Synthesis of 1,2,3-Triazole Elements in Histamine H_3 Receptor Ligands

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Abstract: 1,2,3-Triazole moieties were introduced in a histamine H_3 receptor antagonist pharmacophore blueprint with a versatile click chemistry approach, yielding potent ligands. Azide and alkynes were combined under copper(I) catalysis to provide the triazole element. Conventional synthesis, as well as microwave irradiation, was successfully applied.

Key words: azides, alkynes, copper catalysis, click chemistry, histamine H_3 receptor

In the central nervous system (CNS), the human histamine H_3 receptor (hH$_3$R) controls histamine-mediated neurotransmission. Its autoreceptor function and cross-linking to other neurotransmitter systems via heteroreceptors play a central role in maintaining the neurotransmitter balance.[1] Due to the resulting modulation of numerous (patho)physiological brain functions, such as vigilance, memory processes and food intake, the H_3R might be an attractive target for the therapy of a multitude of CNS disorders.[2]

The common pharmacophore blueprint of H_3R antagonists/inverse agonists offers an amine moiety in the western part of the molecule linked by an alkyl spacer to a mostly lipophilic central core structure. This receptor-targeting part can be substituted by a broad range of structural elements, defining the activity of the compound (Figure 1).[3]

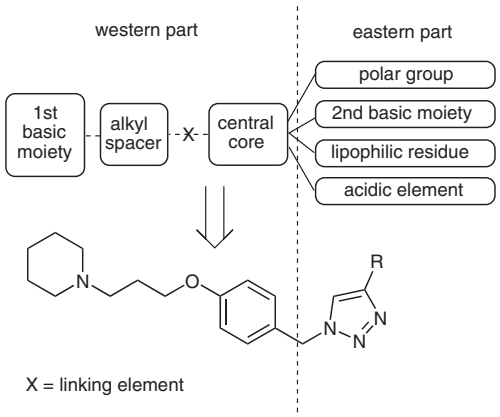

Figure 1 Structural blueprint of H_3R antagonists[3] and general pharmacophore of presented ligands

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So far, different azole moieties have been successfully introduced in hH$_3$R ligands.[4] Due to their favorable physicochemical properties, triazoles are highly recommended in drug discovery. Huisgen's 1,3-dipolar cycloaddition describes the synthesis of 1,2,3-triazoles by the reaction of azides and alkynes.[5] Despite their high energy, azides and alkynes belong to the least reactive functional groups, leading to inefficient reaction times and low yields. Copper(I) catalysis enables an easy introduction of the triazoles in a multitude of molecules, which makes this reaction highly applicable in compound variations for drug development.[6,7]

Using this click chemistry approach on H_3R antagonists, we identified 1,2,3-triazole moieties as suitable structural elements on the eastern part of the H_3R antagonist construction pattern, but these were insufficient as a linking element (X, cf. Figure 1).[8] Based on these findings, the aim of the present work was the structural variation of the 1,2,3-triazole moiety in the eastern part of the molecule by using polar alkynes (Figure 1). The influence of different polar substituents on the binding behavior towards the receptor was easily evaluated. The hH$_3$R affinities were determined in a radioligand competitive binding assay, described previously.[9,10]

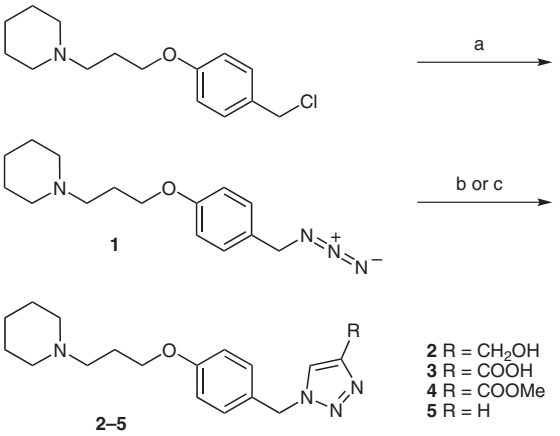
The cycloaddition of azide and alkynes under copper(I) catalysis was used for the synthesis of compounds **2**–**4** (Scheme 1).[7,11] First, the H_3R core fragment was prepared according to the literature.[12] The azide functionality was incorporated using sodium azide in *N*,*N*-dimethylformamide. The resulting 1-{3-[4-(azidomethyl)phenoxy]propyl}piperidine (**1**) was used as a versatile precursor for the click chemistry reaction performed with different alkynes (namely, prop-2-yn-1-ol, propiolic acid and methyl propiolate), in a mixture of *N*,*N*-dimethylformamide and water or isopropyl alcohol and water as solvent.[8] Copper(I), which was obtained in situ by reduction of copper(II) sulfate with sodium ascorbate, enabled the 1,3-dipolar cycloaddition by forming copper acetylides, activating the azide.[11] The alcohol-containing derivative **2** and the ester compound **4** were obtained by conventional synthesis in a round-bottom flask upon stirring at room temperature. Microwave irradiation was used for the preparation of acid derivative **3**.[13]

Compound **5** was obtained by an alternative method (Scheme 1).[14] The conventional cycloaddition of azide derivative **1** and vinyl acetate was performed under microwave conditions without catalysis.

Table 1 In Vitro Binding Affinities of Compounds **1–5** on hH_3R

Compound	Chemical formula	Molecular weight (g/mol)	hH_3R K_i[a] [nM], (*n*)
1	$C_{15}H_{22}N_4O\cdot(COOH)_2$	364.41	28 ± 0.6 (2)
2	$C_{18}H_{26}N_4O_2$	330.42	8.7 ± 0.1 (2)
3	$C_{18}H_{24}N_4O_3$	344.41	432 ± 27 (2)
4	$C_{19}H_{26}N_4O_3$	358.43	17 ± 4.2 (2)
5	$C_{17}H_{24}N_4O\cdot1.5(COOH)_2$	435.46	30 ± 12 (4)

[a] [^{3}H]N^α-Methylhistamine competitive binding assay on HEK-293 cells stably expressing hH_3R;[9] K_d = 2.98 nM;[10] values are means ± SD of two to four independent experiments performed at least in duplicate (number of experiments in parentheses).



Scheme 1 Preparation of **1–5**. *Reagents and conditions*: (a) NaN_3, DMF, microwave (MW), 120 °C, 40 min, 98%; (b) Compounds **2** and **4**: prop-2-yn-1-ol or methyl propiolate, $CuSO_4$, sodium ascorbate, DMF–H_2O (2:1), r.t., 16 h, **2**: 64%, **4**: 42%; compound **3**: propiolic acid, $CuSO_4$, sodium ascorbate, *i*-PrOH–H_2O (1:1), MW, 125 °C, 10 min, 48%; (c) Compound **5**: vinyl acetate, MW, 120 °C, 18 h, 26%.

All compounds prepared offered a good to excellent binding behavior to hH_3R in the nanomolar concentration range (Table 1). Compared to the unsubstituted 1,2,3-triazole (compound **5**) with a K_i value of 30 nM, an additional alcohol or ester structure enhances affinity (K_i values of 8.7 nM and 17 nM, respectively). Introduction of the acidic element in carboxylic acid **3** decreases receptor binding (K_i value of 432 nM). This impairment most likely demonstrates a limitation of the substitution pattern in the eastern part of the hH_3R antagonist blueprint for ionic elements.

In summary, the click chemistry approach offers an advantageous synthetic way for the incorporation of 1,2,3-triazoles in the H_3R pharmacophore. Copper(I) catalysis enables shorter reaction times, especially in the microwave approach (compound **3**), and higher yields compared to the alternative cycloaddition (compound **5**). Whereas lipophilic alkynes have been preferred in the literature for 1,3-dipolar cycloreactions, we have successfully transferred the synthetic procedure to polar structures, leading to high affine H_3R antagonists/inverse agonists.

All chemicals were obtained from Sigma-Aldrich, ABCR and Acros Organics, and were used without further purification. Precursor 1-{3-[4-(chloromethyl)phenoxy]propyl}piperidine was obtained according to the literature.[12] Melting points were determined on a Büchi 510 melting point apparatus (Büchi, Switzerland) and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker AMX 250 (250 MHz) or AV 300 (300 MHz) spectrometer (Bruker, Germany). ^{1}H NMR data are reported in the following order: chemical shift (δ) in ppm relative to TMS as internal reference; multiplicity (s, singlet; d, doublet; t, triplet; m, multiplet); approximate coupling constants (*J*) in hertz (Hz); number and assignment of protons (ox, oxalate; ph, phenyl; pip, piperidine; prop, propyl; trz, triazole). ^{13}C NMR spectra were recorded on a Bruker AV 300 (75 MHz) spectrometer (Bruker, Germany). DMSO-d_6 was used as the solvent. ESI-MS was performed on a Fisons Instruments VG Platform II spectrometer (Manchester, Great Britain) in positive polarity. Data are listed as mass number ($[M + H]^+$) and relative intensity (%). Elemental analyses (C, H, N) were measured on a CHN-Rapid analyzer (Heraeus, Germany) and are within ±0.4% of the theoretical values for all final compounds. Preparative column chromatography was performed on silica gel (63–200 μM; Merck, Germany). Flash chromatography was carried out on Varian SuperFlash silica gel (50 μM). TLC was performed on Merck plastic-backed silica gel plates (DC-Plastikfolien 60, F254; layer thickness: 0.2 mm) that were visualized with UV light (254 nm) or by staining with ninhydrin solution. Microwave irradiation was conducted in a Biotage Initiator 2.0 microwave reactor (Biotage, Sweden).

1-{3-[4-(Azidomethyl)phenoxy]propyl}piperidine (1)

1-{3-[4-(Chloromethyl)phenoxy]propyl}piperidine[12] (1.2 g, 4.48 mmol) and NaN_3 (0.641 g, 9.86 mmol) in DMF (8 mL) was placed in a 10–20 mL vial. The reaction mixture was stirred with a magnetic stirrer bar and subjected to microwave irradiation at 120 °C for 40 min. The mixture was diluted with 2 N aq NaOH (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The organic layers were combined, dried (Na_2SO_4) and filtered. The solvent was evaporated to dryness. Azide **1** was obtained as a brown oil; yield: 1.06 g (86%).

Crystallization as the salt of oxalic acid led to a white solid; mp 177.7 °C.

R_f = 0.77 (CH_2Cl_2–ammoniacal MeOH, 9:1).

^{1}H NMR (250 MHz, DMSO-d_6): δ = 7.28 (d, *J* = 8.6 Hz, 2 H, ph-3,5*H*), 6.97 (d, *J* = 8.6 Hz, 2 H, ph-2,6*H*), 4.35 (s, 2 H, C*H*$_2$N$_3$), 4.04 (t, *J* = 6.0 Hz, 2 H, prop-3H_2), 3.15–3.10 (m, 6 H, pip-2,6H_2, prop-1H_2), 2.13–2.06 (m, 2 H, prop-2H_2), 1.72–1.70 (m, 4 H, pip-3,5H_2), 1.53 (m, 2 H, pip-4H_2).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 164.32 (ox-*C*OOH), 158.17 (ph-1*C*), 130.10 (ph-3,5*C*), 127.69 (ph-4*C*), 114.60 (ph-2,6*C*),

65.00 (prop-3*C*), 53.45 (prop-1*C*), 53.13 (*C*H_2N_3), 52.16 (pip-2,6*C*), 23.50 (prop-2*C*), 22.66 (pip-3,5*C*), 21.45 (pip-4*C*).

ESI-MS: *m*/*z* (%) = 275.2 (100) $[M + H]^+$.

Anal. Calcd for $C_{15}H_{22}N_4O\cdot(COOH)_2$: C, 56.03; H, 6.64; N, 15.37. Found: C, 55.78; H, 6.55; N, 15.21.

{1-[4-(3-Piperidin-1-ylpropoxy)benzyl]-1*H*-1,2,3-triazol-4-yl}methanol (2)

In a 100 mL round-bottomed flask, azide **1** (1 g, 3.64 mmol), $CuSO_4$ (0.291 g, 1.822 mmol) and sodium ascorbate (0.361 g, 1.822 mmol) were dissolved in DMF–H_2O (2:1, total: 30 mL). Prop-2-yn-1-ol (0.307 g, 5.47 mmol) was added under ice cooling and argon atmosphere. The reaction mixture was stirred with a magnetic stir bar at r.t. overnight. The residue was filtered off and the solution was diluted with 2 N NaOH (80 mL). The aqueous layer was extracted with EtOAc (3 × 100 mL). The organic layers were combined, dried (Na_2SO_4) and filtered. The solvent was evaporated to dryness. The crude product was added to a silica gel column and eluted with CH_2Cl_2–ammoniacal MeOH (99:1 to 9:1). Alcohol **2** was obtained as a white solid; yield (crude product): 770 mg (64%).

Mp 96 °C; R_f = 0.67 (CH_2Cl_2–ammoniacal MeOH, 9:1).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.01 (s, 1 H, trz-5*H*), 7.32 (d, *J* = 9.0 Hz, 2 H, ph-2,6*H*), 6.99 (d, *J* = 9.0 Hz, 2 H, ph-3,5*H*), 5.53 (s, 2 H, CH_2-trz), 5.21 (br s, 1 H, O*H*), 4.54 (s, 2 H, CH_2OH), 4.03 (t, *J* = 6.0 Hz, 2 H, prop-1H_2), 2.48–2.40 (m, 6 H, pip-2,6H_2, prop-3H_2), 1.97–1.86 (m, 2 H, prop-2H_2), 1.57–1.53 (m, 4 H, pip-3,5H_2), 1.34–1.30 (m, 2 H, pip-4H_2).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 158.56 (ph-4*C*), 148.34 (trz-4*C*), 129.55 (ph-2,6*C*), 128.27 (ph-1*C*), 122.43 (trz-5*C*), 114.59 (ph-3,5*C*), 65.87 (prop-1*C*), 55.01 (*C*H_2-trz), 54.95 (prop-3*C*), 53.83 (pip-2,6*C*), 52.37 (*C*H_2OH), 26.09 (prop-2*C*), 25.36 (pip-3,5*C*), 23.72 (pip-4*C*).

ESI-MS: *m*/*z* (%) = 331.0 (100) $[M + H]^+$.

Anal. Calcd for $C_{18}H_{26}N_4O_2$: C, 65.43; H, 7.93; N, 16.96. Found: C, 65.23; H, 7.87; N, 16.96.

1-[4-(3-Piperidin-1-ylpropoxy)benzyl]-1*H*-1,2,3-triazole-4-carboxylic Acid (3)

$CuSO_4$ (0.7 mg, 0.073 mmol) and sodium ascorbate (11.90 mg, 0.073 mmol) in H_2O (1.5 mL) was added to a 2–5-mL vial. Azide **1** (200 mg, 0.729 mmol) suspended in *i*-PrOH (1.5 mL) was added. The mixture was aerated with argon and the vial was locked. Propiolic acid (0.067 mL, 1.093 mmol) was added to the vial via syringe. The reaction mixture was stirred with a magnetic stir bar and subjected to microwave irradiation at 125 °C for 10 min. The mixture was concentrated to dryness. The crude product was added to a silica gel column and eluted with CH_2Cl_2–ammoniacal MeOH (2:1). Acid **3** was obtained as a light brownish solid; yield: 120 mg (48%).

Mp 192 °C; R_f = 0.35 (CH_2Cl_2–ammoniacal MeOH, 2:1).

^{1}H NMR (250 MHz, DMSO-d_6): δ = 8.41 (s, 1 H, trz-5*H*), 7.28 (d, *J* = 8.6 Hz, 2 H, ph-2,6*H*), 6.93 (d, *J* = 8.6 Hz, 2 H, ph-3,5*H*), 5.51 (s, 2 H, CH_2-trz), 3.97 (t, *J* = 6.4 Hz, 2 H, prop-1H_2), 2.46–2.43 (m, 6 H, pip-2,6H_2, prop-3H_2), 1.90–1.82 (m, 2 H, prop-2H_2), 1.54–1.50 (m, 4 H, pip-3,5H_2), 1.41–1.39 (m, 2 H, pip-4H_2).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 162.87 (*C*OOH), 158.40 (ph-4*C*), 143.19 (trz-4*C*), 129.61 (ph-2,6*C*), 127.78 (ph-1*C*), 127.36 (trz-5*C*), 114.62 (ph-3,5*C*), 65.64 (prop-1*C*), 54.26 (prop-3*C*), 53.10 (pip-2,6*C*), 52.37 (*C*H_2-trz), 25.01 (prop-2*C*), 24.27 (pip-3,5*C*), 23.07 (pip-4*C*).

ESI-MS: *m*/*z* (%) = 345.1 (100) $[M + H]^+$.

Anal. Calcd for $C_{18}H_{24}N_4O_3$: C, 62.77; H, 7.02; N, 16.27. Found: C, 62.47; H, 7.32; N, 16.01.

Methyl 1-[4-(3-Piperidin-1-ylpropoxy)benzyl]-1*H*-1,2,3-triazole-4-carboxylate (4)

In a 100 mL round-bottomed flask, azide **1** (1.0 g, 3.64 mmol), $CuSO_4$ (0.291 g, 1.822 mmol) and sodium ascorbate (0.361 g, 1.822 mmol) were dissolved in DMF–H_2O (2:1, total: 15 mL). Methyl propiolate (0.457 mL, 5.47 mmol) was added under ice cooling and argon atmosphere. The reaction mixture was stirred with a magnetic stir bar at r.t. overnight. The residue was filtered off and the solution was diluted with 2 N NaOH (pH 10, 50 mL). The aqueous layer was extracted with EtOAc (3 × 70 mL). The organic layers were combined, dried (Na_2SO_4) and filtered. The solvent was evaporated to dryness. The residue was heated with EtOH (10 mL) at 80 °C for 30 min, and the product was collected by filtration. Ester **4** was obtained as a white solid; yield: 550 mg (42%).

Mp 126 °C; R_f = 0.38 (CH_2Cl_2–ammoniacal MeOH, 9:1).

^{1}H NMR (250 MHz, DMSO-d_6): δ = 8.85 (s, 1 H, trz-5*H*), 7.30 (d, *J* = 10.0 Hz, 2 H, ph-2,6*H*), 6.95 (d, *J* = 10.0 Hz, 2 H, ph-3,5*H*), 5.57 (s, 2 H, CH_2-trz), 3.98 (t, *J* = 6.3 Hz, 2 H, prop-1H_2), 3.83 (s, 3 H, OCH_3), 2.38–2.25 (m, 6 H, pip-2,6H_2, prop-3H_2), 1.89–1.78 (m, 2 H, prop-2H_2), 1.48–1.46 (m, 4 H, pip-3,5H_2), 1.39–1.37 (m, 2 H, pip-4H_2).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 160.62 (*C*OOCH$_3$), 158.63 (ph-4*C*), 138.68 (trz-4*C*), 129.68 (ph-2,6*C*), 128.85 (ph-1*C*), 127.22 (trz-5*C*), 114.64 (ph-3,5*C*), 65.93 (prop-1*C*), 55.05 (prop-3*C*), 54.06 (pip-2,6*C*), 52.65 (*C*H_2-trz), 51.73 (*C*H_3), 26.18 (prop-2*C*), 25.54 (pip-3,5*C*), 24.09 (pip-4*C*).

ESI-MS: *m*/*z* (%) = 359.1 (100) $[M + H]^+$.

Anal. Calcd for $C_{19}H_{26}N_4O_3$: C, 63.67; H, 7.31; N, 15.63. Found: C, 63.45; H, 7.37; N, 15.53.

1-{3-[4-(1*H*-1,2,3-Triazol-1-ylmethyl)phenoxy]propyl}piperidine (5)

Azide **1** (0.75 g, 2.73 mmol) was placed in a 2–5 mL vial and excess vinyl acetate (5 mL, 54.2 mmol) was added. The reaction mixture was stirred with a magnetic stir bar and subjected to microwave irradiation at 120 °C for 18 h. The mixture was concentrated and the crude product was purified by flash chromatography (CH_2Cl_2–ammoniacal MeOH, 99:1 to 9:1). The resulting brown oil [yield: 214 mg (26%)] was crystallized as the salt of oxalic acid, which was obtained as a white solid; mp 104 °C.

R_f = 0.74 (CH_2Cl_2–ammoniacal MeOH, 9:1).

^{1}H NMR (250 MHz, DMSO-d_6): δ = 8.15 (br s, 1 H, trz-4*H*), 7.73 (br s, 1 H, trz-5*H*), 7.27 (d, *J* = 10.05 Hz, 2 H, ph-3,5*H*), 6.96 (d, *J* = 10.05 Hz, 2 H, ph-2,6*H*), 5.54 (s, 2 H, CH_2-trz), 4.03 (t, *J* = 6.25 Hz, 2 H, prop-3H_2), 3.18–3.12 (m, 6 H, pip-2,6H_2, prop-1H_2), 2.17–2.06 (m, 2 H, prop-2H_2), 1.74 (m, 4 H, pip-3,5H_2), 1.55 (m, 2 H, pip-4H_2).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 163.39 (ox-*C*OOH), 158.04 (ph-1*C*), 133.44 (trz-5*C*), 129.47 (ph-3,5*C*), 128.45 (ph-4*C*), 124.61 (trz-4*C*), 114.66 (ph-2,6*C*), 64.99 (prop-3*C*), 53.36 (*C*H_2-trz), 52.10 (prop-1*C*), 52.08 (pip-2,6*C*), 23.37 (prop-2*C*), 22.53 (pip-3,5*C*), 21.32 (pip-4*C*).

ESI-MS: *m*/*z* (%) = 301.1 (100) $[M + H]^+$.

Anal. Calcd for $C_{17}H_{24}N_4O\cdot1.5(COOH)_2$: C, 55.17; H, 5.87; N, 12.87. Found: C, 54.94; H, 6.04; N, 12.93.

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