RESEARCH PAPER

Synthesis, in vitro Antimicrobial assay and Molecular Docking Studies of some new Symmetrical Bis-Schiff Bases and their 2-Azetidinones.

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ABSTRACT:

Four membered cyclic amides that are a broadly utilized class of antimicrobial agents up to now. Moreover, Symmetrical Bis-Schiff bases constitute an extraordinary class of strained compounds with varied applications and building blocks for the synthesis of 2-Azetidinones antibiotics. Because of those over biological significance, this study concludes a versatile synthetic precursor for the synthesis of the new Symmetrical Bis-Schiff bases and 2-Azetidinones in an exceedingly high yield. 2-Azetidinones were synthesized through [2+2] dichloroketene-imine cycloaddition reaction. The structures of the synthesized compounds were characterized by FT-IR, ¹H-NMR, and ¹³C-NMR. Additionally, the products were assayed against two antibacterial types Gram-positive (S. aureus) and Gram-negative (E. coli) microorganisms and two varieties of fungal strains A. niger, T. mentagrophytes by broth microdilution method. As a result, all synthesized compounds displayed good antimicrobial activities against resistant strains. Finally, molecular docking studies were explained the inhibitory activities for the new products with the target (PDB ID: 1MWU) methicillin acyl-Penicillin binding protein 2a from methicillin-resistant Staphylococcus aureus strain 27r at 2.60 Å resolution.

KEY WORDS: Symmetrical Bis-Schiff Base, 2-Azetidinone, Antimicrobial assay, and Molecular Docking Studies.

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1. INTRODUCTION:

The development of new antimicrobial organic compounds might afford further opportunities for the treatment of diverse microorganism infections that uncountable folks worldwide affected (Kumar et al., 2017). Conversely, heterocyclic Schiff bases are well-known to human treatment when illnesses are affecting for a protracted time (Azzawi and Al-Obiadi). For that reason, researchers and pharmaceuticals are synthesizing and studying Schiff bases that are one of the most significant synthetic usages in organic chemistry which is used as intermediate for the synthesis of different compounds (Ali et al., Shockravi et al., 2009).

Schiff bases are known as imines or azomethines which had been discovered by Hugo Schiff in 1864 (Ahmad et al., 2020). The functional group of (C=N) is the functional group of Schiff base which are commonly synthesized through the condensation of active carbonyl groups and primary amines (Bhuyar et al., 2013, Sharma et al., 2012). Symmetrical bis-azomethines (Ar-N=CH-Ar=CH=Ar) have a similar synthetic mono Schiff base’s pathway but by using the different molar ratio (Ozdemir Gungor, 2017). Schiff bases have broad variability applications in a medicinal field that possess a wide spectrum of biological activities such as antibacterial (Ziwar and Musheer), antioxidant (Hassan, 2019), antifungal (Noori et al., 2019), anti-inflammatory,
analgesic, anticancer (Kajal et al., 2013), antitumor (Ibrahim, 2015), anticonvulsant antimalarial, anti-tubercular (Khudr and Zimam, 2018a), and anti-diabetic (Al-Masoudi et al., 2016).

The chemistry of 2-Azetidinone has involved a crucial site in organic chemistry, it is four-membered heterocyclic amidates (Singh and Sudheesh, 2014, Van Brabandt et al., 2005). The (N) atom is linked to the 2-carbon atom neighboring to the carbonyl so it referred to Azetidin-2-one. Staudinger had synthesized 2-Azetidinone in 1907 for the first time through [2+2] ketene-imine cycladdition reaction (Khudr and Zimam, 2018a). Azetidin-2-one is based on the varieties of the important antibiotics on an individual basis human and varied medicines (Singh and Sudheesh, 2014). Azetidin-2-one antibiotics action by inhibiting the microorganism cytomembrane in each gram-positive and gram-negative microorganism caused by their sturdy binding affinity to energetic penicillin-binding proteins (PBPs) (Piens, 2017). To date, researchers still improvements and discovering new drugs as a result of vying a vital role in the therapeutic field owing to their broader spectrum of biological activities (Jurčík et al., 2011) such as antibacterial, antifungal (Mehta et al., 2006), antioxidant (Hassan, 2019), anticancer, analgesic and antiviral activities (Deep et al., 2016), anti-inflammatory (Ayyash, 2019), antimalarial (Borazjani et al., 2020).

In a read of that overhead biotic importance, the current study has been focused on the synthesis of the Bis-Schiff bases and their 2-Azetidinone. All the synthesized compounds were tested for antibacterial and antifungal activities and additionally the screened activities supported by their Molecular Docking studies.

2. MATERIALS AND METHODS

Chemical compounds were bought from Sigma-Aldrich, Fluka, and Merck chemical companies and used without further purification. Melting points were determined by electrothermal melting point apparatus (Stuart, normal power 75 W, model: ST15 OSA at Raparin University/ Kurdistan/Iraq) in capillaries and were uncorrected. Thin-layer chromatography (TLC) on pre-coated SiO₂ gel (HF254, 200 mesh) aluminum plate was used to check the progress of the reactions, a mixture of n-hexane: ethyl acetate (7:3) was used as eluent. TLC plates were visualized by UV light (CSL-MDOCBASIC at Raparin University/ Kurdistan/Iraq). The Ultrasonic cleaner was used for sonication (DIGITAL PRO+, 40 kHz, and a standard power 180 W at Raparin University/ Kurdistan/Iraq). FT-IR spectra were recorded on the Thermo Scientific Spectrometer (Model: Nicolet iS 10 at Raparin University/ Kurdistan/Iraq). ¹H-NMR and ¹³C-NMR spectra were carried out on a Brukner (400 MHz at Tehran University/ Iran), DMSO-d₆ was used as a solvent with TMS as an inner standard), data were reported as chemical shift in ppm, apparent multiplicity (s = singlet, d = doublet, t = triplet, br= broad, J= coupling constant, Hz = Hertz). A microplate reader (BioTek-ELx808 at Raparin University) was used for the detection of antimicrobial activity of the synthesized compounds.

2.1. A general synthetic method for the synthesis of symmetrical Bis-Schiff bases (2-8)

All the symmetrical Schiff bases were synthesized via the condensing between amines and terephthaldehyde. An appropriate synthetic method was used with a slight modification (Turan and Sekerci, 2009). An amine ethyl alcohol solution (2 mmol in ethanol 5 mL) was added to a warm ethyl alcohol solution of terephthaldehyde (1 mmol in 5 ml ethanol). A catalytic amount of glacial acetic acid was used (10 mol %). The reaction mixture was sonicated for 35-75 minutes. The completion of the reaction was checked by TLC plates. The precipitate was collected through filtration. The products were recrystallized several times from absolute ethanol to obtain pure products (2-8), the reaction conditions are shown in the (Scheme 1).

2.1.1. 4,4’-(1,4-phenylenebis(methaneylylidene))bis(azaneylylidene))bis(N-(thiazol-2-yl) benzene sulfonamide) (2)

Pale yellow color solid, m.p. = 254-255 °C, yield= 83%, time= 40 minutes. FT-IR (cm⁻¹): 3194 (NH str.), 3010 (CH Ar. St.), 1620 (C=N str. imine), 1578 (C=C Ar. St.), 1303 (SO₂ asym. str.), 1146 (SO₂ sym. str.). ¹H-NMR (DMSO-d₆): δ 12.680 (s, br, 2H (NH)), 8.101 (s, 2H (CH=N)), 8.731 (s, 4H (H2, H3, H5, H6)), 7.891 (d, 4H (H3', H5')), J= 8
Hz), 7.436 (d, 4H (H2', H6')), J= 8 Hz), 7.297 (d, 2H (H4'')), J= 7.6 Hz), 6.875 (d, 2H (H5'')), J= 8.4 Hz). 13C-NMR (DMSEO-d6): δ 169.37 (2C (C=N')), 143.5 (2C (C1'')), 137.19 (2C (C1, C4')), 132.92 (2C (4'a)), 130.11 (2C (C6')), 129.98 (4C (C3', C5')), 124.64 (2C (C1')), 121.46 (2C (C3')), 116.78 (2C (C7')).

2.1.3. 4,4'-(1,4-phenylenbis(methanethylenedimethylene))bis(N-phenylaniiline) (4)
Dark green color solid, m.p. = 122-123 °C, yield = 78%, time = 65 minutes. FT-IR (cm⁻¹): 3382 (OH str.), 3049 (NH str.), 2917 (C-H str.), 1581 (C=C str.), 1335 (SO₂ asym. str.).

1H-NMR (DMSEO-d6): δ 8.753 (s, 2H (CH=N)), 8.382 (d, 2H (H4'')), J= 8.4 Hz), 7.985 (d, 2H (H7')), J= 7.8 Hz), 7.961 (s, 4H (H2, H3, H5, H6')), 7.883 (d, 2H (H5'), J= 7.6 Hz), 7.812 (s, 2H (H1')), 7.781 (d, 2H (H3')), J= 8.4 Hz), 7.487 (t, 2H (H6'), J= 7.6 Hz, J= 8 Hz). 13C-NMR (DMSEO-d6): δ 161.03 (2C (C=N)), 151.43 (2C (C8'')), 142.78 (2C (C2'')), 137.18 (2C (C1, C4')), 132.92 (2C (4'a)), 130.11 (2C (C6'')), 129.92 (2C (C4'')), 129.06 (4C (C2, C3, C5, C6')), 126.91 (2C (C5')), 126.66 (2C (C8'a)), 124.64 (2C (C1')), 121.46 (2C (C3'')), 116.78 (2C (C7'')).

2.1.4. 1,4'-1,4-phenylenebis(N-(4-(phenylidiazene yl)phenyl)methanimine) (5)
Orange color solid, m.p. = 191-192 °C, yield = 76%, time = 70 minutes. FT-IR (cm⁻¹): 3037 (CH Ar. str.), 1615 (C=N str. imine), 1581 (C=C Ar. str.).
2.1. 4.4’-((1,4-phenylenebis(methaneylylidene))bis(azaneylylidene))bis-2’-benzothiazol (8)
Green color solid, m.p. = 181-182 °C, yield= 85%, time= 35 minutes. FT-IR (cm⁻¹): 2999 (CH Ar. Str.), 1622 (C=N str. imine), 1588 (C=C Ar. Str.). 1H-NMR (DMSO-d₆): δ 8.865 (s, 2H (CH=N)), 7.951 (d, 2H (H4’)), J= 8.4 Hz), 7.767 (s, 4H (H2, H3, H5, H6’)), 7.503 (d, 2H (H7’), J= 8 Hz), 7.140 (t, 2H (H5’), J= 8 Hz, J= 8 Hz), 6.954 (t, 2H (H6’), J= 8.4 Hz, J= 8 Hz). 13C-NMR (DMSO-d₆): δ 169.10 (2C (C2’)), 159.74 (2C (C=)), 149.41 (2C (C3’a)), 137.34 (2C (C1, C4’)), 129.70 (4C (C2, C3, C5, C6’)), 126.89 (2C (C7’a)), 124.98 (2C (C5’)), 122.55 (2C (C6’)), 121.41 (2C (C7’)), 120.84 (2C (C4’)).

2.2. A general synthetic method for the synthesis of 2-Azetidinones (10-16)
A convenient synthetic pathway was used (Turan et al., 2016). A solution was prepared from the mixing trichloroacetyl chloride (2 mmol) and activated zinc (0.04 g) in 50 mL of diethyl ether, the mixture was sonicated for 30 minutes at 25 °C. The Schiff base (1 mmol) was added to the mixture and refluxed for 8-12 hours under a nitrogen atmosphere. A TLC plate was used to monitor the progress of the reaction. The excess zinc was filtered off. The solvent was evaporated via a rotary evaporator and washed products in absolute ethanol to remove zinc salt. The products were purified by column chromatography silica gel (n-hexane: ethyl acetate 65:35) to obtain the pure 2-Azetidinones. The reaction conditions are illustrated in (Scheme 2).

2.2.1. 4.4’-((1,4-phenylenebis(3,3-dichloro-4-oxazetidin-1,4-diyl))bis-(N-thiazol-2-yl) benzenesulfonamide) (10)
Brown color solid, m.p. = 231-232 °C, yield= 78%, time= 8.5hrs. FT-IR (cm⁻¹): 3202 (NH str.), 3009 (CH Ar. Str.), 1745 (C=O str. 2-Azetidinone ring), 1593 (C=C Ar. Str.), 1326 (SO₂ asym. str.), 1135 (SO₂ sym. str.). 1H-NMR (DMSO-d₆): δ 12.767 (s, br, 2H (NH)), 7.904 (d, 4H (H3’, H5’)), J= 8.4 Hz), 7.704 (d, 4H (H2’, H6’)), J= 8.8 Hz), 8.549 (s, 4H (H2, H3, H5, H6)), 7.302 (d, 2H (H4”, J= 8.4 Hz)), 7.024 (d, 2H (H5”)), J= 7.6 Hz), 5.774 (s, 2H (CH 2-Azetidinone ring)). 13C-NMR (DMSO-d₆): δ 169.64 (2C (C2’’)), 161.20 (2C (C=O 2-Azetidinone ring)), 150.54 (2C (C1’)), 140.58 (2C (C1, C4’)), 136.91 (2C (C4’’)), 133.09 (2C (C4’)), 129.81 (4C (C3’, C5’)), 125.03 (4C (C2, C3, C5, C6’)), 122.74 (4C (C2’, C6’’)), 111.33 (2C (C5”’)), 94.95 (2C (C=Cl₂ 2-Azetidinone ring)), 75.47 (2C (CH 2-Azetidinone ring)).

2.2.2. 8,8’-((1,4-phenylenebis(3,3-dichloro-2-oxazetidine-4,1-diyl))bis(naphthalene-2-sulfonic acid) (11)
Soil color solid, m.p. = 290-291 °C, yield= 65%, time= 12 hrs. FT-IR (cm⁻¹): 3324 (OH str.), 3041 (CH Ar. Str.), 1704 (C=O str. 2-Azetidinone ring), 1597 (C=C Ar. Str.), 1331 (SO₂ asym. str.), 1143 (SO₂ sym. str.). 1H-NMR (DMSO-d₆): δ 8.548 (d, 2H (H4’), J= 8.8 Hz), 8.506 (s, 2H (OH)), 8.185 (s, 2H (H1’)), 8.156 (d, 2H (H5’), J=7.6 Hz), 8.078 (d, 2H (H7’), J=7.2 Hz), 7.597 (d, 2H (H3’), J=8 Hz), 7.493 (t, 2H (H6’), J= 8 Hz, J= 7.6 Hz), 7.008 (s, 4H (H2, H3, H5, H6’)), 5.461 (s, 2H (CH 2-Azetidinone ring)). 13C-NMR (DMSO-d₆): δ 158.80 (2C (C=O 2-Azetidinone ring)), 147.84 (2C (C8’)), 146.95 (2C (C1, C4’)), 141.40 (2C (C2’)), 138.46 (2C (C4’)), 130.50 (2C (C4’’)), 129.51 (2C (C6’)), 124.55 (4C (C2, C3, C5, C6’)), 124.10 (2C (C3’)), 121.84 (2C (C8’a’)), 118.21 (2C (C1’)), 117.99 (2C (C5’’)) 108.62 (2C (C7’’)), 94.77 (2C (C=Cl₂ 2-Azetidinone ring)), 79.11 (2C (CH 2-Azetidinone ring)).

2.2.3. 4.4’-((1,4-phenylenebis(3,3-dichloro-2-oxazetidine-4,1-diyl))bis(N-phenylaniline) (12)
Dark brown color solid, m.p. = 108-109 °C, yield= 70%, time= 10.5 hrs. FT-IR (cm⁻¹): 3431 (NH str.), 3028 (CH Ar. Str.), 1725 (C=O str. 2-Azetidinone ring), 1594 (C=C Ar. Str.). 1H-NMR (DMSO-d₆): δ 8.818 (s, 2H (NH)), 8.535 (t, 4H (H3’, H5’)), J= 5.6 Hz, J= 6 Hz), 8.288 (s, 4H (H2, H3, H5, H6’)), 7.771 (d, 4H (H3’, H5’), J= 8 Hz), 7.079 (d, 4H (H2’, H6’’), J= 7.6 Hz), 7.032 (t, 2H (H4’)), J= 7.6 Hz, J= 8 Hz), 6.902 (d, 4H (H2’, H6’), J= 8.8 Hz), 5.866 (s, 2H (CH 2-Azetidinone ring)). 13C-NMR (DMSO-d₆): δ 159.25 (2C (C=O 2-Azetidinone ring)), 143.15 (2C (C1’)), 138.16 (2C (C1, C4’)), 137.02 (2C (C4’’)), 132.65 (4C (C2’, C6’’)), 129.56 (4C (C3’, C5’’)), 128.20 (2C (C1’’)), 125.31 (4C (C2, C3, C5, C6’’)), 122.35 (2C (C4’’’)), 121.73 (4C (C2’, C6’)), 120.16 (4C (C3’, C5’’)), 92.17 (2C (C=Cl₂ 2-Azetidinone ring)), 75.94 (2C (CH 2-Azetidinone ring)).

2.2.4. 4.4’-((1,4-phenylenebis(3,3-dichloro-1-(4-(phenyl diazenyl)phenyl)azetidin-2-one) (13)
Oily color solid, m.p. = 154-155 °C, yield= 67%, time= 11 hrs. FT-IR (cm⁻¹): 3038 (CH Ar Str.), 1740 (C=O str. 2-Azetidine ring), 1595 (C=O Ar Str.). ¹H-NMR (DMSO-d6): δ 8.380 (d, 4H (H3', H5')), J = 8 Hz), 8.070 (d, 4H (H2', H6')), J = 8 Hz), 7.848 (t, 4H (H3'', H5''), J = 7.2 Hz), 7.466 (s, 4H (H2, H3, H4, H5)), 7.086 (t, 2H (H4'), J = 7.6 Hz, J = 8 Hz), 6.883 (d, 4H (H2', H6')), J = 8 Hz), 5.537 (s, 2H (CH 2-Azetidine ring)). ¹³C-NMR (DMSO-d6): δ 159.87 (2C (C=O 2-Azetidine ring)), 151.06 (2C (C1'')), 149.93 (2C (C4'')), 139.81 (2C (C1')) 138.95 (2C (C1, C4)), 131.11 (2C, (C4'')), 130.32 (4C (C2', C6')), 129.51 (4C (C3', C5'')), 126.72 (4C (C2, C3, C5, C6)), 124.57 (4C (C3', C5')), 123.63 (4C (C2', C6'')), 90.53 (2C (C-Cl2 2-Azetidine ring)), 74.60 (2CH 2-Azetidine ring)).

2.2.5. 4,4'-(1,4-phenylenebis(3,3-dichloro-2-oxoazetidine-4,1-diyi)bis(N-(pyrimidin-2-yl)benzenesulfonamide) (14)

Deep brown color solid, m.p. = 261-262 °C, yield= 75%, time= 9 hrs. FT-IR (cm⁻¹): 3254 (NH str.), 3021 (CH Ar Str.), 1722 (C=O str. 2-Azetidine ring), 1593 (C=C Ar Str.), 1326 (SO₂ asym.str.), 1134 (SO₂ sym.str.). ¹H-NMR (DMSO-d6): δ 11.938 (s, br, 2H (NH)), 8.545 (d, 4H (H3'', H5''), J = 7.2 Hz), 8.070 (d, 4H (H3', H5'), J = 8 Hz), 7.562 (d, 4H (H2', H6'), J = 8 Hz), 7.288 (s, 4H (H2', H3, H5, H6)), 7.147 (t, 2H (H4''), J = 8.4 Hz, J = 7.6 Hz), 5.615 (s, 2H (CH 2-Azetidine ring)). ¹³C-NMR (DMSO-d6): δ 170.19 (2C (C1''), 160.81 (2C (C=O 2-Azetidine ring)), 158.88 (4C (C3'', C5'')), 143.40 (2C (C1''), 142.08 (2C (C1, C4)), 135.66 (2C (C4''), 129.61 (4C (C3', C5'')), 124.29 (4C (C2, C3, C5, C6)), 122.34 (4C (C2', C6'')), 116.93 (2C (C4''), 92.99 (2C (C-Cl2 2-Azetidine ring)), 76.65 (2CH 2-Azetidine ring)).

2.2.6. 4,4'-(1,4-phenylenebis(3,3-dichloro-2-oxoazetidine-4,1-diyi)bis(1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one) (15)

Coffey color solid, m.p. = 129-130 °C, yield= 72%, 10 hrs. FT-IR (cm⁻¹): 3035 (CH Ar Str.), 2808, 2941 (CH Aliph. Str.), 1731 (C=O str. 2-Azetidine ring), 1672 (C=O str.), 1580 (C=C Ar Str.). ¹H-NMR (DMSO-d6): δ 7.696 (t, 4H (H3'', H5''), J = 7.2 Hz, J = 8 Hz), 7.506 (d, 4H (H2'', H6''), J = 8.8 Hz), 7.454 (t, 2H (H4''), J = 8.8 Hz), J = 8.4 Hz), 7.311 (s, 4H (H2, H3, H5, H6)), 5.153 (s, 2H (CH 2-Azetidine ring)), 3.261 (s, 6H (N-CH₃)), 2.077 (s, 6H (C-CH₃)). ¹³C-NMR (DMSO-d6): δ 162.65 (2C (C3''), 159.09 (2C (C=O 2-Azetidine ring)), 145.97 (2C (C1, C4''), 136.94 (2C (C1'')), 134.05 (2C (C5''), 129.71 (4C (C3'', C5''))), 124.56 (4C (C2, C3, C5, C6'')), 122.18 (4C (C2', C6'')), 121.70 (2C (C4''), 105.43 (2C (C4''), 94.56 (2C (C-Cl2 2-Azetidine ring)), 73.81 (2C (CH 2-Azetidine ring)), 35.72 (2C (N-CH₃)), 21.10 (2C (C-CH₃)).

2.2.7. 4,4'-(1,4-phenylenebis(1-(benzothiazol-2-yl)-3,3-dichloroazetidin-2-one) (16)

Bronzy color solid, m.p. = 145-146 °C, yield= 79%, time= 8 hrs. FT-IR (cm⁻¹): 3033 (CH Ar Str.), 1715 (C=O str. 2-Azetidine ring), 1593 (C=C str.), 151.06 (2C (C1'')), 149.93 (2C (C4'')), 139.81 (2C (C1')), 138.95 (2C (C1, C4)), 131.11 (2C, (C4'')), 130.32 (4C (C2', C6')), 129.51 (4C (C3', C5'')), 126.72 (4C (C2, C3, C5, C6)), 124.57 (4C (C3', C5')), 123.63 (4C (C2', C6'')), 90.53 (2C (C-Cl2 2-Azetidine ring)), 74.60 (2CH 2-Azetidine ring).

2.3. In Vitro Antimicrobial (antibacterial and antifungal) assay

The broth microdilution method was utilized to test the antibacterial and antifungal assays. The synthesized compounds (2-8) and (10-16) were screened a great capacity to inhibition strains against gram-positive strain (S. aureus), and gram-negative strains (E. coli) of bacterial and A. niger (natural isolates) and T. mentagrophytes. A common medication, Amoxicillin and Penicillin were used as standard drugs (Aziz and Azeez, 2020).

2.4. Molecular docking software

PubChem (https://pubchem.ncbi.nlm.nih.gov/) and ChemDraw Professional 16.0 were used to design of the synthesized compounds (ligands) as the SDF type file format, Protein Data Bank (https://www.rcsb.org/), online tools were used for download of a protein (ID code: 1MWU). The zinc (http://zinc.docking.org/) website was used for the design and download of standard drugs (amoxicillin and penicillin G). PyRx (AutoDockTools-1.5.6) and BIOVIA Discovery Studio 2020 were employed to imagine and adapt receptor and ligand structures (Beg and Athar, 2020, My et al., 2011).
3. RESULTS AND DISCUSSION

3.1. Chemistry

3.1.1. Symmetrical Bis-Schiff bases (2-8)

A convenient synthetic method was applied for the preparation of symmetrical Bis-Schiff base compounds that are depicted in (Scheme 1). Terephthaldehyde was preferred for the synthesis of new Symmetrical Bis-Schiff bases as the starting material. Symmetrical Bis-Schiff bases (2-8) were synthesized via a condensation reaction of terephthaldehyde (1) with seven various aromatic primary amines. Acetic acid was used as an acid catalyst (Shinde et al.). The ultrasonic technique was used for a few purposes such as reducing the time of the reactions, utilizing the least amounts of ethanol dissolvable and, getting a good product yields (Bendale et al., 2011).

Within the spectrum of Bis-Schiff bases, the characteristic absorption around 1610-1626 cm\(^{-1}\) can be related to stretching vibration of (C=N) Schiff bases, which could be a sensible affirmation to the synthesis of Bis-Schiff bases, the vanishing of a carbonyl (C=O) of the terephthaldehyde around 1700 cm\(^{-1}\), and two peaks of primary amines (NH\(_2\)) at 3300 and 3400 cm\(^{-1}\) were implied that the pure Bis-Schiff bases were formed (Shaygan et al., 2018). Moreover, a carbonyl peak showed up at 1640 cm\(^{-1}\) for compound (7) but it is not carbonyl of aldehyde, this carbonyl group is a portion of the 4-aminoantipyrine compound. Within the compounds (2, 4, and 6) a band NH stretching vibration seemed at 3194, 3415 and 3226 cm\(^{-1}\) respectively (Hamdan et al., 2018). A broad hydroxide (OH) peak showed up at 3382 cm\(^{-1}\) for the compound (2) (Singh et al., 2018).

In the \(^1\)H-NMR spectrums, singlet peaks appeared at 8.10-9.67 ppm for an identical to two protons of (H-C=N) Schiff bases. A singlet and broad singlet bands did not appear for the proton of (CH=O) of terephthaldehyde and protons of (NH\(_2\)) amines, meaning the pure symmetrical Bis-Schiff bases were formed without any reactants (Mohammed and Taha, 2017). The broad singlet band was shown for every (NH) protons of compounds (2, 6, and 4) at 12.680, 8.392, and 11.830 ppm, separately (Elsayed et al., 2014). A single peak appeared at 8.481 ppm that is doled out to the (O–H) groups of compound (2). The equivalence
aromatic protons were shown at 8.777-6.491 ppm. Also, two corresponding singlet peaks at 3.362 and 2.525 ppm were conjointly displayed due to the CH₃ groups of the compound (7). ¹³C-NMR spectrums are shown with these next data. The carbon of (C=N) of symmetrical Schiff bases is recorded at 162.55-159.39 ppm. The aromatic carbons are seen at 171.01-111.91 ppm (Krátký et al., 2017). The two lowest signals appeared at 36.97 and 19.07 ppm due to the CH₃ groups of the compound (7). The two symmetrical carbons of carbonyl groups of compound (7) are shown at 159.54 ppm, high chemical shift due to neighboring oxygen atoms. Because of electronegativity the neighbor atom is influenced by the linkage of carbons. Those carbon atoms that are linked to two nitrogen atoms or nitrogen and sulfur atoms were shown the most elevated chemical shift as the compounds (6 and 2) (Anacona et al., 2015, Krátký et al., 2012).

3.1.2. 2-Azetidinones (10-16)

The synthetic method for the synthesis of 2-Azetidinones is based on [2+2] dichloroketene-imine cycloaddition reaction. The conditions of the reactions are shown in (Scheme 2), and mechanism of the reaction is illustrated in (Scheme 3). One mole of symmetrical Bis-Schiff bases (2-8) was reacted with two moles with trichloroacetyl chloride (9). Activated zinc was as a catalyst, diethyl ether as solvent (Turan et al., 2016).

Scheme 2. 2-Azetidinones synthesis (10-16)
Scheme 3. Mechanism of the synthesis 2-Azetidinones (10-16) (Khdur and Zimam, 2018b, Turan et al., 2016)

In the view of spectrums of 2-Azetidinones, the most effective instructive to indicate the formation of 2-Azetidinones by FT-IR is that the vanished of imine vibrational stretching (C=N) groups of symmetrical bis-Schiff bases and appeared of carbonyl (C=O) group of 2-Azetidinones at 1745-1704 cm⁻¹. Concealed the peak of imine groups is good evidence for the formation of pure 2-Azetidinones without bis-Schiff bases reactant (Ayyash, 2019). A vibrational stretching peak appeared at 1672 cm⁻¹ for the ketone carbonyl group of the compound (7). The NH stretching vibrational peak appeared at 3202, 3431, and 3254 cm⁻¹ for the compounds (10, 12, and 14), severally (Mehta et al., 2014). A broad vibrational stretching peak appeared at 3324 cm⁻¹ for the hydroxide (OH) compound (11). ¹H-NMR spectrums were shown the properties of the protons band. An identical two singlet bands appeared at 5.774-5.53 ppm for (CH) protons of the 2-Azetidinone ring and disappeared the singlet band of imine (CH=N) groups (Khajavi, 1998, Turan et al., 2016). The broad singlet band of NH protons of compounds (10, 12, and 14) were shown at 12.767, 8.818, 11.938 ppm, individually. A single band appeared for (O–H) protons of the compound (2) at 8.506 ppm. The equivalence aromatic protons are shown at 8.548-6.883 ppm.

Two singlet bands seem at 3.261 and 2.077 ppm due to CH₃ groups of the compound (7). Within the ¹³C-NMR spectrums of 2-Azetidinones, carbon of the carbonyl of 2-Azetidinone rings seemed at 161.20-158.80 ppm. The aromatic carbons appeared at 170.19-105.43 ppm (Khdur and Zimam, 2018a). Two signals appeared for the carbons of (C-Cl and CH) 2-Azetidinone rings at 79.11-73.23 ppm and 94.95-89.11 ppm, respectively. Two signal bands appeared at 35.72 and 21.10 ppm because of the CH₃ groups of the compound (15).

3.2. In vitro Antimicrobial assay

All synthesized compounds were evaluated for their in vitro antibacterial activities against gram-positive strain, Staphylococcus aureus (ATCC 9144), and gram-negative Escherichia coli (ATCC 8739), and surveyed for their antifungal activity against Aspergillus niger and Trichophyton mentagrophytes (Sharma et al., 2012). The antimicrobial of the synthesized compounds assessed through the broth microdilution technique, the results were detailed by the (MIC) minimum inhibitory concentration, and the results are shown in (Table 1).

| Table 1. In vitro antimicrobial assay of the synthesized compounds (MIC μg/mL) |
|-----------------------------------------------|
| Compounds | MIC for Microorganisms (μg/ml) |
| | Bacterial strains | Fungal strains |
| | S.aureus | E.coli | A.niger | T. mentagrophytes |
| 2 | 1.5 | 1.8 | 2.5 | 2.7 |
| 3 | 0.8 | 0.7 | 1.8 | 2.3 |
| 4 | 3 | 4 | 4 | 3.3 |
| 5 | 4 | 3.5 | 3 | 3.5 |
| 6 | 2 | 1.5 | 2.7 | 2.9 |
| 7 | 4.5 | 4 | 4.5 | 5 |

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All synthesized compounds screened good antibacterial and antifungal activities as compared to standard amoxicillin, penicillin, and nystatin drugs. As inspected the antibacterial of the synthesized compounds higher than their antifungal. The 2-Azetidinones possessed higher antimicrobial activity than Schiff bases. The compound (11) exhibited the most elevated antibacterial activity against *Escherichia coli* and *Staphylococcus aureus* bacteria and showed the most noteworthy activity against *Aspergillus niger* and *Trichophyton mentagrophytes* fungi. The compound (8) exhibited the lowest antibacterial activity against *Escherichia coli* and *Staphylococcus aureus* bacteria. The compound (7) displayed the lowest antifungal *Aspergillus niger* and *Trichophyton mentagrophytes* fungi. The P values are equal to 0.00512 and 0.00399 for Schiff bases (2-8) and 2-Azetidinones (10-16) against *Staphylococcus aureus*, respectively. They are less than 0.05 and statistically significant.

### 3.3. Molecular docking study

To provision the *in vitro* antimicrobial activity of the synthesized compounds a molecular docking study was applied to identify binding affinities and interactions between synthesized compounds and the target protein. For this purpose, methicillin acyl-Penicillin binding protein 2a (PDB ID: 1MWU) was selected as a fitting molecular docking target (My et al., 2011). The minimum binding energy value reflects affinity and high stability of ligands to tie with the receptor (Abbas et al., 2018). Corresponding to the docking studies, the synthesized compounds showed good interactions and binding energy as compared to drug references ( Amoxicillin and Penicillin G), which shown in (Table 2).

| Compound | Binding energy (kcal/mol) | Interactions | Other Interactions |
|----------|--------------------------|--------------|--------------------|
| 2        | -5.10                    | GLU¹³⁹, GLU¹⁵⁹, SER³⁹¹, SER³⁷⁶, ASP²²¹ | VAL²¹⁷ | LYS²¹⁵ (Pi-cation) |
| 3        | -6.00                    | LYS¹⁸⁷, LYS¹²⁵ | TYE¹⁶⁶ | LEU³⁸⁵, LYS³⁸², PRO³⁷⁰, VAL²¹⁷ |
| 4        | -4.40                    | GLU³⁷⁹, ASP²²¹, LYS²¹⁸ | VAL²¹⁷, PRO³⁷⁰, LEU²⁴⁴ | LYS²¹⁵ (Pi-cation), MET³⁷⁵ (Pi-sulfur), TYR²²³ (pi-pi) |
| 5        | -4.10                    | ASP³⁵⁷ | LYS¹¹⁹ | LEU³⁸³, PRO³⁷⁰, LYS³⁸² | LYS²¹⁹ (Pi-cation), GLU³⁷⁸ (Pi-anion) |
| 6        | -4.90                    | MET¹⁷⁵, PHE¹⁷¹, PRO³⁵⁸, TYR¹⁹⁶, GLY²⁵⁷ | PRO²⁵⁸ | LYS²⁰⁰ (Pi-cation) |
| 7        | -5.00                    | ASP³⁵² | LYS²⁶⁰ | LEU¹³⁵, LYS¹³², LYS¹¹⁹ | LYS²⁸⁹ (Pi-amide), ASP³²³ (Pi-anion), GLU¹⁶¹ (Pi-anion) |
|   | 8    | -4.00 | GLU<sup>259</sup>, SER<sup>280</sup> | THR<sup>395</sup> | LYS<sup>213</sup> | TYR<sup>173</sup> (pi-pi) |
|---|------|-------|-----------------------------------|-----------------|-----------------|------------------------|
| 10| -7.00|       | GLU<sup>189</sup>, SER<sup>391</sup> | LYS<sup>215</sup> | PRO<sup>170</sup>, VAL<sup>217</sup> | GLU<sup>189</sup> (Pi-anion), GLU<sup>189</sup> (Pi-anion), LEU<sup>383</sup> (Pi-sigma), ASP<sup>367</sup> (Halogen) |
| 11| -8.20|       | TYR<sup>289</sup>, TYR<sup>296</sup>, GLN<sup>396</sup>, ASN<sup>393</sup> | LYS<sup>280</sup>, LYS<sup>281</sup> | LYS<sup>281</sup> (Pi-cation) |
| 12| -7.30|       | GLU<sup>259</sup>, LYS<sup>280</sup>, PRO<sup>258</sup>, ASP<sup>295</sup>, | | LYS<sup>281</sup> (Pi-cation), ARG<sup>298</sup> (Pi-cation), VAL<sup>277</sup> (Pi-sigma), SER<sup>240</sup> (Pi-amaid) |
| 13| -6.50| SER<sup>193</sup> | TYR<sup>296</sup>, PRO<sup>258</sup>, LYS<sup>280</sup> (Pi-cation) |
| 14| -7.00|       | SER<sup>193</sup>, MET<sup>172</sup>, THR<sup>216</sup>, PHE<sup>271</sup>, TYR<sup>255</sup>, GLY<sup>257</sup> | PRO<sup>258</sup> | TYR<sup>299</sup> (pi-pi) |
| 15| -7.70|       | TYR<sup>380</sup>, ASN<sup>393</sup>, GLN<sup>396</sup>, HIS<sup>251</sup> | PRO<sup>497</sup>, LEU<sup>286</sup>, LEU<sup>391</sup> | - |
| 16| -6.80|       | MET<sup>172</sup>, THR<sup>216</sup>, PRO<sup>258</sup>, MET<sup>372</sup>, PRO<sup>372</sup>, VAL<sup>277</sup> | - | |
| Amoxicillin | -7.4 |       | LYS<sup>148</sup>, THR<sup>215</sup>, SER<sup>149</sup>, GLY<sup>239</sup>, VAL<sup>258</sup>, SER<sup>288</sup>, LEU<sup>391</sup> | PRO<sup>258</sup>, MET<sup>372</sup> | TYR<sup>173</sup> (pi-pi) |
| Penicillin G | -7.2 |       | GLU<sup>256</sup>, GLY<sup>282</sup>, TYR<sup>296</sup>, ASN<sup>393</sup>, LEU<sup>391</sup>, TYR<sup>295</sup>, TYR<sup>296</sup>, LYS<sup>281</sup> | LYS<sup>285</sup>, LEU<sup>386</sup> (Pi-sigma) | |
All synthesized compounds screened a good binding score (-4.00 to -8.20 kcal/mole) as compared to standard drugs. As shown in the table (2), the 2-Azetidinones exhibited the lower binding energy than Schiff bases, meaning 2-Azetidinone more stable than Schiff bases whereas it interacted with the active site of the protein. Commonly, the number of the interactions was expanded while the Schiff bases were converted to the 2-Azetidinone due to chlorine atoms and oxygen atoms of 2-Azetidinone rings as seen in the compound (11) figure (2 and 6), two hydrogen bond were formed with amino acid residues TYR496, GLN396 due to oxygen atom of the 2-Azetidinone’s carbonyl, and chlorine formed hydrogen and halogen bonds in a few of the synthesized compounds such as compound (10). Because of the best orientation seen in compound (11) as presented better docking scores (-8.20 kcal/mole) and more interactions with amino acid residues, which formed as four hydrogen bonds with these active receptor sites TYR269, TYR496, TYR499, and GLN396, two van der Waals forces with GLN396 and ASN393, two pi-alkyl interactions (LYS280 and LYS281) and a pi-cation interaction LYS281. For Schiff bases, the compound (3) showed the lowest binding energy of Schiff bases (-6.00 kcal/mole), the interactions shown in the figure (1 and 5). The lower binding affinities were taken note for compounds (8 and 16).
4. CONCLUSIONS

Within the current investigation, helpful synthetic methods were applied for the synthesis of seven new symmetrical Bis-Schiff bases and 2-Azetidinones in good yield. The structures of synthesized compounds were fully characterized by FT-IR and NMR. Antimicrobial activities were assessed for all synthesized compounds. All the synthesized compounds showed good antimicrobial activity as compared to reference drugs. According to the in vitro antimicrobial tests, the compound (3) for Schiff bases and compound (11) for 2-Azetidinones exhibited highest antimicrobial activity. The part of this research study focused on supporting the antimicrobial activity, to affirm the interactions and supporting the antimicrobial activity, a molecular docking study was utilized for this reason, synthesized compounds showed good binding energy and interactions. The compound (11) screened better binding energy and most active to create interactions with acceptor sites, which supported to their antimicrobial activity. The binding energy and antimicrobial activity of 2-Azetidinones were better than Schiff bases due to Chlorine and oxygen atoms of 2-Azetidinones rings, which formed the interactions with protein acceptors like, Hydrogen bond, van der Waals forces, and halogen interactions. Sulfonamides (compounds 2, 6, 10 and 14) and hydroxide groups (compounds 3 and 11) expanded the activity of the compounds for antimicrobial activity and docking studies. Furthermore, the newly synthesized compounds can use in pharmaceutical fields for treatments of some infections afterward some further assessments.
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Appendix

Fig. 7. FT-IR Spectrum of the compound (2)

Fig. 8. FT-IR Spectrum of the compound (10)

Fig. 9. $^1$H-NMR spectrum of the compound (2)
Fig. 10. $^1$H-NMR spectrum of the compound (10)

Fig. 11. $^{13}$C-NMR Spectrum of the compound (2)
Fig. 12. $^{13}$C-NMR Spectrum of the compound (10)