Design and synthesis of cyclic dinucleotide analogues containing triazolyl C-nucleosides

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Abstract

Natural Cyclic dinucleotide (CDN) is the secondary messenger involving bacterial hemostasis, human innate immunity, and bacterial antiphage immunity. Synthetic CDN and its analogues are key molecular probes and potential immunotherapeutics. Several CDN analogues are under clinical research for antitumor immunotherapy. A myriad of synthetic methods has been developed and reported to prepare CDN and its analogues. Chemical modifications of phosphate, ribose, and nucleo-base of natural CDN have been investigated using solid phase or solution phase strategy. However, most of the protocols take multisteps and only one CDN or its analogue could be prepared in one time. In this paper, a strategy based on a macrocyclic ribose phosphate skeleton containing a 1'-alkynyl group was designed and developed to prepare CDN analogues containing triazolyl C-nucleosides by Click chemistry. Combinatorial application of Click chemistry and sulfonylation cascade to the macrocyclic skeleton extended the diversity of CDN analogues. This macrocyclic skeleton strategy could rapidly and efficiently provide CDN analogues to facilitate the research of microbiology, immunology, and the development of immunotherapeutics.

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