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De Novo Conception of Small Molecule Modulators Based on Endogenous Peptide Ligands: Pyrrolodiazepin-2-one γ-Turn Mimics That Differentially Modulate Urotensin II Receptor-Mediated Vasoconstriction *ex Vivo*

Julien Dufour-Gallant,[†,‡] David Chatenet,*[,‡] and William D. Lubell*[,†]

[†]Département de Chimie, Université de Montréal, C.P. 6128, Succursale Centre-Ville, Montréal, Québec H3C 3J7, Canada

[‡]INRS—Institut Armand-Frappier, Groupe de Recherche en Ingénierie des Peptides et en Pharmacothérapie (GRIPP), Université du Québec, Ville de Laval, Québec H7V 1B7, Canada

Supporting Information

ABSTRACT: A proof-of-concept library of pyrrolodiazepinone small molecules was designed based on the Bip-Lys-Tyr motif found in a recently described modulator of the urotensinergic system. Solid-phase synthesis provided 13 analogues, which were tested for their ability to modulate selectively and differentially the potency (EC_{50}) and efficacy (E_{max}) of hUII and URP *ex vivo* in a rat aortic ring bioassay. Notably, at 14 μM, pyrrolodiazepinone *R*-**4a** inhibited completely hUII-induced contractions and increased URP-associated vasoconstriction. Pyrrolodiazepinone *R*-**4a** represents, to the best of our knowledge, a first-in-class small molecule that exerts a probe-dependent effect on hUII and URP biological activities and proves that UT modulators of the urotensin II receptor (UT) can be rationally designed. The importance of the UT system in the pathogenesis and progression of cardiovascular diseases highlights the utility of pyrrolodiazepinones such as *R*-**4a**, which exhibit promising potential as tools for differentiating the respective roles, signaling pathways, and phenotypic outcomes of UII and URP in the UT system.