Organic LETTERS

Concise Synthesis of Tetrazole Macrocycle

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S Supporting Information

ABSTRACT: A concise two step synthesis of tetrazole containing macrocycles from readily accessible starting materials is presented. The first step comprises a chemoselective amidation of amino acid derived isocyanocarboxylicacid esters with unprotected symmetrical diamines to afford diverse α-isocyano-ω-amines. In the second step, the α-isocyano-ω-amines undergo an Ugi tetrazole reaction to close the macrocycle. Advantageously, this strategy allows short access to 11−19-membered macrocycles in which substituents can be independently varied at three different positions.
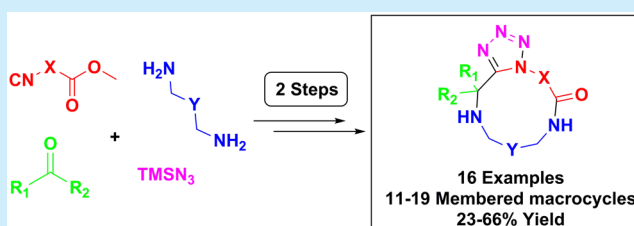
Protein−protein interactions (PPIs) are a highly interesting but challenging class of pharmaceutical targets.[1−4] However, they are mostly undruggable by conventional small molecules due to their inappropriate size and shape.[5,6] Therefore, receptor interactions are the classical targets of monoclonal antibodies (mAbs). mAbs seem to better mimic the large network of endogenous small interactions in the interface of receptors. While mAbs are a highly successful class of drugs, they also show inherent disadvantages, including potential immunogenicity, minor tissue penetration, high cost-of-goods and restriction to cell surface targets. Development of novel classes of molecules with properties in between small molecules and biologics is therefore an area of intensive research. Examples of such emerging classes are peptidomimetics, modified peptides, cyclic peptides, including stapled peptides. Peptides, however, suffer often from similar deficiencies as biologics such as reduced biological stability, lengthy syntheses, poor or no oral bioavailability and potential immunogenicity.

Therefore, several groups have developed elegant approaches toward artificial macrocycles which are not built on peptides nor involving complex multistep syntheses.[7−11] For example, we have recently described the shortest 2-step synthesis of artificial macrocycles.[12,13] In order to expand our previous work and increase the number of macrocyclic scaffolds a concise and general approach toward artificial tetrazole containing macrocycles based on the Ugi tetrazole multicomponent reaction (MCR) was designed. The reaction design is based on our recently published concept of building a macrocycle from an acyclic precursor through a MCR, while the precursor is built from an efficient linear or exponential diversification step.[14] In light of potential issues of passive membrane permeation, we decided to replace a secondary amide group by the bioisosteric

tetrazole cycle which is devoid of hydrogen bond donors.[15] The current work is thus also an extension of our recent reports of tetrazole macrocycles, which however did require up to 5 sequential reaction steps including two MCR reactions (Scheme 1).[12] In this study, we report the isocyanide based

Scheme 1. Comparison of the Previous Work and New Strategy toward Synthesis of Tetrazole Macrocycles
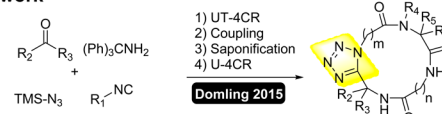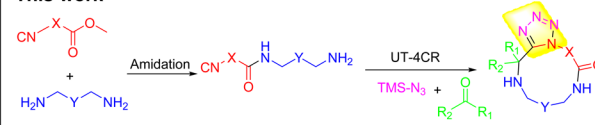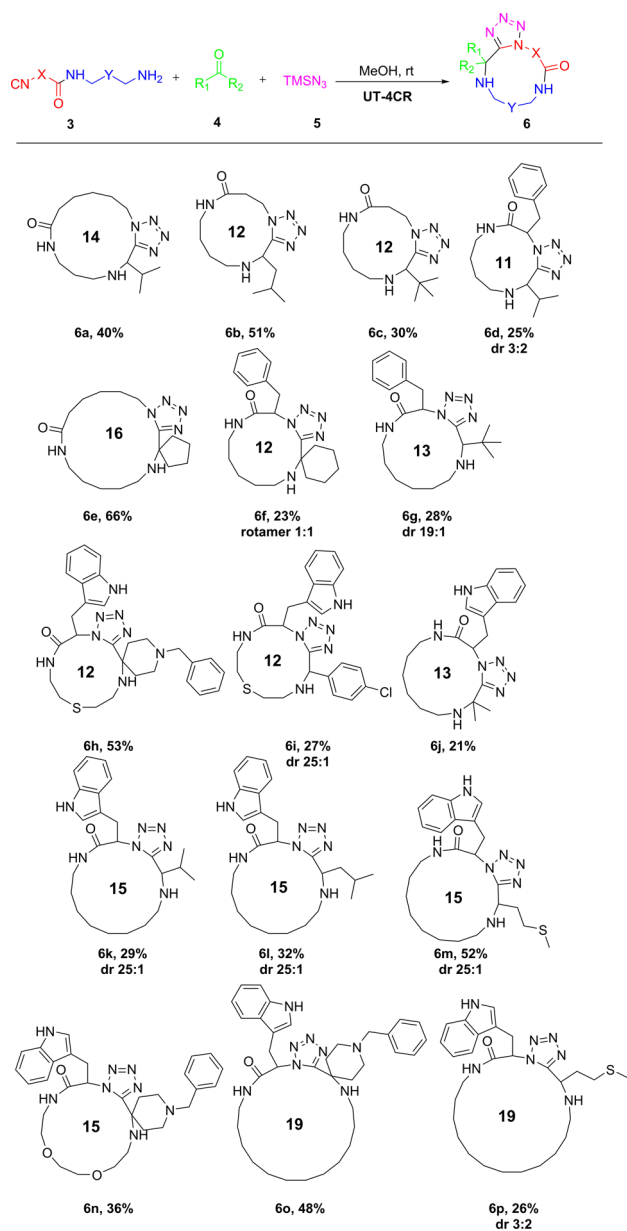

multicomponent reactions (IMCRs) involving simple starting materials like α-isocyano-ω-amine and aldehyde in the presence of the azide source TMSN$_3$ to access tetrazole macrocycle scaffolds in a convergent method and to use, for the first time, the Ugi-tetrazole reaction for macrocyclizing 16 macrocycles (Scheme 2).

We started the study by optimizing the first step in our 2-step protocol, the synthesis of amino isocyanide by the coupling of the diamine and isocyanide ester under protecting group free conditions. This turned out to be challenging due to the

Scheme 2. Azido-Ugi-4CR Derived Macrocycle Synthesis Pathway and Products with Isolated Yields

Table 1. α-Isocyano-ω-amine Synthesis Strategy and the Isolated Yields

entry	isocyanide	diamine	yield (%)*
3a			60
3b			55
3c			65
3d			42
3e			48
3f			56
3g			49
3h			56
3i			56
3j			54
3k			54

*Isolated yield.

polarity of our products which resulted in unreacted and double reacted diamine side products. To overcome this problem, some optimization of the coupling reaction was necessary, by trying different solvents, including chloroform, dichloromethane, methanol, water, tetrahydrofuran, ethanol and trifluoroethanol. It was observed that the use of dioxane gave the best results, while other solvents resulted either in multiple product formation, low yields or no product formation at all (SFC-MS, TLC). As the products are quite polar in nature, we faced difficulties in their isolation. Finally, the product purification was accomplished on silica (60−200 μm) using 1:1 dichloromethane:ethyl acetate as eluent A and ammonia in methanol as eluent B in a gradient method. With this optimized method in hand, ten different α-isocyano-ω-amines of different length were synthesized from their commercially available diamines with excellent purity and good yields ranging from 42 to 65% on a gram scale (Table 1). It is interesting to note that the unprecedented class of α-isocyano-ω-amines are stable

compounds and similar to other isocyanides it is possible to store them in the fridge at low temperature for a long time.

Next, the macrocyclic ring closure by tetrazole Ugi MCR was carried out under optimized conditions using 1 equiv of an oxo component to yield the macrocycles (Scheme 2). Different conditions were extensively screened by varying concentration, temperature, solvent and time. Methanol as solvent in 0.01 M

dilution, after 48 h at room temperature was found to be optimal condition for this macrocylization reaction. Surprisingly, the yield was dramatically increased while after 24 h the solvent volume was reduced to 50% under nitrogen, and it was stirred in 0.02 M dilution for an additional 24 h. For example, for compound **6f** the yield was increased from 10% to 23% by reducing the solvent volume and therefore increasing the concentration to 0.02 M. This can be explained by the continuous decrease in concentration of the starting materials as the reaction proceeds. On the other hand, it is well-known that Ugi reaction run best in high concentrations, as four components have to react with each other.[16] Here the situation is even further complicated due to the diluted conditions for the macrocyclization reaction.

To investigate substrate scope and limitations, a total of 16 examples was synthesized which are shown in Scheme 2. The last step of the macrocycle synthesis was performed by using several commercially available aliphatic, aromatic, and heterocyclic aldehydes and ketones as oxo-components to afford macrocyclic derivatives in moderate yields of 21−66% after purification by column chromatography. Diastereomer formation was also investigated by using D,L-tryptophan and phenylalanine derived isocyanides. In these cases, surprisingly mixtures of diastereomers were observed and compounds **6d**, **6g**, **6i**, **6k**, **6l**, **6m** and **6p** were obtained in poor to very good diastereomeric ratios of 3:2 to 25:1, determined by ^{1}H NMR.

In order to confirm the product formation and to gain insight into ring conformation and hydrogen bondings, two products (**6a** and **6h**) were crystallized and their solid-state structure were determined by X-ray crystallography (Figure 1). In **6a** structure, the tetrazole N-3 forms a short hydrogen bond (2.3 Å) to a neighboring molecule amide NH. Additionally, the hydrophobic moieties of the macrocycle undergo multiple van
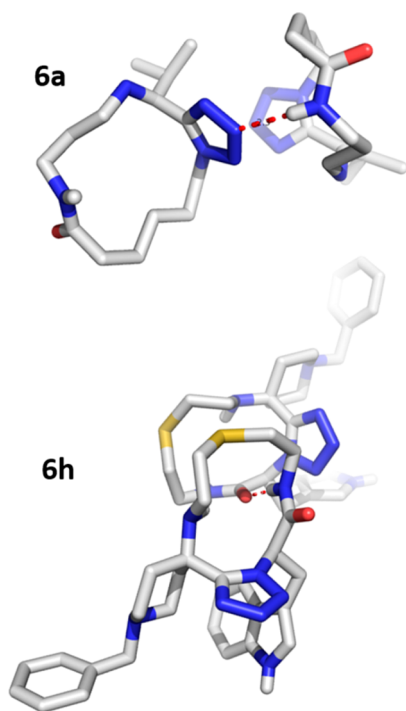

Figure 1. Representative MCR-derived 14-membered-**6a** and 12-membered-**6h** macrocycles in solid state featuring intermolecular hydrogen bonding contacts.

der Waals interactions to neighboring rings. In **6h** the macrocycle secondary amide undergoes a hydrogen bonding (2.0 Å) with the same amide group of a neighboring macrocycle. Solid state hydrogen bonds can help to inform about solution phase behavior of the molecules. Such intermolecular hydrogen bonds and hydrophobic interactions potentially improve chameleonic properties of macrocycles, which enables them to change their conformation in aqueous solution and while passing through lipid cell membranes. This chameleonic ability improves passive membrane permeability by exposing polar groups in aqueous solution and burying them while traveling lipid membranes.[17]

The plausible mechanism for this Ugi cyclization reaction is shown in Scheme 3. It is conceivable that initially the

Scheme 3. Possible Mechanism for the Formation of Products by the Azido-Ugi Reaction
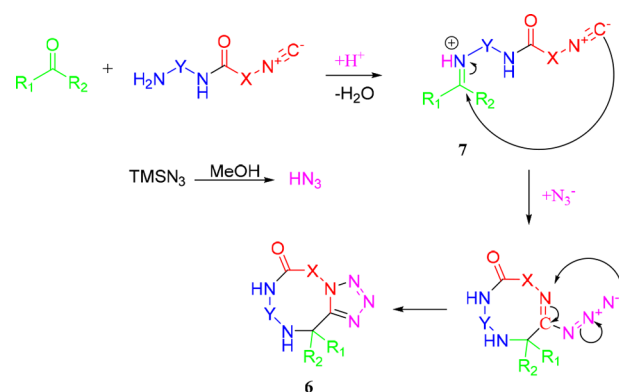
condensation of the oxo-component and amino group affords the Schiff base **7**. Then, nucleophilic addition of carbenoid C atom of the isocyanide onto the iminium group followed by the addition of the azide anion onto the C atom of the nitrillium ion and 1,5-dipolar electrocyclization leads to the formation of the products **6**. The low yields in this reaction are due to the presence of unreacted starting materials even after stirring the reaction for a long time.

The passive membrane permeation and the connected bioavailability of macrocycles is a major concern for drug discovery.[18] While there seems to be a MW cutoff of 1000 Da for passive membrane transportation of cyclic peptides,[19] there is also indication that specifically the macrocyclic space between 500 and 1000 Da is virtually unexplored but promises to harbor a large number of macrocycles with drug-like ADMET properties.[20] Here we provide a novel synthesis strategy to access specifically the space of 500 to 1000 Da using convergent MCR chemistries toward tetrazole macrocycles. A MW vs cLogP plot (Figure 2) of a random library based on the herein proposed macrocycle chemistry indicates an average MW of 408 Da and clogP of 1.8, which is quite interesting for searching for compounds with drug-like properties (SI).[21]

In conclusion, a very mild, straightforward, sequential, rapid and highly diverse tetrazole macrocycle synthesis pathway is introduced via MCRs. To the best of our knowledge this is the first report of using a tetrazole Ugi reaction for the macrocyclization step. 11−19-Membered macrocyles containing various side chains were synthesized in two steps by using readily available starting materials. A simple chemoinformatic analysis of the macrocycle space predicts drug-like properties. We are currently venturing into these new territories of drug
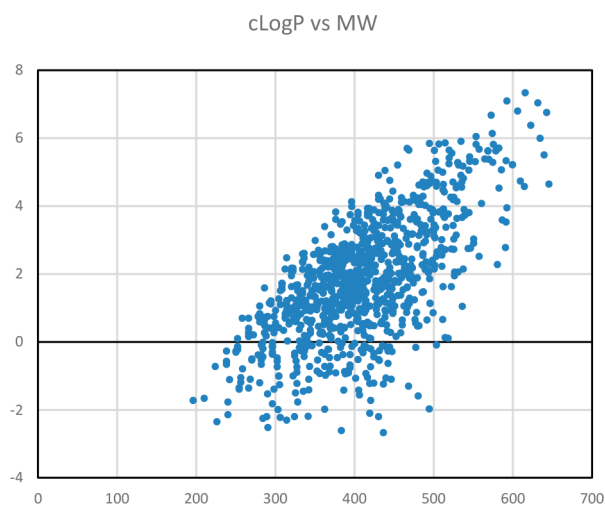
cLogP vs MW

Figure 2. Molecular weight against calculated lipophilicity plot of 1.000 randomly generated macrocycles.

discovery by preparing libraries of such macrocyclic derivatives and screening them for biological activity.

ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02319.

> General procedures, characterization data of all the compounds, crystal structure determination and virtual library synthesis (PDF)

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Notes

The authors declare no competing financial interest.

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