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Investigation of the Antimicrobial Activities of Schiff Bases Containing Triazoles

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Abstract

Objective: Pathogen parasites and bacteria are microorganisms that have existed throughout human history and cause different diseases. Various antimicrobial agents have become one of the treatment options in the fight against these diseases. With the increase in the number of resistant microorganisms, existing agents became ineffective and there was a need to synthesize or produce new antibiotics, antiparasitic, antiviral and antifungal drugs. There are many studies showing that Schiff base derivatives have antimicrobial properties and proving the existence of their biological activities. In this study, it was aimed to determine the antimicrobial activity of two originally synthesized compounds, a triazole-containing Schiff base, against 16 different bacterial isolates and one different Leishmania species.

Methods: In our study, the biological activities of two different newly synthesized triazole-containing Schiff base derivatives against selected one Leishmania and 16 bacteria species were evaluated by the microdilution broth (alamar blue added) method. In the study, the in vitro antibacterial activities of the compounds were determined by measuring their Minimum Inhibitory Concentration (MIC) values.

Results: Leishmanicidal activity of *Leishmania infantum* parasite was determined by measuring its Leishmanicidal Concentration. The compounds were found to have antimicrobial activity against bacteria and parasite at different concentrations.

Conclusion: It was concluded that the in vitro antimicrobial activity results obtained in our study will be of significant benefit to future research due to the resistance detected against drugs used in the treatment of infectious diseases and health problems arising due to the side effects of the drugs. If in vivo animal experiments and toxicity studies are as expected; We believe that the in vitro antimicrobial activity results obtained in our study will make a significant contribution to future research due to the resistance detected against drugs used in the treatment of infectious diseases and the health problems caused by their side effects.

Keyword: Triazole-containing Schiff bases, antimikrobiyal activity, Leishmania infantum, MIC value

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INTRODUCTION

Infections have been seen since the beginning of humanity. Antibacterial agents have been used extensively for years, starting from the early 20th century. Bacteria have developed serious resistance over the years. Antibiotic resistance has also become a global problem today. Millions of people lose their lives due to different infections caused by bacteria. The loss of effectiveness of antimicrobial agents due to the rapid increase in the development of resistance of microorganisms to existing agents puts these drugs in danger (1). At the same time, the effects of these drugs lead to the failure of treatments associated with bacteria that are resistant to many drugs. With the emergence of antibiotic-resistant strains over the years, the production of different antimicrobial agents has increased (2). As a global consequence of this, alarming consequences arise for public health. Therefore, it is necessary to develop alternative antimicrobial drugs and to widely evaluate these drugs with antimicrobial susceptibility methods.

The Leishmania vector, a female phlebotomine sand fly, transmits parasites to humans during blood feeding (3). The disease affects both animals and humans (4). According to WHO, more than 98 countries and territories are endemic for leishmaniasis. Estimates suggest that 0.3 million new cases of visceral leishmaniasis (VL) and one million new cases of cutaneous leishmaniasis (CL) are diagnosed annually worldwide. The majority of cases are seen in countries such as Ethiopia, Syria, Bolivia, Brazil, Costa Rica, Iran, Peru, Sudan Nepal, Bangladesh, Colombia, India, and Algeria. Since our country is located in the Mediterranean basin, the disease is also seen in our country. Leishmaniasis is considered among the 6 most important infectious diseases worldwide (5). Visceral (VL, Kala-Azar) leishmaniasis is a highly fatal form that progresses in severe and untreated cases.

The disease has a geographical distribution in certain regions and is increasing due to climate change (6). There is no effective prophylactic vaccine against leishmaniasis yet. Due to the toxic side effects seen in the drugs used for treatment and the increased resistance seen in parasites, the discovery and development of new drugs is very important.

It has been reported that 1,2,4-triazole derivatives, among triazole-containing compounds, have significant antimicrobial, antituberculosis, anti-inflammatory, antihypertensive, antidepressant, enzyme inhibitor, antioxidant, and antitumor biological activities (7-9). Especially in the structure of drugs used as antifungal drugs today, there are structures containing imidazole, expressed as triazole and triazol-5-one nucleus or its bio isoester (10).

In this context, the study aimed to evaluate, for the first time, the antimicrobial activity of two originally synthesized compounds, triazole-containing Schiff bases, against 16 different bacterial isolates and one different Leishmania species.

METHODS

Supply of Triazole Schiff Some compounds

Compound I (5-methyl-4-((pyridin-4-ylmethylene)amino)-2,4-dihydro-3H-1,2,4-triazol-3-one) (Figure 1) and Compound II (5-benzyl-4- ((pyridine-4-ylmethylene)amino)-2,4-dihydro-3H-1,2,4-triazol-3-one) (figure 2) were previously synthesized and published in an article (11).

The antimicrobial activities of these compounds were evaluated in vitro against 16 standard ATCC bacterial isolates and 1 standard Leishmania isolate stored in the deep freezer. Bacterial isolates were obtained from the American Type Culture Collection (ATCC); ATCC 43300 Methicillin-resistant *Staphylococcus aureus* (MRSA), ATCC 29213 *Staphylococcus aureus*, ATCC 49619 *Streptecoccus pneumonia*, ATCC 13813 *Streptecoccus agalactiae*, ATCC 29212 *Enterococcus faecalis*, ATCC 700327 *Enterococcus casseliflavus*, ATCC 40247 *Haemophilus influenzae*, ATCC 700603 *Klebsiella pneumoniae*, ATCC 25933 *Proteus mirabilis*, ATCC 14028 *Salmonella typhimurium*, ATCC 13076 *Salmonella enterica*, ATCC 12022 *Shigella flexneri*, ATCC 9610 *Yersinia enterocolitica*, ATCC 8090 *Citorobacter freundii*, ATCC 13047 *Enterobacter cloacae*, ATCC 19606 *Acinetobacter baumannii*. The standard *Leishmania infantum* parasite isolate was included in the study.

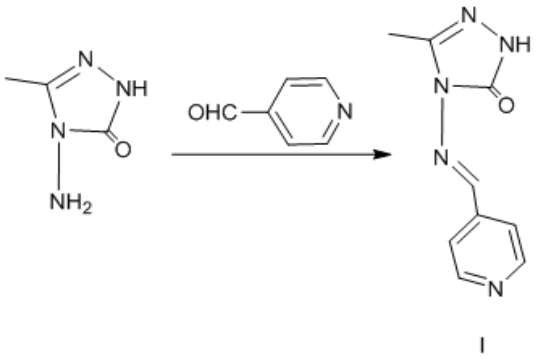

Figure 1. 5-methyl-4-((pyridin-4-ylmethylene)amino)-2,4-dihydro-3H-1,2,4-triazol-3-one

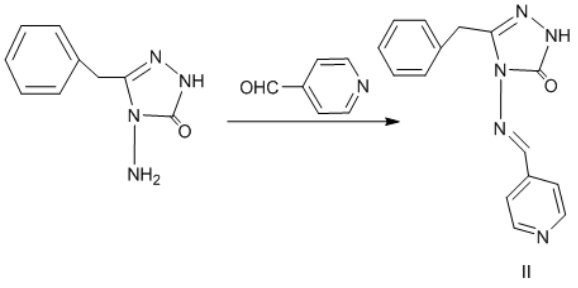

Figure 2. 5-benzyl-4-((pyridin-4-ylmethylene)amino)-2,4-dihydro-3H-1,2,4-triazol-3-one

Sixteen standard ATCC bacterial isolates stored in the deep freezer were removed from the freezer and thawed. After vortexing, the bacteria were passaged onto Blood Agar and Eosin Methilen Blue (EMB) Agar media using a sterile loop and cultured. The next day, the growths were checked, and their viability and purity were checked.

The synthesized compounds I and II, which were in powder form, were weighed and predissolved with dimethylsulfoxide. Then, distilled water was added, and the stock solution was diluted to 80 mg/ml. Compound solutions were sterilized by passing them through a membrane filter with a diameter of 0.45 micrometers.

In vitro Antibacterial Activity Test

The revived standard ATCC bacterial isolates were placed in a sterile tube containing 5 ml of physiological saline and mixed homogeneously. Bacterial density was adjusted in the McFarland device according to the McFarland 0.5 turbidity chart ($1.5x10^8$ CFU/ml).

Flat-bottomed 96-well sterile microplates were used to determine the minimum inhibitory concentration (MIC) of the compounds.

Briefly for antibacterial activity test; 100 µL of previously prepared and sterile MHB medium was added to all wells. 100 µL of the stock solution of the compound was added to the first well and mixed to ensure homogeneity. To dilute the compound concentration by 1/2, 100 µL was taken from the first well and transferred to the second well. This application was made in 10 wells. Thus, serial dilution of the compound was made in the microplates with a concentration range between 40 mg/ml and 78 µg/ml. Then, 100 µL of the previously prepared standard bacterial suspension was added to each diluted well and incubated. Wells 11 and 12 were used as negative and positive control wells, respectively. The microplate was incubated at 37°C in the incubator for 20 hours. When the incubation period was over, 20 µL of alamar blue was added to all wells and placed back in the incubator, and the color change was observed and waited for another 4 hours. During the evaluation of antibacterial activity, at the end of the incubation period, the indicator dye in the mixture in the wells turning pink was interpreted as positive bacterial growth, while the color of alamar blue remaining unchanged was interpreted as bacterial growth stopping. The last well in which the blue color did not change to the pink color was recorded as the MIC value. MIC values against all bacteria studied were determined by observation between approximately 21-24 hours. The antibacterial activity experiment of both compounds was repeated twice. In addition, Amikacin antibiotic was used as a standard drug for control purposes in the bacterial activity study.

In vitro Antiparasitic Activity Test

Whether compounds I and compound II had leishmanicidal activities on *L.infantum* promastigotes was evaluated by tests. In the study, for the culture of axenic standard *L.infantum* isolates 10% Fetal Bovine Serum, streptomycin, penicillin and fluconazole (100.000 units of penicillin, 10 mg streptomycin, fluconazole 2 mg/ml) were added to RPMI-1640 liquid medium to falcon tubes and kept at 26°C was also incubated. Reproducing parasites were washed three times in Phosphate Buffered Saline (PBS). Then, the final concentrations of promastigotes were adjusted by diluting them with RPMI-1640 medium using a thoma slide (hemocytometer) to $1x10^5$ cells.

Leishmanicidal activity in vitro

In the leishmanicidal activity (LA) study, stock solution concentrations of the compounds were prepared in the same way as for the antibacterial activity study. 100 µL of RPMI-1640 (FBS added) medium was added to all wells in the microplate. 100 µL of the stock solution of the sterile compound was added to the first well of the microplate and after mixing, 100 µL was taken from this well and transferred to the second well and diluted by 1/2. The application was made in this way, including the 10th well. The concentration range of the compounds was between 40 mg/ml and 78 µg/ml by serial dilution. 100 µl of *L. infantum* promastigotes was added to the wells. Negative control and positive control wells were added to the study. Microplates were incubated for 20 hours in the incubator at 26ºC. After 20 hours, 20 µl of sterile alamar blue (0.1 mg/ml) was added to all wells and incubated in the oven for another 4 hours at the same temperature. The results of the test were evaluated at the end of the 1st, 2nd, and 3rd day and the results were recorded. Microplates were incubated for 20 hours in the incubator at 26ºC. Amphotericin B was evaluated as the control drug in the study. The antiparasitic activity study was repeated twice. If the indicator dye turned pink at the end of the incubation period, it was interpreted as positive parasite growth, and if the dye remained unchanged, it meant that parasite growth had stopped. The last well in which the blue color did not change to pink color was recorded as the LA value. In addition, samples were taken from all wells, and the viability (motion) status of the promastigotes was evaluated under the microscope at forty-degree magnification between slides and coverslips and confirmed by comparing them with the alamar blue test results.

RESULTS

Antibacterial Activity Results

The 16 bacteria evaluated were studied in two different microplate groups. The 1st microplate *S. typhimurium, S. flexneri, E. faecalis, H. influenzae, S. enterica, K. pneumoniae,* MRSA and *S. aureus,* the 2nd microplate *Y. enterocolitica, C. freundii, E. clocae, A.*

baumannii, S. agalactiae, S. pneumoniae, E. caselliflavus, and *P. mirabilis* were present. Both compounds were found to be effective at different concentrations against 11 of the 16 bacterial isolates we studied. Since some bacteria have longer incubation periods, the positive controls were taken into consideration and incubated for another day and re-evaluated.

When the study results obtained after 48 hours were evaluated; Compound I exhibited antibacterial activity at different concentrations against MRSA, *S. aureus, S. pneumoniae, S. agalactiae, E. faecalis, E. casseliflavus, H. influenzae, S. flexneri, E. cloacae, C. freundii,* and *Y. enterocolitica* isolates. MIC values were found to be 625 µg/ml, 2500 µg/ml, <39 µg/ml, 312 µg/ml, 78 µg/ml, <39 µg/ml, <39 µg/ml, <39 µg/ml, 10.000 µg/ml , 312 µg/ml, and 312 µg/ml, respectively. It was determined that they had no antibacterial activity even at the highest compound concentrations studied against *S. typhimurium, S. enterica, K. pneumoniae, P.mirabilis,* and *A. baumannii* isolates. Compound II showed antibacterial activity at different concentrations against MRSA, *S. aureus, S. pneumoniae, S. agalactiae, E. casseliflavus, H.influenzae, S. typhimurium, S. flexneri, E. cloacae, C. freundii,* and *Y. enterocolitica* isolates. MIC values were found to be 625 µg/ml, 2500 µg/ml, <39 µg/ml, 312 µg/ml, <39 µg/ml, <39 µg/ml, 312 µg/ml, <39 µg/ml, 10000 µg/ml, 312 µg/ml, and 312 µg/ml, respectively. It was determined that they did not have antibacterial activities even at the highest compound concentrations studied against *E. faecalis, S. enterica, K. pneumoniae, P.mirabilis* and *A. baumannii* isolates. In Table 1, the determined MIC values of the compounds against all bacterial isolates studied are given (Table 1, Figure 3).

Leishmanicidal activity results

The antiparasitic activities of Compounds I and II against *L.infantum* promastigotes were determined in vitro by the alamar blue-supplemented broth microdilution method. In the evaluation of leishmanicidal activity, it was evaluated according to whether the indicator dye changed color or not. LA values obtained as a result of the test are given in Table 2. According to the data, Compound I was found to be effective against the studied leishmania specie at a concentration of 10000 µg/mL. It was observed that Compound II was effective against *L.infantum* promastigotes at the highest concentration studied (MIC: 20000). It was determined that amphotericin B, used as a control drug, was effective against leishmania specie, even at the lowest concentration studied (MIC: <39) (Table 2, Figure 4).

Table 1. The determined MIC values of the compounds against all bacterial isolates

Bacterial Isolates	MIC values (µg/ml)	
	Compound I	**Compound II**
Staphylococcus arueus (MRSA)	625	625
Staphylococcus aureus	2500	2500
Streptococcus pneumoniae	<39	<39
Streptococcus agalactiae	312	312
Enterococcus faecalis	78	>20000
Enterococcus casseliflavus	<39	<39
Haemophilus influenzae	<39	<39
Salmonella typhimurium	>20000	312
Salmonella enterica	>20000	>20000
Shigella flexneri	<39	<39
Enterobacter cloacae	10000	10000
Citrobacter freundii	312	312
Yersinia enterocolitica	312	312
Klebsiella pneumoniae	>20000	>20000
Proteus mirabilis	>20000	>20000
Acinetobacter baumannii	>20000	>20000

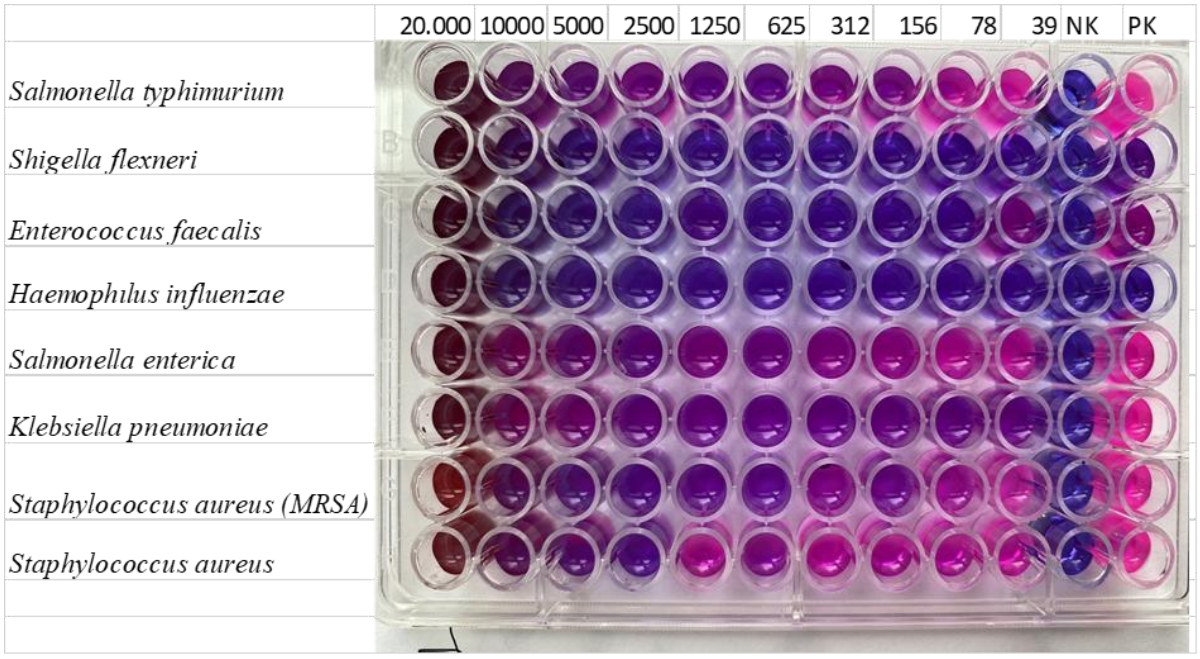

Figure 3. Antibacterial activities of Compound I against group 1 bacterial samples

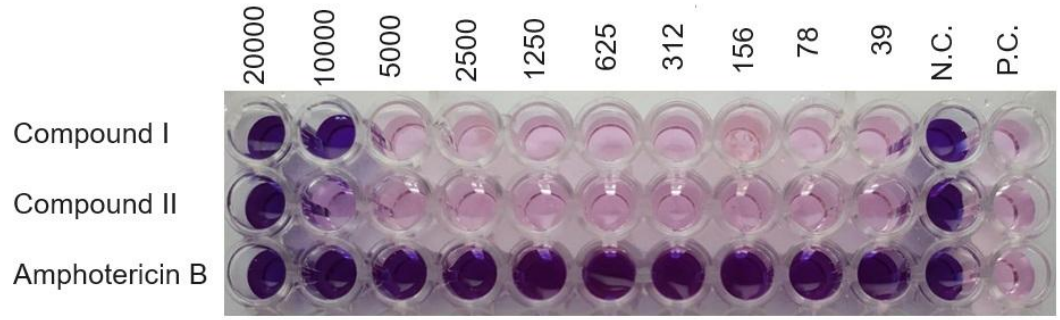

Figure 4. In vitro leishmaniacidal activities against *L.infantum* promastigotes

Table 2. Leishmaniacidal activity (LA) concentration values of the compounds against *Leishmania infantum* promastigotes.

	LA (**µg/ml**)
Compound I	10000
Compound I	20000
Amphotericin B	<39

DISCUSSION

Despite advances in the field of treatments for microbial infections, resistance to antimicrobial drugs is occurring faster than the introduction of new chemical compounds into clinical practice, resulting in increased mortality rates due to various microbial infections. The rapid development of drug-resistant microorganisms, in addition to the biofilm formation of some microorganisms, has attracted the attention of pharmaceutical chemists and other scientists working in this field, leading them to design and develop chemical structures with increased efficacy along with various modes of action. Antimicrobial drugs currently used to treat different microbial infectious diseases have therapeutic limitations such as narrow spectrum, drug toxicity, and variable bioavailability, in addition to increased microbial resistance (12).

The number and structure of drugs used in the treatment of infectious diseases are constantly changing. This change is progresses in direct proportion to the resistance created by microorganisms. The need for drugs, disinfectants, and antimicrobial agents used today arises from the resistance of microorganisms to these substances (13).

Studies have reported that the *E. faecalis* strain has become resistant to many antibiotics (14, 15). In our study, compound I was observed to be effective even at a low concentration (MIC: 78), while compound II was found to be ineffective even at the highest concentration. Additionally, it was observed that both compounds were highly effective against the other Enterococcus specie, *E. casseliflavus*.

According to a study, it is stated that *A.baumannii* creates resistance against many agents (16). Likewise, similar studies report high resistance to *S.typhimurium, S.enterica, K.pneumonia*, and *P.mirabilis*. In our current study, *A. baumanni, K. pneumonia, S. enterica* and *P. mirabilis* were found to be highly resistant to both compounds.

Similar to our study, Benkli et al. (17.) reported in their study on fourteen different triazole derivatives, they reported that no major differences were observed between the compounds in terms of antibacterial and antifungal activity.

In another study, when the antimicrobial activity of 17 different triazole derivatives was tested, it was reported that MIC values could be determined only against *E. coli*, and no activity was observed against other bacterial and fungal species (18).

The effectiveness of the triazole derivative Schiff base in anticancer, antibacterial, and

antiapoptotic studies was evaluated, and it was reported that its activities against Gram positives were higher than those against Gram negatives (19).

In another study, when the antibacterial and antifungal properties of new thiazolyl-triazole Schiff bases were tested, Schiff bases showed good antibacterial activity against *L. monocytogenes* and *P. aeruginosa*; It has been stated that it is twice as active as ciprofloxacin, and its anti-Candida activity is twice as high compared to fluconazole (20).

Chohan and Hanif synthesized a new series consisting of four biologically active triazole derivative Schiff base ligands (l1–l4) and their cobalt (II), nickel (II), copper (II) and zinc (II) complexes (1–16). Antibacterial activity against four Gram-negative (*E. coli, S. sonnei, P. aeruginosa, S. typhi*) and two Gram-positive (*S. aureus, B. subtilis*) bacteria, and antifungal activity against to *T.longifusus, C.albicans, A.flavus, M.canis, F.solani* and *C.glabrata* were tested. They stated that metal (II) complexes showed stronger antibacterial and antifungal activity than the parent Schiff bases against one or more species of bacteria and fungi. Antibacterial activities of metal (II) complexes indicated that metal (II) complexes 1, 3–8, 10 and 12–14 showed significant activity (54–82%) against all observed bacterial strains (21).

In the study conducted by Strzelecka and Swiatek in Switzerland, it was shown that the compounds have strong antibacterial activity in the study conducted on 1,2,4-triazole and its quinolone agents and hybrids, as well as 4-amino-, 3-mercapto- and 1,2,4-triazole derivatives. They reported that these compounds inhibit the growth of both Gram-positive and Gram-negative bacteria, and that the most active compounds are equal to or more effective than antibacterial drugs commonly used on the market (22).

In a study by Holanda et al. (23), they evaluated the antileishmanial activities of 4-phenyl-1-[2-(phthalimido-2-yl)ethyl]-1H-1,2,3-triazole (PT4) derivatives against *Leishmania amazonensis* and *Leishmania braziliensis* amastigotes and promastigotes. They stated that PT4 and PI compounds had an effect on the parasite membranes of both parasite species. They emphasized that it has well-predicted pharmacokinetic properties that may be useful in the development of oral formulations, especially for the treatment of cutaneous leishmaniasis.

Meinel et al. (24) synthesized a series of 1,2,3-triazolium salts (TS) and corresponding 1,2,3-triazole (T) precursors containing novel epoxide derivatives and were tested against promastigote and intracellular amastigote forms of *Leishmania amazonensis*. Among these compounds, compound TS-6 exhibited promising activity on promastigotes (IC50 = 3.61 μM) and intracellular amastigotes (IC50 = 7.61 μM) of *L. amazonensis*, which was

superior to miltefosine (IC50 > 10.0 μM) used as the reference drug stated.

Almeida et al., (25) as in our study, synthesized seven new acetyl-functionalized 1,2,3-triazolium salts and four 1,2,3-triazole precursors, and investigated their effects against different *L. infantum* strains from dogs and humans. 1,2,3-triazolium salts have been reported to exhibit better activity than 1,2,3 triazole derivatives with an IC50 range of 0.12 to 8.66 μM. Among these compounds, compound 5 has been reported to show significant activity against promastigotes (IC50 between 4.55 and 5.28 μM) and is effective against intracellular amastigotes with the best selective index (SI~ 6-9) and reduced toxicity (5 IC50 from 0.36 to 7.92 μM)

Süleymanoğlu et al. (10) 1,2,4-triazole derivatives with morpholine; 4-((3-methylthiophene–2-yl)methyleneamino)-1-((4-(3-methylthiophene–2-yl)methyleneamino)-1-(morpholinomethyl)-5-thioxo-4,5-dihydro-1H -1,2,4-triazol-3-yl)methyl)-3-(thiophene-2-ylmethyl)-1H-1,2,4-triazol-5(4H)-one (compound I) and 1-((1-(morpholinomethyl)–4-(5-nitrothiophene–2-yl)methyleneamino)-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)methyl)-4- In vitro antileishmanial activities of ((5-nitrothiophene–2-yl)methyleneamino)-3-(thiophene–2-ylmethyl)-1H-1,2,4-triazol-5(4H)-one (compound II) evaluated their antilesihmanial activity against *L. infantum* promastigotes by microdilution broth method with Alamar Blue dye. They stated that both compounds are antiparasitic and especially compound II has significant antileishmanial activity due to its MIC value of 312 μg/mL.

In a study in which thiol-thion tautomeric forms of 1,2,4-triazole derivatives were synthesized with the Schiff base, in vitro antileishmanial activity against *L. infantum* promastigotes was evaluated by microdilution method with Alamar Blue Dye. It has been emphasized that the 1,2,4-triazole derivative exhibits antiparasitic activity due to its MIC value of 1250 mg/mL (26).

Chen et al. (27) designed and synthesized a series of new myricetin derivatives containing the 1,2,4-triazole Schiff base. During antibacterial bioassays, 6f, 6i, and 6q showed a good inhibitory effect against *Xanthomonas axonopodis* pv at 10.0, 9.4 and 8.8 mg mL, respectively, and also in antiviral bioassays, most compounds showed excellent against tobacco mosaic virus (TMV) at a concentration of 500 mg mL-1. They revealed that it exhibited antiviral activity. It was determined that the triazole derivative Schiff bases we studied were highly effective against *S. flexneri*, *H. influenzae*, and *S. pneumoniae* (MIC <39).

CONCLUSION

With the ever-increasing antibiotic resistance and bacterial infections, the development of effective antibiotics to treat these infectious diseases has become a necessity. Schiff bases

and their derived complexes are reported to be important in medicinal chemistry. Triazole Schiff base ligands have applications as biological probes and potent drug agents.

In this study, it was observed that both of the newly produced triazole-containing Schiff bases were effective against *S.pneumonia, S.flexneri,* and *H.infulienzae*, which are known to be common infectious agents, at every concentration. The two Schiff base derivatives that we have studied can be investigated as a new drug derivative to be developed against these three types. It can also be considered among the new generation drugs to be produced against these microorganisms.

Neither compound was found to be effective against Gram-negative bacteria such as S. enteridis, *K.pneumoniae, A.baumannii,* and *P.mirabilis* at any concentration. Additionally, while compound 1 did not show activity against *S. typhimurium*, compound 2 was found to be ineffective against *E. faecalis*.

Both compounds whose antiparasitic activity was studied were determined to have leishmanicidal activity against *L. infantum*, albeit at high concentrations. In order for the synthesized compounds to be used in the treatment of leishmaniasis, *in vivo* control studies and toxicity tests in experimental animal models are required.

It is very important to discover new agents because the emergence of resistant isolates detected in microorganisms negatively affects human health. There are serious problems in the treatment of diseases caused by the spread of microorganisms showing multiple antibiotic resistance. This increases the need for the discovery of new antimicrobial agents. Therefore, we can positively evaluate the effectiveness of these two synthesized Schiff bases containing triazoles. We hope that this study will study the antimicrobial activities of these compounds for the first time and shed light on future studies.

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Peer-review: Externally peer-reviewed

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