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SYNTHESIS AND ANTI-CANCER ACTIVITY OF NOVEL 3-ARYL THIOPHENE-2-CARBALDEHYDES AND THEIR ARYL/HETEROARYL CHALCONE DERIVATIVES

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ABSTRACT

A new series of 3-aryl thiophene-2-aryl and hetero aryl chalcones were synthesised and evaluated for their invitro antiproliferative activity against human colon cancer cell lines. The synthesis of the key intermediate required for the preparation of the final compounds was achieved by employing tetrakis(triphenylphosphine)palladium (0) mediated cross couplings using Suzuki reaction for the smooth formation of C-C bond between 3-bromothiophene-2-Carbaldehyde 1 and 2 or 3 substituted phenylboronic acids (**2a-d**) to offer 3-aryl-thiophene-2-carboxaldehyde (**3a-d**) in efficient manner with excellent yeilds. 3-(3-Methoxyphenyl)thiophene-2-carbaldehyde further underwent condensation with a variety of aryl and heteroaryl methyl ketones to give 3-aryl-thiophene-2-aryl/heteroaryl chalcones. Quite a good number of these final candidates have shown superior anticancer activity when compared to the reference compound. In the series tested, best anti tumour activity was shown by **5a** with IC_{50} value of 21 µg/mL compared to the IC_{50} value of the reference doxorubicin at 25 µg/mL. Compound **5g** had the IC_{50} value of 22.8 µg/mL indicating the potential cytotoxic properties of the new compounds against HCT-15 human colon cancer cells.

Keywords: 3-Aryl thiophene, 2-aryl and heteroaryl chalcones, aryl-boronicacids, anti-cancer activity, 3 bromothiophene-2-carbaldehyde, LDA, tetrakis-catalyst, Suzuki coupling reaction.

INTRODUCTION

Chalcones are flavonoid and isoflavonoid precursors[1] which are abundant in edible plants and are considered as important intermediate in the flavonoid biosynthesis. Chalcones of heterocycles from nature or synthetic origin exhibit wide and diverse pharmacological activities like antioxidant[2], antibacterial[3], antileishmanial[4-5] anticancer[6-8] antiangiogenic [9] anti-infective, anti-inflammatory activities[10] and are widely used in traditional medicine practices[11]. In addition, chalcones are very important compounds as a Michael acceptor in organic syntheses. The Michael addition reaction is one of the most fundamental C-C bond-forming reactions in the synthesis of various synthons[12] which are desirable starting materials for generating many heterocyclic and polyfunctional compounds.Chalcones of thiophenes are also associated with various activities[13]. Our interest in the sulphur and nitrogen heterocycles[14] prompted us to take up the present study.Synthesis of aryl thiophenes involve palladium-catalyzed cross-coupling reactions of 3-bromothiophene-2-carbaldehyde with aryl-boronic-acids which are considered as the most powerful methods for the preparation of aryl thiophenes. The efficiency of palladium-catalyzed Suzuki cross-coupling for the reaction of aryl boronicacids were well documented in the literature[15-16] in exception to 3-bromothiophene-2-carbaldehyde derivatives, which are not explored.

The chemistry of 3-arylations of 3-bromothiophene-2-carbaldehyde derivatives via palladium catalyzed bimolecular couplings 3-bromothiophene-2-carbaldehyde derivatives has not been reported. Over the past few years, new palladium-catalyzed procedure for the functionalization of hetero aromatics has emerged[17-20]. It consists of directly arylating hetero aromatics via a C-H bond activation of the heteroarenes[21-23]. This procedure proceeds smoothly for coupling of several thiophene derivatives with aryl halides. For such couplings, preparation of an organometallic derivative is not required. Moreover, this reaction provides only HX associated to a base as by-product, instead of a metallic salt, and therefore is very interesting both in terms of atom–economy and non-toxic wastes [24-28]. However, so far, most of the results reported for this reaction were obtained with 2-substituted thiophene and gave 5-arylated thiophene. Herein, we report synthetic details of the preparation of the 3-aryl thiophene chalcone derivatives via direct 3-arylations of thiophenes using 2-substituted thiophenes and the analysis of the structure – activity relationships in terms of their anti-cancer activities.

EXEPERIMENTAL

Materials and Metheds

All the chemicals are commercially available and have been carried forward without purification. Melting points were determined by open glass capillary method on a Cintex melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer spectrometer in KBr pellets. ^{1}H NMR spectra were recorded on a Varian 300 MHz spectrometer using $CDCl_3$ as a solvent. Chemical shift (δ) values are presented as singlet (s), doublet (d), triplet (t) quartet (q) or multiplet (m). Mass spectra were recorded on a LC-MSD-Trap-SL instrument in the electrospray ionization (ESI) mode. All the reactions were monitored by TLC on pre-coated silica gel plates (60F 254; Merck). Column chromatography was performed on 100-200 mesh silica gel (SRL, India) using 10-20 fold excess (by weight) of the crude product. The organic extracts were dried over anhydrous Na_2SO_4.

General procedure for the synthesis of 3-bromothiophene-2-carbaldehyde (**1**)

3-Bromothiophene (10g, 61.349 mmol) is dissolved in THF stirred and added LDA (30 mL) dropwise at 0 ^{0}C and stiired for 30 min and added N-formyl piperidine (6.9g, 61.349 mmol). The mixture was stirred further until TLC analysis indicated that all the starting material had been consumed 3hr. The resulting reaction mass was quenched with 20% aq. ammonium chloride and extracted with diethyl ether, dried in Na_2SO_4 and concentrated to get the crude. The crude was purified by column chromatography using 5% EtOAC/ Hexane, the pure product is (9g, 78%).

General procedure for the synthesis of 3-(3-methoxyphenyl) thiophene-2carboxaldehyde (3a-d)

To a solution of 3-Bromothiophene-2-carboxyaldehyde (9g, 47.12 mmol) and 3-methoxyphenyl boronicacid (9.3g, 61.25 mmol) are dissolved in 1,2-dimethoxyethane (DME, 90ml) and added a 2M $NaHCO_3$ solution (26g, 188.48 mmol) $Pd(Ph_3)_4$ and (14g, 1.413 mmol) perched with nitrogen gas and the Mixture was heated at 80 ^{0}C for 4hr. The reaction mixture was filtered in celite bed and washed with ethyl acetate to separated layers and The Organic layer was washed with water, and brine sol. dried in Na_2SO_4 and evaporated, the residue was purified by silica gel Colum chromatography (Hexane/EtOAC (5:1) to give **1** (9.5g, 93.2%) as a off white solid.

3-(3-Methoxyphenyl) thiophene-2-carbaldehyde (3a)

Off white solid, yield 93%, M.p. 95 °C IR (KBR): 1658 cm^{-1}, 1490 cm^{-1}, 1414 cm^{-1}, 1361 cm^{-1}, 1263 cm^{-1}, 1023 cm^{-1}, 895 cm^{-1}, 756 cm^{-1}. ^{1}H-NMR δ 9.8 (s, 1H, -CHO) δ 7.83 (d, 1H, =CHS), δ 7.52 (d, 1H, Ar-H) δ 7.45 (s, 1H, Ar-H) δ 7.32 (d, 1H, Ar-H) δ 7.09 (d, 1H, Ar-H), δ 6.93 (d, 1H, Ar-H) δ 3.35 (s, 3H). ^{13}C NMR δ 184.65, 162.04, 160.45, 160.10, 149.71, 145.45, 132.99, 131.71, 131.08, 128.00, 114.28, 28.2. LC-MS (m/z) 219 (M+1).

3-(3-Fluroyphenyl) thiophene-2-carbaldehyde (3b)
Off white solid, yield 65%, M.p.90 °C IR (KBR):1652cm^{-1}, 1480cm^{-1}, 1410cm^{-1}, 1325cm^{-1}, 1270cm^{-1}, 1020cm^{-1}.^{1}H-NMR δ 9.871 (1H, s, -CHO), δ 7.759 (d, 1H, Ar-H), δ 7.46 (d, 1H, Ar-H), δ 7.179 (dd, 1H, Ar-H), δ 7.12 (d, 1H, Ar-H), δ 7.10 (d, 1H, Ar-H), δ 6.89 (d, 1H, Ar-H). ^{13}C-NMR δ 183.67, 163.99, 149.66, 138.94, 135.91, 134.36, 131.45, 130.75, 125.46, 116.55, 115.86. LC-MS (m/z): 207 (M+1).

3-*m*-Tolythiophene-2-carbaldehyde (3c)
Off white solid, yield 66%, M.p. 92 °C IR (KBR):1658cm^{-1}, 1458cm^{-1}, 1413cm^{-1}, 1320cm^{-1}, 1260cm^{1}, 1030cm^{1}. ^{1}HNMR δ 9.861 (1H, s, -CHO), δ 7.694 (d, 1H, Ar-H), δ 7.343 (d, 3H, Ar-H), δ 7.258 (dd, 1H, Ar-H), δ 7.232 (d, 1H, Ar-H), δ 7.191 (d, 1H, Ar-H), δ 7.18 (d, 1H, Ar-H), δ 2.406 (CH_3, 3H, s); ^{13}C-NMR δ 184.41, 151.72, 139.42, 134.00, 133.12, 130.72, 129.06, 125.45, 120.24, 128.21, 126.73, 21.44, LC-MS (m/z) 203 (M+1).

3-(2-Methoxyphenyl) thiophene-2-carbaldehyde (3d)
Off white solid, yield 93%, M.p. 90 °C IR (KBR): 1658cm^{-1}, 1490cm^{-1}, 1414cm^{-1}, 1361cm^{-1}, 1263cm^{-1}, 1023cm^{-1}, 895 cm^{-1}, 756 cm^{-1}. ^{1}H-NMR δ 9.8 (s, 1H, -CHO) δ 7.8 (d, 1H, =CHS), δ 7.5 (d, 1H, Ar-H) δ 7.4 (s, 1H, Ar-H) δ 7.32 (d, 1H, Ar-H) δ 7.12 (d, 1H, Ar-H), δ 6.9 (d, 1H, Ar-H) δ 3.3 (s, 3H). ^{13}C NMR δ 184.65, 162.04, 160.45, 160.10, 149.71, 145.45, 132.99, 131.71, 131.08, 128.00, 114.28, 28.2, LC-MS (m/z) 219 (M+1).

General procedure for the synthesis of 3-(3-(3-methoxyphenyl) thiophene-2-yl)-1-phenylprop-2-en-1-one (5a-l)
Acetophenones **(4a-l)** (389mg, 2.29 mmol) were dissolved in alkaline methanolic solution (2 molor) and stirred for 10 min then added 3-(3-Methoxyphenyl) thiophene-2-carbaldehyde (**3a**) (500mg, 2.290 mmol) the resulting mixture was stirred at ambient temperature for 5-8 hr. The reaction mixture was diluted with water (10ml) and filtered to get the solid and air dried to give (**5a-l**).

3-(3-(3-Methoxyphenyl) thiophen-2-yl)-1-phenylprop-2-en-1-one (5a)
Yellow solid, yield 93%, M.p.98 °C IR (KBR): (C=O) 1658 cm^{-1}, (C=C) 1597cm^{-1}, Ring vibrations – 1565 cm^{-1}, 1468 cm^{-1}, 1261 cm^{-1}. ^{1}H-NMR: δ 9.236 (s, 1H, Ar-H), δ 8.817 (d, 1H), δ 8.415 (d, 1H), δ 7.893 (d, 1H), δ 7.88 (d , 2H), δ 7.577 (m, 2H), δ 7.478 (d, J=7.6, 1H), δ 7.3 (d, J=7.6, 1H), δ 7.035 (3H, m, Ar-H), δ 3.808 (OCH_3, s, 3H), ^{13}C-NMR δ 187.94, 159.44, 153.21, 149.42, 146.98, 136.38 , 136.03, 135.83, 134.11, 132.68, 130.63, 129.92, 129.85, 123.85, 121.58, 120.77, 114.12, 113.83, 55.19. LC-MS (m/z): 322 (M+1).

1-(3-Methoxyphenyl)-3-(3-(3-methoxyphenyl) thiophen-2-yl)-1-phenylprop-2-en-1-one (5b)
Yellow solid, yield 90%, M.p.80 °C, IR:(C=O) 1652cm^{-1},(C=C)1565cm^{-1}, Ringvibrations -1565cm^{-1}, 1462cm^{-1}, 1265cm^{-1}. ^{1}H-NMR: δ 7.849 (s, 1H) δ 7.646 (d, 1H) δ 7.474 (m, 4H), δ 7.404 (d, 1H), δ 7.303 (d, J=7.6, 1H), δ 7.195 (d, J=7.6, 1H), δ 6.99 (m, 2H), 6.95 (m, 1H) δ 3.807 (s, 3H, CH_3), δ 3.789 (s, 3H, CH_3). ^{13}C NMR δ 188.46, 159.51, 159.43, 146.47, 138.88, 136.10, 135.84, 134.25,130.59, 129.92,129.88, 129.32,121.53,121.13,120.82, 119.08, 114.63,113.75,112.77,55.18,39.53. LCMS; (m/z): 351(M+1).

1-(4-Methoxyphenyl)-3-(3-(3-methoxyphenyl) thiophen-2-yl)-1-phenylprop-2-en-1-one (5c)
Yellow solid, yield 92%, M.p.85 °C, IR (KBR):(C=O) 1658 cm^{-1},(C=C) 1565cm^{-1}, Ring vibrations -1565cm^{-1}, 1480 cm^{-1}, 1260cm^{-1}. ^{1}H-NMR δ 8.829 (m, 2H), δ 7.858 (d, 1H), δ 7.508 (m, 4H), δ 7.424 (d, J=7.6, 1H), 7.22 (d, J=7.6, 1H), δ 6.987 (m, 3H), δ 3.808 (s, 3H, OCH_3), 3.790 (s, 3H, OCH_3). ^{13}C NMR δ 188.46, 159.51, 159.43, 146.47, 138.88, 136.10, 135.84, 134.25, 130.59, 129.92, 129.88, 129.32, 121.53, 121.13, 120.82, 119.08, 114.63, 113.75, 112.77, 55.18, 39.53 LC-MS (m/z) Mass: 351 (M+1).

1-(4-Bromophenyl)-3-(3-(3-methoxyphenyl) thiophen-2-yl)-1-phenylprop-2-en-1-one (5d)
Yellow solid, yield 92%, M.p.136 °C, IR(KBR): (C=O) 1652 cm^{-1}, (C=C) 1567cm^{-1}, Ring vibrations-1567cm^{-1}, 1472 cm^{-1},1241 cm^{-1}. ^{1}H-NMR δ 8.0135 (d, 2H), δ 7.867 (d, 2H), δ 7.759 (d, 2H), δ 7.546 (1H, s), δ 7.508 (1H, s), δ 7.446 (d, J=7.6, 1H), δ 7.335 (d, J=7.6, 1H), δ 6.9 (m, 2H) δ 3.822 (s, 3H, CH_3); ^{13}C NMR δ 187.70, 159.43, 146.74, 136.37, 136.19, 136.05, 134.20, 131.82, 130.62, 130.36, 129.91, 129.57, 127.18, 121.57, 120.57, 114.67, 113.75, 112.53, 55.19, 39.90. LC-MS (m/z): 399,401 (M+1).

1-(4-Chlorophenyl)-3-(3-(3-methoxyphenyl)thiophen-2-yl)-1-phenylprop-2-en-1-one (5e)

Yellow solid, yield 94%, M.p.123 °C, IR (KBR): (C=O) 1685cm^{-1}, (C=C) 1557cm^{-1}, Ringvibrations:1557cm^{-1}, 1482 cm^{1},1261 cm^{1}. ^{1}HNMR δ 8.095 (d, 2H), δ 7.877 (d, 2H), δ 7.612 (m, 2H), δ 7.557 (d, J=7.6, 1H), δ 7.519 (m,1H), δ 7.449 (d, J=7.6, 1H), δ 7.337 (3H ,m) δ 3.8 (s, 3H, OCH_3). ^{13}C NMR δ 187.47, 159.42, 146.70, 138.00, 136.08, 136.03, 136.05,134.21, 130.59, 130.22, 129.88, 129.50, 128.84, 121.55, 120.58, 114.66,113.72,55.17,39.9.LC-MS (m/z): 355 (M+1).

1-(4-Iodophenyl)-3-(3-(3-methoxyphenyl) thiophen-2-yl)-1-phenylprop-2-en-1-one (5f)
Yellow solid, yield 95%, M.p.97 °C, IR (KBR): (C=O) 1662Cm^{-1}, (C=C) 1557 cm^{-1}, 1482 cm^{-1}, 1261 cm^{-1}. ^{1}H-NMR δ 8.863 (s, 1H), δ 8.214 (d, 1H), δ 8.056 (m, 2H), δ 7.978 (m, 1H), δ 7.888 (s, 1H), δ 7.779 (m, 2H), δ 7.723 (d, J=7.6, 1H), δ 7.704 (d, J=7.6, 1H), δ 7.682 (m, 2H), 3.829 (s, 3H). ^{13}C NMR δ 18842, 159.43, 146.46, 136.14, 135.69, 134.99, 134.37, 132.27, 130.62, 130.12, 129.90, 129.64, 129.26, 128.45, 127.64, 124.01, 121.59, 121.10, 114.68, 55.17; LC-MS (m/z): 446 (M+1).

3-(3-(3-Methoxyphenyl) thiophen-2-yl)-1-(2,4,6 -Trimethylphenyl)-prop-2-en-1-one (5g)
Yellow solid, yield 93%, M.p.120 °C, IR (KBR): (C=O) 1663cm^{-1}, (C=C) 1560cm^{-1}, Ring vibrations: 1560cm^{-1}, 1462cm^{-1}, 1251cm^{-1}. ^{1}H-NMR δ 7.860 (s, 1H), δ 7.307 (m, 3H), δ 6.858 (m, 6H, Ar-H), δ 3.73 (s, 3H, CH_3), δ 2.223 (s, 9H). ^{13}C NMR δ 199.29, 159.34, 146.16, 138.03 137.72, 136.74, 135.60, 133.34, 133.22, 130.65, 129.98, 129.69, 128.06, 126.95, 121.22, 114.24, 113.92, 55.06, 20.58, 18.75. LC-MS (m/z): 363 (M+1).

3-(3-(3-Methoxyphenyl) thiophen-2-yl)-1-(1-napthalene-6-yl)-prop-2-en-1-one (5h)
Yellow solid, yield 94%, M.p.119 °C, IR (KBR): (C=O) 1662cm^{-1}, (C=C) 1545cm^{-1}, Ring vibrations: 1545cm^{-1}, 1462cm^{-1}, 1241cm^{-1}. ^{1}H-NMR δ 8.12 (s, 1H,) δ8.01 (d, 1H , Ar-H) δ 7.9 (d, 2H, Ar-H) δ 7.8 (d, J=7.6, 1H) δ 7.5 (d, 3H, Ar-H) δ7.4 (d, 4H, Ar-H), 7.3 (d, J=7.6, 1H) δ7.01 (s, 1H, Ar-H) δ 3.8 (s, 3H, CH_3), ^{13}C-NMR δ 196.00, 187.94, 159.44, 159.06, 153.21, 149.41, 141.42, 138.14, 136.17, 136.05, 132.68, 130.46, 129.83, 129.65, 129.25, 127.21, 121.56, 120.77, 114.12, 113.65, 55.19, 45.84.

3-(3-(3-Methoxyphenyl) thiophen-2-yl)-1-(1-napthalene-2-yl)-prop-2-en-1-one (5i)
Yellow solid, yield 94%, M.p.119 °C, IR (KBR): (C=O) 1662cm^{-1}, (C=C) 1545cm^{-1}, Ring vibrations: 1545cm^{-1}, 1462cm^{-1}, 1241cm^{-1}. ^{1}H-NMR δ 8.12 (s, 1H,) δ8.01 (d, 1H , Ar-H) δ 7.9 (d, 2H, Ar-H) δ 7.8 (d, 2H) δ7.5 (d, 3H, Ar-H) δ7.4 (d, 3H, Ar-H), δ7.32 (d, J=7.6, 1H), δ7.01 (d, J=7.6, 1H), δ 3.8 (s, 3H, CH3), ^{13}C-NMR δ 196.00, 187.94, 159.44, 159.06, 153.21, 149.41, 141.42, 138.14, 136.17, 136.05, 132.68, 130.46, 129.83, 129.65, 129.25, 127.21, 121.56, 120.77, 114.12, 113.65, 55.19, 45.84. LC-MS (m/z): 371.

3-(3-(3-Methoxyphenyl) thiophen-2-yl)-1-(pyridin-2-yl)-prop-2-en-1-one (5j)
Yellow solid, yield 92%, M.p.158 °C, IR (KBR): (C=O) 1682cm^{-1}, (C=C) 1567cm-1, Ring vibrations: 1567cm^{-1}, 1482cm-1, 1261cm^{-1}, Trans (CH=CH) 975cm^{-1}. ^{1}H-NMR δ 8.817 (d, 1H, Ar-H) δ 8.042 (m, 3H, Ar-H) δ 7.946 (s, 1H) δ 7.859 (d, J=7.6, 1H) δ 7.68 (d, J=7.6, 1H) δ 7.465 (s, 1H) δ 7.343 (d, 1H, Ar-H) δ 7.034 (m, 3H, Ar-H) δ 3.8 (s, 3H, CH3), ^{13}C-NMR δ 187.90, 159.44, 153.14, 149.16, 146.77,

137.72, 136.01, 135.57, 134.57, 130.81, 129.92, 129.40, 127.62, 122.36, 121.56, 119.78, 114.65, 113.82, 55.19. LC-MS (m/z): 322 (M+1).

3-(3-(3-Methoxyphenyl) thiophen-2-yl)-1-(pyridin-3-yl)-prop-2-en-1-one (5k)
Yellow solid, yield 92%, M.p.140 °C, IR (KBR): (C=O) 1682cm^{-1}, (C=C) 1567cm^{-1}, Ring vibrations: 1567cm^{-1}, 1482cm^{-1}, 1261cm^{-1}, Trans (CH=CH) 975cm^{-1}. ^{1}H-NMR δ 9.235 (S, 1H Py-H), δ 8.802 (d, 1H, Py-H), δ 8.402 (d, 1H, Py-H), δ 7.903 (2H, m), δ 7.65 (m, 2H), δ 7.43-7.09 (m, 3H), 7.42 (d, 1H, J=7.6, =CH-), 7.30 (d, 1H, J=7.6, =CH-), δ 3.8 (S, 3H, O-CH_3), ^{13}CNMR-DMSO-d6 δ ppm 187.90, 159.44, 153.14, 149.16, 146.77,137.72, 136.01, 135.57,134.57, 130.81,129.40, 127.62, 122.36, 121.56, 119.78, 114.65, 113.82, 55.19. LC-MS (m/z): 322 (M+1).

3-(3-(3-Methoxyphenyl) thiophen-2-yl)-1-(thiophen-2-yl)-prop-2-en-1-one (5l)
Yellow solid, yield 94%, M.p.129 °C, IR (KBR): (C=O) 1642 cm^{-1}, (C=C) 1546 cm^{-1}, Ring vibrations: 1546 cm^{-1}, 1462 cm^{-1}, 1261cm^{-1}. ^{1}H-NMR δ 8.254 (s, 1H), δ 8.24 (d, 1H, Ar-H), δ 7.85 (d, 2H), δ 7.53 (m, 2H, Ar-H), δ 7.49 (d, J=7.6, 1H), 7.49 (d, J=7.6, 1H), δ 7.43 (m, 3H), δ 3.82 (s, 3H, O-CH_3). ^{13}C-NMR δ 180.91, 159.42, 146.49, 145.07, 136.09, 135.46, 134.85, 134.07, 133.36, 130.58, 129.90, 129.33, 128.90, 121.55, 120.79, 114.64, 113.74, 55.17. LC-MS (m/z): 327 (M+1).

RESULTS AND DISCUSSION

Chemistry

3-Bromothiophene-2-carboxaldehyde (**1**) was synthesized from 3-bromothiophene in the presence of LDA, N-formyl piperidine in THF. The structure of the compound obtained was confirmed by comparing the analytical data with the reported literature. Compound (**1**) was reacted with 2,3-substituted aryl boronicacids (**2a-d**) in 1,2-dimethoxyethane in the presence of tetrakis palladium tri phenyl phosphine and $NaHCO_3$ under nitrogen atmosphere at 80 ^{0}C for 4h to give 3-aryl thiophene-2-carboxaldehyde (**3a-d**) in good yields. As a representative example, 3-(3-methoxyphenyl) thiophene-2-carboxaldehyde (**3a**) was formed in 93% yield, M.p. 95-96 °C. The structure of compound **3a** was confirmed based on the following analytical data as 3-(3-methoxyphenyl) thiophene-2-carboxaldehyde. IR (KBR) spectrum of **3a** displayed stretching frequency of unsaturated aldehyde group at 1655cm^{-1}. The ^{1}H NMR spectrum of **3a** gave signals at ^{1}H-NMR δ 9.8 (s, 1H, -CHO) δ 7.83 (d, 1H, =CHS), δ 7.52 (d, 1H, Ar-H) δ 7.45 (s, 1H, Ar-H) δ 7.32 (d, 1H, Ar-H) δ 7.09 (d, 1H, Ar-H), δ 6.93 (d, 1H, Ar-H) δ 3.35 (s, 3H). ^{13}C NMR δ 184.65, 162.04, 160.45, 160.10, 149.71, 145.45, 132.99, 131.71, 131.08, 129.38, 128.00, 114.28, 28.2, LC-MS (m/z) 218 (M+1). LC-MS showed M+1 at (m/z) 219 and fragmentation pattern was in accordance with the assigned structure (Scheme-1).

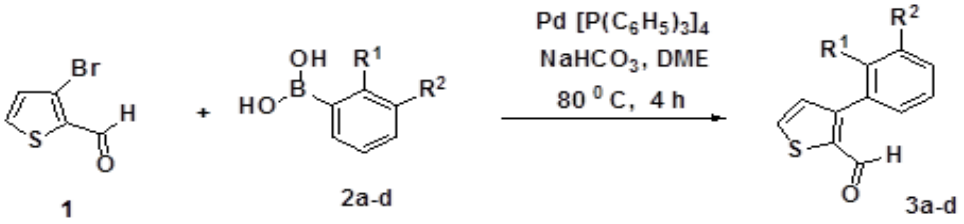
3-(3-methoxyphenyl) thiophene-2-carboxaldehyde (**3a**) is allowed to react with substituted arylmethylketones (**4a-l**) in alcoholic sodium hydroxide to give a variety of chalcones (**5a-l**) in good yields. **Scheme 2**. To represent the series 3-(3-(3-methoxyphenyl) thiophen-2-yl)-1-(pyridin-3-yl)-prop-2-en-1-one (**5k**) is formed as pale yellow with 92% yield and M.p. 140 °C. IR (KBR): (C=O) 1682 cm^{-1}, (C=C) 1567 cm^{-1}. ^{1}H-NMR δ 9.235 (s, 1H, Py-H), δ 8.802 (d, 1H, Py-H), δ 8.402 (d, 1H, Py-H), δ 7.903 (2H, m, Ar-H), δ 7.65 (m, 2H, Ar-H), δ 7.43-7.09 (m, 3H, Ar-H), 7.42 (d, J=7.6, 1H, =CH-), 7.30 (d, J=7.6, 1H, =CH-), δ 3.8 (S, 3H, O-CH_3), ^{13}CNMR-DMSO-d6 δ ppm 187.90, 159.44, 153.14, 149.16, 146.77, 137.72, 136.01, 135.57, 134.57, 130.81, 129.40, 127.62, 122.36, 121.56, 119.78, 114.65, 113.82, 55.19. LC-MS (m/z): 322 (M+1) confirms the assigned structure (Scheme-2).

Biological Evaluation

Anti-cancerActivity

3-aryl thiophene chalcones which were designed and synthesized are evaluated in vitro for their anti-proliferative activity against Human colon cancer cell lines (HCT-15) using MTT assay (3,4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide taking Doxorubicin (DRI) a known anticancer

drug as a reference compound. Quite a good number of the final candidates have shown superior anticancer activity when compared to the reference compound. Among the new derivatives tested **5a, 5d, 5g,** and **5j** exhibited most potent growing inhibitory activity With IC_{50} values in the range of 21 to 23.8 µg/mL which is more promising and superior than the reference compound Doxorubicin (DRI) 25 µg/mL. The percentage of cell death along with IC_{50} (half maximal inhibitory concentration) values were measured at various concentrations (**Table 1**). In the series tested, best anti tumor activity was shown by **5a** with IC_{50} value of 21 µg/mL compared to the IC_{50} value of the reference compound doxorubicin with 25 µg/mL. Compound **5g** had IC_{50} value of 22.8 µg/mL indicating the potential cytotoxic properties of the new compounds against HCT-15 human colon cancer cells. The promising/ encouraging results of the present study have provided a rational for for the further development of this class of compounds as novel cancer chemotherapeutic agents (Table-1).



a = R^1 = H ; R^2 = OCH_3

b = R^1 = H ; R^2 = F

c = R^1 = H ; R^2 = CH_3

d = R^1 = OCH_3 ; R^2 = H

Scheme-1: Synthesis of compounds **3a-3d**

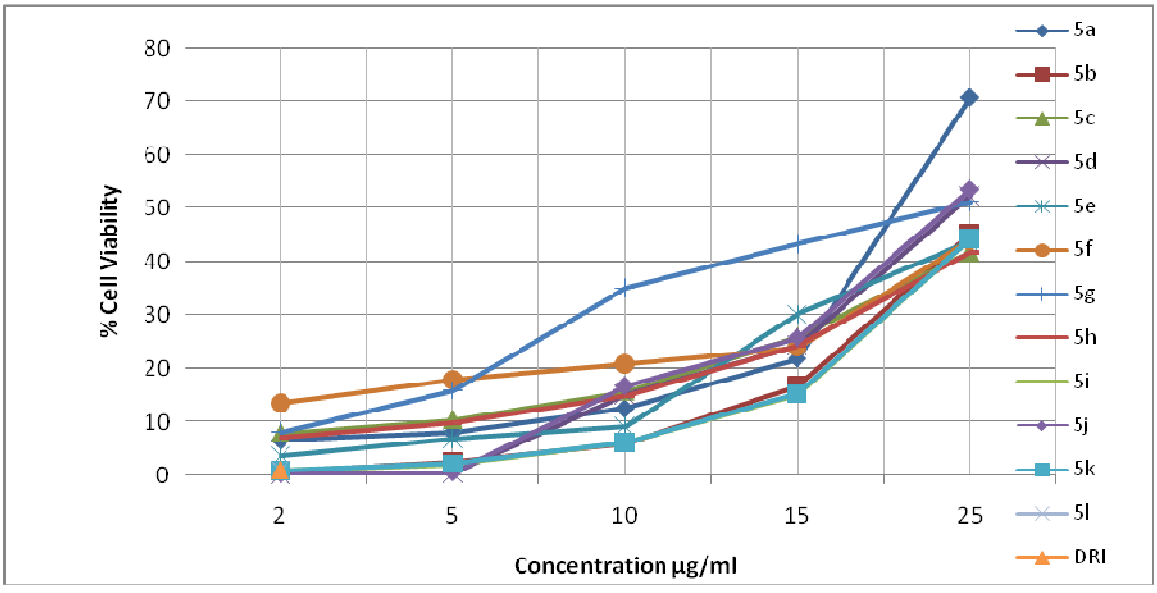
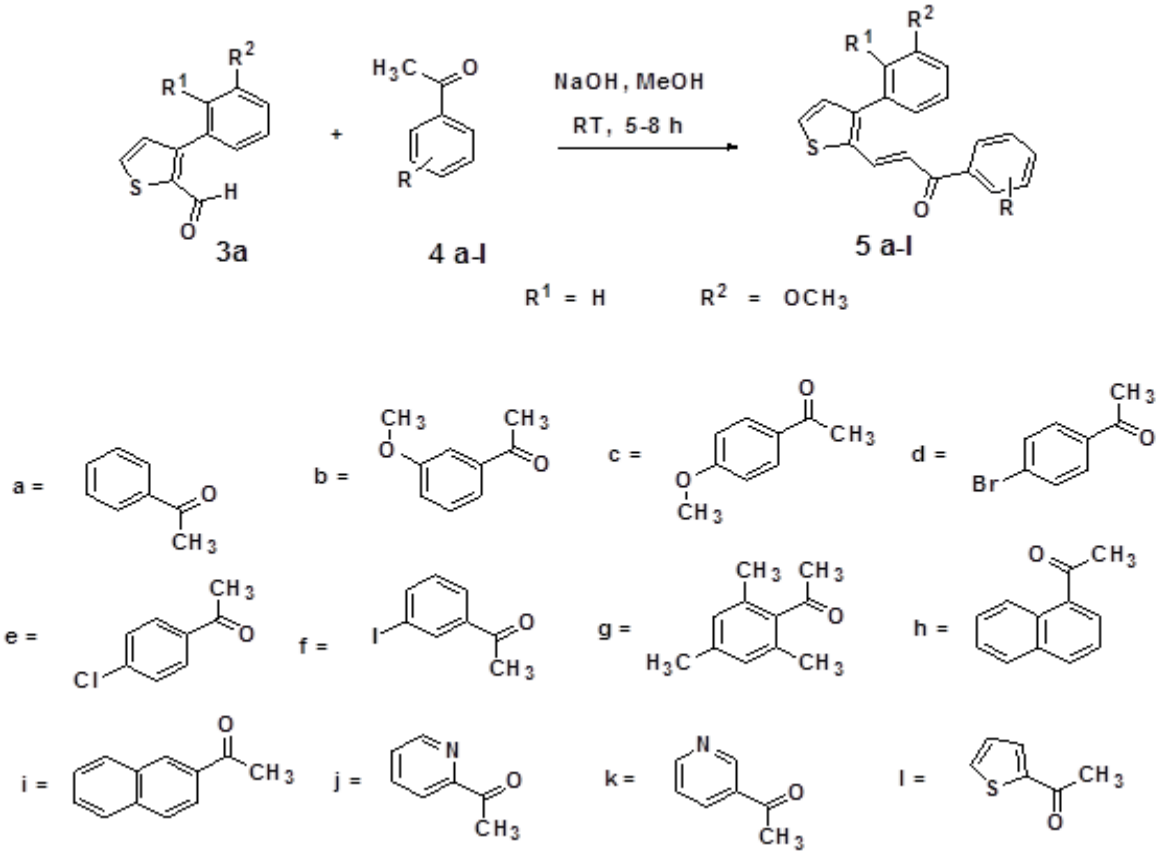


Fig.-1: Anticancer activity of 3-aryl thiophene chalcones by MTT assay



Scheme-2: Synthesis of compounds **5a**-**5l**

Biological assay

Cell Line and Culture Conditions

HCT15 (Human colon cancer cell line) was procured from NCCS, Pune, India. The cell line was grown in the RPMI-1640 with 2mM L-glutamine, supplemented with 10% FBS, penicillin (100IU/mL) and streptomycin (100µg/mL) at 37 ^{0}C in a 95% humidified CO_2 incubator with 5% CO_2 atmosphere The cell line was passaged twice weekly for maintaining sub-confluent state.

Cell Viability Assay

MTT assay was used as cell viability assay [29,30,31,32]. The principle of the assay lies in the fact that the MTT is reduced to Formazan crystals by mitochondrial dehydrogenize of the viable cells. The treated and untreated cells were washed with PBS (Phosphate buffer saline) and MTT (100µg/ml) was added and incubated at 37 ^{0}C for 5hr. The MTT was then removed and the formazan crystals were dissolved by adding DMSO (DimethylSulfoxide). The absorbance at 540nm represents the viable cells. The absorbance was taken using multiscan spectrum from Thermo scientific. The absorbance from the untreated cells was defined as 100% viable cells. The % viable cells were plotted (Y axis) against concentration (X axis). The IC_{50} values can be interpolated from the graph. (Human colon cancer cell line) cancer cell lines.

CONCLUSIONS

A new efficient approach to the synthesis of 3-aryl thiophene chalcones has been developed.3-Aryl thiophene-2-carboxaldehydes, the key intermediates for the final step has been prepared by Suzuki cross

coupling reactions employing tetrakis (triphenylphosphine) palladium (0). The current methodology allows for the incorporation of many substitution patterns not available from the few previously reported approaches of this class. The robustness of this step was demonstrated by synthesizing a large number of compounds The final compounds have shown superior anticancer activity when compared to the reference compound doxorubicin.

Table-1: *In vitro* Cytotoxic Activities of Compounds 5a and 5l Against Human Cancer Cell Lines (HCT-15).

Compound	% of cell death of various concentrations (µg/mL)					IC_{50} (µg/mL)
	2.0	5.0	10.0	15.0	25	
5a	6.61	8.09	12.53	21.88	70.73	21
5b	0.76	2.54	6.10	16.79	45.29	-
5c	7.88	10.43	15.77	25.95	41.73	-
5d	0.25	0.50	15.26	24.42	52.41	23
5e	3.56	6.87	9.16	30.27	43.76	-
5f	13.48	17.81	20.86	23.91	44.02	-
5g	8.09	15.80	34.99	43.24	51.12	22.8
5h	7.09	9.89	14.78	24.25	41.73	-
5i	0.92	2.15	6.14	15.24	44.25	-
5j	0.32	0.60	16.72	25.74	53.41	23.8
5k	21.65	27.71	46.76	48.06	49.79	25
5l	7.09	9.89	14.78	24.25	41.73	-
DRI	21.65	21.65	21.65	21.65	21.65	21.65

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