RESEARCH ARTICLE

Synthesis, Characterization of New Sulfamethoxazole Derivatives containing β-lactam Ring and Preliminary Evaluation of their Antimicrobial Activity

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ABSTRACT

Sulfamethoxazole (SMX) is the most significant antibiotic in the sulfonamide family. It was chosen as the representative of this category because of its widespread use. Starting with sulfamethoxazole, a new series of 2-Azetidinone (M1-M6) was synthesized, the structure of these new derivatives was confirmed using spectral methods, starting with the synthesis of Schiff's bases by reflux of different aromatic benzaldehydes, separately, with Sulfamethoxazole in ethanol with few drops of acetic acid. The final compounds were obtained by ketene-imine synthesis of β-lactam using chloroacetyl chloride. The designed chemicals' synthesis has been completed successfully. Physical parameters (melting points and Rf values), Fourier transform infrared (FT-IR) spectroscopy, and Proton nuclear magnetic resonance (^{1}H-NMR) spectroscopy were used to establish the purity and characterization of these derivatives. When compared to standard antibiotics (Sulfamethoxazole, Ciprofloxacin, and Fluconazole), the preliminary antimicrobial activity tests on four different bacteria strains and one type of fungus demonstrated that the final compounds (M1-M6) have significant activity. Finally, the new derivatives (M3 and M5) are the most potent than the other ones and more active than the standard drugs.

Keywords: 2-Azetidinone, β-lactam synthesis, Antimicrobial Activity, Sulfamethoxazole.

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INTRODUCTION

From Alexander Fleming's discovery of Penicillin in 1929 to Domak's discovery of sulfa medicines in 1932, the story of antibiotics has been evolving.[1] The β-lactam ring, known as the 2-azetidinone skeleton, has long been recognized as a significant building block in the synthesis of biologically relevant molecules. Antifungal, antibacterial,[1-4] antitubercular,[5,6] analgesic, anti-inflammatory,[7,8] chymase inhibitory,[9] antitumor,[10-12] antiviral,[13] antidiabetic,[14] and cholesterol absorption inhibitory effects,[15] are some of the biological actions of azetindin-2-one derivatives. The presence of a 2-azetidinone ring is responsible for the activity of well-known antibiotic classes such as penicillins, cephalosporins, carumonam, aztreonam, thienamycin, nocardicin, and carbapenems.[2]

Unfortunately, the most extensively used ones create selective pressure on bacteria, allowing resistant organisms to grow.[16] Due to the increasing resistance of bacteria to traditional β-lactam antibiotics and the need for medications with more specific antibacterial activity, several synthetic and semi-synthetic β-lactam antibiotics were created.[17] Schiff bases have been reported for their wide range of biological activities, such as antitumor, anti-tuberculosis, and antimicrobial activity.[18] Sulfonamides' biological activity has also been widely documented, antibacterial, antifungal, anticancer agents, diuretics, carbonic anhydrase inhibitors, hypoglycemic medication, thyroid inhibitors, anticonvulsants, and protease inhibitors have all been discovered to be useful.[19,20]

In the sulfonamide family, Sulfamethoxazole (SMX) is the most important antibiotic. Because of its widespread use, detection frequency, and widespread use in the aquatic environment, it was chosen as the category's representative.[21] (SMX) acts as a folic acid synthesis inhibitor by resembling p-aminobenzoic acid (PABA) as false substrates, the bacteriostatic activity of sulfonamides facing essential challenges by emerging resistant microorganisms.[22]

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Different researches revealed that derivatives of sulphathiazole bearing lactam ring[23] and SMX containing thiazolidinone moiety[24] were more active than the parent sulfonamide. Therefore, the combination of the β-lactam ring with the sulfonamide group of SMX by preparation of the Schiff bases appears to be interesting for many biological and chemical considerations.

MATERIAL AND METHODS

Sulfamethoxazole was obtained from Pioneer (Iraqi pharmaceutical company), Solvent, and other reagents that were used through reaction were bought from commercial sources. (TLC) (GF254, Merk-Germany) was used to check the purity of the products and monitor the reactions under UV light (254 nm). Two solvent systems were utilized.

(a) Ethyl acetate: n-hexane: glacial acetic acid (6:3.5:0.5)[25].

(b) Ethyl acetate: n-hexane: methanol (6:4:1).[26]

The melting points were determined in open capillary tubes with the Stuart SMP3 melting point instrument and are uncorrected. The Fourier transform infrared (FT-IR) spectrophotometer from Shimadzu, Japan, was used to create the infrared spectra. With tetramethylsilane as an internal standard, Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on the nuclear magnetic resonance (NMR-500) spectrometer model; chemical shifts (δ) were represented in ppm.

Synthesis

General procedure for the synthesis of Schiff's bases (A1-A6):[27]

Five drops of glacial acetic acid were added to an ethanolic solution of 5 mL containing (5 mmol) of each following aldehydes: 4-methoxybenzaldehyde **(**1) (0.76 g), 4-chlorobenzylaldehyde (2) (0.7 g), 4-dimethylaminobenzaldehyde (3) (0.74 g), 3,4,5-trimethoxybenzaldehyde (4) (0.98 g), 4-hydroxy-3-methoxybenzaldehyde (5) (0.6 g) and 2-hydroxybenzaldehyde (6) (0.54 g) contained in a 100 mL round bottom flask equipped with a magnetic stirrer. Then (5mmol, 1.29 g) of aromatic amine (Sulfamethoxazole) dissolved in (10mL) of absolute ethanol added drop by drop to mixtures as mentioned above, separately, after that, the reaction mixtures reflux at 80°C for 6 to 8 hours. At the end of reflux time, the mixture is left to cool at room temperature or in crushed ice; the formed precipitate is collected, filtered, and then recrystallized with hot ethanol to give the intended Schiff's bases.

4-((4-methoxybenzylidene)amino)-N-(5-methylisoxazol-3-yl) benzenesulfonamide (Compound A1)

Yellow powder, Yield: 88%, M.P: (172-174°C), Rf: 0.6 (A), IR (υ cm^{-1}): 3200 (NH) str. of sulfonamide, 3055 (CH) str. of aromatic, 2951 (CH_3) str. of methoxy group, 2835 (CH_3) str. of oxazole ring, 1608 (C=N) str. of imine, 1570 (C=N) str. of oxazole ring, 1512 (C=C) str. of the aromatic ring.

4-((4-chlorobenzylidene)amino)-N-(5-methylisoxazol-3-yl) benzenesulfonamide (Compound A2)

White powder, Yield: 75%, M.P: (192-194°C), Rf: 0.72 (A), IR (υ cm^{-1}): 3200 (NH) str. of sulfonamide, 3055 (CH) str. of aromatic, 2835 (CH_3) str. of oxazole ring, 1620 (C=N) str. of imine, 1581 (C=N) str. of oxazole ring, 1566 (C=C) str. of the aromatic ring, 661 (C-Cl) str.

4-((4-(dimethylamino)benzylidene)amino)-N-(5-methylisoxazol-3-yl)benzenesulfonamide (Compound A3)

Pale yellow powder, Yield: 90%, M.P: (185-187°C), Rf: 0.56 (A), IR (υ cm^{-1}): 3286 (NH) str. of sulfonamide, 3143 (CH) str. of aromatic, 2835 (CH_3) str. of oxazole ring, 2897,2858 (CH_3) of N-methyl groups, 1604 (C=N) str. of imine, 1573 (C=N) str. of oxazole ring, 1531 (C=C) str. of the aromatic ring.

N-(5-methylisoxazol-3-yl)-4-((3,4,5-trimethoxybenzylidene) amino)benzenesulfonamide (Compound A4)

Pinkish-white powder, Yield: 85%, M.P: (195-197°C), RF: 0.75 (A), IR (υ cm^{-1}): 3200 (NH) str. of sulfonamide, 3005 (CH) str. of aromatic, 2981 (CH_3) str. of methoxy groups, 2877 (CH3) str. of oxazole ring, 1620 (C=N) str. of imine, 1577 (C=N) str. of oxazole ring, 1512 (C=C) str. of the aromatic ring.

4-((3-hydroxy-4-methoxybenzylidene)amino)-N-(5-methylisoxazol-3-yl)benzenesulfonamide (Compound A5)

Greenish-white powder, Yield: 95%, M.P: (203-205°C), Rf: 0.83 (A), IR (υ cm^{-1}): 3537 (OH) str. of hydroxyl group, 3200 (NH) str. of sulfonamide, 3005 (CH) str. of aromatic, 2985 (CH_3) str. of methoxy group, 2877 (CH_3) str. of oxazole ring, 1623 (C=N) str. of imine, 1577 (C=N) str. of oxazole ring, 1512 (C=C) str. of the aromatic ring.

4-((2-hydroxybenzylidene)amino)-N-(5-methylisoxazol-3-yl) benzenesulfonamide (Compound A6)

Red powder, Yield: 90%, M.P: (190-191°C), Rf: 0.74 (A), IR (υ cm^{-1}): 3587 (OH) str. of hydroxyl group, 3223 (NH) str. of sulfonamide, 3089 (CH) str. of aromatic, 2877 (CH3) str. of oxazole ring, 1612 (C=N) str. of imine, 1593 (C=N) str. of oxazole ring, 1504 (C=C) str. of the aromatic ring.

General procedure to synthesis 2-Azetidinone derivatives (M1-M6):[28, 29]

Chloroacetyl chloride (1 mmol) was added slowly to mixture of dry CH_2Cl_2 (15 mL) and (1 mmol of Schiff bases) (A1; 0.371 g, A2; 0.375 g, A3; 0.384 g, A4; 0.431 g, A5; 0.387 g, A6; 0.357 g), separately, and in the presence of (1mmol) triethylamine, at (-5°C). The reaction mixture was allowed to be warmed at room temperature and then refluxed for (12 hours.). Finally, the mixture was washed successively with saturated sodium bicarbonate (20 mL) and brine water (20 mL), dried with (Na_2SO_4) and the solvent was evaporated to give a crude product which was then recrystallized with ethyl acetate.

4-(3-chloro-2-(4-methoxyphenyl)-4-oxoazetidin-1-yl)-N-(5-methylisoxazol-3-yl) benzenesulfonamide (Compound M1)

Brown powder, Yield: 75%, M.P: (233-235°C), Rf: 0.9 (B), IR (υ cm^{-1}): 3317 (NH) str. of sulfonamide, 3136 (CH) str. of

aromatic, 2877 (CH_3) str. of oxazole ring, 1720 (C=O) str. of β-lactam, 1589 (C=N) str. of oxazole ring, 1539 (C=C) str. of the aromatic ring, 678 (C-Cl) str.
^{1}H-NMR: 2.3 (3H, s, CH_3 of oxazole ring), 3.8 (3H, s, CH_3 of methoxy group), 4.29 (1H, d, CH-N azetidinone ring), 4.35 (1H, d, CH-Cl of azetidinone ring), 6.14 (1H, s, CH of oxazole ring), 6.74-7.8 (4H, d, d, protons of aromatic ring that have methoxy group), 7.9-8.5 (4H, d, d, protons of another aromatic ring), 10.94 (1H, s, NH proton).

4-(3-chloro-2-(4-chlorophenyl)-4-oxoazetidin-1-yl)-N-(5-methylisoxazol-3-yl) benzenesulfonamide (Compound M2)

Reddish-brown powder, Yield: 60%, M.P: (257-259°C), Rf: 0.92 (B), IR (υ cm^{-1}): 3344 (NH) str. of sulfonamide, 3136(CH) str. of aromatic, 2877 (CH_3) str. of oxazole ring, 1720 (C=O) str. of β-lactam, 1589 (C=N) str. of oxazole ring, 1533 (C=C) str. of the aromatic ring, 688 (C-Cl) str. of azetidinone ring, 678 (C-Cl) str. of the aromatic ring.
^{1}H-NMR: 2.3 (3H, s, CH_3 of oxazole ring), 4.29 (1H, d, CH-N azetidinone ring), 4.35 (1H, d, CH-Cl of azetidinone ring), 6.14 (1H, s, CH of oxazole ring), 6.72-7.81 (4H, d, d, protons of aromatic ring that have chlorine group), 7.9-8.02 (4H, d, d, protons of another aromatic ring), 10.94 (1H, s, NH proton).

4-(3-chloro-2-(4-(dimethylamino)phenyl)-4-oxoazetidin-1-yl)-N-(5-methylisoxazol-3-yl) benzenesulfonamide (Compound M3)

Orange powder, Yield: 80%, M.P: (205-207°C), Rf: 0.83 (B), IR (υ cm^{-1}): 3340 (NH) str. of sulfonamide, 3130 (CH) str. of aromatic, 2985, 29833 (CH_3) str. of N-methyl groups, 2877 (CH_3) str. of oxazole ring, 1747 (C=O) str. of β-lactam, 1589 (C=N) str. of oxazole ring, 1533 (C=C) str. of the aromatic ring, 688 (C-Cl) str. of azetidinone ring.
^{1}H-NMR: 2.3 (3H, s, CH_3 of oxazole ring), 3.05 (6H, s, CH_3 of dimethylamine), 4.27 (1H, d, CH-N azetidinone ring), 4.37 (1H, d, CH-Cl of azetidinone ring), 6.14 (1H, s, CH of oxazole ring), 6.75-7.83 (4H, d, d, protons of aromatic ring that have dimethylamine group), 7.9-8.02 (4H, d, d, protons of another aromatic ring), 10.94 (1H, s, NH proton).

4-(3-chloro-2-oxo-4-(3,4,5-trimethoxyphenyl)azetidin-1-yl)-N-(5-methylisoxazol-3-yl)benzenesulfonamide (Compound M4)

Brown powder, Yield: 83%, M.P: (212-214°C), Rf: 0.78 (B), IR (υ cm^{-1}): 3332 (NH) str. of sulfonamide, 3136 (CH) str. of aromatic, 2985 (CH_3) str. of O-methyl groups, 2877 (CH_3) str. of oxazole ring, 1720 (C=O) str. of β-lactam, 1589 (C=N) str. of oxazole ring, 1535 (C=C) str. of the aromatic ring, 663 (C-Cl) str. of azetidinone ring.
^{1}H-NMR**:** 2.3 (3H, s, CH3 of oxazole ring), 3.55 (9H, s, CH3 of O-methyl groups), 4.27 (1H, d, CH-N azetidinone ring), 4.37 (1H, d, CH-Cl of azetidinone ring), 6.14 (1H, s, CH of oxazole ring), 6.75 (2H, s, protons of aromatic ring that have O-methyl groups), 7.9-8.02 (4H, d, d, protons of another aromatic ring), 10.94 (1H, s, NH proton).

4-(3-chloro-2-(3-hydroxy-4-methoxyphenyl)-4-oxoazetidin-1-yl)-N-(5-methylisoxazol-3-yl) benzenesulfonamide (Compound M5):

Red powder, Yield: 77%, M.P: (195-197°C), Rf: 0.88 (B), IR (υ cm^{-1}): 3332 (OH) str. of hydroxyl group, 3201 (NH) str. of sulfonamide, 3143 (CH) str. of aromatic, 2993 (CH_3) str. of methoxy group, 2877 (CH_3) str. of oxazole ring, 1720 (C=O) str. of β-lactam, 1593 (C=N) str. of oxazole ring, 1535 (C=C) str. of the aromatic ring, 665 (C-Cl) str. of azetidinone ring.
^{1}H-NMR: 2.3 (3H, s, CH_3 of oxazole ring), 3.38 (9H, s, CH_3 of methoxy group), 4.22 (1H, d, CH-N azetidinone ring), 4.33 (1H, d, CH-Cl of azetidinone ring), 6.14 (1H, s, CH of oxazole ring), 6.37 (1H of OH group), 7.79 (3H, m, protons of aromatic ring that have O-methyl group and hydroxyl group), 7.9-8.02 (4H, d, d, protons of another aromatic ring), 10.94 (1H, s, NH proton).

4-(3-chloro-2-(2-hydroxyphenyl)-4-oxoazetidin-1-yl)-N-(5-methylisoxazol-3-yl)benzene sulfonamide (Compound M6)

Pale brown powder, Yield: 90%, M.P: (197-199°C), Rf: 0.9 (B), IR (υ cm^{-1}): 3317(OH) str. of hydroxyl group, 3205 (NH) str. of sulfonamide, 3143 (CH) str. of aromatic, 2877 (CH_3) str. of oxazole ring, 1720 (C=O) str. of β-lactam, 1593 (C=N) str. of oxazole ring, 1535 (C=C) str. of the aromatic ring, 668 (C-Cl) str. of azetidinone ring.
^{1}H NMR: 2.3 (3H, s, CH_3 of oxazole ring), 3.38 (9H, s, CH_3 of methoxy group), 4.25 (1H, d, CH-N azetidinone ring), 4.37 (1H, d, CH-Cl of azetidinone ring), 6.14 (1H, s, CH of oxazole ring), 6.37 (1H of OH group), 7.62-7.8 (4H, d, d, protons of aromatic ring that have hydroxyl group), 7.9-8.02 (4H, d, d, protons of another aromatic ring), 10.94 (1H, s, NH proton).

Antimicrobial Assay

The antimicrobial activities of each derivative compound were assessed using an agar well diffusion method with pure isolates of four bacteria strains and one fungus strain, which was first subcultures in brain heart infusion broth at 37°C for 18–24 hours.

One hundred microliters of standardized inoculum bacterial suspension (1.510^8 CFU/mL) were obtained from the McFarland turbidity standard (number 0.5). Each bacteria and fungus were seeded on the surface of Mueller Hinton Agar (MHA) plates using a glass spreader. The extra liquid was either air-dried under a sterile hood or spread out again. After allowing the plate to dry, 5–6 mm diameter wells were punched into the agar. Following that, five wells were formed in each agar plate of tested bacteria and fungus, and (100 µL) of dilutions of derivative compounds were put into wells on the MHA plate. The negative controller was DMSO.

The plates were incubated for 24 hours at 37°C, and the antimicrobial effect was calculated by measuring the diameter of the inhibition zone (IZ) all over the disc in millimeters. The diameter of the inhibition zone created all around the well was used to determine the antibacterial and antifungal action.[30]

RESULTS AND DISCUSSION

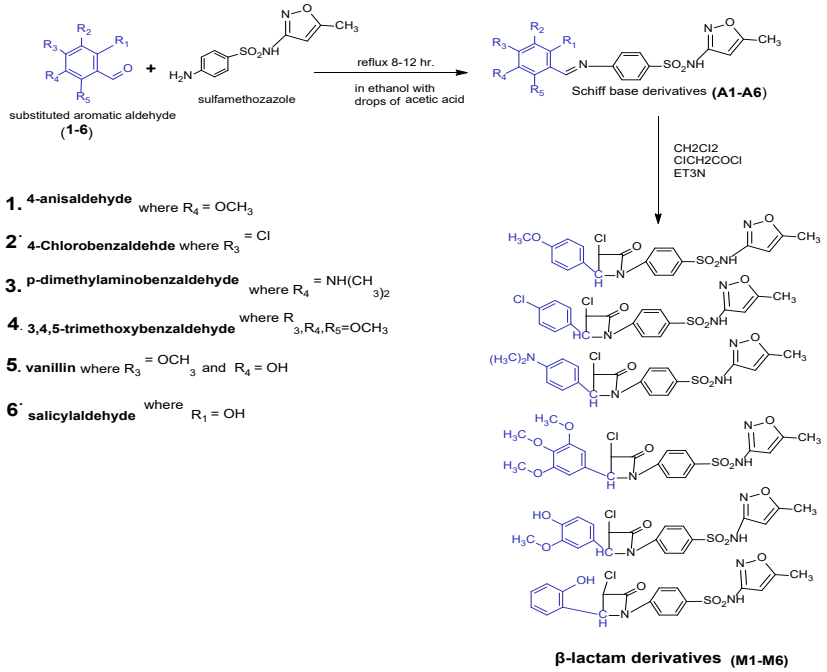
Chemistry

The steps of the synthesis of new 2- azetidinone derivatives (M1-M6), starting from (SMX) are demonstrated in scheme 1. Schiff's bases (A1-A6) were prepared by refluxing different aromatic aldehydes (1-6) with (SMX) in ethanol in presence of acetic acid as catalyst. The final compounds (M1-M6) were obtained by refluxing compounds (A1-A6) with chloroacetyl chloride in dry CH_2Cl_2 in presence of triethylamine as a catalyst.

Antimicrobial Evaluation

The antimicrobial activities of the 2-azetidinone derivatives (M1-M6) were determined using a well diffusion technique, using G(+ve) and G(-ve) bacteria and *Candida albicans*, in comparison to (SMX), Ciprofloxacin, and Fluconazole. DMSO was used as a solvent and as a negative control, as shown in Table 1.

Most of the synthesized derivatives showed greater activity than Sulfamethoxazole against all types of bacteria, particularly against *Pseudomonas aeruginosa*; among all derivatives, the compound (M5) has the highest activity against



Scheme 1: Pathway synthesis of target compounds (M1-M6)

Table (1): Antimicrobial activity of target compounds (M1-M6) with a concentration of 500 µg/mL

Compound No.	*Inhibition zone (IZ) in mm*				
	Escherichia coli (G-ve)	*Pseudomonas aeruginosa (G-ve)*	*Staphylococcus aureus (G+ve)*	*Streptococcus pyogenes (G+ve)*	*Candida ablicans*
Sulfamethoxazole*	20	5	23	18	----------
Ciprofloxacin*	22	----------	18	15	----------
Fluconazole**					25
DMSO	-------	----------	----------	----------	-----
M1	22	15	17	20	23
M2	20	17	25	23	25
M3	23	20	24	20	27
M4	17	20	16	18	20
M5	25	19	23	20	23
M6	20	18	25	23	24

* Standard for bacterial strains, ** Standard for fungi.
(----) = No activity, slightly active (inhibition zone between 5-10 mm), moderately active= (inhibition zone between 10-20 mm), highly active= (inhibition zone more than 20 mm).[33]

most of the examined types of bacteria and the compound (M3) coming in the second degree of activity.

In comparison the antibacterial activity of Ciprofloxacin (Table 1), it shows no activity against *P. aeruginosa*, while most of the β-lactam derivatives give moderate activity against *P. aeruginosa*, and the compounds M5 and M3 showed the highest activity than other synthesized derivatives, these observed results seem logical because a previous study was showed that vanillin - β-lactam derivative has activity better than the parent β- lactam drug (amoxicillin),31 in another study; Gaidhane MK *et al.* [32] demonstrate that 2-Azetidinone derivative bearing 4-(dimethylamino)phenyl group showed better activity against *E. coli* and *Staphylococcus aureus* than the other prepared derivatives.

The antifungal activity of the new compounds was examined against *C. albicans* species, resulted in most of them being highly active compared to Fluconazole; moreover, compound (M3) has greater activity than Fluconazole.

CONCLUSION

The new 2-Azetidinone derivatives have been successfully synthesized. Their chemical structures were confirmed by using FT-IR spectroscopy and 1HNMR. The antimicrobial activity of target compounds (M1-M6) has been examined by the well-diffusion method. Most newly synthesized compounds are more active than standard drugs with greater activity shown by (M3 and M5) compounds as antibacterial agents, whereas the compound (M3) has better activity as an antifungal agent when compared with standard (Fluconazole).

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