Available online at www.joac.info

ISSN: 2278-1862

Journal of Applicable Chemistry

2014, 3 (3):1260-1267

(International Peer Reviewed Journal)

Synthesis and Antimicrobial Activity of Novel Chalcone Analogues Bearing 2-Furan Trifluoromethyl Ring

M.Rajasekhar[1*], T.S.V. Prasad Reddy[1] and Anima Sunil Dadhich[1]

1. Department of Chemistry, Institute of Science, GITAM University, Visakhapatnam- 530045, A.P., **INDIA**

Email: sai.rajsekhar.m@gmail.com

Accepted on 20th May 2014

ABSTRACT

Synthetic fluorinated chalcones have been found to exhibit several pharmacological activities, including: antioxidant and anticancer activity, NO inhibition, tropomycin-related kinase B (TrkB) brain imaging, antibacterial activity. The present paper describes the synthesis, characterization and antibacterial activity of novel chalcone derivatives ***7a-7m*** *prepared from commercially available key starting materials such as Ethyl 4,,4,4-trifluoro acetoacetate and 3-methoxy-4-hydroxy acetophenone. All the compounds,* ***7a-7m*** *were screened in-vitro (at a concentration: 10 µg/disc) for their antibacterial activity against two Gram-positive strains (Staphylococcus aureus and Bacillus subtilis) and two Gram-negative strains (Escherichia coli and Pseudomonas aeruginosa). Results of the antibacterial data revealed that among all the compounds tested, compound* ***7d*** *to* ***7h*** *showed excellent activity, while compounds* ***7c, 7i, 7j*** *and* ***7k*** *displayed good activity against all the tested bacteria.*

Keywords: Antibacterial Activity, Synthesis, 3-methoxy-4-hydroxy acetophenone, ethyl 2,2,2-trifluoroacetate .

INTRODUCTION

Chalcones constitute an important class of natural products belonging to the flavonoid family. Chemically, chalcones are 1, 3-diphenylpropenones in which the two aromatic rings are connected by third carbon α, β-unsaturated carbonyl system [1]. Natural occurring or synthetic chalcones have been found to exhibit several pharmacological activities [2], including: anti-inflammatory, antioxidant, cytotoxicity, antimicrobial, analgesic, antipyretic, ant malarial and anti-allergic activities [3]. This wide-range of biological properties is mainly attributed to the, *β*-unsaturated ketone moiety [3]. Synthetic fluorinated chalcones have been found to exhibit several pharmacological activities [4], including: antioxidant and anticancer activity [5,6], NO inhibition [7], tropomycin-related kinase B(TrkB) [8] brain imaging and antibacterial activity [9].

Several antibiotics have been prescribed and found to be effective on various infectious disorders. However, the appearance of multidrug resistant Gram-positive bacteria, in particular, methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant Enterococci (VRE) are causing a serious menace. As pathogenic bacteria continuously evolve mechanisms of resistance to currently use antibacterial drugs, the discovery of novel and potent antibacterial agents is the best way to overcome

bacterial resistance and develop effective therapies [10]. Some other references referred are [12-16]. The present study was designed to synthesize novel chalcone derivatives bearing 2-trifluoro methyl furan ring and evaluate its anti-bacterial activity.

MATERIALS AND METHODS

Chemical and solvents used were purchased either from Fluka or Merck. All the reagents were of analytical grade. Thin-layer chromatography (TLC) was performed on E.Merck AL silica gel 60 F254 plates and visualized under UV light. IR spectra were recorded as KBr pellet with a PerkinElmer spectrum gx-FTIR instrument and only diagnostic and/or intense peaks are reported. ^{1}H NMR spectra were recorded in DMSO- d_6 with a Varian Mercury plus 400 MHz instrument. ^{13}C NMR spectra were recorded in DMSO- d_6 with a Varian Gemini 100 MHz instrument. Signals due to the solvent (^{13}C NMR) or residual protonated solvent (^{1}H NMR) served as the internal standard. All the chemical shifts were reported in δ (ppm) using TMS as an internal standard. . The ^{1}H NMR chemical shifts and coupling constants were determined assuming first-order behavior. Multiplicity is indicated by one or more of the following: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad); the list of coupling constants (*J*) corresponds to the order of multiplicity assignment. Mass spectra were recorded with a PE Sciex model API 3000 instrument. All the reactions were carried out under argon atmosphere.

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 1,2-dimethoxy ethane (30 mL) was added chloroacetone (6g, 0.065 mol) at 75^{o}C. The reaction mixture was heated to 90 ^{o}C for 20 h. After completion of the reaction (judged by TLC), the reaction mixture was cooled to room temperature and quenched with saturated NH_4Cl solution and extracted with isopropyl acetate (2 x 10mL). The organic layer was separated and washed with water (2x15 mL) followed by brine solution (15 mL), dried over Na_2SO_4, filtered and evaporated and 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);

2-(trifluoromethyl)-5-methylfuran-3-carboxylic acid 3: To a stirred solution of p-toluene sulphonamide monohydrate (582 mg, 3.06 mmol.) in toluene (20 mL) at 110 ^{o}C (and azeaotroped to remove water) was added a pre-mixed solution of compound **3** (3.55g, 14.80 mmol) in toluene and heated to reflux for 17 h. The reaction mixture was cooled to room temperature, added sodium bicarbonate (1g) followed by water (15 mL) and extracted with toluene (2 x 20 mL). The combined organic layer was separated and washed with brine solution and taken to the next step without isolation. To the above reaction mixture was added methanol (20 mL), water (10 mL) followed by NaOH (0.88g, 22 mmol.) and 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).

2-(trifluoromethyl)-5-methylfuran 4: A mixture of compound **3** (2g, 10.30 mmol.), copper sulphate (100 mg) in NMP (4 mL) was heated to 150 ^{o}C for 2 h and concomitantly distilled to isolate compound **4**. Yield: 1.35g, 95%.

2-(bromomethyl)-5-(trifluoromethyl)furan 5: To a stirred solution of compound **4** (1.58 g, 10.52 mmol.) in chloroform (8 mL) was added NBS (2 g, 11.24 mmol.) followed by AIBN (0.86g, 5.24 mmol.) and heated to 65 ^{o}C for 2h. The reaction mixture was filtered and the organic layer was washed with water (2x 15 mL) followed by brine solution, 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).

1-(4-((5-(trifluoromethyl)furan-2-yl)methoxy)-3-methoxyphenyl)ethanone 6: To a solution of apocynin (1g, 6.02 mmol.) in DMF (7 mL) was added potassium carbonate (1 g, 7.23 mmol.) followed by compound **5** (1.45 g, 6.32 mmol.) at room temperature. The reaction mixture was heated to 80 ^{o}C for 3 h. The reaction mixture was cooled to room temperature and diluted with ethylacetate (25 mL), the organic layer was washed with water (2 x 25 mL) followed by brine solution (15 mL). The organic layer was separated, dried over anhydrous sodium sulphate, filtered and evaporated under reduced pressure to obtain the crude compound. The crude compound was purified by column chromatography (6 % EtOAc in n-Hexane), yielding the compound **7**. 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-7m) : To a stirred solution of methanol containing compound **6** (100 mg, 0.32 mmol.) was added sodium hydroxide (52 mg, 1.28 mmol.) followed by various fluorinated benzaldehydes (1.90 mmol.) and the contents were stirred at room temperatures for 5 h. The reaction mixture was diluted with water and the precipitated solids were filtered at the pump, washed with water followed by pet-ether to obtain the pure compounds. Yields of the products varied between 88 and 94%.

(E)-1-(4-((5-(trifluoromethyl)furan-2-yl)methoxy)-3-methoxyphenyl)-3-(4-chlorophenyl)prop-2-en-1-one (7a): Yellow solid; Yield: 90%; M.R: 97-98 ^{o}C; IR (KBr): υ_{max} 3112, 1654, 1602, 1591, 1576, 1513, 1490, 1465, 1407, 1381, 1349, 1323, 1274, 1261, 1245, 1202, 1179, 1168, 1038, 1023, 1003, 961, 935, 848, 806, 775, 736, 688 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.80 (d, *J* = 12.6 Hz, 1 H), 7.68 (d, *J* = 5.8 Hz, 2 H), 7.58 (d, *J* = 6.0 Hz, 2 H), 7.54 (d, *J* = 15.8 Hz, 1 H), 7.08 (d, *J* = 7.2 Hz, 1 H), 6.80 (s, 1H), 6.56 (s, 1H), 5.20 (s, 2 H), 3.98 (s, 3H).

(E)-1-(4-((5-(trifluoromethyl)furan-2-yl)methoxy)-3-methoxyphenyl)-3-(4-bromophenyl)prop-2-en-1-one (7b): Yellow solid; Yield: 90%; M.R: 111-112 ^{o}C; IR (KBr): υ_{max} 3110, 2942, 1655, 1603, 1575, 1588, 1564, 1513, 1487, 1465, 1402, 1382, 1348, 1324, 1293, 1274, 1203, 1181, 1169, 1132, 1072, 1024, 1006, 970, 962, 934, 847, 836, 805, 772, 736, 684, 655 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.80 (d, *J* = 12.4 Hz, 1 H), 7.68 (d, *J* = 5.8 Hz, 2 H), 7.58-7.50 (m, 5H), 7.08 (d, *J* = 7.2 Hz, 1 H), 6.80 (s, 1H), 6.58 (s, 1H), 5.20 (s, 2 H), 3.98 (s, 3H); ESI-MS: m/z, 481 (M+1), 483 (M+2).

(E)-1-(4-((5-(trifluoromethyl)furan-2-yl)methoxy)-3-methoxyphenyl)-3-(4-Fluorophenyl)prop-2-en-1-one (7c): Yellow solid; Yield: 92%; M.R: 101-108 ^{o}C; IR (KBr): υ_{max} 2943, 1655, 1574, 1594, 1508, 1466, 1414, 1382, 1350, 1323, 1278, 1263, 1236, 1202, 1171, 1130, 1104, 1024, 1004, 971, 934, 963, 808, 738, 689 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.80 (d, *J* = 12.4 Hz, 1 H), 7.65-7.64 (m, 4H), 7.48 (d, *J* = 12.4 Hz, 1 H), 7.13-7.10 (m, 2H), 7.04 (d, *J* = 6.4 Hz, 1H), 6.78 (s, 1H), 6.54 (s, 1H), 5.20 (s, 2 H), 3.98 (s, 3H); ESI-MS: m/z, 421.1 (M+1).

(E)-1-(4-((5-(trifluoromethyl)furan-2-yl)methoxy)-3-methoxyphenyl)-3-(2-(trifluoro methyl) phenyl) prop-2-en-1-one (7d): Pale yellow solid; Yield: 88%; M.R: 98-100 ^{o}C; IR (KBr): υ_{max} 3122, 1655, 1591, 1576, 1513, 1488, 1419, 1381, 1349, 1312, 1277, 1202, 1162, 1102, 1038, 1022, 1004, 973, 961, 934, 828, 813, 794, 759 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.12 (d, *J* = 15.6 Hz, 1H), 7.81 (d, *J* = 7.6 Hz, 1H), 7.72 (d, J = 7.6 Hz, 1H), 7.63-7.59 (m, 3H), 7.59-7.48 (m, 1H), 7.42 (d, *J* = 15.6 Hz, 1H), 7.03 (d, *J* = 4. 4 Hz, 1H), 6.78 (d, *J* = 3.4 Hz, 1H), 6.53 (d, *J* = 3.2 Hz, 1H), 5.20 (s, 1H), 3.95 (s, 3H); ESI-MS: m/z, 471.04 (M+1).

(E)-1-(4-((5-(trifluoromethyl)furan-2-yl)methoxy)-3-methoxyphenyl)-3-(3-(trifluoromethyl)phenyl) prop-2-en-1-one (7e): Yellow solid; Yield: 90%; M.R: 106-107 ^{o}C; IR (KBr): υ_{max} 2943, 1657, 1605, 1593, 1574, 1466, 1380, 1351, 1337, 1321, 1277, 1246, 1218, 1163, 1126, 1105, 1037, 1022, 1005, 969, 934, 843, 816, 736, 692 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.89 (s, 1H), 7.82-7.78 (m, 2H), 7.54-7.48 (m, 2H), 7.04 (d, *J* = 8.0 Hz, 1H), 6.78 (d, *J* = 3.6 Hz, 1H), 6.54 (d, *J* = 3.2 Hz, 1H), 5.20 (s, 2H), 3.97 (s, 3H); ESI-MS: m/z, 471.04 (M+1).

(E)-1-(4-((5-(trifluoromethyl)furan-2-yl)methoxy)-3-methoxyphenyl)-3-(4-(trifluoromethyl)phenyl) prop-2-en-1-one (7f): Pale yellow solid; Yield: 90%; M.R: 100-103 ^{o}C; IR (KBr): υ_{max} 1658, 1606, 1576, 1513, 1468, 1424, 1409, 1355, 1321, 1273, 1205, 1163, 1100, 1068, 1038, 1023, 1005, 965, 935, 830, 811, 744 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.82-7.57 (m, 8H), 7.04 (d, *J* = 8.0 Hz, 1H), 6.78 (d, *J* = 3.2 Hz, 1H), 6.53 (d, *J* = 5.2 Hz, 1H), 5.20 (s, 2H), 3.96 (s, 3H); ESI-MS: m/z, 471.0 (M+1).

(E)-1-(4-((5-(trifluoromethyl)furan-2-yl)methoxy)-3-methoxyphenyl)-3-(4-(trifluoromethoxy)phenyl) prop-2-en-1-one (7g): Yellow solid; Yield: 89%; M.R: 119-120 ^{o}C; IR (KBr): υ_{max} 3111, 1603, 1574, 1507, 1467, 1419, 1380, 1351, 1326, 1258, 1218, 1200, 1161, 1106, 1023, 1004, 972, 961, 935, 813, 802, 762, 737, 691 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.80 (d, *J* = 12.4 Hz, 1 H), 7.68-7.65 (m, 4H), 7.50 (d, *J* = 12.4 Hz, 1 H), 7.26 (d, *J* = 6.0 Hz, 1H), 7.03 (d, *J* = 6.4 Hz, 1H), 6.78 (s, 1H), 6.54 (s, 1H), 5.20 (s, 2 H), 3.98 (s, 3H); ESI-MS: m/z, 487.1 (M+1).

(E)-1-(4-((5-(trifluoromethyl)furan-2-yl)methoxy)-3-methoxyphenyl)-3-(4-(difluoromethoxy)phenyl) prop-2-en-1-one (7h): Pale yellow solid; Yield: 88%; M.R: 97-98 ^{o}C; IR (KBr): υ_{max} 1665, 1601, 1574, 1508, 1467, 1422, 1380, 1352, 1308, 1324, 1279, 1240, 1202, 1176, 1125, 1103, 1037, 1003, 972, 962, 847, 764, 736, 691, 659 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.76 (d, *J* = 15.2 Hz, 1H), 7.66-7.63 (m, 4H), 7.50 (d, *J* = 15.6 Hz, 1H), 7.16 (d, *J* = 8.8 Hz, 2H), 7.02 (d, *J* = 9.2 Hz, 1H), 6.68 (d, *J* = 3.2 Hz, 1H), 6.56 (d, *J* = 3.4 Hz, 1H), 5.20 (s, 2H), 3.98 (s, 3H); ESI-MS: m/z, 468.94 (M^{+1}).

(E)-1-(4-((5-(trifluoromethyl)furan-2-yl)methoxy)-3-methoxyphenyl)-3-(2,4-difluorophenyl)prop-2-en-1-one (7i): Pale yellow solid; Yield: 94%; M.R: 122-123 ^{o}C; IR (KBr): υ_{max} 2944, 1655, 1597, 1574, 1466, 1409, 1351,1323, 1271, 1243, 1209, 1176, 1129, 1103, 1023, 1003, 969, 935, 880, 843, 779, 692 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.81 (d, *J* = 15.6 Hz, 1H), 7.66-7.57 (m, 4H), 7.52-7.42 (m, 2H), 7.04-6.88 (m, 3H), 6.88 (d, *J* = 3.4 Hz, 1H), 6.53 (d, *J* = 5.2 Hz, 1H), 5.20 (s, 2H), 3.96 (s, 3H); ESI-MS: m/z, 439.93 (M^{+1}).

(E)-1-(4-((5-(trifluoromethyl)furan-2-yl)methoxy)-3-methoxyphenyl)-3-(2,6-difluorophenyl)prop-2-en-1-one (7j): Yellow solid; Yield: 94%; M.R: 124-125 ^{c}o; IR (Ker): m_{ix} 3122, 1654, 1601, 1589, 1573, 1513, 1463, 1379, 1348, 1322, 1292, 1269, 1245, 1200, 1174, 1119, 1106, 1024, 1003, 979, 963, 935, 848, 835, 811, 782, 742, 728, 693 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.91-7.82 (m, 2H), 7.66-7.63 (m, 2H), 7.36-7.31 (m, 1H), 7.04-7.02 (m, 3H), 6.78 (s, 1H), 6.54 (s, 1H), 5.20 (s, 2 H), 3.98 (s, 3H); ESI-MS: m/z, 439.05 (M+1).

(E)-1-(4-((5-(trifluoromethyl)furan-2-yl)methoxy)-3-methoxyphenyl)-3-(3,4-difluorophenyl)prop-2-en-1-one (7k): Pale yellow solid; Yield: 90%; M.R: 116-117 ^{o}C; IR (KBr): υ_{max} 2942, 1655, 1597, 1574, 1466, 1409, 1351,1323, 1271, 1243, 1209, 1176, 1129, 1103, 1023, 1003, 969, 935, 880, 843, 779, 692 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.68 (d, *J* = 15.6 Hz, 1H), 7.65-7.54 (m, 2H), 7.52-7.42 (m, 2H), 7.38-7.32 (m, 1H), 7.28-7.18 (m, 1H), 7.04 (d, *J* = 8.0 Hz, 1H), 6.80 (d, *J* = 3.6 Hz, 1H), 6.56 (d, *J* = 3.2 Hz, 1H), 5.20 (s, 2H), 3.97 (s, 3H); ESI-MS: m/z, 439.05 (M^{+1}).

(E)-1-(4-((5-(trifluoromethyl)furan-2-yl)methoxy)-3-methoxyphenyl)-3-(5-bromo-2-fluorophenyl) prop-2-en-1-one (7l): Yellow solid; Yield: 88%; M.R: 122-123 ^{o}C; IR (KBr): υ_{max} 1657, 1599, 1576, 1513, 1470, 1424, 1355, 1263, 1166, 1125, 1102, 1078, 1038, 1024, 1001, 982, 934, 840, 816, 802, 742

cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.82-7.58 (m, 2H), 7.66-7.59 (m, 3H), 7.52-7.46 (m, 1H), 7.06-7.01 (m, 2H), 6.78 (d, *J* = 3.2 Hz, 1H), 6.54 (d, *J* = 5.2 Hz, 1H), 5.20 (s, 2H), 3.98 (s, 3H); ESI-MS: m/z, 498.89 (M^{+1}).

(E)-1-(4-((5-(trifluoromethyl)furan-2-yl)methoxy)-3-methoxyphenyl)-3-(2-chloro-3-(trifluoromethyl) phenyl) prop-2-en-1-one (7m): Yellow solid; Yield: 92%; M.R: 117-118 ^oC; IR (KBr): υ_{max} 2942, 1654, 1602, 1573, 1514, 1466, 1422, 1380, 1351, 1320, 1268, 1240, 1203, 1164, 1128, 1102, 1048, 1036, 1021, 1003, 963, 934, 898, 846, 766, 735, 705, 690 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 8.22 (d, *J* = 15.2 Hz, 1H), 7.88 (d, *J* = 7.2 Hz, 1H), 7.74 (d, *J* = 7.2 Hz, 1H), 7.64-7.62 (m, 2H), 7.42-7.48 (m, 2H), 7.02 (d, *J* = 8.2 Hz, 1H), 6.78 (d, *J* = 3.2 Hz, 1H), 6.54 (d, *J* = 3.4 Hz, 1H), 5.20 (s, 2H), 3.96 (s, 3H); ESI-MS: m/z, 504.95 (M+1).

Antimicrobial activity: The antimicrobial activity was determined using disc diffusion method by measuring zone of inhibition in mm [11]. All the compounds, **7a-7m** were screened *in-vitro* (at a concentration: 10 μg/mL) for their antibacterial activity against two Gram-positive strains (*Staphylococcus aureus* and *Bacillus subtilis*) and two Gram-negative strains (*Escherichia coli* and *Pseudomonas aeruginosa*). Standard antibacterial drug ciprofloxacin (10μg/mL) 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 highly active (≥25 mm), moderately active (12-24 mm) and least active (<11 mm). The results of antibacterial activity are expressed in terms of zone of inhibition and presented in **Table 1**.

Table 1. Results of Antibacterial Evaluation of Hydrazone derivatives **7a – 7m**

Compound[a]	R	Zone of inhibition (mm)			
		E.coli	*P.aeruginosa*	*S.aureus*	*B.subtilis*
7a	4-Cl	-	-	-	-
7b	4-Br	-	-	-	-
7c	4-F	22	24	23	22
7d	2-CF_3	27	25	25	25
7e	3-CF_3	26	25	25	25
7f	4-CF_3	25	26	25	26
7g	4-OCF_3	27	25	25	26
7h	4-$OCHF_2$	25	25	25	25
7i	2,4-di-Fluoro	19	18	21	19
7j	3,4-di-Fluoro	20	21	20	21
7k	2,6-di-Fluoro	22	22	21	20
7l	2-Fluoro-5-Bromo	11	10	11	9
7m	2-Chloro-3-CF_3	11	11	10	10
Ciprofloxacin		28	25	26	26

--: no activity

RESULTS AND DISCUSSION

Chemistry: Condensation of 1,3-diketone with chloroacetone in presence of NaH in ethyleneglycol dimethylether resulted in the formation of coupled product **2**. Cyclization of compound **2** in toluene in presence of p-TSA produced 2-(trifluoromethyl)-5-methylfuran-3-carboxylic acid **3**, which upon hydrolysis and de-carboxylation gave 2-(trifluoromethyl)-5-methylfuran **4**. Bromination of compound **4** using NBS in chloroform in presence of AIBN gave bromide derivative **5**. Coupling of bromide derivative **5** with apocynin (3-methoxy-4-hydroxy-acetophenone) gave subsequent acetophenone derivative **6**. Claisen-Schmidt reaction of compound **6** with various fluorinated benzaldehydes in presence of NaOH in

methanol resulted in the formation of novel chalcone analogues **7a-7m**. The reaction scheme associated with these novel chalcone derivatives **7a-7m** is depicted in Scheme **1.** The structures of the synthesized chalcones derivatives **7a-7m** and its related intermediate compounds were confirmed by ^{1}H NMR, Mass and IR spectral data.

As a representative example, the ^{1}H NMR spectrum of the key intermediate, 1-(4-((5-(trifluoromethyl)furan-2-yl)methoxy)-3-methoxyphenyl)ethanone **6** indicated the following signals: the singlets at 2.58 ppm, 3.98 ppm and 5.20 ppm indicated the presence of a methyl, methoxy and a methylene (-CH_2) group respectively, while the presence of the following signals at 7.58 ppm (singlet, 2H), 7.0 ppm (doublet, 1H), 6.80 pp (singlet, 1H) and 6.56 (singlet, 1H) corresponds to apocynin and furan ring. The mass spectral data of the key intermediate **6** also confirms the expected structure [Molecular weight, 314.99 (M+1)] correlating to ^{1}H NMR data. All the other aromatic protons were observed at expected regions. Furthermore, the formation of chalcone derivatives **7a-7m** is confirmed by ^{1}H NMR, Mass and IR data. As an example, the absence of characteristic signal at 2.58 ppm (in intermediate **6**) and formation of the prominent oelifin functional group –CH=CH-, two doublets with coupling constant: J = 12.4 Hz, confirms the desired chalcone derivative 7c. All the other aromatic and aliphatic are found to be in the expected region.

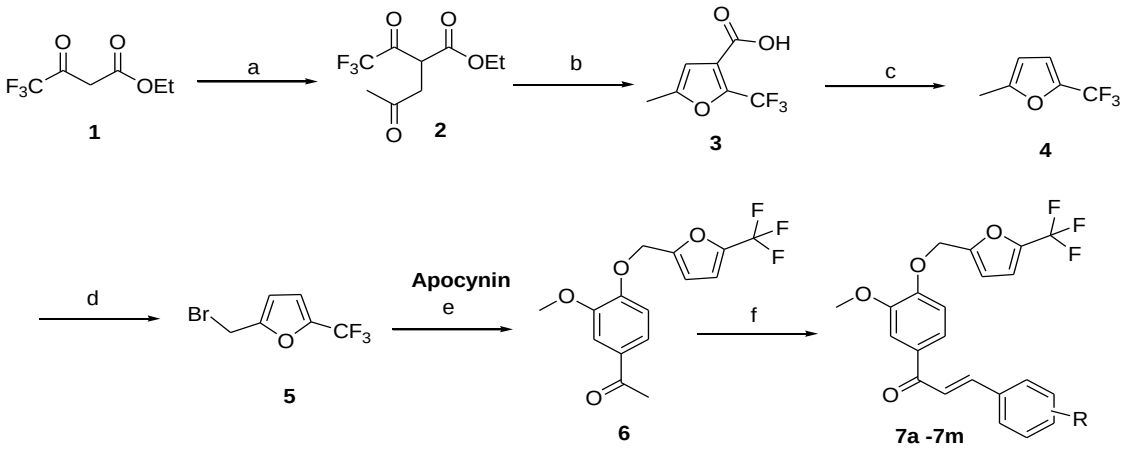
In Vitro Antibacterial Activity: The newly synthesized compounds were tested to evaluate their antibacterial activity. All these compounds were found to exhibit excellent to moderate antibacterial activity against different species of bacteria. From the activity data (**Table 1**) it was observed that among all the compounds tested, compound **7d** to **7h** showed excellent activity, while compounds 7**c, 7i, 7j** and **7k** displayed good activity against all the tested bacteria. Among the other compounds **7l, 7m** showed weak activity whiles the compounds **7a** and **7b** indicated no bacterial activity against all the tested pathogens. Mode of action of antibacterial activity of these compounds **7a-7m** is still uncertain and further exploration in this regard is the future scope of the work.

APPLICATIONS

The newly synthesized chalcone derivatives **7a-7m** was screened for their antibacterial activity and the results revealed that most of the compounds showed encouraging antibacterial activity. Thus, these chalcone analogs can be further evaluated for various desired biological activities.

CONCLUSIONS

The present paper reports the synthesis of newly prepared chalcone derivatives **7a-7m** and was screened *in-vitro* (at a concentration: 10 µg/mL) for their antibacterial activity against the bacterial strains viz., *Staphylococcus aureus, Bacillus subtilis, Escherichia coli* and *Pseudomonas aeruginosa*. The results of the antibacterial data revealed that compound **7d** to **7h** showed excellent activity, while compounds 7**c, 7i, 7j** and **7k** displayed good activity against all the tested bacteria strains.



Reaction conditions: a) chloroacetone, NaH, Ethyleneglycol dimethyl ether, 90 ^{o}C, 20 h; b) (i) p-PTSA, toluene, reflux, 17 h; ii) NaOH, H_2O, Ethanol, 70 ^{o}C, 3 h; c) NMP, Copper sulphate, NMP, 150 ^{o}C, 2 h; d) NBS, AIBN, $CHCl_3$, 65 ^{o}C, 3 h; e) **apocynin**, K_2CO_3, DMF, 80 ^{o}C, 3 h; f) NaOH, benzaldyhydes (**a-m**), MeOH, r.t., 5 h.

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