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## Preliminary Communication

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# Design, synthesis, and anticancer activity of novel aryl/heteroaryl chalcone derivatives

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**Abstract:** A new series of chalcones **5a–l** were synthesized and evaluated for *in vitro* antiproliferative activity against human colon cancer cell lines. The synthesis of the key intermediate compounds **3a–d** was achieved by tetrakis(triphenylphosphine) palladium(II) mediated Suzuki cross coupling reaction. Chalcone **5a** shows superior anticancer activity with $IC_{50}$ value of 21.0 μg/mL compared to the $IC_{50}$ value of the reference drug doxorubicin at 21.65 μg/mL.

**Keywords:** anti-cancer; arylboronic acids; 3-arylthiophene; 3-bromothiophen-2-carbaldehyde; chalcones; LDA.

This publication is dedicated to Professor G.S.R. Subba Rao.

Synthetic and natural aryl/heteroaryl chalcones exhibit wide and diverse pharmacological activities including antioxidant, anti-HIV, antibacterial, antileishmanial, antiplatelet, anti-infective, anti-inflammatory, antimalarial, antifungal, anticancer, and antiangiogenic properties and are widely used in traditional medicine practices [1]. Their anticancer activity is due to the involvement with multi-drug resistance (MDR) channels [2], p53 degradation [3], JAK/STAT signaling pathway [4], angiogenesis [5], and VEGFR-2 kinase inhibition [6]. Selected naturally occurring and synthetic chalcones with numerous biological activities are shown in Figure 1 [7]. Most of the clinically useful anticancer drugs have genotoxic effects due to interaction with the amino groups of nucleic acids but aryl/heteroaryl chalcones have not been found to show such undesired side effects [8]. Recent development of anticancer agents involves structural modification of chalcones with heteroaryl substituents [9]. In particular, chalcones of thiophenes exhibit various activities [10, 11]. In this work we designed and synthesized a series of 3-arylthiophene chalcone derivatives **5a–l** which were not explored earlier and investigated their cytotoxicity against human colon cancer cell line HCT-15.

As depicted in Scheme 1, new 3-arylthiophene-2-carboxaldehydes **3a–d** were synthesized by carrying out palladium catalyzed Suzuki cross coupling reaction [12–15] of 3-bromothiophene-2-carboxaldehyde (**1**) and arylboronic acids **2a–d**. In literature, most of the results reported for this reaction have been obtained with 2-bromothiophene [16]. In this work, 3-arylthiophene carboxaldehyde derivatives **3a–d** were synthesized. The starting material, 3-bromothiophene-2-carboxaldehyde (**1**), was synthesized from 3-bromothiophene and *N*-formylpiperidine in the presence of LDA. The structure of the compound obtained was confirmed by comparing the analytical data with those reported [17]. Compound **1** was allowed to react with commercially available 2,3-disubstituted arylboronic acids **2a–d** in the presence of a palladium catalyst and $NaHCO_3$ under nitrogen atmosphere to give the corresponding 3-arylthiophene-2-carboxaldehydes **3a–d** in good yields. We initially directed our efforts towards the synthesis of a new series of 3-[3-(3-methoxyphenyl) thiophen-2-yl]-1-phenylprop-2-en-1-one derivatives **5a–l** (Scheme 2) from 3-(3-methoxyphenyl)thiophene-2-carboxaldehyde (**3a**). The aldehyde **3a** was allowed to react with commercially available substituted aryl methyl ketones **4a–l** in alcoholic sodium hydroxide to give the corresponding chalcones **5a–l** with *E*-geometry of olefin in good yields. The *E*-configuration was confirmed by analysis of the $^1H$ NMR spectral data. Briefly, two doublets at around $\delta$ 7.00 and 7.85 for the adjacent olefinic protons show a coupling of 14.0–14.5 Hz, which is fully consistent with the *E*-geometry of the olefin fragment in chalcone compounds.

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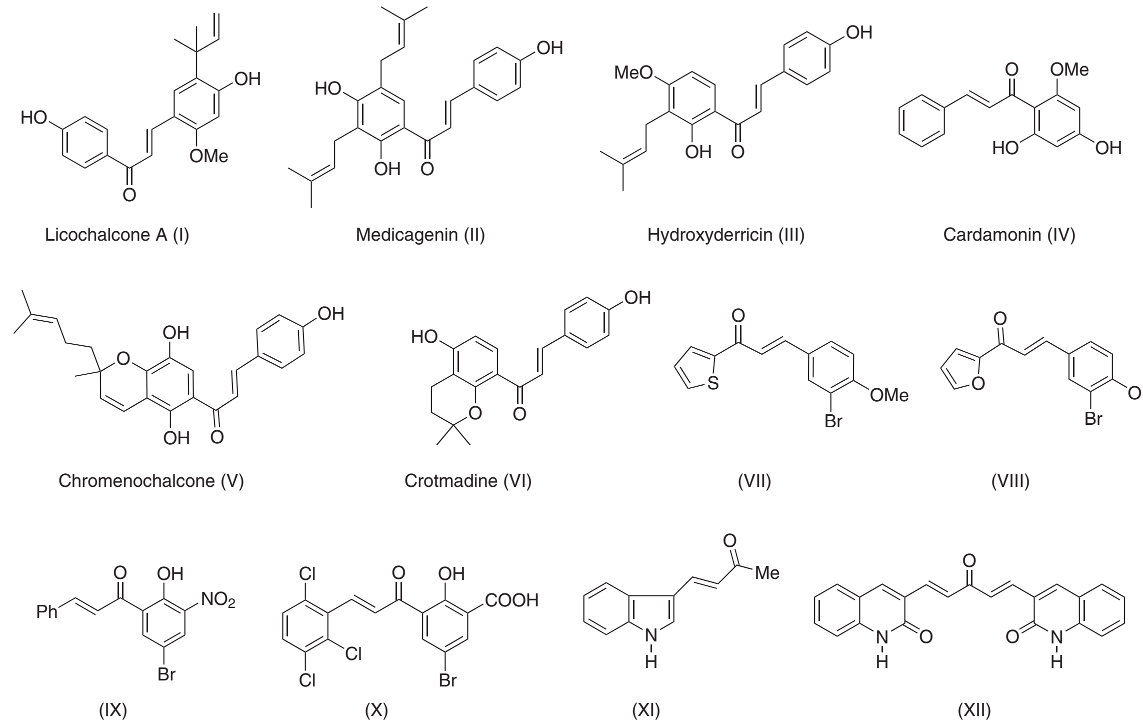
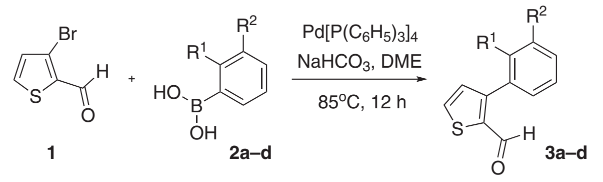
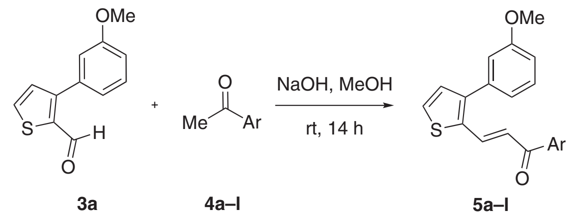


**Figure 1** Naturally occurring (I–VI) and synthetic aryl/heteroaryl chalcones (VII–XII).



**a**: $R^1$ = H; $R^2$ = OMe
**b**: $R^1$ = H; $R^2$ = F
**c**: $R^1$ = H; $R^2$ = Me
**d**: $R^1$ = OMe; $R^2$ = H

**Scheme 1** Synthesis of compounds **3a–d**.



**4a**, **5a**: Ar = Ph
**4b**, **5b**: Ar = 3-MeO-$C_6H_4$
**4c**, **5c**: Ar = 4-MeO-$C_6H_4$
**4d**, **5d**: Ar = 4-Br-$C_6H_4$
**4e**, **5e**: Ar = 4-Cl-$C_6H_4$
**4f**, **5f**: Ar = 4-I-$C_6H_4$
**4g**, **5g**: Ar = 2,4,6-triMe-$C_6H_2$
**4h**, **5h**: Ar = 1-napthyl
**4i**, **5i**: Ar = 2-napthyl
**4j**, **5j**: Ar = 2-pyridyl
**4k**, **5k**: Ar = 3-pyridyl
**4l**, **5l**: Ar = 2-thienyl

**Scheme 2** Synthesis of chalcones **5a–l**.

The 3-arylthiophene chalcones **5a–l** were evaluated *in vitro* for anti-proliferative activity against human colon cancer cell lines (HCT-15) using an MTT (3,4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay and doxorubicin (DRI) as a reference anticancer drug. Many chalcones show superior anticancer activity when compared to the reference compound. Compounds **5a, 5d, 5g,** and **5j** exhibit the most potent growing inhibitory activity with $IC_{50}$ values in the range from 21.0 to 23.8 μg/mL which is comparable to the activity of 21.65 μg/mL of doxorubicin. The percentage of cell

**Table 1** *In vitro* anticancer activity of compounds **5a-l.**

| Compound | % of cell death at various concentrations (μg/mL) of compound | | | | | $IC_{50}$ (μg/mL) |
|---|---|---|---|---|---|---|
| | 2.0 | 5.0 | 10.0 | 15.0 | 25.0 | |
| **5a** | 6.61 | 8.09 | 12.53 | 21.88 | 70.73 | 21.0 |
| **5b** | 0.76 | 2.54 | 6.10 | 16.79 | 45.29 | – |
| **5c** | 7.88 | 10.43 | 15.77 | 25.95 | 41.41 | – |
| **5d** | 0.25 | 0.50 | 15.26 | 24.42 | 52.73 | 23.0 |
| **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 | 25.0 |
| **5l** | 7.09 | 9.89 | 14.48 | 24.25 | 41.73 | – |
| **DRI**[a] | 6.68 | 8.42 | 11.98 | 20.75 | 70.10 | 21.65 |

[a] Dioxorubicin.

death along with $IC_{50}$ (half maximal inhibitory concentration) values were measured at various concentrations (Table 1). In the series tested, compound **5a** shows the best antitumor activity with the $IC_{50}$ value of 21.0 μg/mL, which is better than the $IC_{50}$ value of 21.65 μg/mL of the reference drug. Compound **5g** with the $IC_{50}$ value of 22.8 μg/mL is also highly active. The results of the present study provide a rationale for the further development of this class of compounds as novel cancer chemotherapeutic agents.

## Experimental

All chemicals and solvents were commercially available and used 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. $^1H$ NMR (300 MHz or 400 MHz) spectra and $^{13}C$ NMR spectra (100 MHz) were recorded on Varian spectrometers. Elemental analyses were performed on a LECO-932 analyzer. Mass spectra were recorded on a LC-MSD-Trap-SL instrument in the electrospray ionization (ESI) mode. All 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).

### Biological assay

HCT-15 (human colon cancer cell line) was procured from NCCS (Pune, India). The cell line was grown in the RPMI-1640 with 2 mM L-glutamine, supplemented with 10% FBS, penicillin (100 IU/mL) and streptomycin (100 μg/mL) at 37°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.

MTT assay was used as cell viability assay [18]. The principle of the assay lies in the fact that MTT is reduced to formazan crystals by mitochondrial dehydrogenase of the viable cells. The treated and untreated cells were washed with PBS (phosphate buffer saline) and after addition of MTT (100 μg/mL) the mixture was incubated at 37°C for 5 h. The remaining MTT was then removed and the formazan crystals were dissolved in DMSO. The absorbance at 540 nm represents the viable cells. The absorbance was taken using multi-scan spectrum from Thermo Scientific. The absorbance from the untreated cells was defined as 100% viable cells. The percentage of viable cells was plotted (Y axis) against concentration (X axis). The $IC_{50}$ values were then interpolated from the graph.

### Synthesis of 3-bromothiophene-2-carboxaldehyde (1)

A solution of 3-bromothiophene (10 g, 61.35 mmol) in THF (100 mL) was stirred and treated dropwise with a solution of LDA in hexanes (62 mmol) at 0°C and the mixture was stirred for an additional 30 min before the addition of *N*-formylpiperidine (6.9 g, 61.35 mmol). The mixture was stirred further for 3 h, after which time the TLC analysis indicated that all starting material had been consumed. The mixture was quenched with 20% aqueous ammonium chloride and extracted with diethyl ether. The extract was dried with $Na_2SO_4$ and concentrated. The residue was purified by column chromatography eluting with 5% ethyl acetate-hexanes. The yield was 9 g (78%) [17].

### General procedure for the synthesis of 3-(3-methoxyphenyl)thiophene-2-carboxaldehydes 3a–d

A solution of 3-bromothiophene-2-carboxaldehyde (**1**, 9.0 g, 47.12 mmol) and 3-methoxy-phenylboronic acid (9.3 g, 61.25 mmol) in 1,2-dimethoxyethane (90 mL) was treated with $NaHCO_3$ (26.0 g, 188.5 mmol), water (90 mL), $Pd(PPh_3)_4$ (14 g, 1.41 mmol), and the mixture was heated at 80°C for 12 h under a nitrogen atmosphere. The mixture was then filtered on a celite bed and extracted with ethyl acetate. The extract was washed with water and brine, dried with $Na_2SO_4$ and concentrated. The residue was purified by silica gel column chromatography eluting with a mixture of hexanes and ethyl acetate (5:1) to give **3a–d** as an off-white solid.

**3-(3-Methoxyphenyl)thiophene-2-carboxaldehyde (3a)** Yield 93%; mp 95°C; IR: ν 1658, 1490, 1414, 1361, 1263, 1023, 895, 756 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 9.80 (s, 1H, -CHO), 7.83 (d, 1H, =CHS), 7.52 (d, 1H, Ar-H), 7.45 (s, 1H, Ar-H), 7.32 (d, 1H, Ar-H), 7.09 (d, 1H, Ar-H), 6.93 (d, 1H, Ar-H), 3.35 (s, 3H); $^{13}C$ NMR (DMSO-$d_6$): δ 184.6, 162.0, 160.4, 160.1, 149.7, 145.4, 132.9, 131.7, 131.0, 128.0, 114.3, 28.0; MS: *m/z* 219.0 (M+1). Anal. Calcd for $C_{12}H_{10}O_2S$: C, 66.03; H, 4.62. Found: C, 66.13; H, 4.59.

**3-(3-Fluorophenyl)thiophene-2-carboxaldehyde (3b)** Yield 65%; mp 90°C; IR: ν: 1652, 1480, 1410, 1325, 1270, 1020 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 9.87 (1H, s, -CHO), 7.75 (d, 1H, Ar-H), 7.46 (d, 1H, Ar-H), 7.17 (dd, 1H, Ar-H), 7.12 (d, 1H, Ar-H), 7.10 (d, 1H, Ar-H), 6.89 (d, 1H, Ar-H); $^{13}C$ NMR ($CDCl_3$): δ 183.7, 164.0, 149.6, 138.9, 135.9, 134.4, 131.4, 130.7, 125.4, 116.5, 115.8; MS: *m/z* 207.2 (M+1). Anal. Calcd for $C_{11}H_7FOS$: C, 64.06; H, 3.42. Found: C, 63.98; H, 3.49.

**3-*m*-Tolylthiophene-2-carboxaldehyde (3c)** Yield 66%; mp 92°C; IR: ν 1658, 1458, 1413, 1320, 1260, 1030 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 9.86 (1H, s, CHO), 7.68 (d, 1H, Ar-H), 7.34 (d, 3H, Ar-H), 7.25 (dd, 1H, Ar-H), 7.23 (d, 1H, Ar-H), 7.19 (d, 1H, Ar-H), 7.18 (d, 1H, Ar-H), 2.40 ($CH_3$, 3H, s); $^{13}C$ NMR ($CDCl_3$): δ 184.4, 184.2, 151.7, 138.6, 138.4, 138.4, 134.5, 133.9, 129.6, 128.7, 126.8, 21.4; MS: (*m/z*) 203.2 (M+1). Anal. Calcd for $C_{12}H_{10}OS$: C, 71.25; H, 4.98. Found: C, 71.15; H, 5.01.

**3-(2-Methoxyphenyl)thiophene-2-carboxaldehyde (3d)** Yield 93%; mp 90°C; IR: ν 1658, 1490, 1414, 1361, 1263, 1023, 895, 756 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 9.81 (s, 1H, -CHO), 7.82 (d, 1H, =CH-S), 7.52 (d, 1H, Ar-H), 7.40 (s, 1H, Ar-H), 7.32 (d, 1H, Ar-H), 7.12 (d, 1H, Ar-H), 6.90 (d, 1H, Ar-H), 3.32 (s, 3H); $^{13}C$ NMR (DMSO-$d_6$): δ 184.6, 162.1, 160.4, 160.10, 149.7, 145.4, 133.0, 131.7, 131.1, 128.0, 114.3, 28.2; MS: *m/z* 219.0 (M+1). Anal. Calcd for $C_{12}H_{10}O_2S$: C, 66.03; H, 4.62. Found: C, 66.13; H, 4.59.

### General procedure for the synthesis of chalcones 5a–l

A solution of acetophenone **4a–l** (389 mg, 2.29 mmol) in methanolic solution of NaOH (2 M) was treated with 3-(3-methoxyphenyl)thiophene-2-carboxaldehyde (**3a,** 500 mg, 2.29 mmol) and the mixture was stirred at ambient temperature for 14 h. After addition of water

(10 mL) the resultant yellow precipitate was filtered and air dried to give analytically pure compound **5a–l**.

**3-(3-(3-Methoxyphenyl)thiophen-2-yl)-1-phenylprop-2-en-1-one (5a)** Yield 93%; mp 98°C; IR: ν 1658 (C=O), 1597, 1565 (C=C), 1468, 1261 cm$^{-1}$; $^1$H NMR (DMSO-$d_6$): $\delta$ 9.23 (s, 1H, Ar-H), 8.81 (d, 1H), 8.41 (d, 1H), 7.89 (d, 1H), 7.88 (d, 2H), 7.57 (m, 2H), 7.47 (d, 1H, *J* = 14.5 Hz, CH of olefin), 7.32 (d, 1H, *J* = 14.5 Hz, CH of olefin), 7.03 (3H, m, Ar-H), 3.80 (s, 3H, $OCH_3$); $^{13}$C NMR (DMSO-$d_6$): $\delta$ 187.9, 159.4, 153.2, 149.4, 146.9, 136.4, 136.0, 135.8, 134.1, 132.7, 130.6, 129.9, 129.8, 123.8, 121.6, 120.7, 114.1, 113.8, 55.2; MS: *m/z* 322.21 (M+1). Anal. Calcd for $C_{20}H_{16}O_2S$: C, 74.97; H, 5.03. Found: C, 74.89; H, 5.08.

**1-(3-Methoxyphenyl)-3-(3-(3-methoxyphenyl)thiophen-2-yl) prop-2-en-1-one (5b)** Yield 90%; mp 80°C; IR: ν 1652 (C=O), 1565 (C=C), 1462, 1265 cm$^{-1}$; $^1$H NMR: (DMSO-$d_6$): $\delta$ 7.84 (s, 1H), 7.64 (d, 1H), 7.47 (m, 4H), 7.40 (d, 1H), 7.30 (d, 1H, *J* = 14.5 Hz, CH of olefin), 7.19 (d, 1H, *J* = 14.5 Hz, CH of olefin), 6.99 (m, 2H), 6.95 (m, 1H), 3.80 (s, 3H, $CH_3$), 3.789 (s, 3H, $CH_3$); $^{13}$C NMR (DMSO-$d_6$): $\delta$ 188.5, 159.5, 159.4, 146.5, 138.9, 136.1,135.8, 134.2, 130.6, 129.9, 129.9, 129.3, 121.5, 121.1, 120.8, 119.1, 114.6, 113.7, 112.8, 55.2, 39.5; MS: *m/z* 351.10 (M+1). Anal. Calcd for $C_{21}H_{18}O_3S$: C, 71.98; H, 5.18. Found: C, 72.01; H, 5.21.

**1-(4-methoxyphenyl)-3-(3-(3-methoxyphenyl)thiophen-2-yl) prop-2-en-1-one (5c)** Yield 92%; mp 85°C; IR: ν 1658 (C=O), 1565 (C=C), 1480, 1260 cm$^{-1}$; $^1$H NMR (DMSO-$d_6$): $\delta$ 8.29 (m, 2H), 7.85 (d, 1H), 7.50 (m, 4H), 7.45 (d, 1H, *J* = 14.5 Hz, CH of olefin), 7.21 (d, 1H, *J* = 14.5 Hz, CH of olefin), 6.98 (m, 3H), 3.80 (s, 3H, $OCH_3$), 3.79 (s, 3H, $OCH_3$); $^{13}$C NMR (DMSO-$d_6$): $\delta$ 188.4, 159.6, 159.3, 146.5, 138.8, 136.1, 135.8, 134.3, 130.6, 129.9, 129.9, 129.3, 121.5, 121.1, 120.8, 119.1, 114.6, 113.7, 112.8, 79.1, 55.3, 55.1; MS: *m/z* 351.20 (M+1). Anal. Calcd for $C_{21}H_{18}O_3S$: C, 71.98; H, 5.18. Found: C, 71.81; H, 5.16.

**1-(4-Bromophenyl)-3-(3-(3-methoxyphenyl)thiophen-2-yl)prop-2-en-1-one (5d)** Yield 92%; mp 136°C; IR: (KBr, cm$^{-1}$) ν: 1652 (C=O), 1567 (C=C), 1472, 1241 cm$^{-1}$; $^1$H NMR (DMSO-$d_6$): $\delta$ 8.013 (d, 2H), 7.86 (d, 2H), 7.75 (d, 2H), 7.54 (1H, s), 7.50 (1H, s), 7.44 (d, 1H, *J* = 14.5 Hz, CH of olefin), 7.33 (d, 1H, *J* = 14.5 Hz, CH of olefin), 6.9 (m, 2H), 3.82 (s, 3H, $CH_3$); $^{13}$C NMR (DMSO-$d_6$): $\delta$ 187.7, 159.4, 146.7, 136.4, 136.2, 136.0, 134.2, 131.8, 130.6, 130.4, 129.9, 129.2, 127.2, 121.6, 120.5, 114.7, 113.7, 112.5, 55.2, 39.9. MS: *m/z* 399.18, 401.16 (M+2). Anal. Calcd for $C_{20}H_{15}BrO_2S$: C, 60.16; H, 3.79. Found: C, 60.24; H, 3.82.

**1-(4-Chlorophenyl)-3-[3-(3-methoxyphenyl)thiophen-2-yl]prop-2-en-1-one (5e)** Yield 94%; mp 123°C; IR: ν 1685 (C=O), 1557 (C=C), 1482, 1261 cm$^{-1}$; $^1$H NMR (DMSO-$d_6$): $\delta$ 8.09 (d, 2H), 7.87 (d, 2H), 7.61 (m, 2H), 7.55 (d, 1H, *J* = 14.0 Hz, CH of olefin), 7.51 (m, 1H), 7.44 (d, 1H, *J* = 14.0 Hz, CH of olefin), 7.33 (3H, m), 3.8 (s, 3H, $OCH_3$); $^{13}$C NMR (DMSO-$d_6$): $\delta$ 187.5, 159.4, 146.7, 138.0, 136.1, 136.0, 136.0,134.2, 130.6, 130.2, 129.9, 129.5, 128.8, 121.5, 120.6, 114.6, 113.7, 55.2, 39.9; MS: *m/z* 355.11 (M+1). Anal. Calcd for $C_{20}H_{15}ClO_2S$: C, 67.69; H, 4.28. Found: C, 67.62; H, 4.31.

**1-(4-Iodophenyl)-3-(3-(3-methoxyphenyl)thiophen-2-yl)prop-2-en-1-one (5f)** Yield 95%; mp 97°C; IR: ν 1662 (C=O), 1557 (C=C), 1482, 1261 cm$^{-1}$; $^1$H NMR (DMSO-$d_6$): $\delta$ 8.86 (s, 1H), 8.21 (d, 1H), 8.05 (m, 2H), 7.97 (m, 1H), 7.88 (s, 1H), 7.77 (m, 2H), 7.72 (d, 1H, *J* = 14.0 Hz, CH of olefin), 7.70 (d, 1H, *J* = 14.0 Hz, CH of olefin), 7.68 (m, 2H), 3.82 (s, 3H); $^{13}$C NMR (DMSO-$d_6$): $\delta$ 188.4, 159.4, 146.5, 136.1, 135.7, 134.5, 134.4, 132.2, 130.6, 130.1, 129.9, 129.6, 129.2, 128.4, 127.6, 124.0, 121.6, 121.1, 114.7, 55.2; MS: *m/z* 446.30 (M+1). Anal. Calcd for $C_{20}H_{15}IO_2S$: C, 53.82; H, 3.39. Found: C, 53.98; H, 3.43.

**3-(3-(3-Methoxyphenyl)thiophen-2-yl)-1-(2,4,6-trimethylphenyl) prop-2-en-1-one (5g)** Yield 93%; mp 120°C; IR: ν 1663 (C=O), 1560 (C=C), 1462, 1251 cm$^{-1}$; $^1$H NMR (DMSO-$d_6$): $\delta$ 7.86 (s, 1H), 7.30 (d, 1H, *J* = 14.0 Hz, CH of olefin), 6.94 (d, 1H, *J* = 14.0 Hz, CH of olefin), 6.85 (m, 6H, Ar-H), 3.73 (s, 3H, $CH_3$), 2.22 (s, 9H); $^{13}$C NMR (DMSO-$d_6$): $\delta$ 199.3, 159.3, 146.1, 138.0 137.7, 136.7, 135.6, 133.3, 133.2, 130.6, 129.9, 129.7, 128.0, 126.9, 121.2, 114.2, 113.9, 55.1, 20.6, 18.7; MS: *m/z* 363.28 (M+1). Anal. Calcd for $C_{23}H_{22}O_2S$: C, 76.21; H, 6.12. Found: C, 76.12; H, 6.21.

**3-(3-(3-methoxyphenyl)thiophen-2-yl)-1-(napthalene-1-yl)prop-2-en-1-one (5h)** Yield 94%; mp 119°C; IR: ν 1662 (C=O), 1545 (C=C), 1462, 1241 cm$^{-1}$; $^1$H NMR (DMSO-$d_6$): $\delta$ 8.12 (s, 1H), 8.01 (d, 1H, Ar-H), 7.90 (d, 2H, Ar-H), 7.81 (d, 1H, *J* = 14.0 Hz, CH of olefin), 7.58 (d, 3H, Ar-H), 7.46 (d, 4H, Ar-H), 7.33 (d, 1H, *J* = 14.0 Hz, CH of olefin), 7.01 (s, 1H, Ar-H), 3.82 (s, 3H, $CH_3$); $^{13}$C NMR (DMSO-$d_6$): $\delta$ 196.0, 187.9, 159.4, 159.0, 153.2, 149.4, 141.4, 138.1, 136.1, 136.0, 132.7, 130.4, 129.8, 129.6, 129.2, 127.2, 121.5, 120.7, 114.1, 113.6, 55.2, 45.8; MS: *m/z* 371.15 (M+1). Anal. Calcd for $C_{24}H_{18}O_2S$: C, 77.81; H, 4.90. Found: C, 78.31; H, 4.94.

**3-(3-(3-methoxyphenyl)thiophen-2-yl)-1-(napthalene-2-yl)-prop-2-en-1-one (5i)** Yield 94%; mp 119°C; IR: ν 1662 (C=O), 1545 (C=C), 1462, 1241 cm$^{-1}$; $^1$H NMR (DMSO-$d_6$): $\delta$ 8.07 (s, 1H), 8.02 (d, 1H, Ar-H), 7.94 (d, 2H, Ar-H), 7.83 (d,2H), 7.54 (d, 3H, Ar-H), 7.42 (d, 3H, Ar-H), 7.32 (d, 1H, *J* = 14.0 Hz, CH of olefin), 7.01 (d, 1H, *J* = 14.0 Hz, CH of olefin), 3.82 (s, 3H, $CH_3$); $^{13}$C NMR (DMSO-$d_6$): $\delta$ 197.0, 187.5, 159.4, 159.4, 159.1, 146.8, 141.4, 139.3, 138.1, 136.4, 136.0, 134.2, 130.8, 130.6, 130.6, 129.9, 129.6, 129.2, 127.7, 127.1, 120.9, 114.6, 113.7, 95.2, 55.1, 54.9, 45.8. MS: *m/z* 371.15, 372.17 (M+1). Anal. Calcd for $C_{24}H_{18}O_2S$: C, 77.81; H, 4.90. Found: C, 77.62; H, 4.87.

**3-(3-(3-methoxyphenyl)thiophen-2-yl)-1-(pyridin-2-yl)-prop-2-en-1-one (5j)** Yield 92%; mp 158°C; IR: ν 1675 (C=O), 1576, 1525 (C=C), 1482, 1224, 970 cm$^{-1}$; $^1$H NMR (DMSO-$d_6$): $\delta$ 8.81 (d, 1H, Ar-H), 8.04 (m, 3H, Ar-H), 7.94 (s, 1H), 7.85 (d, 1H, *J* = 14.3 Hz, CH of olefin), 7.68 (d, 1H, *J* = 14.3 Hz, CH of olefin), 7.46 (s, 1H), 7.34 (d, 1H, Ar-H), 7.034 (m, 3H, Ar-H), 3.83 (s, 3H, CH3); $^{13}$C NMR (DMSO-$d_6$): $\delta$ 187.9, 159.4, 153.1, 149.1, 146.7, 137.7, 136.0, 135.5, 134.5, 130.8, 129.9, 129.4, 127.6, 122.3, 121.5, 119.8, 114.6, 113.8, 55.2; MS: *m/z* 322.0 (M+1). Anal. Calcd for $C_{19}H_{15}NO_2S$: C, 71.00; H, 4.70; N, 4.36. Found: C, 71.12; H, 4.65; N, 4.28.

**3-(3-(3-methoxyphenyl)thiophen-2-yl)-1-(pyridin-3-yl)prop-2-en-1-one (5k)** Yield 92%; mp 140°C; IR: ν 1682 (C=O), 1567 (C=C), 1482, 1261, 975 cm$^{-1}$; $^1$H NMR (DMSO-$d_6$): $\delta$ 9.23 (S, 1H Py-H), 8.80 (d, 1H, Py-H), 8.40 (d, 1H, Py-H), 7.90 (2H, m), 7.65 (m, 2H), 7.43-7.09 (m, 3H), 7.42 (d, 1H, *J* = 14.0 Hz, CH of olefin), 7.30 (d, 1H, *J* = 14.0 Hz, CH of olefin), 3.8 (s, 3H, $OCH_3$); $^{13}$C NMR (DMSO-$d_6$): $\delta$ 187.9, 159.4, 153.1, 149.1, 146.7, 137.7, 136.0, 135.5, 134.6, 130.8, 129.4, 127.6, 122.3, 121.5, 119.8, 114.6, 113.8, 55.2; MS: *m/z* 322.0 (M+1). Anal. Calcd for $C_{19}H_{15}NO_2S$: C, 71.00; H, 4.70; N, 4.36. Found: C, 71.15; H, 4.61; N, 4.30.

**3-(3-(3-Methoxyphenyl)thiophen-2-yl)-1-(thiophen-2-yl)-prop-2-en-1-one (5l)** Yield 94%; mp 129°C; IR: ν 1642 (C=O), 1546 (C=C), 1462, 1261 cm$^{-1}$; $^1$H NMR (DMSO-$d_6$): $\delta$ 8.25 (s, 1H), 8.24 (d, 1H, Ar-H), 7.85 (d, 2H), 7.53 (m, 2H, Ar-H), 7.49 (d, 1H, *J* = 14.5 Hz, CH of olefin), 7.49 (d, 1H, *J* = 14.5 Hz, CH of olefin), 7.43 (m, 3H), 3.82 (s, 3H, $OCH_3$); $^{13}$C NMR (DMSO-$d_6$): $\delta$ 180.9, 159.4, 146.5, 145.1, 136.1, 135.4, 134.8, 134.1, 133.4, 130.6, 129.9, 129.3, 128.9, 121.5, 120.8, 114.6, 113.7, 55.2; MS: *m/z* 327.10 (M+1). Anal. Calcd for $C_{18}H_{14}O_2S_2$: C, 66.23; H, 4.32. Found: C, 66.18; H, 4.28.

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