Assembly of small molecule PAC_1 receptor antagonists as a potential anxiolytic

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Recent work done at the University of Vermont has implicated the neuropeptide pituitary adenylate cyclase-activating peptide (PACAP) and a corresponding receptor, PAC_1 that is localized in the bed nucleus of the stria terminalis (BNST), as possible players in the development of stress-related anxiety. (Hammack, et al., 2009) Here we explore the synthesis and preparation of several small molecule antagonists to the PAC_1 receptor to determine whether receptor modulation will attenuate anxiety-like behavior. A common feature of these molecules is an acyl hydrazide linker that connects a substituted aryl ring with an indole ring. The indole ring acts as a linker and in turn is substituted on the indole nitrogen with a functionalized benzyl ring. To date, eleven analogues have been prepared and qualitatively analyzed to determine relative binding affinities using a western blot assay. Quantitative analysis is underway using radioactive isoptope binding assays to determine the compounds with the best receptor affinity. *In vivo* testing will take place in rats or mice using a light enhanced startle paradigm with intracranial drug administration once the best-matched molecules are determined. It is anticipated that there will be an observable reduction in stress-based anxiety for subjects that received the PAC_1 antagonist. Analysis of *in vivo* and *in vitro* testing will provide insight into possible creation of more potent analogues, as well as the role of PACAP in the development of stress-related anxiety.

Hammack, S. E., Cheung, J., Rhodes, K. M., Schutz, K. C., Falls, W. A., Brass, K. M., et al. (2009). *Psychoneuroendocrinology, 34*, 833-843.