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Synthetic Communications

An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: http://www.tandfonline.com/loi/lsyc20

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To cite this article: Ramasamy Anandhan, Ayyavoo Kannan & Perumal Rajakumar (2016): Synthesis and Anti-Inflammatory Activity of Triazole Based Macrocyclic Amides through Click Chemistry, Synthetic Communications, DOI: 10.1080/00397911.2016.1254800

To link to this article: http://dx.doi.org/10.1080/00397911.2016.1254800

Synthesis and anti-inflammatory activity of triazole based macrocyclic amides through click chemistry

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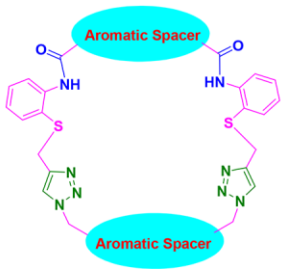
Abstract

Triazole based macrocyclic amides **1-12** with amide group as the intrannular functionality has been synthesized through click chemistry. Triazole based macrocyclic amides **1**–**12** show good anti-inflammatory activity even at low concentration (50 µg/mL) when compared to that of the reference drug prednisolone. BINOL based chiral macrocyclic amides and pyridine based macrocyclic amides show better anti-inflammatory activity than the other synthesized macrocyclic amides.

Graphical Abstract

Triazole based macrocyclic amides with amide group as the intrannular functionality has been synthesized through click chemistry. All the triazole based macrocyclic amides show good anti-inflammatory activity even at low concentration (50 µg/mL) when compared to that of the reference drug prednisolone.



KEYWORDS: click chemistry, macrocyclic amides, anti-inflammatory, NSAIDs

1. INTRODUCTION

Cyclophane amides are biologically active supramolecular motifs[1] used as molecular clefts,[2] molecular receptors[3] and for molecular recognition. [4]In particular cyclophane amides[5] can form complexes with fluoride, chloride, bromide and phosphate anions, and also can exhibit antimicrobial activity with various human pathogenic bacteria and plant pathogenic fungi. Incorporation of chiral unit into cyclophanes is an essential phenomenon in the field of chiral separations and analysis,[6] asymmetric synthesis,[7] supramolecular material science,[8] host–guest chemistry[9] and chiral biomolecules such as proteins, nucleic acids and carbohydrates. On the other hand, the synthesis of amide functionalized cyclophaneshas received considerable attention due to their biological importance includinganti-inflammatory,[10] cytotoxic,[11] and anticonvulsant activities.[12]

NSAIDs (NonSteroidal Anti-Inflammatory Drugs) such as aspirin, ibuprofen, naproxen and fenbufenare commonly used for the treatment of pain, fever, and inflammation particularly arthritis.[13] Such common NSAIDs gives only temporary relief[14] and have many side effects such as dyspepsia, gastrointestinal bleeding, perforation in addition to renal failure and distinct salicylate intoxication.[15] To overcome such side effects, 1,2,3-triazoleas drug delivery system has been developed to enhance the activity of NSAIDs and limit their side effects, which promise to be safer than their traditional NSAID counterparts over the years.[16] During recent times considerable attentionhas been focused on the synthesize and anti-inflammatory activity of various novel ‘clickable’’1,2,3-triazole based cyclophanes. The main challenge in preparing macrocyclic compound using “click” cyclization is to find a macrocyclic amenable to

efficient end-group modification at opposite ends of azides and alkynes. 1,2,3-Triazole can serve as hydrogen bond acceptors and can function as an effective amide mimicin various biological applications.[17] "Click" reaction results from the ligation of azides and alkynes to give a 1,2,3-triazole moiety and has great potentialfor the synthesis of macrocyclic molecules. On the other hand, during recent years Cu(I) has been utilizedas an efficient protocol to generate macrocycles of different sizes by the formation of 1,2,3-triazole ring system.[18] In particular, the synthesis and *in vitro* anti-arthritic[19] andanti-inflammatory activities of amide based cyclophanes has been reported from our laboratory.[20] Recently, our research focus on the utility of Cu(I) catalyzed click chemistry for the synthesis of macrocylic amides. Therefore, we wish to report herein the synthesis and In-vitro anti-inflammatory activity of triazole based macrocyclic amides **1-12** by click chemistry approach (Figure 1).

RESULTS AND DISCUSSION

2-Aminothiophenol **13** on *S*-alkylation with propargyl bromide in the presence of KOH and catalytic amount of TBAB (10 mg) in a mixture of toluene/H_2O (1:1) afforded *S*-propargyloxy-2-aminothiophenol **14** in 83% yield. Further, reaction of 2.1 equiv. of *S*-propargyloxy-2-aminothiophenol **14** with one equiv. of isophthaloyl chloride **15,** pyridine-2,6-dicarboxylic acid chloride **16,** thiophenedicarboxylic acid chloride **17** and (S)-BINOL diacid chloride **18** in the presence of triethylamine in DCM for 12 h at room temperature afforded the precyclophane amides **19, 20, 21** and **22** in 65%, 71%, 64% and 68% yields, respectively.

The ^{1}H NMR spectrum of the precyclophane amide **20** displayed a triplet at δ 2.00 for acetylenic protons and singlet at δ 10.70 for amide NH protons in addition to the signals for the other aliphatic and aromatic protons. In the ^{13}C NMR spectrum, the amide precyclophane **20** showed the acetylenic carbons at δ 72.4 and 79.0 and the amide carbonyl carbon at δ 160.4 in addition to the signals for the other aliphatic and aromatic carbons. The mass spectrum (ESI-MS) of **20** showed the molecular ion peak at m/z 457. Further, the structure of the precyclophane amide **20** was also confirmed from elemental analysis. Similarly, the structure of precyclophane amides **19, 21** and **22** was confirmed from the spectral and analytical data.

Triazole based macrocylic amides**1-6** were synthesized in 72%, 71%, 58%, 55%, 75% and 73% yields, respectively by treating one equiv. of precyclophane amide **19** and **20** with one equiv. of 1,4-xylenediazide **23,** 1,4-dimethoxy-2,5-xylenyldiazide **24** and 1,3-azidomethylprydine **25** in the presence of 5 mol % $CuSO_4.5H_2O$ with 10 mol % sodium ascorbate (Scheme 2). In ^{1}H NMR spectrum, macrocyclic amide **4** showed sharp singlets at δ 3.57, 4.00 and 5.21 for *O*-methyl, *S*-methylene and *N*-methylene protons respectively and a singlet at δ 10.71 for the amide NH proton in addition to the signals for fifteen aromatic protons. The ^{13}C NMR spectrum of macrocyclic amide **4** showed *O*-methyl, *S*-methylene and *N*-methylene carbons at δ 28.6, 46.5 and 53.9 respectively and amide carbonyl at δ 159.6 in addition to the signals for fourteen aromatic carbons. The mass spectrum (ESI-MS) of **4** showed the molecular ion peak at *m/z* 705 (M^{+}). Further, the structure of the macrocyclic amide **4** was also confirmed from elemental analysis.

In ^{1}H NMR spectrum, macrocyclic amide **5** showed sharp singlets at δ 4.18 and 5.43 for *S*-methylene and *N*-methylene protons respectively and a singlet at δ 9.29 for the amide NH proton in addition to the signals for the other aliphatic and aromatic protons. The ^{13}C NMR spectrum of macrocyclic amide **5** showed *S*-methylene and *N*-methylene carbons at δ 32.6 and 55.0 respectively and amide carbonyl carbon at δ 163.5 in addition to the signals for the other aliphatic and aromatic carbons. The mass spectrum (ESI-MS) of **5** showed the molecular ion peak at *m/z* 646 (M^+). Further, the structure of the macrocyclic amide **5** was also confirmed from elemental analysis. Similarly, the structure of macrocyclic amide **1**, **2**, **3**, and **6** was confirmed from spectral and analytical data.

Next, we focussed our attention on the synthesis of thiophene based macrocyclic amides **7**, **8** and **9**. Reaction of the precylophane **21** with one equivalent of 1,4-xylenediazide **23,** 1,4-dimethoxy-2,5-xylenyldiazide **24** and 1,3-azidomethylprydine **25** gave themacrocyclic amide **7**, **8** and **9** in 72%, 63% and 77% yields, respectively (Scheme 3).

In ^{1}H NMR spectrum, the macrocyclic amide **8** showed sharp singlets at δ 3.71, 4.12 and 5.30 for *O*-methyl, *S*-methylene and *N*-methylene protons respectively and a singlet at δ 9.22 for the amide NH proton in addition to the signals for the other aliphatic and aromatic protons. The ^{13}C NMR spectrum of macrocyclic amide **8** showed *O*-methyl, *S*-methylene and *N*-methylene carbons at δ 29.7, 49.5 and 56.2 respectively and amide carbonyl carbon at δ 158.6 in addition to the signals for the other aliphatic and aromatic carbons. The mass spectrum (ESI-MS) of **8** showed the molecular ion peak at *m/z* 711 (M^+). Further, the structure of the macrocyclic amides **8** was also confirmed from

elemental analysis. Similarly, the structure of other triazole based macrocyclic amides **7** and **9** was also confirmed from the spectral and analytical data.

Incorporation of chiral (S)-BINOL unit in the cyclophanes amide would be more promising with reference to the biological application.[21] Triazole based chiral macrocyclic amides **10-12** were obtainedin 63%, 59% and 69% yields, respectively by the reaction of one equiv. of the chiral precyclophane amide **20** with one equiv. of 1,4-xylenyldiazide **21** 1,4-dimethoxy-2,5-xylenyldiazide **22** and 1,3-azidomethylprydine **25** under click reaction conditions (Scheme4).

In the ^{1}H NMR spectrum, the triazole based macrocyclic amide **10** showed sharp singlets at δ 3.42 and 5.15 for *S*-methylene and *N*-methylene protons respectively, a pair of doublets at δ 4.46 and 4.53 for *O*-methylene protons attached to the S(-)-BINOL unit and a singlet at δ 8.72 for amide NH protons in addition to the signals for the aromatic protons. The ^{13}C NMR spectrum of the triazole based chiralmacrocyclic amide **10** showed *S*-methylene, *N*-methylene and *O*-methylene carbons attached to the S(-)-BINOL unit at δ 29.7, 53.2 and 69.71 respectively, amide carbonyl at δ 166.2 in addition to the signals for nineteen aromatic carbons. The mass spectrum (ESI-MS) of **10** showed the molecular ion peak at *m/z* 880 (M^{+}). Further, the structure of the triazole based chiralmacrocyclic amide **10** was also confirmed from elemental analysis. Similarly, the structures of the triazole based macrocyclic amides **11** and **12** were also confirmed from the spectral and analytical data.

ANTI-INFLAMMATORY ACTIVITY

The lysosomal enzymes released during inflammation produce a variety of disorders. The extracellular activity of these enzymes is related to acute or chronic inflammation. Since the HRBC membranes are similar to lysosomalmembrane components, the prevention of hypotonicity induced HRBC membrane lysis is taken as a measure of anti-inflammatory activity of drug. The triazole based cyclophane amides **1-12** were screened for *in-vitro* anti-inflammatory activity.Percentage stabilization of the membrane in the presence of macrocyclic amides **1-12** at various concentration levels of 2.5, 5, 10, 50, 100, 400, 800 and 1000 µg/mL is shown in Figure 2. The anti-inflammatory activities of all the macrocyclic amides are concentration dependent. All the cyclophane amides **1-12** showed better anti-inflammatory activity at lower concentration of 50 µg/mL than at all other concentrations. Chiral BINOL macrocyclic amides and thiophene macrocyclic amides showed better anti-inflammatory activity than the other cyclophanes amides.

Anti-inflammatory of activity BINOL amides could be due to their binding on to the erythrocyte membrane with subsequent alteration of the charges. In particular chiral (S)-BINOL macrocyclic amides **10**, **11**, and **12** exhibits better anti-inflammatory activity than all other macrocyclic amides at all concentrations which shows that their binding on to the membrane of the erythrocyte is very effective which could be due to the presence of rigid chiral BINOL unit and more number of triazoles units. This might have prevented physical interaction with aggregating agents or promote dispersal by mutual repulsion of like charges which are involved in the haemolysis of red blood cells.

EXPERIMENTAL SECTION

Materials And Methods

All reagents were commercially available and used as such unless otherwise stated. The diacid chlorides **15**, **16,17** and **18** were prepared from corresponding diacid, as reported earlier from our laboratory.[22] All melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded with BRUKER 300MHz instruments in deuterated chloroform ($CDCl_3$) with Tetramethylsilane (TMS) as internal standard. Elemental analyses were carried out using a Perkin- Elmer CHNS 2400 instrument. Column chromatography was performed on silica gel (ACME, 100–200 mesh). Routine monitoring of the reaction was made using thin layer chromatography developed on glass plates coated with silica gel-G (ACME) of 25 mm thickness and visualized with iodine.

General Procedure For The Cu (I) Catalyzed Click Reaction

A mixture of azide (1.0 mmol, 1 equiv.), alkyne (1.0 mmol, 1 equiv.) was dissolved in THF/H_2O (1:1; 20 mL) and added NaAsc (0.4 mmol, 0.4 equiv.) followed by the addition of $CuSO_4.5H_2O$ (0.2 mmol, 0.2 equiv.). The reaction mixture was stirred overnight at room temperature. The solvent was evaporated and the crude product obtained was dissolved in EtOAc (2 X 100 mL), washed with brine solution (50 mL), dried over Na_2SO_4 and concentrated to give a residue, which was purified by column chromatography (SiO_2).

Triazole Based Cyclophane Amide 1

Yield: 72%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.14 (s, 4H), 5.45 (s, 4H), 6.89 (s, 1H), 6.97 (s, 4H), 7.17 (t, *J* = 7.5 Hz, 2H), 7.26 (s, 3H), 7.41 (s, 2H), 7.72-7.77 (m, 2H), 8.07 (dd, *J* = 6.3 Hz, *J* = 1.5 Hz, 2H), 8.39-8.42 (m, 2H), 9.41 (s, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 32.0, 53.5, 119.7, 121.8, 122.5, 124.7, 125.4, 128.0, 130.7, 134.8, 134.9, 136.5, 140.3, 163.4 ppm. MS (EI): *m/z*= 644 [M^+]. Elemental Anal.Calcd for $C_{34}H_{28}N_8O_2S_2$: C, 63.33; H, 4.38; N, 17.38 %. Found: C, 63.19; H, 4.32; N, 17.40 %.

CONCLUSION

In conclusion, the triazole based macrocyclic amides **1-12** with amide group as the intrannular functionality have been synthesised through click chemistry. All the triazole based cyclophane amides **1-12** show good anti inflammatory activity even at low concentration of 50 µg/mL than the reference drug prednisolone. The BINOL based chiral macrocyclic amides and thiophene based macrocyclic amides show better anti-inflammatory activity than the other macrocyclic amides.

ACKNOWLEDGMENTS

The authors thank CSIR, New Delhi, India, for financial assistance and DST-FIST for providing NMR facility to the department and Prof. D. Chamundeeswari, Ph.D., Department of Pharmacognozy, College of Pharmacy, Sri Ramachandra University, Chennai-600 116, for the *in vitro* anti-inflammatory studies.

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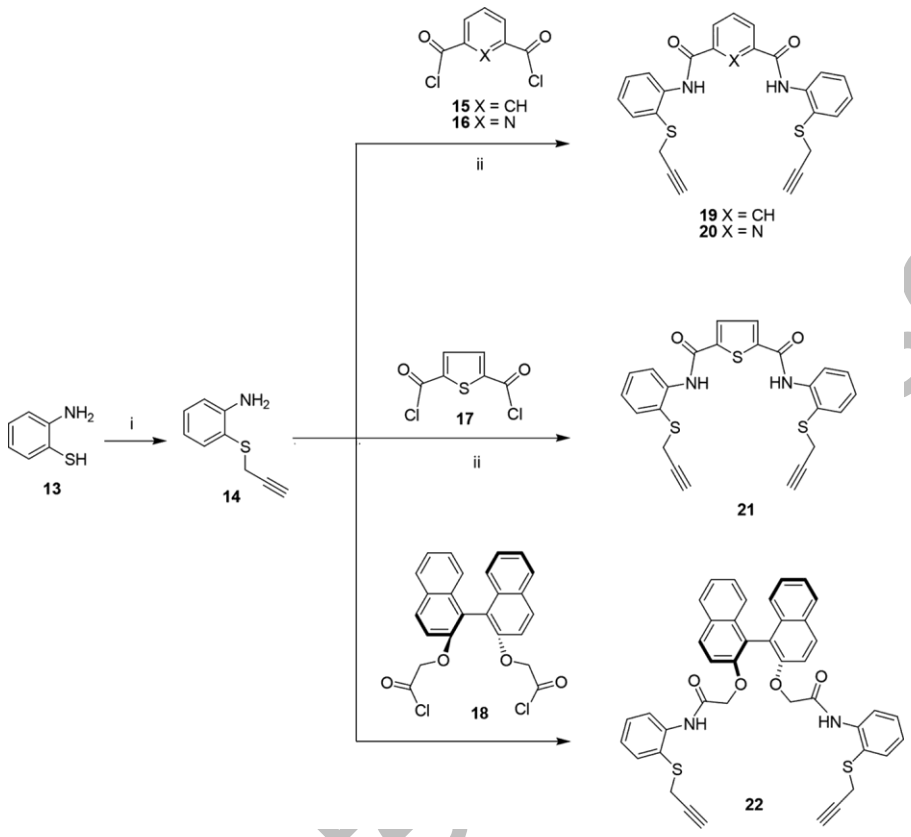
Table 1. *In vitro* anti-inflammatory activity of cyclophanes amideson HRBC membrane stabilization

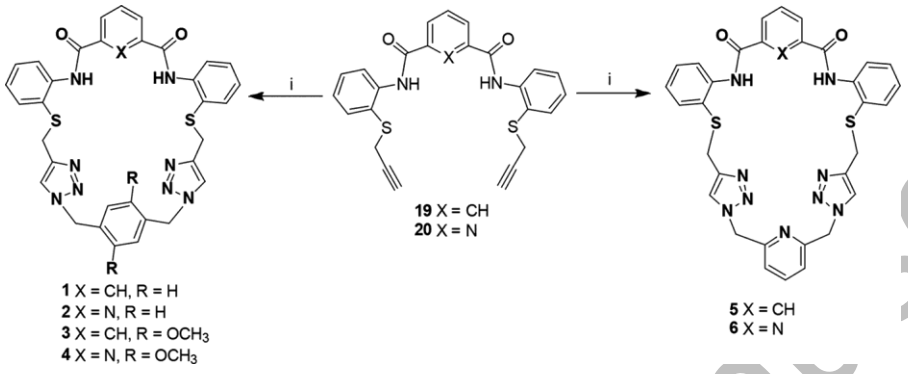
Cyclophanes amides	Activity (% prevention of lysis)						
	5 µg/mL	10 µg/mL	50 µg/mL	100 µg/mL	400 µg/mL	800 µg/mL	1000 µg/mL
1	46.24 ± 0.80	57.34 ± 1.00	82.95 ± 0.77	80.05 ± 0.81	79.41 ± 0.43	80.00 ± 0.55	80.05 ± 1.01
2	47.19 ± 1.10	65.00 ± 0.63	84.80 ± 0.52	84.00 ± 0.90	81.00 ± 0.80	80.00 ± 1.04	80.80 ± 0.83
3	65.25 ± 0.99	65.84 ± 0.55	91.01 ± 0.41	87.63 ± 0.35	88.14 ± 0.71	90.32 ± 0.78	90.84 ± 0.55
4	67.97 ± 0.77	80.27 ± 0.80	93.00 ± 0.99	89.22 ± 0.92	84.05 ± 0.65	84.98 ± 0.74	84.27 ± 0.87
5	48.52 ± 0.27	56.79 ± 0.74	85.74 ± 0.33	83.11 ± 0.98	80.70 ± 0.66	81.90 ± 0.49	72.17 ± 0.77
6	49.54 ± 0.41	79.67 ± 0.45	85.14 ± 0.70	85.08 ± 0.54	82.52 ± 0.61	84.39 ± 1.08	79.67 ± 0.73
7	70.25 ± 0.78	88.54 ± 0.90	96.74 ± 0.47	91.00 ± 0.93	91.14 ± 0.63	88.48 ± 1.01	89.4 ± 0.33
8	63.52 ± 0.41	81.41 ± 0.86	95.84 ± 0.51	89.19 ± 0.38	93.37 ± 0.54	93.52 ± 0.75	94.41 ± 0.86
9	71.97 ± 0.76	90.00 ± 0.40	95.08 ± 0.54	93.82 ± 0.49	93.46 ± 0.92	91.69 ± 1.11	91.00 ± 0.30

10	70.24 ± 0.58	80.42 ± 0.82	95.28 ± 0.36	93.94 ± 0.27	89.87 ± 0.59	91.39 ± 0.62	93.42 ± 0.82
11	76.10 ± 0.60	82.54 ± 0.81	98.21 ± 0.30	94.63 ± 0.25	95.67 ± 0.51	96.23 ± 0.66	95.54 ± 0.81
12	77.64 ± 0.91	87.27 ± 0.92	98.74 ± 0.49	94.22 ± 0.32	96.05 ± 0.60	95.98 ± 0.81	95.27 ± 0.92
Prednisolone	15.27 ± 0.76	25.16 ± 0.76	40.05 ± 0.76	59.34 ± 0.76	86.37 ± 0.76	-	-

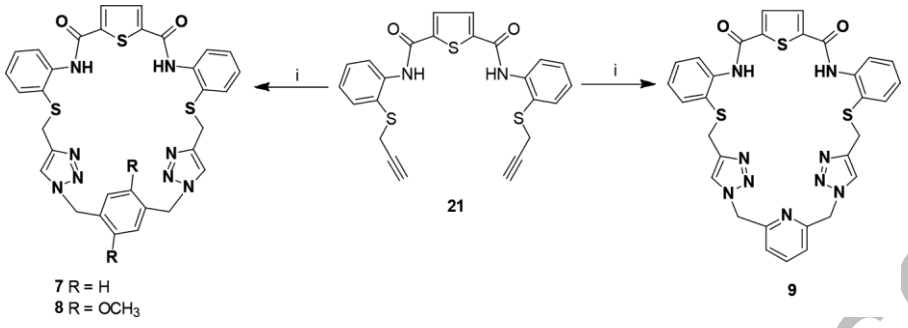
Scheme 1. **Reagents and conditions**: (i) Propargyl bromide (1.2 equiv), KOH, TBAB(cat), Toluene-H_2O (1:1), reflux, 5 h, **14** (83%); (ii) TEA, DCM (dry), 12 h. **19** (65%), **20** (71%), **21** (64%) and **22** (68%).



Scheme 2. **Reagents and conditions**: (i) 1,4-xylenediazide **23,** 1,4-dimethoxy-2,5-xylenyldiazide **24** and 1,3-azidomethylprydine **25,** $CuSO_4$ (5 mol %), sodium ascorbate (10 mol %), H_2O/THF (1:1) r.t., 10 h; **1 (**72%), **2** (71%), **3** (58%), **4** (55%), **5** (75%) and **6** (73%).



Scheme 3. **Reagents and conditions**: (i) 1,4-xylenediazide **23,** 1,4-dimethoxy-2,5-xylenyldiazide **24** and 1,3-azidomethylprydine **25,** $CuSO_4$ (5 mol %), sodium ascorbate (10 mol %), H_2O/THF (1:1) r.t., 10 h; **7 (**72%), **8** (63%) and **9** (77%).



Scheme 4. **Reagents and conditions**: (i) 1,4-xylenediazide **23,** 1,4-dimethoxy-2,5-xylenyldiazide **24** and 1,3-azidomethylprydine **25,** $CuSO_4$ (5 mol %), sodium ascorbate (10 mol %), H_2O/THF (1:1) r.t., 10 h; **10 (**63%), **11** (59%) and **12** (69%).

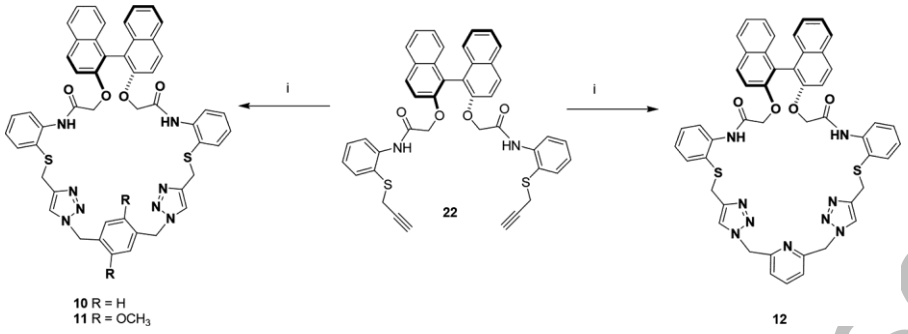
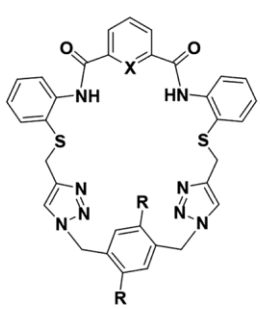
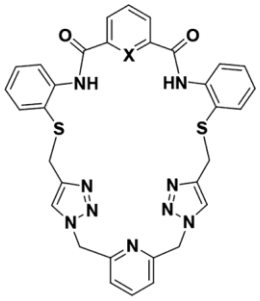


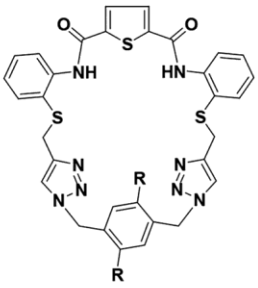
Figure 1. Structure of triazole based macrocyclic amides **1-12**



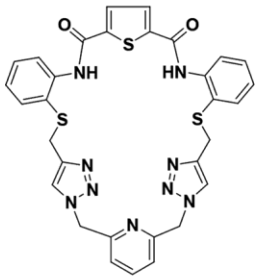
1 X = CH, R = H
2 X = N, R = H
3 X = CH, R = OCH_3
4 X = N, R = OCH_3



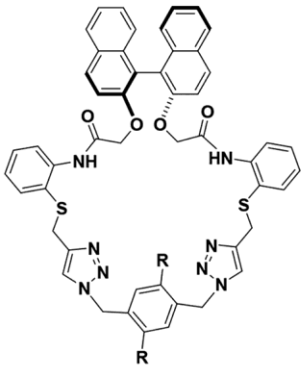
5 X = CH
6 X = N



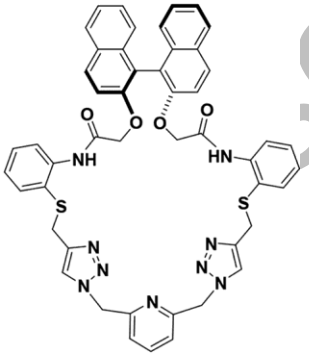
7 R = H
8 R = OCH_3



9



10 R = H
11 R = OCH_3



12

Figure 2. Anti-inflammatory activity of macrocyclic amides **1-12**