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Design and synthesis of cyclic depsipeptides containing triazole (CDPT) rings†

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We report the synthesis of cyclic depsipeptides containing triazole (CDPT) rings using click chemistry. 1,3-Dipolar cyclization *via* Cu^{I}-catalyzed alkyne–azide coupling gave the CDPT ring in a 58–64% yield.

Cyclic peptides are a large and diverse class of natural products which can contain both proteinogenic and nonproteinogenic amino acids, and whose equally diverse range of biological activities makes them and their analogues important targets for organic synthesis.[1] Considering the vast application of cyclic peptides and their analogues in synthetic as well as in medicinal chemistry, cyclic peptides remain an important area of study for both academic and industrial laboratories. Head-to-tail or cyclization *via* peptide bond formation poses significant challenges, such as oligomerization (a possible side reaction), and ring strain in the transition state which can prohibit cyclization altogether.[2] Despite this, cyclic peptides containing triazole have been developed. This method involves the use of a 1,4-disubstituted-1,2,3-triazole as an amide bond surrogate and cyclization aid. These triazoles have atom placement and electronic properties similar to those of a peptide bond,[3] and are accessible in one step *via* Cu^{I}-catalyzed alkyne–azide cycloaddition.[4] Furthermore, the increased ring size of the triazole analogue and the apparent "ring contraction" mechanism of Cu^{I}-catalyzed alkyne–azide cycloaddition[5] may help to promote cyclization.[6] The literature also reveals that the incorporation of other functional groups into the cyclic peptide enhances the membrane permeability and bioavailability *in vivo*.[7] Maarseveen *et al.* incorporated triazole rings in place of an amide linkage to synthesise the triazole analogue (**2**) of a naturally occurring cyclic peptide (**1**) which is a potent tyrosinase inhibitor.[8] On the other hand, sansalvamide A is a natural cyclic depsipeptide (**3**) which has *in vitro* cytotoxicity towards COLO 205 colon and SK-MEL-2 melanoma cancer cell lines.[9] A number of amide derivatives (**4**) (ref. 10) and macrocyclic analogues of sansalvamide A (ref. 11) have been synthesized and evaluated against various cancerous cell lines, many of which have been found to be more potent than the natural compound (Fig. 1).

To demonstrate the cyclization potential of click chemistry on peptides as part of our ongoing program of synthesising a new class of bioactive molecules,[12] we have designed and synthesized a series of cyclic depsipeptides containing triazole (CDPT) rings. The CDPT ring (**10**) was designed as a hybrid of **2** and **3** with a bicyclic/14-membered ring structure. We proposed a pathway to synthesise the CDPT ring analogue **10** (Scheme 1),

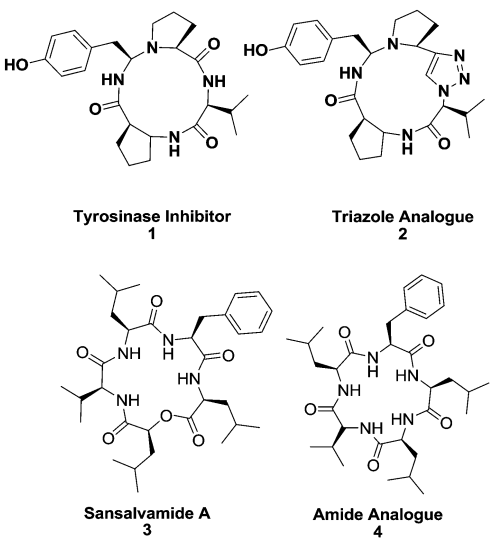

Fig. 1 Structure of natural and synthesized cyclic peptides.

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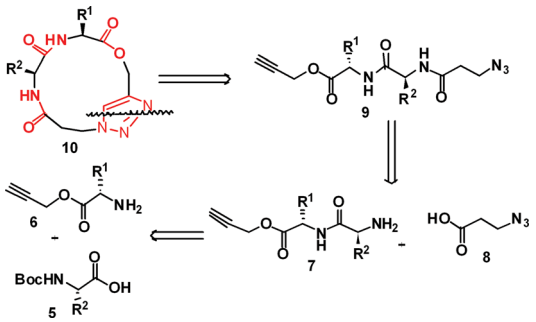
‡ Crystal data of **10e**: $C_{17}H_{27}N_5O_4$; $M = 365.44$ g mol^{-1}, orthorhombic, $P2_12_12_1$, colourless, thin plate 0.16 × 0.10 × 0.05 mm, $T = 150(2)$ K, $a = 9.359(4)$ Å, $b = 10.657(4)$ Å, $c = 19.105(7)$ Å, $V = 1905.4(13)$ Å^3, $\rho = 1.274$ g cm^{-3}, $Z = 4$, $\mu = 0.092$ mm^{-1}, no. unique/observed reflections = 3104/1664, no. of parameters = 240, $R_1 = 0.0719$, $wR_2 = 0.1679$, GoF = 0.906, $\Delta\rho_{min/max}$(e Å^{-3}) = −0.231/0.262.



Scheme 1 Retrosynthetic analysis of the CDPT ring.

disconnecting the lone triazole ring retrosynthetically to give a linear azido–alkyne depsipeptide **9**, because the literature suggests that the cyclization of triazole analogues of a cyclic peptide *via* click chemistry is feasible through cyclization *via* peptide bond formation.[6e,8] The linear depsipeptide (**9**) was disconnected further to the propargyl ester containing dipeptide **7**, and 3-azido propionic acid **8**.[13] **7** was finally disconnected to Boc protected amino acid **5** and propargyl amino ester **6**.

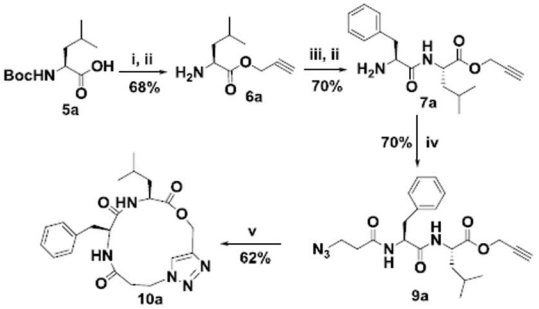
We set out initially to synthesize CDPT **10a**, in order to evaluate the viability of the proposed route and its efficiency relative to the cyclization method (Scheme 2, see ESI†). Synthesis of **6a** was achieved *via* 1,1′-carbonyl diimidazole (CDI) mediated esterification of Boc–Leu–OH (**5a**) with propargyl alcohol, followed by trifluoroacetic acid (TFA) removal of the Boc group in quantitative yield. Boc–Phe–OH (**5b**) was then coupled with **6a** to give the Boc protected propargyl ester containing dipeptide, which on treatment with TFA gave the TFA salt of propargyl ester containing dipeptide **7a**. EDC·HCl/HOBt mediated peptide coupling of 3-azido propionic acid[13] with **7a** gave the linear azido–alkyne depsipeptide **9a** cleanly in 70% yield. Addition of copper(I) bromide to a refluxing solution of **9a** in toluene and DBU led to the formation of the desired cyclic depsipeptide containing triazole ring **10a** in 62% yield. With the optimized reaction conditions in hand, the scope of the methodology was explored for the synthesis of a library of CDPT rings and is given in Table 1.

Table 1 Synthesis of cyclic depsipeptides containing triazole (CDPT) rings

			Yield[a] (%)			
Entry	R^1	R^2	**6**	7	**9**	**10**
a	Leu	Phe	68	70	70	62
b	Val	Ile	72	75	73	58
c	Ile	Phe	67	65	69	60
d	Val	Phe	74	76	72	64
e	Ile	Val	62	67	65	61
f	Val	Leu	75	69	72	59
g	Val	Val	72	76	70	62
h	Val	Gly	68	73	68	59
i	Val	Ala	65	65	74	58
j	Ile	Tyr	69	68	72	64
k	Ile	Ser(OBz)	70	72	70	62

[a] Isolated yield for each step.

As shown in Table 1 the desired cyclic peptides were isolated in 58–64% yield. All the azido–alkyne acyclic peptides (**9a–k**) and cyclic peptides (**10a–k**) were characterized by ^{1}H-NMR, ^{13}C-NMR, FT-IR, ESI-MS and the purity of the compounds was checked by HPLC. Remarkable differences were observed in the NMR and IR spectra for the azido–alkyne acyclic peptides **9** and the cyclic peptides **10**; the alkyne proton peak for **9** was observed at δ 2.5 ppm by ^{1}H-NMR whilst for **10** it had disappeared and a new peak was observed at δ 7.6 ppm from the triazole proton. A sharp peak from the azide in **9** was observed at 2103 cm^{-1} by FT-IR which was not present in **10**. In addition, the melting point (mp) of **9a-k** was around 100 °C while the mp of cyclic peptide **10a-k** was much higher *i.e.* around 250 °C. Furthermore, in the HPLC analysis **9** showed two different values for absorbance, at 244 nm and 215 nm for the azide and amide group respectively, while for **10** a sharp peak appeared at 215 nm. The exact three dimensional crystal structure of **10e** was established by X-ray diffraction (Fig. 2(a), ESI‡) and the crystal geometry was compared with the optimized gas phase geometry (Fig. 2(b)), highlighting the differences in molecular conformation (see ESI†). Furthermore, COSY, DEPT, TOCSY and HSQC experiments were also performed (see ESI†).



Scheme 2 Synthesis of CDPT ring **10a**. *Reagents and conditions*: (i) Propargyl alcohol, CDI, THF, 0 °C, 1 h, rt, 8 h, (ii) TFA, DCM, 0 °C, 2 h, (iii) BocNH–CH(CH_2Ph)–COOH **5b**, CDI, THF, 0 °C, 1 h, rt, 8 h, (iv) Azido propionic acid **8**, EDC·HCl/HOBt, DCM, 0 °C, 12 h, (v) Copper(I) bromide, DBU, toluene, 110 °C, 14 h.

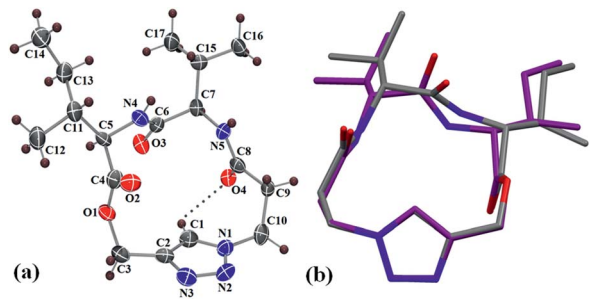


Fig. 2 (a) ORTEP diagram of **10e** drawn with 50% ellipsoidal probability. The dotted line indicates the weak intramolecular C–H···O hydrogen bond. (b) Structure overlay of solid state geometry (C-atoms are gray) of **10e** with optimized geometry of the isolated molecule (C-atoms are purple) at MP2/6-311G**.

In summary, we have demonstrated application of click chemistry for the synthesis of a new class of cyclic depsipeptides containing triazole rings. The methodology has been explored for the synthesis of a library of CDPTs and structural evidence was obtained from IR, ESI-MS, NMR, COSY, DEPT, TOCSY and HSQC and X-ray crystallography. We also anticipate that the proposed protocol can be useful for the synthesis of various diverse cyclic peptides.

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