

Design, synthesis and evaluation of new hybrid derivatives of 5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolin-2(1*H*)-one as potential dual inhibitors of blood coagulation factors Xa and XIa

Anna A. Skoptsova ¹, Athina Geronikaki ², Nadezhda P. Novichikhina ¹, Alexey V. Sulimov ³, Ivan S. Ilin ³, Vladimir B. Sulimov ³, Georgii A. Bykov ⁴, Nadezhda A. Podoplelova ⁵, Oleg V. Pyankov ⁶ and Khidmet S. Shikhaliev¹

¹ Department of Organic Chemistry, Faculty of Chemistry, Voronezh State University, 1 Universitetskaya Sq., 394018 Voronezh, Russia

² School of Pharmacy, Aristotle University of Thessaloniki, 54124 Thessaloniki, Greece

³ Research Computing Center, Lomonosov Moscow State University, 119992 Moscow, Russia

⁴ Department of Biophysics at the Faculty of Physics, Lomonosov Moscow State University, 119992 Moscow, Russia

⁵ Center for Theoretical Problems of Physicochemical Pharmacology, 119991 Moscow, Russia

⁶ State Research Center of Virology and Biotechnology "Vector", 630559 Koltsovo, Russia;

* Correspondence: geronik@pharm.auth.gr (A.G.); shikh1961@yandex.ru (K.S.S.)

Contents.

Copies of spectral data of synthesized compounds.....	S4
¹ H, ¹³ C NMR and data HPLC-HRMS-ESI spectra of methyl (Z)-2-(4-oxo-2-(2-((Z)-4,4,6-trimethyl-2-oxo-5,6-dihydro-4 <i>H</i> -pyrrolo[3,2,1- <i>ij</i>]quinolin-1(2 <i>H</i>)-ylidene)hydrazineyl)thiazol-5(4 <i>H</i>)-ylidene)acetate 3a.....	S4
¹ H, ¹³ C NMR and data HPLC-HRMS-ESI spectra of methyl (Z)-2-(2-(2-((Z)-8-methoxy-4,4,6-trimethyl-2-oxo-5,6-dihydro-4 <i>H</i> -pyrrolo[3,2,1- <i>ij</i>]quinolin-1(2 <i>H</i>)-ylidene)hydrazineyl)-4-oxothiazol-5(4 <i>H</i>)-ylidene)acetate 3b.....	S6
¹ H, ¹³ C NMR and data HPLC-HRMS-ESI spectra of methyl (Z)-2-(2-(2-((Z)-8-chloro-4,4,6-trimethyl-2-oxo-5,6-dihydro-4 <i>H</i> -pyrrolo[3,2,1- <i>ij</i>]quinolin-1(2 <i>H</i>)-ylidene)hydrazineyl)-4-oxothiazol-5(4 <i>H</i>)-ylidene)acetate 3c	S8
¹ H, ¹³ C NMR and data HPLC-HRMS-ESI spectra of methyl (Z)-2-(2-(2-((Z)-8-bromo-4,4,6-trimethyl-2-oxo-5,6-dihydro-4 <i>H</i> -pyrrolo[3,2,1- <i>ij</i>]quinolin-1(2 <i>H</i>)-ylidene)hydrazineyl)-4-oxothiazol-5(4 <i>H</i>)-ylidene)acetate 3d.....	S10
¹ H, ¹³ C NMR and data HPLC-HRMS-ESI spectra of methyl 2-(2-(2-(8-iodo-4,4,6-trimethyl-2-oxo-5,6-dihydro-4 <i>H</i> -pyrrolo[3,2,1- <i>ij</i>]quinolin-1(2 <i>H</i>)-ylidene)hydrazineyl)-4-oxothiazol-5(4 <i>H</i>)-ylidene)acetate 3e	S12

¹ H, ¹³ C NMR and data HPLC-HRMS-ESI spectra of methyl (Z)-2-(4-oxo-2-(2-((Z)-4,4,6,8,9-pentamethyl-2-oxo-5,6-dihydro-4 <i>H</i> -pyrrolo[3,2,1- <i>ij</i>]quinolin-1(2 <i>H</i>)-ylidene)hydrazineyl)thiazol-5(4 <i>H</i>)-ylidene)acetate 3f	S14
¹ H, ¹³ C NMR and data HPLC-HRMS-ESI spectra of methyl (Z)-2-(2-(2-(8-chloro-4,4,6,9-tetramethyl-2-oxo-5,6-dihydro-4 <i>H</i> -pyrrolo[3,2,1- <i>ij</i>]quinolin-1(2 <i>H</i>)-ylidene)hydrazineyl)-4-oxothiazol-5(4 <i>H</i>)-ylidene)acetate 3g	S16
¹ H, ¹³ C NMR and data HPLC-HRMS-ESI spectra of methyl (Z)-2-(2-(2-(8-bromo-4,4,6,9-tetramethyl-2-oxo-5,6-dihydro-4 <i>H</i> -pyrrolo[3,2,1- <i>ij</i>]quinolin-1(2 <i>H</i>)-ylidene)hydrazineyl)-4-oxothiazol-5(4 <i>H</i>)-ylidene)acetate 3h	S18
¹ H, ¹³ C NMR and data HPLC-HRMS-ESI spectra of methyl (Z)-2-(2-(2-((Z)-6-(4-chlorophenyl)-4,4,6-trimethyl-2-oxo-5,6-dihydro-4 <i>H</i> -pyrrolo[3,2,1- <i>ij</i>]quinolin-1(2 <i>H</i>)-ylidene)hydrazineyl)-4-oxothiazol-5(4 <i>H</i>)-ylidene)acetate 3i	S20
¹ H, ¹³ C NMR and data HPLC-HRMS-ESI spectra of methyl 2-(2-(2-(6-(4-chlorophenyl)-4,4,6,8-tetramethyl-2-oxo-5,6-dihydro-4 <i>H</i> -pyrrolo[3,2,1- <i>ij</i>]quinolin-1(2 <i>H</i>)-ylidene)hydrazineyl)-4-oxothiazol-5(4 <i>H</i>)-ylidene)acetate 3j	S22
¹ H, ¹³ C NMR and data HPLC-HRMS-ESI spectra of methyl (Z)-2-(2-(2-((Z)-8-chloro-6-(4-chlorophenyl)-4,4,6-trimethyl-2-oxo-5,6-dihydro-4 <i>H</i> -pyrrolo[3,2,1- <i>ij</i>]quinolin-1(2 <i>H</i>)-ylidene)hydrazineyl)-4-oxothiazol-5(4 <i>H</i>)-ylidene)acetate 3k	S24
¹ H, ¹³ C NMR and data HPLC-HRMS-ESI spectra of methyl (Z)-2-(2-(2-((Z)-8-bromo-6-(4-chlorophenyl)-4,4,6-trimethyl-2-oxo-5,6-dihydro-4 <i>H</i> -pyrrolo[3,2,1- <i>ij</i>]quinolin-1(2 <i>H</i>)-ylidene)hydrazineyl)-4-oxothiazol-5(4 <i>H</i>)-ylidene)acetate 3l	S26
¹ H, ¹³ C NMR and data HPLC-HRMS-ESI spectra of methyl 2-(2-(2-(6-(4-chlorophenyl)-8-fluoro-4,4,6-trimethyl-2-oxo-5,6-dihydro-4 <i>H</i> -pyrrolo[3,2,1- <i>ij</i>]quinolin-1(2 <i>H</i>)-ylidene)hydrazineyl)-4-oxothiazol-5(4 <i>H</i>)-ylidene)acetate 3m	S28
¹ H, ¹³ C NMR and data HPLC-HRMS-ESI spectra of methyl (Z)-2-(4-oxo-2-(2-((Z)-4,4,6-trimethyl-2-oxo-6-phenyl-5,6-dihydro-4 <i>H</i> -pyrrolo[3,2,1- <i>ij</i>]quinolin-1(2 <i>H</i>)-ylidene)hydrazineyl)thiazol-5(4 <i>H</i>)-ylidene)acetate 3n	S30
¹ H, ¹³ C NMR and data HPLC-HRMS-ESI spectra of methyl (Z)-2-(2-(2-((Z)-8-chloro-4,4,6-trimethyl-2-oxo-6-phenyl-5,6-dihydro-4 <i>H</i> -pyrrolo[3,2,1- <i>ij</i>]quinolin-1(2 <i>H</i>)-ylidene)hydrazineyl)-4-oxothiazol-5(4 <i>H</i>)-ylidene)acetate 3o	S32
¹ H, ¹³ C NMR and data HPLC-HRMS-ESI spectra of methyl (Z)-2-(2-(2-((Z)-8-bromo-4,4,6-trimethyl-2-oxo-6-phenyl-5,6-dihydro-4 <i>H</i> -pyrrolo[3,2,1- <i>ij</i>]quinolin-1(2 <i>H</i>)-ylidene)hydrazineyl)-4-oxothiazol-5(4 <i>H</i>)-ylidene)acetate 3p	S34

¹ H, ¹³ C NMR and data HPLC-HRMS-ESI spectra of methyl (Z)-2-(2-(2-((Z)-8-fluoro-4,4,6-trimethyl-2-oxo-6-phenyl-5,6-dihydro-4 <i>H</i> -pyrrolo[3,2,1- <i>ij</i>]quinolin-1(2 <i>H</i>)-ylidene)hydrazineyl)-4-oxothiazol-5(4 <i>H</i>)-ylidene)acetate 3q.....	S36
The dependence of inhibition of factor Xa- and XIa-induced chromogenic substrate hydrolysis on the compound concentration.	S38
The dependence of inhibition of factor Xa- and XIa-induced chromogenic substrate hydrolysis on the concentration of 3b	S38
The dependence of inhibition of factor Xa- and XIa-induced chromogenic substrate hydrolysis on the concentration of 3c.....	S39
The dependence of inhibition of factor Xa- and XIa-induced chromogenic substrate hydrolysis on the concentration of 3e.....	S40
The dependence of inhibition of factor Xa- and XIa-induced chromogenic substrate hydrolysis on the concentration of 3f.....	S41
The dependence of inhibition of factor Xa- and XIa-induced chromogenic substrate hydrolysis on the concentration of 3k	S42
The dependence of inhibition of factor Xa- and XIa-induced chromogenic substrate hydrolysis on the concentration of 3l	S43
The dependence of inhibition of factor Xa- and XIa-induced chromogenic substrate hydrolysis on the concentration of 3n	S44
The dependence of inhibition of factor Xa- and XIa-induced chromogenic substrate hydrolysis on the concentration of 3o	S45
The dependence of inhibition of factor Xa- and XIa-induced chromogenic substrate hydrolysis on the concentration of 3p	S46
LCMS analysis of the reaction mass after 1 h of interaction of compound 1b with thiosemicarbazide to obtain 2b.....	S47

¹H, ¹³C NMR and data HPLC-HRMS-ESI spectra of methyl (Z)-2-(4-oxo-2-(2-((Z)-4,4,6-trimethyl-2-oxo-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolin-1(2*H*)-ylidene)hydrazineyl)thiazol-5(4*H*)-ylidene)acetate 3a



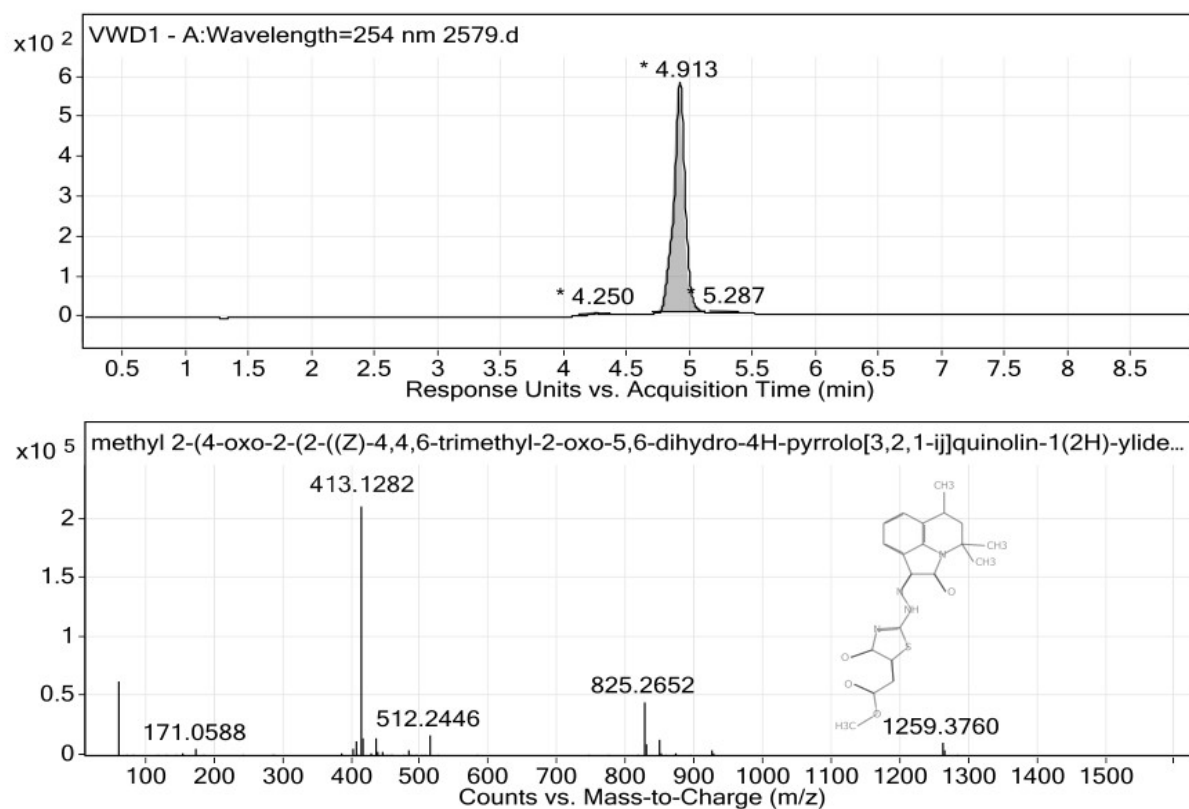


Figure S3. Data of HPLC-MS-ESI analysis of **3a**

[illegible]

Chemical shift (ppm): 165.750, 156.341, 155.525, 147.482, 142.077, 134.850, 126.561, 118.326, 116.144, 115.608, 115.303, 111.987, 103.960, 55.745, 53.566, 52.509, 51.739, 49.733, 48.133, 40.094, 39.524, 39.885, 39.672, 39.677, 39.506, 39.469, 38.297, 38.260, 38.088, 39.052, 38.880, 38.444, 38.444, 25.528, 23.814, 17.969.

Chemical structure: COc1ccc2c(c1)c3c(c2)c(=O)[nH]c3N=C4C(=O)N(C)C(C)C4C5=CC(=O)SC5=CC(=O)OC

Chemical shift (ppm): 165.750, 156.341, 155.525, 147.482, 142.077, 134.850, 126.561, 118.326, 116.144, 115.608, 115.303, 111.987, 103.960, 55.745, 53.566, 52.509, 51.739, 49.733, 48.133, 40.094, 39.524, 39.885, 39.672, 39.677, 39.506, 39.469, 38.297, 38.260, 38.088, 39.052, 38.880, 38.444, 38.444, 25.528, 23.814, 17.969.

S6

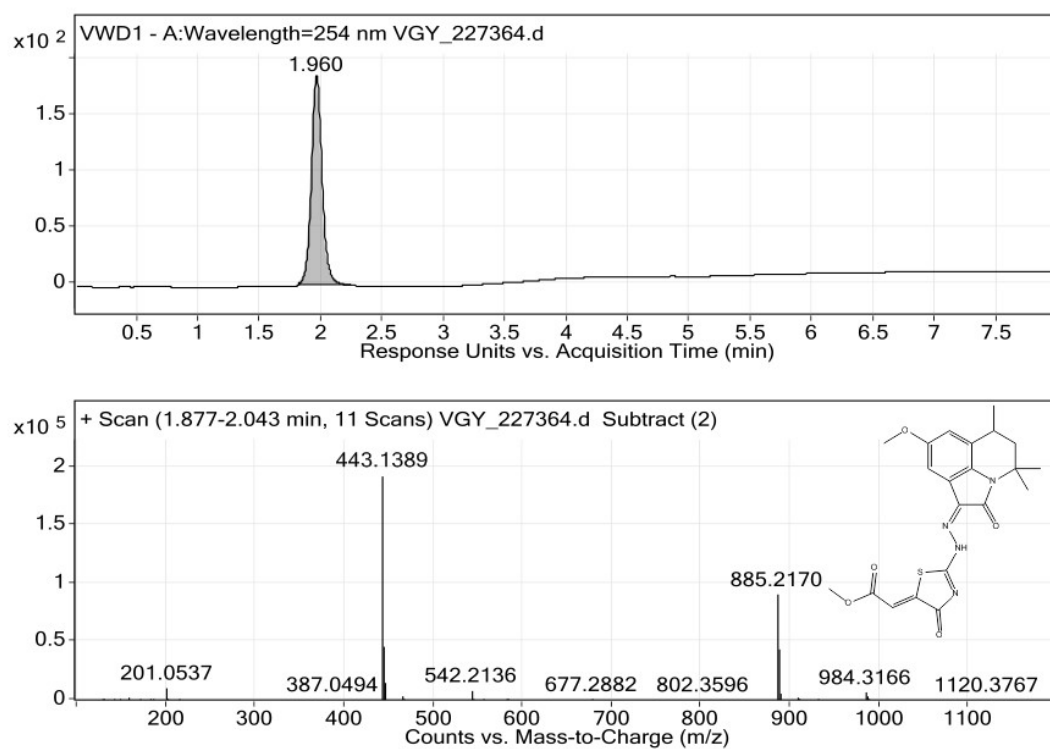


Figure S6. Data of HPLC-MS-ESI analysis of **3b**

^1H , ^{13}C NMR and data HPLC-HRMS-ESI spectra of methyl (Z)-2-(2-((Z)-8-chloro-4,4,6-trimethyl-2-oxo-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolin-1(2*H*)-ylidene)hydrazineyl)-4-oxothiazol-5(4*H*)-ylidene)acetate **3c**

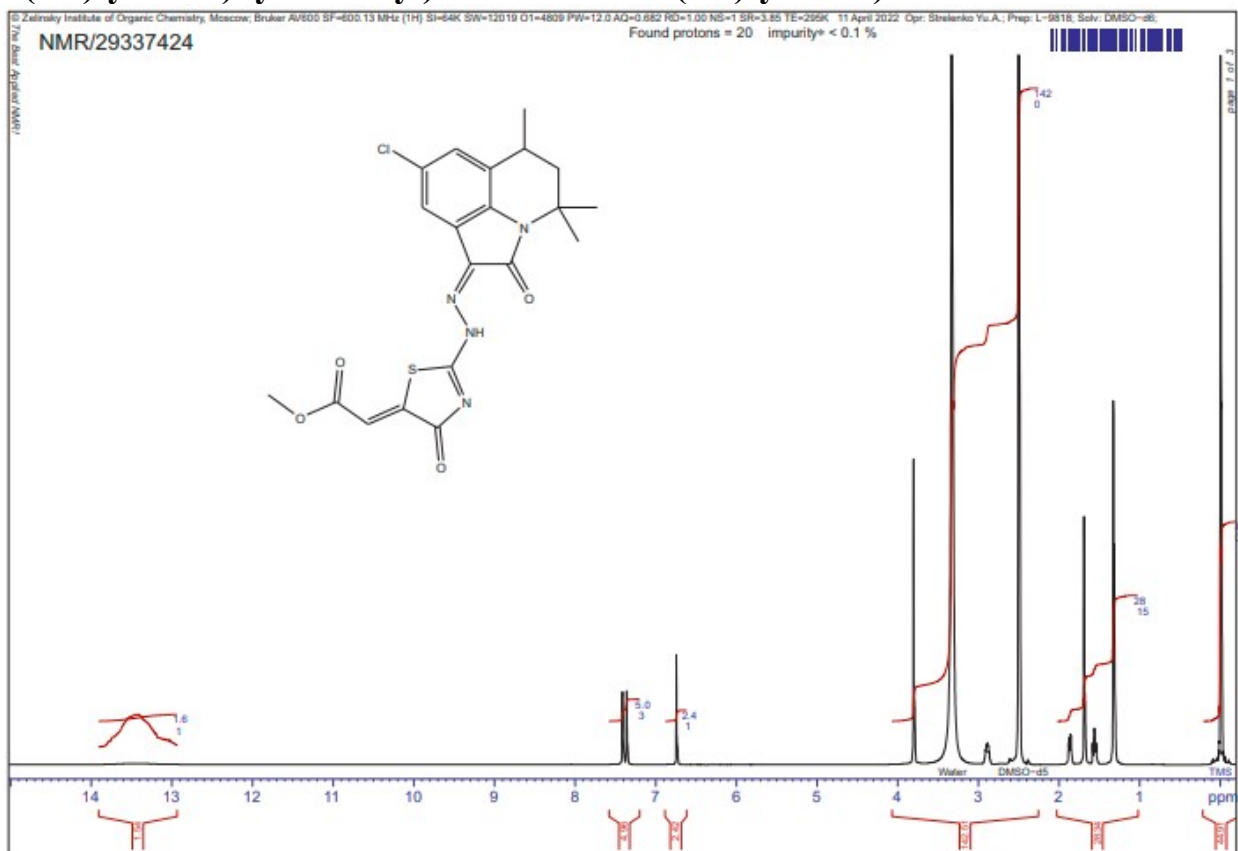


Figure S7. ^1H NMR spectrum of compound **3c**

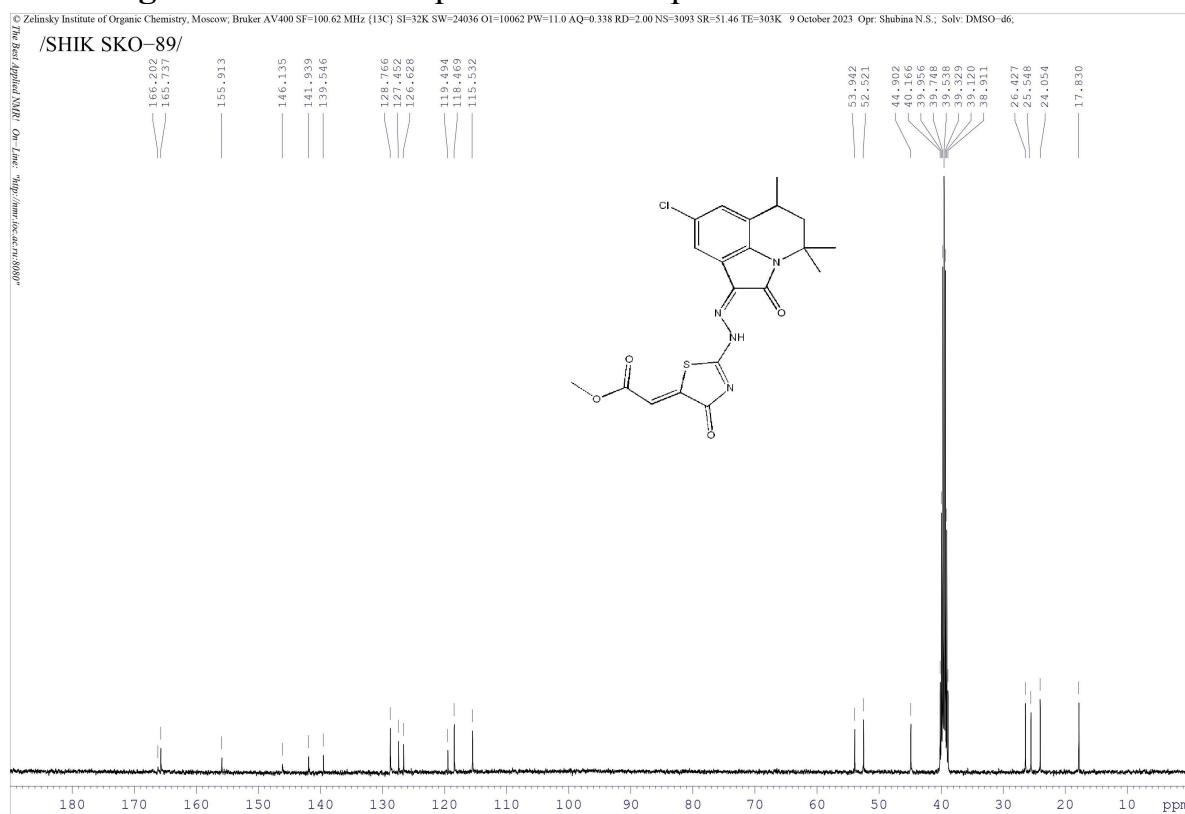


Figure S8. ^{13}C NMR spectrum of compound **3c**

^1H , ^{13}C NMR and data HPLC-HRMS-ESI spectra of methyl (Z)-2-(2-(2-((Z)-8-bromo-4,4,6-trimethyl-2-oxo-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolin-1(2*H*)-ylidene)hydrazineyl)-4-oxothiazol-5(4*H*)-ylidene)acetate **3d**

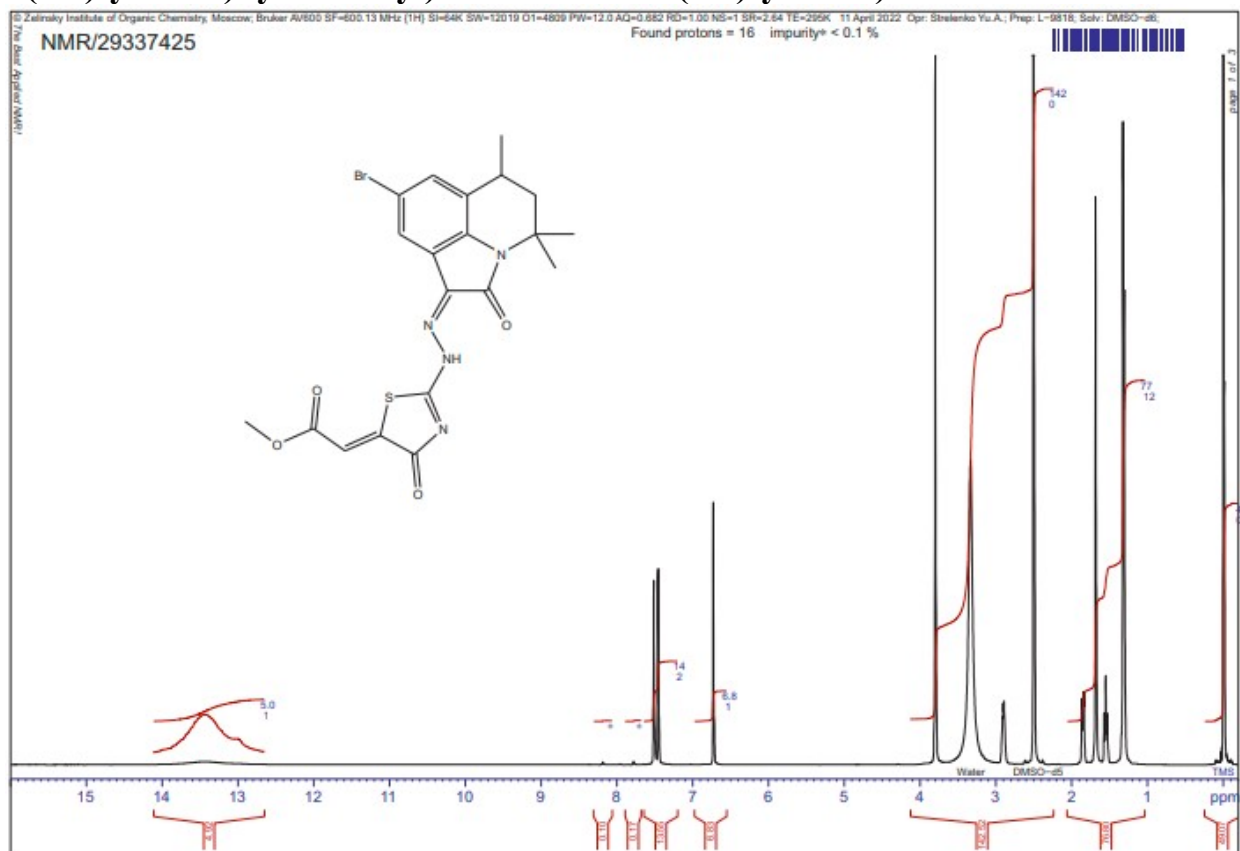


Figure S10. ^1H NMR spectrum of compound **3d**

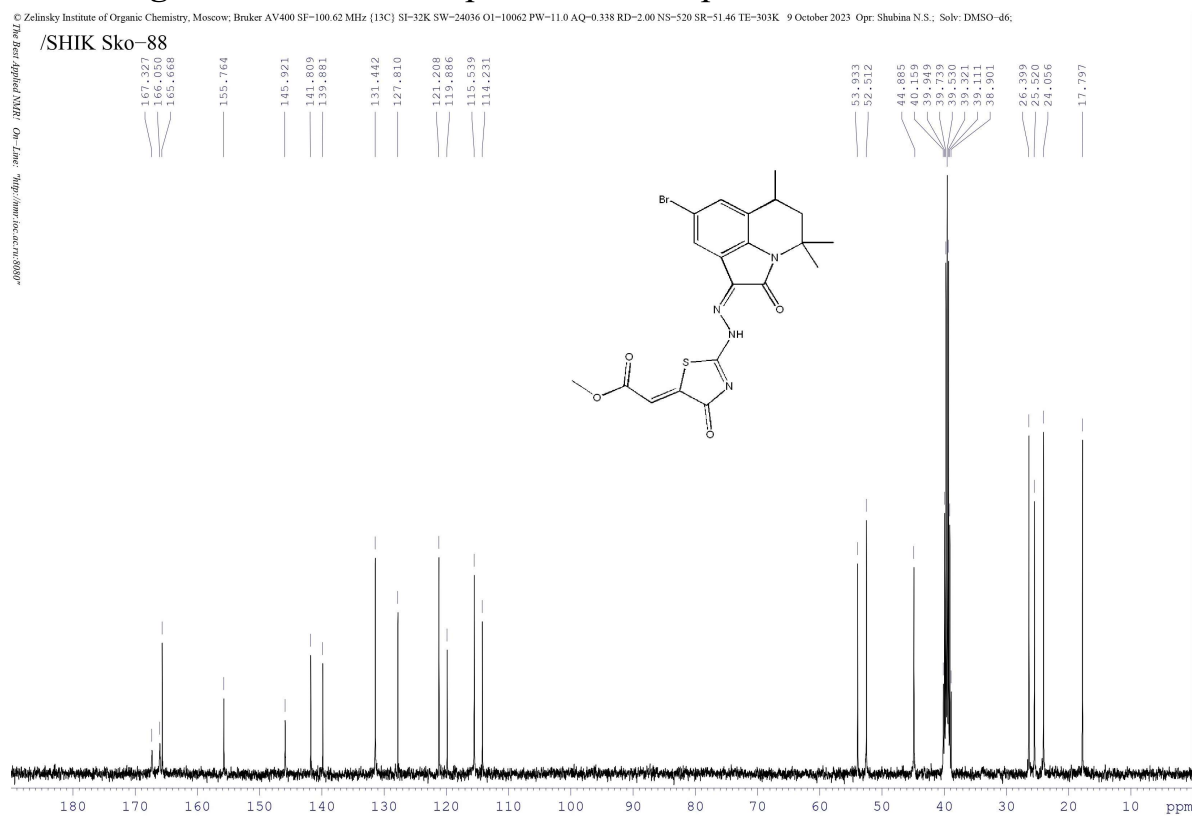


Figure S11. ^{13}C NMR spectrum of compound **3d**

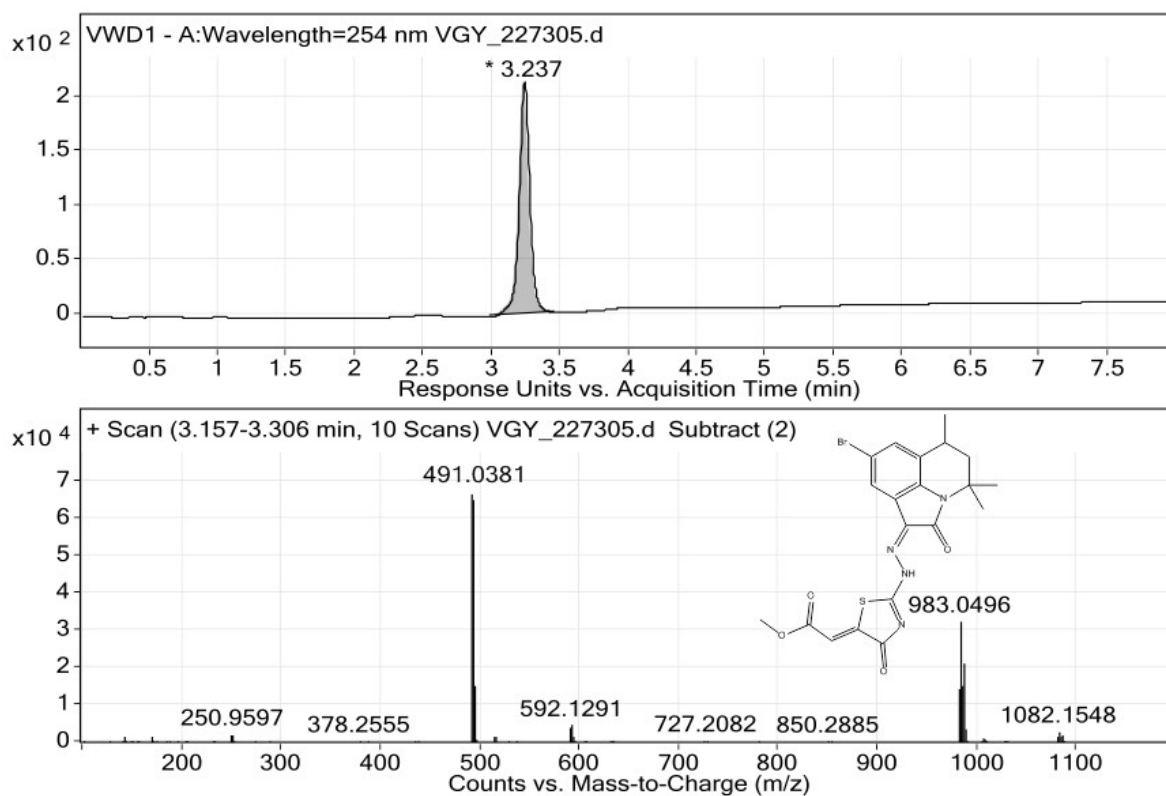


Figure S12. Data of HPLC-MS-ESI analysis of **3d**

^1H , ^{13}C NMR and data HPLC-HRMS-ESI spectra of methyl 2-(2-(2-(8-iodo-4,4,6-trimethyl-2-oxo-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolin-1(2*H*)-ylidene)hydrazineyl)-4-oxothiazol-5(4*H*)-ylidene)acetate **3e**

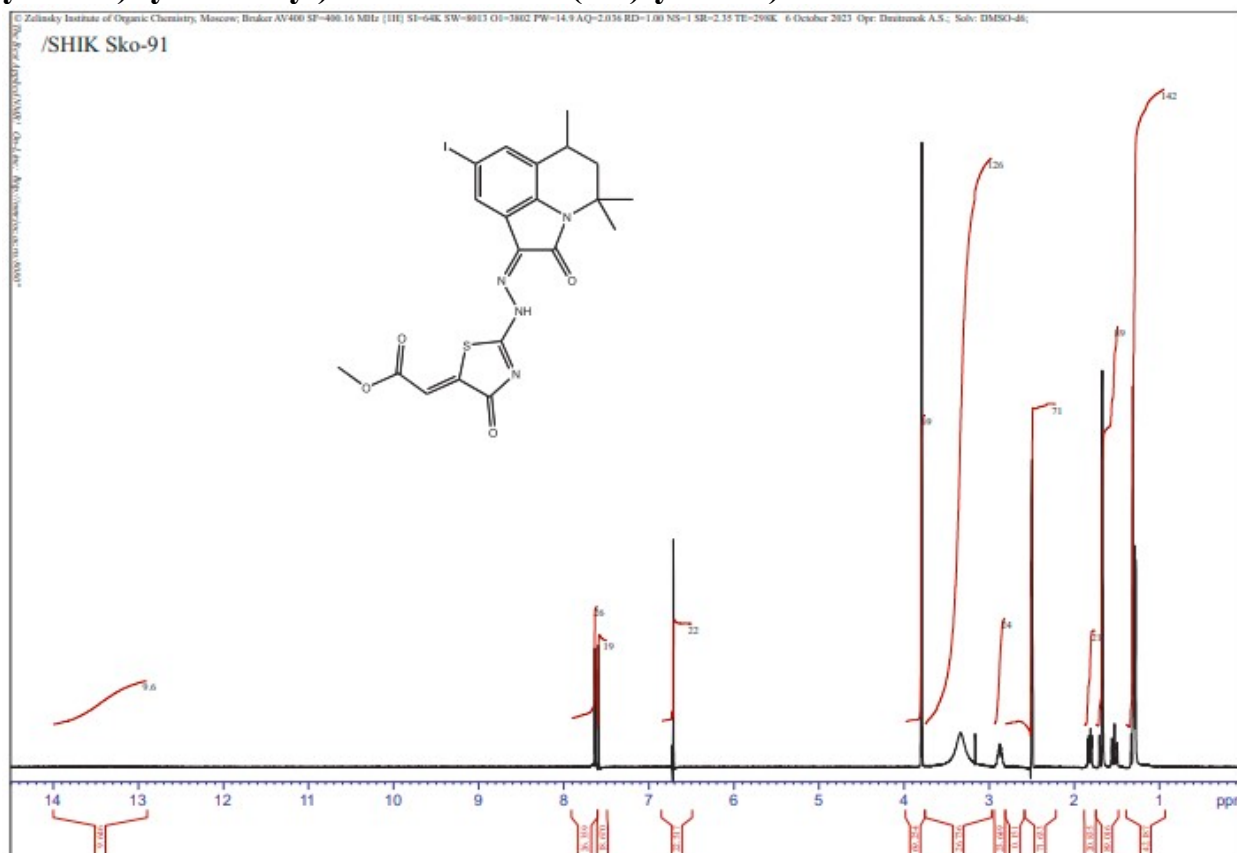


Figure S13. ^1H NMR spectrum of compound **3e**

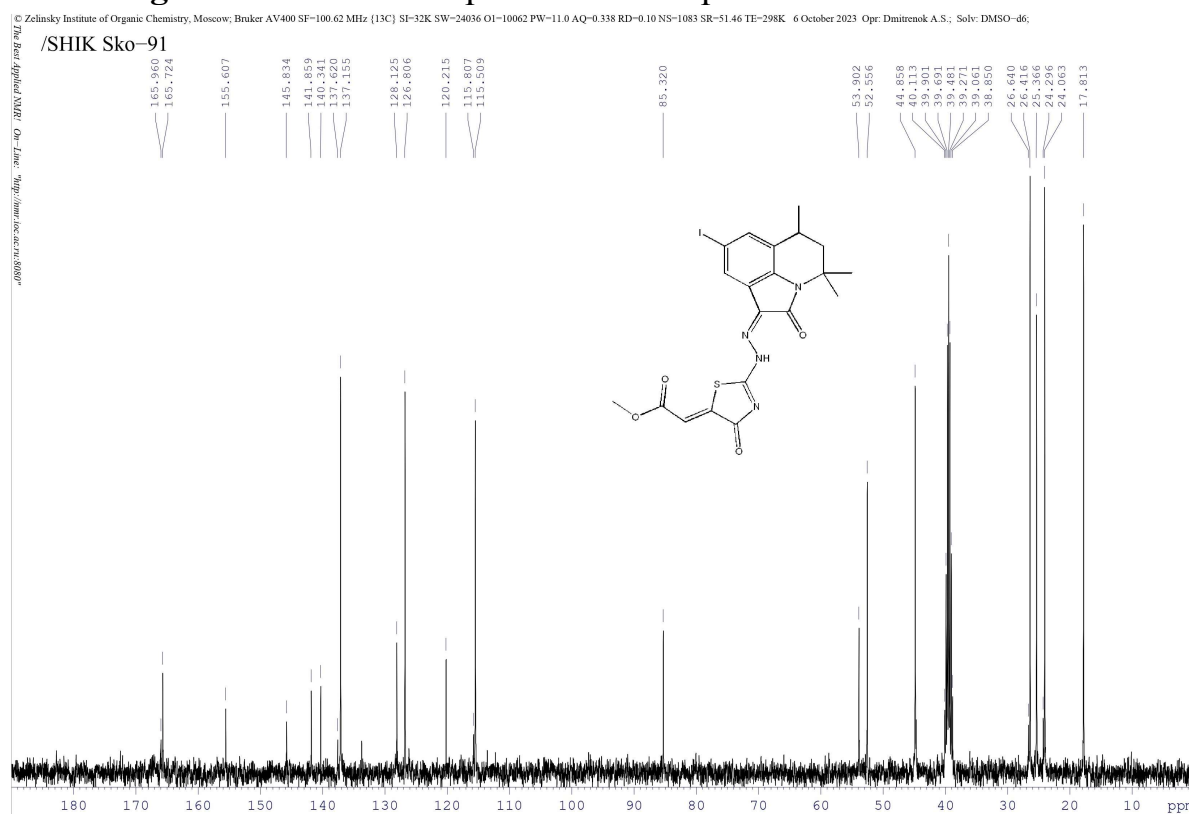


Figure S14. ^{13}C NMR spectrum of compound **3e**

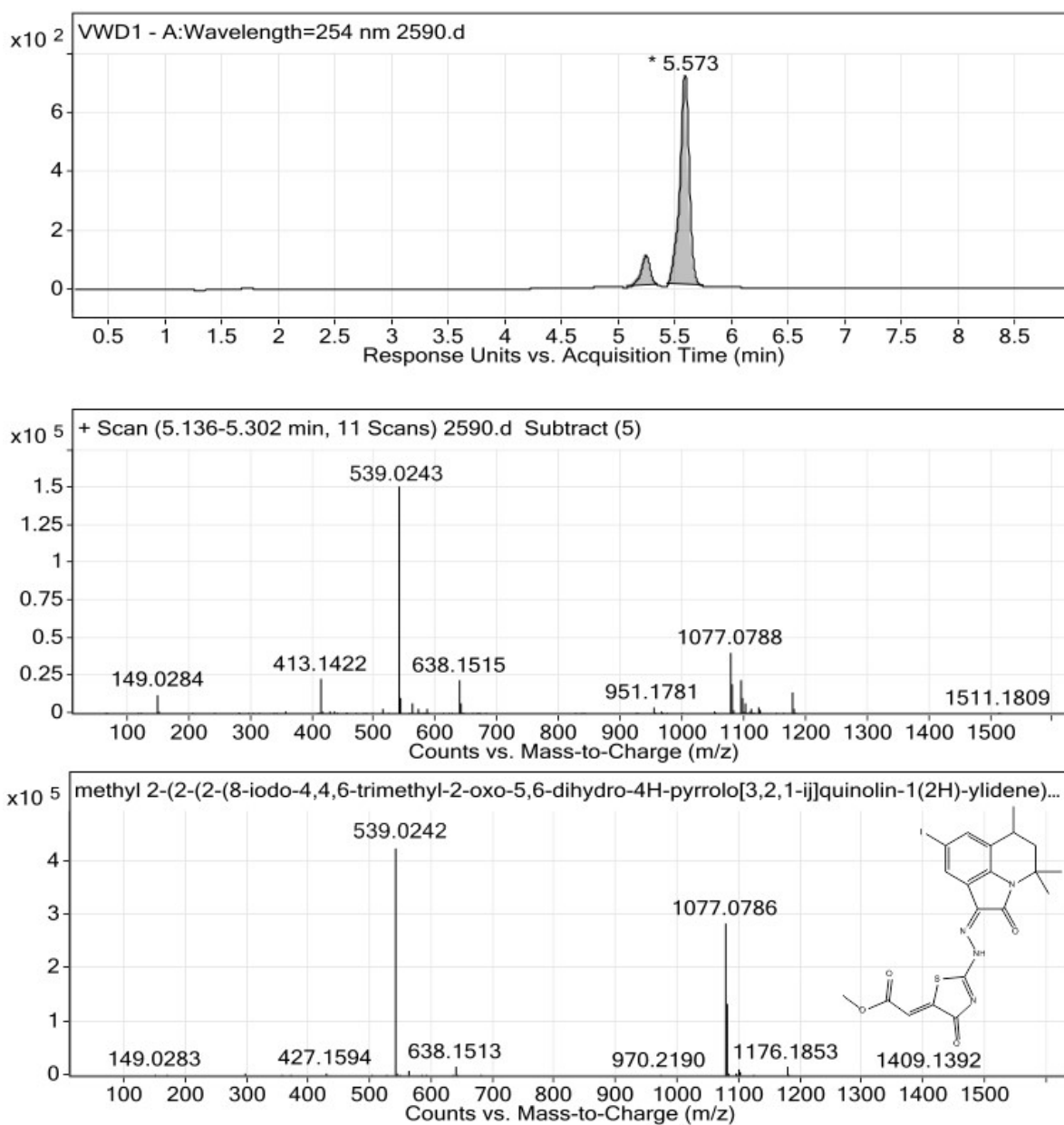


Figure S15. Data of HPLC-MS-ESI analysis of **3e**

^1H , ^{13}C NMR and data HPLC-HRMS-ESI spectra of methyl (Z)-2-(4-oxo-2-(2-((Z)-4,4,6,8,9-pentamethyl-2-oxo-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolin-1(2*H*)-ylidene)hydrazineyl)thiazol-5(4*H*)-ylidene)acetate 3f

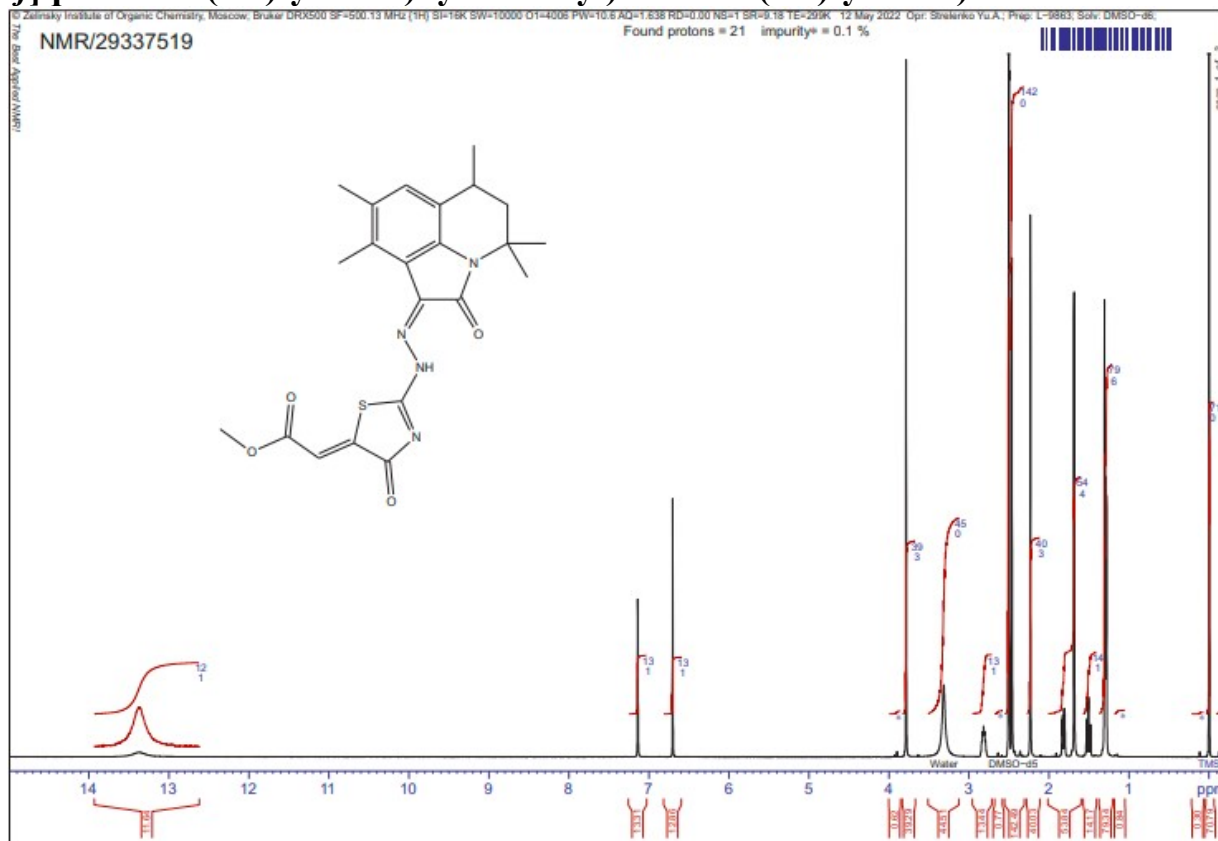


Figure S16. ^1H NMR spectrum of compound 3f

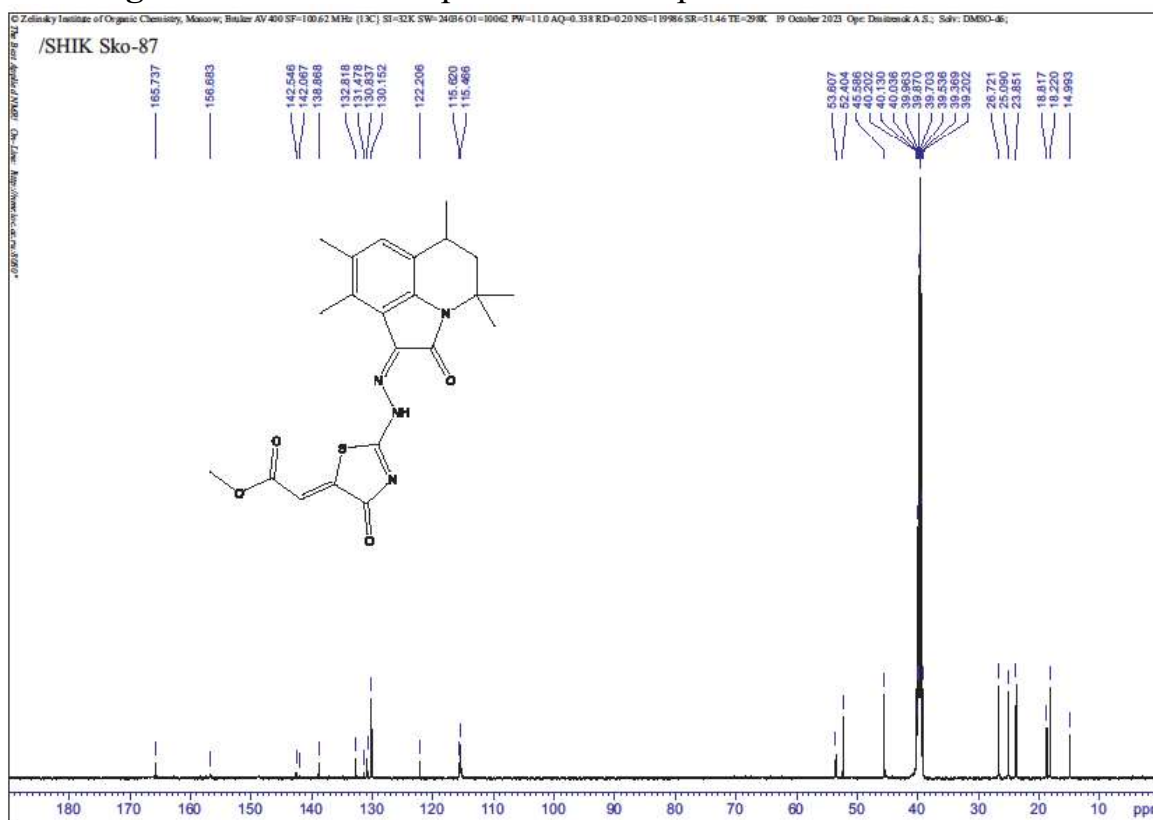


Figure S17. ^{13}C NMR spectrum of compound 3f

^1H , ^{13}C NMR and data HPLC-HRMS-ESI spectra of methyl (Z)-2-(2-(2-(8-chloro-4,4,6,9-tetramethyl-2-oxo-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolin-1(2*H*)-ylidene)hydrazineyl)-4-oxothiazol-5(4*H*)-ylidene)acetate **3g**

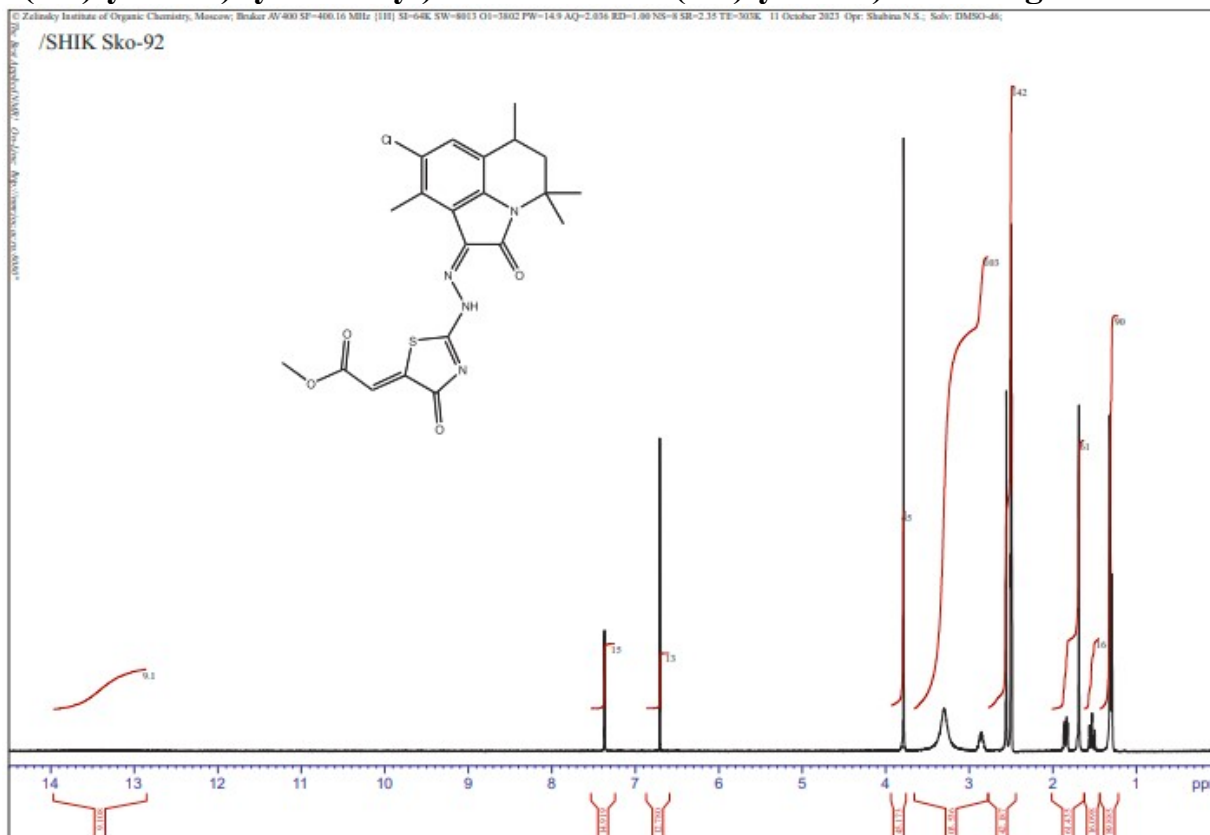


Figure S19. ^1H NMR spectrum of compound **3g**

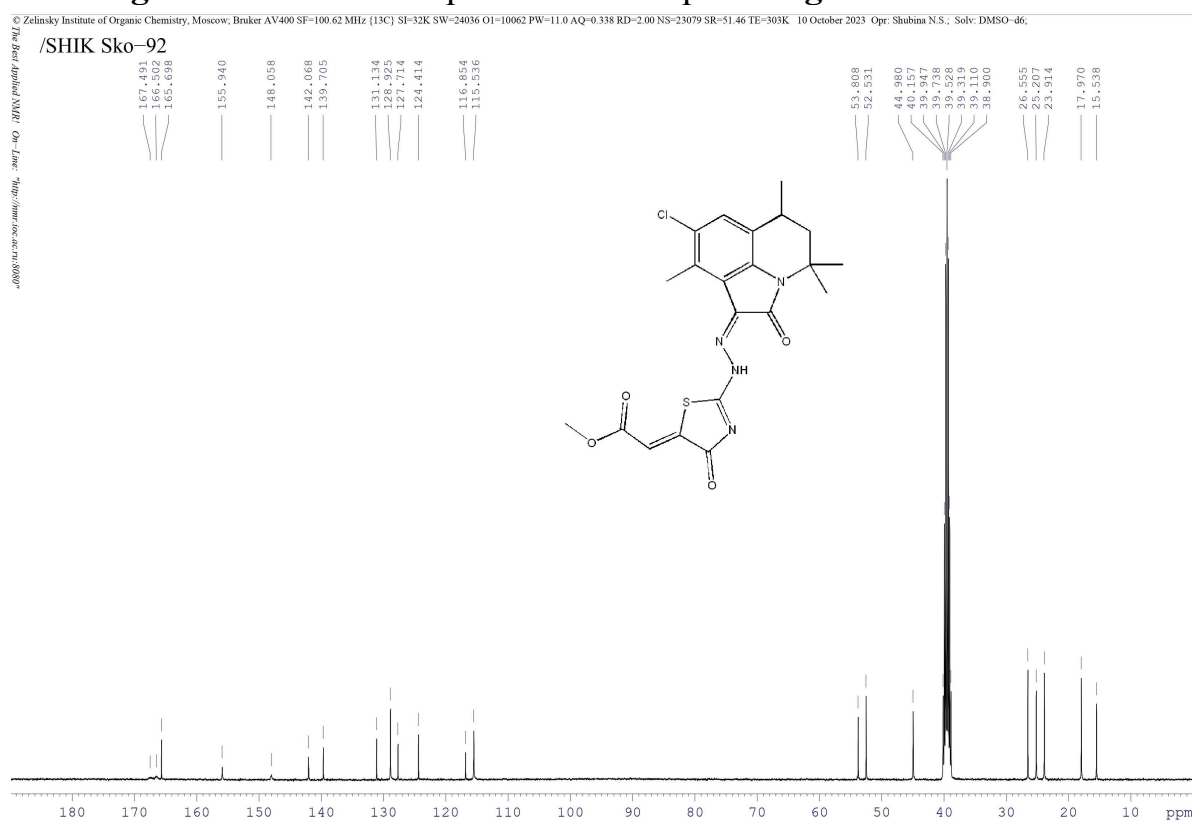


Figure S20. ^{13}C NMR spectrum of compound **3g**

^1H , ^{13}C NMR and data HPLC-HRMS-ESI spectra of methyl (Z)-(2-(2-(2-(8-bromo-4,4,6,9-tetramethyl-2-oxo-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolin-1(2*H*)-ylidene)hydrazineyl)-4-oxothiazol-5(4*H*)-ylidene)acetate **3h**

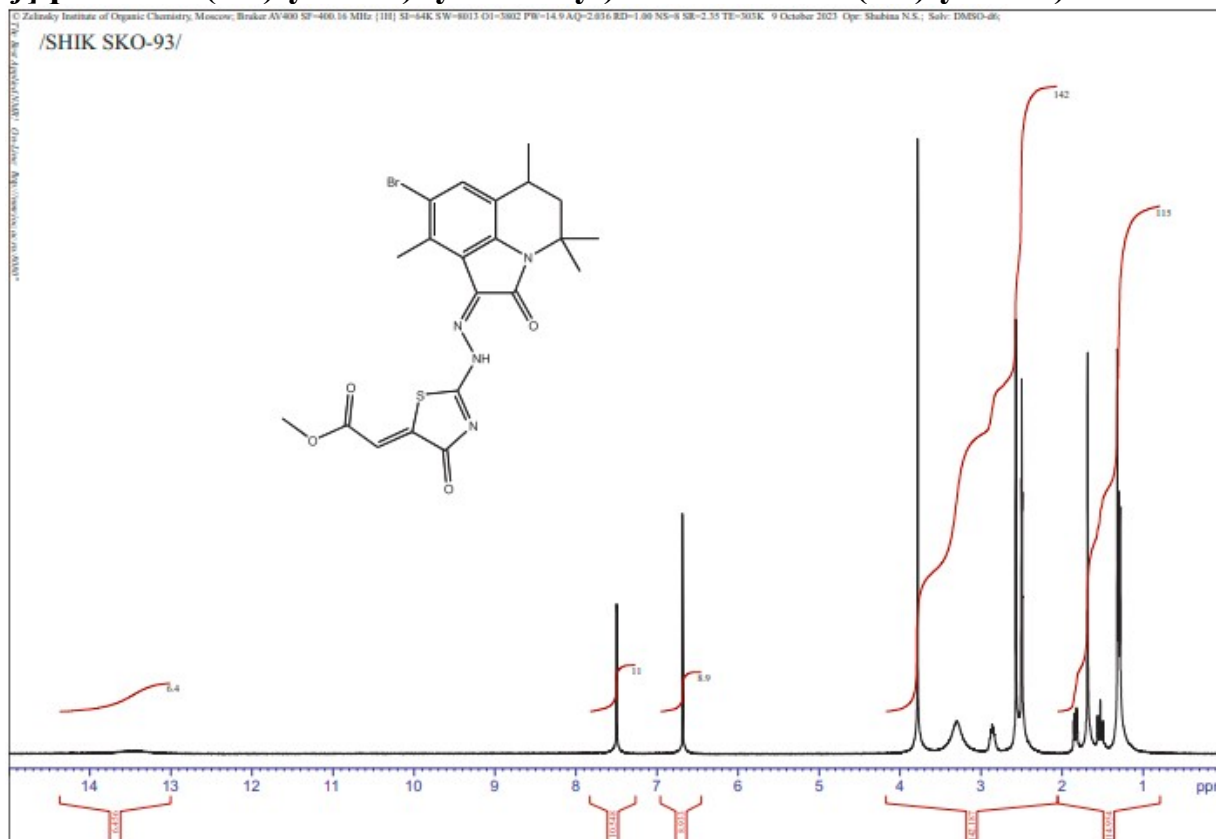


Figure S22. ^1H NMR spectrum of compound **3h**

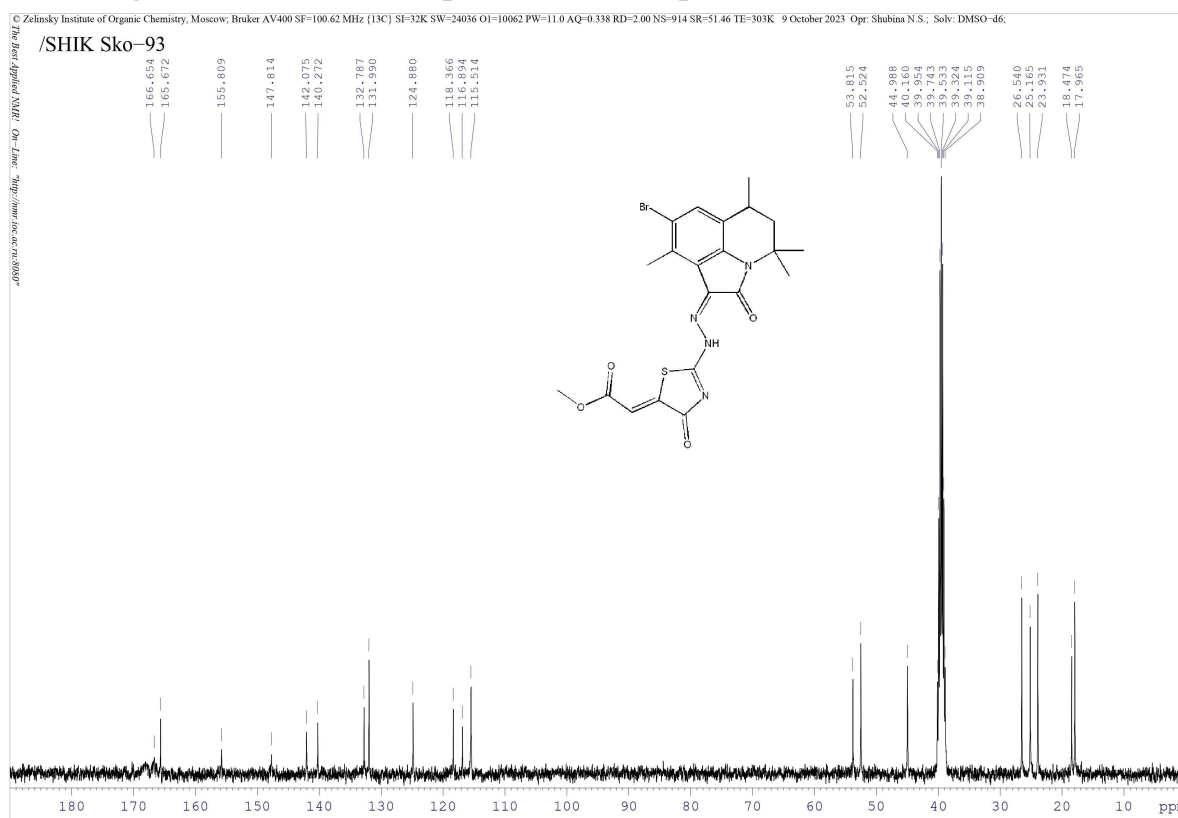


Figure S23. ^{13}C NMR spectrum of compound **3h**

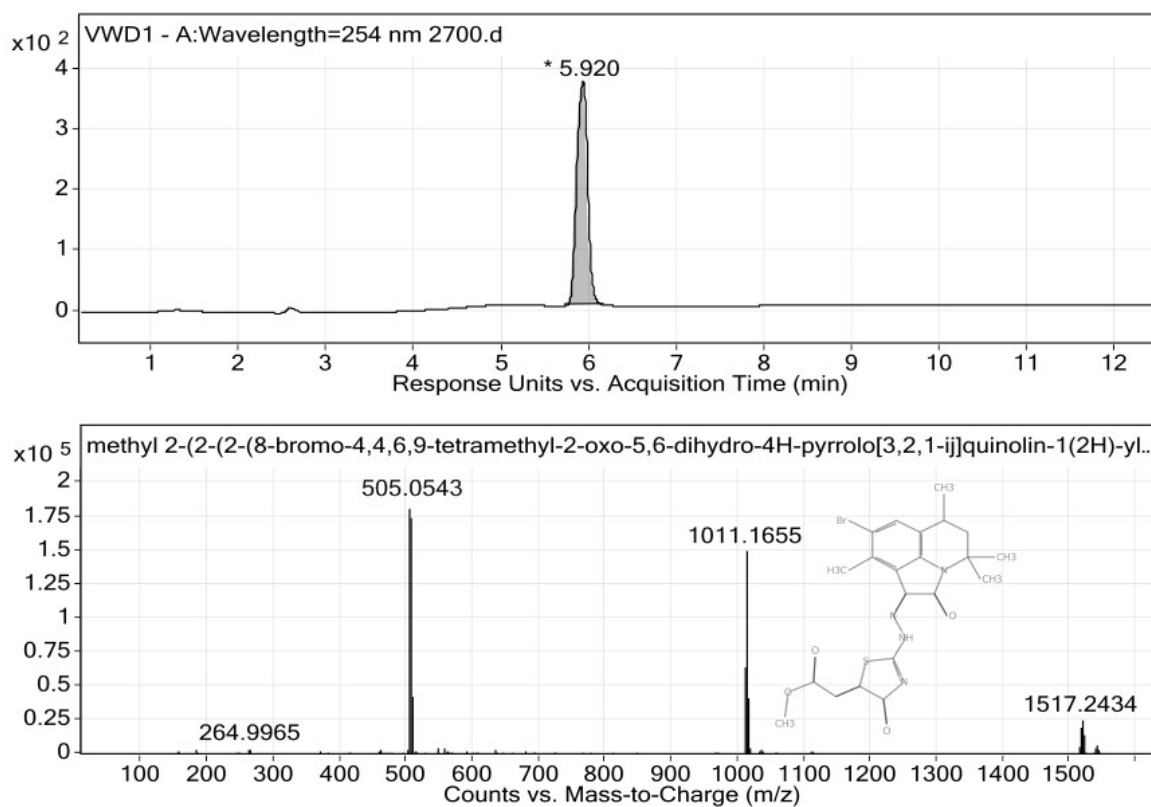


Figure S24. Data of HPLC-MS-ESI analysis of **3h**

^1H , ^{13}C NMR and data HPLC-HRMS-ESI spectra of methyl (Z)-2-(2-((Z)-6-(4-chlorophenyl)-4,4,6-trimethyl-2-oxo-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolin-1(2*H*)-ylidene)hydrazineyl)-4-oxothiazol-5(4*H*)-ylidene)acetate **3i**

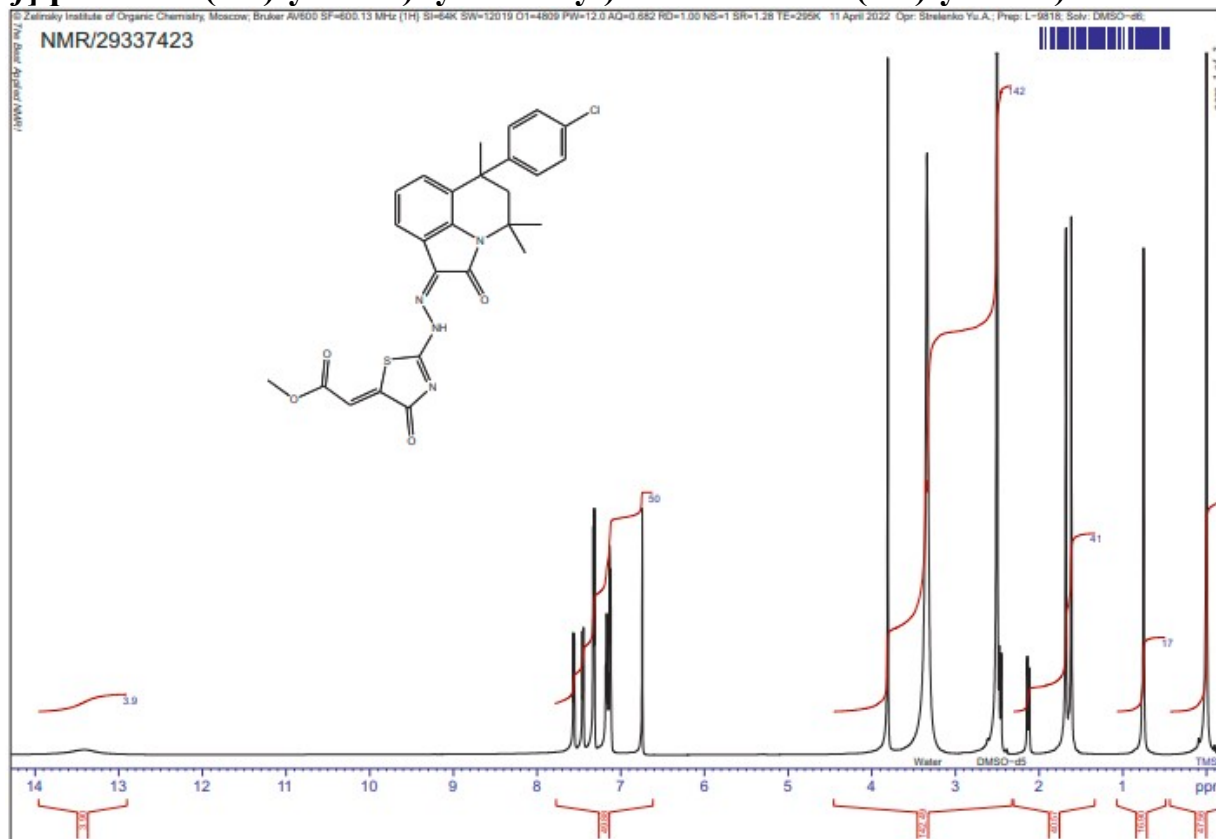


Figure S25. ^1H NMR spectrum of compound **3i**

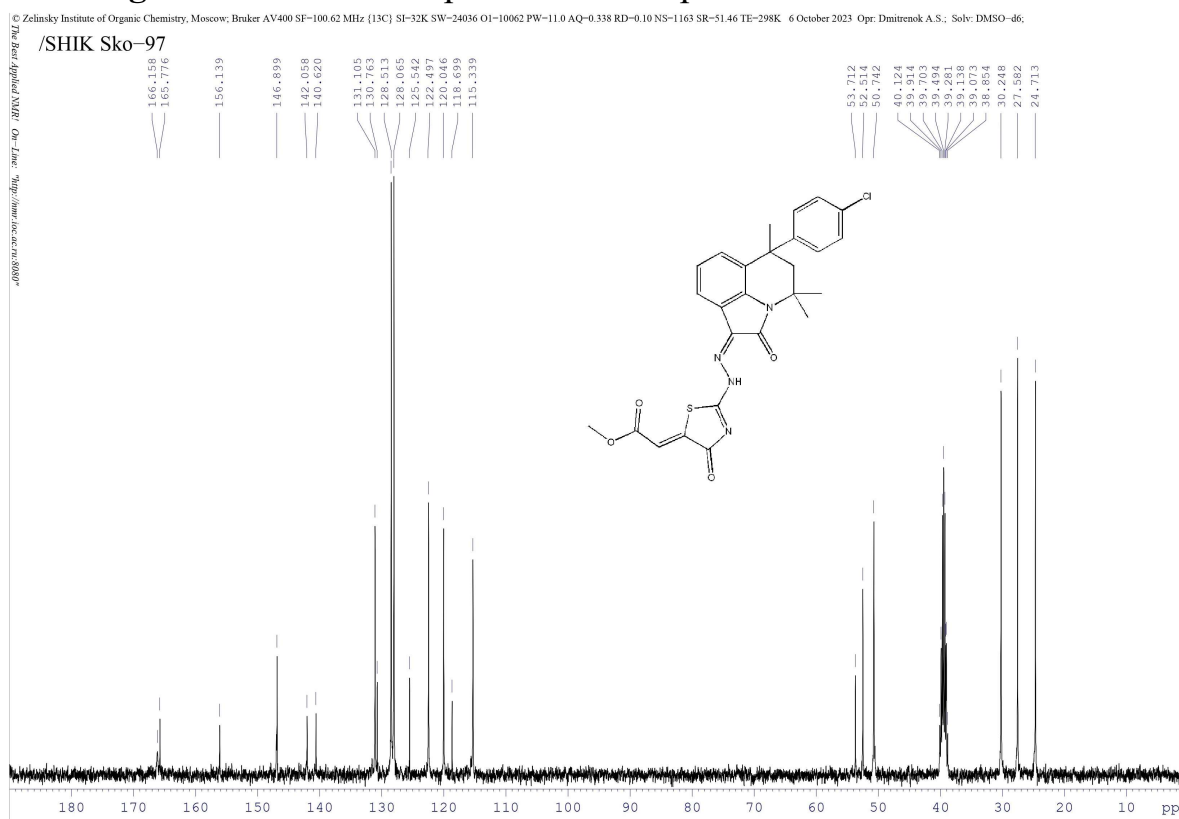


Figure S26. ^{13}C NMR spectrum of compound **3i**

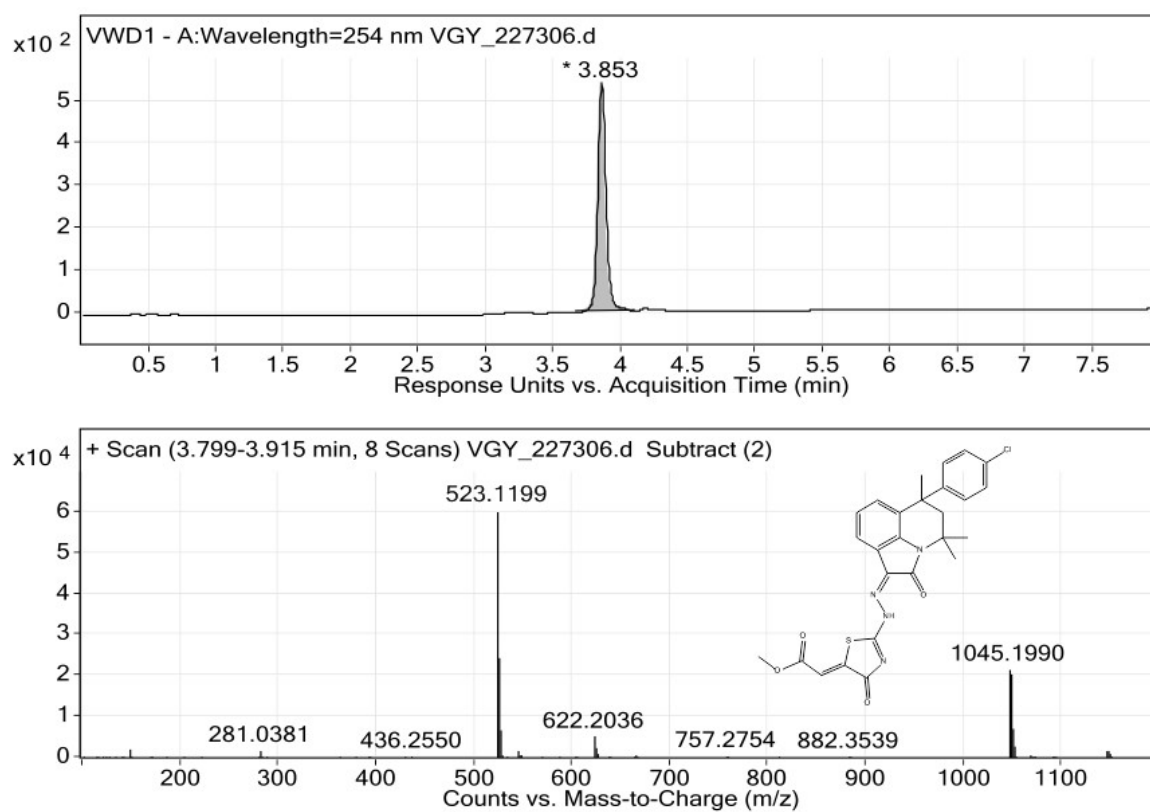


Figure S27. Data of HPLC-MS-ESI analysis of **3i**

^1H , ^{13}C NMR and data HPLC-HRMS-ESI spectra of methyl 2-(2-(2-(6-(4-chlorophenyl)-4,4,6,8-tetramethyl-2-oxo-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolin-1(2*H*)-ylidene)hydrazineyl)-4-oxothiazol-5(4*H*)-ylidene)acetate **3j**

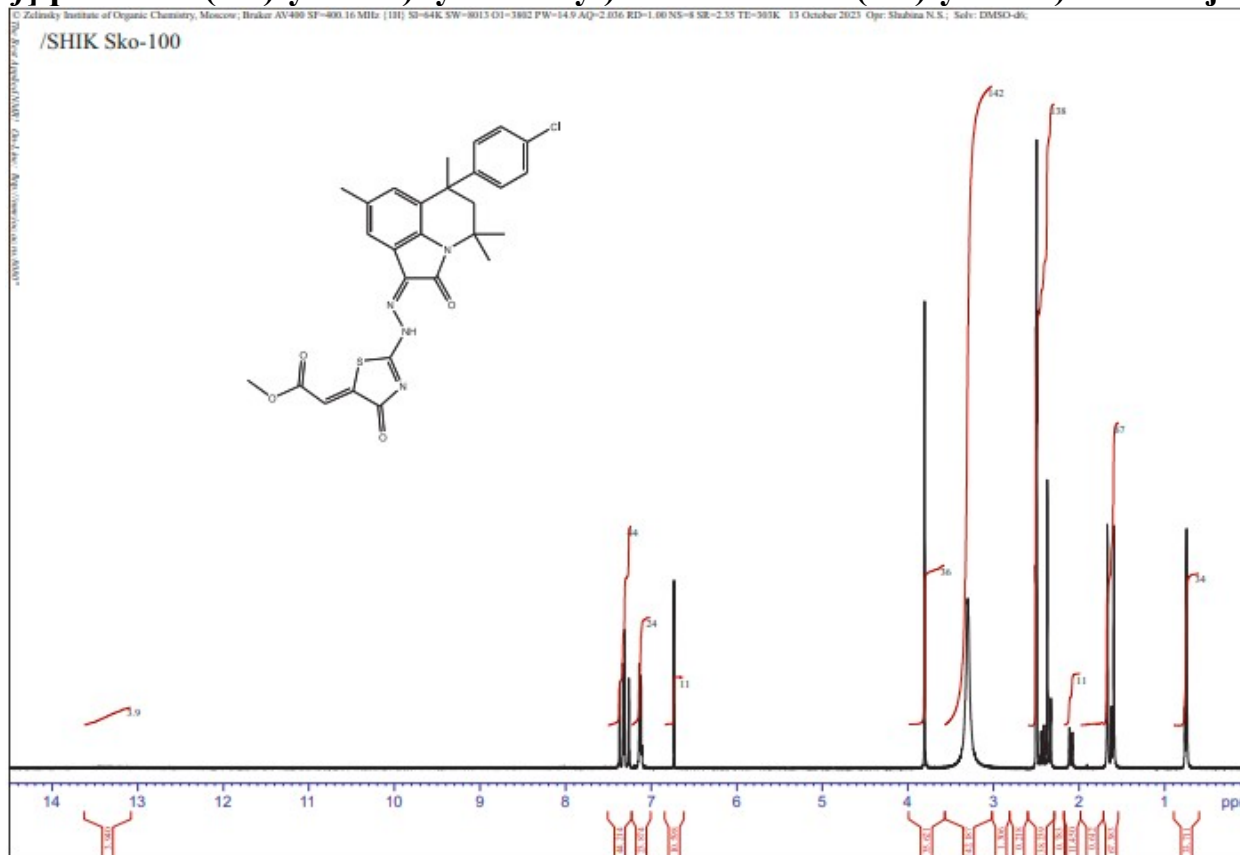


Figure S28. ^1H NMR spectrum of compound **3j**

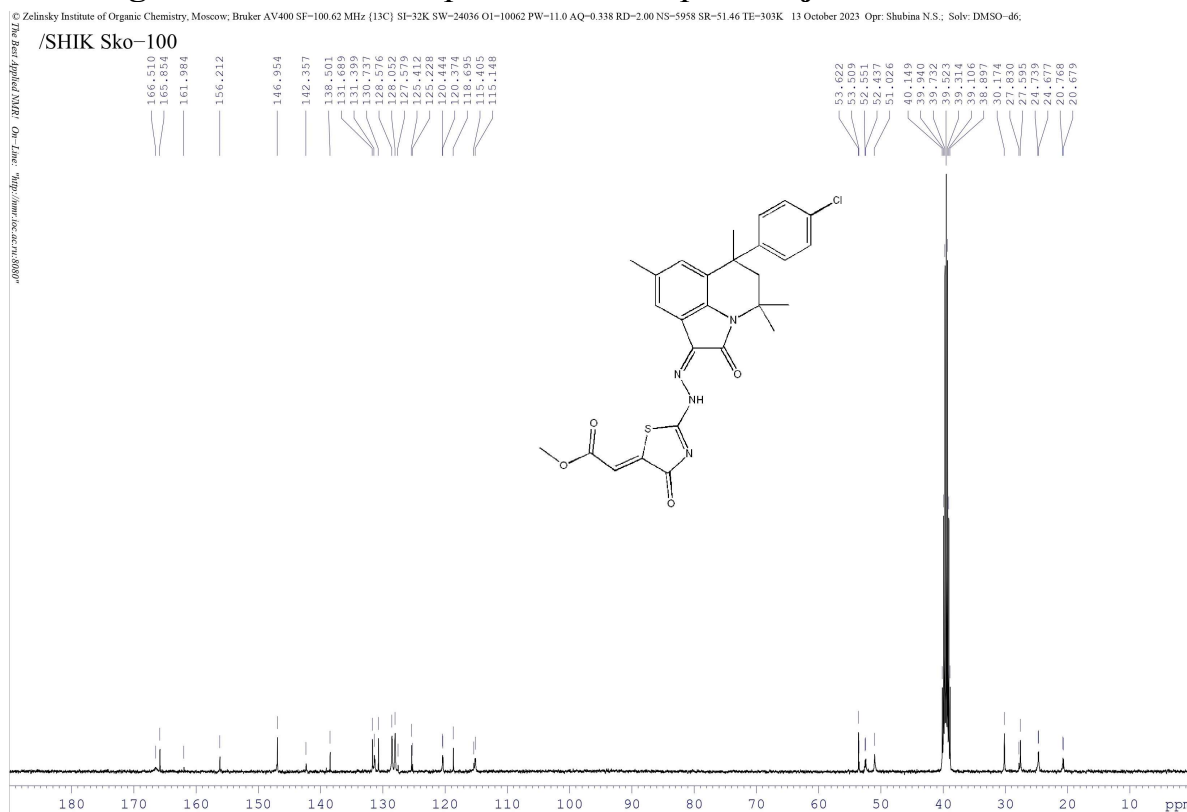


Figure S29. ^{13}C NMR spectrum of compound **3j**

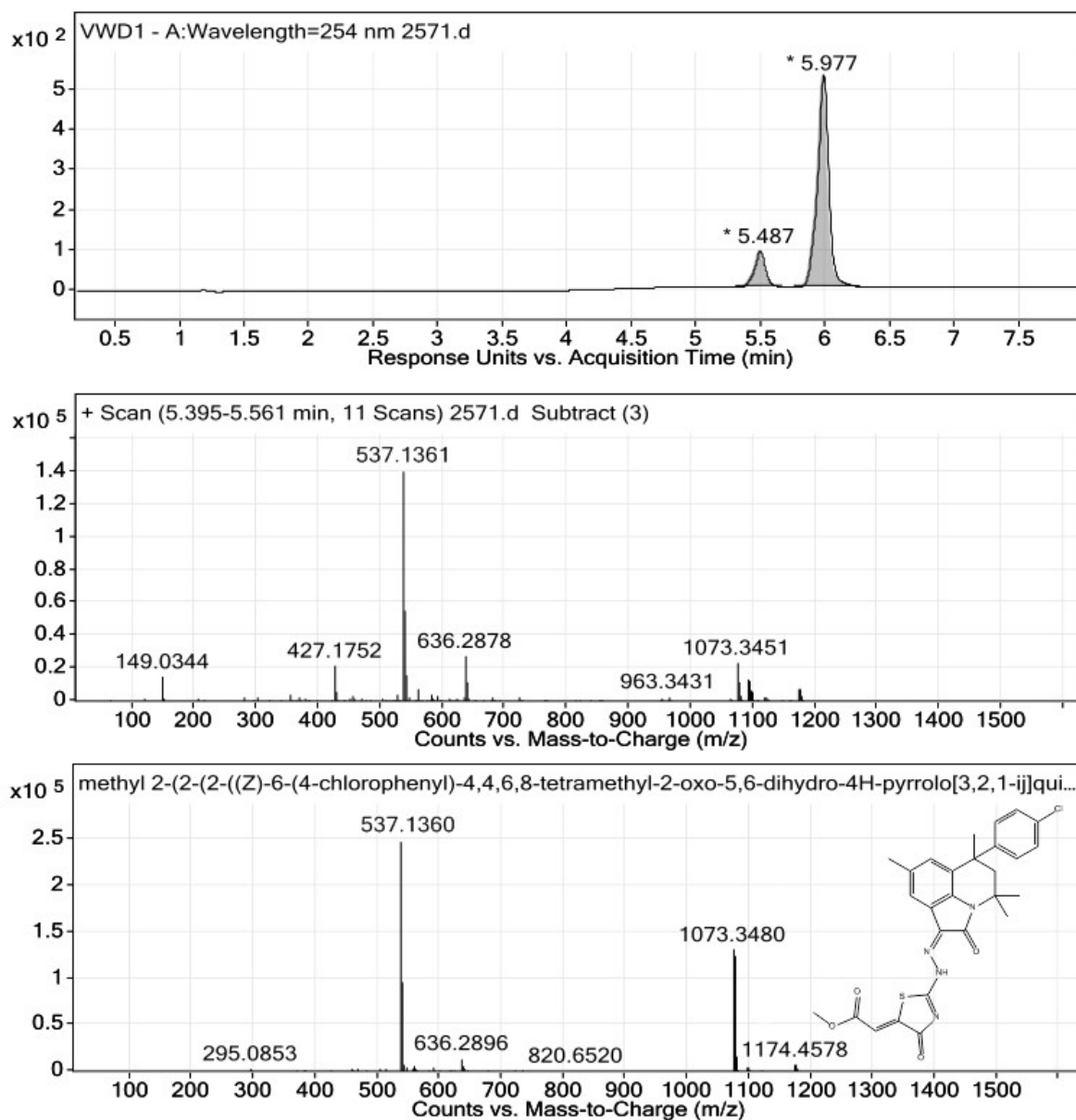


Figure S30. Data of HPLC-MS-ESI analysis of **3j**

© Zelinsky Institute of Organic Chemistry, Moscow; Bruker AV-400 51~400.16 MHz ¹H; 51~64K SW~8013 GJ~5802 PH~14.9 AQ~2.036 RD~1.08 NS~8 SR~2.35 TE~303K 12 October 2023 Op: Shabina N.S.; Solv: DMSO-d₆
/SHIK Sko-98

Chemical structure of compound 13 is shown above the spectrum. The spectrum displays peaks from 0 to 14 ppm with corresponding integrations. A small peak at 13.1 ppm is labeled '1.1'. Peaks in the aromatic region (6.5-7.5 ppm) are labeled with integrations 2.9, 4.0, and 1.1. A large peak at 3.42 ppm is labeled '4.2'. Other peaks are labeled with integrations 1.6, 1.2, 2.2, and 3.6.

© Zelinsky Institute of Organic Chemistry, Moscow; Bruker AV400 SF-100.62 MHz [13C] SF-32K SW-24036 O1-10062 PW-11.0 AQ-0.338 RD-0.50 NS-24576 SR-51.46 TE-303K 12 October 2023 Opr: Shubina N.S.; Solv: DMSO-d6; /SHIK Sko-98

167.442
166.168
165.765

155.727

146.346
145.364
141.924
139.477

130.924
130.234
130.175
128.807
128.123
127.641
126.807
120.358
119.415
115.634
115.555

53.896
52.599
52.487
50.659

40.151
39.942
39.733
39.526
39.315
39.107
38.899

29.951
27.467
24.747
24.685

180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

Chemical structure of compound 98 is shown above the spectrum.

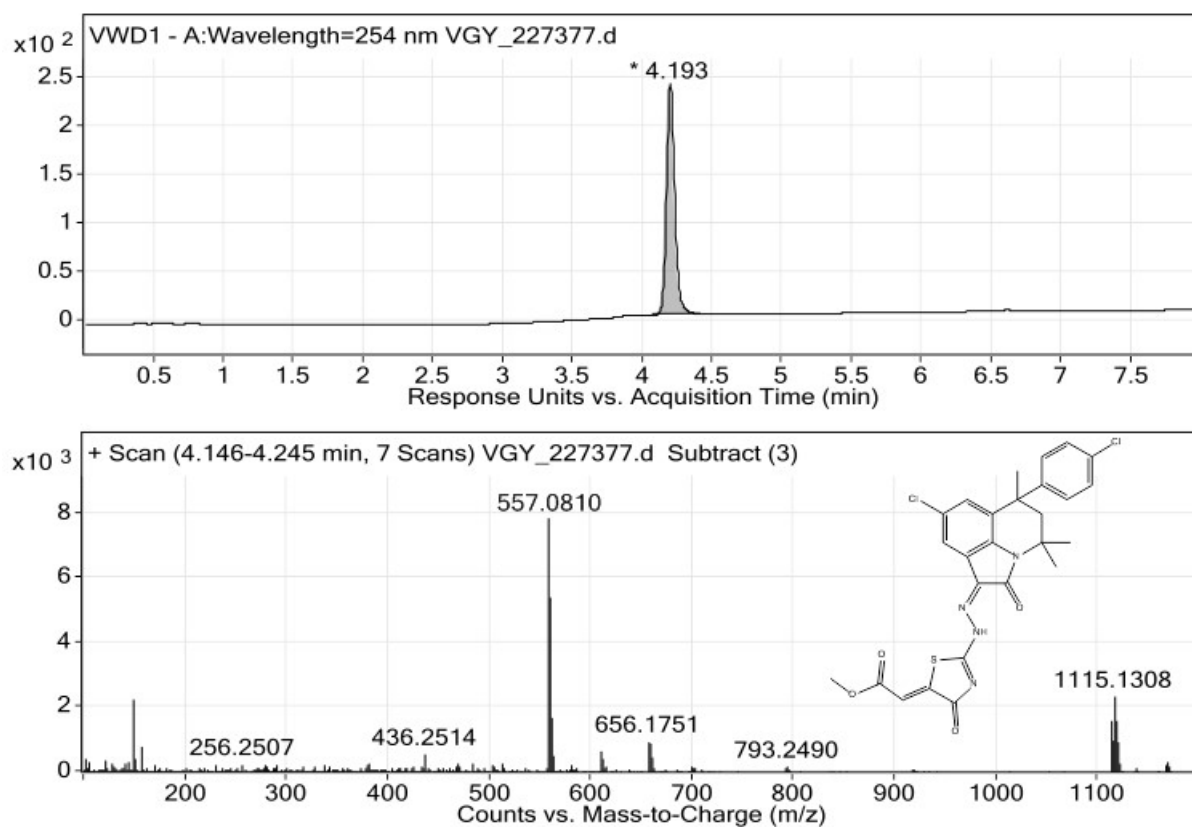
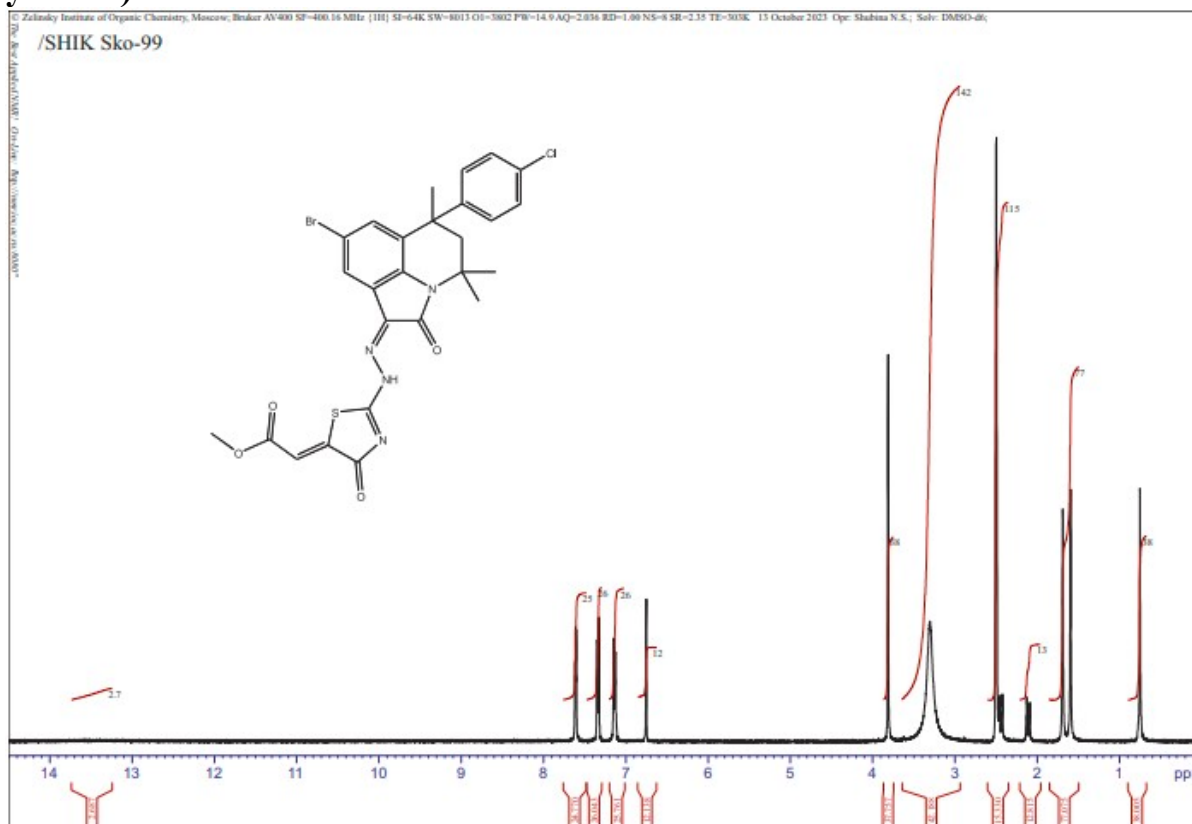


Figure S33. Data of HPLC-MS-ESI analysis of **3k**

^1H , ^{13}C NMR and data HPLC-HRMS-ESI spectra of methyl (Z)-2-(2-((Z)-8-bromo-6-(4-chlorophenyl)-4,4,6-trimethyl-2-oxo-5,6-dihydro-4H-pyrrolo[3,2,1-*ij*]quinolin-1(2H)-ylidene)hydrazineyl)-4-oxothiazol-5(4H)-ylidene)acetate **3l**



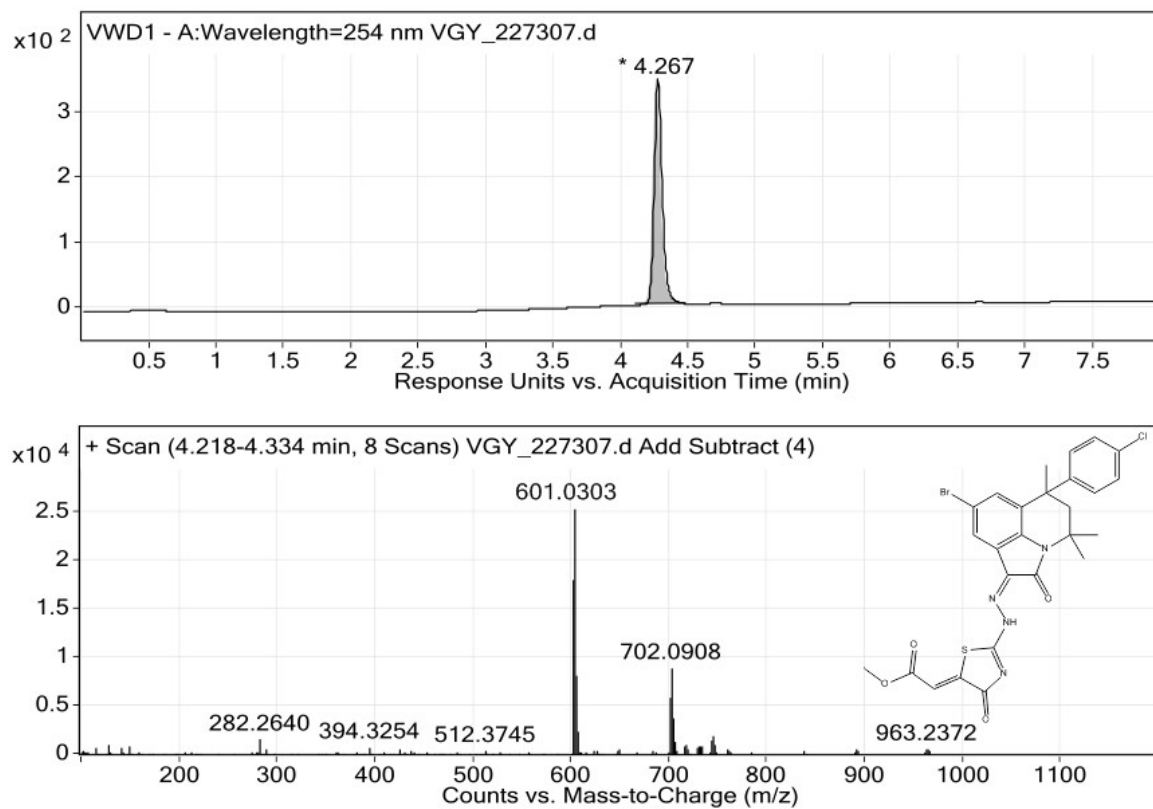


Figure S36. Data of HPLC-MS-ESI analysis of **31**

^1H , ^{13}C NMR and data HPLC-HRMS-ESI spectra of methyl 2-(2-(2-(6-(4-chlorophenyl)-8-fluoro-4,4,6-trimethyl-2-oxo-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolin-1(2*H*)-ylidene)hydrazineyl)-4-oxothiazol-5(4*H*)-ylidene)acetate **3m**

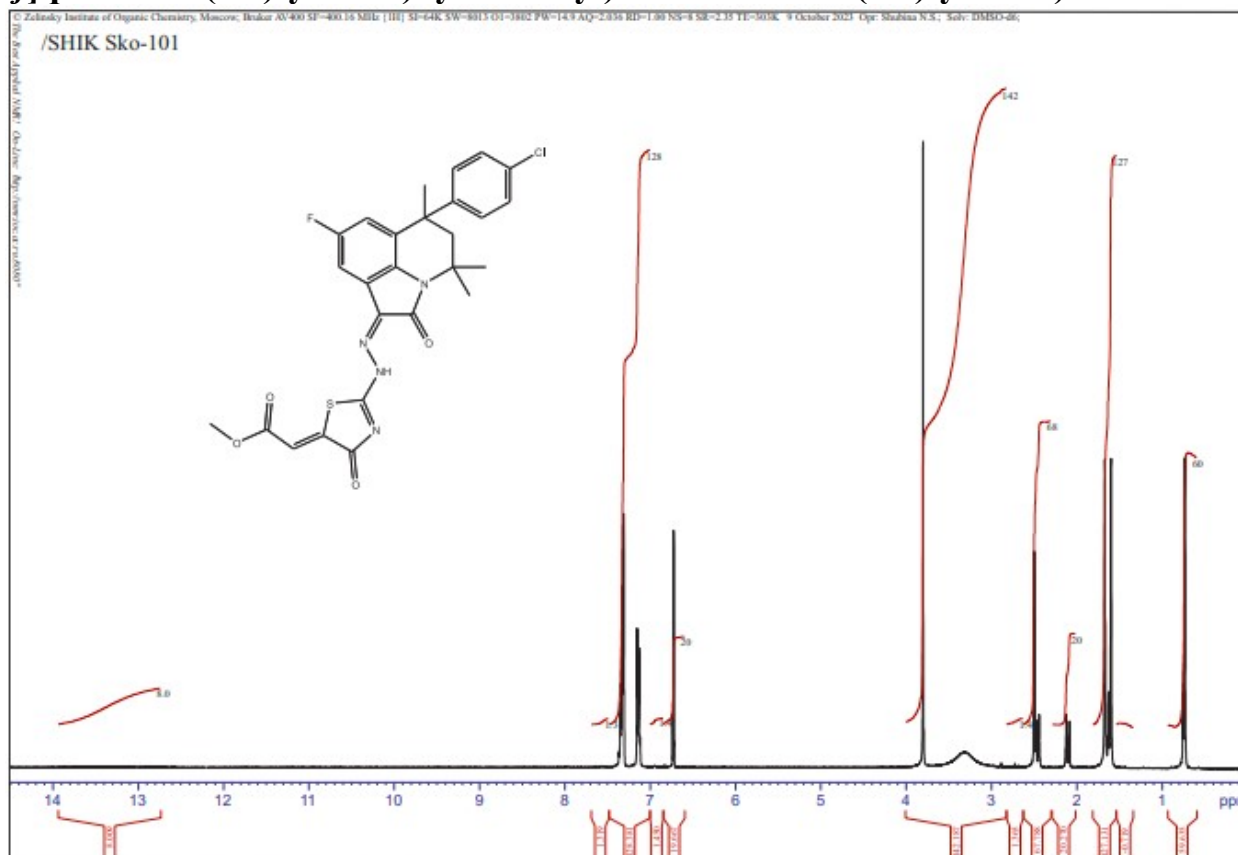


Figure S37. ^1H NMR spectrum of compound **3m**

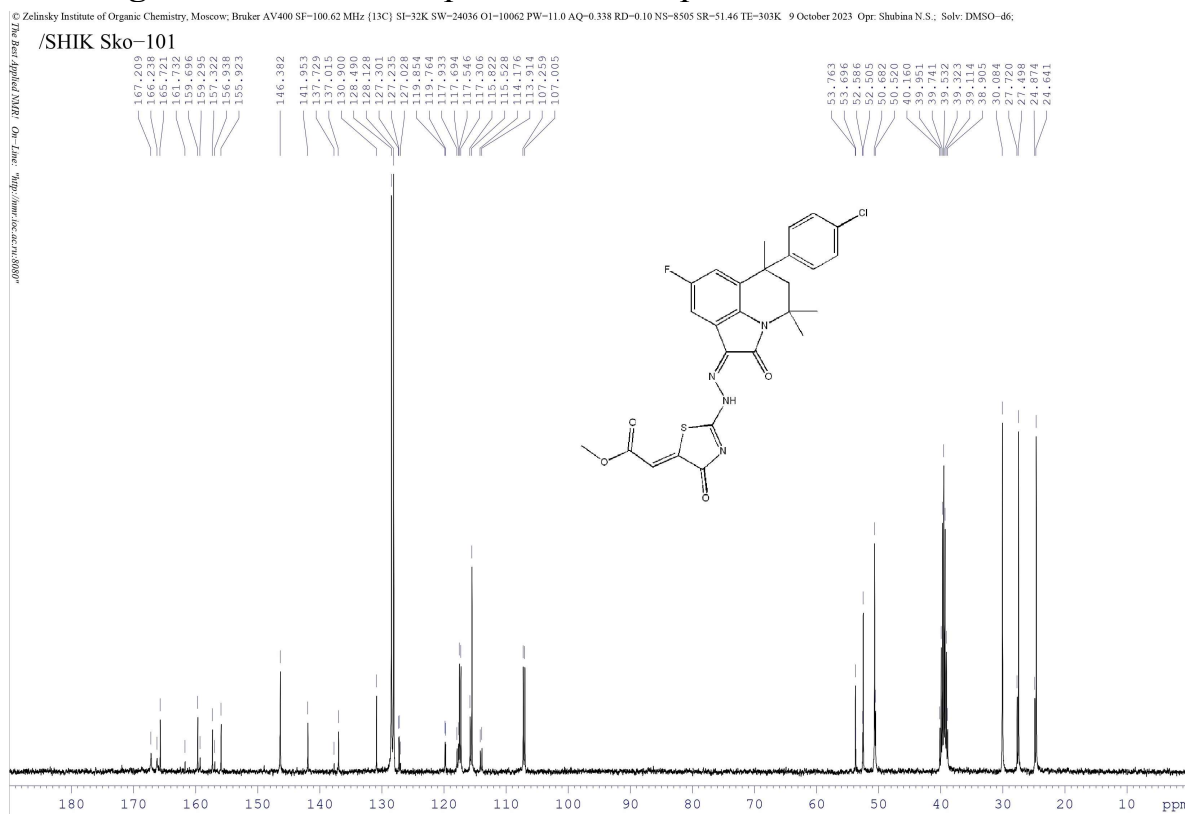


Figure S38. ^{13}C NMR spectrum of compound **3m**

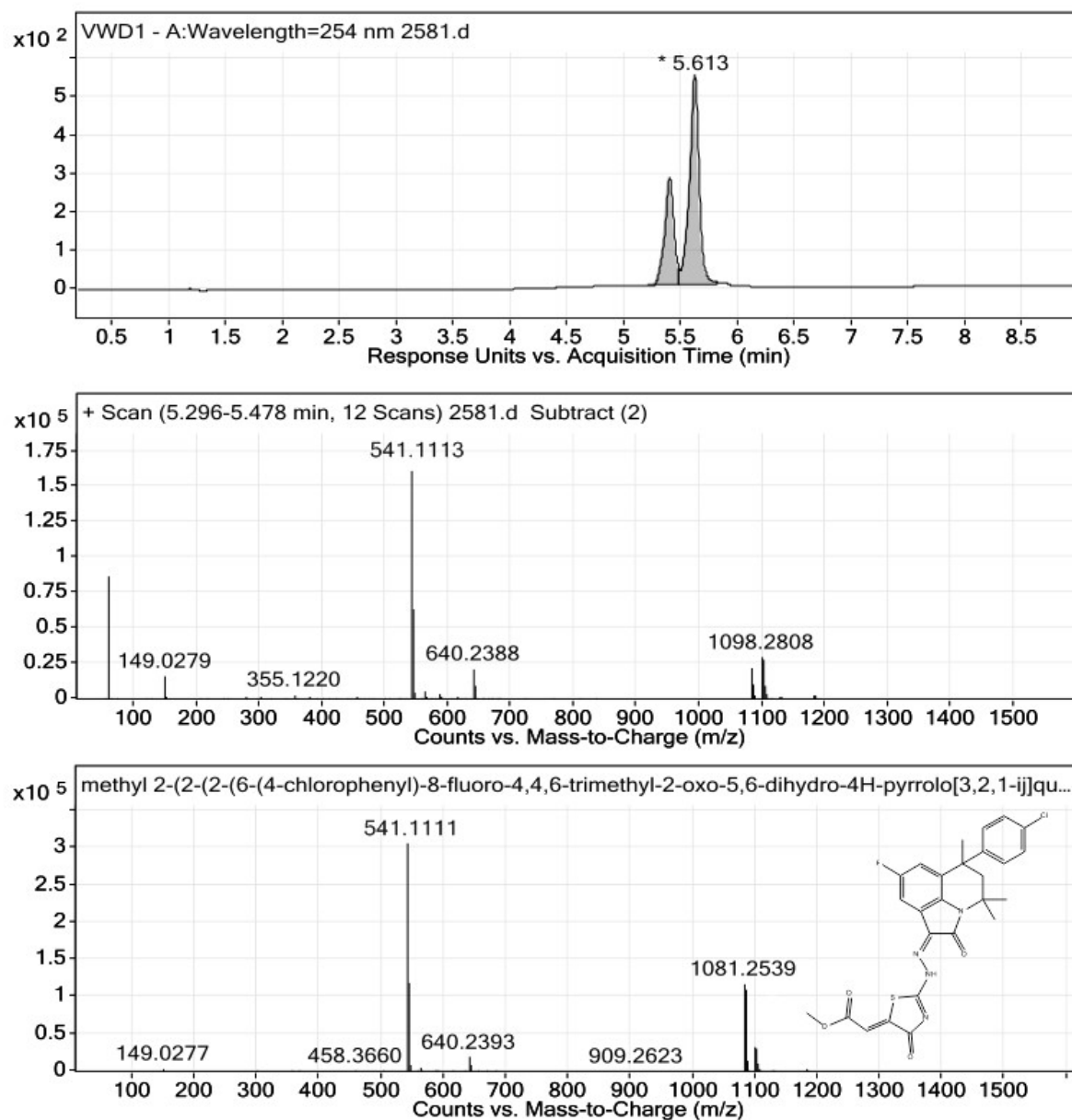


Figure S39. Data of HPLC-MS-ESI analysis of **3m**

^1H , ^{13}C NMR and data HPLC-HRMS-ESI spectra of methyl (Z)-2-(4-oxo-2-(2-((Z)-4,4,6-trimethyl-2-oxo-6-phenyl-5,6-dihydro-4H-pyrrolo[3,2,1-*ij*]quinolin-1(2H)-ylidene)hydrazineyl)thiazol-5(4H)-ylidene)acetate 3n

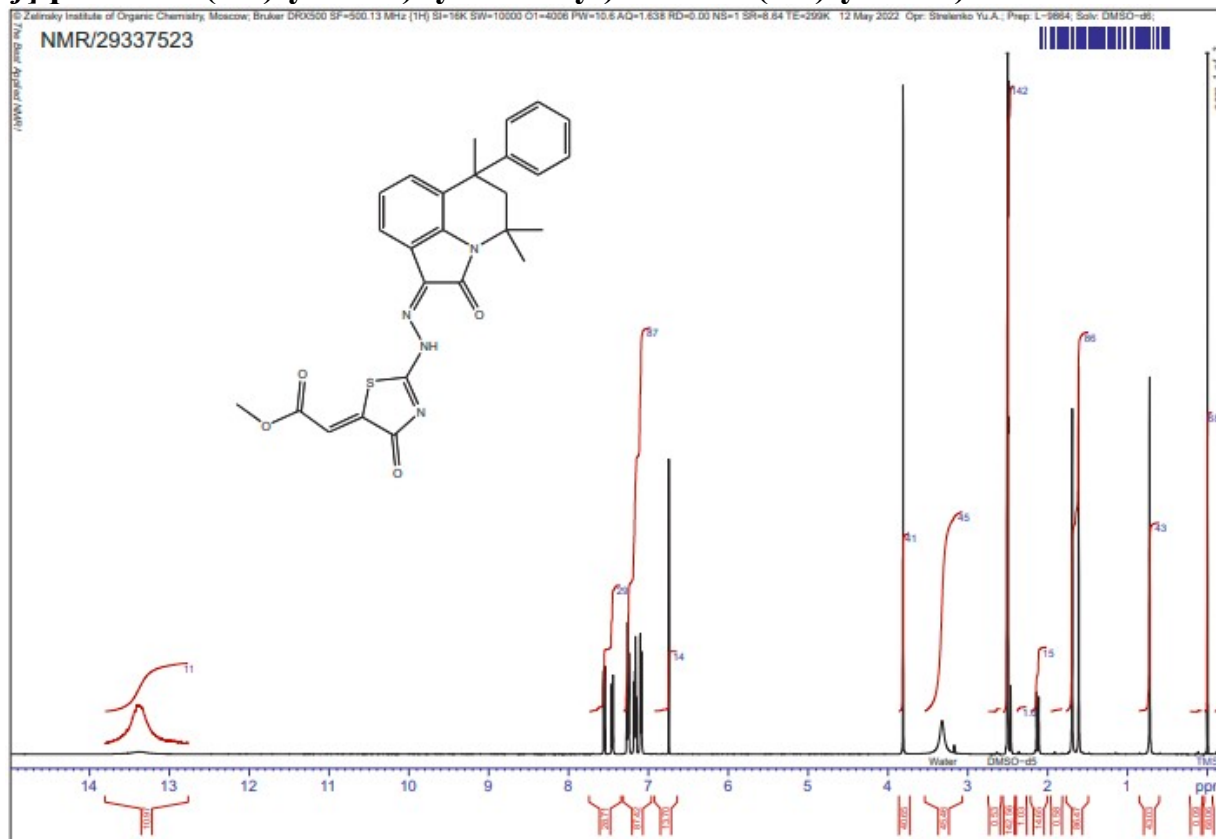


Figure S40. ^1H NMR spectrum of compound 3n

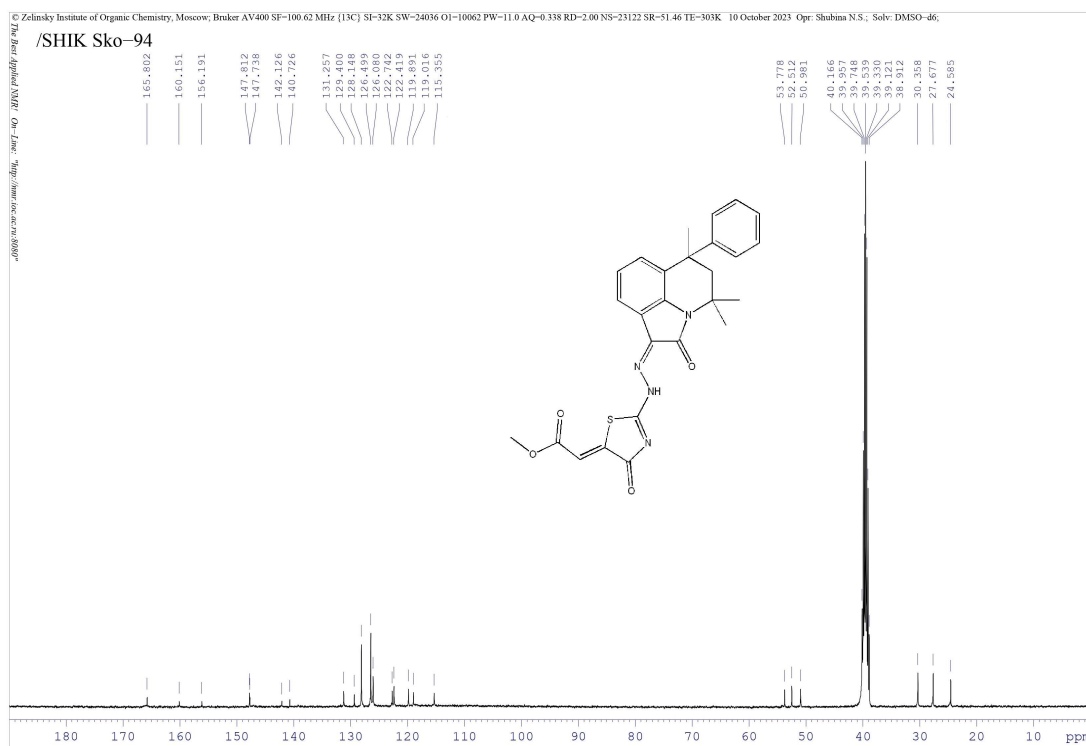


Figure S41. ^{13}C NMR spectrum of compound 3n

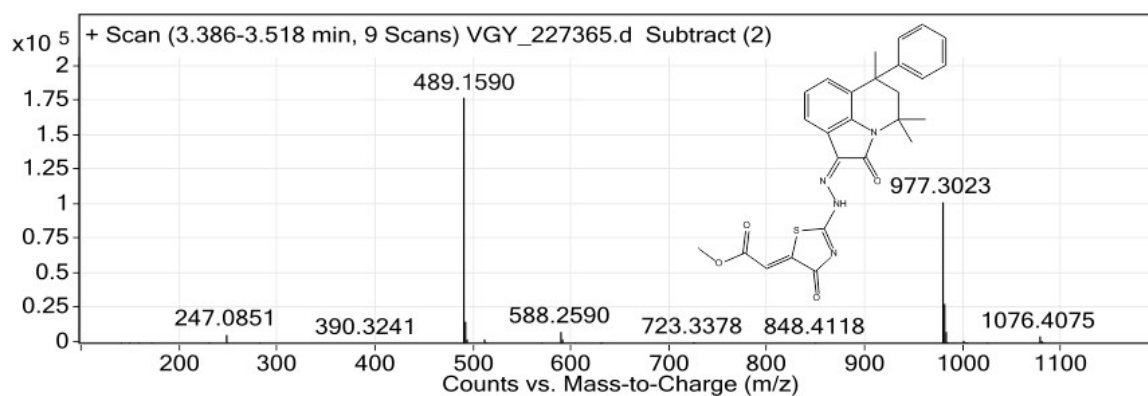
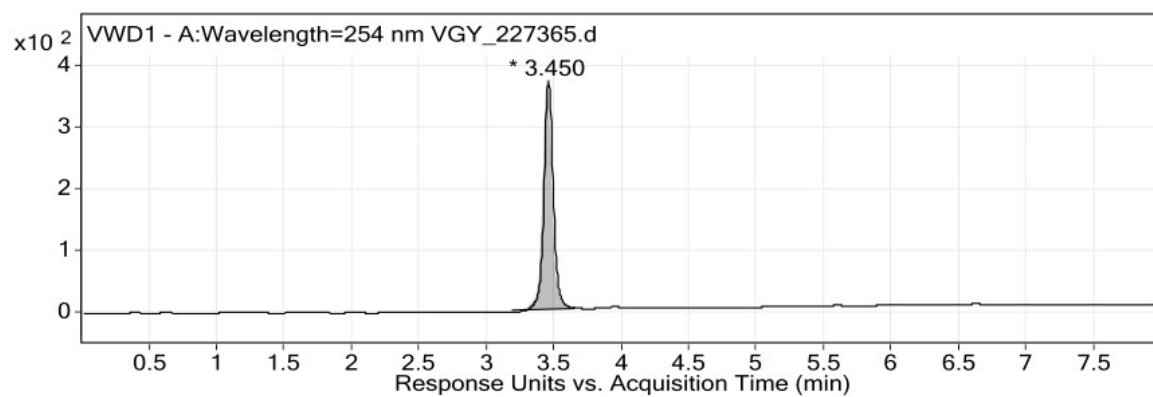


Figure S42. Data of HPLC-MS-ESI analysis of **3n**

^1H , ^{13}C NMR and data HPLC-HRMS-ESI spectra of methyl (Z)-2-(2-((Z)-8-chloro-4,4,6-trimethyl-2-oxo-6-phenyl-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolin-1(2*H*)-ylidene)hydrazineyl)-4-oxothiazol-5(4*H*)-ylidene)acetate **3o**

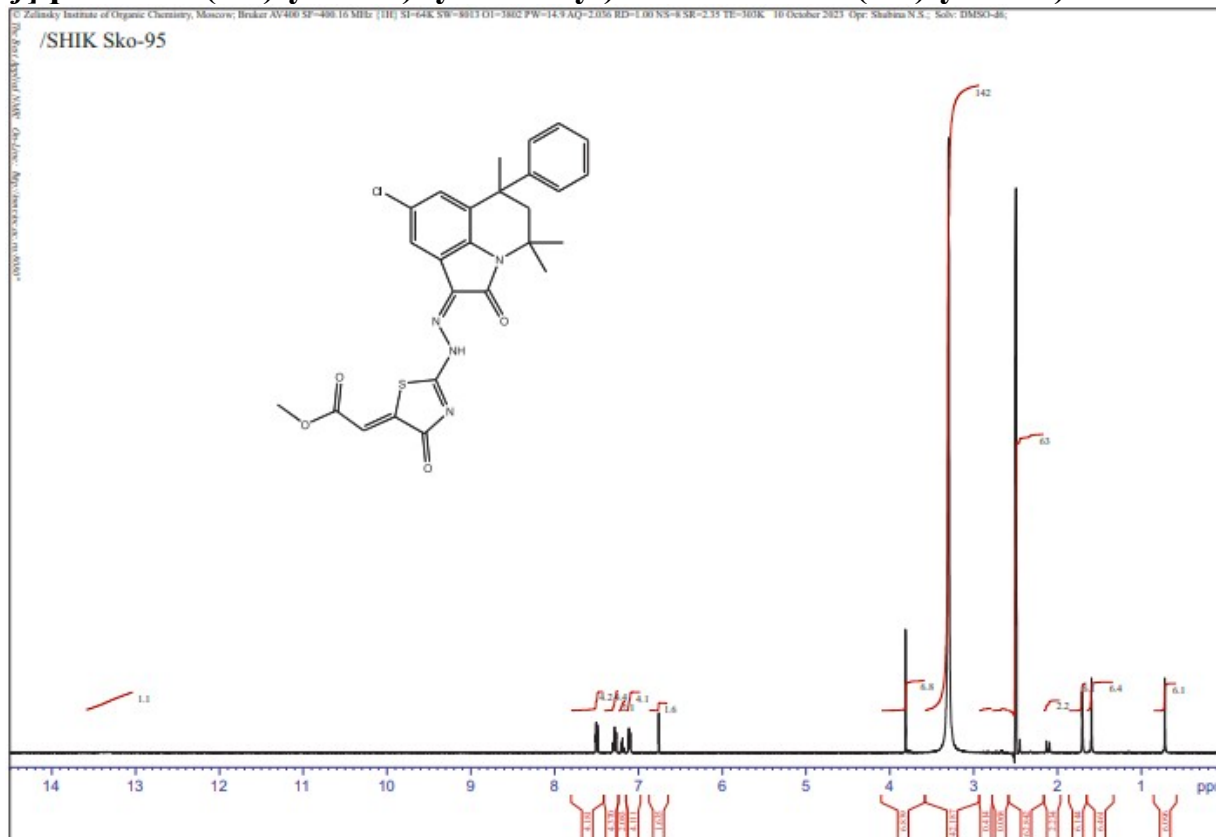


Figure S43. ^1H NMR spectrum of compound **3o**

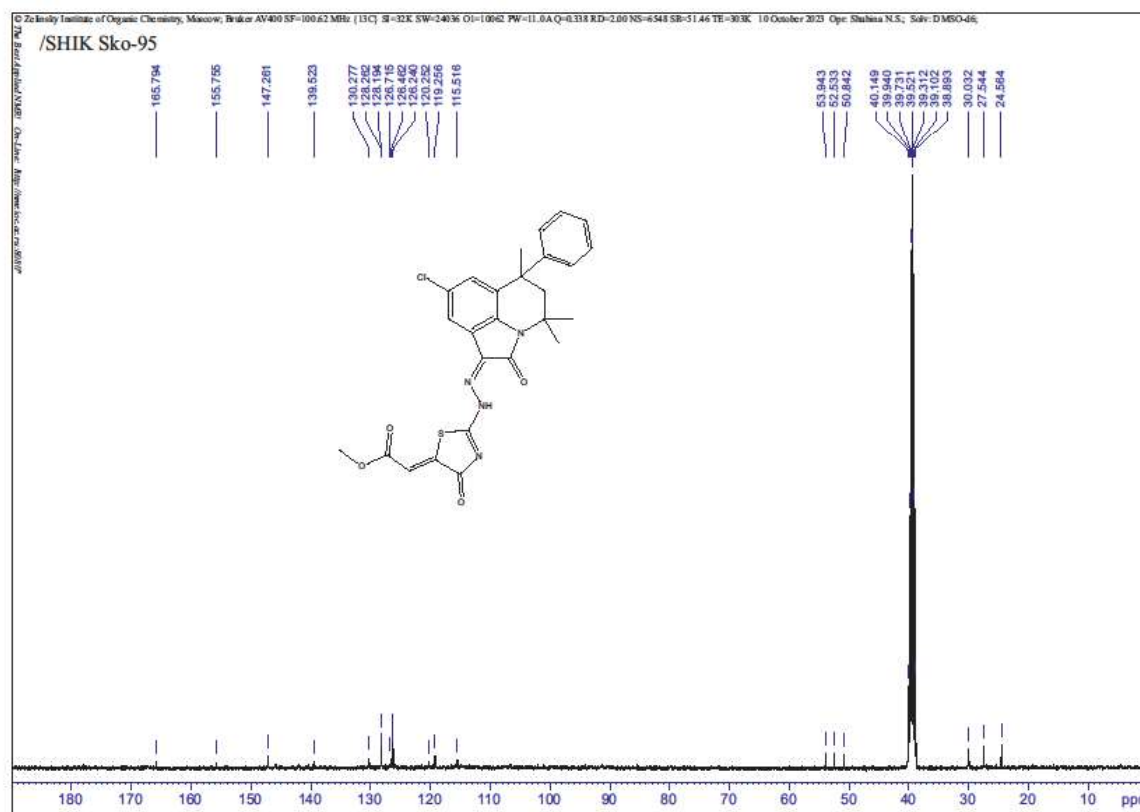


Figure S44. ^{13}C NMR spectrum of compound **3o**

© Zelinsky Institute of Organic Chemistry, Moscow; Bruker DPX350 SP-500.13 MHz (1H) SI-16K SW-10500 C1-400K PW-10.8 AQ-1.638 RD-0.00 NS-1 SP-6.75 TE-299K 12 May 2022 Opr: Shalenko Yu.A.; Prep: L-9894; Solv: DMSO-d6;

NMR/29337522

Found protons = 22 impurity = 0.5 %

Chemical structure of compound **1**: COC(=O)/C=C1/C(=O)N=C1N2C(=O)N(C(C)(C)C)C(C)(C)C2c3ccc(Br)cc3

¹H NMR spectrum (DMSO-d₆) showing peaks and integration values:

Chemical Shift (ppm)	Integration
~13.5	10.1
~8.2	2.2
~7.5	7.3
~7.2	1.3
~3.8	3.0
~3.3	1.4
~2.5	42.0
~2.0	5.4
~1.5	4.2

[illegible]

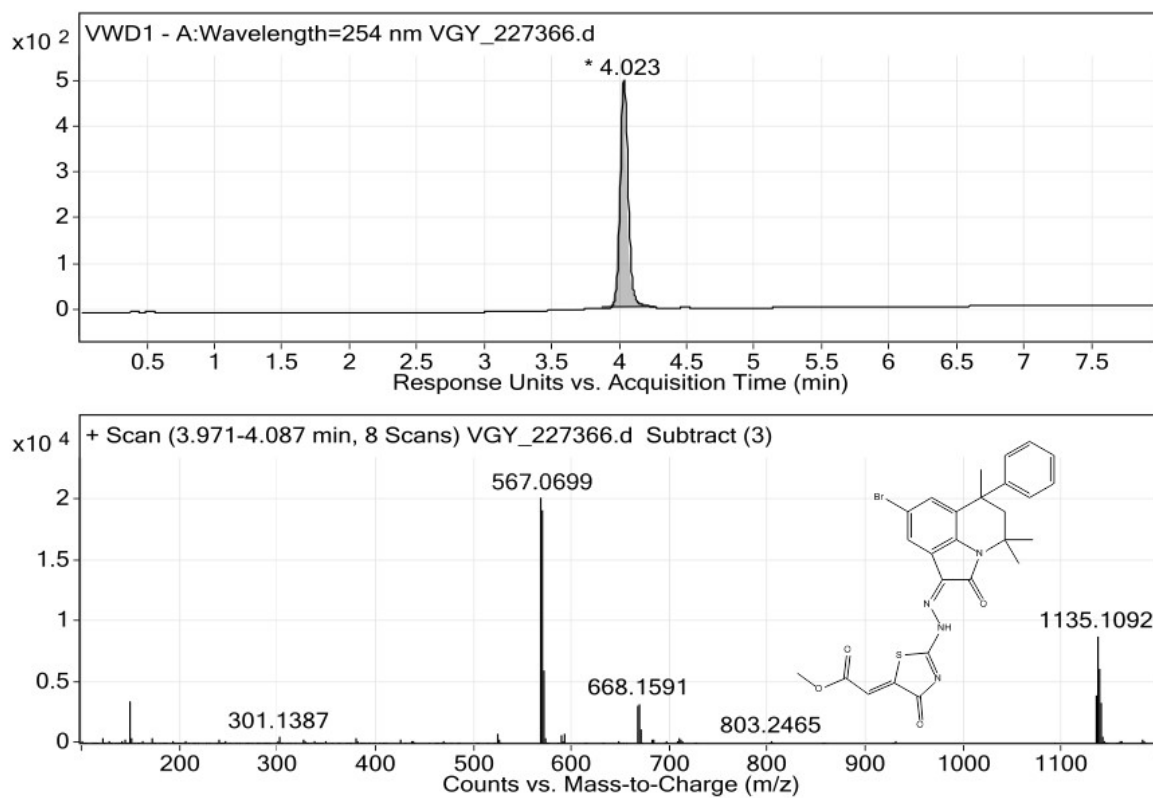


Figure S48. Data of HPLC-MS-ESI analysis of **3p**

^1H , ^{13}C NMR and data HPLC-HRMS-ESI spectra of methyl (Z)-2-(2-(2-((Z)-8-fluoro-4,4,6-trimethyl-2-oxo-6-phenyl-5,6-dihydro-4H-pyrrolo[3,2,1-*ij*]quinolin-1(2H)-ylidene)hydrazineyl)-4-oxothiazol-5(4H)-ylidene)acetate 3q

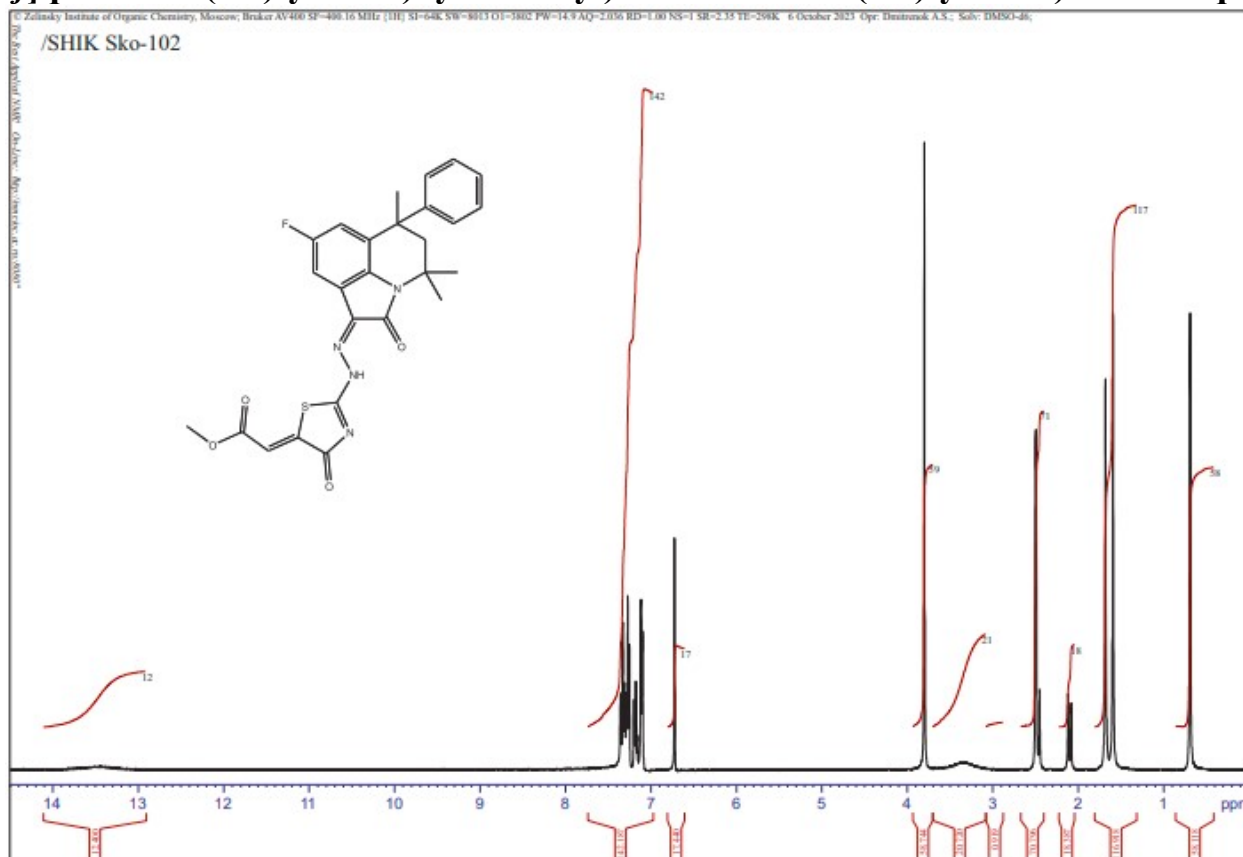


Figure S49. ^1H NMR spectrum of compound 3q

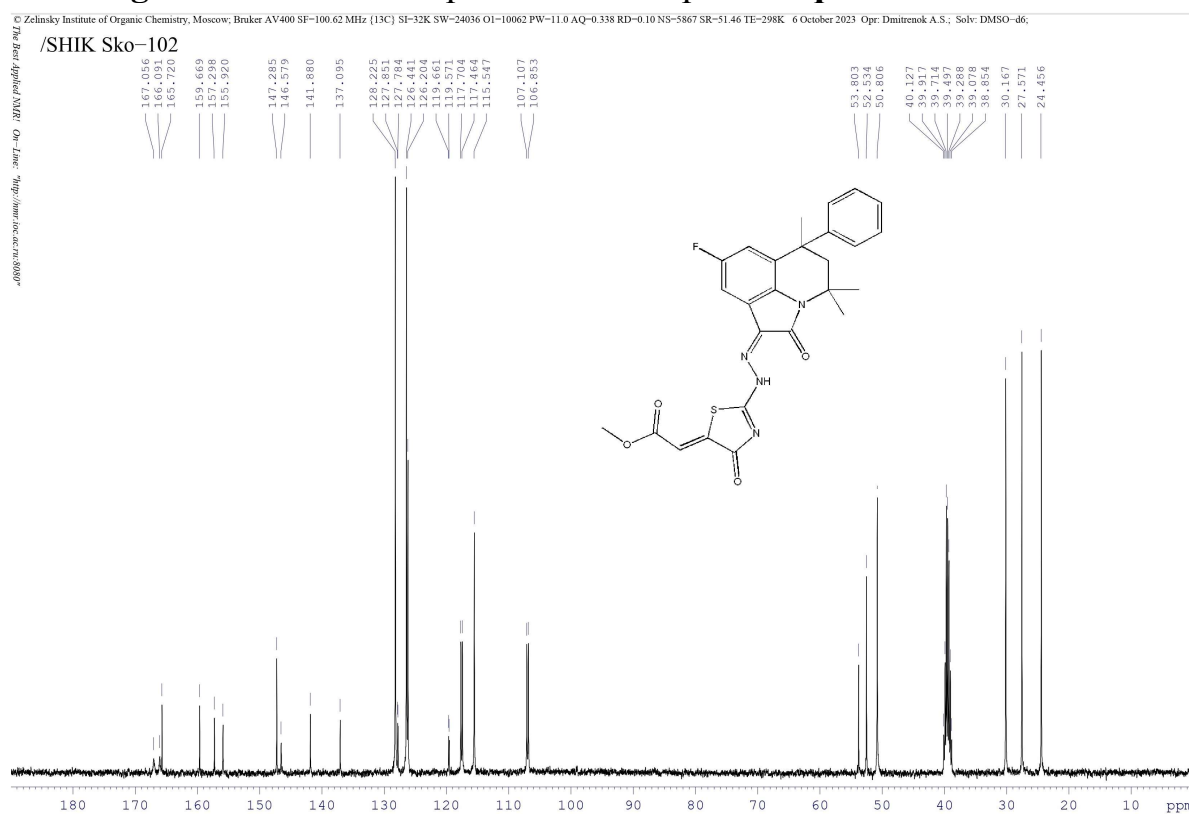


Figure S50. ^{13}C NMR spectrum of compound 3q

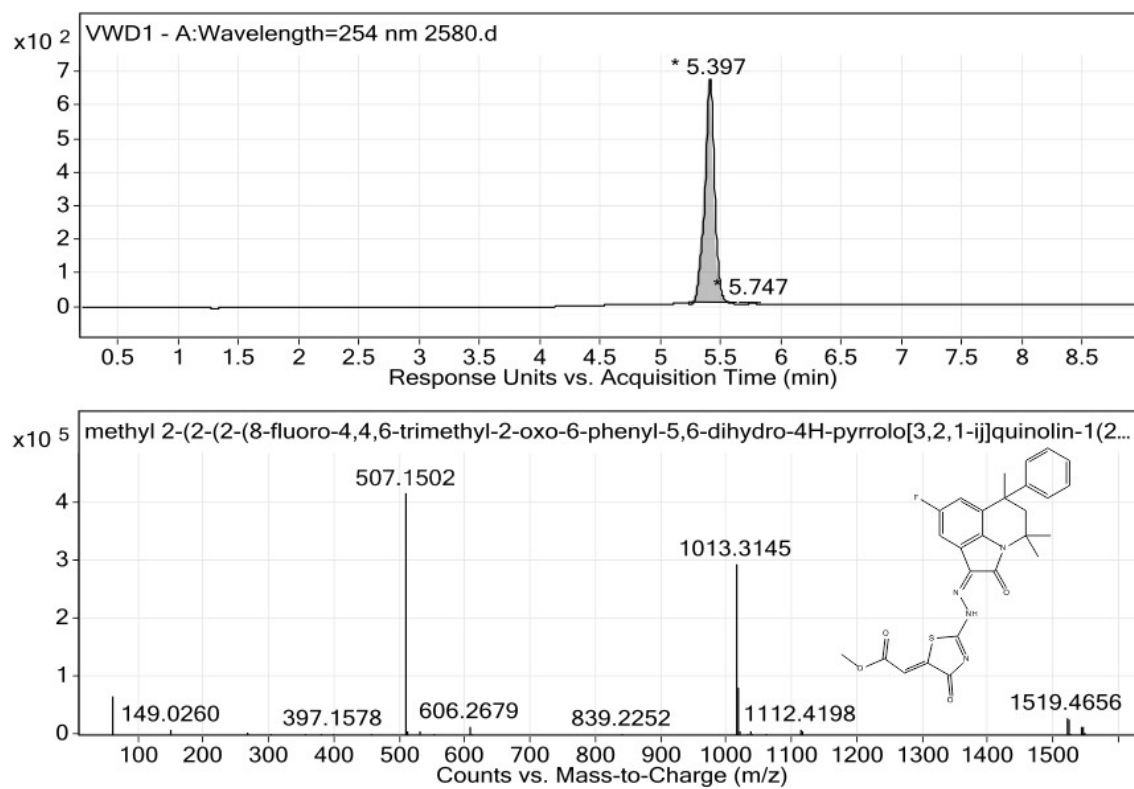


Figure S51. Data of HPLC-MS-ESI analysis of **3q**

The dependence of inhibition of factor Xa- and XIa-induced chromogenic substrate hydrolysis on the compound concentration.

The dependence of inhibition of factor Xa- and XIa-induced chromogenic substrate hydrolysis on the concentration of 3b

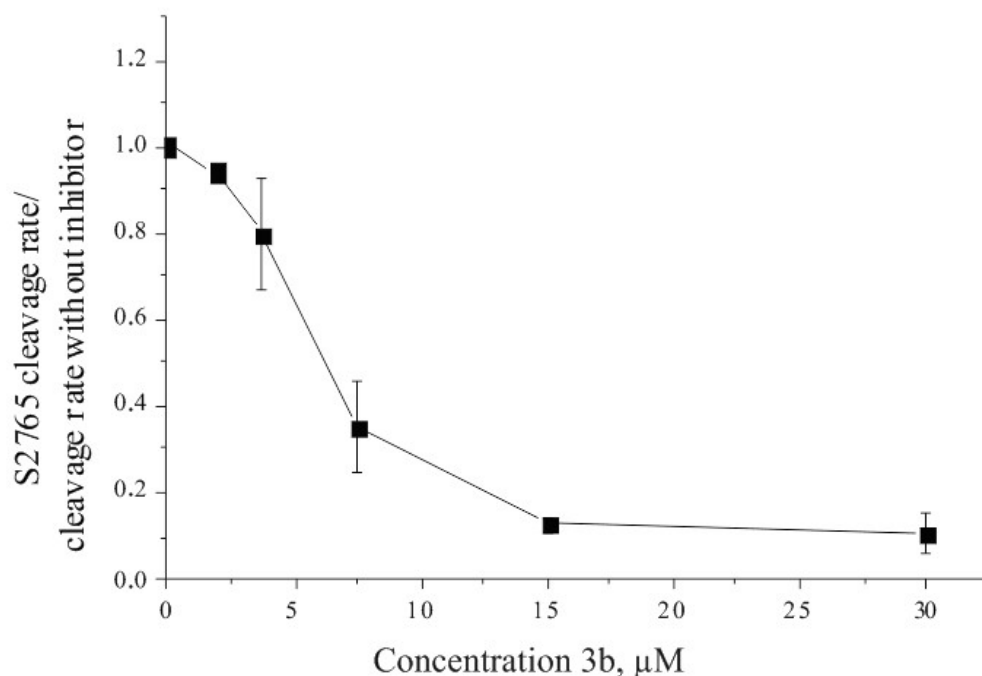


Figure S52. The dependence of inhibition of factor Xa-induced chromogenic substrate hydrolysis on the concentration of **3b**

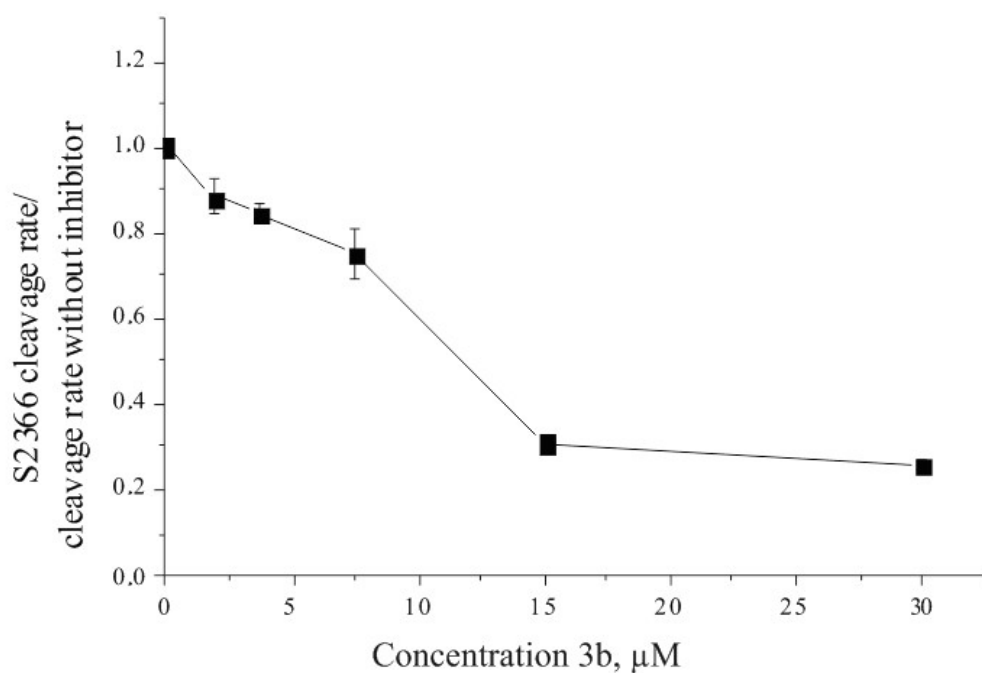


Figure S53. The dependence of inhibition of factor XIa-induced chromogenic substrate hydrolysis on the concentration of **3b**

The dependence of inhibition of factor Xa- and XIa-induced chromogenic substrate hydrolysis on the concentration of 3c

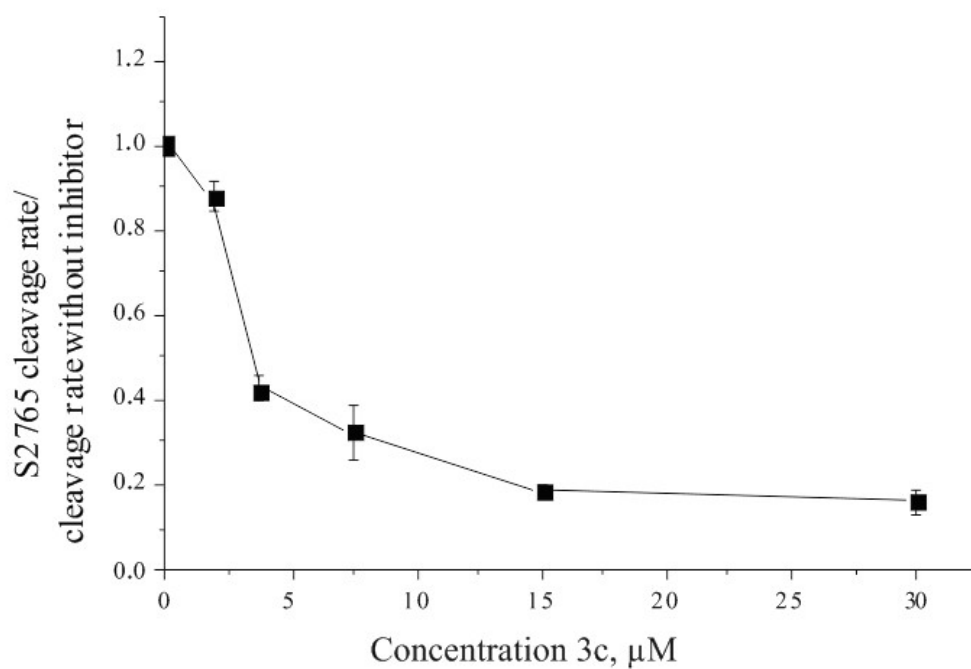


Figure S54. The dependence of inhibition of factor Xa-induced chromogenic substrate hydrolysis on the concentration of 3c

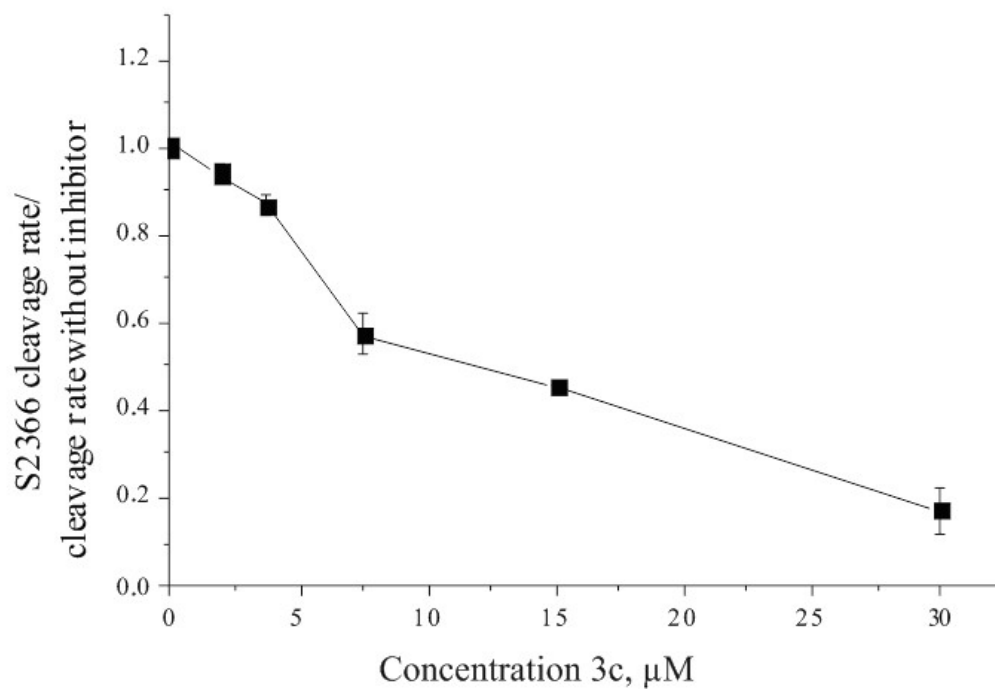


Figure S55. The dependence of inhibition of factor XIa-induced chromogenic substrate hydrolysis on the concentration of 3c

The dependence of inhibition of factor Xa- and XIa-induced chromogenic substrate hydrolysis on the concentration of 3e

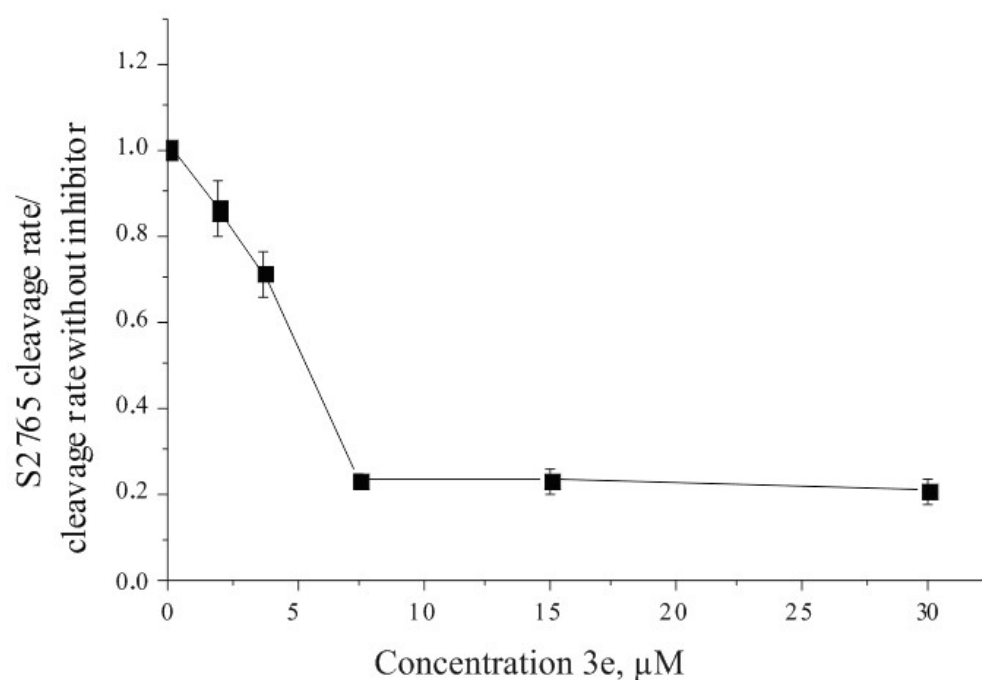


Figure S56. The dependence of inhibition of factor Xa-induced chromogenic substrate hydrolysis on the concentration of 3e

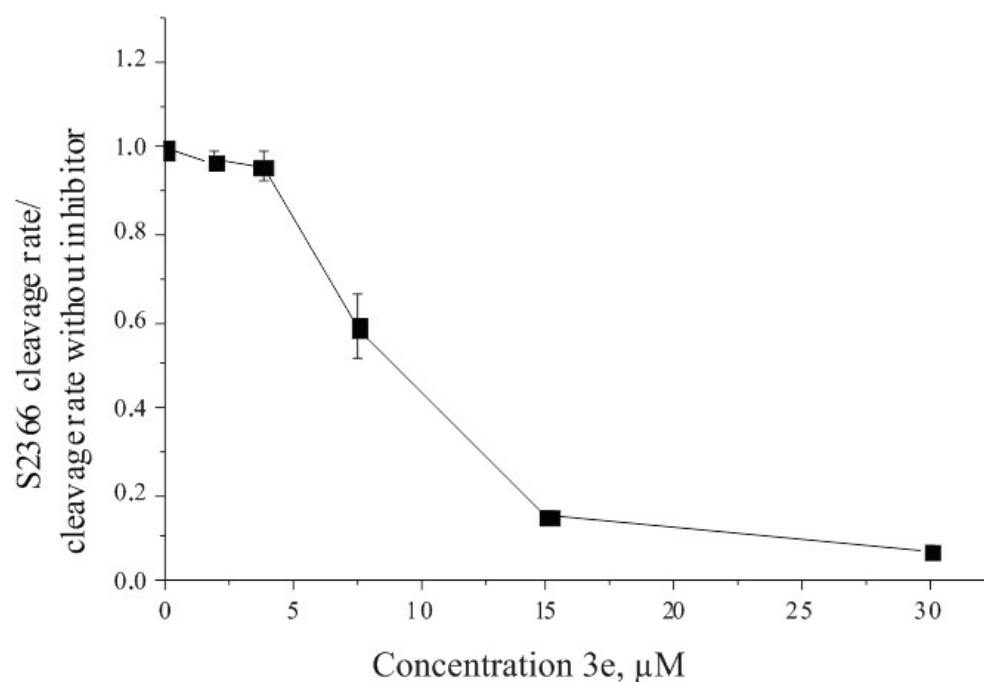


Figure S57. The dependence of inhibition of factor XIa-induced chromogenic substrate hydrolysis on the concentration of 3e

The dependence of inhibition of factor Xa- and XIa-induced chromogenic substrate hydrolysis on the concentration of 3f

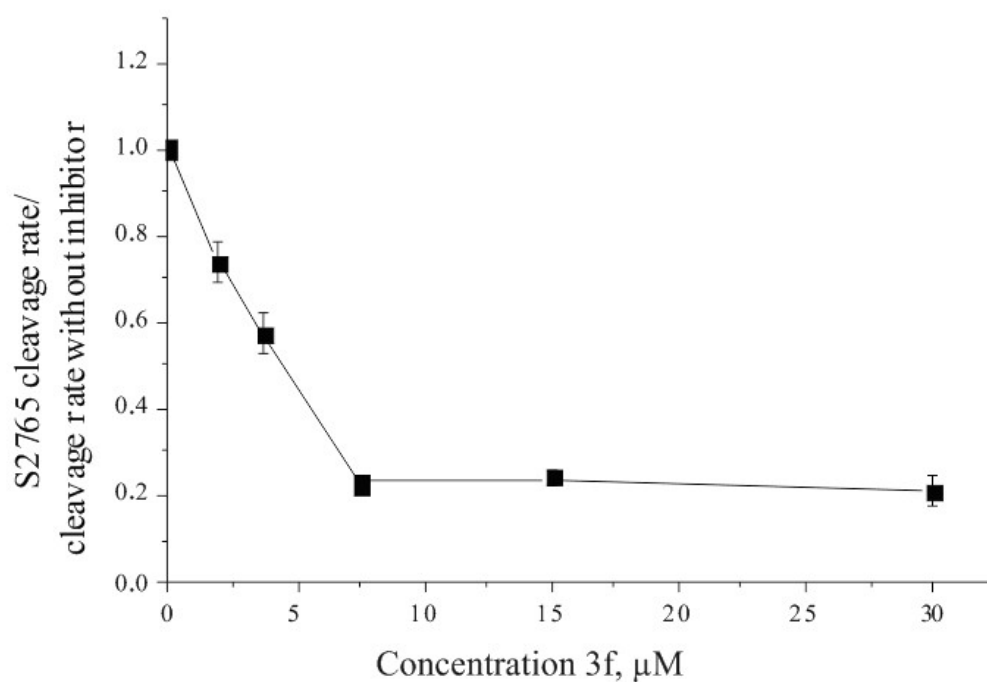


Figure S58. The dependence of inhibition of factor Xa-induced chromogenic substrate hydrolysis on the concentration of 3f

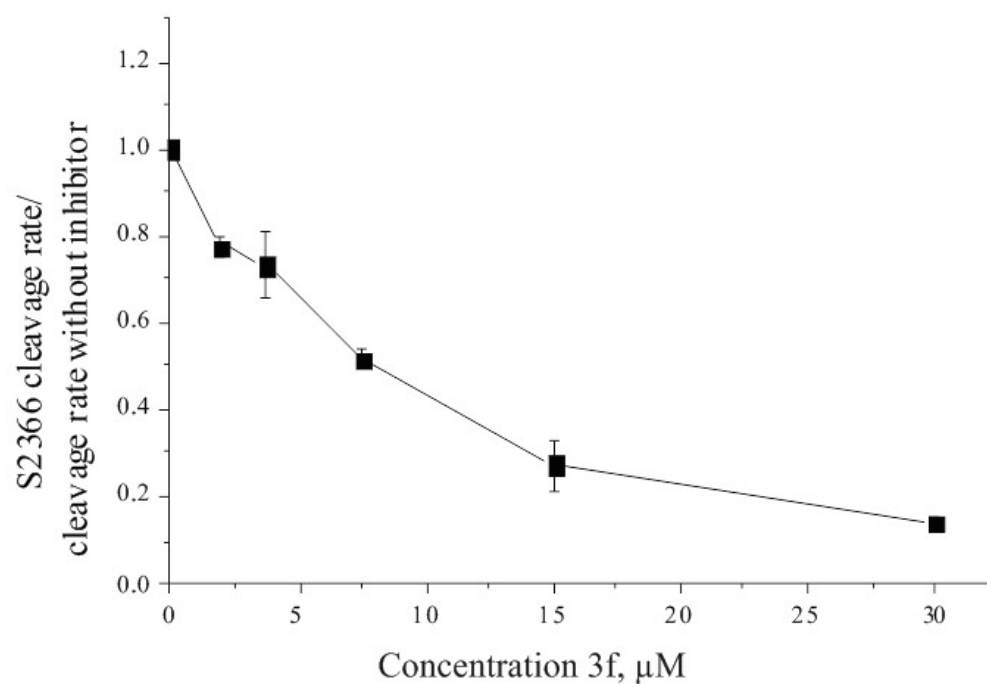


Figure S59. The dependence of inhibition of factor XIa-induced chromogenic substrate hydrolysis on the concentration of 3f

The dependence of inhibition of factor Xa- and XIa-induced chromogenic substrate hydrolysis on the concentration of 3k

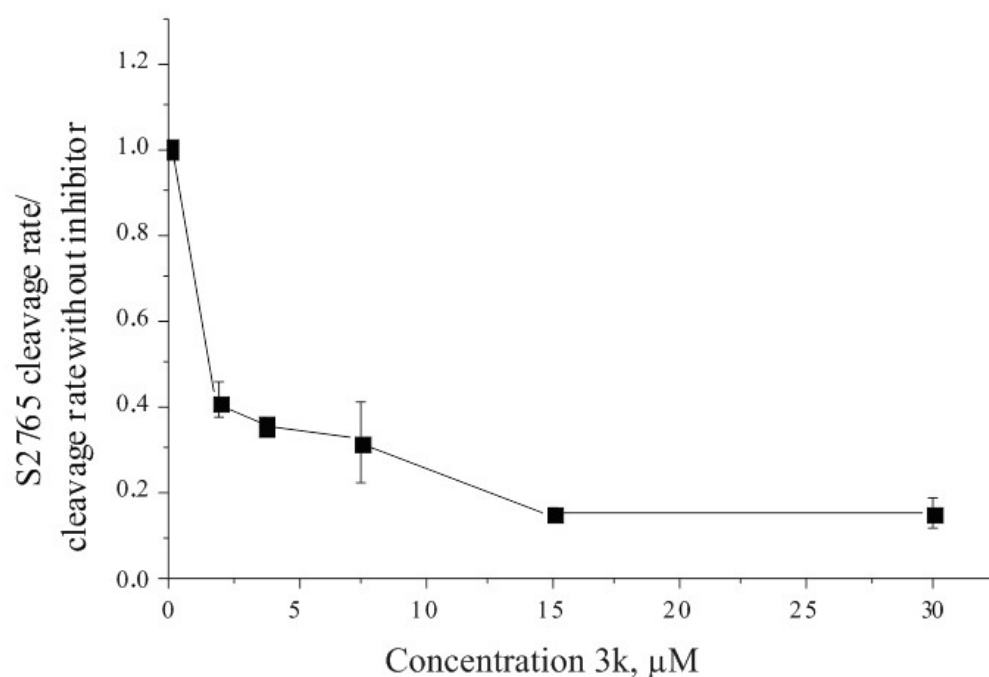


Figure S60. The dependence of inhibition of factor Xa-induced chromogenic substrate hydrolysis on the concentration of 3k

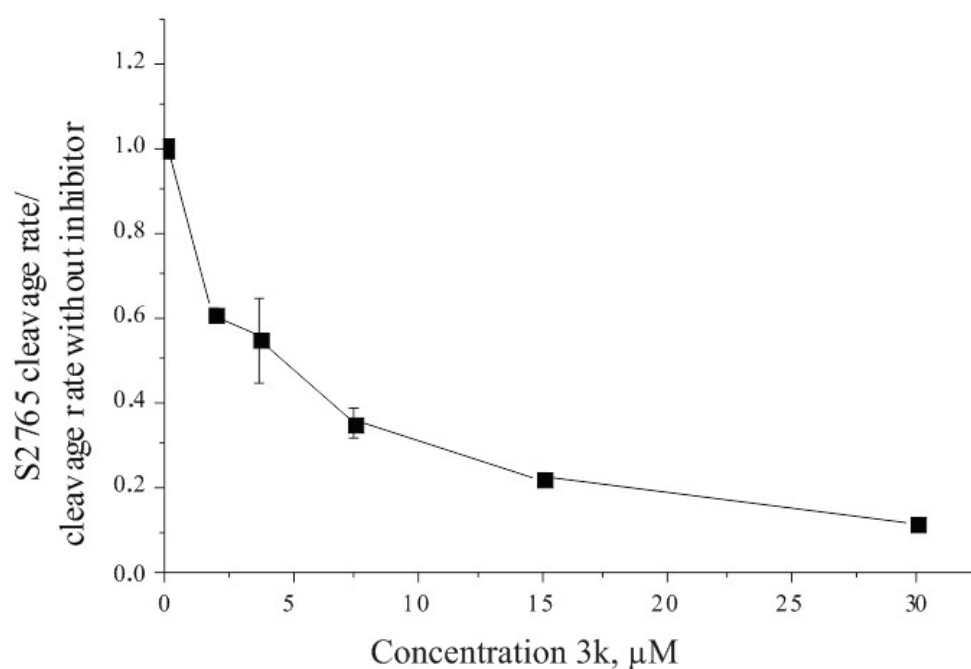


Figure S61. The dependence of inhibition of factor XIa-induced chromogenic substrate hydrolysis on the concentration of 3k

The dependence of inhibition of factor Xa- and XIa-induced chromogenic substrate hydrolysis on the concentration of 3l

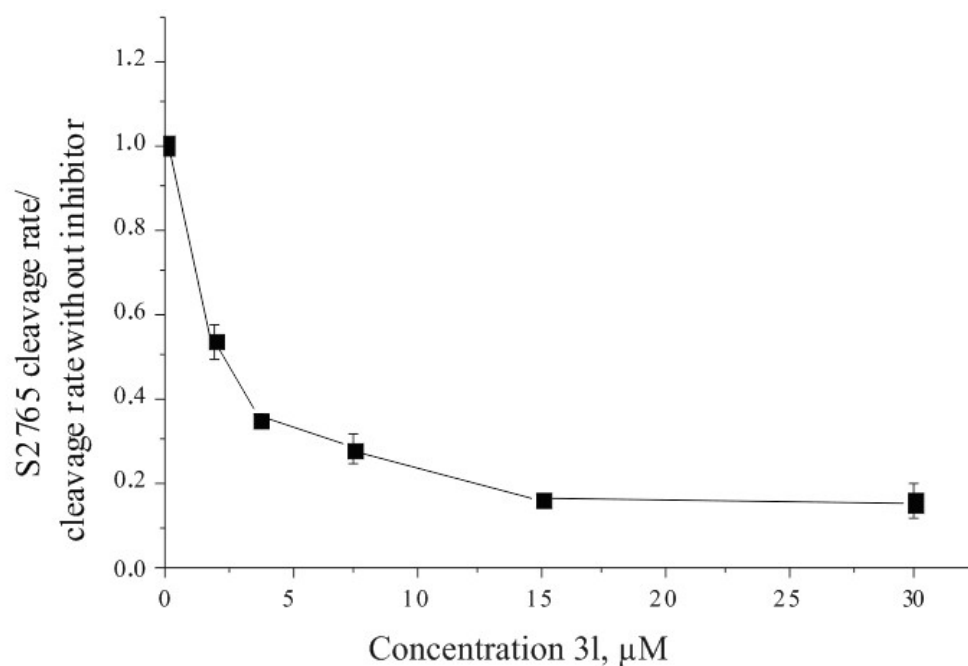


Figure S62. The dependence of inhibition of factor Xa-induced chromogenic substrate hydrolysis on the concentration of 3l

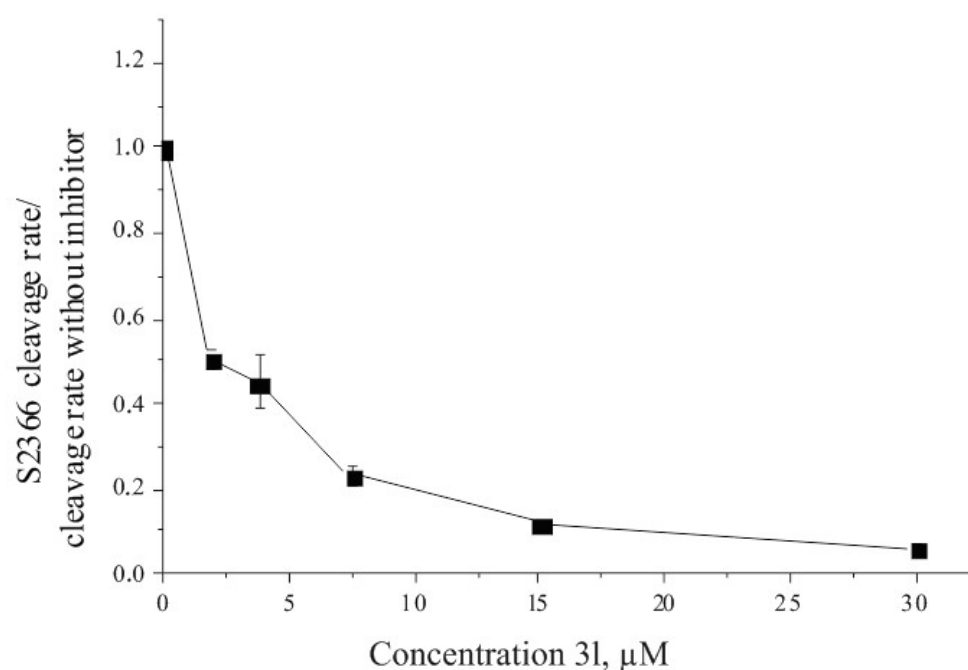


Figure S63. The dependence of inhibition of factor XIa-induced chromogenic substrate hydrolysis on the concentration of 3l

The dependence of inhibition of factor Xa- and XIa-induced chromogenic substrate hydrolysis on the concentration of 3n

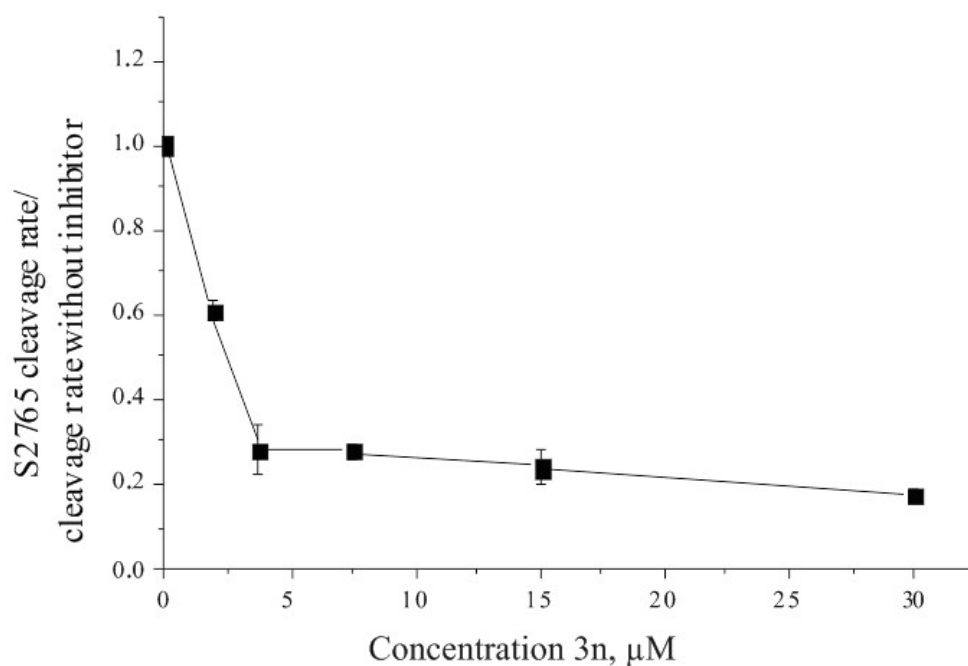


Figure S64. The dependence of inhibition of factor Xa-induced chromogenic substrate hydrolysis on the concentration of 3n

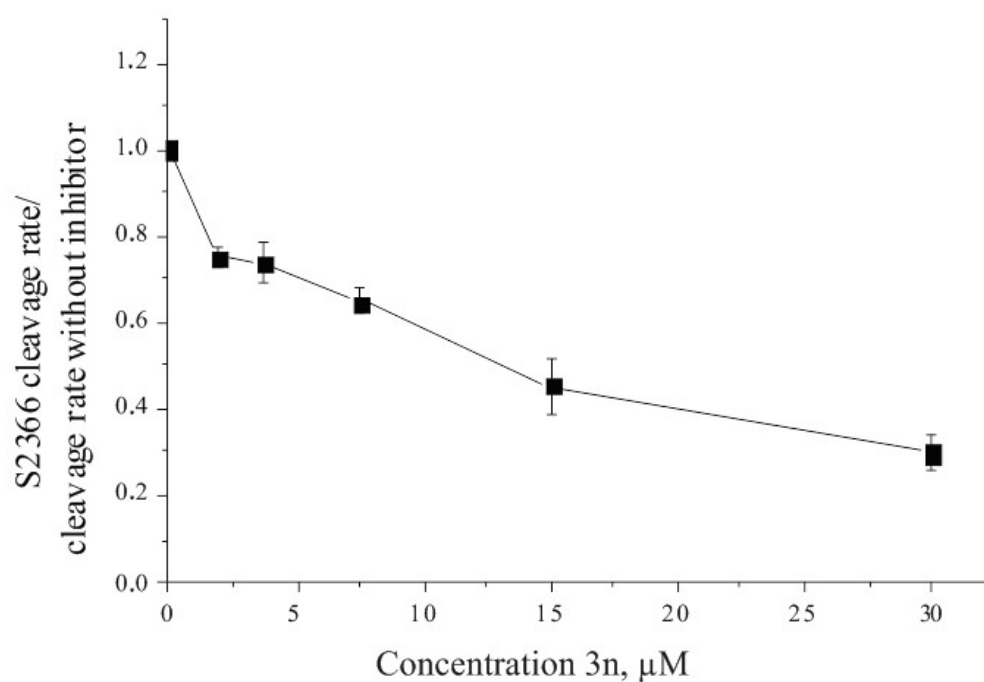


Figure S65. The dependence of inhibition of factor XIa-induced chromogenic substrate hydrolysis on the concentration of 3n

The dependence of inhibition of factor Xa- and XIa-induced chromogenic substrate hydrolysis on the concentration of 3o

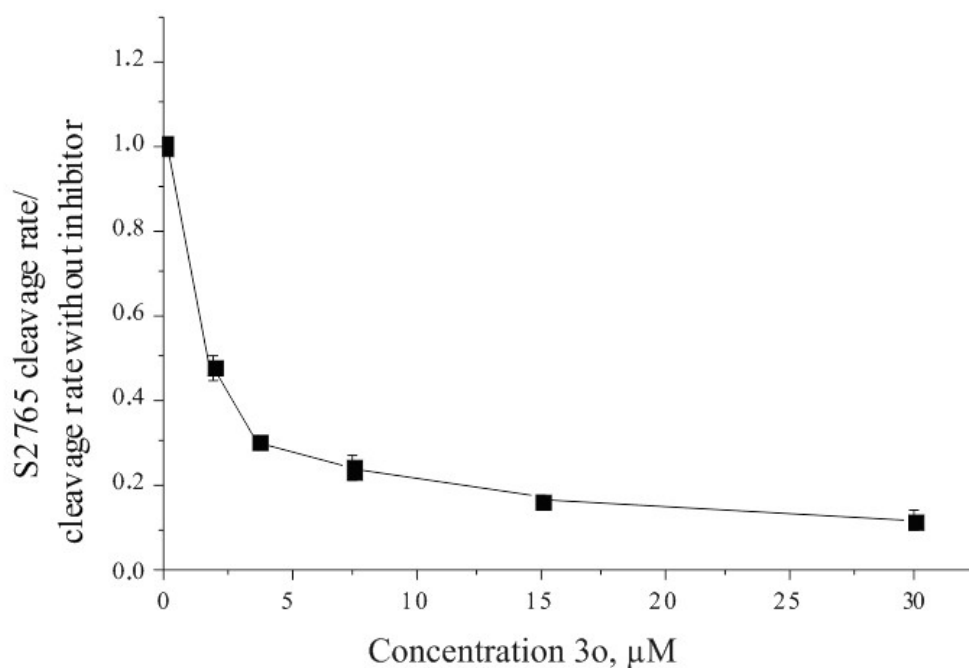


Figure S66. The dependence of inhibition of factor Xa-induced chromogenic substrate hydrolysis on the concentration of **3o**

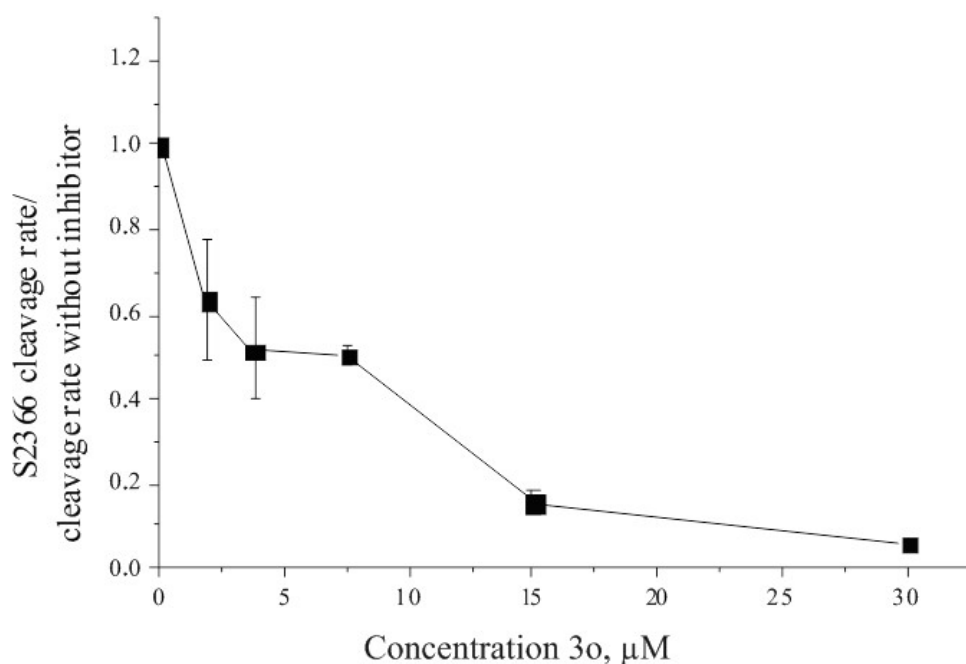


Figure S67. The dependence of inhibition of factor XIa-induced chromogenic substrate hydrolysis on the concentration of **3o**

The dependence of inhibition of factor Xa- and XIa-induced chromogenic substrate hydrolysis on the concentration of 3p

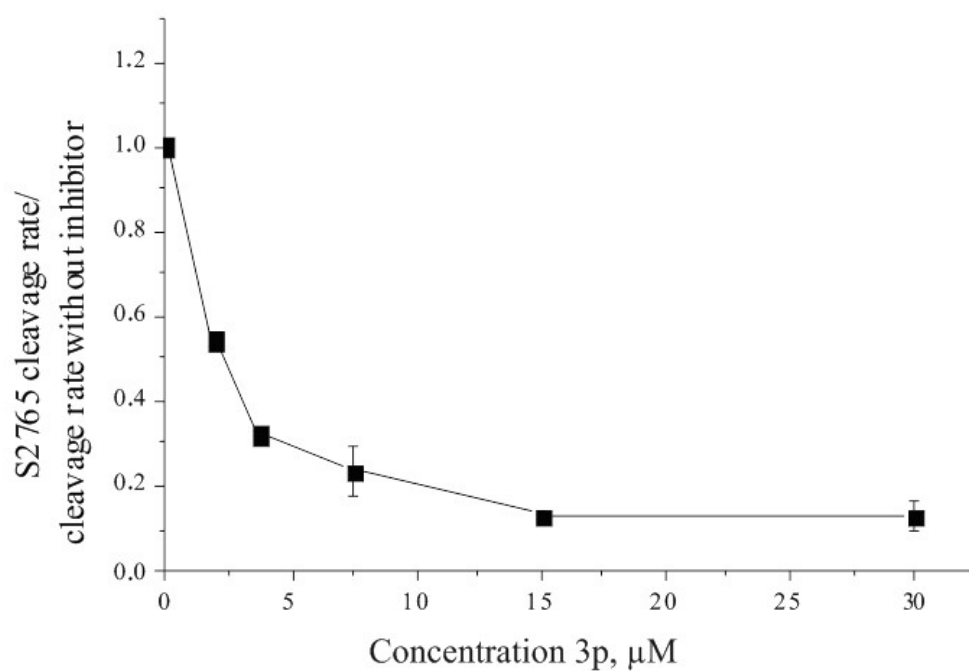


Figure S68. The dependence of inhibition of factor Xa-induced chromogenic substrate hydrolysis on the concentration of **3p**

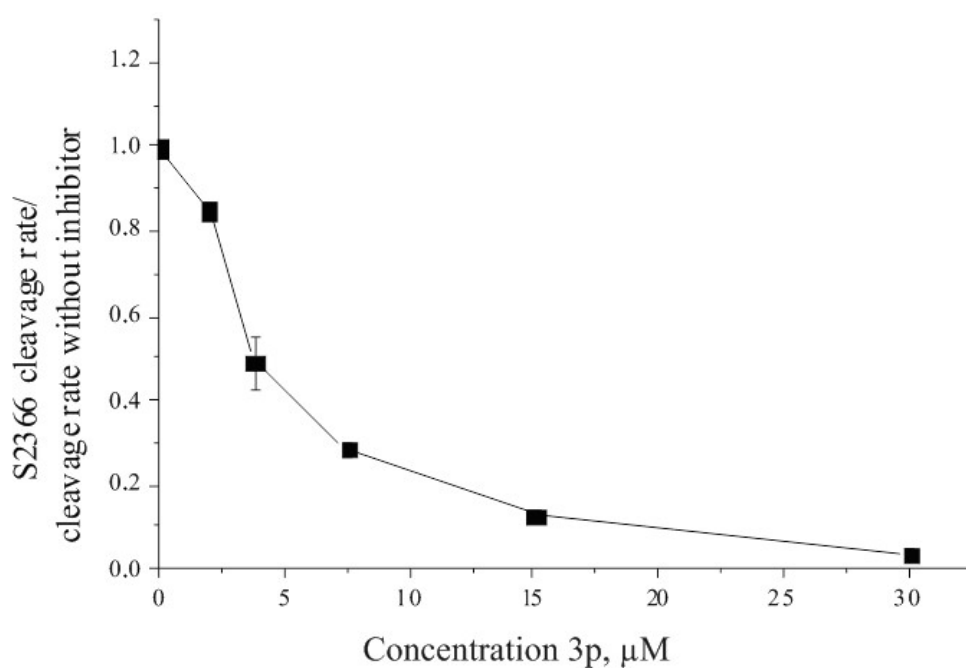


Figure S69. The dependence of inhibition of factor XIa-induced chromogenic substrate hydrolysis on the concentration of **3p**

LCMS analysis of the reaction mass after 1 h of interaction of compound 1b with thiosemicarbazide to obtain 2b

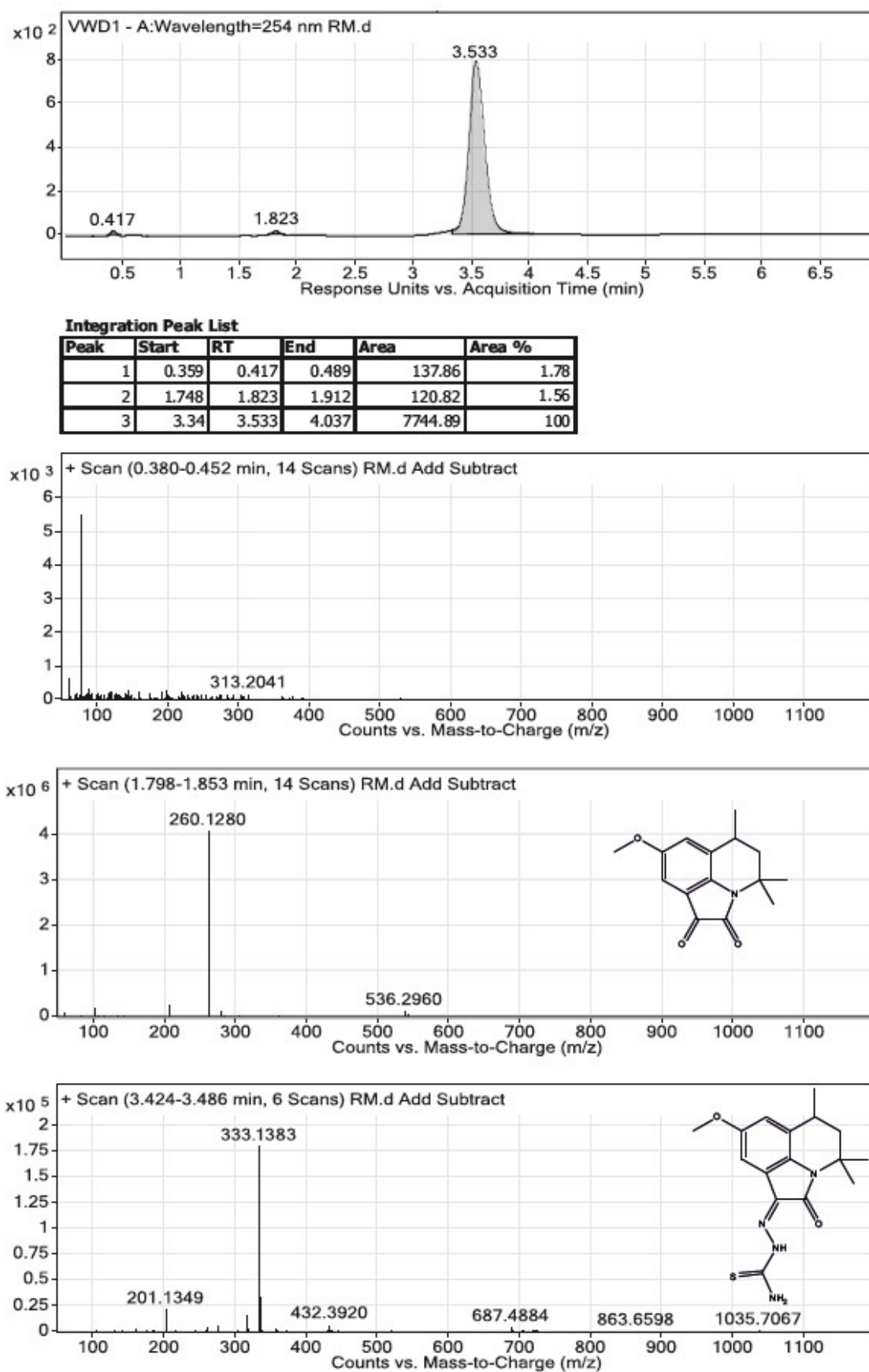


Figure S70. LCMS analysis of the reaction mass after 1 h of interaction of compound 1b with thiosemicarbazide to obtain 2b