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Synthesis, characterisation and antibacterial evaluation of chalcone derivatives linked with 2-trifluoromethyl furan

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ABSTRACT

*The present paper describes the synthesis and antibacterial activity of 2-trifluoromethyl furan chalcones **7a-7r** against a panel of two Gram-positive strains (Staphylococcus aureus and Streptococcus pyogenes) and two Gram-negative strains (Escherichia coli and Pseudomonas aeruginosa). The structures of the synthesized chalcones derivatives **7a-7r** and its related intermediate compounds were confirmed by ^{1}H NMR, Mass and IR spectral data. Claisen-Schmidt reaction of compound **6** with various aromatic and hetroaromatic aldehydes **a-r** was carried out by grinding (mortal and pestle) compound **6** in presence of NaOH at room temperature for 3-5 min resulting in the formation of chalcone derivatives **7a-7r**. Within the series of chalcone derivatives, compounds **7p**, **7q** and **7r**, exhibited excellent antibacterial activity (++++), while the compounds **7f**, **7i**, **7k**, **7l**, **7m**, **7n** showed good antibacterial activity (+++).*

Keywords: Antibacterial activity, Apocynin, Green methods, Synthesis

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INTRODUCTION

Chalcones and its derivatives have fascinated medicinal chemist due to numerous pharmacological applications. They have been reported to exert a broad spectrum of pharmacological activities which include, antioxidant [2-4], anti-inflammatory [5-6], antimalarial [7-10], antiprotozoal (antileishmanial and antitrypanosomal) [11], antibacterial [12, 13], antifilarial [14], antifungal [15, 16], antimicrobial [17], larvicidal [18], anticonvulsant [19], and anticancer [20-24] activities.

Resistance to antimicrobial drugs has become an increasingly important global problem [25, 26]. Structural modification of resistant antimicrobial drugs has proven to be an effective means of extending the lifespan of antifungal antiviral and antibacterial agents such as azoles, non-nucleoside reverse transcriptase inhibitors [26] and lactams & quinolones [27], respectively. Broad empirical screening of chemical entities for antimicrobial activity represents a strategy for the development of novel drugs.

Encouraged by the various pharmacological profiles of chalcones and in continuation to our work in search of novel antibacterial activity [28], we report here in the synthesis and antibacterial activity of certain chalcone derivatives bearing 2-trifluoromethylfuran moiety against a panel of two Gram-positive strains (*Staphylococcus aureus* and *Streptococcus pyogenes*) and two Gram-negative strains (*Escherichia coli* and *Pseudomonas aeruginosa*). Furthermore, the present paper describes the synthesis of chalcones and its associated intermediates utilizing green methods.

MATERIALS AND METHODS

The solvents were purified according to standard procedures prior to use, and all commercial chemicals were used as received. For thin-layer chromatography (TLC) analysis, Merck pre-coated Plates (silica gel 60 F254) were used and spots were visualized with UV light. Merck silica gel 60 (230-400 mesh) was used for flash column chromatography and the eluting solvents are indicated in the procedures. Melting point (mp) determinations were performed by using Mel-temp apparatus and are uncorrected. ^{1}H NMR spectra were recorded on Varian MR-400 MHz instrument. Chemical shifts are reported in δ parts per million (ppm) downfield from with reference to tetramethylsilane (TMS) internal standard and the signals were reported as s (singlet), d (doublet), dd (doublet of doublet), t (triplet), q (quartet), m (multiplet) and coupling constants in Hz. The mass spectra were recorded on Agilent ion trap MS. Infrared (IR) spectra were recorded on a Perkin Elmer FT-IR spectrometer.

Preparation of ethyl 2-(2,2,2-trifluoroacetyl)-4-oxopentanoate (2)

To a stirred suspension of NaH (60%, 65.20 mmol.), Ethyl 4,,4,4-trifluoro acetoacetate (10 g, 54.32 mmol) in 2-methyltetrahydrofuran (30 mL) and chloroacetone (6g, 0.065 mol) were added at 75 ^{o}C. The reaction mixture was refluxed for 18 h. After completion of the reaction (judged by TLC), the reaction mixture was cooled to room temperature and quenched with saturated NH_4Cl solution. It was then extracted with isopropyl acetate (2 x 10mL). The organic layer was separated and washed with water (2x15 mL) followed by brine solution (15 mL). It was dried over Na_2SO_4, filtered and evaporated under reduced pressure to obtain pale yellow oily liquid. Yield: 50%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.38 (d, *J* = 5.6 Hz, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 3.38 (dd, *J* = 2.6 Hz, 5.6 Hz, 1H), 3.18 (d, *J* = 5.6 Hz, 1H), 2.20 (s, 3H), 1.30 (t, *J* = 7.2 Hz, 3H).

Preparation of 2-(trifluoromethyl)-5-methylfuran-3-carboxylic acid (3)

To a stirred solution of methanesulphonic acid (10% w/w) in acetic acid (15 mL) compound **3** (3.55g, 14.80 mmol) was added and refluxed for 24 h at 110° C. The reaction mixture was cooled to room temperature. Sodium bicarbonate (1g)was added to it followed by water (15 mL) and extraction with 2-methyl tetrahydrofuran (2 x 20 mL). The combined organic layer was separated, washed with brine solution and evaporated under reduced pressure to obtain the crude compound which was taken to the next step without further purification. To the above reaction mixture, methanol (20 mL) and water (10 mL) were added followed by NaOH (0.88g, 22 mmol). It was then heated to 70 ^{o}C for 3h. The organic layer was separated and evaporated under reduced pressure and further diluted with water. The aqueous reaction mixture was cooled to 15-20 ^{o}C and acidified to pH<2 using conc. HCl to obtain pale yellow solid. The precipitated solids was further washed with Hexane and dried under vacuum at 60 ^{o}C. Yield: 99%; M.R. 153-154 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.5 (br.s, 1H), 6.60 (s, 1H), 2.38 (s, 3H).

Preparation of 2-(trifluoromethyl)-5-methylfuran (4)

A mixture of compound **3** (2g, 10.30 mmol.), copper sulphate (100 mg) in NMP (4 mL) , and 4A ^{o} molecular sieves (20% w/w) were heated in a sealed tube at 150 ^{o}C for 45 min to isolate compound **4**. Yield: 1.35g, 95%.

Preparation of 2-(bromomethyl)-5-(trifluoromethyl)furan (5)

To a stirred solution of compound **4** (1.58 g, 10.52 mmol.) in chloroform (8 mL), 1,3-DBH (1,3-dibromo-5,5-dimethylhydantoin) (11.24 mmol.) followed by AIBN (0.86g, 5.24 mmol) was added and heated to 65 ^{o}C for 30 min. The reaction mixture was filtered and the organic layer was washed with water (2x 15 mL) followed by brine solution. It was dried over Na_2SO_4, filtered and evaporated under reduced pressure to obtain the crude compound **5**. Vacuum distillation of the crude compound yielded the pure bromide derivative **5**. Yield: 1.2g, 50%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.78 (s, 1H), 6.52 (s, 1H), 4.50 (s, 2H).

Preparation of 1-(4-((5-(trifluoromethyl)furan-2-yl)methoxy)-3-methoxyphenyl)ethanone (6)

To a stirred solution of compound **5** (1.2 eq.) and apocynin (1g, 6.02 mmol) in [bmim][PF_6] (4.15 mL) was added a pre-mixed solution of NaOH (17.90 mmol) in water (9.0 mL) . The reaction mixture was vigorously stirred at room temperature for 36 h in a sealed tube. The progress of the reaction was followed by TLC (eluent: n-hexane/ethyl acetate, 80:20). The reaction mixture was extracted with cyclopentyl methylether (5 x 3 mL). The combined organic phases were dried over $MgSO_4$, filtered & evaporated in *vacuo*. The residue was passed through a small flash chromatography and compound **6 was** isolated**.** Yield: 82%. Yellow solid; Yield: 85%; M.R.: 107-108 ^{o}C; IR (KBr): υ_{max} 3103, 3072, 1681, 1587, 1568, 1512, 1471, 1456, 1419, 1382, 1360, 1338, 1315, 1268, 1218, 1179, 1129, 1103, 1084, 1023, 1000, 964, 933, 905, 881, 832, 804, 732, 682 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.58 (s, 2 H), 7.0 (d, *J* = 7.2 Hz, 1 H), 6.80 (s, 1H), 6.56 (s, 1H), 5.20 (s, 2 H), 3.98 (s, 3H), 2.58 (s, 3H); ESI-MS: m/z, 314.99 (M+1).

General Experimental Procedure for the Synthesis of Chalcone derivatives (7a-7r)

A mixture of compound **6** (100mg, 0.32 mmol), aromatic / heteroaromatic aldehyde **a-r** (0.32 mmol), and sodium

hydroxide (1.28 mmol) was thoroughly ground with a pestle in an open mortar at room temperature for 3-5 min until the mixture transformed into a syrupy liquid. The initial syrupy reaction mixture solidified within 3–5 min. Grindingwas continued for 5–8 min more, and the reaction was monitored by TLC. The solid was washed with cold water to remove the sodium hydroxide and recrystallized from ethanol to give the corresponding chalcone derivatives. Yields of the products varied between 88 and 94%.

(E)-1-(4-((5-(trifluoromethyl)furan-2-yl)methoxy)-3-methoxyphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (7a):
White solid; M.p.: 117-118 ^{o}C; Yield: 79%; IR (KBr): υ_{max} 2937, 2049, 1653, 1595, 1571, 1508, 1463, 1421, 1347, 1373, 1318, 1251, 1161, 1146, 1105, 1129, 1022, 987, 966, 934, 825, 794, 741, 695 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.86 (m, 3H), 7.76 (s, 1H), 7.65 (s, 1H), 7.62 (s, 1H), 7.25 (s, 1H), 7.00 (d, 2H, *J* = 8.0 Hz), 6.82 (s, 1H), 5.27 (s, 2H), 3.81 (s, 6H); ESI-MS: m/z (rel.abund.%) 433.23 (M+,100).

(E)-1-(4-((5-(trifluoromethyl)furan-2-yl)methoxy)-3-methoxyphenyl)-3-(2,4-dimethoxyphenyl)prop-2-en-1-one (7b):
Pale yellow solid; M.p: 112-113 ^{o}C; Yield: 86%; IR (KBr): υ_{max} 2997, 1651, 1596, 1567, 1502, 1466, 1420, 1390, 1372, 1327, 1299, 1232, 1255, 1200, 1162, 1147, 1110, 1057, 1028, 998, 954, 935, 882, 831, 802, 750, 731, 693 cm^{-1}; ^{1} H NMR (400 MHz, DMSO-d_6): δ 8.02 (d, J = 12.4 Hz, 1H), 7.63-7.52 (m, 4H), 7.00 (d, J = 6.0 Hz, 1H), 6.75 (s, 1H), 6.54-6.48 (m, 3H), 5.18 (s, 2H), 3.92 (s, 3H), 3.90 (s, 3H), 3.86 (s, 3H); ESI-MS: m/z (rel.abund.%) 463.16 (M+, 100).

(E)-1-(4-((5-(trifluoromethyl)furan-2-yl)methoxy)-3-methoxyphenyl)-3-(2,5-dimethoxyphenyl)prop-2-en-1-one (7c):
Yellow solid; M.p: 128-129 ^{o}C; Yield: 82%; IR (KBr): υ_{max} 3146, 3078, 2935, 2837, 2603, 2516, 1649, 1599, 1575, 1514, 1504, 1460, 1414, 1382, 1319, 1261, 1236, 1207, 1171, 1146, 1121, 1103, 1055, 1031, 1009, 978, 960, 933, 917, 870, 851, 841, 820, 799, 747, 718, 699, 660 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.10- 7.75 (m, 3H), 7.50 (d, J = 16 Hz, 2H), 7.3 (s, 2H), 7.10 (s, 2H), 6.80 (s, 1H), 5.30 (s, 2H), 3.90 (s, 6H); ESI-MS: m/z (rel.abund.%) 463.16 (M+,100).

(E)-1-(4-((5-(trifluoromethyl)furan-2-yl)methoxy)-3-methoxyphenyl)-3-(2,6-dimethoxyphenyl)prop-2-en-1-one (7d):
Yellow solid; M.p: 118-119 ^{o}C; Yield: 86%; IR (KBr): υ_{max} 3114, 2943, 1649, 1595, 1573, 1512, 1476, 1466, 1418, 1390, 1376, 1320, 1297, 1277, 1234, 1196, 1162, 1146, 1120, 1106, 1029, 990, 959, 933, 888, 858, 829, 811, 727, 743 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.22 (d, 1H, J = 12.4 Hz), 7.96 (d, J = 12.4 Hz, 1H), 7.65 (s, 2H), 7.26 (d, J = 12.4 Hz, 1H), 6.77 (s, 1H), 6.59-6.52 (m, 3H), 5.17 (s, 2H), 3.92 (s, 3H), 3.83 (s, 3H); ESI-MS: m/z (rel.abund.%) 463.0 (M+,100).

(E)-1-(4-((5-(trifluoromethyl)furan-2-yl)methoxy)-3-methoxyphenyl)-3-(3,4-dimethoxyphenyl)prop-2-en-1-one (7e):
Yellow solid; M.p: 105-106 ^{o}C; Yield: 80%; IR (KBr): υ_{max} 3107, 3002, 2939, 2848, 2604, 1656, 1569, 1512, 1462, 1421, 1377, 1341, 1317, 1284, 1258, 1119, 1104, 1013, 976, 960, 934, 914, 834, 809, 791, 767, 734 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.90 - 6.80 (m, 10H), 5.30 (s, 2H), 3.90 (s, 9H); ESI-MS: m/z (rel.abund.%) 463.16 (M+,100).

E)-1-(4-((5-(trifluoromethyl)furan-2-yl)methoxy)-3-methoxyphenyl)-3-(3,4,5-dimethoxyphenyl)prop-2-en-1-one (7f):
White solid; M.p: 142-143 ^{o}C; Yield: 85%; IR (KBr): υ_{max} 3501, 3115, 3009, 2940, 2844, 1653, 1581, 1504, 1455, 1419, 1373, 1350, 1318, 1275, 1243, 1258, 1171, 1147, 1119, 1025, 1002, 934, 801, 733, 676 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.0 - 7.80 (m, 2H), 7.60-7.56 (m, 2H), 7.35-7.20 (m, 4H), 6.80 (s, 1H), 5.30 (s, 2H), 3.90 (s, 9H), 3.70 (s, 3H); ESI-MS: m/z (rel.abund.%) 493.16 (M+,100).

(E)-1-(4-((5-(trifluoromethyl)furan-2-yl)methoxy)-3-methoxyphenyl)-3-(4-ethoxy-3-methoxyphenyl)prop-2-en-1-one (7g):
Yellow solid; M.p: 129-130 ^{o}C; Yield: 86%; IR (KBr): υ_{max} 3111, 2941, 1656, 1592, 1571, 1513, 1463, 1421, 1392, 1370, 1339, 1318, 1257, 1234, 1196, 1177, 1162, 1146, 1131, 1119, 1028, 1013, 976, 961, 912, 934, 881, 849, 834, 807, 791, 733, 719 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.74 (d, 1H, J = 12.4 Hz), 7.64 (s, 2H), 7.37 (d, J = 12.4 Hz, 1H), 7.26-7.21 (m, 3H), 7.02 (d, J = 6.4 Hz, 1H), 6.88 (d, J = 6.4 Hz, 1H), 6.77 (s, 1H), 6.52 (s, 1H), 5.18 (s, 2H), 4.16 (q, 2H, J = 5.2 Hz), 3.94 (s, 6H), 1.54 (t, J = 5.2 Hz, 3H); ESI-MS: m/z (rel.abund.%) 477.0 (M+,100).

(E)-1-(4-((5-(trifluoromethyl)furan-2-yl)methoxy)-3-methoxyphenyl)-3-(3-methoxy-4-propoxyphenyl)prop-2-en-1-one (7h):
Brown solid; M.p: 122-124 ^{o}C; Yield: 78%; IR (KBr): υ_{max} 3112, 2941, 2872, 1652, 1594, 1582, 1569, 1511, 1466, 1417, 1380, 1349, 1323, 1263, 1246, 1232, 1201, 1165, 1129, 1119, 1108, 1021, 971, 961, 935, 866, 838, 822, 797, 767, 735, 724 cm^{-1};^{1}H NMR (400 MHz, DMSO-d_6): δ 7.98- 7.30 (m, 8H), 6.95 (d, J = 15 Hz, 2H), 5.3 (s, 2H), 3.99 (t, J = 7.2 Hz, 2H), 3.87 (s, 6H), 1.70-1.68 (m, 2H), 1.09 (t, J = 7.0, 3H); ESI-MS: m/z (rel.abund.%) 491.18 (M+,100).

(E)-1-(4-((5-(trifluoromethyl)furan-2-yl)methoxy)-3-methoxyphenyl)-3-(2-hydroxy-3-methoxyphenyl)prop-2-en-1-one (7i):
Pale Brown solid; M.p.: 136-137^{o}C; Yield: 83%; IR (KBr): υ_{max} 3374, 2920, 2943, 1648, 1575, 1512, 1480, 1418, 1439, 1361, 1315, 1257, 1175, 1150, 1127, 1107, 1074, 1026, 1006, 963, 935, 841, 805, 776, 732, 712 cm^{-1};^{1}H NMR (400 MHz, DMSO-d_6): δ 8.0 (d, J = 15.5 Hz, 1H), 7.73 (d, J = 15.5 Hz, 1H), 7.66 (d, J = 7.0 Hz, 2H), 7.26 (s, 1H), 7.19 (s, 1H), 7.02- 6.89 (m, 3H), 6.77 (s, 1H), 6.52 (br, 1H), 5.18 (s, 2H), 3.95-3.93 (s, 6H); ESI-MS: m/z (rel.abund.%) 449.16 (M+,100).

(E)-1-(4-((5-(trifluoromethyl)furan-2-yl)methoxy)-3-methoxyphenyl)-3-(3-chlorophenyl)prop-2-en-1-one (7j):
White solid; M.p.: 110-111 ^{o}C; Yield: 83%; IR (KBr): υ_{max} 3114, 2943, 1655, 16050, 1592, 1572, 1513, 1479, 1467, 1410, 1381, 1349, 1323, 1302, 1278, 1262, 1246, 1201, 1177, 1163, 1131, 1106, 965, 984, 892, 878, 840, 826, 812, 782, 736, 691, 670 cm^{-1};^{1}H NMR (400 MHz, DMSO-d_6): δ 8.05 (d, J = 8.0 Hz, 1H), 8.02 (s, 1H), 7.94 (d, J = 8.0 Hz, 1H), 7.82 (d, J = 6.0 Hz, 1H), 7.48-7.46 (m, 2H), 7.46 (d, J = 7.0 Hz, 2H), 7.26 (d, J = 9.5 Hz, 2H), 6.87 (s, 1H), 5.29 (s, 2H), 3.85 (s, 3H); ESI-MS: m/z (rel.abund.%) 437.19 (M+,100).

(E)-1-(4-((5-(trifluoromethyl)furan-2-yl)methoxy)-3-methoxyphenyl)-3-(2-nitrophenyl)prop-2-en-1-one (7k):
Pale yellow solid; M.p.: 125-126 ^{o}C; Yield: 77%; IR (KBr): υ_{max} 3114, 2941, 1797, 1655, 1593, 1574, 1517, 1464, 1414, 1389, 1379, 1341, 1276, 1263, 1170, 1128, 1100, 1023, 1003, 933, 872, 837, 813, 755, 736, 711, 676 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.27 (d, J = 7.0 Hz, 2H), 8.14-8.12 (m, 3H), 7.85 (d, J = 8.0 Hz, 1H), 7.77 (d, J = 15.0 Hz, 1H), 7.64 (s, 1H), 7.25 (d, J = 8.0 Hz, 2H), 6.87 (s, 1H), 5.29 (s, 2H), 3.86 (s, 3H); ESI-MS: m/z (rel.abund.%) 448.19 (M+,100).

(E)-1-(4-((5-(trifluoromethyl)furan-2-yl)methoxy)-3-methoxyphenyl)-3-(4-nitrophenyl)prop-2-en-1-one (7l):
Yellow solid; M.p: 127-128 ^{o}C; Yield: 87%; IR (KBr): υ_{max} 3120, 2944, 2618, 2449, 2219, 1655, 1574, 1594, 1517, 1415, 1378, 1341, 1263, 1276, 1169, 1318, 975, 933, 837, 769, 736,676 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.76 (d, J = 15 Hz, 2H), 8.65 – 8.60 (m, 3H), 7.98 (d, J = 7 Hz, 1H), 7.76 (d, J = 15 Hz, 1H), 7.60-7.58 (m, 2H), 6.80 (s, 1H), 5.03 (s, 2H), 3.90 (s, 3H); ESI-MS: m/z (rel.abund.%) 448.16 (M+,100).

(E)-1-(4-((5-(trifluoromethyl)furan-2-yl)methoxy)-3-methoxyphenyl)-3-(4-(dimethylamino)phenyl)prop-2-en-1-one (7m):
Pale Brown solid; M.p: 134-135 ^{o}C; Yield: 84%; IR (KBr): υ_{max} 3030, 2893, 2802, 2557, 2077, 1871, 1644, 1584, 1510, 1352, 1323, 1262, 1164, 1104, 996, 934, 828, 728, 704 cm^{-1};^{1}H NMR (400 MHz, DMSO-d_6): δ 7.90 (d, J = 7.0 Hz, 2H), 7.80-7.60 (m, 5H), 7.03 (s, 2H), 6.90 (s, 1H), 6.70 (d, J = 7.0 Hz, 2H), 5.20 (s, 2H), 3.89 (s, 3H), 3.20 (s, 6H); ESI-MS: m/z (rel.abund.%) 446.18 (M+,100).

(E)-1-(4-((5-(trifluoromethyl)furan-2-yl)methoxy)-3-methoxyphenyl)-3-(4-(methylsulfonyl)phenyl)prop-2-en-1-one (7n):
White solid; M.p.: 100-101 ^{o}C; Yield: 80%; IR (KBr): υ_{max} 3001, 1652, 1599, 1565, 1505, 1467, 1421, 1392, 1331, 1321, 1301, 1257, 1202, 1164, 1148, 1108, 1060, 1025, 986, 932, 830, 804, 753 cm^{-1};^{1}H NMR (400 MHz, DMSO-d_6): δ 8.00 (d, 2H, *J* = 10.8 Hz), 7.86-7.82 (m, 3H), 7.66-7.54 (, 3H), 7.06 (d, 1H, *J* = 6.4 Hz), 6.78 (s, 1H), 6.52 (d, 1H, *J* = 10.0 Hz), 5.20 (s, 2H), 3.96 (s, 3H), 3.09 (s, 3H); ESI-MS: m/z (rel.abund.%) 480.8 (M+,100).

N-(4-((E)-3-(4-((5-(trifluoromethyl)furan-2-yl)methoxy)-3-methoxyphenyl)-3-oxoprop-1-enyl)phenyl)acetamide (7o):
Pale Yellow solid; M.p.: 124-125^{o}C; Yield: 76%; IR (KBr): υ_{max} 3345, 3111, 2231, 1689, 1645, 1595, 1567, 1512, 1468, 1411, 1355, 1316, 1282, 1219, 1167, 1158, 1125, 1099, 1028, 1003, 975, 934, 873, 824, 805, 755, 742, 692, 661 cm^{-1};^{1}H NMR (400 MHz, DMSO-d_6): δ 7.75 (d, J = 15.5 Hz, 1H), 7.60 (d, J = 15.0 Hz, 1H), 7.48-7.33 (m, 4H), 7.03 (s, 1H), 6.77 (s, 1H), 6.55 (s, 1H), 5.18 (s, 2H), 3.95 (s, 3H), 2.21 (s, 3H); ESI-MS: m/z (rel.abund.%) 460.17 (M+,100).

(E)-1-(4-((5-(trifluoromethyl)furan-2-yl)methoxy)-3-methoxyphenyl)-3-(5-methylfuran-2-yl)prop-2-en-1-one (7p):
Pale Yellow solid; M.p: 112-113 ^{o}C; Yield: 75%; IR (KBr): υ_{max} 3138, 2932, 1681, 1655, 1587, 1511, 1453, 1419, 1390, 1316, 1265, 1219, 1176, 1126, 1104, 1023, 1002, 962, 934, 906, 873, 805, 761cm^{-1};^{1}H NMR (400 MHz, DMSO-d_6): δ 7.74 (t, J = 8.0 Hz, 1H), 7.55 (s, 1H), 7.49 (d, J = 9.5 Hz, 2H), 7.25 (d, J = 8.0 Hz, 2H), 6.98 (d, J = 3.5 Hz, 1H), 6.85 (d, *J* = 3.5 Hz, 1H,), 6.32 (d, J = 2.5 Hz, 1H), 5.27 (s, 2H), 3.84 (s, 3H), 2.37 (s, 3H); ESI-MS: m/z (rel.abund.%) 407.19 (M+,100).

(E)-1-(4-((5-(trifluoromethyl)furan-2-yl)methoxy)-3-methoxyphenyl)-3-(benzofuran-2-yl)prop-2-en-1-one (7q):
Yellow solid; M.p.: 104-105^{o}C; Yield: 96%; IR (KBr): υ_{max} 3112, 1655, 1596, 1574, 1509, 1467, 1450, 1420, 1354, 1316, 1265, 1235, 1124, 1103, 1026, 1001, 965, 934, 801, 786, 734, 691 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.72 (s, 1H), 8.076 (s, 2H), 7.86-7.55 (m, 8H), 7.26 (s, 1H), 7.04 (s, 1H), 6.78 (s, 1H), 6.53 (s, 1H), 5.18 (s, 2H), 3.97 (s, 3H); ESI-MS: m/z (rel.abund.%) 443.17 (M+,100).

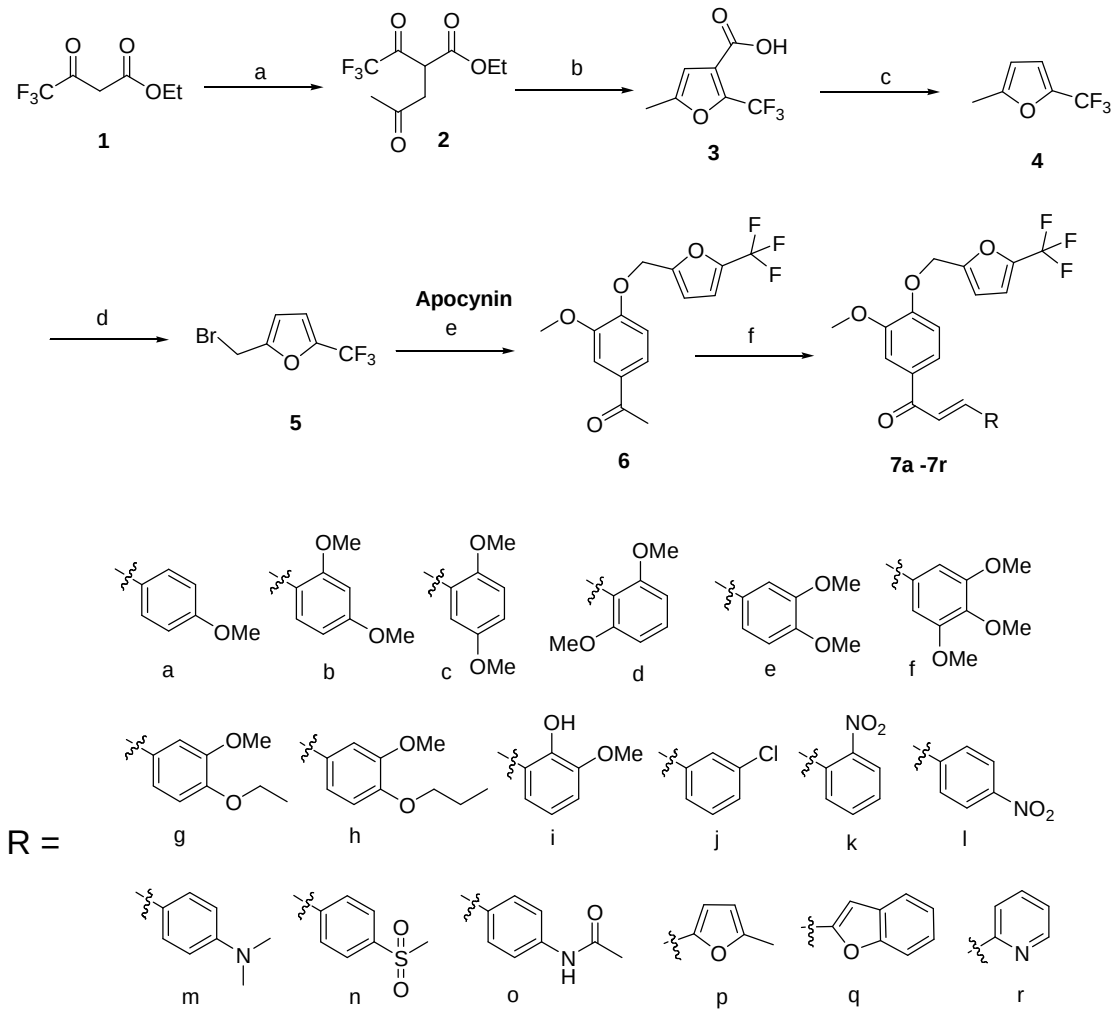
(E)-1-(4-((5-(trifluoromethyl)furan-2-yl)methoxy)-3-methoxyphenyl)-3-(pyridin-2-yl)prop-2-en-1-one (7r):
Pale Yellow solid; M.p.: 124-125^{o}C; Yield: 76%; IR (KBr): υ_{max} 3113, 1653, 1600, 1573, 1512, 1468, 1434, 1408, 1349, 1325, 1279, 1203, 1171, 1134, 1109, 1023, 1007, 972, 962, 935, 873, 835, 810, 775, 736, 726, 694 cm^{-1};^{1}H NMR (400 MHz, DMSO-d_6): δ 7.75 (dd, J = 1.6, 6.8 Hz, 3H), 7.71 (d, J = 1.2 Hz, 1H), 7.68 (s, 1H), 7.62 (d, J = 6.0 Hz, 1H), 7.52 (d, J = 6.4 Hz, 1H), 7.40 (s, 1H), 7.26 (d, J = 8.0 Hz, 1H), 7.04 (d, J = 8.0 Hz, 1H), 6.78 (s, 1H), 6.54 (s, 1H), 5.18 (s, 2H), 3.97 (s, 3H); ESI-MS: m/z (rel.abund.%) 480.21 (M+,100).

***In-vitro* Antibacterial Assay**
The antimicrobial activity of the synthesized chalcone derivatives was determined using disc diffusion method by measuring zone of inhibition in mm [29]. They were screened *in-vitro* (at a concentration: 10 µg/disc) for antibacterial activity against a panel of two Gram-positive strains (*Staphylococcus aureus* and *Streptococcus pyogenes*) and two Gram-negative strains (*Escherichia coli* and *Pseudomonas aeruginosa*). Standard antibacterial drug ciprofloxacin (10µg/disc) were also tested under similar conditions against these organisms. Each experiment was done in triplicate and the average reading was taken. The antibacterial activity was classified as, **weak activity** (+, ZI< 10 - 12 mm), **good activity** (**++,** ZI = 12 - 19 mm), **moderate activity** (**+++,** ZI = 20 – 25 mm)**; excellent activity** (++++, ZI = 25 – 30 mm). The results of antibacterial activity are expressed in terms of zone of inhibition and presented in **Table 1**.

RESULTS AND DISCUSSION

Chemistry
Condensation of 1,3-diketone with chloroacetone in presence of NaH in 2-Methyl tetrahydrofuran and refluxing for 18 h resulted in the formation of compound **2**. Cyclization of compound **2** was done by refluxing for 24 h in 2-Methyltetrahydrofuran in presence of methanesulphonic acid followed by base hydrolysis resulting in 2-(trifluoromethyl)-5-methylfuran-3-carboxylic acid **3.** The de-carboxylation of compound **3** in presence of copper sulphate, molecular sieves in NMP at 150 ^{o}C for 45 min in sealed tube gave rise to 2-(trifluoromethyl)-5-methylfuran **4**. Treatment of compound **4** with 1,3-DBH (1,3-Dibromo-5,5-dimethyl hydantoin), AIBN in $CHCl_3$ at 65 ^{o}C for 30 min gave bromide derivative **5**. Coupling of bromide derivative **5** with apocynin (3-methoxy-4-hydroxy-acetophenone) in presence of NaOH in [bmim][PF_6] gave acetophenone derivative **6**. Claisen-Schmidt reaction of compound **6** with various aromatic and hetroaromatic aldehydes **a-r** was carried out by grinding (mortar and pestle) compound **6** in presence of NaOH at room temperature for 3-5 min resulted in the formation of chalcone derivatives **7a-7r**. The reaction scheme associated with the chalcone derivatives **7a-7r** is depicted in Scheme **1.** During the course of the synthesis of chalcone derivative, successful attempts were made utilizing green reaction conditions and during this process some green solvents such as 2-Methyltetrahydrofuran and RTIL's were used [30-32]. The structures of the synthesized chalcones derivatives **7a-7r** and its related intermediate compounds were confirmed by ^{1}H NMR, Mass and IR spectral data.

***In vitro* Antibacterial Activity**
The results of the antibacterial activity of chalcone derivatives is presented in **Table-I**. Compounds **7p**, **7q** and **7r** exhibited excellent antibacterial activity (++++), while the compounds **7f**, **7i**, **7k**, **7l**, **7m**, **7n** showed good antibacterial activity (+++) and the compounds **7b**, **7c**, **7d**, **7e**, **7o** displayed moderate antibacterial activity (++). The remaining compounds in the series *viz.*, **7g**, **7h**, **7a** and **7j** either showed weak antibacterial activity or nil antibacterial actively respectively.



Scheme 1: Synthesis of chalcone derivatives 7a-7r

Reaction conditions: *a) chloroacetone, NaH, 2-Methyltetrahydrofuran, reflux, 18 h; b) (i) methanesulphonic acid (10% w/w), 2-Methyltetrahydrofuran, reflux, 24 h; ii) NaOH, H_2O, Ethanol, 70 ^oC, 3 h; c) NMP, Copper sulphate, 4A^o molecular sieves, 150 ^oC, 45 min; d) 1,3-DBH (1,3-Dibromo-5,5-dimethyl hydantoin), AIBN, $CHCl_3$, 65 ^oC, 30 min; e)* ***apocynin****, [bmim][PF_6], NaOH, water, room temperature, 36 h ; f) Grinding, NaOH, benzaldyhydes (**a-t**), r.t., 5-8 min.*

Table I- Antibacterial Activity of the synthesized compounds 7a-r

Compound No	Gram negative bacteria		Gram positive bacteria	
	E.coli MTCC 443	*P.aeruginosa MTCC 424*	*S.aureus MTCC 96*	*S.pyogenes MTCC 442*
	Zone of inhibition in mm (ZI)			
7a	-	-	-	-
7b	++	++	++	++
7c	++	++	++	++
7d	++	++	++	++
7e	++	++	++	++
7f	+++	+++	+++	+++
7g	+	+	+	+
7h	+	+	+	+
7i	+++	+++	+++	+++
7j	-	-	-	-
7k	+++	+++	+++	+++
7l	+++	+++	+++	+++
7m	+++	+++	+++	+++
7n	+++	+++	+++	+++
7o	++	++	++	++
7p	++++	++++	++++	++++
7q	++++	++++	++++	++++
7r	++++	++++	++++	++++
Ciprofloxacin	28	25	26	26
Control (DMSO)	-	-	-	-

-: no activity; +: weak activity (ZI< 10 - 12 mm); ++: good activity (ZI = 12 - 19 mm) ; +++: moderate activity (ZI = 20 – 25 mm); ++++: excellent activity (ZI = 25 – 30 mm)

CONCLUSION

In summary, the present paper reports the synthesis, characterization and antibacterial activity of new chalcone derivatives 7a-7t, synthesized by coupling 2-(bromomethyl)-5-(trifluoromethyl)furan **5** and apocynin**.** The results of the antibacterial activity of chalcone derivatives revealed that compounds **7p**, **7q** and **7r** exhibited excellent antibacterial activity (++++), while the compounds **7f**, **7i**, **7k**, **7l**, **7m**, **7n** showed good antibacterial activity (+++).

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