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Synthesis and Antibacterial Activity of (*E*)-N'-[4-{2-(4-Fluorophenylthio)ethoxy}-3-cyano-5-methoxybenzylidene]-substituted benzohydrazide Derivatives

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Commercially available vanillin was used as the starting material for the preparation of some new (*E*)-N'-[4-{2-(4-fluorophenylthio)-ethoxy}-3-cyano-5-methoxybenzylidene]-4-substituted benzohydrazide derivatives (**8.1** to **8.10**) in quantitative yields. The structural confirmations of all the newly synthesized hydrazone derivatives were established on the basis of ^{1}H NMR, mass and IR data. Hydrazides such as (*E*)-N'-[4-{2-(4-fluorophenylthio)ethoxy}-3-cyano-5-methoxybenzylidene]-2,5-dichlorobenzohydrazide (**8.6**), (E)-N'-[4-{2-(4-fluorophenylthio)ethoxy}-3-cyano-5-methoxybenzylidene]-2,5-difluorobenzohydrazide (**8.9**) showed duplication of NMR signals, this was attributed to the presence of *anti* and *syn* periplanar conformers. Antibacterial study against *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli* and *Pseudomonas aeruginosa* with reference to the standard drug (streptomycin) revealed that compounds bearing R = 4-OH (**8.2**), 3,4,5-OMe (**8.3**) and 4-SO_2Me (**8.4**) substituents has shown the good antibacterial sensitivity.

Keywords: Substituted benzohydrazide derivatives, Vanillin.

INTRODUCTION

Vanillin (4-hydroxy-3-methoxybenzaldehyde), a compound isolated from the bean and pod of tropical vanilla orchid is widely used in the food and beverage industry and is responsible for the characteristic vanilla flavour. This substance is also relevant for the synthesis of different agrochemicals, antifoaming and pharmaceutical products [1]. Some of the biological activities exhibited by vanillin are antimicrobial activity [2-4], antimutagenic [5,6] and anticarcinogenic actions [7], conversely, it may also induce oxidative stress in yeast cells [8].

Hydrazide-hydrazones have also attracted a great deal of interest due to their increased importance in medicinal chemistry [9,10]. Isoniazid, a hydrazide derivative, is the front-line drug currently employed in the treatment of tuberculosis [11]. Hydrazone derivatives of isoniazid and other hydrazides have been reported to display significant antimicrobial activity [10-16]. Numerous substituted hydrazone derivatives have also been synthesized and evaluated for their antitumor activity and some promising results were reported [17,18].

Since resistance of pathogenic bacteria towards available antibiotics is rapidly becoming a major worldwide problem, the design of new compounds to deal with resistant bacteria has become one of the most important areas of antibacterial research today. In view of the above biological significance of vanillin and hydrazone chemistry, we report here in the synthesis and antibacterial activity of new hydrazone derivatives prepared from commercially available vanillin.

EXPERIMENTAL

3-Methoxy-4-hydroxy-5-iodo benzaldehyde (2): A mixture of vanillin (5 g, 32.86 mmol), $CaCO_3$ (3.94 g, 39.43 mmol) in cyclopentylmethyl ether (100 mL) was cooled to 0 °C and added benzyltrimethylammonium dichloroiodate (12 g, 34.50 mmol) in seven portions. The reaction mixture was stirred at room temperature for 10 h. The precipitated solids were filtered and dried under vaccum to afford 5-iodo-vanillin (**2**). Yellow solid, m.p.: 183-184 °C, Yield: 8.2 g, 90 %; IR (KBr, ν_{max}, cm^{-1}): 3297, 3076, 2843, 1740, 1663, 1563, 1493, 1458, 1408, 1363, 1290, 1250, 1210, 1128, 1084, 1035, 94, 900, 845, 815, 727, 665, 643; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.04 (s,1 H), 9.73 (s, 1 H), 7.81 (s, 1 H), 7.34 (s, 1 H), 3.98 (s, 3 H); EI-MS: *m/z*, 278 [M+1].

4-(2-Hydroxyethoxy)-3-iodo-5-methoxybenzaldehyde (3): To a stirred solution of compound **2** (5 g, 17.0 mmol) in

cyclopentylmethyl ether (50 mL) was added K_2CO_3 (2.58 g, 18.70 mmol) followed by 1-bromoethanol (18.7 mmol) and heated to reflux for 4 h. After the completion of the reaction (monitored by TLC), the reaction mixture was diluted with water and washed with brine solution, dried on sodium sulphate, filtered and concentrated to obtain compound **3**. Pale yellow solid; m.p.: 64-65 °C, Yield: 4.93 g, 85 %; IR (KBr, ν_{max}, cm^{-1}): 3314, 3074, 2971, 2842, 1689, 1568, 1516, 1458, 1385, 1272, 1235, 1140, 1071, 1034, 998, 899, 853, 787, 738, 665; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.84 (s,1 H), 7.86 (d, *J* = 1.6 Hz, 1H), 7.43 (d, *J* = 2.0 Hz, 1H), 4.28 (t, *J* = 4.4 Hz, 2H), 3.91 (t, *J* = 4.4 Hz, 2H), 3.90 (s, 3H), 2.70 (brs, 1H); EI-MS: *m/z*, 278 [M+1].

2-(4-Formyl-2-iodo-6-methoxyphenoxy)ethyl methanesulfonate (4): To a solution of compound **3** (4 g, 12.42 mmol) in cyclopentyl methyl ether (20 mL) was added triethyl amine (2 mL, 14.90 mmol) followed by methane sulphonyl chloride (1 mL, 13.04 mmol) and stirred at room temperature for 2 h. After completion of the reaction (checked by TLC), the reaction mixture was diluted with water and washed with brine solution, dried on sodium sulphate, filtered and concentrated to obtain compound **4**. Pale yellow viscous liquid; Yield: 4.5 g, 90 %; IR (KBr, ν_{max}, cm^{-1}): 3074, 2969, 2878, 1738, 1686, 1562, 1455, 1387, 1339, 1271, 1222, 1168, 1139, 1108, 1040, 977, 923, 893, 862, 786, 730, 659; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.84 (s, 1H), 7.86 (d, *J* = 1.6 Hz, 1H), 7.43 (d, *J* = 2.0 Hz, 1H), 4.62-4.60 (m, 2H), 4.40-4.38 (m, 2H), 3.93 (s, 3H), 3.13 (s, 3H); EI-MS: *m/z*, 401 [M+1].

4-[2-(4-Fluorophenylthio)ethoxy]-3-iodo-5-methoxybenzaldehyde (5): To a solution of compound **4** (2 g, 10 mmol) in DMF (15 mL), cooled to 5 °C was added sodium methoxide (0.65 g, 12 mmol) followed by a pre-mixed solution of *p*-fluorothiophenol (1.28 g, 10 mmol) in DMF (5 mL) for 30 min and stirred at room temperature for 5 h. The reaction mixture was quenched with water and extracted with cyclopentyl methyl ether. The organic layer was washed with water (20 mL), brine solution and dried over sodium sulphate, filtered and concentrated to obtain compound **5.** Yellow solid; Yield 1.72 g, 80 %; m.p.: 92-94 °C; IR (KBr, ν_{max}, cm^{-1}): 3073, 2985, 2848, 1724, 1696, 1582, 1485, 1460, 1414, 1386, 1271, 1220, 1137, 1090, 1038, 977, 853, 823, 742, 664, 619; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.82 (s, 1H), 7.84 (d, *J* = 1.2 Hz, 1H), 7.38 (d, *J* = 2.0 Hz, 1H), 7.42 (t, *J* = 9.2 Hz, 2H), 7.01 (t, *J* = 8.4 Hz, 2H), 4.21 (t, *J* = 7.6 Hz, 2H), 3.85 (s, 3H), 3.31 (t, *J* = 7.6 Hz, 2H); EI-MS: *m/z*, 432 [M+1].

2-[2-(4-Fluorophenylthio)ethoxy]-5-formyl-3-methoxybenzonitrile (6): To a solution of compound **5** (1.5 g, 3.48 mmol) in dimethyl formamide (10 mL) was added cuprous cyanide (0.38 g, 4.18 mmol) and heated to 130-135 °C for 3 h. The reaction mixture was cooled to room temperature and diluted with diethyl ether (50 mL) followed by water (100 mL). The organic layer was washed with water (2 × 25 mL) followed by brine solution, dried over Na_2SO_4, filtered and concentrated to afford compound **5** as pale yellow solid. Yield 94 %; m.p.: 148-150 °C; IR (KBr, ν_{max}, cm^{-1}): 3069, 2954, 2842, 2232, 1731, 1697, 1579, 1486, 1428, 1387, 1332, 1296, 1224, 1142, 1076, 1042, 1011, 966, 924, 870, 811, 751, 699, 631; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.88 (s, 1H), 7.63 (d, *J* = 1.2 Hz, 1H), 7.59 (d, *J* = 2.0 Hz, 1H), 7.42 (t, *J* = 9.2 Hz, 2H), 7.01 (t, *J* = 8.6 Hz, 2H), 4.43 (t, *J* = 7.4 Hz, 2H), 3.89 (s, 3H), 3.27 (t, *J* = 7.4 Hz, 2H); EI-MS: *m/z*, 332 [M+1].

General experimental procedure for the synthesis of hydrazones (8.1-8.10): A mixture of compound **6** (0.23 mmol), benzohydrazides **7.1** to **7.10** (0.23 mmol), respectively was refluxed in ethanol for 1 h. The precipitated solids obtained were filtered and washed with pet-ether and dried at the pump to obtain hydrazones **8.1-8.9** in quantitative yields.

(*E*)-N'-[4-{2-(4-Fluorophenylthio)ethoxy}-3-cyano-5-methoxybenzylidene]benzohydrazide (8.1): Off white solid; Yield: 86 %; m.p.: 111-112 °C; IR (KBr, ν_{max}, cm^{-1}): 3276, 3224, 3066, 2963, 2844, 2233, 1653, 1599, 1557, 1485, 1419, 1381, 1296, 1220, 1164, 1070, 1001, 962, 895, 865, 823, 744, 697, 660, 626; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.0 (s, 1H), 8.42 (s, 1H), 7.92 (d, *J* = 7.2 Hz, 2H), 7.70 (s, 1H), 7.62 (d, *J* = 6.8 Hz, 2H), 7.60 (d, *J* = 7.2 Hz, 2H), 7.45 (t, *J* = 8.0 Hz, 2H), 7.20 (d, *J* = 8.4 Hz, 2H), 4.32 (t, *J* = 6.8 Hz, 2H), 3.88 (s, 3H), 3.30 (t, *J* = 6.8 Hz, 2H); ESI-MS: *m/z*, 450 (M+1).

(*E*)-N'-[4-{2-(4-Fluorophenylthio)ethoxy}-3-cyano-5-methoxybenzylidene]-4-hydroxybenzohydrazide (8.2): White solid; Yield: 80 %; m.p.: 99-100 °C; IR (KBr, ν_{max}, cm^{-1}): 3320, 3081, 2945, 2803, 2238, 1641, 1602, 1566, 1481, 1451, 1376, 1323, 1270, 1228, 1170, 1150, 1109, 1073, 995, 939, 891, 841, 756, 624; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.80 (s, 1H), 10.15 (s, 1H), 8.39 (s, 1H), 7.80 (d, *J* = 8.4 Hz, 2H), 7.66 (s, 1H), 7.59 (s, 1H), 7.45 (dd, *J* = 5.2, 8.4 Hz, 2H), 7.20 (t, *J* = 9.2 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 4.31 (t, *J* = 6.8 Hz, 2H), 3.88 (s, 3H), 3.30 (t, *J* = 6.8 Hz, 2H); ESI-MS: *m/z*, 464.0 (M-1).

(*E*)-N'-[4-{2-(4-Fluorophenylthio)ethoxy}-3-cyano-5-methoxybenzylidene]-3,4,5-trimethoxybenzohydrazide (8.3): Brown solid; Yield: 85 %; m.p.: 122-123 °C; IR (KBr, ν_{max}, cm^{-1}): 3314, 3079, 2943, 2841, 2235, 1669, 1580, 1545, 1492, 1416, 1373, 1324, 1293, 1221, 1179, 1123, 1081, 999, 957, 869, 831, 745, 697, 663; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.88 (s, 1H), 7.68 (s, 1H), 7.62 (s, 1H), 7.45 (t, *J* = 8.0 Hz, 2H), 7.23 (s, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 4.32 (t, *J* = 6.0 Hz, 2H), 3.88 (s, 3H), 3.86 (s, 3H), 3.73 (s, 3H), 3.31 (t, *J* = 6.0 Hz, 2H); ESI-MS: *m/z*, 540.0 (M+1).

(*E*)-N'-[4-{2-(4-Fluorophenylthio)ethoxy}-3-cyano-5-methoxybenzylidene}-4-(methylsulfonyl)benzohydrazide (8.4): Pale yellow solid; Yield: 80 %; m.p.: 106-108 °C; IR (KBr, ν_{max}, cm^{-1}): 3275, 3068, 2974, 2232, 1661, 1612, 1578, 1543, 1483, 1456, 1416, 1382, 1288, 123, 1148, 1083, 1006, 959, 895, 858, 828, 779, 746, 707, 651, 623; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.24 (s, 1H), 8.42 (s, 1H), 8.15 (d, *J* = 8.4 Hz, 2H), 8.10 (d, *J* = 8.4 Hz, 2H), 7.70 (s, 1H), 7.66 (s, 1H), 7.45 (t, *J* = 8.8 Hz, 3H), 7.20 (t, *J* = 9.2 Hz, 2H), 4.32 (t, *J* = 6.8 Hz, 2H), 3.88 (s, 3H), 3.30 (t, *J* = 6.8 Hz, 2H); ESI-MS: *m/z*, 526.0 (M+1).

***(E)*-N'-[4-{2-(4-Fluorophenylthio)ethoxy}-3-cyano-5-methoxybenzylidene]-3-nitrobenzohydrazide (8.5):** Yellow solid; Yield: 86 %; m.p.: 78-80 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.33 (s, 1H), 8.75 (s, 1H), 8.47 (s, 1H), 8.44 (s, 1H), 8.38 (d, *J* = 7.2 Hz, 1H), 7.85 (t, *J* = 8.0 Hz, 1H), 7.71 (s, 1H), 7.66 (s, 1H), 7.46 (t, *J* = 8.8 Hz, 2H), 7.20 (t, *J* = 7.6 Hz, 2H), 4.33 (t, *J* = 6.8 Hz, 2H), 3.89 (s, 3H), 3.30 (t, *J* = 6.8 Hz, 2H); ESI-MS: *m/z*, 493.0 (M-1).

(*E*)-N'-[4-{2-(4-Fluorophenylthio)ethoxy}-3-cyano-5-methoxybenzylidene]-2,5-dichlorobenzohydrazide (8.6): White solid; Yield: 84 %; m.p.: 78-80 °C; IR (KBr, ν_{max}, cm^{-1}): 3176, 2996, 2851, 2234, 1742, 1653, 1567, 1426, 1419, 1373, 1292, 1223, 1164, 1072, 1002, 967, 924, 877, 825, 785, 745, 697, 661, 625; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.31 (* 12.15, s, 1H), 8.22 (* 8.0, s, 1H), 7.73 (* 7.70, s, 1H), 7.64-7.55 (m, 3H), 7.47-7.40 (m, 2H), 7.34 (* 7.27, s, 1H), 7.22-7.15 (m, 2H), 4.32 (* 4.25, t, *J* = 6.8 Hz, 2H), 3.88 (* 3.66, s, 3H), 3.33 (* 3.25, t, *J* = 6.8 Hz, 2H); ESI-MS: *m/z*, 518.0 (M-1).

(*E*)-N'-[4-{2-(4-Fluorophenylthio)ethoxy}-3-cyano-5-methoxybenzylidene]-3,5-dichlorobenzohydrazide (8.7): White solid; Yield: 82 %; m.p.: 78-80 °C; IR (KBr, ν_{max}, cm^{-1}): 3326, 3081, 2965, 2851, 2904, 2232, 2087, 1676, 1603, 1553, 1487, 1459, 1418, 1368, 1301, 1249, 1184, 1117, 1080, 997, 935, 865, 808, 744, 697, 662, 621; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.16 (s, 1H), 8.38 (s, 1H), 7.93 (d, *J* = 1.2 Hz, 2H), 7.90 (s, 1H), 7.68 (s, 1H), 7.65 (s, 1H), 7.45 (dd, *J* = 4.8, 8.4 Hz, 2H), 7.20 (t, *J* = 8.4 Hz, 2H), 4.32 (t, *J* = 6.0 Hz, 2H), 3.88 (s, 3H), 3.30 (t, *J* = 6.0 Hz, 2H); ESI-MS: *m/z*, 516.0 (M+1).

(*E*)-N'-[4-{2-(4-Fluorophenylthio)ethoxy}-3-cyano-5-methoxybenzylidene]-4-chlorobenzohydrazide (8.8): Pale yellow solid; Yield: 84 %; m.p.: 131-132 °C; IR (KBr, ν_{max}, cm^{-1}): 3223, 3069, 2955, 2888, 2843, 2237, 1653, 1597, 1551, 1484, 1417, 1377, 1298, 1220, 1168, 1068, 1004, 959, 894, 837, 754, 670, 625; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.09 (s, 1H), 8.41 (s, 1H), 7.95 (d, *J* = 8.0 Hz, 2H), 7.68 (s, 1H), 7.62 (d, *J* = 8.4 Hz, 3H), 7.45 (t, *J* = 8.0 Hz, 2H), 7.20 (t, *J* = 8.0 Hz, 2H), 4.32 (t, *J* = 6.0 Hz, 2H), 3.88 (s, 3H), 3.31 (t, *J* = 6.0 Hz, 2H); ESI-MS: *m/z*, 484.0 (M+1).

(*E*)-N'-[4-{2-(4-Fluorophenylthio)ethoxy}-3-cyano-5-methoxybenzylidene]-2,5-difluorobenzohydrazide (8.9): White solid; Yield: 86 %; m.p.: 88-89 °C; 3262, 3071, 2947, 2231, 1653, 1581, 1549, 1485, 1417, 1369, 1286, 1225, 1188, 1159, 1069, 1003, 962, 903, 853, 819, 782, 752, 699, 662, 625; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.28 (* 12.10, s, 1H), 8.28 (* 8.02, s, 1H), 7.69 (* 7.64, s, 1H), 7.54 (* 7.44, s, 1H), 7.45-7.41 (m, 4H), 7.37 (* 7.33, s, 1H), 7.20 (t, *J* = 9.2 Hz, 2H), 4.32 (* 4.26, t, *J* = 6.4 Hz, 2H), 3.88 (* 3.69, s, 3H), 3.30 (* 3.26, t, *J* = 6.4 Hz, 2H); ESI-MS: *m/z*, 486.0 (M+1).

(*E*)-N'-[4-{2-(4-Fluorophenylthio)ethoxy}-3-cyano-5-methoxybenzylidene]-4-methoxybenzohydrazide (8.10): White solid; Yield: 80 %; m.p.: 117-118 °C; IR (KBr, ν_{max}, cm^{-1}): 2232 (–C≡N str),1740 (C=O str), 1645 (CONH), 1604 (C=N str), 1576 (NH bending), 1486, 146, 1415, 1371, 1295, 1253, 1225, 1176, 1114, 1074, 1030, 995, 950, 903, 833, 756, 707, 622; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.90 (s, 1H), 8.41 (s, 1H), 7.92 (d, *J* = 8.0 Hz, 2H), 7.67 (s, 1H), 7.60 (s, 1H), 7.45 (t, *J* = 8.0 Hz, 2H), 7.20 (t, *J* = 8.0 Hz, 2H), 7.07 (d, *J* = 8.0 Hz, 2H), 4.30 (t, *J* = 6.0 Hz, 2H), 3.88 (s, 3H), 3.84 (s, 3H), 3.30 (t, *J* = 6.0 Hz, 2H); ESI-MS: *m/z*, 484.0 (M+1).

Antibacterial bioassay: The *in vitro* antibacterial activity of the newly synthesized compounds (**8.1** to **8.10**) were screened for the antibacterial activity against several pathogenic representative Gram-positive bacteria (*Staphylococcus aureus*, MTCC 902 and *Bacillus subtilis*, MTCC 441); Gram-negative bacteria (*Escherichia coli*, MTCC 2692 and *Pseudomonas aeruginosa*, MTCC 2453) using disc diffusion sensitivity test [19,20]. Mueller-Hinton agar media were sterilized (15 min at 121 °C) and poured into the plates to a uniform depth of 5 mm and allow it to solidify. The microbial suspension (1.2×10^8 CFU/mL) (0.5 McFarland Nephelometery Standards) was streaked over the surface of media using a sterile cotton swab (15 min at 180 °C) to ensure confluent growth of the organisms. The tested compounds **8.1-8.10** were dissolved in DMSO at 200 μg mL^{-1} concentration. The discs measuring 6.25 mm in diameter (Whatman no. 1 filter paper) were impregnated with prepared solution of compounds (**8.1-8.10**) by 1 mL of the chemical solution which was added to each bottle contained 12 discs and placed on Muller-Hinton agar media previously inoculated with bacterial suspension. The inhibition zones as a criterion for anti-microbial activity were measured in millimeter at the end of an incubation period of 24 h at 37 °C. The results of these evaluations are given in Table-1. Streptomycin was chosen as a standard drug at a concentration of 10 μg mL^{-1}.

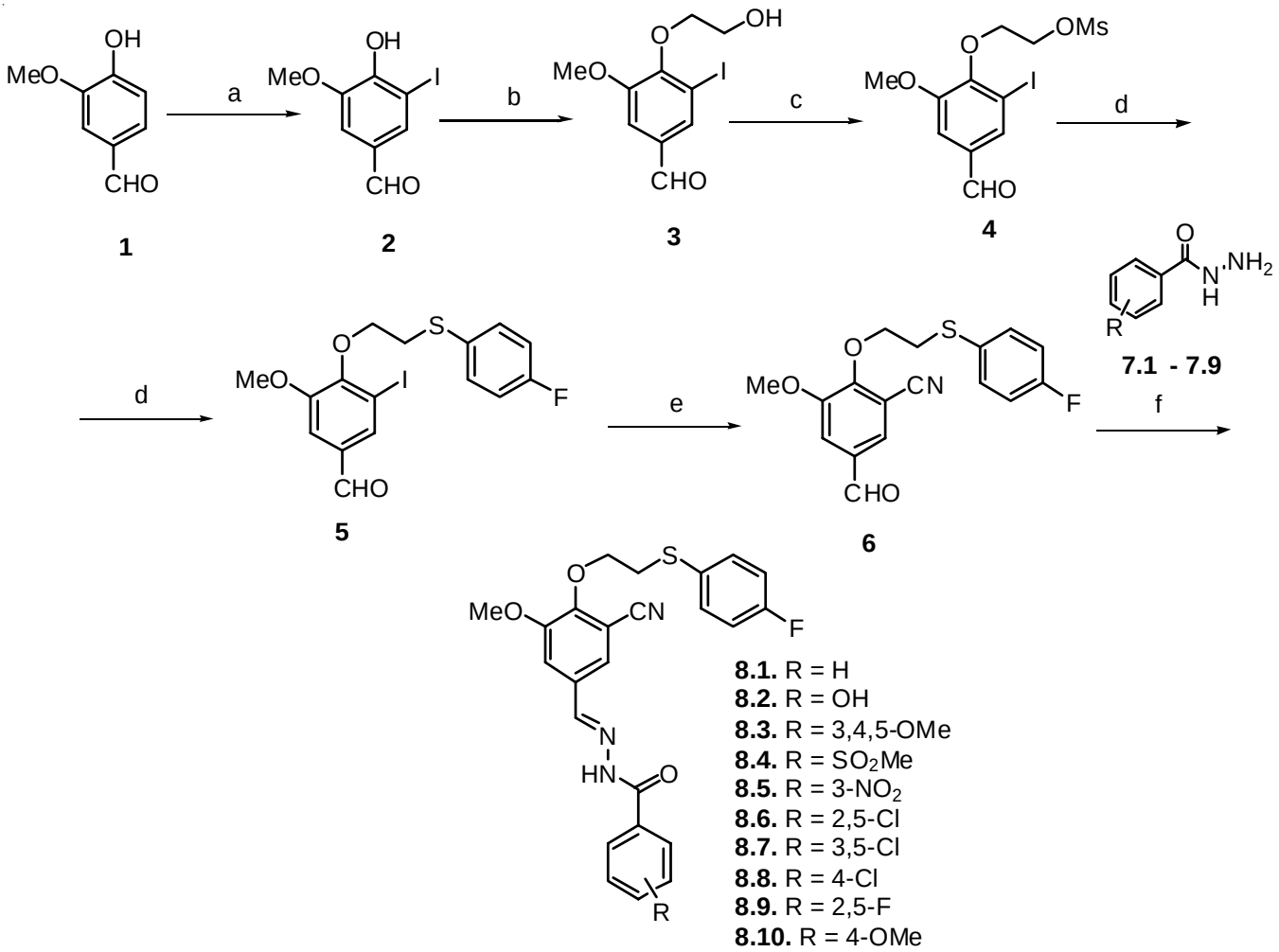
TABLE-1
ANTIBACTERIAL ACTIVITY OF INTERMEDIATES AND COMPOUNDS **8.1- 8.10**

Compd. No.	Zone of inhibition (mm)			
	Gram negative bacteria		Gram positive bacteria	
	E. coli MTCC 2692	*P. aeruginosa* MTCC 2453	*S. aureus* MTCC 902	*B. subtilis* MTCC 441
8.1	6	**1**	11	11
8.2	**13**	**8**	**21**	**21**
8.3	**11**	**6**	**20**	**19**
8.4	**10**	**5**	**18**	**18**
8.5	–	–	7	–
8.6	–	–	5	–
8.7	–	–	5	–
8.8	**4**	**1**	4	–
8.9	**8**	4	15	16
8.10	**8**	4	14	15
[a]Streptomycin	15	10	24	25

[a]Concentration: 10 μg mL^{-1}

RESULTS AND DISCUSSION

The hydrazone derivatives **8.1 to 8.10** were prepared in six steps from commercially available vanillin as starting material (**Scheme-I**). Iodination of vanillin was carried out at room temperature in presence of benzyltrimethylammonium perchloroiodate and $CaCO_3$ to afford 5-iodo vanillin in 90 % yield. This method is superior over the recently reported literature method [21]. Alkylation of 5-iodovanillin in presence of 1-bromoethanol gave 4-(2-hydroxyethoxy)-3-iodo-5-methoxybenzaldehyde **3** in 85 % yield. Reaction of alcohol **3** with methanesulphonyl chloride followed by alkylation with *p*-fluorothiophenol in presence of sodium methoxide gave 4-(2-(4-fluorophenylthio)ethoxy)-3-iodo-5-methoxybenzaldehyde **5** in 80 % yield. Reaction of iodide **5** with cuprous cyanide in DMF at 130-135 °C resulted in 2-(2-(4-fluorophenylthio)ethoxy)-5-formyl-3-methoxybenzonitrile **6** in 94 %



Reaction conditions: a) Benzyltrimethylammonium dichloroiodate, $CaCO_3$, cyclopentylmethyl ether, room temperature, 10 h; b) 1-bromoethanol, K_2CO_3, cyclopentylmethyl ether, reflux, 4 h; c) methanesulphonyl chloride, triethyl amine, cyclopentyl methyl ether, room temperature, 2 h; d) *p*-fluorothiophenol, NaOMe, DMF, room temperature, 5 h; e) CuI, DMF, 130-135 °C, 3 h; f) Benzohydrazides **7.1-7.10**, ethanol, reflux, 1 h

Scheme-I: Synthesis of hydrazone derivatives **8.1** to **8.10**

yield [22,23]. Condensation of aldehyde **6** with substituted benzohydrazides **7.1-7.10** resulted in the formation of (*E*)-N'-[4-{2-(4-fluorophenylthio)-ethoxy}-3-cyano-5-methoxybenzylidene]benzohydrazide derivatives **8.1** to **8.10**. The structural confirmations of all the newly synthesized hydrazone derivatives were confirmed by ^{1}H NMR, mass and IR data. The molecular weight of all the synthesized intermediates and the final compounds is in agreement with the desired molecular formula and also, the IR spectral data has confirmed the presence of the expected functional groups. Furthermore, the ^{1}H NMR spectral data is in accordance with the desired structure. For example, ^{1}H NMR determination of (*E*)-N'-(4-(2-(4-fluorophenylthio)ethoxy)-3-cyano-5-methoxybenzylidene)-3,4,5-trimethoxybenzohydrazide (**8.3**) is described here, the protons resonating at 11.88 ppm, 8.44 ppm corresponds to –CONH, –CH=N- groups and the protons resonating at 7.68, 7.62 and 7.23 ppm is assigned for the benzonitrile ring and 3,45-trimethoxy phenyl ring. The *para*-fluorothiophenol ring protons resonated at 7.45 and 7.19 ppm as doublets, the methylene protons resonated 4.32 and 3.31 ppm as triplets and the methoxylated protons resonated at 3.88, 3.86 and 3.73 ppm, thus confirming the structure of the hydrazone compound **8.3**.

It is noteworthy to mention that hydrazones such as **8.6** (R = 2,5-dichloro) and **8.9** (R = 2,5-difluoro) showed duplication of NMR signals [24-27] and is attributed to the presence of mixture of *anti*- and *syn*-periplanar conformers. The possibility of conformers arises from the increase in rotational barrier due to the decoplanarization of the aromatic ring and carbonyl group (induced by *ortho* substituent) and electron withdrawing nature of aromatic ring [26]. Ratio of signal integration of duplicate peaks of certain proton in ^{1}H NMR spectra of N-acylhydrazones gives the information about the fraction of each conformer in the mixture of hydrazones.

Antibacterial activity: From Table-1, as it can be put forth from the data, the hydrazone compounds bearing R = 4-OH (**8.2**), 3,4,5-OMe (**8.3**) and 4-SO_2Me (**8.4**) substituents has shown the good antibacterial sensitivity, compounds (**8.9**) and (**8.10**) with substituents 2,5-difluoro and 4-OMe, respectively exhibited the moderate while the remaining compounds in the series showed either nil activity or weak activity. The good activity can be ascribed to the presence of groups 4-OH, 4-SO_2Me and 3,4,5-OMe which are directly attached to the phenyl ring of the hydrazone moiety. All the other compounds were found to weak to moderate activities against the tested organisms.

Conclusion

In conclusion, we have prepared some new hydrazone derivatives **8.1** to **8.10** from vanillin as the starting material in seven steps with good yields. The synthesized hydrazones (at 200 μg mL^{-1}) were further screened against Gram-positive bacteria (*Staphylococcus aureus*, MTCC 902 and *Bacillus subtilis*, MTCC 441); Gram-negative bacteria (*Escherichia coli*, MTCC 2692 and *Pseudomonas aeruginosa*, MTCC 2453) using disc diffusion sensitivity. The antibacterial activity data revealed that, the hydrazone compounds bearing R = 4-OH (**8.2**), 3,4,5-OMe (**8.3**) and 4-SO_2Me (**8.4**) substituents has shown the good antibacterial sensitivity, compounds (**8.9**) and (**8.10**) with substituents 2,5-difluoro and 4-OMe, respectively exhibited the moderate while the remaining compounds in the series showed either no activity or weak activity.

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