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Synthesis of novel tryptamine-based macrocycles using a Ugi 4-CR/microwave assisted click-cycloaddition reaction protocol

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Lizbeth Chavez-Acevedo[a] and Luis D. Miranda.[a]*

A practical synthesis of novel tryptamine-based macrocycles using a Ugi 4-CR/click-cycloaddition sequential reaction protocol is described. The main features of the macrocyclic scaffolds are a peptoid moiety, a 1,3-substituted indole nucleus, and a triazole ring.

The impact of macrocyclic structures on modern medicinal chemistry is demonstrated by the diverse structures that display significant biological properties.[1] The prevalence of macrocyclic structures in natural products[2] and synthetic derivatives[3] has stimulated the development of elegant and efficient syntheses, particularly as applied to the search for new drugs.[1] The indole heterocyclic system is found in several natural and synthetic macrocyclic structues, many of them with remarkable biological functions.[4] The indole heterocyclic platform is frequently found in alkaloid compounds, especially those that regulate biological functions.[4-6] The biosynthesis of most of the these natural alkaloids derives from the amino acid tryptophan and/or its decarboxylated derivative tryptamine.[7]

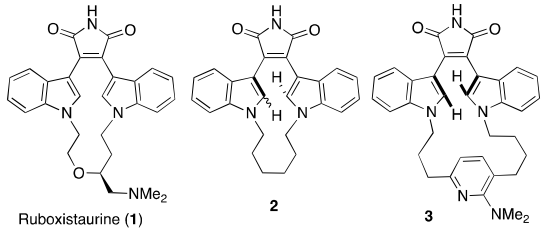
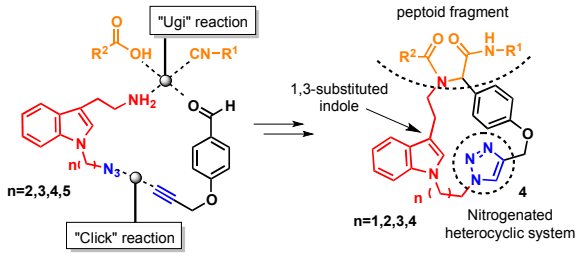


Figure 1. Indole-based macrocycles.

Ruboxistaurin **1** (Figure 1), for example, is a synthetic bis-1,3-disubstituted indole macrocyclic molecule found to selectively inhibit protein kinase C beta (PKC-β) and has been proposed for the treatment of diabetic retinopathy and macular edema.[8] Interestingly in related inhibitory molecules **2** and **3**, the kinase selectivity could be modulated by changing the size of the macrocycle. Shorter chains caused a conformational change of the bis-indoles leading to preference for the *anti*-conformer **2** (Figure 1) and providing some selectivity towards inhibition of GSK3-β. In contrast, longer chains favored *syn*-conformer **3**, resulting in enhanced PKC-β inhibition.[8] In the active macrocycle 3, three main structural motifs are anticipated: a 1,3-substituted indole, an imide, and a 1,4-substituted pyridine ring (nitrogenated heterocyclic system). Encouraged by the interest in the macrocyclic 1,3-substituted indole units, we developed a methodology for the synthesis of macrocyclic structures with various ring sizes that would contain a peptoid moiety, a 1,3-substituted indole (tryptamine-based), and a triazole ring, with the general structure of **4** (Scheme 1).

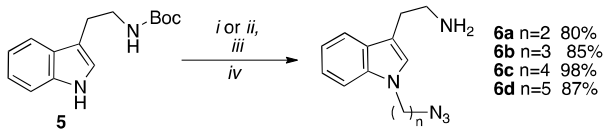


Scheme 1. Construction of macrocycles containing a 1,3-substituted indole, a peptoid moiety and a triazole..

In recent years both the Ugi four component reaction (4-CR) and the copper(I)-catalyzed azide alkyne cycloaddition (CuAAC), the most frequently used "click" reaction, have emerged as efficient methodologies for the construction of a range of different

macrocyclic structures for different purposes.[9] It is worth noting that both methodologies produce adducts with important pharmacological properties. Accordingly, the Ugi 4-CR reaction represents a highly convergent and effective methodology for the construction of peptoid backbones from four different starting materials (an aldehyde, a carboxylic acid, an amine, and an isocyanide).[10] The structure of the peptoid motif, obtained in a Ugi 4-CR, can be modulated by choosing the appropriate structures for the four component-input set. On the other hand, CuAAC have been utilized as an efficient protocol to close macrocycles of different sizes by formation of 1-4 triazoles.[11] In this report, we describe a practical approach for rapid access to a tryptamine-based macrocyclic skeleton containing a peptoid Ugi-adduct and a 1,4-substituted triazole.

The structure of N-alkylated tryptamine **6a-d** was chosen as the template from which the macrocycle would be constructed in accordance with the Scheme 2. Accordingly, the *N*-Boc tryptamine was alkylated with the corresponding alkyldihalide reagent (for n=2, 1,2-dichloroethane, for n=3, 1-bromo-3-chloropropane, for n=4 1,4-dibromobutane and for n=5, 1,5-dibromopentane were used; Scheme 2). Then, the remaining halide in the side alkyl chain was substituted by an azide group under standard conditions, and finally, removal of the Boc protection of the amine (Scheme 2). In the case of the alkylation with 1-bromo-3-chloropropane (n=3), NaH was used as a base in anhydrous THF to avoid the competing bromo elimination process. It is worth pointing out that starting amines **6a-d** could be obtained in gram scale in good overall yields over the three steps, and required only one column chromatography purification (Scheme 2).

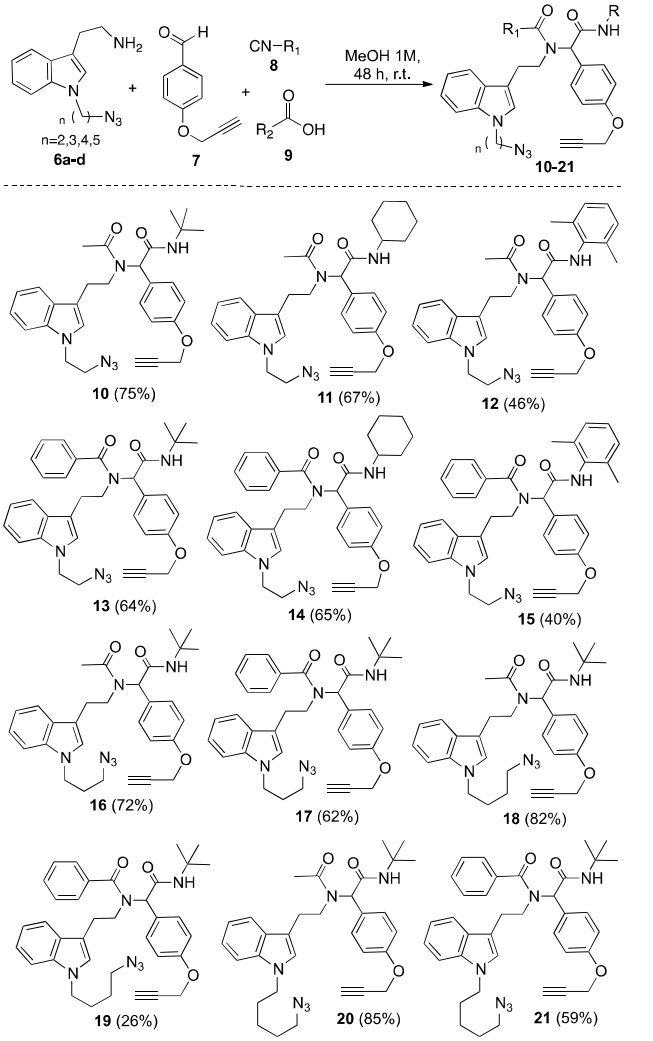


Scheme 2. *Conditions*. i. $X(CH_2)_nX$, *n*-Bu_4NI, NaOH 50%, THF, 50 °C, 8 h. ii. For n=3, NaH, THF, r.t. iii. NaN_3, DMSO, 80 °C, 3 h. iv. HCOOH 0.3M, 0.5 h

We chose propargyl aldehyde **7** as the aldehyde input in the Ugi reaction. This reagent was prepared by propargylation of 4-hydroxybenzaldehyde under previously reported reactions conditions.[12]

With the amines **6a-d** and aldehyde **7** components in hand, we sought to optimize the Ugi four-component reaction conditions. We first investigated our previously reported conditions[13] by performing the reaction at room temperature in methanol in the presence of $InCl_3$ as catalyst. Under these conditions the Ugi adduct was isolated in 60% along with recovery of starting materials. Later a brief survey of conditions indicated that the presence of $InCl_3$ was not necessary. High temperature also was not beneficial for the reaction. The use of dichloromethane or acetonitrile as the solvent did not improve the product yield (See S11 in supporting information). Thus the transformation proceeded in acceptable 75% yield, in a 1M solution of 1 equivalent of each component, using methanol as the solvent and during 48 h, at room temperature. Under these conditions, twelve Ugi adducts were prepared from amines **6a-d** and benzaldehyde **7** using acetic (**10-12**, **16**, **18**, **20**) or benzoic acid (**13-15**, **17**, **19**, **21**) in combinations with three different isonitriles, including *tert*-butylisonitrile (**10**, **13**, **16-18**, **19-21**), cyclohexylisonitrile (**11** and **14**), and 2,6-dimethylphenylisonitrile (**12**, **15**); these were all commercially available reagents. Yields and structures of the products of these reactions are presented in Table 1. Except for the adduct **19** which was obtained in a low 26% yield, most the other products were obtained in moderate to good yields (Table 1).

Table 1. Ugi four-component reactions.



Conditions: 1 eq amine, 1 eq aldehyde, 1 eq isocyanide, 1 eq acid in MeOH 1M, 48 h, r.t.

We then undertook the macrocyclization process using the Ugi adducts as substrates in the copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC). Thus, Ugi adduct **10** was chosen as the model compound to optimize the reaction conditions to obtain the 18-membered macrocyclic scaffold **22** (Table 2). The first attempt for the cyclization process was based on the methodology reported by Marcaurelle and coworkers[14] using Amberlyst 21/$CuPF_6$ in toluene at 0.02M concentration (entry 1). Under these conditions the starting material at room temperature was recovered unchanged; however, when the reaction was heated to reflux (entry 2), 48% yield of the desired product was obtained along with 52% of recovered

starting material. The use of TBTA (tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine) and $Cu(MeCN)_4BF_4$ in dichloroethane, as reported by James and Chouhan[15] (entry 3), yielded the macrocyclic product in a similar 50%. In the absence of the TBTA, formation of the product was not observed (entry 4) and with shorter reaction time under microwave irradiation, the product yield was slightly decreased (entry 5). We increased the temperature of the reaction to 110 ºC by using toluene as the solvent and the reaction was carried out using 20 mol% of inexpensive CuBr[16] and DBU as a base, under a more dilute concentration (0.005M); under these conditions, we initially recovered only the starting material (entry 6). However, when microwave irradiation was used, the expected macrocycle **22** was obtained in 32% (entry 7). Finally, the use of 40 mol% of CuBr under microwave conditions lead to the isolation of the product in a satisfactory 75% yield (entry 8).

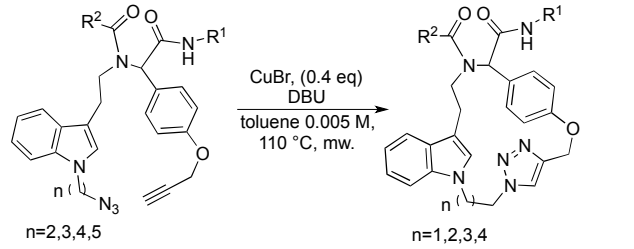
Table 2. Optimization of the azide-alkyne cycloadditions for the transformation of **10** into **22**.

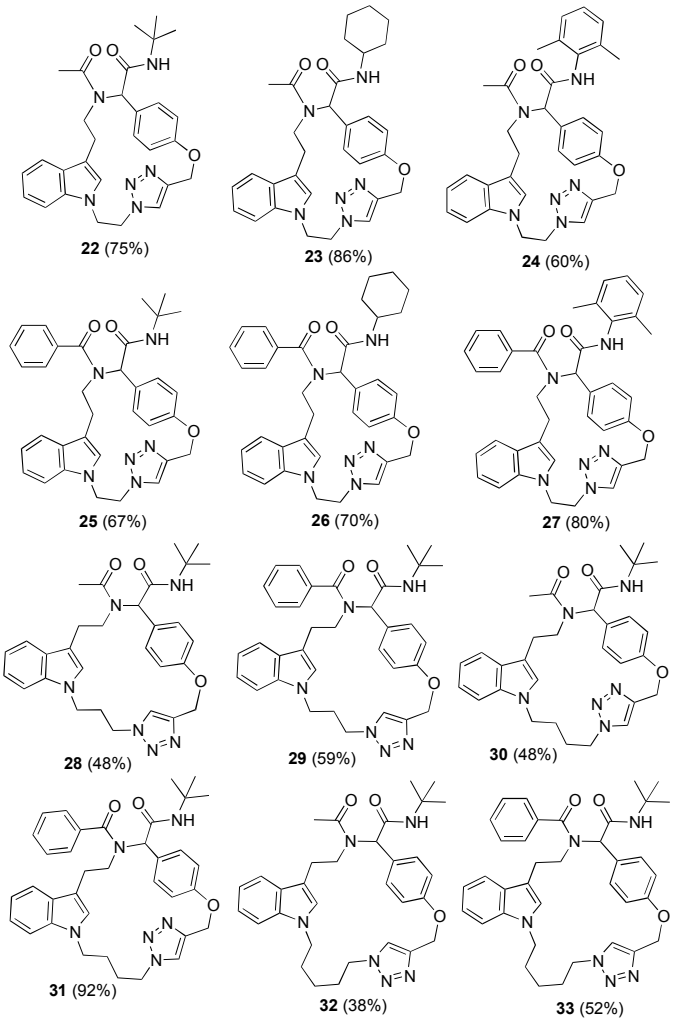
Ex	copper source	additive	solvent	temp. (ºC)	time (h)	Yield (%)
1	Amberlyst 21/$CuPF_6$	-	Toluene 0.02M	25	72	-
2[a]	Amberlyst 21/$CuPF_6$	-	Toluene 0.02M	110	72	48%
3[a]	$Cu(MeCN)_4BF_4$ 5 mol%	TBTA 5 mol%	DCE 0.01M	55	72	50%
4[a]	$Cu(MeCN)_4BF_4$ 5 mol%	-	DCE 0.02M	55	72	-
5[b]	$Cu(MeCN)_4BF_4$ 5 mol%	TBTA 5 mol%	DCE 0.02M	55	4	42%
6[a]	CuBr 20 mol%	DBU 100 mol%	Toluene 0.005M	110	72	-
7[b]	CuBr 20 mol%	DBU 100 mol%	Toluene 0.005M	110	4	32%
8[b]	CuBr 40 mol%	DBU 100 mol%	Toluene 0.005M	110	4	75%

[a] *Conventional heat.* [b] *Microwave*

Once the optimized conditions were established, the remaining Ugi adducts were submitted to the macrocyclic process. Thus, macrocycles **23** and **24** where the isonitrile moiety was varied (cyclohexyl and 2,6-dimethylphenyl substituents) were obtained both in good yields from **11** and **12**, respectively. The structure of **24** was confirmed by single-crystal X-ray diffraction analysis (Figure 2).[17] Likewise, introduction of the benzoic acid moiety did not affect the performance of the macrocyclization process and **25**-**27** were obtained also in good yields from the corresponding azide-alkyne **13**-**15**. Parent homologues **28** and **29** were obtained from the respective Ugi adducts **16** and **17**, though in lower yields. A remarkable difference in the macrocyclization process was observed when adduct **18** and **19**, bearing four carbon atoms in the N-alkyl chain of the indole, were submitted to the macrocyclization process. Acetic acid derivative **18** afforded macrocycle **30** in 48% yield, while the analog derived from benzoic acid **19** gave the corresponding product **31** in superior 92% yield. Interestingly, the addition of one more atom in the chain allowed the macrocyclization process and **32** and **33** were obtained from adducts **20** and **21** in 38% and 52% yields, respectively. Table 3 summarizes twelve novel tryptamine- derived macrocycles obtained through the Ugi reaction followed by a click-macrocyclization process. It is worth noting that the present protocol opens up a practical entry to explore structural diversity in this later class of macrocycles, not only by further variation of the isonitrile and carboxylic acid moieties, but also by the alternative use of different alkynyl-aldehydes (analogs of **7)** with a different aromatic system (i.e., 1,3-substituted indole) and/or with variations in chain length. These experiments along with the study of cytotoxic activity of these macrocycles are in progress in our laboratory and will be reported in due course.

Table 3. Microwave assisted click-cycloaddition reaction protocol.





Conditions: 1eq Ugi adduct, 1eq DBU, 0.4 eq CuBr in toluene 0.005 M, 6 h, 110 °C, mw.

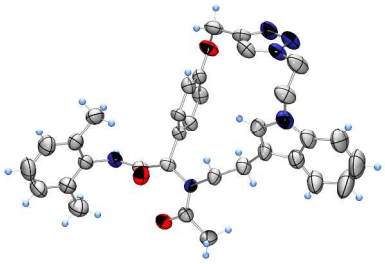


Figure 2. ORTEP representation of the molecular structure of compound **24**.[17]

Conclusions

In closing, we have achieved a practical synthesis of novel tryptamine-based macrocycles using a Ugi 4-CR/click-cycloaddition sequential reaction protocol. The main features of the macrocyclic scaffolds are a peptoid moiety, a 1,3-substituted indole nucleus, and a triazole ring. The present protocol offered the opportunity to explore structural diversity by variation of the isonitriles and carboxylic acids in the four-component set in the Ugi reaction, and leaves room for further exploration of structural and biological functional diversity in these novel macrocyclic scaffolds.

Notes and references

[a] Instituto de Química, Universidad Nacional Autónoma de México, Circuito Exterior S.N., Ciudad Universitaria, Coyoacán, México, D.F. O4510, México.

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Electronic Supplementary Information (ESI) available: Experimental procedures, NMR spectra and characterization for new materials. See DOI: 10.1039/c000000x/

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17. ORTEP representation of the molecular structure of compound X in the crystal with 30% ellipsoid probability. The hydrogen atoms are omitted for clarity. CCDC1043211 contain the supplementary crystallography data for this paper. Copies of these data can be obtained, free of charge, from the Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.