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Synthesis, characterization and investigation of antibacterial and antifungal activities of novel 1,3-butadiene compounds

Serdar Goksin Aydinli[a], Yasemin Ozdamar[a], Cigdem Sayil[a], Nahide Gulsah Deniz[a], Maryna Stasevych[b], Viktor Zvarych[b], Olena Komarovska-Porokhnyavets[b], and Volodymyr Novikov[b]

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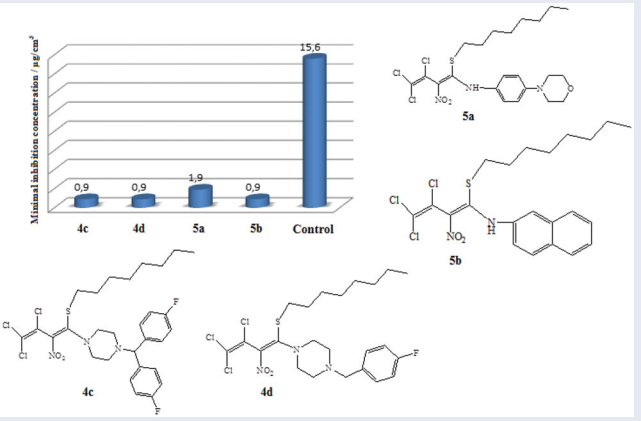
ABSTRACT

The nitro group–substituted perhalogenobuta-1,3-diene (**1**) is important synthetic precursor in the synthesis of different heterocycles groups with high biological activity. Firstly, new N,S-substituted-perhalonitro-1,3-butadiene compounds were synthesized by the reactions of various amino or thiol containing nucleophiles with **1**. The structures of all new compounds have been identified by using spectroscopic techniques (FT-IR, ^{1}H-NMR, ^{13}C-NMR, MS and microanalysis). Secondly, their antimicrobial properties were tested as potential antibacterial and antifungal agents. Antimicrobial activity of synthesized N,S-substituted perhalonitrobutadienes **4a–j** and **5a–d** was evaluated against *Escherichia coli* B-906, *Staphylococcus aureus* 209-P, and *Mycobacterium luteum* B-917 bacteria and *Candida tenuis* VKM Y-70 and *Aspergillus niger* F-1119 fungi and the compounds **4c**, **4d**, **5a** and **5b** with high antifungal action against test-culture *Aspergillus niger* at MIC values 0.9–1.9 μg/cm^3 were identified as the most potent.

GRAPHICAL ABSTRACT



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KEYWORDS

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Introduction

The chemistry of nitro group–substituted perhalogeno-1,3-butadienes has been widely studied over the years. Particular interest in this class of compounds mainly arises from their modifiability potential as multi directional starting materials in the synthesis of various heterocycles groups with high biological activity. An additional nitro substituent to perhalobutadienes to provide the corresponding perhalonitrobutadienes effecting the biological activity and also addition of halogens to conjugated systems should increase the chemical stability of these compounds due to the steric and electronic properties of the halogen atom. So, perhalogeno-1,3-butadienes turn into powerful electrophiles that react well with nucleophiles. The conjugated systems of butadiene unit are often structural components of most bioactive active compounds, including intermediates and natural products, as well as pharmaceuticals. Most perhalonitro-1,3-butadiene derivatives show biological activity as a drug or plant protective agent.[1–6]

The six-membered saturated moiety containing nitrogen atoms as some morpholine, thiomorpholine and piperazine analogs have been reported as a great interest for their biological activities in a number of different therapeutic areas such as anticancer, antifungal, antibacterial and antimalarial.[7–8] These heterocyclic amine derivatives owing to important activity properties are also used in psychological and neurological researching fields to obtain the new molecules with more better biological effect as to treat disorders like psychosis, schizophrenia, depression and anxiety.[9–10]

Perhalonitro-1,3-butadienes readily reacts with various thiols or secondary aliphatic amines, such as morpholine, thiomorpholine and piperazine. Thus, N,S-substituted perhalonitro-1,3-butadiene derivatives can be obtained by the click synthesis of polyhalonitro-1,3-butadiene with nucleophilies in nucleophilic vinylic substitution reaction. So, the synthesis of hetero group substituted 1,3-butadine compounds starts with nucleophile attack as thiols or amines to perhalonitrobutadiene molecules. Some of the S-, S,S- and N,S-substituted perhalonitrobutadiene derivatives have been synthesized in the literature before.[11–28]

Firstly, the aim of this study was the synthesis of new N,S-substituted-nitro-1,3-butadiene compounds and characterization of their structures by using the various spectroscopic techniques. We inspired by the biological importance of mono-(S)-substituted-nitro-1,3-butadiene compounds and nucleophilies such as piperazine, aniline, thiol, etc. Secondly, we know that there were very few related literature on investigation of biological properties of 1,3-butadiene compounds that allowed us to synthesize new N, S-substituted butadiene compounds. It should be noted, that only two works about biological properties of N,S-substituted-1,3-butadiene compounds, which belong to our group, was published.[14,19] Therefore, the aim of our study was the synthesis and characterization of novel N,S-substituted perhalo-nitro-1,3-butadiene compounds and their study as perspective antibacterial and antifungal agents.

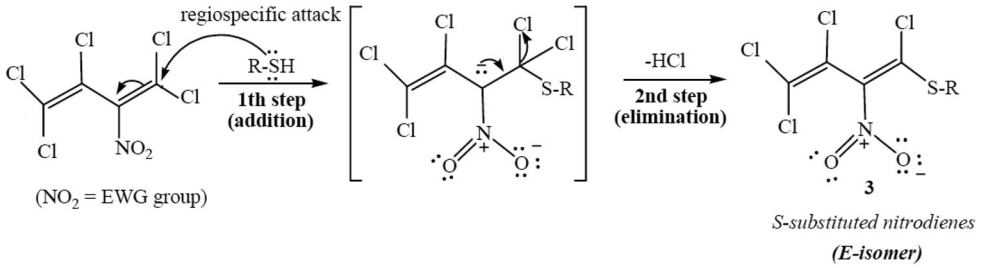
Results and discussion

Chemistry

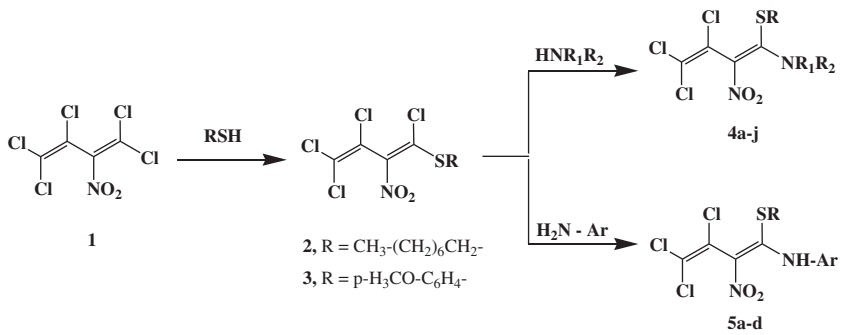
The SN_{vin} reactions of the nitro-substituted perhalobuta-1,3-diene (**1**) with one molar equivalent of thiols such as 1-octanethiol or 4-methoxythiophenol without any solvent gave

mono(thio)substituted perhalonitrobutadienes (**2** and **3**) at room temperature. The nitro-substituted perhalobuta-1,3-diene which are interesting with their electronic structure can be used for different synthetic applications because the reactions can be carried out by various methods with nucleophilic vinylic substitution (SN_{Vin}) via additional-elimination routes. The proposed mechanism for the synthesis of mono-*S*-substituted nitrodienes was given on the Scheme 1. These substitution reaction continues with the addition-elimination reaction mechanism (Scheme 1). First, the reagent attacking the C, C double bond is added, and in a second step the intermediate is stabilized by removing hydrogen chloride.

2-Nitro-1,3,4,4-tetrachloro-1-octylthio-1,3-butadiene (**2**)[27] and 2-nitro-1,3,4,4-tetrachloro-1-(4-methoxyphenylthio)-1,3-butadiene (**3**)[28] reacted with the piperazine derivatives to give the new compounds **4a–j** and with amine derivatives to give the new compounds **5a–d** (Scheme 2). We know that mono- and N,S-substituted nitrobutadiene compounds yielded as a single *E*-isomer instead of mixture of *E/Z* isomer according to our previously related literature.[18–21,29–37] The exact structures of our mono- and N,S-substituted nitro butadiene compounds were investigated by all spectroscopic data and also especially X-ray single-crystal diffraction method in our previously literature.[34–36] In the crystal structures of mono(thio)- and N, S-substituted nitrodienes reported in



Scheme 1. The proposed mechanism for the synthesis of *S*-substituted nitrodienes [18].



4a: R = CH_3-$(CH_2)_6CH_2$-, R_1R_2 = furan-3-carbonyl piperazino
4b: R = CH_3-$(CH_2)_6CH_2$-, R_1R_2 = 3,4-dichlorophenyl piperazino
4c: R = CH_3-$(CH_2)_6CH_2$-, R_1R_2 = bis(4-fluorophenyl)methyl piperazino
4d: R = CH_3-$(CH_2)_6CH_2$-, R_1R_2 = 4-fluorobenzyl piperazino
4e: R = CH_3-$(CH_2)_6CH_2$-, R_1R_2 = 2-pyridyl piperazino
4f: R = p-H_3CO-C_6H_4-, R_1R_2 = furan-3-carbonyl piperazino
4g: R = p-H_3CO-C_6H_4-, R_1R_2 = 3,4-dichlorophenyl piperazino
4h: R = p-H_3CO-C_6H_4-, R_1R_2 = bis(4-fluorophenyl)methyl piperazino
4i: R = p-H_3CO-C_6H_4-, R_1R_2 = 4-fluorobenzyl piperazino
4j: R = p-H_3CO-C_6H_4-, R_1R_2 = 2-pyridyl piperazino

5a: R = CH_3-$(CH_2)_6$-CH_2-, Ar = 4-morpholino anilino
5b: R = CH_3-$(CH_2)_6$-CH_2-, Ar = 2-naphthyl amino
5c: R = p-H_3CO-C_6H_4-, Ar = 4-morpholino anilino
5d: R = p-H_3CO-C_6H_4-, Ar = 2-naphthyl amino

Scheme 2. Synthesis of S- and N,S-substituted-2-nitro-1,3-butadienes (**4a–j** and **5a–d**).

our previous studies, it was proved that mono(thio)substituted nitrobutadienes were *E*-isomers and N, S-substituted nitrobutadienes were also *E*-isomers.[18–21,24,29–36] As a consequence, it might be thought that the derived new nitrodiene products were probably *E*-isomers.

In the IR spectra of synthesized compounds **4a–j** and **5a–d** symmetrical vibrations of nitro groups appear as strong bands in the region 1235–1294 cm^{-1}, to asymmetrical vibrations correspond the bands within 1504–1548 cm^{-1}. The IR spectra showed a characteristic >C=O band at 1713 cm^{-1} for **4a** and at 1749 cm^{-1} for **4f**. In compounds **5a–d**, the (N-H) stretching bands occur at 3165 cm^{-1}, 3172 cm^{-1}, 3150 cm^{-1} and 3177 cm^{-1}, respectively.

In the ^{1}H NMR spectra of compounds synthesized **4a–j** and **5a–d**, aromatic protons usually show up in the range of $\delta = 6.30–8.30$ ppm and compounds **4a**, **4b**, **4c**, **4d**, **4h** and **4i** which contain the piperazine ring, the piperazine ring protons were observed as two broad singlet in the regions at $\delta = 2.12–3.73$ and $\delta = 3.52–3.98$ ppm, respectively. In compound **4e**, piperazine protons were observed as one broad singlet in the region at $\delta = 3.74$ ppm. In compounds **4f** and **4j**, piperazine protons appear as multiplet in two regions at $\delta = 3.46–3.58$ and at $\delta = 3.00–3.75$ ppm, respectively. In compound **4g**, piperazine protons were observed as one broad singlet and multiplet in two regions at $\delta = 2.91$ ppm and $\delta = 3.55–3.70$ ppm, respectively. In compounds **5a** and **5c** which contain the morpholine ring showed the morpholine ring protons (N-CH_2 and O–CH_2) as two signals as tertiary at $\delta = 3.22$, 3.89 and at $\delta = 3.13$, 3.87 ppm, respectively. Compounds **5a-d** gave a characteristic singlet bands at $\delta = 12.04$, 12.16, 11.72 and 11.84 ppm for the protons of the (–NH) group, respectively.

In the ^{13}C NMR spectra of compounds **4a–j** signals were observed at $\delta = 44.11–53.41$ ppm for the methylene carbon atoms of the piperazine ring and also for the compounds **5a** and **5j**, signals were observed at $\delta = 48.65–68.13$ ppm for the methylene carbon atoms of the morpholine ring. For the compounds **4a** and **4f**, due to the aromatic ring of furoyl, signals for were observed at $\delta = 147.22$ and $\delta = 147.24$ ppm for the furoyl (C–O) carbons and $\delta = 158.97$ and $\delta = 166.06$ ppm for carbonyl (>C=O) carbons, respectively.

The MS[+ESI] mass spectrum of the compounds **4b** and **4g**, the respective molecular ion peaks was observed at *m/z* (%) 575.9 (100) $[M]^+$ and *m/z* (%) 569.8 (100) $[M]^+$, respectively. The compounds **4a**, **4c**, **4d**, **4f** and **4h** revealed at *m/z* (%) 547.9 (100) $[M+23]^+$, *m/z* (%) 655.9 (100) $[M+23]^+$, *m/z* (%) 561.9 (100) $[M+23]^+$, *m/z* (%) 541.9 (100) $[M+23]^+$ and *m/z* (%) 649.8 (100) $[M+23]^+$, respectively which corresponds to the addition of one sodium ion. The results of MS[+ESI] mass spectrum of all the remaining compounds agree well with corresponding fragments in similar compounds.

Antibacterial and antifungal activities

New synthesized N,S-substituted-polyhalo-2-nitro-1,3-butadiene compounds **4a–j** and **5a–d** were evaluated for their antibacterial and antifungal activity against test cultures of *Escherichia coli* B-906, *Staphylococcus aureus* 209-P, and *Mycobacterium luteum* B-

917 bacteria and *Candida tenuis* VKM Y-70 and *Aspergillus niger* F-1119 fungi using diffusion method[38] and serial dilution method[39] to search new perspective antimicrobial agents. Results of the biological study were presented in Tables 1 and 2. Biological activities of heteroatom-substituted 1,3-butadiene compounds **4a–j** and **5a–d** were compared with the known antibacterial agent vancomycin and antifungal agent nystatin (as control C).

The *S. aureus* bacteria strain was sensitive to compound **5b** at a concentrations of 0.5% and 0.1% and the diameter of the inhibition zone was 15.0 and 13.0 mm, respectively. Compounds **4a–j** and **5a–d** (at 0.1% concentration) have no antibacterial and antifungal activity against *E. coli, M. luteum* bacteria and *C. tenuis* fungus (using diffusion method, Table 1). Compounds **5b** and **5d** have moderate activity against test culture *M. luteum* (10.0 mm at a concentration of 0.5%). For compounds **4a–j** and **5a–d**, antifungal activity against *A. niger* was observed between 7.0 and 10.0 mm at concentrations of 0.5% and 0.1%. The *S. aureus* bacteria strain was sensitive to compound **5d** at a concentration of 0.5% and the diameter of the inhibition zone was 13.0 mm (Table 1).

The biological activity results of the synthesized compounds (**4a–j** and **5a–d)** using serial dilution method were classified as follows: the antibacterial/antifungal activity was considered as significant, when the minimum inhibition concentration (MIC) was

Table 1. Antimicrobial activity of the synthesized compounds determined by diffusion method.

		Inhibition diameter of microorganism growth, mm				
		Bactericidal activity			Fungicidal activity	
Compound	Concentration/%	*E. coli*	*S. aureus*	*M. luteum*	*C. tenuis*	*A. niger*
4a	0.5	0	0	0	0	7.0
	0.1	0	0	0	0	0
4b	0.5	0	0	0	0	10.0
	0.1	0	0	0	0	0
4c	0.5	0	0	0	0	10.0
	0.1	0	0	0	0	7.0
4d	0.5	0	0	0	0	10.0
	0.1	0	0	0	0	7.0
4e	0.5	0	0	0	0	10.0
	0.1	0	0	0	0	8.0
4f	0.5	0	0	0	0	7.0
	0.1	0	0	0	0	0
4g	0.5	0	0	0	0	10.0
	0.1	0	0	0	0	0
4h	0.5	0	0	0	0	7.0
	0.1	0	0	0	0	0
4i	0.5	0	0	0	0	7.0
	0.1	0	0	0	0	0
4j	0.5	0	0	0	0	10.0
	0.1	0	0	0	0	0
5a	0.5	0	0	0	0	7.0
	0.1	0	0	0	0	0
5b	0.5	0	15.0	10.0	0	10.0
	0.1	0	13.0	0	0	7.0
5c	0.5	0	0	0	0	10.0
	0.1	0	0	0	0	8.0
5d	0.5	0	13.0	10.0	0	10.0
	0.1	0	0	0	0	7.0
C*	0.5	14.0	15.0	18.0	19.0	20.0

*Vancomycin was used as a control in the tests of antibacterial activity of the synthesized compounds and Nystatin was used in the tests of antifungal action.

Table 2. Bactericidal and fungicidal activity of the synthesized compounds determined by serial dilution method (only compounds with positive results are included in the table).

	Minimal inhibition concentration MIC, μg/cm^3				
Compound	*E. coli*	*S. aureus*	*M. luteum*	*C. tenuis*	*A. niger*
4c	+	+	+	+	0.9
4d	+	+	+	+	0.9
5a	+	+	+	+	1.9
5b	+	62.5	125.0	+	0.9
5d	+	500.0	500.0	+	+
C*	31.2	3.9	7.8	7.8	15.6

*Vancomycin was used as a control in the tests of antibacterial activity of the synthesized compounds and Nystatin was used in the tests of antifungal action.
"+" - Growth of microorganisms

100 μg/cm^3 or less; moderate, when the MIC was 100.0–500.0 μg/cm^3; weak, when the MIC was 500.0–1.000 μg/cm^3; and inactive when the MIC was above 1.000 μg/cm^3. Vancomycin and nystatin were used as controls. Evaluation of antibacterial activity of synthesized compounds **5b** and **5d** showed that **5b** and **5d** have MIC = 62.5 and 500.0 μg/cm^3, for *S. aureus* and also have MIC = 125.0 μg/cm^3 and 500.0 μg/cm^3 for strain of *M. luteum* bacteria (using serial dilution method, Table 2). Compounds **4c**, **4d**, **5a**, **5b** and **5d** have no antimicrobial activity against Gram-negative bacteria *E. Coli*. The only compounds **4c**, **4d**, **5a**, **5b** and **5d** with positive results are included in the Table 2.

Investigation of the antifungal activity of the synthesized compounds showed that **4c, 4d**, **5b** and **5a** were the most potent for fungus *A.niger* with MIC = 0.9 μg/cm^3 and 1.9 μg/cm^3, respectively. Compounds **4c**, **4d**, **5a** and **5b** (Fig. 1) had more lower MIC values against test culture of *A.niger,* when nystatin (control) has MIC = 15.6 μg/cm^3 (Fig. 2). It was determined, that these compounds have no antifungal activity against *C. tenuis* fungus.

Therefore, octylthio and piperazine ring substituted polyhalo-nitro-1,3-butadiene derivatives **4c**, **4d**, **5a** and **5b** have synthesized that are the good promising candidates with respect to biological activity as potential antifungal agents against *A. niger* (Figs. 1, 2).

Materials and methods

Apparatus

Melting points were measured on a Buchi B-540 melting point apparatus. TLC plates silica 60 F_{254} (Merck, Darmstadt), detection with ultraviolet light (254 nm). Elemental analyses were performed on a Thermo Finnigan Flash EA 1112 Elemental analyzer. Infrared (IR) spectra were recorded in ATR method on a Perkin Elmer Precisely Spectrum One FTIR spectrometry. ^{1}H and ^{13}C NMR spectra were recorded on Varian UNITYINOVA operating at 500 MHz. Mass spectra were obtained on a Thermo Finnigan LCQ Advantage MAX LC/MS/MS spectrometer according to ESI probe. Products were isolated by column chromatography on Silica gel (Fluka Silica gel 60, particle size 63–200 μm). All chemicals were reagent grade and used without further purification. Moisture was excluded from the glass apparatus using $CaCl_2$ drying tubes.

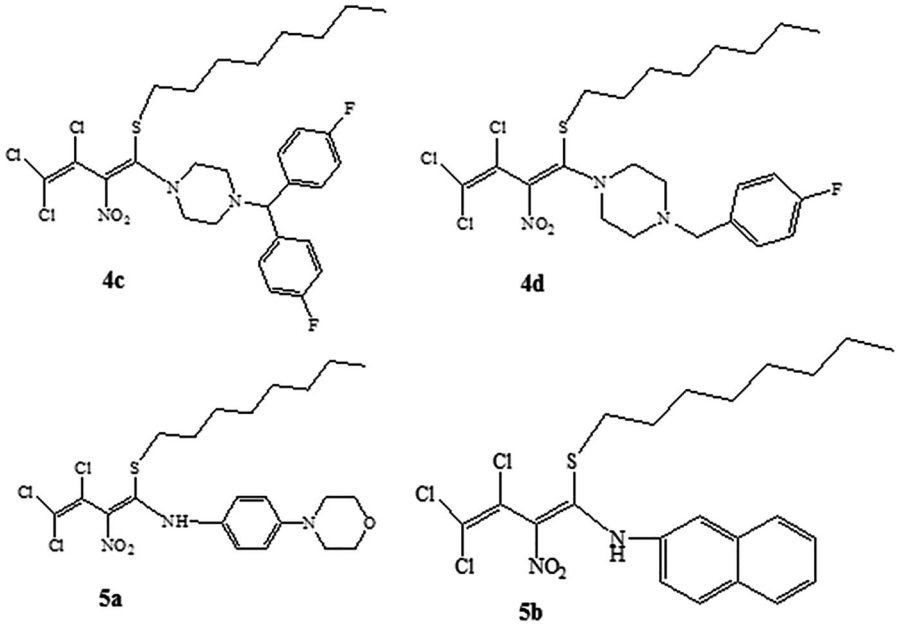


Figure 1. Structures of **4c**, **4d**, **5a** and **5 b** as potential antifungal agents against test-culture *A. niger*.

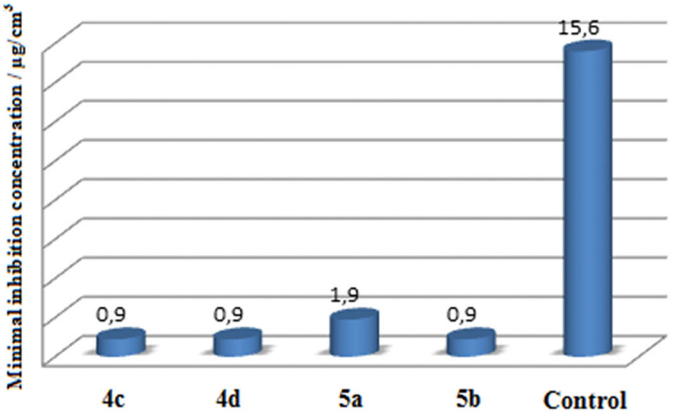


Figure 2. Minimal inhibition concentrations (µg/cm^3) of **4c**, **4d**, **5a**, **5 b** and Nystatin against test-culture *A. niger*.

Solvents, unless otherwise specified, were of reagent grade and distilled once prior to use.

Synthesis

Preparation of compounds (4a–j and 5a–d)

As starting materials, 2-nitro-1,3,4,4-tetrachloro-1-octylthio-1,3-butadiene (**2**) and 2-nitro-1,3,4,4-tetrachloro-1-(4-methoxyphenylthio)-1,3-butadiene (**3**) were prepared from reactions of pentachloro-2-nitro-1,3-butadiene (**1**) with alkylthiols.[26–28] To a solution

Table 3. Parameters of results evaluation by the method of compound diffusion in agar.

Zone diameter of microorganisms growth inhibition, mm	Degree of microorganism sensitivity
11–15	Low sensitive
16–25	Sensitive
>25	Highly sensitive

of **2** or **3** in 10 mL of dichloromethane as a solvent was added in equimolar amount with vigorous stirring the respective aromatic and heterocyclic amine derivatives in 10 mL of dichloromethane at room temperature until completion of the reaction. The mixture was stirred for 4 h and the crude products were extracted with chloroform (3×50 mL). The combined organic phases were washed with water (2×30 mL) and dried over anhydrous calcium chloride or magnesium sulfate in vacuo. The products were purified by column chromatography over silica gel.

Biological studies

Determination of antimicrobial and antifungal activity by diffusion method in agar

Antimicrobial and antifungal activity has been studied by diffusion in agar on solid nutrient medium (beef-extract agar for bacteria, wort agar for fungi). Petri plates containing 20 mL of nutrient medium were used for all the microorganism tested. The inoculums (the microbial loading – 109 cells (spores)/1 mL) was spread on the surface of the solidified media and Whatman no.1 filter paper disks (6 mm in diameter) impregnated with the test compound (0.1 and 0.5%) were placed on the plates. The duration of bacteria incubation was 24 h at 35°C and of fungi incubation 48–72 h at 28–30°C. The antimicrobial effect and degree of activity of the tested compounds were evaluated by measuring the zone diameters and the results were compared with well-known drugs (Table 1). Every experiment was repeated three times. Parameters of results evaluation by the method of compound diffusion in agar were given on the Table 3.

Determination of minimal inhibitory (MIC) concentrations using serial dilution method

The tested compounds were added to the nutrient medium (beef-extract broth for bacteria and wort for fungi) as solutions in dimethyl sulfoxide (DMSO) in ensuring needed concentration (0.9–500.0 μg/mL). Bacteria and fungi inoculum was inoculated into nutrient medium (the microbial loading was 10^6 cells (spores)/1 mL). The duration of bacteria incubation was 24 h at 35°C and of fungi incubation 48–72 h at 28–30°C. The results were estimated by the microorganism growth measured by degree of microbial turbidity in nutrient medium. Minimal inhibitory concentration (MIC) of any compound is defined as the lowest concentration which completely inhibits visible growth (turbidity on liquid nutrient medium) (Table 2).

Conclusion

The aim of this study, firstly, we synthesized and characterized of novel N,S-substituted 2-nitro-1,3-butadiene compounds (**4a–j** and **5a–d)** by using SN_{Vin} reaction in moderate to good yields. Their structures were characterized by using the various spectroscopic techniques (FT-IR, ^{1}H-NMR, ^{13}C-NMR, MS and microanalysis). These derivatives were obtained as yellow solids or oils. We inspired by the biological importance of mono-(S)-substituted-nitro-1,3-butadiene compounds and also nucleophilies possessing bio-active such as piperazine, aniline, etc.

Second part of this study, the antimicrobial properties of the synthesized of new N,S-substituted were investigated such as antibacterial and antifungal properties. The study of synthesized compounds (**4a–j** and **5a–d)** for their *in vitro* antimicrobial and antifungal activity against bacteria *Escherichia coli B-906, Staphylococcus aureus 209-P, Mycobacterium luteum B-917* and fungi *Candida tenuis VCM Y-70, Aspergillus niger VCM F-1119* showed that the compound **5b** has good antibacterial activity against test culture *S. aureus* at concentration of 0.5% and the diameter of the inhibition zone was 15 mm using diffusion method (for vancomycin was 15 mm). Evaluation of the antifungal activity using dilution method (for control compound was 15.6 μg/cm^3) of the synthesized N,S-substituted 2-nitrodienes showed that compounds **4c**, **4d**, **5b** and derivative **5a** had high antifungal effect against *A. niger* with MIC 0.9 μg/cm^3 and 1.9 μg/cm^3, respectively. Therefore, we have synthesized a series of N,S-substituted-1,3-butadiene derivatives as potential anti-*Aspergillus* agents.

Full experimental detail, ^{1}H and ^{13}C NMR spectra, MS and FTIR spectra. This material can be found via the "Supplementary Content" section of this article's webpage.

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