CHAPTER IV
DEVELOPMENT OF BENZOXAZINE MACROCYCLES FOR SUPRAMOLECULES/MOLECULAR NECKLACE VIA CLICK CHEMISTRY

4.1 Abstract

Molecular necklace based on benzoxazine macrocycle unit containing alkyne group and alkyl chain containing diazide group connected together via Click chemistry is proposed. By using propargyl amine in preparation of benzoxazine monomer, followed by the ring opening dimerization and the polycondensation with diacid chloride, benzoxazine macrocycle containing mono- or di alkyne groups can be obtained. The modification of dibromobutane with sodium azide leads to diazidobutane compound which allows the final step of the Click chemistry between macrocyclic benzoxazine and diazido compound with Cu catalyst to obtain molecular necklace.

4.2 Introduction

Supramolecules are defined in term of polymolecules that result from intermolecular association based on molecular recognition of individual molecules as host-guest interaction.[1] Normally, structure of supramolecules can be acyclic structure; cholic acid[2], cyclic structure; crown ether (G.W. Gokel *et al.*, 2004)[3], cyclodextrin[4], and calixarenes[5] and hierarchical structure, sophisticated mechanically interlocked compounds with complicated structures, such as molecular shuttles[6], molecular elevators[7] and molecular necklace[8].

Molecular necklace is development of topological structure based on connected macrocycles. The preparation of molecular necklace has been proposed in terms of aggregation[9], complexation[10] and copolymerization[11], e.g.

For the past several years, our group has established benzoxazine supramolcular chemistry especially the benzoxazine dimer-based supramolecular structures and macrocycles.[12, 13] The reaction of benzoxazine with alkyl chain

containing diacid chloride or ditosyl group leads to a quantitative macrocyclization with the average yield (80-85%).

The present work, therefore, proposes the molecular necklace based on the benzoxazine macrocycles linked with alkyl chains. As Click chemistry is a convenient pathway to combine the molecules with alkyne and azide group via triazole linkage since the reaction is a selective reaction carried out in mild condition as room temperature[14, 15], the present work demonstrates how this reaction is practical to obtain benzoxazine molecular necklace when the components of the molecules are mono- and/or dialkyne containing benzoxazine macrocycles and diazide containing alkane.

4.3 Experimental

4.3.1 Chemical

2,4-Dimethylphenol and 1,4-dibromobutane were purchased from Merck Millipore. Formaldehyde solution was purchased from RCI Labscan, Thailand. Propargylamine, terephthaloyl chloride and sodium hydroxide were purchased from Sigma Aldrich. Deuterated chloroform ($CDCl_3$) and deuterium oxide (D_2O) were purchased from Sigma Aldrich. Sodium hydroxide and sodium sulphate anhydrous were purchased from Ajax Finechem. Dichloromethane, dimethtylformamide, isopropanol, 1,4-dioxane and acetone were purchased from RCI Labscan, Thailand.

4.3.2 Instruments

Fourier transform infrared spectra (FTIR) were recorded by a Nicolet Nexus 670 FT-IR spectrometer in the range 4000-400 cm^{-1} Proton nuclear magnetic resonance spectra (^{1}H-NMR) were obtained from a Bruker Avance nuclear magnetic resonance (NMR) spectrometer (Germany) operating at Larmor frequencies of 500.13 MHz. Mass spectroscopy was analysed by a Bruker a micrOTOF II electrospray ionization mass spectrometer (ESI-MS) and a Bruker Autoflex III Matrix-assisted laser desorption/ionization-time of flight mass spectrometer (MALDI-TOF).

4.3.3 Syntheses

4.3.3.1 Preparation of Benzoxazine Monomer

Benzoxazine monomer was prepared according to the previous report (Laobuthee *et al.*, 2001). In brief, propagylamine (0.54 mL, 0.01 mol) and formaldehyde solution (3.06 mL, 0.04 mol) were dissolve in dioxane (20 mL) and stirred while being chilled in an ice bath for 30 min. 2,4-Dimethylphenol (1.20 mL, 0.01 mol) was added into the reaction mixture and stirred further at 110 °C for 12 hr. The solution obtained was dissolved in diethyl ether, and washed with 0.1 M sodium hydroxide (NaOH) and distilled water several times. The solution was dried over by sodium sulfate anhydrous, and the solvent was removed to obtain the **1**, 3,4-dihydro-6,8-dimethyl-3-propargyl-2H-1,3-benzoxazine.

4.3.3.2 Preparation of Benzoxazine Dimer

Benzoxazine dimer, as reported in the past(Laobuthee *et al.*, 2001). In brief, 2,4-dimethylphenol (1.20 mL, 0.01 mol) was added into solution of **1** (2.01 g, 0.01 mol) in 20 mL of dioxane and allowed stirring at 110 °C for 20 hr. The solvent was removed under reduced pressure and the crude product was crystallized in a 1:1 isopropanol/chloroform mixture to obtain a colorless crystalline product, **2**, N,N-bis(3,5-dimethyl-2-hydroxybenzyl)propargylamine.

4.3.3.3 Preparation of Benzoxazine Macrocycle

Benzoxazine macrocycle was prepared by interfacial polycondensation. Here, 0.15 M solution of **2** in water in the presence of NaOH, and 0.15 M solution of terephthaloyl dichloride in dichloromethane in separate syringes were added dropwisely into the mixture of dichloromethane (35 mL), water (10 mL) and hexadecyltrimethylammonium bromide (CTAB), and stirred at room temperature for 7 days. The solution obtained was washed with distilled water several times. The solvent was removed under reduced pressure to obtain the crude product. The crude product was purified by column chromatography to obtain benzoxazine macrocycle **3**.

4.3.3.4 Preparation of Molecular Necklace based on Benzoxazine Macrocycle.

Benzoxazine macrocycle, **3**, (0.070 mg, 0.07mol) was dissolved in DMF (5 ml) containing CuI/pyridine complex under nitrogen

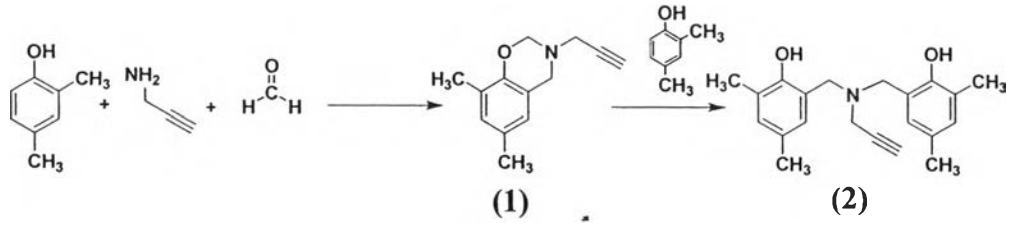
atmosphere at room temperature for a half hour. 1,4-Diazidobutane(9.8 mg,0.007 mol) was added into solution mixture and stirred further for 24 hr. The solution obtained was poured into water for purification. The precipitates were washed by distilled water several times.

4.4 Results and Discussion

4.4.1 Benzoxazine Dimer

Benzoxazine monomer containing alkyne unit, **1**, was prepared by Mannich reaction of 2,4-dimethyl phenol, formaldehyde and propargylamine (Scheme 1). Propagylamine was used as a starting material since it is a commercially available amine compound containing a alkyne unit. From FT-IR data, **1** shows the peaks at 1228 cm^{-1}, 924 cm^{-1} (asymmetric stretching of Ar–O–C and -CH out of plane of benzene ring (oxazine ring)) and 3261 cm^{-1} (–C≡CH of propargyl group)(Figure 1a). The ^{1}H-NMR spectrum of compound **1** shows signals of methylene groups of oxazine ring at 4.09 and 4.93 ppm as singlet resonances (Figure 2a). In the case of benzoxazine dimer, **2**, compound **1** was further reacted with 2,4-dimethyl phenol for ring opening reaction (Scheme 1). The FT-IR spectra show disappearance of the peaks at 1228 cm^{-1} and 924 cm^{-1} implying the cleavage of oxazine ring and appearance of the new peak at 3433 cm^{-1} (hydroxyl group) implied to formation of **2** (Figure 2). The ^{1}H-NMR spectra (Figure 2) show a signal at 3.83 ppm (methylene group in Mannich bridge) and the disappearance of the signal at 4.93 ppm (methylene group in oxazine ring).

Scheme 4.1



(1) (2)

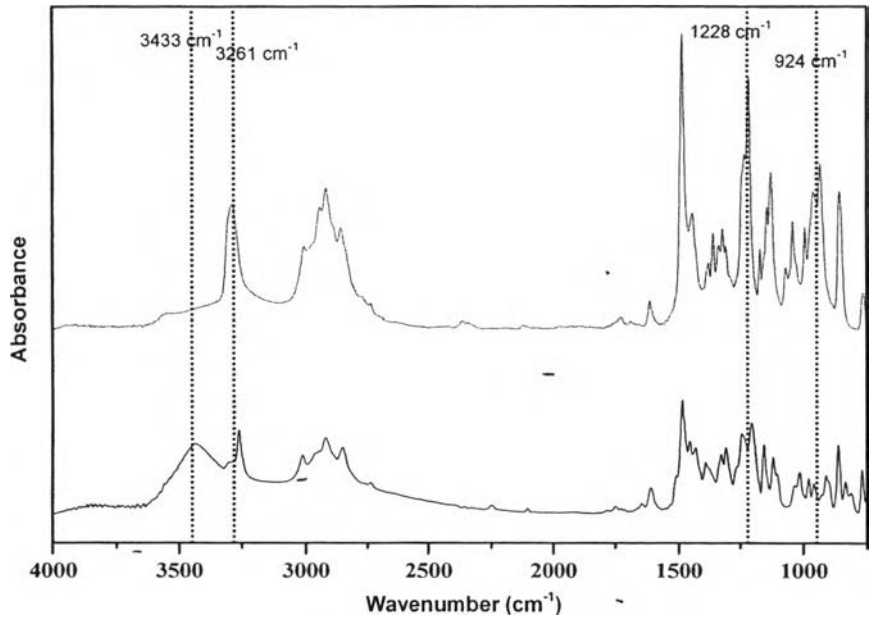


Figure 4.1. FT-IR spectra of :(a) **1,** and (b) **2**.

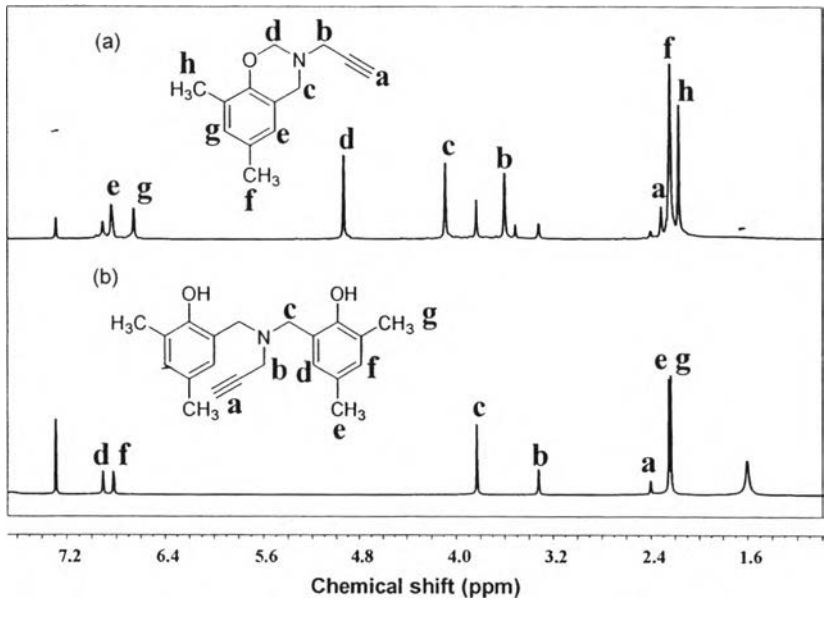
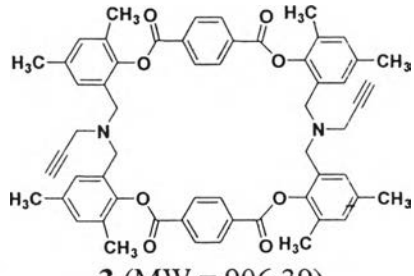


Figure 4.2. ^{1}H-NMR spectra of :(a) **1**, and (b) **2**.

4.4.2 Benzoxazine Macrocycle

In the past, macrocyclic acylate dimer was prepared by interfacial polycondensation of *o*-phthaloyl dichloride with bisphenol-A [11]. In our case, benzoxazine macrocyle was synthesized by interfacial polycondensation of terephthaloyl dichloride with **2**. The ^{1}H-NMR spectrum (Figure 4.3) shows a peak of

aza-methylene bridge at δ_H = 3.57 ppm and the peak at δ = 8.34 ppm that belong aromatic protons of diacaid chloride. The ^{13}C-NMR spectrum shows the peak at δ = 163.79 ppm that belongs to carbonyl group of diacid chloride. Moreover, ESI mass spectrum (Figure 4.5.) shows the parent peaks ($M+Na^+$) at *m/z* = 929.32 that confirms the structure of product obtained is [2+2] macrocyclic, **3**.



3 (MW = 906.39)

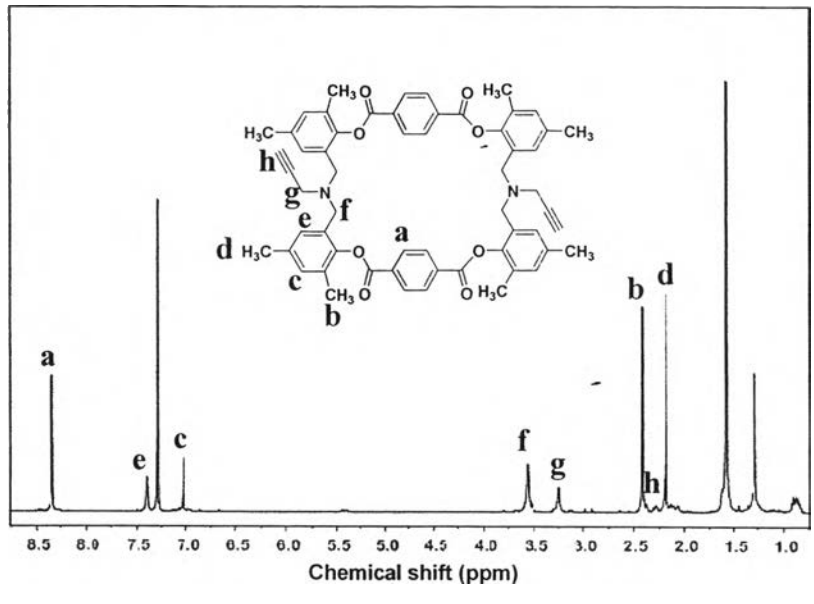


Figure 4.3. ^{1}H-NMR spectrum of **3**.

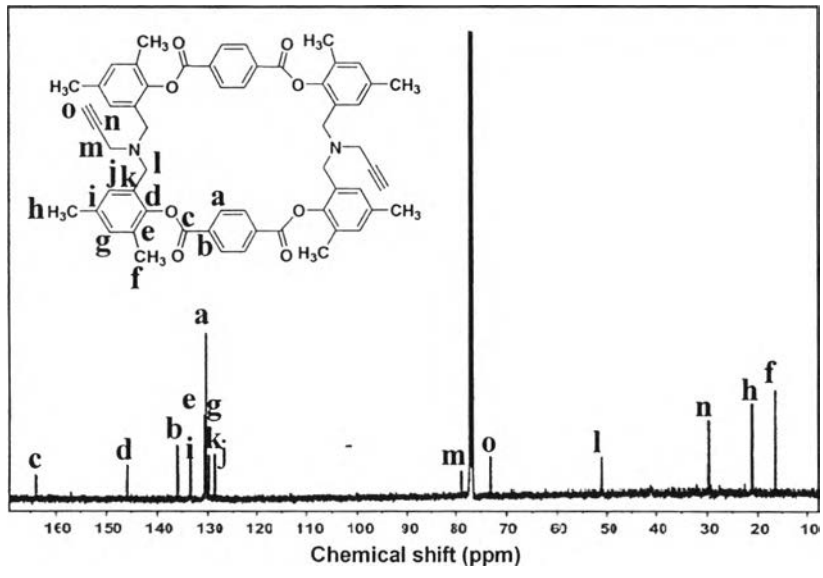


Figure 4.4. ^{13}C-NMR spectrum of **3**.

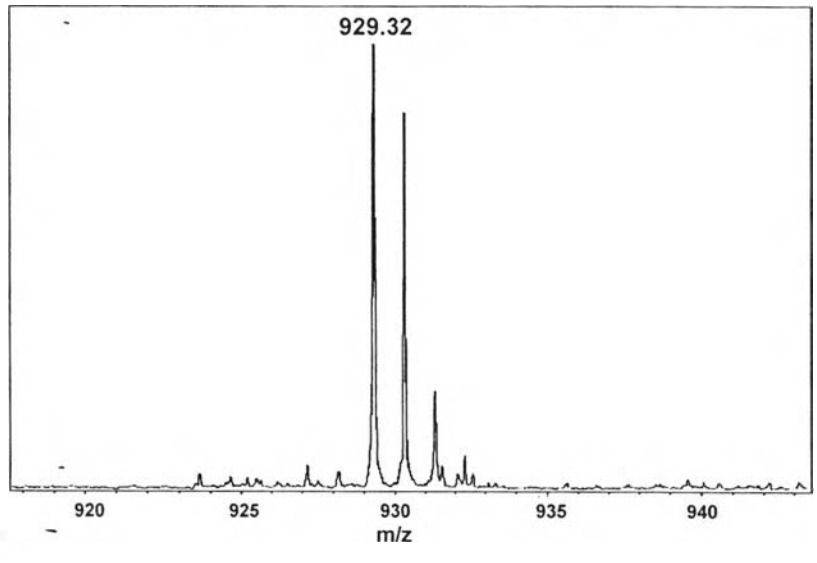


Figure 4.5. ESI mass spectrum of **3**.

4.4.3 1,4-diazidobutane

1,4-diazidobutane was used for Click chemistry since the structure contains azide unit. The FT-IR spectrum (Figure 4.5b) shows the strong peak at 2058 cm^{-1} referring to the characteristic peak of azide group. The ^{1}H-NMR spectra (Figure 4.6) show the chemical shifts at 3.46 ppm (BrCH_2) and 2.05 ppm

($CH_2CH_2CH_2CH_2$) shifting to 3.34 ppm (NCH_2) and 1.70 ppm ($CH_2CH_2CH_2CH_2$), respectively,-implying the successful functionalization of azide group.

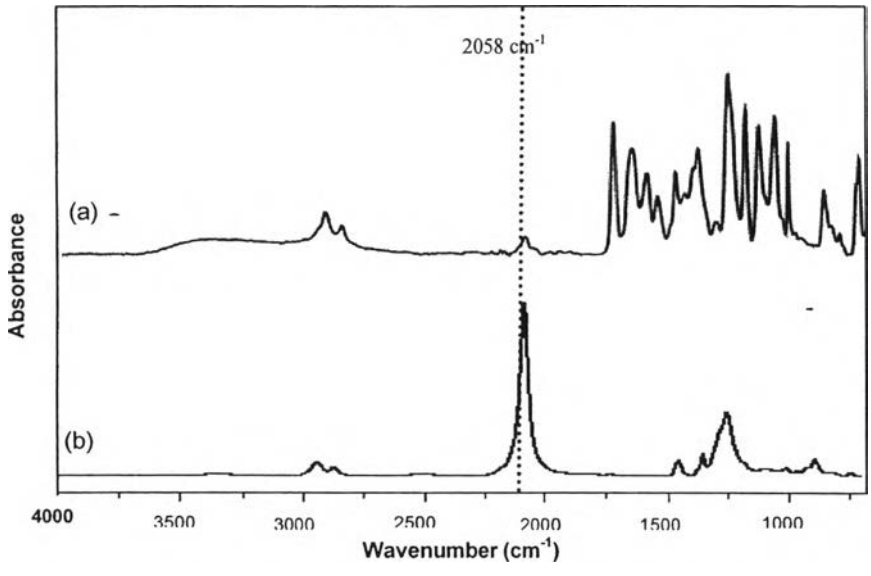


Figure 4.6. FT-IR spectra of (a) the product obtained from Click chemistry and (b) 1,4-diazidobutane.

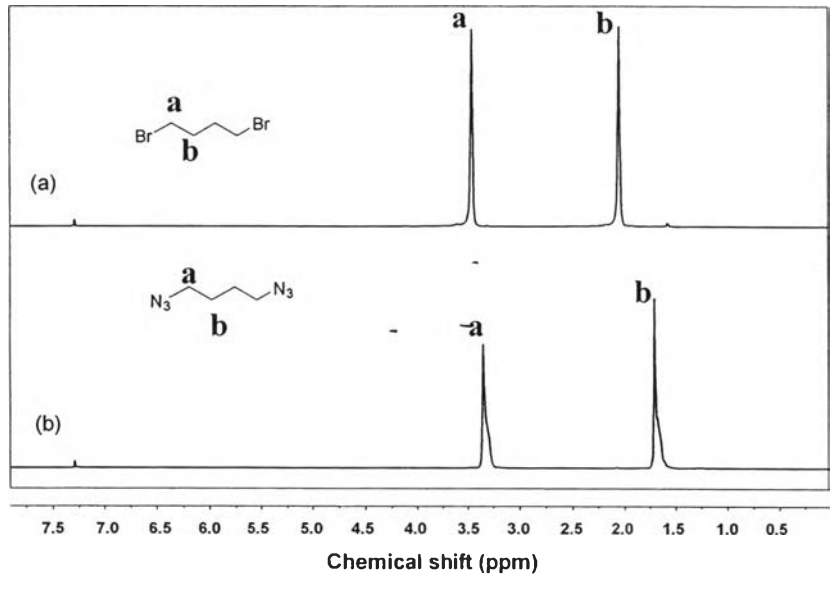
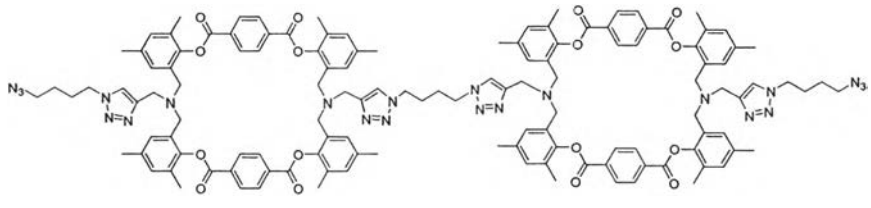


Figure 4.7. ^{1}H-NMR spectra of :(a) 1,4-dibromobutane, (b) 1,4-diazidobutane.

4.4.4 Molecular Necklace based on Benzoxazine Macrocycle

Click chemistry between **3** and 1,4-dazidobutane was carried out at room temperature in the presence of Cu(I). The FT-IR spectra (Figure 4.5) show that the decreasing of azide peak (-N=N=N) at 2058 cm^{1} implying that the azide group was developed to 1,2,3-triazole linkage. Moreover, ESI-MS was applied to clarify structure. The ESI mass spectrum (Figure 4.8) shows the important parent peaks ($M+2Cu^{+}$) at *m/z* = 2358 referring to the structures of **4** as connecting of two benzoxazine macrocycles via 1,2,3-triazole linkage.



4 (MW = 2233)

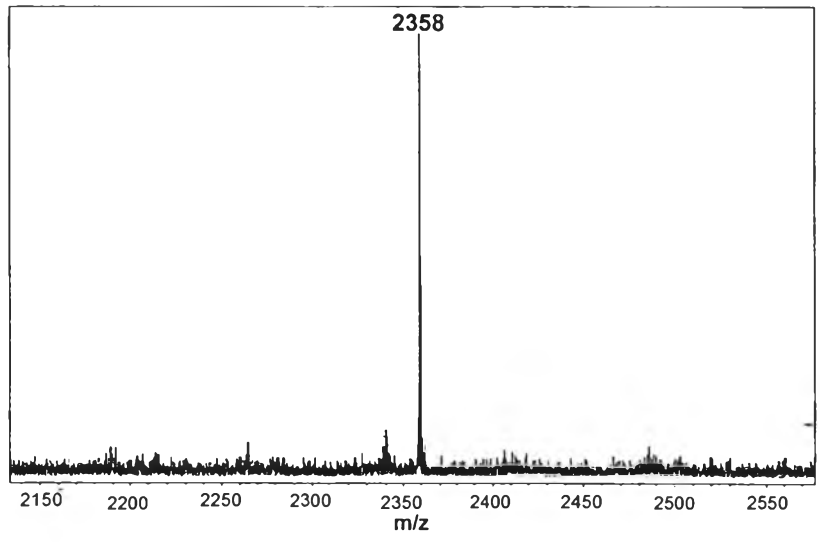


Figure 4.8. ESI mass spectrum of **4**.

4.5 Conclusions

The present work showed an achievement of connecting benzoxazine macrocycles with alkyl chain using Click chemistry. The key of the success was the

use of propargyl amine to obtain benzoxazines with the alkyne group and the modification of dibromobutane with sodium azide to obtain the alkyl chain with azide group. The fact that the purification of the crude macrocycles from interfacial reaction to obtain [2+2] benzoxazine macrocyclic was difficult, the present work carried out Click chemistry between [2+2] benzoxazine macrocyclic. Obtaining two types of the products **4**, was a proof to the concept of molecular necklace based on Click chemistry.

4.6 Acknowledgements

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4.7 References

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