Synthesis, Antimicrobial and Anti-HIV Activity of Some Novel Benzenesulfonamides Bearing 2,5-Disubstituted-1,3,4-oxadiazole Moiety

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Twelve novel primary (**4a-c**, **5a-c**) and secondary (**4d-f, 5d-f**) benzenesulfonamides bearing 2,5-disubstituted-1,3,4-oxadiazole moiety have successfully been prepared by direct chlorosulfonation of phenyl substitutent present on the 2-position of 5-mercapto-1,3,4-oxadiazoles **2a-c** and their methylhio derivatives **3a-c** using chlorosulfonic acid under anhydrous conditions. Structures of the synthesized compounds were established by their physical and spectral data. Some of the synthesized compounds have been screened in vitro for their antimicrobial and anti-HIV activity; the results were in accordance with SAR.

Keywords: Benzenesulfonamides; 1,3,4-Oxadiazole; Methylthio derivatives; Chlorosulfonation; Antimicrobial and Anti-HIV activity.

INTRODUCTION

The sulfonamides constitute an important class of drugs, with several types of pharmacological agents possessing antibacterial, antifungal, diuretic, anticarbonic anhydrase, antithyroid, hypoglycemic and antitumour activity[1-5] among others. The reports of Krebs[6] that mainly the unsubstituted (primary) aromatic sulfonamides of type $ArSO_2NH_2$ act as strong carbonic anhydrase inhibitors (CAIs), and that potency of such compounds is drastically reduced by N-substitution of the sulfonamide moiety. This was the beginning of extensive structure-activity correlations, which led to some valuable drugs during a short period of time: the carbonic anhydrase inhibitor acetazolamide (**A**) (clinically used for over 45 years),[7,8] the widely used diuretic furosemide (**B**),[9] the anticancer sulfonamide E7070 (**C**),[10] and the HIV protease inhibitor amprenavir (**D**)[11] (used for the treatment of AIDS and HIV infections). Secondly, the 1,3,4-oxadiazole nucleus is of significant interest due to its chemotherapeutic history.[12-14]

Despite improvements in the synthesis of aromatic and heterocyclic sulfonamides, there is a desperate need to develop new more effective sulfonamides. The standard method, commonly used to synthesize aromatic sulfonamides involves the chlorosulfonation of an arene to give sulfonyl chloride and subsequent reaction with an amine.[15] Herein we report the synthesis of novel benzenesulfonamides bearing 2,5-disubstituted-1,3,4-oxadiazole moiety in 41-82% yields, Scheme I. This is a simple, efficient and novel approach of direct chlorosulfonation of phenyl substituent present on the 2-position of 5-mercapto-1,3,4-oxadiazoles **2a-c** and their methylthio derivatives **3a-c** using chlorosulfonic acid. A common theme in these benzenesulfonamides **4a-f** is the requirement for a free -SH/ mercaptoaryl group for an enhanced antiviral and antimicrobial activity.[16] Therefore, special emphasis was made on the synthesis of primary benzenesulfonamides with a free –SH group at position 5 of the oxadiazole ring.

RESULTS AND DISCUSSIONS

Following Scheme I, the 2,5-disubstituted-1,3,4-oxadiazoles **2a-c** were prepared by the reported method.[17] Methylthio derivatives **3a-c** of these 2,5-disubstituted-1,3,4-oxadiazoles were synthesized by a new approach using triethylamine and 4-(N,N-dimethylamino) pyridine (DMAP) in excellent yields (90-93%).

Various sulfonylchlorides obtained by direct chlorosulfonation of 2,5-disubstituted-1,3,4-oxadiazoles **2a-c**

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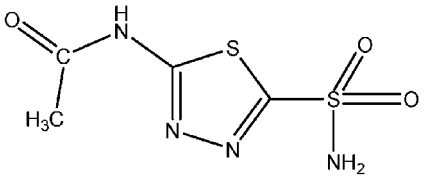
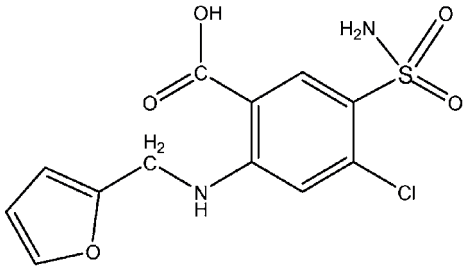
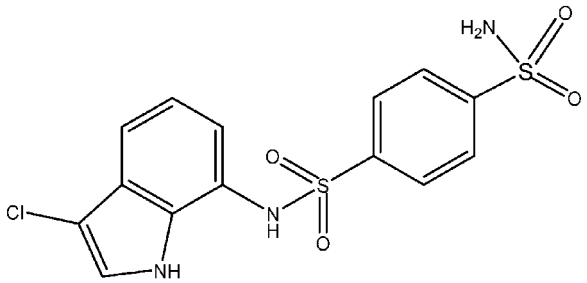


A:Acetazolamide



B:Furosemide



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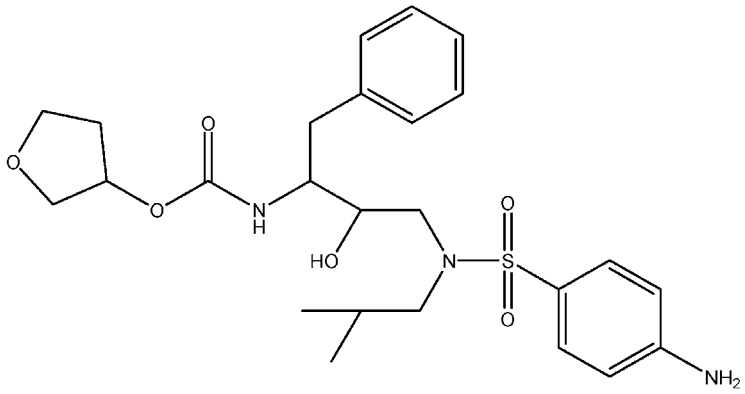
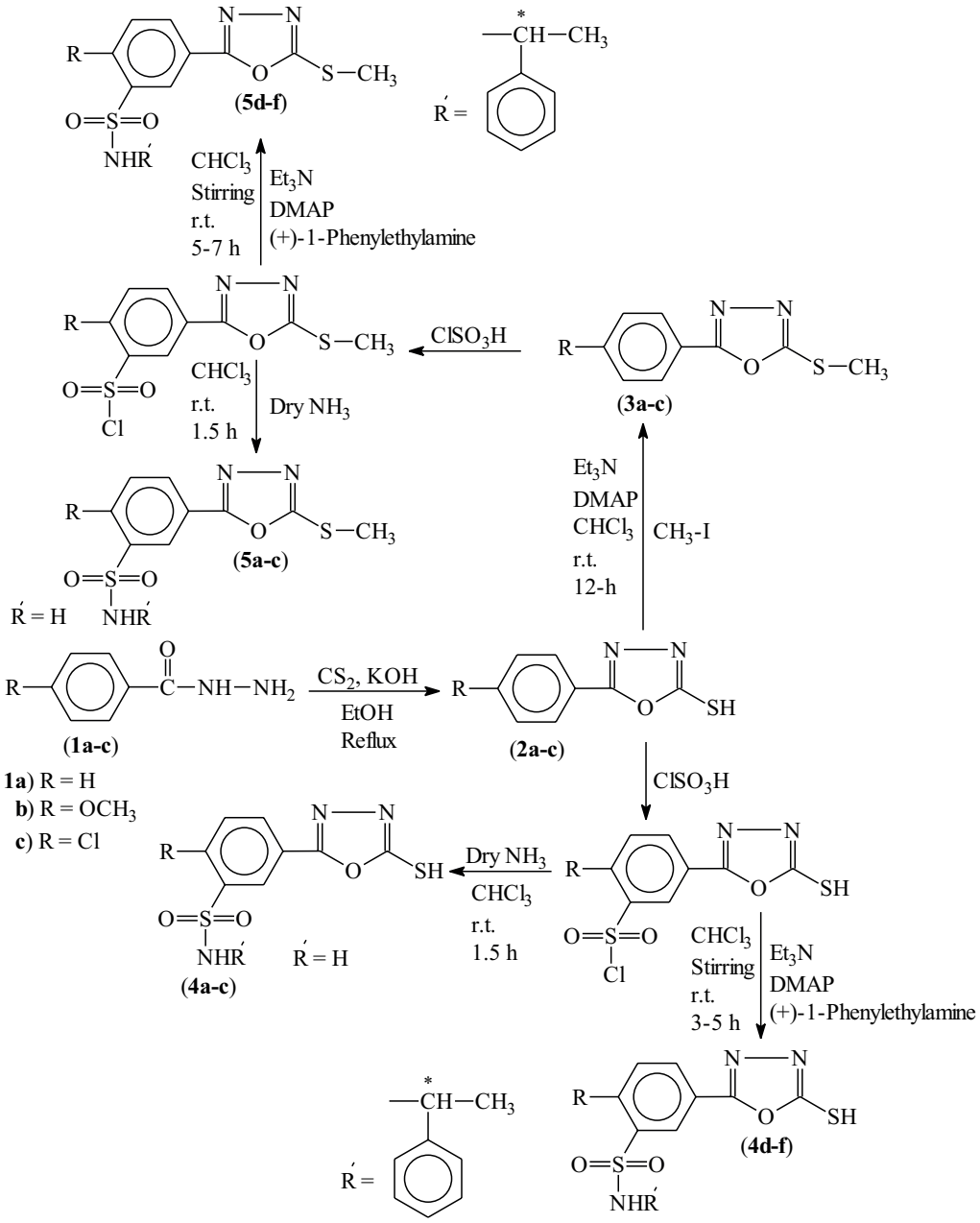


D:Amprenavir

and their methylthio derivatives **3a-c** were converted to primary benzenesulfonamides **4a-c** and **5a-c** using dry ammonia. Secondary benzenesulfonamides **4d-f** and **5d-f** were prepared by the reaction of sulfonylchlorides with (+)-1-phenylethylamine in the presence of triethylamine and DMAP. Preparation of primary benzenesulfonamides **4a-c** and **5a-c** is an improved and unique synthesis. Incorporation of a chiral centre, in case of secondary benzenesulfonamides **4d-f** and **5d-f**, may serve the purpose of selectivity in various chemotherapeutic actions. All the synthesized compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. The IR spectrum of primary sulfonamide **4a** revealed the presence of characteristic bands for NH_2 at 3287 cm^{-1}, 3265 cm^{-1} and 2565 cm^{-1} for SH in addition to the SO_2 functional group. In the mass spectrum of **4a** a molecular ion peak was observed at *m/z* 257 (M^+, 27). In the ^{1}H NMR spectrum of **4a**, measured in acetone-d_6, the following signals were observed: δ 7.5-7.6 (m, 3H, ArH), 7.9 (s, 1H, ArH), 12.30 (bs, H, NH).

^{13}C NMR spectrum of **4a** revealed the presence of aromatic carbon (δ 141.3) attached to a -SO_2NH_2 group. Spectroscopic data of all primary sulfonamides is given in Table 1. In the case of secondary sulfonamide **5d**, an IR characteristic band for NH at 3265 cm^{-1} was observed. The

Scheme I



4d) R = H, **4e)** R = OCH_3, **4f)** R = Cl

structure of **5d** was further supported by its mass spectrum which exhibited a molecular ion peak at *m/z* 375 (M^+, 8) and a base peak at *m/z* 105. The ^{1}H NMR spectrum of **5d** revealed a doublet at δ 1.41 assigned to CH_3 attached to the chiral centre CH, singlet at δ 2.36 for SCH_3 and multiplet at δ 4.43-4.46 assigned to chiral centre CH. ^{13}C NMR data of **5d** shows the presence of aromatic carbon (δ 142.9) attached to a -SO_2NHR group, SCH_3 (14.9), CH_3 (20.8) and CH (46.0). Spectroscopic data of all secondary sulfonamides is given in Table 1.

It was also found that yields of sulfonamides in the case of activated phenyl ring (with electron donating

Table 1. Characterization data of the synthesized compounds

Compd.	M.P. (°C)/ (Yield: %)	Formula (M.W.)	Spectral data
4a	181-83 (45)	$C_8H_7O_3N_3S_2$ (257)	IR (cm^{-1}, KBr) 3287, 3265 (NH), 2565 (SH), 1601 (C=N), 1331, 1170 (SO_2), 723 (C–S); ^{1}H NMR (400 MHz, Acetone-d_6) δ 7.5-7.6 (m, 3H, ArH), 12.30 (bs, H, NH); ^{13}C NMR: δ 124.7, 126.5, 127.9, 129.8, 130.8, 141.3 (Ar-C), 168.7 (C=N), 176.7 (C-S); EI-MS (%) 257 (M^+, 27), 193 (57), 176 (19), 155 (8), 105 (100).
4b	192-93 (57)	$C_9H_9O_4N_3S_2$ (287)	IR (cm^{-1}, KBr) 3259, 3254 (NH), 2567 (SH), 1695 (C=N), 1354, 1157 (SO_2), 718 (C–S); ^{1}H NMR (400 MHz, Acetone-d_6) δ 3.77 (s, 3H, OCH_3), 5.16 (br.s, 1H, SH), 7.39 (d, J = 8.1, 1H, ArH), 7.65 (d, J = 8 Hz, 1H, ArH), 8.12 (s, 1H, ArH), 12.88 (bs, H, NH); ^{13}C NMR: δ 55.7 (OCH_3) 116.5, 119.3, 121.7, 126.1, 132.2, 158.7 (Ar-C), 166.2 (C=N), 176.4 (C- S); EI-MS (%) 287 (M^+, 19), 223 (2.6), 192 (79), 135 (100), 131 (79), 91 (61).
4c	210-12 (41)	$C_8H_6O_3N_3S_2Cl$ (291)	IR (cm^{-1}, KBr) 3292, 3286 (NH), 2585 (SH), 1605 (C=N), 1332, 1175 (SO_2), 723 (C–S); ^{1}H NMR (400 MHz, Acetone-d_6) δ 7.67 (d, J = 8.0 Hz, 1H, ArH), 7.90 (d, J = 8.0 Hz, 1H, ArH), 8.05 (s, 1H, ArH), 13.30 (bs, H, NH); ^{13}C NMR: δ 125.7, 126.5, 130.5, 131.6, 132.8, 144.3 (Ar-C), 169.1 (C=N), 178.3 (C-S); EI-MS (%) 291 (M^+, 7), 155 (8), 139 (100), 111 (94), 89 (18), 75 (45).
4d	155-57 (55)	$C_{16}H_{15}O_3N_3S_2$ (361)	IR (cm^{-1}, KBr) 3286 (NH), 2551 (SH), 1602 (C=N), 1331, 1167 (SO_2), 723 (C–S); ^{1}H NMR (400 MHz, Acetone-d_6) δ 1.40 (d, J = 7.0 Hz, 3H, CH_3), 3.65 (s, 1H, SH), 4.42-4.45 (m, 1H, CH), 7.54-7.63 (m, 6H, ArH), 7.92 (d, J = 8.0 Hz, 1H, ArH), 7.97 (d, J = 8.0, = 8.0 Hz, 1H, ArH), 8.0 (s, 1H, ArH), 12.89 (bs, H, NH); ^{13}C NMR: δ 20.6 (CH_3), 45.3 (CH), 116.0, 119.1, 120.7, 125.3, 127.1, 127.3, 127.8, 128.7, 128.8, 132.0, 145.1, 158.3, (Ar-C), 167.0 (C=N), 176.9 (C-S); EI-MS (%) 361 (M^+, 2.2), 297 (7), 234 (6), 192 (32), 178 (100), 118 (84), 120 (9), 91 (41), 77 (81).
4e	172-73 (61)	$C_{17}H_{17}O_4N_3S_2$ (391)	IR (cm^{-1}, KBr) 3265 (NH), 2585 (SH), 1610 (C=N), 1344, 1159 (SO_2), 735 (C–S); ^{1}H NMR (400 MHz, Acetone-d_6) δ 1.43 (d, J = 7.0 Hz, 3H, CH_3), 3.77 (s, 3H, OCH_3), 3.94 (m, 1H, CH), 7.06-7.39 (m, 6H, ArH), 7.64 (d, J = 8.1 Hz, 1H, ArH), 8.07 (s, 1H, ArH), 12.37 (s, 1H, NH); ^{13}C NMR: δ 20.5 (CH_3), 45.4 (CH), 55.4 (OCH_3), 115.2, 119.3, 120.2, 126.1, 127.0, 127.4, 127.6, 128.1, 128.2, 131.9, 144.1, 157.5 (Ar-C), 166.0 (C=N), 176.7 (C-S); EI-MS (%) 391 (M^+, 3.2), 327 (100), 312 (12), 256 (12), 120 (99), 91 (19), 77 (8), 65 (15).
4f	182-84 (41)	$C_{16}H_{14}O_3N_3S_2Cl$ (395)	IR (cm^{-1}, KBr) 3287 (NH), 2555 (SH), 1597 (C=N), 1321, 1161 (SO_2), 704 (C–S); ^{1}H NMR (400 MHz, Acetone-d_6) δ 2.0 (d, J = 8.0 Hz, 1H, ArH), 7.98 (s, H, ArH), 13.3 (s, 1H, NH); ^{13}C NMR: δ 20.9 (CH_3), 46.3 (CH), 124.9, 125.7, 127.0, 127.1, 127.2, 128.7, 128.8, 130.3., 132.1, 133.5, 140.6, 144.3 (Ar-C), 168.7 (C=N), 179.0 (C-S); EI-MS (%) 395 (M^+, 9), 239 (27), 212 (100), 195 (181), 91 (20), 77 (9).
5a	142-43 (71)	$C_9H_9O_3N_3S_2$ (271)	IR (cm^{-1}, KBr) 3286, 3266 (NH), 1605 (C=N), 1333, 1165 (SO_2), 692 (C–S); ^{1}H NMR (400 MHz, Acetone-d_6) δ 2.5 (s, 3H, S–Me), 7.5-7.6 (m, 3H, ArH), 7.9 (s, 1H, ArH), 12.30 (bs, H, NH); ^{13}C NMR: δ 14.3 (SCH_3), 123.7, 125.8, 127.7, 130.1, 131.2, 140.9 (Ar-C), 165.1 (C=N), 171.3 (C-S); EI-MS (%) 271 (M^+, 28), 226 (57), 207 (100), 179 (56), 76 (15), 75 (46), 57 (17).

5b	151-53 (82)	$C_{10}H_{11}O_3N_3S_2$ (301)	IR (cm^{-1}, KBr) 3256, 3254 (NH), 1601 (C=N), 1355, 1157 (SO_2), 693 (C–S); ^{1}H NMR (400 MHz, Acetone-d_6) δ 2.64 (s, 3H, S–Me), 3.78 (s, 3H, OCH_3), 7.41 (d, J = 8.2 Hz, 1H, ArH), 7.66 (d, J = 8.1 Hz, 1H, ArH), 13.53 (bs, H, NH); ^{13}C NMR: δ 14.3 (SCH_3), 55.8 (OCH_3), 115.2, 118.8, 124.8, 125.1, 130.9, 158.1 (Ar-C) 165.1 (C=N), 168.3 (C-S); EI-MS (%) 301 (M^+, 21), (2.7), 192 (61) 135 (100), 105 (7), 91 (61), 77 (11).
5c	145-47 (64)	$C_9H_8O_3N_3S_2Cl$ (305)	IR (cm^{-1}, KBr) 3287, 3281 (NH), 1604 (C=N), 1332, 1172 (SO_2), 723 (C–S); ^{1}H NMR (400 MHz, Acetone-d_6) δ 2.81 (s, 3H, S–Me), 7.65 (d, J = 8.1 Hz, 1H, ArH), 7.90 (d, J = 8.0 Hz, 1H, ArH), 8.05 (s, 1H, ArH), 13.30 (bs, H, NH); ^{13}C NMR: δ 14.8 (SCH_3), 124.7, 125.9, 127.7, 130.4, 131.7, 140.6 (Ar-C), 167.1 (C=N), 172.2 (C-S); EI-MS (%) 305 (M^+, 2.6), 241 (21), 194 21), 139 (100), 131 (79), 105 (18), 91 (61), 77 (13), 66 (17).
5d	Brown oil (61)	$C_{17}H_{17}O_3N_3S_2$ (375)	IR (cm^{-1}) 3265 (NH), 1605 (C=N), 1333, 1175 (SO_2), 723 (C-S); ^{1}H NMR (400 MHz, Acetone-d_6) δ 1.41 (d, J = 7.1 Hz, 3H, CH_3), 2.36 (s, 3H, S–Me), 4.43-4.46 (m, 1H, CH), 7.54-7.64 (m, 6H, ArH), 7.92-7.95 (m, 2H, ArH), 7.98 (d, J = 8.0 Hz, 1H, ArH), 10.75 (bs, H, NH); ^{13}C NMR: δ 14.9 (SCH_3), 20.8 (CH_3), 46.0 (CH), 123.8, 126.4, 126.6, 127.3, 127.4, 127.7, 128.5, 128.7, 129.1, 130.5, 140.5, 142.9 (Ar-C), 166.5 (C=N), 170.9 (C-S); EI-MS (%) 375 (M^+, 8), 311 (7), 234 (69), 192 (37), 178 (77), 120 (3), 105 (100), 77 (71), 57 (6).
5e	Brown oil (69)	$C_{18}H_{19}O_4N_3S_2$ (405)	IR (cm^{-1}) 3267 (NH), 1605 (C=N), 1338, 1174 (SO_2), 721 (C–S); ^{1}H NMR (400 MHz, Acetone-d_6) δ 1.44 (d, J = 7.1 Hz, 3H, CH_3), 2.36 (s, 3H, S–Me), 3.73 (s, 3H, OCH_3), 4.43-4.46 (m, 1H, CH), 7.54-7.69 (m, 6H, ArH), 7.92-7.96 (m, 1H, ArH), 11.21 (bs, H, NH); ^{13}C NMR: δ 14.4 (SCH_3), 20.8 (CH_3), 45.3 (CH), 56.0 (OCH_3), 115.4, 119.4, 120.5, 125.3, 127.0, 127.2, 127.5, 128.7, 128.8, 131.9, 143.6, 157.8 (Ar-C), 165.0 (C=N), 169.0 (C-S); EI-MS (%) 405 (M^+, 17), 342 (9), 234 (69), 192 (37), 178 (77),120 (3), 135 (100), 77 (7), 65 (16).
5f	Brown oil (47)	$C_{16}H_{14}O_3N_3S_2Cl$ (409)	IR (cm^{-1}) 3277 (NH), 1608 (C=N), 1323, 1149 (SO_2), 704 (C–S); ^{1}H NMR (400 MHz, Acetone-d_6) δ 1.43 (d, J = 7.2 Hz, 3H, CH_3), 2.71 (s, 3H, S–Me), 4.45-4.47 (m, 1H, CH), 7.67 (d, J = 8.0 Hz, 1H, ArH), 7.92 (d, J = 8.0 Hz, 1H, ArH), 8.08 (s, 1H, ArH), 12.65 (bs, H, NH); ^{13}C NMR: δ 14.7 (SCH_3), 21.0 (CH_3), 46.9 (CH), 124.7, 125.9, 127.4, 128.7, 128.9, 130.0, 132.0, 128.7, 132.3, 132.5, 141.1, 145.3, (Ar-C), 168.1 (C=N), 171.9 (C-S); EI-MS (%) 409 (M^+, 2.6), 345 (21), 241 (19), 193 (55), 139 (100), 131 (79), 120 (13), 9 (61), 77 (13), 57 (8).

groups such as methoxy) are greater than those counterpart sulfonamides bearing 4-chlorophenyl substituent. Finally this method (Scheme I) enabled us to synthesize sulfonamides in fewer steps (two steps less) than the common available route, i.e., first making sulfonamides from substituted aromatic carboxylic acids[18] and then cyclization to a heterocyclic ring. This new approach can prompt synthetic chemists to develop a cost effective method for the synthesis of this important class of drugs. Some of the synthesized compounds were screened *in vitro* for their antimicrobial and anti-HIV activities; the results are presented in Tables 2, 3 and 4.

ANTIMICROBIAL ACTIVITY

All the synthesized sulfonamides have been tested *in vitro* for their antibacterial activity against *Staphylococcus aureus*, *Bacillus subtilis* (Gram + ve) and *E. coli,* and *Pseudomonas aeruginosa* (Gram – ve) bacteria by agar diffusion method.[19] DMF was used as a control solvent and Chloramphenicol as a standard drug. After 24 hrs of incubation at 37 °C, the zone of inhibition was measured in mm. The investigation results are listed in Table 2. The results showed that all compounds were active against both the gram positive and gram negative bacteria. Compounds

Table 2. Antibacterial activity of synthesized benzenesulfonamides **4a-f** and **5a-f**

Compd. No.	*Staphylococcus aureus*	*Bacillus subtilis*	*Pseudomonas aeruginosa*	*E. coli*
4a	14	16	11	17
4b	15	13	-	12
4c	17	21	15	19
4d	10	11	-	-
4e	13	16	-	12
4f	16	19	14	17
5a	-	12	-	13
5b	14	16	10	15
5c	15	21	12	17
5d	11	-	-	12
5e	14	16	-	11
5f	11	17	14	16
Chloramphenicol (Standard)	24	24	23	24

Zone diameter of growth inhibition (mm): <10 mm (-), Concentration 2 mg/mL in DMF.

Table 3. Antifungal activity of some synthesized compounds and inhibition zones (%)

Name of Fungi	Compd. No.					Standard drug
	4a	**4b**	**4c**	**4f**	**5d**	
Trichphyton longifusus	35	50	90	0	0	Miconazole
Candida albicans	0	0	100	0	0	Miconazole
Aspergillus flavus	0	0	0	0	0	Amphotericin
Microsporum canis	40	0	60	0	0	Miconazole
Fusarium solani	40	0	100	50	40	Miconazole
Candida glabrata	0	0	0	0	0	Miconazole

Conc. of sample 200 μg/mL of DMSO at 27 °C, Incubation period 07 days.

4a-c, **4f** and **5c** showed significant activity against both the gram positive and gram negative bacteria. The investigation on the structure-activity relationship (SAR) shows that free -SH at position 5 of the oxadiazole ring, free -NH_2 of the sulfonamido moiety and presence of chloro group at position 4 of the phenyl substituent of the oxadiazole ring enhanced the antibacterial action of the synthesized sulfonamides. Five selected representatives of newly synthesized sulfonamides **4a-c**, **4f** and **5d** were screened *in vitro* for their antifungal activity against six species using the agar plate technique.[20] The linear growth of the fungus was obtained by measuring the diameter of the fungal colony after seven days. The amount of growth inhibition in each case was calculated as percentage inhibition. The screening results given in Table 3 indicated that compounds **4a-c** and **4f** exhibit moderate to significant activities. It is worthwhile to note that compound **4c** exhibits significant (maximum) antibacterial and antifungal activities due to the presence of a chloro group on position 4 of the phenyl substituent, free -SH at position 5 of the oxadiazole ring, and free -NH_2 of the sulfonamido moiety. Whereas, in the case of **5d** the substitution at free SH and NH_2 diminished the antimicrobial activity as given in Tables 2, 3. Therefore, the antimicrobial results are in accordance with SAR.

Table 4. The anti-HIV activity and cellular toxicity of some synthesized compounds

Compd. No.	% Reduction of HIV-1[a]			CD50[b] (μg/mL)
	50 μg/mL	25 μg/mL	5 μg/mL	
4a	11	5	0	>100
4b	23	7	0	>100
4c	27	9	5	>100
4f	62	21	14	67
5d	0	0	0	>100

[a] Percentage inhibition of virus replication at each of the indicated concentrations.
[b] The cytotoxic dose (the dose which gives 50% inhibition of growth of uninfected cells).

ANTI-HIV ACTIVITY

Five synthesized sulfonamides **4a-c**, **4f** and **5d** were screened against human immunodeficiency virus type 1 (HIV-1) using the XTT assay in MT-4 cells.[21]

The anti-HIV-1 activity of compounds **4a-c**, **4f** and **5d** at 50, 25, and 5 μg/mL concentrations and the cytotoxic doses CD_{50} are given in Table 4. The results revealed that compound **4f** was the most active among the tested compounds; it produced 62%, 21%, and 14% reduction of viral replication at 50, 25, and 5 μg/mL concentrations, respectively. Compounds **4a**, **4b** and **4c** exhibited non-significant antiviral activity, whereas, **5d** was totally inactive. All the tested sulfonamides were found to be noncytotoxic with CD_{50} > 100 μg/mL except compound **4f** whose CD_{50} was 67 μg/mL.

EXPERIMENTAL SECTION

Melting points were determined on a Gallenkamp digital melting point apparatus and are uncorrected. IR spectra were recorded in a KBr disc on a FT-IR model FTS 300 MX spectrometer. NMR spectra were recorded in acetone-d_6 or $CDCl_3$ on a Bruker (^{1}H, 400 MHz and ^{13}C, 75 MHz) spectrophotometer. The chemical shifts of proton signals are in parts per million (ppm) downfield from tetramethylsilane (TMS) as an internal standard. EI-MS spectra were recorded on a MAT 311A mass spectrometer (EI at 70 eV). Thin layer chromatography (TLC) was performed on precoated silica gel 60 F_{254} aluminum sheets (Merck).

Compounds **2a-c** were prepared as described in the literature.[12]

2-(4-Chlorophenyl)-5-(methylthio)-1,3,4-oxadiazole 3c

Compound **2c** (0.01 mole), triethylamine (0.02 mole) and DMAP (25 mg) in dry chloroform (Scheme I) were stirred at room temperature for half an hour. Methyl iodide (0.011 moles) was then added and the reaction mixture was stirred at room temperature for 12 hrs. The reaction mixture was washed with dil. HCl, brine, water and dried over anhyd. Na_2SO_4. The solvent was distilled off and the product was recrystallized with aqueous ethanol. Compounds **3a-b** were prepared in a similar fashion. **3c**, m.p. 105-107 ^oC , yield 93%, IR (cm^{-1}, KBr) 1597 (C=N), 702 (C–S); ^{1}H NMR (400 MHz, Acetone-d_6) δ 2.81 (s, 3H, S–Me), 7.58 (d, J = 8 Hz, 2H, ArH), 7.83 (d, J = 8 Hz, 2H, ArH); EI-MS (%) 226 (M^+, 7), 139 (100).

3-(5-Mercapto-1,3,4-oxadiazol-2-yl)-2-R-benzenesulfonamides 4a-c. General procedure

Chlorosulfonic acid (0.025 moles) was gradually added to **2a-c** (0.005 moles) at 0 ^{o}C under anhydrous conditions. The reaction mixture was warmed (50-70 ^{o}C) for 2 hrs, poured on ice and extracted twice with chloroform. The combined extract was washed with brine, water and dried over anhyd. Na_2SO_4. This chloroform mixture (containing sulfonyl chloride) was partitioned into two portions; one was treated directly with dry ammonia for 1.5 hrs, and concentrated to afford primary sulfonamide **4a-c**. Each primary sulfonamide was purified by recrystallization with aqueous ethanol. Physical and spectroscopic data of **4a-c** are given in Table 1.

3-(5-Mercapto-1,3,4-oxadiaziol-2-yl)-N-(1-phenylethyl)-2-R-benzenesulfonamides 4d-f. General procedure

The second portion (containing sulfonylchloride) was stirred at room temperature for 7 hrs with equimolar (+)-1-phenylethylamine in the presence of triethylamine and DMAP (25 mg). The reaction mixture was washed with dil. HCl, brine, water and dried over anhyd. Na_2SO_4. The solvent was distilled off to get crude secondary sulfonamide **4d-f**. Each was purified by preparative thin layer chromatography using petroleum ether: ethyl acetate (4:1) as eluent. Physical and spectroscopic data of **4d-f** is presented in Table 1.

2-R-5-(5-(methylthio)-1,3,4-oxadiazol-2-yl)benzenesulfonamide 5a-c. General procedure

Chlorosulfonic acid (0.025 moles) was gradually added to **3a-c** (0.005 moles) at 0 ^{o}C under anhydrous condi-

tions. The reaction mixture was warmed (50-70 °C) for 2 hrs, poured on ice and extracted twice with chloroform. The combined extract was washed with brine and dried over anhyd. Na_2SO_4. This chloroform mixture (containing sulfonyl chloride) was partitioned into two portions; one was treated directly with dry ammonia for 1.5 hrs, and concentrated to afford primary sulfonamide **5a-c**. Each primary sulfonamide was purified by recrystallization with aqueous ethanol. Characterization data of **5a-c** is given in Table 1.

2-R-5-(5-(methylthio)-1,3,4-oxadiazol-2-yl)-N-(1-phenylethyl)benzenesulfonamide 5d-f. General procedure

The second portion (containing sulfonylchloride) was stirred at room temperature for 7 hrs with equimolar (+)-1-phenylethylamine in the presence of triethylamine and DMAP (25 mg). The reaction mixture was washed with dil. HCl, brine, water and dried over anhyd. Na_2SO_4. The solvent was distilled off to get crude secondary sulfonamide **5d-f**. Each was purified by preparative thin layer chromatography using petroleum ether: ethyl acetate (4:1) as eluent. Characterization data of **5d-f** is given in Table 1.

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