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Synthesis and Antibacterial, Antioxidant and DNA Cleavage Evaluation of Triazenes Containing Sulfathiazole Moiety

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Abstract

Triazenes are one of the most important linker groups that recently investigated as potential enzyme inhibitors. For this reason, in the present work, a series of 1,3-diaryltriazene-substituted sulfathiazole derivatives were re-synthesized by condensation of diazonium salt of sulfathiazole and substituted aromatic amines under optimized conditions. The obtained compounds were tested for their antibacterial, DNA cleavage, and antioxidant properties (including several bioanalytical methods such as DPPH free radical scavenging assay, ABTS cation radical decolarization, metal chelating and cupric reducing antioxidant capacity (CUPRAC)). In general, compounds were more susceptible to gram (-) bacteria strain (P. aeruginosa) with two compounds ST-4 and ST-10 have minimal inhibitory concentration (MIC) values of 15.6μg/mL as compared standard sulfathiazole (MIC: 125μg/mL). On the other hand, all compounds showed weak to moderate antioxidant activity against tested methods.

Keywords: Sulfathiazole; Triazen; Antibacterial; DNA cleavage; Antioxidant

Introduction

The sulfonamide group containing compounds and their isosters (sulfamides, sulfamates) was designed, synthesized and developed as antibacterial agents to treat a broad spectrum of bacterial diseases for decades [1]. Among these studies, many drugs came out and used as potent antimicrobial drugs [1-3]. In the current century, sulfonamides are still a hot topic to discover new and biologically more potent compounds. More specifically, in recent studies, sulfonamides were used as powerful pharmacophore to develop more potent carbonic anhydrase inhibitors (this enzyme is related to many diseases such as, diuretic, cancer, glaucoma, epilepsy, obesity, Alzheimer, etc.) [4-8], antibacterial agents [9,10], and antioxidants [11,12].

Triazenes are a diverse group of compounds contains three contiguous nitrogene atoms that can be easily synthesized from amines or alkyl azides [13,14]. This linker is one of the most important groups for many compounds due to their easy preparation and great pharmaceutical properties in medicinal chemistry research. When the literature studies are examined, it can be seen that the 1,3-diaryl-substituted triazenes gained more importance, more specifically in potent and selective enzyme inhibition studies, in recent years [15,16]. On the other hand, triazene substituted compounds were extensively used in the many drugs design and development studies as anticancer [17,18], antibacterial [19], carbonic anhydrase inhibitors [20-22], acetylcholinesterase inhibitors [23], and antioxidant agents [24].

In our previous study, we have successfully designed and synthesized 1,3-diaryltriazene-substituted sulfathiazole derivatives and enzyme inhibition properties of compounds were evaluated against metabolic enzymes; α-glycosidase (α-GLY), human carbonic anhydrase (*h*CA I and *h*CA II), and acetylcholinesterase (AChE) [22]. Among the tested series, some

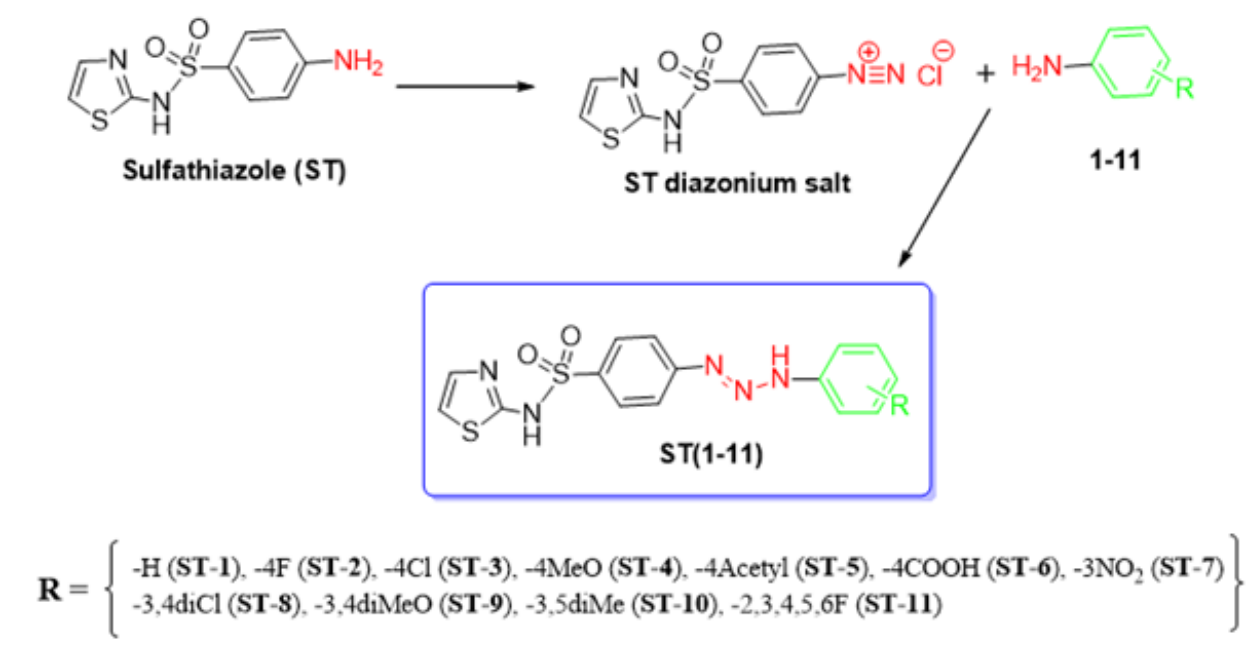
of the compounds greatly inhibited enzymes with nanomolar range [22]. In the present study, we aimed to investigate antibacterial (toward two Gram-positive bacteria and two Gram-negative), antioxidant (four different methods such as, DPPH free radical scavenging assay, ABTS cation radical decolarization, metal chelating and CUPRAC) and DNA cleavage activities of re-synthesized 1,3-diaryltriazene-substituted sulfathiazole derivatives.

Material and Methods

All chemicals and anhydrous solvents were purchased and used without any further purification. Reactions were monitored by thin-layer chromatography (TLC) on Merck silica gel 60 F_{254} plated visualizing with ultraviolet light and appropriate solvents were used as mobile phase. IR spectra were recorded by using PerkinElmer Spectrum 100 FT-IR spectrum and are expressed in cm^{-1} (400-4000 cm^{-1}). ^{1}H-NMR and ^{13}C-NMR spectra were recorded using a Bruker Advance III 300 MHz spectrometer using DMSO-d6 as a solvent; the chemical shifts are referenced to tetramethylsilane (TMS). Melting points (mp) were recorded with SMP30 melting point apparatus in open capillary tubes and were uncorrected.

Chemistry

Compounds **ST(1-11)** were synthesized by diazo reaction as previously described by us [22]. Briefly, the diazonium salt of sulfathiazole was reacted with various substituted aromatic amines to obtain targeted compounds **ST(1-11)** as summarized in Scheme 1. Physicochemical and spectroscopic characteristic of all the synthesized compounds were previously reported by us [22].



Scheme 1: General synthetic route for the re-synthesis of the 1,3-diaryltriazene-substituted sulfathiazole derivatives ST(1-11).

Scheme 1 General synthetic route for the re-synthesis of the 1,3-diaryltriazene-substituted sulfathiazole derivatives **ST(1-11)**.

Antibacterial activities

The microdilution susceptibility tests were carried out in Nutrient broth for the evaluation of antibacterial activity. The freshly synthesized, 1,3-diaryltriazene-substituted sulfathiazole derivatives **ST(1-11)** were evaluated for their antimicrobial activity against four pathogenic bacterial strains, including Gram-positive (Staphylococcus *aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212) and Gram-negative bacteria (*Pseudomonas aeruginosa* ATCC 10231, *Escherichia coli* ATCC 25912).

The antimicrobial analyzes were carried out by modifying according to Al blewi et al. [25]. Briefly, the synthesized compounds were dissolved in DMSO compounds and 5mg/mL stock solution was prepared and were tested at eight different concentrations diluted seven times. The bacterial strain (100µL) was added to each microplate well to be approximately 106 CFU/mL bacteria, adjusting the density with a McFarland densitometer. Sulfathiazole was used as a standard compound for comparison reasons and the same procedures were applied to it. Microplates were incubated for 24 hours at 37°C to measure antibacterial activity, then optical densities were measured at 600 nm (OD600) using a microplate reader (Biotek ELX800 elisa reader). MIC assessments were repeated three times for each microorganism and each compound.

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Minimal inhibitory concentrations (MICs) were determined at the end of the 24-hour incubation period. Control experiments with standard antimicrobial agents (positive control) and unvaccinated media (negative control) were performed in parallel and in the same manner as the compounds examined conditions.

Antioxidant activity assays

The in vitro method was followed in the literature and previous studies reported by us, for DPPH free radical scavenging activity assay [26-28], ABTS cation radical decoloriaztion activity assay [29, 30], and CUPRAC activity assay [31]. On the other hand, BHA, BHT and α-TOC were used as standards for comparison. The metal chelating activity assay was also applied as reported in the literature and EDTA was used as standard [32,33].

Plasmid DNA cleavage studies

The plasmid DNA cleavage assay was performed with pET21a (Novagen) plazmid DNA by using the agarose gel electrophoresis method. *Escherichia coli* Dh5α cells carrying pET21a (Novagen) plasmid were inoculated into fresh LB medium containing 100μg/mL ampicillin and the culture was grown at 220rpm for overnight at 37°C. Plasmid DNA was extracted by using plasmid DNA isolation kit (K0502, Thermo Fisher Scientific™) and stored at 4°C until needed. In order to examine the plasmid cleavage activity of the re-synthesized compounds; 1μg plasmid DNA, 50μM of each of the derivatives dissolved in 25μM in 10 mM TrisHCl/1mM EDTA buffer pH 8.0 and 0.4M dimethyl sulfoxide (DMSO) were mixed in an Eppendorf tube.

Plasmid DNA with no compound and DMSO as a hydroxy radical scavenger and plasmid DNA and only DMSO were used for control. The samples were incubated at 37°C. After 3h incubation; the samples were mixed with 6X bromophenol blue loading dye (Fermentas) and loaded on a 0.8% agarose gel containing 2.0μg/mL ethidium bromide. The gel was run for 30 min in 0.5X Tris-Borate-EDTA (TBE) buffer at 120V. The gel was visualized by UV with Quantum ST5 gel documentation system.

Results and Discussion

All the re-synthesized triazene containing sulfathiazole derivatives **ST(1-11)** were assessed for their antibacterial properties against Gram-positive (*Staphylococcus aureus ATCC 29213, Enterococcus faecalis* ATCC 29212) and Gram-negative bacteria (*Pseudomonas aeruginosa* ATCC 10231, *Escherichia coli* ATCC 25912) by obtaining their minimum inhibitory concentration (MIC) values demonstrated in Table 1. The starting compound, sulfathiazole, was used as a reference drug. Among the tested series, some compounds showed greater antibacterial activity, comparing with standard drug sulfathiazole against gram-positive bacteria strains including **ST-11** (*against S. aureus with* 31.3μg/mL) and **ST-2** (against *E. faecalis* with 31.3 μg/mL) which is interestingly, both of them have flor atom in their structure (2,3,4,5,6-penta-F, and 4-F, respectively). Another halogeno atom chlor (4-Cl and 3,4di-Cl) did not show same potential effect on gram (+) strains. On the other hand, compounds **ST-6, ST-7** and **ST-8** against S. aureus strain and compound ST-8 against *E. faecalis* strain showed any activity. Also, for gram (-) strains, the compounds **ST-4** (4-MeO) and **ST-10** (3,5di-Me) were more potent than the reference drug with MIC = 15.6μg/mL, while only one compound was less active than the sulfathiazole at MIC = 250μg/mL against *P. aeruginosa* (ATCC 10231).

Table 1: Antibacterial activity of triazene containing sulfathiazole derivatives ST(1-11) against Gram-positive and Gram-negative Bacterial Strains.

Compounds	Antibacterial Activity, Minimal Inhibitory Concentration (μg/mL)			
	Gram (+) Bacteria Strains		Gram (-) Bacteria Strains	
	S. aureus	*E. faecalis*	*P. aeruginosa*	*E. coli*
ST-1	250	125	31.3	125
ST-2	62.5	31.3	62.5	125
ST-3	125	125	250	62.5
ST-4	62.5	125	15.6	62.5
ST-5	125	125	31.3	125
ST-6	nd	500	31.3	125
ST-7	nd	250	125	250
ST-8	nd	nd	31.3	125
ST-9	250	500	31.3	250
ST-10	250	500	15.6	250
ST-11	31.3	125	62.5	250
Sulfathiazole	31.3	125	125	62.5

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Antioxidant capacities of the re-synthesized compounds were also assessed by using several different bioanalytical methods, including DPPH free radical scavenging assay, ABTS cation radical decolarization, methal chelating, and CUPRAC. In general, all compounds showed weak to moderate antioxidant activity against tested methods. More specifically, any compounds showed DPPH free radical and metal chelating activity by having IC50 value of >1000 µM, which table 2 demonstrates that our compounds not susceptible to these methods. The best antioxidant activity was observed with ABTS cation radical method among the tested series, which is also weak as compared with standards BHT and BHA. The moderate activity was observed with the compounds **ST-5**, **ST-9** and **ST-11** with IC_{50} values of 54.54±0.80, 48.30±0.64, and 43.69±0.78µM, respectively.

Table 2: Antioxidant activities of triazene containing sulfathiazole derivatives ST(1-11).

Compounds	DPPH Free Radical	ABTS Cation Radical	Metal Chelating	CUPRAC $A_{0.5}$ (µM)
	IC_{50} (µM)	IC_{50} (µM)	IC_{50} (µM)	
ST-1	>1000	185.77±0.79	>1000	332.57±0.93
ST-2	>1000	190.05±0.30	>1000	97.09±0.49
ST-3	>1000	179.49±0.92	>1000	97.48±0.89
ST-4	>1000	97.63±0.11	>1000	101.68±0.73
ST-5	>1000	54.54±0.80	>1000	91.03±0.24
ST-6	>1000	74.14±0.60	>1000	105.41±0.60
ST-7	>1000	67.32±0.23	>1000	87.30±0.82
ST-8	>1000	119.54±0.82	>1000	162.43±0.57
ST-9	>1000	48.30±0.64	>1000	161.31±0.71
ST-10	>1000	75.19±0.89	>1000	98.65±0.66
ST-11	>1000	43.69±0.78	>1000	61.68±0.44
BHA[a]	48.37±0.58	10.22±0.12	-	33.32±0.70
BHT[a]	354.31±1.23	16.19±0.17	-	39.37±0.12
EDTA[a]	-	±	26.82±0.10	-

*Values expressed are the means ± standard deviation of three parallel measurements ($p<0.05$) [a]standard compounds

The plasmid DNA cleavage assay was performed to determine the DNA protection ability of each of the re-synthesized compounds ST(1-11) to protect pET21a plasmid DNA from the damaging effects of hydroxyl radicals [34]. Agarose gel electrophoresis method is used frequently in order to reveal the activity of the compounds as chemical nucleases. Circular plasmid DNA is faster than its linear form in agarose gel electrophoresis [35]. If the scission is on one strand of the plasmid, then open circular form (oc DNA; form 2) occurs. If the scission is on on both strands, a linear conformation (form 3) occurs and this configuration will migrate between Form I and II [36]. In the present study, the ability of triazene containing sulfathiazole derivatives **ST(1-11)** to cleave plasmid DNA was studied by means of gel electrophoresis with supercoiled pET21a in 10mM TrisHCl/1 mM EDTA buffer (pH 8.0) and with DMSO activation.

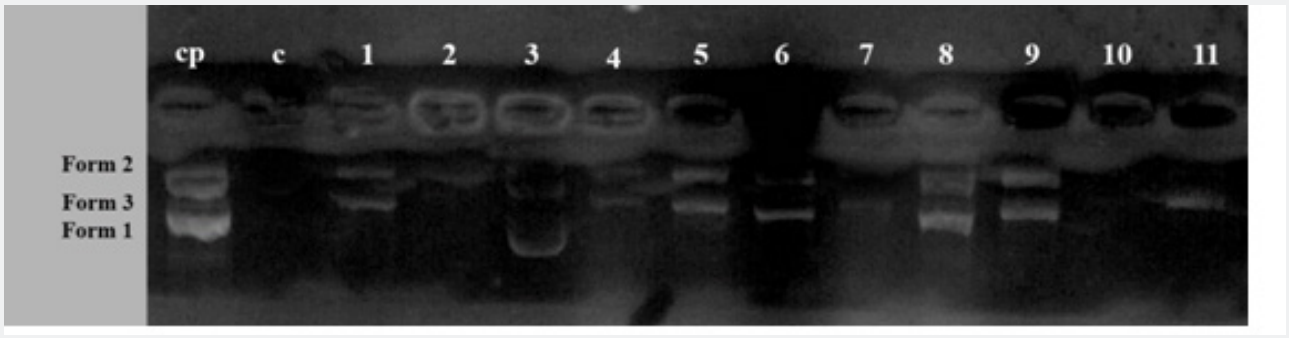

Figure 1: DNA cleavage study of triazene containing sulfathiazole derivatives ST(1-11). Cp; circular plasmid, c; control (contains circular plasmid, 0.4 M DMSO and 10 mM TrisHCl/1 mM EDTA buffer pH 8.0, 1-12; ST series compounds 1 to 12. Each one contained 50 µM of the complex dissolved in 25 µM in 10 mM TrisHCl/1 mM EDTA buffer pH 8.0, 0.4 M DMSO.

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According to our results presented in Figure 1, the addition of hydroxyl radical scavengers (lane 2) significantly attenuates DNA strand scission. A decrease in the percentage of form I was observed in compounds (Figure 1). **ST-2** caused only the formation of Form II. **ST-1**, **ST-4**, **ST-5**, b, and **ST-11** caused the formation of Form II and Form III together in the presence of DMSO. On the other hand, **ST-3** and **ST-6** showed Form I and Form II configuration occured together. **ST-10** had an interesting formation in which any DNA fragment was seen was similar to the control group that was the lack of any compounds. The result of the plasmid DNA cleavage activity of our re-synthesized triazene containing sulfathiazole derivatives revealed that our compounds are effective in DNA cleavage with the help of hydroxy radicals.

Conclusion

Herein, we report a series of 1,3-diaryltriazene-substituted sulfathiazole derivatives, which were re-synthesized for their antibacterial, DNA cleavage, and antioxidant properties. Two Gram-positive (*Staphylococcus aureus, Enterococcus faecalis*) and two Gram-negative bacteria (*Pseudomonas aeruginosa, Escherichia coli*) were used for antibacterial testing and in general most of the compounds showed moderate to high antibacterial activity as compared with standard sulfathiazole. More specifically, compounds **ST-4** and **ST-10** have MIC values of 15.6μg/mL against Gram (-) bacteria strain P. aeruginosa. On the other hand, all compounds showed no DPPH free radical scavenging and metal chelating activity by having IC_{50} value of >1000μM. The re-synthesized compounds were more susceptible to ABTS cation radical decolarization and CUPRAC assays. Also, our compounds were efficient in DNA cleavage activity. As a result, these types of compounds might be investigated and improved as potent and effective antibacterial agents.

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