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Synthesis, structural elucidation and biological activities of some novel sulfonyl hydrazones as antibacterial agents

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ABSTRACT: In this study, some *N*'-(substituted arylmethylidene)-4-nitrobenzenesulfonohydrazide derivatives were synthesis by reacting various aldehydes and 4-nitrobenzenesulfonohydrazide. The structural characterization of the compounds was performed by IR, ^{1}H-NMR and TOF-MS (compounds **3b** and **3e**) spectroscopic data besides elementel analyses results. The antibacterial activities of these compounds were examined against some bacteria species. The compounds showed the highest activity against *Pseudomonas aeruginosa* ATCC 27853. Also, anti-quorum sensing activities have been determined using a biosensor bioassay with *Chromobacterium violaceum* CV026 and the signaling molecule *N*-hexanoyl-L-homoserine lactone. All the compounds were subjected for ADME predictions by computational method.

KEYWORDS: Sulfonyl hydrazone; hydrazide; MIC; antibacterial activity; quorum sensing.

1. INTRODUCTION

The infection created by microorganisms, for example bacteria or fungi, has been regarded as one of the major worldwide medical conditions. Currently, antimicrobial resistance causes 700,000 deaths by the year, and the number is anticipated to rise to 10 million in 2050 [1]. Because of the antibiotic resistance, biofilm formation and increasing number of multi-drug microbial pathogens, scientists have focused on creating novel, less toxic more significant antimicrobial drugs.

Quorum sensing, is a bacterial communication mechanism that regulates gene expression depending on population density and signal molecule secretion [2], also assumed to be responsible for bacterial virulence [3]. In Gram negative bacteria, quorum sensing occurs via acyl homoserine lactone (AHL) signal molecules. While *Chromobacterium violaceum* (*C. violaceum*, wild type) is a strain capable of producing short chain AHL and purple colored violacein pigment; mutant *C. violaceum* CV02 is a biosensor strain that does not produce AHL and pigments but can produce violacein pigment by recognizing short-chain AHL molecules (AHL molecules with chain length C4 to C8) [4]. Quorum sensing inhibition is a powerful route for anti-pathogenic drugs development and control of microbial infections [5].

Ever since the discovery of antibacterial properties of the red dye Prontosil, sulfonamide drugs have been used to treat and prevent bacterial infections in humans [6,7]. Sulfonamides and related sulfonyl derivatives are established in a number of active pharmacophores and shows wide-ranging property (Figure 1). Sulfonyl hydrazones derived from sulfonamides have similar chemical and biological properties and exhibited antidepressant [8], antioxidant [9], anticancer [10] anti-carbonic anhydrase [11,12] and especially antibacterial activities [13,14].

In continuation of our researchs on bioactive molecules, we designed the synthesis with a series of sulfonyl hydrazone derivatives with the antibacterial activity evaluation. Many antibacterial activity studies indicate the electron-withdrawing groups on hydrazone compounds enhance antibacterial activity [15–17].

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The presence of fluorine and nitro groups in the targeted compounds has been chosen due to activity-enhancing properties. We obtained a series of original sulfonyl hydrazones **(3a-h)** and characterized their structures by spectroscopic techniques. We investigated their antibacterial activities against *Escherichia coli* ATCC 25922, *Staphylococcus aureus* ATCC 29213, methicillin-resistant *Staphylococcus aureus* ATCC 43300, *Pseudomonas aeruginosa* ATCC 27853, *Enterococcus faecalis* ATCC 29212 and *Klebsiella pneumoniae* ATCC 13883, by minimal inhibition concentration (MIC) methods for comparison. Additionaly, anti-quorum sensing activity of the derivatives was determined using the reporter biosensor strain *Chromobacterium violaceum* CV026 reporter strain and the signaling molecule *N*-hexanoyl-L-homoserine lactone agar diffusion assay.

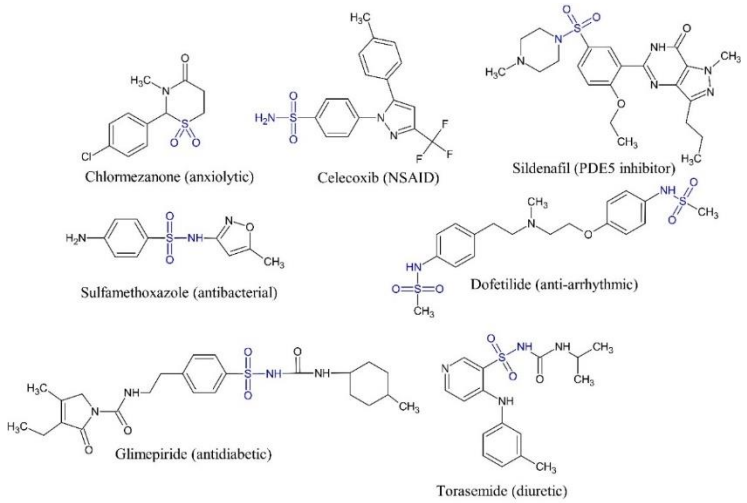

Figure 1. Selected examples of bioactive sulfonyl/sulfonamide derivatives.

2. RESULTS AND DISCUSSION

2. 1. Chemistry

In this present work, new sulfonyl hydrazone derivatives **(3a-h)** were synthesized for the first time. At first, 4-nitrobenzenesulfonohydrazide **(2)** was obtained by stirring p-nitrobenzenesulfonyl chloride **(1)** with hydrazine hydrate in tetrahydrofuran [18]. The reaction of **2** with different aldehydes furnished the corresponding 4-nitro-*N*'-(substituted arylmethylidene)benzenesulfonohydrazides **(3a-h)** (Scheme 1) [10,19]. The structures of newly synthesized compounds were supported by spectral data. The FT-IR, ^{1}H-NMR, TOF-MS spectra (for **3b** and **3e**) and elementel analysis results are in aggrement with the proposed structures. In the FT-IR spectra, sharp bands at 3159- 3325 cm^{-1} due to N-H group and 1602-1626 cm^{-1} due to C=N group are characteristic for sulfonyl hydrazone moiety [10]. In the ^{1}H-NMR spectra, the signals due to N-H and CH=N protons are common in all of the compounds appeared as a singlet at δ= 11.89-12.25 ppm and δ= 7.92-8.12 ppm, respectively. The mass spectrum of the compounds **3b** and **3e** chosen as prototypes showed protonated molecular ion peaks ([M+H]$^+$) in agreement with their molecular formulae.

2. 2. Biological evaluation

2.2.1. Antimicrobial activity

The antimicrobial activity of bacterial species against the compounds are given in Table 1. All of the compounds demonstrated acceptable activity against all microorganisms tested with MIC values varying between 6.25 and 25 µg/mL. The best inhibitory effects of all compounds were observed against *Pseudomonas aeruginosa* having the MIC 6.25 µg/ml. According to the results, we may conclude that compounds **3a-h** have noticeable antibacterial activities.

Additionally, the literature surveys indicated that, sulfonamides have wide antimicrobial activity against Gram-positive and certain Gram-negative bacteria, such as *Escherichia coli, Klebsiella, Salmonella* and *Enterobacter* species but show no inhibitory activity against *Pseudomonas aeruginosa* [20]. This study observed discovery of the more active compounds against *Pseudomonas aeruginosa* though structural modifications and derivatization.

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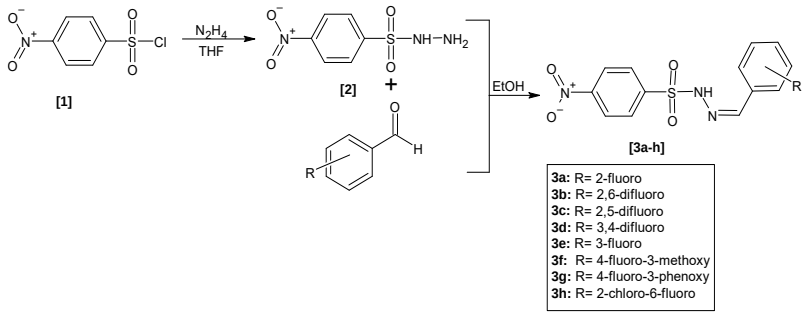

Scheme 1. Synthesis of title compounds **(3a-h)**.

Table 1. Antibacterial activities of the compounds as MIC values (µg/ml).

Compounds	Microorganisms					
	E.c.	*S.a.*	*S.a.**	*P.a.*	*E.f.*	*K.p.*
3a	25	12.5	12.5	12.5	12.5	12.5
3b	25	12.5	12.5	6.25	12.5	12.5
3c	12.5	12.5	12.5	6.25	12.5	12.5
3d	12.5	12.5	12.5	6.25	12.5	12.5
3e	12.5	12.5	12.5	6.25	12.5	12.5
3f	12.5	12.5	12.5	6.25	12.5	12.5
3g	25	12.5	12.5	6.25	12.5	12.5
3h	25	12.5	12.5	6.25	12.5	25

E.c., Escherichia coli ATCC 25922; *S.a., Staphylococcus aureus* ATCC29213; *S.a.**, Methicillin-resistant *Staphylococcus aureus* ATCC 43300; *P.a., Pseudomonas aeruginosa* ATCC 27853; E.f., *Enterococcus faecalis* ATCC 29212; *K.p., Klebsiella pneumoniae ATCC 13883*

2.2.2. Anti-quorum sensing activity

In this study, anti-quorum sensing activity of the test materials at highest and subMIC concentrations was evaluted. It was determined that compounds at subMIC concentrations did not effective activity on quorum sensing mechanism signal molecule *N*-hexanoyl-L-homoserine lactone but the stock concentrations (400 µg/mL) of the compounds showed quorum sensing inhibitory activity. This effect has appeared in the form of inhibition of violacein pigment formation without stopping the growth of bacteria although *N*-hexanoyl-L-homoserine lactone signal molecule and *C. violaceum* CV026 were together in the environment (Figure 2). The best activity result was obtained from compound **3g** with 4-fluoro-3-phenoxyphenyl substitutent. Other substances were found to have anti-quorum sensing activity at 400 µg/mL concentration.

2.3. ADME properties

Lately, research groups have used the potential of chemoinformatics tools to develop a rational drug design method. Currently, these tools have been used in conjunction with experimental testing. Therefore, *in silico* pharmacokinetic properties of all the novel compounds were evaluated using the Osiris Property Explorer (http://www.openmolecules.org/datawarrior/) and Swiss ADME programs http://www.swissadme.ch/) (Table 2) [21].

According to our prediction result, all of the compounds presented a non-toxic risk profile regarding mutagenic, tumourigenic, irritant and reproductive effects. Also, none of the compounds violated rule of five, that proposed for an acceptable theoretical bioavailability [22]. The predicted log P values of the compounds were in the range of 1.38-2.06, less than 5. The calculated percent absorption (%ABS) of all derivatives ranged between 66.92% and 70.11%, indicating that these compounds have good permeability in the cellular membrane. The topological polar surface area (TPSA) is known as a good mark of absorption in the intestine (less than 140 Å^2) and blood-brain barrier penetration (≤ 60Å^2). ABS% was calculated according to the corresponding literature method [23]. According to predicted data, these compounds have good intestinal absorption and do not have sufficient blood-brain barrier penetration.

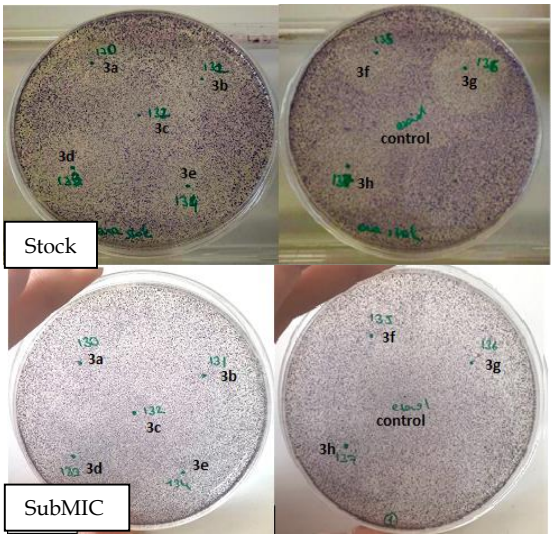

Figure 2. Anti-quorum sensing activity of test materials on violacein pigment production.

Table 2. Lipinski's rule and pharmacokinetic parameters for compounds **3a-h**.

Comp.	Toxicity Risks[a]				ADME properties[b]								
	M	T	IR	RE	MW ≤500	cLog*P* [a] <5	logS[a] >-4	RB[b] ≤10	HD[b] ≤5	HA[b] ≤10	MR[b] 40-130	%Abs	TPSA[b] ≤140Å ^{2}
3a					323	1.45	-2.69	5	1	6	79.29	70.11	112.73
3b					341	1.55	-3.00	5	1	7	79.25	70.11	112.73
3c					341	1.55	-3.00	5	1	7	79.25	70.11	112.73
3d					341	1.55	-3.00	5	1	7	79.25	70.11	112.73
3e					323	1.45	-2.69	5	1	6	79.79	70.11	112.73
3f					353	1.38	-2.70	6	1	7	85.78	66.92	121.96
3g					357	2.06	-3.42	7	1	7	105.81	66.92	121.96
3h					357	2.06	-3.42	5	1	6	84.30	70.11	112.73

: not toxic ; M: mutagenic; T: tumorigenic; IR: irritant; RE: reproductive effective; MW: Molecular weight; cLog*P*: calculated Log*P*; S: Solubility; RB: Number of rotatable bonds; HD: Number of hydrogen donors; HA: Number of hydrogen acceptors; MR: Molar refractivity; TPSA: Topological polar surface area; [a]Parameters calculated using OSIRIS [b] Parameters calculated using SwissADME

3. CONCLUSION

In this study, our results displayed that aromatic sulfonyl hydrazones with a nitro group had remarkable antibacterial activity and were active against drug-resistant pathogens, such as methicillin-resistant *Staphylococcus aureus (MRSA)* and *Pseudomonas aeruginosa*. Additionaly, the stock concentrations of the compounds showed inhibitory activity on *N*-hexanoyl-L-homoserine lactone QS signal molecule. It is thought that, more extensive study is needed to optimize the effectiveness of this series of molecules.

4. MATERIALS AND METHODS

4.1. Synthesis

All chemicals used in this work were purchased from Sigma Aldrich (St. Louis, MO, USA) or Merck (Darmstadt, Germany). Melting points were estimated with a SMP II melting point apparatus and uncorrected. ^{1}H-NMR spectra were taken on Bruker 300 MHz Ultrashield and Bruker Avance III HD 600 MHz spectrometers. Infrared (IR) spectra were performed using a Shimadzu FTIR 8400S spectrometer. Elemental analysis was performed using a LECO CHNS-932 analysis system. Mass spectra were recorded on a Xevo G2-XS QTof mass spectrometer. Liquid chromatographic system consists of an Agilent Technologies 1100 series and data acquisition was done with the Agilent Chemstation Plus software. Chromatographic separation was performed using a reverse phase Zorbax C8 (4.0×250 mm) column. The wavelength reading was 254 nm and the working flow rate was 1 ml/min. All experiments were performed in gradient mode using acetonitrile and water (ACN/H_2O system was used as gradient system: 0-3 min (50:50 ACN/H_2O); 3-6 min (75:25 ACN/H_2O); 6-12 min (100:0 ACN/H_2O).

4.1.1. General procedure for the synthesis of 4-nitrobenzenesulfonohydrazide (2)

The 4-nitrobenzenesulfonohydrazide was produced in good yields (85%) by adding the corresponding p-nitrobenzenesulfonyl chloride in tetrahydrofuran to a slightly excess of hydrazine hydrate solution (80%).

4.1.2. General procedure for the synthesis N'-(substituted arylmethylidene)-4-nitrobenzenesulfono hydrazides (3a-h)

The compounds were synthesized as shown in Scheme 1. A mixture of *p*-nitrobenzenesulfonohydrazide **(2)** (0.001 mol) and substituted aldehydes (0.001 mol) in ethanol was refluxed for 3-4 hours. After completion of reaction, the solvent was evaporated and the solid that formed was filtered, dried and recrystallized from ethanol.

N'-(2-Fluorobenzylidene)-4-nitrobenzenesulfonohydrazide (3a)

Off-white solid; Yield 73% ; m.p. 144-145 °C, Rt (min.): 4.79; FT-IR υ_{max} (cm^{-1}): 3585 (OH, H_2O), 3325 (NH), 1606 (C=N), 1537, 1352 (NO_2), 1329, 1165 (SO_2); ^1H NMR (300 MHz), (DMSO-d_6/TMS) δ ppm: 7.22-7.29 (2H, m), 7.43-7.51 (1H, m), 7.70-7.76 (1H, td, J_1=6 Hz, J_2=1.5 Hz), 8.12-8.17 (3H, m), 8.41-8.46 (2H, m), 12.08 (1H, s, NH). Anal. Calcd for $C_{13}H_{10}FN_3O_4S.H_2O$: C, 45.75; H, 3.54; N, 12.32; S, 9.39 Found: C, 45.45; H, 3.68; N, 11.88; S, 9.73.

N'-(2,6-Difluorobenzylidene)-4-nitrobenzenesulfonohydrazide (3b)

Yellow solid; Yield 78% ; m.p. 160-162 °C, Rt (min.): 4.73; FT-IR υ_{max} (cm^{-1}): 3190 (NH), 1626 (C=N), 1519, 1348 (NO_2), 1307, 1166 (SO_2); ^1H NMR (300 MHz), (DMSO-d_6/TMS) δ ppm: 7.11-7.21 (2H, m), 7.44-7.54 (1H, m), 8.02 (1H, s), 8.10 (2H, d, *J*=9 Hz), 8.44 (2H, d, *J*=9 Hz), 12.16 (1H, s, NH). Anal. Calcd for $C_{13}H_9F_2N_3O_4S.1/2C_2H_5OH$: C, 46.15; H, 3.32; N, 11.53; S, 8.80 Found: C, 46.24; H, 2.98; N, 11.29; S, 8.65. TOF/MS: m/z for $C_{13}H_9F_2N_3O_4S$ $[M+H]^+$: Calc. 342.0354, Found 342.0344.

N'-(2,5-Difluorobenzylidene)-4-nitrobenzenesulfonohydrazide (3c)

Light yellow solid; Yield 86% ; m.p. 150-151 °C, Rt (min.): 4.74; FT-IR υ_{max} (cm^{-1}): 3159 (NH), 1604 (C=N), 1529, 1346 (NO_2), 1327, 1163 (SO_2); ^1H NMR (300 MHz), (DMSO-d_6/TMS) δ ppm: 7.11-7.21 (2H, m), 7.44-7.54 (1H, m), 8.07 (1H, s), 8.16 (2H, d, *J*=9 Hz), 8.43 (2H, d, *J*=9 Hz), 12.21 (1H, s, NH). Anal. Calcd for $C_{13}H_9F_2N_3O_4S.2/3H_2O$: C, 44.19; H, 2.95; N, 11.89; S, 9.08 Found: C, 44.23; H, 3.27; N, 11.19; S, 9.27.

N'-(3,4-Difluorobenzylidene)-4-nitrobenzenesulfonohydrazide (3d)

Light yellow solid; Yield 88% ; m.p. 174-176 °C, Rt (min.): 4.70; FT-IR υ_{max} (cm^{-1}): 3171 (NH), 1606 (C=N), 1527, 1348 (NO_2), 1305, 1163 (SO_2); ^1H NMR (300 MHz), (DMSO-d_6/TMS) δ ppm: 7.45-7.62 (2H, m), 7.62-7.68 (1H, m), 7.94 (1H, s), 8.16 (2H, d, *J*=9 Hz), 8.44 (2H, d, *J*=9 Hz), 12.03 (1H, s, NH). Anal. Calcd for $C_{13}H_9F_2N_3O_4S$: C, 45.75; H, 266; N, 12.31; S, 9.40 Found: C, 45.98; H, 2.77; N, 12.26; S, 9.66.

N'-(3-Fluorobenzylidene)-4-nitrobenzenesulfonohydrazide (3e)

Off-white solid; Yield 87% ; m.p. 147-148 °C, Rt (min.): 4.80; FT-IR υ_{max} (cm^{-1}): 3578 (OH, H_2O), 3190 (NH), 1606 (C=N), 1537, 1352 (NO_2), 1311, 1165 (SO_2); ^1H NMR (300 MHz), (DMSO-d_6/TMS) δ ppm: 7.26-7.38 (1H, m), 7.39-7.49 (3H, m), 7.97 (1H, s), 8.15 (2H, d, *J*=9 Hz), 8.44 (2H, d, *J*=9 Hz), 12.03 (1H, s, NH). Anal. Calcd for $C_{13}H_{10}FN_3O_4S.H_2O$: C, 45.75; H, 3.54; N, 12.31; S, 9.39 Found: C, 45.67; H, 3.51; N, 12.11; S, 9.14. TOF/MS: m/z for $C_{13}H_9F_2N_3O_4S$ $[M+H]^+$: Calc. 324.0448, Found 324.0425.

N'-(4-Fluoro-3-methoxybenzylidene)-4-nitrobenzenesulfonohydrazide (3f)

Yellow solid; Yield 74% ; m.p. 165-167 °C, Rt (min.): 5.40; FT-IR υ_{max} (cm^{-1}): 3200 (NH), 1602 (C=N), 1518, 1357 (NO_2), 1346, 1165 (SO_2); ^1H NMR (300 MHz), (DMSO-d_6/TMS) δ ppm: 3.86 (3H, s, CH_3), 7.18-7.36 (3H, m), 7.93 (1H, s), 8.14 (2H, d, *J*=9 Hz), 8.43 (2H, d, *J*=9 Hz), 11.89 (1H, s, NH). Anal. Calcd for $C_{14}H_{12}FN_3O_5S$: C, 47.59; H, 3.42; N, 11.89; S, 9.08 Found: C, 48.07; H, 3.56; N, 11.71; S, 9.00.

N'-(4-Fluoro-3-phenoxybenzylidene)-4-nitrobenzenesulfonohydrazide (3g)

Off-white solid; Yield 85% ; m.p. 147-148 °C, Rt (min.): 5.42; FT-IR υ_{max} (cm^{-1}): 3182 (NH), 1608 (C=N), 1535, 1336 (NO_2), 1303, 1166 (SO_2); ^1H NMR (600 MHz), (DMSO-d_6/TMS) δ ppm: 7.01 (2H, d, *J*=9 Hz), 7.19 (2H, t, *J*= 8.4 Hz), 7.40- 7.47 (4H, m), 7.92 (1H, s), 8.06 (2H, d, *J*=9 Hz), 8.39 (2H, d, *J*=9 Hz), 11.94 (1H, s, NH). Anal. Calcd for $C_{19}H_{14}FN_3O_5S$: C, 54.94; H, 3.40; N, 10.12; S, 7.72 Found: C, 55.30; H, 3.53; N, 9.97; S, 7.72.

N'-(2-Chloro-6-fluorobenzylidene)-4-nitrobenzenesulfonohydrazide (3h)

Dark green solid; Yield 89% ; m.p. 186-188 °C, Rt (min.): 4.87; FT-IR υ_{max} (cm^{-1}): 3176 (NH), 1604 (C=N), 1519, 1355 (NO_2), 1307, 1170 (SO_2); ^{1}H NMR (600 MHz), (DMSO-d_6/TMS) δ ppm: 7.26 (1H, t, *J*=9 Hz), 7.19 (1H,d, *J*= 7.8 Hz), 7.44- 7.47 (1H, m), 8.11 (2H, d, *J*=9 Hz), 8.12 (1H, s), 8.45 (2H, d, *J*=9 Hz), 12.25 (1H, s, NH). Anal. Calcd for $C_{19}H_{14}FN_3O_5S.1/3\ C_2H_5OH$: C, 54.94; H, 3.40; N, 10.12; S, 7.72 Found: C, 44.36; H, 2.77; N, 9.97; S, 7.72.

4.2. Biological studies

4.2.1. Antibacterial activity test

The synthesized compounds were tested for *in vitro* antibacterial activity against *Escherichia coli* ATCC 25922, *Staphylococcus aureus* ATCC 29213, methicillin-resistant *Staphylococcus aureus* ATCC 43300, *Pseudomonas aeruginosa* ATCC 27853, *Enterococcus faecalis* ATCC 29212 and *Klebsiella pneumoniae ATCC 13883* with using micro broth dilution method according to the methodology described in the literature [24]. The minimum concentration that inhibits bacterial growth accepted as minimal inhibition concentration (MIC). The results were evaluated according to the EUCAST clinical control tables [25].

4.2.2. Anti-quorum sensing activity determination

N-Hexanoyl-L-homoserine lactone was used as signal molecule for biosensor strain. The fresh culture of *C. violaceum* CV026 at 30°C for 18 hours was taken, and adjusted to Mc Farland 0.5 density (10^8 cfu/mL). 100 µL *C. violaceum* CV026, and 50 µL *N*-hexanoyl-L-homoserine lactone was added to 10 mL soft Luria Bertani agar (0.9%) medium and poured into petri plates after vortexing thoroughly. The test materials at highest concentrations (stock) and subMIC concentrations was dropped on (20 µL) agar plates and incubated 30°C for 48 hours. The test was carried out three times and ethanol was used as control [26].

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