# 4-Alkynylphenyl Imidazolylpropyl Ethers as Selective Histamine $H_3$-Receptor Antagonists with High Oral Central Nervous System Activity

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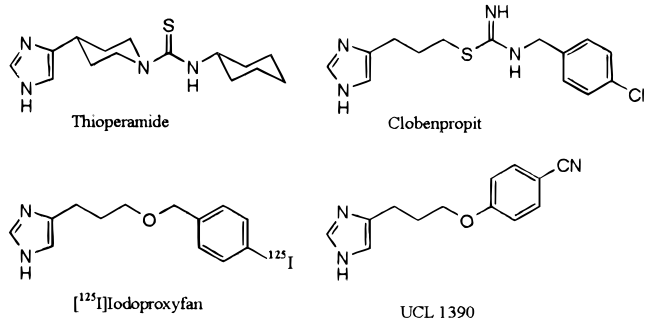
In search for potent and therapeutically useful $H_3$-receptor antagonists, we prepared novel 4-alkynylphenyl ether derivatives of 3-(1*H*-imidazol-4-yl)propanol in a convenient synthetic route. All compounds were tested for in vitro and in vivo $H_3$-receptor antagonist activity as well as for $H_3$-receptor selectivity versus $H_1$- and $H_2$-receptors. The presented 4-alkynylphenyl ethers are highly potent and selective $H_3$ antagonists showing oral activity and improved brain penetration. Particularly 4-ethynylphenyl 3-(1*H*-imidazol-4-yl)propyl ether (**14a**) displays striking in vitro and in vivo activity with a $-\log K_i$ value of 8.6 and an $ED_{50}$ value of 0.12 mg/kg. At present **14a** is the most potent $H_3$-receptor antagonist in vivo and may therefore be a potential drug for the therapy of $H_3$-receptor-dependent diseases of the central nervous system (CNS).

## Introduction

The histamine $H_3$-receptor was demonstrated to be located presynaptically on histaminergic neurons in the central nervous system (CNS) where it regulates histamine synthesis and release as an inhibitory autoreceptor.[1,2] Inhibition of this negative feedback mechanism by $H_3$-receptor antagonists thus increases concentration of the neurotransmitter histamine released.[3] Moreover, $H_3$-receptors function as heteroreceptors on nonhistaminergic neurons in the brain and the periphery inhibiting the release of neuropeptides[4] and several other neurotransmitters.[5] In radiolabeling studies the highest density of $H_3$-receptors was found in distinct areas of the CNS,[6] and it is thus suggested that the potential therapeutic role of $H_3$-receptor antagonists may be the treatment of various neurological and psychiatric diseases, e.g., epilepsy, narcolepsy, schizophrenia, or dementia.[7]

The first selective $H_3$-receptor antagonist, thioperamide,[8] which has become a useful tool for the pharmacological investigation of $H_3$-receptors, does not appear to be suitable for clinical studies because of hepatotoxicity that is probably related to its thiourea group (Chart 1). Similar drawbacks are likely to occur with the isothiourea derivative clobenpropit[9] which is more active than thioperamide in vitro but less effective in vivo presumably as a consequence of limited bioavailability (cf. Table 1). To circumvent the toxicological and bioavailability problems at $H_3$-receptors, a number of histamine $H_3$-receptor antagonists that are devoid of sulfur-containing functionalities were developed, e.g., amides, carbamates, esters, ethers, guanidines, heteroaryl compounds,[7] and less polar alkynes derived from the marine natural product verongamine.[10]

**Chart 1.** Histamine $H_3$-Receptor Antagonists




The aim of the present study was to design potent histamine $H_3$-receptor antagonists that exhibit improved oral bioavailability and brain penetration and lack potentially toxic sulfur-containing functionalities. The current research focused on imidazolylpropyl ethers because their potency was clearly pointed out in previous studies. In particular, the para-iodinated benzylic ether iodoproxyfan was selected for radiolabeling from a series of recently described aliphatic imidazolylalkyl ethers due to its in vitro potency and selectivity (Chart 1).[6,11] In an attempt to explore structure−activity relationships of $H_3$-receptor ligands, Ganellin et al. reported aromatic imidazolylalkyl ethers to be potent $H_3$-receptor antagonists that provide high in vitro activity at $H_3$-receptors.[12] Thus, para-substituted phenyl ether derivatives such as 4-cyanophenyl 3-(1*H*-imidazol-4-yl)propyl ether (UCL 1390; Chart 1) served as lead compounds in the search for novel antagonists. To obtain selective, orally active, and centrally penetrating $H_3$-receptor antagonists, we introduced alkynyl moieties in the para-position of phenyl ether derivatives of 3-(1*H*-imidazol-4-yl)propanol. The synthetical approach and pharmacological evaluation of those 4-alkynylphenyl ethers are presented, all of which were screened for their in vitro and in vivo $H_3$-receptor

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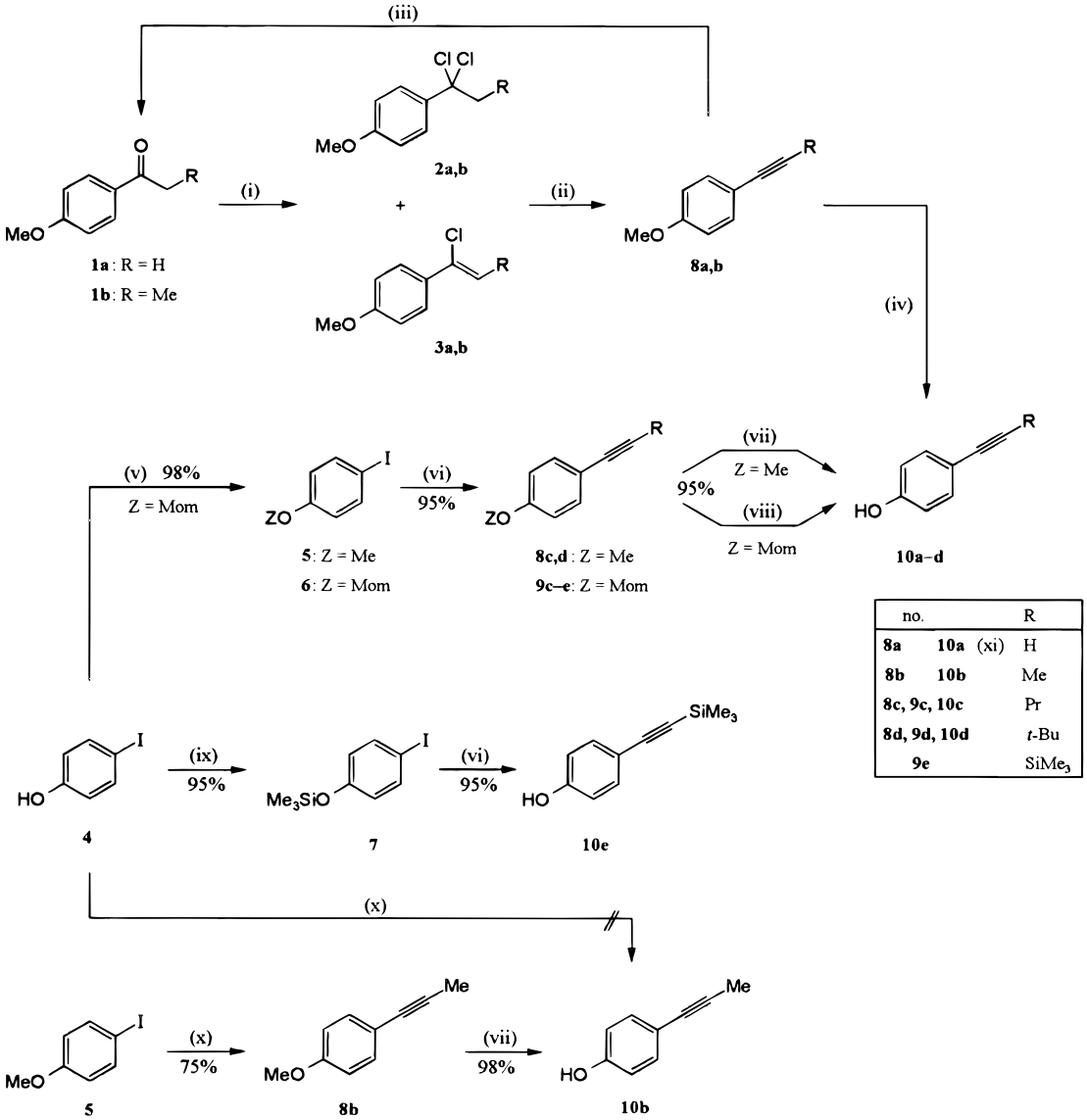
**Scheme 1.** Synthetic Pathways To Obtain 4-Alkynylphenols **10a**−**e**[a]




[a] (i) $PCl_5$, benzene, 24 h at ambient temperature; (ii) *t*-BuOK, 18-crown-6, $C_6H_{12}$, 0 °C → reflux, 3 h; (iii) $Me_3SiBr$ or $Me_3SiI$, $CH_2Cl_2$, 48 h at ambient temperature → 50 °C, 30 min, MeOH/$H_2O$; (iv) EtSNa, DMF, reflux, 1 h; (v) MomCl, $Et_3N$, $Et_2O$, 48 h at ambient temperature; (vi) HC≡CR, $Pd^{II}Cl_2(PPh_3)_2$, CuI, $Et_3N$, 1 h at ambient temperature; (vii) EtSNa, DMF, reflux, 1 h; (viii) HCl, MeOH, THF, 24 h at ambient temperature; (ix) $Me_3SiCl$, $Et_3N$, $Et_2O$, reflux, 18 h; (x) $Me_3SiC{\equiv}CMe$, ($\eta^3$-$C_3H_5Pd^{II}Cl)_2$, TBAF, THF, ambient temperature → 50 °C, 15 min; (xi) identified by TLC but not isolated due to instability.

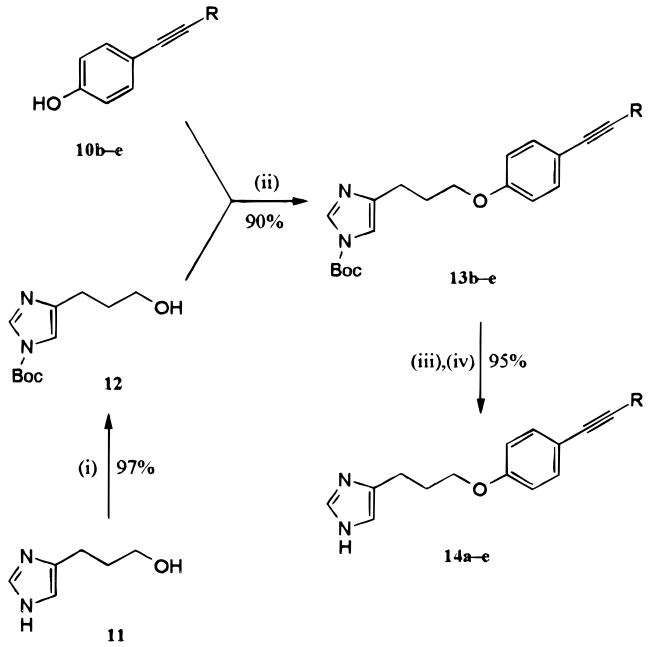
antagonist activity as well as for their $H_3$-receptor selectivity versus $H_1$- and $H_2$-receptors.

## Chemistry

The classical route to prepare aromatic alkynes **8a**,**b** proceeds from aromatic ketones **1a**,**b** which are converted to *gem*-dichlorides **2a**,**b** by treatment with $PCl_5$ (Scheme 1). $\beta$-Elimination of HCl may follow, and vinylic chlorides **3a**,**b** are frequent side products. The C≡C triple bond formation is accomplished by successive dehydrohalogenation in the presence of potassium *tert*-butanolate. Although this method was optimized by means of phase-transfer catalysis as recently reported,[13] the alkynes **8a**,**b** were obtained with overall yields of only about 20%. Cleavage of the phenol protecting methyl ether was finally achieved by treatment with sodium ethanethiolate in refluxing dimethylformamide[14] because the procedure with trimethysilyl bromide or iodide[15] led to hydration of the triple bond giving the corresponding ketones **1a**,**b**. In contrast to 4-propynylphenol (**10b**) the ethynyl analogue **10a** was found to be too labile to be isolated from solution due to polymerization, although its formation was clearly proved by means of TLC.

An efficient and mild alternative route is provided by arylation of alkynes, known as the Heck reaction,[16] which was achieved by treatment with an "arylpalladium" reagent (Scheme 1). The latter was generated in situ by treatment of an aryl iodide (**5**, **6**) with a palladium(II)−triphenylphosphine complex in the presence of triethylamine and cuprous(I) iodide as cocatalyst.[17] The reaction was facilitated by cuprous(I) iodide so that it was completed after 30 min at room temperature. Subsequent cleavage of the protecting groups, either methyl or methoxymethyl (Mom),[18] yielded the stable internal alkynes **10c**,**d**. As the trimethysilyl protecting group of **9e** was not stable under the hydrolytic conditions used,[19] the labile terminal 4-alkynylphe-

**Scheme 2.** Synthesis of 4-Alkynylphenyl Ethers **14**[a]




[a] (i) $Boc_2O$, MeCN, $Et_3N$, dioxane, $H_2O$, DMAP, 2 h at ambient temperature; (ii) $PPh_3$, DEAD, THF, 72 h at ambient temperature; (iii) $NH_3$, MeOH, 6 h at ambient temperature; (iv) $H_2NNH_2$, MeOH, 30 min at ambient temperature.

nol **10a** was formed instead of **10e** but could not be isolated as mentioned above.

Synthesis of the desired trimethylsilyl-protected alkyne **10e** was accomplished by Heck reaction using trimethylsilyl-protected 4-iodophenol (**7**) as substrate (Scheme 1). During the reaction the trimethylsilyl protecting group of the phenol was cleaved, hence giving **10e** almost quantitatively in a tandem reaction.

Although gaseous propyne could have been used effectively under these conditions, the Heck reaction did not seem to be attractive for the synthesis of **10b** due to its problematic utilization. However, the fluoride-mediated cross-coupling reaction of trimethylsilylpropyne with 4-iodoanisole yielding **8b** is an efficient alternative to dehydrohalogenation (Scheme 1).[20] Although this cross-coupling reaction was reported to be highly chemoselective in the presence of an unprotected hydroxy group, we found protection of the phenol to be essential because coupling of 4-iodophenol (**4**) failed to give **10b**. Compound **8b** was deprotected by sodium ethanethiolate in the final stage to give **10b** with an overall yield of 74%.

To obtain the desired 4-alkynylphenyl ethers **14**, the phenol precursors **10** were coupled to *tert*-butoxycarbonyl (Boc)-protected 3-(1*H*-imidazol-4-yl)propanol (**12**)[21] according to the Mitsunobu protocol (Scheme 2).[22] The Boc protection of the imidazole was readily accomplished at ambient temperature by means of di-*tert*-butyl dicarbonate in the presence of 4-(*N*,*N*-dimethylamino)pyridine. The Boc residue was primarily chosen as protecting group because the commonly used trityl group could not be cleaved without affecting the C≡C triple bond, neither hydrolytically under various acidic conditions nor hydrogenolytically in the presence of palladium on charcoal. However, cleavage of the Boc group by methanolic ammonia or hydrazine at ambient temperature proved to be ideal in this reaction sequence. Even desilylation of the alkyne **13e**, which was expected to occur quantitatively under these conditions, came about just partially so that not only the unprotected target compound 4-ethynylphenyl 3-(1*H*-imidazol-4-yl)-propyl ether (**14a**) was obtained (60% yield) but also its trimethylsilyl-protected analogue **14e** (30% yield), separation of which was performed by means of column chromatography.

## Pharmacological Results and Discussion

**In Vitro Testing.** The presented compounds were tested for their antagonist potency at $H_3$-receptors in an assay with $K^+$-evoked [$^3$H]histamine release from synaptosomes of rat cerebral cortex.[23]

The novel 4-alkynylphenyl ethers **14** show moderate to high $H_3$-receptor antagonist potency, which was found to be dependent on the residue of the aromatic alkyne (Table 1). The terminal alkyne **14a** is the most potent compound of this series, whereas substitution of the aromatic alkyne decreased antagonist activity. It is assumed that the affinity to $H_3$-receptors is reduced most likely due to steric effects as the methyl group in **14b** led only to a slight decrease in potency as compared to the bulkier propyl (**14c**), *tert*-butyl (**14d**), and trimethylsilyl (**14e**) groups, respectively. The ethynyl derivative **14a**, however, which has a $-\log K_i$ value of 8.6 appears to be even more potent than the standard $H_3$-receptor antagonist thioperamide ($-\log K_i = 8.4$).[8] The pronounced in vitro potency of **14a** was further substantiated in a functional $H_3$-receptor assay on the guinea pig ileum,[6] in which it acts as a competitive antagonist displaying a $pA_2$ value of 8.1 ± 0.15 ($\bar{x}$ ± SEM, $n = 16$).

**In Vivo Results on Mice.** The in vivo antagonist activity at $H_3$-receptors was screened in an assay measuring the effect on brain histamine turnover after oral application to mice.[23]

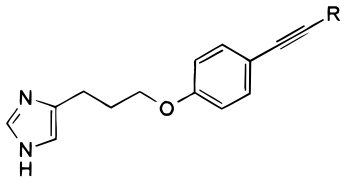
Corresponding to the effects observed in vitro, the 4-ethynylphenyl ether **14a** showed improved potency as compared to the internal alkyne derivatives **14b**−**e**, which are nevertheless highly effective $H_3$-receptor antagonists exhibiting about the same potency as thioperamide (Table 1). However, the striking CNS activity following oral administration of **14a** is clearly pointed out by these results as it is approximately 6.5 times higher on a molar basis than thioperamide. It is even more potent than any other $H_3$-receptor antagonist published so far and might thus become a potential therapeutic agent in neurology or psychiatry.

**Screening at Other Histamine Receptor Subtypes.** In addition, compounds **14a**−**e** were tested for their $H_1$-receptor activity on the guinea pig ileum as well as for their $H_2$-receptor activity on the guinea pig atrium.[24] As a result, all compounds were observed to be moderately or highly selective for the $H_3$-receptor versus $H_1$- and $H_2$-receptors, respectively (Table 1). Particularly the most potent compound (**14a**) exhibits pronounced selectivity for the $H_3$-receptor at a ratio of approximately 6000/1 vs $H_1$- and 1250/1 vs $H_2$-receptors.

## Conclusions

The presented 4-alkynylphenyl ether derivatives of 3-(1*H*-imidazol-4-yl)propanol were prepared in a mild and convenient synthetic route providing almost quan-

**Table 1.** Chemical Data and Pharmacological Results of Screening for Histamine $H_3$-Receptor Antagonist Activity and Selectivity




| | | | | | | in vivo | in vitro | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | −log *K* | | |
| compd | R | yield (%) | mp[c] (°C) | formula | $M_r$ | $ED_{50}$[a] (mg $kg^{-1}$) $\bar{x} \pm$ SEM | $K_i$[b] (nM) $\bar{x} \pm$ SEM | $H_3$[b] | $H_2$[d] | $H_1$[e] |
| **14a** | H | 60[f] | 150 | $C_{14}H_{14}N_2O \cdot C_4H_4O_4 \cdot 0.25H_2O$ | 346.9 | 0.12 ± 0.07 | 2.3 ± 0.8 | 8.6 | <4.8 | <5.5 |
| **14b** | Me | 87 | 137 | $C_{15}H_{16}N_2O \cdot C_4H_4O_4 \cdot 0.5H_2O$ | 365.4 | 1.3 ± 0.4 | 7.5 ± 1.2 | 8.1 | <4.7 | <5.0 |
| **14c** | Pr | 85 | 126 | $C_{17}H_{20}N_2O \cdot C_4H_4O_4 \cdot 0.25H_2O$ | 388.9 | 2.2 ± 0.9 | 140 ± 58 | 6.9 | <4.7 | <5.9 |
| **14d** | *t*-Bu | 95 | 132 | $C_{18}H_{22}N_2O \cdot C_4H_4O_4 \cdot 0.5H_2O$ | 407.5 | 2.2 ± 0.3 | 123 ± 17 | 6.9 | <4.6 | <5.6 |
| **14e** | $SiMe_3$ | 30[f] | 126 | $C_{17}H_{22}N_2OSi \cdot C_4H_4O_4 \cdot 0.75H_2O$ | 428.1 | 1.1 ± 0.3 | 36 ± 15 | 7.4 | <4.6 | <5.0 |
| thioperamide | | | | | | 1.0 ± 0.5[g] | 4 ± 1[h] | | | |
| clobenpropit | | | | | | 26 ± 7[i] | 0.6 ± 0.1[j] | | | |

[a] In vivo screening on central $H_3$-receptor activity after po application to mice.[23] $ED_{50}$ values expressed in mg of base $kg^{-1}$. [b] Functional $H_3$-receptor test in vitro on synaptosomes of rat cerebral cortex.[23] [c] Crystallization solvent: $Et_2O$/EtOH. [d] Functional $H_2$-receptor test on guinea pig atrium.[24] [e] Functional $H_1$-receptor test on guinea pig ileum.[24] [f] Compounds **14a**,**e** obtained from a single experiment. [g] Reference 12. [h] Reference 8. [i] Reference 11. [j] Reference 6.

titative yields in each step, except for compounds **14a**,**e** which were obtained together from a single experiment. In vitro studies proved their $H_3$-receptor antagonist potency and selectivity for $H_3$-receptors versus $H_1$- and $H_2$-receptors. Furthermore, the new compounds display high oral CNS activity with particularly the terminal alkyne being 6.5 times more active on a molar basis than thioperamide and more effective than any other $H_3$-receptor antagonist published to date. Although increasing substitution of the alkyne reduced both in vitro and in vivo activity, the internal alkynes proved to be almost equipotent with thioperamide. These data clearly indicate the efficacy of the structural modifications applied. Furthermore, the (trimethylsilyl)ethynyl derivative **14e** is, to our knowledge, the first compound containing a silyl moiety which shows $H_3$-receptor antagonist activity.

## Experimental Section

**Chemistry. General Procedures.** Melting points were determined on an Electrothermal IA 9000 digital melting point apparatus and are uncorrected. $^1$H NMR spectra were recorded on a Bruker AC 300 (300 MHz) spectrometer. Chemical shifts are expressed in ppm downfield from internal $Me_4Si$ as reference. $^1$H NMR data are reported in the order: multiplicity (br, broad; s, singlet; d, doublet; t, triplet; m, multiplet; *, exchangeable by $D_2O$), number of protons, and approximate coupling constants in hertz. A Finnigan MATCH/A (EI; 170 °C, 70 eV) or a Finnigan MAT CH5DF ($FAB^+$; Xe, $Me_2SO$/glycerol) mass spectrometer was used. IR spectra were obtained on a Perkin-Elmer spectrophotometer 297. Elemental analyses (C, H, N) were measured on a Perkin-Elmer 240 C instrument and were within ±0.4% of the theoretical values unless otherwise indicated. Analytical TLC was performed on silica gel $F_{254}$ plates (Merck). Preparative column chromatography was carried out using silica gel, 63−200 $\mu$m (Merck).

**1-Ethynyl-4-methoxybenzene (8a).**[25] A solution of 4-methoxyphenylethanone (**1a**; 50 mmol, 7.51 g) in 10 mL of benzene was added to a suspension of $PCl_5$ (50 mmol, 10.43 g) in 100 mL of benzene. The mixture was stirred for 24 h at ambient temperature, hydrolyzed on ice, and extracted with light petroleum (bp 50−70 °C). The organic layer was washed ($H_2O$, $NaHCO_3$, $H_2O$), dried ($MgSO_4$), and evaporated to dryness. The resulting oil (**2a**; 44 mmol, 9.0 g) was dissolved in 40 mL of cyclohexane and cooled in an ice bath. Then *t*-BuOK (88 mmol, 9.87 g) and 18-crown-6 (0.09 mmol, 23 mg) were added at 0−5 °C followed by an additional 3 h under reflux. After the mixture was hydrolyzed on ice, the organic layer was separated, washed ($H_2O$), dried ($MgSO_4$), and evaporated. The resulting product was subjected to column chromatography [eluent: $CH_2Cl_2$ (25%), light petroleum (75%)] to afford the title compound as an oil which was crystallized from light petroleum (yield, 1.5 g, 25%): mp 29 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.42 (d, $J$ = 8.7 Hz, 2H, Ph-2-H, Ph-6-H), 6.83 (d, $J$ = 8.7 Hz, 2H, Ph-3-H, Ph-5-H), 3.81 (s, 1H, Me), 2.99 (s, 1H, C≡CH); MS *m*/*z* 132 ($M^{\bullet+}$, 100), 117 (27), 89 (26); IR (KBr) $\tilde{\nu}$ 3287 (s, C≡C−H), 2959 (m, C−H), 2838 (m, C−H), 2105 (m, C≡C), 1605 (s, C═C), 1570 (w, C═C), 1507 (s, C═C). Anal. ($C_9H_8O \cdot 0.2H_2O$) C, H, N.

**4-Methoxy-1-propynylbenzene (8b).**[26] **Method A:** Prepared according to **8a** (yield, 20%). **Method B:** To a solution of 4-iodoanisole (**5**; 10 mmol, 2.34 g) in 40 mL of THF were subsequently added (trimethylsilyl)propyne (10 mmol, 1.18 g), TBAF (10 mmol, 2.61 g), and ($\eta^3$-$C_3H_5PdCl)_2$ (0.25 mmol, 0.09 g) followed by 15 min of stirring at 50 °C under argon atmosphere. The cooled mixture was filtered and evaporated under reduced pressure. The resulting product was purified as described for **8a** (yield, 1.1 g, 75%): mp 22 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.32 (d, $J$ = 8.8 Hz, 2H, Ph-2-H, Ph-6-H), 6.81 (d, $J$ = 8.8 Hz, 2H, Ph-3-H, Ph-5-H), 3.79 (s, 3H, O-Me), 2.03 (s, 3H, C≡C-Me); MS *m*/*z* 146 ($M^{\bullet+}$, 43), 131 (18), 111 (100), 90 (22); IR (KBr) $\tilde{\nu}$ 2955 (m, C−H), 2850 (m, C−H), 2043 (w, C≡C), 1607 (s, C═C), 1567 (m, C═C), 1510 (vs, C═C). Anal. ($C_{10}H_{10}O \cdot 0.25H_2O$) C, H, N.

**4-Methoxy-1-pentynylbenzene (8c).** To a solution of 4-iodoanisole (**5**; 20 mmol, 4.68 g) in 50 mL of $Et_3N$ were subsequently added $(PPh_3)_2PdCl_2$ (0.2 mmol, 0.14 g), CuI (0.2 mmol, 0.04 g), and pentyne (40 mmol, 2.72 g) followed by stirring for 1 h at ambient temperature under Ar atmosphere. The mixture was then filtered, concentrated under reduced pressure, and subjected to column chromatography (eluent: light petroleum). The product was obtained as a light-yellow oil (yield, 3.4 g, 98%): $^1$H NMR ($CDCl_3$) $\delta$ 7.32 (d, $J$ = 8.8 Hz, 2H, Ph-2-H, Ph-6-H), 6.81 (d, $J$ = 8.8 Hz, 2H, Ph-3-H, Ph-5-H), 3.79 (s, 3H, O-Me), 2.36 (t, $J$ = 7.0 Hz, 2H, C≡C−$CH_2$), 1.63 (m, 2H, C$H_2$-Me), 1.04 (t, $J$ = 7.4 Hz, 3H, $CH_2$-*Me*); MS *m*/*z* 174 ($M^{\bullet+}$, 85), 145 (100), 102 (13). Anal. ($C_{12}H_{14}O$) C, H, N.

**1-(3,3-Dimethylbutynyl)-4-methoxybenzene (8d):** prepared according to **8c**; crystallized from light petroleum (yield, 93%); mp 39 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.32 (d, $J$ = 8.8 Hz, 2H, Ph-2-H, Ph-6-H), 6.79 (d, $J$ = 8.8 Hz, 2H, Ph-3-H, Ph-5-H), 3.78 (s, 3H, O-Me), 1.30 (s, 9H, *t*-Bu); MS *m*/*z* 188 ($M^{\bullet+}$, 81), 175 (100), 160 (21), 133 (11), 115 (15). Anal. ($C_{13}H_{16}O$) C, H, N.

**4-(Methoxymethoxy)-1-pentynylbenzene (9c):** prepared according to **8c** (yield, 98%); oil; $^1$H NMR ($CDCl_3$) $\delta$ 7.32 (d, $J$ = 8.7 Hz, 2H, Ph-2-H, Ph-6-H), 6.94 (d, $J$ = 8.7 Hz, 2H, Ph-3-H, Ph-5-H), 5.16 (s, 2H, O-$CH_2$), 3.47 (s, 3H, O-Me), 2.36 (t, $J$ = 7.0 Hz, 2H, C≡C−$CH_2$), 1.61 (m, 2H, C$H_2$-Me), 1.04 (t, $J$ = 7.4 Hz, 3H, $CH_2$-*Me*); MS *m*/*z* 204 ($M^{\bullet+}$, 43), 145 (11), 45 (100). Anal. ($C_{13}H_{16}O_2$) C, H, N.

**1-(3,3-Dimethylbutynyl)-4-(methoxymethoxy)benzene (9d):** prepared according to **8c** (yield, 98%); oil; $^1$H NMR ($CDCl_3$) $\delta$ 7.31 (d, $J$ = 8.8 Hz, 2H, Ph-2-H, Ph-6-H), 6.93 (d, $J$ = 8.8 Hz, 2H, Ph-3-H, Ph-5-H), 5.16 (s, 2H, $CH_2$), 3.46 (s, 3H, O-Me), 1.30 (s, 9H, *t*-Bu); MS *m*/*z* 218 ($M^{\bullet+}$, 49), 203 (10), 173 (27), 45 (100). Anal. ($C_{14}H_{18}O_2 \cdot 0.2H_2O$) C, H, N.

**4-(Methoxymethoxy)-1-[(trimethylsilyl)ethynyl]benzene (9e):** prepared according to **8c** (yield, 79%); oil; $^1$H NMR ($CDCl_3$) $\delta$ 7.39 (d, $J$ = 8.6 Hz, 2H, Ph-2-H, Ph-6-H), 6.95 (d, $J$ = 8.6 Hz, 2H, Ph-3-H, Ph-5-H), 5.17 (s, 2H, $CH_2$), 3.47 (s, 3H, O-Me), 0.24 (s, 9H, Si-$Me_3$); MS *m*/*z* 234 ($M^{\bullet+}$, 41), 219 (15), 189 (17), 130 (25), 45 (100). Anal. ($C_{13}H_{18}O_2Si$) C, H, N.

**4-Propynylphenol (10b).** A solution of **8b** (20 mmol, 3.0 g) in 100 mL of DMF was heated together with EtSNa (50 mmol, 4.21 g) under reflux for 1 h. The resulting suspension was then concentrated under reduced pressure, extracted with $CH_2Cl_2$, filtered, and evaporated again. Column chromatography (eluent: $CH_2Cl_2$) afforded the title compound as a light-yellow oil (yield, 2.67 g, 98%): $^1$H NMR ($CDCl_3$) $\delta$ 7.27 (d, $J$ = 8.6 Hz, 2H, Ph-3-H, Ph-5-H), 6.81 (d, $J$ = 8.6 Hz, 2H, Ph-2-H, Ph-6-H), 5.22 (br*, 1H, OH), 2.02 (s, 3H, Me); MS *m*/*z* 132 ($M^{\bullet+}$, 100), 103 (18). Anal. ($C_9H_8O \cdot 0.8H_2O$) C, H, N.

**4-Pentynylphenol (10c). Method A:** Prepared according to **10b** (yield, 98%). **Method B:** To a solution of **9c** (10 mmol, 2.04 g) in 20 mL of THF was added 5 mL of 10% methanolic HCl followed by stirring at ambient temperature for 24 h. Removal of the solvent under reduced pressure and purification by column chromatography (eluent: $CH_2Cl_2$) afforded the product as a light-yellow oil (yield, 1.52 g, 95%): $^1$H NMR ($CDCl_3$) $\delta$ 7.27 (d, $J$ = 8.7 Hz, 2H, Ph-3-H, Ph-5-H), 6.74 (d, $J$ = 8.7 Hz, 2H, Ph-2-H, Ph-6-H), 4.99 (s*, 1H, OH), 2.36 (t, $J$ = 7.0 Hz, 2H, C≡C−$CH_2$), 1.61 (m, 2H, C$H_2$-Me), 1.04 (t, $J$ = 7.3 Hz, 3H, $CH_2$-*Me*); MS *m*/*z* 160 ($M^{\bullet+}$, 79), 131 (100). Anal. ($C_{11}H_{12}O \cdot 0.25H_2O$) C, H, N.

**4-(3,3-Dimethylbutynyl)phenol (10d). Method A:** Prepared according to **10b** (yield, 95%). **Method B:** Prepared according to **10c** (yield, 90%); crystallized from light petroleum; mp 90 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.26 (d, $J$ = 8.6 Hz, 2H, Ph-3-H, Ph-5-H), 6.73 (d, $J$ = 8.6 Hz, 2H, Ph-2-H, Ph-6-H), 4.86 (br*, 1H, OH), 1.30 (s, 9H, *t*-Bu); MS *m*/*z* 174 ($M^{\bullet+}$, 57), 159 (100), 144 (13). Anal. ($C_{12}H_{14}O$) C, H, N.

**4-[(Trimethylsilyl)ethynyl]phenol (10e):** prepared from (4-iodophenoxy)trimethylsilane (**7**) according to **8c**; crystallized from light petroleum (yield, 85%); mp 68 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.33 (d, $J$ = 8.6 Hz, 2H, Ph-3-H, Ph-5-H), 6.72 (d, $J$ = 8.6 Hz, 2H, Ph-2-H, Ph-6-H), 5.43 (br*, 1H, OH), 0.23 (s, 9H, Si-$Me_3$); MS *m*/*z* 190 ($M^{\bullet+}$, 31), 175 (100), 116 (13). Anal. ($C_{11}H_{14}$-OSi) C, H, N.

**4-(3-Hydroxypropyl)-1*H*-imidazole-1-carboxylic Acid 1,1-Dimethylethyl Ester (12).**[27] 3-(1*H*-Imidazol-4-yl)propanol (**11**; 10 mmol, 3.7 g)[11] was dissolved in 20 mL of MeCN and 5 mL of dioxane/$H_2O$ (1:1). After addition of 5 mL of $Et_3N$, DMAP (1 mmol, 0.12 g), and $Boc_2O$ (12 mmol, 2.62 g), the solution was stirred at ambient temperature for 2 h followed by evaporation to dryness. The residue was subjected to column chromatography [eluent: $CH_2Cl_2$ (90%), MeOH (10%)] to give the title compound as an oil which crystallized at 4 °C (yield, 2.21 g, 97%): mp 76−78 °C; $^1$H NMR ($Me_2SO$-$d_6$) $\delta$ 8.08 (s, 1H, Im-2-H), 7.21 (s, 1H, Im-5-H), 4.47 (t, $J$ = 5.1 Hz, 1H, OH), 3.43 (m, 2H, O-$CH_2$), 2.50 (t, $J$ = 7.7 Hz, 2H, Im-$CH_2$), 1.71 (m, 2H, Im-$CH_2$-C$H_2$), 1.56 (s, 9H, *t*-Bu); MS *m*/*z* ($FAB^+$) 227 (M + $H^{\bullet+}$, 17), 171 (81), 127 (40), 109 (15), 81 (11). Anal. ($C_{11}H_{18}N_2O_3 \cdot 0.5H_2O$) C, H, N.

**4-Ethynylphenyl 3-(1*H*-imidazol-4-yl)propyl ether (14a):** for preparation see **14e**; crystallized as hydrogen maleate from EtOH/$Et_2O$; $^1$H NMR ($Me_2SO$-$d_6$) $\delta$ 8.89 (s, 1H, Im-2-H), 7.42 (m, 3H, Im-5-H, Ph-2-H, Ph-6-H), 6.94 (d, $J$ = 8.4 Hz, 2H, Ph-3-H, Ph-5-H), 6.07 (s, 2H, Mal), 4.06 (m, 3H, O-$CH_2$, CH), 2.82 (t, $J$ = 7.4 Hz, 2H, Im-$CH_2$), 2.09 (m, 2H, Im-$CH_2$-C$H_2$); MS *m*/*z* 226 ($M^{\bullet+}$, 12), 209 (1), 153 (1), 109 (100), 82 (36). Anal. ($C_{14}H_{14}N_2O \cdot C_4H_4O_4 \cdot 0.25H_2O$) C, H, N.

**3-(1*H*-Imidazol-4-yl)propyl 4-Propynylphenyl Ether (14b).** Triphenylphosphine (6 mmol, 1.57 g) was dissolved in 20 mL of THF under $N_2$ atmosphere together with **12** (5 mmol, 1.13 g) and **10c** (5 mmol, 0.80 g) and cooled in an ice bath. Then diethyl azodicarboxylate (6 mmol, 0.95 mL) was added dropwise followed by additional stirring for 72 h at ambient temperature. Evaporation under reduced pressure and purification by column chromatography (eluent: EtOAc) afforded the Boc-protected product **13b** which was deprotected by stirring in 25 mL of methanolic $NH_3$ (10%) at ambient temperature for 6 h. The residue was concentrated under reduced pressure and subjected to column chromatography [eluent: $CH_2Cl_2$ (90%), MeOH (10%)] to give the title compound as an oil, which was crystallized as hydrogen maleate from EtOH/$Et_2O$: $^1$H NMR ($Me_2SO$-$d_6$) $\delta$ 8.88 (s, 1H, Im-2-H), 7.42 (s, 1H, Im-5-H), 7.30 (d, $J$ = 8.6 Hz, 2H, Ph-2-H, Ph-6-H), 6.87 (d, $J$ = 8.6 Hz, 2H, Ph-3-H, Ph-5-H), 6.04 (s, 2H, Mal), 4.01 (t, $J$ = 6.1 Hz, 2H, O-$CH_2$), 2.78 (t, $J$ = 7.5 Hz, 2H, Im-$CH_2$), 2.06 (m, 2H, Im-$CH_2$-C$H_2$), 2.00 (s, 3H, Me); MS *m*/*z* 240 ($M^{\bullet+}$, 16), 158 (100), 109 (100), 82 (23). Anal. ($C_{15}H_{16}N_2O \cdot C_4H_4O_4 \cdot 0.5H_2O$) C, H, N.

**3-(1*H*-Imidazol-4-yl)propyl 4-pentynylphenyl ether (14c):** prepared according to **14b**; crystallized as hydrogen maleate from EtOH/$Et_2O$; $^1$H NMR ($Me_2SO$-$d_6$) $\delta$ 8.89 (s, 1H, Im-2-H), 7.43 (s, 1H, Im-5-H), 7.30 (d, $J$ = 8.6 Hz, 2H, Ph-2-H, Ph-6-H), 6.87 (d, $J$ = 8.6 Hz, 2H, Ph-3-H, Ph-5-H), 6.05 (s, 2H, Mal), 4.01 (t, $J$ = 6.1 Hz, 2H, O-$CH_2$), 2.79 (t, $J$ = 7.4 Hz, 2H, Im-$CH_2$), 2.36 (t, $J$ = 7.0 Hz, 2H, C≡C−$CH_2$), 2.06 (m, 2H, Im-$CH_2$-C$H_2$), 1.53 (m, 2H, C$H_2$-Me), 0.98 (t, $J$ = 7.3 Hz, 3H, Me); MS *m*/*z* 268 ($M^{\bullet+}$, 13), 131 (6), 109 (100), 82 (14). Anal. ($C_{17}H_{20}N_2O \cdot C_4H_4O_4 \cdot 0.25H_2O$) C, H, N.

**4-(3,3-Dimethylbutynyl)phenyl 3-(1*H*-imidazol-4-yl)-propyl ether (14d):** prepared according to **14b**; crystallized as hydrogen maleate from EtOH/$Et_2O$; $^1$H NMR ($Me_2SO$-$d_6$) $\delta$ 8.90 (s, 1H, Im-2-H), 7.43 (s, 1H, Im-5-H), 7.27 (d, $J$ = 8.7 Hz, 2H, Ph-2-H, Ph-6-H), 6.87 (d, $J$ = 8.7 Hz, 2H, Ph-3-H, Ph-5-H), 6.06 (s, 2H, Mal), 4.01 (t, $J$ = 6.1 Hz, 2H, O-$CH_2$), 2.80 (t, $J$ = 7.5 Hz, 2H, Im-$CH_2$), 2.07 (m, 2H, Im-$CH_2$-C$H_2$), 1.27 (s, 9H, *t*-Bu); MS *m*/*z* 282 ($M^{\bullet+}$, 14), 267 (4), 159 (7), 109 (100), 82 (11). Anal. ($C_{18}H_{22}N_2O \cdot C_4H_4O_4 \cdot 0.5H_2O$) C, H, N.

**3-(1*H*-Imidazol-4-yl)propyl 4-[(Trimethylsilyl)ethynyl]-phenyl Ether (14e).** This was prepared according to **14b**. The Boc-protected product **13e** was deprotected by stirring in 25 mL of methanolic hydrazine solution (10%) at ambient temperature for 30 min. The residue was concentrated under reduced pressure and subjected to column chromatography [eluent: $CH_2Cl_2$ (90%), MeOH (10%)] to separate the title compound from **14a** giving it as an oil which was crystallized as hydrogen maleate from EtOH/$Et_2O$: $^1$H NMR ($Me_2SO$-$d_6$) $\delta$ 8.86 (s, 1H, Im-2-H), 7.42 (m, 3H, Im-5-H, Ph-2-H, Ph-6-H), 6.93 (d, $J$ = 8.5 Hz, Ph-3-H, Ph-5-H), 6.06 (s, 2H, Mal), 4.06 (t, 2H, O-$CH_2$), 2.81 (t, $J$ = 7.3 Hz, 2H, Im-$CH_2$), 2.09 (m, 2H, Im-$CH_2$-C$H_2$), 0.23 (s, 9H, Si-$Me_3$); MS *m*/*z* 298 ($M^{\bullet+}$, 6), 283 (3), 175 (5), 147 (4), 109 (100), 82 (23); IR (KBr) $\tilde{\nu}$ 3432 (br), 3141 (m), 2957 (m, C−H), 2877 (m, C−H), 2155 (w, C≡C), 1574 (vs, C═C), 1510 (vs, C═C). Anal. ($C_{17}H_{22}N_2OSi \cdot C_4H_4O_4 \cdot 0.75H_2O$) C, N; H: calcd, 6.48; found, 6.04.

**Pharmacology. General Methods: Histamine $H_3$-Receptor Assay on Synaptosomes from Rat Cerebral Cortex.** The new compounds were tested for their $H_3$-receptor antagonist activity at least in triplicate in an assay with $K^+$-evoked depolarization-induced release of [$^3$H]histamine from synaptosomes according to Garbarg et al.[23]

**Histamine $H_3$-Receptor Antagonist Activity in Vivo in Mouse.** In vivo testing of all compounds was performed at least in triplicate after oral administration to Swiss mice as described by Garbarg et al.[23]

**In Vitro Screening at Other Histamine Receptors.** All compounds were screened in duplicate for histamine $H_2$-receptor activity at isolated spontaneously beating guinea pig right

atrium as well as for $H_1$-receptor activity at isolated guinea pig ileum by standard methods described by Hirschfeld et al.[24]

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## References

(1) Arrang, J.-M.; Garbarg, M.; Schwartz, J.-C. Auto-Inhibition of Brain Histamine Release Mediated by a Novel Class ($H_3$) of Histamine Receptor. *Nature (London)* **1983**, *302*, 832−837.

(2) Arrang, J.-M.; Garbarg, M.; Schwartz, J.-C. Autoinhibition of Histamine Synthesis Mediated by Presynaptic $H_3$-Receptors. *Neuroscience* **1987**, *23*, 149−157.

(3) Arrang, J.-M.; Garbarg, M.; Schwartz, J.-C. Autoregulation of Histamine Release in Brain by Presynaptic $H_3$-Receptors. *Neuroscience* **1985**, *15*, 553−562.

(4) Burgaud, J. L.; Oudart, N. Effect of an Histaminergic $H_3$ Agonist on the Nonadrenergic Noncholinergic Contraction in the Guinea-pig Perfused Bronchioles. *J. Pharm. Pharmacol.* **1993**, *45*, 955−958.

(5) Schlicker, E.; Malinowska, B.; Kathmann, M.; Göthert, M. Modulation of Neurotransmitter Release via Histamine $H_3$ Heteroreceptors. *Fundam. Clin. Pharmacol.* **1994**, *8*, 128−137.

(6) Ligneau, X.; Garbarg, M.; Vizuete, M. L.; Diaz, J.; Purand, K.; Stark, H.; Schunack, W.; Schwartz, J.-C. [$^{125}$I]Iodoproxyfan, a New Antagonist to Label and Visualize Cerebral Histamine $H_3$ Receptors. *J. Pharmacol. Exp. Ther.* **1994**, *271*, 452−459.

(7) Stark, H.; Schlicker, E.; Schunack, W. Developments of Histamine $H_3$-Receptor Antagonists. *Drugs Future* **1996**, *21*, 507−520.

(8) Arrang, J.-M.; Garbarg, M.; Lancelot, J.-C.; Lecomte, J.-M.; Pollard, H.; Robba, M.; Schunack, W.; Schwartz, J.-C. Highly Potent and Selective Ligands for Histamine $H_3$ Receptors. *Nature (London)* **1987**, *327*, 117−123.

(9) Van der Goot, H.; Schepers, M. J. P.; Sterk, G. J.; Timmermann, H. Isothiourea Analogues of Histamine as Potent Antagonists of the Histamine $H_3$ Receptor. *Eur. J. Med. Chem.* **1992**, *27*, 511−517.

(10) Ali, S. M.; Tedford, C. E.; Gregory, R.; Yates, S. L.; Phillips, J. G. New Acetylene Based Histamine $H_3$ Receptor Antagonists Derived from the Marine Natural Product Verongamine. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1133−1138.

(11) Stark, H.; Purand, K.; Hüls, A.; Ligneau, X.; Garbarg, M.; Schwartz, J.-C.; Schunack, W. [$^{125}$I]Iodoproxyfan and Related Compounds: A Reversible Radioligand and Novel Classes of Antagonists with High Affinity and Selectivity for the Histamine $H_3$ Receptor. *J. Med. Chem.* **1996**, *39*, 1220−1226.

(12) Ganellin, C. R.; Fkyerat, A.; Bang-Andersen, B.; Athmani, S.; Tertiuk, W.; Garbarg, M.; Ligneau, X.; Schwartz, J.-C. A Novel Series of (Phenoxyalkyl)imidazoles as Potent $H_3$-Receptor Histamine Antagonists. *J. Med. Chem.* **1996**, *39*, 3806−3813.

(13) Dehmlow, E. V.; Lissel, M. Preparation of Alkynes from Alkyl Halides with Solid Potassium *tert*.-Butoxide and Crown Ether. *Liebigs Ann. Chem.* **1980**, 1−13.

(14) Feutrill, G. I.; Mirrington, R. N. Demethylation of Aryl Methyl Ethers with Thioethoxide Ion in Dimethyl Formamide. *Tetrahedron Lett.* **1970**, 1327−1328.

(15) Jung, M. E.; Lyster, M. A. Quantitative Dealkylation of Alkyl Ethers via Treatment with Trimethylsilyl Iodide. A New Method for Ether Hydrolysis. *J. Org. Chem.* **1977**, *42*, 3761−3764.

(16) Dieck, H. A.; Heck, F. R. Palladium Catalyzed Synthesis of Aryl, Heterocyclic and Vinylic Acetylene Derivatives. *J. Organomet. Chem.* **1975**, *93*, 259−263.

(17) Sonogashira, K.; Tohda, Y.; Hagihara, N. A Convenient Synthesis of Acetylenes: Catalytic Substitutions of Acetylenic Hydrogen with Bromoalkenes, Iodoarenes, and Bromopyridines. *Tetrahedron Lett.* **1975**, 4467−4470.

(18) Rall, G. J. H.; Oberholzer, M. E.; Ferreira, D.; Roux, D. G. Crown Ethers. Application in the Synthesis of Chalcones. *Tetrahedron Lett.* **1976**, 1033−1036.

(19) Takahashi, S.; Kuroyama, Y.; Sonogashira, K.; Hagihara, N. A Convenient Synthesis of Ethynylarenes and Diethynylarenes. *Synthesis* **1980**, 627−630.

(20) Hatanaka, Y.; Hiyama, T. Highly Selective Cross-Coupling Reactions of Organosilicon Compounds Mediated by Fluoride Ion and a Palladium Catalyst. *Synlett* **1991**, 845−853.

(21) Grehn, L.; Ragnarsson, U. A Convenient Method for the Preparation of 1-(*tert*-Butyloxycarbonyl)pyrroles. *Angew. Chem.* **1984**, *96*, 291−292.

(22) Mitsunobu, O. The Use of Diethyl Azodicarboxylate and Triphenylphosphine in Synthesis and Transformation of Natural Products. *Synthesis* **1981**, 1−28.

(23) Garbarg, M.; Arrang, J.-M.; Rouleau, A.; Ligneau, X.; Dam Trung Tuong, M.; Schwartz, J.-C.; Ganellin, C. R. *S*-[2-(4-Imidazolyl)-ethyl]Isothiourea, a Highly Specific and Potent Histamine $H_3$-Receptor Agonist. *J. Pharmacol. Exp. Ther.* **1992**, *263*, 304−310.

(24) Hirschfeld, J.; Buschauer, A.; Elz, S.; Schunack, W.; Ruat, M.; Traiffort, E.; Schwartz, J.-C. Iodoaminopotentidine and Related Compounds: A New Class of Ligands with High Affinity and Selectivity for Histamine $H_2$ Receptors. *J. Med. Chem.* **1992**, *35*, 2231−2238.

(25) Smissman, E. E.; Johnson, R. H.; Carlson, A. W.; Aycock, B. F. The Acid-Catalyzed Rearrangement of Phenylethynylcarbinols. *J. Am. Chem. Soc.* **1956**, *78*, 3395−3400.

(26) Naves, Y. R. Volatile Plant Materials. CLXV. Synthesis of cis-Anethole from trans-Anethole. *Helv. Chim. Acta* **1960**, *43*, 230−232.

(27) Ryono, D. E.; Petrillo, E. W., Jr. (Squibb, E. R., and Sons) U.S. Patent Appl. 357,941, March 15, 1982; *Chem. Abstr.* **1984**, *100*, P86121h.

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