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Regioselective synthesis of novel imidazo[1,5-*b*]pyridazine derivatives from diaminoimidazoles and α-acylacrylonitriles

Dmitriy Yu. Vandyshev, Evgeniya A. Kosheleva, Vladimir A. Polikarchuk, Daria A. Mangusheva, Gleb L. Denisov and Khidmet S. Shikhaliev

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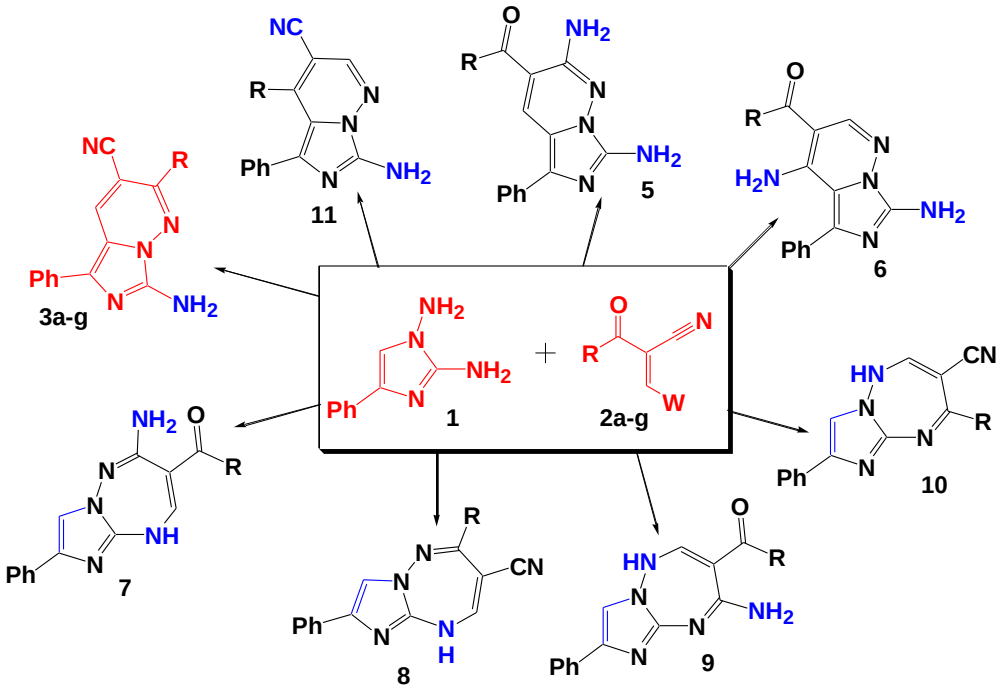
Discussion of regioselectivity, chemoselectivity and process mechanism

Considering the polynucleophilic nature of the initial 1,2-diamino-4-phenylimidazole **1**, whose structure contains several asymmetric dinucleophilic centres, namely 1,3-C,N (C^5-N^1-NH_2), 1,3-N,N (HN^3-C^2=NH), 1,4-N,N (NH_2-N^1-C^2-NH_2), and the theoretical possibility of difference in the sequence of attacks by bielectrophilic reagents. Scheme S1 shows structures of all possible products of its reaction with 2-dimethylaminomethylidene-3-(het)aryl-3-oxopropanenitriles **2a-f** and 2-dimethylaminomethylidene-3-oxobutanonitrile **2g**. Alternative imidazopyridazines **3** and **11** or imidazotriazepines **8** and **10** can be formed due to the difference in the initial attachment of **1** to **2** with CH- or NH_2 – groups respectively, followed by intramolecular condensation with the participation of carbonyl groups**.** In turn, the competitive formation of imidazopyridazines **5** and **6** or imidazotriazepines **7** and **9** is associated with the possibility of the nitrile group of oxopropanenitriles taking part in the final stage of the cyclisation process**.**



R: Ph (**a**); 2-$MeOC_6H_4$ (**b**); 4-$MeOC_6H_4$ (**c**); 4-ClC_6H_4 (**d**); naphtalen-2-yl (**e**); thiophen-2-yl (**f**); CH_3 (**g**).
W = NMe_2 or EtO.

Scheme S1.

The IR spectra of the obtained compounds demonstrates a stretching vibration band of the nitrile group in the region ≈ 2205-2220 cm^{-1}. The presence of the CN-group allowed us to exclude the formation of diaminoimidazotriazepines **5** and **6,** and imidazotriazipynes **7** and **9**.

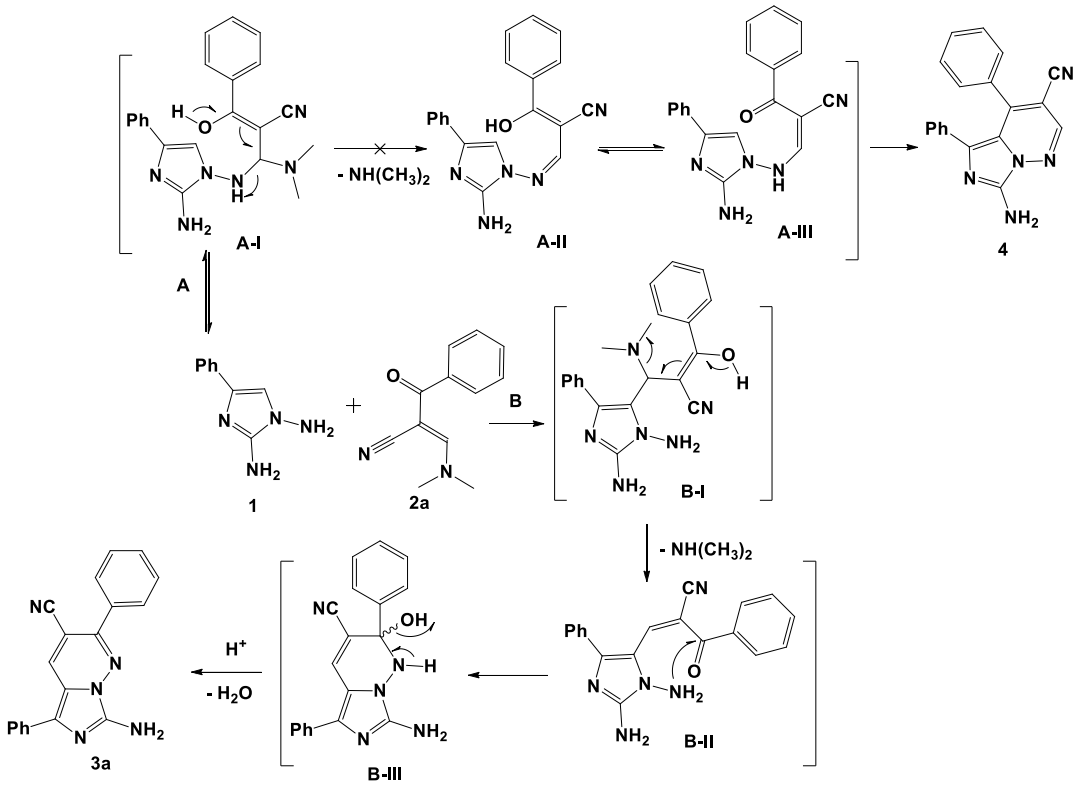
The presence in the ^1H NMR spectra of the obtained compounds of the singlet of the NH_2 group with C-7 in the region of 6.84-6.97 ppm, and a peak of the pyridazine cycle at 8.85-8.99 ppm (with no proton signal of the imidazole cycle at C-5) also allowed us to exclude imidazotriazipynes **7-10** from further consideration.

It appeared to be impossible to choose between isomers **3** and **11** using IR, ^1H, ^{13}C NMR and two-dimensional correlation spectroscopy. Therefore, to determine the structure of the obtained compounds, we performed an X-ray diffraction analysis of the compound **3a**. It demonstrated that during the studied cascade reaction 7-amino-2-(het)aryl-5-phenylimidazo[1,5-b]pyridazine-3-carbonitriles **3a-g** are formed

The obtained results allow us to suggest the following mechanism of the studied reaction (Scheme S2) using the example of the reaction of the initial diaminoimidazole **1** and 2-dimethylaminomethylidene-3-phenypropanonitrile **2a** with the possible alternative formation of the two most common regioisomers, **3** and **11**. During the first stage, the attack of an NH- or CH-proton of the imidazole cycle and a subsequent elimination of the dimethylamine group can result in the formation of intermediates **A-I**, **A-II** and **A-III** (path A) or **B-I, B-II** and **B-III** (path B).

We assume that the process mostly takes place under thermodynamic control, i.e. according to path B, and results in the formation of a more thermodynamically stable (due to steric difficulties) regioisomer, **3a**. This is proved by the fact that the substitution of aryl with

less bulky methyl in oxopropanenitriles significantly increases the speed of the reaction under the same conditions. During the first stage **B-I**, which is a product of a classical Michael-type reaction, separates the dimethylamine molecule and transforms into an intermediate **B-II**. During the last stage, there is an acid-catalysed nucleophillic attack of the N-1 amino group on the carbonyl group followed by the dehydration and formation of the final product **3a** (see Scheme S2).



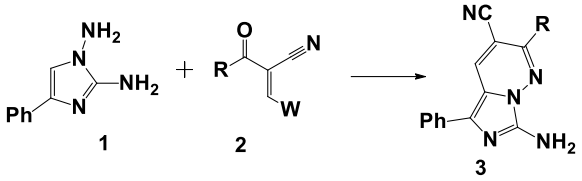
Scheme S2.

General information (instrumentation)

IR spectra were recorded on a Bruker Vertex 70 spectrometer with a Platinum ATR accessory. ^{1}H NMR, ^{13}C NMR, NOESY spectra were recorded on Bruker DRX-500 devices (500.13 and 125.75 MHz, respectively) in DMSO-d_6 and TFA-d with the internal TMS standard. Melting temperatures were taken on a Stuart SMP30 device. HPLC/MS spectra were recorded on an AgilentInfinity 1260 chromatograph with MS interface Agilent 6230 TOFLC/MS. Conditions for the separation: mobile phase MeCN/H_2O + 0.1% formic acid, gradient elution, column - Poroshell 120 EC-C18 (4.6 x 50 mm, 2.7 μm), thermostat 23-28°C, flow rate of 0.3-0.4 ml/min. Electrospray ionisation (capillary – 3.5 kV; fragmentor + 191V; OctRF + 66V – positive polarity). The reaction progress and purity of the obtained compounds were controlled by TLC on Merck TLC Silica gel 60 F254 plates in a 20:1 $CHCl_3$–MeOH system (visualisation under UV light). The commercially available reagents were purchased from Lancaster.

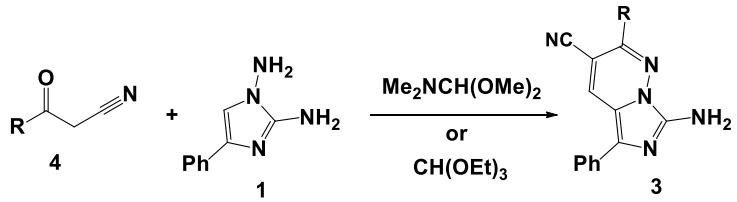
Synthesis and analytical data for imidazo[1,5-*b*]pyridazine-3-carbonitriles 3a-g

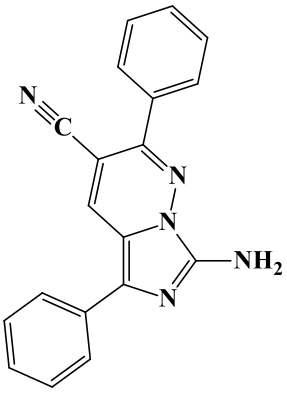
Procedure A: A solution of diaminoimidazole **1** (5 mmol), and the appropriate α-acylacrylonitrile **2** (5 mmol), in Pr^{i}OH–DMF mixture (3:1, 5 ml) with the addition of 1-2 drops of acetic acid was boiled for 2 hours in a retort with reflux condenser. The precipitate was filtered and recrystallised from the Pr^{i}OH–DMF mixture, 2:1.



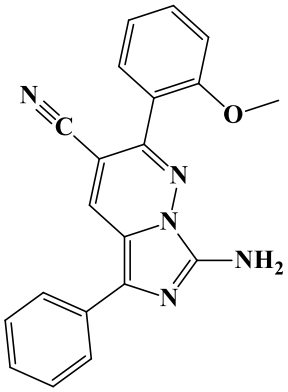
Procedure B: A solution of diaminoimidazole **1** (5 mmol), the appropriate β-oxo nitrile **4** (5 mmol) and triethyl orthoformate (5 mmol) in Pr^{i}OH -DMF mixture (3:1, 5 ml) with the addition of 1-2 drops of acetic acid was boiled for 2 hours in a flask with a reflux condenser. The precipitate was filtered and recrystallised from the Pr^{i}OH – DMF mixture, 2:1.

Procedure C: A solution of the appropriate β-oxo nitrile **4** (5 mmol**)**, dimethylformamide dimethylacetal (5 mmol), in DMF (1 ml) was left for 6 hours at room temperature. Then, diaminoimidazole **1** (5 mmol), Pr^{i}OH (3 ml), and 2 drops of acetic acid were added and the mixture was boiled for 2 hours in a retort with a reflux condenser. The precipitate was filtered and recrystallised from the Pr^{i}OH – DMF mixture, 2:1.

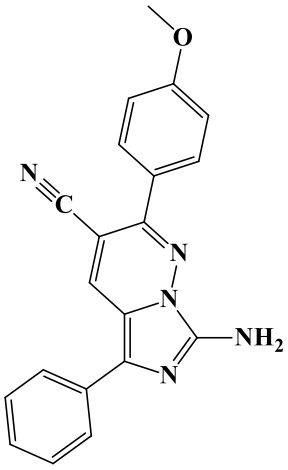




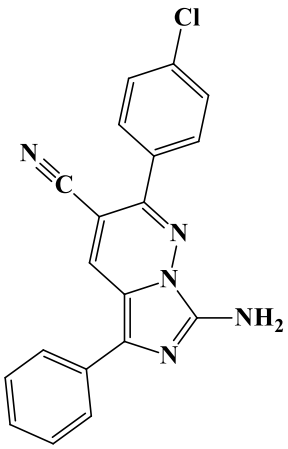
7-Amino-2,5-diphenylimidazo[1,5-*b*]pyridazine-3-carbonitrile 3a. Yield: A - 1061 mg (68%); B/C - 1029 mg (66%), red crystals, mp. 298-300 °C. IR, (ν, см$^{-1}$): 3439, 3288 (NH_2); 3056 (br, C-H + associated N-H); 2208 (CN); 1652 (NH); 1596 (Ph); 1558 (C=N imidazole); 1496 (Ph); 1222 (C-N amin); 1161 (C-N amin); 766 (C-H Ph); 694 (C-H Ph + N-H). ^{1}H NMR, (δ, ppm, *J*, Hz): 6.94 (s, 2H, NH_2); 7.34-7.38 (m, 1H, Ar-H); 7.46 (t, *J* 7.9 Hz, 2H, Ar-H); 7.55-7.60 (m, 3H, Ar-H); 7.81-7.84 (m, 2H, Ar-H); 7.97-8.00 (m, 2H, Ar-H); 8.95 (s, 1H, H^4). ^{13}C NMR, (δ, ppm): 90.4, 115.2, 118.3, 126.5, 128.0, 128.5, 128.6, 128.9, 130.3, 133.1; 134.1, 134.2, 136.9, 146.6, 151.0. HRMS (ESI), *m/z*: 312.1246 $[M+H]^+$. (calc. for $C_{19}H_{14}N_5$, *m/z*: 312.1244).



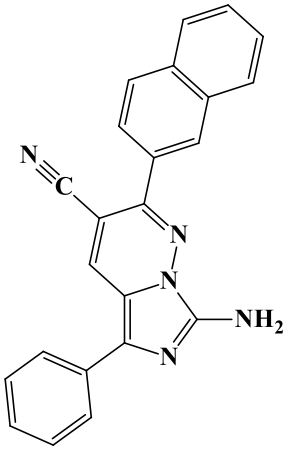
7-Amino-2-(2-methoxyphenyl)-5-phenylimidazo[1,5-*b*]-pyridazine-3-carbonitrile 3b. Yield: A - 1368 mg (80%); B/C - 1334 mg (78%), red crystals, mp. 288-290 °C. IR, (ν, см$^{-1}$): 3401, 3301 (NH_2); 3084 (br, C-H + associated N-H); 2211 (CN); 1653 (NH); 1598 (Ar); 1562 (C=N imidazole); 1497 (Ar); 1243 (Ar-O-Me); 1223 (C-N amin); 1161 (C-N amin); 747 (o-C_6H_4); 697 (C-H Ph + N-H). ^{1}H NMR, (δ, ppm, *J*, Hz): 3.84 (s, 3H, OCH_3); 6.86 (s, 2H, NH_2); 7.11 (t, *J* 7.5 Hz, 1H, Ar-H); 7.22 (d, *J* 8.3 Hz, 1H, Ar- H); 7.33-7.37 (m, 1H, Ar-H); 7.43-7.48 (m, 3H, Ar-H); 7.53-7.57 (m, 1H, Ar-H); 7.96-7.99 (m, 2H, Ar-H); 8.85 (s, 1H, H^4). ^{13}C NMR, (δ, ppm): 55.7, 93.3, 111.7, 114.9, 117.8, 120.6, 123.5, 126.5, 127.9, 128.9, 130.4, 131.9, 133.21, 133.8, 135.3, 146.5, 150.6, 157.3. HRMS (ESI), *m/z*: 342.1347 $[M+H]^+$. (calc. for $C_{20}H_{16}N_5O$, *m/z*: 342.1355).



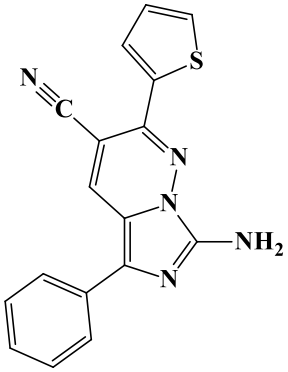
7-Amino-2-(4-methoxyphenyl)-5-phenylimidazo[1,5-*b*]-pyridazine-3-carbonitrile 3c. Yield: A - 1471 mg (86%); B/C - 1419 mg (83%), red crystals, mp. 270-272 °C. IR, (ν, см$^{-1}$): 3457, 3284 (NH_2); 3076 (br, C-H + associated N-H); 2213 (CN); 1650 (NH); 1596 (Ar); 1559 (C=N imidazole); 1514 (Ar); 1262 (Ar-O-Me); 1223 (C-N amin); 1163 (C-N amin); 838 (p-C_6H_4); 696 (C-H Ph + N-H). ^{1}H NMR, (δ, ppm, *J*, Hz): 3.85 (s, 3H, OCH_3); 6.90 (s, 2H, NH_2); 7.12 (dt, *J* 8.8, 2.1 Hz, 2H, Ar-H); 7.34-7.37 (m, 1H, Ar-H); 7,46 (t, *J* 7.6 Hz, 2H, Ar-H); 7.81 (dt, *J* 8.8, 2.1 Hz, 2H, Ar-H); 7.97-7.99 (m, 2H, H-Ar); 8.91 (s, 1H, H^4). ^{13}C NMR, (δ, ppm): 55.4, 90.4, 113.8, 115.1, 118.5, 126.4, 126.5, 127.9, 128.9, 130.1, 133.15, 134.0, 136.8, 146.5, 150.4, 160.9. HRMS (ESI), *m/z*: 342.1349 $[M+H]^+$. (calc. for $C_{20}H_{16}N_5O$, *m/z*: 342.1355).



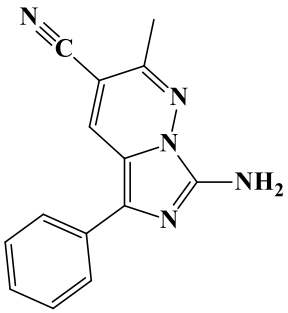
7-Amino-2-(4-chlorophenyl)-5-phenylimidazo[1,5-*b*]-pyridazine-3-carbonitrile 3d. Yield: A - 1296 mg (75%); B/C - 1246 mg (72%), red crystals, mp. 280-282 °C. IR, (ν, см$^{-1}$): 3288, 3147 (NH_2); 3072 (br, C-H + associated N-H); 2210 (CN); 1650 (NH); 1593 (Ar); 1558 (C=N imidazole); 1495 (Ar); 1222 (C-N amin); 1162 (C-N amin); 838 (p-C_6H_4); 696 (C-H Ph + N-H). ^{1}H NMR, (δ, ppm, *J*, Hz): 6.97 (s, 2H, NH_2); 7.35-7.38 (m, 1H, Ar-H); 7.46 (t, *J* 7.8 Hz , 2H, Ar-H); 7.66 (dt, *J* 8.5, 2.0 Hz, 2H, Ar-H); 7.86 (dt, *J* 8.5, 2.0 Hz, 2H, Ar-H); 7.97-8.00 (m, 2H, Ar-H); 8.96 (s, 1H, H^4). ^{13}C NMR, (δ, ppm): 90.1, 115.2, 118.2, 126.5, 128.0, 128.6, 128.9, 130.5, 132.4; 133.0, 134.4, 135.3, 136.9, 146.6, 150.0. HRMS (ESI), *m/z*: 346.0852 $[M+H]^+$. (calc. for $C_{19}H_{13}ClN_5$, *m/z*: 346.0854).



7-Amino-2-(naphthalene-2-yl)-5-phenylimidazo[1,5-*b*]-pyridazine-3-carbonitrile 3e. Yield: A - 1683 mg (93%); B/C - 1629 mg (90%), red crystals, mp. >300 °C. IR, (ν, см$^{-1}$): 3447, 3287 (NH_2); 3049 (br, C-H + associated N-H); 2210 (CN); 1650 (NH); 1593 (Ar); 1497 (Ar); 1559 (C=N imidazole); 1513 (Ar); 1224 (C-N amin); 1158 (C-N amin); 770 (C-H Ar); 693 (C-H Ph + N-H). ^{1}H NMR, (δ, ppm, *J*, Hz): 6.98 (s, 2H, NH_2); 7.37 (t, *J* 7.3 Hz, 1H, Ar-H); 7.48 (t, *J* 7.8 Hz, 2H, Ar-H); 7.62-7.68 (m, 2H, Ar-H); 7.94 (dd, *J* 8.5, 1.7 Hz, 1H, Ar-H); 8.00-8.08 (m, 4H, Ar-H); 8.11 (d, *J* 8.6 Hz, 1H, Ar-H); 8.42 (s, 1H, Ar-H); 8.99 (s, 1H, H^4). ^{13}C NMR, (δ, ppm): 90.6, 115.2, 118.4, 125.7, 126.5, 126.9, 127.6, 127.8, 128.0, 128.1, 128.5, 128.6, 128.9, 131.6, 132.3, 133.1, 133.5, 134.3, 136.9, 146.6, 150.9. HRMS (ESI), *m/z*: 362.1401 [M+H]$^+$. (calc. for $C_{23}H_{16}N_5$, *m/z*: 362.1401).



7-Amino-5-phenyl-2-(thiophen-2-yl)imidazo[1,5-*b*]-pyridazine-3-carbonitrile 3f. Yield: A - 1018 mg (64%); B/C - 1017 mg (63%), red crystals, mp. >300 °C. IR, (ν, см$^{-1}$): 3410, 3287 (NH_2); 3073 (br, C-H + associated N-H); 2212 (CN); 1649 (NH); 1594 (Ar); 1559 (C=N imidazole); 1223 (C-N amin); 1164 (C-N amin); 753 (C-H Ph); 695 (C-H Ph + C-H thiophene + N-H). ^{1}H NMR, (δ, ppm, *J*, Hz): 6.92 (s, 2H, NH_2); 7.27 (t, *J* 4.4 Hz, 1H, thiophen-H); 7.37 (t, *J* 7.3 Hz, 1H, Ar-H); 7.46 (t, *J* 7.4 Hz, 2H, Ar-H); 7.86 (d, *J* 5.1 Hz,1H, thiophen-H); 7.98 (d, *J* 7.7 Hz, 2H, Ar-H); 8.01 (d, *J* 3.7 Hz, 1H, thiophen-H); 8.93 (s, 1H, H^4). ^{13}C NMR, (δ, ppm): 88.6, 115.0, 118.6, 126.5, 128.1, 128.2, 128.9, 129.7, 130.3, 132.4, 134.8, 136.5, 137.4, 144.5, 146.4. HRMS (ESI), *m/z*: 318.0802 [M+H]$^+$. (calc. for $C_{17}H_{12}N_5S$, *m/z*: 318.0808).



7-Amino-2-methyl-5-phenylimidazo[1,5-*b*]pyridazine-3-carbonitrile 3g. Yield: A - 1046 mg (84%); B/C - 1108 mg (89%), red crystals, mp. 260-262 °C. IR, (ν, см$^{-1}$): 3453, 3288 (NH_2); 3096 (br, C-H + associated N-H); 2210 (CN); 1646 (NH); 1604 (Ph); 1559 (C=N imidazole); 1497 (Ph); 1227 (C-N amin); 1158 (C-N amin); 767 (C-H Ph); 699 (C-H Ph + N-H). ^{1}H NMR, (δ, ppm, *J*, Hz): 2.41 (s, 3H, CH_3), 6.79 (s, 2H, NH_2); 7.27 (t, *J* 6.9 Hz,1H, Ar-H); 7.43 (t, *J* 7.5 Hz, 2H, Ar-H); 7.92 (d, *J* 7.7 Hz, 2H, Ar-H); 8.78 (s, 1H, H^4). ^{13}C NMR, (δ, ppm): 20.4, 91.6, 115.2, 117.9, 126.3, 127.8, 128.8, 133.2, 133.9, 135.2, 146.1, 150.0. HRMS (ESI), *m/z*: 250.1088 [M+H]$^+$. (calc. for $C_{14}H_{11}N_5$, *m/z*: 250.1088).

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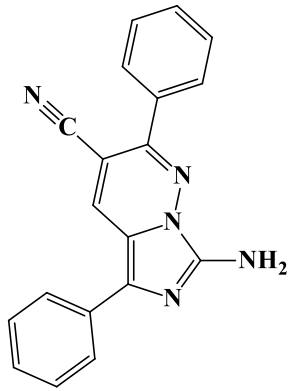
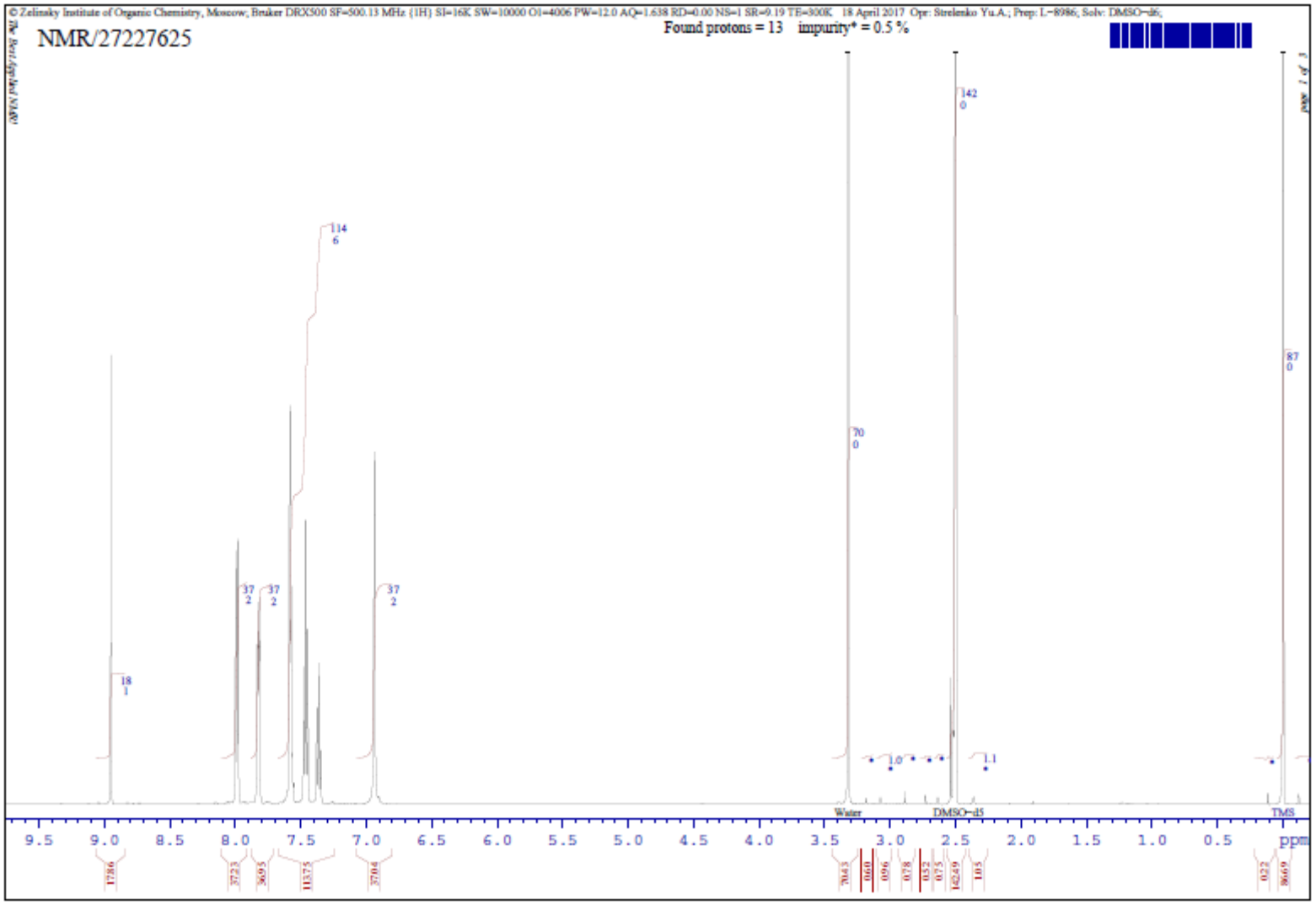
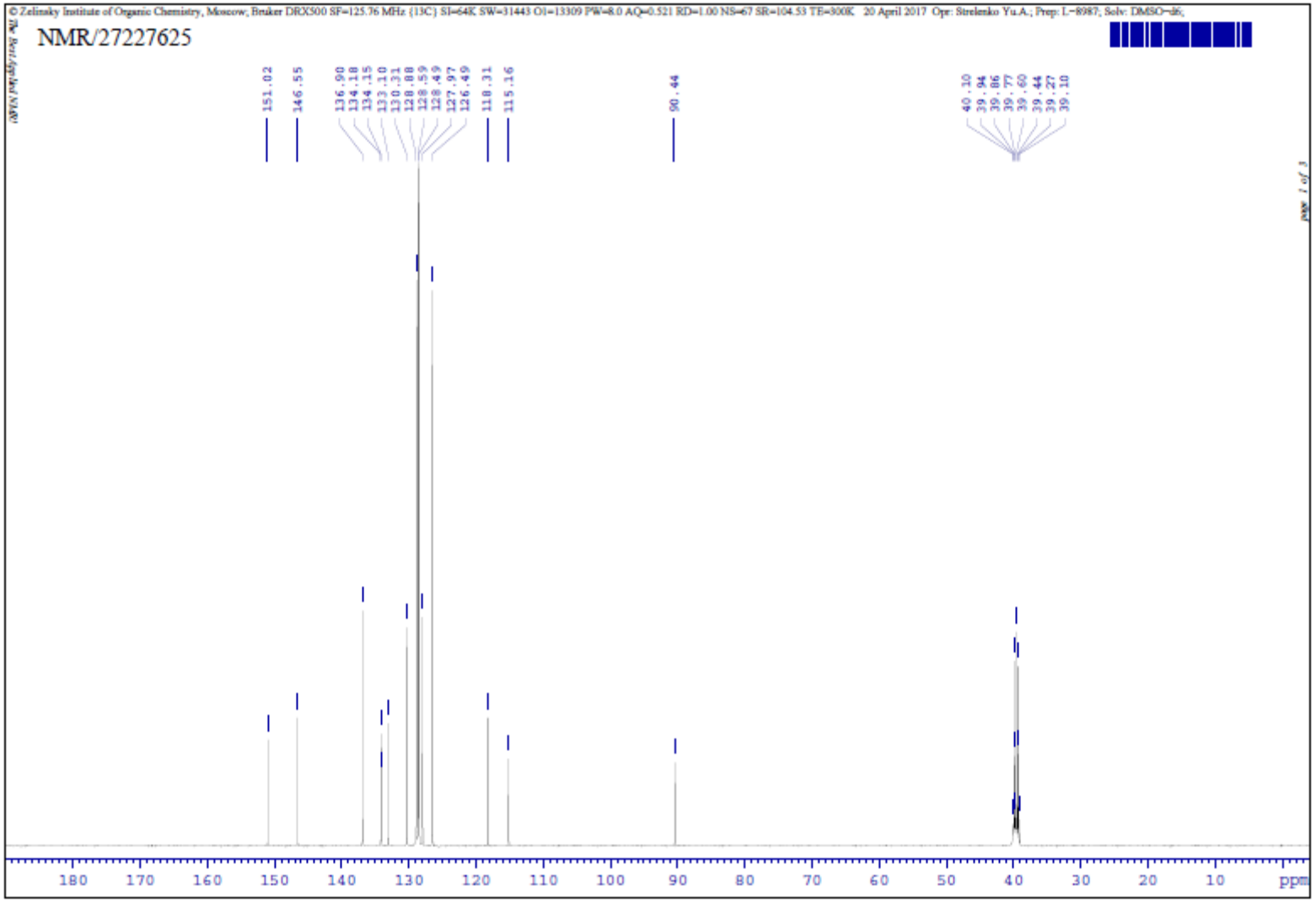
Table S1. Spectra of compound 3a






© Zelinsky Institute of Organic Chemistry, Moscow, Bruker DRX500 SF=125.76 MHz (13C) SI=64K SW=31443 O1=13309 PW=8.0 AQ=0.521 RD=1.00 NS=67 SR=104.53 TE=300K 20 April 2017 Opr: Strelenko Yu.A., Prep: L-8987, Solv: DMSO-d6;
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134.18
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40
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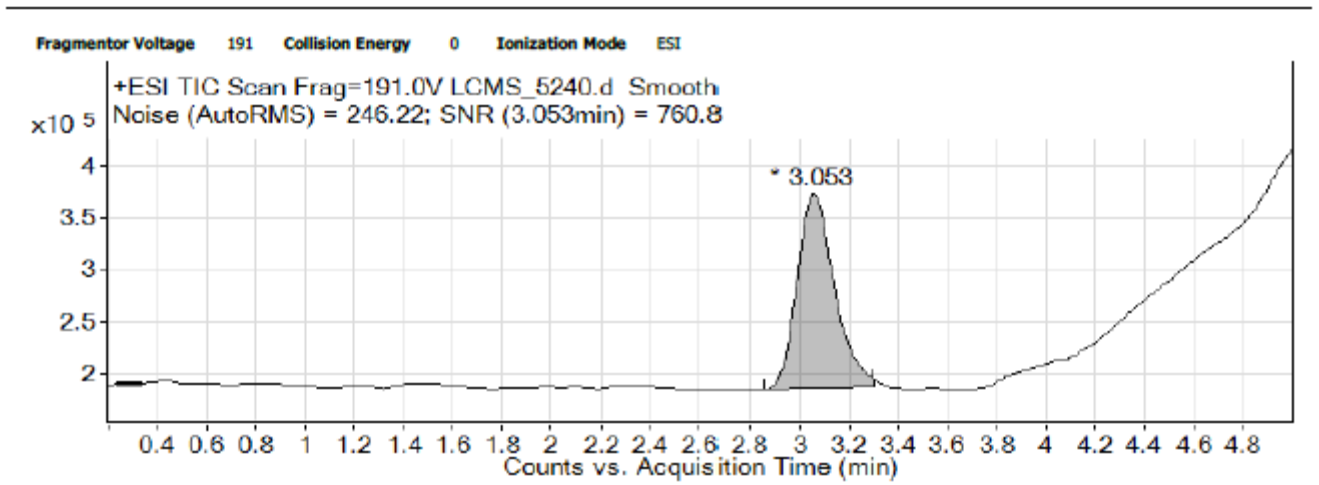
20
10
ppm


Fragmentor Voltage 191 Collision Energy 0 Ionization Mode ESI
+ESI TIC Scan Frag=191.0V LCMS_5240.d Smooth
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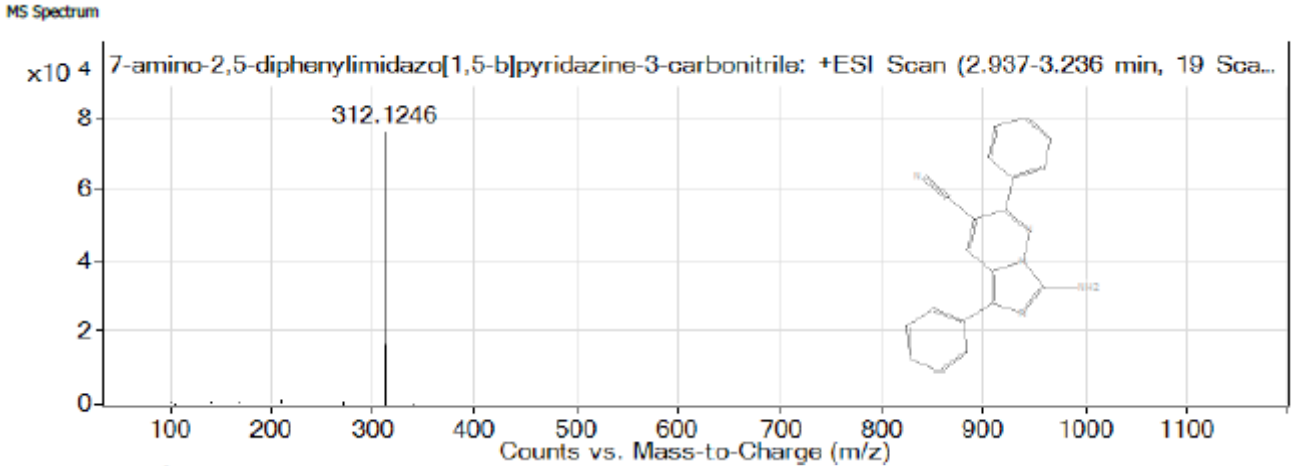
x10 5
* 3.053
Counts vs. Acquisition Time (min)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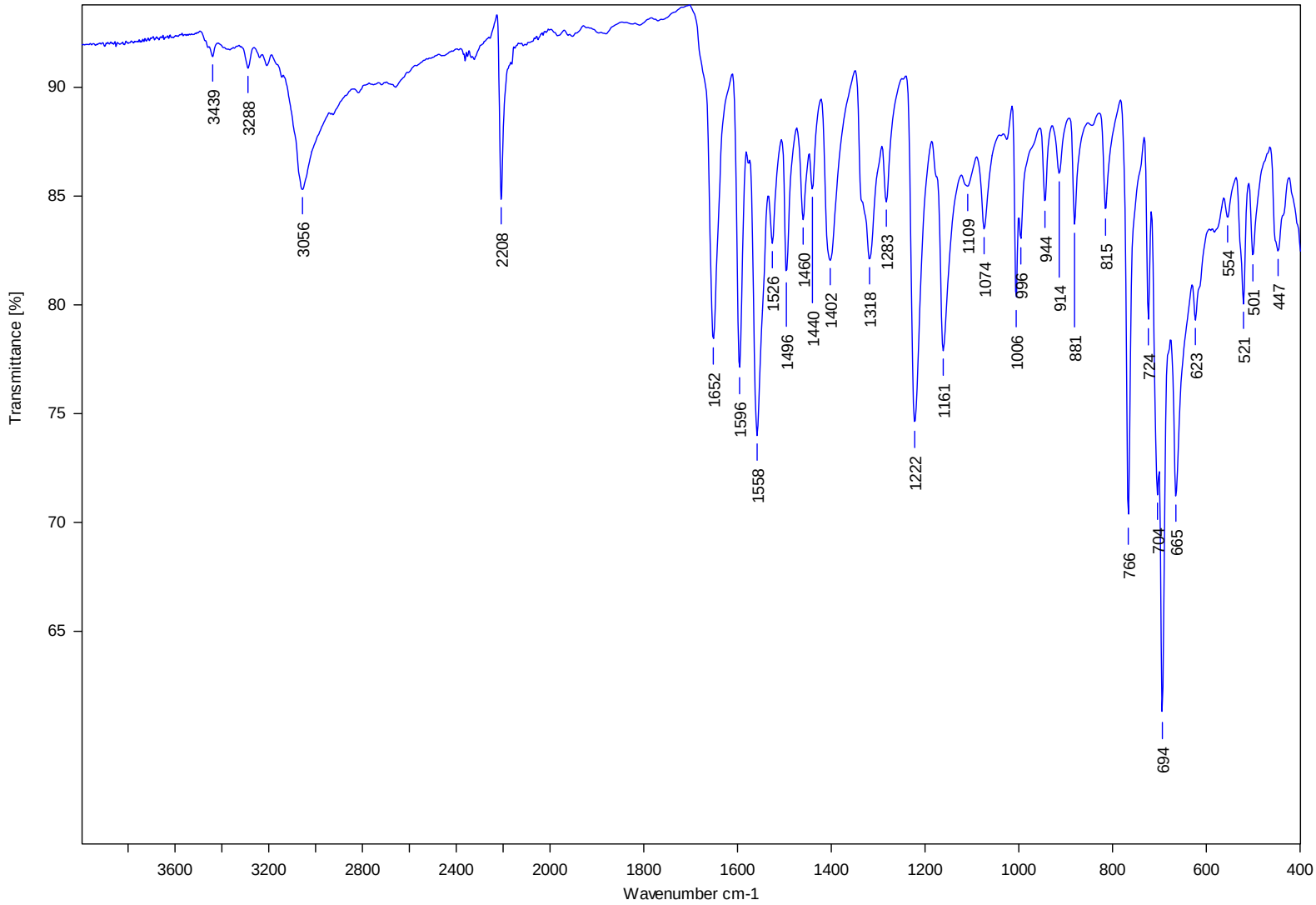
x10 4
312.1246
Counts vs. Mass-to-Charge (m/z)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75
70
65
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1440
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1318
1283
1222
1161
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996
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944
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694
665
623
554
521
501
447
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2000
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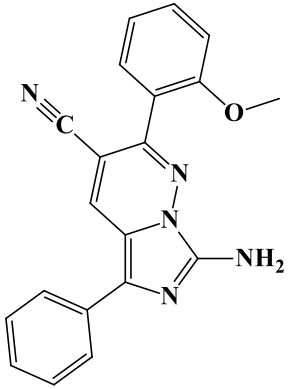
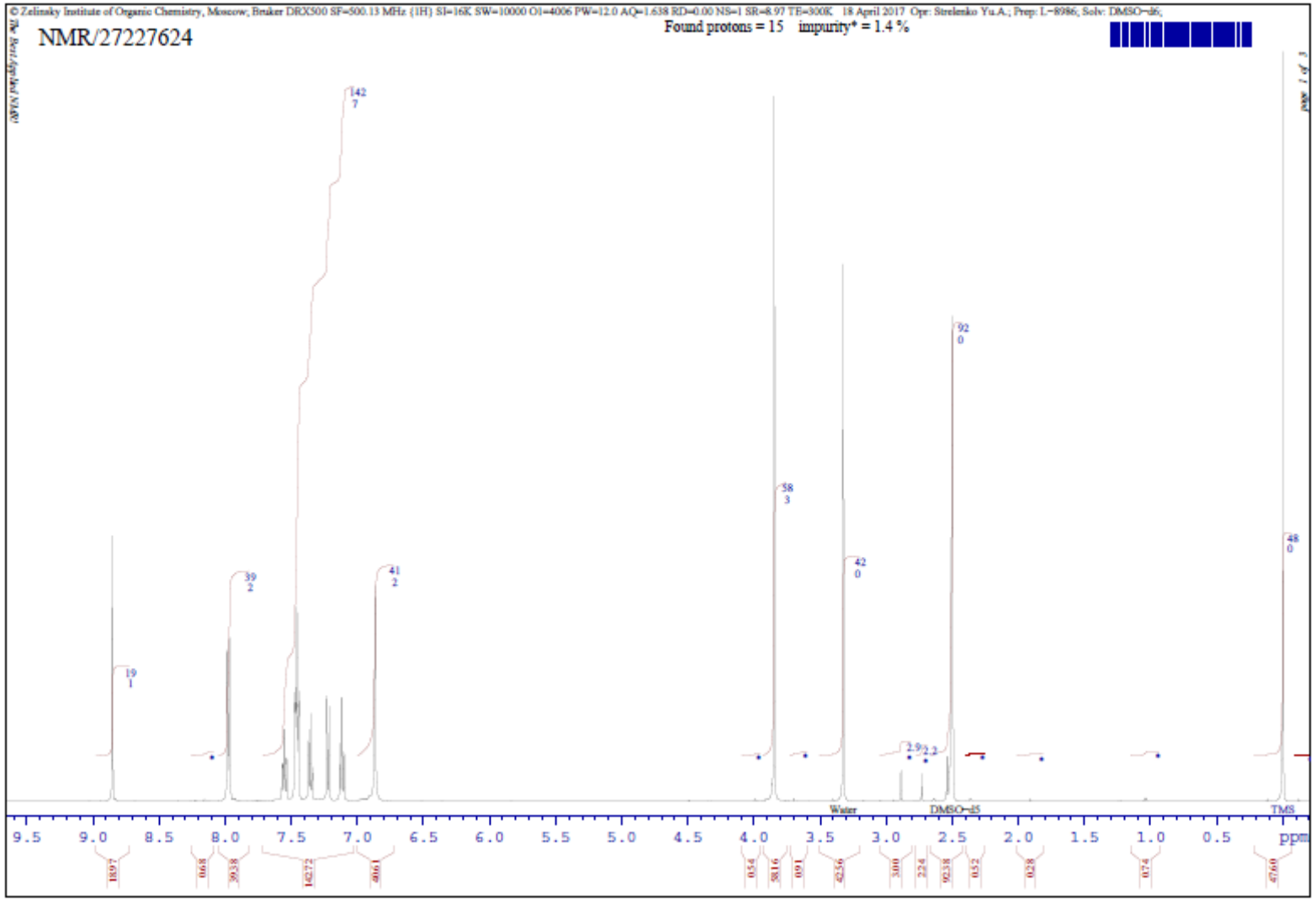
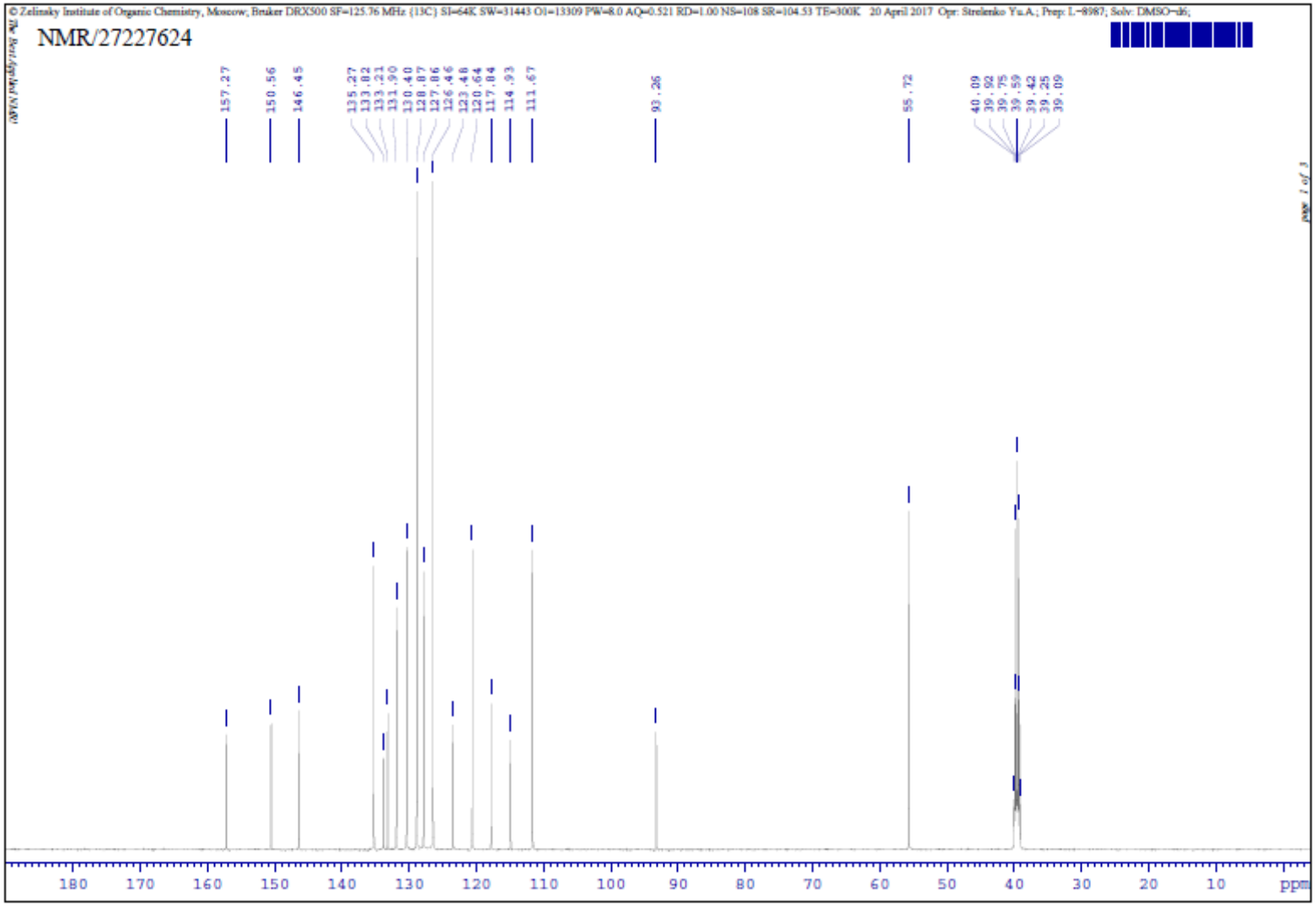
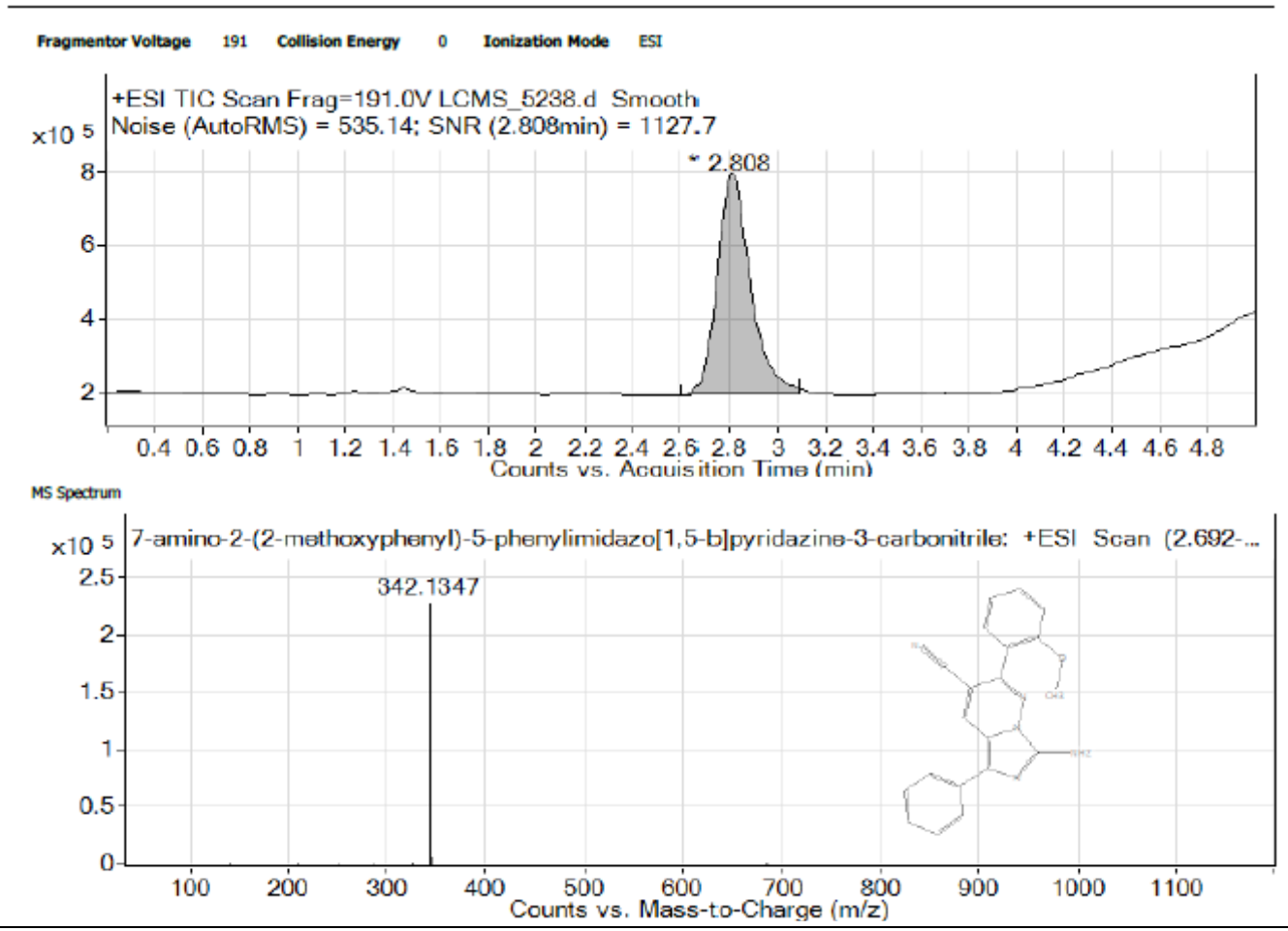
1400
1200
1000
800
600
400
Wavenumber cm-1

Table S2. Spectra of compound 3b






© Zelinsky Institute of Organic Chemistry, Moscow, Bruker DRX500 SF=125.76 MHz {13C} SI=64K SW=31443 O1=13309 PW=8.0 AQ=0.521 RD=1.00 NS=108 SR=104.53 TE=300K 20 April 2017 Opr: Strelenko Yu.A.; Prep: L-8987; Solv: DMSO-d6;
NMR/27227624
157.27
150.56
146.45
135.27
133.82
133.21
131.90
130.40
128.87
127.06
126.46
123.46
120.64
117.84
114.93
111.67
93.26
55.72
40.09
39.92
39.75
39.59
39.42
39.25
39.09
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


Fragmentor Voltage 191 Collision Energy 0 Ionization Mode ESI
+ESI TIC Scan Frag=191.0V LCMS_5238.d Smooth
Noise (AutoRMS) = 535.14; SNR (2.808min) = 1127.7
x10 5
2.808
Counts vs. Acquisition Time (min)
MS Spectrum
7-amino-2-(2-methoxyphenyl)-5-phenylimidazo[1,5-b]pyridazine-3-carbonitrile: +ESI Scan (2.692-...
342.1347
Counts vs. Mass-to-Charge (m/z)

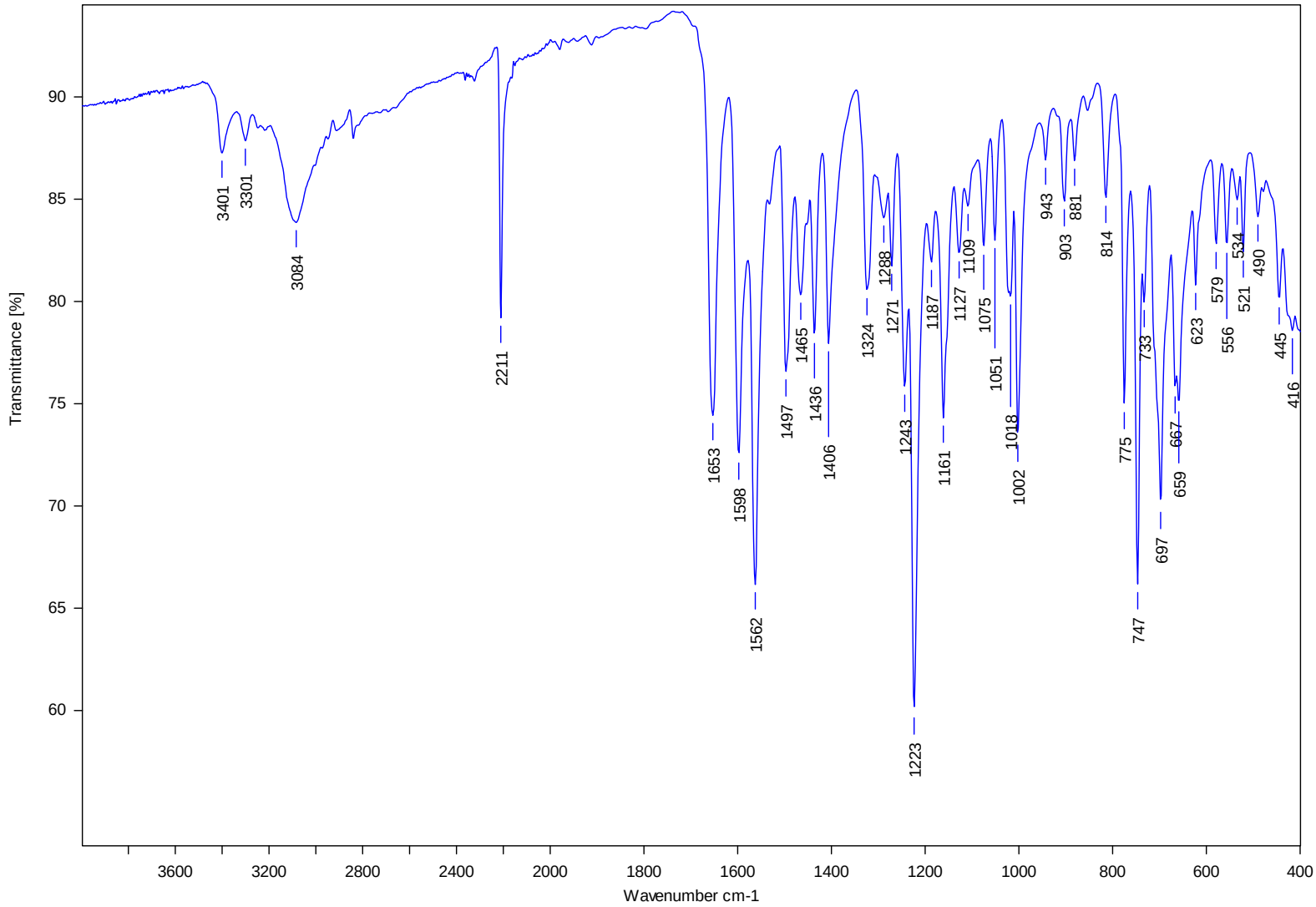
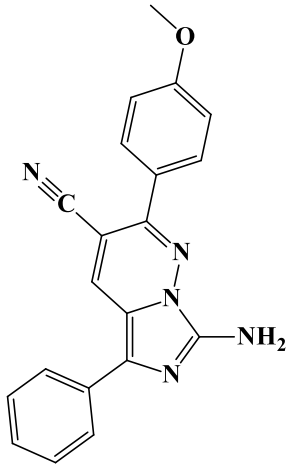
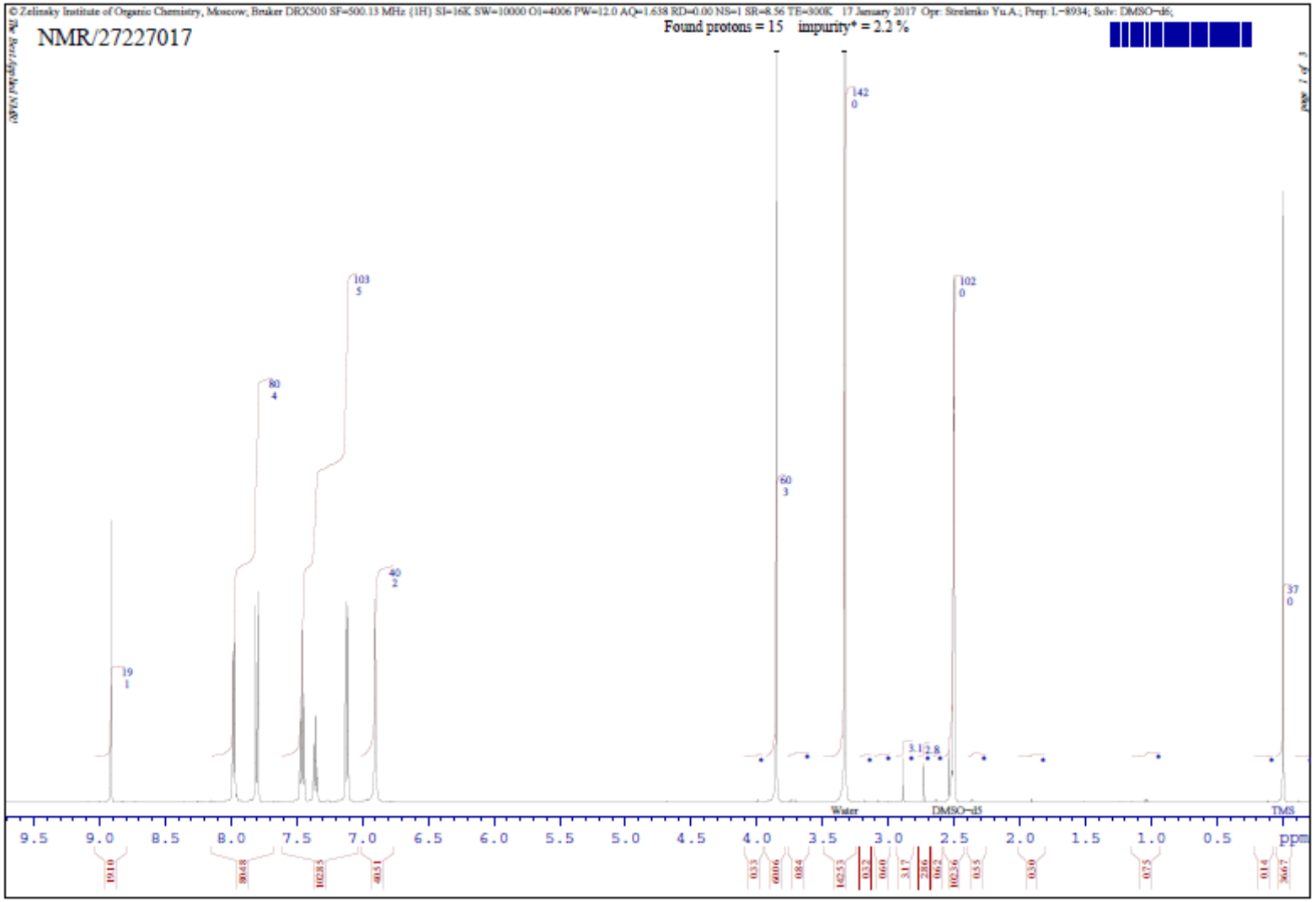
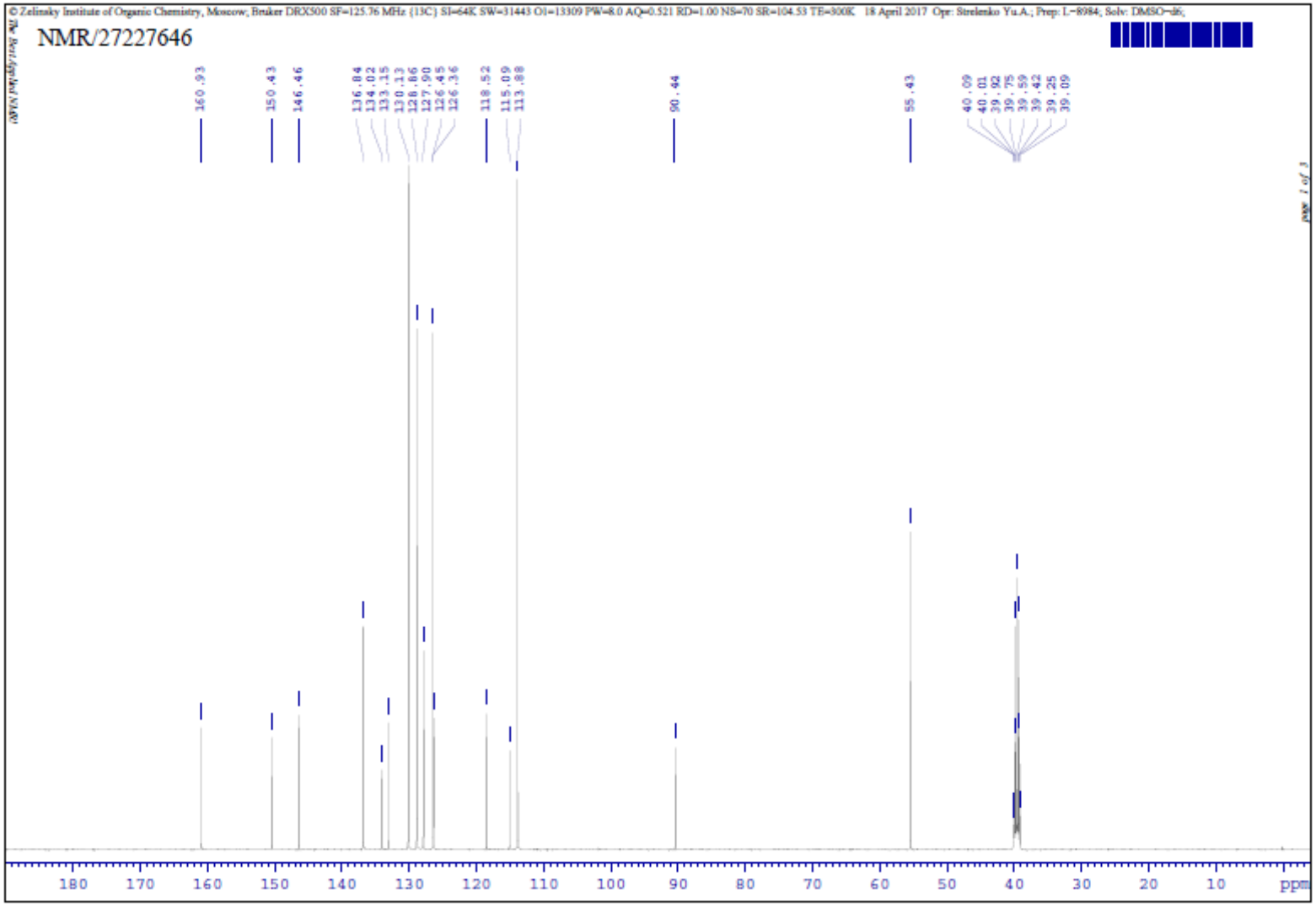
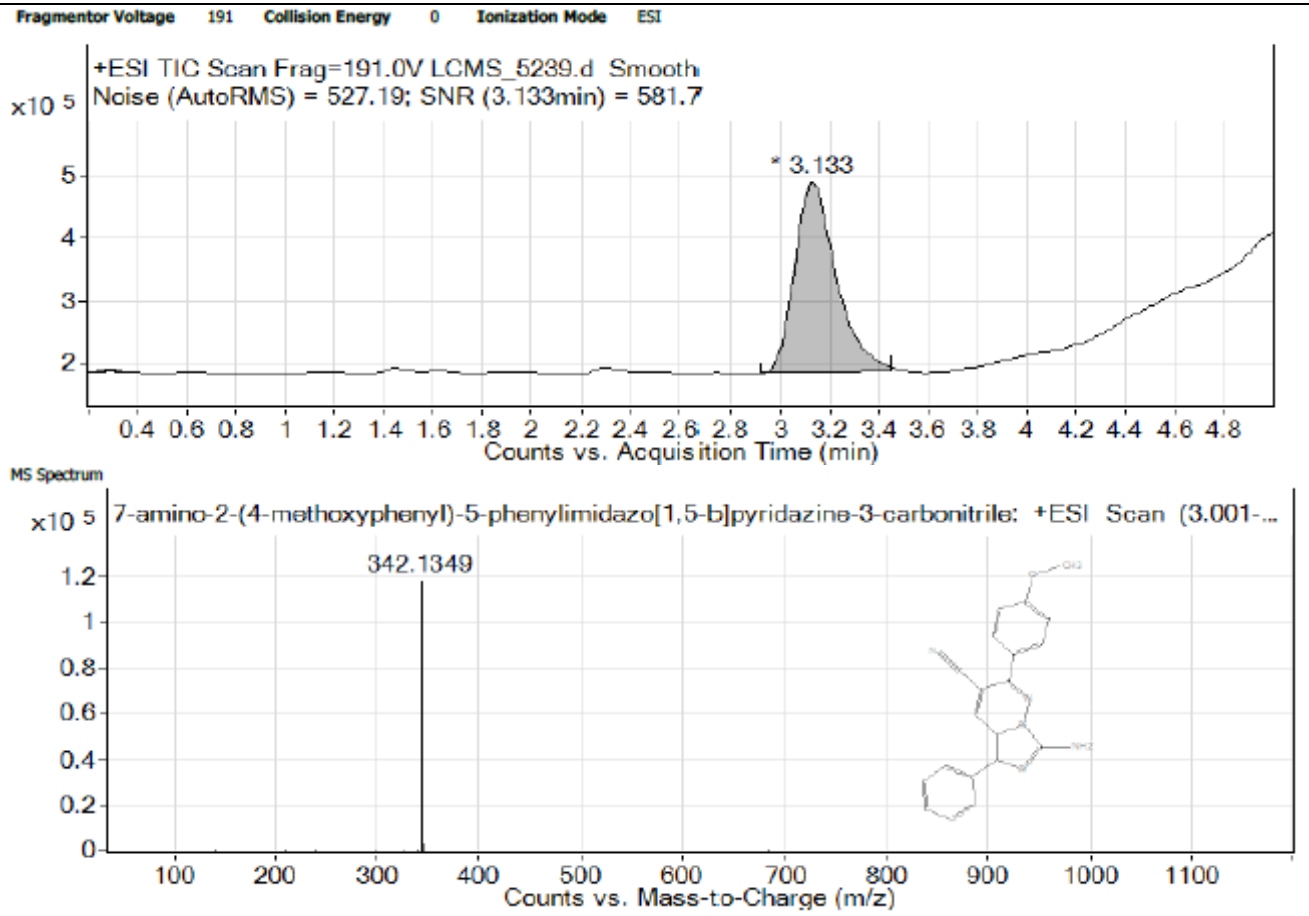

Transmittance [%]
90
85
80
75
70
65
60
3401
3301
3084
2211
1653
1598
1562
1497
1465
1436
1406
1324
1288
1271
1243
1223
1187
1161
1127
1109
1075
1051
1018
1002
943
903
881
814
775
747
733
697
667
659
623
579
556
534
521
490
445
416
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600
400
Wavenumber cm-1

Table S3. Spectra of compound 3c






© Zelinsky Institute of Organic Chemistry, Moscow, Bruker DRX500 SF=125.76 MHz (13C) SI=64K SW=31443 O1=13309 PW=8.0 AQ=0.521 RD=1.00 NS=70 SR=104.53 TE=300K 18 April 2017 Opr: Strelenko Yu.A.; Prep: L-8984; Solv: DMSO-d6;
NMR/27227646
160.93
150.43
146.46
136.84
134.02
133.15
130.13
128.66
127.90
126.45
126.36
118.52
115.09
113.88
90.44
55.43
40.09
40.01
39.92
39.75
39.59
39.42
39.25
39.09
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


Fragmentor Voltage 191 Collision Energy 0 Ionization Mode ESI
+ESI TIC Scan Frag=191.0V LCMS_5239.d Smooth
Noise (AutoRMS) = 527.19; SNR (3.133min) = 581.7
x10 5
* 3.133
Counts vs. Acquisition Time (min)
MS Spectrum
7-amino-2-(4-methoxyphenyl)-5-phenylimidazo[1,5-b]pyridazine-3-carbonitrile: +ESI Scan (3.001-...
342.1349
Counts vs. Mass-to-Charge (m/z)

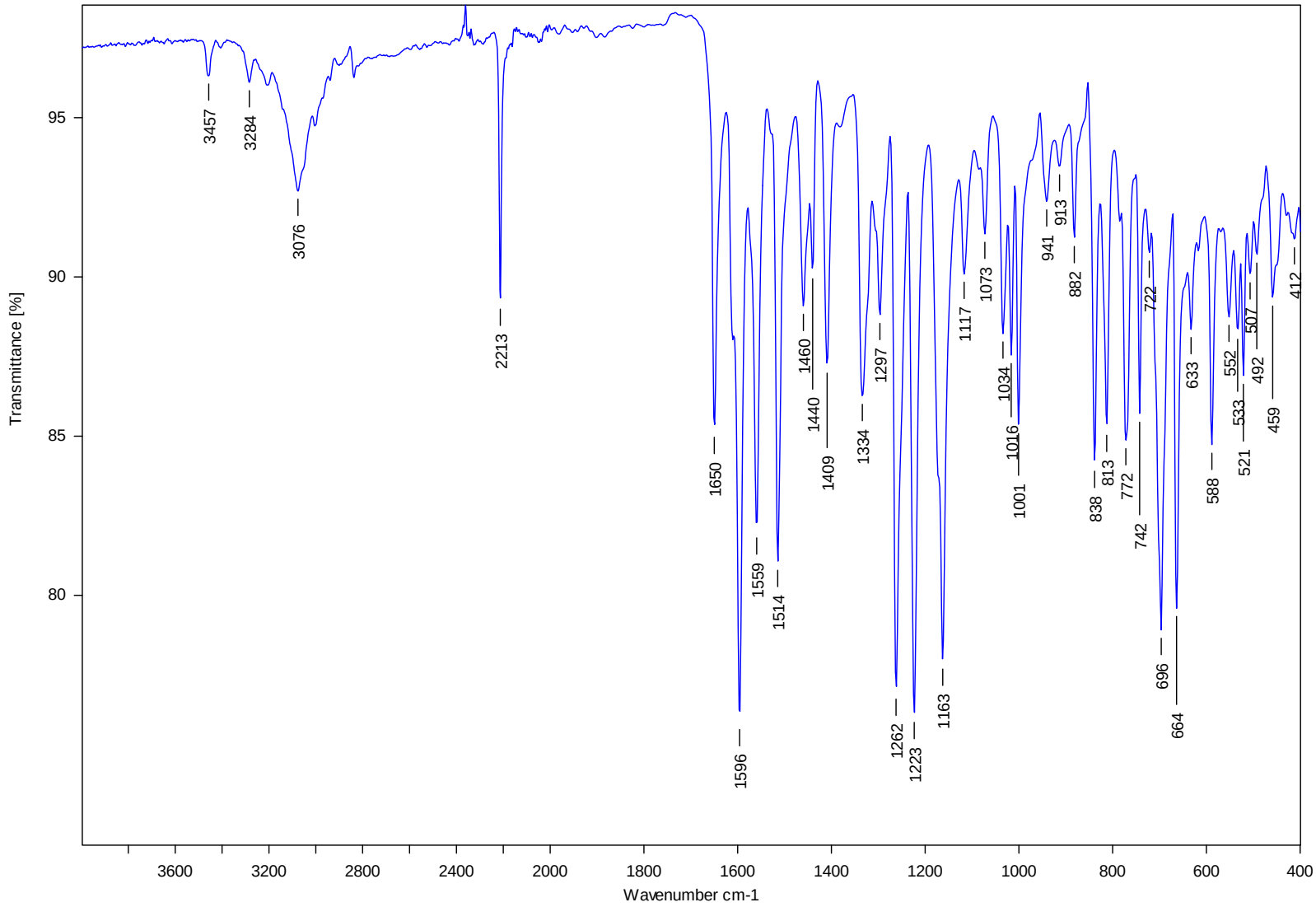
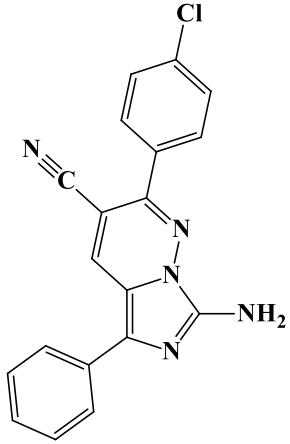
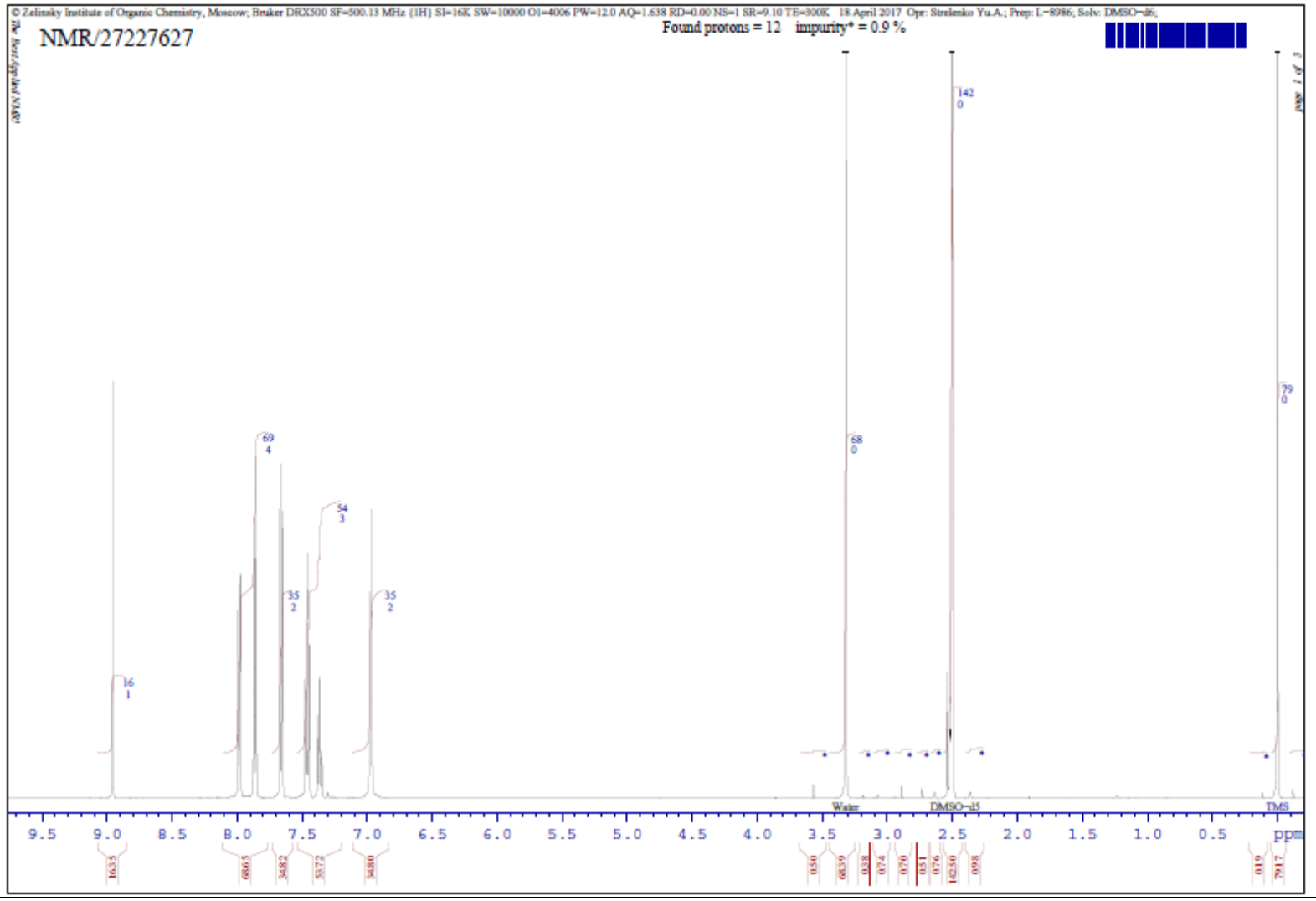
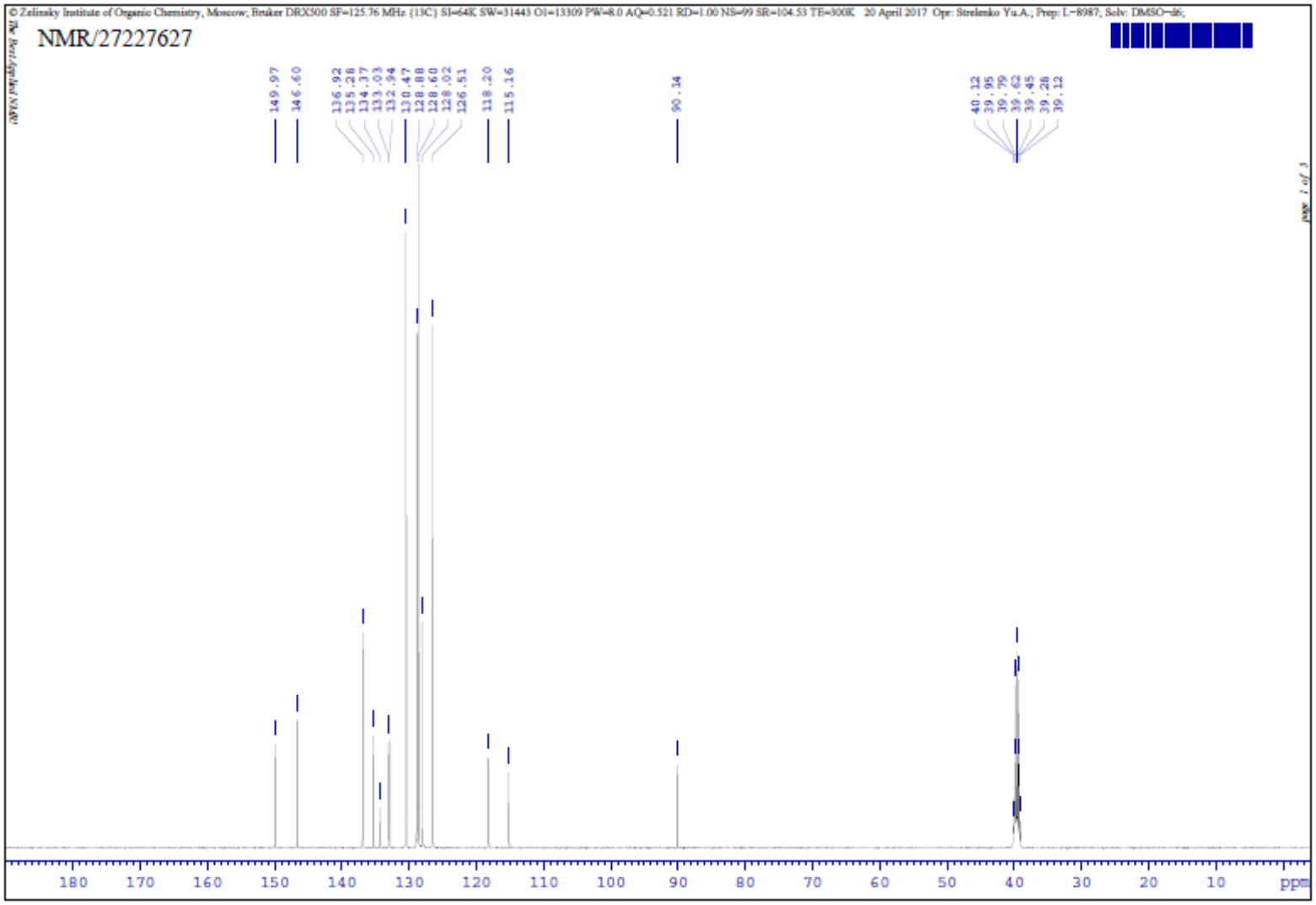
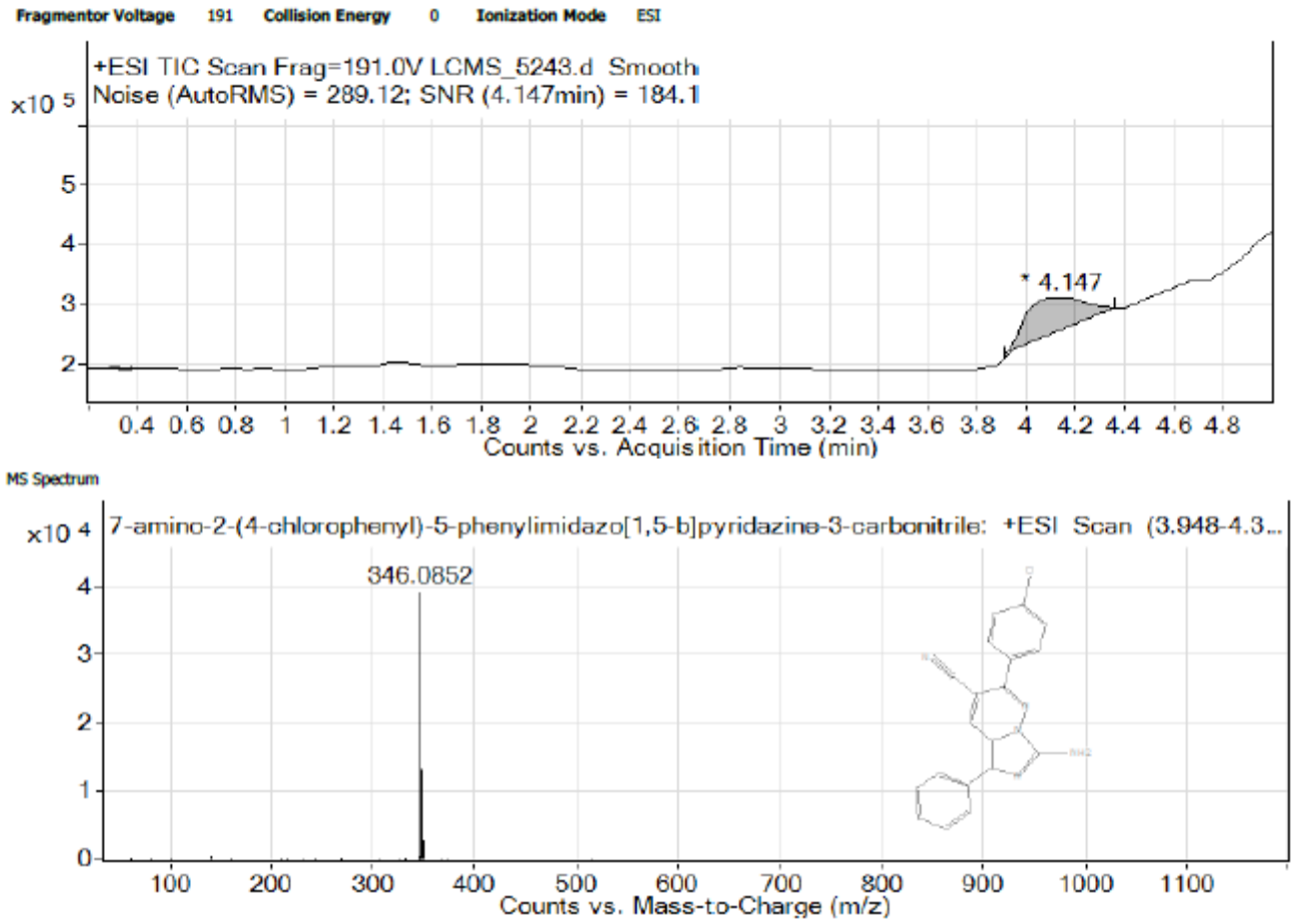

Transmittance [%]
95
90
85
80
3457
3284
3076
2213
1650
1596
1559
1514
1460
1440
1409
1334
1297
1262
1223
1163
1117
1073
1034
1016
1001
941
913
882
838
813
772
742
722
696
664
633
588
552
533
521
507
492
459
412
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600
400
Wavenumber cm-1

Table S4. Spectra of compound 3d






© Zelinsky Institute of Organic Chemistry, Moscow, Bruker DRX500 SF=125.76 MHz (13C) SI=64K SW=31443 O1=13309 PW=8.0 AQ=0.521 RD=1.00 NS=99 SR=104.53 TE=300K 20 April 2017 Opr: Strelenko Yu.A.; Prep: L-8987; Solv: DMSO-d6;
NMR/27227627
149.97
146.60
136.92
135.26
134.37
133.03
132.94
130.47
128.88
128.60
128.02
126.51
118.20
115.16
90.34
40.12
39.95
39.79
39.62
39.45
39.28
39.12
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


Fragmentor Voltage 191 Collision Energy 0 Ionization Mode ESI
+ESI TIC Scan Frag=191.0V LCMS_5243.d Smooth
Noise (AutoRMS) = 289.12; SNR (4.147min) = 184.1
x10 5
* 4.147
Counts vs. Acquisition Time (min)
MS Spectrum
7-amino-2-(4-chlorophenyl)-5-phenylimidazo[1,5-b]pyridazine-3-carbonitrile: +ESI Scan (3.948-4.3...
x10 4
346.0852
Counts vs. Mass-to-Charge (m/z)

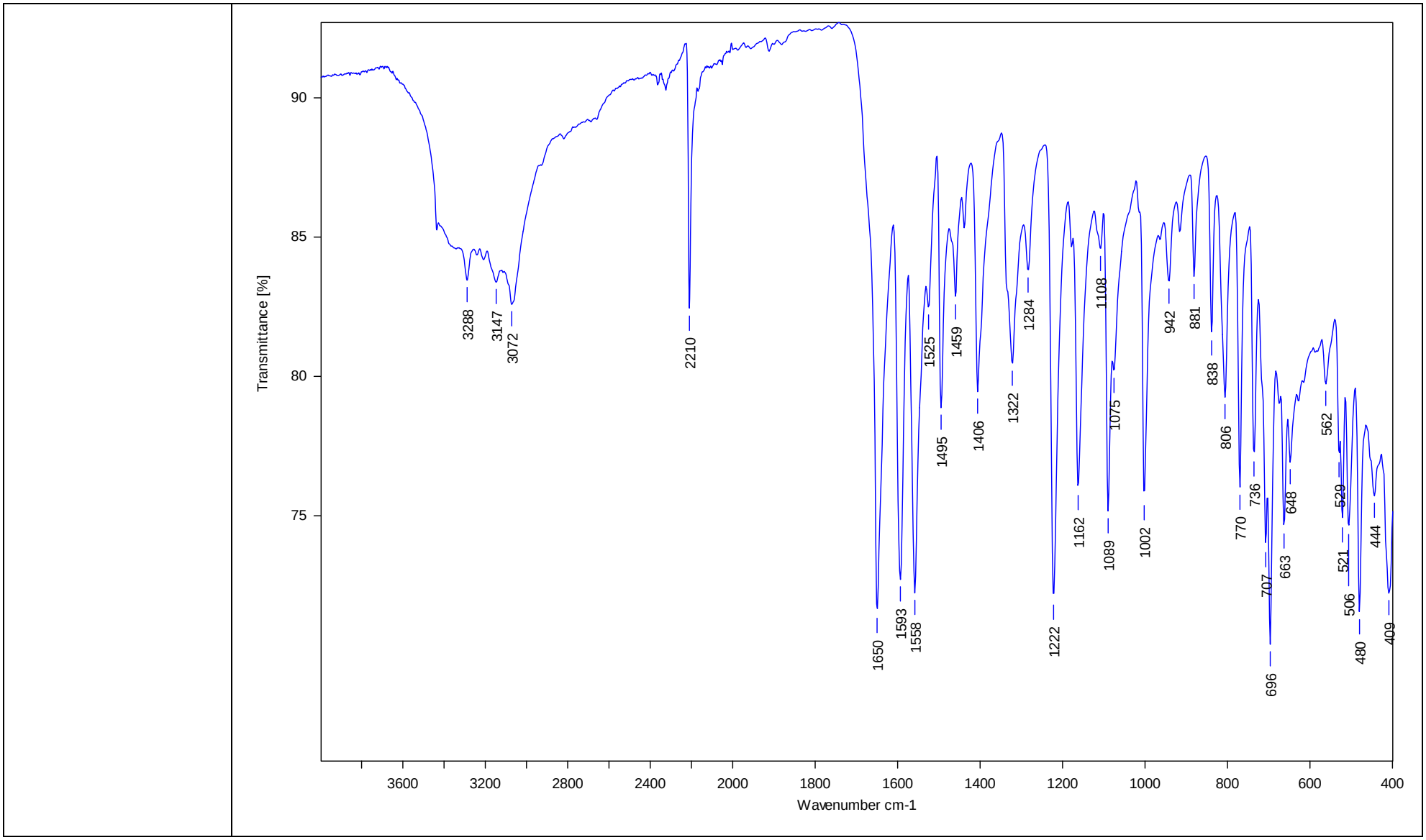
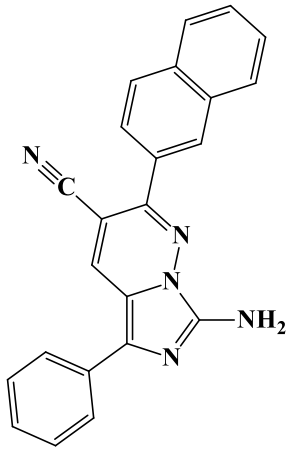
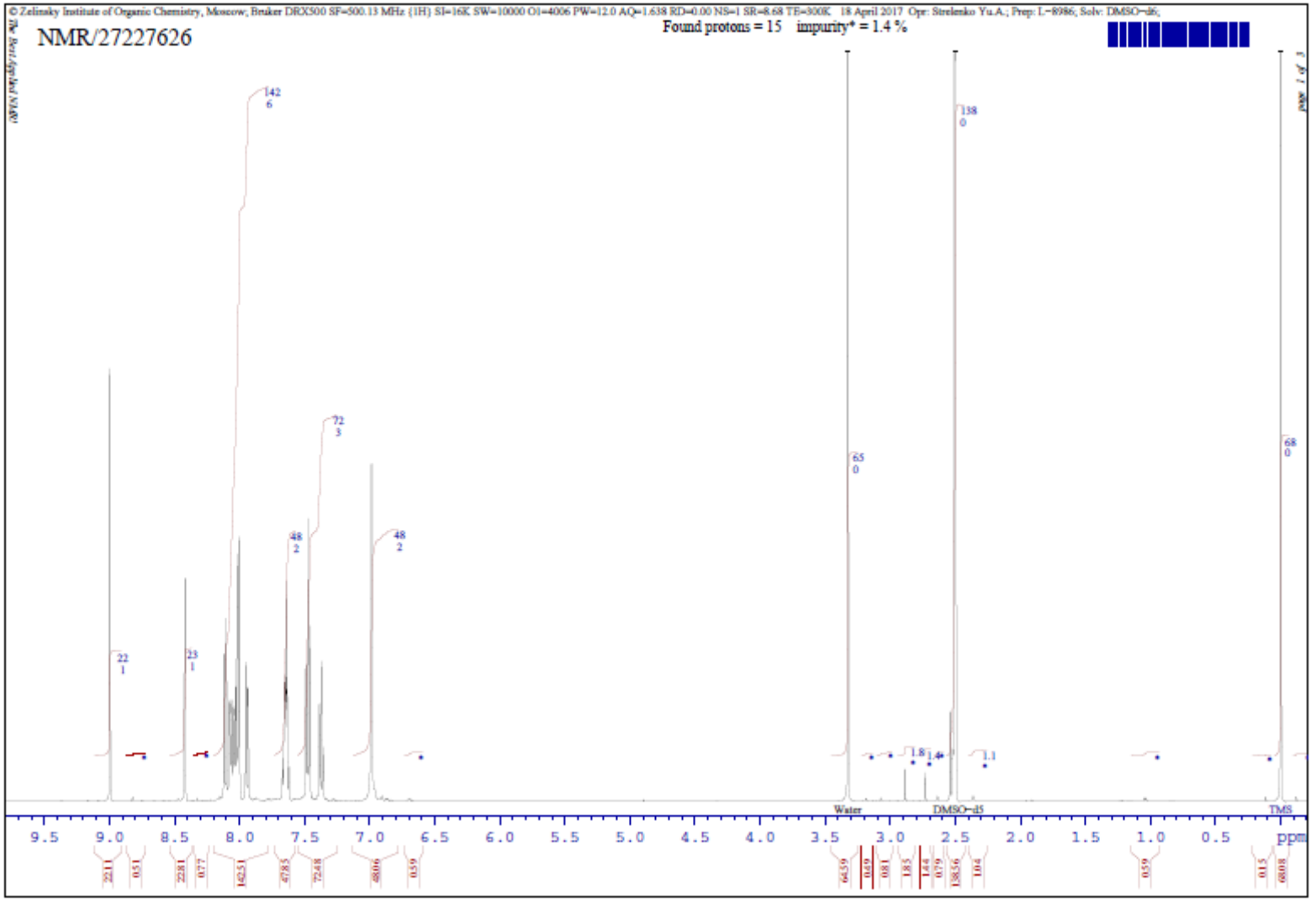
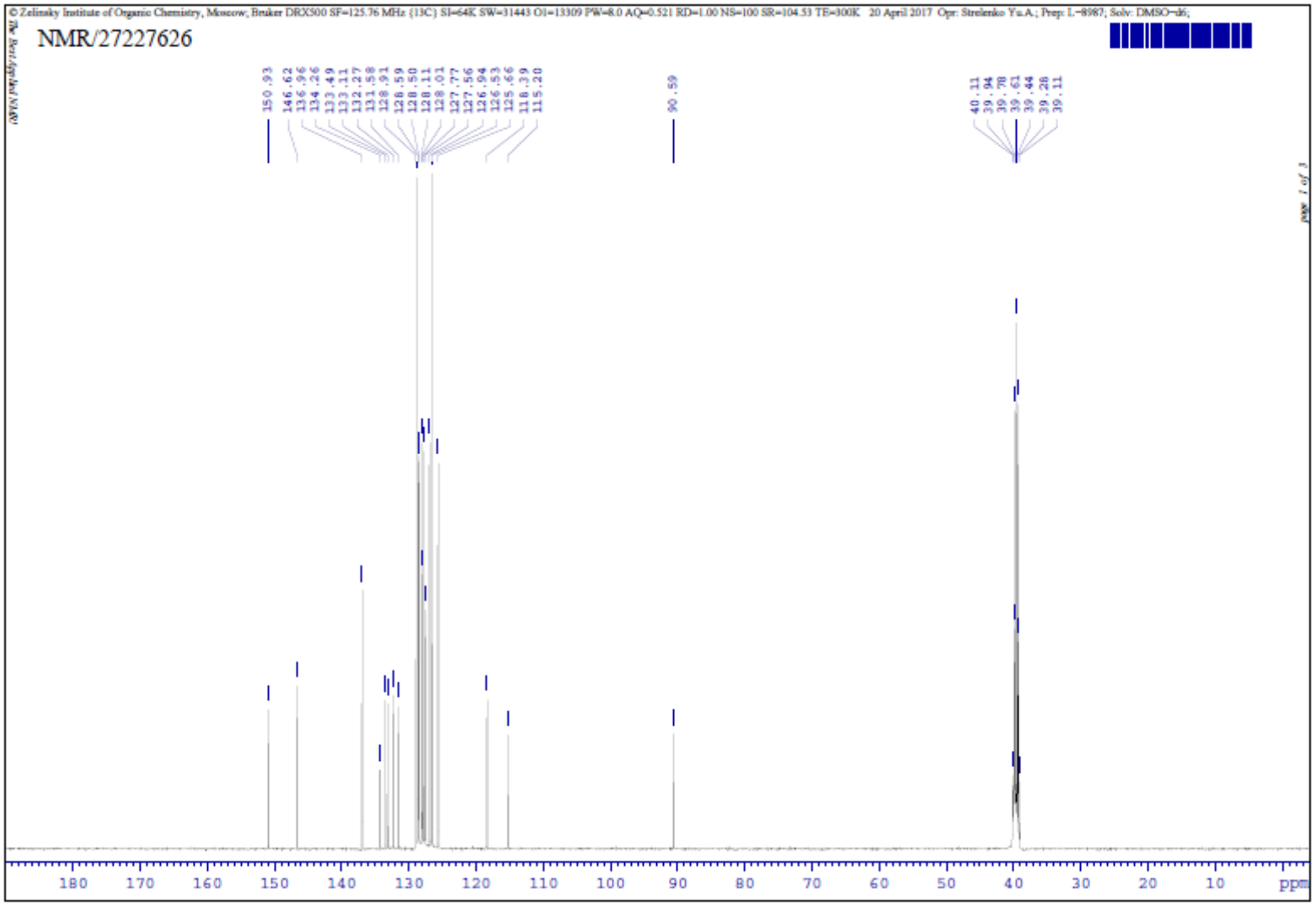
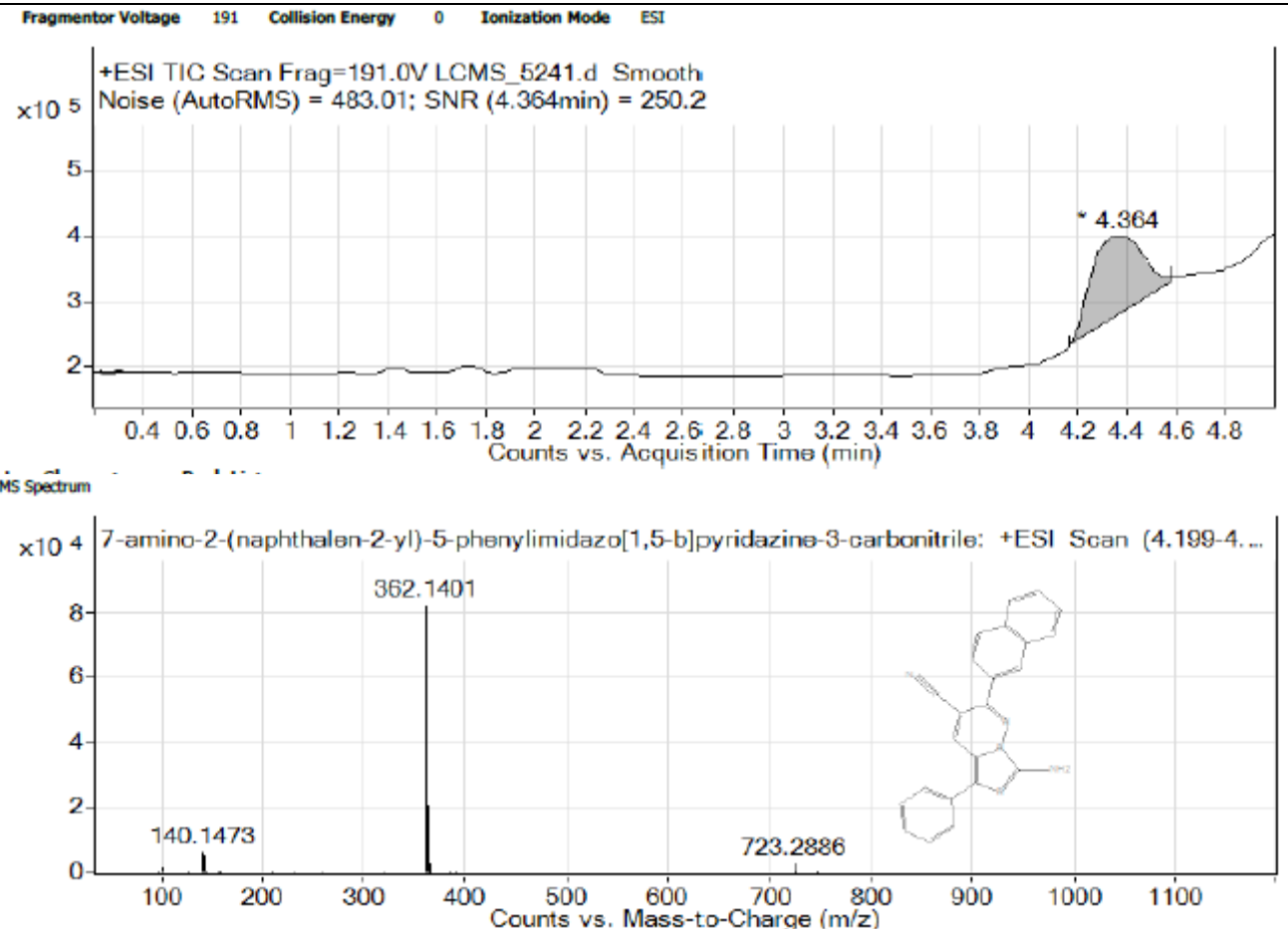

Transmittance [%]
90
85
80
75
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600
400
Wavenumber cm-1
3288
3147
3072
2210
1650
1593
1558
1525
1495
1459
1406
1322
1284
1222
1162
1108
1089
1075
1002
942
881
838
806
770
736
707
696
663
648
562
529
521
506
480
444
409

Table S5. Spectra of compound 3e






© Zelinsky Institute of Organic Chemistry, Moscow, Bruker DRX500 SF=125.76 MHz (13C) SI=64K SW=31443 O1=13309 PW=8.0 AQ=0.521 RD=1.00 NS=100 SR=104.53 TE=300K 20 April 2017 Opr: Strelenko Yu.A.; Prep: L-8987; Solv: DMSO-d6;
NMR/27227626
150.93
146.62
136.96
134.26
133.49
133.11
132.27
131.58
128.91
128.59
128.50
128.11
128.01
127.77
127.56
126.94
126.53
125.66
116.39
115.20
90.59
40.11
39.94
39.78
39.61
39.44
39.28
39.11
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


Fragmentor Voltage 191 Collision Energy 0 Ionization Mode ESI
+ESI TIC Scan Frag=191.0V LCMS_5241.d Smooth
Noise (AutoRMS) = 483.01; SNR (4.364min) = 250.2
x10 5
* 4.364
Counts vs. Acquisition Time (min)
MS Spectrum
x10 4
7-amino-2-(naphthalen-2-yl)-5-phenylimidazo[1,5-b]pyridazine-3-carbonitrile: +ESI Scan (4.199-4.
362.1401
140.1473
723.2886
Counts vs. Mass-to-Charge (m/z)

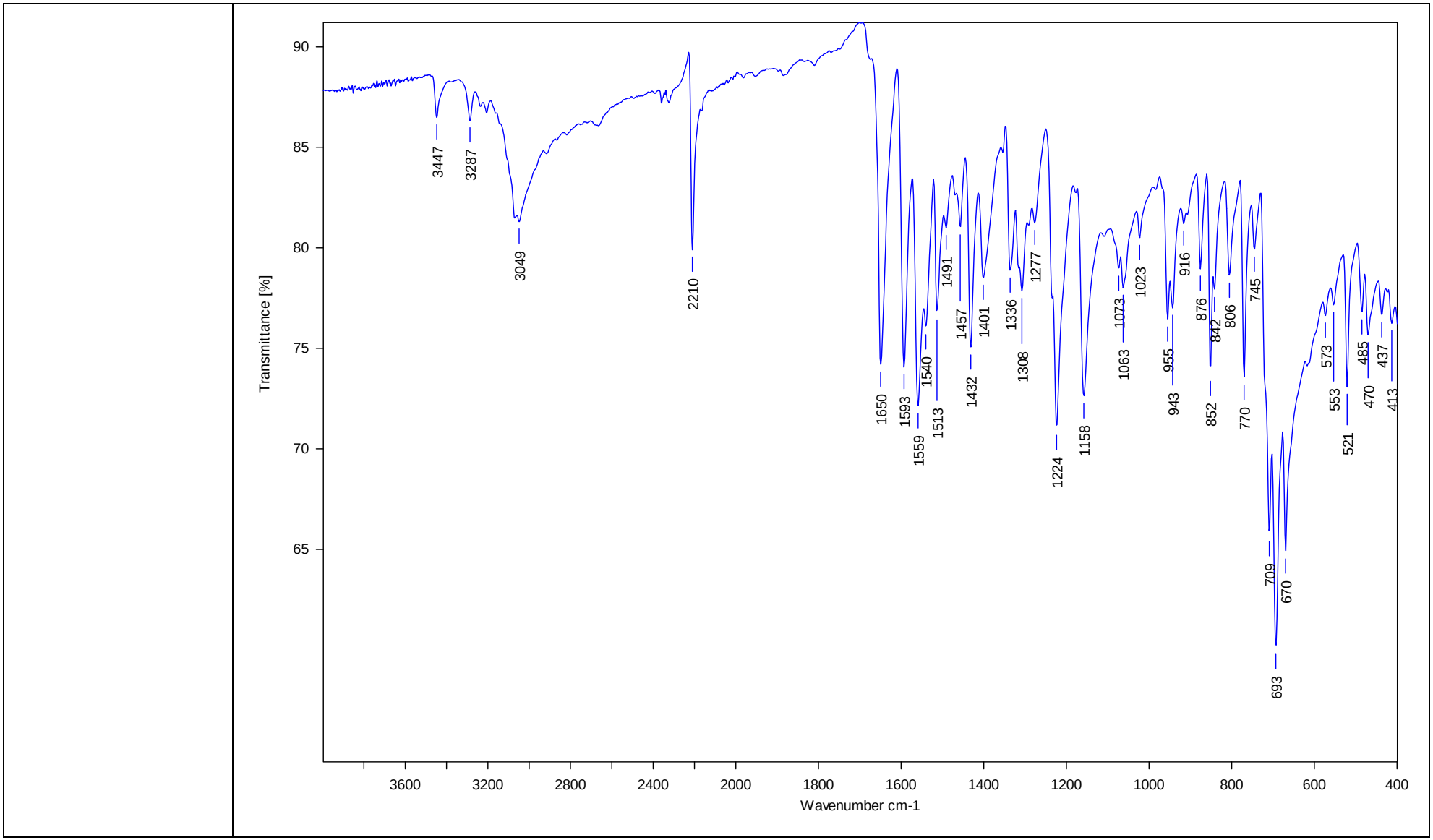
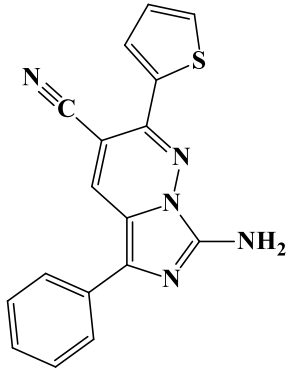
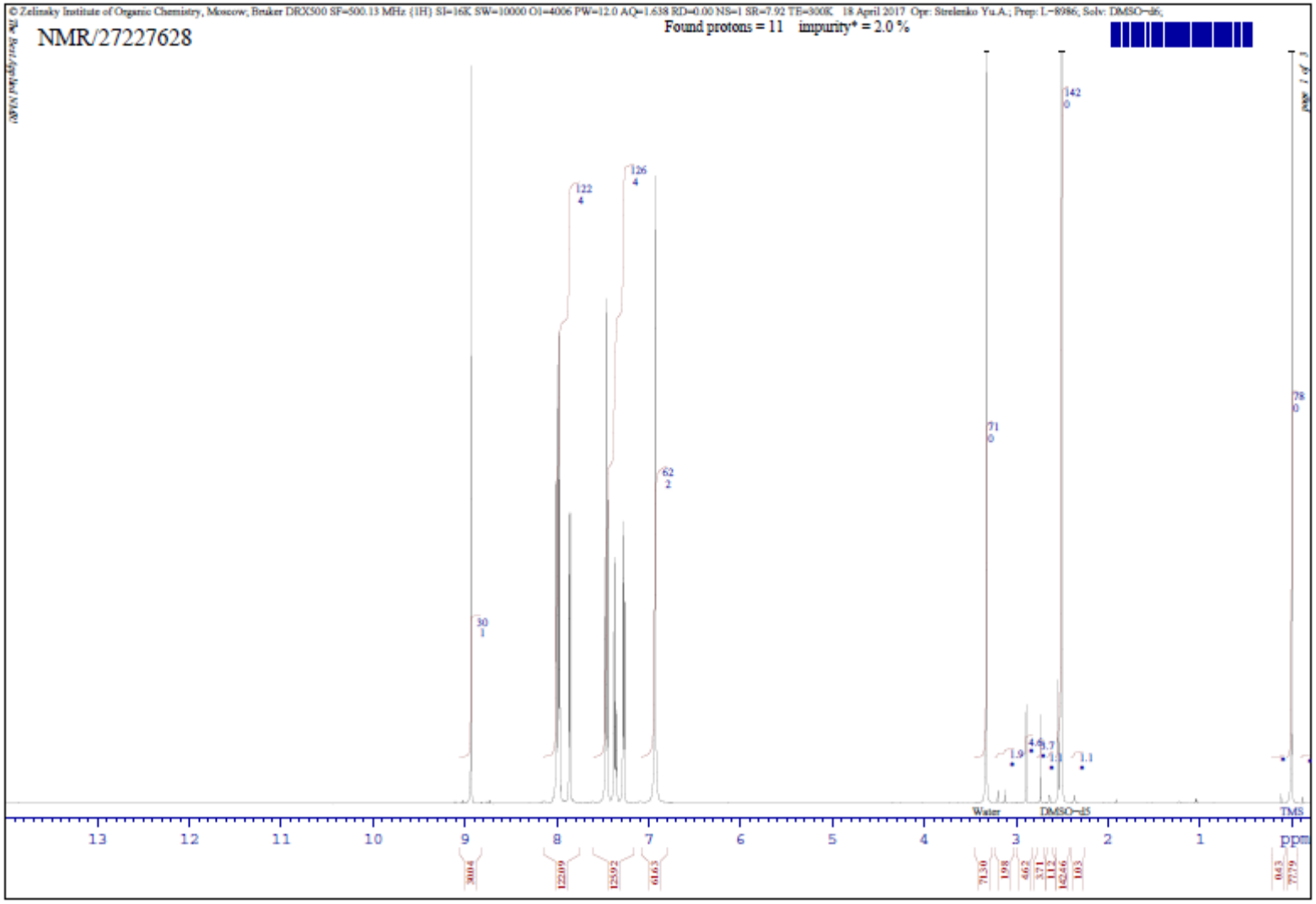
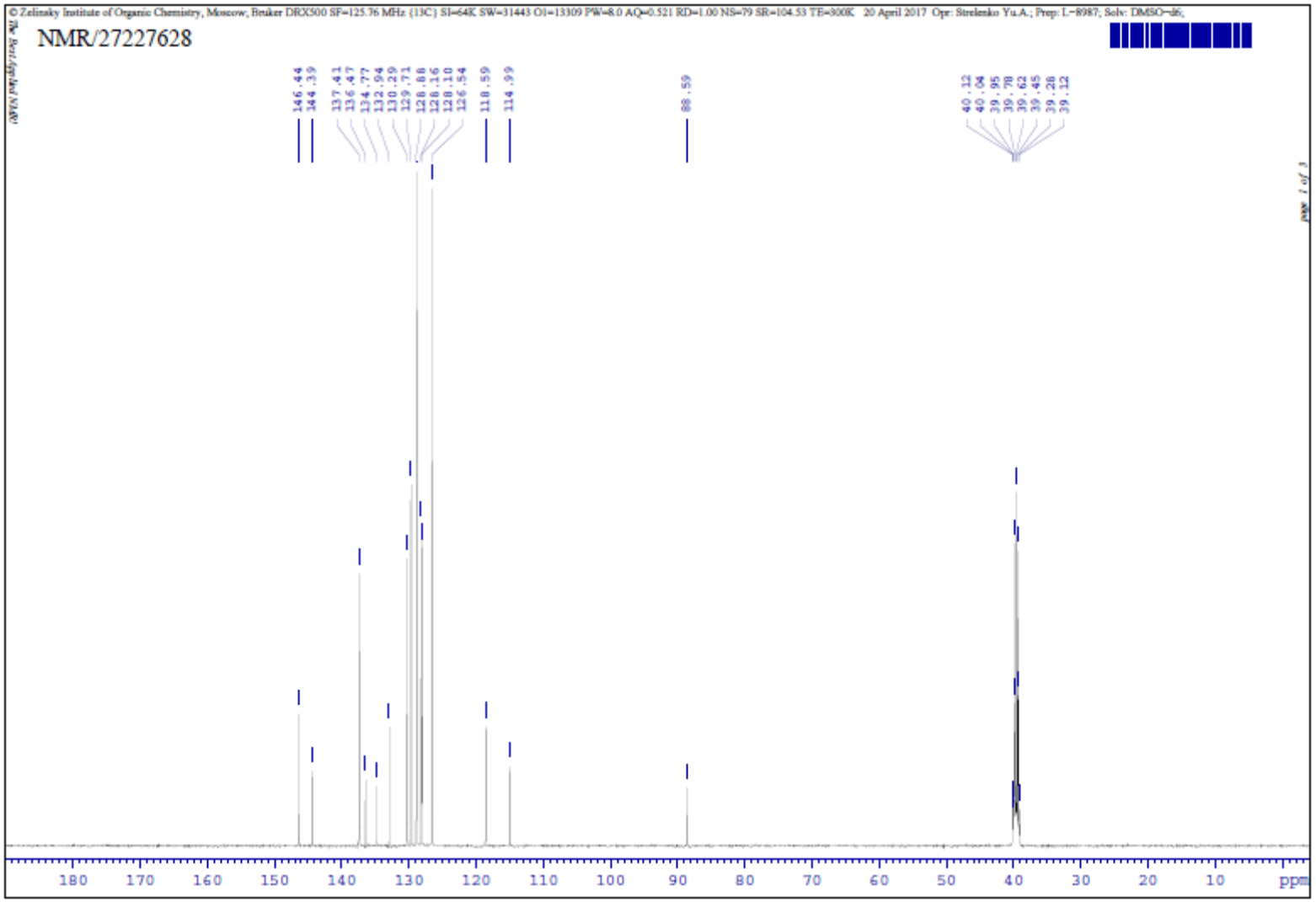
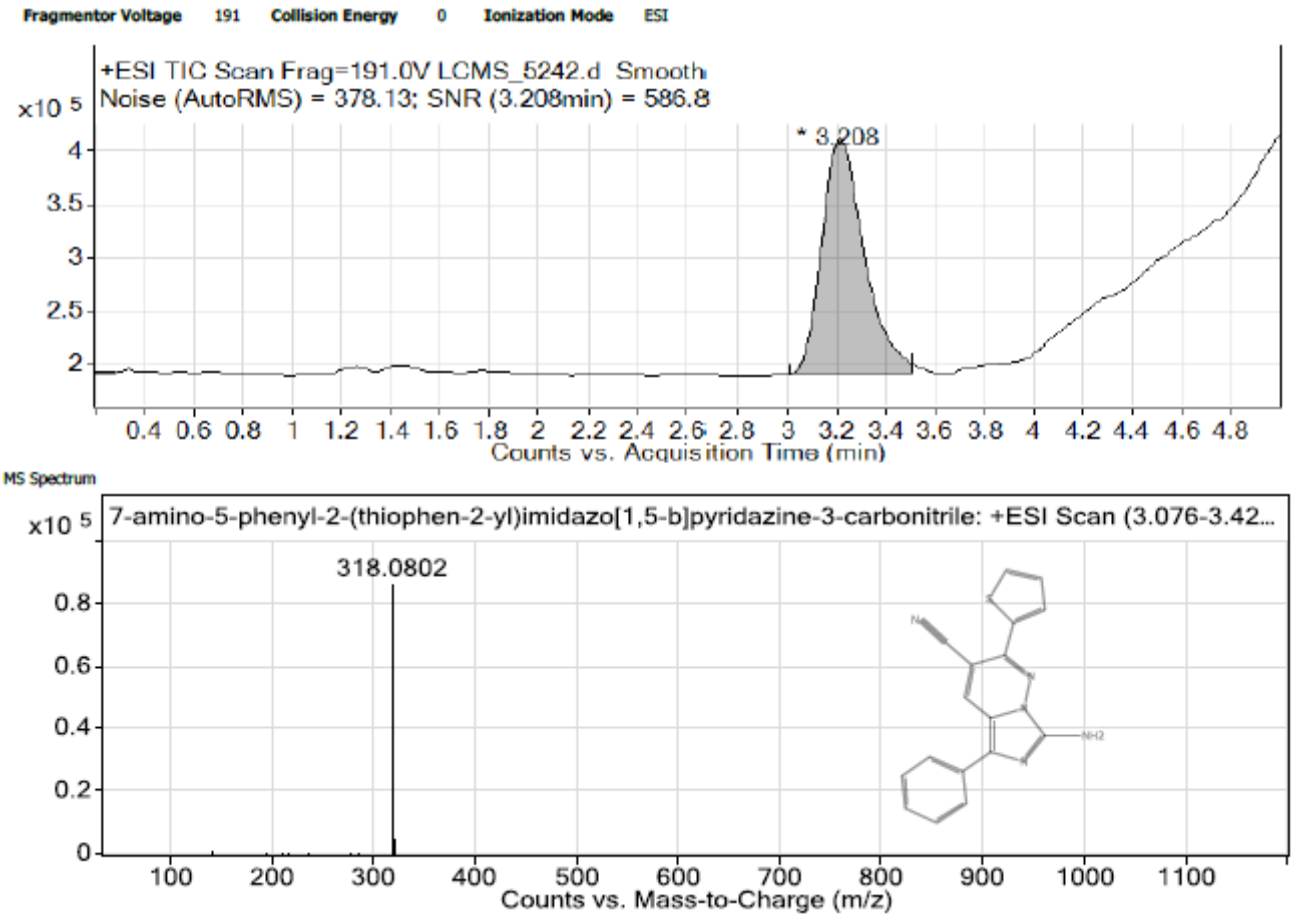

Transmittance [%]
90
85
80
75
70
65
3447
3287
3049
2210
1650
1593
1559
1540
1513
1491
1457
1432
1401
1336
1308
1277
1224
1158
1073
1063
1023
955
943
916
876
852
842
806
770
745
709
693
670
573
553
521
485
470
437
413
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600
400
Wavenumber cm-1

Table S6. Spectra of compound 3f






© Zelinsky Institute of Organic Chemistry, Moscow, Bruker DRX500 SF=125.76 MHz (13C) SI=64K SW=31443 O1=13309 PW=8.0 AQ=0.521 RD=1.00 NS=79 SR=104.53 TE=300K 20 April 2017 Ope: Strelenko Yu.A.; Prep: L-8987; Solv: DMSO-d6;
NMR/27227628
146.44
144.39
137.41
136.47
134.77
132.94
130.29
129.71
128.66
128.16
128.10
126.54
118.59
114.99
88.59
40.12
40.04
39.95
39.78
39.62
39.45
39.28
39.12
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


Fragmentor Voltage 191 Collision Energy 0 Ionization Mode ESI
+ESI TIC Scan Frag=191.0V LCMS_5242.d Smooth
Noise (AutoRMS) = 378.13; SNR (3.208min) = 586.8
x10 5
* 3.208
Counts vs. Acquisition Time (min)
MS Spectrum
7-amino-5-phenyl-2-(thiophen-2-yl)imidazo[1,5-b]pyridazine-3-carbonitrile: +ESI Scan (3.076-3.42...
318.0802
Counts vs. Mass-to-Charge (m/z)

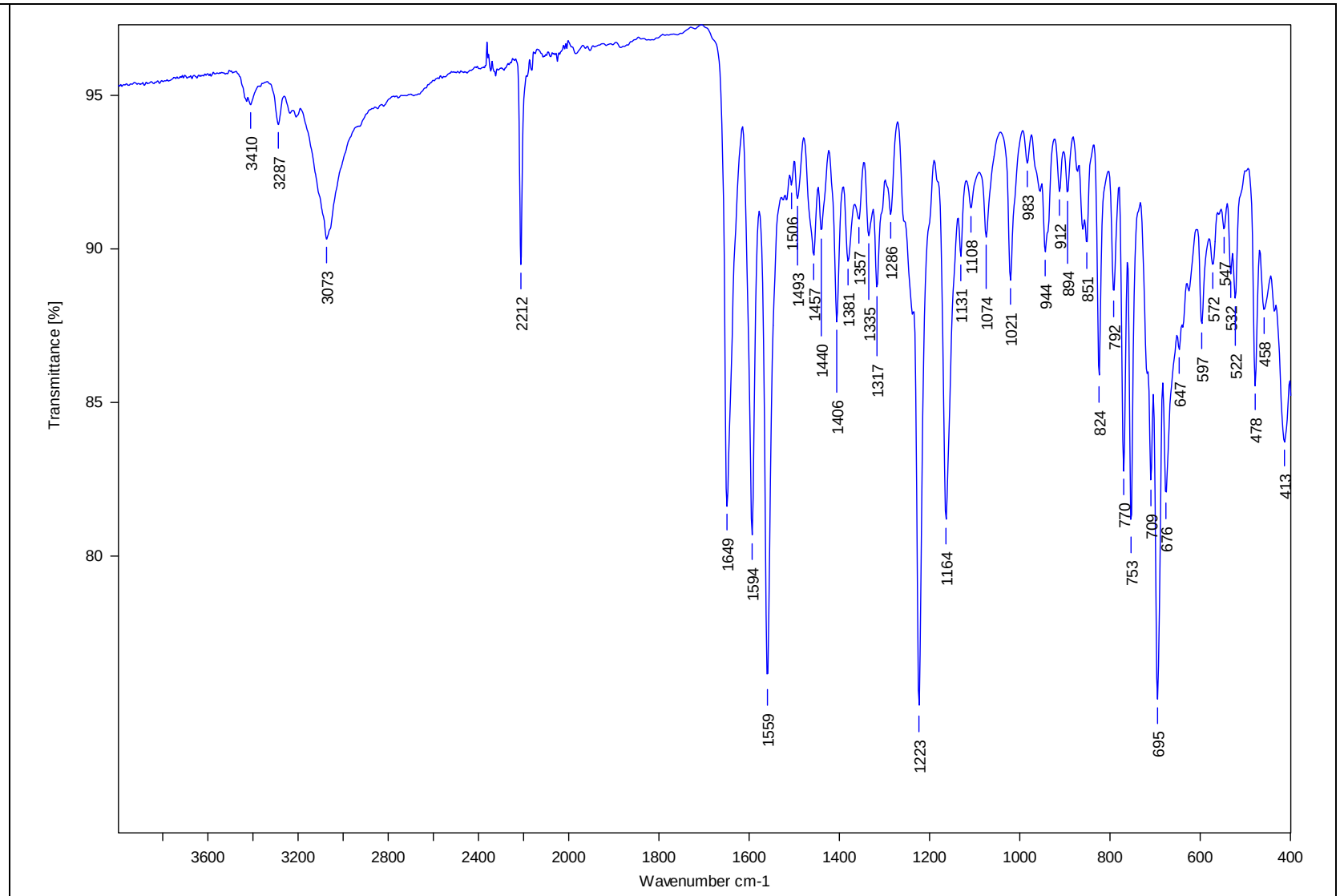
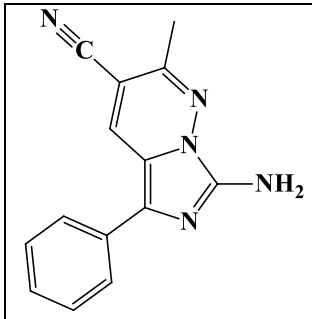
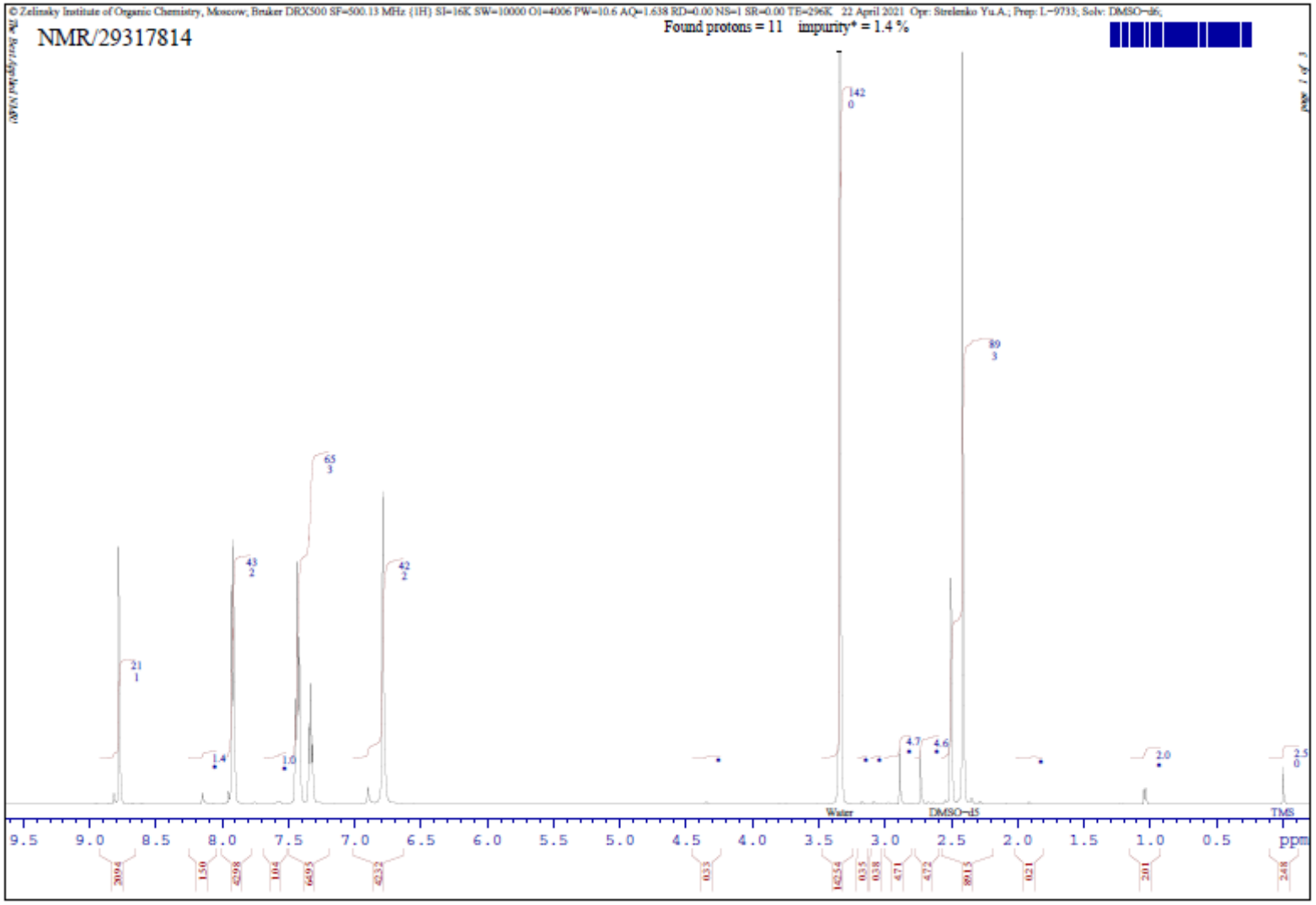
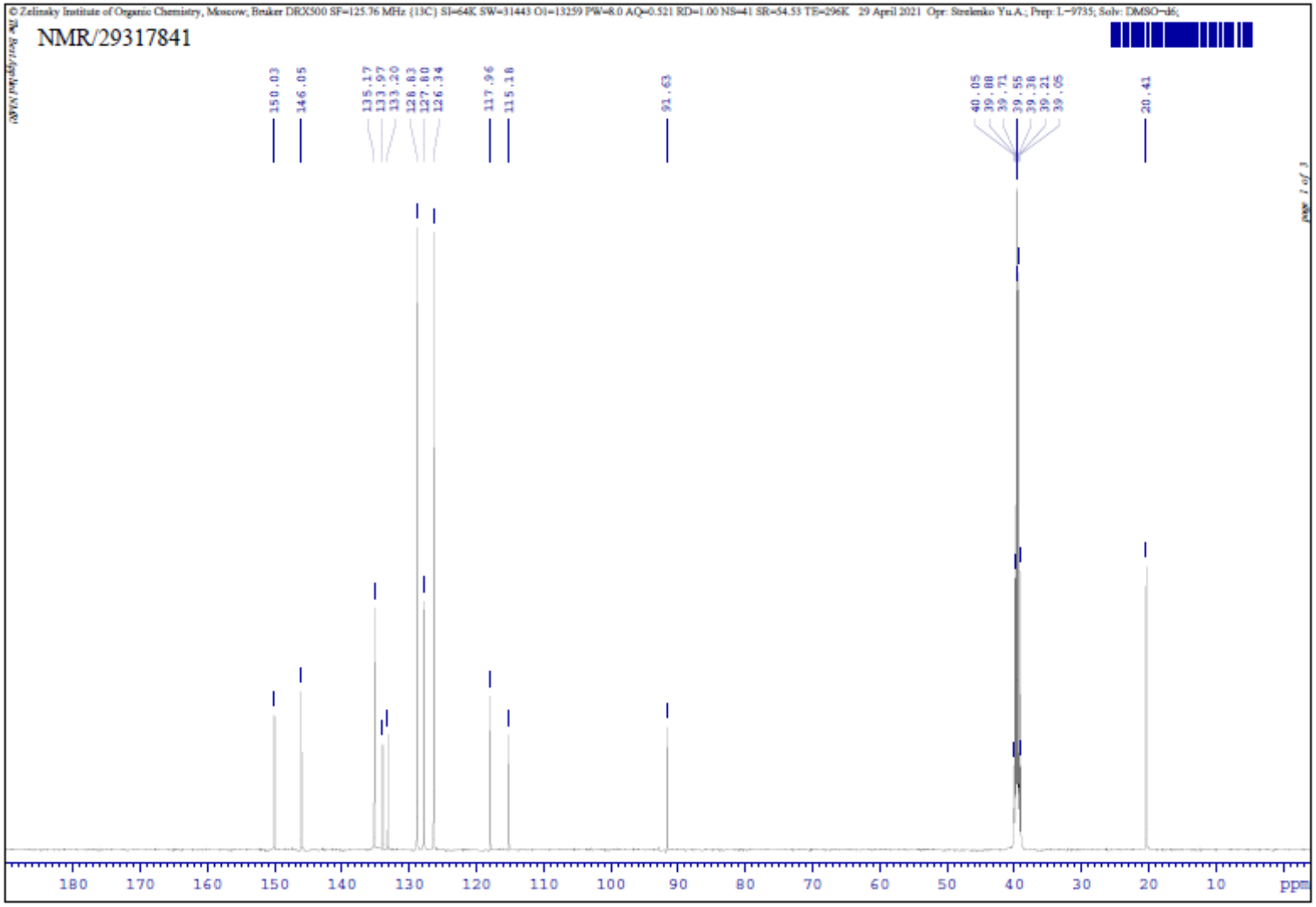
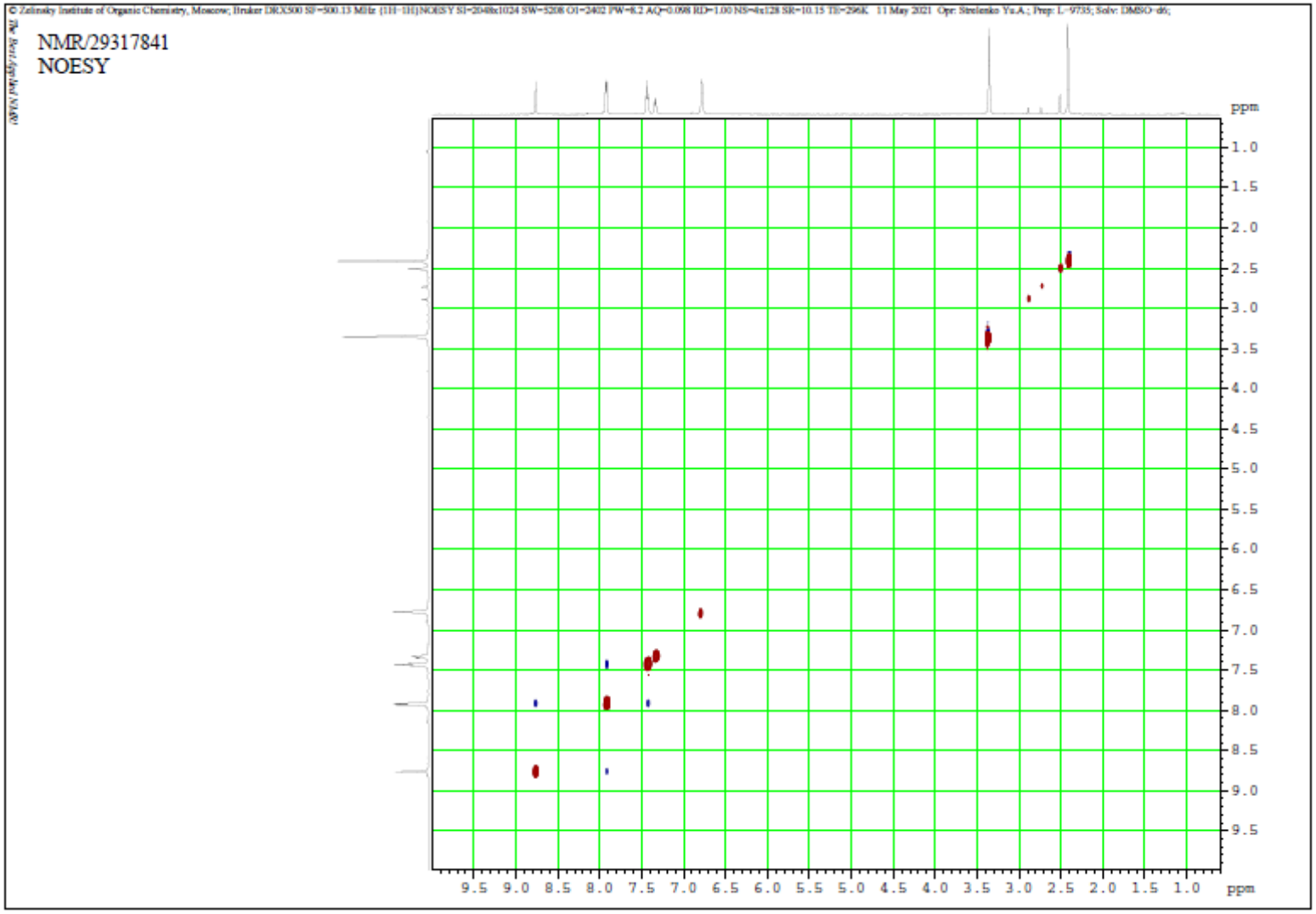


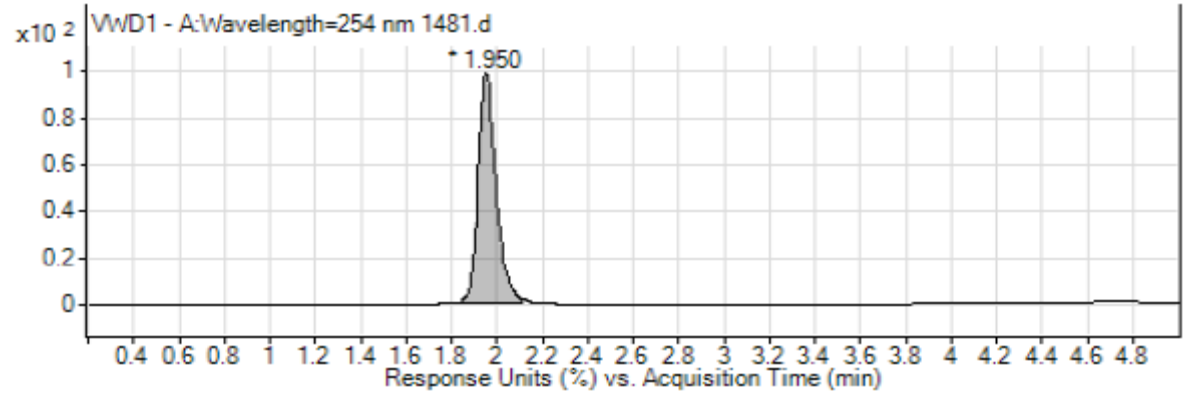
Table S7. Spectra of compound 3g


N
C
N
N
N
NH2

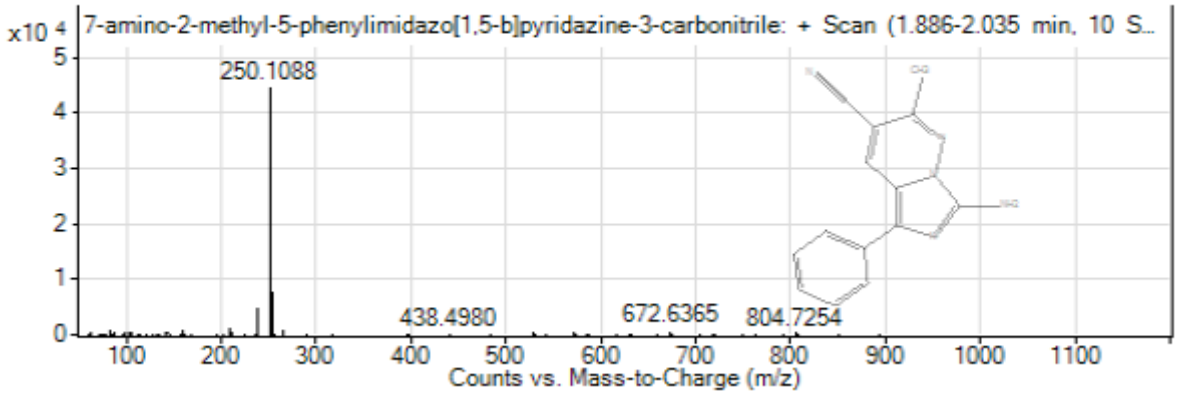

NMR/29317814
Found protons = 11 impurity* = 1.4 %
Water
DMSO-d5
TMS
ppm

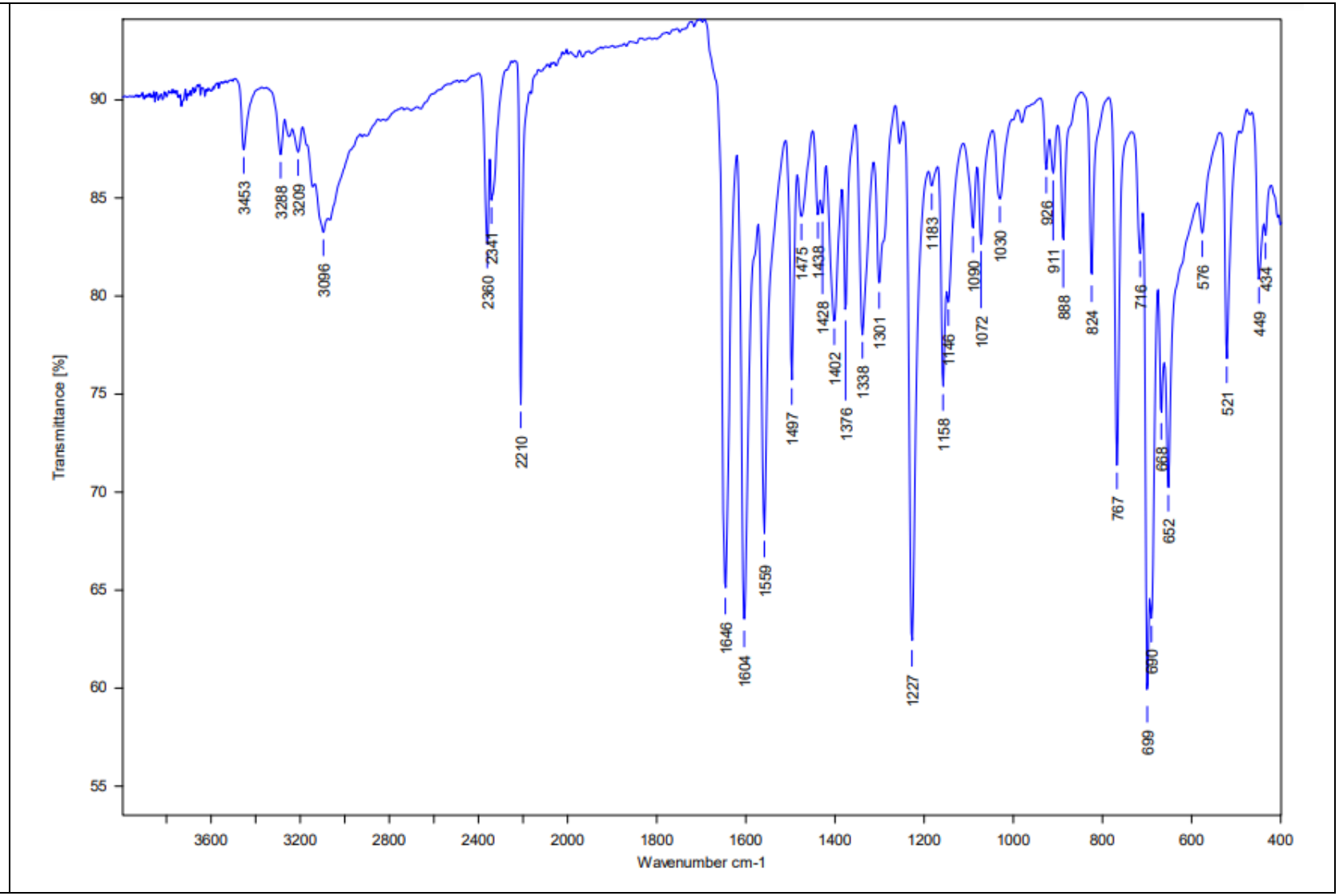

© Zelinsky Institute of Organic Chemistry, Moscow, Bruker DRX500 SF=125.76 MHz (13C) SI=64K SW=31443 O1=13259 PW=8.0 AQ=0.521 RD=1.00 NS=41 SR=54.53 TE=296K 29 April 2021 Opr: Strelenko Yu.A.; Prep: L-9735; Solv: DMSO-d6;
NMR/29317841
150.03
146.05
135.17
133.97
133.20
126.83
127.60
126.34
117.96
115.16
91.63
40.05
39.88
39.71
39.55
39.38
39.21
39.05
20.41
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


NMR/29317841
NOESY
ppm
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
ppm



Fragmentor Voltage	Collision Energy	Ionization Mode
191	0	ESI




Transmittance [%]
90
85
80
75
70
65
60
55
3453
3288
3209
3096
2360
2341
2210
1646
1604
1559
1497
1475
1438
1428
1402
1376
1338
1301
1227
1183
1158
1146
1090
1072
1030
926
911
888
824
767
716
699
690
668
652
576
521
449
434
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600
400
Wavenumber cm-1