

## **Aroyl-isothiocyanate/isoselenocyanate as precursors to afford novel *cis*-3- aroyl-thiourea/urea-b-lactams: Design, synthesis, docking and biological evaluation**

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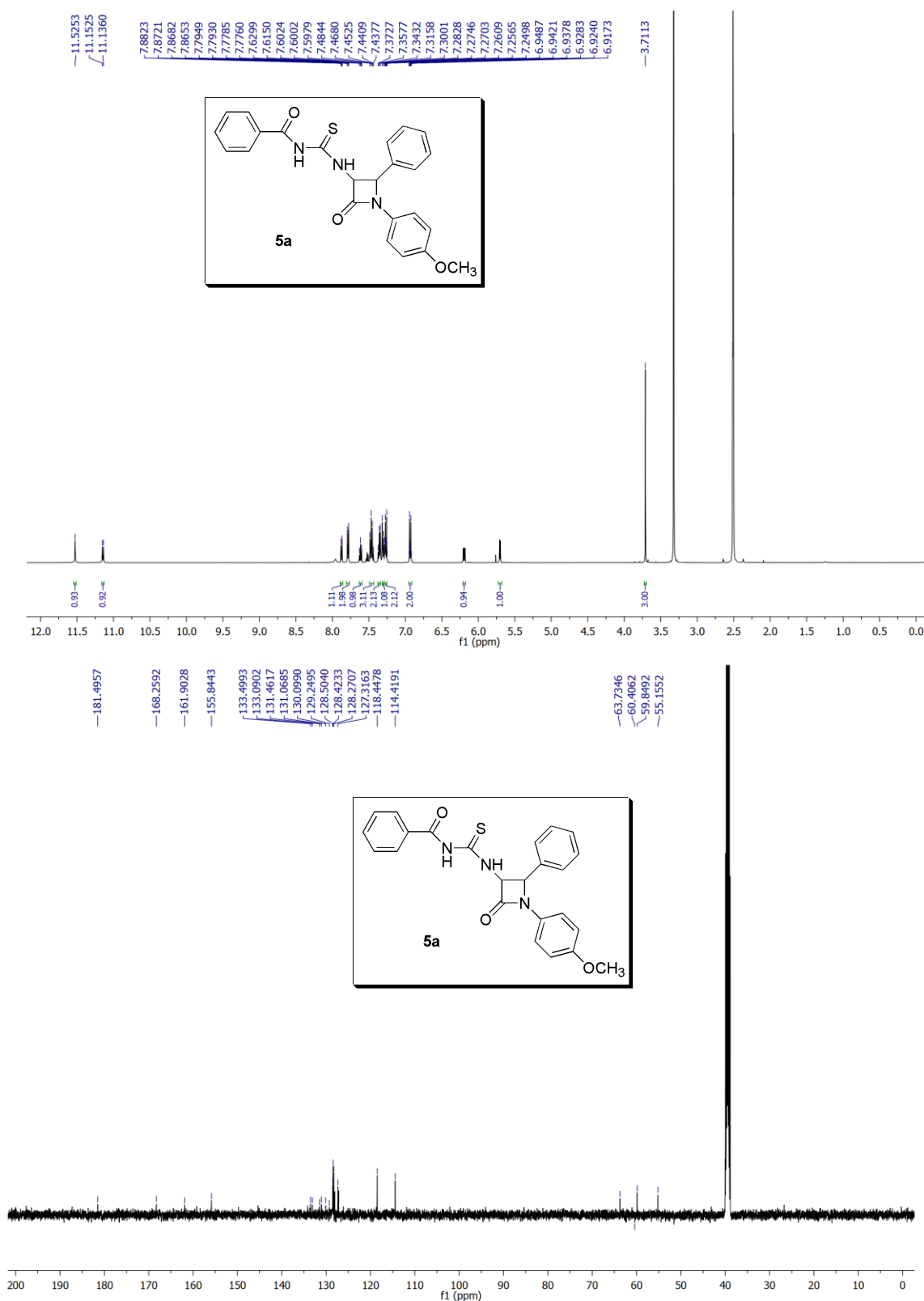
\* Corresponding author.

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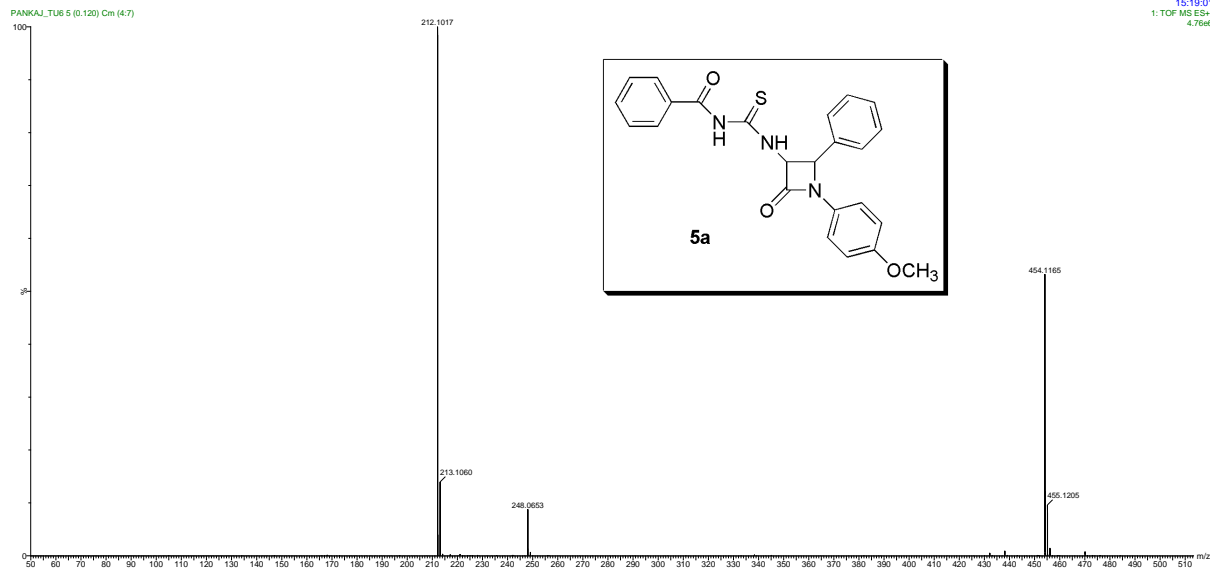
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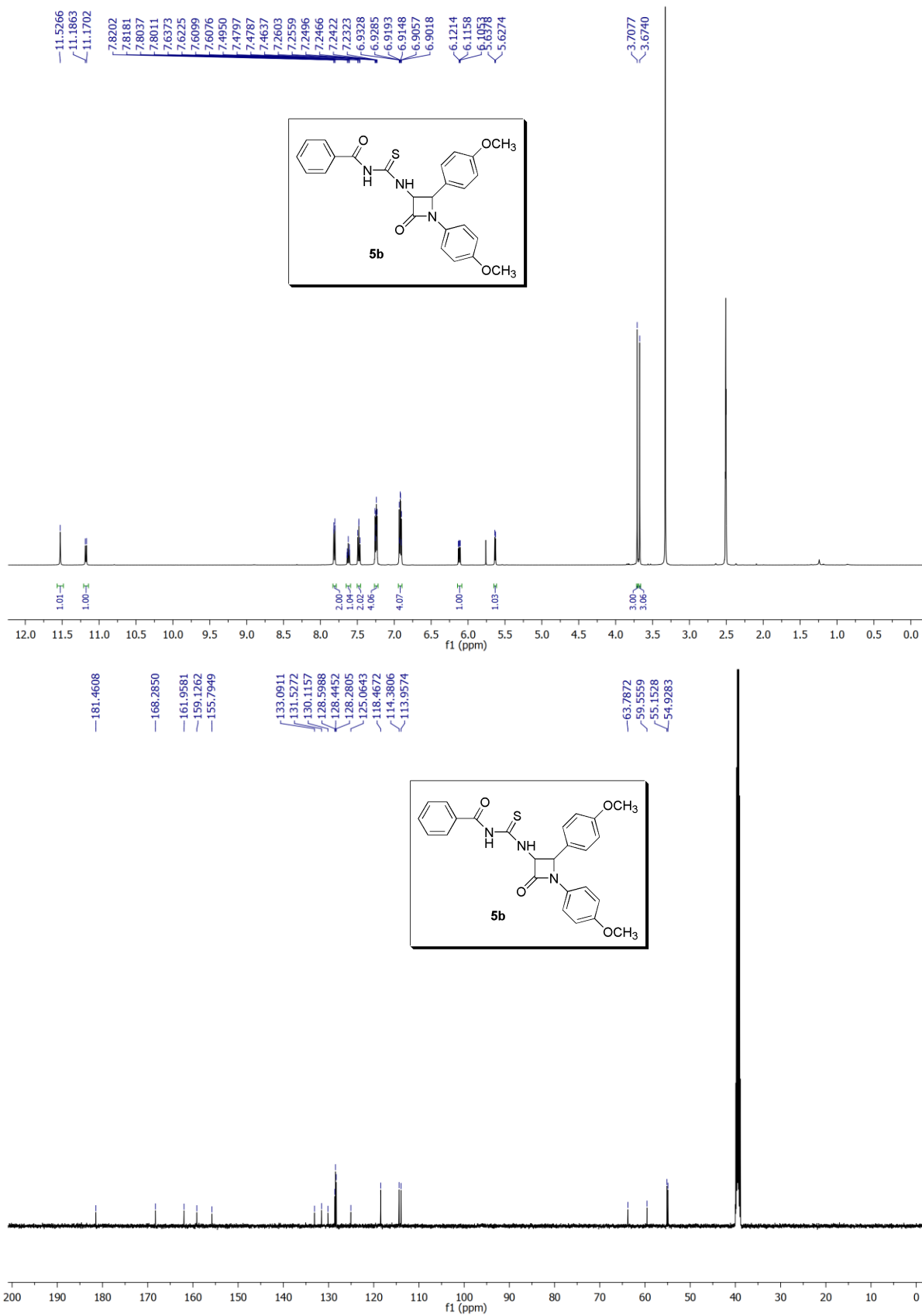
# 1. $^1\text{H}$ , $^{13}\text{C}$ -NMR and HRMS spectra of 3-arylthiourea- $\beta$ -lactams 5a-f



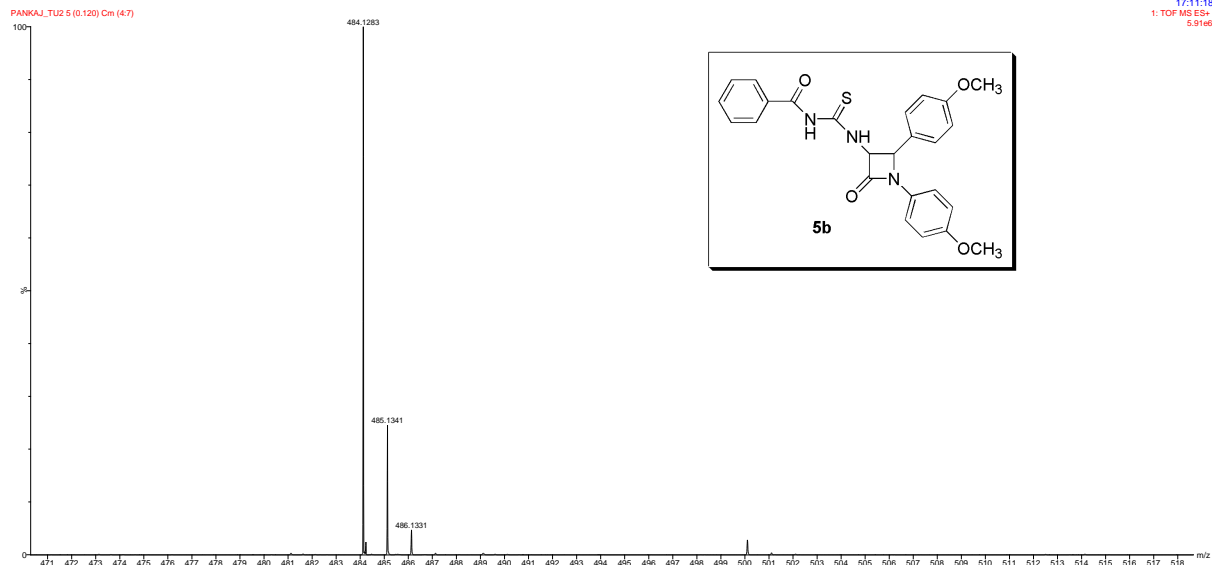
**Figure S1:**  $^1\text{H}$  and  $^{13}\text{C}$ -NMR spectra of 1-Benzoyl-3-[1-(4-methoxy-phenyl)-2-oxo-4-phenyl-azetidin-3-yl]-thiourea **5a** in DMSO



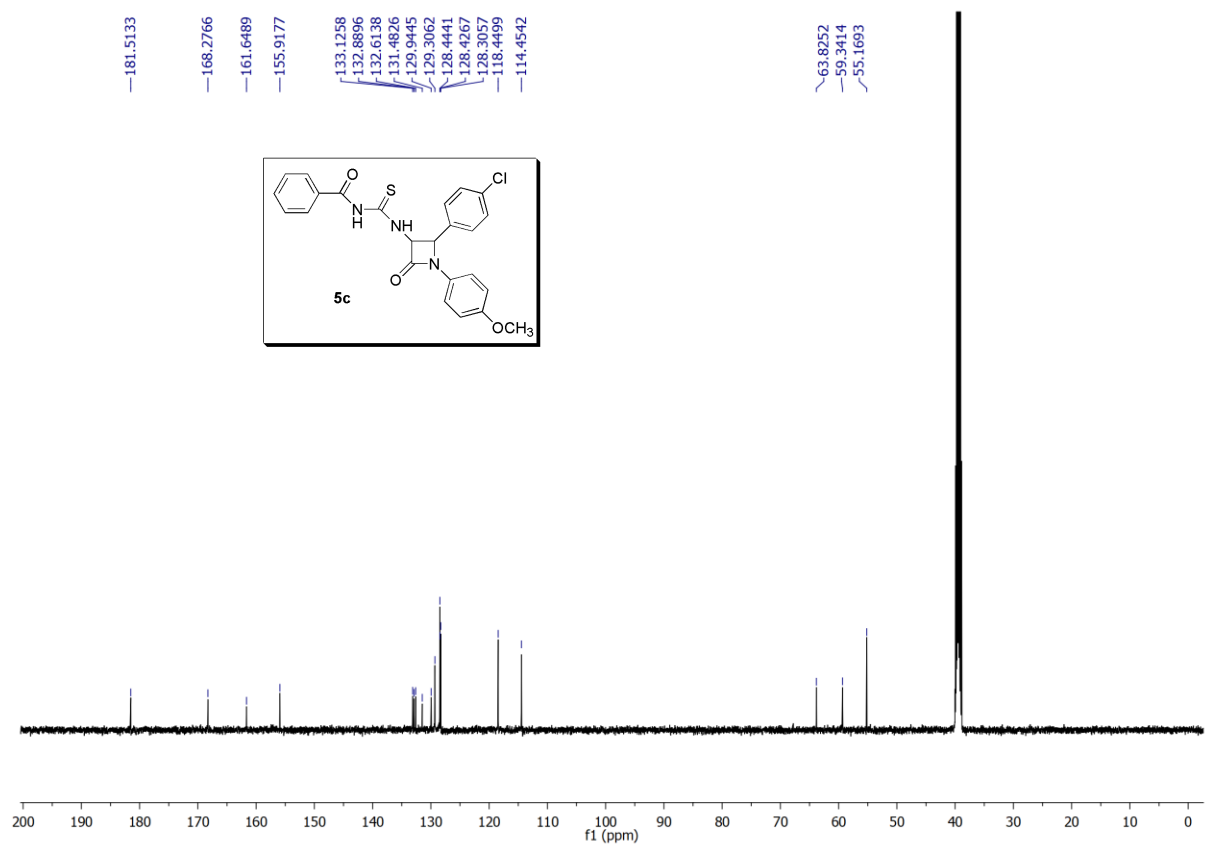
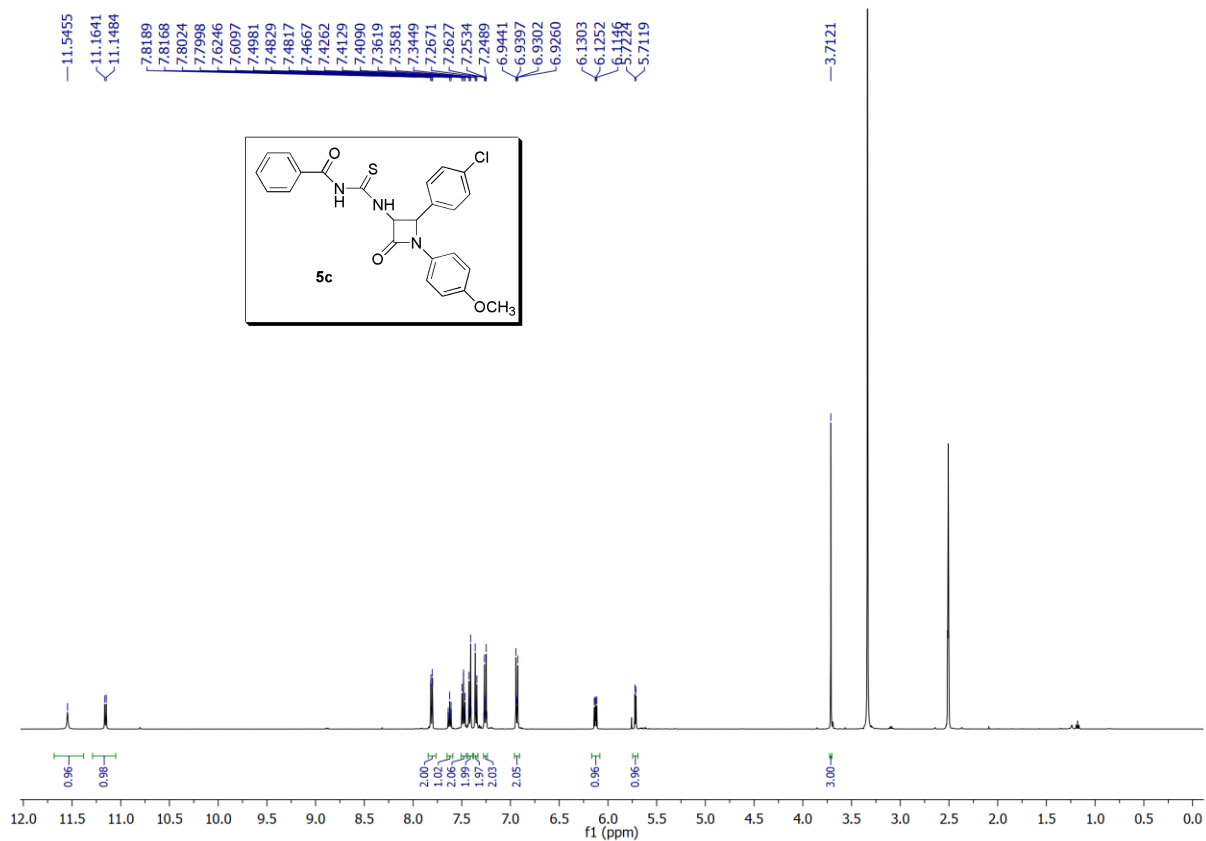
**Figure S2:** HRMS spectra of 1-Benzoyl-3-[1-(4-methoxy-phenyl)-2-oxo-4-phenyl-azetidin-3-yl]-thiourea **5a**



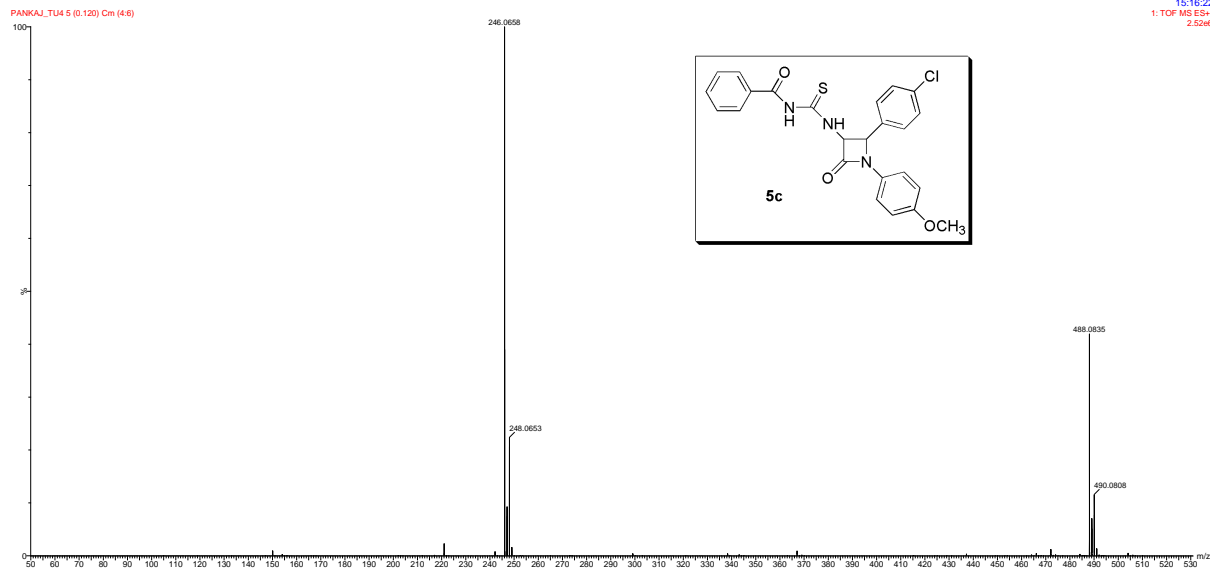
**Figure S3:**  $^1\text{H}$  and  $^{13}\text{C}$ -NMR spectra of 1-Benzoyl-3-[1,2-bis-(4-methoxy-phenyl)-4-oxo-azetidin-3-yl]-thiourea **5b** in DMSO



**Figure S4:** HRMS spectra of 1-Benzoyl-3-[1,2-bis-(4-methoxy-phenyl)-4-oxo-azetidin-3-yl]-thiourea **5b**

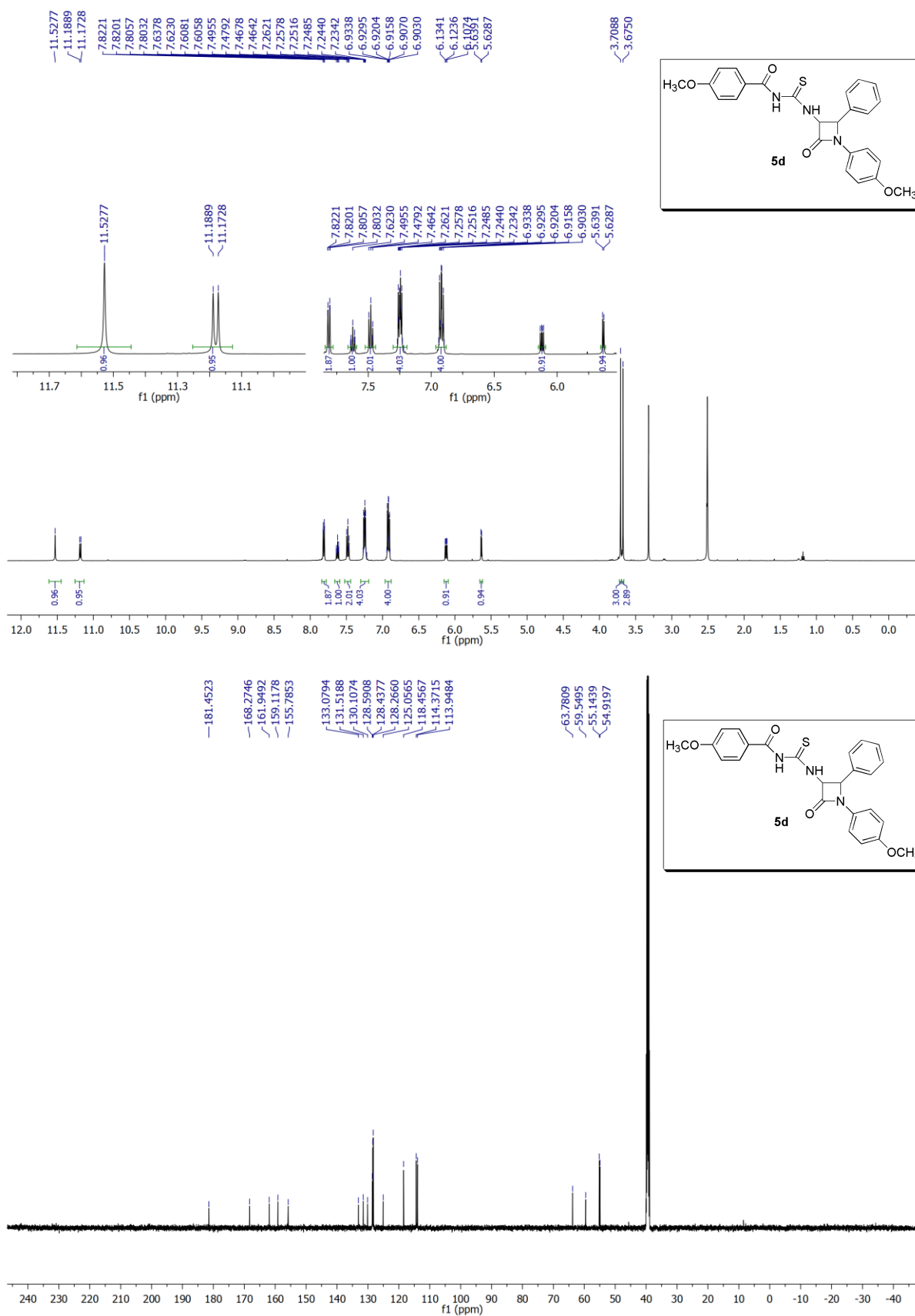


**Figure S5:** <sup>1</sup>H and <sup>13</sup>C-NMR spectra of 1-Benzoyl-3-[2-(4-chloro-phenyl)-1-(4-methoxy-phenyl)-4-oxo-azetidin-3-yl]-thiourea **5c** in DMSO

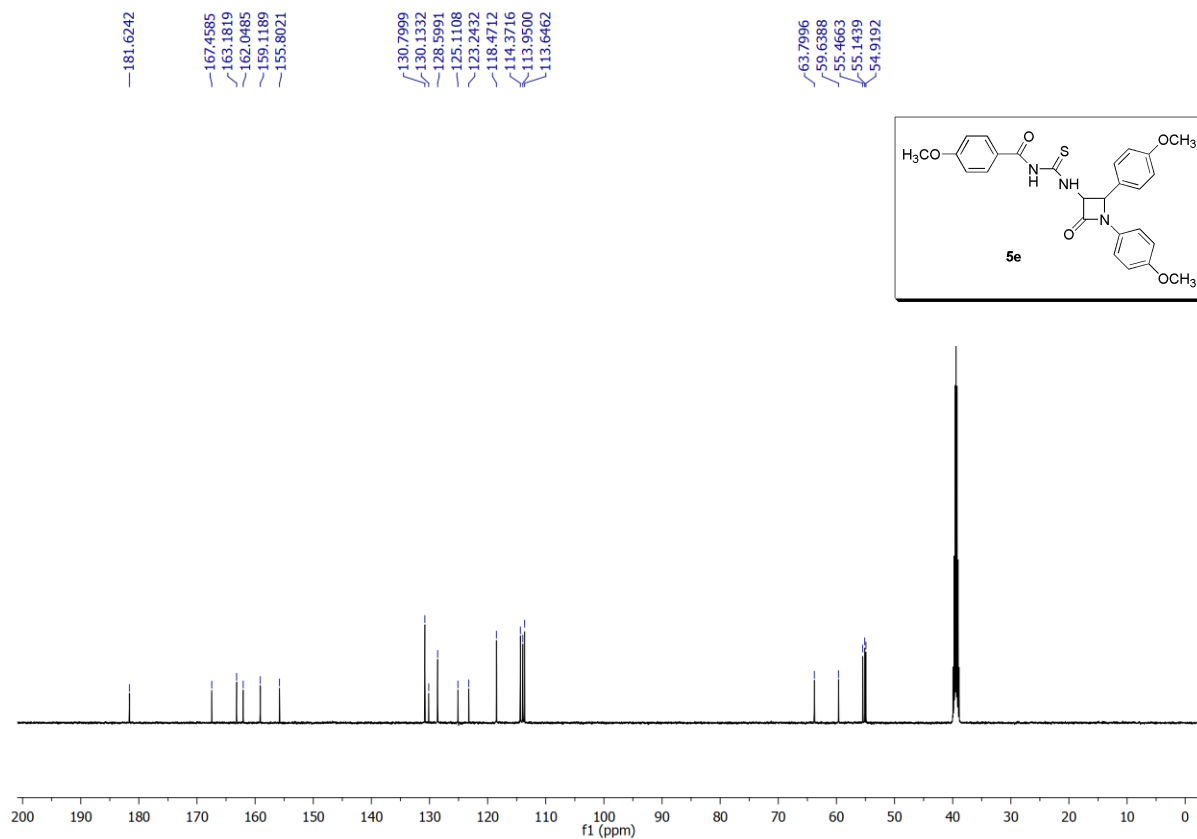
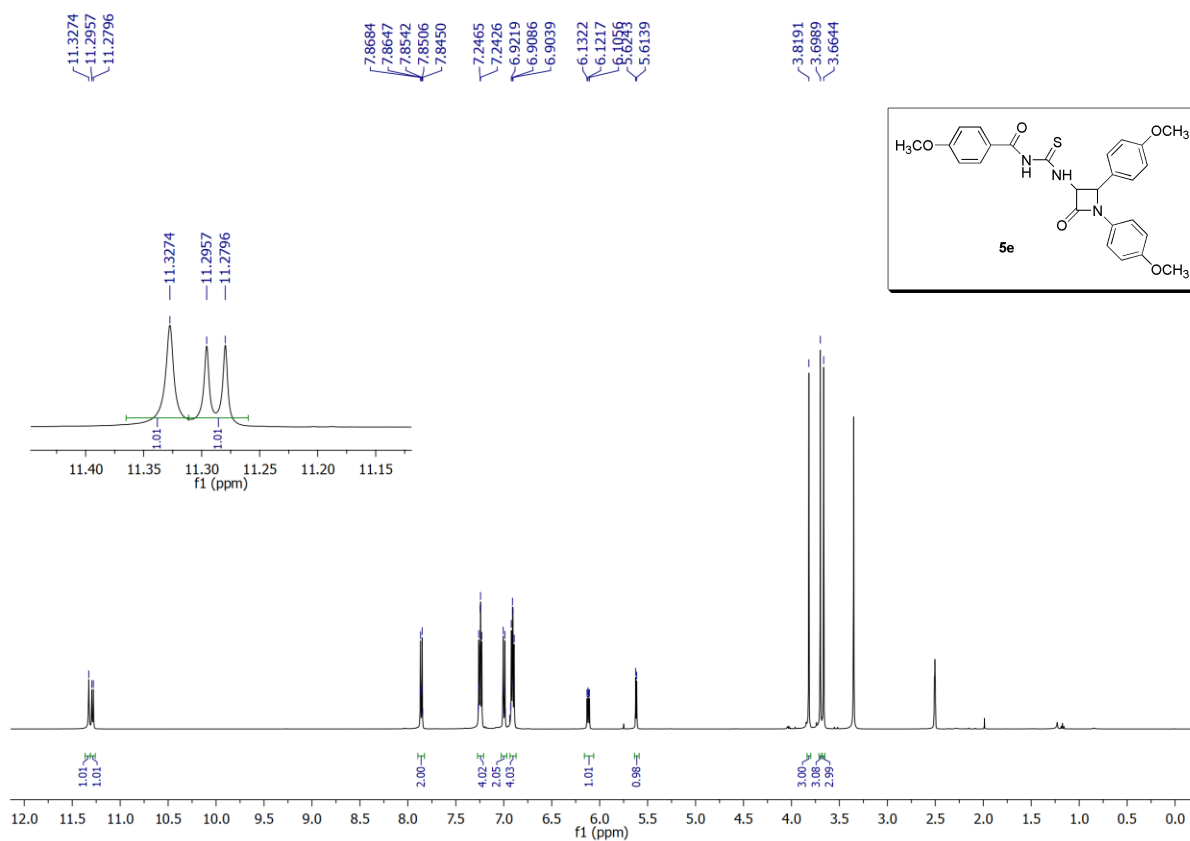


**Figure S6:** HRMS spectra of 1-Benzoyl-3-[2-(4-chloro-phenyl)-1-(4-methoxy-phenyl)-4-oxo-azetidin-3-yl]-thiourea **5c**

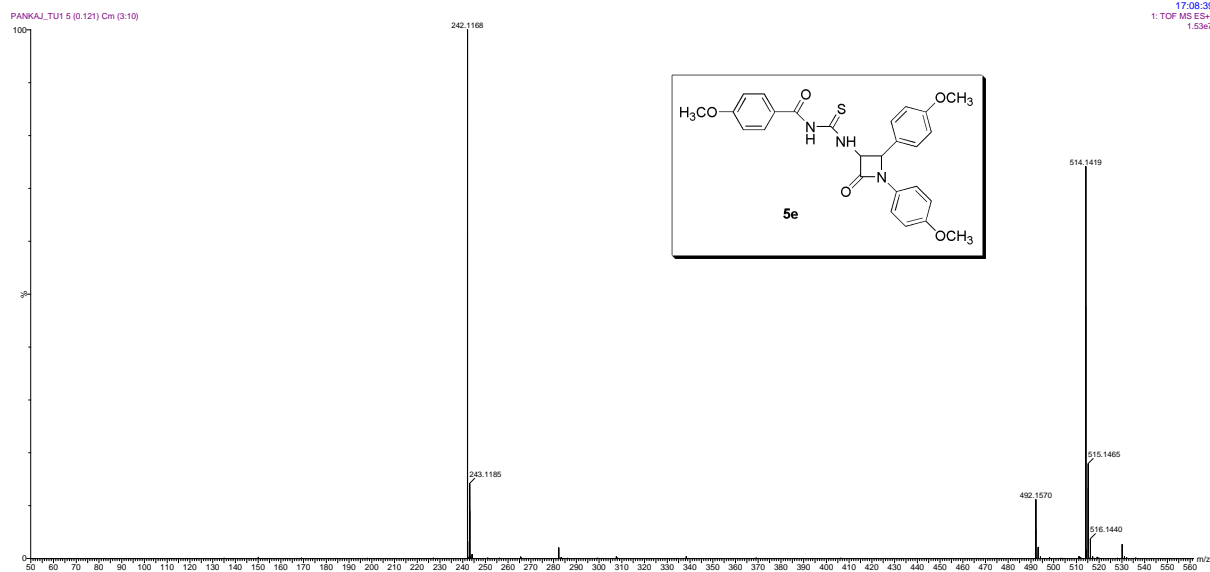




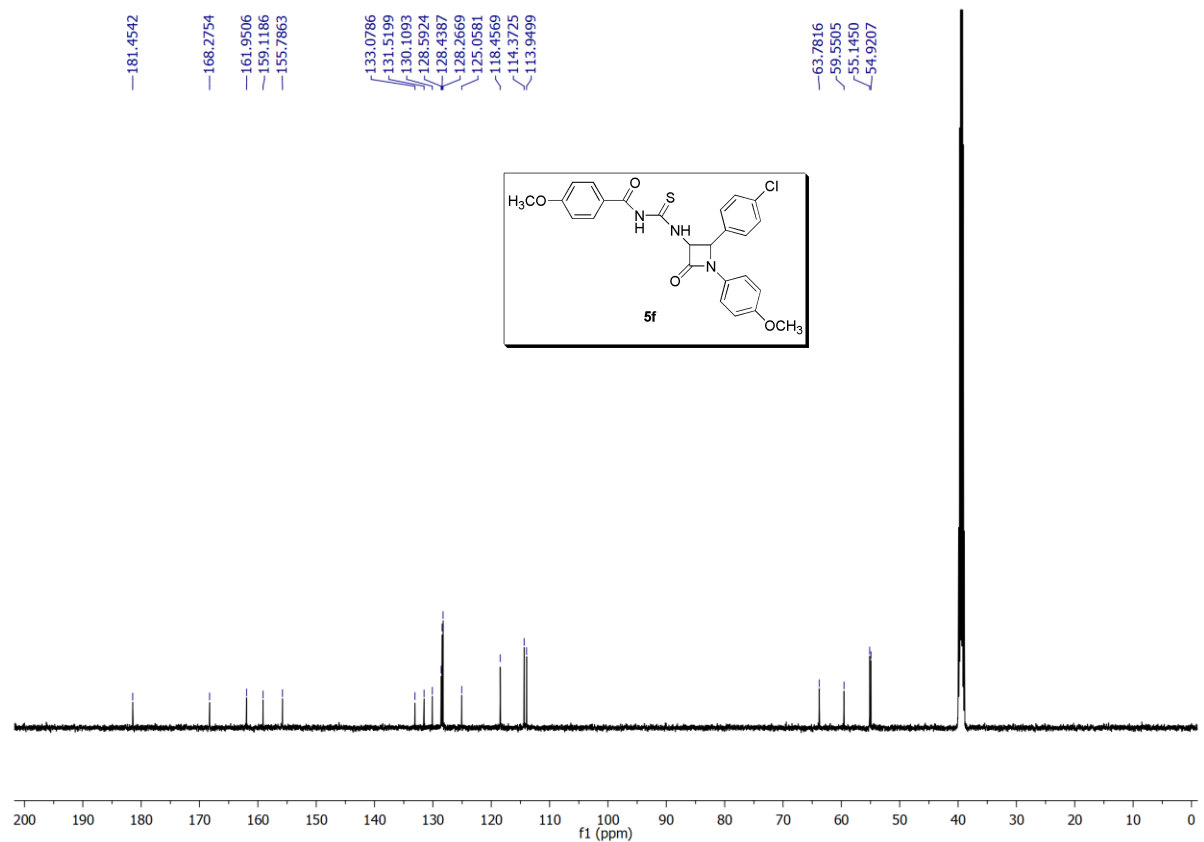
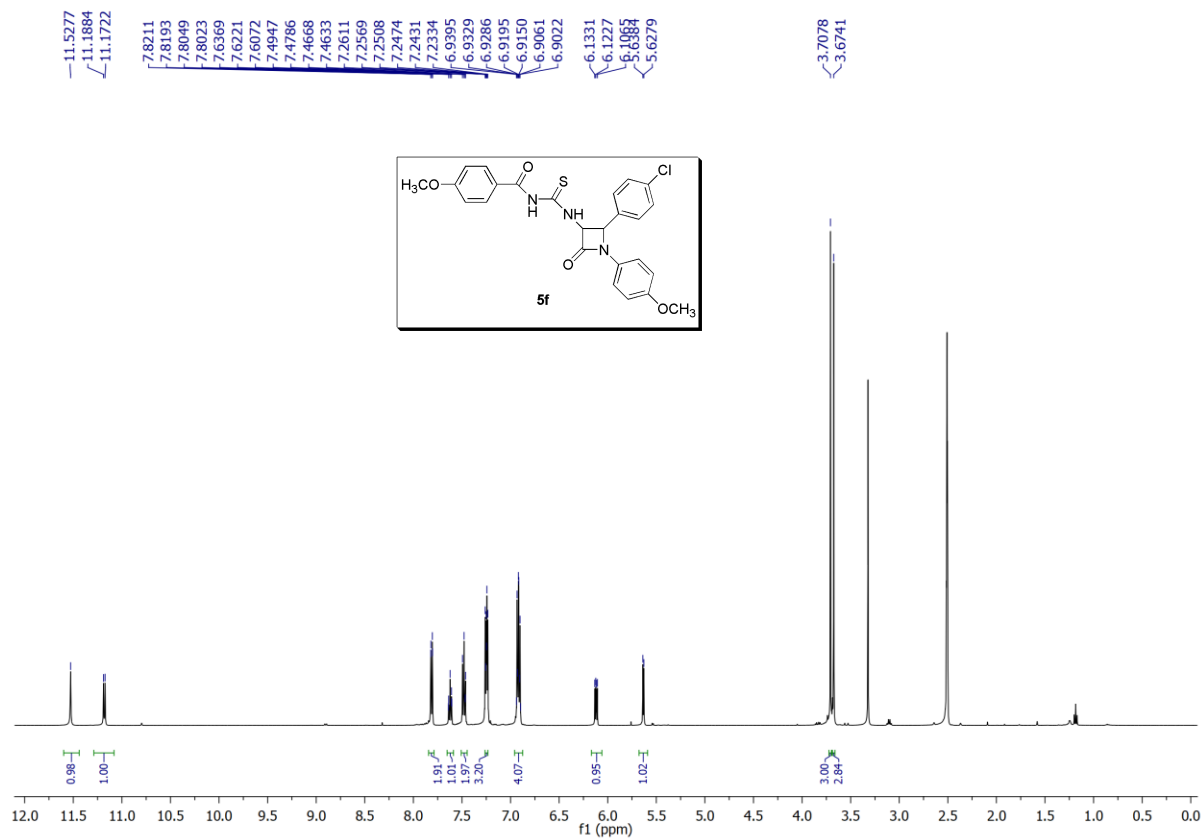
**Figure S7:** <sup>1</sup>H and <sup>13</sup>C-NMR spectra of 1-(4-Methoxy-benzoyl)-3-[1-(4-methoxy-phenyl)-2-oxo-4-phenyl-azetidin-3-yl]-thiourea **5d** in DMSO



**Figure S8:** <sup>1</sup>H and <sup>13</sup>C-NMR spectra of 1-[1,2-Bis-(4-methoxy-phenyl)-4-oxo-azetidin-3-yl]-3-(4-methoxy-benzoyl)-thiourea **5e** in DMSO

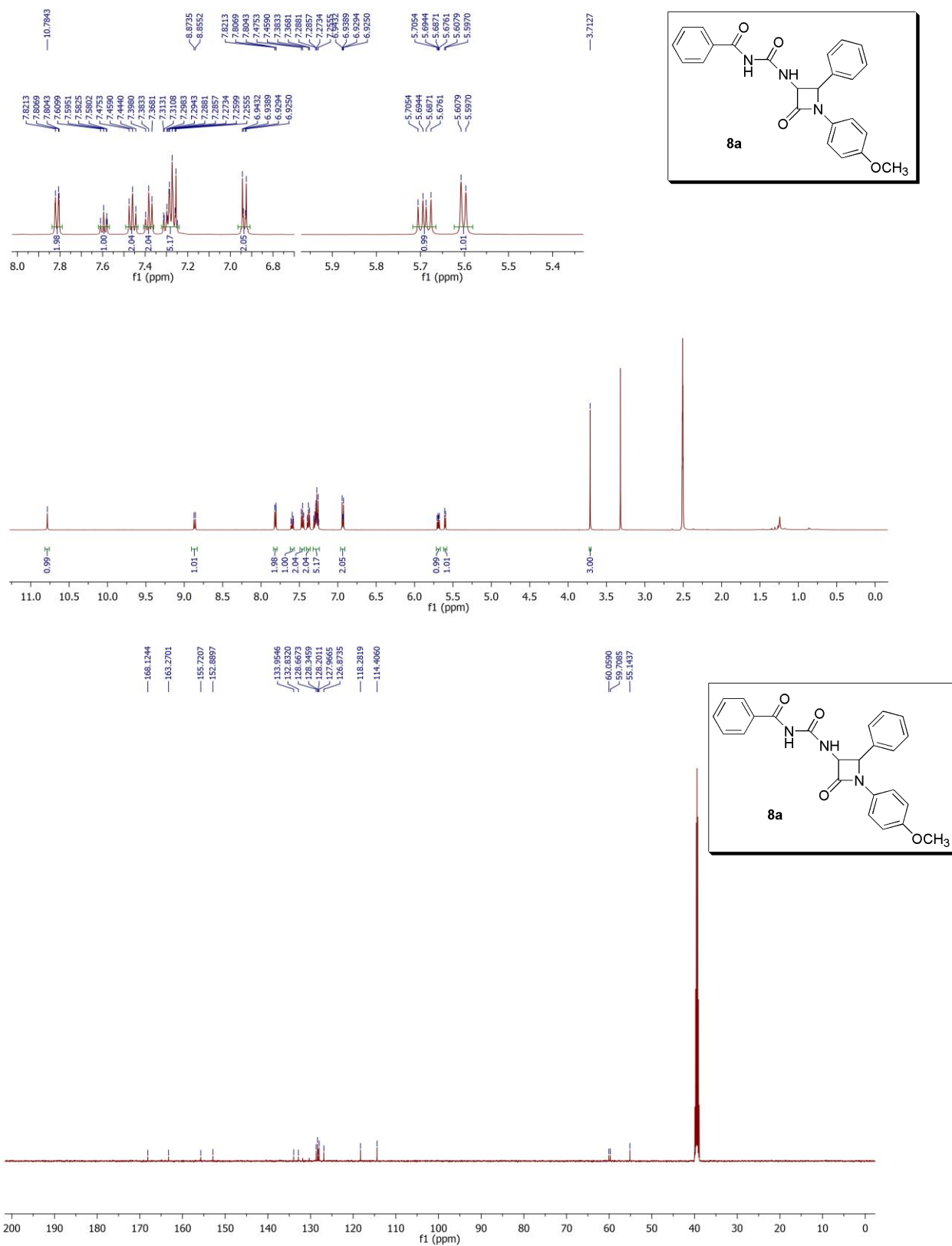


**Figure S9:** HRMS spectra of 1-[1,2-Bis-(4-methoxy-phenyl)-4-oxo-azetidin-3-yl]-3-(4-methoxy-benzoyl)-thiourea **5e**

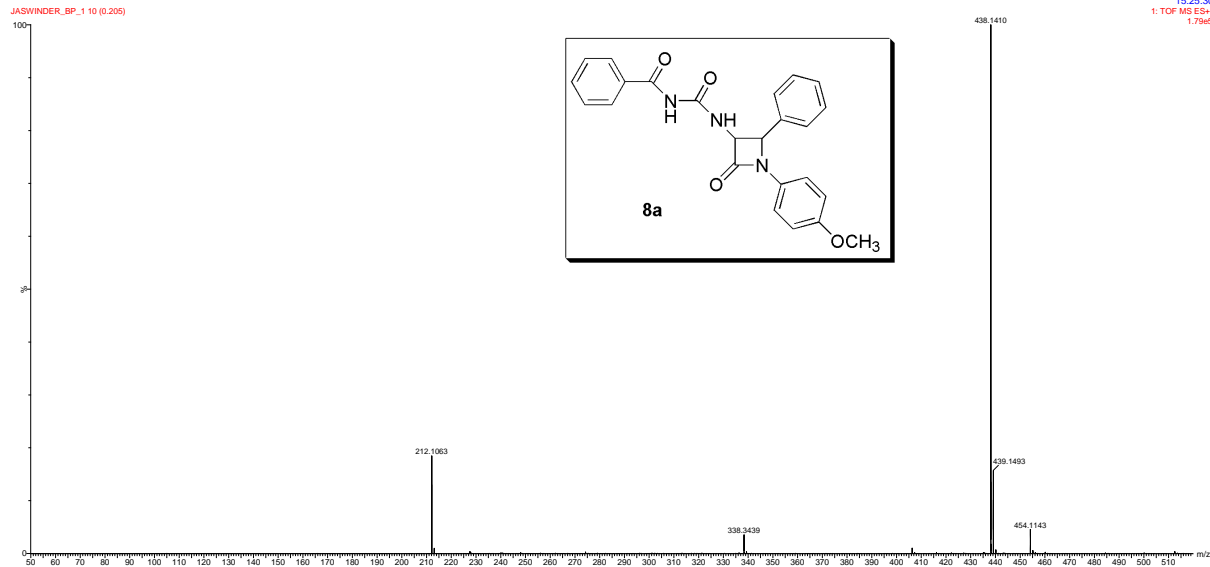


**Figure S10:** <sup>1</sup>H and <sup>13</sup>C-NMR spectra of 1-[2-(4-Chloro-phenyl)-1-(4-methoxy-phenyl)-4-oxo-azetidin-3-yl]-3-(4-methoxy-benzoyl)-thiourea **5f** in DMSO

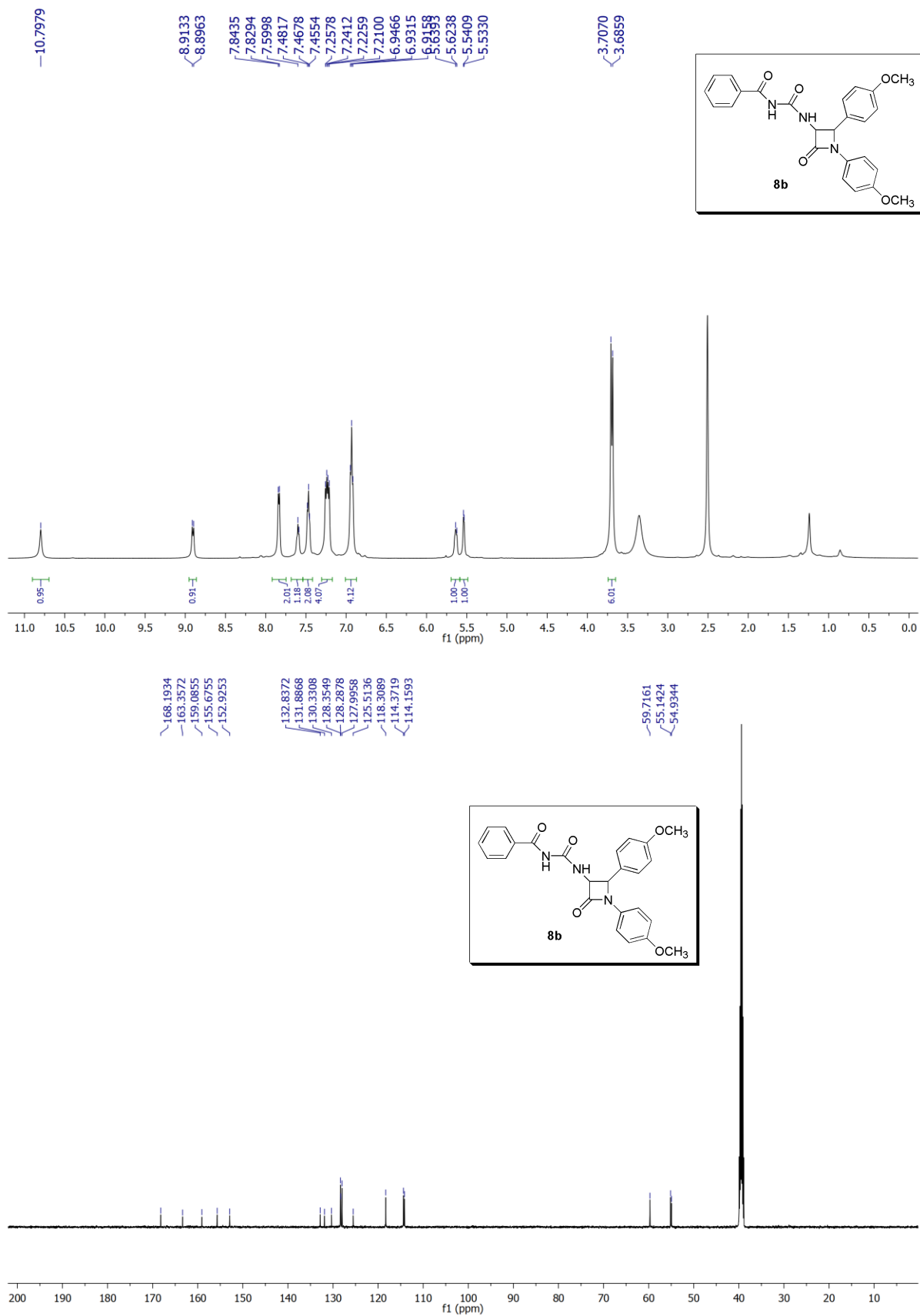
## 2. $^1\text{H}$ , $^{13}\text{C}$ -NMR and HRMS spectra of 3-aryollurea- $\beta$ -lactams **8a-f**



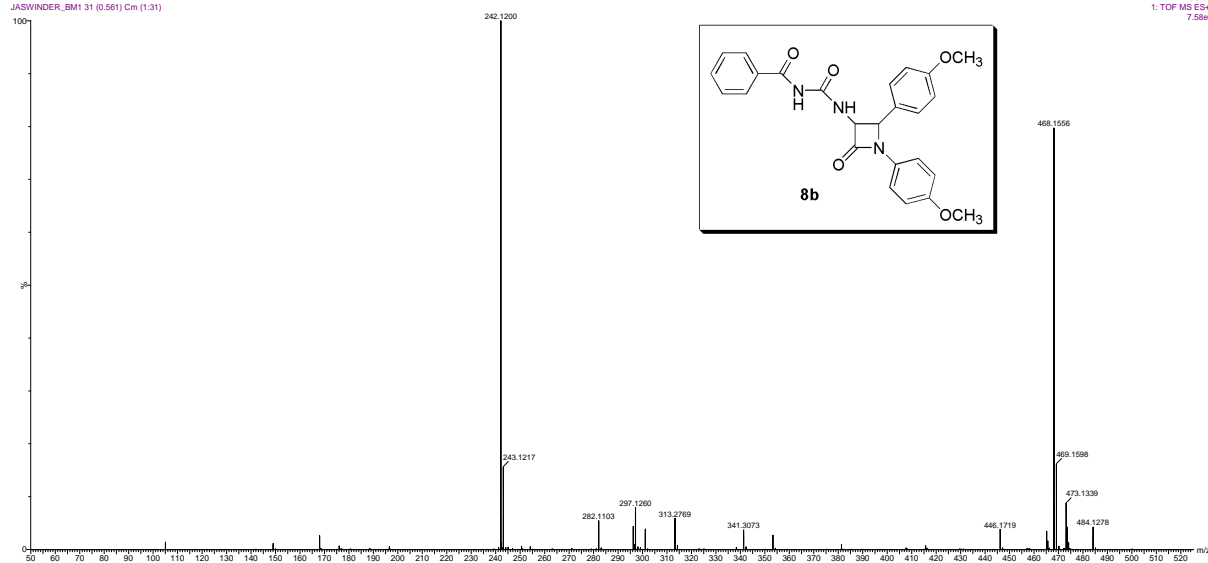
**Figure S11:**  $^1\text{H}$  and  $^{13}\text{C}$ -NMR spectra of 1-Benzoyl-3-[1-(4-methoxy-phenyl)-2-oxo-4-phenyl-azetidin-3-yl]-urea **8a** in DMSO



**Figure S12:** HRMS spectra of 1-Benzoyl-3-[1-(4-methoxy-phenyl)-2-oxo-4-phenyl-azetidin-3-yl]-urea **8a**

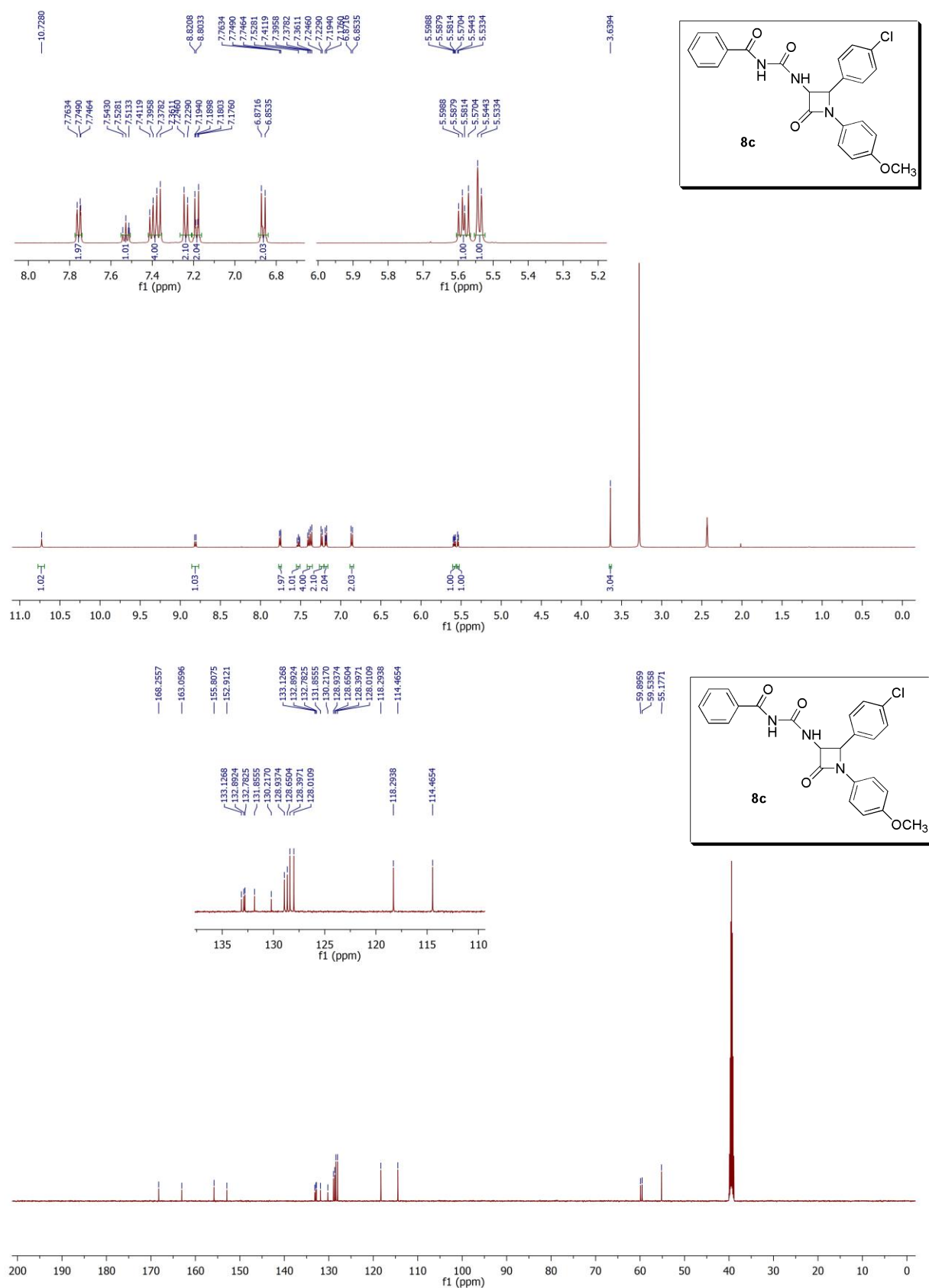


**Figure S13:** <sup>1</sup>H and <sup>13</sup>C-NMR spectra of 1-Benzoyl-3-[1,2-bis-(4-methoxy-phenyl)-4-oxo-azetidin-3-yl]-urea **8b** in DMSO

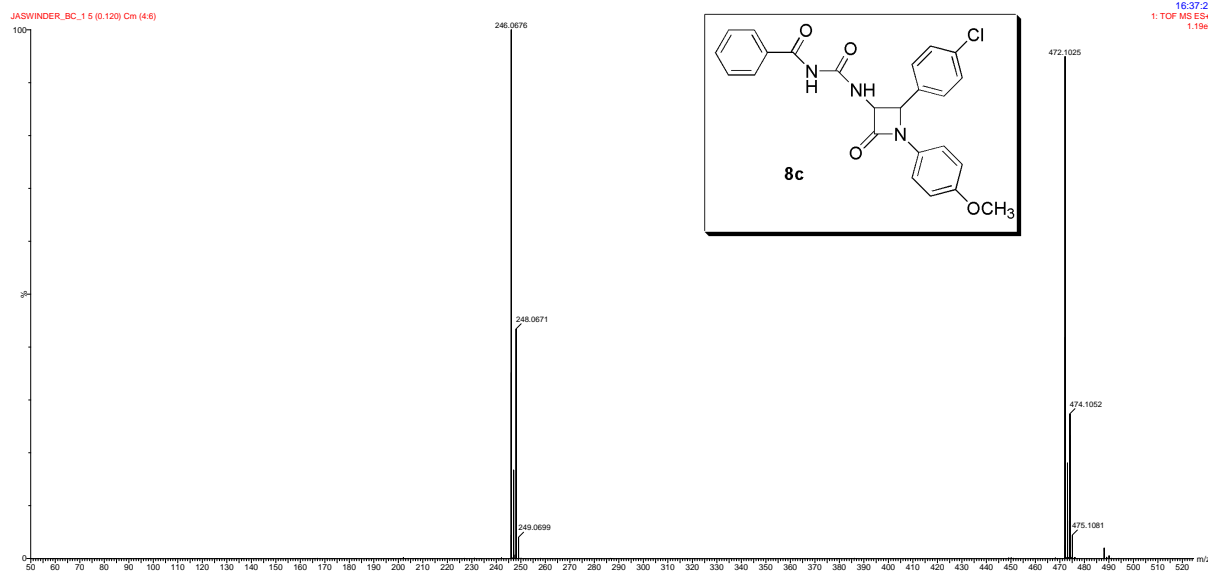


**Figure S14:** HRMS spectra of 1-Benzoyl-3-[1,2-bis-(4-methoxy-phenyl)-4-oxo-azetidin-3-yl]-urea **8b**

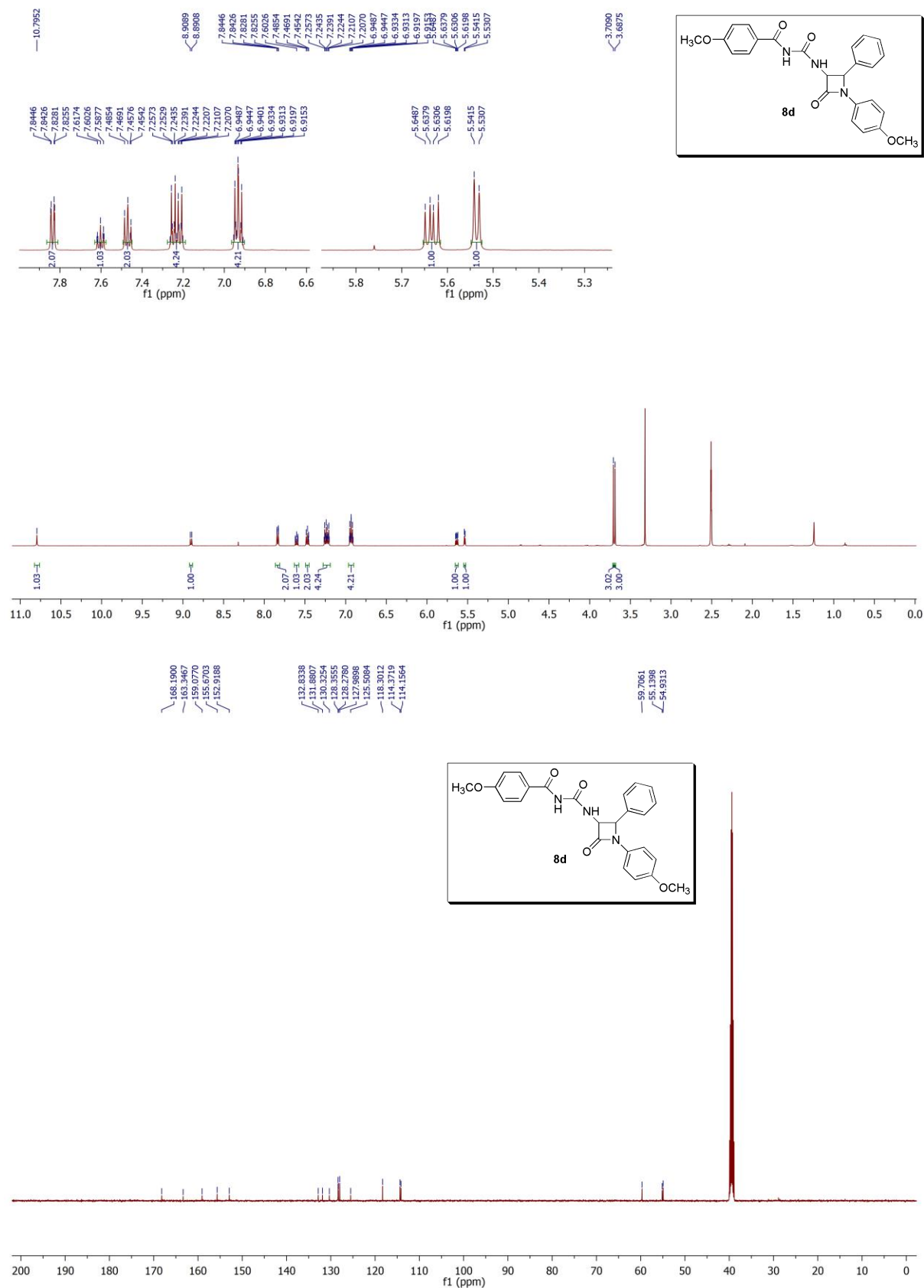




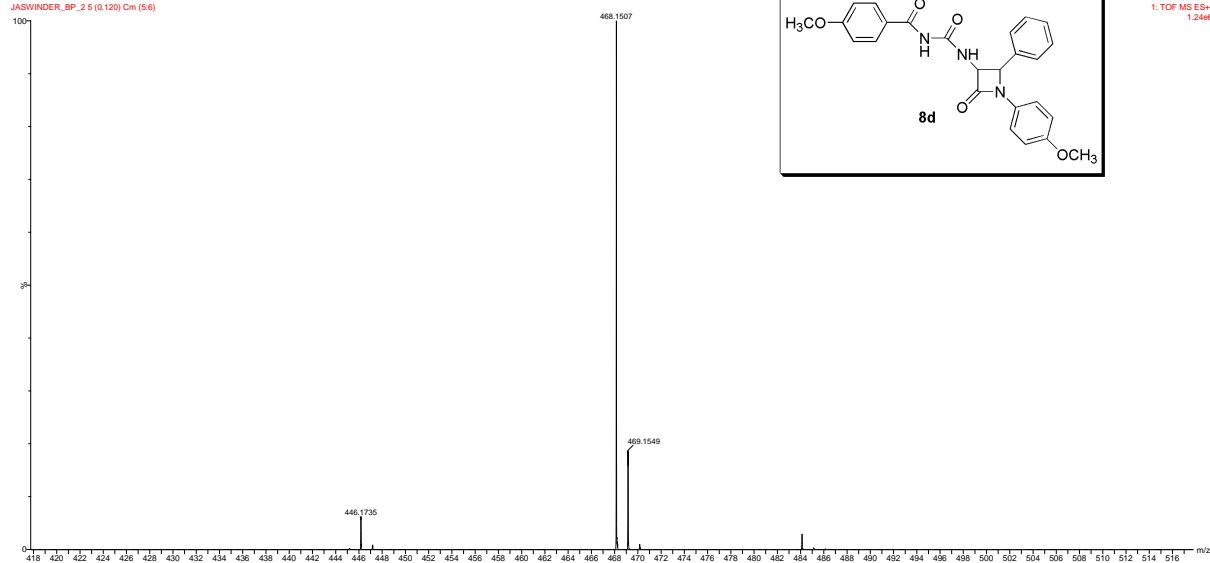
**Figure S15:** <sup>1</sup>H and <sup>13</sup>C-NMR spectra of 1-Benzoyl-3-[2-(4-chloro-phenyl)-1-(4-methoxy-phenyl)-4-oxo-azetidin-3-yl]-urea **8c** in DMSO



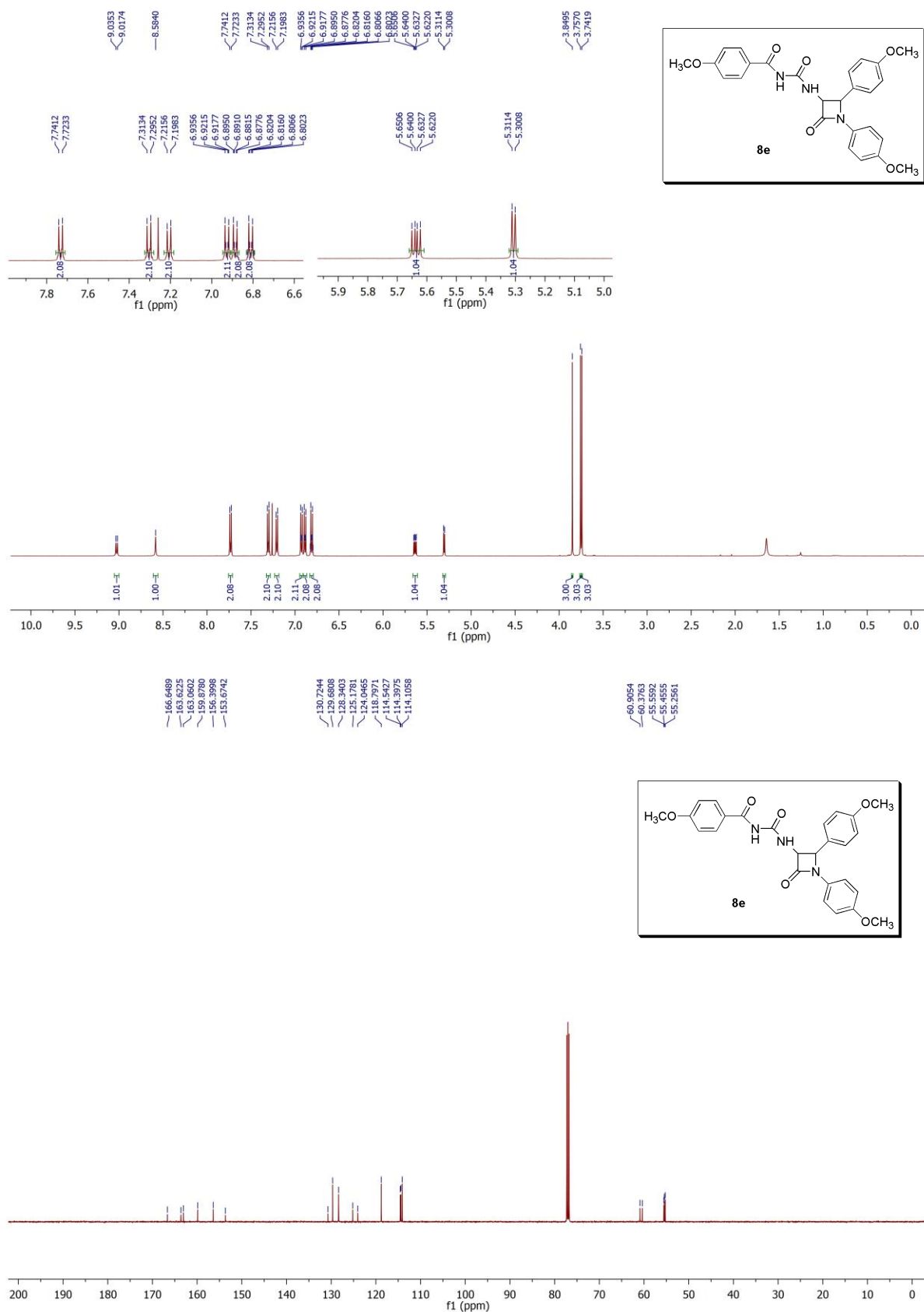
**Figure S16:** HRMS spectra of 1-Benzoyl-3-[2-(4-chloro-phenyl)-1-(4-methoxy-phenyl)-4-oxo-azetidin-3-yl]-urea **8c**



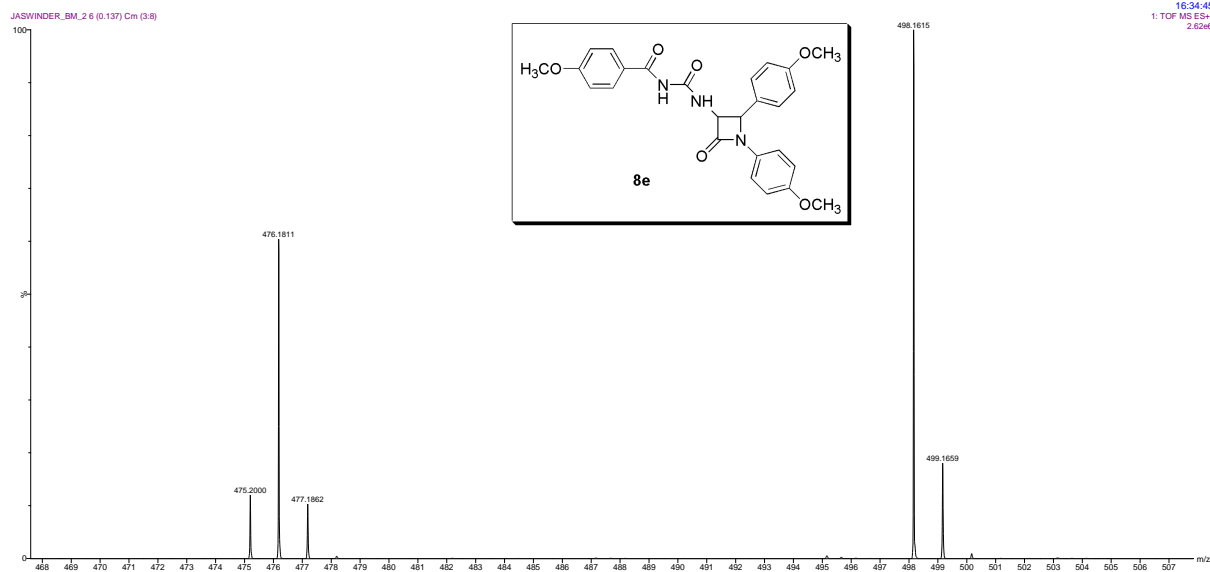
**Figure S17:** <sup>1</sup>H and <sup>13</sup>C-NMR spectra of 1-(4-Methoxy-benzoyl)-3-[1-(4-methoxy-phenyl)-2-oxo-4-phenyl-azetidin-3-yl]-urea **8d** in DMSO



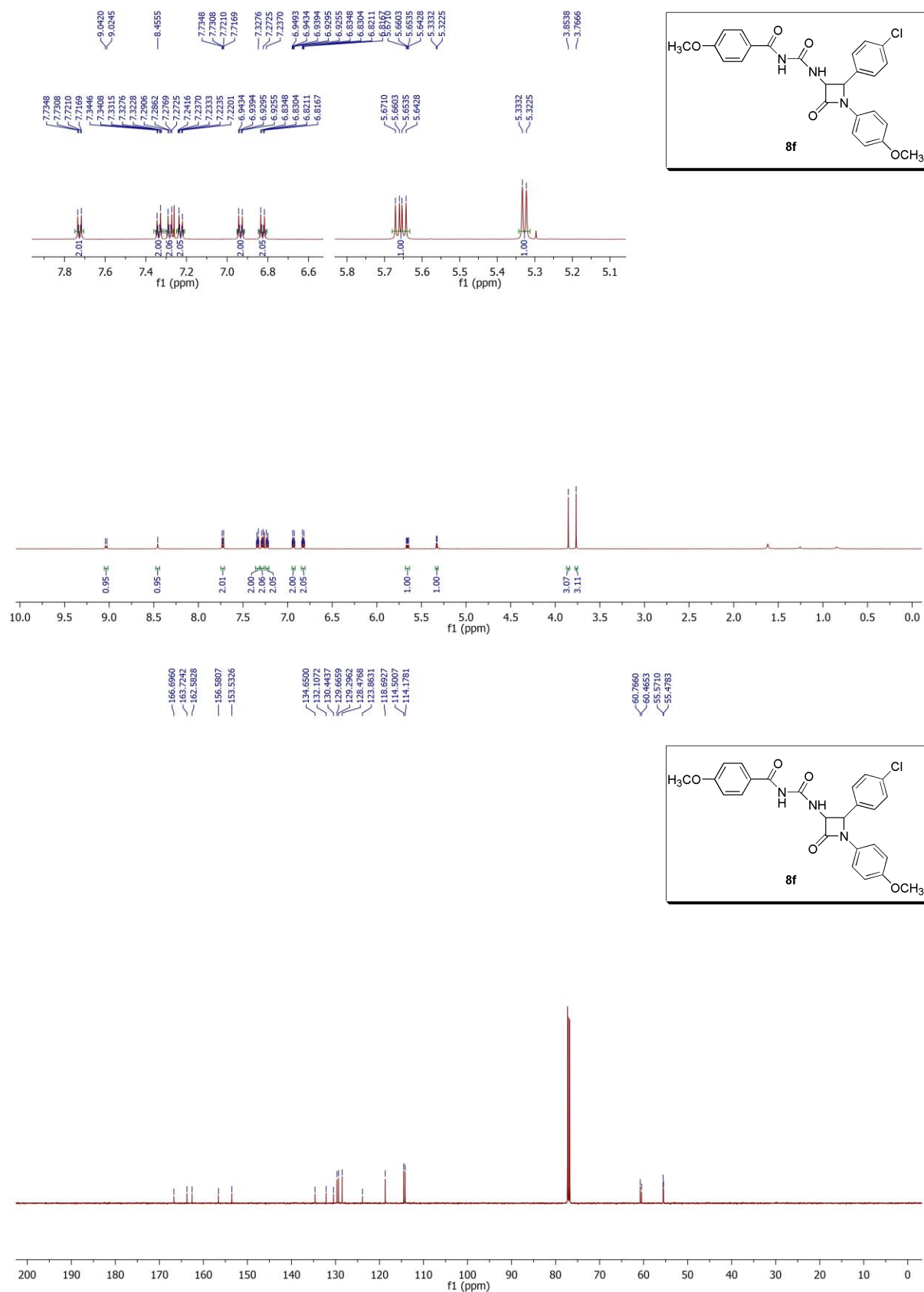
**Figure S18:** HRMS spectra of 1-(4-Methoxy-benzoyl)-3-[1-(4-methoxy-phenyl)-2-oxo-4-phenyl-azetidin-3-yl]-urea **8d**



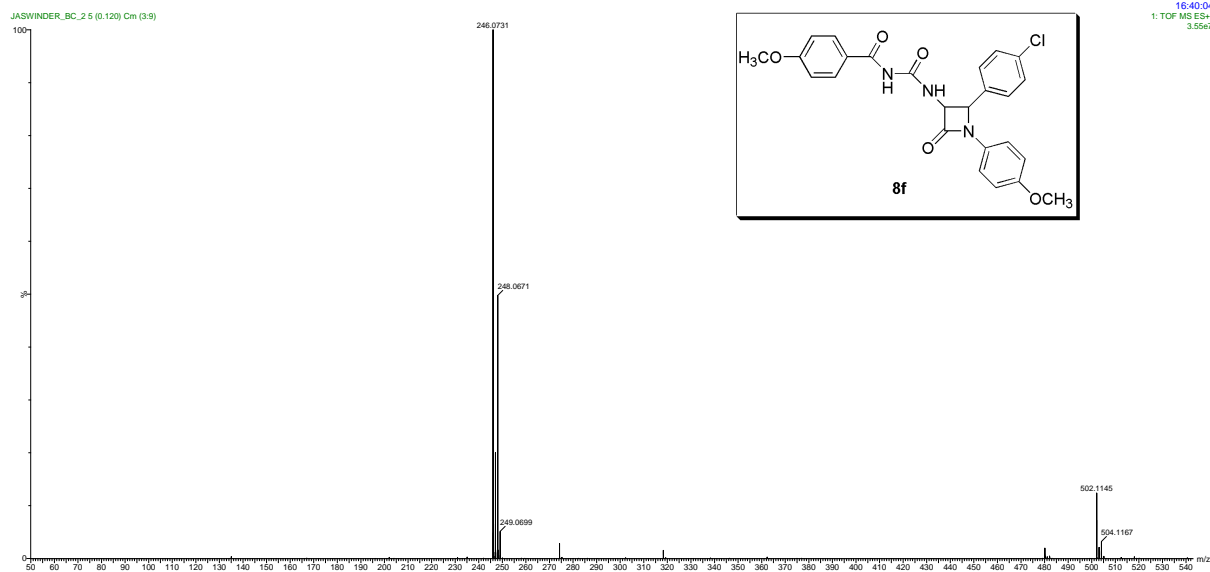
**Figure S19:** <sup>1</sup>H and <sup>13</sup>C-NMR spectra of 1-[1,2-Bis-(4-methoxy-phenyl)-4-oxo-azetidin-3-yl]-3-(4-methoxy-benzoyl)-urea **8e** in CDCl<sub>3</sub>



**Figure S20:** HRMS spectra of 1-[1,2-Bis-(4-methoxy-phenyl)-4-oxo-azetidin-3-yl]-3-(4-methoxy-benzoyl)-urea **8e**



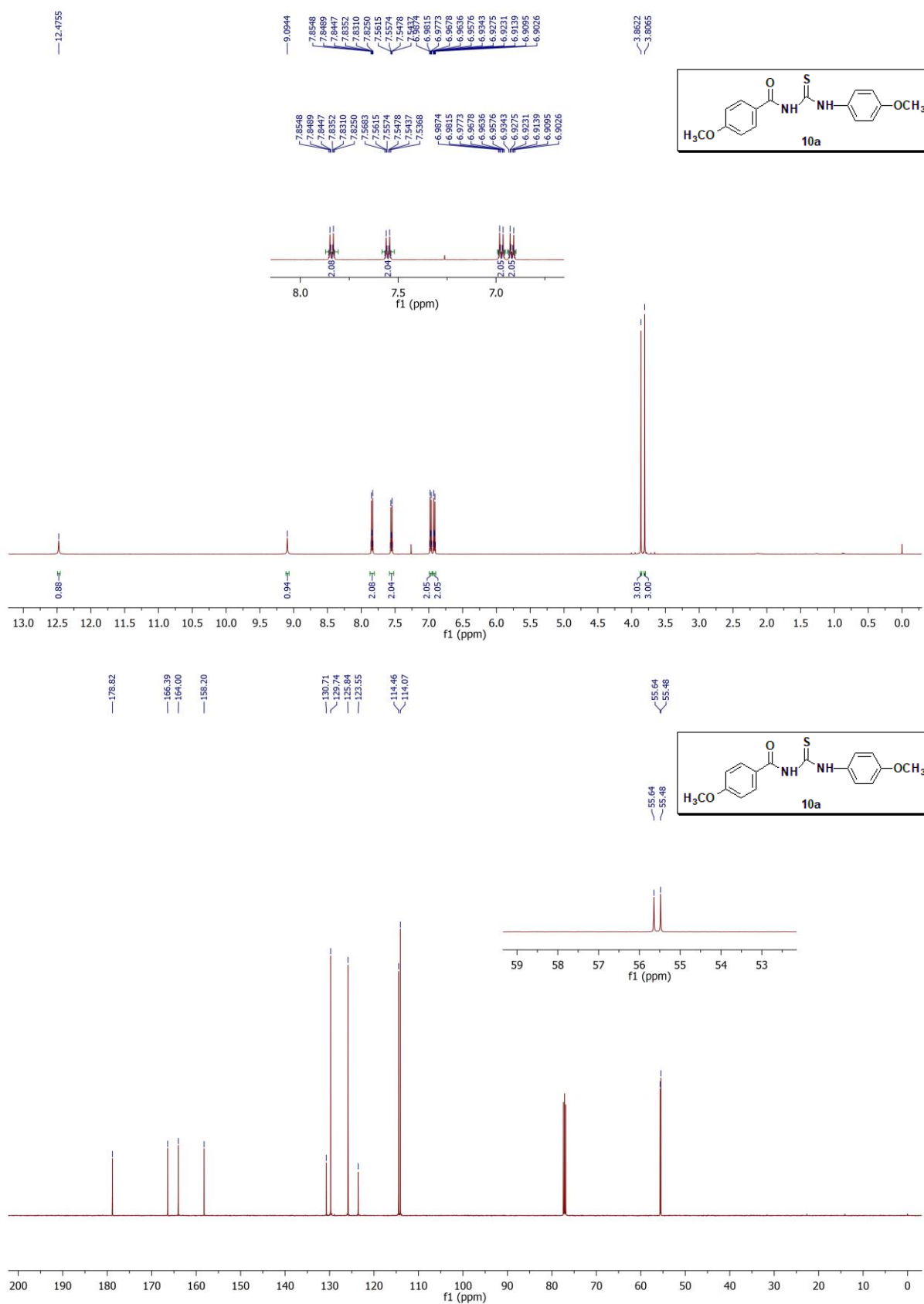
**Figure S21:** <sup>1</sup>H and <sup>13</sup>C-NMR spectra of 1-[2-(4-Chloro-phenyl)-1-(4-methoxy-phenyl)-4-oxo-azetidin-3-yl]-3-(4-methoxy-benzoyl)-urea **8f** in CDCl<sub>3</sub>



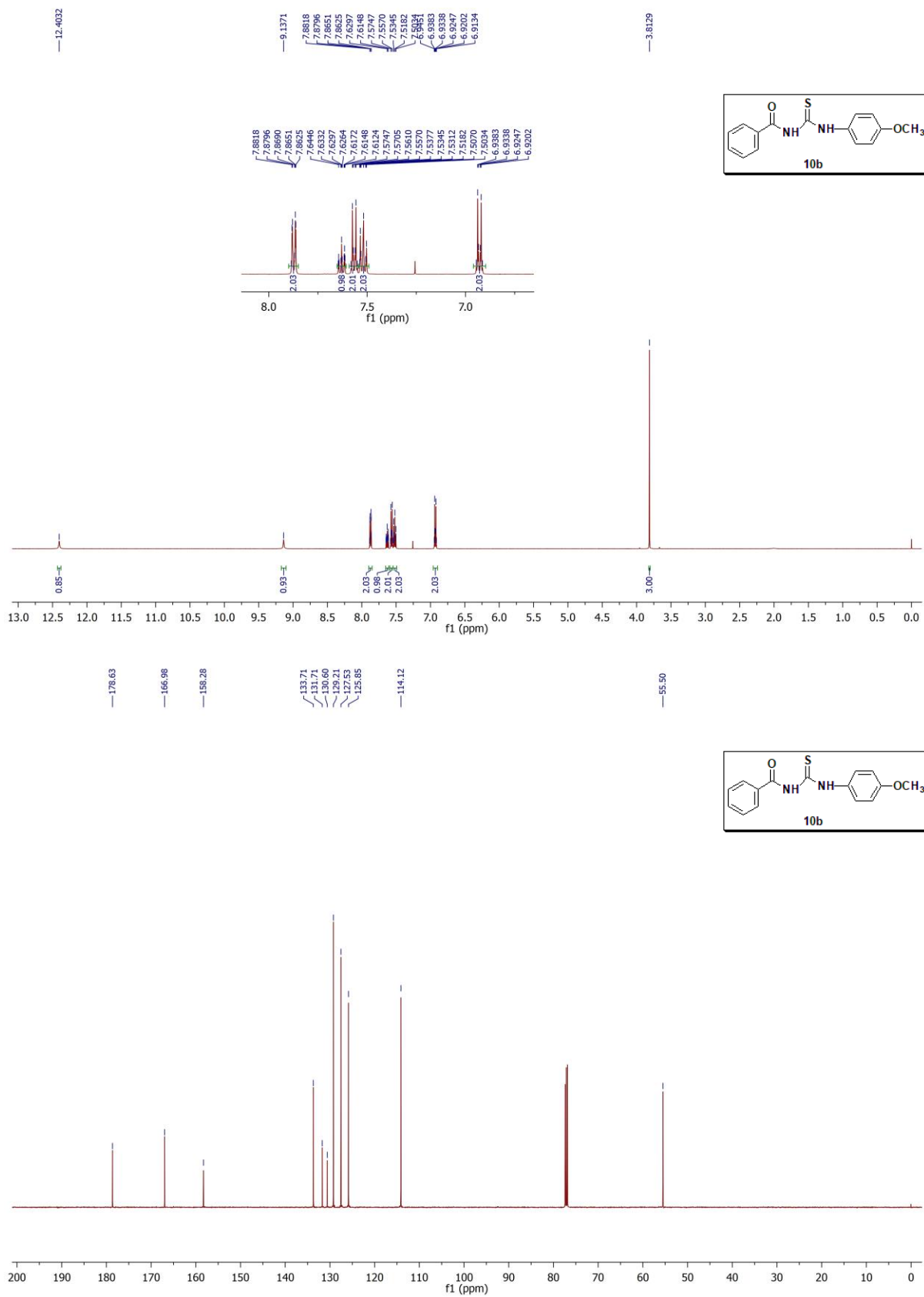
**Figure S22:** HRMS spectra of 1-[2-(4-Chloro-phenyl)-1-(4-methoxy-phenyl)-4-oxo-azetidin-3-yl]-3-(4-methoxy-benzoyl)-urea **8f**



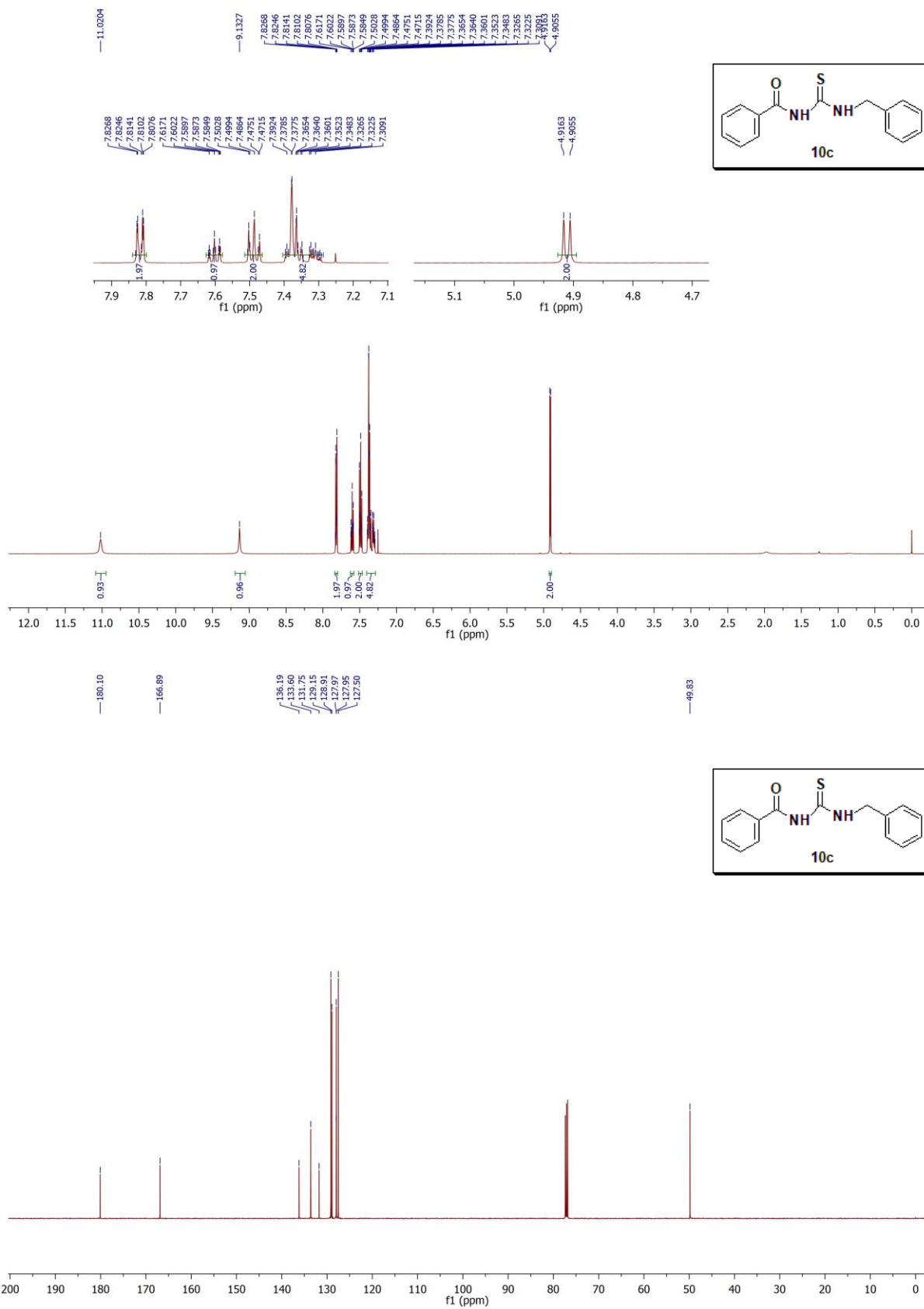
### 3. $^1\text{H}$ and $^{13}\text{C}$ -NMR spectra of thiourea derivatives 10a-c



**Figure S23:**  $^1\text{H}$  and  $^{13}\text{C}$ -NMR spectra of 1-(4-methoxy-benzoyl)-3-(4-methoxy-phenyl)-thiourea **10a** in  $\text{CDCl}_3$



**Figure S24:** <sup>1</sup>H and <sup>13</sup>C-NMR spectra of 1-Benzoyl-3-(4-methoxy-phenyl)-thiourea **10b** in CDCl<sub>3</sub>



**Figure S25:** <sup>1</sup>H and <sup>13</sup>C-NMR spectra of 1-Benzoyl-3-benzyl-thiourea **10c** in CDCl<sub>3</sub>

#### 4. $^1\text{H}$ and $^{13}\text{C}$ -NMR spectra of amide derivatives 11a-c

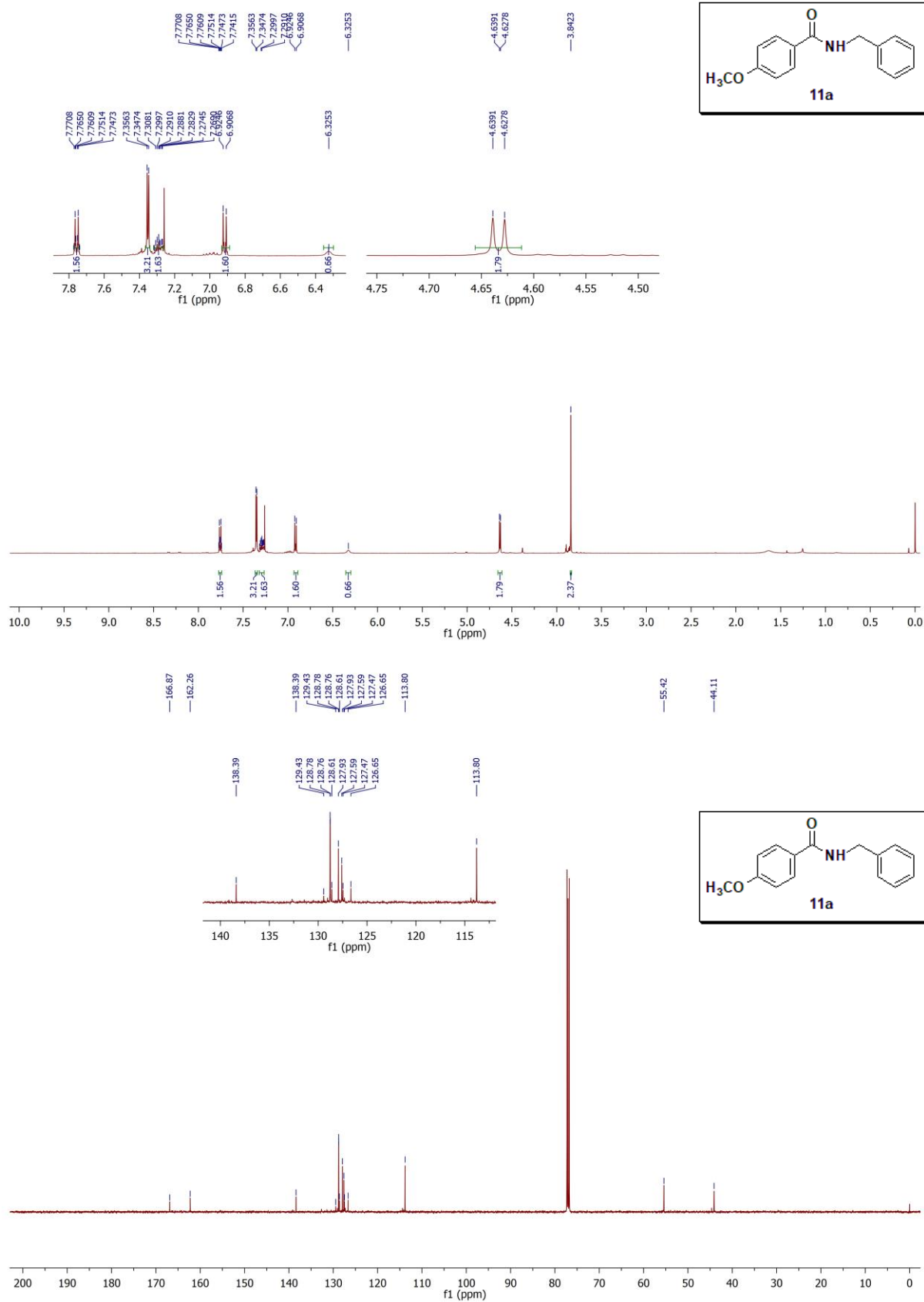
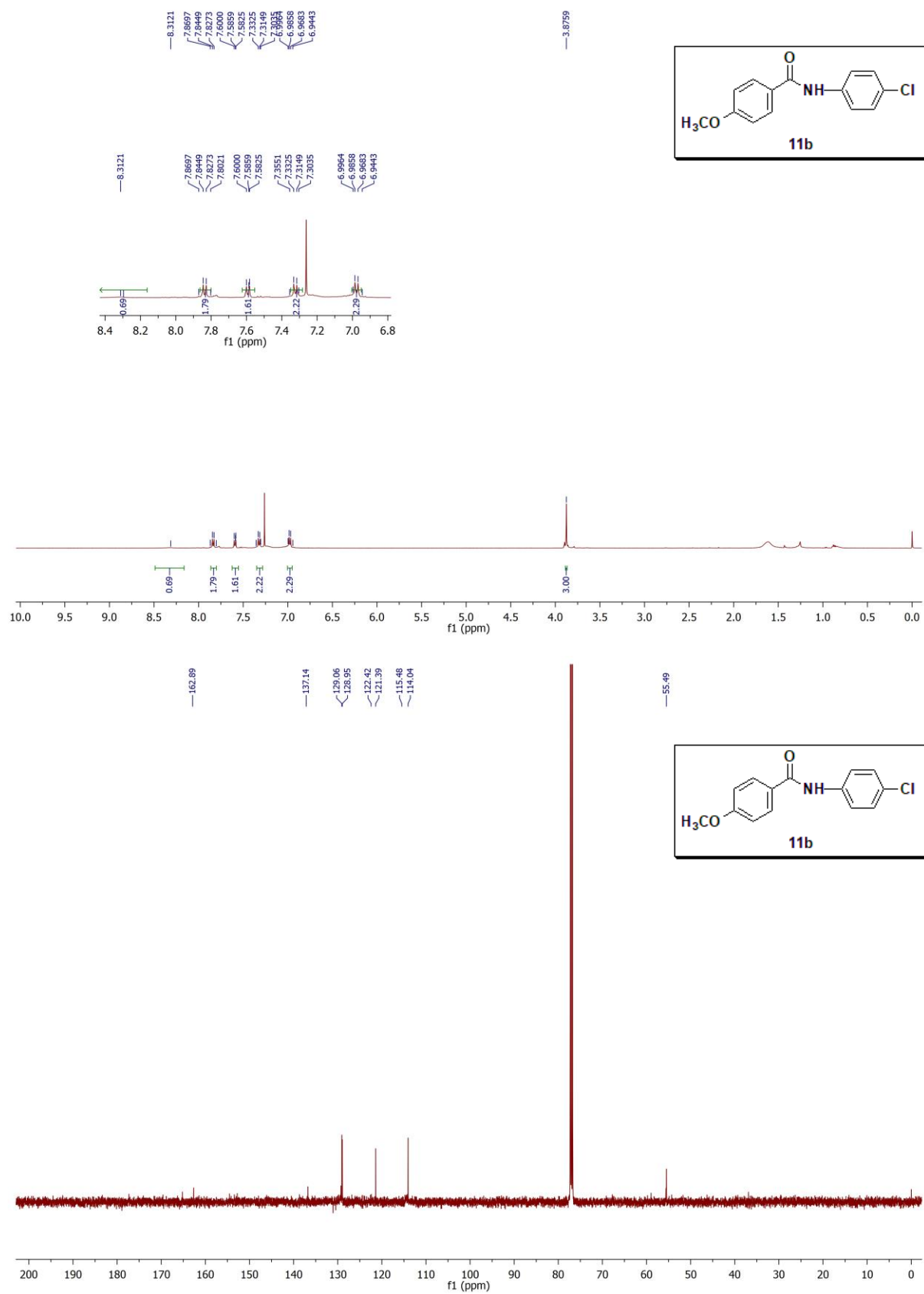
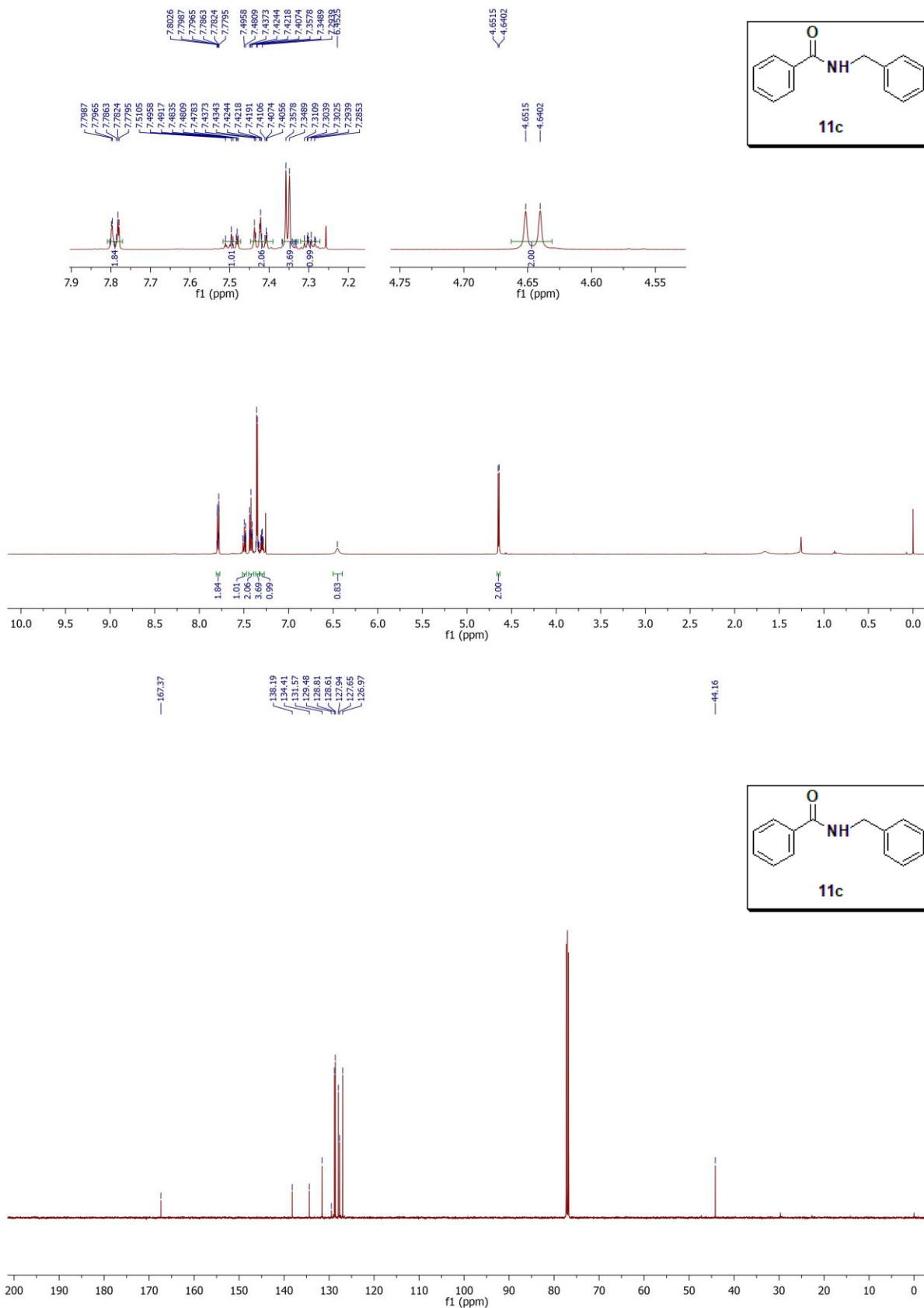


Figure S26:  $^1\text{H}$  and  $^{13}\text{C}$ -NMR spectra of N-Benzyl-4-methoxy-benzamide **11a** in  $\text{CDCl}_3$



**Figure S27:** <sup>1</sup>H and <sup>13</sup>C-NMR spectra of N-Benzyl-benzamide **11b** in CDCl<sub>3</sub>



**Figure S28:** <sup>1</sup>H and <sup>13</sup>C-NMR spectra of N-(4-Chloro-phenyl)-4-methoxy-benzamide **11c** in CDCl<sub>3</sub>

## 5. ADME parameters

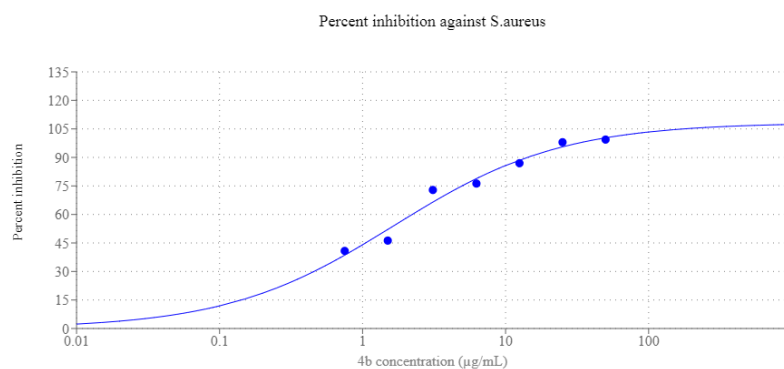
	5a	5b	5c	5d	5e	5f	8a	8b	8c	8d	8e	8f	Ampicillin
MW	431.51	461.53	465.95	461.53	491.56	491.56	415.44	445.47	449.89	445.47	475.49	479.91	349.4
RB	8	9	8	9	10	10	8	9	8	9	10	9	5
HBA	3	4	3	4	5	5	4	5	4	5	6	5	5
HBD	2	2	2	2	2	2	2	2	2	2	2	2	3
TPSA	102.76	111.99	102.76	111.99	121.22	121.22	87.74	96.97	87.74	96.97	106.2	96.97	138.03
iLOGP	3.01	3.88	3.26	3.81	4.03	4.03	2.29	3.02	2.36	2.7	3.05	2.63	1.15
GIA	High	High	High	High	High	High	High	High	High	High	High	High	Low
BBBP	No	No	No	No	No	No	No	No	No	No	No	No	No
PGP	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
CYP1A2 inhibitor	No	No	No	No	No	No	No	No	No	No	No	No	No
CYP2C19 inhibitor	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
CYP2C9 inhibitor	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
CYP2D6 inhibitor	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
CYP3A4 inhibitor	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
log Kp (cm/s)	-5.84	-6.04	-5.61	-6.04	-6.25	-6.25	-6.17	-6.37	-5.93	-6.37	-6.57	-6.14	-9.23
Lipinski #violations	0	0	0	0	0	0	0	0	0	0	0	0	0
Veber #violations	0	0	0	0	0	0	0	0	0	0	0	0	0
Muegge #violations	0	0	0	0	0	0	0	0	0	0	0	0	0

**Figure S29:** ADME parameters of *cis*-3-aryyl-thiourea/urea- $\beta$ -lactams **5a-f/8a-f**

## 6. IC50 Graphs

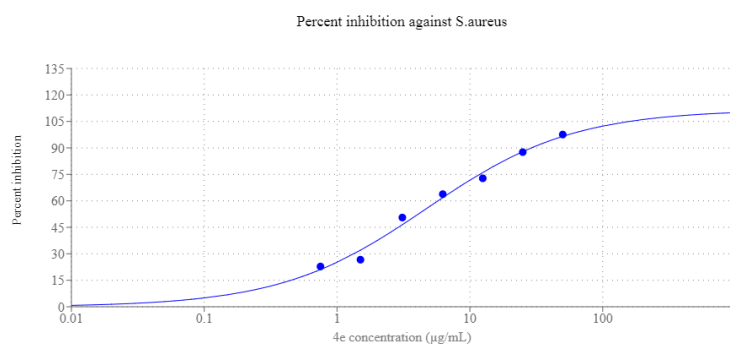
### 6.1 IC50 graphs against *S. aureus*

IC50= 1.66  $\mu\text{g/ml}$



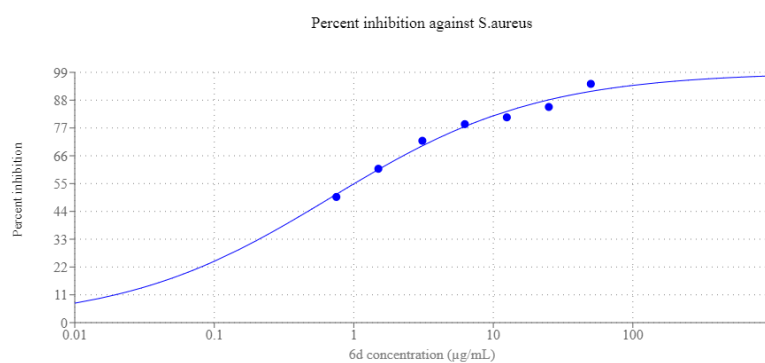
**Figure S30:** IC50 curve of compound **5b**.

IC50= 4.74  $\mu\text{g/ml}$



**Figure S31:** IC50 curve of compound **5e**.

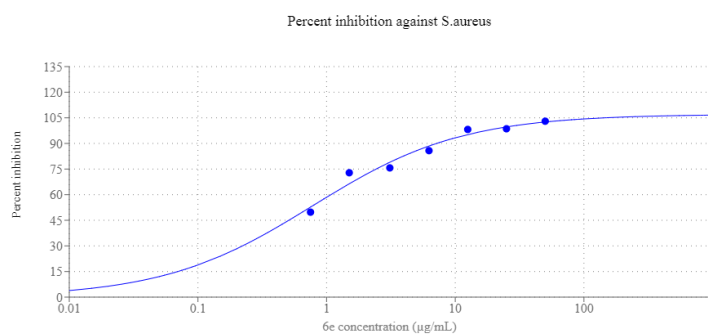
IC50= 0.685  $\mu\text{g/ml}$



**Figure S32:** IC50 curve of compound **8d**.



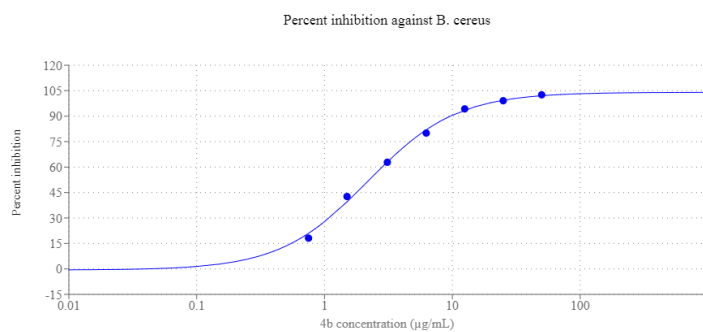
IC<sub>50</sub> = 0.78 μg/ml



**Figure S33:** IC<sub>50</sub> curve of compound **8e**.

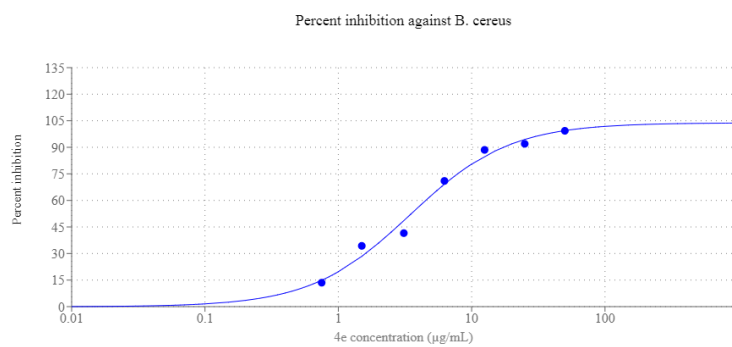
## 6.2 IC50 graphs against *B. cereus*

IC50= 2.19  $\mu\text{g/ml}$



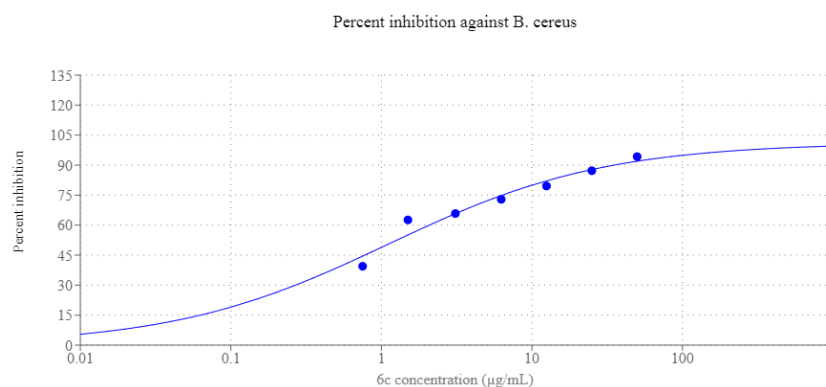
**Figure S34:** IC50 curve of compound 5b.

IC50= 3.45  $\mu\text{g/ml}$



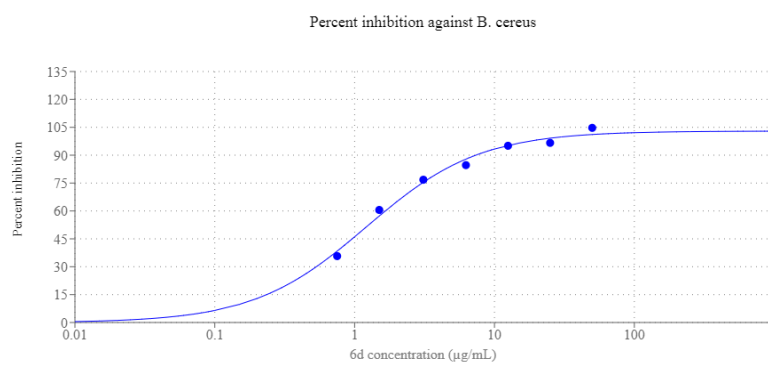
**Figure S35:** IC50 curve of compound 5e.

IC50= 1.11  $\mu\text{g/ml}$



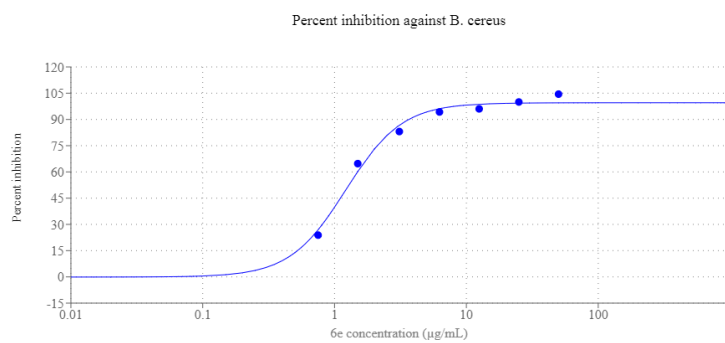
**Figure S36:** IC50 curve of compound 8c.

IC50= 1.21  $\mu\text{g/ml}$



**Figure S37:** IC50 curve of compound **8d**.

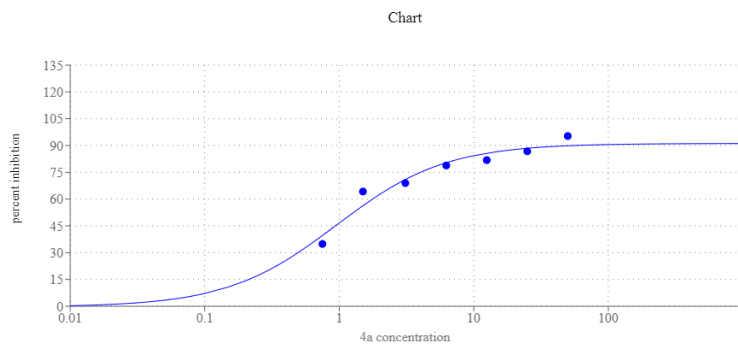
IC50= 1.22  $\mu\text{g/ml}$



**Figure S38:** IC50 curve of compound **8e**.

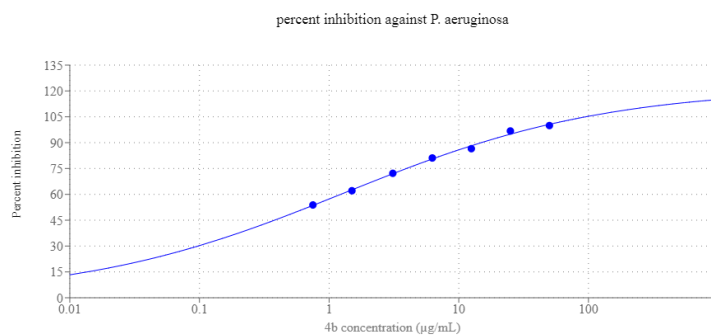
### 6.3 IC50 graphs against *P. aeruginosa*

IC50= 0.95  $\mu\text{g/ml}$



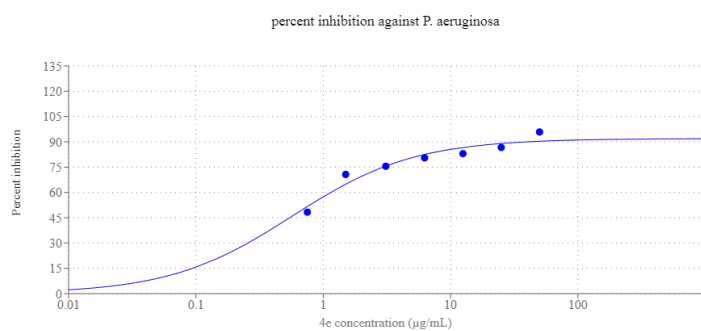
**Figure S39:** IC50 curve of compound 5a.

IC50= 1.31  $\mu\text{g/ml}$



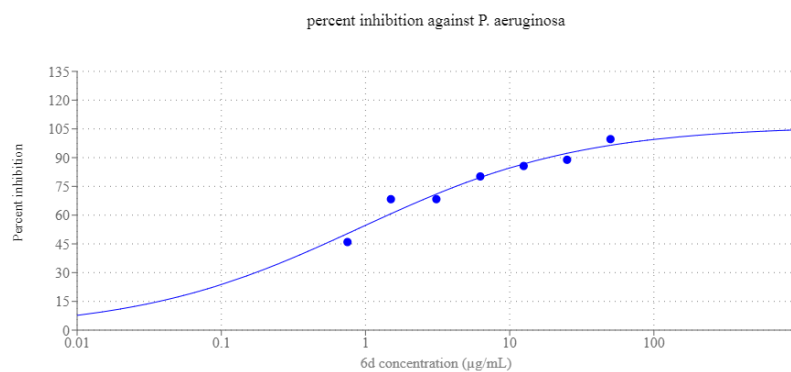
**Figure S40:** IC50 curve of compound 5b.

IC50= 0.57  $\mu\text{g/ml}$



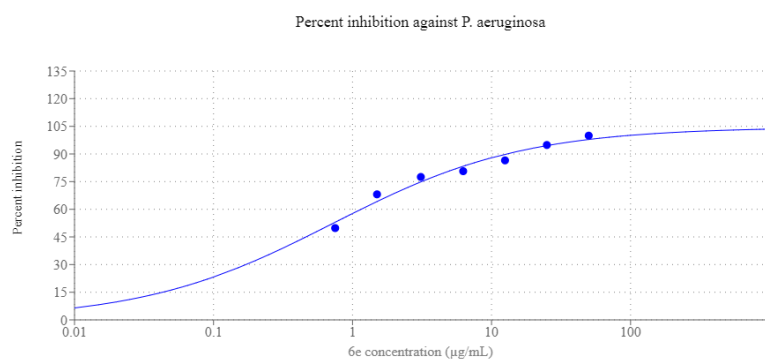
**Figure S41:** IC50 curve of compound 5e.

IC50= 0.91  $\mu\text{g/ml}$



**Figure S42:** IC50 curve of compound **8d**.

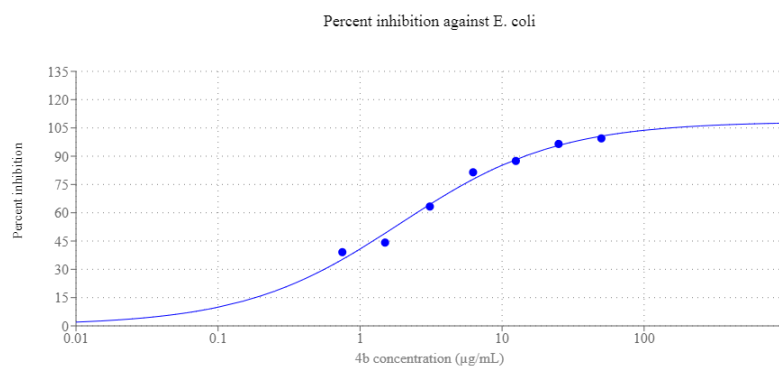
IC50= 0.72  $\mu\text{g/ml}$



**Figure S43:** IC50 curve of compound **8e**.

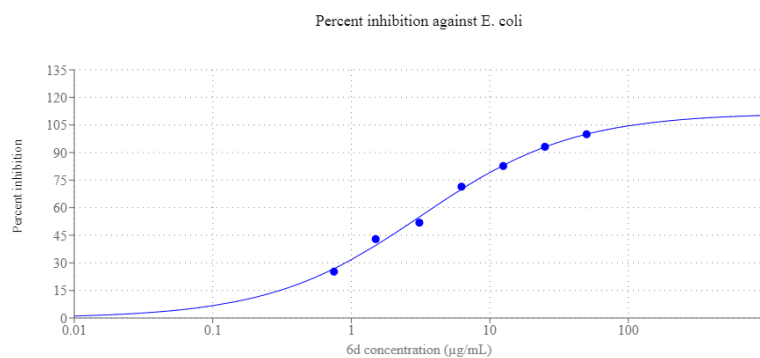
## 6.4 IC50 graphs against *E. coli*

IC50= 1.92  $\mu\text{g/ml}$



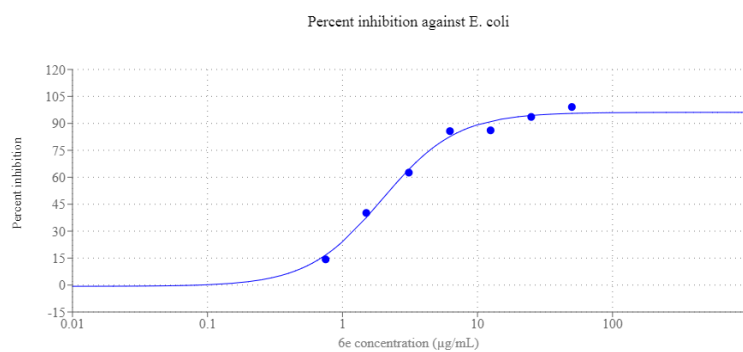
**Figure S44:** IC50 curve of compound **5b**.

IC50= 3.2  $\mu\text{g/ml}$



**Figure S45:** IC50 curve of compound **8d**.

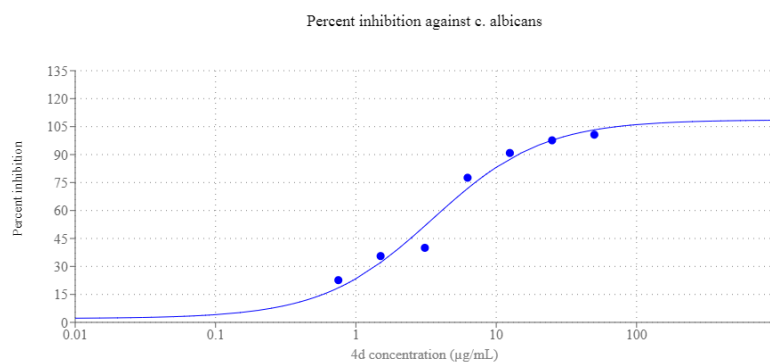
IC50= 1.97  $\mu\text{g/ml}$



**Figure S46:** IC50 curve of compound **8e**.

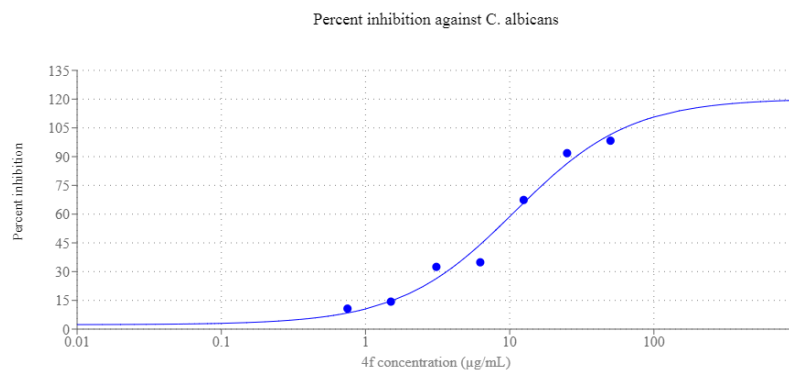
## 6.5 IC50 graphs against *C. albicans*

IC50= 3.5  $\mu\text{g/ml}$



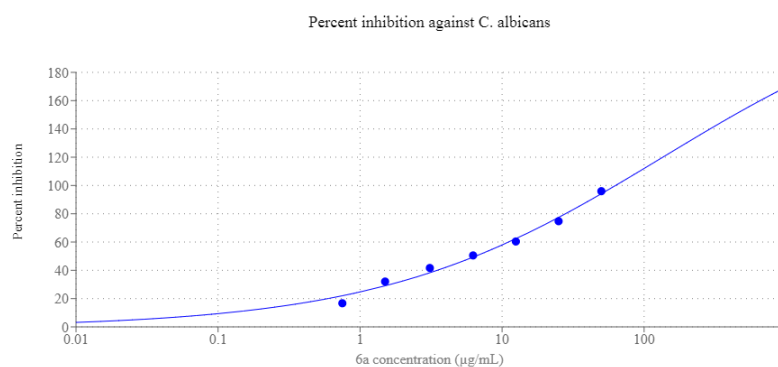
**Figure S47:** IC50 curve of compound **5d**.

IC50= 10.84  $\mu\text{g/ml}$



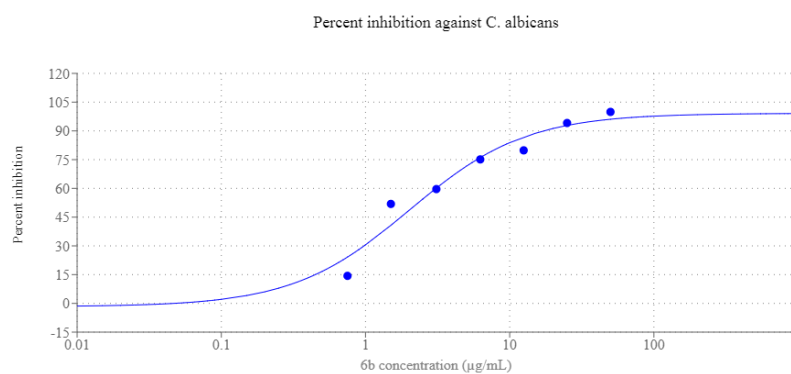
**Figure S48:** IC50 curve of compound **5f**.

IC50= 6.25  $\mu\text{g/ml}$



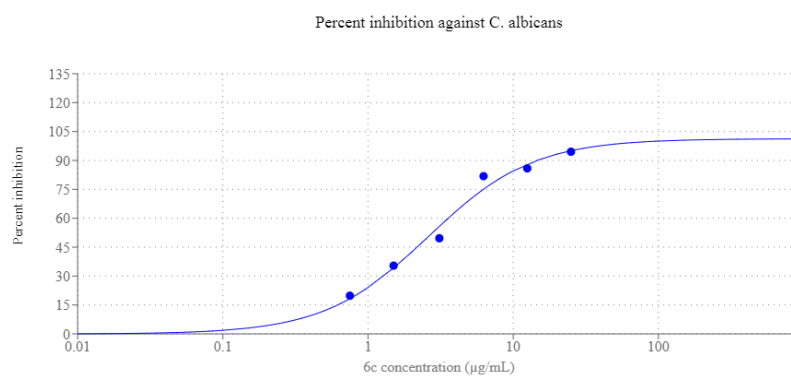
**Figure S49:** IC50 curve of compound **8a**.

IC50= 2.02  $\mu\text{g/ml}$



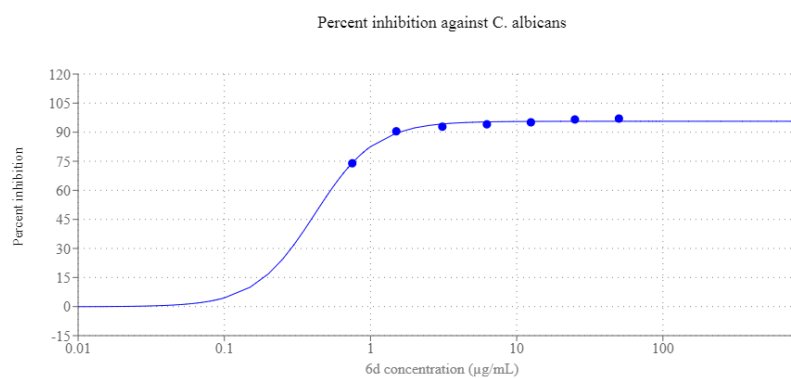
**Figure S50:** IC50 curve of compound **8b**.

IC50= 2.61  $\mu\text{g/ml}$



**Figure S51:** IC50 curve of compound **8c**.

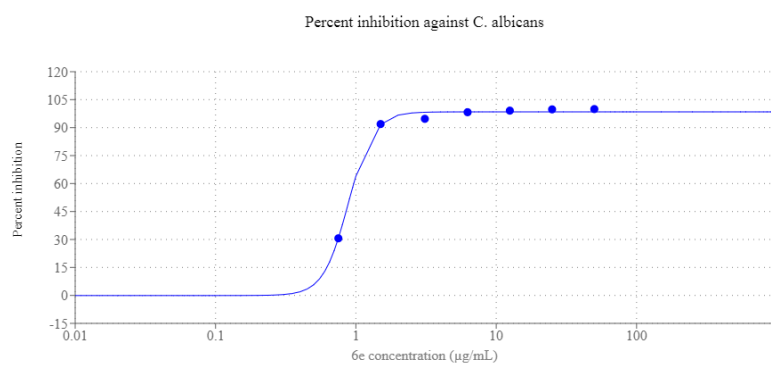
IC50= 0.42  $\mu\text{g/ml}$



**Figure S52:** IC50 curve of compound **8d**.

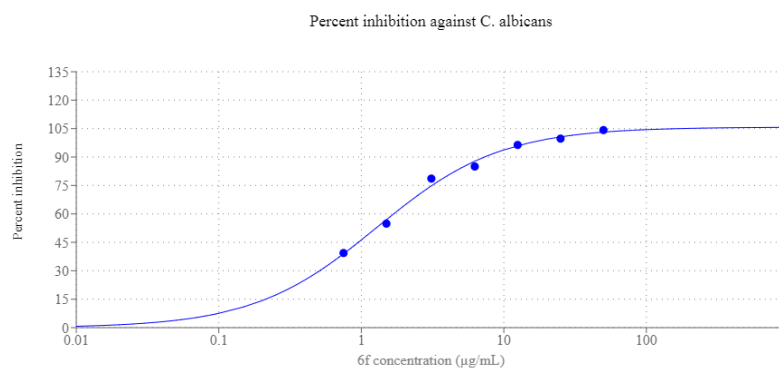


IC50= 0.88  $\mu\text{g/ml}$



**Figure S53:** IC50 curve of compound **8e**.

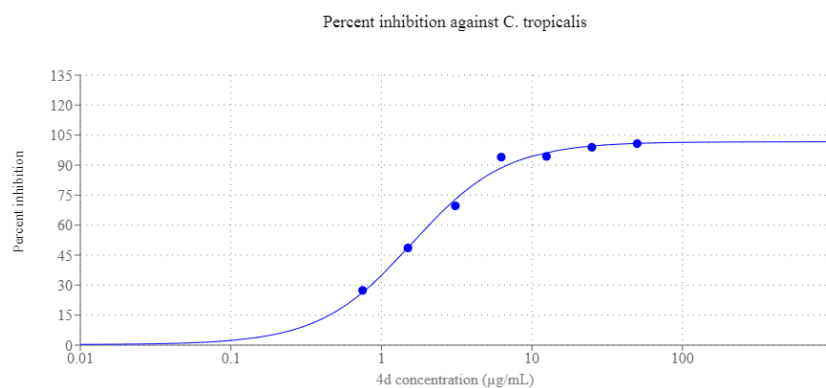
IC50= 1.28  $\mu\text{g/ml}$



**Figure S54:** IC50 curve of compound **8f**.

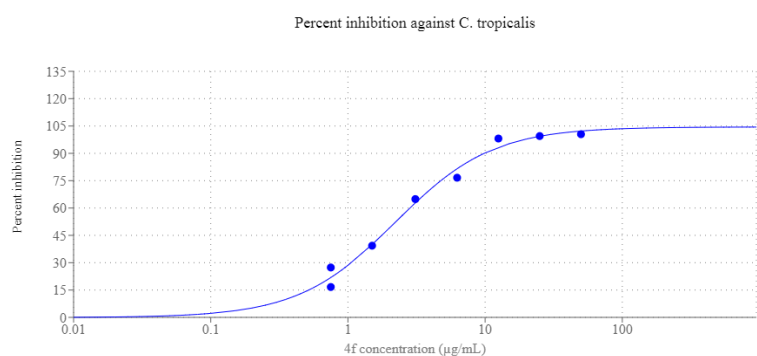
## 6.6 IC50 graphs against *C. tropicalis*

IC50= 1.6  $\mu\text{g/ml}$



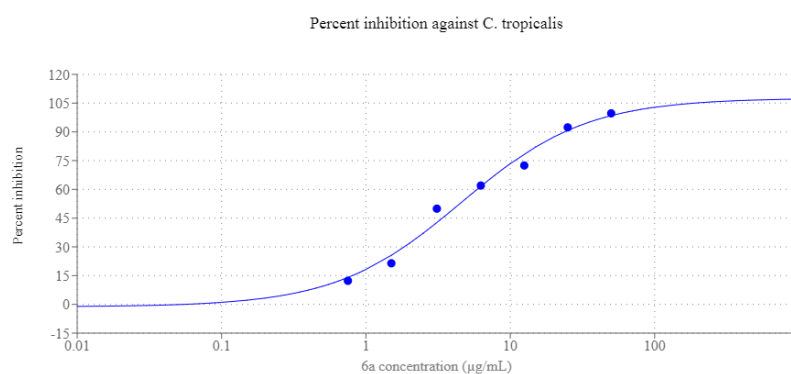
**Figure S55:** IC50 curve of compound **5d**.

IC50= 2.21  $\mu\text{g/ml}$



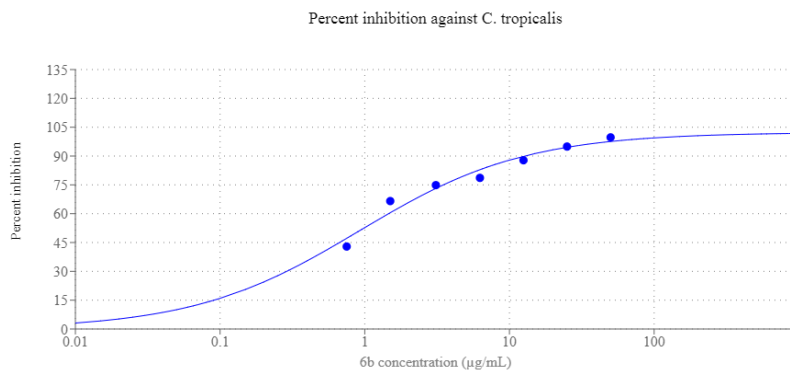
**Figure S56:** IC50 curve of compound **5f**.

IC50= 4.58  $\mu\text{g/ml}$



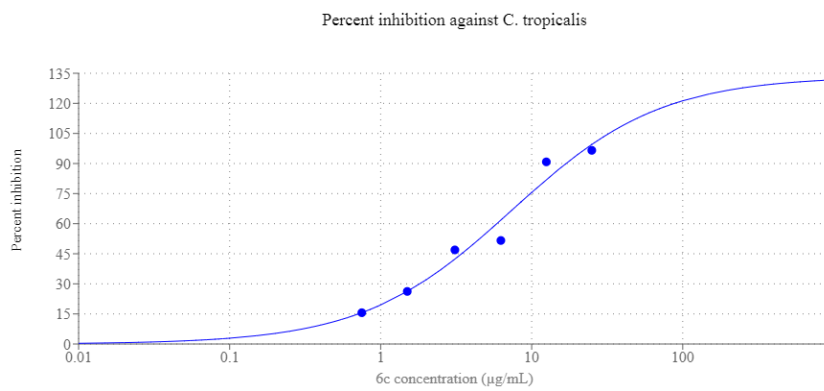
**Figure S57:** IC50 curve of compound **8a**.

IC50= 0.92  $\mu\text{g/ml}$



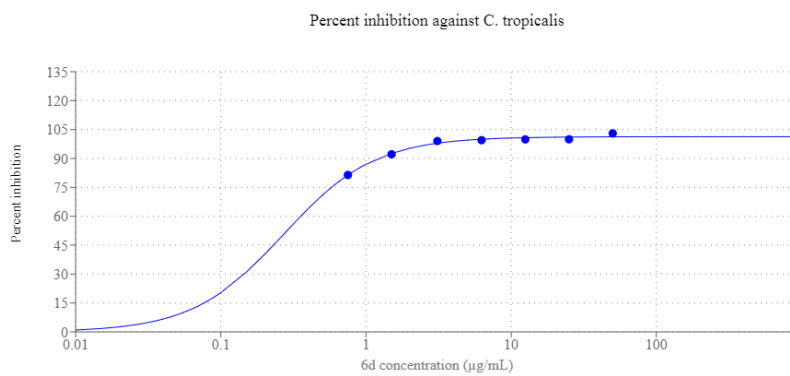
**Figure S58:** IC50 curve of compound **8b**.

IC50= 7.38  $\mu\text{g/ml}$



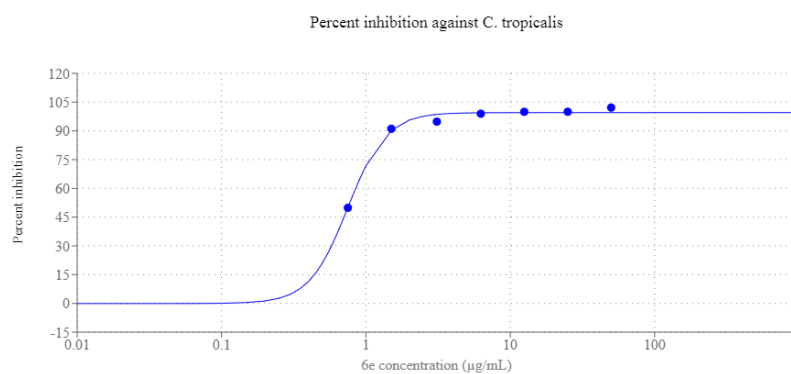
**Figure S59:** IC50 curve of compound **8c**.

IC50= 0.27  $\mu\text{g/ml}$



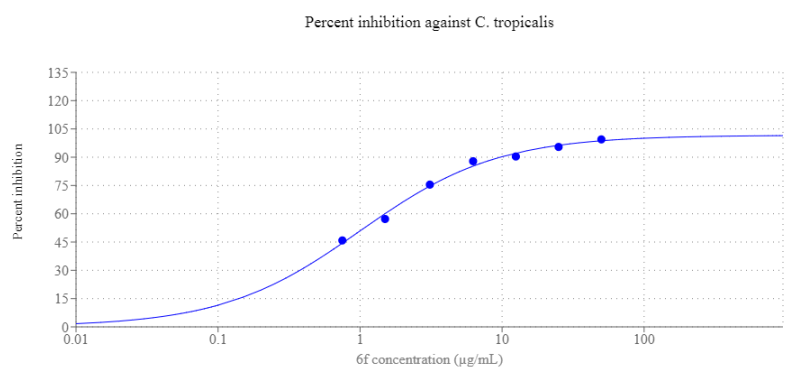
**Figure S60:** IC50 curve of compound **8d**.

IC50= 0.75  $\mu\text{g/ml}$



**Figure S61:** IC50 curve of compound **8e**.

IC50= 0.997  $\mu\text{g/ml}$



**Figure S62:** IC50 curve of compound **8f**.