Supplementary Material

A practical synthesis of *N*-allyl/propargyl-substituted 5-fluorouracils

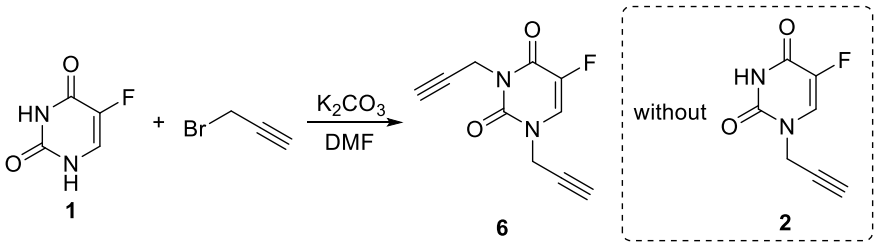
Shijie Zhang,[a,b] Huhui Xia,[c] Jian Sun,[d] and Wei Zhou*[c]

[a]Academy of Chinese Medical Sciences, Zhejiang Chinese Medical University, Hangzhou 310053, China. [b]Zhejiang Medicine Co., Ltd. Xinchang Pharmaceutical Factory, Shaoxing 312500, China. [c]College of Pharmaceutical Science, Zhejiang University of Technology, Hangzhou 310014, China [d]Quanjiao NATA Opto Electronic Materials Ltd., Chuzhou 239514, China.
Email: zhouwei@zjut.edu.cn

Table of Contents

1. Optimization of reaction conditions

Table S1. Optimization of reaction conditions of 5-FU and bromopropyne



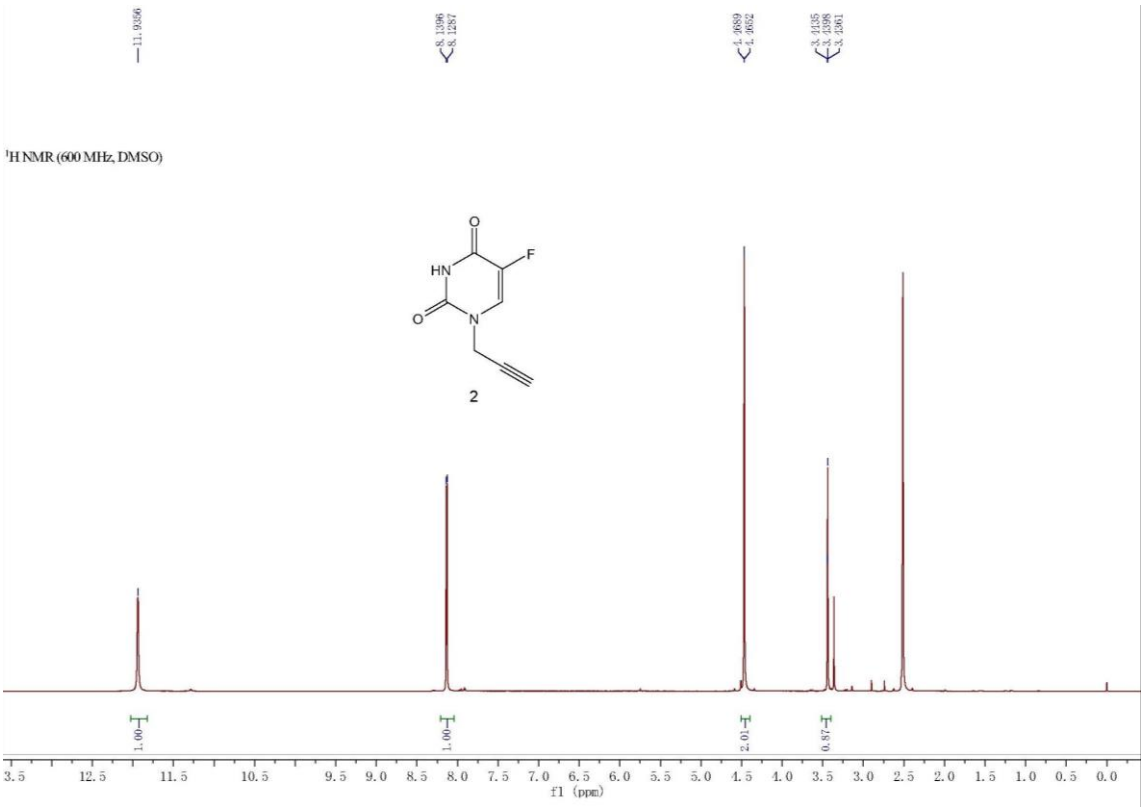
Ratio of bromopropyne and 5-FU	Reaction time (d)	Yield of **6** (%)[a,b]
0.5:1	2	13
1:1	2	23
1.5:1	2	50
2:1	2	74
2.5:1	2	81
2:1	0.5	65
2:1	1	71
2:1	3	81
2:1	4	82

[a] characterization of compound **6**: colorless needle crystal, mp 97–98°C [lit[1] 96.3-97.8°C]; IR (KBr) cm^{-1}: 3200, 3098, 2832, 1758, 1700, 1289, 1153, 903, 842; ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.29 (d, *J* = 6.6 Hz, 1H, ArH), 4.563 (d, *J* = 2.4 Hz, 2H, N-CH_2-C), 4.556 (d, *J* = 2.4 Hz, 2H, N-CH_2-C), 3.50 (t, *J* = 2.4 Hz, 1H, C≡CH), 3.20 (t, *J* = 2.4 Hz, 1H, C≡CH).; ^{13}C NMR (150 MHz, DMSO-d_6) δ 156.3 (d, *J* = 27.2 Hz), 148.9, 139.6 (d, *J* = 227.4 Hz), 128.8 (d, *J* = 33.8 Hz), 78.8, 78.3, 77.0, 74.0, 38.7, 31.2.

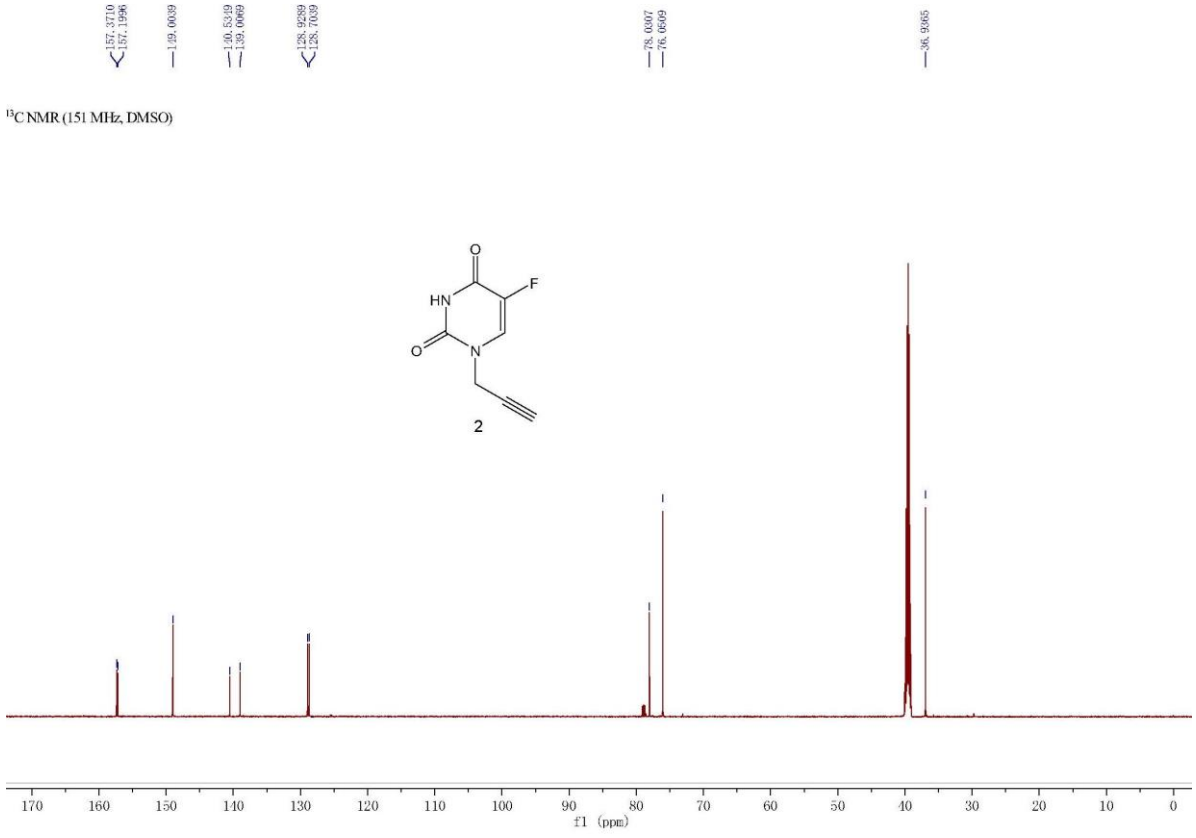
[b] no compound **2** was detected by ^{1}H NMR characterization.

2. Copies of ^{1}H and ^{13}C NMR spectra

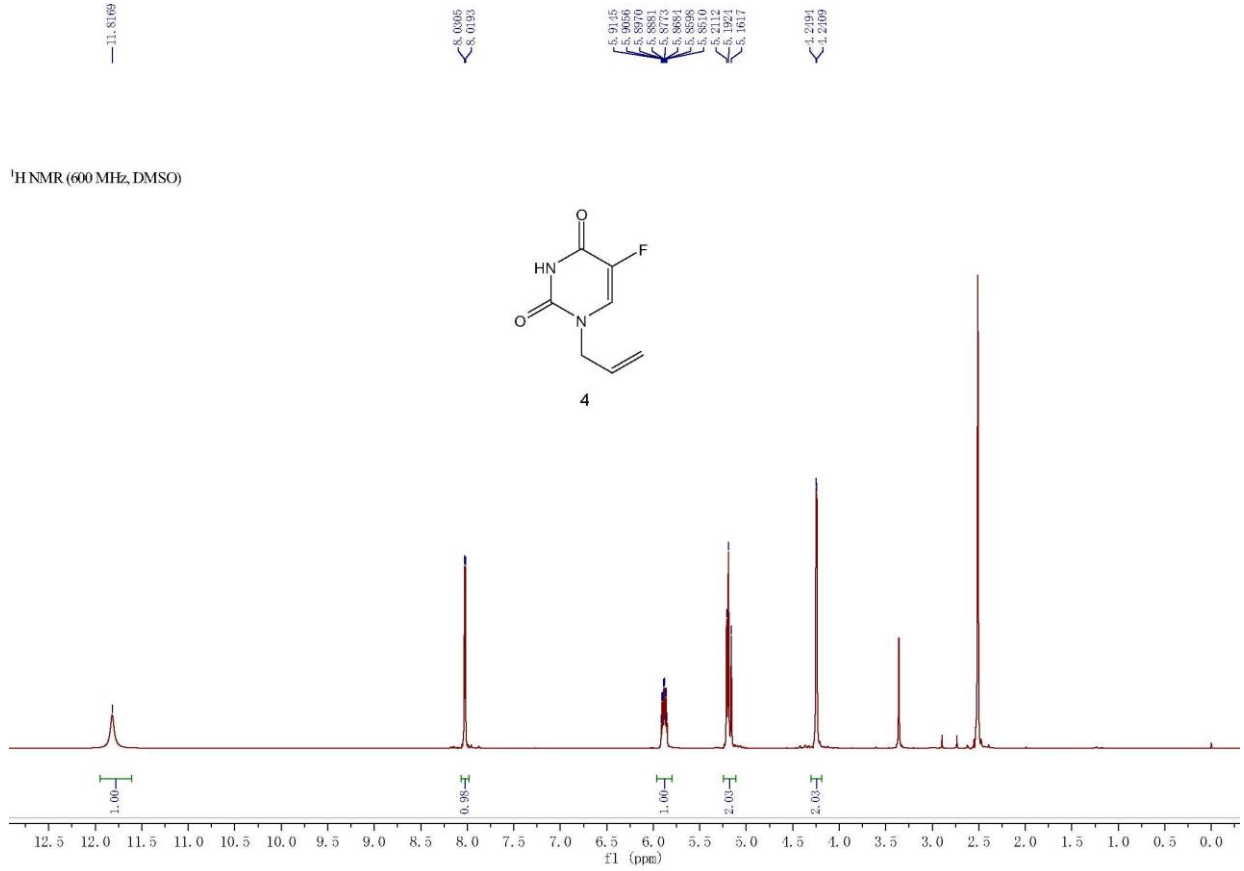
^{1}H NMR spectra of 1-propargyl-3H-5-FU (**2**)



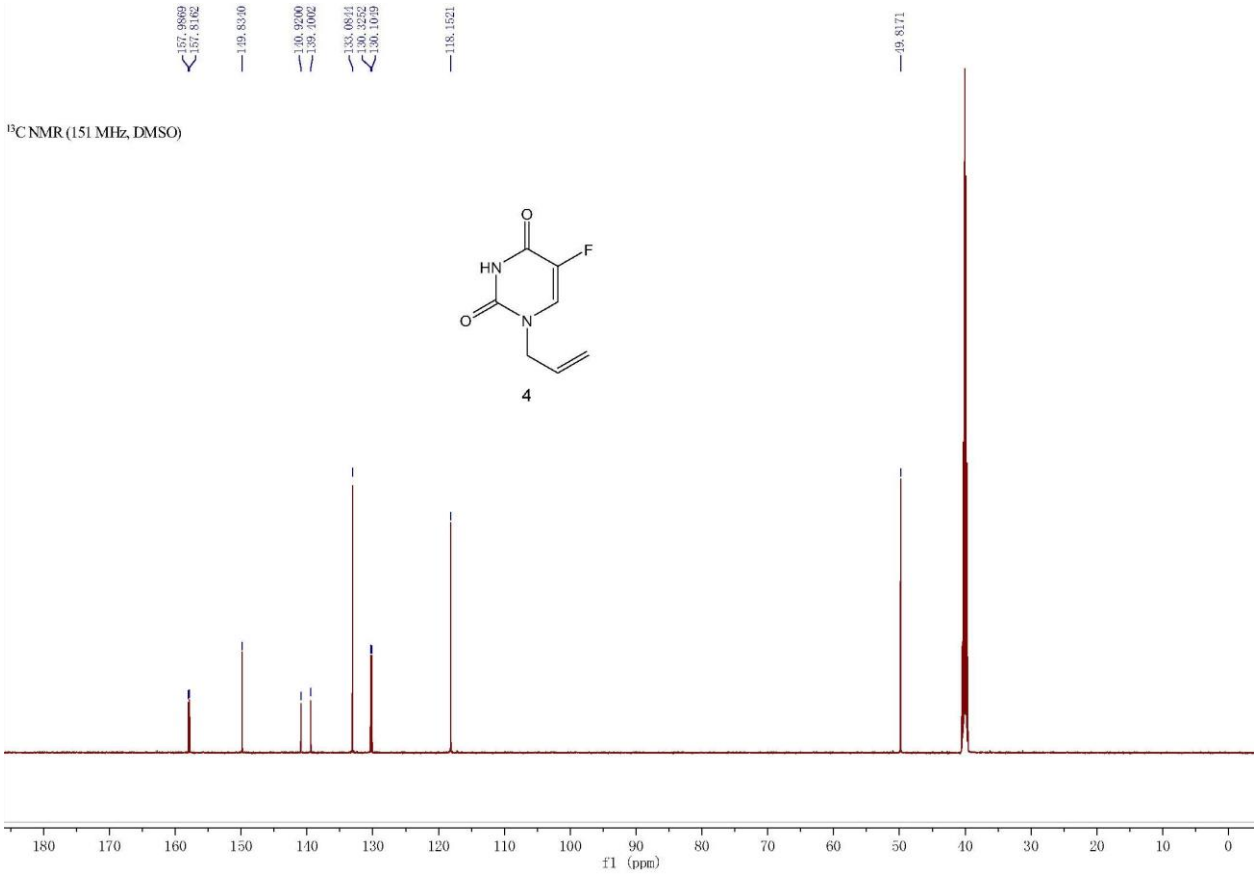
^{13}C NMR spectra of 1-propargyl-3H-5-FU (**2**)



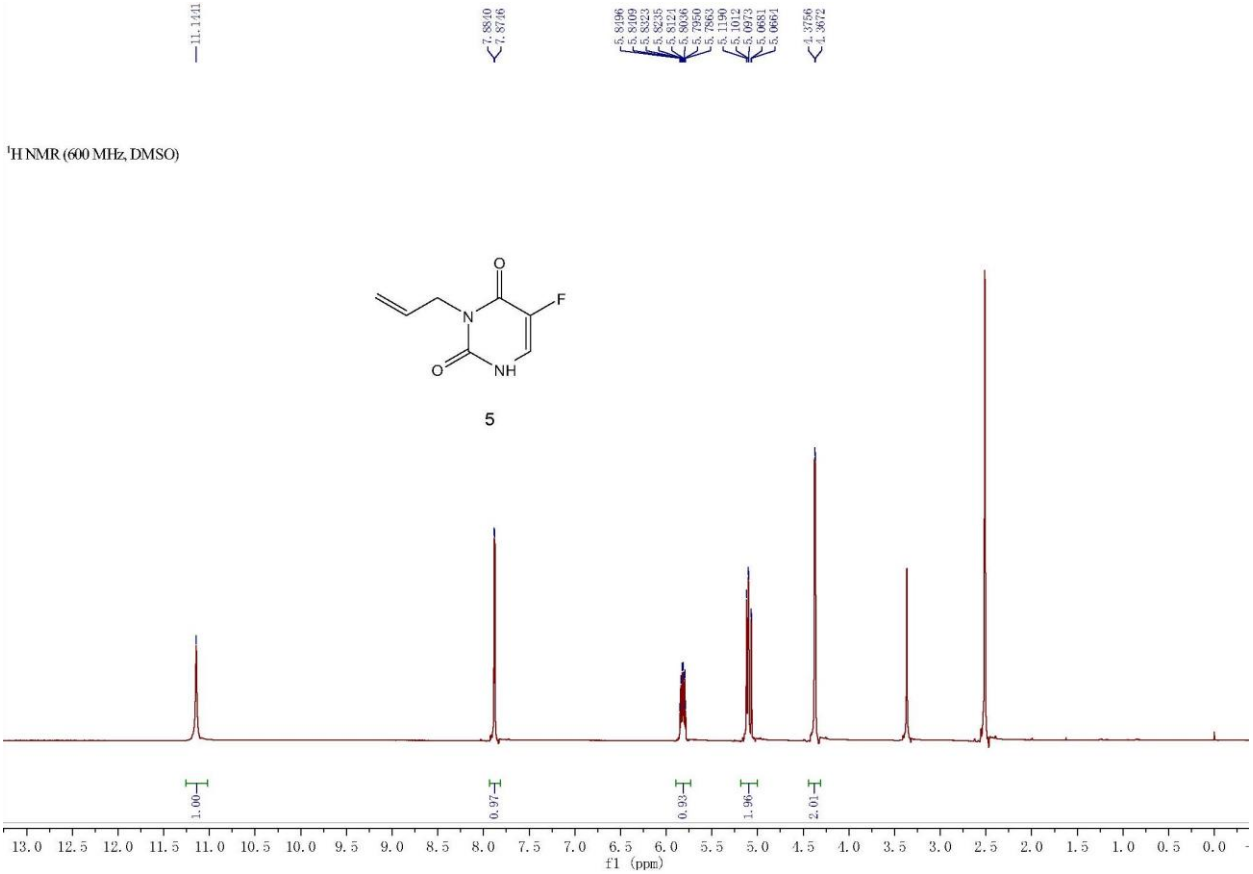
^{1}H NMR spectra of 1-allyl-5-Fu (4)



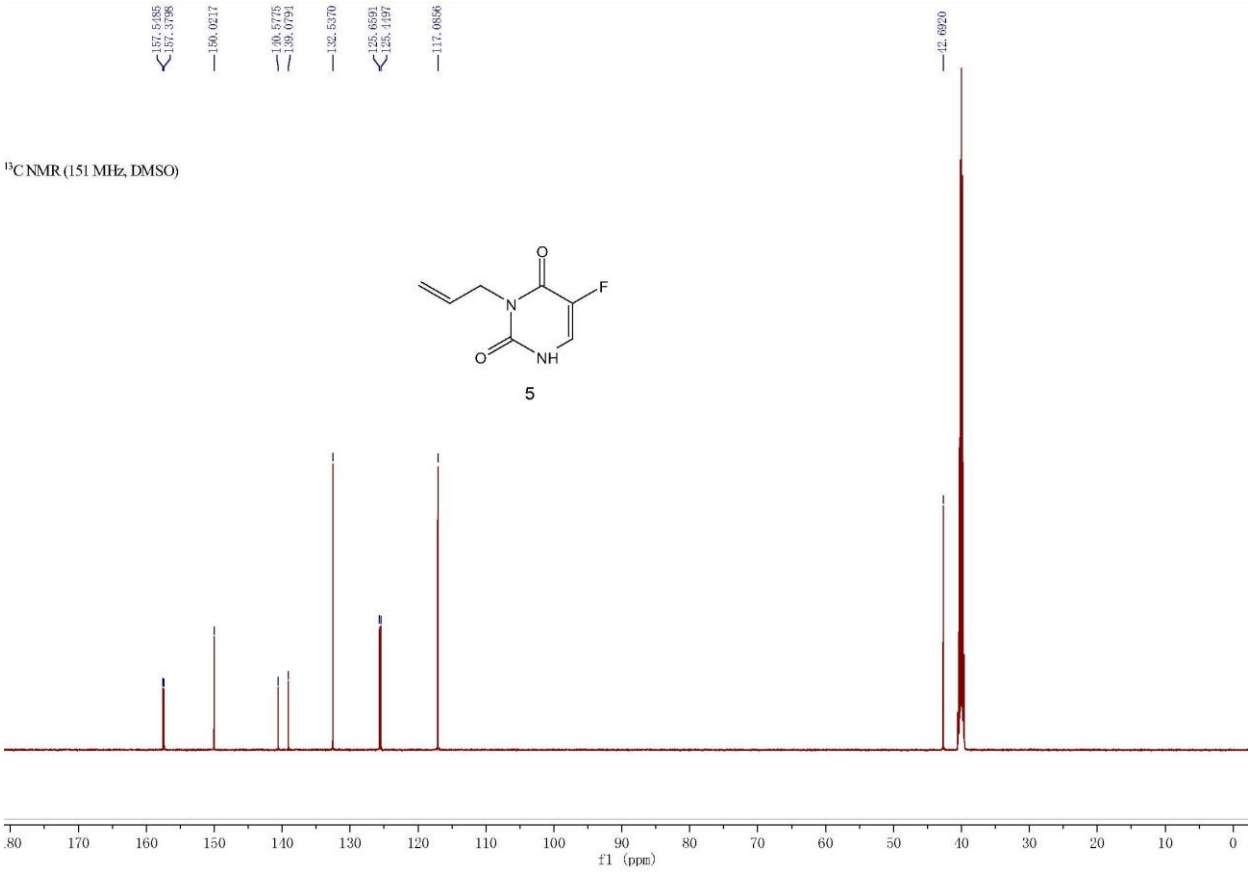
^{13}C NMR spectra of 1-allyl-5-Fu (**4**)



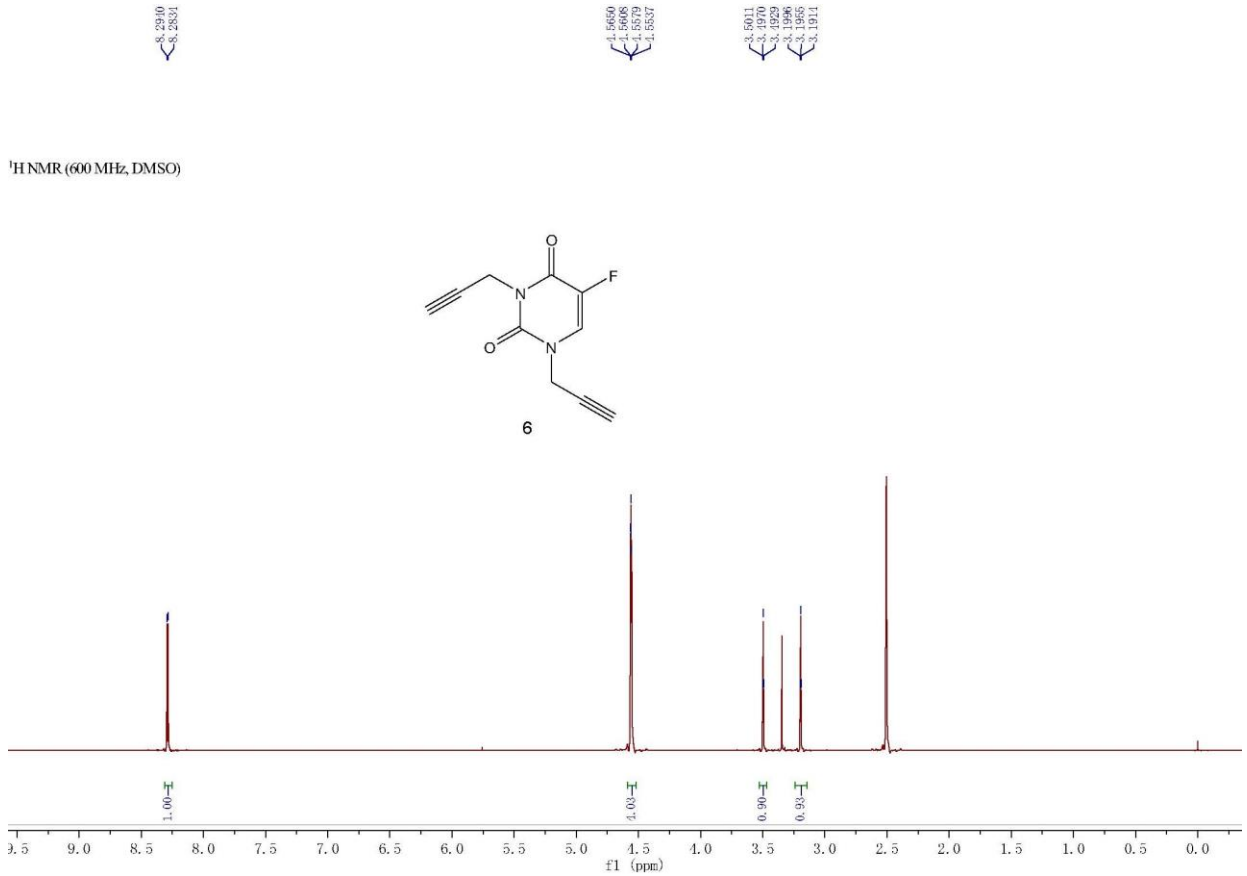
^{1}H NMR spectra of 3-allyl-5-Fu (**5**)



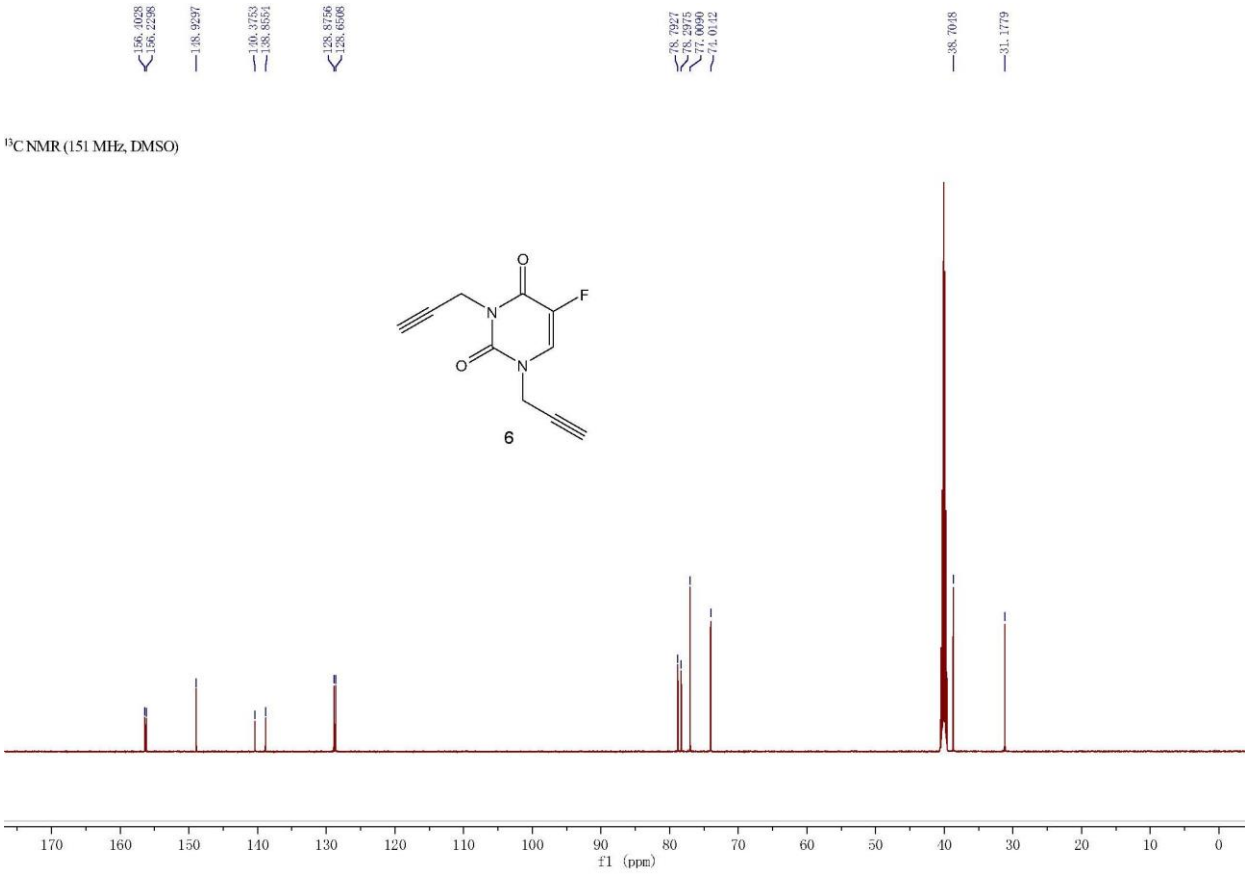
^{13}C NMR spectra of 3-allyl-5-Fu (**5**)



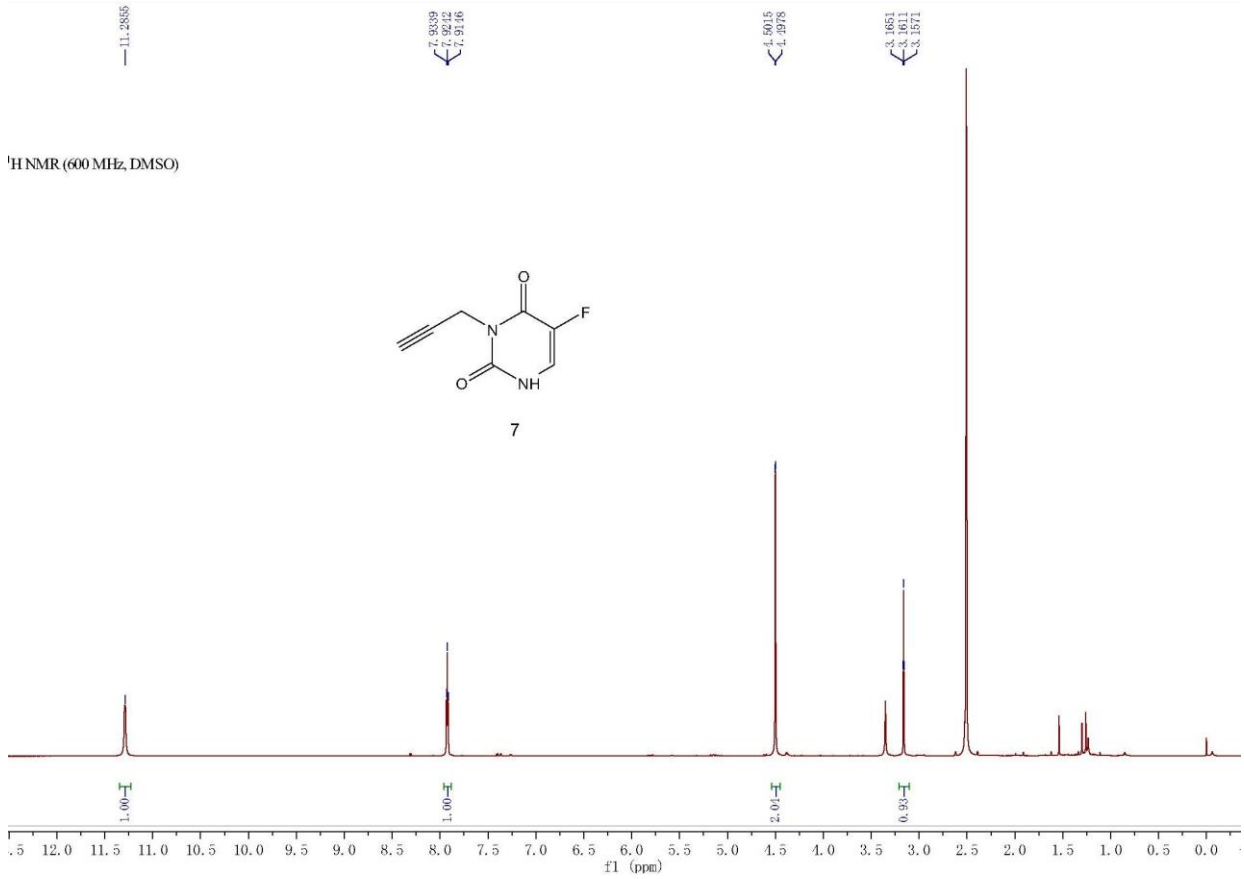
^{1}H NMR spectra of 1-propargyl-3-propargyl-5-FU (**6**)



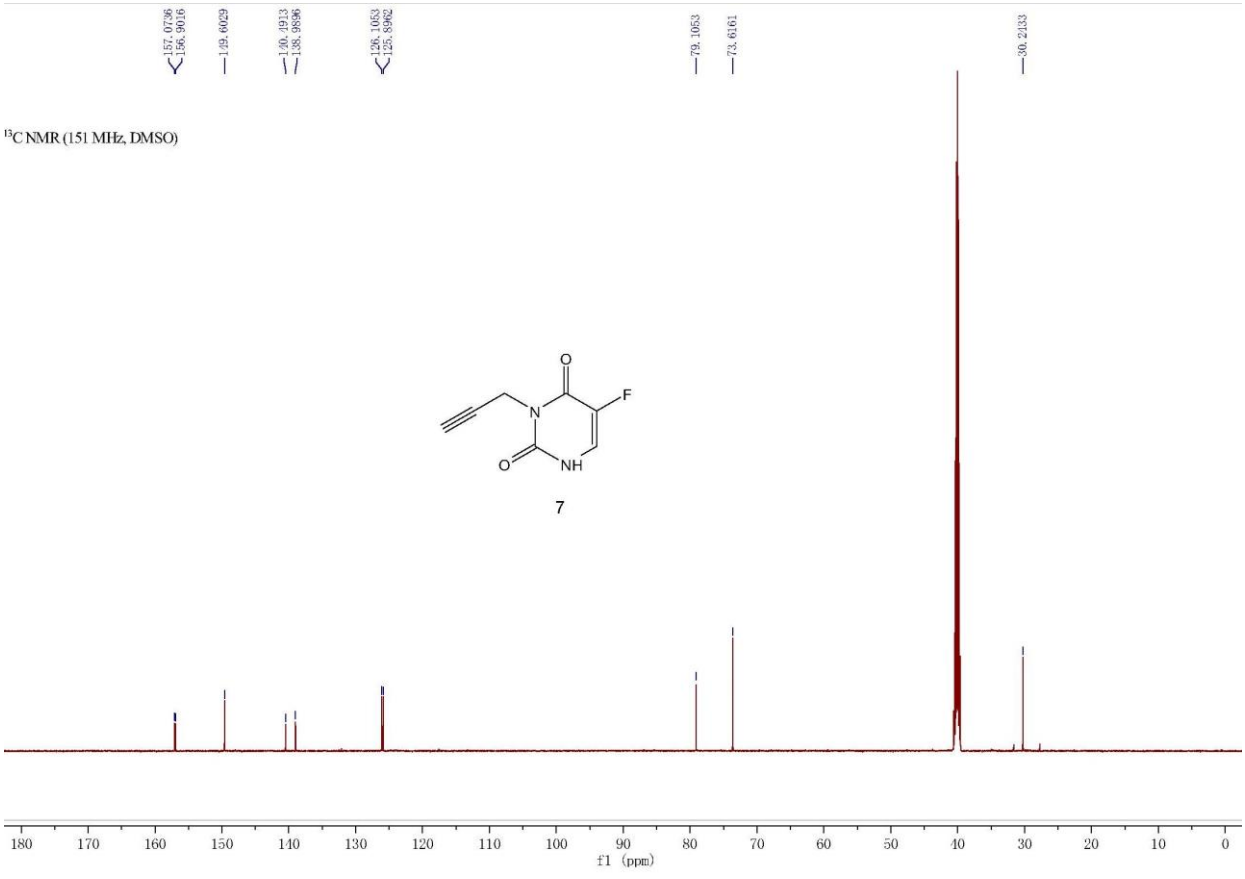
^{13}C NMR spectra of 1-propargyl-3-propargyl-5-FU (**6**)



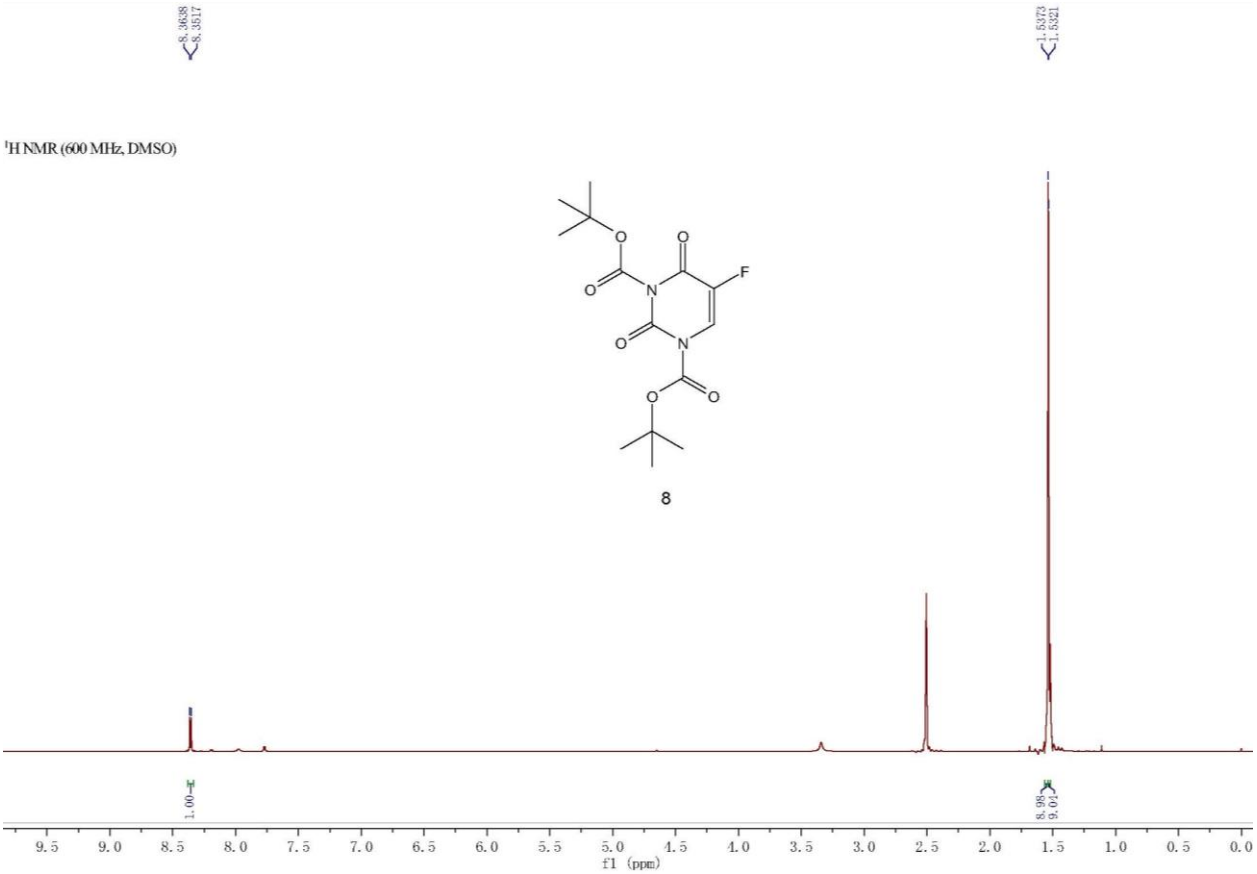
^{1}H NMR spectra of 3-propargyl-5-Fu (**7**)



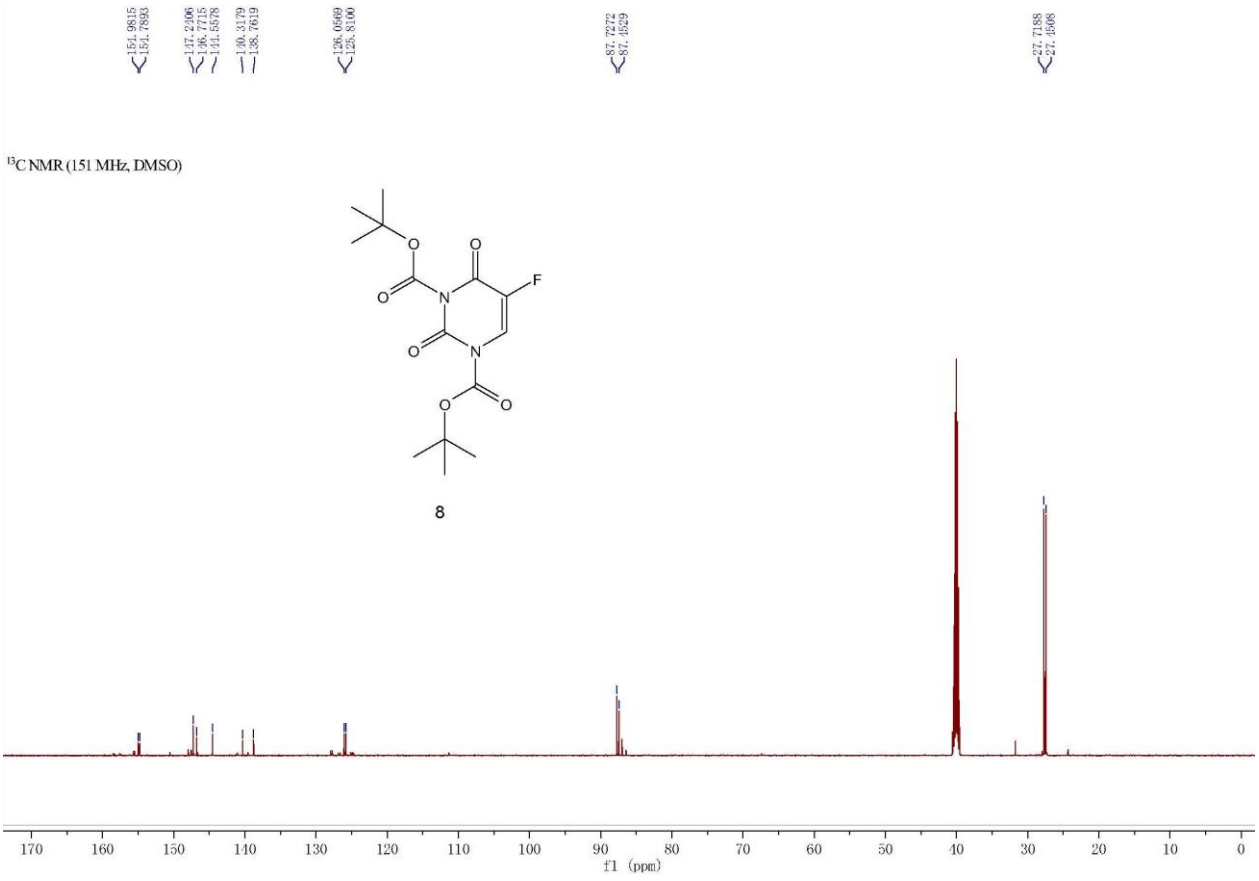
^{13}C NMR spectra of 3-propargyl-5-Fu (**7**)



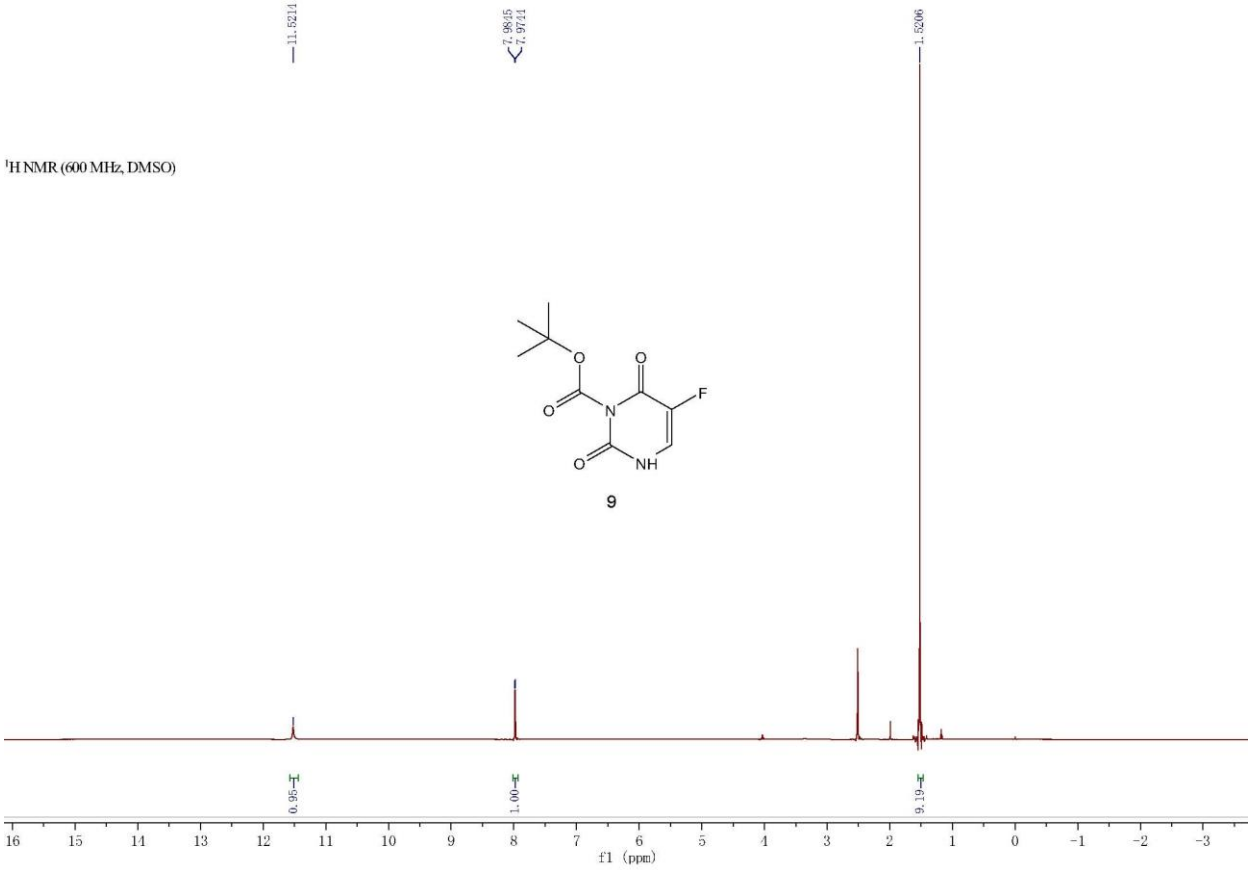
^{1}H NMR spectra of 1-N-Boc-3-N-Boc-5-FU (**8**)



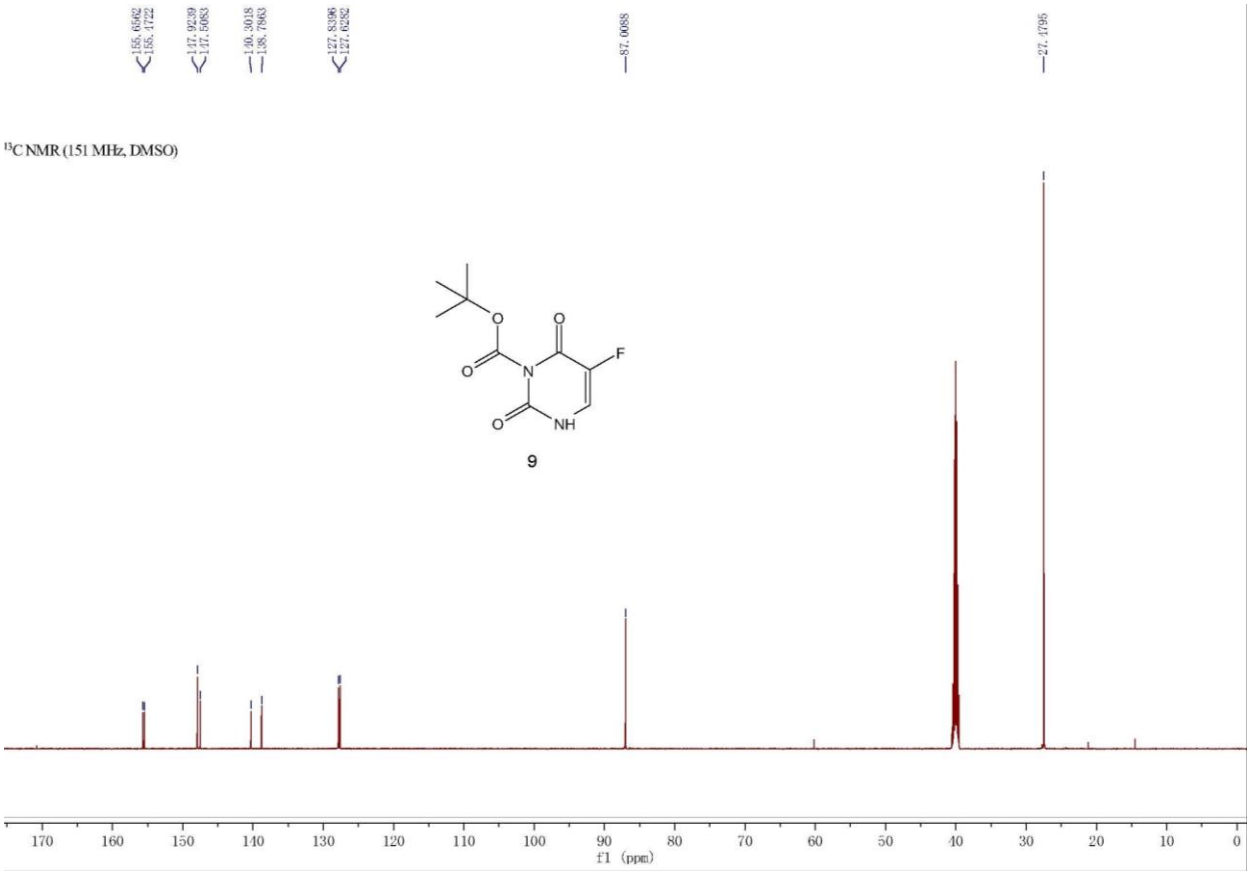
^{13}C NMR spectra of 1-N-Boc-3-N-Boc-5-FU (**8**)



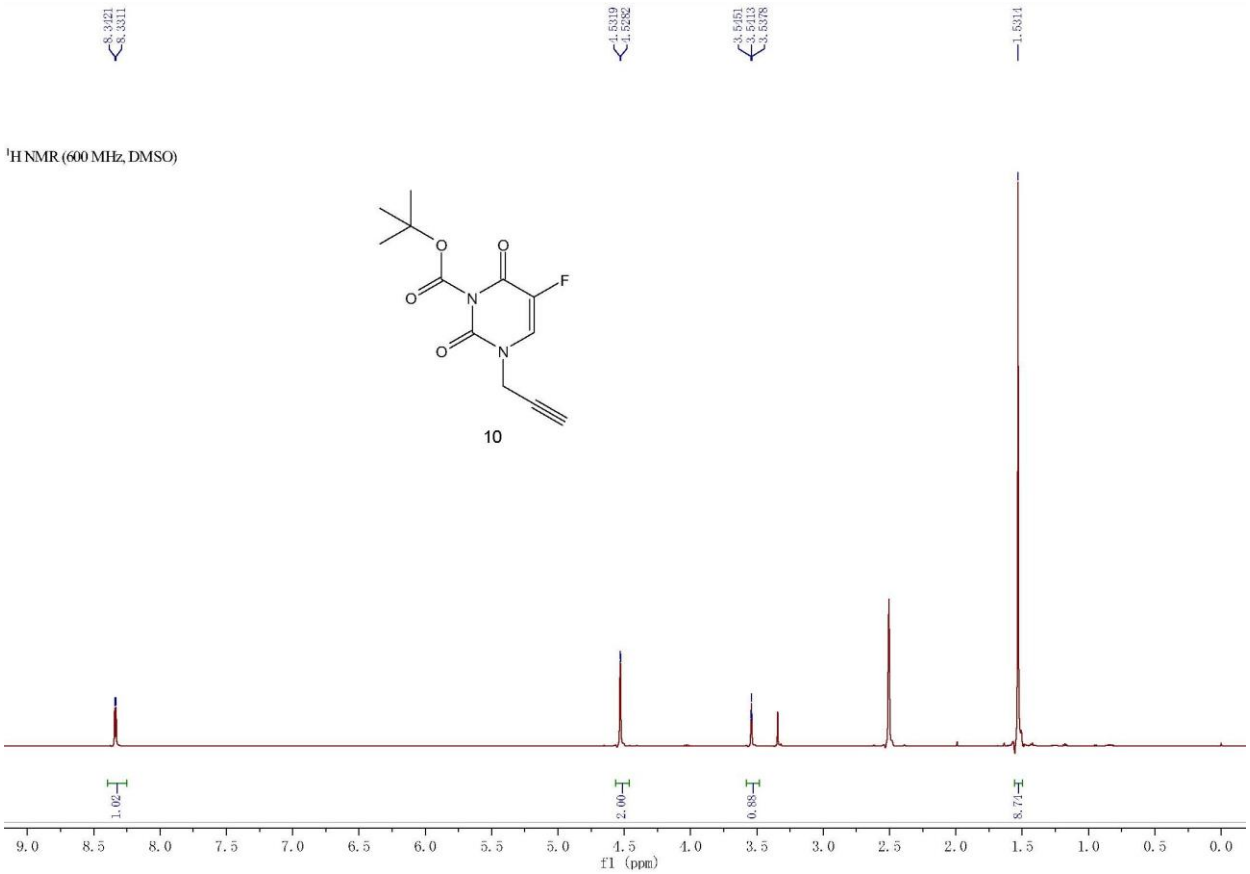
^{1}H NMR spectra of 3-N-Boc-1H-5-FU (**9**)



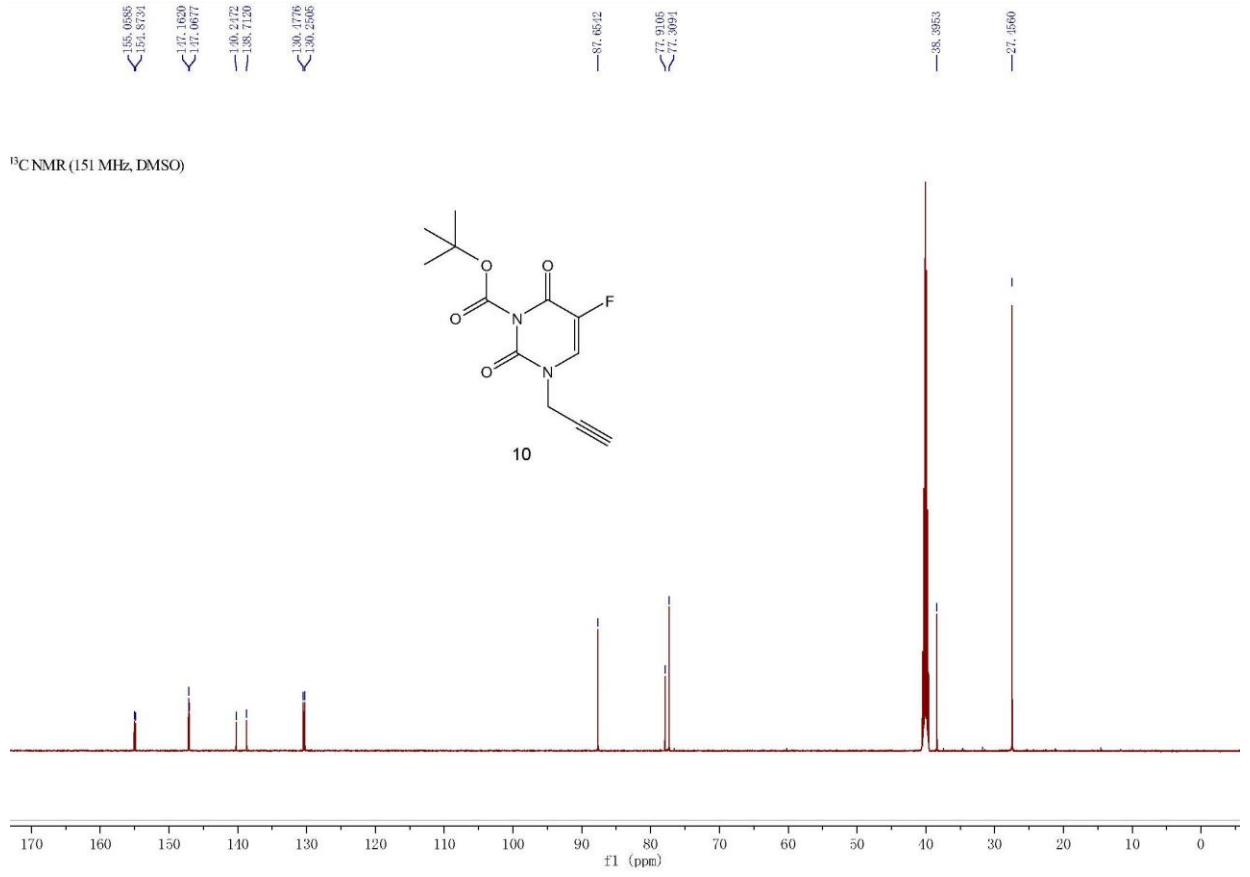
^{13}C NMR spectra of 3-N-Boc-1H-5-FU (**9**)



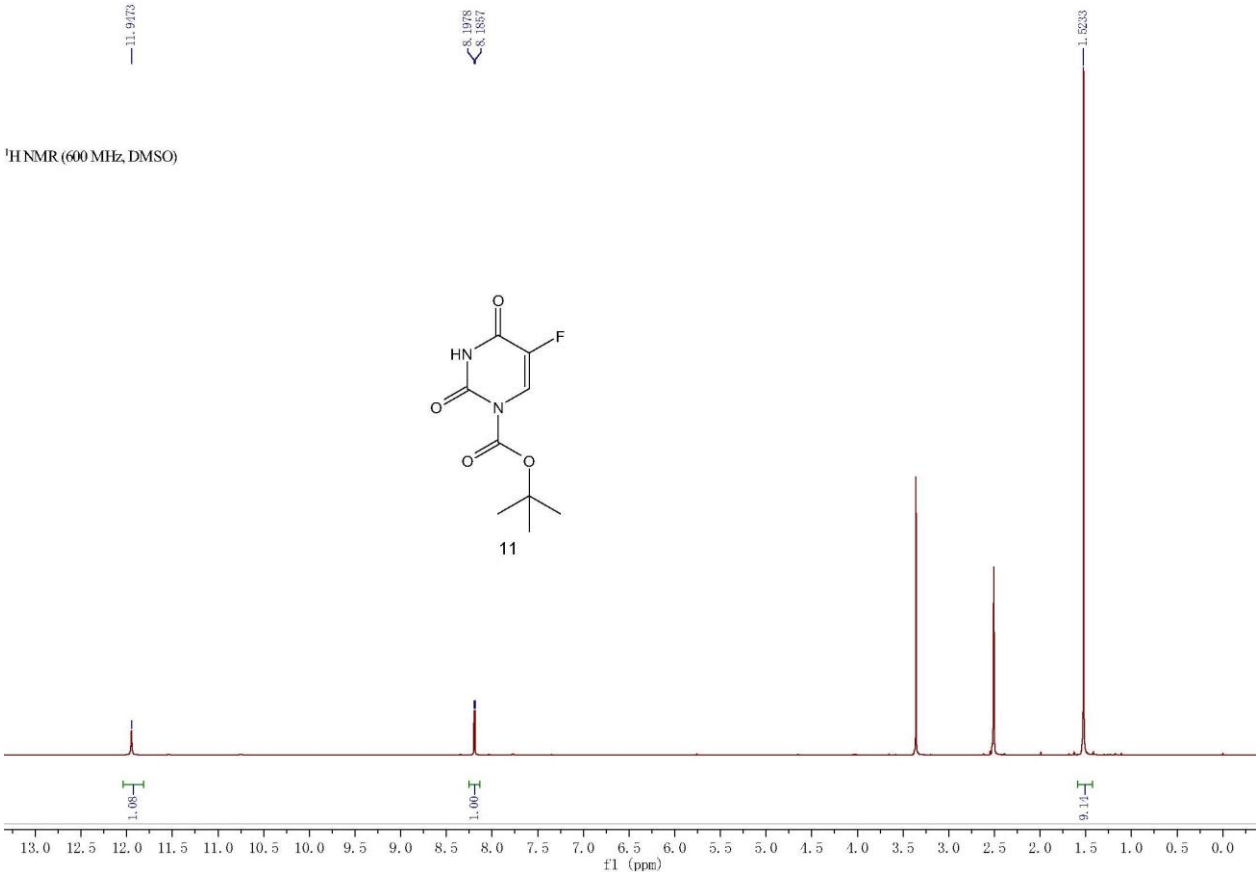
^{1}H NMR spectra of 3-N-Boc-1-propargyl-5-FU (**10**)



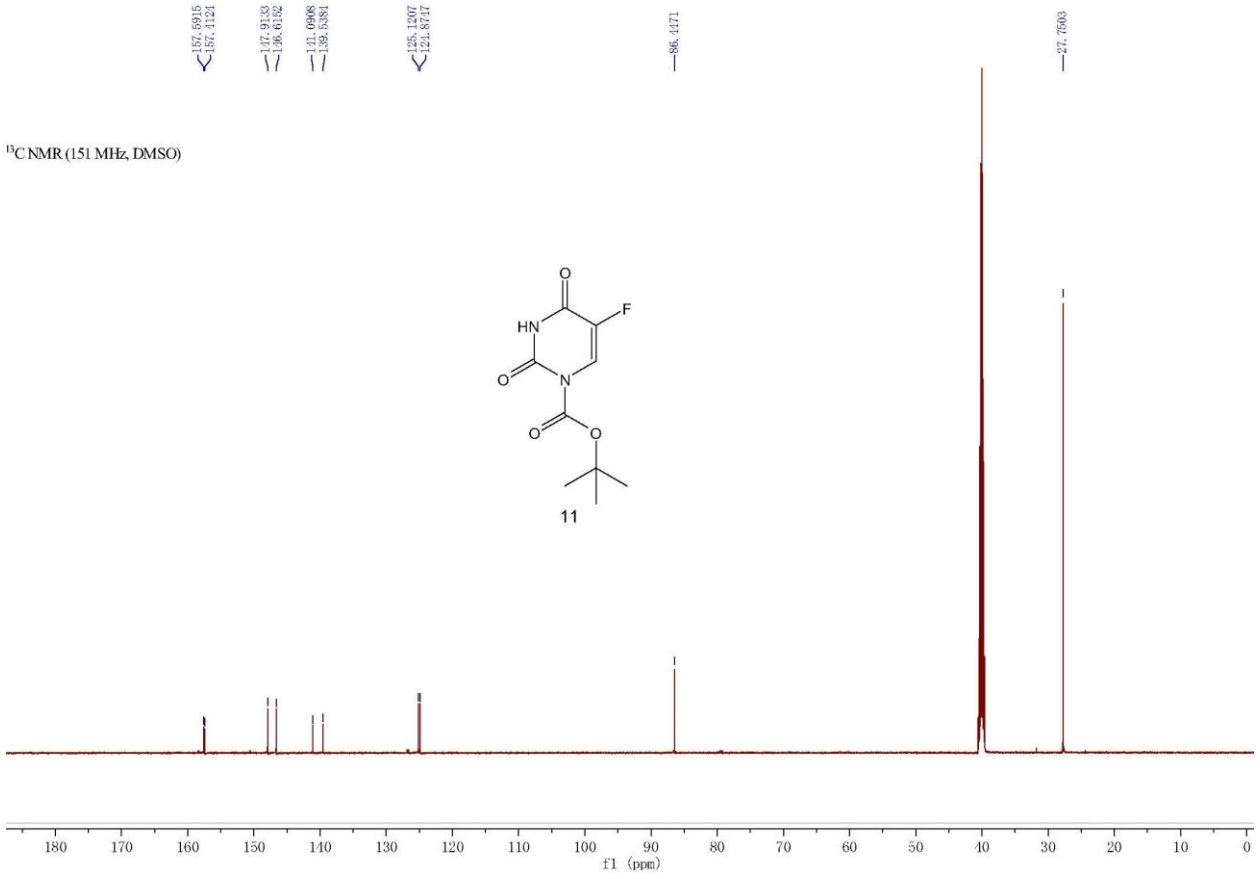
^{13}C NMR spectra of 3-N-Boc-1-propargyl-5-FU (**10**)



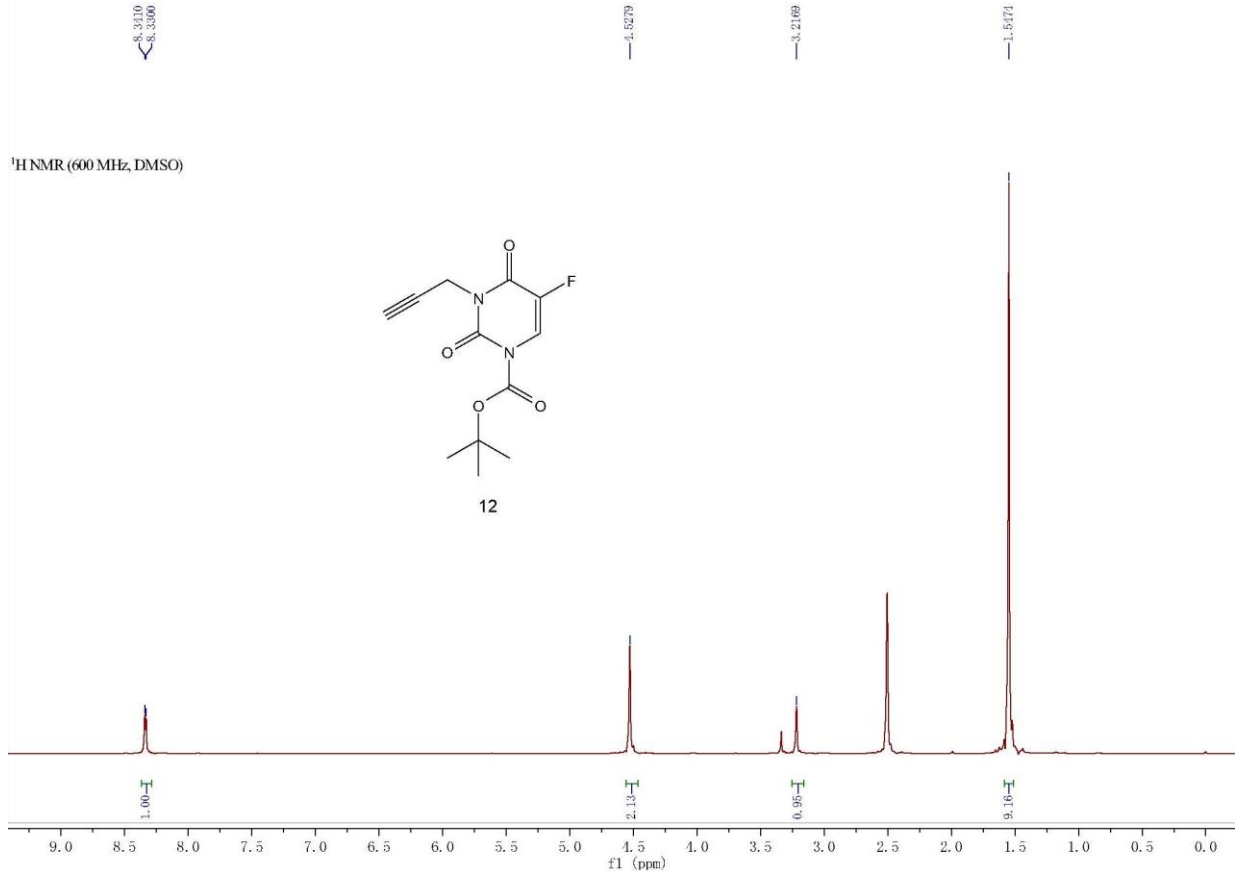
^{1}H NMR spectra of 1-N-Boc-3H-5-FU (**11**)



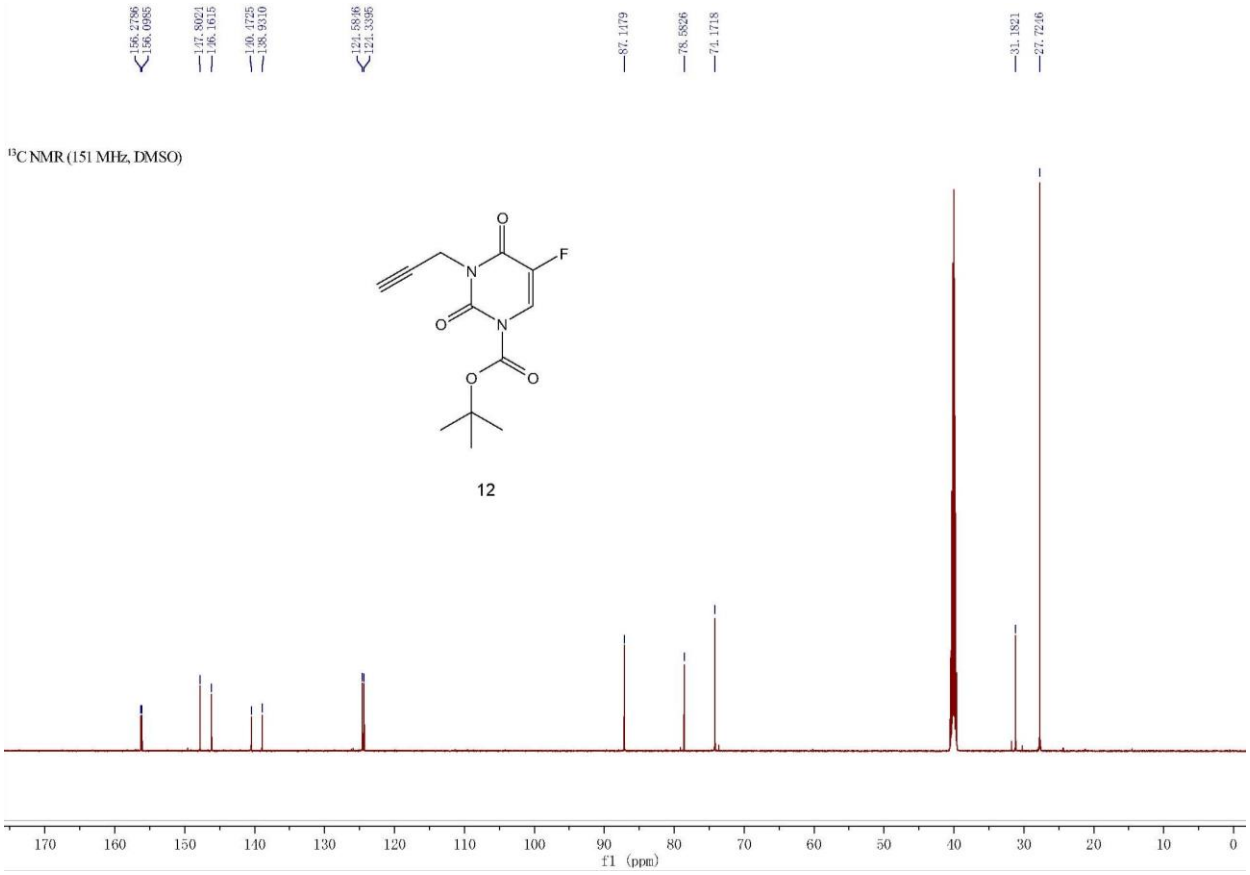
^{13}C NMR spectra of 1-N-Boc-3H-5-FU (**11**)



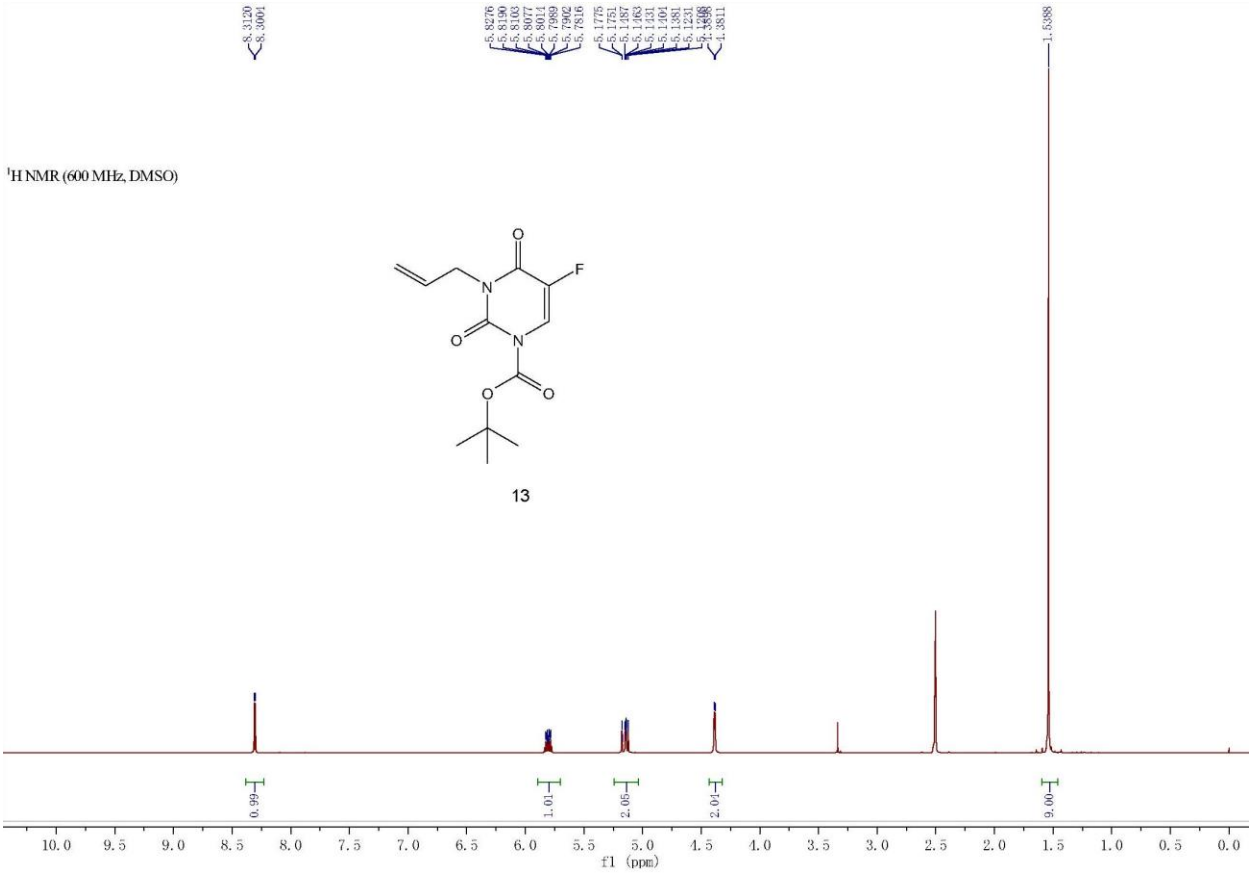
^{1}H NMR spectra of 1-N-Boc-3-propargyl-5-FU (**12**)



^{13}C NMR spectra of 1-N-Boc-3-propargyl-5-FU (**12**)



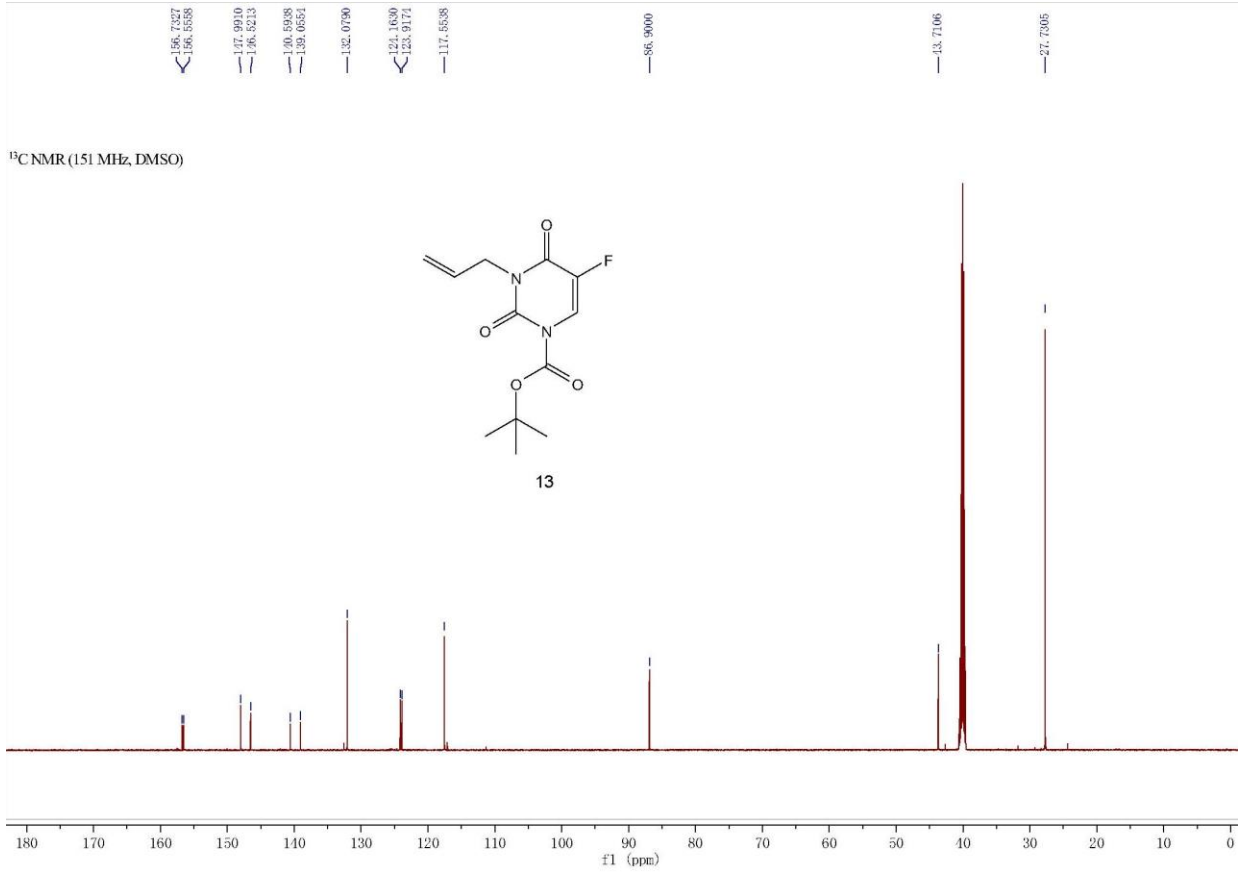
^{1}H NMR spectra of 1-N-Boc-3-allyl-5-FU (**13**)



^{1}H NMR (600 MHz, DMSO)

13

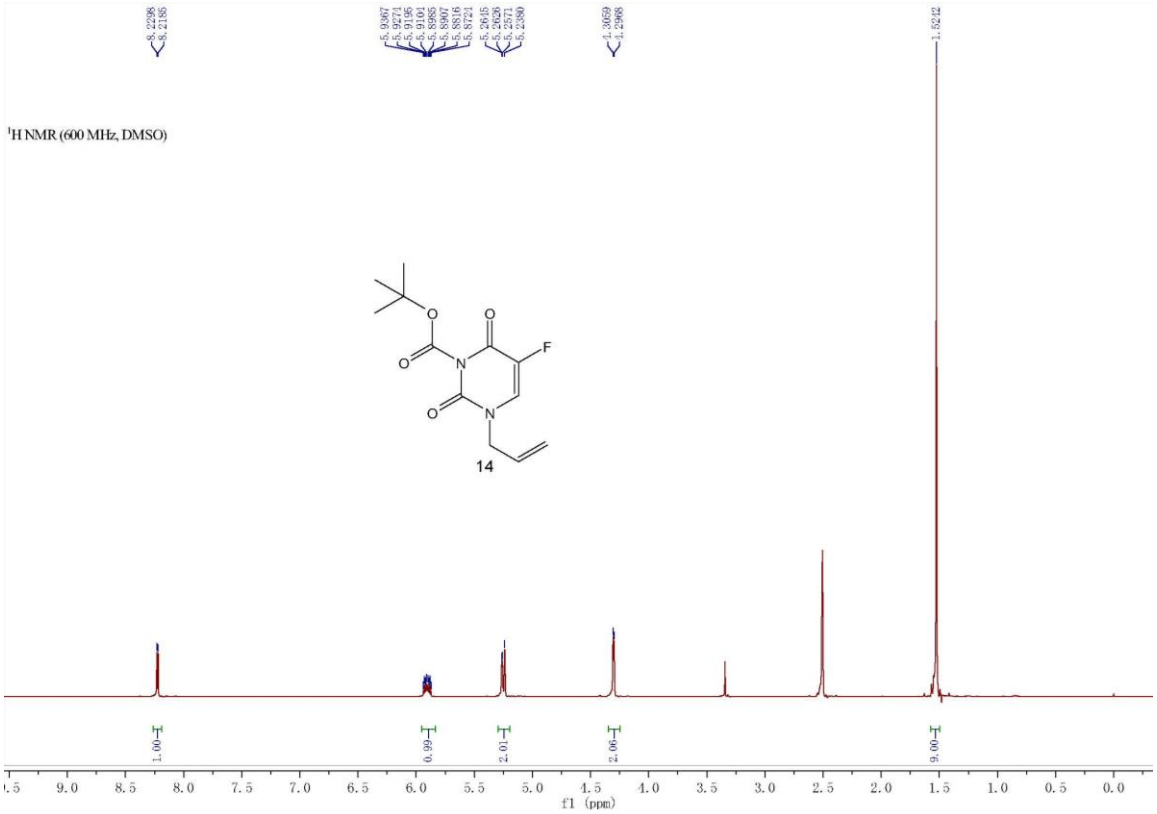
^{13}C NMR spectra of 1-N-Boc-3-allyl-5-FU (**13**)



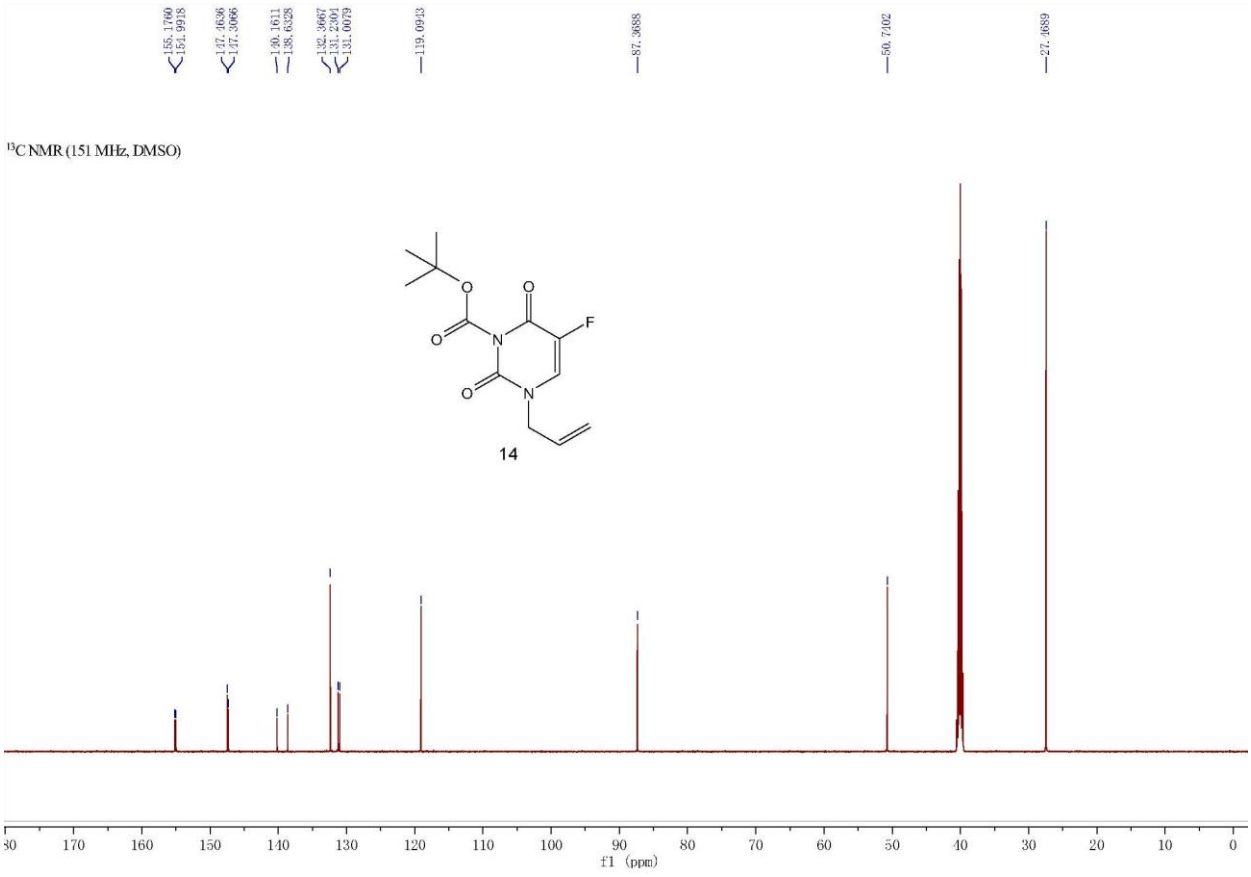
^{13}C NMR (151 MHz, DMSO)

13

^{1}H NMR spectra of 3-N-Boc-1-allyl-5-FU (**14**)

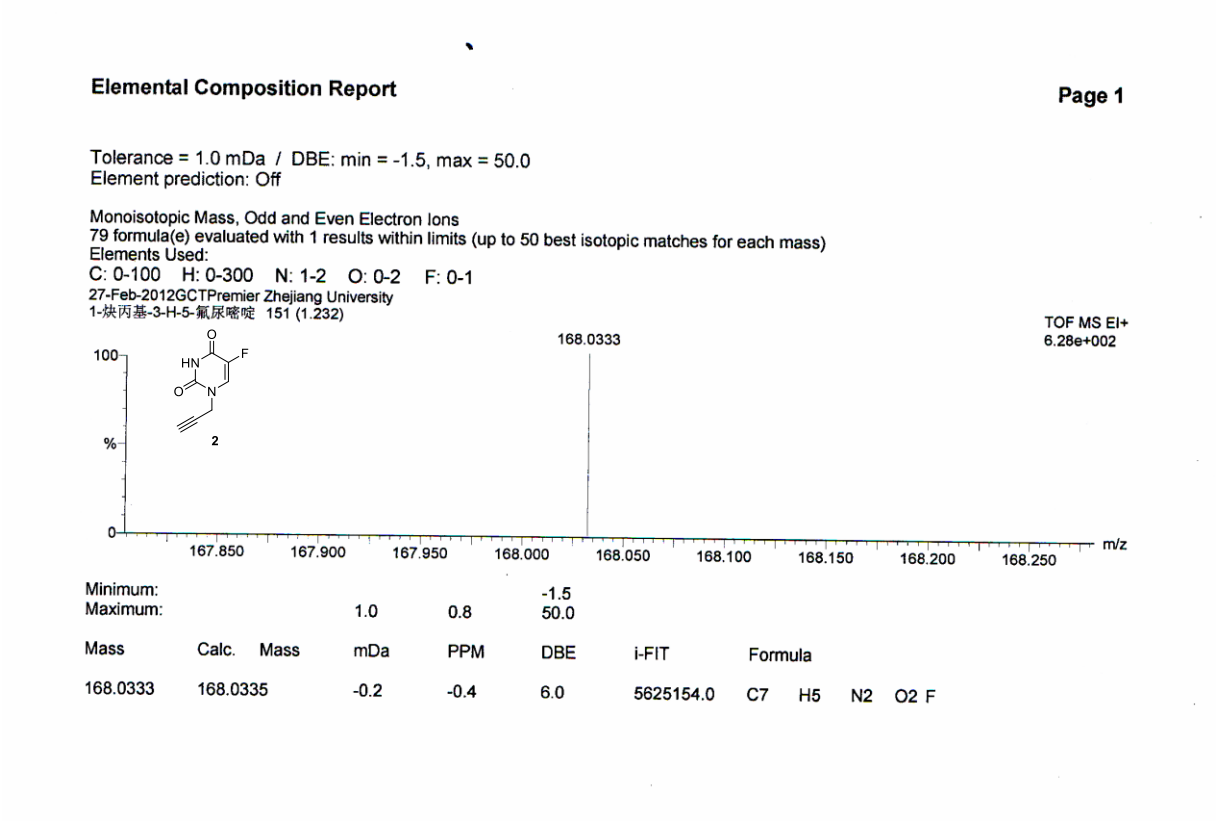


^{13}C NMR spectra of 3-N-Boc-1-allyl-5-FU (**14**)



3. HRMS spectral data

HRMS spectra of 1-propargyl-5-Fu(**2**)



Elemental Composition Report **Page 1**

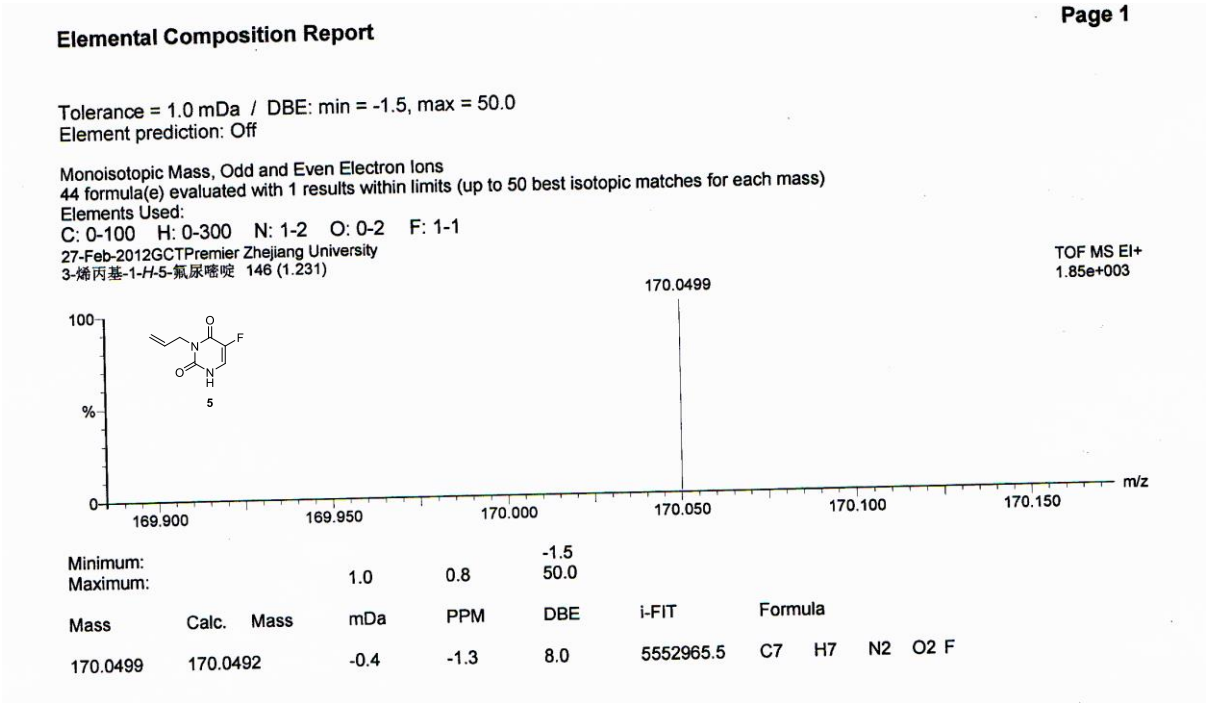
Tolerance = 1.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off

Monoisotopic Mass, Odd and Even Electron Ions
79 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 0-100 H: 0-300 N: 1-2 O: 0-2 F: 0-1
27-Feb-2012GCTPremier Zhejiang University
1-炔丙基-3-H-5-氟尿嘧啶 151 (1.232)

TOF MS EI+
6.28e+002

Minimum:					-1.5					
Maximum:			1.0	0.8	50.0					
Mass	Calc. Mass		mDa	PPM	DBE	i-FIT	Formula			
168.0333	168.0335		-0.2	-0.4	6.0	5625154.0	C7	H5	N2	O2 F

HRMS spectra of 3-allyl-5-Fu(**5**)



Elemental Composition Report **Page 1**

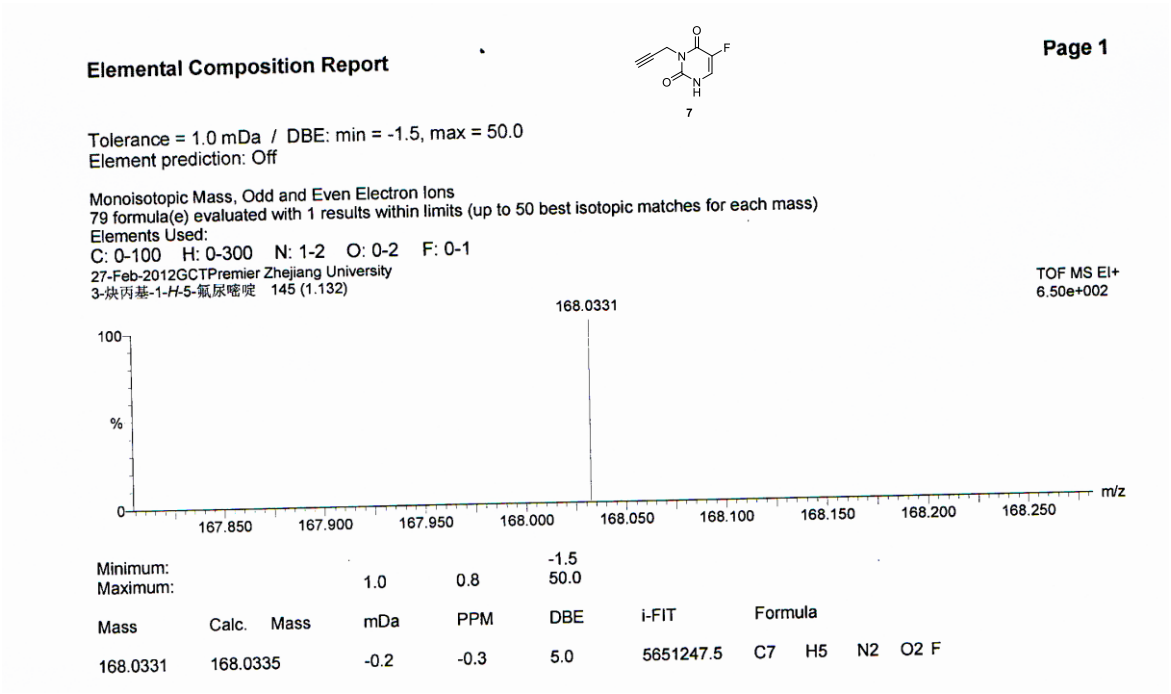
Tolerance = 1.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off

Monoisotopic Mass, Odd and Even Electron Ions
44 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 0-100 H: 0-300 N: 1-2 O: 0-2 F: 1-1
27-Feb-2012GCTPremier Zhejiang University
3-烯丙基-1-*H*-5-氟尿嘧啶 146 (1.231)

TOF MS EI+
1.85e+003

Minimum:					-1.5					
Maximum:			1.0	0.8	50.0					
Mass	Calc. Mass		mDa	PPM	DBE	i-FIT	Formula			
170.0499	170.0492		-0.4	-1.3	8.0	5552965.5	C7	H7	N2	O2 F

HRMS spectra of 3-propargyl-5-Fu(**7**)



Elemental Composition Report Page 1

7

Tolerance = 1.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off

Monoisotopic Mass, Odd and Even Electron Ions
79 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 0-100 H: 0-300 N: 1-2 O: 0-2 F: 0-1
27-Feb-2012GCTPremier Zhejiang University
3-炔丙基-1-*H*-5-氟尿嘧啶 145 (1.132)

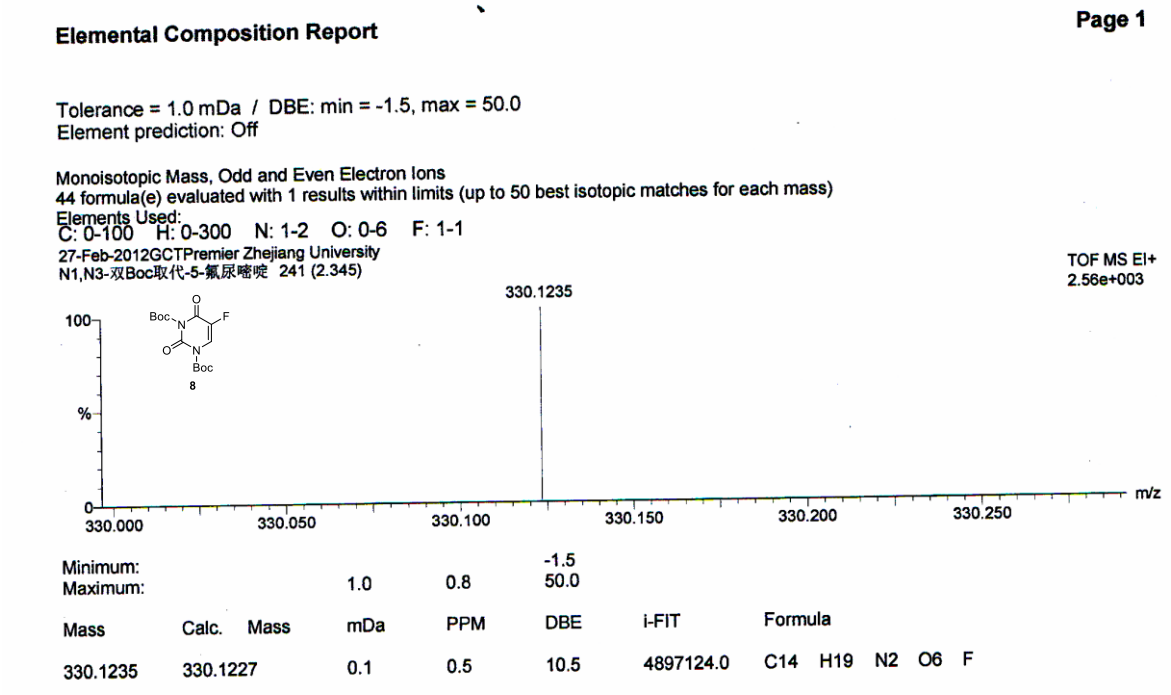
TOF MS EI+
6.50e+002

168.0331

100
%
0
167.850 167.900 167.950 168.000 168.050 168.100 168.150 168.200 168.250 m/z

Minimum:			1.0	0.8	-1.5					
Maximum:					50.0					
Mass	Calc. Mass		mDa	PPM	DBE	i-FIT	Formula			
168.0331	168.0335		-0.2	-0.3	5.0	5651247.5	C7	H5	N2	O2 F

HRMS spectra of 1,3-diBoc-5-Fu(**8**)



Elemental Composition Report Page 1

Tolerance = 1.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off

Monoisotopic Mass, Odd and Even Electron Ions
44 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 0-100 H: 0-300 N: 1-2 O: 0-6 F: 1-1
27-Feb-2012GCTPremier Zhejiang University
N1,N3-双Boc取代-5-氟尿嘧啶 241 (2.345)

TOF MS EI+
2.56e+003

330.1235

8

100
%
0
330.000 330.050 330.100 330.150 330.200 330.250 m/z

Minimum:			1.0	0.8	-1.5					
Maximum:					50.0					
Mass	Calc. Mass		mDa	PPM	DBE	i-FIT	Formula			
330.1235	330.1227		0.1	0.5	10.5	4897124.0	C14	H19	N2	O6 F

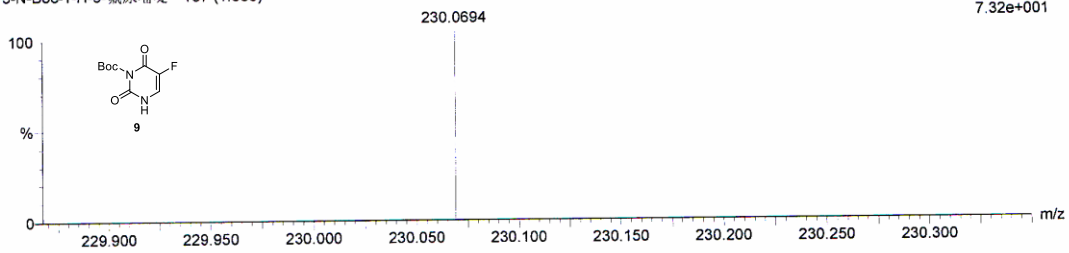
HRMS spectra of 3-Boc-5-Fu(**9**)

Elemental Composition Report **Page 1**

Tolerance = 0.5 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off

Monoisotopic Mass, Odd and Even Electron Ions
82 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 0-100 H: 0-300 N: 1-2 O: 0-4 F: 0-1
27-Feb-2012GCTPremier Zhejiang University
3-N-Boc-1-H-5-氟尿嘧啶 187 (1.655)

TOF MS EI+
7.32e+001



Minimum:					-1.5					
Maximum:			0.5	0.8	50.0					
Mass	Calc. Mass		mDa	PPM	DBE	i-FIT	Formula			
230.0694	230.0703		-0.3	-0.5	4.0	5556785.5	C9	H11	N2	O4 F

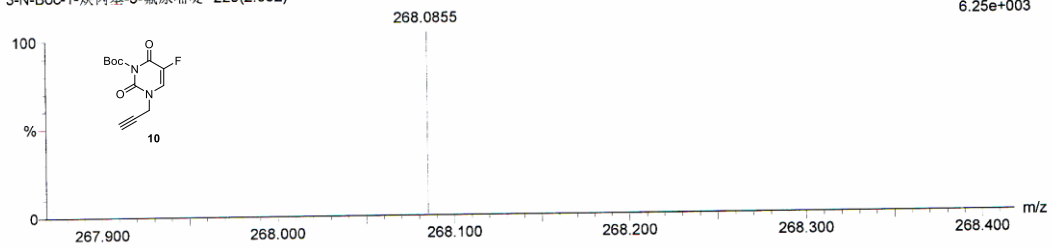
HRMS spectra of 1-propargyl-3-Boc-5-Fu(**10**)

Elemental Composition Report **Page 1**

Tolerance = 1.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off

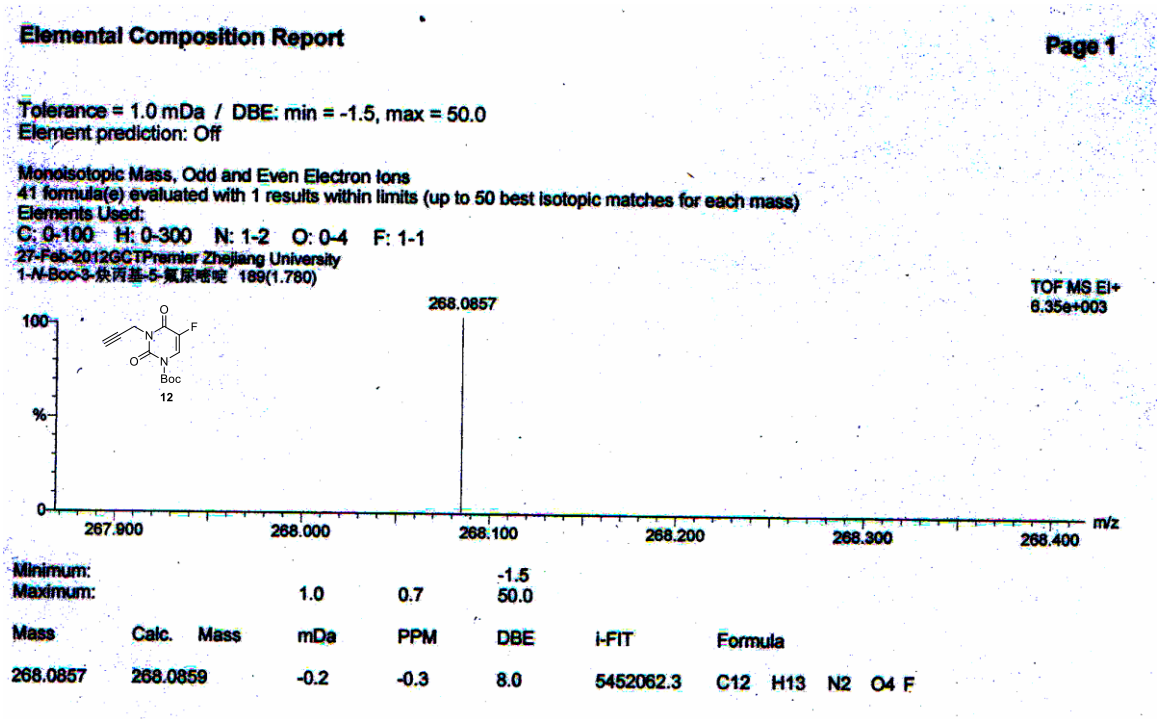
Monoisotopic Mass, Odd and Even Electron Ions
41 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 0-100 H: 0-300 N: 1-2 O: 0-4 F: 1-1
27-Feb-2012GCTPremier Zhejiang University
3-N-Boc-1-炔丙基-5-氟尿嘧啶 225(2.032)

TOF MS EI+
6.25e+003

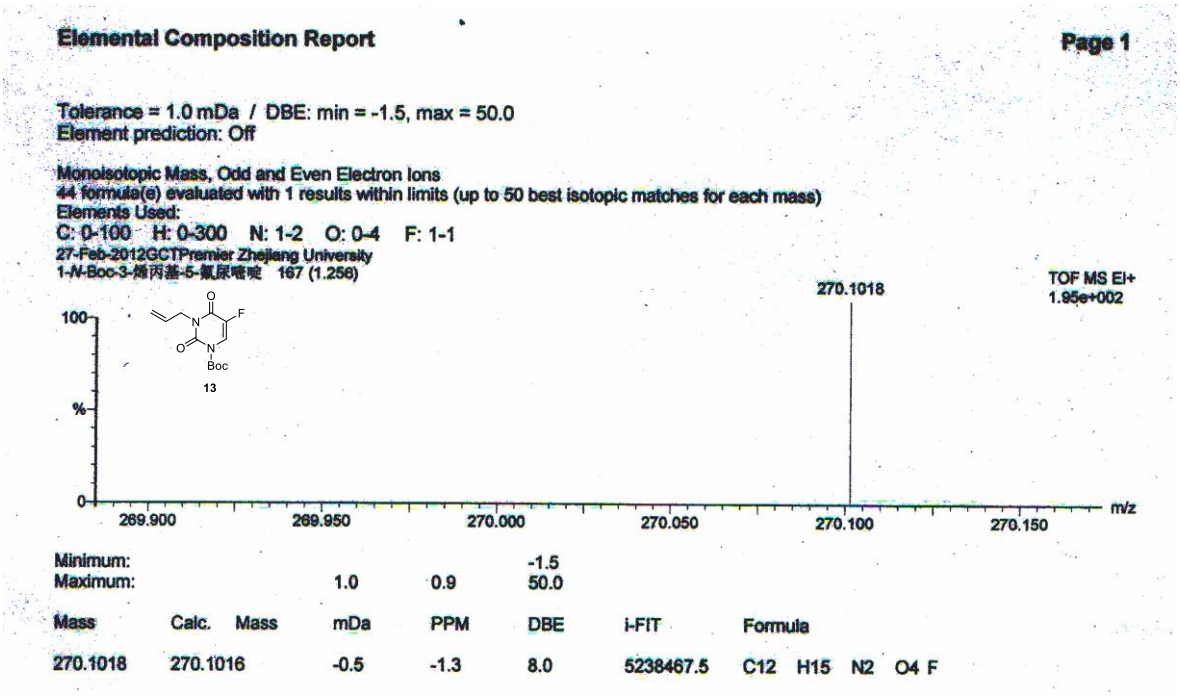


Minimum:					-1.5					
Maximum:			1.0	0.7	50.0					
Mass	Calc. Mass		mDa	PPM	DBE	i-FIT	Formula			
268.0855	268.0859		-0.2	-0.3	8.0	5231234.3	C12	H13	N2	O4 F

HRMS spectra of 1-Boc-3-propargyl-5-Fu(**12**)



HRMS spectra of 1-Boc-3-allyl-5-Fu(**13**)

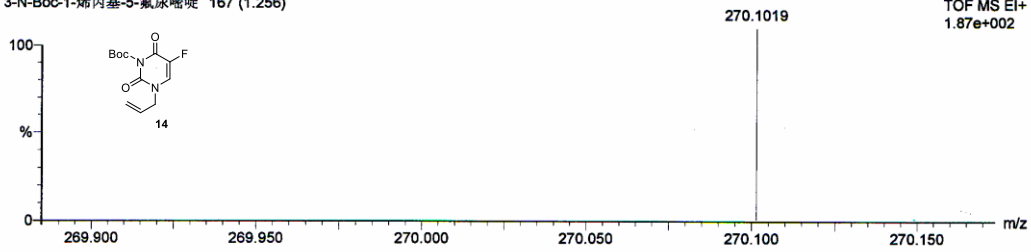


HRMS spectra of 1-allyl-3-Boc-5-Fu(**14**)

Elemental Composition Report **Page 1**

Tolerance = 1.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off

Monoisotopic Mass, Odd and Even Electron Ions
44 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 0-100 H: 0-300 N: 1-2 O: 0-4 F: 1-1
27-Feb-2012GCTPremier Zhejiang University
3-N-Boc-1-烯丙基-5-氟尿嘧啶 167 (1.256)



Minimum:				-1.5			
Maximum:		1.0	0.9	50.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula	
270.1019	270.1016	-0.4	-1.2	8.0	5238467.5	C12 H15 N2 O4 F	

4. Reference

1. Yu, B.; Qi, P. P.; Shi, X. J.; Huang, R. L.; Guo, H.; Zheng, Y. C.; Yu, D. Q.; Liu, H. M. *Eur. J. Med. Chem*. **2016**, *117*, 241-255. https://doi.org/10.1016/j.ejmech.2016.04.024

