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Synthesis, Characterization and Antimicrobial Activity of Thiazolo-oxazine Fused Heterocyclic Derivatives, Based on Benzene Sulfonyl Hydrazide

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ABSTRACT

Schiff bases of Benzene sulfonyl hydrazide (SBSZ) (1a-e) were prepared by using various benzaldehyde derivatives. (1a-e) SBSZ were then condensed with mercapto acetic acid. The obtained resultant 2-thiazolidinone derivatives (2a-e) were then condensed with 5-nitro-2-furfuralidine derivatives i.e. (Z)-N-(5-((5-nitrofuran-2-yl) methylene)-4-oxo-2-substitutedthiazolidin-3-yl) benzenesulfonamide (3a-e). These derivatives were further condensed with phenyl urea to yield fused heterocyclic derivatives i.e. N-(2-substituted-7-(5-nitrofuran-2-yl)-5-(phenylamino)-2H-thiazolo[5,4-e][1,3]oxazin-3(3aH)-yl) benzene sulfonamide (4a-e). All the derivatives were characterised by C, H, N elemental analyser and IR-NMR-Mass Spectra. The antimicrobial properties of all the derivatives were studied for selected common microbes. The results of antibacterial activity of all three series (i.e. 2a-e, 3a-e, and 4a-e) of compounds indicate that all compounds are toxic for bacteria. However, the chlorine containing compounds are more toxic than others.

Keywords: Hydrazide, Schiff base, Thiazolidinone, Spectral features, Antimicrobial activity, Elemental analysis.

INTRODUCTION

Recently, the chemistry of sulfohydrazide ($-SO_2NHNH_2$) received more attention by the chemists and biochemists.[1-4] Various heterocyclic compounds are documented from aryl sulfonyl hydrazides[5-7] and tested for their potent biological activities. The aryl sulfonyl hydrazones are found to be antitubercular and anticancer agents.[8-10] The pyrrole derivatives are more pertinent to antitubercular activity reported recently.[11] It was found regarding the Schiff bases of benzene sulfonyl hydrazide with common benzaldehyde not being heterocyclised as well as fused derivatives. However, the disubstituted benzaldehyde-based Schiff bases of benzene sulfonyl hydrazide have been reported as antitumor agents.[12] With these excellent medicinal properties of heterocyclic derivatives of aryl sulfonyl hydrazides[5-11] were explored in the field of hetereocyclization with Schiff bases of benzene sulfonyl hydrazides. Thus,

the study comprises with the post heterocyclization of Schiff bases of benzene sulfonyl hydrazide. The Schematic diagram of the synthesis scheme is shown in Results and discussion part.

MATERIAL AND METHODS

Analytical grade chemicals were used in all experiments. The melting point (uncorrected) of all compounds were determined by using an open capillary method. TLC method was used for purity of compounds. All compounds were scanned for FTIR and ^{1}H NMR spectra were scanned on Bruker using DMSO-d_6 solvent and TMS as reference. Elemental content of all compounds determined by Thermofinigan Flash EA (Italy). The sulfur and halogen determined by Carious method. The antibacterial activity of all the three series of compounds were evaluated by agar cup method[13-15] against the *Gram-positive* and *Gram-negative* bacteria shown in Table 1.

General procedure

Synthesis of benzenesulfonyl hydrazide Schiff base formation of (1a-e)

The Schiff base (1a-e) were prepared (Scheme 1) by refluxing a solution of benzene sulfonyl hydrazide and benzaldehyde derivatives (shown is Scheme 1) in THF solvent for 6 hours. The solvent THF was vacuum distilled. The solid was washed by water and used for further reaction.

Preparation of N-(4-oxo-2-substituted thiazolidin-3-yl) benzenesulfonamide (2a-e)

The mixture of Schiff base (1a-e) (0.01 mole), Mercapto acetic acid (0.0125 mole), DMF Solvent (10 mL) with a little of dry zinc chloride was heated up to boiling for 8 to 9 hours.

The product was then isolated from reaction mixture and washed. The product obtained was purified by chromatographically. Finally crystallized from methanol to give 4-thiazolidinones (2a-e), which were obtained in 70-80% yield.

Synthesis of (Z)-N-(5-((5-nitrofuran-2-yl) methylene)-4-oxo-2-substituted thiazolidin-3-yl) benzenesulfonamide (3a-e)

A mixture of 4-thiazolidinone derivatives (2a-e) (0.01 mole) and 5-Nitro-2-furaldehyde (0.01 mole) in ethanolic sodium hydroxide solution (35 mL) was boiled for 5 hours.

The solid mass was isolated from reaction mixture and washed. Finally recrystallized from ethanol to get 5-(5-nitrofurylidine) derivatives (3a-e).

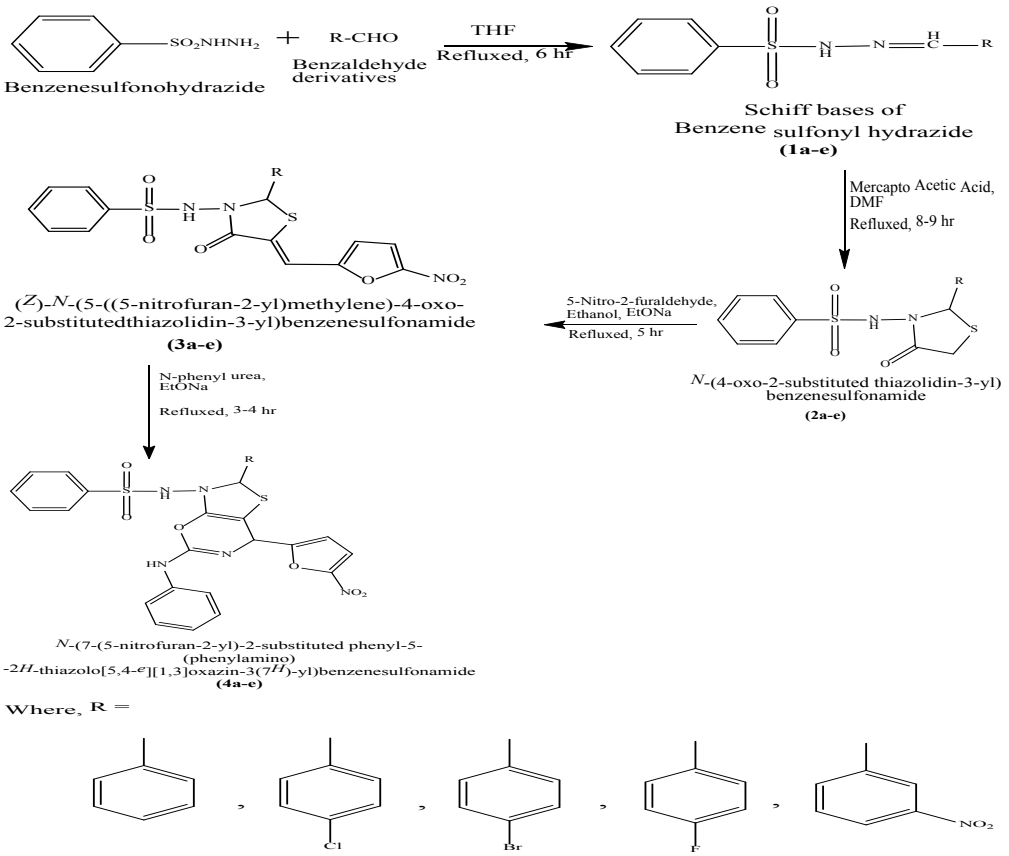
Synthesis of N-(7-(5-nitrofuran-2-yl)-2-substituted phenyl-5-(phenylamino)-2H-thiazolo [5,4-e][1,3] oxazin-3(7H)-yl)benzenesulfonamide (4a-e)

5-nitrofurylidine thiazolidinone (3a-e) (0.02 mole) and N-phenyl urea (0.02 mole) were dissolved in sodium ethanolate solution in ethanol (30 mL). The resultant solution was stirred on magnetically for 4 h and then added to crushed ice with gentle stirring for 4 hours. It was kept in cooling chamber (15) for 24 hours. The crystals were obtained and further recrystallised from ethyl alcohol.

RESULTS AND DISCUSSION

Table 1: Result of Antibacterial activity of 2a-e, 3a-e and 4a-e derivatives

Compound code	Zone of Inhibition of Growth of Bacteria (in mm)			
	Gram +Ve		*Gram -Ve*	
	Staphylococcus aureus	*Bacillus subtills*	*Pseudomonas aeruginosa*	*E. coli*
2a	8	7	9	7
2b	16	15	16	14
2c	19	18	17	18
2d	15	14	13	12
2e	10	11	11	12
3a	7	8	8	6
3b	17	15	15	15
3c	20	19	16	17
3d	15	14	14	13
3e	11	10	10	12
4a	8	9	7	6
4b	14	16	16	15
4c	18	18	17	18
4d	13	14	15	16
4e	10	12	13	14
Neomycin (Standard Drug)	23	24	24	23



Schematic diagram of preparation of thiazolidinone and thiazolo-oxazine fused derivatives based on Schiff bases of benzene sulfonyl hydrazide

2a: N-(4-oxo-2-phenylthiazolidin-3-yl) benzenesulfonamide-Product: 75%, m.p. 203-205, FT-IR (KBr): 1725-1758 (Cyclic C=O), 1200-1250 (S=O), 3310-3350 (-NH), ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.85, 3.95 (d, 2H, -CH_2 Thiazolidinone), 5.91 (s, 1H, -CH Thiazolidinone), 7.26-7.71 (m, 10H, Aromatic), LC-MS : m/z 335.40, Theoretical for $C_{15}H_{14}N_2O_3S_2$: C-53.87, H-4.22, N-4.22, N-8.38, S-19.18 Obtained: C-53.90, H-4.20, N-8.40, S-19.20%.

2b: N-(2-(4-chlorophenyl)-4-oxothiazolidin-3yl)benzenesulfonamide-Product: 76%, m. p. 196-199, FT-IR (KBr): 1725-1755 (Cyclic C=O), 1200-1245 (S=O), 3310-3340 (-NH), ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.80, 3.92 (d, 2H, -CH_2 Thiazolidinone), 5.90 (s, 1H, -CH Thiazolidinone), 7.26-7.65 (m, 9H, Aromatic), LC-MS : m/z 369.90, Theoretical for $C_{15}H_{13}ClN_2O_3S_2$: C-48.84, H-3.55, N-7.59, S-17.39, Cl-9.61% Obtained: C-48.90, H-3.50, N-7.50, S-17.40, Cl-9.60%.

2c: N-(2-(4-bromophenyl)-4-oxothiazolidin-3yl)benzenesulfonamide-product: 74%, m. p. 188-190, δ FT-IR (KBr: 1727-1757 (Cyclic C=O), 1210-1250 (S=O), 3310-3345 (-NH), ^{1}H NMR (400 MHz, DMSO-d_6): 3.85, 3.90 (d, 2h, -CH_2 Thaizolidinone), 5.85 (s, 1H, -CH Thiazolidinone), 7.20-7.60 (m, 9H, Aromatic), LC-MS : m/z 423.31, Theoretical for $C_{15}H_{13}BrN_2O_3S_2$: C-43.59, H-3.17, N-6.78, S-15.52, Br-19.33% Obtained: C-43.60, H-3.00, N-6.80, S-15.50, Br-19.30%.

2d: N-(2-(4-fluorophenyl)-4-oxothiazolidin-3-yl)benzenesulfonamide-Product: 75%, m. p. 178-182 , FT-IR (KBr): 1725-1755 (Cyclic C=O), 1205-1250 (S=O), 3310-3347 (-NH), ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.84, 3.92 (d, 1H, -CH_2 Thiazolidinone), 5.83 (s, 1H, -CH Thiazolidinone), 7.81-7.55 (m, 9H, Aromatic), LC-MS : m/z 352.40, Theoretical for $C_{15}H_{13}FN_2O_3S_2$: C-51.12, H-3.72, N-7.95, S-18.20, F-5.39% Obtained: C-51.10, H-3.70, N-8.00, S-18.20, Br-5.40%.

2e: N-(2-(3-nitrophenyl)-4-oxothiazolidin-3-yl)benzenesulfonamide-Product: 73%, m. p. 205-208, FT-IR (KBr): 1735-1765 (Cyclic C=O), 1210-1250 (S=O), 3320-3355 (-NH), ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.85, 3.98 (d, 2H, -CH_2 Thiazolidinone), 5.93 (s, 1H, -CH Thiazolidinone), 7.25-7.65 (m, 9H, Aromatic), LC-MS : m/z 379.41 Theoretical for $C_{15}H_{13}N_3O_5S_2$: C-47.48, H-3.45, N-11.08, S-16.90% Obtained: C-47.50, H-3.50, N-11.00, S-16.90%.

3a: N-(5-((5-nitrofuran-2-yl)methylene)-4-oxo-2-pheynlthiazolidin-3-yl)benzenesulfonamide-Product: 87%, m. p. 155-157, FT-IR (KBr): 1568 (C=C), 1730-1670 (C=O), 1250-1200 (S=O), 3310-3350 (-NH), ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.71 (s, 1H, CH=C), 5.91 (s, 1H, -CH Thiazolidinone), 7.26-7.71 (m, 10H, Aromatic), LC-MS : m/z 458.50, Theoretical for $C_{20}H_{15}N_3O_6S_2$: C-52.51, H-3.30, N-9.19, S-14.02 Obtained: C-52.50, H-3.30, N-9.20, S-14.00%.

3b: N-(2-(4-chlorophenyl)-5-((5-nitrofuran-2-yl)methylene)4-oxothiazolidin-3-yl)-benzene sulfonamide-Product: 88%, m. p. 153-155, FT-IR (KBr): 1569 (C=C), 1720-1660 (C=O), 1250-1200 (S=O), 3315-3350 (-NH), ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.73 (s, 1H, CH=C), 5.90 (s, 1H, -CH Thiazolidinone), 7.30-7.70 (m, 9H, Aromatic), LC-MS : m/z 492.90, Theoretical for $C_{20}H_{14}ClN_3O_6S_2$: C-48.83, H-2.87, N-8.54, S-13.04, Cl-7.21 Obtained: C-48.80, H-2.90, N-8.50, S-13.10, Cl-7.20%.

3c: N-(2-(4-bromophenyl)-5-((5-nitrofurnan-2-yl)methylene)-4-oxothiazolidin-3-yl)-benzene sulfonamide-Product: 89%, m. p. 145-147, FT-IR (KBr): 1570 (C=C), 1730-1650 (C=O), 1240-1200 (S=O), 3325-3350 (-NH), ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.65 (s, 1H, CH=C), 5.85 (s, 1H, -CH Thiazolidinone), 7.40-7.70 (m, 9H, Aromatic), LC-MS : m/z 536.5, Theoretical for $C_{20}H_{14}BrN_3O_6S_2$: C-44.78, H-2.63, N-7.83, S-11.96, Br-14.90 Obtained: C-44.80, H-2.60, N-7.80, S-12.00, Br-14.90%.

3d: N-(2-(4-fluorophenyl)-5-((5-nitrofuran-2-yl)methylene)-4-oxothiazolidin-3-yl)-benzene sulfonamide-Product: 90%, m. p. 142-145 , FT-IR (KBr): 1560 (C=C), 1740-1660 (C=O), 1240-1190 (S=O), 3320-3350 (-NH), ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.70 (s, 1H, CH=C), 5.75 (s, 1H, -CH Thiazolidinone), 7.40-7.70 (m, 9H, Aromatic), LC-MS : m/z 476.50, Theoretical for $C_{20}H_{14}FN_3O_6S_2$: C-50.52, H-2.97, N-8.84, S-13.49, F-4.00 Obtained C-50.50, H-3.00, N-8.80, S-13.50, F-4.00%.

3 : N-(2-(3-nitrophenyl)-5-((5-nitrofuran-2-yl)methylene)-4-oxothiazolidin-3-yl)-benzene-sulfonamide-Product: 92%, m. p. 158-160, FT-IR (KBr): 1570 (C=C), 1750-1670 (C=O), 1245-1185 (S=O), 3320-3350 (-NH), ^{1}H NMR (400 MHZ, DMSO-d_6): δ 7.60 (s, 1H, CH=C), 5.70 (s, 1H, -CH Thiazolidinone), 7.45-7.75 (m, 9H, Aromatic), LC-MS, m/z 503.50, Theoretical for $C_{20}H_{14}N_4O_8S_2$: C-47.81, H-2.81, N-11.15, S-12.76 Obtained: C-47.80, H-2.80, N-11.10, S-12.80%.

4a: N-(7-(5-nitrofuran-2yl)-2-phenyl-5-(phenylamino)-2H-thiazolo[5,4-e][1,3]oxazin-3(7H)-yl)benzenesulfonamide-Product: 64%, m. p. 182-185, FT-IR (KBr): 1158 (C-N), 1024, 1126 (C-O-C), 1460, 1510, 1585 (C=C), 1250-1200 (S=O), 3310-3350 (-NH), ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.7 (s, 1H, oxazin ring), 4.0 (s broad, 1H, -NH), 4.23 (s, 1H, Thiazolo ring), 6.43-7.86 (m, 17H, Aromatic & furan), LC-MS:m/z 576.60, Theoretical for $C_{27}H_{21}N_5O_6S_2$:C-56.34, H-3.68, N-12.17, S-11.14 Obtained: C-56.30, H-3.70, N-12.20, S-11.10%.

4b: N-(2-(4-chlorophenyl)-7-(5-nitrofuran-2-yl)-5-(phenylamino)-2H-thiazolo[5,4-e][1,3] oxazin-3(7H)-ylbenzenesulfonamide-Product: 65%, m. p. 178-180, FT-IR (KBr): 1156 (C-N), 1025, 1228 (C-O-C), 1458, 1505, 1580 (C=C), 1240-1200 (S=O), 3310-3345 (-NH), ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.65 (s, 1H, oxazin ring), 4.2 (s broad, 1H, -NH), 4.25 (s, 1H, Thiazolo ring), 6.40-7.85 (m, 16H, Aromatic & furan), LC-MS : m/z 611.10 Theoretical for $C_{27}H_{20}ClN_5O_6S_2$:C-53.16, H-3.30, N-11.48, S-10.51, Cl-5.81 Obtained: C-53.20, H-3.30, N-11.50, S-10.50, Cl-5.80%.

4c: N-(2-(4-bromophenyl)-7-(5-nitrofuran-2-yl)-5-(phenylamino)-2H-thiazolo[5,4-e][1,3]oxazin-3(7H)-ylbenzenesulfonamide-Product: 66%, m. p. 164-166, FT-IR (KBr): 1155 (C-N), 1022, 1230, (C-O-C), 1462, 1507, 1568 (C=C), 1245-1200 (S=O), 3310-3347 (-NH), ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.67 (s, 1H, oxazin ring), 4.15 (s broad, 1H, -NH), 4.30 (s, 1H, Thiazolo ring), 6.45-7.80 (m, 16H, Aromatic & furan), LC-MS : m/z 655.50 Theoretical for $C_{27}H_{20}BrN_5O_6S_2$:C-49.55, H-3.08, N-10.70, S-9.80, Br-12.21 Obtained: C-49.60, H-3.00, N-10.70, S-9.70, Br-12.20%.

4d: N-(2-4-fluorophenyl)-7-(5-nitrofuran-2yl)-5-(phenylamino)-2H-thiazolo[5,4-e][1,3]oxaxzin-3(7H)-yl)benzenesulfonamide-Product: 65%, m. p. 154-156 , FT-IR (KBr): 1152 (C-N), 1020, 1234 (C-O-C), 1461, 1508, 1583 (C=C), 1247-1208 (S=O),

3310-3343 (-NH), ^{1}H NMR (400 MHz, DMSO-d6): δ 3.64 (s, 1H, oxazin ring), 4.12 (s broad, 1H, -NH), 4.28 (s, 1H, Thiazolo ring), 6.48-7.78 (m, 16H, Aromatic & furan), LC-MS : m/z 594.60 Theoretical for $C_{27}H_{20}FN_5O_6S_2$:C-54.63, H-3.40, N-11.80, F-3.20 Obtained: C-54.70, H-3.50, N-11.80, S-10.80, Br-3.20%.

4e: N-(2-(3-nitrophenyl)-7-(5-nitrofuran-2-yl)-5-(phenylamino)-2H-thiazolo[5,4-e][1,3]oxazin-3-(7H)-yl)benzenesulfonamide-Product: 67%, m. p. 162-164 , FT-IR (KBr): 1157 (C-N), 1022, 1236, (C-O-C), 1465, 1512, 1580 (C=C), 1247-1208 (S=O), 3310-3345 (-NH), ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.62 (s, 1H, oxazin ring), 4.12 (s broad, 1H, -NH), 4.28 (s, 1H, Thiazolo ring), 6.48-7.75 (m, 16H, Aromatic & furan), LC-MS : m/z 621.60, Theoretical for $C_{27}H_{20}N_6O_8S_2$: C-52.25, H-3.25, N-13.54, S-10.33 Obtained: C-52.20, H-3.20, N-13.50, S-10.30%.

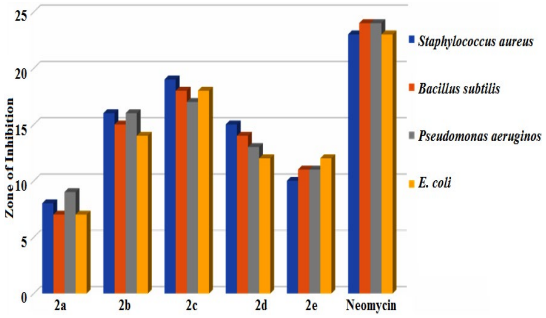


Fig. 1. Histogram of Antibacterial Activity of derivatives 2(a-e)

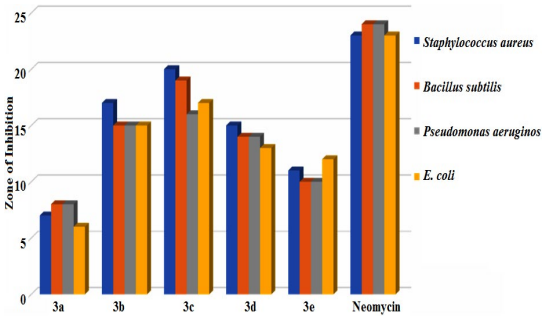


Fig. 2. Histogram of Antibacterial Activity of derivatives 3(a-e)

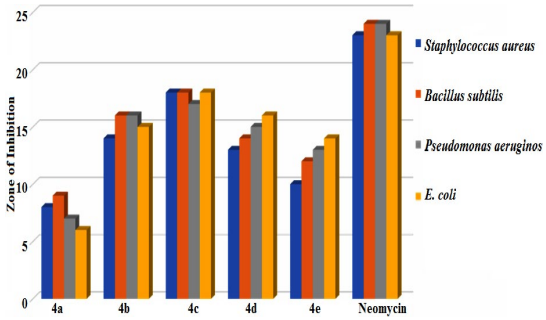


Fig. 3. Histogram of Antibacterial Activity of derivatives 4(a-e)

CONCLUSION

Schiff bases of Benzene sulfonyl hydrazide (SBSZ) were prepared and then post heterocyclization to 4-thiazolidinone derivatives. Further, fused heterocyclised derivatives i.e. thiazolo-oxazine were prepared by condensation of 4-thiazolidinone with 5-nitrofuraldehyde/phenyl urea. All these compounds were characterised duly. The antibacterial activity of all these compounds is good and more particularly chlorine containing derivatives have more antibacterial activity.

Antibacterial activity

All the three series of compounds viz; 2a-e, 3a-e and 4a-e were monitored for antimicrobial activity. The common *Gram+Ve* and *Gram-Ve* bacteria (Shown in Table 1) were used for the study. Sample solution in DMF was placed in a petri dish with nutrient agar and culture media. The zone of inhibition of growth of bacteria by a compound was measured. After on day incubation at[27]. The result (Table 1) are compared with standard Neomycin.

The inspection of the results of the all derivatives reveals that the derivatives 2b, c; 3b, c and 4b, c have excellent toxicity for bacteria used. The other derivatives have moderate toxicity for bacteria. The more toxicity of 2b, c; 3b, c and 4b, c may be responsible to presence of halogen in the structure.

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Conflict of Interest

There is no any conflict of interest.

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