Design, Synthesis, and Apoptotic Evaluation of Spiro[indoline-3,3'-pyrazolo[1,2-a]indazole] Derivatives via [3+2] *N,N*-Cycloaddition

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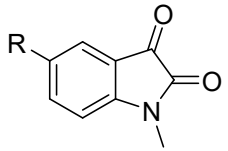
1. Materials and methods

1.1. General procedures and instrumentation

All available starting materials were purchased from Sigma-Aldrich and used without any further purification. The solvents involved in this work were purchased from either Merk/Sigma-Aldrich and purified as per the standard procedures. The ^{1}H and ^{13}C NMR spectra were recorded by utilizing Avance Neo Nanobay 400 MHz spectrometer and $CDCl_3$ serving as the solvent. Chemical shifts were determined in parts per million (ppm) relative to the residual solvent signals, which were used as references for both ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra ($CDCl_3$ = 7.26 ppm for ^{1}H and 77.2 ppm for ^{13}C, with reference to downfield shift from TMS as an internal standard). Coupling constants (*J* values) were expressed in hertz (Hz). For analytical Thin-layer chromatography (TLC) analysis, silica-gel plates (Merck DC Silica plates 60 GF254) were employed. Visualization of compounds was achieved by exposing them to 254 nm UV light. Flash column chromatography was conducted using silica gel (mesh size: 100-200) and the specified solvents. Furthermore, substituted 2-(1-methyl-2-oxoindolin-3-ylidene) malononitriles (**1a-1f**) and substituted 2-(1-allyl-2-oxoindolin-3-ylidene) malononitriles (**1g-1m**) were generated as per the literature procedures.[1]

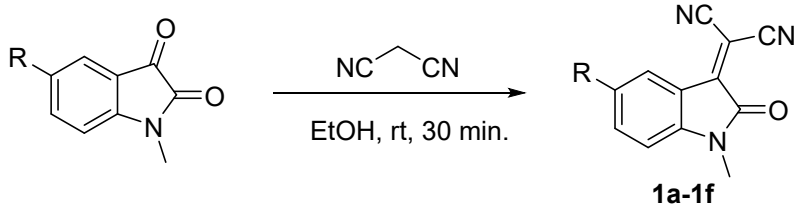
1.2. General information - I



R = H, F, Cl, Br, Me, OMe

Note: All substituted 1-methylindoline-2,3-dione were procured from commercially available sources.

1.3. General procedure for synthesis of 2-(1-methyl-2-oxoindolin-3-ylidene)malononitrile intermediates:



1a-1f

To a stirred solution of 1-methylindoline-2,3-dione (1.0 equiv.) in ethanol (10 v) was added malononitrile (1.0 equiv.) and the resulting reaction mixture was stirred at room temperature for 30 minutes. The progress of the reaction was monitored by TLC and LCMS. After completion, the solid was filtered, washed with n-pentane and dried to afford the titled compound.

2-(1-methyl-2-oxoindolin-3-ylidene)malononitrile (1a): Brown solid (97% yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.12 (d, J = 8.4 Hz, 1H), 7.58 (td, J = 7.6, 1.2 Hz, 1H), 7.15 (td, J = 8.0, 0.8 Hz, 1H), 6.86 (d, J = 8.0 Hz, 1H), 3.25 (s, 3H); (LCMS) m/z $(M + H)^+$ = 210.13

2-(5-fluoro-1-methyl-2-oxoindolin-3-ylidene)malononitrile (1b): Brown solid (99% yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.87 (dd, J = 7.6, 2.4 Hz, 1H), 7.32 (td, J = 8.8, 2.4 Hz, 1H), 6.85 (dd, J = 8.8, 4.0 Hz, 1H), 3.27 (s, 1H); (LCMS) m/z $(M + H)^+$ = 228.06

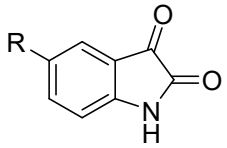
2-(5-chloro-1-methyl-2-oxoindolin-3-ylidene)malononitrile (1c): Brown solid (97% yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.08 (d, J = 2.0 Hz, 1H), 7.55 (dd, J = 8.4, 2.0 Hz, 1H), 6.82 (d, J = 8.8 Hz, 1H), 3.25 (s, 3H); (LCMS) m/z $(M + H)^+$ = 244.09

2-(5-bromo-1-methyl-2-oxoindolin-3-ylidene)malononitrile (1d): Pale brown solid (98% yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.21 (d, J = 2.0 Hz, 1H), 7.70 (dd, J = 8.4, 1.6 Hz, 1H), 6.77 (d, J = 8.4 Hz, 1H), 3.24 (s, 3H); (LCMS) m/z $(M + H)^+$ = 288.17

2-(5-methyl-1-methyl-2-oxoindolin-3-ylidene)malononitrile (1e*):* Brown solid (98% yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.90 (s, 1H), 7.38 – 7.36 (m, 1H), 6.75 (d, J = 8.0 Hz, 1H), 3.22 (s, 3H), 2.36 (s, 3H); (LCMS) m/z $(M + H)^+$ = 224.08

2-(5-methoxy-1-methyl-2-oxoindolin-3-ylidene)malononitrile (1f*):* Brown solid (97% yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.65 (d, J = 2.4 Hz, 1H), 7.13 (dd, J = 8.8, 2.8 Hz, 1H), 6.77 (d, J = 8.8 Hz, 1H), 3.83 (s, 3H), 3.21 (s, 3H); (LCMS) m/z $(M + H)^+$ = 240.13

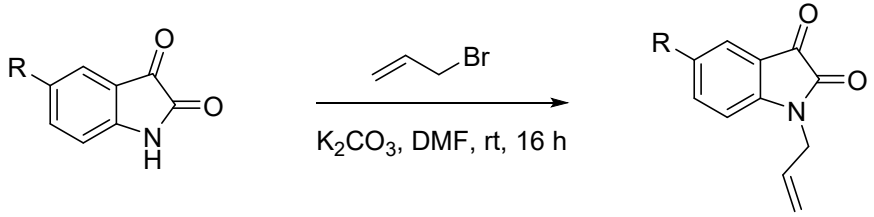
1.4. General Information - II



R = F, Cl, Br, Me, OMe, CF_3

Note: All substituted indoline-2,3-dione were procured from commercially available sources.

1.5. General procedure for synthesis of 1-allylindoline-2,3-dione intermediates:



R = F, Cl, Br, Me, OMe, CF_3

To a stirred solution of indoline-2,3-dione (1.0 equiv.) in DMF (10 v) was added K_2CO_3 (2.0 equiv.) followed by 3-bromoprop-1-ene (1.0 equiv.) and the resulted reaction mixture was stirred at room temperature for 16 h. The progress of the reaction was monitored by TLC and LCMS After completion, ice-cold water was added and the resulting solid was filtered and dried to afford the titled compound.

Note: 1-allylindoline-2,3-dione was procured from commercially available sources.

1-allyl-5-fluoroindoline-2,3-dione: Brown gummy (97% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.33 – 7.26 (m, 2H), 6.86 (dd, J = 8.4, 3.4 Hz, 1H), 5.88 - 5.78 (m, 1H), 5.34 – 5.30 (m 2H), 4.37 – 4 36 (m, 2H); (LCMS) m/z $(M + H)^+$ = 206.04

1-allyl-5-chloroindoline-2,3-dione*:* Orange solid (96% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.58 (d, J = 1.6 Hz, 1H), 7.53 (dd, J = 8.4, 1.6 Hz, 1H), 6.85 (d, J = 8.4 Hz, 1H), 5.87 - 5.78 (m, 1H), 5.34 – 5.30 (m, 2H), 4.36 (d, J = 4.8 Hz, 2H); (LCMS) m/z $(M + H)^+$ = 222.0

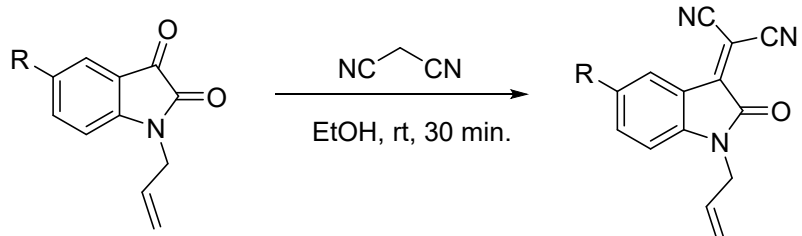
1-allyl-5-bromoindoline-2,3-dione: Orange solid (98% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.73 (d, *j* = 2.0 Hz, 1H), 7.68 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.80 (d, *J* = 8.4 Hz, 1H), 5.87 – 5.78 (m, 1H), 5.33 – 5.29 (m, 2H), 4.37 – 4.35 (m, 2H); (LCMS) m/z $(M + H)^+$ = 266.06

1-allyl-5-methylindoline-2,3-dione: Brown solid (99% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.43 (s, 1H), 7.36 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.78 (d, *J* = 8.4 Hz, 1H), 5.89 - 5.78 (m, 1H), 5.33 – 5.27 (m 2H), 4.36 – 4 33 (m, 2H); (LCMS) m/z $(M + H)^+$ = 202.19

1-allyl-5-methoxyindoline-2,3-dione: Brown gummy (97% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.16 (d, *J* = 2.8 Hz, 1H), 7.12 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.81 (d, *J* = 8.4 Hz, 1H), 5.90 - 5.80 (m, 1H), 5.34 – 5.28 (m, 2H), 4.35 – 4 33 (m, 2H), 3.81 (s, 3H); (LCMS) m/z $(M + H)^+$ = 218.24

1-allyl-5-(trifluoromethyl)indoline-2,3-dione: Brown solid (98% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.88 (s, 1H), 7.84 (d, *J* = 8.4 Hz, 1H), 7.02 (d, *J* = 8.4 Hz, 1H), 5.85 - 5.80 (m, 1H), 5.36 – 5.32 (m 2H), 4.43 – 4 41 (m, 2H); (LCMS) m/z $(M + H)^+$ = 256.16

1.6. General procedure for synthesis of 2-(1-allyl-2-oxoindolin-3-ylidene)malononitrile intermediates:



R = H, F, Cl, Br, Me, OMe, CF_3 **1g-1m**

To a stirred solution of 1-allylindoline-2,3-dione (1.0 equiv.) in ethanol (10 v) was added malononitrile (1.0 equiv.) and the reaction mixture was stirred at room temperature for 30 minutes. The progress of the reaction was monitored by TLC and LCMS. After completion, the resulting solid was filtered, washed with n-pentane and dried to afford the titled compound.

2-(1-allyl-2-oxoindolin-3-ylidene)malononitrile (1g): Brown solid (98% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.13 (d, *J* = 8.0 Hz, 1H), 7.54 (td, *J* = 8.0, 1.2 Hz, 1H), 7.14 (td, *J* = 7.6, 0.8 Hz, 1H), 6.86 (d, *J* = 8.0 Hz, 1H), 5.80 - 5.76 (m, 1H), 5.32 – 5.27 (m 2H), 4.37 – 4 35 (m, 2H); (LCMS) m/z $(M + H)^+$ = 236.20

2-(1-allyl-5-fluoro-2-oxoindolin-3-ylidene)malononitrile (1h): Brown liquid (98% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.86 (dd, *J* = 7.6, 2.4 Hz, 1H), 7.29 – 7.24 (m, 1H), 6.82 (dd, *J* = 8.8, 4.0 Hz, 1H), 5.85 - 5.72 (m, 1H), 5.33 – 5.27 (m 2H), 4.36 – 4 34 (m, 2H); (LCMS) m/z $(M + H)^+$ = 254.04

2-(1-allyl-5-chloro-2-oxoindolin-3-ylidene)malononitrile (1i): Orange solid (99% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.09 (d, *J* = 2.0 Hz, 1H), 7.50 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.82 (d, *J* = 8.4 Hz, 1H), 5.78 - 5.74 (m, 1H), 5.32 – 5.26 (m 2H), 4.36 – 4 34 (m, 2H); (LCMS) m/z $(M + H)^+$ = 270.10

2-(1-allyl-5-bromo-2-oxoindolin-3-ylidene)malononitrile (1j): Pale brown solid (95% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.23 (d, *J* = 2.0 Hz, 1H), 7.65 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.77 (d, *J* = 8.4 Hz, 1H), 5.79 - 5.74 (m, 1H), 5.33 – 5.26 (m 2H), 4.36 – 4 34 (m, 2H); (LCMS) m/z $(M + H)^+$ = 314.14

2-(1-allyl-5-methyl-2-oxoindolin-3-ylidene)malononitrile (1k): Brown solid (97% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.92 (s, 1H), 7.35 – 7.32 (m, 1H), 6.75 (d, *J* = 8.4 Hz, 1H), 5.85 - 5.75 (m, 1H), 5.29 – 5.25 (m 2H), 4.33 – 4 31 (m, 2H); (LCMS) m/z $(M + H)^+$ = 250.13

2-(1-allyl-5-methoxy-2-oxoindolin-3-ylidene)malononitrile (1l): Orange solid (97% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.66 (d, *J* = 2.4 Hz, 1H), 7.09 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.76 (d, *J* = 8.8 Hz, 1H), 5.79 - 5.75 (m, 1H), 5.30 – 5.26 (m 2H), 4.32 – 4 31 (m, 2H), 3.83 (s, 3H); (LCMS) m/z $(M + H)^+$ = 266.19

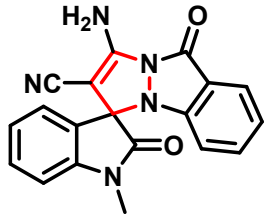
2-(1-allyl-2-oxo-5-(trifluoromethyl)indolin-3-ylidene)malononitrile (1m): Brown solid (98% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.37 (s, 1H), 7.81 (dd, *J* = 8.4, 0.8 Hz, 1H), 7.0 (d, *J* = 8.4 Hz, 1H), 5.86 - 5.76 (m, 1H), 5.35 – 5.29 (m 2H), 4.43 – 4 40 (m, 2H); (LCMS) m/z $(M + H)^+$ = 304.27

Note: All above mentioned data was matched with the referenced data

1.7. General procedure for synthesis of substituted 1'-amino-1-methyl-2,9'-dioxo-9'H-spiro[indoline-3,3'-pyrazolo[1,2-a]indazole]-2'-carbonitrile (3a-3f):

To a stirred solution of substituted 2-(1-methyl-2-oxoindolin-3-ylidene) malononitrile (**1a-1f**) (1.0 equiv.) in CH_2Cl_2 (10v) was added 1,2-dihydro-3H-indazol-3-one (1.0 equiv.) followed by Et_3N (0.5 equiv.) and the resulted reaction mixture was stirred at room temperature for 4 h. The progress of the reaction was monitored by TLC and LCMS. After that, the reaction mixture was concentrated under reduced pressure to obtain crude compound. The crude compound was purified by column chromatography (silica gel; 100-200 mesh: 0-40% ethyl acetate in pet ether as eluent) to afford the titled compound.

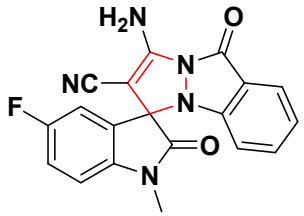
1'-amino-1-methyl-2,9'-dioxo-9'H-spiro[indoline-3,3'-pyrazolo[1,2-a]indazole]-2'-carbonitrile (3a):



3a

Pale yellow solid (95% yield); m.p.180-190 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.84 (d, *J* = 8.0 Hz, 1H), 7.49 – 7.45 (m, 1H), 7.42 – 7.38 (m, 2H), 7.17 (t, *J* = 7.6 Hz, 2H), 6.98 (d, *J* = 8.0 Hz, 1H), 6.33 (d, *J* = 8.4 Hz, 1H), 6.07 (br s, 2H), 3.24 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ (ppm): 171.6, 161.0, 150.5, 146.7, 143.8, 134.4, 131.8, 126.0, 125.4, 124.2, 124.1, 123.4, 119.7, 114.0, 111.1, 109.2, 71.3, 64.6, 26.7; HRMS (ESI) m/z Calculated for $C_{19}H_{14}N_5O_2$ $[H]^+$: 344.1148, found: 344.1141

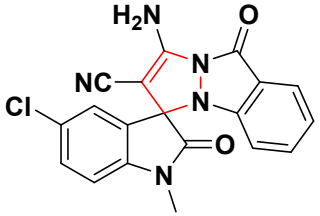
1'-amino-5-fluoro-1-methyl-2,9'-dioxo-9'H-spiro[indoline-3,3'-pyrazolo[1,2-a]indazole]-2'-carbonitrile (3b):



3b

Orange solid (92% yield); m.p. 180-190 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.85 (d, J = 8.0 Hz, 1H), 7.46 – 7.42 (m, 1H), 7.22 – 7.16 (m, 3H), 6.94 – 6.90 (m, 1H), 6.36 (d, J = 8.4 Hz, 1H), 6.13 (br s, 2H), 3.22 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ (ppm): 171.4, 161.0, 150.6, 146.7, 139.7, 134.6, 125.9, 125.5, 123.7, 119.8, 118.4, 118.1, 113.9, 111.0, 110.0, 71.3, 64.1, 29.7, 26.8; HRMS (ESI) m/z Calculated for $C_{19}H_{13}FN_5O_2$ $[H]^+$: 362.1054, found: 362.1043

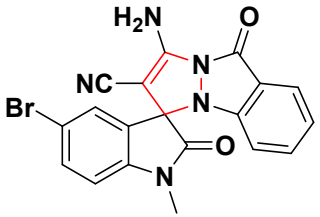
1'-amino-5-chloro-1-methyl-2,9'-dioxo-9'H-spiro[indoline-3,3'-pyrazolo[1,2-a]indazole]-2'-carbonitrile (3c):



3c

Pale yellow solid (90% yield); m.p. 200-210 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.85 (d, J = 7.6 Hz, 1H), 7.46 – 7.42 (m, 3H), 7.21 (t, J = 7.6 Hz, 1H), 6.91 (d, J = 8.4 Hz, 1H), 6.36 (d, J = 8.0 Hz, 1H), 6.14 (br s, 2H), 3.22 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ (ppm): 171.3, 161.0, 146.7, 142.3, 134.6, 131.7, 129.7, 126.4, 125.9, 125.5, 123.8, 119.8, 113.8, 111.0, 110.3, 71.1, 64.0, 29.7, 26.8; HRMS (ESI) m/z Calculated for $C_{19}H_{13}ClN_5O_2$ $[H]^+$: 378.0759, found: 378.0742

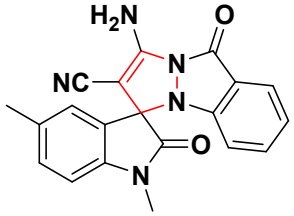
1'-amino-5-bromo-1-methyl-2,9'-dioxo-9'H-spiro[indoline-3,3'-pyrazolo[1,2-a]indazole]-2'-carbonitrile (3d):



3d

Brown solid (91% yield); m.p. 190-200 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.85 (d, *J* = 7.6 Hz, 1H), 7.60 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.57 (d, *J* = 1.6 Hz, 1H), 7.46 – 7.42 (m, 1H), 7.21 (t, *J* = 7.6 Hz, 1H), 6.87 (d, *J* = 8.4 Hz, 1H), 6.36 (d, *J* = 8.4 Hz, 1H), 6.07 (br s, 2H), 3.22 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ (ppm): 171.2, 160.9, 146.6, 142.8, 134.6, 129.2, 126.2, 125.5, 123.7, 119.8, 116.9, 113.9, 111.0, 110.7, 71.0, 63.9, 31.9, 29.7, 26.7; HRMS (ESI) m/z Calculated for $C_{19}H_{13}BrN_5O_2$ [H]$^+$: 422.0253, found: 422.0245

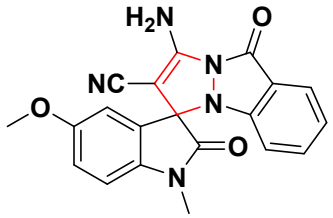
1'-amino-1,5-dimethyl-2,9'-dioxo-9'H-spiro[indoline-3,3'-pyrazolo[1,2-a]indazole]-2'-carbonitrile (3e):



3e

White solid (97% yield); m.p. 190-200 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.83 (d, *J* = 8.0 Hz, 1H), 7.42 – 7.38 (m, 1H), 7.24 – 7.23 (m, 2H), 7.17 (t, *J* = 8.0 Hz, 1H), 6.86 (d, *J* = 8.0 Hz, 1H), 6.35 (d, *J* = 8.4 Hz, 1H), 6.09 (br s, 2H), 3.20 (s, 3H), 2.34 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ (ppm): 171.6, 160.8, 146.6, 141.4, 134.3, 134.0, 132.0, 126.6, 125.3, 124.0, 123.3, 119.7, 114.3, 111.1, 108.9, 71.3, 64.4, 60.4, 26.6, 21.0; HRMS (ESI) m/z Calculated for $C_{20}H_{16}N_5O_2$ [H]$^+$: 358.1305, found: 358.1294

1'-amino-5-methoxy-1-methyl-2,9'-dioxo-9'H-spiro[indoline-3,3'-pyrazolo[1,2-a]indazole]-2'-carbonitrile (3f):



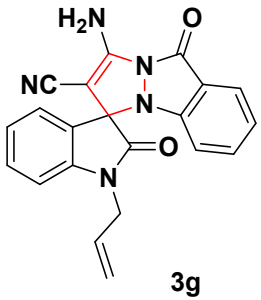
3f

Brown solid (94% yield); m.p. 190-200 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.84 (d, *J* = 8.0 Hz, 1H), 7.44 – 7.39 (m, 1H), 7.18 (t, *J* = 7.6 Hz, 1H), 7.01 – 6.97 (m, 2H), 6.88 (d, *J* = 7.6 Hz, 1H), 6.37 (d, *J* = 8.4 Hz, 1H), 6.04 (br s, 2H), 3.79 (s, 3H), 3.20 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ (ppm): 171.5, 160.9, 157.0, 150.6, 146.6, 136.9, 134.4, 125.3, 123.4, 119.7, 116.7, 114.2, 112.3, 111.1, 109.9, 71.5, 64.3, 55.8, 29.6, 26.7; HRMS (ESI) m/z Calculated for $C_{20}H_{16}N_5O_3$ $[H]^+$: 374.1254, found: 374.1243

1.8. General procedure for synthesis of substituted 1-allyl-1'-amino-2,9'-dioxo-9'H-spiro[indoline-3,3'-pyrazolo[1,2-a]indazole]-2'-carbonitrile and derivatives (3g-3m):

To a stirred solution of substituted 2-(1-allyl-2-oxoindolin-3-ylidene) malononitriles (**1g-1m**) (1.0 equiv.) in CH_2Cl_2 (10v) were added 1,2-dihydro-3H-indazol-3-one (1.0 equiv.) followed by Et_3N (0.5 equiv.) and the resulted reaction mixture was stirred at room temperature for 4 h. The progress of the reaction was monitored by TLC and LCMS. After that, the reaction mixture was concentrated under reduced pressure to obtain crude compound. The crude compound was purified by column chromatography (silica gel; 100-200 mesh: 0-40% ethyl acetate in pet ether as eluent) to afford the titled compound.

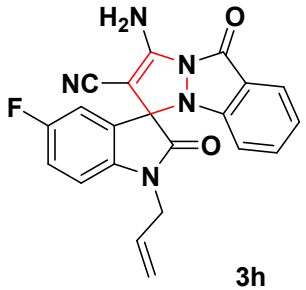
1-allyl-1'-amino-2,9'-dioxo-9'H-spiro[indoline-3,3'-pyrazolo[1,2-a]indazole]-2'-carbonitrile (3g):



3g

Brown solid (90% yield); m.p. 190-200 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.84 (d, *J* = 8.0 Hz, 1H), 7.45 – 7.42 (m, 1H), 7.41 – 7.39 (m, 2H), 7.20 – 7.14 (m, 2H), 6.97 (d, *J* = 8.0 Hz, 1H), 6.37 (d, *J* = 8.4 Hz, 1H), 6.04 (br s, 2H), 5.85 – 5.76 (m, 1H), 5.35 – 5.28 (m, 2H), 4.35 – 4.32 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ (ppm): 171.4, 161.0, 150.5, 146.7, 143.0, 134.3, 131.6, 130.5, 126.1, 125.4, 124.1, 124.0, 123.5, 119.7, 118.8, 111.3, 110.2, 71.2, 64.8, 42.9, 29.7; HRMS (ESI) m/z Calculated for $C_{21}H_{16}N_5O_2$ $[H]^+$: 370.1305, found: 370.1296

1-allyl-1'-amino-5-fluoro-2,9'-dioxo-9'H-spiro[indoline-3,3'-pyrazolo[1,2-a]indazole]-2'-carbonitrile (3h):

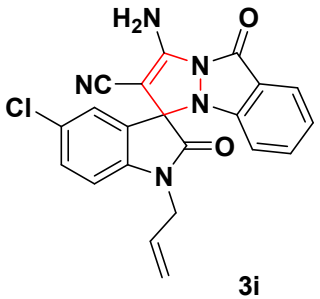


3h

Brown solid (89% yield); m.p. 158-168 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.86 (d, *J* = 8.0 Hz, 1H), 7.46 – 7.42 (m, 1H), 7.23 – 7.19 (m, 2H), 7.14 (td, *J* = 8.4, 2.4 Hz, 1H), 6.91 (dd, *J* = 8.8, 4.0 Hz, 1H), 6.40 (d, *J* = 8.4 Hz, 1H), 6.09 (br s, 2H), 5.81 – 5.73 (m, 1H), 5.34 – 5.29 (m, 2H), 4.33 – 4.30(m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ (ppm): 171.5, 160.9, 158.5, 150.6, 146.5, 138.8, 134.4,

130.4, 125.9, 125.5, 123.7, 119.9, 118.9, 118.2, 118.0, 114.1, 113.9, 111.1, 71.2, 63.6, 43.0; HRMS (ESI) m/z Calculated for $C_{21}H_{15}FN_5O_2$ $[H]^+$: 388.1211, found: 388.1202

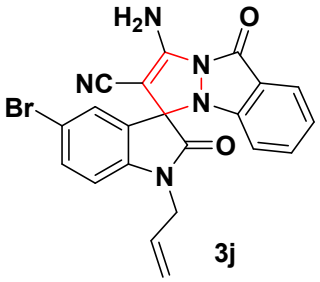
1-allyl-1'-amino-5-chloro-2,9'-dioxo-9'H-spiro[indoline-3,3'-pyrazolo[1,2-a]indazole]-2'-carbonitrile (3i):



3i

Off-white solid (92% yield); m.p. 185-190 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.85 (d, *J* = 8.0 Hz, 1H), 7.46 – 7.39 (m, 3H), 7.23 – 7.19 (m, 1H), 6.90 (d, *J* = 8.4 Hz, 1H), 6.40 (d, *J* = 8.4 Hz, 1H), 6.17 (br s, 2H), 5.82 – 5.72 (m, 1H), 5.33 – 5.29 (m, 2H), 4.32 – 4.29 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ (ppm): 171.2, 160.8, 150.6, 146.5, 141.4, 136.4, 131.5, 130.2, 129.7, 126.4, 125.9, 125.5, 123.7, 119.9, 118.9, 114.1, 111.3, 111.1, 71.0, 63.7, 43.0; HRMS (ESI) m/z Calculated for $C_{21}H_{15}ClN_5O_2$ $[H]^+$: 404.0915, found: 404.0907

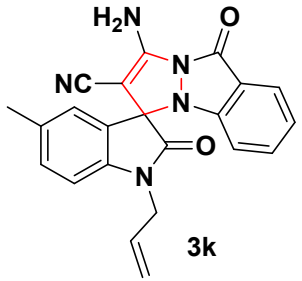
1-allyl-1'-amino-5-bromo-2,9'-dioxo-9'H-spiro[indoline-3,3'-pyrazolo[1,2-a]indazole]-2'-carbonitrile (3j):



3j

Orange solid (91% yield); m.p. 180-190 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.86 (d, *J* = 8.0 Hz, 1H), 7.59 – 7.55 (m, 2H), 7.47 – 7.43 (m, 1H), 7.23 – 7.19 (m, 1H), 6.85 (d, *J* = 8.4 Hz, 1H), 6.40 (d, *J* = 8.0 Hz, 1H), 6.04 (br s, 2H), 5.82 – 5.72 (m, 1H), 5.33 – 5.29 (m, 2H), 4.32 – 4.29 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ (ppm): 171.1, 160.8, 150.6, 146.5, 141.9, 134.5, 130.1, 129.2, 126.2, 125.5, 123.7, 119.9, 119.0, 116.8, 114.1, 111.7, 111.1, 70.9, 63.7, 42.9; HRMS (ESI) m/z Calculated for $C_{21}H_{15}BrN_5O_2$ $[H]^+$: 448.0410, found: 448.0400

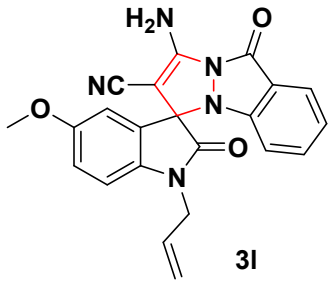
1-allyl-1'-amino-5-methyl-2,9'-dioxo-9'H-spiro[indoline-3,3'-pyrazolo[1,2-a]indazole]-2'-carbonitrile (3k):



3k

Pale yellow solid (95% yield); m.p. 190-200 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.84 (d, *J* = 8.0 Hz, 1H), 7.43 – 7.39 (m, 1H), 7.23 – 7.16 (m, 3H), 6.85 (d, *J* = 8.0 Hz, 1H), 6.40 (d, *J* = 8.0 Hz, 1H), 6.03 (br s, 2H), 5.84 – 5.74 (m, 1H), 5.33 – 5.26 (m, 2H), 4.32 – 4.29 (m, 2H), 2.33 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ (ppm): 171.6, 160.6, 150.5, 146.4, 140.5, 134.1, 133.8, 131.8, 130.6, 126.6, 125.3, 124.0, 123.3, 119.8, 118.5, 114.4, 111.2, 109.9, 71.2, 64.1, 42.9, 20.9; HRMS (ESI) m/z Calculated for $C_{22}H_{18}N_5O_2$ $[H]^+$: 384.1461, found: 384.1449

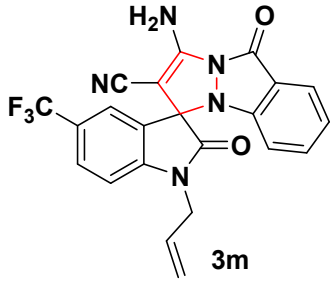
1-allyl-1'-amino-5-methoxy-2,9'-dioxo-9'H-spiro[indoline-3,3'-pyrazolo[1,2-a]indazole]-2'-carbonitrile (3l):



3l

Brown solid (93% yield); m.p. 170-180 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.84 (d, *J* = 8.0 Hz, 1H), 7.44 – 7.40 (m, 1H), 7.20 – 7.16 (m, 1H), 7.01 (d, *J* = 2.8 Hz, 1H), 6.95 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.87 (d, *J* = 8.4 Hz, 1H), 6.41 (d, *J* = 8.4 Hz, 1H), 6.06 (br s, 2H), 5.84 – 5.74 (m, 1H), 5.33 – 5.27 (m, 2H), 4.32 – 4.29 (m, 2H), 3.78 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ (ppm): 171.4, 160.8, 156.9, 150.6, 146.5, 136.0, 134.2, 130.7, 125.3, 123.4, 119.8, 118.6, 116.7, 114.3, 112.2, 111.3, 110.9, 71.5, 64.2, 55.8, 42.9; HRMS (ESI) m/z Calculated for $C_{22}H_{18}N_5O_3$ $[H]^+$: 400.1410, found: 400.1399

1-allyl-1'-amino-2,9'-dioxo-5-(trifluoromethyl)-9'H-spiro[indoline-3,3'-pyrazolo[1,2-a]indazole]-2'-carbonitrile (3m):



3m

White solid (85% yield); m.p. 195-200 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.87 (d, *J* = 8.0 Hz, 1H), 7.74 – 7.72 (m, 2H), 7.47 – 7.43 (m, 1H), 7.22 (t, *J* = 7.6 Hz, 1H), 7.06 (d, *J* = 8.4 Hz, 1H), 6.37 (d, *J* = 8.4 Hz, 1H), 6.09 (br s, 2H), 5.82 – 5.74 (m, 1H), 5.35 – 5.31 (m, 2H), 4.36 – 4.30 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ (ppm): 171.4, 161.2, 150.6, 146.8, 145.9, 134.6, 129.9, 129.3,

125.6, 125.1, 123.9, 123.3, 119.9, 119.3, 113.6, 111.2, 110.2, 70.9, 65.8, 64.1, 43.1, 15.2; HRMS (ESI) m/z Calculated for $C_{22}H_{15}F_3N_5O_2$ $[H]^+$: 438.1179, found: 438.1170

1.9. X-ray crystallographic study of spirooxindole derivative (3m)

Single crystals suitable for X-ray diffraction analysis of spirooxindole derivative **3m** was obtained at room temperature under non-inert atmospheric conditions. Single crystals of suitable dimensions were mounted on a CryoLoop (Hampton Research Corp.) with a layer of light mineral oil and placed in a nitrogen stream at 298.0 K and all measurements were made on Rigaku Oxford Diffraction, GUI svn.r1 with graphite monochromatic Mo-Kα (0.71073 Å) radiation. Crystal data and structure refinement parameters are summarized in Table S1 in the supplementary information. The structure was solved by direct methods (SIR2014)[2] and refined on F^2 by full-matrix least-squares methods; using SHELXL-2018.[3,4] Non-hydrogen atoms were anisotropically refined. H atoms were included in the refinement in calculated positions riding on their carrier atoms. The function minimized was $[\sum w(F_o^2 - F_c^2)^2]$ ($w = 1/[\sigma^2(F_o^2) + (aP)^2 + bP]$), where $P = (\max(F_o^2,0) + 2F_c^2)/3$ with $\sigma^2(F_o^2)$ from counting statistics. The functions R_1 and wR_2 were $(\sum||F_o| - |F_c||)/\sum|F_o|$ and $[\sum w(F_o^2 - F_c^2)^2/\sum(wF_o^4)]^{1/2}$. The Diamond-3 program was used to draw the molecule. Crystallographic data (excluding structural factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 2346438.

1.10. References

1. B. R. Patil, C. B. Nichinde, G. R. Krishna and A. K. Kinage, *RSC Adv*., 2024, **14**, 2873–2877.
2. M. C. Burla, R. Caliandro, B. Carrozzini, G. L. Cascarano, C. Cuocci, C. Giacovazzo, M. Mallamo, A. Mazzone and G. G. Polidori, *J. Appl. Cryst*., 2015, **48**, 306–309.
3. G. M. Sheldrick, *Acta, Crystallogr. Sect. CStruct. Chem*., 2015, **71**, 3–8.
4. C. B. Hübschle, G. M. Sheldrick and B. Dittrich, *J. Appl. Crystallogr*., 2011, **44**, 1281–1284.

Table S1. Crystal data and structure refinement for **3m**.

Crystal data and structure refinement for 3m			
Identification code (CCDC)	2346438	μ/mm^{-1}	0.108
Empirical formula	$C_{22}H_{14}F_3N_5O_2$	F(000)	896
Formula weight	437.38	Crystal size/mm^3	0.213 × 0.211 × 0.194
Temperature/K	298	Radiation	MoKα (λ = 0.71073)
Crystal system	orthorhombic	2Θ range for data collection/°	4.234 to 55.23
Space group	$P2_12_12_1$	Index ranges	$-14 \leq h \leq 14$, $-15 \leq k \leq 15$, $-22 \leq l \leq 22$
a/Å	10.798(3)	Reflections collected	59592
b/Å	11.682(4)	Independent reflections	4945 [R_{int} = 0.0644, R_{sigma} = 0.0539]
c/Å	16.946(5)	Data/restraints/parameters	4945/0/271
α/°	90	Goodness-of-fit on F^2	1.176
β/°	90	Final R indexes [I>=2σ (I)]	R_1 = 0.0910, wR_2 = 0.2815
γ/°	90	Final R indexes [all data]	R_1 = 0.1155, wR_2 = 0.3049
Volume/$Å^3$	2137.7(10)	Largest diff. peak/hole / e $Å^{-3}$	0.72/-0.81
Z	4	Flack parameter	0.5(7)
$\rho_{calc}g/cm^3$	1.359		

Table S2. Molecular docking interactions of test compound (3l) with CDK-2 (PDB ID: 2FVD) and with EGFR-TKD (PDB ID: 4hjo).

Compound Id	Docking score (kcal/mol)	Protein-ligand interactions
3l with CDK-2 (PDB ID: 2FVD)	-6.63	**H-bond:** Asp86(2.27Å), Asp86(2.50Å) & Lys89(2.10Å); **Hydrophobic:** Ile10(3.0Å), Phe82(3.24Å), Leu134(3.31Å), Leu134 & (3.82Å); **Stacking:** Phe82(5.18Å)
3l with EGFR-TKD (PDB ID: 4hjo)	-6.86	**H-bond:** Arg817(2.53Å), Asn818(2.65Å), &Asn818(1.97Å); **Hydrophobic:** Va1702(3.38Å)

3. NMR and HRMS Spectra

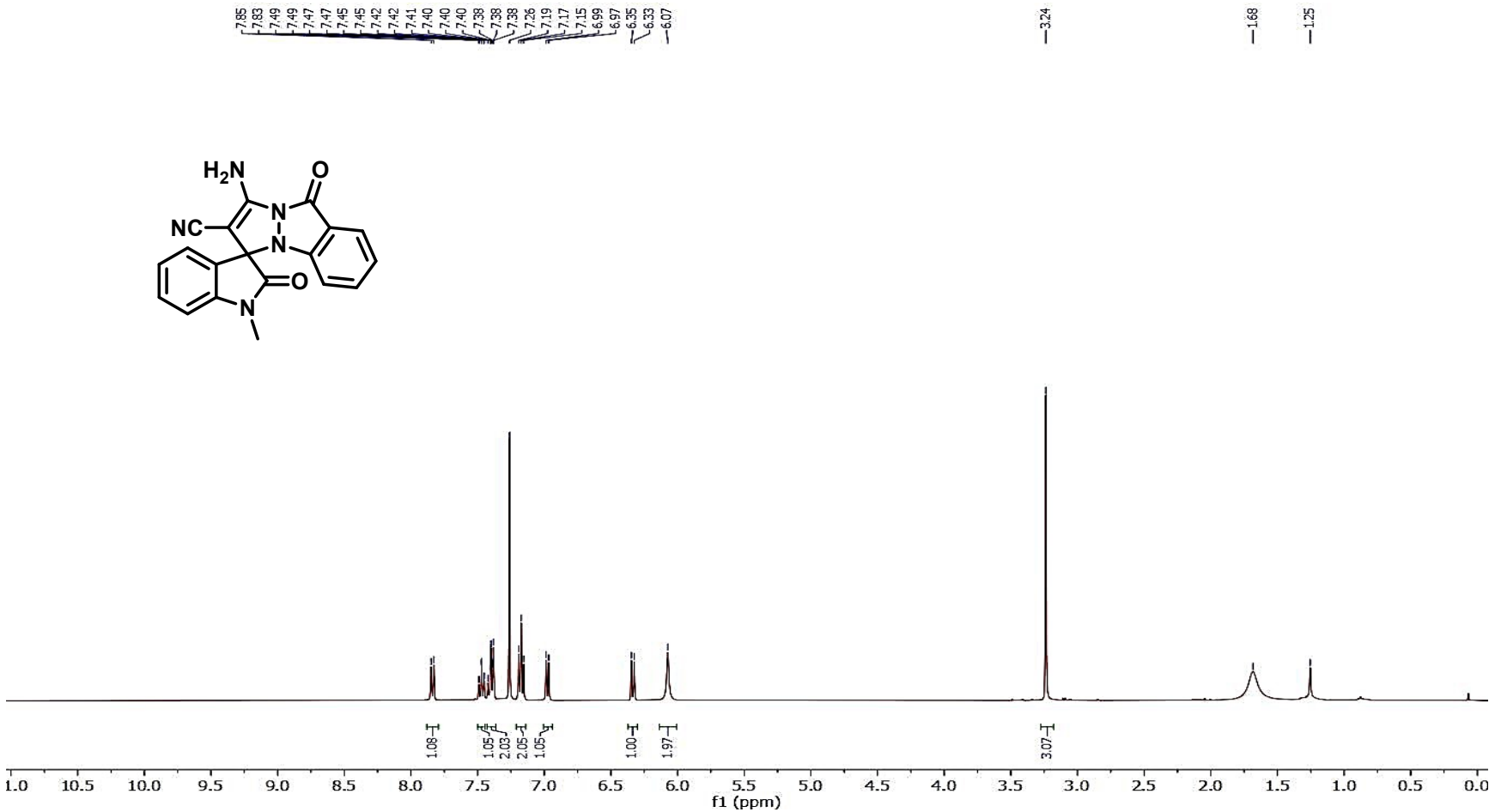


Fig. S1. ^{1}H NMR of 1'-amino-1-methyl-2,9'-dioxo-9'*H*-spiro[indoline-3,3'-pyrazolo[1,2-a]indazole]-2'-carbonitrile (**3a**):

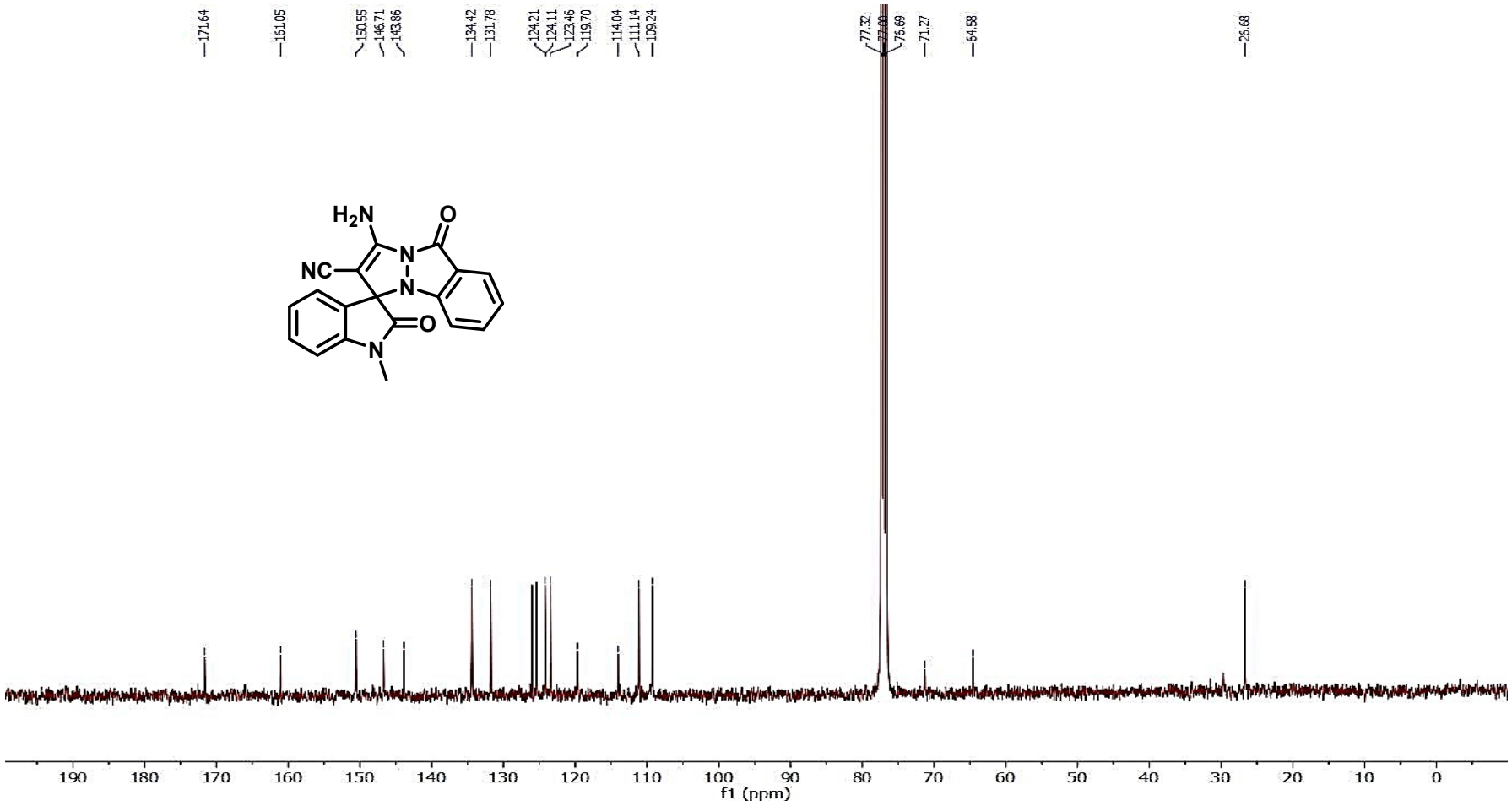


Fig. S2. ^{13}C NMR of 1'-amino-1-methyl-2,9'-dioxo-9'*H*-spiro[indoline-3,3'-pyrazolo[1,2-a]indazole]-2'-carbonitrile (**3a**):

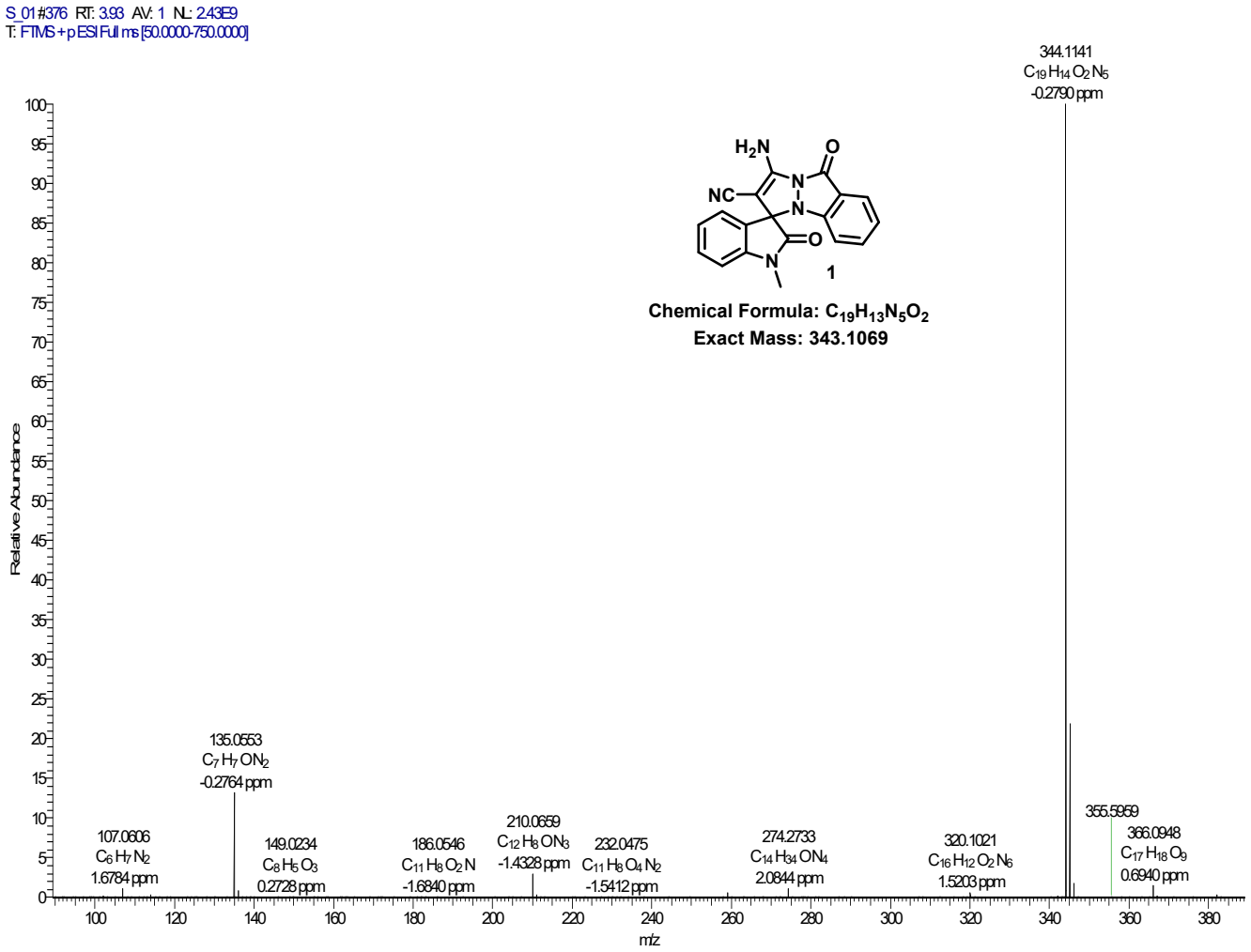


Fig. S3. HRMS of 1'-amino-1-methyl-2,9'-dioxo-9'*H*-spiro[indoline-3,3'-pyrazolo[1,2-a]indazole]-2'-carbonitrile (**3a**):

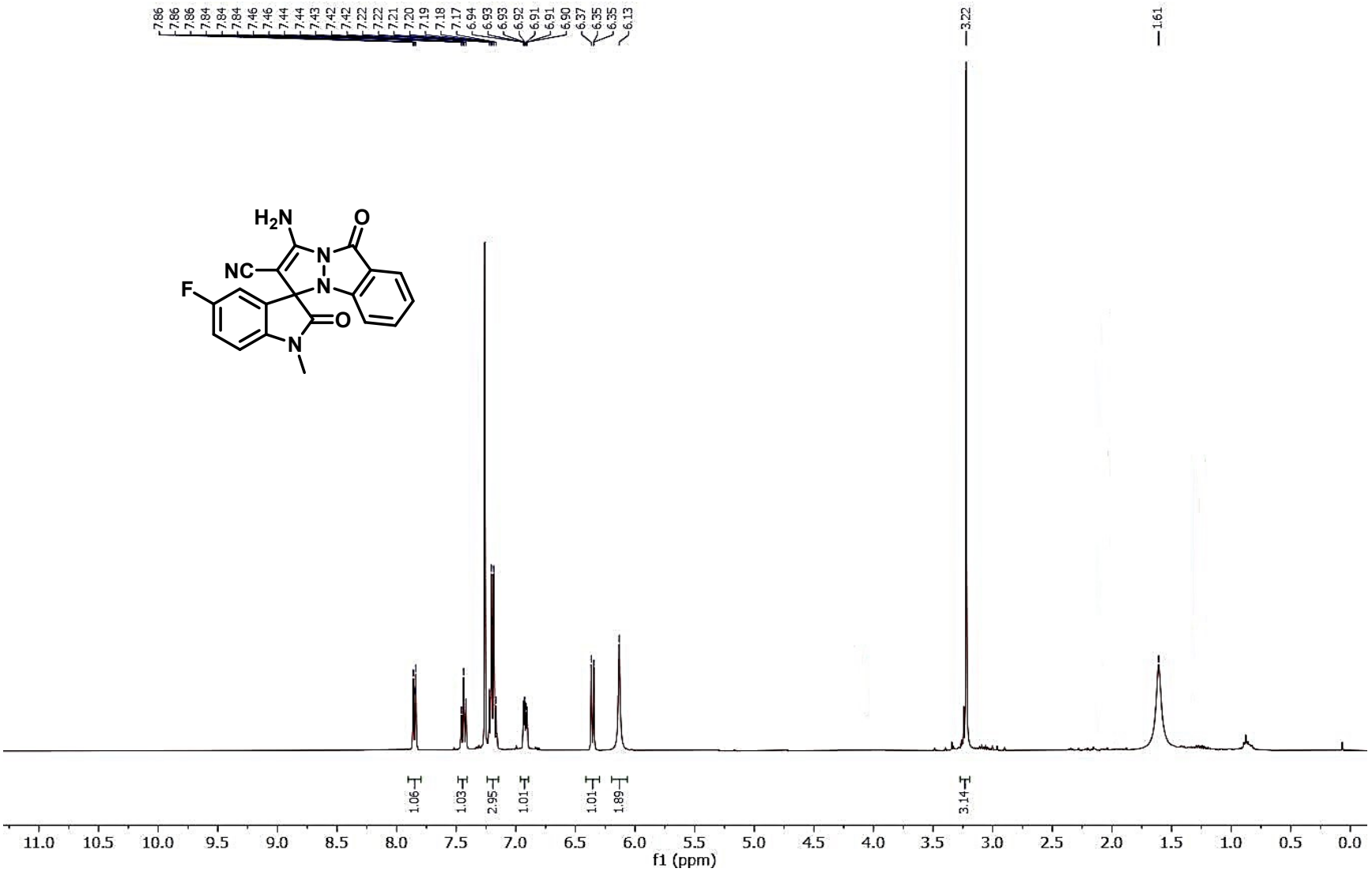


Fig. S4. [1]H NMR of 1'-amino-5-fluoro-1-methyl-2,9'-dioxo-9'*H*-spiro[indoline-3,3'-pyrazolo[1,2-a]indazole]-2'-carbonitrile (**3b**):

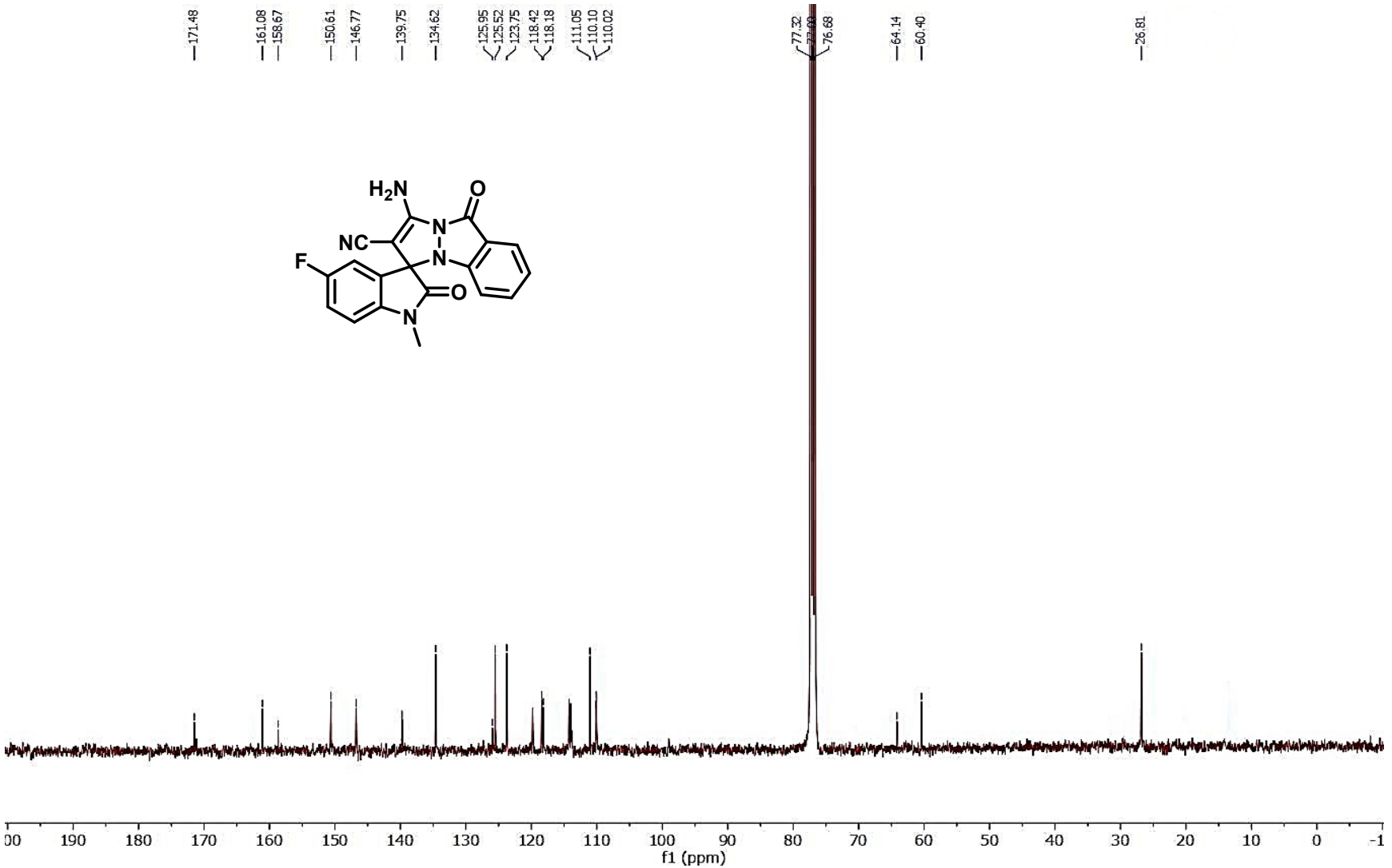


Fig. S5. ^{13}C NMR of 1'-amino-5-fluoro-1-methyl-2,9'-dioxo-9'*H*-spiro[indoline-3,3'-pyrazolo[1,2-a]indazole]-2'-carbonitrile (**3b**):

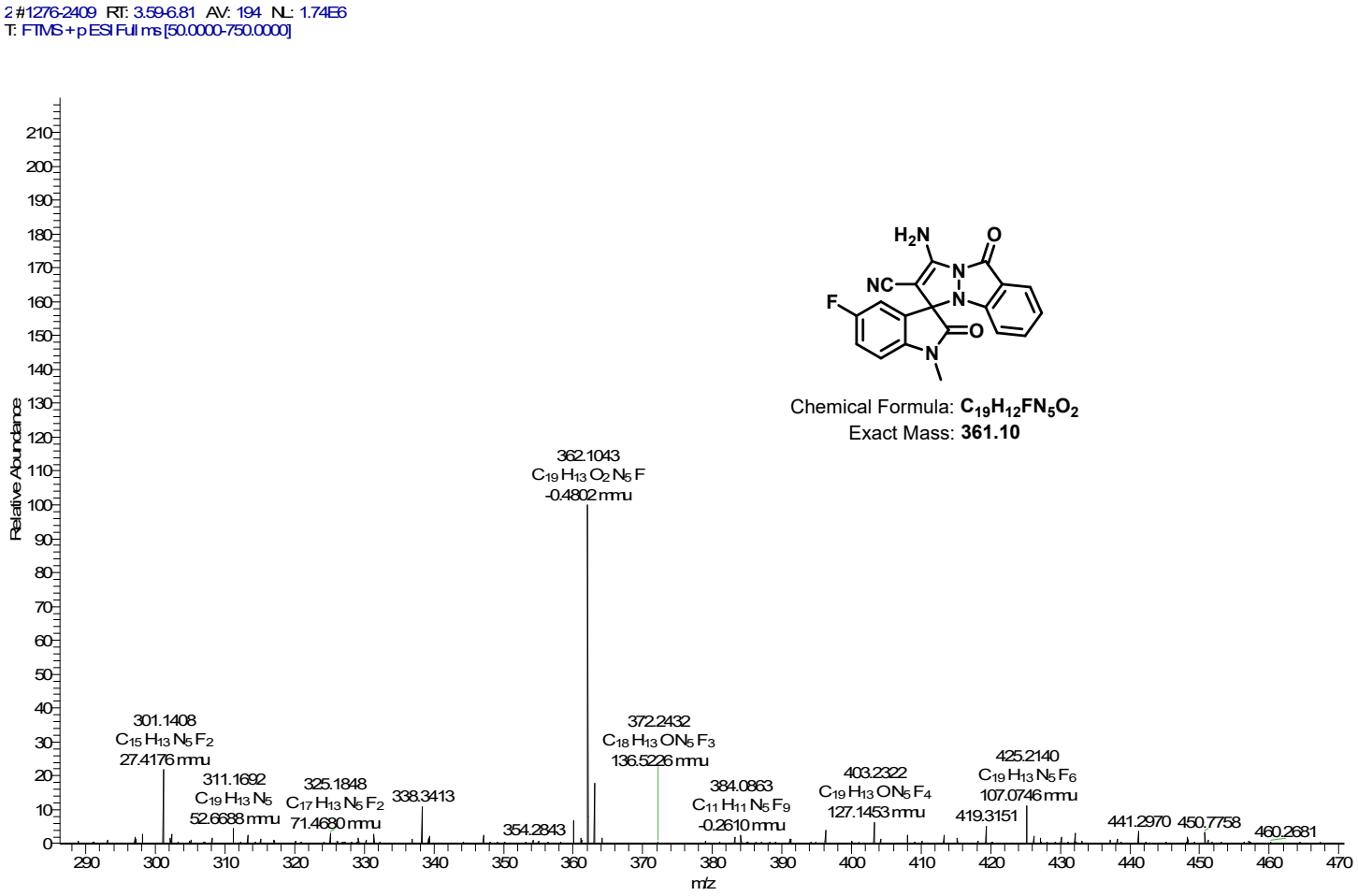


Fig. S6. HRMS of 1'-amino-5-fluoro-1-methyl-2,9'-dioxo-9'*H*-spiro[indoline-3,3'-pyrazolo[1,2-a]indazole]-2'-carbonitrile (**3b**):

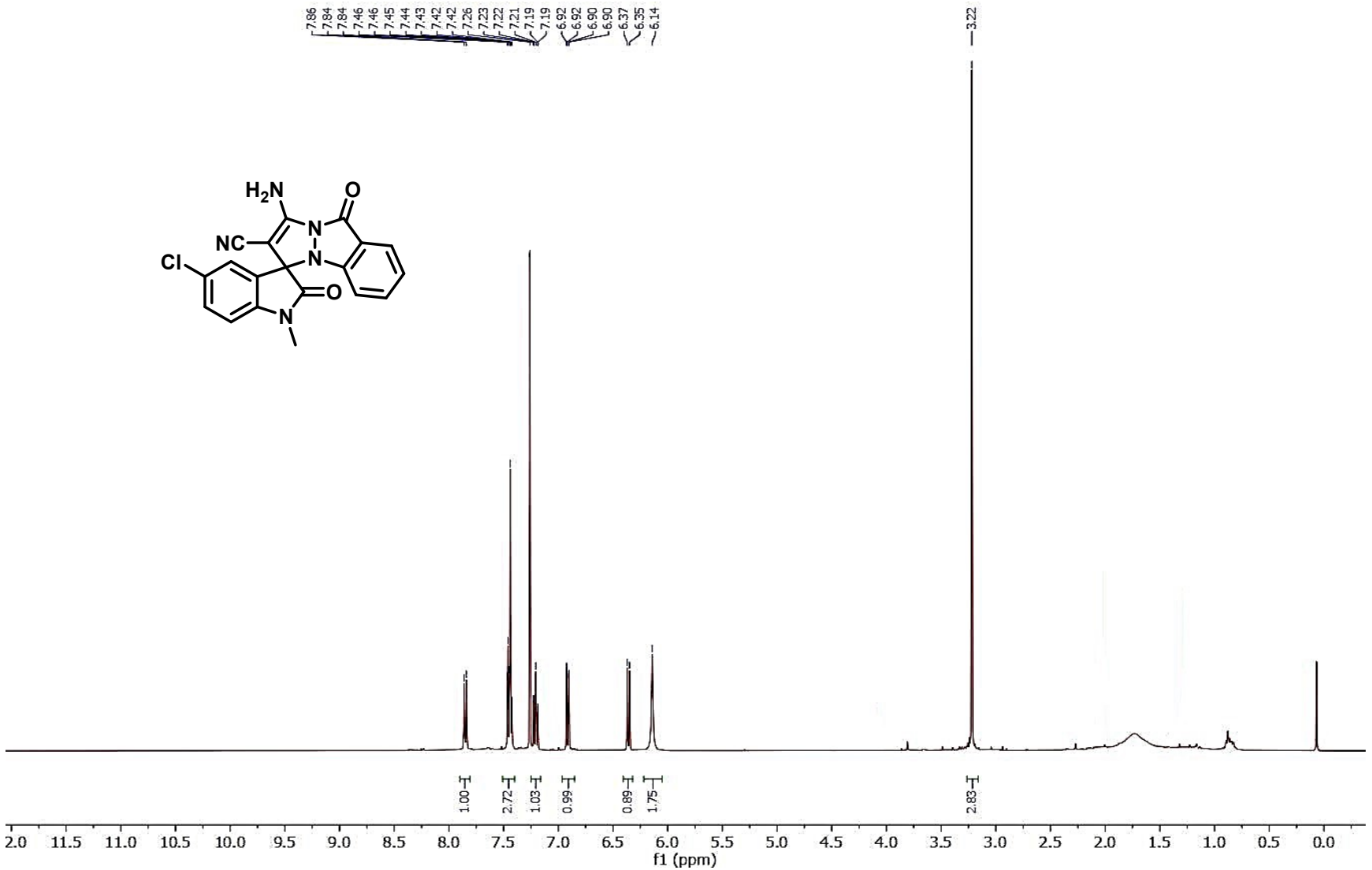


Fig. S7. ^{1}H NMR of 1'-amino-5-chloro-1-methyl-2,9'-dioxo-9'*H*-spiro[indoline-3,3'-pyrazolo[1,2-a]indazole]-2'-carbonitrile (**3c**):

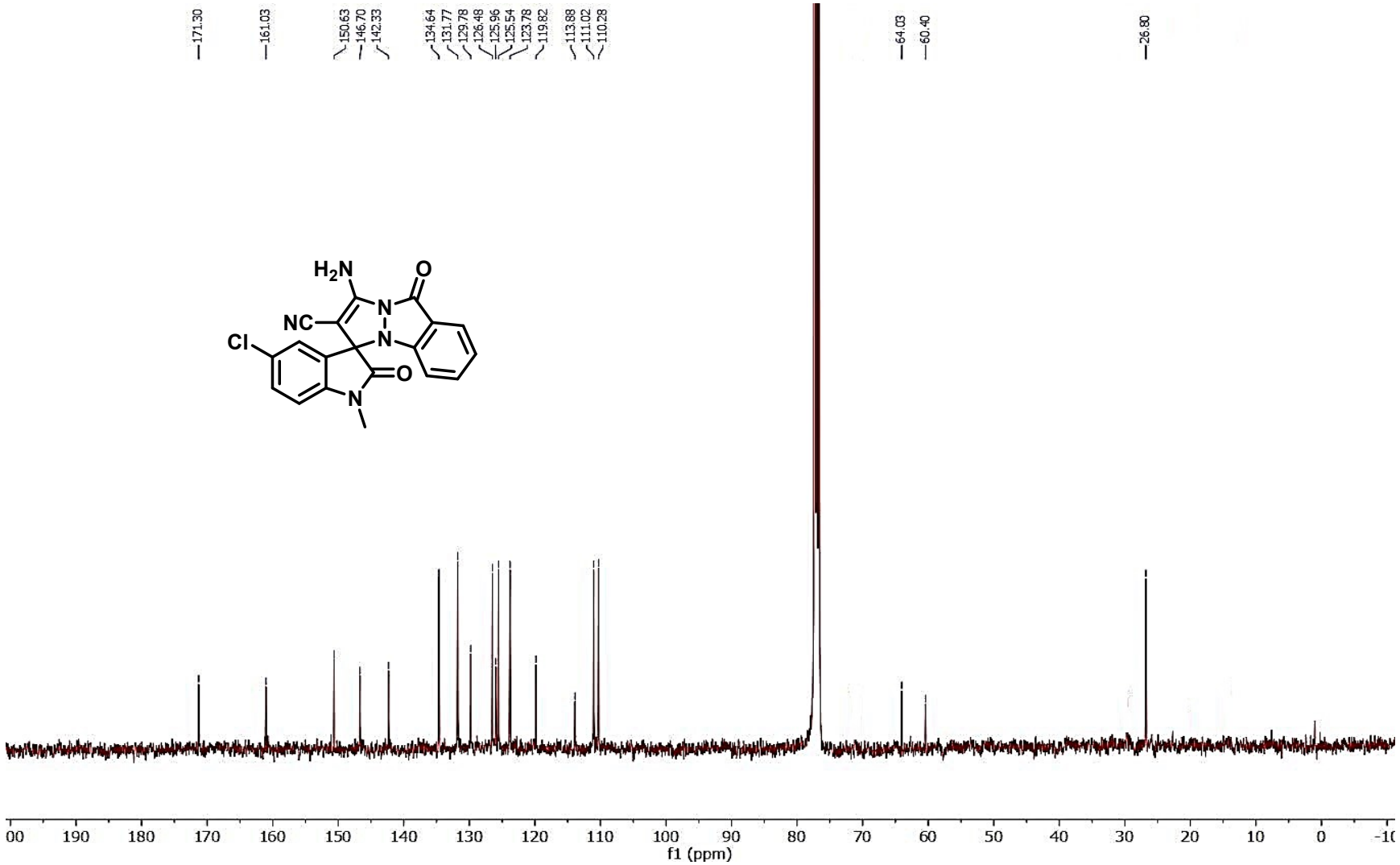


Fig. S8. ^{13}C NMR of 1'-amino-5-chloro-1-methyl-2,9'-dioxo-9'*H*-spiro[indoline-3,3'-pyrazolo[1,2-a]indazole]-2'-carbonitrile (**3c**):

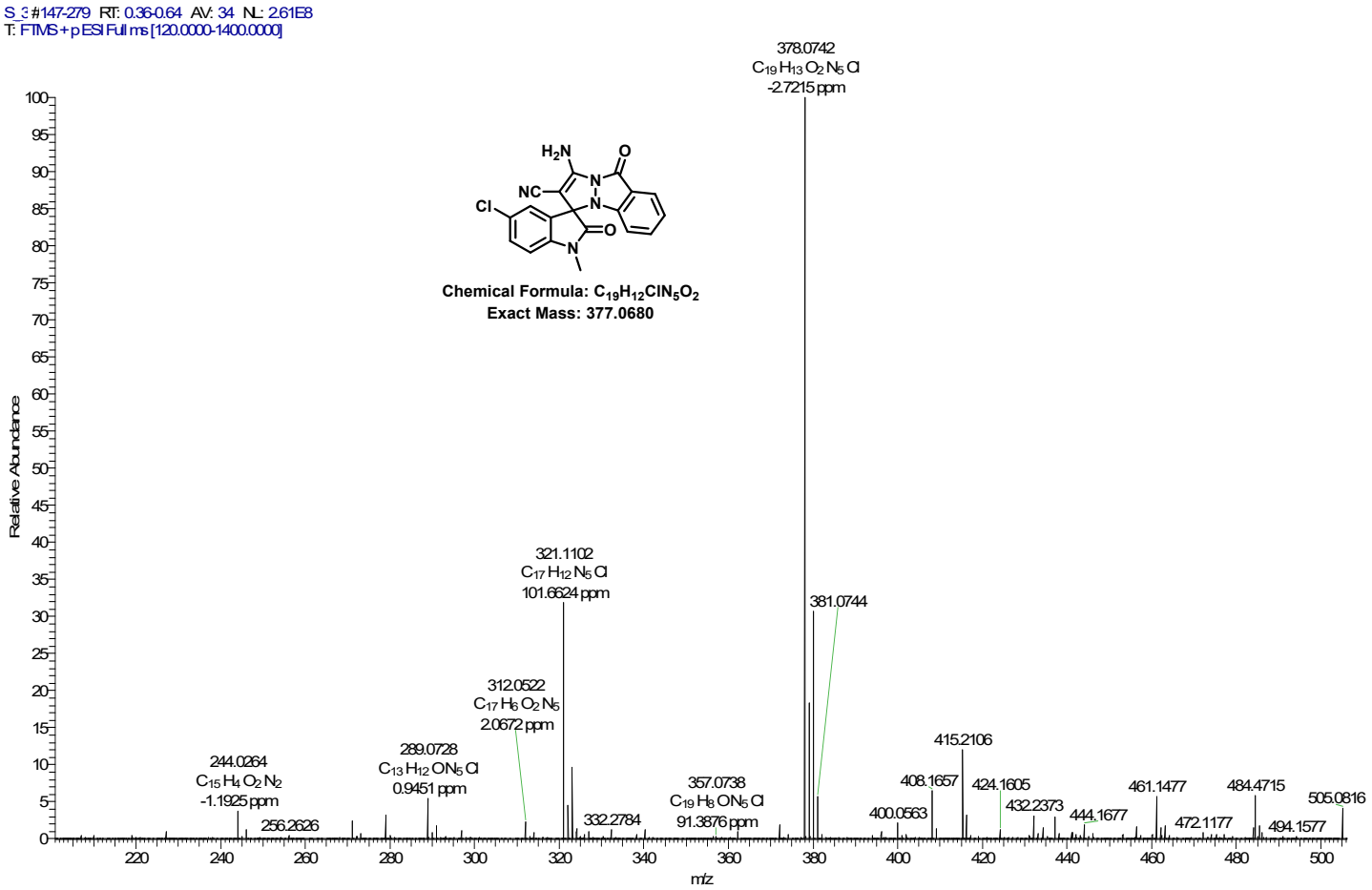


Fig. S9. HRMS of 1'-amino-5-chloro-1-methyl-2,9'-dioxo-9'*H*-spiro[indoline-3,3'-pyrazolo[1,2-a]indazole]-2'-carbonitrile (**3c**):

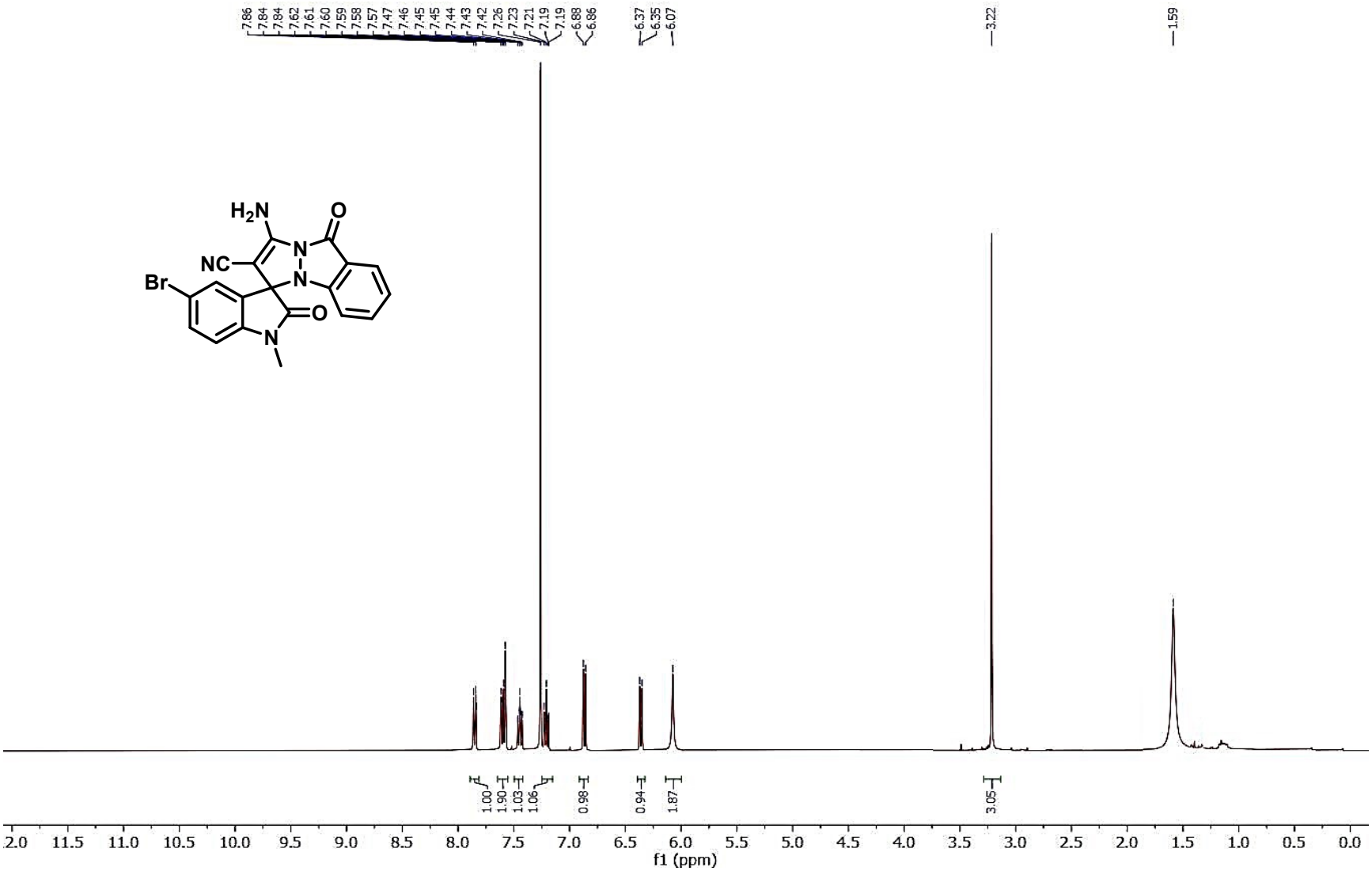


Fig. S10. [1]H NMR of 1'-amino-5-bromo-1-methyl-2,9'-dioxo-9'*H*-spiro[indoline-3,3'-pyrazolo[1,2-a]indazole]-2'-carbonitrile (**3d**):

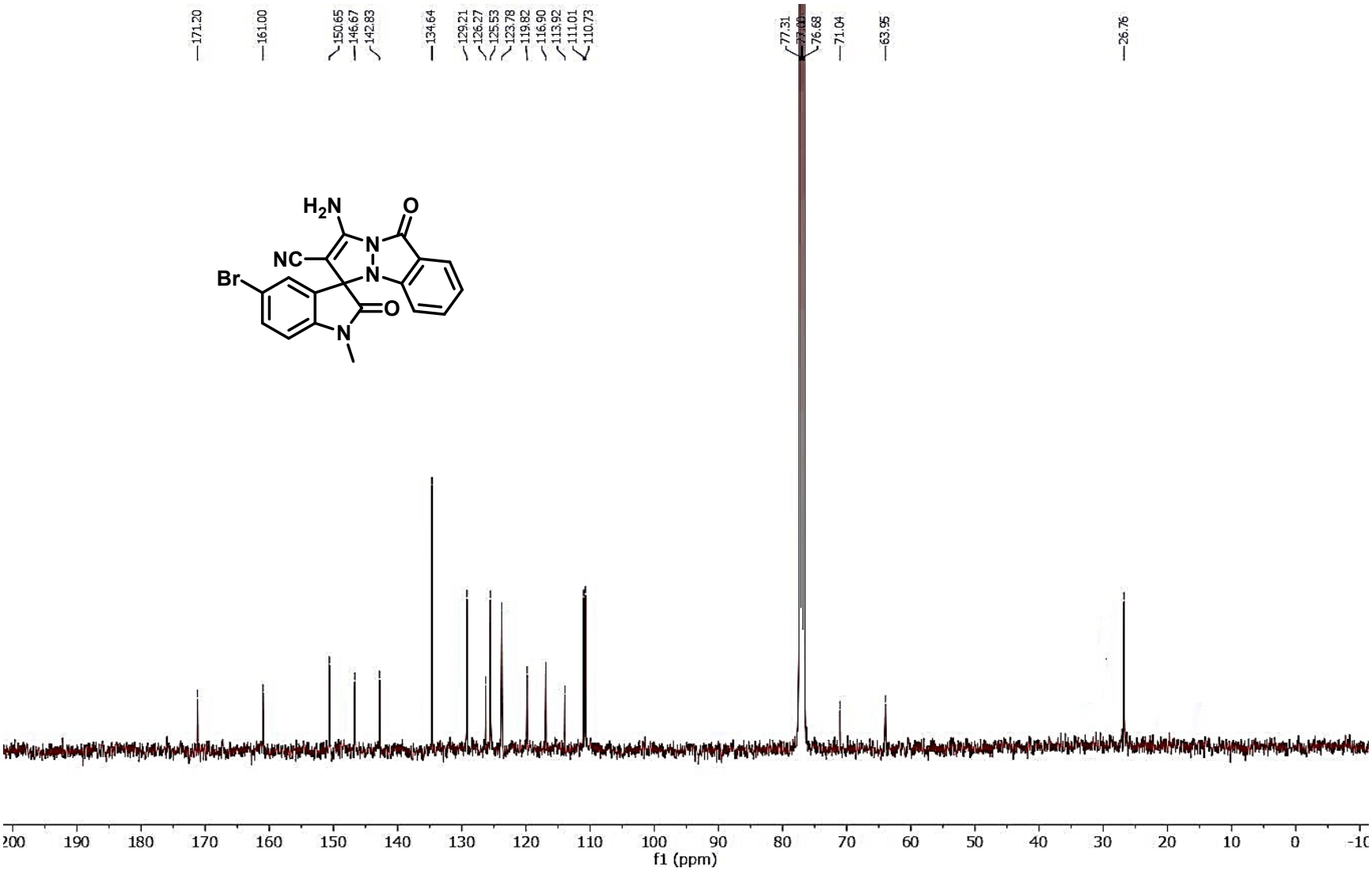


Fig. S11. ^{13}C NMR of 1'-amino-5-bromo-1-methyl-2,9'-dioxo-9'*H*-spiro[indoline-3,3'-pyrazolo[1,2-a]indazole]-2'-carbonitrile (**3d**):

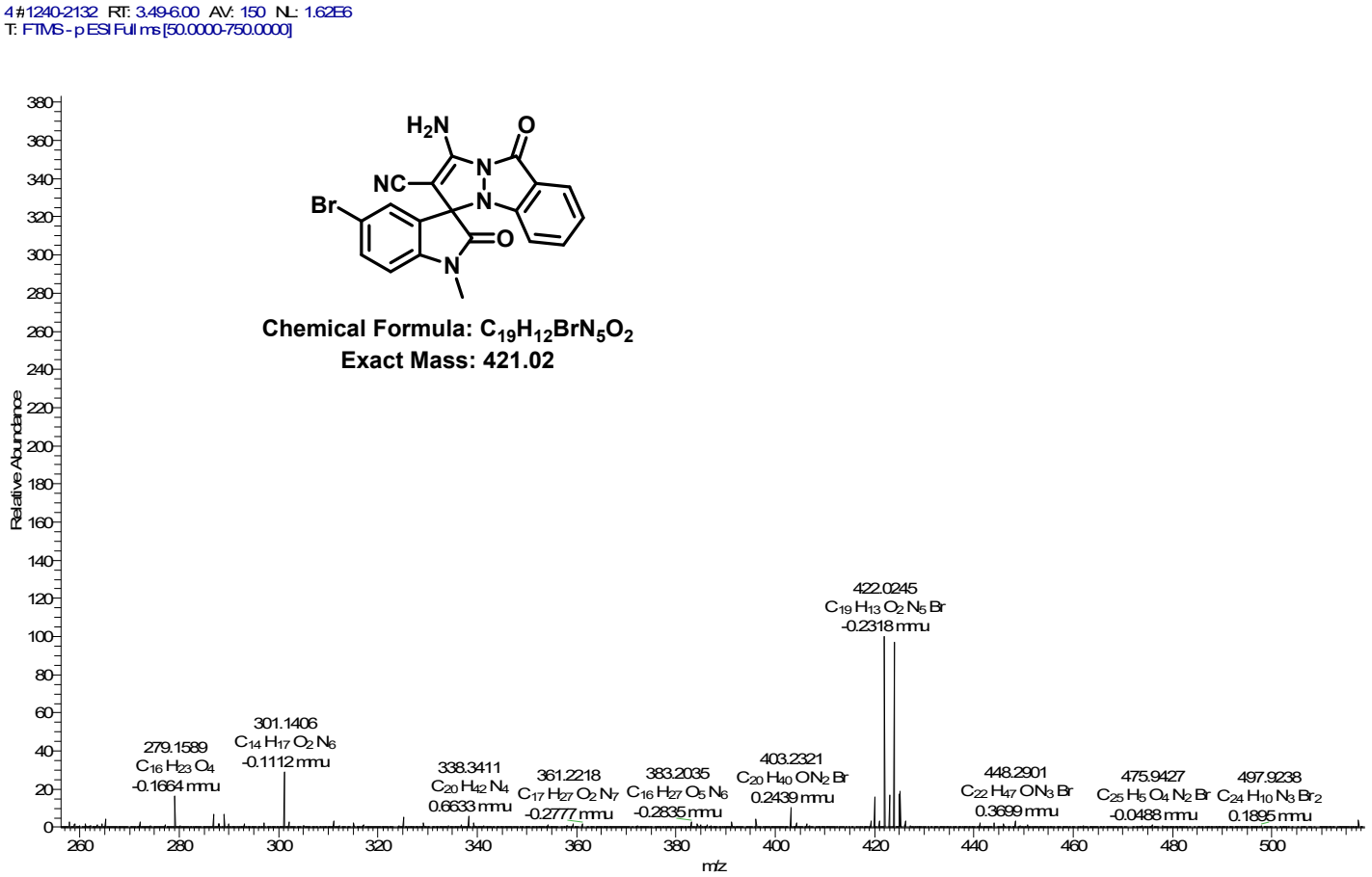


Fig. S12. HRMS of 1'-amino-5-bromo-1-methyl-2,9'-dioxo-9'*H*-spiro[indoline-3,3'-pyrazolo[1,2-a]indazole]-2'-carbonitrile (**3d**):

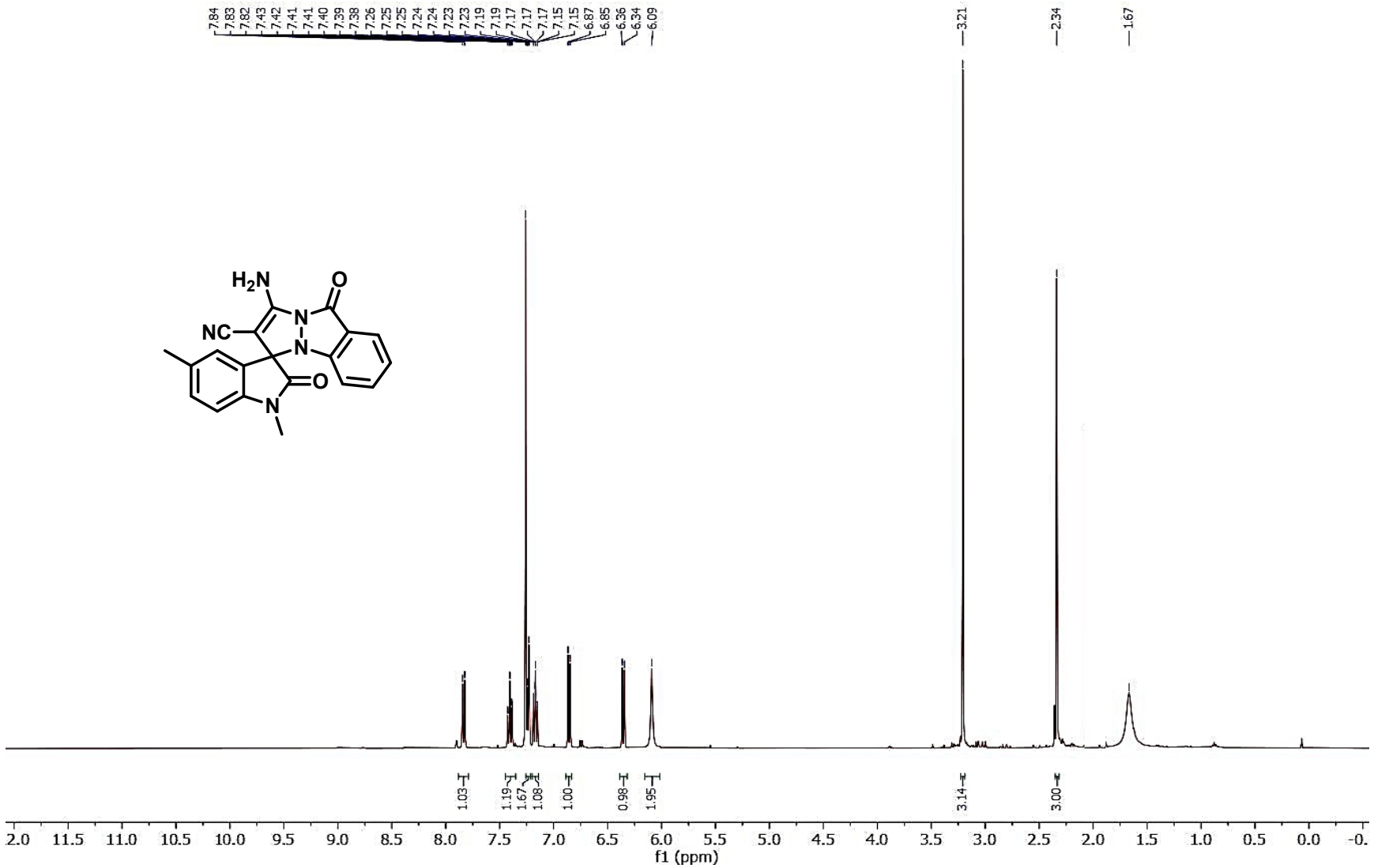


Fig. S13. ^{1}H NMR of 1'-amino-1,5-dimethyl-2,9'-dioxo-9'*H*-spiro[indoline-3,3'-pyrazolo[1,2-a]indazole]-2'-carbonitrile (**3e**):

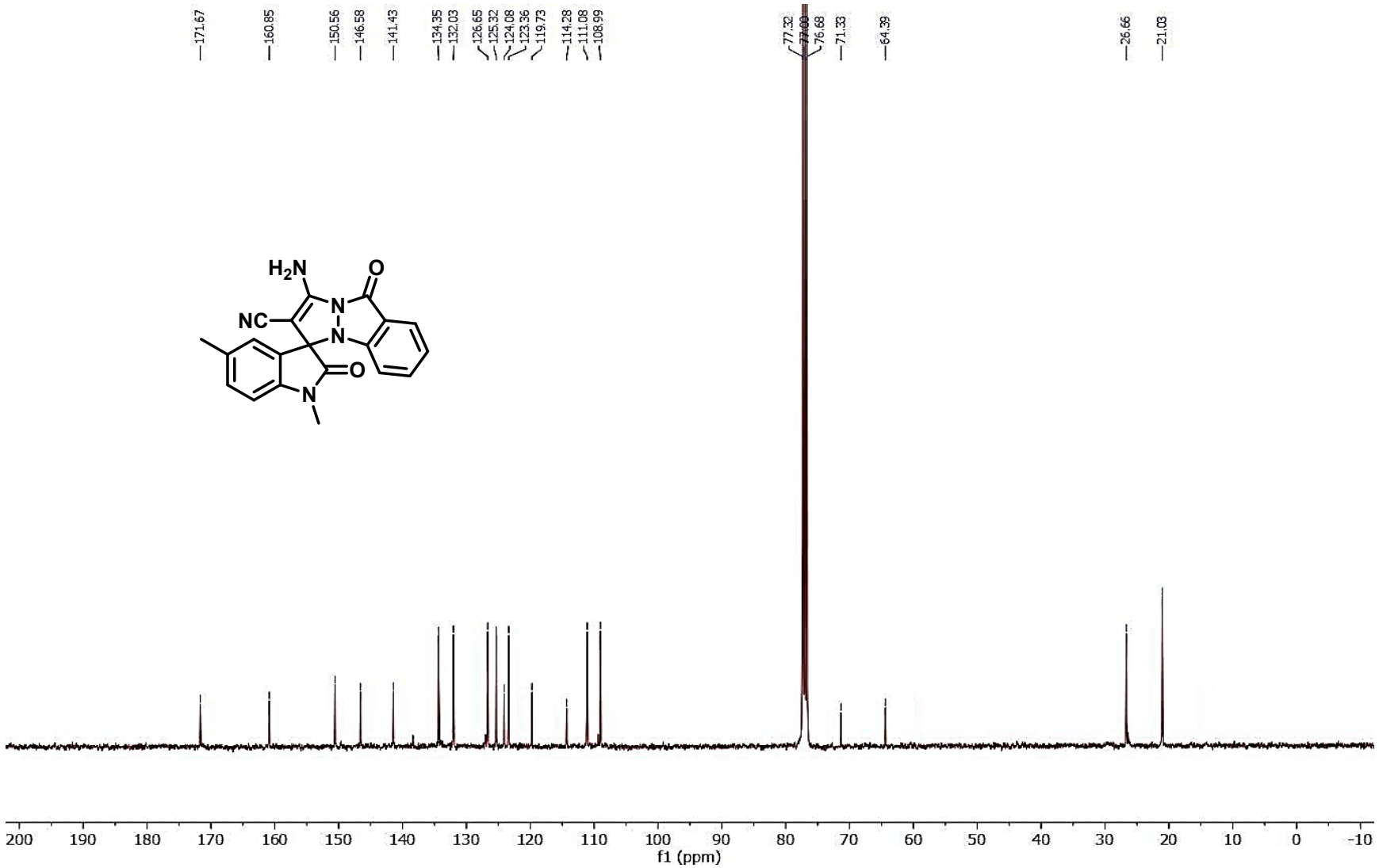


Fig. S14. ^{13}C NMR of 1'-amino-1,5-dimethyl-2,9'-dioxo-9'*H*-spiro[indoline-3,3'-pyrazolo[1,2-a]indazole]-2'-carbonitrile (**3e**):

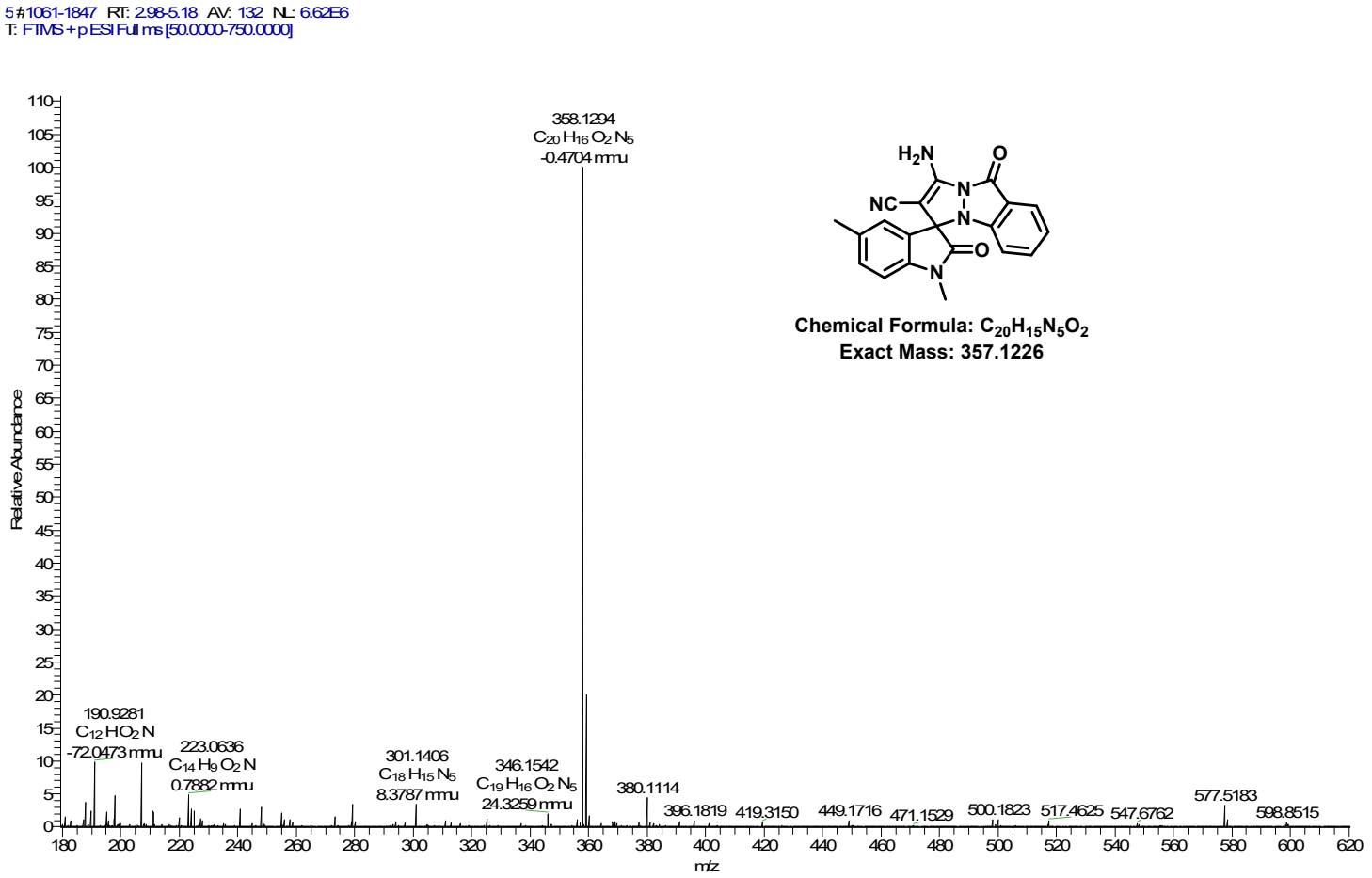


Fig. S15. HRMS of 1'-amino-1,5-dimethyl-2,9'-dioxo-9'*H*-spiro[indoline-3,3'-pyrazolo[1,2-a]indazole]-2'-carbonitrile (**3e**):

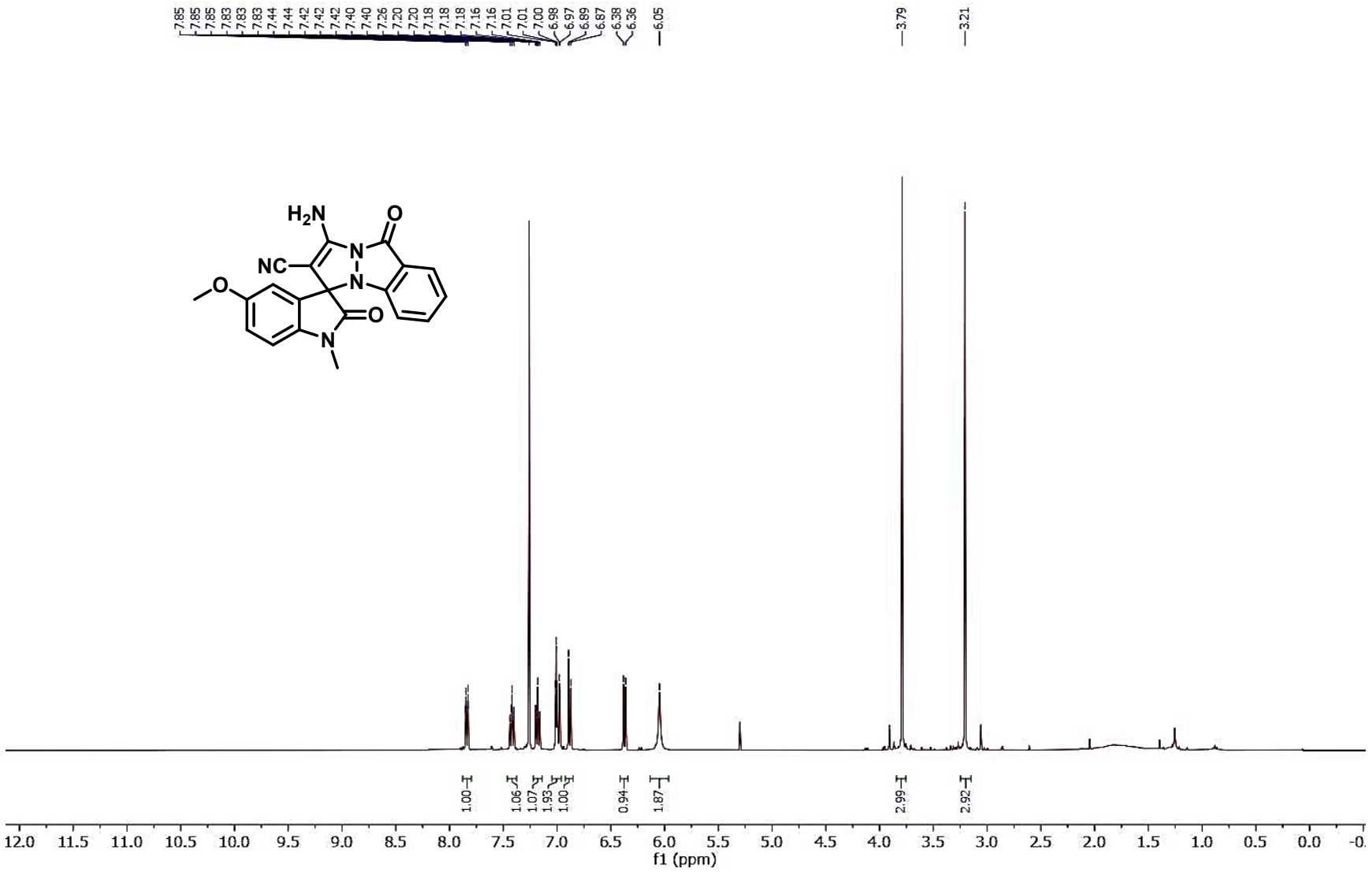


Fig. S16. ^{1}H NMR of 1'-amino-5-methoxy-1-methyl-2,9'-dioxo-9'*H*-spiro[indoline-3,3'-pyrazolo[1,2-a]indazole]-2'-carbonitrile (**3f**):

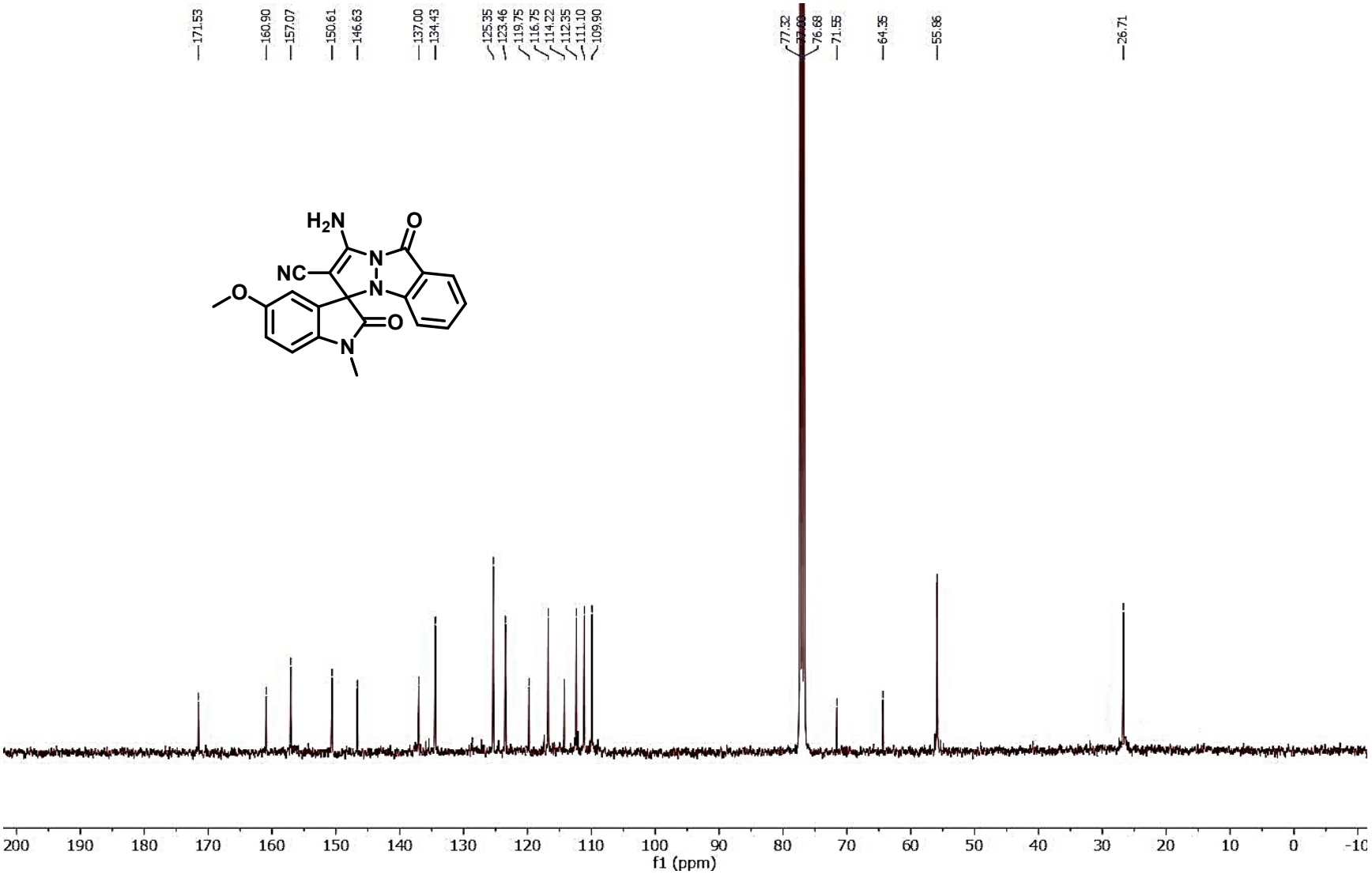


Fig. S17. ^{13}C NMR of 1'-amino-5-methoxy-1-methyl-2,9'-dioxo-9'*H*-spiro[indoline-3,3'-pyrazolo[1,2-a]indazole]-2'-carbonitrile (**3f**):

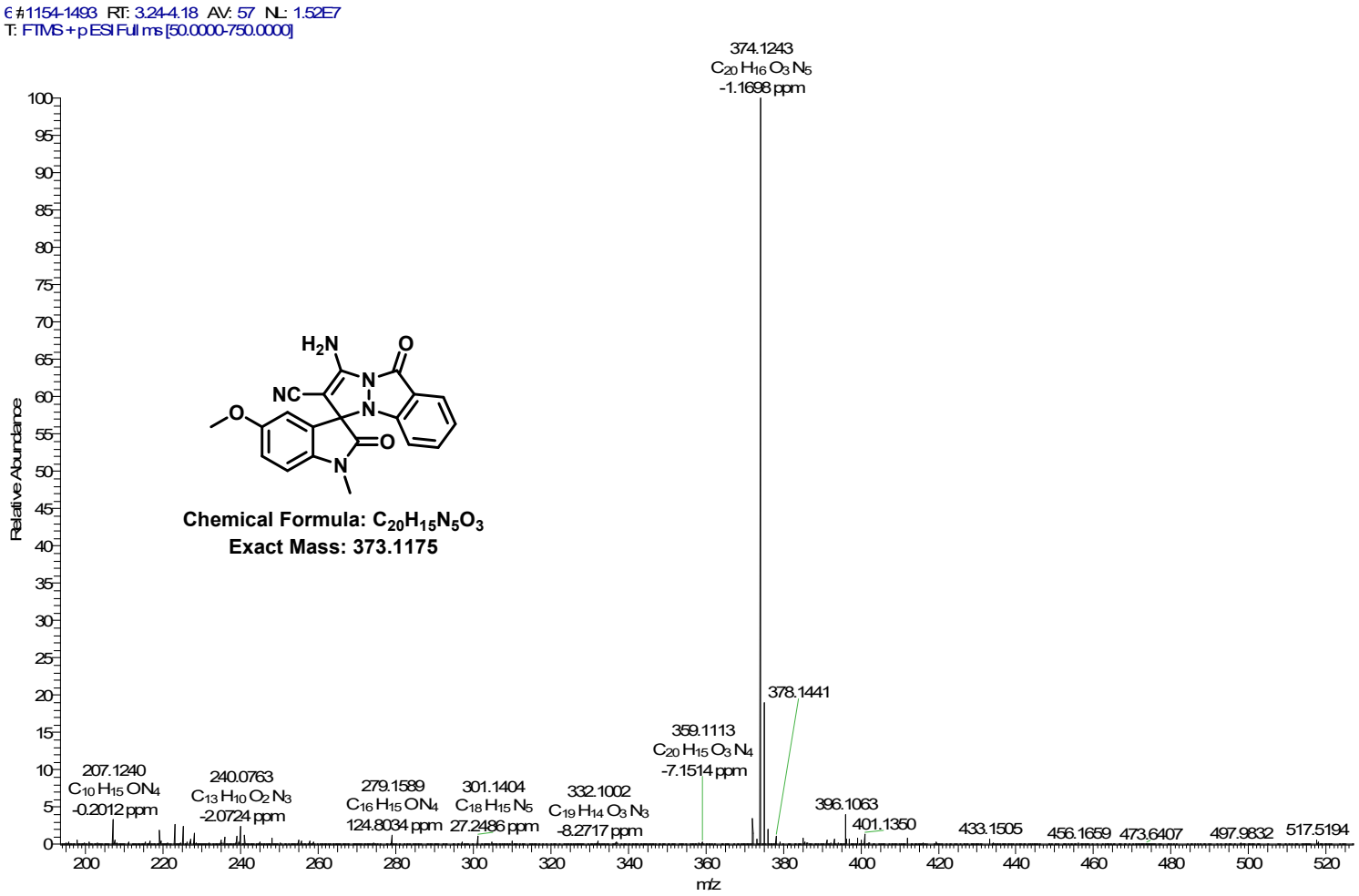


Fig. S18. HRMS of 1'-amino-5-methoxy-1-methyl-2,9'-dioxo-9'*H*-spiro[indoline-3,3'-pyrazolo[1,2-a]indazole]-2'-carbonitrile (**3f**):

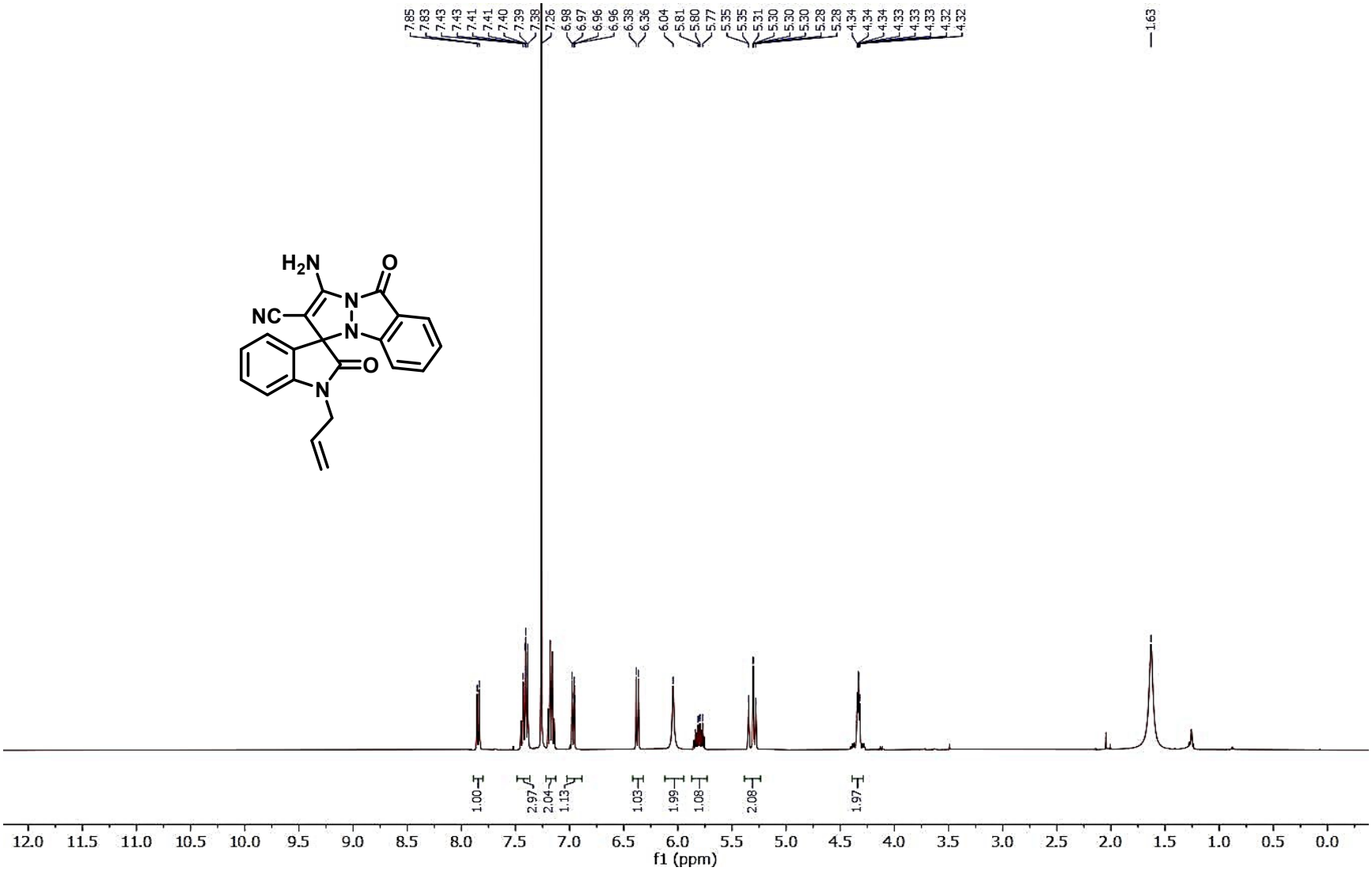


Fig. S19. ^{1}H NMR of 1-allyl-1'-amino-2,9'-dioxo-9'*H*-spiro[indoline-3,3'-pyrazolo[1,2-a]indazole]-2'-carbonitrile (**3g**):

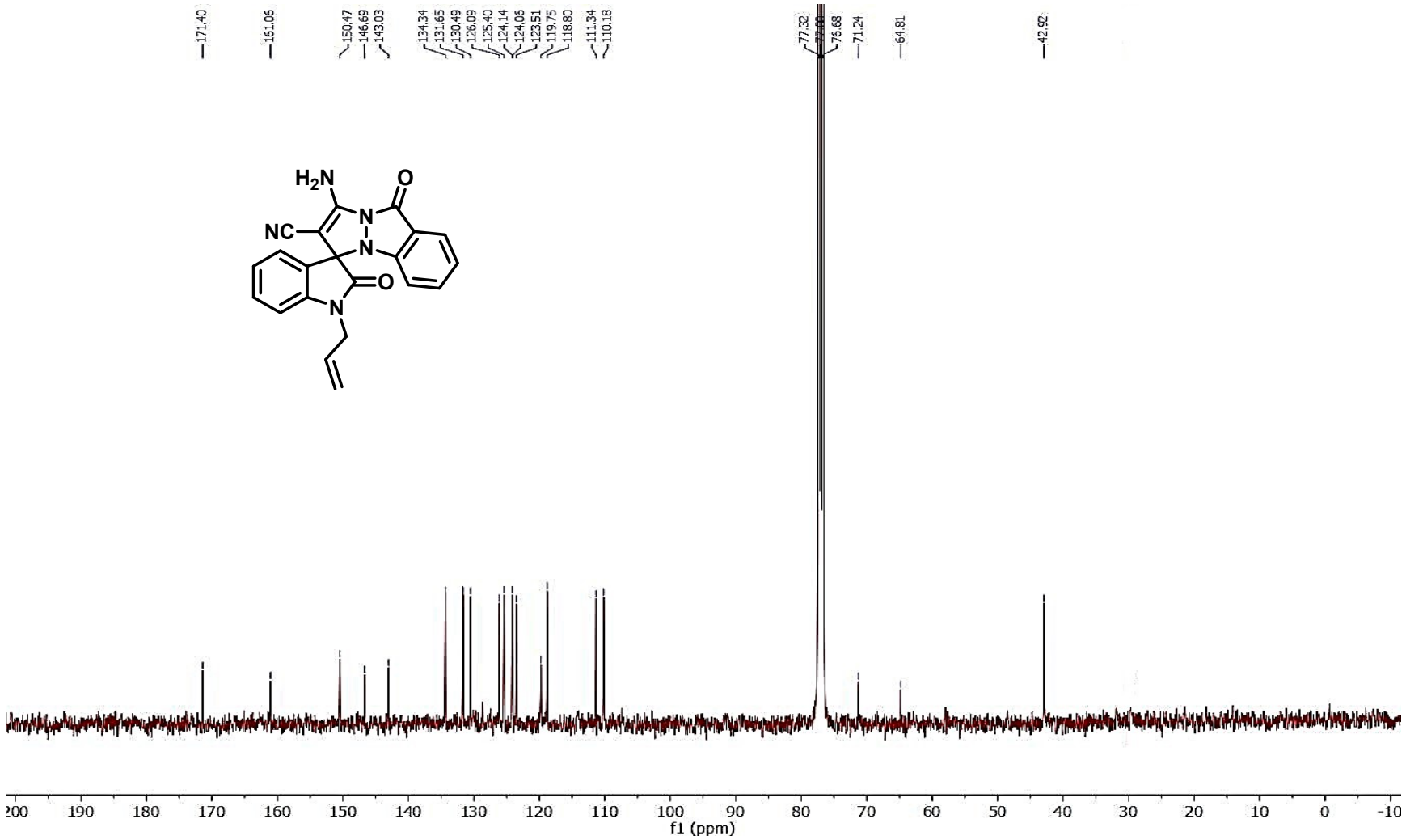


Fig. S20. ^{13}C NMR of 1-allyl-1'-amino-2,9'-dioxo-9'*H*-spiro[indoline-3,3'-pyrazolo[1,2-a]indazole]-2'-carbonitrile (**3g**):

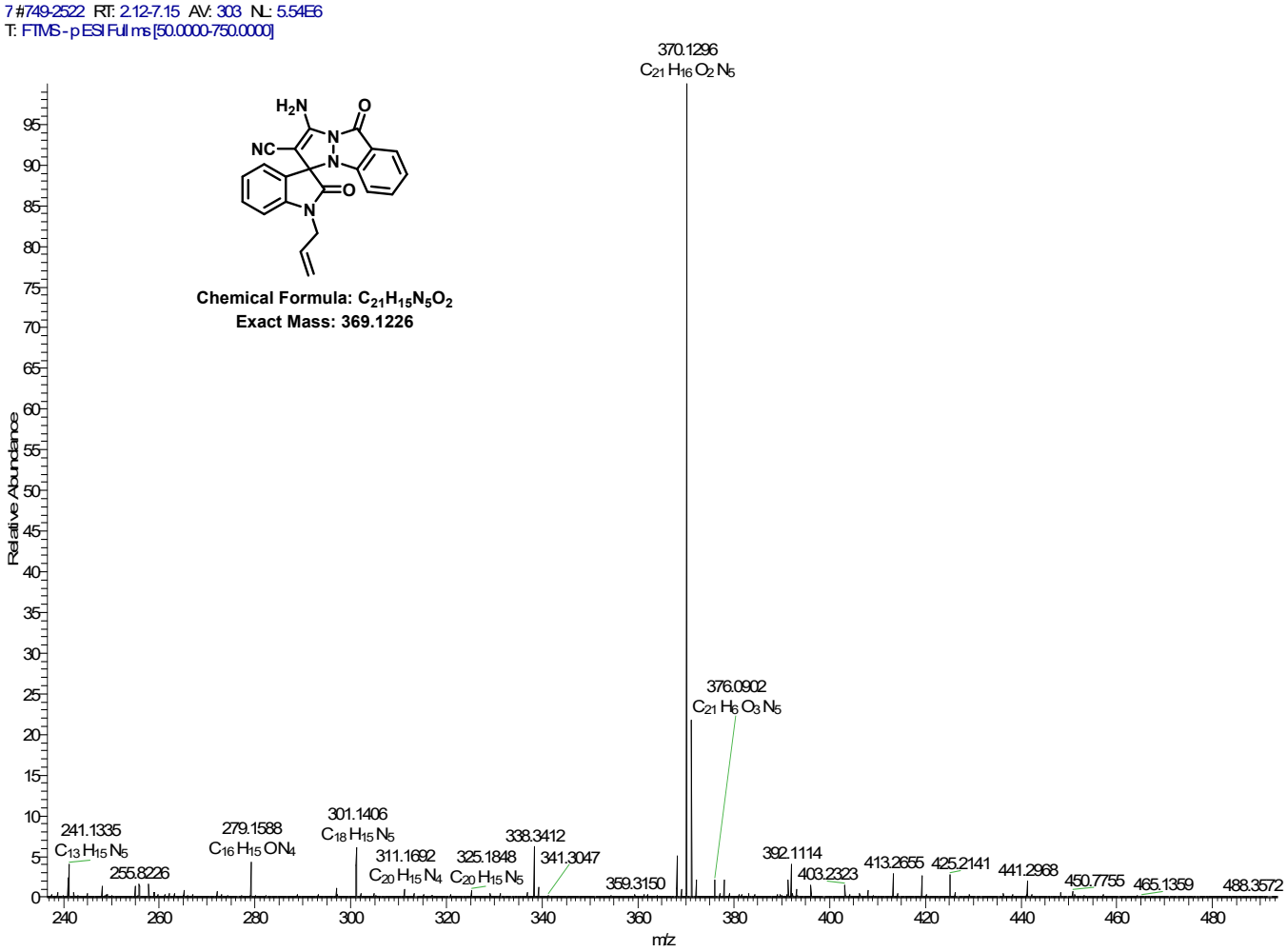


Fig. S21. HRMS of 1-allyl-1'-amino-2,9'-dioxo-9'*H*-spiro[indoline-3,3'-pyrazolo[1,2-a]indazole]-2'-carbonitrile (**3g**):

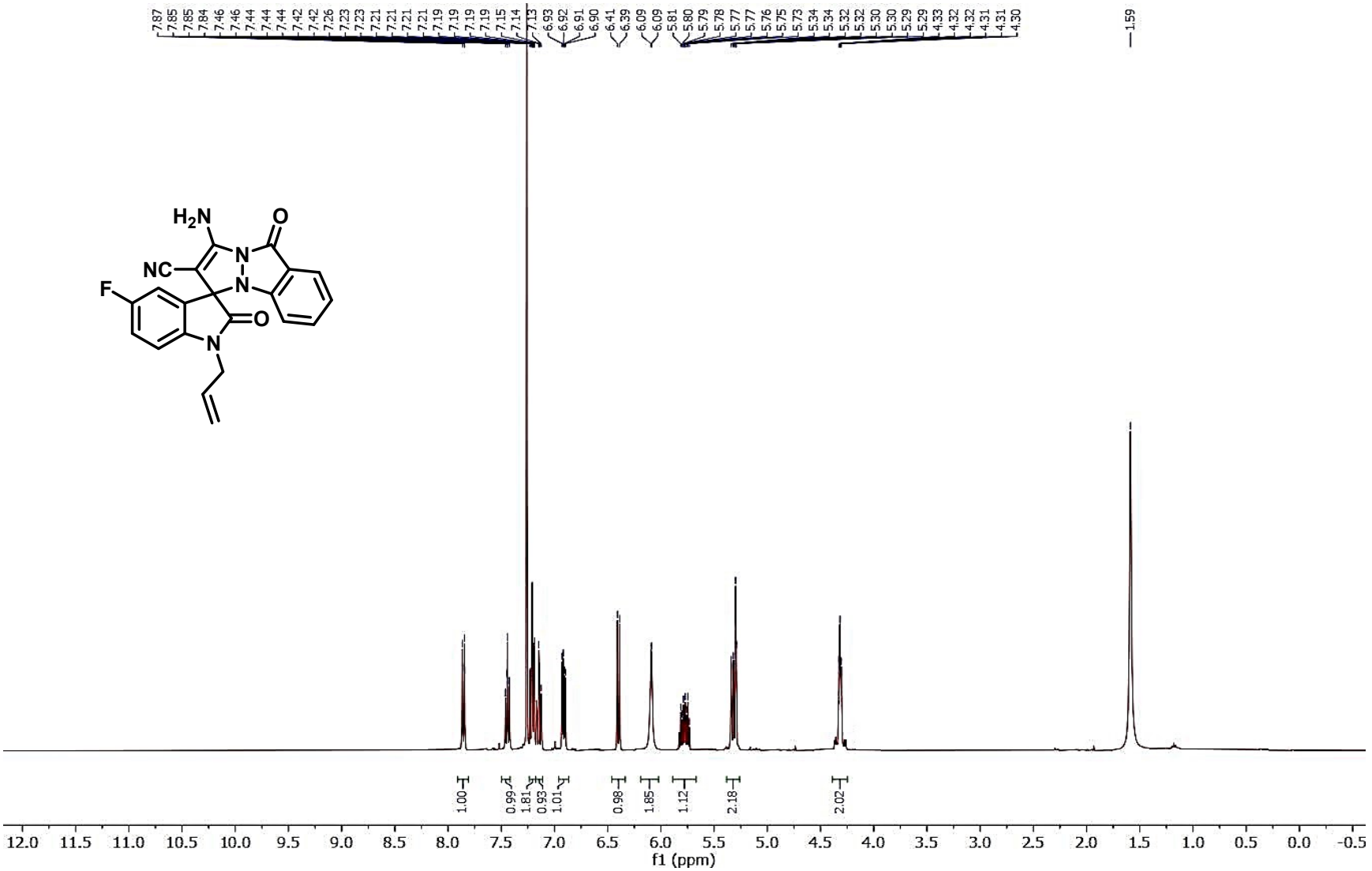


Fig. S22. [1]H NMR of 1-allyl-1'-amino-5-fluoro-2,9'-dioxo-9'*H*-spiro[indoline-3,3'-pyrazolo[1,2-a]indazole]-2'-carbonitrile (**3h**):

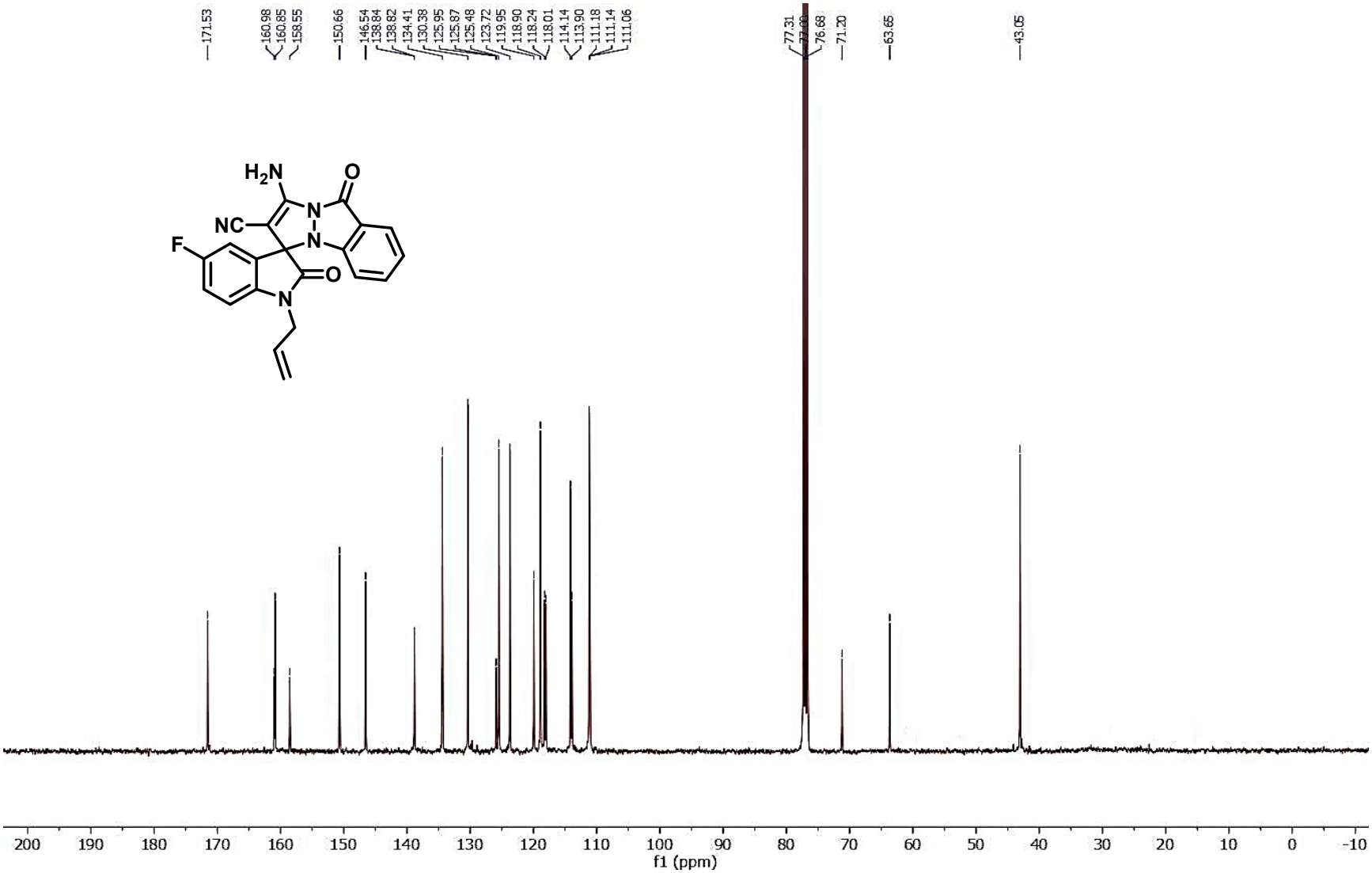


Fig. S23. ^{13}C NMR of 1-allyl-1'-amino-5-fluoro-2,9'-dioxo-9'*H*-spiro[indoline-3,3'-pyrazolo[1,2-a]indazole]-2'-carbonitrile (**3h**):

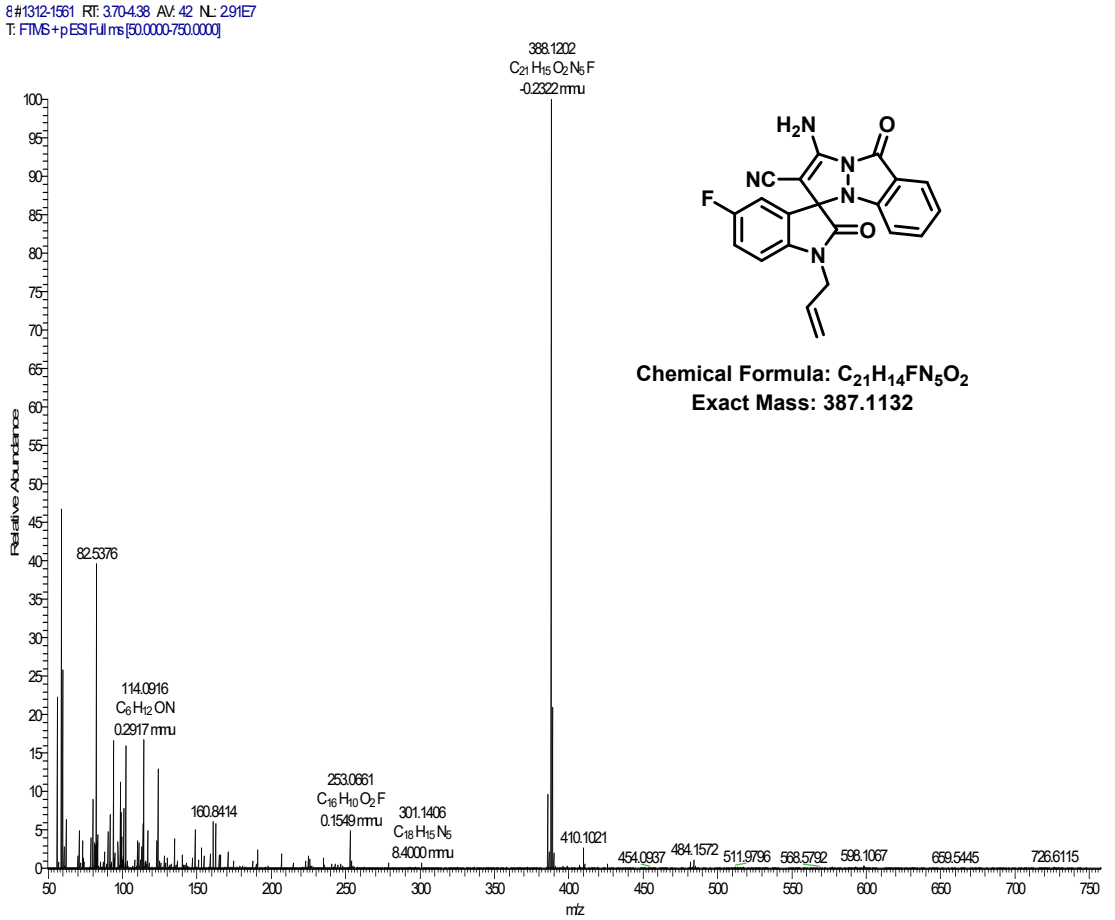


Fig. S24. HRMS of 1-allyl-1'-amino-5-fluoro-2,9'-dioxo-9'*H*-spiro[indoline-3,3'-pyrazolo[1,2-a]indazole]-2'-carbonitrile (**3h**):

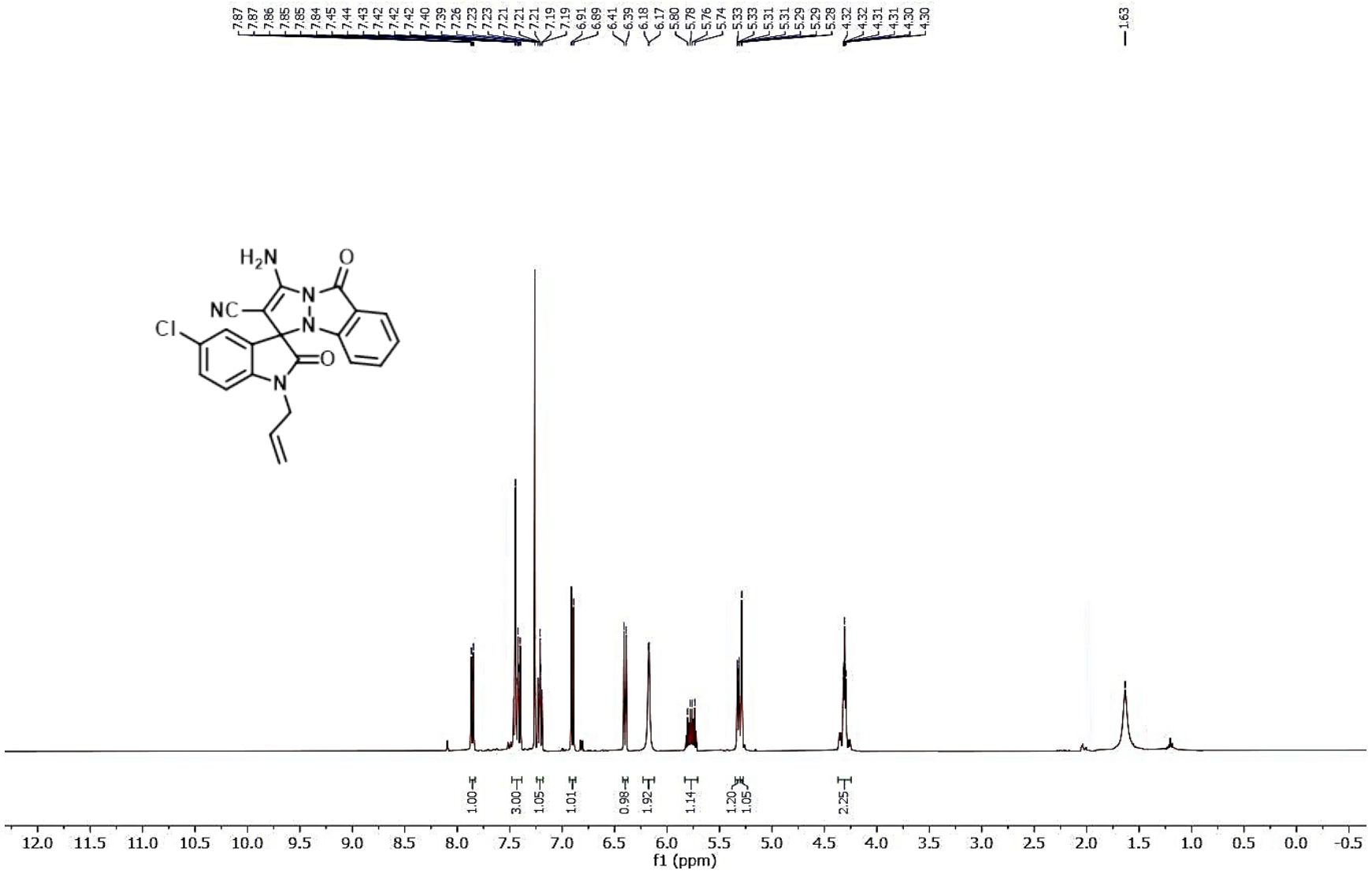


Fig. S25. ^{1}H NMR of 1-allyl-1'-amino-5-chloro-2,9'-dioxo-9'*H*-spiro[indoline-3,3'-pyrazolo[1,2-a]indazole]-2'-carbonitrile (**3i**):

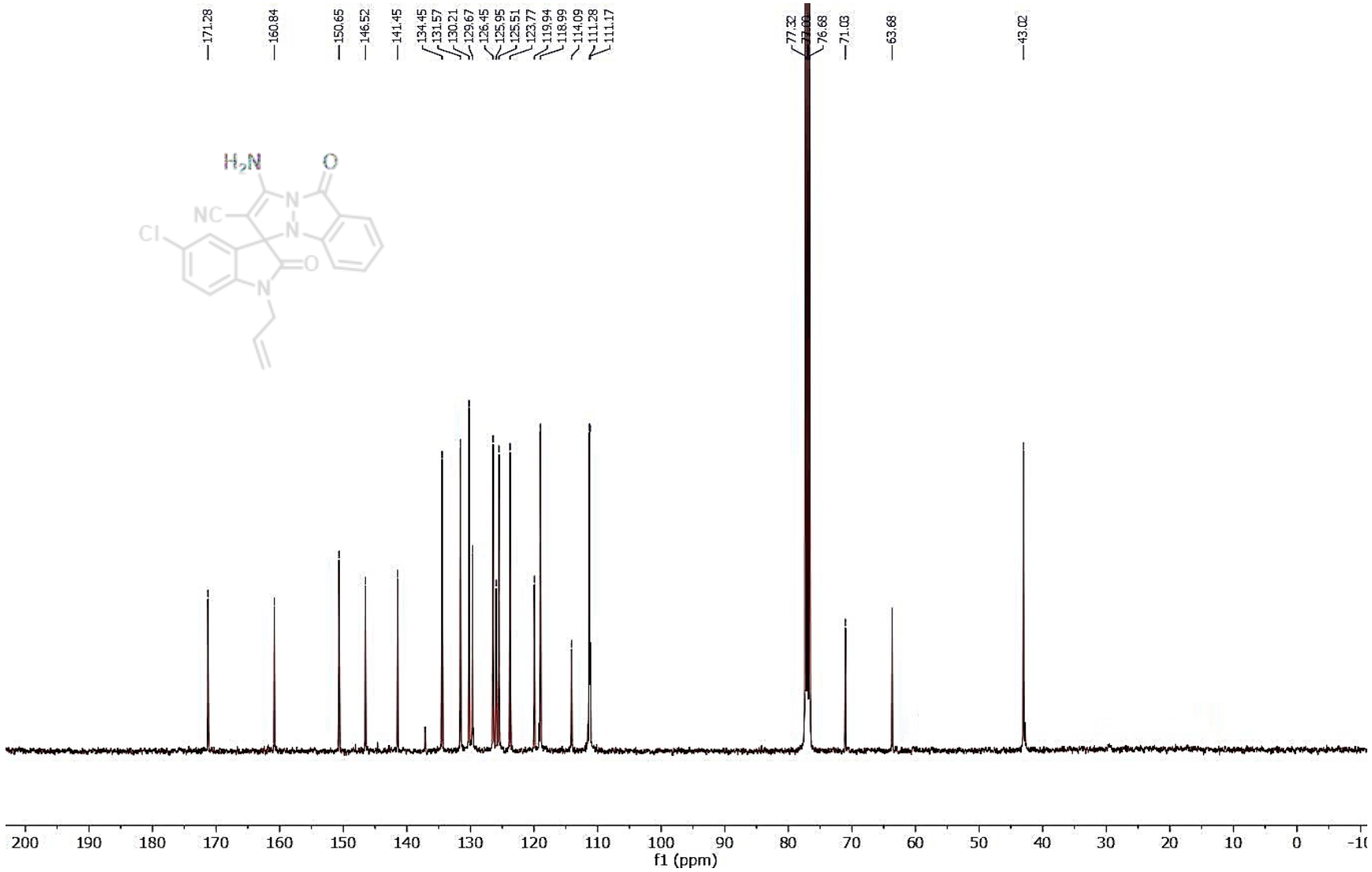


Fig. S26. ^{13}C NMR of 1-allyl-1'-amino-5-chloro-2,9'-dioxo-9'*H*-spiro[indoline-3,3'-pyrazolo[1,2-a]indazole]-2'-carbonitrile (**3i**):

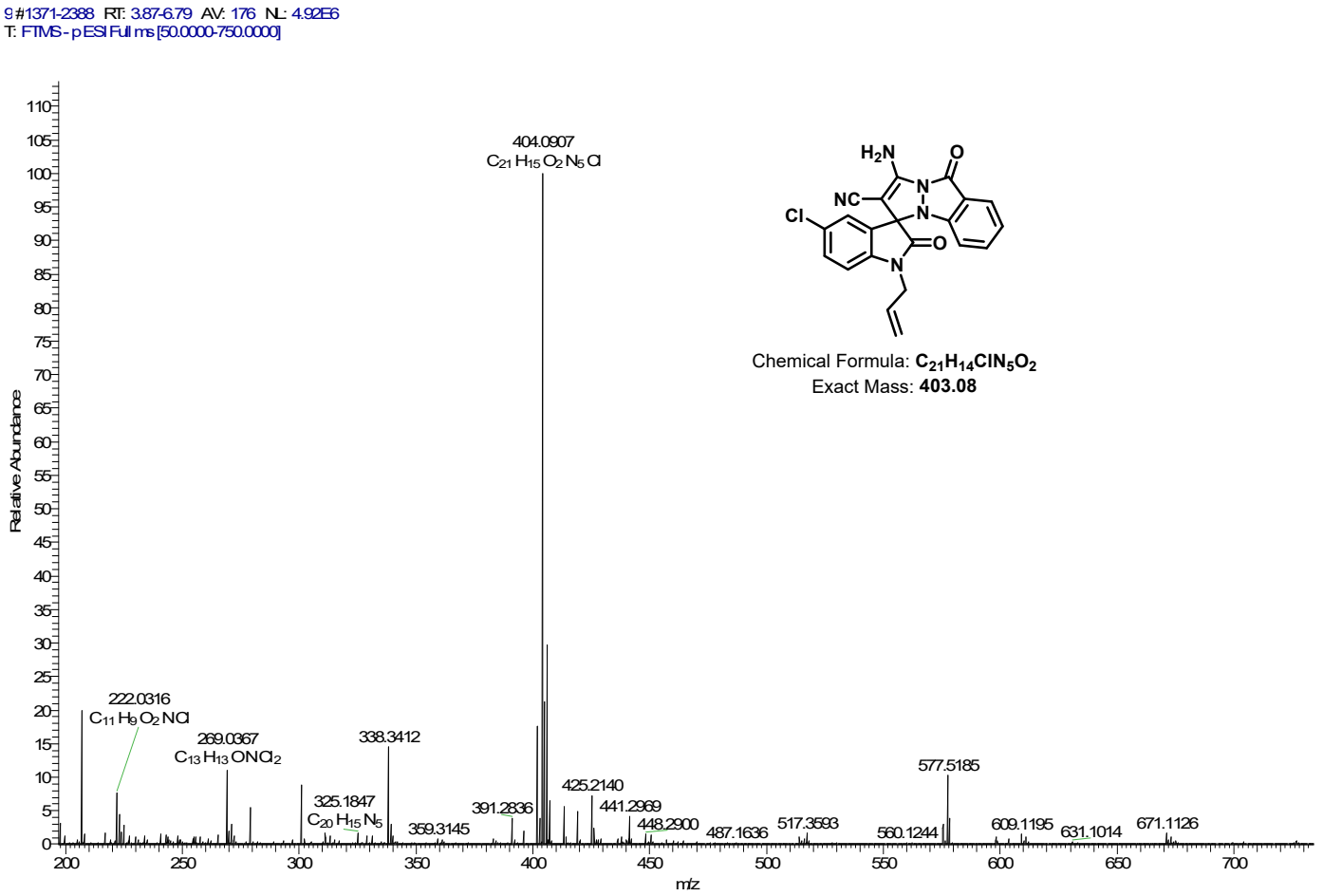


Fig. S27. HRMS of 1-allyl-1'-amino-5-chloro-2,9'-dioxo-9'*H*-spiro[indoline-3,3'-pyrazolo[1,2-a]indazole]-2'-carbonitrile (**3i**):

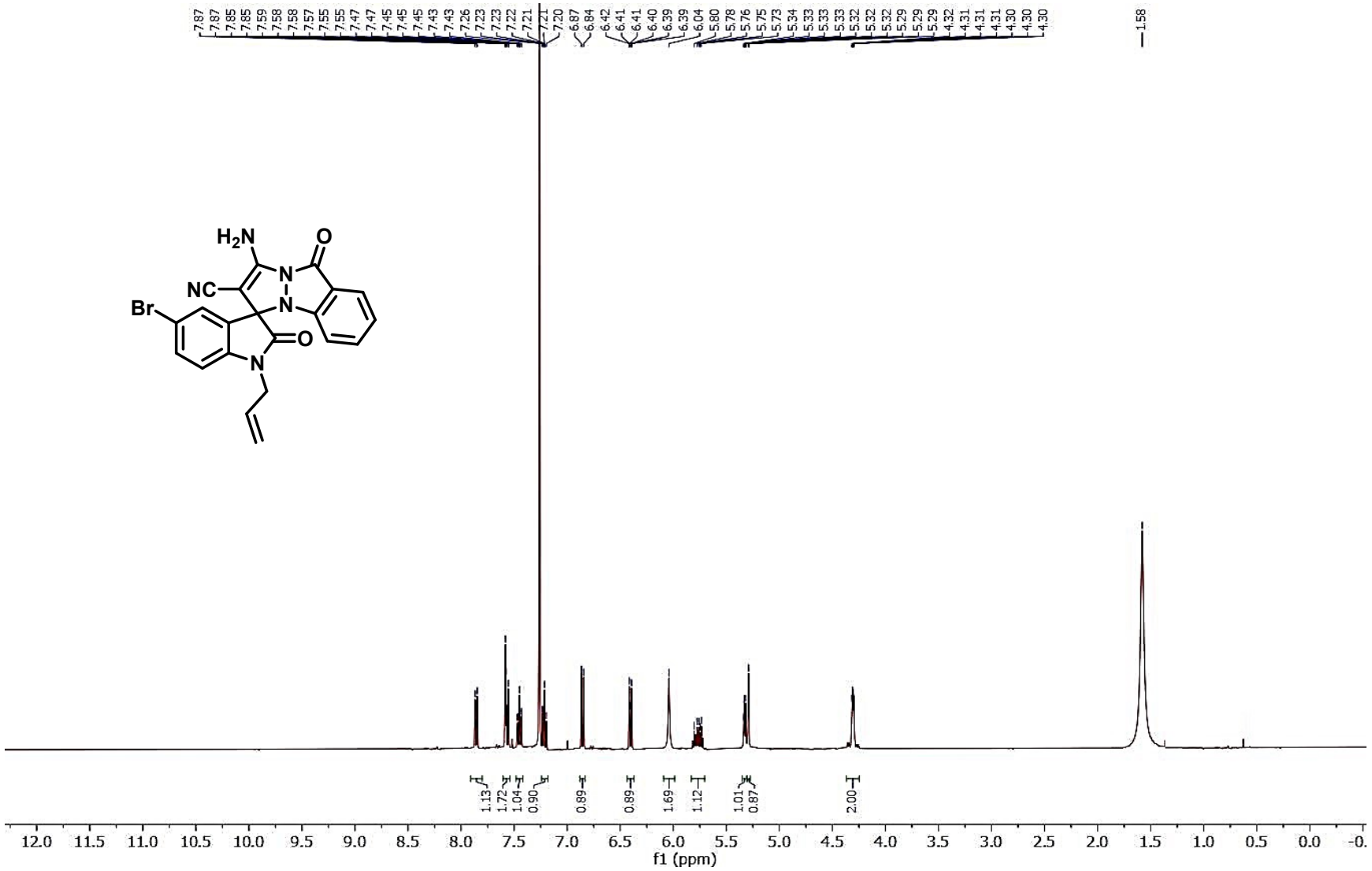


Fig. S28. ^{1}H NMR of 1-allyl-1'-amino-5-bromo-2,9'-dioxo-9'H-spiro[indoline-3,3'-pyrazolo[1,2-a]indazole]-2'-carbonitrile (**3j**):

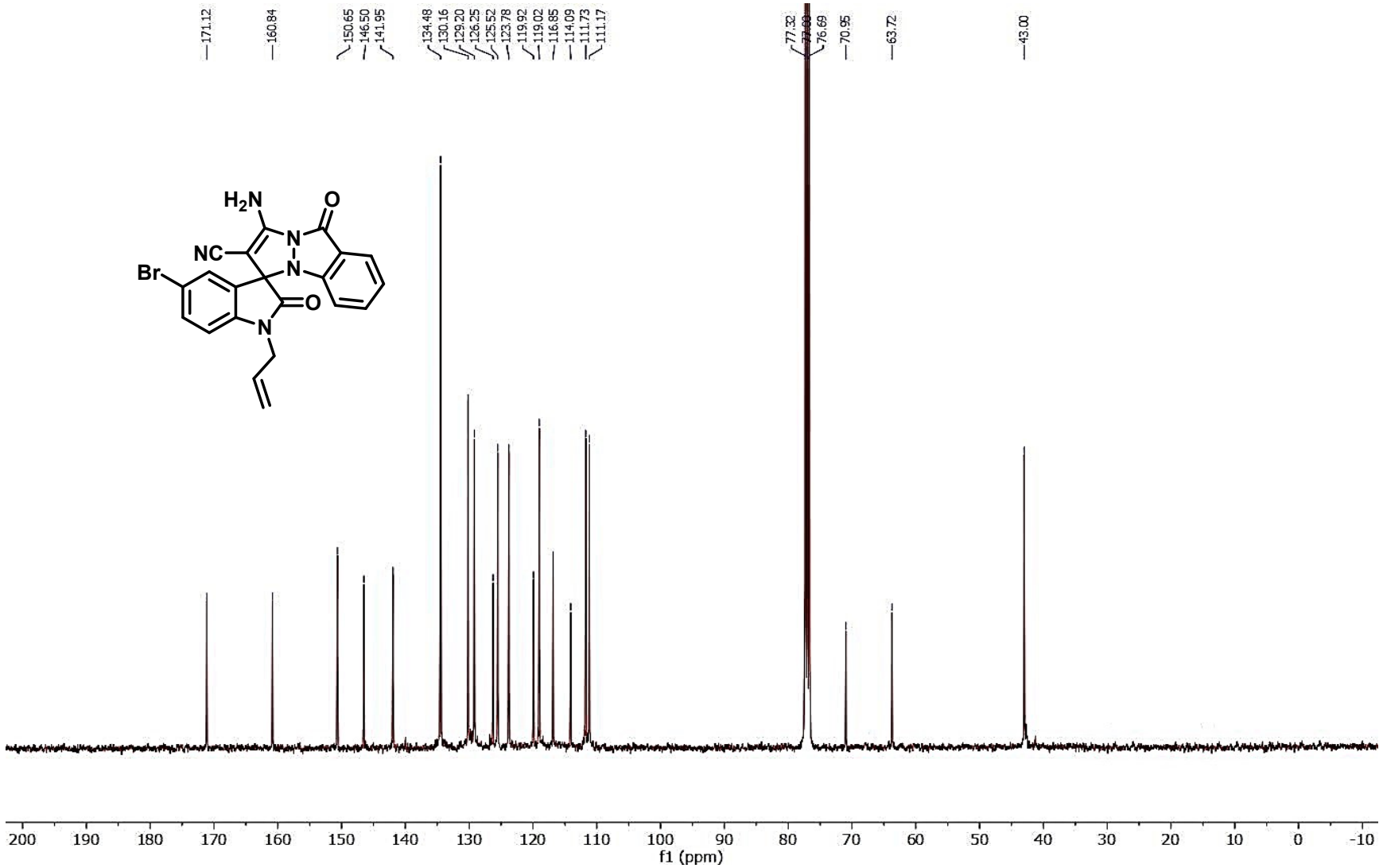


Fig. S29. ^{13}C NMR of 1-allyl-1'-amino-5-bromo-2,9'-dioxo-9'*H*-spiro[indoline-3,3'-pyrazolo[1,2-a]indazole]-2'-carbonitrile (**3j**):

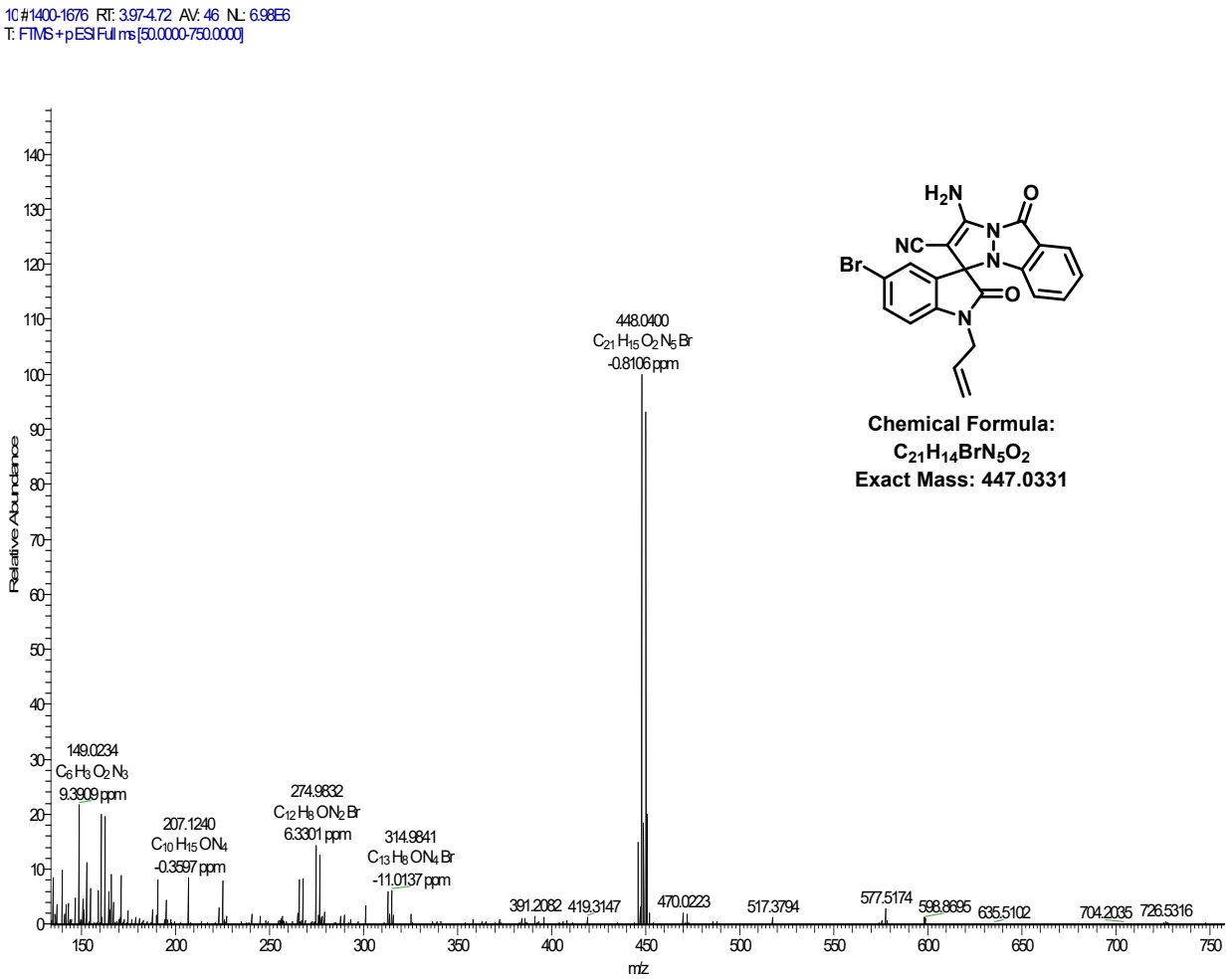


Fig. S30. HRMS of 1-allyl-1'-amino-5-bromo-2,9'-dioxo-9'*H*-spiro[indoline-3,3'-pyrazolo[1,2-a]indazole]-2'-carbonitrile (**3j**):

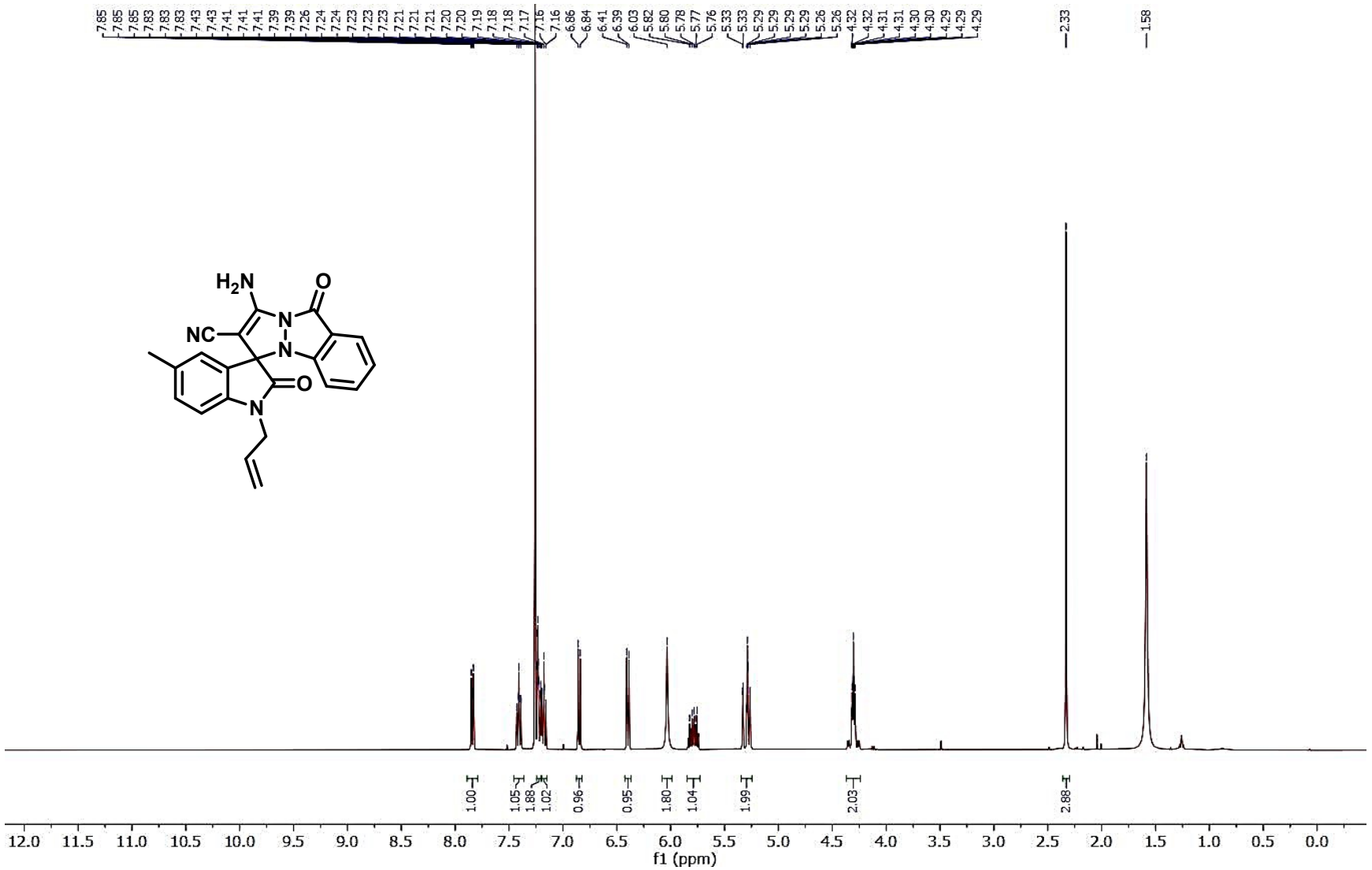


Fig. S31. [1]H NMR of 1-allyl-1'-amino-5-methyl-2,9'-dioxo-9'*H*-spiro[indoline-3,3'-pyrazolo[1,2-a]indazole]-2'-carbonitrile (**3k**):

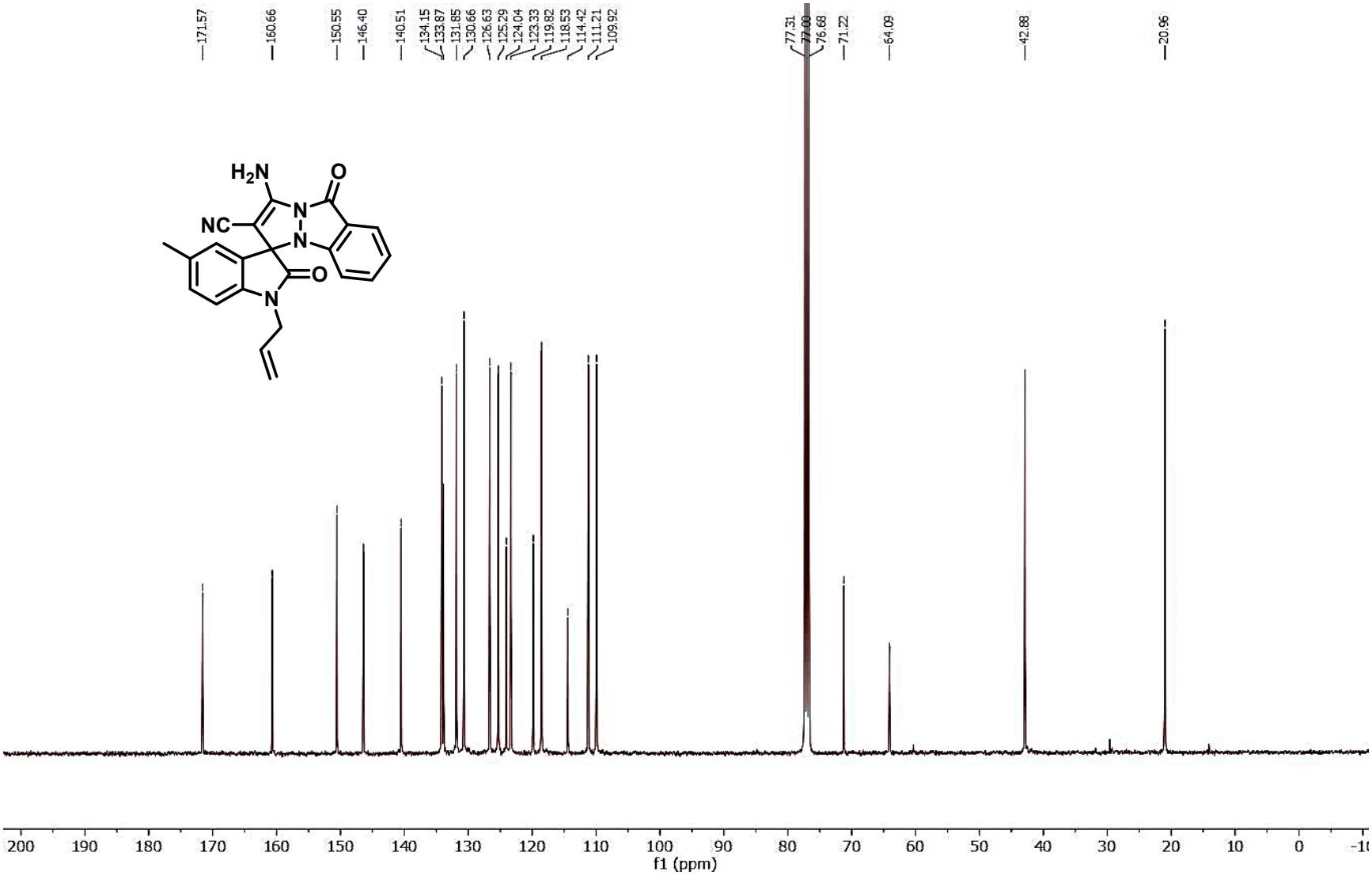


Fig. S32. ^{13}C NMR of 1-allyl-1'-amino-5-methyl-2,9'-dioxo-9'*H*-spiro[indoline-3,3'-pyrazolo[1,2-a]indazole]-2'-carbonitrile (**3k**):

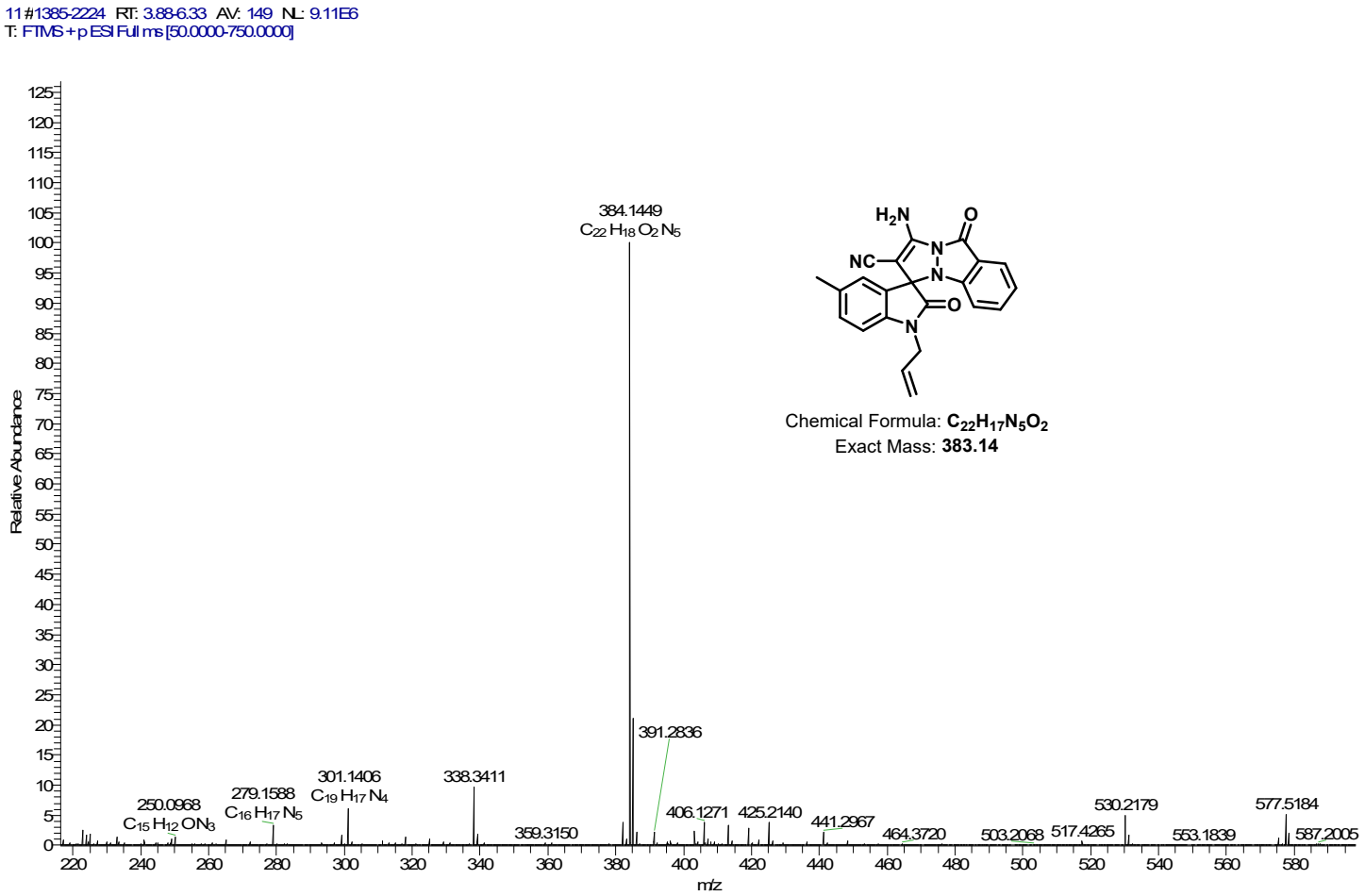


Fig. S33. HRMS of 1-allyl-1'-amino-5-methyl-2,9'-dioxo-9'*H*-spiro[indoline-3,3'-pyrazolo[1,2-a]indazole]-2'-carbonitrile (**3k**):

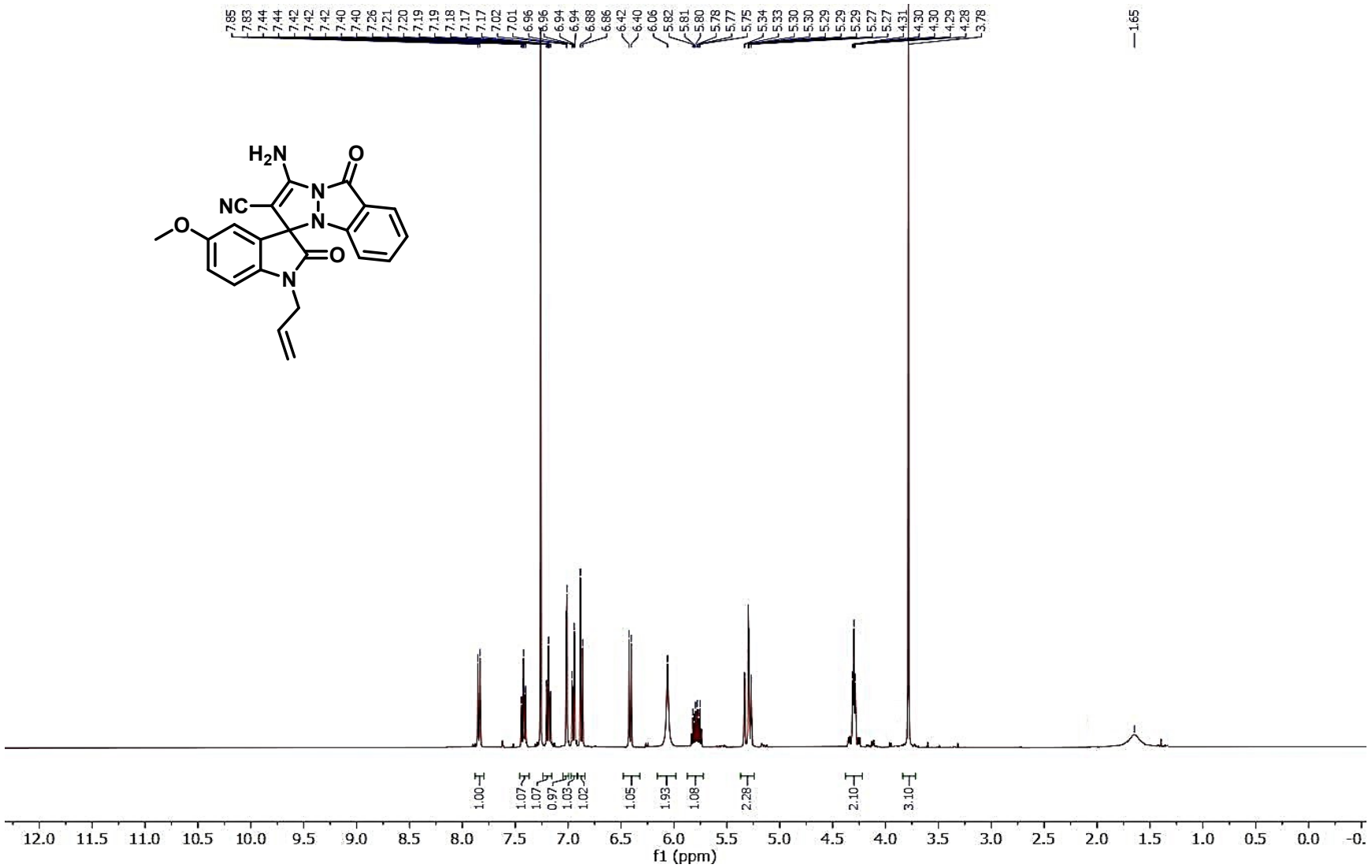


Fig. S34. [1]H NMR of 1-allyl-1'-amino-5-methoxy-2,9'-dioxo-9'*H*-spiro[indoline-3,3'-pyrazolo[1,2-a]indazole]-2'-carbonitrile (**3l**):

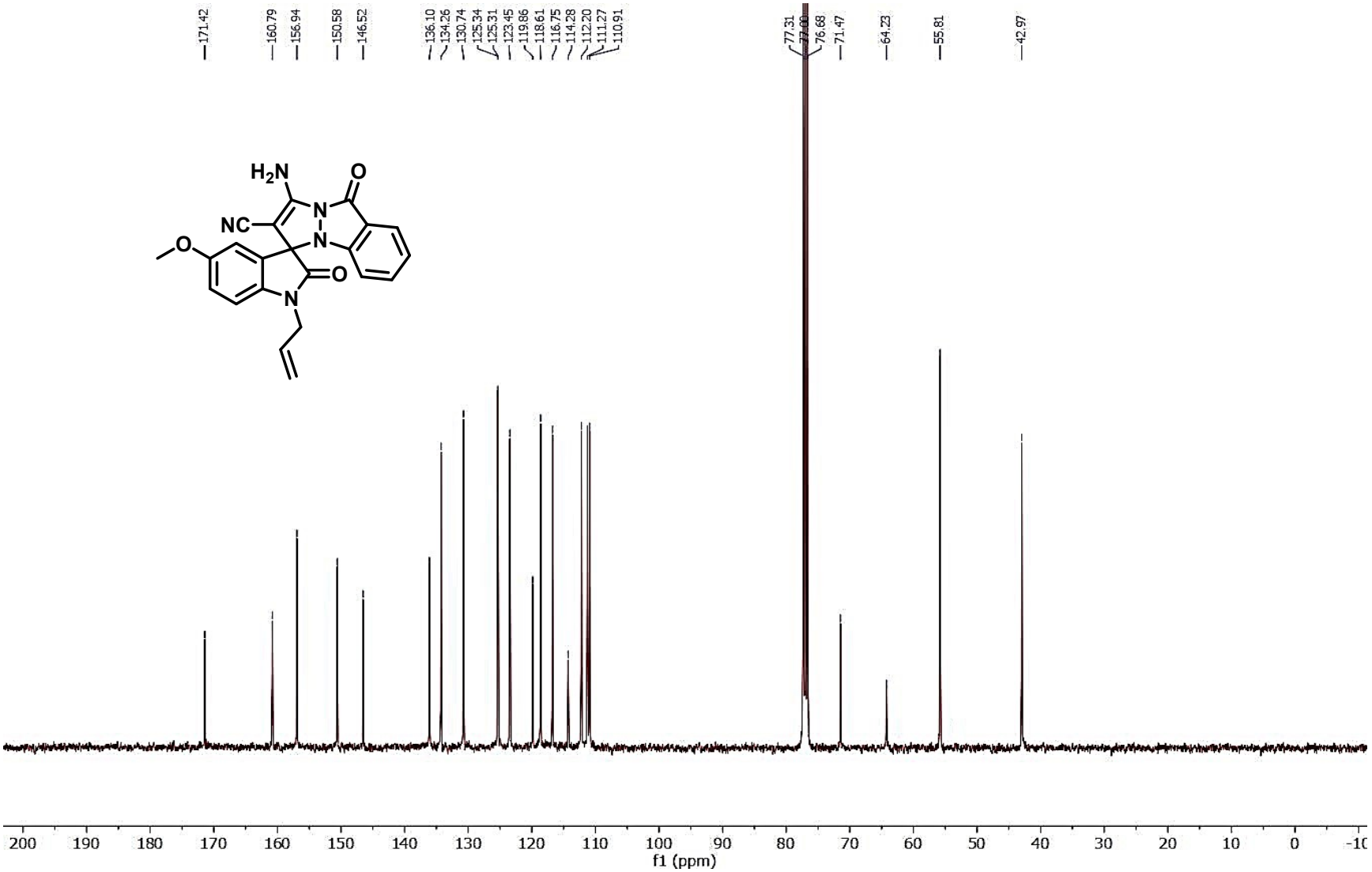


Fig. S35. ^{13}C NMR of 1-allyl-1'-amino-5-methoxy-2,9'-dioxo-9'*H*-spiro[indoline-3,3'-pyrazolo[1,2-a]indazole]-2'-carbonitrile (**3l**):

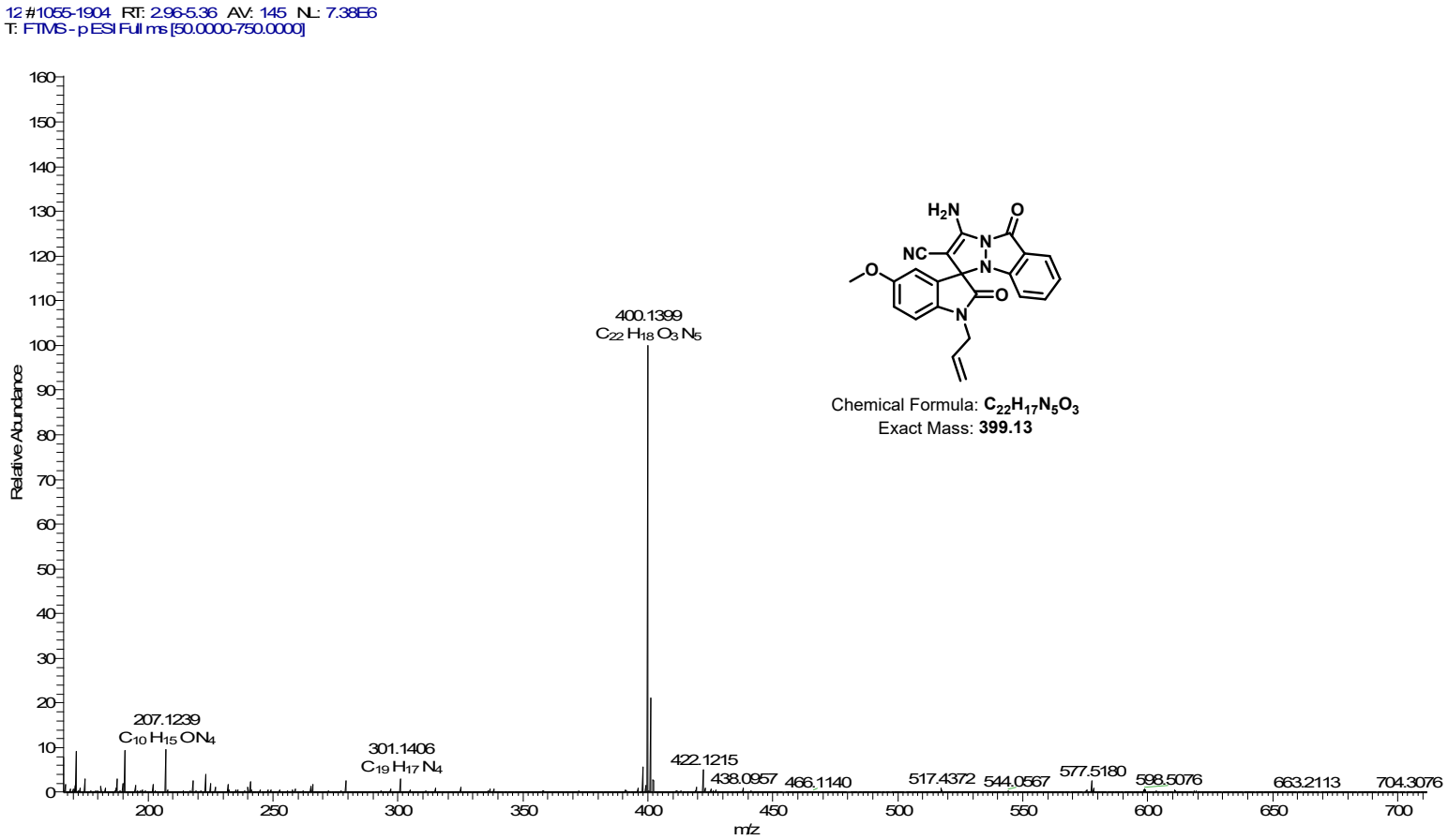


Fig. S36. HRMS of 1-allyl-1'-amino-5-methoxy-2,9'-dioxo-9'*H*-spiro[indoline-3,3'-pyrazolo[1,2-a]indazole]-2'-carbonitrile (**3l**):

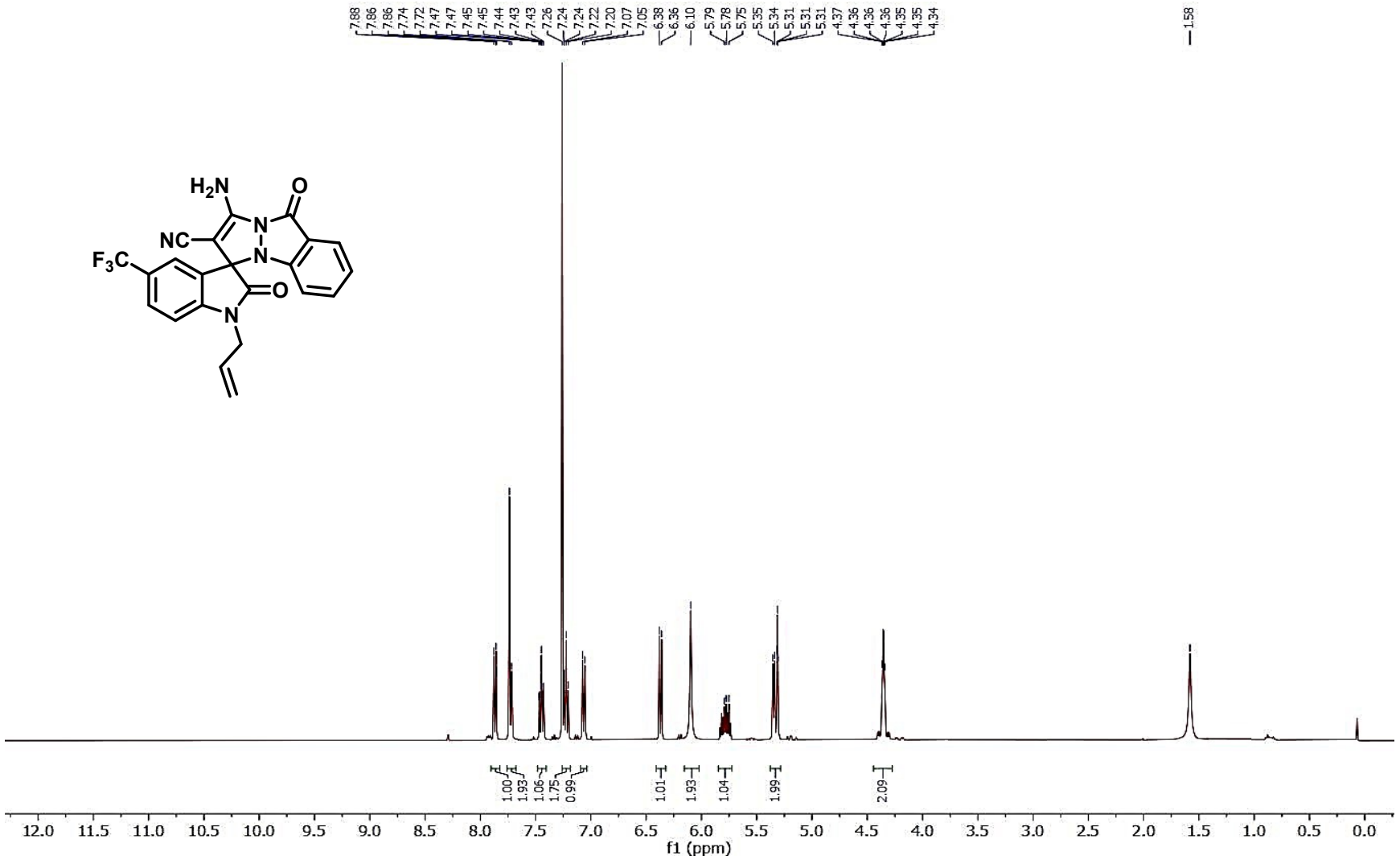


Fig. S37. ^{1}H NMR of 1-allyl-1'-amino-2,9'-dioxo-5-(trifluoromethyl)-9'*H*-spiro[indoline-3,3'-pyrazolo[1,2-a]indazole]-2'-carbonitrile (**3m**):

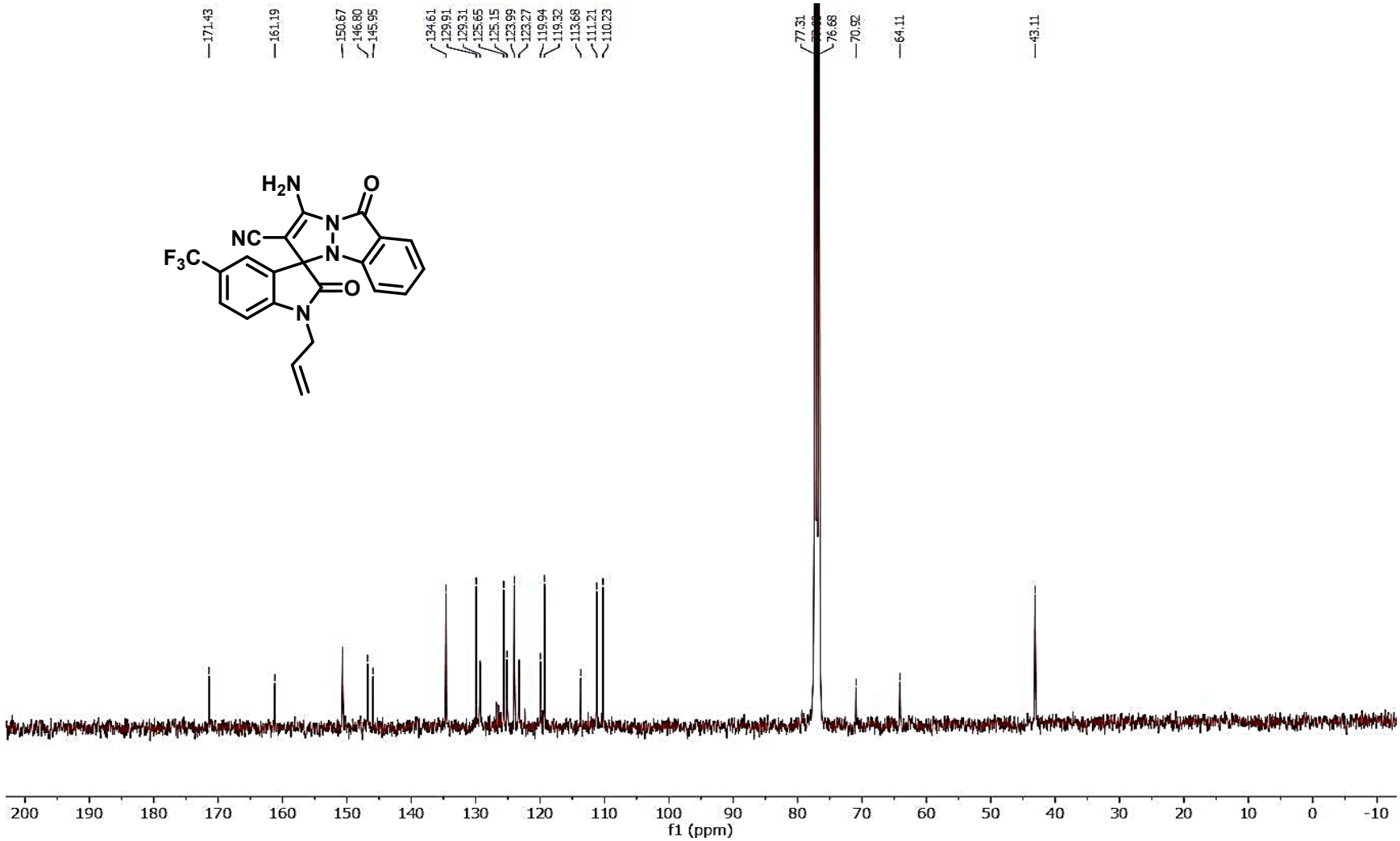


Fig. S38. ^{13}C NMR of 1-allyl-1'-amino-2,9'-dioxo-5-(trifluoromethyl)-9'*H*-spiro[indoline-3,3'-pyrazolo[1,2-a]indazole]-2'-carbonitrile (**3m**):

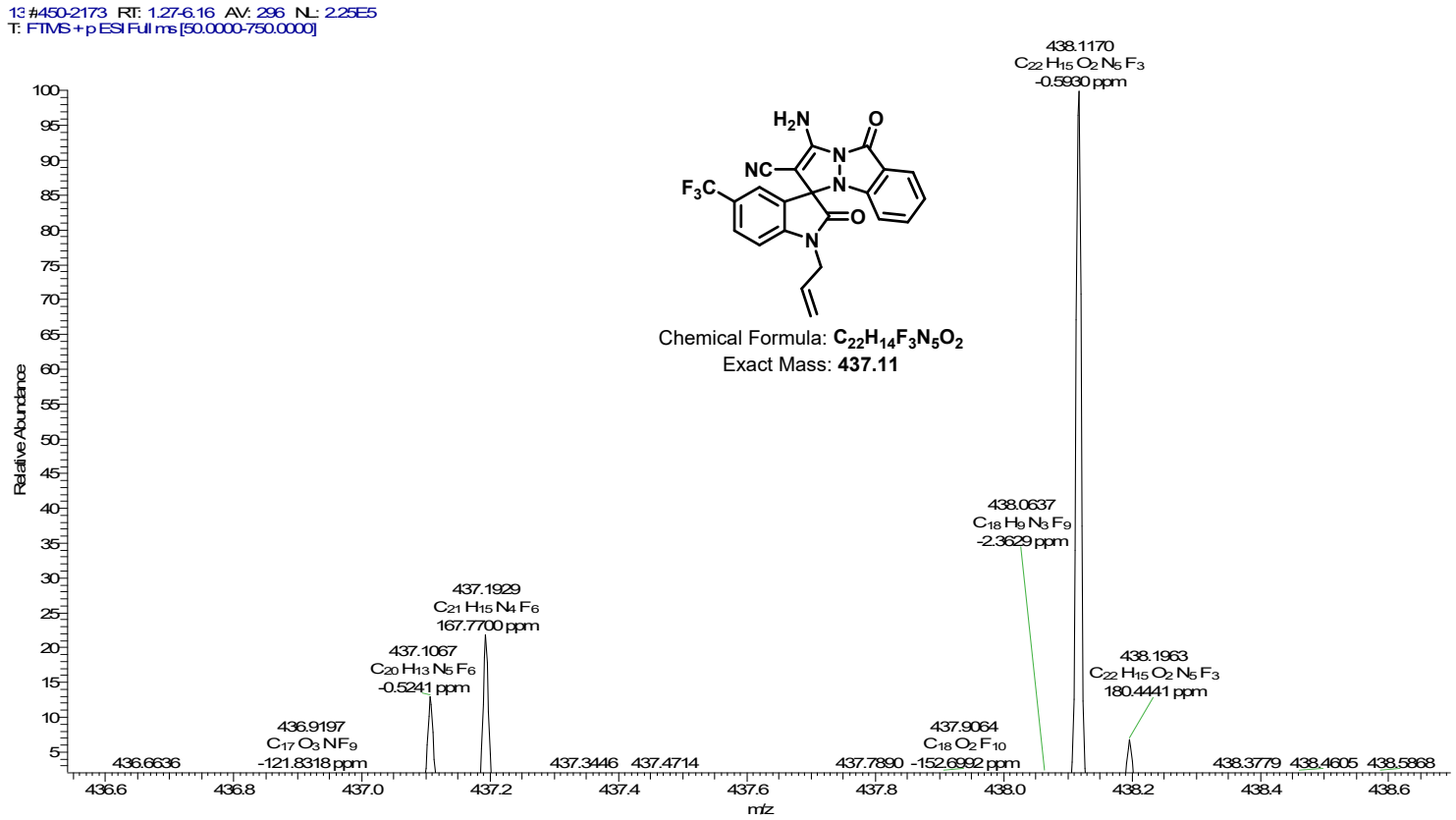


Fig. S39. HRMS of 1-allyl-1'-amino-2,9'-dioxo-5-(trifluoromethyl)-9'*H*-spiro[indoline-3,3'-pyrazolo[1,2-a]indazole]-2'-carbonitrile (**3m**):