Design and Microwave Assisted Synthesis of Novel 2-Phenyl/2-Phenylethynyl-3-aroyl thiophenes as Potent Antiproliferative Agents

Rupinder Kaur Gill[a,b,c], Ramandeep Kaur[a], Virender Kumar[d], Vivek Gupta[e], Gagandeep Singh[f] and Jitender Bariwal[a,g*]

[a]*Department of Pharmaceutical Chemistry, ISF College of Pharmacy, Moga-142001, Punjab, India.*

[b]*I. K. Gujral Punjab Technical University, Kapurthala, Jalandhar -144 601, Punjab, India.*

[c]*Department of Pharmaceutical Sciences, Guru Nanak Dev University, Amritsar-143 005, Punjab, India.*

[d]*Department of Pharmaceutical Sciences, University of Nebraska Medical Center, Omaha, Nebraska, USA, 68198.*

[e]*Post-Graduate Department of Physics & Electronics, University of Jammu, Jammu Tawi-180 006, India.*

[f]*Bio-Organic and Photochemistry Laboratory, Department of Pharmaceutical Sciences, Guru Nanak Dev University, Amritsar-143 005, Punjab, India.*

[g]*Satiate Research & Anatech Pvt. Ltd., HSIIDC, Barwala, Panchkula-134118, Haryana, India.*

***Corresponding author**: Dr. Jitender Bariwal. Tel.: +91 1636 324200; fax: +91 1636 239515

E-mail: jitender.bariwal@gmail.com

Supporting Information Available: Tables and characterization data.

Table of contents:

Experimental Section

Chemistry

The starting materials and solvents were commercially purchased from Sigma Aldrich and SD fine and the reagents were used without further purification. Solvents used in reaction were dried before use and stored over activated molecular sieves (4A˚). ^{1}HNMR and ^{13}C NMR spectra were carried out on Bruker Avance II 400 and 500 MHz spectrometer, operating at 400, 500 MHz and 100, 125 MHz, respectively. Chemical shifts (δ) are expressed in ppm relative to TMS (Tetramethylsilane, δ=0) as an internal standard and $CDCl_3$ as a solvent. The coupling constants (*J*) were given in Hertz (Hz) and signals are represented by singlet (s), doublet (d), triplet (t) and multiplet (m). The mass spectra were recorded on a Bruker microTOF QII Mass spectrometer. The melting points were determined in open capillary method on Buchi 535 electronic apparatus and are uncorrected. The IR spectra of synthesized compounds were recorded on NICOLET-380 FTIR spectrophotometer in potassium bromide discs. The progress of the reaction was monitored by TLC on precoated silica-gel plates (Silica gel 60 F_{254}) using hexane: ethyl acetate as solvent. Column chromatography was performed on 60–120 mesh silica gel.

Microwave Irradiation Experiments

All the microwave irradiation experiments were performed in a dedicated CEM-Discover monomode microwave apparatus, with continuous irradiation power from 0 to 300 W and utilization of the standard absorbance level of 300W maximum power. The 10-mL glass tube sealed with Teflon septum was used for performing all the reactions and the reaction mixture was irradiated at a required ceiling temperature using maximum power for the stipulated time. Then the mixture was cooled to ambient temperature with gas jet cooling.

General Procedures and Characterization data of Synthesized compounds

***General procedure for the preparation of substituted 2-aminothiophenes 9(a-m)*[1,2]**

The substituted 2-aminothiophenes ***9a-m*** were synthesized according to the literature procedure.[1,2] 3-Oxopropanenitrile 2.0 g (0.01 mol, 1.0 eq.)[1] was dissolved in 20 ml of dried ethanol and then 1.35 g of (1.42 ml, 0.01 mol, 1.0 eq.) cyclohexanone and 0.44 g of (0.013 mol, 1.0 eq.) sulfur was added to it. Further, morpholine 12.8 g (12.7 ml, 0.14 mol, 10.7 eq.) was added dropwise on heating to dissolve elemental sulphur and then refluxed it for 10-15 h. The completion of reaction was checked by TLC. After cooling down to room temperature,

the reaction mixture was poured into ice-cold water with vigorous shaking. The solid precipitate obtained were filtered, washed, dried and recrystallized from methanol.

***(2-Amino-4,5-dimethylthiophen-3-yl)(phenyl)methanone* (9*a*)**: Mp: 132-135°C; IR (KBr) ν: 3239, 3138, 2919, 1660, 1582, 1237 cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$): 7.76 (*d*, *J* = 7.0 Hz, 2H, Ar-H), 7.54 (t, *J* = 6.8 Hz, 1H, Ar-H), 7.48 (t, *J* = 6.8 Hz, 2H, Ar-H), 7.44 (s, 2H, NH_2), 2.30 (s, 3H, CH_3), 2.15 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 193.29, 158.71, 136.07, 132.59, 132.37, 131.96, 129.49 (X2), 128.20 (X2), 111.30, 12.56, 12.34.

(2-Amino-4,5-dimethylthiophen-3-yl)(*p*-tolyl)methanone (9*b*): Mp: 103-105°C; IR (KBr) ν: 3270, 3129, 2930, 1679, 1577, 1232 cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$): 7.75 (*d*, *J* = 7.0 Hz, 2H, Ar-H), 7.44 (d, *J* = 7.0 Hz, 2H, Ar-H), 7.40 (s, 2H, NH_2), 2.36 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 2.13 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 193.18, 156.34, 140.59, 136.21, 134.38, 130.65, 129.22 (X2), 128.88 (X2), 109.19, 22.34, 12.51, 12.20.

(2-Amino-4,5-dimethylthiophen-3-yl)(4-nitrophenyl)methanone (9*c*): Mp: 153-155°C; IR (KBr) ν: 3240, 3135, 2965, 1666, 1513, 1232 cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$): 7.99 (*d*, *J* = 7.1 Hz, 2H, Ar-H), 7.81 (d, *J* = 7.0 Hz, 2H, Ar-H), 7.49 (s, 2H, NH_2), 2.40 (s, 3H, CH_3), 2.25 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 193.19, 158.74, 148.69, 140.07, 138.55, 134.38, 129.33 (X2), 123.69 (X2), 114.27, 13.30, 12.56.

(2-Amino-4,5-dimethylthiophen-3-yl)(4-methoxyphenyl)methanone (9*d*): Mp: 133-135°C; IR (KBr) ν: 3239, 3123, 2935, 1689,1216 cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$): 7.67 (*d*, *J* = 7.2 Hz, 2H, Ar-H), 7.46 (d, *J* = 6.8 Hz, 2H, Ar-H), 3.81 (s, 3H, OCH_3), 2.30 (s, 3H, CH_3), 2.14 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 193.19, 155.79, 154.23, 140.09, 134.73, 130.21 (X2), 125.76, 115.29 (X2), 105.64, 54.80, 12.87, 12.19.

(2-Amino-4,5-dimethylthiophen-3-yl)(3,4,5-trimethoxyphenyl)methanone (9*e*): Mp: 169-173°C; IR (KBr) ν: 3241, 2927, 1671, 1214 cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$): δ = 8.10 (s, 2H, NH_2), 6.87 (*d*, *J* = 6.8 Hz, 2H, Ar-H), 3.85 (s, 9H, OCH_3), 2.27 (s, 3H, CH_3), 2.16 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 193.22, 155.65, 149.10 (X2), 146.72, 140.14, 134.69, 128.75, 105.41 (X2), 109.02, 59.46, 59.42, 56.04, 12.87, 12.22.

(2-Amino-4,5,6,7-tetrahydrobenzo[*b*]thiophen-3-yl)(phenyl)methanone (9*f*): Mp: 150-155°C; IR (KBr) ν: 3239, 3138, 2925, 1669, 1273 cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$): δ = 7.79-7.68 (*m*, 3H, Ar-H), 7.49 (t, *J* = 7.0 Hz, 2H, Ar-H), 7.47 (s, 2H, NH_2), 2.74 (t, *J* = 6.2 Hz, 2H, CH_2), 2.40 (t, *J* = 6.0 Hz, 2H, CH_2), 1.85-1.78 (m, 2H, CH_2), 1.70-1.66 (m, 2H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): 193.27, 157.50, 142.73, 133.41, 131.26, 129.50 (X2), 128.25 (X2), 126.32, 111.32, 23.76, 22.84, 22.60, 21.51.

(2-Amino-4,5,6,7-tetrahydrobenzo[*b*]thiophen-3-yl)(*p*-tolyl)methanone (9*g*): Mp: 110-113°C; IR (KBr) ν: 3275, 3130, 2935, 1688, 1234 cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$): δ = 7.72 (*d*, *J* = 7.0 Hz, 2H, Ar-H), 7.41 (d, *J* = 6.8 Hz, 2H, Ar-H), 2.72 (t, *J* = 6.2 Hz, 2H, CH_2), 2.47 (t, *J* = 6.2 Hz, 2H, CH_2), 2.36 (s, 3H, CH_3), 1.79-1.75 (m, 2H, CH_2), 1.62-1.54 (m, 2H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): 193.18, 156.41, 145.18, 140.02, 129.67, 129.34 (X2), 128.92 (X2), 126.45, 109.23, 23.77, 23.10, 22.87, 22.52, 22.33.

(2-Amino-4,5,6,7-tetrahydrobenzo[*b*]thiophen-3-yl)(4-nitrophenyl)methanone (9*h*): Mp: 159-162 °C; IR (KBr) ν: 3239, 3130, 2962, 1674, 1514, 1235 cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$): δ = 8.15 (*d*, *J* = 7.8 Hz, 2H, Ar-H), 7.65 (d, *J* = 7.5 Hz, 2H, Ar-H), 2.73 (t, *J* = 6.2 Hz, 2H, CH_2), 2.64 (t, *J* = 6.0 Hz, 2H, CH_2), 1.87-1.70 (m, 4H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): 193.22, 158.40, 148.82, 140.64, 140.20, 129.30 (X2), 126.37, 123.77 (X2), 114.29, 23.60, 23.27, 22.56, 22.36.

(2-Amino-4,5,6,7-tetrahydrobenzo[*b*]thiophen-3-yl)(4-methoxyphenyl)methanone (9*i*): Mp: 140-144 °C; IR (KBr) ν: 3241, 3128, 2941, 1689 cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$): δ = 7.75 (*d*, *J* = 7.0 Hz, 2H, Ar-H), 7.42 (d, *J* = 6.8 Hz, 2H, Ar-H), 3.87 (s, 3H, OCH_3), 2.71 (t, *J* = 6.0 Hz, 2H, CH_2), 2.42 (t, *J* = 6.0 Hz, 2H, CH_2), 1.74-1.65 (m, 2H, CH_2), 1.57-1.45 (m, 2H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): 193.15, 155.82, 150.21, 141.36, 129.83 (X2), 128.04, 127.70, 115.05 (X2), 105.71, 54.78, 24.68, 23.33, 22.47, 22.45.

(2-Amino-4,5,6,7-tetrahydrobenzo[*b*]thiophen-3-yl)(3,4,5-trimethoxyphenyl)methanone (9*j*): Mp: 176-180; IR (KBr) ν: 3243, 2932, 1671 cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$): δ = 8.10 (s, 2H, NH_2), 6.87 (*d*, *J* = 7.5 Hz, 2H, Ar-H), 3.85 (s, 9H, OCH_3), 2.65 (t, *J* = 6.2 Hz, 2H, CH_2), 2.34 (t, *J* = 6.0 Hz, 2H, CH_2), 1.66-1.57 (m, 4H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): 193.24, 155.71, 149.34 (X2), 146.73, 140.12, 128.70, 126.08, 105.45 (X2), 109.11, 59.47, 59.38, 56.00, 24.75, 23.31, 22.47, 22.43.

(2-Amino-5,6,7,8-tetrahydro-4*H*-cyclohepta[*b*]thiophen-3-yl)(phenyl)methanone (9*k*): Mp: 128-130°C; IR (KBr) ν: 3248, 3139, 2915, 1679 cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$): δ = 7.79 (*d*, *J* = 7.5 Hz, 2H, Ar-H), 7.58 (t, *J* = 7.0 Hz, 1H, Ar-H), 7.53 (t, *J* = 7.5 Hz, 2H, Ar-H), 2.68 (t, *J* = 6.0 Hz, 2H, CH_2), 2.40 (t, *J* = 6.0 Hz, 2H, CH_2), 1.66-1.57 (m, 6H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): 193.26, 155.43, 145.10, 133.45, 131.30, 129.43 (X2), 128.25 (X2), 126.12, 111.46, 30.15, 29.68, 26.51, 25.77, 18.36.

(2-Amino-5,6,7,8-tetrahydro-4*H*-cyclohepta[*b*]thiophen-3-yl)(*p*-tolyl)methanone (9*l*): Mp: 118-120°C; IR (KBr) ν: 3271, 3130, 2932, 1678 cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$): δ = 7.76 (*d*, *J* = 7.2 Hz, 2H, Ar-H), 7.51 (s, 2H, NH_2), 7.39 (d, *J* = 7.0 Hz, 2H, Ar-H), 2.67 (t, *J* = 6.0 Hz, 2H, CH_2), 2.36 (t, *J* = 5.8 Hz, 2H, CH_2), 2.37 (s, 3H, CH_3), 1.62-1.48 (m, 6H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): 193.18, 156.72, 141.99, 141.60, 129.31, 129.24 (X2), 128.89 (X2), 126.29, 109.27, 30.18, 29.80, 27.00, 26.46, 22.36, 19.13.

(2-Amino-5,6,7,8-tetrahydro-4*H*-cyclohepta[*b*]thiophen-3-yl)(4-nitrophenyl)methanone (9*m*): Mp: 151-155 °C; IR (KBr) ν: 3241, 3133, 2963, 1666 cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$): δ = 8.12 (*d*, *J* = 7.5 Hz, 2H, Ar-H), 8.06 (s, 2H, NH_2), 7.74 (d, *J* = 7.2 Hz, 2H, Ar-H), 2.79 (t, *J* = 6.5 Hz, 2H, CH_2), 2.40 (t, *J* = 6.0 Hz, 2H, CH_2), 1.76-1.63 (m, 6H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): 193.21, 158.10, 148.73, 140.34, 140.06, 129.36 (X2), 126.30, 123.77 (X2), 114.42, 30.11, 29.85, 26.70, 26.65, 16.49.

General procedure for the preparation of substituted 2-iodo-thiophenes* (10*a-m*)[3]:** To a stirred solution of *p*-toluene sulfonic acid (*p*-TSA) (2.21 g, 0.01 mol, 3.0 eq.) in MeCN (10 ml) was added the corresponding 2-aminothiophene **9*a-m (1.0 g, 0.004 mol, 1.0 eq.) at 0°C to get paste like suspension. To this suspension, solution of $NaNO_2$ (0.53 g, 0.008 mol, 2.0 eq.) in water was added and N_2 fumes evolved (diazotization was checked by starch-iodide paper; its color changes from white to brown). Then, immediately added the solution of KI (1.99 g, 0.012 mol, 3.0 eq.) in H_2O (5 ml). Afterward, the mixture was stirred for 15 min at 0°C then for 15 min at room temperature. The reaction mixture was neutralized with dil. ammonia solution and extracted with ethyl acetate (30 ml×3). The organic layers were combined, dried over anhydrous Na_2SO_4, and evaporated under low pressure. The crude product was purified by column chromatography using 9:1 hexane/ethyl acetate.

(2-Iodo-4,5-dimethylthiophen-3-yl)(phenyl)methanone (**10*a***): Mp: 245-247°C; IR (KBr) ν: 3052, 2940, 1708, 647 cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$): 7.80 (*d*, *J* = 7.1 Hz, 2H, Ar-H), 7.63 (t, *J* = 6.8 Hz, 1H, Ar-H), 7.52 (t, *J* = 6.8 Hz, 2H, Ar-H), 2.29 (s, 3H, CH_3), 2.13 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 193.34, 149.28, 140.11, 134.49, 133.44, 131.30, 129.49 (X2), 128.22 (X2), 84.22, 13.64, 12.71. HRMS (microTOF-QII, MS, ESI): *m/z* $[M]^+$ Calcd for $C_{13}H_{11}IOS$: 342.1953, found: 342.1950.

(2-Iodo-4,5-dimethylthiophen-3-yl)(p-tolyl)methanone (**10*b***): Mp: 270-273°C; IR (KBr) ν: 3049, 2940, 1711, 643 cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$): 7.72 (*d*, *J* = 7.0 Hz, 2H, Ar-H), 7.46 (d, *J* = 6.8 Hz, 2H, Ar-H), 2.38 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 2.10 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 193.21, 151.52, 141.80, 138.94, 134.78, 130.18, 129.24 (X2), 128.89 (X2), 84.23, 22.34, 13.40, 12.53. HRMS (microTOF-QII, MS, ESI): *m/z* $[M]^+$ Calcd for $C_{14}H_{13}IOS$: 356.2219, found: 356.2213.

(2-Iodo-4,5-dimethylthiophen-3-yl)(p-nitrophenyl)methanone (**10*c***): Mp: 286-289°C; IR (KBr) ν: 3053, 2920, 1668, 644 cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$): 7.93 (*d*, *J* = 7.2 Hz, 2H, Ar-H), 7.75 (d, *J* = 6.8 Hz, 2H, Ar-H), 2.41 (s, 3H, CH_3), 2.23 (s, 3H, CH_3). ^{13}C NMR (100

MHz, $CDCl_3$): 193.23, 151.40, 148.67, 140.01, 139.84, 134.40, 129.33 (X2), 123.72 (X2), 84.18, 13.36, 12.59. HRMS (microTOF-QII, MS, ESI): *m/z* $[M+H]^+$ Calcd for $C_{13}H_{10}INO_3S$: 388.1929, found: 388.1933.

(2-Iodo-4,5-dimethylthiophen-3-yl)(p-methoxyphenyl)methanone (**10*d***): Mp: 290-293°C; IR (KBr) ν: 3050, 2918, 1706, 646 cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$): 7.69 (*d*, *J* = 7.0 Hz, 2H, Ar-H), 7.51 (d, *J* = 6.5 Hz, 2H, Ar-H), 3.82 (s, 3H, OCH_3), 2.28 (s, 3H, CH_3), 2.15 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 193.22, 151.73, 148.91, 140.12, 134.86, 130.24 (X2), 125.74, 115.33 (X2), 84.16, 54.81, 13.62, 12.58. HRMS (microTOF-QII, MS, ESI): *m/z* $[M]^+$ Calcd for $C_{14}H_{13}IO_2S$: 372.2213, found: 372.2217.

(2-Iodo-4,5-dimethylthiophen-3-yl)(3,4,5-trimethoxyphenyl)methanone (**10*e***): Mp: Above 300°C; IR (KBr) ν: 3055, 2923, 1711, 644 cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$): δ = 6.85 (*d*, *J* = 7.0 Hz, 2H, Ar-H), 3.87 (s, 9H, OCH_3), 2.29 (s, 3H, CH_3), 2.17 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 193.25, 147.54, 147.33 (X2), 146.79, 140.17, 134.88, 128.79, 105.44 (X2), 84.30, 59.44, 59.41, 56.04, 13.64, 12.59. HRMS (microTOF-QII, MS, ESI): *m/z* $[M]^+$ Calcd for $C_{16}H_{17}IO_4S$: 432.2732, found: 432.2735.

(4,5,6,7-Tetrahydro-2-iodobenzo[b]thiophen-3-yl)(phenyl)methanone (**10*f***): Mp: 285-288°C; IR (KBr) ν: 3054, 1710, 650 cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$): δ = 7.83 (*d*, *J* = 7.1 Hz, 2H, Ar-H), 7.61 (t, *J* = 7.0 Hz, 1H, Ar-H), 7.45 (t, *J* = 7.0 Hz, 2H, Ar-H), 2.76 (t, *J* = 6.0 Hz, 2H, CH_2), 2.43 (t, *J* = 6.0 Hz, 2H, CH_2), 1.88-1.80 (m, 2H, CH_2), 1.72-1.66 (m, 2H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): 193.29, 149.33, 144.77, 133.50, 131.29, 129.50 (X2), 128.26 (X2), 126.40, 84.24, 23.79, 22.88, 22.64, 21.56. HRMS (microTOF-QII, MS, ESI): *m/z* $[M+H]^+$ Calcd for $C_{15}H_{13}IOS$: 369.2326, found: 369.2325.

(4,5,6,7-Tetrahydro-2-iodobenzo[b]thiophen-3-yl)(p-tolyl)methanone (**10*g***): Mp: Above 300°C; IR (KBr) ν: 3052, 2941, 1715, 646 cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$): δ = 7.74 (*d*, *J* = 7.2 Hz, 2H, Ar-H), 7.41 (d, *J* = 7.0 Hz, 2H, Ar-H), 2.74 (t, *J* = 6.2 Hz, 2H, CH_2), 2.51 (t, *J* = 6.0 Hz, 2H, CH_2), 2.36 (s, 3H, CH_3), 1.82-1.74 (m, 2H, CH_2), 1.65-1.57 (m, 2H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): 193.23, 151.47, 145.27, 140.13, 129.60, 129.31 (X2), 128.93 (X2), 126.42, 84.21, 23.79, 23.12, 22.91, 22.56, 22.31. HRMS (microTOF-QII, MS, ESI): *m/z* $[M]^+$ Calcd for $C_{16}H_{15}IOS$: 382.2592, found: 382.2595.

(2-Iodo-4,5,6,7-tetrahydrobenzo[b]thiophen-3-yl)(4-nitrophenyl)methanone (**10*h***): Mp: Above 300°C; IR (KBr) ν: 3050, 1666, 640 cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$): δ = 8.09 (*d*, *J* = 7.5 Hz, 2H, Ar-H), 7.60 (d, *J* = 7.1 Hz, 2H, Ar-H), 2.78 (t, *J* = 5.6 Hz, 2H, CH_2), 2.66 (t, *J* = 5.6 Hz, 2H, CH_2), 1.89-1.71 (m, 4H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): 193.26, 151.49, 148.79, 146.67, 140.03, 129.33 (X2), 126.38, 123.77 (X2), 84.16, 23.69, 23.34, 22.58, 22.17.

HRMS (microTOF-QII, MS, ESI): *m/z* $[M]^+$ Calcd for $C_{15}H_{12}INO_3S$: 413.2302, found: 416.2305.

(4,5,6,7-Tetrahydro-2-iodobenzo[b]thiophen-3-yl)(p-methoxyphenyl)methanone (**10*i***): Mp: Above 300°C; IR (KBr) ν: 3054, 2917, 1709, 645 cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$): δ = 7.76 (*d*, *J* = 6.8 Hz, 2H, Ar-H), 7.42 (d, *J* = 6.8 Hz, 2H, Ar-H), 3.89 (s, 3H, OCH_3), 2.73 (t, *J* = 5.8 Hz, 2H, CH_2), 2.46 (t, *J* = 6.0 Hz, 2H, CH_2), 1.77-1.68 (m, 2H, CH_2), 1.59-1.44 (m, 2H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): 193.21, 151.74, 148.87, 146.74, 129.87 (X2), 128.01, 127.75, 115.06 (X2), 84.14, 54.78, 24.72, 23.38, 22.53, 22.47. HRMS (microTOF-QII, MS, ESI): *m/z* $[M]^+$ Calcd for $C_{16}H_{15}IO_2S$: 398.2586, found: 398.2591.

(2-Iodo-4,5,6,7-tetrahydrobenzo[b]thiophen-3-yl)(3,4,5-trimethoxyphenyl)methanone (**10*j***): Mp: Above 300°C; IR (KBr) ν: 3053, 2919, 1708, 644 cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$): δ = 6.86 (*d*, *J* = 7.0 Hz, 2H, Ar-H), 3.87 (s, 9H, OCH_3), 2.68 (t, *J* = 6.0 Hz, 2H, CH_2), 2.39 (t, *J* = 6.0 Hz, 2H, CH_2), 1.74-1.64 (m, 4H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): 193.24, 147.56, 147.34 (X2), 146.79, 144.34, 128.68, 126.11, 105.46 (X2), 84.37, 59.46, 59.41, 56.04, 24.74, 23.38, 22.50, 22.48. HRMS (microTOF-QII, MS, ESI): *m/z* $[M+H]^+$ Calcd for $C_{18}H_{19}IO_4S$: 459.3105, found: 459.3109.

(5,6,7,8-Tetrahydro-2-iodo-4H-cyclohepta[b]thiophen-3-yl)(phenyl)methanone (**10*k***): Mp: 290-295°C; IR (KBr) ν: 3053, 2943, 1709, 648 cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$): δ = 7.81 (*d*, *J* = 7.0 Hz, 2H, Ar-H), 7.58 (t, *J* = 6.8 Hz, 1H, Ar-H), 7.50 (t, *J* = 7.0 Hz, 2H, Ar-H), 2.71 (t, *J* = 5.8 Hz, 2H, CH_2), 2.38 (t, *J* = 5.8 Hz, 2H, CH_2), 1.74-1.59 (m, 6H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): 193.31, 149.31, 144.79, 133.51, 131.32, 129.50 (X2), 128.25 (X2), 126.42, 84.24, 30.21, 29.98, 26.76, 26.01, 18.34. HRMS (microTOF-QII, MS, ESI): *m/z* $[M+H]^+$ Calcd for $C_{16}H_{15}IOS$: 382.2592, found: 382.2599.

(5,6,7,8-Tetrahydro-2-iodo-4H-cyclohepta[b]thiophen-3-yl)(p-tolyl)methanone (**10*l***): Mp: Above 300°C; IR (KBr) ν: 3053, 2941, 1714, 648 cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$): δ = 7.76 (*d*, *J* = 7.5 Hz, 2H, Ar-H), 7.41 (d, *J* = 7.0 Hz, 2H, Ar-H), 2.64 (t, *J* = 6.1 Hz, 2H, CH_2), 2.40 (t, *J* = 6.1 Hz, 2H, CH_2), 2.38 (s, 3H, CH_3), 1.68-1.52 (m, 6H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): 193.24, 151.49, 144.68, 142.77, 129.36, 129.24 (X2), 128.91 (X2), 126.36, 84.19, 30.21, 29.84, 27.05, 26.54, 22.36, 19.10. HRMS (microTOF-QII, MS, ESI): *m/z* $[M+H]^+$ Calcd for $C_{17}H_{17}IOS$: 397.2858, found: 397.2862.

(5,6,7,8-Tetrahydro-2-iodo-4H-cyclohepta[b]thiophen-3-yl)(p-nitrophenyl)methanone (**10*m***): Mp: Above 300°C; IR (KBr) ν: 3049, 2921, 1666, 642 cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$): δ = 7.95 (*d*, *J* = 7.0 Hz, 2H, Ar-H), 7.67 (d, *J* = 6.6 Hz, 2H, Ar-H), 2.76 (t, *J* = 6.0 Hz, 2H, CH_2), 2.43 (t, *J* = 5.8 Hz, 2H, CH_2), 1.84-1.68 (m, 6H, CH_2). ^{13}C NMR (100 MHz,

$CDCl_3$): 193.24, 151.42, 148.66, 146.70, 140.00, 129.34 (X2), 126.38, 123.79 (X2), 84.16, 30.13, 29.98, 26.74, 26.65, 16.55. HRMS (microTOF-QII, MS, ESI): *m/z* $[M]^+$ Calcd for $C_{16}H_{14}INO_3S$: 427.2567, found: 427.2573.

***General procedure for the preparation of 2-phenyl-3-aroyl thiophenes* (12*a-j*)**

A suspension of iodothiophene **10** (0.1 g, 0.00027 mol), phenylboronic acid (**11**, 0.042 g, 0.00035 mol, 1.3 eq.) and tetrakis(triphenylphosphane)palladium(0) (16 mg, 5 mol%) in DMF (1.5 ml) were loaded into the microwave vial. To this suspension, K_2CO_3 (111 mg, 0.1 mol, 3.0 eq.) and water (1.5 ml) was added and vessel was sealed. The mixture was irradiated with stirring at a ceiling temperature of 140°C, at a maximum power level of 100W for 20 min. After the reaction, the vessel was cooled to 60°C by air jet cooling. The reaction mixture was poured into water and extracted with diethyl ether (25 ml × 3). The combined organic layers were dried on Na_2SO_4 and solvent was removed under reduced pressure. The crude product obtained was purified using column chromatography (5% ethyl acetate-hexane) to afford the desired compound.

(4,5-Dimethyl-2-phenylthiophen-3-yl)(phenyl)methanone (**12*a***): IR (KBr) ν: 3028, 1650, 1594 cm^{-1}. ^{1}HNMR (500 MHz, $CDCl_3$): δ: 7.75 (d, *J* = 7.0 Hz, 2H, Ar-H), 7.44 (t, *J* = 6.8 Hz, 1H, Ar-H), 7.26-7.21 (m, 4H, Ar-H), 7.18-7.10 (m, 3H, Ar-H), 2.33 (s, 3H, CH_3), 2.24 (s, 3H, CH_3). ^{13}C NMR (120 MHz, $CDCl_3$): 194.37, 143.01, 138.51, 137.08, 136.94, 135.86, 133.32, 128.81 (X2), 128.63, 127.66 (X2), 127.18 (X2), 127.01 (X2), 126.99, 12.35, 11.76; HRMS (microTOF-QII, MS, ESI): *m/z* $[M+Na]^+$ Calcd for $C_{19}H_{16}OS$: 315.3947, found: 315.3943.

(*4,5-Dimethyl-2-phenylthiophen-3-yl)(p-tolyl)methanone* (**12*b***): IR (KBr) ν: 3033, 1650, 1603 cm^{-1}; ^{1}HNMR (500 MHz, $CDCl_3$): δ: 7.68 (d, *J* = 7.0 Hz, 2H, Ar-H), 7.22-7.15 (m, 4H, Ar-H), 7.15-7.07 (m, 3H, Ar-H), 2.45 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 2.28 (s, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): 189.63, 141.53, 136.95, 136.69, 136.27, 132.56, 129.53, 127.19, 126.64 (X2), 125.99 (X2), 125.13, 124.78 (X2), 124.34 (X2), 23.41, 11.33, 10.62; HRMS (microTOF-QII, MS, ESI): *m/z* $[M]^+$ Calcd for $C_{20}H_{18}OS$: 306.4213, found: 306.4216.

(4,5-Dimethyl-2-phenylthiophen-3-yl)(p-nitrophenyl)methanone (**12*c***): IR (KBr) ν: 3033, 1650, 1596 cm^{-1}. ^{1}HNMR (500 MHz, $CDCl_3$): 8.04 (*d*, *J* = 7.1 Hz, 2H, Ar-H), 7.52 (d, *J* = 6.8 Hz, 2H, Ar-H), 7.41 (d, *J* = 6.8 Hz, 2H, Ar-H), 7.21-7.15 (m, 3H, Ar-H), 2.46 (s, 3H, CH_3), 2.27 (s, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): 194.81, 144.25, 140.42, 138.34, 137.04, 136.37, 134.34, 129.48, 128.94 (X2), 128.06 (X2), 127.73, 127.25 (X2), 127.01 (X2), 12.38, 11.71; HRMS (microTOF-QII, MS, ESI): *m/z* $[M]^+$ Calcd for $C_{19}H_{15}NO_3S$: 337.3923, found: 337.3925.

(4,5,6,7-Tetrahydro-2-phenylbenzo[b]thiophen-3-yl)(phenyl)methanone (**12*d***):

IR (KBr) ν: 3030, 1648, 1596 cm^{-1}; ^{1}HNMR (500 MHz, $CDCl_3$): δ: 7.77 (d, *J* = 7.5 Hz, 2H, Ar-H), 7.42 (t, *J* = 7.0 Hz, 1H, Ar-H), 7.30-7.27 (m, 4H, Ar-H), 7.17-7.11 (m, 3H, Ar-H), 2.85 (t, *J* = 6.0 Hz, 2H, CH_2), 2.52 (t, *J* = 6.0 Hz, 2H, CH_2), 1.91-1.89 (m, 2H, CH_2), 1.80-1.78 (m, 2H, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): 195.56, 141.42, 137.48, 136.25, 135.93, 133.73, 133.01, 129.81 (X2), 129.53 (X2), 128.55, 128.38 (X2), 128.23 (X2), 127.62, 29.70, 25.03, 23.22, 22.48; HRMS (microTOF-QII, MS, ESI): *m/z* $[M+Na]^+$ Calcd for $C_{21}H_{18}OS$: 341.4320, found: 341.4322.

***(4,5,6,7-Tetrahydro-2-phenylbenzo[b]thiophen-3-yl)(p-tolyl)methanone* (12*e*):** IR (KBr) ν: 3035, 1646, 1603 cm^{-1}. ^{1}HNMR (500 MHz, $CDCl_3$): δ: 7.72 (d, *J* = 7.0 Hz, 2H, Ar-H), 7.26 (d, *J* = 6.8 Hz, 2H, Ar-H), 7.21 (d, *J* = 7.0 Hz, 2H, Ar-H), 7.07-6.98 (m, 3H, Ar-H), 2.78 (t, *J* = 6.1 Hz, 2H, CH_2), 2.46 (t, *J* = 6.1 Hz, 2H, CH_2), 2.40 (s, 3H, CH_3) 1.89-1.84 (m, 2H, CH_2), 1.78-1.73 (m, 2H, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): 190.84, 141.82, 137.25, 135.67, 135.28, 133.54, 132.24, 127.38 (X2), 126.97 (X2), 126.63 (X2), 126.17, 126.05 (X2), 125.73, 27.97, 24.76, 22.92, 22.45, 21.94; HRMS (microTOF-QII, MS, ESI): *m/z* $[M]^+$ Calcd for $C_{22}H_{20}OS$: 332.4586, found: 332.4580.

(*4,5,6,7-Tetrahydro-2-phenylbenzo[b]thiophen-3-yl)(p-nitrophenyl)methanone* (12*f*): IR (KBr) ν: 3034, 1652, 1601 cm^{-1}; ^{1}HNMR (500 MHz, $CDCl_3$): δ: 8.11 (d, *J* = 7.5 Hz, 2H, Ar-H), 7.64 (d, *J* = 7.0 Hz, 2H, Ar-H), 7.59 (d, *J* = 7.0 Hz, 2H, Ar-H), 7.26-7.19 (m, 3H, Ar-H), 2.86 (t, *J* = 6.3 Hz, 2H, CH_2), 2.56 (t, *J* = 6.3 Hz, 2H, CH_2), 1.97-1.83 (m, 4H, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): 195.68, 142.36, 138.52, 138.11, 136.26, 134.82, 134.54, 133.02 (X2), 129.67 (X2), 129.13, 128.66 (X2), 128.23 (X2), 126.76, 29.64, 24.91, 23.20, 22.51; HRMS (microTOF-QII, MS, ESI): *m/z* $[M]^+$ Calcd for $C_{21}H_{17}NO_3S$: 363.4296, found: 363.4293.

***(4,5,6,7-Tetrahydro-2-phenylbenzo[b]thiophen-3-yl)(p-methoxyphenyl)methanone* (12*g*)**: IR (KBr) ν: 3035, 1644, 1595 cm^{-1}; ^{1}HNMR (500 MHz, $CDCl_3$): δ: 7.66 (d, *J* = 7.2 Hz, 2H, Ar-H), 7.24 (d, *J* = 7.0 Hz, 2H, Ar-H), 7.14-7.09 (m, 3H, Ar-H), 6.89 (d, *J* = 7.1Hz, 2H, Ar-H), 3.64 (s, 3H, OCH_3), 2.75 (t, *J* = 6.1 Hz, 2H, CH_2), 2.44 (t, *J* = 6.1 Hz, 2H, CH_2), 1.88-1.80 (m, 2H, CH_2), 1.75-1.68 (m, 2H, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): 189.16, 141.21, 136.71, 136.13, 135.24, 131.67, 130.19 (X2), 129.73 (X2), 128.45, 126.37 (X2), 126.10, 126.03, 114.34 (X2), 53.42, 27.41, 23.17, 22.42, 21.80; HRMS (microTOF-QII, MS, ESI): *m/z* $[M]^+$ Calcd for $C_{22}H_{20}O_2S$: 348.4580, found: 348.4584.

(5,6,7,8-Tetrahydro-2-phenyl-4*H*-cyclohepta[*b*]thiophen-3-yl)(phenyl)methanone (12*h*): IR (KBr) ν: 3033, 1648, 1580 cm^{-1}. ^{1}HNMR (500 MHz, $CDCl_3$): δ: 7.80 (d, *J* = 7.0 Hz, 2H, Ar-H), 7.43-7.31 (m, 3H, Ar-H), 7.25 (d, *J* = 7.0 Hz, 2H, Ar-H), 7.18-7.12 (m, 3H, Ar-H),

2.83 (t, *J* = 6.0 Hz, 2H, CH_2), 2.50 (t, *J* = 6.0 Hz, 2H, CH_2), 1.70-1.58 (m, 6H, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): 188.52, 145.51, 136.28, 137.17, 136.67, 135.75, 133.51, 129.87, 128.34, 127.61, 127.24, 126.94, 125.72, 30.56, 25.94, 24.71, 24.58, 21.73; HRMS (microTOF-QII, MS, ESI): *m/z* $[M+Na]^+$ Calcd for $C_{22}H_{20}OS$: 355.4586, found: 355.4587.

(5,6,7,8-Tetrahydro-2-phenyl-4H-cyclohepta[b]thiophen-3-yl)(p-tolyl)methanone (**12*i***): IR (KBr) ν: 3033, 1650, 1603 cm^{-1}. ^{1}HNMR (500 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 7.1 Hz, 2H, Ar-H), 7.34 (d, *J* = 6.9 Hz, 2H, Ar-H), 7.19 (d, *J* = 6.9 Hz, 2H, Ar-H), 7.06-6.98 (m, 3H, Ar-H), 2.78 (t, *J* = 6.1 Hz, 2H, CH_2), 2.49 (t, *J* = 6.1 Hz, 2H, CH_2), 2.43 (s, 3H, CH_3), 1.62-1.49 (m, 6H, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): 190.49, 143.67, 136.71, 135.38, 134.92, 133.07, 130.21, 129.29 (X2), 128.48 (X2), 127.82 (X2), 127.77, 126.41 (X2), 126.03, 30.41, 25.91, 24.68, 24.53, 23.25, 21.64; HRMS (microTOF-QII, MS, ESI): *m/z* $[M]^+$ Calcd for $C_{23}H_{22}OS$: 346.4852, found: 346.4852.

(5,6,7,8-Tetrahydro-2-phenyl-4H-cyclohepta[b]thiophen-3-yl)(p-nitrophenyl)methanone **(12*j*):** IR (KBr) ν: 3033, 1650, 1600 cm^{-1}. ^{1}HNMR (500 MHz, $CDCl_3$): δ = 8.08 (*d*, *J* = 7.5 Hz, 2H, Ar-H), 7.67 (d, *J* = 7.1 Hz, 2H, Ar-H), 7.55 (d, *J* = 7.1 Hz, 2H, Ar-H), 7.28-7.21 (m, 3H, Ar-H), 2.85 (t, *J* = 6.2 Hz, 2H, CH_2), 2.53 (s, 3H, CH_3), 1.70-1.59 (m, 6H, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): 189.73, 148.52, 140.38, 138.65, 138.16, 137.31, 134.74, 130.21 (X2), 128.85 (X2), 128.40, 127.31 (X2), 126.98, 125.57 (X2), 31.53, 26.06, 24.79, 24.64, 21.75; HRMS (microTOF-QII, MS, ESI): *m/z* $[M]^+$ Calcd for $C_{22}H_{19}NO_3S$: 377.4562, found: 377.4561.

General procedure for the preparation of 2-phenylethynl-3-aroyl thiophenes* 14*(a-q)

A suspension of 2-iodothiophene (**10*a-m***, 0.1 g), substituted alkyne (**13*a,b***, 1.2 equiv.), tetrakis(triphenylphosphane)palladium(0) (2 mol%) and CuI (3 mol%) in DMF (1.5 ml) and diethylamine (1.5 ml) were loaded into the microwave vial equipped with a magnetic stirrer. The vessel was placed in the microwave reactor and irradiated with stirring at a ceiling temperature of 80°C for 20-40 min. After the reaction, the vessel was cooled to 60°C by air jet cooling. The reaction mixture was poured into water and extracted with ethyl acetate (25 ml × 3). The combined organic layers were dried on Na_2SO_4 and solvent was removed under reduced pressure. The crude product obtained was purified using column chromatography (2% ethyl acetate-hexane) to afford the desired compound.

(*4,5-Dimethyl-2-(phenylethynyl)thiophen-3-yl)(phenyl)methanone* (14*a*): IR (KBr) ν: 3059, 2925, 2360, 2203, 1724, 1653 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 7.5 Hz, 2H, Ar-H), 7.61 (t, *J* = 7.5 Hz, 1H, Ar-H), 7.49 (d, *J* = 7.5 Hz, 2H, Ar-H), 7.25-7.17 (m, 3H, Ar-H), 6.94 (d, *J* = 7.7 Hz, 2H, Ar-H), 2.42 (s, 3H, CH_3), 2.17 (s, 3H, CH_3). ^{13}C NMR (125 Hz,

$CDCl_3$): δ = 193.41, 143.85, 138.21, 136.59, 133.11, 131.07 (X2), 130.28 (X2), 130.26, 128.37 (X2), 128.31 (X2), 128.07, 122.49, 121.54, 97.84, 82.05, 13.26, 12.83. HRMS (microTOF-QII, MS, ESI): *m/z* $[M+H]^+$ Calcd for $C_{21}H_{16}OS$: 317.4161, found: 317.4163.

(4,5-Dimethyl-2-(phenylethynyl)thiophen-3-yl)(p-tolyl)methanone **(14*b*):** IR (KBr) ν: 3059, 2925, 2360, 1724, 1653 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.82 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.31 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.20-7.16 (m, 3H, Ar-H), 6.91 (d, *J* = 8.5 Hz, 2H, Ar-H), 2.43 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 2.15 (s, 3H, CH_3). ^{13}C NMR (125 Hz, $CDCl_3$): δ = 193.19, 143.67, 142.50, 138.29, 135.90, 135.72, 131.04 (X2), 130.26 (X2), 128.56 (X2), 128.90, 128.68 (X2), 122.53, 121.41, 98.04, 82.47, 21.62, 13.25, 12.80. HRMS (microTOF-QII, MS, ESI): *m/z* $[M]^+$ Calcd for $C_{22}H_{18}OS$: 330.4427, found: 330.4424.

(4,5-Dimethyl-2-(phenylethynyl)thiophen-3-yl)(4-nitrophenyl)methanone (**14*c***): IR (KBr) ν: 3059, 2967, 2213, 1703, 1532 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 8.34 (d, *J* = 8.5 Hz, 2H, Ar-H), 8.10 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.58 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.32-7.25 (m, 3H, Ar-H), 2.43 (s, 3H, CH_3), 2.20 (s, 3H, CH_3). ^{13}C NMR (125 Hz, $CDCl_3$): δ = 192.84, 149.87, 142.25, 140.01, 138.97, 136.13, 133.46 (X2), 129.60 (X2), 128.83, 128.79 (X2), 125.20, 124.12 (X2), 122.83, 98.39, 82.34, 13.31, 12.96. HRMS (microTOF-QII, MS, ESI): *m/z* $[M]^+$ Calcd for $C_{21}H_{15}NO_3S$: 361.4137, found: 361.4131.

(4,5-Dimethyl-2-(phenylethynyl)thiophen-3-yl)(4-methoxyphenyl)methanone (**14*d***): IR (KBr) ν: 2959, 2360, 1712 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.81 (d, *J* = 7.5 Hz, 2H, Ar-H), 7.34 (d, *J* = 7.5 Hz, 2H, Ar-H), 7.13-7.09 (m, 3H, Ar-H), 6.79 (d, *J* = 8.0 Hz, 2H, Ar-H), 3.75 (s, 3H, OCH_3), 2.39 (s, 3H, CH_3), 2.34 (s, 3H, CH_3). ^{13}C NMR (125 Hz, $CDCl_3$): δ = 192.38, 147.64, 143.46, 138.66, 134.21, 131.63 (X2), 130.80 (X2), 129.07, 128.76 (X2), 128.91, 125.67, 121.33, 116.16 (X2), 96.75, 84.03, 56.62, 13.23, 12.80. HRMS (microTOF-QII, MS, ESI): *m/z* $[M+H]^+$ Calcd for $C_{22}H_{18}O_2S$: 347.4421, found: 347.4423.

(4,5-Dimethyl-2-(phenylethynyl)thiophen-3-yl)(3,4,5-trimethoxyphenyl)methanone (**14*e***): IR (KBr) ν: 3055, 2960, 2360, 1715 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.41 (d, *J* = 7.5 Hz, 2H, Ar-H), 7.20-7.15 (m, 3H, Ar-H), 6.91 (d, *J* = 7.5 Hz, 2H, Ar-H), 3.78 (s, 9H, OCH_3), 2.37 (s, 3H, CH_3), 2.35 (s, 3H, CH_3). ^{13}C NMR (125 Hz, $CDCl_3$): δ = 192.43, 148.34 (X2), 144.69, 143.51, 140.09, 134.21, 132.30 (X2), 129.21, 128.35, 128.27 (X2), 125.62, 122.33, 105.20 (X2), 96.73, 84.03, 59.24, 56.47 (X2), 13.25, 12.81. HRMS (microTOF-QII, MS, ESI): *m/z* $[M+1]^+$ Calcd for $C_{24}H_{22}O_4S$: 407.4941, found: 407.4940.

Phenyl(2-(phenylethynyl)-4,5,6,7-tetrahydrobenzo[b]thiophen-3-yl)methanone (**14*f***): IR (KBr) ν: 3057, 2360, 1724 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 7.5 Hz, 2H, Ar-H), 7.60 (t, *J* = 7.5 Hz, 1H, Ar-H), 7.56-7.48 (m, 2H, Ar-H), 7.27-7.15 (m, 3H, Ar-H),

6.92 (d, *J* = 7.0 Hz, 2H, Ar-H), 2.81 (t, *J* = 6.0 Hz, 2H, CH_2), 2.68 (t, *J* = 6.0 Hz, 2H, CH_2), 1.91-1.80 (m, 4H, CH_2). ^{13}C NMR (125 Hz, $CDCl_3$): δ = 192.82, 142.19, 138.58, 138.28, 136.03, 131.09, 129.53 (X2), 128.81 (X2), 128.32, 128.23 (X2), 128.05 (X2), 122.88, 122.50, 98.40, 82.32, 25.25, 25.18, 23.00, 22.36. HRMS (microTOF-QII, MS, ESI): *m/z* $[M]^+$ Calcd for $C_{23}H_{18}OS$: 342.4534, found: 342.4534.

(2-(Phenylethynyl)-4,5,6,7-tetrahydrobenzo[b]thiophen-3-yl)(p-tolyl)methanone (**14*g***): IR (KBr) ν: 3054, 2357, 1722 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.85 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.29 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.23-7.18 (m, 3H, Ar-H), 6.94 (d, *J* = 8.5 Hz, 2H, Ar-H), 2.80 (t, *J* = 6.2 Hz, 2H, CH_2), 2.66 (t, *J* = 6.2 Hz, 2H, CH_2), 2.44 (s, 3H, CH_3), 1.91-1.80 (m, 4H, CH_2). ^{13}C NMR (125 Hz, $CDCl_3$): δ = 192.57, 143.79, 142.51, 138.47, 135.92, 135.67, 131.05 (X2), 130.90 (X2), 128.95 (X2), 128.83, 128.79 (X2), 122.59, 122.42, 98.06, 82.45, 25.23, 23.76, 23.00, 22.35, 21.64. HRMS (microTOF-QII, MS, ESI): *m/z* $[M]^+$ Calcd for $C_{24}H_{20}OS$: 356.4800, found: 356.4807.

(4-Nitrophenyl)(2-(phenylethynyl)-4,5,6,7-tetrahydrobenzo[b]thiophen-3-yl)methanone (**14*h***): IR (KBr) ν: 3061, 2219, 1708, 1532 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 8.31 (d, *J* = 8.5 Hz, 2H, Ar-H), 8.07 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.61 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.34-7.26 (m, 3H, Ar-H), 2.83 (t, *J* = 6.2 Hz, 2H, CH_2), 2.71 (t, *J* = 6.2 Hz, 2H, CH_2), 1.92-1.84 (m, 4H, CH_2). ^{13}C NMR (125 Hz, $CDCl_3$): δ = 192.85, 149.89, 142.27, 140.06, 138.99, 136.10, 133.46 (X2), 129.61 (X2), 128.86, 128.84 (X2), 125.21, 124.17 (X2), 122.90, 98.42, 82.36, 25.23, 25.22, 23.04, 22.39. HRMS (microTOF-QII, MS, ESI): *m/z* $[M]^+$ Calcd for $C_{23}H_{17}NO_3S$: 387.4510, found: 387.4513.

(4-Methoxyphenyl)(2-(phenylethynyl)-4,5,6,7-tetrahydrobenzo[b]thiophen-3-yl)methanone (**14*i***): IR (KBr) ν: 3054, 2934, 2360, 1712 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.79 (d, *J* = 7.5 Hz, 2H, Ar-H), 7.31 (d, *J* = 7.5 Hz, 2H, Ar-H), 7.17-7.12 (m, 3H, Ar-H), 6.82 (d, *J* = 8.0 Hz, 2H, Ar-H), 3.76 (s, 3H, OCH_3), 2.79 (t, *J* = 6.0 Hz, 2H, CH_2), 2.63 (t, *J* = 6.0 Hz, 2H, CH_2), 1.89-1.82 (m, 4H, CH_2). ^{13}C NMR (125 Hz, $CDCl_3$): δ = 192.42, 147.63, 143.50, 138.69, 134.24, 131.67 (X2), 130.82 (X2), 129.04, 128.76 (X2), 128.90, 125.69, 121.34, 116.20 (X2), 96.79, 84.00, 56.63, 25.21, 23.72, 22.90, 22.68. HRMS (microTOF-QII, MS, ESI): *m/z* $[M+H]^+$ Calcd for $C_{24}H_{20}O_2S$: 373.4794, found: 373.4792.

(2-(Phenylethynyl)-4,5,6,7-tetrahydrobenzo[b]thiophen-3-yl)(3,4,5-trimethoxyphenyl)methanone (**14*j***): IR (KBr) ν: 3053, 2928, 2360, 1724 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.39 (d, *J* = 7.5 Hz, 2H, Ar-H), 7.21-7.17 (m, 3H, Ar-H), 6.94 (d, *J* = 7.5 Hz, 2H, Ar-H), 3.79 (s, 9H, OCH_3), 2.78 (t, *J* = 6.0 Hz, 2H, CH_2), 2.66 (t, *J* = 6.0 Hz, 2H, CH_2), 1.90-1.84 (m, 4H, CH_2). ^{13}C NMR (125 Hz, $CDCl_3$): δ = 192.45, 148.37 (X2), 144.68,

143.55, 140.06, 134.27, 132.29 (X2), 129.21, 128.36, 128.30 (X2), 125.69, 122.37, 105.26 (X2), 96.73, 83.96, 59.22, 56.49 (X2), 25.13, 23.40, 22.84, 22.61. HRMS (microTOF-QII, MS, ESI): *m/z* $[M]^+$ Calcd for $C_{26}H_{24}O_4S$: 432.5314, found: 432.5318.

(4,5-dimethyl-2-(p-tolylethynyl)thiophen-3-yl)(phenyl)methanone (**14*k***): IR (KBr) ν: 3058, 2926, 2360, 1724, 1654 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.59-7.49 (m, 3H, Ar-H), 7.00 (d, *J* = 7.5 Hz, 2H, Ar-H), 6.83 (d, *J* = 7.2 Hz, 2H, Ar-H), 2.41 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 2.16 (s, 3H, CH_3). ^{13}C NMR (125 Hz, $CDCl_3$): δ = 193.43, 143.69, 138.36, 138.11, 135.45, 133.72, 133.02, 130.97 (X2), 130.27 (X2), 128.83 (X2), 128.31 (X2), 121.69, 119.04, 97.99, 81.25, 21.47, 13.23, 12.82. HRMS (microTOF-QII, MS, ESI): *m/z* $[M]^+$ Calcd for $C_{22}H_{18}OS$: 330.4427, found: 330.4420.

(4,5-Dimethyl-2-(p-tolylethynyl)thiophen-3-yl)(p-tolyl)methanone (**14*l***): IR (KBr) ν: 3058, 2928, 2360, 1721, 1650 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.85 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.29 (d, *J* = 7.0 Hz, 2H, Ar-H), 7.00 (d, *J* = 8.0 Hz, 2H, Ar-H), 6.85 (d, *J* = 8.0 Hz, 2H, Ar-H), 2.40 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 2.19 (s, 3H, CH_3), 2.14 (s, 3H, CH_3). ^{13}C NMR (125 Hz, $CDCl_3$): δ = 193.17, 143.89, 138.44, 135.60, 135.33, 133.56, 130.96 (X2), 130.47 (X2), 129.94, 128.99 (X2), 128.93 (X2), 121.42, 119.52, 97.78, 81.55, 21.67, 21.45, 13.22, 12.80. HRMS (microTOF-QII, MS, ESI): *m/z* $[M]^+$ Calcd for $C_{23}H_{20}OS$: 344.4693, found: 344.4696.

(4,5-Dimethyl-2-(p-tolylethynyl)thiophen-3-yl)(4-nitrophenyl)methanone (**14*m***):IR (KBr) ν: 3057, 2357, 1721, 1531 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 8.04 (d, *J* = 8.5 Hz, 2H, Ar-H), 7.59 (d, *J* = 8.5 Hz, 2H, Ar-H), 7.46 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.19 (d, *J* = 8.0 Hz, 2H, Ar-H), 2.40 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 2.21 (s, 3H, CH_3). ^{13}C NMR (125 Hz, $CDCl_3$): δ = 193.17, 151.35, 141.18, 138.97, 138.72, 137.30, 131.63 (X2), 131.37 (X2), 129.64, 129.45 (X2), 129.20 (X2), 128.12, 119.65, 92.55, 88.12, 21.55, 14.32, 13.01. HRMS (microTOF-QII, MS, ESI): *m/z* $[M]^+$ Calcd for $C_{22}H_{17}NO_3S$: 375.4403, found: 375.4406.

Phenyl(2-(p-tolylethynyl)-4,5,6,7-tetrahydrobenzo[b]thiophen-3-yl)methanone (**14*n***): IR (KBr) ν: 3057, 2934, 2360, 1724, 1649 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 7.5 Hz, 2H, Ar-H), 7.49-7.47 (m, 3H, Ar-H), 7.00 (d, *J* = 8.0 Hz, 2H, Ar-H), 6.82 (d, *J* = 8.5 Hz, 2H, Ar-H), 2.81 (t, *J* = 6.2 Hz, 2H, CH_2), 2.69 (t, *J* = 6.2 Hz, 2H, CH_2), 2.30 (s, 3H, CH_3), 1.92-1.79 (m, 4H, CH_2). ^{13}C NMR (125 Hz, $CDCl_3$): δ = 192.88, 141.87, 138.57, 138.31, 138.27, 136.00, 132.90 (X2), 131.00 (X2), 130.25, 129.54 (X2), 128.85 (X2), 123.31, 119.41, 98.76, 81.75, 25.23, 25.21, 23.02, 22.38, 21.48. HRMS (microTOF-QII, MS, ESI): *m/z* $[M+H]^+$ Calcd for $C_{24}H_{20}OS$: 357.4800, found: 357.4808.

p-Tolyl(2-(p-tolylethynyl)-4,5,6,7-tetrahydrobenzo[b]thiophen-3-yl)methanone (**14*o***):IR (KBr) ν: 2930, 2360, 1715, 1647, 1606 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.84 (d, *J* = 7.5 Hz, 2H, Ar-H), 7.29 (d, *J* = 7.0 Hz, 2H, Ar-H), 7.02 (d, *J* = 7.5 Hz, 2H, Ar-H), 6.86 (d, *J* = 7.5 Hz, 2H, Ar-H), 2.78 (t, *J* = 6.0 Hz, 2H, CH_2), 2.68 (t, *J* = 6.0 Hz, 2H, CH_2), 2.19 (s, 3H, CH_3), 2.16 (s, 3H, CH_3), 1.87-1.79 (m, 4H, CH_2). ^{13}C NMR (125 Hz, $CDCl_3$): δ = 192.72, 143.83, 138.52, 136.69, 136.41, 136.00, 132.84 (X2), 131.10, 130.53 (X2), 129.91 (X2), 128.82 (X2), 123.22, 119.38, 97.82, 81.59, 25.21, 25.17, 23.01, 22.35, 21.67, 21.47. HRMS (microTOF-QII, MS, ESI): *m/z* $[M+H]^+$ Calcd for $C_{25}H_{22}OS$: 371.5066, found: 371.5065.

(4-Nitrophenyl)(2-(p-tolylethynyl)-4,5,6,7-tetrahydrobenzo[b]thiophen-3-yl)methanone (**14*p***): IR (KBr) ν: 3055, 2356, 1721, 1531 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 8.04 (d, *J* = 8.5 Hz, 2H, Ar-H), 7.59 (d, *J* = 8.5 Hz, 2H, Ar-H), 7.46 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.19 (d, *J* = 8.0 Hz, 2H, Ar-H), 2.85 (t, *J* = 6.5 Hz, 2H, CH_2), 2.71 (t, *J* = 6.5 Hz, 2H, CH_2), 2.40 (s, 3H, CH_3), 1.87-1.81 (m, 4H, CH_2). ^{13}C NMR (125 Hz, $CDCl_3$): δ = 193.16, 151.37, 141.20, 138.97, 138.74, 137.29, 131.63 (X2), 131.37 (X2), 129.64, 129.45 (X2), 129.20 (X2), 128.12, 119.65, 92.56, 88.12, 25.25, 25.22, 23.06, 22.40, 21.55. HRMS (microTOF-QII, MS, ESI): *m/z* $[M]^+$ Calcd for $C_{24}H_{19}NO_3S$: 401.4776, found: 401.4777.

(2-(p-Tolylethynyl)-4,5,6,7-tetrahydrobenzo[b]thiophen-3-yl)(3,4,5-trimethoxyphenyl)methanone (**14*q***): IR (KBr) ν: 3055, 2927, 2360, 1722 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.36 (d, *J* = 7.5 Hz, 2H, Ar-H), 7.16 (d, *J* = 8.0 Hz, 2H, Ar-H), 6.86 (d, *J* = 7.5 Hz, 2H, Ar-H), 3.80 (s, 9H, OCH_3), 2.77 (t, *J* = 6.0 Hz, 2H, CH_2), 2.65 (t, *J* = 6.0 Hz, 2H, CH_2), 2.39 (s, 3H, CH_3), 1.89-1.86 (m, 4H, CH_2). ^{13}C NMR (125 Hz, $CDCl_3$): δ = 192.43, 148.38 (X2), 144.68, 143.51, 140.04, 137.63, 134.27, 132.20 (X2), 129.20, 128.36 (X2), 125.59, 120.04, 105.18 (X2), 96.54, 83.68, 59.24, 56.37 (X2), 25.14, 23.37, 22.84, 22.60. HRMS (microTOF-QII, MS, ESI): *m/z* $[M]^+$ Calcd for $C_{27}H_{26}O_4S$: 446.5579, found: 446.5573.

Biology Experiments

Antiproliferative assays

All the synthesized compounds **12*a-j*** and **14*a-q*** were submitted to the MTT assay to assess the growth inhibition against A-375, MIA PaCa-2, Caco-2, A-549 and PC-3 cancer cell lines.[4] Cells were cultured in DMEM medium supplemented with 10% fetal bovine serum (FBS) and 1% penicillin/streptomycin, at 37°C in a humidified atmosphere with 5% CO_2. Cells were seeded into a 96-well plate at a density of 5000 cells per well. After incubation for 24 h, culture medium was replaced with 100 µl of fresh medium containing the treatments.

The cells were incubated for 48 h and 100 µL of FBS-free medium containing 0.5 mg/mL of MTT was added, which was discarded after 4 h incubation at 37 ºC. The resulting formazan blue formed in the cells was dissolved in DMSO and absorbance (optical density, OD) of the solution was measured at 562 nm using a microplate reader (Spectramax M5, CA, USA). The relation between surviving fraction and drug concentration was plotted to get the percentage cell proliferation of tested compounds against each cancer cell line. The concentration required to inhibit cell proliferation by 50% (IC_{50}) was calculated from concentration-response curves using linear regression analysis and compared with the reference drug paclitaxel.

Calcein AM Assay

This assay was performed according to the manufacturer's instructions mentioned in Live/Dead Viability/Cytotoxicity assay kit (Invitrogen, CA, USA). After the treatment for 24 h, cells were washed with 1x PBS for 5 min; and incubated with Calcein acetoxymethyl (Calcein AM) 2 µM and Ethidium homodimer-1 (EthD-1) 4 µM for 15 min at 37°C in the dark. Cells were then washed again with 1x PBS for 5 min and images were acquired by a confocal microscope Fluoview FV1000 (Olympus). The live and dead cells ratio was determined by quantifying the number of cells in 3 fields at the same magnification for tested compounds **12*j*** and **14*h***.

Plate Colony Forming Assay

A-375 and MIAPaCa-2 cells were seeded at about 500 cells per well of a six-well plate and incubate it for 12h. Cells were then treated with compounds **12*j*** and **14*h*** and incubated for 10–14 days. After washing with PBS twice, cells were fixed with 10% formaldehyde for 15 min, and stained with 0.5% crystal violet for 15 min at room temperature and washed with running water. The colony is defined to consist of at least 50 cells and visible colonies were counted using microscope.

Colony formation rate = (number of colonies/number of seeded cells) × 100%.

Cell-cycle analysis

A-375 and MIA PaCa-2 cells were cultured overnight in a six-well plate followed by thymidine blockade was carried out for 12 h. Cells were then incubated with compounds **12*j*** and **14*h*** for 48 h. Treated cells were then harvested by trypsinization and fixed in 80% ice-cold ethanol at 4 °C overnight. After washing with PBS containing RNase (1 mg/mL), cell pellet was resuspended in 5 µg/mL propidium iodide staining solution for 30 min at room temperature. Finally, the cell cycle distribution was measured by flow cytometry (Becton, Dickinson, NJ, USA) and percentage of cells in the G0/G1, S, and G2/M phases was

determined by using Cell Quest acquisition software. 10,000 fluorescent events were recorded for each group and experiment was performed in triplicates.

Table S1 Crystal and experimental data

Crystal description	white block
Crystal size	0.3 X 0.2 X 0.2 mm
Empirical formula	$C_{21}H_{16}OS$
Formula weight	316.40
Radiation, Wavelength	Mo *K*α, 0.71073 Å
Unit cell dimensions	a= 13.3396(10), b= 13.3396(10), c= 13.3396(10), β= 94.937(8)
Crystal system	monoclinic
Space group	P 2_1/n
Unit cell volume	1698.7(2)
No. of molecules per unit cell, Z	4
Temperature	293(2) K
Absorption coefficient	0.192 mm^{-1}
F(000)	664
Scan mode	ω scan
θ range for entire data collection	3.62 <θ< 26.00
Range of indices	h= -13 to 16, k= -10 to 6, l= -16 to 19
Reflections collected / unique	6451/ 3333
Reflections observed (I > 2σ(I))	1948
R_{int}	0.0385
R_{sigma}	0.0680
Structure determination	Direct methods
Refinement	Full-matrix least-squares on F^2
No. of parameters refined	210
Final R	0.0523
wR(F^2)	0.1212

Contd.

Weight	$1/[\sigma^2(F_o^2)+(0.0596P)^2 + 0.0000P]$ Where $P=[F_o^2 +2F_c^2] / 3$
Goodness-of-fit	0.985
Final residual electron density	$-0.297 < \Delta\rho < 0.173$ eÅ^{-3}
Measurement	*X'calibur system-Oxford diffraction make, U.K*
Software for structure solution:	SHELXS97 (Sheldrick, 2008)
Software for refinement:	SHELXL97 (Sheldrick, 2008)
Software for molecular plotting:	ORTEP-3 (Farrugia, 1997) PLATON
Software for geometrical calculation	PLATON (Spek, 2009) PARST (Nardelli, 1995)

Table S2. Cell cycle effect of compounds **12*j*** and **14*h*** on A-375 and MIA PaCa-2 cell lines.

Compd	**Cell cycle distribution (%)[a]**							
	Sub G1		**G0G1**		**S**		**G2/M**	
	A-375	**MIA PaCa -2**	**A-375**	**MIA PaCa -2**	**A-375**	**MIA PaCa -2**	**A-375**	**MIA PaCa -2**
Control	1.1±0.4	1.53±0.4	64.18±2.6	66.05±2.2	30.48±1.4	17.29±1.8	8.18±2.2	16.66±0.8
12*j*	10.92±1.6	7.95±1.5	50.85±2.0	46.27±1.5	34.51±0.8	16.71±1.2	44.96±0.7	38.46±3.1
14*h*	23.59±0.8	20.32±1.4	42.36±1.5	38.20±2.1	33.02±1.0	20.17±2.4	52.34±1.3	52.89±2.5

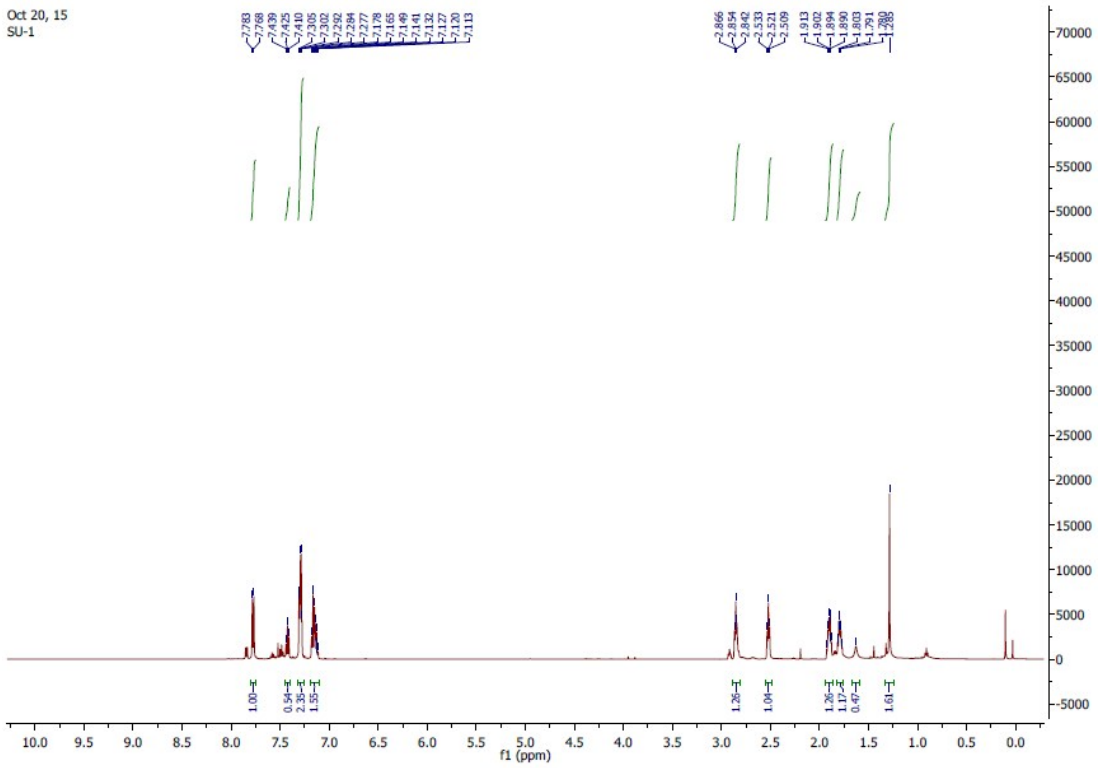
[a]Percentage of the cell population in G1, G2 and S phase respectively, determined by flow cytometry.

Table S3 *In silico* physicochemical ADME properties of all synthesized compounds.[5]

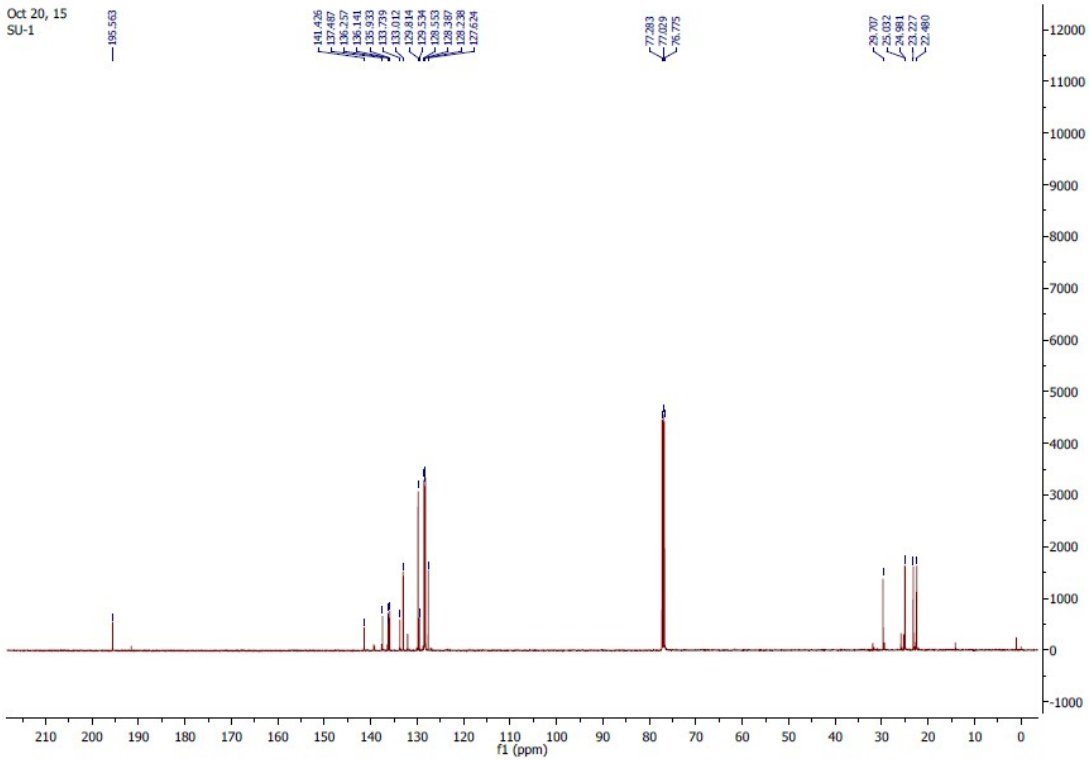
Code	miLog*P*	TPSA (A^2)	nON	nOHNH	n-violations	Nrotb	Mol. wt.
Rule	≤5	-	<10	<5	≤1	-	<500
12*a*	5.50	17.07	1	0	1	3	292.39
12*b*	5.95	17.07	1	0	1	3	306.42
12*c*	5.46	62.90	4	0	1	4	337.39
12*d*	6.08	17.07	1	0	1	3	318.43
12*e*	6.52	17.07	1	0	1	3	332.45
12*f*	6.03	62.90	4	0	1	4	363.42
12*g*	6.13	26.30	2	0	1	4	348.45
12*h*	6.58	17.07	1	0	1	3	332.45
12*i*	7.03	17.07	1	0	1	3	346.48
12*j*	6.54	62.90	4	0	1	4	377.45
14*a*	5.25	17.07	1	0	1	2	316.41
14*b*	5.70	17.07	1	0	1	2	330.44
14*c*	5.21	62.90	4	0	1	3	361.41
14*d*	5.30	26.30	2	0	1	3	346.44
14*e*	4.88	44.77	4	0	0	5	406.49
14*f*	5.82	17.07	1	0	1	2	342.45
14*g*	6.27	17.07	1	0	1	2	356.48
14*h*	5.78	62.90	4	0	1	3	387.45
14*i*	5.88	26.30	2	0	1	3	372.47
14*j*	5.46	44.77	4	0	1	5	432.53
14*k*	5.70	17.07	1	0	1	2	330.44
14*l*	6.14	17.07	1	0	1	2	344.46
14*m*	5.65	62.90	4	0	1	3	375.44
14*n*	6.27	17.07	1	0	1	2	356.48
14*o*	6.72	17.07	1	0	1	2	370.50
14*p*	6.23	62.90	4	0	1	3	401.47
14*q*	5.90	44.77	4	0	1	5	446.55

^{1}H and ^{13}C NMR Spectra:

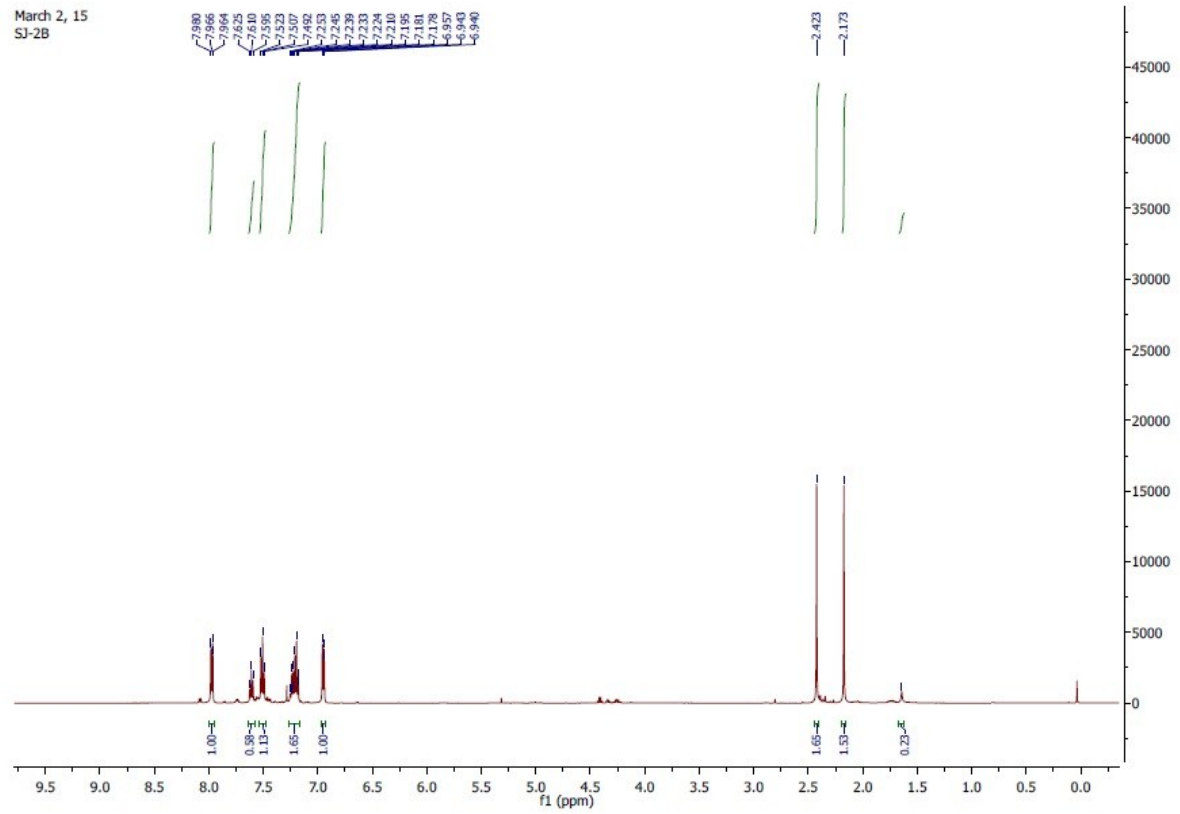
^{1}H NMR of 12*d*



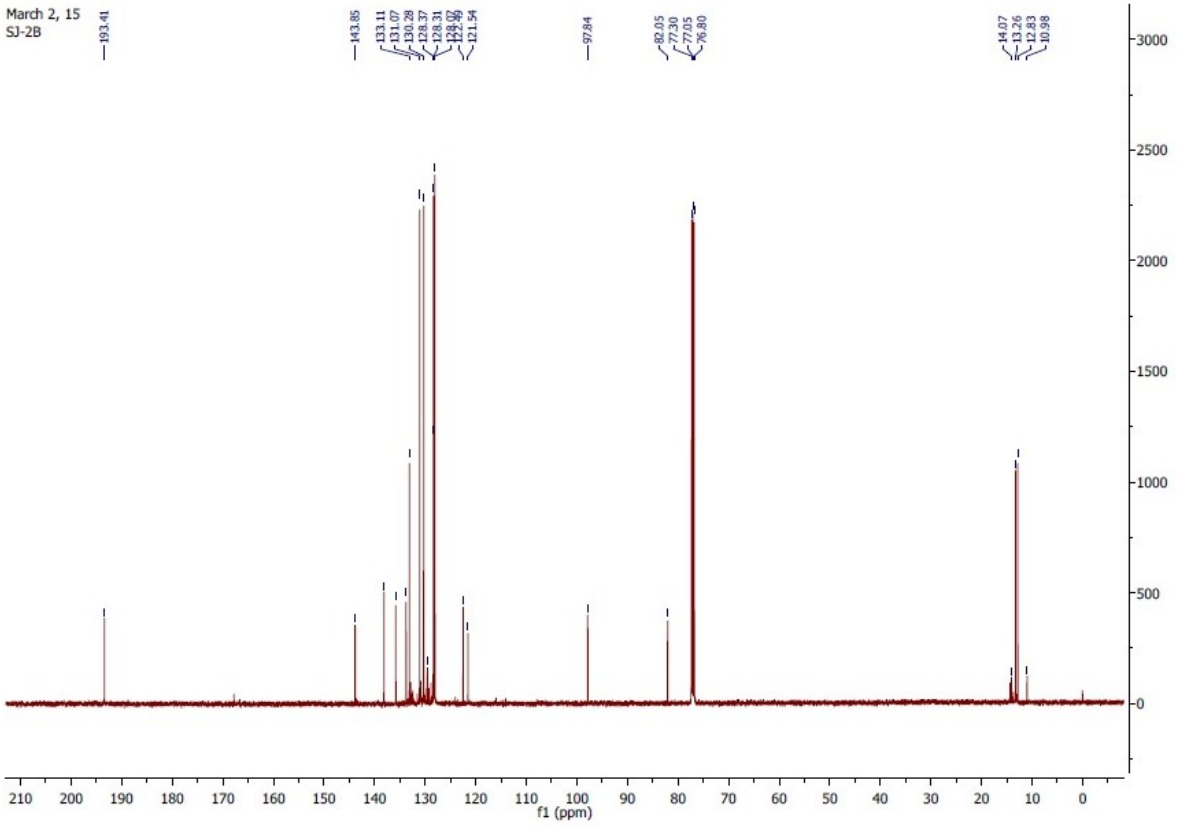
^{13}C NMR of 12*d*



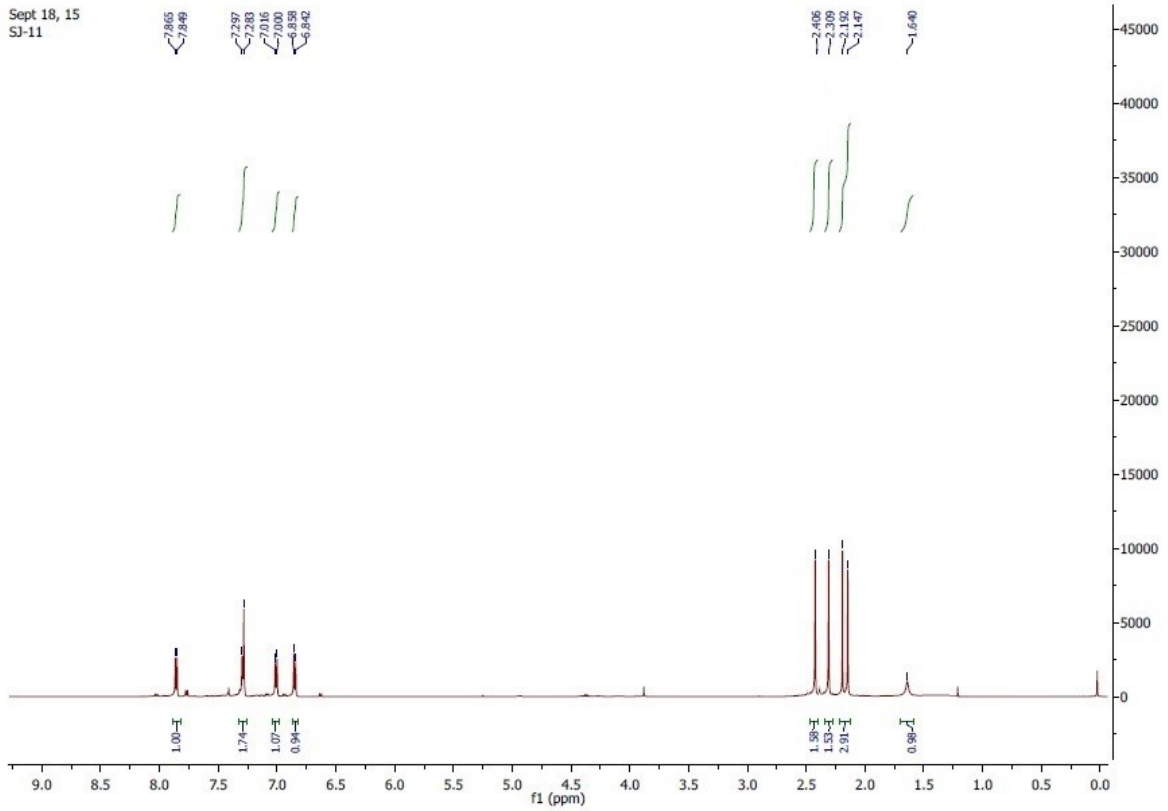
^{1}H NMR of 14*a*



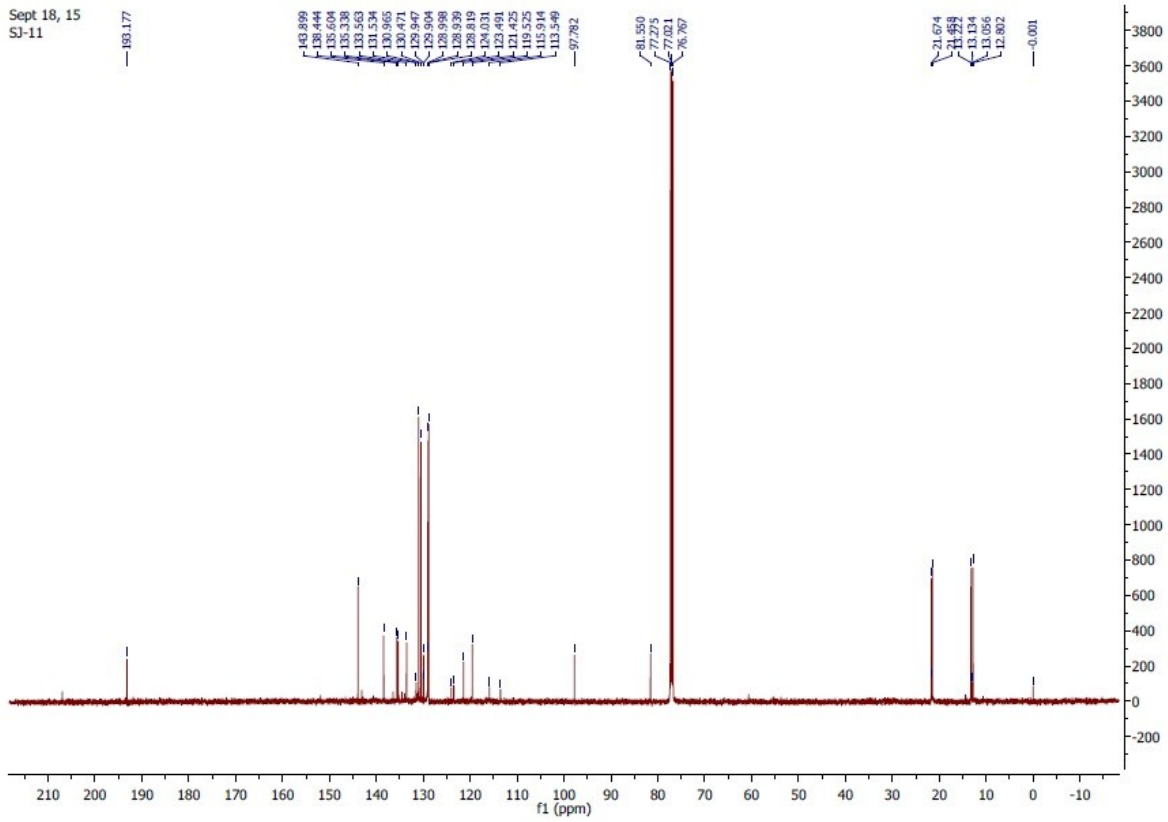
^{13}C NMR of 14*a*



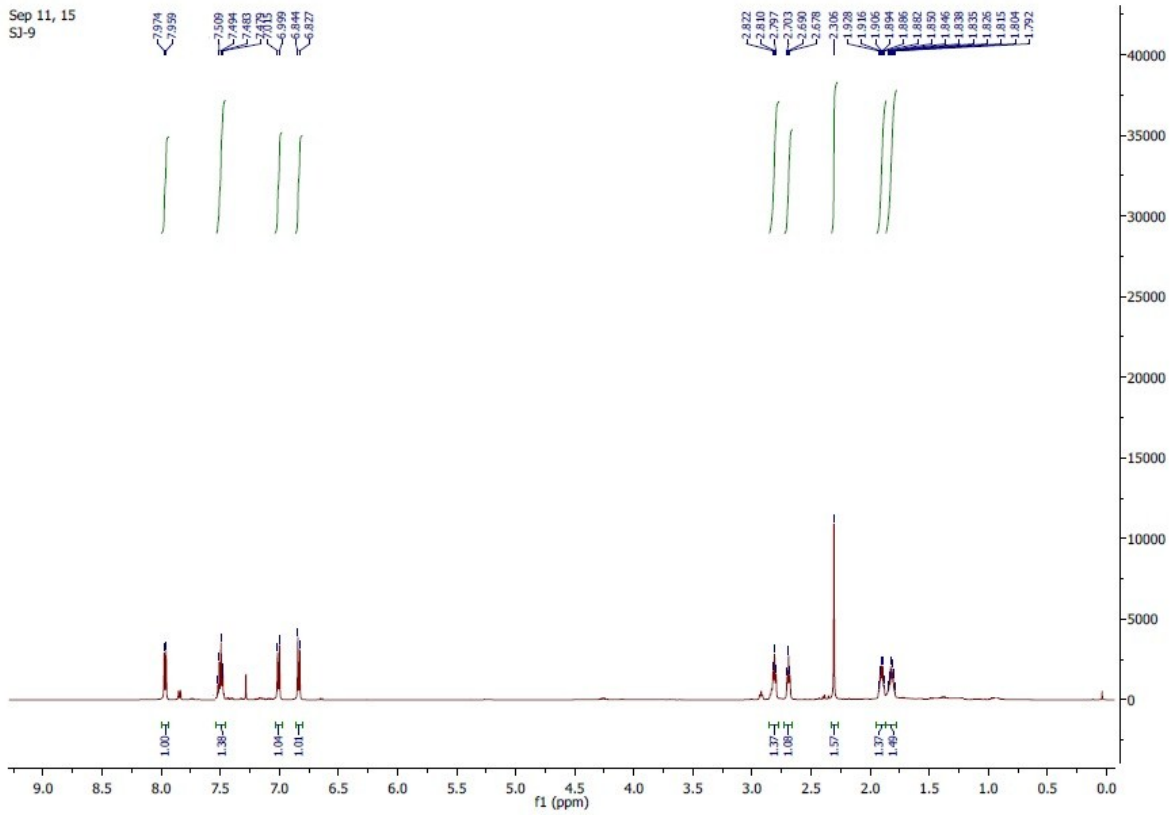
^{1}H NMR of 14*l*



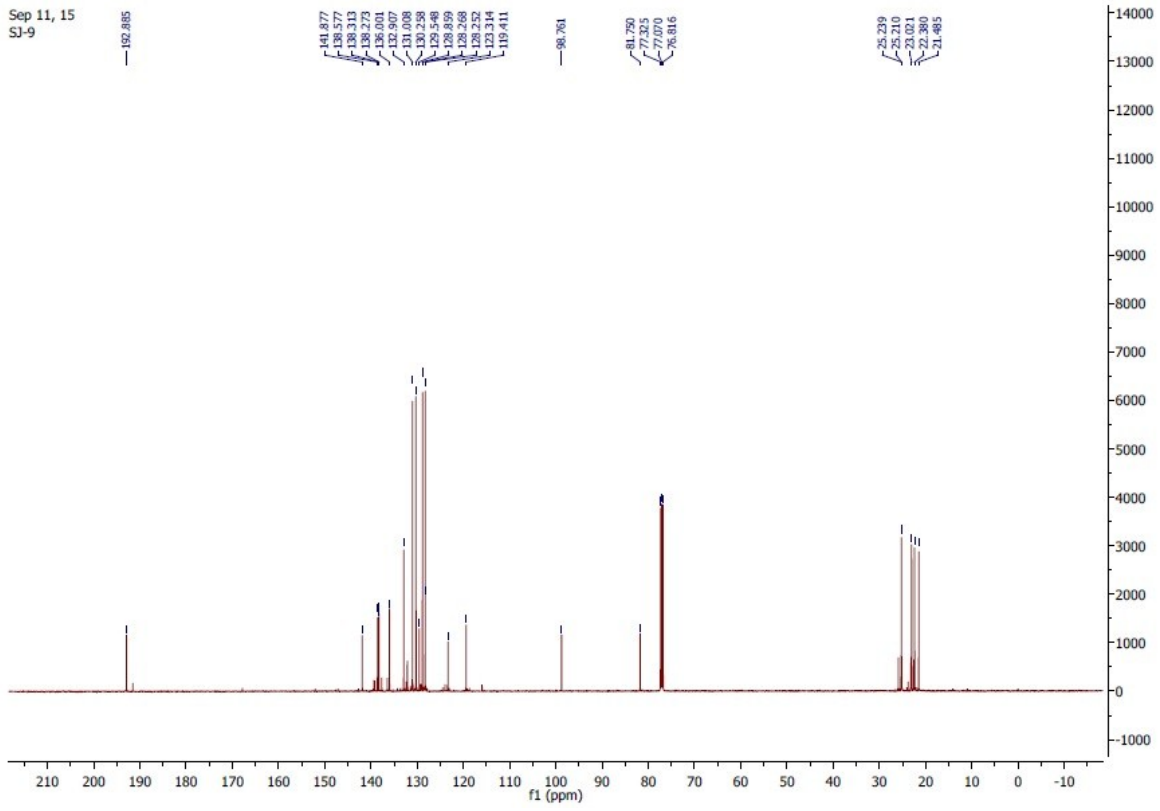
^{13}C NMR of 14*l*



^{1}H NMR of 14*n*



^{13}C NMR of 14*n*



References

1. Z. Puterová, A. Andicsová and D. Végh, Tetrahedron, 2008, 64(49), 11262-11269.
2. Y. Huang and A. Dömling, Mol. Divers., 2011, 15(1), 3-33.
3. A. Nakhi, R. Adepu, D. Rambabu, R. Kishore, G. Vanaja, A. M. Kalle and M. Pal, Bioorg. Med. Chem. Lett., 2012, 22(13), 4418-4427.
4. T. Mosmann, J. Immunol. Methods, 1983, 65(1-2), 55-63.
5. S. R. Molinspiration Chemoinformatics Brastislava, Available from: http://www.molinspiration.com/cgi-bin/properties (Accessed on 10-03-2016).