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RESEARCH PAPER

Evaluation of Biological Activity of 5-Fluoro-Isatin Thiosemicarbazone Derivatives

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ABSTRACT

Isatin based materials can exhibit a wide range of biological activities including antimicrobial, antiviral, antifungal, anthelmintic, antitumor, anti-HIV, anti-inflammatory, antidepressant, antioxidant, anticonvulsant, antitubercular, analgesic, and central nervous system depressant activities. In this study, four compounds containing 5-Fluoro-isatin thiosemicarbazone with methoxyphenyl or methoxyphenyl in different positions and zinc complexes were evaluated based on their biological activities. **Compound 2** was the strongest compound affecting gram-negative bacteria compared to the other compounds. Also, **this compound** indicated better antimicrobial activity than positive control antibiotics. Besides, **compound 3** was the only compound that inhibited the growth of Salmonella spp. such as *Salmonella enteritidis* ATCC 13076 and *Salmonella typhimurium* NRRLE 4463. 5-Fluoro-Isatin thiosemicarbazone and its derivatives also showed DNA protection property from moderate to good protections. Among them, **compound 4** displayed the highest DNA binding affinity. These compounds possessed a capacity for utilization as drugs or drug additives based on their effects on bacteria strains and DNA binding affinity.

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INTRODUCTION

Bacterial infections, antibiotic resistance, and cancer cases are increasing nowadays, and researchers are working on developing new drug therapies to reverse this. Isatin (2,3-dioxindole) which is a derivative of indole is among the substrates which can be used as raw material in drug treatment. It is also a synthetic substance which can be utilized for obtaining some other derivatives [1,2]. Isatin material is found in some plant species such as *Couroupita guianensis* and *Calanthe discolor* (Lindl.). Joaquim et al. showed that the mammalian tissues and bufo frogs were secreted in the parotid glands. Also, they detected the metabolic adrenal of isatin derivatives in humankind [2]. Further, indigo

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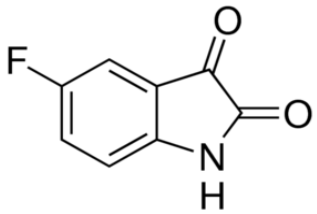

Fig. 1. Chemical structure of 5– Fluoro-isatin.

dye was oxidized by some acid derivatives and discovered isatin material [3]. Because of the highly reactive property of the carbonyl group at C-3 position, isatin is essential and is preferred in organic synthesis studies [4,5]. This group of isatin generally binds to the prochiral center [5]. Isatin has a unique feature for acetylcholine regulation in the brain. This is achieved by raising the dopamine level under stress conditions [6].

Isatin and its derivatives can exhibit a wide range of biological activities. They can be listed as antimicrobial, antiviral, anthelmintic, antitumor, anti-HIV, anti-inflammatory, antioxidant, anticonvulsant, analgesic and central nervous system depressant activities [3,6,15,7–14]. Thiosemicarbazones are a compound produced by the condensation of thiosemicarbazone with suitable ketones or aldehydes. Thiosemicarbazones can be linked to many complex metals using hydrazine nitrogen and sulfur atoms [16]. Thiosemicarbazones are among the therapeutic agents for human diseases. Also, antiviral compounds are employed against DNA and RNA viruses because they are a large spectrum against antiviral agents [17].

Thiosemicarbazones have been utilized for antimicrobial, antiviral, antifungal and antitumor activity as well as blocking sodium channels [18]. Today, one of the most important threats to human health in the world is accepted as antimicrobial resistance. The best example of this is *Staphylococcus aureus* (MRSA) which has developed resistance to methicillin. This bacterium causes many people to die every year. Also, as a result of the misuse of antibiotics, this wrong use of antibiotics rather than disease agents is seen as the most important public health problem to be treated. In addition to these problems, resistance against antibiotics has increased, not only among the public but also in hospital settings.

Furthermore, this situation causes an increase in mortality and morbidity rates [19]. Anti-microbial agents lose their effectiveness in the formation and spread of antibiotic resistance compared to other pharmaceutical compounds [20]. Therefore, no class of antibiotics could not move away from this negative effect. Besides, the effects of this condition on gram-positive bacteria are more common than gram-negative bacteria [21].

Fluorinated heterocyclic compounds are important intermediates in the synthesis of various pharmaceuticals and therefore play an important role in these and similar technological developments. Al-Romaizan (2014) had reported that the combination of fluorine atoms with a heterocyclic nitrogen molecule frequently give properties of pharmacological interest when compared with their non-fluorinated analogs. The molecular formula of 5-Fluoro isatin is $C_8H_4FNO_2$ as shown in Fig. 1 with a molecular weight = 165.12 Mol.

Numerous reports have been carried out to search the biological properties of isatin, thiosemicarbazones and their different derivatives. However, the examination of some biological features of 5-Fluoro-isatin thiosemicarbazone its derivatives has been limited. For this purpose, we performed different biological activity studies including antimicrobial and DNA protective properties of these compounds. These compounds may be beneficial for toxicity testing and therapeutic targets in the future.

MATERIAL AND METHODS

Chemical compounds

All isatin derivative compounds utilized in this research were re-synthesized [22] and controlled their chemical structure again before starting biological activity analyses. Four compounds namely 5-Fluoro-isatin thiosemicarbazone with methoxyphenyl or methoxyphenyl in different positions and zinc were used in this study and their properties were indicated in Table 1.

Antimicrobial activity

The antibacterial activity of four different compounds was investigated. A total of 21 bacterial strains including gram-positive and gram-negative bacteria strains were utilized in this study. The strains were obtained from the Department of Genetics and Bioengineering at Kastamonu University and the Department of Microbiology at Gazi University. These strains and their gram staining properties are seen in Table 2.

Table 1. Properties and abbreviations of 5-Fluoro-isatin 3 derivatives.

Compound No	Compound name	Abbreviations	Molecular weight (g/mol)
1	5-Fluoro-isatin 3-[(N-4-methoxyphenyl)-thiosemicarbazone]	5-F-I3-[(N-4-MXP)-TSC]	344,3634
2	5-Fluoro-isatin 3-[(N-2-methoxyphenyl)-thiosemicarbazone]	5-F-I3-[(N-2-MP)-TSC]	344,3634
3	5-Fluoro-isatin 3-[(N-3-methoxyphenyl)-thiosemicarbazone]	5-F-I3-[(N-3-MXP)-TSC]	344,3634
4	5-Fluoro-isatin 4-(3-methoxyphenyl)3-thiosemicarbazone) zinc (II)	5-F-I4-(3MXP)-3-TSC)Z(II)	735.1084

Table 2. Bacterial strains used in this study.

	Bacterial Strains	Abbreviations	G. Stain
1	Klebsiella pneumoniae	K. pneumoniae	-
2	Staphylococcus aureus ATCC 25923	S. aureus ATCC 25923	+
3	Staphylococcus aureus	S. aureus	+
4	Proteus vulgaris	P. vulgaris	-
5	Escherichia coli	E. coli	-
6	Serratia marcescens	S. marcescens	-
7	Staphylococcus epidermis	S. epidermis	+
8	Alpha haemolytic Streptococcus	Alpha h. Streptococcus	+
9	Enterococcus faecium	E. faecium	+
10	Pseudomonas aeruginosa	P. aeruginosa	-
11	Listeria monocytogenes ATCC 7644	L. monocytogenes ATCC 7644	+
12	Enterococcus durans	E. durans	+
13	Enterococcus aerogenes ATCC 13048	E. aerogenes ATCC 13048	-
14	Staphylococcus aureus ATCC 43300	S. aureus ATCC 43300	+
15	Salmonella enteritidis ATCC 13076	S. enteritidis ATCC 13076	-
16	Streptococcus pneumoniae ATCC 10015	S. pneumoniae ATCC 10015	+
17	Sarcina lutea ATCC 9341	S. lutea ATCC 9341	+
18	Salmonella typhimurium NRRLE 4463	S. typhimurium NRRLE 4463	-
19	Yersinia enterocolitica ATCC 1501	Y. enterocolitica ATCC 1501	-
20	Proteus mirabilis ATCC 25933	P. mirabilis ATCC 25933	-
21	Enterococcus faecalis ATCC 25212	E. faecalis ATCC 25212	+

Preparation of stock solutions

Stock solutions of the four compounds were set according to their molecular weight by dissolving the compounds in 1 ml of Dimethyl Sulfoxide (DMSO) in sterile test tubes to give a final concentration of 0.4 M. For the minimum inhibitory concentrations (MICs) analysis, DMSO was used for dilution of chemical compounds to prepare a series of descending concentrations down. We performed MIC analysis as previously indicated in our different study [22]. It was found that 0.4 M of each compound was more suitable for MIC analysis. First, 50 µl of the stock solution was added to the sterile filter paper. The filter papers loaded with the solution were then dried at 30 °C for 3 hours to dry under constant temperature and sterile conditions. DMSO was directly used as a negative control to see if there is any effect on these types of bacteria. Filter paper discs loaded with DMSO were kept drying 3 hours at 30 °C in sterile conditions to evaporate the solvent and left at room temperature with the same ways of the compounds. A wide spectrum of antibiotics, such as Zosyn and Levofloxacin, were used as positive controls [22].

Inoculation procedures

The four compounds, positive control Levofloxacin and Zosyn antibiotics and negative control DMSO were tested against the 21 types of bacterial strains, using a disk-diffusion method [23]. All bacterial strains were transferred to 5 ml of prepared broth media and then allowed to incubate at 37 °C for 18-24 hours. Preparation and sterilization of sterile saline solution were performed in 5 ml test tubes. Suspension of each bacterial strain was poured on the sterile saline solution tube drop by drop. The visible turbidity

was adjusted to 0.5 McFarland standards which approximately equal to 10^8 cells forming unit (CFU). The accuracy of the density of McFarland Standards was used by a spectrophotometer with a 1 cm light path, and a 0.5 McFarland. Standard had an absorbance reading of (0.08 to 0.1 at 625-nm). Muller Hinton Media Agar was sterilized and poured into 100 mm sterile Petri dishes [24]. In sterile Petri dishes, the medium was ready for the cultivation of bacteria. Bacteria were cultured with sterile cotton swabs to transfer them on plate. After bacterial cultivation, sterile antibiotic discs were placed in the required areas, and chemical compounds were absorbed into these discs. Incubation was left for 18-24 hours at 37 °C to be left to incubation. The incubation period was achieved for 18-24 hours at 37 °C. Finally, the data of the antibacterial activity was calculated by comparing inhibition sites.

DNA Protection Test

The DNA protection analysis was carried out using pUC19 isolated from *E. coli*, and the DNA concentration was confirmed spectrophotometrically. Fenton's reagent was prepared by using 80 mM $FeCl_3$, 50 mM ascorbic acid, and 30 mM H_2O_2 then adding distilled water up to the final be 10 ml [24]. Horizontal agarose gel electrophoresis method was used to obtain DNA fragments which were illuminated with ethidium bromide. Every compound was prepared in 1 mL of absolute ethanol at two concentrations 0.0165 M and 0.102 M and kept for 24 hours, then centrifuged at 600 rpm for 5 minutes and the supernatant was collected.

The concentration of the pDNA was 230 ng/µl. The plasmid was prepared according to the purification protocols of the Gene JET Plasmid Miniprep Kit (Thermo Scientific, USA Company). The mixture formed for the preparation of the samples contains 3 µl Fenton's reagent, 4 µl pDNA, 3 µl chemical and 10 µl distilled water. Also, only 4 µl pDNA and 16 µl distilled water were used for the negative control. The mixture prepared for a positive control sample contains 3 µl Fenton reagent, 4 µl pDNA and 13 µl distilled water. In the next step, all samples were left at 37 ° C for 30 minutes to be incubated, and then 4 µl loading dye (Thermo Scientific, USA) was added. DNA was run on 1% agarose gels for 45 minutes and then visualized under ultraviolet light. All experiments were repeated three times, and band density was determined by gel image analysis software (Quantum, Vision-Capt., Vilber Lourmat SAS, and France).

Statistical Analysis

All experiments were performed in triplicate with technical replicates. Standard error of mean (SEM) analysis was performed using Minitab version 17.

RESULTS AND DISCUSSION

Antimicrobial property of compounds

In the levofloxacin's positive control study, *E. faecium* and *K. pneumonia* species were found to be resistant to Levofloxacin, while other bacterial strains had different inhibition regions. Zosyn had also lethal effect on some of the bacteria except for *P. vulgaris, E. coli, S. marrescens, E. aerogenes* ATCC 13048, *P. aeruginosa, E. durans, L. monocytogenes* ATCC 7644*, S. Enteritidis* ATCC 13076*, S. lutea* ATCC 9341*, P. mirabilis* ATCC 25933, *S. pneumonia* ATCC 10015 (Fig. 2).

Levofloxacin is one of the group of antibiotics called fluoroquinolones. Zosyn is a combination of piperacillin and tazobactam that are broad-spectrum antibiotics. Levofloxacin is an effective agent against gram-positive and gram-negative bacteria. It is also preferred because it has a broad antimicrobial activity. It is first used in the treatment of many bacterial infections compared to ciprofloxacin. However, it is better than ciprofloxacin thanks to proven clinical effects such as the low incidence of adverse gastrointestinal reactions. DMSO was used as a negative control because it did not show any effect on all strains of bacteria used in this study. To clarify any participating role of DMSO in the biological screening, separate studies were carried out with the solutions alone of DMSO, and they showed no activity against any bacterial strains.

Compound 1 which contains N-4-methoxyphenyl with fluoro isatin and thiosemicarbazone did not show any effect on all types of bacteria strains, and no inhibition zone appear.

In contrast to **compound 1**, **compound 2** indicated very good antimicrobial activity when compared to Levofloxacin and Zosyn which were used for positive control. Also, **compound 2** caused the formation of wide inhibition zones for nine strains of gram-positive and gram-negative bacteria which ranged between 11 and 30 mm in

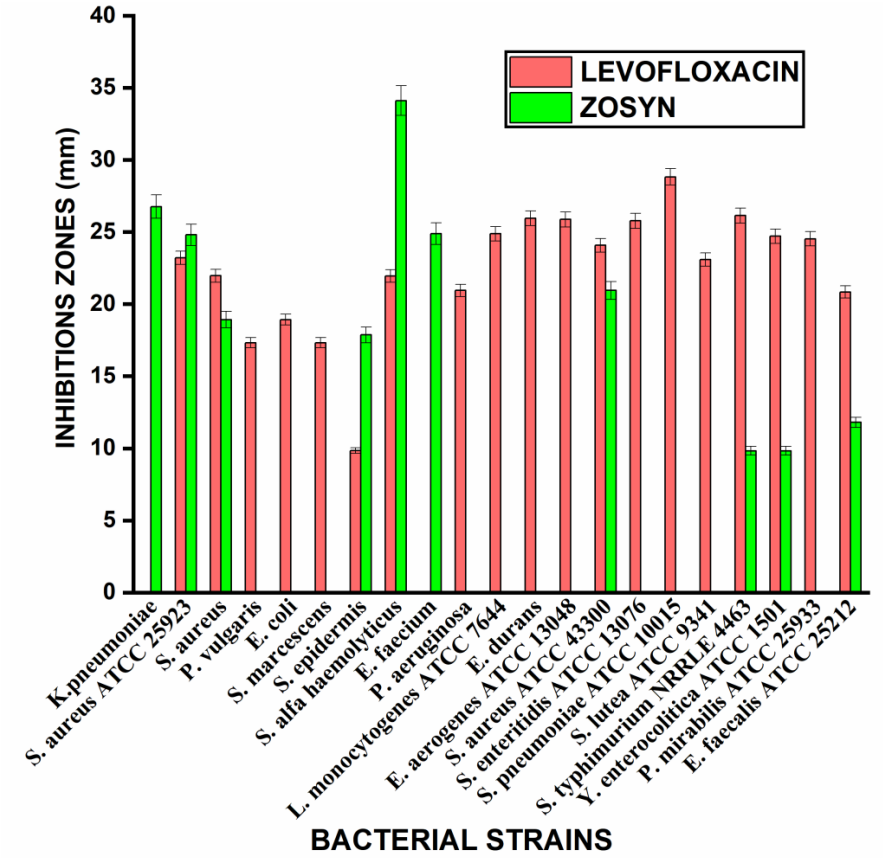

Fig. 2. Antimicrobial activity of Levofloxacin and Zosyn antibiotics against the different bacterial strains.

diameter. The affected bacteria were *P. vulgaris, S. aureus* ATCC 25923*, E. faecium, Alpha hemolytic Streptococcus, E. coli, S. aureus, L. monocytogenes* ATCC 7644*, S. marrescens,* and *E. aerogenes* ATCC 13048*.* **Compound 2** gave better inhibition zones than Levofloxacin for gram-negative bacteria *P. vulgaris, E. coli* and *S. marrescens* with inhibition zones 30, 20, and 23 respectively. Also, **compound 2** was better than Levofloxacin on gram-positive bacteria strains including *E. faecium, E. aerogenes* ATCC 13048 and *L. monocytogenes* ATCC 7644. **Compound 2** also indicated better antimicrobial activity than Zosyn antibiotic because Zosyn did not give any action on five strains of bacteria (Fig. 3).

Compound 2 was the strongest compound affecting gram-negative bacteria (about 44.4% of the total bacteria) compared to the other compounds. **Compound 2** nearly resembles **compound 1** on its structure which did not display any bacterial actions or inhibition zone in all bacteria. The only difference between them that the first one is composed of methoxyphenyl on the second position instead of methoxyphenyl on the fourth position. It can be concluded that the type and position of derivatives might directly affect the antimicrobial activity of the compound.

Compound 3 share the same chemical structure except that the methoxyphenyl is present in the position of three. **Compound 3** showed inhibition zones for both gram-positive and gram-negative bacteria strains including *K. pneumonia, S. Enteritidis* ATCC 13076, *S. marrescens, S. epidermis, E. coli, S. aureus* ATCC 25923*, S. aureus* ATCC 43300*, S. lutea* ATCC 9341*, S. typhimurium* NRRLE 4463*.* On the other hand, the inhibition zone of **compound 3** indicated mild inhibition zones with 6-9 mm in diameter compared with **compound 2** whose inhibition zones were ranged between 11 to 30 mm in diameter. This situation can be explained by the presence of methoxyphenyl instead of methoxyphenyl groups.

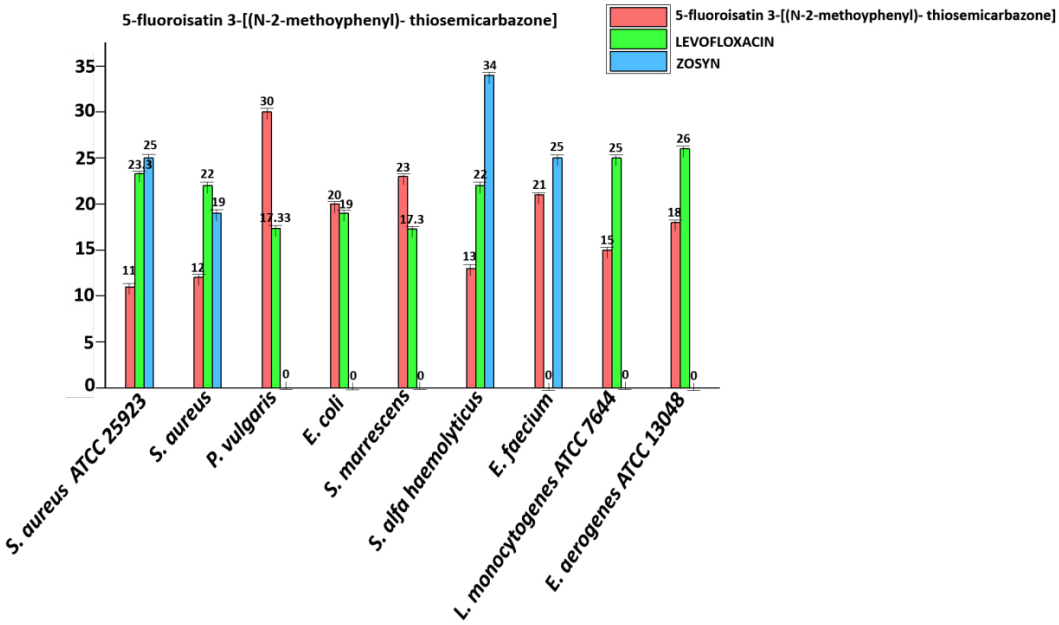

Fig. 3. Antibacterial property of compound 2.

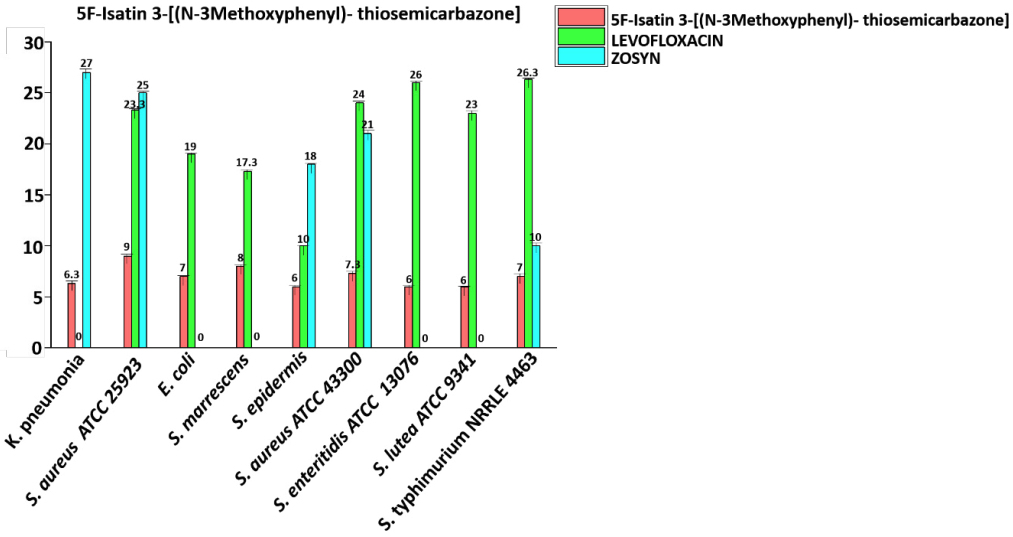

Fig. 4. Antibacterial property of compound 3.

Also, **compound 3** is more affecting gram-negative than gram-positive bacteria and is the only compound that inhibited Salmonella spp. such as *S. enteritidis* ATCC 13076 and *S. typhimurium* NRRLE 4463. Although some bacteria strains were not affected by Zosyn, **compound 3** affected them even if it had a mild effect on these bacteria including *E. coli, S. marrescens, S. enteritidis* ATCC 13076 and *S. lutea* ATCC 9341 (Fig. 4).

In this study, one metal complex of 5-Fluoro-isatin thiosemicarbazone was also created by adding zinc to the complex. It was called Although many articles suggest that the addition of some metals caused an increase in their effect on

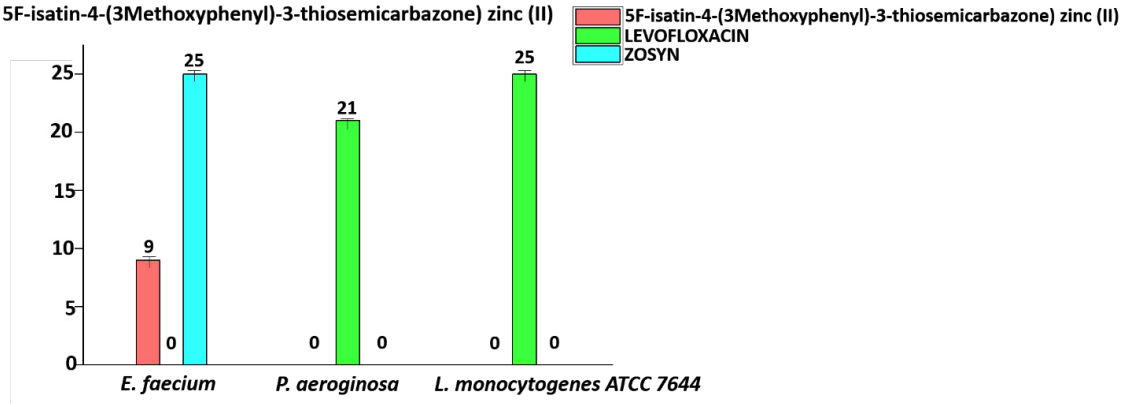

Fig. 5. Antibacterial property of compound 4.

bacteria and inhibition zones, **Compound 4** with zinc (II) did not show a wide range of antimicrobial activity. **Compound 4** affected only one strain of gram-positive bacteria (*E. faecium*) with 9 mm diameter of inhibition zone and gave a better result than Levofloxacin based on their effect on *E. faecium* bacteria as shown in Fig. 5.

Although many articles suggest that the addition of some metals caused an increase in their effect on bacteria and inhibition zones, **Compound 4** with zinc (II) did not show a wide range of antimicrobial activity. These groups of compounds contained 5 Fluoro-Isatin thiosemicarbazones with methoxyphenyl or methoxyphenyl on different positions of their chemical structures as well as zinc. They displayed different antimicrobial activities except **compound 1** which did not show any inhibition zone for all tested bacteria strains. Although there is no certain explanation for this situation, it may arise from the position of the N-4- methoxyphenyl. Patela *et al*. (2006) reported an antimicrobial study in which substitution in the 5th position of isatin with fluorine, chlorine, and bromine produced more active compounds in a series [25]. These compounds provided good action compared to positive control antibiotics against some bacteria strains. For example, **compound 2** brought about the formation of 30 mm in diameter inhibition zones in *P. vulgaris*. Other compounds also formed great inhibition zones against *L. monocytogenes* ATCC 7644, *E. aerogenes* ATCC 13048*, S. marrescens, E. coli* and *E. faecium.* Also, this group of compounds was mostly affected by gram-negative bacteria strains. Saito *et al.* (2007) reported that *P. vulgaris* is often persistent nosocomial microorganism and difficult to treat due to its resistance to many antibiotics. It was also detected that progressive increase in resistance to fluoroquinolones and broad-spectrum cephalosporin had been seen in clinical isolates of this species [26]. However, 5-Fluoro-isatin thiosemicarbazone derivatives provided very good action against *P. vulgaris*. *S. enteritidis* ATCC 13076 and *S. typhimurium* NRRLE 4463*,* which are considered one of the world problems as antibiotics resistance were also affected by these groups of compounds. **Compound 4** was the weakest one in this group and inhibited only one gram-positive bacteria *E. faecium* with a small inhibition zone. This outcome is contrary to that of Varkey et al. (2013) and Vaidya et al. (2017) who found that the compounds with metal had more effects on bacterial actions [27,28]. Surprisingly, it was consistent with a study reported by Hobman and Crossman (2014) who indicated metal ion resistance on antimicrobial activity [29]. It is difficult to explain this result, but it might be related to the chemical structure of compounds and the position of derivatives.

DNA protection activity

The DNA protection test was conducted to indicate the protection feature of various compounds against hydroxyl radical damage generated by Fenton Reagents. DNA protection capacity of the 5-Fluoro-Isatin thiosemicarbazone and its derivatives were examined in this study. Although there were some variations, it was observed that compounds indicated average DNA protection activity. The **compound 4** gave the best

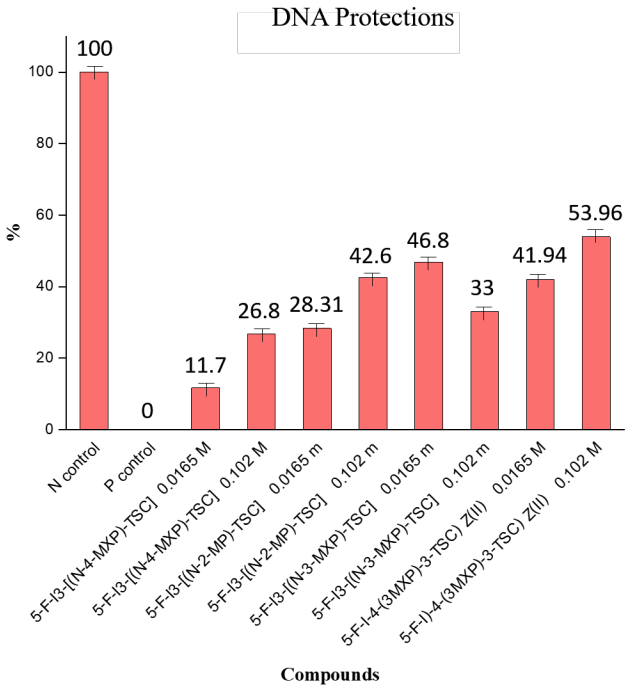

Fig. 6. DNA protection activity of 5 Fluoro-Isatin thiosemicarbazone and its derivatives.

DNA protection activity with 54% followed by **compound 3** with 46.8% (Fig. 6).

Because of the presence of zinc metal in **compound 4,** it might tightly bind to DNA and protected from Fenton's reagent.

Contrary to expectations, **compound 3** performed better protection activity at low concentration rather than higher concentration. Also, **compound 1** which was the only compound that did not have antimicrobial activity also showed the lowest DNA protection percentage. Although there was no significant relationship between the antimicrobial and DNA protection activities, a similar study indicated the same correlation. Şener et al. (2018) reported that 2,4-dihydroxyquinoline derived disazo dyes had the same effect on both activities [30]. The compounds which possessed lower DNA binding capacity also displayed limited antimicrobial activity. A possible explanation for these results may be the binding affinity of compounds to biomolecules. The lower binding capacity to macromolecules or biomolecules may result in reduced antimicrobial activity.

CONCLUSIONS

In the fight against bacterial infections, antibiotic resistance occurs are especially important. The prevalence of the diseases caused by these infections is evaluated urgently for medical research in the treatment process. Therefore, the different biological effects of 5-fluoro-isatin thiosemicarbazone and its derivatives were examined in this study to find out combating bacterial infections. **Compound 2** possessed a promising effect on both Gram-positive and negative bacteria strains. Besides, DNA protective activity of these compounds was also investigated and found that **Compound 4** had high DNA binding affinity. A possible explanation for these results may be the presence of different functional groups and their positions in compounds. Furthermore, some *in vivo* tests should be performed for further evidence of their antimicrobial activity or DNA binding property. Also, it is necessary to examine more structure-activity relationships on derivatives of isatin-thiosemicarbazone. Thus, more efficient drugs might be improved for both bacterial infections and cancer treatments.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this manuscript.

REFERENCES

1. Mishra AP, Mishra R, Jain R, Gupta S. Synthesis of New VO(II), Co(II), Ni(II) and Cu(II) Complexes with Isatin-3-Chloro-4-Floroaniline and 2-Pyridinecarboxylidene-4-Aminoantipyrine and their Antimicrobial Studies. Mycobiology. 2012;40(1):20-6.
2. Silva JFMd, Garden SJ, Pinto AC. The chemistry of isatins: a review from 1975 to 1999. Journal of the Brazilian Chemical Society. 2001;12(3):273-324.
3. Pal M, Sharma NK, Priyanka P, Jha KK. ChemInform Abstract: Synthetic and Biological Multiplicity of Isatin. ChemInform. 2011;42(44):no-no.
4 M. Shyam, B. Debnath, P. Devbhuti, Search for Biological Active Thiazolidinedione: A Short Review, Indo Am. J. Pharm. Res. 6 (2016) 5282–5311.
5. Borad MA, Bhoi MN, Prajapati NP, Patel HD. ChemInform Abstract: Review of Synthesis of Multispiro Heterocyclic Compounds from Isatin. ChemInform. 2014;45(25):no-no.
6. Nain S. Recent Advancement in Synthesis of Isatin as Anticonvulsant Agents: A Review. Medicinal Chemistry. 2014;4(4).
7. Pakravan P, Kashanian S, Khodaei MM, Harding FJ. Biochemical and pharmacological characterization of isatin and its derivatives: from structure to activity. Pharmacological Reports. 2013;65(2):313-35.
8. Glover V, Halket JM, Watkins PJ, Clow A, Goodwin BL, Sandier M. Isatin: Identity with the Purified Endogenous Monoamine Oxidase Inhibitor Tribulin. Journal of Neurochemistry. 1988;51(2):656-9.
9. Bhattacharya SK, Glover V, McIntyre I, Oxenkrug G, Sandler M. Stress causes an increase in endogenous monoamine oxidase inhibitor (tribulin) in rat brain. Neuroscience Letters. 1988;92(2):218-21.
10. Bhattacharya SK, Mitra SK, Acharya SB. Anxiogenic activity of isatin, a putative biological factor, in rodents. Journal of Psychopharmacology. 1991;5(3):202-6.
11. Gil-Turnes M, Hay M, Fenical W. Symbiotic marine bacteria chemically defend crustacean embryos from a pathogenic fungus. Science. 1989;246(4926):116-8.
12. Pandeya SN, Sriram D, Nath G, De Clercq E. Synthesis, antibacterial, antifungal and anti-HIV evaluation of Schiff and Mannich bases of isatin derivatives with 3-amino-2-methylmercapto quinazolin-4(3H)-one. Pharmaceutica Acta Helvetiae. 1999;74(1):11-7.
13. Pandeya SN, Sriram D, Nath G, De Clercq E. Synthesis, antibacterial, antifungal and anti-HIV activities of norfloxacin Mannich bases. European Journal of Medicinal Chemistry. 2000;35(2):249-55.
14 S.N. Pandeya, D. Sriram, G. Nath, E. De Clercq, HIV Evaluation of Schiff and Mannich Bases of Isatin and its Derivatives with Triazole, Drug Res. 50 (2000) 55–59.
15. Pignatello R, Panico A, Mazzone P, Pinizzotto MR, Garozzo A, Fumeri PM. Schiff bases of N-hydroxy-N′-aminoguanidines as antiviral, antibacterial and anticancer agents. European Journal of Medicinal Chemistry. 1994;29(10):781-5.
16 D. N-arylmaleimides, Synthesis of Novel Thiosemicarbazide Derivatives of, 5 (2016) 172–180. doi:10.20959/wjpr20164-5848.
17. Wu D, Chen Z. Study on the interaction between ginsenoside Rh2 and calf thymus DNA by spectroscopic techniques. Luminescence. 2015;30(8):1212-8.
18 E.M. Jouad, G. Larcher, A. Allain, A. Riou, G.M. Bouet, M.A. Khan, X. Do Thanh, Synthesis, structure and biological activity of nickel(II) complexes of 5-methyl 2-furfural thiosemicarbazone, J. Inorg. Biochem. 86 (2001) 565–571. doi:10.1016/S0162-0134(01)00220-3.
19 J.N. Pendleton, S.P. Gorman, B.F. Gilmore, Patogenos Eskape Er, 11 (2013) 297–308. doi:10.1586/eri.13.12.
20. Rossolini GM, Arena F, Pecile P, Pollini S. Update on the antibiotic resistance crisis. Current Opinion in Pharmacology. 2014;18:56-60.
21. Fernández J, Bert F, Nicolas-Chanoine M-H. The challenges of multi-drug-resistance in hepatology. Journal of Hepatology. 2016;65(5):1043-54.
22. Ganim MA, Baloglu MC, Aygun A, Altunoglu YC, Sayiner HS, Kandemirli F, et al. Analysis of DNA protection, interaction and antimicrobial activity of isatin derivatives. International Journal of Biological Macromolecules. 2019;122:1271-8.
23. Andrews JM. BSAC standardized disc susceptibility testing method (version 4). Journal of Antimicrobial Chemotherapy. 2005;56(1):60-76.
24. Özkan OE, Zengin G, Akça M, Baloğlu MC, Olgun Ç, Altuner EM, et al. DNA protection, antioxidant, antibacterial and enzyme inhibition activities of heartwood and sapwood extracts from juniper and olive woods. RSC Advances. 2015;5(89):72950-8.
25 P. Ankur, B. Sanjay, T. Gokul, P. Jitendra, S. Manda, Synthesis and Antimicrobial Activity of Some New Isatin Derivatives, Iran. J. Pharm. Res. 5 (2006) 249–254.
26. Saito R, Okugawa S, Kumita W, Sato K, Chida T, Okamura N, et al. Clinical epidemiology of ciprofloxacin-resistant Proteus mirabilis isolated from urine samples of hospitalised patients. Clinical Microbiology and Infection. 2007;13(12):1204-6.
27. Varkey AJ, Dlamini MD, Mansuetus AB, Tiruneh AT. Germicidal Action of Some Metals/Metal Ions in Combating E. coli Bacteria in Relation to Their Electro-Chemical Properties. Journal of Water Resource and Protection. 2013;05(12):1132-43.
28. Vaidya MY, McBain AJ, Butler JA, Banks CE, Whitehead KA. Antimicrobial Efficacy and Synergy of Metal Ions against Enterococcus faecium, Klebsiella pneumoniae and Acinetobacter baumannii in Planktonic and Biofilm Phenotypes. Scientific Reports. 2017;7(1).
29. Hobman JL, Crossman LC. Bacterial antimicrobial metal ion resistance. Journal of Medical Microbiology. 2015;64(5):471-97.
30. Şener N, Mohammed HJA, Yerlikaya S, Celik Altunoglu Y, Gür M, Baloglu MC, et al. Anticancer, antimicrobial, and DNA protection analysis of novel 2,4-dihydroxyquinoline dyes. Dyes and Pigments. 2018;157:11-9.