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Antimicrobial Activity Studies of 3-Substituted Indole-2-one and -thione derivatives and Molecular Docking and ADME Evaluations

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Abstract

Increasing antibiotic resistance is an important problem for public health therefore new antimicrobial compounds are needed. In this study, the antimicrobial effects of 3-Substituted Indole-2-one and -thione derivatives were investigated. Antimicrobial effects of previously synthesized 18 different 3-substituted indole-2-one and 2-thione derivatives against 5 different microorganisms were investigated and the structure-activity relationships and drug-like properties of compounds were analyzed by molecular docking and in silico prediction studies. The *in vitro* antimicrobial activities of compounds were tested by microdilution method. The most active compounds were found as 2, 3, 4, 5, 6, 7, 8 at 125 µg/mL of MIC value. Compounds 2 and 3 were found to be active against *S. enterica* and compounds 4, 5, 6, 7, and 8 were found to be active against methicillin-resistant *S. aureus*. According to molecular docking studies, all compounds presented weaker binding properties than ciprofloxacin, ampicillin and gentamicin. The predicted values for molecular weight, log P, PSA, crossing the BBB, GI absorption properties and type of CYPP450 inhibition data of compounds were found promising for drug-like properties. 3-Substituted Indole-2-one and -thione derivatives can proivide an important contribution to develop alternative antimicrobial agents.

Keywords

Antimicrobial activity: Minimum inhibitory concentration: Molecular docking: Structure-activity relationship: 3-Substituted-indole-2-on and 2-thione

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INTRODUCTION

Indole is an important scaffold that shows a variety of biological activities. Among the indole derivatives, oxoindole, thioindole, isatine and spiro oxoindole frameworks containing derivatives especially cover important pharmacological activities such as antimicrobial, antifungal, anti-tumor, antiproliferative and tyrosine kinase activities useful for the treatment of cancer (Bhaskar *et al.*,2012). Isatin derivatives were found that antimicrobial activity against a variety of pathogens (Khan and Maalik, 2015). According to study of thiosemicarbazone and dispiro pyrrolidine derivatives of isatin showed that these compounds inhibit the growth of *Mycobacterium tuberculosis* (Kumar *et al.*, 2010; Banerjee *et al.*, 2011). In the another study found that isatin-3- phenylhydrazone showed antimicrobial activity compared to amoxicillin and norfloxacin against *Proteus vulgaris, Escherichia coli, Pseudomonas aeruginosa* and *Staphylococcus aureus* (Konstantinović *et al.,* 2008). Lanthanide complexes with isatin bis hydrazones derivatives were found to have antifungal properties depending on the lipophilicity of the molecules (Mohanan *et al.,* 2008). New isatin derivatives condensed with benzoyl hydrazides were found active against some bacterial strains including *M. tuberculosis* and fungi. In the another study it was found that 5,5-Disubstituted-1,2,4-Triazolidin-3-one showed good antimicrobial activity against Gram positive bacteria (Sudha *et al.*, 2015). Some mono and bis-[3,3-di(indolyl)indolinone] derivatives were assayed for in-vitro antimicrobial activity. Although they were active against *S. aureus*, they were not found active against *E. coli*, *P. aeruginosa* and *Candida albicans* (Karimi *et al.*, 2015). According to another study it is showed that Schiff bases of 1*H*-indole-2,3-dione derivatives with 4-amino-N-(5,6-dimethoxypyrimidine-4-yl) benzenesulfonamides has considerable antimicrobial activities in comparison to reference drug sulfadoxine (Singh *et al.,* 2010). Other types of Schiff bases of isatin were studied by the same research group. It was reported that these compounds have higher activity against several bacteria and fungi in comparison to norfloxacin (Pandeya et al., 2008). Sixteen substituted indole-2,3-diones hydrazones were tested for antimicrobial activity. Some compounds exhibited good inhibitory activity against *Salmonella Typhi*, *Staphylococcus haemolyticus*, *Mycobacterium paratuberculosis* 607, *Aspergillus niger*, *C. albicans*, and *Saccharomyces cerevisiae* (Piscopo *et al.*, 1986; Piscopo *et al.*, 1987). A series of spirooxoindoles obtained from isatin showed moderate to good

antimicrobial activity against several bacterial and fungal strains (Nandakumar *et al.*, 2010). 5-Fluoro and 5-iodo indole-2,3-dione derived from spiro-4-thiazolidinones were reported to be potent compounds against bacteria and fungi (Hussain *et al.*, 2016).

All the above findings of indole-2- one derivatives obtained from literature prompted us to test our previously synthesized 18 compounds against 5 different bacterial strains. The activity results were evaluated based on their structure by using computer-assisted methods. A docking study was run to explain the interaction of indole-2-one derivatives with the binding site of DNA gyrase enzymes of microorganisms. Swiss Absorption, distribution, metabolism, and excretion (ADME) (http://swissadme.ch/) prediction was also used to calculate physicochemical properties of compounds to explain drug-like properties.

MATERIALS AND METHODS

Methanol (Sigma-Aldrich) and Mueller-Hinton broth (MHB) (Difco, Detroit, USA) were used for biological assays. Autodock vina 4.2.6 was used for the calculation of receptor-ligand interactions and the 3D compound-protein docking posses were analyzed by using Pymol 4.2.6 software. The Physico-chemical data were calculated using Swiss ADME (http://swissadme.ch/) online prediction program.

In Vitro Antimicrobial Assay

Test Microorganisms

Gram-negative bacteria (*Acinetobacter baumannii* ATCC 19606, *Salmonella Typhi* clinical isolate ve *Salmonella enterica* – clinical isolate) and Gram-positive bacteria (*Staphylococcus haemolyticus* ATCC 43252, *Methicillin-resistant Staphylococcus aureus* ATCC 43300) were used to determine the antimicrobial activity of eighteen previously synthesized indole derivatives.

Determination of the minimum inhibitory concentration (MIC) by microdilution tests

MIC values of the compounds on the bacteria cultures used in the study were determined according to the broth microdilution method (Sanli-Yurudu *et al.*, 2012). 24-hour fresh cultures of all bacteria were prepared in Mueller Hinton Broth (MHB), and the bacterial concentration was adjusted as 0.5 McFarland (CLSI, 2018). The all compounds are dissolved in methanol. The dilutions of the compounds and standards in the test medium were prepared using Muller Hinton Broth at the required quantities of 1000, 500, 250, 125,

62.5, 31.25, 15.7, 7.8, 3.9, 1.95, 0.98, and 0.5 µg/mL and added onto the tested microorganisms in 96 microcell plate and incubated at 37±0.1 °C for 24 hours. In addition, a mixture containing only methanol and microorganisms was added to the microplates to examine the antimicrobial effect of methanol on microorganisms. Then 50 µL of 2,3,5-triphenyl tetrazolium chloride from a 2 mg/mL stock solution was added to each cell and MIC values of compounds were determined by colorimetric measurement. Streptomycin, gentamicin, ampicillin and ciprofloxacin (1000 µg/mL -0.5 µg/mL dilution range) were used for controls (Kang *et al.*, 2008).

Chemistry

3-Substituted benzylidene indolin-2-one and 2-thione derivatives (1-18) were previously synthesized in two steps starting from indole-2-one and indole-2-thione (Figure 1).

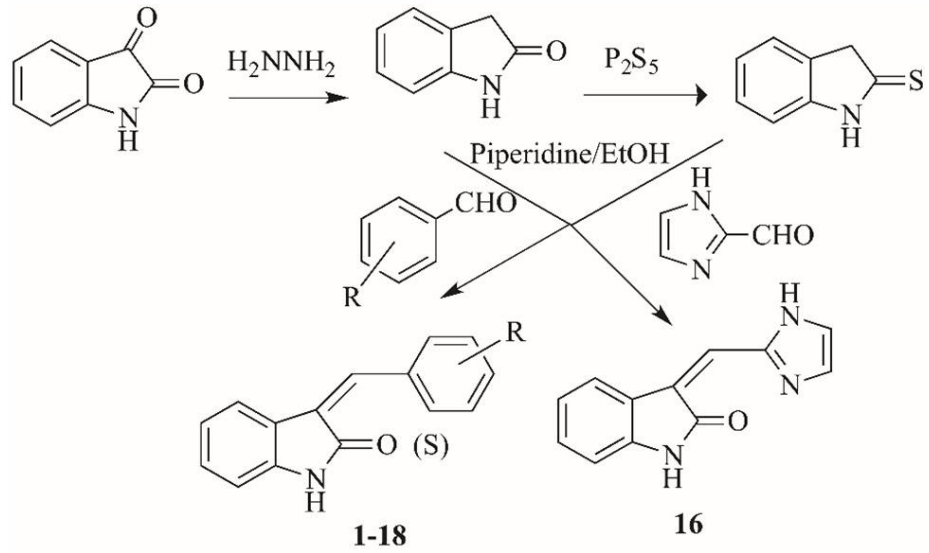


Figure 1: 3-Substituted benzylidene indolin-2-one and 2-thione derivatives tested for antimicrobial activity.

Oxoindole was synthesized by Wolff-Kishner like reduction of isatin and indole-2-thione was derived from indole-2-one by using P_2S_5. The tested compounds were synthesized by condensation of oxoindole and thioindole with several aldehydes in the presence of piperidine as a basic catalyst (Olgen *et al.*, 2005).

Molecular Docking

The crystal structures of the DNA gyrases of related microorganisms were taken from the Protein Databank (PDB, http://www.rcsb.org). The PDB ID for studied microorganisms was used as follows: *S. haemolyticus*: 2RHS, *S. thypi*: 6J90, *S. aureus*: 5CDQ, *A. baumannii*: 2XKJ, *S. enterica*: 6AEP).

After drawing the three-dimensional structure of the compounds by using ChemDraw Ultra 15.9, the energy minimizations of compounds were done by ChemBio Ultra 15.9. Then all water molecules were discarded and the polar hydrogens were added. The grid box was adjusted with a volumetric space of 30x30x30 for corresponding DNA gyrases of microorganisms. The docking study was run in AutoDock vina 4.2.6 software and the 3D compound-protein interactions were analyzed by using Pymol 4.2.6.

Calculation of molecular properties

To evaluate the structure-activity relationships of compounds, physicochemical features such as polar surface area (PSA), type of metabolizing enzymes, Blood-Brain Barrier (BBB) parameter, Lipinski's rule of five and Log P values were calculated by using Swiss ADME (http://swissadme.ch/) online software program (Swiss ADMET Prediction) (Lipinski et al., 2012).

RESULTS AND DISCUSSION

Determination of in vitro Antimicrobial Activities of Compounds

In this study, 18 different compounds were tested against 5 different microorganisms in comparison to reference drugs ampicillin, streptomycin, gentamicin and ciprofloxacin for determining antibacterial activities. The in vitro antimicrobial activities of compounds were determined by the microdilution method (CLSI, 2018) and the results were shown in Table 1. Accordingly, the activity data of the tested 18 compounds presented different profiles against the microorganisms. Compounds showed slight activity against Gram (+) bacteria of *S. haemolyticus* ATCC 43252 strain at 250-1000 µg/mL and Methicillin-resistant Staphylococcus aureus ATCC 43300 (MRSA ATCC 43300) strain at 125-500 µg/mL concentrations. They were also found active against Gram (-) bacteria of *A. baumannii* ATCC 19606 strains at 125-500 µg/mL, *S. Typhi* clinical isolate at 250-1000 µg/mL and against *S. enterica* clinical isolate at 125-250 µg/mL concentrations.

Table 1: MIC (µg/ml) values of tested compounds and standard drugs.

Results MIC (µg/ml)	*S. haemolyticus* ATCC 43252	MRSA ATCC 43300	*A. baumannii* ATCC 19606	*S. enterica* (clinical isolate)	*S. Typhi* (clinical isolate)
1	500	500	500	250	500
2	250	250	125	125	250
3	250	250	250	125	250
4	250	125	250	250	250
5	250	125	250	250	250
6	250	125	250	250	250

7	250	125	250	250	500
8	500	125	500	250	250
9	250	500	250	250	500
10	250	500	250	250	500
11	250	250	250	250	500
12	250	250	250	250	500
13	250	250	250	250	500
14	250	250	250	250	500
15	250	250	250	250	500
16	250	250	250	250	500
17	1000	500	500	250	500
18	1000	500	500	250	1000
Ampicillin	>1000	125	125	3,2	500
Gentamycin	31,25	<0,5	3,9	125	1,9
Streptomycin	500	0,9	125	62,5	31,25
Ciprofloxacin	0,48	0,97	31,25	0,48	0,48

*ND: Non Determined

As seen in Table 1 , the most active compounds showed their activities at 125 µg/mL of MIC value. Among them, compounds 2 and 3 were found to have activities against *S. enterica* and compounds 4, 5, 6, 7, and 8 were found to be active against MRSA. The reference compound ampicillin was found effective against MRSA and *A. baumannii* at 125 µg/mL and *S. enterica* at 3.2 µg/mL concentrations. Ciprofloxacin showed activity at 0.48 µg/mL of MIC value against *S. haemolyticus*, *S. enterica*, and *S. Typhi*. According to these results, it can be concluded that compounds are more active against *S. enterica* with a value of 125- 250 µg/mL than other bacteria tested in this study. In addition, the MIC values of compounds 4, 5, 6, 7 and 8 were determined in 125 µg/mL against MRSA ATCC *43300*, which represented more effective than other compounds against all tested microorganisms in the study. The MIC values of compounds 2,3,4,5,6,7,9,10,11,12,13,14,15,16 were determined 250 µg/ml against *Staphylococcus haemolyticus* ATCC 43252. Similarly, the MIC values of compounds 2,3,4,5,6,8 were determined 250 µg/ml MIC against *S. Typhi*. The MIC value of compound 2 was determined 125 µg/ml against *Acinetobacter baumannii* ATCC 19606. When the tested all compound was compared with reference drugs gentamicin and ciprofloxacin, they showed a weaker antimicrobial effect. In generally, it has seen that all compound showed a weaker antimicrobial effect compared with reference drugs gentamicin and ciprofloxacin. However, compound 2 showed similar antimicrobial effect againist *S. enterica* compared with gentamicin

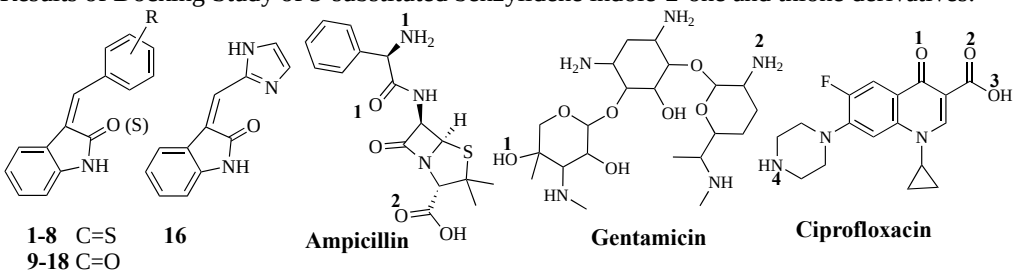
The antibacterial activity of compounds was observed better with 3-substituted benzylidene indol-2-thione derivatives than

with 3-substituted benzylidene indol-2-one derivatives.

Molecular Docking Studies

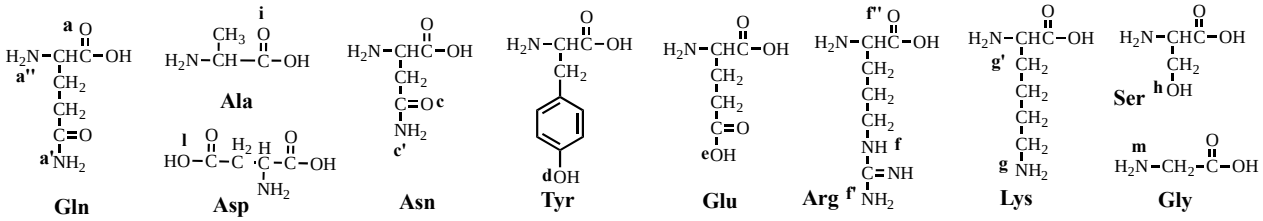
Antimicrobial efficacies of compounds were determined with molecular docking studies and the obtained best-docked poses were evaluated. To evaluate the effectiveness of compounds by molecular docking studies, the lowest binding energies, hydrogen bond capabilities, root-mean- square deviation (RMSD) value and MIC values of compounds were assessed. Since ciprofloxacin shows its effect via binding DNA gyrase, the docking studies of compounds were evaluated based on the data of biological and molecular interaction studies in comparison to ciprofloxacin**.** The best binding affinity and receptor-ligand interactions of each compound were assessed and well-established good interactions in the receptor's active pocket of the target receptor DNA gyrase of related microorganisms were shown in Table 2.

Table 2: Results of Docking Study of 3-substituted benzylidene indole-2-one and thione derivatives.



Comp No	R	Energy score	RMSD value	H-bond (distance Å)	Microorganisms
1	2-Cl	-7.00	0.11	NH of indole with e of GLU216 (2.054)	*S. heamolyticus*
2	4-COOH	-8.55	1.25	C=O with g' of LYS103 (2.107)	*S. enterica*
		-6.42	0.26	NH of indole with d of TYR1051 (1.900) C=O with m of GLY1143 (1.795)	*A. baumanii*
4	2-OH	-6.90	0.14	Ph-OH with O-l of ASP437 (2.108)	*S. aureus*
6	3-F	-7.13	0.12	-	*S. aureus*
7	4-OCH_3	-7.08	0.06	-	*S. aureus*
8	3-NO_2	-9.42	0.25	Ph-NO_2 with H-a' of GLN177 (1.842)	*S. heamolyticus*
		-9.33	0.32	Ph-NO_2 with H-c' of ASN46 (2.003)	*S. enterica*
12	3,4-DiCl	-9.02	0.22	C=O with H-h of SER174 (1.755)	*S. heamolyticus*
Amp		-12.11	0.70	O-1 with g of LYS103 (2.088) H-1 with i of ALA100 (2.095)	*S. enterica*
Gn		-10.88	1.99	H-1 with i of ALA100 (1.858) H-1 with e of GLU50 (2.143)	*S. typhi*
Cp		-7.00	0.44	O-2 with d of TYR1051 (2.155) O-2 with g' of LYS1156 (2.148)	*A. baumanii*
Cp		-10.54	0.09	O-2 with H-f' of ARG122 (1.761) O-2 with H-n of SER84 (2.176)	*S. aureus*
Cp		11.48	0.88	H-4 with O-i of ALA100 (2.151)	*S. enterica*
Cp		11.10	0.80	O-1 with H-h of SER174 (1.677)	*S. heamolyticus*

Amp.: Ampicillin; Gn: Gentamicin; Cp: Ciprofloxacin



The binding energy and RMSD value of most of the compounds were found to be very close to reference compounds ciprofloxacin. According to docking results, compounds showed better binding properties with the receptor active site of MRSA and *S. haemolyticus*. The effectiveness of compounds was evaluated based on the lowest binding energy capabilities and MIC values of compounds. The most active compounds (2, 3, 4, 5, 6, 7, and 8) were found effective at 125 µg/L concentration against *A. baumanii*, *S. enterica*, and *MRSA*. To confirm these results, docking studies were done and remarkable binding affinity values were found for compound 8 as interaction with *S. haemolyticus* at -9.42 kcal/mol and interaction with *S. enterica* at -9.33 kcal/mol.

Compound 2 showed good interaction with the receptor active site of *A. baumanii*, and *S. enterica*, with values at -6.42 kcal/mol and -8.55 kcal/mol, respectively. Good binding properties and biological activity showing compounds also presented good hydrogen-bonding ability and RMSD values and these findings were found to be mutually supportive. The reference compound ampicillin also showed good binding interaction with receptors of *S. enterica*, at -12.11 kcal/mol. This result confirms the good activity result of ampicillin with 3.2 µg/mL of MIC value against *S. enterica*. Gentamycin showed good binding property with the receptor of *S. Typhi* at -10.88 kcal/mol and also presented good activity at 1.9 µg/mL concentration. Although streptomycin did not show any interaction with the tested receptors in docking studies, it was found very active against all microorganisms in the range of 0.9-500 µg/mL concentrations. Although streptomycine is not a DNA gyrase inhibitor and does not interact with DNA gyrase active sites, it was used as a reference compound because of its strong and variety of antimicrobial spectrum. Ciprofloxacin showed good binding energies against all tested bacterial gyrase enzymes and was found as the most active compound in the range of 0.48-31.25 µg/mL. In terms of the way it binds to the receptor active site, some other compounds showed good binding properties. Figure 2 depicts the 3D structural interaction details

of the most active compounds 4, 5, 6, 7, and 8 with DNA gyrase of MRSA against *S. aureus* comparison to the reference compound ciprofloxacin.

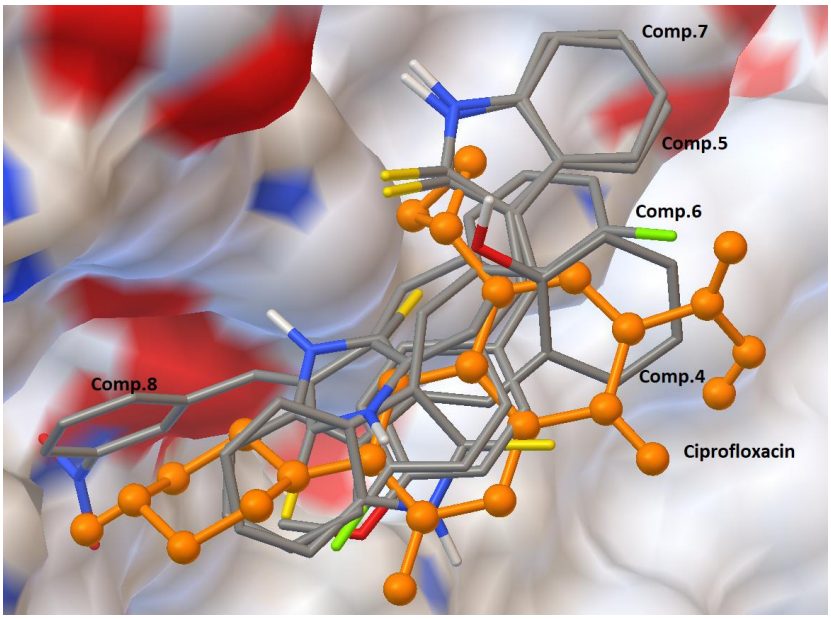


Figure 2: Three dimensional structural interaction of the most active compounds 4, 5, 6, 7, 8 and reference compound ciprofloxacin (orange) with DNA gyrase of MRSA.

As seen from the figures, compounds bonded to the active site by overlapping with reference compounds. These results proved that compounds presented the parallel results due to ligand-receptor binding interactions and therapeutic potence in *in-vitro* studies.

Drug-like properties

Swiss ADME online prediction program was used to calculate physicochemical features and drug-likeness properties of tested compounds to clarify the structure-activity relationships. The predicted values such as molecular weight, log P, PSA, crossing the BBB, GI absorption properties and type of CYPP450 inhibition of compounds were shown in Table 3.

Table 3: Drug-like properties of **1-18** calculated by Swiss ADME online software program.

Comp. No	MW (g/mol)[a]	LogP [b]	TPSA [c]	BBB [d]	GI Abs.[e]	Type of CYP Inh.[f]	Rule of Five [g]
1	273.78	4.37	54.59 Å	Yes	High	CYP1A2, CYP2C19, CYP2C9, CYP3A4	Yes
2	283.34	3.34	91.89 Å²	No	High	CYP1A2, CYP2C19, CYP2C9, CYP3A	Yes
3	308.23	4.88	54.59 Å²	Yes	High	CYP1A2, CYP2C19, CYP2C9, CYP3A	Yes
4	255.33	3.41	74.82 Å	Yes	High	CYP1A2, CYP2C19, CYP2C9, CYP3A	Yes
5	273.78	4.37	54.59 Å	Yes	High	CYP1A2, CYP2C19, CYP2C9, CYP3A	Yes
6	257.33	4.15	54.59 Å	Yes	High	CYP1A2, CYP2C19, CYP2C9, CYP3A	Yes
7	269.36	3.80	63.82 Å	Yes	High	CYP1A2, CYP2C19, CYP2C9, CYP2D6	Yes
8	284.33	3.22	100.41 Å²	No	High	CYP1A2, CYP2C19, CYP2C9, CYP3A4	Yes
9	257.71	3.86	36.02 Å²	Yes	High	CYP1A2, CYP2C19, CYP2D6 ,CYP3A4	Yes
10	239.27	2.84	56.25 Å²	Yes	High	CYP1A2, CYP2D6, CYP3A4	Yes
11	302.71	3.23	81.84 Å	No	High	CYP1A2, CYP2C19, CYP2C9	Yes
12	292.16	4.34	36.02 Å	Yes	High	CYP1A2, CYP2D6, CYP3A4	Yes
13	241.26	3.60	36.02 Å²	Yes	High	CYP1A2, CYP2C19, CYP2D6 ,CYP3A4	Yes
14	268.27	2.68	81.84 Å²	No	High	CYP1A2, CYP2C19, CYP2C9, CYP2D6	Yes
15	257.71	3.82	36.02 Å	Yes	High	CYP1A2, CYP2C19, CYP2D6 ,CYP3A4	Yes
16	213.24	1.78	64.70 Å²	Yes	High	CYP1A2, CYP2D6	Yes
17	308.23	4.87	54.59 Å²	Yes	High	CYP1A2, CYP2C19, CYP2C9, CYP3A4	Yes
18	282.40	3.81	57.83 Å²	Yes	High	CYP1A2, CYP2C19, CYP2C9, CYP2D6	Yes
Ampicillin	349.40	0.88	138.03 Å²	No	Low	CYP3A4	Yes
Gentamycin	477.60	-1.6	199.73 Å²	No	Low	-	No
Streptomycin	581.57	-5.86	336.43 Å²	No	Low	-	No
Ciprofloxacin	331.34	1.10	74.57 Å²	No	High	CYP3A4	Yes

[a]Molecular weight (recommended value <500)
[b] Logarithm of the partition coefficient of the compound between n-octanol and water (recommended value <5)
[c] Polar surface area (recommended value ≤140Å²)
[d] Indicates whether the compound pass blod Brain Barrier or not
[e] Degree of Gastrointestinal Absorption
[f] Represent the ınhıbıtıon of CYP450 subtypes
[g] Indicates whether the compound obeys Lipinski's Rule of Five or not.

Except for compounds 2, 8, 11 and 14, the other compounds showed good hydrophobic properties to pass lipid barrier. Lipophilicity values of compounds were

determined lower than the recommended value of 5 which obey Lipinski's Rules (Lipinski *et al.,* 2012). Compounds also exhibited good pharmacokinetic features

such as high gastrointestinal absorption (GI), Partition coefficient (LogP), Molecular weight (MW) and PSA which all obeys Lipinski's rule of five. Similar to our study, Mendoza-Figueroa et al. investigated the antibacterial activity of fluorine-substituted indole-based imidazolines against *Escherichia coli, Staphylococcus*

aureus, Pseudomonas aeruginosa and *Listeria monocytogenes* strains by broth dilution method and they found that one substance showed the highest antibacterial effect on *S. aureus* strain with a MIC value of 80 µg/ml (Mendoza-Figueroa *et al.,* 2018). Shirinzadeh et al. investigated the antibacterial effect of new indole derivatives containing 1,2,4-Triazole, 1,3,4-Thiadiazole and carbothioamide on *S. aureus, Bacillus subtilis, E. coli* and MRSA and they reported that they had an antibacterial effect with a MIC value of 6.25 µg/ml (Shirinzadeh *et al.,* 2018). In another

study, Chodvadiya *et al.* investigated the antibacterial effect of N-methyl indole derivatives on *E. coli, S. Typhi, Bacillus megaterium, Micrococcus spp.* by agar diffusion method and they showed that 3 substances had high antibacterial effects against *S. Typhi* (Chodvadiya *et al.,* 2019). Shaker et al. investigated the antibacterial effects of 2-(4-methylsulfonyl phenyl) indole derivatives on MRSA, *E. coli, P. aeruginosa and A. baumanni* and they reported that MIC values of 3 substances were found 8, 1, 2 µg/ml against MRSA strain and MIC value of 3 substances were found 16.44 µg/ml against *A. baumannii* (Shaker et al., 2020). Doganay *et al.* investigated the antibacterial effect of 16 different indole amide derivatives on 14 different bacteria by agar diffusion and broth dilution method and found that the tested compounds were most effective (25 µg/ml) against *S. aureus* and *Aeromonas hydrophila* (Doganay *et al.,* 2022). Olgen *et al.* investigated the antibacterial effect of 3-substituted benzylidene-1,3-dihydro-indoline derivatives against *K. pneumoniae, P. aeruginosa, E. coli, B. subtilis, S. aureus* by broth dilution method. As a result of their studies, a high activity was observed (15.62 – 62.5 µg/ml) against *B. subtilis* and *S. aureus* strains (Olgen and Ozkan 2009). According to the results of the study, it was determined that the examined substances had antibacterial effects against the test bacteria, albeit in low amounts. In the

literature, it was observed that the indole derivatives tested on different bacterial strains were more effective than the indole derivatives tested in the study. In order to evaluate the structure-activity relationship of compounds, it was evaluated that the electron-withdrawing or electron-giving substituent effects might not play a role in the potency of compounds. The overall evaluation of the molecular docking and activity results indicates that the results are parallel with activity results and show that most compounds have activity against the *S. aureus*. The docking results also supported that most compounds bind the related active site with the expected properties in terms of binding energy, hydrogen bond capability, Van Der Waals interactions, and RMSD values. Since antimicrobial activity studies have not been performed on many compounds with 3-substituted benzylidene indole-2-one and thion structure in literature, it was not possible to make a comparative structure-activity interpretation of the compounds. However, the findings obtained in this study give clues about the possibility of obtaining more effective molecules when modifications with further substitutions are made on these main structures.

Several predicted descriptors such as the molecular weight, percent human oral absorption, PSA and logarithm octanol-water partition coefficient (QPlogPo/w) showed that all compounds have drug-likeness properties and good oral absorption values. As a result, it can be concluded that compounds might have good bioavailability and drug-likeness properties. All compounds tested in the study were found to exhibit less, equivalent, or greater antibacterial activities than the reference drugs used in the study.

CONCLUSION

None of indole-2-one and indole-2-thion compounds showed strong inhibitor effects against used microorganisms in this study. The presence of antimicrobial effects of structurally similar compounds in the literature and the lack of antibacterial activity in our compounds showed that small changes in the structure significantly affect the activity results. These results suggest that further studies of receptor interaction such as molecular dynamic are required to design rational novel compounds. However, it can be considered to test some of the compounds against other microorganisms in *in-vitro* studies. It is thought that the results of the study will contribute significantly to the development of antimicrobial drugs related to indole

derivatives.

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