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# Antibacterial activity of some 1,2,3,4-tetrasubstituted pyrrole derivatives and molecular docking studies

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**Abstract:** Pyrrole compounds are important classes of heterocycle compounds in the search for effective agents against multidrug-resistant bacterial infections. With an approach to reduce the growing bacterial resistance and to discover more active antibacterial agents with fewer side effects, the previously synthesized 1,2,3,4-tetrasubstituted pyrrole derivatives were screened for their *in vitro* antibacterial activity by disc diffusion method against some Gram-positive and Gram-negative bacteria, for the first time. The results indicated that compounds **4, 11, and 12** showed promising antibacterial activity against Gram-positive *S. aureus* and *B. cereus* bacteria equal or more than standard as tetracycline. Molecular docking studies were employed both to explain the activity results of the more active compounds at the level of protein-ligand interactions and to compare the interactions of these compounds with the interactions of tetracycline. The relationship between structure and antibacterial activity was also discussed.

**Keywords:** Antibacterial activity; 1,2,3,4-tetrasubstituted pyrroles; tetracycline; disc diffusion method; molecular docking. 

## 1. Introduction

Infectious diseases caused by bacteria are still a major worldwide problem due to the increase in the morbidity, mortality, and costs connected to its healing along with the rapid development of resistance to the existing antibacterial drugs. The improper and irrational utilization of antibacterial medicines has resulted in resistant bacteria becoming prominent.[1-5] A wide range of antibacterial classes has been identified during the search of antibacterial agents in 1950s-70s after the successful outcomes obtained by the discovery of early antibacterial drugs such as penicillin and sulfa drugs. However, no new classes of antibacterial agents have been discovered since this era.[6,7] Since pathogenic bacteria continuously evolve mechanisms of resistance to currently used antibiotics, the discovery of novel and potent antibacterial classes and agents is vital to help in the battle against pathogenic microorganisms and develop effective therapies.[8]

Pyrrole and its derivatives are important heterocycles that are found in many natural products such as heam, chlorophyll, vitamin B12, and bile pigments. Also, numerous natural products containing pyrrole core display diverse biological properties.[9] Due to the chemical functionality of the

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pyrrole scaffold in biologically active molecules, they have been widely used in drug development for the treatment as antibacterial, anti-inflammatory, antiviral, antitumor, and antioxidant agent.[10] Pyrrole derivatives as antibacterial agents have been investigated for several decades. For instances, some tetrasubstituted pyrrole derivatives were synthesized and evaluated for their biological potential against *Escherichia coli* and *S. aureus* by Abdul Jamal Abdul Nasser et al. They found that 3,5-dimethyl-$N^2$, $N^4$-bis(4-(4-nitrophenyl)thiazol-2-yl)-1*H*-pyrrole-2,4-dicarboxamide displays excellent activity against *E. coli* relative to the standard ciprofloxacin (Figure 1).[11a,b] A series of new pyrroles and pyrrolo[2,3-d] pyrimidine derivatives were also reported as compounds having potent antimicrobial activity against various Gram-positive and Gram-negative bacteria.[12] 1,2,3,5-tetrasubstituted pyrroles, especially 1,2,3-tris(4-fluorophenyl)-5-phenyl-1*H*-pyrrole, has significant activity against the *Chlamydia strain* which is a group of bacterial pathogens, as proved by Bao *et al.* (Figure 1).[13] Also, a naturally occurring halogenated pyrrole derivative such as pyoluteorin was found to have antibacterial activity, and many 4,5-dihalopyrrole derivatives derived from pyoluteorin were synthesized and reported as potential antibacterial agents.[14,15] (*R*)-Reutericyclin,(*2R*)-4-acetyl-1,2-dihydro-5-hydroxy-2-(2-methyl-propyl)-1-[(*2E*)-1-oxodec-2-enyl]-3*H*-pyrrol-3-one was found as another bactericidal natural compound with a trisubstituted tetramic acid moiety which shows a broad spectrum antibacterial activity against Gram-positive bacteria.[16] Recently, pseudoceratidine and 64 closely-related analogues were synthesized to be evaluated against Gram-positive and Gram-negative bacteria by Barker et al. They highlighted that these analogues are most effective against Gram-positive bacteria and two pyrrole units in their structure are essential for the good antibacterial activity.[17] Masci et al. reported the identification, synthesis, and antibacterial evaluation of some novel 1,5-diphenylpyrrole derivatives. The synthesized pyrrole compounds exhibited high activity against Gram-positive and Gram-negative bacteria at a concentration similar or lower than levofloxacin by targeting the bacterial DNA gyrase. Also, they showed similar inhibitory activity to levofloxacin against the wild-type enzyme and retaining activity against the fluoroquinolone-resistant enzyme.[18]

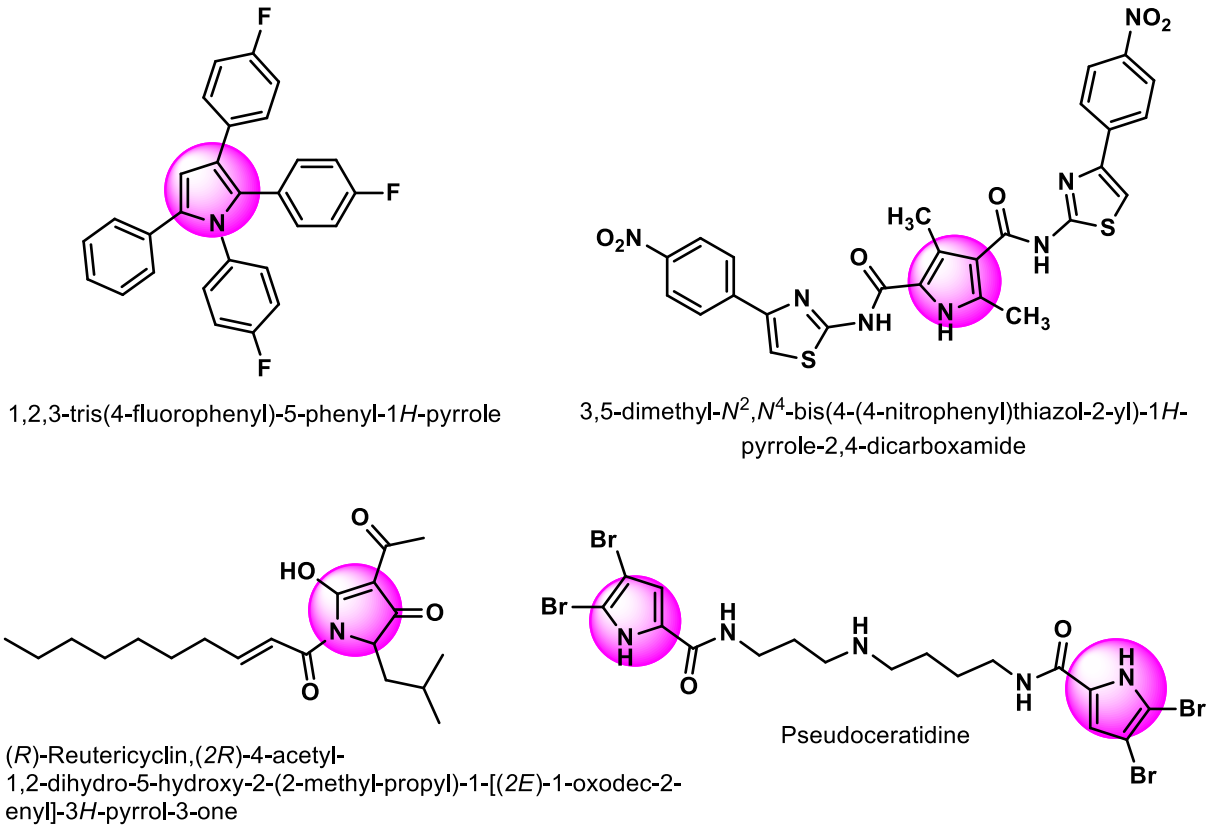



**Figure 1.** Pyrrole-based antibacterial derivatives

The extraordinary interest in pyrrole derivatives as antimicrobial agents, as it is seen in the literature survey, has led us to check our previously synthesized 1,2,3,4 tetrasubstituted pyrrole derivatives for their antibacterial properties.[19] Here, for the first time, this kind of pyrrole derivatives was evaluated for their *in vitro* antibacterial effects on Gram-positive bacteria; *Staphylococcus aureus, Bacillus cereus,* and Gram-negative bacteria; *Escherichia coli, Pseudomonas fluorescens, Salmonella typhimurim.* It is found that some of the 1,2,3,4-tetrasubstituted pyrrole derivatives demonstrated an inhibitory effect on Gram-positive bacteria, with compounds **4, 11, 12** being the most effective in comparison to tetracycline. The structure-activity relationship was determined by comparing their activity results. Also, molecular docking studies were performed to explain the antibacterial activities of active compounds at the level of protein-ligand interactions. The interactions of the compounds and reference molecule with docking studies were used Maestro 11.8 program. The result of studies showed in a good binding affinity of the molecules with the bacterial target.

## 2. Experimental

### *2.1. Chemistry*

Unless noted otherwise, all starting materials and solvents were used as provided without further purification. All synthesized compounds were characterized by NMR, IR, and elemental analyses. Nuclear magnetic resonance (NMR) spectra are recorded in parts per million from internal tetramethylsilane on the δ scale. $^{1}H$ and $^{13}C$ NMR spectra were recorded in $CDCl_3$ or $DMSO_4$-$d_6$ [using the solvent peak as internal reference ($CDCl_3$: δ H 7.24; δ C 77.23, $DMSO_4$-$d_6$ : δ H 2.50; δ C 39.51)] on a Bruker 300 MHz Ultrashield TM spectrometer operating at 300 MHz and 75 MHz, respectively or a Bruker Avance III 400 MHz spectrometer operating at 400 MHz and 100 MHz, respectively. IR spectra were recorded on a Perkin-Elmer 55148 spectrometer. Melting points were determined in capillary tubes using an Electrothermal 9100 instrument; they are uncorrected. Elemental analyses were measured on a Thermo Flash 2000 Organic Elemental Analyzer. The purity of the synthesized compounds was checked on silica gel TLC plates using petroleum ether and ethyl acetate as a solvent system. The visualization of the spot was done under UV light.

The 1,2,3,4-tetrasubstituted pyrrole derivatives (1–24) were synthesized and isolated as previously described.[19] They were characterized by spectroscopic analysis (see Supporting Information).

### *2.2. Antibacterial Activity*

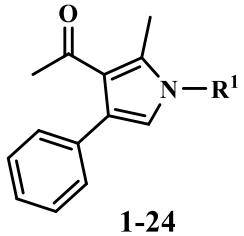
The antibacterial activity of the synthesized compounds was determined on Mueller-Hinton agar (MHA) medium by disk diffusion method against Gram-positive bacteria; *Staphylococcus aureus* (25923), *Bacillus cereus* (NRRL 3711) and Gram-negative bacteria; *Escherichia coli* (ATCC 25922), *Pseudomonas fluorescens* (NRRL 2641), *Salmonella typhimurim* (25923) [20,21] The bacterial zone of inhibition was measured in mm. Tetracycline was used as the standard antibiotic for comparison due to its structural similarity to the pyrrole derivatives. DMSO was kept as a negative control. All synthesized compounds were dissolved in DMSO to make a stock solution of 2500 µg/mL. Eight sterile discs of diameter 6 mm were placed on the medium. Two different dosages of each synthesized compound solution (5 and 10 µL) were added to the previously labeled discs and the petri dishes were incubated at 37°C for 24 h. The diameter of the zone of inhibition around each disk was measured by the scale for each compound. The average of three readings of bacterial zones of inhibition (mm) values is presented in Table 1.

### *2.3. Molecular Docking Studies*

Maestro 11.8 (Schrodinger, USA, 2018) program was used in molecular docking studies. To evaluate the antibacterial activities of the synthesized compounds, the two different crystal structure of 2ZCO, and 5BS8 PDB encoded proteins was used. Crystal structures of proteins are taken from www.rscb.org. Protein Preparation Wizard software of Maestro was used for the preparation of protein

crystal structures.[22, 23] While preparing the proteins, first of all, the water molecules and ligands in the protein structure were deleted and hydrogen atoms were added. Then the proteins were minimized using the OPLS3 force filed. Active regions of each protein (2ZCOand 5BS8) were determined according to the literature data, and grid box maps were created using the Grid Map Generator software. The X, Y, Z coordinates of the proteins (2ZCO and 5BS8) are respectively; 52.91, 8.93, 48.6 and 36.33, 19.36, 15.52.[24-26] Ligands and reference molecule (tetracycline) were drawn with the 2D Sketcher software of Maestro program and prepared for docking studies using LigPrep software. The possible ionization states were generated at the target site at pH 7.0 ± 2.0. The prepared ligands and tetracycline were docked 100 times to the active site of three different proteins with extra precision. 3D images of protein-ligand interactions were obtained using Schrodinger's XP visualizer.[27]

**Table 1.** *In vitro* antibacterial property of pyrrole compounds **1-24** against Gram-positive and Gram-negative bacteria




**1-24**

| Pyrrole Compounds | $R^1$ | Zone of Inhibition (mm) | | | | |
|---|---|---|---|---|---|---|
| | | Gram-positive bacteria | | Gram-negative bacteria | | |
| | | ***S. aureus*** | ***B. cereus*** | ***E. coli*** | ***P. fluorescens*** | ***S. typhimurium*** |
| **1** | $C_6H_5$ | - | - | - | - | - |
| **2** | 4-$OCH_3$-$C_6H_4$ | - | 7 | - | - | - |
| **3** | 4-OH-$C_6H_4$ | 7 | 10 | - | - | - |
| **4** | 4-COOH-$C_6H_4$ | 30 | 19 | - | - | - |
| **5** | 4-$OC_2H_5$-$C_6H_4$ | - | - | - | - | - |
| **6** | 4-$NO_2$-$C_6H_4$ | 13 | 9 | - | - | - |
| **7** | 4-$CH_3$-$C_6H_4$ | 11 | 7 | - | - | - |
| **8** | 4-F-$C_6H_4$ | - | - | - | - | - |
| **9** | 4-Cl-$C_6H_4$ | - | - | - | - | - |
| **10** | 4-Br-$C_6H_4$ | - | - | - | - | - |
| **11** | 3-$NO_2$-$C_6H_4$ | 24 | 16 | - | - | - |
| **12** | 3-$CF_3$-$C_6H_4$ | 21 | 12 | - | - | - |
| **13** | 3-Cl-$C_6H_4$ | - | - | - | - | - |
| **14** | 3-F-$C_6H_4$ | - | - | - | - | - |
| **15** | 3-Br-$C_6H_4$ | - | - | - | - | - |
| **16** | 2-OH-$C_6H_4$ | 13 | 12 | - | - | - |
| **17** | 2-$CH_3$-$C_6H_4$ | 8 | - | - | - | - |
| **18** | 2-F-$C_6H_4$ | 12 | - | - | - | - |
| **19** | $C_6H_5$-$CH_2$ | 12 | - | - | - | - |
| **20** | 4-$CH_3$-$C_6H_4$-$CH_2$ | - | - | - | - | - |
| **21** | 4-$OCH_3$-$C_6H_4$-$CH_2$ | - | - | - | - | - |
| **22** | cyclohexyl | - | - | - | - | - |
| **23** | 2-furfuryl | 9 | 8 | - | - | - |
| **24** | 2-naphthyl | - | - | - | - | - |
| Tetracycline (Standard) | | 23 | 20 | 23 | 25 | 20 |

Significant activities are bold. - No *activity was observed*

*S.aureus: Staphylococcus aureus (25923), B.cereus*: *Bacillus cereus* (NRRL 3711), *E.coli*: *Escherichia coli* (ATCC 25922), *P. fluorescens*: *Pseudomonas fluorescens* (NRRL 2641), S. *typhim*urium: *Salmonella typhimurium* (25923)

## 3. Results and Discussion

All the synthesized 1,2,3,4-tetrasubstituted pyrrole derivatives were initially screened for their *in vitro* antibacterial effects on Gram-positive and Gram-negative bacteria using the disk diffusion method. The zone inhibitions were evaluated by comparison to standard ‘‘tetracycline’’ as reference antibiotic which showed zone inhibition 23, 20, 23, 25, and 20 mm against *S.aureus, B. cereus, E. coli, P. fluorescens,* and *S. typhimurium* respectively. To ensure that the solvent (DMSO) did not affect bacteria; a negative control test was also performed with only DMSO at the same dilutions with the compounds and found inactive in the culture medium. The results of *in vitro* antibacterial activity (zone of inhibition) were reported in Table 1. In general, the antibacterial screening data revealed that some 1,2,3,4-tetrasubstituted pyrrole derivatives displayed moderate to excellent inhibition against Gram-positive bacteria while they did not show any inhibitory effect on Gram-negative bacteria. The non-activity of the pyrrole derivatives against Gram-negative bacteria could be explained with either the low permeability of Gram-negative outer membrane which poses an obstacle the molecules reaching the target or the unsuitable chemical structure of pyrrole derivatives for binding the bacterial target. Among all compounds, compound **4** was found to be the most potent one against both Gram-positive *S. aureus* and *B. cereus* with inhibition zones of 30 and 19 mm, respectively. Compound **11** (24 mm in *S. aureus*) showed inhibition more than the standard drug tetracycline (zone of inhibition: 23 mm in *S. aureus),* meanwhile, the inhibition of compound **12** (21 mm in *S. aureus*) was nearer to the standard. However, both these compounds were less active towards *B. cereus* relative to the reference. Compounds **17, 18,** and **19** displayed inhibition only against S. aureus with a small zone whereas they did not show any inhibition against *B. cereus*. Compound **2** was weakly active only towards *B. cereus* and compounds **3, 6, 7, 16**, and **23** exhibited poor activities against both Gram-positive bacteria. Besides, the remaining synthesized compounds (**1, 5, 8-10, 13-15, 20-22,** and **24**) were determined not to show any inhibition against the same organisms.

An insight into the structures of the active compounds indicated that the variation of the electronic properties of functional groups on phenyl ring attached to the nitrogen atom of pyrrole core and their position did not have any obvious effect on the inhibition of the growth bacteria. The presence of electron-withdrawing substituents (3-$NO_2$, 3-$CF_3$, 4-COOH) at para and meta position on the phenyl ring led to enhance the antibacterial potential of the pyrrole derivatives. Especially, compound **4** containing the carboxyl group at para position displayed the highest antibacterial activity profile against Gram-positive bacteria. When the electron-donating substituents (4-OH, 4-$OCH_3$, 4-$CH_3$, 2-OH, 2-$CH_3$) were at para and ortho position, the compounds illustrated poor to moderate activity against the same Gram-positive bacteria. Furthermore, the introduction of weakly electron-deficient halogens did not make any change in the spectrum of antibacterial activity of the pyrrole compounds. These results demonstrated that generally, 1,2,3,4-tetrasubstituted pyrrole derivatives possess antibacterial activity against Gram-positive *S. aureus* and *B. cereus*, whereas they do not show any inhibition on Gram-negative *E. coli, P. fluorescens,* and *S. typhimurim* bacteria. Also, the correlation ship between the antibacterial activity and the position and nature of substituents on the phenyl ring at the *N*-position of pyrrole cannot be drawn exactly.

Molecular docking studies have been carried out to explain the antibacterial activities of the synthesized new compounds at the level of protein-ligand interactions and to compare the interactions of these compounds with the interactions of tetracycline (reference molecule). Docking studies were performed using 2ZCO (Crystal structure of the C(30) carotenoid dehydrosqualene synthase from Staphylococcus aureus), and 5BS8 (topoisomerase II complex) PDB encoded proteins. Maestro 11.8 program was used in all stages of molecular docking studies. The results of docking studies with two different proteins are given in Table 2.

**Table 2.** Docking scores of compounds (kcal/mol) against two target proteins

| | **Docking Scores (kcal/mol)** | |
|---|---|---|
| **Compounds** | **2ZCO** | **5BS8** |
| **4** | -5,500 | -2,982 |
| **11** | -6,629 | -3,235 |
| **12** | -6,700 | -3,683 |
| Tetracycline | -6,371 | -3,832 |

In the docking study performed with the 2ZCO PDB coded protein, it was observed that the docking scores of the compounds **11** and **12** (-6,629; -6,700, respectively) were higher than tetracycline. Tetracycline has a salt bridge with ARG 45, hydrogen bonding with TYR129; has charged (negative) interaction with ASP48, ASP49, ASP52, ASP114; charged (positive) interaction with ARG181; has hydrophobic interaction with ILE51, VAL111, TYR129, VAL133, ALA134, TYR183; has polar interaction with HIE18, GLN115, GLN165, ASN179. Compound **12** has pi-cation interaction with ARG45; hydrogen bonding with TYR129; has charged (negative) interaction with ASP48, ASP114 ASP172; charged (positive) interaction with ARG45; has hydrophobic interaction with CYS44, TYR41, PHE22, VAL111, TYR129, VAL133, ALA134, TYR183; has polar interaction with HIE18, THR110, GLN165, ASN168. When the interactions of compound **4** in the active site of the protein were examined, it was observed that it did not make strong interactions with residues in this region (Figure 2). It is thought that the reason for the low activity of compound **4** is that this compound does not make these strong interactions.

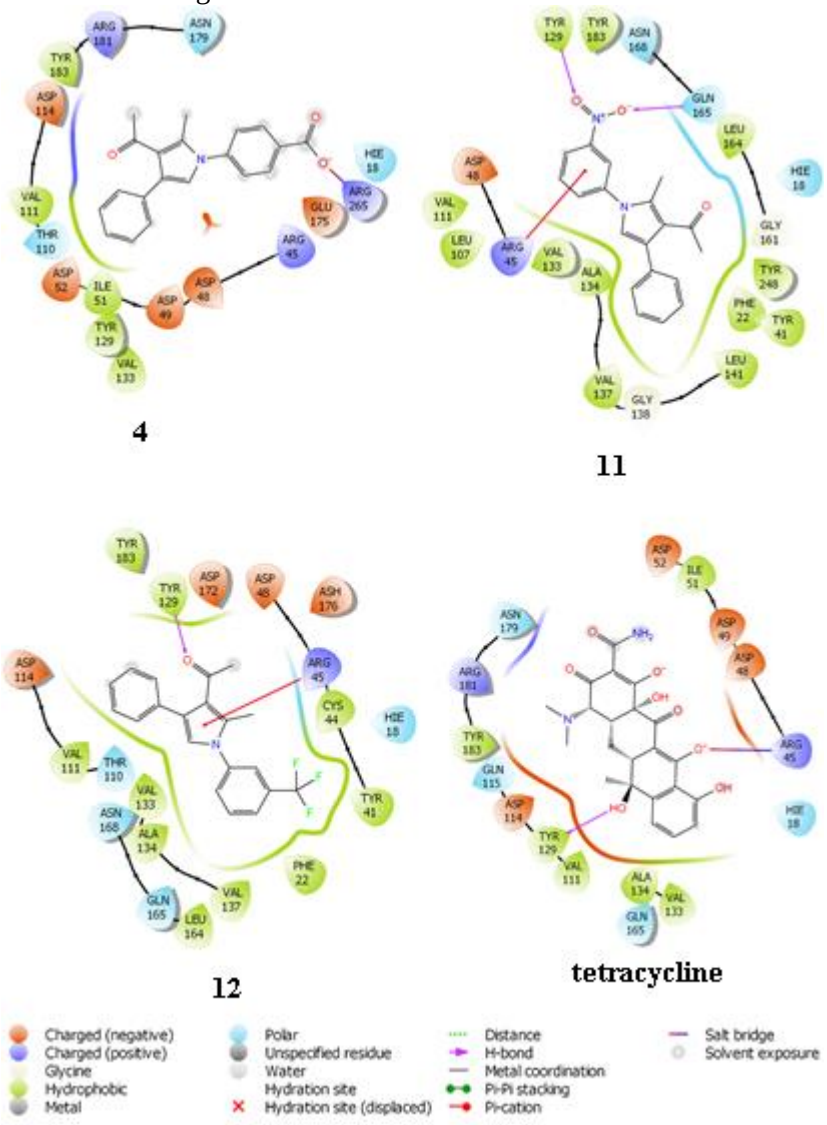



**Figure 2.** 2D interaction compounds 4, 11, 12, and Tetracycline with the active site of protein (**2ZCO**)

In the docking study performed with 5BS8 coded protein, the docking scores of the synthesized compounds **4, 11, 12**, respectively -2.98, -3.235, and -3.683 kcal/mol were calculated to lower than the tetracycline docking score (-3,832). However, *in vitro* antibacterial activity studies on *S. aureus*, compounds **11** and **12** were found more active than tetracycline. When the interactions of the compounds with the receptor are examined, it is seen that compounds **11** and **12** have similar

interactions (Figure 3). Compounds **11** and **12** have pi-cation interaction with ARG128 and LYS484; hydrogen bonding with GLY483; have charged (negative) interaction with ASP461, GLU459, ASP532, ASP536; have charged (positive) interaction with ARG482, ARG39; hydrophobic interaction with LEU481, and ILE540. On the other hand, tetracycline has a salt bridge with ARG482 and ARG128; hydrogen bonding with GLY88; has charged (negative) interaction with ASP461, GLU459, ASP532, ASP536; has charged (positive) interaction with LYS484; has hydrophobic interaction with PRO86, ALA90, ALA126, ILE540; has polar interaction with HIS87, SER91, and SER462. Although the docking scores of compounds **11** and **12** are lower than tetracycline, the reason for the low antibacterial activity of tetracycline may be the different interactions compounds have in the active site of the protein. Among these interactions, especially hydrogen bonding with GLY483 is thought to be related to antimicrobial activity.

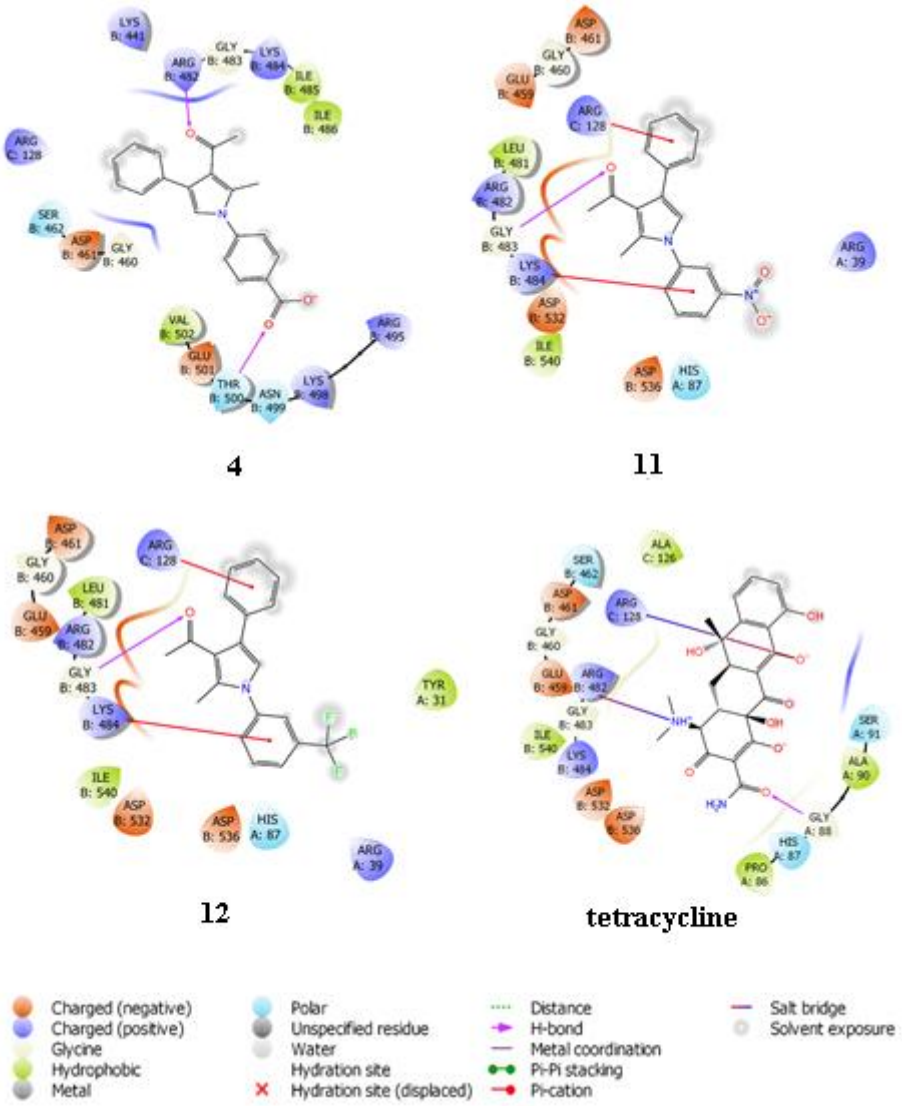



**Figure 3.** 2D interaction compounds 4, 11, 12 and Tetracycline with the active site of protein (**5BS8**)

## 4. Conclusion

In the present study, some 1,2,3,4-tetrasubstituted pyrrole derivatives were evaluated for their antibacterial activity with the hope of discovering new bioactive molecules that could be useful as potent antibacterial agents. Among all the tested compounds, compounds **4** and **11** exhibited excellent

antibacterial activity against Gram-positive *S. aureus*, which were 30% and 4% more than tetracycline respectively, whereas compound **12** displayed inhibition very close to the standard antibiotic tetracycline. Also, these compounds have good activity against *B. cereus*. Unfortunately, all tested 1,2,3,4-tetrasubstituted pyrroles did not have any inhibitory effect on the Gram-negative *E. coli*, *P. fluorescens*, *S. typhimurim*. Furthermore, the binding affinity of compounds was carried out by docking studies. The results may be instructive to researchers to gain more understanding of the antibacterial activity of pyrrole derivatives.

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## Supporting Information

Supporting information accompanies this paper on https://www.acgpubs.org/journal/bioorganic-medicinal-chemistry-reports

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