Synthesis, characterization and antibacterial activity of some new 3-(2-hydroxy-5-methylphenyl)-3-phenylpropanehydrazide-hydrazone derivatives


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ABSTRACT
Tolterodine is a muscarinic receptor antagonist for the treatment of over active bladder including urinary incontinence and is marketed under the trademarks DETROL and DETRUSITOL. The present paper describes the synthesis, characterization and antibacterial activity of ten new hydrazide-hydrazone 5a-5j, from commercially available cinnamic acid and p-cresol. From the results of the antibacterial data, it is observed that compounds 5g, 5h, 5i and 5j with substitution R = 4-NO2, 2-hydroxy, 2-methoxy, 2-methoxy-3-ethoxy and 3,4-diethoxy respectively exhibited excellent antibacterial activity when tested against all the bacterial strains.

Key words: Tolterodine, Cinnamic acid, p-cresol, synthesis, antibacterial activity

INTRODUCTION
Hydrazides and hydrazones have been demonstrated to possess, anticonvulsant, analgesic, antiinflammatory, antiplatelet, antitubercular, and antitumoral activities [1, 2]. Iproniazid, like isoniazid is used in the treatment of tuberculosis (TB) and also showed antidepressant. Another effective hydrazide-hydrazone is nifuroxazide, which is used as an intestinal antiseptic [3, 4].

The antibacterial activity of hydrazine derivatives showed significant potency against various pathogenic bacterial strains [5, 6]. Benzimidazole derivatives with hydrazone moiety [7], chloropyrrole derivatives of aroylhydrazone [8] and some hydrazonoyl substituted
pyrimidinones showed antibacterial activity [9]. Vanillin based hydrazines showed antibacterial activity against *S. aureus* and *P. aeruginosa* [10]. 2-Quinoxalinone-3- hydrazine derivative exhibited antibacterial activities against different bacterial strains [11].

Even though many antibiotics and chemotherapeutics are available, the treatment of bacterial infections still remains a demanding therapeutic problem because of rising infectious diseases and the increasing number of multidrug-resistant microbial pathogens. The emergence of old and new antibiotic-resistant bacterial strains in the last decades constitutes a substantial need for new classes of anti-bacterial agents [12]. The rapid rise in bacterial resistance to the traditional antibiotics such as penicillin’s [13] and tetracycline [14] has encouraged a continuing search for new classes of compounds with novel modes of antibacterial activity.

Tolterodine is a muscarinic receptor antagonist for the treatment of over active bladder including urinary incontinence. It gained its first marketing approval (as the tartrate salt) in 1997 and was launched in many markets under the trademarks DETROL and DETRUSITOL. A process for the production of tolterodine comprises, condensing p-cresol with cinnamic acid resulting a lactone formation [15]. The aim of the present work is to prepare and utilize the lactone 3 (scheme 1) and further transforming it to novel hydrazide-hydrazone derivatives 5a-5j and evaluate for antibacterial activity studies.

**MATERIALS AND METHODS**

Solvents and reagents were obtained from commercial source and used without purification. The IR spectra (\(\nu_{\text{max}}, \text{cm}^{-1}\)) were recorded in solid state KBr dispersion using Perkin Elmer FT-IR spectrometer. The \(^1\)H-NMR spectra was recorded on Varian 500 MHz spectrometer. The chemical shifts were reported in \(\delta/\text{ppm}\) relative to TMS. The mass spectra were recorded on API 2000 Perkin Elmer PE-Sciex mass spectrometer. The reactions were monitored by Thin–layer chromatography (TLC). Melting points were determined on polman melting point apparatus (Model No MP96) by open capillary method and are uncorrected. All the reactions were carried out under nitrogen atmosphere. All the substituted benzaldehydes a-j utilized for the preparation of 5a-4j were purchased from commercial sources.

*Preparation of 3, 4-dihydro-6-methyl-4-phenylchromen-2-one (3)*

A mixture of cinnamic acid (20 g, 0.135 mol), p-cresol (15.32 g, 0.142 mol) and a catalytic amount of conc H\(_2\)SO\(_4\) (4.63 g, 0.0472 mol) was heated to 110˚C for 12 h. After completion of reaction (judged by T.L.C), the reaction mixture was cooled to room temperature and diluted with toluene (2 x 100 mL) and water (100 mL) and stirred for 5 minutes. The aqueous layer and separated and adjusted the
pH to 7.0 - 7.5 using 10% NaHCO₃ (at 0-5°C) and stirred for 1 h at the same temperature. The precipitated solids were filtered and washed with water (100 mL). The crude compound was recrystallized by isopropyl alcohol. White solid, Yield: 27.33 g, 85%; M.P: 48-50°C.

Preparation of 3-(2-hydroxy-5-methylphenyl)-3-phenylpropanehydrazide (4)

To a solution of 3, 4-dihydro-6-methyl-4-phenylchromen-2-one 3 (20 g, 0.084 mol) in methanol (100 mL) was added hydrazine hydrate (12.5 g, 0.252 mol) and heated to 50°C for 5 h. After completion of the reaction (checked by T.L.C), the reaction mixture was cooled to 0-5°C and filtered to obtain the crude compound. The crude compound was dissolved in ethanol (100 mL) at 45°C to get clear solution and cooled to 10°C and filtered at the pump to obtain pure compound 4. White solid, Yield: 16.5 g, 83%. M.p: 192-193°C; IR (KBr): \( \nu_{\text{max}} \) 3313, 3250, 3164, 3053, 3025, 2945, 2924, 2864, 2736, 1747, 1643, 1611, 1539, 1511, 1495, 1452, 1429, 1379, 1366, 1351, 1327, 1273, 1257, 1226, 1206, 1183, 1146, 1101, 1077, 1047, 1029, 1006, 997, 956, 924, 909, 875, 821, 795, 776, 737, 697 \text{ cm}^{-1}; \^1\text{H NMR (400 MHz, DMSO-d}_6\text{)}: \delta 9.09 (s, 1H), 8.97 (s, 1H), 7.22 - 7.21 (m, 4H), 7.09 (t, J = 3.6 Hz, 1H), 6.89 (d, J = 1.2 Hz, 1H), 6.77 (t, J = 1.2 Hz, 1H), 6.62 (d, J = 6.4 Hz, 1H), 6.77 (t, J = 1.2 Hz, 1H), 6.62 (d, J = 6.4 Hz, 1H), 4.80 (dd, J = 5.6, 6.8 Hz, 1H), 4.06 (s, 1H), 2.74 (dd, J = 7.2, 11.6 Hz), 2.65 (dd, J = 6.0, 11.2 Hz), 2.15 (s, 3H); ESI-MS: m/z, 269.1 (M+1).

General Experimental Procedure for the Synthesis of Hydrazones derivatives (5a-5j)

To a suspension of 3-(2-hydroxy-5-methylphenyl)-3-phenylpropanehydrazide (1g, 3.70 mmol) in methanol (10 mL) at 25-27°C was added benzaldehydes (a-j) (0.411 g, 3.80 mmol) and heated to 50°C for 5h. After completion of the reaction (checked by T.L.C), the reaction mixture was cooled to 0-5°C and maintained for 30 min. The precipitated solids were filtered at the pump and dried. The yields of the products varied from 80-88%.

\((E)\)-N’-benzylidene-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanehydrazide (5a)

Yellow solid; Yield: 85%; M.p: 193-194°C; IR (KBr): \( \nu_{\text{max}} \) 3546, 3160, 3059, 3028, 2969, 1639, 1613, 1514, 1493, 1450, 1434, 1409, 1349, 1342, 1314, 1286, 1270, 1251, 1221, 1186, 1157, 1133, 1116, 1078, 1030, 971, 949, 937, 912, 895, 870, 843, 786, 757, 734, 698, 690, 660 cm\(^{-1}\); \^1\text{H NMR (400 MHz, DMSO-d}_6\text{)}: \delta 11.41 (* 11.16, s, 1H), 9.17 (* 9.13, s, 1H), 8.13 (* 7.96, s, 1H), 7.70 (s, 1H), 7.63 (d, J = 6.4 Hz, 1H), 7.44-7.40 (m, 3H), 7.29-7.23 (m, 4H), 7.22 (d, J = 6.4 Hz, 1H), 7.12 (d, J = 6.0 Hz, 1H), 6.97 (d, J = 6.4 Hz, 1H), 6.78 (t, J = 6.0 Hz, 1H), 6.64 (d, J = 6.8 Hz, 1H), 4.93 (* 4.87, t, J = 6.4 Hz, 1H), 3.35 (* 3.33, t, J = 6.4 Hz, 1H), 2.95 (* 2.89, t, J = 6.4 Hz), 2.17 (* 2.10, s, 3H); ESI-MS: m/z, 359.4 (M+1).
(E)-N'-{(2-methoxybenzylidene)-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanehydrazide}

(5b)
White solid; Yield: 88%; M.p: 176-178 °C; IR (KBr): \( \nu_{\text{max}} \) 3541, 3334, 3182, 3080, 3019, 2967, 2930, 2906, 2861, 2838, 2042, 1659, 1743, 1612, 1497, 1485, 1465, 1451, 1435, 1417, 1398, 1350, 1339, 1323, 1304, 1287, 1255, 1226, 1212, 1180, 1164, 1154, 1134, 1102, 1078, 1046, 1028, 975, 956, 906, 896, 884, 871, 846, 836, 790, 753, 709, 677, 657 cm\(^{-1}\); \(^1\)H NMR (400 MHz, DMSO-d\(_6\)): \( \delta \) 11.41 (*11.12, s, 1H), 9.18 (* 9.13, s, 1H), 8.46 (* 8.28, s, 1H), 7.88 (* 7.73, s, 1H), 7.41-7.38 (m, 1H), 7.26-7.20 (m, 4H), 7.11-7.02 (m, 4H), 6.78 (t, J = 8.4 Hz, 1H), 6.65 (t, J = 6.4 Hz, 1H), 4.93 (* 4.86, t, J = 6.2 Hz, 1H), 3.83 (s, 1H), 3.36 (* 3.32, t, J = 6.2 Hz, 1H), 2.92 (* 2.86, t, J = 6.0 Hz, 1H), 2.10 (* 2.08, s, 3H); ESI-MS: m/z, 389.3 (M+1).

(E)-N'-{(4-methoxybenzylidene)-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanehydrazide} (5c)
White solid; Yield: 82%; M.p: 195-196 °C; IR (KBr): \( \nu_{\text{max}} \) 3174, 3084, 3029, 2967, 2932, 2834, 1647, 1610, 1514, 1496, 1451, 1437, 1407, 1349, 1310, 1300, 1250, 1178, 1167, 1117, 1107, 1085, 972, 955, 930, 895, 874, 817, 790, 735, 702, 659 cm\(^{-1}\); \(^1\)H NMR (400 MHz, DMSO-d\(_6\)): \( \delta \) 11.26 (*11.02, s, 1H), 9.15 (* 9.11, s, 1H), 8.06 (* 7.90, d, J = 7.6 Hz, 1H), 7.50 (d, J = 7.6 Hz, 1H), 7.28-7.20 (m, 4H), 7.11 (d, J = 8.8 Hz, 1H), 7.09-6.96 (m, 3H), 6.78 (t, d = 12.4 Hz, 1H), 6.63 (d, J = 6.0 Hz, 1H), 4.94 (* 4.86, t, J = 6.0 Hz, 1H), 3.35 (* 3.31, t, J = 6.0 Hz, 1H), 2.94 (* 2.86, t, J = 6.0 Hz, 1H), 2.16 (* 2.10, s, 3H); ESI-MS: m/z, 389.6 (M+1).

(E)-N'-{(3-chlorobenzylidene)-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanehydrazide} (5d)
White solid; Yield: 84%; M.p: 174-175 °C; IR (KBr): \( \nu_{\text{max}} \) 3578, 3296, 3186, 3088, 3023, 2986, 2910, 2861, 1662, 1604, 1563, 1487, 1464, 1449, 1419, 1397, 1349, 1339, 1323, 1297, 1270, 1230, 1154, 1137, 1112, 1079, 1050, 1031, 952, 940, 906, 895, 883, 872, 821, 791, 751, 736, 727, 699, 663 cm\(^{-1}\); \(^1\)H NMR (400 MHz, DMSO-d\(_6\)): \( \delta \) 11.66 (*11.36, s, 1H), 9.19 (* 9.15, s, 1H), 8.52 (* 8.34, s, 1H), 8.05 (* 7.89, d, J = 7.6 Hz, 1H), 7.50 (d, J = 7.6 Hz, 1H), 7.44-7.39 (m, 2H), 7.27-7.22 (m, 4H), 7.10 (d, J = 6.0 Hz, 1H), 6.98 (s, 1H), 6.78 (t, J = 8.4 Hz, 1H), 6.65 (d, J = 6.4 Hz, 1H), 4.95 (* 4.86, t, J = 6.2 Hz, 1H), 3.34 (* 3.30, t, J = 6.0 Hz, 1H), 3.0 (* 2.96, t, J = 6.2 Hz, 1H), 2.17 (* 2.10, s, 3H); ESI-MS: m/z, 393.2 (M+1).

(E)-N'-{(3-chlorobenzylidene)-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanehydrazide} (5e)
Pale yellow solid; Yield: 88%; M.p: 184-185 °C; IR (KBr): \( \nu_{\text{max}} \) 3582, 3185, 3060, 3029, 2968, 2916, 2859, 1775, 1650, 1609, 1596, 1565, 1496, 1470, 1433, 1405, 1353, 1330, 1292,
1262, 1249, 1236, 1224, 1167, 1138, 1117, 1087, 1077, 1055, 1031, 998, 970, 946, 937, 908, 889, 816, 789, 761, 749, 734, 723, 709, 687 cm\(^{-1}\); \(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta\) 11.55 (*11.27, s, 1H), 9.20 (* 9.14, s, 1H), 8.11 (* 7.93, s, 1H), 7.74 (s,1H), 7.70 (s, 1H), 7.47-7.44 (m, 2H), 7.29-7.23 (m, 4H), 7.29 (d, J = 6.4 Hz, 1H), 7.0 (d, J = 1.2 Hz, 1H), 6.96 (d, J = 1.2 Hz, 1H), 6.78 (d, J = 1.2 Hz, 1H), 6.64 (d, J = 6.2 Hz, 1H), 4.92 (* 4.86, t, J = 6.2 Hz, 1H), 3.36 (* 3.31, t, J = 6.0 Hz, 1H), 3.0 (* 2.96, t, J = 6.0 Hz, 1H), 2.17 (* 2.10, s, 3H); ESI-MS: m/z, 393.4 (M+1).

(E)-N’-(3-bromobenzylidene)-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanehydrazide (5f)

Pale yellow solid; Yield: 88%; M.p: 169-170 °C; IR (KBr): \(v_{\text{max}}\) 3779, 3188, 3059, 3028, 2965, 2918, 2859, 1650, 1608, 1560, 1538, 1496, 1467, 1404, 1353, 1330, 1292, 1262, 1249, 1224, 1167, 1138, 1117, 1087, 1077, 1055, 1031, 998, 970, 946, 937, 908, 889, 816, 789, 761, 749, 734, 723, 709, 687 cm\(^{-1}\); \(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta\) 11.54 (*11.26, s, 1H), 9.17 (* 9.12, s, 1H), 8.09 (* 7.92, s, 1H), 7.88 (d, J = 7.4 Hz, 1H), 7.70-7.58 (m, 1H), 7.26-7.21 (m, 4H), 7.12 (d, J = 6.4 Hz, 1H), 7.0 (d, J = 1.2 Hz, 1H), 6.78 (d, J = 1.2 Hz, 1H), 6.64 (d, J = 6.2 Hz, 1H), 4.96 (* 4.92, t, J = 6.2 Hz, 1H), 3.36 (* 3.34, t, J = 6.0 Hz, 1H), 3.0 (* 2.96, t, J = 6.0 Hz, 1H), 2.17 (* 2.10, s, 3H); ESI-MS: m/z, 438.4 (M+1).

(E)-N’-(4-nitrobenzylidene)-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanehydrazide (5g)

Pale yellow solid; Yield: 82%; M.p: 205-206 °C; IR (KBr): \(v_{\text{max}}\) 3488, 3181, 3029, 2973, 283, 2455, 1666, 1613, 1584, 1509, 1452, 1429, 1387, 1341, 1300, 1285, 1266, 1252, 1229, 1188, 1174, 1147, 1107, 1099, 1025, 958, 940, 921, 865, 851, 838, 816, 748, 699, 674 cm\(^{-1}\); \(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta\) 11.72 (*11.45, s, 1H), 9.19 (* 9.15, s, 1H), 8.09 (* 7.92, s, 1H), 7.88 (d, J = 7.2 Hz, 2H), 8.04 (* 7.90, s, 1H), 7.28-7.22 (m, 4H), 7.12 (s, 1H), 6.96 (d, J = 7.2 Hz, 1H), 6.78 (d, J = 2.2 Hz, 1H), 6.66 (s, 1H), 4.94 (* 4.86, t, J = 6.2 Hz, 1H), 3.35 (* 3.30, t, J = 6.2 Hz, 1H), 2.94 (* 2.86, t, J = 6.2 Hz, 1H), 2.16 (* 2.10, s, 3H); ESI-MS: m/z, 404.6 (M+1).

(E)-N’-(2-hydroxy-3-methoxybenzylidene)-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanehydrazide (5h)

Pale yellow solid; Yield: 80%; M.p: 198-199 °C; IR (KBr): \(v_{\text{max}}\) 3544, 3269, 3064, 3020, 2999, 2940, 2904, 2838, 1700, 1678, 1611, 1579, 1552, 1512, 1495, 1459, 1423, 1374, 1353, 1247, 1209, 1186, 1176, 1167, 1150, 1121, 1093, 1079, 1034, 1007, 969, 956, 947, 899, 858, 836, 818, 782, 754, 735, 712, 695, 657 cm\(^{-1}\); \(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta\) 11.61 (*11.14, s, 1H), 10.76 (* 9.44, s, 1H), 9.17 (* 9.11, s, 1H), 8.32 (* 8.27, s, 1H), 7.28 (* 7.28, d, J = 12.8 Hz, 1H), 7.26-7.21 (m, 4H), 7.12 (d, J = 6.4 Hz, 1H), 7.10-7.06 (m, 2H), 6.99-6.80 (m, 2H), 6.64 (d, J = 6.6 Hz, 1H), 4.92 (* 4.86, t, J = 6.2 Hz, 1H), 3.33 (* 3.30, t, J = 6.2 Hz, 1H), 3.0 (* 2.96, t, J = 6.2 Hz, 1H), 2.16 (* 2.10, s, 3H); ESI-MS: m/z, 405.6 (M+1).
(E)-N’-(4-ethoxy-3-methoxybenzylidene)-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanehydrazide (5i)

White solid; Yield: 84%; M.p: 157-158 °C; IR (KBr): $\nu_{\text{max}}$ 3779, 3182, 3060, 3027, 2977, 2933, 2025, 1641, 1608, 1559, 1538, 1510, 1474, 1451, 1420, 1405, 1351, 1328, 1265, 1235, 1167, 1140, 1033, 948, 921, 889, 816, 788, 755, 735, 699 cm$^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 11.27 (*11.04, s, 1H), 9.16 (* 9.10, s, 1H), 8.03 (* 7.86, s, 1H), 7.28-7.22 (m, 5H), 7.22-7.0 (m, 4H), 6.80 (t, J = 7.6 Hz, 1H), 6.64 (t, J = 6.8 Hz, 1H), 4.96 (* 4.80, t, J = 6.4 Hz, 1H), 4.02 (q, J = 7.2 Hz, 2H), 3.80 (s, 3H), 3.35 (* 3.30, t, J = 6.2 Hz, 1H), 2.94 (*2.86, t, J = 6.2 Hz, 1H), 2.16 (* 2.10, s, 3H), 1.35 (t, J =7.2 Hz, 3H); ESI-MS: m/z, 433.6 (M+1).

(E)-N’-(3, 4-diethoxybenzylidene)-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanehydrazide (5j)

White solid; Yield: 84%; M.p: 160-161 °C; IR (KBr): $\nu_{\text{max}}$ 3180, 3079, 3027, 2979, 2926, 1650, 1578, 1512, 1497, 1474, 1435, 1410, 1392, 1354, 1327, 1264, 1233, 1183, 1141, 1087, 1041, 972, 950, 924, 897, 862, 821, 791, 770, 750, 736, 700 cm$^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 11.26 (*11.04, s, 1H), 9.16 (* 9.10, s, 1H), 8.01 (* 7.85, s, 1H), 7.28-7.22 (m, 5H), 7.22-7.18 (m, 2H), 7.16-7.14 (m, 2H), 6.98 (d, J = 7.6 Hz, 1H), 6.64 (t, J = 6.8 Hz, 1H), 4.94 (* 4.86, t, J = 6.4 Hz, 1H), 4.04 (q, J = 10.4 Hz, 4H), 3.36 (* 3.32, t, J = 6.2 Hz, 1H), 2.94 (* 2.86, t, J = 6.2 Hz, 1H), 2.16 (* 2.10, s, 3H), 1.32 (t, J =10.4 Hz, 6H); ESI-MS: m/z, 445.6 (M+1).

**Antimicrobial Screening**

The antimicrobial activity was determined using disc diffusion method by measuring zone of inhibition in mm [16]. All the compounds, 5a-5j were screened in-vitro at a concentration of 250 μg/mL for antibacterial activity against two Gram-positive pathogenic organisms: *Staphylococcus aureus* and *Staphylococcus pyogenes*, two Gram-negative organisms: *Escherichia coli* and *Pseudomonas aeruginosa* (Table 1). Standard antibacterial drug ciprofloxacin (250 μg/disc) was also tested under similar conditions against these organisms. Each experiment was done in triplicate and the average reading was taken. Growth inhibition was calculated with reference to positive control. Hydrazide-hydrazone (5a – 5j) were dissolved in dimethyl sulphoxide at 250 μg/mL concentration. The inhibition zones were measured in millimeters at the end of an incubation period of 48 hours at (35±2) °C. DMSO alone showed no inhibition. The composition of nutrient agar medium was Bactotryptone (10 g), yeast extract (5 g), NaCl (10 g), final pH 7.4.
RESULTS AND DISCUSSION
The synthesis of ten new hydrazide-hydrazone derivatives is presented as shown in Scheme-1. Condensation of cinnamic acid 1 with p-cresol 2 in presence of catalytic quantity of conc; H₂SO₄ afforded lactone (3,4-dihydro-6-methyl-4-phenylchromen-2-one) 3 in 85% yield. Reaction of lactone 3 with hydrazine hydrate in methanol at 50 °C for 5 h resulted in 3-(2-hydroxy-5-methylphenyl)-3-phenylpropanehydrazone 4 in 83% yield. The structures of compounds 5a-5j were established on the basis of their spectral data. Each compound was characterized by ¹H NMR, IR and mass spectrometry (MS). In the IR spectra, all derivatives (5a-5j) had a strong, characteristic band in the region 1700-1647 cm⁻¹ due to the C=O stretching vibration. The N-H stretching vibration of the compounds (5a - 5j) gave rise to a band at 3488-3180 cm⁻¹. The stretching bands for C=C and C=N groups were observed at 1609-1496 cm⁻¹. In general, the IR stretching frequencies for –OH groups varied for the compounds 5a–5j, observed at 3200-3600 cm⁻¹ (H-bonded) and 3500-3700 cm⁻¹ (free, H-bonded) respectively. In the ¹H NMR spectra of the compounds, all of the aromatic and aliphatic protons were observed at the expected ppm scale. Aromatic protons were observed at about 6.64-8.28 ppm. Because hydrazones exist as couple of diastereoisomers E/Z, [17] – OH, -N-H, -CH=N-N, –CH₃, -CH₂ab, -CHa and –CH₃ protons were observed as couples [18] of peaks at 11.41-11.16 ppm, 9.17-9.13, 8.13-7.96, 4.93-4.87, 3.35-3.33, 2.95-2.87, and 2.95-2.89 respectively. To confirm the identification of each hydrazide-hydrazone 5a-5j, (ESI) MS analysis was performed in the positive ion mode, showing peaks at m/z, corresponding to the expected monoisotopic mass of the [M+H]+ ion.

Reaction Scheme

![Reaction Scheme](image)

**SCHEME-1**: Synthesis of novel hydrazide-hydrazone derivatives 5a – 5j
EXPERIMENTAL CONDITIONS: a) catalytic; conc; H₂SO₄, 110 °C, 12 h; b) hydrazine-hydrate, methanol, 50°C, 5 h; c) Aromatic benzaldehydes a-j, methanol, 50 °C, 5 h.

Antibacterial Activity

The results of the antibacterial data of novel hydrazide-hydrazine derivatives 5a-5j is presented in Table 1. The antibacterial activity was measured in terms of zone of inhibition (ZI, in mm). In case of E.coli and P.aeruginosa, the ZI is classified as excellent activity (ZI: >27-28 mm), good activity (ZI: 21-25 mm) and weak activity (ZI: 9-12 mm), while in case of S.aureus and S.pyogenes, ZI with 23-25 mm, 16-19 mm and 6-8 mm is considered as excellent, good and weak activity respectively. From table-1, it is noteworthy to observe that, in general, compounds 5g, 5h, 5i and 5j with substitution R = 4-NO₂, 2-hydroxy-2-methoxy, 2-methoxy-3-ethoxy and 3,4-diethoxy respectively exhibited excellent antibacterial activity when tested against all the bacterial strains. Compounds 5a (R =H), 5b (R = 2-OMe) and 5c (R = 4-OMe) displayed good antibacterial activity while compounds 5d (R = 2-Cl), 5e (R = 3-Cl) and 5f (R = 3-Br) showed weak antibacterial activity.

Table 1: Antibacterial activity data of novel hydrazide-hydrazine derivatives (5a-5j)

<table>
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<th>Compound no.</th>
<th>R</th>
<th>E. coli MTCC 443</th>
<th>P. aeruginosa MTCC 424</th>
<th>S.aureus MTCC 96</th>
<th>S.pyogenes MTCC 442</th>
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<td>9</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>5g</td>
<td>4-NO₂</td>
<td>30</td>
<td>29</td>
<td>24</td>
<td>25</td>
</tr>
<tr>
<td>5h</td>
<td>2-OH- 2-OMe</td>
<td>31</td>
<td>30</td>
<td>25</td>
<td>23</td>
</tr>
<tr>
<td>5i</td>
<td>2-OMe- 3-OEt</td>
<td>29</td>
<td>29</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>5j</td>
<td>3,4-OEt</td>
<td>30</td>
<td>28</td>
<td>23</td>
<td>24</td>
</tr>
<tr>
<td>SD* Ciprofloxacin (Conc. 250 μg/mL)</td>
<td>--</td>
<td>28</td>
<td>27</td>
<td>22</td>
<td>22</td>
</tr>
</tbody>
</table>
CONCLUSION

In conclusion, we have synthesized, characterized and evaluated ten new hydrazide-hydrazone derivatives 5a-5j, from one of the key intermediate used for the preparation of Tolterodine drug. The antibacterial activity data revealed that compounds 5g, 5h, 5i and 5j R = 4-NO2, 2-hydroxy- 2-methoxy, 2-methoxy- 3-ethoxy and 3,4-dithoxy respectively exhibited excellent antibacterial activity when tested against all the bacterial strains (Staphylococcus aureus and Staphylococcus pyogenes, two Gram-negative organisms: Escherichia coli and Pseudomonas aeruginosa).

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REFERENCES

