

ADRENOMEDULLIN: A NEW TARGET FOR THE DESIGN AND SYNTHESIS OF DRUGS

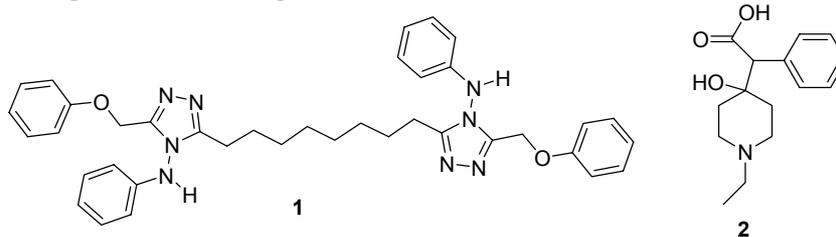
S. Martín-Santamaría,^a M. A. García,^a M. Cacho,^a J. J. Rodríguez,^a V. Roldós,^a M. Julián,^a A. Martínez,^b A. Ramos,^a B. de Pascual-Teresa.^a

^aDepartamento de Química. Facultad de Farmacia, Universidad San Pablo CEU, Urbanización Montepríncipe, 28668-Boadilla del Monte, Madrid, Spain

^bInstituto de Neurobiología Ramón y Cajal, Av. Doctor Arce, 37. 28002-Madrid, Spain.

Adrenomedullin (AM) is a biologically active peptide isolated in 1993 from extracts of a human pheochromocytoma cell line, a cancer derived from the adrenal gland and whose function is related to several diseases, such as diabetes, hypertension and cancer.[1] AM levels are dysregulated in many human pathologies such as hypertension, heart failure, sepsis, cancer or diabetes. Several studies have demonstrated that changes in AM levels have opposite effects depending on the particular disease studied. Thus, while AM is a protective agent against cardiovascular disorders, it behaves as a stimulating factor in other pathologies such as cancer and diabetes.[2] Therefore, AM is a new and promising target in the development of molecules which, through their ability to positively or negatively regulate AM activity, could be used in the treatment of these pathologies.

In a recent study of High Throughput Screening for the search of positive and negative modulators of AM, several compounds have been detected, among them positive modulator **1** and negative modulator **2**.[3] Structurally related families of compounds, available from the small molecules NCI library, have been evaluated together with new series which have been synthesized in our laboratory, following a classical approach of molecular modulation. Three-dimensional structure-activity relationship 3D-QSAR analysis techniques, together with conformational and molecular dynamics studies have also been performed, in order to rationalize the chemical aspects required to bind AM, and to scrutinize the anchoring points that compose the binding site. This approach will help us in the further design of new analogues.



[1] Kitamura, K.; Kangawa, K.; Kawamoto, M.; Ichiki, Y.; Nakamura, S.; Matsuo, H.; Eto, T. *Biochem. Biophys. Res. Commun.* **1993**, *192*, 553-560.

[2] a) López, J.; Martínez, A. *Int. Rev. Cytol.* **2002**, *221*, 1-92. b) Dobrzynski, E.; Wang, C.; Chao, J.; Chao, L. *Hypertension* **2000**, *36*, 995-1001.

[3] Martínez, A.; Julián, M.; Bregonzio, C.; Notari, L.; Moody, T.; Cuttita, F. *Endocrinology* **2004**, *145*, 3858-3865.

[4] García, M. A.; Martín-Santamaría, S.; Cacho, M.; Moreno de la Llave, F.; Julián, M.; Martínez, A.; de Pascual-Teresa, B.; Ramos, A. *J. Med. Chem.* **2005**, submitted.