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Exploring macrocyclization strategies to design novel octreotate-based radioconjugates

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ABSTRACT

Peptides derived from the cyclic tetradecapeptide somastostatin exhibit a strong affinity primarily towards the G-protein coupled somatostatin receptor subtype 2 (SSTR2), which is overexpressed in neuroendocrine tumors. These somatostatin analogs, such as octreotide (TOC) or octreotate (TATE), are typically cyclized through a disulfide bridge. To address the potential fragility of this linkage in vivo, four distinct stapling strategies were explored to develop novel TATE derivatives with improved stability. Each approach induced a different distance between the two sulfhydryl groups involved into the macrocyclization. Additionally, the stapling linkers were designed to present a third functional group required for the regioselective insertion of a metal chelate. Ultimately, six stapled octreotate derivatives (**stTATE-01/06**), possessing 3 to 6 chemical bonds between the two cysteine residues, were synthesized and radiolabeled with indium-111. Evaluation of their affinity to SSTR2, conducted through a competitive binding assay, aimed to identify the most effective stapling strategy. However, a significant loss of affinity was observed for all stapled peptides compared to the gold standard DOTA-TATE, confirming that these macrocyclization approaches were detrimental to the biological activity of the new SSTR2 ligands.

Introduction

Over the past two decades, there has been significant growth in the field of peptides [1]. Peptide development is typically approached through two strategies: one involves modifying existing natural peptides to enhance their pharmacological and pharmacokinetic characteristics, while the other entails the creation of extensive libraries of peptides for screening and identification of novel biologically active compounds. Despite these efforts, only a limited number of peptides receive approval for clinical use due to challenges, such as instability or loss of affinity [2]. Various methods have been employed to enhance the biochemical properties of peptides, among which the stapled strategy stands out as a promising approach.

The stapled strategy was initially pioneered by H. Blackwell and R. Grubbs, who reported a metastasis reaction for ring-closure. This approach has since been further developed by G. Verdine and his colleagues over the past 15 years [3,4]. Two main stapling techniques have been employed in the macrocyclization of linear peptides. The first technique involves "single-compound stapling", where an intramolecular reaction occurs between two unnatural amino acids containing complementary functionalized side chains, such as the cycloaddition between an azido group of one amino acid and an alkyne of another one [5]. The second technique consists of the "two-compound stapling", which involves a linear peptide containing two non-canonical amino acids with functionalized side chains and a small molecule, referred to as a stapling linker, possessing two functional groups complementary to the amino acid side chains. In this scenario, the same linear peptide can be used to generate a library of stapled peptides using different stapling linkers with diverse physical and chemical properties. For instance, D. Greenbaum et al. followed this approach to screen various stapling linkers, aiming to identify the optimal length for maximal helicity and stability [6]. Additionally, this technique offers the possibility to use a trifunctional stapling linker, allowing the selective attachment of a payload (e.g., drugs, dyes, or chelators). These stapling strategies confer conformations to peptides that enhance enzymatic resistance to degradation, target binding affinity, cell internalization, and overall improve pharmacokinetic characteristics. Cysteine residues are particularly well-suited for chemical modification due to the high

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reactivity of thiolates, which act as nucleophiles in a plethora of reactions [7,8]. Reacting thiol groups from cysteine residues with suitable reagents results in the formation of stable bis-thioethers [7]. These stapled peptides usually exhibit enhanced binding affinity to biomarkers compared to their reduced linear counterparts [9,10].

Somatostatin, also known as somatotropin release-inhibiting factor (SRIF), is a cyclic peptide characterized by a disulfide bridge connecting two cysteine residues within its structure. SRIF interacts with the somatostatin receptor subtypes 1–5, and particularly with the somatostatin receptor subtype 2 (SSTR2) in the context of neuroendocrine tumors. Analogs of somatostatin, such as octreotide (TOC) or octreotate (TATE), share a common feature, which is the presence of a disulfide bridge to form cyclic peptides. Studies have shown that this bridge in the somatostatin analogs stabilizes a type II' β-turn structure, essential for effective interaction with SSTR2 [11,12]. However, this disulfide linkage is also responsible for their relatively poor in vivo stability. In fact, the disulfide bridge is susceptible to reduction by enzymes, such as glutathione reductase and thioredoxin reductase, as well as attack by nucleophiles and basic agents, leading to β-elimination, homolytic cleavage, and polymerization [13,14]. Additionally, another challenge arises from the sensitivity of the somatostatin analogs to *N*-terminal chemical modifications, the favored position for the attachment of a payload, which can lead to a decrease of binding affinity to SSTR2 [15,16].

Herein, we describe novel octreotate analogs in which disulfide-mediated cyclization of the octamer peptide was replaced by "two-compound" stappling approaches (Fig. 1). Four distinct trifunctional stapling linkers were involved in the macrocyclization processes, allowing to adjust the distance between the two thiol groups of the cysteine residues, and to facilitate the regioselective coupling of a bifunctional chelate. The linear octamer peptide was subjected to macrocyclization using either dibromomaleimide, 1,3-dichloroacetone, 3,6-dichlorotetrazine, or 1,3,5-tribromo-methyl-benzene. The remaining functional group reacted with modified DOTA chelators via strain-promoted alkyne-azide cycloaddition (SPAAC), oxime formation, inverse electron-demand Diels-Alder (IEDDA), and SN1 reaction. Finally, in vitro competition assay was carried out to determine if these stappling approaches could afford a cyclic peptide that conserved its binding affinity to SSTR2.

Results and discussion

Our initial objective was to substitute the disulfide bridge with four distinct stapling strategies and subsequently assess the impact of these modifications on the affinity to SSTR2. Four different functionalized stapling reagents were employed for the macrocyclization of the linear peptide D-Phe-Cys-Tyr-D-Trp-Lys-Thr-Cys-Thr (**2**), obtained by conventional solid-phase peptide synthesis (Scheme S1). These reagents provided cyclic peptides owning 3 to 6 chemical bonds between the two thiols, as well as a reactive group for the orthogonal incorporation of the DOTA chelator. We selected DOTA, as it is known to form stable complexes with various radionuclides, such as ^{68}Ga, ^{111}In, ^{161}Tb, ^{177}Lu and ^{225}Ac, commonly used in nuclear medicine applications.

Initially, we investigated the macrocyclization of the linear octamer peptide **2** using a stapling linker, allowing the shortest distance (3 chemical bonds) between the two cysteine residues. The cyclization was achieved through the reaction of the peptide's thiol groups with a *N*-functionalized bromomaleimide reagent (**5**). This reagent was synthesized in two steps, adapted from the method described by Baker et al. (Scheme S2) [17]. The first step involved the conversion of 3,4-dibromomaleimide to a carbamate by treatment with methyl chloroformate in the presence of *N*-methylmorpholine. Subsequently, the intermediate **4** reacted with 3-azidopropylamine to yield the functionalized stapling agent, *N*-(3-azidopropyl)-3,4-dibromomaleimide (**5**), with a high yield of 68 % over the two steps. The cyclization of the linear peptide **2** followed the procedure outlined by Wilson and coworkers [9]. Briefly, **2** was combined with the dibromomaleimide stapling reagent **5** in a water-acetonitrile solution at room temperature (Scheme 1). The cyclic peptide **18** was obtained with a moderate yield of 32 %. It was noted that the reaction progressed slowly, with no further advancement observed after 16 h, while the reaction reported by Wilson et al. was completed within 4 h. Subsequently, the modified DOTA chelators (**7** and **8**) were attached to the cyclized peptide **18**. DBCO-DOTA (**7**) and BCN-PEG$_2$-DOTA (**8**) were synthesized by an amidation reaction between DOTA-NHS ester and the corresponding amines containing a click handle, namely dibenzocyclooctyne-amine (DBCO-amine) and *N*-[(1R,8S,9s)-bicyclo [6.1.0]non-4-yn-9-ylmethyloxycarbonyl]-1,8-diamino-3,6-dioxaoctane (BCN-PEG$_2$-amine), in the presence of triethylamine (Scheme S3). Both compounds were obtained with yields of 60 % and 62 %, respectively. Finally, the strain-promoted alkyne-azide cycloaddition (SPAAC) between the azido group of **18** and the alkyne of either DBCO-DOTA or BCN-PEG$_2$-DOTA produced the clicked peptides **stTATE-1** and **stTATE-2** with yields of 64 % and 94 %, respectively. The SPAAC reaction was chosen as it does not require the use of a copper catalyst, which could potentially be complexed by the DOTA chelator [18]. Monitoring of these reactions revealed that the SPAAC reaction between BCN-PEG$_2$-DOTA (**8**) and **18** proceeded slower than the corresponding reaction with DBCO-DOTA (**7**). This outcome was anticipated, as it is known that the kinetics of the SPAAC reaction are slightly faster when the azide reacts with DBCO compared to BCN ($k \sim 0.34\ M^{-1}\ s^{-1}$ vs $0.14\ M^{-1}\ s^{-1}$, respectively) [18,19]. To assess the impact of the position of the chelator on the peptide's affinity, the chelator was positioned either close to the bridge (**stTATE-01**) or distanced from the peptide by using a polyethylene glycol (PEG) linker (**stTATE-02**).

The second method involved macrocyclization using 1,3-dichloroacetone (Scheme 2). Philips et al. detailed the conditions for cyclizing peptides with 1,3-dichloroacetone in a basic phosphate buffer (NaH_2PO_4) [20]. However, this approach resulted in a limited conversion rate (30 %), likely due to peptide solubility issues. Therefore, we opted for DMF and DIPEA, as solvent and base, respectively. Under these conditions, the reaction yielded cyclic peptide **21** with 84 % yield. Next, we synthesized two variants of the DOTA chelator, **16** and **11**, both featuring an oxoamine group designed to react with the ketone of **21**. Compound **11** was synthesized with a 20 % yield by amidation of **6** with *tert*-butyl-(2-aminoethoxy)carbamate, followed by deprotection of the Boc protective group under acidic conditions (Scheme S3). **16** differed from **11** by the inclusion of a *p*-xylylenediamine spacer [21]. The synthesis of the oxoamine **16** involved a series of amidation and deprotection steps, resulting in an overall yield of 9 %. The initial step consisted of the NHS activation of 2-((bis(*tert*-butoxycarbonyl)amino) oxy)acetic acid in the presence of dicyclohexylcarbodiimide (DCC), following the protocol reported by Dumy et al. [22]. Intermediate **14** was obtained with an 80 % yield without further purification. Concurrently, amidation of *N*-Boc-*p*-xylylenediamine with DOTA NHS ester produced **12** with a yield of 57 %. Subsequent removal of the Boc group and coupling of **14** in the presence of triethylamine yielded **15** with a 39 % yield. Finally, removal of the Boc protective group gave **16** with a 52 % yield.

The oxyamine derivatives **16** and **11** were coupled to the cyclic peptide **21** in an ammonium acetate buffer (pH 4.5) to yield the final products **stTATE-03** and **stTATE-04**. Aniline, known as a nucleophilic catalyst compatible with biomolecules, was used to promote the reaction. However, under these conditions, a low yield of approximately 20 % was obtained after 48 h for the oxyamine **11**, and no product was detected for **16**. Consequently, post-purification, **stTATE-03** was obtained with a very low yield of 2 %. A new strategy was thus adopted, involving the sequential execution of the oxime formation followed by the cyclization. This method, introduced by Ng and Derda, was initiated with the oxime formation by treatment of **16** with 1,3-dichloroacetone [18]. No catalyst was employed, and the reaction proceeded gradually, yielding product **17** with a 54 % yield. The subsequent step involved cyclization between the dichlorooxime **17** and linear peptide **2**.

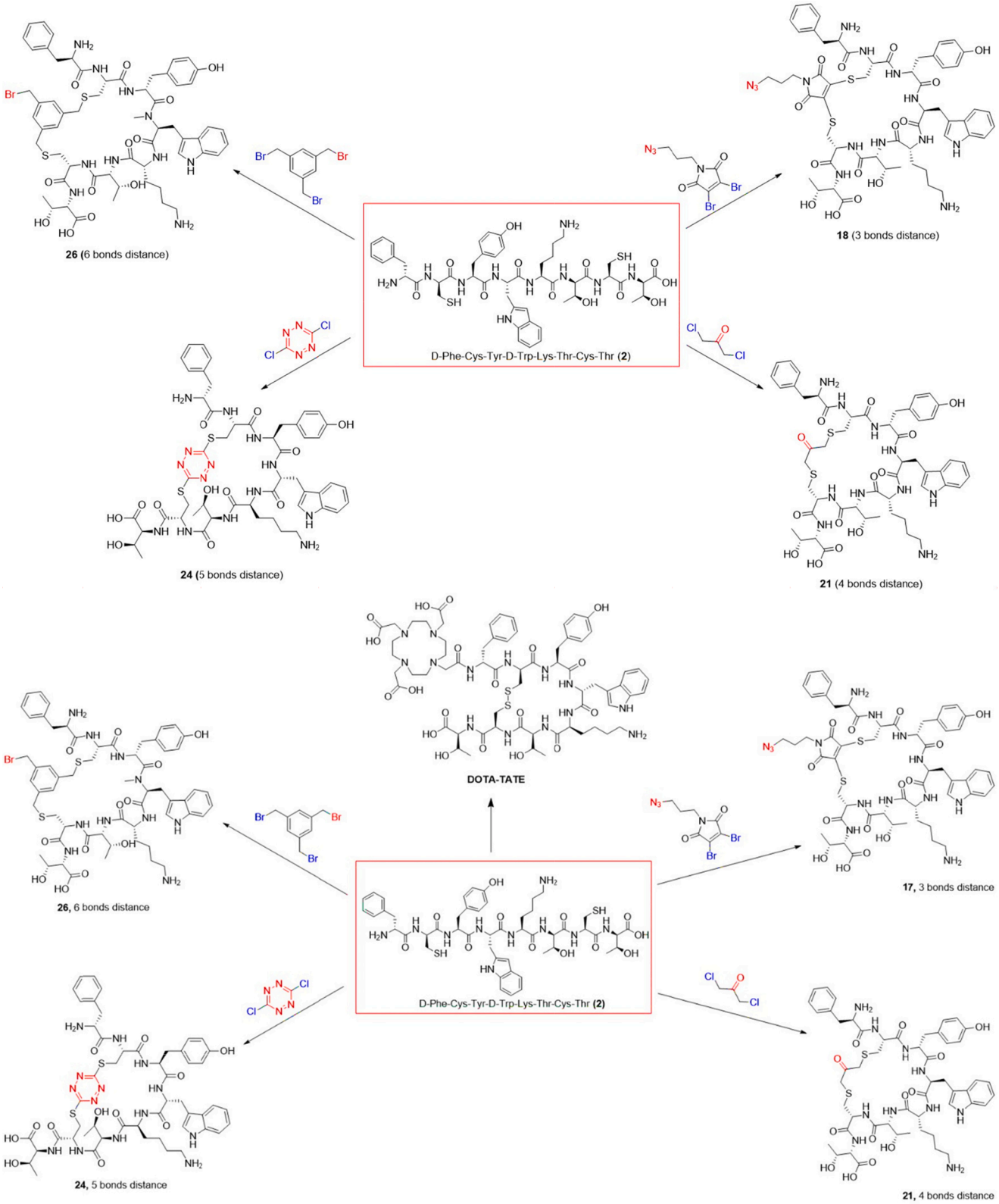
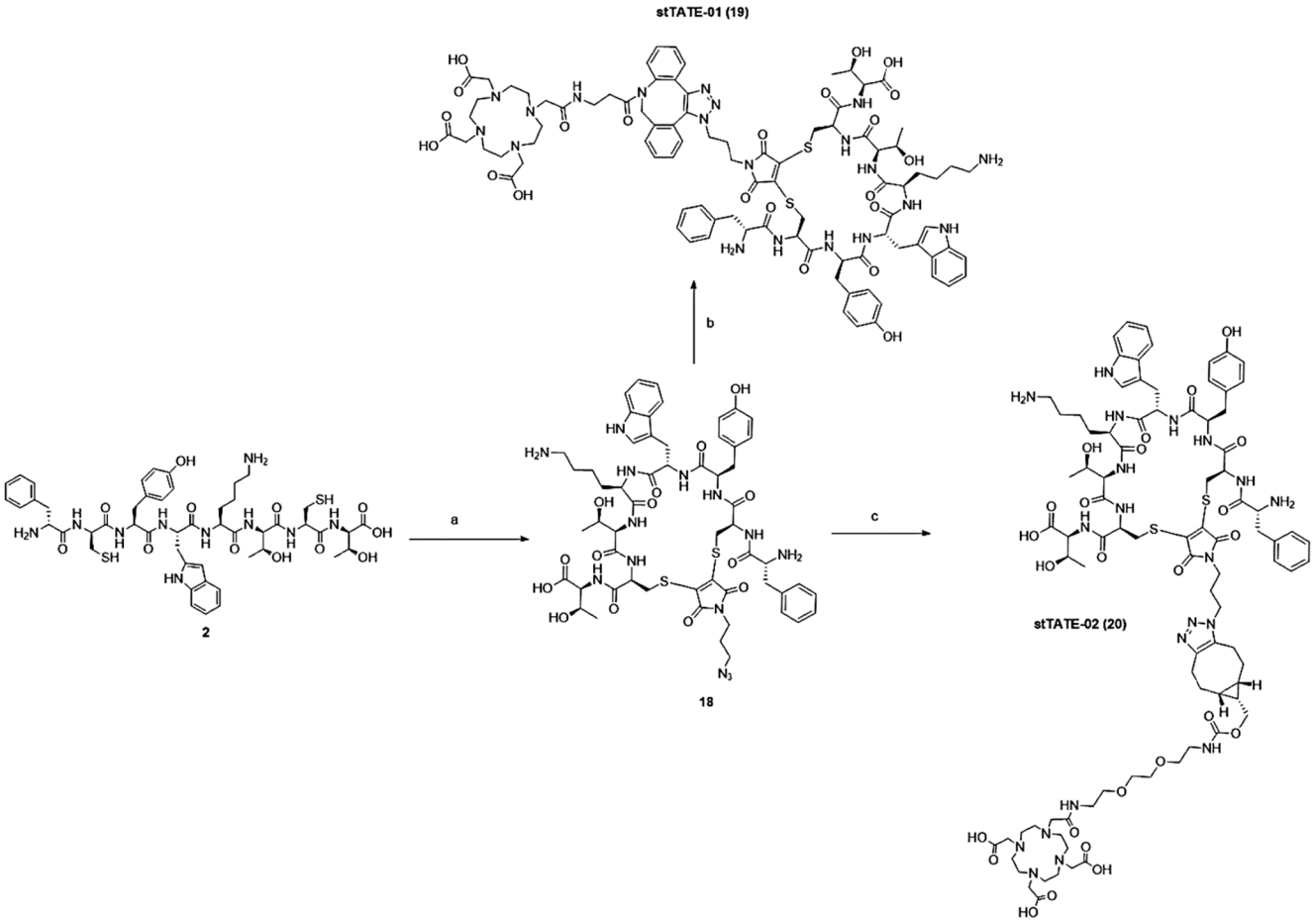


Fig. 1. Four stapling strategies were explored to form cyclic peptides with various distances between the cysteines' sulfhydryl groups. in blue, the chemical groups that interacted with the side-chains of the cysteine residues, and in red the orthogonal functions allowing the attachment of the bifunctional chelator DOTA. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)



Scheme 1. Synthesis of the **stTATE-01** and **stTATE-02**. Reagents and conditions: (a) *N*-(3-azidopropyl)-3,4-dibromomaleimide, H_2O/ACN (1:1 v/v), 16 h, rt, 32 %; (b) **7**, H_2O/ACN (1:1 v/v), 37 °C, 1 h, 64 %; (c) **8**, H_2O/ACN (1:1 v/v), 37 °C, 16 h, 94 %.

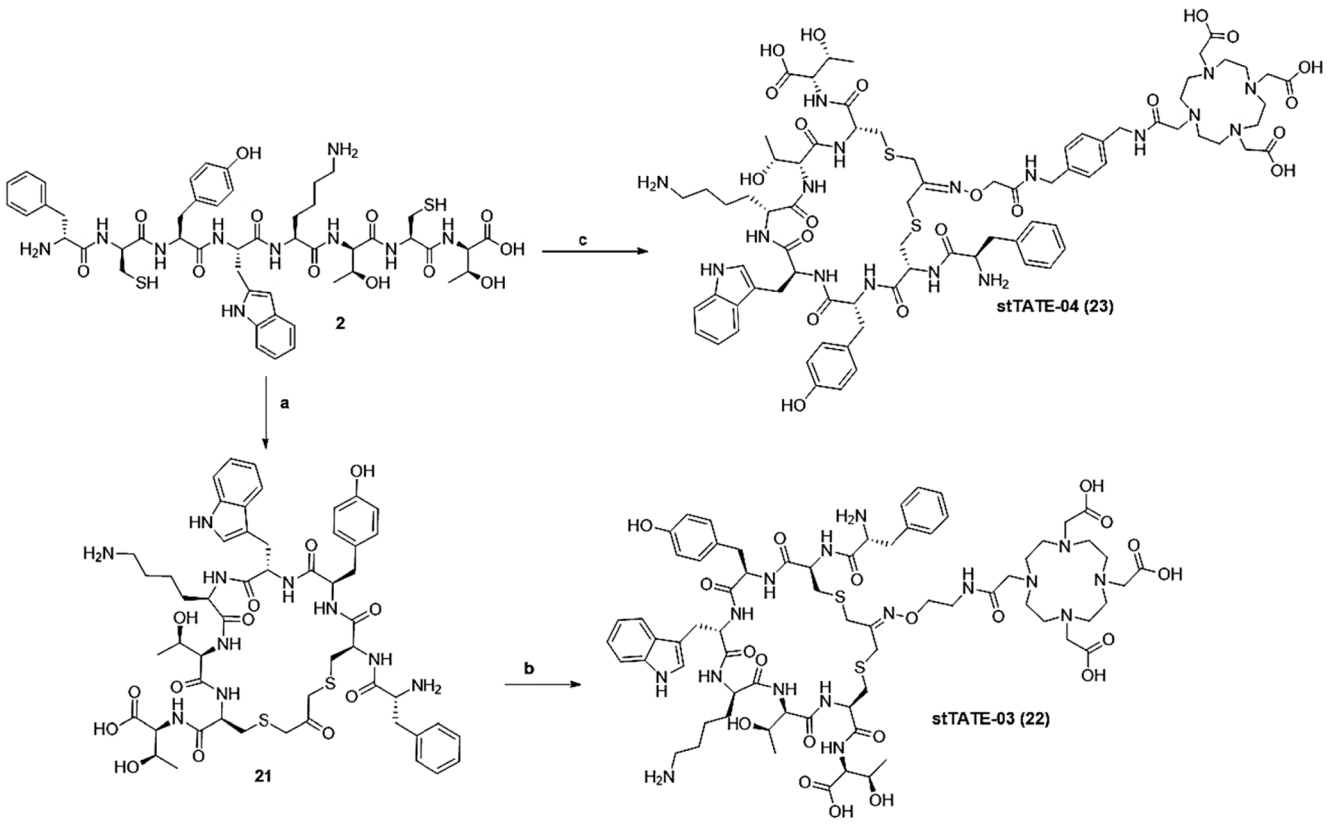
The resulting stapled peptide **stTATE-4** was obtained with an 11 % yield, notably lower than the yield achieved in the cyclization of **2** with 1,3-dichloroacetone.

The third macrocyclization approach of the linear peptide **2** was achieved with the stapling reagent 3,6-dichloro-1,2,4,5-tetrazine (Scheme 3). Displacement of two chlorides by nucleophilic attack of the sulfhydryl groups facilitated peptide cyclization by bridging the two cysteine residues, while the tetrazine facilitated the attachment of the DOTA chelator via an inverse electron-demand Diels-Alder reaction.

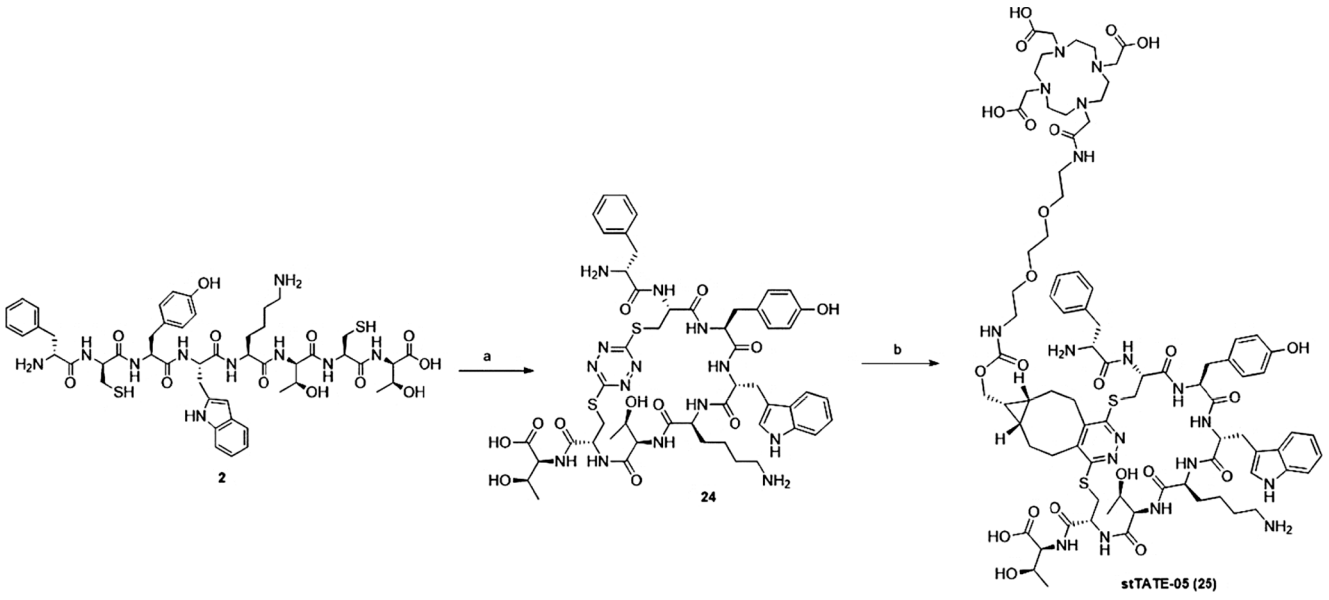
The cyclization was performed according to a diphasic protocol inspired by the work of Brown and Smith [19]. In essence, peptide **2** was dissolved in an acidic phosphate buffer (pH 5), while the dichlorotetrazine was dissolved in an organic solvent (chloroform). After vortexing for a minute, the product formed in the aqueous phase. The reaction was conducted in the dark due to the sensitivity of the tetrazine to light. The cyclic peptide **24** was obtained with a yield of 60 %. The final product, **stTATE-05**, resulted from the IEDDA reaction between BCN-PEG_2-DOTA (**8**) and the tetrazine peptide **24**. This reaction occurred over 22 h, a duration consistent with findings reported in the literature. The IEDDA reaction between a *trans*-cyclooctyne (TCO) and a tetrazine is significantly faster, typically lasting a few minutes [23]. However, unlike BCN-PEG_2-DOTA, TCO-DOTA can easily isomerize to its cys-conformer, which is known to be significantly less reactive towards tetrazines. This was further confirmed when attempting the IEDDA reaction between TCO-DOTA and tetrazine peptide **24**, resulting in multiple impurities without the possibility of isolation. In contrast, the reaction with **8** gave a single product, **stTATE-05**, obtained with a global yield of 41 %.

The final stapled peptide **stTATE-06** was obtained by cyclization of linear peptide **2** with tris(bromomethyl)benzene (TBMB). This stapling agent induced a distance of six chemical bonds between the two cysteine residues. In this process, two bromo leaving groups of TBMB participated in the cyclization, while the remaining one enabled the attachment of the DOTA chelator (Scheme 4). First, the linear peptide **2** was cyclized using TBMB, following the conditions outlined by Albericio et al. [20]. However, we chose to perform the reaction in DMF and DIPEA due to the solubility of our peptide instead of a basic buffer, as described by Albericio and coworkers. The cyclization proceeded rapidly, taking only 10–15 min. To prevent hydrolysis of the remaining bromo-substituent, we quenched the reaction using TFA. The cyclic product **26** was obtained with a yield of 26 %. In parallel, we synthesized cysteamine-DOTA (**9**). Cysteamine presents both an amine and a thiol function that could react, respectively, with DOTA-NHS ester and TBMB. **9** was obtained with a yield of 71 % using the amidation method previously described for DBCO-DOTA (**7**) (Scheme S3). The final step entailed coupling of compound **9** with the cyclic peptide **26** through a nucleophilic substitution. Despite the rapid reaction, taking approximately 30 min, hydrolysis competed with the desired reaction, resulting in a yield of only 23 %. **stTATE-06** was obtained with an overall yield of 6 %.

To evaluate the impact of the stapling strategies and the repositioning of the chelator, we conducted binding affinity studies with our six new ligands (**stTATE-01/06**) and compared them to the gold standard, DOTA-TATE. DOTA-TATE is characterized by a conventional disulfide bridge (1 chemical bond distance between the two cysteine residues) and a DOTA chelator located at the *N*-terminus [24]. Affinity values (IC_{50}) were determined through a competitive binding assay in U2OS cells overexpressing the somatostatin receptor subtype 2 (SSTR2),



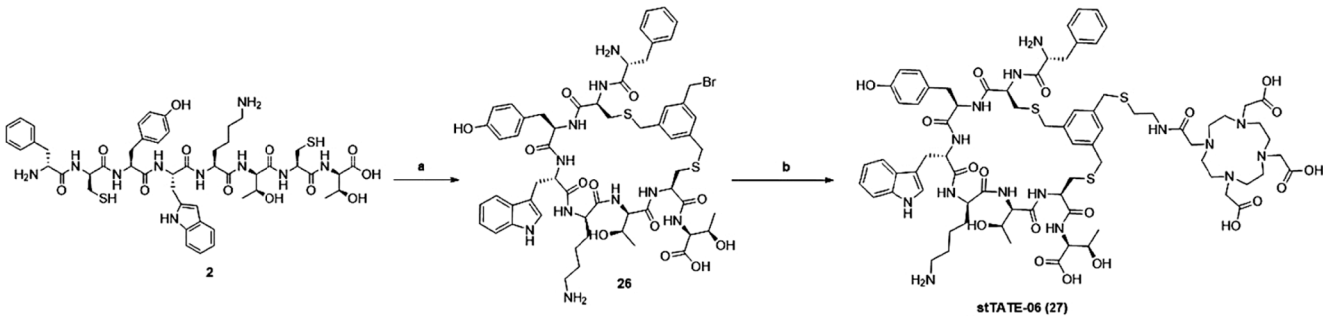
Scheme 2. Synthesis of **stTATE-03** and **stTATE-04**. Reagents and conditions: (a) 1,3-dichloroacetone, DIPEA, DMF, rt, 3 h, 84 %; (b) **11**, 50 mM ammonium acetate, 100 mM aniline (pH 4.5), 48 h, 2 %; (c) **17**, DIPEA, DMF, 3 h, 11 %.



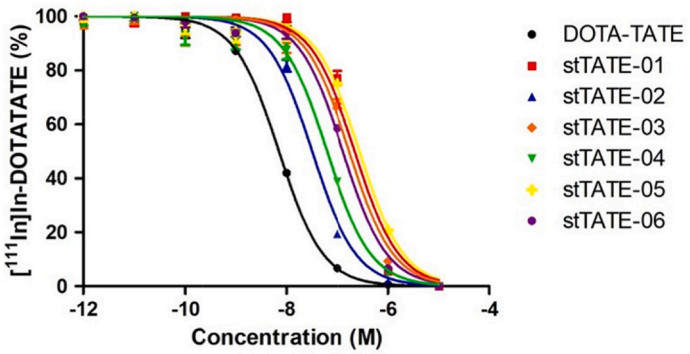
Scheme 3. Synthesis of **stTATE-05**. Reagents and conditions: (a) 3,6-dichloro-1,2,4,5-tetrazine, 50 mM NaH_2PO_4 (pH 5)/chloroform (1:1 v/v), 1 min, 60 %, rt; (b) **8**, H_2O/ACN (1:1 v/v), 37 °C, 16 h, 69 %.

using [^{111}In]In-DOTA-TATE as radioligand (Fig. 2) [25]. The ligands demonstrated affinities ranging from 42 to 279 nM to SSTR2. These IC_{50} values were 7 to 49-fold higher than the value observed for DOTA-TATE. Notably, the first and second strategies led to compounds exhibiting IC_{50} values 7 and 8-fold higher, respectively, than DOTA-TATE ($P < 0.05$). However, these compounds featured the chelate positioned distantly from the cyclization linkage. In contrast, when the chelate was closer to the peptide, binding affinity dropped, reaching values comparable to other strategies.

Somatostatin analogs, such as SSTR14 and octreotate, are known for their cyclic form involving a disulfide bridge which induce a β-sheet structure, facilitating specific interactions between the binding domain of octreotate (Tyr-D-Trp-Lys-Thr) and the binding pocket of SSTR2 [12,26,27]. However, stapling of a linear peptide typically induces an



Scheme 4. Synthesis of **stTATE-06**. Reagents and conditions: (a) tris(bromomethyl)benzene, DIPEA, DMF, 15 min, rt, 26 %; (b) **9**, DIPEA, DMF, 30 min, 23 %.



Compound	IC_{50} (nM) (n=3)
DOTA-TATE	6.05 ± 1.43
stTATE-01	207.20 ± 22.06
stTATE-02	42.05 ± 14.21
stTATE-03	198.10 ± 64.80
stTATE-04	70.20 ± 10.47
stTATE-05	122.07 ± 7.60
stTATE-06	278.87 ± 52.03

Fig. 2. IC_{50} curves and IC_{50} values of the in vitro competitive binding assay for **stTATE-01/06**.

α-helix structure [2,28,29]. Consequently, post-stapling, octreotate may adopt a different conformation, potentially leading to a loss of crucial interactions with the SSTR2 binding pocket and, consequently, a decline in affinity. To investigate this hypothesis, circular dichroism spectroscopy can be employed to determine the helicity. Furthermore, the distance between the two sulfurs, from 3 to 6 bonds vs. 1 for the native disulfide bridge, significantly affect the conformation of the six cyclic peptides, compromising their ability to fit into the binding pocket and to establish the correct interactions with the receptor. Depending on this distance, it resulted in a more or less important drop of affinity for SSTR2. Additionally, for the first (stTATE-01 vs. stTATE-02) and second (stTATE-03 vs. stTATE-04) strategies, we observed that the distance of the chelate from the cyclization linkage is critical, as longer distances correlate with improved affinity. This observation may be attributed to the opening of the peptide cycle, allowing the chelate to readily interact with the binding pocket, potentially interfering with the peptide's binding. Previous studies have demonstrated that not only the position but also the distance of the chelator from the peptide's binding domain can significantly influence affinity to the target [30–32]. However, to understand the impact of the chelate's position relative to the cyclization center on binding affinity, the other two strategies also need to be verified. For SSTR2 ligands, it is well-established that modifications in the *N*-terminus can significantly impact peptide interactions, which is explaining why we opted to attach the chelator at the macrocyclization center [15,16]. Further investigations, particularly employing circular dichroism spectroscopy and structural analyses, are warranted to elucidate the structural implications of stapling on peptide conformation and binding interactions. Even if these approaches did not provide a lead compound for SSTR2, they could be useful for other cyclic peptides, particularly seeing the interest for bicyclic peptides [33,34].

Conclusion

Six ligands were successfully synthesized using four distinct stapling strategies, involving modification of the size of the cyclic peptide and the position of the DOTA chelator. Ultimately, the evaluation of these ligands centered on their affinity to the somatostatin receptor subtype 2. All our observations showed that a one bond distance is ideal to preserve affinity for SSTR2. Intriguingly, when the chelate was positioned close to the cyclization linkage, regardless of the size, a decrease in affinity was observed. Conversely, when the chelate was distanced, an improvement in affinity was noted, particularly for stapling linkage of 3 and 4 bonds. Further investigations are needed to unravel the mechanisms underlying the interaction of these ligands with the binding pocket, providing deeper insights into the design of new stapled SSTR2 (radio)ligand with improved stability.

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CRediT authorship contribution statement

Dylan Chapeau: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Investigation, Formal analysis, Data curation. **Angelos Iroidis:** Writing – review & editing, Investigation, Data curation. **Savanne Beckman:** Writing – review & editing, Software, Investigation, Data curation. **Yann Seimbille:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Resources, Project administration, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2024.155162.

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