



**Trip Report for**

**“Second RSC/SCI Symposium: G-Protein Coupled Receptors (GPCRs)  
in Medicinal Chemistry”**

**Gothenburg, Sweden  
September 8-10, 2008**

**Kevin Fitzpatrick, Ph.D**

**December 4, 2008**

## AMRI Memorandum

TO: Barnes, Keith; Earley, Bill; Gauuan, Joli; Geiss, Bill; Guaciario, 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; Khmelnitsky, Yuri; Cotterill, Ian

FROM: Kevin Fitzpatrick, Ph.D.

DATE: September 8-10, 2008

RE: "Second RSC/SCI Symposium: G-Protein Coupled Receptors (GPCRs) in Medicinal Chemistry," Gothenburg, Sweden.

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**Abstract:** All work, presented herein is for review purposes only and remains the sole intellectual property of the originating authors and their respective institutions.

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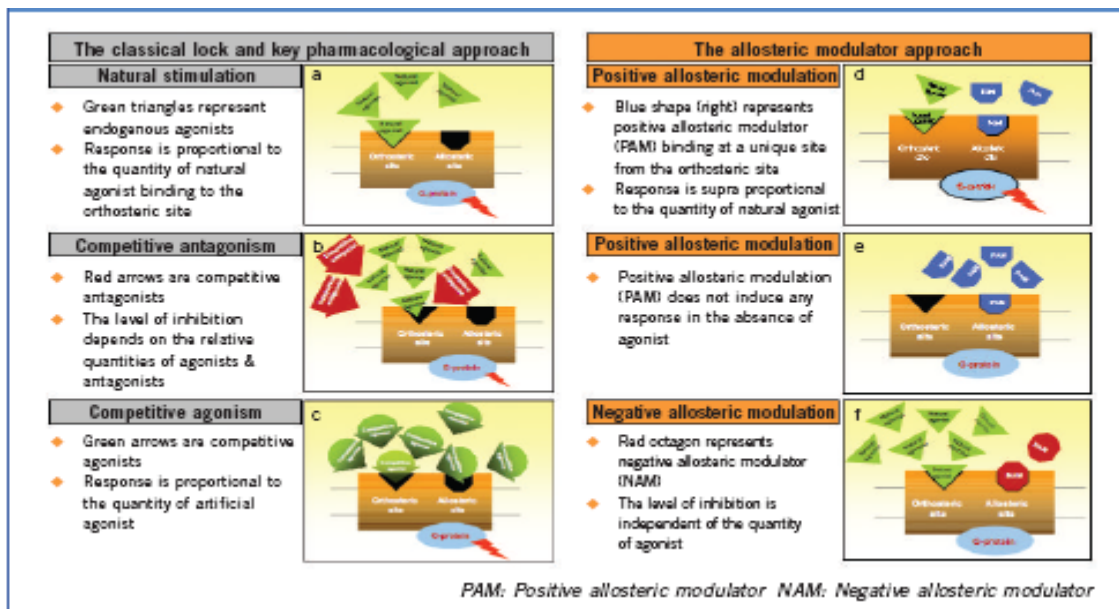
### **"Allosteric Modulators of GPCRs: Focus on a Novel Series of Highly Selective mGluR5 Negative Allosteric Modulators,"**

*Jean Phillipe Rocher, Ph.D., (Addex Pharmaceuticals S.A), Geneva, Switzerland.*

This talk by Dr. Rocher was very interesting in which the benefits of allosteric modulators were discussed.

Traditionally, approaches to drug discovery have focused on the use of small molecule competitive agonists/antagonists to modulate the activity at the target receptor binding site (orthosteric binding site) normally controlled by the endogenous ligand. Significant challenges remain to produce therapeutically useful GPCR small molecule competitive modulators due to the lack of receptor specificity or the complex interactions of the endogenous ligand with the receptors, often leading to undesirable side effects. Recent advances in allosteric modulators, particularly in the GPCR class of receptors where the allosteric sites are less conserved, have allowed the amelioration of side-effects by preserving normal physiological signaling patterns (Figure 1).

Figure 1



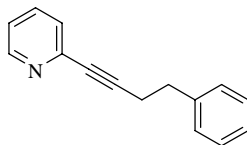
Allosteric modulation (Figure 1) –A Novel Approach (reproduced from Innovations in Pharmaceutical Technology Journal available through Addex Pharmaceutical’s web site at <http://www.addexpharma.com/allosteric-modulation>).

Positive allosteric modulators (PAM) binding at the allosteric site in the presence of endogenous ligand (or competitive agonists) binding at the orthosteric site result in >100% biological response as compared with the endogenous ligand alone. However, in the absence of agonist/endogenous ligand no biological response occurs. Negative allosteric modulators (NAM) on the other hand can inhibit biological response to sub basal levels; the degree of inhibition is independent of agonist/endogenous ligand concentration.

Therefore full and or partial allosteric modulators may allow the receptor activity to be potentiated to the desired level while minimizing undesirable side effects.

Dr Rocher went on to talk about one of the programs at Addex Pharmaceuticals involving NAMs of mGluR5 receptors. These compounds represent potential therapies for depression, movement disorders such as Parkinson’s disease, neuroprotection (stroke and head trauma) as well as addiction. The initial hit **ADX10728** from a HTS screen is shown below (Figure 2).

**Figure 2**



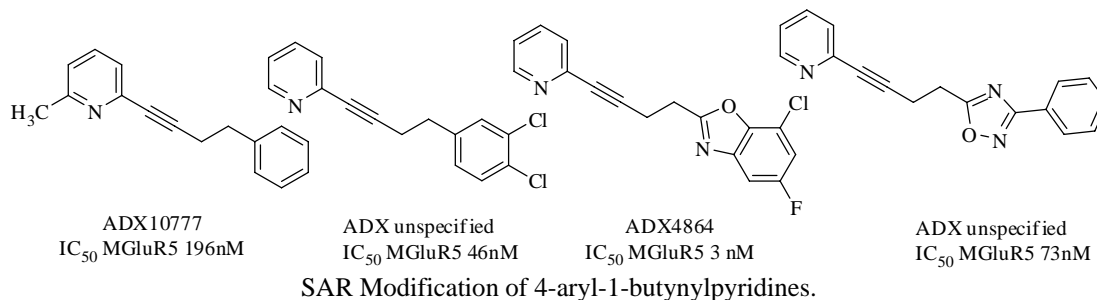
ADX10728

IC<sub>50</sub> Rat mGluR<sub>5</sub> = 120 nM  
Initial Lead from mGluR5 HTS screen

Subsequent SAR elaboration of **ADX10728** indicated that the pyridine functionality by suitable surrogates (pyrimidine, benzoazole) could not be replaced without dramatic loss of activity. Also, pyridine functionalities performed well in subsequent second generation analog metabolic stability studies.

The ethylene spacer between the alkyne and the aromatic rings was also examined. Use of either a methylene or propylene spacer was found to have much inferior affinities. The right hand side of the molecule was examined and found be more amenable to modifications (Figure 3).

**Figure 3**



These SAR modifications resulted in structure **ADX48621** which had a suitable pharmacokinetic properties (IC<sub>50</sub> Rat mGluR<sub>5</sub> = 21 nM, tPSA 28, cLog P 2.37), good metabolic stability as well as functional activity profile. The structure of **ADX48621** was not disclosed but the following comment (below) was described on the Addex Pharmaceuticals' website regarding the status of **ADX48621**.

“**ADX48621** is a metabotropic glutamate receptor 5 (mGluR5) negative allosteric modulator (NAM), which may have potential in multiple indications. The lead indication for the product is levodopa associated dyskinesia in Parkinson's disease. **ADX48621** also is a backup for **ADX10059**, which is in Phase II development for GERD & migraine. **ADX48621** has completed an initial Phase I trial. In this first-in-man single ascending dose study, the orally administered product was well tolerated. The **ADX48621** Phase I

program is scheduled to be completed in 2008. Phase **II** proof of concept studies in levodopa associated dyskinesia in Parkinson's patients are schedule to start in the first half of 2009.”

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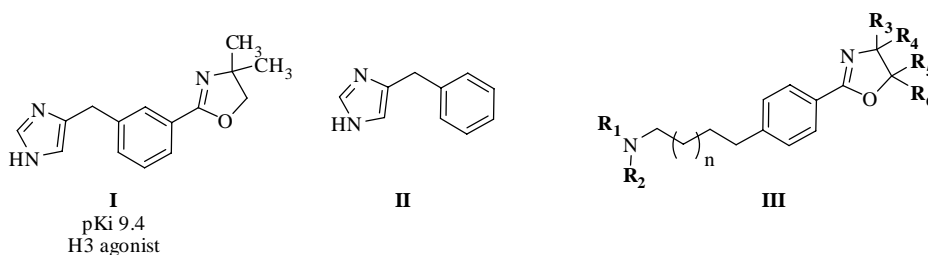
**“A Journey from Agonists to Inverse Agonists of the Histamine H<sub>3</sub> Receptor,”**

*Frederic Denome, Ph.D., (UCB), Braine L'Alleud, Belgium.*

The Histamine H<sub>3</sub> receptor is a less clinically validated target than The H<sub>1</sub> and H<sub>2</sub> receptors. Recently, H<sub>3</sub> inverse agonists have advanced to the clinical phase for the treatment of CNS disorders such as narcolepsy, ADHD and dementia, while H<sub>3</sub> agonists may be useful for indications in food-intake regulation and obesity.

Dr Denome and co-workers at UCB carried out a screening campaign where the initial hit **I** allowed the elaboration to two chemical families **II** and **III** (Figure 4).

**Figure 4**



Family of H<sub>3</sub> agonists/ inverse H<sub>3</sub> agonists developed by UCB

Altering the oxazoline side chain of **I** led to the discovery of a family of H<sub>3</sub> agonists **II** with affinities in the nM range.

Replacement of the imidazole of **I** with cyclic/acyclic aminoalkyl groups led to another series **III** of H<sub>3</sub> inverse agonists. These compounds were in good agreement with a pharmacophores model devised by workers at F-Hoffmann la Roche (Figure 5).<sup>1</sup>

Figure 5

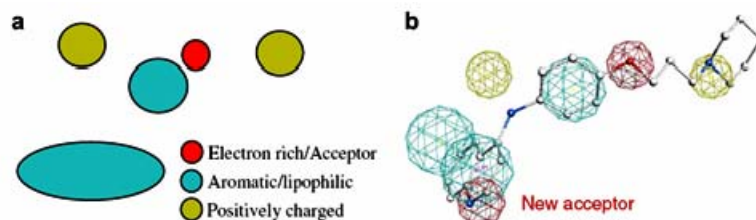
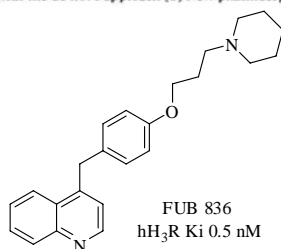


Figure 1. (a) Pharmacophore model used with the de novo approach (b) New pharmacophore model used in this study with FUB 836 fitted



Homology Model of H<sub>3</sub> receptor for **FUB 836** devised by workers at F.Hoffmann-La Roche and outlined by M. Nettekoven *et al* in Bioorg. Med. Chem. Lett. **2008**, *18*, 4377-4379.

These H<sub>3</sub> inverse agonists display anti-amnesiac properties in a mouse cognition model and are currently under further investigation.

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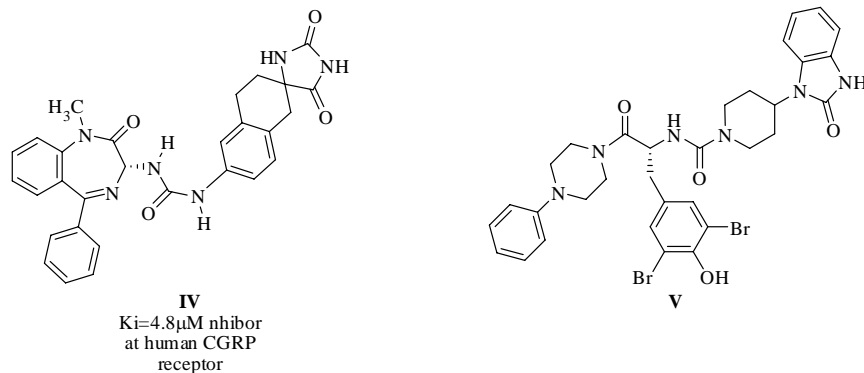
### “The Discovery of Telcagepant (MK-0974) an Orally Active Calcitonin Gene-Related Peptide Receptor Antagonist for the Treatment of Migraine,”

*Theresa M Williams, Ph.D., (Merck), West Pont PA, USA.*

Calcitonin Gene-Related Peptide (CGRP) is a 37 amino acid neuropeptide implicated in the pathogenesis of migraine headache. CGRP antagonists do not directly induce vasoconstriction and therefore could offer clinical advantage over the current gold standard triptan class of 5-HT<sub>1B/1D</sub> receptor agonists (Imitrex<sup>®</sup> and Treximet<sup>®</sup>).

The initial benzodiazapinone hit **IV** was found from a HTS screening campaign (Figure 6). This compound although not particularly potent was unique compared with the published CGRP antagonist **V**.

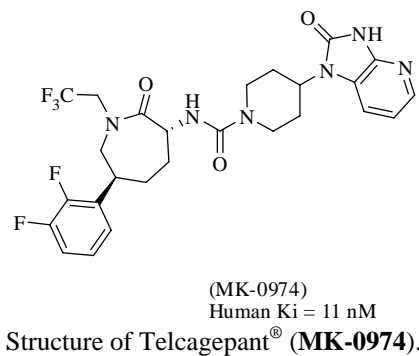
**Figure 6**



Initial CGRP Antagonists **IV** and **V**.

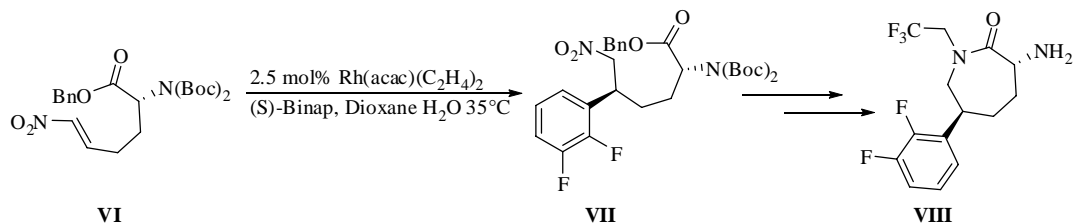
Hybrid structures of **IV** and **V** were prepared and subsequent extensive SAR analysis led to a (3*R*)-amino-(6*S*)-phenylcaprolactam moiety replacement for privileged structure **V** resulting in orally active Telcagepant<sup>®</sup>, **MK-0974** (Figure 7).<sup>2</sup>

**Figure 7**



The (3*R*)-amino-(6*S*)-phenylcaprolactam moiety required a viable multi-gram route to be developed. The key step involved a Hayasji-Miyaura catalysed arylboronic acid addition to nitroalkene **VI** which has been recently described (Figure 8).<sup>3</sup>

**Figure 8**



Asymmetric Hayasji-Miyaura catalysed arylboronic acid addition to nitroalkene **VI**.

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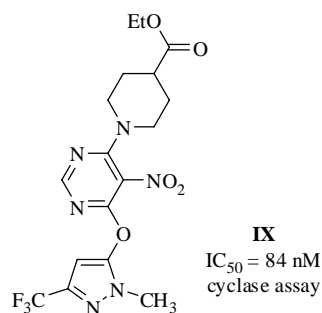
## “Discovery and Pharmacological Evaluation of Agonists of the Orphan Receptor GDIR (GPR119),”

(Graeme Semple Arena Pharmaceuticals).

This talk investigated the approach of identifying a novel class A  $G\alpha_s$ -coupled GPCR that would have similar  $\beta$ -cell expression and G-protein function as the GLP-1 receptor (glucagon-like peptide receptor 1) injectable anti diabetic peptide agonists such as exenatide<sup>®</sup>. This approach identified GPR119 (recently termed glucose-dependent insulinotropic receptor or GDIR) as a constitutively active,  $\beta$ -expressed receptor capable of elevating intracellular cAMP levels in either transfected CHO cells or pancreatic  $\beta$ -cell lines.

Initial screening using a 96 well plate Flashplate membrane cyclase assay capable of distinguishing both agonist and inverse agonist identified hit **IX** as an inverse agonist (Figure 9).<sup>4</sup>

**Figure 9**

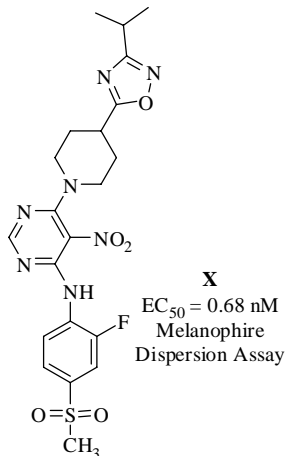


Initial screening hit **IX** as an inverse agonist of GDIR.

Although compound **IX** had significant issues including the fact that it was an inverse agonist rather than the required agonist as well as having an undesirable ester and nitro functionalities in the molecule, the group at Arena Pharmaceuticals set about modifying compound **IX** with a view to deriving a suitable agonist of GDIR.

After some level of manipulation a suitable agonist **X** was discovered (Figure 10).

**Figure 10**



Compound **X** an agonist of GDIR

Profiling of compound **X** indicated the compound to be a highly selective ligand for GDIR with no off-target liabilities against a panel; of 76 receptors (Cerep) as well as 140 known and orphan GPCRs in-house, no CYP nor <10 $\mu$ M activity at the hERG channel. Furthermore compound **X** did not show activity against dipeptidyl peptidase 4 (DPP4) a well validated target for the treatment of diabetes. To date compound **X** has proven to be an excellent tool compound for target validation studies in mice and ultimately may make GDIR a more attractive target for further drug development.

<sup>1</sup> Roche, O.; Nettekoven, M.; Vifian, W.; Sarmiento R. M. R.; *Biorg. Med. Chem. Lett.* **2008**, *18*, 4377-4379 and references cited therein.

<sup>2</sup>(a) Paone, D.V.; Shaw, A. W.; Nguyen, D. N.; Burgey, C. S.; Deng, J. Z.; Kane, S. A.; Koblan, K. S.; Salvatore, C. A.; Mosser, S. D.; Johnston, V. K.; Wong, B. K.; Miller-Stein, C. M.; Hershey, J. C.; Graham, S. L.; Vacca, J. P. and Williams, T. M. *J. Med. Chem.* **2007**, *50*, 5564-5567; (b) Williams, T. M.; Stump, C. A.; Nguyen, Quigley, A. G.; Bell, I. M.; Gallicchio, S. N.; Zartman, B.; Wan, B-L.; Penna, K. D.; Kunapili, P.; Kane, S. A.; Koblan, K. S.; Mosser, S. D.; Rutledge, R. Z.; Salvatore, C. A.; Fay, J. F.; Vacca, J. P. and Graham, S. L. *Biorg. Med. Chem. Lett.* **2006**, *16*, 2595-2598.

<sup>3</sup> Burgey, C. S.; Paone, D.V.; Shaw, A. W.; Deng, J. Z.; Nguyen, D. N.; Potteiger, C. M.; Graham, S. L.; Vacca, J. P. and Williams, T. M. *Org. Lett.* **2008**, *10*, 3235-3238.

<sup>4</sup> Semple, G.; Fioravanti, B.; Pereira, G.; Calderon, I.; Uy, J.; Choi, K.; Xiong, Y.; Ren, A.; Morgan, M.; Dave, V.; Thomsen, W.; Unett, D. J.; Xing, C.; Bossie, S.; Carroll, C.; Chu, Z-L.; Grottick, A. J.; Hauser, E. K.; Leonard, J. and Jones, R. M. *J. Med. Chem.* **2008**, *51*, 5172-5175 and references cited therein.