Egypt. J. Chem. Vol. 67, SI: M. R. Mahran, pp. **1317 - 1331** (2024)

Egyptian Journal of Chemistry

http://ejchem.journals.ekb.eg/

1,2,3-Triazole-Based Chitosan Derivatives: Recent Aspects, Synthesis and Therapeutic Potential

Abdulmohsen S. Altuwayjiri[1], Yassine El-Ghoul[1,*], Sobhi M. Gomha[2*] and Wael A El-Sayed[1]

[1] Department of Chemistry, College of Science, Qassim University, Buraidah 51452, Saudi Arabia

[2]Department of Chemistry, Faculty of Science, Islamic University of Madinah, Madinah, 42351, Saudi Arabia

Abstract

The integration of 1,2,3-triazole derivatives into medicinal chemistry has emerged as a promising strategy for enhancing the efficacy of therapeutic agents. These compounds demonstrate a broad spectrum of biological effects, such as antifungal, antimicrobial, anti-inflammatory, and anticancer activities. Chitosan, a biocompatible and biodegradable polymer derived from chitin, provides an excellent matrix for the development of functionalized materials. The incorporation of triazole moieties into chitosan and its derivatives through click chemistry enhances their therapeutic potential and expands their applications in biomedical fields. These chitosan-based materials can be engineered for drug delivery systems, improving the solubility and stability of therapeutic agents, as well as for wound healing applications, due to their inherent antimicrobial properties. This review highlights the recent advancements in the application of triazole derivatives in medicinal chemistry and the innovative use of click chemistry in developing chitosan and chitosan derivative-based materials. The synergy between triazole chemistry and chitosan functionality presents exciting opportunities for the design of novel therapeutics and delivery systems, addressing key challenges in contemporary pharmaceutical research.

Keywords: Chitosan; Polymers; synthesis; Click chemistry; Triazole derivatives; Biocompatibility; Antimicrobial; Cancer therapy.

Introduction:

The creation of new synthetic drug candidates has captured the attention of researchers in medicinal chemistry. The identification of therapeutically active heterocyclic compounds has ushered in a new era in medicinal chemistry, largely due to their strong bioactive profiles, researchers are still working in this field. The most common heteroatoms are nitrogen, oxygen, and sulfur. On the other hand, heterocyclic rings containing different heteroatoms are widely recognized [1]. Numerous drugs, vitamins, natural products, and bioactive compounds include heterocyclic structures. Pharmaceuticals and agricultural chemicals frequently use synthetic heterocyclic compounds as a structural motif[2-6]. Heterocycles have been studied and discovered to have a wide range of biological and chemical activity [7-15].

Clinical therapy extensively utilizes a variety of triazole analogues. In medicinal chemistry, triazole derivatives represent an important class of heterocyclic compounds that are particularly valuable as therapeutic agents [16]. Due to their strong dipole moments, triazoles are effective amide carriers in bioactive molecules[14]. Triazole-based compounds are of significant interest due to their unique structural characteristics and their ability to interact with a variety of biological targets. These compounds exhibit remarkable versatility in terms of both their chemical architecture and their potential for modulating biological processes, making them a focal point for research in drug development and therapeutic applications. Their distinct molecular features enable them to bind effectively to specific biomolecules, influencing various biological pathways and offering promise for the treatment of a wide range of diseases. It is well-established that 1,2,3-triazole derivatives possess a range of beneficial properties, including anti-HIV, anti-inflammatory, anticancer, antiviral, antimicrobial, antidepressant, antioxidant, and antifungal activities. It also inhibits the activities of a variety of enzymes [17-19, 23]. Triazole compounds have been applied across diverse areas such as additives, polymer science and technology, supramolecular chemical engineering, and photoinhibition [24,25].

1. Chitosan: Advancements in Biomedical Applications and Polymer Chemistry

Derived from chitin, an abundant and renewable source, chitosan is a polysaccharide with appealing biopolymer characteristics that make it ideal for a variety of biomedical applications due to its non-toxicity, biocompatibility, and ability to biodegrade [26,27]

In 1811, chitin was first identified by Henri Braconnot in mushrooms. Later, in 1823, Odier discovered the same substance in insect cuticles and named it 'Chitin,' deriving the term from the Greek word for tunic, covering, or envelope [28]. This marked the start of a new line of

*Corresponding author e-mail: waelshendy@gmail.com.; (Wael A El-Sayed).

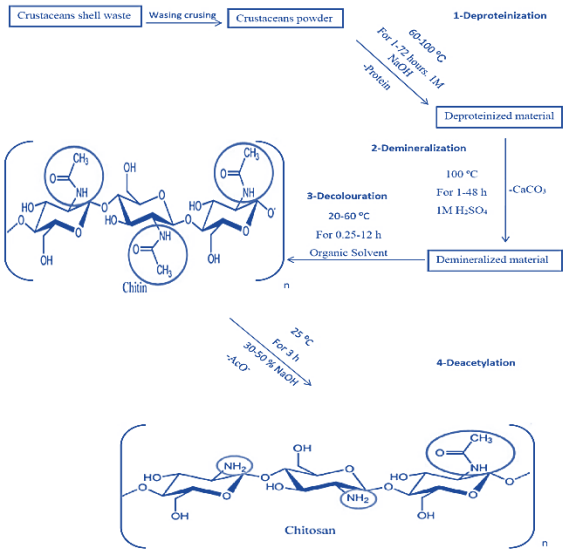
Receive Date: 08 November 2024, Revise Date: 27 November 2024, Accept Date: 03 December 2024

DOI: 10.21608/ejchem.2024.334736.10761

research into naturally occurring polymers. Over time, in 1859, Professor C. Rouget identified a novel biopolymer, derived from the previously discovered chitin, which he named 'Chitosan.' Chitosan, a linear and hydrophilic biopolymer, is essentially chitin in its partially deacetylated state, which ranks as the second most abundant natural biopolymer [29].

Polysaccharides, widespread natural polymers on Earth, comprise materials like cellulose, chitosan, alginate, dextran, and hyaluronic acid. Presently, they are employed in various coating applications and are the focus of extensive research, including studies on their modified versions [31-37]. Additionally, they contribute importantly to drug delivery and the advancement of biomedical materials [38-42]. Chitosan is known for its antimicrobial properties [43,44], and regenerative capabilities [45] as an absorption enhancer, chitosan is also applied in drug delivery systems [46] [47]. Chitosan exhibits not only improved solubility but also significant biocompatibility and degradability [48]. Furthermore, chitosan possesses a wide range of pharmacological and biological qualities, such as bacteriostatic, antioxidant, immunomodulatory, and anti-tumor activities [49-51].

A very active area of research involves chemically altering chitosan to enhance its properties for the intended use or biological activity [52-55]. The presence of the amino group in chitosan facilitates various chemical reactions, including alkylation, acetylation, metal chelation, quaternization, and interactions with aldehyde and ketone functional groups.



Scheme 1. Chitosan production from chitin [30]

These reactions contribute to the formation of a diverse range of products that exhibit antibacterial, antifungal, antiviral, anti-acid, anti-ulcer properties, and are characterized by their non-toxicity, non-allergenic nature, and complete biocompatibility or biodegradability [56-58].

The various grades of chitosan, a copolymer composed of N-acetyl-D-glucosamine and D-glucosamine units, are differentiated by their degree of acetylation[59]. In each repeating glucosidic residue of chitosan, there are two hydroxyl groups and one amino group. Specific chemical changes can be applied to these hydroxyl groups to improve their solubility [60].

1.1. Synthesis of Chitosan-based 1,2,3-triazole compounds

Chitosan, a widely available and renewable polysaccharide, is known for its appealing
bioactivities and natural characteristics. However, chemical functionalization of chitosan is frequently required to enhance its utility. Li et al**.** have designed and synthesized three new water-soluble chitosan derivatives featuring 1,2,3-triazole, either with or without halogens.

The antifungal activity of these derivatives against three types of phytopathogens was evaluated using hyphal measurement in vitro. The results showed that the synthesized chitosan derivatives exhibited significantly improved inhibitory properties and water solubility compared to unmodified chitosan [62]. They hypothesized that the presence of thiazolyl groups contributed to the enhanced antifungal potential of the modified chitosan.

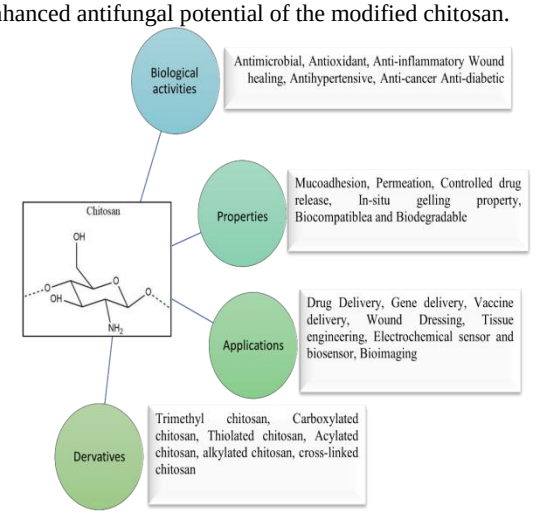
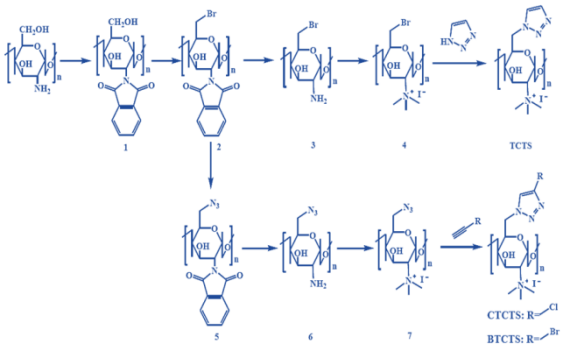


Figure 1. Biological Activities, Properties, Applications, and Derivatives of Chitosan [61]



Scheme 2. Synthetic pathway for the synthesis of chitosan derivatives.

Furthermore, the derivatives BTCTS and CTCTS, which contain halogens at the polymer periphery, demonstrated even greater effectiveness in inhibiting the development of the tested phytopathogens, with inhibitory effects ranging from 81% to 93%. The study suggests the presence of a synergistic impact between the halogens and the triazole moiety, enhancing the antifungal potential due to their antifungal properties and electron-withdrawing capacity, which further improved the overall performance of the made chitosan derivatives.

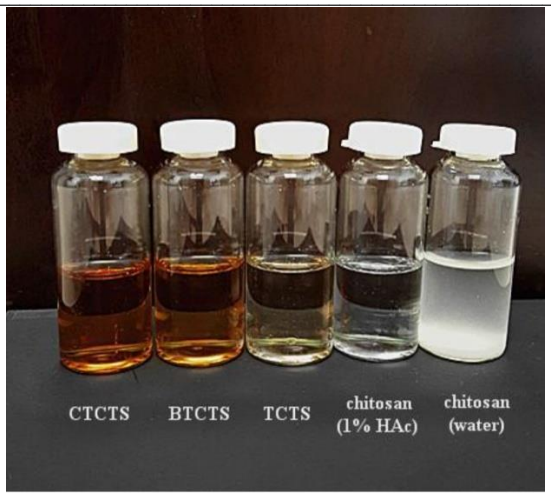


Figure 2. Different producedsolutions of the designed chitosan derivatives prepared in neutral water at a concentration of 1.0 mg/mL, alongside a chitosan solution in neutral water supplemented with 1% acetic acid (HAc) [62].

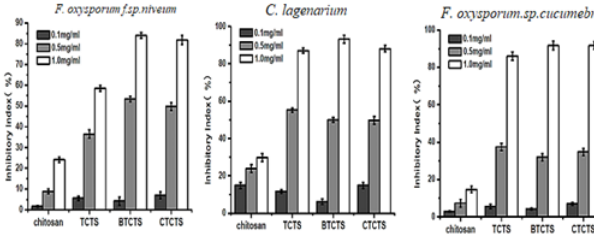
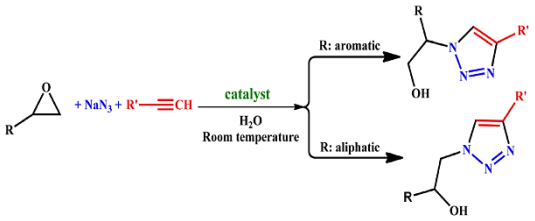


Figure 3. Assessment of the antifungal potential of chitosan biopolymer and its different derivatives against the three types of phytopathogens ($P < 0.05$).

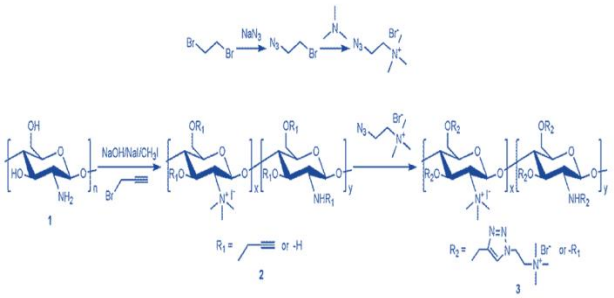


Scheme3. Synthesis of 1,2,3-triazoles via the $Cs/CuFe_2O_4$ polymeric hydrogel as an effective heterogeneous catalyst.

Ajormal et al. investigated the preparation of an innovative nanocomposite based-chitosan derivative ($CS/CuFe_2O_4$ NCH) which revealed an excellent effectiveness in its application as a heterogeneous catalyst. They employed this hydrogel for the azide-alkyne-epoxide synthesis of1,2,3-triazoles derivatives. Different techniques of characterization were performed on the made hydrogel including FT-IR, TGA, SEM, EDS, XRD, HRTEM, and DLS. Furthermore, single-crystal X-ray diffraction analysis was used to confirm the structure of the synthesized 1,2,3-triazoles [63].

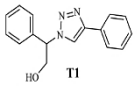
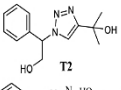
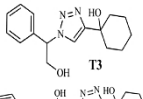
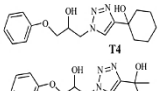
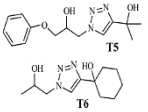
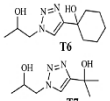
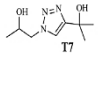
The study highlighted several advantages of the nanocomposite hydrogel, including its easy regeneration and numerous reuses without important lossin catalytic application. Additionally, the high catalytic efficiency, use of environmentally friendly solvents, and easy separation of the catalyst were noted as key benefits. This method provides both financial and environmental advantages, further showcasing the potential of chitosan-based nanocomposites in green chemistry applications.

Tan et al. [64] modified the chitosan biopolymer by incorporating a quaternary ammonium group through a click chemistry approach. The resulting functionalized polymer is a cationic chitosan derivative with a 1,2,3-triazole moiety. Different structural, elemental, and chemical techniques were performed to characterize the created polymers. Turbidity measurements were used to evaluate the water solubility of the chitosan derivatives at different pH values. Moreover, the antifungal effectiveness of the cationic polymers produced was assessed against various phytopathogenic strains, showing promising results.



Scheme 4. Synthetic approaches to produce modified cationic chitosan biopolymers

Table 1. Evaluation the click chemistry resulting rates produced with the polymeric hydrogel CS/CuFe2O4 as a heterogeneous catalyst

Entry	Epoxide	Allyne	Product	Time (h)	Yield (%)	Selectivity (%)
1			 T1	8	96	>99
2			 T2	12	92	98
3			 T3	12	87	98
4			 T4	12	79	92
5			 T5	12	82	94
6			 T6	12	68	89
7			 T7	12	73	91

Furthermore, antioxidant activity was evaluated through superoxide radical scavenging and reducing power assays. The chitosan derivative incorporating a 1,2,3-triazole group demonstrated notably enhanced water solubility, particularly in basic conditions, compared to native chitosan. It also exhibited potent antifungal activity, with inhibition rates exceeding 70% against the chosen fungi at a concentration of 1 mg/mL. Additionally, it demonstrated improved antioxidant properties, with higher superoxide radical scavenging at 1.6 mg/mL, attributed to the presence of the 1,2,3-triazole and quaternary ammonium functions. These promising biological properties suggest that this chitosan derivative could be a valuable candidate for antifungal and antioxidant applications.

1.2. Biological applications of chitosan-based 1,2,3-triazole compounds

The development of chitosan-based biomaterials through the CuAAC reaction has garnered considerable interest for their potential in biological applications. Sahariah and colleagues explored the CuAAC method to create anoplin-chitosan conjugates, achieving substantial control over the rate of grafting. These conjugates demonstrated a significant increase in antibacterial effectiveness compared to anoplin alone, while maintaining a very low level of hemolytic activity [65].

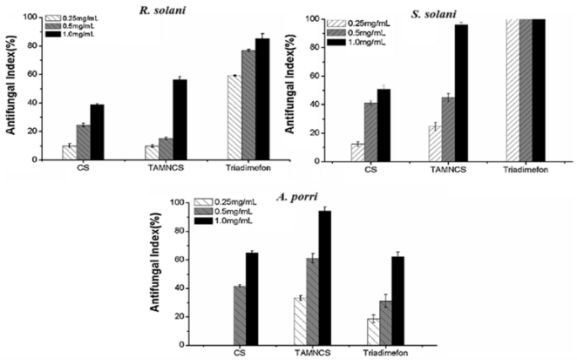


Figure 4. Evaluation of the antifungal effects of chitosan and its cationic derivatives on *the different pathogen strains*

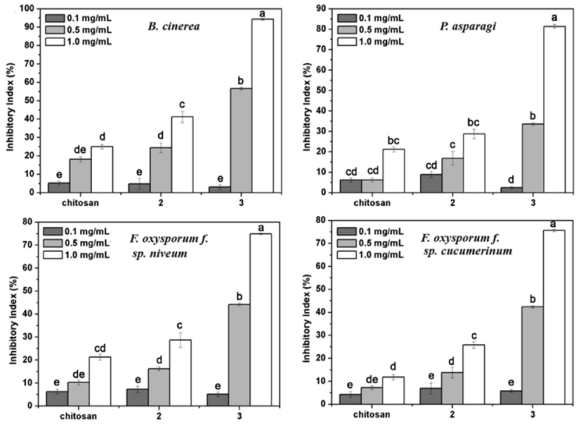
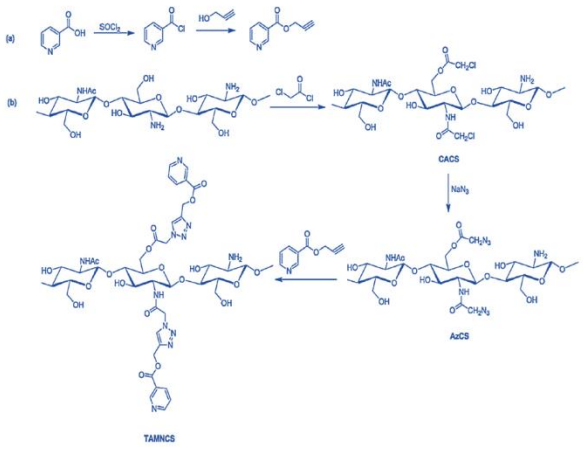


Figure 5. Antifungal efficacy of TAMNCS on the different tested pathogens at various concentrations.

Qinet al. [66] aimed to create new chitosan derivatives having potent antifungal activity against fungi that threaten crops by synthesizing (1,2,3-triazol-4-yl)methyl nicotinate chitosan (TAMNCS) through a click chemistry reaction. The structure of the TAMNCS chitosan derivative was analyzed using different chemical (NMR and IR), elemental, thermal (DSC) and morphological (SEM) characterizations. The antifungal activity was tested against *three different pathogens* at various varied concentrations. Results showed that TAMNCS had significantly enhanced antifungal activity compared to unmodified chitosan. Notably, TAMNCS inhibited the growth of *A. porri* by 94.2% at aa higher concentration of 1mg/mL, outperforming the commonly used fungicide triadimefon, which had an inhibitory rate of 62.2% at the same concentration. These initial antifungal findings indicate that TAMNCS could be a promising antifungal agent for agricultural applications.



Scheme 5. Synthetic approach for preparing the TAMNCS chitosan derivative.

Li et al. recently investigated the synthesis and radical scavenging potential of chitosan derivatives modified with triazole and triazolium groups. Their results demonstrated a notable enhancement in radical scavenging activity in the modified chitosans compared to the unmodified version. Furthermore, the activity was further increased following the N-methylation of the 1,2,3-triazole units, highlighting the effectiveness of these modifications in improving the biopolymer's functionality [67].

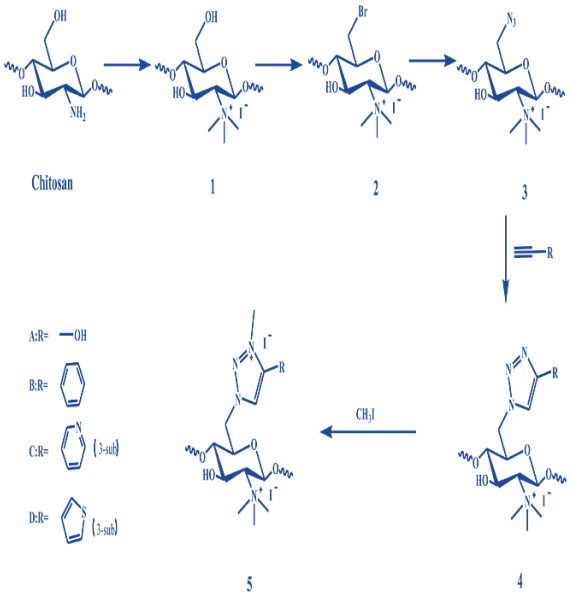
Aljohani et al**.** [68] focused on adressing the challenge of treating *Toxoplasma gondii* (*T. gondii*), a widespread parasite for which current treatments are either ineffective or have significant side effects, lacking a reliable gold-standard option. To overcome this, they synthesized different types of sulfonamide-1,2,3-triazole hybrids (3a–c) via a copper-catalyzed 1,3-dipolar cycloaddition between prop-2-yn-1-alcohol (1) and sulfa drug azides (2a–c). The synthesized compounds were thoroughly analyzed using multiple spectroscopic techniques and subsequently incorporated onto chitosan nanoclusters to create innovative nanomaterials for various anti-Toxoplasma evaluation.

In addition, the research demonstrated the efficacy of these derivatives in mice with experimental infections. Among the evaluated formulations, the sulfonamide-1,2,3-triazole nanoformulation labeled as 3c, showed the most auspicious results for the treatment of toxoplasmosis, achieving 100% survival, complete parasite reduction, and remarkable histopathological improvement in all examined organs compared to the standard treatment with sulfadiazine.

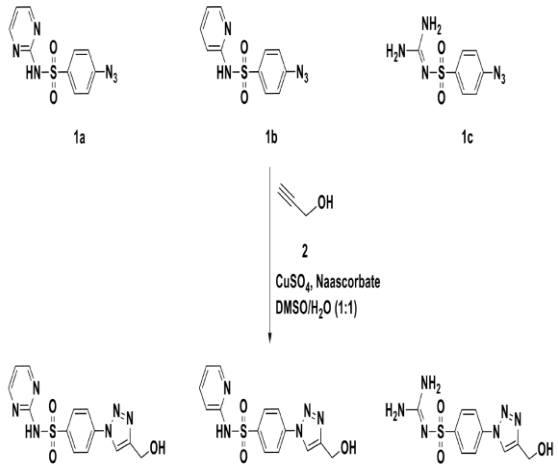
2. Functionalized chitosan-based 1,2,3-triazole derivatives.

Daraie et al**.**[69] prepared a novel hybrid composite compound by reacting the poly(styrene-co-maleic anhydride) with the folic acid (FA) and ionic liquid. The resulting product was polymerized with the chitosan and next the Copper(I) was incorporated onto the system to provide the nanocatalyst the Cu@SMA-FA-CS-IL. The

nanocatalyst was then analyzed using different chemical, structural, elemental, analytical and thermal characterizations. This heterogeneous prepared catalyst showed an excellent effectiveness when used in the reaction of sodium azide, terminal alkynes, and alkyl halides or α-haloketones in water to produce 1,4-disubstituted-1,2,3-triazoles. Additionally, the nanocatalyst revealed the possibility of its efficiently reuse up to 5 times.



Scheme 6. Synthetic routes for the preparation of chitosan derivatives.



115a: R_1 = isopropylidene, R_2 = H

Scheme 7. Preparation of the different molecular conjugates 3a–c containing 1,2,3-triazole and sulfonamide groups.

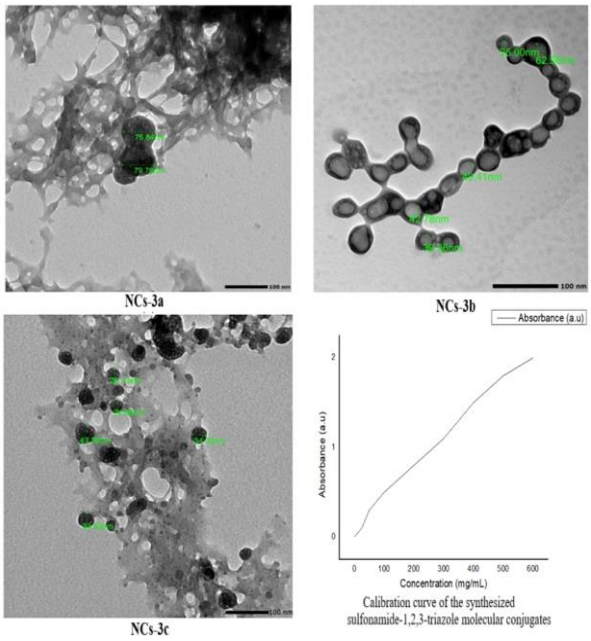
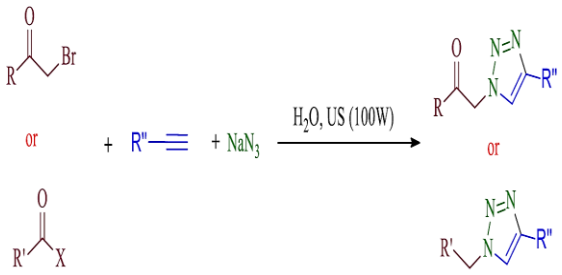


Figure 6. TEM images of the different chitosan nanoclusters (100,000×) [69]

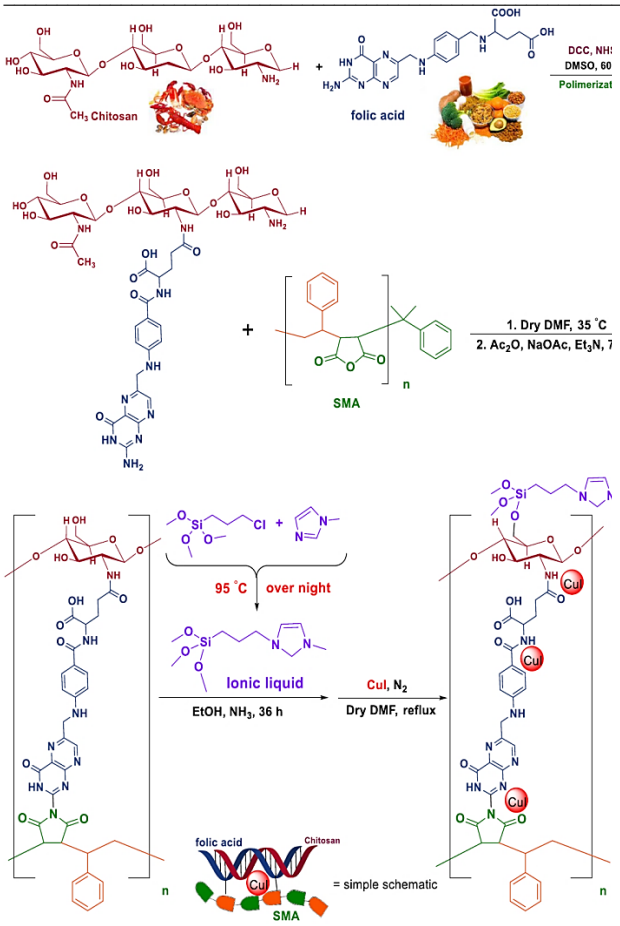
Table 2. Various evaluated characteristics of the produced nanoformula.

Nano Formulations	PS (nm)	ζ Potential (mV)	PDI	Entrapment Efficiency % (EE%)	Loading Efficiency (LE%)
NCs-3a	76.3 ± 10.9	+36.4 ± 2.7	0.34 ± 0.1	78.11 ± 1.70	38.42 ± 0.8
NCs-3b	50.4 ± 7.3	+37.2 ± 0.8	0.36 ± 0.03	80.15 ± 1.10	38.70 ± 0.5
NCs-3c	36.0 ± 10.4	+39.3 ± 1.9	0.35 ± 0.1	89.27 ± 1.23	43.31 ± 1.0

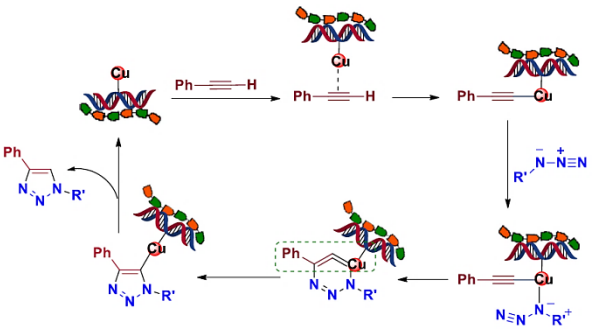


Scheme 8. Synthetic routes of the 1,4-disubstituted 1,2,3-triazoles.

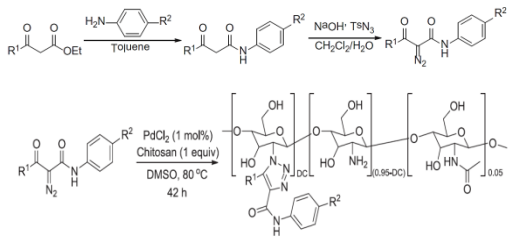
Zhang et al. [70] developed a synthetic strategy using a modified Wolff's cyclocondensation to produce 1,2,3-triazole functionalized chitosans. By employing this method, a series of multi-substituted 1,2,3-triazole-modified chitosans were synthesized, achieving degrees of conversion (DC) between 42.1% and 53.9%. FTIR spectroscopy and 1H NMR analysis were used to confirm the chemical structures of these functionalized chitosans, and amino titration was used to ascertain the DC measurements. Additionally, the effect of the 1,2,3-triazole groups on the thermal characteristics of the chitosan derivatives was analyzed through TGA and DSC thermal analysis.



Scheme 9. Scheme of the synthesis process of the Cu@SMA-FA-CS-ILnanocatalyst.



Scheme 10. Possible mechanism for click reaction



Scheme 11. Developed synthesis route of α-diazo-β-oxoamides.

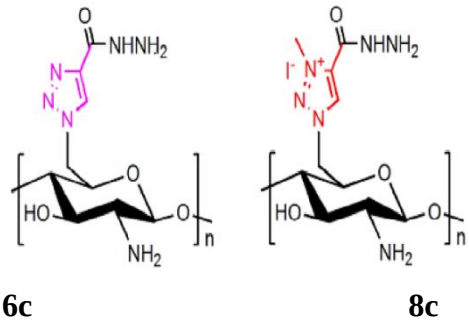
Table 3. 1,2,3-Triazole grafted chitosan synthesis

Entry	2	R^1	R^2	3	$[NH_2]^a$	DC[b]
1	2a	Me	H	3a	2.5%	53.9%
2	2b	Ph	H	3b	3.1%	42.5%
3	2c	Me	CF_3	3c	2.3%	52.6%
4	2d	Ph	CF_3	3d	2.7%	44.3%
5	2e	Me	$n\text{-}C_{12}H_{25}$	3e	2.1%	49.8%
6	2f	Ph	$n\text{-}C_{12}H_{25}$	3f	2.5%	42.1%

[a]The NH_2 content was measured using the titration method.
[b]The degrees of conversion (DCs) were estimated based on the NH_2 content.

Tan et al. [71] explored the increasing interest in amino groups for the chemical modification of polysaccharides, particularly regarding their possible applications in biomedicine. In their research, the authors developed innovative antioxidant materials derived from chitosan derivatives with amino-functional groups. They introduced 1,2,3-triazole and 1,2,3-triazolium units using a click chemistry approach followed by N-methylation. Different techniques were performed to characterize the produced derivatives including elemental analysis, FTIR, and NMR spectroscopy. The chitosan derivatives containing 1,2,3-triazoles exhibited significantly enhanced antioxidant potential compared to unmodified chitosan. Moreover, the antioxidant performance of the derivatives was enhanced following the N-methylation of the 1,2,3-triazole groups with iodomethane, achieving levels comparable to those of ascorbic acid. Among the created compounds, those functionalized with acylhydrazine and amino groups demonstrated higher antioxidant activity than hydroxylated chitosan with the employed concentrations. Additionally, the cytotoxicity of the derivatives was assessed in vitro using HaCaT cells, indicating their potential for safe use. These findings suggest that acylhydrazine- and amino-grafted chitosan derivatives with 1,2,3-triazolium moieties hold promise as innovative and efficient antioxidant materials for future biomedical applications.

The following scheme 13 shows the chemical structures of chitosan modified material**6c** and **8c**. These compounds exhibited ultra-strong antioxidant properties, comparable to the effect of **ascorbic acid,** which was used as a positive control. This superior activity is assigned to the combined influence of the **acylhydrazine** functions and the **1,2,3-triazole** groups in compound **6c,** and the **1,2,3-triazolium** groups in compound **8c**.



Scheme 12. Structure of 7c and 9c chitosan derivatives

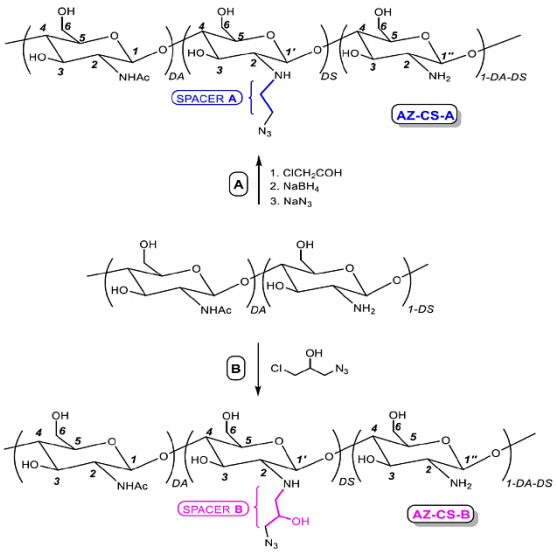
Tan et al. [72] identified chitosan as a highly efficient biopolymer with diverse possible applications, owing to its distinctive chemical, physical, and biological characteristics. To improve its water solubility and biological performance, chitosan was functionalized to produce new derivatives. In their study, the researchers introduced a triphenylphosphonium function to chitosan via click chemistry approach, exploring its potential as an antifungal biomaterial for agricultural use.

Different methods of characterization including NMR, FTIR spectroscopy and UV-vis spectroscopy were performed to evaluate the impact of the applied chemical functionalization on the final properties of the modified chitosan.

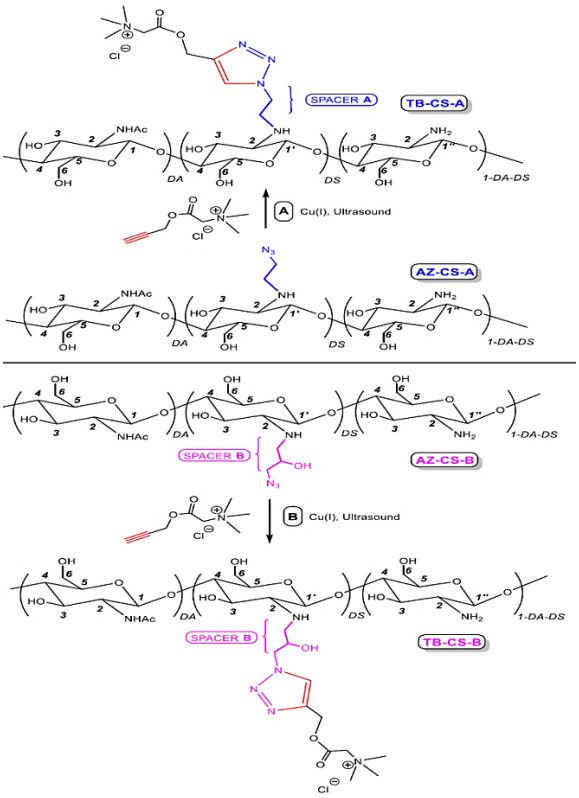
Additionally, the microbial properties of the synthesized chitosan biomaterial were tested using different pathogen strains that pose a threat to plants. In vitro experiments showed that the triphenylphosphonium-modified chitosan exhibited significantly enhanced antifungal activity compared to unmodified chitosan and intermediate derivatives. Notably, the modified chitosan demonstrated a strong antifungal activity, with an inhibitory index exceeding 80% against *Botrytis cinerea* at a concentration of 1.0 mg/mL. The findings of this comprehensive antifungal investigation indicate that the modified chitosan biomaterial, which incorporates both 1,2,3-triazole and triphenylphosphonium groups, provides a promising foundation for the creation of innovative antifungal biomaterials for agricultural applications.

3. Chitosan Nanoparticles based 1,2,3-triazole

Kritchenkov et al. [73] utilized ultrasound-assisted click chemistry (CuAAC) for the modification of chitosan. The ultrasound-facilitated click reaction applied on the propargyl ester group of betaine and an azido-modified chitosan biopolymer occurred swiftly in water in aerobic conditions, leading to the creation of new triazole betaine chitosan biomaterial with improved solubility in water. The resulting chitosan derivatives were then used to prepare nanoparticles through the ionic gelation method, which were subsequently characterized. The antibacterial and transfection properties of the novel chitosan derivatives and their nanoparticles were evaluated. The nanoparticles, which had an average diameter of around 100 nm and a ζ-potential of approximately +65 mV, demonstrated outstanding antibacterial effectiveness. Their activity exceeded that of the native triazole betaine derivatives and was on par with the efficacy of standard antibiotics like ampicillin and gentamicin. Conversely, the native triazole chitosan derivatives demonstrated significantly increasing transfection potential higher than that of their nanoparticle form. The derivatives with moderate molecular weight and substitution levels showed the highest activity. These chitosan-based biomaterials exhibited exceptionally high transfection efficiency, achieving results comparable to those of Lipofectin, a widely used commercial gene delivery agent. Kritchenkov et al. [73] emphasized several important aspects of their study, notably their successful advancement of ultrasound-assisted CuAAC in the field of chitosan chemistry. By optimizing the click reaction, the authors demonstrated that tuning the ultrasound power and frequency could greatly speed up the CuAAC process, even in the presence of oxygen, while preserving the reaction's selectivity and preventing ultrasonic degradation of the chitosan polymer chain. Using this method, they successfully synthesized new triazole betaine chitosan derivatives with varying substitution degrees, starting with chitosans of different molecular weights. These resulting biopolymers exhibited outstanding water solubility. Next, the researchers employed ionic gelation of triazole betaine chitosan derivatives with TPP to create spherical nanoparticles with a uniform size distribution. They then assessed both the antibacterial and transfection activities of the modified chitosan biopolymers and their nanoparticle formulations.



Scheme 13. Synthetic route for the designing of chitosan azido compounds AZ-CS-A and AZ-CS-B.



Scheme 14. Synthetic pathway for the preparation of TB-CS-A and TB-CS-B derivatives

Table 4. Antimicrobial properties of the triazole derivatives and their nanoparticle formulations

Sample	Tested bacteria	
	S. aureus	*E. coli*
	Inhibition zone, mm[a]/MIC	
Triazole	11.5 ± 0.13/3.23	7.2 ± 0.44/5.42
Betain	2.1 ± 0.11/15.71	1.5 ± 0.24/26.71
Triazolbetaine	33.3 ± 0.41/1.26	14.8 ± 0.11/2.67
Chitosan	13.5 ± 0.3/2.69	10.4 ± 0.2/3.81
TB-CS-A-I-L	19.2 ± 0.32/1.66	9.6 ± 0.40/2.76
TB-CS-A-I-M	21.3 ± 0.43/1.32	12.3 ± 0.32/2.68
TB-CS-A-I-H	18.7 ± 0.25/1.77	10.1 ± 0.26/2.83
TB-CS-B-I-L	21.9 ± 0.22/1.51	12.8 ± 0.46/2.45
TB-CS-B-I-M	24.3 ± 0.36/1.26	15.6 ± 0.15/2.23
TB-CS-B-I-H	22.7 ± 0.37/1.48	13.5 ± 0.11/2.52
TB-CS-A-II-L	25.1 ± 0.34/1.34	16.1 ± 0.22/2.09
TB-CS-A-II-M	27.9 ± 0.13/1.14	18.8 ± 0.19/1.71
TB-CS-A-II-H	26.1 ± 0.51/1.29	16.1 ± 0.34/2.14
TB-CS-B-II-L	28.8 ± 0.47/1.15	19.0 ± 0.25/1.63
TB-CS-B-II-M	32.1 ± 0.17/1.01	20.1 ± 0.39/1.21
TB-CS-B-II-H	30.1 ± 0.23/1.17	18.9 ± 0.33/1.62
TB-CS-A-III-L	33.3 ± 0.41/0.98	25.1 ± 0.21/1.15
TB-CS-A-III-M	36.5 ± 0.12/0.69	28.2 ± 0.25/0.74
TB-CS-A-III-H	34.1 ± 0.11/0.93	24.6 ± 0.15/1.13
TB-CS-B-III-L	38.7 ± 0.45/0.58	32.5 ± 0.19/0.87
TB-CS-B-III-M	41.3 ± 0.17/0.25	34.2 ± 0.22/0.37
TB-CS-B-III-H	39.2 ± 0.22/0.61	31.3 ± 0.27/0.91
NP-A-1	45.6 ± 0.11/0.11	36.8 ± 0.14/0.20
NP-A-2	41.4 ± 0.19/0.22	31.7 ± 0.18/0.35
NP-A-3	28.7 ± 0.21/1.10	23.2 ± 0.19/1.24
NP-A-4	33.2 ± 0.32/0.84	28.3 ± 0.14/0.89
NP-A-5	34.1 ± 0.10/0.83	28.0 ± 0.11/0.93
NP-B-1	44.8 ± 0.19/0.12	36.4 ± 0.09/0.21
NP-B-2	40.9 ± 0.24/0.23	31.2 ± 0.13/0.36
NP-B-3	29.2 ± 0.33/1.11	23.2 ± 0.21/1.22
NP-B-4	33.7 ± 0.12/0.84	28.6 ± 0.17/0.88
NP-B-5	34.5 ± 0.14/0.82	28.0 ± 0.14/0.92
Ampicillin	30.2 ± 0.19/0.12	—
Gentamicin	—	22.1 ± 0.24/0.21

The produced nanoparticles, measuring approximately 100 nm in size and possessing a ζ-potential of around +65 mV, demonstrated exceptional antibacterial properties, outperforming the native triazole betaine derivatives and exhibiting activity on par with, or slightly greater than, that of ampicillin and gentamicin. In contrast, the native triazole betaine chitosan derivatives exhibited superior transfection efficiency compared to their nanoparticle counterparts. The most effective derivatives were those derived from moderate molecular weight chitosan with an intermediate degree of substitution, showing transfection activity comparable to Lipofectin, a widely used commercial gene delivery vector. Additionally, both the modified chitosan biopolymers and their nanoparticle formulations were determined to be non-toxic. The researchers highlighted that their findings represent some of the most promising results to date in the areas of transfection and antimicrobial potential for chitosan-based systems. They suggested that these chitosan-based systems, with potential applications in both antibacterial and transfection fields, warrant further in vivo studies. Finally, their findings once again confirmed the efficacy of ultrasonic and click-reaction approaches in the field of chitosan chemistry, and they expressed optimism that these methods could be extended to further bioactive macromolecules.

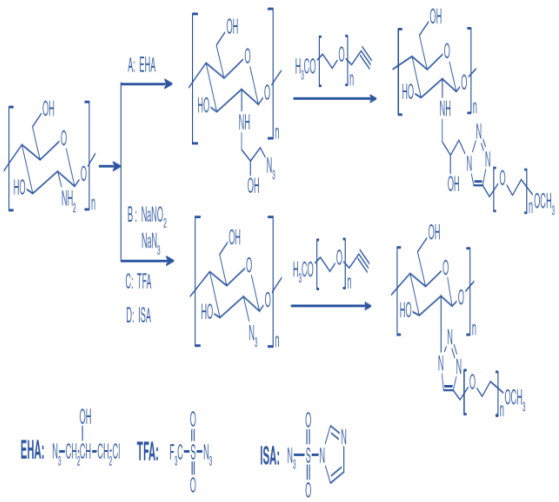
4. Enhancing Chitosan through Click Chemistry: Methods and Biomedical Impacts

Up to this point, the synthesis of 1,2,3-triazole functionalized chitosans has been exclusively focused on the amino groups in chitosan, employing click chemistry techniques. Kulbokaite et al**.** [74] synthesized azido-chitosan polymer via different methods including the use of azido epichlorohydrin, sodium azide with sodium nitrite, trifluoromethanesulfonyl azide, and imidazole-1-sulfonyl azido hydrochloride. The highest degrees of azidation (DA) of chitosan, were around 65%, and achieved with the last two reagents used. N-azidatedchitosans with approximately 60% DA were insoluble in both water and common organic solvents, but they dissolved in a 5% LiCl solution in N-methyl-2-pyrrolidone, a solvent rarely used for chitin. For the first time, chitosan-methoxy poly(ethylene glycol) derivatives containing triazolyl groups (chitosan-N-TMPEG comb copolymers) were synthesized through click reaction, linking the azide groups on chitosan with the terminal alkyne functions on MPEG.

The chitosan-N-TMPEG materials were synthesized with degrees of substitution (DS) corresponding to the degree of azidation (DA) of the chitosan, achieving a DS of up to 40% by using excess MPEG alkyne. The "click" reaction between MPEG alkyne and azido chitosan was successful in a binary mixture of water and methylene chloride, but it did not occur in a 5% LiCl solution in N-methyl-2-pyrrolidone. Furthermore, the use of a Cu(II)/ascorbate catalyst led to crucial degradation of the chitosan backbone during the click reaction, resulting in grafted copolymers. The resulting chitosan-N-TMPEG copolymers contained residual copper and were soluble in acetate buffer at pH 3.7. These new combined copolymers were characterized by 1H NMR and infrared spectroscopy, size exclusion chromatography, viscosity measurements, and elemental analysis.

Table 5. Evaluation of the different methods for azido-chitosan synthesis

Method of azidation	N (%)	NH_2 (%)	DA (N) (%)	DA (NH_2) (%)	DA (FT-IR) (%)
Procedure A	11.5	3.5	25.7	27.4	28.4
Procedure B	8.9	5.8	5.2	8.6	-
Procedure C	13.7	2.7	40.1	41.1	40.3



Scheme 15. Synthetic route of theN-MPEGylation of the chitosan biopolymer using click cycloaddition reactions.

Table 6. Evaluation of the azido-chitosan synthesis via the Procedure D

Alkaline comp. X	X (mmol)	0.1 M HCl (ml)	Chitosan (mmol)	ISA (mmol)	$CuSO_4.5H_2O$ (mmol)	MeOH (ml)	Time (days)	Yield (%)	DA[b]
TEA[a]	9.38	80	5.780	17.4	0.174	35.5	8	91.3	13.6
Na_2CO_3	15.4	80	5.780	6.94	0.0578	30.0	16	96.0	59.2
$NaHCO_3$	67.2	80	5.780	59.2	0.592	10.0	1	86.7	64.4
$NaHCO_3$	67.2	105	11.56	59.2	0.482	20.0	2	96.3	61.3
$NaHCO_3$	8.26	-	0.578	5.78	0.0578	24.0	2	54.4	49.7

[a] Triethyl amine.
[b] The degree of azidation (DA) was determined using FT-IR spectroscopy.

Table 7. The findings of the chitosan-N-TMPEG copolymer analysis

No.	Azidation of chitosan	Molar ratio			NH_2 (%)	DS (%) (NH_2)	DS (%) (NMR)	$[\eta]$ (dL/g)
		Chitosan[a]	Azide[b]	MPEG				
1	Procedure A	1	0.27	0.20	1.82	15	13	1.52
2		1	0.27	0.30	1.42	21	20	1.41
3		1	0.27	0.40	0.91	28	26	0.58
4	Procedure C	1	0.40	0.20	1.64	17	15	1.59
5		1	0.40	0.40	0.68	35	32	0.77
6		1	0.40	0.50	0.47	41	40	0.49

Table 8. Molecular parameters of chitosan and its derivatives and Cu content

No.[a]	Polymer	DS (%) (NH_2)	$M_W \times 10^{-3}$	$M_n \times 10^{-3}$	M_W/M_n	Cu (ppm)
	Chitosan	-	305	218	1.40	-
2	Chitosan-I-TMPEG	21	212	89	2.38	157±3
3	Chitosan-I-TMPEG	28	189	79	2.39	86±1
5	Chitosan-I-TMPEG	35	448	105	4.27	75±2

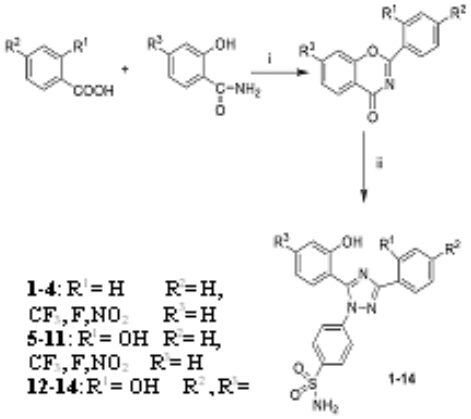
[a] Corresponds to No. in Table 5.

In recent years, the use of Cuprous-catalyzed azide-alkyne cycloaddition (CuAAC) has gained prominence as an effective and appealing method for chitosan functionalization. Consequently, there has been an increasing focus on applying the CuAAC reaction to modify chitosan derivatives[75, 76]**.**

Additionally, Tan et al. describe a new method for synthesizing chitosan derivatives that are functionalized with both amino and acylhydrazine groups, incorporating 1,2,3-triazole and 1,2,3-triazolium functionalities. The synthesis process employed the CuAAC reaction, along with N-methylation using iodomethane. The antioxidant properties of these derivatives were evaluated by testing their ability to scavenge OH radicals, DPPH radicals, and superoxide radicals, as well as assessing their reducing power. These tests aimed to investigate how the presence of 1,2,3-triazoles, their N-methylation, and the inclusion of various amino groups influence the radical scavenging activities of the modified chitosan biopolymers [71].

The azide-alkyne cycloaddition catalyzed by copper (I), was established by Sharpless and has seen extensive application in the modification of polysaccharides [76]. Polysaccharides modified through click chemistry exhibit various biological activities, including antibacterial, anti-inflammatory, antitubercular, and anticancer properties [62]. Moreover, 1,2,3-triazole is regarded as a compelling bridging moiety capable of linking pharmacophores to form novel bioactive compounds. Numerous studies have concentrated on the highly regioselective functionalization of different types of polysaccharides, including chitosan, via click reactions.[52, 77].

Modifications of chitosan using CuAAC have primarily targeted reactions involving azides at the C-2 amine and C-6 position, with the C-2 amine being shielded by phthaloyl functions [78, 79].



Scheme 16. Synthesis of triazole derivatives.

The amino function in chitosan has been modified by attaching acyl moieties with terminal alkyne or azido functions. These modified groups can then undergo transformation into triazoles through the CuAAC reaction, a method that has been employed for the grafting of peptides[65, 80]Polyethylene glycols, often abbreviated as PEGs. [74] as well as conjugates of drugs and nanoparticles [65, 81, 82]**.**

Liao et al. [83] developed a range of 1,2,4-triazole derivatives (1–14) to explore their neuroprotective properties and underlying mechanisms. Compounds 5–11 showed significant protection of PC12 cells against cytotoxicity induced by H_2O_2 or sodium nitroprusside, with product 11 proving the highest effectiveness. Compound 11 demonstrated the ability to chelate Fe(II) ions, scavenge reactive oxygen species, and reinstated the mitochondrial membrane potential. Moreover, it boosted antioxidant defense by elevating serum superoxide dismutase levels and facilitating the nuclear translocation of the nuclear factor erythroid 2-related factor 2.

Table 9. IC50 values of products 5-11 in the inhibition of Ferrozine-Fe2+ interaction

Compound	IC_{50} (μM) [a]	Compound	IC_{50} (μM)[a]
5	42.94 ± 0.11	9	35.99 ± 0.49
6	22.61 ± 0.54	**10**	35.12 ± 0.67
7	46.17 ± 3.88	11	36.27 ± 1.74
8	27.53 ± 0.43		

[a]The values are expressed as the mean ± SD of three independent experiments.

Table 10. Compound 11's impact on GSH, GSH-px, and SOD levels in PC12 cells treated with H_2O_2 or SNP.

	GSH (nM/mg)	GSH-px (mU/mg)	SOD (U/mg)		GSH (nM/mg)	GSH-px (mU/mg)	SOD (U/mg)
Control	88.85 ± 1.47	80.89 ± 5.68	42.59 ± 1.86	**Control**	94.76 ± 2.23	55.70 ± 3.38	42.87 ± 1.82
H_2O_2(500 μM)	65.52 ± 1.44***	45.92 ± 3.64**	29.69 ± 1.65**	**SNP (300 μM)**	75.78 ± 1.74**	37.70 ± 2.88*	23.74 ± 2.02**
H_2O_2+11(2.5 μM)	70.42 ± 2.05	51.03 ± 3.82	36.30 ± 2.35	**SNP+11(2.5 μM)**	79.07 ± 1.99	42.45 ± 7.76	34.63 ± 1.88
H_2O_2+11(5 μM)	72.51 ± 1.15#	65.15 ± 2.54#	38.85 ± 1.90#	**SNP+11(5 μM)**	86.74 ± 1.86#	44.38 ± 6.56	34.85 ± 2.74#
H_2O_2+11(10 μM)	80.57 ± 1.16##	77.94 ± 1.62##	41.19 ± 1.40##	**SNP+11(10 μM)**	89.16 ± 1.72##	52.78 ± 3.46#	39.07 ± 3.83#

Compound 11 altered blood levels of important biochemical markers (TNF-α, IL-1β, SOD, and MDA), decreased the extent of cerebral infarction, and enhanced behavior in a rat model of middle cerebral artery occlusion (MCAO). When compound 11 was administered intraperitoneally to mice, the fatal dose (LD_{50}) was more than 400 mg/kg. Pharmacokinetic studies also showed high bioavailability after oral and intravenous injection and an extended half-life (4.26 hours for oral and 5.11 hours for intravenous administration).

5. Hybrid 1,2,3-Triazole Chitosan Derivatives as efficient Anticancer Agents: Mechanisms and Structure-Activity Relationships

Anticancer drugs are essential for treating cancer, but the negative effects and drug resistance linked to existing therapies highlight the pressing need for new medications with enhanced effectiveness and reduced adverse effects.

Triazole-based scaffold materials serve as important building blocks in the design of novel anticancer agents, with several derivatives either currently in clinical use or in the process of clinical studies. Hybrid molecules are crucial in cancer therapy, and the integration of the 1,2,3-triazole structure with other anticancer pharmacophores holds promise for developing new therapeutic strategies, particularly for drug-resistant cancers. Anticancer drugs play a critical role in managing and eliminating cancer, yet the increasing prevalence of drug-resistant and multidrug-resistant cancers presents a significant strain on healthcare systems worldwide.

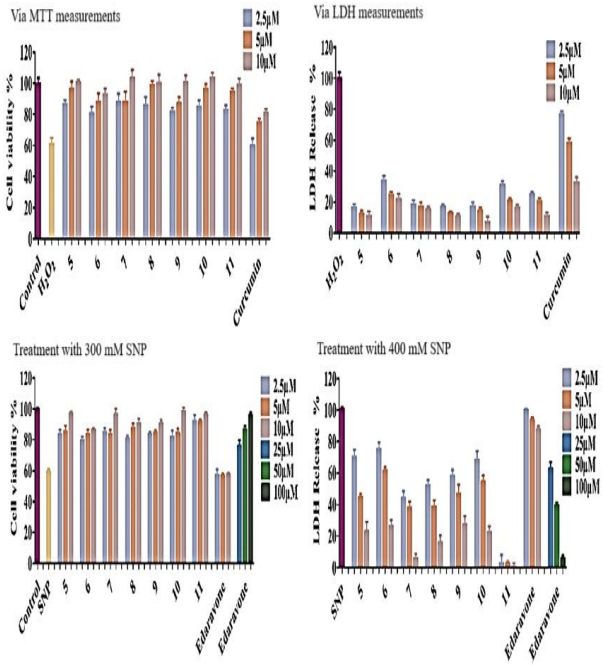


Figure 7. Neuroprotective effect of active compounds **5-11** on H2O2 or SNP induced PC12 damage. (Data are expressed as the mean ± SD of three independent assays).

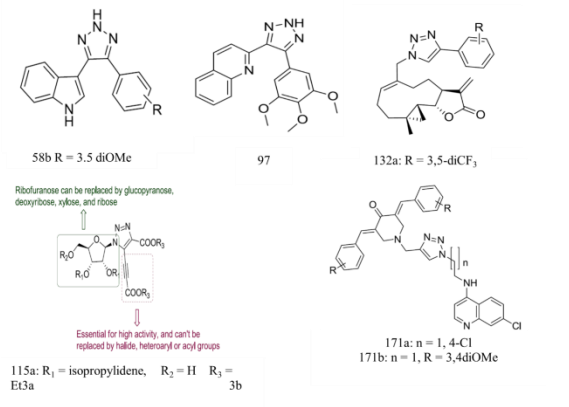


Figure 8. Some novel efficient anticancer products based-triazole moiety.

As a result, it is vital to develop new anticancer agents that are not only effective against both drug-sensitive and resistant cancers but also have minimal side effects. Xu et al. [84] have focused on 1,2,3-triazole, a versatile moiety that has shown significant potential in the development of new drugs for cancer treatment. Hybridizing 1,2,3-triazole with other anticancer pharmacophores could offer promising new therapeutic possibilities. Over the past five years, Xu et al. [84] have synthesized a variety of 1,2,3-triazole-based hybrids for this purpose. Notable among these are compounds like 58b, 97, 132a, 115a, and 171a,b, which have shown potent anticancer activity across a broad spectrum.

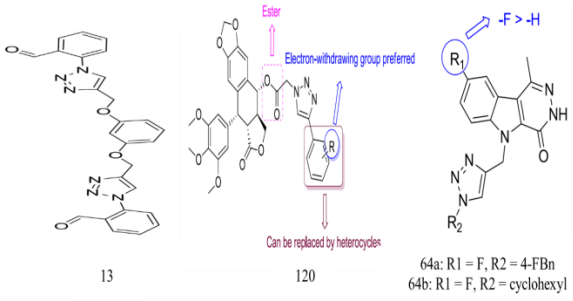


Figure 9. Some novel efficient anticancer products based-triazole moiety.

Furthermore, conjugates like 13, 64 (a-b), and 120**,** with IC50 values in the nanomolar range, have shown strong activity against various cancer cells.

Compounds 57a, 72a, 99a-c, 115a, 133a, and 137a demonstrated remarkable potency in both in vitro and in vivo models, effectively targeting both drug-sensitive and drug-resistant cancers. These findings underscore the promising potential of these

1,2,3-triazole hybrids as innovative candidates for cancer therapy. Their review summarizes 1,2,3-triazole-containing hybrids that have shown potential anticancer activity in both in vitro and in vivo studies developed over the past five years.

The review also explores the structure-activity relationships (SARs) and mechanisms of action, providing guidance for the design and optimization of 1,2,3-triazole-based hybrids with greater efficacy and lower toxicity [84].

Recent studies have introduced innovative nanocarriers (NCs) that are bioconjugated with trastuzumab (Tras) using click chemistry techniques. Specifically, click reactions were employed to link CS-Mal/SH-ALG NCs with Tras, acting as a receptor-targeting ligand, after synthesizing chitosan-maleimide (CHI-Mal) and thiolated alginate.

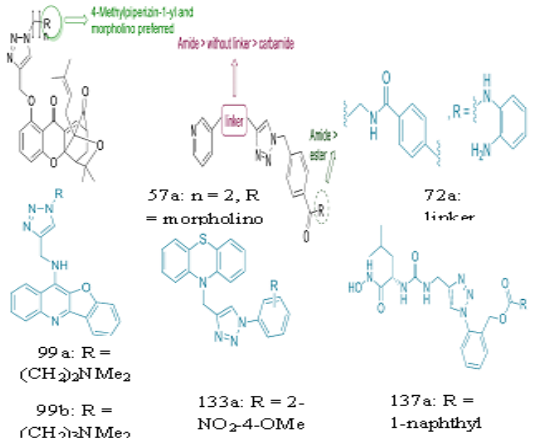


Figure 10. Some novel efficient anticancer products based-triazole moiety.

The SK-BR-3 HER2-positive breast cancer cell line was utilized to evaluate the NCs in terms of cell viability, targeting efficiency, biocompatibility, and anticancer activity. The resulting NCs exhibited a positive surface charge, a nearly spherical morphology, and nanoscale dimensions. Notably, the release of curcumin (Cur) from Cur-loaded CHI-Mal/SH-ALG NCs (Cur-NCs) was significantly higher in an acidic cancer environment (pH 5.5; 98%) compared to physiological conditions (pH 7.4; 57%) over a 7-day period. Tras-conjugated Cur-NCs (Tras-Cur-NCs) demonstrated superior anticancer effects and increased cellular uptake, outperforming both free Cur and non-targeted Cur-NCs.

A recent study conducted by Antoniraj et al. [86] proposed a pH-responsive copolymer based on chitosan and mPEG, which was loaded with prednisolone. The study revealed that the resulting polymeric nanoparticles (PNPs) effectively reduced the levels of inflammatory mediators such as ROS and NO in RAW264.7 cell lines. The results highlighted the potential of the pH-responsive properties of the PNPs and their promising ability to treat both cancer and inflammatory conditions through this innovative delivery system.

6. Conclusion

In summary, the application of triazole derivatives in medicinal chemistry and the development of chitosan-based materials using click chemistry highlight the progressive and transformative aspects of polymer and pharmaceutical research. These innovative compounds improve upon current therapeutic methods and introduce new ways to combat a wide range of diseases. Meticulous investigation and teamwork have led to the fusion of triazole chemistry with chitosan enhancements, advancing powerful solutions for both existing and forthcoming health issues. This rapidly growing area promises significant advances in creating more efficient and specific treatments, emphasizing the necessity for ongoing research and utilization of these adaptable chemical structures.

7. References

[1] A.R. Katritzky, Handbook of Heterocyclic Chemistry. Pergamon, 1985.

[2] R. Dahm, "Discovering DNA: Friedrich Miescher and the early years of nucleic acid research," Jan. 2008. doi: 10.1007/s00439-007-0433-0.

[3] M.B. Davies, D.A. Partridge, J.A. Austin, *VITAMIN C Its Chemistry and Biochemistry*. Royal Society of Chemistry, OCT. 2007.

[4] Y. El Ghoul, R. Renia, I. Faye, S. Rassou, N. Badi, V. Bennevault-Celton, C. Huin, and P. Guégan, Biomimetic artificial ion channels based on beta-cyclodextrin. Chemical Communications, 49(99), pp. 11647-11649, 2013, doi: org/10.1039/C3CC47071G

[5] P. FüRst and P. Stehle, "3rd Amino Acid Workshop What Are the Essential Elements Needed for the Determination of Amino Acid Requirements in Humans? 1." [Online]. Available: https://academic.oup.com/jn/article-abstract/134/6/1558S/4688841

[6] M. S. Saini, A. Kumar, J. Dwivedi, and R. Singh, A review: biological significances of heterocyclic compounds. Int. J. Pharm. Sci. Res, 4(3), pp.66-77.

[7] K. M. J. A. Joule, *Heterocyclic Chemistry*. Blackwell Science, Oxford, ©2000.

[8] S. M. Gomha and H. A. Abdel-Aziz, "Enaminones as building blocks in heterocyclic preparations: Synthesis of novel pyrazoles, pyrazolo[3,4-d]pyridazines, pyrazolo[1,5-a]pyrimidines, pyrido[2,3-d]pyrimidines linked to imidazo[2,1-b]thiazole system," Heterocycles, vol. 85, no. 9, pp. 2291–2303, 2012.

[9]H. R. M. Rashdan, A. H. Abdelmonsef, I. A. Shehadi, S. M. Gomha, A. M. M. Soliman, and H. K. Mahmoud, "Synthesis, molecular docking screening and anti-proliferative potency evaluation of some new imidazo[2,1-b]thiazole linked thiadiazole conjugates," Molecules, vol. 25, pp. 4997, 2020.

[10] D.D. Nekrasov, "Biological Activity of 5-and 6-Membered Azaheterocycles and Their Synthesis from 5-Aryl-2, 3-Dihydrofuran-2, 3-diones. Chemistry of Heterocyclic Compounds, 37, pp.263-275, 2001, doi.org/10.1023/A:1017505929583.

[11] J.B. Sperry and D.L. Wright, "Furans, thiophenes and related heterocycles in drug discovery. Current opinion in drug discovery & development, 8(6), pp.723-740, 2005, PMID: 16312148.

[12] W.G. Zhao, "Synthesis of Pyrazolyl-heterocycles and Their Fungicidal Activities," *Chin. J. Chem*, pp. 942–939, 2001.

[13] H. R. M. Rashdan, S. M. Gomha, M. S. El-Gendey, M. A. El-Hashash, and A. M. M. Soliman, "Eco-friendly one-pot synthesis of some new pyrazolo[1,2-b]phthalazinediones with antiproliferative efficacy on human hepatic cancer cell lines," Green Chem. Lett. Rev., vol. 11, no. 3, pp. 264–274, 2018.

[14] A. S. Shawali and S. M. Gomha, "Regioselectivity in 1,5-electrocyclization of N-[as-triazin-3-yl]nitrilimines: Synthesis of s-triazolo[4,3-b]-as-triazin-7(8H)-ones," Tetrahedron, vol. 58, pp. 8559–8564, 2002.

[15] S. M. Gomha, S. M. Riyadh, E. A. Mahmmoud, and M. M. Elaasser, "Synthesis and anticancer activity of arylazothiazoles and 1,3,4-thiadiazoles using chitosan-grafted-poly(4-vinylpyridine) as a novel copolymer basic catalyst," Chem. Heterocycl. Compd., vol. 51, no. 11, pp. 1030–1038, 2015.

[16] H. Li, R. Aneja, and I. Chaiken, "Click chemistry in peptide-based drug design," Aug. 2013. doi: 10.3390/molecules18089797.

[17] S. M. Gomha, S. A. Ahmed, and A. O. Abdelhamid, "Synthesis and cytotoxicity evaluation of some novel thiazoles, thiadiazoles, and pyrido[2,3-d][1,2,4]triazolo[4,3-a]pyrimidin-5(1H)-one incorporating triazole moiety," Molecules, vol. 20, pp. 1357–1376, 2015.

[18] K. D. Khalil, S. M. Riyadh, S. M. Gomha, and I. Ali, "Synthesis, characterization and application of copper oxide chitosan nanocomposite for green regioselective synthesis of [1,2,3]triazoles," Int. J. Biol. Macromol., vol. 130, pp. 928–937, 2019.

[19] S. A. Osman, M. A. Abdallah, H. Salah, A. M. M. Soliman, S. M. Gomha, H. Bassiony, and H. R. M. Rashdan, "Chitosan (CS)/polyvinyl alcohol (PVA) films loaded with novel synthesized 1,2,3-triazole derivative for cancer treatment," Egypt. J. Chem., vol. 67, pp. 279–288, 2024.

[20] B. S. Holla, M. Mahalinga, M. S. Karthikeyan, B. Poojary, P. M. Akberali, and N. S. Kumari, "Synthesis, characterization and antimicrobial activity of some substituted 1,2,3-triazoles," *Eur J Med Chem*, vol. 40, no. 11, pp. 1173–1178, Nov. 2005, doi: 10.1016/j.ejmech.2005.02.013.

[21] I. Khan, M. A. Tantray, H. Hamid, M. S. Alam, A. Kalam, and A. Dhulap, "Synthesis of benzimidazole based thiadiazole and carbohydrazide conjugates as glycogen synthase kinase-3β inhibitors with anti-depressant activity," *Bioorg Med Chem Lett*, vol. 26, no. 16, pp.4020–4024, 2016, doi: 10.1016/j.bmcl.2016.06.084.

[22] S. Narsimha, K. S. Battula, and V. R. Nagavelli, "One-pot synthesis of novel 1,2,3-triazole-pyrimido[4,5-c]isoquinoline hybrids and evaluation of their antioxidant activity," *Synth Commun*, vol. 48, no. 10, pp. 1220–1226, May 2018, doi: 10.1080/00397911.2018.1440315.

[23] W. Yan *et al.*, "Design, synthesis, and antifungal activity of carboxamide derivatives possessing 1,2,3-triazole as potential succinate dehydrogenase inhibitors," *PesticBiochemPhysiol*, vol. 156, pp. 160–169, May 2019, doi: 10.1016/j.pestbp.2019.02.017.

[24] D. Dheer, V. Singh, and R. Shankar, "Medicinal attributes of 1,2,3-triazoles: Current developments," Apr. 01, 2017, *Academic Press Inc.* doi: 10.1016/j.bioorg.2017.01.010.

[25] J. R. Johansson, T. Beke-Somfai, A. Said Stålsmeden, and N. Kann, "Ruthenium-Catalyzed Azide Alkyne Cycloaddition Reaction: Scope, Mechanism, and Applications," Dec. 14, 2016, *American Chemical Society*. doi: 10.1021/acs.chemrev.6b00466.

[26] M. Z. Elsabee and E. S. Abdou, "Chitosan based edible films and coatings: A review," May. 2013. doi: 10.1016/j.msec.2013.01.010.

[27] R. Jayakumar, M. Prabaharan, S. V. Nair, and H. Tamura, "Novel chitin and chitosan nanofibers in biomedical applications," Jan. 2010. doi: 10.1016/j.biotechadv.2009.11.001.

[28] C. Ammar, Y. El Ghoul, and A. El Achari, 2015. Finishing of polypropylene fibers with cyclodextrins and polyacrylic acid as a crosslinking agent. Textile

Research Journal, 85(2), pp.171-179. doi.org/10.1177/0040517514540769.

[29] Y. El Ghoul, F. Salah, H. Majdoub, and F. Sakli, 2017. Synthesis and study of drug delivery system obtained via β-cyclodextrin functionalization of viscose/polyester dressings. Journal of Industrial Textiles, 47(4), pp.489-504. doi.org/10.1177/1528083716652833.

[30] Z. A. Raza, S. Khalil, A. Ayub, and I. M. Banat, "Recent developments in chitosan encapsulation of various active ingredients for multifunctional applications," *Carbohydr Res*, vol. 492, Jun. 2020, doi: 10.1016/j.carres.2020.108004.

[31] Y. El-Ghoul, A.S. Altuwayjiri, and G.A. Alharbi, "Synthesis and characterization of new electrospun medical scaffold-based modified cellulose nanofiber and bioactive natural propolis for potential wound dressing applications," *RSC advances*, *14*(36), pp.26183-26197, 2024, doi: 10.1039/D4RA04231J.

[32] L. A. Alshabanah, S. M. Gomha, L. A. Al-Mutabagani, T. Z. Abolibda, N. A. Abd El-Ghany, W. A. M. A. El-Enany, A. K. El-Ziaty, R. S. Ali, and N. A. Mohamed, "Cross-linked chitosan/multi-walled carbon nanotubes composite as eco-friendly biocatalyst for synthesis of some novel benzil bis-thiazoles," Polymers, vol. 13, pp. 1728, 2021.

[33] K. D. Khalil, H. A. Ahmed, A. H. Bashal, S. Bräse, A. Nayl, and S. M. Gomha, "Efficient, recyclable, heterogeneous base nanocatalyst for thiazoles with chitosan-capped calcium oxide nanocomposite," Polymers, vol. 14, pp. 3347, 2022.

[34] J. Y. Al-Humaidi, S. M. Gomha, N. A. Abd El-Ghany, B. Farag, M. E. A. Zaki, T. Z. Abolibda, and N. A. Mohamed, "Green synthesis and molecular docking study of some new thiazoles using terephthalohydrazide chitosan hydrogel as eco-friendly biopolymeric catalyst," Catalysts, vol. 13, pp. 1311, 2023.

[35] K. D. Khalil, S. M. Riyadh, A. H. Bashal, T. Abolibda, and S. M. Gomha, "Green synthetic approaches of 2-hydrazonothiazol-4(5H)-ones using sustainable barium oxide-chitosan nanocomposite catalyst," Polymers, vol. 15, no. 18, pp. 3817, 2023.

[36] S. M. Gomha, N. A. Abd El-Ghany, M. S. Ebaid, T. Z. Abolibda, M. E. A. Zaki, M. Alhilal, S. Alhilal, and N. A. Mohamed, "Eco-friendly synthesis of thiazole derivatives using a recyclable cross-linked chitosan hydrogel biocatalyst under ultrasonic irradiation as anti-hepatocarcinogenic agents," Catalysts, vol. 14, pp. 840, 2024.

[37] B. Karpagam, J. Rajesh, G. Rajagopal, Use of Dextran in Pharmaceutical and Cosmetic Compositions. *Biopolymers in Pharmaceutical and Food Applications*, *2*, pp.451-469, 2024, doi: org/10.1002/9783527848133.ch21.

[38] K. J. Edgar, "Cellulose esters in drug delivery," *Cellulose*, vol. 14, no. 1, pp. 49–64, Feb. 2007, doi: 10.1007/s10570-006-9087-7.

[39] V. R. Sinha and R. Kumria, "Polysaccharides in colon-specific drug delivery," *International journal of pharmaceutics*, *224*(1-2), pp.19-38, 2001, doi: org/10.1016/S0378-5173(01)00720-7.

[40] F.M. Alminderej, C. Ammar, and Y. El-Ghoul, Functionalization, characterization and microbiological performance of new biocompatible cellulosic dressing grafted chitosan and Suaedafruticosa polysaccharide extract. Cellulose, 28(15), pp.9821-9835, 2021, doi: org/10.1007/s10570-021-04155-4.

[41] Y. El-Ghoul and F.M, Alminderej, Bioactive and superabsorbent cellulosic dressing grafted alginate and Carthamus tinctorius polysaccharide extract for the treatment of chronic wounds. Textile Research Journal, 91(3-4), pp.235-248, 2021, doi: org/10.1177/0040517520935.

[42] Y. El-Ghoul, M.S. Al-Fakeh, and N.S. Al-Subaie, Synthesis and Characterization of a New Alginate/Carrageenan crosslinked biopolymer and Study of the Antibacterial, Antioxidant, and Anticancer Performance of its Mn (II), Fe (III), Ni (II), and Cu (II) polymeric complexes. Polymers, 15(11), p.2511, 2023, doi: org/10.3390/polym15112511.

[43] S. Shi, W. Shi, B. Zhou, S. Qiu, Research and Application of Chitosan Nanoparticles in Orthopedic Infections. International Journal of Nanomedicine, pp.6589-6602, 2024, doi: org/10.2147/IJN.S468848.

[44] P. Poznanski, A. Hameed, W. Orczyk, Chitosan and chitosan nanoparticles: parameters enhancing antifungal activity. Molecules, 28(7), p.2996, 2023, doi: org/10.3390/molecules28072996.

[45] M. Dash, F. Chiellini, R. M. Ottenbrite, E. Chiellini, "Chitosan - A versatile semi-synthetic polymer in biomedical applications," *Progress in polymer science*, *36*(8), pp.981-1014, 2011, doi: 10.1016/j.progpolymsci.2011.02.001.

[46] A.F. Kotze, H.L. Lueßen, A.G. De Boer, J. C. Verhoef, and H. E. Junginger, "Chitosan for enhanced intestinal permeability: Prospects for derivatives soluble in neutral and basic environments," European journal of pharmaceutical sciences, 7(2), pp.145-151, 1999, doi: org/10.1016/S0928-0987(98)00016-5.

[47] S. Rathinam, M. Hjálmarsdóttir, M. B. Thygesen, and M. Másson, "Chitotriazolan (poly(β(1-4)-2-(1H-1,2,3-triazol-1-yl)-2-deoxy-D-glucose)) derivatives: Synthesis, characterization, and evaluation of antibacterial activity," *CarbohydrPolym*, vol. 267, Sep. 2021, doi: 10.1016/j.carbpol.2021.118162.

[48] C. K. S. Pillai, W. Paul, and C. P. Sharma, "Chitin and chitosan polymers: Chemistry, solubility and fiber formation," Jul. 2009. doi: 10.1016/j.progpolymsci.2009.04.001.

[49] G. N. Shi *et al.*, "Enhanced antitumor immunity by targeting dendritic cells with tumor cell lysate-loaded chitosan nanoparticles vaccine," *Biomaterials*, vol. 113, pp. 191–202, Jan. 2017, doi: 10.1016/j.biomaterials.2016.10.047.

[50] R.M.C. Udayangani, S. H. S. Dananjaya, C. Nikapitiya, G. J. Heo, J. Lee, and M. De Zoysa, "Metagenomics analysis of gut microbiota and immune modulation in zebrafish (Danio rerio) fed chitosan silver nanocomposites," *Fish Shellfish Immunol*, vol. 66, pp. 173–184, Jul. 2017, doi: 10.1016/j.fsi.2017.05.018.

[51] L. Wei, W. Tan, G. Wang, Q. Li, F. Dong, and Z. Guo, "The antioxidant and antifungal activity of chitosan derivatives bearing Schiff bases and quaternary ammonium salts," *CarbohydrPolym*, vol. 226, Dec. 2019, doi: 10.1016/j.carbpol.2019.115256.

[52] Y. El-Ghoul, Biological and microbiological performance of new polymer-based chitosan and synthesized amino-cyclodextrin finished polypropylene abdominal wall prosthesis

biomaterial. Textile Research Journal, 90(23-24), pp.2690-2702, 2020, doi: org/10.1177/0040517520926624.

[53] G.I. Edo, E. Yousif, M.H. Al-Mashhadani, Chitosan: An overview of biological activities, derivatives, properties, and current advancements in biomedical applications. *Carbohydrate Research*, p.109199, 2024, doi: org/10.1016/j.carres.2024.109199.

[54] B. Zhang, W. Lan, Z. Wang, Z. Shao, J. Xie, Modified chitosan with different phenolic acids: Characterization, physicochemical properties, and biological activity. *Food Chemistry*, *441*, p.138337, 2024, doi: org/10.1016/j.foodchem.2023.138337.

[55] M.E. Ahmed, M.I. Mohamed, H.Y. Ahmed, M.M. Elaasser, N.G. Kandile, Fabrication and characterization of unique sustain modified chitosan nanoparticles for biomedical applications. *Scientific Reports*, *14*(1), p.13869, 2024, doi: org/10.1038/s41598-024-64017-4.

[56] M. Dash, F. Chiellini, R. M. Ottenbrite, and E. Chiellini, "Chitosan - A versatile semi-synthetic polymer in biomedical applications," *Progress in polymer science*, *36*(8), pp.981-1014, 2011, doi: 10.1016/j.progpolymsci.2011.02.001.

[57] C.K.S. Pillai, W. Paul, and C.P. Sharma, "Chitin and chitosan polymers: Chemistry, solubility and fiber formation," *Progress in polymer science*, *34*(7), pp.641-678 Jul. 2009. doi: 10.1016/j.progpolymsci.2009.04.001.

[58] F.M. Alminderej, Y. El-Ghoul, Synthesis and study of a new biopolymer-based chitosan/hematoxylin grafted to cotton wound dressings. Journal of Applied Polymer Science, 136(23), p.47625, 2019, doi: org/10.1002/app.47625.

[59] H.K.S. Panahi, M. Dehhaghi, H. Amiri, G.J. Guillemin, V.K. Gupta, A. Rajaei, Y. Yang, W. Peng, J. Pan, M. Aghbashlo, M. Tabatabaei, Current and emerging applications of saccharide-modified chitosan: a critical review. Biotechnology advances, 66, p.108172, 2023, doi: org/10.1016/j.biotechadv.2023.108172.

[60] S. Dumitriu, *Polysaccharides in Medicinal Applications*. Routledge, 2017. doi: 10.1201/9780203742815.

[61] A. Harugade, A. P. Sherje, and A. Pethe, "Chitosan: A review on properties, biological activities and recent progress in biomedical applications," *React FunctPolym*, vol. 191, p. 105634, Oct. 2023, doi: 10.1016/j.reactfunctpolym.2023.105634.

[62] Q. Li, W. Tan, C. Zhang, G. Gu, and Z. Guo, "Synthesis of water-soluble chitosan derivatives with halogeno-1,2,3-triazole and their antifungal activity," *Int J Biol Macromol*, vol. 91, pp. 623–629, Oct. 2016, doi: 10.1016/j.ijbiomac.2016.06.006.

[63] F. Ajormal, R. Bikas, H. Ghasemzadeh, N. Noshiranzadeh, and A. Kozakiewicz-Piekarz, "Green and recyclable catalyst based on chitosan/CuFe2O4 nanocomposite hydrogel for one-step synthesis of 1,2,3-triazoles," *RSC Adv*, vol. 14, no. 43, pp. 31320–31331, Oct. 2024, doi: 10.1039/d4ra05626d.

[64] W. Tan, J. Zhang, Y. Mi, F. Dong, Q. Li, and Z. Guo, "Synthesis, characterization, and evaluation of antifungal and antioxidant properties of cationic chitosan derivative via azide-alkyne click reaction," *Int J Biol Macromol*, vol. 120, pp. 318–324, Dec. 2018, doi: 10.1016/j.ijbiomac.2018.08.111.

[65] P. Sahariah*et al.*, "Antimicrobial peptide shows enhanced activity and reduced toxicity upon grafting to chitosan polymers," *Chemical Communications*, vol. 51, no. 58, pp. 11611–11614, Jul. 2015, doi: 10.1039/c5cc04010h.

[66] Y. Qin, S. Liu, R. Xing, K. Li, H. Yu, and P. Li, "Synthesis and antifungal evaluation of (1,2,3-triazol-4-yl) methyl nicotinate chitosan," *Int J Biol Macromol*, vol. 61, pp. 58–62, 2013, doi: 10.1016/j.ijbiomac.2013.05.023.

[67] Q. Li, X. Sun, G. Gu, and Z. Guo, "Novel water soluble chitosan derivatives with 1,2,3-Triazolium and their free radical-scavenging activity," *Mar Drugs*, vol. 16, no. 4, Apr. 2018, doi: 10.3390/md16040107.

[68] F.S. Aljohani*et al.*, "Synthesis, Characterization and Nanoformulation of Novel Sulfonamide-1,2,3-triazole Molecular Conjugates as Potent Antiparasitic Agents," *Int J Mol Sci*, vol. 23, no. 8, Apr. 2022, doi: 10.3390/ijms23084241.

[69] M. Daraie and M. M. Heravi, "A biocompatible chitosan-ionic liquid hybrid catalyst for regioselective synthesis of 1,2,3-triazols," *Int J Biol Macromol*, vol. 140, pp. 939–948, Nov. 2019, doi: 10.1016/j.ijbiomac.2019.08.162.

[70] Z. Zhang *et al.*, "A novel approach to 1,2,3-triazole grafted chitosans via modified Wolff's cyclocondensation," *EurPolym J*, vol. 98, pp. 492–498, Jan. 2018, doi: 10.1016/j.eurpolymj.2017.11.047.

[71] W. Tan, J. Zhang, X. Zhao, F. Dong, Q. Li, and Z. Guo, "Synthesis and antioxidant action of chitosan derivatives with amino-containing groups via azide-alkyne click reaction and N-methylation," *CarbohydrPolym*, vol. 199, pp. 583–592, Nov. 2018, doi: 10.1016/j.carbpol.2018.07.056.

[72] W. Tan, J. Zhang, Y. Mi, F. Dong, Q. Li, and Z. Guo, "Enhanced antifungal activity of novel cationic chitosan derivative bearing triphenylphosphonium salt via azide-alkyne click reaction," *Int J Biol Macromol*, vol. 165, pp. 1765–1772, Dec. 2020, doi: 10.1016/j.ijbiomac.2020.10.019.

[73] A.S. Kritchenkov*et et al.*, "Ultrasound-assisted Cu(I)-catalyzed azide-alkyne click cycloaddition as polymer-analogous transformation in chitosan chemistry. High antibacterial and transfection activity of novel triazol betaine chitosan derivatives and their nanoparticles," *Int J Biol Macromol*, vol. 137, pp. 592–603, Sep. 2019, doi: 10.1016/j.ijbiomac.2019.06.190.

[74] R. Kulbokaite, G. Ciuta, M. Netopilik, and R. Makuska, "N-PEG'ylation of chitosan via 'click chemistry' reactions," *React FunctPolym*, vol. 69, no. 10, pp. 771–778, Oct. 2009, doi: 10.1016/j.reactfunctpolym.2009.06.010.

[75] X. Meng and K. J. Edgar, "'Click' reactions in polysaccharide modification," Progress in Polymer Science, 53, pp.52-85, Feb. 2016, *Elsevier Ltd*. doi: 10.1016/j.progpolymsci.2015.07.006.

[76] V. K. Tiwari, B. B. Mishra, K. B. Mishra, N. Mishra, A. S. Singh, and X. Chen, "Cu-Catalyzed Click Reaction in Carbohydrate Chemistry," Mar. 2016, *American Chemical Society*. doi: 10.1021/acs.chemrev.5b00408.

[77] K. González *et al.*, "Starch/graphene hydrogels via click chemistry with relevant electrical and

antibacterial properties," *CarbohydrPolym*, vol. 202, pp. 372–381, Dec. 2018, doi: 10.1016/j.carbpol.2018.09.007.

[78] Y. Gao, Z. Zhang, L. Chen, W. Gu, Y. Li, "Synthesis of 6-N,N,N-trimethyltriazole chitosan via 'click chemistry' and evaluation for gene delivery," *Biomacromolecules*, vol. 10, no. 8, pp. 2175–2182, Aug. 2009, doi: 10.1021/bm900341d.

[79] F. Luan *et al.*, "Preparation and characterization of quaternized chitosan derivatives and assessment of their antioxidant activity," *Molecules*, 23(3), p.516, 2018, doi: 10.3390/molecules23030516.

[80] M. Barbosa, N. Vale, F.M.T.A. Costa, M.C.L. Martins, and P. Gomes, "Tethering antimicrobial peptides onto chitosan: Optimization of azide-alkyne 'click' reaction conditions," *CarbohydrPolym*, vol. 165, pp. 384–393, Jun. 2017, doi: 10.1016/j.carbpol.2017.02.050.

[81] Q. Li, W. Tan, C. Zhang, G. Gu, and Z. Guo, "Novel triazolyl-functionalized chitosan derivatives with different chain lengths of aliphatic alcohol substituent: Design, synthesis, and antifungal activity," *Carbohydr Res*, vol. 418, pp. 44–49, Dec. 2015, doi: 10.1016/j.carres.2015.10.005.

[82] A. Sarwar, H. Katas, S. N. Samsudin, and N. M. Zin, "Regioselective sequential modification of chitosan via azide-alkyne click reaction: Synthesis, characterization, and antimicrobial activity of chitosan derivatives and nanoparticles," *PLoS One*, vol. 10, no. 4, Apr. 2015, doi: 10.1371/journal.pone.0123084.

[83] L. Liao *et al.*, "Synthesis and biological evaluation of 1,2,4-triazole derivatives as potential neuroprotectant against ischemic brain injury," *Eur J Med Chem*, vol. 190, Mar. 2020, doi: 10.1016/j.ejmech.2020.112114.

[84] Z. Xu, S. J. Zhao, and Y. Liu, "1,2,3-Triazole-containing hybrids as potential anticancer agents: Current developments, action mechanisms and structure-activity relationships," European journal of medicinal chemistry, 183, p.111700, Dec, 2019, *Elsevier Masson SAS*. doi: 10.1016/j.ejmech.2019.111700.

[85] C. Pornpitchanarong, Y.Y. Myat, N. Sahatsapan, S. Pengnam, T. Rojanarata, P. Opanasopit, T. Ngawhirunpat, P. Patrojanasophon, "Bioconjugated clicked chitosan/alginate nanocarriers with trastuzumab: Unlocking curcumin's potential in targeting breast cancer," *Carbohydrate Polymer Technologies and Applications, 8*, p.100563, 2024, doi: org/10.1016/j.carpta.2024.100563.

[86] M.G. Antoniraj, H.L.J. Kumari, A. Shanmugarathinam, R. Kandasamy, pH-responsive chitosan copolymer synthesized via click chemistry for design of polymeric nanoparticles for targeted drug delivery. Carbohydrate Research, 542, p.109200, 2024, doi: org/10.1016/j.carres.2024.109200.