



Trip Report for
“236th American Chemical Society Meeting”
Philadelphia, PA
August 17-21, 2008

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December 2, 2008

AMRI Memorandum

TO: Barnes, Keith; Earley, Bill; Gauuan, Joli; Geiss, Bill; Guaciaro, Michael; Herr, Jason; Molino, Bruce; Reilly, John; Schaffer, Malissa; Voss, Matthew; Yang, Zhicai; Sargent, Bruce; Guzzo, Pete; Michels, Pete; Carr, Grant; Manning, Dave; Surman, Matthew; Henderson, Alan; Wolf, Mark; Liu, Shuang; Luche, Michele; Mocek, Ursula; Chase, Matthew; Khmel'nitsky, Yuri; Cotterill, Ian

FROM: Kristen Ryan, Ph.D.

DATE: August 17-21, 2008

RE: "236th American Chemical Society Meeting," Philadelphia, PA.

Abstract: The 236th American Chemical Society Meeting was held in Philadelphia, PA on August 17-21, covering a variety of topics pertaining to chemists in all disciplines. This report highlights a few seminar presentations of interest to medicinal chemists.

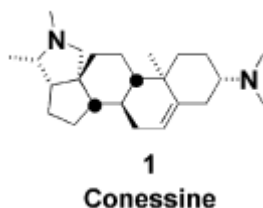
"Discovery of New Histamine H₃ Receptor Antagonists: From a Complex Natural Product to Small Molecule Leads"

Vincent Santora, (Arena Pharmaceuticals), San Diego, CA, USA.

In a session devoted entirely to Histamine H₃ antagonists, Dr. Santora discussed the potential use of H₃ antagonists and inverse agonists in the treatment of excessive daytime sleepiness associated with narcolepsy, depression, sleep apnea, etc. H₃ receptors are located mainly presynaptically in the CNS where they regulate the synthesis and release of histamine and other neurotransmitters. Many early H₃ antagonists contained an imidazole group (similar to histamine itself) and, unfortunately, imidazole-containing ligands tend to be potent CYP inhibitors. Therefore, efforts have turned toward the development of second generation H₃ antagonists lacking this group.

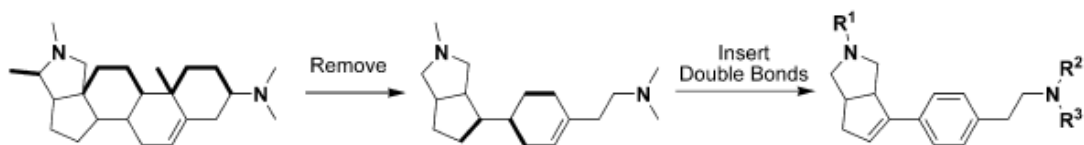
A high-throughput screen of Arena's compound collection identified a natural product called Conessine (Figure 1) as a fairly potent H₃ antagonist, with a K_i of 66 nM in a rat cortex membrane assay. It was determined that the relative positioning of the two amines in Conessine was necessary for activity and, therefore, the scientists at Arena set out to design a series of compounds that would retain two amines in positioning similar to the natural product.

Figure 1



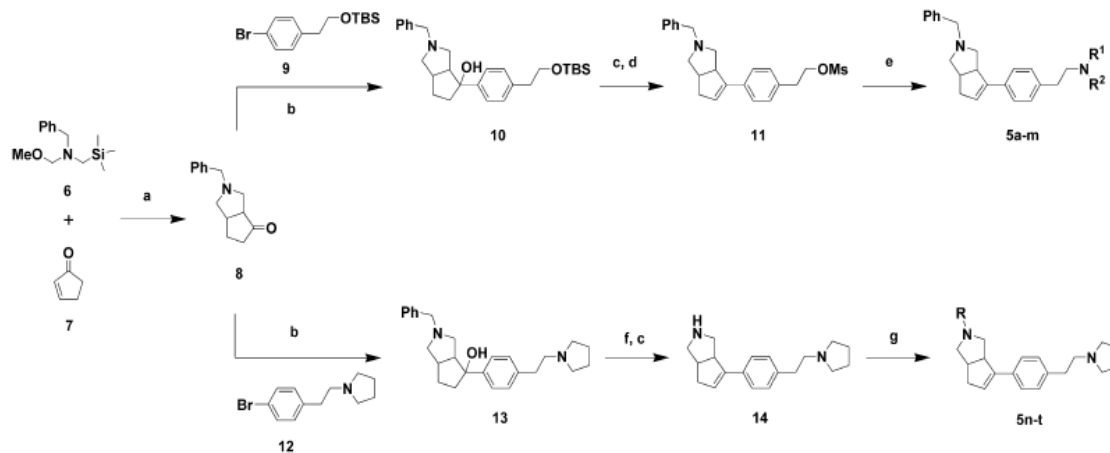
As a starting point, Arena chose to simplify the structure of Conessine as shown in Figure 2. The approach included aromatization of the central six-membered ring, removal of a number of carbon atoms, and incorporation of a double bond in the remaining bicyclic portion of the scaffold.

Figure 2



Synthesis of the initial target compounds is shown in Figure 3. The commercially available azomethine ylide **6** was treated with cyclopentenone **7** to give bicyclic ketone **8**. Reaction of this ketone with the alkyllithium reagent derived from compound **9** resulted in the formation of alcohol **10**, which was dehydrated and deprotected and then converted to mesylate **11**. Reaction of the mesylate with various secondary amines provided compounds **5a-m**, allowing exploration of the effects of phenethylamine substituents on binding. Alternatively, ketone **8** underwent reaction with the alkyllithium reagent derived from 4-bromo-phenethylamine **12** to give alcohol **13**. Deprotection and dehydration afforded compound **14**, which then underwent various reductive amination and arylation reactions to give compounds **5n-t**.

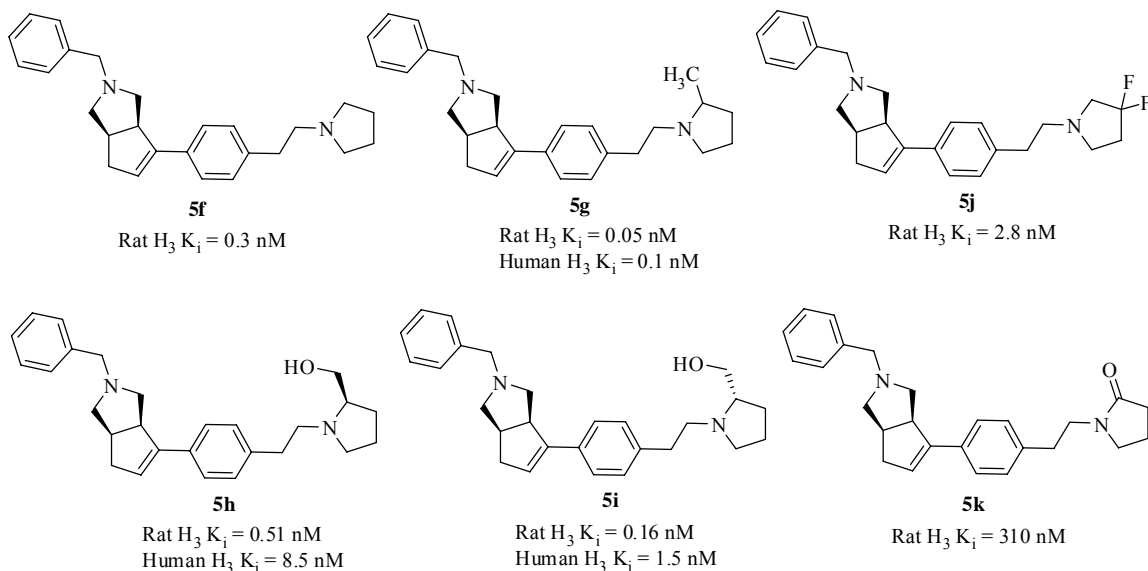
Figure 3



Scheme 1. Synthesis of target compounds **5**. Reagents and conditions: (a) CH₃CN, rt, 69%; (b) *n*-BuLi, THF, -78 °C, 64–66%; (c) HCl, *t*-PrOH, 60 °C, 98%; (d) MsCl, Et₃N, CH₂Cl₂, rt, 82%; (e) HNR₁R₂, Na₂CO₃, CH₃CN, microwave, 120 °C, 25–60%; (f) NH₄CHO₂, Pd(OH)₂/C, MeOH, 98%; (g) i—RCHO or R₂CO, NaBH(OAc)₃, AcOH, CH₂Cl₂, rt, 22–88%; or ii—ArBr, Pd(dba)₂, *t*-BuOK, DMSO, 175 °C, 8–31%.

Several compounds in the initial series showed potent binding, with the basicity of the nitrogens as well as the substitution patterns proving to be important for activity. A few select examples are shown in Figure 4.

Figure 4



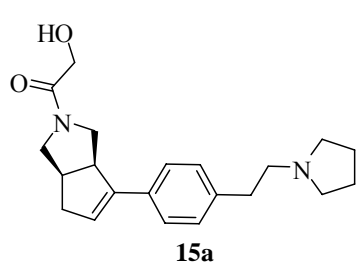
The phenethylpyrrolidine analog, **5f**, was about ten-fold more potent than the difluoropyrrolidine analog **5j** and 1000 times more potent than the amide (**5k**). The influence of substitution is evident in the fact that the methylpyrrolidine analog **5g** demonstrated 6-fold greater potency than the unsubstituted pyrrolidine analog (**5f**).

In addition, there seemed to be a preference for the *S*-hydroxymethyl in **5i** as compared to the *R*-isomer (**5h**).

Though the compounds shown in Figure 4 proved useful in terms of preliminary *in vivo* studies, they generally exhibited delayed absorption and long half-lives. Since the goal of this program was the development of a rapidly absorbed, fast-acting drug, focus next turned to the development of a new series aimed at achieving a more desirable PK profile. After determining that the basic phenethylamine portion was required for activity at the H₃ receptor, modifications were next made to the bicyclic core, incorporating functional groups such as ureas, amides, and sulfonamides.

In general, the urea and sulfonamide analogs were significantly less potent than the previously prepared diamines and the ureas continued the trend of long half-lives and fairly low oral bioavailability. The amides, however, fared better in that potency was retained and PK profiles improved considerably. Two select amide analogs and their corresponding binding affinities and PK data are shown in Figure 5.

Figure 5

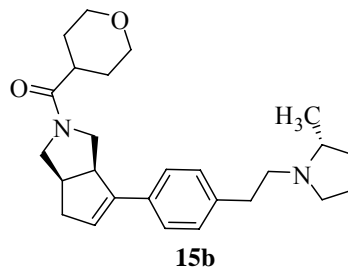


Rat H₃ K_i = 6 nM

t_{1/2} = 1.8 h

T_{max} = 0.6 h

%F = 39



Rat H₃ K_i = 0.7 nM

t_{1/2} = 2.5 h

T_{max} = 0.3 h

%F = 66

Both **15a** and **15b** displayed short half-lives, rapid absorption, and good bioavailability. In addition, the THP-amide analog, **15b**, showed potent inverse agonist activity (K_i = 4 nM) at the human H₃ receptor and >1000-fold selectivity for the H₃ receptor versus a panel of >100 human GPCRs (this panel also included the histamine H₁, H₂, and H₄ receptors). Finally, Dr. Santora mentioned that this compound demonstrated a good dose response in the rat drinking model with a minimum efficacious dose (MED) of 1 mg/kg, as well as low CYP and hERG inhibition.

References:

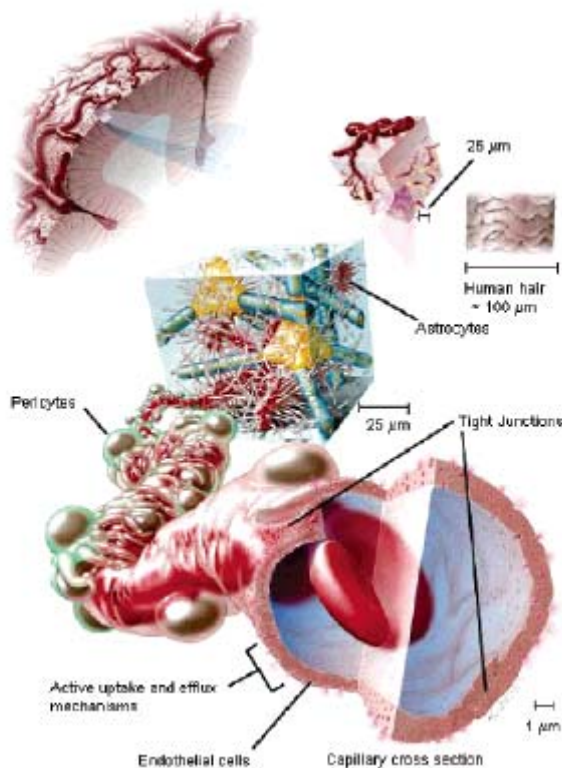
- 1) Santora, V.J. *et al. Bioorg. Med. Chem. Lett.* **2008**, *18*, 1490-1494.
- 2) Santora, V.J. *et al. Bioorg. Med. Chem. Lett.* **2008**, *18*, 4133-4136.

“Blood-Brain Barrier Permeability Considerations for CNS-Targeted Compound Design”

Stephen Hitchcock, (Amgen Inc.), Thousand Oaks, CA, USA.

The blood-brain barrier is estimated to be ~600 km in length and ~12 m² in surface area. Diffusion of molecules across this barrier is particularly difficult due to the continuous tight junctions (Figure 6). Transport proteins ensure the uptake of essential nutrients; however, efflux transport proteins recognize an array of diverse substrates and restrict their access to the brain.

Figure 6: Blood-Brain Barrier



A number of studies have attempted to link physicochemical properties of compounds with their ability to cross the blood-brain barrier. Certainly, lipophilicity plays a role, but it was suggested that there has possibly been too much emphasis on optimizing this single property at the expense of other considerations. Overemphasis on lipophilicity and its affect on passive diffusion fails to account for the influence of active transport.

A few years ago, a study was performed which compared a set of 48 drugs for CNS indications with a set of 45 drugs for non-CNS indications, investigating their P-gp substrate profiles and apparent permeability. For CNS delivery, a drug should ideally have an *in vitro* passive permeability > 150 nm/s and not be a good P-gp substrate (B→A/A→B ratio < 2.5). Only 4.2% of the CNS drugs (2 of 48) had passive

permeability values <150 nm/s compared to 28.9% of the non-CNS drugs (13 of 45). Also, the CNS drug set (7 of 48, 14.6%) had a three-fold lower incidence of P-gp-mediated efflux than the non-CNS drug set (19 of 45, 42.2%).

Analysis revealed that the CNS drugs had fewer hydrogen bond donors, lower polar surface area, higher calculated log P values, and fewer rotatable bonds compared to the non-CNS compounds (the mean molecular weights were approximately the same for both groups). Interestingly, Dr. Hitchcock noted that hydrogen bond donors seem to be more influential than hydrogen bond acceptors.

Finally, Dr. Hitchcock mentioned that their strategy often involves trying to predict BBB penetration and designing CNS-preferred compounds even before compound screening takes place. Figure 7 shows a number of ranges for physicochemical properties that may increase the probability of attaining improved BBB permeability.

Figure 7

property	top 25 CNS drugs mean values	suggested limits	% of top 25 CNS drugs in suggested range	preferred range	% of top 25 CNS drugs in preferred range
PSA (Å ²)	47	<90	96	<70	76
HBD	0.8	<3	100	0–1	92
cLogP	2.8	2–5	68	2–4	52
clogD (pH 7.4)	2.1	2–5	61	2–4	61
MW	293	<500	100	<450	100

References:

- 1) Hitchcock, S.A and Pennington, L.D. *J. Med. Chem.* **2006**, *49*, 7559-7583.
- 2) Polli, J.W. *et al. J. Pharmacol. Exp. Ther.* **2002**, *303*, 1029-1037.

“Design of CNS Penetrant Bradykinin Antagonists”

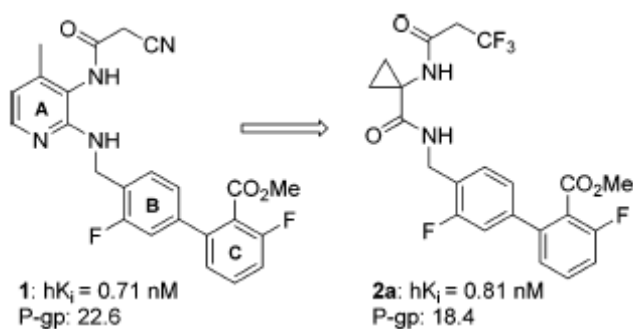
Scott Kuduk, (Merck), Westpoint, PA, USA.

Bradykinin peptides are rapidly produced in the plasma following tissue injury and produce a variety of physiological effects, including pain and inflammation. These effects are regulated by two known GPCRs, designated B₁ and B₂. It is believed that the B₂ receptor is responsible for the initial acute pain response and is mediated by the peptides bradykinin and kallidin. Their corresponding metabolites serve as agonists for the B₁ receptor, which is induced in the hours following the injury. Animal models have subsequently shown that bradykinin B₁ receptor antagonists are able to attenuate response to painful stimuli. Many of the B₁ receptor mediated effects involve peripheral mechanisms; however, this receptor is also expressed in the CNS, suggesting a central

component in pain perception. Dr. Kuduk and co-workers have theorized that CNS B₁ receptor antagonists may prove more efficacious than peripheral B₁ antagonists in treating arthritis, painful neuromas (nerve cell tumors), etc.

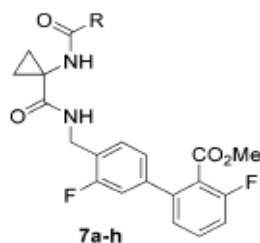
Figure 8 shows one of the group's initial leads, compound **1**, which exhibited a high affinity for the human B₁ receptor. However, the 2, 3-diaminopyridine core led to high levels of bioactivation both in vitro and in vivo. When that core was replaced with a cyclopropylamide, compound **2** retained the desired activity and displayed a number of promising pharmacokinetic properties; unfortunately, this analog proved to be a significant substrate for P-gp mediated efflux.

Figure 8



In an effort to reduce the affinity for P-gp, the trifluoropropionamide was replaced with various amides and the most promising proved to be a series of polyhaloacetamides as shown in Figure 9. All of the compounds shown proved to be selective for the B₁ receptor over B₂. Though some loss of binding affinity occurred for most of the analogs, overall the P-gp affinity was significantly reduced. In addition, the passive permeability was also determined for the set of compounds since compounds with low permeability tend to diminish the reliability that a P-gp transport assay can be used to predict CNS distribution. A passive permeability value of 15×10^{-6} cm/s or greater will typically indicate that the compound will exhibit good CNS penetration and all of the compounds shown met or exceeded this value.

Figure 9



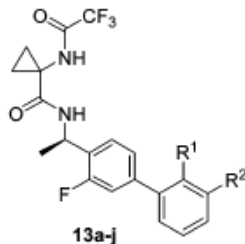
compound	R	hBK ₁ ^a	P-gp ^b	Papp ^c
2a	CH ₂ CF ₃	0.81	18.4	23
7a	CF ₂ CF ₃	2.95	2.2	31
7b	CF ₃	1.47	4.1	23
7c	CHF ₂	13.5	3.4	33
7d	CH ₃	11.6	6.3	24
7e	CHCl ₂	0.54	2.8	21
7f	CCH ₂ Cl ₂	119	nd	nd
7g	CClF ₂	2.5	2.8	29
7h	CHClF	2.8	nd	nd

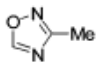
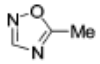
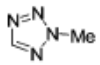
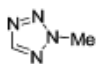
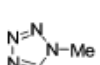
^a Values represent the numerical average of at least two experiments. Interassay variability was $\pm 25\%$ (K_i , nM). ^b MDR1 directional transport ratio (B/A)/(A/B). Values represent the average of three experiments, and interassay variability was $\pm 20\%$. ^c Passive permeability (10^{-6} cm/s).

In trying to rationalize why the polyacetamides proved to be less susceptible to P-gp transport, Dr. Kuduk and coworkers suggested that the fewer hydrogen bond acceptors a compound possesses, the less likely it is to be a substrate for P-gp. They feel that the electron deficient amide is a poorer hydrogen bond acceptor, making it less prone to recognition by P-gp.

The group chose to focus on the trifluoroacetamide group and turned their efforts toward fine-tuning the PK properties of the series. Hydrolysis of the methyl ester proved to be the major metabolic clearance pathway and a number of alterations to the C-ring ester and halogen substituents were made as summarized in Figure 10.

Figure 10



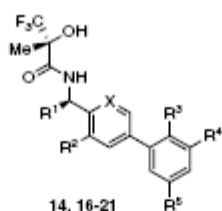
Compound	R ¹	R ²	hBK ₁ ^a (nM)	h FLIPR (nM)	P-gp ^b	P _{app} (10 ⁻⁶ cm/s) ^c	Rat PK ^d F%, t _{1/2} , Cl
2b	CO ₂ Me	F	0.13	nd	8.6	25	14, 1.44, 25
12b	CO ₂ Me	F	0.57	1.9	2.3	20	21, 0.5, 42
13a	CO ₂ Me	H	10.3	nd	2.2	34	nd
13b	CO ₂ Me	Cl	0.44	1.52	1.9	34	34, 0.4, 40
13c	CO ₂ Et	Cl	1.35	9.1	2.1	25	45, 1.1, 8.4
13d		F	0.51	0.89	5.6	37	27, 0.35, 28
13e		F	0.68	nd	3.7	28	44, 0.34, 27
13f		F	0.6	0.65	4	33	48, 0.7, 11
13g		Cl	0.66	nd	5.5	29	50, 0.7, 12
13h		F	62.5	nd	15.5	19	nd
13i	CF ₃	F	1.44	7.3	2	32	30, 2.6, 10
13j	COEt	Cl	1.95	nd	1.6	27	nd

Removal of the fluorine atom ortho to the ester resulted in a 20-fold loss in binding and had little impact on the P-gp affinity. Replacement with a chlorine atom, however, resulted in an improvement in both P-gp affinity and passive permeability, while maintaining a very high affinity for the B₁ receptor. In addition, this analog exhibited improved oral bioavailability and reduced clearance. Increasing the size of the ester resulted in a decrease in activity. Replacement with a bioisostere such as an oxadiazole maintained good binding affinity but, unfortunately, resulted in an increase in P-gp efflux. The same held true for tetrazoles and it has been suggested that this may be due to the additional nitrogen atoms serving as hydrogen bond acceptors (again referring to

their suggestion that the fewer hydrogen bond acceptors a compound possesses, the less likely it is to be a good P-gp substrate.)

Further exploration eventually resulted in the series of compounds shown in Figure 11, where the cyclopropylamino acid amide functionality was replaced by a simpler α -hydroxy amide. In addition, a nitrogen has been inserted into the B ring phenyl group.

Figure 11



Compound	R ¹	R ²	X	R ³	R ⁴	R ⁵	h K _i ^a (nM)	h FLIPR IC ₅₀ ^b (nM)	P _{gp} ratio	P _{app} ^b (10 ⁻⁶ cm/s)
14	H	F	CH	CO ₂ Me	F	H	24.5	43.6	1.6	32
16	Me	F	N	CO ₂ Me	Cl	Cl	0.35	3.93	1.6	23
17	Me	F	N		Cl	Cl	0.79	6.65	1.3	33
18	Me	F	N		F	Cl	0.66	6.65	1.7	35
19	Me	F	N		F	Cl	0.59	4.90	2.8	36
20	Me	Cl	N		F	Cl	0.43	—	1.8	26
21	Me	F	N		F	Cl	0.66	4.47	1.6	27

^a Values represent the numerical average of at least two experiments. Interassay variability was $\pm 10\%$ for the binding assay and $\pm 25\%$ for the FLIPR experiments.

^b Values represent the numerical average of at least three experiments. Interassay variability was $\pm 20\%$.

The analogs shown displayed subnanomolar binding affinities and a new bioisostere for the ester, a 3-methyl oxadiazole, lacked the P-gp affinity that the previously examined isosteres seemed to cause. Ultimately, compound **21** was chosen to progress to preclinical development and demonstrated an Occ₉₀ value of 140 nM (one of the lowest values determined to date). This value represents the concentration required to occupy 90% of the human B₁ receptors expressed in the rat CNS in a rat transgenic model. This compound has since advanced to clinical trials for the treatment of inflammatory pain.

References:

- 1) Kuduk, S.D. *et al. J. Med. Chem.* **2007**, *50*, 272-282.
- 2) Kuduk, S.D. *et al. Bioorg. Med. Chem. Lett.* **2008**, *18*, 716-720.