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# Synthesis of C8–C8/C2–C8-linked triazolo pyrrolobenzodiazepine dimers by employing 'click' chemistry and their DNA-binding affinity

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**Abstract**

A series of 1,2,3-triazole-containing pyrrolo[2,1-*c*][1,4]benzodiazepine dimers have been prepared efficiently by employing a 'click' chemistry protocol. This method involves 1,3-dipolar cycloaddition of terminal alkynes with organic azides using a Cu(I)-catalyst. Further, these molecules exhibited interesting DNA-binding affinity profiles.


*Keywords:* Pyrrolo[2,1-*c*][1,4]benzodiazepines; 1,2,3-Triazoles; DNA-binding affinity; 'Click' chemistry

DNA interstrand cross-linking agents have attracted the attention of many researchers because of their potent anticancer activity as exhibited in most compounds with a pyrrolobenzodiazepine (PBD) ring system.[1] There has been considerable interest in the past few years in the design and synthesis of symmetrical and unsymmetrical cross-linking agents, particularly those based on PBDs.[2] In the literature, a number of PBD dimers have been designed and synthesized that exhibit varying degrees of cytotoxicity and DNA cross-linking activity.[3] The PBD antitumor antibiotics are produced by various *Streptomyces* species and are generally referred to as the anthramycin family, which comprise of representative members including DC-81 (**1**), anthramycin, tomaymycin, and chicamycin. These PBD dimers are linked through different positions such as *A*-C7/*A*-C7′, *A*-C8/*A*-C8′, and *C*-C2/*C*-C2′, among these *A*-C8/*A*-C8-linked PBD dimers have shown promising cytotoxicity and efficient cross-linking properties. Further, extensive studies have been carried out on both the solution[4] and solid-phase[5] synthesis of PBDs, and a sound understanding of structure–activity relationships within the family has been developed.[6] In a recent development, Thurston and co-workers[7] tethered two DC-81 units at the C8-positions[8] by using different alkane spacers to give bisfunctional–alkylating agents capable of cross-linking DNA. One of these dimers, DSB-120 **2a**, forms an irreversible interstrand cross-link between two guanine bases within the minor groove of DNA via their exocyclic N2 atoms and spans six base pairs, thereby actively recognizing a central 5′-GATC sequence.[9] Moreover, in this laboratory, mixed imine–amide PBD dimers such as **2b** have been designed and synthesized which shows efficient DNA binding ability with significant anticancer activity in a number of human cancer cell lines.[10] In continuation of these efforts toward the design and synthesis of nitrogen-rich PBD dimer analogues, as well as the development of new synthetic strategies,[11] we became interested in exploring the DNA-binding ability of C8–C8/C2–C8-linked 1,2,3-triazole-containing PBD dimers (Fig. 1).

1,2,3-Triazoles are heterocycles with a wide range of applications that are receiving growing attention in biological activity studies and are employed widely as pharmaceuticals and agrochemicals.[12] Earlier studies have revealed that the azole group due to the aromaticity and lone-pair electrons provides great potential for several

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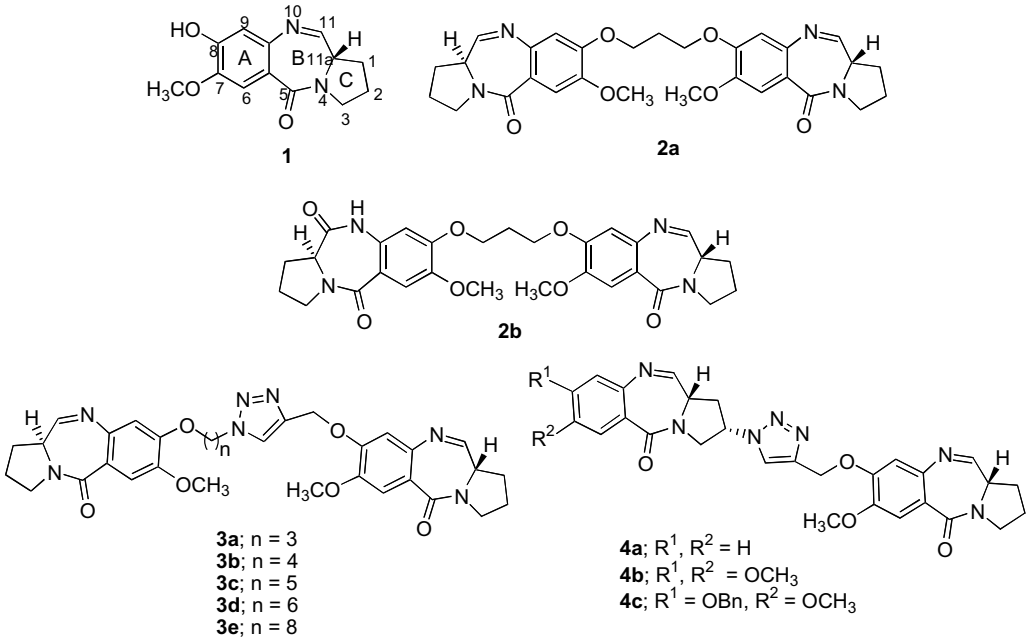


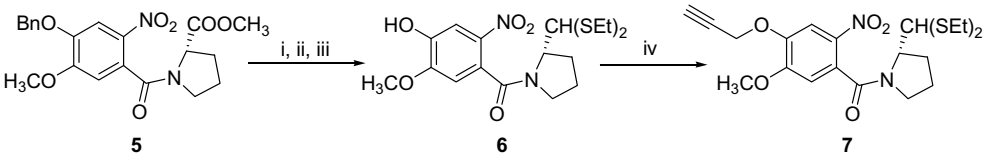

Fig. 1. Chemical structures of DC-81 (**1**), DSB-120 (**2a**), imine-amide PBD dimer (**2b**), and 1,2,3-triazole-PBD dimer analogues (**3a**–**e** and **4a**–**c**).

applications. Interestingly, the in situ generated triazole unit is revealed as a very active pharmacophore instead of a passive linker.[13a] Furthermore, dimerization of biologically useful molecules having a triazole moiety can take place easily.[13b] In recent years, alkylating agents have been studied extensively with regard to cancer chemotherapy, and this has led to the development of many new and more selective alkylating agents including molecules that are based on the triazole moiety.[14] The conventional route to 1,2,3-triazoles is the Huisgen dipolar cycloaddition of alkynes with organic azides.[15] This process provides biologically diverse molecules in a single-step and is also an example of 'click' chemistry. In this connection, we herein report a new class of C8–C8/C2–C8-linked pyrrolo[2,1-*c*]-[1,4]benzodiazepine dimers that are linked through 1,2,3-triazoles units, which are prepared by employing the 'click' reaction. Moreover, one of compound **3d** has shown enhanced DNA binding ability compared to the previously reported PBD dimer, DSB-120.

The synthesis of these 1,2,3-triazole-containing C8–C8-linked PBD dimers **3a**–**e** was carried out by employing the (2*S*)-*N*-[4-benzyloxy-5-methoxy-2-nitrobenzoyl]proline methyl ester (**5**), which was obtained according to the literature method starting from vanillin.[16] This, upon selective reduction employing DIBAL-H and protection with TMSCl/EtSH followed by deprotection using $BF_3{\cdot}OEt_2$/EtSH gave sulfide **6**. The etherification of **6** with propargyl bromide in the presence of $K_2CO_3$ afforded the required intermediate **7** in excellent yield (93%) as shown in Scheme 1.

The synthesis of the other starting substrates **8a**–**e** was accomplished using the similar procedures. Etherification of compound **6** with various dibromoalkanes followed by azidation with $NaN_3$ gave azides **8a**–**e**. Alkyne **7** and azides **8a**–**e** underwent the 'click' reaction in the presence of Cu(I) catalyst (1 mol %) and sodium ascorbate (5 mol %) to afford 1,2,3-triazole-containing PBD intermediates **9a**–**e**. Next, **9a**–**e** were reduced with $SnCl_2{\cdot}2H_2O$ followed by deprotection with $HgCl_2/CaCO_3$ to give the target molecules **3a**–**e**[17] in good yields as depicted in Scheme 2.

We next turned our attention to the exploration of the diversity at the C2-position. The C2–C8-linked triazole-containing PBD dimers **4a**–**c** were thus prepared by employing substrates **11a**–**c** , which were prepared using a reported method.[18] Thus, mesylation of the C2-hydroxy group of **11a**–**c** followed by azidation via $S_N2$ reaction with $NaN_3$ afforded azides. These upon selective reduction with DIBAL-H followed by protection with TMSCl/EtSH gave




Scheme 1. Reagents and conditions: (i) DIBAL-H, dry $CH_2Cl_2$, −78 °C, 1 h, 72%; (ii) TMSCl/EtSH, dry $CH_2Cl_2$, rt, 12 h, 92%; (iii) $BF_3{\cdot}OEt_2$/EtSH, dry $CH_2Cl_2$, rt, 12 h, 85%; (iv) $K_2CO_3$, propargyl bromide, dry DMF, rt, 12 h, 93%.