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Synthesis and Antibacterial Activity of Some Novel *N*,*N*-Di-Oxalamide Derivatives

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Abstract

Novel *N*,*N*-di-oxalamide derivatives 1-6 were synthesized and characterized by the spectroscopic techniques. These derivatives showed good antibacterial activities against Gram-negative organism *Escherichia coli* and Gram-positive organisms *Staphylococcus aureus* and *Bacillus subtilus*. However, compounds 3 and 4 showed potent antibacterial activity against Gram-negative organism*Escherichia coli*and Gram-positive organism *Staphylococcus aureus*. In addition to that, we compared their antibacterial profiles with previously synthesized *N*,*N*-di-oxalamide derivatives 7-9. The new compounds showed superior antibacterial activities compared to moderate activities for 7-9.

Keywords: Synthesis, *N*, *N*-Di-oxalamide derivatives. *Escherichia coli*, *Staphylococcus aureus*, *Bacillus subtilus*, Antibacterial activity.

1. Introduction

Emergence of new microbial infections resulted in a massive increase in the rate of mortality, mainly in immune compromised individuals, such as tuberculosis, cancer or AIDS patients. Fungal and bacterial infections represent large proportion of the infectious diseases resulting in 13 million deaths each year worldwide (Purewal *et al.*, 2011).

The alarming rates of bacterial resistance to classically used antibiotics and increasing prevalence of multidrug-resistant bacteria necessitates the development of new highly effective and safe antimicrobial agents to combat infections by these bacteria (Park *et al.*, 2009).

Sulfanilamide derivatives are considered for glaucoma therapy and as antimicrobial agents (Turkmen *et al.*, 2011). Sulfonamides were the first drugs acting selectively that could be used in a systematic manner as preventive and therapeutic agents against various bacteiral diseases (Sköld, 2000). Their antibacterial effects are enhanced by combination with trimethoprim through a well known synergistic effect. For example, sulfamethoxazole was used in combination with trimethoprim (Co-trimoxazole) as first choice treatment of pneumonia, urinary tract bacterial infections and toxoplasmosis.

Approaches to produce highly effective antimicrobial agents include the development of structurally new classes of antimicrobial agents with novel mechanisms of action and structural modifications of existing agents by improving both the binding affinity and spectrum of activity while retaining bioavailability and safety profiles.

Recently, potent antimicrobial agents were developed via combining two different active fragments in one molecule. This strategy achieves several advantages by binding independently two different biological targets and synchronously accumulates at both target sites. Dual-action drugs propose the possibility to beat the current resistance and reduce the appearance of new resistant strains (Wang *et al.*, 2002).

Prompted by the quickly developing bacterial resistance to antibacterial chemotherapeutic agents we decided to implement a design strategy that combine sulfonamide scaffold with mixed *N*,*N*-di-oxalamide derivatives (compounds 1-6) based on the combined antibacterial properties of sulfanilamides (Thiele-Bruhn and Beck, 2005; Özdemir *et al.*, 2009; Alsughayer *et al.*, 2011; Becheker *et al.*, 2014) and the metal chelating properties of *N*,*N*-di-oxalamide derivatives (Costa *et al.*, 2004; Vajpayee *et al.*, 2013). Metal chelation provides prospective antibacterial and antiviral activity [We anticipated that the combined sulfonamide / *N*,*N*-di-oxalamide scaffold should enhance the antibacterial properties of the sulfonamide fragments by

potentiating the antibacterial activity with metal chelation. We compared antimicrobial profiles of the new compounds with standard antibacterial antibiotic, i.e., streptomycin.

2.Experimental

2.1. General

^{1}H-NMR and ^{13}C-NMR spectra were collected on a Bruker NMR-300 MHz spectrometer. High resolution mass spectrometry was performed using LC Mass Bruker Apex-IV mass spectrometer utilizing an electrospray interface. Infrared spectra were recorded using WQF-520 FTIR spectrometer. The samples were analyzed as KBr pellets. Analytical thin layer chromatography (TLC) was carried out using pre-coated alumina plates and visualized by UV light (at 254 and / or 360 nm) using different combinations of mobile phase to ensure purity. Chemicals and solvents were used without further purification.

General procedure for the synthesis of *N*,*N*-di-oxalamide derivatives 1-6

To a magnetically stirred ice-bath cooled solution of the selected succinic anhydride (4 mmol) in anhydrous dioxane (20 mL) neat oxalyl chloride was added (8 mmol). After stirring over 30 min the reaction mixture was warmed to room temperature. Two hours later, the reaction mixture was re-cooled to 0 ^{o}C in ice bath followed by drop wise addition of the particular aromatic amine (4 mmol) in pyridine (10 mL) to the reaction mixture. After stirring over 30 min the reaction mixture was warmed to room temperature and allowed to stir over 24 h. Subsequently, the reaction was carefully quenched with saturated sodium bicarbonate solution (200 mL). Finally, the mixture was filtered to offer the products as whitish to gray solids that were re-crystallized from acetone.

N-*o*-Tolyl-succinamic acid (1)

Yield (1.07 gm, 0.01 mmol) to yield the title compound as white powder (1.4 gm, 70%): mp: 144-146 ^{o}C (cryst. diethylether); $\nu_{\mu\alpha\xi}$ (KBr): 3300-2700, 1655 cm^{-1}. HRMS-ESI *m/z* [*M*-H]$^{+}$ calcd for C11H12NO$_3$: 206.08172 found 206.08227

N-*p*-anisidine-succinamic acid (3)

Yield (1.4 gm, 70%): mp: 167-170 ^{o}C (cryst. diethylether); $\nu_{\mu\alpha\xi}$ (KBr): 3300-2700, 1701 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-*d6*): δ 2.48 (m ,2H, CH$_2$), 3.01 (m ,2H, CH$_2$), 3.70 (s, 3H, OCH$_3$), 6.85 (m, 2H), 7.45 (m,2H), 10.00 (brs, 1H, NH), 11.10 ppm (brs, 1H, OH) ppm; ^{13}C NMR (75 MHz, DMSO-*d6*): δ 55.82 (OCH$_3$), 44.14 (CH$_2$), 46.18 (CH$_2$), 114.56 (2 x CH), 121.27 (2 x CH), 132.67 (C), 156.01 (C), 164.22 (C=O), 168.47 (C=O) ppm.HRMS-ESI *m/z* [*M*-H]$^{+}$ calcd for C11H12NO$_4$: 222.07663 found 222.07718

N-(4-Sulfamoyl-phenyl)-*N*-*o*-tolyl-oxalamide (7)

Compound 1 was prepared from commercially available sulfanilamide (4 mmol), *o*-toluidine (4 mmol)and oxalyl chloride (8.0 mmol) in dioxane (20 ml) to yield the compound as faint off-white powder (71 %). mp: Decompose at 180 ^{o}C. FTIR: ν_{max} (KBr disc) 3302, 1670, 1621 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d$_6$): δ 2.25 (3H, s), 7.18 (2H, d, *J* = 9.0 Hz), 7.21 (1H, m), 7.26 (1H, m), 7.51 (1H, m), 7.80 (2H, d, *J* = 9.0 Hz), 8.01 (1H, m). ^{13}C-NMR (300 MHz, DMSO-d$_6$): δ 18.1 (CH$_3$), 121.0 (2 × CH), 125.1 (CH), 126.5 (CH), 126.7 (2 ×CH), 126.9 (CH), 130.9 (CH), 132.6, 135.6, 139.8, 142.6, 159.2, 159.7. HRESI-MS m/z [M - H]$^{+}$ calcd for C$_{15}$H$_{14}$N$_3$O$_4$S$_1$: 332.07105, found: 332.07105.

N-(2-Methoxy-phenyl)-*N*-(4-sulfamoyl-phenyl)-oxalamide (2)

Compound 2 was prepared from commercially available sulfanilamide (4 mmol), *o*-anisidine (4 mmol)and oxalyl chloride (8.0 mmol) in dioxane (20 ml) to yield the compound as faint off-white powder (73 %). mp: Decompose at 180 ^{o}C. FTIR: ν_{max} (KBr disc) 3317, 1679, 1595 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d$_6$): δ 3.82 (3H, s), 6.86 (1H, m), 7.03 (1H, m), 7.73 (2H, m), 7.79 (2H, m), 7.94 (1H, m), 7.97 (1H, m). ^{13}C-NMR (300 MHz, DMSO-d$_6$): δ 56.1 (CH$_3$), 111.6 (CH), 118.9 (CH), 120.6 (CH), 121.0 (2 × CH), 126.9 (2 × CH), 127.1 (CH), 138.5, 139.3, 142.7, 149.9, 170.9, 171.5.

N-(4-Methoxy-phenyl)-*N*-(4-sulfamoyl-phenyl)-oxalamide(3)

Compound 3 was prepared from commercially available sulfanilamide (4 mmol), *p*-anisidine (4 mmol)and oxalyl chloride (8.0 mmol) in dioxane (20 ml) to yield the compound as faint off-white powder (73 %). mp: Decompose at 180 ^{o}C. FTIR: ν_{max} (KBr disc) 3416, 1622 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d$_6$): δ 3.81 (3H, s), 7.06 (2H, d, *J* = 7.8 Hz), 7.35 (2H, d, *J* = 7.2 Hz), 7.92 (4H, d). ^{13}C-NMR (300 MHz, DMSO-d$_6$): δ 55.9 (CH$_3$), 114.6 (2 × CH), 123.8 (2 CH), 124.9, 129.2 (2 CH), 132.1, 135.1 (2 CH), 159.3, 167.7. HRESI-MS m/z [M - H]$^{+}$ calcd for C$_{15}$H$_{14}$N$_3$O$_5$S: 348.06597, found: 348.06596.

N-(2,6-Dimethyl-phenyl)-*N*-(4-sulfamoyl-phenyl)-oxalamide(4)

Compound 4 was prepared from commercially available sulfanilamide (4 mmol), 2,6-dimethylaniline (4 mmol)and oxalyl chloride (8.0 mmol) in dioxane (20 ml) to yield the compound as faint off-white powder (72 %). mp: Decompose at 180 ^{o}C. FTIR: ν_{max} (KBr disc) 3450, 1640 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d$_6$): δ 2.16 (6H, s), 7.79 (1H, t, *J* = 7.8 Hz), 7.80 (2H, d, *J* = 7.2 Hz), 7.95 (2H, d, *J* = 9.0 Hz), 8.02 (2H, d, *J* = 8.4 Hz). ^{13}C-NMR (300 MHz, DMSO-d$_6$): δ 18.5 (2

× CH_3), 120.8 (CH), 121.0 (2 × CH), 126.9 (2 × CH), 128.3 (2 × CH), 135.6. HRESI-MS m/z $[M + Na]^+$ calcd for $C_{16}H_{17}N_3NaO_4S$: 370.08320, found: 370.08320.

N-(2-Chloro-phenyl)-*N*-(4-sulfamoyl-phenyl)-oxalamide(5)

Compound 5 was prepared from commercially available sulfanilamide (4 mmol), 2-chloroaniline (4 mmol)and oxalyl chloride (8.0 mmol) in dioxane (20 ml) to yield the compound as faint off-white powder (67 %). mp: Decompose at 180 ^oC. ^1H-NMR (300 MHz, DMSO-d_6): δ 7.18 (1H, t, *J* = 7.5 Hz), 7.32 (1H, t, *J* = 6.6 Hz), 7.47 (2H, d, *J* = 7.5 Hz), 7.71 (1H, m), 7.74 (1H, m), 7.92 (2H, m). ^{13}C-NMR (300 MHz, DMSO-d_6): δ 118.9 (2 × CH), 121.3 (CH), 121.0 (2 ×CH), 126.5 (CH), 127.8 (CH), 129.9 (CH), 135.5, 138.5, 139.4, 142.7, 171.2, 171.4. HRESI-MS m/z $[M - H]^+$ calcd for $C_{14}H_{11}ClN_3O_4S$: 352.01588, found: 352.01643.

N-(4-Methoxy-phenyl)-*N*-(4-sulfamoylmethyl-phenyl)-oxalamide(6)

Compound 6 was prepared from commercially available mafenide (4 mmol), *p*-anisidine (4 mmol)and oxalyl chloride (8.0 mmol) in dioxane (20 ml) to yield the compound as faint off-white powder (73 %). mp: Decompose at 180 ^oC. FTIR: ν_{max} (KBr disc) 3337, 1716, 1683 cm^{-1}. ^1H-NMR (300 MHz, DMSO-d_6): δ 3.55 (2H, s), 3.80 (3H, s), 7.06 (2H, d, *J* = 8.7 Hz), 7.34 (2H, d, *J* = 8.7 Hz), 7.80 (2H, d, *J* = 8.4 Hz), 7.99 (2H, d, *J* = 9.0 Hz). ^{13}C-NMR (300 MHz, DMSO-d_6): δ 55.9 (CH_3), 66.8 (CH_2), 114.6 (2 × CH), 123.8 (2 ×CH), 129.2 (2 CH), 132.1, 135.1 (2 × CH), 159.3, 167.7. HRESI-MS m/z $[M + 2H]^+$ calcd for $C_{16}H_{19}N_3O_5S$: 365.10344, found: 365.10399.

N,*N*-Bis-(2-methoxy-4-methyl-phenyl)-oxalamide (7)

Compound 7 was prepared from commercially available 2-methoxy-4-methylaniline (4 mmol) and oxalyl chloride (8.0 mmol) in dioxane (20 ml) to yield the compound as faint off-white powder (0.3 g, 19 %). mp: Decompose at 180 ^oC (Habash and Taha, 2011). HRMS-ESI m/z $[M+Na]^+$ calcd for $C_{18}H_{20}N_2NaO_4$: 351.13207, found 351.13152.

N-Naphthalen-1-yl-*N*′-*o*-tolyl-oxalamide (8)

Compound 8 was prepared from commercially available 1-naphthylamine (4 mmol), *o*-toluidine and oxalyl chloride (8.0 mmol) in dioxane (20 ml) to yield the compound as faint off-white powder (0.3 g, 21 %). mp: 125-129 ^oC (Habash and Taha, 2011). Anal. Calcd for $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30; N, 9.20. Found: C, 72.06; H, 5.41; N, 9.16.

N-Naphthalen-1-yl-*N*′-*p*-tolyl-oxalamide (9)

Compound 9 was prepared from commercially available 1-naphthylamine (4 mmol), *p*-toluidine and oxalyl chloride (8.0 mmol) in dioxane (20 ml) to yield the compound as faint off-white powder (0.2 g, 14 %). mp: 166-170 ^oC (Habash and Taha, 2011). Anal. Calcd for $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30; N, 9.20. Found: C, 71.35; H, 5.07; N, 8.83.

2.2. Antibacterial Assay

The Standard bacterial strains used for this study were *Escherichia coli* (ATCC 8739) *Staphylococcus aureus* (ATCC 6538P) and *Bacillus subtilus* (ATCC 6633). Cultures of the strains were maintained at 4º C on nutrient agar plates. All tested agents were prepared by dissolving certain amount in 50 mL of dimethyl sulfoxide (DMSO) then stirred and sonicated for 2 hours until homogenous suspensions were formed.

The minimum inhibitory concentration (MIC) was determined according to the broth micro dilution susceptibility assay which was originally described by the National Committee of Clinical Laboratory Standards currently known as Clinical and Laboratory Standard Institute (CLSI), with some modifications. MIC test was performed in 96 flat bottom microtiter plates (TPP, Switzerland). Each test-well was filled with a volume of 100 µL nutrient broth. Tested preparation (100 µL) was added to the first column of test-well and mixed. A series of two fold dilutions of each tested preparation was then carried out across the plate using micropipette, changing the tips at each dilution step. Then, 10 µL of pre-adjusted overnight microbial culture was used to inoculate each well in the microtiter plate to achieve a final inoculum size of $5x10^6$ cfu / mL. The stock solutions of the tested agents were used.

In all assays, positive growth controls (wells with overnight culture, nutrient broth and bacterial inoculum but without any testing agents) and negative controls (wells with broth but without inoculum) were included.

MICs were expressed as the average of two successive concentrations of the antimicrobial agent showing no growth and growth, respectively. The microorganism's growth was detected as turbidity, visualized by naked eyes, relative to the negative and positive controls. The following equation expresses the calculated MIC.

$$MIC = \frac{Cn + C(n+1)}{2}$$

Where Cn is the concentration at well number n, where no turbidity occurs. C (n+1) is the concentration at well number (n+1), where turbidity occurs. MIC determination was carried out in duplicate (in same 96-well plate) and repeated twice for each microorganism and each tested agent.

The agar diffusion method was performed. A sterile cotton swab was dipped into the overnight bacterial culture, pressed firmly against the inside wall of the tube just above the fluid

level and rotated to remove excess liquid. This was then streaked over the entire surface of freshly prepared nutrient agar (20 mL to give uniform depth) plates. The streaking procedure was repeated three times, rotating the plate approximately 60 degree after each application to ensure an even distribution of the inoculation. Finally, the swab was applied to all around the edge of the agar surface. Agar wells were performed using cork porer. Each pore was filled with 1 mL of the tested agent. The plates were put in an upright position and incubated at 37 °C for 24 hour.

Zone diameters (mm) of complete inhibition (including the diameter of the disc) were measured with a ruler on the under surface of the plate without opening the lid and recorded.

3. Results and Discussion

Novel *N*,*N*-di-oxalamide derivatives1-6 were synthesized by reaction of some selected aromatic amines with oxalyl chloride (Figure-1). In this study, one of the selected aromatic amines; sulfanilamide was used to enhance the antibacterial activity of the resulting *N*,*N*-di-oxalamide derivatives1-6. Succinic anhydride was employed as amine donor to allow mono-substitution of the oxalyl chloride. The mixed anhydride intermediate of succiniamide undergoes azalactonization reaction to yield cyclic isoimide intermediate. Subsequently, the isoimide intermediate apparently acts as imine nucleophile and attacks a second oxalyl-chloride molecule to form isoimidium-oxalylchloride adduct. The second amine attacks the isoimidium-oxalylchloride adduct to form isoimidium-oxalyl-amide adduct which is hydrolyzed to *N*,*N*-di-oxalamide products 1-6 and succinic anhydride. The proposed mechanism for the synthesis of *N*,*N*-di-oxalamide derivatives1-6 is shown in scheme-1 and was reported by Habash and Taha (2011).

However, compounds 1-6 were successfully prepared according to the previous procedure and the novel mechanism reported by Habash and Taha, 2011. These compounds were characterized with the help of spectroscopic techniques.Compounds 1-6 were produced in good yields with about 70 %. However, Compounds 2, 3 and 6 were found to be the major products with 73 % yield.

The antimicrobial activity of a selected group of the previously synthesized compounds 7-9 (Figure-2) was reported here for the first time. These compounds showed moderate antibacterial activities against Gram-positive and Gram negative organisms (Tables-1 and -2). Moreover, the antibacterial activities of novel *N*,*N*-di-oxalamide derivatives1-6 were also studied. Compounds 1-6 exhibited good antibacterial activities against Gram-positive and Gram negative organisms (Tables-1 and -2) in comparison to reported MIC (µg/mL) values of streptomycin antibiotic (Roy *et al.*, 2014). However, compounds 3 and 4 showed potent antibacterial activity against Gram-negative organism*Escherichia coli*and Gram-positive organism*Staphylococcus aureus*.

Compound 1 was synthesized by reaction of *o*-toluidine with succinic anhydride in dioxane followed by addition of oxalyl chloride and sulfanilamide. Compound 1 was produced with 71 % yield. The HRESI-MS spectrum of compound 1 exhibited an $[M - H]^+$ at m/z 332.07105, corresponding to the formula $C_{15}H_{14}N_3O_4S_1$ (calcd. 332.07105). Compound 1 showed good antibacterial activity against Gram-negative organism *E. coli* and moderate activity against Gram-positive organisms *S. aureus* and *B. subtilus* in comparison to streptomycin antibiotic.

Compound 2 was synthesized by reaction of *o*-anisidine with succinic anhydride in dioxane followed by addition of oxalyl chloride and sulfanilamide. Compound 2 was produced with 73 % yield. Compound 2 showed potent antibacterial activity against Gram-positive organism *S. aureus* and good activity against Gram-negative organism *E. coli* and Gram-positive organism *B. subtilus*. Apparently, the presence of electron-donating methoxy group at ortho position of aniline in compound 2 significantly enhances the antibacterial activity.

Compound 3 was synthesized by reaction of *p*-anisidine with succinic anhydride in dioxane followed by addition of oxalyl chloride and sulfanilamide. Compound 3 was produced with 73 % yield. The HRESI-MS spectrum of compound 3 exhibited an $[M - H]^+$ at m/z 348.06596, corresponding to the formula $C_{15}H_{14}N_3O_5S$ (calcd. 348.06597). Compound 3 showed potent antibacterial activity against Gram-positive organism *S. aureus* (MIC = 3.37 µg/mL) and Gram-negative organism *E. coli*, (MIC = 3.37 µg/mL), while compound 3 showed good activity against Gram-positive organism *B. subtilus*. Apparently, the presence of electron-donating methoxy group at para position of aniline in compound 3 significantly enhances the antibacterial activity against both Gram-positive and Gram-negative organisms.

Compound 4 was synthesized by reaction of 2,6-dimethylaniline with succinic anhydride in dioxane followed by addition of oxalyl chloride and sulfanilamide. Compound 4 was produced with 72 % yield. The HRESI-MS spectrum of compound 4 exhibited an $[M + Na]^+$ at m/z 370.08320, corresponding to the formula $C_{16}H_{17}N_3NaO_4S$ (calcd. 370.08320). Compound 4 showed potent antibacterial activity against Gram-positive organism *S. aureus* (MIC = 6.75 µg/mL) and Gram-negative organism *E. coli*(MIC = 3.38 µg/mL), while compound 4 showed good activity against Gram-positive organism *B. subtilus*. Apparently, the presence of two electron-releasing methyl groups at para position of aniline in compound 4 significantly enhances the antibacterial activity against both Gram-positive and Gram-negative organisms compared to compound 1.

Compound 5 was synthesized by reaction of 2-chloroaniline with succinic anhydride in dioxane followed by addition of oxalyl chloride and sulfanilamide. Compound 5 was produced

with 67 % yield. The HRESI-MS spectrum of compound 5 exhibited an $[M - H]^+$ at m/z 352.01643, corresponding to the formula $C_{14}H_{11}ClN_3O_4S$ (calcd. 352.01588). Compound 5 showed good antibacterial activity against Gram-positive organisms *S. aureus* and *B. subtilus* and Gram-negative organism *E. coli*. Apparently, the presence of electron-withdrawing Cl group attached to aniline in compound 5 significantly reduces the antibacterial activity against both Gram-positive and Gram-negative organisms.

Compound 6 was synthesized by reaction of *p*-anisidine with succinic anhydride in dioxane followed by addition of oxalyl chloride and mafenide. Compound 6 was produced with 73 % yield. The HRESI-MS spectrum of compound 6 exhibited an $[M + 2H]^+$ at m/z 365.10399, corresponding to the formula $C_{16}H_{19}N_3O_5S$ (calcd. 365.10344). Compound 6 showed potent antibacterial activity against Gram-positive organism *S. aureus* and good activity against Gram-negative organism *E. coli* and Gram-positive organism *B. subtilus*.

The previously synthesized compounds 7-9 showed moderate antibacterial activity against Gram-positive organismsand Gram-negative organism.

4.Conclusion

In conclusion we have reported the synthesis of *N*,*N*-di-oxalamide derivatives1-6 for the first time. The antibacterial activities of the newly synthesized derivatives 1-6 and the reported synthesized compounds 7-9 (Habash and Taha, 2011) were evaluated. These compounds showed good antibacterial activities against Gram-positive and Gram-negative organisms. However, compounds 3 and 4 showed potent antibacterial activity against Gram-negative organism*Escherichia coli*and Gram-positive organism*Staphylococcus aureus*.

5.Acknowledgments

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6. Contribution

This study originates new and novel *N*,*N*-di-oxalamide compounds with acceptable antibacterial activity. This study opens future work for further exploration of other dual combinations using different known antibacterial drugs for the design and synthesis of novel potnt antibacterial agents.

Table-1. The antimicrobial activity and MIC (µg/mL) against *E. coli*, *S. aureus* and *B. subtilus* for novel compounds 1–6and reported compounds 7-9 *.

Gram-positive B. subtilus	Gram-positive S. aureus	Gram-negative E. coli	Compound
9.00	18.00	9.00	1
7.87	7.87	15.75	**2**
6.75	3.37	3.37	3
6.75	6.75	3.38	4
9.75	9.75	9.75	5
7.12	7.12	14.25	6
10.44	22.15	22.15	7
18.98	37.96	9.49	8
45.32	22.66	45.32	9
1.50	12.50	6.25	Streptomycin

* Values are mean of duplicate.

Table-2. Antibacterial activity (Inhibition zone diameter in mm) of novel compounds 1–6and reported compounds 7-9 *.

Gram-positive B. subtilus	Gram-positive S. aureus	Gram-negative E. coli	Compound
20.0	13.0	15.0	**1**
20.0	16.0	13.0	**2**
21.0	16.0	15.0	**3**
16.0	15.0	16.0	**4**
17.0	11.0	15.0	**5**
20.0	15.0	16.0	**6**
10.0	20.0	11.0	**7**
15.0	19.0	13.0	**8**
18.0	18.0	14.0	**9**
17.0	23.0	16.0	Streptomycin

Results were recorded after 24 hour of treatment and inhibitory zone diameters were measured in mm.
* Values are mean of duplicate.

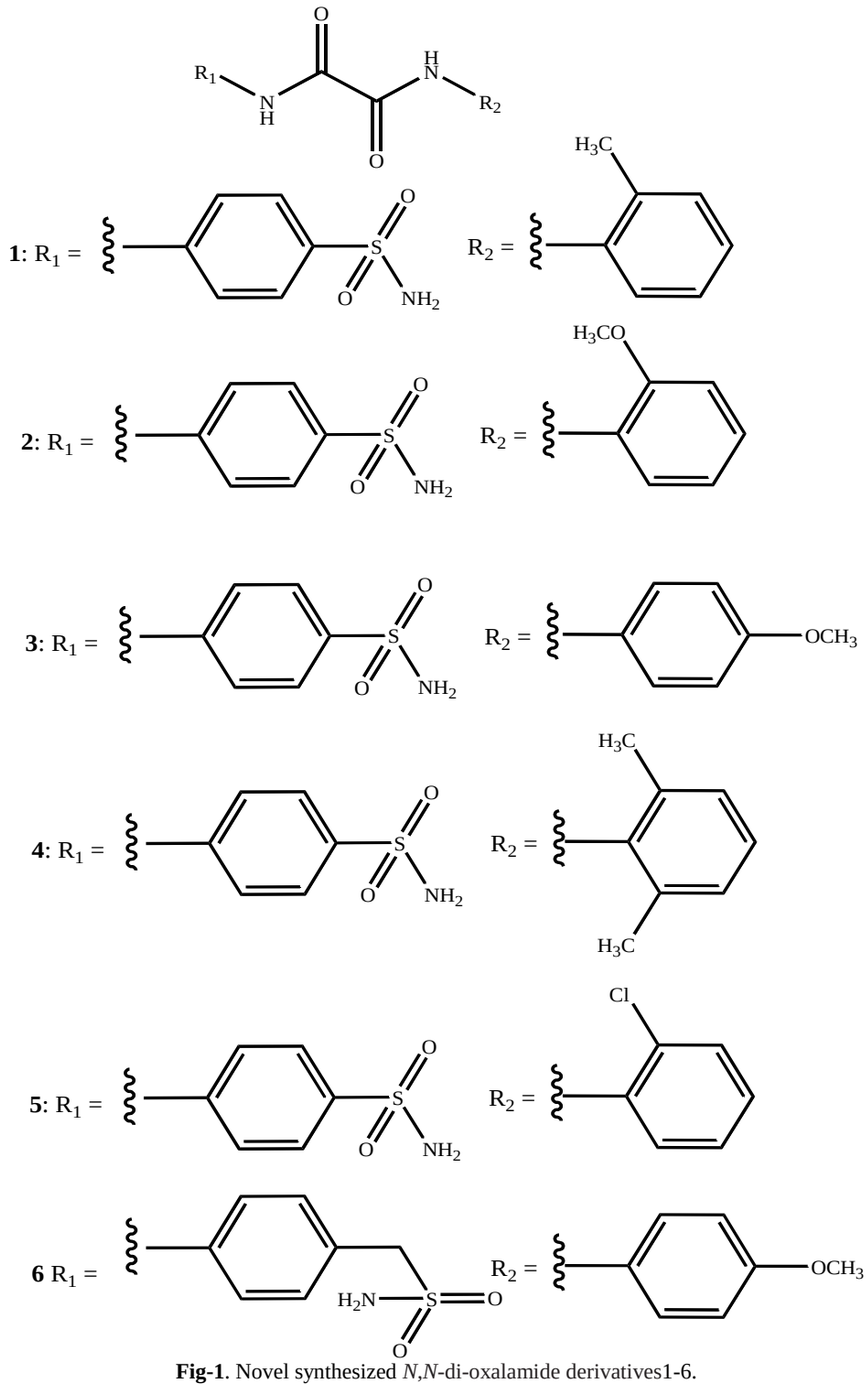


Fig-1. Novel synthesized *N*,*N*-di-oxalamide derivatives1-6.

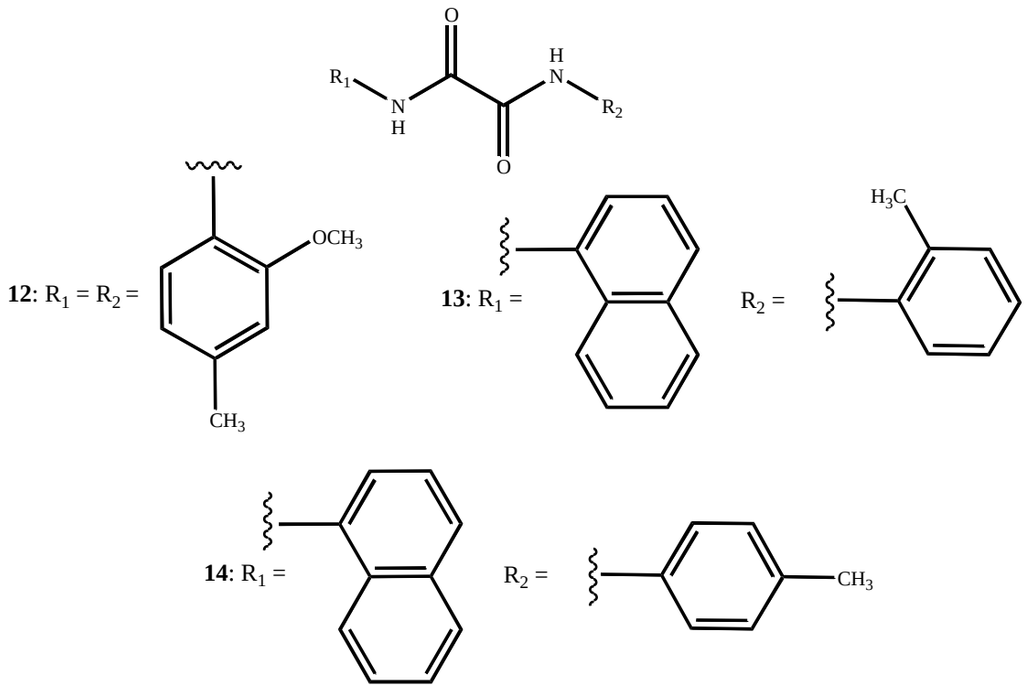
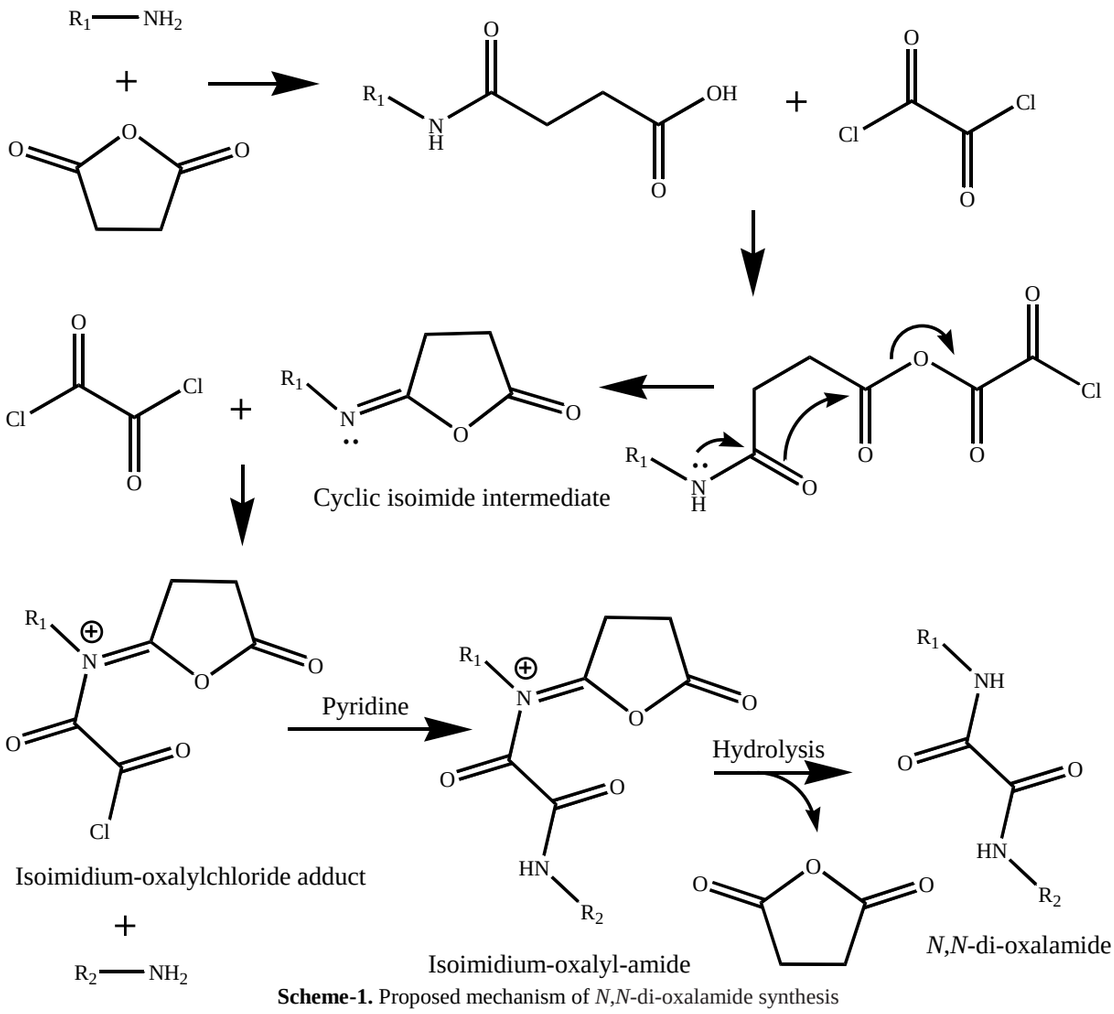


Fig-2. Previously synthesized *N*,*N*-di-oxalamide derivatives**7**-**9**.



Scheme-1. Proposed mechanism of *N*,*N*-di-oxalamide synthesis

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