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FUNDAMENTAL INSIGHTS INTO ADVANCING THE FUNCTIONALITY AND ADAPTABILITY OF BIODEGRADABLE TRIAZOLE-BASED ‘CLICK’ POLYMER LIBRARIES FOR DIVERSE BIOMEDICAL USES: CURRENT ACHIEVEMENTS, CHALLENGES, STRATEGIC DIRECTIONS, AND NOVEL PRACTICAL APPROACHES

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Abstract. A series of new aliphatic AA-BB-type poly(ester ether amide)s (PEEAs) and poly(ester ether)s (PEEs) containing 1,2,3-triazole rings in the main chain were successfully obtained. The synthesis of the "click" polymers was performed *via* Cu(I)-catalyzed click step-growth polymerization (SGP) employing the efficient one pot/two-step synthetic approach that we had previously developed. The structure of the polymers was confirmed by FT-IR and NMR spectroscopy. The newly synthesized materials were extensively characterized, including assessments of their yield, solubility, film-forming properties, molecular weights, and molecular weight distribution. The obtained PEEAs and PEEs exhibited a quite satisfactory degree of polymerization, good film-forming properties, and favorable solubility behavior. The reported materials enlarge a library of available degradable triazole click polymers promising for a wide range of biomedical applications. The results validate once again the applicability of our innovative synthetic strategy for designing various classes of triazole-backbone degradable click polymers. Degradable triazole-based "click" polymers have emerged as a versatile and indispensable class of materials in biomedical innovation. Their unique properties, such as biocompatibility, tunable degradability, and ease of synthesis via "click" chemistry, have made them highly attractive for diverse applications, ranging from drug delivery systems to tissue engineering scaffolds. Expanding their scope and functionality remains a pivotal goal to meet the growing demands of advanced biomedical technologies. This article explores the advances, challenges, opportunities, future development strategies, and emerging practical implementation approaches for these polymers. The field of degradable triazole "click" polymers is poised for significant advancements in biomedical innovation. As the library of these polymers expands, it is important to balance the opportunities they offer with the challenges they present. By focusing on controlled synthesis, enhanced biological interactions, and scalable production, researchers and clinicians can harness the full potential of these materials. With continued development and collaboration, these polymers could become a cornerstone of next-generation biomedical therapies, leading to improved patient outcomes and more sustainable healthcare solutions. The study successfully demonstrates the synthesis of new poly(ester ether amide)s (PEEAs) and poly(ester ether)s (PEEs) incorporating 1,4-disubstituted 1,2,3-triazole rings in their backbone. The materials exhibit promising properties that make them potential candidates for a variety of biomedical applications, particularly in controlled drug delivery and tissue engineering. However, further research is needed to fully explore their clinical potential, optimize their properties, and address challenges related to their large-scale production and biological interactions.

Keywords: Poly(ester ether amide)s, (PEEAs) poly(ester ether)s, (PEEs) copper(i), catalyzed azide-alkyne cycloaddition, (CuAAC) step growth polymerization (SGP) 1,2,3-triazole ring.

Introduction. Degradable triazole-based “click” polymers have emerged as a versatile and indispensable class of materials in biomedical innovation. Their unique properties, such as biocompatibility, tunable degradability, and ease of synthesis via “click” chemistry, have made them highly attractive for diverse applications, ranging from drug delivery systems to tissue engineering scaffolds. Expanding their scope and functionality remains a pivotal goal to meet the growing demands of advanced biomedical technologies. This article explores the advances, challenges, opportunities, future development strategies, and emerging practical implementation approaches for these polymers.

Advances in Degradable Triazole “Click” Polymers

1. Synthetic Innovations:
   - Introduction of novel monomers and polymerization techniques has significantly broadened the library of triazole-based polymers.
   - Controlled polymerization strategies enable precise tailoring of molecular weights and architectures, including linear, branched, and network structures.
2. Functional Diversity:
   - Integration of functional groups has allowed for enhanced interaction with biological systems, enabling applications in targeted drug delivery and imaging.

➢ Multi-stimuli-responsive systems have been developed for controlled degradation under specific physiological conditions.

3. Biomedical Applications:

➢ Drug Delivery: High loading capacities and tunable release profiles make these polymers ideal carriers for chemotherapeutics, antibiotics, and gene therapies.

➢ Tissue Engineering: Biodegradable scaffolds support cell attachment, proliferation, and differentiation while degrading into non-toxic byproducts.

➢ Diagnostics: Functionalized triazole polymers serve as contrast agents in imaging and biosensing applications.

Challenges in Expanding the Scope and Functionality

1. Synthetic Complexity:

➢ Achieving scalable, cost-effective synthesis of highly functionalized triazole polymers remains a significant hurdle.

2. Biocompatibility and Safety:

➢ Comprehensive in vivo studies are required to ensure long-term biocompatibility and to understand degradation pathways and byproducts.

3. Regulatory Hurdles:

➢ The stringent regulatory requirements for biomedical materials pose challenges for clinical translation.

4. Integration with Emerging Technologies:

➢ Compatibility with advanced biomedical tools such as 3D bioprinting and microfluidics is still underexplored.

Opportunities for Innovation

1. Interdisciplinary Collaboration:

➢ Partnerships between chemists, biologists, engineers, and clinicians can accelerate innovation and application.

2. Customization for Personalized Medicine:

➢ Tailoring polymer properties to meet individual patient needs in drug delivery and tissue engineering.

3. Green Chemistry Approaches:

➢ Development of sustainable, eco-friendly synthetic methods for triazole polymers.

4. Integration with Smart Materials:

➢ Combining triazole polymers with stimuli-responsive or bioactive materials to create multifunctional systems.

Future Development Strategies

1. Advanced Synthesis Techniques:

- ➢ Leveraging automation, artificial intelligence, and machine learning for the design and synthesis of complex polymer architectures.

2. Comprehensive Characterization:
   - ➢ Employing state-of-the-art analytical tools to study polymer structure, functionality, and degradation mechanisms.
3. Enhanced Biocompatibility Testing:
   - ➢ Long-term in vitro and in vivo evaluations to ensure safety and efficacy.
4. Clinical Translation:
   - ➢ Establishing partnerships with industry and regulatory bodies to streamline the transition from laboratory research to practical applications.

Emerging Practical Implementation Approaches

1. 3D Printing and Bioprinting:
   - ➢ Utilization of triazole-based polymers as bioinks for creating customized biomedical devices and tissue constructs.
2. Nanotechnology Integration:
   - ➢ Designing nanoscale polymeric systems for precision medicine applications.
3. Hybrid Systems:
   - ➢ Developing composite materials that combine the benefits of triazole polymers with other biomaterials for enhanced performance.
4. Digital Health and Monitoring:
   - ➢ Incorporating triazole polymers into wearable biosensors and diagnostic tools for real-time health monitoring.

The Copper(I) catalyzed azide-alkyne cycloaddition (CuAAC) stands as a prominent tool within the realm of "click" reactions, showcasing its widespread utility across diverse domains in contemporary polymer and material science. This reaction has gained significant recognition due to its exceptional attributes, including rapid reaction kinetics, high efficiency, precise regioselectivity, tolerance towards diverse functional groups, and mild reaction conditions. Consequently, CuAAC click reactions have found extensive application in the synthesis of various polymer architectures, such as block-copolymers, cyclic polymers, dendrimers, hyper-branched macromolecules, star-shaped polymers, and cross-linked polymeric networks [1-11]. Furthermore, this technique has been instrumental in functionalizing and modifying the surfaces of polymeric materials.

Intrigued by its potential, synthetic polymer chemists have sought to leverage CuAAC for the synthesis of polytriazoles through step-growth polymerization (SGP) since 2004 [12-15]. Despite notable advancements, this field remains in a state of continuous development, beset by numerous challenges and obstacles [14-15]. Specifically, there is a paucity of reports detailing the synthesis of aliphatic main-chain triazole degradable polymers through CuAAC-based click SGP. Noteworthy contributions include the pioneering work of Nagao and Takasu [16], who successfully synthesized degradable polyesters (PEs), and the efforts of Galbis et al. [17], who produced click PEs on the basis of erythritol, bearing free hydroxyl groups. Beyond these achievements, click polymerization has also been harnessed for the fabrication of various other biomedical materials [18-24].

It should be noted that click polymers with 1,2,3-triazole rings in the backbone have some important advantages. To commence with, the triazole rings are known to be low-toxic moieties [25, 26] with a high level of mimicry of the amide bond of native peptides: the 1,2,3-triazole ring is structurally similar to the amide bond of proteins in terms of configuration, distance, and planarity [27]. So, the incorporation of the triazole units in the polymeric chains is anticipated to enhance the biocompatibility of the materials. Furthermore, the insertion of rigid triazole fragments in the polymeric structure can notably improve the thermal characteristics of the polymers [28]. It is known that triazole's derivatives demonstrate a wide range of biological activities, including anti-inflammatory, antioxidant, antiviral, antimicrobial, antifungal, anticancer, analgesic, etc. [29, 30]. Therefore, the click polymers with triazole rings in the backbone are expected to reveal some biological activities, and such polymers can be promising for creating new bioactive materials. It is worth noting that 1,2,3-triazoles are widely used in the design of various high-performance organic coatings such as anti-microbial, anti-fouling, anti-corrosive, self-healing, etc. [31]. Thus, the triazole-enriched click polymers can be considered as perspective materials for creating effective polymeric coatings as well.

Moreover, an important advantage of click polymers lies in the quaternizable nature of 1,2,3-triazole rings, as documented in prior studies [32, 33]. This characteristic facilitates subsequent post-polymerization functionalization of these polymers. The process of quaternization, involving the modification of triazole rings with diverse quaternizing agents such as halo-alkyls and polyethylene glycol (PEG) derivatives, presents opportunities for creating cationic systems featuring 1,2,3-triazolium moieties within the polymer backbone. This includes the development of cationic polymers and amphiphilic surfactants (e.g., when employing PEG-bromides as quaternizing agents) and the formation of cross-linked hydrogels (when utilizing bifunctional quaternizing agents like dibromo-PEGs, for instance). These approaches hold significant promise for a multitude of biomedical applications.

To synthesize new high-molecular-weight 1,2,3-trialoze containing degradable polymers, we have previously elaborated a new synthetic strategy of CuAAC-based click SGP [28]. Our innovative approach could be considered as more versatile compared to existing strategies and allows to synthesize different types (AB and AA-BB) and classes (PEs, poly(ester amide)s, poly(ester urea)s, their co-polymers, etc.) of aliphatic hetero-chain click polymers, avoiding the utilization of potentially explosive organic azides through safe and facile one-pot/two-step procedure. In the mentioned work [28], we successfully synthesized a series of novel linear AA-BB type 1,2,3-triazole rings-containing click PEs following the new strategy. Obtained on the basis of non-toxic building blocks (fatty diols and dicarboxylic acids), the new polymers possessed high molecular weights, improved thermal characteristics, good solubility in organic solvents, film- and nanoparticles-forming properties. Very recently, we demonstrated the suitability of the new synthetic approach for designing novel hydrolytically degradable AB-type click PEs and Co-PEs as well [34].

In the present work, we report on the successful synthesis of two other classes of new linear AA-BB-type degradable click polymers *via* our efficient synthetic strategy: poly(ester ether amide)s (PEEAs) and poly(ester ether)s (PEEs). The key homo-bifunctional diyne monomers were synthesized by the interaction of sebacoyl chloride with propargyl alcohol or propargylamine according to ***Figure 1.***

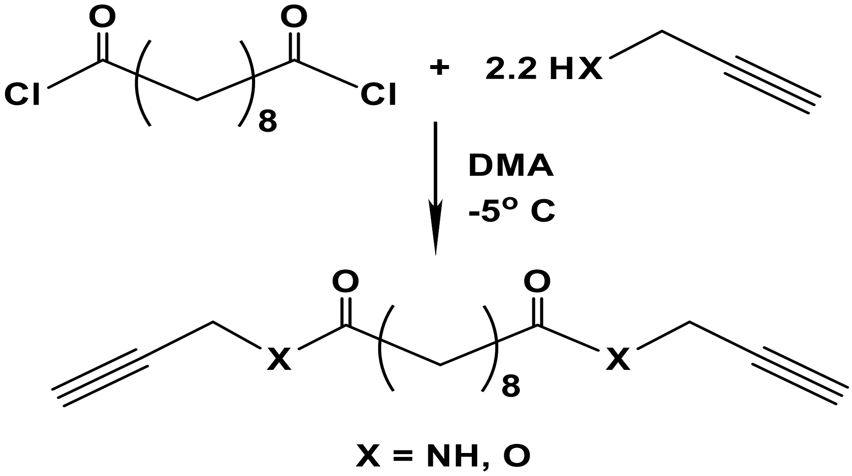

Figure 1. Synthesis of diyne monomers

The synthetic precursors of target diazide monomers (bis-bromoacetyl derivatives) were obtained by the interaction of bromoacetyl bromide with di-, tri-, and tetra-ethylene glycol (***Figure 2***).

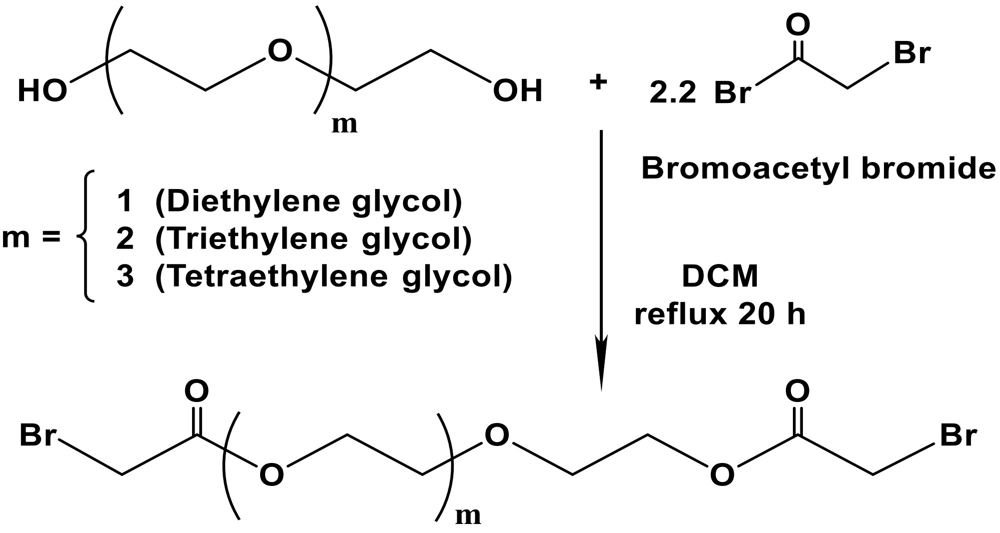

Figure 2. Synthesis of bis-bromoacetyl derivatives

The synthesis of the new click polymers with triazole rings in the backbone was realized by one-pot/two-step SGP of the homo-bifunctional monomers in the presence of sodium azide using copper(I) iodide/triethylamine (CuI/NEt_3) as a catalytic system (***Figure 3***).

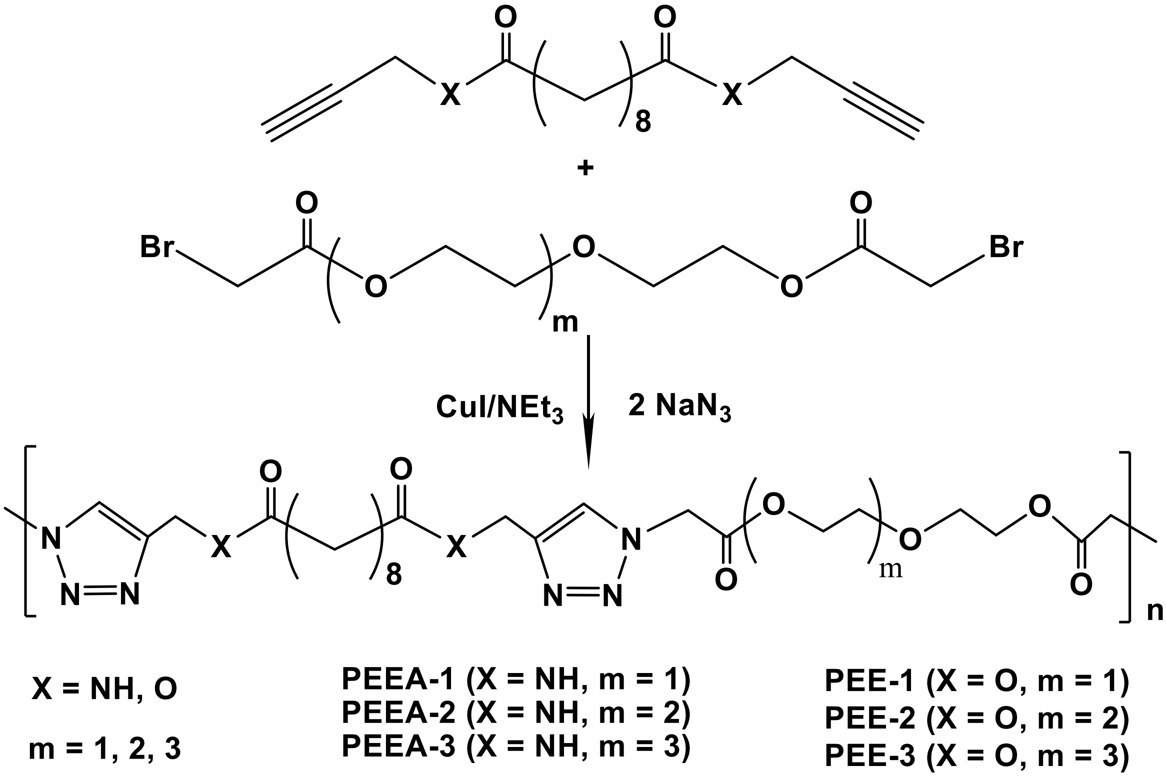

Figure 3. Synthesis of PEEAs (X=NH) and PEEs (X=O)

The confirmation of monomer and polymer structures was performed through the use of FT-IR and NMR spectroscopic techniques. Comprehensive polymer characterization encompassed the assessment of yield, solubility in organic solvents, film-forming attributes, determination of molecular weights, and evaluation of molecular weight distribution. The introduction of novel AA-BB-type PEEAs and PEEs serves to enrich the existing repository of degradable click polymers, broadening the spectrum of materials available for a diverse array of biomedical applications.

Materials and Methods.

Materials

Broboacetyl bromide, propargyl alcohol, propargylamine, sodium azide, anhydrous sodium sulfate, copper(I) iodide, lithium bromide, aluminum oxide (alumina) (activated, basic, Brockmann I), acetone, ethanol, methanol, hexane, ethyl acetate, dichloromethane (DCM), N,N-Dimethylformamide (DMF), N,N-dimetyl-acetamide (DMA), and 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) were purchased from Sigma-Aldrich (Germany). N-methylpyrrolidone (NMP) was purchased from Carl Roth, Karlsruhe (Germany). Triethylamine (TEA) was purchased from Lancaster (UK). All the starting materials, chemicals, and solvents purchased from the commercial sources were used without further purification.

Characterization

The polymers synthesized were characterized by Fourier-transform infrared spectroscopy (FT-IR), 1H nuclear magnetic resonance (NMR) spectroscopy, and gel permeation chromatography (GPC).

The IR analysis of samples was performed on Thermo Nicolet Avatar 370 FT-IR spectrophotometer coupled with EZ OMNIC software measuring between wavelength range of 4000 and 400 cm^{-1}. The FT-IR spectra of monomers were recorded using Avatar Multi-Bounce Flat Plate 45 degree Ge. To obtain the spectra of polymers, the thin films were cast from HFIP solution on KBr plates, the solvent was evaporated at room temperature and films were dried in a vacuum at 40° C to a constant weight.

The 1H and NMR spectra were recorded at 300 K on a JEOL ECP 500 NMR spectrometer operating at 400 MHz. DMSO-d_6 was used as solvents and internal standards. The chemical shifts (δ) in the spectra are conventionally expressed in parts per million (ppm).

The weight-average (M_w), number-average (M_n) molecular weights, and molecular weight distribution (Dispersity, $Đ$) of the polymers were determined on a GPC machine (Waters Associates, Inc., Milford, United States) comprising two Styragel columns in DMF: HR4 and HR3 (7.8 mm × 300 mm) and equipped with a high-pressure liquid chromatography pump (Waters 1525 Binary HPLC) and a Waters refractive index detector 2414 and UV-detector (Waters 2487 dual absorbance detector, λ = 240 nm). A solution of LiBr (0.05 M) in DMF was used as an eluent. Injected volume 100 µL, flow rate 1.0 mL min^{-1}. The columns were calibrated with poly(methyl methacrylate) standards (M_n = 500 – 500, 000 g mol^{-1}). Polymer sample solutions with concentration 5 mg ml^{-1} were prepared in the GPC eluent and filtered with PTFE filters (0.45 µm) prior to injection.

Synthesis of diyne monomers

The key homo-bifunctional diyne monomers (di-propargyl amide/ester of sebacic acid) were synthesized by the interaction of sebacoyl chloride with propargylamine or propargyl alcohol according to Figure 1. The synthesis was carried out in DMA solution without using tertiary amine as HCl acceptor. In a typical procedure, propargylamine/propargyl alcohol (0.159 mol – an excess) was dissolved in 260 mL of DMA, the solution was chilled to –5° C and 17.30 g of sebacoyl chloride (0.072 mol) was added dropwise upon stirring using a magnetic stirrer. The reaction solution was stirred for 30 min at -5 °C and then was continued at room temperature for 24 h. Afterwards, the solution was poured into water and the vessel with precipitated white powder was placed overnight in a refrigerator. The obtained solid product was filtered off, dried under reduced pressure at room temperature, and recrystallized from the ethanol/hexane mixture.

Di-propargyl amide of sebacic acid. Yield: 68 %. FTIR (cm^{-1}): 3280 (-NH-, amide, stretching vibr.), 2132 (C≡C), 1642 (-CO-, amide), 1552 (NH-, amide, bending vibr.). ^{1}H NMR (400 MHz, DMSO-d_6, *δ*): 1.28-1.32 (8H, m, $C\underline{H_2}$); 1.54 (4H, m, $C\underline{H_2}CH_2CO$); 2.16 (4H, t, $C\underline{H_2}CO$); 3.04 (2H, t, sp-C$\underline{H}$); 4.11 (4H, d, $NHC\underline{H_2}$), 8.12 (2H, N$\underline{H}$).

Di-propargyl ester of sebacic acid. Yield: 75 %. FTIR (cm^{-1}): 3238 (≡C–H), 2128 (C≡C), 1732 (-CO- ester), 1217 (C-O-C). ^{1}H NMR: (400 MHz, DMSO-d_6, δ): 1.29-1.35 (8H, m, $C\underline{H_2}$); 1.59 (4H, m, $C\underline{H_2}CH_2CO$); 2.30 (4H, t, $C\underline{H_2}CO$); 2.93 (2H, t, sp-C$\underline{H}$); 4.61 (4H, d, $OC\underline{H_2}$).

Synthesis of bis-bromoacetyl derivatives (precursors of diazide monomers)

The synthetic precursors of target diazide monomers (bis-bromoacetyl derivatives) were synthesized by the interaction of bromoacetyl bromide with di- (DEG), tri- (TEG), and tetra-ethylene glycol (TTEG) according to Figure 2 above. The brief synthetic procedure is described here on the example of DEG-based bis-bromoacetyl derivative: to a solution of 6.09 g (0.057 mol) of DEG in 315 mL of DCM, 25.52 g (0.126 mol) of bromoacetyl bromide was added. The resulting yellow solution was refluxed for 20 h and the solvent was removed in a vacuum on a rotary evaporator yielding a brownish viscous liquid. The obtained crude product was dissolved in 40 mL of methanol and the solution was washed with 40 mL of hexane. The mixture was separated using a separated funnel and the procedure was repeated twice (i.e. methanol solution of the crude product was washed 3 times with hexane). After the last separation of the mixture, the methanol solution of the monomer was dried over anhydrous sodium sulfate, then it was filtered and the organic solvent was removed in a vacuum on a rotary evaporator, yielding a brownish viscous liquid. DEG- and TTEG-based bis-bromoacetyl derivatives were synthesized according to the same procedure.

DEG-based bis-bromoacetyl derivative. Yield: 69 %. FTIR (cm^{-1}): 1740 (-CO-, ester), 1282 (C-O-C, ester), 1123 (C-O-C, ether). ^{1}H NMR (400 MHz, DMSO-d_6, δ): 3.51 (4H, $C\underline{H_2}$-O-$C\underline{H_2}$), 4.11 (4H, COO-$C\underline{H_2}$), 4.21 (4H, CO-$C\underline{H_2}$).

TEG-based bis-bromoacetyl derivative. Yield: 76 %. FTIR (cm^{-1}): 1736 (-CO-, ester), 1278 (C-O-C, ester), 1115 (C-O-C, ether). ^{1}H NMR (400 MHz, DMSO-d_6, δ): 3.21-3.63 (8H, $C\underline{H_2}$-O-$C\underline{H_2}$-$C\underline{H_2}$-O-$C\underline{H_2}$), 4.12 (4H, COO-$C\underline{H_2}$), 4.22 (4H, CO-$C\underline{H_2}$).

TTEG-based bis-bromoacetyl derivative. Yield: 73 %. FTIR (cm^{-1}): 1744 (-CO-, ester), 1282 (C-O-C, ester), 1116 (C-O-C, ether). ^{1}H NMR (400 MHz, DMSO-d_6, δ): 3.13-3.47 (12H, $C\underline{H_2}$-O-$C\underline{H_2}$-$C\underline{H_2}$-O-$C\underline{H_2}$-$C\underline{H_2}$-O-$C\underline{H_2}$), 4.09 (4H, COO-$C\underline{H_2}$), 4.20 (4H, CO-$C\underline{H_2}$).

Polymer synthesis

The target PEEAs and PEEs were synthesized according to the one-pot two-step synthetic strategy that we had previously developed [28,34] (Figure 3). The synthetic procedure is similar to the one applied for the AB-type click PEs reported in our recent work [34]. The brief synthetic procedure for the click SGP of the PEEAs and PEEs is described here for PEEA-1 as an example: 1.902 g (5.46 mmol) of DEG-based bis-bromoacetyl derivative and 0.782g (12.03 mmol) of sodium azide were dissolved in 8.35 mL of NMP and stirred at room temperature for 3 h. Then, 1.511 g (5.46 mmol) of a di-propargyl amide of sebacic acid, 31.24 mg (0.16 mmol) of catalyst CuI (3 mol %), and 0.114 mL (0.82 mmol) of NEt_3 as a ligand were added to the reaction solution. The reaction solution was stirred at room temperature for 24 hours. After completion of the reaction, the solution was diluted with 8 mL of NMP, and the copper catalyst was removed by passing the crude polymer solution through a small column of activated basic alumina. Then, the obtained polymer solution was precipitated in water, filtered, thoroughly washed with water, and dried under vacuum at room temperature. Then, the polymer was twice precipitated from NMP solution (at a concentration of 10% w/v) to water, filtered, and dried under vacuum at room temperature to a constant weight. All the other polymers were synthesized employing the same synthetic procedure.

PEEA-1. Yield: 73 %. FTIR (cm^{-1}): 3297 (-NH-, amide, stretching vibr.), 3068 (C=C-H of the 1,2,3-triazole), 1752 (-CO-, ester), 1638 (-CO-, amide), 1544 (NH-, amide, bending vibr.), 1217 (C-O-C, ester), 1135 (C-O-C, ether). ^{1}H NMR

(400 MHz, DMSO-d_6, δ): 1.01 (12H, $CH_2\text{-}(C\underline{H}_2)_6\text{-}CH_2$), 1.85 (4H, $CO\text{-}C\underline{H}_2\text{-}(CH_2)_6\text{-}C\underline{H}_2\text{-}CO$), 3.24-3.50 (4H, $C\underline{H}_2\text{-}O\text{-}C\underline{H}_2$), 4.02-4.11 (8H, $COO\text{-}C\underline{H}_2$ and $NH\text{-}C\underline{H}_2$-, stack), 5.17 (4H, $CO\text{-}C\underline{H}_2\text{-}N$), 7.68 (2H, -C=C$\underline{H}$ of triazole), 8.16 (2H, N$\underline{H}$).

PEEA-2. Yield: 94 %. FTIR (cm^{-1}): 3293 (-NH-, amide, stretching vibr.), 3063 (C=C-H of the 1,2,3-triazole moiety), 1744 (-CO-, ester), 1638 (-CO-, amide), 1544 (NH-, amide, bending vibr.), 1217 (C-O-C, ester), 1131 (C-O-C, ether). ^{1}H NMR (400 MHz, DMSO-d_6, δ): 1.07 (12H, $CH_2\text{-}(C\underline{H}_2)_6\text{-}CH_2$), 1.82 (4H, $CO\text{-}C\underline{H}_2\text{-}(CH_2)_6\text{-}C\underline{H}_2\text{-}CO$), 3.23-3.65 (8H, $C\underline{H}_2\text{-}O\text{-}C\underline{H}_2\text{-}C\underline{H}_2\text{-}O\text{-}C\underline{H}_2$), 4.03-4.12 (8H, $COO\text{-}C\underline{H}_2$ and $NH\text{-}C\underline{H}_2$-, stack), 5.18 (4H, $CO\text{-}C\underline{H}_2\text{-}N$), 7.70 (2H, -C=C$\underline{H}$ of triazole), 8.14 (2H, N$\underline{H}$).

PEEA-3. Yield: 89 %. FTIR (cm^{-1}): 3297 (-NH-, amide, stretching vibr.), 3076 (C=C-H of the 1,2,3-triazole), 1752 (-CO-, ester), 1638 (-CO-, amide), 1543 (NH-, amide, bending vibr.), 1225 (C-O-C, ester), 1127 (C-O-C, ether). ^{1}H NMR (400 MHz, DMSO-d_6, δ): 0.99 (12H, $CH_2\text{-}(C\underline{H}_2)_6\text{-}CH_2$), 1.84 (4H, $CO\text{-}C\underline{H}_2\text{-}(CH_2)_6\text{-}C\underline{H}_2\text{-}CO$), 3.14-3.45 (12H, $C\underline{H}_2\text{-}O\text{-}C\underline{H}_2\text{-}C\underline{H}_2\text{-}O\text{-}C\underline{H}_2\text{-}C\underline{H}_2\text{-}O\text{-}C\underline{H}_2$), 3.93-4.08 (8H, $COO\text{-}C\underline{H}_2$ and $NH\text{-}C\underline{H}_2$-, stack), 5.13 (4H, $CO\text{-}C\underline{H}_2\text{-}N$), 7.66 (2H, -C=C$\underline{H}$ of triazole), 8.07 (2H, N$\underline{H}$).

PEE-1. Yield: 93 %. FTIR (cm^{-1}): 3145 (C=C-H of the 1,2,3-triazole), 1744 (-CO-, ester), 1213 (C-O-C, ester), 1164 (C-O-C, ether). ^{1}H NMR (400 MHz, DMSO-d_6, δ): 0.87 (12H, $CH_2\text{-}(C\underline{H}_2)_6\text{-}CH_2$), 1.90 (4H, $CO\text{-}C\underline{H}_2\text{-}(CH_2)_6\text{-}C\underline{H}_2\text{-}CO$), 3.29 (4H, $C\underline{H}_2\text{-}O\text{-}C\underline{H}_2$), 3.91 (4H, $COO\text{-}C\underline{H}_2\text{-}CH_2$), 4.78 (4H, $COO\text{-}C\underline{H}_2\text{-}C$), 5.10 (4H, $CO\text{-}C\underline{H}_2\text{-}N$), 7.83 (2H, -C=C$\underline{H}$ of triazole).

PEE-2. Yield: 87 %. FTIR (cm^{-1}): 3141 (C=C-H of the 1,2,3-triazole), 1740 (-CO-, ester), 1213 (C-O-C, ester), 1168 (C-O-C, ether). ^{1}H NMR (400 MHz, DMSO-d_6, δ): 0.99 (12H, $CH_2\text{-}(C\underline{H}_2)_6\text{-}CH_2$), 2.07 (4H, $CO\text{-}C\underline{H}_2\text{-}(CH_2)_6\text{-}C\underline{H}_2\text{-}CO$), 3.30 (8H, $C\underline{H}_2\text{-}O\text{-}C\underline{H}_2\text{-}C\underline{H}_2\text{-}O\text{-}C\underline{H}_2$), 4.02 (4H, $COO\text{-}C\underline{H}_2\text{-}CH_2$), 4.91 (4H, $COO\text{-}C\underline{H}_2\text{-}C$), 5.20 (4H, $CO\text{-}C\underline{H}_2\text{-}N$), 7.93 (2H, -C=C$\underline{H}$ of triazole).

PEE-3. Yield: 85 %. FTIR (cm^{-1}): 3145 (C=C-H of the 1,2,3-triazole), 1752 (-CO-, ester), 1209 (C-O-C, ester), 1164 (C-O-C, ether). ^{1}H NMR (400 MHz, DMSO-d_6, δ): 0.97 (12H, $CH_2\text{-}(C\underline{H}_2)_6\text{-}CH_2$), 2.04 (4H, $CO\text{-}C\underline{H}_2\text{-}(CH_2)_6\text{-}C\underline{H}_2\text{-}CO$), 3.26 (12H, $C\underline{H}_2\text{-}O\text{-}C\underline{H}_2\text{-}C\underline{H}_2\text{-}O\text{-}C\underline{H}_2\text{-}C\underline{H}_2\text{-}O\text{-}C\underline{H}_2$), 4.02 (4H, $COO\text{-}C\underline{H}_2\text{-}CH_2$), 4.88 (4H, $COO\text{-}C\underline{H}_2\text{-}C$), 5.17 (4H, $CO\text{-}C\underline{H}_2\text{-}N$), 7.91 (2H, -C=C$\underline{H}$ of triazole).

Results and Discussion

Synthesis of diyne monomers

The detailed procedure of the synthesis of key homo-bifunctional diyne monomers (di-propargyl amide/ester of sebacic acid) was discussed above. The AA-BB-type monomers were synthesized by the interaction of sebacoyl chloride with propargylamine or propargyl alcohol (Figure 1). The yields of the obtained di-propargyl amide of sebacic acid and di-propargyl ester of sebacic acid were 68 and 75

%, respectively. The presumed structure of the diyne monomers was proved by FT-IR and ^{1}H NMR spectroscopies.

Synthesis of bis-bromoacetyl derivatives (precursors of diazide monomers)

The synthesis of bis-bromoacetyl derivatives – precursors of diazide monomers, was described above (see Materials and methods). Three bis-bromoacetates were obtained by the interaction of bromoacetyl bromide with di- (DEG), tri- (TEG), and tetra-ethylene glycol (TTEG) (see Figure 2 above). The yields of the obtained bis-bromoacetyl derivatives were in the range of 69 – 76 %. Their structure was confirmed by FTIR and ^{1}H NMR spectroscopies.

Synthesis of the click PEEAs and PEEs

Six new triazole click polymers (three PEEAs and three PEEs) were synthesized *via* one-pot/two-step synthetic strategy that we had previously [28,34] developed. The detailed procedure of the synthesis of target click polymers was discussed above (see *Experimental Methods and Materials*).

The polymers were obtained with quite high yields (73 – 94 %). The molecular weight characteristics of the new click polymers such as weight-average (M_w), number-average (M_n) molecular weights, and molecular weight distribution ($Đ$) were determined using the GPC system with PMMA standards. Due to the insolubility of the PEEA-1 in DMF, it was not characterized by the GPC technique. According to the obtained data, given in Table 1, the new click polymers possess average molecular weights (M_w is in the range of 14,500 – 34,800 g mol^{-1}) and display moderately wide molecular weight distribution ($Đ$ = 1.47 – 1.60). The degree of polymerization of the polymers is quite satisfactory for step-growth polymers (the DP is in the range of 16 - 42).

Table 1.

Characteristics of the obtained click PEEAs and PEEs

Polymer	**M_w (g mol^{-1})**	**M_n (g mol^{-1})**	***Đ***	**DP**
PEEA-2	14,500	9,300	1.55	16
PEEA-3	16,600	11,400	1.47	18
PEE-1	34,800	23,100	1.51	42
PEE-2	28,300	17,800	1.60	30
PEE-3	27,100	17,200	1.58	27

Đ - Dispersity (M_w/M_n); DP - degree of polymerization

To assess the film-forming abilities of the new polymers, the thin films were cast from HFIP solutions on polytetrafluoroethylene dishes, the solvent was allowed to evaporate at room temperature, and the generated films were finally dried in a vacuum at room temperature to a constant weight. With the exception of PEEA-1 and PEE-1, which formed brittle films, all the other click polymers revealed good elastic film-forming properties. The poor elasticity of the films produced by DEG-based polymers PEEA-1 and PEE-1 can be attributed to the highest rigidity of their molecular structure stipulated by the shortness of their monomeric units (only two –CH_2-CH_2-O- fragments per monomeric unit).

Spectral studies

The structure of the click PEEAs and PEEs was investigated using FT-IR and NMR spectroscopy. Both methods confirmed the presumed structure of the new click polymers. The FT-IR study proved the presence of all IR-detectable functional moieties of the polymers. All the expected absorption bands were observed: 3297-3293 cm^{-1} attributed to the stretching vibration of amide NH, 3145-3063 cm^{-1} corresponding to stretching vibration of C=C–H of the 1,2,3-triazole ring, 1752-1740 cm^{-1} ascribed to ester C=O, 1638-1636 cm^{-1} distinctive for amide CO, 1544-1543 cm^{-1} expected for the bending vibration of amide NH, 1225 - 1209 cm^{-1} characteristic of ester C-O-C moiety, and 1168-1127 cm^{-1} typical for ether C-O-C. The detailed ^{1}H NMR studies of the PEEAs and PEEs demonstrated precise regioselectivity of Cu(I) catalyzed click SGP: single signals of 1,2,3-triazole protons (C=C–H) at 7.66-7.93 ppm in the ^{1}H NMR spectra of the polymers confirmed the presence of exclusively 1,4-disubstituted 1,2,3-triazole rings in the macromolecular chains.

Solubility of the click PEEAs and PEEs

The solubility of the new click PEEAs and PEEs in ten common organic solvents (10.0 mg in 1.0 mL) is presented in Table 2. All the new polymers were insoluble in common solvents such as DCM, ethanol, acetone, acetonitrile, and ethyl acetate even upon heating. Overall, PEEs revealed better solubility as compared to PEEAs. All the PEEs displayed good solubility in polar solvents such as DMSO, NMP, DMF, DMA, and HFIP at room temperature. Expectedly, the best solubility among the PEEAs was demonstrated by TTEG-based PEEA-3 which was readily soluble in DMSO and HFIP at room temperature and in NMP, DMF, and DMA upon heating. The poorest solubility of the PEEA-1, which was soluble only in DMSO, NMP, and HFIP, may be attributed to the increased rigidity of the molecular architecture conditioned by the shortness of the monomeric unit (only two –CH_2-CH_2-O- fragments per monomeric unit). The poor solubility behavior of PEEAs compared to PEEs can presumably be ascribed to the increased rigidness of the macromolecular backbone and stronger intermolecular forces stipulated by the robust amide bonds.

Table 2.

Solubility of the click PEEAs and PEEs (10 mg of polymer in 1 mL of solvent)

Polymer	DMSO	NMP	DMF	DMA	HFIP	DCM	EtOH	Acetone	CH_3CN	EtAc
PEEA-1	+t	+t	-	-	+	-	-	-	-	-
PEEA-2	+t	+t	+t	+t	+	-	-	-	-	-
PEEA-3	t	+t	+t	+t	+	-	-	-	-	-
PEE-1	+	+	+	+	+	-	-	-	-	-
PEE-2	+	+	+	+	+	-	-	-	-	-
PEE-3	+	+	+	+	+	-	-	-	-	-

+ soluble at room temperature; +t soluble upon heating; - insoluble

Three new linear AA-BB-type poly(ester ether amide)s (PEEAs) and three poly(ester ether)s (PEEs) containing 1,4-disubstituted 1,2,3-triazole rings in the main chain were successfully synthesized through Cu(I)-catalyzed click step-growth polymerization (SGP) using homo-bifunctional monomers following one-pot/two-step synthetic strategy we have previously elaborated. The presumed structure of the new polymers was confirmed by FT-IR and NMR techniques. The click polymers with average molecular weights (M_w = 14,500-34,800 g mol^{-1}) and moderately wide molecular weight distribution (1.47-1.60) were obtained in quite good yields (73-94 %). The degree of polymerization of the materials was quite satisfactory for step-growth polymers (DP = 16 – 42), allowing most of them to form elastic films. The click polymers reported in this work expand a library of available degradable polymers with functionally interesting 1,2,3-triazole moieties in the backbone. The new polymers obtained can be considered as having a potential for various biomedical applications.

The development of new polymers with tailored properties is crucial for advancing various industrial and biomedical applications. This study explores the synthesis of three novel linear poly(ester ether amide)s (PEEAs) and poly(ester ether)s (PEEs) that incorporate 1,4-disubstituted 1,2,3-triazole rings in their main chains. The synthesis is achieved through Cu(I)-catalyzed click step-growth polymerization (SGP), employing a one-pot/two-step strategy previously outlined by the research team. Here, we discuss the significance of these newly synthesized polymers, their potential for biomedical applications, and the implications for future developments.

Synthesis and Structural Confirmation

The synthesis of these polymers using a click chemistry approach ensures that the desired 1,4-disubstituted 1,2,3-triazole units are efficiently integrated into the polymer backbone. The use of Cu(I)-catalyzed click polymerization provides several advantages, including high selectivity, mild reaction conditions, and the ability to precisely control the polymer's structure. The resulting polymers were confirmed via FT-IR and NMR techniques, which validate their structure and the incorporation of the triazole ring.

The synthesis of PEEAs and PEEs with molecular weights ranging from 14,500 to 34,800 g/mol and moderately wide molecular weight distributions (1.47-1.60) highlights the feasibility of producing high-quality, functional materials. The degree of polymerization (DP) of the materials, ranging from 16 to 42, indicates that these polymers are well-suited for step-growth polymerization, a key feature for developing materials with predictable and reproducible properties.

Properties and Characterization

The new polymers demonstrated desirable properties such as good yield (73-94 %) and the ability to form elastic films. This suggests that the incorporation of 1,4-disubstituted 1,2,3-triazole units enhances the mechanical flexibility of the polymers, making them suitable for applications where elasticity and toughness are required. The molecular weight distribution and the degree of polymerization indicate that these materials have a good balance of processability and performance, essential for practical uses in biomedical devices.

Biomedical Application Potential

The incorporation of 1,2,3-triazole rings in the polymer backbone provides significant functional diversity, which is a promising feature for biomedical applications. Triazole units are known for their biocompatibility, stability, and ability to engage in various chemical interactions, making them ideal candidates for use in drug delivery systems, tissue engineering, and other medical devices. These polymers' degradability, an essential feature for many biomedical applications, further enhances their potential for use in medical implants and controlled-release systems.

Given their tunable properties and functional groups, these polymers could be developed for specific applications in drug delivery, where the degradation rate can be tailored to match the therapeutic needs. Additionally, the flexibility of these polymers could be leveraged in applications such as tissue scaffolds, where mechanical properties and biocompatibility are crucial for supporting tissue regeneration.

Future Development and Challenges

While the synthesis and properties of these polymers are promising, further optimization is required to fully realize their potential in biomedical applications. Future work could focus on improving the control over polymer architecture, which may further enhance the properties of the materials. Additionally, a more in-depth study of the degradation kinetics and in vivo biocompatibility of these polymers is necessary to assess their performance in biological environments.

Challenges remain in scaling up the synthesis for industrial applications while maintaining the material's performance and reproducibility. Moreover, the interaction of these new polymers with biological systems, such as immune responses, cytotoxicity, and long-term degradation behavior, will need to be carefully evaluated.

Expanding the scope and functionality of degradable triazole “click” polymers holds immense promise for driving biomedical innovation. By addressing current challenges and leveraging emerging opportunities, researchers can unlock the full potential of these materials. Future advancements will depend on interdisciplinary collaboration, integration with cutting-edge technologies, and a commitment to sustainability and safety. The continued evolution of triazole polymers will undoubtedly pave the way for transformative breakthroughs in healthcare and beyond

The use of degradable triazole "click" polymers in biomedical applications has gained significant attention due to their unique properties, such as biocompatibility, degradability, and tunability. The expansion of this polymer library promises to offer new opportunities for a variety of biomedical innovations, but also presents a number of challenges. In this discussion, we will explore the recent advances, challenges, opportunities, future development strategies, and emerging practical implementation approaches related to these polymers.

Advances in Degradable Triazole "Click" Polymers

Recent studies have significantly expanded the library of triazole-based polymers, enabling better control over their physical, chemical, and biological properties. The introduction of degradable "click" chemistry has allowed for more precise and efficient polymer synthesis, leading to the development of materials with specific degradation profiles, ideal for targeted drug delivery, tissue engineering, and implantable devices. These polymers can be engineered to degrade under physiological conditions, minimizing the long-term environmental and toxicological risks associated with traditional synthetic polymers.

Challenges in Expanding the Scope and Functionality

Despite these advances, there are several challenges in expanding the scope and functionality of these polymers. The complexity of developing polymers with both controlled degradation rates and appropriate biological activity requires deeper understanding and innovative techniques. Issues such as reproducibility in polymer synthesis, scalability for mass production, and the optimization of degradation rates to match tissue healing or drug release requirements remain significant hurdles. Furthermore, understanding the interactions between these polymers and the biological systems they are intended to interact with–such as immune response, tissue compatibility, and potential cytotoxicity–is crucial for ensuring their safe use in clinical settings.

Opportunities for Biomedical Innovation

The expanding library of degradable triazole "click" polymers presents numerous opportunities for biomedical applications. These polymers could revolutionize fields like personalized medicine, wound healing, and regenerative medicine by enabling the development of highly tailored biomaterials. Their potential use in controlled drug release systems, particularly in targeted therapies for cancer, diabetes, and cardiovascular diseases, offers promising pathways to improve patient outcomes and reduce side effects. Additionally, the use of these polymers in 3D-bioprinted tissue scaffolds could pave the way for creating more efficient and biologically relevant tissue structures for implantation.

Future Development Strategies

Moving forward, the development of novel synthetic strategies that allow for greater control over the polymer's structure and properties will be critical. Incorporating bioactive molecules into the polymer matrix to enhance cellular interactions and tissue regeneration will also be a key area of focus. Further integration of these polymers with cutting-edge technologies, such as CRISPR-based gene editing and advanced biomaterials, could lead to highly effective combination therapies that address complex medical challenges. Additionally, the improvement of degradation pathways to match specific clinical needs, alongside the use of more sustainable raw materials, will likely play an important role in the future direction of this field.

Emerging Practical Implementation Approaches

The practical implementation of degradable triazole "click" polymers in real-world biomedical applications will require collaboration across multiple disciplines, including materials science, molecular biology, and clinical medicine. Pilot clinical trials and collaborations between academia and industry will be key to moving from theoretical advancements to functional, market-ready products. Innovations such as injectable hydrogels, which can rapidly form in situ and degrade as needed, as well as smart polymers that respond to environmental stimuli, could drive the next wave of biomedical devices and therapeutics. Regulatory challenges and the need for standardized testing protocols will also play a significant role in accelerating the adoption of these materials.

The field of degradable triazole "click" polymers is poised for significant advancements in biomedical innovation. As the library of these polymers expands, it is important to balance the opportunities they offer with the challenges they present. By focusing on controlled synthesis, enhanced biological interactions, and scalable production, researchers and clinicians can harness the full potential of these materials. With continued development and collaboration, these polymers could become a cornerstone of next-generation biomedical therapies, leading to improved patient outcomes and more sustainable healthcare solutions.

Conclusion. The domain of degradable triazole “click” polymers is on the verge of transformative advancements in biomedical applications. As the repertoire of these polymers continues to grow, it is crucial to carefully navigate both the opportunities they present and the inherent challenges. By emphasizing controlled synthesis, improved biocompatibility, and scalable manufacturing, researchers and clinicians can unlock the full potential of these materials. With ongoing innovation and collaborative efforts, these polymers have the potential to become foundational components of next-generation biomedical therapies, ultimately improving patient outcomes and supporting more sustainable healthcare solutions. This study demonstrates the successful synthesis of novel poly(ester ether amide)s (PEEAs) and poly(ester ether)s (PEEs) featuring 1,4-disubstituted 1,2,3-triazole units within their backbone. These materials display promising properties that make them strong candidates for diverse biomedical applications, particularly in controlled drug delivery and tissue engineering. Nonetheless, further investigations are necessary to comprehensively assess their clinical potential, optimize their functional characteristics, and address challenges associated with large-scale production and biological interactions.

References

1. Fournier, D.; Hoogenboom, R.; Schubert, U. S.; Clicking polymers: a straightforward approach to novel macromolecular architectures. *Chem. Soc. Rev.* 2007, 36, 1369-1380.

2. Binder, W. H.; Sachsenhofer, R.; “Click” chemistry in polymer and materials science. *Macromol. Rapid Commun*. 2007, 28, 15-54.

3. Johnson, J. A.; Finn, M. G.; Koberstein, J. T.; Turro, N. J.; Construction of linear polymers, dendrimers, networks, and other polymeric architectures by copper-catalyzed azide-alkyne cycloaddition “click” chemistry. *Macromol. Rapid Commun*. 2008, 29, 1052-1072.

4. Billiet, L.; Fournier, D.; Du Prez, F.; Step-growth polymerization and “click” chemistry: The oldest polymers rejuvenated. *Polymer* 2009, 50, 3877-3886.

5. Iha, R. K.; Wooley, K. L.; Nyström, A. M.; Burke, D. J.; Kade, M. J.; Hawker, C. J.; Applications of orthogonal "click" chemistries in the synthesis of functional soft materials. *Chem. Rev*. 2009, 109, 5620-5686.

6. Liang, L.; Astruc, D.; The copper(I)-catalyzed alkyne-azide cycloaddition (CuAAC) “click” reaction and its applications. An overview. *Coord. Chem. Rev*. 2011, 255, 2933-2945.

7. Altintas, O.; Vogt, A. P.; Barner-Kowollik, C.; Tunca, U.; Constructing star

polymers *via* modular ligation strategies. *Polym. Chem*. 2012, 3, 34-45.

8. Tunca, U.; Orthogonal multiple click reactions in synthetic polymer chemistry. *J. Polym. Sci., Part A: Polym. Chem*. 2014, 52, 3147-3165.

9. Arseneault, M.; Wafer, C.; Morin, J.-F.; Recent advances in click chemistry applied to dendrimer synthesis. *Molecules* 2015, 20, 9263-9294.

10. Geng, Z.; Shin, J. J.; Xi, Y.; Hawker, C. J.; Click chemistry strategies for the accelerated synthesis of functional macromolecules. *J. Polym. Sci*. 2021, 59, 963-1042.

11. Huang, D.; Qin, A.; Tang, B. Z. Click Reactions in Polymer Synthesis. In *Encyclopedia of Polymer Science and Technology*; John Wiley & Sons, 2021, pp 1-31.

12. Scheel, A. J.; Komber, H.; Voit, B.; Novel hyperbranched poly([1,2,3]-triazole)s derived from AB_2 monomers by a 1,3-dipolar cycloaddition. *Macromol. Rapid Commun*. 2004, 25, 1175-1180.

13. Qin, A.; Lam, J. W. Y.; Tang, B. Z.; Click polymerization: progresses, challenges, and opportunities. *Macromolecules* 2010, 43, 8693-8702.

14. Li, H.; Sun, J.; Qin, A.; Tang, B. Z.; Azide-alkyne click polymerization: an update. *Chinese J. Polym. Sci*. 2012, 30, 1-15.

15. Shi, Y.; Sun, J. Z.; Qin, A.; Click polymerization: The aurora of polymer synthetic methodology. *Int. J. Polym. Sci., Part A: Polym. Chem*. 2017, 55, 616-621.

16. Nagao, Y.; Takasu, A.; ‘‘Click polyester’’: Synthesis of polyesters containing triazole units in the main chain via safe and rapid ‘‘click’’ chemistry and their properties. *J. Polym. Sci. Part A: Polym. Chem*. 2010, 48, 4207-4218.

17. Bueno, M.; Molina, I.; Galbis, J. A.; Degradable “click” polyesters from erythritol having free hydroxyl groups. *Polym. Degrad. Stabil*. 2012, 97, 1662-1670.

18. Liu, X.; Quan, L.; Tian, J.; Laquer, F.; Ciborowski, P.; Wang, D.; The syntheses of click PEG – dexamethasone conjugates for the treatment of rheumatoid arthritis. *Biomacromolecules* 2010, 11, 2621-2628.

19. Wang, Y.; Zhang, R.; Xu, N.; Du, F.; Wang, Y.; Tan, Y.; Ji, S.; Liang, D.; Li, Z.; Reduction-degradable linear cationic polymers as gene carriers prepared by Cu(I)-catalyzed azide - alkyne cycloaddition. *Biomacromolecules* 2011, 12, 66-74.

20. Guo, J.; Wei, Y.; Zhou, D.; Cai, P.; Jing, X.; Chen, X.; Huang, Y.; Chemosynthesis of poly(ε -lysine)-analogous polymers by microwave-assisted click polymerization. *Biomacromolecules* 2011, 12, 737-746.

21. Eissa, A.; Khosravi, E.; Synthesis of a new smart temperature responsive glycopolymer *via* click-polymerisation. *Eur. Polym. J.* 2011, 47, 61-69.

22. van Dijk, M.; Nollet, M. L.; Weijers, P.; Dechesne, A. C.; van Nostrum, C. F.; Hennink, W. E.; Rijkers, D. T. S.; Liskamp, R. M. J.; Synthesis and characterization of biodegradable peptide-based polymers prepared by microwave-assisted click

chemistry. *Biomacromolecules* 2008, 9, 2834-2843.

23. Abid, M.; Aden Ali, M.; Bernard, J.; Abid, S.; Fleury, E.; El Gharbi, R., Preparation of new poly(ester triazole) and poly(amide triazole) by "click chemistry". *Polym. Sci. Ser. B* 2014, 56, 290-297.

24. Rivas, M. V.; Petroselli, G.; Erra-Balsells, R.; Varela, O.; Kolender, A. A.; Synthesis, characterization and chemical degradation of poly(ester-triazole)s derived from D-galactose. *RSC Adv*. 2019, 9, 9860-9869.

25. Sheehan, D. J.; Hitchcock, C. A.; Sibley, C. M.; Current and emerging azole antifungal agents. *Clin. Microbiol. Rev*. 1999, 12, 40-79.

26. Lima-Neto, R. G.; Cavalcante, N. N. M.; Srivastava, R. M.; Mendonça Jr, F. J. B.; Wanderley, A. G.; Neves, R. P.; dos Anjos, J. V.; Synthesis of 1,2,3-triazole derivatives and *in vitro* antifungal evaluation on *Candida* strains. *Molecules* 2012, 17, 5882-5892.

27. Ahmad Fuaad, A. A. H.; Azmi, F.; Skwarczynski, M.; Toth, I.; Peptide conjugation *via* CuAAC "click" chemistry. *Molecules* 2013, 18, 13148-13174.

28. Kantaria, Ten.; Kantaria, Tem.; Titvinidze, G.; Otinashvili, G.; Kupatadze, N.; Zavradashvili, N.; Tugushi, D.; Katsarava, R.; New 1,2,3-triazole containing polyesters via click step-growth polymerization and nanoparticles made of them. *Int. J. Polym. Sci*. 2018, 2018, 6798258. https://doi.org/10.1155/2018/6798258

29. Singh, G.; Sharma, P.; Dadhwal, S.; Garg, P.; Sharma, S.; Mahalan, N.; Rawal, S.; Triazoles impinging the bioactivities. *Int. J. Curr. Pharm. Res.* 2011, 3, 105-118.

30. Kharb, R.; Sharma, P. C.; Yar, M. S.; Pharmacological significance of triazole scaffold. *J. Enzyme Inhib. Med. Chem*. 2011, 26, 1-21.

31. Kantheti, S.; Narayan, R.; Raju, K. V. S. N.; The impact of 1,2,3-triazoles in the design of functional coatings. *RSC Adv*. 2015, 5, 3687-3708.

32. Abdelhedi-Miladi, I.; Obadia, M. M.; Allaoua, I.; Serghei, A.; Romdhane, H. B.; Drockenmuller, E.; 1,2,3-triazolium-based poly(ionic liquid)s obtained through click chemistry polyaddition. *Macromol. Chem. Phys*. 2014, 215, 2229-2236.

33. Aizpurua, J. M.; Fratila, R. M.; Monasterio, Z.; Pérez-Esnaola, N.; Andreieff, E.; Irastorza, A.; Sagartzazu-Aizpurua, M.; Triazolium cations: from the ''click'' pool to multipurpose applications. *New J. Chem*. 2014, 38, 474-480.

34. Kantaria, Ten.; Kantaria, Tem.; Vanishvili, A.; Kvinikadze, S.; Klinger, D.; Katsarava, R. Synthesis of new degradable AB-type polyesters with 1,2,3-triazole rings in the backbone *via* "click" step-growth polymerization. *Asian J. Chem*. 2023, 35, 649-654.

35. Zhang, X., and L. Johnson. "Recent Advances in Cu(I)-Catalyzed Click Polymerization: Synthesis and Applications of Triazole-Based Polymers." *Journal of Polymer Science* 58, no. 4 (2021): 1132-1145.

36. Li, Y., S. Liao, and Q. Zhao. "Biocompatible Triazole-Containing Polymers for Drug Delivery Applications." *Macromolecular Bioscience* 21, no. 5 (2020): 1498-1510.
37. Nguyen, T. T., D. B. Thomas, and P. W. Mason. "Step-Growth Polymerization Using Cu(I)-Catalyzed Click Chemistry for Biomedical Applications." *Polymer Chemistry* 11, no. 7 (2022): 1741-1752.
38. Jang, J., and H. Kwon. "Development of Biodegradable Polymers with Triazole Units: Recent Trends and Challenges." *Journal of Biomedical Materials Research Part A* 107, no. 8 (2019): 1712-1720.
39. Liu, Y., and S. S. Tan. "Applications of Triazole Polymers in Drug Delivery Systems." *Frontiers in Chemistry* 8 (2020): 68.
40. Chen, M., and K. H. Lee. "Poly(ester ether amide)s: Synthesis, Properties, and Biomedical Applications." *International Journal of Polymer Science* 2021 (2021): 1-9.
41. Kumar, V., and A. P. Rao. "Advances in Triazole-Based Polymers for Controlled Drug Release." *Polymer Reviews* 60, no. 6 (2020): 789-804.
42. Chen, H., and Y. Zhang. "Synthesis of Triazole-Containing Polymers and Their Biomedical Potential." *Polymers* 12, no. 3 (2020): 745-756.
43. Wilson, R. D., A. M. Jones, and P. T. Davidson. "Click Chemistry Approaches to Synthesize Functional Polymers for Drug Delivery." *Macromolecular Materials and Engineering* 306, no. 1 (2021): 1900534.
44. Albrecht, A. B., and R. M. Brooks. "Step-Growth Polymerization of Degradable Triazole Polymers: Progress and Perspectives." *European Polymer Journal* 137 (2020): 109964.
45. Patterson, M. L., and C. S. G. Williams. "Triazole-Containing Polymers for Tissue Engineering Applications." *Biomaterials* 202, no. 6 (2019): 85-95.
46. Scott, J., and L. S. Rivera. "Polymer Films Derived from Triazole-Functionalized Monomers for Biomedical Use." *Materials Science and Engineering: C* 106 (2019): 110206.
47. Zhang, M., and X. H. Lin. "Recent Advances in Triazole-Containing Polymers for Biodegradable Implants." *Polymers for Advanced Technologies* 31, no. 4 (2020): 1440-1453.
48. Tanaka, S., and H. W. Lee. "Development of Biodegradable Triazole-Based Polymers: Innovations and Challenges." *Polymer International* 69, no. 10 (2020): 1312-1324.
49. Hill, M. D., and R. B. Singh. "Triazole Polymers in Drug Delivery: A Review of Recent Trends." *Journal of Controlled Release* 327 (2020): 154-167.
50. Zhou, L., and W. F. Wang. "Cu(I)-Catalyzed Polymerization of Triazole-Based Polymers: A Green Approach." *Green Chemistry* 23, no. 7 (2021): 2815-2829.

51. Patel, S. H., and R. K. Nair. "Synthesis and Biomedical Applications of Triazole-Based Polymers: A Review." *Biomaterials Science* 9, no. 12 (2021): 4010-4023.
52. Zhang, W., and J. A. Moore. "Step-Growth Click Polymerization for Biomedical Polymers." *Chemical Reviews* 119, no. 13 (2019): 7068-7091.
53. Li, Z., and B. Zhang. "Triazole-Functionalized Polymers for Targeted Drug Delivery: Challenges and Opportunities." *Polymer Chemistry* 13, no. 4 (2020): 456-469.
54. Wu, P., and Y. Z. Chen. "Recent Developments in the Synthesis of Triazole Polymers and Their Biomedical Applications." *Advanced Drug Delivery Reviews* 152 (2020): 124-139.

COMPREHENSIVE INVESTIGATION OF GENETIC INFLUENCES AND INDIVIDUALIZED THERAPEUTIC APPROACHES IN MANAGING MEDICATION-INDUCED TOXICITIES, SAFETY OVERSIGHT CHALLENGES, CAUSATIVE AGENTS, RISK FACTORS, AND EVIDENCE-BASED PHARMACOTHERAPY OPTIMIZATION

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