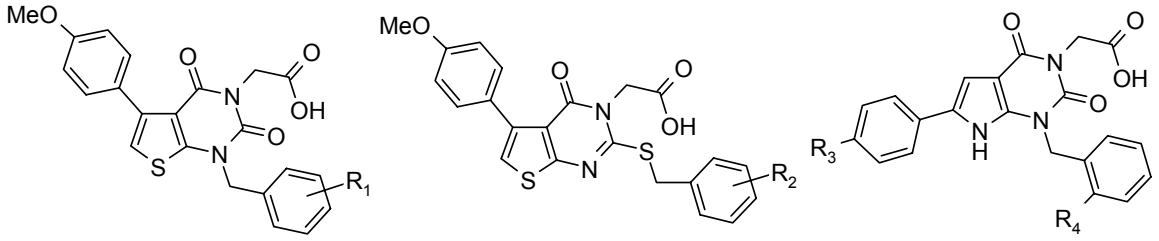
DESIGN AND SYNTHESIS OF NOVEL POTENTIAL LIGANDS FOR ENDOTHELIN RECEPTORS

Valeria Pittalà[a], Maria Modica[a], Giuseppe Romeo[a], Luisa Materia[a], Loredana Salerno[a], Maria Angela Siracusa[a], Ilario Mereghetti[b], Alfredo Cagnotto[b], Tiziana Mennini[b], and Filippo Russo[a]

[a]Dipartimento di Scienze Farmaceutiche, Università di Catania, v.le A. Doria 6, 95125 Catania, Italy
[b]Istituto di Ricerche Farmacologiche " Mario Negri ", via Eritrea 62, 20157 Milano, Italy

The endothelin (ET) system has been extensively studied over the last several years for its key role in physiological functions in normal tissue, acting as modulators of vasomotor tone, tissue differentiation, development, cell proliferation and hormone production and for its involvement in a variety of pathological conditions such us high blood pressure, pulmonary hypertension, acute myocardial infarction, congestive heart failure, renal failure and atherosclerosis. ETs comprise a family of three small peptides (ET-1, ET-2, ET-3) that exert their activities via specific seven-transmembrane, G-protein coupled receptors. To date two receptor subtypes, ET_A and ET_B, have been identified and cloned. Several literature reports indicate that blocking the ET receptors is a novel and powerful therapeutic approach for the treatment of the aforementioned diseases. In the last years, our research group had been involved in the synthesis of novel ligands for endothelin receptors [1-2].



Recently Cho et al. reported the synthesis of some thieno[2,3-*d*]pyrimidine-3-acetic acid derivatives as a new class of endothelin receptor ligands [3]. We now report the synthesis of novel thienopyrimidine and pyrrolopyrimidine derivatives as new ligands for endothelin receptors. Binding assays for the synthesized compounds were performed on recombinant human endothelin receptors (ET_{Ah} and ET_{Bh}) expressed in CHO-K1 cells. Complete binding profile for these new ligands will be reported at the symposium.

[1] V. Pittalà, M. Modica, G. Romeo, L. Materia, L. Salerno, M. Siracusa, F. Russo, A. Cagnotto, T. Mennini. Acidi (E)-[(1*H*-Indol-3-il)metilene]benzeneacetici: una Nuova Classe di Ligandi per i Recettori delle Endoteline. *XXVII Convegno Nazionale della Divisione di Chimica Farmaceutica della Società Chimica Italiana.* Pisa, Italia, 6-10 Settembre **2004**, P-149.
[2] V. Pittalà, M. Modica, G. Romeo, L. Materia, F. Guerrera, L. Salerno, M. Siracusa, I. Mereghetti, A. Cagnotto, T. Mennini, F. Russo. Searching for Novel Endothelin Receptors Ligands. *Joint Meeting on Medicinal Chemistry,* Krakow, Poland, 15-18 Ottobre **2003**, P55.
[3] N. Cho, Y. Nara, M. Harada, T. Sugo, Y. Masuda, A. Abe, K. Kusumoto, Y. Itoh, T. Ohtaki, T. Watanabe, S. Furuya. *Chem. Pharm. Bull.* 46, **1998**, 1724-1737.