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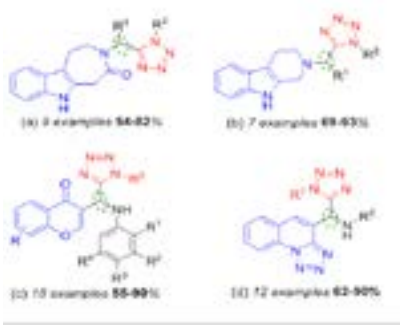
Rocío Gámez-Montaño

University of Guanajuato, México

Synthesis of methane-linked *bis*-heterocycles containing the 1,5-disubstituted-tetrazole moiety via Ugi-azide based methodologies

Bis-heterocycles are structurally complex compounds having two linked, fused, merged or bound heterocyclic frameworks, which have attracted much attention of synthetic community due to their potential applications in agrochemistry, optics, material science, and medicinal chemistry. Moreover, 1,5-disubstituted-tetrazoles (1,5-DS-T's) are known as resistant bioisosteres of the *Cis*-amide bond of peptides, which are present in numerous valuable drugs like the 3rd generation cephalosporin antibiotic Latamoxef. Besides, 1,5-DS-T's are suitable precursors of a plethora of prime ligands and chelating agents. Thus, according to our ongoing program to develop short and versatile Ugi-azide based methodologies toward a variety of methane-linked bis-heterocycles containing the 1,5-DS-T moiety, we herein disclose our most recent published results. In 2013, we described the synthesis of azepino[4,5-*b*]indol-4-one-1,5-1H-tetrazoles in two steps: i) one pot (Ugi-azide/*N*-acylation/S_N2), and ii) free radical mediated cyclization, as well as *in silico* studies as 5-Ht_6R ligands using docking techniques (Figure 1a). In 2014, we reported the synthesis of 2,3,4,9-tetrahydro-β-carboline-1,5-1H-tetrazoles by a one pot Ugi-azide/Pictet-Spengler process (Figure 1b). In 2014, we reported the synthesis of chromen-4-ones-1,5-1H-tetrazoles via the Ugi-azide reaction and *in vitro* studies of antiparasitic properties against *E. histolytica, G. lamblia* and *T. vaginalis*. Then, in 2015 we extended this work synthesizing some fluorinated analogs, which together with the previously synthesized bis-heterocycles were assayed *in vitro* against *P. aeruginosa, S. aureus, S. schenckii, C. albicans* and *C. tropicalis* (Figure 1c). Finally, in 2016, we reported the synthesis of novel 3-tetrazolyl-tetrazolo[1,5-α]quinolines via a novel one pot Ugi-azide/S_NAr/ring-chain azido-tautomerization process (Figure 1d). As seen, the Ugi-azide reaction or its combination with further cyclization processes allows the rapid synthesis of a variety of methane-linked bis-heterocycles with potential application mainly in medicinal chemistry because 1,5-DS-T framework has been suitably combined with other heterocyclic systems, which are present in numerous bioactive products, even in commercial drugs.



Biography

Rocío Gámez-Montaño got her PhD in 2001 under the guidance of Professor Raymundo Cruz-Almanza in UNAM, CDMX, México. After a Post-doctoral fellowship in 2002 under the guidance of Professor Jieping Zhu at Gif-Sur-Yvette, France, she joined the University of Guanajuato, México, where, she is a Full-time Researcher-Professor (Class B). Her scientific interest includes the synthesis of heterocycles and poly-heterocycles via MCR, *in vitro* and *in silico* studies of biological properties, applications in optics, as well as study of reaction mechanisms.

rociogm@ugto.mx