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RECORDS OF PHARMACEUTICAL AND BIOMEDICAL SCIENCES

Synthesis and Antimicrobial Evaluation of Novel Hydrazones and 1,3,4-Oxadiazoles Incorporating Bumetanide Derivatives.

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Abstract

The aim of this study is to synthesize new benzenesulfonamide derivatives that possess antibacterial activity using Bumetanide as a precursor of benzenesulfonamide. A novel series of hydrazones containing benzenesulfonamides **(4_{a-i})** and 1,3,4 oxadiazole containing benzenesulfonamides **(5_{a-e})** were prepared and their antibacterial and antifungal activities were measured using microplate broth assay against Gram-positive: *Staphylococcus aureus*, Gram-negative: *Escherichia coli* and *Pseudomonas aeruginosa* and Fungi: *Aspergillus fumigates* and *Candida albicans*. The results showed that some of the prepared compounds exhibit a good to excellent activity against the mentioned bacteria, however all the series showed no activity against fungi. Among the series, Compound **(4_i)** demoed an excellent antibacterial activity better than that of the standard reference (Sulfamethoxazole) against *Escherichia coli*, while compounds **(4_c, 4_e, 4_g)** showed good activity against all tested bacterial strains equals to Sulfamethoxazole activity. Moreover, compounds **(4_g, 5_d)** exert an antimicrobial activity equals to that of Sulfamethoxazole against *Pseudomonas aeruginosa*, while compounds **(4_a, 4_b, 4_c, 4_f, 4_g, 4_h)** exhibit similar activity to Sulfamethoxazole against *Escherichia coli*.

Keywords: Bumetanide; Hydrazones; 1,3,4-oxadiazole; antimicrobial activity; benzenesulfonamide.

1. Introduction

The antimicrobial resistance has turned into a menace that confronts the community over the last few decades. The use and misuse of antimicrobial agents incited the bacteria to develop resistance against them through different defensive mechanisms like enzymatic degradation, modulation of the drug targets or modifying bacterial cell membrane permeability

(Sefton; 2002). Thus a great number of infectious diseases have become uncontrollable which contributes to high levels of morbidity and mortality (El-Sayed et al.; 2017). According to the Centers for Disease Control and Prevention (CDC), the resistant bacteria could infect up to two million patients in the United States every year, while around 23000 person of them meet their fate due to the treatment failure (Srinivasan et al., 2012). On the other hand, the World Health Organization (WHO) stated that though the antimicrobial agents lose their activity, there are insufficient researches that stand up to this catastrophe which means that our competence to overcome the antimicrobial resistance declines dramatically (Gorton et al., 2017).

The researches in the field of medicinal chemistry evolved a limited number of substantial moieties, frequently present in several drug molecules and interestingly, sulfonamide moiety (SO_2NH_2) is one of them (Scozzafava et al., 2012). Sulfonamides are a pharmacologically active class of drugs that exert different pharmacological activities like antibacterial (Kamal et al. 2013; Zhang et al., 2017), antifungal (Saha et al., 2000; Zaidi et al., 2007), anticarbonic anhydrase (Saluja et al., 2014; Supuran et al., 2018), diuretics (Fravolini et al., 1991; Al-Kahtani et al., 2016), anti-inflammatory (Rodge et al., 2012; Brusco et al., 2015) and anticancer (Ahmed et al., 2015; Alafeefy et al., 2016). Among this class of drugs are sulfa drugs that are the first successfully synthesized antimicrobial agents that exert their action via competitive inhibition of folic acid synthesis, and consequently turn off the microbial nucleic acid replication. So far, a group of clinically tried sulfa drugs comprised of benzenesulfonamides bearing antibacterial active aromatic heterocycles are now widely used (Scozzafava et al., 2012). For instance, Sulfamethoxazole, Sulfathiazole, Sulfadiazine and Sulfachloropyridazine are composed of benzenesulfonamide conjugated with isoxazole, thiazole, pyrimidine and pyridazine moieties respectively. Thus, new researches were conducted to discover novel benzenesulfonamide derivatives of antimicrobial action to overcome the antimicrobial resistance problem. For example, addition of coumarin ring to benzenesulfonamide contributed to the antimicrobial activity of compounds **(1, 2)** as displayed in **figure (1)** (Patecl et al., 2010).

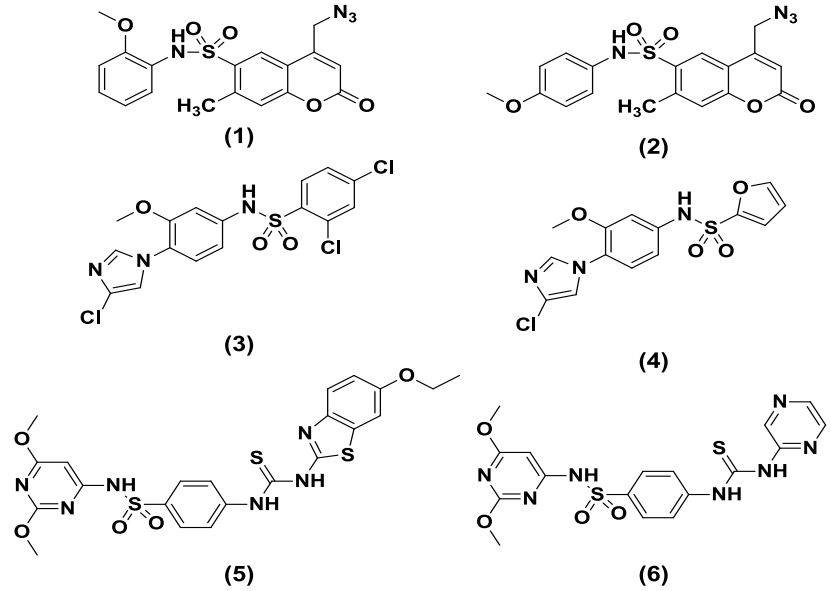


Figure 1: Benzenesulfonamide derivatives of antibacterial activity

Moreover, incorporation a chloro substituted imidazole derivative into benzensulfonamide moiety has enhanced antimicrobial and antitubercular activity of compounds **(3, 4)** shown in **figure (1**). (Pakkath et al., 2014). Recently, Ghorab et al. (Soliman et al., 2019) could prepare new antimicrobial agents compounds **(5,6)** through conjugating thioureidobenzensulfonamide moiety with substituted pyrimidine as shown in **figure (1).**

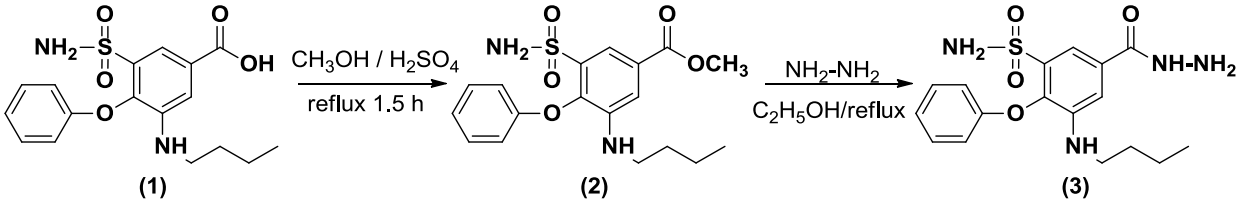
On a parallel approach, in the present investigation, we aimed at introducing new antimicrobial agents to face the antimicrobial resistance challenge. Our research is based on incorporation of well reputed antimicrobial moieties like hydrazones (Mazi et al., 2003) and 1,3,4-oxadiazoles (Othman et al., 2014) into Bumetanide as a precursor of benzenesulfonamide.

2. Results and discussion

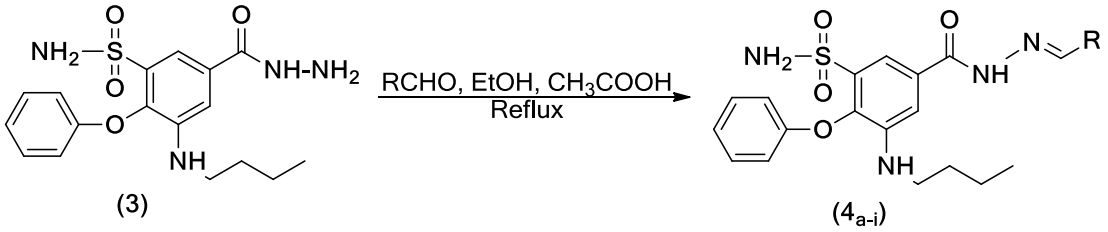
2.1. *Chemistry*

The starting material of this investigation is Bumetanide; 3-(butylamino)-4-phenoxy-5-sulfamoylbenzoic acid **(1)** which was esterified with methanol in presence of sulfuric acid to afford methyl 3-(butylamino)-4-phenoxy-5-sulfamoylbenzoate **(2)**.The ester form **(2)** underwent hydrazinolysis with hydrazine hydrate in ethanol to yield 3-(butylamino)-5-(hydrazinocarbonyl)-2-phenoxy-benzenesulfonamide **(3)** as shown in **scheme (1).**

The acid hydrazide derivative **(3)** was condensed with series of different aldehydes to afford *N'*-arylidene-3-(butylamino)-2-phenoxy-benzenesulfonamide-5-carbonylhydrazides (**4_{a-i}**) as shown in **scheme (2).**



Scheme 1: Synthesis of the key intermediate acid hydrazide (3)

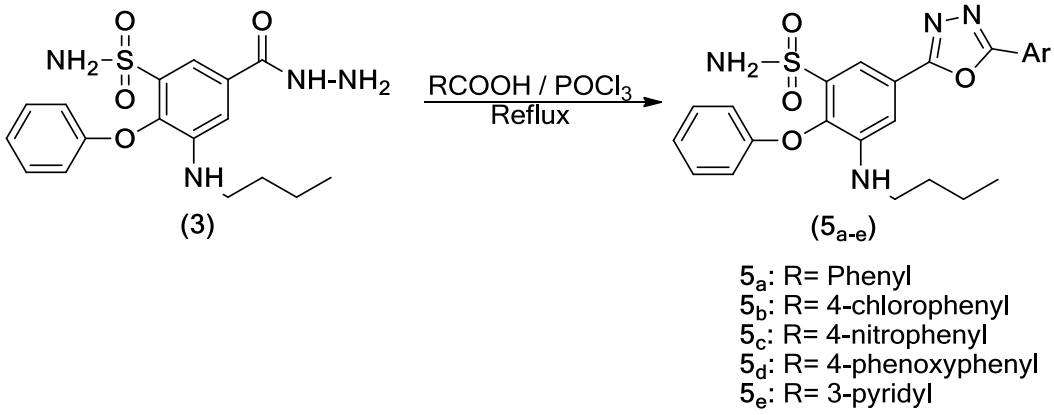


4_a: R= 3-indolyl
4_b: R= 2-furyl
4_c: R= 4-pyridyl
4_d: R= 2-thienyl
4_e: R= 4-nitrophenyl
4_f: R= 4-methoxyphenyl
4_g: R= 4-chlorophenyl
4_h: R= 4-benzyloxyphenyl
4_i: R= 3,4,5-trimethoxyphenyl

Scheme 2: Synthesis of the hyrazone series (4_{a-i})

On the other hand, compound **(3)** was condensed with different aromatic acids in presence of phosphorous oxychloride ($POCl_3$) to produce a novel series of oxadiazoles of substituted-3-(butylamino)-2-phenoxy-5-(5-aryl-1,3,4-oxadiazol-2-yl)-benzenesulfonamide **(5_{a-e})** as shown in **scheme (3)**.

The structures of the novel compounds were confirmed from their spectral and micro analytical data. Structure of compound **(2)** was confirmed by the presence of one singlet signal in H^1NMR spectrum at 3.87 ppm due to (OCH_3) protons. Furthermore, its ^{13}CNMR spectra revealed one additional signal of aliphatic carbon at 52.5 due to (OCH_3) carbon. Formation of compound **(3)** was indicated in ^{1}HNMR spectrum by disappearance of singlet signal of (OCH_3) protons and appearance of the signals of $NHNH_2$ protons at 2.49 ppm (NH-N<u>H</u>$_2$) and 9.88ppm (N<u>H</u>NH_2), while ^{13}CNMR spectrum elucidate disappearance of one signal of aliphatic carbon of (OCH_3) group which clarifies the nucleophilic substitution reaction. Moreover, the structures of compounds **(4_{a-i})** were confirmed by^{1}HNMR spectra that showed disappearance of the signal of primary amino group protons (NHN<u>H</u>$_2$) in compound **(3)** spectrum which proved the condensation with different aldehydes. Moreover, an increase in the number of signals in the aromatic region with one signal corresponding to a methylidene proton at the region between 8.30-8.80 ppm except compound **(4_h)** it exhibited at 10.65 ppm. ^{13}CNMR spectra of compounds **(4_{a-i})** revealed additional signals due to carbons of aromatic rings of different aromatic aldehydes, besides a methylidene carbon of hydrazone at different values between 143.3 and 148.1. In another direction, compounds **(5_{a-e})** were demonstrated in ^{1}HNMR spectra by disappearance of two signals of (NH-NH_2) which were present at compound **(3)** ^{1}HNMR spectrum at 2.49, 9.88 ppm and appearance of signals of the new aromatic rings protons of different aromatic acids. Moreover, ^{13}CNMR spectra showed the presence of two carbon signals at the region between 161.1 and 167.4referring to the C_2, C_5 of the newly formed 1,3,4 oxadiazole ring and absence of the carbonyl signal of compound **(3)** which was appeared at 165.0 ppm. Moreover, the ^{13}CNMR spectra demoed an increase in the number of aromatic signals at the region between 129.0 and 130.0 corresponding to the additional carbons of aromatic acids at position 5 of the oxadiazole ring.



Scheme 3: Synthesis of 1,3,4 oxadizaole series (5_{a-e})

2.2. *Antimicrobial Activity*

The antimicrobial activity of the newly synthesized compounds were screened against several pathogenic microbes representative Gram-positive bacteria: *Staphyllococcus aureus* (RCMB010010), Gram-negative bacteria: *Pseudomonas aeruginosa* (RCMB 010049) and *Escherichia coli* (RCMB 010058) and Fungi: *Aspergillusfumigatus*(RCMB 02568) and *Candida albicans* (RCMB 05036).The microbial suspensions equivalent to the turbidity of 0.5 McFarland (10^8 CFU/ml) standard were prepared from a fresh subculture of tested bacteria in Mueller Hinton Broth (MHB) and tested fungi in Sabouraud Dextrose Broth (SDB) then this suspension was diluted to 10^6 CFU/ml using MHB for bacteria and Sabourand dextrose Broth (SDB) for tested fungi. The adjusted microbial inoculums (100 µl) were added to each well of sterile 96-well flat-bottomed micro titer plate containing the tested concentration of tested samples (100 µl/well). As a result,last inoculum concentration of 5 X 10^5 CFU/ml was obtained in each well. Three wells containing microbial suspension with no sample using DMSO employed for dissolving the tested compound (Growth control) and two wells containing only media (background control) were included in this plate. Optical densities were measured after 24 hours at 37 $^\circ$C for bacteria and after 48 hours at 28°C for fungi using a multi-detection microplate reader at The Regional Center for Mycology and biotechnology (sun Rise - Tecan, USA) at 600 nm. Sulfamethoxzole and Amphotericin B were used as standards for Gram positive bacteria, Gram negative bacteria and fungi respectively. The inhibitory percentage of the tested compounds were illustrated in the **Table (1)** (Ankem et al., 2009).

2.2.1 *Determination of minimum inhibitory concentration (MIC) and inhibitory concentration 50 (IC50):*

The antibacterial activities of the tested compounds were studied adopting the broth micro dilution method (Valgas et al., 2007) using Mueller Hinton brothatthe department of microbiology, Faculty of pharmacy, Port Said University. The inoculums of 3 different clinical isolates including Gram-positive bacteria: *Staphyllococcus aureus* (RCMB010010), Gram-negative bacteria: *Pseudomonas aeruginosa* (RCMB 010049) and *Escherichia coli* (RCMB 010058) and Fungi: *Aspergillusfumigatus*(RCMB 02568) and *Candida albicans* (RCMB 05036).

The microbial suspensions equivalent to the turbidity of 0.5 McFarland (108 CFU/ml) standard were prepared from a fresh subculture of tested bacteria in Mueller Hinton Broth (MHB) and tested fungi in Sabouraud Dextrose Broth (SDB) then this suspension was diluted to 106 CFU/ml using MHB for bacteria and Sabourand dextrose Broth (SDB) for tested fungi. The adjusted microbial inoculums (100 µl) were added to each well of sterile 96-well flat-bottomed micro titer plate containing the tested concentration of tested samples (100µl/well). As a result, last inoculum concentration of 5 X 105 CFU/ml was obtained in each well. Three wells containing microbial suspension with no sample using DMSO (Sigma-Aldrich, Germany) employed for dissolving the tested compound (Growth control) and two wells containing only media (background control) were included in this plate.

Optical densities were measured after 24 hours at 37 ○C for bacteria and after 48 hours at 28°C for fungi using a multi-detection microplate reader at 600 nm. Sulfamethoxazole and Amphotericin B were used as standards for Gram positive bacteria, Gram negative bacteria and Fungi respectively. The inhibitory percentage of the tested compounds was illustrated in the **Table (2)**.

IC50 for each compound were measured during measuring the MIC, The values of IC50 **IC50** for each compound were measured during measuring the MIC, The values of IC50 were illustrated in **Table (3)**.

Table (1): Mean of inhibitory % ± standard derivation produced on a range of clinically pathogenic microorganisms using (125 µg) concentration of tested samples. Results are depicted in the following table:

Tested samples/ M.O.	Fungi		Gram positive bacteria	Gram negative bacteria	
	Asp. fumigatus (RCMB 02568)	C. albicans (RCMB 05036)	*Staph. aureus* (RCMB010010)	*Ps. aeruginosa* (RCMB 010043)	*E. coli* (RCMB 010052)
Standards	**Amphotericin B**		**Sulfamethoxazole**		
	90.31 ± 0.58	**95.21 ± 0.44**	**90.32 ± 0.68**	**72.12 ± 0.32**	**85.75 ± 0.56**
Bumetanide	**NA**	**NA**	**45.66 ± 0.83**	**34.42 ± 0.69**	**38.61 ± 0.69**
2	NA	NA	18.24 ± 0.87	22.14 ± 0.66	27.17 ± 0.60
3	NA	NA	38.13 ± 0.92	18.28 ± 0.69	24.25 ± 0.76
4_a	NA	NA	26.24 ± 0.94	12.67 ± 0.74	84.62 ± 0.66
4_b	NA	NA	22.25 ± 0.88	19.32 ± 0.70	85.21 ± 0.59
4_c	NA	NA	89.68 ± 0.58	74.37 ± 0.73	83.89 ± 0.44
4_d	NA	NA	19.21 ± 0.91	12.21 ± 0.77	71.08 ± 0.58
4_e	NA	NA	68.26 ± 0.68	68.56 ± 0.55	62.38 ± 0.74
4_f	NA	NA	26.25 ± 0.94	12.34 ± 0.88	86.26 ± 0.58
4_g	NA	NA	84.32 ± 0.89	76.34 ± 0.52	85.52 ± 0.61
4_h	NA	NA	32.14 ± 0.97	22.03 ± 0.72	82.14 ± 0.54
4_i	NA	NA	27.14 ± 0.74	19.14 ± 0.68	95.26 ± 0.32
5_a	NA	NA	12.35 ± 0.87	23.21 ± 0.91	11.14 ± 0.79
5_b	NA	NA	18.23 ± 0.88	13.37 ± 0.79	82.14 ± 0.66
5_c	NA	NA	14.29 ± 0.99	9.14 ± 0.92	74.25 ± 0.62
5_d	NA	NA	21.17 ± 0.82	70.74 ± 0.59	14.22 ± 0.78
5_e	NA	NA	10.34 ± 0.94	18.14 ± 0.83	11.13 ± 0.90

N.A.: no activity, *Asp. fumigatus: Aspergillus fumigatus, C. albicans: Candida albicans, Staph. aureus: Staphyllococcusaureus, Ps. aeruginosa: Pseudomonas aeruginosa,E. coli: Escherichia coli.*

Table (2): Antimicrobial Activity as MIC (µg/ml) of tested samples against tested microorganism:

Tested samples/ M.O.	Fungi		Gram positive bacteria	Gram negative bacteria	
	Asp. fumigatus (RCMB 02568)	*C. albicans* (RCMB 05036)	*Staph. aureus* (RCMB010010)	*Ps. aeruginosa* (RCMB 010043)	*E. coli* (RCMB010052)
Standards	**Amphotericin B**		**Sulfamethoxazole**		
	1.2	**0.6**	**6.4**	**12.8**	**12.8**
Bumetanide	**NA**	**NA**	**>100**	**>100**	**>100**
2	NA	NA	>100	>100	>100
3	NA	NA	>100	>100	>100
4_a	NA	NA	>100	>100	12.8
4_b	NA	NA	>100	>100	12.8
4_c	NA	NA	12.8	25.6	12.8
4_d	NA	NA	>100	>100	25.6
4_e	NA	NA	51.2	25.6	51.2
4_f	NA	NA	>100	>100	12.8
4_g	NA	NA	25.6	12.8	12.8
4_h	NA	NA	>100	>100	12.8
4_i	NA	NA	>100	>100	6.4
5_a	NA	NA	>100	>100	>100
5_b	NA	NA	>100	>100	51.2
5_c	NA	NA	>100	>100	25.6
5_d	NA	NA	>100	12.8	>100
5_e	NA	NA	>100	>100	>100

N.A.: no activity, *Asp. fumigatus: Aspergillus fumigatus, C. albicans: Candida albicans, Staph. aureus: Staphyllococcus aureus, Ps. aeruginosa: Pseudomonas aeruginosa,E. coli: Escherichia coli.*

Table (3): Antimicrobial Activity as IC50 (µg/ml) of tested samples against tested microorganism:

Tested samples/ M.O.	Fungi		Gram positive bacteria	Gram negative bacteria	
	Asp. fumigatus (RCMB 02568)	C. albicans (RCMB 05036)	*Staph. aureus* (RCMB010010)	*Ps. aeruginosa* (RCMB 010043)	*E. coli* (RCMB 010052)
Standards	**Amphotericin B**		**Sulfamethoxazole**		
	9.2	**2.1**	**13.07**	**32.9**	**29.8**
Bumetanide	**NA**	**NA**	**>100**	**>100**	**>100**
2	NA	NA	>100	>100	>100
3	NA	NA	>100	>100	>100
4_a	NA	NA	>100	>100	30.1
4_b	NA	NA	>100	>100	29.4
4_c	NA	NA	31.3	54.9	26.2
4_d	NA	NA	>100	>100	42.7
4_e	NA	NA	>100	45.5	99.8
4_f	NA	NA	>100	>100	38.5
4_g	NA	NA	45.7	19.9	20.6
4_h	NA	NA	>100	>100	32.2
4_i	NA	NA	>100	>100	17.8
5_a	NA	NA	>100	>100	>100
5_b	NA	NA	>100	>100	>100
5_c	NA	NA	>100	>100	69.8
5_d	NA	NA	>100	17.5	>100
5_e	NA	NA	>100	>100	>100

N.A.: no activity, *Asp. fumigatus: Aspergillus fumigatus, C. albicans: Candida albicans, Staph. aureus: Staphyllococcus aureus, Ps. aeruginosa: Pseudomonas aeruginosa,E. coli: Escherichia coli*.

The results clarified that all of tested compounds had no activity against the used fungal strains. Most of the newly synthesized compounds show significant antibacterial activity against *Escherichia coli* and *Pseudomonas aeruginosa* with MIC values ranging from 6.4 to 51.2µg/mL. However, compounds **(4_c, 4_e, 4_g)** showed activity against all tested bacterial strains. Interestingly, compound **(4_i)** showed an excellent antibacterial activity against *Escherichia coli* (6.4µg/mL) that exceed Sulfamethoxazole reference standard (12.8µg/mL). Moreover, compounds **(4_a, 4_b, 4_c, 4_f, 4_g, 4_h)** showed similar activity to Sulfamethoxazole against *Escherichia coli* (12.8µg/mL). Furthermore, compounds **(4_g, 5_d)** exert similar activity to Sulfamethoxazole against *Pseudomonas aeruginosa* (12.8µg/mL). Compounds **(1, 2, 3, 5_a, 5_e)** did not exhibit any activity against all the tested strains.

The structure activity relationship (SAR) analysis revealed that benzenesulfonamides bearing hydrazone moieties carrying electron-withdrawing groups or atoms like pyridine (N), Nitro and Chloro at position 4 as compounds **(4_c, 4_e, 4_g)** conferred a significant antibacterial activity against all the tested bacterial strains. While compounds possessing electron-donating groups like 3-indolyl, 2-furyl, 2-thienyl, methoxy, benzyloxy or timethoxy as compounds **(4_a, 4_b, 4_d, 4_f, 4_h, 4_i)** exhibited antibacterial activity against *Escherichia coli* only. On the other side, benzenesulfonamides bearing oxadiazoles having electron-withdrawing groups like Chloro and Nitro at position 4 of the aromatic ring as compounds **(5_b, 5_c)** exhibit a good antibacterial effect against *Escherichia coli* only, while only compounds attached to electron-donating groups at position 4 of aromatic ring like phenoxy group as compound **(5_d)** resulted in a good activity against *Pseudomonas aeruginosa*.

3. Experimental

3.1. General techniques

All starting materials in this investigation from (Sigma-Aldrich, Germany).Melting points (°C) were determined with a Gallenkamp melting point apparatus (London, UK), and are uncorrected. Elemental analysis was performed in the Regional center for Mycology and Biotechnology, Faculty of Science, Al Azhar University, Nasr city, Cairo, Egypt. ^{1}HNMR and ^{13}CNMR were performed in NMR department, Faculty of Science, Al Mansora University. ^{1}HNMR spectra were recorded on Jeol resonance DELTA2-NMR (500 MHz) (Japan) using dimethyl sulfoxide (DMSO)-d_6 as a solvent and tetramethylsilane (TMS) as internal standard (chemical shift in δ, ppm). ^{13}CNMR spectra were recorded on Jeol resonance DELTA2-NMR (100 MHz) (Japan). All reactions were monitored by thin-layer chromatography (TLC) using Silica gel 60 GF245 (E-Merck-Germany) and were visualized by iodine vapors or by UV-lamp at wavelength λ 254 nm.

3.2. Elemental and experimental analysis

3.2.1 Methyl 3-(butylamino)-4-phenoxy-5-sulfamoylbenzoate (2). To a solution of Bumetanide (1.2 g, 3.2 mmol) in methanol, 1 mL of concentrated H_2SO_4 was slowly added using a glass pipette. The reaction mixture was refluxed at 65^{o}C for 1 hour. Allow the reaction mixture to cool to room temperature then pour into a 200 mL beaker containing ice water and add 10% Na_2CO_3 solution till the pH reach approximately 8. (88%), m.p.= 150-152^{o}C; ^{1}HNMR (500 MHz, DMSO-d_6) δ: 0.75 (t, 3H, J = 3.5 Hz, CH_3), 1.07-1.13 (m, 2H, CH_2), 1.32-138 (m, 2H, CH_2), 2.49 (s, 2H, $SO_2N\underline{H_2}$), 3.05 (q, 2H, $C\underline{H_2}$-NH), 3.87 (s , 3H, $OC\underline{H_3}$), 5.13 (t, 1H, J = 6 Hz, NH), 6.83 (d, 2H, J = 8 Hz, Ar-H), 7.00 (t, 1H, J = 7.5 Hz, Ar-H), 7.25 (t, 2H, J = 7.5 Hz, Ar-H), 7.37 (s, 1H, Ar-H), 7.68 (s, 1H, Ar-H) ppm; ^{13}CNMR(100 MHz, DMSO-d_6) δ: 13.6 (CH_2-CH_2-CH_2-$\underline{C}H_3$), 19.3 (CH_2-CH_2-$\underline{C}H_2$-CH_3), 30.1 (CH_2-$\underline{C}H_2$-CH_2-CH_3), 42.0 ($\underline{C}H_2$-CH_2-CH_2-CH_3), 52.5 ($O\underline{C}H_3$), 114.5 (Ar-C), 114.9 (Ar-C), 115.6 (2 Ar-C), 122.3 (Ar-C), 126.9 (Ar-C), 129.1 (Ar-C), 137.9 (2 Ar-C), 139.9 (Ar-C), 142.6 (Ar-C), 156.3 (Ar-C), 165.6 ($\underline{C}$=O) ppm.Anal. Calcd. for $C_{18}H_{22}N_2O_5S$: C, 57.13; H, 5.86; N, 7.40, Found: C, 57.38; H, 5.81; N, 7.6%.

3.2.2. 3-(Butylamino)-5-(hydrazinocarbonyl)-2-phenoxy-benzenesulfonamide (3). To a solution of compound **(2)** (1 g, 2.6 mmol) in ethanol (20 mL), hydrazine hydrate (3 mL, 61.2 mmol) was added then the mixture was refluxed for 6 hours. After cooling, the formed precipitate was filtered, washed with ethanol, dried then recrystallized from ethanol. (90%), m.p.= 215-217 °C; ^{1}HNMR (500 MHz, DMSO-d_6) δ: 0.77 (t, 3H, *J* = 3.5 Hz, CH_3), 1.01-1.13 (m, 2H, CH_2), 1.32-1.38 (m, 2H, CH_2), 2.49 (s, 4H, $SO_2N\underline{H}_2$, NH-$N\underline{H}_2$), 3.06 (q, 2H, $C\underline{H}_2$-NH), 4.92 (t, 1H, *J* = 6 Hz, NH), 6.82 (d, 2H, *J* = 8 Hz, Ar-H), 6.99 (t, 1H, *J* = 7 Hz, Ar-H), 7.25 (t, 2H, *J* = 7.5 Hz, Ar-H), 7.35 (s, 1H, Ar-H), 7.58 (s, 1H, Ar-H), 9.88 (s, 1H, N<u>H</u>-NH_2) ppm; ^{13}CNMR(100 MHz, DMSO-d_6) δ: 13.7 (CH_2-CH_2-CH_2-$\underline{C}H_3$), 19.4 (CH_2-CH_2-$\underline{C}H_2$-CH_3), 30.4 (CH_2-$\underline{C}H_2$-CH_2-CH_3), 42.0 ($\underline{C}H_2$-CH_2-CH_2-CH_3), 112.6 (Ar-C), 113.3 (Ar-C), 115.6 (2 Ar-C), 122.2 (Ar-C), 129.1 (Ar-C), 130.6 (2 Ar-C), 137.5 (Ar-C), 138.1 (Ar-C), 142.2 (Ar-C), 156.5 (Ar-C), 165.0 (<u>C</u>=O) ppm. Anal. Calcd. for $C_{17}H_{22}N_4O_4S$: C, 53.95; H, 5.86; N, 14.80, Found: C, 54.31; H, 5.99; N, 14.97%.

3.2.3. General procedures for synthesis of N'- Arylidene-3-(butylamino)-2-phenoxy-benzenesulfonamide -5-carbonylhydrazide (4_{a-i})

To a solution of compound **(3)** (0.5 g, 1.07 mmol) in ethanol (20 mL), the appropriate aldehyde (0.114 mmol) was added. The reaction mixture was refluxed for 3 hours. The separated solid was filtered, washed with diethyl ether, and crystallized from ethanol.

3.2.3.1. 3-(Butylamino)-5-{2-[(3a,7a-dihydro-1H-indol-3-yl)methylene]hydrazine-1-carbonyl}-2-phenoxybenzenesulfonamide (4a). (87%), m.p. = 275-277^{o}C; ^{1}HNMR (500 MHz, DMSO-d_6) δ: 0.78 (t, 3H, *J* = 3 Hz, CH_3), 1.12-1.15 (m, 2H, CH_2), 1.38-1.41 (m, 2H, CH_2), 2.490 (s, 2H, $SO_2N\underline{H}_2$), 3.12 (q, 2H, CH_2 next to NH), 5.00 (t, 1H, *J* = 6.5 Hz, NH), 6.87 (d, 2H, *J* = 8 Hz, Ar-H), 7.01 (t, 1H, *J* = 7.5 Hz, Ar-H), 7.16 (t, 1H, *J* = 7.5 Hz, Ar-H), 7.21 (t, 1H,*J* = 8 Hz,CH, indole), 7.27 (t, 2H, *J* = 8 Hz, Ar-H), 7.43 (d, 1H, *J* = 7.4 Hz, Ar-H), 7.45 (s, 1H, Ar-H), 7.66 (s, 1H, Ar-H), 7.84 (s, 1H, Ar-H), 8.30 (d, 1H, *J* = 7.5 Hz, Ar-H), 8.64 (s, 1H, C<u>H</u>=N), 11.62 (s, 2H, CON<u>H</u>, N<u>H</u> of indole) ppm; ^{13}CNMR (100 MHz, DMSO-d_6) δ: 13.7 (CH_2-CH_2-CH_2-$\underline{C}H_3$), 19.4 (CH_2-CH_2-$\underline{C}H_2$-CH_3), 30.3 (CH_2-$\underline{C}H_2$-CH_2-CH_3), 42.1 ($\underline{C}H_2$-CH_2-CH_2-CH_3), 111.7 (Ar-C), 111.8 (C_3-indole), 113.4 (Ar-C), 115.6 (Ar-C), 120.4 (2 Ar-C), 122.0 (Ar-C), 122.2 (2 Ar-C), 122.7 (Ar-C), 124.3 (Ar-C), 129.1 (2 Ar-C), 130.4 (C_2-indole), 131.5 (Ar-C), 137.0 (Ar-C), 137.5 (Ar-C), 138.3 (<u>C</u>H=N), 142.2 (Ar-C), 145.4 (Ar-C), 156.5 (Ar-C), 161.8 (<u>C</u>=O) ppm. Anal. Calcd for $C_{26}H_{27}N_5O_4S$: C, 61.77; H, 5.38; N, 13.85, Found: C, 61.65; H, 5.44; N, 13.72%.

3.2.3.2. 3-(Butylamino)-5-[2-(furan-2-ylmethylene)-hydrazinecarbonyl]-2-phenoxy-benzenesulfonamide (4_b). (82%), m.p. =153-155 ^{o}C; ^{1}HNMR (500 MHz, DMSO-d_6) δ: 0.77 (t, *J* = 3.5 Hz, 3H, CH_3), 1.08-1.11 (m, 2H, CH_2), 1.36-1.39 (m, 2H, CH_2), 2.49 (s, 2H, $SO_2N\underline{H}_2$), 3.07-3.11 (q, 2H, $C\underline{H}_2$-NH), 5.02 (t, 1H, *J* = 5.5 Hz, NH), 6.65 (t, 1H, *J* = 5.5 Hz, furan), 6.85 (d, 2H, *J* = 7.5 Hz, Ar-H), 6.95 (d, 1H, *J* = 6 Hz, furan), 7.01 (t, 1H, *J* = 7 Hz, Ar-H), 7.27 (t, 2H, *J* = 7.5 Hz, Ar-H), 7.38 (s, 1H, Ar-H), 7.62 (d, 1H, *J* = 2.5 Hz, C<u>H</u>-O, furan), 7.87 (s, 1H, Ar-H), 8.36 (s, 1H, C<u>H</u>=N), 11.87 (s, 1H, CO-N<u>H</u>) ppm; ^{13}CNMR (100 MHz, DMSO-d_6) δ: 13.7 (CH_2-CH_2-CH_2-$\underline{C}H_3$), 19.3 (CH_2-CH_2-$\underline{C}H_2$-CH_3), 30.3 (CH_2-$\underline{C}H_2$-CH_2-CH_3), 42.1 ($\underline{C}H_2$-CH_2-CH_2-CH_3), 112.3 (Ar-C), 113.4 (Ar-C), 113.8 (Ar-C), 115.6 (C_4-furan), 122.2 (2 Ar-C), 128.8 (C_3-furan), 129.1 (Ar-C), 130.7 (2 Ar-C), 137.6 (<u>C</u>H=N), 137.9 (Ar-C), 138.7 (Ar-C), 142.3 (C_5-furan), 145.3 (Ar-C), 149.4 (C_2-furan), 156.4 (Ar-C), 162.3 (<u>C</u>=O) ppm. Anal. Calcd. for $C_{22}H_{24}N_4O_5S$: C, 57.88; H, 5.30; N, 12.27, Found: C, 57.84; H, 4.92; N, 11.96%.

3.2.3.33-(Butylamino)-2-phenoxy-5-[2-(pyridin-4-ylmethylene)-hydrazinecarbonyl]-

benzenesulfonamide (4_c). (91%), m.p. = 260--264°C; ^{1}HNMR (500 MHz, DMSO-d_6) δ: 0.77 (t, 3H, *J* = 3 Hz, CH_3), 1.09-1.11 (m, 2H, CH_2), 1.37- 1.40 (m, 2H, CH_2), 2.49 (s, 2H, $SO_2N\underline{H}_2$), 3.09-3.11 (q, 2H, $C\underline{H}_2$-NH), 5.05-5.07 (t, 1H, *J* =5.5 Hz, NH), 6.86 (d, 2H, *J* = 8.5 Hz, Ar-H), 7.01 (t, 1H, *J* = 7.5 Hz, Ar-H), 7.27 (t, 2H, *J* = 8 Hz, Ar-H), 7.41 (s, 1H, Ar-H), 7.66 (s, 1H, Ar-H), 7.68 (d, 2H, *J* = 6.5 Hz, pyridine), 8.47 (s, 1H, C<u>H</u>=N), 8.66 (d, 2H, *J* = 6.5 Hz, pyridine), 12.21 (s, 1H, CO-N<u>H</u>) ppm; ^{13}CNMR (100 MHz, DMSO-d_6) δ: 13.7 (CH_2-CH_2-CH_2-<u>C</u>H_3), 19.3 (CH_2-CH_2-<u>C</u>H_2-CH_3), 30.2 (CH_2-<u>C</u>H_2-CH_2-CH_3), 42.1 (<u>C</u>H_2-CH_2-CH_2-CH_3), 113.6 (Ar-C), 115.6 (Ar-C), 121.0 (2 Ar-C), 122.7 (C_3, C_5-pyridine), 129.1 (Ar-C), 130.4 (Ar-C), 137.6 (3 Ar-C), 138.9 (Ar-C), 141.4 (C_4-pyridine), 142.4 (<u>C</u>H=N), 145.7 (C_2, C_6-pyridine), 150.3 (Ar-C), 156.4 (Ar-C), 162.7 (<u>C</u>=O) ppm. Anal. Calcd. for $C_{23}H_{25}N_5O_4S$: C, 59.09; H, 5.39; N, 14.98, Found: C, 59.11; H, 5.42; N, 14.90%.

3.2.3.4. 3-(Butylamino)-2-phenoxy-5-[2-(thiophen-2-yl-methylene)-hydrazinecarbonyl]-benzenesulfonamide (4_d). (86%), m.p. =218-220°C; ^{1}HNMR (500 MHz, DMSO-d_6) δ: 0.77 (t, 3H, *J* = 3.5 Hz, CH_3), 1.09-1.13 (m, 2H, CH_2), 1.35-1.39 (m, 2H, CH_2), 2.49 (s, 2H, $SO_2N\underline{H}_2$), 3.08-3.11 (q, 2H, $C\underline{H}_2$-NH), 5.02 (t, 1H, *J* = 6 Hz, NH), 6.85 (d, 2H, *J* = 7.5 Hz, Ar-H), 7.00 (t, 1H, *J* = 7.5 Hz, Ar-H), 7.15 (t, 1H, *J* = 6.5 Hz, thiophene), 7.27 (t, 2H, *J* = 7.5 Hz, Ar-H), 7.39 (s, 1H, Ar-H), 7.48 (d, 1H, *J* = 7 Hz, thiophene), 7.63 (s, 1H, Ar-H), 7.69 (d, 1H, *J* = 6 Hz, thiophene), 8.70 (s, 1H, C<u>H</u>=N), 11.92 (s, 1H, CO-N<u>H</u>) ppm; ^{13}CNMR (100 MHz, DMSO-d_6) δ: 13.7 (CH_2-CH_2-CH_2-<u>C</u>H_3), 19.3 (CH_2-CH_2-<u>C</u>H_2-CH_3), 30.3 (CH_2-<u>C</u>H_2-CH_2-CH_3), 42.1 (<u>C</u>H_2-CH_2-CH_2-CH_3), 113.4 (Ar-C), 113.5 (Ar-C), 115.6 (2 Ar-C), 122.2 (Ar-C), 127.9 (Ar-C), 129.1 (<u>C</u>H=N), 130.8 (C_4-thiophene), 131.1 (2 Ar-C, C_5-thiophene), 137.6 (C_3-thiophene), 138.6 (Ar-C), 139.1 (Ar-C), 142.3 (C_2-thiophene), 143.3 (Ar-C), 156.4 (Ar-C), 162.2 (<u>C</u>=O) ppm. Anal. Calcd. for $C_{22}H_{24}N_4O_5S$: C, 55.92; H, 5.12; N, 11.86, Found: C, 55.81; H, 5.36; N, 12.29%.

3.2.3.5. 3-(Butylamino)-5-[2-(4-nitrobenzylidene)-hydrazinecarbonyl]-2-phenoxy-benzenesulfonamide (4_e). (93%), m.p. = 277-281°C; ^{1}HNMR (500 MHz, DMSO-d_6) δ: 0.77 (t, 3H, *J* = 3.5 Hz, CH_3), 1.08-1.12 (m, 2H, CH_2), 1.34-1.39 (m, 2H, CH_2), 2.49 (s, 2H, $SO_2N\underline{H}_2$), 3.09-3.12 (q, 2H, $C\underline{H}_2$-NH), 5.04 (t, 1H, *J* = 6 Hz, NH), 6.87 (d, 2H, *J* = 7.5 Hz, Ar-H), 7.01 (t, 1H, *J* = 7.5 Hz, Ar-H), 7.28 (t, 2H, *J* = 8 Hz, Ar-H), 7.33 (s, 1H, Ar-H), 7.58 (s, 1H, Ar-H), 8.11 (d, 2H, *J* = 8 Hz, Ar-H), 8.28 (d, 2H, *J* = 8 Hz, Ar-H), 8.77 (s, 1H,C<u>H</u>=N), 11.089 (s, 1H, CO-N<u>H</u>) ppm; ^{13}CNMR (100 MHz, DMSO-d_6) δ: 13.6 (CH_2-CH_2-CH_2-<u>C</u>H_3), 19.3 (CH_2-CH_2-<u>C</u>H_2-CH_3), 30.2 (CH_2-<u>C</u>H_2-CH_2-CH_3), 42.0 (<u>C</u>H_2-CH_2-CH_2-CH_3), 113.8 (Ar-C), 115.6 (Ar-C), 122.2 (2 Ar-C), 123.6 (Ar-C), 127.6 (3 Ar-C), 129.1 (2 Ar-C), 131.3 (3 Ar-C), 138.6 (Ar-C), 142.1 (Ar-C), 144.2 (Ar-C), 147.7 (<u>C</u>H=N), 152.9 (Ar-C), 156.5 (Ar-C), 162.4 (<u>C</u>=O) ppm. Anal. Calcd. for $C_{24}H_{25}N_5O_6S$: C, 56.35; H, 4.93; N, 13.69, Found: C, 56.91; H, 5.22; N, 14.09%.

3.2.3.6. 3-(Butylamino)-5-[2-(4-methoxybenzylidene)-hydrazinecarbonyl]-2-phenoxy-benzenesulfonamide (4_f). (74%), m.p. =213-215°C; ^{1}HNMR (500 MHz, DMSO-d_6) δ: 0.75-0.78 (t, 3H, *J* = 3.5 Hz, CH_3), 1.09-1.13 (m, 2H, CH_2), 1.37-1.39 (m, 2H, CH_2), 2.49 (s, 2H, $SO_2N\underline{H}_2$), 3.09-3.10 (q, 2H, $C\underline{H}_2$-NH), 3.81 (s, 3H, $OC\underline{H}_3$), 5.00 (t, 1H, *J* = 6 Hz, NH), 6.85 (d, 2H, *J* = 8.5 Hz, Ar-H), 7.02 (t, 1H, *J* = 8 Hz, Ar-H), 7.03 (d, 2H, *J* = 8.5 Hz, Ar-H), 7.27 (t, 2H, *J* = 8 Hz, Ar-H), 7.31 (s, 1H, Ar-H), 7.65 (s, 1H, Ar-H), 7.68 (d,2H, *J* = 8.5 Hz, Ar-H), 8.43 (s, 1H, C<u>H</u>=N), 11.84 (s, 1H, CO-N<u>H</u>) ppm.^{13}CNMR (100 MHz, DMSO-d_6) δ: 13.7 (CH_2-CH_2-CH_2-<u>C</u>H_3), 19.3 (CH_2-CH_2-<u>C</u>H_2-CH_3), 30.3 (CH_2-<u>C</u>H_2-CH_2-CH_3), 42.1 (<u>C</u>H_2-CH_2-CH_2-CH_3), 55.3 ($O\underline{C}H_3$), 113.5 (Ar-C), 114.4 (Ar-C), 115.6 (2 Ar-C), 122.2 (2 Ar-C), 126.8 (Ar-C), 128.8 (Ar-C), 129.1 (Ar-C), 131.0 (2 Ar-C), 131.8 (2 Ar-C), 137.5 (Ar-C), 138.6 (Ar-C), 142.3 (Ar-C), 148.1 (<u>C</u>H=N), 156.4 (Ar-C), 160.9 (Ar-C), 162.2 (<u>C</u>=O) ppm. Anal. Calcd. for $C_{25}H_{28}N_4O_5S$: C, 60.47; H,

5.68; N, 11.28, Found: C, 60.77; H, 5.88; N, 11.58%.

3.2.3.7. 3-(Butylamino)-5-[2-(4-chlorobenzylidene)-hydrazinecarbonyl]-2-phenoxy-benzenesulfonamide (4_g). (86%), m.p. =230-234°C; ^{1}HNMR (500 MHz, DMSO-d_6) δ: 0.75-0.78 (t, 3H, *J* = 3.5 Hz, CH_3), 1.09-1.13 (m, 2H, CH_2), 1.35-1.40 (m, 2H, CH_2), 2.49 (s, 2H, $SO_2N\underline{H}_2$), 3.08-3.12 (q, 2H, $C\underline{H}_2$-NH), 5.03 (t, 1H, *J* = 6 Hz, NH), 6.86 (d, 2H, *J* = 7.5 Hz, Ar-H), 7.01 (t, 1H, *J* = 7.5 Hz, Ar-H), 7.27 (t, 2H, *J* = 7.5 Hz, Ar-H), 7.40 (s, 1H, Ar-H), 7.53 (d, 2H, *J* = 8.5 Hz, Ar-H), 7.65 (s, 1H, Ar-H), 7.77 (d, 2H, *J* = 8.5 Hz, Ar-H), 8.47 (s, 1H,C<u>H</u>=N), 12.00 (s, 1H, CO-N<u>H</u>) ppm; ^{13}CNMR (100 MHz, DMSO-d_6) δ: 13.6 (CH_2-CH_2-CH_2-<u>C</u>H_3), 19.3 (CH_2-CH_2-<u>C</u>H_2-CH_3), 30.3 (CH_2-<u>C</u>H_2-CH_2-CH_3), 42.1 (<u>C</u>H_2-CH_2-CH_2-CH_3), 113.5 (Ar-C), 115.6 (Ar-C), 122.2 (2 Ar-C), 128.8 (Ar-C), 129.0 (Ar-C), 129.1 (3 Ar-C), 130.7 (2 Ar-C), 133.2 (2 Ar-C), 134.6 (Ar-C), 137.6 (Ar-C), 138.7 (Ar-C), 142.3 (Ar-C), 146.8 (<u>C</u>H=N), 156.4 (Ar-C), 162.4 (<u>C</u>=O) ppm. Anal. Calcd. for $C_{24}H_{25}ClN_4O_4S$: C, 57.54; H, 5.03; N, 11.18, Found: C, 57.81; H, 5.34; N, 11.51%.

3.2.3.8. 5-{2-[4-(benzyloxy)-benzylidene]-hydrazinecarbonyl}-3-(butylamino)-2-phenoxy-benzenesulfonamide (4_h). (73%), m.p. =286-289°C; ^{1}HNMR (500 MHz, DMSO-d_6) δ: 0.76 (t, 3H, *J* = 3.5 Hz, CH_3), 1.10-1.13 (m, 2H, CH_2), 1.35-1.38 (m, 2H, CH_2), 2.49 (s, 2H, $SO_2N\underline{H}_2$), 3.07-3.11 (q, 2H, $C\underline{H}_2$-NH), 5.02 (t, 1H, *J* = 6 Hz, NH), 5.13 (s, 2H, $C\underline{H}_2$-O), 6.85 (d, 2H, *J* = 7.5 Hz, Ar-H), 6.99 (t, 1H, *J* = 6.5 Hz, Ar-H), 7.01 (d, 2H, *J* = 8.5 Hz, Ar-H), 7.16 (t, 1H, *J* = 6.5 Hz, Ar-H), 7.26 (t, 2H, *J* = 8 Hz, Ar-H), 7.30 (s, 1H, Ar-H), 7.38 (t, 2H, *J* = 7 Hz, Ar-H), 7.43 (d, 2H, *J* = 7 Hz, Ar-H), 7.68 (s, 1H, Ar-H), 7.70 (d, 2H, *J* = 8.5 Hz, Ar-H), 10.65 (s, 1H, C<u>H</u>=N), 11.748 (s, 1H, CO-N<u>H</u>) ppm; ^{13}CNMR (100 MHz, DMSO-d_6) δ: 13.7 (CH_2-CH_2-CH_2-<u>C</u>H_3), 19.4 (CH_2-CH_2-<u>C</u>H_2-CH_3), 30.3 (CH_2-<u>C</u>H_2-CH_2-CH_3), 42.0 (<u>C</u>H_2-CH_2-CH_2-CH_3), 69.3 (O-<u>C</u>H_2), 113.8 (Ar-C), 115.1 (Ar-C), 115.6 (2 Ar-C), 118.6 (2 Ar-C), 122.2 (Ar-C), 126.9 (Ar-C), 127.7 (Ar-C), 128.5 (2 Ar-C), 129.1 (Ar-C), 129.9 (2 Ar-C), 130.1 (2 Ar-C), 131.4 (2 Ar-C), 136.0 (Ar-C), 136.8 (Ar-C), 138.6 (Ar-C), 139.3 (Ar-C), 143.9 (<u>C</u>H=N), 156.4 (Ar-C), 164.4 (Ar-C), 168.4 (<u>C</u>=O) ppm. Anal. Calcd. for $C_{31}H_{32}N_4O_5S$: C, 65.02; H, 5.63; N, 9.78, Found: C, 65.37; H, 5.69; N, 9.72%.

3.2.3.9. 3-(Butylamino)-2-phenoxy-5-[2-(3,4,5-trimethoxybenzylidene)-hydrazinecarbonyl]-benzenesulfonamide (4_i). (77%), m.p. = 254-257°C; ^{1}HNMR (500 MHz, DMSO-d_6) δ: 0.78 (t, 3H, *J* = 3.5 Hz, CH_3), 1.09-1.13 (m, 2H, CH_2), 1.36-1.41 (m, 2H, CH_2), 2.49 (s, 2H, $SO_2N\underline{H}_2$), 3.08-3.11 (q, 2H, $C\underline{H}_2$-NH), 3.71 (s, 3H, $OC\underline{H}_3$), 3.84 (s, 6H, $2OC\underline{H}_3$), 5.02 (t, 1H, *J* = 6 Hz, NH), 6.86 (d, 2H, *J* = 8 Hz, Ar-H), 7.01 (t, 1H, *J* = 7.5 Hz, Ar-H), 7.03 (s, 2H, Ar-H), 7.27 (t, 2H, *J* = 8 Hz, Ar-H), 7.39 (s, 1H, Ar-H), 7.64 (s, 1H, Ar-H), 8.41 (s, 1H, C<u>H</u>=N), 11.91 (s, 1H, CO-N<u>H</u>) ppm; ^{13}CNMR (100 MHz, DMSO-d_6) δ: 13.6 (CH_2-CH_2-CH_2-<u>C</u>H_3), 19.3 (CH_2-CH_2-<u>C</u>H_2-CH_3), 30.3 (CH_2-<u>C</u>H_2-CH_2-CH_3), 42.1 (<u>C</u>H_2-CH_2-CH_2-CH_3), 56.0 (3, 5 O<u>C</u>H_3), 60.1 (4 O<u>C</u>H_3), 104.3 (2 Ar-C), 113.5 (Ar-C), 115.6 (Ar-C), 122.2 (2 Ar-C), 129.1 (Ar-C), 129.8 (Ar-C), 130.9 (Ar-C), 137.6 (3 Ar-C), 138.6 (Ar-C), 139.3 (Ar-C), 142.2 (Ar-C), 148.2 (<u>C</u>H=N), 153.2 (2 Ar-C), 156.4 (Ar-C), 162.4 (<u>C</u>=O) ppm. Anal. Calcd. for $C_{27}H_{32}N_4O_7S$: C, 58.26; H, 5.79; N, 10.07, Found: C, 58.23; H, 5.77; N, 10.09%.

3.2.4. General procedures for synthesis of substituted-3-(butylamino)-2-phenoxy-5-(5-aryl-1,3,4-oxadiazol-2-yl)-benzenesulfonamide (5_{a-e}):

To a solution of compound **(3)** (10 mmol), phosphorus oxychloride and an equivalent amount of aromatic acid (10 mmol) were added and the mixture was refluxed for 24 hours. Excess phosphorus oxychloride was distilled off under reduced pressure and the residue was quenched in ice. Sodium carbonate was added till neutralization takes place and the separated solid was filtered and crystallized from methylene chloride and petroleum ether.

3.2.4.1. 3-(Butylamino)-2-phenoxy-5-(5-phenyl-1,3,4-oxadiazol-2-yl)-benzenesulfonamide (5_a). (82%), m.p.= 153-155°C; ^{1}HNMR (500 MHz, DMSO-d_6) δ: 0.77 (t, 3H, *J* = 3 Hz, CH_3), 1.07-1.15 (m, 2H, CH_2), 1.31-1.43 (m, 2H, CH_2), 2.49 (s, 2H, $SO_2N\underline{H}_2$), 3.01-3.11 (q, 2H, $C\underline{H}_2$-NH), 4.66 (t, 1H, *J* = 6 Hz NH), 6.80 (d, 2H, *J* = 8 Hz, Ar-H), 6.94 (t, 1H, *J* = 8 Hz, Ar-H), 7.21 (t, 2H, *J* = 8 Hz, Ar-H), 7.27 (d, 2H, *J* = 7 Hz, Ar-H), 7.33 (s, 1H, Ar-H), 7.54 (t, 1H, *J* = 7 Hz, Ar-H), 7.64 (s, 1H, Ar-H), 7.80 (t, 2H, *J* = 7 Hz, Ar-H) ppm. Anal. Calcd. for $C_{24}H_{24}N_4O_4S$: C, 62.06; H, 5.21; N, 12.06, Found: C, 62.20; H, 5.37; N, 12.17%.

3.2.4.2. 3-(Butylamino)-5-[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]-2-phenoxy-benzenesulfonamide (5_b). (82%), m.p.= 244-246°C; ^{1}HNMR (500 MHz, DMSO-d_6) δ: 0.77 (t, 3H, *J* = 3 Hz, CH_3), 1.06-1.11 (m, 2H, CH_2), 1.22-1.28 (m, 2H, CH_2), 2.49 (s, 2H, $SO_2N\underline{H}_2$), 3.06-3.11 (q, 2H, $C\underline{H}_2$-NH), 4.91 (t, 1H, *J* = 6 Hz, NH), 6.82 (d, 2H, *J* = 8 Hz, Ar-H), 7.06 (t, 1H, *J* = 8.5 Hz, Ar-H), 7.14 (d, 2H, *J* = 7.5 Hz, Ar-H), 7.23 (s, 1H, Ar-H), 7.29 (t, 2H, *J* = 8 Hz, Ar-H), 7.59 (s, 1H, Ar-H), 7.83 (d, 2H, *J* = 8 Hz, Ar-H) ppm; ^{13}CNMR (100 MHz, DMSO-d_6) δ: 14.0 (CH_2-CH_2-CH_2-$\underline{C}H_3$), 19.9 (CH_2-CH_2-$\underline{C}H_2$-CH_3), 30.4 (CH_2-$\underline{C}H_2$-CH_2-CH_3), 42.7 ($\underline{C}H_2$-CH_2-CH_2-CH_3), 112.7 (Ar-C), 116.3 (Ar-C), 117.9 (2 Ar-C), 118.5 (Ar-C), 119.5 (Ar-C), 125.9 (2 Ar-C), 129.6 (2 Ar-C), 129.8 (2 Ar-C), 130.7 (Ar-C), 135.1 (Ar-C), 145.3 (Ar-C), 147.2 (Ar-C), 152.1 (Ar-C), 156.1 (Ar-C), 161.5 (C_5-oxadiazole), 161.8 (C_2-oxadiazole) ppm. Anal. Calcd. for $C_{24}H_{23}ClN_4O_4S$: C, 57.77; H, 4.65; N, 11.23, Found: C, 57.80; H, 4.58; N, 11.29%.

3.2.4.3. 3-(Butylamino)-5-[5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl]-2-phenoxy-benzenesulfonamide (5_c). (90%), m.p.= 289-292°C; ^{1}HNMR (500 MHz, DMSO-d_6) δ: 0.77 (t, 3H, *J* = 3.5 Hz, CH_3), 1.00-1.12 (m, 2H, CH_2), 1.22-1.38 (m, 2H, CH_2), 2.49 (s, 2H, $SO_2N\underline{H}_2$), 3.00-3.10 (q, 2H, $C\underline{H}_2$-NH), 5.21 (t, 1H, *J* = 6 Hz, NH), 6.88 (d, 2H, *J* = 8.5 Hz, Ar-H), 7.01 (t, 1H, *J* = 8 Hz, Ar-H), 7.28 (t, 2H, *J* = 7.5 Hz, Ar-H), 7.53 (s, 1H, Ar-H), 7.73 (d, 2H, *J* = 8.5 Hz, Ar-H), 7.80 (s, 1H, Ar-H), 8.16 (d, 2H, *J* = 7 Hz, Ar-H) ppm; ^{13}CNMR (100 MHz, DMSO-d_6) δ: 13.6 (CH_2-CH_2-CH_2-$\underline{C}H_3$), 19.3 (CH_2-CH_2-$\underline{C}H_2$-CH_3), 30.6 (CH_2-$\underline{C}H_2$-CH_2-CH_3), 42.2 ($\underline{C}H_2$-CH_2-CH_2-CH_3), 128.3 (Ar-C), 129.1 (Ar-C), 130.3 (2 Ar-C), 131.8 (Ar-C), 134.7 (Ar-C), 136.4 (Ar-C), 136.7 (2 Ar-C), 137.7 (2 Ar-C), 138.8 (2 Ar-C), 139.6 (Ar-C), 146.4 (Ar-C), 147.6 (Ar-C), 151.9 (Ar-C), 156.3 (Ar-C), 161.9 (C_5-oxadiazole), 162.5 (C_2-oxadiazole) ppm. Anal. Calcd. for $C_{24}H_{23}N_5O_6S$: C, 56.57; H, 4.55; N, 13.74, Found: C, 56.36; H, 4.48; N, 13.54%.

3.2.4.4. 3-(Butylamino)-2-phenoxy-5-[5-(4-phenoxyphenyl)-1,3,4-oxadiazol-2-yl]-benzenesulfonamide (5_d). (91%), m.p.= 326-328°C; ^{1}HNMR (500 MHz, DMSO-d_6) δ: 0.77 (t, 3H, *J* = 3.5 Hz, CH_3), 1.01-1.11 (m, 2H, CH_2), 1.34-1.37 (m, 2H, CH_2), 2.49 (s, 2H, $SO_2N\underline{H}_2$), 3.06-3.08 (q, 2H, $C\underline{H}_2$-NH), 4.92 (t, 1H, *J* = 6 Hz NH), 6.82 (d, 4H, *J* = 8.5 Hz, Ar-H), 6.99 (t, 1H, *J* = 7.5 Hz, Ar-H), 7.09 (t, 1H, *J* = 7.5 Hz, Ar-H), 7.21 (s, 1H, Ar-H), 7.25 (t, 2H, *J* = 7 Hz, Ar-H), 7.33 (t, 2H, *J* = 7.5 Hz, Ar-H), 7.57 (d, 2H, *J* = 8.5 Hz, Ar-H), 7.68 (s, 1H, Ar-H), 8.01(d, 2H, *J* = 8.5 Hz, Ar-H) ppm; ^{13}CNMR (100 MHz, DMSO-d_6) δ: 13.6 (CH_2-CH_2-CH_2-$\underline{C}H_3$), 19.3 (CH_2-CH_2-$\underline{C}H_2$-CH_3), 30.4 (CH_2-$\underline{C}H_2$-CH_2-CH_3), 42.0 ($\underline{C}H_2$-CH_2-CH_2-CH_3), 115.5 (Ar-C), 122.1 (Ar-C), 122.8 (2 Ar-C), 129.1 (2 Ar-C), 129.3 (4 Ar-C), 129.6 (Ar-C), 139.1 (2 Ar-C), 147.1 (Ar-C), 148.3 (4 Ar-C), 156.7 (Ar-C), 157.1 (3 Ar-C), 157.9 (Ar-C), 159.4 (Ar-C), 162.8 (C_5-oxadiazole), 165.1 (C_2-oxadiazole) ppm. Anal. Calcd. for $C_{30}H_{28}N_4O_5S$: C, 64.73; H, 5.07; N, 10.07, Found: C, 64.23; H, 4.77; N, 9.71%.

3.2.4.5. 3-(Butylamino)-2-phenoxy-5-[5-(pyridin-3-yl)-1,3,4-oxadiazol-2-yl]-benzenesulfonamide (5_e). a (89%), m.p.= 263-265°C; ^{1}HNMR (500 MHz, DMSO-d_6) δ: 0.78 (t, 3H, *J* = 3.5 Hz, CH_3), 1.08-1.11 (m, 2H, CH_2), 1.36-1.39 (m, 2H, CH_2), 2.49 (s, 2H, $SO_2N\underline{H}_2$), 3.06-3.11 (q, 2H, $C\underline{H}_2$-NH), 4.67 (t,

1H, *J* = 6 Hz NH), 6.81 (d, 2H, *J* = 8 Hz, Ar-H), 6.94 (t, 1H, *J* = 7.5 Hz, Ar-H), 7.20 (t, 2H, *J* = 7.5 Hz, Ar-H), 7.37 (s, 1H, Ar-H), 7.68 (t, 1H, *J* = 8.5 Hz, pyridine), 7.83 (s, 1H, Ar-H), 8.50 (d, 2H, *J* = 7 Hz, pyridine), 9.32 (s, 1H, pyridine) ppm; ^{13}CNMR (100 MHz, DMSO-d_6) δ: 13.6 (CH_2-CH_2-CH_2-$\underline{C}H_3$), 19.3 (CH_2-CH_2-$\underline{C}H_2$-CH_3), 30.3 (CH_2-$\underline{C}H_2$-CH_2-CH_3), 42.2 ($\underline{C}H_2$-CH_2-CH_2-CH_3), 114.5 (Ar-C), 115.8 (Ar-C), 119.2 (2 Ar-C), 121.4 (Ar-C), 124,4 (Ar-C), 128.9 (C_3, C_5-pyridine), 130.0 (Ar-C), 134.3 (2 Ar-C), 134.4 (C_4-pyridine), 142.6 (Ar-C), 147.4 (Ar-C), 150.2 (C_6-pyridine), 152.3 (C_2-pyridine), 156.9 (C_6-pyridine), 162.6 (C_5-oxadiazole), 167.4 (C_2-oxadiazole) ppm. Anal. Calcd. for $C_{23}H_{23}N_5O_4S$: C, 59.34; H, 4.98; N, 15.04, Found: C, 59.82; H, 5.33; N, 15.43%.

4. Conclusion.

We have synthesized a series of benzenesulfonamides bearing hydrazones and benzenesulfonamides bearing oxadiazoles. The investigation of antibacterial screening data reveals that the synthesized compounds showed promising antibacterial activity to both Gram-positive and Gram-negative species. Compound **(4_i)**exerts higher antibacterial activity than sulfamethoxazole against *Escherichia coli*. Many compounds showed equivalent antibacterial activity to Sulfamethoxazole either against *Escherichia coli* as compounds **(4_a, 4_b, 4_c, 4_f, 4_g, 4_h)** or against *Pseudomonas aeruginosa* like compounds **(4_g, 5_d)**. Moreover, there was no any antifungal activity for all tested samples. Hence, the newly synthesized compounds could be considered for further improvement as lead compounds in the future to develop more potent antibacterial agents.

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6. Conflict of interest.

All authors of this manuscript state that there is no any potential conflict of interest.

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