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Synthesis and SAR of Aminoalkoxy-biaryl-4-carboxamides: Novel and Selective Histamine H_3 Receptor Antagonists

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Abstract—Novel 4′-[(NR1R2-1-yl)]-propoxy-biaryl-4-carboxamides were designed and synthesized. All compounds were tested for affinity at histamine H_3receptors. Most compounds were highly potent and selective for human and rat H_3 receptors and selected examples such as A-349821 showed functional antagonism of H_3 receptors in vitro and in a mouse dipsogenia model.

Histamine mediates its action both in the CNS and the periphery through 4 distinct receptors (H_1–H_4) known to date.[1] Histamine H_1 and H_2 receptor blockers are important medicines in clinical use today. The H_3-receptor, primarily located in the CNS, is a presynaptic receptor, which modulates the production and release of histamine. Blockade of this receptor leads to increased levels of histamine and other neurotransmitters throughout the brain via effects on pre- and post-synaptic H_3 heteroreceptors.[2] The wide distribution of H_3 receptors in the mammalian CNS indicates the physiological role of this receptor. Therefore the therapeutic potential as a novel drug development target in indications associated with neurological disorders such as attention-deficit hyperactivity disorder (ADHD), Alzheimer's disease (AD), Parkinson disease and epilepsy as well as metabolic disorders such as obesity have been proposed.[3]

We describe herein chemical, radioligand binding, in vitro and in vivo pharmacological data on a novel non-imidazole H_3-receptor antagonist series,[4] typified by A-349821. This series of compounds is characterized by high, but approximately equal, affinity for both the human and rat receptor, in contrast to several previous series from our own laboratories[4b] as well as to previously described imidazole-based H_3 antagonists such as GT-2331[5] (pK_i of 8.67 ± 0.05 and 9.71 ± 0.11 at human cloned[7] and rat cortical H_3 receptors[8]) and ciproxifan[6] (pK_i of 7.22 ± 0.05 and 9.22 ± 0.04).

During our efforts to develop a selective H_3-blocker, we investigated the chemistry of several biaryl systems.[4a] By treatment of chloropropyloxy-biarylnitrile with pyrrolidine in a sealed-tube for 24 h at 120 °C we obtained both the displacement product (**1**) and a small amount ($\sim$10%) of the corresponding carboxamide **2** as a minor component (Scheme 1). Affinity measurements at the H_3-receptor revealed carboxamide **2** with pK_i of 8.95 ± 0.06 and 8.18 ± 0.02 at human cloned and rat cortical H_3 receptors. Additional screening revealed excellent selectivity vis-à-vis other histaminergic receptors with pK_i ≤ 5.72 at human H_1 and H_2 receptors.

Solution-phase parallel synthesis and a matrix approach were employed to prepare analogues of **2** quickly. Given this lead molecule consists of, both amide and amine functionalities, variation of each of these elements allowed a practical, systematic strategy toward the rapid delineation of the SAR of this biphenyl-amide series (Scheme 2).

Thus, commercially available methyl-4′-hydroxy[1,1′-biphenyl]-4-carboxylate (Scheme 2) was treated with 1-bromo-3-chloropropane in the presence of K_2CO_3 in

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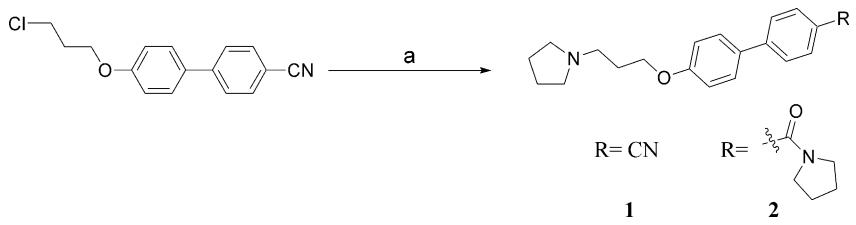
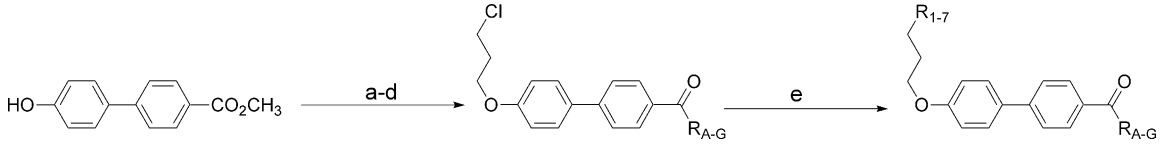


Scheme 1. (a) Pyrrolidine, 120 °C, sealed tube, 24 h, 10%.



Scheme 2. (a) Cl–$(CH_2)_3$–Br, K_2CO_3, 2-butanone, reflux, 24 h, 100%; (b) LiOH, THF/H_2O (3:1), rt, 98%; (c) $SOCl_2$, 90 °C, 4 h, 99%; (d) amines (A–G) Hunig's base, CH_2Cl_2, 0 °C, 70–92%; (e) amines (1–7), K_2CO_3, KI, 2-butanone, reflux, 72 h, 60–88%.

refluxing 2-butanone for 24 h. The resulting *O*-alkyl chloride was further treated, without purification, with lithium hydroxide to give the desired acid in 98% yield after silica-gel chromatoghraphy-filtration. Thionyl chloride treatment of the biaryl carboxylic acid provided the biphenyl-acyl chloride ready for parallel synthesis (Scheme 2). A group of 49 biphenyl-*O*-propylamine amides were prepared in a matrix-parallel fashion using the above set of 7×7 amines (Fig. 1).

The resulting products were purified using high throughput-HPLC-MS techniques, and assayed in a binding experiment using human cloned H_3 and rat cortex H_3 receptors. Data from Table 1 indicate a fairly well defined pharmacophore. While the lead **2** had good affinity for human and rat H_3R, several other substitutions altering various physicochemical properties of the molecule showed better binding (i.e., morpholine amide: **A6**; 4-methylpiperidine amide **B6** or *N,N*- diethylamide **G6**).

Overall, the amide portion can tolerate wide structural alterations but the basic site seems to be more restrictive, favoring small substituted pyrrolidines such as (*R,R*)-dimethylpyrrolidine. From the above studies we selected A-349821 (i.e., **A6**) based on its high affinity and selectivity for human and rat H_3 receptors. Compound **A6** (A-349821) demonstrated excellent selectivity towards other histaminergic receptors with pK_i of 5.63±0.036 at human H_1 and pK_i of 5.00 at human H_2 and H_4[11] receptors. A-349821 was tested at a number of biogenic amine receptors and transporters including different subtypes (Table 2).

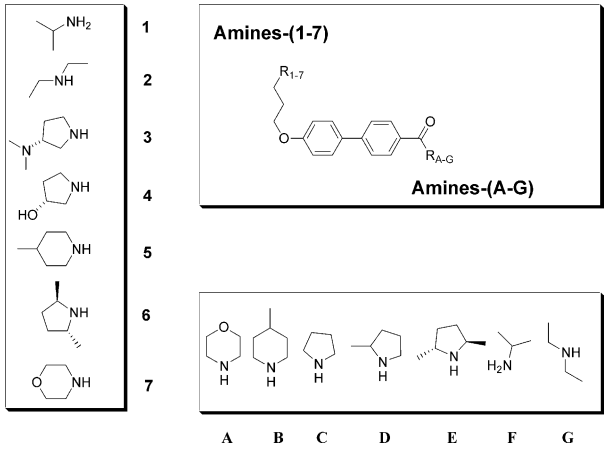


Figure 1.

A-349821 demonstrated low affinity at all of these sites. Since A-349821 fulfilled our requirement of in-vitro potency and selectivity, it was further evaluated in models of in-vitro functional activity. In vitro functional antagonism was demonstrated in assays in which inhibition of forskolin-stimulated cyclic AMP formation could be inhibited by (*R*)-α-methylhistamine, and reversed by H_3 antagonists.[8] At cloned human and rat H_3 receptors, compound **A6** blocked the H_3 agonist with pA_2 values of 8.67±0.25 and 8.71±0.20, consistent with similar affinities for these two receptors in radioligand binding assays. A-349821 was tested for H_3 receptor antagonist activity in an assay with K^+-evoked depolarization-induced release of [^{3}H]-histamine from

Table 1. Binding affinities[a] (pK_i) at human cloned and rat cortical H_3 receptors

Compd[b]	hH_3	rH_3	Compd	hH_3	rH_3	Compd	hH_3	rH_3
A1	7.49	6.89	**C4**	8.19	7.48	**E7**	7.43	6.94
A2	8.62	8.05	**C5**	8.44	7.99	**F1**[c]	ND	ND
A3	8.26	7.56	**C6**	9.16	8.29	**F2**	8.21	7.79
A4	8.21	7.49	**C7**	7.39	6.75	**F3**	8.22	7.69
A5	8.14	8.06	**D1**	8.01	7.37	**F4**	8.09	7.54
A6	9.31	8.78	**D2**	8.67	8.14	**F5**	8.68	8.42
A7	7.74	7.28	**D3**	8.19	7.67	**F6**	9.07	8.55
B1	6.74	6.32	**D4**	8.08	7.59	**F7**	7.41	6.87
B2	8.46	8.08	**D5**	8.43	8.55	**G1**	6.96	6.39
B3	8.41	7.53	**D6**	9.11	8.99	**G2**[c]	ND	ND
B4	8.16	7.51	**D7**	7.61	6.95	**G3**	8.16	7.55
B5	7.97	7.68	**E1**	6.64	6.66	**G4**	8.09	7.37
B6	9.22	8.53	**E2**	8.29	7.86	**G5**	8.32	8.04
B7	7.63	7.15	**E3**	8.36	7.76	**G6**	9.11	8.69
C1[c]	ND	ND	**E4**	7.95	7.24	**G7**	7.79	7.01
C2	8.52	7.89	**E5**	8.33	8.44	**1**	8.14	7.38
C3	8.54	7.73	**E6**	9.01	8.38	**2**	8.95	8.18

[a]Values were estimated from at least three separate competition experiments (SEM < 0.08).
[b]Satisfactory ^{1}H NMR, MS spectra were obtained for all new compounds. Compounds were tested as TFA salts.
[c]Lost during purification.

Table 2. Binding affinities[a] (pK_i) at human biogenic amine receptors and transporters

Compd	$hD_{4.2}$	hM_1	hM_2	hM_3	$h\alpha_2C_{10}$	UPTK-NE	UPTK- 5HT	UPTK-DA
A-349821[b]	5.01	5.79	6.03	5.78	5.79	5.01	5.45	5.31

[a]Values were estimated from at least three separate competition experiments (SEM $\leq$ 0.14).
[b]Compound was tested as L-tartaric acid salt.

rat synaptosomes[9] with pK_b of 9.23 ± 0.16. The compound also blocked (*R*)-α-methylhistamine-induced inhibition of electrical field-stimulation induced twitch responses in the isolated guinea pig ileum with a pA_2 value of 9.47 ± 0.56.

To demonstrate functional antagonism at the H_3 receptor in vivo, we employed a previously characterized mouse dipsogenia model in which pronounced drinking, elicited acutely in response to the H_3 receptor agonist (*R*)-α-methylhistamine, can be attenuated by pre-administration of H_3 receptor blockers[10] (Fig. 2).

A-349821, administered 5 min prior to (*R*)-α-methylhistamine, dose-dependently attenuated agonist-induced dipsogenia over a dose range 0.001–10 μmoles/kg, ip A-349821 had no effect on basal drinking response when administered 5 min prior to vehicle instead of (*R*)-α-methylhistamine.

On the basis of its excellent characteristics, A-349821 was evaluated for oral bioavailability in both monkey and dog. After a 2.5 mg/kg oral dose, A-349821 showed an excellent bioavailability of 78% in monkey. The compound was characterized by low plasma clearance (CLp = 1.0 L/h kg), an apparent elimination half-life of 5.3 h and a volume of distribution (V_β) = 7.5 L/kg. The peak plasma concentration after 5 h was 0.17 mcg/mL. A-349821 pharmacokinetics following a 2.5 mg/kg oral dose in dog was characterized by low clearance values (CLp = 0.6 L/h kg) with an apparent elimination half-life of 2.6 h. Peak blood concentrations averaged 0.31 mcg/mL after oral dosing, with 33.0% bioavailability. A-349821 was further advanced to in vivo studies (to be described elsewhere).

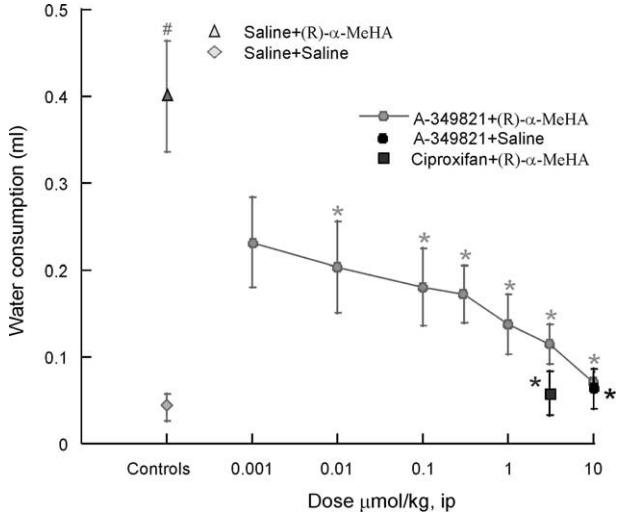


Figure 2.

In summary, we have discovered highly potent ligands for both human and rat H_3 receptors, with several exemplary compounds showing some of the highest affinity for human H_3 receptors reported to date.[12] The high potency of some of these compounds (e.g., **A6** or A-349821) for human receptors, coupled with other favorable physiological and pharmacodynamic properties make these compounds prime candidates for clinical studies in various CNS disorders.

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