

Supporting information for

Synthesis, molecular docking, *in vitro* and *in vivo* studies of novel dimorpholinoquinazoline-based potential inhibitors of PI3K/Akt/mTOR pathway

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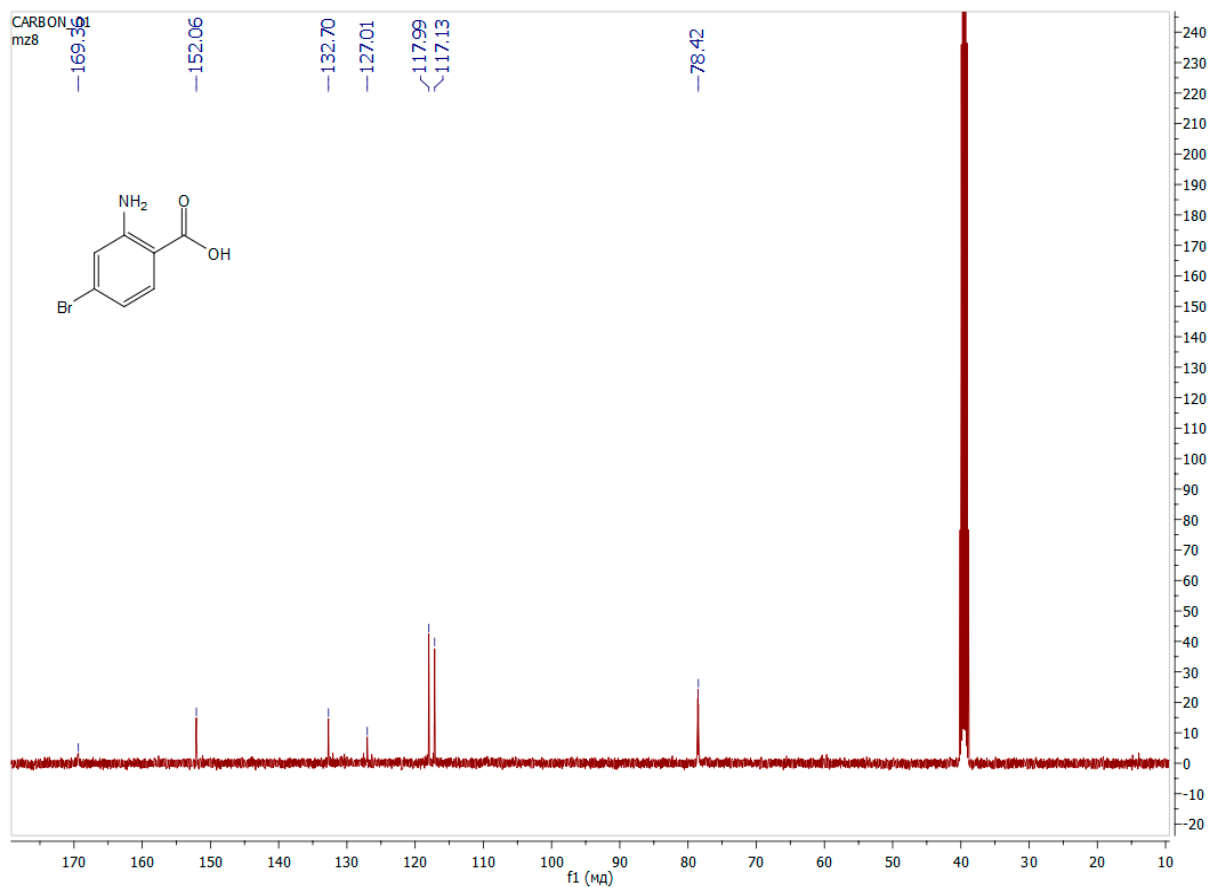
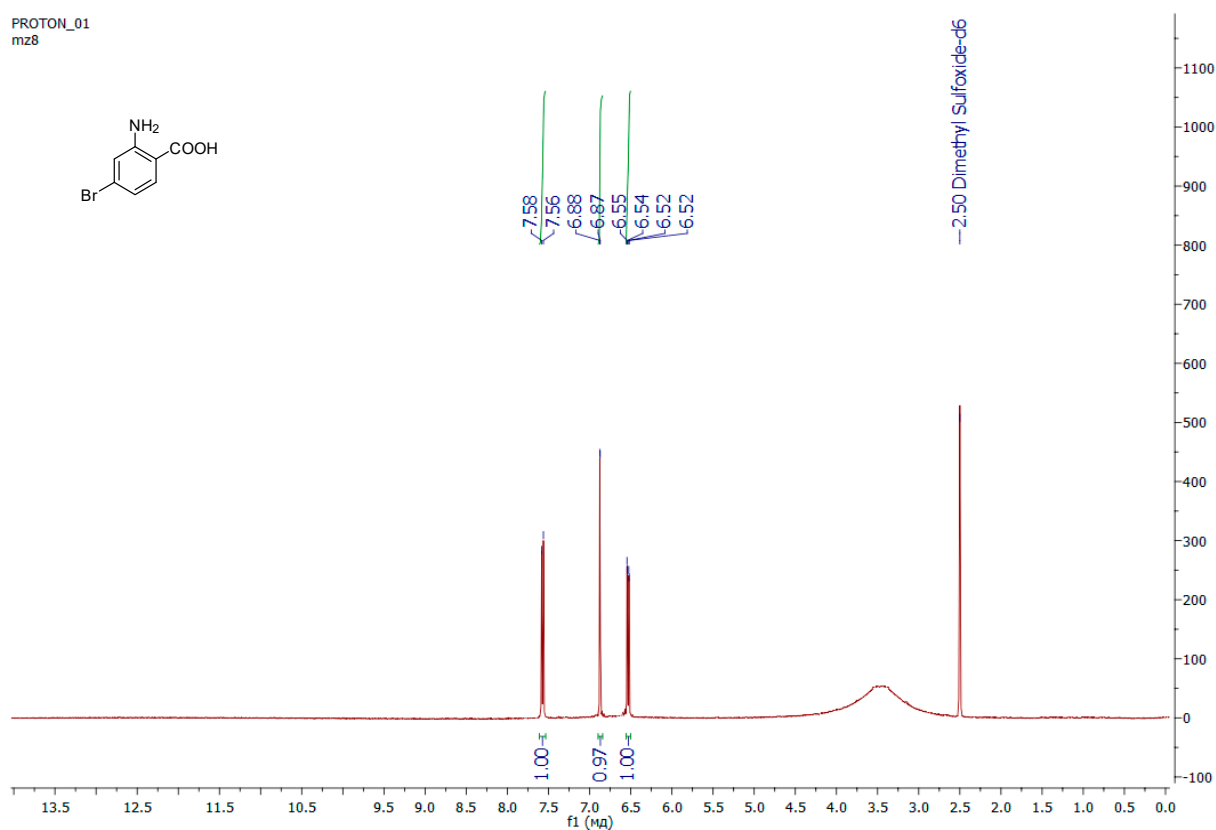
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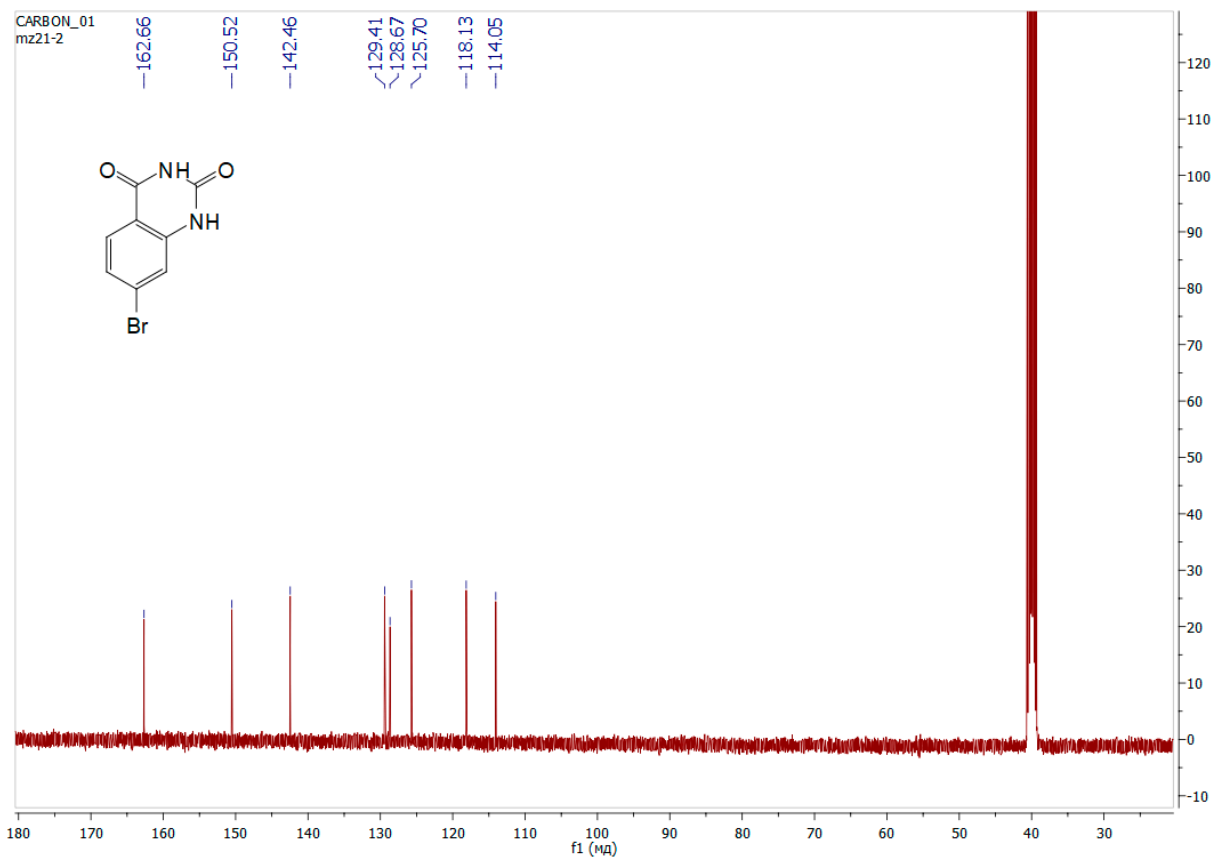
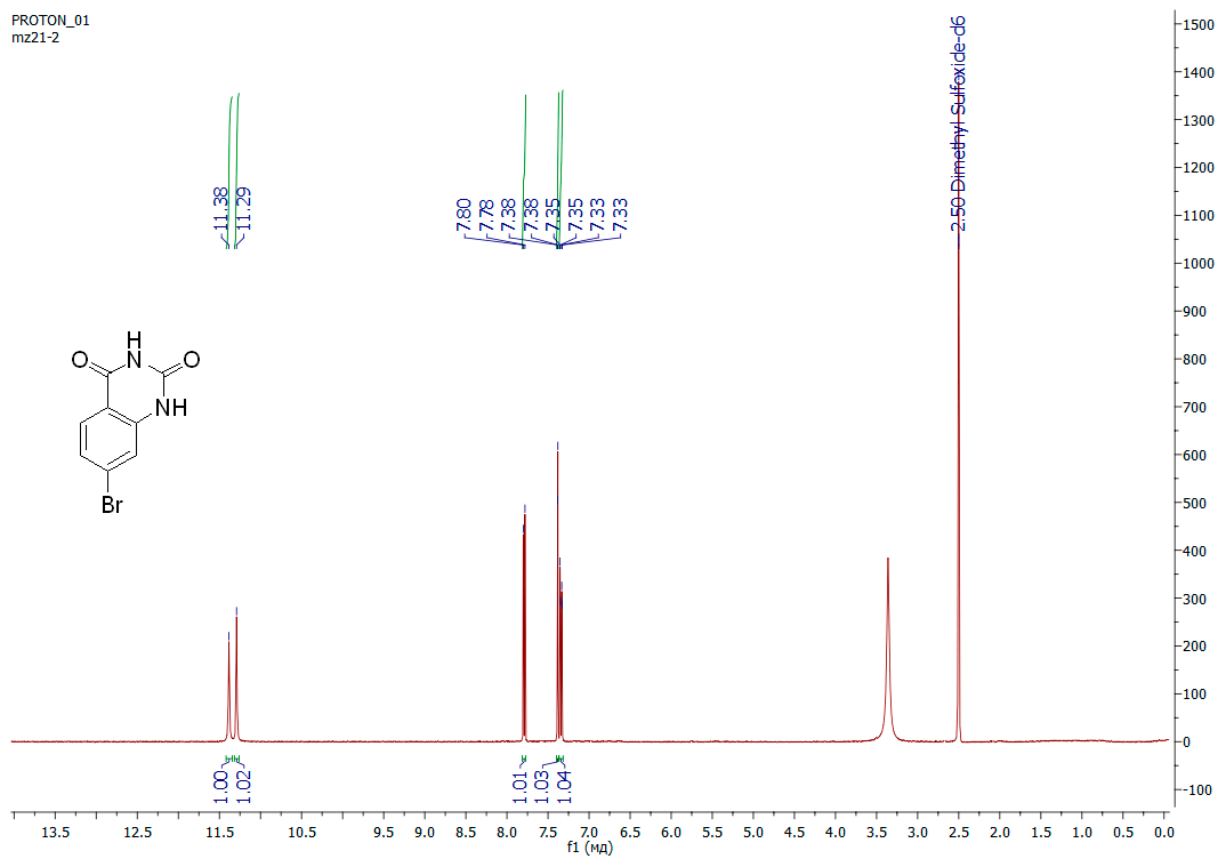
NMR spectra for compounds 2-6, 7a-l

2-amino-4-bromobenzoic acid 2

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mz8

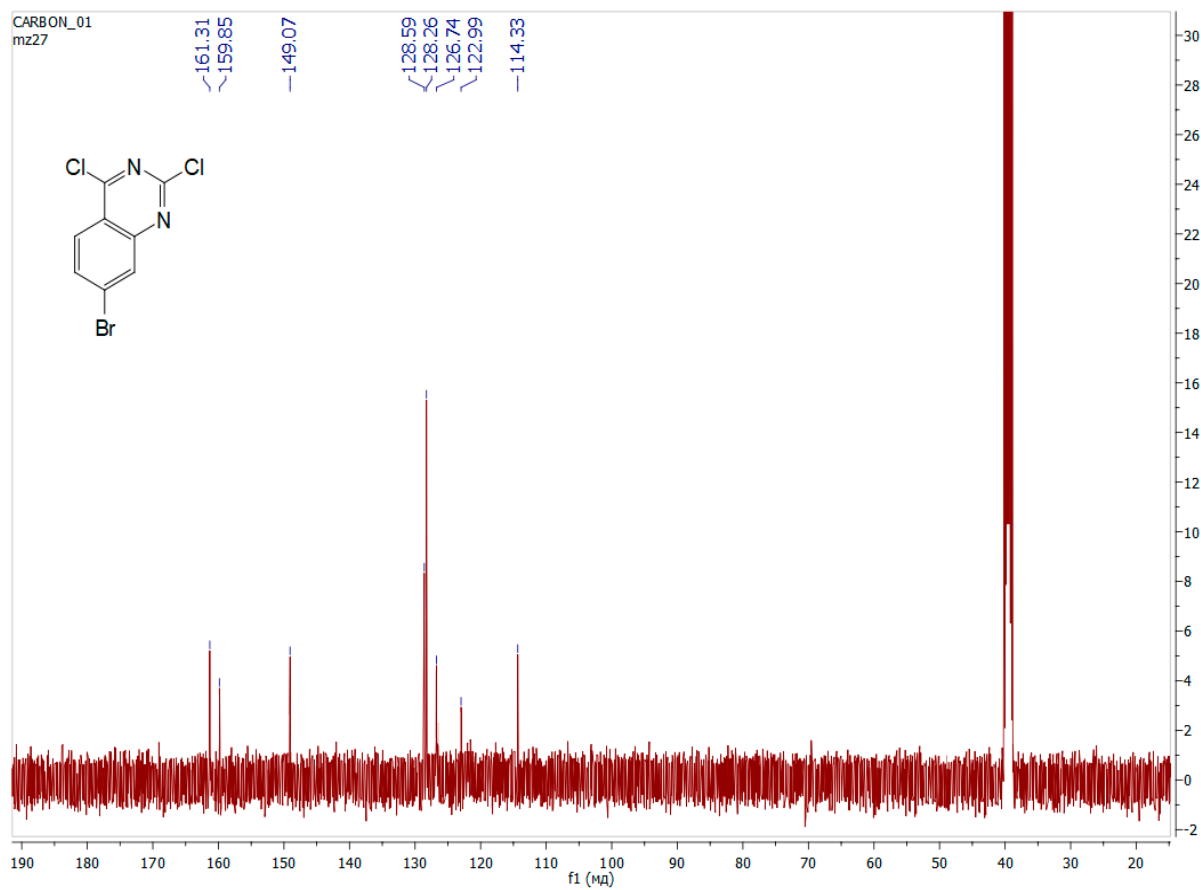
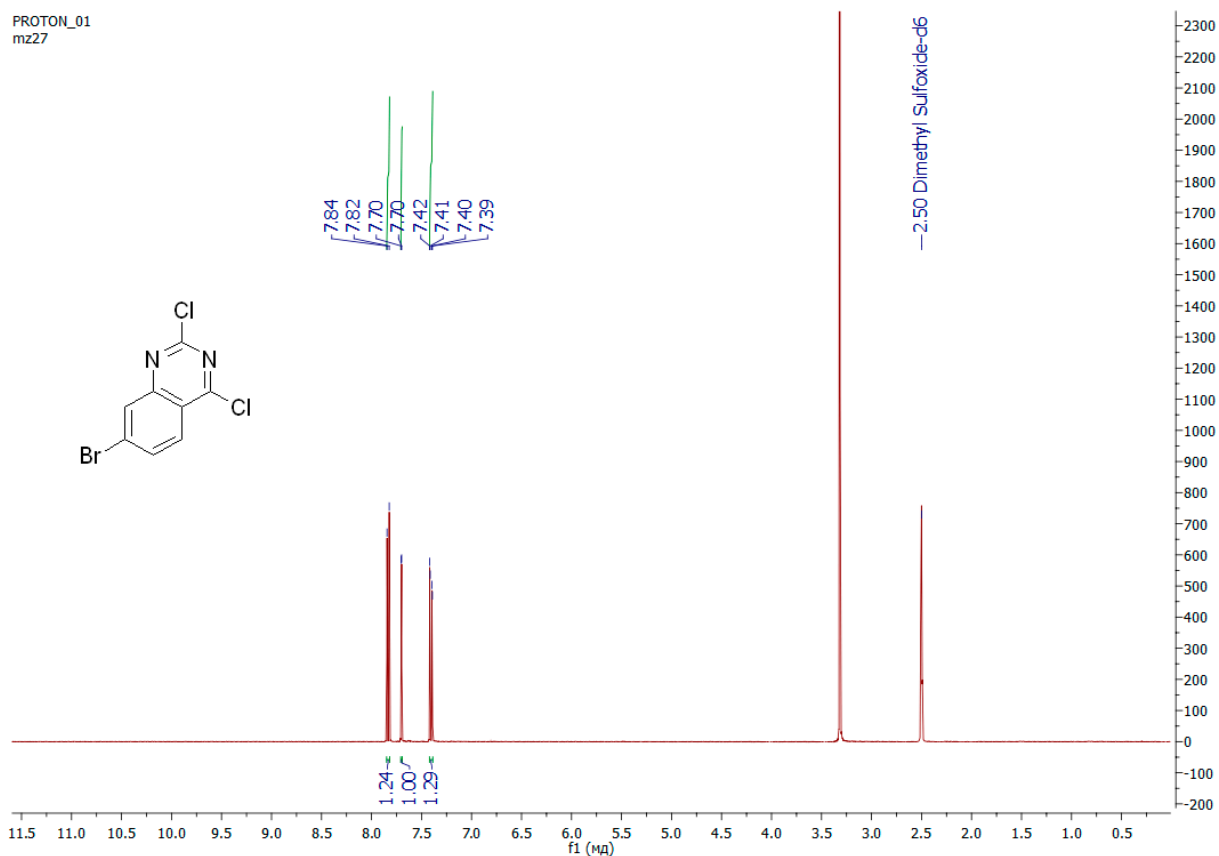


7-bromoquinazoline-2,4(1H,3H)-dione **3**



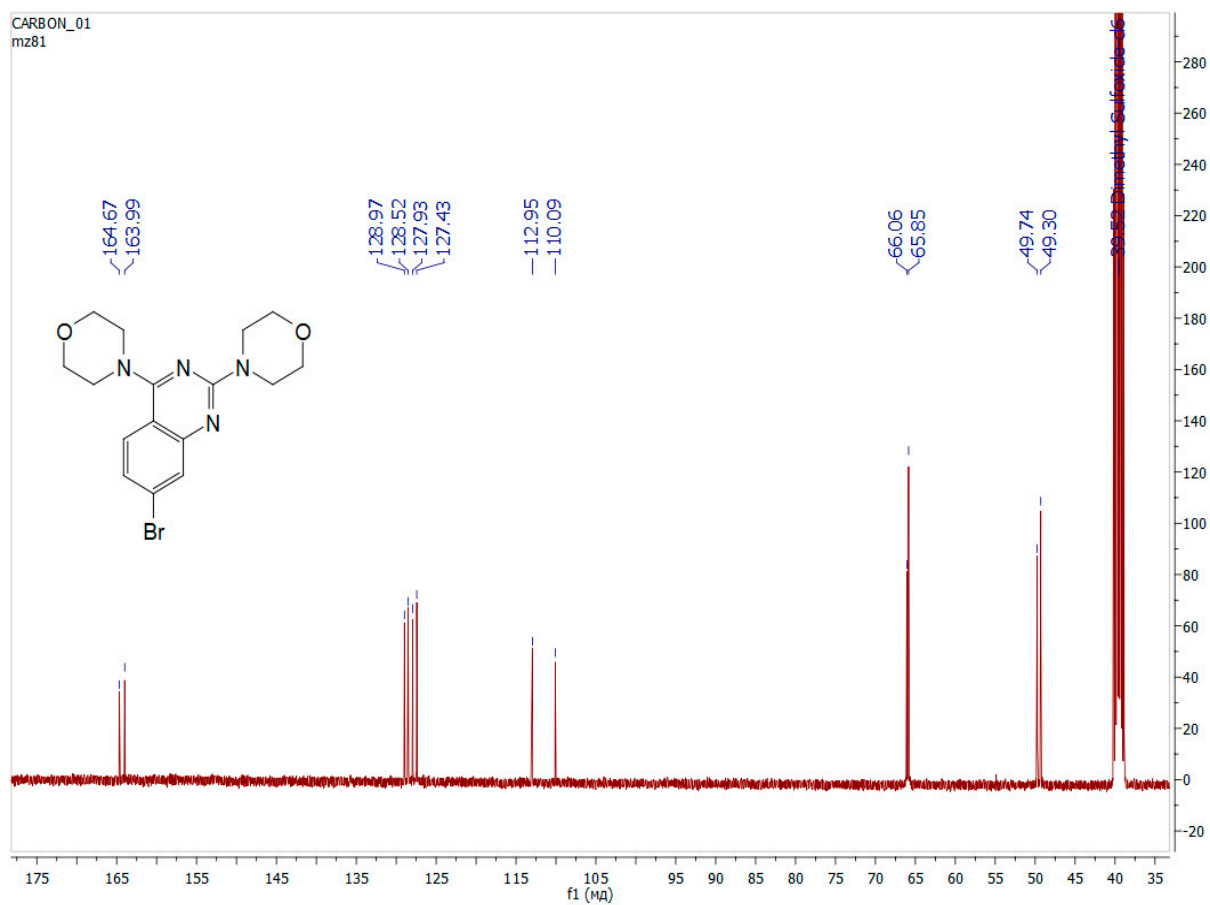
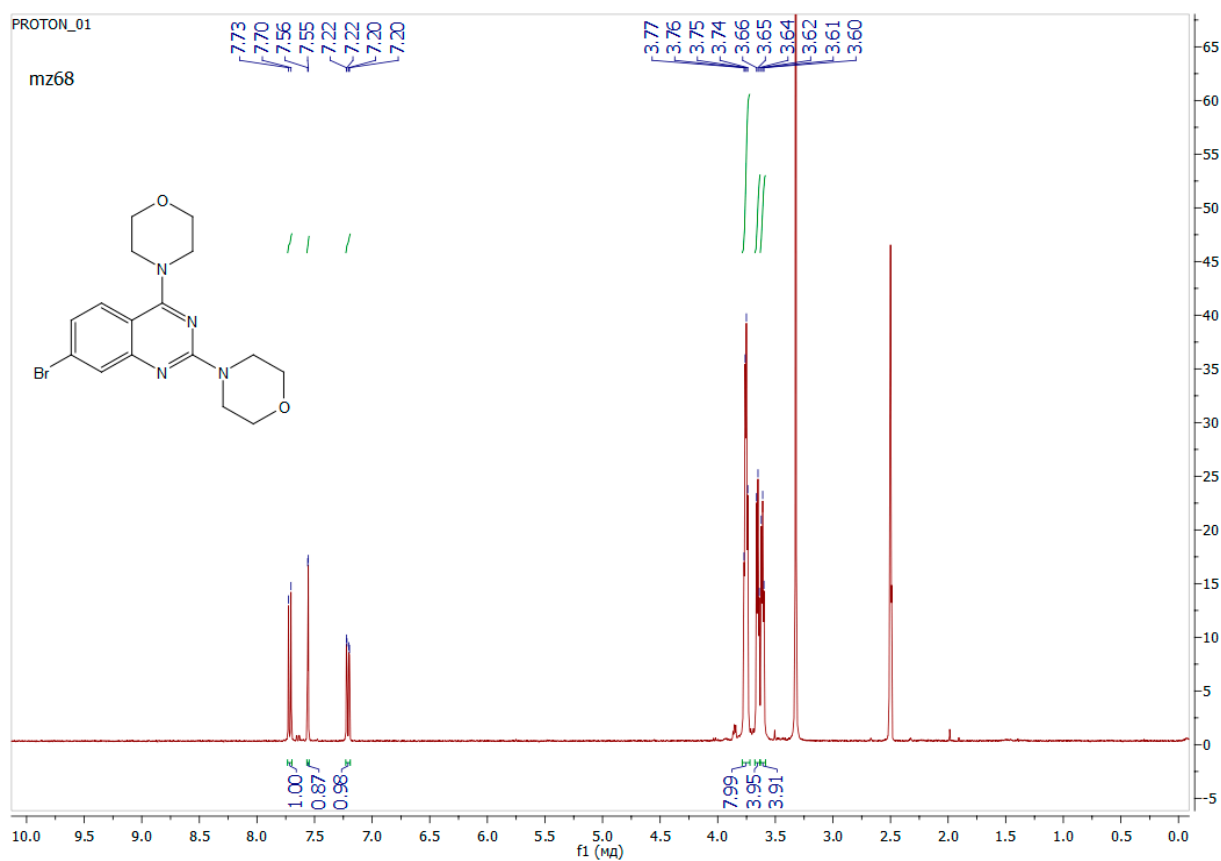
7-bromo-2,4-dichloroquinazoline

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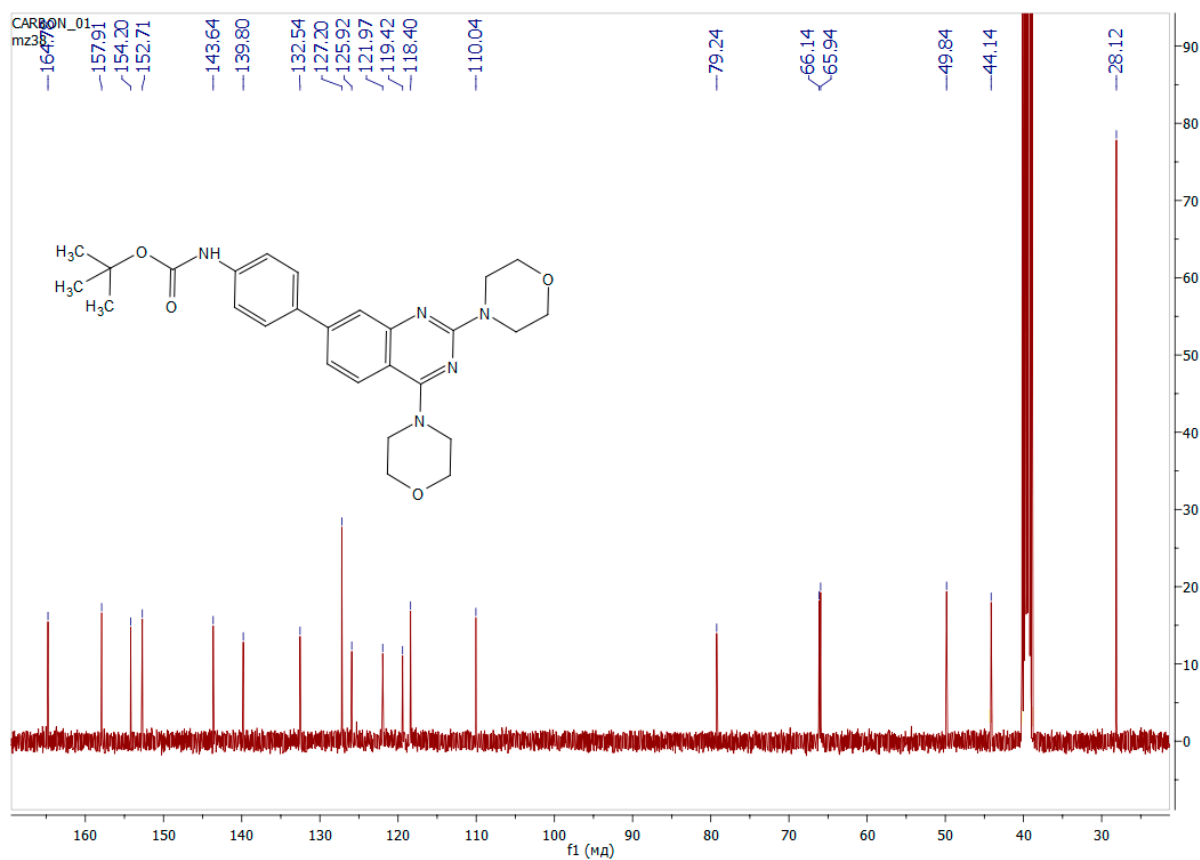
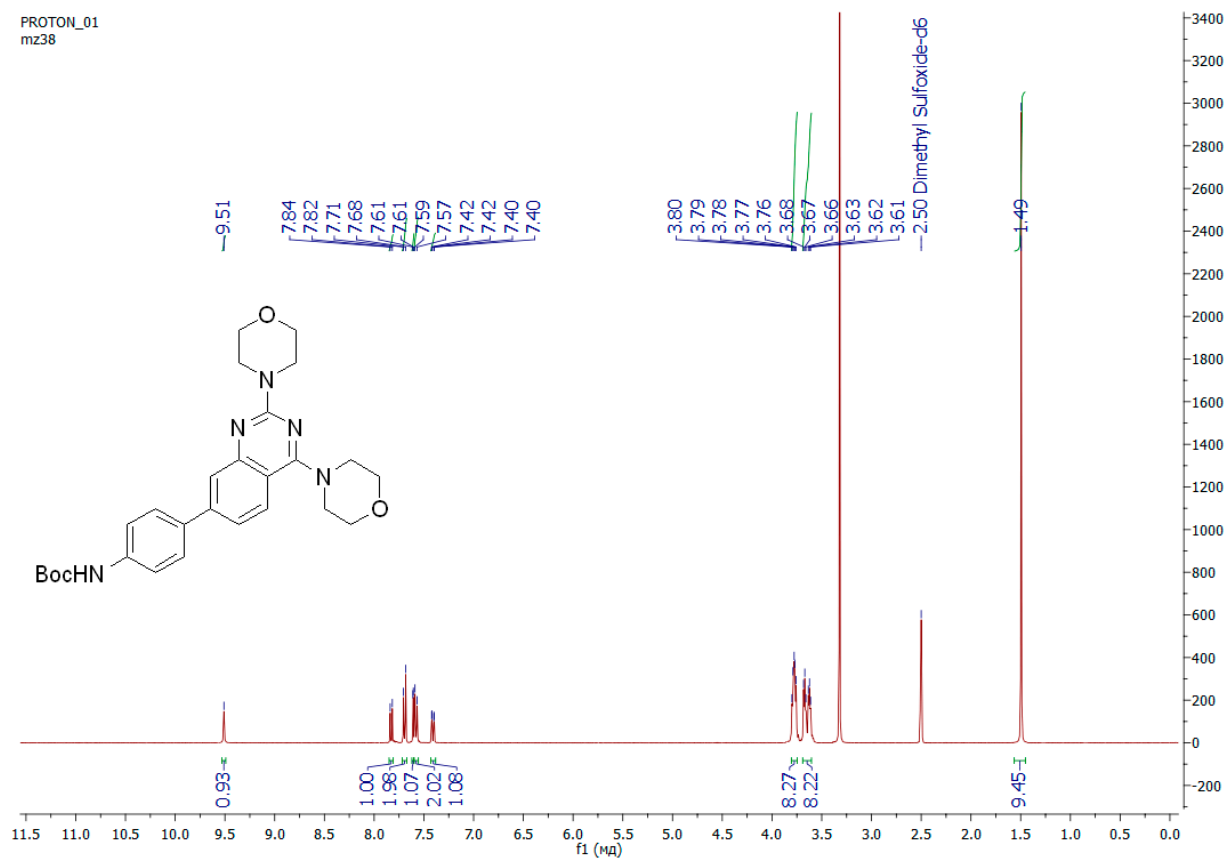


4,4'-(7-bromoquinazoline-2,4-diyl)dimorpholine

5

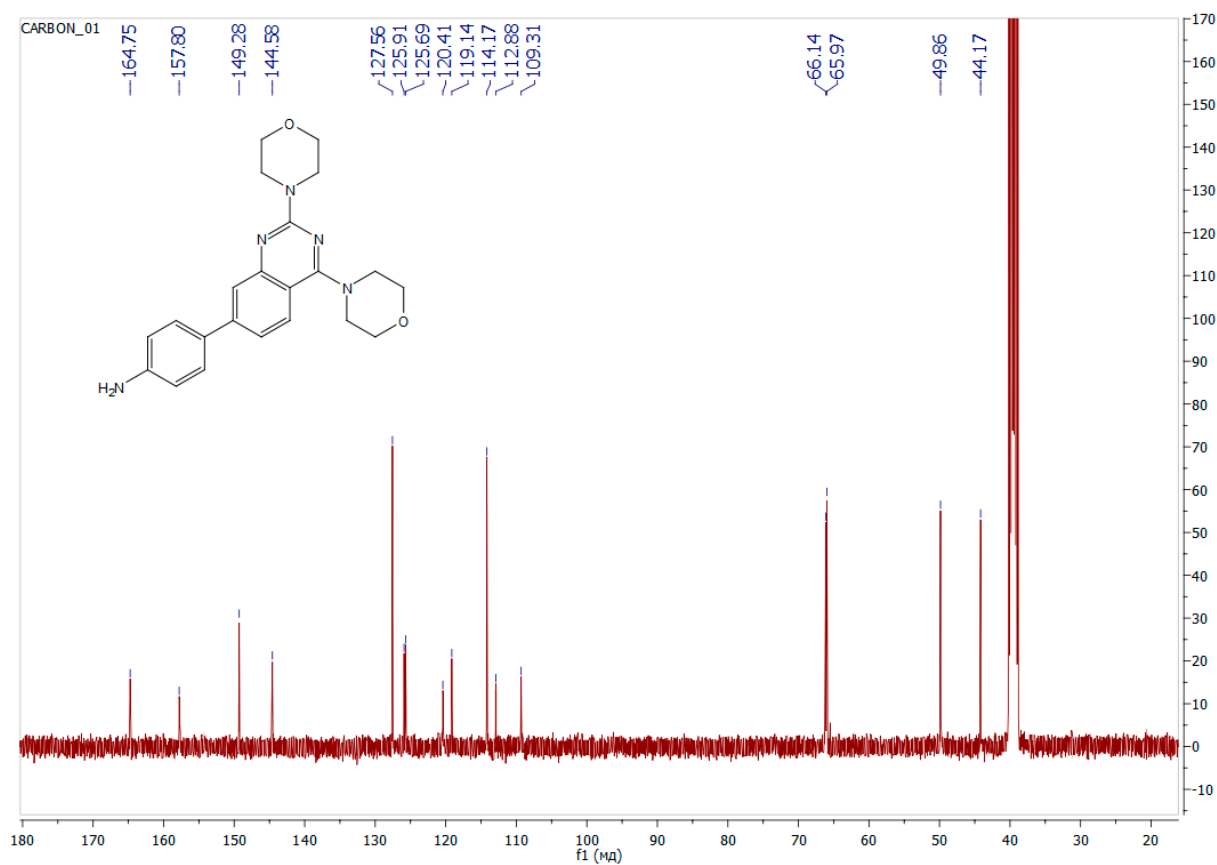
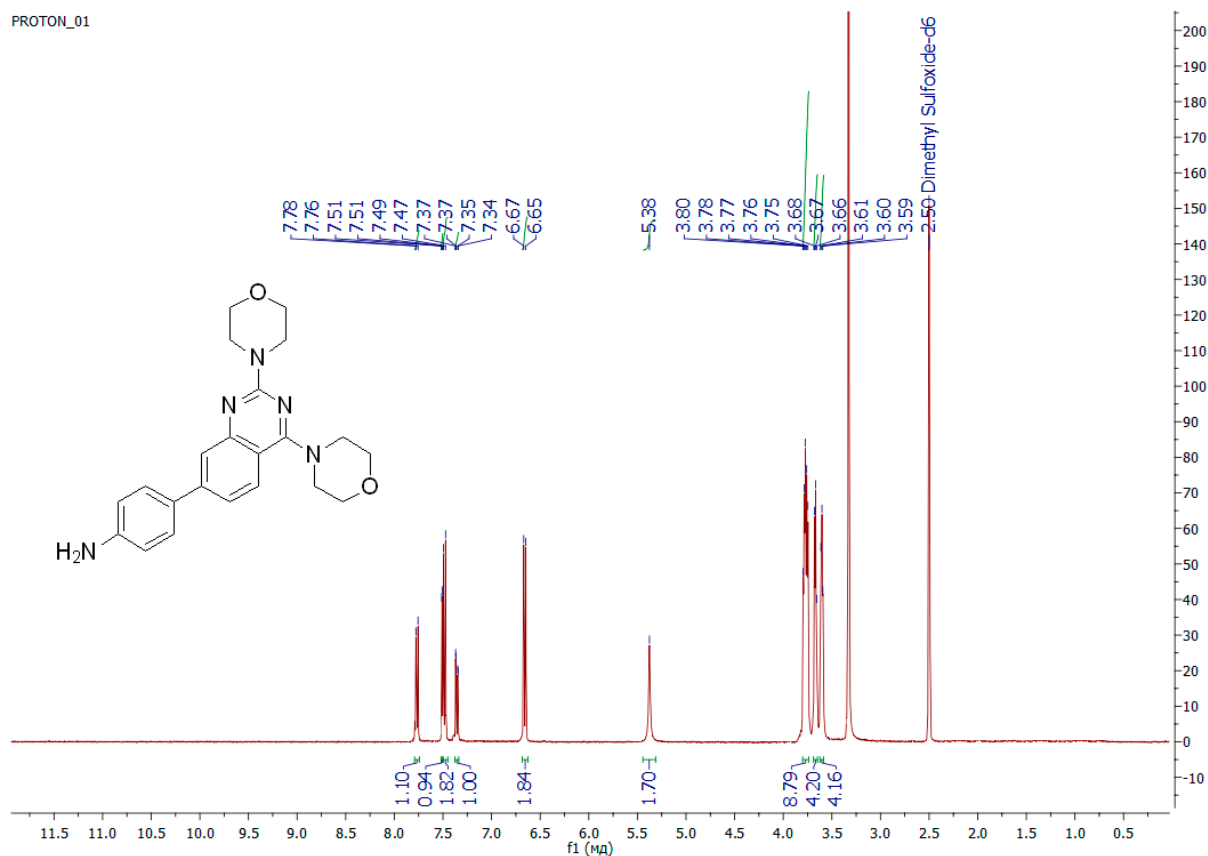


tert-butyl (4-(2,4-dimorpholinoquinazolin-7-yl)phenyl)carbamate



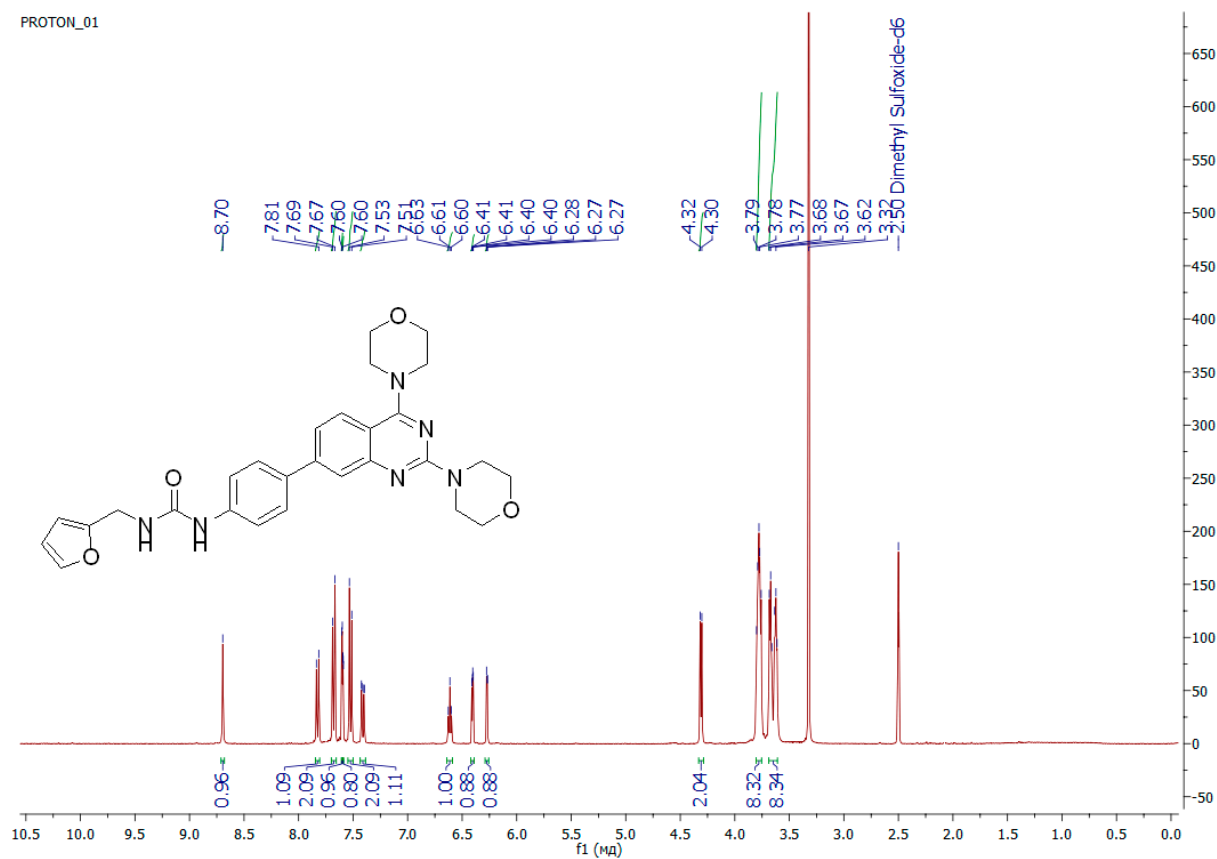
4-(2,4-dimorpholinoquinazolin-7-yl)aniline

6

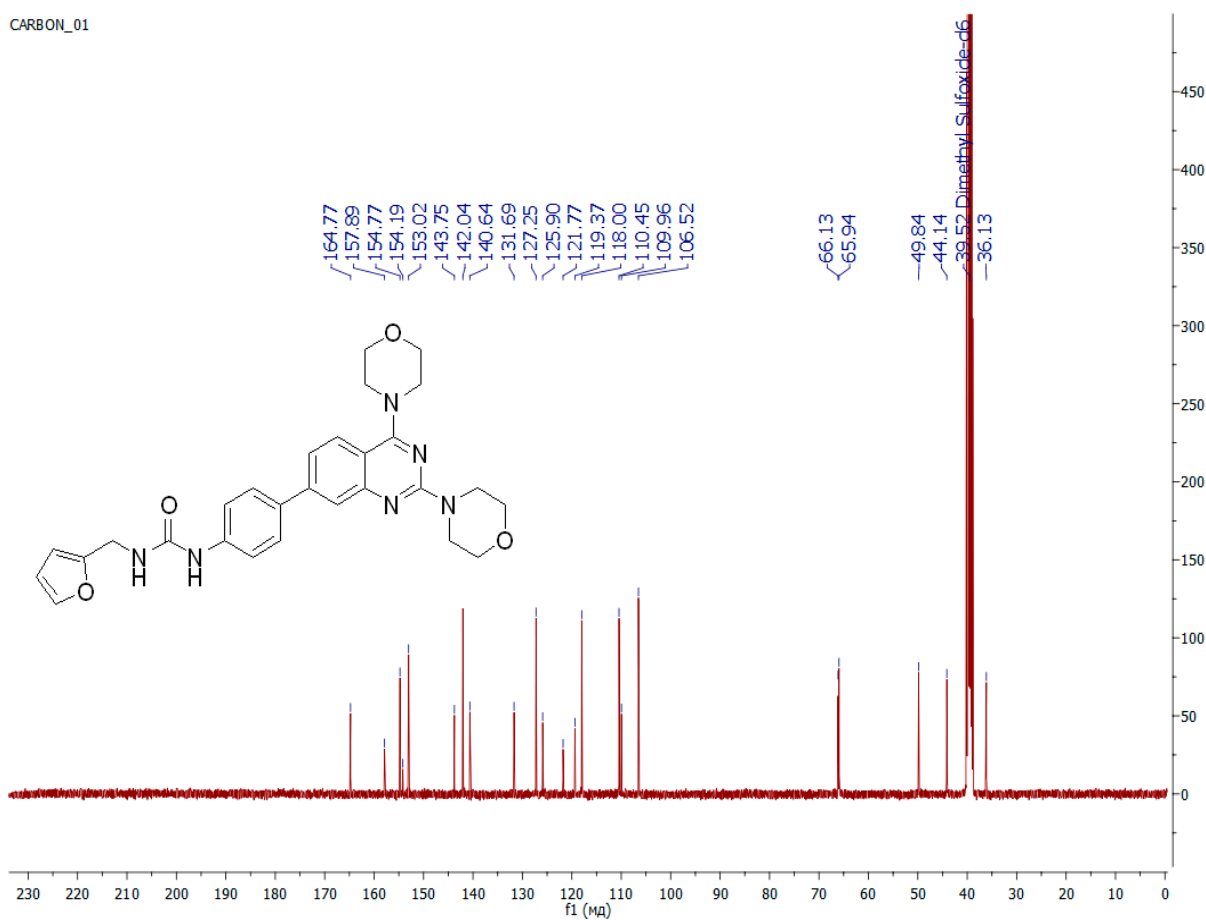


1-(4-(2,4-dimorpholinoquinazolin-7-yl)phenyl)-3-(furan-2-ylmethyl)urea **7a**

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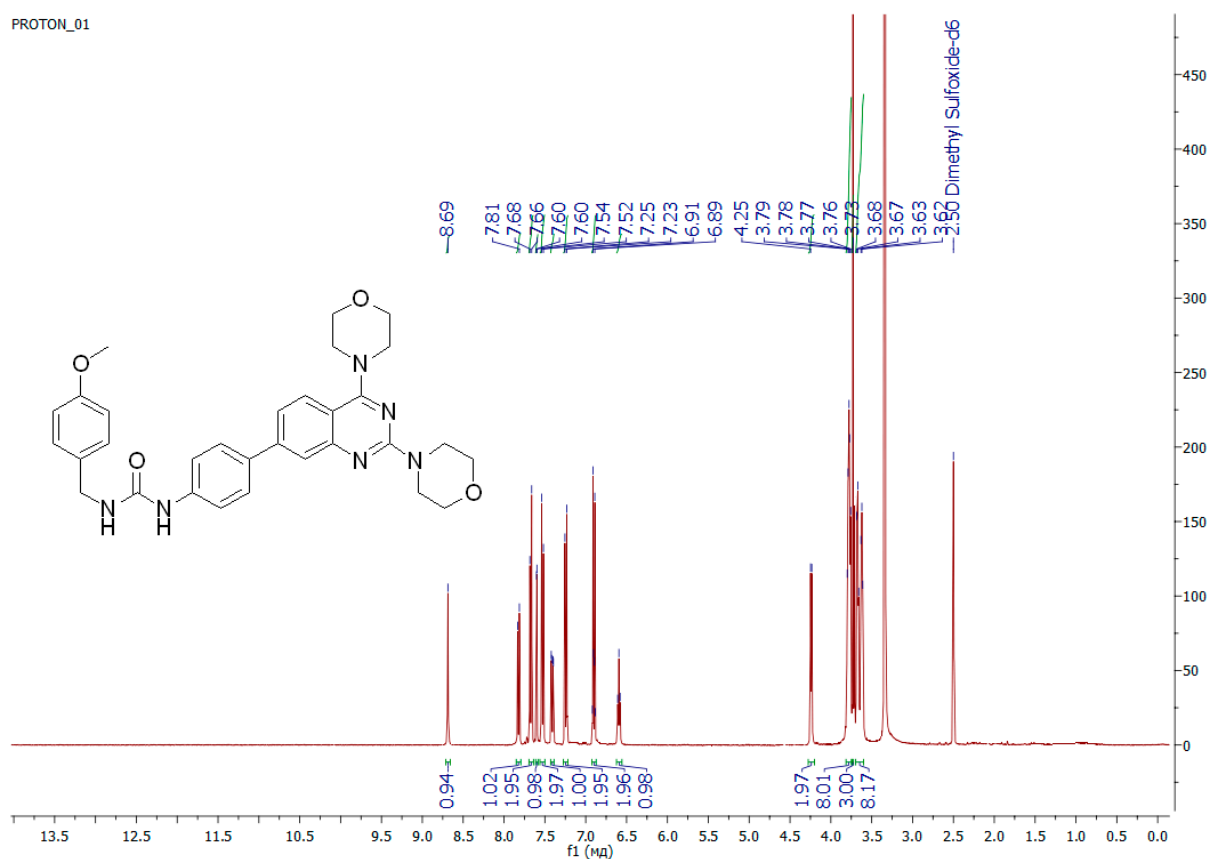


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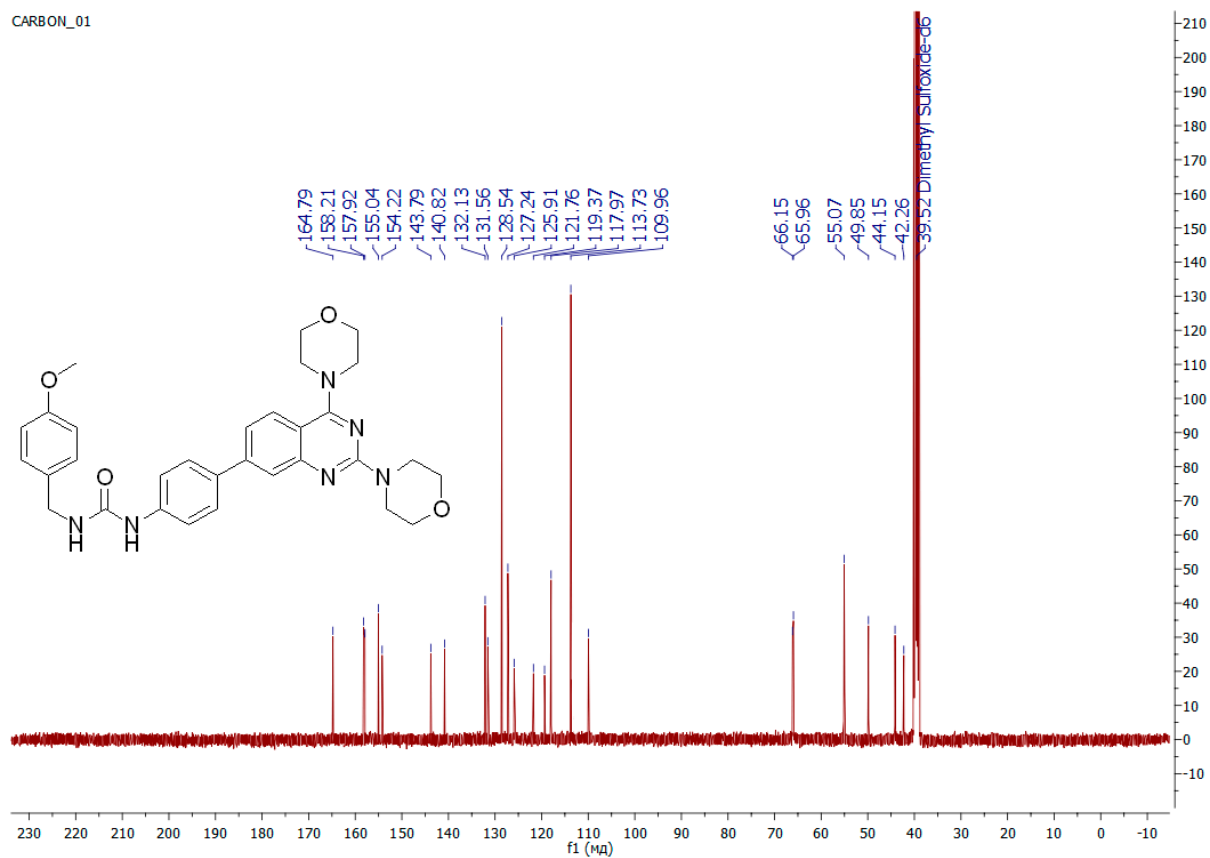


1-(4-(2,4-dimorpholinoquinazolin-7-yl)phenyl)-3-(4-methoxybenzyl)urea
7b

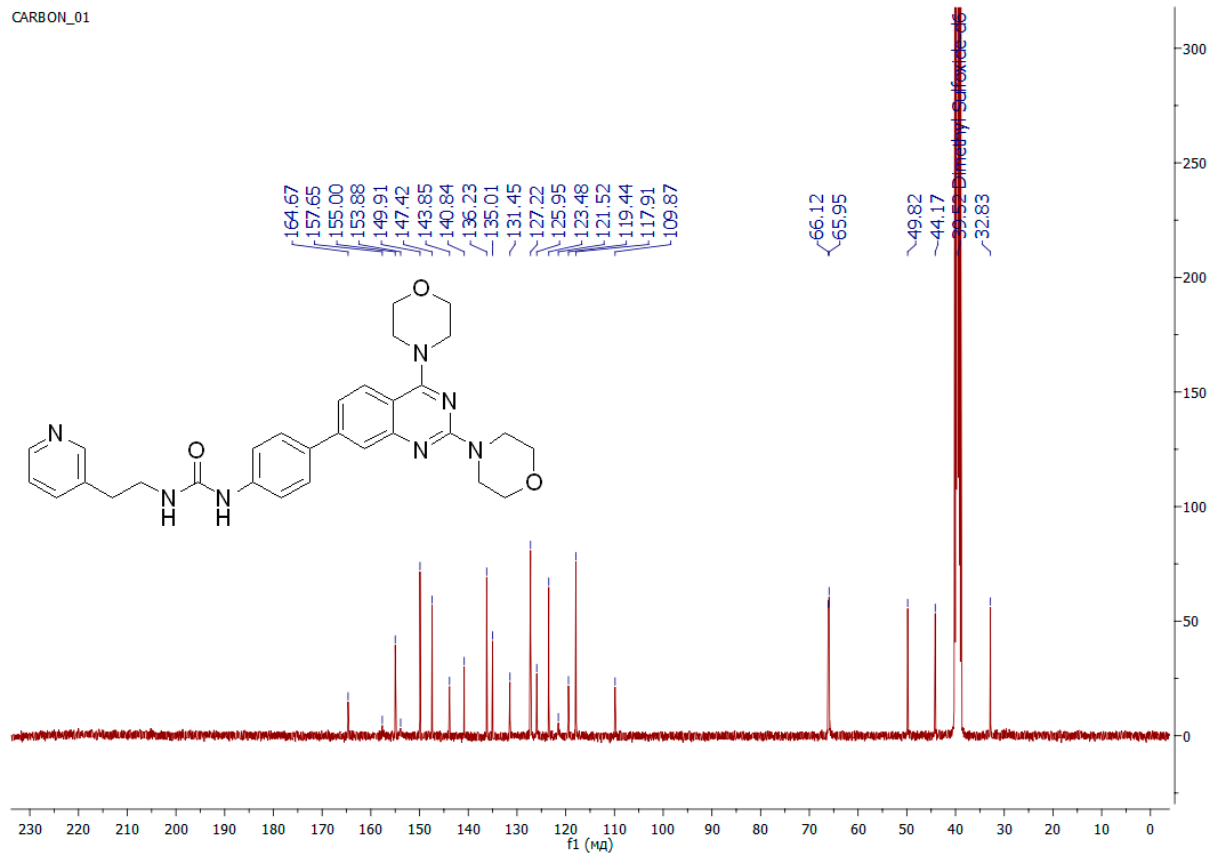
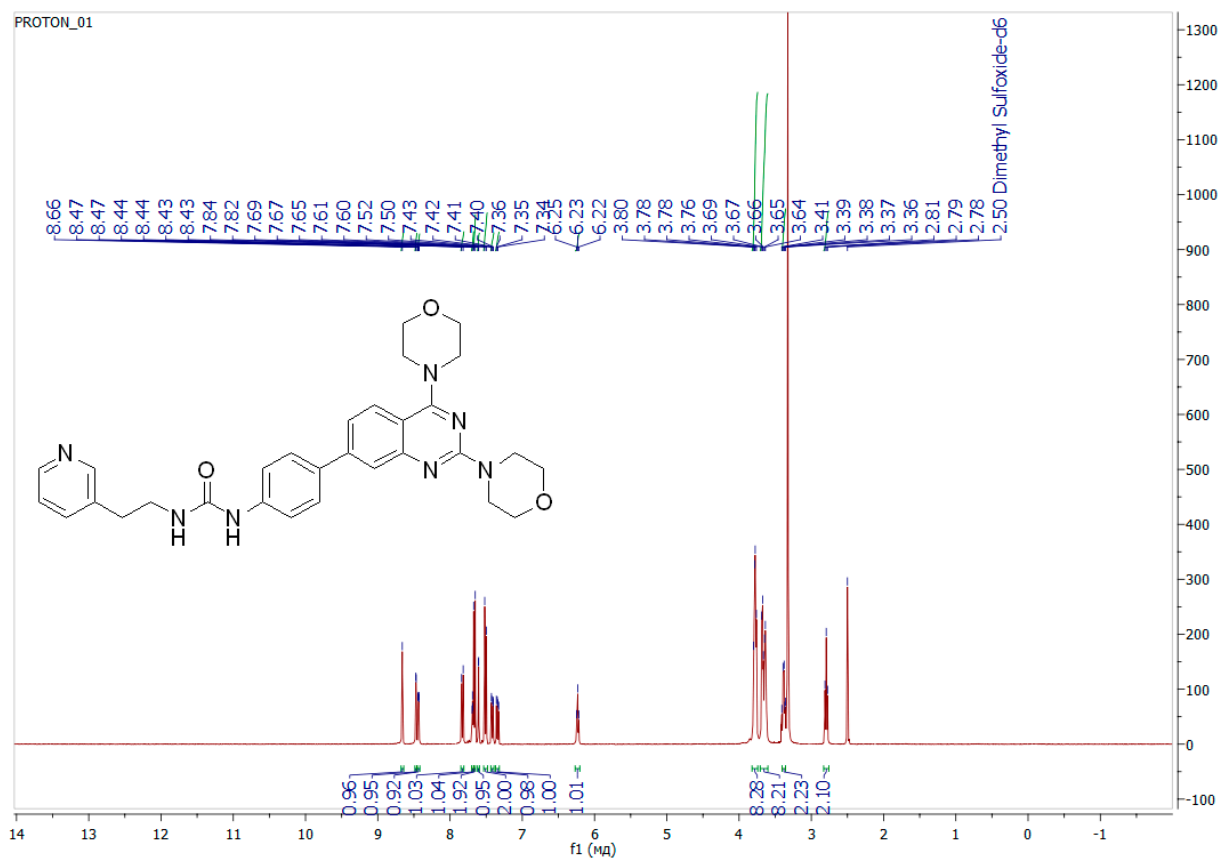
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CARBON_01

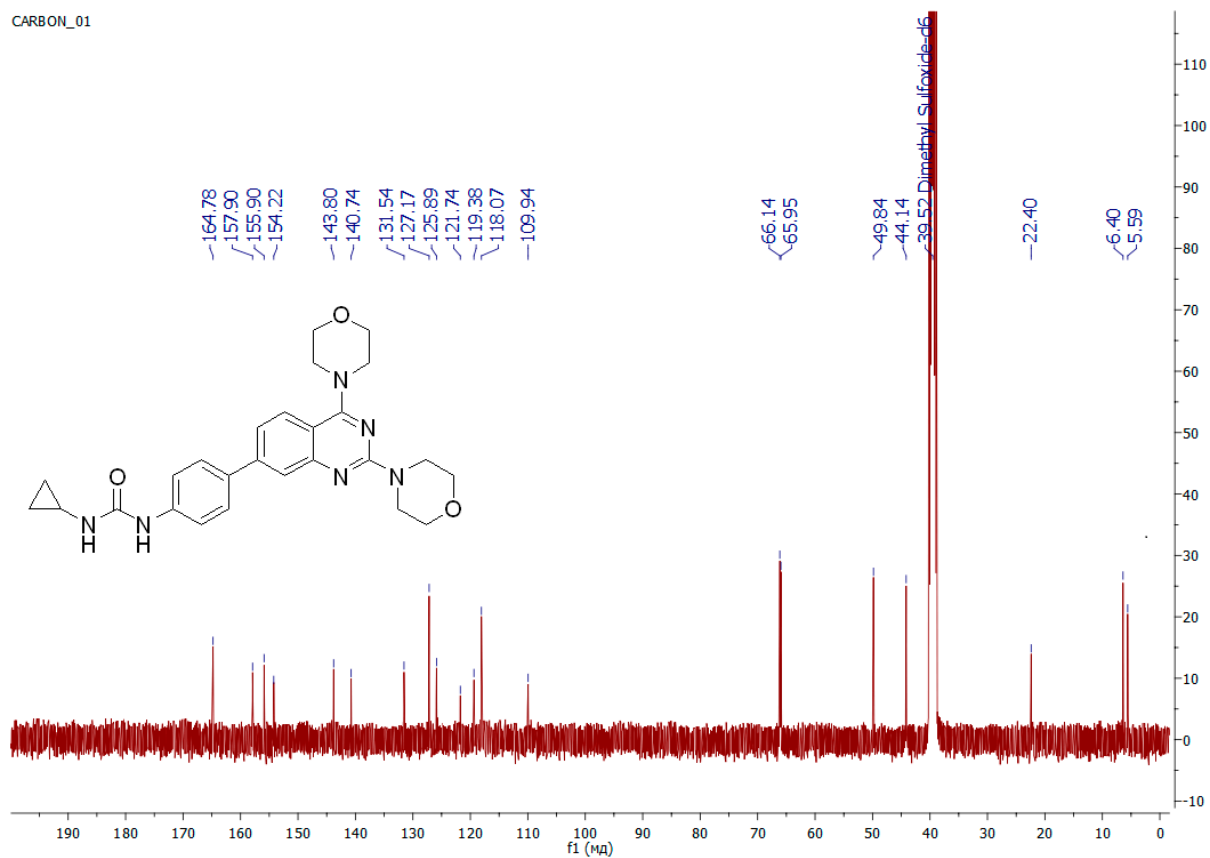
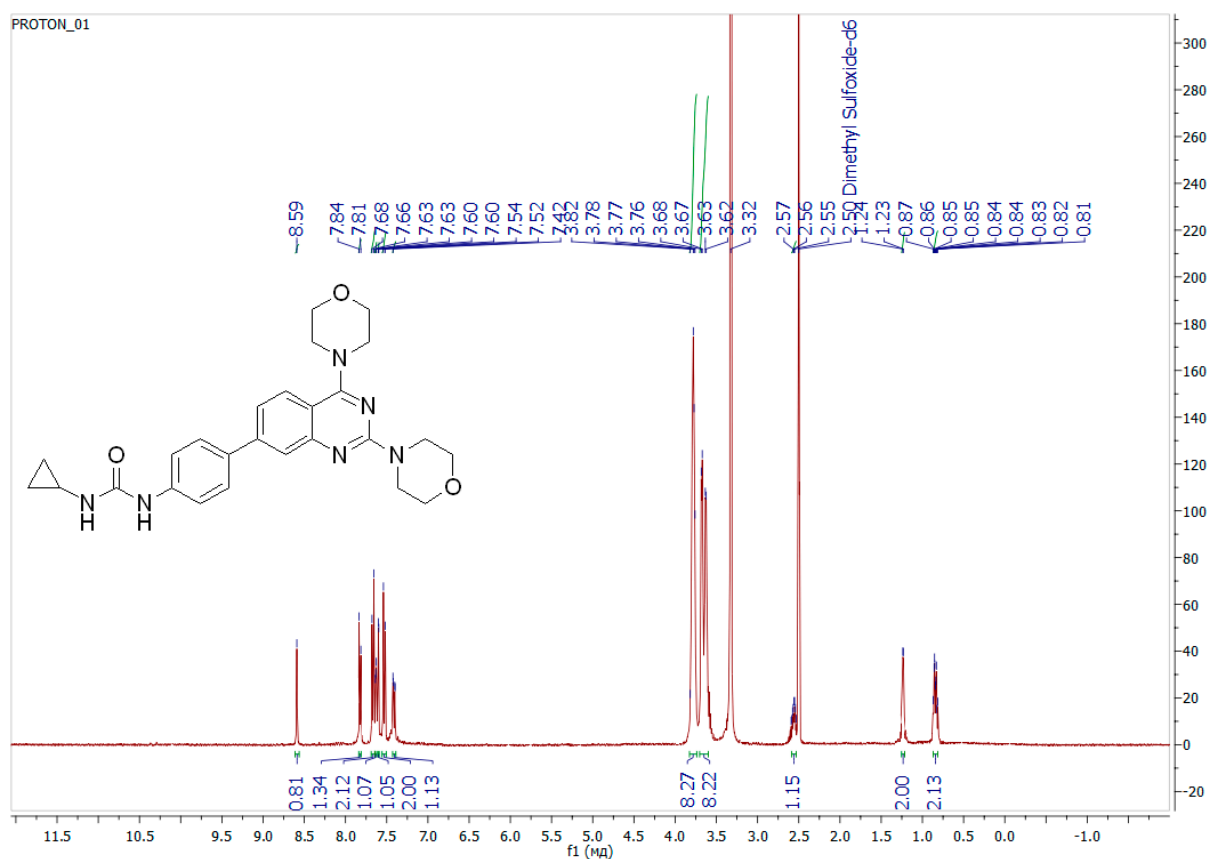


1-(4-(2,4-dimorpholinoquinazolin-7-yl)phenyl)-3-(2-(pyridin-3-yl)ethyl)urea **7c**



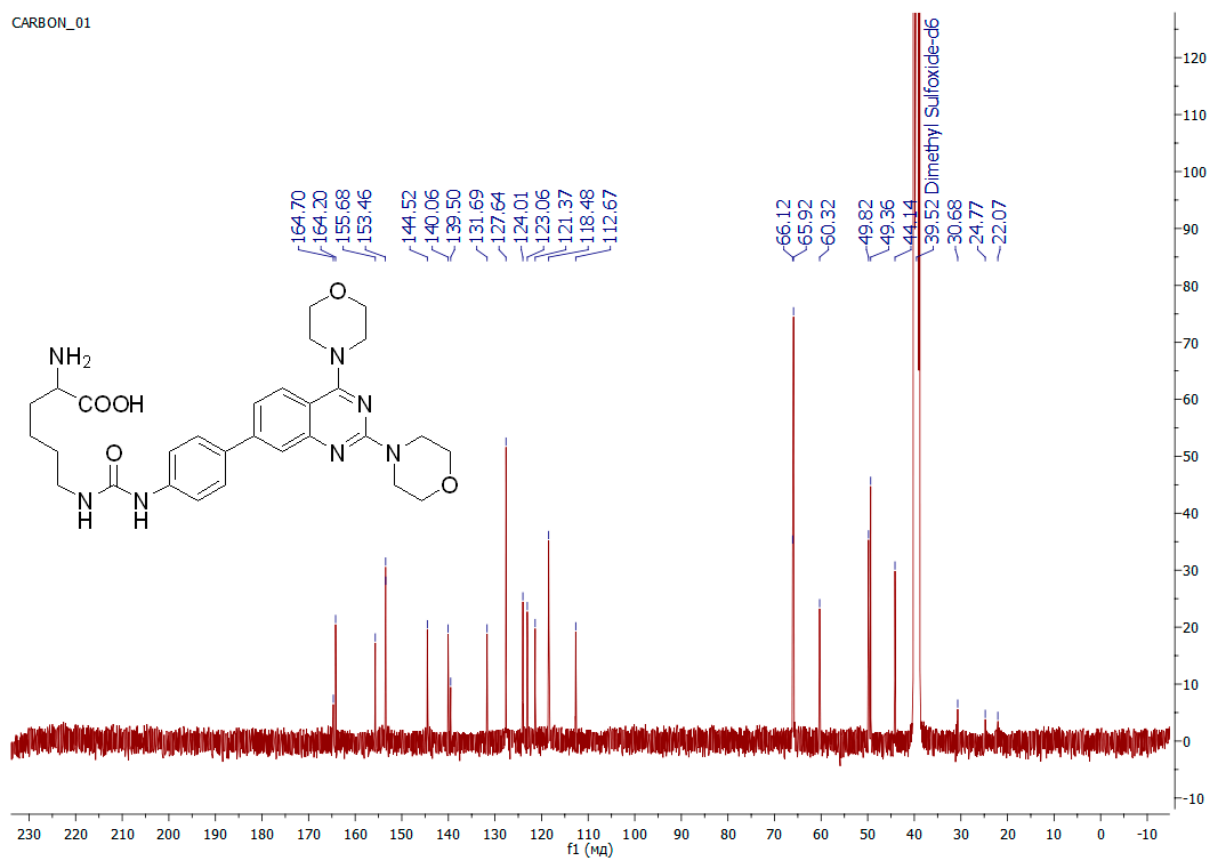
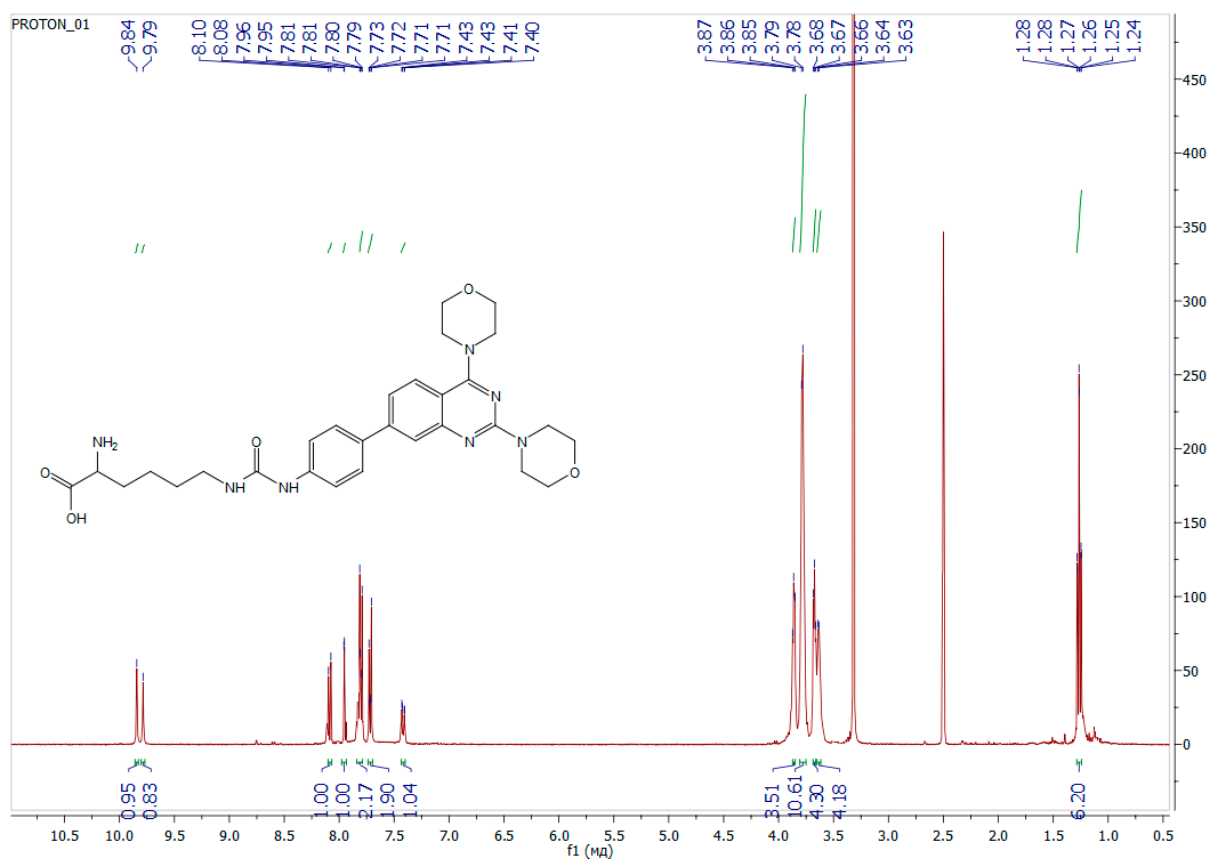
1-cyclopropyl-3-(4-(2,4-dimorpholinoquinazolin-7-yl)phenyl)urea

7d



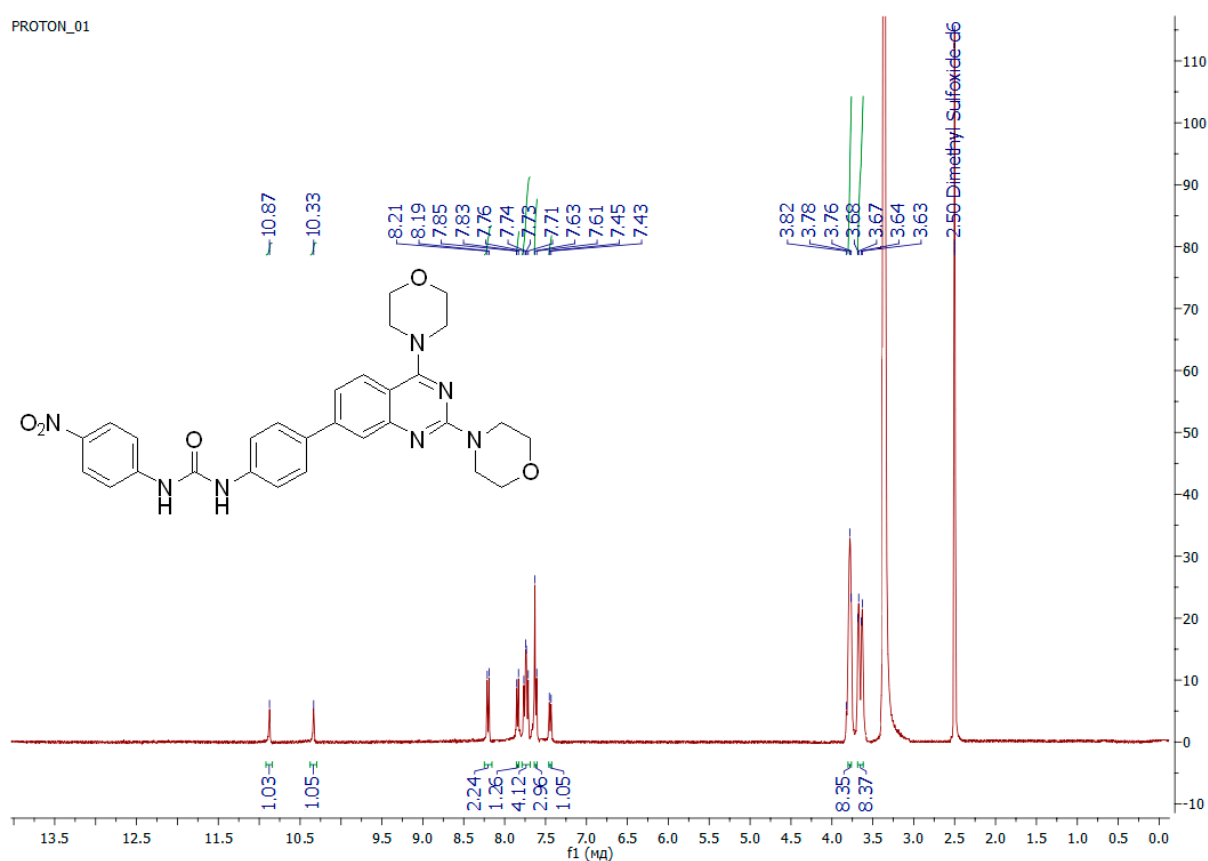
N6-((4-(2,4-dimorpholinoquinazolin-7-yl)phenyl)carbamoyl)lysine

7e

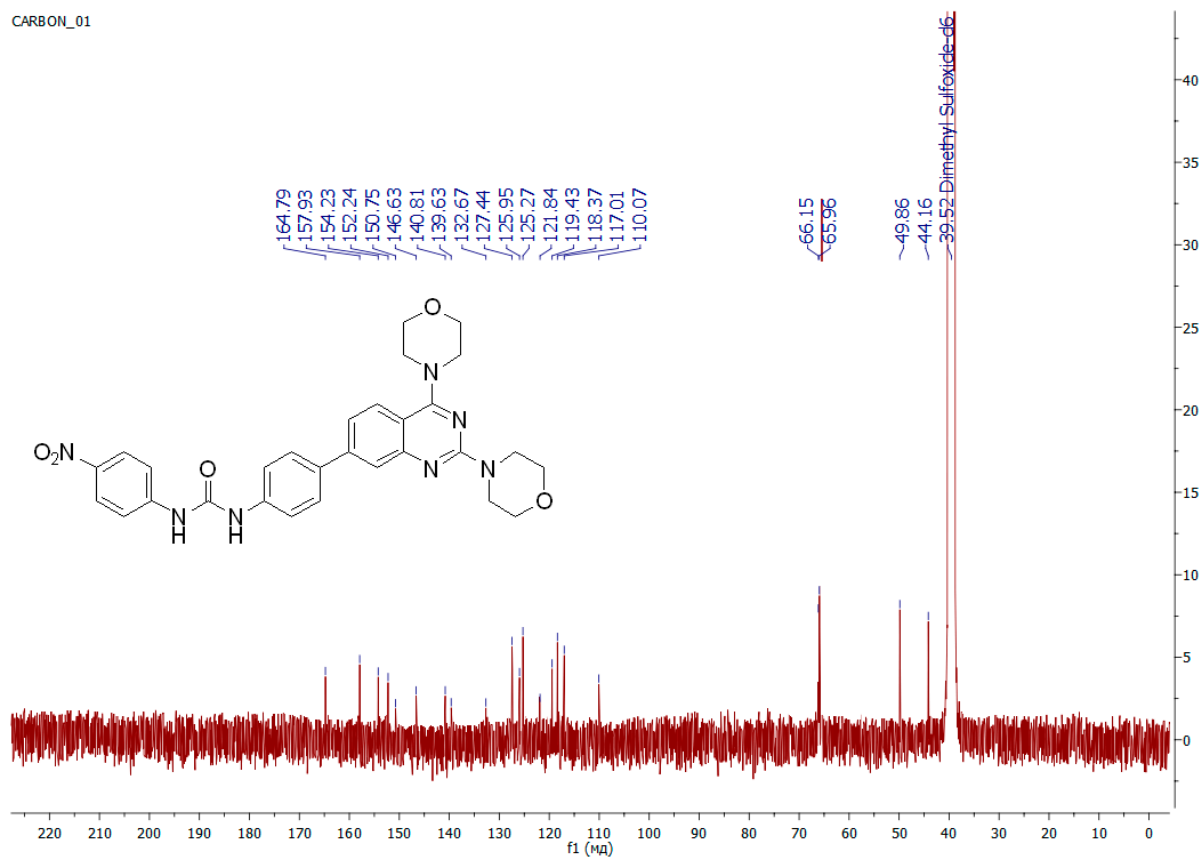


1-(4-(2,4-dimorpholinoquinazolin-7-yl)phenyl)-3-(4-nitrophenyl)urea
7f

PROTON_01

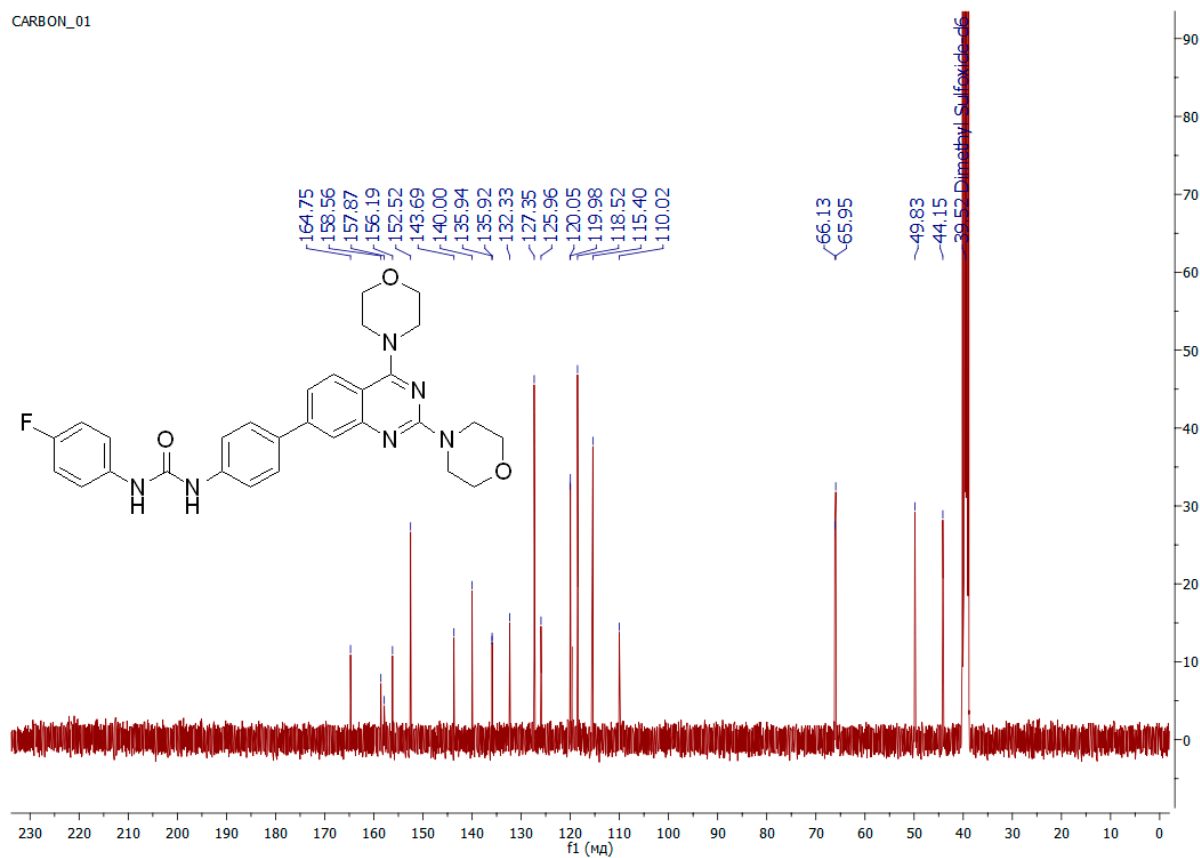
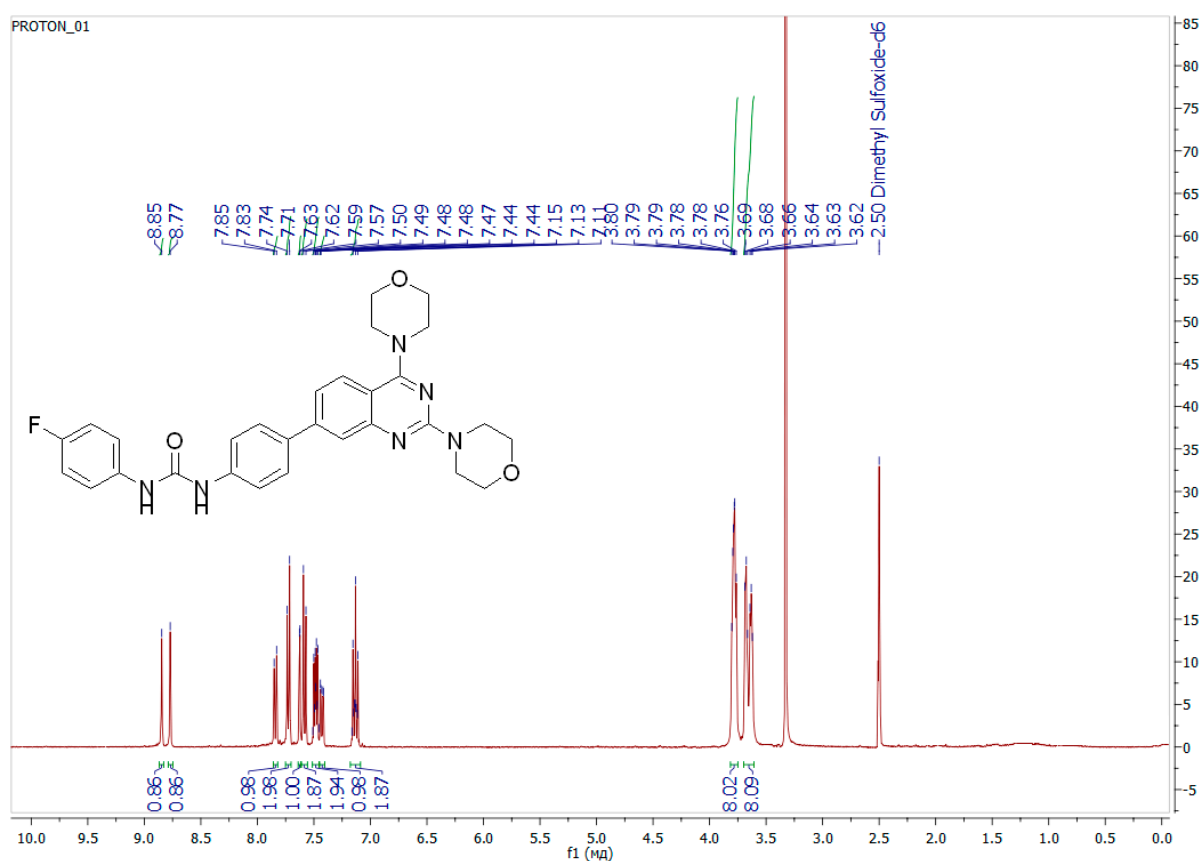


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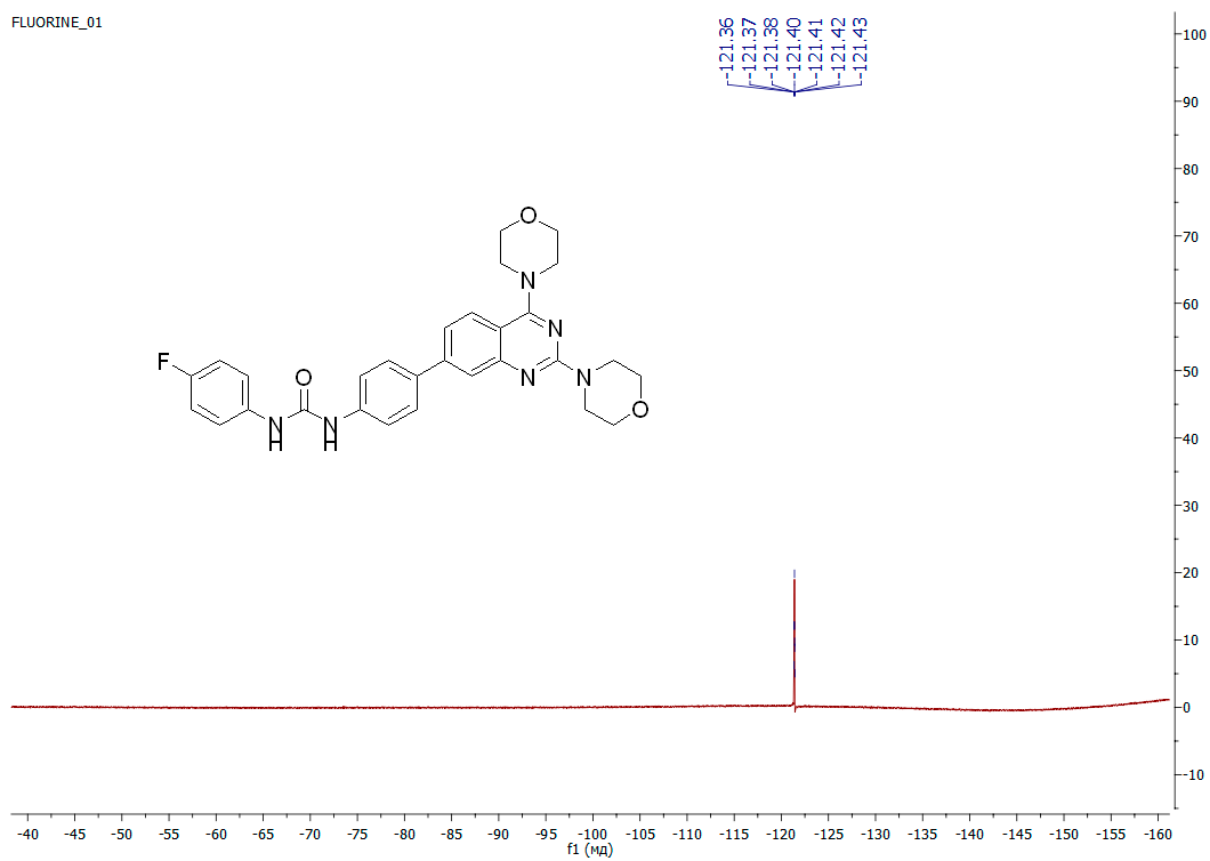


1-(4-(2,4-dimorpholinoquinazolin-7-yl)phenyl)-3-(4-fluorophenyl)urea

7g

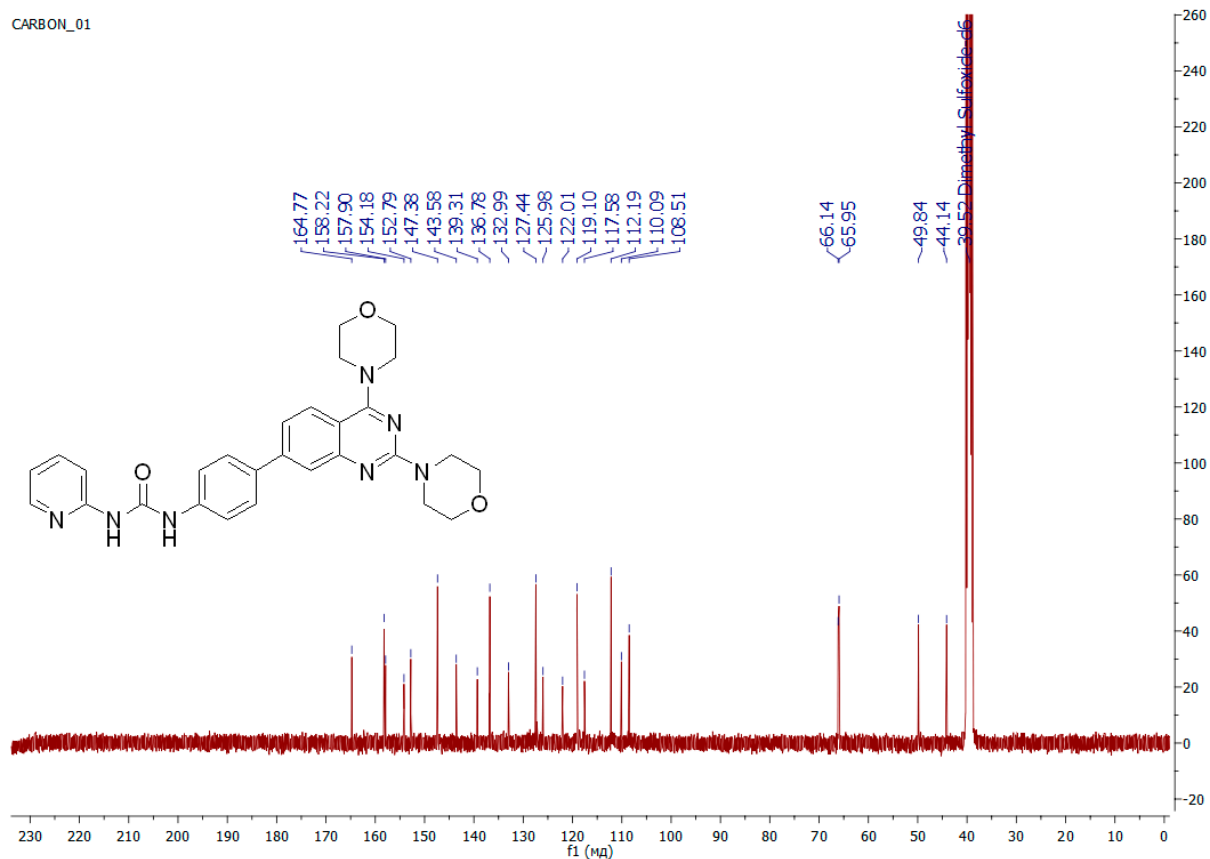
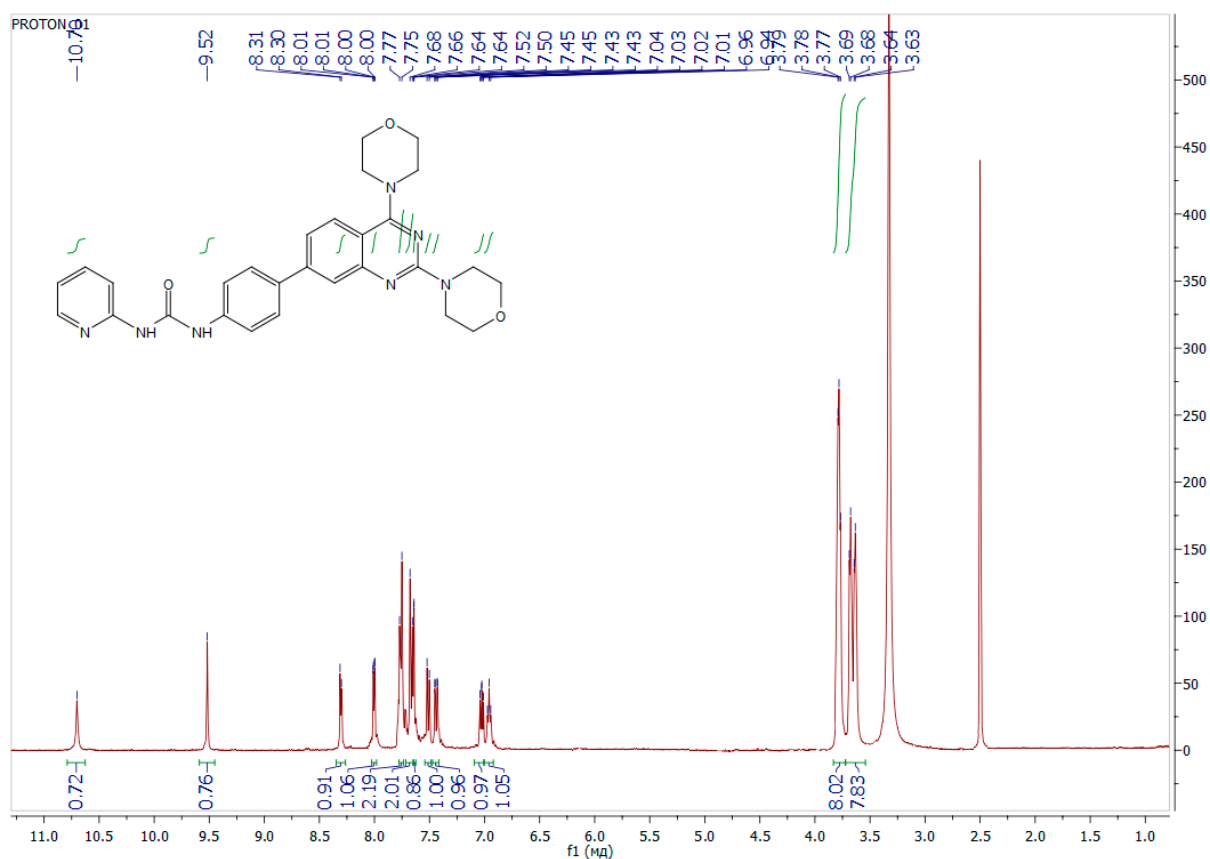


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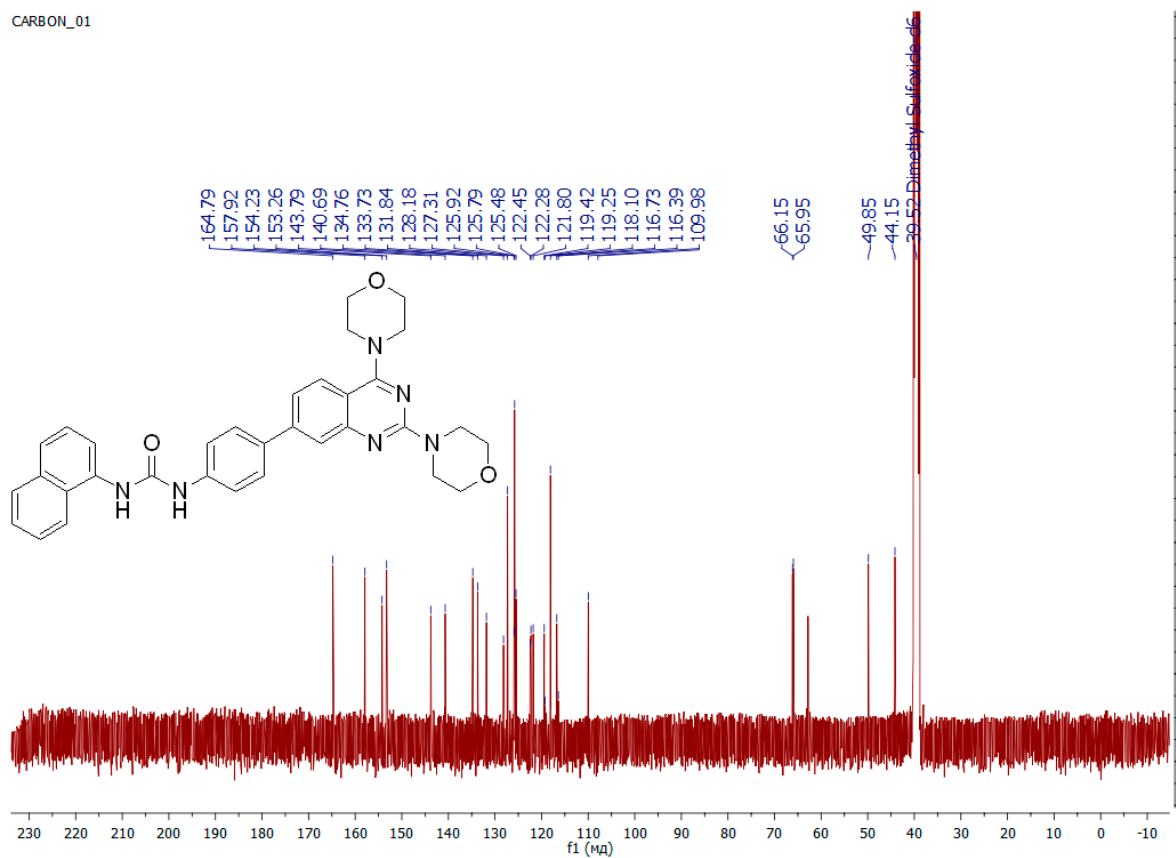
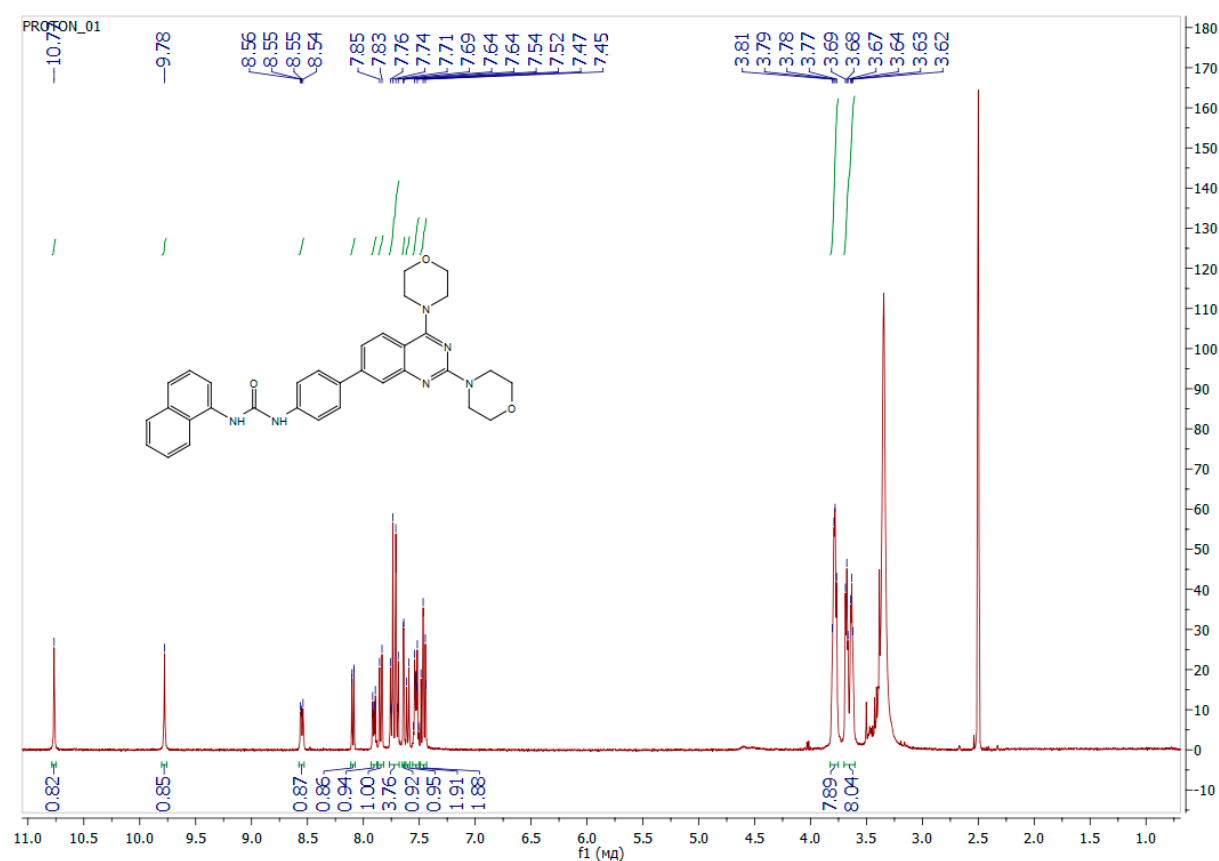
1-(4-(2,4-dimorpholinoquinazolin-7-yl)phenyl)-3-(pyridin-2-yl)urea

7h



1-(4-(2,4-dimorpholinoquinazolin-7-yl)phenyl)-3-(naphthalen-1-yl)urea

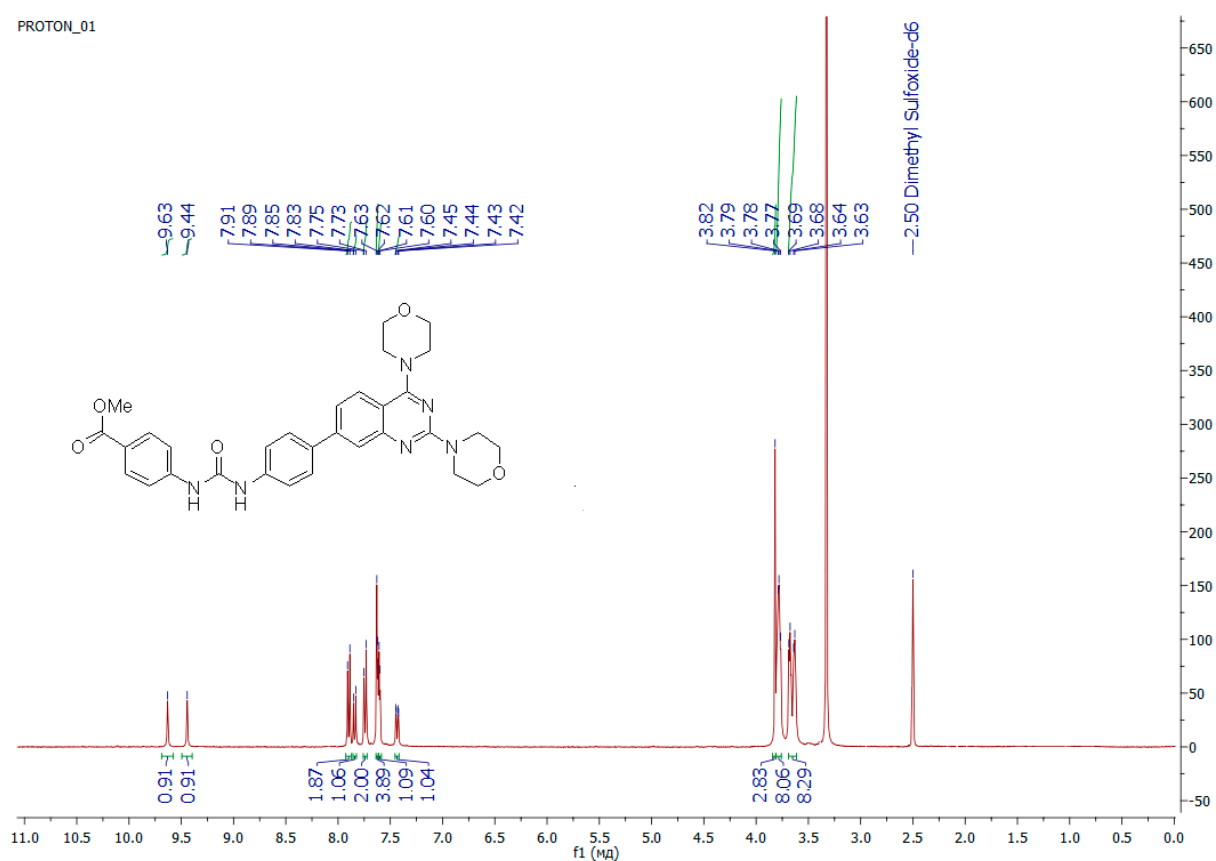
7i



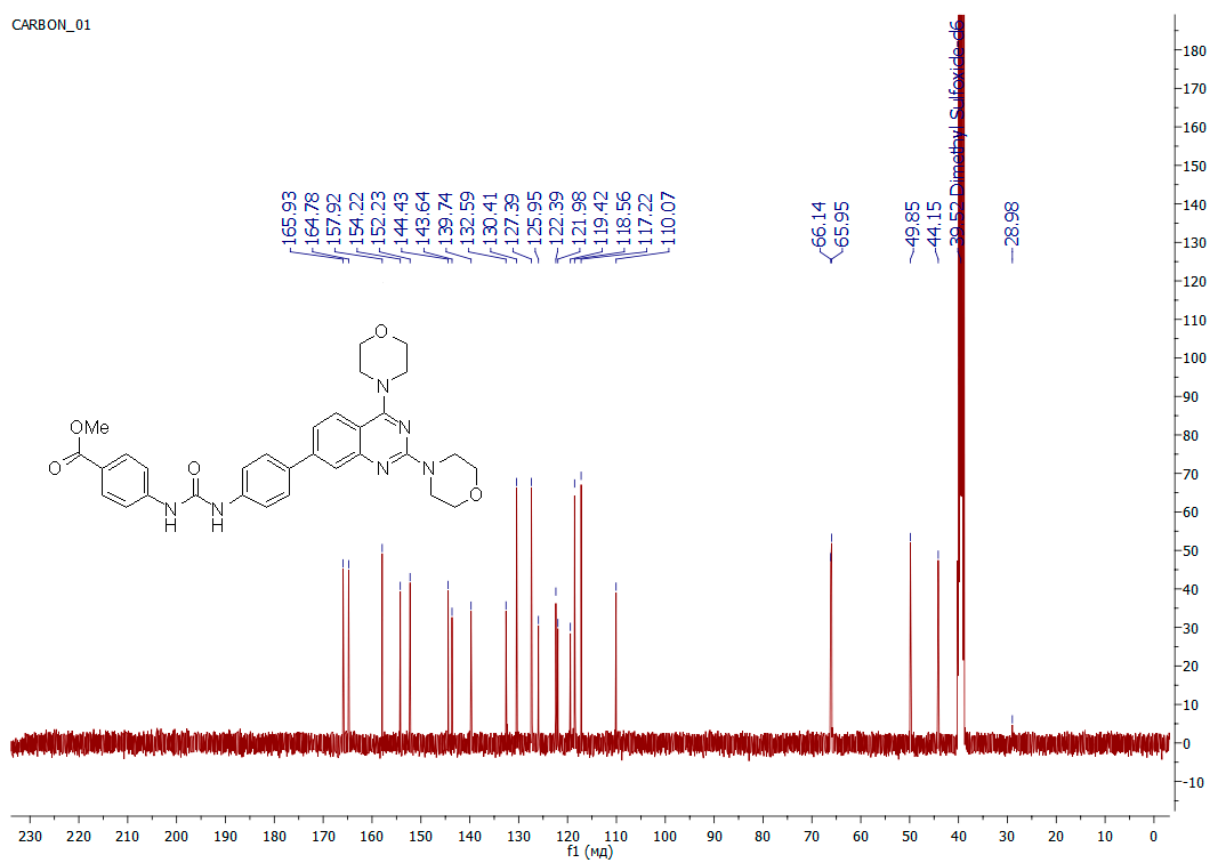
Methyl 4-(3-(4-(2,4-dimorpholinoquinazolin-7-yl)phenyl)ureido)benzoate

7j

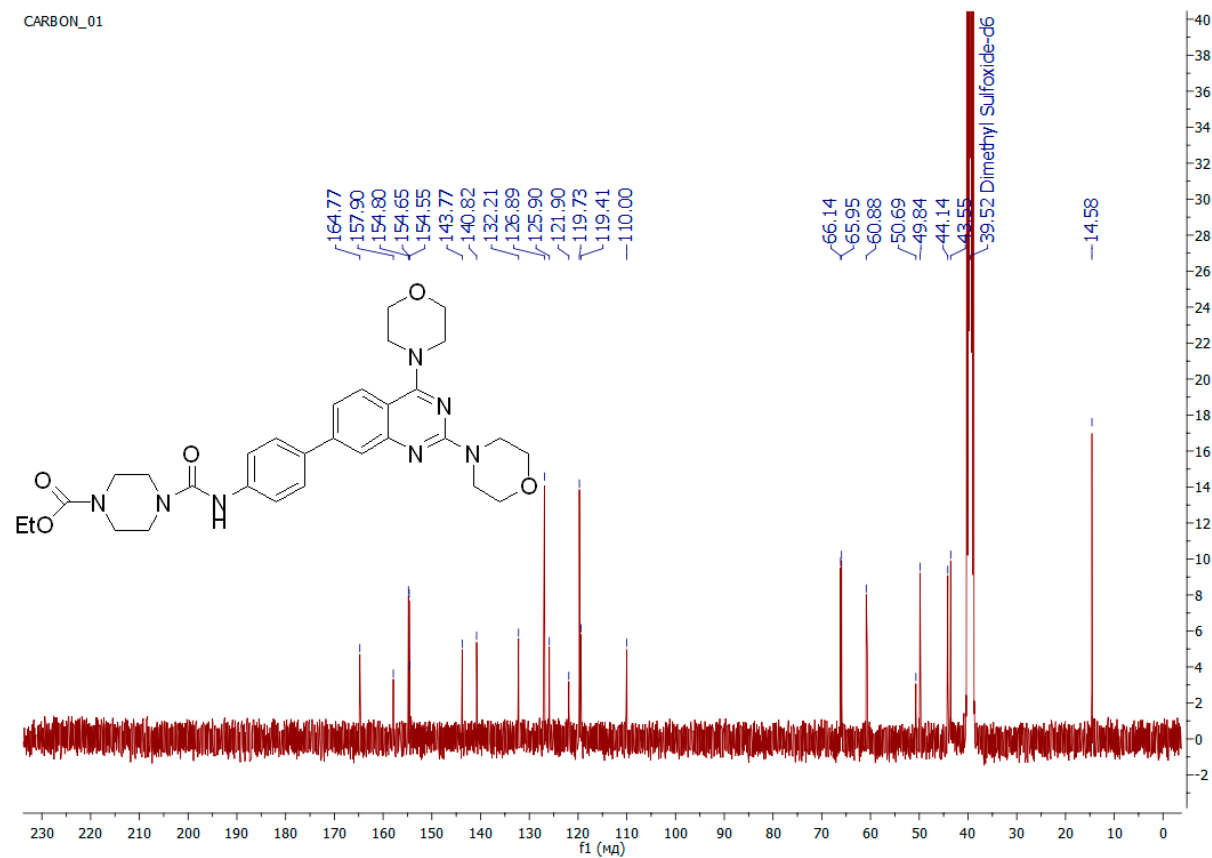
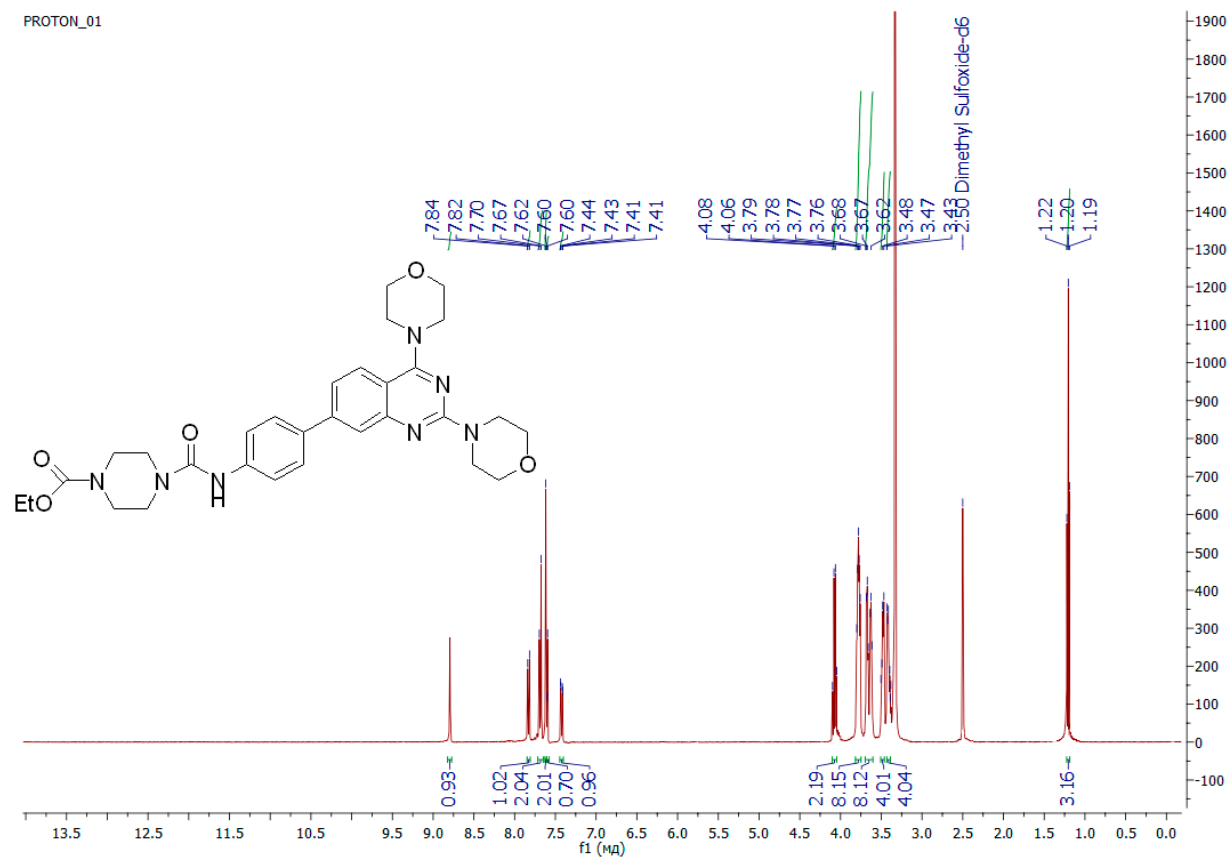
PROTON_01



CARBON_01



Ethyl 4-((4-(2,4-dimorpholinoquinazolin-7-yl)phenyl)carbamoyl)piperazine-1-carboxylate **7k**



1-(4-(2,4-dimorpholinoquinazolin-7-yl)phenyl)-3-(prop-2-yn-1-yl)urea

7l

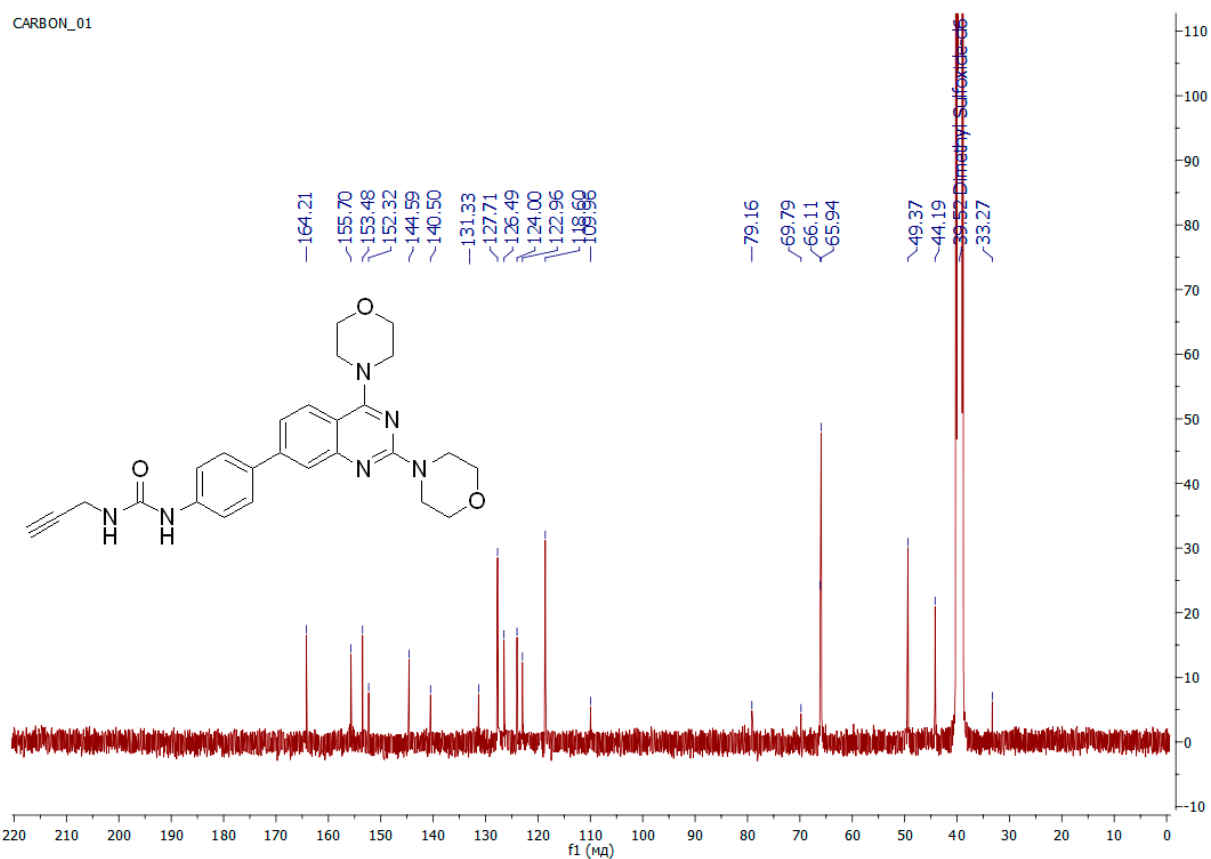
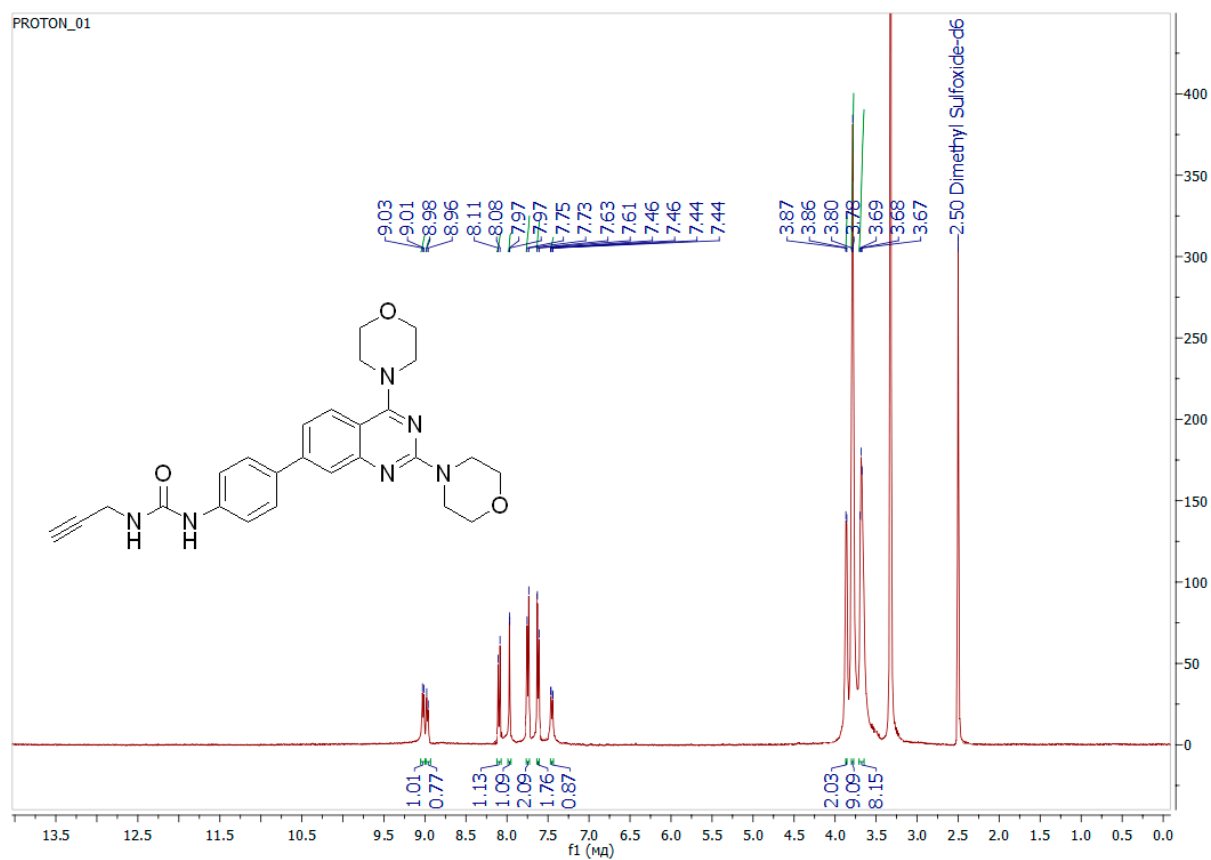
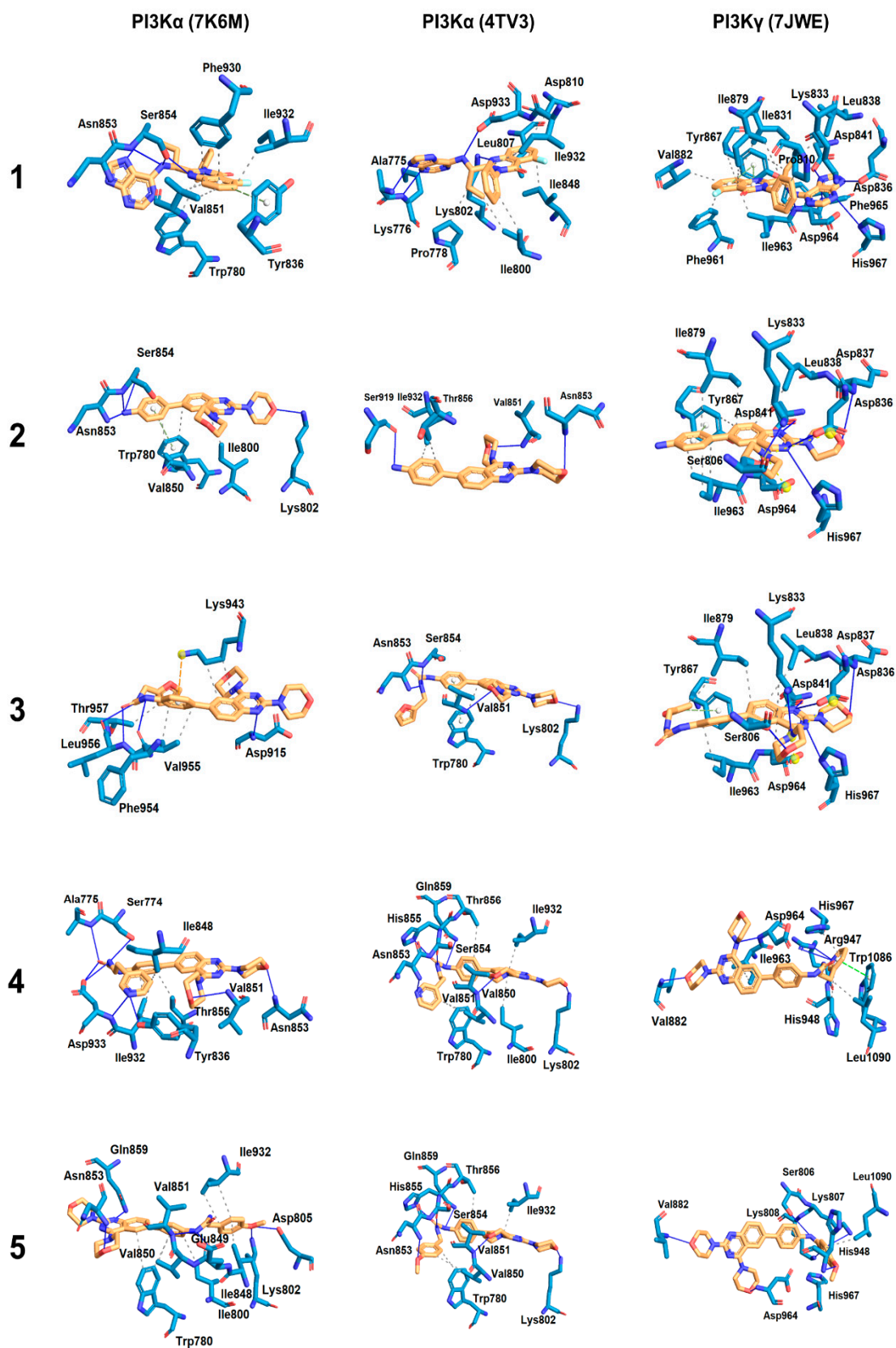


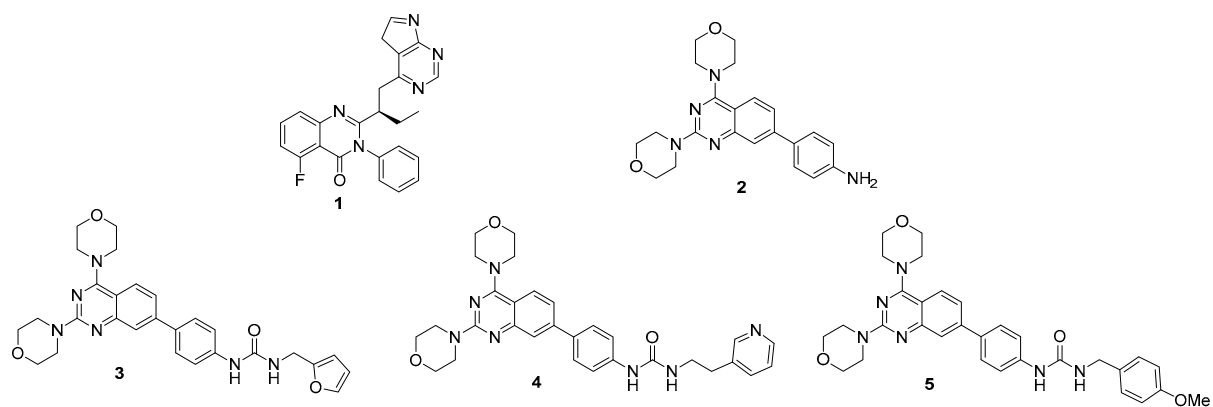
Table S1

Predicted ADME features of target compounds

Compound	c Log P	Solubility in water (ESOL)	Log Kp (skin permeation)	Number of H-bond donors	Number of H-bond acceptors
7a	2.90	9.00×10^{-3} mg/ml	-7.36 cm/s	2	6
7b	3.53	1.85×10^{-3} mg/ml	6.99 cm/s	2	6
7c	3.08	5.07×10^{-3} mg/ml	-7.31 cm/s	2	6
7d	2.74	1.57×10^{-2} mg/ml	7.14 cm/s	2	5
7e	1.22	1.08 mg/ml	-9.87 cm/s	4	8
7f	2.81	1.77×10^{-3} mg/ml	-7.05 cm/s	2	7
7g	3.84	1.35×10^{-3} mg/ml	-6.68 cm/s	2	6
7h	2.94	5.49×10^{-3} mg/ml	-7.18 cm/s	2	6
7i	4.45	1.58×10^{-4} mg/ml	-6.07 cm/s	2	5
7j	3.54	1.71×10^{-3} mg/ml	-7.11 cm/s	2	7
7k	2.48	1.12×10^{-2} mg/ml	-7.99 cm/s	1	7
7l	2.61	3.05×10^{-2} mg/ml	-7.44 cm/s	2	5

Docking of reference (line 1) and synthesized compounds (lines 2-5) in active site of PI3K α and PI3K γ isoforms. Structures of compounds are represented below.





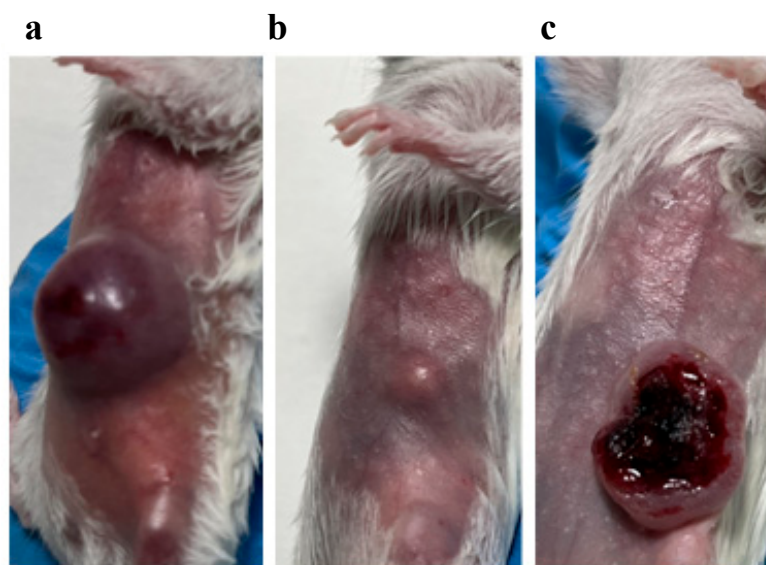
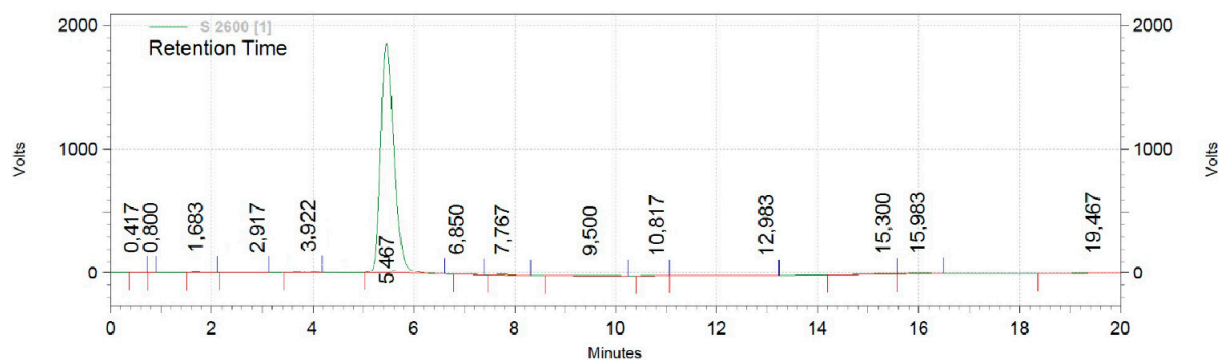


Figure S1. **Effect of the compound 7c on tumor growth.** BALB/c mice were s.c. inoculated with colorectal Colon-26 cells. a-c: Overview of the tumors in control (a), at early (b) and late (c) treatment at day 28 post tumor transplantation.

Area % Report

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Retention time	Area	Area, %	Height	Height, %
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2,917	11892	0,03	414	0,01
3,922	539435	1,52	9047	0,73
5,467	33970229	95,89	1852504	97,45
6,850	33576	0,10	762	0,03
7,767	128543	0,34	6251	0,31
9,500	152964	0,42	3672	0,18
10,817	27283	0,08	1260	0,05
12,983	51771	0,15	724	0,03
15,300	164994	0,47	6506	0,31
15,983	211220	0,57	7880	0,35
19,467	88348	0,25	2518	0,12
Total	35 420 983	100	1899938	100