База даних фізико-хімічних та спектральних властивостей синтезованих сполук-лідерів, перспективних інгібіторів протеаз M^{pro} та PL^{pro} коронавірусу SARS CoV 2

Я. В. Колесник, А.О. Гелеверя, П.В. Тростянко, С.М. Коваленко, Л.В. Євсєєва, А.Б. Захаров, В.В. Іванов, К.О. Логачева, О.В. Кириченко, Т.В. Черножук, О.М. Калугін

Науково-навчальний інститут хімії, Харківський національний університет імені В.Н. Каразіна, Харків, Україна
onkalugin@karazin.ua

Ключові слова: COVID-19, SARS-CoV-2, protease, M^{pro}, PL^{pro}; dual inhibitors

Abstract

This paper presents a series of molecular structures that demonstrate potential as inhibitors acting on M^{pro} proteases or simultaneously on M^{pro} and PL^{pro} proteases of the SARS-CoV-2 coronavirus.

In silico screening, pharmacophore filtering, and molecular docking of an evolutionary library based on the known inhibitor ML300 were performed. Virtual libraries were created using an evolutionary algorithm. By using pharmacophore filtering, we selected candidates that were subsequently ranked based on molecular docking calculations. The selected compounds were synthesized for further research.

This work contains data on the general physicochemical properties of the synthesized leading compounds, spectral characteristics, and chemical purity parameters of the samples.

Реферат

У даній роботі представлено серію молекулярних структур, які демонструють потенціал як інгібітори, що діють на протеази M^{pro} або одночасно на протеази M^{pro} і PL^{pro} коронавірусу SARS-CoV-2.

Було проведено *in silico* скринінг, фармакофорне фільтрування та молекулярний докінг еволюційної бібліотеки на основі відомого інгібітору ML300. Були створені віртуальні бібліотеки за допомогою еволюційного алгоритму. За допомогою фармакофорного фільтрування ми відібрали кандидати, які згодом були проранжовані на основі розрахунків молекулярного докінгу. Відібрані сполуки були синтезовані для подальших досліджень.

Дана робота містить дані щодо загальних фізико-хімічних властивостей синтезованих сполук-лідерів, спектральні характеристики та параметри хімічної чистоти зразків.

Зміст

Вступ

У даній роботі представлено серію молекулярних структур, які демонструють потенціал як інгібітори, що діють на протеази M^{pro} або одночасно на протеази M^{pro} і PL^{pro} коронавірусу SARS-CoV-2. Роботу виконано у рамках проекту «Молекулярний дизайн, синтез та скринінг нових потенційних противірусних фармацевтичних інгредієнтів для терапії інфекційного захворювання COVID-19» (Grant No. 96/0062 (2021.01/0062).

Ми провели *in silico* скринінг, фармакофорне фільтрування та молекулярний докінг еволюційної бібліотеки на основі відомого інгібітору ML300. Віртуальні бібліотеки з 2565 та 11367 аналогами ML300 були створені за допомогою еволюційного алгоритму, що імітує природну еволюцію лікарських сполук. За допомогою фармакофорного фільтрування ми відібрали кандидати, які згодом були проранжовані на основі розрахунків молекулярного докінгу. Крім того, ми оцінили силу зв'язування вибраних кандидатів до звичайних та резистентних до ліків варіантів SARS-CoV-2, включаючи Delta та Omicron.

Відібрані сполуки були синтезовані [1-3] для подальших досліджень.

У даній роботі наведено дані щодо загальних фізико-хімічних властивостей синтезованих сполук-лідерів, спектральні характеристики та параметри хімічної чистоти зразків. У таблицях 1-2 наведено обчислені енергії зв’язування обраних сполук з протеазами M^{pro} і PL^{pro}.

Подяки

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Таблиця 1. Результати молекулярного докінгу досліджуваних лігандів (енергія зв'язування з M^{pro}

Ліганд	Енергія зв'язування, kcal/mol	
	PDB: 7LME	PDB: 8R24
ML300	-7.8	-8.0
1a	-7.0	-7.5
1b	-6.7	-7.6
1c	-6.8	-7.2
1d	-7.3	-7.3
1e	-7.2	-7.2
1f	-7.3	-7.2
1g	-7.6	-7.8
1h	-6.9	-7.7
1i	-7.3	-7.4
1j	-5.9	-6.6
1k	-6.4	-6.7
1l	-6.9	-6.8
1m	-6.1	-6.6
1o	-6.8	-6.6
1p	-6.5	-6.7
1r	-6.5	-6.6
1s	-6.0	-6.5
1t	-7.0	-6.8
1u	-6.7	-6.5
1w	-6.4	-6.5
1x	-6.8	-6.6
2a	-6.7	-6.4
2b	-6.2	-6.3
2c	-7.9	-7.7
2d	-8.1	-8.1
3a	-7.0	-6.9
3b	-7.0	-7.0
3c	-7.1	-8.1
3d	-8.5	-8.4
4a	-6.5	-7.0
4b	-7.0	-7.0
4c	-6.8	-7.0
4d	-6.8	-7.1
4e	-6.6	-6.8
4f	-6.8	-6.7
4g	-7.3	-7.3
4h	-7.1	-7.5
4i	-7.1	-7.9

6a		-8.3

Таблиця 2. Результати молекулярного докінгу перспективних дуальних інгібіторів (енергія зв'язування з M^{pro} та PL^{pro}) для структур **5a-5q**.

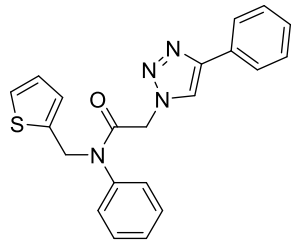
Ліганд	Енергія зв'язування, kcal/mol	
	PL^{pro} PDB ID: 7LBR	M^{pro} PDB ID: 7EN9
Reference *	-9.5	-8.7
5a	-9.9	-9.0
5b	-9.6	-8.6
5c	-9.8	-8.6
5d	-9.9	-9.4
5e	-10.1	-8.9
5f	-10.1	-9.6
5g	-10.0	-8.4
5h	-10.2	-7.9
5i	-10.2	-7.8
5j	-9.6	-7.5
5k	-10.2	-8.9
5l	-9.7	-9.8
5m	-10.6	-7.6
5n	-9.7	-7.9
5o	-10.2	-8.5
5p	-9.6	-8.4
5q	-10.2	-8.5

* - binding parameters of the reference ligands (WU-02 for 7EN9 and XR8-89 for 7LBR, designated as "Reference")

Похідні 1*H*-1,2,3-триазолацетамідів 1a-1x

Речовина **1a**. Нековалентний інгібітор головної протеази SARS-CoV-2 M^{pro}.

Назва: *N-Phenyl-2-(4-phenyl-1H-1,2,3-triazol-1-yl)-N-(thiophen-2-ylmethyl)acetamide*



White solid. Yield 87 %

Спектральні параметри:

^{1}H NMR (400 MHz, DMSO-D_6) δ 8.42 (s, 1H), 7.84 – 7.77 (m, 2H), 7.51 – 7.37 (m, 7H), 7.36 – 7.23 (m, 4H), 6.88 (dd, *J* = 5.1, 3.4 Hz, 1H), 6.82 (d, *J* = 3.4 Hz, 1H), 5.03 (d, *J* = 13.5 Hz, 4H).

^{13}C NMR (101 MHz, DMSO-D_6) δ 165.50, 146.55, 140.22, 139.31, 131.25, 130.43, 129.47, 129.26, 128.88, 128.36, 128.00, 127.13, 126.87, 125.63, 123.55, 51.67, 48.02

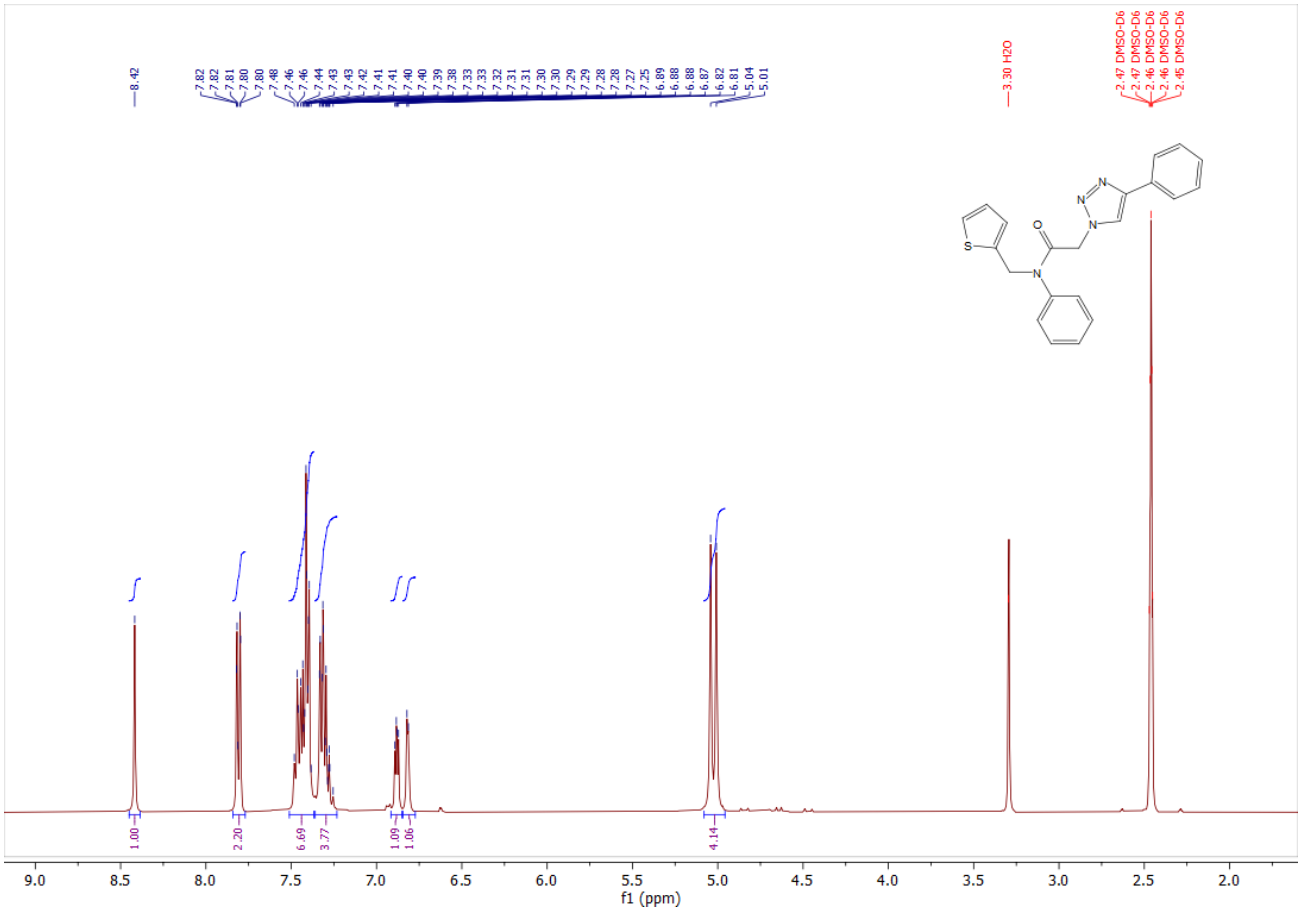


Рисунок 1. ^{1}H NMR spectrum (400 MHz, DMSO-D_6) *N-Phenyl-2-(4-phenyl-1H-1,2,3-triazol-1-yl)-N-(thiophen-2-ylmethyl)acetamide* **1a**

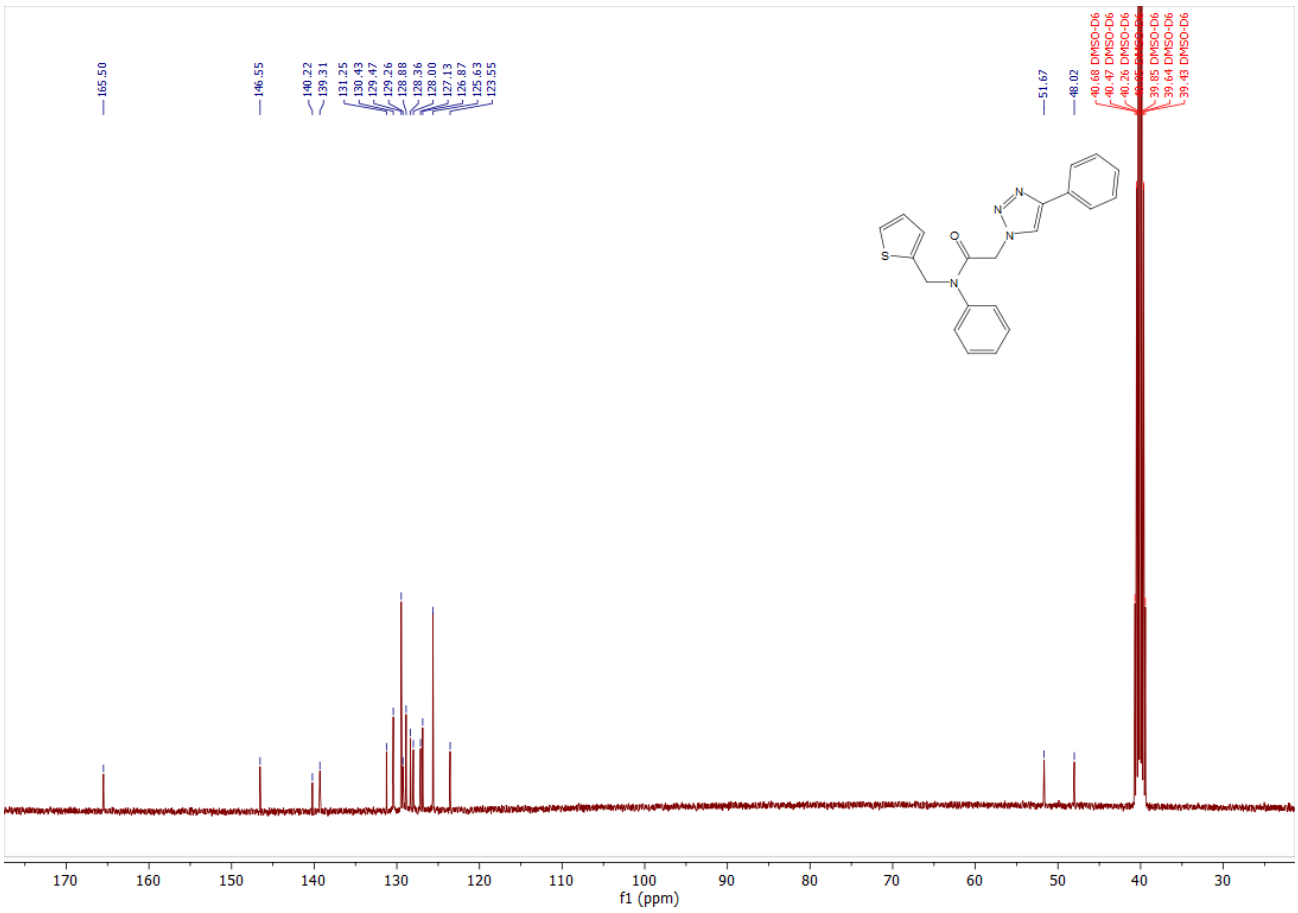
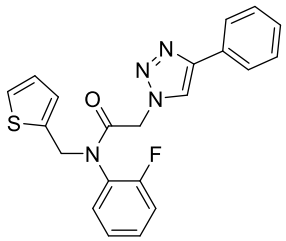


Рисунок 2. ^{13}C NMR spectrum (101 MHz, DMSO-D_6) *N-Phenyl-2-(4-phenyl-1H-1,2,3-triazol-1-yl)-N-(thiophen-2-ylmethyl)acetamide* **1a**

Речовина **1b**. Нековалентний інгібітор головної протеази SARS-CoV-2 M^{pro}.

Назва: *N-(2-Fluorophenyl)-2-(4-phenyl-1H-1,2,3-triazol-1-yl)-N-(thiophen-2-ylmethyl)acetamide*



Yellow solid. Yield 93 %

Спектральні параметри:

^{1}H NMR (400 MHz, DMSO-D_6) δ 8.46 (s, 1H), 7.83 – 7.79 (m, 2H), 7.52 – 7.45 (m, 1H), 7.44 – 7.36 (m, 6H), 7.32 – 7.25 (m, 3H), 6.87 (dd, J = 5.1, 3.4 Hz, 1H), 6.81 (dd, J = 3.5, 1.2 Hz, 1H), 5.20 – 5.05 (m, 2H), 4.91 (dd, J = 37.1, 16.0 Hz, 2H).

^{13}C NMR (101 MHz, DMSO-D_6) δ 165.85, 159.39, 156.91, 146.61, 138.50, 131.87, 131.79, 131.41, 131.20, 129.52, 129.47, 128.37, 127.22, 127.14, 127.08, 126.34, 126.22, 126.18, 125.64, 123.65, 117.68, 117.48, 51.44, 47.21.

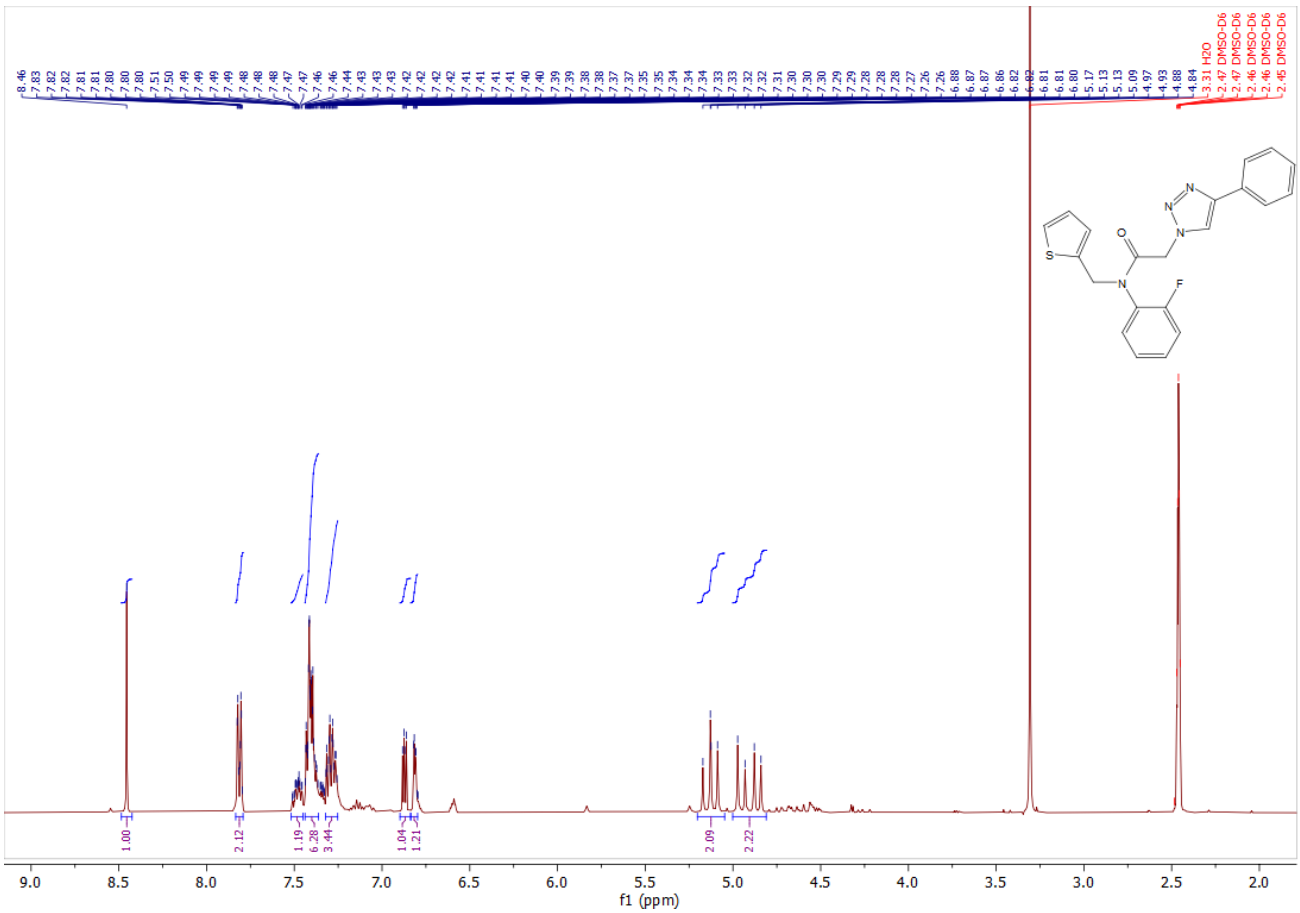


Рисунок 3. ^{1}H NMR spectrum (400 MHz, DMSO-D_6) *N-(2-Fluorophenyl)-2-(4-phenyl-1H-1,2,3-triazol-1-yl)-N-(thiophen-2-ylmethyl)acetamide* **1b**

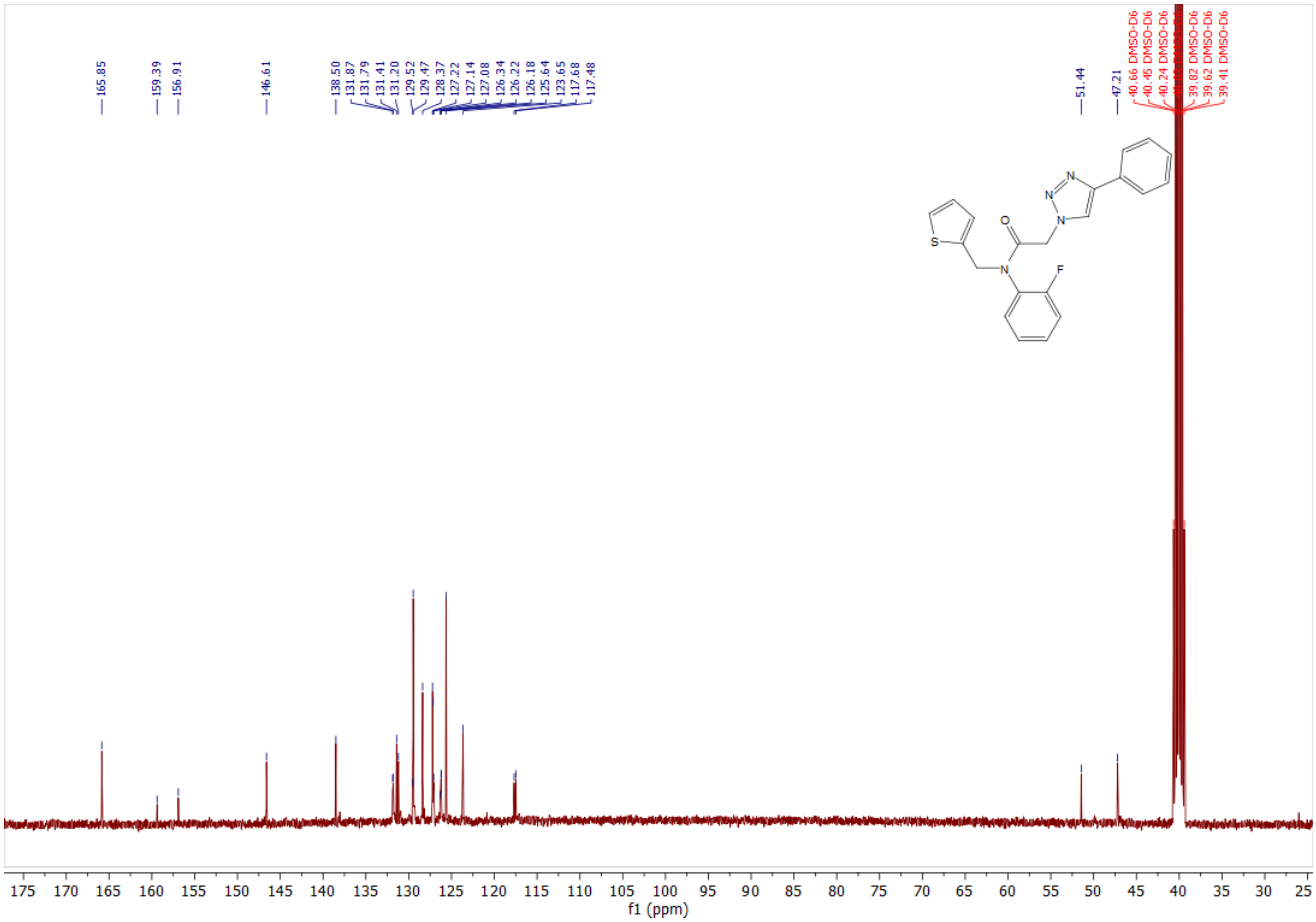
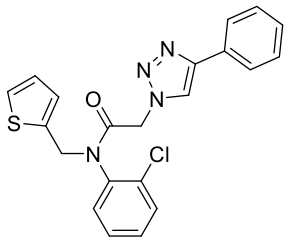


Рисунок 4. ^{13}C NMR spectrum (101 MHz, DMSO-D_6) *N-(2-Fluorophenyl)-2-(4-phenyl-1H-1,2,3-triazol-1-yl)-N-(thiophen-2-ylmethyl)acetamide* **1b**

Речовина **1c**. Нековалентний інгібітор головної протеази SARS-CoV-2 M^{pro}.

Назва: *N-(2-Chlorophenyl)-2-(4-phenyl-1H-1,2,3-triazol-1-yl)-N-(thiophen-2-ylmethyl)acetamide*



Yellow solid. Yield 92 %

Спектральні параметри:

^{1}H NMR (400 MHz, DMSO-D_6) δ 8.44 (s, 1H), 7.86 – 7.78 (m, 2H), 7.69 (dd, J = 7.9, 1.5 Hz, 1H), 7.48 (td, J = 7.7, 1.8 Hz, 1H), 7.42 (dddd, J = 9.7, 6.1, 3.3, 1.8 Hz, 4H), 7.32 – 7.25 (m, 2H), 6.89 (dd, J = 5.1, 3.4 Hz, 1H), 6.82 (dd, J = 3.4, 1.2 Hz, 1H), 5.27 (d, J = 0.8 Hz, 1H), 5.09 (d, J = 16.9 Hz, 1H), 4.79 (d, J = 16.8 Hz, 1H), 4.59 (d, J = 15.1 Hz, 1H).

^{13}C NMR (101 MHz, DMSO-D_6) δ 165.63, 146.65, 138.27, 136.84, 132.82, 131.97, 131.60, 131.31, 131.20, 129.46, 129.31, 128.73, 128.38, 127.35, 127.17, 125.66, 123.61, 51.63, 46.73.

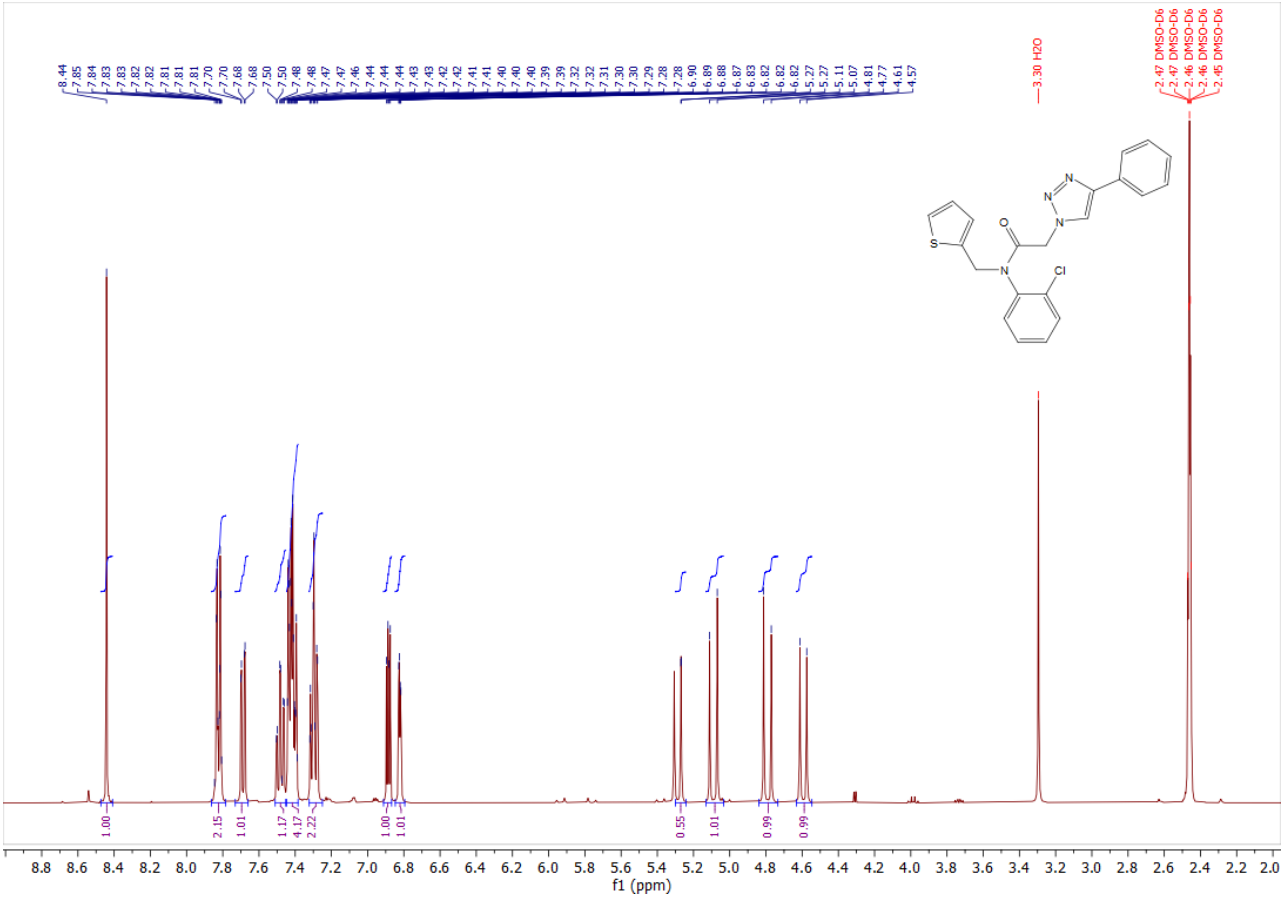


Рисунок 5. ^{1}H NMR spectrum (400 MHz, DMSO-D_6) *N-(2-Chlorophenyl)-2-(4-phenyl-1H-1,2,3-triazol-1-yl)-N-(thiophen-2-ylmethyl)acetamide* **1c**

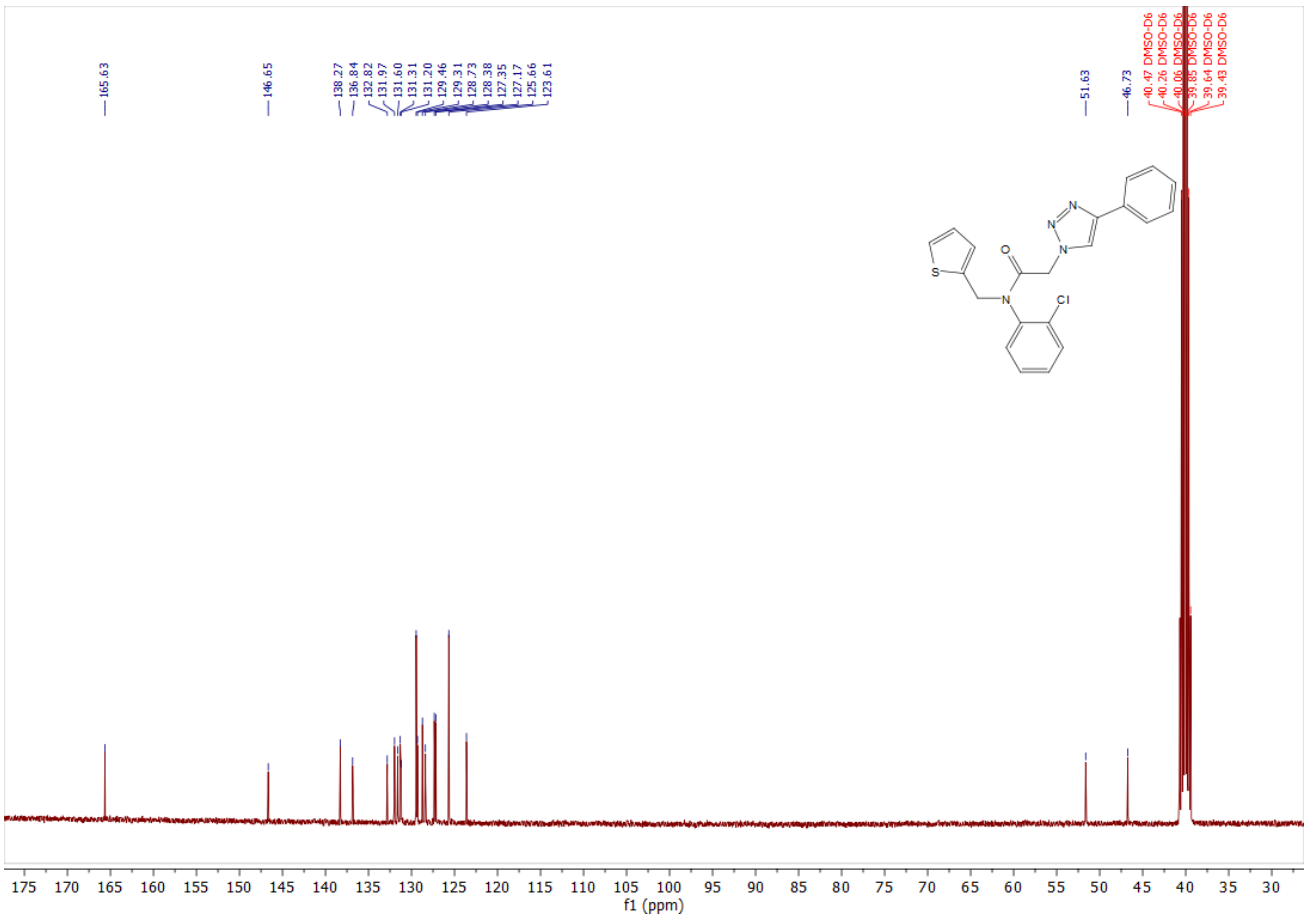
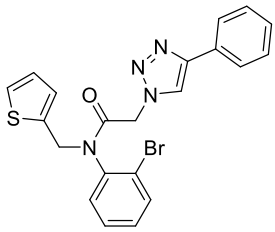


Рисунок 6. ^{13}C NMR spectrum (101 MHz, DMSO-D_6) *N-(2-Chlorophenyl)-2-(4-phenyl-1H-1,2,3-triazol-1-yl)-N-(thiophen-2-ylmethyl)acetamide* **1c**

Речовина **1d**. Нековалентний інгібітор головної протеази SARS-CoV-2 M^{pro}.

Назва: *N-(2-Bromophenyl)-2-(4-phenyl-1H-1,2,3-triazol-1-yl)-N-(thiophen-2-ylmethyl)acetamide*



White solid. Yield 87 %

Спектральні параметри:

^{1}H NMR (400 MHz, DMSO-D_6) δ 8.45 (s, 1H), 7.84 – 7.77 (m, 2H), 7.55 – 7.32 (m, 7H), 7.28 (td, *J* = 7.1, 1.6 Hz, 1H), 7.14 (ddt, *J* = 6.4, 1.8, 0.9 Hz, 1H), 6.98 (dd, *J* = 6.5, 5.3 Hz, 1H), 5.24 (d, *J* = 0.9 Hz, 2H), 5.08 (d, *J* = 0.9 Hz, 2H).

^{13}C NMR (101 MHz, DMSO-D_6) δ 166.61, 150.60, 139.05, 138.19, 133.67, 130.38, 129.65, 129.30, 128.92, 128.79, 127.33, 127.23, 125.58, 125.56, 124.81, 120.54, 119.85, 52.83, 44.17.

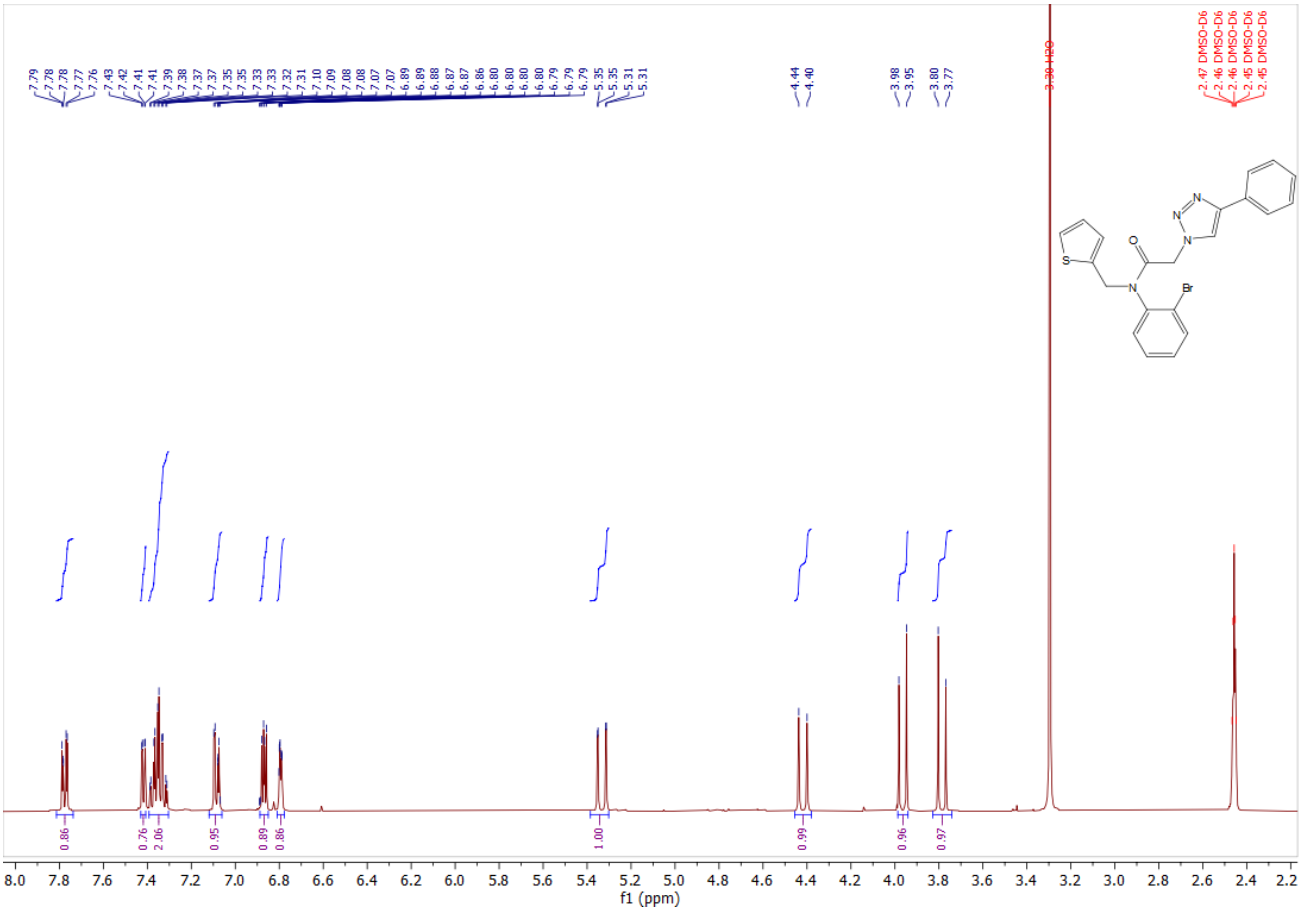


Рисунок 7. ^{1}H NMR spectrum (400 MHz, DMSO-D_6) *N-(2-Bromophenyl)-2-(4-phenyl-1H-1,2,3-triazol-1-yl)-N-(thiophen-2-ylmethyl)acetamide* **1d**

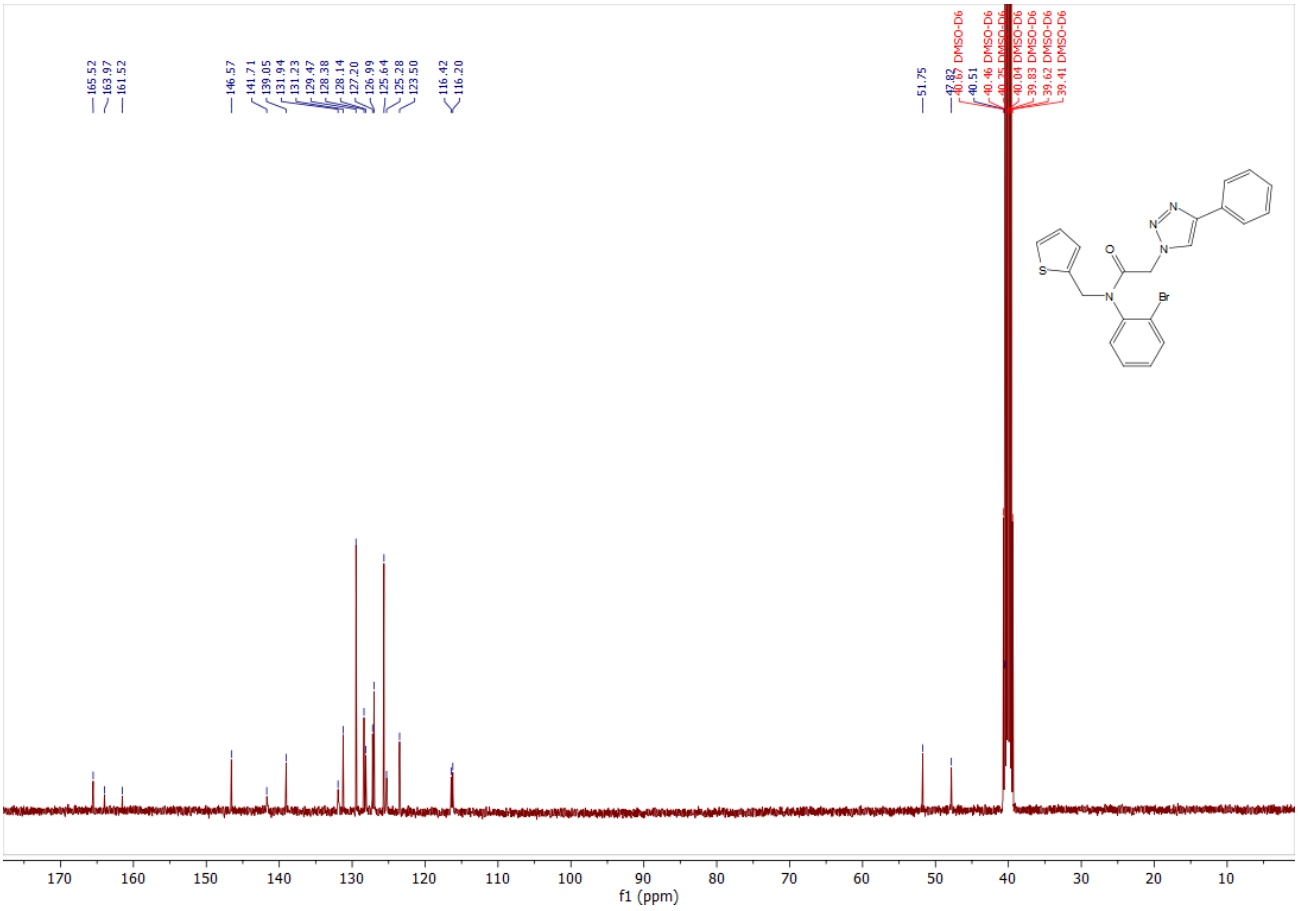
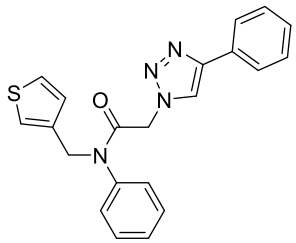


Рисунок 8. ^{13}C NMR spectrum (101 MHz, DMSO-D_6) *N-(2-Bromophenyl)-2-(4-phenyl-1H-1,2,3-triazol-1-yl)-N-(thiophen-2-ylmethyl)acetamide* **1d**

Речовина **1e**. Нековалентний інгібітор головної протеази SARS-CoV-2 M^{pro}.

Назва: *N-Phenyl-2-(4-phenyl-1H-1,2,3-triazol-1-yl)-N-(thiophen-3-ylmethyl)acetamide*



White solid. Yield 89 %

Спектральні параметри:

^{1}H NMR (400 MHz, DMSO-D_6) δ 8.43 (s, 1H), 7.86 – 7.76 (m, 2H), 7.48 – 7.22 (m, 10H), 6.99 – 6.91 (m, 1H), 5.06 (s, 2H), 4.85 (s, 2H).

^{13}C NMR (101 MHz, DMSO-D_6) δ 165.54, 146.54, 140.67, 138.01, 131.27, 130.38, 129.47, 129.10, 128.81, 128.35, 128.26, 127.07, 125.62, 123.93, 123.56, 51.75, 48.61.

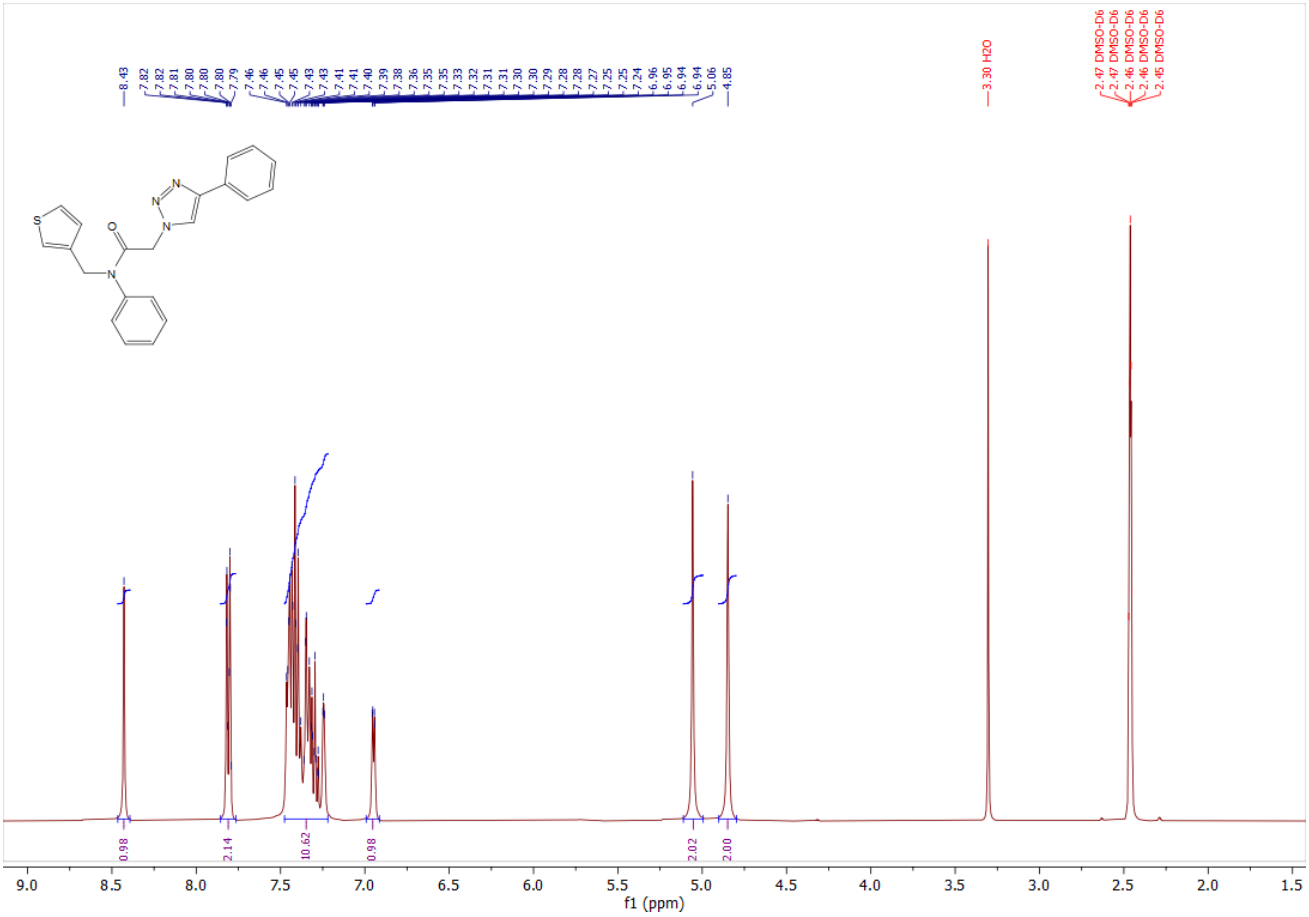


Рисунок 9. ^{1}H NMR spectrum (400 MHz, DMSO-D_6) *N-Phenyl-2-(4-phenyl-1H-1,2,3-triazol-1-yl)-N-(thiophen-3-ylmethyl)acetamide* **1e**

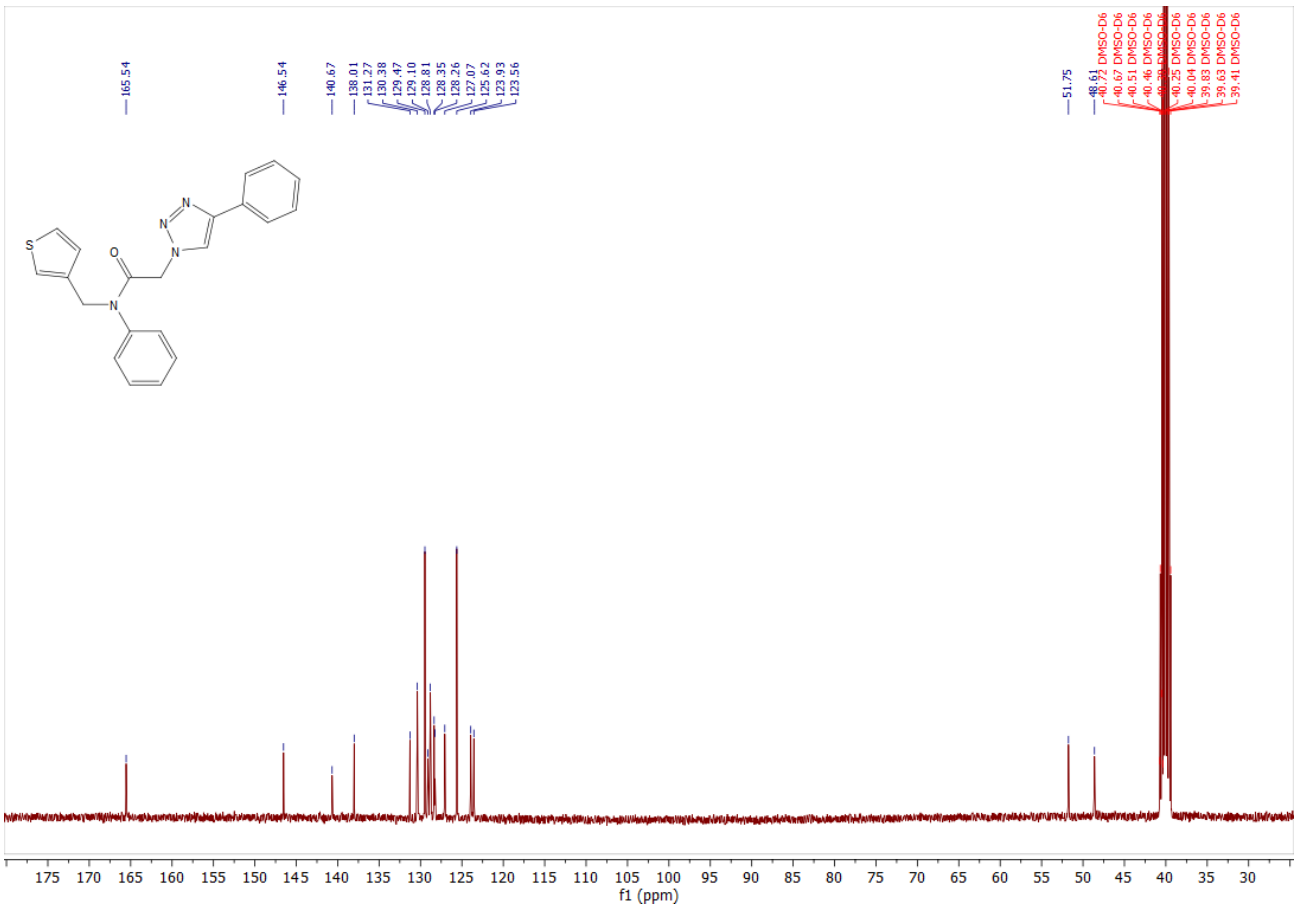
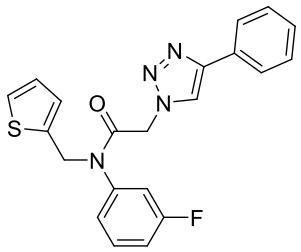


Рисунок 10. ^{13}C NMR spectrum (101 MHz, DMSO-D_6) *N-Phenyl-2-(4-phenyl-1H-1,2,3-triazol-1-yl)-N-(thiophen-3-ylmethyl)acetamide* **1e**

Речовина **1f**. Нековалентний інгібітор головної протеази SARS-CoV-2 M^{pro}.

Назва: *N-(3-Fluorophenyl)-2-(4-phenyl-1H-1,2,3-triazol-1-yl)-N-(thiophen-2-ylmethyl)acetamide*



White solid. Yield 88 %

Спектральні параметри:

^{1}H NMR (400 MHz, DMSO-D_6) δ 8.41 (s, 1H), 7.85 – 7.77 (m, 2H), 7.49 (q, J = 7.6 Hz, 1H), 7.44 – 7.38 (m, 3H), 7.34 – 7.22 (m, 3H), 7.20 – 7.14 (m, 1H), 6.93 – 6.79 (m, 2H), 5.08 (d, J = 39.2 Hz, 4H).

^{13}C NMR (101 MHz, DMSO-D_6) δ 165.52, 163.97, 161.52, 146.57, 141.71, 139.05, 131.94, 131.23, 129.47, 128.38, 128.14, 127.20, 126.99, 125.64, 125.28, 123.50, 116.42, 116.20, 51.75, 47.82.

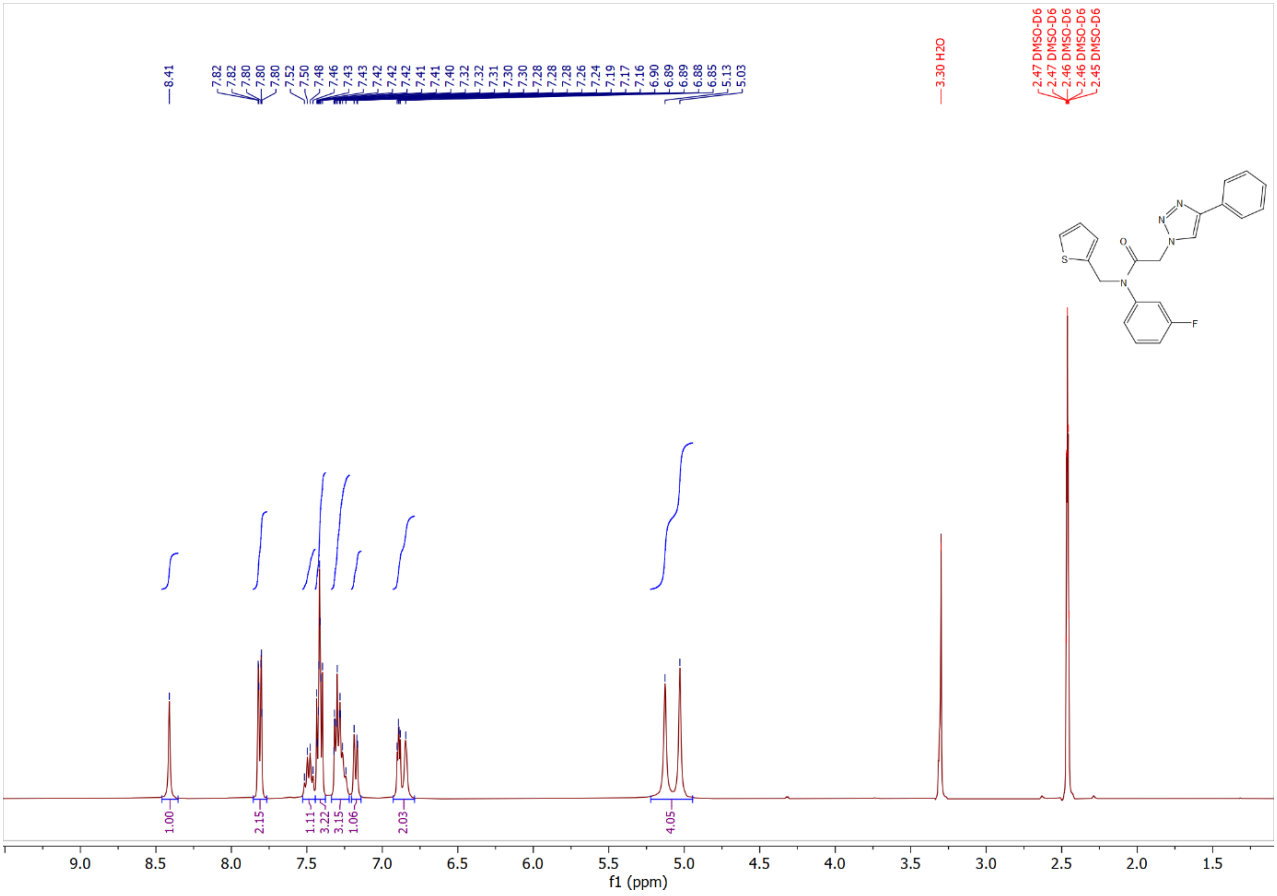


Рисунок 11. ^{1}H NMR spectrum (400 MHz, DMSO-D_6) *N-(3-Fluorophenyl)-2-(4-phenyl-1H-1,2,3-triazol-1-yl)-N-(thiophen-2-ylmethyl)acetamide* **1f**

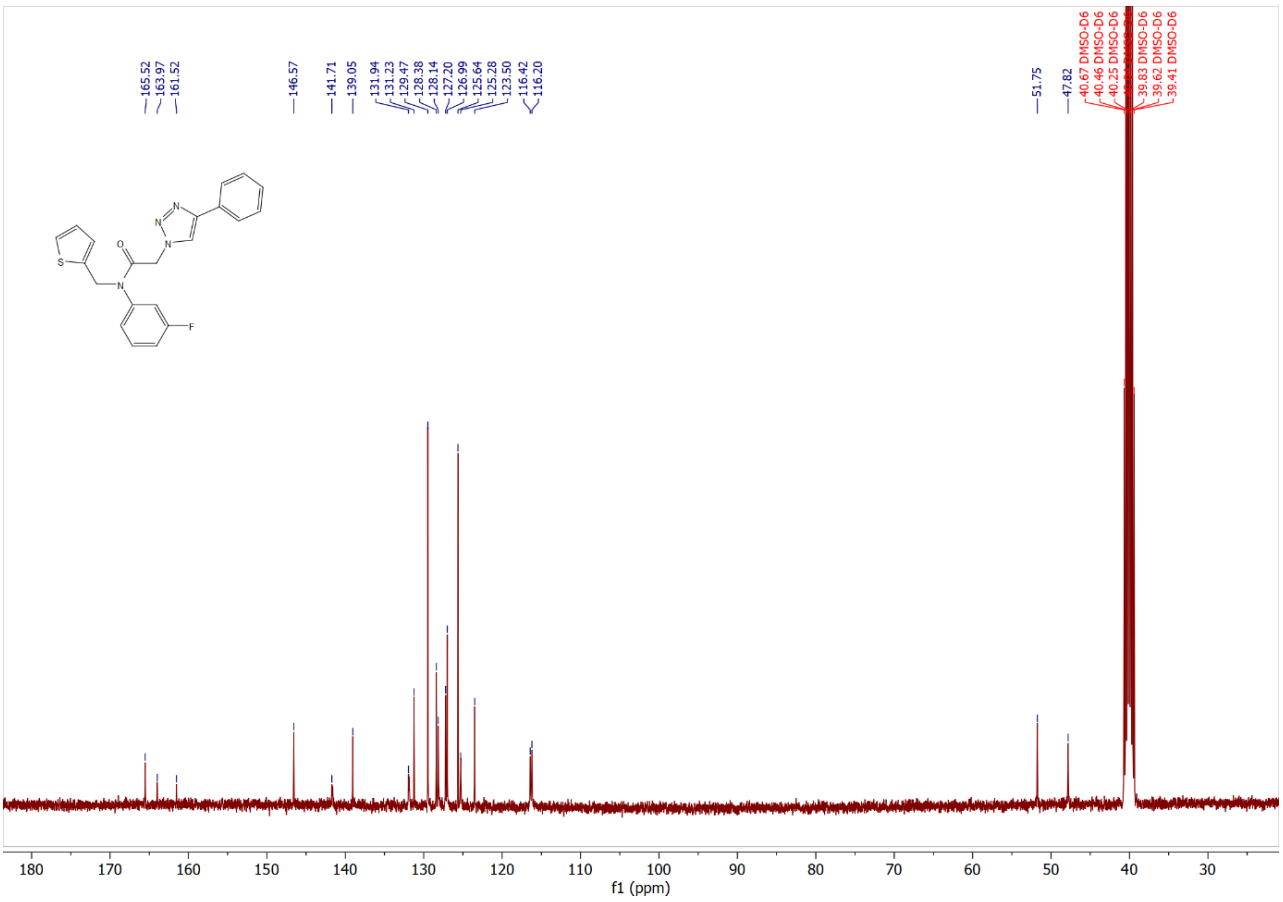
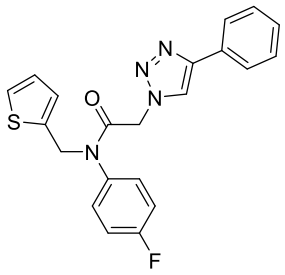


Рисунок 12. ^{13}C NMR spectrum (101 MHz, DMSO-D_6) *N-(3-Fluorophenyl)-2-(4-phenyl-1H-1,2,3-triazol-1-yl)-N-(thiophen-2-ylmethyl)acetamide* **1f**

Речовина **1g**. Нековалентний інгібітор головної протеази SARS-CoV-2 M^{pro}.

Назва: *N-(4-Fluorophenyl)-2-(4-phenyl-1H-1,2,3-triazol-1-yl)-N-(thiophen-2-ylmethyl)acetamide*



White solid. Yield 92 %.

Спектральні параметри:

^{1}H NMR (400 MHz, DMSO-D_6) δ 8.42 (s, 1H), 7.84 – 7.76 (m, 2H), 7.55 – 7.46 (m, 5H), 7.33 – 7.26 (m, 4H), 6.98 (dd, J = 6.5, 5.3 Hz, 1H), 5.22 (d, J = 0.8 Hz, 2H), 5.06 (d, J = 0.7 Hz, 2H).

^{13}C NMR (101 MHz, DMSO-D_6) δ 165.93, 162.64, 158.20, 150.59, 138.11, 136.88, 136.85, 130.38, 129.30, 128.92, 127.23, 125.69, 125.61, 125.58, 125.57, 124.79, 120.52, 117.56, 117.34, 52.75, 43.14.

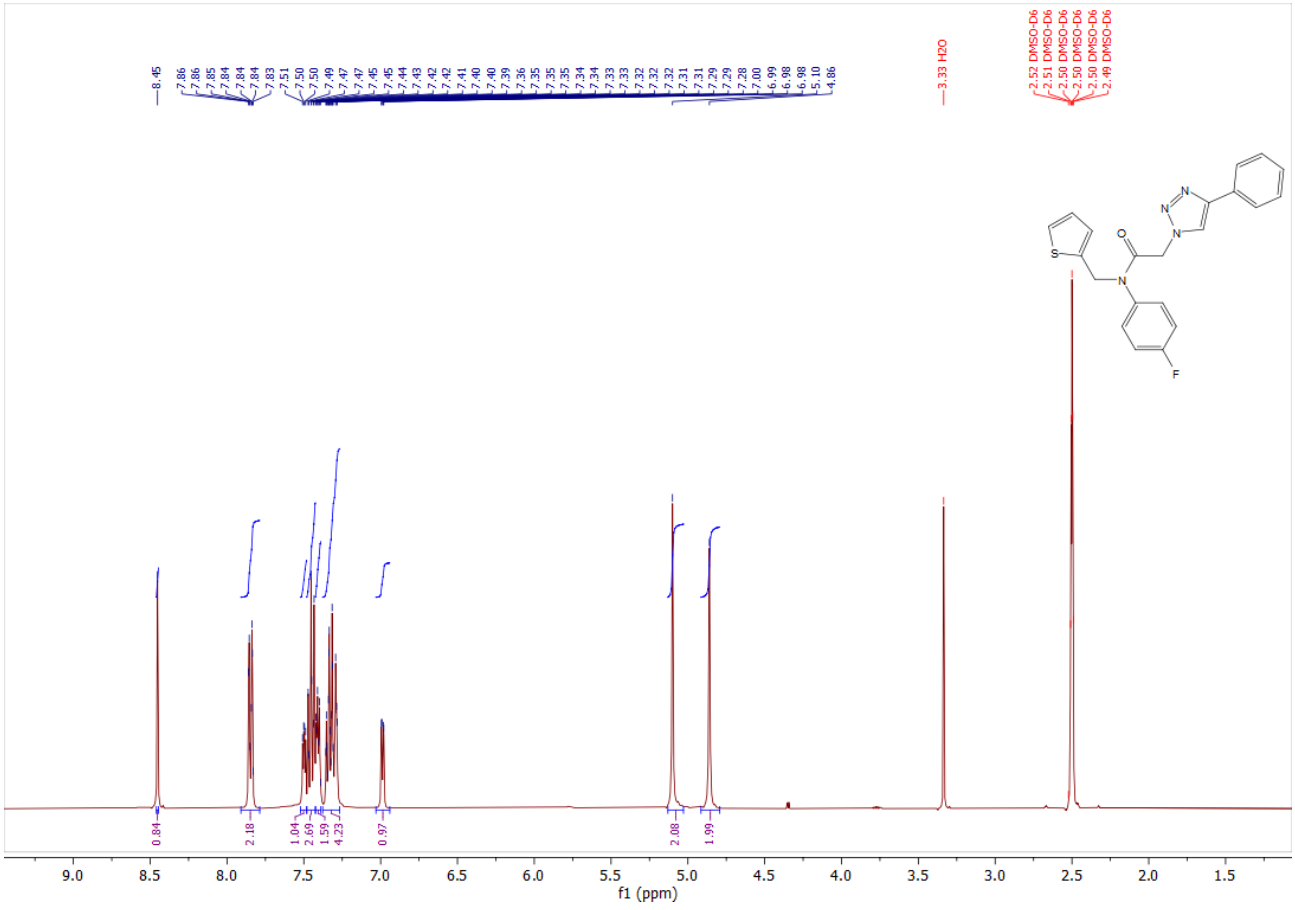


Рисунок 13. ^{1}H NMR spectrum (400 MHz, DMSO-D_6) *N-(4-Fluorophenyl)-2-(4-phenyl-1H-1,2,3-triazol-1-yl)-N-(thiophen-2-ylmethyl)acetamide* **1g**

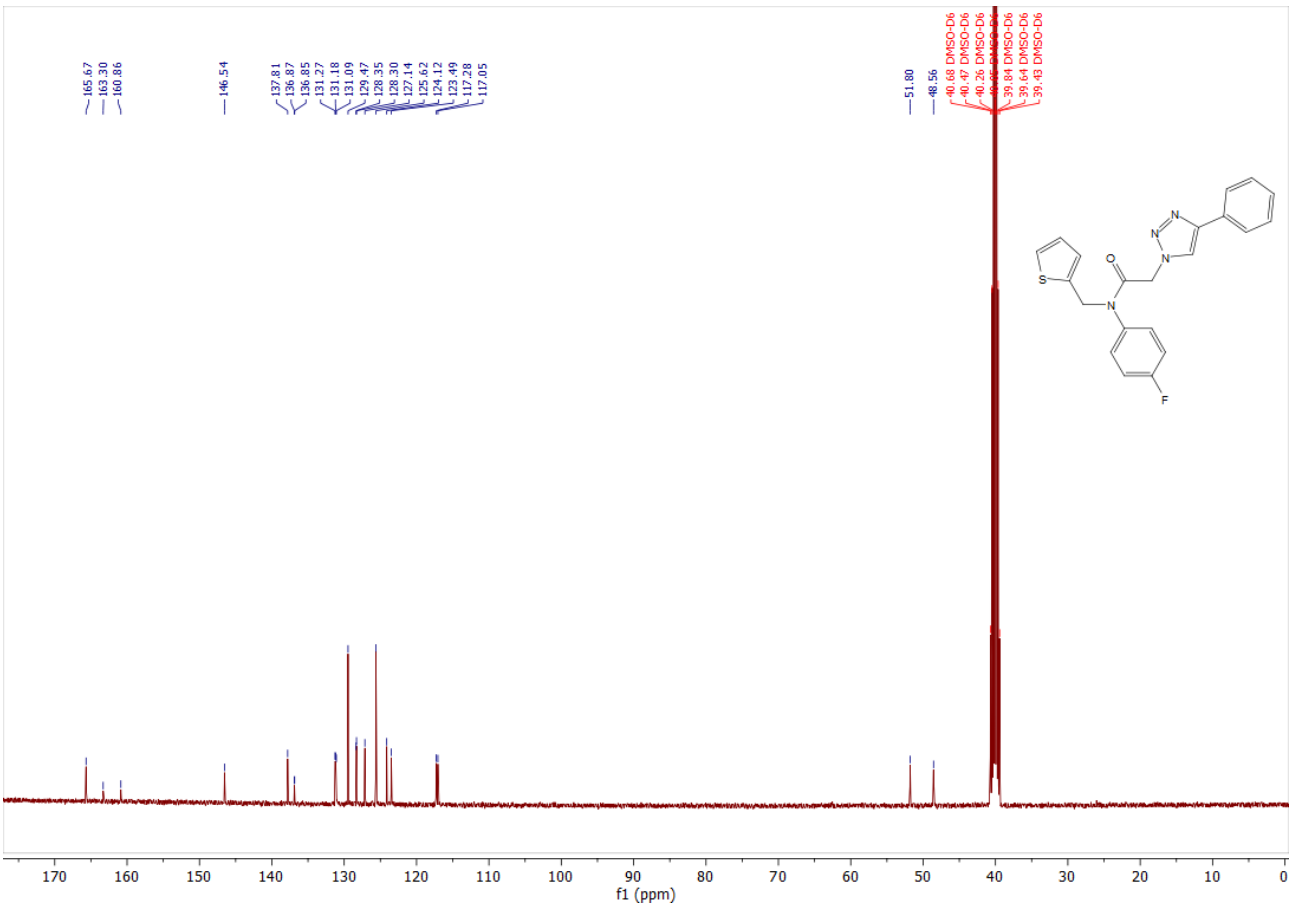
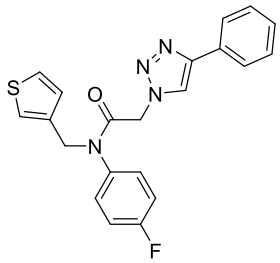


Рисунок 14. ^{13}C NMR spectrum (101 MHz, DMSO-D_6) *N-(4-Fluorophenyl)-2-(4-phenyl-1H-1,2,3-triazol-1-yl)-N-(thiophen-2-ylmethyl)acetamide* **1g**

Речовина **1h**. Нековалентний інгібітор головної протеази SARS-CoV-2 M^{pro}.

Назва: *N-(4-Fluorophenyl)-2-(4-phenyl-1H-1,2,3-triazol-1-yl)-N-(thiophen-3-ylmethyl)acetamide*



White solid. Yield 93 %

Спектральні параметри:

^{1}H NMR (400 MHz, DMSO-D_6) δ 8.41 (s, 1H), 7.84 – 7.78 (m, 2H), 7.47 – 7.35 (m, 5H), 7.32 – 7.23 (m, 4H), 6.95 (dd, J = 4.9, 1.3 Hz, 1H), 5.06 (s, 2H), 4.82 (s, 2H).

^{13}C NMR (101 MHz, DMSO-D_6) δ 165.67, 163.30, 160.86, 146.54, 137.81, 136.87, 136.85, 131.27, 131.18, 131.09, 129.47, 128.35, 128.30, 127.14, 125.62, 124.12, 123.49, 117.28, 117.05, 51.80, 48.56.

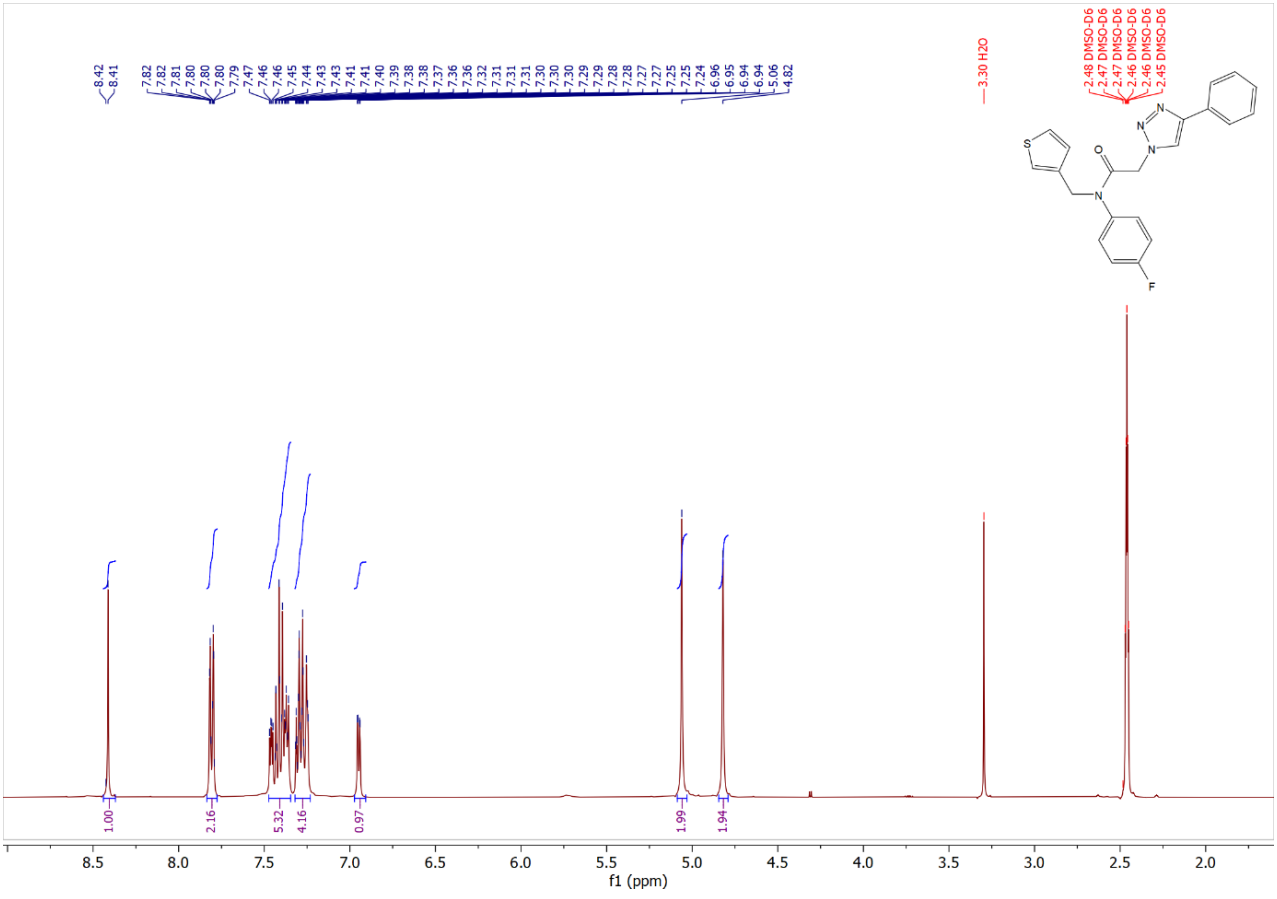


Рисунок 15. ^{1}H NMR spectrum (400 MHz, DMSO-D_6) *N-(4-Fluorophenyl)-2-(4-phenyl-1H-1,2,3-triazol-1-yl)-N-(thiophen-3-ylmethyl)acetamide* **1h**

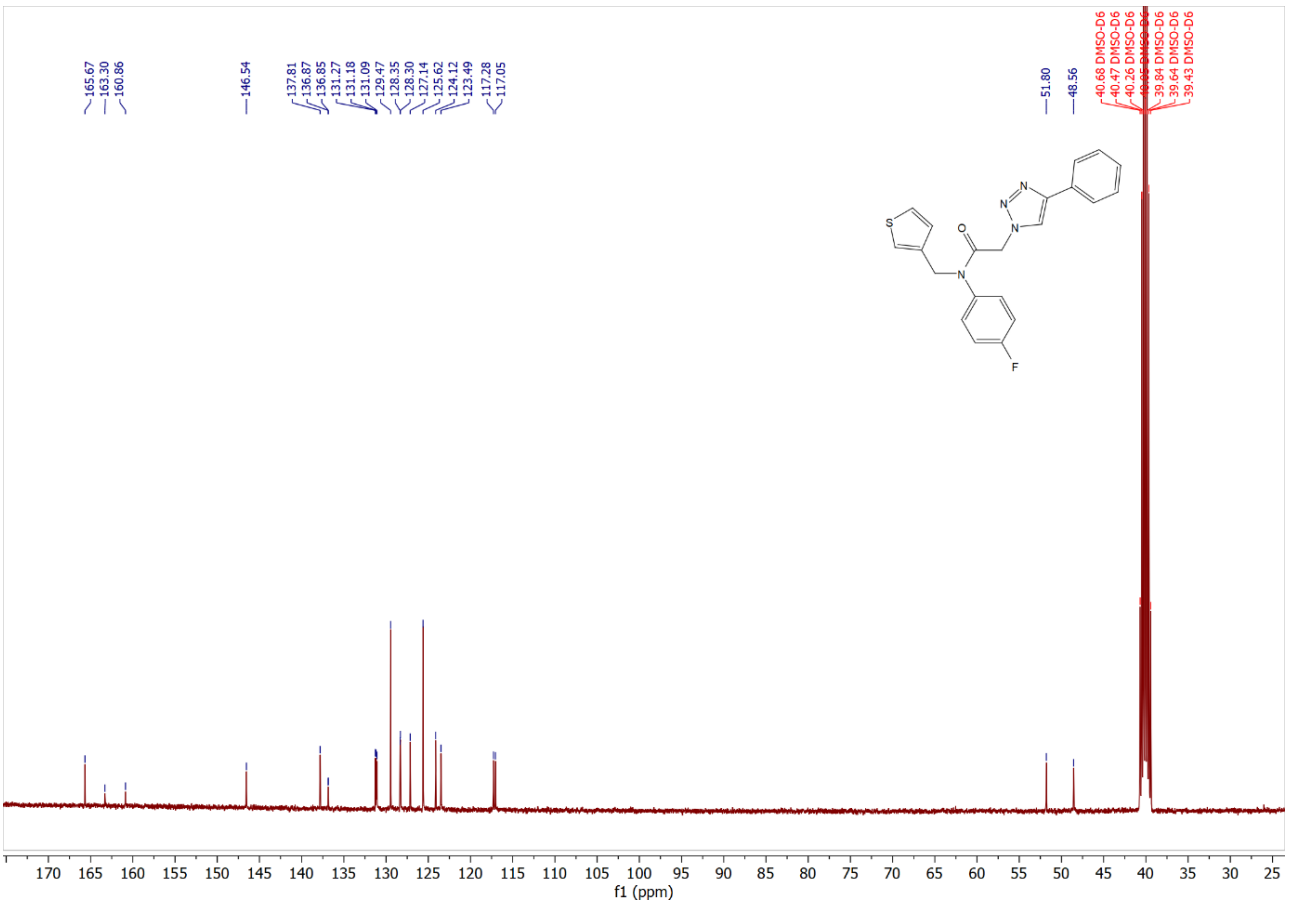
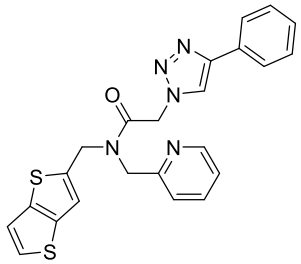


Рисунок 16. ^{13}C NMR spectrum (101 MHz, DMSO-D_6) *N-(4-Fluorophenyl)-2-(4-phenyl-1H-1,2,3-triazol-1-yl)-N-(thiophen-3-ylmethyl)acetamide* **1h**

Речовина **1i**. Нековалентний інгібітор головної протеази SARS-CoV-2 M^{pro}.

Назва: *2-(4-Phenyl-1H-1,2,3-triazol-1-yl)-N-(pyridin-2-ylmethyl)-N-(thieno[3,2-b]thiophen-2-ylmethyl)acetamide*



Yellow solid. Yield 92 %

Спектральні параметри:

^{1}H NMR (400 MHz, DMSO-D_6) δ 8.58 – 8.49 (m, 1H), 8.43 (d, J = 0.9 Hz, 1H), 7.85 – 7.73 (m, 1H), 7.59 – 7.54 (m, 2H), 7.54 (s, 1H), 7.47 – 7.38 (m, 1H), 7.36 – 7.28 (m, 2H), 7.02 (d, J = 1.0 Hz, 1H), 4.99 (d, J = 0.7 Hz, 1H), 4.68 (d, J = 0.8 Hz, 1H), 4.51 (d, J = 0.8 Hz, 1H).

^{13}C NMR (101 MHz, DMSO-D_6) δ 167.62, 156.18, 150.63, 149.74, 142.68, 139.11, 138.91, 137.07, 130.84, 130.38, 129.30, 128.92, 125.01, 124.79, 122.76, 122.57, 122.18, 120.61, 52.24, 50.63, 47.16.

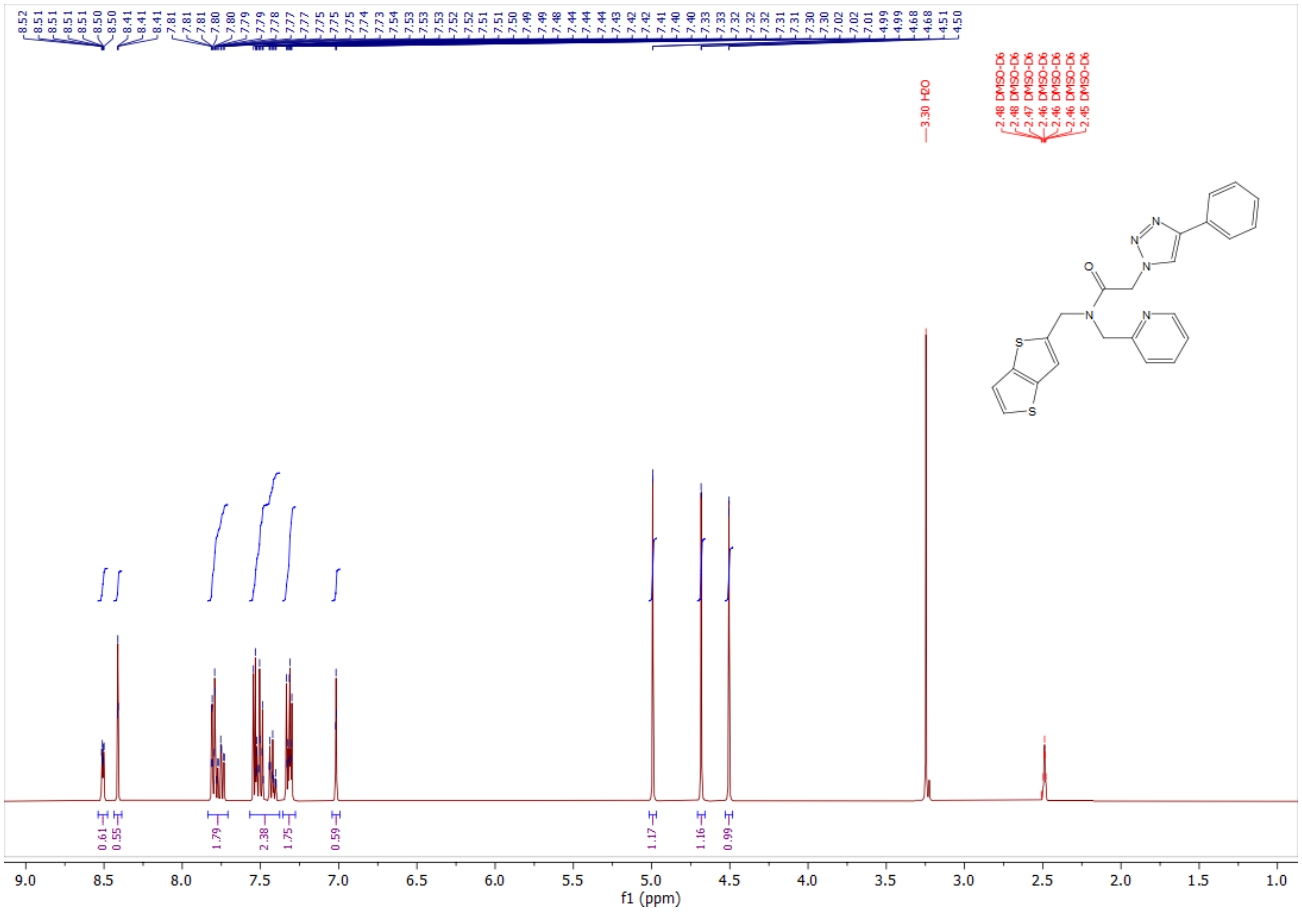


Рисунок 17. ^{1}H NMR spectrum (400 MHz, DMSO-D_6) *2-(4-Phenyl-1H-1,2,3-triazol-1-yl)-N-(pyridin-2-ylmethyl)-N-(thieno[3,2-b]thiophen-2-ylmethyl)acetamide* **1i**

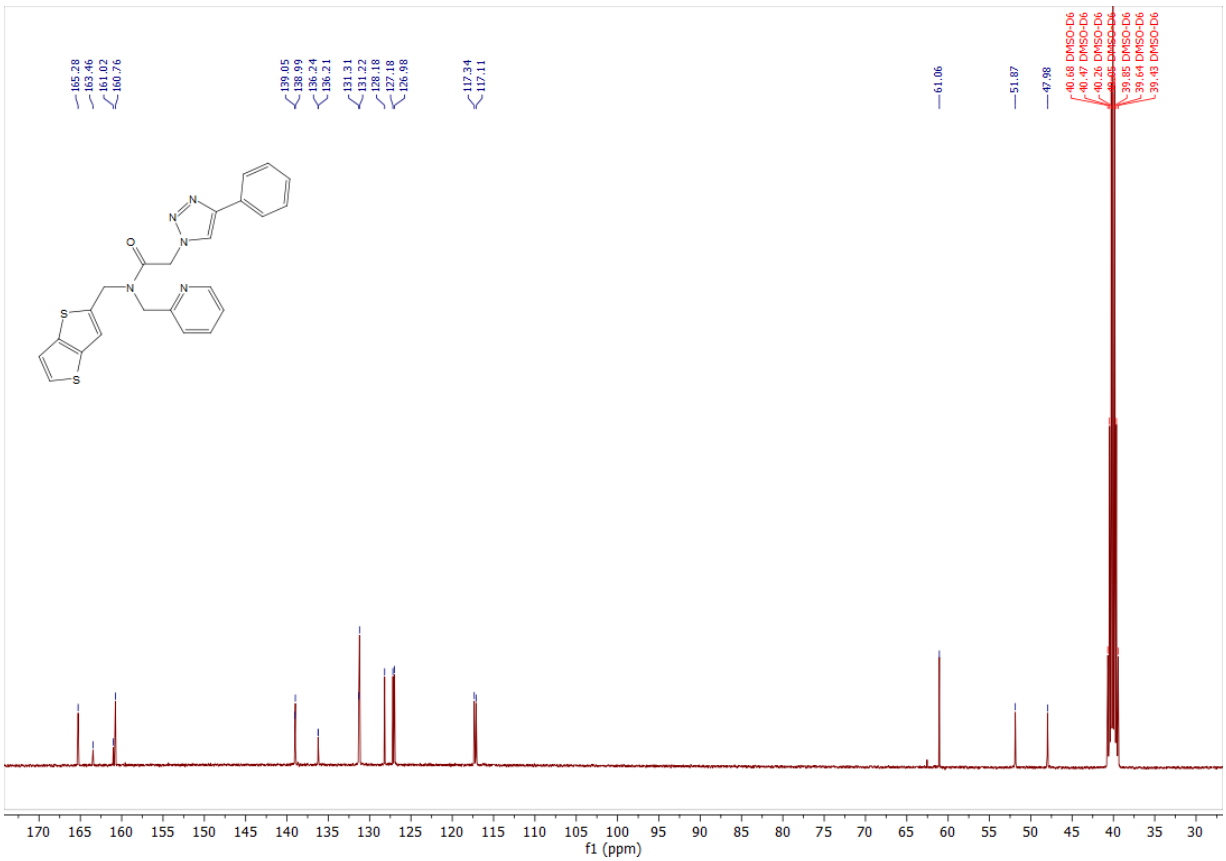
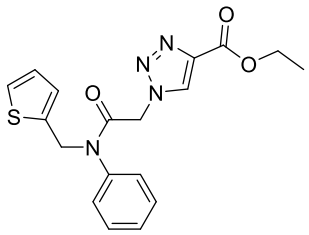


Рисунок 18. ^{13}C NMR spectrum (101 MHz, DMSO-D_6) *2-(4-Phenyl-1H-1,2,3-triazol-1-yl)-N-(pyridin-2-ylmethyl)-N-(thieno[3,2-b]thiophen-2-ylmethyl)acetamide* **1i**

Речовина **1j**. Нековалентний інгібітор головної протеази SARS-CoV-2 M^{pro}.

Назва: *Ethyl 1-(2-oxo-2-(phenyl(thiophen-2-ylmethyl)amino)ethyl)-1H-1,2,3-triazole-4-carboxylate*



White solid. Yield 90 %

Спектральні параметри:

^{1}H NMR (400 MHz, DMSO-D_6) δ 8.52 (s, 1H), 7.36 (dd, J = 5.3, 1.7 Hz, 1H), 7.25 (s, 2H), 7.31 – 7.11 (m, 4H), 6.98 (dd, J = 6.5, 5.3 Hz, 1H), 5.20 (d, J = 0.7 Hz, 2H), 5.06 (d, J = 0.8 Hz, 2H), 4.34 (q, J = 6.4 Hz, 2H), 1.29 (t, J = 6.4 Hz, 3H).

^{13}C NMR (101 MHz, DMSO-D_6) δ 166.64, 161.06, 144.30, 140.11, 138.11, 129.24, 127.29, 127.23, 125.58, 125.57, 124.72, 123.62, 61.48, 52.24, 43.12, 14.31.

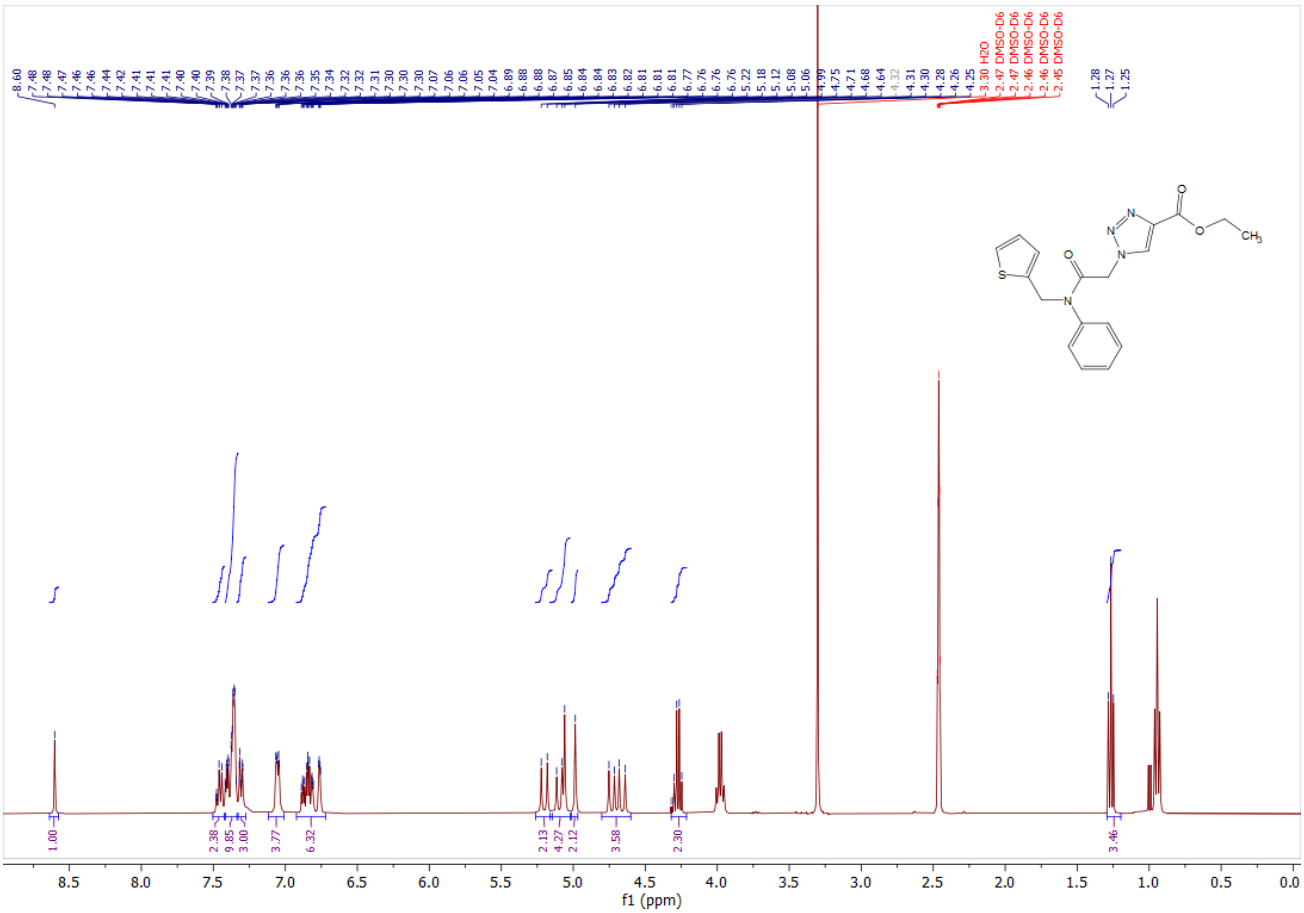


Рисунок 19. ^{1}H NMR spectrum (400 MHz, DMSO-D_6) *Ethyl 1-(2-oxo-2-(phenyl(thiophen-2-ylmethyl)amino)ethyl)-1H-1,2,3-triazole-4-carboxylate* **1j**

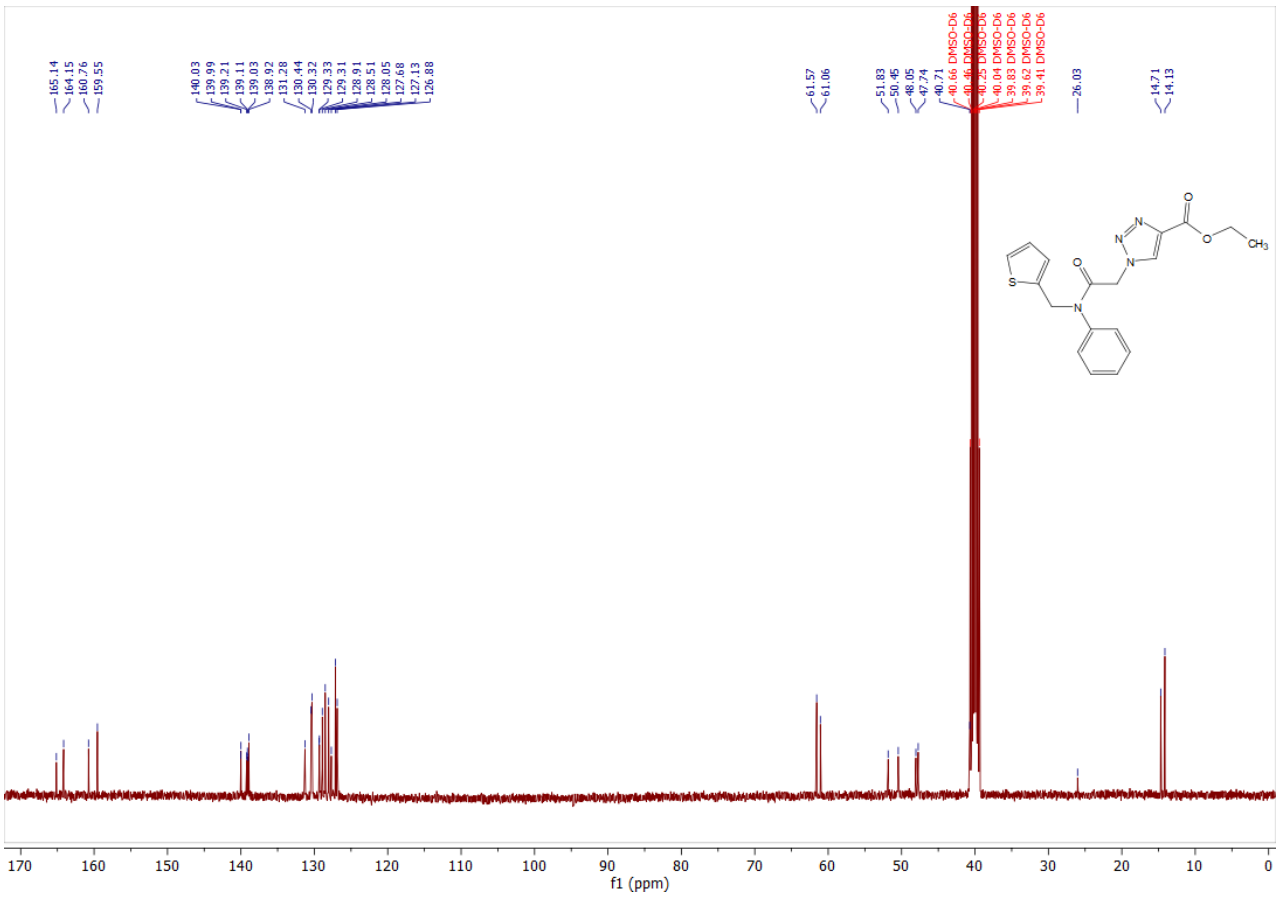
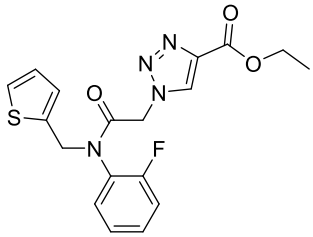


Рисунок 20. ^{13}C NMR spectrum (101 MHz, DMSO-D_6) *Ethyl 1-(2-oxo-2-(phenyl(thiophen-2-ylmethyl)amino)ethyl)-1H-1,2,3-triazole-4-carboxylate* **1j**

Речовина **1k**. Нековалентний інгібітор головної протеази SARS-CoV-2 M^{pro}.

Назва: *Ethyl 1-(2-((2-fluorophenyl)(thiophen-2-ylmethyl)amino)-2-oxoethyl)-1H-1,2,3-triazole-4-carboxylate*



White solid. Yield 91 %

Спектральні параметри:

^{1}H NMR (400 MHz, DMSO-D_6) δ 8.64 (s, 1H), 7.48 (m, 1H), 7.43 – 7.34 (m, 3H), 7.28 (td, *J* = 7.7, 1.5 Hz, 1H), 6.87 (dd, *J* = 5.1, 3.4 Hz, 1H), 6.81 (dd, *J* = 3.5, 1.2 Hz, 1H), 5.13 (dd, *J* = 29.7, 16.0 Hz, 2H), 4.99 (d, *J* = 16.8 Hz, 1H), 4.85 (d, *J* = 15.1 Hz, 1H), 4.27 (q, *J* = 7.1 Hz, 2H), 1.27 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, DMSO-D_6) δ 165.48, 160.73, 159.40, 156.92, 139.09, 138.40, 131.93, 131.85, 131.37, 128.39, 127.22, 127.14, 127.04, 126.91, 126.22, 126.18, 117.70, 117.51, 61.09, 51.55, 47.23, 14.69.

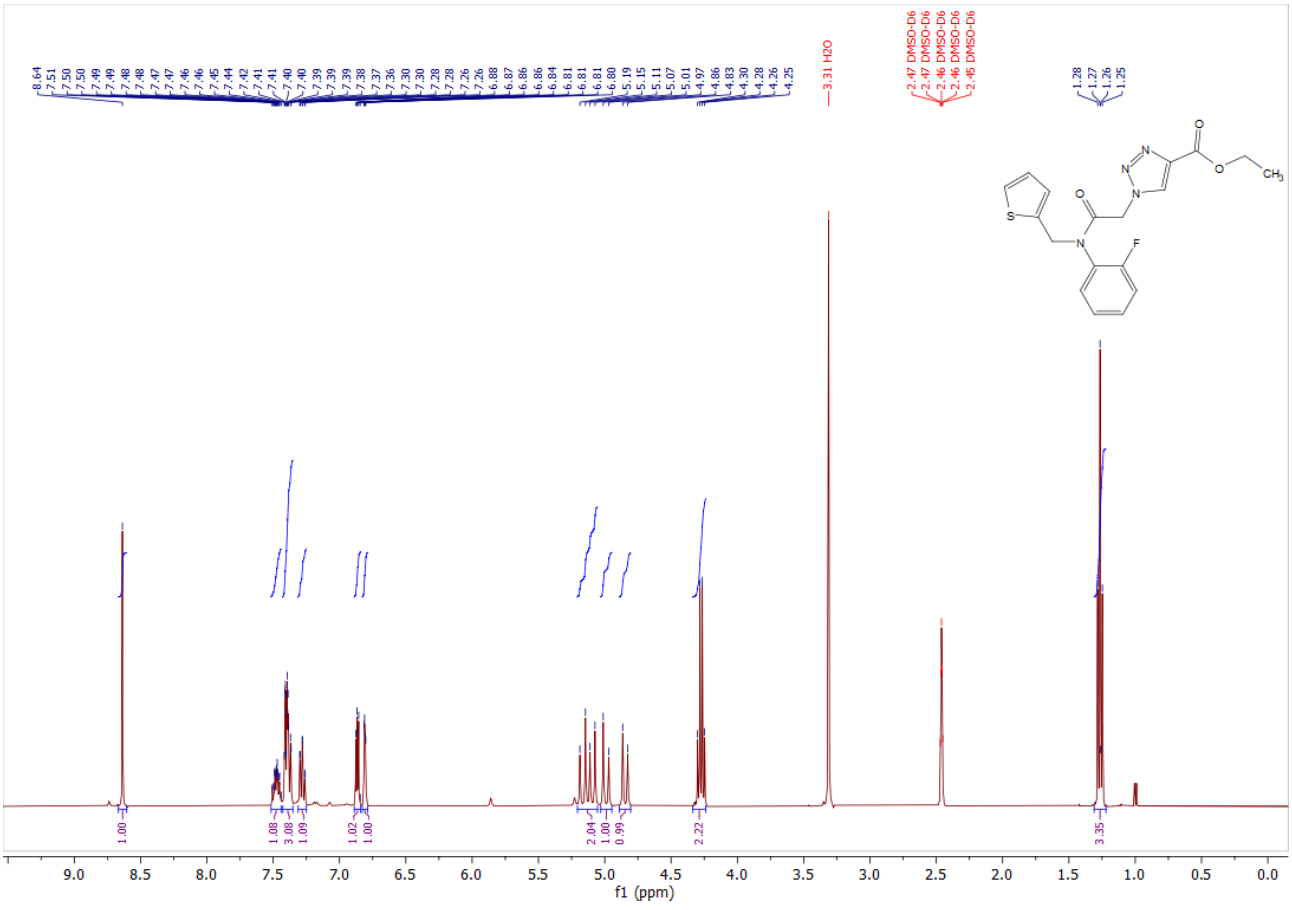


Рисунок 21. ^{1}H NMR spectrum (400 MHz, DMSO-D_6) *Ethyl 1-(2-((2-fluorophenyl)(thiophen-2-ylmethyl)amino)-2-oxoethyl)-1H-1,2,3-triazole-4-carboxylate* **1k**

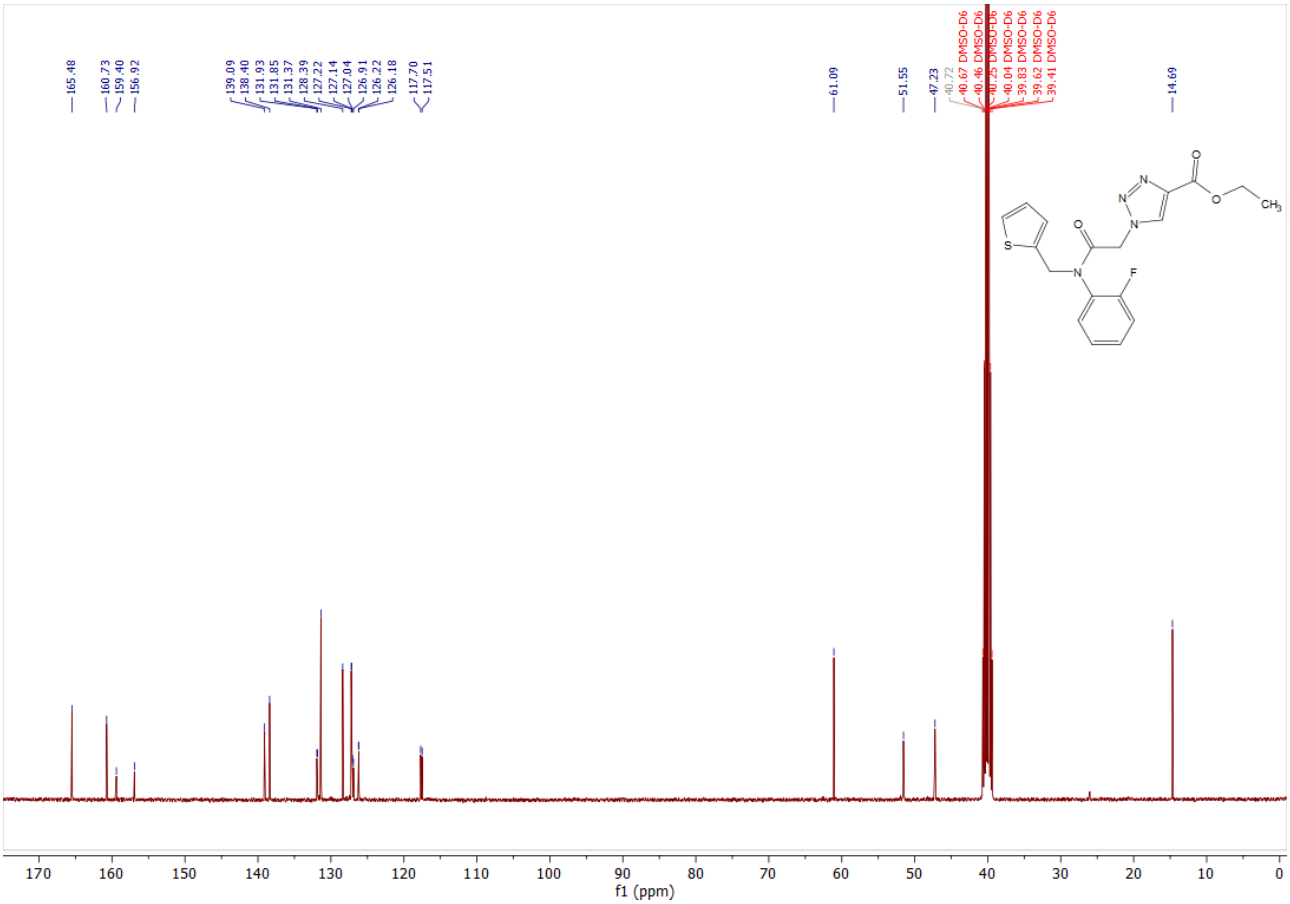
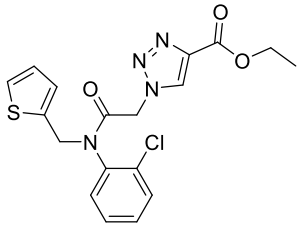


Рисунок 22. ^{13}C NMR spectrum (101 MHz, DMSO-D_6) *Ethyl 1-(2-((2-fluorophenyl)(thiophen-2-ylmethyl)amino)-2-oxoethyl)-1H-1,2,3-triazole-4-carboxylate* **1k**

Речовина **1l**. Нековалентний інгібітор головної протеази SARS-CoV-2 M^{pro}.

Назва: *Ethyl 1-(2-((2-chlorophenyl)(thiophen-2-ylmethyl)amino)-2-oxoethyl)-1H-1,2,3-triazole-4-carboxylate*



Yellow solid. Yield 90 %

Спектральні параметри:

^{1}H NMR (400 MHz, DMSO-D_6) δ 8.62 (s, 1H), 7.69 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.48 (td, *J* = 7.7, 1.8 Hz, 1H), 7.45 – 7.39 (m, 2H), 7.26 (dd, *J* = 7.8, 1.7 Hz, 1H), 6.88 (dd, *J* = 5.1, 3.4 Hz, 1H), 6.82 (dd, *J* = 3.5, 1.3 Hz, 1H), 5.27 (dd, *J* = 15.0, 0.8 Hz, 1H), 5.10 (d, *J* = 16.8 Hz, 1H), 4.83 (d, *J* = 16.8 Hz, 1H), 4.58 (d, *J* = 15.1 Hz, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 1.27 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, DMSO-D_6) δ 165.26, 160.72, 139.10, 138.15, 136.66, 132.84, 131.93, 131.67, 131.35, 129.31, 128.76, 127.38, 127.17, 61.09, 60.29, 51.72, 46.74, 14.70.

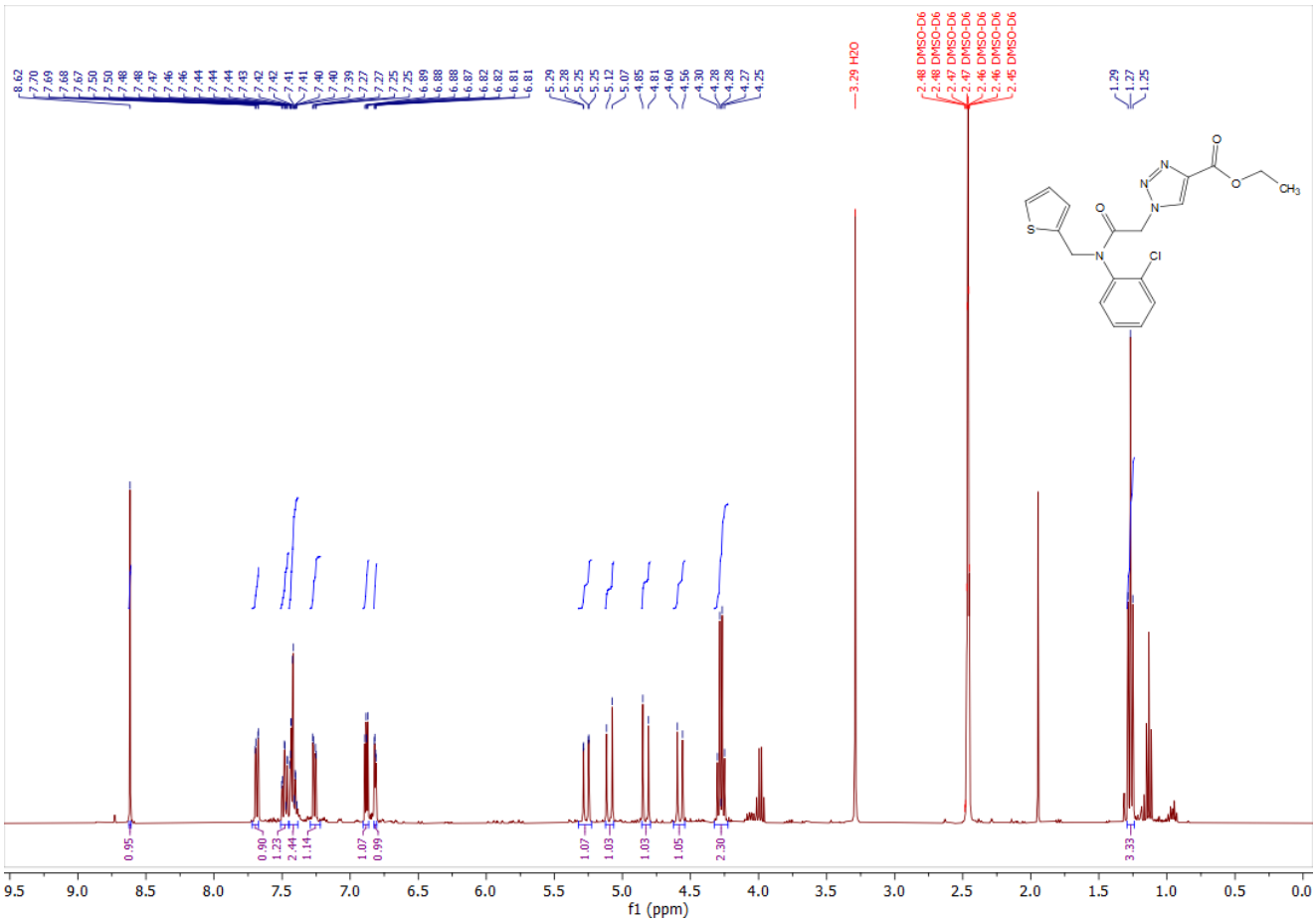


Рисунок 23. ^{1}H NMR spectrum (400 MHz, DMSO-D_6) *Ethyl 1-(2-((2-chlorophenyl)(thiophen-2-ylmethyl)amino)-2-oxoethyl)-1H-1,2,3-triazole-4-carboxylate* **1l**

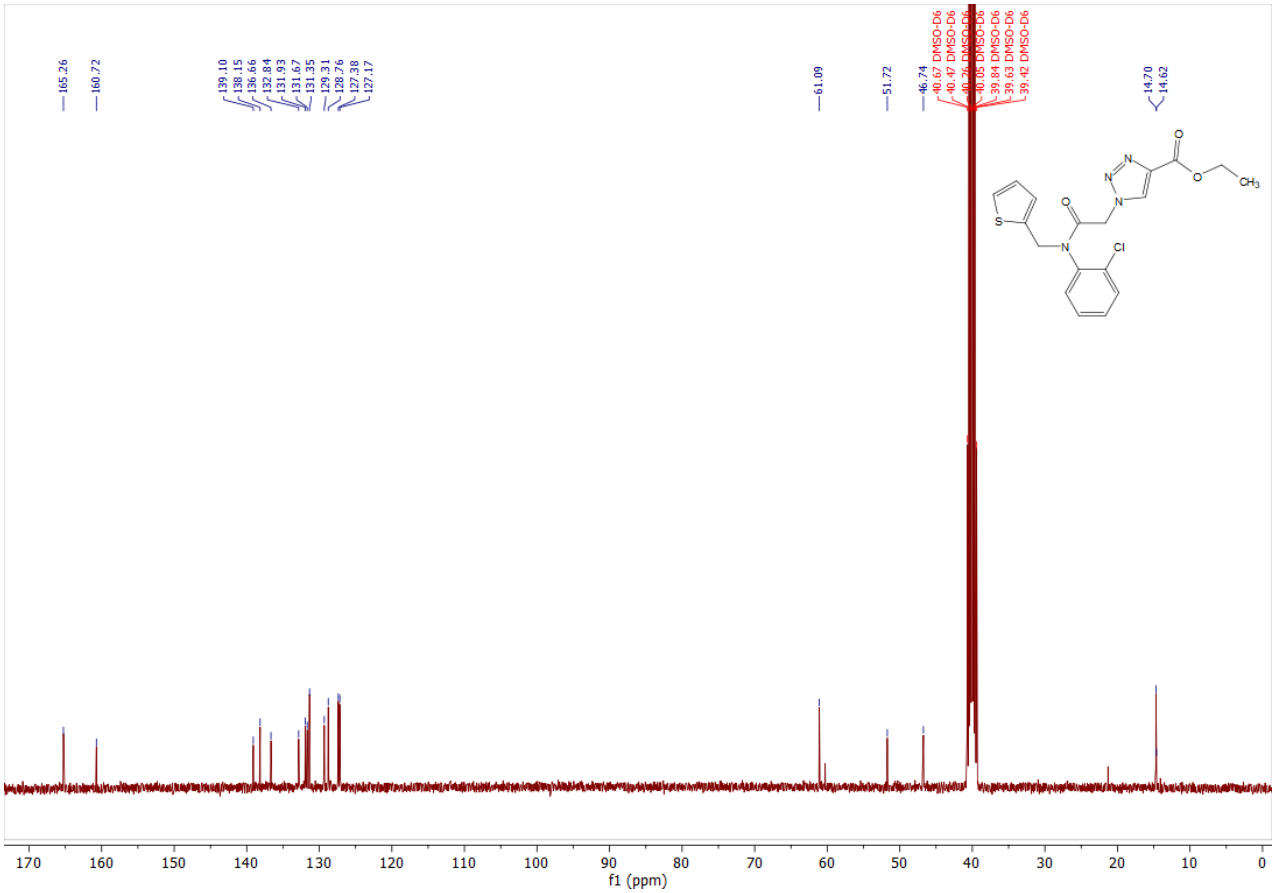
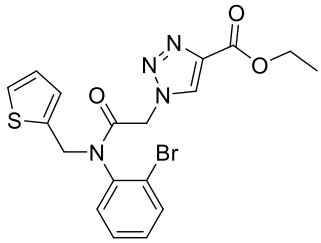


Рисунок 24. ^{13}C NMR spectrum (101 MHz, DMSO-D_6) *Ethyl 1-(2-((2-chlorophenyl)(thiophen-2-ylmethyl)amino)-2-oxoethyl)-1H-1,2,3-triazole-4-carboxylate* **1l**

Речовина **1m**. Нековалентний інгібітор головної протеази SARS-CoV-2 M^{pro}.

Назва: *Ethyl 1-(2-((2-bromophenyl)(thiophen-2-ylmethyl)amino)-2-oxoethyl)-1H-1,2,3-triazole-4-carboxylate*



Yellow solid. Yield 92 %

Спектральні параметри:

^{1}H NMR (400 MHz, DMSO-D_6) δ 8.60 (s, 1H), 7.45 (ddd, J = 8.5, 7.1, 1.5 Hz, 1H), 7.44 – 7.32 (m, 3H), 7.28 (td, J = 7.1, 1.6 Hz, 1H), 7.14 (ddt, J = 6.4, 1.8, 0.9 Hz, 1H), 6.98 (dd, J = 6.5, 5.3 Hz, 1H), 5.18 (d, J = 0.7 Hz, 2H), 5.05 (d, J = 0.8 Hz, 2H), 4.34 (q, J = 6.4 Hz, 2H), 1.29 (t, J = 6.4 Hz, 3H).

^{13}C NMR (101 MHz, DMSO-D_6) δ 166.29, 161.06, 144.30, 139.05, 138.19, 133.67, 129.65, 128.79, 127.33, 127.29, 127.23, 125.58, 125.57, 119.83, 61.48, 52.13, 44.15, 14.31.

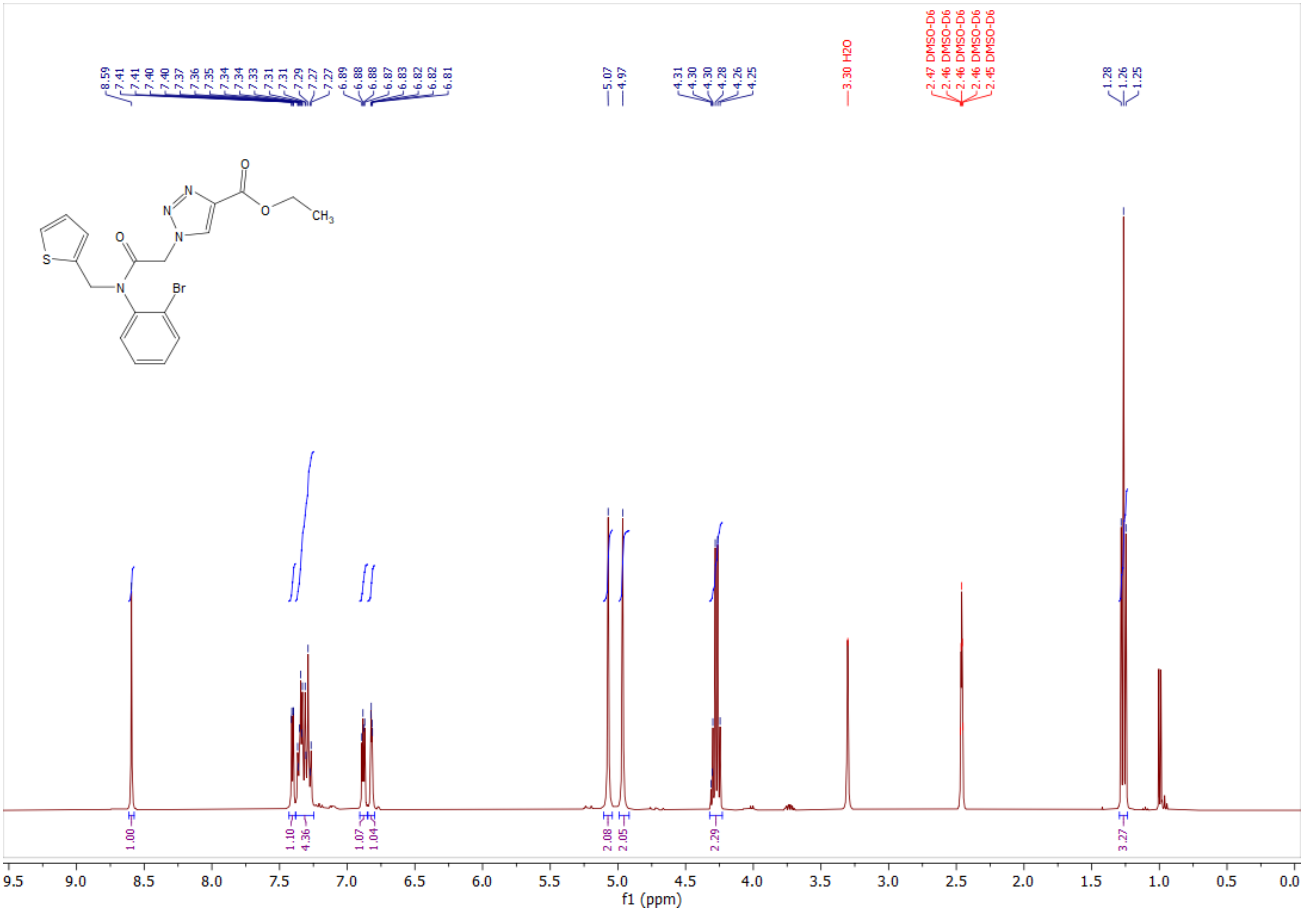


Рисунок 25. ^{1}H NMR spectrum (400 MHz, DMSO-D_6) *Ethyl 1-(2-((2-bromophenyl)(thiophen-2-ylmethyl)amino)-2-oxoethyl)-1H-1,2,3-triazole-4-carboxylate* **1m**

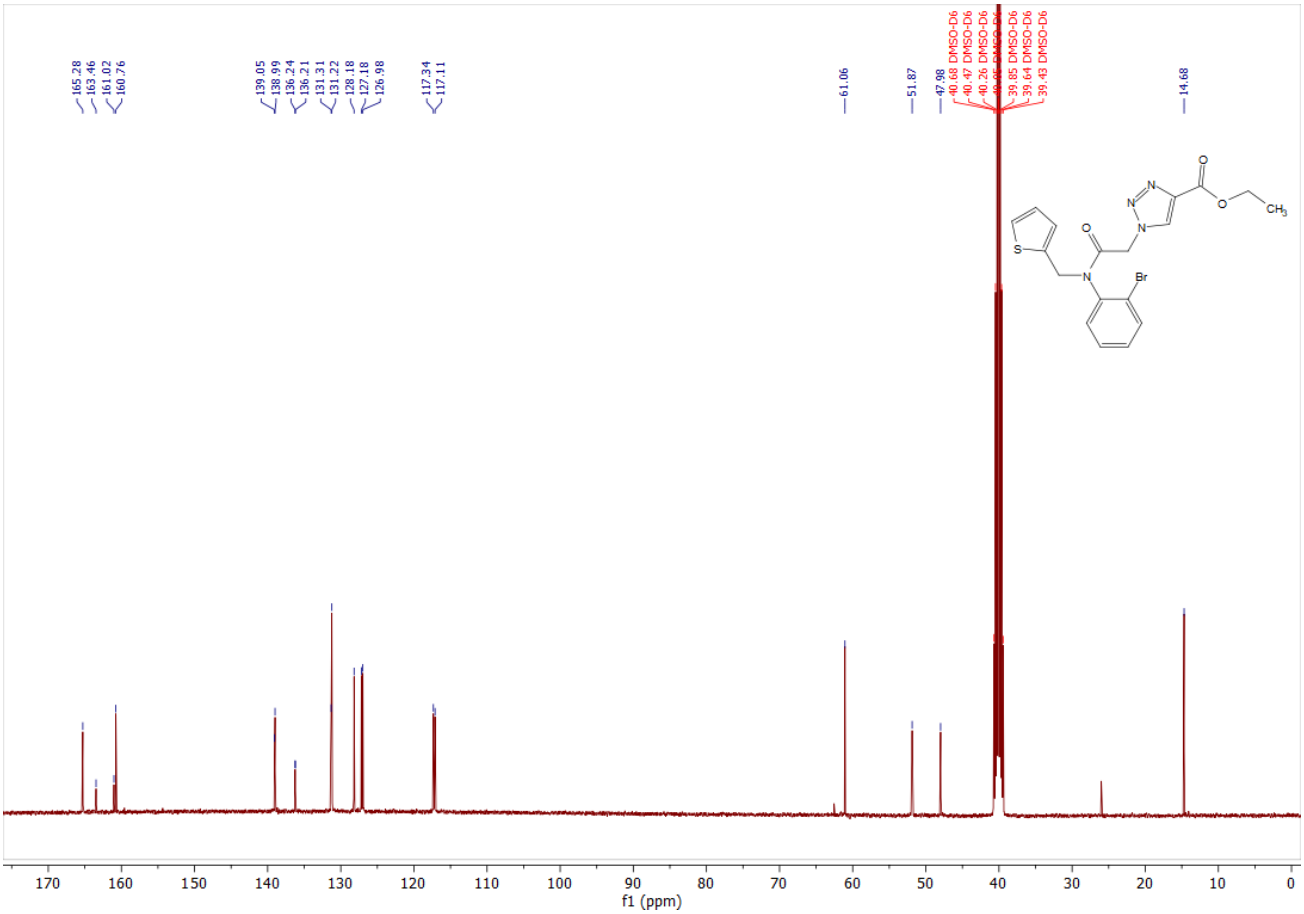
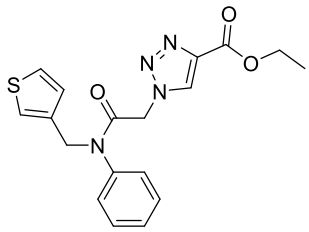


Рисунок 26. ^{13}C NMR spectrum (101 MHz, DMSO-D_6) *Ethyl 1-(2-((2-bromophenyl)(thiophen-2-ylmethyl)amino)-2-oxoethyl)-1H-1,2,3-triazole-4-carboxylate* **1m**

Речовина **1n**. Нековалентний інгібітор головної протеази SARS-CoV-2 M^{pro}.

Назва: *Ethyl 1-(2-oxo-2-(phenyl(thiophen-3-ylmethyl)amino)ethyl)-1H-1,2,3-triazole-4-carboxylate*



White solid. Yield 89 %

Спектральні параметри:

^{1}H NMR (400 MHz, DMSO-D_6) δ 8.59 (s, 1H), 7.41 (dd, J = 5.2, 1.7 Hz, 1H), 7.35 (tt, J = 1.6, 0.9 Hz, 1H), 7.25 (s, 2H), 7.31 – 7.20 (m, 3H), 7.23 – 7.13 (m, 1H), 5.20 (d, J = 0.8 Hz, 2H), 5.04 (t, J = 0.9 Hz, 2H), 4.34 (q, J = 6.4 Hz, 2H), 1.29 (t, J = 6.4 Hz, 3H).

^{13}C NMR (101 MHz, DMSO-D_6) δ 166.92, 161.06, 144.30, 140.36, 135.71, 129.24, 127.29, 127.11, 126.70, 124.72, 123.63, 123.25, 61.48, 52.26, 44.83, 14.31.

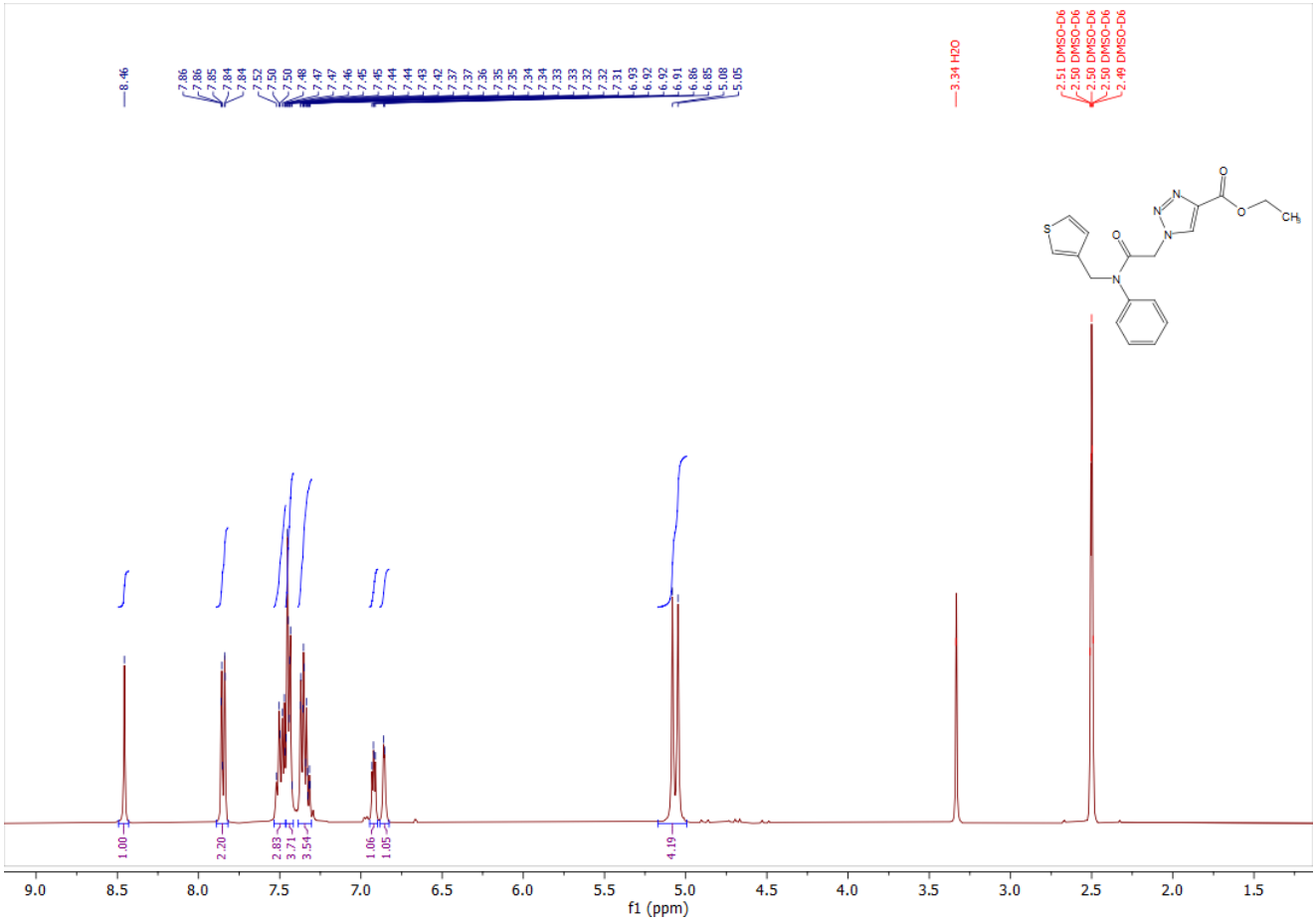


Рисунок 27. ^{1}H NMR spectrum (400 MHz, DMSO-D_6) *Ethyl 1-(2-oxo-2-(phenyl(thiophen-3-ylmethyl)amino)ethyl)-1H-1,2,3-triazole-4-carboxylate* **1n**

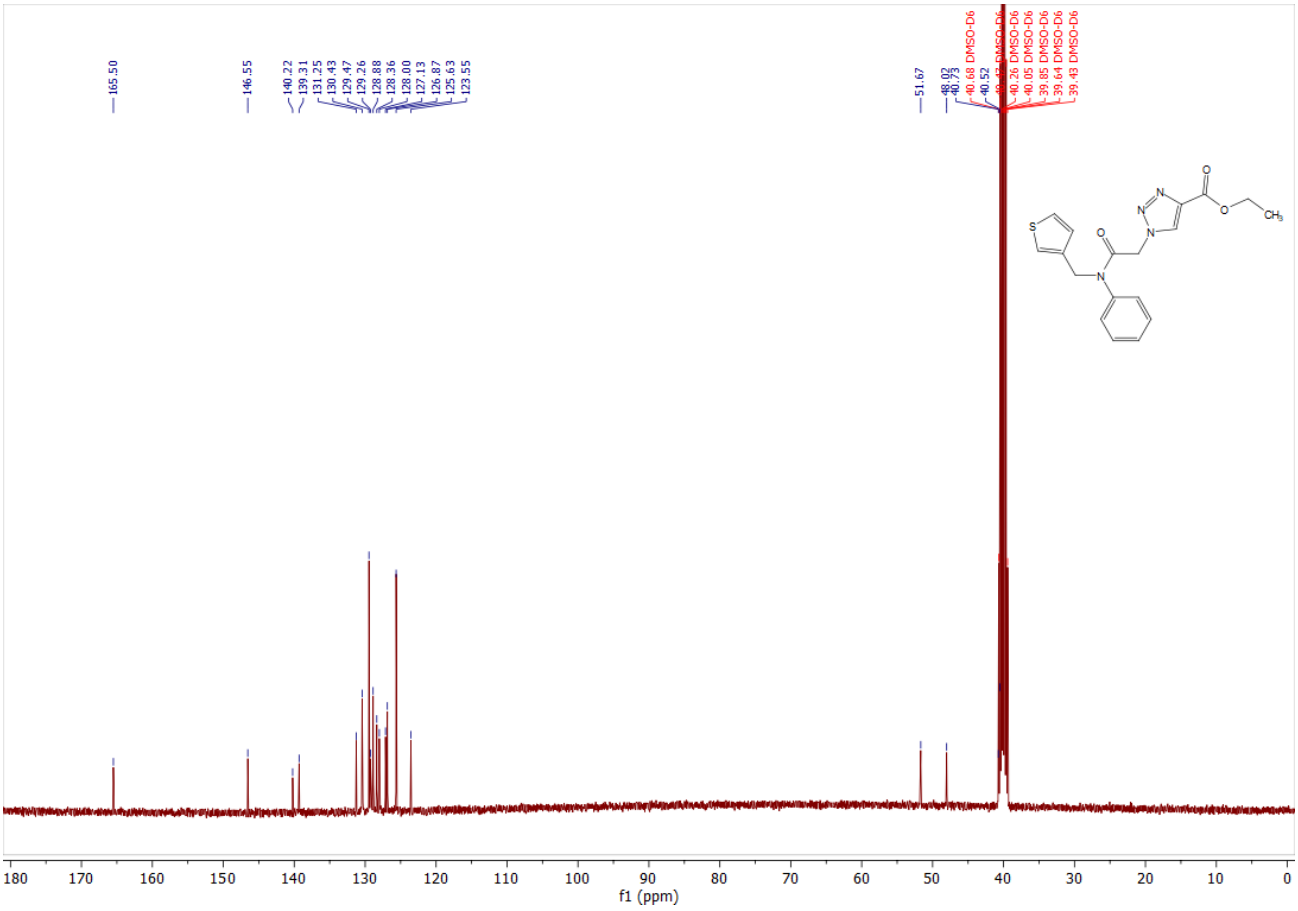
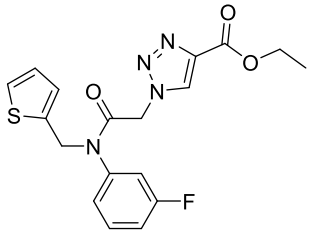


Рисунок 28. ^{13}C NMR spectrum (101 MHz, DMSO-D_6) *Ethyl 1-(2-oxo-2-(phenyl(thiophen-3-ylmethyl)amino)ethyl)-1H-1,2,3-triazole-4-carboxylate* **1n**

Речовина **1o**. Нековалентний інгібітор головної протеази SARS-CoV-2 M^{pro}.

Назва: *Ethyl 1-(2-((3-fluorophenyl)(thiophen-2-ylmethyl)amino)-2-oxoethyl)-1H-1,2,3-triazole-4-carboxylate*



White solid. Yield 90 %

Спектральні параметри:

^{1}H NMR (400 MHz, DMSO-D_6) δ 8.60 (s, 1H), 7.47 (t, J = 7.5 Hz, 1H), 7.41 (dd, J = 5.0, 1.3 Hz, 1H), 7.27 (d, J = 9.3 Hz, 2H), 7.16 (dd, J = 7.8, 1.5 Hz, 1H), 6.95 – 6.77 (m, 2H), 5.14 (s, 2H), 5.01 (s, 2H), 4.27 (q, J = 7.1 Hz, 2H), 1.27 (t, J = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, DMSO-D_6) δ 165.17, 163.95, 161.50, 160.76, 141.52, 141.43, 139.06, 138.94, 131.94, 131.85, 131.22, 128.16, 127.19, 126.99, 125.34, 116.48, 116.26, 61.07, 51.89, 47.85, 14.69.

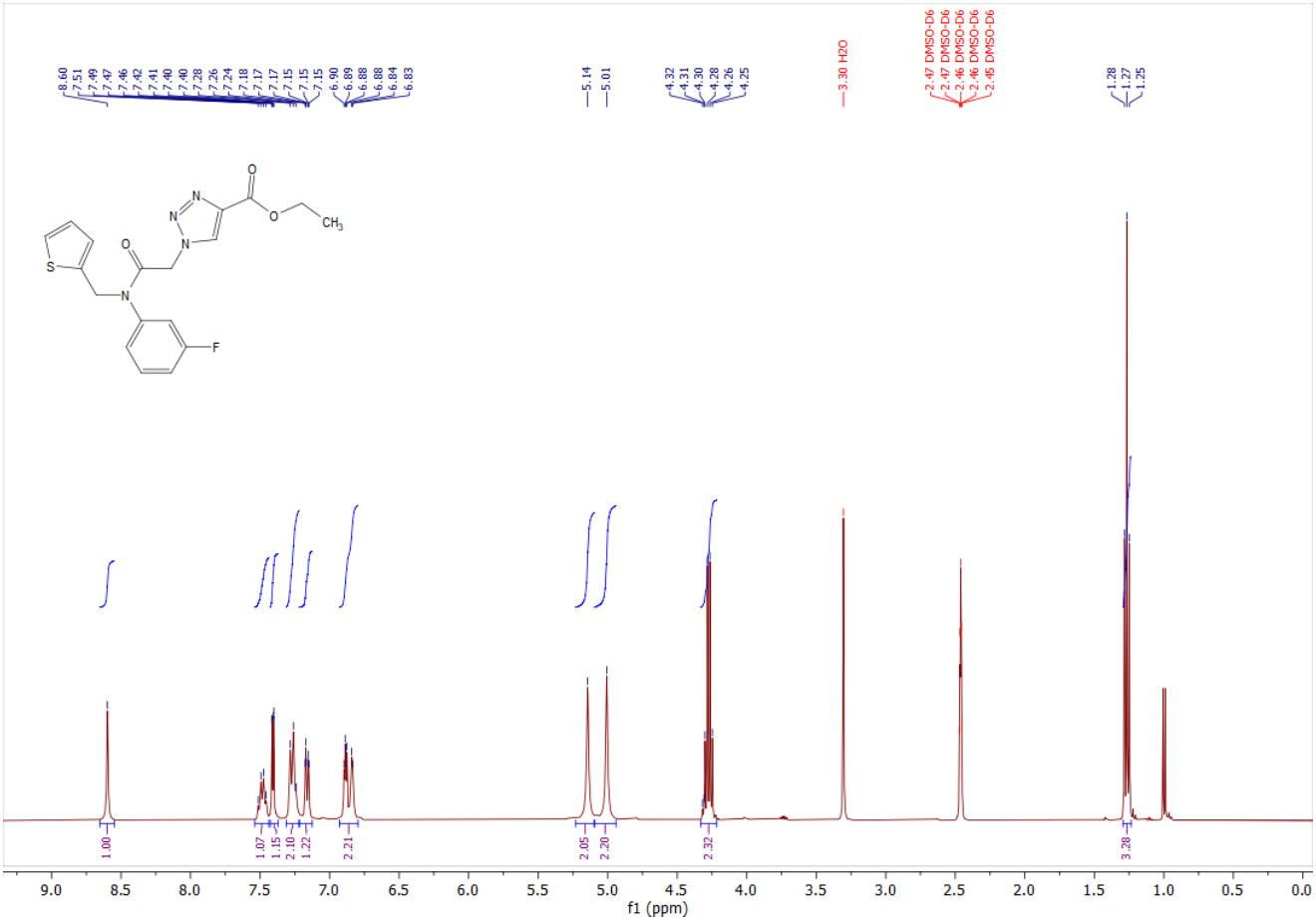


Рисунок 29. ^{1}H NMR spectrum (400 MHz, DMSO-D_6) *Ethyl 1-(2-((3-fluorophenyl)(thiophen-2-ylmethyl)amino)-2-oxoethyl)-1H-1,2,3-triazole-4-carboxylate* **1o**

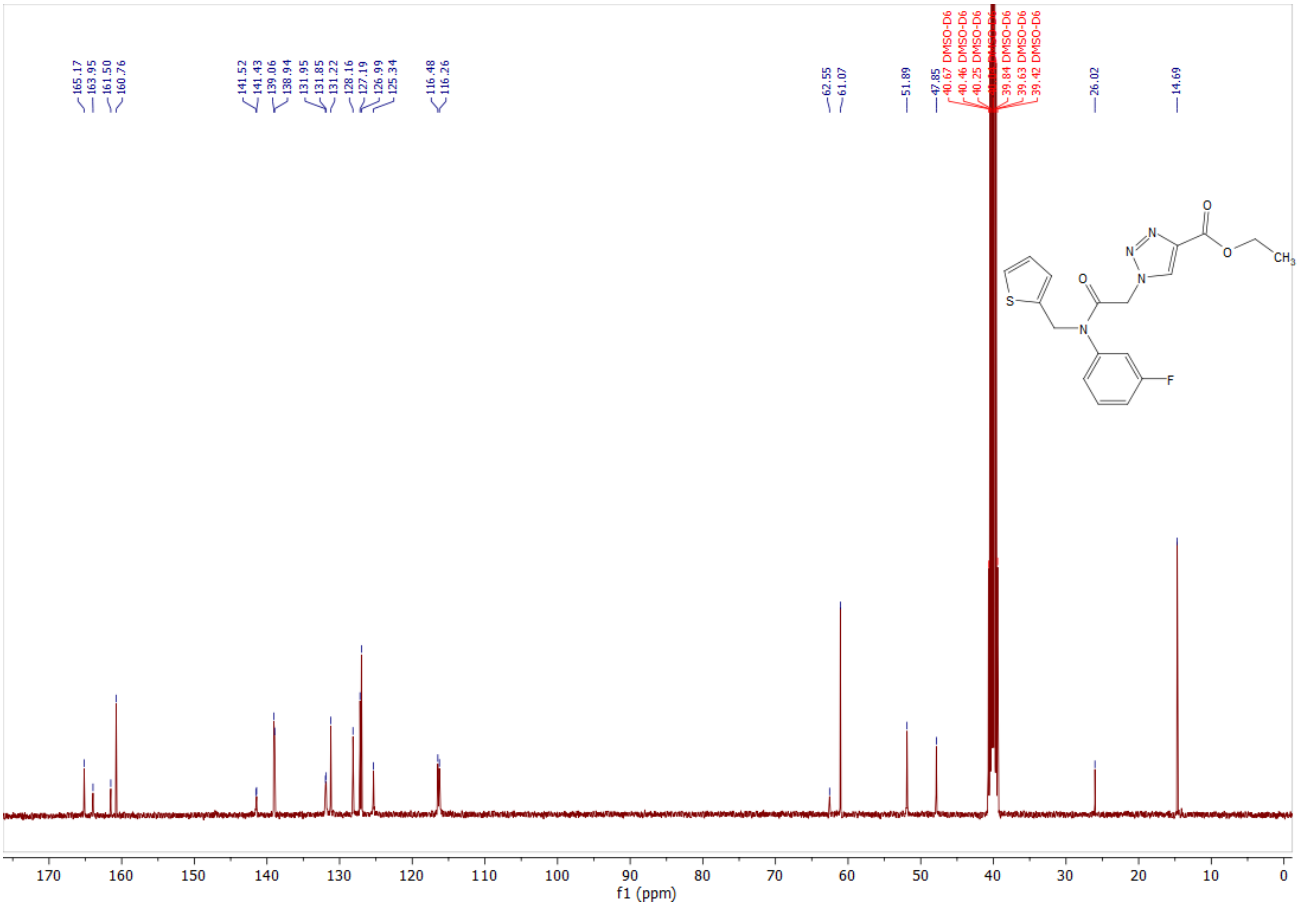
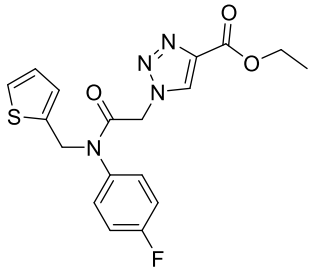


Рисунок 30. ^{13}C NMR spectrum (101 MHz, DMSO-D_6) *Ethyl 1-(2-((3-fluorophenyl)(thiophen-2-ylmethyl)amino)-2-oxoethyl)-1H-1,2,3-triazole-4-carboxylate* **1o**

Речовина **1p**. Нековалентний інгібітор головної протеази SARS-CoV-2 M^{pro}.

Назва: *Ethyl 1-(2-((4-fluorophenyl)(thiophen-2-ylmethyl)amino)-2-oxoethyl)-1H-1,2,3-triazole-4-carboxylate*



White solid. Yield 92 %

Спектральні параметри:

^{1}H NMR (400 MHz, DMSO-D_6) δ 8.59 (s, 1H), 7.40 (dd, J = 5.1, 1.3 Hz, 1H), 7.35 (dd, J = 8.9, 5.2 Hz, 2H), 7.29 (t, J = 8.7 Hz, 2H), 6.88 (dd, J = 5.1, 3.4 Hz, 1H), 6.82 (dd, J = 3.5, 1.2 Hz, 1H), 5.07 (s, 2H), 4.97 (s, 2H), 4.26 (t, J = 7.1 Hz, 2H), 1.26 (t, J = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, DMSO-D_6) δ 165.28, 160.76, 139.05, 138.99, 136.24, 136.21, 131.31, 131.22, 128.18, 127.18, 126.98, 117.34, 117.11, 61.06, 51.87, 47.98, 14.68.

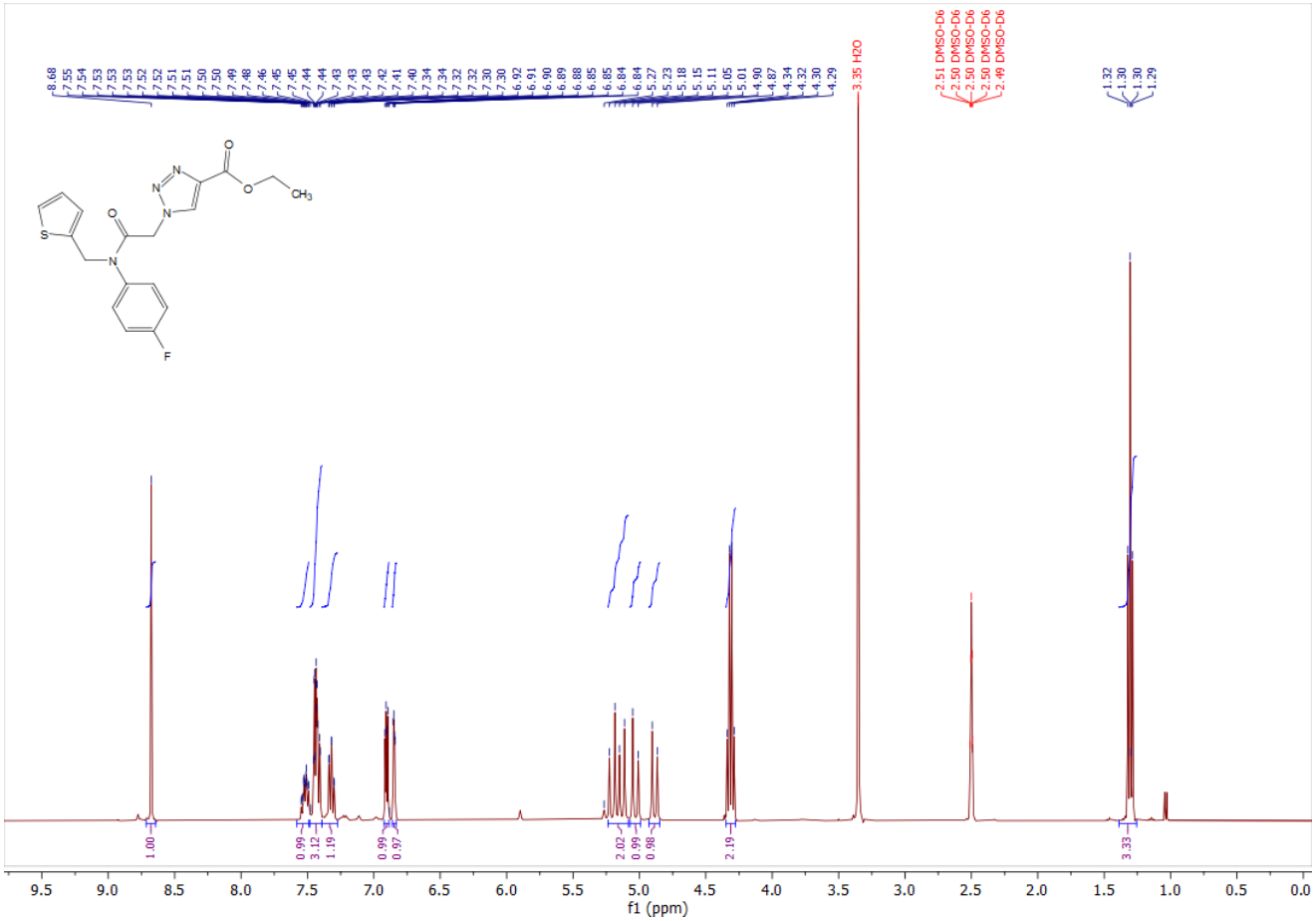


Рисунок 31. ^{1}H NMR spectrum (400 MHz, DMSO-D_6) *Ethyl 1-(2-((4-fluorophenyl)(thiophen-2-ylmethyl)amino)-2-oxoethyl)-1H-1,2,3-triazole-4-carboxylate* **1p**

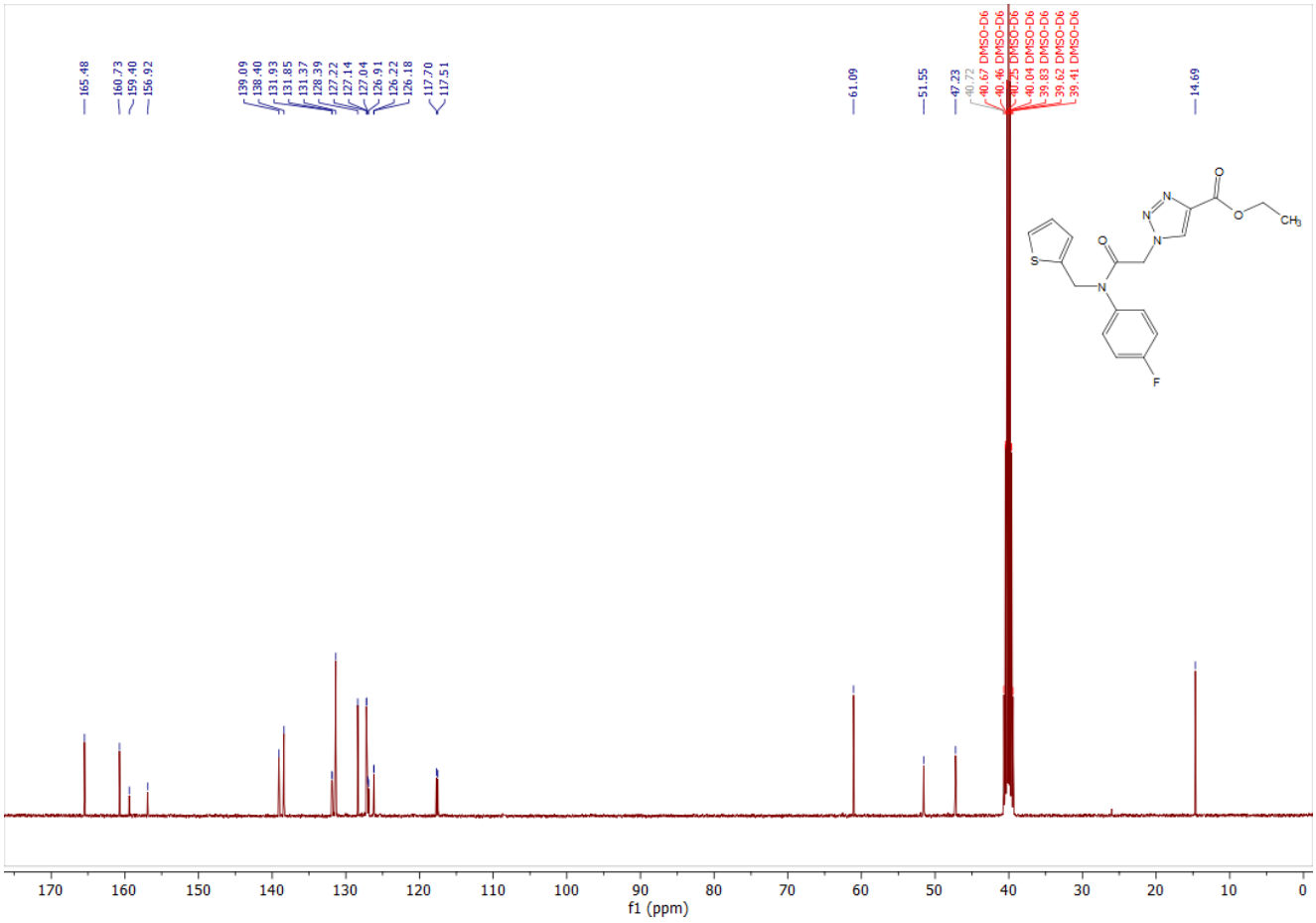
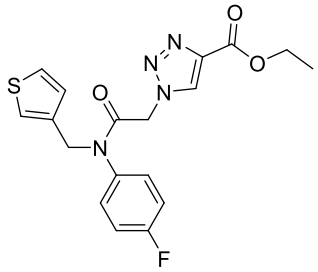


Рисунок 32. ^{13}C NMR spectrum (101 MHz, DMSO-D_6) *Ethyl 1-(2-((4-fluorophenyl)(thiophen-2-ylmethyl)amino)-2-oxoethyl)-1H-1,2,3-triazole-4-carboxylate* **1p**

Речовина **1q**. Нековалентний інгібітор головної протеази SARS-CoV-2 M^{pro}.

Назва: *Ethyl 1-(2-((4-fluorophenyl)(thiophen-3-ylmethyl)amino)-2-oxoethyl)-1H-1,2,3-triazole-4-carboxylate*



White solid. Yield 92 %

Спектральні параметри:

^{1}H NMR (400 MHz, DMSO-D_6) δ 8.52 (s, 1H), 7.41 (dd, J = 5.2, 1.7 Hz, 1H), 7.35 (tt, J = 1.6, 0.9 Hz, 1H), 7.34 – 7.26 (m, 2H), 7.23 (ddt, J = 5.3, 1.6, 0.8 Hz, 1H), 7.10 – 7.00 (m, 2H), 5.20 (d, J = 0.8 Hz, 2H), 5.04 (t, J = 0.9 Hz, 2H), 4.34 (q, J = 6.4 Hz, 2H), 1.29 (t, J = 6.4 Hz, 3H).

^{13}C NMR (101 MHz, DMSO-D_6) δ 166.75, 161.06, 160.65, 158.19, 144.30, 137.30, 137.27, 135.69, 127.29, 127.11, 126.70, 125.59, 125.50, 123.25, 117.52, 117.30, 61.48, 52.26, 44.60, 14.31.

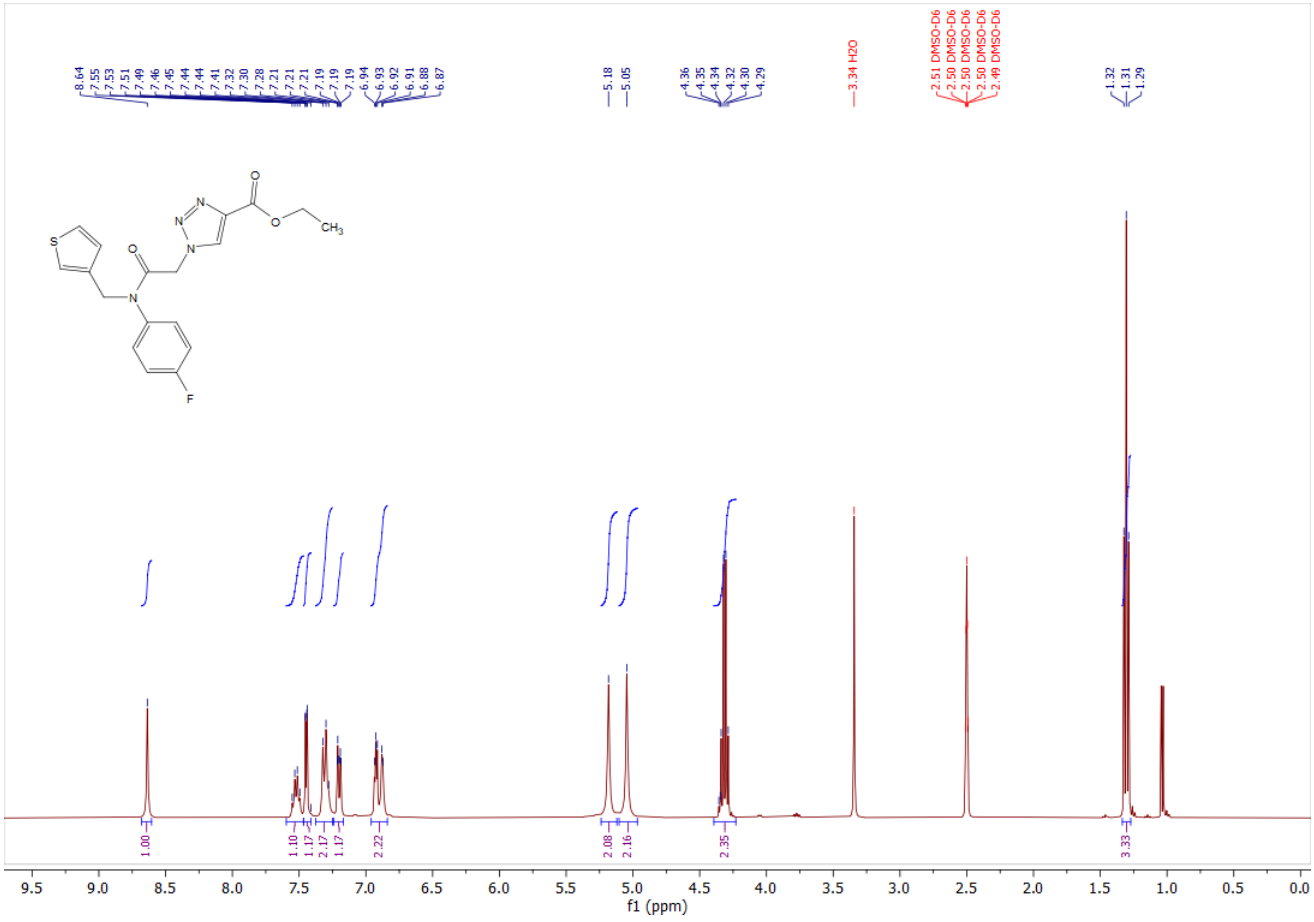


Рисунок 33. ^{1}H NMR spectrum (400 MHz, DMSO-D_6) *Ethyl 1-(2-((4-fluorophenyl)(thiophen-3-ylmethyl)amino)-2-oxoethyl)-1H-1,2,3-triazole-4-carboxylate* **1q**

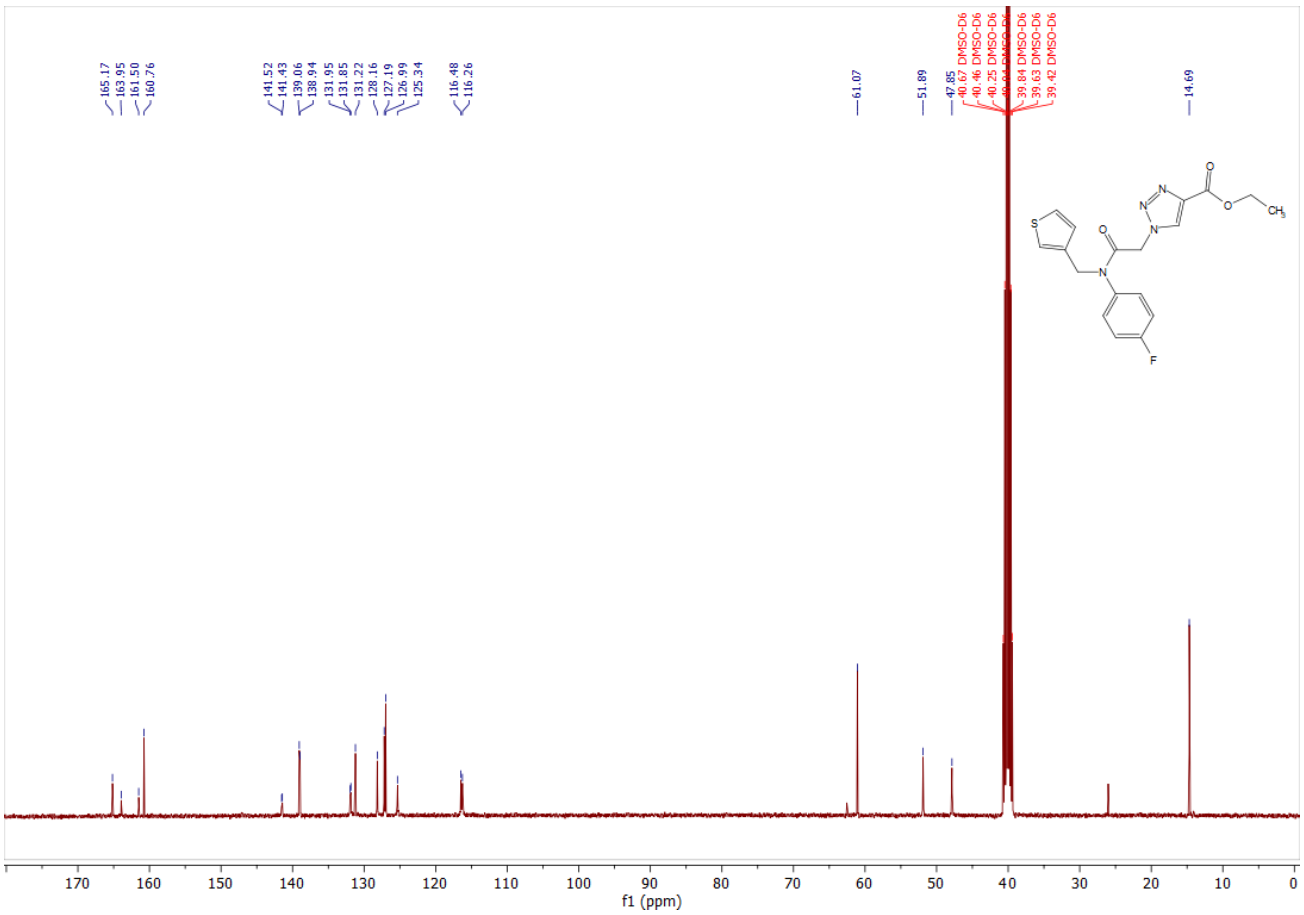
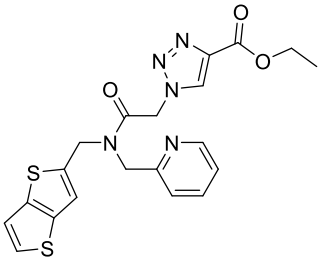


Рисунок 34. ^{13}C NMR spectrum (101 MHz, DMSO-D_6) *Ethyl 1-(2-((4-fluorophenyl)(thiophen-3-ylmethyl)amino)-2-oxoethyl)-1H-1,2,3-triazole-4-carboxylate* **1q**

Речовина **1r**. Нековалентний інгібітор головної протеази SARS-CoV-2 M^{pro}.

Назва: *Ethyl 1-(2-oxo-2-((pyridin-2-ylmethyl)(thieno[3,2-b]thiophen-2-ylmethyl)amino)ethyl)-1H-1,2,3-triazole-4-carboxylate*



White solid. Yield 89 %

Спектральні параметри:

^{1}H NMR (400 MHz, DMSO-D_6) δ 8.54 – 8.45 (m, 2H), 7.80 – 7.71 (m, 1H), 7.54 (d, J = 5.0 Hz, 1H), 7.36 – 7.28 (m, 3H), 7.02 (d, J = 1.2 Hz, 1H), 4.97 (d, J = 0.8 Hz, 2H), 4.68 (d, J = 0.8 Hz, 2H), 4.51 (d, J = 0.7 Hz, 2H), 4.34 (q, J = 6.4 Hz, 2H), 1.29 (t, J = 6.4 Hz, 3H).

^{13}C NMR (101 MHz, DMSO-D_6) δ 167.50, 161.06, 156.18, 149.74, 144.30, 142.68, 139.11, 138.91, 137.07, 130.84, 127.36, 125.01, 122.76, 122.57, 122.18, 61.48, 51.99, 50.63, 47.16, 14.31.

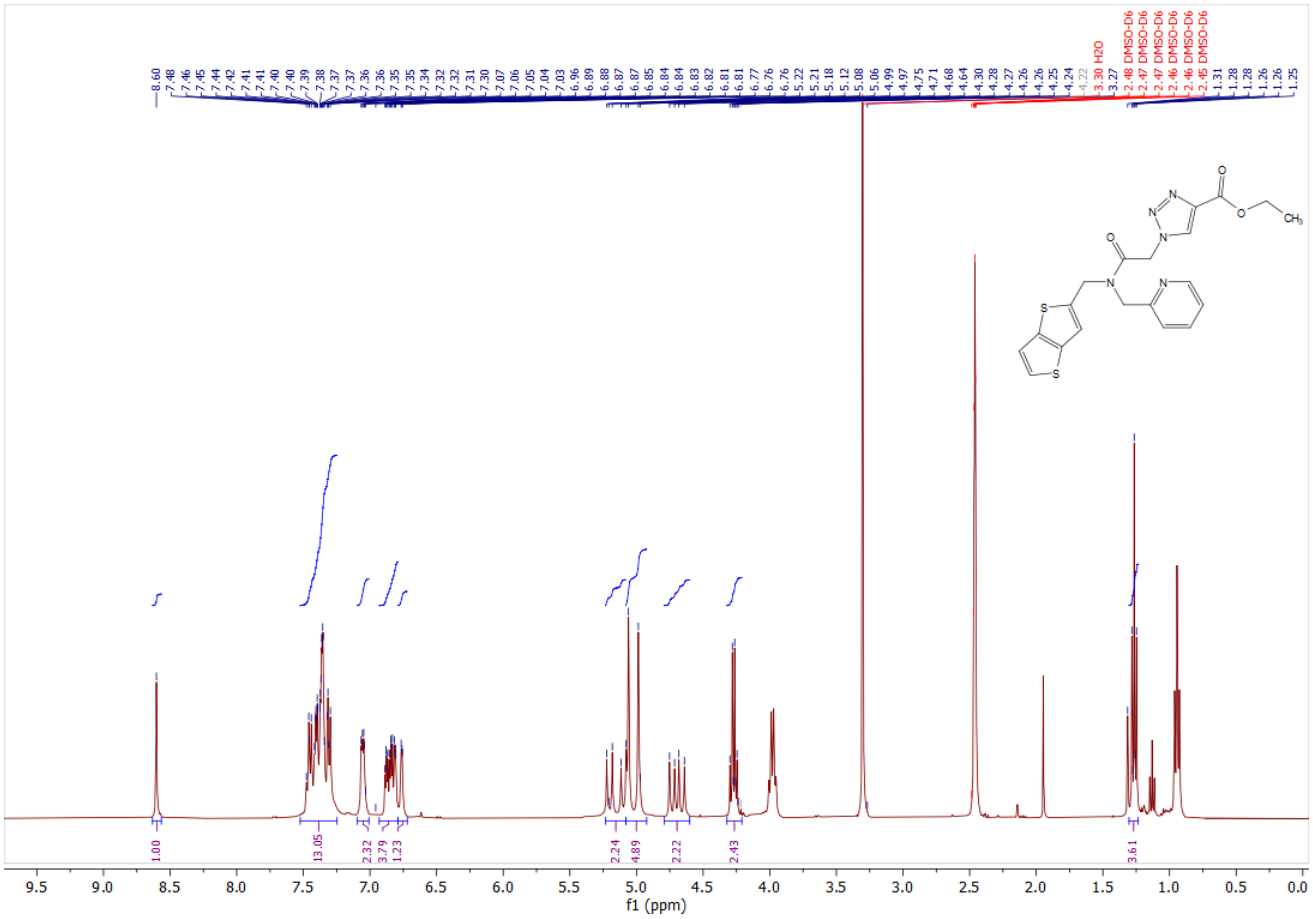


Рисунок 35. ^{1}H NMR spectrum (400 MHz, DMSO-D_6) *Ethyl 1-(2-oxo-2-((pyridin-2-ylmethyl)(thieno[3,2-b]thiophen-2-ylmethyl)amino)ethyl)-1H-1,2,3-triazole-4-carboxylate* **1r**

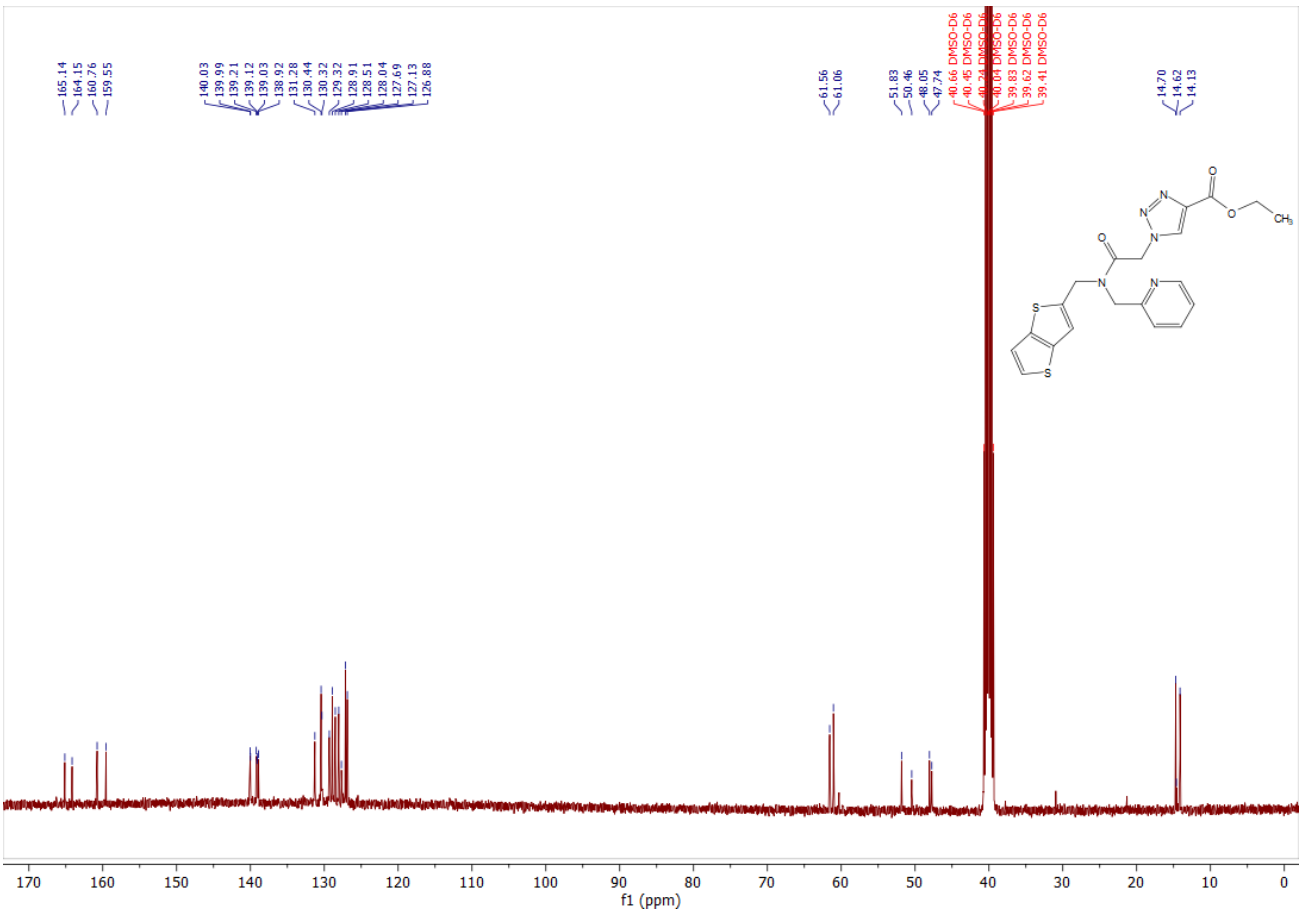
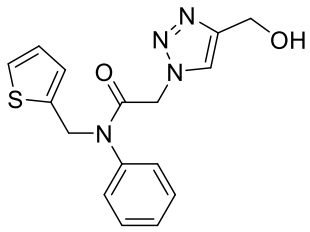


Рисунок 36. ^{13}C NMR spectrum (101 MHz, DMSO-D_6) *Ethyl 1-(2-oxo-2-((pyridin-2-ylmethyl)(thieno[3,2-b]thiophen-2-ylmethyl)amino)ethyl)-1H-1,2,3-triazole-4-carboxylate* **1r**

Речовина **1s**. Нековалентний інгібітор головної протеази SARS-CoV-2 M^{pro}.

Назва: *2-(4-(Hydroxymethyl)-1H-1,2,3-triazol-1-yl)-N-phenyl-N-(thiophen-2-ylmethyl)acetamide*



White solid. Yield 92 %

Спектральні параметри:

^{1}H NMR (400 MHz, DMSO-D_6) δ 7.80 (s, 1H), 7.36 (dd, J = 5.3, 1.7 Hz, 1H), 7.25 (s, 2H), 7.31 – 7.11 (m, 4H), 6.98 (dd, J = 6.5, 5.3 Hz, 1H), 5.23 (d, J = 0.7 Hz, 2H), 5.06 (d, J = 0.7 Hz, 2H), 4.81 (dd, J = 6.1, 5.0 Hz, 1H), 4.77 – 4.71 (m, 2H).

^{13}C NMR (101 MHz, DMSO-D_6) δ 167.84, 148.21, 141.07, 139.14, 129.45, 127.32, 126.61, 125.57, 124.72, 123.62, 120.54, 52.81, 51.74, 43.12.

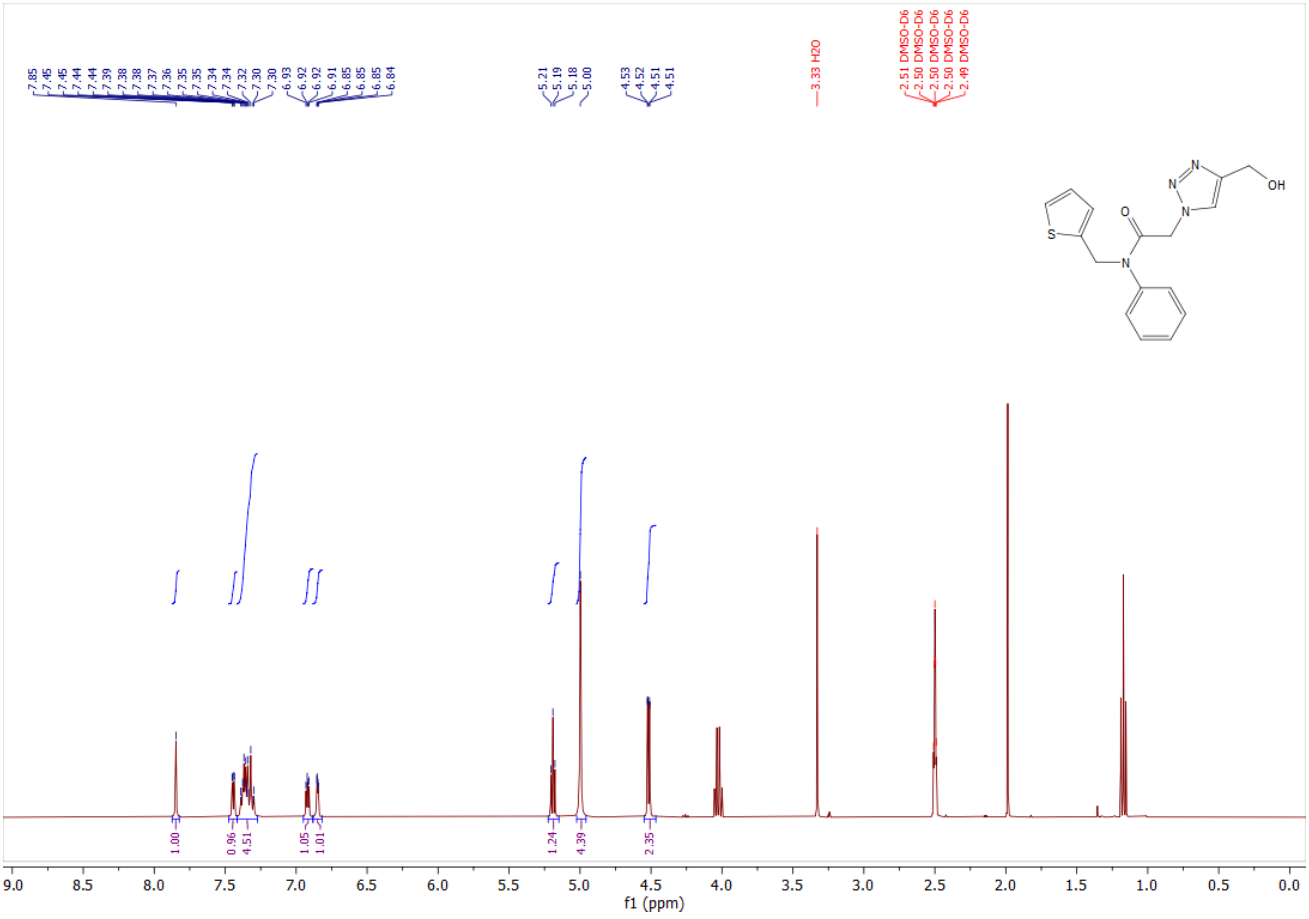


Рисунок 37. ^{1}H NMR spectrum (400 MHz, DMSO-D_6) *2-(4-(Hydroxymethyl)-1H-1,2,3-triazol-1-yl)-N-phenyl-N-(thiophen-2-ylmethyl)acetamide* **1s**

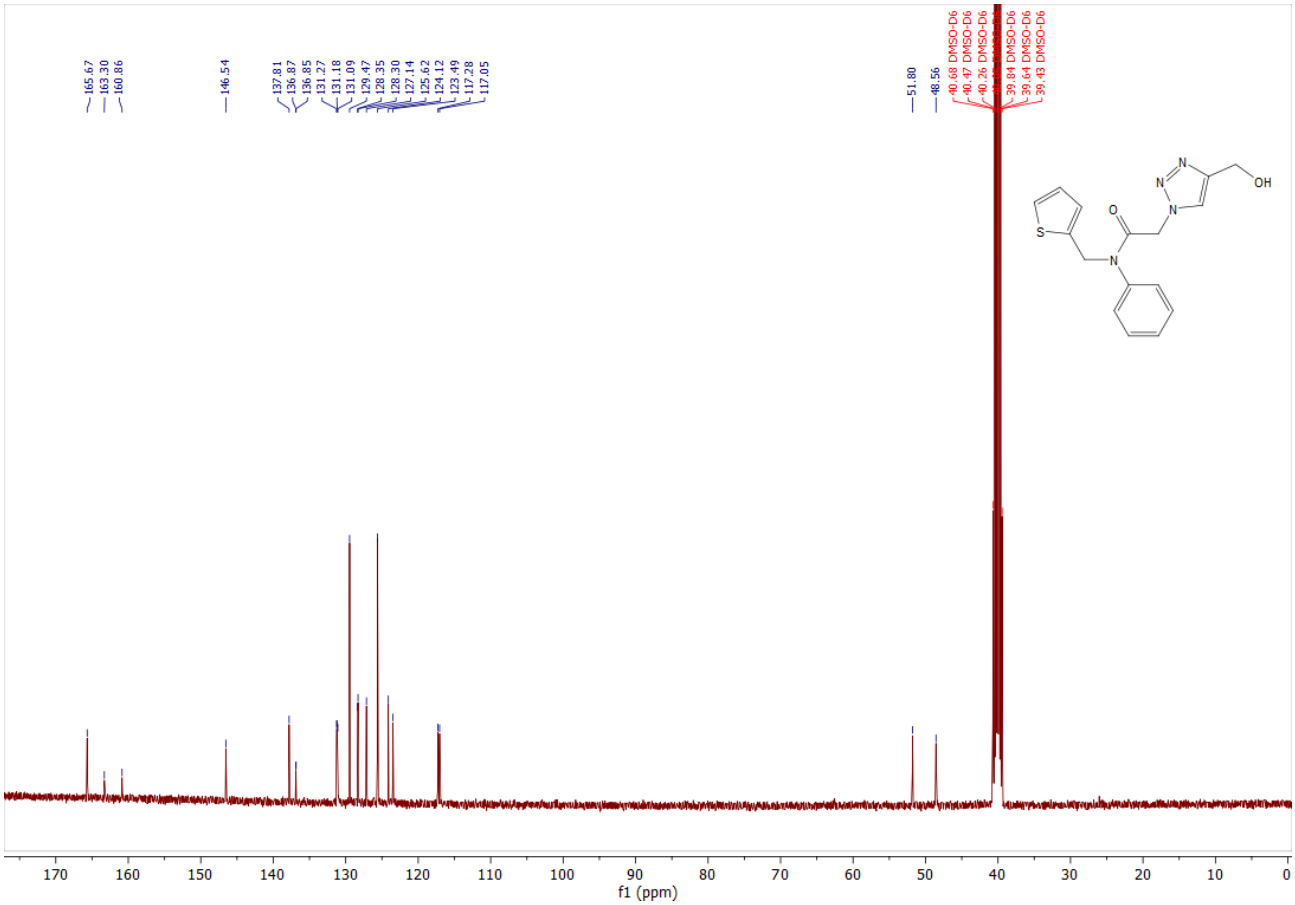
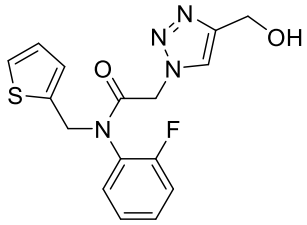


Рисунок 38. ^{13}C NMR spectrum (101 MHz, DMSO-D_6) *2-(4-(Hydroxymethyl)-1H-1,2,3-triazol-1-yl)-N-phenyl-N-(thiophen-2-ylmethyl)acetamide* **1s**

Речовина **1t**. Нековалентний інгібітор головної протеази SARS-CoV-2 M^{pro}.

Назва: *N-(2-Fluorophenyl)-2-(4-(hydroxymethyl)-1H-1,2,3-triazol-1-yl)-N-(thiophen-2-ylmethyl)acetamide*



White solid. Yield 88 %

Спектральні параметри:

^{1}H NMR (400 MHz, DMSO-D_6) δ 7.82 (s, 1H), 7.50 – 7.40 (m, 1H), 7.39 – 7.22 (m, 2H), 7.17 – 6.94 (m, 2H), 5.20 (d, J = 0.8 Hz, 1H), 5.02 (d, J = 0.8 Hz, 1H), 4.84 – 4.71 (m, 2H).

^{13}C NMR (101 MHz, DMSO-D_6) δ 168.24, 166.11, 159.08, 155.66, 147.27, 138.28, 131.32, 131.12, 129.65, 129.58, 127.56, 126.64, 125.67, 125.59, 125.54, 125.19, 125.14, 120.54, 115.82, 115.61, 52.69, 51.74, 44.26, 44.23.

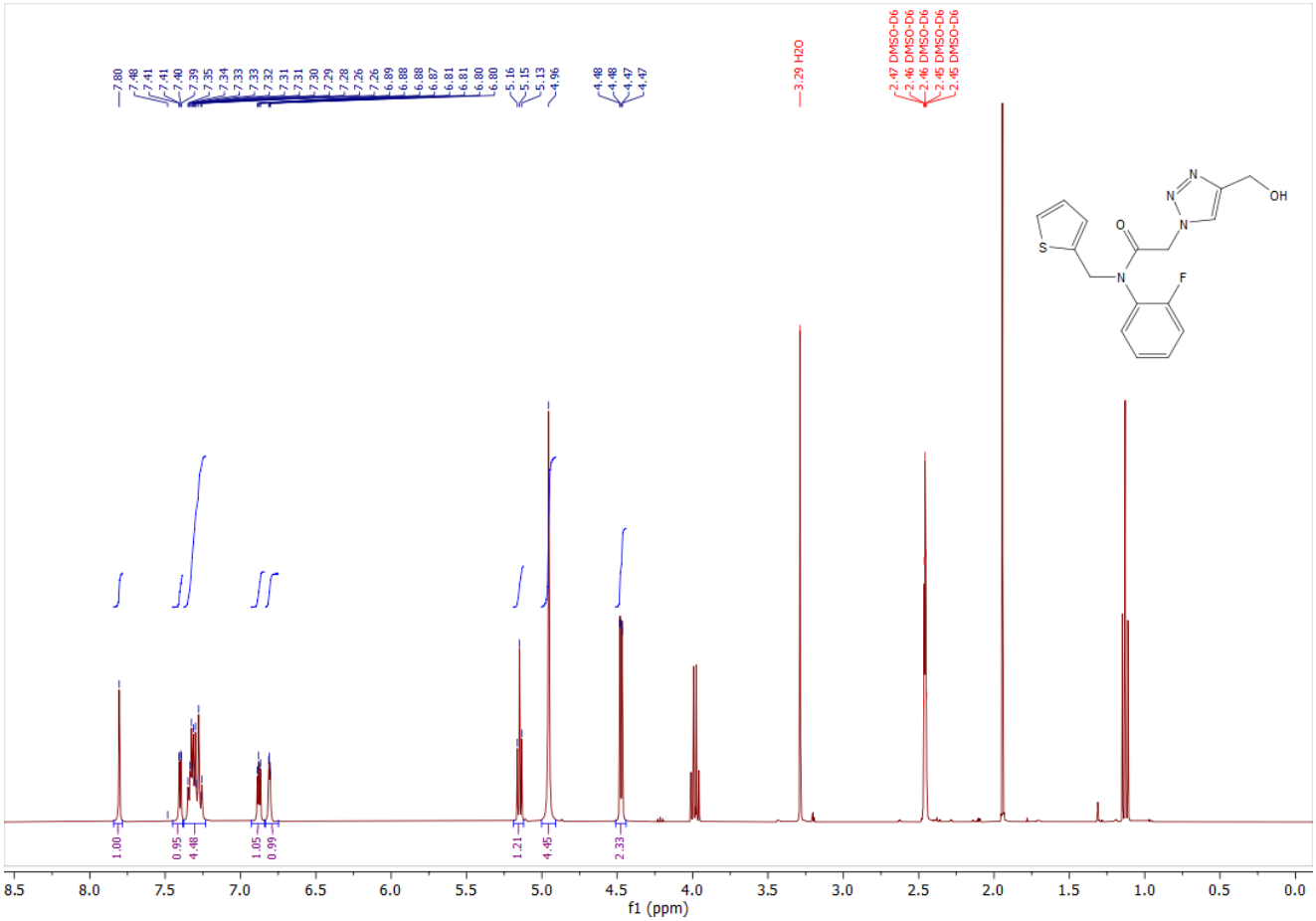


Рисунок 39. ^{1}H NMR spectrum (400 MHz, DMSO-D_6) *N-(2-Fluorophenyl)-2-(4-(hydroxymethyl)-1H-1,2,3-triazol-1-yl)-N-(thiophen-2-ylmethyl)acetamide* **1t**

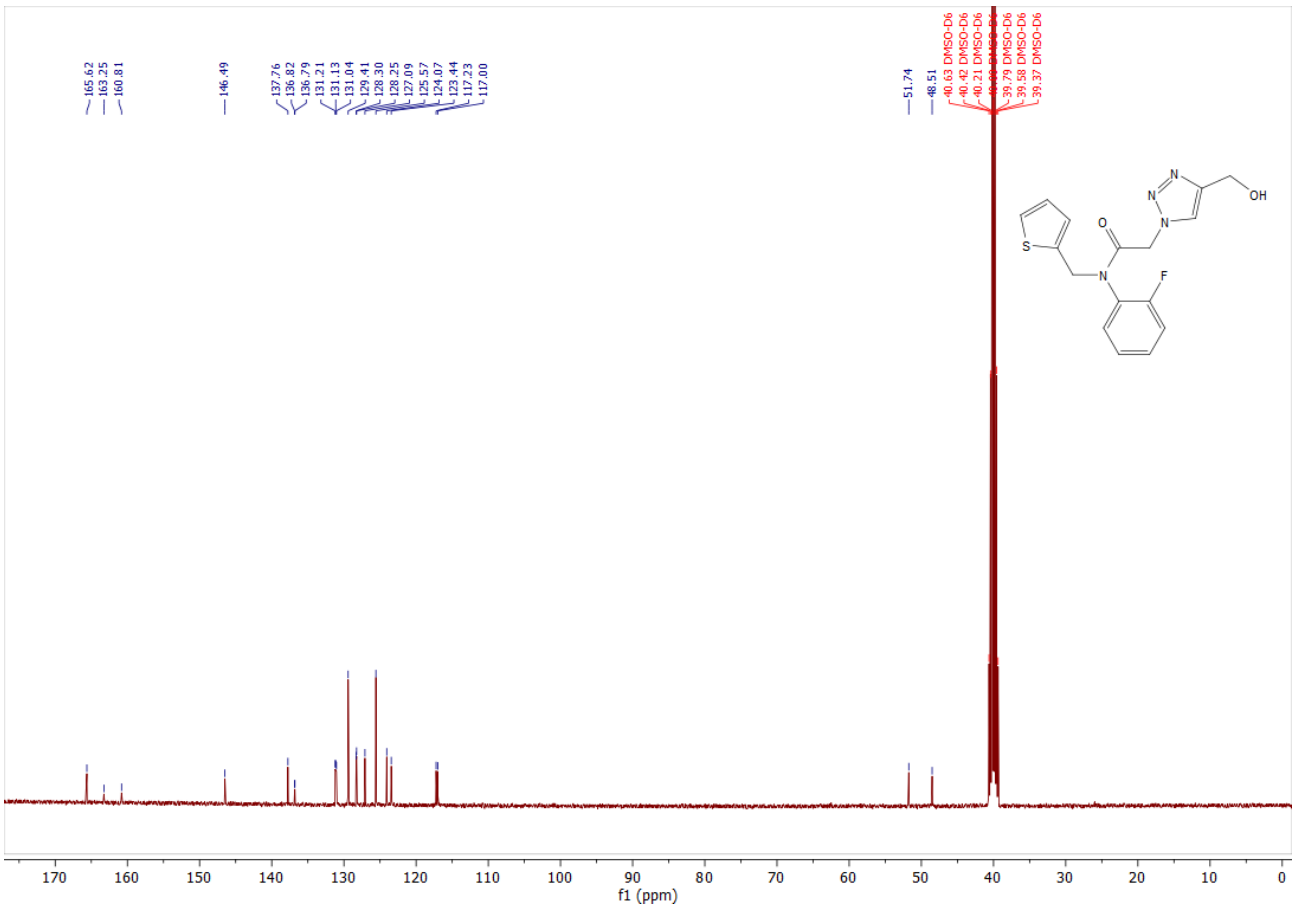
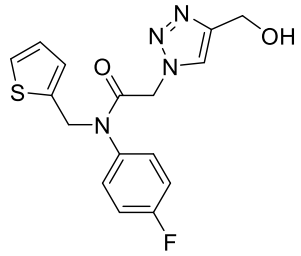


Рисунок 40. ^{13}C NMR spectrum (101 MHz, DMSO-D_6) *N-(2-Fluorophenyl)-2-(4-(hydroxymethyl)-1H-1,2,3-triazol-1-yl)-N-(thiophen-2-ylmethyl)acetamide* **1t**

Речовина **1u**. Нековалентний інгібітор головної протеази SARS-CoV-2 M^{pro}.

Назва: *N-(4-Fluorophenyl)-2-(4-(hydroxymethyl)-1H-1,2,3-triazol-1-yl)-N-(thiophen-2-ylmethyl)acetamide*



White solid. Yield 87 %

Спектральні параметри:

^{1}H NMR (400 MHz, DMSO-D_6) δ 7.80 (s, 1H), 7.40 (dd, J = 5.1, 1.3 Hz, 1H), 7.36 – 7.22 (m, 4H), 6.88 (dd, J = 5.1, 3.4 Hz, 1H), 6.81 (dd, J = 3.4, 1.2 Hz, 1H), 5.15 (t, J = 5.7 Hz, 1H), 4.96 (s, 4H), 4.47 (dd, J = 5.7, 0.7 Hz, 2H), 1.94 (s, 2H).

^{13}C NMR (101 MHz, DMSO-D_6) δ 166.91, 160.65, 158.19, 147.19, 138.11, 136.88, 136.85, 127.23, 125.69, 125.61, 125.58, 125.57, 120.54, 117.57, 117.34, 52.81, 51.74, 43.14.

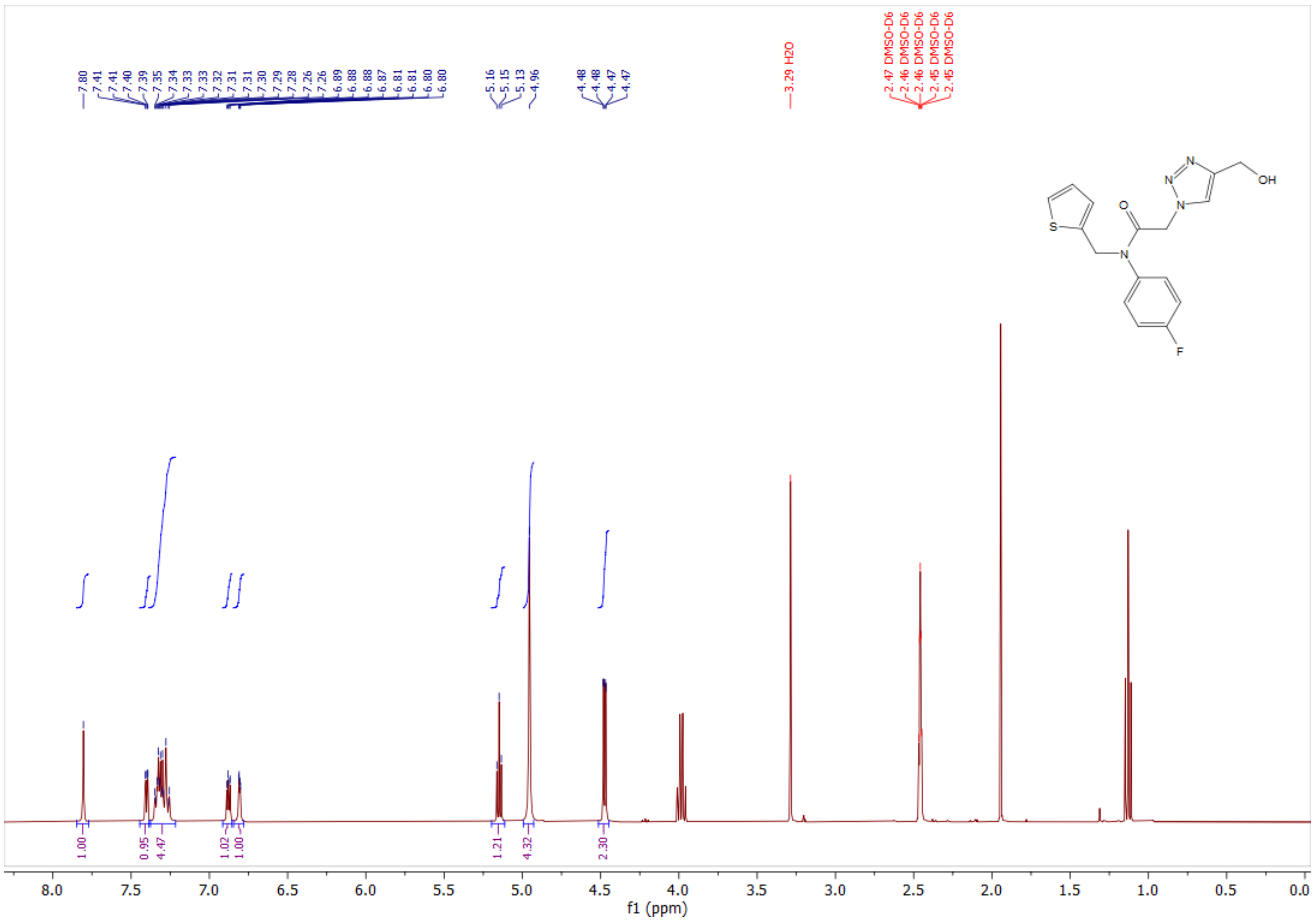


Рисунок 41. ^{1}H NMR spectrum (400 MHz, DMSO-D_6) *N-(4-Fluorophenyl)-2-(4-(hydroxymethyl)-1H-1,2,3-triazol-1-yl)-N-(thiophen-2-ylmethyl)acetamide* **1u**

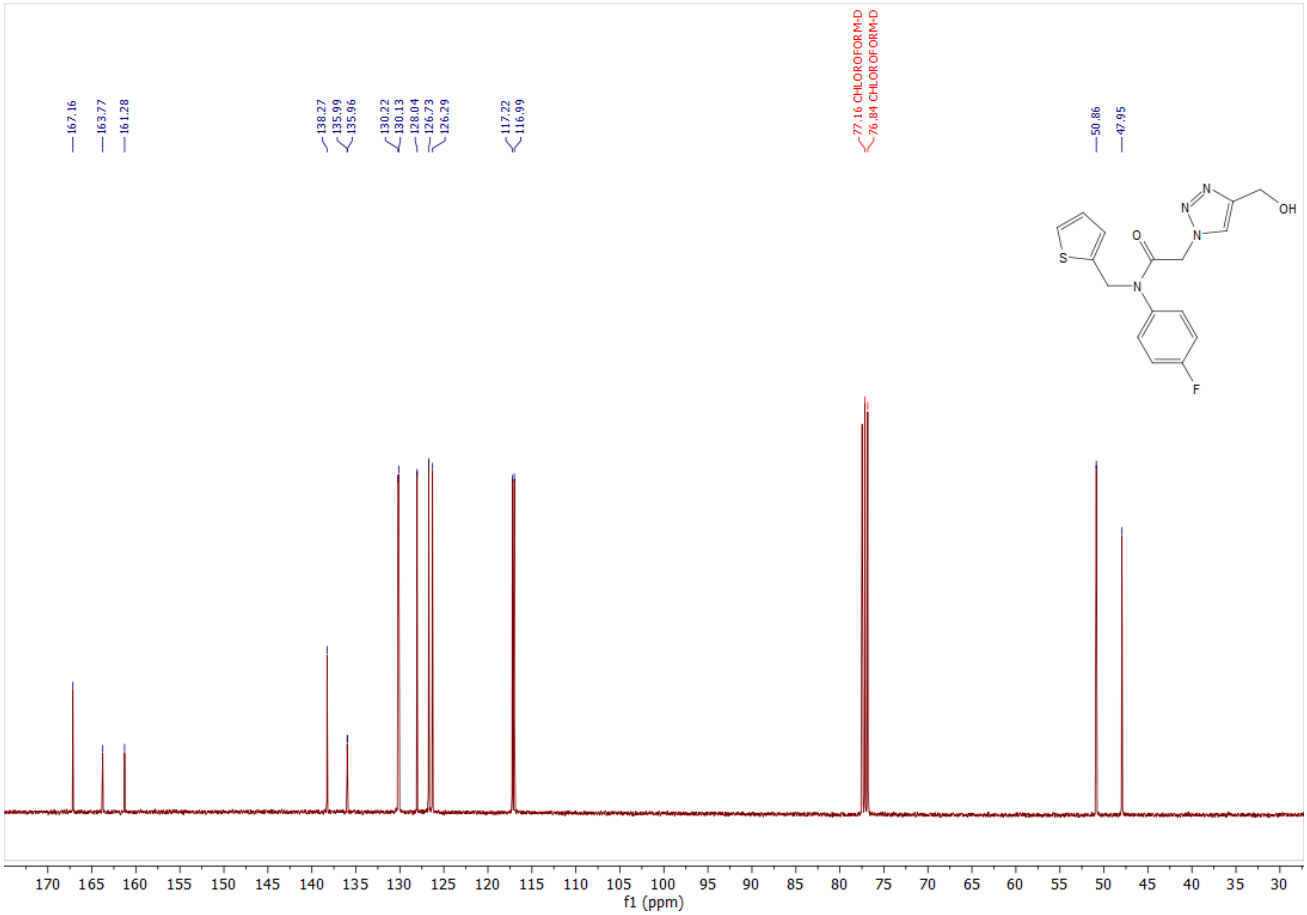
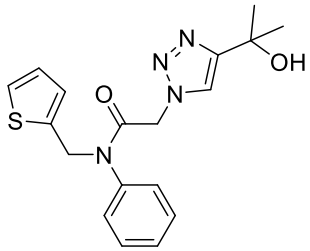


Рисунок 42. ^{13}C NMR spectrum (101 MHz,, $CDCl_3$) *N-(4-Fluorophenyl)-2-(4-(hydroxymethyl)-1H-1,2,3-triazol-1-yl)-N-(thiophen-2-ylmethyl)acetamide* **1u**

Речовина **1v**. Нековалентний інгібітор головної протеази SARS-CoV-2 M^{pro}.

Назва: *2-(4-(2-Hydroxypropan-2-yl)-1H-1,2,3-triazol-1-yl)-N-phenyl-N-(thiophen-2-ylmethyl)acetamide*



White solid. Yield 89 %

Спектральні параметри:

^{1}H NMR (400 MHz, DMSO-D_6) δ 7.70 (t, J = 0.8 Hz, 1H), 7.36 (dd, J = 5.3, 1.7 Hz, 1H), 7.31 – 7.14 (m, 5H), 7.15 (ddt, J = 6.5, 1.8, 0.8 Hz, 1H), 6.98 (dd, J = 6.5, 5.3 Hz, 1H), 5.22 (d, J = 0.8 Hz, 2H), 5.12 – 5.03 (m, 3H), 1.76 (s, 5H).

^{13}C NMR (101 MHz, DMSO-D_6) δ 166.82, 157.10, 140.05, 138.11, 129.24, 127.23, 125.58, 125.57, 124.72, 123.62, 118.60, 68.33, 52.82, 43.12, 29.57.

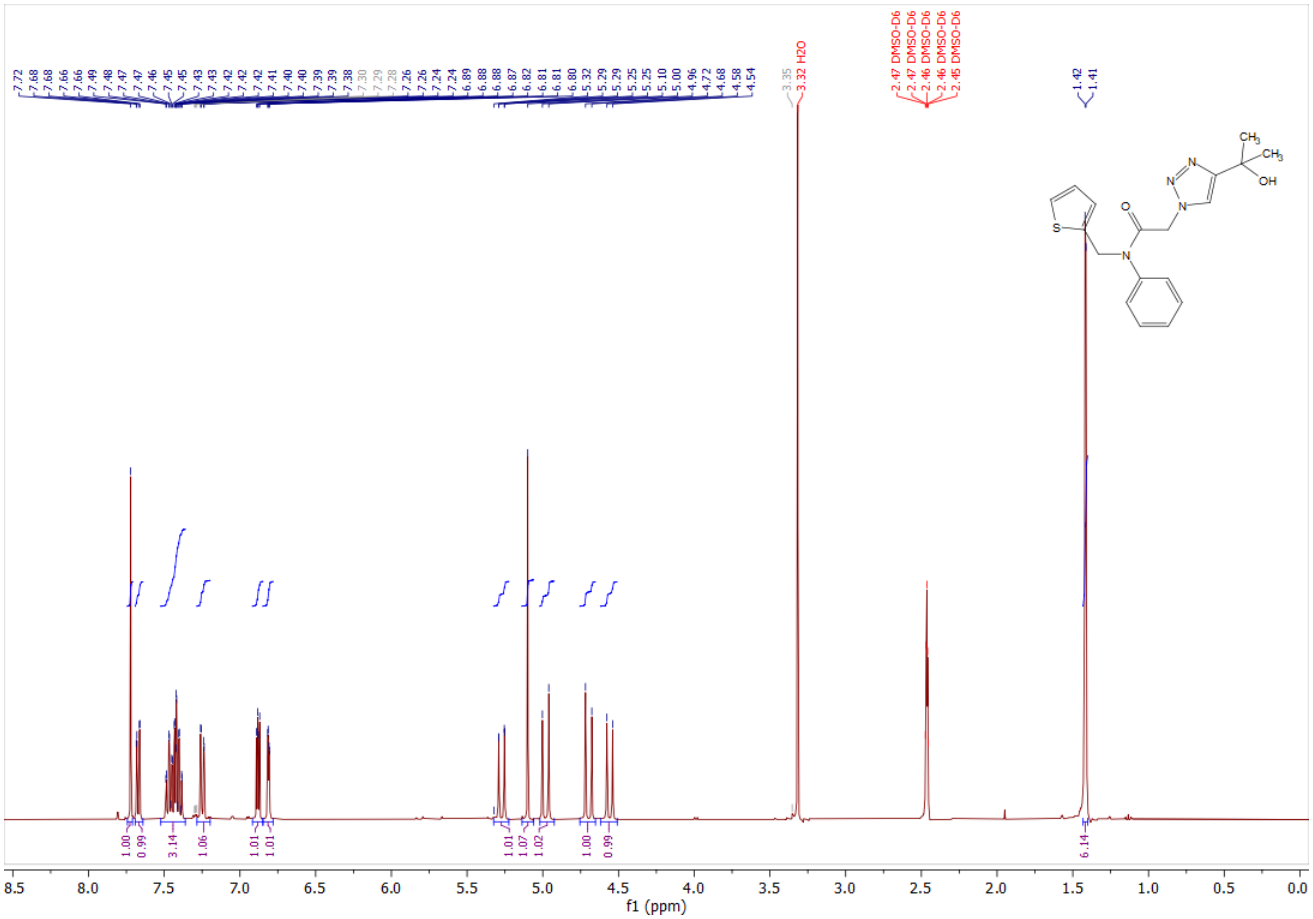


Рисунок 43. ^{1}H NMR spectrum (400 MHz, DMSO-D_6) *2-(4-(2-Hydroxypropan-2-yl)-1H-1,2,3-triazol-1-yl)-N-phenyl-N-(thiophen-2-ylmethyl)acetamide* **1v**

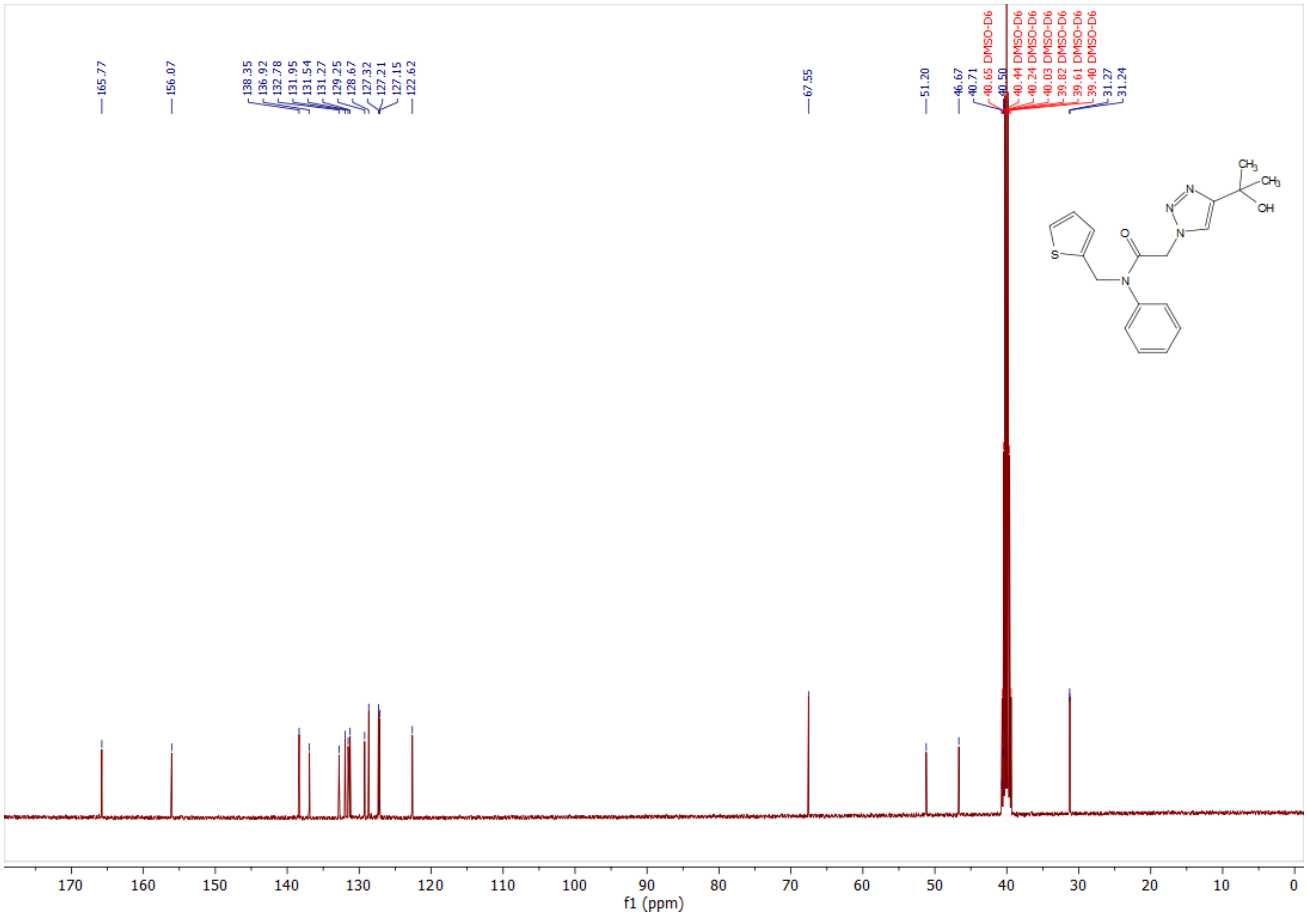
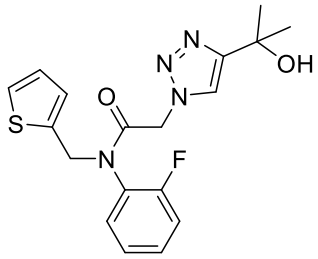


Рисунок 44. ^{13}C NMR spectrum (101 MHz, DMSO-D_6) *2-(4-(2-Hydroxypropan-2-yl)-1H-1,2,3-triazol-1-yl)-N-phenyl-N-(thiophen-2-ylmethyl)acetamide* **1v**

Речовина **1w**. Нековалентний інгібітор головної протеази SARS-CoV-2 M^{pro}.

Назва: *N-(2-Fluorophenyl)-2-(4-(2-hydroxypropan-2-yl)-1H-1,2,3-triazol-1-yl)-N-(thiophen-2-ylmethyl)acetamide*



White solid. Yield 87 %

Спектральні параметри:

^{1}H NMR (400 MHz, DMSO-D_6) δ 7.72 (s, 1H), 7.51 – 7.42 (m, 1H), 7.39 – 7.22 (m, 3H), 7.14 (ddt, *J* = 6.5, 1.7, 0.9 Hz, 1H), 7.11 – 7.01 (m, 1H), 6.98 (dd, *J* = 6.4, 5.3 Hz, 1H), 5.09 (s, 1H), 5.02 (d, *J* = 8.2 Hz, 4H), 1.76 (s, 6H).

^{13}C NMR (101 MHz, DMSO-D_6) δ 166.27, 165.19, 158.09, 157.15, 155.63, 138.25, 131.26, 131.12, 129.65, 129.58, 127.23, 125.64, 125.60, 125.59, 125.54, 125.19, 125.14, 118.60, 115.82, 115.61, 68.33, 52.78, 44.26, 44.23, 29.57.

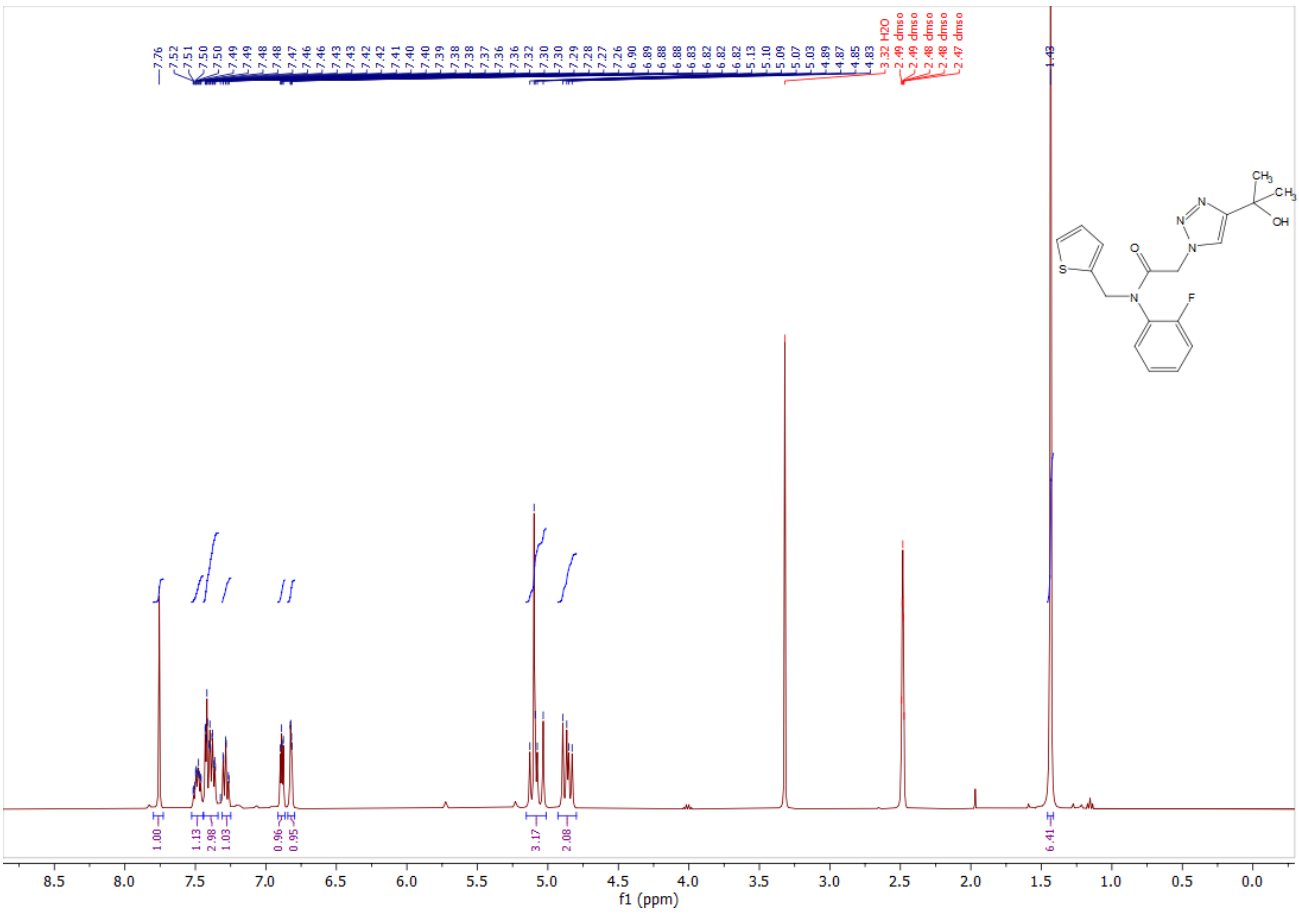


Рисунок 45. ^{1}H NMR spectrum (400 MHz, DMSO-D_6) *N-(2-Fluorophenyl)-2-(4-(2-hydroxypropan-2-yl)-1H-1,2,3-triazol-1-yl)-N-(thiophen-2-ylmethyl)acetamide* **1w**

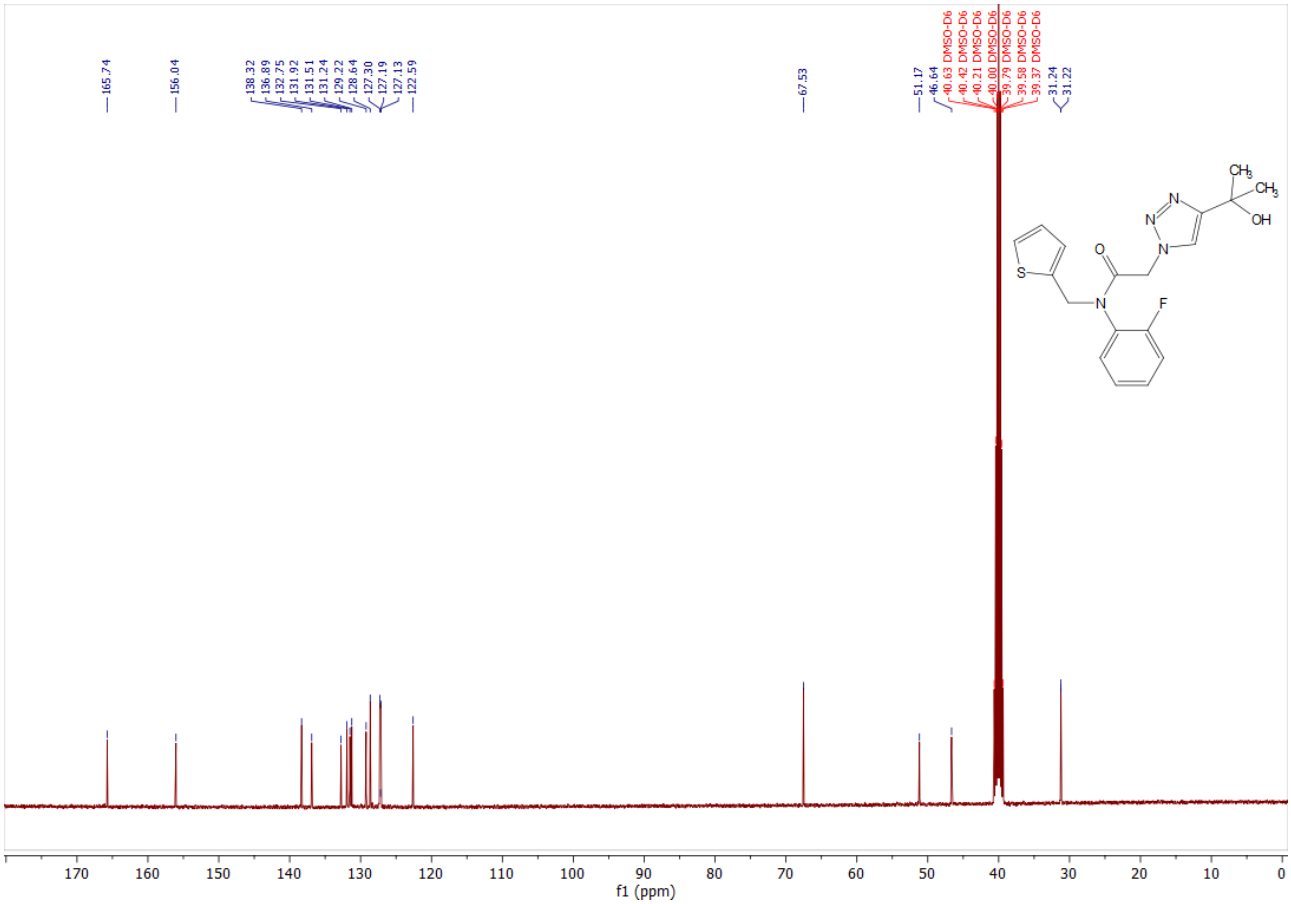
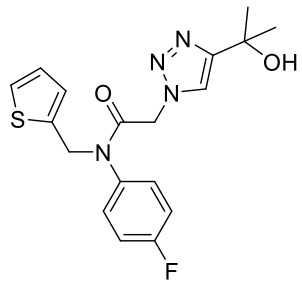


Рисунок 46. ^{13}C NMR spectrum (101 MHz, DMSO-D_6) *N-(2-Fluorophenyl)-2-(4-(2-hydroxypropan-2-yl)-1H-1,2,3-triazol-1-yl)-N-(thiophen-2-ylmethyl)acetamide* **1w**

Речовина **1x**. Нековалентний інгібітор головної протеази SARS-CoV-2 M^{pro}.

Назва: *N-(4-Fluorophenyl)-2-(4-(2-hydroxypropan-2-yl)-1H-1,2,3-triazol-1-yl)-N-(thiophen-2-ylmethyl)acetamide*



White solid. Yield 90 %

Спектральні параметри:

^{1}H NMR (400 MHz, DMSO-D_6) δ 7.70 (s, 1H), 7.40 (dd, J = 5.1, 1.3 Hz, 1H), 7.34 – 7.20 (m, 4H), 6.88 (dd, J = 5.1, 3.4 Hz, 1H), 6.81 (dd, J = 3.4, 1.3 Hz, 1H), 5.06 (s, 1H), 4.94 (d, J = 8.4 Hz, 4H), 1.41 (s, 6H).

^{13}C NMR (101 MHz, DMSO-D_6) δ 166.93, 160.65, 158.19, 157.10, 138.11, 136.88, 136.85, 127.23, 125.69, 125.61, 125.58, 125.57, 118.60, 117.57, 117.34, 68.33, 52.82, 43.14, 29.57.

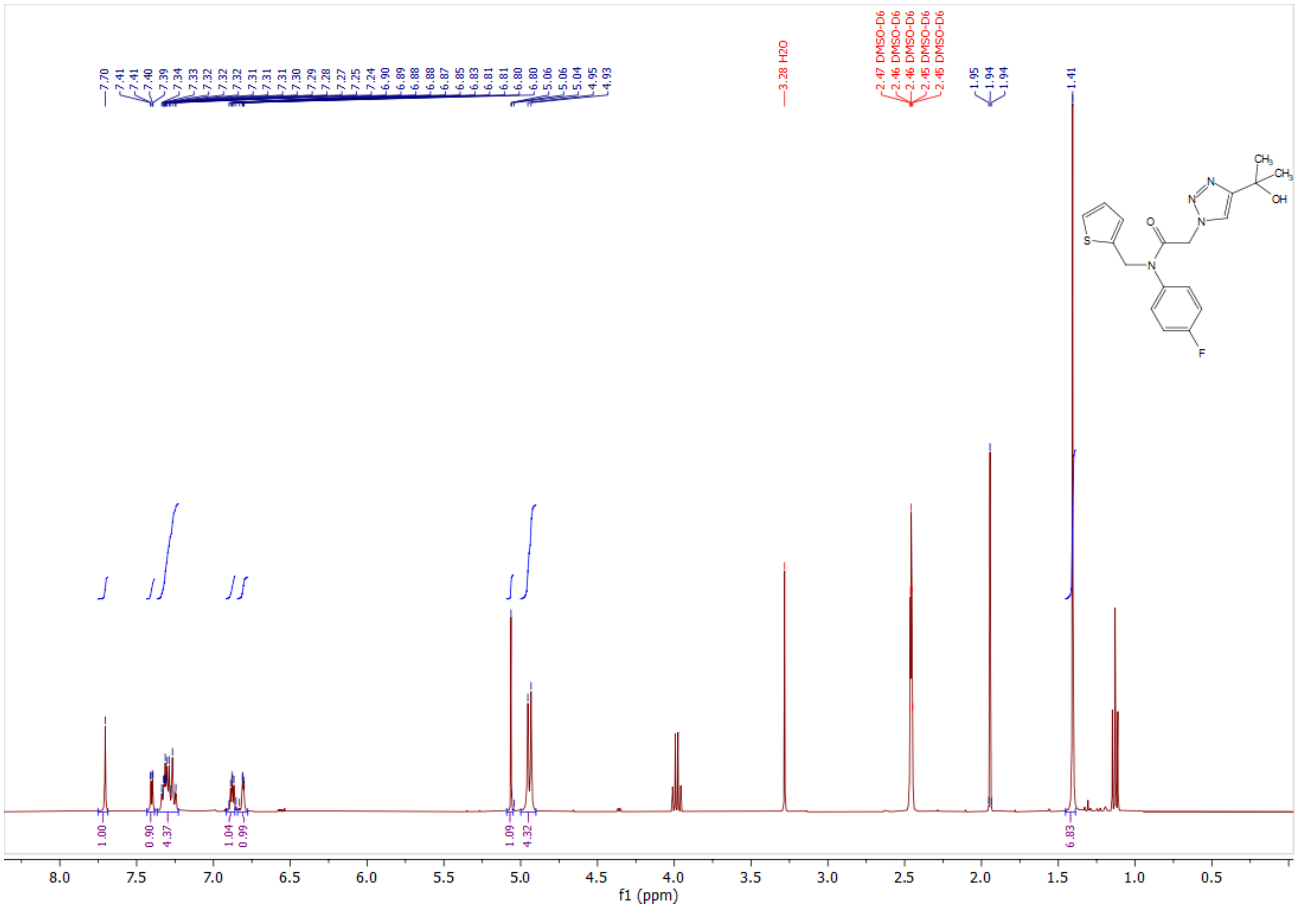


Рисунок 47. ^{1}H NMR spectrum (400 MHz, DMSO-D_6) *N-(4-Fluorophenyl)-2-(4-(2-hydroxypropan-2-yl)-1H-1,2,3-triazol-1-yl)-N-(thiophen-2-ylmethyl)acetamide* **1x**

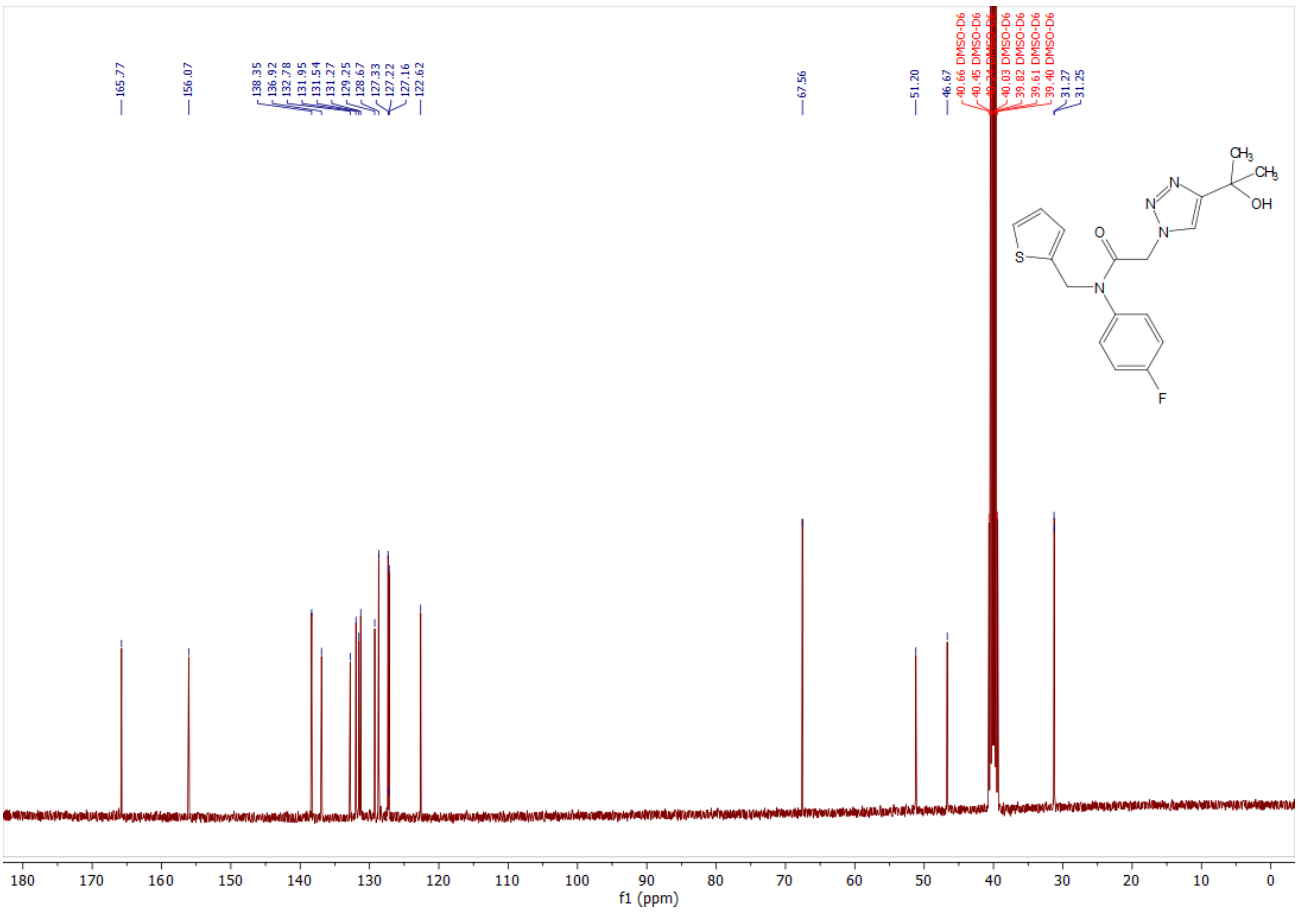
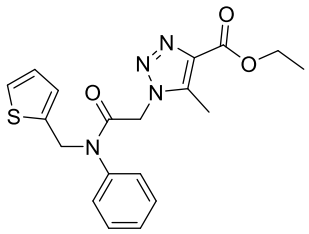


Рисунок 48. ^{13}C NMR spectrum (101 MHz, DMSO-D_6) *N-(4-Fluorophenyl)-2-(4-(2-hydroxypropan-2-yl)-1H-1,2,3-triazol-1-yl)-N-(thiophen-2-ylmethyl)acetamide* **1x**

Похідні етил 5-(4-(трифторметил)феніл)-1*H*-1,2,3-триазол-4-карбоксилатів та етил 5-methyl-1*H*-1,2,3-триазол-4-карбоксилатів 2a-2d

Речовина **2a**. Нековалентний інгібітор головної протеази SARS-CoV-2 M^{pro}.

Назва: *Ethyl 5-methyl-1-(2-oxo-2-(phenyl(thiophen-2-ylmethyl)amino)ethyl)-1H-1,2,3-triazole-4-carboxylate*



White solid. Yield 96 %

Спектральні параметри:

^{1}H NMR (400 MHz, DMSO-D_6) δ 7.39 (dd, J = 5.3, 1.7 Hz, 1H), 7.33 – 7.24 (m, 4H), 7.23 – 7.11 (m, 2H), 6.98 (dd, J = 6.5, 5.3 Hz, 1H), 5.20 (s, 2H), 5.06 (d, J = 0.8 Hz, 2H), 4.37 (q, J = 6.4 Hz, 2H), 1.32 (t, J = 6.4 Hz, 3H).

^{13}C NMR (101 MHz, DMSO-D_6) δ 166.20, 162.17, 139.76, 138.11, 137.57, 137.23, 129.24, 127.23, 125.58 (d, J = 1.2 Hz), 124.72, 123.63, 63.82, 50.69, 42.98, 14.09, 11.27.

MS (ESI+) m/z calculated for $C_{19}H_{20}N_4O_3S$ $[M+H]^+$ 385.1, found 385.3.

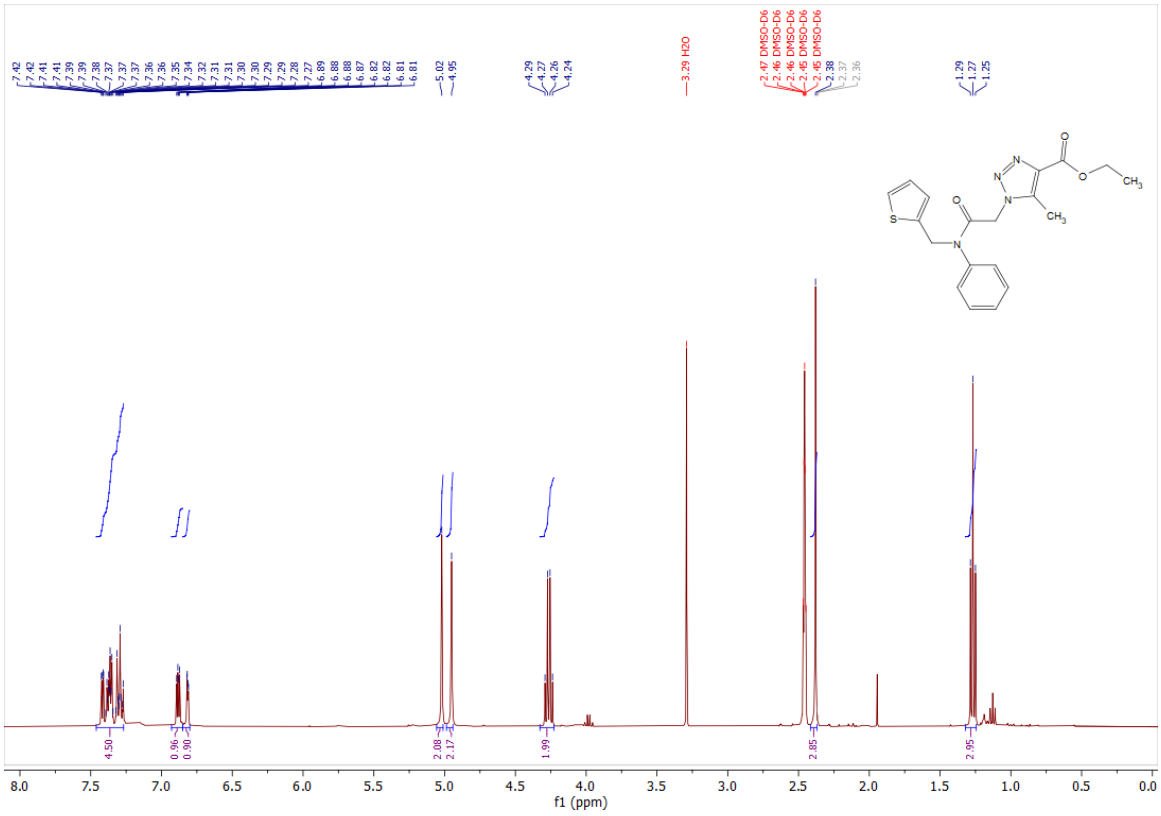


Рисунок 49. ^{1}H NMR spectrum (400 MHz, DMSO-D_6) *Ethyl 5-methyl-1-(2-oxo-2-(phenyl(thiophen-2-ylmethyl)amino)ethyl)-1H-1,2,3-triazole-4-carboxylate* **2a**

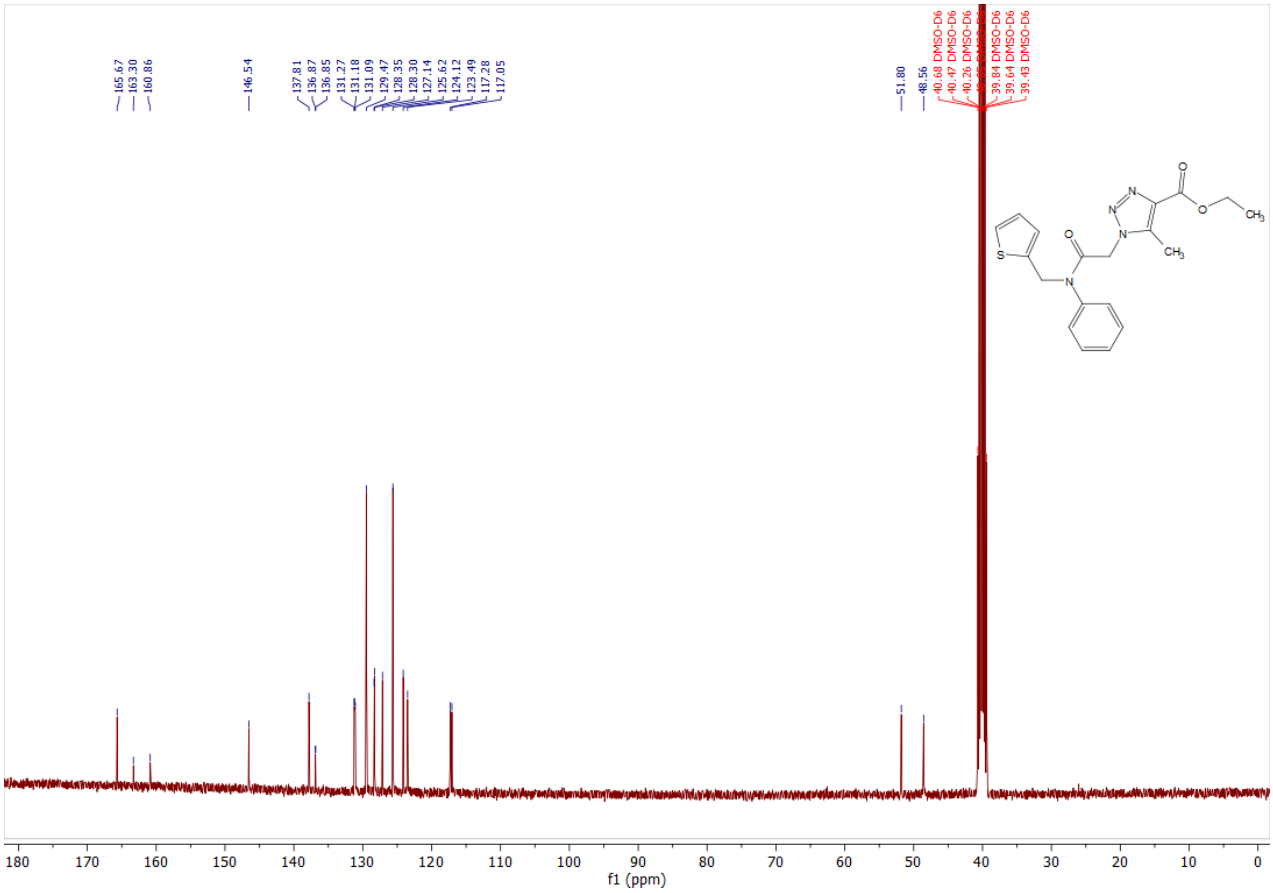
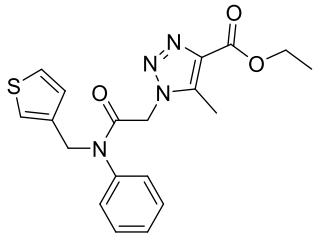


Рисунок 50. ^{13}C NMR spectrum (101 MHz, DMSO-D_6) *Ethyl 5-methyl-1-(2-oxo-2-(phenyl(thiophen-2-ylmethyl)amino)ethyl)-1H-1,2,3-triazole-4-carboxylate* **2a**

Речовина **2b**. Нековалентний інгібітор головної протеази SARS-CoV-2 M^{pro}.

Назва: *Ethyl 5-methyl-1-(2-oxo-2-(phenyl(thiophen-3-ylmethyl)amino)ethyl)-1H-1,2,3-triazole-4-carboxylate*



White solid. Yield 93 %. MS (ESI+) m/z calculated for $C_{19}H_{20}N_4O_3S$ $[M+H]^+$ 385.1, found 385.3.

Спектральні параметри:

^{1}H NMR (400 MHz, DMSO-D_6) δ 7.38 (dd, J = 5.2, 1.7 Hz, 1H), 7.35 (tt, J = 1.6, 0.9 Hz, 1H), 7.31 – 7.22 (m, 5H), 7.22 – 7.13 (m, 1H), 5.20 (s, 2H), 5.04 (t, J = 0.9 Hz, 2H), 4.37 (q, J = 6.4 Hz, 2H), 1.29 (t, J = 6.4 Hz, 3H).

^{13}C NMR (101 MHz, DMSO-D_6) δ 166.35, 162.17, 139.92, 137.57, 137.23, 135.71, 129.24, 127.11, 126.70, 124.72, 123.63, 123.25, 63.82, 50.64, 44.76, 14.09, 11.27

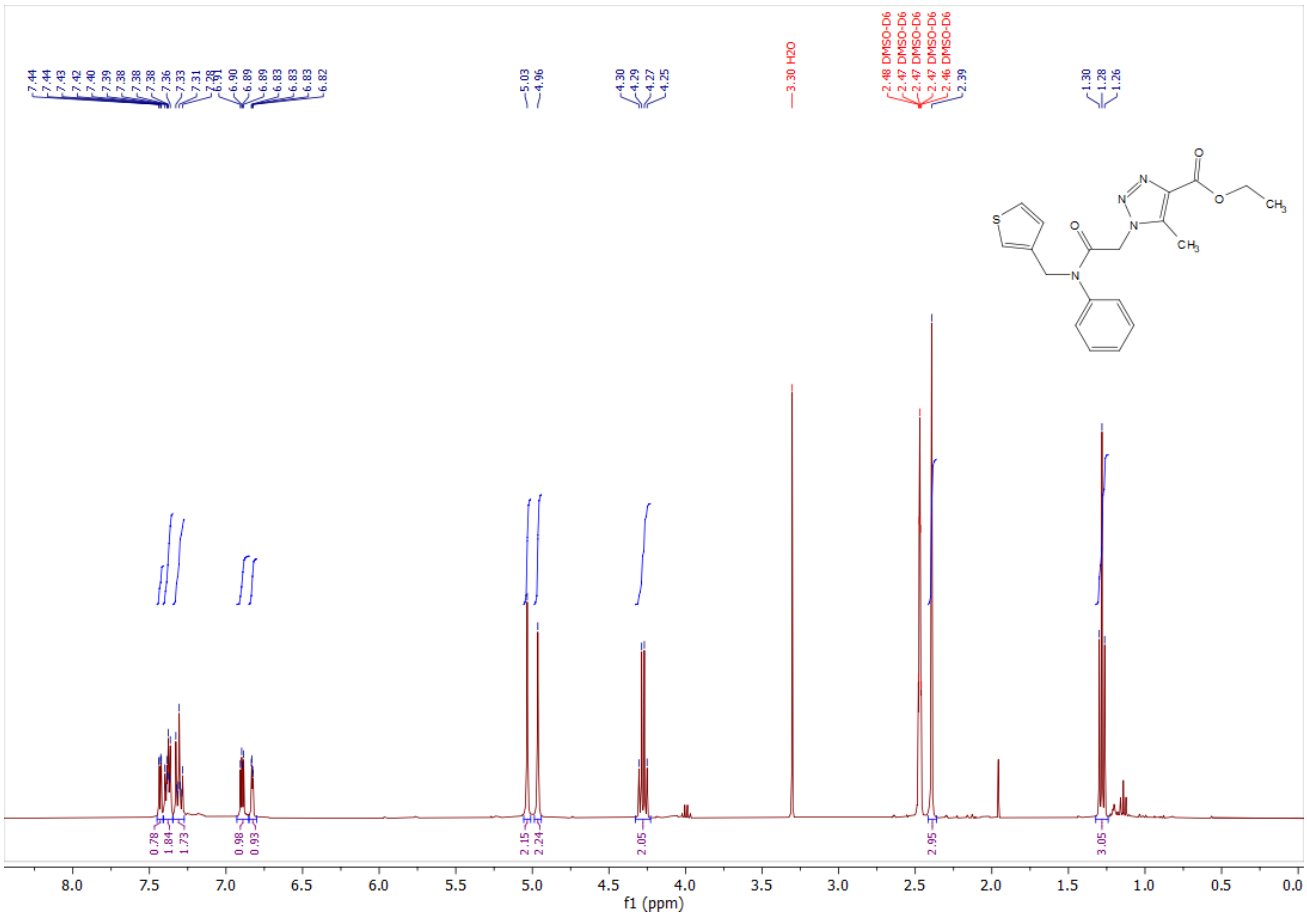


Рисунок 51. ^{1}H NMR spectrum (400 MHz, DMSO-D_6) *Ethyl 5-methyl-1-(2-oxo-2-(phenyl(thiophen-3-ylmethyl)amino)ethyl)-1H-1,2,3-triazole-4-carboxylate* **2b**

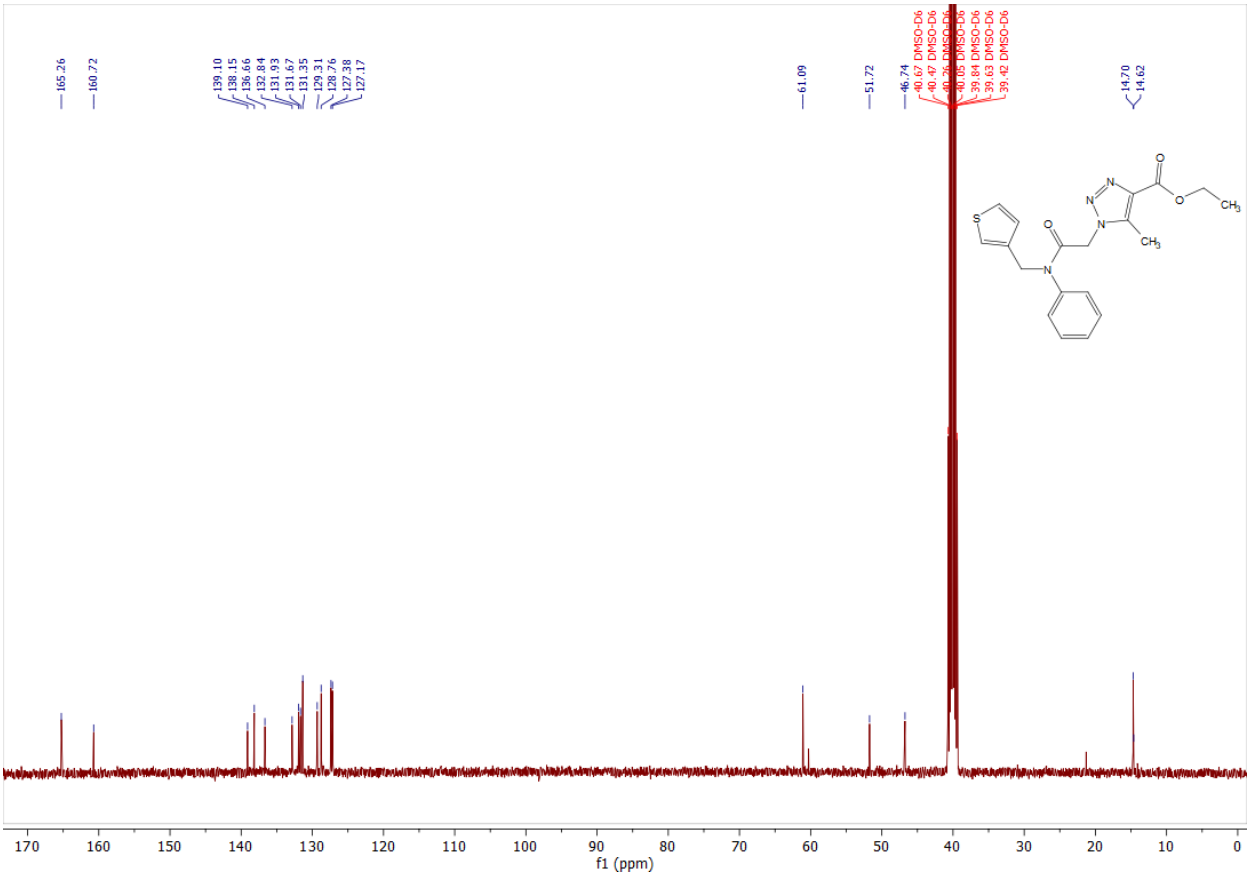
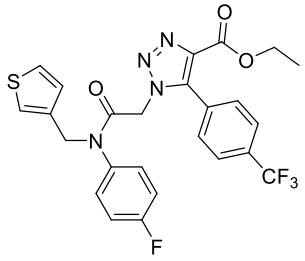


Рисунок 52. ^{13}C NMR spectrum (101 MHz, DMSO-D_6) *Ethyl 5-methyl-1-(2-oxo-2-(phenyl(thiophen-3-ylmethyl)amino)ethyl)-1H-1,2,3-triazole-4-carboxylate* **2b**

Речовина **2c**. Нековалентний інгібітор головної протеази SARS-CoV-2 M^{pro}.

Назва: *Ethyl 1-(2-((4-fluorophenyl)(thiophen-3-ylmethyl)amino)-2-oxoethyl)-5-(4-(trifluoromethyl)phenyl)-1H-1,2,3-triazole-4-carboxylate*



Yellow solid. Yield 88 %. MS (ESI+) m/z calculated for $C_{25}H_{20}F_4N_4O_3S$ $[M+H]^+$ 533.1, found 533.3.

Спектральні параметри:

^{1}H NMR (400 MHz, DMSO-D_6) δ 7.69 (m, 1H), 7.63 – 7.56 (m, 1H), 7.35 – 7.23 (m, 2H), 7.10 – 7.00 (m, 1H), 5.26 (s, 1H), 5.02 (t, *J* = 0.9 Hz, 1H), 4.39 (q, *J* = 6.4 Hz, 1H), 1.29 (t, *J* = 6.4 Hz, 2H).

^{13}C NMR (101 MHz, DMSO-D_6) δ 166.26, 160.68 (d, *J* = 5.1 Hz), 158.19, 139.80, 138.09, 137.36 (d, *J* = 3.0 Hz), 135.69, 133.45, 131.83 (q, *J* = 4.2 Hz), 131.29, 130.97, 127.08 (d, *J* = 4.9 Hz), 126.70, 125.54 (d, *J* = 8.4 Hz), 125.23, 123.25, 122.51, 117.52, 117.30, 61.14, 52.24, 44.49, 14.09.

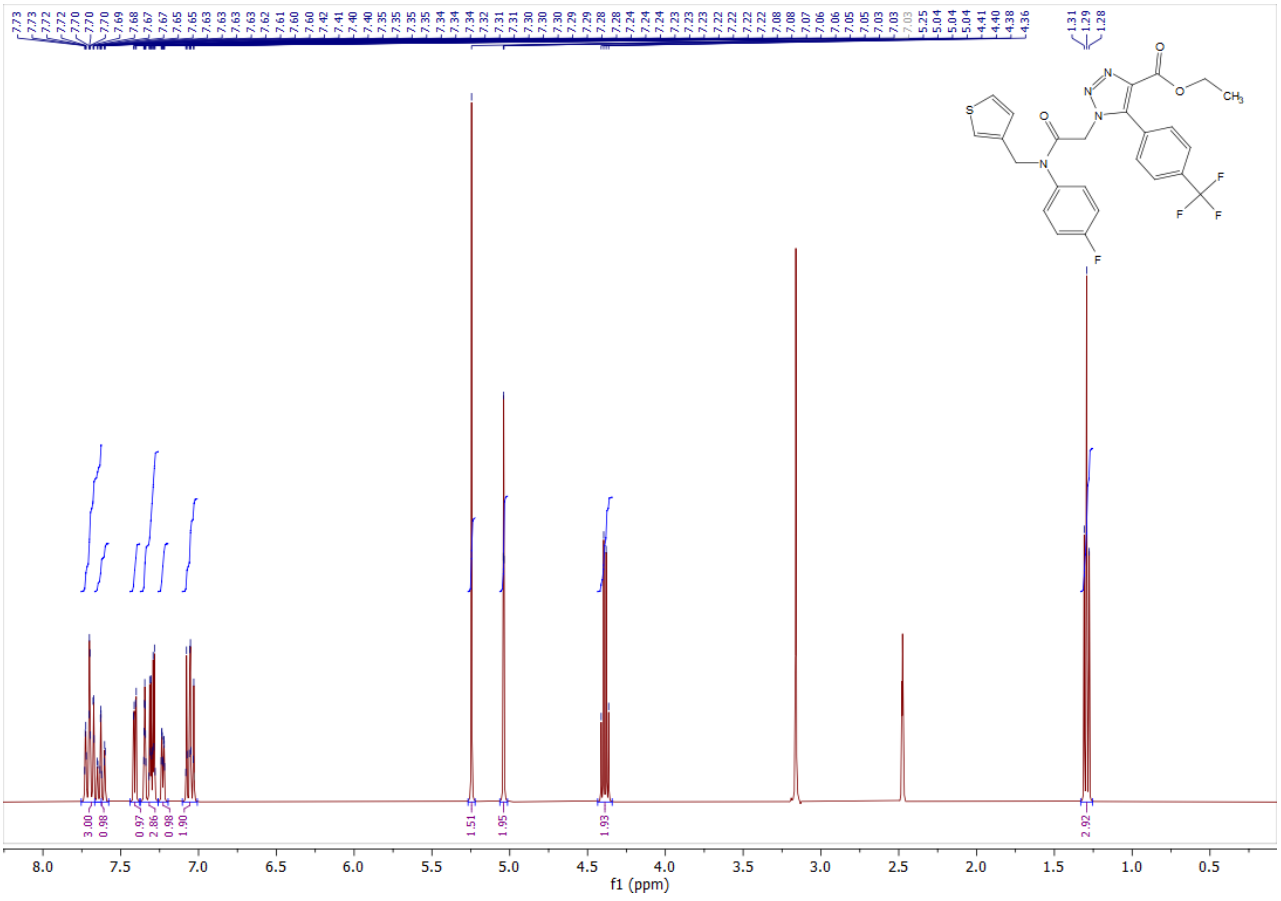


Рисунок 53. ^{1}H NMR spectrum (400 MHz, DMSO-D_6) *Ethyl 1-(2-((4-fluorophenyl)(thiophen-3-ylmethyl)amino)-2-oxoethyl)-5-(4-(trifluoromethyl)phenyl)-1H-1,2,3-triazole-4-carboxylate* **2c**

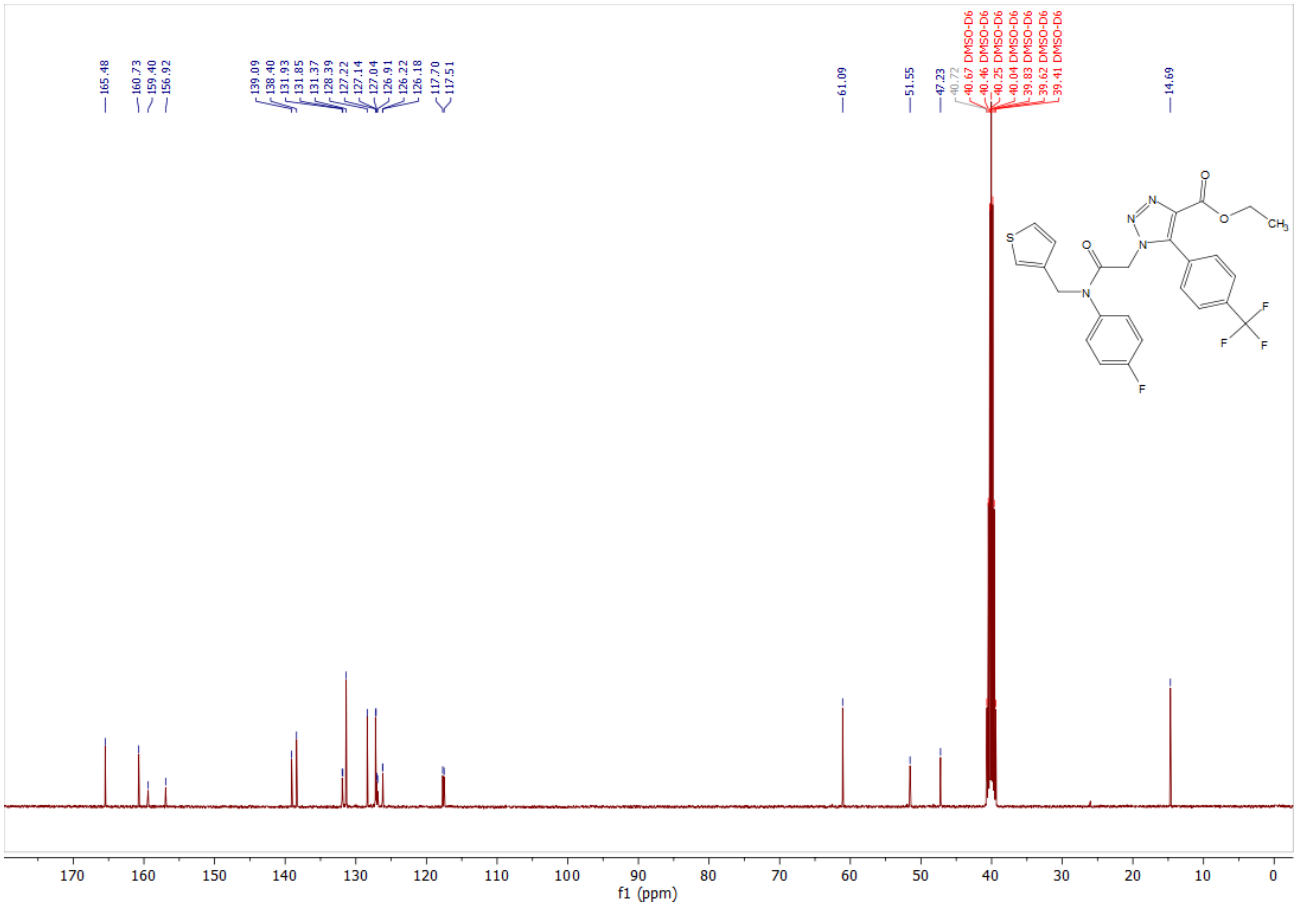
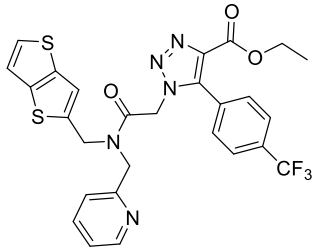


Рисунок 54. ^{13}C NMR spectrum (101 MHz, DMSO-D_6) *Ethyl 1-(2-((4-fluorophenyl)(thiophen-3-ylmethyl)amino)-2-oxoethyl)-5-(4-(trifluoromethyl)phenyl)-1H-1,2,3-triazole-4-carboxylate* **2c**

Речовина **2d**. Нековалентний інгібітор головної протеази SARS-CoV-2 M^{pro}.

Назва: *Ethyl 1-(2-oxo-2-((pyridin-2-ylmethyl)(thieno[3,2-b]thiophen-2-ylmethyl)amino)ethyl)-5-(4-(trifluoromethyl)phenyl)-1H-1,2,3-triazole-4-carboxylate*



Yellow solid. Yield 87 %. MS (ESI+) m/z calculated for $C_{27}H_{22}F_3N_5O_3S_2$ $[M+H]^+$ 586.1, found 586.3.

Спектральні параметри:

^{1}H NMR (400 MHz, DMSO-D_6) δ 8.58 – 8.50 (m, 1H), 7.82 – 7.69 (m, 3H), 7.67 – 7.61 (m, 2H), 7.56 (d, *J* = 5.0 Hz, 1H), 7.04 (d, *J* = 0.9 Hz, 1H), 5.08 (s, 2H), 4.68 (d, *J* = 0.8 Hz, 2H), 4.51 (d, *J* = 0.7 Hz, 2H), 4.39 (q, *J* = 6.4 Hz, 2H), 1.32 (t, *J* = 6.4 Hz, 3H)

^{13}C NMR (101 MHz, DMSO-D_6) δ 168.51, 161.70, 157.02, 149.82, 142.68, 139.62, 139.11, 138.91, 138.09, 137.07, 133.45, 131.83 (q, *J* = 4.2 Hz), 131.29, 130.90 (d, *J* = 13.3 Hz), 127.08 (q, *J* = 4.8 Hz), 125.23, 125.01, 122.86 – 122.38 (m), 122.18, 61.14, 52.01, 50.63, 47.13, 14.09.

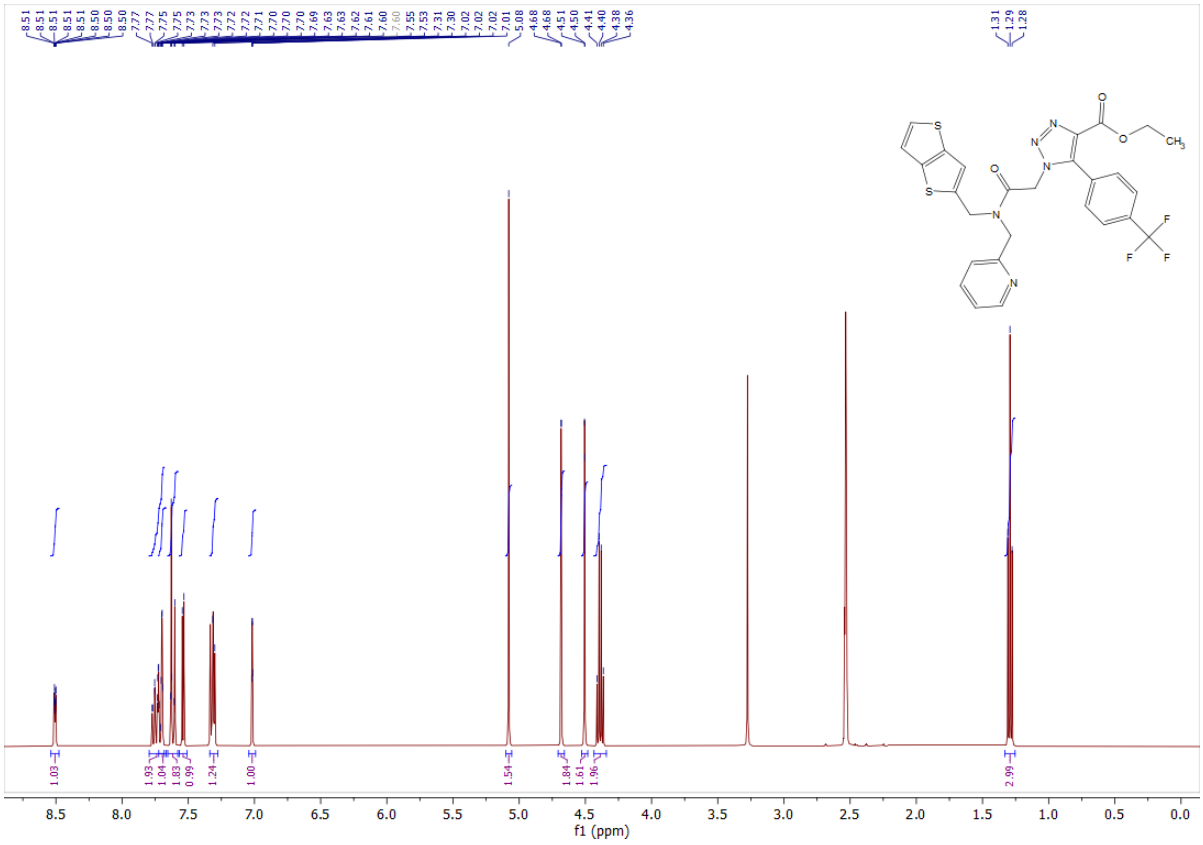


Рисунок 55. ^{1}H NMR spectrum (400 MHz, DMSO-D_6) *Ethyl 1-(2-oxo-2-((pyridin-2-ylmethyl)(thieno[3,2-b]thiophen-2-ylmethyl)amino)ethyl)-5-(4-(trifluoromethyl)phenyl)-1H-1,2,3-triazole-4-carboxylate* **2d**

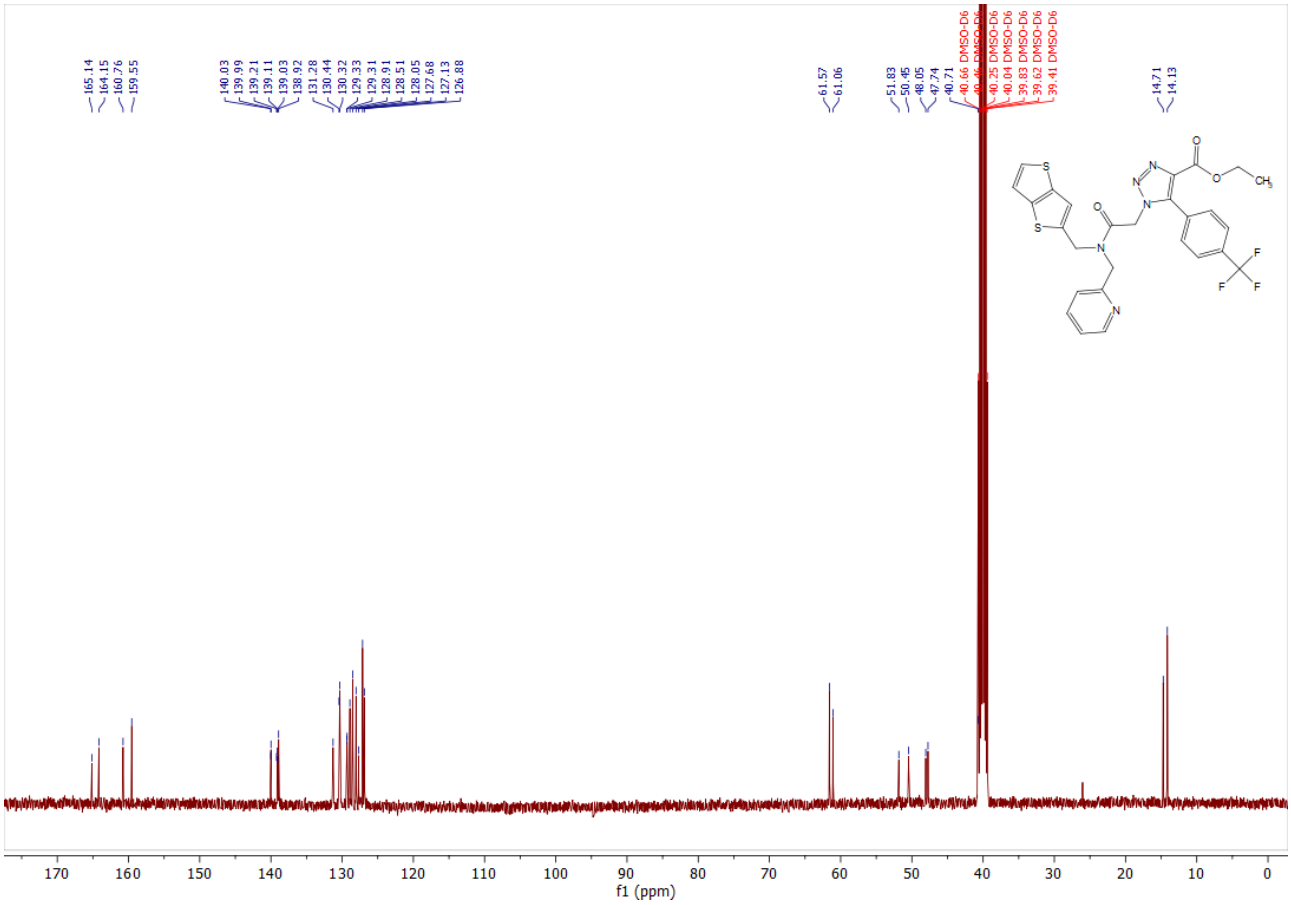
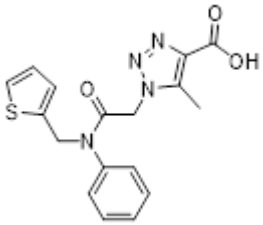


Рисунок 56. ^{13}C NMR spectrum (101 MHz, DMSO-D_6) *Ethyl 1-(2-oxo-2-((pyridin-2-ylmethyl)(thieno[3,2-b]thiophen-2-ylmethyl)amino)ethyl)-5-(4-(trifluoromethyl)phenyl)-1H-1,2,3-triazole-4-carboxylate* **2d**

Похідні 5-(4-(трифторметил)феніл)-1*H*-1,2,3-триазол-4-карбоксилатів та 5-methyl-1*H*-1,2,3-триазол-4-карбоксилатів 3a-3d

Речовина **3a**. Нековалентний інгібітор головної протеази SARS-CoV-2 M^{pro}.

Назва: *5-Methyl-1-(2-oxo-2-(phenyl(thiophen-2-ylmethyl)amino)ethyl)-1H-1,2,3-triazole-4-carboxylic acid*



White solid. Yield 82 %. MS (ESI+) m/z calculated for $C_{17}H_{16}N_4O_3S$ $[M+H]^+$ 357.0, found 357.1.

Спектральні параметри:

^{1}H NMR (400 MHz, DMSO-D_6) δ 7.37 (dd, J = 5.3, 1.7 Hz, 1H), 7.32 – 7.24 (m, 4H), 7.23 – 7.11 (m, 2H), 6.98 (dd, J = 6.5, 5.3 Hz, 1H), 5.20 (s, 2H), 5.06 (d, J = 0.8 Hz, 2H).

^{13}C NMR (101 MHz, DMSO-D_6) δ 167.22, 163.70, 139.74, 138.11, 136.92, 135.34, 129.24, 127.23, 125.58 (d, J = 1.2 Hz), 124.72, 123.63, 50.65, 42.98, 11.05.

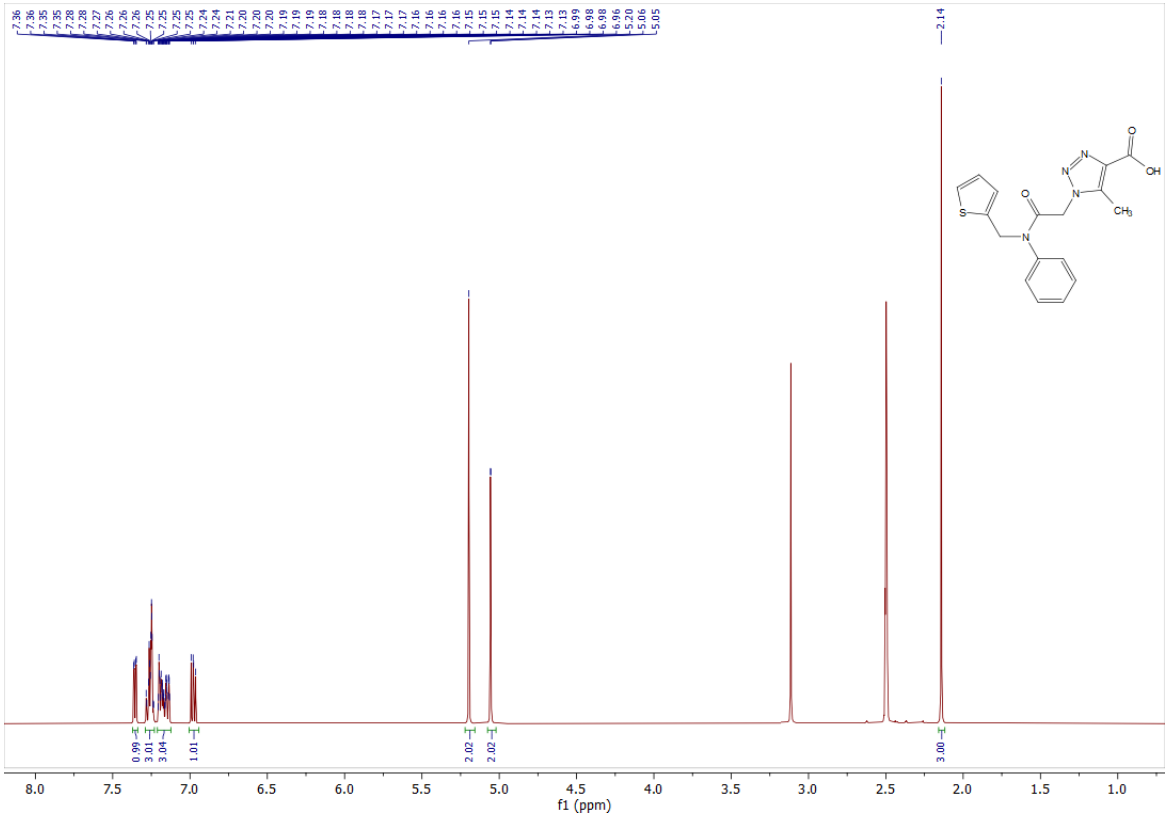


Рисунок 57. ^{1}H NMR spectrum (400 MHz, DMSO-D_6) *5-Methyl-1-(2-oxo-2-(phenyl(thiophen-2-ylmethyl)amino)ethyl)-1H-1,2,3-triazole-4-carboxylic acid* **3a**

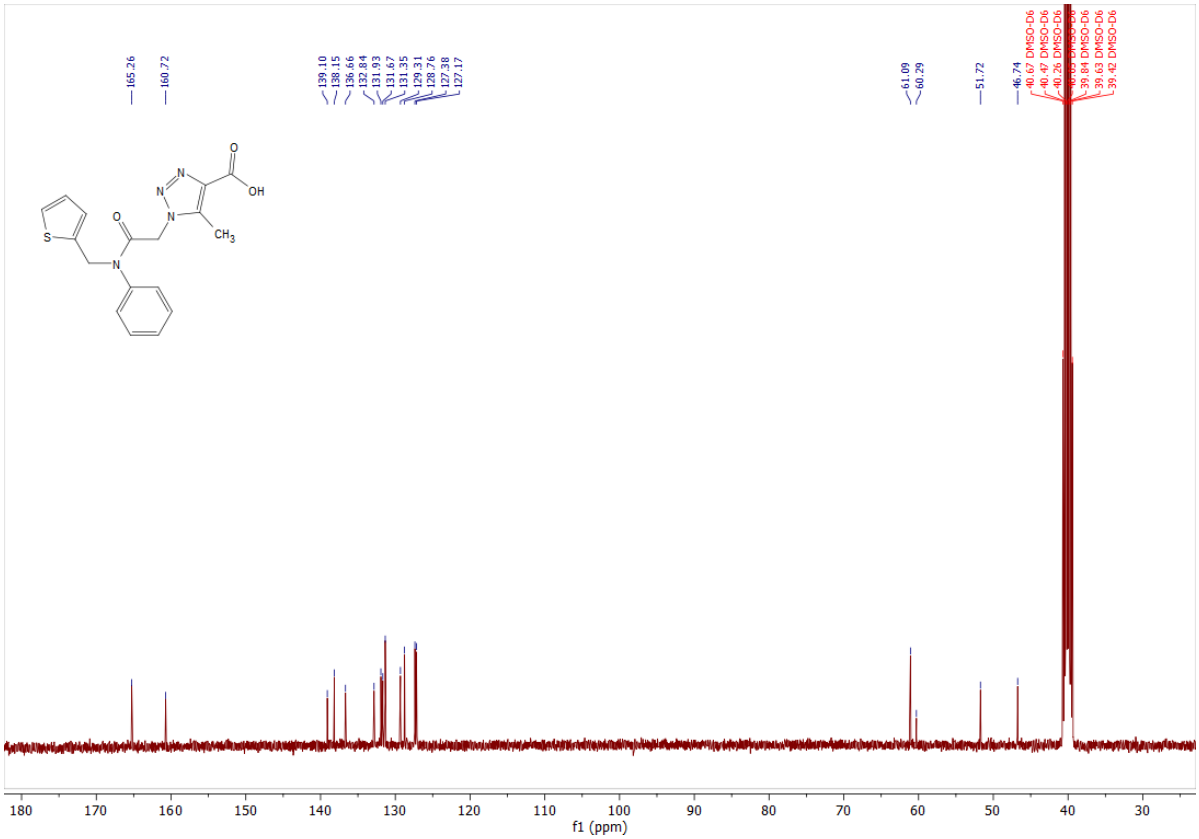
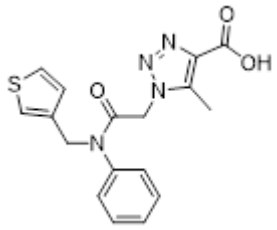


Рисунок 58. ^{13}C NMR spectrum (101 MHz, DMSO-D_6) *5-Methyl-1-(2-oxo-2-(phenyl(thiophen-2-ylmethyl)amino)ethyl)-1H-1,2,3-triazole-4-carboxylic acid* **3a**

Речовина **3b**. Нековалентний інгібітор головної протеази SARS-CoV-2 M^{pro}.

Назва: *5-Methyl-1-(2-oxo-2-(phenyl(thiophen-3-ylmethyl)amino)ethyl)-1H-1,2,3-triazole-4-carboxylic acid*



White solid. Yield 85 %ю MS (ESI+) m/z calculated for $C_{17}H_{16}N_4O_3S$ $[M+H]^+$ 357.0, found 357.1.

Спектральні параметри:

^{1}H NMR (400 MHz, DMSO-D_6) δ 7.41 (dd, J = 5.2, 1.7 Hz, 1H), 7.35 (tt, J = 1.6, 0.9 Hz, 1H), 7.31 – 7.22 (m, 5H), 7.22 – 7.12 (m, 1H), 5.20 (s, 2H), 5.04 (t, J = 0.9 Hz, 2H).

^{13}C NMR (101 MHz, DMSO-D_6) δ 167.36, 163.69, 139.92, 136.92, 135.71, 135.34, 129.24, 127.11, 126.70, 124.72, 123.63, 123.25, 50.60, 44.76, 11.05.

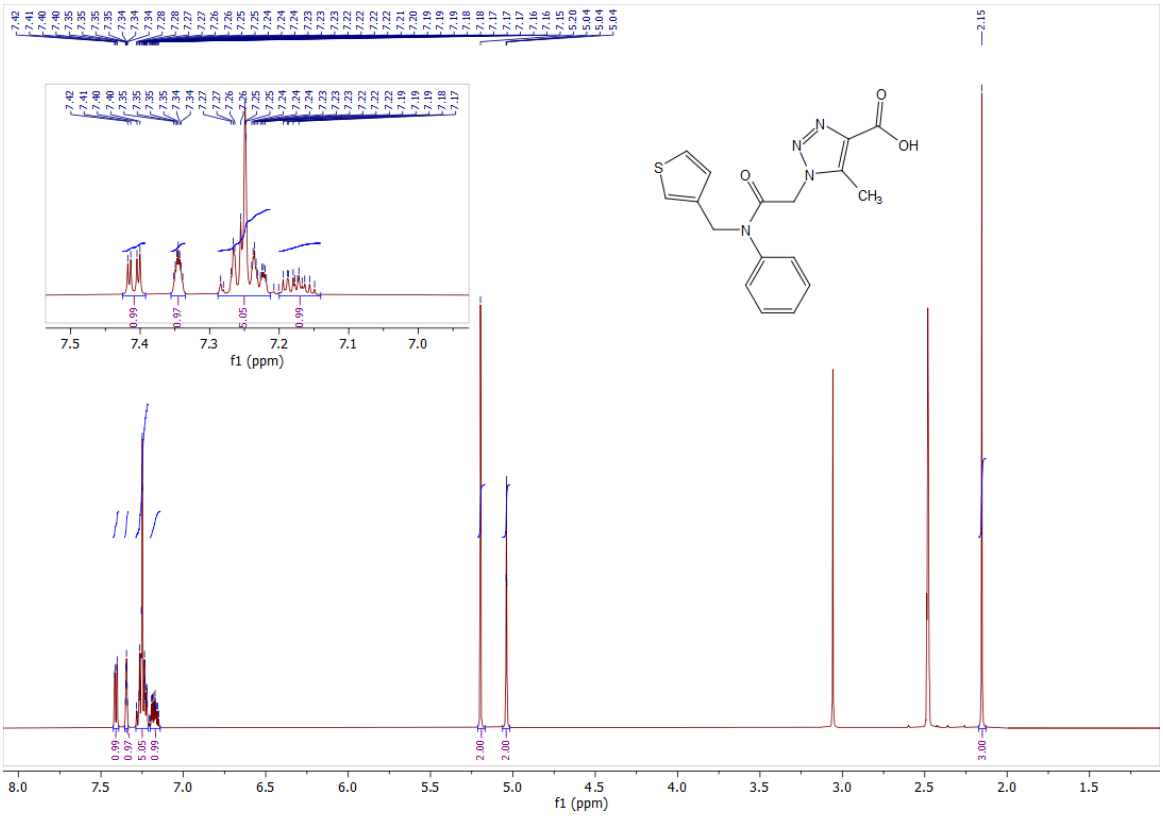


Рисунок 59. ^{1}H NMR spectrum (400 MHz, DMSO-D_6) *5-Methyl-1-(2-oxo-2-(phenyl(thiophen-3-ylmethyl)amino)ethyl)-1H-1,2,3-triazole-4-carboxylic acid* **3b**

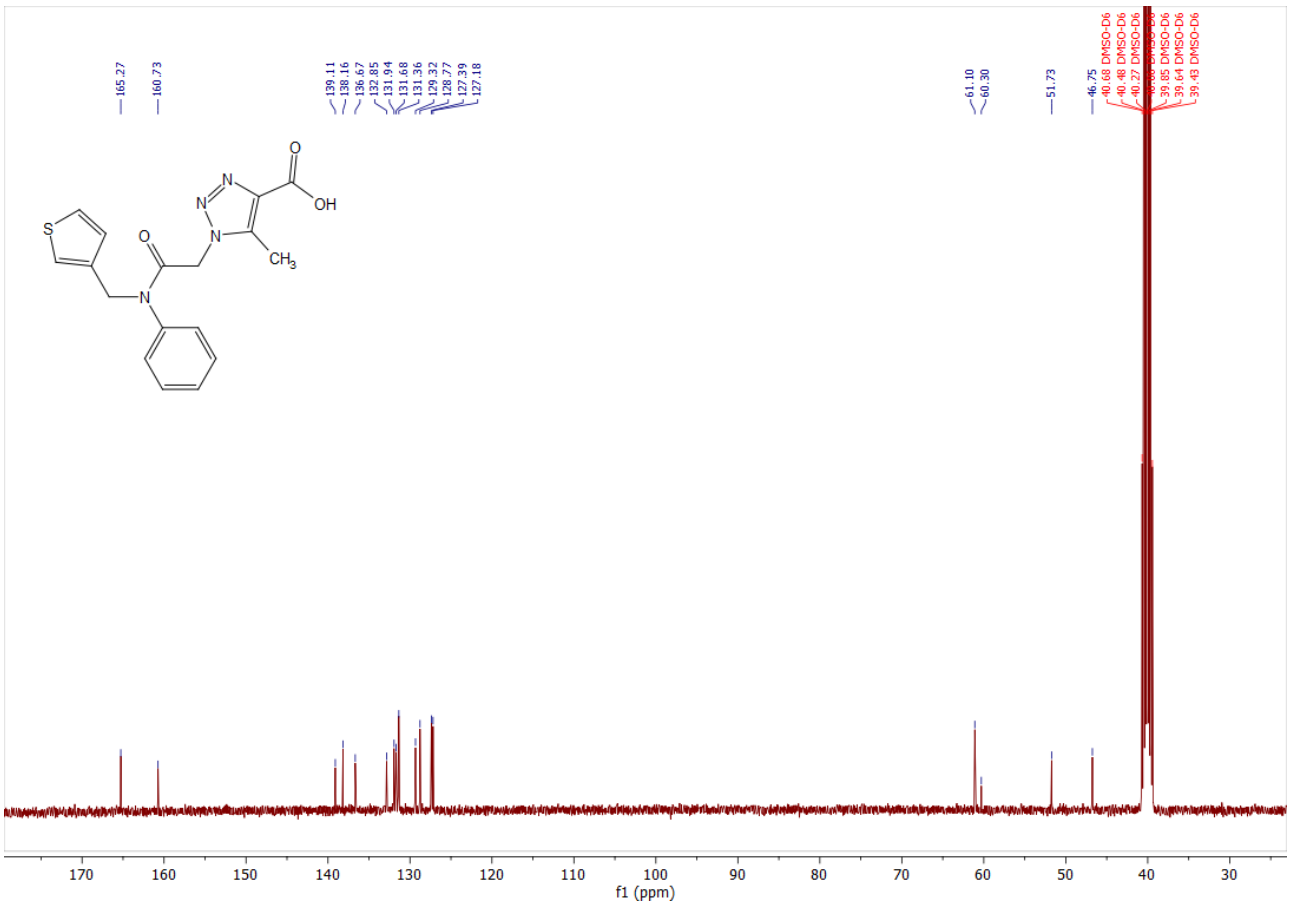
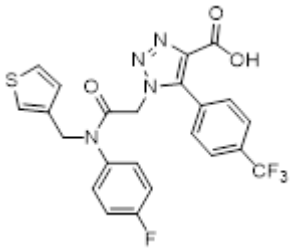


Рисунок 60. ^{13}C NMR spectrum (101 MHz, DMSO-D_6) *5-Methyl-1-(2-oxo-2-(phenyl(thiophen-3-ylmethyl)amino)ethyl)-1H-1,2,3-triazole-4-carboxylic acid* **3b**

Речовина **3c**. Нековалентний інгібітор головної протеази SARS-CoV-2 M^{pro}.

Назва: *1-(2-((4-Fluorophenyl)(thiophen-3-ylmethyl)amino)-2-oxoethyl)-5-(4-(trifluoromethyl)phenyl)-1H-1,2,3-triazole-4-carboxylic acid*



White solid. Yield 87 %ю MS (ESI+) m/z calculated for $C_{23}H_{16}F_4N_4O_3S$ $[M+H]^+$ 505.0, found 505.2.

Спектральні параметри:

^{1}H NMR (400 MHz, DMSO-D_6) δ 7.74 (dq, J = 10.6, 1.4 Hz, 2H), 7.68 – 7.59 (m, 2H), 7.41 (dd, J = 5.2, 1.7 Hz, 1H), 7.37 – 7.27 (m, 3H), 7.23 (m, 1H), 7.10 – 7.00 (m, 2H), 5.25 (s, 2H), 5.04 (t, J = 0.9 Hz, 2H).

^{13}C NMR (101 MHz, DMSO-D_6) δ 166.26, 163.38, 160.65, 158.19, 139.00, 137.36 (d, J = 3.0 Hz), 136.27, 135.69, 133.55, 131.86 (q, J = 4.2 Hz), 131.29, 130.97, 127.34 – 126.85 (m), 126.70, 125.54 (d, J = 8.4 Hz), 125.23, 123.25, 122.51, 117.52, 117.30, 52.14, 44.49.

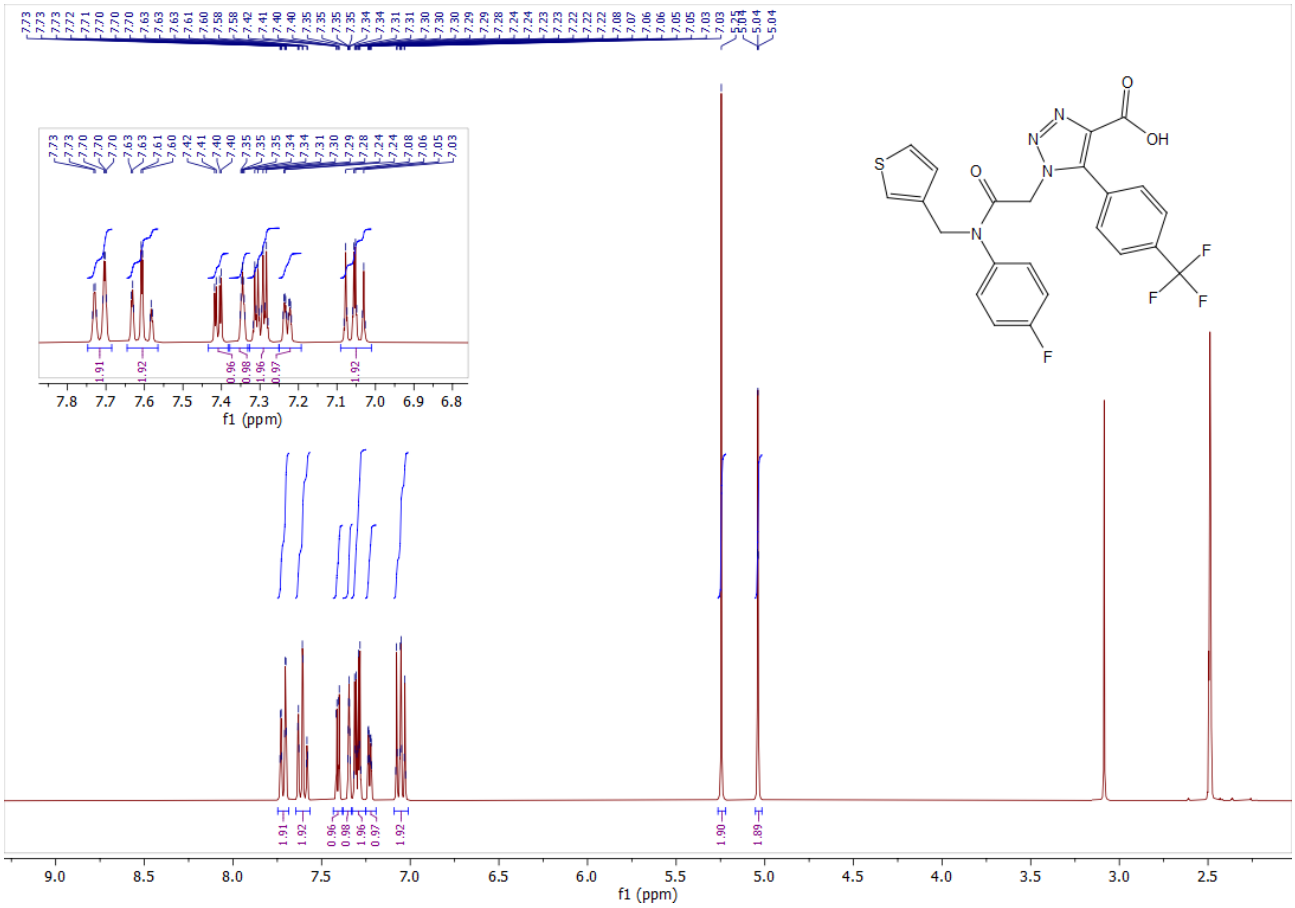


Рисунок 61. ^{1}H NMR spectrum (400 MHz, DMSO-D_6) *1-(2-((4-Fluorophenyl)(thiophen-3-ylmethyl)amino)-2-oxoethyl)-5-(4-(trifluoromethyl)phenyl)-1H-1,2,3-triazole-4-carboxylic acid* **3c**

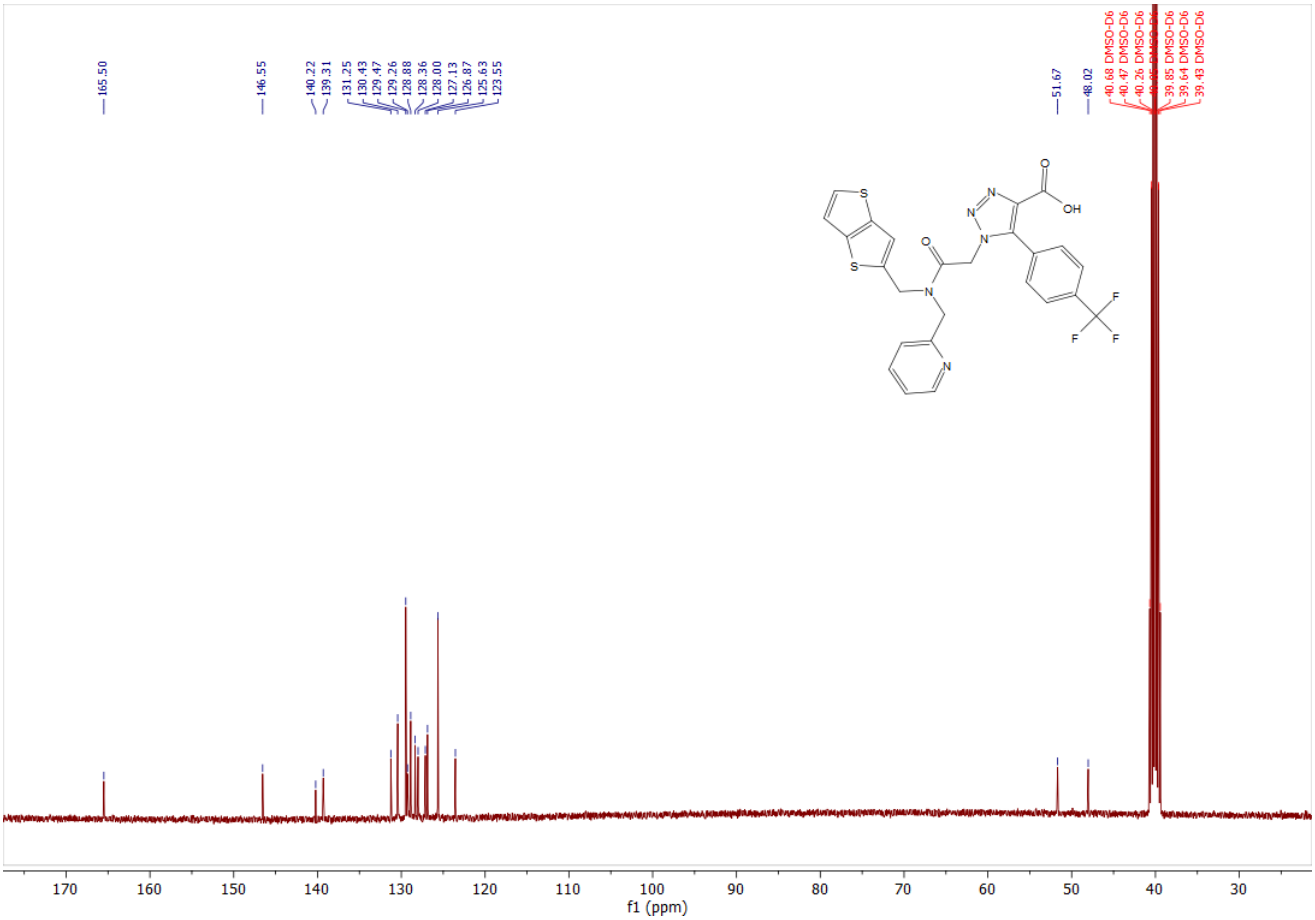
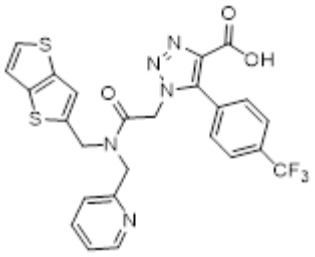


Рисунок 62. ^{13}C NMR spectrum (101 MHz, DMSO-D_6) *1-(2-((4-Fluorophenyl)(thiophen-3-ylmethyl)amino)-2-oxoethyl)-5-(4-(trifluoromethyl)phenyl)-1H-1,2,3-triazole-4-carboxylic acid* **3c**

Речовина **3d**. Нековалентний інгібітор головної протеази SARS-CoV-2 M^{pro}.

Назва: *1-(2-Oxo-2-((pyridin-2-ylmethyl)(thieno[3,2-b]thiophen-2-ylmethyl)amino)ethyl)-5-(4-(trifluoromethyl)phenyl)-1H-1,2,3-triazole-4-carboxylic acid*



Yellow solid. Yield 79 %. MS (ESI+) m/z calculated for $C_{25}H_{18}F_3N_5O_3S_2$ $[M+H]^+$ 558.0, found 558.2.

Спектральні параметри:

^{1}H NMR (400 MHz, DMSO-D_6) δ 8.59 – 8.51 (m, 1H), 7.82 – 7.69 (m, 3H), 7.68 – 7.59 (m, 2H), 7.54 (d, J = 5.0 Hz, 1H), 7.36 – 7.28 (m, 3H), 7.04 – 6.99 (m, 1H), 5.08 (s, 2H), 4.68 (d, J = 0.8 Hz, 2H), 4.51 (d, J = 0.7 Hz, 2H).

^{13}C NMR (101 MHz, DMSO-D_6) δ 168.49, 164.37, 157.05, 149.74, 142.68, 139.24 – 138.81 (m), 137.07, 136.28, 133.55, 131.86 (q, J = 4.2 Hz), 131.29, 130.92 (d, J = 13.3 Hz), 127.09 (q, J = 4.7 Hz), 125.23, 125.01, 122.86 – 122.38 (m), 122.18, 52.00, 50.65, 47.14.

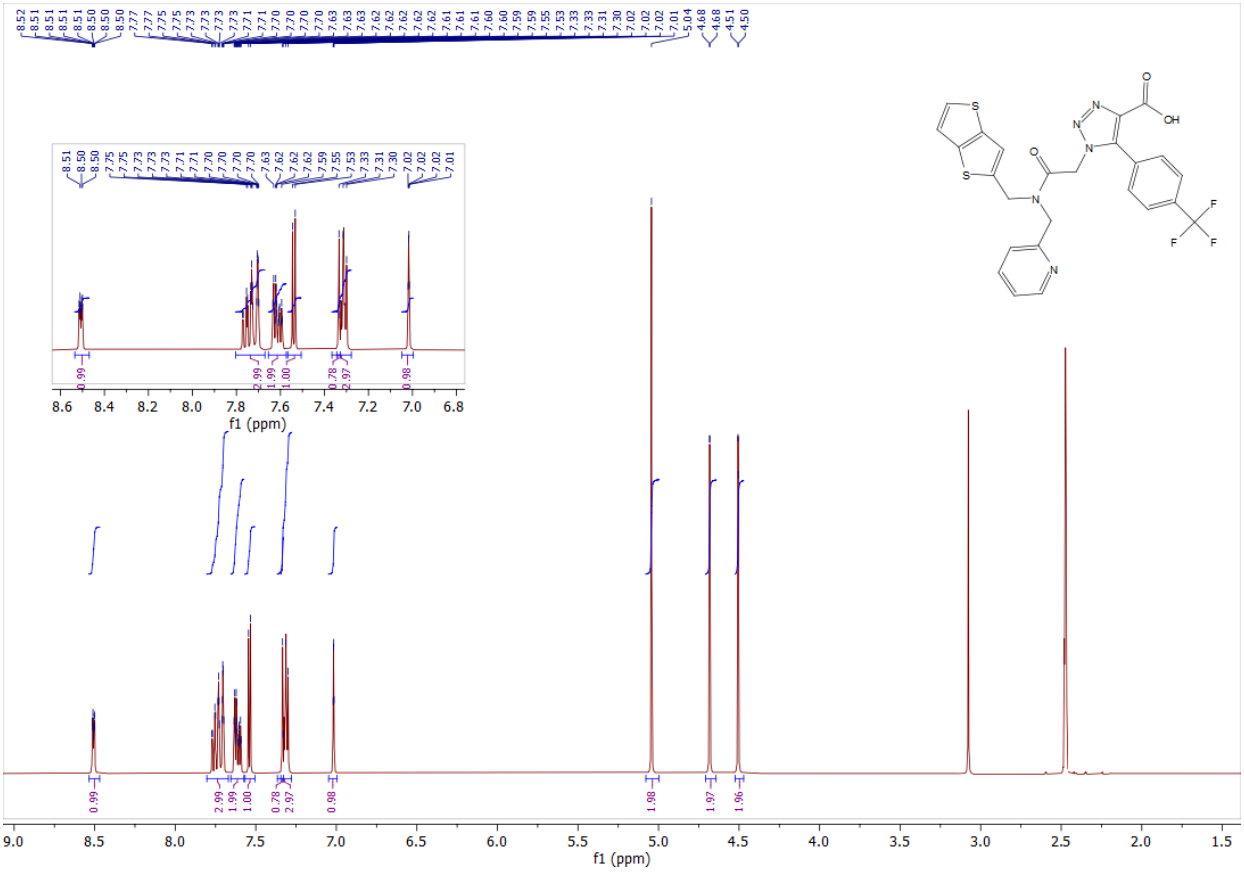


Рисунок 63. ^{1}H NMR spectrum (400 MHz, DMSO-D_6) *1-(2-Oxo-2-((pyridin-2-ylmethyl)(thieno[3,2-b]thiophen-2-ylmethyl)amino)ethyl)-5-(4-(trifluoromethyl)phenyl)-1H-1,2,3-triazole-4-carboxylic acid* **3d**

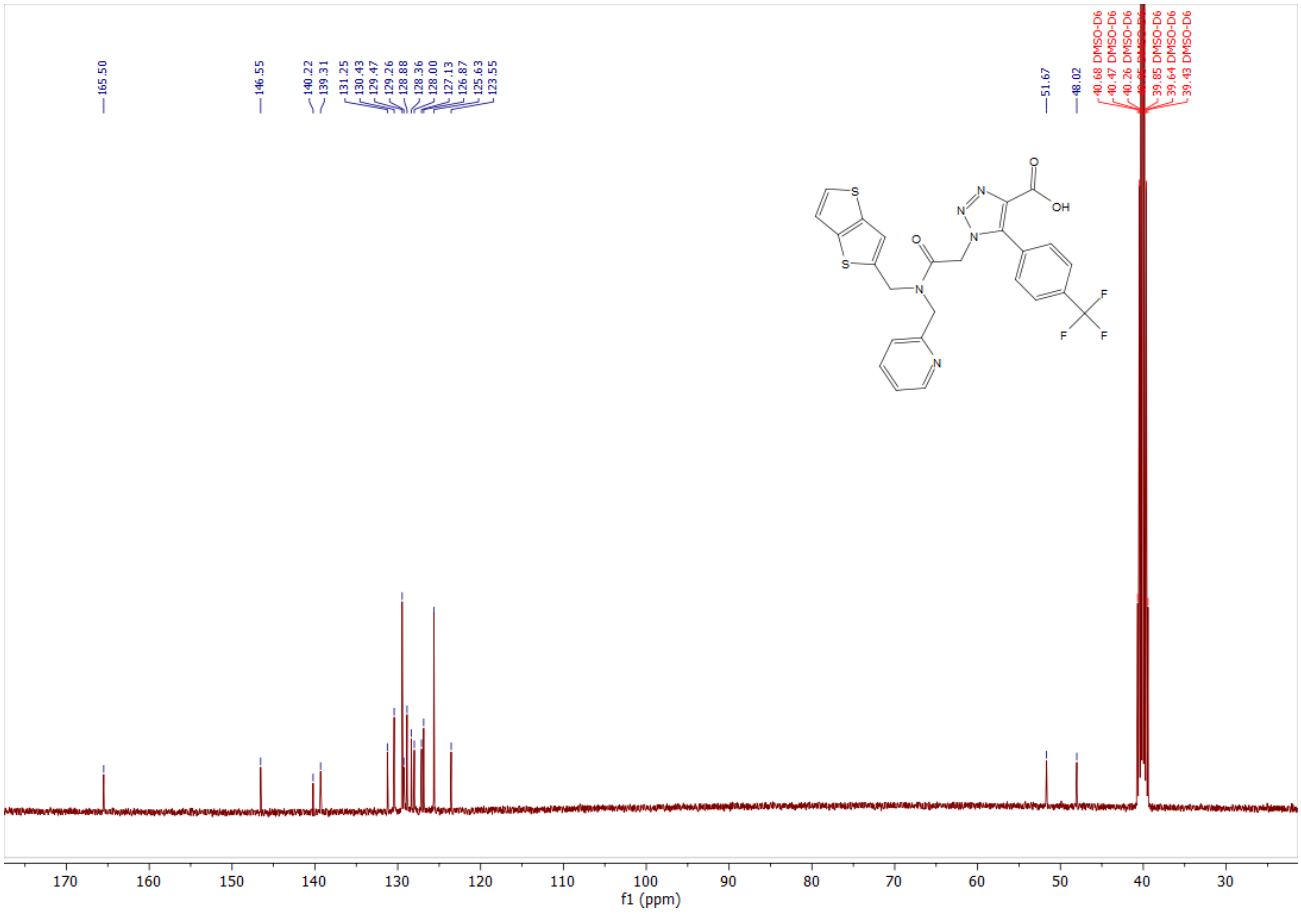
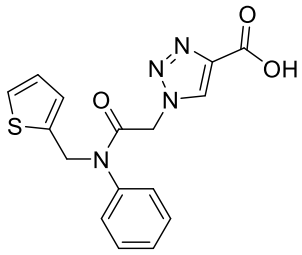


Рисунок 64. ^{13}C NMR spectrum (101 MHz, DMSO-D_6) *1-(2-Oxo-2-((pyridin-2-ylmethyl)(thieno[3,2-b]thiophen-2-ylmethyl)amino)ethyl)-5-(4-(trifluoromethyl)phenyl)-1H-1,2,3-triazole-4-carboxylic acid* **3d**

Похідні 1*H*-1,2,3-триазол-4-карбонової кислоти 4a-4i

Речовина **4a**. Нековалентний інгібітор головної протеази SARS-CoV-2 M^{pro}.

Назва: *1-(2-Oxo-2-(phenyl(thiophen-2-ylmethyl)amino)ethyl)-1H-1,2,3-triazole-4-carboxylic acid*



White solid. Yield 86 %

Спектральні параметри:

^{1}H NMR (400 MHz, DMSO-D_6) δ 8.48 (s, 1H), 7.36 (dd, J = 5.3, 1.7 Hz, 1H), 7.25 (s, 2H), 7.31 – 7.18 (m, 2H), 7.22 – 7.11 (m, 2H), 6.98 (dd, J = 6.5, 5.3 Hz, 1H), 5.20 (d, J = 0.7 Hz, 2H), 5.06 (d, J = 0.8 Hz, 2H).

^{13}C NMR (101 MHz, DMSO-D_6) δ 166.64, 163.17, 140.11, 138.11, 137.07, 129.24, 127.23, 127.21, 125.58, 125.57, 124.72, 123.62, 52.18, 43.12.

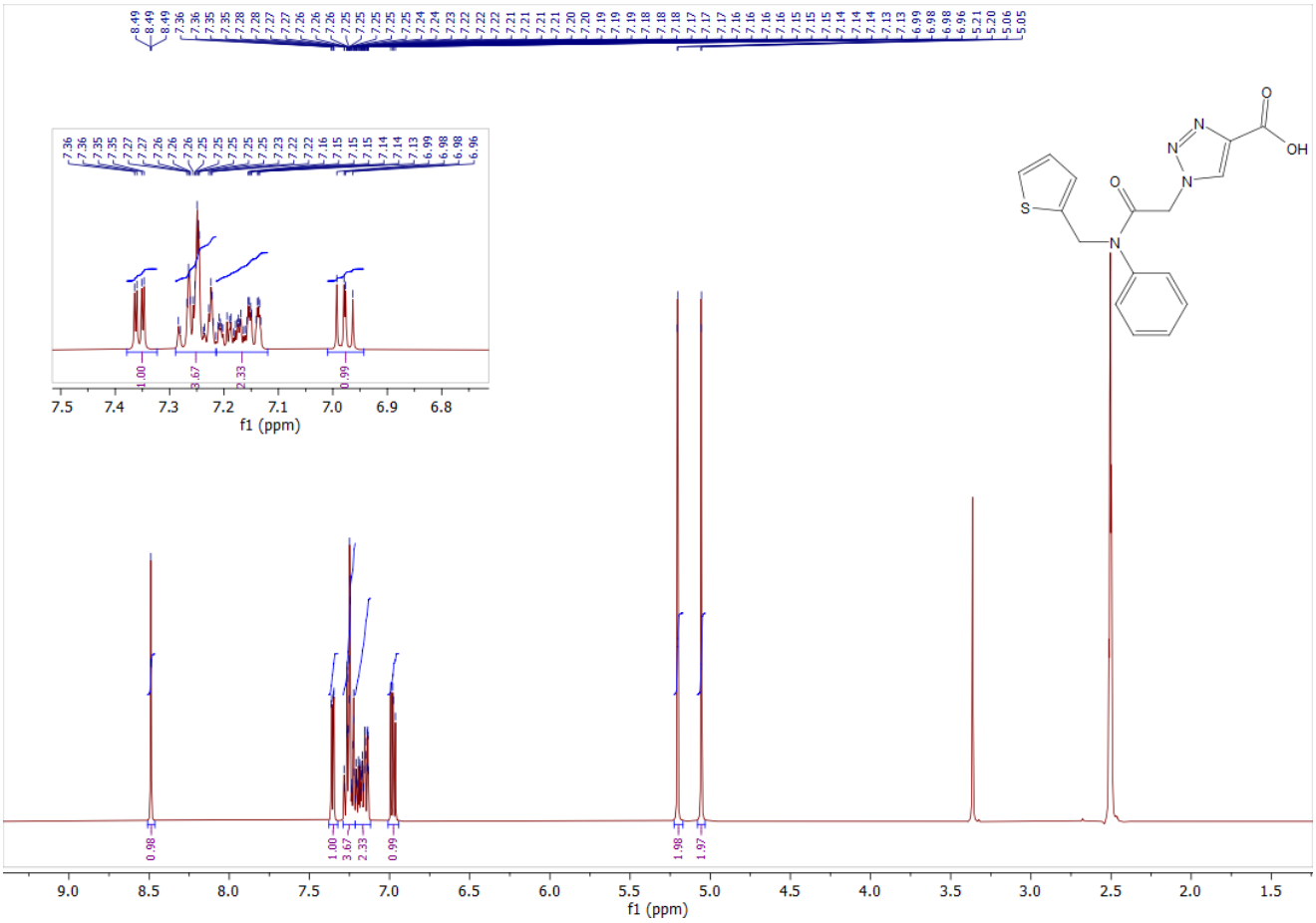


Рисунок 65. ^{1}H NMR spectrum (400 MHz, DMSO-D_6) *1-(2-Oxo-2-(phenyl(thiophen-2-ylmethyl)amino)ethyl)-1H-1,2,3-triazole-4-carboxylic acid* **4a**

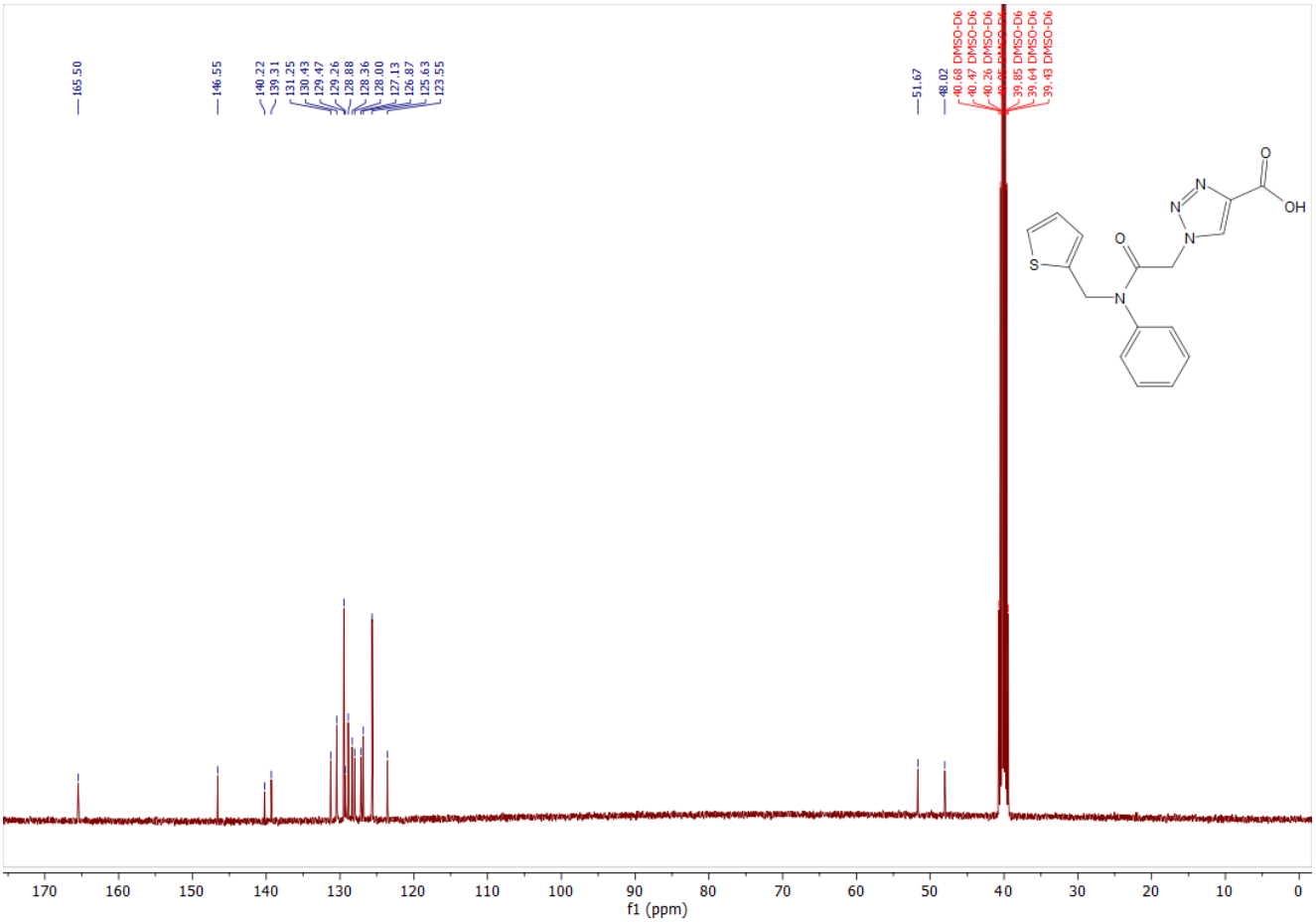
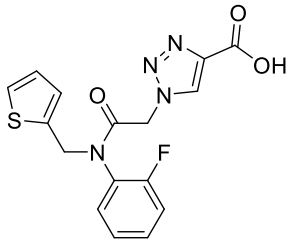


Рисунок 66. ^{13}C NMR spectrum (101 MHz, DMSO-D_6) *1-(2-Oxo-2-(phenyl(thiophen-2-ylmethyl)amino)ethyl)-1H-1,2,3-triazole-4-carboxylic acid* **4a**

Речовина **4b** Нековалентний інгібітор головної протеази SARS-CoV-2 M^{pro}.

Назва: *1-(2-((2-Fluorophenyl)(thiophen-2-ylmethyl)amino)-2-oxoethyl)-1H-1,2,3-triazole-4-carboxylic acid*



White solid. Yield 80 %

Спектральні параметри:

^{1}H NMR (400 MHz, DMSO-D_6) δ 8.48 (s, 1H), 7.50 – 7.40 (m, 1H), 7.36 (dd, J = 5.3, 1.7 Hz, 1H), 7.33 – 7.22 (m, 2H), 7.14 (ddt, J = 6.5, 1.7, 0.9 Hz, 1H), 7.13 – 7.01 (m, 1H), 6.98 (dd, J = 6.4, 5.3 Hz, 1H), 5.18 (d, J = 0.8 Hz, 2H), 5.02 (d, J = 0.8 Hz, 2H).

^{13}C NMR (101 MHz, DMSO-D_6) δ 166.02, 165.91, 163.17, 158.05, 155.60, 138.22, 137.06, 131.28, 131.12, 129.65, 129.58, 127.23, 127.21, 125.64, 125.60, 125.59, 125.54, 125.19, 125.14, 115.82, 115.61, 52.12, 44.26, 44.23.

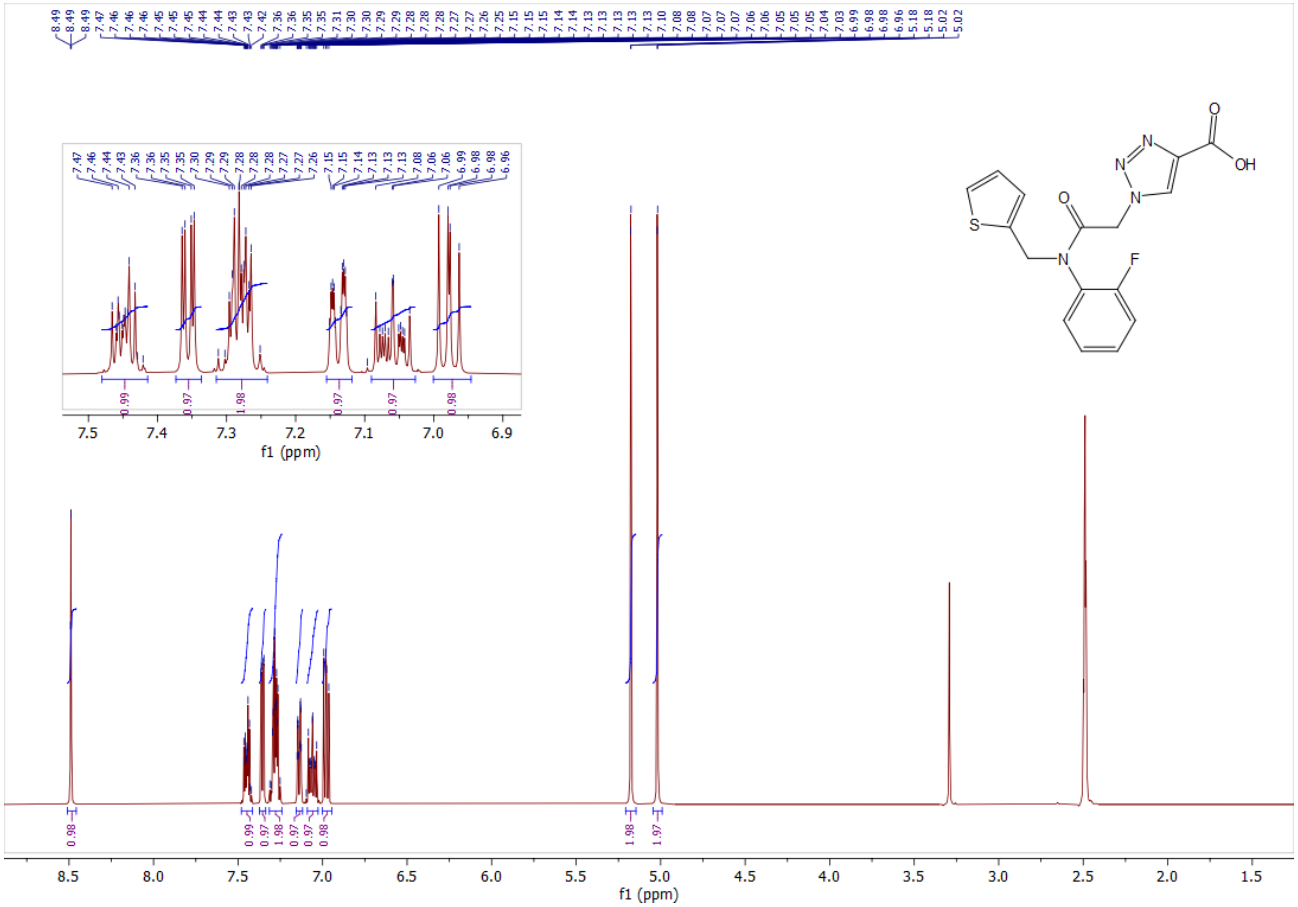


Рисунок 67. ^{1}H NMR spectrum (400 MHz, DMSO-D_6) *1-(2-((2-Fluorophenyl)(thiophen-2-ylmethyl)amino)-2-oxoethyl)-1H-1,2,3-triazole-4-carboxylic acid* **4b**

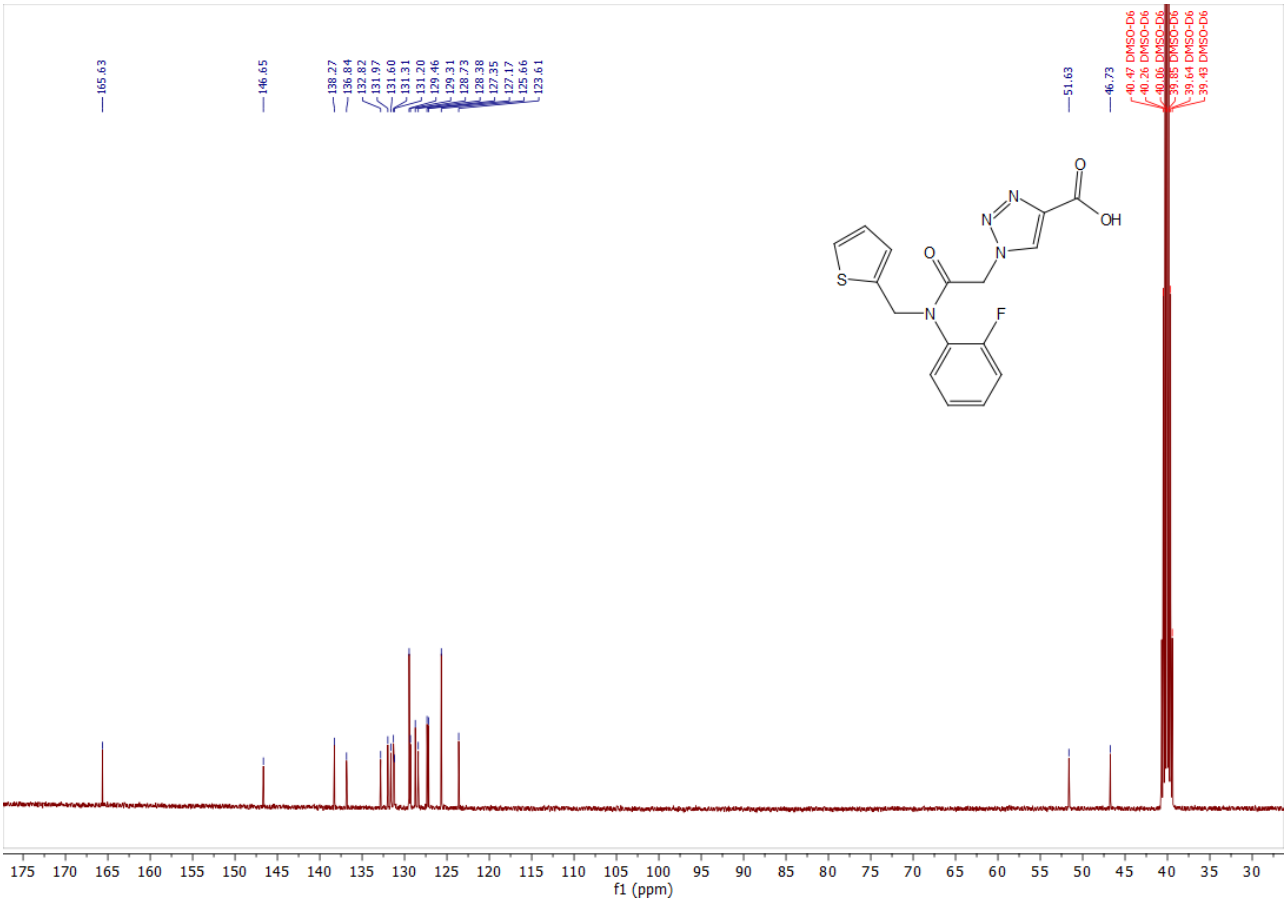
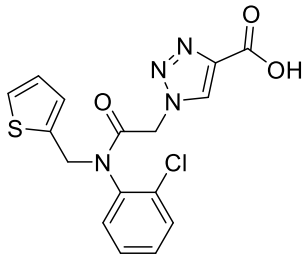


Рисунок 68. ^{13}C NMR spectrum (101 MHz, DMSO-D_6) *1-(2-((2-Fluorophenyl)(thiophen-2-ylmethyl)amino)-2-oxoethyl)-1H-1,2,3-triazole-4-carboxylic acid* **4b**

Речовина **4c**. Нековалентний інгібітор головної протеази SARS-CoV-2 M^{pro}.

Назва: *1-(2-((2-Chlorophenyl)(thiophen-2-ylmethyl)amino)-2-oxoethyl)-1H-1,2,3-triazole-4-carboxylic acid*



White solid. Yield 85 %

Спектральні параметри:

^{1}H NMR (400 MHz, DMSO-D_6) δ 8.48 (s, 1H), 7.40 (dd, J = 7.3, 1.5 Hz, 1H), 7.38 – 7.30 (m, 2H), 7.27 (td, J = 7.4, 1.5 Hz, 1H), 7.20 – 7.10 (m, 2H), 6.98 (dd, J = 6.4, 5.3 Hz, 1H), 5.18 (d, J = 0.7 Hz, 2H), 5.02 (d, J = 0.8 Hz, 2H).

^{13}C NMR (101 MHz, DMSO-D_6) δ 165.96, 163.17, 138.57, 138.19, 137.07, 131.06, 129.75, 129.65, 127.93, 127.23, 127.21, 126.16, 125.58, 125.57, 52.10, 44.20.

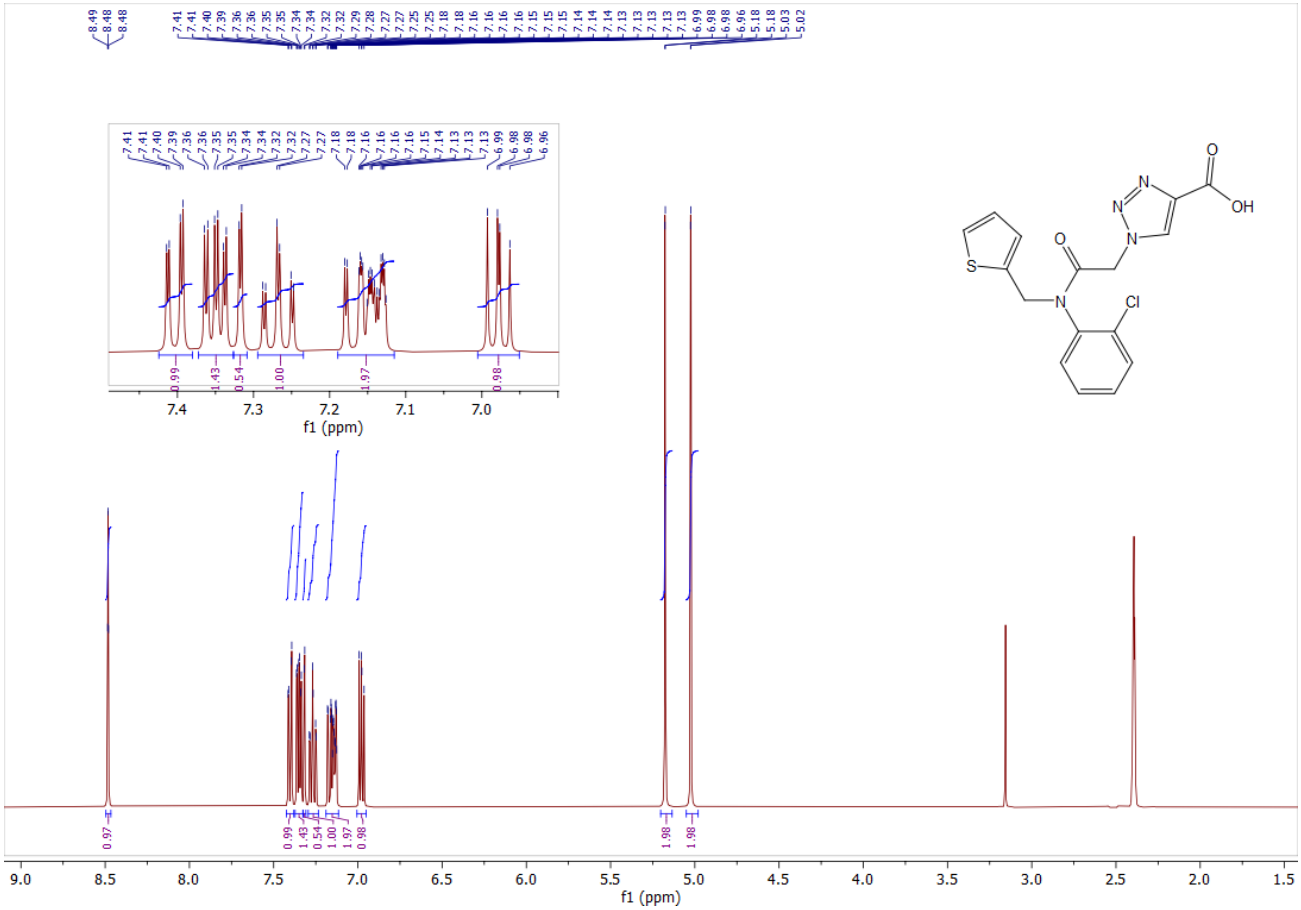


Рисунок 69. ^{1}H NMR spectrum (400 MHz, DMSO-D_6) *1-(2-((2-Chlorophenyl)(thiophen-2-ylmethyl)amino)-2-oxoethyl)-1H-1,2,3-triazole-4-carboxylic acid* **4c**

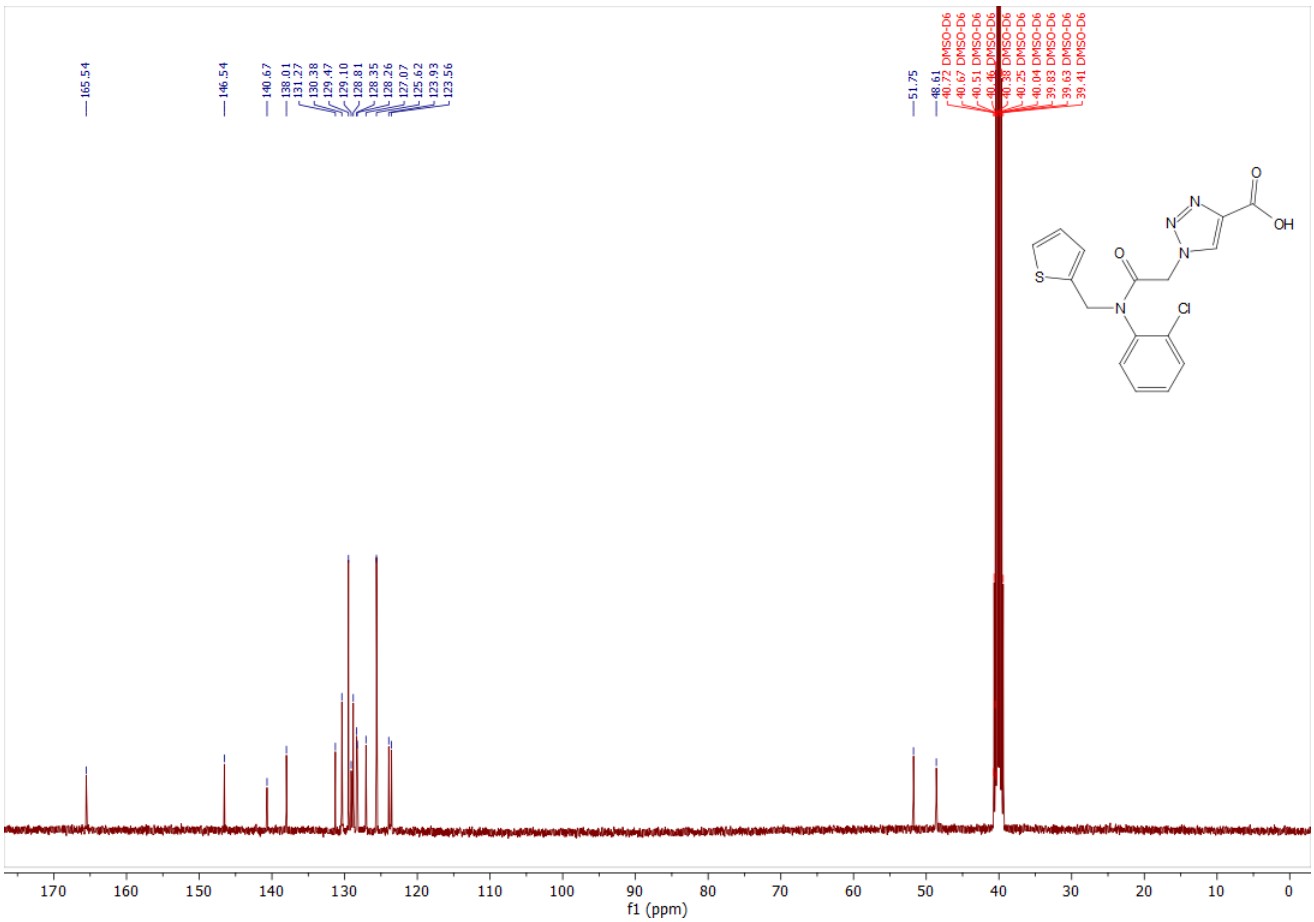
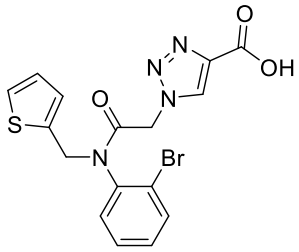


Рисунок 70. ^{13}C NMR spectrum (101 MHz, DMSO-D_6) *1-(2-((2-Chlorophenyl)(thiophen-2-ylmethyl)amino)-2-oxoethyl)-1H-1,2,3-triazole-4-carboxylic acid* **4c**

Речовина **4d**. Нековалентний інгібітор головної протеази SARS-CoV-2 M^{pro}.

Назва: *1-(2-((2-Bromophenyl)(thiophen-2-ylmethyl)amino)-2-oxoethyl)-1H-1,2,3-triazole-4-carboxylic acid*



White solid. Yield 85 %

Спектральні параметри:

^{1}H NMR (400 MHz, DMSO-D_6) δ 8.46 (s, 1H), 7.45 (ddd, J = 8.5, 7.1, 1.5 Hz, 1H), 7.44 – 7.32 (m, 3H), 7.28 (td, J = 7.1, 1.6 Hz, 1H), 7.14 (ddt, J = 6.5, 1.8, 0.9 Hz, 1H), 6.98 (dd, J = 6.5, 5.3 Hz, 1H), 5.18 (d, J = 0.7 Hz, 2H), 5.05 (d, J = 0.8 Hz, 2H).

^{13}C NMR (101 MHz, DMSO-D_6) δ 166.29, 163.17, 139.05, 138.19, 137.07, 133.67, 129.65, 128.79, 127.33, 127.23, 127.21, 125.58, 125.57, 119.83, 52.09, 44.15.

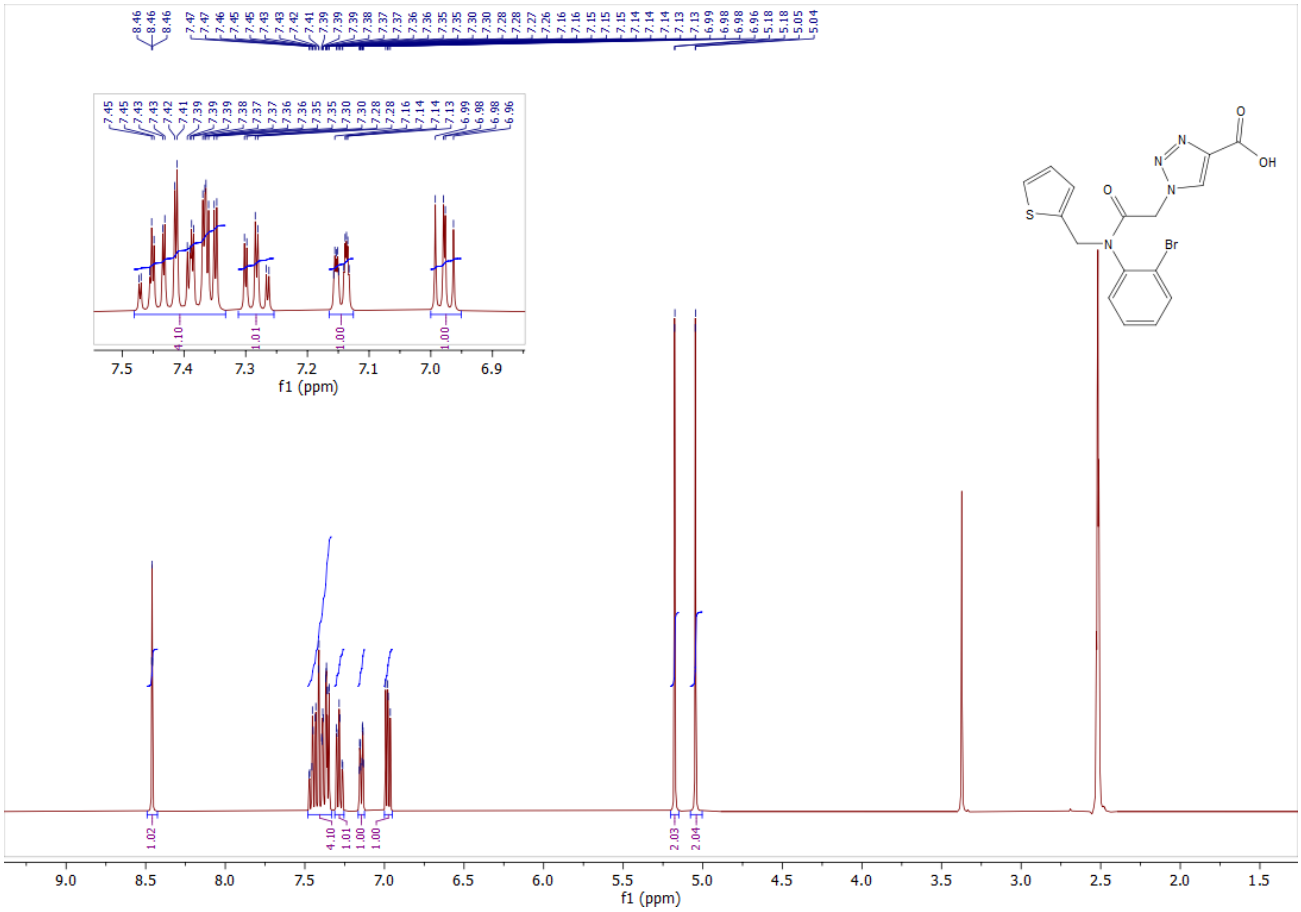


Рисунок 71. ^{1}H NMR spectrum (400 MHz, DMSO-D_6) *1-(2-((2-Bromophenyl)(thiophen-2-ylmethyl)amino)-2-oxoethyl)-1H-1,2,3-triazole-4-carboxylic acid* **4d**

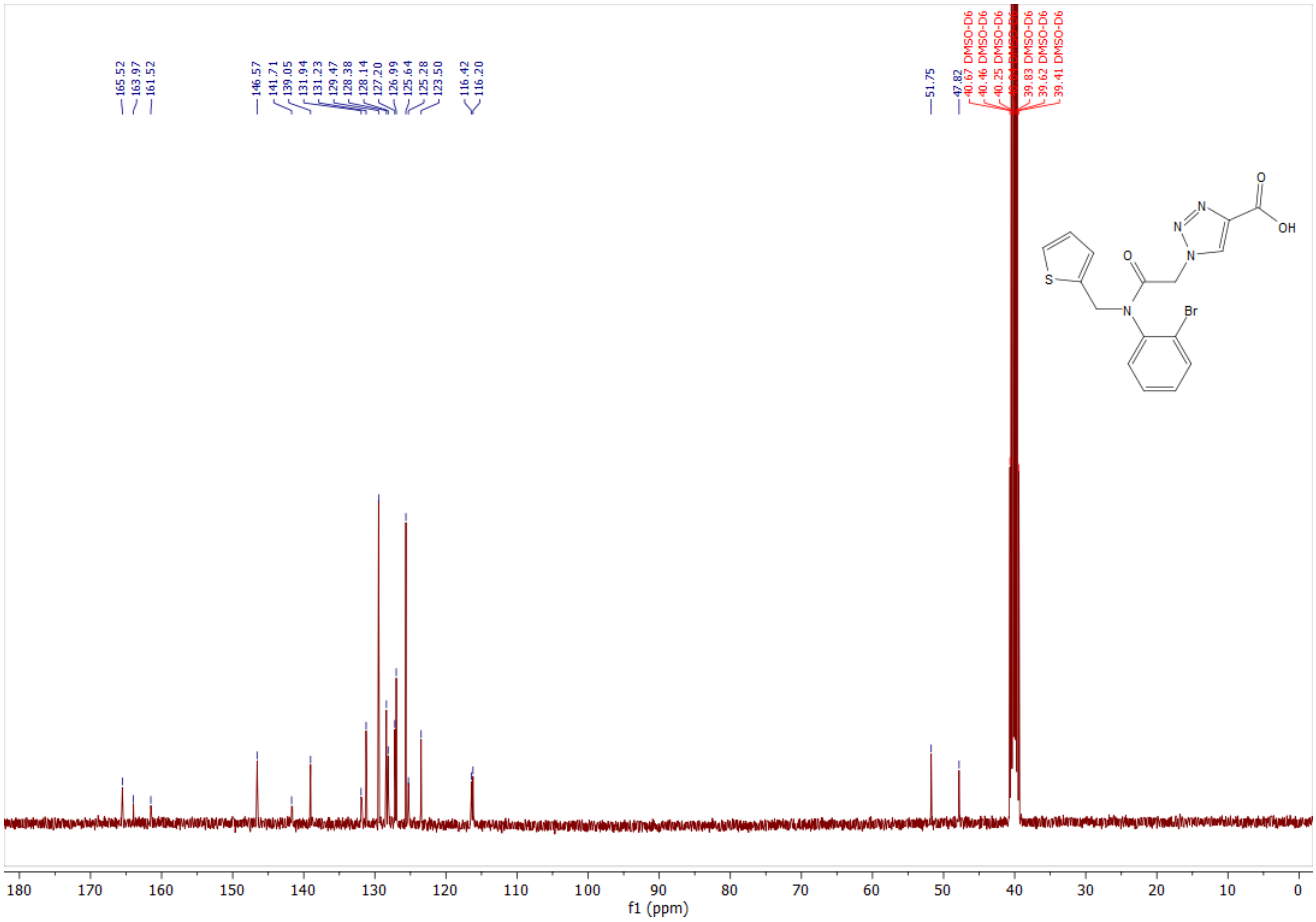
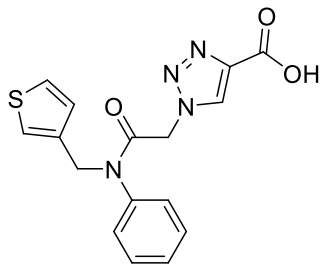


Рисунок 72. ^{13}C NMR spectrum (101 MHz, DMSO-D_6) *1-(2-((2-Bromophenyl)(thiophen-2-ylmethyl)amino)-2-oxoethyl)-1H-1,2,3-triazole-4-carboxylic acid* **4d**

Речовина **4e**. Нековалентний інгібітор головної протеази SARS-CoV-2 M^{pro}.

Назва: *1-(2-Oxo-2-(phenyl(thiophen-3-ylmethyl)amino)ethyl)-1H-1,2,3-triazole-4-carboxylic acid*



White solid. Yield 77 %

Спектральні параметри:

^{1}H NMR (400 MHz, DMSO-D_6) δ 8.47 (s, 1H), 7.41 (dd, J = 5.2, 1.7 Hz, 1H), 7.35 (tt, J = 1.6, 0.9 Hz, 1H), 7.25 (s, 3H), 7.31 – 7.12 (m, 4H), 5.20 (d, J = 0.8 Hz, 2H), 5.04 (t, J = 0.9 Hz, 2H).

^{13}C NMR (101 MHz, DMSO-D_6) δ 166.92, 163.17, 140.36, 137.07, 135.71, 129.24, 127.21, 127.11, 126.70, 124.72, 123.63, 123.25, 52.18, 44.83.

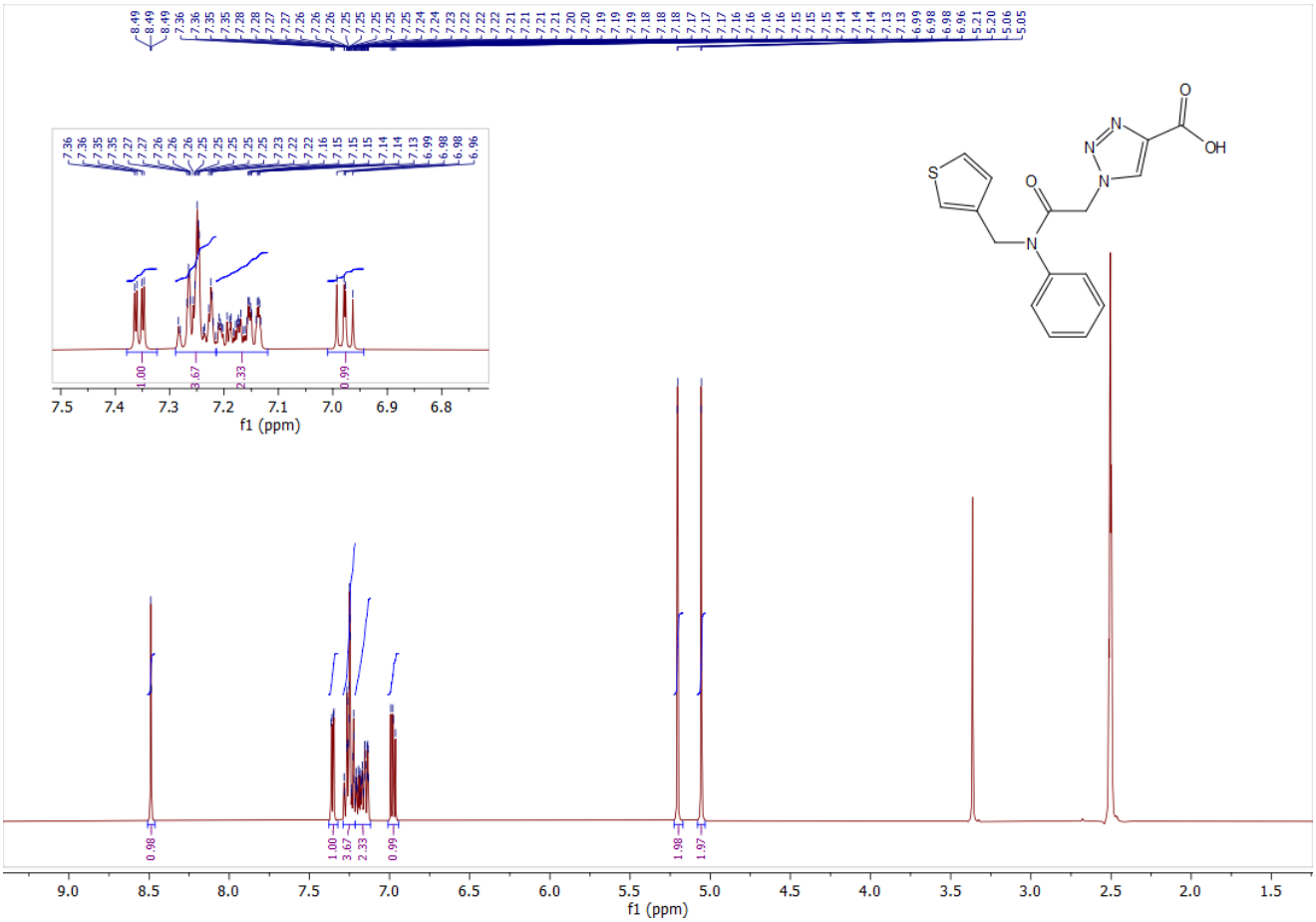


Рисунок 73. ^{1}H NMR spectrum (400 MHz, DMSO-D_6) *1-(2-Oxo-2-(phenyl(thiophen-3-ylmethyl)amino)ethyl)-1H-1,2,3-triazole-4-carboxylic acid* **4e**

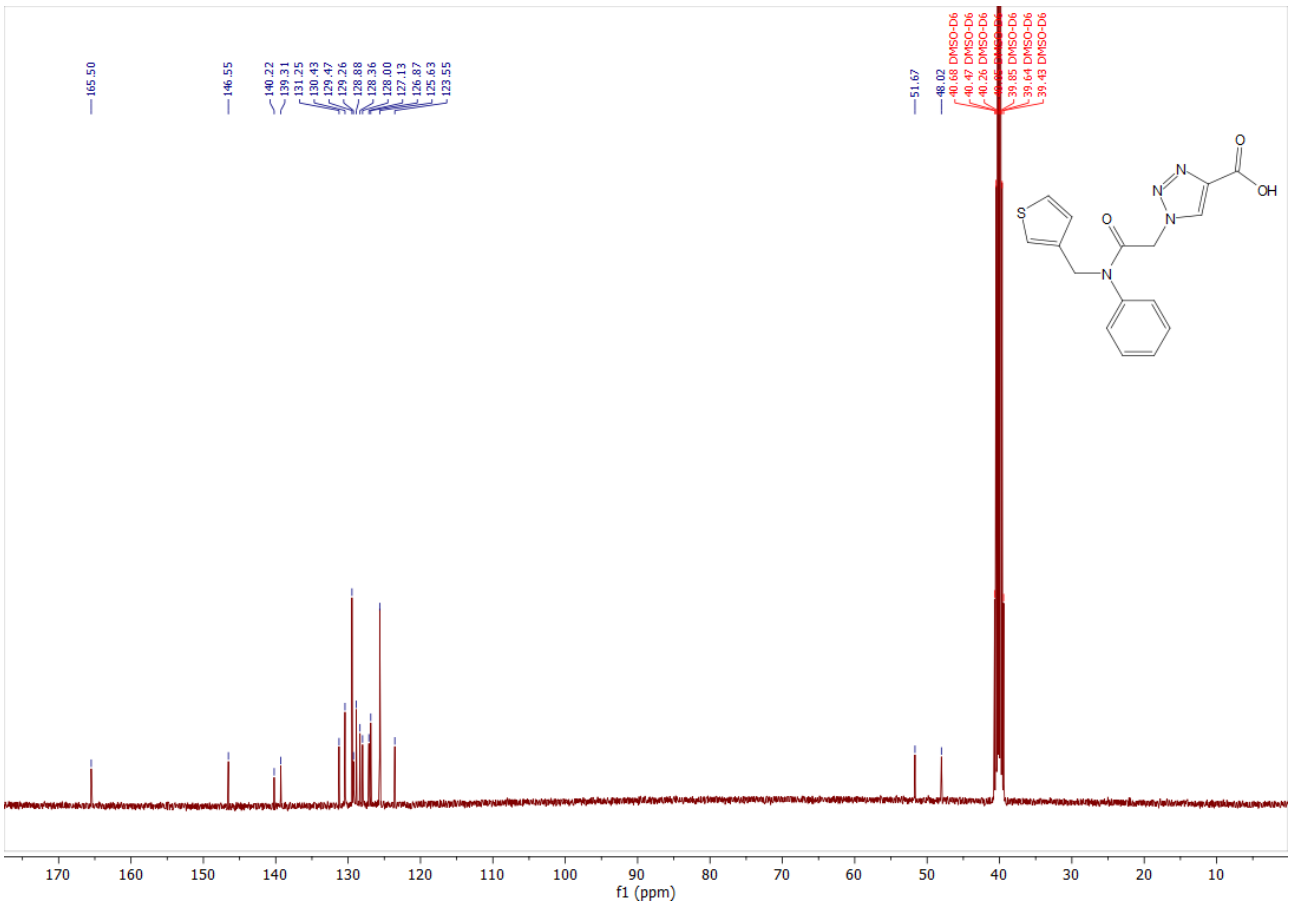
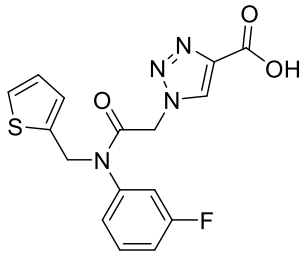


Рисунок 74. ^{13}C NMR spectrum (101 MHz, DMSO-D_6) *1-(2-Oxo-2-(phenyl(thiophen-3-ylmethyl)amino)ethyl)-1H-1,2,3-triazole-4-carboxylic acid* **4e**

Речовина **4f**. Нековалентний інгібітор головної протеази SARS-CoV-2 M^{pro}.

Назва: *1-(2-((3-Fluorophenyl)(thiophen-2-ylmethyl)amino)-2-oxoethyl)-1H-1,2,3-triazole-4-carboxylic acid*



White solid. Yield 84 %

Спектральні параметри:

^{1}H NMR (400 MHz, DMSO-D_6) δ 8.48 (s, 1H), 7.39 – 7.23 (m, 1H), 7.18 – 7.11 (m, 1H), 7.15 – 7.05 (m, 1H), 7.08 – 6.94 (m, 1H), 5.20 (d, J = 0.7 Hz, 1H), 5.00 (d, J = 0.8 Hz, 1H).

^{13}C NMR (101 MHz, DMSO-D_6) δ 166.56, 164.44, 163.17, 161.97, 139.82, 139.69, 138.10, 137.07, 130.61, 130.51, 127.23, 127.21, 125.58, 125.57, 119.85, 119.81, 110.28, 110.04, 109.77, 109.55, 52.17, 43.10.

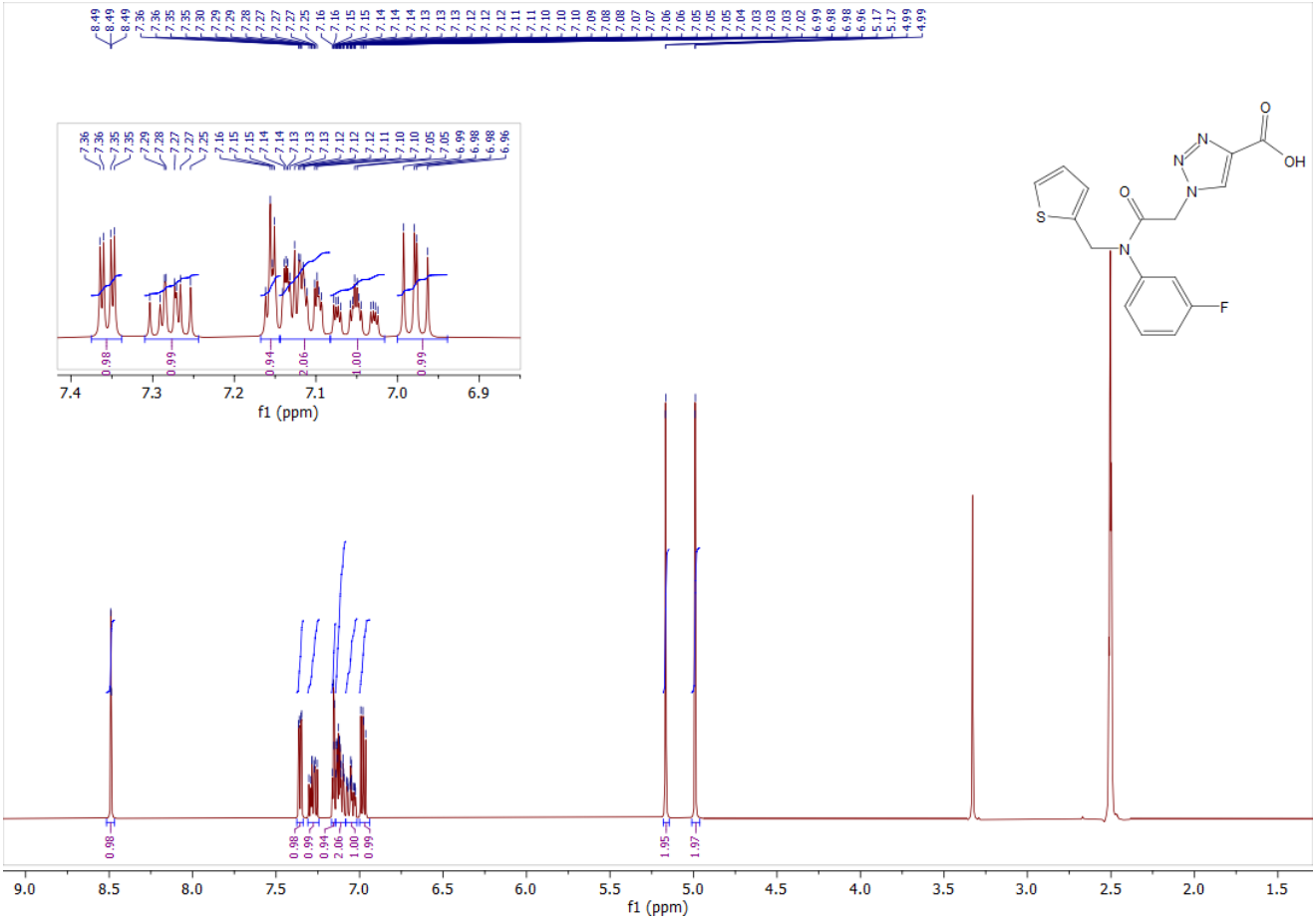


Рисунок 75. ^{1}H NMR spectrum (400 MHz, DMSO-D_6) *1-(2-((3-Fluorophenyl)(thiophen-2-ylmethyl)amino)-2-oxoethyl)-1H-1,2,3-triazole-4-carboxylic acid* **4f**

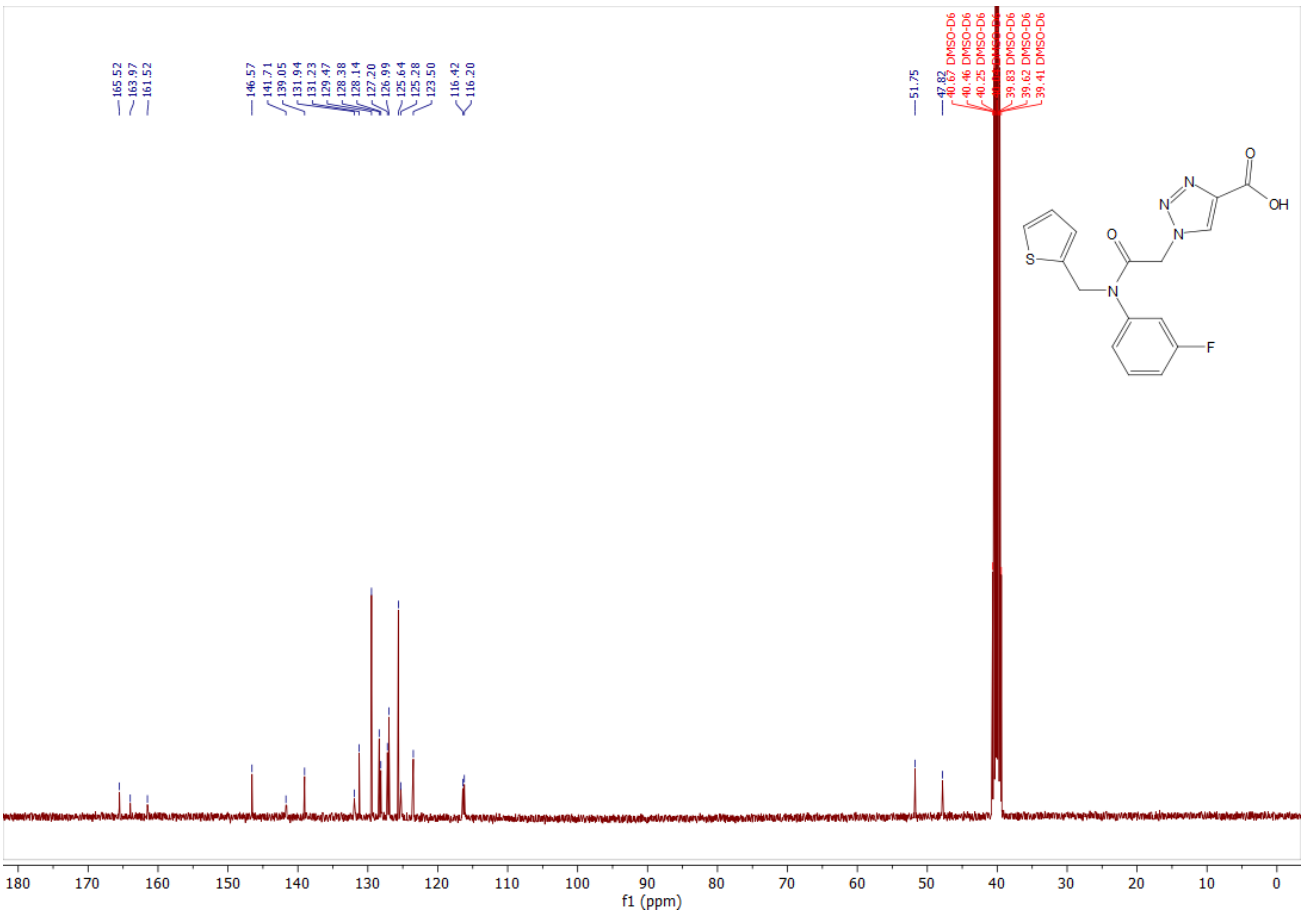
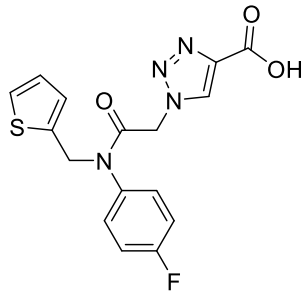


Рисунок 76. ^{13}C NMR spectrum (101 MHz, DMSO-D_6) *1-(2-((3-Fluorophenyl)(thiophen-2-ylmethyl)amino)-2-oxoethyl)-1H-1,2,3-triazole-4-carboxylic acid* **4f**

Речовина **4g**. Нековалентний інгібітор головної протеази SARS-CoV-2 M^{pro}.

Назва: *1-(2-((4-Fluorophenyl)(thiophen-2-ylmethyl)amino)-2-oxoethyl)-1H-1,2,3-triazole-4-carboxylic acid*



White solid. Yield 82 %

Спектральні параметри:

^{1}H NMR (400 MHz, DMSO-D_6) δ 8.46 (s, 1H), 7.36 (dd, J = 5.3, 1.7 Hz, 1H), 7.33 – 7.26 (m, 2H), 7.14 (ddt, J = 6.4, 1.8, 0.9 Hz, 1H), 7.10 – 7.01 (m, 2H), 6.98 (dd, J = 6.5, 5.3 Hz, 1H), 5.20 (d, J = 0.7 Hz, 2H), 5.06 (d, J = 0.8 Hz, 2H).

^{13}C NMR (101 MHz, DMSO-D_6) δ 166.67, 163.17, 160.65, 158.19, 138.11, 137.07, 136.88, 136.85, 127.23, 127.21, 125.69, 125.61, 125.58, 125.57, 117.57, 117.34, 52.18, 43.14.

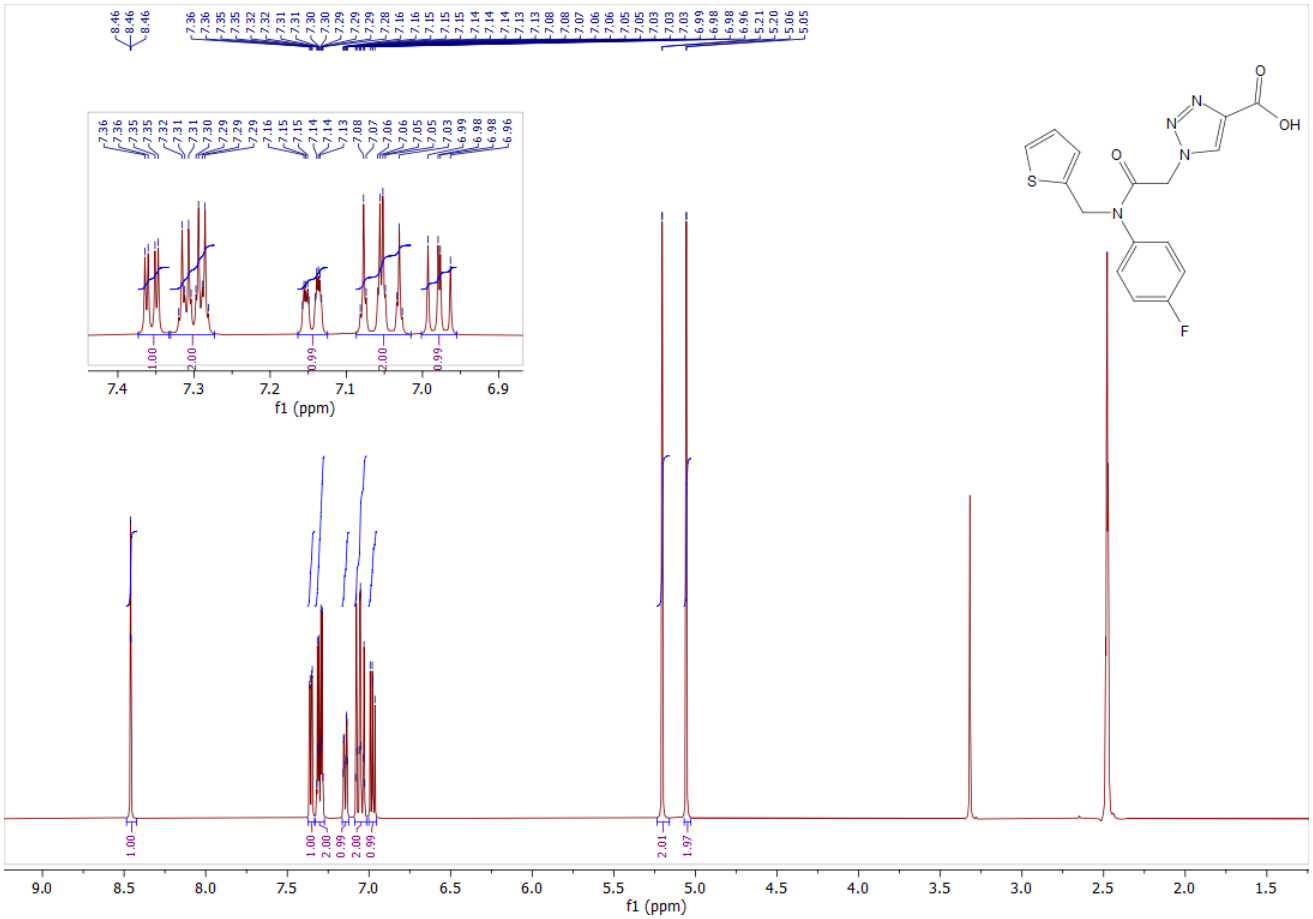


Рисунок 77. ^{1}H NMR spectrum (400 MHz, DMSO-D_6) *1-(2-((4-Fluorophenyl)(thiophen-2-ylmethyl)amino)-2-oxoethyl)-1H-1,2,3-triazole-4-carboxylic acid* **4g**

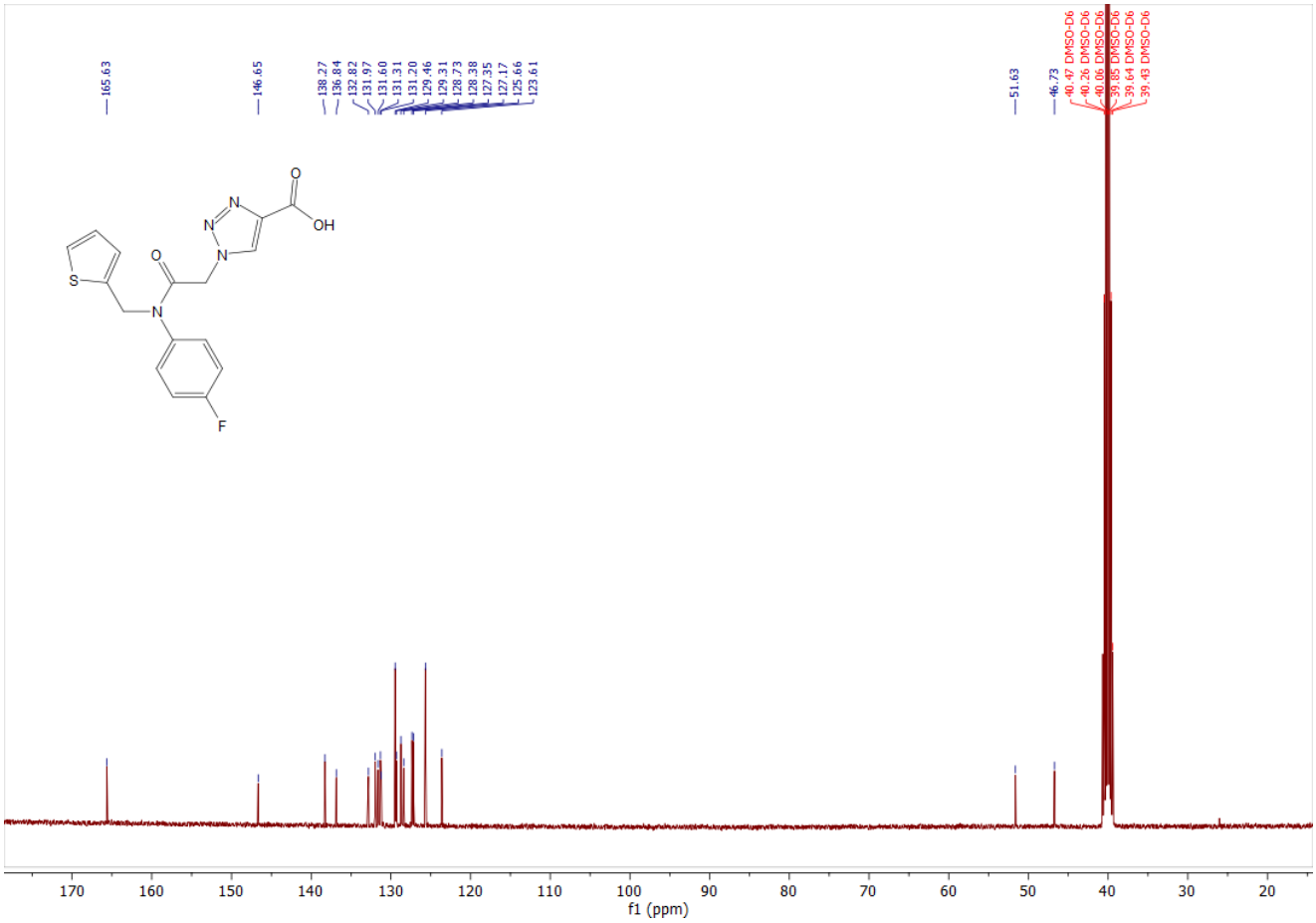
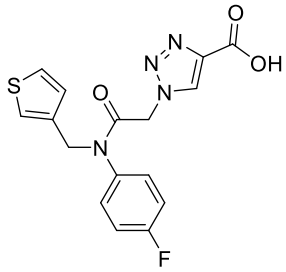


Рисунок 78. ^{13}C NMR spectrum (101 MHz, DMSO-D_6) *1-(2-((4-Fluorophenyl)(thiophen-2-ylmethyl)amino)-2-oxoethyl)-1H-1,2,3-triazole-4-carboxylic acid* **4g**

Речовина **4h**. Нековалентний інгібітор головної протеази SARS-CoV-2 M^{pro}.

Назва: *1-(2-((4-Fluorophenyl)(thiophen-3-ylmethyl)amino)-2-oxoethyl)-1H-1,2,3-triazole-4-carboxylic acid*



White solid. Yield 78 %

Спектральні параметри:

^{1}H NMR (400 MHz, DMSO-D_6) δ 8.48 (d, J = 0.9 Hz, 1H), 7.41 (dd, J = 5.2, 1.7 Hz, 1H), 7.35 (tt, J = 1.6, 0.9 Hz, 1H), 7.34 – 7.26 (m, 2H), 7.23 (ddt, J = 5.3, 1.7, 0.8 Hz, 1H), 7.10 – 7.00 (m, 2H), 5.20 (d, J = 0.8 Hz, 2H), 5.04 (t, J = 0.9 Hz, 2H).

^{13}C NMR (101 MHz, DMSO-D_6) δ 166.75, 163.17, 160.65, 158.19, 137.30, 137.27, 137.07, 135.69, 127.21, 127.11, 126.70, 125.59, 125.50, 123.25, 117.52, 117.30, 52.18, 44.60.

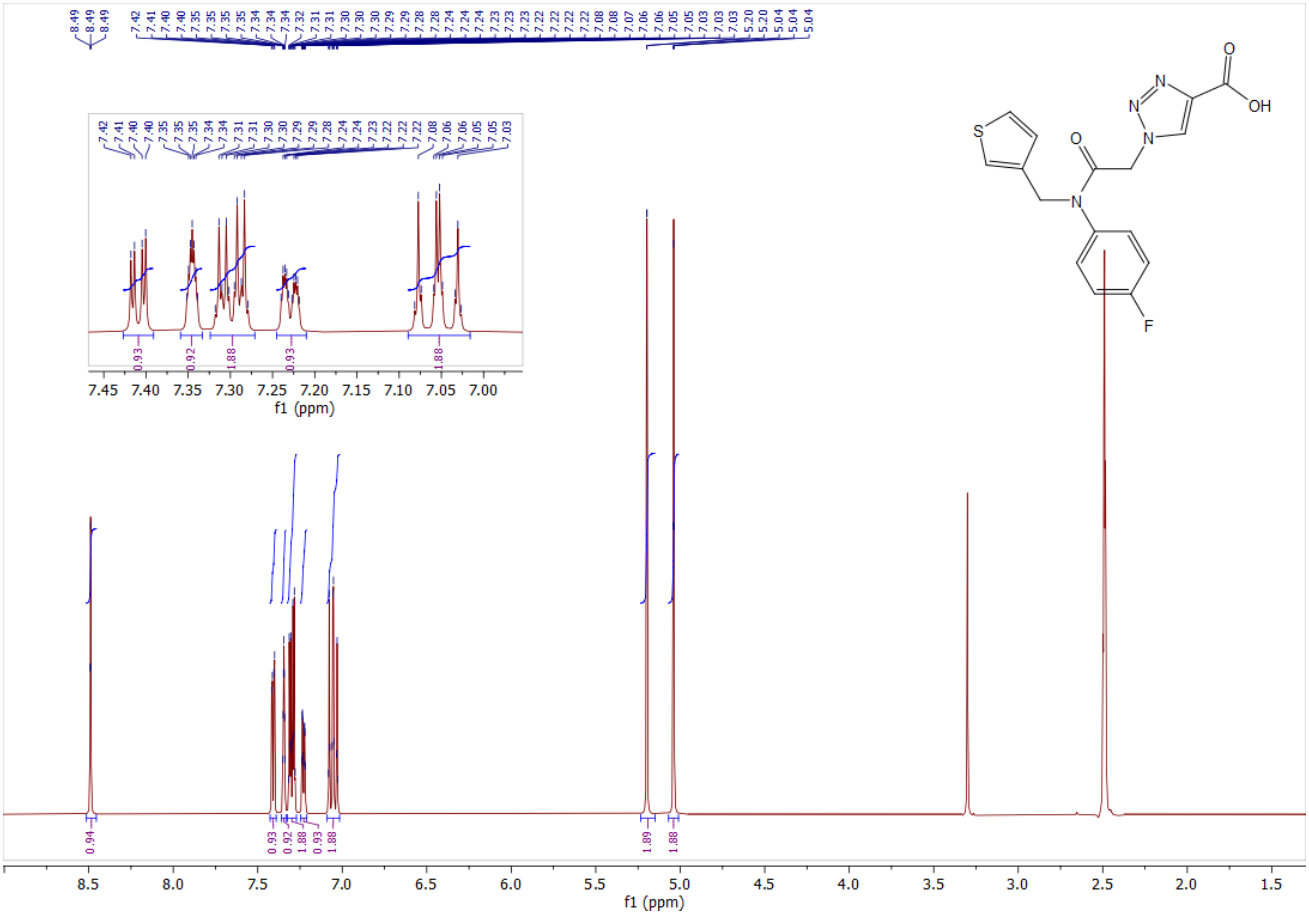


Рисунок 79. ^{1}H NMR spectrum (400 MHz, DMSO-D_6) *1-(2-((4-Fluorophenyl)(thiophen-3-ylmethyl)amino)-2-oxoethyl)-1H-1,2,3-triazole-4-carboxylic acid* **4h**

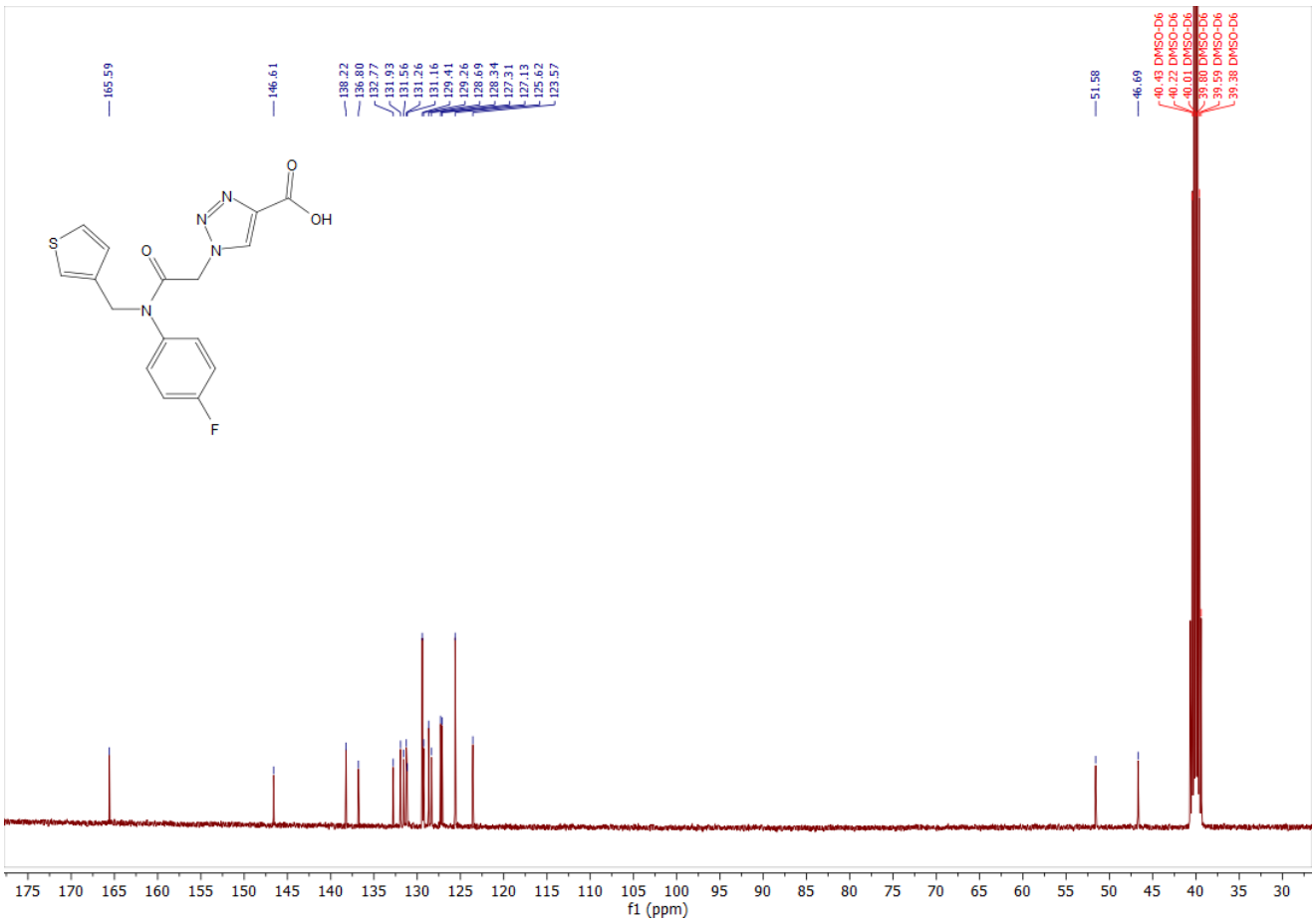
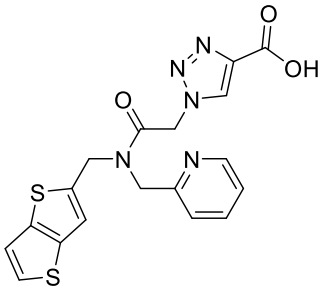


Рисунок 80. ^{13}C NMR spectrum (101 MHz, DMSO-D_6) *1-(2-((4-Fluorophenyl)(thiophen-3-ylmethyl)amino)-2-oxoethyl)-1H-1,2,3-triazole-4-carboxylic acid* **4h**

Речовина **4i**. Нековалентний інгібітор головної протеази SARS-CoV-2 M^{pro}.

Назва: *1-(2-Oxo-2-((pyridin-2-ylmethyl)(thieno[3,2-b]thiophen-2-ylmethyl)amino)ethyl)-1H-1,2,3-triazole-4-carboxylic acid*



White solid. Yield 84 %. MS (ESI+) m/z calculated for $C_{18}H_{15}N_5O_3S_2$ $[M+H]^+$ 414.0, found 414.2.

Спектральні параметри:

^{1}H NMR (400 MHz, DMSO-D_6) δ 8.53 – 8.46 (m, 1H), 8.41 (t, J = 0.9 Hz, 1H), 7.79 – 7.71 (m, 1H), 7.53 (d, J = 5.0 Hz, 1H), 7.35 – 7.28 (m, 3H), 7.01 (d, J = 1.2 Hz, 1H), 4.94 (d, J = 0.8 Hz, 2H), 4.68 (d, J = 0.8 Hz, 2H), 4.51 (d, J = 0.8 Hz, 2H).

^{13}C NMR (101 MHz, DMSO-D_6) δ 167.50, 163.17, 156.18, 149.74, 142.68, 139.11, 138.91, 137.07, 130.84, 127.32, 125.01, 122.76, 122.57, 122.18, 51.92, 50.63, 47.16.

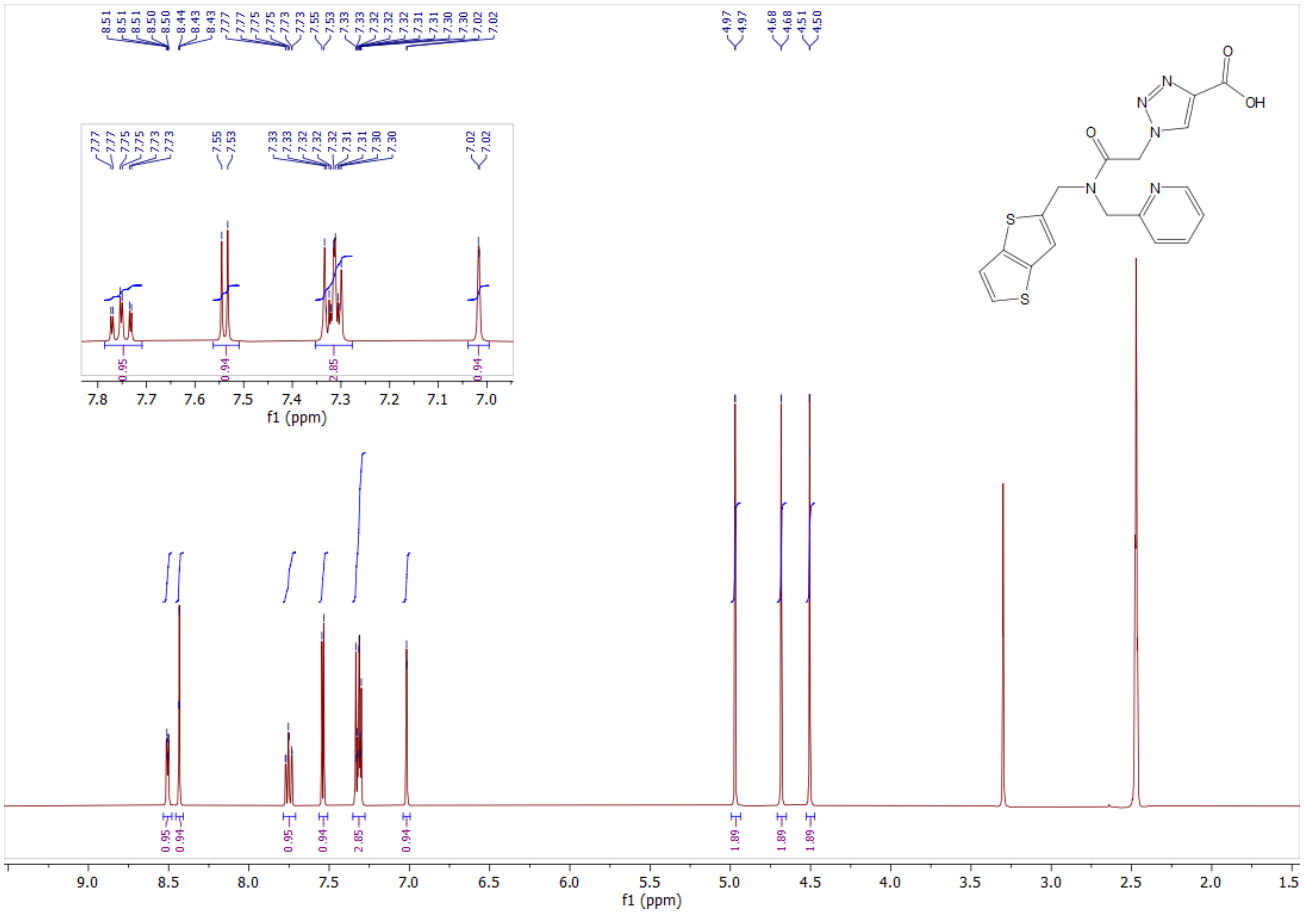


Рисунок 81. ^{1}H NMR spectrum (400 MHz, DMSO-D_6) *1-(2-Oxo-2-((pyridin-2-ylmethyl)(thieno[3,2-b]thiophen-2-ylmethyl)amino)ethyl)-1H-1,2,3-triazole-4-carboxylic acid* **4i**

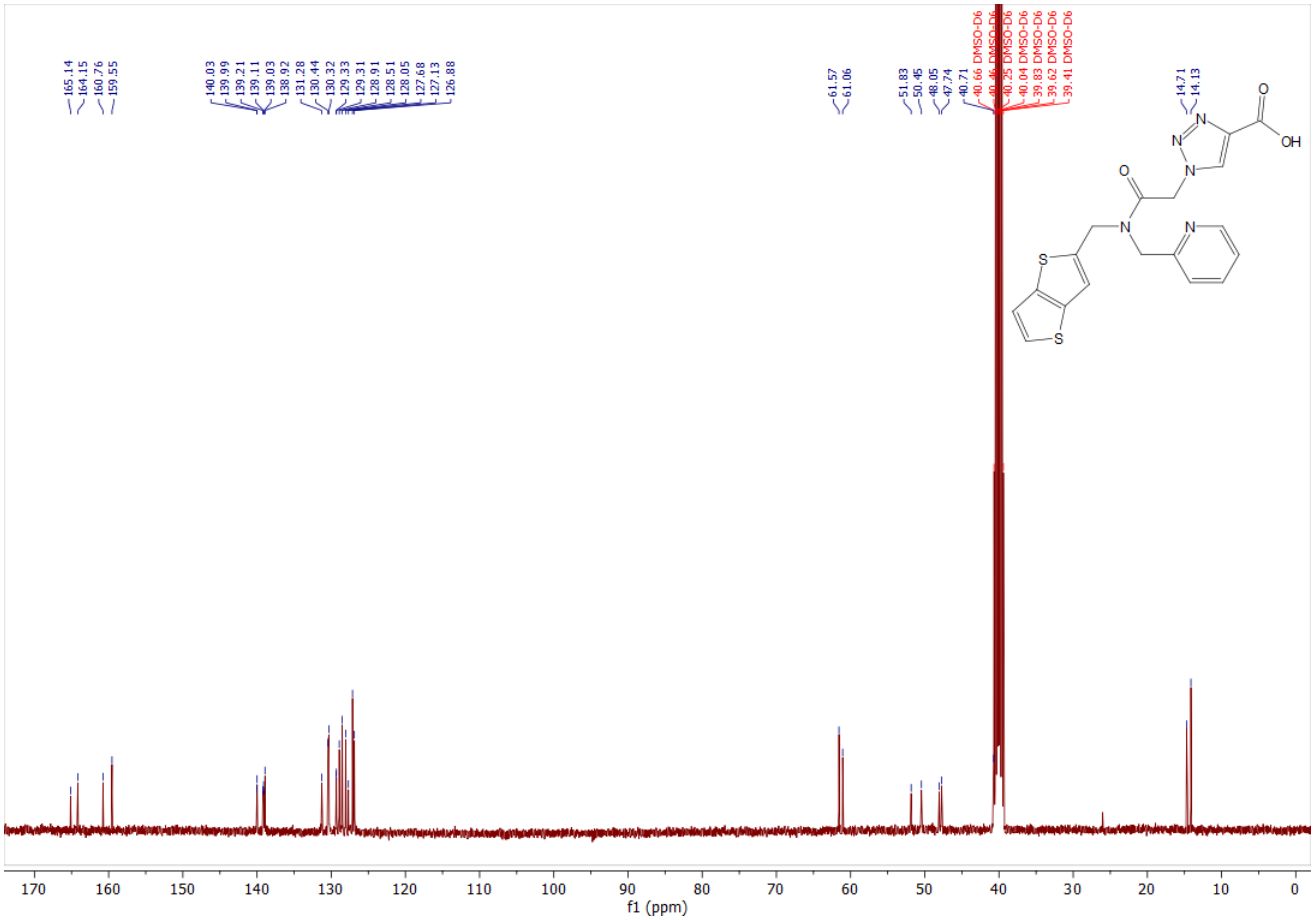
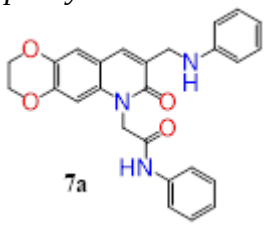


Рисунок 82. ^{13}C NMR spectrum (101 MHz, DMSO-D_6) *1-(2-Oxo-2-((pyridin-2-ylmethyl)(thieno[3,2-b]thiophen-2-ylmethyl)amino)ethyl)-1H-1,2,3-triazole-4-carboxylic acid* **4i**

Сполуки 5a-5q

Речовина **5a**. Дуальний інгібітор протеаз SARS-CoV-2 M^{pro} та PL^{pro}.
Назва: *2-(7-Oxo-8-((phenylamino)methyl)-2,3-dihydro-[1,4]dioxino[2,3-g]quinolin-6(7H)-yl)-N-phenylacetamide*



Yellow powder, Yield 85 %, mp = 238-9°C. $[MH]^+$ m/z = 442.2.
Спектральні параметри:
^{1}H NMR (400 MHz, DMSO-*d6*) δ 10.24 (s, 1H), 7.57 (dd, J = 7.0, 1.2 Hz, 3H), 7.40 – 7.28 (m, 3H), 7.24 (s, 1H), 7.20 – 7.12 (m, 2H), 7.12 – 7.01 (m, 2H), 6.78 (dd, J = 7.9, 1.2 Hz, 2H), 6.75 – 6.68 (m, 1H), 5.10 (s, 2H), 4.50 (dd, J = 5.2, 1.3 Hz, 2H), 4.33 – 4.22 (m, 4H).
^{13}C NMR (100 MHz, DMSO-d_6) δ 166.34, 164.19, 146.03, 145.36, 139.64, 137.08, 133.49, 131.06, 129.61, 129.43, 128.91, 123.75, 120.04, 117.22, 116.74, 113.47, 111.97, 99.39, 64.55, 64.03, 48.23, 45.10, 40.61, 40.45, 40.40, 40.24, 40.19, 40.03, 39.98, 39.78, 39.57, 39.36.

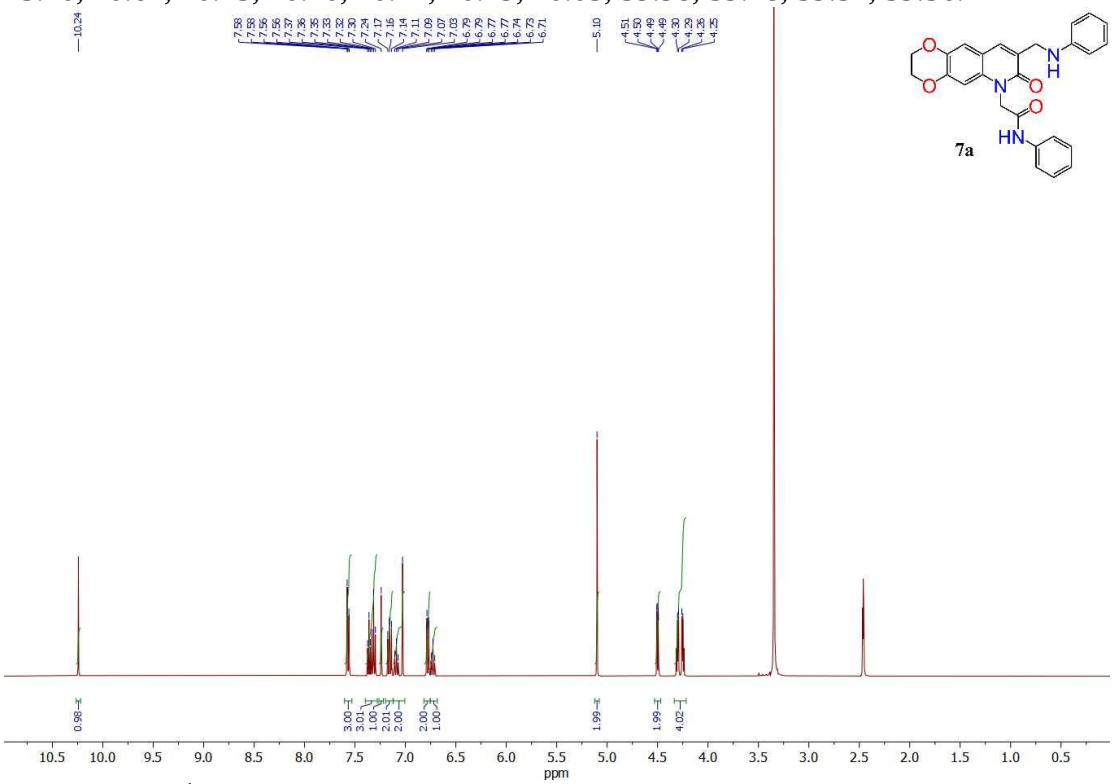


Рисунок 83. ^{1}H NMR spectrum (400 MHz, DMSO-d6) of 2-(7-Oxo-8-((phenylamino)methyl)-2,3-dihydro-[1,4]dioxino[2,3-g]quinolin-6(7H)-yl)-N-phenylacetamide **5a**

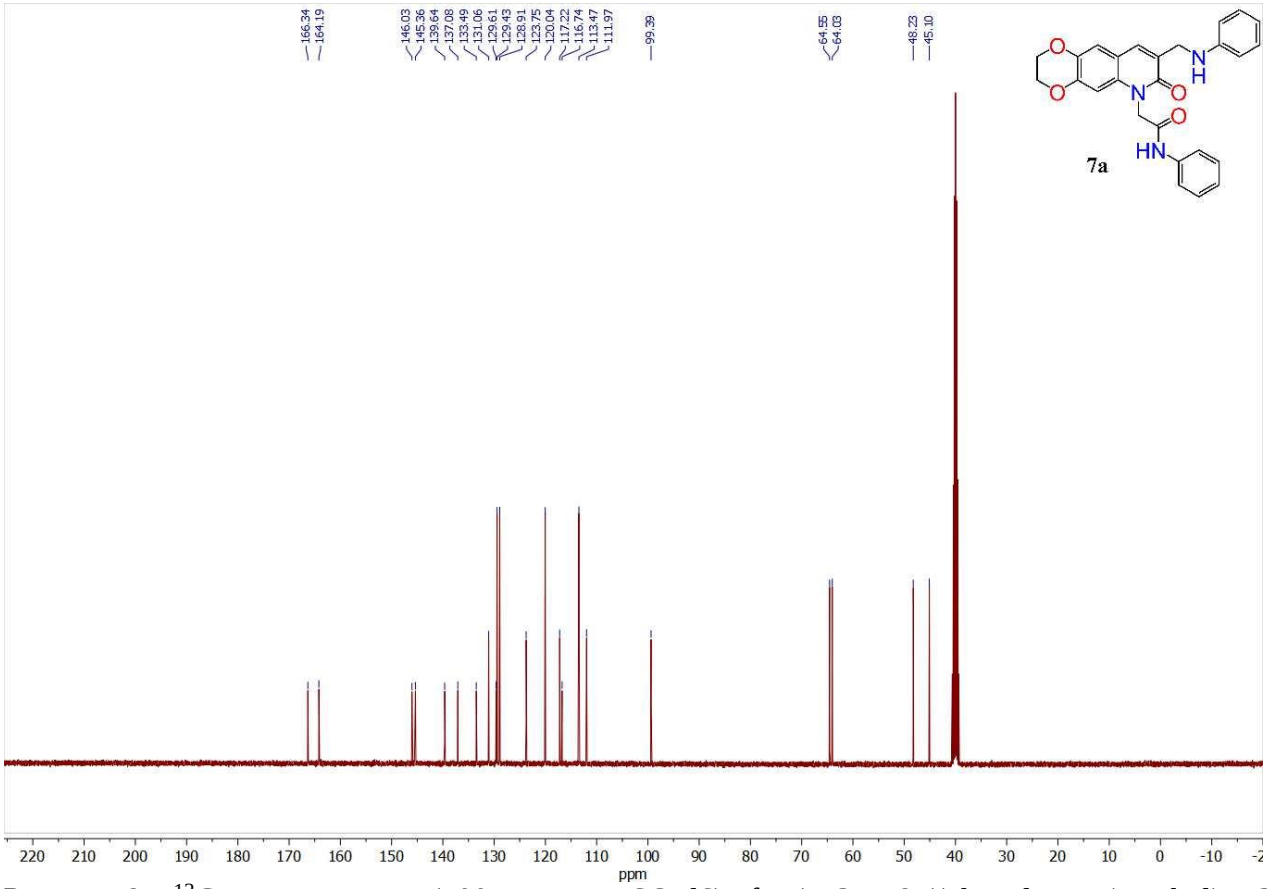
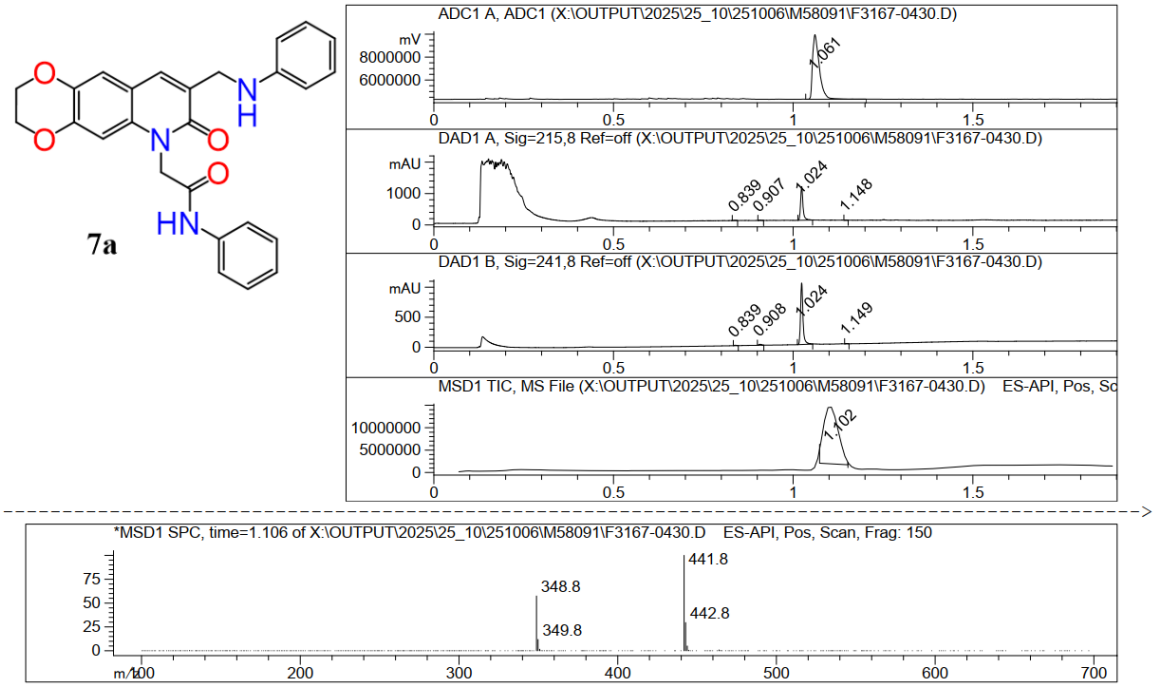


Рисунок 84. ^{13}C NMR spectrum (100 MHz, DMSO-d6) of 2-(7-Oxo-8-((phenylamino)methyl)-2,3-dihydro-[1,4]dioxino[2,3-g]quinolin-6(7H)-yl)-N-phenylacetamide **5a**.

Agilent 1260 LC/MSD SL
Diodearrey G1315B (DAD1A-215nm; DAD1B-241nm)
Mass Quad G6140 (MSD1-Pos, MSD2-Neg)
ELSD Softa 1400 (ADC1 A, ELSD)

Mobile Phase:A-H2O+0.1%HCOOH;B-MeCN+0.1HCOOH
Separation column:
97 %
Cartige 4.6x30mm,
1.8-Micron, Zorbx SB-C18



#	Signal	R.Time	Area %
1	ADC1 A, ADC1	1.061	100.000

#	Signal	R.Time	Area %
1	DAD1 A, Sig=215,8 Ref=off	0.839	0.870
2		0.907	1.192
3		1.024	97.214
4		1.148	0.724

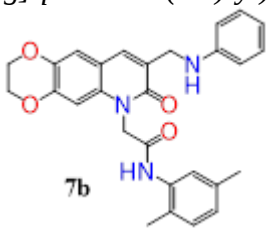
#	Signal	R.Time	Area %
1	DAD1 B, Sig=241,8 Ref=off	0.839	0.649
2		0.908	1.309
3		1.024	97.696
4		1.149	0.346

#	Signal	R.Time	Area %
1	MSD1 TIC, MS File	1.102	100.000

Рисунок 85. LC/MS data of 2-(7-Oxo-8-((phenylamino)methyl)-2,3-dihydro-[1,4]dioxino[2,3-g]quinolin-6(7H)-yl)-N-phenylacetamide **5a**.

Речовина **5b**. Дуальний інгібітор протеаз SARS-CoV-2 M^{pro} та PL^{pro}.

Назва: *N-(2,5-Dimethylphenyl)-2-(7-oxo-8-((phenylamino)methyl)-2,3-dihydro-[1,4]dioxino[2,3-g]quinolin-6(7H)-yl)acetamide*



Yellow powder, Yield 81 %, mp = 231-2°C. $[MH]^+$ m/z = 470.2.

Спектральні параметри:

^{1}H NMR (400 MHz, DMSO-d6) δ 9.55 (s, 1H), 7.58 (t, J = 1.3 Hz, 1H), 7.30 (t, J = 5.3 Hz, 1H), 7.20 – 7.11 (m, 3H), 7.03 (s, 1H), 6.97 – 6.87 (m, 2H), 6.59 – 6.51 (m, 3H), 6.10 (tt, J = 6.9, 1.3 Hz, 1H), 5.15 (s, 2H), 4.35 – 4.15 (m, 4H), 4.12 (d, J = 3.9 Hz, 2H), 2.22 – 2.17 (m, 6H).

^{13}C NMR (101 MHz, DMSO-d6) δ 167.91, 164.19, 146.03, 145.36, 139.64, 138.02, 136.09, 133.49, 131.06, 129.68, 129.61, 129.43, 129.11, 123.35, 120.95, 117.22, 116.74, 113.47, 111.97, 99.39, 64.55, 64.03, 48.13, 45.10, 40.61, 40.45, 40.40, 40.24, 40.19, 40.03, 39.98, 39.78, 39.57, 39.36, 21.33, 17.61.

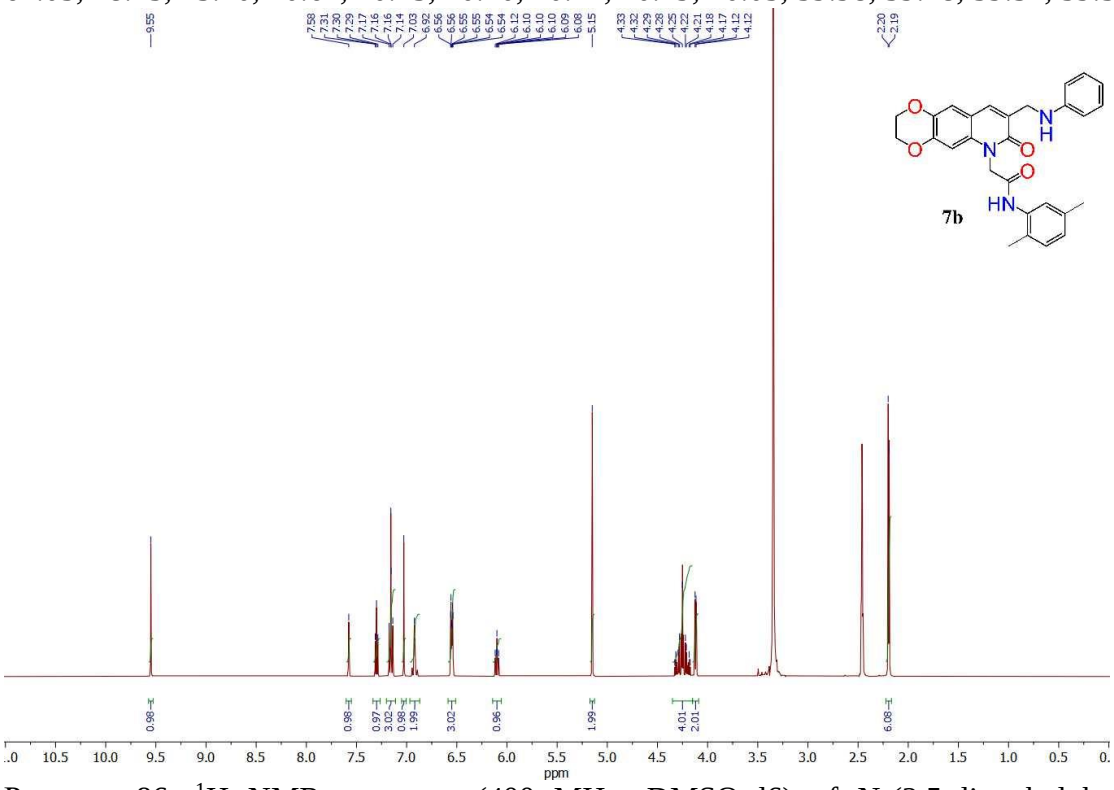


Рисунок 86. ^{1}H NMR spectrum (400 MHz, DMSO-d6) of N-(2,5-dimethylphenyl)-2-(7-oxo-8-((phenylamino)methyl)-2,3-dihydro-[1,4]dioxino[2,3-g]quinolin-6(7H)-yl)acetamide **5b**

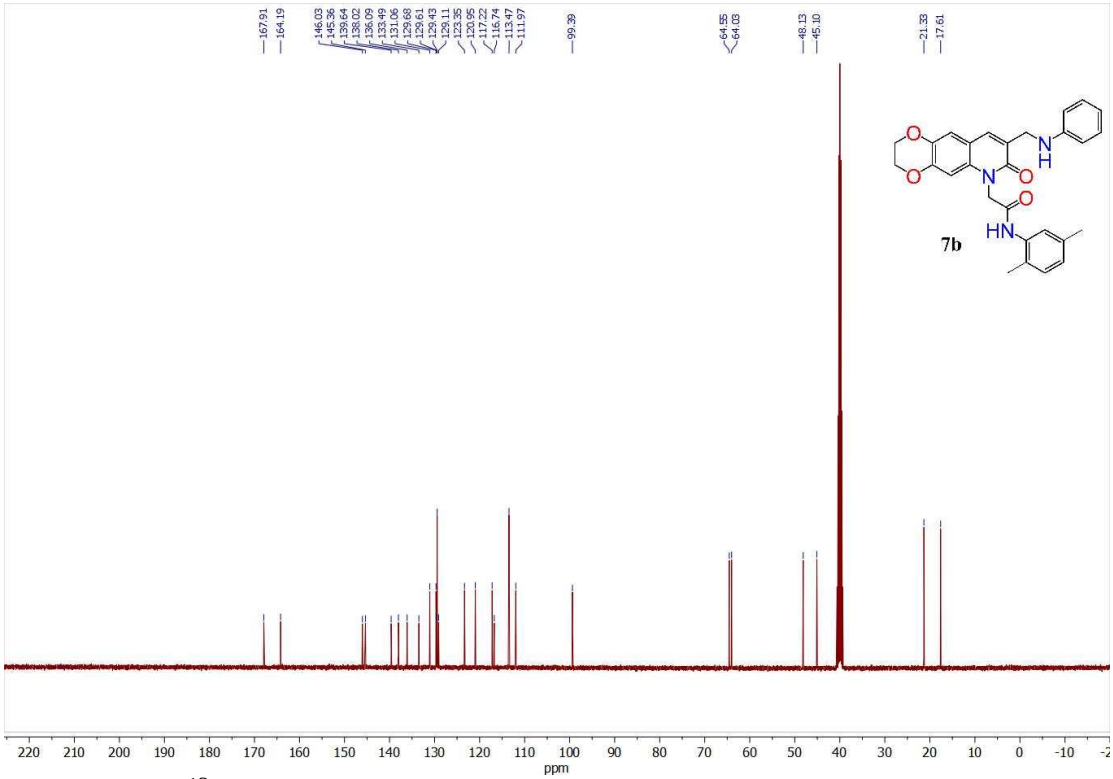
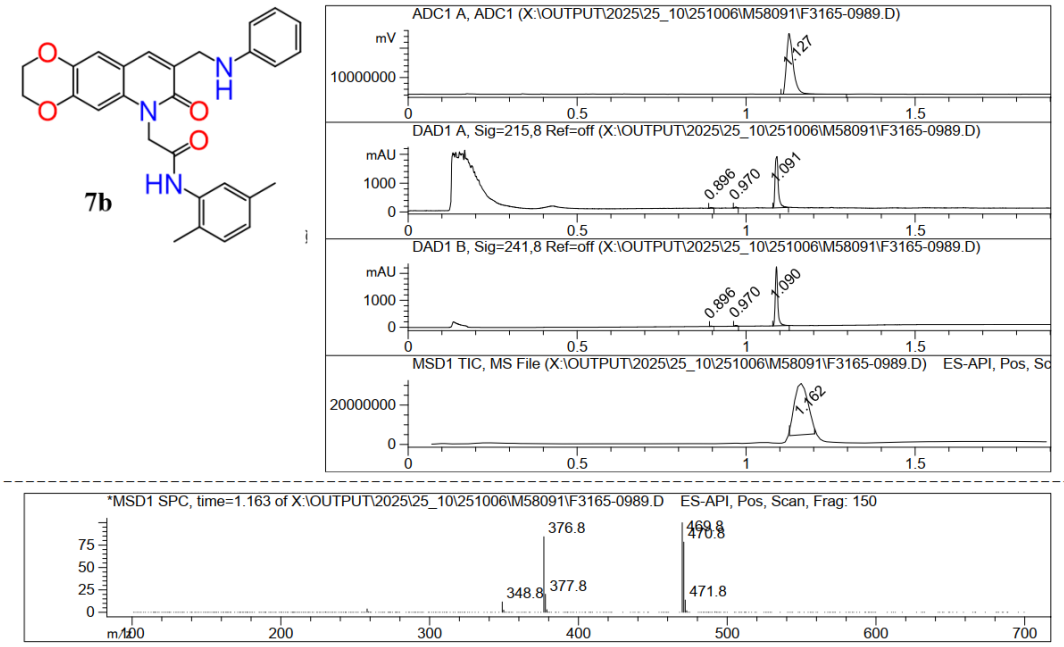


Рисунок 87. ^{13}C NMR spectrum (101 MHz, DMSO-d6) of 2-N-(2,5-dimethylphenyl)-2-(7-oxo-8-((phenylamino)methyl)-2,3-dihydro-[1,4]dioxino[2,3-g]quinolin-6(7H)-yl)acetamide **5b**

Agilent 1260 LC/MSD SL
Diodearrey G1315B (DAD1A-215nm; DAD1B-241nm)
Mass Quad G6140 (MSD1-Pos, MSD2-Neg)
ELSD Softa 1400 (ADC1 A, ELSD)

Mobile Phase:A-H2O+0.1%HCOOH;B-MeCN+0.1HCOOH
97 %
Rapid Resolution HT Cartige 4.6x30mm,
1.8-Micron, Zorbx SB-C18



#	Signal	R.Time	Area %
1	ADC1 A, ADC1	1.127	100.000

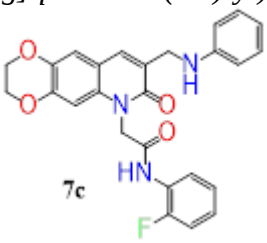
#	Signal	R.Time	Area %
1	DAD1 A, Sig=215,8 Ref=off	0.896	1.049
2		0.970	1.178
3		1.091	97.772

#	Signal	R.Time	Area %
1	DAD1 B, Sig=241,8 Ref=off	0.896	0.357
2		0.970	1.032
3		1.090	98.611

#	Signal	R.Time	Area %
1	MSD1 TIC, MS File	1.162	100.000

Рисунок 88. LC/MS data of 2-N-(2,5-dimethylphenyl)-2-(7-oxo-8-((phenylamino)methyl)-2,3-dihydro-[1,4]dioxino[2,3-g]quinolin-6(7H)-yl)acetamide **5b**

Речовина **5c**. Дуальний інгібітор протеаз SARS-CoV-2 M^{pro} та PL^{pro}.
Назва: *N-(2-Fluorophenyl)-2-(7-oxo-8-((phenylamino)methyl)-2,3-dihydro-[1,4]dioxino[2,3-g]quinolin-6(7H)-yl)acetamide*



Yellow powder, Yield 86 %, mp = 217-8°C. $[MH]^+$ m/z = 460.2.
Спектральні параметри:
^{1}H NMR (400 MHz, DMSO-d6) δ 10.25 (d, J = 3.4 Hz, 1H), 7.36 (t, J = 5.4 Hz, 1H), 7.27 – 7.01 (m, 7H), 6.81 – 6.69 (m, 3H), 5.20 (s, 2H), 4.50 (dd, J = 5.2, 1.3 Hz, 2H), 4.33 – 4.22 (m, 4H).
^{13}C NMR (101 MHz, DMSO-d6) δ 167.80, 167.69, 164.19, 155.06, 152.64, 146.03, 145.36, 139.64, 133.49, 131.06, 129.61, 129.43, 126.62, 126.47, 125.23, 125.19, 123.78, 123.70, 121.66, 121.60, 117.22, 116.74, 115.48, 115.27, 113.47, 111.97, 99.39, 64.55, 64.03, 48.09, 45.10, 40.61, 40.45, 40.40, 40.24, 40.19, 40.03, 39.98, 39.78, 39.57, 39.36.

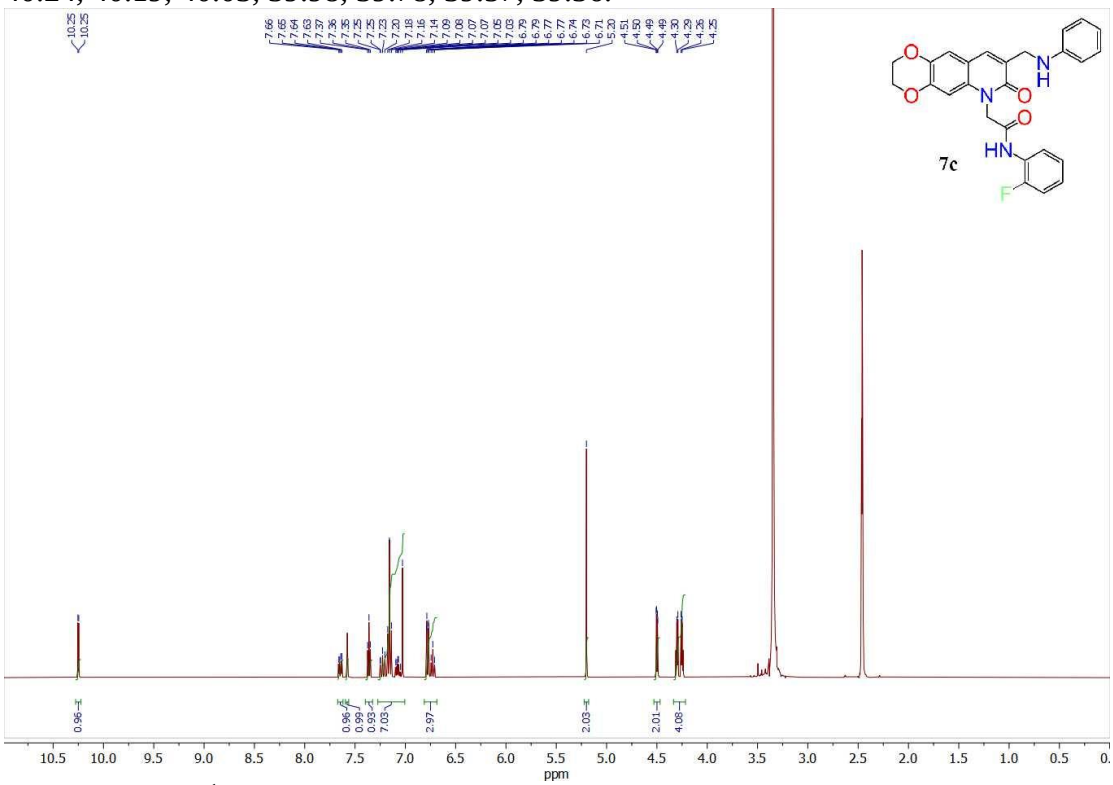


Рисунок 89. ^{1}H NMR spectrum (400 MHz, DMSO-d6) of N-(2-fluorophenyl)-2-(7-oxo-8-((phenylamino)methyl)-2,3-dihydro-[1,4]dioxino[2,3-g]quinolin-6(7H)-yl)acetamide **5c**

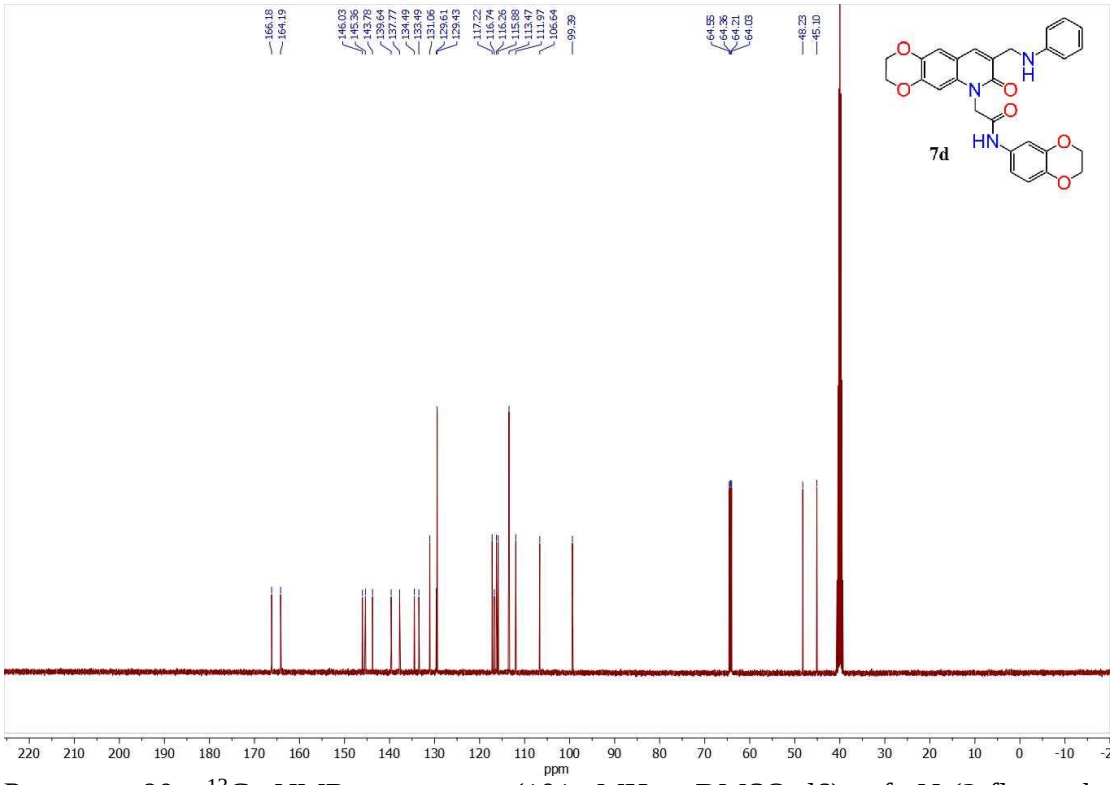
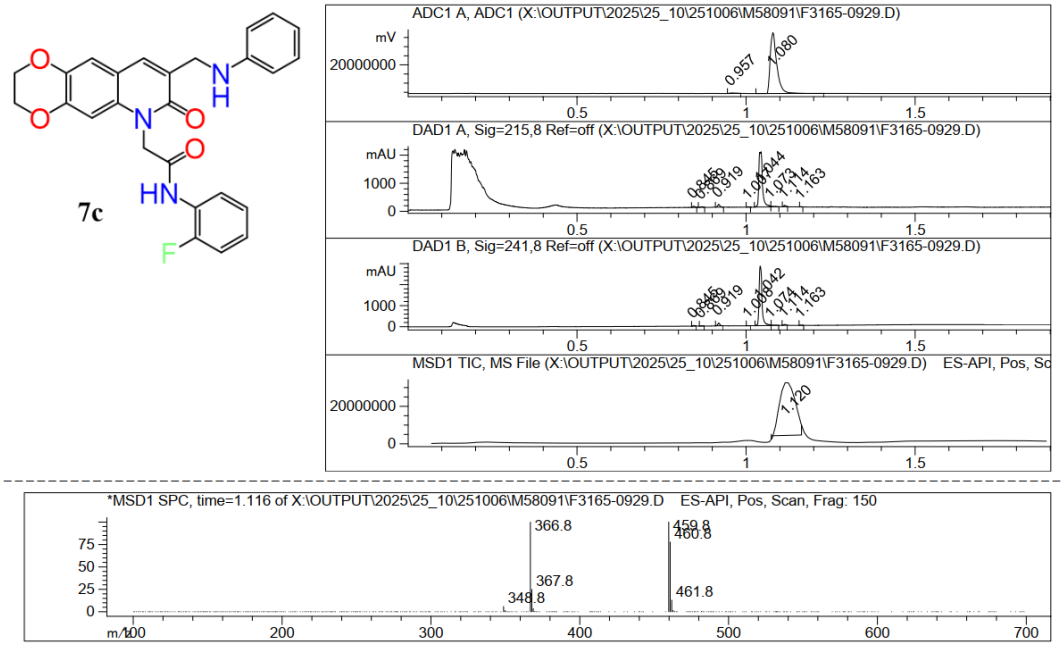


Рисунок 90. ^{13}C NMR spectrum (101 MHz, DMSO-d6) of N-(2-fluorophenyl)-2-(7-oxo-8-((phenylamino)methyl)-2,3-dihydro-[1,4]dioxino[2,3-g]quinolin-6(7H)-yl)acetamide **5c**

Agilent 1260 LC/MSD SL
Diodearrey G1315B (DAD1A-215nm; DAD1B-241nm)
Mass Quad G6140 (MSD1-Pos, MSD2-Neg)
ELSD Softa 1400 (ADC1 A, ELSD)

Mobile Phase:A-H2O+0.1%HCOOH;B-MeCN+0.1HCOOH
Separation column:
92 %
Rapid Resolution HT Cartige 4.6x30mm,
1.8-Micron, Zorbx SB-C18



#	Signal	R.Time	Area %
1	ADC1 A, ADC1	0.957	0.659
2		1.080	99.341

#	Signal	R.Time	Area %
1	DAD1 A, Sig=215,8 Ref=off	0.845	1.136
2		0.869	0.587
3		0.919	2.794
4		1.007	0.307
5		1.044	92.479
6		1.073	1.232
7		1.114	1.258
8		1.163	0.208

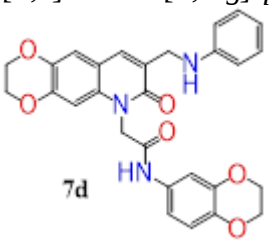
#	Signal	R.Time	Area %
1	DAD1 B, Sig=241,8 Ref=off	0.845	0.577
2		0.869	0.360
3		0.919	2.994
4		1.008	0.271
5		1.042	93.679
6		1.074	1.014
7		1.114	0.897
8		1.163	0.208

#	Signal	R.Time	Area %
1	MSD1 TIC, MS File	1.120	100.000

Рисунок 91. LC/MS data of N-(2-fluorophenyl)-2-(7-oxo-8-((phenylamino)methyl)-2,3-dihydro-[1,4]dioxino[2,3-g]quinolin-6(7H)-yl)acetamide **5c**

Речовина **5d**. Дуальний інгібітор протеаз SARS-CoV-2 M^{pro} та PL^{pro}.

Назва: *N-(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)-2-(7-oxo-8-((phenylamino)methyl)-2,3-dihydro-[1,4]dioxino[2,3-g]quinolin-6(7H)-yl)acetamide*



Yellow powder, Yield 75 %, mp = 234-5°C. $[MH]^+$ m/z = 500.2.

Спектральні параметри:

^{1}H NMR (400 MHz, DMSO-d6) δ 10.07 (s, 1H), 8.84 (t, J = 5.3 Hz, 1H), 7.32 (s, 1H), 7.24 (d, J = 2.1 Hz, 1H), 7.15 (s, 1H), 7.10 (s, 1H), 7.09 – 6.99 (m, 3H), 6.78 (d, J = 8.5 Hz, 3H), 6.67 (d, J = 8.0 Hz, 2H), 4.78 (d, J = 7.0 Hz, 4H), 4.33 – 4.21 (m, 9H).

^{13}C NMR (101 MHz, DMSO-d6) δ 166.18, 164.19, 146.03, 145.36, 143.78, 139.64, 137.77, 134.49, 133.49, 131.06, 129.61, 129.43, 117.22, 116.74, 116.26, 115.88, 113.47, 111.97, 106.64, 99.39, 64.55, 64.36, 64.21, 64.03, 48.23, 45.10.

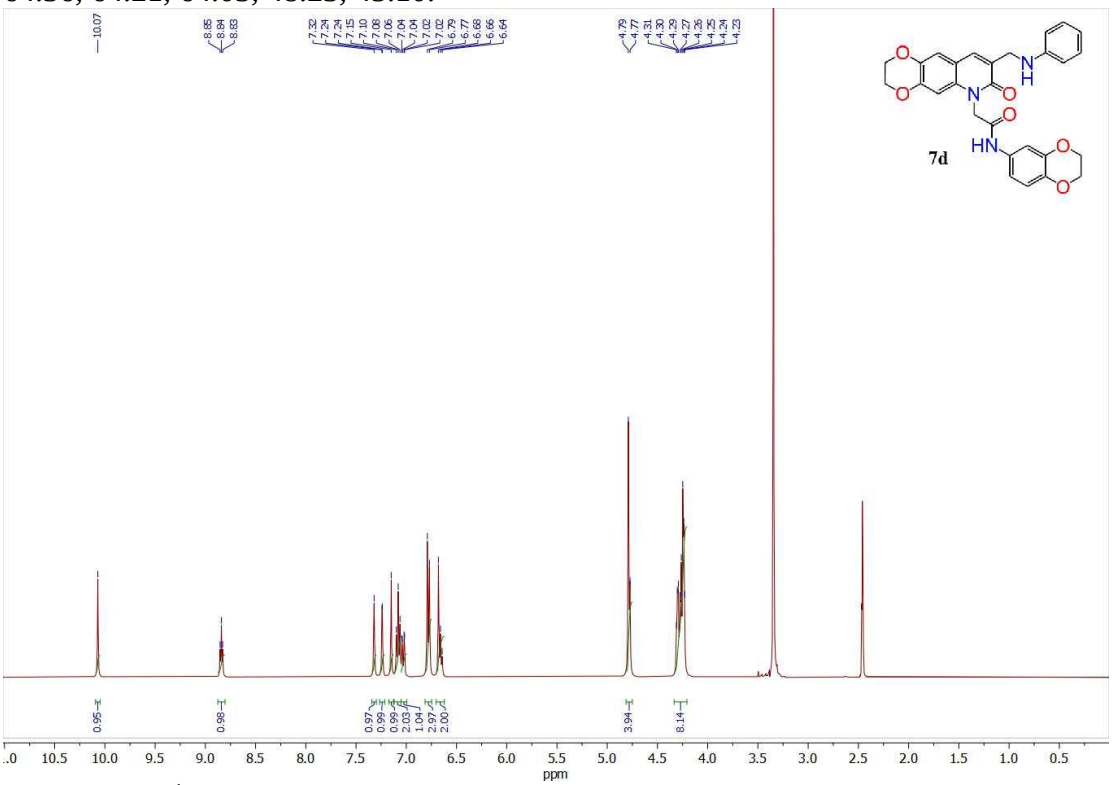


Рисунок 92. ^{1}H NMR spectrum (400 MHz, DMSO-d6) of N-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-(7-oxo-8-((phenylamino)methyl)-2,3-dihydro-[1,4]dioxino[2,3-g]quinolin-6(7H)-yl)acetamide **5d**

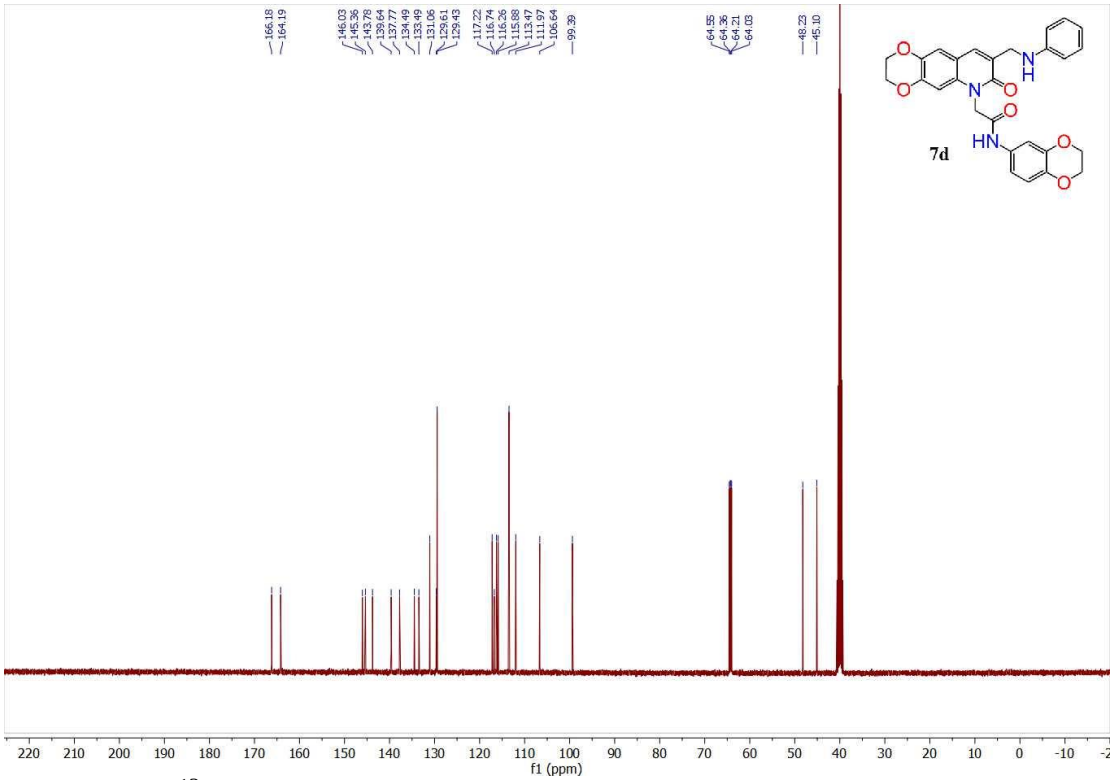
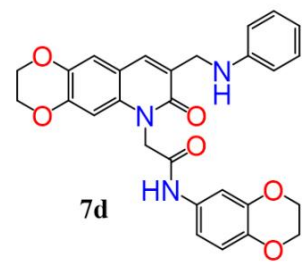
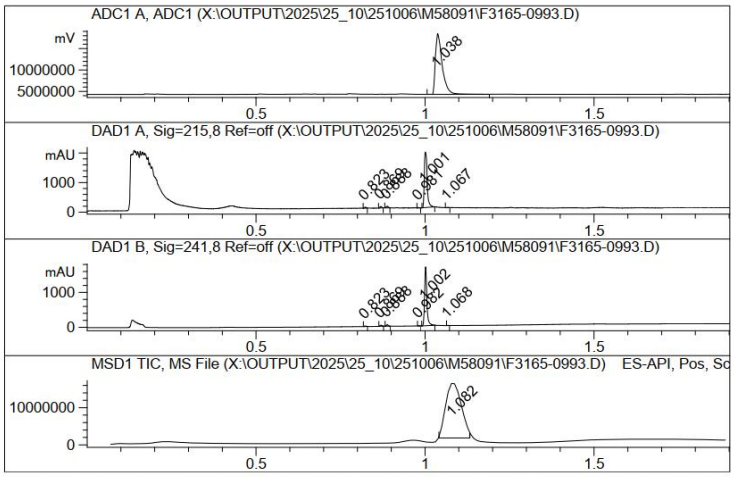


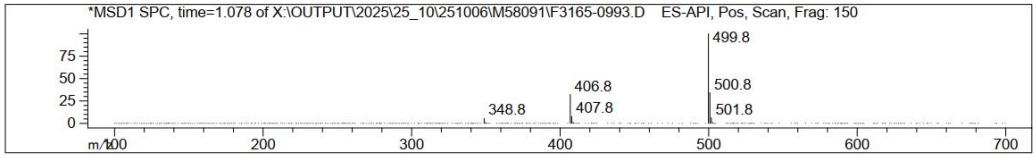
Рисунок 93. ^{13}C NMR spectrum (101 MHz, DMSO-d6) of N-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-(7-oxo-8-((phenylamino)methyl)-2,3-dihydro-[1,4]dioxino[2,3-g]quinolin-6(7H)-yl)acetamide **5d**

Agilent 1260 LC/MSD SL
Diodearrey G1315B (DAD1A-215nm; DAD1B-241nm)
Mass Quad G6140 (MSD1-Pos, MSD2-Neg)
ELSD Softa 1400 (ADC1 A, ELSD)

Mobile Phase:A-H2O+0.1%HCOOH;B-MeCN+0.1HCOOH
Separation column:
94 %
1.8-Micron, Zorbx SB-C18







#	Signal	R.Time	Area %
1	ADC1 A, ADC1	1.038	100.000

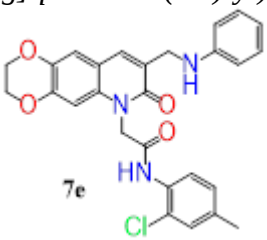
#	Signal	R.Time	Area %
1	DAD1 A, Sig=215,8 Ref=off	0.823	0.984
2		0.869	1.579
3		0.888	2.097
4		0.981	0.439
5		1.001	94.552
6		1.067	0.350

#	Signal	R.Time	Area %
1	DAD1 B, Sig=241,8 Ref=off	0.823	0.683
2		0.869	1.237
3		0.888	1.954
4		0.982	0.258
5		1.002	95.633
6		1.068	0.235

#	Signal	R.Time	Area %
1	MSD1 TIC, MS File	1.082	100.000

Рисунок 94. LC/MS data of N-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-(7-oxo-8-((phenylamino)methyl)-2,3-dihydro-[1,4]dioxino[2,3-g]quinolin-6(7H)-yl)acetamide **5d**

Речовина **5e**. Дуальний інгібітор протеаз SARS-CoV-2 M^{pro} та PL^{pro}.
Назва: *N-(2-Chloro-4-methylphenyl)-2-(7-oxo-8-((phenylamino)methyl)-2,3-dihydro-[1,4]dioxino[2,3-g]quinolin-6(7H)-yl)acetamide*



Yellow powder, Yield 85 %, mp = 219-20°C. $[MH]^+$ m/z = 490.2.
Спектральні параметри:
^{1}H NMR (400 MHz, DMSO-d6) δ 10.06 (s, 1H), 8.84 (t, J = 5.3 Hz, 1H), 7.72 (d, J = 2.1 Hz, 1H), 7.47 (d, J = 8.0 Hz, 1H), 7.32 (s, 1H), 7.18 – 7.12 (m, 2H), 7.08 (t, J = 7.3 Hz, 2H), 6.78 (d, J = 7.3 Hz, 2H), 6.67 (d, J = 8.0 Hz, 2H), 4.78 (d, J = 7.0 Hz, 4H), 4.33 – 4.27 (m, 2H), 4.27 – 4.21 (m, 2H).
^{13}C NMR (101 MHz, DMSO-d6) δ 167.42, 164.19, 146.03, 145.36, 139.64, 134.28, 133.82, 133.49, 131.06, 129.77, 129.61, 129.43, 128.90, 123.71, 122.09, 117.22, 116.74, 113.47, 111.97, 99.39, 64.55, 64.03, 48.03, 45.10, 20.35.

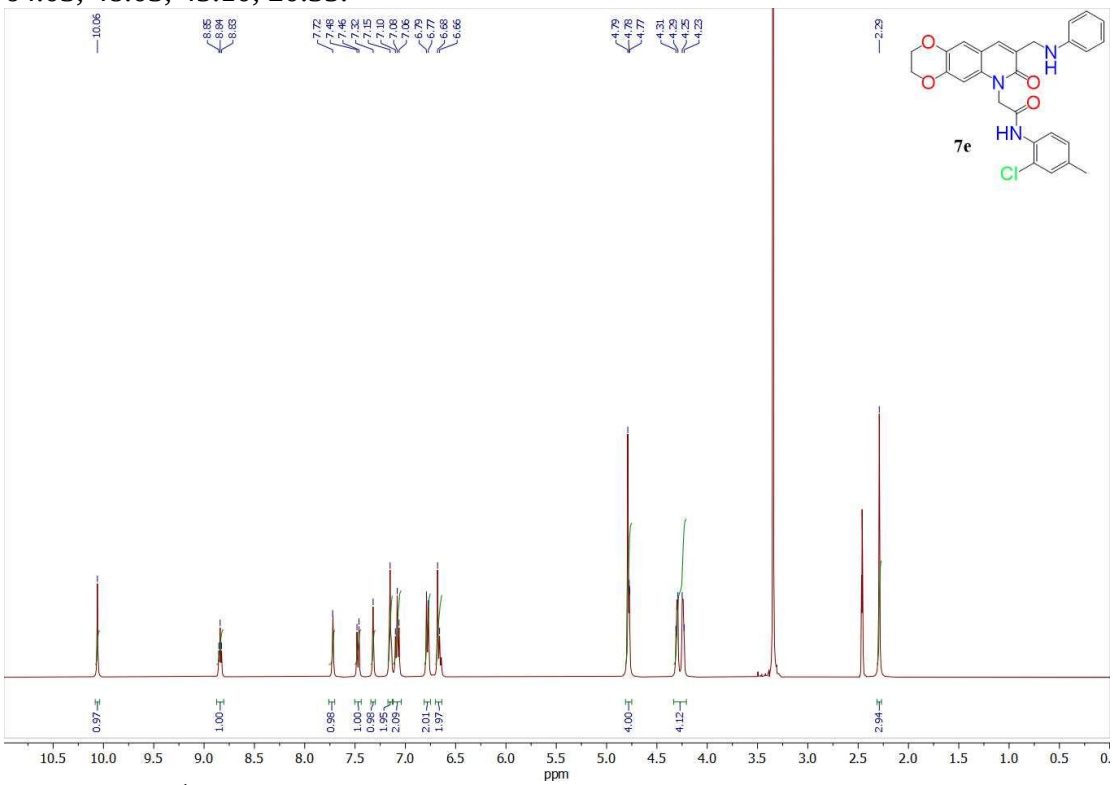


Рисунок 95. ^{1}H NMR spectrum (400 MHz, DMSO-d6) of N-(2-chloro-4-methylphenyl)-2-(7-oxo-8-((phenylamino)methyl)-2,3-dihydro-[1,4]dioxino[2,3-g]quinolin-6(7H)-yl)acetamide **5e**

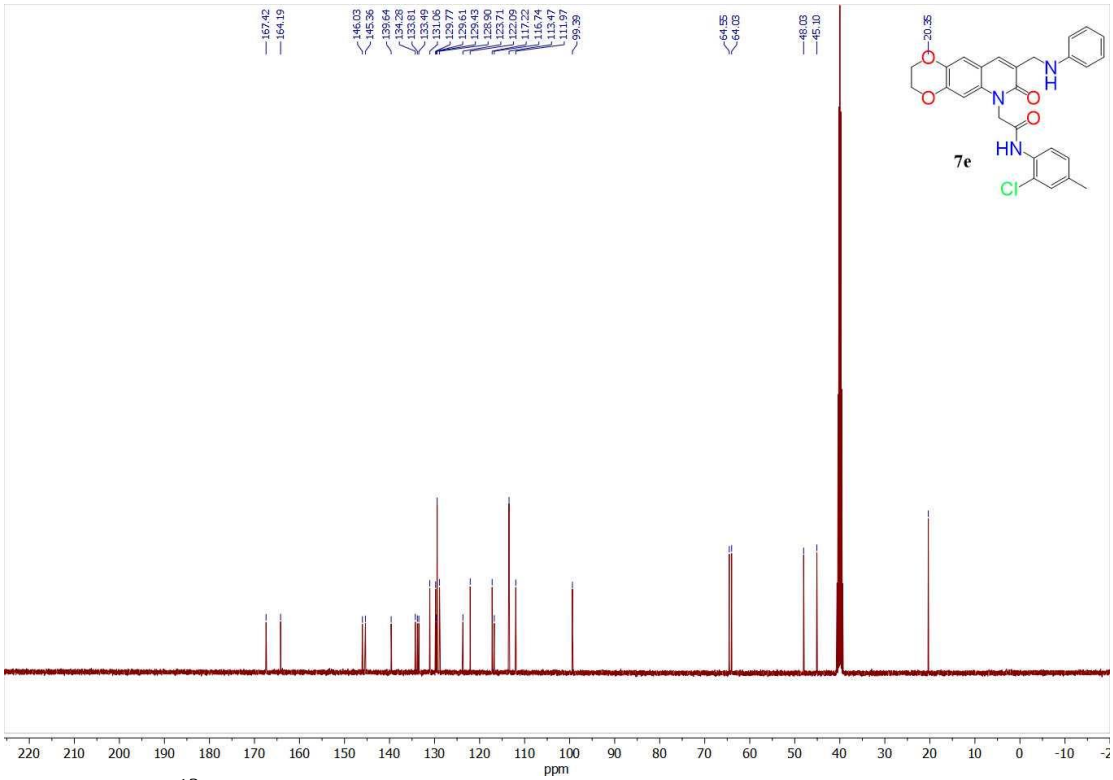
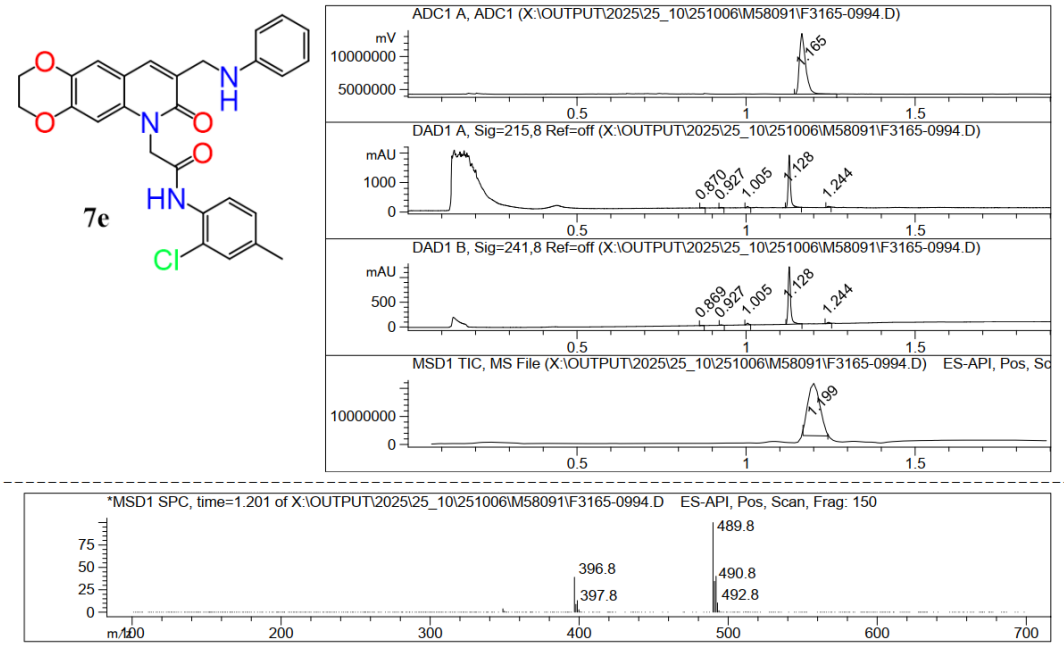


Рисунок 96. ^{13}C NMR spectrum (101 MHz, DMSO-d6) of N-(2-chloro-4-methylphenyl)-2-(7-oxo-8-((phenylamino)methyl)-2,3-dihydro-[1,4]dioxino[2,3-g]quinolin-6(7H)-yl)acetamide **5e**

Agilent 1260 LC/MSD SL
Diodearrey G1315B (DAD1A-215nm; DAD1B-241nm)
Mass Quad G6140 (MSD1-Pos, MSD2-Neg)
ELSD Softa 1400 (ADC1 A, ELSD)

Mobile Phase:A-H2O+0.1%HCOOH;B-MeCN+0.1HCOOH
94 %
Rapid Resolutionn HT Cartige 4.6x30mm,
1.8-Micron, Zorbx SB-C18



#	Signal	R.Time	Area %
1	ADC1 A, ADC1	1.165	100.000

#	Signal	R.Time	Area %
1	DAD1 A, Sig=215,8 Ref=off	0.870	0.560
2		0.927	1.020
3		1.005	2.167
4		1.128	94.464
5		1.244	1.789

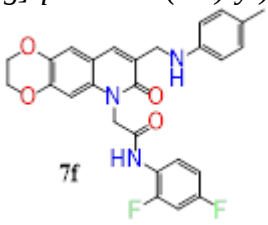
#	Signal	R.Time	Area %
1	DAD1 B, Sig=241,8 Ref=off	0.869	0.437
2		0.927	0.731
3		1.005	2.368
4		1.128	94.424
5		1.244	2.040

#	Signal	R.Time	Area %
1	MSD1 TIC, MS File	1.199	100.000

Рисунок 97. LC/MS data of N-(2-chloro-4-methylphenyl)-2-(7-oxo-8-((phenylamino)methyl)-2,3-dihydro-[1,4]dioxino[2,3-g]quinolin-6(7H)-yl)acetamide **5e**

Речовина **5f**. Дуальний інгібітор протеаз SARS-CoV-2 M^{pro} та PL^{pro}.

Назва: *N-(2,4-Difluorophenyl)-2-(7-oxo-8-((p-tolylamino)methyl)-2,3-dihydro-[1,4]dioxino[2,3-g]quinolin-6(7H)-yl)acetamide*



Yellow powder, Yield 79 %, mp = 217-18°C. $[MH]^+$ m/z = 492.2.

Спектральні параметри:

^{1}H NMR (400 MHz, DMSO-d6) δ 10.06 (d, J = 3.1 Hz, 1H), 8.84 (t, J = 5.3 Hz, 1H), 7.54 (dt, J = 7.8, 4.7 Hz, 1H), 7.32 (s, 1H), 7.17 – 7.06 (m, 2H), 7.02 – 6.90 (m, 3H), 6.68 (s, 1H), 6.52 (d, J = 7.8 Hz, 2H), 4.78 (d, J = 7.0 Hz, 4H), 4.33 – 4.21 (m, 4H).

^{13}C NMR (101 MHz, DMSO-d6) δ 167.84, 167.74, 164.19, 158.29, 158.16, 155.85, 155.71, 155.52, 155.39, 153.08, 152.96, 145.36, 144.68, 139.64, 133.49, 131.06, 129.69, 129.61, 127.41, 124.78, 124.74, 124.64, 124.60, 122.73, 122.67, 122.65, 122.58, 116.74, 114.30, 112.11, 112.07, 111.97, 111.89, 111.85, 104.39, 104.15, 104.13, 103.89, 99.39, 64.55, 64.03, 48.09, 45.10, 20.75.

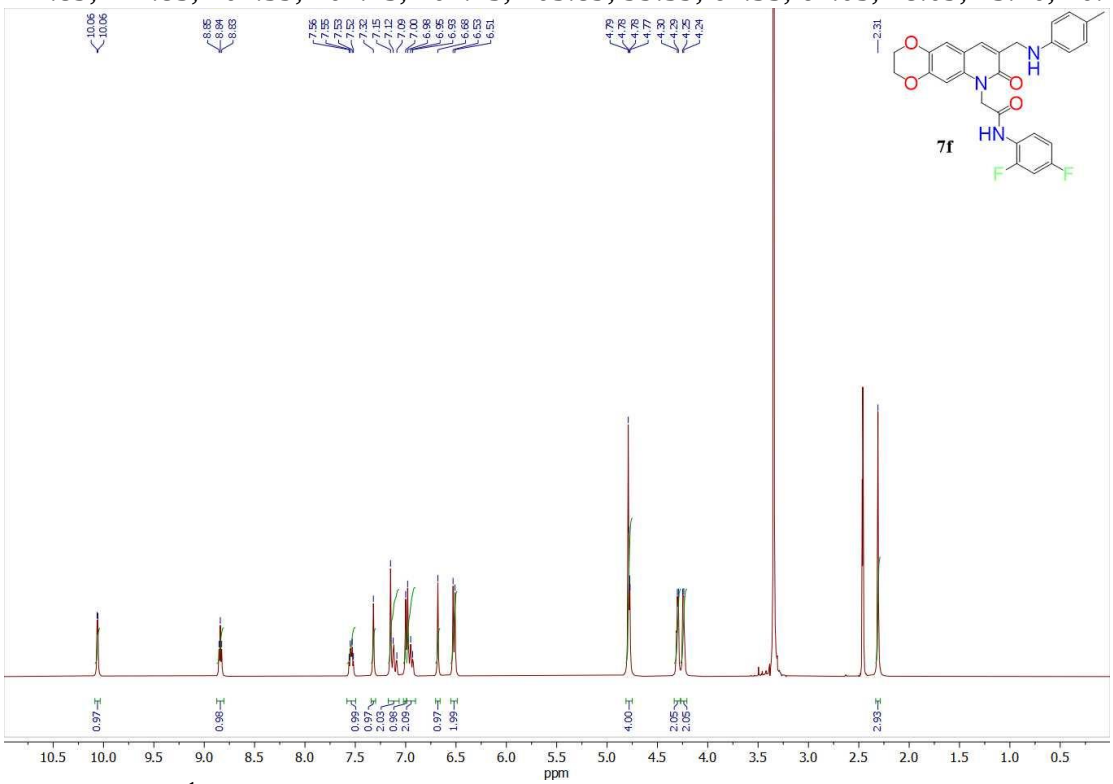


Рисунок 98. ^{1}H NMR spectrum (400 MHz, DMSO-d6) of N-(2,4-difluorophenyl)-2-(7-oxo-8-((p-tolylamino)methyl)-2,3-dihydro-[1,4]dioxino[2,3-g]quinolin-6(7H)-yl)acetamide **5f**

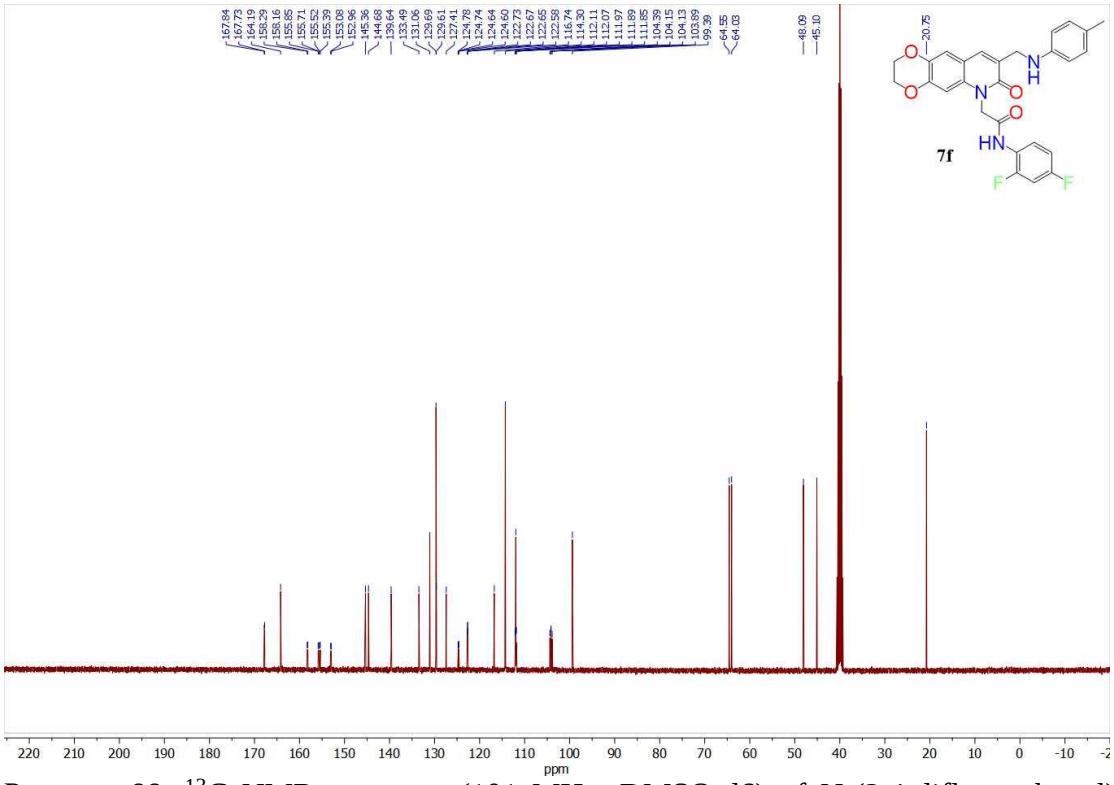
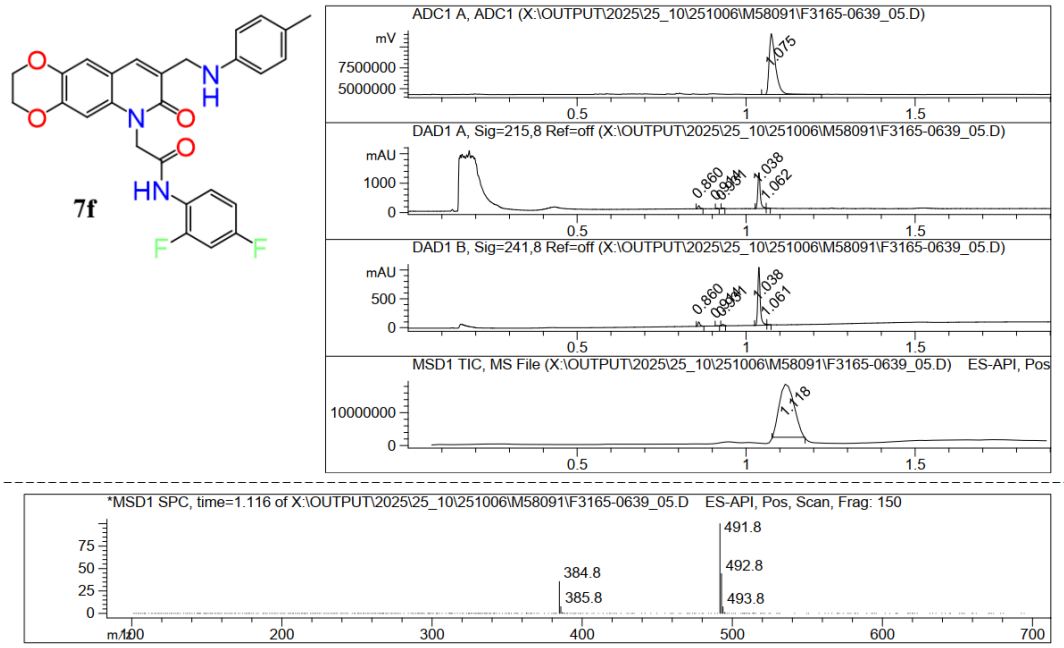


Рисунок 99. ^{13}C NMR spectrum (101 MHz, DMSO-d6) of N-(2,4-difluorophenyl)-2-(7-oxo-8-((p-tolylamino)methyl)-2,3-dihydro-[1,4]dioxino[2,3-g]quinolin-6(7H)-yl)acetamide **5f**

```
Agilent 1260 LC/MSD SL                          Mobile Phase:A-H2O+0.1%HCOOH;B-MeCN+0.1HCOOH
Diodearrey G1315B (DAD1A-215nm; DAD1B-241nm)    Separation column:
Mass Quad  G6140  (MSD1-Pos,  MSD2-Neg)         Rapid Resolutionn HT Cartige 4.6x30mm,
ELSD Softa 1400  (ADC1 A, ELSD)                 1.8-Micron, Zorbx SB-C18
```



#	Signal	R.Time	Area %
1	ADC1 A, ADC1	1.075	100.000

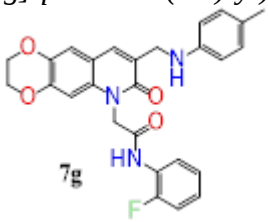
#	Signal	R.Time	Area %
1	DAD1 A, Sig=215,8 Ref=off	0.860	6.123
2		0.914	1.035
3		0.931	0.938
4		1.038	90.920
5		1.062	0.985

#	Signal	R.Time	Area %
1	DAD1 B, Sig=241,8 Ref=off	0.860	5.987
2		0.914	0.322
3		0.931	2.009
4		1.038	90.877
5		1.061	0.805

#	Signal	R.Time	Area %
1	MSD1 TIC, MS File	1.118	100.000

Рисунок 100. LC/MS data of N-(2,4-difluorophenyl)-2-(7-oxo-8-((p-tolylamino)methyl)-2,3-dihydro-[1,4]dioxino[2,3-g]quinolin-6(7H)-yl)acetamide **5f**

Речовина **5g**. Дуальний інгібітор протеаз SARS-CoV-2 M^{pro} та PL^{pro}.
Назва: *N-(2-Fluorophenyl)-2-(7-oxo-8-((p-tolylamino)methyl)-2,3-dihydro-[1,4]dioxino[2,3-g]quinolin-6(7H)-yl)acetamide*



Yellow powder, Yield 87 %, mp = 218-9°C. $[MH]^+$ m/z = 474.2.
Спектральні параметри:
^{1}H NMR (400 MHz, DMSO-d6) δ 10.06 (d, J = 3.1 Hz, 1H), 8.84 (t, J = 5.3 Hz, 1H), 8.00 – 7.92 (m, 1H), 7.32 (s, 1H), 7.19 (td, J = 8.0, 3.8 Hz, 1H), 7.17 – 7.13 (m, 1H), 7.13 – 7.07 (m, 1H), 7.06 – 6.96 (m, 3H), 6.68 (s, 1H), 6.52 (d, J = 7.8 Hz, 2H), 4.78 (d, J = 7.0 Hz, 4H), 4.33 – 4.27 (m, 2H), 4.27 – 4.21 (m, 2H).
^{13}C NMR (101 MHz, DMSO-d6) δ 167.80, 167.69, 164.19, 155.07, 152.63, 145.36, 144.68, 139.64, 133.49, 131.06, 129.69, 129.61, 127.41, 126.62, 126.47, 125.23, 125.19, 123.78, 123.70, 121.66, 121.60, 116.74, 115.48, 115.27, 114.30, 111.97, 99.39, 64.55, 64.03, 48.09, 45.10, 20.75.

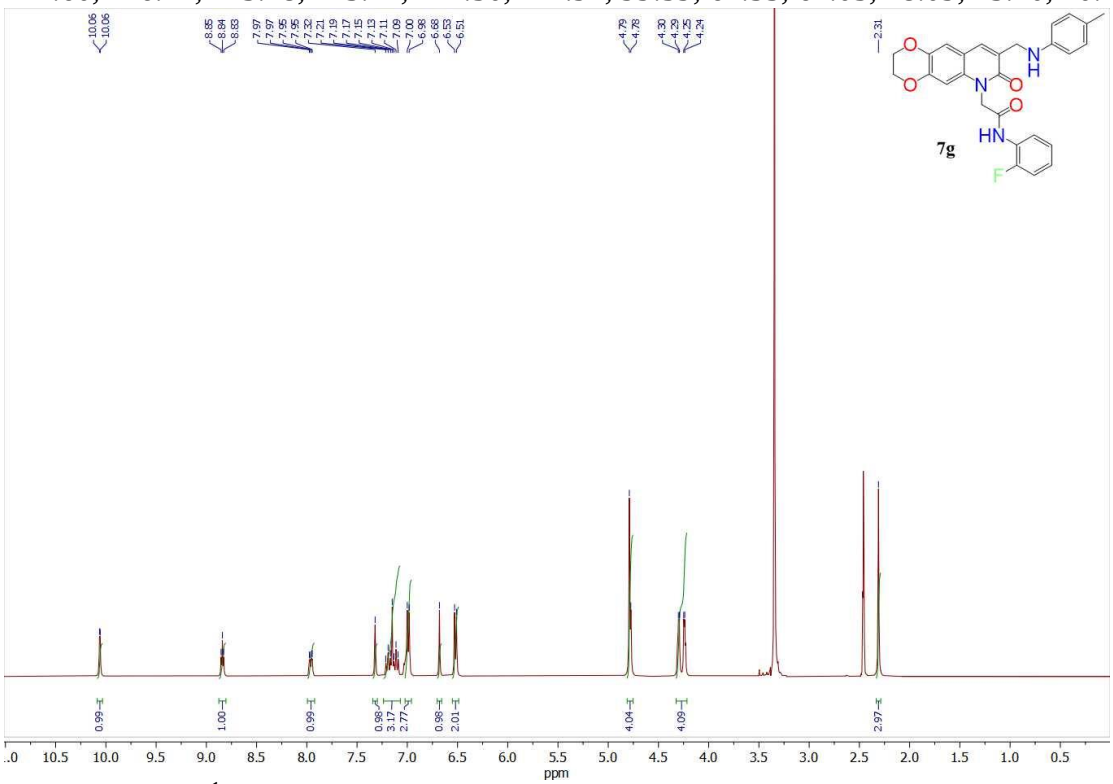


Рисунок 101. ^{1}H NMR spectrum (400 MHz, DMSO-d6) of N-(2-fluorophenyl)-2-(7-oxo-8-((p-tolylamino)methyl)-2,3-dihydro-[1,4]dioxino[2,3-g]quinolin-6(7H)-yl)acetamide **5g**

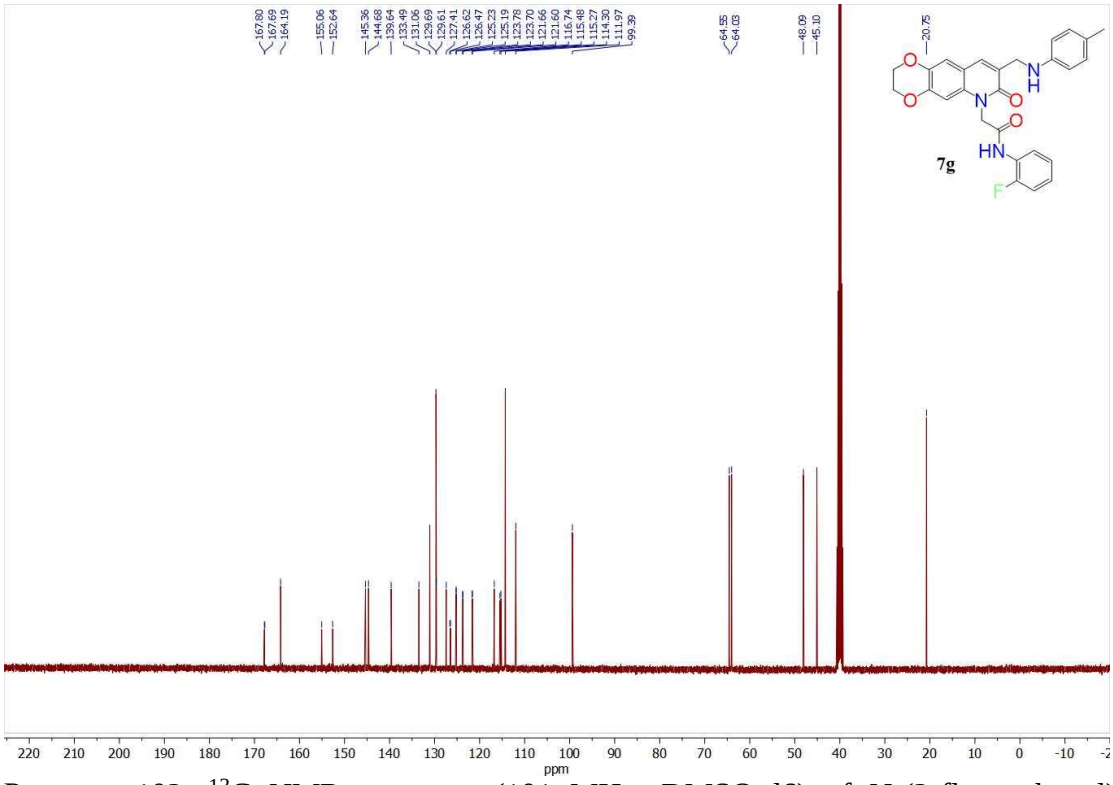
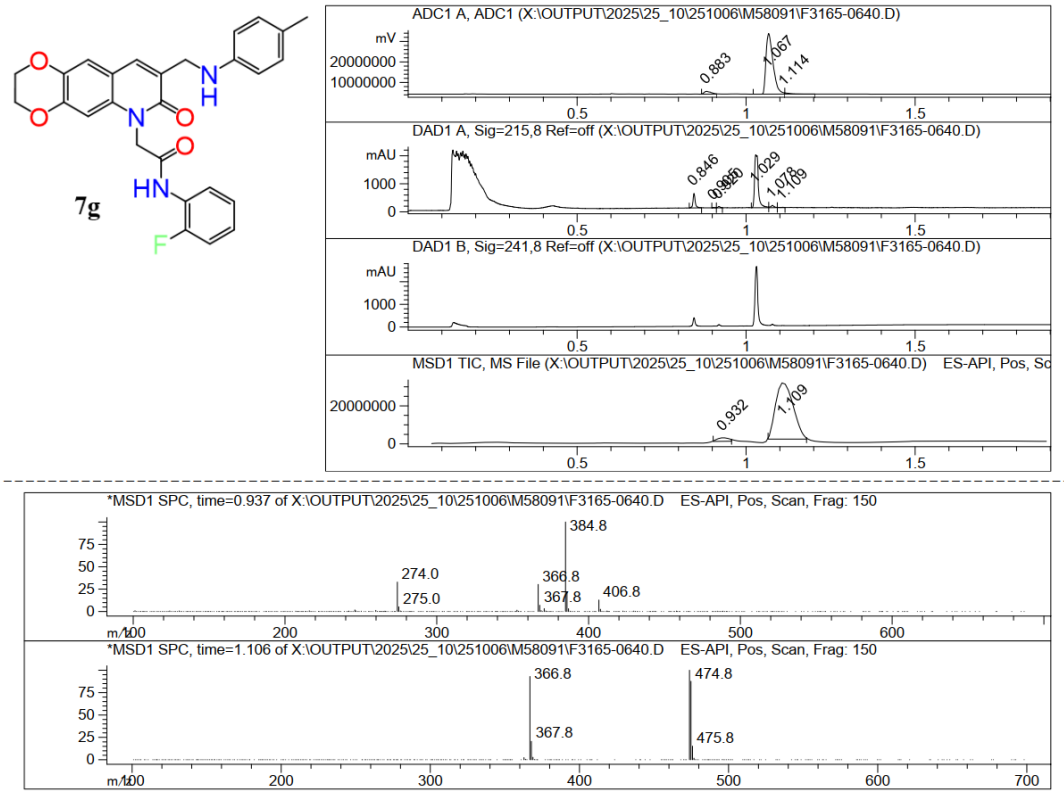


Рисунок 102. ^{13}C NMR spectrum (101 MHz, DMSO-d6) of N-(2-fluorophenyl)-2-(7-oxo-8-((p-tolylamino)methyl)-2,3-dihydro-[1,4]dioxino[2,3-g]quinolin-6(7H)-yl)acetamide **5g**

Agilent 1260 LC/MSD SL
Diodearrey G1315B (DAD1A-215nm; DAD1B-241nm)
Mass Quad G6140 (MSD1-Pos, MSD2-Neg)
ELSD Softa 1400 (ADC1 A, ELSD)

Mobile Phase:A-H2O+0.1%HCOOH;B-MeCN+0.1HCOOH
Separation column:
Rapid Resolutionn HT Cartige 4.6x30mm,
1.8-Micron, Zorbx SB-C18



#	Signal	R.Time	Area %
1	ADC1 A, ADC1	0.883	4.163
2		1.067	94.318
3		1.114	1.519

#	Signal	R.Time	Area %
1	DAD1 A, Sig=215,8 Ref=off	0.846	3.249
2		0.905	0.447
3		0.920	1.324
4		1.029	91.427
5		1.078	2.955
6		1.109	0.598

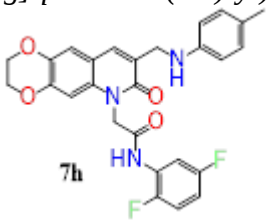
#	Signal	R.Time	Area %

#	Signal	R.Time	Area %
1	MSD1 TIC, MS File	0.932	4.103
2		1.109	95.897

Рисунок 103. LC/MS data of N-(2-fluorophenyl)-2-(7-oxo-8-((p-tolylamino)methyl)-2,3-dihydro-[1,4]dioxino[2,3-g]quinolin-6(7H)-yl)acetamide **5g**

Речовина **5h**. Дуальний інгібітор протеаз SARS-CoV-2 M^{pro} та PL^{pro}.

Назва: *N-(2,5-Difluorophenyl)-2-(7-oxo-8-((p-tolylamino)methyl)-2,3-dihydro-[1,4]dioxino[2,3-g]quinolin-6(7H)-yl)acetamide*



Yellow powder, Yield 81 %, mp = 229-30°C. $[MH]^+$ m/z = 492.2.

Спектральні параметри:

^{1}H NMR (400 MHz, DMSO-d6) δ 10.06 (d, J = 3.1 Hz, 1H), 8.84 (t, J = 5.3 Hz, 1H), 7.81 (dt, J = 11.9, 2.6 Hz, 1H), 7.32 (s, 2H), 7.15 (s, 1H), 6.99 (d, J = 7.8 Hz, 3H), 6.68 (s, 1H), 6.52 (d, J = 7.8 Hz, 2H), 4.78 (d, J = 7.0 Hz, 4H), 4.33 – 4.27 (m, 2H), 4.27 – 4.21 (m, 2H).

^{13}C NMR (101 MHz, DMSO-d6) δ 167.77, 167.66, 164.19, 160.59, 160.57, 158.15, 158.13, 152.59, 152.57, 150.16, 150.14, 145.36, 144.68, 139.64, 133.49, 131.06, 129.69, 129.61, 128.44, 128.33, 128.29, 128.18, 127.41, 116.74, 116.38, 116.30, 116.17, 116.09, 114.30, 111.97, 109.04, 108.97, 108.81, 108.75, 108.56, 108.50, 108.31, 108.25, 99.39, 64.55, 64.03, 48.07, 45.10, 20.75.

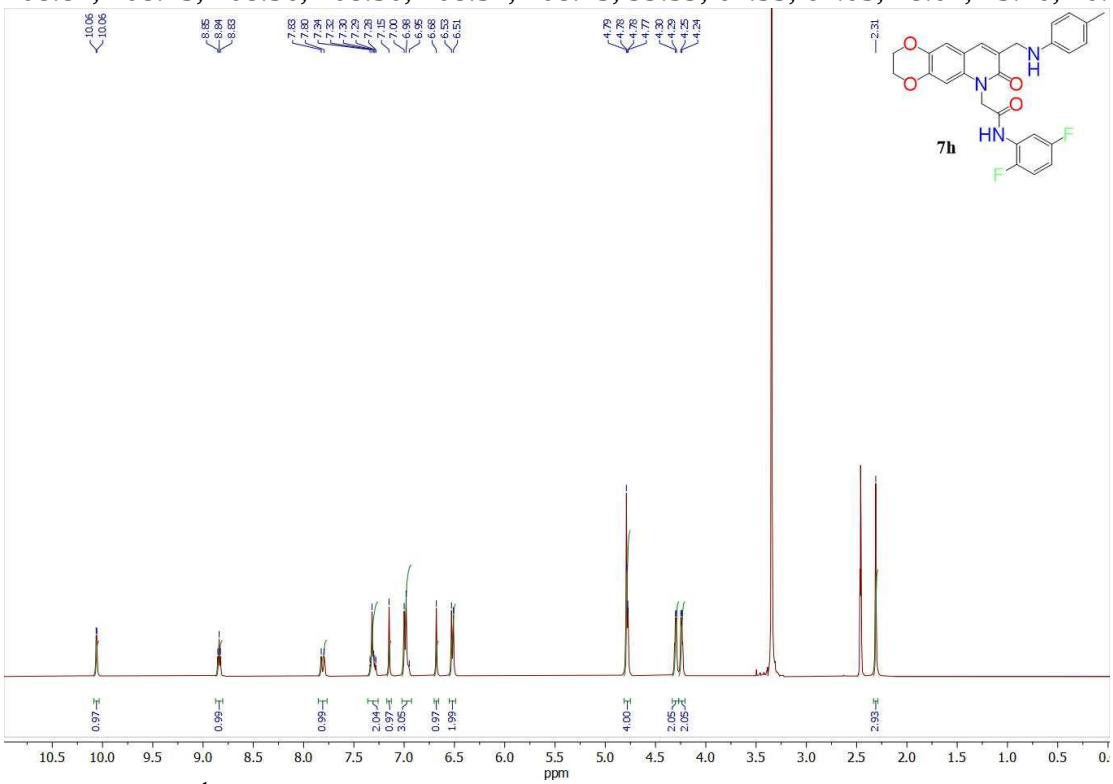


Рисунок 104. ^{1}H NMR spectrum (400 MHz, DMSO-d6) of N-(2,5-difluorophenyl)-2-(7-oxo-8-((p-tolylamino)methyl)-2,3-dihydro-[1,4]dioxino[2,3-g]quinolin-6(7H)-yl)acetamide **5h**

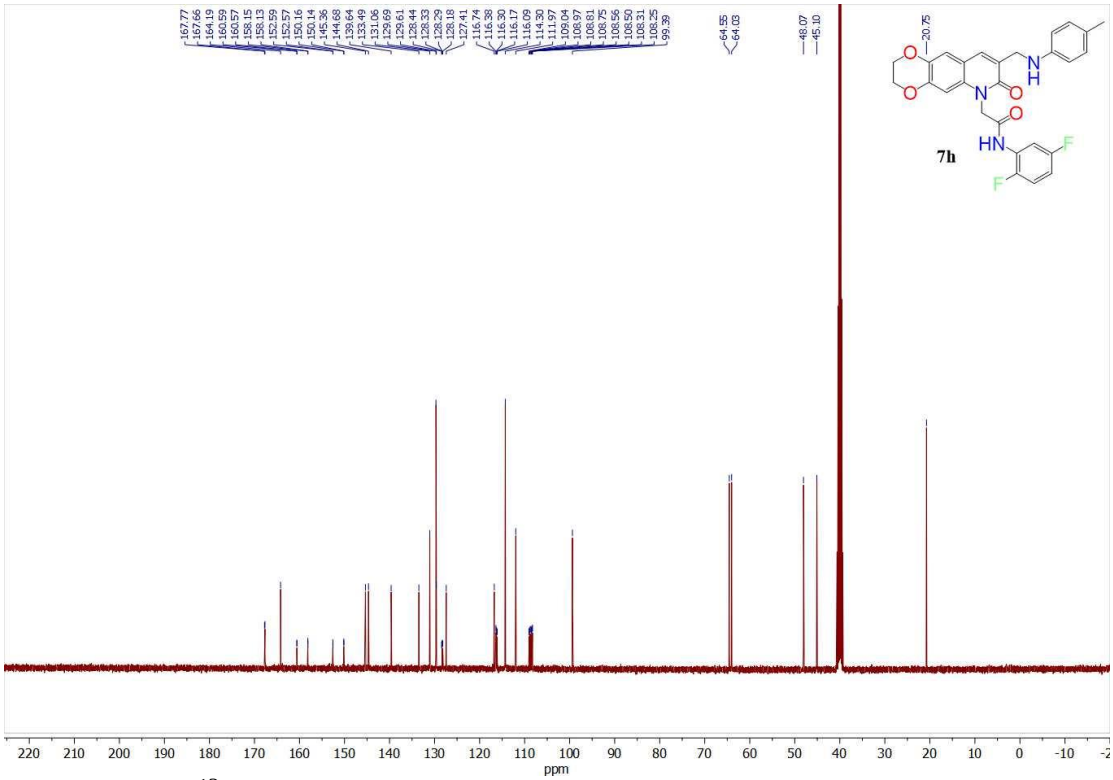
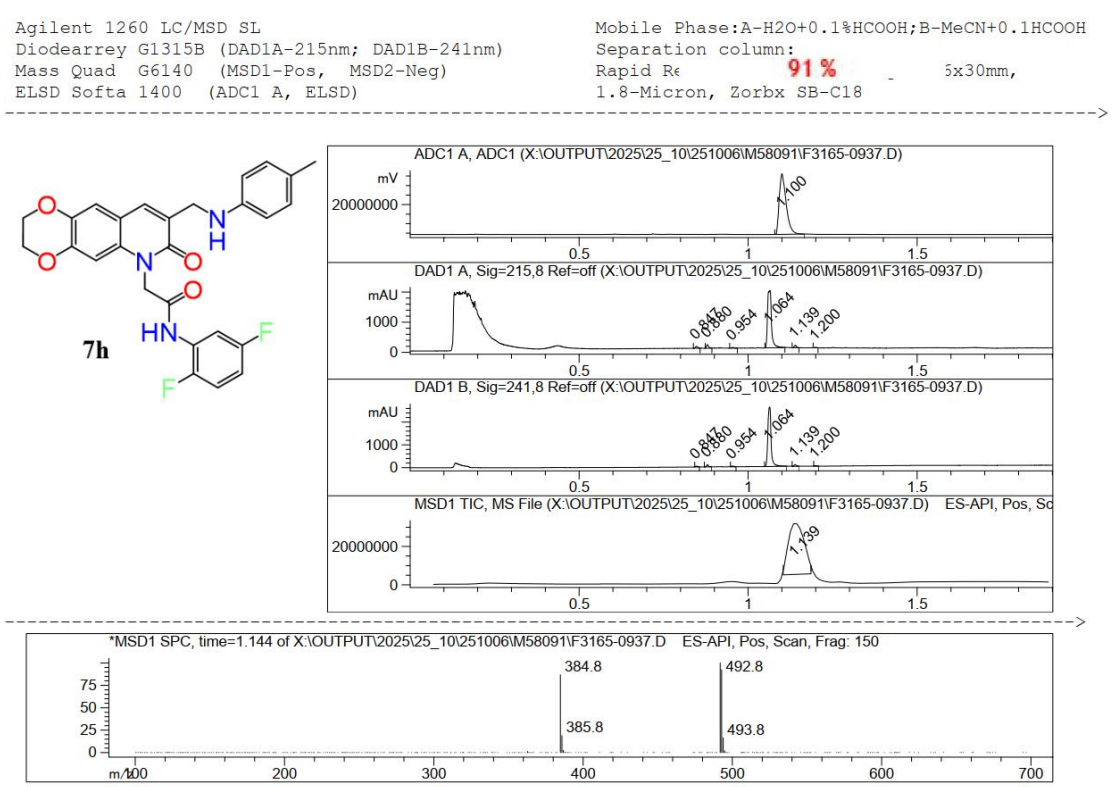


Рисунок 105. ^{13}C NMR spectrum (101 MHz, DMSO-d6) of N-(2,5-difluorophenyl)-2-(7-oxo-8-((p-tolylamino)methyl)-2,3-dihydro-[1,4]dioxino[2,3-g]quinolin-6(7H)-yl)acetamide **5h**



#	Signal	R.Time	Area %
1	ADC1 A, ADC1	1.100	100.000

#	Signal	R.Time	Area %
1	DAD1 A, Sig=215,8 Ref=off	0.847	1.749
2		0.880	3.117
3		0.954	0.927
4		1.064	91.514
5		1.139	2.258
6		1.200	0.436

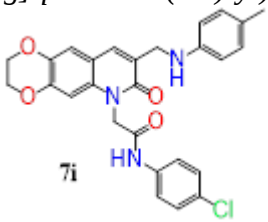
#	Signal	R.Time	Area %
1	DAD1 B, Sig=241,8 Ref=off	0.847	0.775
2		0.880	2.047
3		0.954	0.883
4		1.064	93.924
5		1.139	1.754
6		1.200	0.617

#	Signal	R.Time	Area %
1	MSD1 TIC, MS File	1.139	100.000

Рисунок 106. LC/MS data of N-(2,5-difluorophenyl)-2-(7-oxo-8-((p-tolylamino)methyl)-2,3-dihydro-[1,4]dioxino[2,3-g]quinolin-6(7H)-yl)acetamide **5h**

Речовина **5i**. Дуальний інгібітор протеаз SARS-CoV-2 M^{pro} та PL^{pro}.

Назва: *N-(4-Chlorophenyl)-2-(7-oxo-8-((p-tolylamino)methyl)-2,3-dihydro-[1,4]dioxino[2,3-g]quinolin-6(7H)-yl)acetamide*



Yellow powder, Yield 80 %, mp = 239-40°C. $[MH]^+$ m/z = 490.2.

Спектральні параметри:

^{1}H NMR (400 MHz, DMSO-d6) δ 10.07 (s, 1H), 8.84 (t, J = 5.3 Hz, 1H), 7.59 (d, J = 8.0 Hz, 2H), 7.38 – 7.30 (m, 3H), 7.15 (s, 1H), 6.99 (d, J = 7.8 Hz, 2H), 6.68 (s, 1H), 6.52 (d, J = 7.8 Hz, 2H), 4.78 (d, J = 7.0 Hz, 4H), 4.33 – 4.27 (m, 2H), 4.27 – 4.21 (m, 2H).

^{13}C NMR (101 MHz, DMSO-d6) δ 166.34, 164.19, 145.36, 144.68, 139.64, 137.01, 133.49, 131.06, 129.69, 129.61, 129.15, 128.00, 127.41, 121.33, 116.74, 114.30, 111.97, 99.39, 64.55, 64.03, 48.23, 45.10, 20.75.

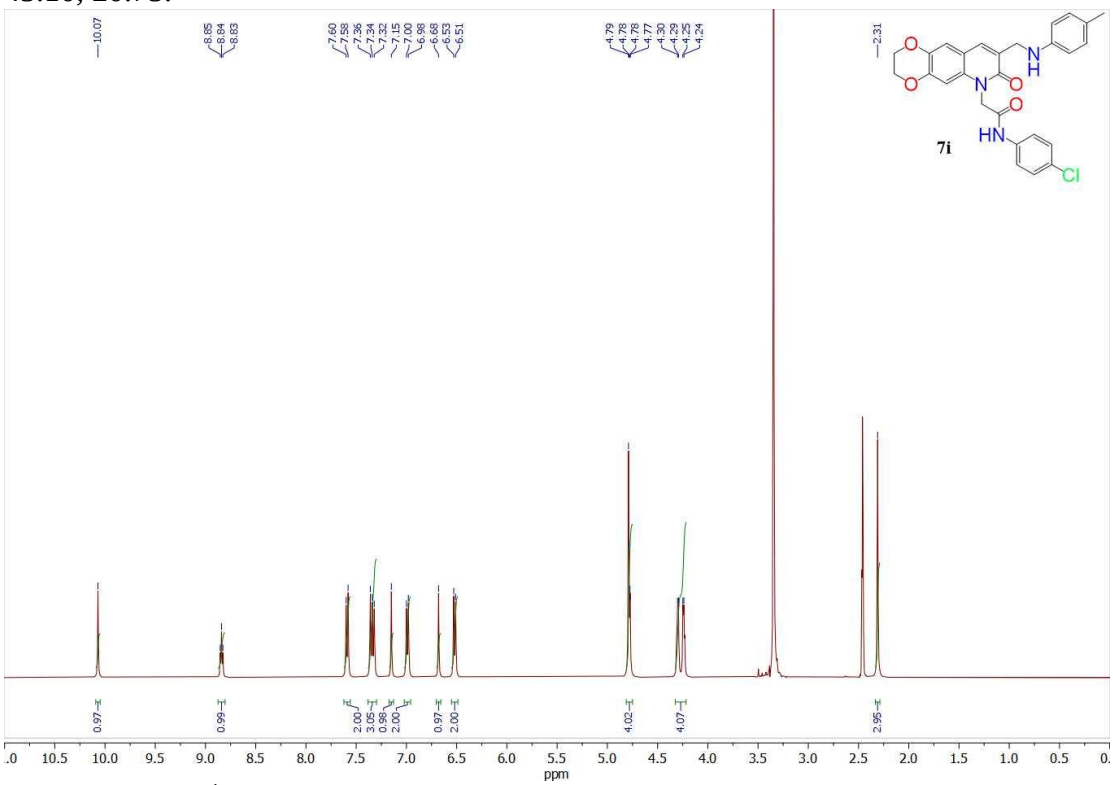


Рисунок 107. ^{1}H NMR spectrum (400 MHz, DMSO-d6) of N-(4-chlorophenyl)-2-(7-oxo-8-((p-tolylamino)methyl)-2,3-dihydro-[1,4]dioxino[2,3-g]quinolin-6(7H)-yl)acetamide **5i**

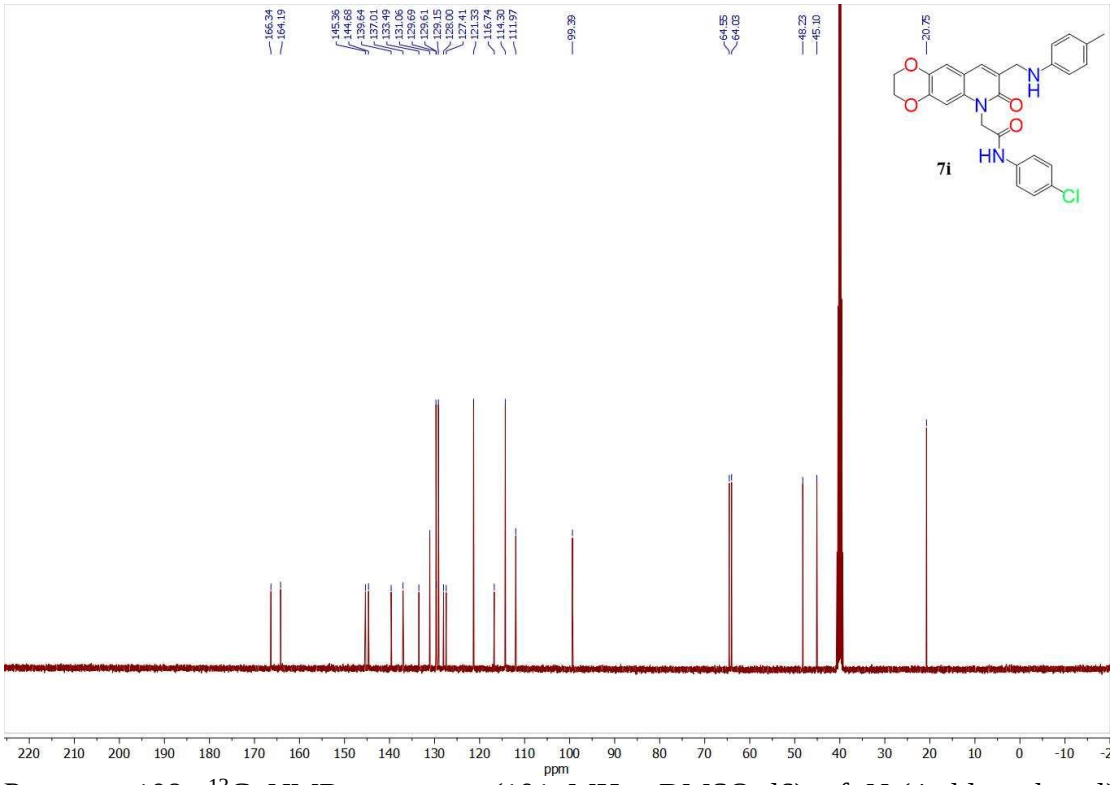
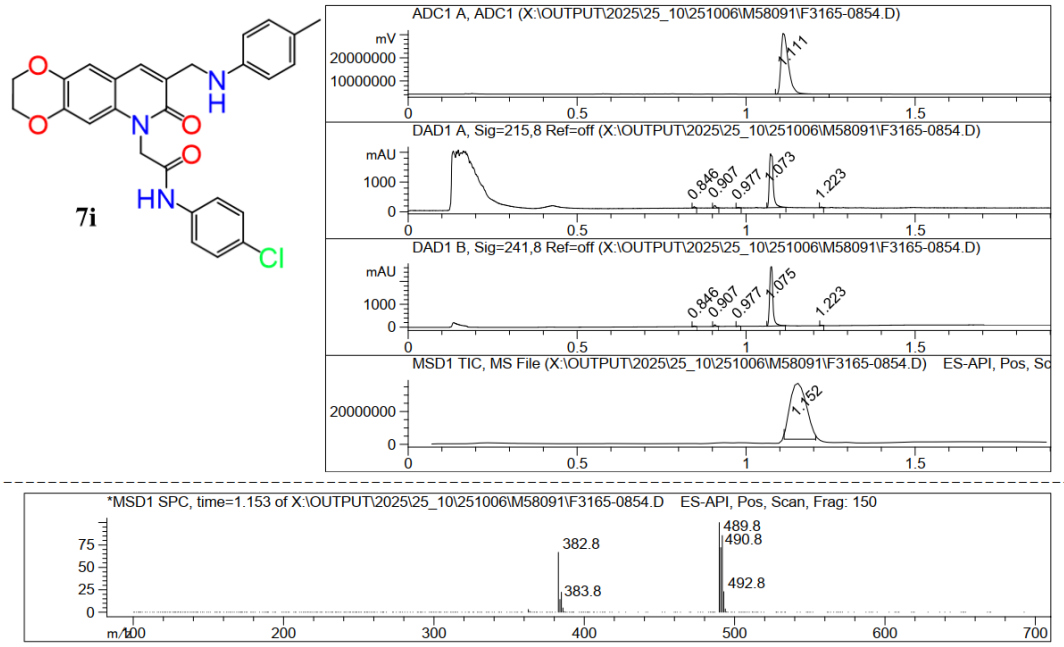


Рисунок 108. ^{13}C NMR spectrum (101 MHz, DMSO-d6) of N-(4-chlorophenyl)-2-(7-oxo-8-((p-tolylamino)methyl)-2,3-dihydro-[1,4]dioxino[2,3-g]quinolin-6(7H)-yl)acetamide **5i**

Agilent 1260 LC/MSD SL
Diodearrey G1315B (DAD1A-215nm; DAD1B-241nm)
Mass Quad G6140 (MSD1-Pos, MSD2-Neg)
ELSD Softa 1400 (ADC1 A, ELSD)

Mobile Phase:A-H2O+0.1%HCOOH;B-MeCN+0.1HCOOH
95 %
Rapid Resolutionn HT Cartige 4.6x30mm,
1.8-Micron, Zorbx SB-C18



#	Signal	R.Time	Area %
1	ADC1 A, ADC1	1.111	100.000

#	Signal	R.Time	Area %
1	DAD1 A, Sig=215,8 Ref=off	0.846	1.048
2		0.907	2.489
3		0.977	0.471
4		1.073	95.342
5		1.223	0.650

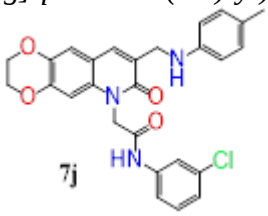
#	Signal	R.Time	Area %
1	DAD1 B, Sig=241,8 Ref=off	0.846	0.608
2		0.907	1.493
3		0.977	0.463
4		1.075	96.941
5		1.223	0.495

#	Signal	R.Time	Area %
1	MSD1 TIC, MS File	1.152	100.000

Рисунок 109. LC/MS data of N-(4-chlorophenyl)-2-(7-oxo-8-((p-tolylamino)methyl)-2,3-dihydro-[1,4]dioxino[2,3-g]quinolin-6(7H)-yl)acetamide **5i**

Речовина **5j**. Дуальний інгібітор протеаз SARS-CoV-2 M^{pro} та PL^{pro}.

Назва: *N-(3-Chlorophenyl)-2-(7-oxo-8-((p-tolylamino)methyl)-2,3-dihydro-[1,4]dioxino[2,3-g]quinolin-6(7H)-yl)acetamide*



Yellow powder, Yield 79 %, mp = 238-9°C. $[MH]^+$ m/z = 490.2.

Спектральні параметри:

^{1}H NMR (400 MHz, DMSO-d6) δ 10.07 (s, 1H), 8.84 (t, J = 5.3 Hz, 1H), 7.55 (t, J = 2.2 Hz, 1H), 7.46 – 7.38 (m, 1H), 7.32 (s, 2H), 7.19 – 7.11 (m, 2H), 6.99 (d, J = 7.8 Hz, 2H), 6.68 (s, 1H), 6.52 (d, J = 7.8 Hz, 2H), 4.78 (d, J = 7.0 Hz, 4H), 4.33 – 4.27 (m, 2H), 4.27 – 4.21 (m, 2H).

^{13}C NMR (101 MHz, DMSO-d6) δ 166.23, 164.19, 145.36, 144.68, 139.64, 138.79, 133.92, 133.49, 131.06, 129.86, 129.69, 129.61, 127.41, 123.53, 120.18, 119.48, 116.74, 114.30, 111.97, 99.39, 64.55, 64.03, 48.23, 45.10, 20.75.

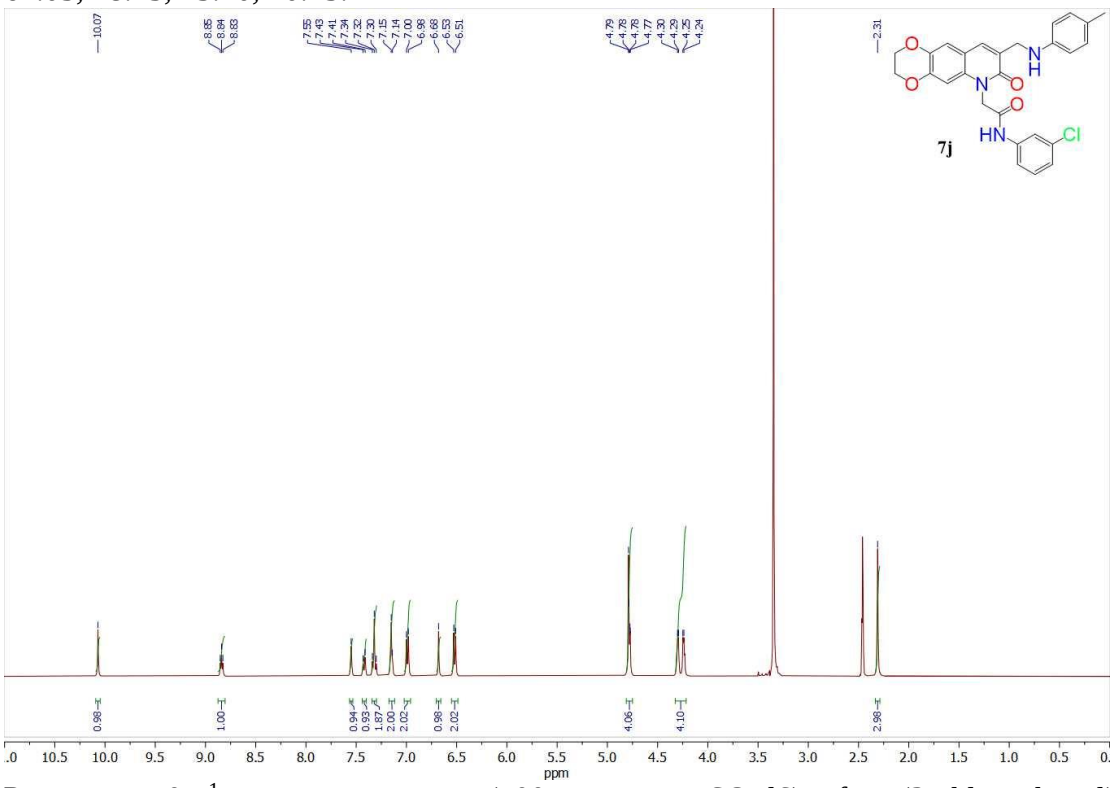


Рисунок 110. ^{1}H NMR spectrum (400 MHz, DMSO-d6) of N-(3-chlorophenyl)-2-(7-oxo-8-((p-tolylamino)methyl)-2,3-dihydro-[1,4]dioxino[2,3-g]quinolin-6(7H)-yl)acetamide **5j**

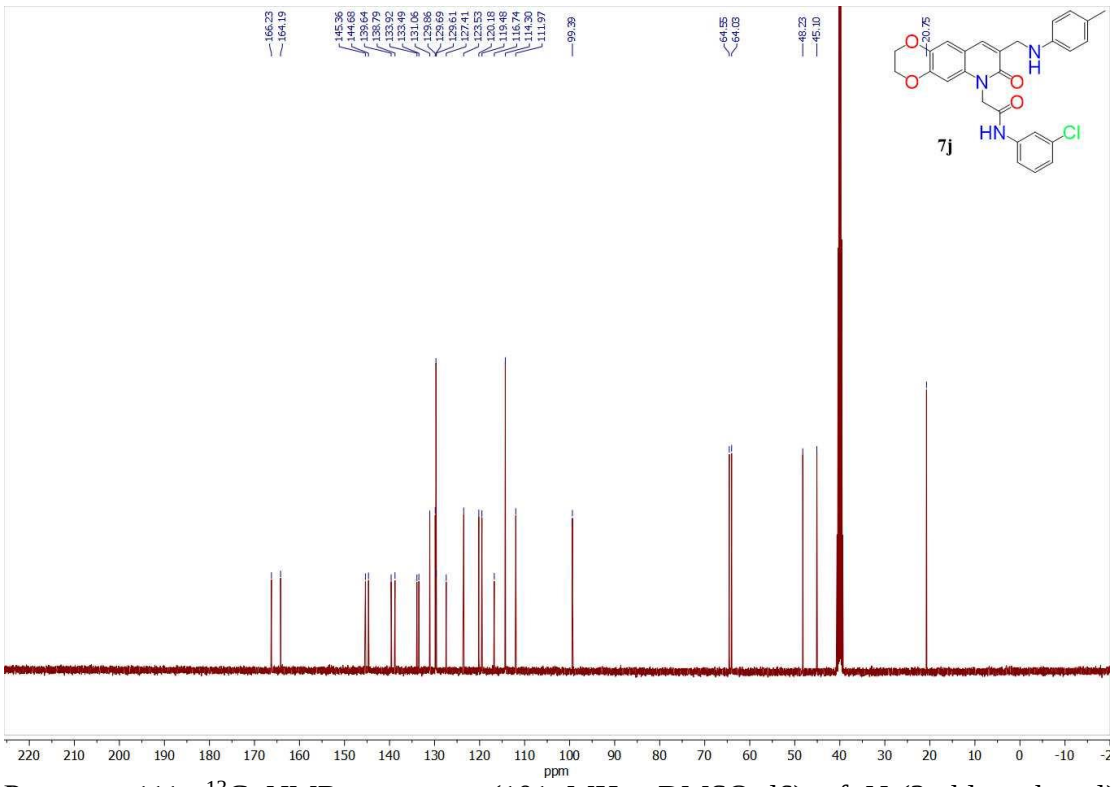
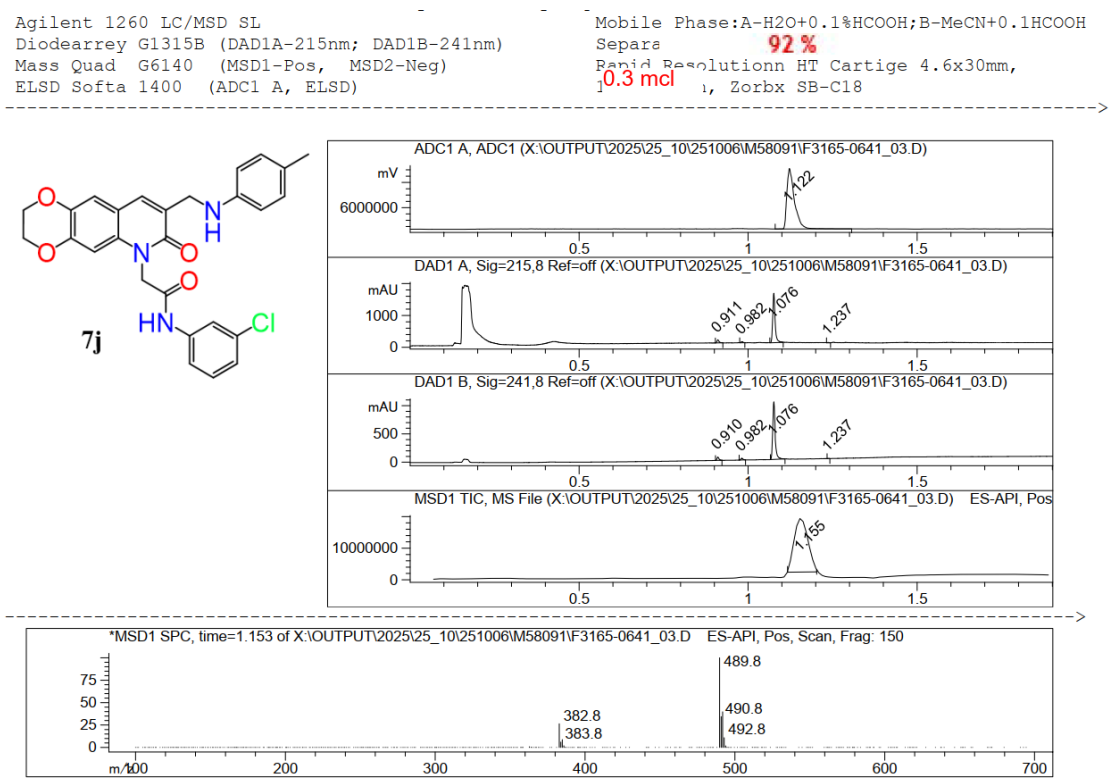


Рисунок 111. ^{13}C NMR spectrum (101 MHz, DMSO-d6) of N-(3-chlorophenyl)-2-(7-oxo-8-((p-tolylamino)methyl)-2,3-dihydro-[1,4]dioxino[2,3-g]quinolin-6(7H)-yl)acetamide **5j**



#	Signal	R.Time	Area %
1	ADC1 A, ADC1	1.122	100.000

#	Signal	R.Time	Area %
1	DAD1 A, Sig=215,8 Ref=off	0.911	5.050
2		0.982	1.596
3		1.076	92.761
4		1.237	0.593

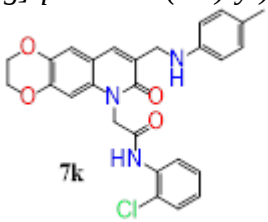
#	Signal	R.Time	Area %
1	DAD1 B, Sig=241,8 Ref=off	0.910	4.433
2		0.982	2.432
3		1.076	92.925
4		1.237	0.209

#	Signal	R.Time	Area %
1	MSD1 TIC, MS File	1.155	100.000

Рисунок 112. LC/MS data of N-(3-chlorophenyl)-2-(7-oxo-8-((p-tolylamino)methyl)-2,3-dihydro-[1,4]dioxino[2,3-g]quinolin-6(7H)-yl)acetamide **5j**

Речовина **5k**. Дуальний інгібітор протеаз SARS-CoV-2 M^{pro} та PL^{pro}.

Назва: *N-(2-Chlorophenyl)-2-(7-oxo-8-((p-tolylamino)methyl)-2,3-dihydro-[1,4]dioxino[2,3-g]quinolin-6(7H)-yl)acetamide*



Yellow powder, Yield 75 %, mp = 205-6°C. $[MH]^+$ m/z = 490.2.

Спектральні параметри:

^{1}H NMR (400 MHz, DMSO-d6) δ 10.06 (s, 1H), 8.84 (t, J = 5.3 Hz, 1H), 7.38 (q, J = 3.8 Hz, 2H), 7.32 (s, 1H), 7.21 (d, J = 7.8 Hz, 1H), 7.17 – 7.08 (m, 2H), 6.99 (d, J = 7.8 Hz, 2H), 6.68 (s, 1H), 6.52 (d, J = 7.8 Hz, 2H), 4.78 (d, J = 7.0 Hz, 4H), 4.33 – 4.21 (m, 4H).

^{13}C NMR (101 MHz, DMSO-d6) δ 167.42, 164.19, 145.36, 144.68, 139.64, 135.37, 133.49, 131.06, 129.69, 129.61, 129.15, 127.78, 127.41, 125.69, 124.84, 122.70, 116.74, 114.30, 111.97, 99.39, 64.55, 64.03, 48.03, 45.10, 20.75.

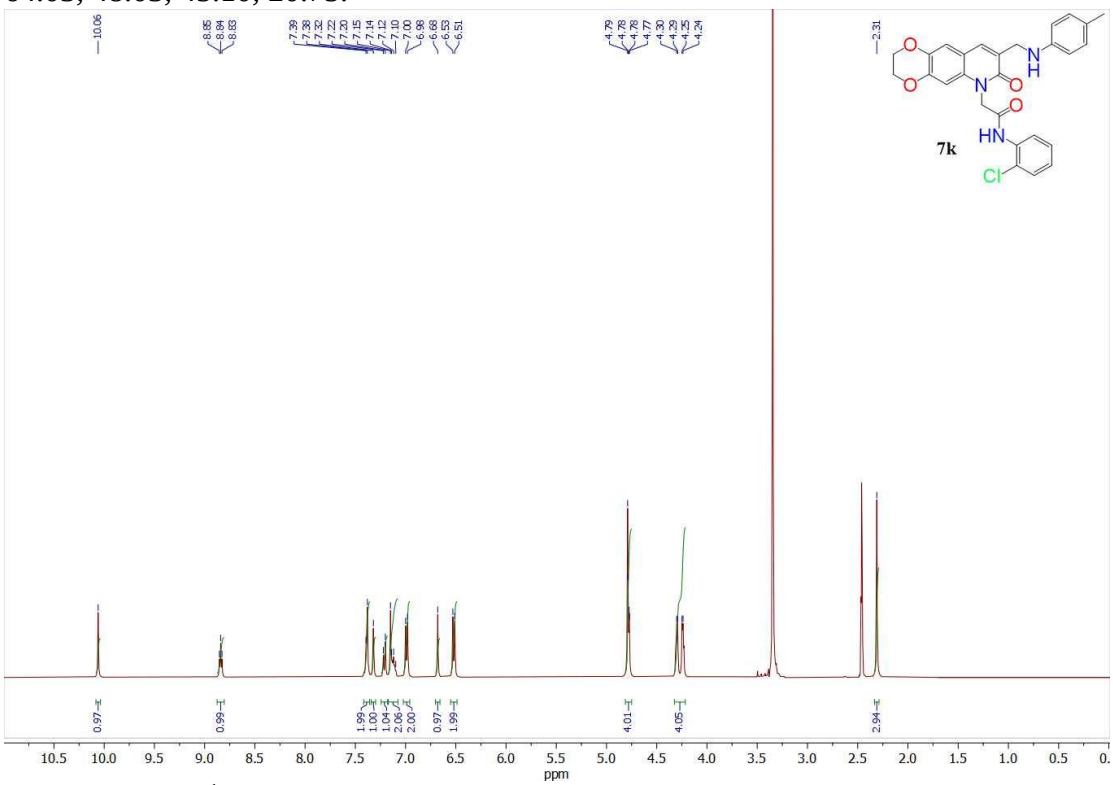


Рисунок 113. ^{1}H NMR spectrum (400 MHz, DMSO-d6) of N-(2-chlorophenyl)-2-(7-oxo-8-((p-tolylamino)methyl)-2,3-dihydro-[1,4]dioxino[2,3-g]quinolin-6(7H)-yl)acetamide **5k**

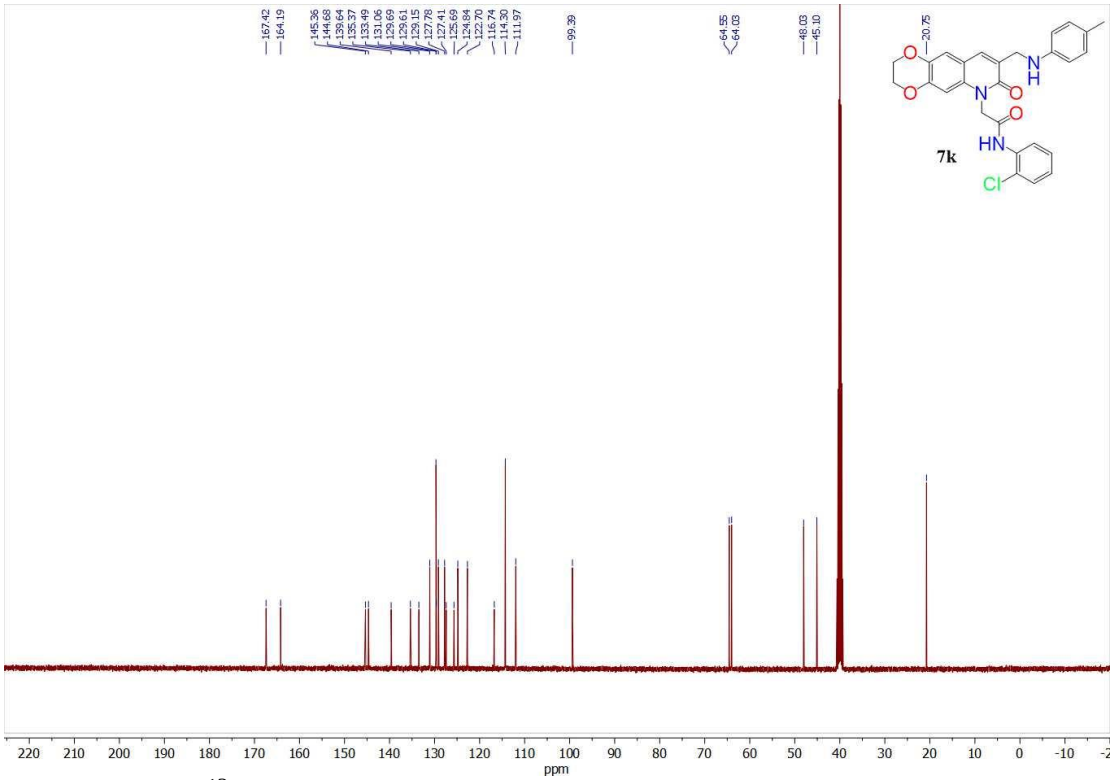
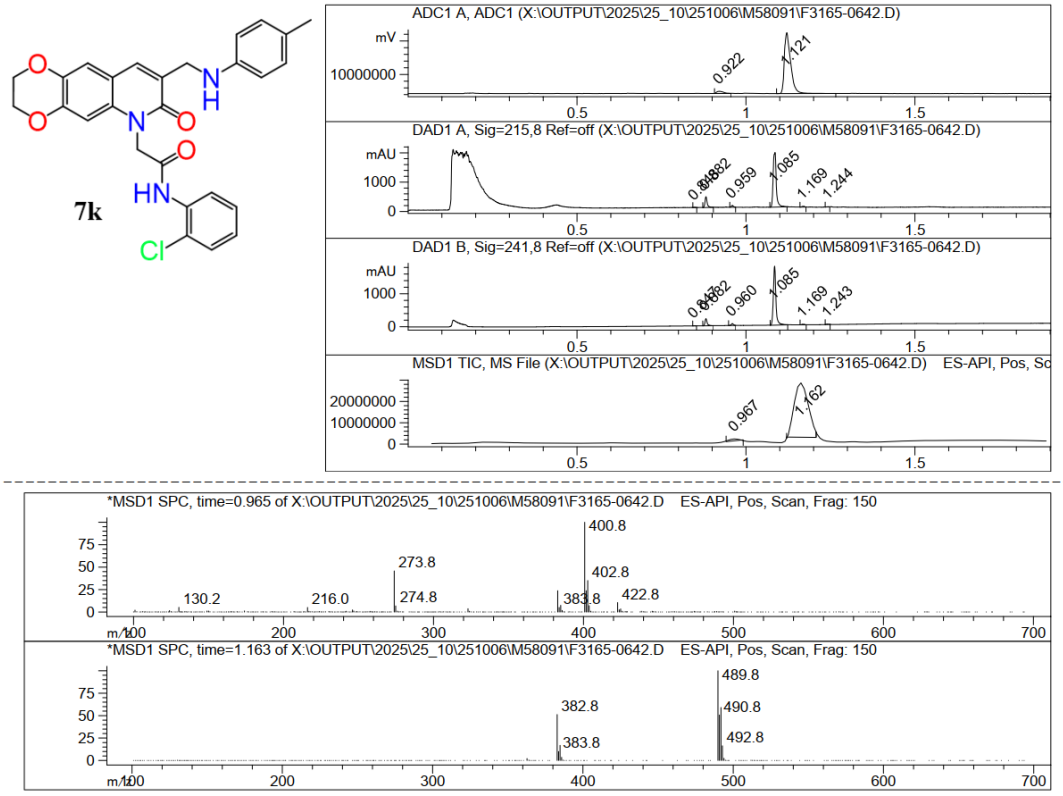


Рисунок 114. ^{13}C NMR spectrum (101 MHz, DMSO-d6) of N-(2-chlorophenyl)-2-(7-oxo-8-((p-tolylamino)methyl)-2,3-dihydro-[1,4]dioxino[2,3-g]quinolin-6(7H)-yl)acetamide **5k**

Agilent 1260 LC/MSD SL
Diodearrey G1315B (DAD1A-215nm; DAD1B-241nm)
Mass Quad G6140 (MSD1-Pos, MSD2-Neg)
ELSD Softa 1400 (ADC1 A, ELSD)

Mobile Phase:A-H2O+0.1%HCOOH;B-MeCN+0.1HCOOH
Separation column:
Rapid Resolutionn HT Cartige 4.6x30mm,
1.8-Micron, Zorbx SB-C18



#	Signal	R.Time	Area %
1	ADC1 A, ADC1	0.922	3.786
2		1.121	96.214

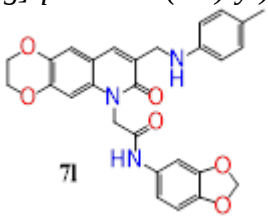
#	Signal	R.Time	Area %
1	DAD1 A, Sig=215,8 Ref=off	0.848	0.353
2		0.882	7.678
3		0.959	1.985
4		1.085	91.692
5		1.169	0.954
6		1.244	0.337

#	Signal	R.Time	Area %
1	DAD1 B, Sig=241,8 Ref=off	0.847	0.210
2		0.882	4.927
3		0.960	2.166
4		1.085	91.574
5		1.169	0.810
6		1.243	0.312

#	Signal	R.Time	Area %
1	MSD1 TIC, MS File	0.967	2.050
2		1.162	97.950

Рисунок 115. LC/MS data of N-(2-chlorophenyl)-2-(7-oxo-8-((p-tolylamino)methyl)-2,3-dihydro-[1,4]dioxino[2,3-g]quinolin-6(7H)-yl)acetamide **5k**

Речовина **5l**. Дуальний інгібітор протеаз SARS-CoV-2 M^{pro} та PL^{pro}.
Назва: *N-(Benzo[d][1,3]dioxol-5-yl)-2-(7-oxo-8-((p-tolylamino)methyl)-2,3-dihydro-[1,4]dioxino[2,3-g]quinolin-6(7H)-yl)acetamide*



Yellow powder, Yield 74 %, mp = 250-1°C. $[MH]^+$ m/z = 500.2.
Спектральні параметри:
^{1}H NMR (400 MHz, DMSO-d6) δ 10.07 (s, 1H), 8.84 (t, J = 5.3 Hz, 1H), 7.32 (s, 1H), 7.25 (d, J = 2.3 Hz, 1H), 7.15 (s, 1H), 7.07 – 6.96 (m, 3H), 6.84 (d, J = 9.1 Hz, 1H), 6.68 (s, 1H), 6.52 (d, J = 7.8 Hz, 2H), 5.97 (s, 2H), 4.78 (d, J = 7.0 Hz, 4H), 4.33 – 4.27 (m, 2H), 4.27 – 4.21 (m, 2H).
^{13}C NMR (101 MHz, DMSO-d6) δ 166.21, 164.19, 147.77, 145.36, 144.68, 142.74, 139.64, 134.41, 133.49, 131.06, 129.69, 129.61, 127.41, 116.74, 115.33, 114.30, 111.97, 109.19, 102.11, 101.07, 99.39, 64.55, 64.16, 48.23, 45.10, 20.75.

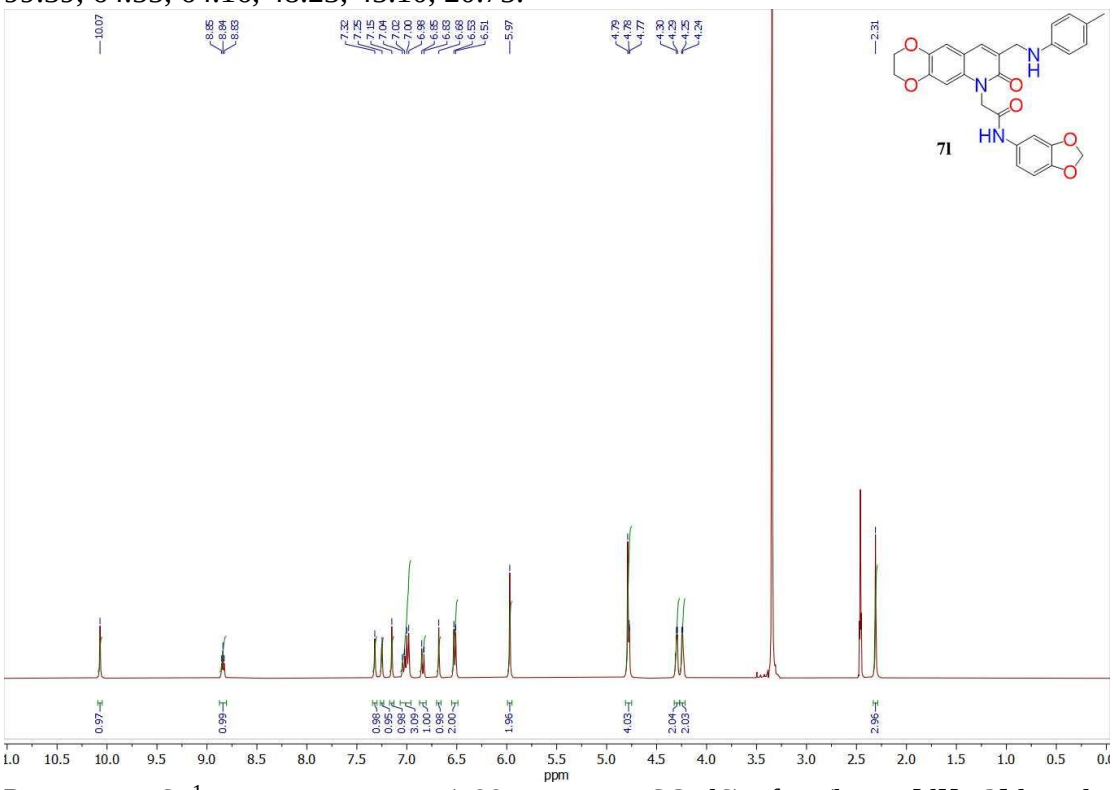


Рисунок 116. ^{1}H NMR spectrum (400 MHz, DMSO-d6) of N-(benzo[d][1,3]dioxol-5-yl)-2-(7-oxo-8-((p-tolylamino)methyl)-2,3-dihydro-[1,4]dioxino[2,3-g]quinolin-6(7H)-yl)acetamide **5l**

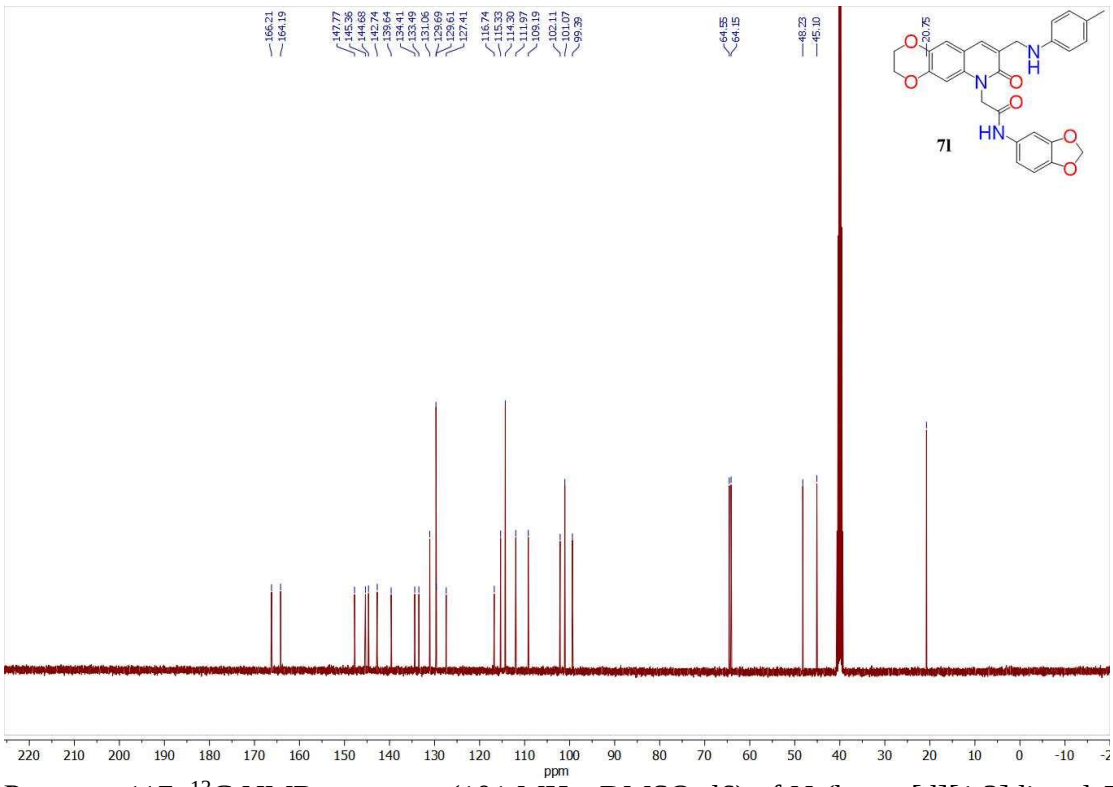
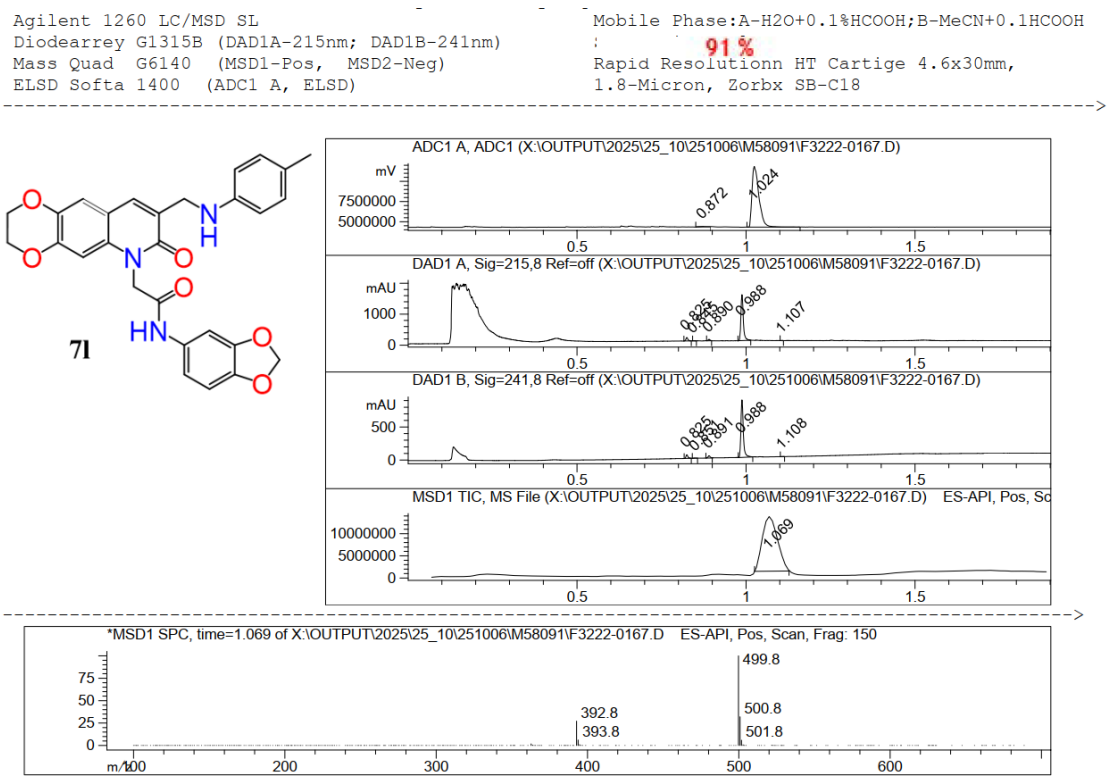


Рисунок 117. ^{13}C NMR spectrum (101 MHz, DMSO-d6) of N-(benzo[d][1,3]dioxol-5-yl)-2-(7-oxo-8-((p-tolylamino)methyl)-2,3-dihydro-[1,4]dioxino[2,3-g]quinolin-6(7H)-yl)acetamide **5l**



#	Signal	R.Time	Area %
1	ADC1 A, ADC1	0.872	0.963
2		1.024	99.037

#	Signal	R.Time	Area %
1	DAD1 A, Sig=215,8 Ref=off	0.825	5.825
2		0.845	0.436
3		0.890	2.128
4		0.988	91.204
5		1.107	0.407

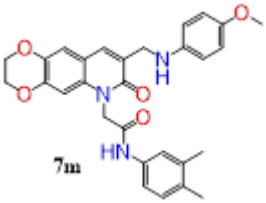
#	Signal	R.Time	Area %
1	DAD1 B, Sig=241,8 Ref=off	0.825	4.750
2		0.851	0.309
3		0.891	3.148
4		0.988	91.536
5		1.108	0.257

#	Signal	R.Time	Area %
1	MSD1 TIC, MS File	1.069	100.000

Рисунок 118. LC/MS data of N-(benzo[d][1,3]dioxol-5-yl)-2-(7-oxo-8-((p-tolylamino)methyl)-2,3-dihydro-[1,4]dioxino[2,3-g]quinolin-6(7H)-yl)acetamide **5l**

Речовина **5m**. Дуальний інгібітор протеаз SARS-CoV-2 M^{pro} та PL^{pro}.

Назва: *O-(3,4Dimethylphenyl)-2-(8-(((4-methoxyphenyl)amino)methyl)-7-oxo-2,3-dihydro-[1,4]dioxino[2,3-g]quinolin-6(7H)-yl)acetamide*



Yellow powder, Yield 76 %, mp = 251-2°C. $[MH]^+$ m/z = 500.2.

Спектральні параметри:

^{1}H NMR (400 MHz, DMSO-d6) δ 10.07 (s, 1H), 8.84 (t, J = 5.3 Hz, 1H), 7.42 (s, 2H), 7.32 (s, 1H), 7.15 (s, 1H), 7.09 (d, J = 7.5 Hz, 1H), 6.79 – 6.66 (m, 5H), 4.78 (d, J = 6.7 Hz, 4H), 4.33 – 4.21 (m, 4H), 3.81 (s, 3H), 2.20 (d, J = 8.0 Hz, 6H).

^{13}C NMR (101 MHz, DMSO-d6) δ 166.21, 164.19, 152.32, 145.36, 140.90, 139.64, 136.82, 136.73, 134.17, 133.49, 131.06, 129.61, 129.51, 120.96, 117.45, 116.74, 114.67, 113.90, 111.97, 99.39, 64.55, 64.03, 55.33, 48.23, 44.98, 19.74, 19.00.

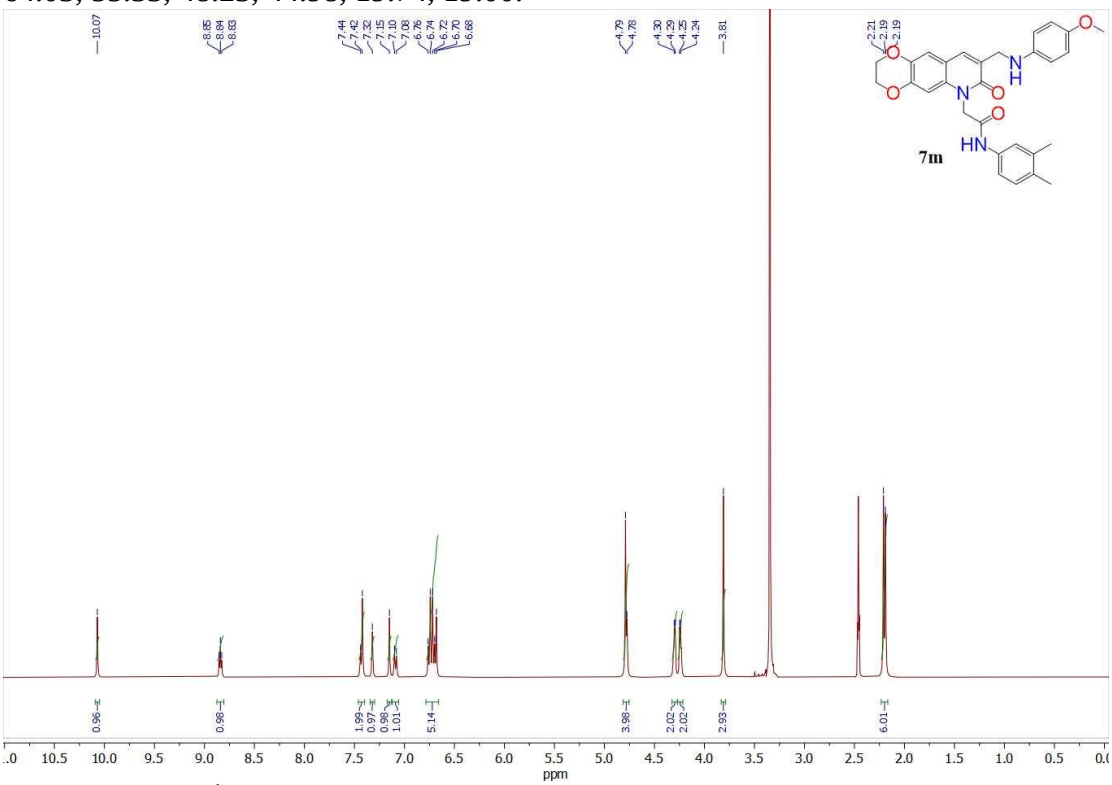


Рисунок 119. ^{1}H NMR spectrum (400 MHz, DMSO-d6) of N-(3,4-dimethylphenyl)-2-(8-(((4-methoxyphenyl)amino)methyl)-7-oxo-2,3-dihydro-[1,4]dioxino[2,3-g]quinolin-6(7H)-yl)acetamide **5m**

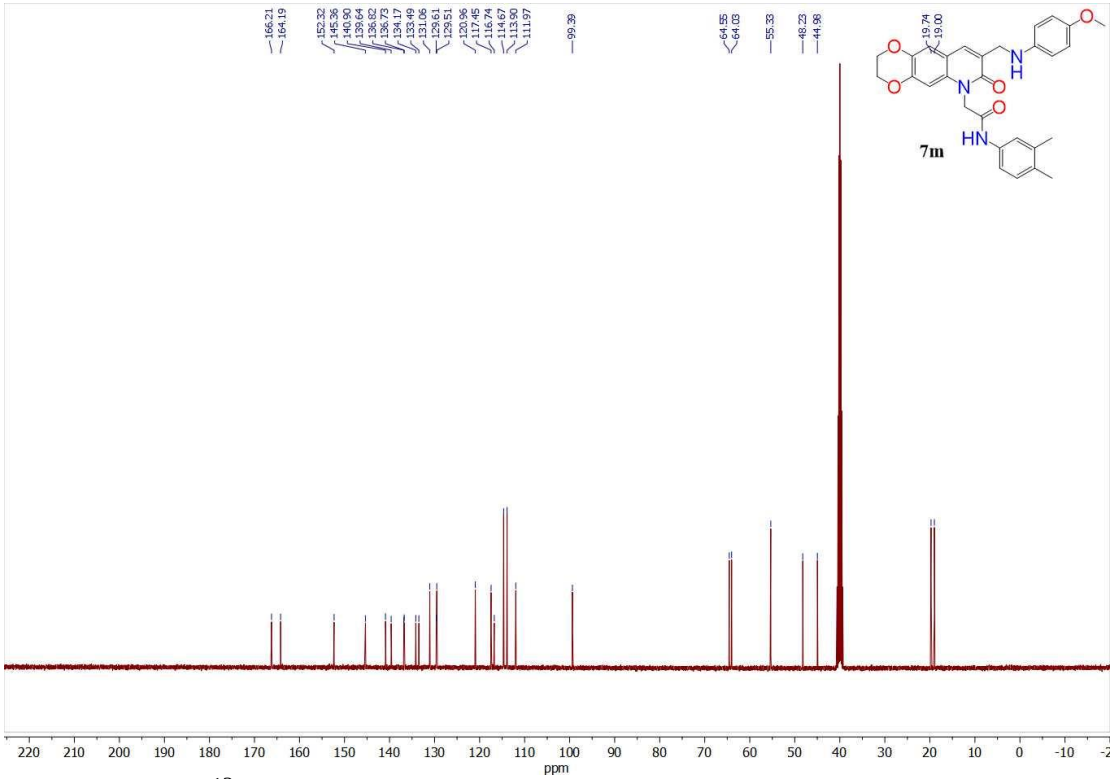
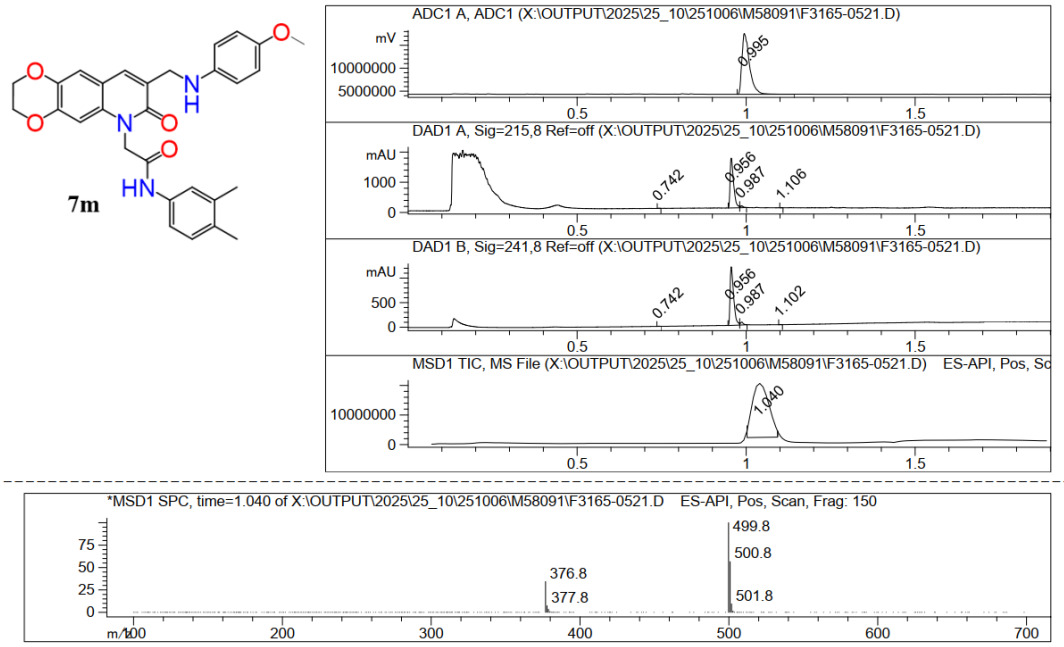


Рисунок 120. ^{13}C NMR spectrum (101 MHz, DMSO-d6) of N-(3,4-dimethylphenyl)-2-(8-(((4-methoxyphenyl)amino)methyl)-7-oxo-2,3-dihydro-[1,4]dioxino[2,3-g]quinolin-6(7H)-yl)acetamide **5m**

Agilent 1260 LC/MSD SL
Diodearrey G1315B (DAD1A-215nm; DAD1B-241nm)
Mass Quad G6140 (MSD1-Pos, MSD2-Neg)
ELSD Softa 1400 (ADC1 A, ELSD)

Mobile Phase:A-H2O+0.1%HCOOH;B-MeCN+0.1HCOOH
Separation column:
Rapid Resolutionn HT Cartige 4.6x30mm,
96 % C18



#	Signal	R.Time	Area %
1	ADC1 A, ADC1	0.995	100.000

#	Signal	R.Time	Area %
1	DAD1 A, Sig=215,8 Ref=off	0.742	0.185
2		0.956	96.805
3		0.987	2.904
4		1.106	0.105

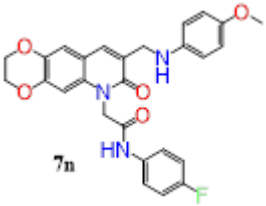
#	Signal	R.Time	Area %
1	DAD1 B, Sig=241,8 Ref=off	0.742	0.139
2		0.956	95.875
3		0.987	3.780
4		1.102	0.206

#	Signal	R.Time	Area %
1	MSD1 TIC, MS File	1.040	100.000

Рисунок 121. LC/MS data of N-(3,4-dimethylphenyl)-2-(8-(((4-methoxyphenyl)amino)methyl)-7-oxo-2,3-dihydro-[1,4]dioxino[2,3-g]quinolin-6(7H)-yl)acetamide **5m**

Речовина **5n**. Дуальний інгібітор протеаз SARS-CoV-2 M^{pro} та PL^{pro}.

Назва: *N-(4-Fluorophenyl)-2-(8-(((4-methoxyphenyl)amino)methyl)-7-oxo-2,3-dihydro-[1,4]dioxino[2,3-g]quinolin-6(7H)-yl)acetamide*



Yellow powder, Yield 83 %, mp = 248-9°C. $[MH]^+$ m/z = 490.2.

Спектральні параметри:

^{1}H NMR (400 MHz, DMSO-d6) δ 10.07 (s, 1H), 7.56 (dd, J = 8.0, 3.6 Hz, 2H), 7.20 – 7.12 (m, 3H), 6.79 – 6.66 (m, 5H), 4.78 (d, J = 7.0 Hz, 4H), 4.33 – 4.27 (m, 2H), 4.27 – 4.21 (m, 2H), 3.81 (s, 3H).

^{13}C NMR (101 MHz, DMSO-d6) δ 166.34, 164.19, 159.25, 156.81, 152.32, 145.36, 140.90, 139.64, 135.29, 135.26, 133.49, 131.06, 129.61, 121.68, 121.60, 116.74, 115.59, 115.37, 114.67, 113.90, 111.97, 99.39, 64.55, 64.03, 55.33, 48.23, 44.98.

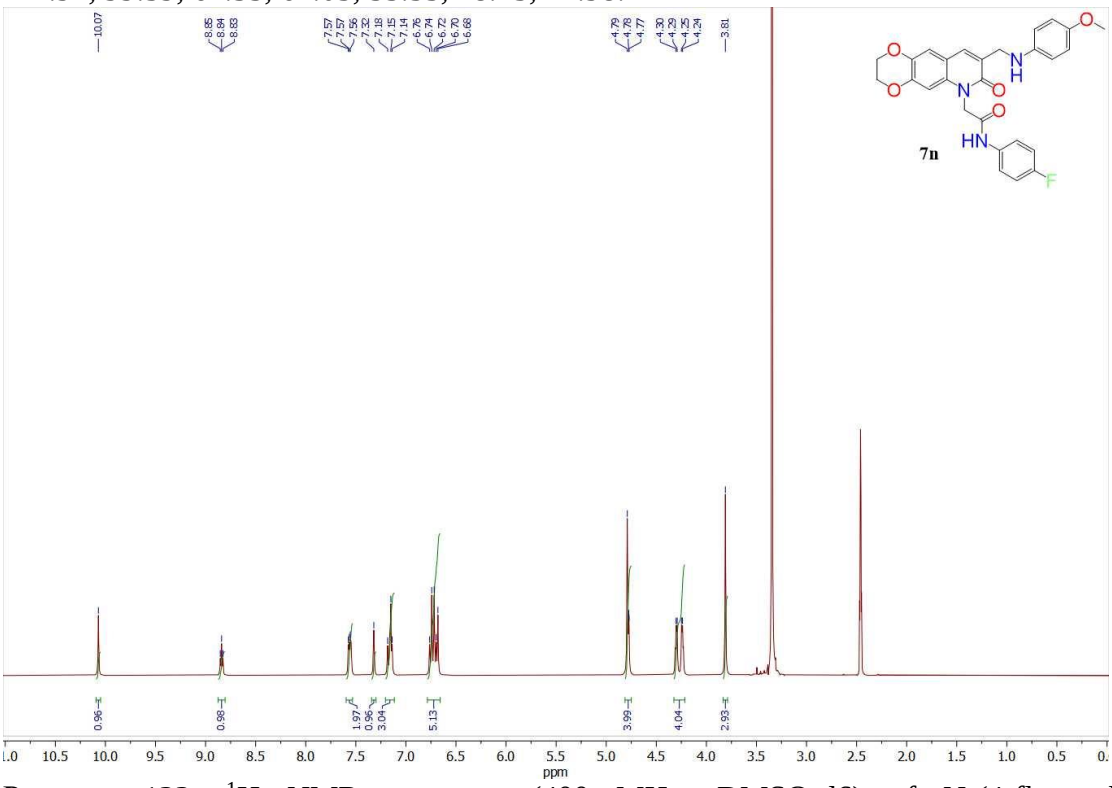


Рисунок 122. ^{1}H NMR spectrum (400 MHz, DMSO-d6) of N-(4-fluorophenyl)-2-(8-(((4-methoxyphenyl)amino)methyl)-7-oxo-2,3-dihydro-[1,4]dioxino[2,3-g]quinolin-6(7H)-yl)acetamide **5n**

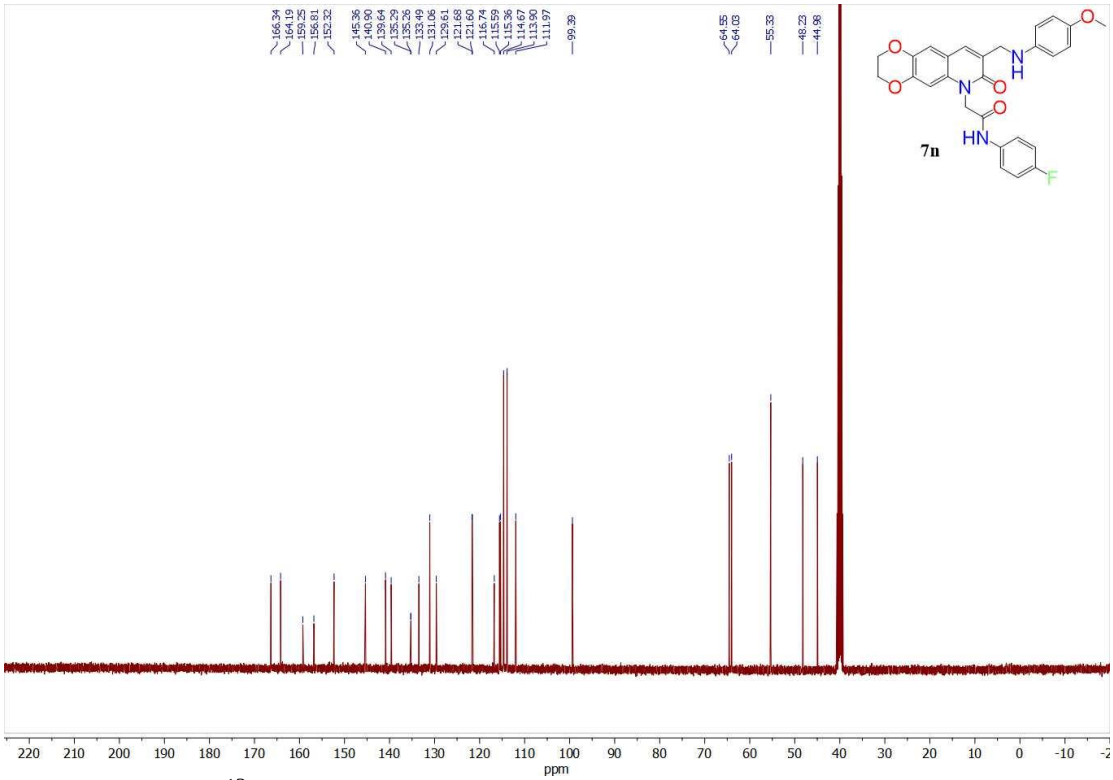
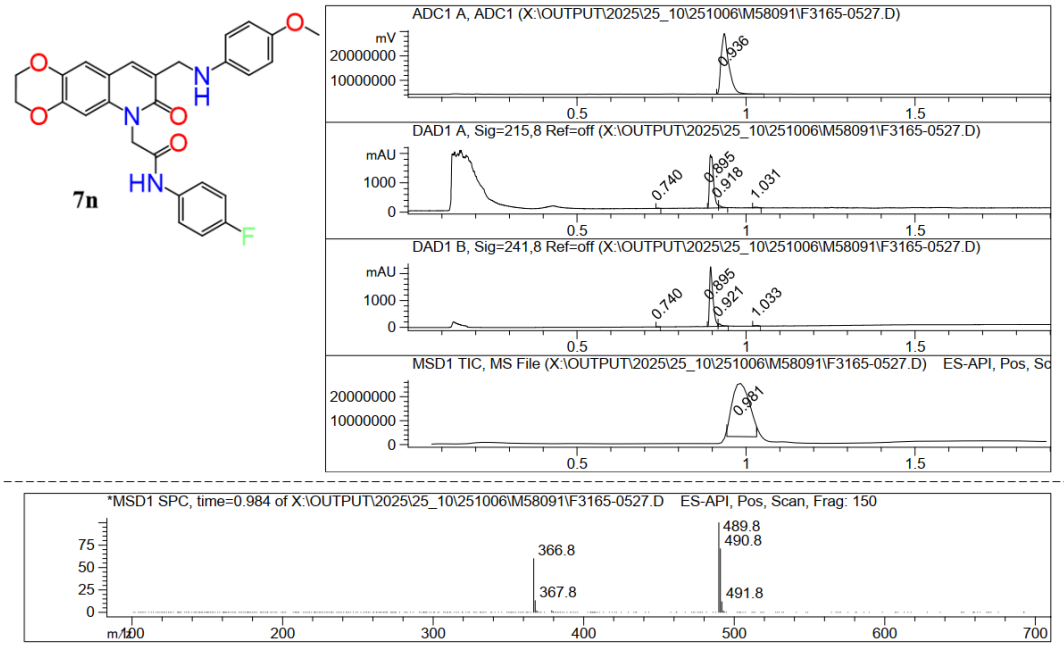


Рисунок 123. ^{13}C NMR spectrum (101 MHz, DMSO-d6) of N-(4-fluorophenyl)-2-(8-(((4-methoxyphenyl)amino)methyl)-7-oxo-2,3-dihydro-[1,4]dioxino[2,3-g]quinolin-6(7H)-yl)acetamide **5n**

Agilent 1260 LC/MSD SL
Diodearrey G1315B (DAD1A-215nm; DAD1B-241nm)
Mass Quad G6140 (MSD1-Pos, MSD2-Neg)
ELSD Softa 1400 (ADC1 A, ELSD)

Mobile Phase:A-H2O+0.1%HCOOH;B-MeCN+0.1HCOOH
Separation column: 95 %
Rapid Resolution HT Cartridge 4.6x30mm,
1.8-Micron, Zorbx SB-C18



#	Signal	R.Time	Area %
1	ADC1 A, ADC1	0.936	100.000

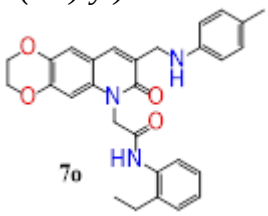
#	Signal	R.Time	Area %
1	DAD1 A, Sig=215,8 Ref=off	0.740	0.440
2		0.895	95.042
3		0.918	3.208
4		1.031	1.310

#	Signal	R.Time	Area %
1	DAD1 B, Sig=241,8 Ref=off	0.740	0.213
2		0.895	95.665
3		0.921	3.249
4		1.033	0.873

#	Signal	R.Time	Area %
1	MSD1 TIC, MS File	0.981	100.000

Рисунок 124. LC/MS data of N-(4-fluorophenyl)-2-(8-(((4-methoxyphenyl)amino)methyl)-7-oxo-2,3-dihydro-[1,4]dioxino[2,3-g]quinolin-6(7H)-yl)acetamide **5n**

Речовина **5о**. Дуальний інгібітор протеаз SARS-CoV-2 M^{pro} та PL^{pro}.
Назва: *N-(2-Ethylphenyl)-2-(7-oxo-8-((p-tolylamino)methyl)-2,3-dihydro-[1,4]dioxino[2,3-g]quinolin-6(7H)-yl)acetamide*



Yellow powder, Yield 80 %, mp = 247-8°C. $[MH]^+$ m/z = 484.2.
Спектральні параметри:
^{1}H NMR (400 MHz, DMSO-d6) δ 10.06 (s, 1H), 8.84 (t, J = 5.3 Hz, 1H), 7.23 – 7.11 (m, 4H), 6.99 (d, J = 7.8 Hz, 2H), 6.84 (d, J = 7.5 Hz, 1H), 6.68 (s, 1H), 6.52 (d, J = 7.8 Hz, 2H), 4.78 (d, J = 7.0 Hz, 4H), 4.33 – 4.21 (m, 4H), 2.58 (q, J = 7.3 Hz, 2H), 1.12 (t, J = 7.3 Hz, 3H).
^{13}C NMR (101 MHz, DMSO-d6) δ 167.84, 164.19, 145.36, 144.68, 139.64, 138.40, 134.22, 133.49, 131.06, 129.69, 129.61, 128.70, 127.43, 127.41, 124.43, 119.72, 116.74, 114.30, 111.97, 99.39, 64.55, 64.03, 48.13, 45.10, 24.39, 20.75, 14.14.

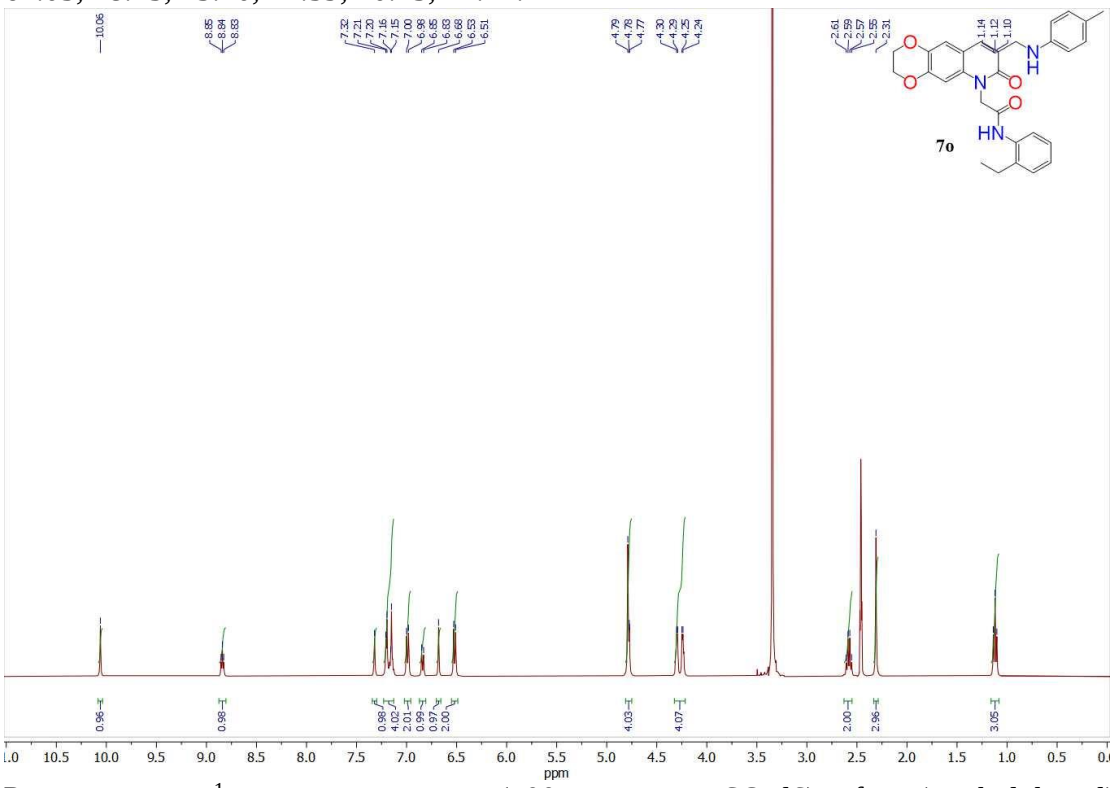


Рисунок 125. ^{1}H NMR spectrum (400 MHz, DMSO-d6) of N-(2-ethylphenyl)-2-(7-oxo-8-((p-tolylamino)methyl)-2,3-dihydro-[1,4]dioxino[2,3-g]quinolin-6(7H)-yl)acetamide **5о**

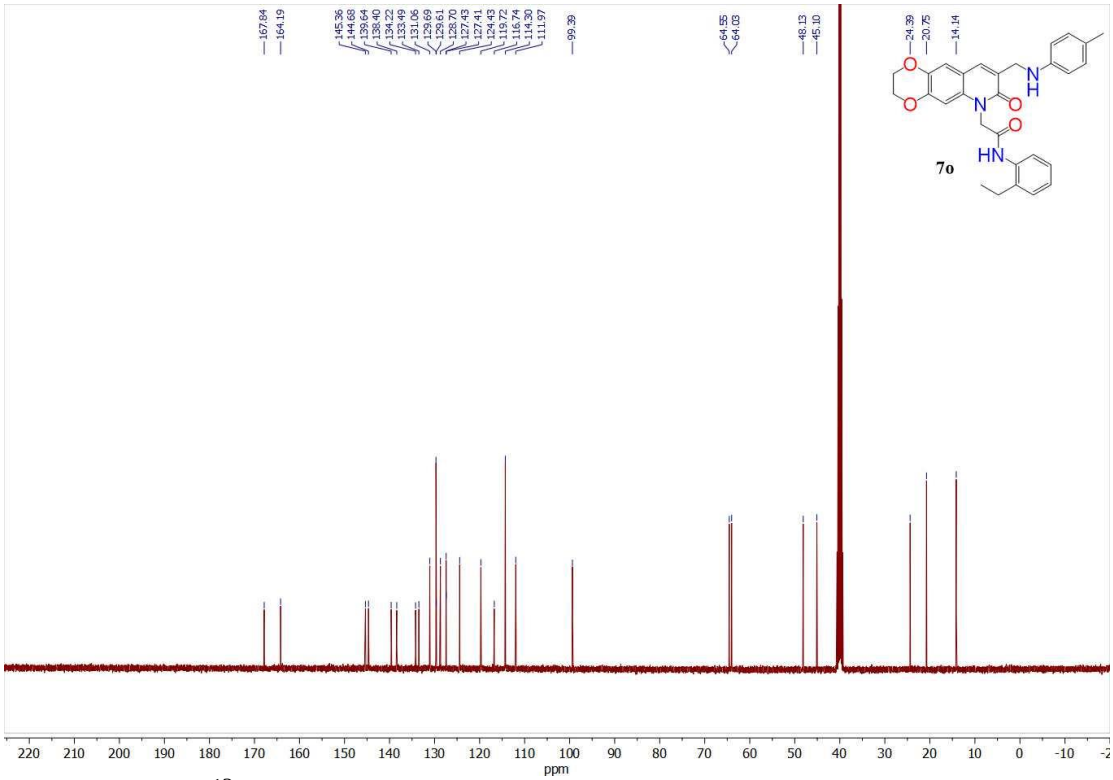
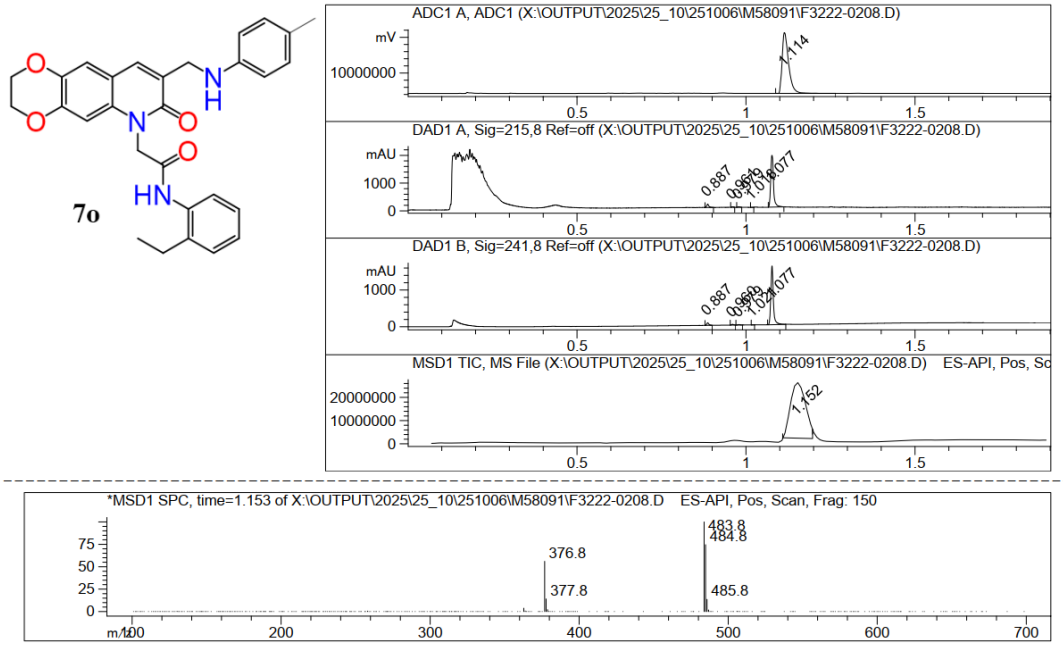


Рисунок 126. ^{13}C NMR spectrum (101 MHz, DMSO-d6) of N-(2-ethylphenyl)-2-(7-oxo-8-((p-tolylamino)methyl)-2,3-dihydro-[1,4]dioxino[2,3-g]quinolin-6(7H)-yl)acetamide **5o**

Agilent 1260 LC/MSD SL
Diodearrey G1315B (DAD1A-215nm; DAD1B-241nm)
Mass Quad G6140 (MSD1-Pos, MSD2-Neg)
ELSD Softa 1400 (ADC1 A, ELSD)

Mobile Phase:A-H2O+0.1%HCOOH;B-MeCN+0.1HCOOH
Separatio 93 %
Rapid Resolutionn HT Cartige 4.6x30mm,
1.8-Micron, Zorbx SB-C18



#	Signal	R.Time	Area %
1	ADC1 A, ADC1	1.114	100.000

#	Signal	R.Time	Area %
1	DAD1 A, Sig=215,8 Ref=off	0.887	4.674
2		0.961	0.597
3		0.979	0.715
4		1.018	0.258
5		1.077	93.756

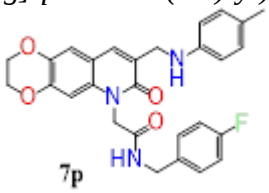
#	Signal	R.Time	Area %
1	DAD1 B, Sig=241,8 Ref=off	0.887	3.368
2		0.960	0.917
3		0.979	0.704
4		1.021	0.168
5		1.077	94.842

#	Signal	R.Time	Area %
1	MSD1 TIC, MS File	1.152	100.000

Рисунок 127. LC/MS data of N-(2-ethylphenyl)-2-(7-oxo-8-((p-tolylamino)methyl)-2,3-dihydro-[1,4]dioxino[2,3-g]quinolin-6(7H)-yl)acetamide **5o**

Речовина **5p**. Дуальний інгібітор протеаз SARS-CoV-2 M^{pro} та PL^{pro}.

Назва: *N-(4-Fluorobenzyl)-2-(7-oxo-8-((p-tolylamino)methyl)-2,3-dihydro-[1,4]dioxino[2,3-g]quinolin-6(7H)-yl)acetamide*



Yellow powder, Yield 84 %, mp = 240-1°C. $[MH]^+$ m/z = 488.2.

Спектральні параметри:

^{1}H NMR (400 MHz, DMSO-d6) δ 8.84 (t, J = 5.3 Hz, 1H), 8.52 (t, J = 5.6 Hz, 1H), 7.39 (dd, J = 7.9, 3.5 Hz, 2H), 7.32 (s, 1H), 7.18 – 7.09 (m, 3H), 6.99 (d, J = 7.8 Hz, 2H), 6.68 (s, 1H), 6.52 (d, J = 7.8 Hz, 2H), 4.81 – 4.72 (m, 4H), 4.33 – 4.27 (m, 2H), 4.27 – 4.18 (m, 4H).

^{13}C NMR (101 MHz, DMSO-d6) δ 168.72, 164.21, 163.26, 160.82, 145.36, 144.68, 139.64, 135.26, 135.23, 133.26, 131.06, 129.69, 129.61, 129.49, 129.40, 127.41, 116.81, 115.23, 115.01, 114.30, 111.97, 99.71, 64.55, 64.03, 48.13, 45.07, 43.19, 20.75.

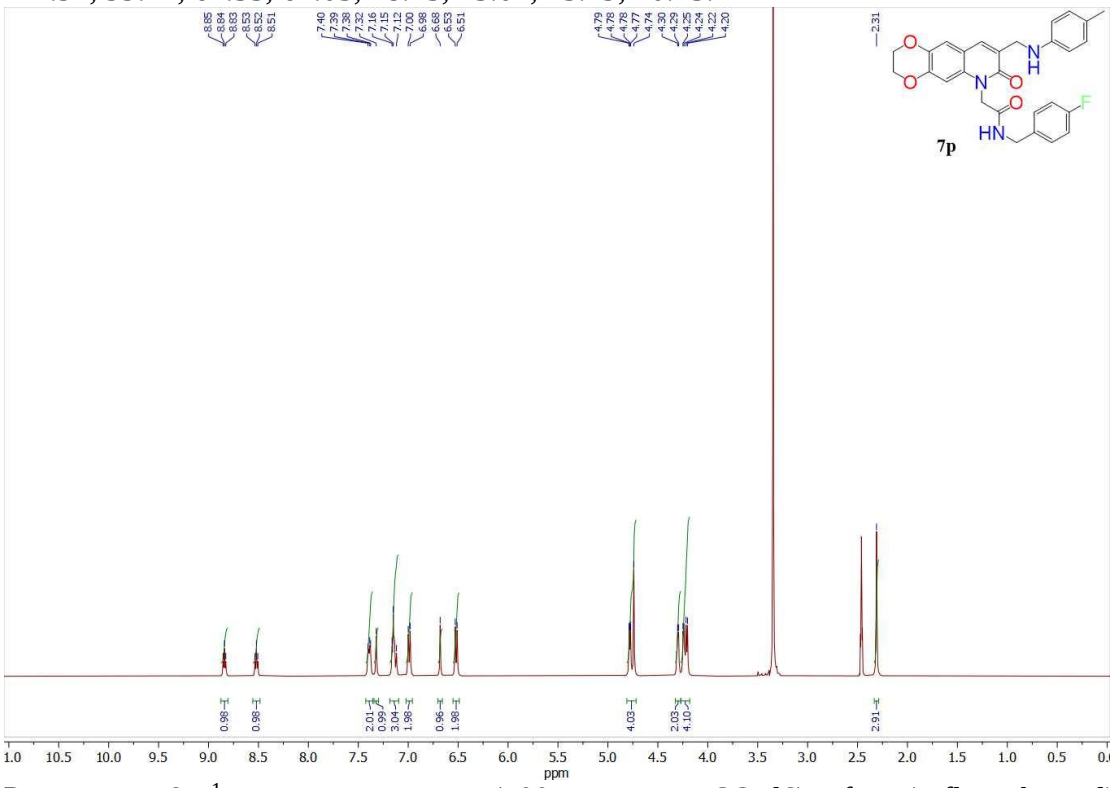


Рисунок 128. ^{1}H NMR spectrum (400 MHz, DMSO-d6) of N-(4-fluorobenzyl)-2-(7-oxo-8-((p-tolylamino)methyl)-2,3-dihydro-[1,4]dioxino[2,3-g]quinolin-6(7H)-yl)acetamide **5p**

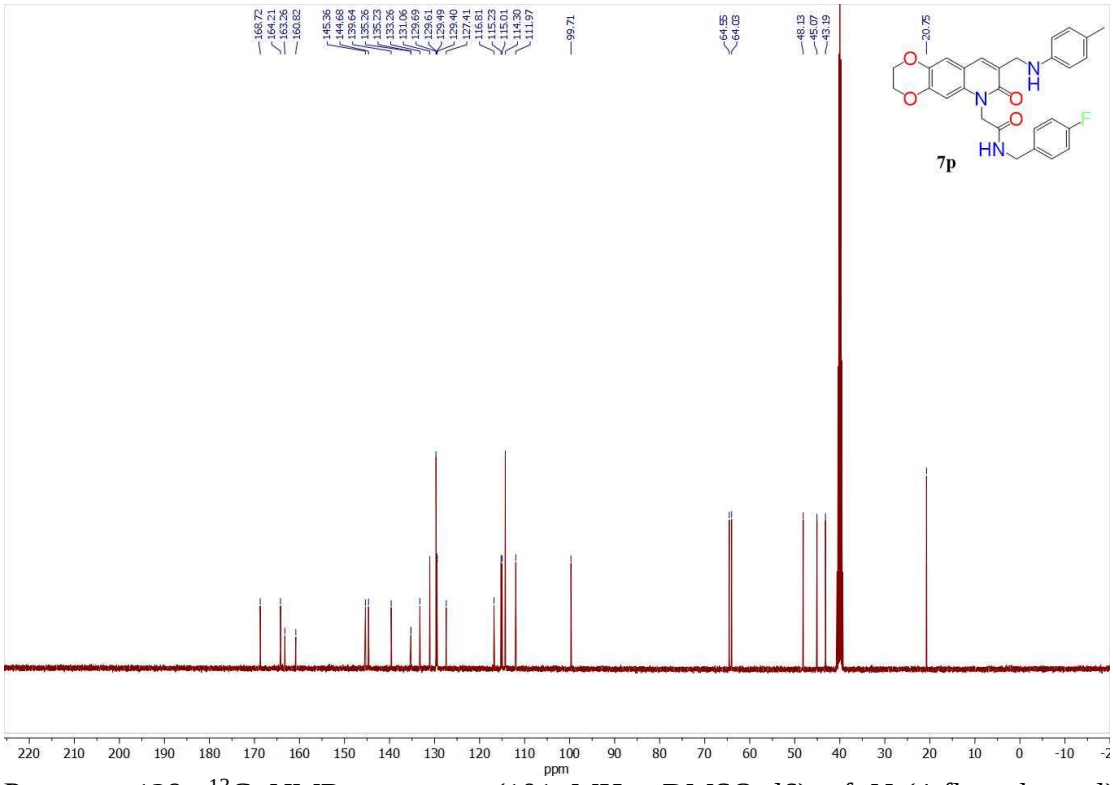
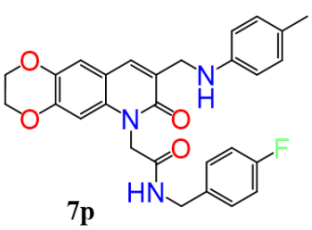
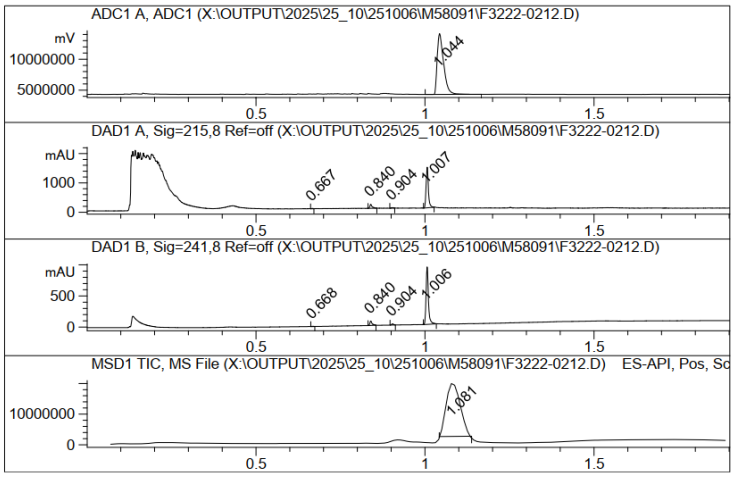


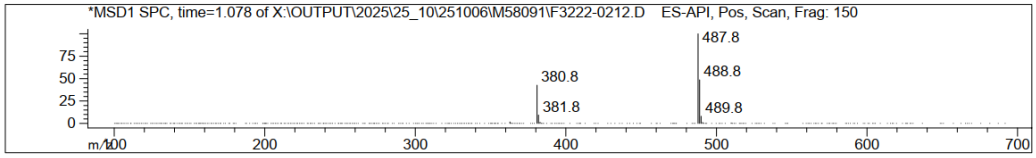
Рисунок 129. ^{13}C NMR spectrum (101 MHz, DMSO-d6) of N-(4-fluorobenzyl)-2-(7-oxo-8-((p-tolylamino)methyl)-2,3-dihydro-[1,4]dioxino[2,3-g]quinolin-6(7H)-yl)acetamide **5p**

Agilent 1260 LC/MSD SL
Diodearrey G1315B (DAD1A-215nm; DAD1B-241nm)
Mass Quad G6140 (MSD1-Pos, MSD2-Neg)
ELSD Softa 1400 (ADC1 A, ELSD)

Mobile Phase:A-H2O+0.1%HCOOH;B-MeCN+0.1HCOOH
Separation column:
Rapid Resolutionn HT Cartige 4.6x30mm,
1.8-Micron, Zorbx SB-C18







#	Signal	R.Time	Area %
1	ADC1 A, ADC1	1.044	100.000

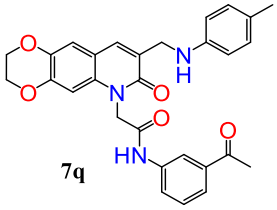
#	Signal	R.Time	Area %
1	DAD1 A, Sig=215,8 Ref=off	0.667	0.584
2		0.840	6.752
3		0.904	1.152
4		1.007	91.512

#	Signal	R.Time	Area %
1	DAD1 B, Sig=241,8 Ref=off	0.668	0.480
2		0.840	6.510
3		0.904	1.348
4		1.006	91.663

#	Signal	R.Time	Area %
1	MSD1 TIC, MS File	1.081	100.000

Рисунок 130. LC/MS data of N-(4-fluorobenzyl)-2-(7-oxo-8-((p-tolylamino)methyl)-2,3-dihydro-[1,4]dioxino[2,3-g]quinolin-6(7H)-yl)acetamide **5p**

Речовина **5q**. Дуальний інгібітор протеаз SARS-CoV-2 M^{pro} та PL^{pro}.
Назва: *N-(3-Acetylphenyl)-2-(7-oxo-8-((p-tolylamino)methyl)-2,3-dihydro-[1,4]dioxino[2,3-g]quinolin-6(7H)-yl)acetamide*



Yellow powder, Yield 72 %, mp = 202-3°C. $[MH]^+$ m/z = 498.2.
Спектральні параметри:
^{1}H NMR (404 MHz, DMSO-d6) δ 10.07 (s, 1H), 8.84 (t, J = 5.3 Hz, 1H), 8.12 (t, J = 2.2 Hz, 1H), 7.90 (dd, J = 7.5, 2.6 Hz, 1H), 7.72 (dd, J = 8.7, 3.0 Hz, 1H), 7.47 (t, J = 8.0 Hz, 1H), 7.32 (s, 1H), 7.15 (s, 1H), 6.99 (d, J = 7.8 Hz, 2H), 6.68 (s, 1H), 6.52 (d, J = 7.8 Hz, 2H), 4.78 (d, J = 7.0 Hz, 4H), 4.33 – 4.21 (m, 4H), 2.31 (s, 3H).
^{13}C NMR (101 MHz, DMSO-d6) δ 199.11, 166.20, 164.19, 145.36, 144.68, 139.64, 138.27, 138.14, 133.49, 131.06, 129.69, 129.61, 128.01, 127.41, 124.48, 123.09, 118.90, 116.74, 114.30, 111.97, 99.39, 64.55, 64.03, 48.23, 45.10, 26.46, 20.75.

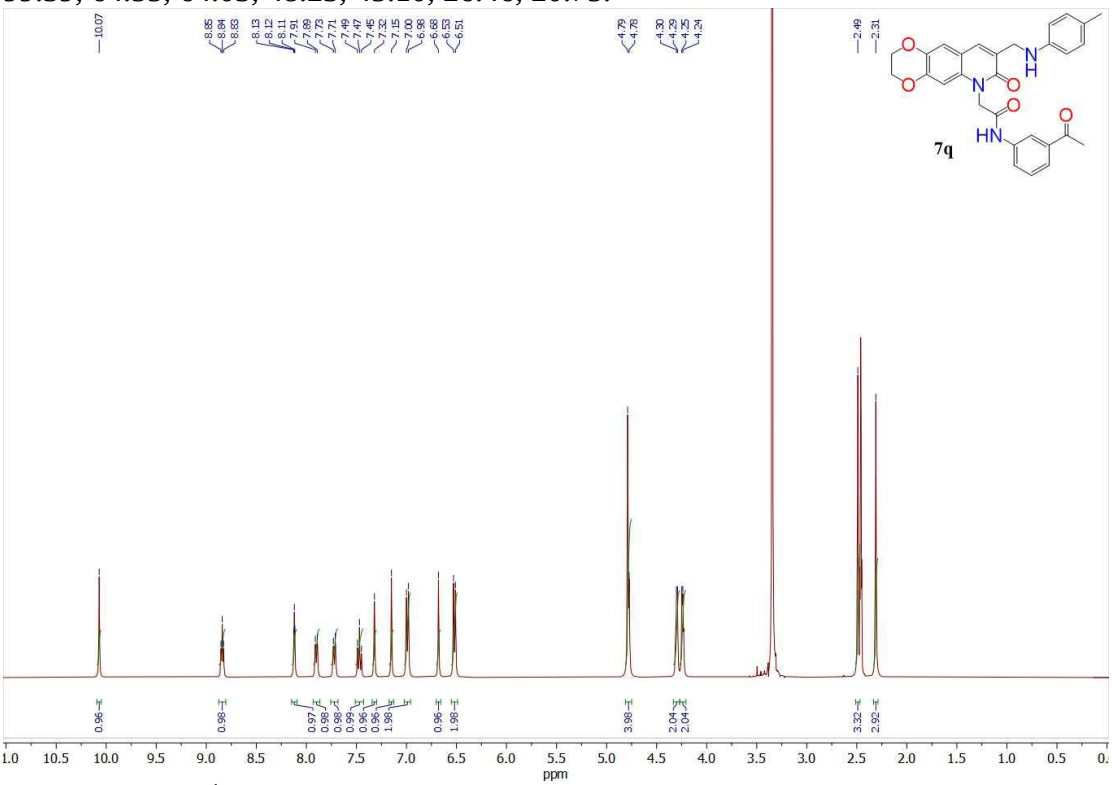


Рисунок 131. ^{1}H NMR spectrum (400 MHz, DMSO-d6) of N-(3-acetylphenyl)-2-(7-oxo-8-((p-tolylamino)methyl)-2,3-dihydro-[1,4]dioxino[2,3-g]quinolin-6(7H)-yl)acetamide **5q**

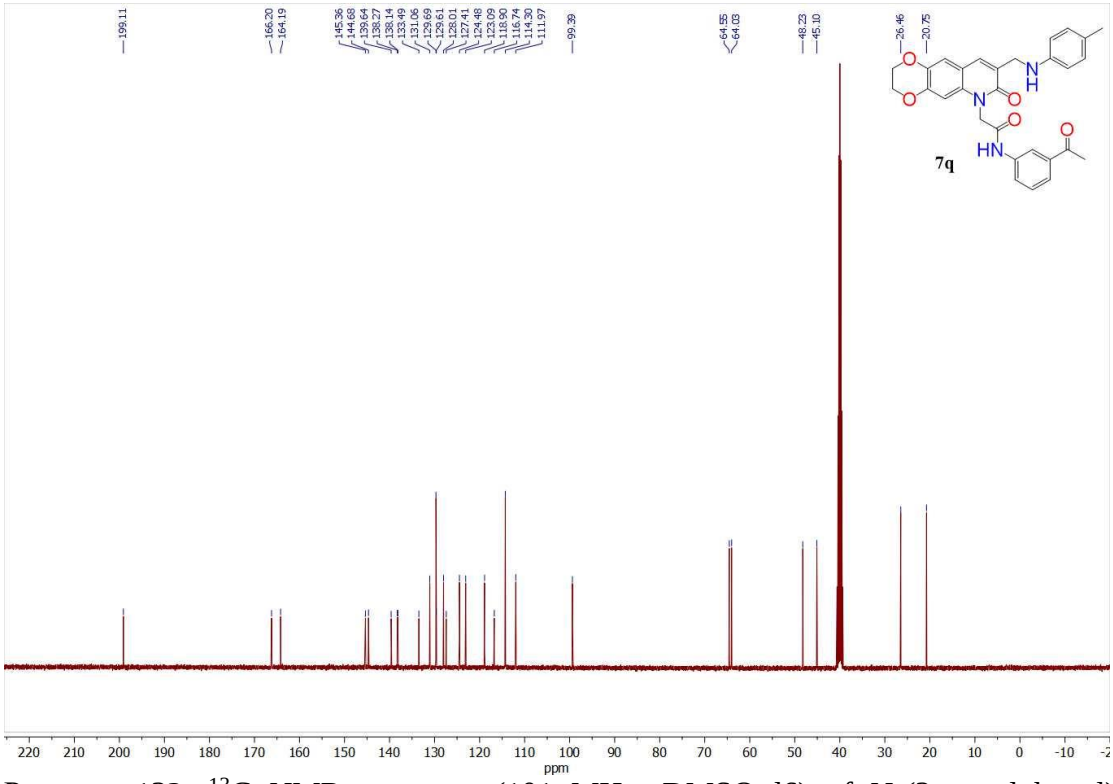
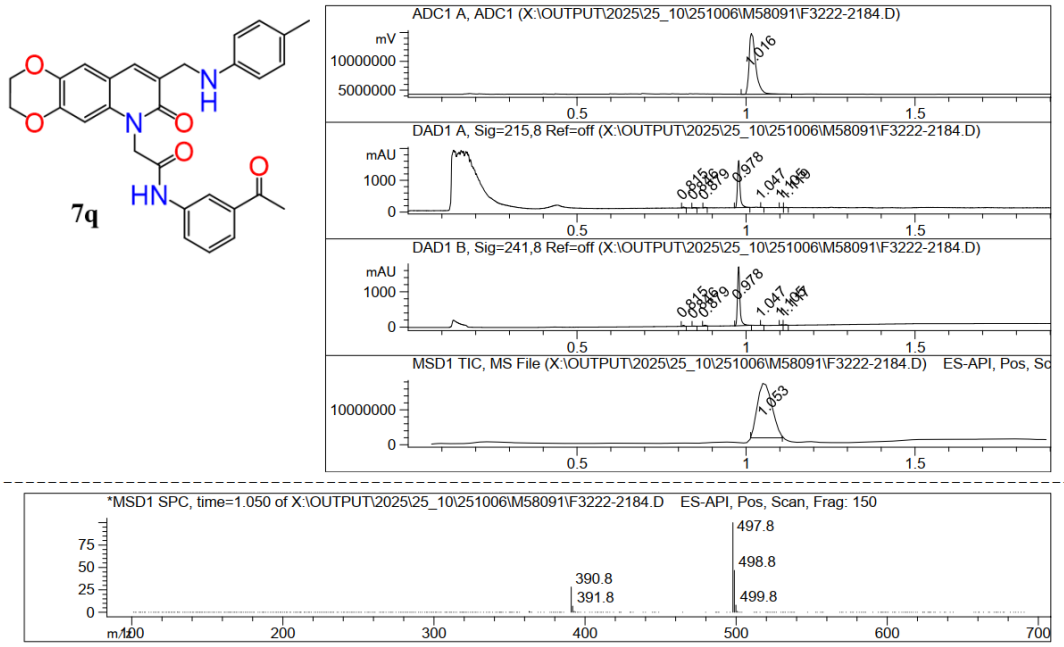


Рисунок 132. ^{13}C NMR spectrum (101 MHz, DMSO-d6) of N-(3-acetylphenyl)-2-(7-oxo-8-((p-tolylamino)methyl)-2,3-dihydro-[1,4]dioxino[2,3-g]quinolin-6(7H)-yl)acetamide **5q**

Agilent 1260 LC/MSD SL
Diodearrey G1315B (DAD1A-215nm; DAD1B-241nm)
Mass Quad G6140 (MSD1-Pos, MSD2-Neg)
ELSD Softa 1400 (ADC1 A, ELSD)

Mobile Phase:A-H2O+0.1%HCOOH;B-MeCN+0.1HCOOH
Separation column:
R[illegible] 95 % ige 4.6x30mm,
1.8-Micron, Zorbx SB-C18



#	Signal	R.Time	Area %
1	ADC1 A, ADC1	1.016	100.000

#	Signal	R.Time	Area %
1	DAD1 A, Sig=215,8 Ref=off	0.815	1.264
2		0.846	0.846
3		0.879	0.706
4		0.978	95.897
5		1.047	0.240
6		1.105	0.592
7		1.119	0.455

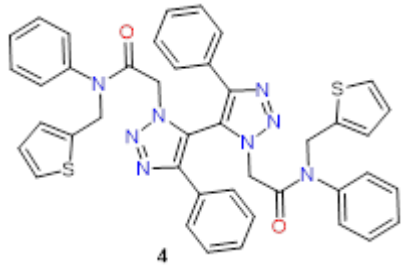
#	Signal	R.Time	Area %
1	DAD1 B, Sig=241,8 Ref=off	0.815	1.254
2		0.846	0.383
3		0.879	1.219
4		0.978	95.612
5		1.047	0.329
6		1.105	0.595
7		1.117	0.607

#	Signal	R.Time	Area %
1	MSD1 TIC, MS File	1.053	100.000

Рисунок 133. LC/MS data of N-(3-acetylphenyl)-2-(7-oxo-8-((p-tolylamino)methyl)-2,3-dihydro-[1,4]dioxino[2,3-g]quinolin-6(7H)-yl)acetamide **5q**

Сполука 6a

Речовина **6a** (димер речовини **1a)** Нековалентний інгібітор головної протеази SARS-CoV-2 M^{pro}.
Назва: 2,2'-(5,5'-diphenyl-3H,3'H-[4,4'-bi(1,2,3-triazole)]-3,3'-diyl)bis(N-phenyl-N-(thiophen-2-ylmethyl)acetamide)



4

White powder (90 % yield). MS (ESI+) m/z calculated for $C_{42}H_{34}N_8O_2S_2$ $[M+H]^+$ 747.2, found 747.4.
Спектральні параметри:
^{1}H NMR (400 MHz, DMSO-D_6) δ 7.38 – 7.32 (m, 6H), 7.32 – 7.21 (m, 12H), 6.95 – 6.90 (m, 4H), 6.81 (dd, J = 5.1, 3.4 Hz, 2H), 6.62 (dd, J = 3.4, 1.2 Hz, 2H), 4.84 (d, J = 16.7 Hz, 2H), 4.70 – 4.57 (q, 4H), 4.46 (d, J = 16.7 Hz, 2H).
^{13}C NMR (101 MHz, DMSO-D_6) δ 164.32, 146.62, 139.71, 138.82, 130.29, 129.47, 129.37, 129.20, 128.38, 127.91, 127.07, 126.83, 126.25, 120.82, 49.96, 47.61.

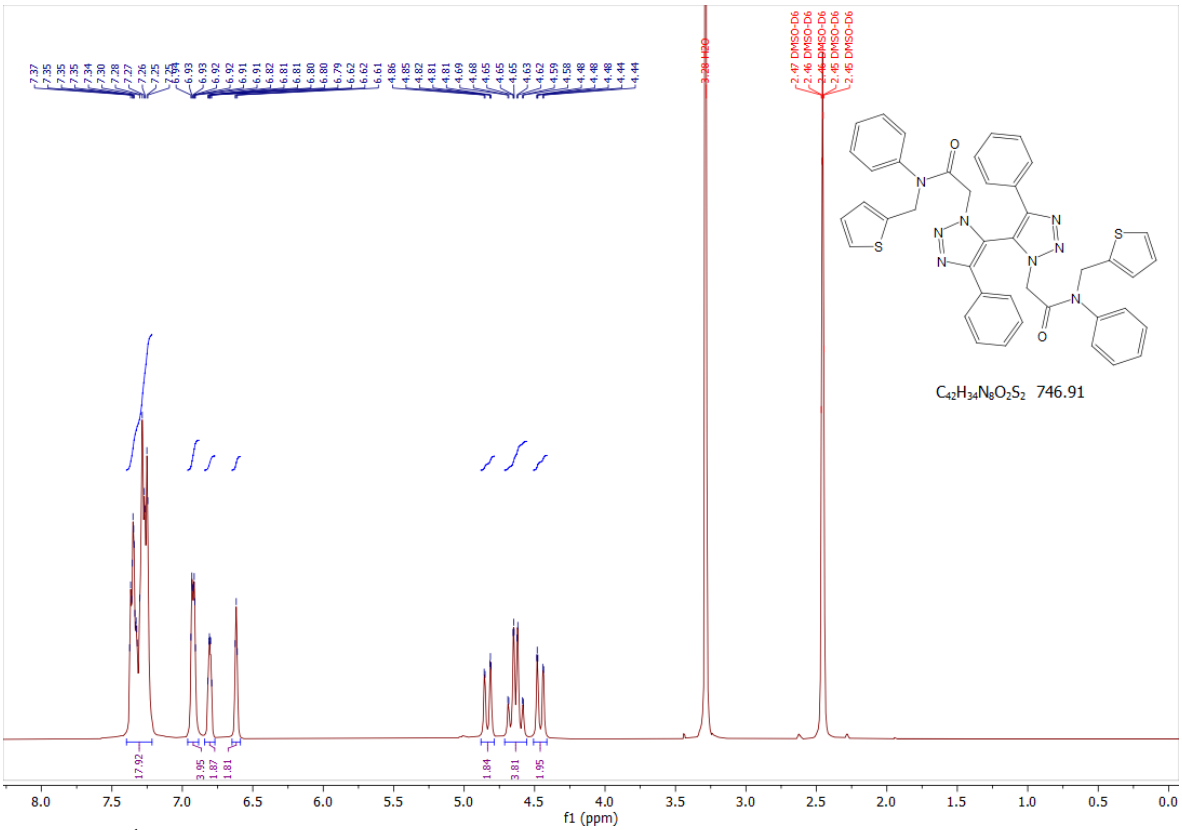


Рисунок 134. ^{1}H NMR spectrum (400 MHz, DMSO-D_6) 2,2'-(5,5'-diphenyl-3H,3'H-[4,4'-bi(1,2,3-triazole)]-3,3'-diyl)bis(N-phenyl-N-(thiophen-2-ylmethyl)acetamide) (**6a**).

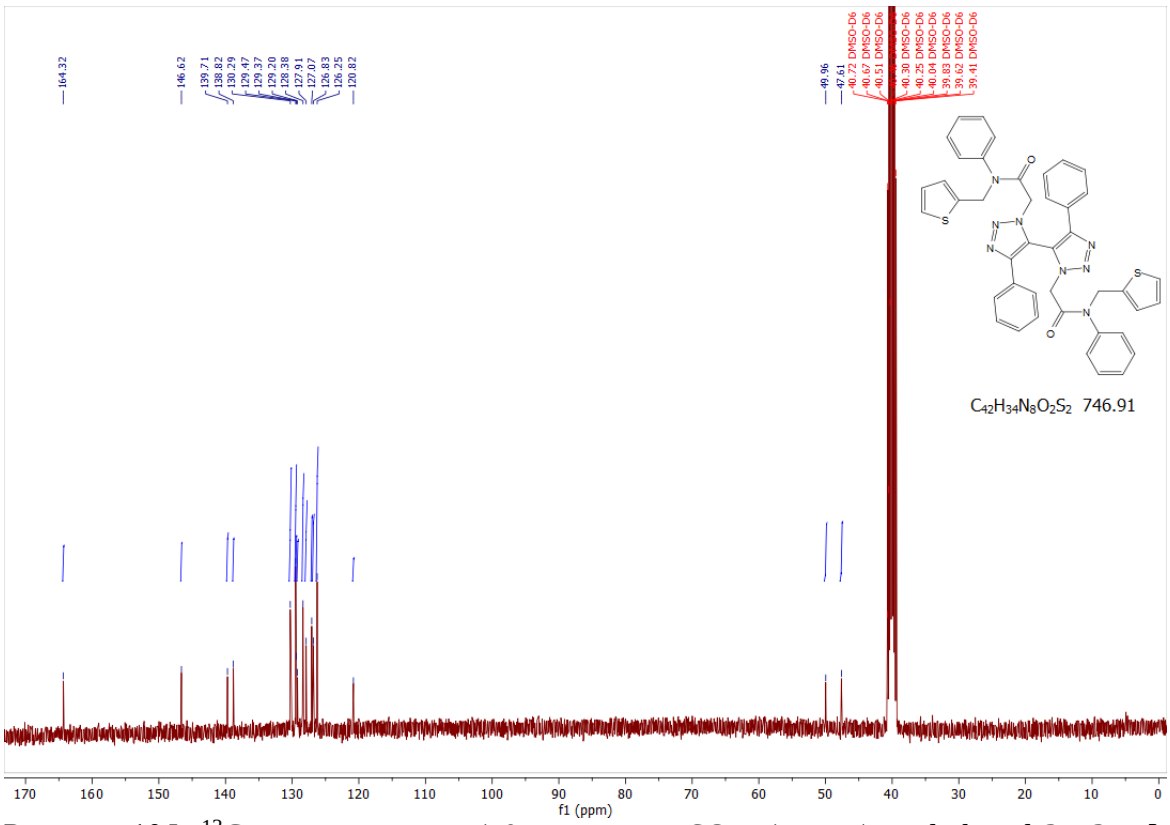


Рисунок 135. ^{13}C NMR spectrum (101 MHz, DMSO-D_6) 2,2'-(5,5'-diphenyl-3H,3'H-[4,4'-bi(1,2,3-triazole)]-3,3'-diyl)bis(N-phenyl-N-(thiophen-2-ylmethyl)acetamide) (**6a**).

Crystal data and structural refinements for **1a** and **6a**.

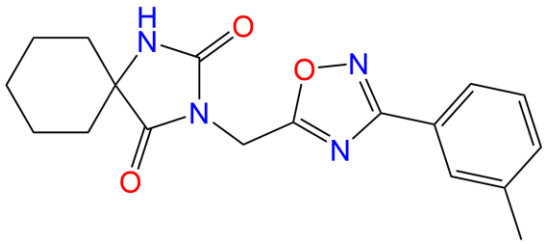
Compound	**1a**	**6a**
formula	$C_{21}H_{18}N_4OS$	$C_{42}H_{34}N_8O_2S_2$
formula weight	374.45	746.68
temperature (K)	150(1)	293(2)
crystal system	orthorhombic	orthorhombic
space group	*Pca*2$_1$	*Pna*2$_1$
a (Å)	16.5168(2)	17.5758(6)
b (Å)	5.5500(1)	20.7815(6)
c (Å)	40.1870(6)	10.5786(3)
V (Å^3)	3683.87(10)	3863.8(2)
Z	8	4
Wavelength/Å	1.54184	0.71073
Radiation type	Cu K_a	Mo *K*α
D_c (g cm^{-3})	1.350	1.284
μ (mm^{-1})	1.708	0.185
F(000)	1568	1559
2θ range (°)	9.06 to 67.96	7.03 to 54.99
GOF on F^2	1.062	1.136
reflections collected	18899	74129
R_{int}	0.0365	0.0725
R_1,^{a} wR_2^{b} [$I > 2\sigma(I)$]	0.0599, 0.1579	0.1091, 0.3115
R_1, wR_2 (all data)	0.0611, 0.1579	0.1741, 0.3648

Похідні гідантоїну, сполуки 7a-7h.

Yevsieieva, L., Kyrychenko, A., Trostianko, P., Ivanov, V., Kovalenko, S. M., & Kalugin, O. (2025). Targeted structural design of molecular scaffolds for dual-action peptidomimetic inhibitors against SARS-CoV-2 MPRO and PLPRO. ScienceRise: Pharmaceutical Science, (5 (57), 56–67. https://doi.org/10.15587/2519-4852.2025.337951

Речовина **7a**. Дуальний пептидоміметичний інгібітор протеаз SARS-COV-2 M^{pro} та PL^{pro}.

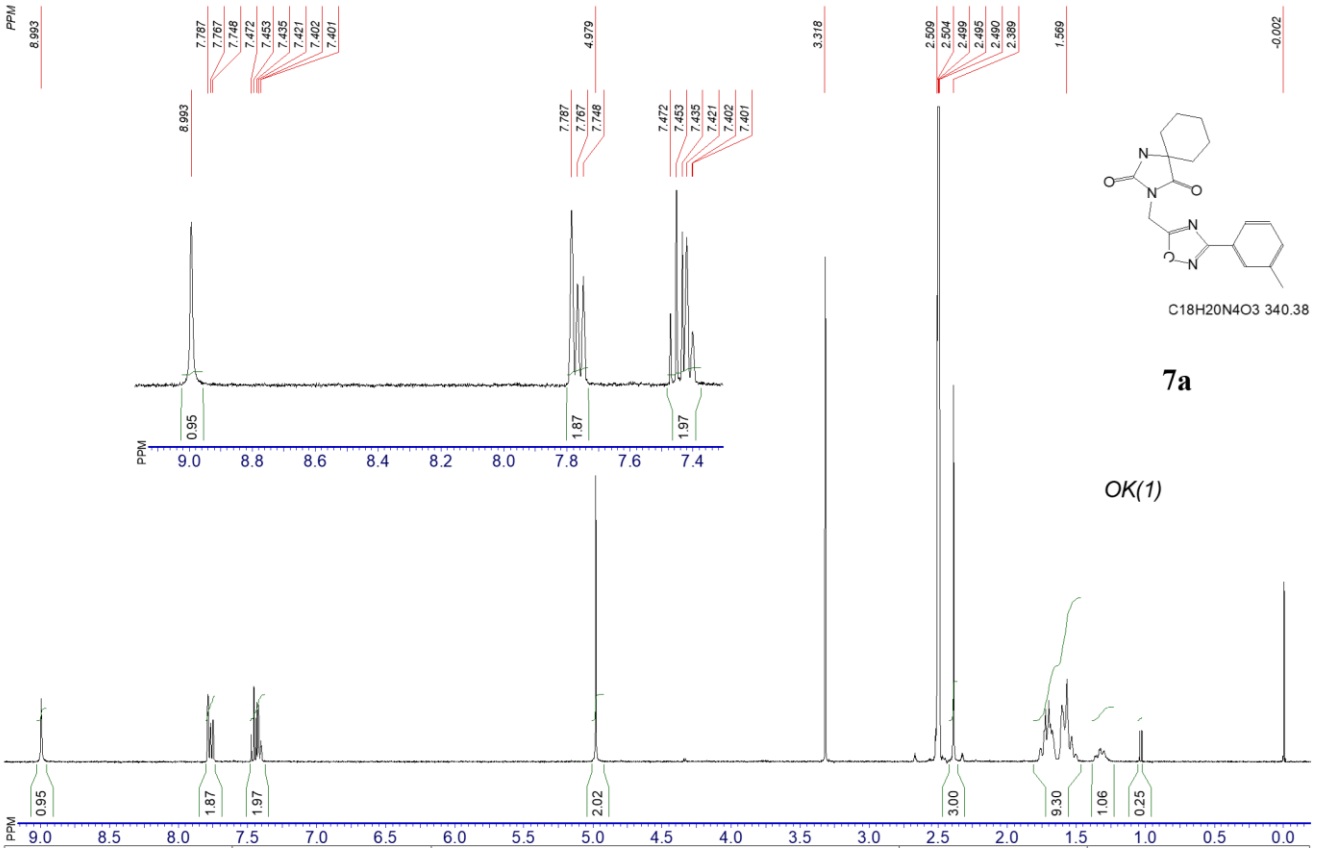
Назва: *3-((3-(M-tolyl)-1,2,4-oxadiazol-5-yl)methyl)-1,3-diazaspiro[4.5]decane-2,4-dione*



White powder, mp > 300°C, 92% yield. $[MH]^+$ m/z = 341.1.

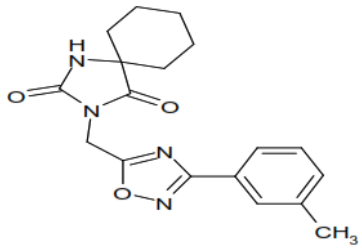
Спектральні параметри:

^{1}H NMR (400 MHz, DMSO-*d6*) δ 9.00 (s, 1H), 7.81 – 7.72 (m, 2H), 7.49 – 7.38 (m, 2H), 4.98 (s, 2H), 2.39 (s, 3H), 1.78 – 1.66 (m, 4H), 1.58 (d, J = 14.0 Hz, 4H), 1.52 (d, J = 12.7 Hz, 1H), 1.31 (d, J = 11.5 Hz, 1H).


C18H20N4O3 340.38
7a
OK(1)

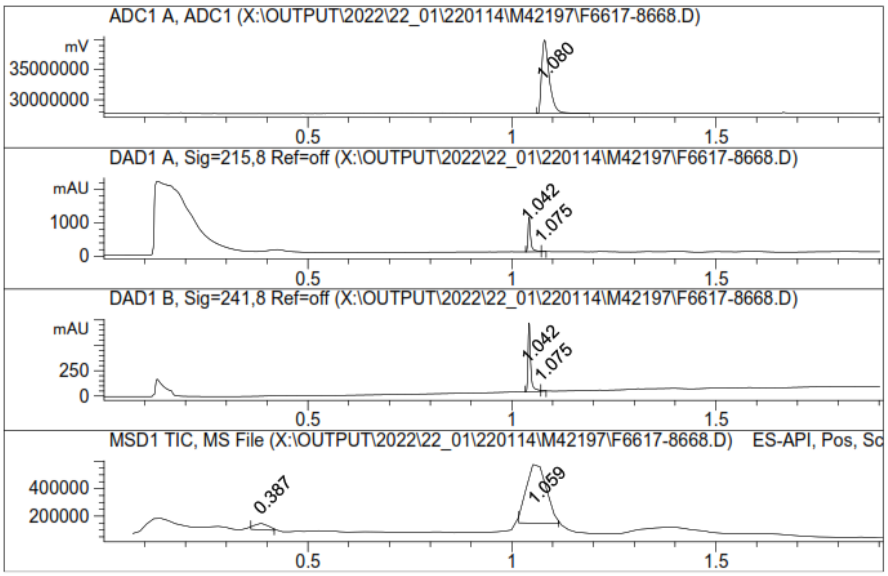
Agilent 1260 LC/MSD SL
Diodearrey G1315B (DAD1A-215nm; DAD1B-241nm)
Mass Quad G6140 (MSD1-Pos, MSD2-Neg)
ELSD Softa 1400 (ADC1 A, ELSD)

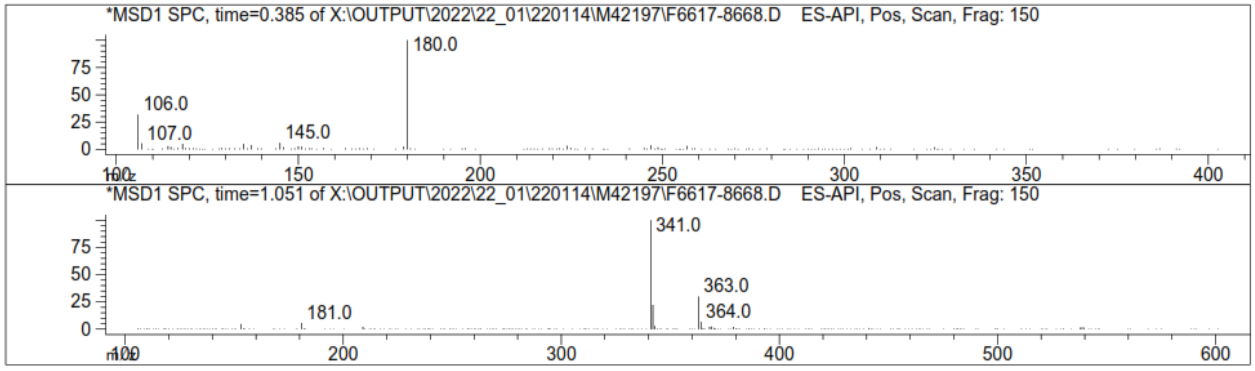
Mobile Phase:A-H2O+0.1%HCOOH;B-MeCN+0.1HCOOH
Separ[illegible] 98 %
Rapid Resolutionn HT Cartige 4.6x30mm,
1.8-Micron, Zorbx SB-C18



Mol.Weight: 340.38
Salt:

7a





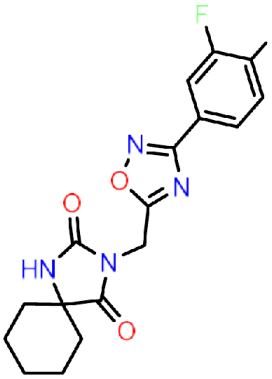
#	Signal	R.Time	Area %
1	ADC1 A, ADC1	1.080	100.000

#	Signal	R.Time	Area %
1	DAD1 A, Sig=215,8 Ref=off	1.042	98.360
2		1.075	1.640

#	Signal	R.Time	Area %
1	DAD1 B, Sig=241,8 Ref=off	1.042	98.635
2		1.075	1.365

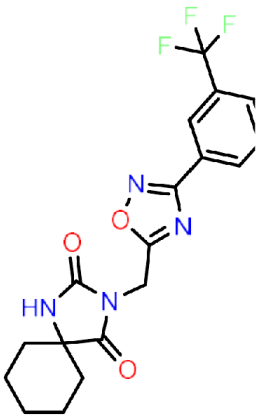
#	Signal	R.Time	Area %
1	MSD1 TIC, MS File	0.387	6.698
2		1.059	93.302

Речовина **7b**. Дуальний пептидоміметичний інгібітор протеаз SARS-COV-2 M^{pro} та PL^{pro}.
Назва: *3-((3-(3,4-Difluorophenyl)-1,2,4-oxadiazol-5-yl)methyl)-1,3-diazaspiro[4.5] decane-2,4-dione*



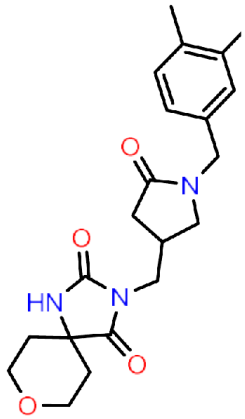
White powder, mp > 300°C, 89% yield. $[MH]^+$ m/z = 363.2.
Спектральні параметри:
^{1}H NMR (400 MHz, DMSO-*d6*) δ 9.01 (s, 1H), 7.96 (ddd, J = 11.1, 7.7, 2.1 Hz, 1H), 7.84 (ddt, J = 7.9, 4.4, 1.7 Hz, 1H), 7.66 (dt, J = 10.5, 8.4 Hz, 1H), 5.00 (s, 2H), 1.72 (dd, J = 14.4, 10.6 Hz, 2H), 1.68 (s, 1H), 1.62 – 1.47 (m, 6H), 1.32 (t, J = 11.7 Hz, 1H).

Речовина **7c**. Дуальний пептидоміметичний інгібітор протеаз SARS-COV-2 M^{pro} та PL^{pro}.
Назва: *3-((3-(3-(Trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)methyl)-1,3-diazaspiro [4.5]decane-2,4-dione*



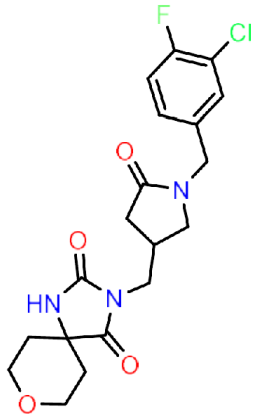
White powder, mp > 300°C, 81% yield. $[MH]^+$ m/z = 395.2.
Спектральні параметри:
^{1}H NMR (400 MHz, DMSO-*d6*) δ 9.01 (s, 1H), 8.27 (d, J = 7.9 Hz, 1H), 8.19 (d, J = 2.2 Hz, 1H), 8.00 (d, J = 7.9 Hz, 1H), 7.84 (t, J = 7.8 Hz, 1H), 5.02 (s, 2H), 1.79 – 1.65 (m, 4H), 1.57 (t, J = 14.3 Hz, 5H), 1.31 (d, J = 11.8 Hz, 1H).

Речовина **7d**. Дуальний пептидоміметичний інгібітор протеаз SARS-COV-2 M^{pro} та PL^{pro}.
Назва: *3-((1-(3,4-Dimethylbenzyl)-5-oxopyrrolidin-3-yl)methyl)-8-oxa-1,3-diazaspiro [4.5]decane-2,4-dione*



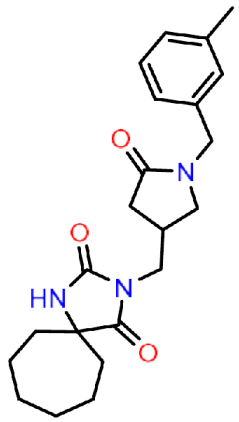
White powder, mp > 300°C, 78% yield. $[MH]^+$ m/z = 386.2.
Спектральні параметри:
^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.78 (s, 1H), 7.13 – 7.06 (m, 1H), 7.05 – 6.96 (m, 2H), 4.49 (dt, J = 12.3, 1.0 Hz, 1H), 4.41 (dt, J = 12.3, 1.0 Hz, 1H), 4.18 (dd, J = 12.5, 4.8 Hz, 1H), 3.90 – 3.78 (m, 2H), 3.70 – 3.48 (m, 5H), 2.66 – 2.48 (m, 2H), 2.37 (ddt, J = 14.4, 6.4, 3.1 Hz, 3H), 2.24 (d, J = 1.0 Hz, 3H), 2.20 (s, 3H), 2.02 (d, J = 14.6, 6.4, 3.7 Hz, 2H).

Речовина **7e**. Дуальний пептидоміметичний інгібітор протеаз SARS-COV-2 M^{pro} та PL^{pro}.
Назва: *3-((1-(3-Chloro-4-fluorobenzyl)-5-oxopyrrolidin-3-yl)methyl)-8-oxa-1,3-diazaspiro[4.5]decane-2,4-dione*



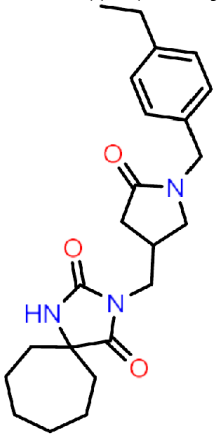
White powder, mp > 300°C, 80% yield. $[MH]^+$ m/z = 410.2.
Спектральні параметри:
^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.90 (s, 1H), 7.46 – 7.33 (m, 2H), 7.22 (ddd, J = 8.1, 4.8, 2.1 Hz, 1H), 4.36 (d, J = 15.1 Hz, 1H), 4.28 (d, J = 15.2 Hz, 1H), 3.81 (dt, J = 11.7, 4.3 Hz, 2H), 3.66 – 3.55 (m, 2H), 3.47 – 3.37 (m, 2H), 3.03 (dd, J = 9.9, 5.3 Hz, 1H), 2.63 (dd, J = 14.6, 7.3 Hz, 1H), 2.43 (dd, J = 16.7, 8.9 Hz, 1H), 2.12 (dd, J = 16.7, 6.3 Hz, 1H), 1.90 – 1.78 (m, 2H), 1.48 (d, J = 13.5 Hz, 2H), 1.24 (d, J = 9.9 Hz, 1H).

Речовина **7f**. Дуальний пептидоміметичний інгібітор протеаз SARS-COV-2 M^{pro} та PL^{pro}.
Назва: *3-((1-(3-Methylbenzyl)-5-oxopyrrolidin-3-yl)methyl)-1,3-diazaspiro[4.6] undecane-2,4-dione*



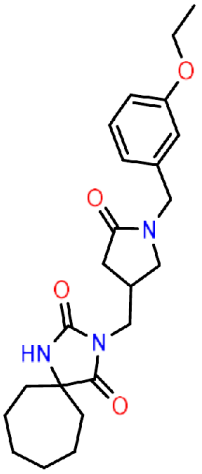
White powder, mp > 300°C, 82% yield. $[MH]^+$ m/z = 383.2.
Спектральні параметри:
^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.98 (s, 1H), 7.27 – 7.12 (m, 3H), 7.11 – 7.04 (m, 1H), 4.50 – 4.42 (m, 1H), 4.42 – 4.34 (m, 1H), 4.18 (dd, J = 12.5, 4.8 Hz, 1H), 3.90 – 3.78 (m, 2H), 3.57 (dd, J = 11.3, 4.4 Hz, 1H), 2.66 – 2.48 (m, 2H), 2.36 (dd, J = 14.5, 6.3 Hz, 1H), 2.29 (s, 3H), 1.85 – 1.73 (m, 2H), 1.61 – 1.31 (m, 10H).

Речовина **7g**. Дуальний пептидоміметичний інгібітор протеаз SARS-COV-2 M^{pro} та PL^{pro}.
Назва: *3-((1-(4-Ethylbenzyl)-5-oxopyrrolidin-3-yl)methyl)-1,3-diazaspiro[4.6]undecane-2,4-dione*



White powder, mp > 300°C, 84% yield. $[MH]^+$ m/z = 397.2.
Спектральні параметри:
^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.91 (s, 1H), 7.23 (dt, J = 8.0, 0.9 Hz, 2H), 7.15 (dt, J = 8.2, 1.0 Hz, 2H), 4.50 (dt, J = 12.6, 1.0 Hz, 1H), 4.46 – 4.38 (m, 1H), 4.18 (dd, J = 12.5, 4.8 Hz, 1H), 3.90 – 3.78 (m, 2H), 3.57 (dd, J = 11.3, 4.4 Hz, 1H), 2.66 – 2.57 (m, 3H), 2.57 – 2.48 (m, 1H), 2.36 (dd, J = 14.5, 6.3 Hz, 1H), 1.85 – 1.73 (m, 2H), 1.59 – 1.31 (m, 10H), 1.20 (t, J = 7.2 Hz, 3H).

Речовина **7h**. Дуальний пептидоміметичний інгібітор протеаз SARS-COV-2 M^{pro} та PL^{pro}.
Назва: *3-((1-(3-Ethoxybenzyl)-5-oxopyrrolidin-3-yl)methyl)-1,3-diazaspiro[4.6] undecane-2,4-dione*



White powder, mp > 300°C, 86% yield. $[MH]^+$ m/z = 413.2.
Спектральні параметри:
^{1}H 1H NMR (400 MHz, DMSO-*d6*) δ 8.81 (s, 1H), 7.23 (t, J = 8.1 Hz, 1H), 7.11 (dd, J = 8.3, 2.1, 1H), 6.95 – 6.88 (m, 1H), 6.85 (td, J = 2.1, 1.0 Hz, 1H), 4.52 (dt, J = 12.3, 1.0 Hz, 1H), 4.45 (dt, J = 12.5, 1.0 Hz, 1H), 4.18 (dd, J = 12.5, 4.8 Hz, 1H), 4.05 (q, J = 6.7 Hz, 2H), 3.90 – 3.78 (m, 2H), 3.57 (dd, J = 11.2, 4.4 Hz, 1H), 2.66 – 2.48 (m, 2H), 2.36 (dd, J = 14.5, 6.3 Hz, 1H), 1.85 – 1.73 (m, 2H), 1.66 – 1.55 (m, 2H), 1.57 – 1.37 (m, 8H), 1.35 (t, J = 6.7 Hz, 3H).