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SULFONAMIDES OF 2-[(2,6-DICHLOROPHENYL)AMINO]PHENYL ACETOXYACETIC ACID AND THEIR ANTIBACTERIAL STUDIES

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Abstract: Reaction of 2-[(2,6–dichlorophenyl)amino]phenylacetoxyacetyl chloride **2** with various N^1-(substituted aryl)-p-aminobenzenesulfonamide derivatives afforded title compounds. All the final compounds were characterized by the IR spectral data and elemental analysis and screened for antibacterial activity against Gram positive and Gram negative bacterial strains.

Keywords: phenylacetoxyacetic acid, sulfonamide, antibacterial

The number of life-threatening infectious diseases caused by multidrug-resistant bacteria has reached an alarming level in many countries around the world. The advent of sulfa drugs and the later discovery of mesoionic compounds in fact accelerated the rate of progress in the field of sulfur containing heterocycles. Sulfa drugs are a group of compounds used for eliminating a wide range of infections in human and other animal systems. Many chemotherapeutically important sulfa drugs like sulfadiazine, sulfathiazole and other sulfonamides possess SO_2NH moiety.

The aforementioned facts are a cause of great concern and create a pressing need for new antibacterial agents. Heterocycles being sulfonamide derivatives have been reported to show broad spectrum of pharmacological properties, such as antitumor (1, 2), anti-HIV (3), antitubercular (4), antimicrobial (5–7), antileukemic (8), carbonic anhydrase inhibitory (9, 10), anti-inflammatory (11), anticonvulsant and analgesic (12) and COX-2 inhibitor (13).

The compound, 2-[(2,6-dichlorophenyl)amino] phenylacetoxyacetic acid (14), is an ester derivative of potent non-steroidal anti-inflammatory analgesic compound of 2-[(2,6-dichlorophenyl)amino]phenylacetic acid; both inhibit the prostaglandin synthesis by decreasing the activity of the enzyme cyclooxygenase, which results in decreased formation of prostaglandin precursors. These compounds are widely used in the long-term treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondilities (15).

In view of these findings, we have seen that the few workers have studied antimicrobial activities of the parent compound. This observation leads us to synthesize new amides of 2-[(2,6-dichlorophenyl) amino]phenylacetoxyacetic acid with sulfonamides to study their activity against different bacterial strains.

EXPERIMENTAL

All melting points were determined in open capillaries and are uncorrected. IR absorption spectra were recorded on Perkin Elmer-838 FT IR spectrometer using KBr pellets and PMR spectra were recorded in DMSO-d_6 on Bruker DRX-300 (300 MHz FT NMR) instrument (chemical shifts in δ ppm). The purity of the compounds was routinely checked by TLC using silica gel and benzene: ethyl acetate (1:1, v/v) as the mobile phase.

The compound, 2-[(2,6-dichlorophenyl)amino] phenylacetoxyacetyl chloride **2**, was prepared from 2-[(2,6-dichlorophenyl)amino]phenylacetoxyacetic acid by reported method (16) and the intermediate N^1-(substituted aryl)-*p*-aminobenzenesulfonamide was also prepared by reported method (17, 18). The synthetic route of the final compounds has been shown in Scheme 1.

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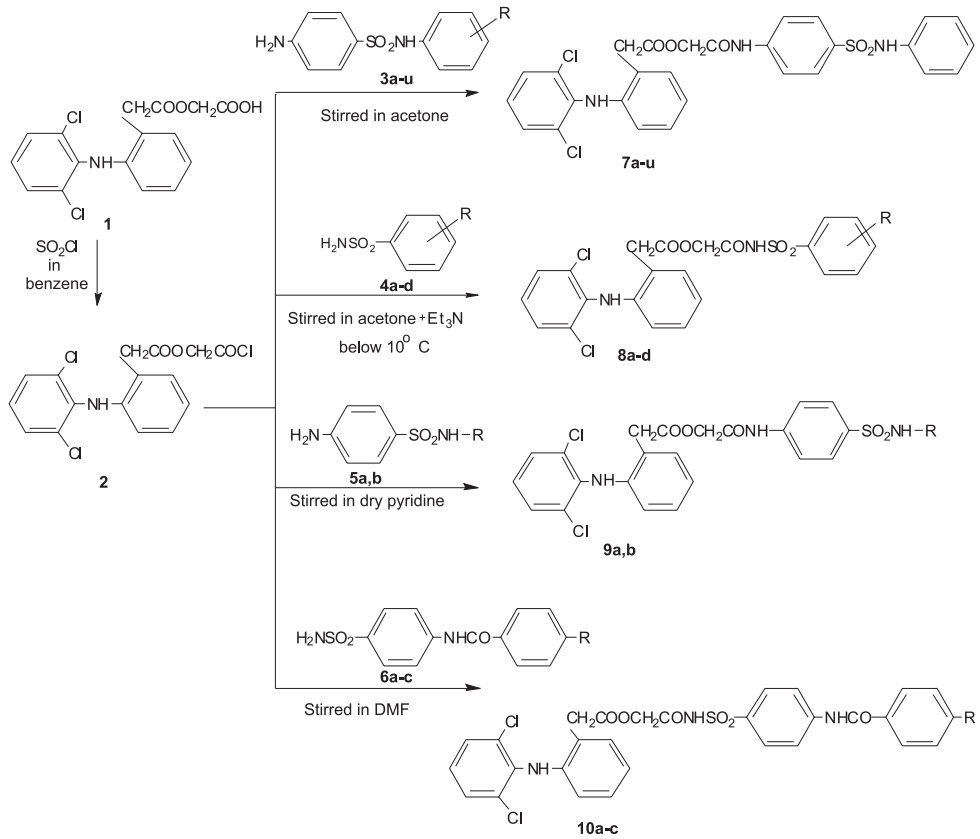

Scheme 1.

General method for the synthesis of 2-[(2,6-dichlorophenyl)amino]-*N*^{1}-(substituted aryl) -*N*^{4}-phenylacetoxyacetamidobenzenesulfonamides 7a-u

The ice cold mixture of *N*^{1}-(substituted aryl) *p*-aminobenzenesulfonamides **3a-u** (0.05 mol) dissolved in DMF (20 mL) was added dropwise into a stirred solution of 2-[(2,6-dichlorophenyl)amino] phenylacetoxyacetyl chloride **2** (0.05 mole) in DMF (20 mL) with occasional stirring. During the addition, the temperature of the reaction mixture was maintained at 10^{o}C and stirring was continued for 6 h and then for 2 h at room temperature. Then, the reaction mixture was heated on oil bath for 16 h at 120–130^{o}C in order to complete the reaction. The mixture was kept overnight at room temperature and on the next day the whole content was poured into the excess of ice cold water with vigorous shaking. The product obtained was filtered and washed successively with cold water followed by 10% aqueous $NaHCO_3$ solution. The crude product was dried and recrystallized from ethanol : chloroform (1:2, v/v).

2-[(2,6-Dichlorophenyl)amino]-*N*^{1}-(phenyl)-*N*^{4}-phenylacetoxyacetamidobenzenesulfonamide **7a**

IR (KBr, cm^{-1}): 785 (C-Cl), 3450 (-NH), 2925, 2845 (-CH_2 sym, asym), 1745 (ester C=O); 1680 (C=O), 1360, 1180 (S=O sym, asym). ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.20 (s, 2H, –CH_2-COO-), 2.51 (s, 2H, -CH_2-CO-), 8.31 (s, 1H, -CONH-), 6.5–7.8 (m, Ar-H), 9.81 (s, 1H, -NH-), 10.51 (s, 1H, -SO_2NH-).

2-[(2,6-Dichlorophenyl)amino]-*N*^{1}-(2-nitrophenyl)-*N*^{4}-phenylacetoxyacetamidobenzenesulfonamide **7b**

IR (KBr, cm^{-1}): 3446 (-NH), 2923, 2841 (-CH_2 sym, asym), 1748 (ester C=O), 1676 (C=O), 1322, 1551 (-NO_2 sym, asym), 1357, 1174 (S=O sym, asym), 780 (C-Cl). ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.21 (s, 2H, –CH_2-COO-), 2.54 (s, 2H, -CH_2-CO-), 8.33 (s, 1H, -CONH-), 6.3–7.9 (m, Ar-H), 9.83 (s, 1H, -NH-), 10.54 (s, 1H, -SO_2NH-).

2-[(2,6-Dichlorophenyl)amino]-N^1-(3-nitrophenyl)-N^4-phenylacetoxyacetamidobenzenesulfonamide **7c**

IR (KBr, cm^{-1}): 3447 (-NH), 2929, 2842 (-CH_2 sym, asym), 1738 (ester C=O), 1672 (C=O), 1326, 1550 (-NO_2 sym, asym), 1352, 1174 (S=O sym, asym), 778 (C-Cl). ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.18 (s, 2H, -CH_2-COO-), 2.47 (s, 2H, -CH_2-CO-), 6.4–7.9 (m, Ar-H), 8.28 (s, 1H, -CONH-), 9.74 (s, 1H, -NH-), 10.47 (s, 1H, -SO_2NH-).

2-[(2,6-Dichlorophenyl)amino]-N^1-(4-nitrophenyl)-N^4-phenylacetoxyacetamidobenzenesulfonamide **7d**

IR (KBr, cm^{-1}): 3445 (-NH), 2921, 2842 (-CH_2 sym, asym), 1741 (ester C=O), 1674 (C=O), 1323, 1551 (-NO_2 sym, asym), 1355, 1178 (S=O sym, asym), 776 (C-Cl). ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.17(s, 2H, -CH_2-COO-), 2.45 (s, 2H, -CH_2-CO-), 6.2–7.7 (m, Ar-H), 8.30 (s, 1H, -CONH-), 9.71 (s, 1H, -NH-), 10.44 (s, 1H, -SO_2NH-).

2-[(2,6-Dichlorophenyl)amino]-N^1-(2-methylphenyl)-N^4-phenylacetoxyacetamidobenzenesulfonamide **7e**

IR (KBr, cm^{-1}): 3446 (-NH.), 2921, 2840 (-CH_2 sym, asym), 1741 (ester C=O), 1672 (C=O), 1358, 1177 (S=O sym, asym), 780 (C-Cl.). ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.18 (s, 2H, -CH_2-COO-), 2.35 (s, 3H, -CH_3), 2.47 (s, 2H, -CH_2-CO-), 6.0–7.6 (m, Ar-H), 8.28 (s, 1H, -CONH-), 9.74 (s, 1H, -NH-), 10.42 (s, 1H, -SO_2NH-).

2-[(2,6-Dichlorophenyl)amino]-N^1-(3-methylphenyl)-N^4-phenylacetoxyacetamidobenzenesulfonamide **7f**

IR (KBr, cm^{-1}): 3443 (-NH.), 2919, 2843 (-CH_2 sym, asym), 1744 (ester C=O); 1677 (C=O), 1351, 1177 (S=O sym, asym), 771 (C-Cl). ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.23 (s, 2H, -CH_2-COO-), 2.32 (s, 3H, -CH_3), 2.54 (s, 2H, -CH_2-CO-), 6.6–7.6 (m, Ar-H), 8.26 (s, 1H, -CONH-), 9.78 (s, 1H, -NH-), 10.48 (s, 1H, -SO_2NH-).

2-[(2,6-Dichlorophenyl)amino]-N^1-(4-methylphenyl)-N^4-phenylacetoxyacetamidobenzenesulfonamide **7g**

IR (KBr, cm^{-1}): 3447 (-NH), 2921, 2847 (-CH_2 sym, asym), 1749 (ester C=O) 1675 (C=O), 1357, 1170 (S=O sym, asym), 774 (C-Cl). ^{1}H-NMR (DMSO-d_6, δ ppm): 1.25 (s, 2H, -CH_2-COO-), 2.30 (s, 3H, -CH_3), 2.54 (s, 2H, -CH_2-CO-), 6.2–7.9 (m, Ar-H), 8.22 (s, 1H, -CONH-), 9.77 (s, 1H, -NH-), 10.54 (s, 1H, -SO_2NH-).

2-[(2,6-Dichlorophenyl)amino]-N^1-(2-methoxyphenyl)-N^4-phenylacetoxyacetamidobenzenesulfonamide **7h**

IR (KBr, cm^{-1}): 3440 (-NH), 2921, 2840 (-CH_2 sym, asym), 1742 (ester C=O) 1672 (C=O), 1352, 1177 (S=O sym, asym), 781 (C-Cl). ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.22 (s, 2H, -CH_2-COO-), 2.53 (s, 2H, -CH_2-CO-), 3.42 (s, 3H, -OCH_3), 6.3–7.1 (m, Ar-H), 8.27 (s, 1H, -CONH-), 9.80 (s, 1H, -NH-), 10.50 (s, 1H, -SO_2NH-).

2-[(2,6-Dichlorophenyl)amino]-N^1-(4-methoxyphenyl)-N^4-phenyl acetoxyacetamidobenzenesulfonamide **7i**

IR (KBr, cm^{-1}): 3441 (-NH), 2920, 2843 (-CH_2 sym, asym), 1740 (ester C=O) 1674 (C=O), 1355, 1175 (S=O sym, asym), 778 (C-Cl). ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.17 (s, 2H, –CH_2-COO-), 2.47 (s, 2H, -CH_2-CO-), 3.45 (s, 3H, -OCH_3), 6.2–7.7 (m, Ar-H), 8.24 (s, 1H, -CONH-), 9.80 (s, 1H, -NH-), 10.45 (s, 1H, -SO_2NH-).

2-[(2,6-Dichlorophenyl)amino]-N^1-(2-chlorophenyl)-N^4-phenylacetoxyacetamidobenzenesulfonamide **7j**

IR (KBr, cm^{-1}): 3446 (-NH), 2917, 2840 (-CH_2 sym, asym), 1736 (ester C=O), 1671 (C=O), 1348, 1168 (S=O sym, asym), 776 (C-Cl). ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.12 (s, 2H, -CH_2-COO-), 2.42 (s, 2H, -CH_2-CO-), 6.1-7.9 (m, Ar-H), 8.20 (s, 1H, -CONH-), 9.82 (s, 1H, -NH-), 10.47 (s, 1H, -SO_2NH-).

2-[(2,6-Dichlorophenyl)amino]-N^1-(3-chlorophenyl)-N^4-phenylacetoxyacetamidobenzenesulfonamide **7k**

IR (KBr, cm^{-1}): 3448 (-NH), 2921, 2842 (-CH_2), 1741 (ester C=O), 1678 (C=O), 1355, 1173 (S=O sym, asym), 781 (C-Cl). ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.18 (s, 2H, -CH_2-COO-), 2.50 (s, 2H, -CH_2-CO-), 6.0–7.3 (m, Ar-H), 8.27 (s, 1H, -CONH-), 9.80 (s, 1H, -NH-), 10.50 (s, 1H, -SO_2NH-).

2-[(2,6-Dichlorophenyl)amino]-N^1-(4-chlorophenyl)-N^4-phenylacetoxyacetamidobenzenesulfonamide **7l**

IR (KBr, cm^{-1}): 3447 (-NH), 2920, 2842 (-CH_2 sym, asym), 1742 (ester C=O), 1676 (C=O), 1357, 1178 (S=O sym, asym), 779 (C-Cl). ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.16 (s, 2H, -CH_2-COO-), 2.47 (s, 2H, -CH_2-CO-), 6.2–7.7 (m, Ar-H), 8.27 (s, 1H, -CONH-), 9.80 (s, 1H, -NH-), 10.46 (s, 1H, -SO_2NH-).

Table 1. Physical and analytical data of synthesized compounds **7a-u**, **8a-d**, **9a**,**b and 10a-c**.

Compd.	R	Molecular formula	M. p. (± 3°C)	Yield %	C H N Analysis Calculated (found)		
					%C	%H	%N
7a	H	$C_{28}H_{23}N_3O_5SCl_2$	195	71	57.54 (57.47)	3.94 (3.89)	7.19 (7.10)
7b	2-NO_2	$C_{28}H_{22}N_4O_7SCl_2$	115	65	53.43 (53.41)	3.49 (3.40)	8.90 (8.81)
7c	3-NO_2	$C_{28}H_{22}N_4O_7SCl_2$	280	60	53.43 (53.38)	3.49 (3.42)	8.90 (8.83)
7d	4-NO_2	$C_{28}H_{22}N_4O_7SCl_2$	195	62	53.43 (53.35)	3.49 (3.41)	8.90 (8.80)
7e	2-CH_3	$C_{29}H_{25}N_3O_5SCl_2$	170	58	58.21 (58.15)	4.18 (4.10)	7.02 (6.93)
7f	3-CH_3	$C_{29}H_{25}N_3O_5SCl_2$	195	59	58.21 (58.19)	4.18 (4.06)	7.02 (7.00)
7g	4-CH_3	$C_{29}H_{25}N_3O_5SCl_2$	252	62	58.21 (58.16)	4.18 (4.06)	7.02 (6.94)
7h	2-OCH_3	$C_{29}H_{23}N_3O_6SCl_2$	210	65	56.68 (56.61)	4.06 (3.98)	6.84 (6.77)
7i	4-OCH_3	$C_{29}H_{23}N_3O_6SCl_2$	141	70	56.68 (56.63)	4.06 (4.00)	6.84 (6.80)
7j	2-Cl	$C_{28}H_{22}N_3O_5SCl_3$	156	61	54.33 (54.27)	3.55 (3.47)	6.79 (6.71)
7k	3-Cl	$C_{28}H_{22}N_3O_5SCl_3$	212	59	54.33 (54.30)	3.55 (3.50)	6.79 (6.69)
7l	4-Cl	$C_{28}H_{22}N_3O_5SCl_3$	175	62	54.33 (54.25)	3.55 (3.49)	6.79 (6.75)
7m	2,6-$(Cl)_2$, 4-NO_2	$C_{28}H_{20}N_4O_7SCl_4$	190	60	48.15 (48.10)	2.86 (2.81)	8.02 (7.97)
7n	6-Cl,2,4-$(NO_2)_2$	$C_{28}H_{20}N_5O_9SCl_3$	>300	56	47.94 (47.89)	2.99 (2.91)	5.99 (5.90)
7o	2-Cl, 4-NO_2	$C_{26}H_{19}N_4O_5SCl_3$	115	68	50.65 (50.59)	3.16 (3.10)	8.44 (8.38)
7p	2,6-$(Br)_2$, 4-CH_3	$C_{29}H_{23}N_3O_5SCl_2Br_2$	160	61	46.06 (46.00)	3.04 (2.98)	5.56 (5.50)
7q	2,6-$(Br)_2$, 4-NO_2	$C_{28}H_{20}N_4O_7SCl_2Br_2$	175	65	42.71 (42.67)	2.54 (2.49)	7.12 (7.01)
7r	2,6-$(NO_2)_2$-	$C_{28}H_{21}N_5O_9SCl_2$	165	62	49.86 (49.80)	3.11 (3.07)	10.38 (10.29)
7s	2-CN, 4-NO_2-	$C_{29}H_{21}N_5O_7SCl_2$	168	59	53.22 (53.17)	3.21 (3.17)	10.70 (10.61)
7t	2-SO_3H, 4-NO_2	$C_{28}H_{22}N_3O_8SCl_2$	240	54	50.68 (50.60)	3.32 (3.26)	6.34 (6.27)
7u	2-SO_3K, 4-NO_2	$C_{26}H_{21}N_3O_8SCl_2K$	>300	51	47.94 (47.88)	2.99 (2.91)	5.99 (5.89)

Table 1. Continued

Compd.	R	Molecular formula	M. p. (± 3°C)	Yield %	C H N Analysis Calculated (found)		
					%C	%H	%N
8a	4-CH_3	$C_{23}H_{20}N_2O_5SCl_2$	195	66	54.44 (54.38)	3.94 (3.89)	5.52 (5.46)
8b	4-OCH_3	$C_{23}H_{20}N_2O_6SCl_2$	160	60	52.78 (52.71)	3.82 (3.79)	5.35 (5.30)
8c	4-OCH_3, 3-Cl	$C_{23}H_{19}N_2O_6SCl_3$	125	56	49.52 (49.48)	3.41 (3.39)	5.02 (5.00)
8d	4-$NHCOCH_3$	$C_{24}H_{21}N_3O_6SCl_2$	110	59	52.37 (52.31)	3.82 (3.77)	7.64 (7.59)
9a	H	$C_{22}H_{19}N_3O_5SCl_2$	>300	70	51.98 (51.90)	3.74 (3.66)	8.26 (8.19)
9b	4,6-$(CH_3)_2$-pyrimidine	$C_{28}H_{25}N_5O_5SCl_2$	290	67	54.73 (54.69)	4.06 (4.00)	11.40 (11.31)
10a	4-Cl	$C_{29}H_{22}N_3O_6SCl_3$	230	56	53.84 (53.79)	3.40 (3.37)	6.49 (6.42)
10b	4-NO_2	$C_{29}H_{22}N_4O_8SCl_2$	156	60	52.98 (52.91)	3.34 (3.30)	8.52 (8.47)
10c	4-$NHCOCH_3$	$C_{31}H_{26}N_4O_7SCl_2$	190	58	55.62 (55.56)	3.88 (3.82)	8.37 (8.29)

2-[(2,6-Dichlorophenyl)amino]-N^1-(2,6-dichloro-4-nitrophenyl)-N^4-phenylacetoxyacetamidobenzenesulfonamide **7m**

IR (KBr, cm^{-1}): 3442 (-NH), 2923, 2845 (-CH_2 sym, asym), 1740 (ester C=O), 1679 (C=O), 1320, 1550 (-NO_2 sym, asym), 1354, 1173 (S=O sym, asym), 778 (C-Cl). ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.18 (s, 2H, -CH_2-COO-), 2.45 (s, 2H, -CH_2-CO-), 6.4–7.3 (m, Ar-H), 8.25 (s, 1H, -CONH-), 9.82 (s, 1H, -NH-), 10.43 (s, 1H, -SO_2NH-).

2-[(2,6-Dichlorophenyl)amino]-N^1-(6-chloro-2,4-dinitrophenyl)-N^4-phenylacetoxyacetamidobenzenesulfonamide **7n**

IR (KBr, cm^{-1}): 3445 (-NH), 2921, 2840 (-CH_2 sym, asym), 1740 (ester C=O), 1672 (C=O), 1325, 1553 (-NO_2 sym, asym), 1355, 1176 (S=O sym, asym), 773 (C-Cl). ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.17 (s, 2H, -CH_2-COO-), 2.42 (s, 2H, -CH_2-CO-), 6.2–7.9 (m, Ar-H), 8.25 (s, 1H, -CONH-), 9.78 (s, 1H, -NH-), 10.43 (s, 1H, -SO_2NH-).

2-[(2,6-Dichlorophenyl)amino]-N^1-(2-chloro-4-nitrophenyl)-N^4-phenylacetoxyacetamidobenzenesulfonamide **7o**

IR (KBr, cm^{-1}): 3444 (-NH), 2925, 2847 (-CH_2 sym, asym), 1743 (ester C=O), 1676 (C=O), 1328, 1555 (-NO_2 sym, asym), 1352, 1171 (S=O sym, asym), 775 (C-Cl). ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.15 (s, 2H, -CH_2-COO-), 2.41 (s, 2H, -CH_2-CO-), 6.4–7.7 (m, Ar-H), 8.27 (s, 1H, -CONH-), 9.80 (s, 1H, -NH-), 10.41 (s, 1H, -SO_2NH-).

2-[(2,6-Dichlorophenyl)amino]-N^1-(2,6-dibromo-4-methylphenyl)-N^4-phenylacetoxyacetamidobenzenesulfonamide **7p**

IR (KBr, cm^{-1}): 3437 (-NH), 2921, 2842 (-CH_2 sym, asym), 1736 (ester C=O), 1677 (C=O), 1352, 1171 (S=O sym, asym), 773 (C-Cl), 639 (C-Br). ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.16 (s, 2H, -CH_2-COO-), 2.40 (s, 2H, -CH_2-CO-), 2.35 (s, 3H, -CH_3), 6.2–7.4 (m, Ar-H), 8.27 (s, 1H, -CONH-), 9.80 (s, 1H, -NH-), 10.45 (s, 1H, -SO_2NH-).

2-[(2,6-Dichlorophenyl)amino]-N^1-(2,6-dibromo-4-nitrophenyl)-N^4-phenylacetoxyacetamidobenzenesulfonamide **7q**

IR (KBr, cm^{-1}): 3433 (-NH), 2923, 2845 (-CH_2 sym, asym), 1737 (ester C=O), 1672 (C=O), 1320, 1554 (-NO_2 sym, asym), 1350, 1174 (S=O sym, asym), 771 (C-Cl), 643 (C-Br). ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.18 (s, 2H, -CH_2-COO-), 2.42 (s, 2H, -CH_2-CO-), 6.1–7.5 (m, Ar-H), 8.26 (s, 1H, -CONH-), 9.78 (s, 1H, -NH-), 10.41 (s, 1H, -SO_2NH-).

2-[(2,6-Dichlorophenyl)amino]-N^1-(2,6-dinitrophenyl)-N^4-phenylacetoxyacetamidobenzenesulfonamide **7r**

IR (KBr, cm^{-1}): 3435 (-NH), 2920, 2840 (-CH_2 sym, asym), 1738 (ester C=O), 1672 (C=O), 1324, 1553 (-NO_2 sym, asym), 1354, 1170 (S=O sym, asym), 770 (C-Cl). ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.15 (s, 2H, -CH_2-COO-), 2.43 (s, 2H, -CH_2-CO-), 6.1–7.5 (m, Ar-H), 8.25 (s, 1H, -CONH-), 9.83 (s, 1H, -NH-), 10.41 (s, 1H, -SO_2NH-).

2-[(2,6-Dichlorophenyl)amino]-N^1-(2-cyano-4-nitrophenyl)-N^4-phenylacetoxyacetamidobenzenesulfonamide **7s**

IR (KBr, cm^{-1}): 3438 (-NH), 2922, 2844 (-CH_2 sym, asym), 1735 (ester C=O), 1675 (C=O), 1322, 1556 (-NO_2 sym, asym), 1350, 1167 (S=O sym, asym), 777 (C-Cl). ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.18 (s, 2H, -CH_2-COO-), 2.38 (s, 2H, -CH_2-CO-), 6.2–7.6 (m, Ar-H), 8.25 (s, 1H, -CONH-), 9.83 (s, 1H, -NH-), 10.42 (s, 1H, -SO_2NH-).

2-[(2,6-Dichlorophenyl)amino]-N^1-(2-sulfo-4-nitrophenyl)-N^4-phenylacetoxyacetamidobenzenesulfonamide **7t**

IR (KBr, cm^{-1}): 3435 (-NH), 2923, 2846 (-CH_2 sym, asym), 1738 (ester C=O), 1673 (C=O), 1320, 1551 (-NO_2 sym, asym), 1354, 1173 (S=O sym, asym), 775 (C-Cl). ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.19 (s, 2H, -CH_2-COO-), 2.43 (s, 2H, -CH_2-CO-), 6.3–7.5 (m, Ar-H), 8.29 (s, 1H, -CONH-), 9.83 (s, 1H, -NH-), 10.47 (s, 1H, -SO_2NH-).

2-[(2,6-Dichlorophenyl)amino]-N^1-(2-potassium sulfonate-4-nitrophenyl)-N^4-phenylacetoxyacetamidobenzenesulfonamide **7u**

IR (KBr, cm^{-1}): 3435 (-NH), 2922, 2842 (-CH_2 sym, asym), 1734 (ester C=O), 1678 (C=O), 1321, 1554 (-NO_2 sym, asym), 1355, 1170 (S=O sym, asym), 770 (C-Cl). ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.17 (s, 2H, -CH_2-COO-), 2.41 (s, 2H, -CH_2-CO-), 6.4–7.4 (m, Ar-H), 8.27 (s, 1H, -CONH-), 9.81 (s, 1H, -NH-), 10.44 (s, 1H, -SO_2NH-).

General method for the synthesis of 2-[(2,6-dichlorophenyl)amino]-*N*-phenylacetoxyacetyl (substituted)benzenesulfonamides 8a-d

A suspension of finely powdered dry substituted benzenesulfonamide **4a-d** in anhydrous 1,4-dioxane (25 mL) was added to ice-cold solution of 2-[(2,6-dichlorophenyl)amino]phenylacetoxyacetyl chloride **2** (0.05 mol) in dry 1,4-dioxane (20 mL) dropwise with constant stirring. The mixture was stirred for 8–9 h at 0–10°C; meanwhile triethylamine (0.055 mol) was added in portions. The reaction mixture was removed from ice-bath and stirred further for 6–8 h at room temperature. The content was refluxed in water bath for 10–12 h, and then the mixture was allowed to stand overnight at room temperature. Triethylamine hydrochloride was removed by filtration and the filtrate was concentrated on a rotary evaporator. The resulting residue was stirred with water and then allowed to stand overnight; the product was washed thoroughly with water and 10% aqueous $NaHCO_3$ solution. The crude product was dried and purified by crystallization from ethanol.

2-[(2,6-Dichlorophenyl)amino]-*N*-phenylacetoxyacetyl-(4-methyl)benzenesulfonamide **8a**

IR (KBr, cm^{-1}): 3447 (-NH), 2920, 2842 (-CH_2 sym, asym), 1742 (ester C=O), 1673 (C=O), 1357, 1174 (S=O sym, asym), 780 (C-Cl). ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.17 (s, 2H, -CH_2-COO-), 2.31 (s, 3H, -CH_3), 2.50 (s, 2H, -CH_2-CO-), 6.4–7.8 (m, Ar-H), 8.28 (s, 1H, -CONH-), 9.77 (s, 1H, -NH-), 10.47 (s, 1H, -SO_2NH-).

2-[(2,6-Dichlorophenyl)amino]-*N*-phenylacetoxyacetyl-(4-methoxy)benzenesulfonamide **8b**

IR (KBr, cm^{-1}): 3445 (-NH), 2921, 2840 (-CH_2 sym, asym), 1742 (ester C=O), 1678 (C=O), 1355, 1174 (S=O sym, asym), 782 (C-Cl). ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.16 (s, 2H, -CH_2-COO-), 2.43 (s, 2H, -CH_2-CO-), 6.2–7.4 (m, Ar-H), 8.27 (s, 1H, -CONH-), 9.80 (s, 1H, -NH-), 10.44 (s, 1H, -SO_2NH-).

2-[(2,6-Dichlorophenyl)amino]-*N*-phenylacetoxyacetyl-(3-chloro-4-methoxy)benzenesulfonamide **8c**

IR (KBr, cm^{-1}): 3448 (-NH), 2920, 2838 (-CH_2 sym, asym), 1744 (ester C=O), 1675 (C=O), 1357, 1172 (S=O sym, asym), 779 (C-Cl). ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.18 (s, 2H, -CH_2-COO-), 3.40 (s, 3H, -OCH_3), 2.47 (s, 2H, -CH_2-CO-), 6.4–7.2 (m, Ar-H), 8.30 (s, 1H, -CONH-), 9.76 (s, 1H, -NH-), 10.48 (s, 1H, -SO_2NH-).

2-[(2,6-Dichlorophenyl)amino]-*N*-phenylacetoxyacetyl-(4-acetamide)benzenesulfonamide **8d**

IR (KBr, cm^{-1}): 3445 (-NH), 2920, 2843 (-CH_2 sym, asym), 1742 (ester C=O), 1677 (C=O), 1355, 1174 (S=O sym, asym), 782 (C-Cl). ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.21 (s, 2H, -CH_2-COO-), 2.52 (s, 2H, -CH_2-CO-), 6.5–7.9 (m, Ar-H), 8.28 (s, 1H, -CONH-), 9.80 (s, 1H, -NH-), 10.53 (s, 1H, -SO_2NH-).

General method for the synthesis of 2-[(2,6-dichlorophenyl)amino](substituted)-N^4-phenylacetoxyacetamidobenzenesulfonamides 9a,b

p-Aminobenzenesulfonamide **5a** (0,005 mol, 0.86 g) was dissolved in anhydrous pyridine (25 mL) and the mixture was immersed in salted ice-bath. A mixture of 2-[(2,6-dichlorophenyl)amino]-phenylacetoxyacetyl chloride **2** (0.05 mol) dissolved in dry pyridine was gradually added with constant stirring at below 10°C for 6 h, and stirred further for 4 h at room temperature. Then the content was refluxed for 6–8 h in an oil bath. After completion of the reaction, the solvent was removed by distillation. The obtained solid mass was transferred into ice cold water containing little amount of HCl. The product was filtered with suction and washed successively with water followed by aqueous $NaHCO_3$ (10%) solution. Finally, the product was dried and recrystallized from ethanol. Similarly **9b** was prepared by the same method.

2-[(2,6-Dichlorophenyl)amino](substituted)-N^4-phenylacetoxyacetamidobenzenesulfonamide **9a**

IR (KBr, cm^{-1}): 3442 (-NH), 2922, 2838 (-CH_2 sym, asym), 1740 (ester C=O), 1676 (C=O), 1359, 1172 (S=O sym, asym), 774 (C-Cl). ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.20 (s, 2H, -CH_2-COO-), 2.48 (s, 2H, -CH_2-CO-), 6.2–7.7 (m, Ar-H), 8.22 (s, 1H, -CONH-), 9.82 (s, 1H, -NH-), 10.47 (s, 1H, -SO_2NH-).

2-[(2,6-Dichlorophenyl)amino]-N^1-(4,6-dimethyl-2-pyrimidinyl)-N^4-phenylacetoxyacetamidobenzenesulfonamide **9b**

IR (KBr, cm^{-1}): 3448 (-NH), 2920, 2842 (-CH_2 sym, asym), 1743 (ester C=O), 1678 (C=O), 1357, 1177 (S=O sym, asym), 780 (C-Cl). ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.22 (s, 2H, -CH_2-COO-), 2.24 (s, 6H, -CH_3,)2.50 (s, 2H, -CH_2-CO-), 6.1–7.9 (m, Ar-H), 8.26 (s, 1H, -CONH-), 9.80 (s, 1H, -NH-), 10.46 (s, 1H, -SO_2NH-).

General method for the synthesis of 2-[(2,6-dichlorophenyl)amino]-N^1-phenylacetoxyacetyl N^2-(*p*-substituted benzoylamino)benzenesulfonamides 10a-c

The compound, N^4-(*p*-substitutedbenzoylamino)benzenesulfonamide, **6a-c** (0.05 mol) was dissolved in anhydrous DMF (25 mL) and the reaction mixture was immersed in salted ice-bath and maintained at the temperature between 0–10°C. Into it, ice cold mixture of 2-[(2,6-dichlorophenyl)-amino]phenylacetoxyacetyl chloride **2** (0.05 mol) in dry DMF was added dropwise with constant stirring. The content was stirred at this temperature for 8–9 h; then the reaction mixture was heated to 120–130°C for 14–16 h in order to complete the reaction. The mixture was kept at room temperature overnight and, on the next day, it was poured on the excess of crushed ice with vigorous shaking. The solid product was filtered and washed successively with cold water followed by 5% $NaHCO_3$ solution. Finally, the product was dried well and recrystallized from the mixture of ethanol and chloroform (1 : 1, v/v).

2-[(2,6-Dichlorophenyl)amino]-N^1-phenylacetoxyacetyl-N^2-(4-chlorobenzoylamino)benzenesulfonamide **10a**

IR (KBr, cm^{-1}): 3448 (-NH), 2922, 2842 (-CH_2 sym, asym), 1741 (ester C=O), 1676 (C=O), 1357, 1178 (S=O sym, asym), 778 (C-Cl). ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.22 (s, 2H, -CH_2-COO-), 2.48 (s, 2H, -CH_2-CO-), 6.3–7.7 (m, Ar-H), 8.30 (s, 1H, -CONH-), 9.80 (s, 1H, -NH-), 10.45 (s, 1H, -SO_2NH-).

2-[(2,6-Dichlorophenyl)amino]-N^1-phenylacetoxyacetyl-N^2-(4-nitrobenzoylamino)benzenesulfonamide **10b**

IR (KBr, cm^{-1}): 3447 (-NH), 2923, 2840 (-CH_2 sym, asym), 1741 (ester C=O), 1675 (C=O), 1357, 1176 (S=O sym, asym), 775 (C-Cl). ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.17 (s, 2H, -CH_2-COO-), 2.47 (s, 2H, -CH_2-CO-), 6.2–7.7 (m, Ar-H), 8.28 (s, 1H, -CONH-), 9.78 (s, 1H, -NH-), 10.43 (s, 1H, -SO_2NH-).

2-[(2,6-Dichlorophenyl)amino]-N^1-phenylacetoxyacetyl-N^2-(4-acetamidebenzoylamino)benzenesulfonamide **10c**

IR (KBr, cm^{-1}): 3453 (-NH), 2925, 2841 (-CH_2 sym, asym), 1740 (ester C=O), 1676 (C=O), 1353, 1178 (S=O sym, asym), 779 (C-Cl). ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.19 (s, 2H, -CH_2-COO-), 2.49 (s, 2H, -CH_2-CO-), 6.4–7.8 (m, Ar-H), 8.26 (s, 1H, -CONH-), 9.76 (s, 1H, -NH-), 10.45 (s, 1H, -SO_2NH-).

Antibacterial activity

All the synthesized compounds were screened for their antibacterial properties against *S. aureus*, *B. subtilis* (Gram positive) and *E. coli*, *P. vulgaris* (Gram negative) strains. The results were compared with the standard drugs penicillin, chloramphenicol, and ampicillin tested under similar conditions. The antibacterial testing was carried out by cup-plate method using DMF solution of compounds at 100

mg/mL concentration. The zones of the inhibition of the test compounds are presented in Table 2.

Amides of 4-amino-N-substituted phenylbenzenesulfonamide **7f**, **7m**, **7n**, **7p**, and **7r** (R = 3-CH_3, 2,6-$(Cl)_2$,4-NO_2, 6-Cl,2,4-$(NO_2)_2$, 2,6-$(Br)_2$,4-CH_3, 2,6-$(NO_2)_2$, respectively) demonstrated good activity. Activity was not improved on mono substitution with electron withdrawing and donating group with exception of -CH_3 at C-3 atom, whereas introduction of halo group with electron withdrawing and donating group and disubstitution with electron withdrawing group demonstrated good activity against *S.*

Table 2. Antimicrobial activity of synthesized compounds **7a-u**, **8a-d**, **9a**,**b and 10a-c**.

Compound	Zone of inhibition in mm			
	Gram-positive		Gram-negative	
	S. aureus	***B. subtilis***	***E. coli***	*P. vulgaris*
7a	14	13	17	19
7b	11	16	18	14
7c	13	20	19	16
7d	12	15	13	11
7e	13	14	15	11
7f	18	12	14	13
7g	16	13	13	14
7h	14	16	20	15
7i	11	14	17	14
7j	14	15	16	13
7k	11	16	19	17
7l	16	18	17	18
7m	19	14	19	16
7n	18	16	18	15
7o	16	14	20	14
7p	19	14	18	16
7q	14	13	16	13
7r	17	16	18	14
7s	12	12	14	14
7t	13	14	16	15
7u	-	-	-	-
8a	14	13	16	13
8b	13	16	18	16
8c	15	14	20	16
8d	14	12	14	15
9a	12	11	16	15
9b	11	19	20	21
10a	20	17	20	19
10b	14	16	19	17
10c	18	14	18	14
Penicillin	30	28	20	21
Chlor.*	28	25	21	20
Ampicillin	26	28	22	21

* Chlor. = Chloramphenicol

aureus. The presence of nitro group in **7c** (R = 3-NO_2) and chloro group in **7l** (R = 4-Cl) represented good activity against *B. subtilis*. Compound bearing methoxy group **7h** (R = 2-OCH_3) and chloro group **7o** (R = 2-Cl) exhibited good activity against *E. coli;* while with *P. vulgaris*, **7a** (R = H) and chloro substituted at C-4 **7l** (R = 4-Cl) possessed good activity.

Amides of substituted benzenesulfonamide showed good to poor activity. Disubstituted compound **8c** (R = 3-Cl, 4-OCH_3) demonstrated good activity against *E. coli;* while remaining all compounds showed moderate to poor activity against all bacterial strains.

Amides of 4-aminobenzenesulfonamide showed poor activity but introduction of dimethylpyrimidinyl group in **9b** (R = 4,6-$(CH_3)_2$-pyrimidine) increased activity against *B. Subtilis, E. coli* and *P. vulgaris*, respectively.

Amides of N^4-(4-substituted benzoylamino) benzenesulfonamide **10a** (R = 4- Cl) demonstrated good activity against all bacteria. Introduction of acetamido group compound in **10c** (R = -$NHCOCH_3$) showed good activity against *S. aureus*, whereas other bacterial strains exhibited moderate to poor activity. Introduction of nitro group in **10b** (R = 4-NO_2) decreased activity against bacterial strains.

Overall conclusion of antimicrobial study is that the introduction of 4-amino-N-substituted phenylbenzenesulfonamide and N^4-(4-substituted benzoylamino)benzenesulfonamide improved the activity, whereas 4-aminobenzenesulfonamide with introduced dimethylpyrimidinyl group improved activity significantly.

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