 0.3H_2O$) C, H, N.

***N*-Methyl-3-phenyl-3-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)-propan-1-amine (8).**[32] Compound **22** (455 mg, 1.33 mmol) via the procedures for **12**, step 1, and **4** and **5**, step 2, provided **8** (300 mg, 96%). ^{1}H NMR ($CDCl_3$) δ 1.79 (m, 4H), 2.19 (q, J = 7.5 Hz, 2H), 2.37 (s, 3H), 2.52 (t, J = 7.1 Hz, 2H), 2.60 (m, 4H), 2.86 (t, J = 6.1 Hz, 2H), 3.94 (t, J=7.7 Hz, 1H), 4.06 (t, J = 5.9 Hz, 2H), 6.83 (d, J = 8.7 Hz, 2H), 7.14 (d, J = 8.3 Hz, 2H), 7.16−7.31 (m, 5H); MS (DCI/NH_3) m/z 339 (M + H)$^+$.

***N*-Methyl-4-phenyl-4-(4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)-butan-1-amine (9).**[32] Compound **23** via the procedures for **12**, step 1, and **4** and **5**, step 2, provided **9**. ^{1}H NMR ($CDCl_3$) δ 1.26−1.51 (m, 2H), 1.79 (m, 4H), 2.04 (q, J = 7.8 Hz, 2H), 2.39 (s, 3H), 2.61 (m, 6H), 2.87 (t, J = 5.9 Hz, 2H), 3.83 (t, J = 7.8 Hz, 1H), 4.06 (t, J = 6.1 Hz, 2H), 6.82 (d, J = 8.8 Hz, 2H), 7.13 (d, J = 8.8 Hz, 2H), 7.15−7.30 (m, 5H); MS (DCI/NH_3) m/z 353 (M + H)$^+$. For salt formation, a solution of **9** (1.71 g, 4.85 mmol) was dissolved in EtOH (10 mL), treated with maleic acid (1.18 g, 10.2 mmol), heated until the solution became homogeneous, filtered, concentrated to ~10 mL total volume, treated with EtOAc (100 mL), and set aside overnight. The solution was decanted off, and the oil was treated with EtOAc. This process was repeated until crystallization occurred. The crystals were collected by filtration, washed with EtOAc, and dried to provide 1.80 g (63%) **9** as the dimaleic acid salt. ^{1}H NMR (DMSO-d_6) δ 1.38−1.52 (m, 2H), 1.82−2.11 (m, 6H), 2.90 (t, J=7.6 Hz, 2H), 2.98−3.46 (m, 7H), 3.52 (bs, 2H), 3.90 (t, J=7.8 Hz, 1H), 4.22 (t, J = 4.7 Hz, 2H), 6.02 (s, 3.1H), 6.92 (d, J=8.8 Hz, 2H), 7.13−7.21 (m, 1H), 7.21−7.32 (m, 4H), 7.25 (d, J=8.8 Hz, 2H), 8.19 (s, 1.5H), 9.59 (s, 0.5H); MS (ESI+) m/z 353 (M + H)$^+$. Anal. ($C_{23}H_{32}N_2O \cdot 2C_4H_4O_4$) C, H, N.

6-(2-(Pyrrolidin-1-yl)ethoxy)naphthalen-1-ol (12). Step 1. A solution of **11**[17] (1.1 g, 4.5 mmol) in DMF (20 mL) under N_2 was treated with NaH (60% dispersion, 1.1 g, 27 mmol), stirred for 15 min, treated with *N*-(2-chloroethyl)pyrrolidine·HCl (1.5 g, 9.0 mmol), stirred for 15 min, heated to 70 °C for 1 h, cooled, treated with water (50 mL), and extracted with Et_2O (3 times). The combined Et_2O layers were washed with brine, dried ($MgSO_4$), filtered, concentrated, and chromatographed, eluting with 2−10% (9:1 MeOH/NH_4OH) in CH_2Cl_2 to provide the intermediate product 1-(2-(5-(benzyloxy)naphthalen-2-yloxy)-ethyl)pyrrolidine (1.27 g, 81%).

Step 2. The intermediate from step 1 (1.26 g, 3.63 mmol) and 10% Pd/C (250 mg) in MeOH (5 mL) was stirred under H_2 (1 atm) for 2 h, diluted to ~100 mL with CH_2Cl_2, stirred under N_2 for 15 min, and filtered to remove the solids. The filtrate was concentrated and chromatographed, eluting with 2−10% (9:1 MeOH/NH_4OH) in CH_2Cl_2 to provide **12** (0.92 g, 98%), which solidified on standing. ^{1}H NMR ($CDCl_3$) δ 1.85 (m, 4H), 2.72 (m, 4H), 2.99 (t, J = 5.8 Hz, 2H), 4.21 (t, J = 5.9 Hz, 2H), 6.64 (dd, J = 6.3, 2.0 Hz, 1H), 7.02−7.07 (m, 2H), 7.18−7.24 (m, 2H), 8.00−8.06 (m, 1H); MS (DCI/NH_3) m/z 258 (M + H)$^+$.

***N*-Phenyl-4-(2-(pyrrolidin-1-yl)ethoxy)aniline (15).** Compound **14** (3.3 g, 18 mmol), NaH (60% dispersion, 0.71 g, 18 mmol), and *N*-(2-chloroethyl)pyrrolidine·HCl (1 g, 5.9 mmol) were processed using the procedures for **12**, step 1. Chromatography, eluting with 3:1 to 0:1 EtOAc/[4:1:1 EtOAc/HCO_2H/H_2O] on silica gel, gave **15** (1.66 g, 100%). ^{1}H NMR ($CDCl_3$) δ 1.81 (m, 4H), 2.63 (m, 4H), 2.89 (t, J = 5.9 Hz, 2H), 4.09 (t, J = 6.1 Hz, 2H), 5.48 (bs, 1H), 6.79−6.93 (m, 5H), 7.02−7.09 (m, 2H), 7.17−7.24 (m, 2H); MS (DCI/NH_3) m/z 283 (M + H)$^+$.

***N*^{1}-Benzyl-*N*^{1}-methyl-*N*^{2}-phenyl-*N*^{2}-(4-(2-(pyrrolidin-1-yl)-ethoxy)phenyl)ethane-1,2-diamine (18).** Compound **15** (170 mg, 0.60 mmol) and NaH (60% dispersion, 240 mg, 6.0 mmol) under N_2 in DMF (3 mL) was stirred for 5 min, treated with **16**[19] (200 mg, 0.90 mmol), stirred for 10 min, heated to 70 °C for 1 h, cooled, and partitioned between Et_2O (75 mL) and 0.1 M NaOH (25 mL). The Et_2O layer was washed with brine, dried ($MgSO_4$), filtered, concentrated, and chromatographed, eluting with 2−10% (9:1 MeOH/NH_4OH) in CH_2Cl_2 to provide **18** (250 mg, 98%). ^{1}H NMR ($CDCl_3$) δ 1.82 (m, 4H), 2.24 (s, 3H), 2.58−2.70 (m, 6H), 2.91 (t, J = 5.9 Hz, 2H), 3.52 (s, 2H), 3.74−3.83 (m, 2H), 4.10 (t, J = 6.1 Hz, 2H), 6.65−6.75 (m, 3H), 6.85−6.93 (m, 2H), 7.00−7.07 (m, 2H), 7.09−7.16 (m, 2H), 7.21−7.33 (m, 5H); MS (DCI/NH_3) m/z 430 (M + H)$^+$.

***N*^{1}-Benzyl-*N*^{1}-methyl-*N*^{3}-phenyl-*N*^{3}-(4-(2-(pyrrolidin-1-yl)-ethoxy)phenyl)propane-1,3-diamine (19).** Compounds **15** (65 mg, 0.23 mmol) and **17**[20] (110 mg, 0.46 mmol) were processed via the procedure for **18** to provide **19** (107 mg, 105%). ^{1}H NMR ($CDCl_3$) δ 1.73−1.89 (m, 6H), 2.16 (s, 3H), 2.42 (t, J = 6.9 Hz, 2H), 2.64 (m, 4H), 2.91 (t, J = 6.1 Hz, 2H), 3.45 (s, 2H), 3.69 (t, J = 7.1 Hz, 2H), 4.10 (t, J = 5.9 Hz, 2H), 6.69−6.79 (m, 3H), 6.85−6.93 (m, 2H), 7.01−7.08 (m, 2H), 7.11−7.19 (m, 2H), 7.20−7.35 (m, 5H); MS (DCI/NH_3) m/z 444 (M + H)$^+$.

***tert*-Butyl 3-(4-Hydroxyphenyl)-3-phenylpropyl(methyl)carbamate (22). Step 1.** Compound **20** (1.76 g, 10.6 mmol) in TFA (5 mL) was treated with phenol (1 g, 10.63 mmol), stirred at room temperature for 3 days, concentrated, treated with 1 M NaOH and extracted with CH_2Cl_2 (3 times). The combined CH_2Cl_2 layers were dried ($MgSO_4$), filtered, concentrated, and chromatographed, eluting with 2%−10% (9:1 MeOH/NH_4OH) in CH_2Cl_2 to provide 4-(3-(methylamino)-1-phenylpropyl)phenol as the more polar isomer (351 mg, 13.7%).

Step 2. This intermediate (343 mg, 1.42 mmol) was treated with Boc_2O (0.37 g, 1.7 mmol) in CH_3CN (5 mL), swirled until homogeneous, heated to near reflux for 1 min, cooled, concentrated, and directly chromatographed, eluting with 5:1 to 1:1 hexane/EtOAc to provide the title compd (462 mg, 95%). ^{1}H NMR ($CDCl_3$) δ 1.41 (s, 9H), 2.22 (q, J = 7.8 Hz, 2H), 2.80 (s, 3H), 3.06−3.22 (m, 2H), 3.81 (t, J = 7.8 Hz, 1H), 6.74

(d, J = 7.8 Hz, 2H), 7.08 (d, J = 8.5 Hz, 2H), 7.21 (d, 5H); MS (DCI/NH_3) m/z 342 $(M + H)^+$.

***tert*-Butyl 4-(4-Hydroxyphenyl)-4-phenylbutyl(methyl)carbamate (23).** Compound **21**[30] (65 mg, 0.36 mmol) and phenol (102 mg, 1.09 mmol) via the procedure for **22**, Step 1, provided a mixture of 4-(4-(methylamino)-1-phenylbutyl)phenol and 2-(4-(methylamino)-1-phenylbutyl)phenol. This mixture of was treated with Boc_2O (38 mg, 0.17 mmol) in CH_3CN (2 mL), heated for 2 min at reflux, cooled, concentrated, and directly chromatographed, eluting with a gradient of 1:1 to 0:1 hexane/[9:1 CH_2Cl_2/EtOAc] to provide **23** as the more polar isomer. ^1H NMR ($CDCl_3$) δ 1.34−1.53 (m, 11H), 1.96 (q, J = 7.5 Hz, 2H), 2.76 (s, 3H), 3.21 (bs, 2H), 3.84 (t, J = 7.7 Hz, 1H), 4.94 (bs, 0.4H), 5.06 (bs, 0.5H), 6.74 (d, J = 8.3 Hz, 2H), 7.08 (d, J = 8.7 Hz, 2H), 7.12−7.30 (m, 5H); MS (DCI/NH_3) m/z 356 $(M + H)^+$.

Supporting Information Available: Analogues of **4**, **5**, and **8**; functional antagonism of **4**−**7**, **9**; estimated receptor occupancy of **5**; full experimental details; alternative syntheses of **5**, **8** and **9**; rat NET binding protocol. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Parsons, M. E.; Ganellin, C. R. Histamine and its receptors. *Br. J. Pharmacol.* **2006**, *147* (S1), S127–S135. (b) Leurs, R.; Bakker, R. A.; Timmerman, H.; de Esch, I. J. P. The histamine H3 receptor: from gene cloning to H3 receptor drugs. *Nat. Rev. Drug Discovery* **2005**, *4*, 107–120.

(2) Arrang, J. M.; Garbarg, M.; Schwartz, J. C. Auto-inhibition of brain histamine release mediated by a novel class (H3) of histamine receptor. *Nature* **1983**, *302*, 832–837.

(3) (a) Barbier, A. J.; Bradbury, M. J. Histaminergic control of sleep−wake cycles: recent therapeutic advances for sleep and wake disorders. *CNS Neurol. Disord.: Drug Targets* **2007**, *6*, 31–43. (b) Gemkow, M. J.; Davenport, A. J.; Harich, S.; Ellenbroek, B. A.; Cesura, A.; Hallett, D. The histamine H3 receptor as a therapeutic drug target for CNS disorders. *Drug Discovery Today* **2009**, *14*, 509–515. (c) Schlicker, E.; Malinowska, B.; Kathmann, M.; Gothert, M. Modulation of neurotransmitter release via histamine H3 heteroreceptors. *Fundam. Clin. Pharmacol.* **1994**, *8*, 128–137.

(4) Sander, K.; Kottke, T.; Stark, H. Histamine H3 receptor antagonists go to clinics. *Biol. Pharm. Bull.* **2008**, *31*, 2163–2181.

(5) (a) Farzin, D.; Asghari, L.; Nowrouzi, M. Rodent antinociception following acute treatment with different histamine receptor agonists and antagonists. *Pharmacol., Biochem. Behav.* **2002**, *72*, 751–760. (b) Malmberg-Aiello, P.; Lamberti, C.; Ghelardini, C.; Giotti, A.; Bartolini, A. Role of histamine in rodent antinociception. *Br. J. Pharmacol.* **1994**, *111*, 1269–1279.

(6) Medhurst, S. J.; Collins, S. D.; Billinton, A.; Bingham, S.; Dalziel, R. G.; Brass, A.; Roberts, J. C.; Medhurst, A. D.; Chessell, I. P. Novel histamine H3 receptor antagonists GSK189254 and GSK334429 are efficacious in surgically-induced and virally-induced rat models of neuropathic pain. *Pain* **2008**, *138*, 61–69.

(7) http://www.clinicaltrials.gov.

(8) Benarroch, E. E. Descending monoaminergic pain modulation: bidirectional control and clinical relevance. *Neurology* **2008**, *71*, 217–221.

(9) Giovannoni, M. P.; Ghelardini, C.; Vergelli, C.; Dal Piaz, V. α2-Agonists as analgesic agents. *Med. Res. Rev.* **2009**, *29*, 339–368.

(10) Zhou, Jia. Norepinephrine transporter inhibitors and their therapeutic potential. *Drugs Future* **2004**, *29*, 1235–1244.

(11) Koch, S.; Hemrick-Luecke, S. K.; Thompson, L. K.; Evans, D. C.; Threlkeld, P. G.; Nelson, D. L.; Perry, K. W.; Bymaster, F. P. Comparison of effects of dual transporter inhibitors on monoamine transporters and extracellular levels in rats. *Neuropharmacology* **2003**, *45*, 935–944.

(12) Fishbain, D.; Berman, K.; Kajdasz, D. K. Duloxetine for neuropathic pain based on recent clinical trials. *Curr. Pain Headache Rep.* **2006**, *10*, 199–204.

(13) (a) Leventhal, L.; Smith, V; Hornby, G.; Andree, T. H.; Brandt, M. R.; Rogers, K. E. Differential and synergistic effects of selective norepinephrine and serotonin reuptake inhibitors in rodent models of pain. *J. Pharmacol. Exp. Ther.* **2007**, *320*, 1178–1185. (b) Krell, H. V.; Leuchter, A. F.; Cook, I. A.; Abrams, M. Evaluation of reboxetine, a noradrenergic antidepressant, for the treatment of fibromyalgia and chronic low back pain. *Psychosomatics* **2005**, *46*, 379–384.

(14) McCleane, G. Antidepressants as analgesics. *CNS Drugs* **2008**, *22*, 139–156.

(15) (a) Keith, J. M.; Gomez, L. A.; Letavic, M. A.; Ly, K. S.; Jablonowski, J. A.; Seierstad, M.; Barbier, A. J.; Wilson, S. J.; Boggs, J. D.; Fraser, I. C.; Mazur, C.; Lovenberg, T. W.; Carruthers, N. I. Dual serotonin transporter/histamine H3 ligands: optimization of the H3 pharmacophore. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 702–706. (b) Apelt, J.; Ligneau, X.; Pertz, H. H.; Arrang, J.-M.; Ganellin, C. R.; Schwartz, J.-C.; Schunack, W.; Stark, H. Development of a new class of nonimidazole histamine H3 receptor ligands with combined inhibitory histamine N-methyltransferase activity. *J. Med. Chem.* **2002**, *45*, 1128–1141.

(16) Bymaster, F. P.; Beedle, E. E.; Findlay, J.; Gallagher, P. T.; Krushinski, J. H.; Mitchell, S.; Robertson, D. W.; Thompson, D. C.; Wallace, L.; Wong, D. T. Duloxetine (Cymbalta), a dual inhibitor of serotonin and norepinephrine reuptake. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4477–4480.

(17) Asakawa, M.; Ashton, P. R.; Boyd, S. E.; Brown, C. L.; Gillard, R. E.; Kocian, O.; Raymo, F. M.; Stoddart, J. F.; Tolley, M. S.; White, A. J. P.; Williams, D. J. Recognition of bipyridinium-based derivatives by hydroquinone- and/or dioxynaphthalene-based macrocyclic polyethers: from inclusion complexes to the self-assembly of [2]catenanes. *J. Org. Chem.* **1997**, *62*, 26–37.

(18) Miyata, S.; Kumamoto, T.; Ishikawa, T. Practical enzymatic desymmetrization of 2-(ethoxycarbonyl)propane-1,3-diyl dihexanoate and model cyclization for the A−D ring system of lysergic acid. *Helv. Chim. Acta* **2007**, *90*, 1420–1438.

(19) Le Bihan, G.; Rondu, F.; Pele-Tounian, A.; Wang, X.; Lidy, S.; Touboul, E.; Lamouri, A.; Dive, G.; Huet, J.; Pfeiffer, B.; Renard, P.; Guardiola-Lemaitre, B.; Manechez, D.; Penicaud, L.; Ktorza, A.; Godfroid, J.-J. Design and Synthesis of imidazoline derivatives active on glucose homeostasis in a rat model of type II diabetes. 2. Syntheses and biological activities of 1,4-dialkyl-, 1,4-dibenzyl, and 1-benzyl-4-alkyl-2-(4′,5′-dihydro-1′*H*-imidazol-2′-yl)piperazines and isosteric analogs of imidazoline. *J. Med. Chem.* **1999**, *42*, 1587–1603.

(20) Bergel, F.; Haworth, J. W.; Morrison, A. L.; Rinderknecht, H. Synthetic analgesics. I. Synthesis of basic benzofuran derivatives and certain 4-phenylpiperidine compounds. *J. Chem. Soc.* **1944**, 261–265.

(21) See Supporting Information for GTPγS data on **4**−**7** and **9**.

(22) See Supporting Information for analogues of **4**, **5**, and **8**.

(23) Esbenshade, T. A.; Krueger, K. M.; Miller, T. R.; Kang, C. H.; Denny, L. I.; Witte, D. G.; Yao, B. B.; Fox, G. B.; Faghih, R.; Bennani, Y. L.; Williams, M.; Hancock, A. A. Two novel and selective nonimidazole histamine H3 receptor antagonists A-304121 and A-317920: I. In vitro pharmacological effects. *J. Pharmacol. Exp. Ther.* **2003**, *305*, 887–896.

(24) Diarylmethane compounds had been previously known as monoamine inhibitors: (a) Manning, J. R.; Sexton, T.; Childers, S. R.; Davies, H. M. L. 1-Naphthyl and 4-indolyl arylalkylamines as selective monoamine reuptake inhibitors. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 58–61. (b) Lucas, M. C.; Carter, D. S.; Cai, H.-Y.; Lee, E. K.; Schoenfeld, R. C.; Steiner, S.; Villa, M.; Weikert, R. J.; Iyer, P. S. Novel, achiral aminoheterocycles as selective monoamine reuptake inhibitors. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4630–4633.

(25) Hsieh, G. C.; Honore, P.; Pai, M.; Wensink, E. J.; Chandran, P.; Salyers, A. K.; Wetter, J. M.; Zhao, C.; Liu, H.; Decker, M. W.; Esbenshade, T. A.; Cowart, M. D.; Brioni, J. D. Antinociceptive effects of histamine H3 receptor antagonist in the preclinical models of pain in rats and the involvement of central noradrenergic systems. *Brain Res.* **2010**, *1354*, 74–84.

(26) (a) Chandran, P.; Pai, M.; Blomme, E. A.; Hsieh, G. C.; Decker, M. W.; Honore, P. Pharmacological modulation of movement-evoked pain in a rat model of osteoarthritis. *Eur. J. Pharmacol.* **2009**, *613*, 39–45. (b) Wensink, E. J.; Salyers, A. K.; Pai, M.; Lewis, L.; Decker, M. W.; Jacobson, P. B.; Hsieh, G. C.; Brioni, J. D. Duloxetine Relieves Osteoarthritic Pain in a Preclinical Rat Model. Presented at Neuroscience 2009, Chicago, IL, Oct 17−21, **2009**; BB11 268.5.

(27) Chappell, A. S.; Ossanna, M. J.; Liu-Seifert, H.; Iyengar, S.; Skljarevski, V.; Li, L. C.; Bennett, R. M.; Collins, H. Duloxetine, a centrally acting analgesic, in the treatment of patients with osteoarthritis knee pain: a 13-week, randomized, placebo-controlled trial. *Pain* **2009**, *146*, 253–260.

(28) Trainor, G. L. The importance of plasma protein binding in drug discovery. *Expert Opin. Drug Discovery* **2007**, *2*, 51–64.

(29) See Supporting Information for estimation of receptor occupancy of **5**.

(30) Augustine, R. L.; Pinto, F. G. Ring-opening reactions of 2-benzoylcyclopropane isocyanate. *J. Org. Chem.* **1975**, *40*, 115–117.

(31) Method for NET binding can be found in the Supporting Information.

(32) See Supporting Information section for alternate synthesis and salt formation of compounds **8** and **9**.