Supplementary Information for

Direct access to pyrazolo(benzo)thienoquinolines. Highly effective palladium catalysts in an intramolecular C-H heteroarylation of arenes

Fátima Churruca, Susana Hernandez, María Pereda, Raul SanMartin* and Esther Domínguez*

Kimika Organikoa II Saila, Zientzia eta Teknologia Fakultatea, Euskal Herriko Unibertsitatea, 644 P.K. 48080 Bilbao, Spain

raul.sanmartin@ehu.es

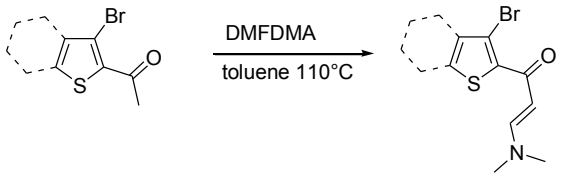
Table of contents

General

All reactions were run under an atmosphere of argon unless otherwise indicated. Room temperature refers to 22°C, ambient pressure to 1013 hPa. All chemicals were purchased and used as received except when indicated. Chromatographic purification was performed as flash chromatography on silica gel 35-70, 60 Å, using a forced flow of eluent (method of Still). Drying of organic extracts during work-up of reactions was performed over anhydrous Na_2SO_4. Concentration under reduced pressure was performed by rotary evaporation at 40°C at the appropriate pressure. Yields refer to chromatographically purified and spectroscopically pure compounds. Chemical shifts δ are reported in ppm with the solvent resonance as the internal standard (d_1-chloroform: 7.260 (^{1}H-NMR), 77.16 (^{13}C-NMR). Coupling constants *J* are given in Hertz (Hz). Multiplicities are classified by the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet and combinations thereof, or m = multiplet or br = broad signal. Melting points were determined in a capillary tube and are uncorrected. TLC was carried out on SiO_2, and the spots were located with UV light.

Experimental procedures

Synthesis of enaminones



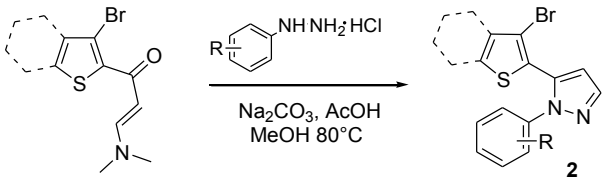
General procedure. *N,N*-Dimethylformamide dimethyl acetal (DMFDMA, 12.24 mmol) was dropwised added to a solution of ketone (7.79 mmol) in dry toluene (13 mL) under argon. The reaction crude was heated to 110ºC until TLC showed the completion of the reaction (23h). After cooling, the solvent was evaporated under reduced pressure and the so-obtained residue was purified by silica gel column chromatography (EtOAc in hexane).

***(E)*-1-(3-Bromobenzo[*b*]thiophen-2-yl)-3-(*N*,*N*-dimethylamino)-2-propen-1-one.** 92%, orange foam: mp 137-139˚C (diethyl ether); IR (film) ν_{max} 1625 (C=O) cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ2.97 (3H, bs, NCH_3), 3.17 (3H, bs, NCH_3), 6.11 (1H, d, *J* 12.3, =CH-CO), 7.40-7.48 (2H, m, H_{arom}), 7.76-7.94 (3H, m, =CH-N, H_{arom}); ^{13}C-NMR (62.8 MHz, $CDCl_3$) δ

37.3, 45.0 (NCH_3), 94.5 (=*C*H-CO), 106.8 (C-3), 122.3, 124.4, 125.0, 126.6 (C_{arom}-H), 138.1, 139.1, 141.3 (C_{arom}-C, C_{arom}-S), 154.4 (=CH-N), 180.5 (C=O); HRMS (*m/z*): $[M]^+$ calcd for $C_{13}H_{12}BrNOS$: 308.9823, found: 308.9818.

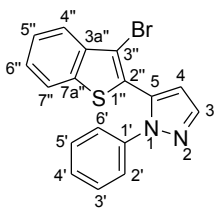
***(E)*-1-(3-Bromothiophen-2-yl)-3-(*N*,*N*-dimethylamino)-2-propen-1-one.** 93%, yellowish solid: mp 56-58˚C (pentane); IR (film) ν_{max} 1631 (C=O) cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ2.88 (3H, bs, NCH_3), 3.10 (3H, bs, NCH_3), 5.95 (1H, d, *J* 12.3, =CH-CO), 6.97 (1H, d, *J* 5.1, H_{arom}), 7.31 (1H, d, *J* 5.1, H_{arom}), 7.76 (1H, d, *J* 12,3, =CH-N); ^{13}C-NMR (62.8 MHz, $CDCl_3$) δ37.3, 45.0 (NCH_3), 94.5 (=*C*H-CO), 106.8 (C-3), 122.3, 124.4, 125.0, 126.6 (C_{arom}-H), 138.1, 139.1, 141.3 (C_{arom}-C, C_{arom}-S), 154.4 (=CH-N), 180.5 (C=O); HRMS (*m/z*): $[M]^+$ calcd for $C_9H_{10}BrNOS$: 258.9666, found: 258.9677.

Synthesis of pyrazoles 2



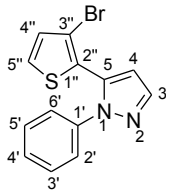
General procedure. Arylhydrazine hydrochloride (6.5 mmol) was added to a solution of enaminoketone (5.9 mmol) and Na_2CO_3 (4.0 mmol) in MeOH (40 mL) and H_2O (8 mL) under stirring at room temperature. The resulting mixture was acidified with glacial acetic acid to pH 5-6 and heated to 135ºC for 2 hours. After cooling, the suspension was diluted with EtOAc (30 mL), the organic layer was washed with H_2O (3 x 10 mL) and the solvent was evaporated under reduced pressure. The so-obtained residue was purified by silica gel column chromatography (hexane in CH_2Cl_2).

5-(3-Bromobenzo[*b*]thiophen-2-yl)-1-phenylpyrazole (2a). 95%, reddish solid: mp 57-58˚C (pentane); IR (film) ν_{max} 1609 (C=N) cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ6.78 (1H, d, *J* 2.0, H-4), 7.28-7.50 (7H, m, H_{arom}), 7.72-7.81 (2H, m, H_{arom}), 7.84 (1H, d, *J* 1.6, H-3); ^{13}C-NMR (62.8 MHz, $CDCl_3$) δ 109.9 (C-3''), 111.1 (C-4), 122.3, 123.8, 124.5, 125.4, 126.1 (C_{arom}-H), 127.1 (C_{arom}-C, C_{arom}-S), 127.7, 129.0 (C_{arom}-H), 134.0, 137.8, 138.7, 139.7



(C_{arom}-C, C_{arom}-S, C_{arom}-N), 140.3 (C-3); HRMS (*m/z*): $[M]^+$ calcd for $C_{17}H_{11}BrN_2S$: 353.9826, found: 353.9821.

5-(3-Bromothiophen-2-yl)-1-phenylpyrazole (2b). 86%, orange solid: mp 68-70˚C (hexane);



IR (film) ν_{max} 1625 (C=N) cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ6.66 (1H, d, *J* 2.0, H-4), 6.99 (1H, d, *J* 5.1, H-4'', H-5''), 7.32-7.34 (6H, m, H_{arom}), 7.76 (1H, d, *J* 1.6, H-3); ^{13}C-NMR (62.8 MHz, $CDCl_3$) δ 110.4 (C-4), 112.3 (C-3''), 124.4, 127.4, 127.7, 128.7, 130.5 (C_{arom}-H), 133.5, 139.5 (C_{arom}-N, C-2''), 139.9 (C-3); HRMS (*m/z*): $[M]^+$ calcd for $C_{13}H_9BrN_2S$: 303.9670, found: 303.9677.

5-(3-Bromobenzo[*b*]thiophen-2-yl)-1-(2-ethylphenyl)pyrazole (2c). 88%, reddish solid: mp 58-60˚C (pentane); IR (film) ν_{max} 1615 (C=N) cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ1.10 (3H, t, *J* 7.5, CH_2CH_3), 2.44 (2H, q, *J* 7.5, CH_2CH_3), 6.99 (1H, d, *J* 2.0, H-4), 7.18-7.46 (6H, m, H_{arom}), 7.61-7.65 (1H, m, H_{arom}), 7.81-7.83 (1H, m, H_{arom}), 7.84 (1H, d, *J* 2.0, H-3); ^{13}C-NMR (62.8 MHz, $CDCl_3$) δ 14.1 (CH_2CH_3), 23.9 (CH_2CH_3), 108.9 (C-3''), 109.4 (C-4), 122.0, 123.8, 125.2, 125.9, 126.2 (C_{arom}-H), 126.6 (C_{arom}-C, C_{arom}-S), 128.4, 129.1, 129.6 (C_{arom}-H), 135.8, 137.6, 137.9, 138.4 (C_{arom}-C, C_{arom}-S, C_{arom}-N), 139.7 (C-3), 141.9 (C_{arom}-S, C_{arom}-N); HRMS (*m/z*): $[M]^+$ calcd for $C_{19}H_{15}BrN_2S$: 382.0139, found: 382.0132.

5-(3-Bromothiophen-2-yl)-1-(2-ethylphenyl)pyrazole (2d). 90%, brown solid: mp 74-76˚C (hexane); IR (film) ν_{max} 1625 (C=N) cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ1.06 (3H, t, *J* 7.5, CH_2CH_3), 2.37 (2H, q, *J* 7.5, CH_2CH_3), 6.87 (1H, d, *J* 1.6, H-4), 6.94 (1H, d, *J* 5.5, H-4'', H-5''), 7.15 (1H, d, *J* 5.5, H-4'', H-5''), 7.21-7.40 (4H, m, H_{arom}), 7.77 (1H, d, *J* 2.0, H-3); ^{13}C-NMR (62.8 MHz, $CDCl_3$) δ 14.0 (CH_2CH_3), 23.7 (CH_2CH_3), 108.3 (C-4), 111.3 (C-3''), 126.1 (C_{arom}-H), 126.3 (C-2', C-2''), 127.1, 128.4, 129.0, 129.5, 130.4 (C_{arom}-H), 135.5, 137.8 (C-2', C-2'', C_{arom}-N), 139.5 (C-3), 141.9 (C_{arom}-N); HRMS (*m/z*): $[M]^+$ calcd for $C_{15}H_{13}BrN_2S$: 331.9983, found: 331.9988.

5-(3-Bromobenzo[*b*]thiophen-2-yl)-1-(4-methylphenyl)pyrazole (2e). 87%, brownish solid: mp 88-89˚C (pentane); IR (film) ν_{max} 1610 (C=N) cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ2.33 (3H, s, CH_3), 6.77 (1H, d, *J* 2.0, H-4), 7.12 (2H, d, *J* 8.3, H-2', H-3'), 7.28 (2H, d, *J* 8.3, H-2', H-3'), 7.38-7.50 (2H, m, H_{arom}), 7.74 (1H, dd, *J* 6.7, *J* 1.2, H-4'', H-7''), 7.81 (1H, d, *J* 1.6, H-3), 7.80-7.84 (1H, m, H_{arom}); ^{13}C-NMR (62.8 MHz, $CDCl_3$) δ 20.9 (CH_3), 109.7 (C-3''),

110.7 (C-4), 122.1, 123.6, 124.3, 125.2, 125.9 (C_{arom}-H), 127.1 (*C*$_{arom}$-C, C_{arom}-S), 129.4 (C_{arom}-H), 133.7 (*C*$_{arom}$-C, C_{arom}-S), 137.1, 137.5, 137.6, 138.6 (*C*$_{arom}$-C, C_{arom}-S, C_{arom}-N), 139.9 (C-3); HRMS (*m/z*): $[M]^+$ calcd for $C_{18}H_{13}BrN_2S$: 367.9983, found: 367.9984.

5-(3-Bromobenzo[*b*]thiophen-2-yl)-1-(4-methoxyphenyl)pyrazole (2f). 82%, brownish solid: mp 104-105˚C (pentane); IR (film) ν_{max} 1609 (C=N) cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ3.77 (3H, s, OCH_3), 6.77 (1H, d, *J* 2.0, H-4), 6.80-6.86 (2H, m, H_{arom}), 7.27-7.33 (2H, m, H_{arom}), 7.37-7.49 (2H, m, H_{arom}), 7.72-7.74 (1H, m, H_{arom}), 7.79 (1H, d, *J* 2.0, H-3), 7.78-7.83 (1H, m, H_{arom}); ^{13}C-NMR (62.8 MHz, $CDCl_3$) δ 55.3 (OCH_3), 109.7 (C-3''), 110.5 (C-4), 114.0, 122.2, 123.8, 125.3, 126.0, 126.1 (C_{arom}-H), 127.1 (*C*$_{arom}$-C, C_{arom}-S), 132.8, 134.0, 137.7, 138.7 (*C*$_{arom}$-C, C_{arom}-S, C_{arom}-N), 139.9 (C-3), 158.8 (C-4'); HRMS (*m/z*): $[M]^+$ calcd for $C_{17}H_{16}BrN_2OS$: 383.9932, found: 383.9943.

5-(3-Bromobenzo[*b*]thiophen-2-yl)-1-(4-trifluoromethylphenyl)pyrazole (2g). 87%, orange solid: mp 113-114˚C (pentane); IR (film) ν_{max} 1607 (C=N) cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ6.76 (1H, d, *J* 1.6, H-4), 7.42-7.60 (6H, m, H_{arom}), 7.77-7.84 (2H, m, H-3, H_{arom}), 7.85 (1H, d, *J* 1.6, H-3); ^{13}C-NMR (62.8 MHz, $CDCl_3$) δ 110.4 (C-3''), 112.0 (C-4), 122.4 (C_{arom}-H), 123.7 (q, *J* 272.9, CF_3), 124.0, 125.6 (C_{arom}-H), 126.2 (q, *J* 3.6, C-3'), 126.4 (C_{arom}-H), 129.3 (q, *J* 32.3, C-4'), 134.1, 137.7, 138.7 (*C*$_{arom}$-C, C_{arom}-S, C_{arom}-N), 141.1 (C-3), 142.2 (C_{arom}-S, C_{arom}-N); HRMS (*m/z*): $[M]^+$ calcd for $C_{18}H_{10}F_3BrN_2S$: 421.9700, found: 421.9695.

5-(3-Bromobenzo[*b*]thiophen-2-yl)-1-(4-*tert*-buthylphenyl)piyrazole (2h). 87%, brown solid: mp 125-127˚C (pentane); IR (film) ν_{max} 1612 (C=N) cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ1.31 (9H, s, $C(CH_3)_3$), 6.77 (1H, d, *J* 2.0, H-4), 7.35-7.49 (6H, m, H_{arom}), 7.72-7-75 (1H, m, H_{arom}), 7.82 (1H, d, *J* 2.0, H-3), 7.82-7.84 (1H, m, H_{arom}); ^{13}C-NMR (62.8 MHz, $CDCl_3$) δ 31.2 ($C(CH_3)_3$), 34.5 ($C(CH_3)_3$), 109.8 (C-3''), 110.8 (C-4), 122.2, 123.7, 123.9, 125.2, 125.8, 125.9 (C_{arom}-H), 127.3 (*C*$_{arom}$-C, C_{arom}-S), 133.7, 137.1, 137.7, 138.7 (*C*$_{arom}$-C, C_{arom}-S, C_{arom}-N), 139.9 (C-3), 150.6 (C-4'); HRMS (*m/z*): $[M]^+$ calcd for $C_{21}H_{19}BrN_2S$: 410.0452, found: 410.0439.

5-(3-Bromothiophen-2-yl)-1-(4-methylphenyl)pyrazole (2i). 87%, brownish solid: mp 66-67˚C (hexane); IR (film) ν_{max} 1600 (C=N) cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ2.35 (3H, s, CH_3), 6.65 (1H, d, *J* 1.6, H-4), 6.98 (1H, d, *J* 5.5, H-4'', H-5''), 7.13 (2H, d, *J* 8.3, H-2', H-

3''), 7.21 (2H, d, *J* 8.3, H-2', H-3''), 7.30 (1H, d, *J* 5.5, H-4'', H-5''), 7.74 (1H, d, *J* 1.6, H-3); ^{13}C-NMR (62.8 MHz, $CDCl_3$) δ 20.9 (CH_3), 110.1 (C-4), 112.2 (C-3''), 124.3 (C_{arom}-H), 126.9 (C-4', C-2''), 127.6, 129.2, 130.4 (C_{arom}-H), 133.4, 137.1, 137.3 (C-4', C-2'', C_{arom}-N), 139.7 (C-3); HRMS (*m/z*): $[M]^+$ calcd for $C_{14}H_{11}BrN_2S$: 317.9826, found: 317.9822.

5-(3-Bromothiophen-2-yl)-1-(4-methoxyphenyl)pyrazole (2j). 77%, brown solid: mp 76-78°C (hexane); IR (film) ν_{max} 1614 (C=N) cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 3.80 (3H, s, OCH_3), 6.66 (1H, d, *J* 2.0, H-4), 6.83-6.87 (2H, m, H_{arom}), 6.98 (1H, d, *J* 5.5, H-4'', H-5''), 7.22-7.26 (2H, m, H_{arom}), 7.30 (1H, d, *J* 5.5, H-4'', H-5''), 7.73 (1H, d, *J* 1.6, H-3); ^{13}C-NMR (62.8 MHz, $CDCl_3$) δ 55.4 (OCH_3), 109.9 (C-4), 112.3 (C-3''), 113.9, 126.3 (C_{arom}-H), 127.0 (C-2''), 127.7, 130.6 (C_{arom}-H), 132.8, 133.8 (C_{arom}-N), 139.7 (C-3), 159.0 (C-4'); HRMS (*m/z*): $[M]^+$ calcd for $C_{14}H_{11}BrN_2OS$: 333.9775, found: 333.9779.

5-(3-Bromothiophen-2-yl)-1-(4-trifluoromethylphenyl)pyrazole (2k). 61%, orange solid: mp 73-74°C (hexane); IR (film) ν_{max} 1608 (C=N) cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 6.72 (1H, d, *J* 2.0, H-4), 7.06 (1H, d, *J* 5.5, H-4'', H-5''), 7.42 (1H, d, *J* 5.5, H-4'', H-5''), 7.53-7.56 (2H, m, H_{arom}), 7.66-7.69 (2H, m, H_{arom}), 7.86 (1H, d, *J* 2.0, H-3); ^{13}C-NMR (62.8 MHz, $CDCl_3$) δ 111.5 (C-4), 112.8 (C-3''), 123.7 (q, *J* 272.9, CF_3), 123.9 (C_{arom}-H), 125.9 (q, *J* 3.6, C-3'), 126.4 (C-2''), 128.1 (C_{arom}-H), 129.1 (q, *J* 32.1, C-4'), 130.8 (C_{arom}-H), 133.6 (C_{arom}-N), 140.7 (C-3), 142.4 (C_{arom}-N); HRMS (*m/z*): $[M]^+$ calcd for $C_{14}H_{18}F_3BrN_2S$: 371.9544, found: 371.9554.

5-(3-Bromothiophen-2-yl)-1-(4-*tert*-buthylphenyl)pyrazole (2l). 78%, brownish solid: mp 102-103°C (hexane); IR (film) ν_{max} 1625 (C=N) cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 1.31 (9H, s, $C(CH_3)_3$), 6.66 (1H, d, *J* 1.6, H-4), 7.00 (1H, d, *J* 5.5, H-4'', H-5''), 7.22-7.37 (5H, m, H_{arom}), 7.75 (1H, d, *J* 2.0, H-3); ^{13}C-NMR (62.8 MHz, $CDCl_3$) δ 31.1 ($C(CH_3)_3$), 34.3 ($C(CH_3)_3$, 110.2 (C-4), 112.2 (C-3''), 123.9, 125.6 (C_{arom}-H), 126.9 (C-2''), 127.6, 130.4 (C_{arom}-H), 133.3, 137.0 (C_{arom}-N), 139.7 (C-3), 150.4 (C-4'); HRMS (*m/z*): $[M]^+$ calcd for $C_{17}H_{17}BrN_2S$: 360.0296, found: 360.0284.

Synthesis of quinolines 1

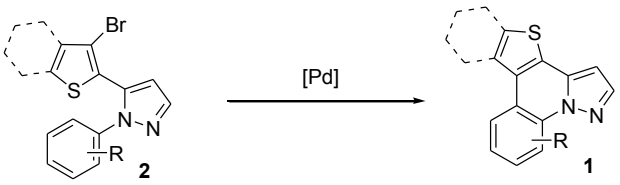
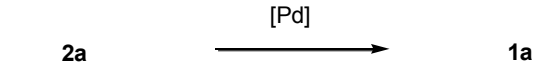


Table S1. Selected assays for the direct arylation of benzothienylphenylpyrazole **2a**



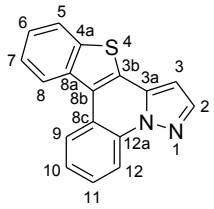
Entry	cat/L (% mol)	base (equiv)	additive	solvent	T (°C)	time (h)	**1a** (%)[a]
1	$Pd(OAc)_2/PPh_3$ (5)	Cs_2CO_3 (2)		dioxane	100	23	41
2	$Pd(OAc)_2$ (5)	K_2CO_3 (3)	18-crown-6	DMF	140	16	22
3	$Pd(PPh_3)_4$ (10)	KOAc (1.5)		toluene	100	22	41
4	$Pd(OAc)_2/PPh_3$ (10)	KOAc (2.5)		DMA	130	20	36
5	$Pd(OAc)_2/PPh_3$ (10)	K_2CO_3 (2.5)	$^nBu_4NBr$	CH_3CN	80	96	12
6	Pd/C (10)	KOAc (1.5)		NMP	100	72	25
7	$Pd(OAc)_2$ (10)	K_2CO_3 (2.5)	$^nBu_4NBr$, LiCl	DMF	130	15	62

[a]Isolated yield. Reaction conditions: **2a** (0.2 mmol), cat/L:1/4, solvent (2 mL) sealed tube under Ar.

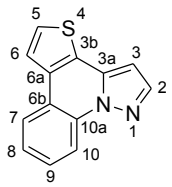
General procedure A (using $Pd(OAc)_2$). Dry degassed DMF (1.5 mL) was added to an oven-dried heavy-wall pressure tube charged with $Pd(OAc)_2$ (0.03 mmol), K_2CO_3 (1.6 mmol), LiCl (0.5 mmol), $^nBu_4NBr$ (0.3 mmol), and pyrazole **2** (0.3 mmol) under argon at room temperature. After the tube was closed, it was heated to 130 °C until TLC showed the completion of the reaction (15-18 h). After cooling, the crude was diluted with CH_2Cl_2 (10 mL), filtered to remove the inorganic salts and the resulting organic layer was washed with H_2O (1 x 5 mL). The organic phase was dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. The so-obtained residue was purified by flash column chromatography (EtOAc in hexane).

General procedure B (using pincers 3a) and C (using pincers 3b). Dry degassed DMA (2 mL) was added to an oven-dried heavy-wall pressure tube charged with complex **3a** or **3b** (0.002 mmol), KOAc (0.3 mmol), and pyrazole **2** (0.2 mmol) under argon at room temperature. After the tube was closed, it was heated to 130 °C until TLC showed the completion of the reaction (16-18 h). After cooling, the crude was diluted with EtOAc (10 mL) and washed with H_2O (1 x 5 mL). The organic phase was dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. The so-obtained residue was purified by flash column chromatography(EtOAc in hexane).

Pyrazolo[1,5-*a*]benzothieno[2,3-*c*]quinoline (1a). 62% (method A), 86% (method B), 92% (method C), yellow solid: mp 80-82˚C (pentane); IR (film) ν_{max} 1632 (C=N) cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 6.77 (1H, d, *J* 2.0, H-3), 7.43-7.59 (3H, m, H_{arom}), 7.64-7.70 (1H, m, H_{arom}), 7.92-7.96 (1H, m, H_{arom}), 8.04 (1H, d, *J* 1.6, H-2), 8.61-8.64 (1H, m, H_{arom}), 8.70-8.76 (2H, m, H_{arom}); ^{13}C-NMR (62.8 MHz, $CDCl_3$) δ 98.9 (C-3), 116.6 (C_{arom}-H), 120.9 (C-3b), 123.3, 123.9, 124.2, 125.1, 125.4, 125.5, 127.9 (C_{arom}-H), 128.5, 133.3, 134.1, 136.1, 139.6 (C_{arom}-C, C-4a, C_{arom}-N), 141.4 (C-2); HRMS (*m/z*): $[M]^+$ calcd for $C_{17}H_{10}N_2S$: 274.0565, found: 274.0570.



Pyrazolo[1,5-*a*]thieno[2,3-*c*]quinoline (1b). 58% (method A), 64% (method B), 83% (method C), yellow solid: mp 151-152˚C (pentane); IR (film) ν_{max} 1596 (C=N) cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 6.76 (1H, d, *J* 1.2, H-3), 7.49-7.55 (1H, m, H-8, H-9), 7.58 (1H, d, *J* 5.2, H-5, H-6), 7.63-7.69 (1H, m, H-8, H-9), 7.82 (1H, d, *J* 5.5, H-5, H-6), 8.02 (1H, d, *J* 1.2, H-2), 8.14-8.17 (1H, m, H-7, H-10), 8.62-8.65 (1H, m, H-7, H-10); ^{13}C-NMR (62.8 MHz, $CDCl_3$) δ 97.8 (C-3), 116.4 (C_{arom}-H), 119.9 (C-3b), 122.4, 124.3, 125.0, 126.4 (C_{arom}-H), 127.0 (C_{arom}-C), 128.3 (C_{arom}-H), 132.8, 133.1, 134.5 (C_{arom}-C, C_{arom}-N), 141.3 (C-2); HRMS (*m/z*): $[M]^+$ calcd for $C_{13}H_8N_2S$: 224.0408, found: 224.0417.



12-Ethylpyrazolo[1,5-*a*]benzothieno[2,3-*c*]quinoline (1c). 65% (method A), 88% (method B), 91% (method C), yellow solid: mp 130-131˚C (pentane); IR (film) ν_{max} 1619 (C=N) cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 1.42 (3H, t, *J* 7.1, CH_2CH_3), 3.71 (2H, q, *J* 7.1, CH_2CH_3), 6.73 (1H, d, *J* 2.0, H-3), 7.38-7.52 (4H, m, H_{arom}), 7.86-7.89 (1H, m, H_{arom}), 8.04 (1H, d, *J* 2.0, H-2), 8.53-8.61 (2H, m, H_{arom}); ^{13}C-NMR (62.8 MHz, $CDCl_3$) δ 16.3 (CH_2CH_3), 30.2 (CH_2CH_3), 98.1 (C-3), 121.9 (C_{arom}-H),122.6 (C-3b), 123.2, 124.2, 124.4, 125.1, 125.2 (C_{arom}-H), 125.8, 128.3 (C_{arom}-C), 130.7 (C_{arom}-H), 132.3, 135.2, 135.5, 136.3, 139.8 (C_{arom}-C, C-4a, C_{arom}-N), 140.5 (C-2); HRMS (*m/z*): $[M]^+$ calcd for $C_{19}H_{14}N_2S$: 302.0878, found: 302.0878.

10-Ethylpyrazolo[1,5-*a*]thieno[2,3-*c*]quinoline (1d). 37% (method A), 78% (method B), 92% (method C), yellow solid: mp 89-90˚C (pentane); IR (film) ν_{max} 1608 (C=N) cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 1.39 (3H, t, *J* 7.5, CH_2CH_3), 3.70 (2H, q, *J* 7.5, CH_2CH_3), 6.74 (1H, d, *J* 2.0, H-3), 7.41-7.50 (2H, m, H_{arom}), 7.51 (1H, d, *J* 5.5, H-5, H-6), 7.76 (1H, d, *J* 5.5, H-5, H-6), 8.02 (1H, d, *J* 2.0, H-2), 8.01-8.05 (1H, m, H_{arom}); ^{13}C-NMR (62.8 MHz, $CDCl_3$) δ 16.3 (CH_2CH_3), 29.7 (CH_2CH_3), 96.8 (C-3), 121.6 (C-3b), 122.6, 122.8, 124.6, 126.0 (C_{arom}-H), 126.8 (C_{arom}-C), 130.9 (C_{arom}-H), 132.0, 133.4, 135.3, 135.6 (C_{arom}-C, C_{arom}-N), 140.2 (C-2); HRMS (*m/z*): $[M]^+$ calcd for $C_{15}H_{12}N_2S$: 252.0721, found: 252.0711.

10-Methylpyrazolo[1,5-*a*]benzothieno[2,3-*c*]quinoline (1e). 73% (method A), 85% (method B), 88% (method C), yellow solid: mp 136-139˚C (pentane); IR (film) ν_{max} 1600 (C=N) cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 2.48 (3H, s, CH_3), 6.61 (1H, d, *J* 2.0, H-3), 7.32-7.44 (3H, m, H_{arom}), 7.77-7.81 (1H, m, H_{arom}), 7.94 (1H, d, *J* 2.0, H-2), 8.21 (1H, s, H-9), 8.35-8.38 (1H, m, H_{arom}), 8.42 (1H, d, *J* 8.7, H-12); ^{13}C-NMR (62.8 MHz, $CDCl_3$) δ 21.6 (CH_3), 98.4 (C-3), 116.1 (C_{arom}-H), 120.6 (C-3b), 123.0, 123.4, 124.0 (C_{arom}-H), 124.9 (C_{arom}-C), 125.0, 125.1 (C_{arom}-H), 128.1 (C_{arom}-C), 128.8 (C_{arom}-H), 131.1, 133.5, 134.4, 135.8, 139.3 (C_{arom}-C, C-4a, C_{arom}-N), 140.8 (C-2); HRMS (*m/z*): $[M]^+$ calcd for $C_{18}H_{12}N_2S$: 288.0721, found: 288.0715.

10-Methoxypyrazolo[1,5-*a*]benzothieno[2,3-*c*]quinoline (1f). 72% (method A), 88% (method B), 90% (method C), yellow solid: mp 170-172˚C (pentane); IR (film) ν_{max} 1614 (C=N) cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 3.98 (3H, s, OCH_3), 6.71 (1H, d, *J* 2.0, H-3), 7.23 (1H, dd, *J* 9.1, *J* 2.8, H-11), 7.41-7.54 (2H, m, H-6, H-7), 7.88-7.92 (1H, m, H-5, H-8), 7.97 (1H, d, *J* 2.4, H-2), 8.05 (1H, d, *J* 2.8, H-9), 8.46-8.49 (1H, m, H-5, H-8), 8.57 (1H, d, *J* 9.1, H-12); ^{13}C-NMR (62.8 MHz, $CDCl_3$) δ 55.6 (OCH_3), 98.5 (C-3), 107.1, 115.2, 117.7 (C_{arom}-H), 121.7 (C-3b), 123.2, 123.7 (C_{arom}-H), 124.8 (C_{arom}-C), 125.2, 125.3 (C_{arom}-H), 127.9, 128.9, 133.2, 135.9, 139.4 (C_{arom}-C, C-4a, C_{arom}-N), 140.7 (C-2), 156.8 (C-10); HRMS (*m/z*): $[M]^+$ calcd for $C_{18}H_{12}N_2OS$: 304.0670, found: 304.0670.

10-Trifluoromethylpyrazolo[1,5-*a*]benzothieno[2,3-*c*]quinoline (1g). 75% (method A), 89% (method B), 92% (method C), yellow solid: mp 185-186˚C (pentane); IR (film) ν_{max} 1625 (C=N) cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 6.70 (1H, d, *J* 2.0, H-3), 7.43-7.58 (2H, m, H_{arom}), 7.82-7.88 (2H, m, H_{arom}), 8.02 (1H, d, *J* 2.0, H-2), 8.40-8.43 (1H, m, H_{arom}), 8.68-8.72 (1H, m, H_{arom}), 8.85 (1H, s, H-9); ^{13}C-NMR (62.8 MHz, $CDCl_3$) δ 99.5 (C-3), 117.2 (C_{arom}-H), 120.3 (C-3b), 121.2 (q, *J* 3.6, C-9, C-11), 123.4, 123.7 (C_{arom}-H), 124.2 (q, *J* 3.6, C-9, C-11), 124.2 (q, *J* 271.1, CF_3), 124.5 (C_{arom}-C), 125.8, 125.9 (C_{arom}-H), 126.9 (q, *J* 32.3, C-10), 129.6, 134.4, 134.7, 135.3, 139.4 (C_{arom}-C, C-4a, C_{arom}-N), 142.3 (C-2); HRMS (*m/z*): $[M]^+$ calcd for $C_{18}H_{19}F_3N_2S$: 342.0439, found: 342.0436.

10-*tert*-Buthylpyrazolo[1,5-*a*]benzothieno[2,3-*c*]quinoline (1h). 55% (method A), 77% (method B), 85% (method C), yellow solid: mp 174-176˚C (pentane); IR (film) ν_{max} 1609 (C=N) cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 1.54 (9H, s, $C(CH_3)_3$), 6.74 (1H, d, *J* 2.0, H-3), 7.41-7.47 (1H, m, H_{arom}), 7.52-7.58 (1H, m, H_{arom}), 7.76 (1H, dd, *J* 8.7, *J* 1.6, H_{arom}), 7.89-7.92 (1H, m, H_{arom}), 8.02 (1H, d, *J* 2.0, H-2), 8.58-8.65 (2H, m, H_{arom}), 8.77 (1H, s, H-9); ^{13}C-NMR (62.8 MHz, $CDCl_3$) δ 31.6 ($C(CH_3)_3$), 35.0 ($C(CH_3)_3$), 98.6 (C-3), 116.2, 120.1 (C_{arom}-H), 120.6 (C-3b), 123.3, 124.0, 125,3 (C_{arom}-H), 125.6 (C_{arom}-C), 125.8 (C_{arom}-H), 128.3, 131.3, 133.9, 136.1, 139.6 (C_{arom}-C, C-4a, C_{arom}-N), 141.1 (C-2), 147.9 (C-10); HRMS (*m/z*): $[M]^+$ calcd for $C_{21}H_{18}N_2S$: 330.1191, found: 330.1205.

8-Methylpyrazolo[1,5-*a*]thieno[2,3-*c*]quinoline (1i). 58% (method A), 79% (method B), 80% (method C), yellow solid: mp 127-129˚C (hexane); IR (film) ν_{max} 1596 (C=N) cm^{-1}; ^{1}H-NMR

(250 MHz, $CDCl_3$) δ 2.53 (3H, s, CH_3), 6.71 (1H, d, *J* 1.6, H-3), 7.42-7.46 (1H, m, H-9, H-10), 7.52 (1H, d, *J* 5.1, H-5, H-6), 7.73 (1H, d, *J* 5.1, H-5, H-6), 7.85 (1H, s, H-7), 7.98 (1H, d, *J* 1.6, H-2), 8.46-8.49 (1H, m, H-9, H-10); ^{13}C-NMR (62.8 MHz, $CDCl_3$) δ 21.3 (CH_3), 97.6 (C-3), 116.2 (C_{arom}-H), 119.8 (C-3b), 122.3, 124.1, 126.2 (C_{arom}-H), 126.9 (C_{arom}-C), 129.6 (C_{arom}-H), 131.2, 132.7, 134.2, 134.6 (C_{arom}-C, C_{arom}-N), 140.9 (C-2); HRMS (*m/z*): $[M]^+$ calcd for $C_{14}H_{10}N_2S$: 238.0565, found: 238.0559.

8-Methoxypyrazolo[1,5-*a*]thieno[2,3-*c*]quinoline (1j). 40% (method A), 80% (method B), 88% (method C), yellow solid: mp 126-127˚C (pentane); IR (film) ν_{max} 1614 (C=N) cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 3.91 (3H, s, CH_3), 6.66 (1H, d, *J* 2.0, H-3), 7.17 (1H, dd, *J* 9.1, 2.4, H-9), 7.37 (1H, d, *J* 2.8, H-7), 7.45 (1H, d, *J* 5.1, H-5, H-6), 7.60 (1H, d, *J* 5.1, H-5, H-6), 7.94 (1H, d, *J* 2.0, H-2), 8.45 (1H, d, *J* 9.1. H-10); ^{13}C-NMR (62.8 MHz, $CDCl_3$) δ 55.6 (OCH_3), 97.4 (C-3), 106.6, 116.3, 117.7 (C_{arom}-H), 120.8 (C-3b), 122.2, 126.1, (C_{arom}-H), 127.4, 127.8, 132.3, 133.6 (C_{arom}-C, C_{arom}-N), 140.5 (C-2), 156.8 (C-9); HRMS (*m/z*): $[M]^+$ calcd for $C_{14}H_{10}N_2OS$: 254.0514, found: 254.0512.

8-Trifluoromethylpyrazolo[1,5-*a*]thieno[2,3-*c*]quinoline (1k). 58% (method A), 76% (method B), 89% (method C), yellow solid: mp 110-113˚C (hexane); IR (film) ν_{max} 1602 (C=N) cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 6.76 (1H, d, *J* 2.0, H-3), 7.61 (1H, d, *J* 5.1, H-5, H-6), 7.79 (1H, d, *J* 5.1, H-5, H-6), 7.85 (1H, d, *J* 8.7, H-9, H-10), 8.04 (1H, d, *J* 2.0, H-2), 8.35 (1H, s, H-7), 8.70 (1H, d, *J* 8.7, H-9, H-10); ^{13}C-NMR (62.8 MHz, $CDCl_3$) δ 98.4 (C-3), 117.2 (C_{arom}-H), 116.9 (C-3b), 121.8 (q, *J* 3.6, C-7, C-9), 122.2 (C_{arom}-H), 124.7 (q, *J* 3.6, C-7, C-9), 126.9 (q, *J* 32.3, C-8), 127.1 (C_{arom}-H), 127.2 (C_{arom}-C, C_{arom}-N), 132.0, 134.7, 134.9 (C_{arom}-C, C_{arom}-N), 142.2 (C-2); HRMS (*m/z*): $[M]^+$ calcd for $C_{14}H_7F_3N_2S$: 292.0282, found: 292.0290.

8-*tert*-Buthylpyrazolo[1,5-*a*]thieno[2,3-*c*]quinoline (1l). 52% (method A), 82% (method B), 87% (method C), yellow solid: mp 71-73˚C (pentane); IR (film) ν_{max} 1602 (C=N) cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 1.46 (9H, s, $C(CH_3)_3$), 6.73 (1H, d, *J* 2.4, H-3), 7.56 (1H, d, *J* 5.1, H-5, H-6), 7.72 (1H, dd, *J* 8.7, 2.0, H-9), 7.84 (1H, d, *J* 5.1, H-5, H-6), 8.00 (1H, d, *J* 2.0, H-2, H-7), 8.10 (1H, d, *J* 2.0, H-2, H-7), 8.54 (1H, d, *J* 8.7, H-10); ^{13}C-NMR (62.8 MHz, $CDCl_3$) δ 31.5 ($C(CH_3)_3$), 34.8 ($C(CH_3)_3$), 97.5 (C-3), 116.1 (C_{arom}-H), 119.5 (C-3b), 120.3, 122.3, 126.2, 126.3 (C_{arom}-H), 126.8, 131.1, 133.0, 134.2 (C_{arom}-C, C_{arom}-N), 141.0 (C-2), 147.9 (C-8); HRMS (*m/z*): $[M]^+$ calcd for $C_{17}H_{16}N_2S$: 280.1034, found: 280.1038.

Catalyst recycling procedure (B, using pincer 3a). Dry degassed DMA (2 mL) was added to an oven-dried heavy-wall pressure tube charged with complex **3a** (0.002 mmol), KOAc (0.3 mmol), and pyrazole **2** (0.2 mmol) under argon at room temperature. After the tube was closed, it was heated to 130 °C until TLC showed the completion of the reaction (16h). After

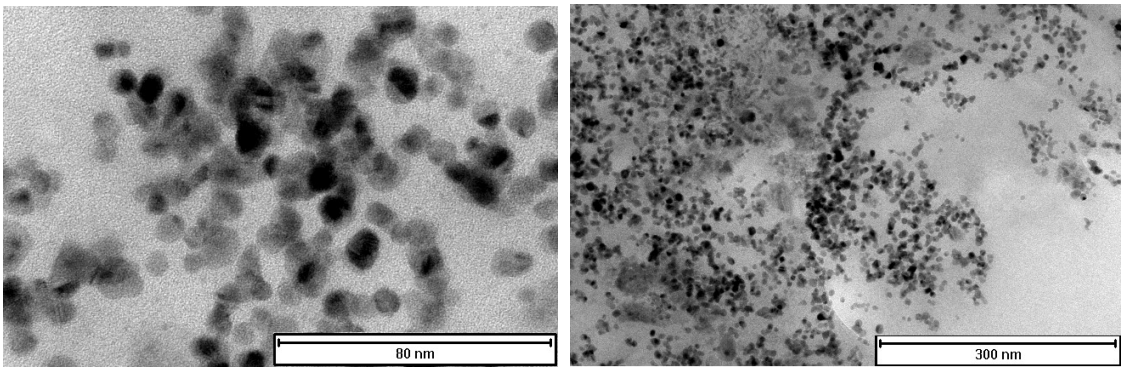
cooling, the crude was diluted with EtOAc (10 mL) and washed with H_2O (10 x 5 mL). The aqueous phase was concentrated in vacuo (T<50ºC) to remove water, and to the resulting DMA yellowish mixture KOAc (0.3 mmol) and pyrazole **2** (0.2 mmol) were added at room temperature and then, after closing, the mixture was heated at 130 °C for 16h. Every time, after cooling and work.up, the reagent and base were added and the reaction repeated. As previously explained in the general procedure, the organic phase was dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure to provide a residue which was purified by flash column chromatography, thus affording benzothienoquinoline **1a** as a yellow powder.

Recycling Experiments for Procedure B (complex **3a**).

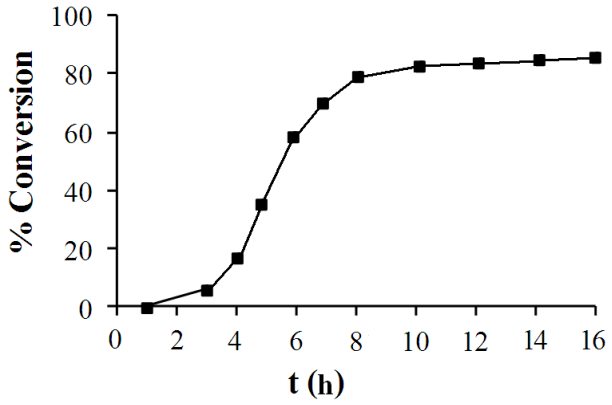
Run	**1a** (%)[a]
1	86
2	80
3	64
4	34
5	<5

[a] Isolated yields.

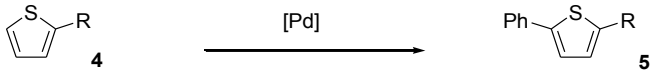
TEM images of the DMA/H_2O layer after extraction with ethyl acetate (Procedure B (complex 3a))



Conversion of benzothienylphenylpyrazole **2a** as a function of time
for intramolecular direct arylation at 130 ºC with complex **3a** (Table 1, entry 7)



Synthesis of thiophenes 5



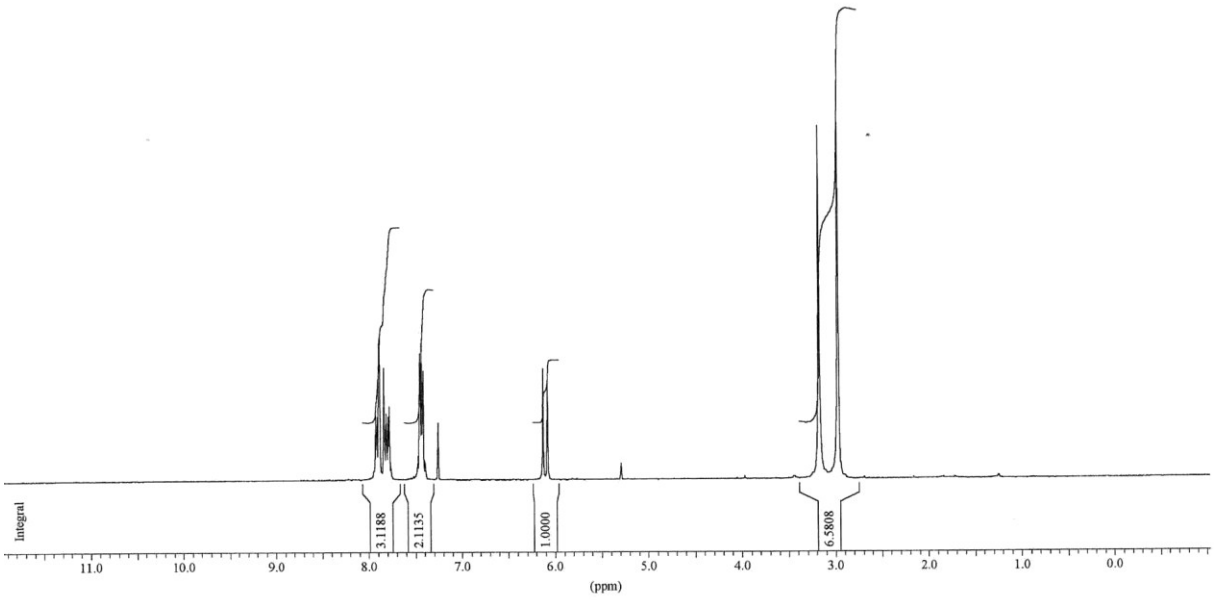
General procedure A (using pincer 3a as catalysts) and B (using pincer 3b as catalysts). Dry degassed DMA (2 mL) was added to an oven-dried heavy-wall pressure tube charged with complex **3a** or **3b**(0.54 μmol), KOAc (0.4 mmol), bromobenzene (0.27 mmol) and thiophene **4** (0.27 mmol) under argon at room temperature. After the tube was closed, it was heated to 130 °C until TLC showed the completion of the reaction (18 h). After cooling, the crude was diluted with CH_2Cl_2 (10 mL) and washed with H_2O (1 x 5 mL). The organic phase was dried and the solvent was evaporated under reduced pressure. The so-obtained residue was purified by silica gel column chromatography (EtOAc in hexane).

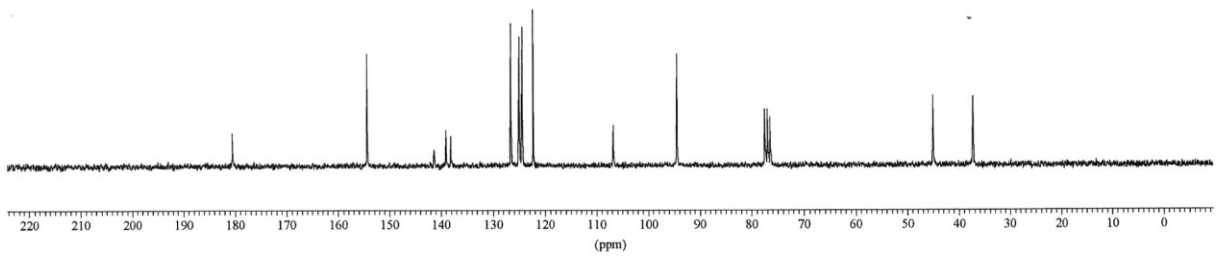
5-Acetyl-2-phenylthiophene 5a. 86% (method A), 83% (method B), yellow needles: mp 113-114˚C (hexane), Lit[1] 114-115˚C.

5-Methyl-2-phenylthiophene 5b. 82% (method A), 78% (method B), white needles: mp 38-40˚C (hexane), Lit[2] 39-41˚C.

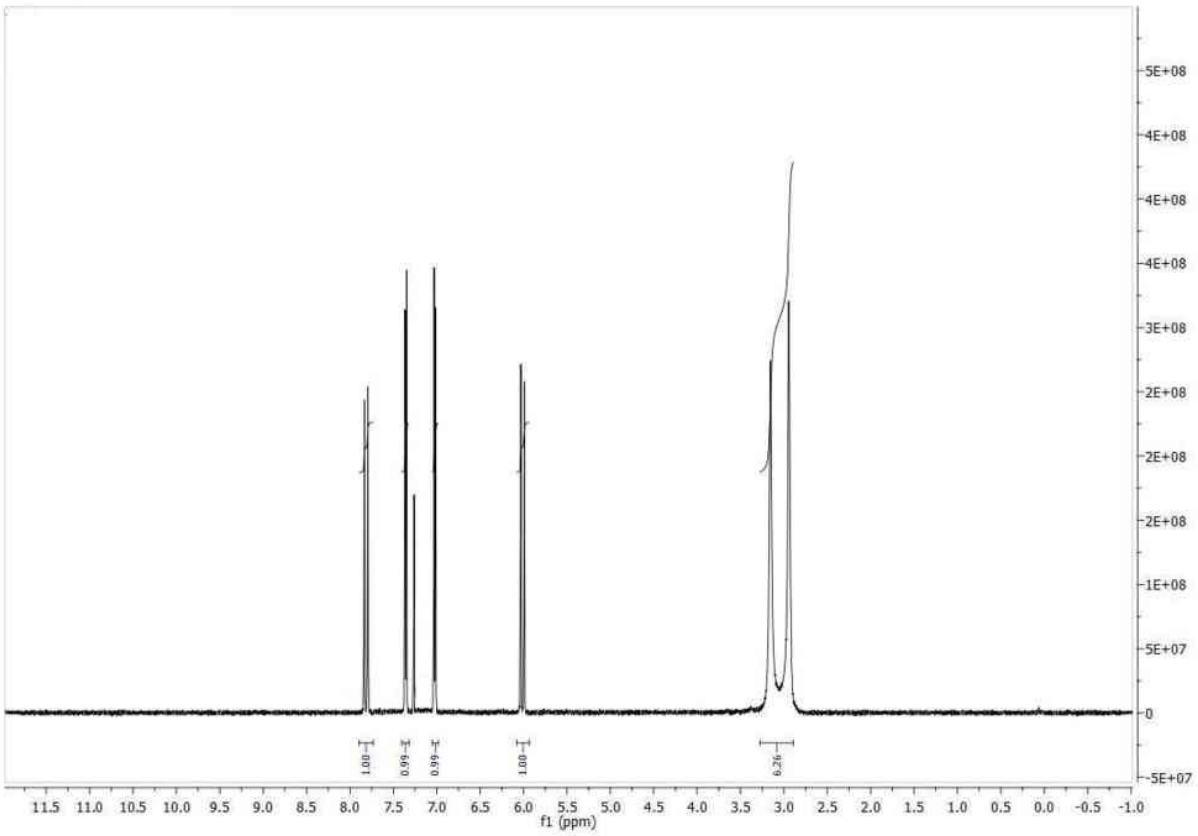
[1] L. Bai, Y. M. Zhang and J.-X. Wang, *QSAR Comb. Sci*., 2004, **23**, 857.
[2] W.-D. Liu, C.-C. Chi, I.-F. Pai, A.-T. Wu and W.-S. Chung, *J. Org. Chem.*, 2002, **67**, 9267.

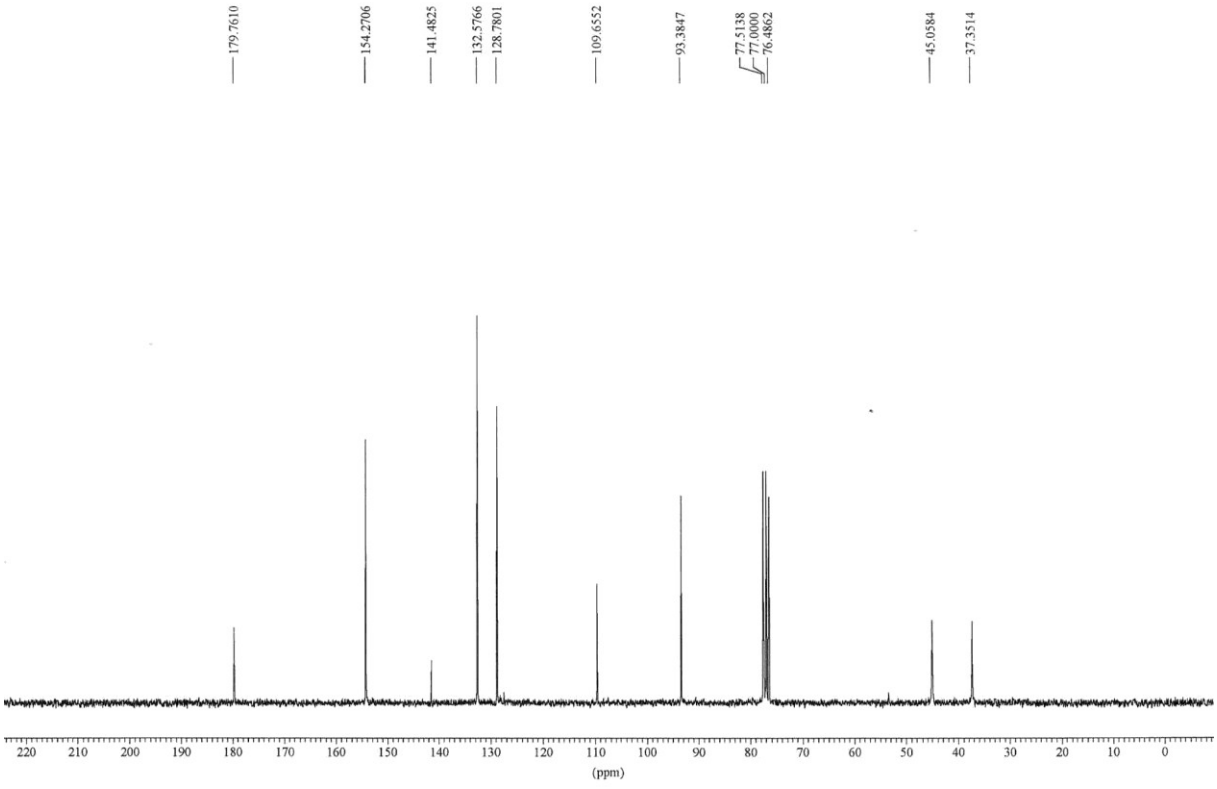
_(E)_-1-(3-Bromobenzo[_b_]thiophen-2-yl)-3-(_N_,_N_-dimethylamino)-2-propen-1-one.



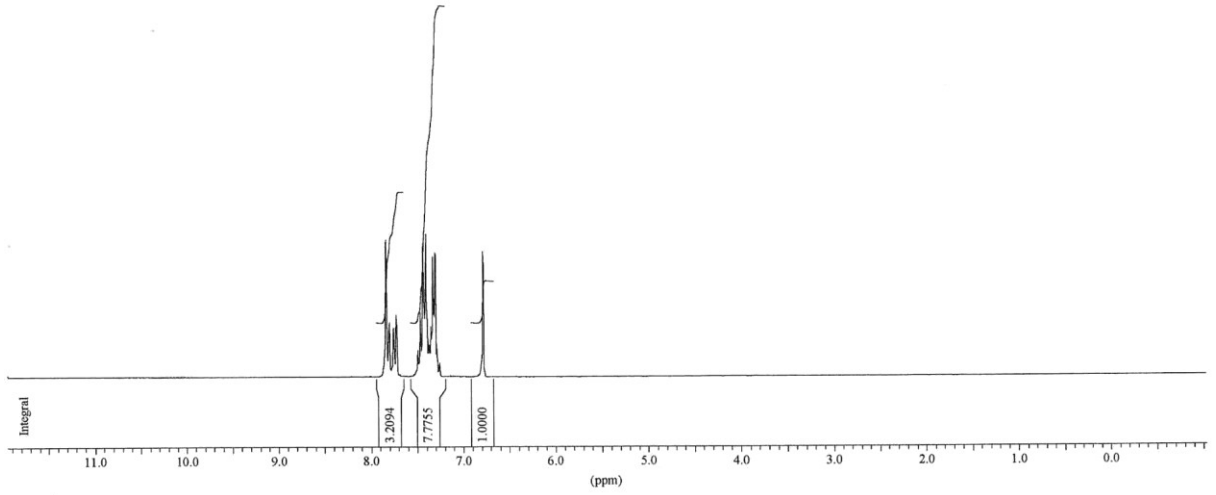


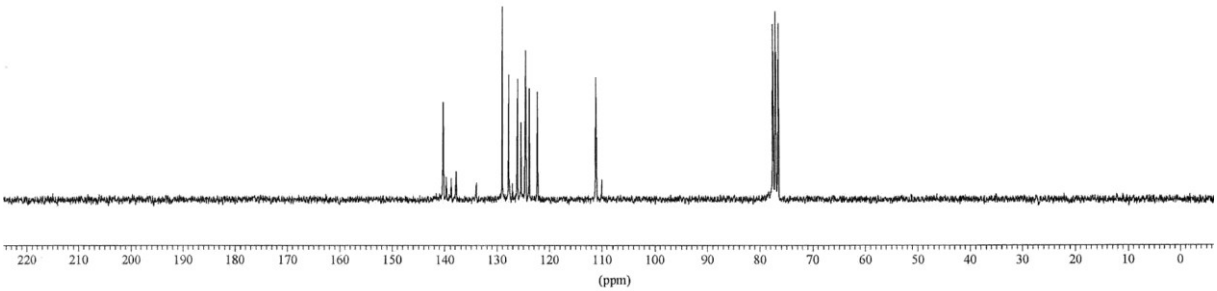
_(E)_-1-(3-Bromothiophen-2-yl)-3-(_N_,_N_-dimethylamino)-2-propen-1-one.



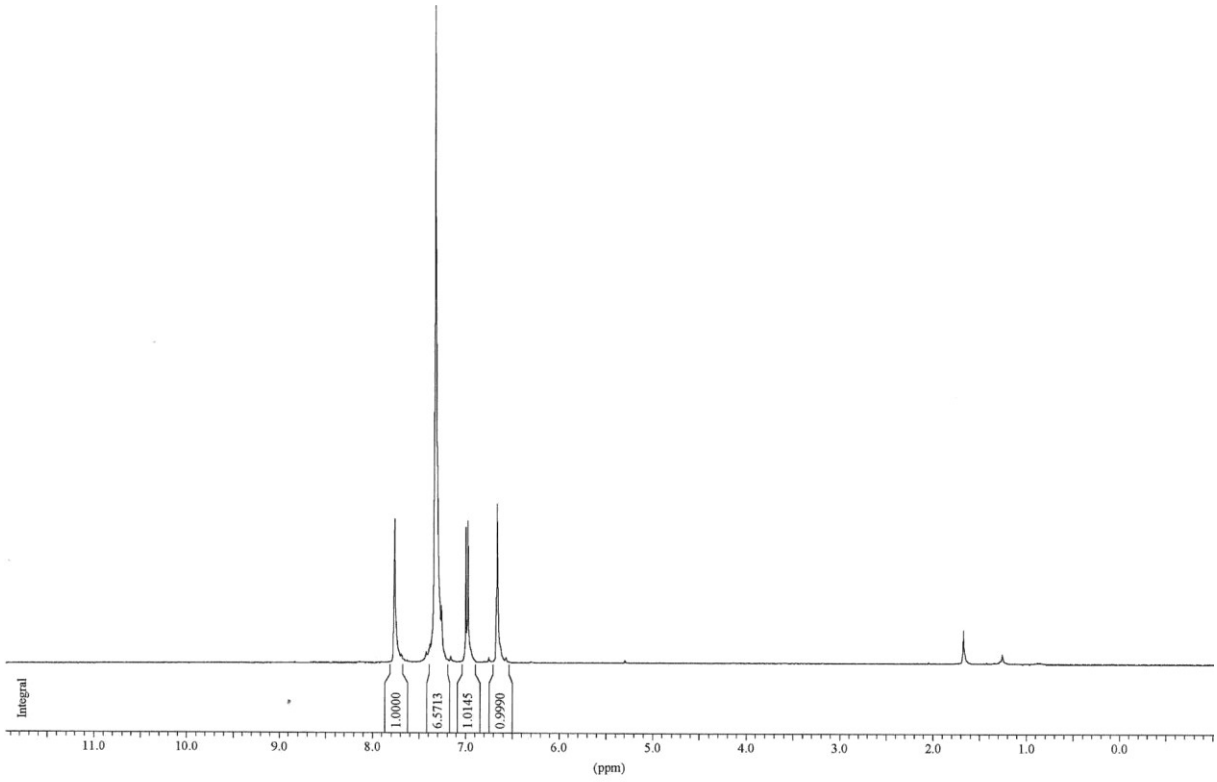


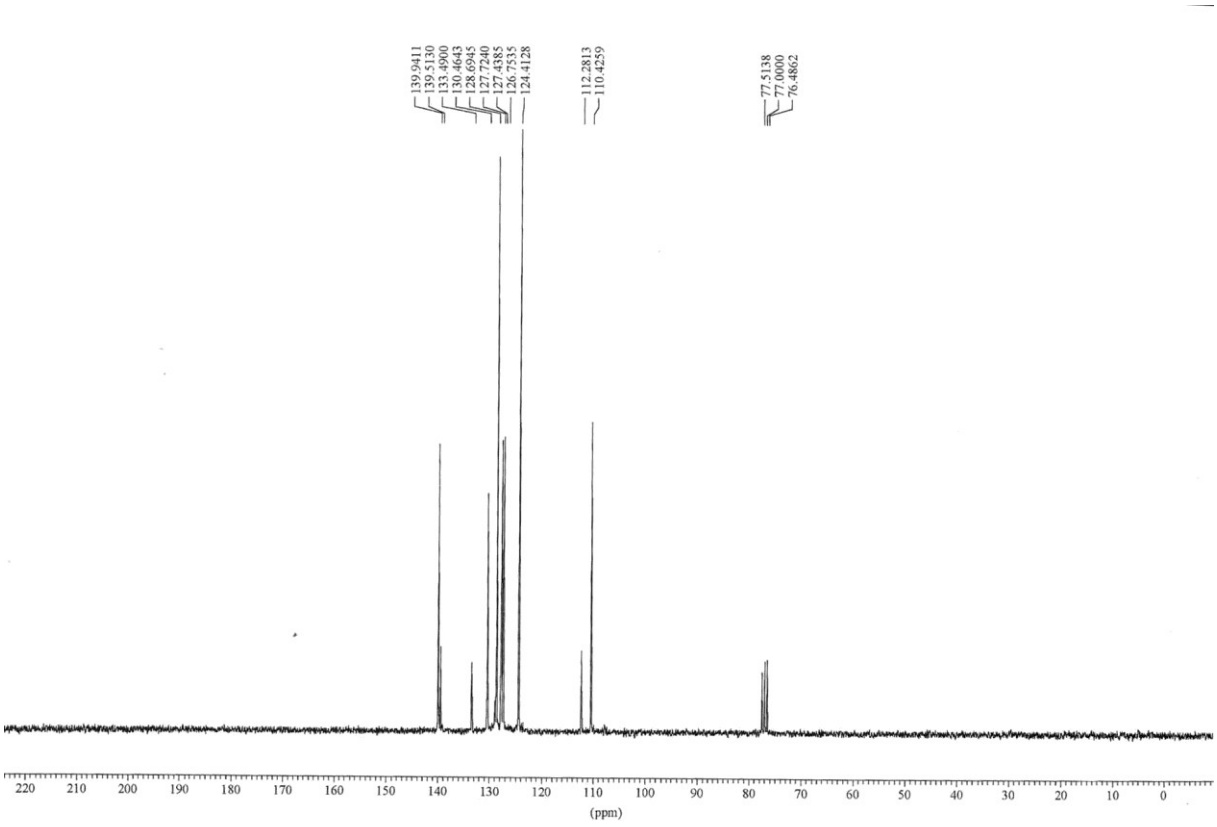
5-(3-Bromobenzo[*b*]thiophen-2-yl)-1-phenylpyrazole (2a).



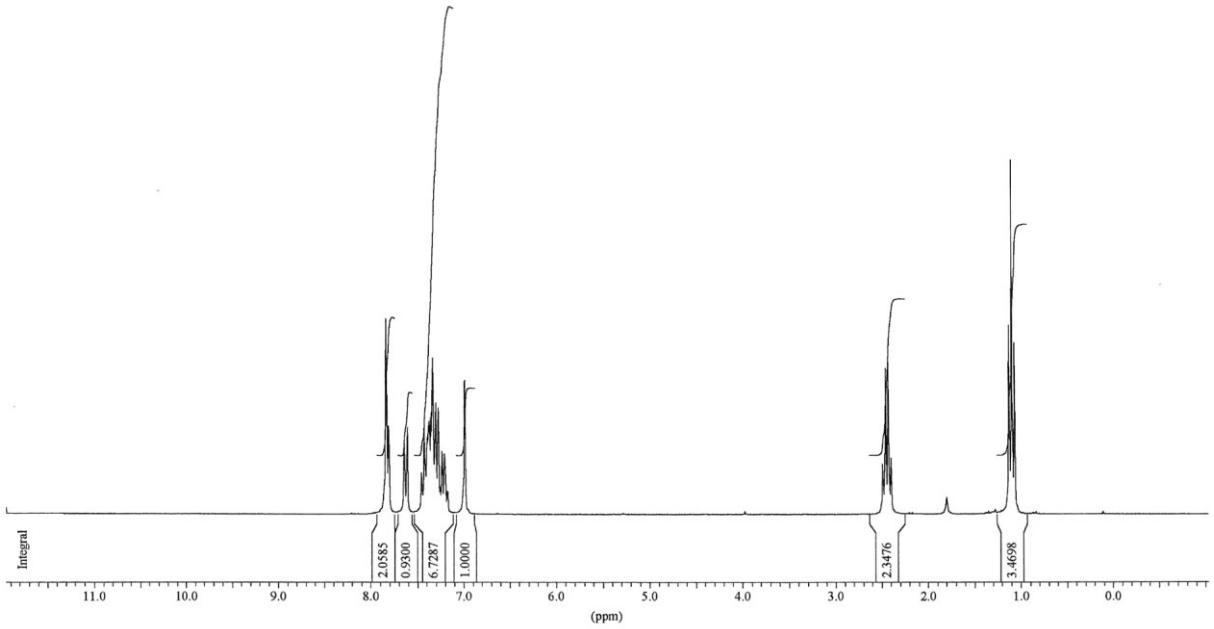


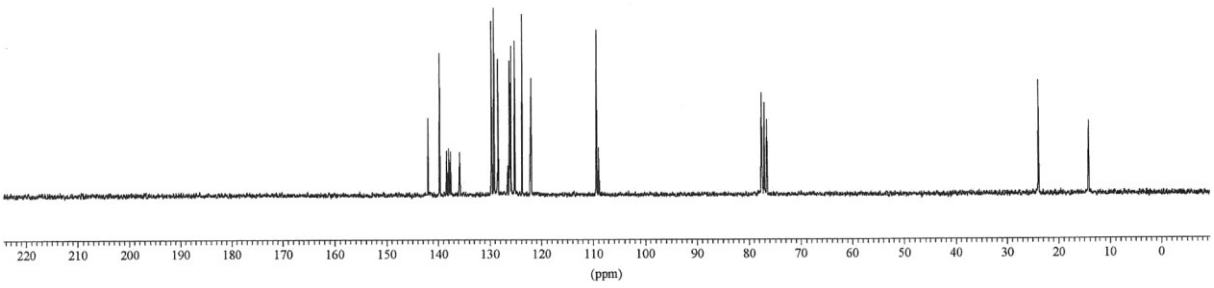
5-(3-Bromothiophen-2-yl)-1-phenylpyrazole (2b).



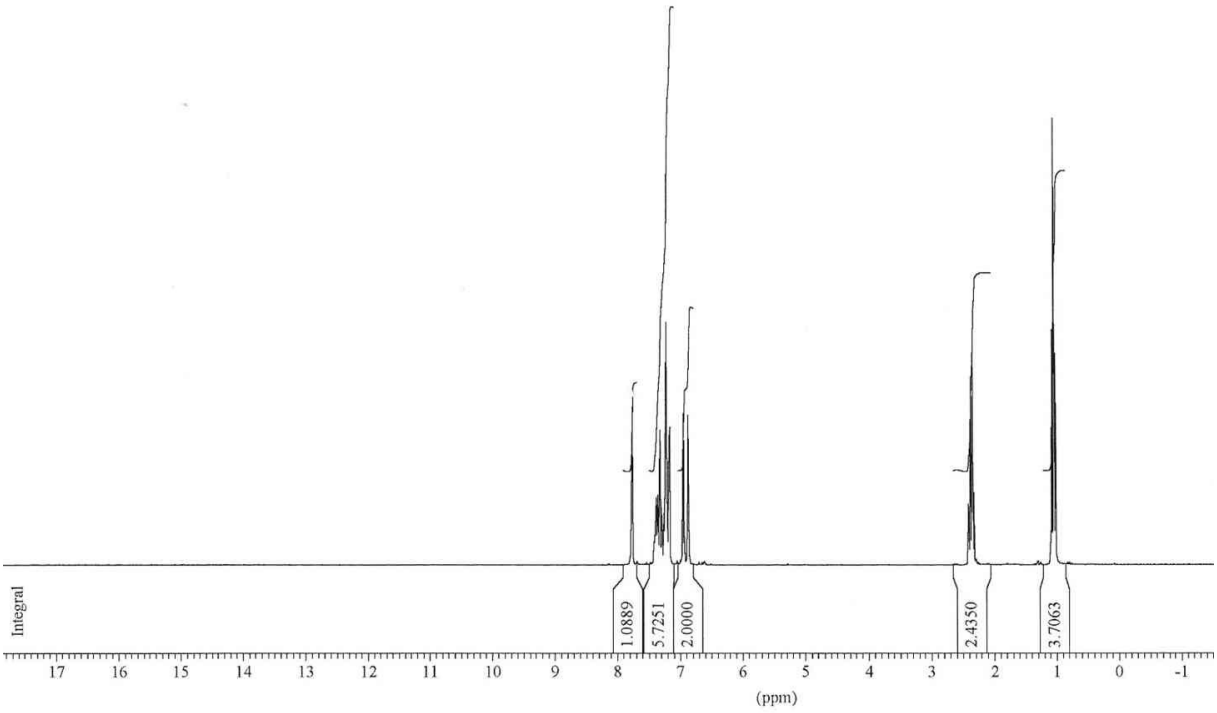


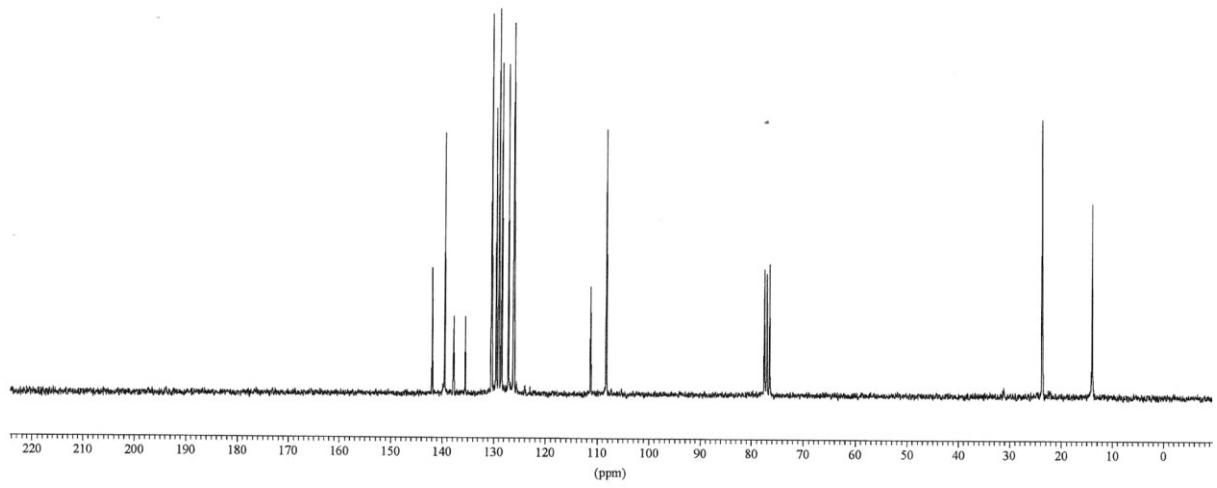
5-(3-Bromobenzo[*b*]thiophen-2-yl)-1-(2-ethylphenyl)pyrazole (2c).



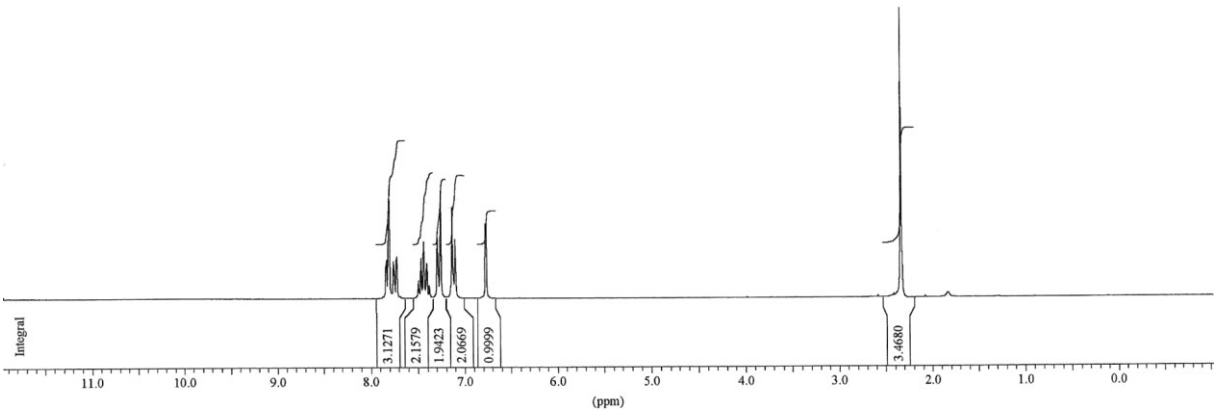


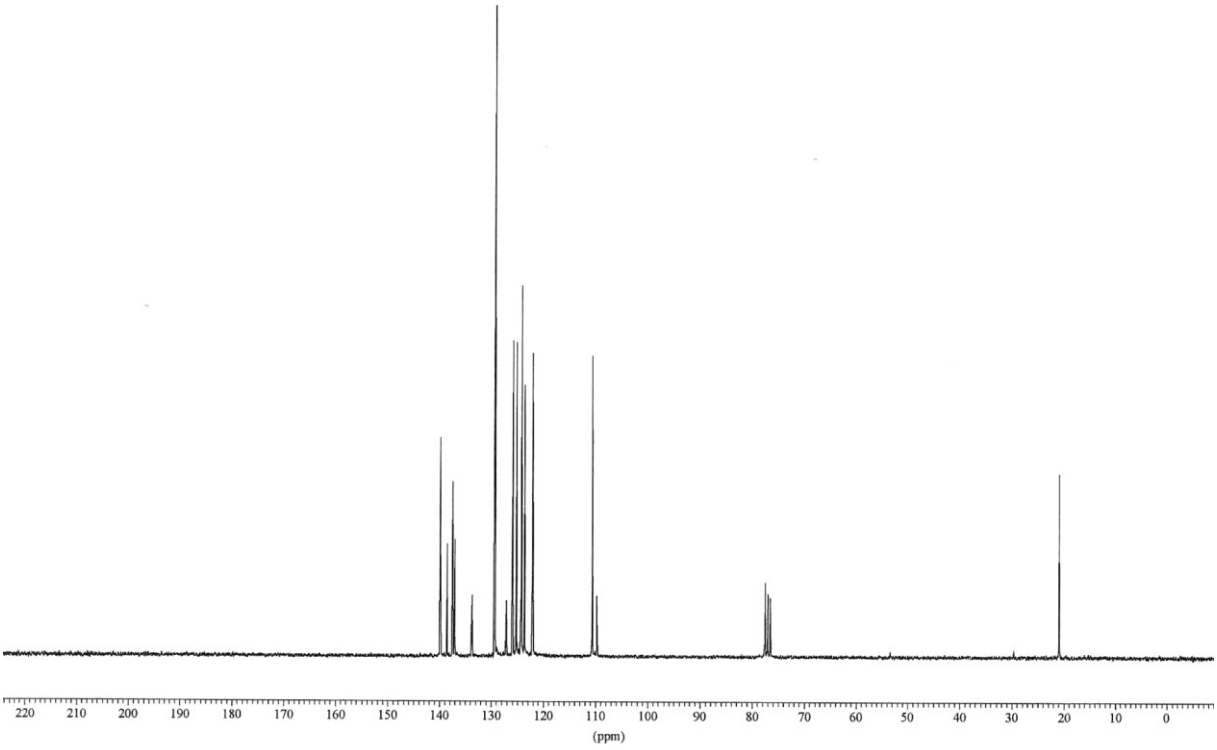
5-(3-Bromothiophen-2-yl)-1-(2-ethylphenyl)pyrazole (2d).



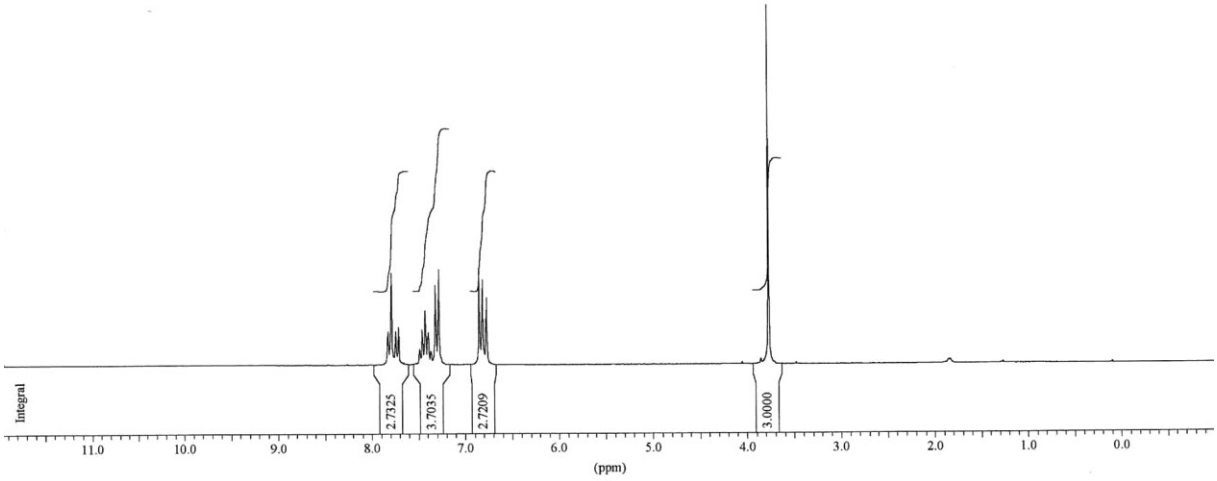


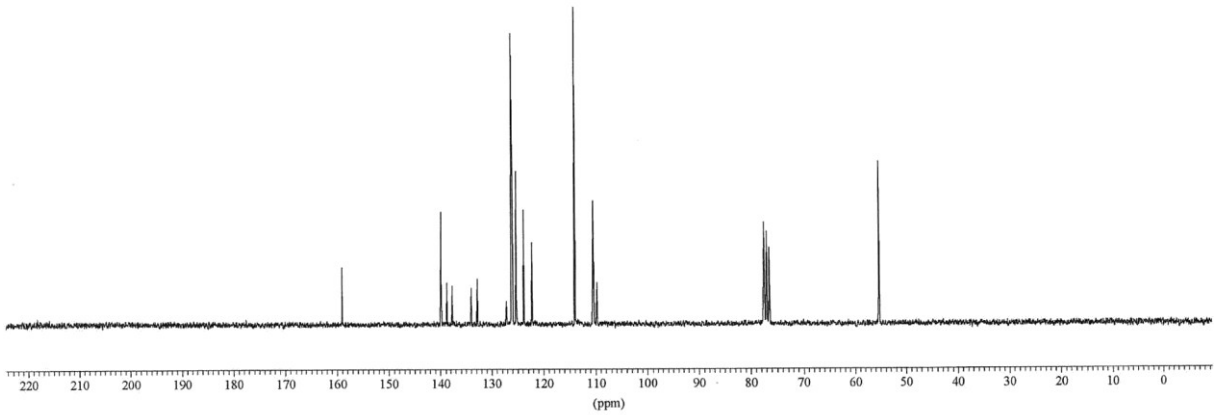
5-(3-Bromobenzo[*b*]thiophen-2-yl)-1-(4-methylphenyl)pyrazole (2e).



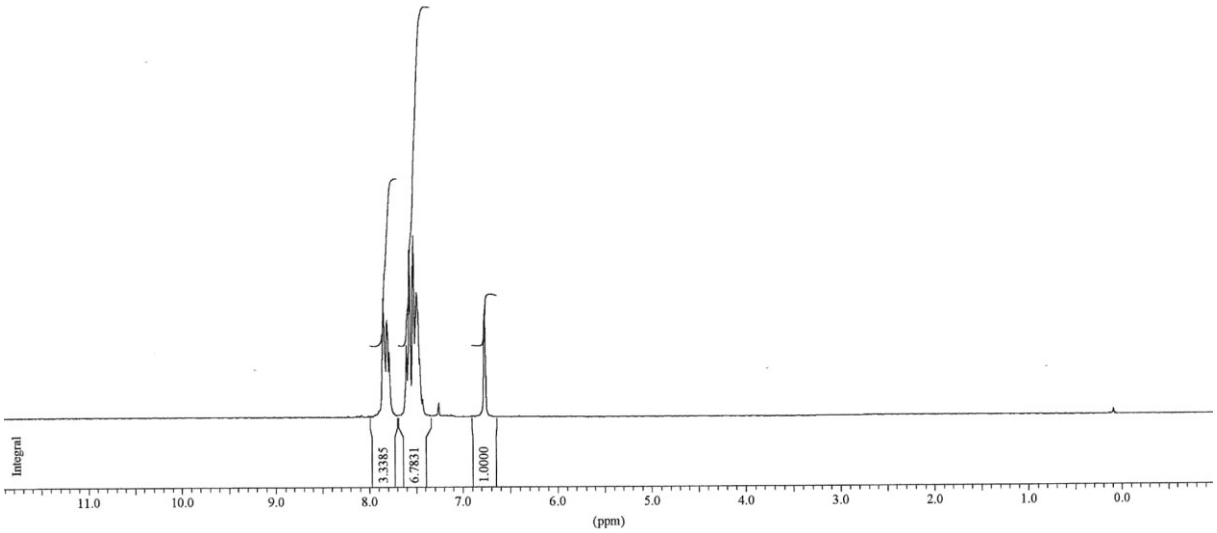


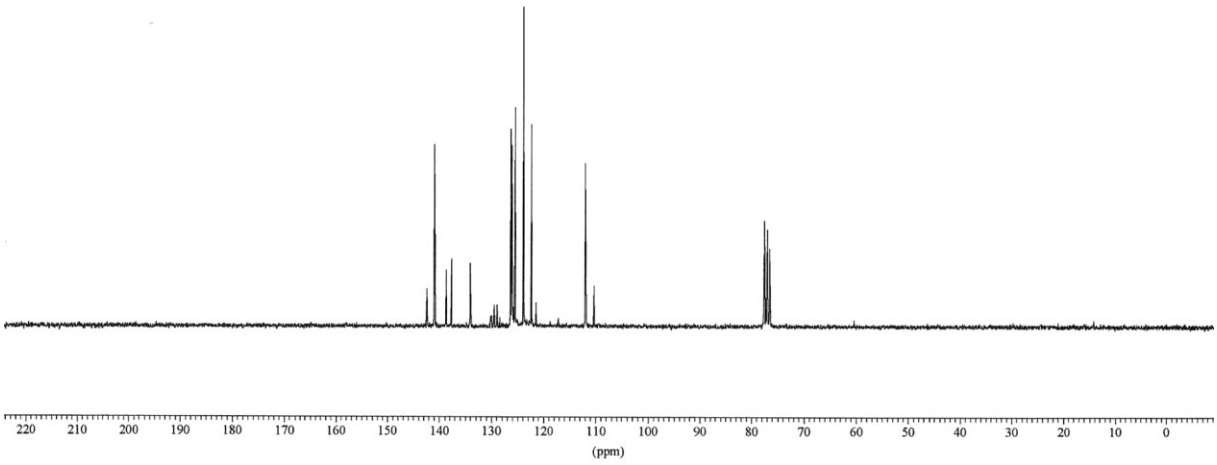
5-(3-Bromobenzo[*b*]thiophen-2-yl)-1-(4-methoxyphenyl)pyrazole (2f).



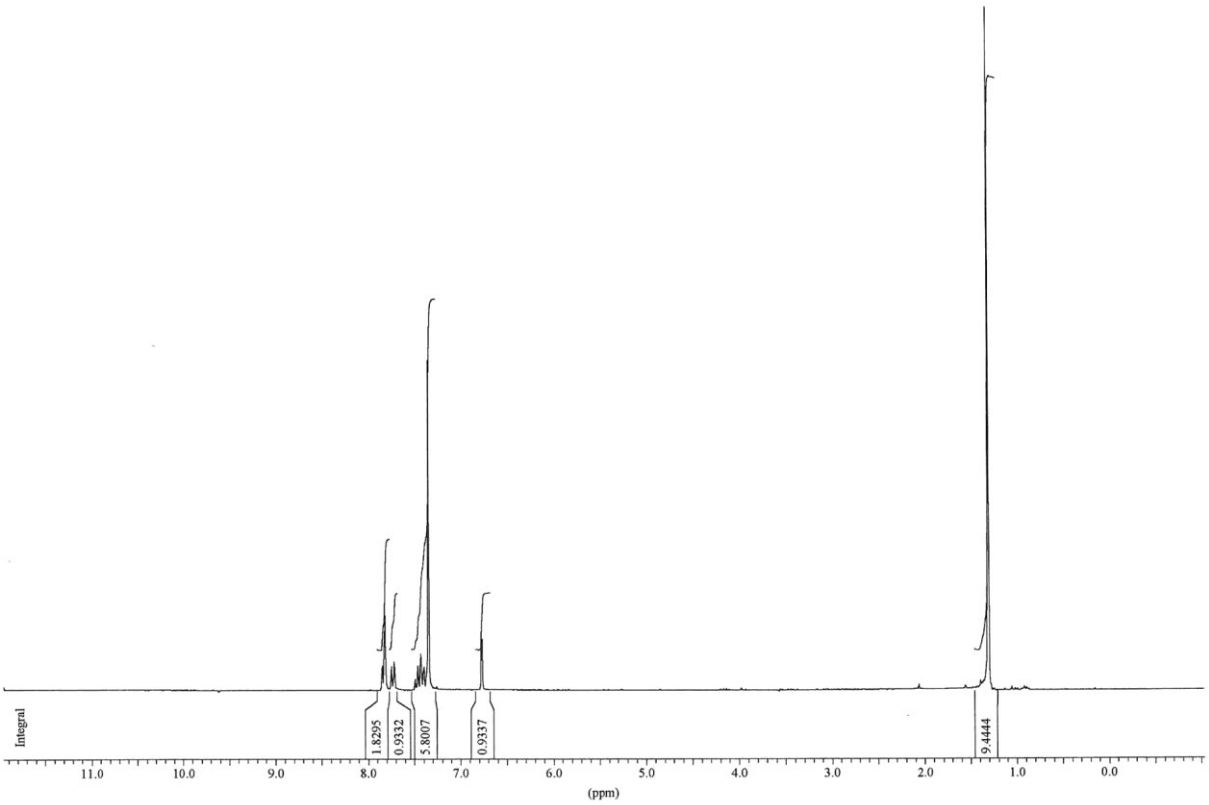


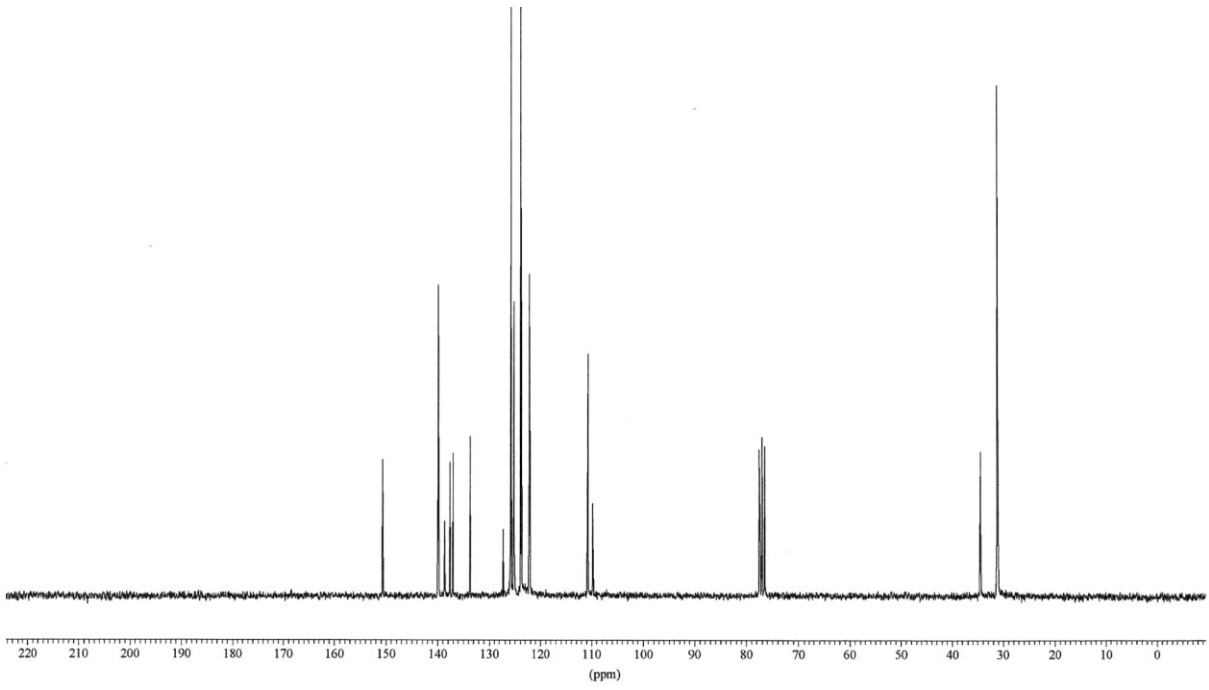
5-(3-Bromobenzo[*b*]thiophen-2-yl)-1-(4-trifluoromethylphenyl)pyrazole (2g).



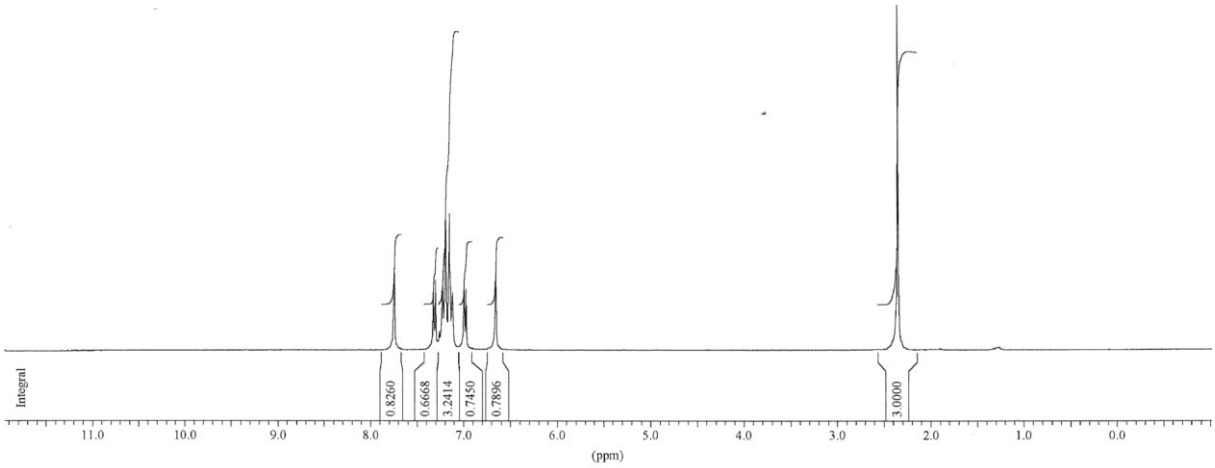


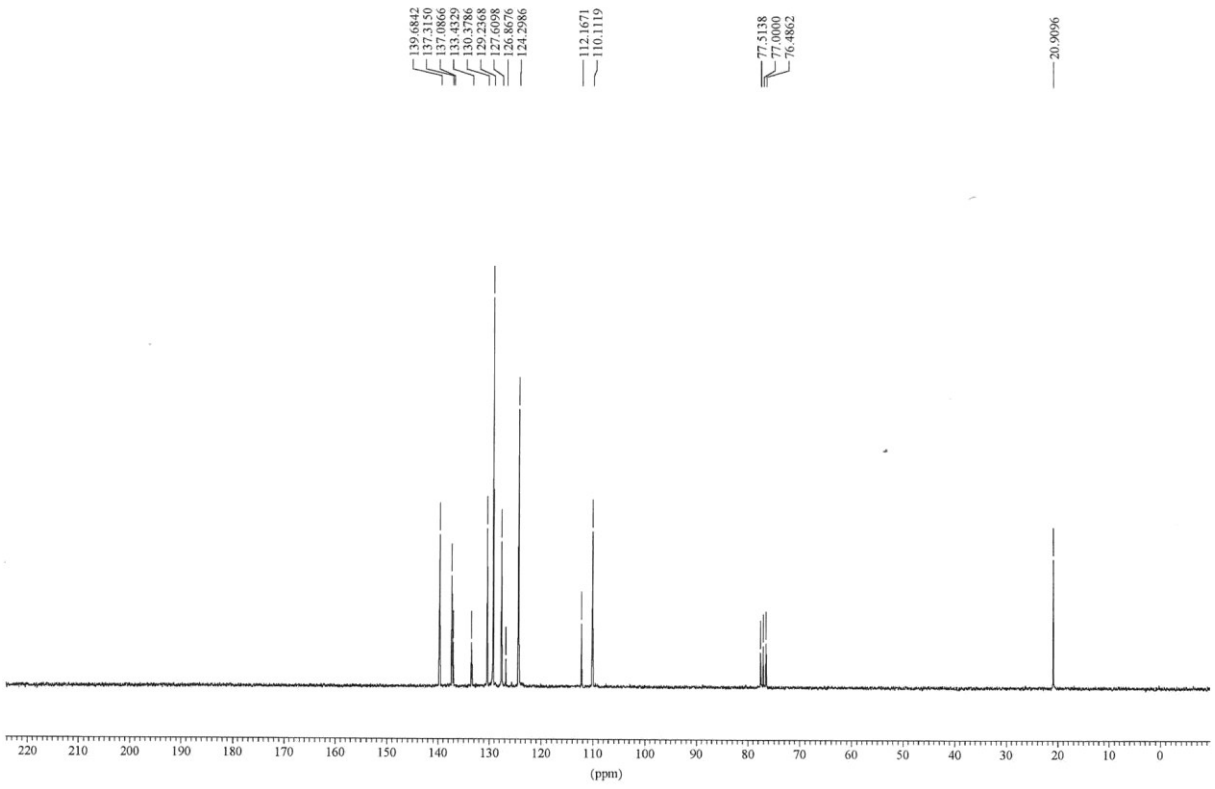
5-(3-Bromobenzo[*b*]thiophen-2-yl)-1-(4-*tert*-buthylphenyl)piyrazole (2h).



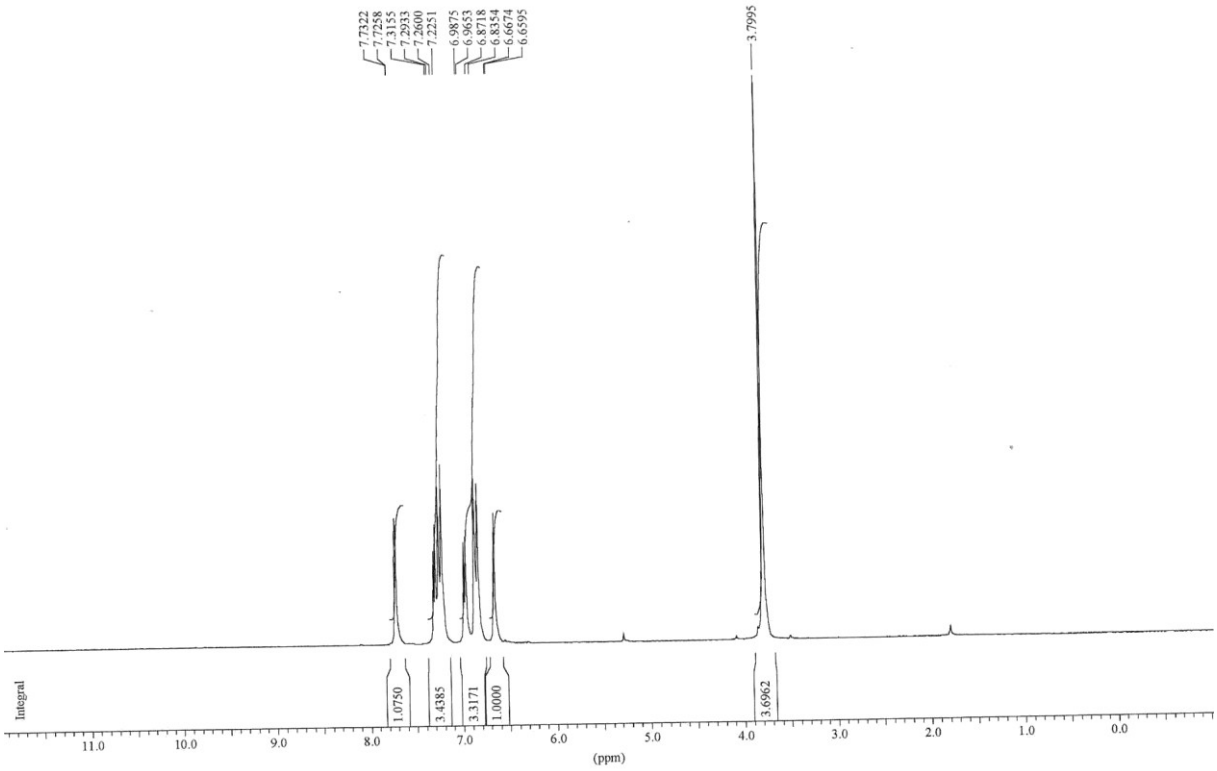


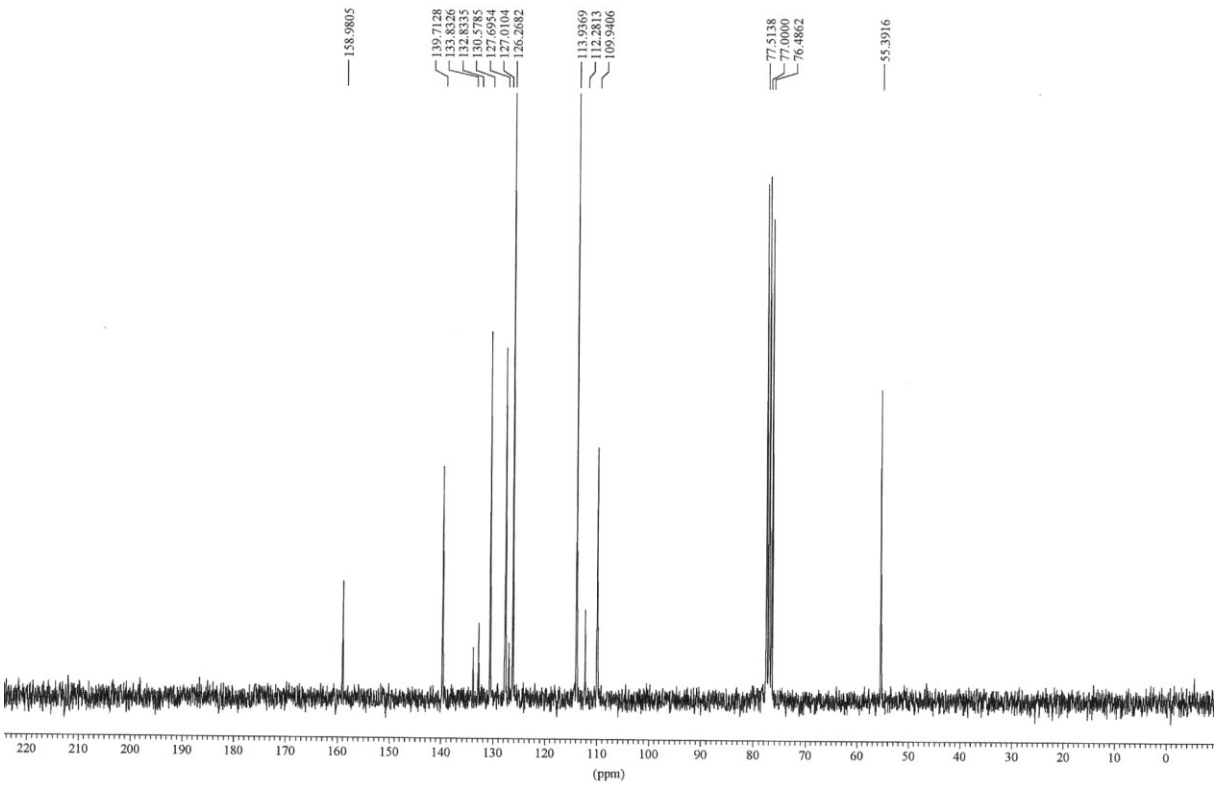
5-(3-Bromothiophen-2-yl)-1-(4-methylphenyl)pyrazole (2i).



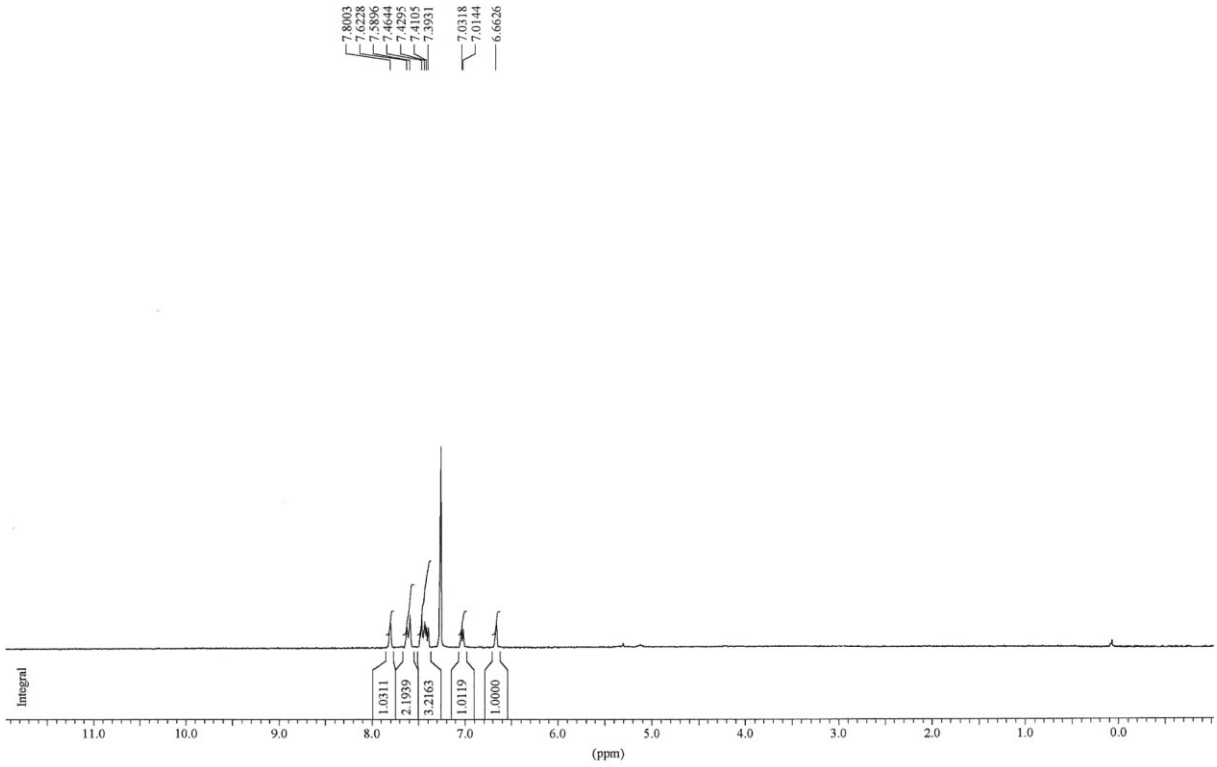


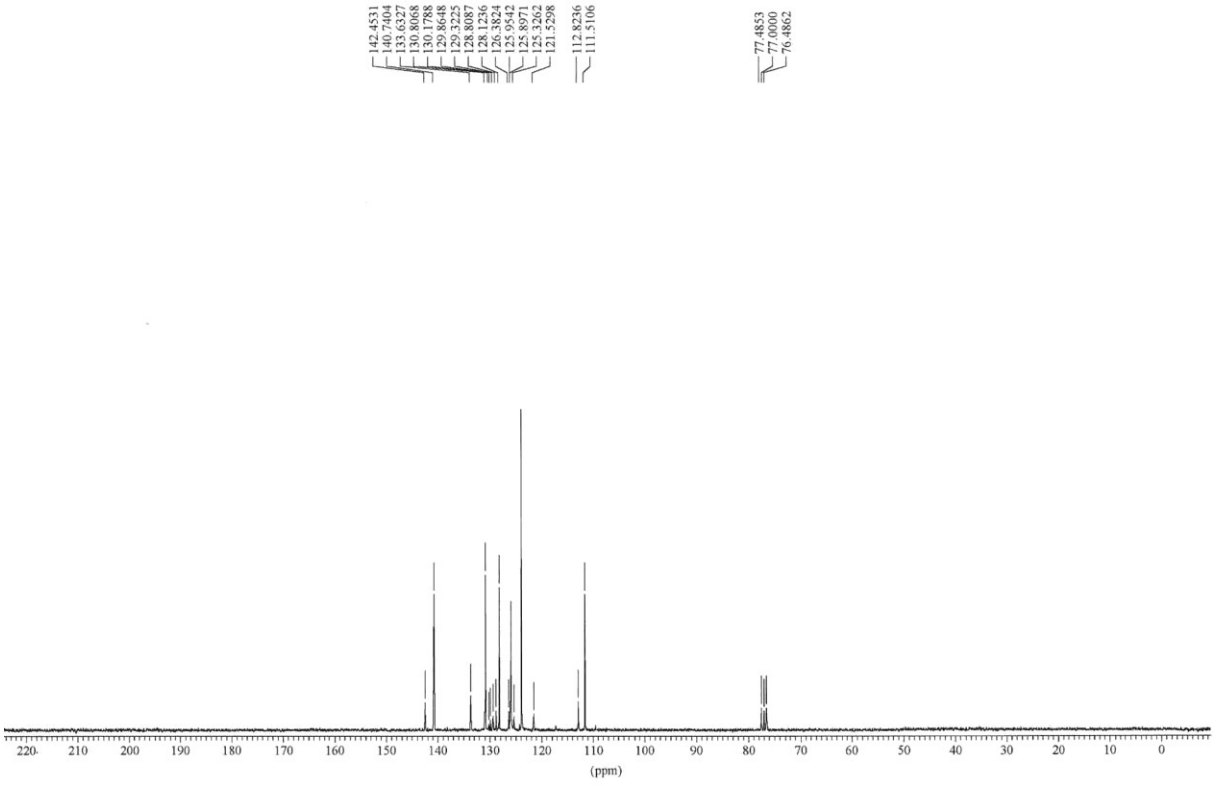
5-(3-Bromothiophen-2-yl)-1-(4-methoxyphenyl)pyrazole (2j).



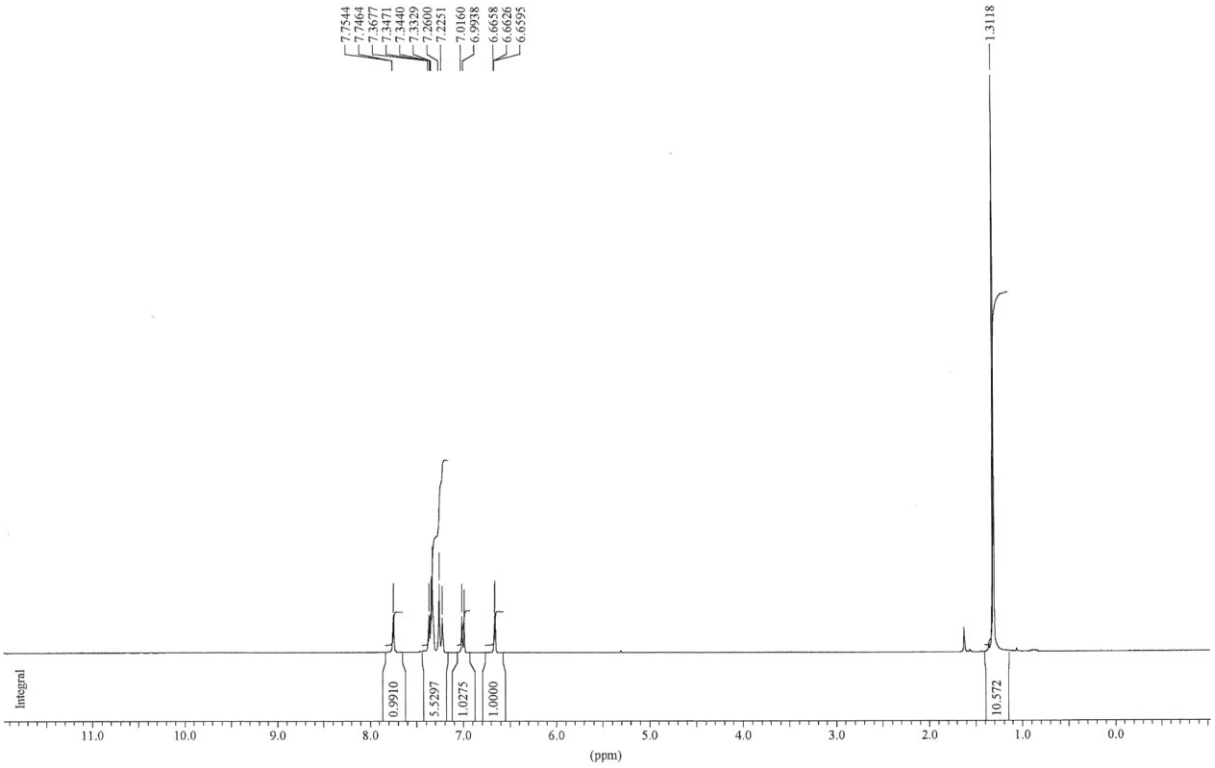


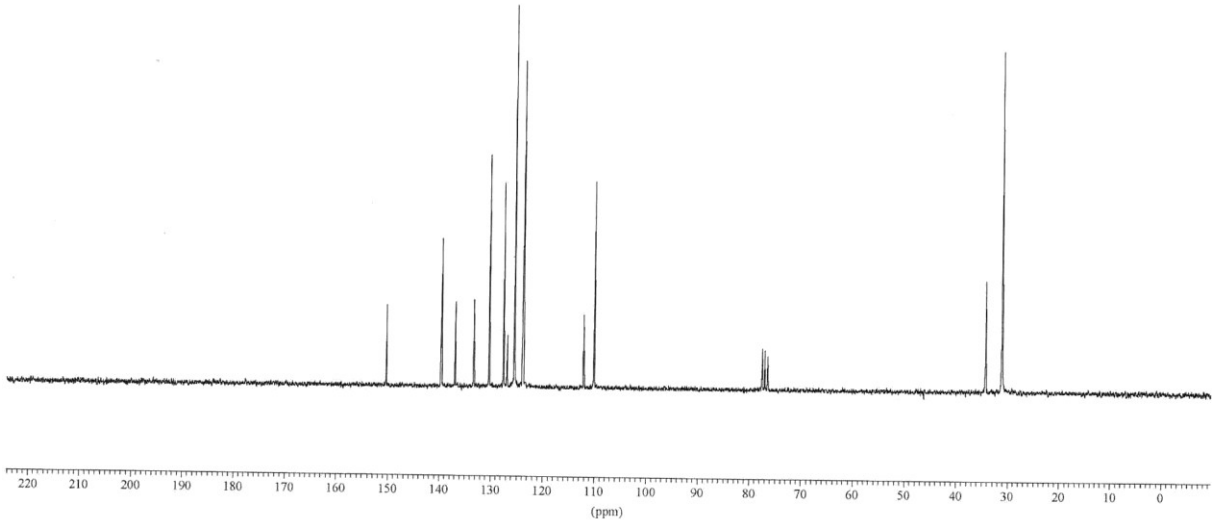
5-(3-Bromothiophen-2-yl)-1-(4-trifluoromethylphenyl)pyrazole (2k).



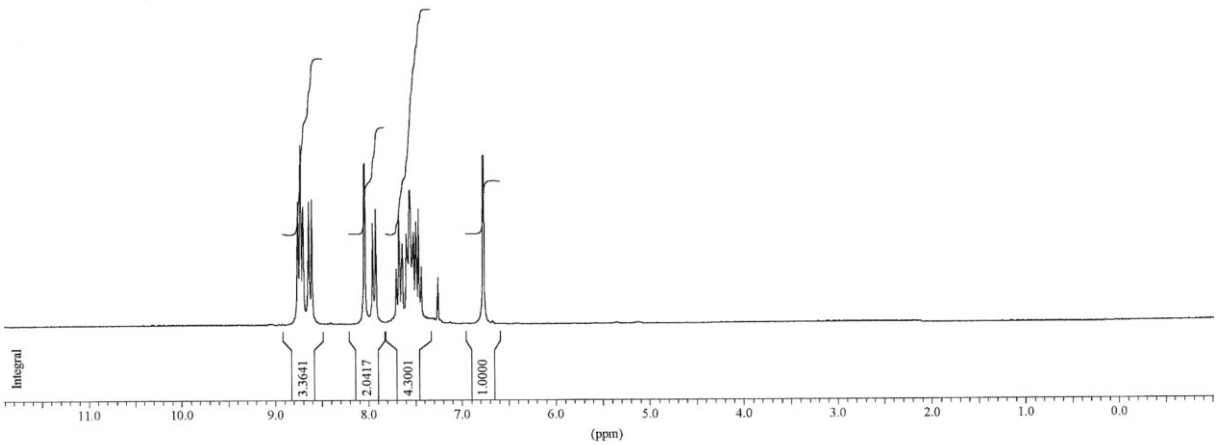


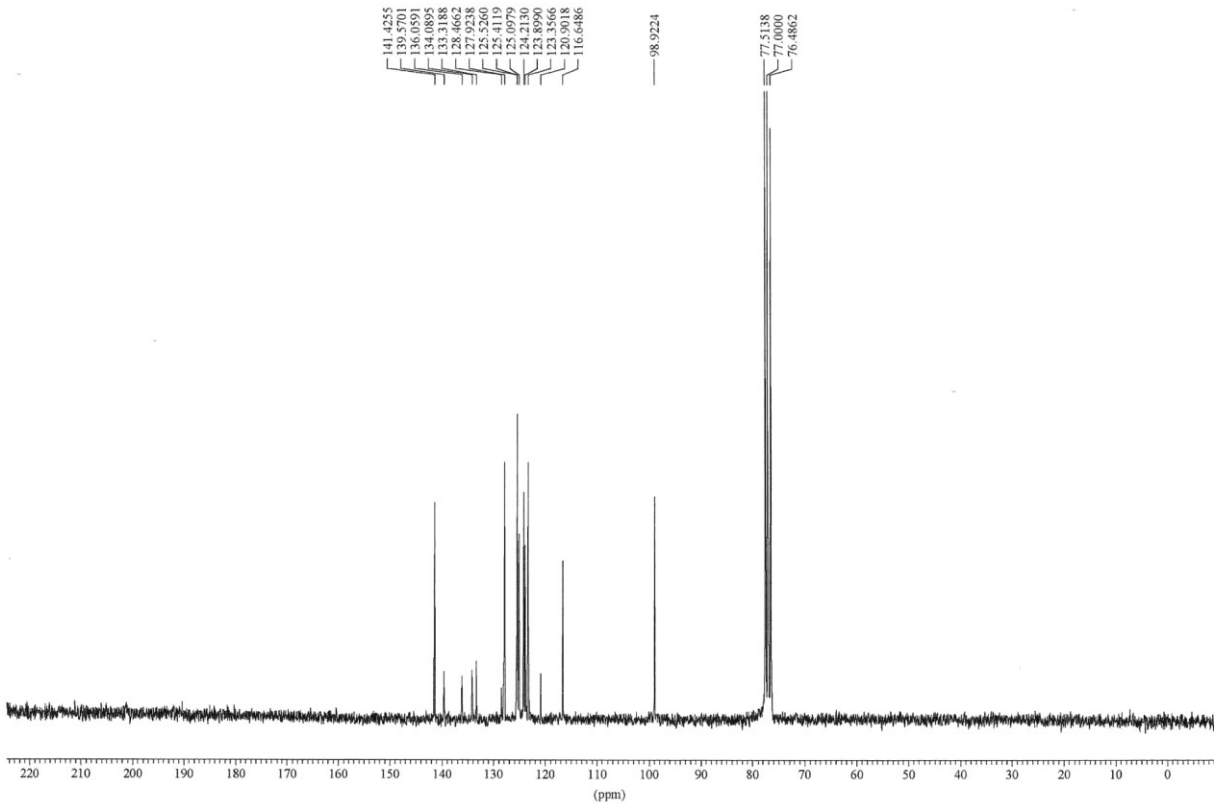
5-(3-Bromothiophen-2-yl)-1-(4-*tert*-buthylphenyl)pyrazole (2l).



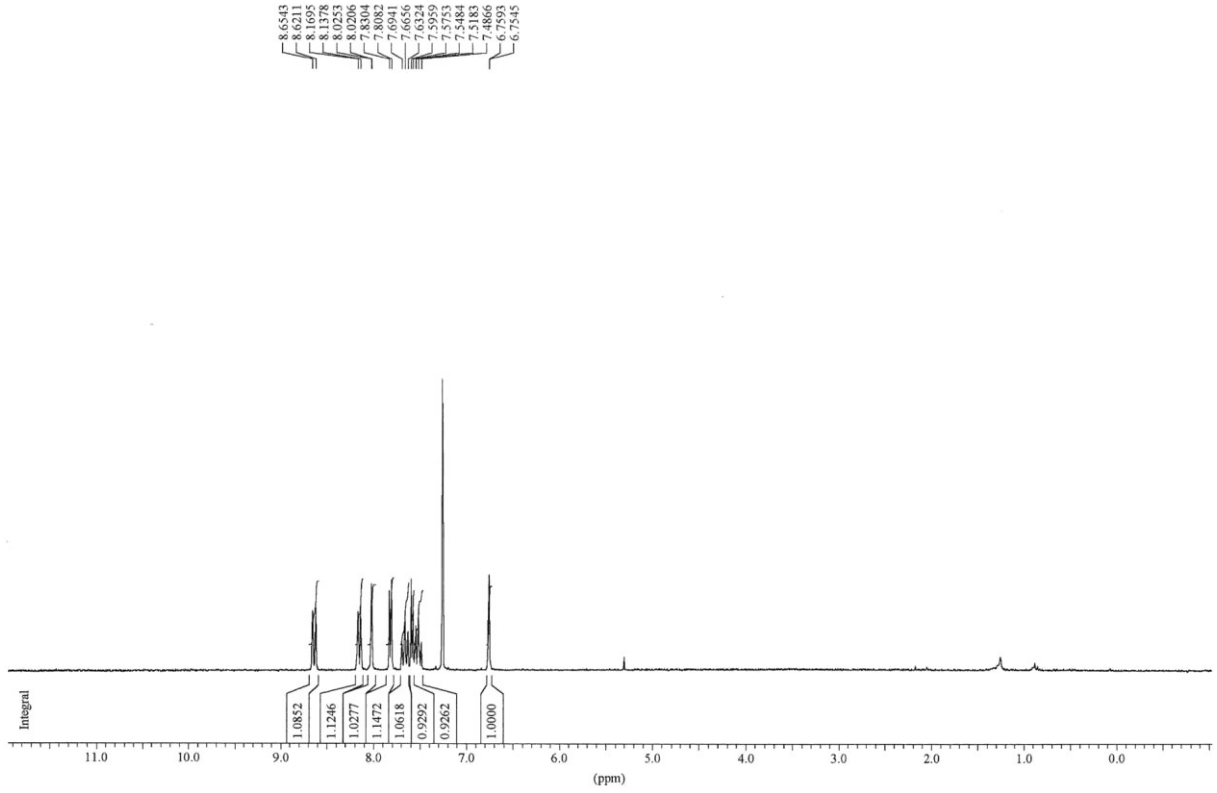


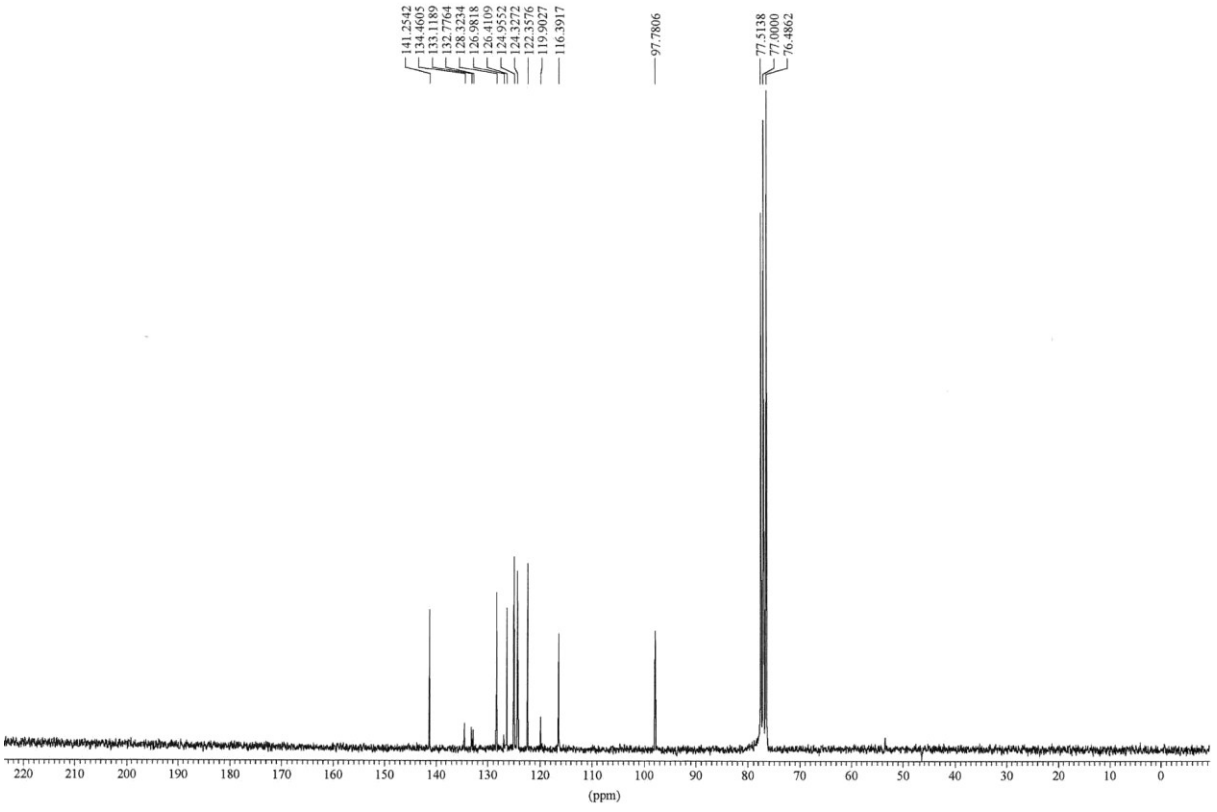
Pyrazolo[1,5-*a*]benzothieno[2,3-*c*]quinoline (1a).



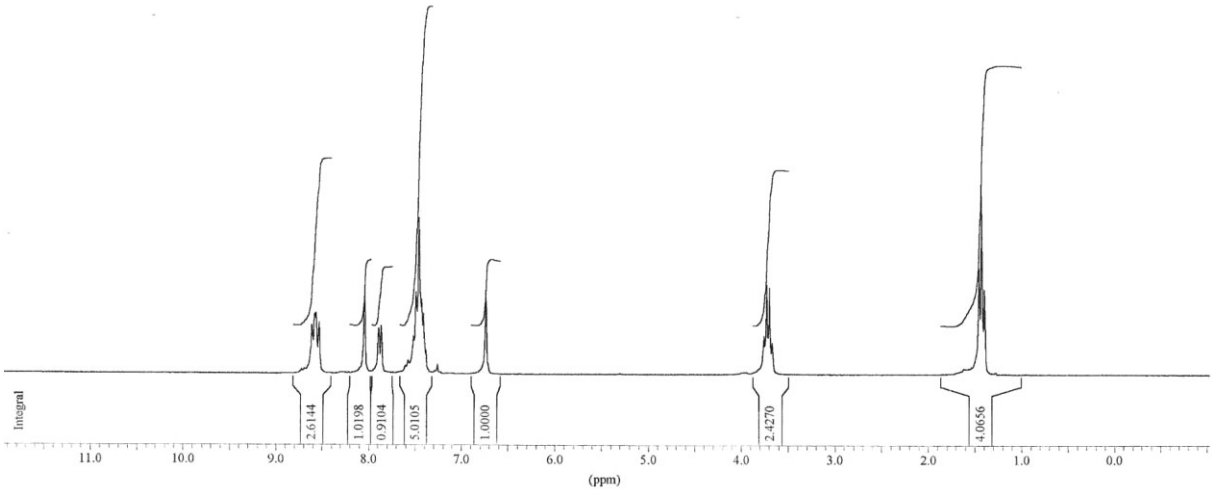


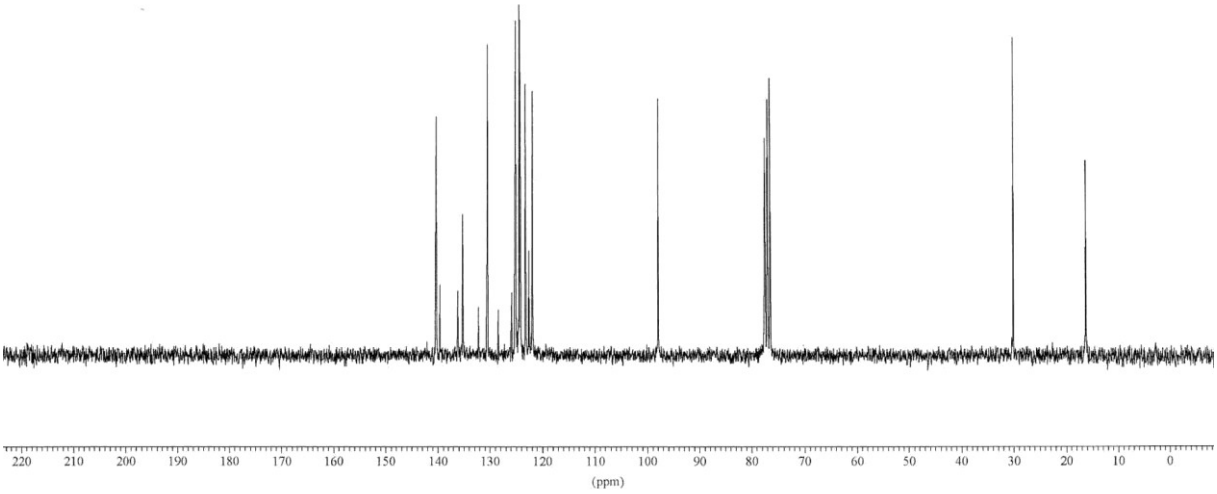
Pyrazolo[1,5-*a*]thieno[2,3-*c*]quinoline (1b).



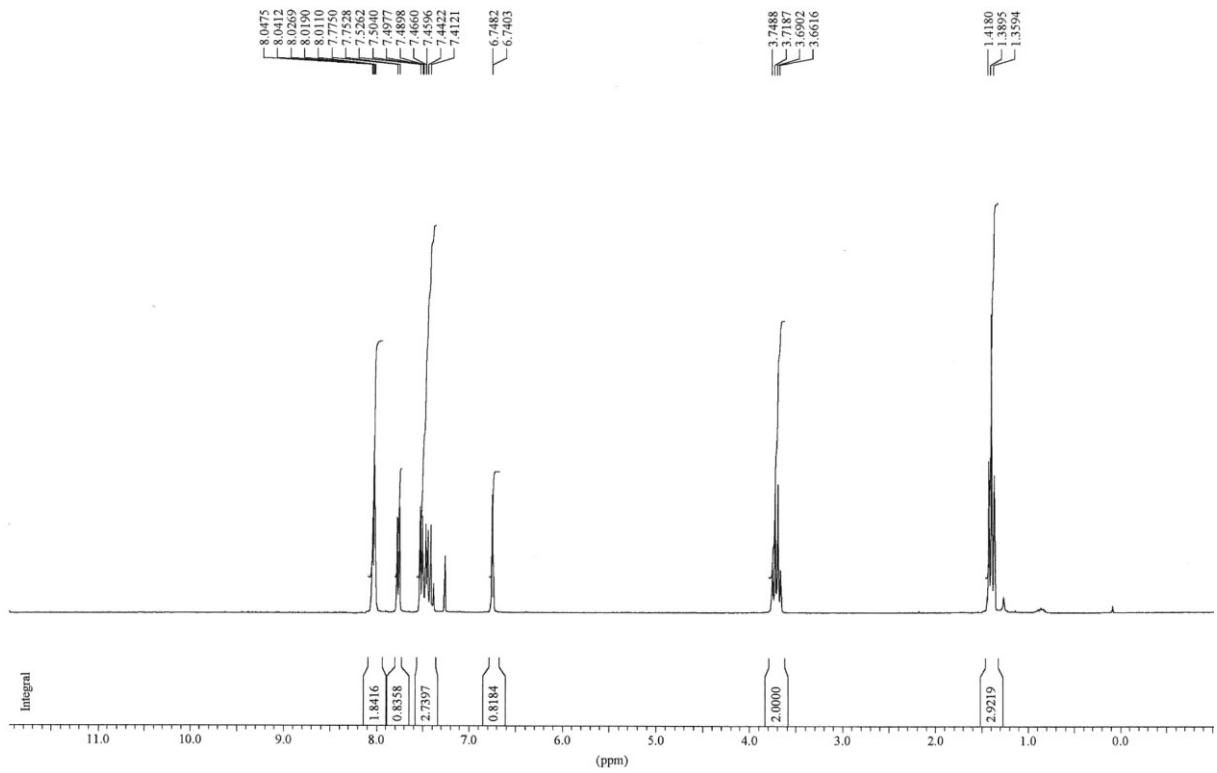


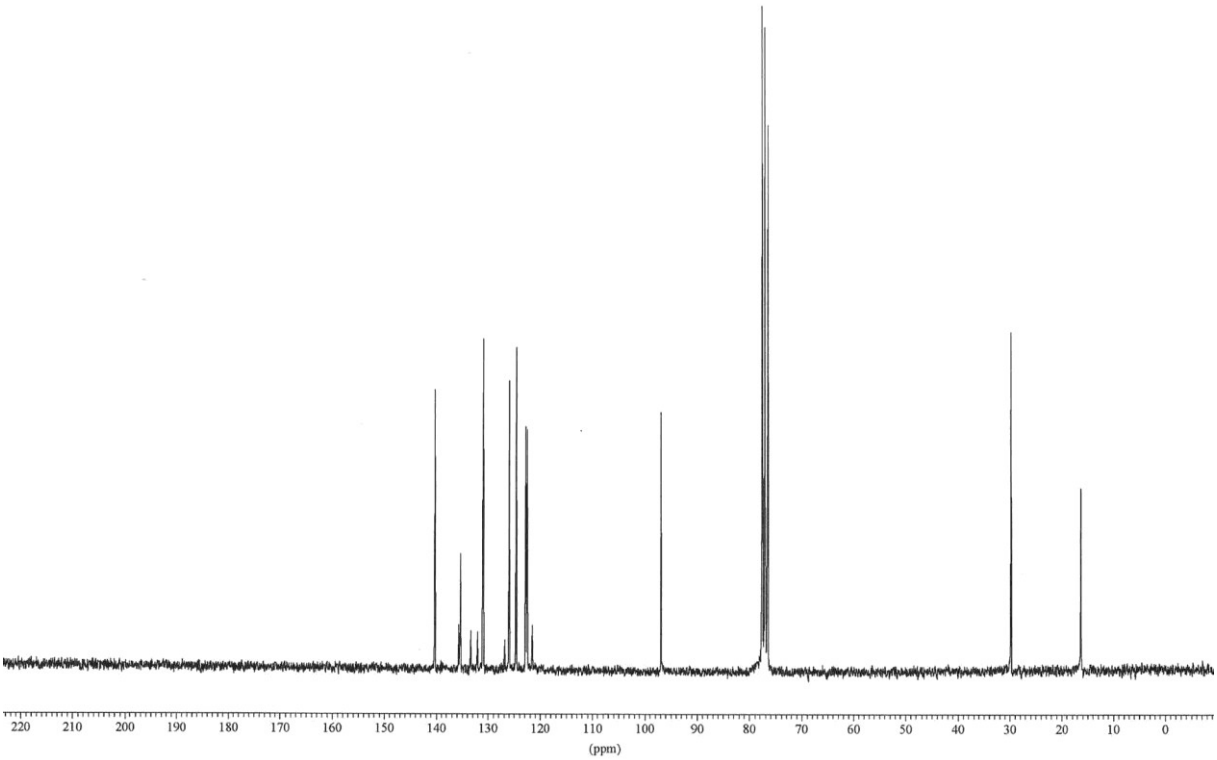
12-Ethylpyrazolo[1,5-*a*]benzothieno[2,3-*c*]quinoline (1c).



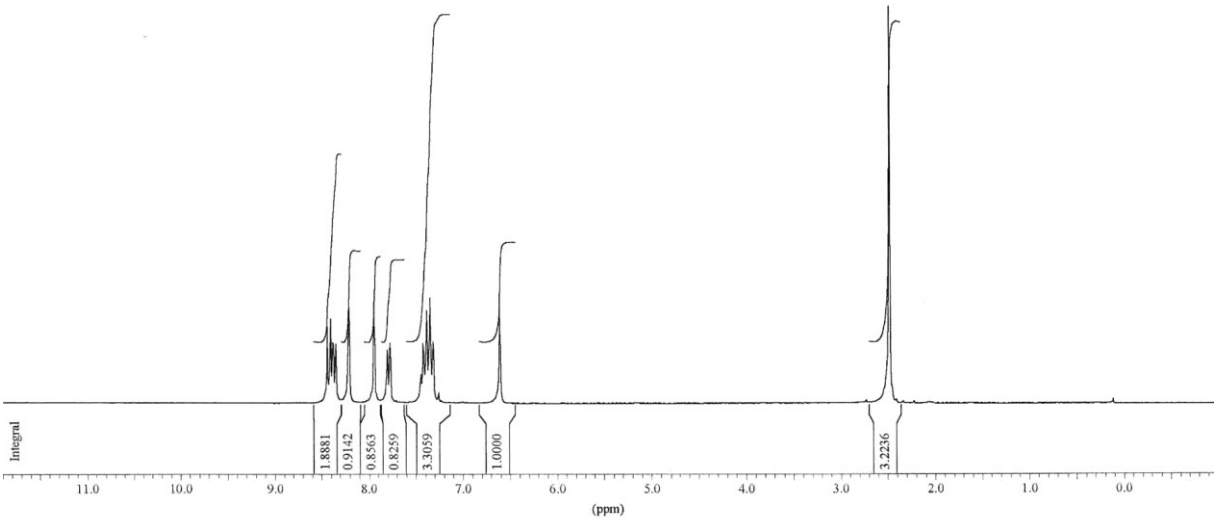


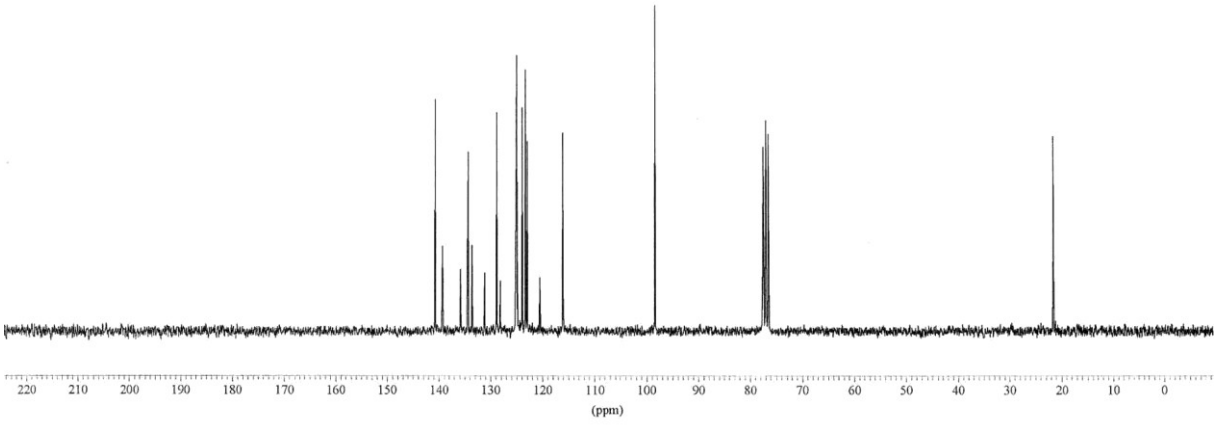
10-Ethylpyrazolo[1,5-*a*]thieno[2,3-*c*]quinoline (1d).



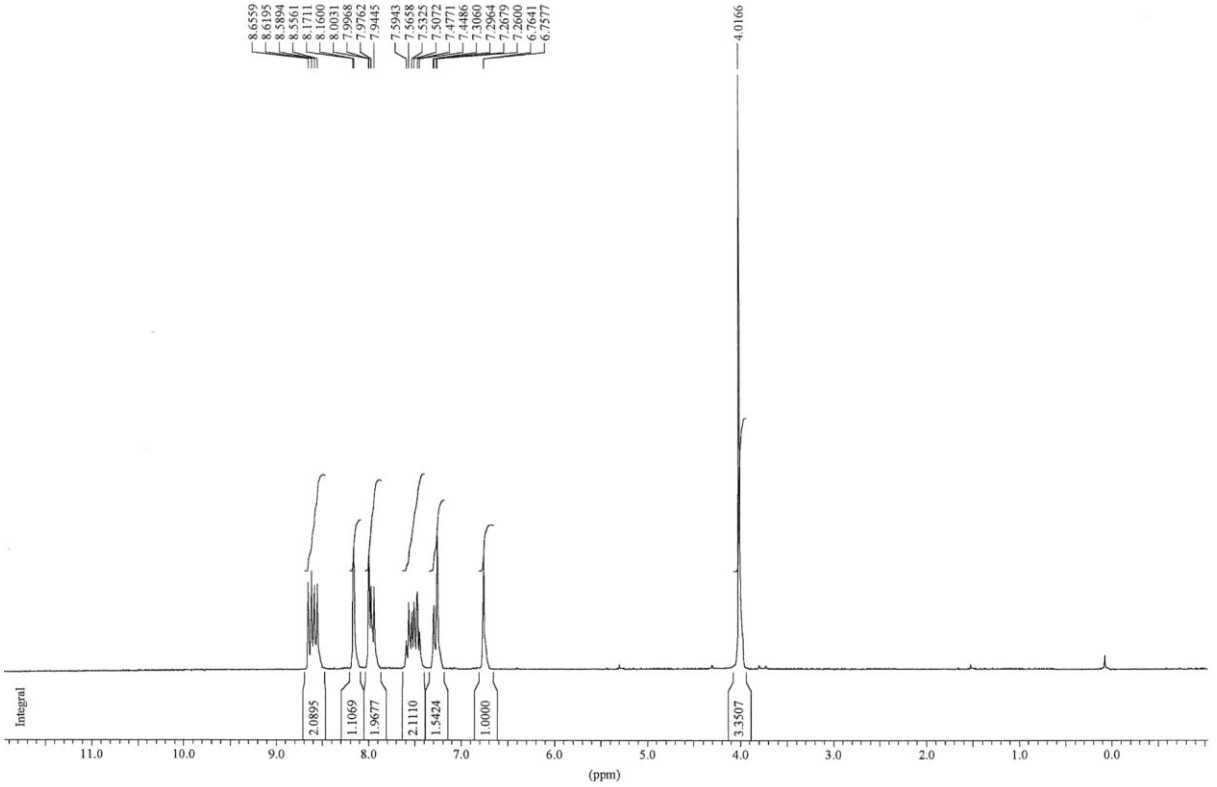


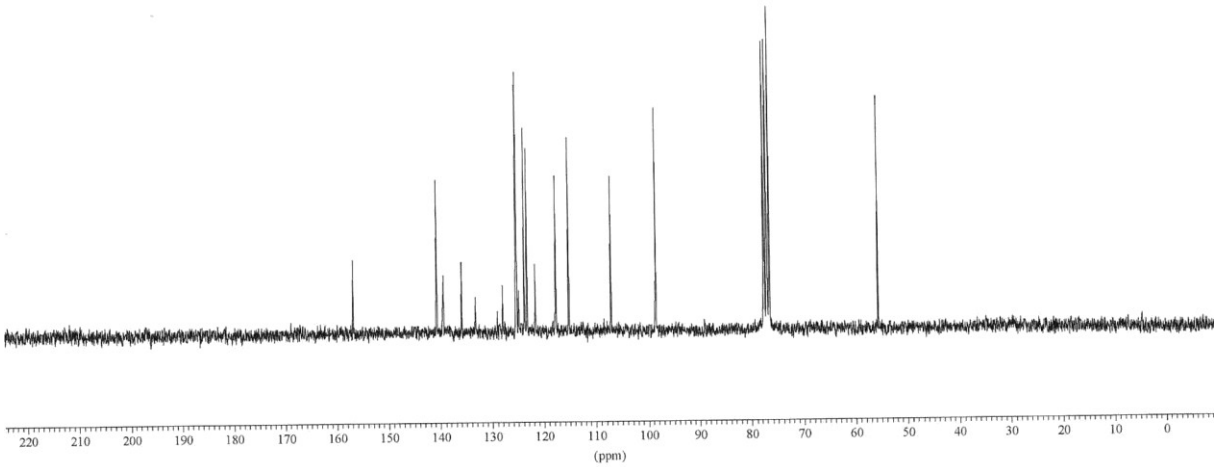
10-Methylpyrazolo[1,5-*a*]benzothieno[2,3-*c*]quinoline (1e).



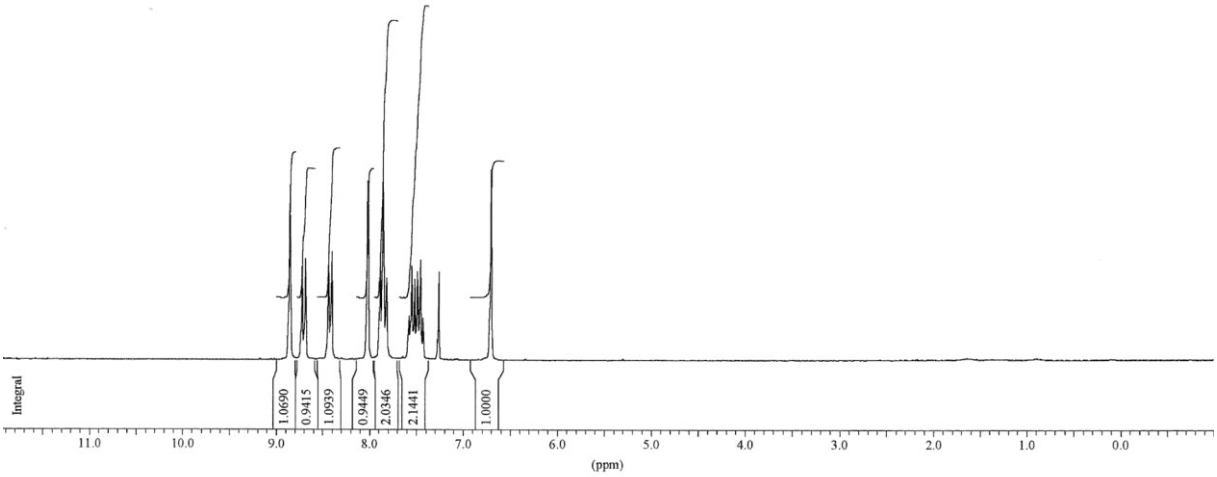


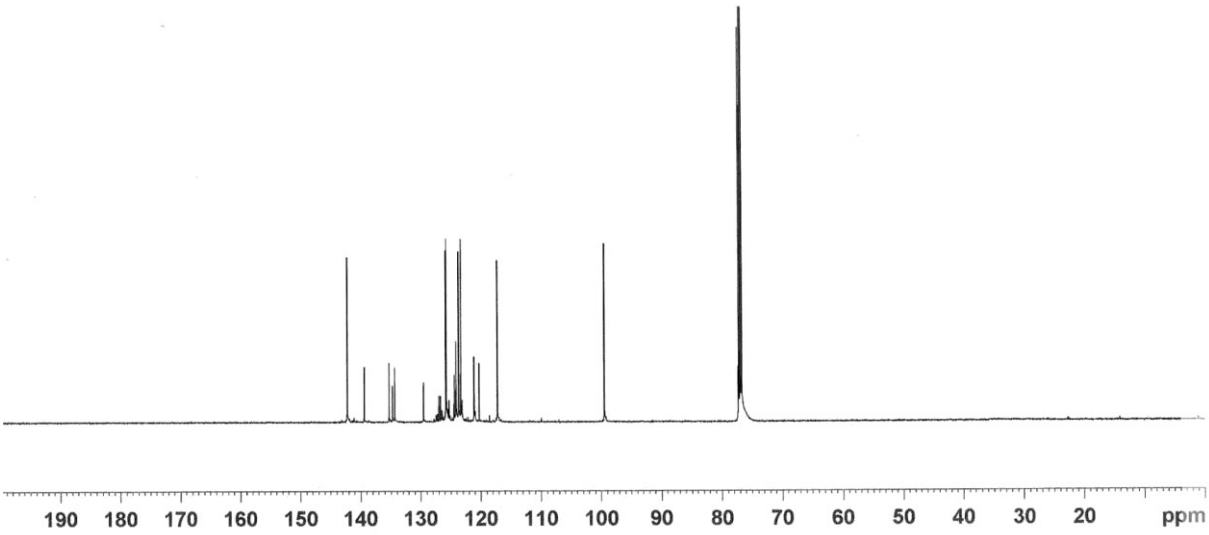
10-Methoxypyrazolo[1,5-*a*]benzothieno[2,3-*c*]quinoline (1f).



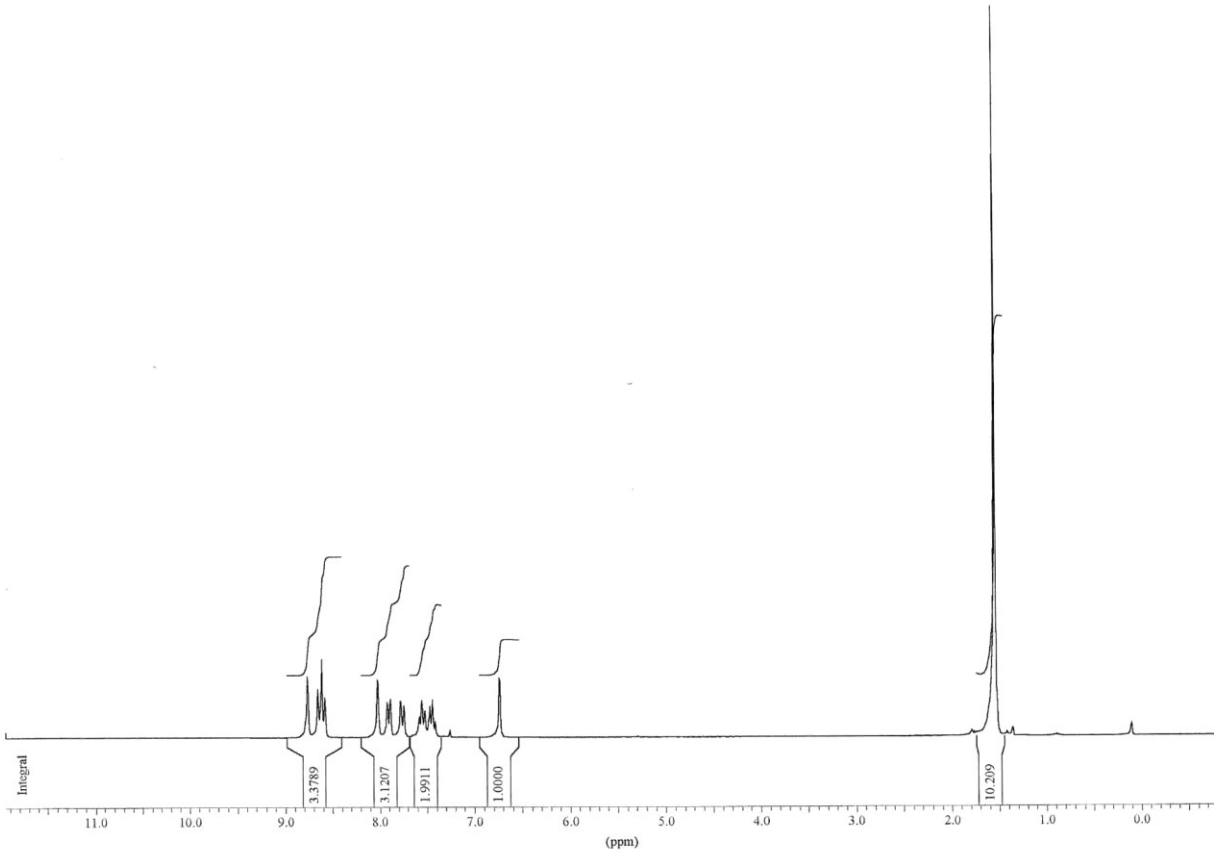


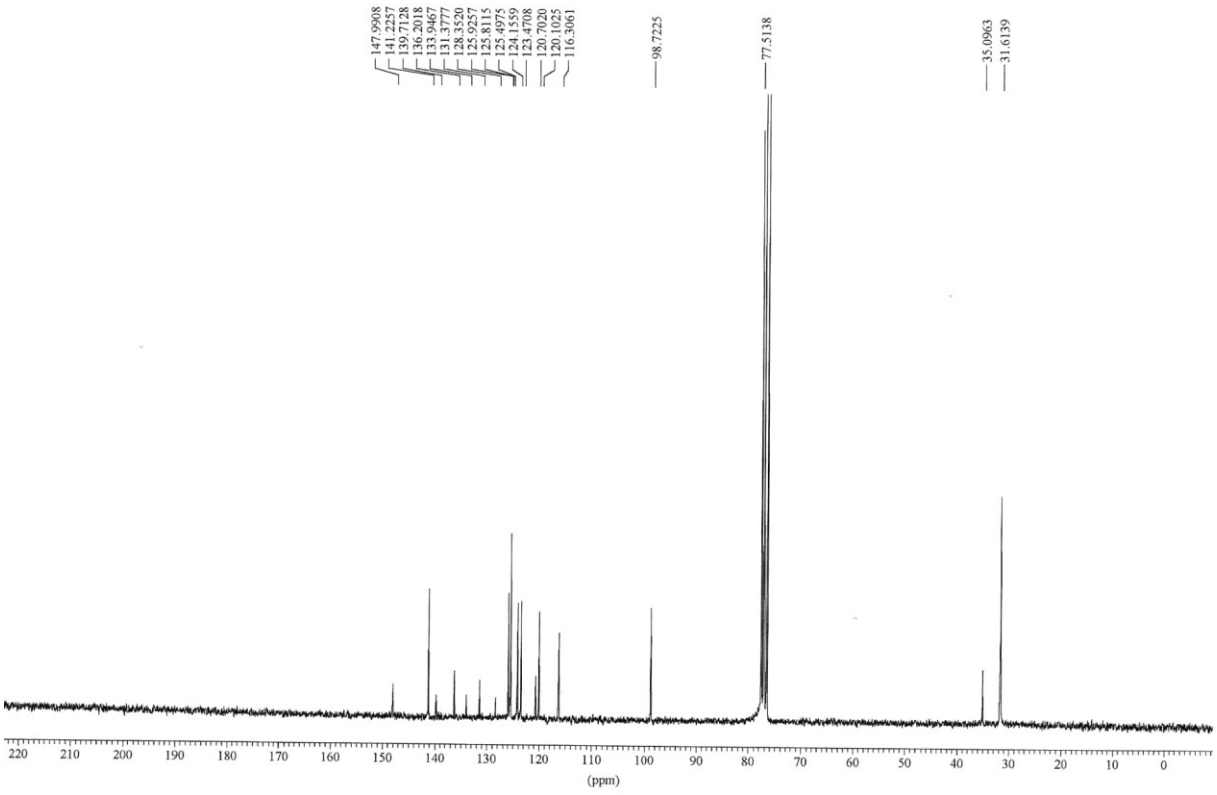
10-Trifluoromethylpyrazolo[1,5-*a*]benzothieno[2,3-*c*]quinoline (1g).



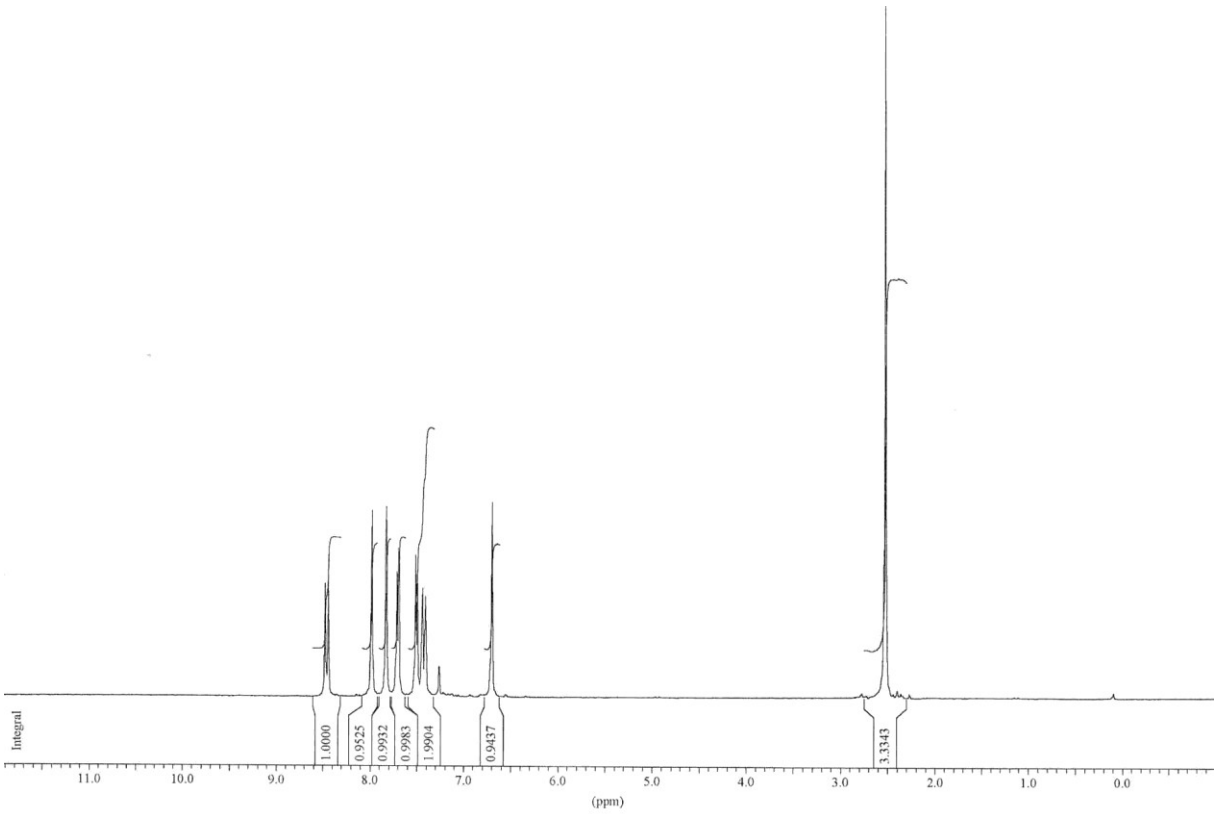


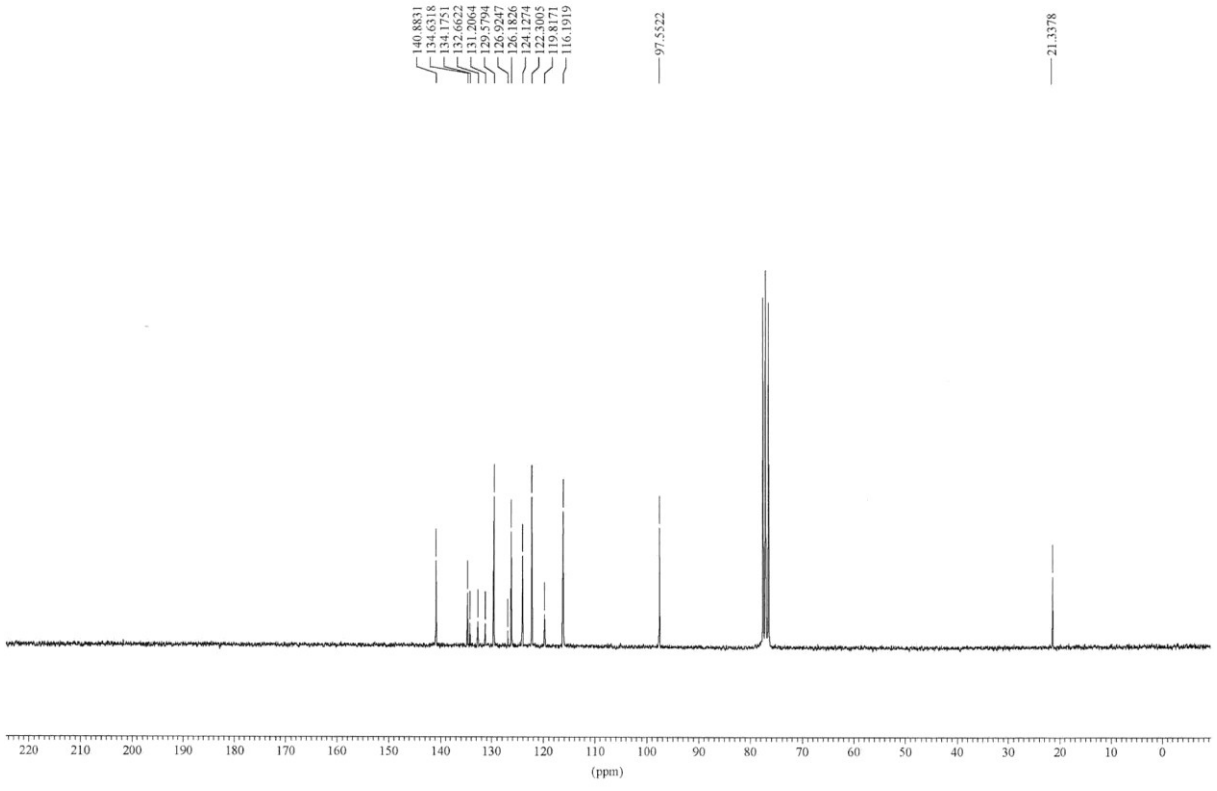
10-*tert*-Buthylpyrazolo[1,5-*a*]benzothieno[2,3-*c*]quinoline (1h).



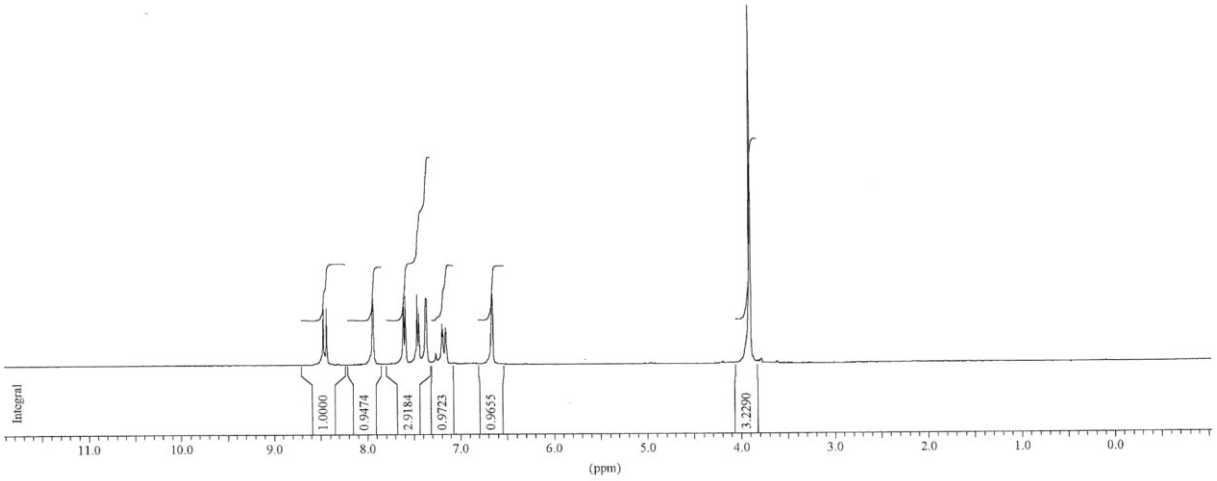


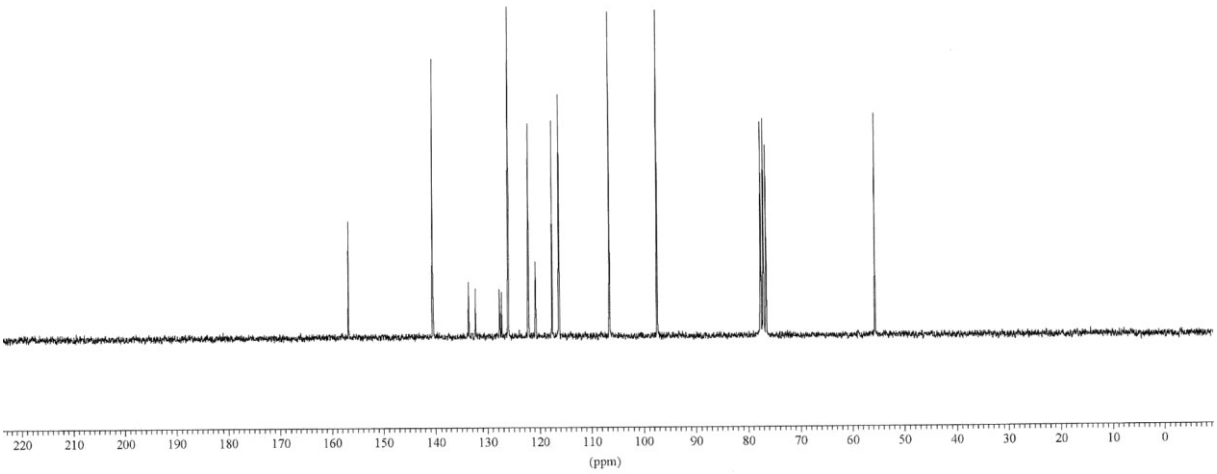
8-Methylpyrazolo[1,5-*a*]thieno[2,3-*c*]quinoline (1i).



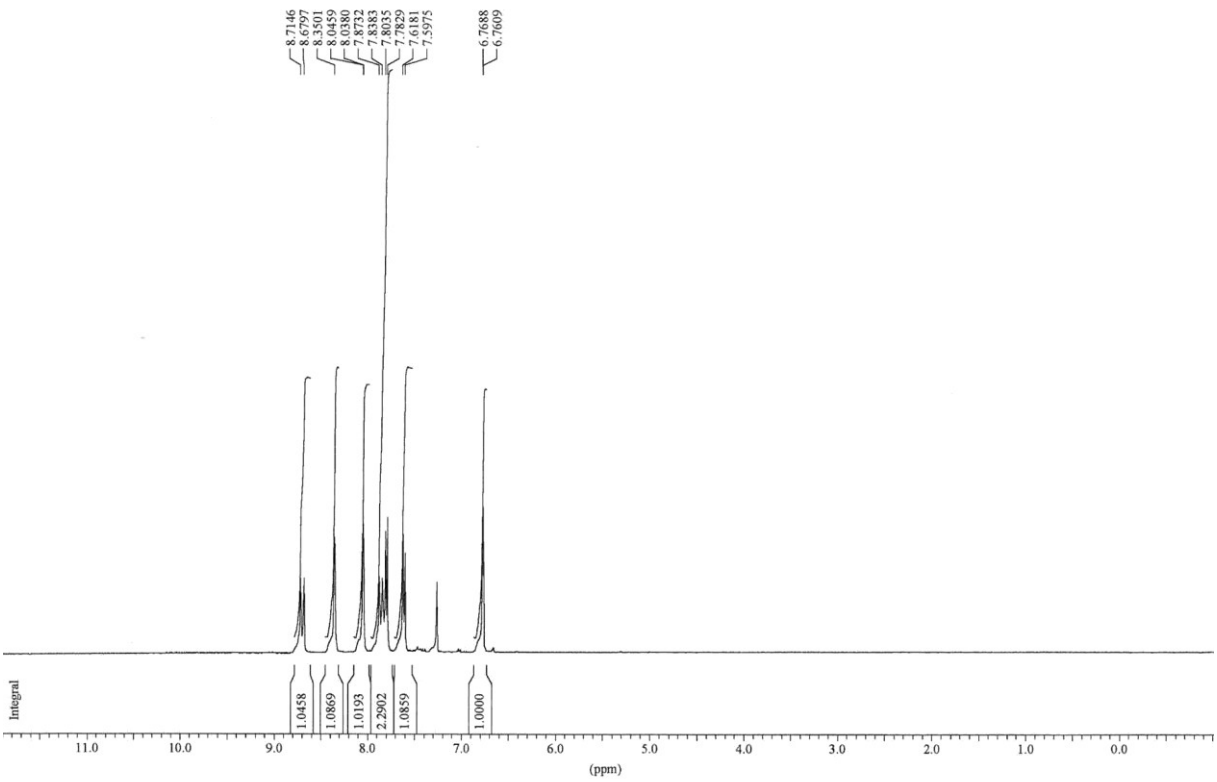


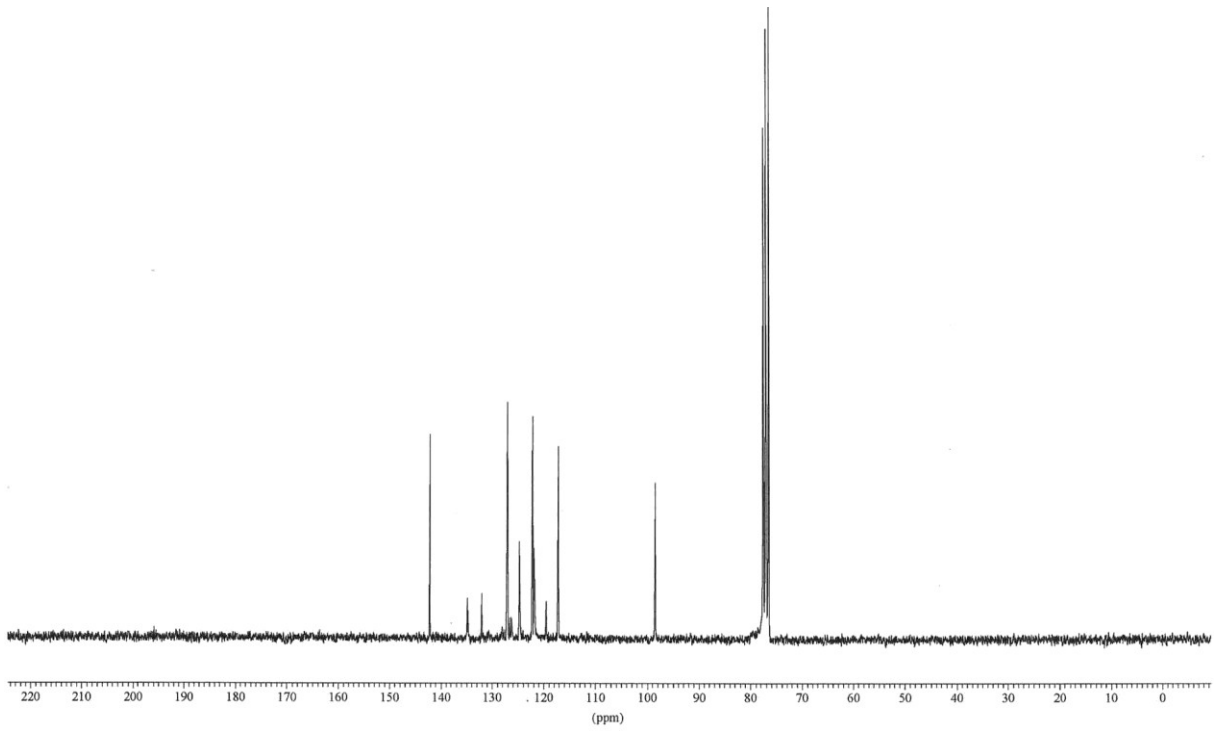
8-Methoxypyrazolo[1,5-*a*]thieno[2,3-*c*]quinoline (1j).



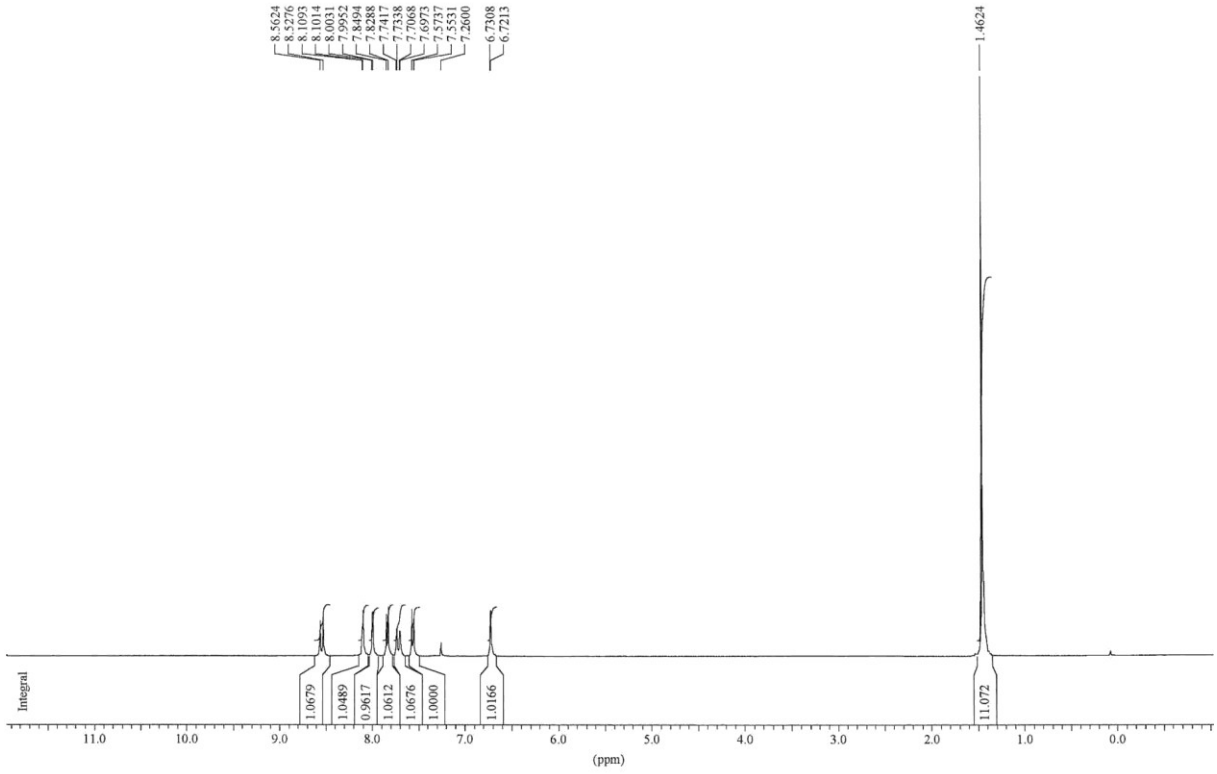


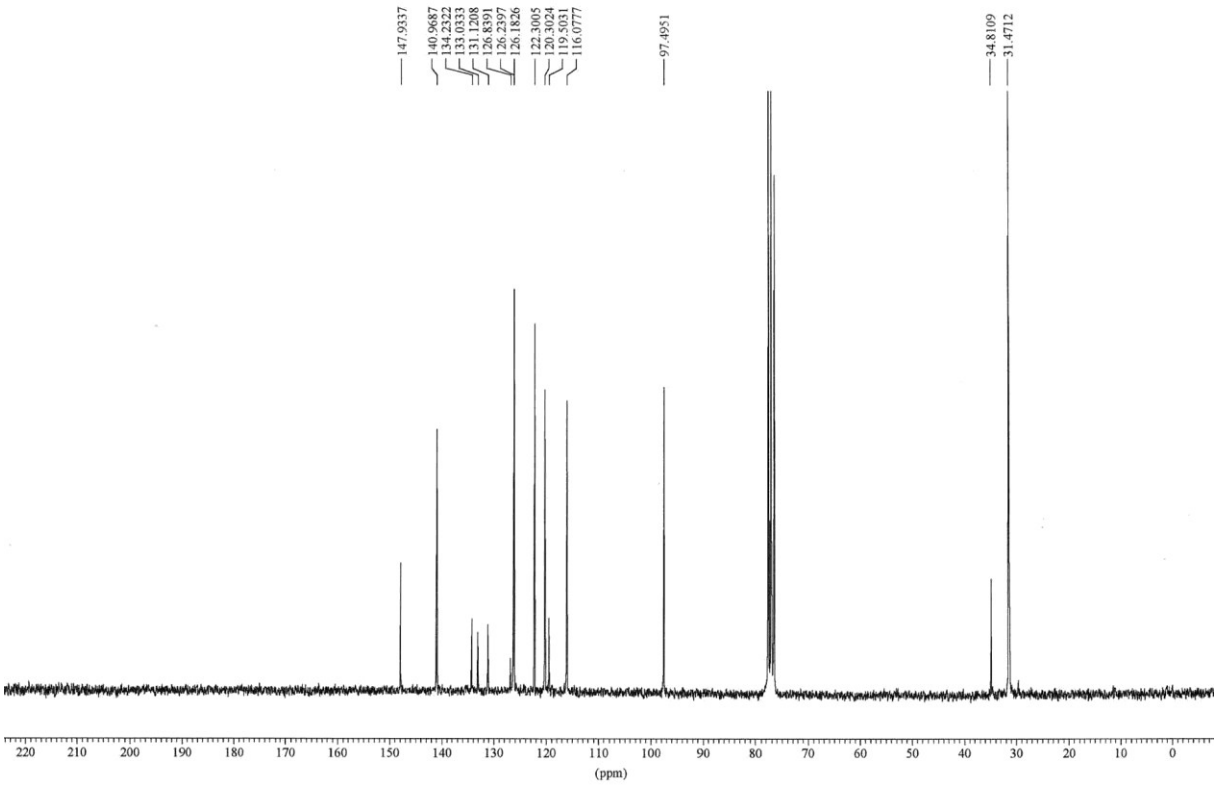
8-Trifluoromethylpyrazolo[1,5-*a*]thieno[2,3-*c*]quinoline (1k).



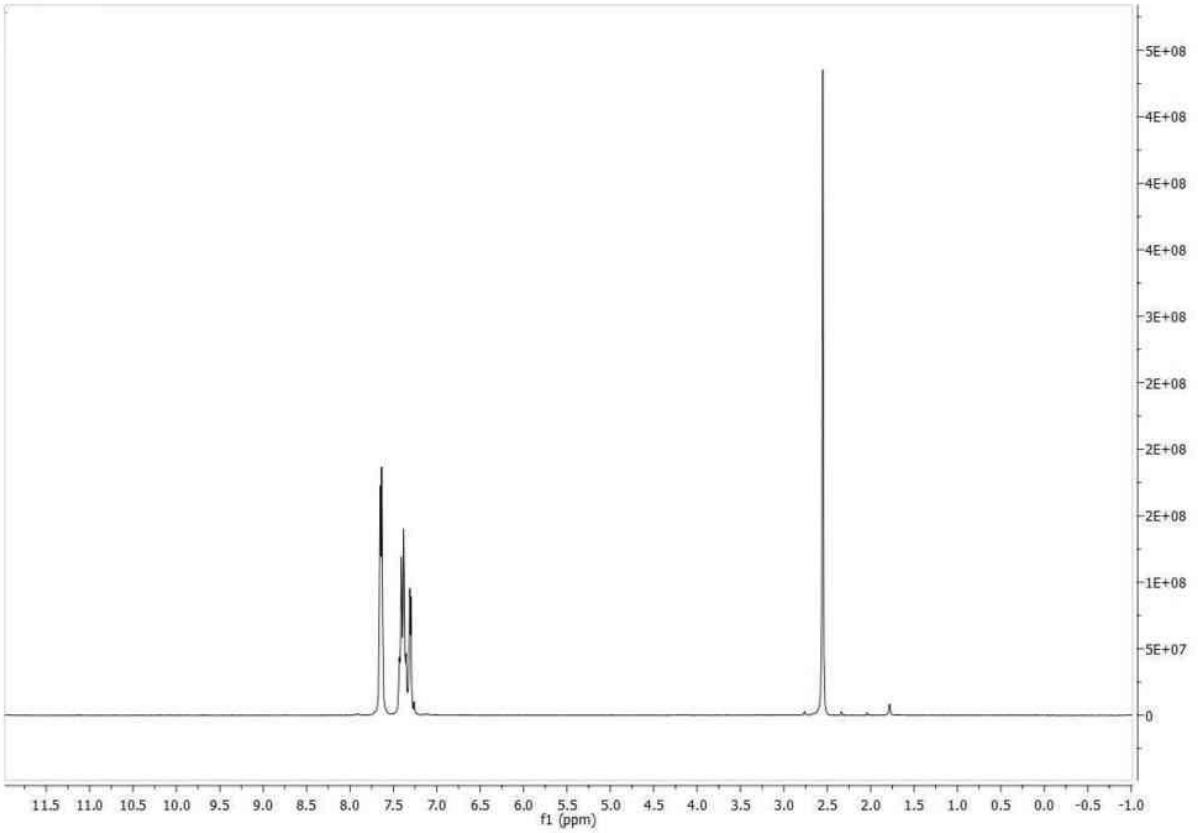


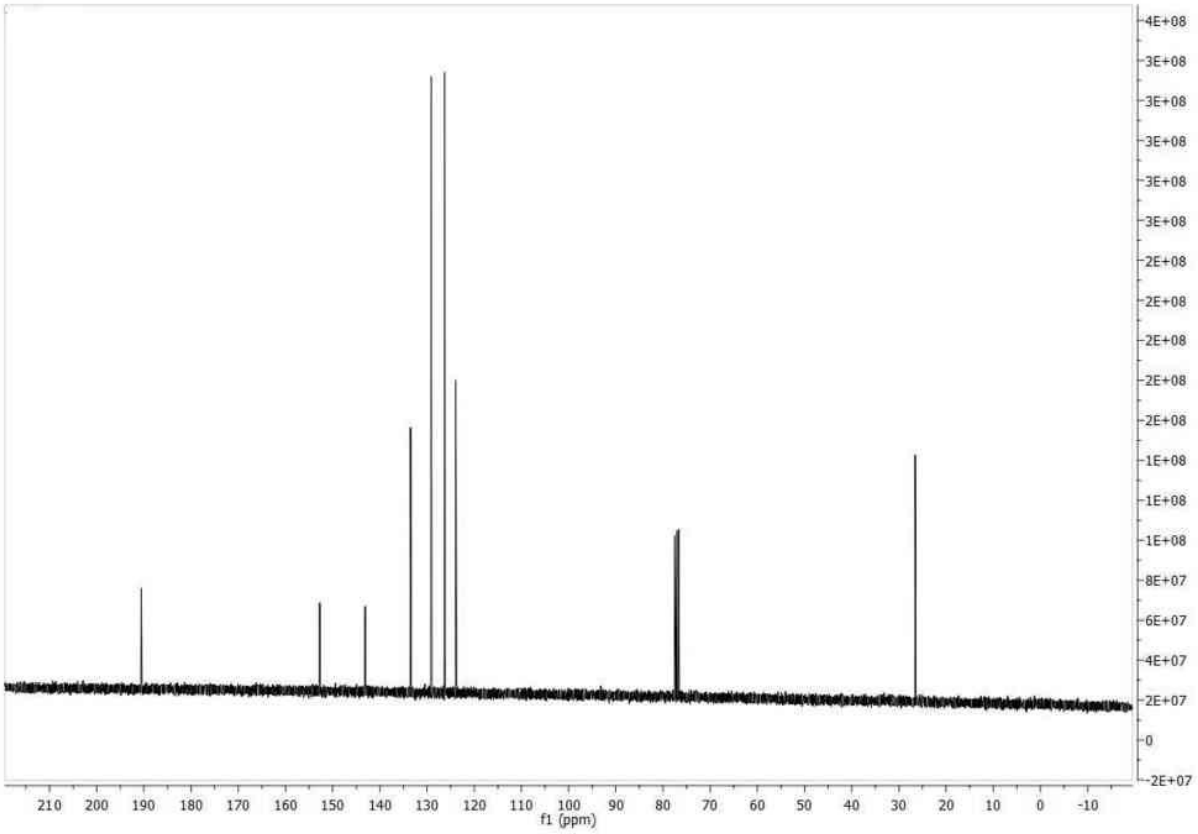
8-*tert*-Buthylpyrazolo[1,5-*a*]thieno[2,3-*c*]quinoline (1l).





5-Acetyl-2-phenylthiophene 5a.





5-Methyl-2-phenylthiophene 5b.