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Original Article

Design, Synthesis, Spectral Characterization, and Study of Biological Effect of Novel *azobenzen-p,p'-di(2-amine-1,3,4-thiadiazol-5-yl*) Derivatives

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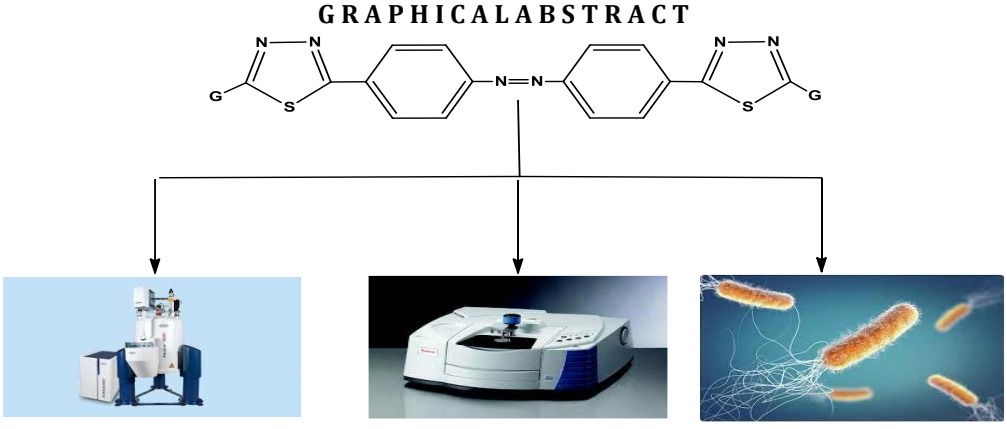
ABSTRACT

The compound azobenzen-p,p'-di(2-amine-1,3,4-thiadiazol-5-yl) (**A**) was formed by reacting 4,4'-(diazene-1,2-diyl)-dibenzoyl chloride with thiosemicarbazide. Ten substituted amino derivatives of azobenzen-p,p'-di(2-amine-1,3,4-thiadiazol-5-yl) were synthesized by reaction of compound (**A**) with formaldehyde and acetaldehyde to give Schiff base. The compound (**A**) reaction with sodiumcyanat and potassiumisothiocyanat gave uredo and thiouredo-1,3,4-thiadizol-5-yl. However, its reaction with benzenesulphonyl chloride and 4-methyl benzene sulphonyl chloride gave sulphonamido compounds, while its reaction with acetylchloride and benzoyl chloride gave acetamido and benzamido derivatives. Its reaction with succinic and glutaric acid gave succinamido and glutaramido, in a 1:2 molar ratio, respectively. All these compounds were characterized by FT-IR, ^{1}H-NMR, ^{13}C-NMR, CHN, and mass spectral analyses. Azobenzen-p,p'-di(2-amine-1,3,4-thiadiazol-5-yl) and its derivatives were examined against two types of *Escherichia coli* gram-negative and *Staphylococcus aurous* gram- positive bacteria and one type of fungus pincilium, the results showed good to moderate strength towards the biological activity comparison with amoxicillin and tetracycline pharmaceutical compounds.

GRAPHICAL ABSTRACT



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Introduction

The organic thiazide compounds are bicyclic structures containing adjacent nitrogen and sulfur atoms on the same ring. There are many previously prepared heterocyclic compounds that showed the good biological activity, especially those among them that are 2,5-disabstituted 1,3,4-thiadiazole, and most likely this activity is due to the -N=C-S-group, which prompted researchers to study its therapeutic importance and the development of selective molecules in which the substituent can be arranged in a pharmacological pattern to exhibit higher pharmacological activities [1-3]. Therefore, many drugs are available that contain the thiazole ring in their composition, such as acetazolamide, carbonic anhydrase inhibitors, and metazolamide [4, 5]. In recent years, the presence of many prepared compounds with a 1,3,4-thiadiazole ring in their main structure has made them able to perform various important pharmacological activities [2-4]. Thiadazole compounds have piqued the interest of chemists due to their biological activity, many of which exhibit antifungal [3, 4], anti-asthmatic [3, 4], anti-parkinsonism [4, 5], anticonvulsant [6], antitumor [7-11], analgesic [12, 13], anti-tubercular [15], antibacterial, and anticancer [16]. The azo compounds, which are prepared by coupling the intermediate diazonium compounds with different aromatic compounds are among the most important industrial compounds used as dyes for many centuries because of their bright and shiny colors [17]. In recent decades, after the preparation of many azo compounds and their derivatives, whose biological effectiveness was tested, especially in metabolic processes [18], many azo derivatives were prepared [19]. Azo and azomethine groups on the azo Schiff base bonds are oriented in such a way that coordination of the two groups to a metal ion is not possible. Thus, the preferential coordination of the azomethine group was observed, while the azo group was left free and uncoordinated [20]. Also, azo compounds were prepared from peanut peel extract, which are agricultural waste and a source of flavonoids used as a corrosion inhibitor in paints and anti-corrosion pigments for the surface coatings. Due to their optical and electrical properties, azobenzene derivatives are an important group of compounds that find applications in various fields [19]. Due to the controllability of trans-cis isomers, azo-bearing structures are an ideal building block for developments such as the smart polymers, nanocomposites, and sensors. The large cyclic compounds that are well-known for their interesting binding properties, super-molecular structure formation, switching, and movement also play an important role [21]. In the present study, a series of novel 1,2,3-thiodizol derivatives containing the azo ring at the C-4 position was developed by using both conventional preparation methods and studying their biological efficacy.

Materials and Methods

In this work, all chemicals used and their suppliers are utilized as received without further purification: P-nitrobenzoic acid from Riedal-Dehaen 99%, glucose from pharmaceutical drug Samara PDS 99%, thiosemicarbazide from Aldrich 99%, and dimethylsulfoxide (DMSO) at 99%. pyridine from BDH 95%, potassium thiocyanate and potassium cyanate from Riedal-Dehaen 99%, petroliumether (60-80) from BDH, ethylacetate from Aldrich, acetylchloride from CDH, benzoyl chloride from Aldrich, succinic and glutaric acid from Aldrich.

Preparation of 4,4'-(diazene-1,2-diyl)dibenzoylchloride

It was prepared by Khalil (2007), and Aiube (2017) [17, 18].

*Synthesis of azobenzen-p,p'-di(2-amine-1,3,4-thiadiazol-5-yl) (**A**)*

The classical or the main method of preparation of compound (**A**), by condensation reaction of thiosemicarbazide (0.182 g, 0.002 mol) with 4,4'-(diazene-1,2-diyl)dibenzoyl chloride (0.307 g, 0.001 mol), with phosphorus oxychloride and sulphuric acid as cyclizing agents: compound (**A**) was obtained with 0.38 g and yielded 83.7% (mp 333 °C).

Preparation of azobenzen-p,p'-di(2-amine-1,3,4-thiadiazol-5-yl) derivatives

*Preparation of azobenzen-p,p'-di(2,N-methyleneimino-1,3,4-thiadiazol-5-yl) (**AI**) and azobenzen-p,p'-di(2,N-ethyleneimino-1,3,4-thiadiazol-5-yl) (**AII**)*

A mixture of azobenzen-p,p'-di(2-amine-1,3,4-thiadiazol-5-yl) (0.380 g, 0.001 mol), formaldehyde or acetaldehyde (0.002 mol), in DMSO (20 mL), which was heated under reflux for 4-5 hours. The reaction completion was followed up using TLC by petroleumether: ethylacetate (6:4). The product was filtered, washed, and recrystallized by DMSO, to give compounds (**AI**) and (**AII**), 0.33, 0.41 g, yield 81.2, 88.5%, mp 223, 292 °C respectively.

*Preparation of azobenzen-p,p'-di(2,N-ureido-1,3,4-thiadiazol-5-yl) (**AIII**) and azobenzen-p,p'-di(2,N-thiouriedo-1,3,4-thiadiazol-5-yl) (**AIV**)*

To a round bottom azobenzen-p,p'-di(2-amine-1,3,4-thiadiazol-5-yl) (0.380 g, 0.001 mol), in DMSO (25 mL), glacial aceticacid (7 mL), sodiumcyanat solution (1.7 g, 0.002 mol) in distilled water (5 mL), was gradually added, and then the reaction mixture was refluxed for 4 hours, The reaction was completed using TLC and petroleum ether: ethylacetate (6:4). The product was filtered, washed, and recrystallized by DMSO. Compound (**AIII**) 0.4 g, yield 71%, melting point 220 °C. The same method was repeated to prepare the compound (**AIV**): sodium isothiocyanate (1.62 g, 0.002 mol), compound (**AIV**) 0.38 g, yield 68%, mp 270 °C.

*Preparation of azobenzen-p,p'-di(2,N-benzensulphonamido-1,3,4-thiadiazol-5-yl) (**AV**) and azobenzen-p,p'-di(2,N-toluenesulphonamido-1,3,4-thiadiazol-5-yl) (**AVI**)*

To a round bottom, azobenzen-p,p'-di(2-amine-1,3,4-thiadiazol-5-yl) (0.380 g, 0.001 mol), in DMSO (20 mL), pyridine (5 mL), and benzenesulfonylchloride (0.2 mL, 0.002 mol), was added in small portions, and then the mixture was refluxed for 8 hours. The completion of the reaction was followed up using TLC by petroleumether: ethylacetate (6:4). The product was cooled, filtered, and kept in the refrigerator for half an hour, and then washed, formed, and recrystallized by DMSO to give the compound (**AV**) 0.30 g, yield 40%, and mp 310 °C. The same method was repeated to prepare the compound (**AVI**) by used 4-methy benzenesulfonylchloride (0.002 mol), give 0.38 g, yield 55.7%, and mp 287 °C.

*Preparation of azobenzen-p,p'-di(2,N-acetamido-1,3,4-thiadiazol-5-yl) (**AVII**) and azobenzen-p,p'-di(2,N-benzamido-1,3,4-thiadiazol-5-yl) (**AVIII**)*

To a round bottom, add azobenzen-p,p'-di(2-amine-1,3,4-thiadiazol-5-yl) (0.380 g, 0.001 mol), in DMSO (25 mL) and distilled acetylchloride (0.25 mL, 0.002 mol) in 5 mL DMSO. The mixture was refluxed for 6 hours. The completion of the reaction was followed up using TLC with petroleum ether: ethylacetate (6:4). The product was cooled, filtered, and kept in a refrigerator for 12 hours, and then washed, formed, and recrystallized by DMSO to give compound (**AVII**) 0.34 g, yield 54%, mp 251 °C. The same method was repeated to prepare the compound (**AVIII**) by used benzoylchloride (0.002 mol), 0.22 g, yield 44 %, and mp 225 °C.

*Preparation azobenzen-p,p'-di(2,N-succinimido-1,3,4-thiadiazol-5-yl) (**AIX**) and azobenzen-p,p'-di(2,N-glutarimido-1,3,4-thiadiazol-5-yl) (**AX**)*

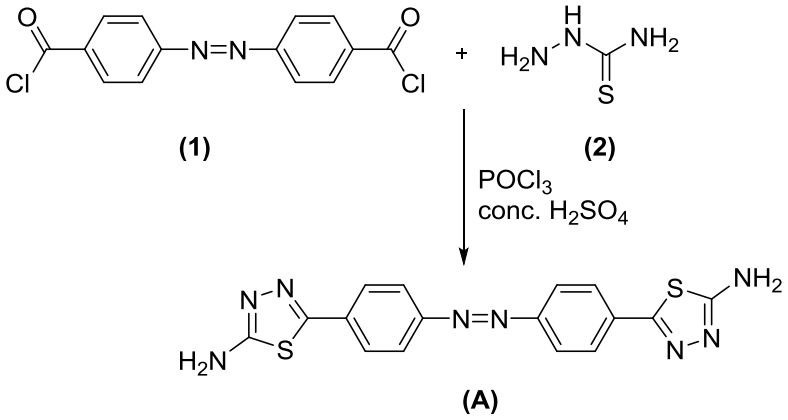
To a round bottom of azobenzen-p,p'-di(2-amine-1,3,4-thiadiazol-5-yl) (0.380 g, 0.001 mol), in DMSO (25 mL), and succinic acid (0.236 g, 0.002 mol). The mixture was refluxed for 6 hours, and then the reaction was completed using TLC and petroleum ether: ethylacetate (6:4). The product was cooled, filtered, and kept in the refrigerator for half an hour, washed, and recrystallized by DMSO to give the compound (**AIX**) 0.48 g, yield 71%, mp 249 °C. The same method was repeated to prepare the compound (**AX**) by used glutoric acid (0.264 g, 0.002 mol), 0.30 g, yield 55%, and mp 255 °C.

Results and Discussion

The literature in the recent years of the scientific research has shown that 1,3,4-thiadiazole has diverse biological effects, and the classical

methods of synthesis have attracted the interest of pharmacologists, chemists, and researchers. We synthesized new di(2,N-substituted-1,3,4-thiadiazol-5-yl) moieties grafted at para-positions of a bridged azobenzene molecule. Many di(2,N-substituted-1,3,4-thiadiazol-5-yl) moiety substituted at the (p,p)-position of the azobenzene molecule were prepared for synthesis [19], as depicted in the following preparation steps.

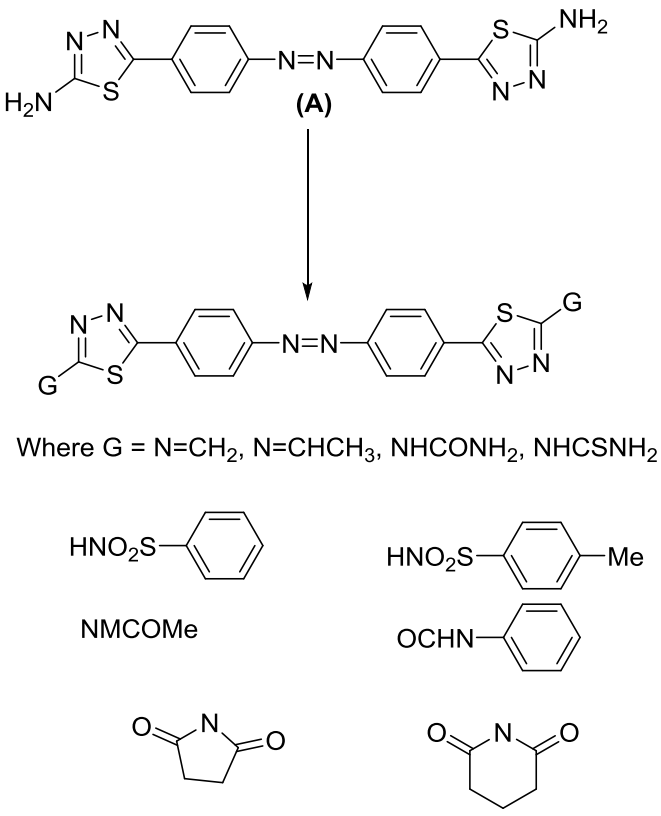
Heating thiosemicarbazide with 4,4'-(diazene-1,2-diyl)dibenzoylchloride the presence of H_2SO_4, showed the excellent yields of compound (**A**), which was diagnosed by CHN analysis and concurred with the data of the theoretical part. The FT-IR spectra showed NH_2 stretching bond vibration at 3300, 3220, and N=N 1450 cm^{-1}. ^{1}HNMR spectra showed (8 H, m) for an aromatic proton at 6.2-9.5 and an amine proton at 10.2 ppm. Aromatic carbons and C=N signals were detected in the ^{13}C-NMR spectrum at 121-153, and 158 ppm, respectively, as displayed in Scheme 1 and Table 1.



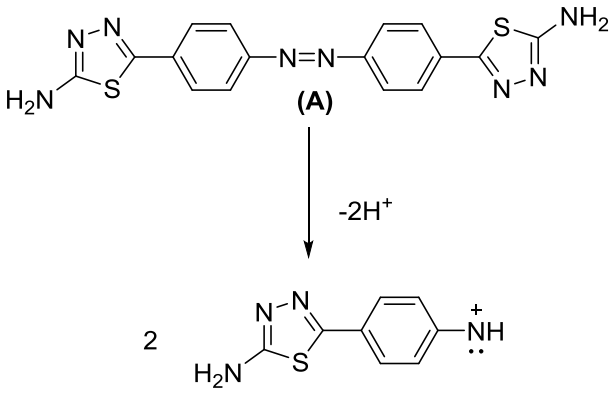
Scheme 1: Preparation of azobenzen-*p,p'*-di(2-amine-1,3,4-thiadiazol-5-yl) (**A**)

The ondensation of compound (**A**) with different-moiety compounds in a molar ratio of 1:2 gives azobenzen-p,p'-di(2N-substituted-1,3,4-thiadiazol-5-yl) derivatives (**AI-AX**), which were identified by IR spectra, and some of them were identified by CHN, ^{1}H-NMR, ^{13}C-NMR, and mass analyses. The FT-IR spectra of compounds (**AI-AX**) showed thiadiazol bonds C-S and C=N at rangs 970-965 and 1645-1555 cm^{-1} and azo stretching bonds (N=N) at ranges of 1458-1445 cm^{-1}, while starching bonds of the other derivative compounds are presented in Table 1. Compounds **V**(**I, III, V, VII**, and **IX**) ^{1}H-NMR spectra revealed an aromatic group connected with proton thiadizole as (8, m) at added 6.2-9.9 ppm. While, ^{13}C-NMR spectral analysis of compounds **A**(**I, III, V, VII**, and **IX**) revealed carbon thiadiazol aromatic signals C=N and C=O at 111-153, 160-179, and 153-158 ppm, respectively, as well as the other carbon signals of derivative compounds provided in Table 1 and Scheme 2.

The mass spectra of azobenzen-p,p'-di(2-amine-1,3,4-thiadiazol-5-yl) (**A**) revealed M+2 ions at m/z 406, whereas compound (**AIII**) revealed chip ions M+1 at m/z 466 and a chip ion at m/z 233. When interpreting the mass spectrum, we notice the fragmentation of this compound, which shows the possibility of ions decomposing the identical molecule due to the presence of the azo bridge connecting the compounds with some of them, which gives a suggestion that the fission is symmetric and the cleavage is equal [20], as demonstrated in the Scheme 3.



Scheme 2: Syntheses of azobenzen-*p,p'*-di(2-amine-1,3,4-thiadiazol-5-yl) derivatives **(AI-AX)**



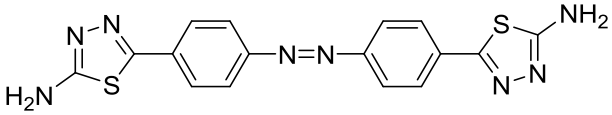
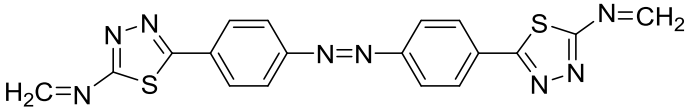
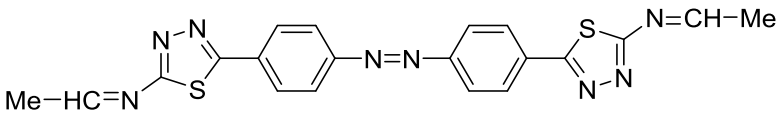
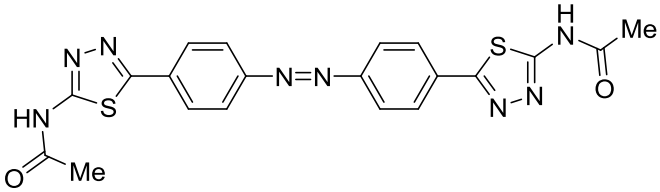
Scheme 3: Mass fragment of azobenzen-p,p'-di(2-amine-1,3,4-thiadiazol-5-yl)

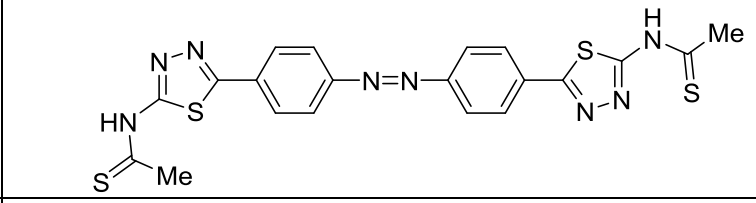
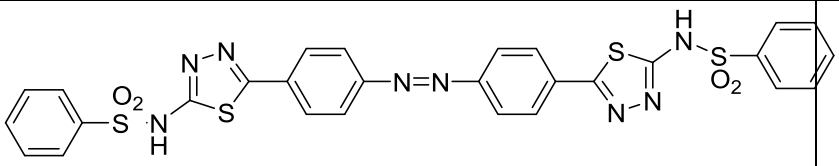
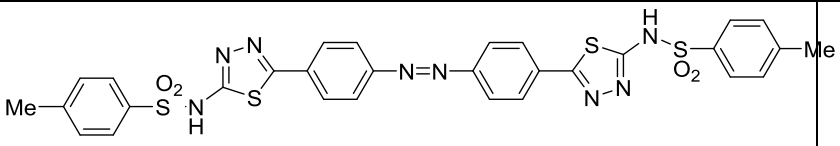
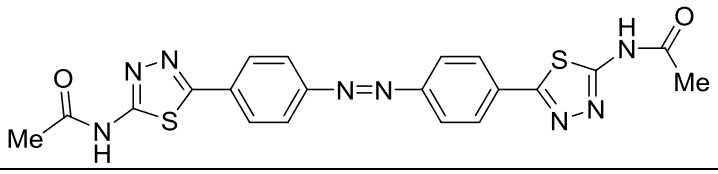
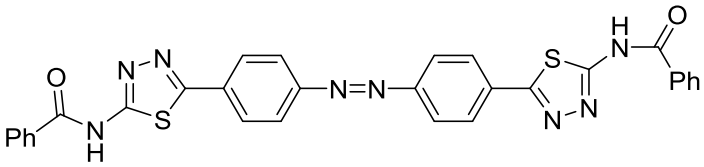
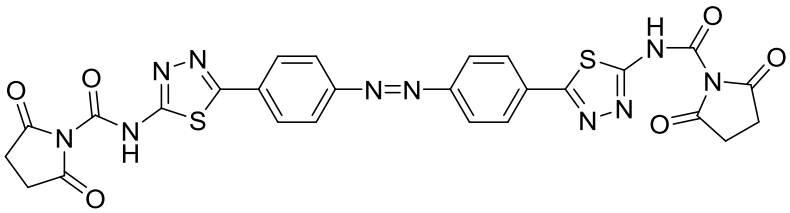
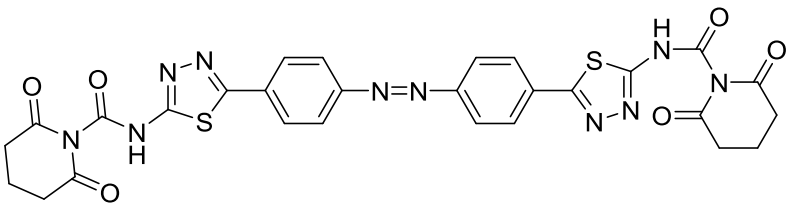
We tested azobenzen substituted thiadiazol and its derivatives against *E. coli* gram-negative and *Staphylococcus aureus* gram-positive bacteria. The results of the biological examination were compared with the antibiotics tetracycline and amoxicillin. When compared with the antibiotics, the results of some of the prepared compounds were found to be good to medium. The same is true when tested against fungi and compared with *Peneiclium* [21], as listed in Table 2.

Table 1: Spectroscopic characterization of azobenzen-*p,p'*-di(2-amine-1,3,4-thiadiazol-5-yl) and derivatives

FT-IR V (cm^{-1})					^{1}H-NMR (ppm)		^{13}C-NMR (ppm)			Analysis found/calculated		
No.	NH_2, NH	CH Ar.	C=O	N=N	CH Ar.	others	CH Ar.	C=N	C=O	C	H	N
A	3300-3220	3051	-	1450	6.2-9.9	8.2 (NH_2)	121-153	153	170	50.5/51.2	3.1/3.1	29.4/29.5
AI	-	3029,2890	-	1480	7.4-8.3	-	119-131	153	168	-	-	-
AII	-	3100-2920	-	1450	-	-	-	-	-	55.5-55.9	3.6/3.7	25.9/25.7
AIII	3433, 3213	3116	1680	1446	6.2-8.4	9.9, 10.7 NH & NH_2	112-152	152	179	-	-	-
AIV	3464 3236	3068	-	1455	-	-	-	-	-	43.3 44.1	2.9/2.8	28.1/28.3
AV	3210	3118	-	1454	7.3/9.9	10.5	111-153	158	170	-	-	-
AVI	3300	3105	-	1450	-	-	-	-	-	52.3/53	3.4/3.4	16.2/16.4
AVII	3398	3178	1670	1450	7.2-8.3	10.5	119-140	153	160	-	-	-
AVIII	3226	2995 3118	1680	1444	-	-	-	-	-	61.2/61.5	3.5/3.4	19/19.1
AIX	-	3095	1620	1450	6.3-8.8	-	119-153	153	162	-	-	-
AX	-	3036	1654	1458	-	-	-	-	-	54.5/54.7	3.5/3.4	19.5/19.6

Table 2: Antimicrobial activity of compounds (**A-AX**)

Compound No.	Compound Names	Average diameter of the retarding area (mm)		
		Staphylococcus aurous	*Escherichia coli*	*Peneicllium*
A		27	13	-
AI		5	8	-
AII		9	10	-
AIII		27	20	13

AIV		25	30	16
AV		20	10	15
AVI		18	8	25
AVII		15	-	10
AVIII		17	7	10
AIX		11	10	-
AX		15	12	-
Tetracycline	$C_{22}H_{24}N_2O_8$	+	–	-
Amoxicillin	$C_{16}H_{19}N_3O_5S$	+	++	-
DMSO	$C_2H_6O_2S$	0	0	0

Conclusion

The major product of the reaction of 4,4'-(diazene-1,2-diyl)-dibenzoyl chloride with thiosemicarbazide is azobenzen-p,p'-di(2-amine-1,3,4-thiadiazol-5-yl) was analyzed. After this, some of their derivatives were prepared. It was concluded that the addition of di(2-amino and/or 2-substituted amino thiadiazolyl) groups to the p.p.'-azobenzene moiety was required to increase the biological effect against gram-positive and gram-negative bacteria and fungi, as compared with the presence of one group of thiadizole in the other derivative compounds.

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Authors' contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

Conflict of Interest

The author declared that they have no conflict of interest.

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