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Sulfonyl derivatives of 1,4-dihydropyrazolo[5,1-*c*][1,2,4]triazines in reactions with acyl/alkyl halides

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General

Control of the individuality of the reagents and the obtained compounds, the qualitative analysis of the reaction mixtures during the reactions was carried out using TLC on Merck TLC Silica gel 60 F_{254} plates, individual solvents (chloroform, ethyl acetate, isopropyl alcohol) and their mixtures were used as eluents. The development of chromatograms was performed in UV light or iodine vapor. Melting points were determined using Stuart SMP30 apparatus. ^{1}H and ^{13}C NMR spectra were recorded using Bruker DRX-500 instrument at frequencies of 500.13 MHz and 125.76 MHz, respectively, at 20 °C in DMSO-d_6 with internal standard Me_4Si. IR spectra were recorded on Vertex 70 FT-IR spectrometer using a Platinum ATR (Bruker) ATR attachment equipped with a diamond prism in the frequency range from 4000 to 400 cm^{-1} with a resolution of 2 cm^{-1}. The result was obtained by averaging 16 scans.

Chromatographic analysis of individual compounds and reaction mixtures was performed using Agilent 1260 Infinity chromatograph with UV and mass detection. The Agilent 6230 time-of-flight LC/MS detector was used as a mass detector, electrospray ionization was performed. Detector: positive ionization, electrospray; capillary 4kV; fragmentator +191; skimmer +65 V.
Chromatographic conditions for individual compounds were as follows: column Poroshell 120 EC-C18 (4.6 × 50 mm); sorbent particle diameter 2.7 μm; linear gradient elution; mobile phase: eluent A - MeCN – H_2O, 2.5: 97.5, 0.1% CF_3COOH, eluent B - MeCN, 0.1% CF_3COOH, mobile phase flow rate 0.4 ml/min; column oven temperature 40 °C; injection volume 1.5 μl.
Conditions for chromatographic analysis of reaction mixtures: column Zorbax Extend-C18 (Rapid Resolution HT 2.1 × 50 mm; 1.8 μm) in the Agilent 1260 Infinity complex (Agilent Technologies, CA, USA). Mobile phase - acetonitrile (A) - water (B) + 0.1% formic acid. Gradient mixing of solvents. Start - 60% (A) for 0.5 min, then 60-95% (A) for 5.5 min, and another 1.5-2 min at 95% (A). Column oven temperature was 25 °C. The volume of the injected sample was 0.5 μL. Rate was 0.4 ml/min.
The eluate was injected directly into ESI-MS detector of Agilent 6230 TOF LC/MS (time-of-flight, ionization - electrospray). Positive polarity signals were recorded; nebulizer (N_2) 20 psig; desiccant gas (N_2), 6 ml/min, 320 °C; the scale of mass determination was 50-3200 m/z. Capillary voltage -4000 V; fragmentator +191 V, skimmer +66 V, OctRF 750 V.

Synthesis of starting compounds

Preparation methods, physicochemical and spectral characteristics, X-ray structural analysis data of the initial 1,4-dihydropyrazolo[5,1-*c*][1,2,4]triazines **2a-c** were described earlier.[S1]
For the synthesis of compounds **3a-c**, **5a-c** commercially available reagents were used: acetyl chloride (Acros, CAS 75-36-5), propionyl chloride (Acros, CAS 79-03-8), methyl iodide (Merck, CAS 74-88-4), ethyl bromide (Merck, CAS 74-96-4), 3-chloroacetonitrile (Acros, CAS 107-14-2). *N*-Aryl-2-chloroacetamides **4d-f** were obtained according to a known method from chloroacetic acid and aromatic amines.

Typical procedure for the synthesis of compounds 3a-c

A corresponding acylating agent (6 mM of acetic or propionic acid chlorides) was added to 3 mmol solution of a sulfonyl derivative of 1,4-dihydropyrazolo[5,1-*c*][1,2,4]triazine **2** in 20 ml of acetic acid (in the case of compounds **3a-b**) or propionic acid (in the case of a compound **3c**). The reaction mixture was boiled under reflux for 2-3 h (the progress of the reaction was monitored by TLC and HPLC-MS). Then the mixture was cooled, 150 ml of water was added, the precipitate formed was filtered off, washed with water (100 ml), dried at room temperature; recrystallized from AcOH (10 ml).

*1-(3-Methylsulfonyl-4,8-diphenylpyrazolo[5,1-c][1,2,4]triazin-1(4H)-yl)ethan-1-one (**3a**).* Light yellow powder, mp 202–204°C (from AcOH), yield 0.97 g (81 %). ^{1}H NMR (500.13 MHz, DMSO-d_6) δ: 3.32, 3.33 (both s, 6H, CH_3 and SO_2CH_3), 6.68 (s, 1H, C^4H), 7.22-7.24 (m, 3H, $3CH_{Ar}$), 7.31-7.35 (m, 4H, $4CH_{Ar}$), 7.39-7.46 (m, 3H, $3CH_{Ar}$), 7.76 (s, 1H, C^7H). ^{13}C NMR (125.76 MHz, DMSO-d_6) δ: 21.7 (CH_3), 41.5 (SO_2CH_3), 58.5 (C^4), 110.5 (C^8), 126.3, 127.2, 127.8, 128.0, 128.2, 129.2, 129.4, 133.1, 135.8, 141.0, 148.9, 166.9 (C=O). IR (neat, ν/cm^{-1}): 1728 (C=O), 1622 (C_{Ar}-C), 1132, 1311 (SO_2CH_3). HPLC-MS (ESI), *m/z*: 395.1176 $[M+H]^+$, (calc. for $C_{20}H_{19}N_4O_3S^+$, *m/z*: 395.1173).

*1-(8-(4-Chlorophenyl)-3-methylsulfonyl-4-phenylpyrazolo[5,1-c][1,2,4]triazin-1(4H)-yl)ethan-1-one (**3b**).* Light yellow powder, mp 208-210°C (from AcOH), yield 1.19 g (93 %). ^{1}H NMR (500.13 MHz, DMSO-d_6) δ: 3.32, 3.35 (both s, 6H, CH_3 and SO_2CH_3), 6.68 (s,1H, C^4H), 7.25 (dt, 2H, $2CH_{Ar}$, *J* 8.5, *J* 2.6 Hz), 7.34-7.42 (m, 7H, CH_{Ar}), 7.77 (s, 1H, C^7H). ^{13}C NMR (125.76 MHz, DMSO-d_6) δ: 21.8 (CH_3), 41.5 (SO_2CH_3), 58.5 (C^4), 109.3 (C^8), 127.4; 127.7; 128.1; 129.2; 129.5; 130.0; 130.9; 132.1; 135.7; 140.9; 148.9; 167.1 (C=O). IR (neat, ν/cm^{-1}): 1741 (C=O), 1575, 1622 (C_{Ar}-C), 1137, 1313 (SO_2CH_3). HPLC-MS (ESI), *m/z*: 429.0785 $[M+H]^+$, (calc. for $C_{20}H_{18}ClN_4O_3S^+$, *m/z*: 429.0784).

*1-(8-(4-Chlorophenyl)-3-methylsulfonyl-4-phenylpyrazolo[5,1-c][1,2,4]triazin-1(4H)-yl)propan-1-one (**3c**).* Beige powder, mp 187–188°C (from AcOH), yield 1.04 g (78 %). ^{1}H NMR (500.13 MHz, DMSO-d_6) δ: 1.08 (t, 3H, CH_2CH_3, *J* 7.4 Hz), 2.93-2.98 (m, 2H, CH_2CH_3), 3.33 (s, 3H, SO_2CH_3), 6.68 (s, 1H, C^4H), 7.24 (dt, 2H, $2CH_{Ar}$, *J* 8.5, *J* 2.6 Hz), 7.32-7.42 (m, 7H, $7CH_{Ar}$), 7.77 (s, 1H, C^7H). ^{13}C NMR (125.76 MHz, DMSO-d_6), δ: 8.6 (CH_2CH_3), 26.8 (CH_2CH_3), 41.5 (SO_2CH_3), 58.5 (C^4), 109.2 (C^8), 127.5, 127.7, 128.1, 129.2, 129.5, 130.0, 130.9, 132.1, 135.8, 140.9, 148.8, 170.3 (C=O). IR (neat, ν/cm^{-1}): 1741 (C=O), 1488, 1610 (C_{Ar}-C), 1141, 1325 (SO_2CH_3). HPLC-MS (ESI), *m/z*: 443.0938 $[M+H]^+$, (calc. for $C_{21}H_{20}ClN_4O_3S^+$, *m/z*: 443.0940).

Typical procedure for the synthesis of compounds 5a-e

Threefold excess (9 mmol) of calcined potassium carbonate and 3.3 mmol of an alkylating agent **4a-e** were added to 3 mmol solution of a sulfonyl derivative of 1,4-dihydropyrazolo[5,1-*c*][1,2,4]triazine **2a-c** in 20 ml of acetonitrile. The reaction mixture was heated to 80 °C and kept at this temperature for 3-4 h (the progress of the reaction was monitored by TLC and HPLC-MS). Then the solution was cooled, 150 ml of water was added, the formed precipitate was filtered off, washed with water (100 ml), dried at room temperature; recrystallized from a mixture Pr^{i}OH-AcOH (2:1).

*1-Methyl-3-methylsulfonyl-4,8-diphenyl-1,4-dihydropyrazolo[5,1-c][1,2,4]triazine (**5a**)* (mixture of enantiomers in the ratio ~ 1:1). Beige powder, mp 78-80°C (from Pr^{i}OH-AcOH), yield 0.78 g (71 %). ^{1}H NMR δ: (500.13 MHz, DMSO-d_6) δ 3.03 (s, 3H, CH_3), 3.39 (s, 2H, SO_2CH_3), 5.75 (s, 1H, C^4H), 6.56* (s, 1H, C^4H), 7.29-7.45 (m, 10H, $10CH_{Ar}$), 7.50 (s, 1H, C^7H). ^{13}C NMR (125.76 MHz, DMSO-d_6) δ: 41.9 (SO_2CH_3), 43.0 (CH_3), 54.8 (C^4), 56.9* (C^4), 105.3 (C^8), 127.3, 127.5, 128.2, 128.8, 130.3, 131.5, 133.2, 137.9, 138.0, 140.9. IR (neat, ν/cm^{-1}): 1504, 1566 (C_{Ar}-C), 1132, 1309 (SO_2CH_3). HPLC-MS (ESI), *m/z*: 367.1205 $[M+H]^+$, (calc. for $C_{19}H_{19}N_4O_2S^+$, *m/z*: 367.1224).

*1-Ethyl-3-methylsulfonyl-4,8-diphenyl-1,4-dihydropyrazolo[5,1-c][1,2,4]triazine (**5b**).* Gray powder, mp 167–169 °C (from Pr^{i}OH-AcOH), yield 0.75 g (66 %). ^{1}H NMR (500.13 MHz, DMSO-d_6) δ: 0.98 (t, 3H, CH_2CH_3, *J* 7.1 Hz), 3.07 (s, 3H, SO_2CH_3), 3.75 (q, 2H, CH_2CH_3, *J* 7.1 Hz), 6.57 (s, 1H, C^4H), 7.27-7.47 (m, 10H, $10CH_{Ar}$), 7.50 (s, 1H, C^7H). ^{13}C NMR (125.76 MHz, DMSO-d_6) δ: 12.6 (CH_2CH_3), 41.8 (SO_2CH_3), 48.6 (CH_2CH_3), 56.8 (C^4),

105.0 (C^8), 127.4, 127.5, 128.3, 128.8, 129.9, 131.8, 132.3, 137.9, 138.9, 140.9. IR (neat, ν/cm^{-1}): 1533, 1568 (C_{Ar}-C), 1153, 1317 (SO_2CH_3). HPLC-MS (ESI), *m/z*: 381.1382 $[M+H]^+$, (calc. for $C_{20}H_{21}N_4O_2S^+$, *m/z*: 381.1381).

*2-(4-Methyl-8-phenyl-3-tosylpyrazolo[5,1-c][1,2,4]triazin-1(4H)-yl)acetonitrile (**5c**).* Gray powder, mp 159–161°C (from Pr^{i}OH-AcOH), yield 0.92 g (76 %). ^{1}H NMR (500.13 MHz, DMSO-d_6) δ: 1.64 (d, 3H, 4-CH_3, *J* 6.6 Hz), 2.43 (s, 3H, CH_3 Tos), 3.33 (s, 3H, C^4-CH_3), 4.65 (q, 2H, CH_2, *J* 18.0), 5.66 (q, 1H, C^4H, *J* 6.5 Hz), 7.39-7.63 (m, 7H, 7CH_{Ar}), 7.73 (s, 1H, C^7H), 7.92 (d, 2H, 2CH_{Ar}, *J* 7.9 Hz). ^{13}C NMR (125.76 MHz, DMSO-d_6) δ: 20.5 (4-CH_3), 21.2 (CH_3 Tos), 42.7 (CH_2), 49.9 (C^4), 105.7 (C^8), 114.9 (CN), 127.9, 128.7; 130.0, 130.3 (CH_{Ar}); 130.8 (C^7); 131.4 (C^{8a}); 135.1, 140.8, 145.1, 145.7 (C^3)*. IR (neat, ν/cm^{-1}): 2364 (CN), 1519, 1573 (C_{Ar}-C), 1137, 1309 (SO_2CH_3). HPLC-MS (ESI), *m/z*: 406.1335 $[M+H]^+$, (calc. for $C_{21}H_{20}N_5O_2S^+$, *m/z*: 406.1333). *The assignments of signals in the ^{13}C NMR spectrum were performed based on the data of two-dimensional correlations.

In 2D ^{1}H-^{1}H NMR spectra of compound **5c** cross peaks between the protons of the methyl group and hydrogen at position 4 of the triazine ring ─ δ 1.64/5.66 ppm (NOESY, COSY) and protons of aromatic nuclei with CH_3 (δ 2.43 ppm) and CH_2 (δ 4.65 ppm) groups (NOESY) were observed. Based on the set of correlations in the heteronuclear HSQC spectrum, the assignments of the signals of carbon atoms directly associated with the corresponding protons were made: 2.43/21.2 ppm (CH_3 of tosyl fragment), 4.65/47.7 ppm (CH_2), 5.66/49.9 ppm (C^4H), 7.73/130.8 ppm (C^7H), as well as unrelated to protons: δ 131.4, 135.1, 140.8, 145.1, 145.7 ppm.

Table S1 Homo- and heteronuclear correlations in two-dimensional spectra of the compound **5c**.

^{1}H NMR signals δ, ppm	Observed correlations			
	^{1}H-^{1}H NOESY	**^{1}H-^{1}H COSY**	**HMBC**	**HSQC**
1.64 (d, 3H, 4-CH_3)	5.66 (q, 1H, C^4H); 7.92 (d, 2H, 2CH_{Ar})	5.66 (q, 1H, C^4H)	20.5 (4-CH_3); 49.9 (C^4); 145.1 (CH_{Ar})	20.5 (4-CH_3)
2.43 (s, 3H, CH_3 Tos)	7.39-7.63 (m, 7H, 7CH_{Ar})	-	21.2 (CH_3 Tos), 130.0, 130.3 (CH_{Ar})	21.2 (CH_3 Tos)
4.65 (q, 2H, CH_2)	7.39-7.63 (m, 7H, 7CH_{Ar})	-	114.9 (CN), 131.4 (C^{8a});	42.7 (CH_2)
5.66 (q,1H, C^4H)	1.64 (d, 3H, 4-CH_3); 7.92 (d, 2H, 2CH_{Ar})	1.64 (d, 3H, 4-CH_3)	20.5 (4-CH_3); 145.1 (CH_{Ar})	49.9 (C^4)
7.39-7.63 (m, 7H, 7CH_{Ar})	2.43 (s, 3H, CH_3 Tos); 4.65 (q, 2H, CH_2); 7.73 (s, 1H, C^7H)	7.92 (d, 2H, 2CH_{Ar})	21.2 (CH_3 Tos), 105.7 (C^8), 127.9, 128.7; 130.0, 130.3 (CH_{Ar}), 135.1, 140.8 (CH_{Ar}) (*cross-peak overlay*)	127.9, 128.7; 130.0, 130.3 (CH_{Ar})
7.73 (s, 1H, C^7H)	7.39-7.63 (m, 7H, 7CH_{Ar})	-	105.7 (C^8), 131.4 (C^{8a})	130.8 (C^7)
7.92 (d, 2H, 2CH_{Ar})	1.64 (d, 3H, 4-CH_3); 5.66 (q, 1H, C^4H); 7.39-7.63 (q, 7H, 7CH_{Ar}); 7.73 (s, 1H, C^7H)	7.39-7.63 (m, 7H, 7CH_{Ar})	128.7 CH_{Ar}); 145.7 (C^3)	128.7 (CH_{Ar})

*2-(3-Methylsulfonyl-4,8-diphenylpyrazolo[5,1-c][1,2,4]triazin-1(4H)-yl)-N-phenylacetamide (**5d**).* Light yellow powder, mp 237–239°C (from Pr^{i}OH-AcOH), yield 1.22 g (83%). ^{1}H NMR (500.13 MHz, DMSO-d_6) δ: 3.35 (s, 3H, SO_2CH_3), 4.56 (q, 2H, CH_2, *J* 17.4 Hz), 6.60 (s, 1H, C^4H), 7.06 (m, 1H, CH_{Ar}), 7.28-7.50 (m, 15H, 14CHAr + C^7H), 9.85 (s, 1H, H NH). NMR ^{13}C (125.76 MHz, DMSO-d_6) δ: 42.1 (SO_2CH_3), 56.2 (CH_2), 57.2 (C^4), 104.9 (C^8), 119.5, 123.7, 127.6, 128.1, 128.4, 128.8, 129.9, 129.0, 130.1, 131.4, 133.0, 138.3, 139.2, 140.8, 165.2 (C=O). IR (neat, ν/cm^{-1}): 3359 (NH), 1735 (C=O), 1531, 1573 (C_{Ar}-C), 1139, 1309 (SO_2CH_3). HPLC-MS (ESI), *m/z*: 486.1600 $[M+H]^+$, (calc. for $C_{26}H_{24}N_5O_3S^+$, *m/z*: 486.1596).

*2-(3-Methylsulfonyl-4,8-diphenylpyrazolo[5,1-c][1,2,4]triazin-1(4H)-yl)-N-(p-tolyl)acetamide (**5e**).* Light yellow powder, mp 209–211°C (from Pr^{i}OH-AcOH), yield 1.18 g (79 %). ^{1}H NMR (500.13 MHz, DMSO-d_6) δ: 2.25 (s, 3H, CH_3), 3.33 (s, 3H, SO_2CH_3), 4.53 (q, 2H, CH_2, *J* 17.3 Hz), 6.59 (s, 1H, C^4H), 7.10 (d, 2H, CH_{Ar}, *J* 8.4 Hz,), 7.28-7.49 (m, 13H, $12CH_{Ar}$ + C^7H), 9.75 (s, 1H, NH); ^{13}C NMR (125.76 MHz, DMSO-d_6) δ: 20.4 (CH_3), 41.9 (SO_2CH_3), 56.0 (CH_2), 57.0 (C^4), 104.8 (C^8), 119.4, 127.4, 127.9, 128.2, 128.7, 129.0, 130.0, 131.3, 132.5, 132.9, 135.6, 138.1, 139.0, 140.6, 164.8 (C=O). IR (neat, ν/cm^{-1}): 3022, 3354 (NH), 1730 (C=O), 1573, 1608 (C_{Ar}-C), 1309, 1137 (SO_2CH_3). HPLC-MS (ESI), *m/z*: 500.1755 $[M+H]^+$, (calc. for $C_{27}H_{26}N_5O_3S^+$, *m/z*: 500.1752).

Typical procedure for the synthesis of compounds 6a,b

Calcined potassium carbonate (3 mmol) and 3.3 mmol of the corresponding chloroacetamide **4e,f** were added to 3 mmol solution of a sulfonyl derivative of 1,4-dihydropyrazolo[5,1-*c*][1,2,4]triazine **2a** in 20 ml of dimethylformamide. The reaction mixture was heated at a temperature of 150 °C for 15-20 min (the progress of the reaction was monitored by TLC and HPLC-MS). The reaction mixture was cooled, 150 ml of water was added, the formed precipitate was filtered off, washed with warm water (200 ml), and dried at room temperature. The product was purified by column chromatography on silica gel, chloroform was used as eluent.

Table S2 Homo- and heteronuclear correlations in two-dimensional spectra of the compound **6a**

^{1}H NMR signals δ, ppm	Observed correlations			
	^{1}H-^{1}H NOESY	**^{1}H-^{1}H COSY**	**HMBC**	**HSQC**
2.32 (s, 3H, CH_3)	7.22-7.25 (m, 3H, $3CH_{Ar}$)	-	129.3 (CH_{Ar}); 133.6 (C-CH_3)	20.5 (CH_3)
5.59 (s, 2H, NH_2)	-	-	129.3; 137.9 (C^6)	-
7.22-7.25 (m, 3H, $3CH_{Ar}$)	2.32 (s, 3H, CH_3); 7.47 (d, 2H, $2CH_{Ar}$); 7.60-7.72 (m, 7H, $7CH_{Ar}$)	7.47 (2H d, H Ar); 7.60-7.72 (7H, m, $7CH_{Ar}$)	20.6 (CH_3); 125.9; 129.3 (CH_{Ar}); 135.2 (C^5)	125.9, 128.6 (CH_{Ar})
7.47 (d, 2H $2CH_{Ar}$)	7.22-7.25 (m, 3H, $3CH_{Ar}$); 7.60-7.72 (m, 7H, $7CH_{Ar}$); 8.18 (d, 2H, $7CH_{Ar}$)	7.22-7.25 (3H, m, $3CH_{Ar}$); 8.18 (2H, d, $2CH_{Ar}$)	128.6 (CH_{Ar}); 131.9 (C^7)	128.2 (CH_{Ar})
7.60-7.72 (m, 7H, $7CH_{Ar}$)	7.22-7.25 (m, 3H, $3CH_{Ar}$); 10.56 (s, 1H, NH)	7.22-7.25 (3H, m, $3CH_{Ar}$)	120.6, 128.2;129.0; 129.8; 129.9 (CH_{Ar}); 133.6 (C-CH_3)	120.6, 128.6-129.9 (CH_{Ar}), (cross-peak overlay)
8.18 (d, 2H, $2CH_{Ar}$)	7.47 (d, 2H, $2CH_{Ar}$); 7.60-7.72 (m, 7H, $7CH_{Ar}$); 8.49 (s, 1H, C^2H)	7.47 (2H d, $2CH_{Ar}$)	110.1 (C^3); 125.9 (CH_{Ar});	125.9 (CH_{Ar})
8.49 (s, 1H, C^2H)	8.18 (d, 2H, $2CH_{Ar}$)	-	110.1 (C^3); 138.2 (C^{3a})	140.8 (C^2)
10.56 (s, 1H, NH)	7.60-7.72 (m, 7H, $7CH_{Ar}$)	-	120.6 (CH_{Ar})	-

In the HSQC spectrum of compound **6a** not a single cross-peak of ^{13}C nuclei with protons at 5.58 ppm was found, which indicates the absence of CH_2 groups in the structure of the product, probably, these protons belong to the exocyclic amino group. The cross-peaks of NH_2 group protons with C^6 and a carbon atom of the benzene ring were found in the two-dimensional HMBC spectrum. The proton at C^2 of the pyrazole ring provides characteristic cross-peaks with the C^3 and C^{3a} atoms, and the hydrogen atom of the amide group shows correlations with the C-atoms of the tolyl fragment. In the NOESY spectrum of the compound **6a** cross-peaks between the NH-proton of the amide group and the protons of the benzene

ring were found. The absence of correlations between the H-atoms of the amino group and NH-protons of the amide group in 2D ^{1}H-^{1}H spectra (NOESY, COSY) was probably associated with the spatial distance of these groups in the molecule.

*6-Amino-3,7-diphenyl-N-(p-tolyl)-4,7-dihydropyrazolo[1,5-a]pyrimidine-5-carboxamide (**6a**).* Orange powder, mp 271–273°C (from *i*-PrOH-AcOH), yield 0.64 g (51 %). ^{1}H NMR (500.13 MHz, DMSO-d_6) δ: 2.32 (s, 3H, CH_3), 5.59 (s, 2H, NH_2), 7.22-7.25 (m, 3H, 3CH_{Ar}), 7.47 (d, 2H, 2CH_{Ar}, *J* 5.9 Hz), 7.60-7.72 (m, 7H, 7CH_{Ar}), 8.18 (d, 2H, 2CH_{Ar}, *J* 6.7 Hz), 8.49 (s, 1H, C^2H), 10.56 (s, 1H, NH). ^{13}C NMR (125.76 MHz, DMSO-d_6) δ: 20.5 (CH_3), 110.1 (C^3), 120.6 (CH_2), 125.9, 128.4, 128.2, 128.6, 129.0, 129.1, 129.3, 129.8, 129.9 (CH_{Ar}), 131.9 (C^7), 133.6 (C_{Ph}-CH_3), 135.2 (C^5), 137.09 (C^6), 138.2 (C^{3a}), 140.9 (C^2), 164.1 (C=O)*. IR (neat, ν/cm^{-1}): 3357, 3477 (NH); 1674 (C=O), 1539, 1568 (C_{Ar}-C). HPLC-MS (ESI), *m*/*z*: 420.1815 $[M+H]^+$, (calc. for $C_{26}H_{22}N_5O^+$, *m*/*z*: 420.1819). *The assignments of signals in the ^{13}C NMR spectrum were performed based on the data of two-dimensional correlations.

*6-Amino-N-(4-methoxyphenyl)-7-methyl-3-phenyl-4,7-dihydropyrazolo[1,5-a]pyrimidine-5-carboxamide (**6b**).* Orange powder, mp 195–197°C (from *i*-PrOH-AcOH), yield 0.65 g (58 %). ^{1}H NMR (500.13 MHz, DMSO-d_6) δ: 2.72 (s, 3H, OCH_3), 3.78 (s, 3H, CH_3), 5.98 (s, 2H, NH_2), 7.00 (dt, 2H, CH_{Ar}, *J* 9.03, *J* 3.42 Hz), 7.23 (m, 1H, CH_{Ar}),7.45 (m, 2H, 2CH_{Ar}), 7.73 (dt, 2H, 2CH_{Ar}, *J* 9.0, *J* 3.4 Hz), 8.19 (dt, 2H, 2CH_{Ar}, *J* 7.2, *J* 1.1 Hz), 8.64 (s, 1H, C^2H), 10.49 (s, 1H, NH). ^{13}C NMR (125.76 MHz, DMSO-d_6) δ: 11.5 (CH_3), 55.3 (OCH_3), 109.6 (C^3), 114.0 (CH_2), 122.3, 125.8, 128.7, 130.1, 130.5, 131.0, 132.0, 136.1, 137.8, 141.0, 156.2, 164.2 (C=O). IR (neat, ν/cm^{-1}): 3354, 3475 (NH), 2852 (OCH_3), 1675 (C=O), 1537, 1566 (C_{Ar}-C). HPLC-MS (ESI), *m*/*z*: 374.1614 $[M+H]^+$, (calc. for $C_{21}H_{20}N_5O_2^+$, *m*/*z*: 374.1612).

*6,10-Diphenyl-3-(p-tolyl)pyrazolo[1,5-a]pyrimido[5,4-d]pyrimidin-4(3H)-one (**6'a**).* Red crystals, mp > 300 °C (from DMF). The compound was obtained by spontaneous cyclocondensation after heating individual product **6a** in DMF for 5-7 min.

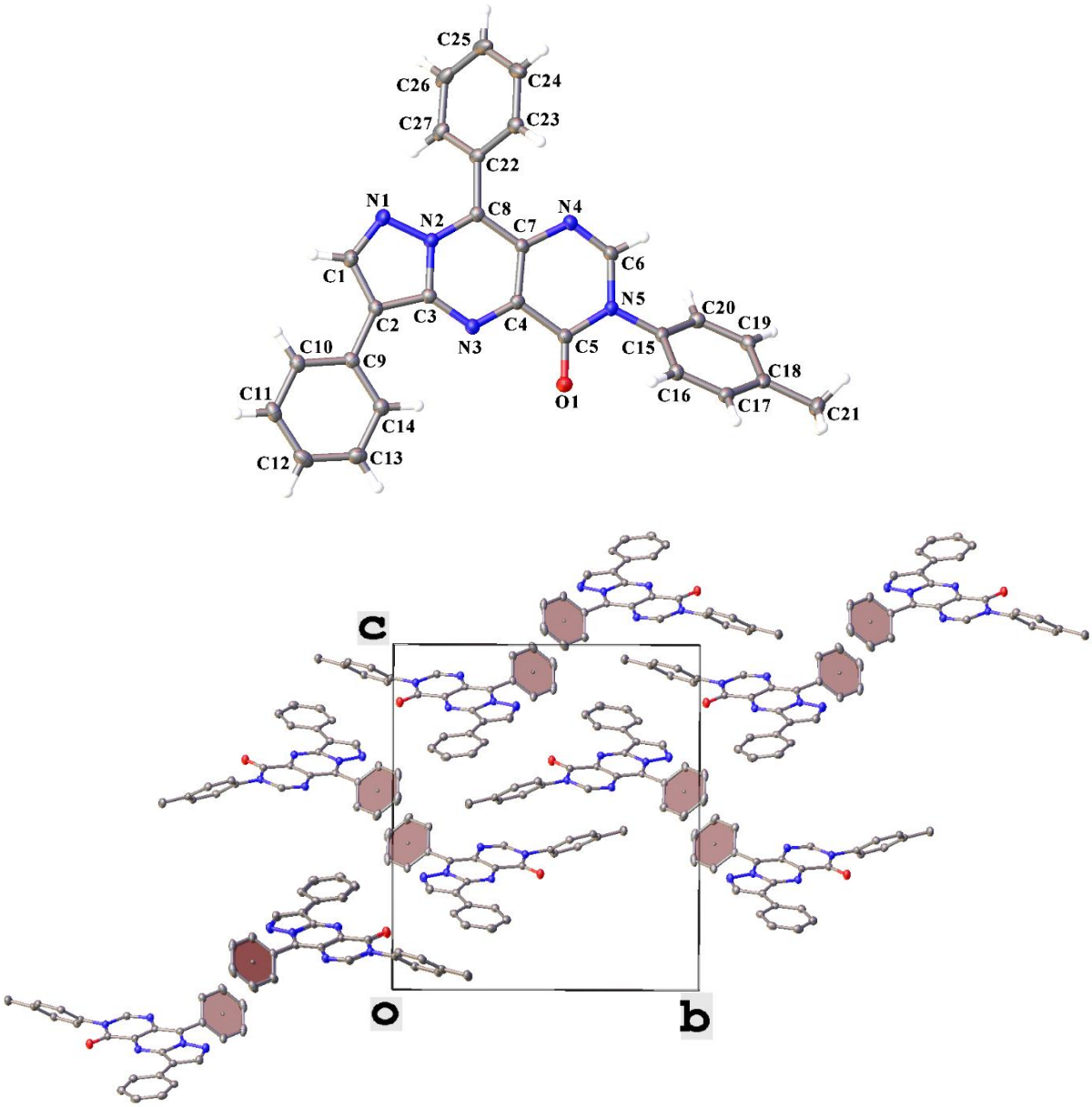


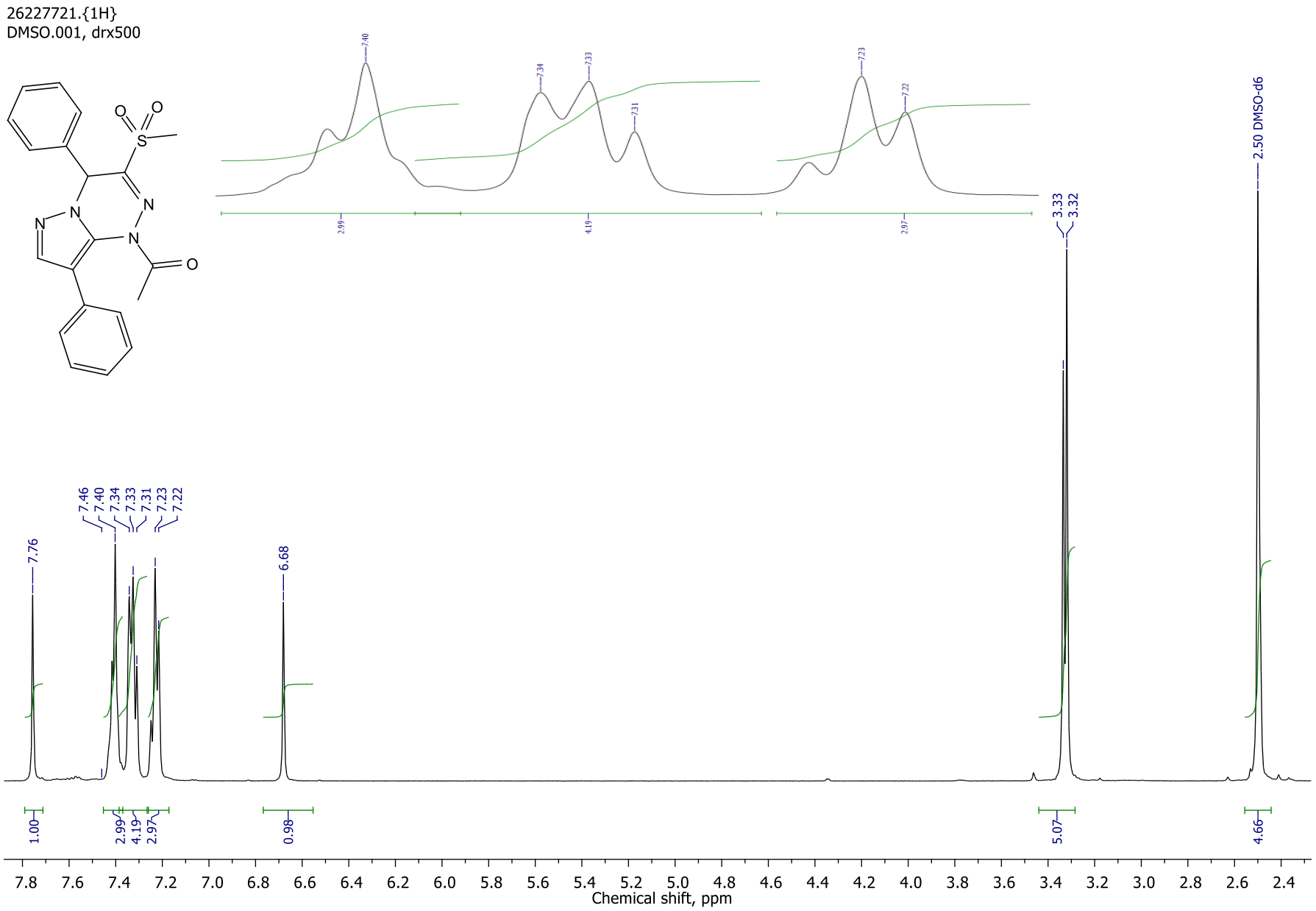
Figure S1. General view of the compound **6′a** (top) and a fragment of its crystal packing (bottom) illustrating the formation of centrosymmetric dimers by intermolecular stacking interactions between phenyl groups highlighted by pink color. Non-hydrogen atoms are shown as thermal ellipsoids at 50% probability level.

The studied compound crystallizes in the monoclinic space group $P2_1/c$ with a single molecule of **6′a** in an asymmetric part of the unit cell. Of the three aryl substituents, one (C9-C14) is nearly coplanar to the planar heterocyclic core (with the angle between the corresponding mean-square planes of 2.56(3)° only) while the two others (C15-C20 and C22-C27) are rotated by 43.57(4) and 48.96(3)°, respectively. The phenyl groups at the carbon atom C(8) in the neighboring molecules form intermolecular parallel-displaced stacking interactions with the inter-centroid and shift distances of 3.8508(11) and 1.631(2) Å, respectively, and the angle between the aromatic planes of 180.00 (7)° to produce centrosymmetric dimers. Those are assembled into a 3D-framework by numerous weaker interactions, such as C-H…N, C-H…O, C-H…C and H…H contacts.

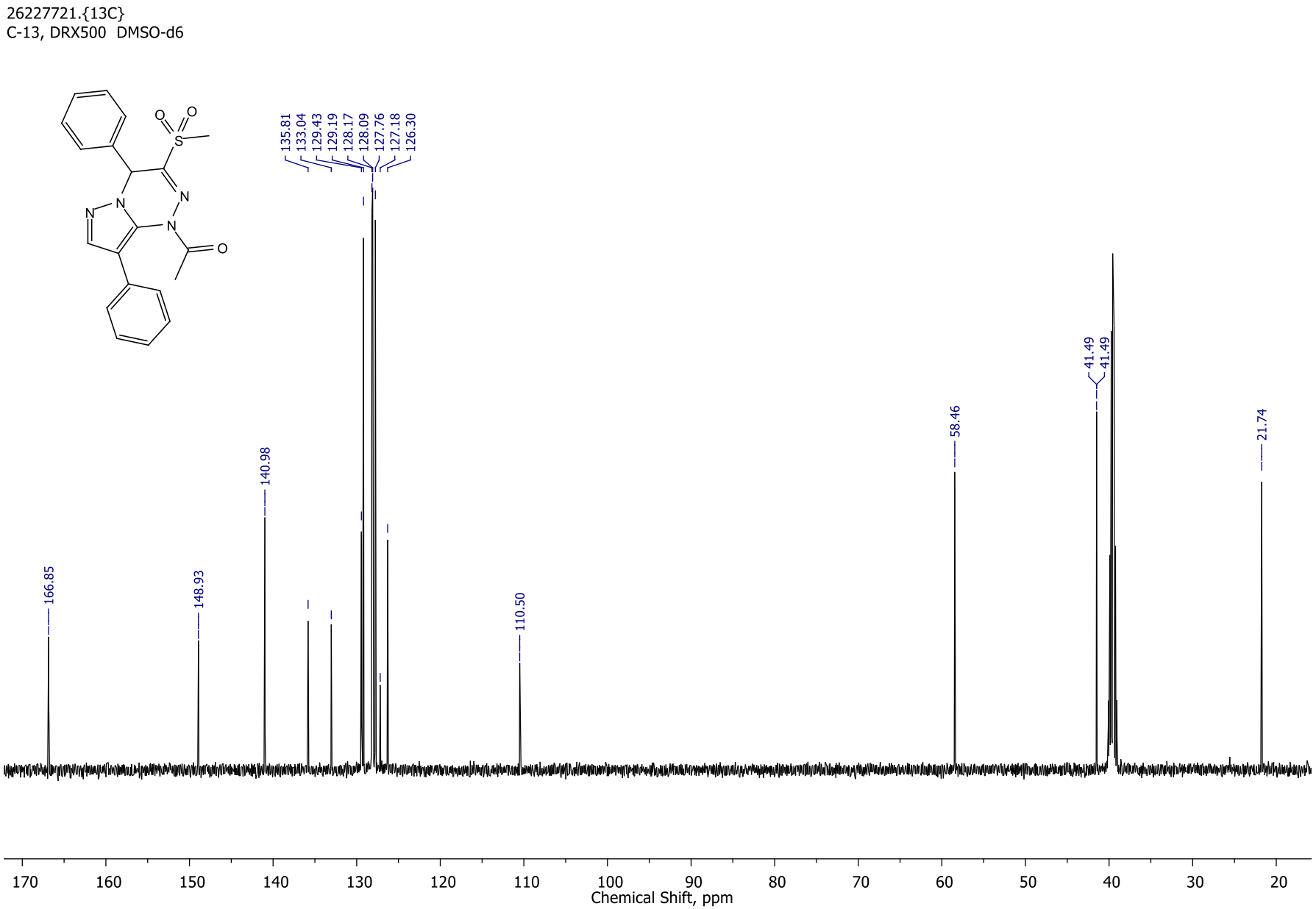
References

S1. I. V. Ledenyova, P. A. Kartavtsev, A. Yu. Egorova and Kh. S. Shikhaliev, *Chem. Heterocycl. Compd.*, 2017, **53**, 1128; https://doi.org/10.1007/s10593-017-2183-9.

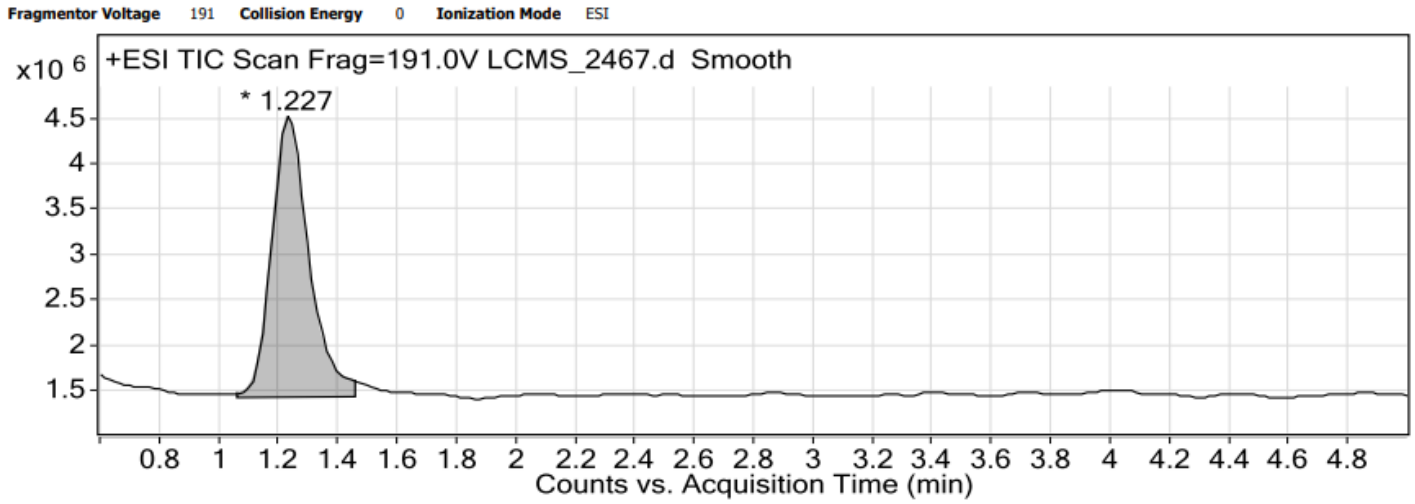
^{1}H NMR spectrum of 1-(3-(methylsulfonyl)-4,8-diphenylpyrazolo[5,1-*c*][1,2,4]triazin-1(4*H*)-yl)ethan-1-one (**3a**) (DMSO-d_6, 500.13 MHz)

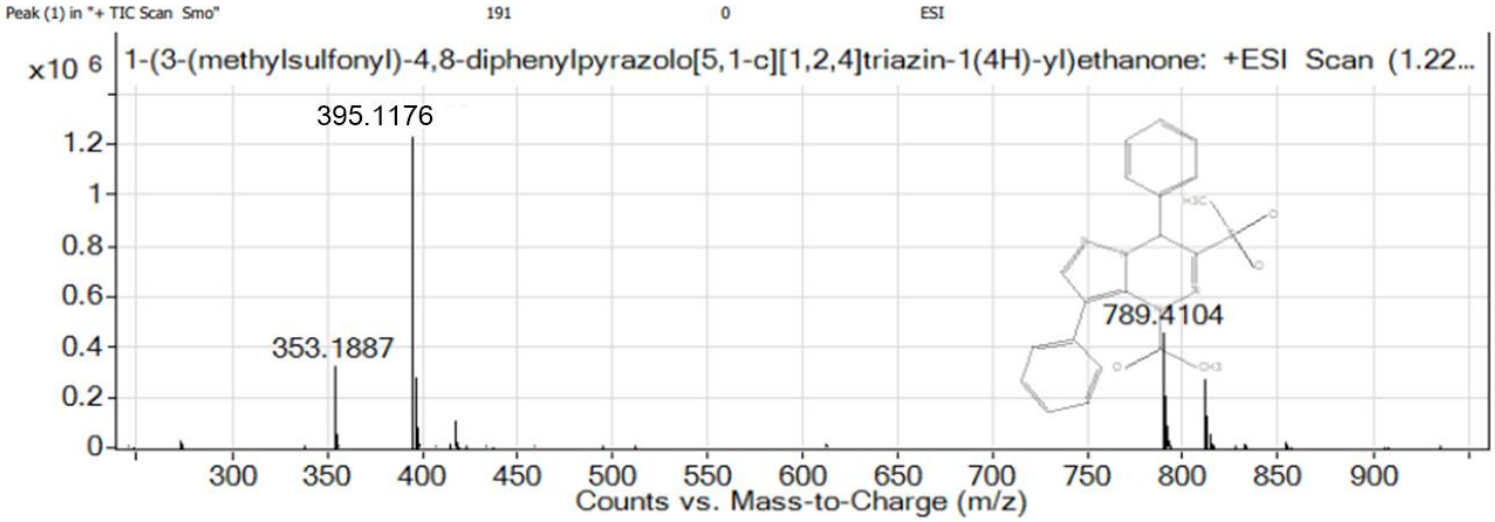


^{13}C NMR spectrum of 1-(3-(methylsulfonyl)-4,8-diphenylpyrazolo[5,1-*c*][1,2,4]triazin-1(4*H*)-yl)ethan-1-one (**3a**) (DMSO-d_6, 125.76 MHz)

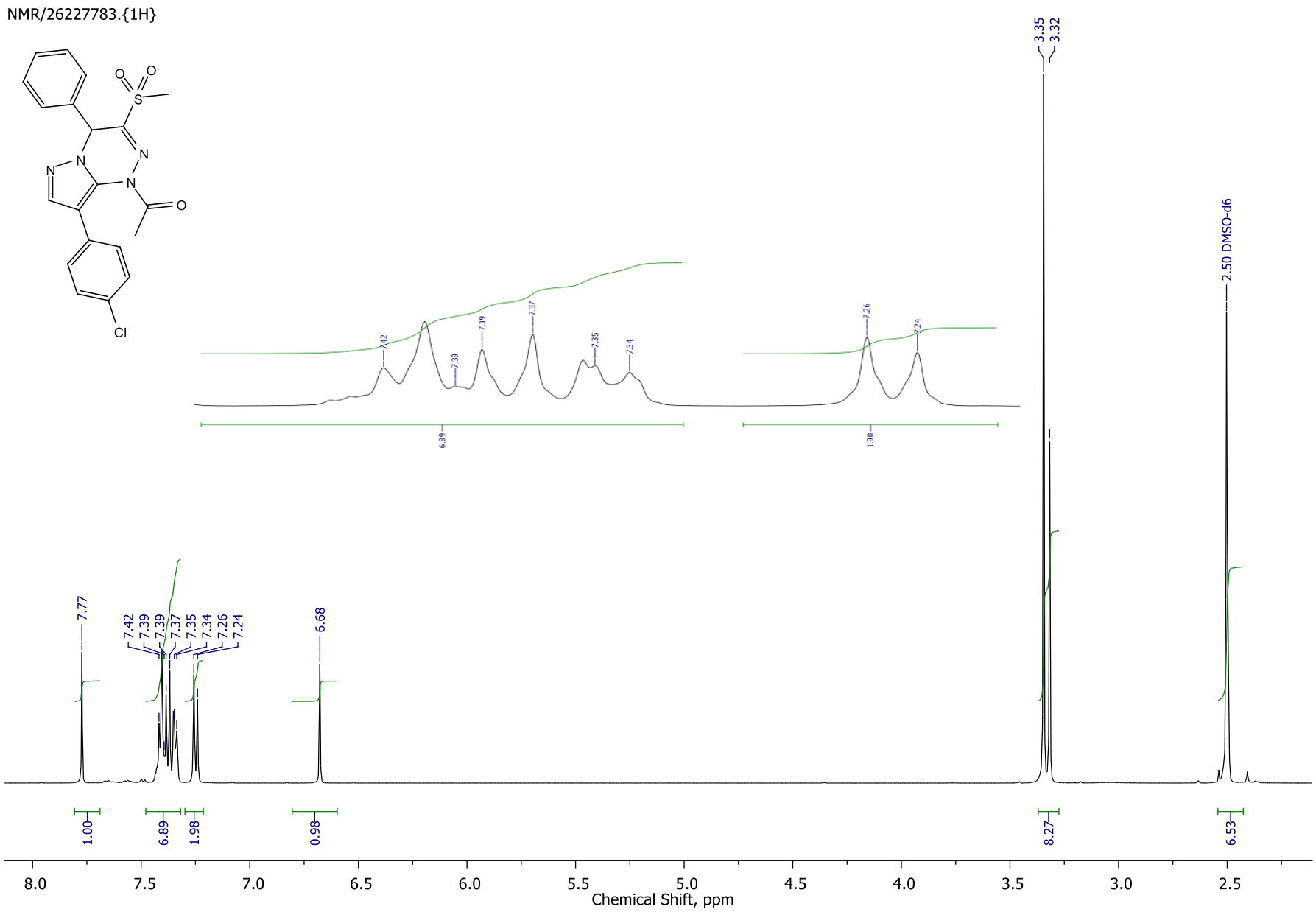


HPLC-MS (ESI) spectrum of 1-(3-(methylsulfonyl)-4,8-diphenylpyrazolo[5,1-*c*][1,2,4]triazin-1(4*H*)-yl)ethan-1-one (**3a**)

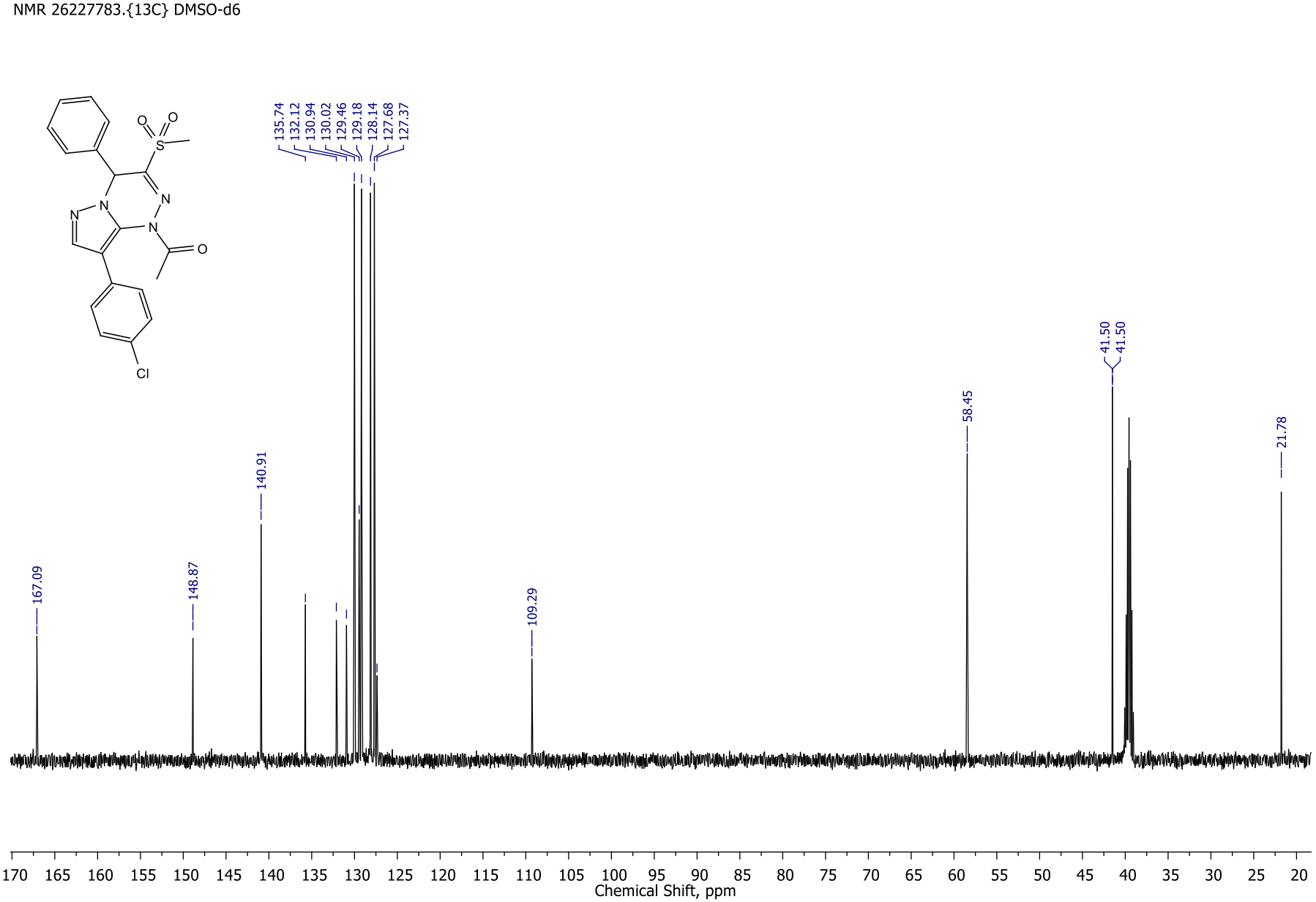




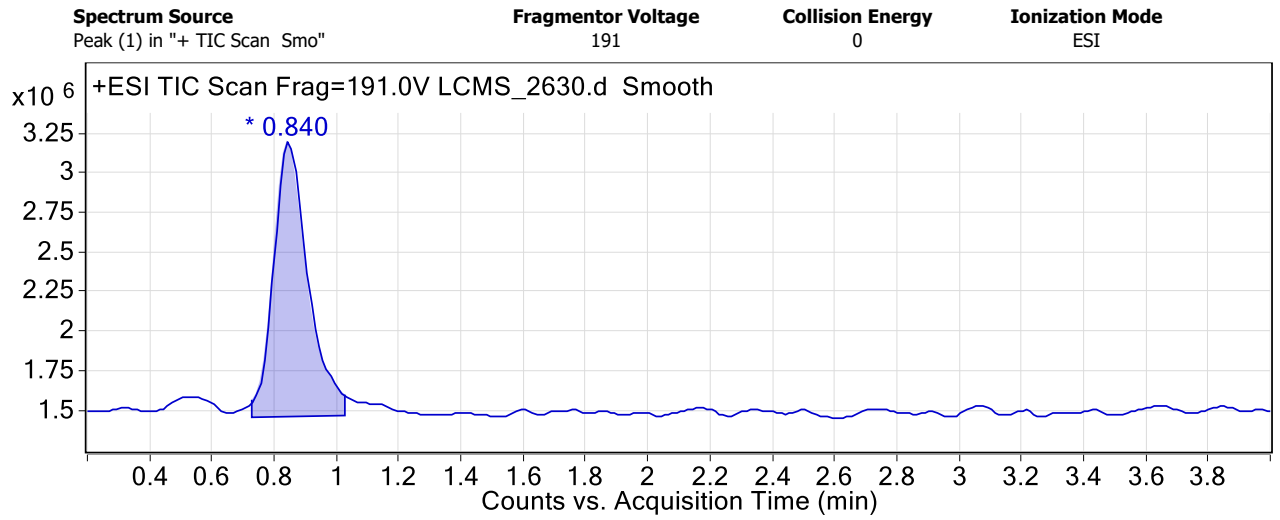
^{1}H NMR spectrum of 1-(8-(4-chlorophenyl)-3-(methylsulfonyl)-4-phenylpyrazolo[5,1-*c*][1,2,4]triazin-1(4*H*)-yl)ethan-1-one (**3b**) (DMSO-d_6, 500.13 MHz)

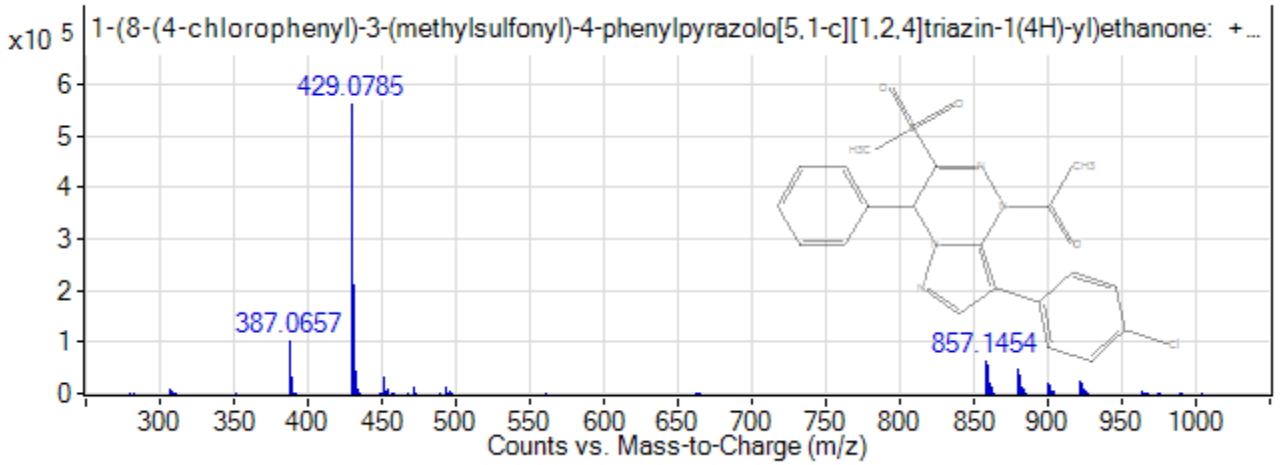


^{13}C NMR spectrum of 1-(8-(4-chlorophenyl)-3-(methylsulfonyl)-4-phenylpyrazolo[5,1-*c*][1,2,4]triazin-1(4*H*)-yl)ethan-1-one (**3b**) (DMSO-d_6, 125.76 MHz)

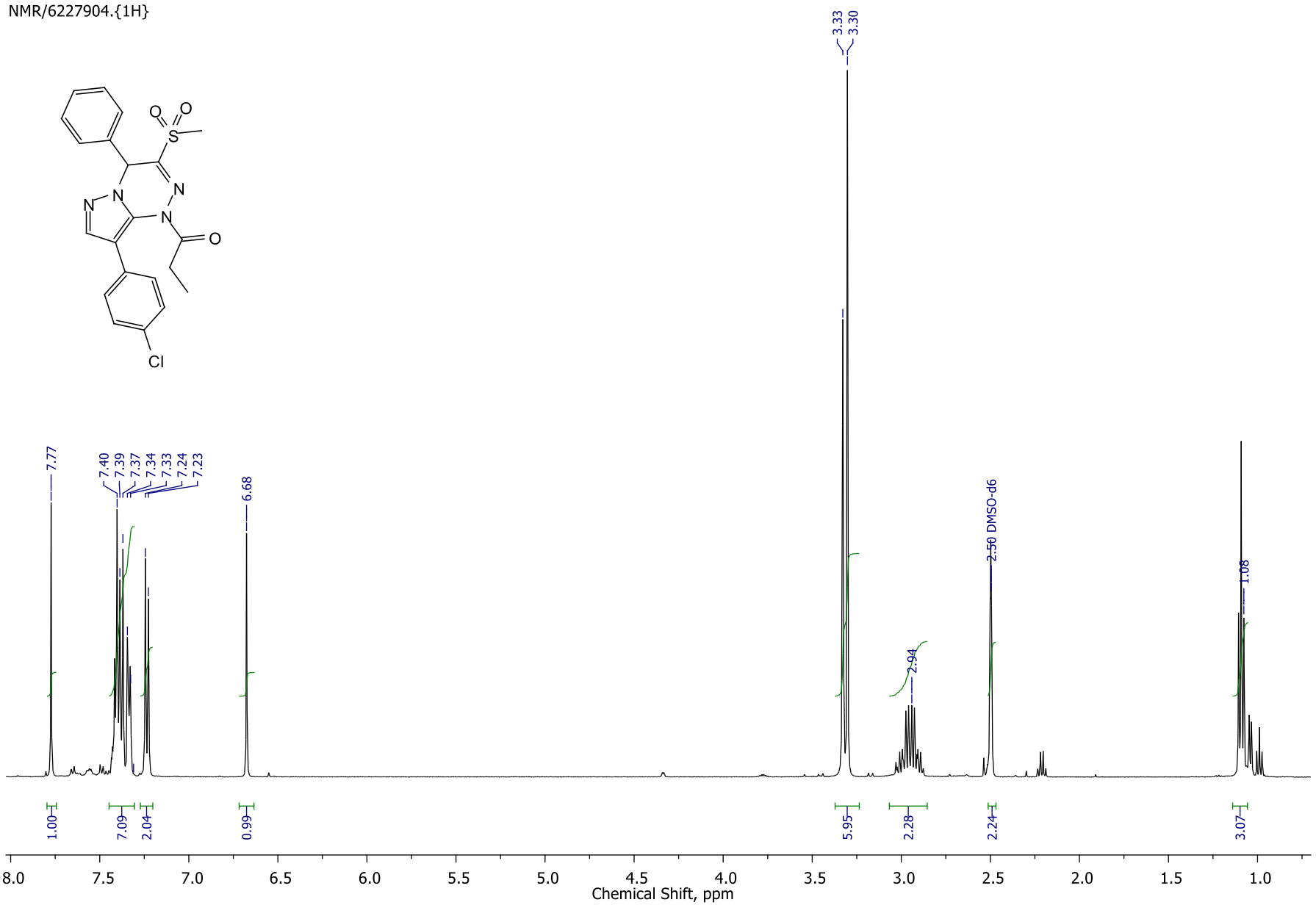


HPLC-MS (ESI) spectrum of 1-(8-(4-chlorophenyl)-3-(methylsulfonyl)-4-phenylpyrazolo[5,1-*c*][1,2,4]triazin-1(4*H*)-yl)ethan-1-one (**3b**)

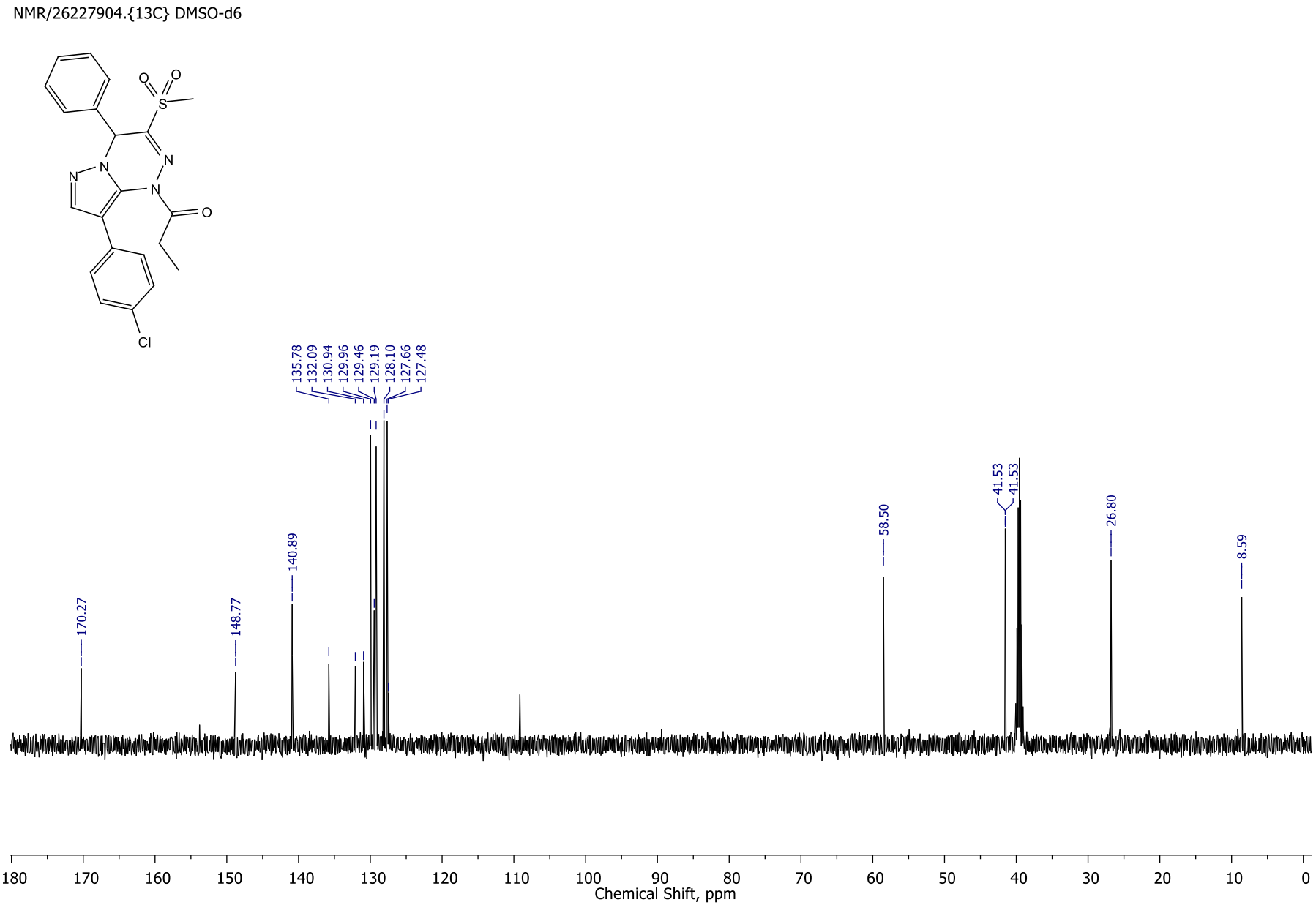




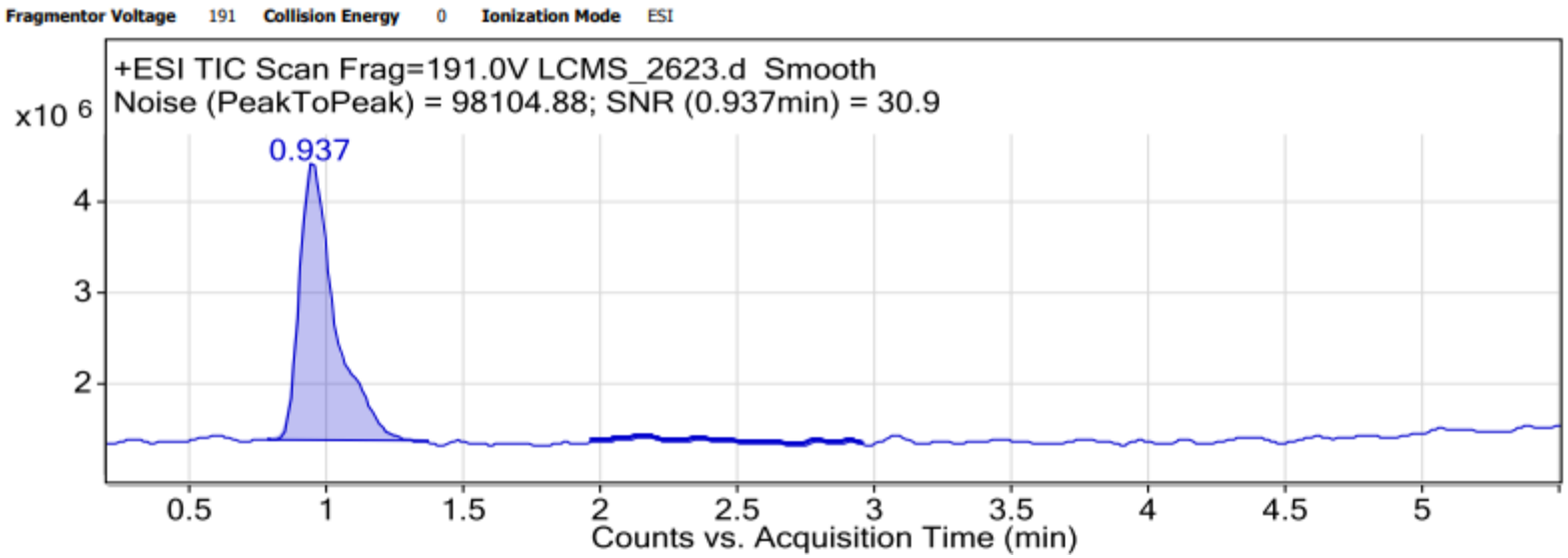
^{1}H NMR spectrum of 1-(8-(4-chlorophenyl)-3-(methylsulfonyl)-4-phenylpyrazolo[5,1-*c*][1,2,4]triazin-1(4*H*)-yl)propan-1-one (**3c**) (DMSO-d_6, 500.13 MHz)

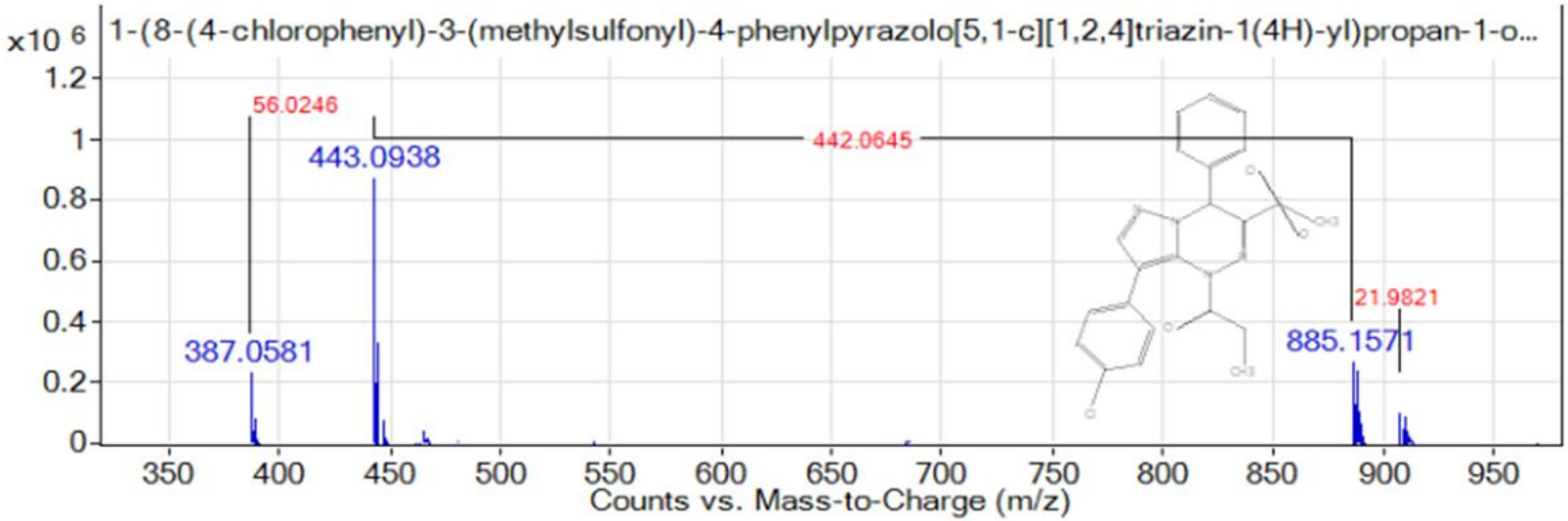


^{13}C NMR spectrum of 1-(8-(4-chlorophenyl)-3-(methylsulfonyl)-4-phenylpyrazolo[5,1-*c*][1,2,4]triazin-1(4*H*)-yl)propan-1-one (**3c**) (DMSO-d_6, 125.76 MHz)

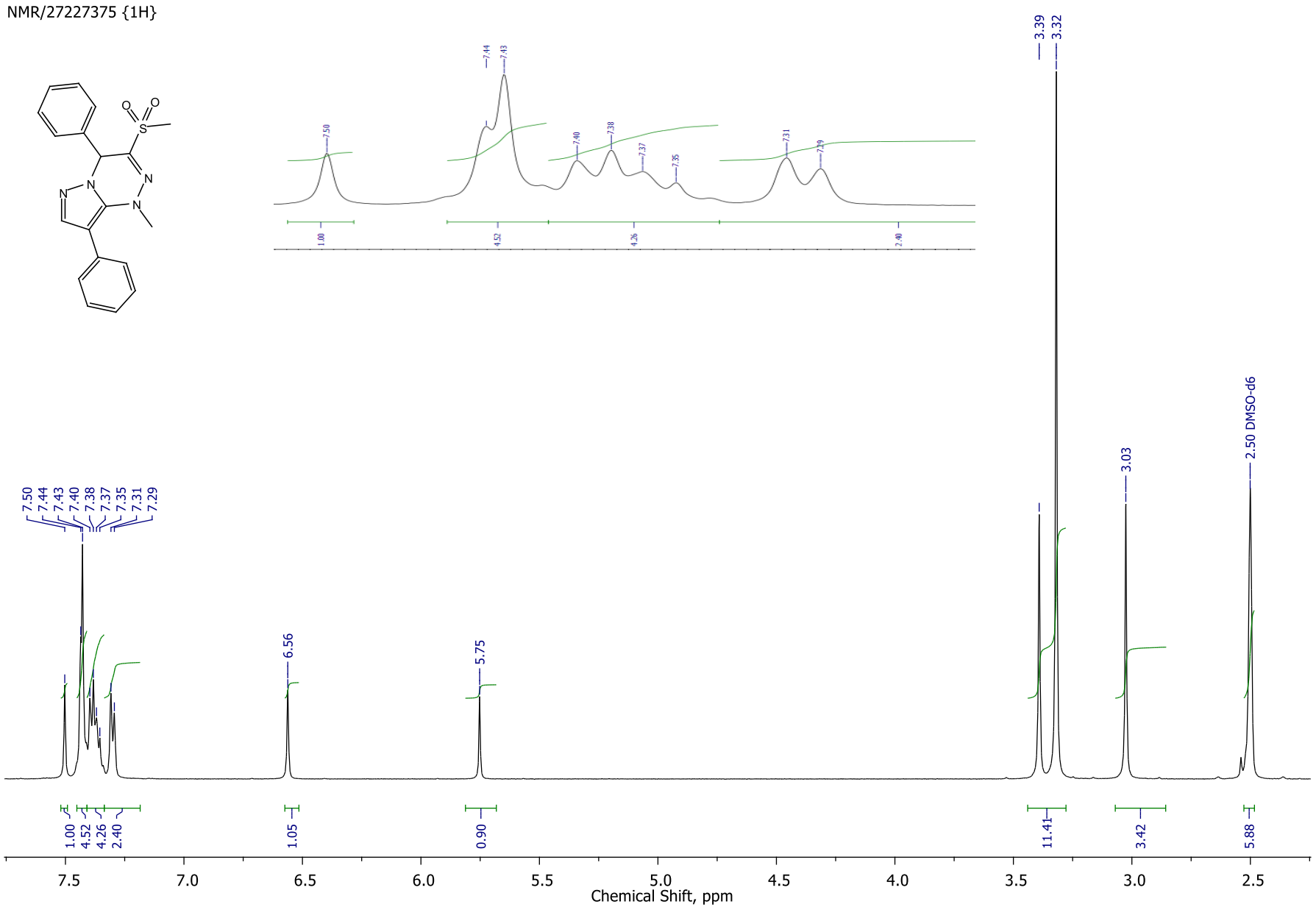


HPLC-MS (ESI) spectrum of 1-(8-(4-chlorophenyl)-3-(methylsulfonyl)-4-phenylpyrazolo[5,1-*c*][1,2,4]triazin-1(4*H*)-yl)propan-1-one (**3c**)

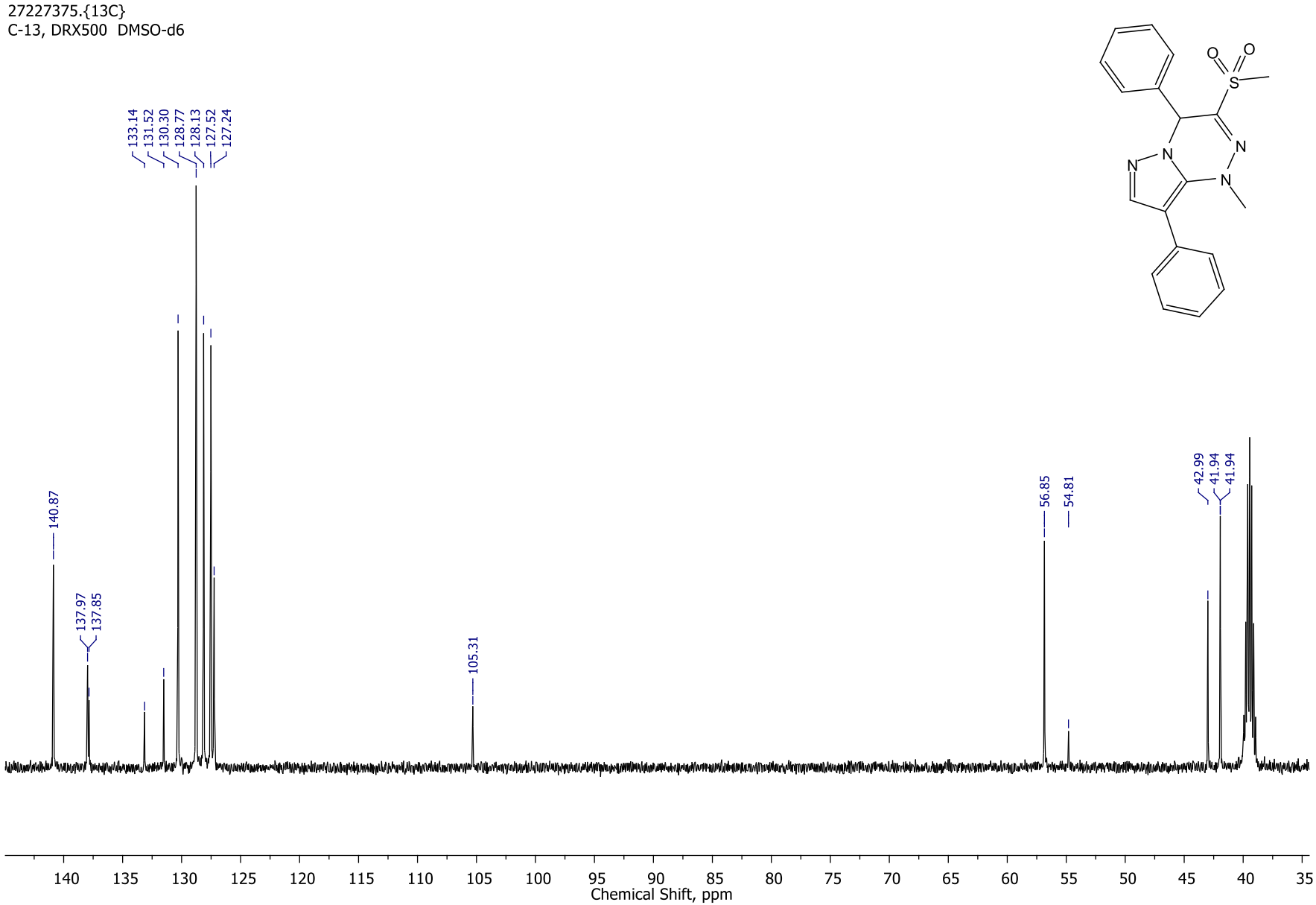




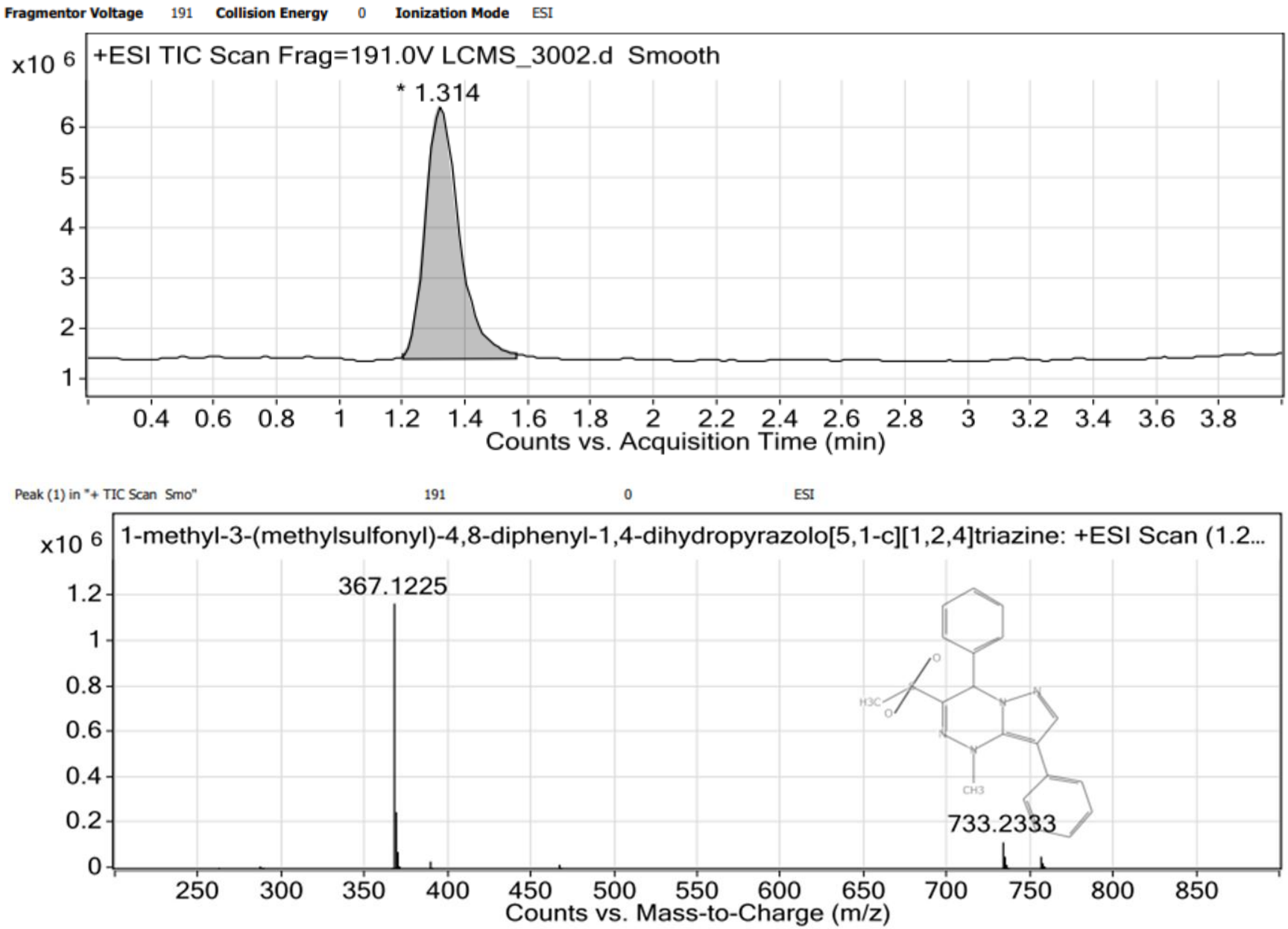
^{1}H NMR spectrum of 1-methyl-3-(methylsulfonyl)-4,8-diphenyl-1,4-dihydropyrazolo[5,1-*c*][1,2,4]triazine (**5a**) (DMSO-d_6, 500.13 MHz) *(mixture of enantiomers)*



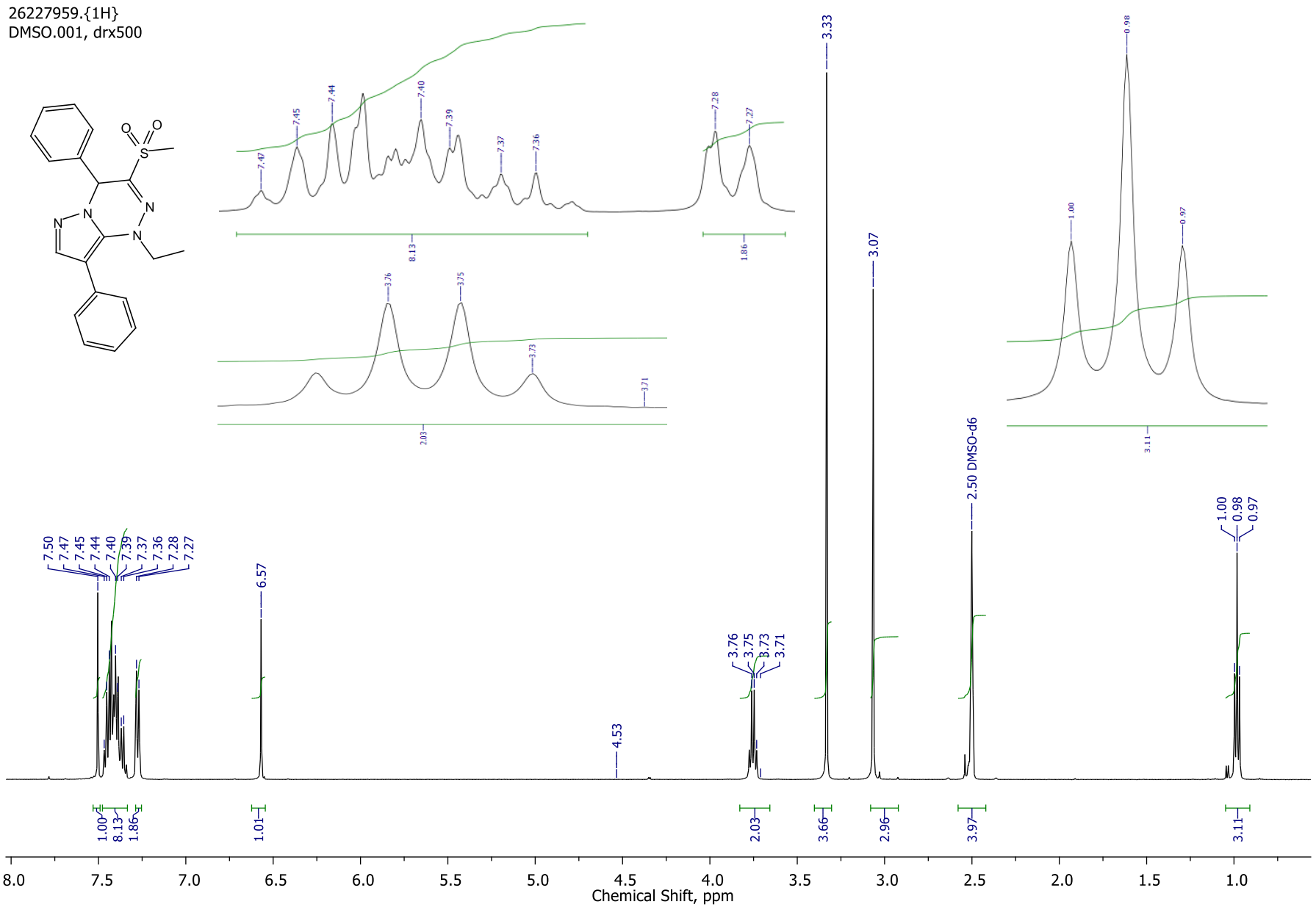
^{13}C NMR spectrum of 1-methyl-3-(methylsulfonyl)-4,8-diphenyl-1,4-dihydropyrazolo[5,1-*c*][1,2,4]triazine (**5a**) (DMSO-d_6, 125.76 MHz) *(mixture of enantiomers)*



HPLC-MS (ESI) spectrum of 1-methyl-3-(methylsulfonyl)-4,8-diphenyl-1,4-dihydropyrazolo[5,1-*c*][1,2,4]triazine (**5a**)

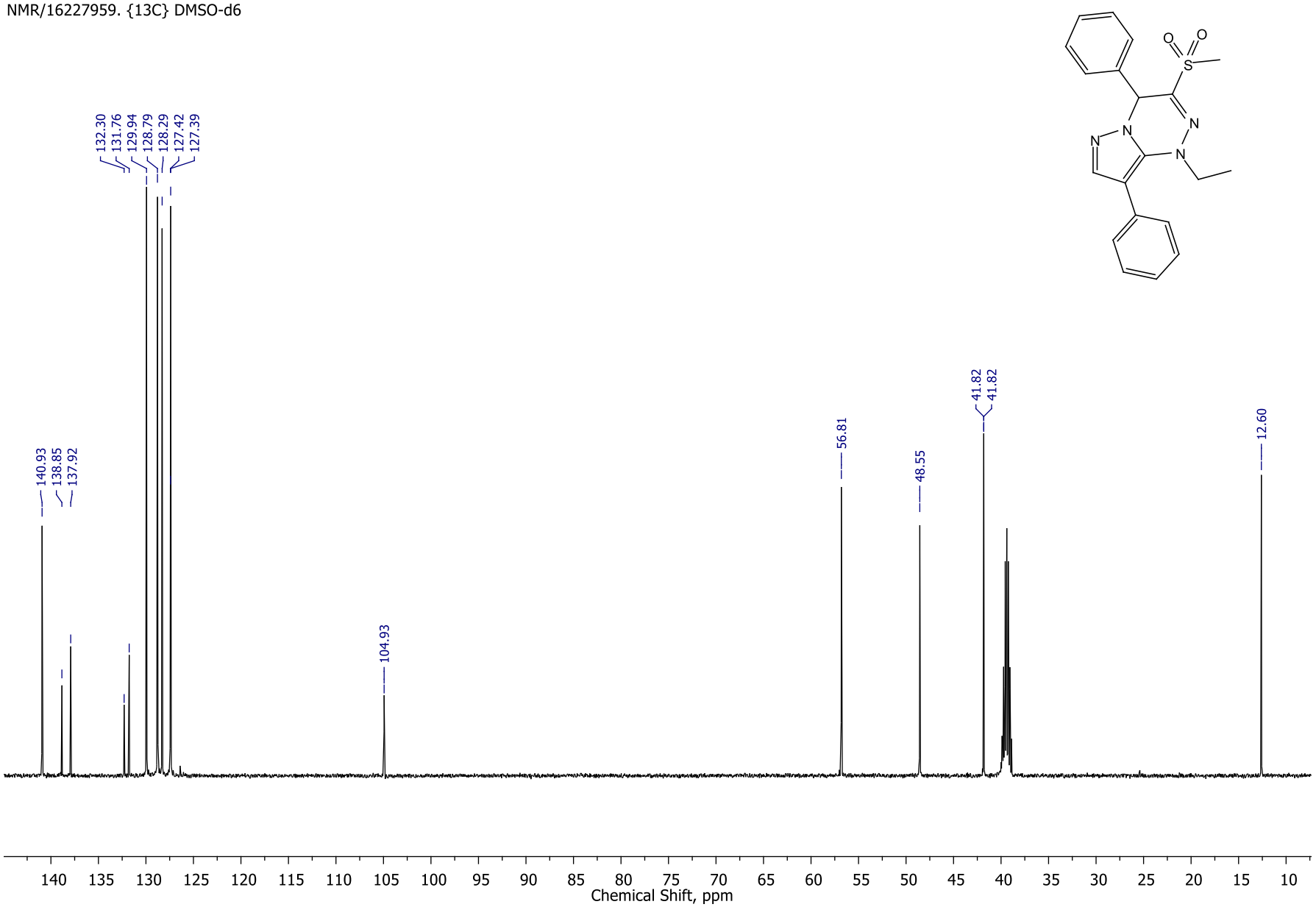


^{1}H NMR spectrum of 1-ethyl-3-(methylsulfonyl)-4,8-diphenyl-1,4-dihydropyrazolo[5,1-*c*][1,2,4]triazine (**5b**) (DMSO-d_6, 500.13 MHz)

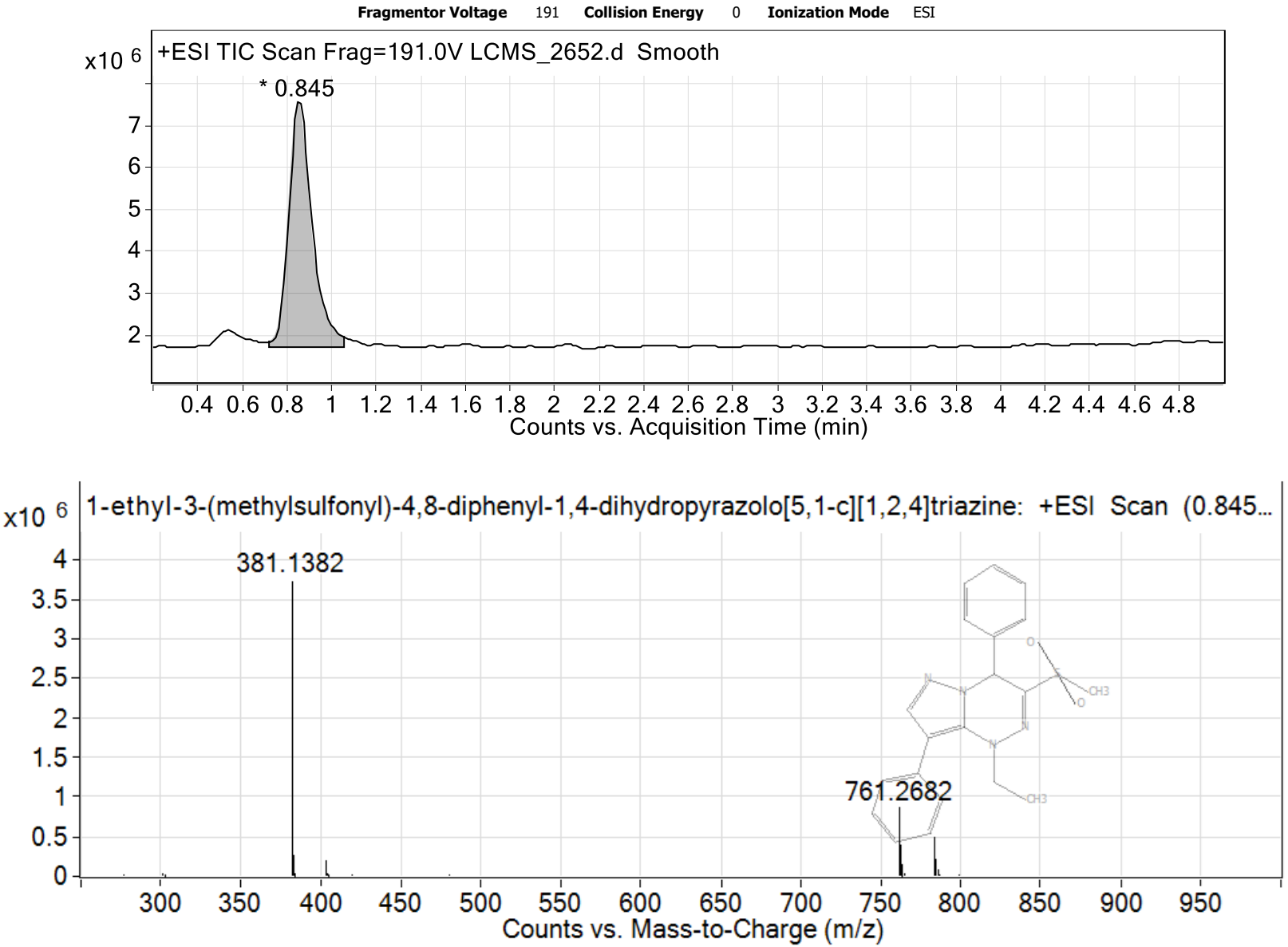


^{13}C NMR spectrum of 1-ethyl-3-(methylsulfonyl)-4,8-diphenyl-1,4-dihydropyrazolo[5,1-*c*][1,2,4]triazine (**5b**)

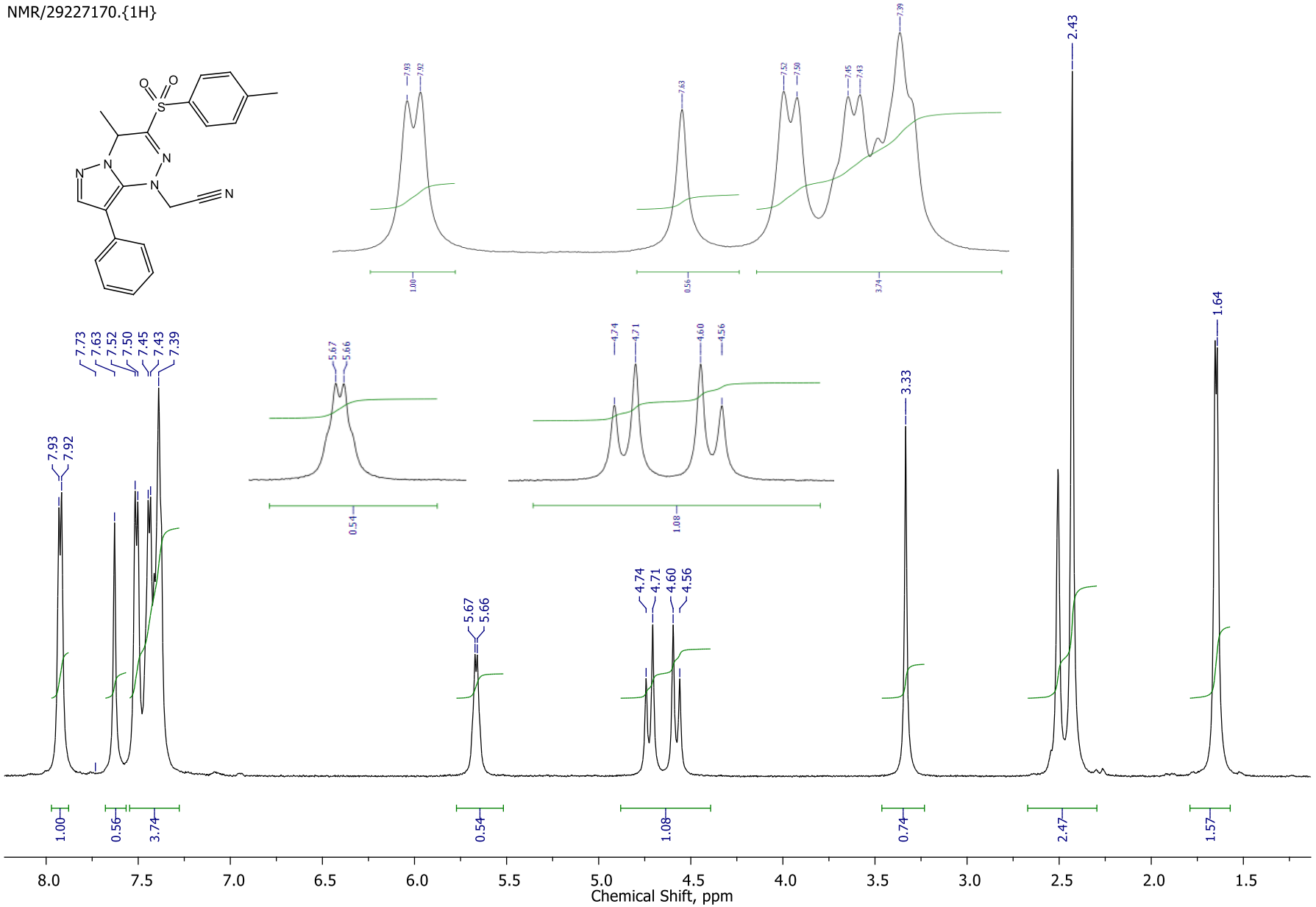
(DMSO-d_6, 125.76 MHz)



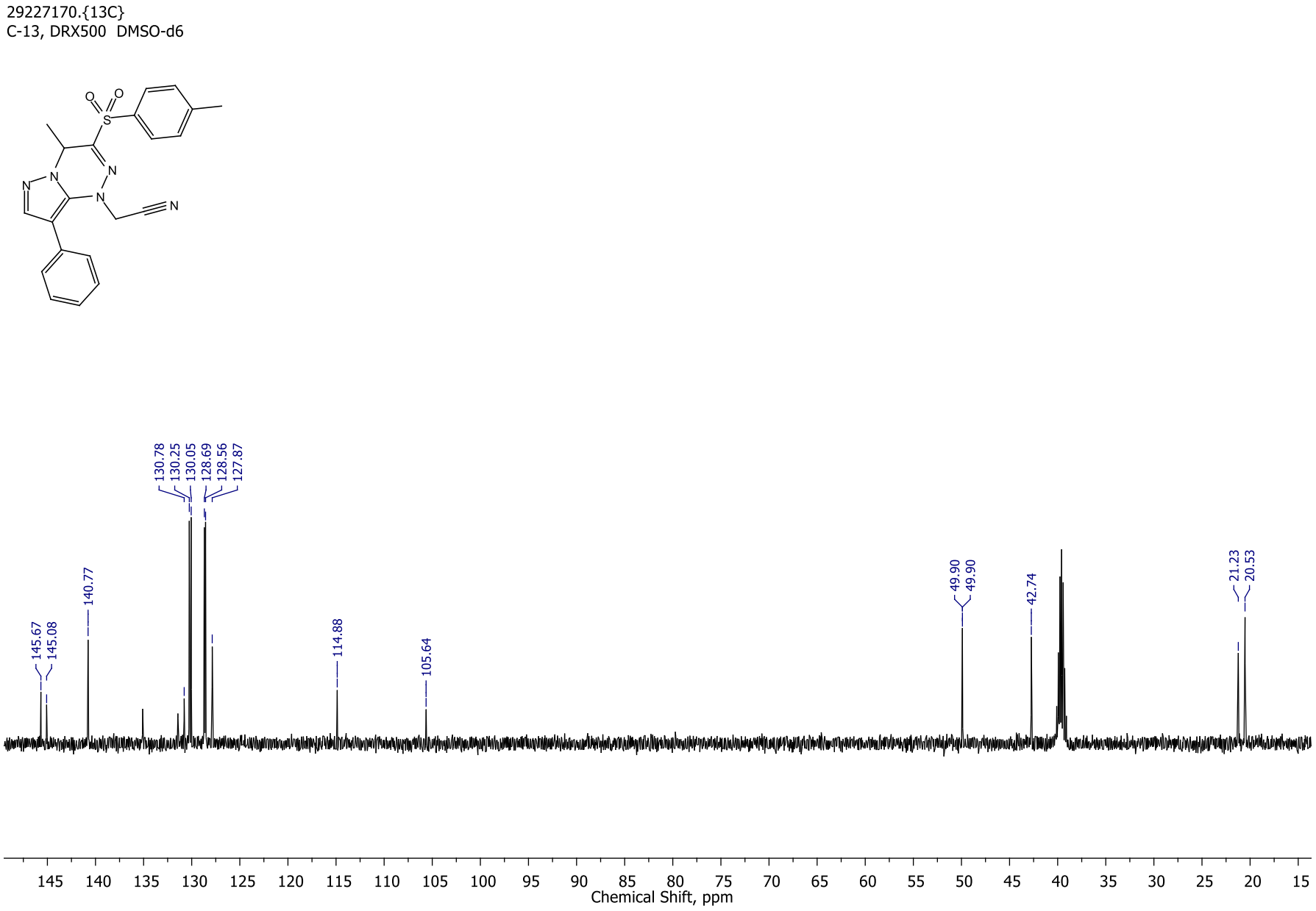
HPLC-MS (ESI) spectrum of 1-ethyl-3-(methylsulfonyl)-4,8-diphenyl-1,4-dihydropyrazolo[5,1-*c*][1,2,4]triazine (**5b**)



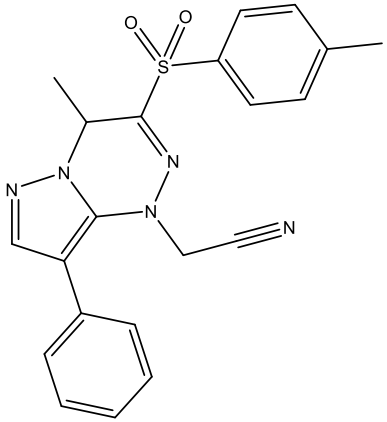
^{1}H NMR spectrum of 2-(4-methyl-8-phenyl-3-tosylpyrazolo[5,1-*c*][1,2,4]triazin-1(4*H*)-yl)acetonitrile (**5c**) (DMSO-d_6, 500.13 MHz)

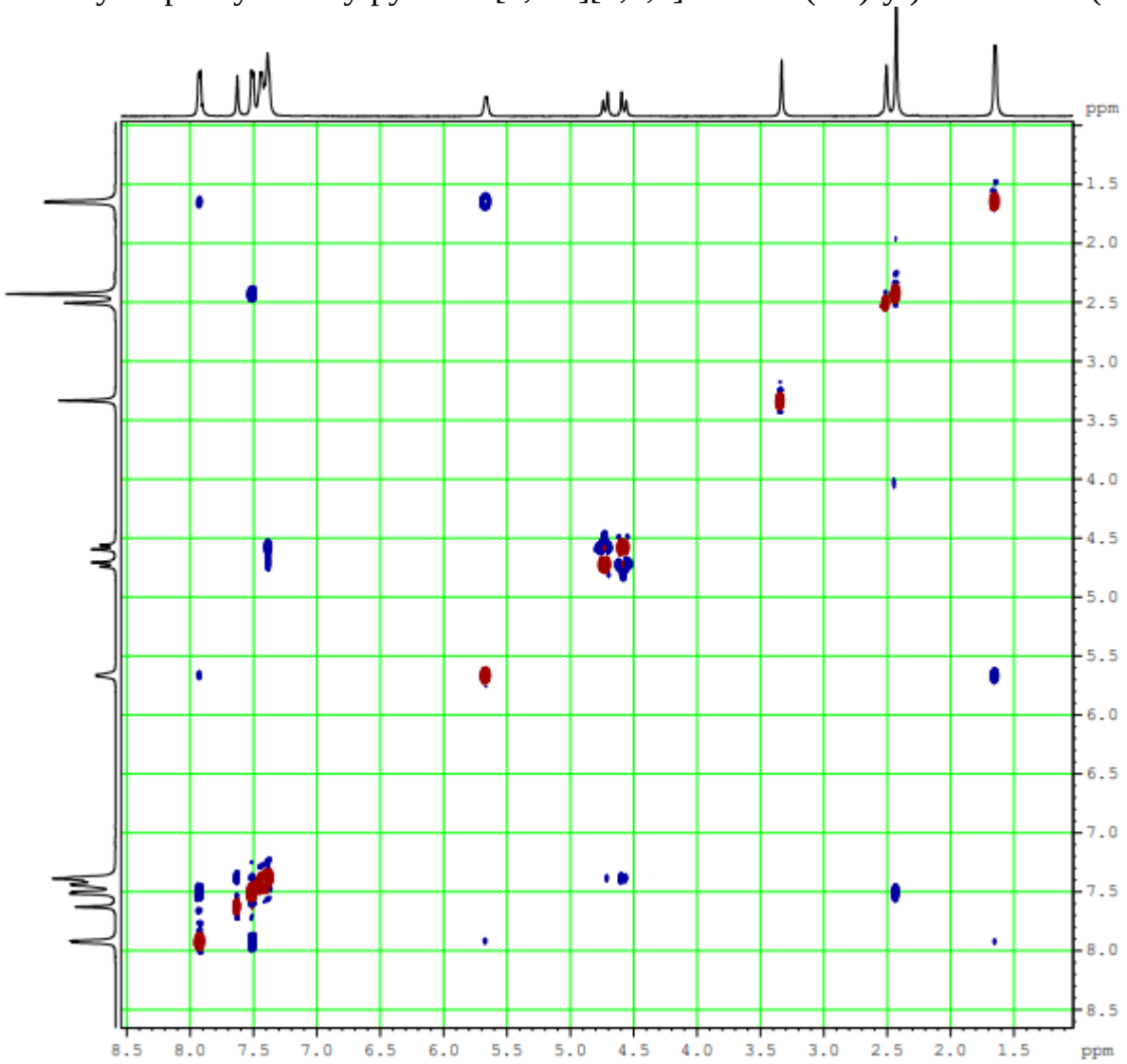


^{13}C NMR spectrum of 2-(4-methyl-8-phenyl-3-tosylpyrazolo[5,1-*c*][1,2,4]triazin-1(4*H*)-yl)acetonitrile (**5c**) (DMSO-d_6, 125.76 MHz)

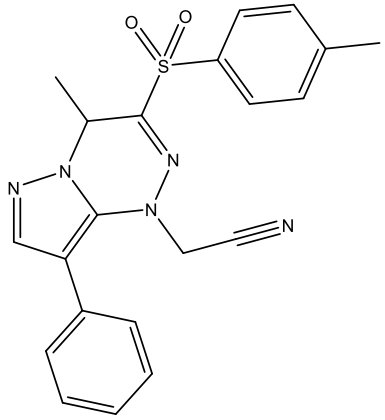


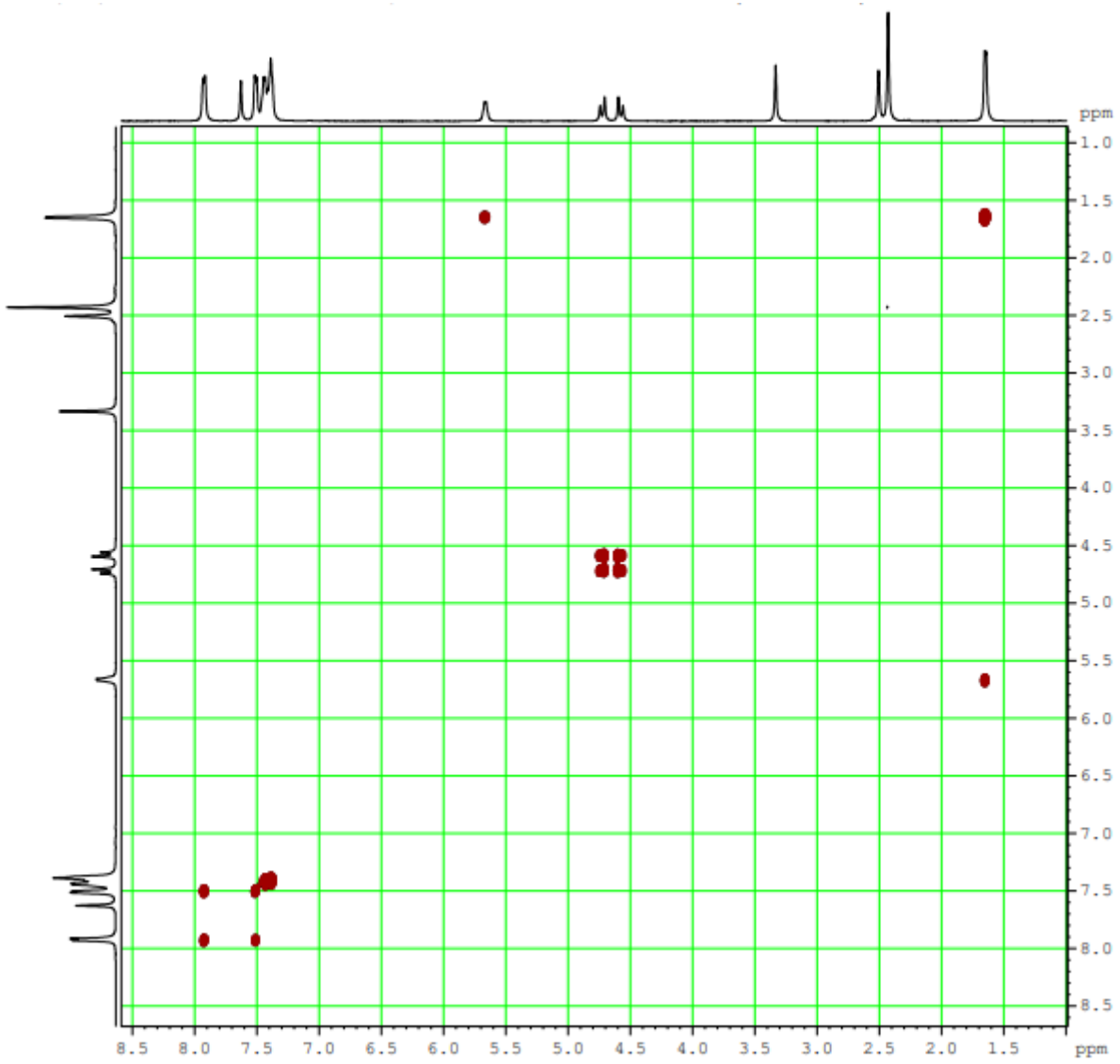
NOESY 2D spectrum of 2-(4-methyl-8-phenyl-3-tosylpyrazolo[5,1-*c*][1,2,4]triazin-1(4*H*)-yl)acetonitrile (**5c**)



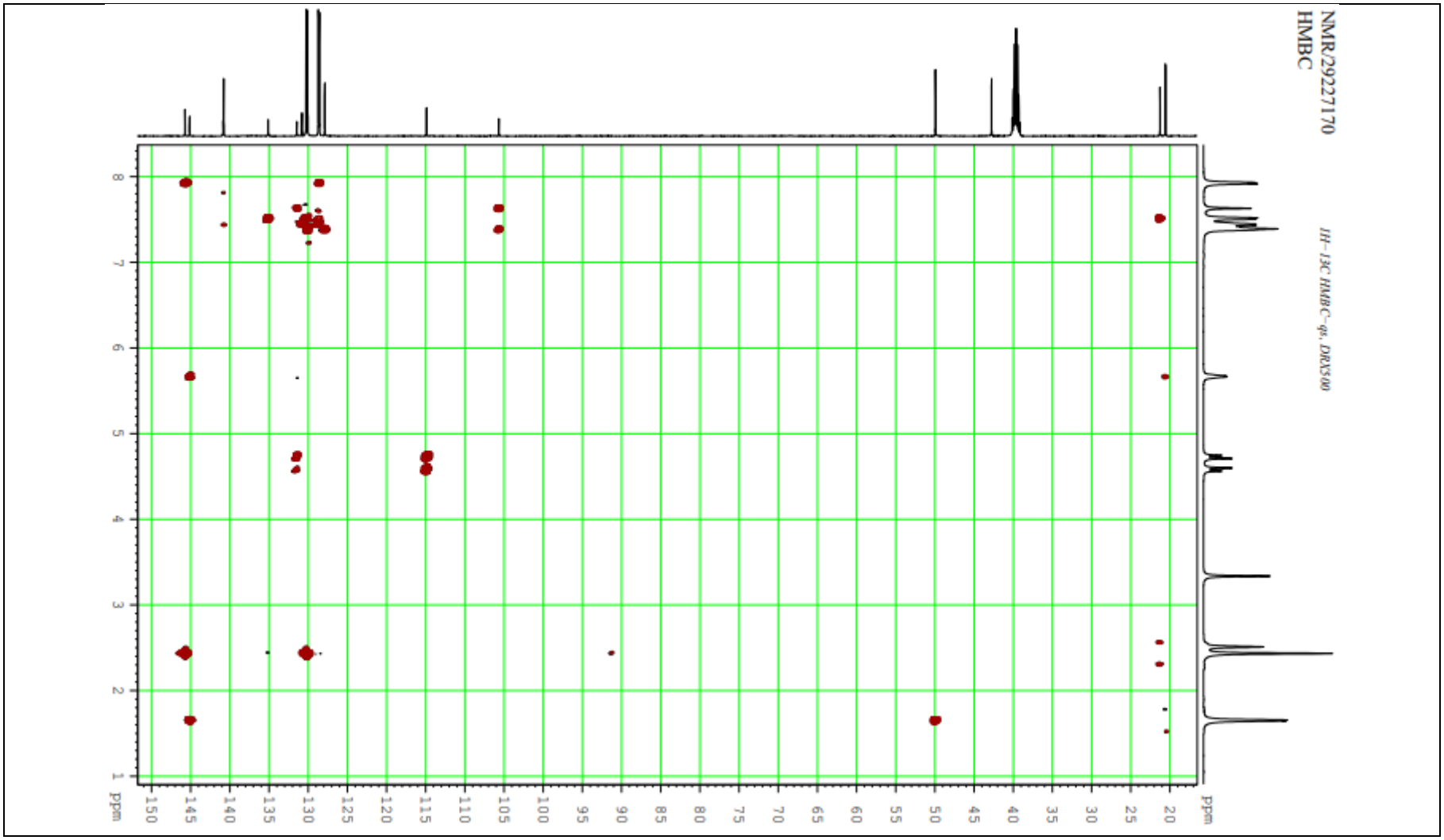


COSY 2D spectrum of 2-(4-methyl-8-phenyl-3-tosylpyrazolo[5,1-*c*][1,2,4]triazin-1(4*H*)-yl)acetonitrile (**5c**)

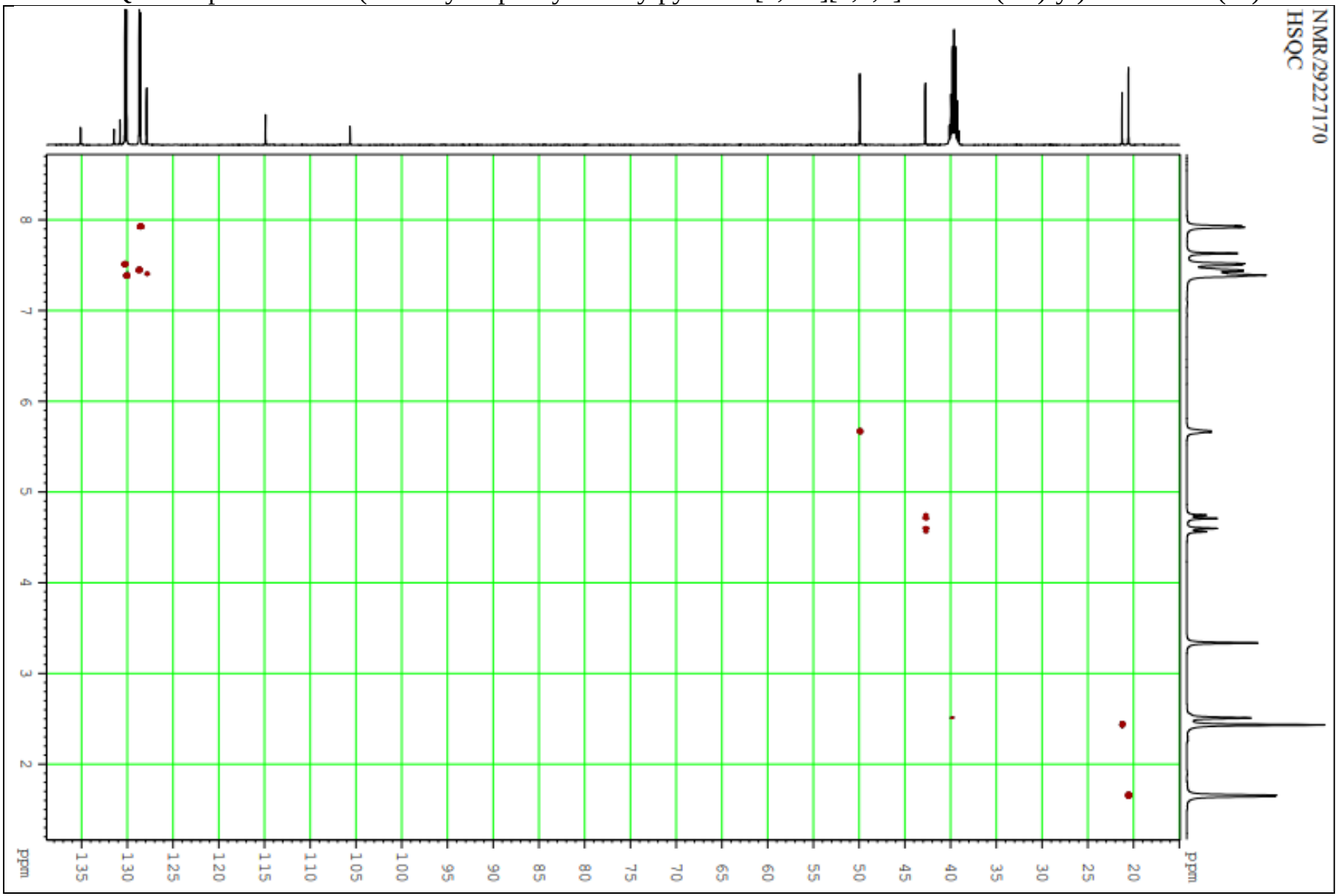




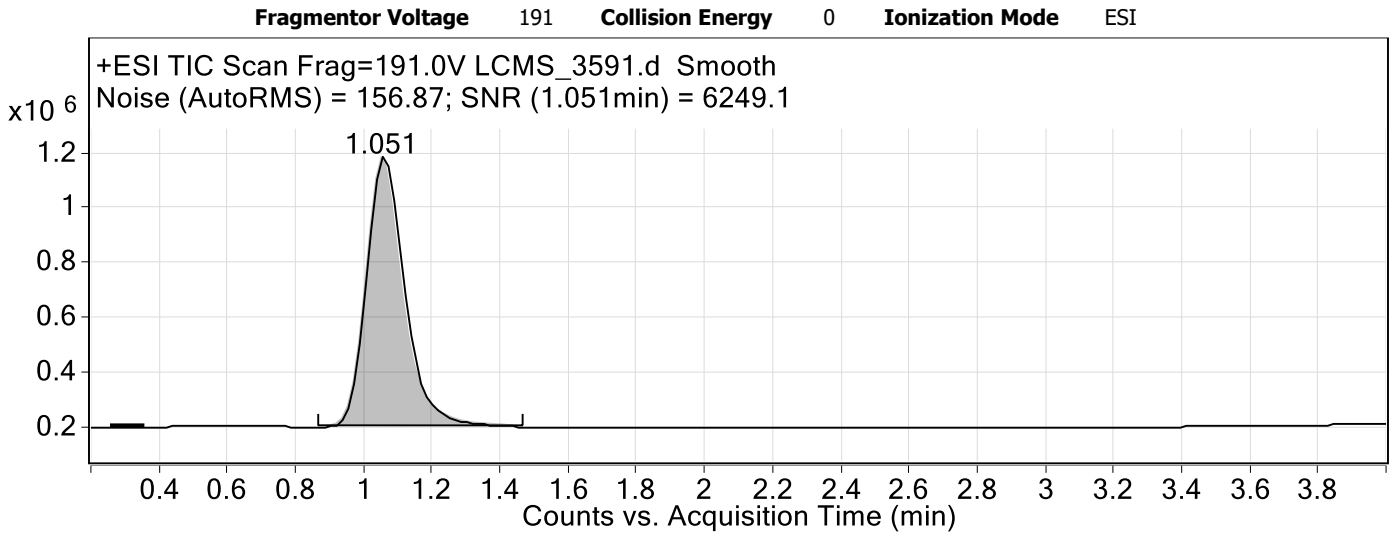
HMBC 2D spectrum of 2-(4-Methyl-8-phenyl-3-tosylpyrazolo[5,1-*c*][1,2,4]triazin-1(4*H*)-yl)acetonitrile (**5c**)

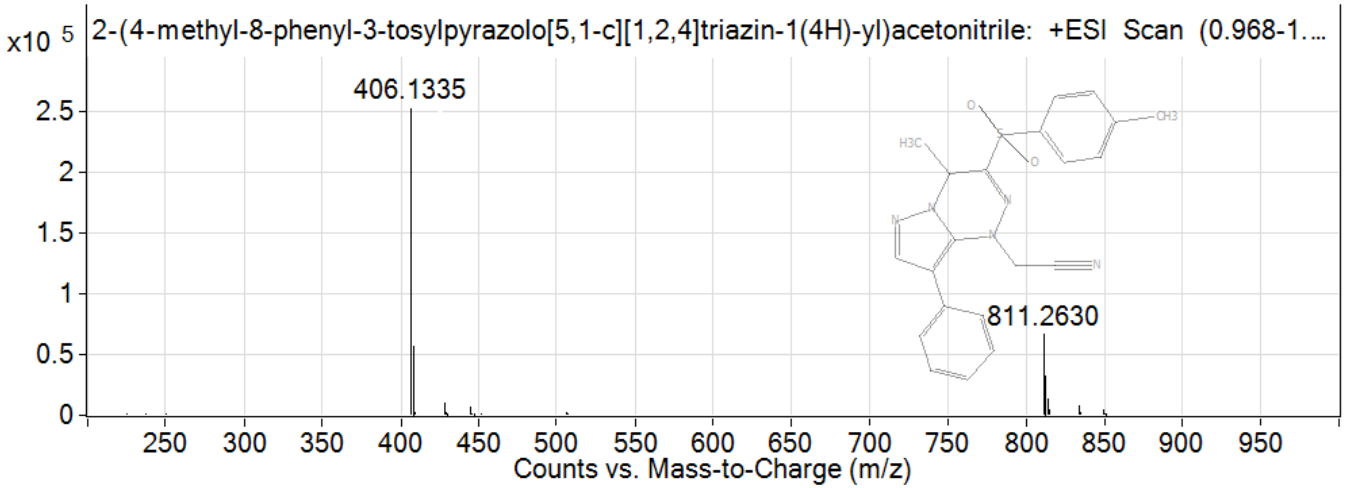


HSQC 2D spectrum of 2-(4-methyl-8-phenyl-3-tosylpyrazolo[5,1-*c*][1,2,4]triazin-1(4*H*)-yl)acetonitrile (**5c**)

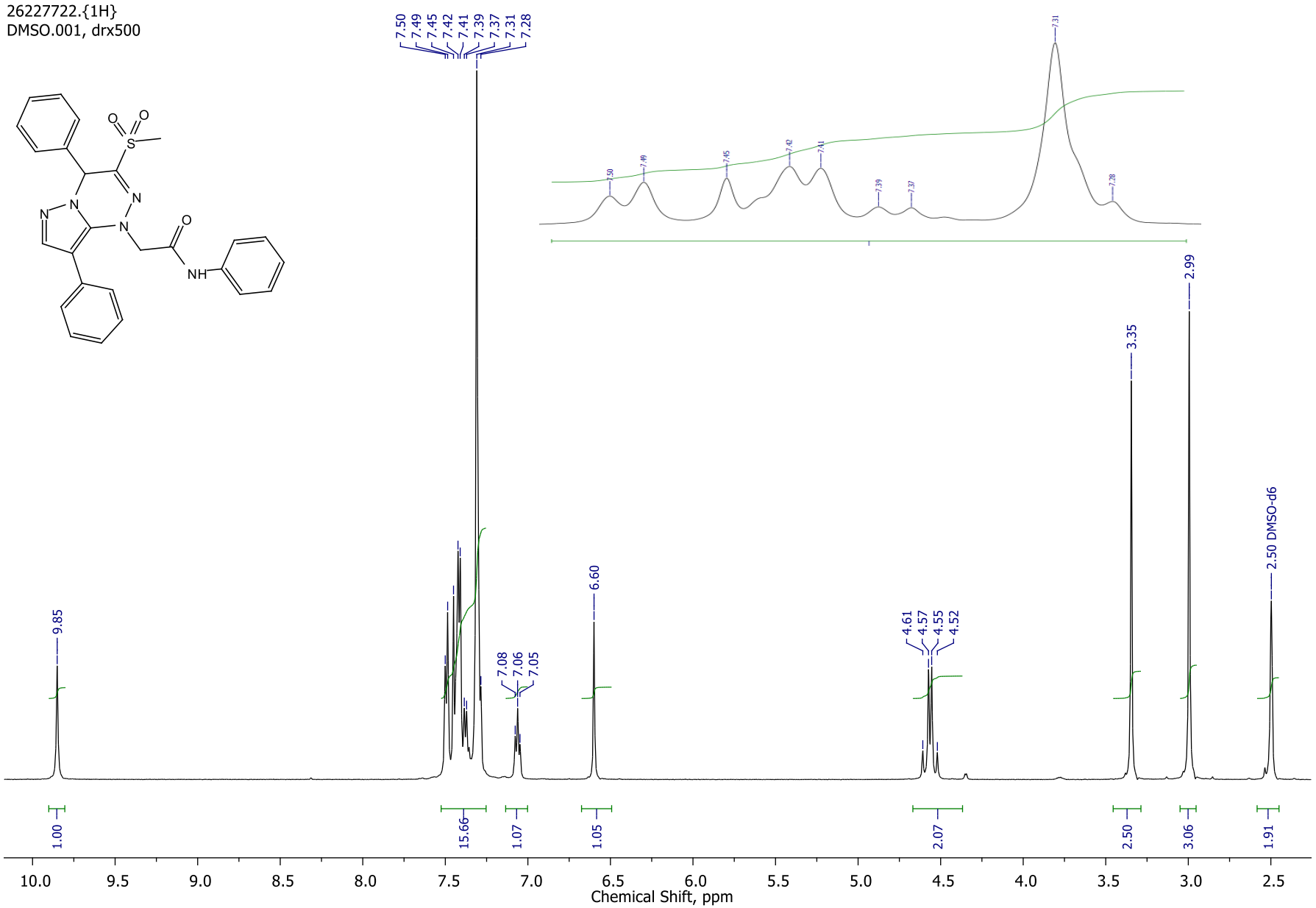


HPLC-MS (ESI) spectrum of 2-(4-methyl-8-phenyl-3-tosylpyrazolo[5,1-*c*][1,2,4]triazin-1(4*H*)-yl)acetonitrile (**5c**)

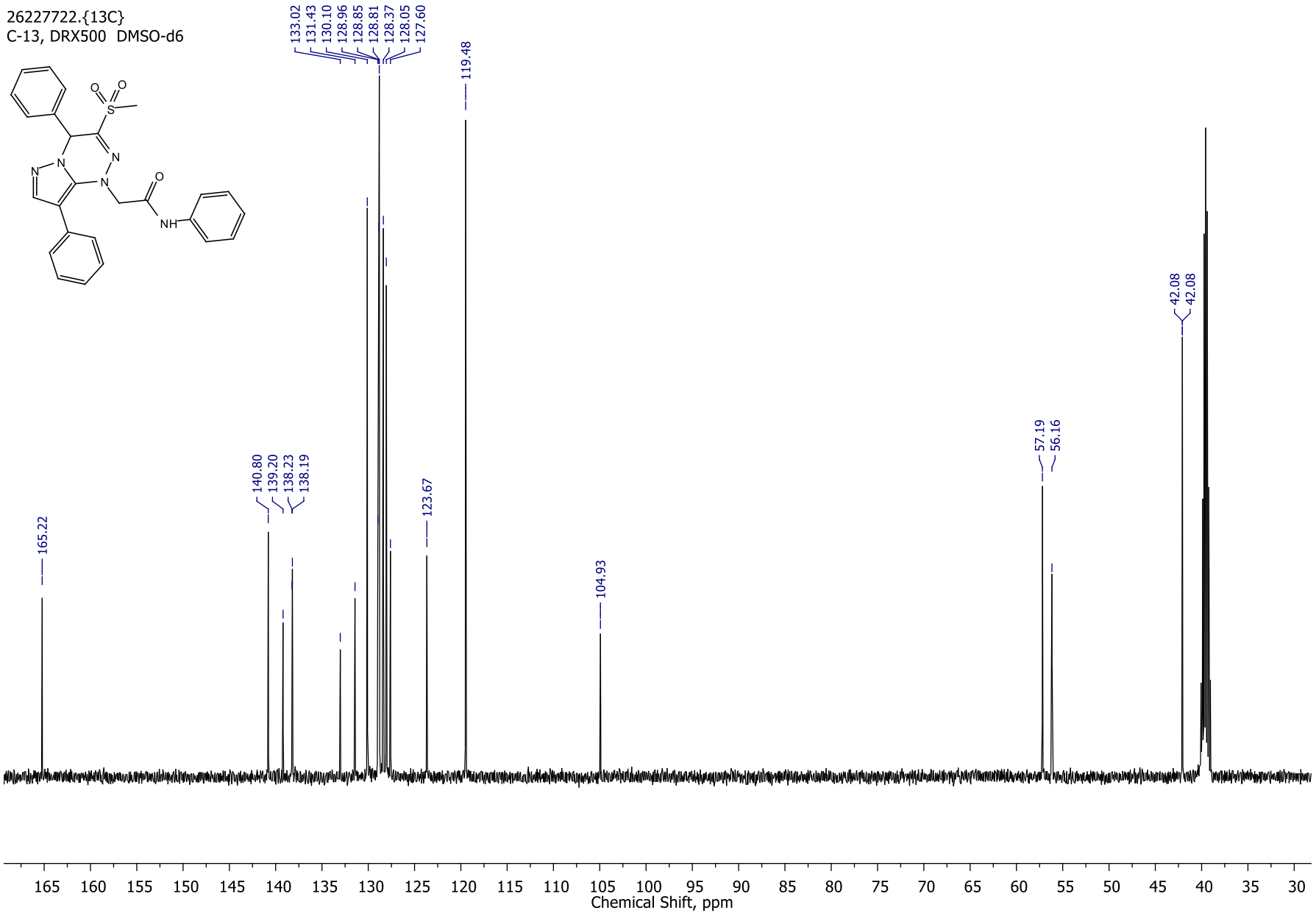




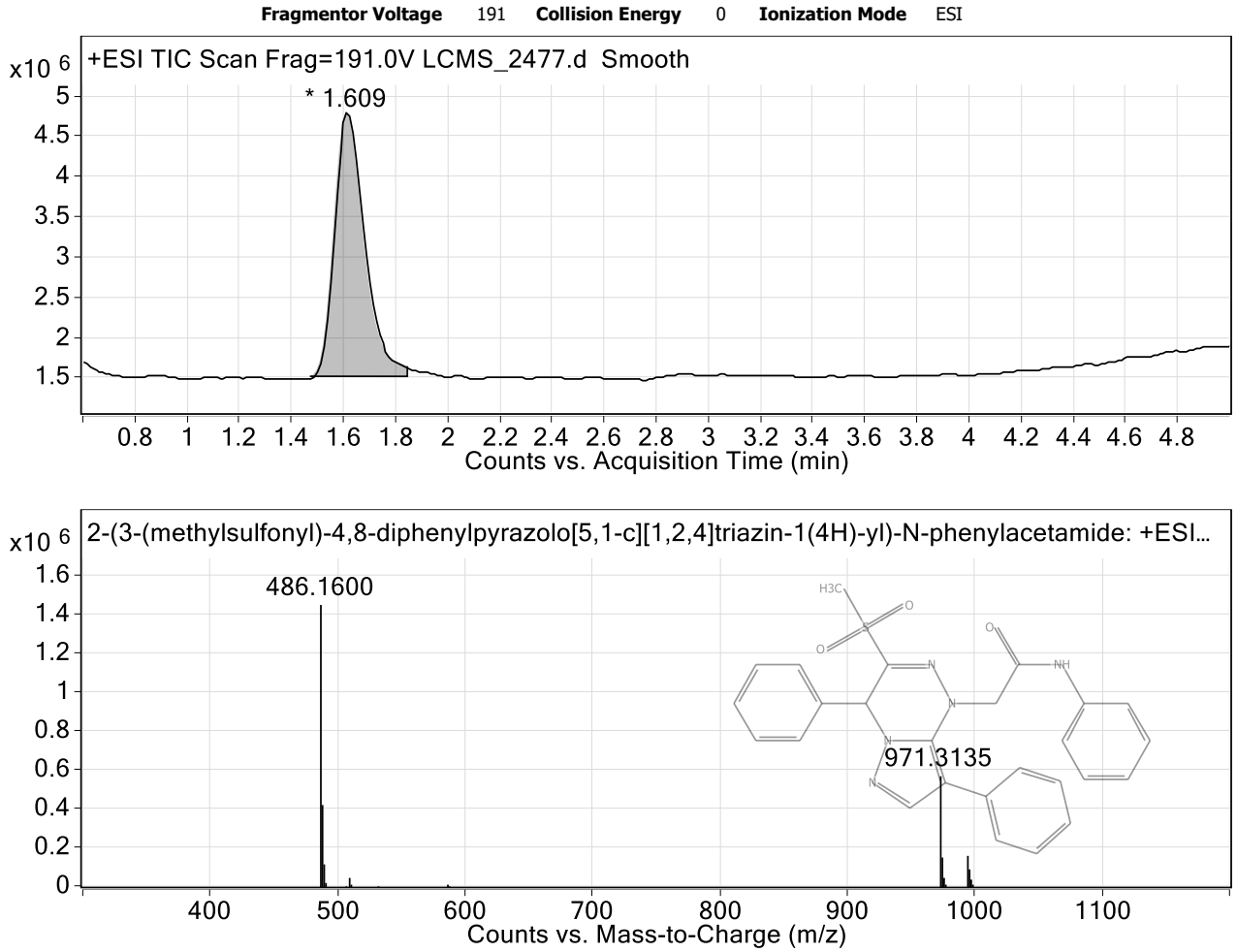
^{1}H NMR spectrum of 2-(3-(methylsulfonyl)-4,8-diphenylpyrazolo[5,1-*c*][1,2,4]triazin-1(4*H*)-yl)-*N*-phenylacetamide (**5d**) (DMSO-d_6, 500.13 MHz)



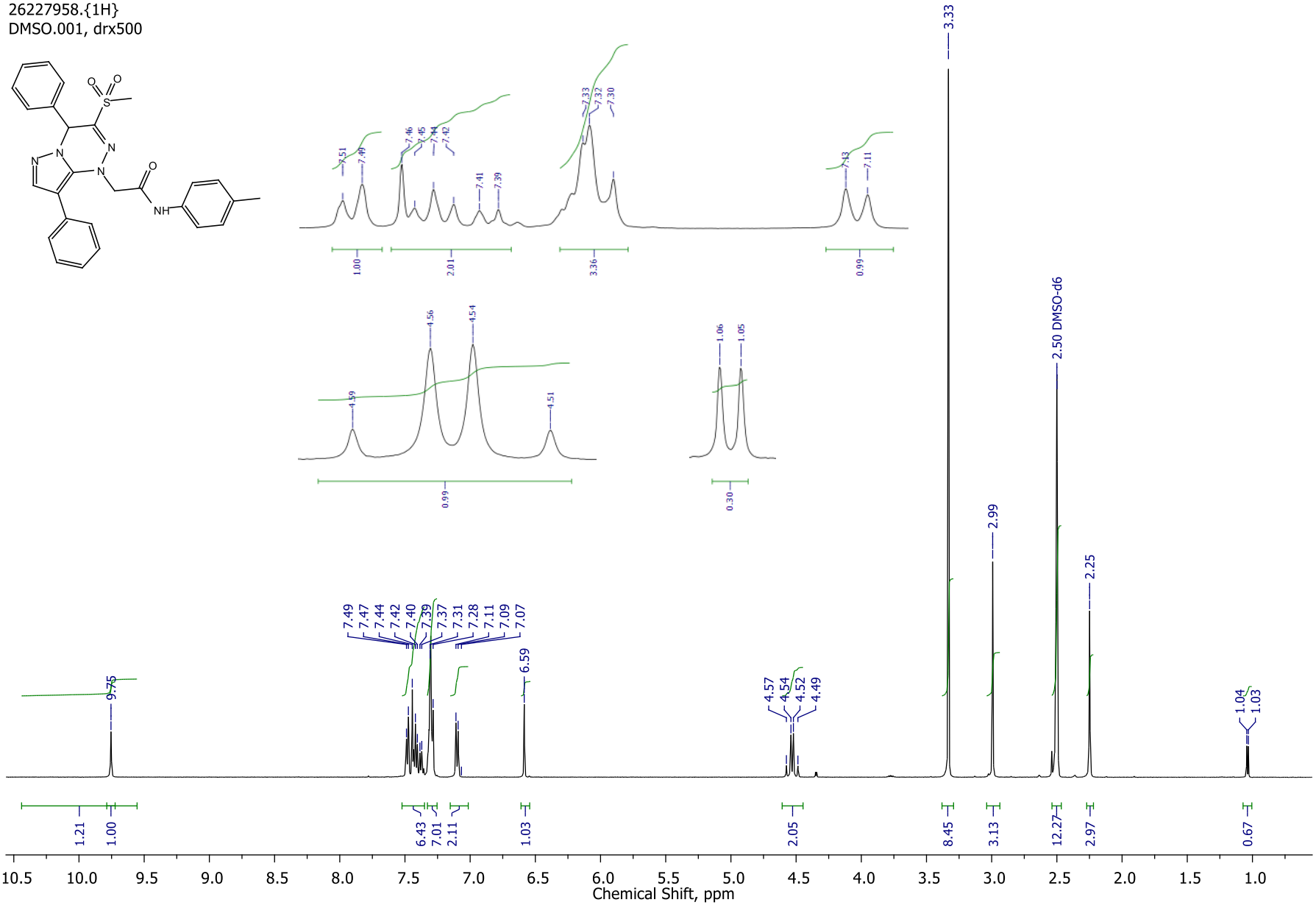
^{13}C NMR spectrum of 2-(3-(methylsulfonyl)-4,8-diphenylpyrazolo[5,1-*c*][1,2,4]triazin-1(4*H*)-yl)-*N*-phenylacetamide (**5d**) (DMSO-d_6, 125.76 MHz)



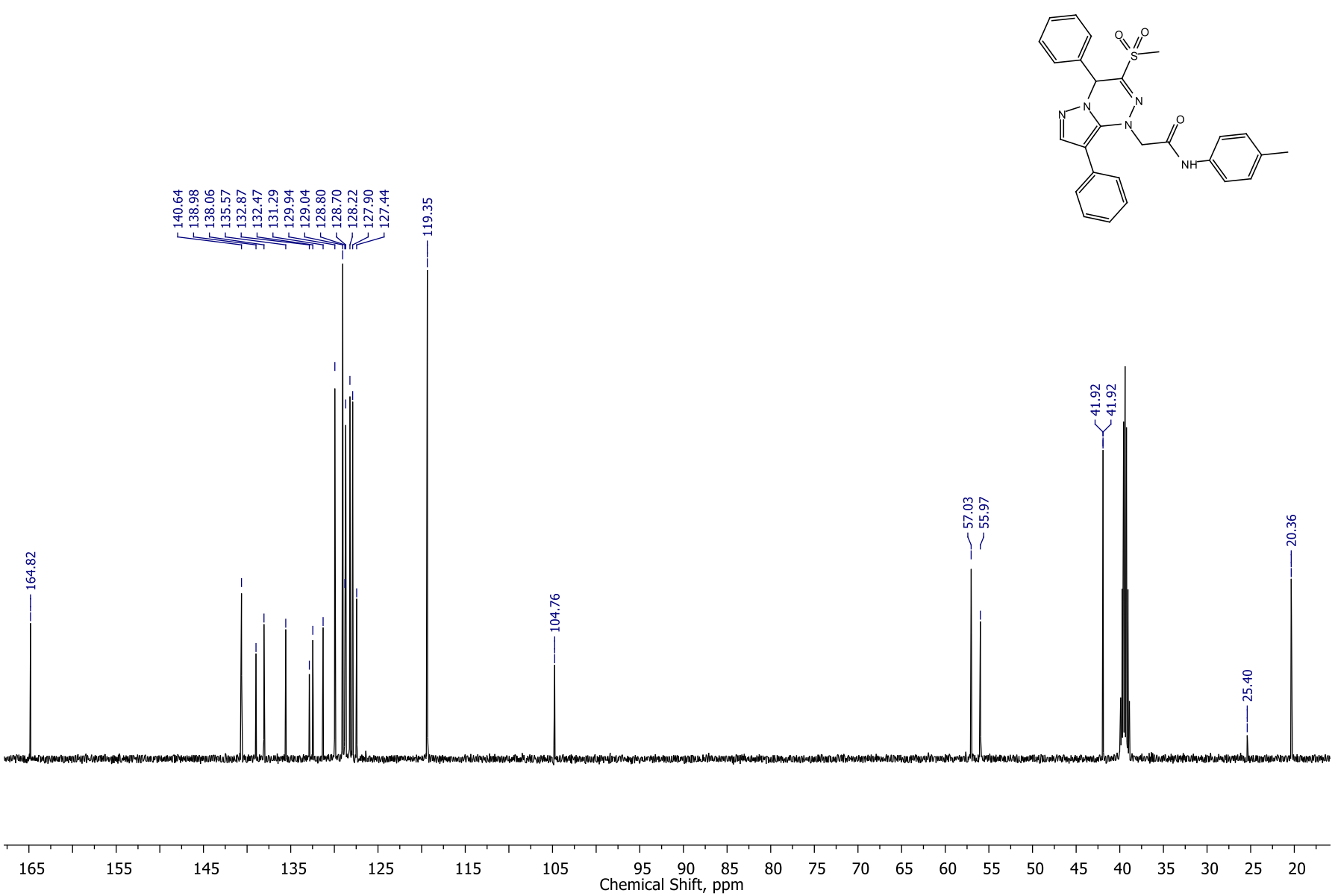
HPLC-MS (ESI) spectrum of 2-(3-(methylsulfonyl)-4,8-diphenylpyrazolo[5,1-*c*][1,2,4]triazin-1(4*H*)-yl)-*N*-phenylacetamide (**5d**)



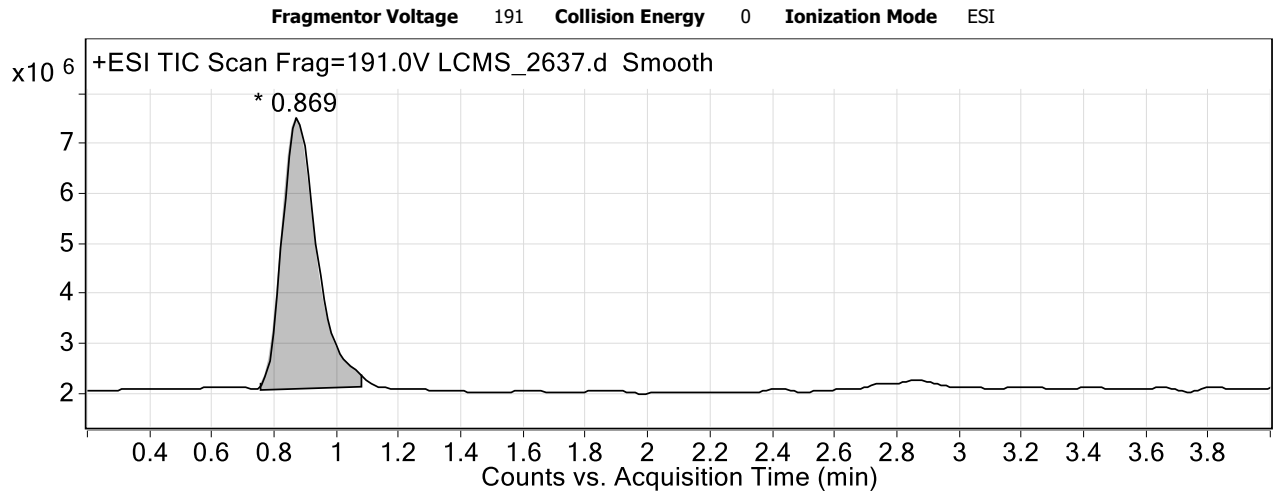
^{1}H NMR spectrum of 2-(3-(methylsulfonyl)-4,8-diphenylpyrazolo[5,1-*c*][1,2,4]triazin-1(4*H*)-yl)-*N*-(*p*-tolyl)acetamide (**5e**) (DMSO-d_6, 500.13 MHz)

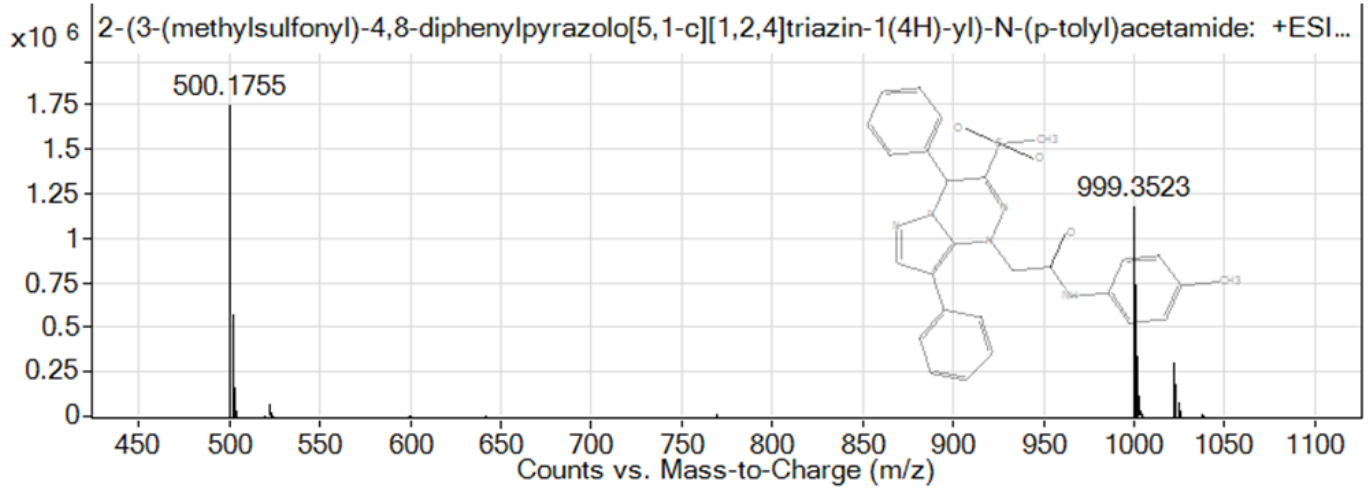


^{13}C NMR spectrum of 2-(3-(methylsulfonyl)-4,8-diphenylpyrazolo[5,1-*c*][1,2,4]triazin-1(4*H*)-yl)-*N*-(*p*-tolyl)acetamide (**5e**) (DMSO-d_6, 125.76 MHz)



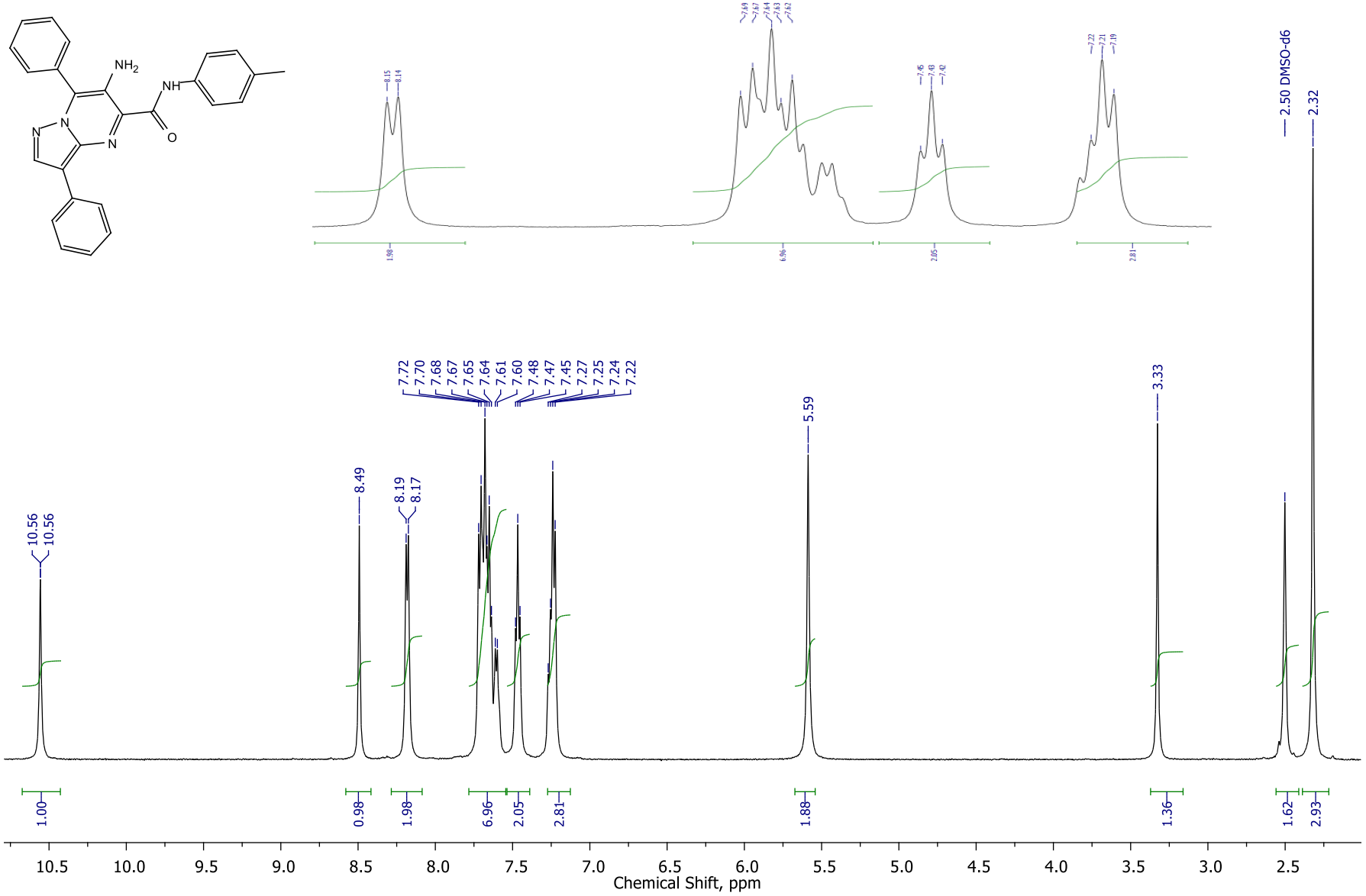
HPLC-MS (ESI) spectrum of 2-(3-(methylsulfonyl)-4,8-diphenylpyrazolo[5,1-*c*][1,2,4]triazin-1(4*H*)-yl)-*N*-(*p*-tolyl)acetamide (**5e**)



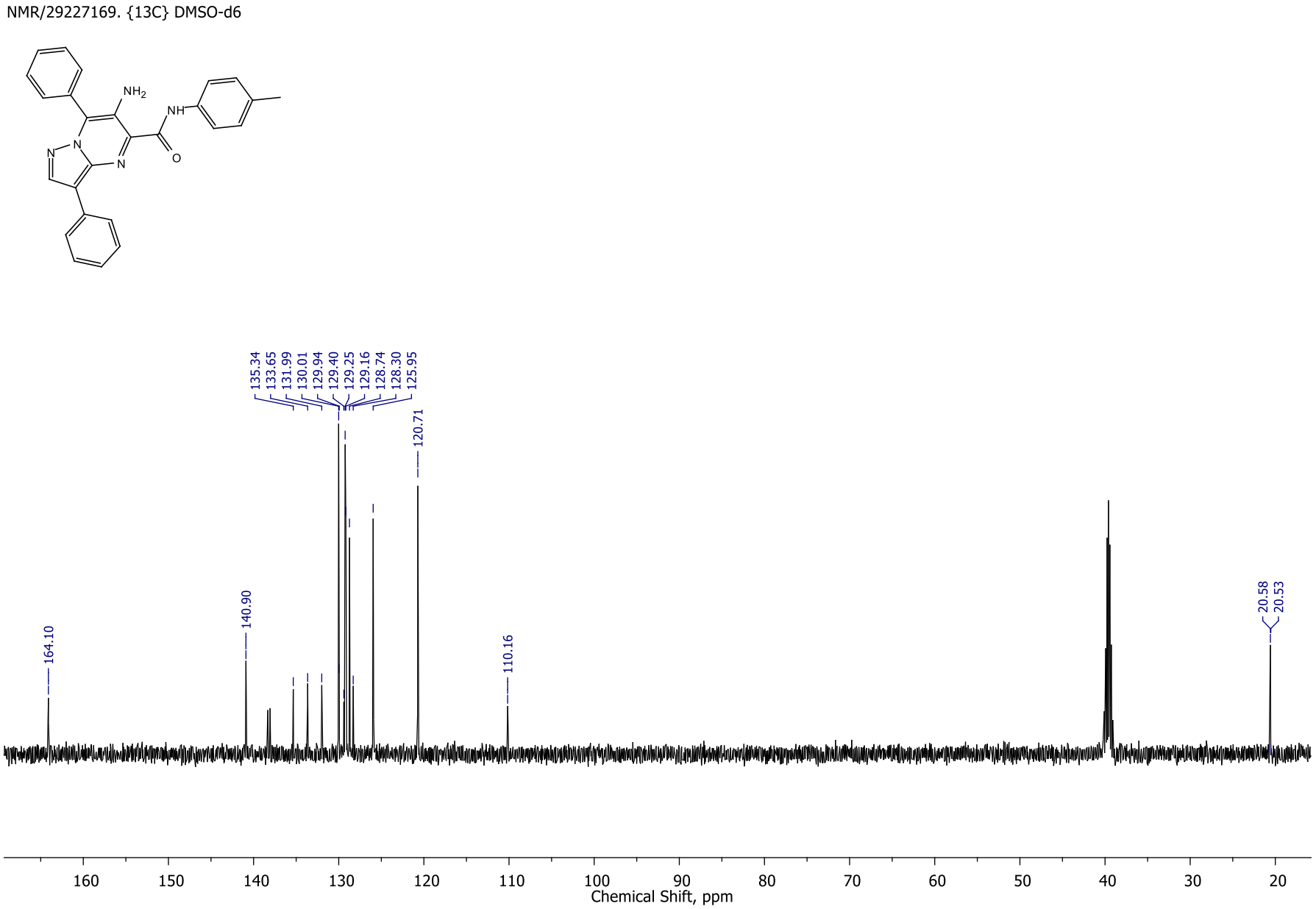


^{1}H NMR spectrum of 6-amino-3,7-diphenyl-*N*-(*p*-tolyl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-5-carboxamide (**6a**) (DMSO-d_6, 500.13 MHz) (note: the compound is not sufficiently soluble in DMSO)

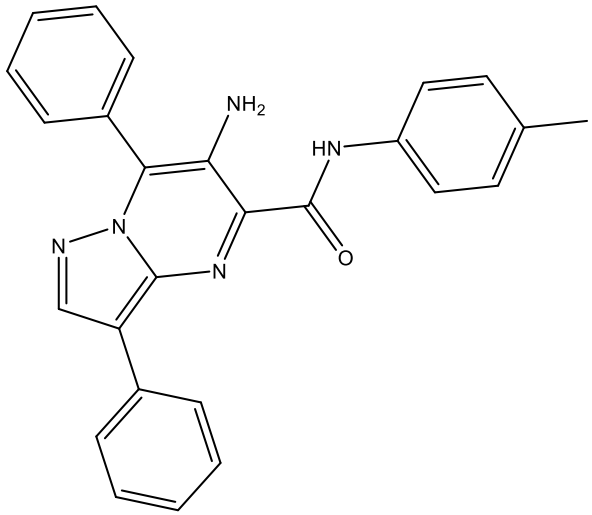
NMR/29227169. {1H} insoluble in DMFA-d6

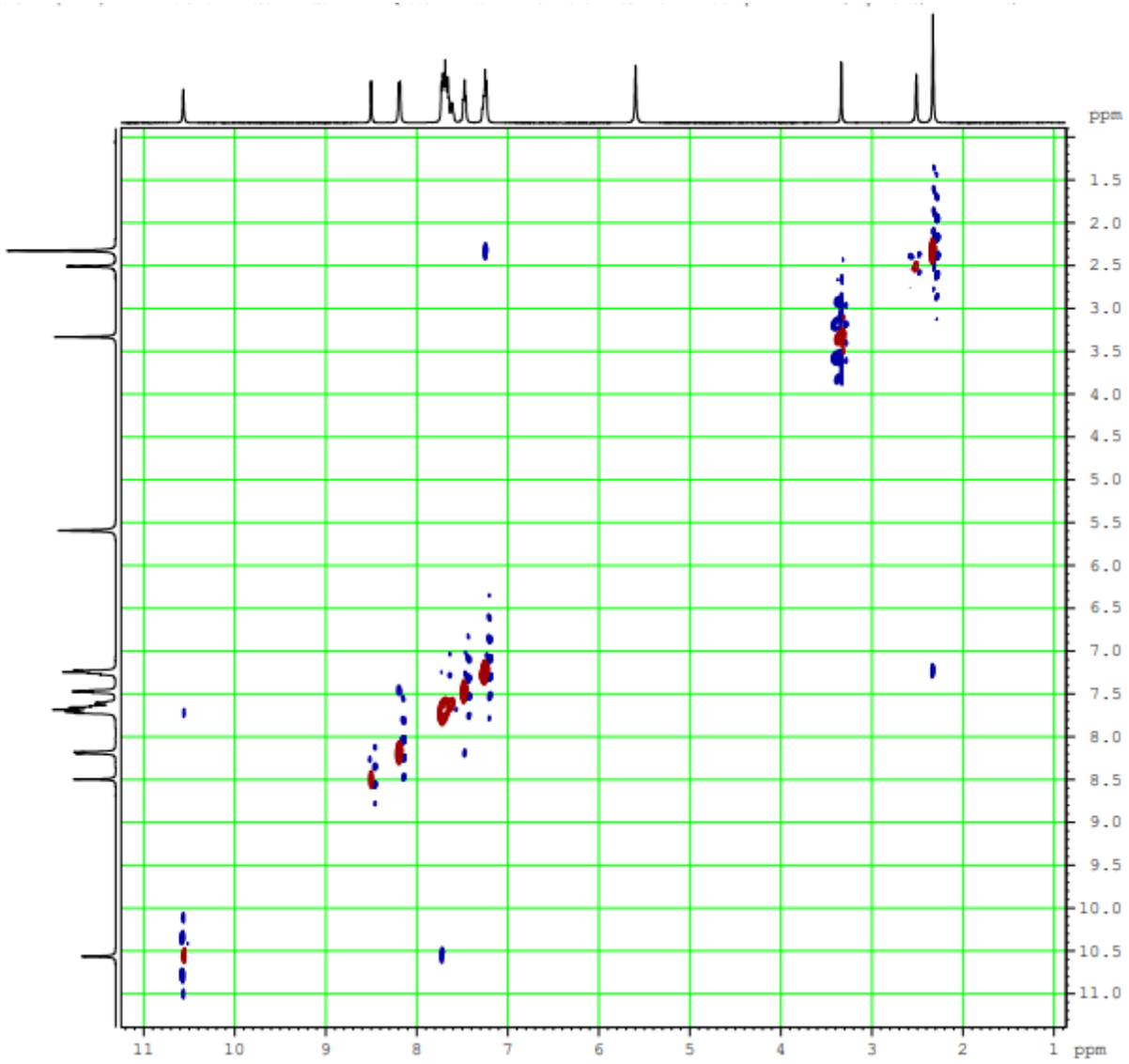


^{13}C NMR spectrum of 6-amino-3,7-diphenyl-*N*-(*p*-tolyl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-5-carboxamide (**6a**) (DMSO-d_6, 125.76 MHz)

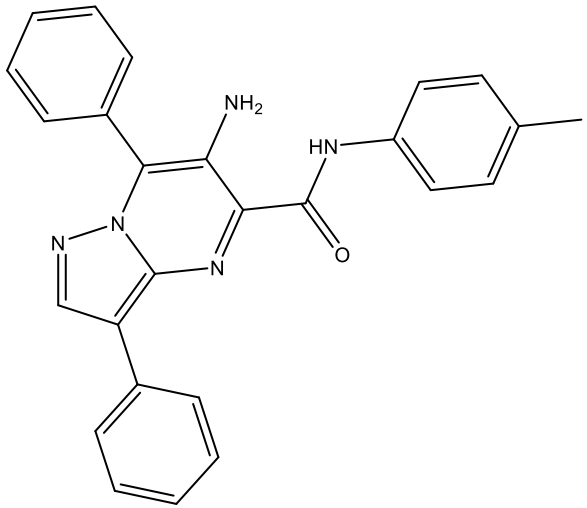


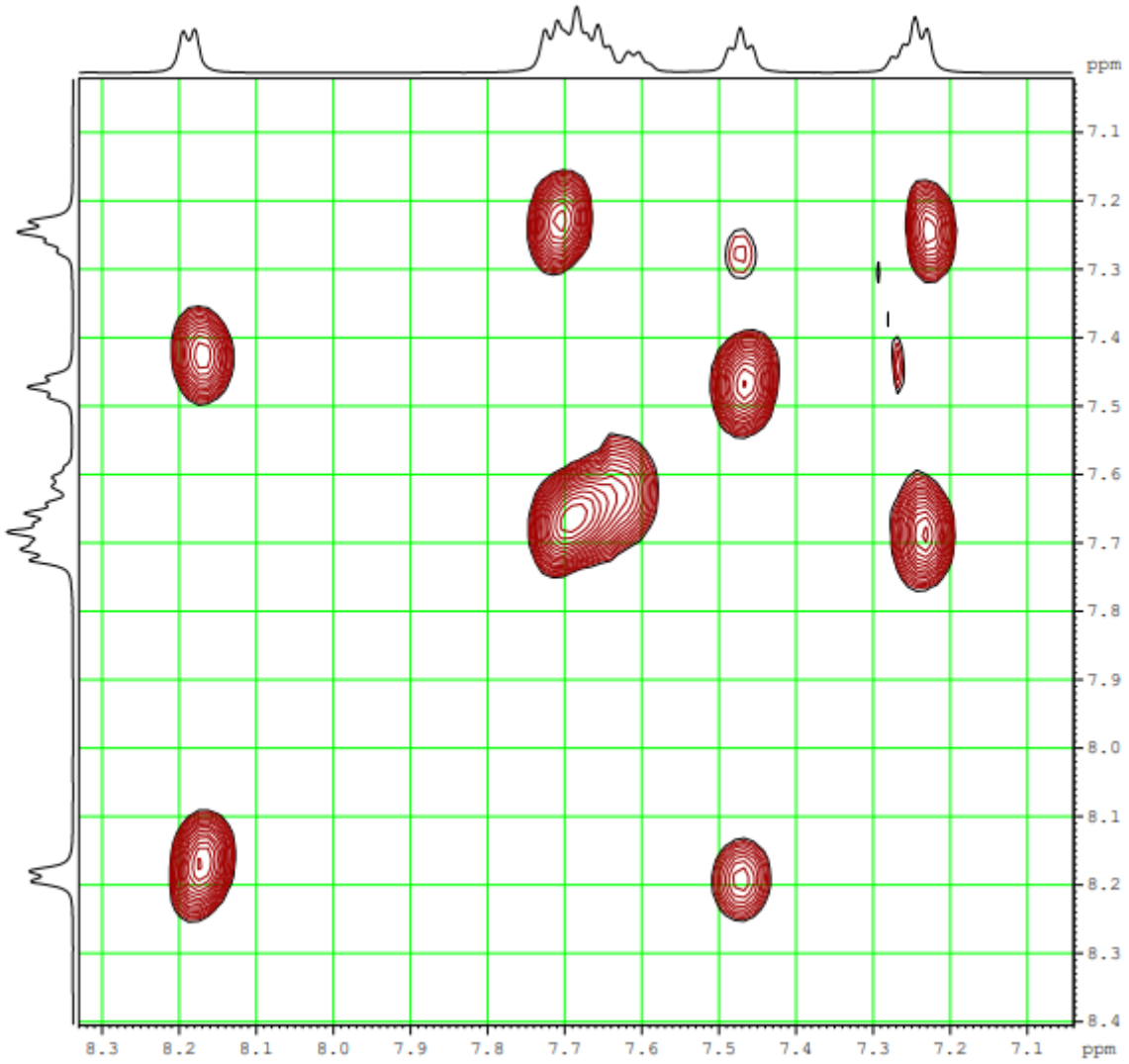
NOESY 2D spectrum of 6-amino-3,7-diphenyl-*N*-(*p*-tolyl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-5-carboxamide (**6a**)



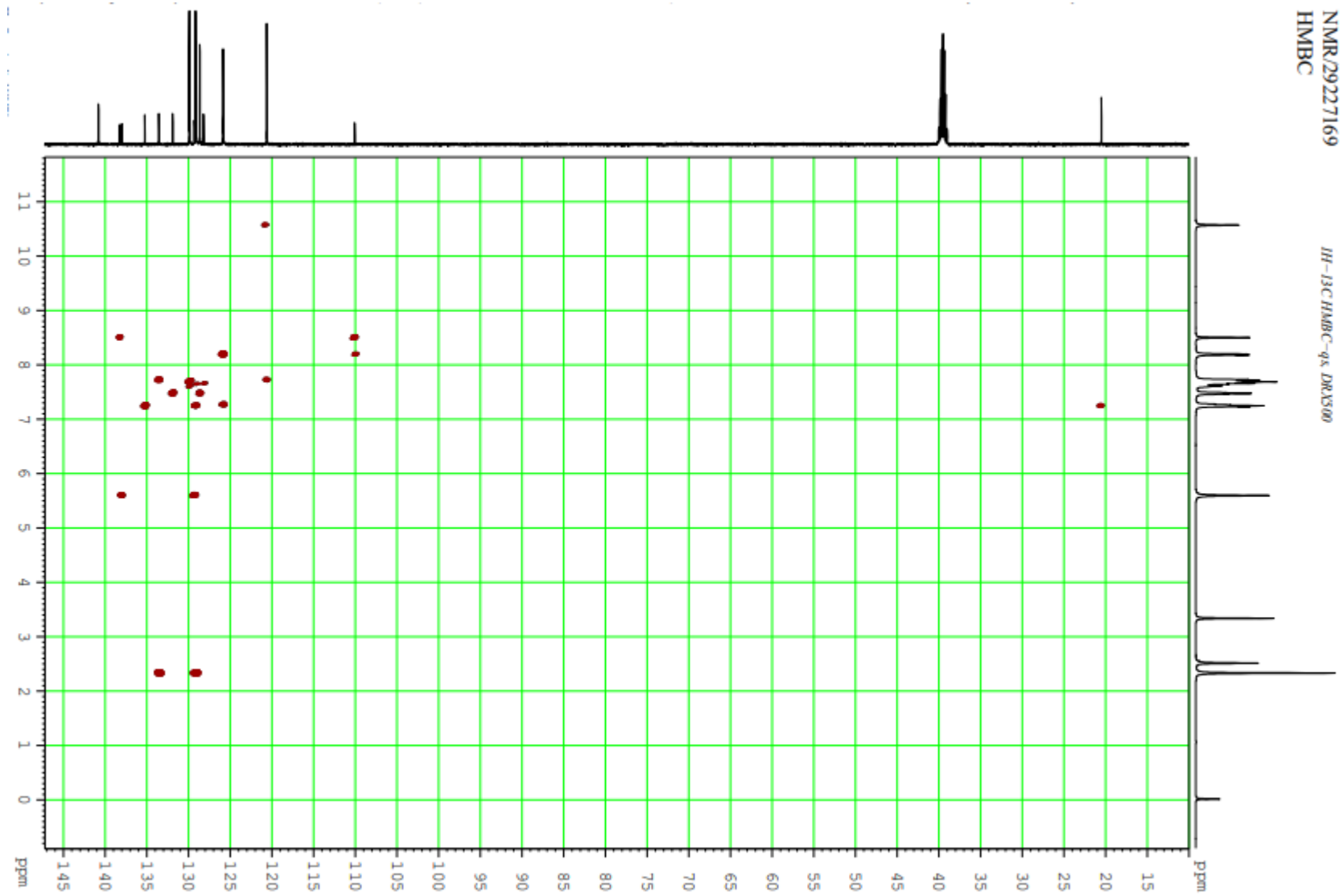


COSY 2D spectrum of 6-amino-3,7-diphenyl-*N*-(*p*-tolyl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-5-carboxamide (**6a**)

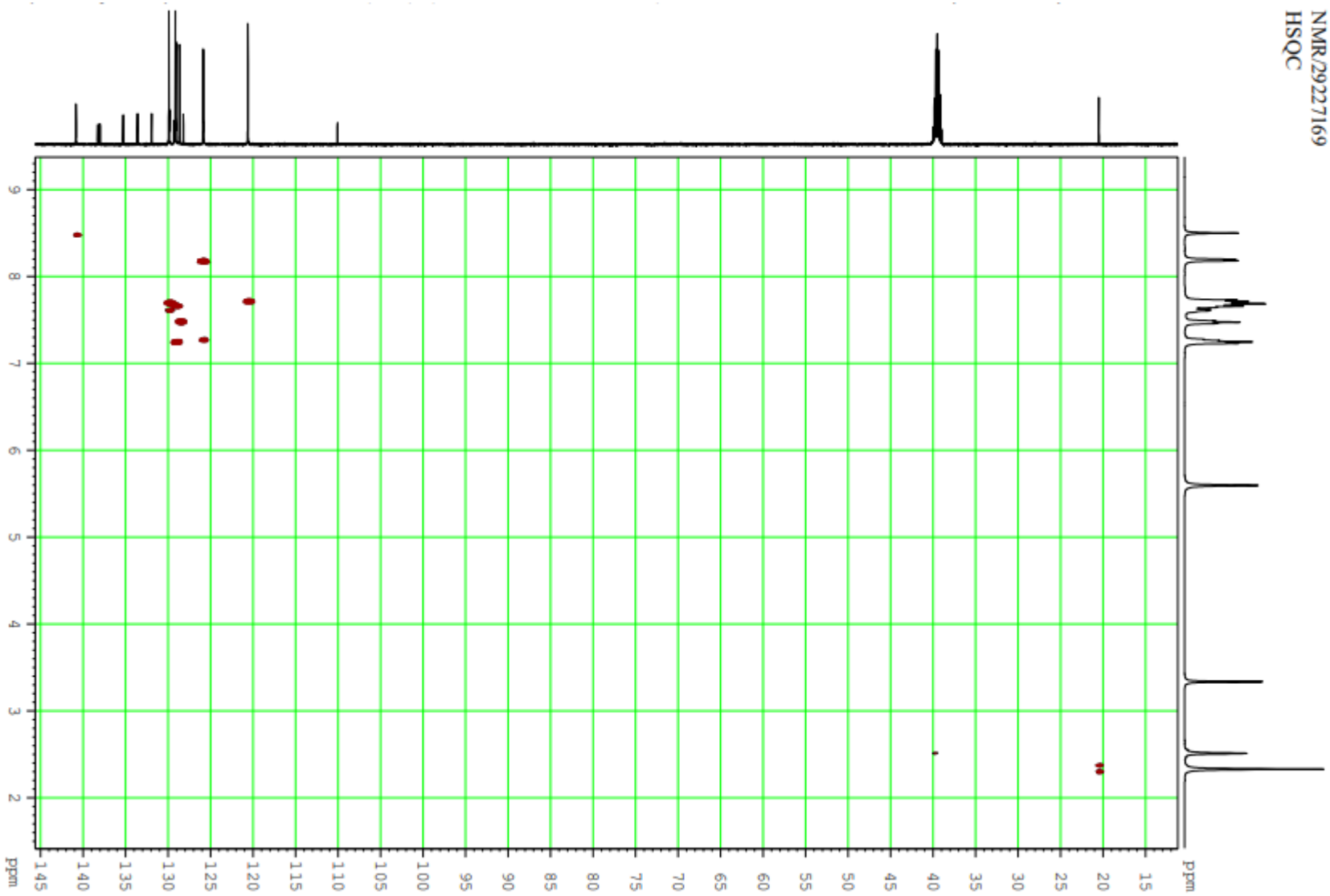




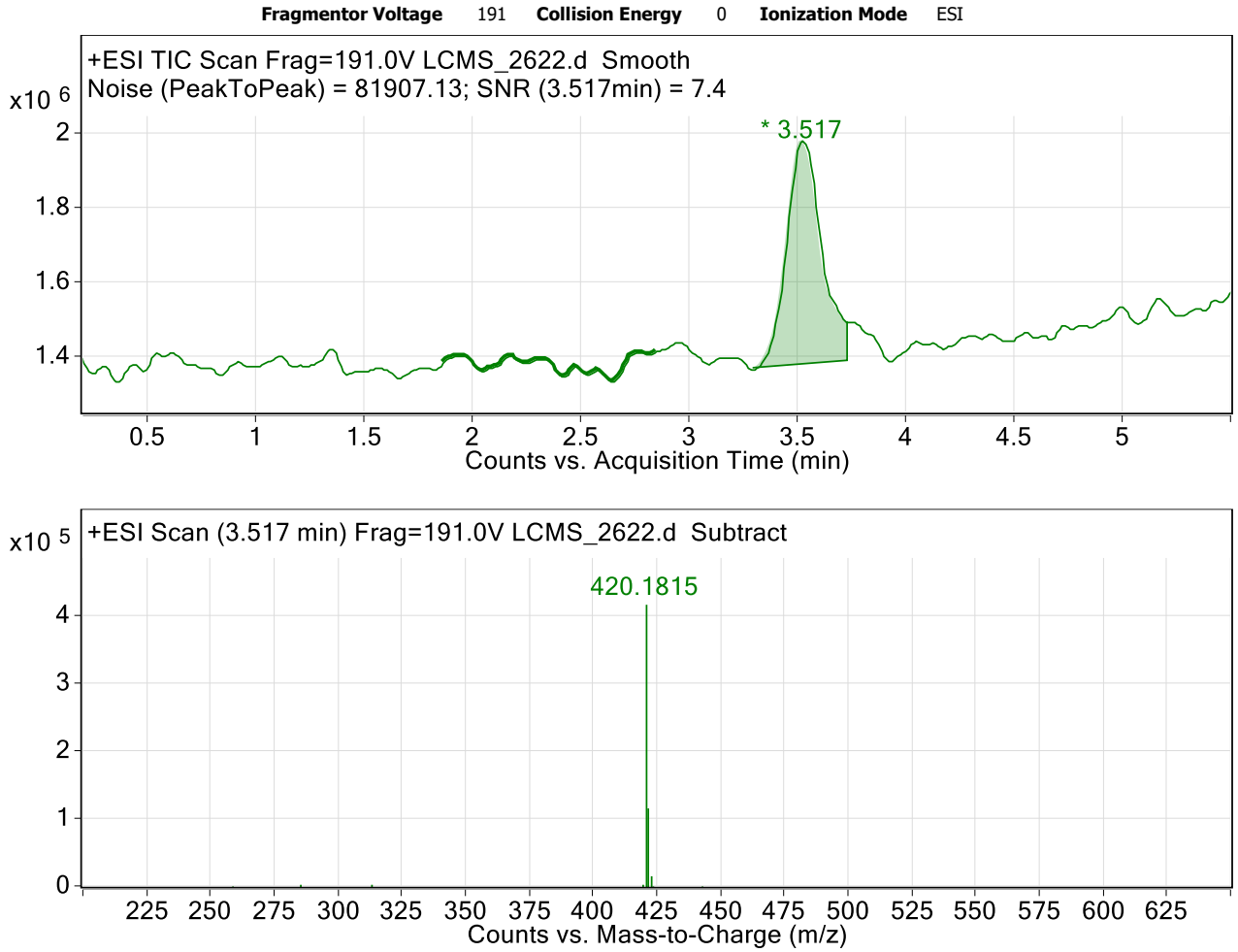
HMBC 2D spectrum of 6-amino-3,7-diphenyl-*N*-(*p*-tolyl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-5-carboxamide (**6a**)



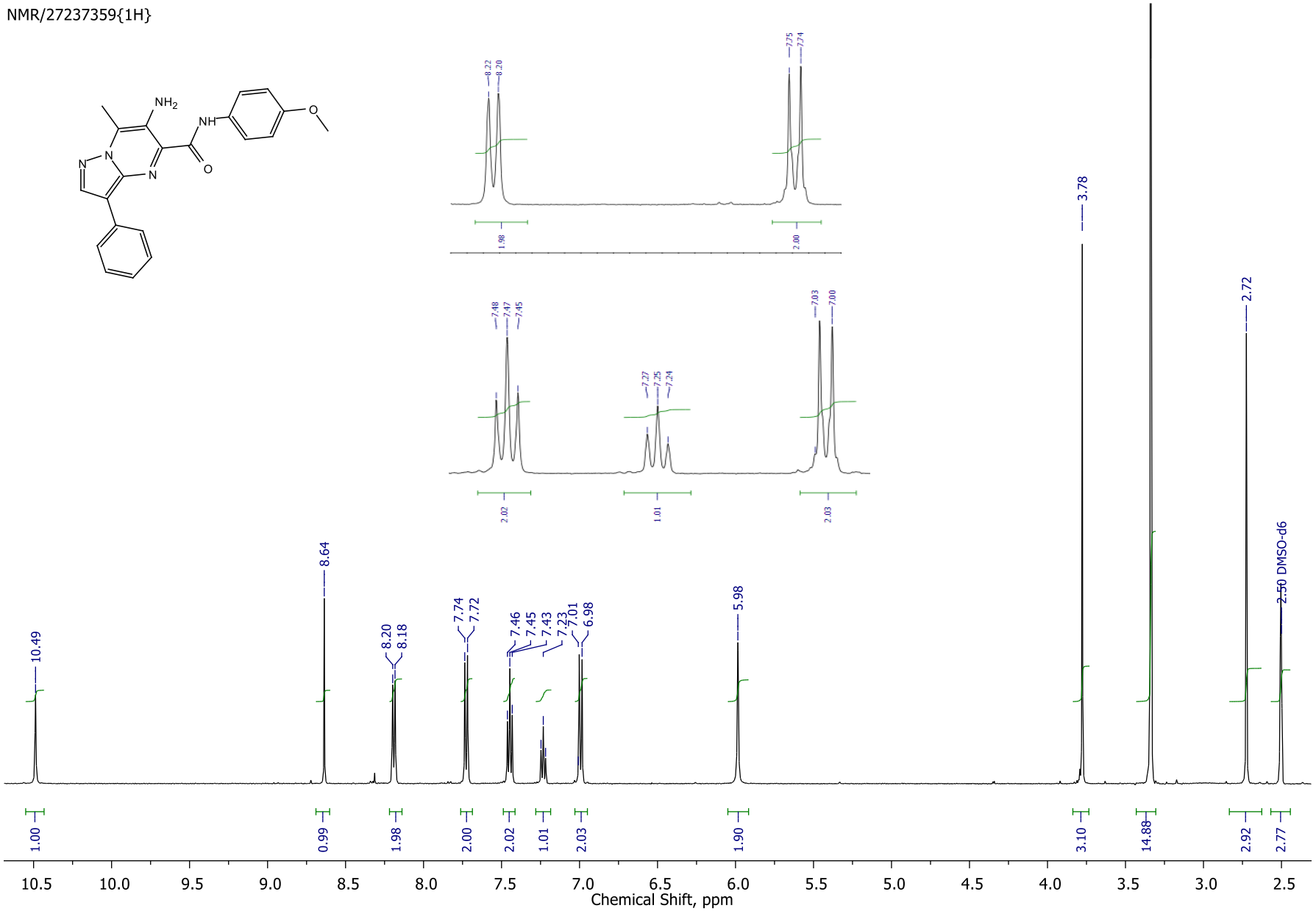
HSQC 2D spectrum of 6-amino-3,7-diphenyl-*N*-(*p*-tolyl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-5-carboxamide (**6a**)



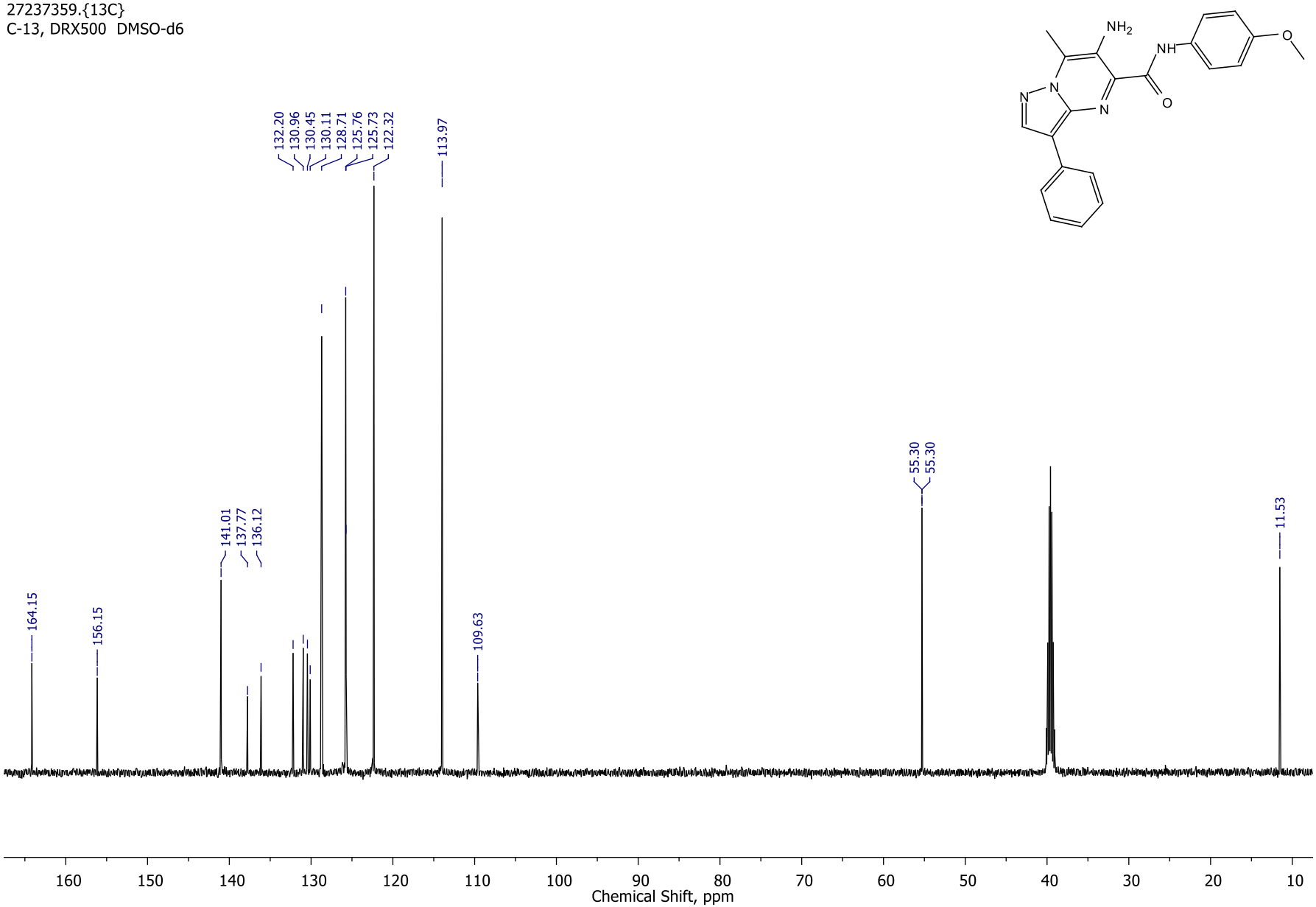
HPLC-MS (ESI) spectrum of 6-amino-3,7-diphenyl-*N*-(*p*-tolyl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-5-carboxamide (**6a**)



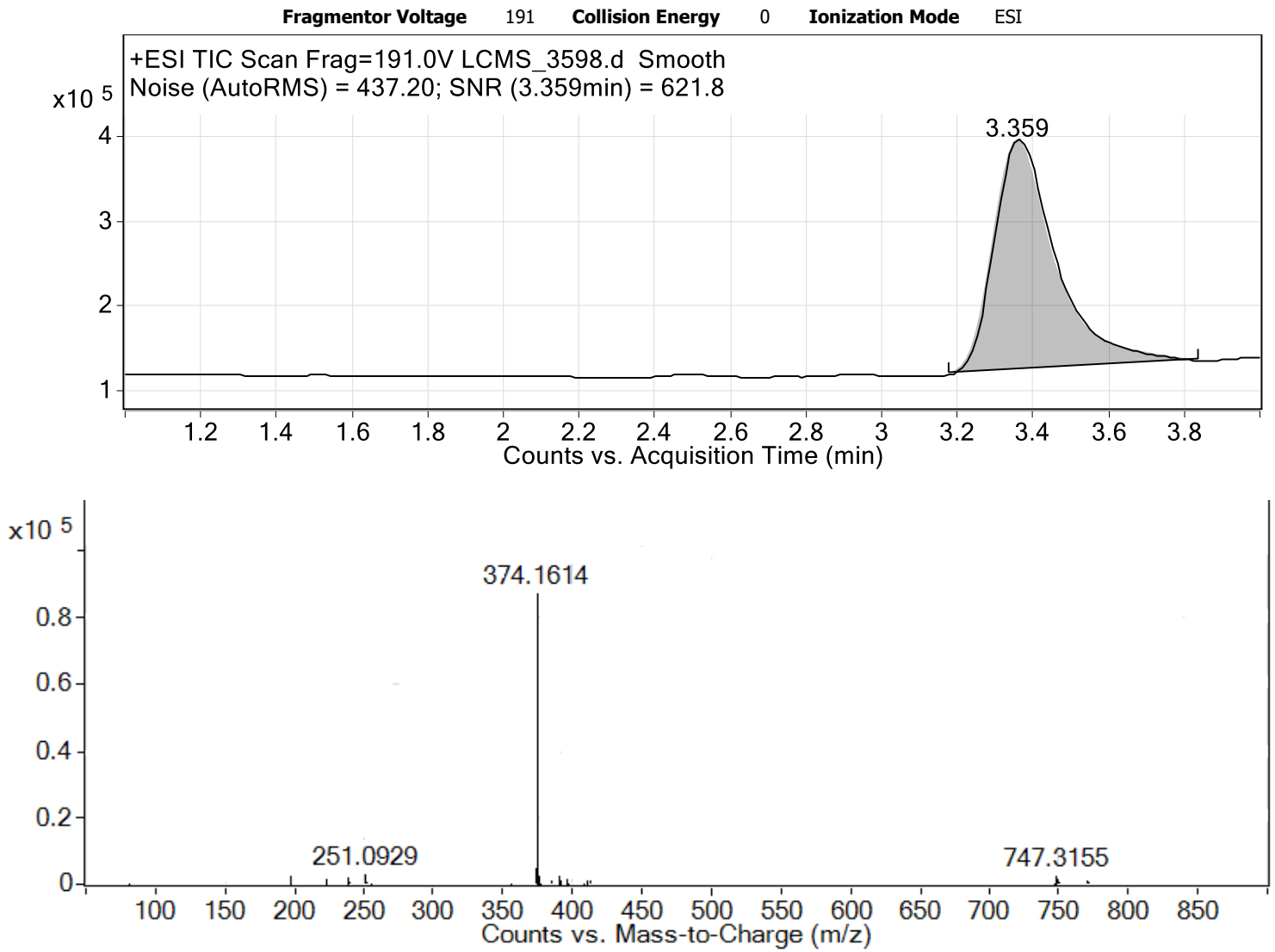
^{1}H NMR spectrum of 6-amino-*N*-(4-methoxyphenyl)-7-methyl-3-phenyl-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-5-carboxamide (**6b**) (DMSO-d_6, 500.13 MHz)



^{13}C NMR spectrum of 6-amino-*N*-(4-methoxyphenyl)-7-methyl-3-phenyl-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-5-carboxamide (**6b**) (DMSO-d_6, 125.76 MHz)



HPLC-MS (ESI) spectrum of 6-amino-N-(4-methoxyphenyl)-7-methyl-3-phenyl-4,7-dihydropyrazolo[1,5-*a*]-pyrimidine-5-carboxamide (**6b**)



X-ray diffraction analysis of 6,10-diphenyl-3-(*p*-tolyl)pyrazolo[1,5-*a*]pyrimido[5,4-*d*]pyrimidin-4(3*H*)-one (**6′a**)

Bond precision: C-C = 0.0019 A Wavelength=0.71073

Cell: a=7.0433(3) b=16.0608(7) c=18.1653(8)
alpha=90 beta=95.891(1) gamma=90
Temperature: 120 K

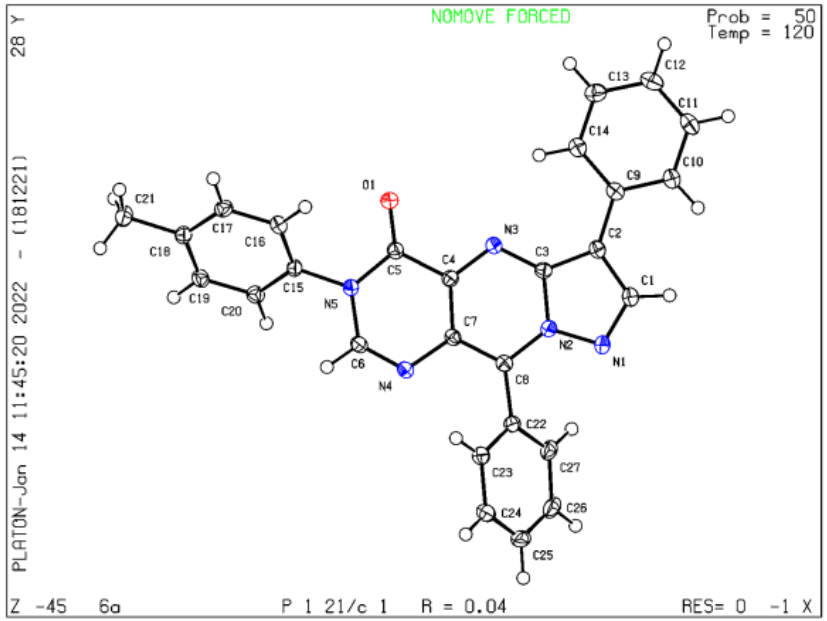
	Calculated	Reported
Volume	2044.03(15)	2044.02(15)
Space group	P 21/c	P 1 21/c 1
Hall group	-P 2ybc	-P 2ybc
Moiety formula	C27 H19 N5 O	C27 H19 N5 O
Sum formula	C27 H19 N5 O	C27 H19 N5 O
Mr	429.47	429.47
Dx,g cm-3	1.396	1.396
Z	4	4
Mu (mm-1)	0.089	0.089
F000	896.0	896.0
F000′	896.32	
h,k,lmax	9,21,23	9,21,23
Nref	4924	4924
Tmin,Tmax	0.974,0.981	0.670,0.746
Tmin′	0.957	

Correction method= # Reported T Limits: Tmin=0.670 Tmax=0.746
AbsCorr = MULTI-SCAN

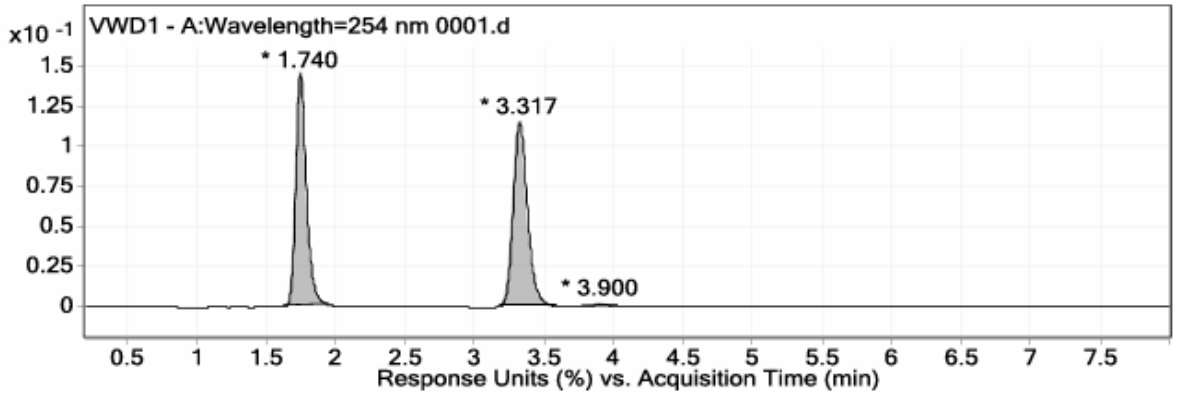
Data completeness= 1.000 Theta(max)= 27.997

R(reflections)= 0.0411(4087) wR2(reflections)= 0.1083(4924)

S = 1.035 Npar= 299



Chromatographic-mass spectrometric study of the reaction pathway of 4-methyl-8-phenyl-3-tosyl-1,4-dihydropyrazolo[5,1-*c*][1,2,4]triazine **2c** with 2-chloro-*N*-(4-methoxyphenyl)acetamide **4f** in K_2CO_3/DMF

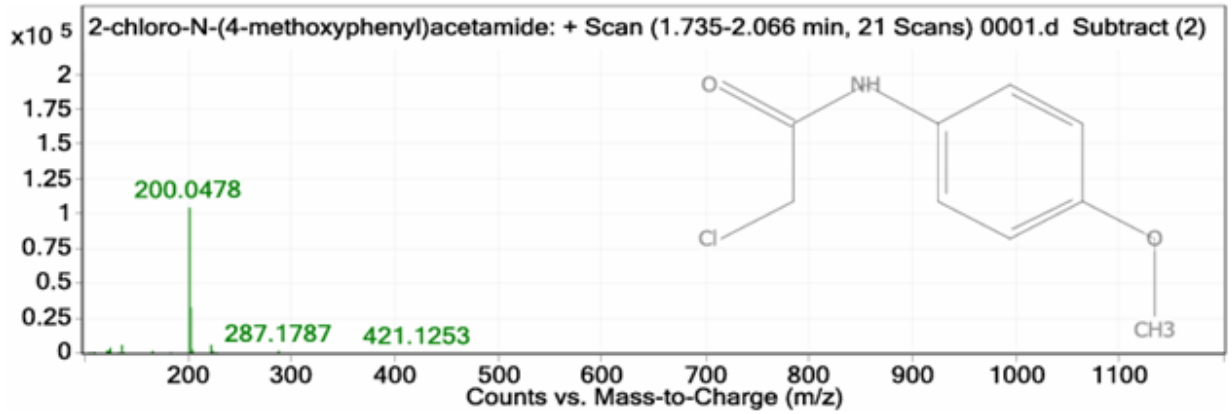


Integration Peak List

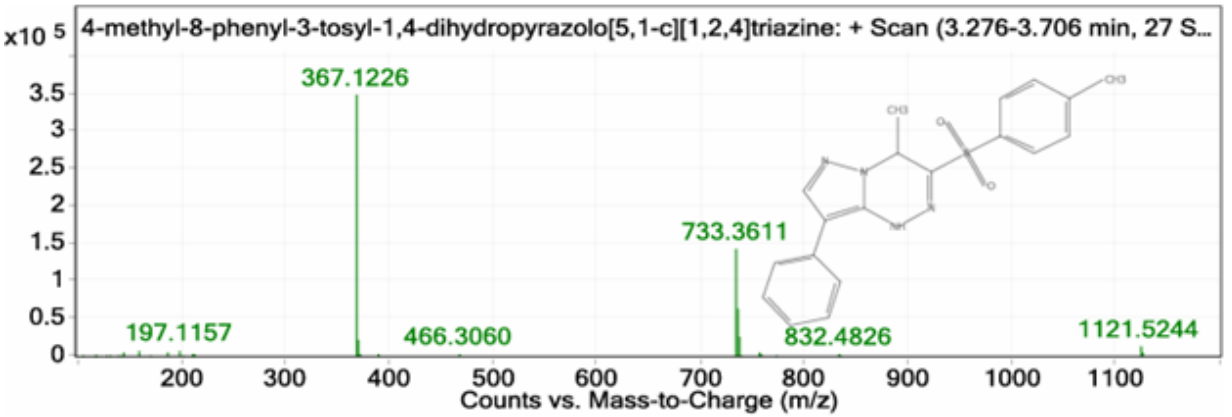
Peak	Start	RT	End	Height	Area	Area %
1	1.623	1.74	1.953	1915.73	10226.51	95.72
2	3.18	3.317	3.59	1508.61	10683.31	100
3	3.77	3.9	4.03	20.14	125.38	1.17

Figure S2. Integrated scanned chromatogram of the total ion current of the reaction mixture after mixing the components without heating

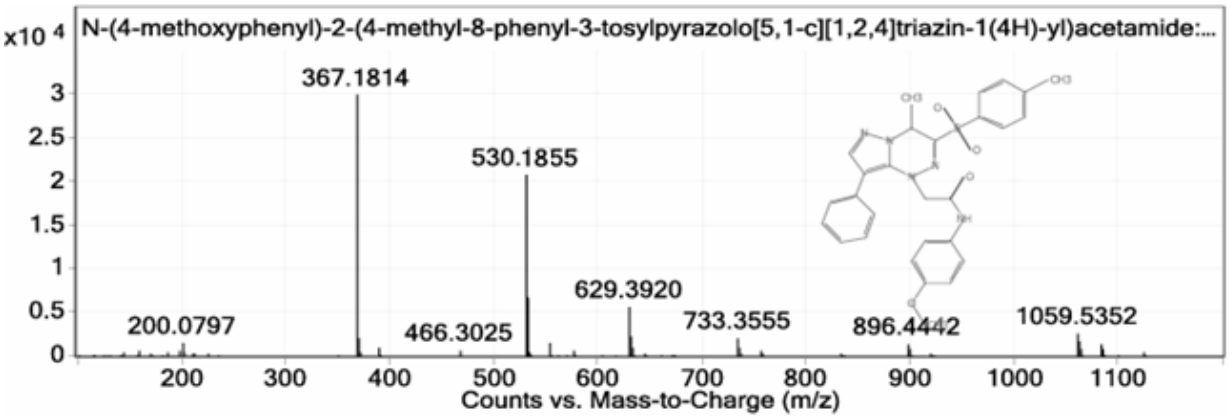
Peak 1

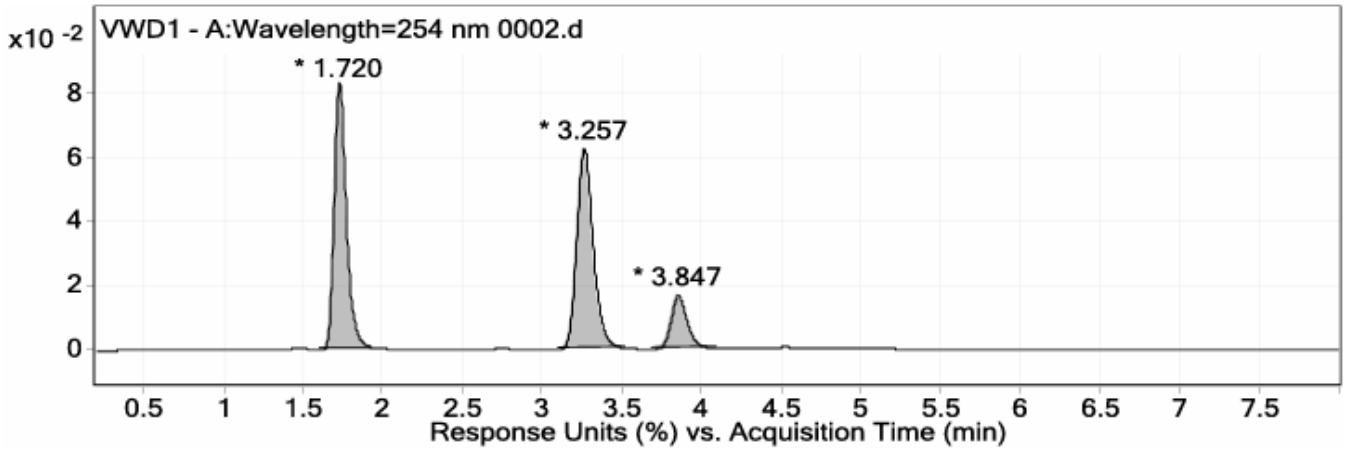


Peak 2



Peak 3



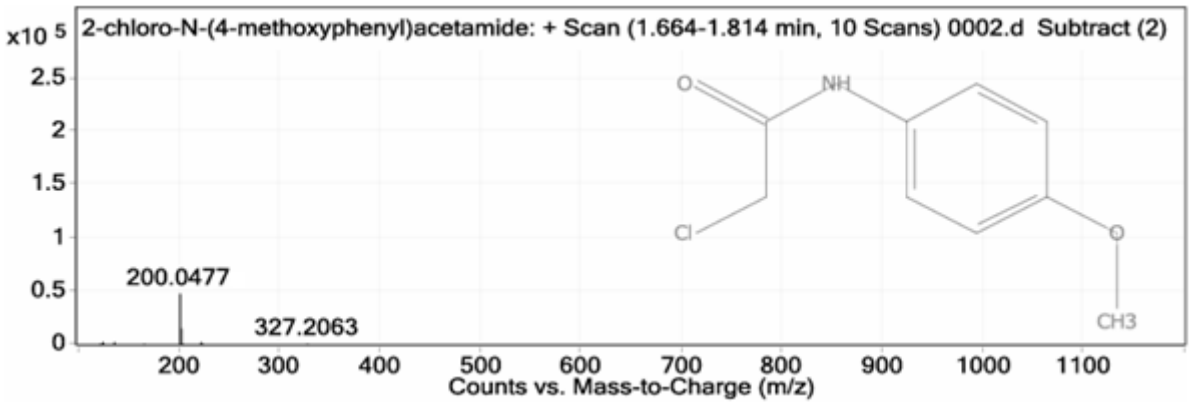


Integration Peak List

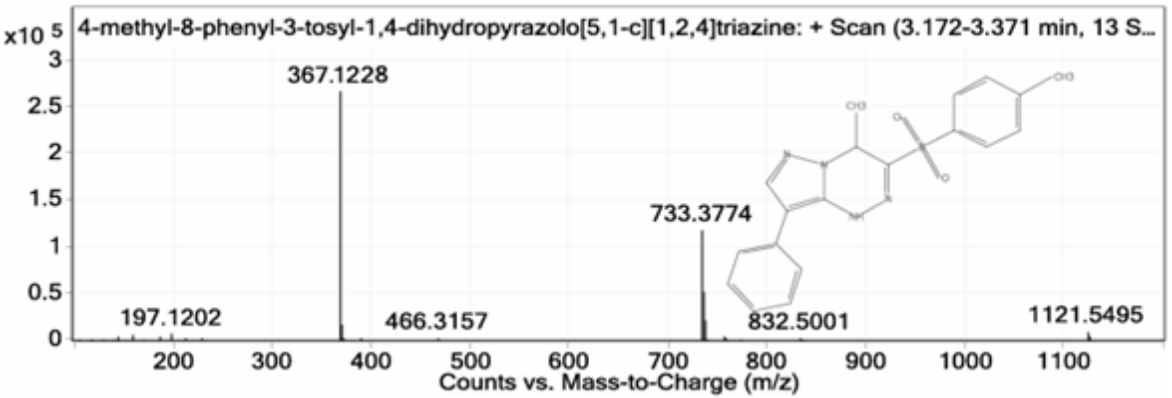
Peak	Start	RT	End	Height	Area	Area %
1	1.6	1.72	1.923	1085.63	5803.17	99.91
2	3.097	3.257	3.52	813.8	5808.33	100
3	3.683	3.847	4.093	215.62	1496.18	25.76

Figure S3. Integrated scanned chromatogram of the total ion current of the reaction mixture after heating for 5 minutes

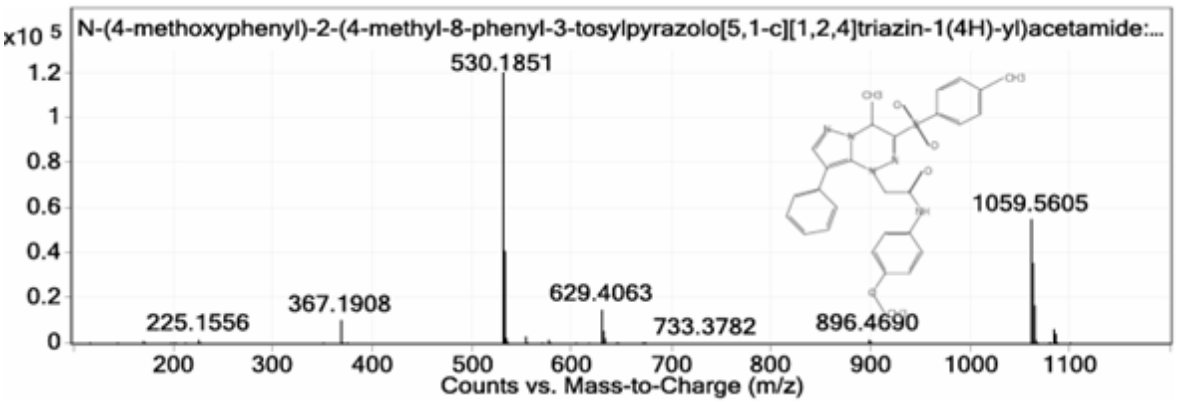
Peak 1

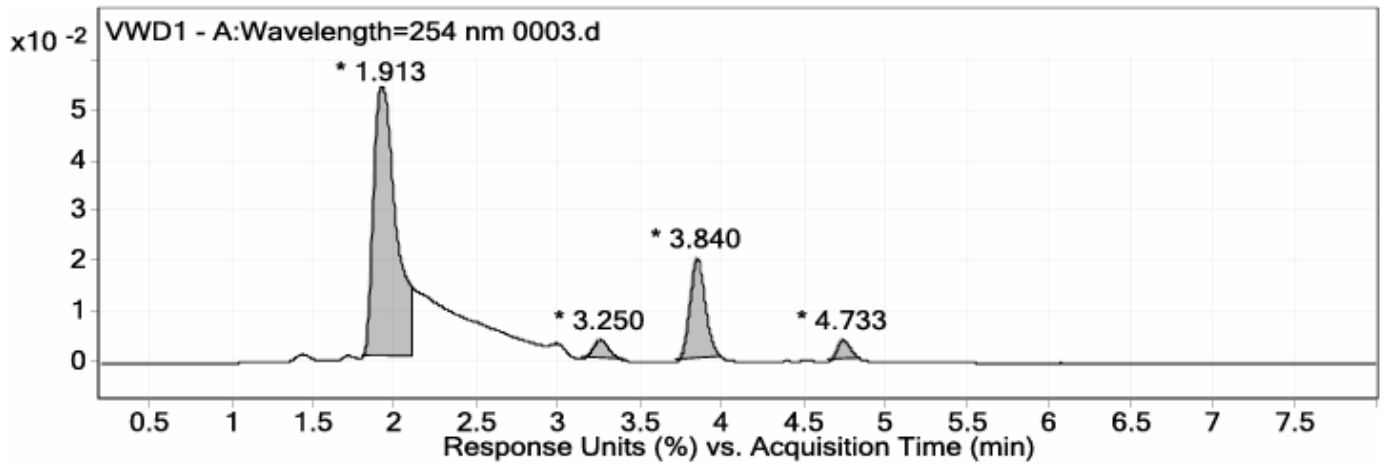


Peak 2



Peak 3



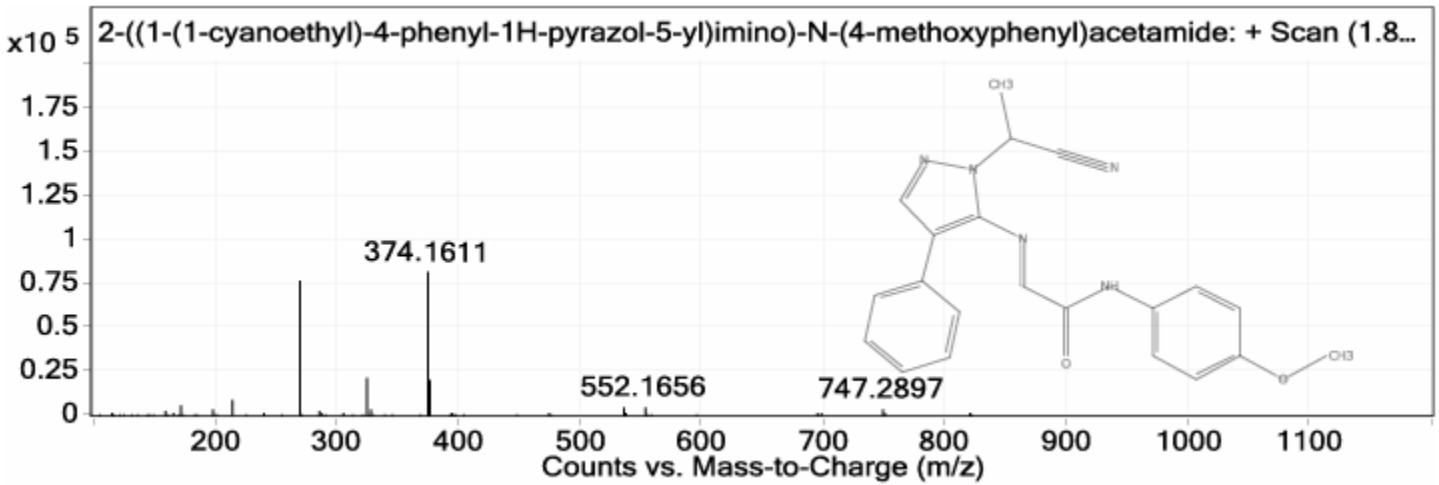


Integration Peak List

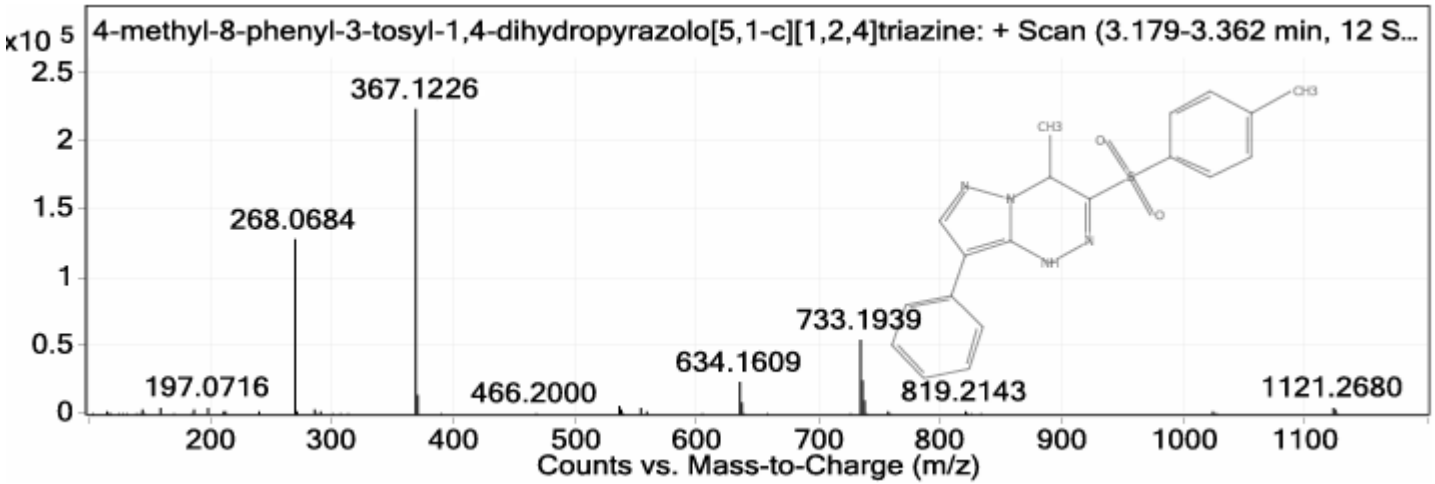
Peak	Start	RT	End	Height	Area	Area %
1	1.797	1.913	2.107	3784.78	36989.2	100
2	3.14	3.25	3.41	273.37	1849.76	5
3	3.717	3.84	3.997	1422.85	9402.17	25.42
4	4.647	4.733	4.847	287.34	1578.98	4.27

Figure S4. Integrated scanned chromatogram of the total ion current of the reaction mixture after heating for 10 minutes (the beginning of boiling)

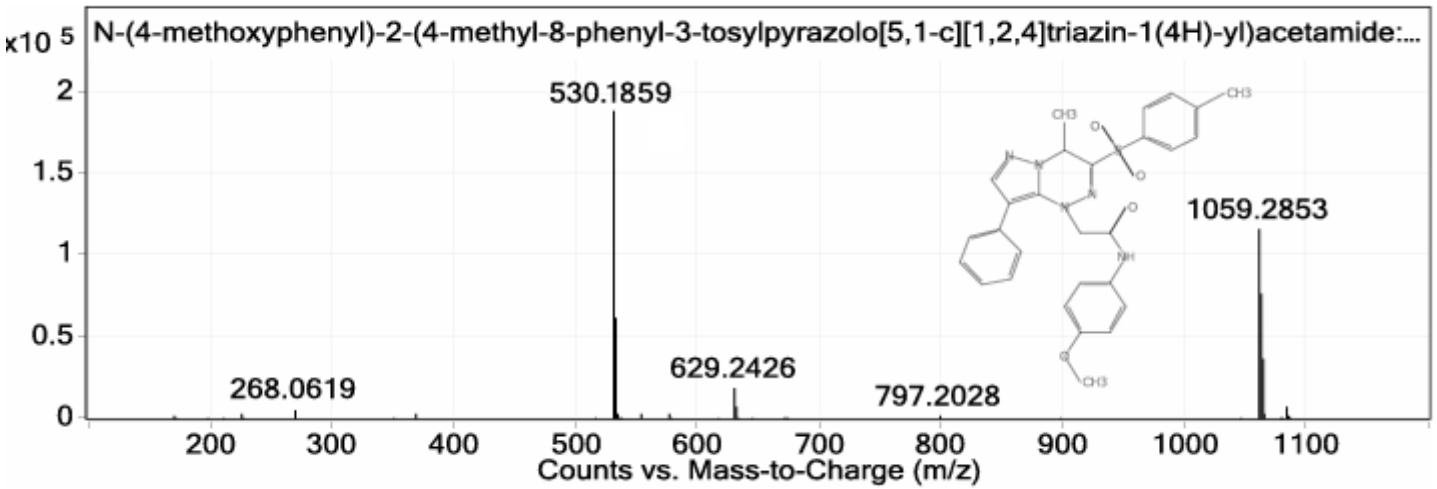
Peak 1


x10 5
2-((1-(1-cyanoethyl)-4-phenyl-1H-pyrazol-5-yl)imino)-N-(4-methoxyphenyl)acetamide: + Scan (1.8...
1.75
1.5
1.25
1
0.75
0.5
0.25
0
374.1611
552.1656
747.2897
200
300
400
500
600
700
800
900
1000
1100
Counts vs. Mass-to-Charge (m/z)

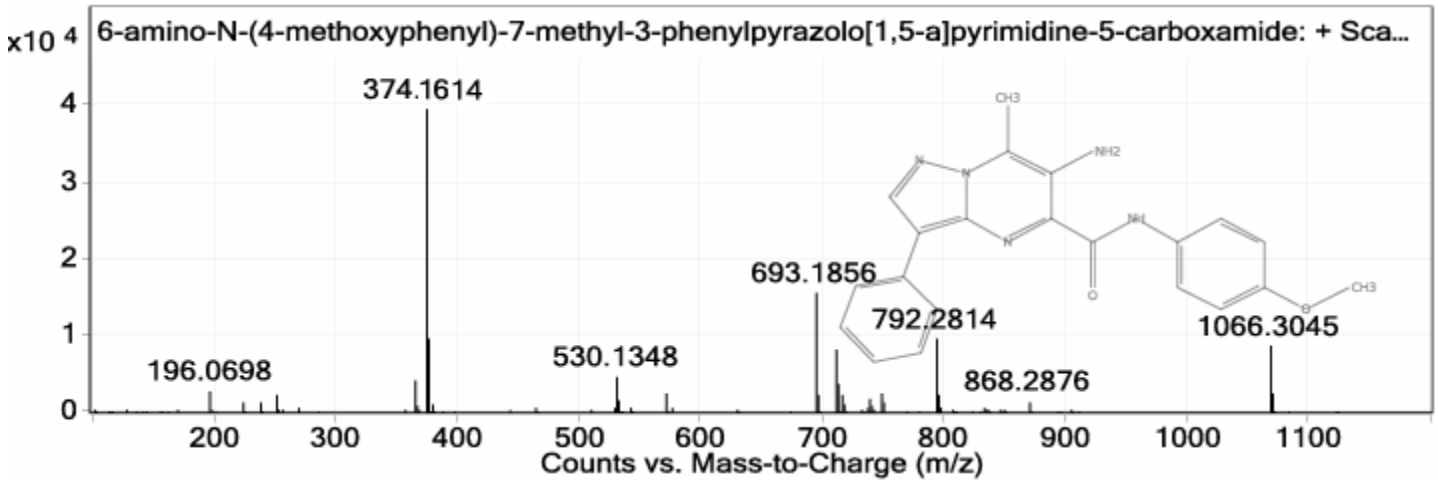
Peak 2

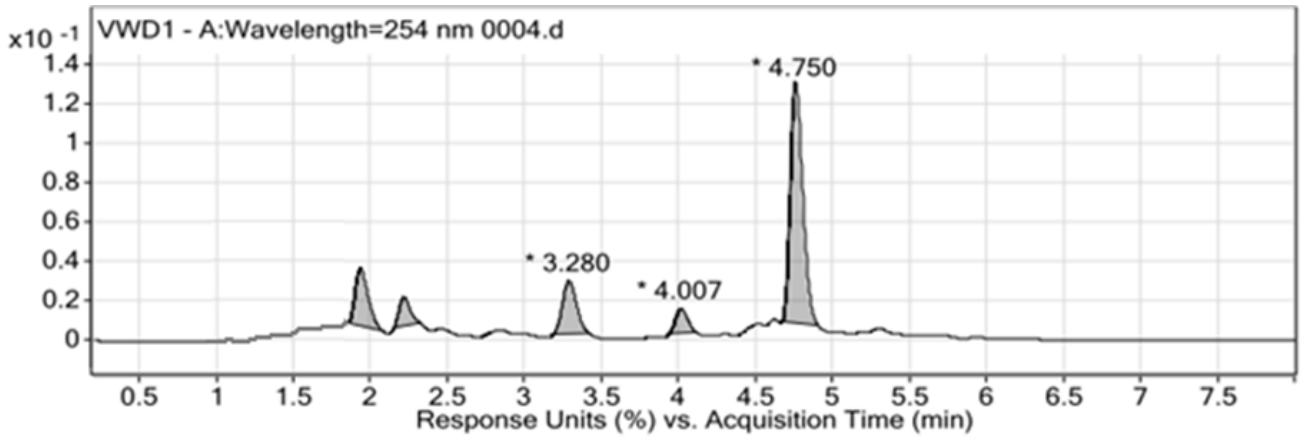

x10 5
4-methyl-8-phenyl-3-tosyl-1,4-dihydropyrazolo[5,1-c][1,2,4]triazine: + Scan (3.179-3.362 min, 12 S...
2.5
2
1.5
1
0.5
0
367.1226
268.0684
733.1939
634.1609
197.0716
466.2000
819.2143
1121.2680
200
300
400
500
600
700
800
900
1000
1100
Counts vs. Mass-to-Charge (m/z)

Peak 3


x10 5
N-(4-methoxyphenyl)-2-(4-methyl-8-phenyl-3-tosylpyrazolo[5,1-c][1,2,4]triazin-1(4H)-yl)acetamide:...
530.1859
1059.2853
629.2426
268.0619
797.2028
Counts vs. Mass-to-Charge (m/z)

Peak 4


x10 4
6-amino-N-(4-methoxyphenyl)-7-methyl-3-phenylpyrazolo[1,5-a]pyrimidine-5-carboxamide: + Sca...
374.1614
693.1856
792.2814
1066.3045
530.1348
196.0698
868.2876
Counts vs. Mass-to-Charge (m/z)

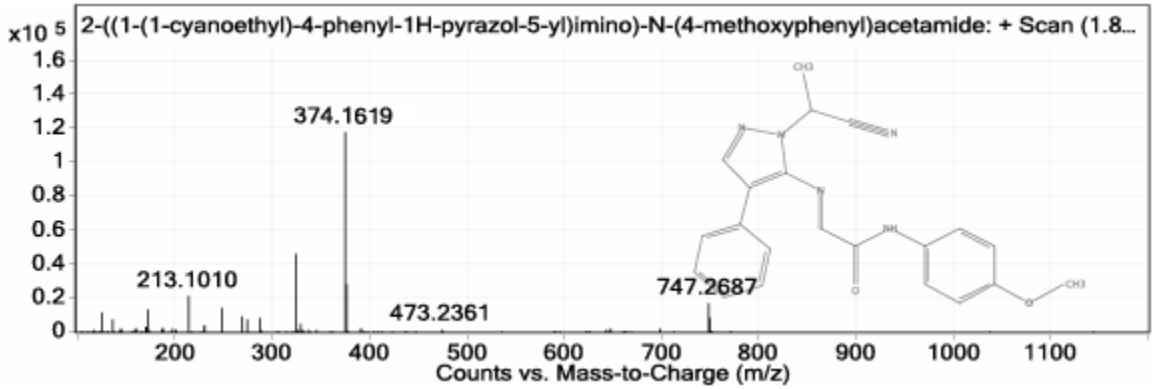


Integration Peak List

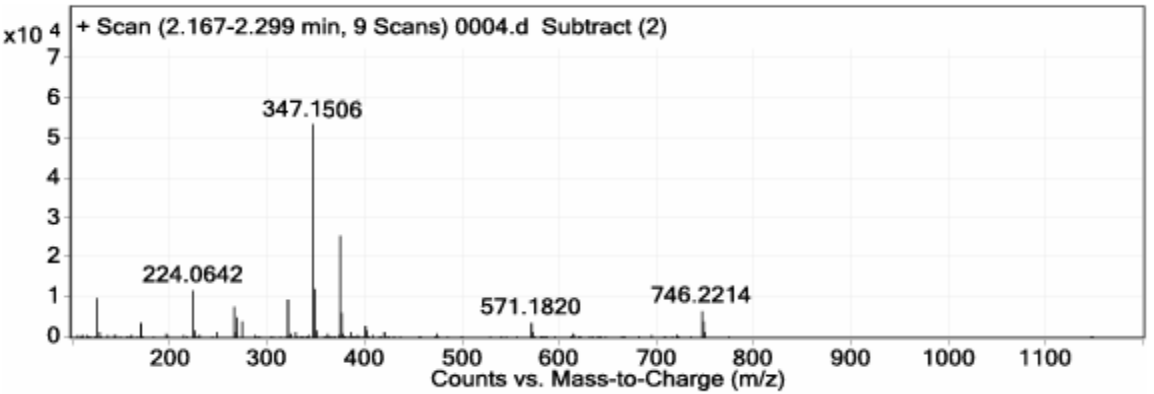
Peak	Start	RT	End	Height	Area	Area %
1	1.84	1.927	2.097	300.04	1826.66	26.3
2	2.14	2.21	2.327	158.19	848.7	12.22
3	3.167	3.28	3.427	278.06	1844.89	26.56
4	3.92	4.007	4.123	133.78	777.72	11.2
5	4.653	4.75	4.903	1237.36	6945.95	100

Figure S5. Integrated scanned chromatogram of the total ion current of the reaction mixture after heating for 20 minutes

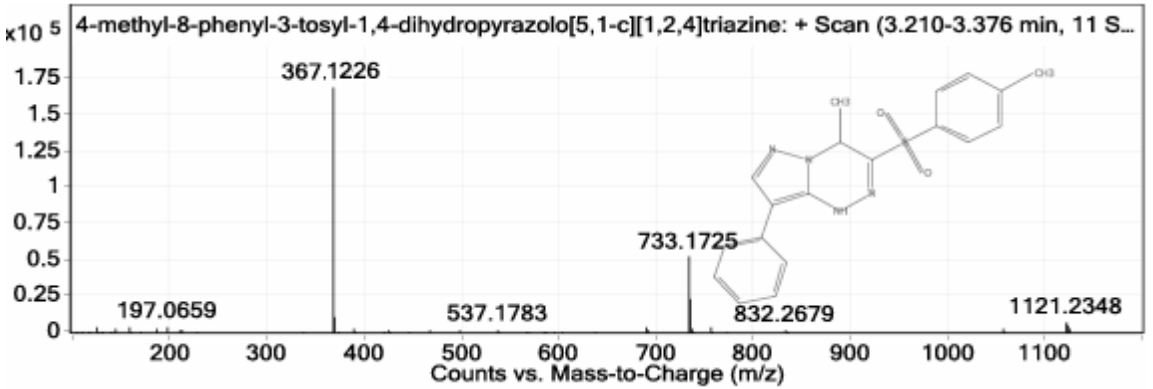
Peak 1



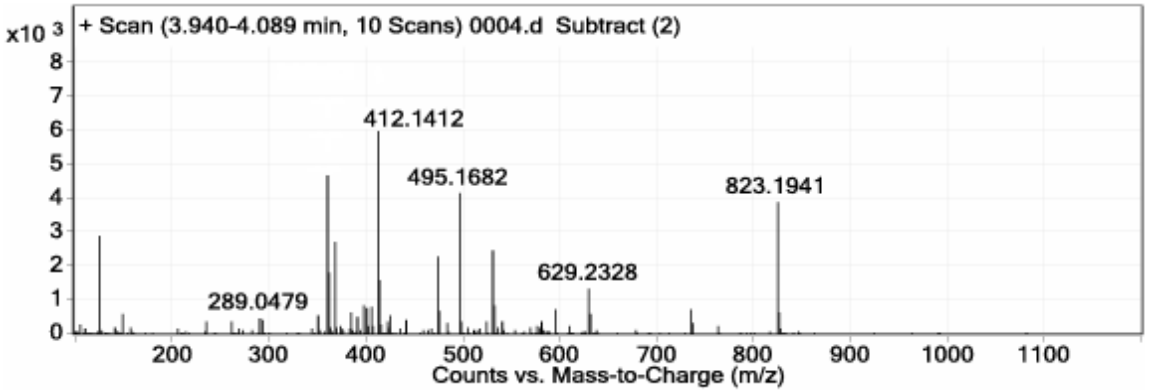
Peak 2



Peak 3



Peak 4


x10 3
+ Scan (3.940-4.089 min, 10 Scans) 0004.d Subtract (2)
412.1412
495.1682
823.1941
629.2328
289.0479
Counts vs. Mass-to-Charge (m/z)

Peak 5

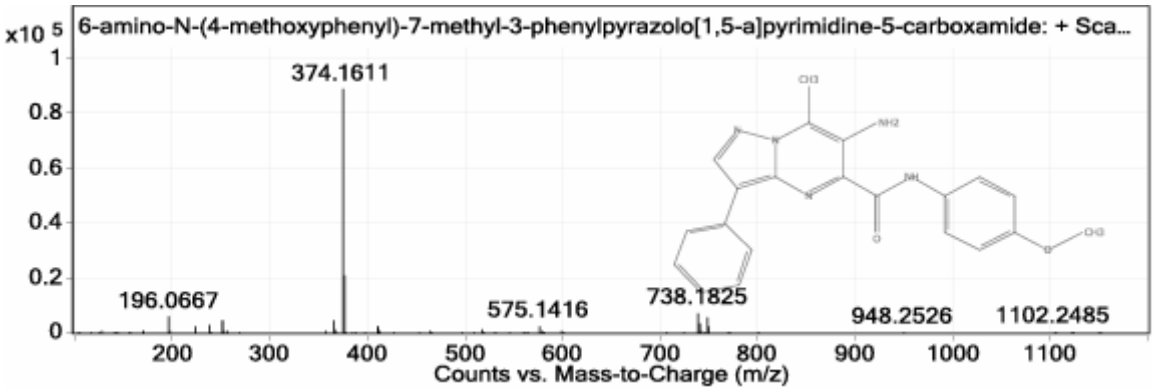

x10 5
6-amino-N-(4-methoxyphenyl)-7-methyl-3-phenylpyrazolo[1,5-a]pyrimidine-5-carboxamide: + Sca...
374.1611
196.0667
575.1416
738.1825
948.2526
1102.2485
Counts vs. Mass-to-Charge (m/z)

Table S3. Generalized data of HPLC-MS study of the reaction mixtures of compounds **2c** and **4f** in K_2CO_3/DMF

Reaction time, min.	Temperature, °C	RT*	$[M+H]^+$, Found / Calculated	Area, %	Substance/ Intermediate (scheme 3)
0	25	1.740	200.0478 200.0473	95.72	**4f**
		3.257	367.1226 367.1224	100	**2c**
		3.900	530.1855 530.1858	1.17	**A**
5	80	1.720	200.0477 200.0473	99.91	**C**
		3.257	367.1228 367.1224	100	**2c**
		3.847	530.1851 530.1858	25.76	**A**
10	150	1.913	374.1611 374.1612	100	**C**
		3.250	367.1226 367.1224	5	**2c**
		3.840	530.1859 530.1858	25.42	**A**
		4.733	374.1614 374.1618	4.27	**6b**
20	150	1.927	374.1619 374.1612	26.30	**C**
		2.210	347.1506 347.1503	12.22	**D**
		3.280	367.1226 367.1224	26.56	**2c**
		4.007	412.1412 412.1405	11.2	**F**
		4.750	374.1611 374.1618	100	**6b**

* Retention time.