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The intramolecular click reaction using ‘carbocontiguous’ precursors

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Abstract

The synthesis and utilization of all carbon-chain ‘carbocontiguous’ azidoalkynyl precursors for an intramolecular click reaction is described. The substrates contain both azidoalkynyl and ethynylmethyl groups which are conjoined by a 2-(phenylsulfonylmethyl)-4,5-diphenyloxazole lynchpin and are suitably disposed for ring closure. On promotion by copper salts, a number of cyclic click products having the 1,4-disubstituted *endo*-fused triazole component and the 4,5-diphenyloxazole component are obtained. In one case, removal of the phenylsulfonylmethyl group from the substrate prior to cyclization gave the 1,5-disubstituted *exo*-fused triazole. The utilization of CuSO₄/sodium ascorbate system appears to be the optimal conditions for closure/cyclization and afforded the cyclized products in yields of 84-95%.

Graphical Abstract

Keywords

click chemistry; cyclic carbohydrates; cyclic peptides; dipolar cycloaddition; 1,2,3-triazole

1. Introduction

Click reactions can facilitate the conjoining of large and small molecular fragments for study and applications in many areas of chemistry, including materials and biomolecular science.¹ The intramolecular click reaction comprises an interesting subset of the fundamental Huisgen 3+2 dipolar cycloaddition reaction whereby a 1,2,3-triazole is formed within a precursor bearing both alkyne and azide moieties to form a ring.² The intramolecular form of the reaction need only utilize a substrate which possesses both necessary reactive

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functionalities as well as entropic favorability for ring closure. At present the most frequent examples of the intramolecular click reaction involve substrates which do have the required reactive functionality, but possess heteroatoms such as oxygen and nitrogen.² For example, when both the azide and alkynyl functionality are built into polypeptides, the stage is set for the cycloaddition to afford cyclic polypeptide analogues containing the signature 1,2,3-triazole ring. Depending on the ring-size potential, the intramolecular click reaction can provide two modes of addition whereby a 1,5- or a 1,4-disubstituted triazole is formed (**Fig. 1**). Specifically, the modes of addition may result in an *exo*-disposed C-C double bond, a.k.a., the 1,5-disubstituted triazole, or the *endo*-disposed C-C double bond or otherwise the 1,4-disubstituted triazole. The *endo* or *exo* products arising from cycloaddition of the azide to the alkyne defines the overall ring size and provides a ring whereby the *endo* product possesses one more carbon in the chain than the *exo*-derived product.³ Moreover, the newly-formed 1,2,3-triazole ring which is common to either cyclic polypeptide or most recently, even cyclic carbohydrate 'click' analogues, may act in additional capacity as a basic, hydrogen bond acceptor or π -stacking site.⁴ We describe herein an intramolecular click reaction in which the azide-alkyne precursor are the reacting components in a contiguous carbon chain thereby yielding two new rings. One of the rings is the connecting triazole which is fused to the second 'major' ring, namely the triazole-fused azecane, azacycloundecane, azacyclododecane, azatridecane or azatetradecane (10-14 membered rings, respectively), depending on the size of the azidoalkyl chain. The functionality of the larger of the newly-formed rings is represented by a 4,5-diphenyloxazole, an established carboxyl group equivalent which also performs as an efficient synthetic scaffold.⁵ The carbon substituted at 2-position of the 4,5-diphenyloxazole acts as a lynchpin which connects both the alkynyl and azido appendages prior to cyclization via the intramolecular click reaction.

2. Results and Discussion

Our synthesis of the click macrocyclization precursors begins with the 2-(phenylsulfonylmethyl)-4,5-diphenyloxazole **1** (**Fig. 2**), a versatile intermediate reported previously from these laboratories which can be utilized to prepare extended oxazoles with diverse functionality.⁶ Using a deprotonation/alkylation sequence, the α -methylenesulfone **1** offers an efficient hinge point for which to attach appendages that carry both the necessary azide and alkynyl functionalities prior to cyclization. Our previous studies showed that alkylation of **1** using potassium *tert*-butoxide/THF followed by addition of 1,6-dibromohexane provided the monoalkylated product **2a** (53%) and not the expected cyclic product from double (intramolecular) alkylation (**Fig. 2**).⁵ This result was in sharp contrast to using 1,3-diiodopentane, 1,4-dibromobutane or 1,5-dibromopentane which gave the cyclic products as a result of intramolecular dialkylation.⁷ Hence, treatment of **1** with potassium *tert*-butoxide in THF followed by addition of 1,6-dibromohexane, 1,7-dibromoheptane, 1,8-dibromooctane or 1,9-dibromononane gave the 2-(bromoalkyl)-2-(phenylsulfonyl)oxazoles **2a-d** in yields of 45-66% after column chromatography (**Scheme 1**). The purified 2-haloalkyl-(phenylsulfonylmethyl)oxazoles **2a-d** were again treated with potassium *tert*-butoxide/THF followed by propargyl bromide to provide the 2-(ethynylmethyl)-2-(haloalkyl)-2-(phenylsulfonylmethyl)oxazoles **3a-d** in 42-80% yield after purification by

column chromatography (**Scheme 1**). Treatment of the haloalkyl-propargylated products **3a-d** with sodium azide/DMF smoothly afforded the 2-(azidoalkyl)-2-(ethynylmethyl)-2-(phenylsulfonylmethyl) oxazoles **5a-d** (77-98%) which now carry the necessary functionality for the intramolecular click reaction. Alternatively, the 2-(haloalkyl)-2-(phenylsulfonylmethyl) oxazoles **2a-d** were treated with sodium azide (DMF/rt/16 h) to give the 2-azidoalkyl-2-(phenylsulfonylmethyl)oxazoles **4a-d** (73-81%). The azides **4a-d** were then propargylated (potassium *tert*-butoxide/propargyl bromide/THF) to provide the click substrates **5a-d** (42-52%) after purification by column chromatography (**Scheme 1**). The route involving the conversion of **2a-d** to substrates **5a-d** through intermediates **3a-d** (**Scheme 1**, conditions b, c) appeared to be the most serviceable, so accordingly, the scale-up preparations of the click substrates were performed through the propargylated haloalkyl intermediates **3a-d**.

The intramolecular click reactions in which the azidoalkyne substrates **5a-d** are converted to the corresponding cyclized products **6a-d** are shown in **Scheme 2**. Utilizing the first member of the homologous substrate series **5a** (**Table 1**), a number of variables, including copper source, reducing agent, base, solvent, reaction time and temperature were examined for the optimization of its cyclization to **6a**. While thermally-promoted click reactions have been reported,⁸ refluxing solvents such as toluene or methanol alone were not sufficient for the cyclization of test substrate **5a** (**Entries 1 and 2, Table 1**)⁹ and starting material was recovered in these experiments. Combinations of copper sulfate pentahydrate (0.1-0.5 eq) sodium ascorbate 0.5-1.0 eq) in a moderately polar solvent/water (THF/H₂O) system gave at best, modest yields of product (38-51%) even after a reaction time of 16-48 h (**Entries 7 and 8, Table 1**). The use of ligand additives such as benzoic acid did not enhance the yields (**Entries 13 and 14, Table 1**), while the use of DMSO as a co-solvent with water did provide a 53% yield (**Entry 12, Table 1**). The employment of bases such as DIPEA or cesium carbonate along with the CuSO₄/ascorbate system (**Entries 3 and 5, Table 1**)¹⁰ did not afford a marked improvement while bases such as DBU resulted in decomposition of starting material (**Entry 4**).¹¹ The optimal conditions utilized copper sulfate pentahydrate (0.2 eq), sodium ascorbate (0.5 eq) in *tert*-butanol:water (2:1) at 90-95 °C whereby the reaction was completed in one hour (96%, **Entry 11, Table 1**).^{12,13,14} Mechanistic studies explain that, in general, the regiochemistry or otherwise mode of addition of the copper-catalyzed azide-alkyne cycloaddition gives the 1,4-triazole cycloadducts. These cases include many copper-catalyzed intramolecular click reactions in which monomeric or dimeric macrocycles result from the *endo* or 1,4 addition. However, with smaller potential ring sizes, the 1,5- or *exo* cycloadducts can result despite the employment of the copper/ascorbate reaction system.³ Consistent with mechanistic studies, we find that in the products **6a-d**, the *endo* or 1,4-disposed regioisomers resulted from the cycloaddition. Routine 400 or 700 MHz ¹H NMR data recorded with products **6a-d** reveal that the lone triazole proton, although obscured by two phenyl groups of the oxazole and one of the phenylsulfonyl group, firmly reside in the δ7.2-7.6 region. To examine the regiochemistry, or *endo* vs *exo* disposition of the intramolecular click cycloaddition reaction, NOESY experiments at 700MHz (CDCl₃) were performed with products **6a-d**.³ The NOESY experiments revealed that in all four example, overlap of the triazole ring proton and the geminal protons of the ring methylene that is α- to the N1 of the triazole. Interestingly, close examination of the

NOESY spectrum of the smallest ring product **6a** revealed additional overlap between the triazole ring proton and the geminal protons of the methylene positioned in between the triazole group and the phenylsulfonylmethyl group. With the precursors of the intramolecular click reaction having a 1,1- or *gem* substitution of both the diphenyloxazole and the phenylsulfonyl group at the quaternary C-4 (numbered from the acetylene end), we surmised that the click cyclization yields of **6a-d** would be higher due to a type of Thorpe-Ingold effect.¹⁵ So a distinct difference in the yield of click-cyclized product might be observed if one of the groups, namely the phenylsulfonyl group, was removed prior to cyclization. Hence, the desulfonylation of the 2-azidoethyl-2-(phenylsulfonylmethyl) oxazole **5a** (Mg/HgCl₂/MeOH/rt/30 min), using conditions optimized for substrates in a previous study,⁷ provided the oxazolyl azidoalkyne **7** in 68% yield after column chromatography (**Scheme 3**). Click cyclization of **7** (CuSO₄·5H₂O/sodium ascorbate/90-95 °C/30 min) afforded the oxazole-substituted 1,2,3-triazole-fused azecane *exo*-**8** in 73% isolated yield, which was markedly less than that of **6a** (derived from sulfonyl-substituted **5a**). Surprisingly, NOESY experiments conducted on isolated product **8** revealed no overlap between the *exo*-disposed triazole ring proton and the protons of the major ring of **8**.³

3. Conclusions

Using an activated 2-substituted-4,5-diphenyloxazole as a central scaffold, and sequentially attaching haloalkyl and propargyl groups followed by nucleophilic azidation, a number of carbocontiguous precursors for a series of intramolecular click reactions were prepared. The sequence of synthetic steps from the starting diphenyloxazole scaffold proved to be interchangeable and gave modest to good yields of the substrate azidoalkynes. The click reactions which afforded the highest yields were mediated with a copper sulfate/sodium ascorbate reagent system, employed a relatively polar aqueous alcohol solvent mixture and yielded the 1,4 *exo*-disubstituted products. The phenylsulfonyl activating group inherent in the ten-carbon starting scaffold could be reductively removed prior to cyclization and provided a click substrate, which in contrast to the other click examples, provided the 1,5 *exo*-disubstituted triazole. Our studies of the intramolecular click reaction of 'carbocontiguous' precursors and their products is the first study of its type in click chemistry. Our studies will continue to include cyclizations of substrates having diverse functionality and will be the topics of future communications from these laboratories.

4. Experimental

Solvents and reagents are ACS grade and were used as commercially supplied. Analytical thin-layer chromatography (TLC) utilized 0.25 mm pre-cut glass-backed plates (Merck, Silica Gel 60 F254). Thin-layer chromatograms were visualized during chromatographic and extraction runs by rapidly dipping the plates in anisaldehyde/ethanol/sulfuric acid stain or phosphomolybdic acid/ethanol stain and heating (hot plate). Gravity-column chromatography was carried out using silica gel 60 (E. Merck 7734, 70-230 mesh). Flash-column chromatography utilized silica gel 60 (E. Merck 9385, 230-400 mesh) with nitrogen gas pressurization. Melting points were taken on a Thomas Hoover apparatus. Extracts and chromatographic fractions were concentrated with a Büchi rotavapor under water aspirator

vacuum. Nuclear magnetic resonance (^1H and ^{13}C NMR) spectra were recorded with Varian VNMRs 400 or 700 MHz instruments using CDCl_3 as a solvent and TMS as internal standard. Infrared spectra (FTIR) were recorded with a Perkin-Elmer Spectrum 100 instrument and spectral values are reported as cm^{-1} . The measurement of high-resolution mass spectra (HRMS) were performed at the Texas A&M University Laboratory for Biological Mass Spectrometry.

General Procedure for synthesis of bromoalkyl-substituted sulfones 2a-d)

To a stirred solution of 2-(phenylsulfonyl)methyl-4,5-diphenyloxazole **1** (500 mg, 1.33 mmol, 1.0 equiv) in dry THF (10 mL) was added potassium *tert*-butoxide (1.60 mmol, 1.2 equiv) at 5 °C. The resulting yellow reaction mixture was stirred under a nitrogen atmosphere (30 min). The dibromo alkane (1.60 mmol, 1.2 equiv) was then slowly added to the reaction mixture by syringe, and reaction mixture was allowed to warm to room temperature and stirring was continued (16 h). After completion of reaction, cold water (10 mL) was poured into the reaction mixture followed by extraction with dichloromethane (2×20 mL). The organic layers were combined, washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The crude residue was submitted to gravity-column chromatography (hexane/ethyl acetate, 9:1) to afford the corresponding products **2a-d**.

2-(7-Bromo-1-(phenylsulfonyl)heptyl)-4,5-diphenyloxazole 2a—colorless oil (380 mg, 53%); $R_f = 0.54$ (hexane/ethyl acetate, 4:1); FT-IR: 3069, 2959, 1690, 1447, 1321, 1148, 687 cm^{-1} ; ^1H NMR (700 MHz, CDCl_3) δ 7.78–7.76 (m, 2H), 7.61 (t, $J = 8.0$ Hz, 1H), 7.52–7.47 (m, 6H), 7.38–7.33 (m, 6H), 4.51 (dd, $J = 10.0$ Hz, 5.2 Hz, 1H), 3.36 (t, $J = 7.2$ Hz, 2H), 2.40–2.37 (m, 2H), 1.83–1.80 (m, 2H), 1.45–1.37 (m, 6H) ppm; ^{13}C NMR (175 MHz, CDCl_3) δ 154.8, 147.0, 137.1, 136.0, 134.0, 131.6, 129.0, 128.92, 128.89, 128.6, 128.5, 128.3, 128.0, 127.8, 126.5, 65.7, 33.6, 32.4, 28.0, 27.6, 26.7, 26.3 ppm; HRMS (ESI-TOF) m/z calcd for $\text{C}_{28}\text{H}_{28}\text{BrNO}_3\text{S}$ $[\text{M}+\text{H}]^+$ 538.1052, found 538.1066.

2-(8-Bromo-1-(phenylsulfonyl)octyl)-4,5-diphenyloxazole 2b—Colorless oil (460 mg, 62%); $R_f = 0.36$ (hexane/ethyl acetate, 4:1); FT-IR: 3067, 2959, 1692, 1443, 1327, 1149, 690 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.76 (d, $J = 7.2$ Hz, 2H), 7.62 (t, $J = 8.0$ Hz, 1H), 7.51–7.46 (m, 6H), 7.35–7.33 (m, 6H), 4.48 (dd, $J = 10.0$ Hz, 7.2 Hz, 1H), 3.36 (t, $J = 6.4$ Hz, 2H), 2.39–2.35 (m, 2H), 1.83–1.77 (m, 2H), 1.42–1.31 (m, 8H) ppm; ^{13}C NMR (175 MHz, CDCl_3) δ 154.9, 147.0, 137.3, 136.0, 134.1, 131.7, 129.1, 129.0, 128.9, 128.7, 128.6, 128.4, 128.1, 127.9, 126.5, 65.9, 33.8, 32.6, 28.7, 28.3, 27.9, 26.8, 26.4 ppm; HRMS (ESI-TOF) m/z calcd for $\text{C}_{29}\text{H}_{30}\text{BrNO}_3\text{S}$ $[\text{M}+\text{Na}]^+$ 574.1022, found 574.1062.

2-(9-Bromo-1-(phenylsulfonyl)nonyl)-4,5-diphenyloxazole 2c—Colorless oil (500 mg, 66%); $R_f = 0.35$ (hexane/ethyl acetate, 4:1); FT-IR: 3058, 2929, 1698, 1447, 1323, 1150, 692 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.77 (d, $J = 8.0$ Hz, 2H), 7.63 (t, $J = 7.2$ Hz, 1H), 7.51–7.46 (m, 6H), 7.36–7.34 (m, 6H), 4.50 (dd, $J = 10.0$ Hz, 4.8 Hz, 1H), 3.37 (t, $J = 6.4$ Hz, 2H), 2.41–2.36 (m, 2H), 1.81 (q, $J = 7.2$ Hz, 2H), 1.38–1.28 (m, 10H) ppm; ^{13}C NMR (175 MHz, CDCl_3) δ 155.0, 147.0, 137.3, 136.0, 134.1, 131.7, 129.1, 129.0, 128.9,

128.7, 128.5, 128.4, 128.2, 127.9, 126.5, 65.9, 33.9, 32.7, 28.9, 28.8, 28.5, 28.0, 26.8, 26.4 ppm; HRMS (ESI-TOF) m/z calcd for $C_{30}H_{32}BrNO_3S$ $[M+Na]^+$ 588.1178, found 588.1198.

2-(10-Bromo-1-(phenylsulfonyl)decyl)-4,5-diphenyloxazole 2d—Colorless oil (350 mg, 45%); R_f = 0.33 (hexane/ethyl acetate, 4:1); FT-IR: 3061, 2927, 1698, 1446, 1323, 1149, 692 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 8.4 Hz, 2H), 7.62 (t, J = 8.0 Hz, 1H), 7.51–7.47 (m, 6H), 7.37–7.34 (m, 6H), 4.51 (dd, J = 9.6 Hz, 5.6 Hz, 1H), 3.37 (t, J = 7.2 Hz, 2H), 2.39–2.36 (m, 2H), 1.84–1.77 (m, 2H), 1.43–1.26 (m, 12H) ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 155.0, 147.0, 137.3, 136.0, 134.1, 131.8, 129.1, 128.99, 128.97, 128.7, 128.6, 128.4, 128.2, 127.9, 126.6, 65.9, 34.0, 32.7, 29.2, 29.0, 28.9, 28.6, 28.1, 26.9, 26.4 ppm; HRMS (ESI-TOF) m/z calcd for $C_{31}H_{34}BrNO_3S$ $[M+Na]^+$ 602.1335.1521, found 602.1366.

General procedure for synthesis of bromoalkyl propargyl intermediates 3a-d

Potassium *tert*-butoxide (50 mg, 0.45 mmol) was added to a stirred solution of bromoalkyl (phenylsulfone) **2a-d** (200 mg, 0.34–0.37 mmol) in THF (15 mL) at 5–10 °C under a nitrogen atmosphere. The reaction mixture was stirred (30 min) then propargyl bromide (0.41–0.44 mmol, 1.2 equiv) was slowly added by syringe under nitrogen. The reaction mixture was allowed to warm to room temperature and stirring was continued overnight after which time TLC indicated that the reaction was complete. The reaction mixture was quenched with cold water (10 mL) and extracted with dichloromethane (2 $\times$ 20 mL). The organic extracts were combined, dried over anhydrous Na_2SO_4 , and concentrated to give a crude oily residue. Submission of the residue to gravity-column chromatography (hexane/ethyl acetate, 4:1) afforded the pure bromohexyl (propargyl)sulfones **3a-d** as colorless oils.

2-(10-Bromo-4-(phenylsulfonyl)dec-1-yn-4-yl)-4,5-diphenyloxazole 3a—

Colorless oil (170 mg, 80%); R_f = 0.51 (hexane/ethyl acetate, 4:1); FT-IR: 3294, 2935, 1447, 1308, 1145, 688 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, J = 7.6 Hz, 2H), 7.57 (t, J = 7.2 Hz, 1H), 7.50–7.43 (m, 6H), 7.41–7.33 (m, 6H), 3.43 (dd, J = 17.6, 2.8 Hz, 1H), 3.40 (t, J = 6.8 Hz, 2H), 3.28 (dd, J = 17.6, 2.8 Hz, 1H), 2.75–2.68 (m, 1H), 2.57–2.50 (m, 1H), 2.10 (t, J = 2.8 Hz, 1H), 1.91–1.84 (m, 2H), 1.80–1.76 (m, 1H), 1.52–1.43 (m, 5H) ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 156.9, 147.0, 135.92, 135.90, 134.1, 131.7, 129.8, 129.0, 128.7, 128.6, 128.5, 128.4, 128.1, 127.9, 126.5, 77.5, 72.1, 69.7, 33.8, 32.5, 29.8, 28.9, 27.7, 23.6, 21.2 ppm. HRMS (ESI-TOF) m/z calcd for $C_{31}H_{30}BrNO_3S$ $[M+H]^+$ 576.1208, found 576.1212.

2-(11-Bromo-4-(phenylsulfonyl)undec-1-yn-4-yl)-4,5-diphenyloxazole 3b—

Colorless oil (121 mg, 57%); R_f = 0.58 (hexane/ethyl acetate, 4:1); FT-IR: 3292, 2930, 1445, 1308, 1145, 689 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, J = 8.8 Hz, 2H), 7.57 (t, J = 7.2 Hz, 1H), 7.50–7.48 (m, 2H), 7.46–7.41 (m, 4H), 7.38–7.34 (m, 6H), 3.42 (dd, J = 17.6, 2.8 Hz, 1H), 3.38 (t, J = 7.2 Hz, 2H), 3.28 (dd, J = 17.6, 2.8 Hz, 1H), 2.75–2.68 (m, 1H), 2.57–2.50 (m, 1H), 2.10 (t, J = 2.8 Hz, 1H), 1.88–1.75 (m, 3H), 1.48–1.42 (m, 7H) ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 156.9, 147.0, 135.94, 135.93, 134.1, 131.7, 129.8, 129.0, 128.74, 128.68, 128.6, 128.4, 128.1, 127.9, 126.6, 77.5, 72.1, 69.8, 33.9, 32.7, 29.9, 29.6, 28.3, 28.0, 23.7, 21.3 ppm. HRMS (ESI-TOF) m/z calcd for $C_{32}H_{32}BrNO_3S$ $[M+H]^+$ 590.1365, found 590.1337.

2-(12-Bromo-4-(phenylsulfonyl)dodec-1-yn-4-yl)-4,5-diphenyloxazole 3c—

Colorless oil (92 mg, 43%); R_f = 0.61 (hexane/ethyl acetate, 4:1); FT-IR: 3305, 2928, 1446, 1308, 1146, 689 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.64 (d, J = 8.8 Hz, 2H), 7.57 (t, J = 7.2 Hz, 1H), 7.50-7.41 (m, 6H), 7.37-7.31 (m, 6H), 3.41 (dd, J = 17.6, 2.4 Hz, 1H), 3.39 (t, J = 7.2 Hz, 2H), 3.27 (dd, J = 17.6, 2.4 Hz, 1H), 2.74-2.67 (m, 1H), 2.57-2.49 (m, 1H), 2.09 (t, J = 2.0 Hz, 1H), 1.87-1.73 (m, 3H), 1.42-1.35 (m, 9H) ppm; ^{13}C NMR (175 MHz, CDCl_3) δ 157.0, 147.0, 135.95, 135.91, 134.1, 131.8, 129.8, 129.0, 128.72, 128.66, 128.55, 128.4, 128.1, 127.9, 126.5, 77.5, 72.1, 69.8, 34.0, 32.7, 29.9, 29.7, 28.9, 28.5, 28.1, 23.7, 21.3 ppm. HRMS (ESI-TOF) m/z calcd for $\text{C}_{33}\text{H}_{34}\text{BrNO}_3\text{S}$ $[\text{M}+\text{H}]^+$ 604.1521, found 604.1490.

2-(13-Bromo-4-(phenylsulfonyl)tridec-1-yn-4-yl)-4,5-diphenyloxazole 3d—

Colorless oil (89 mg, 42%); R_f = 0.62 (hexane/ethyl acetate, 4:1); FT-IR: 3293, 2928, 1446, 1309, 1146, 1064, 689 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.64 (d, J = 8.4 Hz, 2H), 7.57 (t, J = 7.6 Hz, 1H), 7.50-7.41 (m, 6H), 7.37-7.34 (m, 6H), 3.42 (dd, J = 18.0, 2.8 Hz, 1H), 3.39 (t, J = 7.2 Hz, 2H), 3.27 (dd, J = 18.0, 2.8 Hz, 1H), 2.70-2.67 (m, 1H), 2.57-2.50 (m, 1H), 2.09 (t, J = 2.4 Hz, 1H), 1.87-1.73 (m, 3H), 1.42-1.30 (m, 11H) ppm; ^{13}C NMR (175 MHz, CDCl_3) δ 157.0, 147.0, 135.96, 135.91, 134.1, 131.8, 129.8, 129.0, 128.72, 128.65, 128.55, 128.4, 128.1, 127.9, 126.5, 77.5, 72.1, 69.8, 34.0, 32.8, 29.9, 29.8, 29.7, 29.0, 28.7, 28.1, 23.8, 21.3 ppm. HRMS (ESI-TOF) m/z calcd for $\text{C}_{34}\text{H}_{36}\text{BrNO}_3\text{S}$ $[\text{M}+\text{H}]^+$ 618.1678, found 618.1702.

General procedure for synthesis of azidoalkyl substituted sulfones 4a-d)

To a clear solution of bromoalkyl sulfone **2a-d** (350 mg, 0.60 - 0.65 mmol, 1.0 equiv), in dry DMF (10 mL) was added NaN_3 (0.72-0.78 mmol, 1.2 equiv) under a nitrogen atmosphere. The reaction mixture was then stirred overnight at room temperature. Upon completion of reaction as indicated by TLC, the reaction mixture was diluted with cold water (25 mL) and extracted with dichloromethane (2×25 mL). The combined extracts were washed with water then brine and dried over anhydrous Na_2SO_4 . The drying agent was then removed and concentration of the dried extracts gave a crude residue. Submission of the oily crude residue to gravity-column chromatography (hexane/ethyl acetate, 4:1) gave the azidoalkyl oxazoles **4a-d** as white or off-white amorphous solids.

2-(7-Azido-1-(phenylsulfonyl)heptyl)-4,5-diphenyloxazole 4a—Off-white

amorphous solid (260 mg, 80%) mp 58-60 $^\circ\text{C}$; R_f = 0.53 (hexane/ethyl acetate, 4:1); FT-IR: 3058, 2938, 2093, 1446, 1320, 1148, 691 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.75 (d, J = 6.8 Hz, 2H), 7.61 (t, J = 8.0 Hz, 1H), 7.50-7.44 (m, 6H), 7.34-7.32 (m, 6H), 4.47 (dd, J = 10.8 Hz, 5.2 Hz, 1H), 3.21 (t, J = 6.8 Hz, 2H), 2.38-2.35 (m, 2H), 1.56-1.53 (m, 2H), 1.40-1.36 (m, 6H) ppm; ^{13}C NMR (175 MHz, CDCl_3) δ 154.8, 147.1, 137.2, 136.0, 134.1, 131.7, 129.1, 129.01, 128.99, 128.7, 128.6, 128.4, 128.1, 127.9, 126.5, 65.8, 51.3, 28.6, 28.5, 26.8, 26.4, 26.3 ppm; HRMS (ESI-TOF) m/z calcd for $\text{C}_{28}\text{H}_{28}\text{N}_4\text{O}_3\text{S}$ $[\text{M}+\text{Na}]^+$ 523.1774, found 523.1742.

2-(8-Azido-1-(phenylsulfonyl)octyl)-4,5-diphenyloxazole 4b—White amorphous

solid (238 mg, 73%) mp 82-85 $^\circ\text{C}$; R_f = 0.28 (hexane/ethyl acetate, 4:1); FT-IR: 3067, 2931, 2093, 1446, 1321, 1148 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.77 (d, J = 7.6 Hz, 2H), 7.62

(t, $J = 7.2$ Hz, 1H), 7.51-7.46 (m, 6H), 7.37-7.34 (m, 6H), 4.49 (dd, $J = 9.6$ Hz, 4.8 Hz, 1H), 3.21 (t, $J = 6.8$ Hz, 2H), 2.39-2.36 (m, 2H), 1.57-1.53 (m, 2H), 1.40-1.32 (m, 8H) ppm; ^{13}C NMR (125 MHz, CDCl_3) δ 154.9, 147.0, 137.3, 136.0, 134.1, 131.7, 129.1, 129.0, 128.7, 128.6, 128.4, 128.1, 127.9, 126.5, 65.8, 51.3, 28.8, 28.7, 28.6, 26.8, 26.5, 26.4 ppm; HRMS (ESI-TOF) m/z calcd for $\text{C}_{29}\text{H}_{30}\text{N}_4\text{O}_3\text{S}$ $[\text{M}+\text{Na}]^+$ 537.1931, found 537.1917.

2-(9-Azido-1-(phenylsulfonyl)nonyl)-4,5-diphenyloxazole 4c—White amorphous solid (261 mg, 80%) mp 62-64 °C; $R_f = 0.34$ (hexane/ethyl acetate, 4:1); FT-IR: 3062, 2928, 2092, 1446, 1322, 1149 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.76 (d, $J = 7.6$ Hz, 2H), 7.62 (t, $J = 7.6$ Hz, 1H), 7.50-7.45 (m, 6H), 7.35-7.33 (m, 6H), 4.49 (dd, $J = 9.6$ Hz, 4.8 Hz, 1H), 3.21 (t, $J = 7.2$ Hz, 2H), 2.38-2.33 (m, 2H), 1.58-1.51 (m, 2H), 1.42-1.28 (m, 10H) ppm; ^{13}C NMR (125 MHz, CDCl_3) δ 154.9, 147.0, 137.3, 136.0, 134.1, 131.7, 129.1, 129.0, 128.7, 128.6, 128.4, 128.2, 127.9, 126.5, 65.9 (65.8), 51.4, 28.93, 28.89, 28.8, 28.7, 26.9, 26.6, 26.4 ppm; HRMS (ESI-TOF) m/z calcd for $\text{C}_{30}\text{H}_{32}\text{N}_4\text{O}_3\text{S}$ $[\text{M}+\text{Na}]^+$ 551.2087, found 551.2112.

2-(10-Azido-1-(phenylsulfonyl)decyl)-4,5-diphenyloxazole 4d—Colorless oil (265 mg, 81%); $R_f = 0.38$ (hexane/ethyl acetate, 4:1); FT-IR: 3067, 2928, 2093, 1712, 1446, 1322, 1149 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.77 (d, $J = 7.2$ Hz, 2H), 7.62 (t, $J = 7.6$ Hz, 1H), 7.51-7.46 (m, 6H), 7.37-7.32 (m, 6H), 4.50 (dd, $J = 10.4$ Hz, 5.5 Hz, 1H), 3.22 (t, $J = 6.8$ Hz, 2H), 2.41-2.34 (m, 2H), 1.59-1.52 (m, 2H), 1.42-1.26 (m, 12H) ppm; ^{13}C NMR (175 MHz, CDCl_3) δ 154.9, 147.0, 137.3, 136.0, 134.1, 131.7, 129.1, 129.0, 128.9, 128.7, 128.5, 128.4, 128.2, 127.9, 126.5, 65.9, 51.4, 29.2, 29.0, 28.9, 28.8, 28.7, 26.9, 26.6, 26.4 ppm; HRMS (ESI-TOF) m/z calcd for $\text{C}_{31}\text{H}_{34}\text{N}_4\text{O}_3\text{S}$ $[\text{M}+\text{Na}]^+$ 565.2244, found 565.2234.

General procedure for synthesis of azidoalkyl propargyl substituted sulfones 5a-d from azidoalkyl sulfones 4a-d

Potassium *tert*-butoxide (0.44-0.48 mmol, 1.2 equiv) was added to a stirred solution of azidoalkyl (phenylsulfone) **4a-d** (200 mg, 0.37-0.40 mmol, 1.0 equiv) in THF (15 mL) at 5-10 °C under a nitrogen atmosphere. The reaction mixture was stirred (30 min) then propargyl bromide (0.44-0.48 mmol, 1.2 equiv) was slowly added by syringe under nitrogen. The reaction mixture was allowed to stir overnight at room temperature after which time TLC indicated that the reaction was complete. The reaction mixture was quenched with cold water (10 mL) and extracted with dichloromethane (2×20 mL). The organic extracts were combined, dried over anhydrous Na_2SO_4 , and concentrated to give a crude oily residue. Submission of the residue to gravity-column chromatography (hexane/ethyl acetate, 9:1) afforded the pure azidoalkyl (propargyl) sulfones **5a-d** as colorless oils.

General procedure for synthesis of azidoalkyl propargyl substituted sulfones (5a-5d) from bromopropargyl sulfones 3a-3d

To a clear solution of bromoalkyl propargyl sulfones **3a-d** (100 mg, 0.16 - 0.17 mmol, 1.0 equiv), in dry DMF (10 mL) was added NaN_3 (0.19-0.20 mmol, 1.2 equiv) under a nitrogen atmosphere. The reaction mixture was allowed to stir overnight at room temperature. After completion, the reaction mixture was diluted with cold water (25 mL) and extracted with dichloromethane (2×25 mL). The combined extracts were washed with water then brine and dried over anhydrous Na_2SO_4 . Evaporation of organic solvent under vacuum using a

rotary evaporator gave a crude residue. Submission of the oily crude residue to gravity-column chromatography (hexane/ethyl acetate, 4:1) gave the azidoalkyl propargyl sulfonylmethyloxazoles **5a-d**, respectively as colorless oils.

2-(10-Azido-4-(phenylsulfonyl)dec-1-yn-4-yl)-4,5-diphenyloxazole 5a—Colorless oil (99 mg, 46%); R_f = 0.38 (hexane/ethyl acetate, 4:1); FT-IR: 3299, 2937, 2093, 1308, 1145 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.63 (d, J = 8.0 Hz, 2H), 7.57 (t, J = 7.6 Hz, 1H), 7.50-7.41 (m, 6H), 7.37-7.31 (m, 6H), 3.42 (dd, J = 17.6, 2.4 Hz, 1H), 3.28 (dd, J = 17.6 Hz, 2.4 Hz, 1H), 3.26 (t, J = 7.2 Hz, 2H), 2.75-2.69 (m, 1H), 2.57-2.50 (m, 1H), 2.09 (t, J = 2.4 Hz, 1H), 1.80-1.77 (m, 1H), 1.64-1.46 (m, 7H) ppm; ^{13}C NMR (175 MHz, CDCl_3) δ 156.9, 147.0, 135.93, 135.92, 134.1, 131.7, 129.8, 129.0, 128.7, 128.6, 128.5, 128.4, 128.1, 127.9, 126.5, 77.5, 72.1, 69.7, 51.4, 29.8, 29.3, 28.7, 26.3, 23.6, 21.3 ppm; HRMS (ESI-TOF) m/z calcd for $\text{C}_{31}\text{H}_{30}\text{N}_4\text{O}_3\text{S}$ $[\text{M}+\text{H}]^+$ 539.2117, found 539.2124

2-(11-Azido-4-(phenylsulfonyl)undec-1-yn-4-yl)-4,5-diphenyloxazole 5b—Colorless oil (111 mg, 52%); R_f = 0.39 (hexane/ethyl acetate, 4:1); FT-IR: 3302, 2932, 2093, 1446, 1308, 1145 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.63 (d, J = 7.6 Hz, 2H), 7.57 (t, J = 7.2 Hz, 1H), 7.50-7.47 (m, 2H), 7.45-7.41 (m, 4H), 7.37-7.33 (m, 6H), 3.41 (dd, J = 17.2, 2.0 Hz, 1H), 3.27 (dd, J = 17.2, 2.0 Hz, 1H), 3.23 (t, J = 6.8 Hz, 2H), 2.71-2.68 (m, 1H), 2.56-2.49 (m, 1H), 2.09 (t, J = 2.8 Hz, 1H), 1.78-1.74 (m, 1H), 1.60-1.58 (m, 2H), 1.44-1.40 (m, 7H) ppm; ^{13}C NMR (175 MHz, CDCl_3) δ 156.9, 147.0, 135.94, 135.92, 134.1, 131.7, 129.8, 129.0, 128.73, 128.66, 128.55, 128.4, 128.1, 127.9, 126.5, 77.5, 72.1, 69.8, 51.4, 29.8, 29.6, 28.7, 28.6, 26.5, 23.7, 21.3 ppm. HRMS (ESI-TOF) m/z calcd for $\text{C}_{32}\text{H}_{32}\text{O}_3\text{S}$ $[\text{M}+\text{Na}]^+$ 575.2087, found 575.2097.

2-(12-Azido-4-(phenylsulfonyl)dodec-1-yn-4-yl)-4,5-diphenyloxazole 5c—Colorless oil (102 mg, 48%); R_f = 0.40 (hexane/ethyl acetate, 4:1); FT-IR: 3296, 2931, 2095, 1447, 1309, 1146 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.64 (d, J = 7.6 Hz, 2H), 7.57 (t, J = 7.2 Hz, 1H), 7.51-7.48 (m, 2H), 7.46-7.41 (m, 4H), 7.38-7.33 (m, 6H), 3.43 (dd, J = 17.6, 2.8 Hz, 1H), 3.28 (dd, J = 17.6, 2.8 Hz, 1H), 3.24 (t, J = 6.8 Hz, 2H), 2.75-2.68 (m, 1H), 2.57-2.50 (m, 1H), 2.10 (t, J = 2.8 Hz, 1H), 1.79-1.74 (m, 1H), 1.59-1.54 (m, 2H), 1.45-1.35 (m, 9H) ppm; ^{13}C NMR (175 MHz, CDCl_3) δ 157.0, 147.0, 136.0, 135.9, 134.1, 131.8, 129.8, 129.0, 128.7, 128.67, 128.6, 128.4, 128.1, 128.0, 126.6, 77.6, 72.1, 69.8, 51.4, 29.9, 29.7, 29.0, 28.8, 26.6, 23.7, 21.3 ppm. HRMS (ESI-TOF) m/z calcd for $\text{C}_{33}\text{H}_{34}\text{N}_4\text{O}_3\text{S}$ $[\text{M}+\text{Na}]$ 589.2244, found 589.2239.

2-(13-Azido-4-(phenylsulfonyl)tridec-1-yn-4-yl)-4,5-diphenyloxazole 5d—Colorless oil (90 mg, 42%); R_f = 0.42 (hexane/ethyl acetate, 4:1); FT-IR: 3302, 2928, 2092, 1446, 1308, 1145 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.64 (d, J = 7.6 Hz, 2H), 7.57 (t, J = 7.6 Hz, 1H), 7.49-7.47 (m, 2H), 7.46-7.39 (m, 5H), 7.35-7.31 (m, 5H), 3.41 (dd, J = 18.0, 2.8 Hz, 1H), 3.28 (dd, J = 18.0, 2.8 Hz, 1H), 3.24 (t, J = 6.8 Hz, 2H), 2.73-2.67 (m, 1H), 2.56-2.49 (m, 1H), 2.09 (t, J = 2.8 Hz, 1H), 1.77-1.74 (m, 1H), 1.63-1.54 (m, 2H), 1.43-1.31 (m, 11H) ppm; ^{13}C NMR (175 MHz, CDCl_3) δ 157.0, 145.0, 136.0, 135.9, 134.0, 131.8, 129.8, 129.0, 128.7, 128.6, 128.5, 128.4, 128.1, 127.9, 126.5, 77.5, 72.0, 69.8, 51.4, 29.87,

29.78, 29.3, 29.03, 29.02, 28.8, 26.7, 23.8, 21.3 ppm.; HRMS (ESI-TOF) m/z calcd for $C_{34}H_{36}N_4O_3S$ $[M+Na]^+$ 603.2300, found 603.2309.

General procedure for the synthesis of final click compounds 6a-d from phenylsulfonylmethyl azidoalkyne precursors 5a-d

To the clear solution of **5a-d** (0.077-0.235 mmol, 1.0 equiv) in 1.5 mL of t -BuOH:H₂O (2:1) was added CuSO₄·5H₂O (0.015-0.047 mmol, 0.2 equiv) and sodium ascorbate (0.077-0.235 mmol, 1.0 equiv) at room temperature. The reaction mass was then heated to 90-95 °C (oil bath) for 30 min. During the progress of reaction, a light yellow color solid was separated from reaction mass and adhered to the bottom of reaction flask. Upon completion of reaction, as indicated by TLC, the reaction mass was cooled to room temperature, then diluted with water (10 mL) and extracted in dichloromethane (2 × 15 mL). The organic layers were combined, dried over anhydrous Na₂SO₄, filtered and concentrated to give a light yellow solid. The resulted crude solid product s were washed ethyl acetate (1 mL) and ethyl acetate layer was decanted thereafter to obtain the pure cyclized products **6a-d**, respectively. The above described procedure also used for synthesis of cyclic click compound **8** from **7**.

4,5-diphenyl-2-(5-(phenylsulfonyl)-4,5,6,7,8,9,10,11-octahydro-[1,2,3]triazolo[1,5-a]azecin-5-yl)oxazole 6a—Light yellow amorphous solid (95 mg, 95%) mp 138-140 °C (decomp); R_f = 0.4 (chloroform/MeOH, 4:1); FT-IR: 3061, 2932, 1446, 1306, 1142, 689 cm⁻¹; ¹H NMR (700 MHz, CDCl₃) δ 7.56-7.54 (t, J = 3.6 Hz, 2H), 7.48-7.42 (m, 4H), 7.35-7.28 (m, 10H), 4.19-4.14 (m, 2H), 4.06 (d, J = 8.8 Hz, 1H), 3.73 (d, J = 8.8 Hz, 1H), 2.41 (t, J = 6.8 Hz, 1H), 2.11 (t, J = 6.4 Hz, 1H), 1.90-1.88 (m, 1H), 1.79-1.77 (m, 2H), 1.29-1.24 (m, 5H) ppm; ¹³C NMR (175 MHz, CDCl₃) δ 157.5, 146.6, 140.9, 136.8, 135.9, 133.8, 131.7, 129.5, 129.0, 128.7, 128.7, 128.6, 128.4, 128.0, 127.9, 126.5, 124.1, 71.8, 50.1, 29.9, 29.1, 26.5, 25.8, 23.3, 22.6 ppm; HRMS (ESI-TOF) m/z calcd for $C_{31}H_{30}N_4O_3S$ $[M+H]^+$ 539.2117, found 539.2181.

4,5-diphenyl-2-(5-(phenylsulfonyl)-5,6,7,8,9,10,11,12-octahydro-4H-[1,2,3]triazolo[1,5-a][1]azacycloundecin-5-yl)oxazole 6b—Light yellow amorphous solid (120 mg, 92%) mp 142-144 °C (decomp); R_f = 0.47 (chloroform/MeOH, 4:1); FT-IR: 3061, 2932, 1446, 1306, 1142, 689 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.58 (d, J = 7.6 Hz, 2H), 7.49-7.44 (m, 4H), 7.39-7.31 (m, 10H), 4.19-4.14 (m, 2H), 4.10 (d, J = 15.6 Hz, 1H), 3.77 (d, J = 15.2 Hz, 1H), 2.40 (t, J = 6.8 Hz, 1H), 2.16 (t, J = 11.2 Hz, 1H), 1.87-1.76 (m, 3H), 1.36-1.27 (m, 7H) ppm; ¹³C NMR (175 MHz, CDCl₃) δ 157.5, 146.6, 141.0, 136.9, 135.9, 133.8, 131.7, 129.5, 129.0, 128.72, 128.68, 128.6, 128.4, 128.0, 127.9, 126.4, 124.1, 71.8, 50.2, 30.1, 29.9, 29.5, 28.4, 26.7, 26.2, 23.5 ppm.

4,5-diphenyl-2-(5-(phenylsulfonyl)-4,5,6,7,8,9,10,11,12,13-decahydro-[1,2,3]triazolo[1,5-a][1]azacyclododecin-5-yl)oxazole 6c—Light yellow amorphous solid (67 mg, 84%) mp 146-148 °C (decomp); R_f = 0.40 (chloroform/MeOH, 4:1); FT-IR: 3061, 2930, 1446, 1306, 1143, 690 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.58 (d, J = 7.6 Hz, 2H), 7.49-7.45 (m, 4H), 7.39-7.32 (m, 10H), 4.23-4.21 (m, 2H), 4.11 (d, J = 15.2 Hz, 1H), 3.77 (d, J = 15.2 Hz, 1H), 2.40 (t, J = 10.8 Hz, 1H), 2.17 (t, J = 12.0 Hz, 1H), 1.87-1.76 (m,

3H), 1.26-1.22 (m, 9H) ppm; ^{13}C NMR (175 MHz, CDCl_3) δ 157.5, 146.6, 141.0, 136.9, 135.9, 133.8, 131.7, 129.5, 129.0, 128.70, 128.67, 128.6, 128.4, 128.0, 127.9, 126.4, 124.0, 71.8, 50.2, 30.1, 30.0, 29.7, 28.8, 28.7, 26.7, 26.3, 23.6 ppm.

4,5-diphenyl-2-(5-(phenylsulfonyl)-5,6,7,8,9,10,11,12,13,14-decahydro-4H-[1,2,3]triazolo[1,5-a][1]azacyclotridecin-5-yl)oxazole 6d—Light yellow amorphous solid (38 mg, 84%) mp 134-136 °C (decomp); R_f = 0.55 (chloroform/MeOH, 4:1); FT-IR: 3061, 2925, 1445, 1306, 1143, 690 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.59 (d, J = 7.2 Hz, 2H), 7.50-7.47 (m, 4H), 7.38-7.32 (m, 10H), 4.23-4.21 (m, 2H), 4.11 (d, J = 14.7 Hz, 1H), 3.78 (d, J = 14.7 Hz, 1H), 2.41 (t, J = 10.8 Hz, 1H), 2.18 (t, J = 11.2 Hz, 1H), 1.86-1.78 (m, 3H), 1.23-1.19 (m, 11H) ppm; ^{13}C NMR (175 MHz, CDCl_3) δ 157.5, 146.6, 141.1, 136.9, 135.9, 133.8, 131.8, 129.5, 129.0, 128.70, 128.67, 128.6, 128.4, 128.0, 127.9, 126.4, 124.0, 71.9, 50.2, 30.1, 30.0, 29.8, 29.2, 29.0, 28.8, 26.7, 26.4, 23.7 ppm; HRMS (ESI-TOF) m/z calcd for $\text{C}_{34}\text{H}_{36}\text{N}_4\text{O}_3\text{S}$ $[\text{M}+\text{H}]^+$ 581.2586, found 581.2561.

2-(10-azidodec-1-yn-4-yl)-4,5-diphenyloxazole 7—To a stirred solution of 2-(10-azido-4-(phenylsulfonyl) dec-1-yn-4-yl)-4,5-diphenyloxazole **5a** (27 mg, 0.050 mmol, 1.0 equiv) in methanol (5 mL) was added magnesium turnings (18.3 mg, 0.75 mmol, 15 equiv) and crystals of mercuric chloride (1.4 mg, 0.005 mmol, 0.1 equiv) at room temperature. The reaction mixture was stirred at room temperature (3 h) while monitoring the reaction progress by TLC. Upon completion, the reaction mixture was filtered through a Celite bed followed by washing with methanol (2×10 mL). The filtrate was concentrated under vacuum using rotary evaporator and the resultant crude residue was submitted to gravity-column chromatography on silica gel, eluting with combinations of hexane/ethyl acetate (9:1) to afford the pure product 2-(10-azidodec-1-yn-4-yl)-4,5-diphenyloxazole **7** as colorless oil (13.6 mg, 68%); R_f = 0.6 (hexane/ethyl acetate, 4:1); FT-IR: 3301, 3059, 2932, 2093, 1444, 1059, 694 cm^{-1} ; ^1H NMR (700 MHz, CDCl_3) δ 7.64 (d, J = 7.7 Hz, 2H), 7.57 (d, J = 7.0 Hz, 2H), 7.37-7.30 (m, 6H), 3.23 (t, J = 6.3 Hz, 2H), 3.18-3.15 (m, 1H), 2.74 (ddd, J = 19.6, 6.3, 2.1 Hz, 1H), 2.66 (ddd, J = 19.6, 6.3, 2.1 Hz, 1H), 2.01 (t, J = 2.8 Hz, 1H), 1.92 (t, J = 4.9 Hz, 2H), 1.59-1.57 (m, 2H), 1.38-1.34 (m, 6H) ppm; ^{13}C NMR (175 MHz, CDCl_3) δ 164.4, 145.2, 135.0, 132.5, 129.1, 128.6, 128.5, 128.4, 128.0, 128.0, 126.4, 81.5, 70.2, 51.4, 38.7, 32.2, 28.9, 28.7, 26.8, 26.5, 22.8 ppm; HRMS (ESI-TOF) m/z calcd for $\text{C}_{25}\text{H}_{26}\text{N}_4\text{O}$ $[\text{M}+\text{H}]^+$ 399.2185, found 399.2192.

2-(4,5,6,7,8,9,10,11-octahydro-[1,2,3]triazolo[1,5-a]azecin-5-yl)-4,5-diphenyloxazole 8—The same procedure (Entry 11, Table 1) was used for the preparation of **8**: Off-white amorphous solid (9.5 mg, 73%) mp 128-130 °C; R_f = 0.37 (chloroform/MeOH, 4:1); FT-IR: 3059, 2929, 2865, 1444, 1053, 694 cm^{-1} ; ^1H NMR (700 MHz, CDCl_3) δ 7.58 (d, J = 7.7 Hz, 2H), 7.50 (d, J = 7.7 Hz, 2H), 7.34-7.26 (m, 6H), 7.13 (s, 1H), 4.17 (t, J = 7.0 Hz, 2H), 3.30-3.28 (m, 1H), 3.23-3.19 (m, 1H), 3.14-3.12 (m, 1H), 1.82-1.69 (m, 4H), 1.29-1.18 (m, 6H) ppm; ^{13}C NMR (175 MHz, CDCl_3) δ 165.2, 145.2, 144.9, 134.9, 132.5, 128.9, 128.6, 128.5, 128.4, 128.1, 127.89, 126.3, 121.4, 50.1, 39.8, 33.2, 30.1, 29.7, 28.6, 26.8, 26.1 ppm.

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Fig. 1.

Possible *exo* vs *endo* double bond disposition and 1,2,3-triazole substitution in the intramolecular click products of an azido alkyne having ten contiguous carbons.

Fig. 2.
2-(Phenylsulfonylmethyl)-4,5-Diphenyloxazole scaffolds **1** and alkylation products

Reagents/Conditions: (a) 1,6-, 1,7-, 1,8- or 1,9-dihalide/KOt-Bu/THF rt/16 h. (b) propargyl bromide/KOt-Bu/THF/rt/16 h. (c) NaN₃/DMF/rt/16 h. (d) NaN₃/DMF/rt/16 h. (e) propargyl bromide/KOt-Bu/THF/rt/16 h.

Scheme 1.

Synthesis of intramolecular click substrates **5a-d** from intermediate **1**.

Reagents/Conditions: (a) 1,6-, 1,7-, 1,8- or 1,9-dihalide/KOt-Bu/THF rt/16 h. (b) propargyl bromide/KOt-Bu/THF/rt/16 h. (c) NaN₃/DMF/rt/16 h. (d) NaN₃/DMF/rt/16 h. (e) propargyl bromide/KOt-Bu/THF/rt/16 h.

Scheme 2.

Intramolecular click reactions of substrates **5a-d** to give cyclized products **6a-d**. Reagents/
Conditions: (See also **Table 1**): (a) $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ /sodium ascorbate/t-BuOH:H₂O/
90-95 °C/30 min.

Scheme 3.

Synthesis and intramolecular click reaction of nonphenylsulfone-substituted substrate **7** to **8**.

Reagents/conditions: (a) Mg/HgCl₂/MeOH/rt/30 min (68%). (b) CuSO₄·5H₂O/90-95 °C/30 min (73%).

Table 1

Optimization of the intramolecular click reaction of **5a** to **6a**.

Entry/Ref	Cu source (eq)	Reducing agent (eq)	Ligand/Base (eq)	Conditions	Yield (%) / Result ¹
1 ⁹				Toluene/reflux/16 h	NR
2				MeOH/reflux/16h	NR
3 ¹⁰	CuI (1.1)		DIPEA (2.5)	THF/rt	44
4 ¹¹	CuI (1.0)		DBU (20)	Toluene/rt/16 h	Decomp.
5	CuI (0.1)	Na ascorbate (0.2)	C ₅ CO ₃ (2.0)	DMF/60°C/16 h	38
6 ¹²	CuSO ₄ ·5H ₂ O (1 mol%)	Na ascorbate (10 mol%)		t-BuOH-H ₂ O/rt/12 h	40
7	CuSO ₄ ·5H ₂ O (0.1)	Na ascorbate (0.5)		THF/H ₂ O (2:1)/rt/48 h	38
8	CuSO ₄ ·5H ₂ O (0.5)	Na ascorbate (1.0)		THF/H ₂ O (2:1)/rt/16 h	51
9 ¹³	CuSO ₄ ·5H ₂ O (0.1)	Na ascorbate (0.5)		DMSO-t-BuOH-H ₂ O (4:2:1) rt/48 h	28
10 ¹⁴	CuSO ₄ ·5H ₂ O (0.2)	Na ascorbate (0.5)		t-BuOH-H ₂ O (2:1)/60 °C/16 h	43
11 ¹⁴	CuSO ₄ ·5H ₂ O (0.2)	Na ascorbate (1.0)		t-BuOH-H ₂ O (2:1)/90-95 °C/1 h	96
12	CuSO ₄ ·5H ₂ O (0.1)	Na ascorbate (0.5)		DMSO-H ₂ O (1:2)/rt/16 h	53
13	CuSO ₄ ·5H ₂ O (0.2)	Na ascorbate (0.8)	Benzoic acid (0.1)	THF-H ₂ O-t-BuOH (3:1:1)/rt/12 h	45
14	CuSO ₄ ·5H ₂ O (1 mol%)	Na ascorbate (5 mol%)	Urea (2 mol%)		35

¹Yields are for isolated purified compounds