

## Efficient Synthesis of New 1-[Alkyl(aryl)]-5-(3,3,3-trihalo-2-oxopropylidene)pyrrolidin-2-ones

Alex F. C. Flores,\* Darlene C. Flores, Graciela Oliveira, Lucas Pizzuti, Rubia M. S. da Silva,  
Marcos A. P. Martins and Helio G. Bonacorso

NUQUIMHE - Departamento de Química, Universidade Federal de Santa Maria  
97105 900 Santa Maria-RS, Brazil

Este trabalho mostra a síntese, em bons rendimentos (57-95%), de duas séries de 1-alkil(aril) amino-2-oxo-5-(2-oxo-3,3,3-trialopropylidene)-pirrolidinas **5** e **6**, a partir dos intermediários 4-[alkil(aril)amino]-6-oxo-7,7,7-trialo-4-heptenoatos de metila **3** e **4** obtidos por substituição da metoxila- $\beta$  nos precursores 4-metoxi-6-oxo-7,7,7-trialo-4-heptenoatos de metila **1** e **2**, pela série de amins primárias RNH<sub>2</sub>, onde R = PhCH<sub>2</sub>, PhCH<sub>2</sub>CH<sub>2</sub>, Ph, 4-MeC<sub>6</sub>H<sub>4</sub>, 4-MeOC<sub>6</sub>H<sub>4</sub>, 4-ClC<sub>6</sub>H<sub>4</sub>, 4-BrC<sub>6</sub>H<sub>4</sub>, 2-piridil, 5-metil-3-isoxazolil, 4-NH<sub>2</sub>C<sub>6</sub>H<sub>4</sub>. A estrutura molecular dos produtos inéditos foi atribuída a partir dos dados de RMN <sup>1</sup>H, <sup>13</sup>C e espectrometria de massas. A configuração geométrica dos compostos **3d** e **5b** foi confirmada pelos dados de difração de raios-X em monocristal.

Reactions of methyl 4-methoxy-6-oxo-7,7,7-trialo-4-heptenoates **1** and **2** with primary amines RNH<sub>2</sub>, where R = PhCH<sub>2</sub>, PhCH<sub>2</sub>CH<sub>2</sub>, Ph, 4-MeC<sub>6</sub>H<sub>4</sub>, 4-MeOC<sub>6</sub>H<sub>4</sub>, 4-ClC<sub>6</sub>H<sub>4</sub>, 4-BrC<sub>6</sub>H<sub>4</sub>, 2-pyridyl, 5-methyl-3-isoxazolyl, 4-NH<sub>2</sub>C<sub>6</sub>H<sub>4</sub> affording methyl 4-[alkyl(aryl)amino]-6-oxo-7,7,7-trialo-4-heptenoates **3**, **4**, in good yields (57-95%), which suffer quantitative intramolecular cyclocondensation to produce 1-alkyl(aryl)-5-(2-oxo-3,3,3-trialopropylidene)pyrrolidin-2-ones **5**, **6**, are reported. The structures of the isolated new products were assigned by means of <sup>1</sup>H, <sup>13</sup>C NMR measurements and mass spectrometry. The *Z* and *E* configuration of compounds **3d** and **5b** respectively were established from X-ray crystallography.

**Keywords:** pyrrolidin-2-ones, [CCCC+N] cyclisation, methyl 4-methoxy-6-oxo-7,7,7-trialo-4-heptenoates

### Introduction

We have systematically used the acetals acylation method for synthesis of wide range of 4-alkoxy-1,1,1-trialo-3-alken-2-ones. These 1,3-dielectrophilic precursors have proved to be important building blocks for regiospecific synthesis of heterocyclic compounds bearing trihalomethyl group<sup>2,3</sup> with important pharmacological<sup>4,5</sup> and synthetic applications.<sup>6</sup> The levulinic acid (4-oxopentanoic acid) is an important fine organic material from renewable source, with acetyl group attractive for us.<sup>7</sup> Our continuing interest in 1,3-dielectrophilic compounds has led us to study a new aspect of the application of the acetal acylation method for producing methyl 4-methoxy-6-oxo-7,7,7-trialo-4-heptenoates **1** and **2**.<sup>8</sup>

On the other hand, the pyrrolidin-2-ones, have received considerable attention due to their activity in CNS as

nootropic drugs. Piracetam-like nootropics revert amnesia induced by scopolamine and other amnesing drugs, electroconvulsive shock and hypoxia with an unknown mechanism.<sup>9</sup> In general, they show no affinity for the most important central receptors, but are able to modulate the action of these most important central neurotransmitters, in particular acetylcholine and glutamate. Extensive study of the modes of action of the 2-pyrrolidinones has revealed various pharmacological effects, with striking differences between drugs.<sup>10,11</sup>

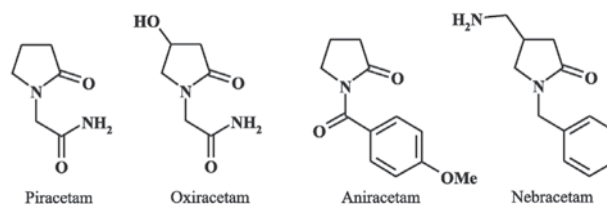


Figure 1. Structures of pyrrolidin-2-one drugs.

\*e-mail: alexflores@smail.ufsm.br

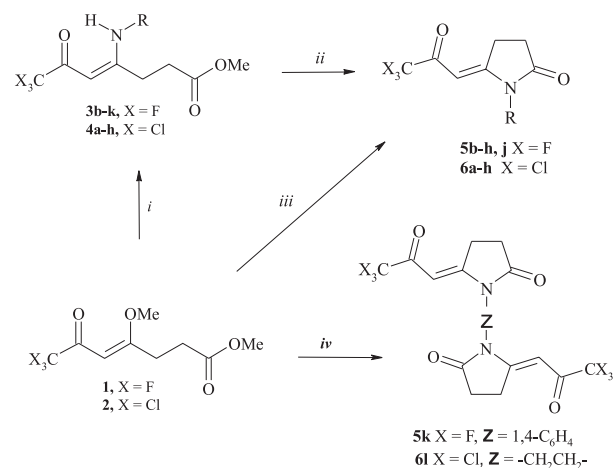
Continuing with our systematic studies on synthesis and application of 4-alkoxy-1,1,1-trihalo-3-alken-2-ones we report an efficient approach for synthesis of a series of 1-[alkyl(aryl)]-5-(3,3,3-trihalo-2-oxopropylidene)pyrrolidin-2-ones from **1** and **2**. This study deals with formation of the methyl 4-alkyl[aryl]amino-6-oxo-7,7,7-trihalo-4-heptenoates **3** and **4**, and their intramolecular cyclisations to new 1-alkyl[aryl]-5-(3,3,3-trihalo-2-oxopropylidene)pyrrolidin-2-ones **5** and **6**.

## Results and Discussion

The precursors methyl 4-methoxy-6-oxo-7,7,7-trihalo-4-heptenoates **1** and **2** were obtained by acetal acylation method as described previously.<sup>8</sup>

The fluorinated enaminones **3** were synthesized and isolated by reaction of the methyl 4-methoxy-6-oxo-7,7,7-trifluoro-4-heptenoate (**1**) with primary alkyl[aryl]amines in CH<sub>3</sub>CN at variable temperatures depending on used amine. The analytical data have demonstrated the formation of the methyl 4-alkyl[aryl]amino-6-oxo-7,7,7-trifluoro-4-heptenoates **3b-k** (Table 1, Supplementary Information), with (*Z*)-4-alkyl[aryl]amino-1,1,1-trifluoro-3-alken-2-one moiety.<sup>2</sup> Primary alkylamines (**b**, **c**) reacted readily with 4-methoxy-1,1,1-trifluoro-3-alken-2-ones in MeOH, EtOH or *i*-PrOH by displacement of β-methoxy substituent, in these cases, the intramolecular cyclocondensation of the resulting methyl 4-alkylamino-6-oxo-7,7,7-trifluoro-4-heptenoates **3b,c** to pyrrolidin-2-ones also took place, affording mixtures of products **3** and **5** at room temperature. However, when the least reactive primary arylamines were employed, and the reaction was carried out in MeOH or EtOH at room temperature, unreacted **1** or mixtures of methyl 4-ethoxy-6-oxo-7,7,7-trifluoro-4-heptenoate and **1** were recovered. The methyl 4-aryl-amino-6-oxo-7,7,7-trifluoro-4-heptenoates **3d-j** were obtained in refluxing MeCN or at room temperature, by addition of equimolar amount of Et<sub>3</sub>N or lutidine (Table 1, Supplementary Information). Reaction of the methyl 4-methoxy-6-oxo-7,7,7-trifluoro-4-heptenoate **1** with 1,4-diaminobenzene in a stoichiometric ratio 1:1 or in 2:1 mol-equiv ratio in MeCN at room temperature lead to the methyl 4-(4-aminophenylamino)-6-oxo-7,7,7-trifluoro-4-heptenoate **3k**, but under reflux conditions the intramolecular cyclisation took place under formation of only 1,1'-(1,4-phenylene)-bis(5-(3,3,3-trifluoro-2-oxopropylidene)-2-pyrrolidin-2-one) **5k** (Scheme 1).

The structures of fluorinated enaminones **3** were confirmed by elemental analysis, mass spectrometry and <sup>1</sup>H, <sup>13</sup>C NMR spectral data. The <sup>1</sup>H NMR spectra showed characteristic broad signals from N-H between 12.4-13.2 ppm, the vinylic hydrogen singlet at 5.47-5.68 ppm



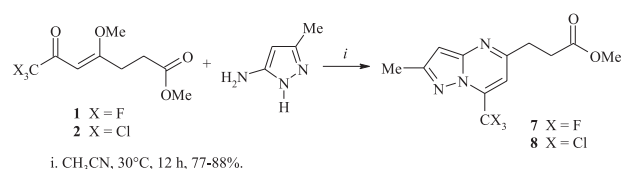
	a	b	c	d	e	f	g
R	n-Pr	CH <sub>2</sub> Ph	(CH <sub>2</sub> ) <sub>2</sub> Ph	Ph	4-Me-C <sub>6</sub> H <sub>4</sub>	4-MeO-C <sub>6</sub> H <sub>4</sub>	4-Cl-C <sub>6</sub> H <sub>4</sub>
	h	i	j	k			
R	4-Br-C <sub>6</sub> H <sub>4</sub>	5-methyl-3-isoxazolyl	2-pyridyl	4-H <sub>2</sub> N-C <sub>6</sub> H <sub>4</sub>			

*i.* RNH<sub>2</sub>, MeCN, 25-80 °C, 6-24h. *ii.* Et<sub>3</sub>N, MeCN, 80 °C, 24h, 75-95%.  
*iii.* (a) RNH<sub>2</sub>, MeCN, 25-80 °C, 12h; (b) Et<sub>3</sub>N, 80 °C, 8-24h  
*iv.* 1,4-diaminobenzene or ethylenediamine, MeCN, 25-80 °C, 12h.

**Scheme 1.**

and for methyl group of ester as intense singlet at 3.64-3.70 ppm.<sup>12,13</sup> The <sup>13</sup>C NMR spectra showed the signals of methoxy group at 51.5-51.9 ppm and carboxylic ester carbon at 169.8 –170.7 ppm confirming the propionyl chain, two characteristic quartets for carbonyl carbon C6, *ca.* 176-178 ppm, <sup>2</sup>J<sub>CF</sub> 34 Hz and trifluoromethyl group C7, *ca.* 116.5-117.5 ppm, <sup>1</sup>J<sub>CF</sub> 288 Hz, all confirming acyclic enaminone structures **3b-k**.

Reacting **1** or **2** with 5-amino-3-methyl-1*H*-pyrazole under conditions described above, the products of cyclocondensation [3 + 3], the methyl 3-(2-methyl-7-(trihalomethyl)pyrazolo[1,5-*a*]pyrimidin-5-yl)propanoates **7** and **8** (Scheme 2). Their structures were confirmed by elemental analysis and <sup>1</sup>H, <sup>13</sup>C NMR data.<sup>15</sup>



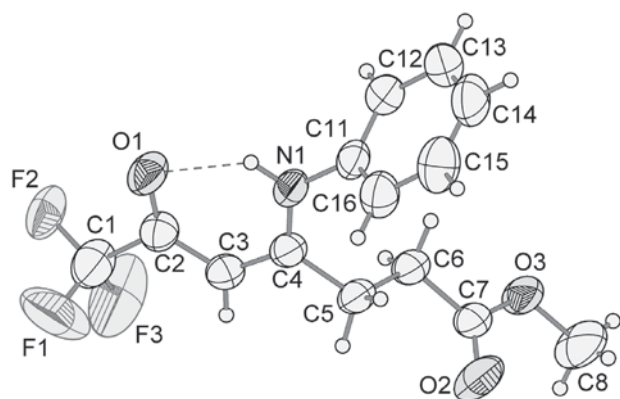
**Scheme 2.** 5-amino-3-methyl-1*H*-pyrazole lead to [CCC + NCN] cyclisation.

The easy intramolecular cyclization of methyl 4-alkylamino-6-oxo-7,7,7-trifluoro-4-heptenoates **3b,c** to pyrrolidin-2-ones **5b,c** occurred in MeOH, EtOH or MeCN. The intramolecular cyclisation of methyl 4-alkylamino-6-oxo-7,7,7-trifluoro-4-heptenoates **3d-j** to 5-(3,3,3-trifluoro-2-oxopropylidene)-pyrrolidin-2-ones **5d-j** occurred only

in refluxing MeCN in the presence of equimolar amount of Et<sub>3</sub>N for reaction periods varying between 8-24 h. The products **5,b-k** can be obtained in *one pot* process by the reaction of precursor **1** and amine in MeCN followed by Et<sub>3</sub>N addition and/or reflux (85 °C) affording similar yields.

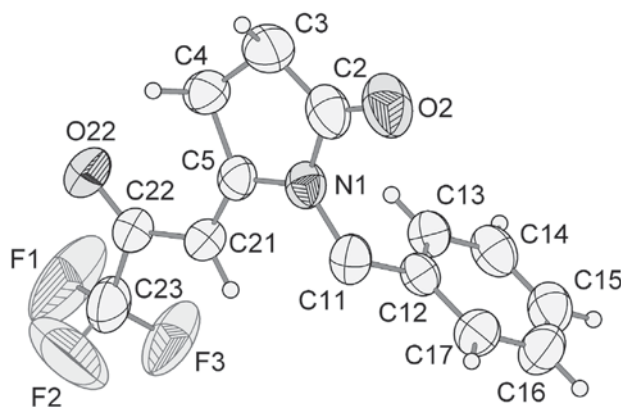
The 1-Alkyl(aryl)-5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-2-ones **5,b-k** were characterised by elemental analysis, mass spectrometry and <sup>1</sup>H, <sup>13</sup>C NMR data. The <sup>1</sup>H NMR spectra showed characteristic signals for vinylic hydrogen at 5.66-5.94 ppm and the signals for cyclic CH<sub>2</sub> as multiplet at 2.67-2.83 and 3.33-3.57 ppm. The <sup>13</sup>C NMR spectra showed the signals of amide carbon at 167.8-169.2 ppm, two characteristic quartets of carbonyl carbon at propylidene chain *ca.* 178-179.3 ppm, <sup>2</sup>J<sub>CF</sub> 34 Hz, for trifluoromethyl group CF<sub>3</sub> *ca.* 116.2-116.4 ppm, <sup>1</sup>J<sub>CF</sub> 291 Hz and for vinylic carbon at 90.3-93.7 ppm, all confirming 1-alkyl[aryl]-5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-2-one structures **5,b-k**.

Compounds **3d** and **5b** were subjected to single crystal X-ray analysis (Tables 4 and 5). This measurement has showed in solid state the molecular structure with *Z*-configuration on alkene moiety and intramolecular hydrogen bond O3---H1—N1 for methyl 6-oxo-4-phenylamino-7,7,7-trifluoro-4-heptenoate (**3d**) (Figure 2). X-ray diffraction analysis performed on 1-benzyl-5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-2-one (**5b**) showed the *E*-configuration for enaminoketone moiety (Figure 3), confirming that the intramolecular cyclisation occurred with the inversion of configuration. In both structures the trifluoromethyl group suffers a rotational disorder and was refined as two components as approximately 60%/40% occupancy (Tables 1 and 2).



**Figure 2.** ORTEP representation of the X-ray molecular structure of methyl 4-benzylamino-2-oxo-7,7,7-trifluoro-4-heptanoate (**3d**).

The methyl 4-methoxy-6-oxo-7,7,7-trichloro-4-heptenoate demonstrated high reactivity for nucleophilic attack of alkylamines at  $\beta$ -carbon of the vinyl group, taking place of methoxy group, followed by fast intramolecular



**Figure 3.** ORTEP representation of the X-ray molecular structure of 1-benzyl-5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-2-one (**5b**).

cyclisation to 1-alkyl-5-(3,3,3-trichloro-2-oxopropylidene)pyrrolidin-2-ones. With the intention to isolate of the methyl 4-alkylamino-6-oxo-7,7,7-trichloro-4-heptenoates **4,a,c**, the heptanoate precursor **2** was reacted with primary alkylamines in dichloromethane or chloroform at -5 - 0 °C for 2 hours. Primary arylamines were reacted in MeCN at room temperature (Scheme 1) for 6 hours, and 4-arylamino-6-oxo-7,7,7-trichloro-4-heptenoates **4,d-j** were isolated in good yields and in high purity (Table 2, Supplementary Information). Reactions in EtOH or *i*-PrOH gave poor yields with complex mixtures of unidentified products, maybe involving transesterification and/or chloroform elimination.

The molecular structures of methyl 4-alkyl[aryl]amino-6-oxo-7,7,7-trichloro-4-heptenoates **4,a,c-j** were confirmed by elemental analysis, mass spectrometry and <sup>1</sup>H, <sup>13</sup>C NMR spectral data. The <sup>1</sup>H NMR spectra showed characteristic broad signals for N-H between 13.4-13.8 ppm, the vinylic hydrogen at 5.85-5.89 ppm and for methoxy group as intense singlet at 3.60-3.67 ppm.<sup>12,13</sup> The <sup>13</sup>C NMR spectra showed the signals of methoxy group at characteristic region 51.9-52.9 ppm, for the carboxylic ester carbon at 181.2-181.7 ppm and low intense signal at 96-99.1 for trichloromethyl carbon confirming the attributed structure for methyl 4-alkyl[aryl]amino-6-oxo-7,7,7-trichloro-4-heptenoates **4,a,c-j**.

The intramolecular cyclisation of isolated methyl 4-alkyl[aryl]amino-6-oxo-7,7,7-trichloro-4-heptenoates **4,a,c** to 5-(3,3,3-trichloro-2-oxopropylidene)pyrrolidin-2-ones **6,a,c** occurred in MeCN, affording quantitative yields without Et<sub>3</sub>N addition. The products **6,d-f** and **6h** were obtained in good yields by stirring of **4** in MeCN at variable temperatures for 2 to 6 h. In general, the products **6** can be readily obtained in excellent yields without isolation of enaminones intermediates, by the reaction of precursor **2** and appropriate amine in MeCN under reflux

temperature (80–85 °C). The 1,1'-(ethane-1,2-diyl)bis(5-(3,3,3-trichloro-2-oxopropylidene)pyrrolidin-2-one) **6l** was obtained by the reaction of **2** and ethylenediamine in 2:1 equiv ratio in MeCN at room temperature (Scheme 1).

The 1-alkyl[aryl]-5-(3,3,3-trichloro-2-oxopropylidene)pyrrolidin-2-ones **6a**, **6c–f** and **6h** were characterised by elemental analysis, mass spectrometry and <sup>1</sup>H, <sup>13</sup>C NMR data. 2D COSY (HH and CH) and DEPT experiments were used for signal assignment.

**Table 1.** Crystal data and structure refinement for **3d** and **5b**

Crystal data	<b>3d</b>	<b>5b</b>
CCDC No. <sup>a</sup>	615368	615367
Formula	C14H14F3NO3	C14H12F3NO2
Habit	Colorless	Colorless
Size (mm)	0.15 x 0.15 x 0.1	0.35 x 0.15 x 0.13
Symmetry	Monoclinic, P2(1)/c	Orthorhombic, Pbca
Unit cell dimensions (Å)		
a, α	11.2299(5), 90°	9.6444(7), 90°
b, β	5.9503(2), 104.22°	15.5012(7), 90°
c, γ	22.8256(10), 90°	17.7423(9), 90°
Volume (Å <sup>3</sup> ), Z	1478.46(10), 4	2652.5(3), 8
D <sub>c</sub> (g.cm <sup>-3</sup> )	1.353	1.419
μ (mm <sup>-1</sup> )	0.119	0.123
θ range for data collection (°)	3.55 < θ < 30.09	2.74 < θ < 27.0
Index ranges	-15 ≤ h ≤ 15 -8 ≤ k ≤ 8 -31 ≤ l ≤ 29	-5 ≤ h ≤ 12 -19 ≤ k ≤ 18 -22 ≤ l ≤ 22
Reflexions collected	17625	14247
Independent reflexions (R <sub>int</sub> )	4275 (0.0313)	2895 0.0396
Completeness to θ	98.4 %	99.8 %
T <sub>min</sub> - T <sub>max</sub>	0.864 - 1.0	0.6937 - 1.0
Solution	Direct methods SHELXS-97	
Refinement method	Full-matrix least-squares on F <sup>2</sup>	
Data, restraints, parameters	4275, 48, 228	2895, 0, 195
Goodness-of-fit on F <sup>2</sup>	1.043	1.072
Final R indices [I > 2σ(I)]	R1 = 0.0494 wR2 = 0.1343	R1 = 0.0662 wR2 = 0.1951
R indices (all data)	R1 = 0.0975 wR2 = 0.1576	R1 = 0.1047 wR2 = 0.2254
Largest diff. peak and hole (e. Å <sup>-3</sup> )	0.23 and -0.227	0.337 and -0.535

<sup>a</sup> CCDC 286548 contains the supplementary crystallographic data for this paper. These data can be made available free of charge via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif), by emailing [data\\_request@ccdc.cam.ac.uk](mailto:data_request@ccdc.cam.ac.uk) or by contacting CCDC.

**Table 2.** Bond lengths [Å] and angles [°] for **3d** and **5b**

	<b>3d</b>	<b>5b</b>		
C7-F1	1.3215(10)	N1-C2	1.398(4)	
C7-F2	1.3219(10)	N1-C5	1.369(3)	
C7-F3	1.3224(10)	N1-C11	1.454(3)	
C7-C6	1.528(2)	C2-O2	1.209(4)	
N1-C4	1.3339(19)	C2-C3	1.488(5)	
N1-C11	1.4287(19)	C3-C4	1.517(5)	
N1-H1	0.86	C3-H3A	0.97	
C6-O3	1.2350(18)	C3-H3B	0.97	
C6-C5	1.400(2)	C4-C5	1.503(4)	
C1-O1	1.190(2)	C4-H4A	0.97	
C5-C4	1.378(2)	C4-H4B	0.97	
C5-H5	0.93	C5-C21	1.356(4)	
C4-C3	1.505(2)	C21-C22	1.432(4)	
C3-C2	1.510(2)	C21-H21	0.93	
C3-H3A	0.97	C22-O22	1.214(3)	
C3-H3B	0.97	C22-C23	1.566(4)	
C2-C1	1.499(2)	C11-C12	1.505(4)	
C2-H2A	0.97	C11-H11A	0.97	
C2-H2B	0.97	C11-H11B	0.97	
C1-O1	1.322(5)	C12-C13	1.372(4)	
C1-O2	1.33(2)	C12-C17	1.386(4)	
O2-C8	1.434(5)	C13-C14	1.386(4)	
C8-H8A	0.96	C13-H13	0.93	
C8-H8B	0.96	C14-C15	1.365(5)	
C8-H8C	0.96	C14-H14	0.93	
C11-C16	1.378(2)	C15-C16	1.366(5)	
C11-C12	1.380(2)	C15-H15	0.93	
C12-C13	1.379(2)	C16-C17	1.379(5)	
C12-H12	0.93	C16-H16	0.93	
C13-C14	1.376(3)	C17-H17	0.93	
C13-H13	0.93	C23-F1	1.3207 (10)	
C14-C15	1.374(3)	C23-F2	1.3210 (10)	
C15-C16	1.378(3)	C23-F3	1.3215 (10)	
F1-C7-F2	106.95(16)	C2-N1-C5	112.6(2)	
F1-C7-C6	115.2(4)	C5-N1-C11	125.9(2)	
C4-N1-C11	126.6(13)	C2-N1-C11	121.5(2)	
C4-N1-H1	116.7	O2-C2-N1	122.3(3)	
C11-N1-H1	116.7	O2-C2-C3	129.4(3)	
O3-C6-C5	127.01(15)	N1-C2-C3	108.3(3)	
O3-C6-C7	115.67(14)	C2-C3-C4	105.4(3)	
C5-C6-C7	117.26(13)	C2-C3-H3A	110.7	
C4-C5-C6	123.25(14)	C4-C3-H3A	110.7	
C4-C5-H5	118.4	H3A-C3-H3B	108.8	
C6-C5-H5	118.4	C5-C4-C3	105.0(2)	

Table 2. continuation

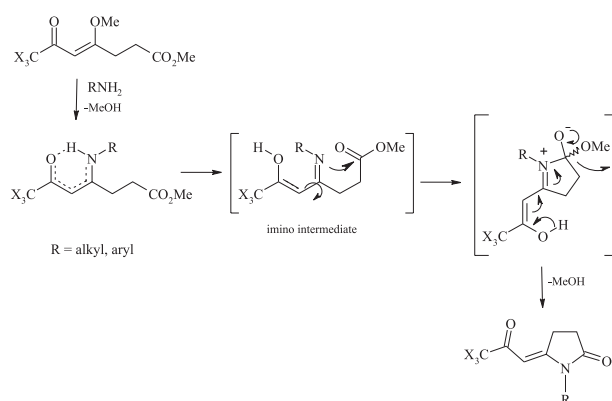
3d		5b	
N1-C4-C5	121.74(14)	C5-C4-H4A	110.8
N1-C4-C3	119.16(14)	C3-C4-H4A	110.8
C5-C4-C3	119.08(13)	H4A-C4-H4B	108.8
C4-C3-C2	113.15(13)	C21-C5-N1	123.8(2)
C4-C3-H3A	108.9	C21-C5-C4	127.5(2)
C2-C3-H3A	108.9	N1-C5-C4	108.7(2)
H3A-C3-H3B	107.8	N1-C11-C12	115.0(2)
C1-C2-C3	111.48(13)	N1-C11-H11A	108.5
O1-C1-O2	122.2(3)	C12-C11-H11A	108.5
O1-C1-C2	124.75(15)	C12-C11-H11B	108.5
O2-C1-C2	113.0(3)	C13-C12-C17	118.5(3)
C1-O2-C8	116.9(4)	C13-C12-C11	123.0(2)
C16-C11-C12	120.13(16)	C17-C12-C11	118.5(2)
C16-C11-N1	121.01(15)	C12-C13-C14	120.6(3)
C12-C11-N1	118.83(15)	C12-C13-H13	119.7
C13-C12-C11	120.06(18)	C14-C13-H13	119.7
C11-C12-H12	120.0	C15-C14-C13	120.2(3)
C14-C13-C12	119.83(19)	C14-C15-C16	120.0(3)
C15-C14-C13	119.93(19)	C15-C16-C17	120.0(3)
C14-C15-C16	120.6(2)	C16-C17-C12	120.7(3)
C11-C16-C15	119.44(19)	C5-C21-C22	122.3(2)
C13-C12-H12	120.0	O22-C22-C21	128.4(3)
C14-C13-H13	120.1	O22-C22-C23	115.7(2)
C14-C15-H15	119.7	C21-C22-C23	116.0(2)

The synthesis of 5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-2-ones from methyl 7,7,7-trihalo-4-methoxy-6-oxo-4-heptenoates and primary amines can be characterised as an Paal-Knorr process for pyrrole heterocyclic from [CCCC + N] building blocks. Mechanistically, it is conceivable that the reaction involves an initial attack from amines to  $\beta$ -position, leading to enaminoketone moiety,<sup>14</sup> then an imino intermediate as shown in Scheme 3, which allow the rotation of trihalocarbonyl group around C4-C5 bond on 4-amino-6-oxo-7,7,7-trihalo-4-heptenoates, and intramolecular nucleophilic attack of imino nitrogen to ester carbonyl lead to pyrrolidin-2-ones.

## Experimental

### General

EtOH, MeOH, MeCN and Et<sub>3</sub>N were purchased from Merck and Aldrich, R<sup>1</sup>NH<sub>2</sub> was purchased from Aldrich, all used as obtained from suppliers. The methyl 7,7,7-trifluoro



Scheme 3.

[chloro]-4-methoxy-6-oxo-4-heptenoates **1** and **2** were prepared according to reference 8. All melting points were determined on a Reichert Thermovar instrument and are uncorrected. <sup>1</sup>H and <sup>13</sup>C NMR spectra were obtained on a Bruker DPX 400 spectrometer (<sup>1</sup>H at 400.13 MHz and <sup>13</sup>C at 100.62 MHz) 5 mm sample tubes, 298 K, digital resolution  $\pm$  0.01 ppm, in CDCl<sub>3</sub> 0.02-0.05 g.mL<sup>-1</sup>, using TMS as internal standard. Mass spectra were registered with a HP 6890 GC connected to a HP 5973 MSD and interfaced by a Pentium PC. The GC was equipped with a capillary column (30 m, 0.32 mm of internal diameter), and helium was used as the carrier gas. The elemental analyses were performed on a Perkin-Elmer 2400 CHN elemental analyser (São Paulo University/Brazil).

### Methyl 4-alkylamino-6-oxo-7,7,7-trifluoro-4-heptenoates (**3b** and **3c**)

To a stirred solution of methyl 7,7,7-trifluoro-4-methoxy-6-oxo-3-heptenoate **1** (5 mmol, 1.28 g) in MeCN (5 mL), kept at 25 °C, was added benzylamine (5.1 mmol, 0.56 mL) or phenethylamine (5.1 mmol, 0.62 mL) in MeCN (5 mL). The mixture was stirred for 6 h. The solvent was evaporated and the solid residue was dried under vacuum. The enaminones **3b** and **3c** were purified on silica-gel chromatographic column using chloroform-hexane (2:1) as eluent, yield refers to purified product.

**3b**: Yield 57 %; oil; Anal. Calcd. for C<sub>15</sub>H<sub>16</sub>F<sub>3</sub>NO<sub>3</sub> (315.29 g.mol<sup>-1</sup>): C, 57.14; H, 5.11, N, 4.44. Found: C, 58.10; H, 5.40; N, 4.65. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  2.56 (m, H2), 2.67 (m, H3), 5.37 (s, H5), 3.69 (s, OMe), 4.61 (d, <sup>2</sup>J<sub>HH</sub> 6.0 Hz, CH<sub>2</sub>), 7.26 - 7.4 (m, Ph), 11.49 (NH, br). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  176.2 (q, <sup>2</sup>J<sub>CF</sub> 33 Hz, C6), 171.6 (C4), 171.3 (C1), 135.9 (C1, Ph), 129.0 (C3 and C5, Ph), 128.1 (C4, Ph), 126.9 (C2 and C6, Ph), 117.5 (q, <sup>1</sup>J<sub>CF</sub> 288 Hz, C7), 87.5 (C5), 51.9 (OMe), 47.2 (-CH<sub>2</sub>-), 31.2 (C2), 26.7 (C3). MS (EI, 70 eV) *m/z* (%): 315 (M<sup>+</sup>, 29), 284 (5), 246(68), 218 (36), 91 (100), 65 (75).



**3c:** Yield 92 %; oil; Anal. Calcd. for  $C_{16}H_{18}F_3NO_3$  (329.32 g.mol<sup>-1</sup>): C, 58.36; H, 5.51, N, 4.25. Found: C, 57.70; H, 5.11; N, 4.44. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.93 (t, <sup>3</sup>J<sub>HH</sub> 7.0 Hz, H2), 2.48 (m, 4H, H3, CH<sub>2</sub>), 5.25 (s, H5), 3.66 (s, OMe), 3.64 (t, <sup>3</sup>J<sub>HH</sub> 7.5 Hz, CH<sub>2</sub>), 7.18 - 7.3 (m, Ph), 11.25 (NH, br). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 175.6 (q, <sup>2</sup>J<sub>CF</sub> 33 Hz, C6), 171.5 (C4), 171.1 (C1), 137.2 (C1, Ph), 128.6 (C3 and C5, Ph), 128.5 (C2 and C6, Ph), 126.8 (C4, Ph), 117.5 (q, <sup>1</sup>J<sub>CF</sub> 288 Hz, C7), 87.1 (C5), 51.7 (OMe), 44.9 (NCH<sub>2</sub>-), 36.0 (-CH<sub>2</sub>Ph), 31.0 (C2), 26.3 (C3). MS (EI, 70 eV): *m/z* (%): 329 (M<sup>+</sup>, 38), 298 (23), 238 (92), 206 (92), 178 (84), 104 (100), 77 (39).

*Methyl 4-arylamino-6-oxo-7,7,7-trifluoro-4-heptenoates (3,d-k)*

To a stirred solution of methyl 7,7,7-trifluoro-4-methoxy-6-oxo-3-heptenoate **1** (5 mmol, 1.28 g) in MeCN (5 mL), was added the appropriate arylamine (Aldrich, 5.1 mmol) in MeCN (5 mL). The mixture was refluxed for 6 to 24 h. Then the solvent was evaporated and solid residue was dried under vacuum. Enaminones **3,d-k** were recrystallised from hexane-chloroform (2:1), yield refers to purified product.

**3d:** Yield 76 %; mp 51-53 °C; Anal. Calcd. for  $C_{14}H_{14}F_3NO_3$  (301.27 g.mol<sup>-1</sup>): C, 55.82; H, 4.68, N, 4.65. Found: C, 56.07; H, 4.65; N, 4.35. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.53 (t, <sup>3</sup>J<sub>HH</sub> 7.5 Hz, H2), 2.72 (t, <sup>3</sup>J<sub>HH</sub> 7.6 Hz, H3), 5.54 (s, H5), 3.64 (s, OMe), 7.14 - 7.5 (m, Ph), 12.6 (NH, br). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 177.0 (q, <sup>2</sup>J<sub>CF</sub> 33 Hz, C6), 171.5 (C4), 170.0 (C1), 136.4 (C1, Ph), 129.6 (C3 and C5, Ph), 127.1, (C4, Ph), 125.7 (C2 and C6, Ph), 117.3 (q, <sup>1</sup>J<sub>CF</sub> 288 Hz, C7), 88.6 (C5), 51.8 (OMe), 31.4 (C2), 27.1 (C3). MS (EI, 70 eV): *m/z* (%): 301 (M<sup>+</sup>, 39), 270 (19), 200 (82), 172 (78), 144 (48), 130 (49), 77 (100).

**3e:** Yield 92 %; mp 43-45 °C; Anal. Calcd. for  $C_{15}H_{16}F_3NO_3$  (315.29 g.mol<sup>-1</sup>): C, 57.14; H, 5.11, N, 4.44. Found: C, 57.48; H, 4.99; N, 4.65. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.52 (t, <sup>3</sup>J<sub>HH</sub> 7.0 Hz, H2), 2.70 (t, <sup>3</sup>J<sub>HH</sub> 7.2 Hz, H3), 5.51 (s, H5), 3.66 (s, OMe), 2.38 (s, 4-CH<sub>3</sub>), 7.07 (m, 2H, Ph), 7.23 (m, 2H, Ph), 12.5 (NH, br). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 177.0 (q, <sup>2</sup>J<sub>CF</sub> 33 Hz, C6), 170.6 (C4), 170.0 (C1), 137.9 (C1, Ph), 133.8 (C4, Ph), 130.2 (C3 and C5, Ph), 125.6 (C2 and C6, Ph), 117.4 (q, <sup>1</sup>J<sub>CF</sub> 288 Hz, C7), 88.5 (C5), 51.9 (OMe), 31.4 (C2), 27.1 (C3), 20.9 (4-CH<sub>3</sub>). MS (EI, 70 eV): *m/z* (%): 315 (M<sup>+</sup>, 61), 284 (16), 228 (25), 214 (100), 186 (73), 158 (34), 144 (41), 91 (59).

**3f:** Yield 74 %; mp 52-54 °C; Anal. Calcd. for  $C_{15}H_{16}F_3NO_4$  (331.29 g.mol<sup>-1</sup>): C, 54.38; H, 4.87, N, 4.23. Found: C, 54.25; H, 4.93; N, 3.87. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.51 (t, <sup>3</sup>J<sub>HH</sub> 7.8 Hz, H2), 2.66 (t, <sup>3</sup>J<sub>HH</sub> 7.8 Hz, H3),

5.50 (s, H5), 3.66 (s, OMe), 3.83 (s, 4-OMe), 6.93 (m, 2H, Ph), 7.11 (m, 2H, Ph), 12.4 (NH, br). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 176.9 (q, <sup>2</sup>J<sub>CF</sub> 33 Hz, C6), 171.6 (C4), 170.5 (C1), 159.1 (C4, Ph), 129.2 (C1, Ph), 127.2 (C3 and C5, Ph), 117.4 (q, <sup>1</sup>J<sub>CF</sub> 288 Hz, C7), 114.8 (C2 and C6, Ph), 88.4 (C5), 55.5 (4-OMe), 51.9 (OMe), 31.5 (C2), 27.2 (C3). MS (EI, 70 eV): *m/z* (%): 331 (M<sup>+</sup>, 100), 300 (15), 272 (24), 230 (78), 202 (38), 160 (27), 132 (13), 92 (15).

**3g:** Yield 98 %; mp 81-83 °C; Anal. Calcd. for  $C_{14}H_{13}ClF_3NO_3$  (335.71 g.mol<sup>-1</sup>): C, 50.09; H, 3.90, N, 4.71. Found: C, 50.18; H, 3.91; N, 4.97. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.54 (t, <sup>3</sup>J<sub>HH</sub> 7.2 Hz, H2), 2.70 (t, <sup>3</sup>J<sub>HH</sub> 7.2 Hz, H3), 5.55 (s, H5), 3.66 (s, OMe), 7.16 (m, 2H, Ph), 7.40 (m, 2H, Ph), 12.5 (NH, br). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 177.3 (q, <sup>2</sup>J<sub>CF</sub> 33 Hz, C6), 171.4 (C4), 169.8 (C1), 135.0 (C1, Ph), 133.5 (C4, Ph), 129.7 (C3 and C5, Ph), 127.0 (C2 and C6, Ph), 117.2 (q, <sup>1</sup>J<sub>CF</sub> 288 Hz, C7), 88.9 (C5), 51.8 (OMe), 31.3 (C2), 26.9 (C3). MS (EI, 70 eV): *m/z* (%): 335 (M<sup>+</sup>, 31), 304 (14), 276 (18), 234 (100), 206 (96), 178 (60), 143 (39), 111 (81), 75 (82).

**3h:** Yield 95 %; mp 77-79 °C; Anal. Calcd. for  $C_{14}H_{13}BrF_3NO_3$  (380.16 g.mol<sup>-1</sup>): C, 44.23; H, 3.45, N, 3.68. Found: C, 44.37; H, 3.44; N, 3.57. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 2.54 (t, <sup>3</sup>J<sub>HH</sub> = 7.2 Hz, H2), 2.70 (t, <sup>3</sup>J<sub>HH</sub> = 7.2 Hz, H3), 5.55 (s, H5), 3.67 (s, OMe), 7.10 (m, 2H, Ph), 7.56 (m, 2H, Ph), 12.5 (NH, br). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 177.3 (q, <sup>2</sup>J<sub>CF</sub> 34 Hz, C6), 171.4 (C4), 169.7 (C1), 135.4 (C1, Ph), 132.7 (C3 and C5, Ph), 127.3 (C2 and C6, Ph), 121.4 (C4, Ph), 117.1 (q, <sup>1</sup>J<sub>CF</sub> 288 Hz, C7), 88.9 (C5), 51.9 (OMe), 31.2 (C2), 26.9 (C3). MS (EI, 70 eV): *m/z* (%): 380 (M<sup>+</sup>, 69), 348 (21), 310 (34), 278 (100), 250 (52), 231 (57), 199 (61), 172 (70), 143 (86), 76 (77).

**3i:** Yield 95 %; mp 68-70 °C; Anal. Calcd. for  $C_{12}H_{13}F_3N_2O_4$  (306.24 g.mol<sup>-1</sup>): C, 47.06; H, 4.28, N, 9.15. Found: C, 46.97; H, 4.19; N, 8.98. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.72 (t, <sup>3</sup>J<sub>HH</sub> 7.6 Hz, H2), 3.13 (t, <sup>3</sup>J<sub>HH</sub> 7.6 Hz, H3), 5.68 (s, H5), 3.70 (s, OMe), 2.43 (s, 3-CH<sub>3</sub>, isox), 5.98 (s, H5, isox), 12.4 (NH, br). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 178.5 (q, <sup>2</sup>J<sub>CF</sub> 34 Hz, C6), 171.6 (C4), 170.7 (C1), 168.3 (C5, isox), 157.6 (C3, isox), 116.6 (q, <sup>1</sup>J<sub>CF</sub> 288 Hz, C7), 96.7 (C4, isox), 92.2 (C5), 51.5 (OMe), 31.3 (C2), 29.4 (C3), 11.9 (3-Me, isox). MS (EI, 70 eV): *m/z* (%): 306 (M<sup>+</sup>, 9), 275 (18), 237 (100), 278 (100), 205 (60), 149 (43), 135 (47), 119 (46), 68 (58).

**3j:** Yield 95 %; mp 65-68 °C; Anal. Calcd. for  $C_{13}H_{13}F_3N_2O_3$  (302.26 g.mol<sup>-1</sup>): C, 51.66; H, 4.34, N, 9.27. Found: C, 51.41; H, 4.18; N, 9.30. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.76 (t, <sup>3</sup>J<sub>HH</sub> 7.2 Hz, H2), 3.33 (t, <sup>3</sup>J<sub>HH</sub> 7.2 Hz, H3), 5.61 (s, H5), 3.70 (s, OMe), 7.0, 7.1, 7.7, 8.4 (2-pyridyl), 12.9 (NH, br). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 177.8 (q, <sup>2</sup>J<sub>CF</sub> 34 Hz, C6), 172.1 (C4), 168.7 (C1), 151.1 (C2, pyr), 148.3 (C6, pyr), 138.4 (C4, pyr),

120.2 (C3, pyr), 115.5 (C5, pyr), 117.0 (q,  $^1J_{CF}$  288 Hz, C7), 92.5 (C5), 51.1 (OMe), 32.3 (C2), 29.5 (C3). MS (EI, 70 eV):  $m/z$  (%): 271 ( $M^+$ -OMe, 34), 233 (21), 205 (100), 173 (98), 131 (88), 96 (18), 78 (97), 51 (38).

**3k**: Yield 95 %; mp 65-68 °C; Anal. Calcd. for  $C_{14}H_{15}F_3N_2O_3$  (316.28 g.mol<sup>-1</sup>): C, 53.17; H, 4.78, N, 8.86. Found: C, 55.00; H, 5.28; N, 9.90. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.50 (t,  $^3J_{HH}$  7.5 Hz, H2), 2.66 (t,  $^3J_{HH}$  7.5 Hz, H3), 5.47 (s, H5), 3.66 (s, OMe), 6.68 (m, 2H, Ph), 6.96 (m, 2H, Ph), 13.2 (NH, br). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 177.6 (q,  $^2J_{CF}$  34 Hz, C6), 171.7 (C4), 170.8 (C1), 146.3 (C4, Ph), 126.9 (C3, C4 and C5, Ph), 115.4 (C2 and C6, Ph), 88.2 (C5), 31.5 (C2), 27.2 (C3). MS (EI, 70 eV):  $m/z$  (%): 316 ( $M^+$ , 100), 285 (10), 257 (15), 215 (36), 187 (33), 173 (32), 92 (19).

*Methyl 7,7,7-trichloro-4-alkylamino-6-oxo-4-heptenoates (4a and 4c)*

To a stirred solution of methyl 7,7,7-trichloro-4-methoxy-6-oxo-3-heptenoate **2** (5 mmol, 1.52 g) in CHCl<sub>3</sub> (5 mL), kept at 25 °C, was added n-propylamine (Aldrich, 18570-1, 5.1 mmol, 0.42 mL) or phenethylamine (Aldrich, 24095-8, 5.1 mmol, 0.62 mL) in CHCl<sub>3</sub> (5 mL). The mixture was stirred for 2 h. Then the solvent was evaporated and solid residue was dried under vacuum. The enaminones **4a** and **4c** were purified on silica-gel chromatographic column using chloroform-hexane (2:1) as eluent, yield refers to purified product.

**4a**: Yield 94 %; Oil; Anal. Calcd. for  $C_{11}H_{16}Cl_3NO_3$  (316.61 g.mol<sup>-1</sup>): C, 41.73; H, 5.09, N, 4.42. Found: C, 41.39; H, 4.95; N, 4.30. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.69 (m, H2 and H3), 5.67 (s, H5), 3.73 (s, OMe), 3.36 (t, CH<sub>2</sub>), 1.72 (q, CH<sub>2</sub>), 1.05 (t, CH<sub>3</sub>), 12.8 (NH, br). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 180.1 (C6), 171.6 (C4), 170.3 (C1), 96.9 (C7), 84.2 (C5) 51.8 (OMe), 44.9 (NCH<sub>2</sub>-), 31.2 (C2), 27.0 (C3), 22.7 (-CH<sub>2</sub>-), 11.1 (Me). MS (EI, 70 eV):  $m/z$  (%): 318 ( $M^+$ + 2, 10), 316 ( $M^+$ , 10), 252 (39), 198 (100), 166 (36).

**4c**: Yield 98 %; Oil; Anal. Calcd. for  $C_{16}H_{18}Cl_3NO_3$  (378.69 g.mol<sup>-1</sup>): C, 50.75; H, 4.79, N, 3.70. Found: C, 52.0; H, 4.97; N, 4.0. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.53 (t,  $^3J_{HH}$  7.2 Hz, H2), 2.95 (t,  $^3J_{HH}$  7.2 Hz, H3), 5.64 (s, H5), 3.69 (s, OMe), 2.53 (CH<sub>2</sub>), 3.61 (CH<sub>2</sub>), 7.2 - 7.33 (Ph), 12.8 (NH, br). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 180.3 (C6), 171.6 (C4), 170.2 (C1), 137.3 (C1, Ph), 128.6 (C3 and C5, Ph), 128.5 (C4, Ph), 126.8 (C2 and C6, Ph), 96.9 (C7), 84.5 (C5), 51.9 (OMe), 45.0 (NCH<sub>2</sub>-), 36.1 (-CH<sub>2</sub>Ph), 31.2 (C2), 26.8 (C3). MS (EI, 70 eV):  $m/z$  (%): 381 ( $M^+$ + 2, 13), 379 ( $M^+$ , 10), 314 (44), 286 (50), 260 (100), 228 (23), 105 (100), 77 (50).

*Methyl 7,7,7-trichloro-4-arylamino-6-oxo-4-heptenoates (4d-4i)*

To a stirred solution of methyl 7,7,7-trichloro-4-methoxy-6-oxo-3-heptenoate **2** (5 mmol, 1.52 g) in MeCN (5 mL), kept at 25 °C, was added appropriate arylamine (Aldrich, 5.1 mmol) in MeCN (5 mL). The mixture was refluxed for 2 to 6 h. The solvent was evaporated and the solid residue was dried under reduced pressure. The enaminones **4d-i**, **4k** were recrystallised from hexane: CHCl<sub>3</sub> (2:1), yield refers to purified product.

**4d**: Yield 73 %; mp 79-82 °C; Anal. Calcd. for  $C_{14}H_{14}Cl_3NO_3$  (350.63 g.mol<sup>-1</sup>): C, 47.96; H, 4.02, N, 3.99. Found: C, 48.0; H, 4.50; N, 3.90. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.52 (t,  $^3J_{HH}$  7.0 Hz, H2), 2.75 (t,  $^3J_{HH}$  7.0 Hz, H3), 5.88 (s, H5), 3.66 (s, OMe), 7.2 - 7.44 (Ph), 13.8 (NH, br). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 181.4 (C6), 171.6 (C4), 168.8 (C1), 136.8 (C1, Ph), 129.6 (C3 and C5, Ph), 127.5 (C4, Ph), 125.7 (C2 and C6, Ph), 96.9 (C7), 86.5 (C5), 51.9 (OMe), 31.6 (C2), 27.5 (C3). MS (EI, 70 eV):  $m/z$  (%): 352 ( $M^+$ + 2, <5), 350 ( $M^+$ , 10), 232 (85), 200 (100), 172 (61), 144 (27), 77 (60).

**4e**: Yield 76 %; mp 53-55 °C; Anal. Calcd. for  $C_{14}H_{14}Cl_3NO_3$  (364.66 g.mol<sup>-1</sup>): C, 49.41; H, 4.42, N, 3.84. Found: C, 49.90; H, 5.0; N, 3.55. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.52 (t,  $^3J_{HH}$  7.7 Hz, H2), 2.73 (t,  $^3J_{HH}$  7.5 Hz, H3), 5.86 (s, H5), 3.65 (s, OMe), 2.37 (4-Me), 7.1 (3H, Ph), 7.3 (2H, Ph), 13.6 (NH, br). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 181.2 (C6), 171.7 (C4), 169.2 (C1), 137.6 (C1, Ph), 134.1 (C3 and C5, Ph), 130.1 (C4, Ph), 125.5 (C2 and C6, Ph), 96.9 (C7), 86.2 (C5) 51.9 (OMe), 31.7 (C2), 27.5 (C3), 20.9 (4-Me). MS (EI, 70 eV):  $m/z$  (%): 367 ( $M^+$ +2, 7), 365 ( $M^+$ , 7), 246 (70), 214 (100), 186 (47), 158 (14), 91 (39).

**4f**: Yield 70 %; mp 79-81 °C; Anal. Calcd. for  $C_{15}H_{16}Cl_3NO_4$  (380.66 g.mol<sup>-1</sup>): C, 47.33; H, 4.24, N, 3.68. Found: C, 47.10; H, 4.20; N, 4.0. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.52 (t,  $^3J_{HH}$  7.5 Hz, H2), 2.70 (t,  $^3J_{HH}$  7.5 Hz, H3), 5.86 (s, H5), 3.66 (s, OMe), 3.84 (4-OMe), 6.9 (3H, Ph), 7.13 (2H, Ph), 13.6 (NH, br). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 181.2 (C6), 171.7 (C4), 169.5 (C1), 158.9 (C4, Ph), 129.2 (C1, Ph), 127.2 (C3 and C5, Ph), 114.7 (C2 and C6, Ph), 97.0 (C7), 86.0 (C5), 55.4 (4-OMe), 51.9 (OMe), 31.7 (C2), 27.5 (C3). MS (EI, 70 eV):  $m/z$  (%): 381 ( $M^+$ +2, 15), 379 ( $M^+$ , 14), 262 (75), 230 (100), 202 (28), 174 (10), 77 (16).

**4g**: Yield 88 %; mp 105-107 °C; Anal. Calcd. for  $C_{14}H_{13}Cl_4NO_3$  (385.08 g.mol<sup>-1</sup>): C, 43.67; H, 3.40, N, 3.64. Found: C, 44.87; H, 4.10; N, 3.90. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.54 (t,  $^3J_{HH}$  7.8 Hz, H2), 2.73 (t,  $^3J_{HH}$  7.6 Hz, H3), 5.89 (s, H5), 3.66 (s, OMe), 7.15 (3H, Ph), 7.40 (2H, Ph), 13.4 (NH, br). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 181.7

(C6), 171.5 (C4), 168.6 (C1), 135.4 (C1, Ph), 133.3 (C3 and C5, Ph), 129.8 (C4, Ph), 127.0 (C2 and C6, Ph), 96.8 (C7), 86.9 (C5), 52.0 (OMe), 31.6 (C2), 27.4 (C3). MS (EI, 70 eV):  $m/z$  (%): 385 ( $M^{+}+2$ , 10), 383 ( $M^{+}$ , 6), 266 (70), 234 (100), 206 (40), 178 (10), 111 (10).

**4h:** Yield 85 %; mp 97-100 °C; Anal. Calcd. for  $C_{14}H_{13}BrCl_3NO_3$  (429.53 g.mol<sup>-1</sup>): C, 39.15; H, 3.05, N, 3.26. Found: C, 39.17; H, 3.10; N, 3.50. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.54 (t, <sup>3</sup> $J_{HH}$  7.5 Hz, H2), 2.74 (t, <sup>3</sup> $J_{HH}$  7.6 Hz, H3), 5.89 (s, H5), 3.67 (s, OMe), 7.1 (3H, Ph), 7.56 (2H, Ph), 13.0 (NH, br). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 181.6 (C6), 171.5 (C4), 168.4 (C1), 135.4 (C1, Ph), 133.3 (C3 and C5, Ph), 129.8 (C4, Ph), 127.0 (C2 and C6, Ph), 96.7 (C7), 86.9 (C5), 52.0 (OMe), 31.5 (C2), 27.4 (C3). MS (EI, 70 eV):  $m/z$  (%): 430 ( $M^{+}+2$ , 16), 428 ( $M^{+}$ , 10), 310 (86), 278 (100), 250 (30), 231 (70).

**4k:** Yield 90 %; mp 114-116 °C; Anal. Calcd. for  $C_{14}H_{15}Cl_3N_2O_3$  (366.65 g.mol<sup>-1</sup>): C, 45.99; H, 4.13, N, 7.66. Found: C, 47.17; H, 4.83; N, 8.20. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.57 (t, <sup>3</sup> $J_{HH}$  7.0 Hz, H2), 2.74 (t, <sup>3</sup> $J_{HH}$  7.2 Hz, H3), 5.85 (s, H5), 3.60 (s, OMe), 6.75 (3H, Ph), 7.0 (2H, Ph), 13.8 (NH, br). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 181.7 (C6), 173.3 (C4), 172.3 (C1), 149.6 (C4, Ph), 128.6 (C3 and C5, Ph), 127.5 (C1, Ph), 116.4 (C2 and C6, Ph), 99.1 (C7), 86.6 (C5), 52.9 (OMe), 33.0 (C2), 29.0 (C3). MS (EI, 70 eV):  $m/z$  (%): 366 ( $M^{+}+2$ , 16), 364 ( $M^{+}$ , 15), 247 (46), 215 (100), 187 (38), 173 (50), 159 (12), 92 (16).

*1-[Alkyl(aryl)]-5-(3,3,3-trifluoro[chloro]-2-oxopropylidene)pyrrolidin-2-ones (5, 6)*

To a stirred solution of appropriate methyl 7,7,7-trihalo-4-alkyl(aryl)amino-6-oxo-3-heptenoate (**3** or **4**, 2 mmol) in MeCN (5 mL), kept at 25 °C, was added Et<sub>3</sub>N (2 mmol, 0.3 mL) in MeCN (1 mL). The mixture was refluxed for 1 to 24 h and the solvent was removed under reduced pressure. The residue was crystallised from hexane, yield refers to purified product.

**5b:** Yield 69 %; mp 96-98 °C; Anal. Calcd. for  $C_{14}H_{12}F_3NO_2$  (283.25 g.mol<sup>-1</sup>): C, 59.37; H, 4.27, N, 4.94. Found: C, 60.10; H, 4.01; N, 5.03. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.67 (m, H3), 3.33 (m, H4), 5.89 (s, CH), 4.79 (s, CH<sub>2</sub>), 7.23 (3H, Ph), 7.4 (2H, Ph). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 178.6 (<sup>2</sup> $J_{CF}$  34 Hz, C2, propylidene), 177.1 (C5, pyrrolidin-2-one), 167.8 (C2, pyrrolidin-2-one), 133.9 (C1, Ph), 128.9 (C4, Ph), 128.1 (C2 and C6, Ph), 127.3 (C3 and C5, Ph), 116.3 (<sup>1</sup> $J_{CF}$  292 Hz, C3, propylidene), 92.0 (C1, propylidene), 44.5 (-CH<sub>2</sub>-), 27.2 (C4, pyrrolidin-2-one), 26.6 (C3, pyrrolidin-2-one). MS (EI, 70 eV):  $m/z$  (%): 283 ( $M^{+}$ , 5), 214 (28), 186 (17), 91 (100), 65 (22).

**5c:** Yield 87 %; mp 103-105 °C; Anal. Calcd. for  $C_{15}H_{14}F_3NO_2$  (297.28 g.mol<sup>-1</sup>): C, 60.61; H, 4.75, N, 4.71. Found: C, 60.41; H, 4.60; N, 4.57. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.56 (m, H3, pyrrolidin-2-one), 3.29 (m, H4, pyrrolidin-2-one), 5.78 (s, H1, propylidene), 2.88 (CH<sub>2</sub>), 3.82 (CH<sub>2</sub>), 7.1 - 7.4 (Ph). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 178.6 (<sup>2</sup> $J_{CF}$  34 Hz, C2, propylidene), 176.8 (C5, pyrrolidin-2-one), 168.2 (C2, pyrrolidin-2-one), 137.0 (C1, Ph), 128.7 (C3 and C5, Ph), 128.6 (C2 and C6, Ph), 127 (C4, Ph), 116.4 (<sup>1</sup> $J_{CF}$  292 Hz, C3, propylidene), 91.0 (C1, propylidene), 42.3 (NCH<sub>2</sub>), 32.6 (CH<sub>2</sub>Ph), 26.7 (C3, pyrrolidin-2-one), 27.1 (C4, pyrrolidin-2-one). MS (EI, 70 eV):  $m/z$  (%): 297 ( $M^{+}$ , 5), 228 (24), 178 (10), 104 (100), 77 (13).

**5d:** Yield 77 %; mp 146-149 °C; Anal. Calcd. for  $C_{13}H_{10}F_3NO_2$  (269.23 g.mol<sup>-1</sup>): C, 58.00; H, 3.74, N, 5.20. Found: C, 57.78; H, 3.81; N, 4.90. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.83 (m, H3), 3.53 (m, H4), 5.66 (s, CH), 7.2 (3H, Ph), 7.5 (2H, Ph). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 179.2 (<sup>2</sup> $J_{CF}$  34 Hz, C2, propylidene), 176.5 (C5, pyrrolidin-2-one), 169.2 (C2, pyrrolidin-2-one), 133.2 (C1, Ph), 130.1 (C3 and C5, Ph), 129.8 (C2 and C5, Ph), 127.1 (C4, Ph), 116.4 (<sup>1</sup> $J_{CF}$  292 Hz, C3, propylidene), 92.7 (C1, propylidene), 27.8 (C4, pyrrolidin-2-one), 26.9 (C3, pyrrolidin-2-one). MS (EI, 70 eV):  $m/z$  (%): 269 ( $M^{+}$ , 13), 200 (100), 172 (68), 144 (29), 77 (69), 51 (41).

**5e:** Yield 86 %; mp 129-131 °C; Anal. Calcd. for  $C_{14}H_{12}F_3NO_2$  (283.25 g.mol<sup>-1</sup>): C, 59.37; H, 4.27, N, 4.94. Found: C, 59.28; H, 4.38; N, 4.79. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.80 (m, H3, pyrrolidin-2-one), 3.50 (m, H4, pyrrolidin-2-one), 5.67 (s, H1, propylidene), 2.43 (4-Me), 7.06 (3H, Ph), 7.34 (2H, Ph). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 179.0 (<sup>2</sup> $J_{CF}$  34 Hz, C2, propylidene), 176.7 (C5, pyrrolidin-2-one), 169.5 (C2, pyrrolidin-2-one), 139.9 (C1, Ph), 130.7 (C2 and C6, Ph), 130.4 (C4, Ph), 126.8 (C3 and C5, Ph), 116.2 (<sup>1</sup> $J_{CF}$  291 Hz, C3, propylidene), 92.6 (C1, propylidene), 27.7 (C4, pyrrolidin-2-one), 26.9 (C3, pyrrolidin-2-one), 21.1 (4-Me). MS (EI, 70 eV):  $m/z$  (%): 283 ( $M^{+}$ , 24), 214 (100), 186 (53), 158 (17), 91 (43).

**5f:** Yield 91 %; mp 88-90 °C; Anal. Calcd. for  $C_{14}H_{12}F_3NO_3$  (299.25 g.mol<sup>-1</sup>): C, 56.19; H, 4.04, N, 4.68. Found: C, 55.91; H, 4.10; N, 4.51. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.81 (m, H3), 3.50 (m, H4), 5.66 (s, CH), 3.87 (OMe), 7.05 (3H, Ph), 7.12 (2H, Ph). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 178.9 (<sup>2</sup> $J_{CF}$  34 Hz, C2, propylidene), 176.6 (C5, pyrrolidin-2-one), 169.7 (C2, pyrrolidin-2-one), 160.3 (C4, Ph), 128.2 (C1, Ph), 125.6 (C3 and C5, Ph), 115.3 (C2 and C6, Ph), 116.3 (<sup>1</sup> $J_{CF}$  291 Hz, C3, propylidene), 92.4 (C1, propylidene), 55.4 (OMe), 27.6 (C4, pyrrolidin-2-one), 26.8 (C3, pyrrolidin-2-one). MS (EI, 70 eV):  $m/z$  (%): 299 ( $M^{+}$ , 53), 230 (100), 202 (28), 188 (31), 159 (24), 131 (14), 77 (21).



**5g:** Yield 70 %; mp 163-165 °C; Anal. Calcd. for  $C_{13}H_9ClF_3NO_2$  (303.67 g.mol<sup>-1</sup>): C, 56.19; H, 4.04, N, 4.68. Found: C, 55.91; H, 4.10; N, 4.51. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) δ 2.82 (m, H3), 3.52 (m, H4), 5.66 (s, CH), 7.16 (3H, Ph), 7.54 (2H, Ph). <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>) δ 168.7 (C2), 26.9 (C3), 27.7 (C4), 176.3 (C5), 92.7 (CH) 178.0 (<sup>2</sup>J<sub>CF</sub> 35 Hz, C=O), 116.2 (<sup>1</sup>J<sub>CF</sub> 291 Hz, CF<sub>3</sub>), 128.5, 130.4, 131.5, 135.8 (Ph). MS (EI, 70 eV): *m/z* (%): 303 (M<sup>+</sup>, 23), 234 (100), 206 (62), 178 (21), 143 (23), 111 (28), 75 (41).

**5h:** Yield 95 %; mp 151-153 °C; Anal. Calcd. for  $C_{13}H_9BrF_3NO_2$  (348.12 g.mol<sup>-1</sup>): C, 44.85; H, 2.61, N, 4.02. Found: C, 44.75; H, 2.63; N, 3.95. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) δ 2.82 (m, H3), 3.52 (m, H4), 5.66 (s, CH), 7.1 (3H, Ph), 7.7 (2H, Ph). <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>) δ 168.5 (C2), 26.9 (C3), 27.8 (C4), 176.2 (C5), 92.9 (CH) 179.2 (<sup>2</sup>J<sub>CF</sub> 35 Hz, C=O), 116.2 (<sup>1</sup>J<sub>CF</sub> 291 Hz, CF<sub>3</sub>), 124.0, 128.8, 132.1, 133.5 (Ph). MS (EI, 70 eV): *m/z* (%): 348 (M<sup>+</sup>, 29), 278 (100), 250 (29), 222 (14), 199 (37), 143 (39), 76 (41).

**5j:** Yield 73 %; mp 165-167 °C; Anal. Calcd. for  $C_{12}H_9F_3N_2O_2$  (270.21 g.mol<sup>-1</sup>): C, 53.34; H, 3.36, N, 10.37. Found: C, 53.30; H, 3.50; N, 10.60. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) δ 2.83 (m, H3), 3.54 (m, H4), 5.94 (s, CH), 7.36 (1H, Py), 7.46 (1H, Py), 7.95 (1H, Py), 8.69 (1H, Py). <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>) δ = 167.1 (C2), 26.9 (C3), 28.0 (C4), 176.3 (C5), 93.7 (CH) 179.2 (<sup>2</sup>J<sub>CF</sub> 34 Hz, C=O), 116.2 (<sup>1</sup>J<sub>CF</sub> 292 Hz, CF<sub>3</sub>), 122.5, 124.5, 139.1, 147.2, 150.1 (Py). MS (EI, 70 eV): *m/z* (%): 201 (18), 173 (100), 145 (20), 131 (43), 78 (52), 69 (8).

**5k:** Yield 71 %; mp 256-258 °C; Anal. Calcd. for  $C_{20}H_{14}F_6N_2O_4$  (460.34 g.mol<sup>-1</sup>): C, 52.18; H, 3.07, N, 6.09. Found: C, 52.80; H, 3.10; N, 6.50. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.88 (m, H3), 3.57 (m, H4), 5.77 (s, CH), 7.4 (Ph). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 179.3 (<sup>2</sup>J<sub>CF</sub> 35 Hz, C2, propylidene), 176.2 (C5, pyrrolidin-2-one), 168.2 (C2, pyrrolidin-2-one), 134.2 (2C, C1, Ph), 129.1 (4C, C2, C3, Ph), 116.2 (<sup>1</sup>J<sub>CF</sub> 291 Hz, C3, propylidene), 93.0 (C1, propylidene), 27.8 (C4, pyrrolidin-2-one), 26.9 (C3, pyrrolidin-2-one). MS (EI, 70 eV): *m/z* (%): 460 (M<sup>+</sup>, 36), 391 (100), 363 (10), 161 (20), 143 (15), 69 (15), 55 (33).

**6a:** Yield 75 %; mp 78-80 °C; Anal. Calcd. for  $C_{10}H_{12}Cl_3NO_2$  (284.57 g.mol<sup>-1</sup>): C, 42.21; H, 4.25, N, 4.92. Found: C, 42.80; H, 4.50; N, 5.30. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.63 (m, H3), 3.35 (m, H4), 6.17 (s, CH), 3.6 (CH<sub>2</sub>), 1.65 (CH<sub>2</sub>), 0.95 (Me). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 180.2 (C2, propylidene), 177.0 (C5, pyrrolidin-2-one), 167.2 (C2, pyrrolidin-2-one), 97.4 (C3, propylidene), 90.3 (C1, propylidene), 42.5 (NCH<sub>2</sub>), 27.5 (C4, pyrrolidin-2-one), 26.3 (C3, pyrrolidin-2-one), 19.9 (CH<sub>2</sub>), 11.3 (Me). MS (EI, 70 eV): *m/z* (%): 285 (M<sup>+</sup>+2, 10), 283 (M<sup>+</sup>, 10), 220 (22), 166 (100), 124 (73), 68 (61).

**6c:** Yield 87 %; mp 145-148 °C; Anal. Calcd. for  $C_{10}H_{12}Cl_3NO_2$  (346.64 g.mol<sup>-1</sup>): C, 51.97; H, 4.07, N, 4.04. Found: C, 51.30; H, 3.80; N, 4.00. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.58 (m, H3), 3.32 (m, H4), 6.18 (s, CH), 2.9 (CH<sub>2</sub>), 3.85 (CH<sub>2</sub>), 7.1- 7.4 (Ph). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 180.0 (C2, propylidene), 176.6 (C5, pyrrolidin-2-one), 166.8 (C2, pyrrolidin-2-one), 137 (C1, Ph), 128.7 (C3 and C5, Ph), 128.5 (C4, Ph), 126.9 (C2 and C6, Ph), 97.3 (C3, propylidene), 90.3 (C1, propylidene), 42.2 (NCH<sub>2</sub>), 32.7 (CH<sub>2</sub>Ph), 27.4 (C4, pyrrolidin-2-one), 26.2 (C3, pyrrolidin-2-one). MS (EI, 70 eV): *m/z* (%): 347 (M<sup>+</sup>+2, 7), 345 (M<sup>+</sup>, 7), 282 (20), 228 (100), 124 (35), 105 (90).

**6d:** Yield 93 %; mp 158-160 °C; Anal. Calcd. for  $C_{13}H_9Cl_3NO_2$  (318.59 g.mol<sup>-1</sup>): C, 49.01; H, 3.16, N, 4.40. Found: C, 50.05; H, 3.20; N, 3.80. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) δ 2.82 (m, H3), 3.53 (m, H4), 5.97 (s, CH), 7.2 (2H, Ph), 7.56 (3H, Ph). <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>) δ 180.4 (C2, propylidene), 176.5 (C5, pyrrolidin-2-one), 167.9 (C2, pyrrolidin-2-one), 133.3 (C1, Ph), 130 (C3 and C5, Ph), 129.6 (C2 and C6, Ph) 127.1 (C4, Ph), 97 (C3, propylidene), 92 (C1, propylidene), 28 (C4, pyrrolidin-2-one), 26.4 (C3, pyrrolidin-2-one). MS (EI, 70 eV): *m/z* (%): 319 (M<sup>+</sup>+2, <5), 317 (M<sup>+</sup>, <5), 256 (5), 254 (10), 202 (15), 200 (100), 172 (30), 77 (20).

**6e:** Yield 95 %; mp 175-178 °C; Anal. Calcd. for  $C_{14}H_{12}Cl_3NO_2$  (332.62 g.mol<sup>-1</sup>): C, 50.56; H, 3.64, N, 4.21. Found: C, 50.30; H, 3.50; N, 4.60. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) δ 2.83 (m, H3), 3.52 (m, H4), 5.98 (s, CH), 2.43 (4-Me), 7.1 (2H, Ph), 7.35 (3H, Ph). <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>) δ 180.5 (C2, propylidene), 176.5 (C5, pyrrolidin-2-one), 168.2 (C2, pyrrolidin-2-one), 133.3 (C1, Ph), 130.0 (C3 and C5, Ph), 129.6 (C4, Ph), 127.1 (C2 and C6, Ph), 97.0 (C3, propylidene), 92.0 (C1, propylidene), 28.0 (C4, pyrrolidin-2-one), 26.4 (C3, pyrrolidin-2-one), 21.2 (4-Me). MS (EI, 70 eV): *m/z* (%): 333 (M<sup>+</sup>+2, <5), 331 (M<sup>+</sup>, <5), 270 (7), 268 (10), 216 (15), 214 (100).

**6f:** Yield 95 %; mp 169-171 °C; Anal. Calcd. for  $C_{14}H_{12}Cl_3NO_3$  (348.62 g.mol<sup>-1</sup>): C, 48.24; H, 3.47, N, 4.02. Found: C, 48.90; H, 4.0; N, 3.78. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) δ 2.79 (m, H3), 3.50 (m, H4), 5.98 (s, CH), 3.86 (4-OMe), 7.05 (2H, Ph), 7.15 (3H, Ph). <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>) δ 168.4 (C2), 26.4 (C3), 27.9 (C4), 176.7 (C5), 92.0 (CH) 180.5 (C=O), 97.1 (CCl<sub>3</sub>), 55.5 (4-Me), 115.3, 125.8, 128.3, 160.2 (Ph). MS (EI, 70 eV): *m/z* (%): 349 (M<sup>+</sup>+2, 15), 347 (M<sup>+</sup>, 15), 284 (22), 230 (100), 188 (78), 159 (44).

**6h:** Yield 86 %; mp 167-170 °C; Anal. Calcd. for  $C_{13}H_9BrCl_3NO_2$  (397.49 g.mol<sup>-1</sup>): C, 39.28; H, 2.28, N, 3.52. Found: C, 39.73; H, 2.5; N, 3.70. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) δ 2.83 (m, H3), 3.53 (m, H4), 5.98 (s, CH), 3.86 (4-OMe), 7.10 (2H, Ph), 7.69 (3H, Ph). <sup>13</sup>C NMR (50

MHz, CDCl<sub>3</sub>) δ 167.2 (C2), 26.4 (C3), 27.9 (C4), 176.2 (C5), 92.2 (CH) 180.3 (C=O), 96.9 (CCl<sub>3</sub>), 123.6, 128.8, 132.3, 133.3 (Ph). MS (EI, 70 eV): *m/z* (%): 398 (M<sup>+</sup>+2, < 5), 396 (M<sup>+</sup>, < 5), 280 (100), 278 (100), 252 (10), 250 (10), 199 (15).

**6l**: Yield 85 %; mp > 300 °C; Anal. Calcd. for C<sub>16</sub>H<sub>14</sub>Cl<sub>6</sub>N<sub>2</sub>O<sub>4</sub> (511.02 g.mol<sup>-1</sup>): C, 37.61; H, 2.76, N, 5.48. Found: C, 37.41; H, 2.90; N, 5.70. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.52 (m, H3), 3.17 (m, H4), 6.22 (s, CH), 3.83 (CH<sub>2</sub>). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 169.1 (C2), 26.7 (C3), 28.0 (C4), 177.6 (C5), 88.0 (CH) 179.3 (C=O), 97.1 (CCl<sub>3</sub>), 37.2 (CH<sub>2</sub>). MS (EI, 70 eV): *m/z* (%): 359 (70), 357 (100), 236 (20), 234 (35), 150 (32).

## Supplementary Information

Supplementary data shown in Tables S1 and S2, <sup>1</sup>H, <sup>13</sup>C NMR and mass spectra are available free of charge as PDF file at <http://jbcs.sbgq.org.br>

## Acknowledgments

Thanks are due to financial support from Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) and Fundação de Amparo à Pesquisa do Rio Grande do Sul (FAPERGS). The Bruker X-ray diffractometer was funded by infrastructure grant from the Financiadora de Estudos e Projetos (CT-INFRA/FINEP). Students thank CNPq for fellowships.

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- Data for methyl 3-(2-methyl-7-(trifluoromethyl)pyrazolo-[1,5-*a*]-pyrimidin-5-yl)propanoate (**7**) yield 94 %, mp 124-125 °C, anal. calcd for C<sub>12</sub>H<sub>12</sub>F<sub>3</sub>N<sub>3</sub>O<sub>2</sub>: C, 50.18; H, 4.21; N, 14.63, found C, 50.35; H, 4.02; N, 13.83, <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 2.55 (s, Me), 2.91 (t, <sup>3</sup>J<sub>HH</sub> 7.5 Hz, CH<sub>2</sub>), 3.20 (t, <sup>3</sup>J<sub>HH</sub> 7.5 Hz, CH<sub>2</sub>), 3.7 (s, OMe), 6.51 (s, 1H), 6.99 (s, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 14.7 (Me), 31.2 (CH<sub>2</sub>), 32.4 (CH<sub>2</sub>), 51.8 (OMe), 96.9 (Pyrim), 105.7 (Pyr), 119.4 (q, <sup>1</sup>J<sub>CF</sub> 285 Hz, CF<sub>3</sub>), 133.3 (q, <sup>1</sup>J<sub>CF</sub> 32 Hz, C7), 156.4 (C2), 159.1 (C5), 150.5 (C3a) 172.9 (COOR) and 3-(2-methyl-7-(trichloromethyl)pyrazolo-[1,5-*a*]-pyrimidin-5-yl)propanoate (**8**) yield 84 %, mp 191-193 °C, anal. calcd for C<sub>12</sub>H<sub>12</sub>Cl<sub>3</sub>N<sub>3</sub>O<sub>2</sub>: C, 42.82; H, 3.59; N, 12.48, found C, 42.55; H, 4.00; N, 12.20, <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 2.25 (s, Me), 2.72 (t, <sup>3</sup>J<sub>HH</sub> 7.2 Hz, CH<sub>2</sub>), 2.99 (t, <sup>3</sup>J<sub>HH</sub> 7.2 Hz, CH<sub>2</sub>), 3.57 (s, OMe), 5.59 (s, 1H), 5.91 (s, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 14.1 (Me), 28.0 (CH<sub>2</sub>), 32.1 (CH<sub>2</sub>), 51.9 (OMe), 89.6 (CCl<sub>3</sub>), 94.6 (Pyrim), 102.1 (Pyr), 142.2 (C7), 152.8 (C3a), 153.4 (C2), 157.9 (C5), 172.3 (COOR). For experimental details see Martins, M. A. P.; Cunico, W.; Scapin, E.; Emerich, D. J.; Fiss, G. F.; Rosa, F. A.; Zanatta, N.; Bonacorso, H. G.; Flores, A. F. C.; *Lett. Org. Chem.* **2006**, *3*, 358.

Received: June 26, 2007

Published on the web: January 31, 2008

## Efficient Synthesis of New 1-[Alkyl(aryl)]-5-(3,3,3-trihalo-2-oxopropylidene) pyrrolidin-2-ones

Alex F. C. Flores,\* Darlene C. Flores, Graciela Oliveira, Lucas Pizzuti, Rubia M. S. da Silva,  
Marcos A. P. Martins and Helio G. Bonacorso

NUQUIMHE - Departamento de Química, Universidade Federal de Santa Maria  
97105 900 Santa Maria-RS, Brazil

<sup>1</sup>H and <sup>13</sup>C NMR spectra were acquired on a Bruker DPX 400 spectrometer (<sup>1</sup>H at 400.13 MHz and <sup>13</sup>C at 100.62 MHz) 5 mm sample tubes, 298-305 K, digital resolution ± 0.01 ppm, in CDCl<sub>3</sub> 0.02-0.05 g mL<sup>-1</sup>, using TMS as internal reference.

**Table S1.** Reaction conditions for isolation of the methyl 4-alkyl[aryl]amino-6-oxo-7,7,7-trifluoro-4-heptenoates (**3**) in CH<sub>3</sub>CN

RNH <sub>2</sub>	Time (h)	Temperature (°C)	Product (ratio, yield <sup>a</sup> %)
benzylamine	6	85	<b>3b</b> + <b>5b</b> (1: 2, 85)
benzylamine	24	25	<b>3b</b> (87)
Phenethylamine	6	80	<b>3c</b> + <b>5c</b> (10:1, 83)
Phenethylamine	24	25	<b>3c</b> (80)
Aniline	6	85	RNH <sub>2</sub> + <b>1</b> + <b>3d</b> (3:1, 25)
Aniline	24	85	<b>3d</b> (87)
4-methoxyaniline	24	30	RNH <sub>2</sub> + <b>1</b> + <b>3f</b> traces
4-methoxyaniline	6	85	<b>3f</b> (79)
3-amino-5-methylisoxazole	6	30	RNH <sub>2</sub> + <b>1</b> + <b>3h</b> (1:10, 60)
3-amino-5-methylisoxazole	12	30	<b>3h</b> (75)
3-amino-5-methylisoxazole	6	85	<b>3h</b> (85)

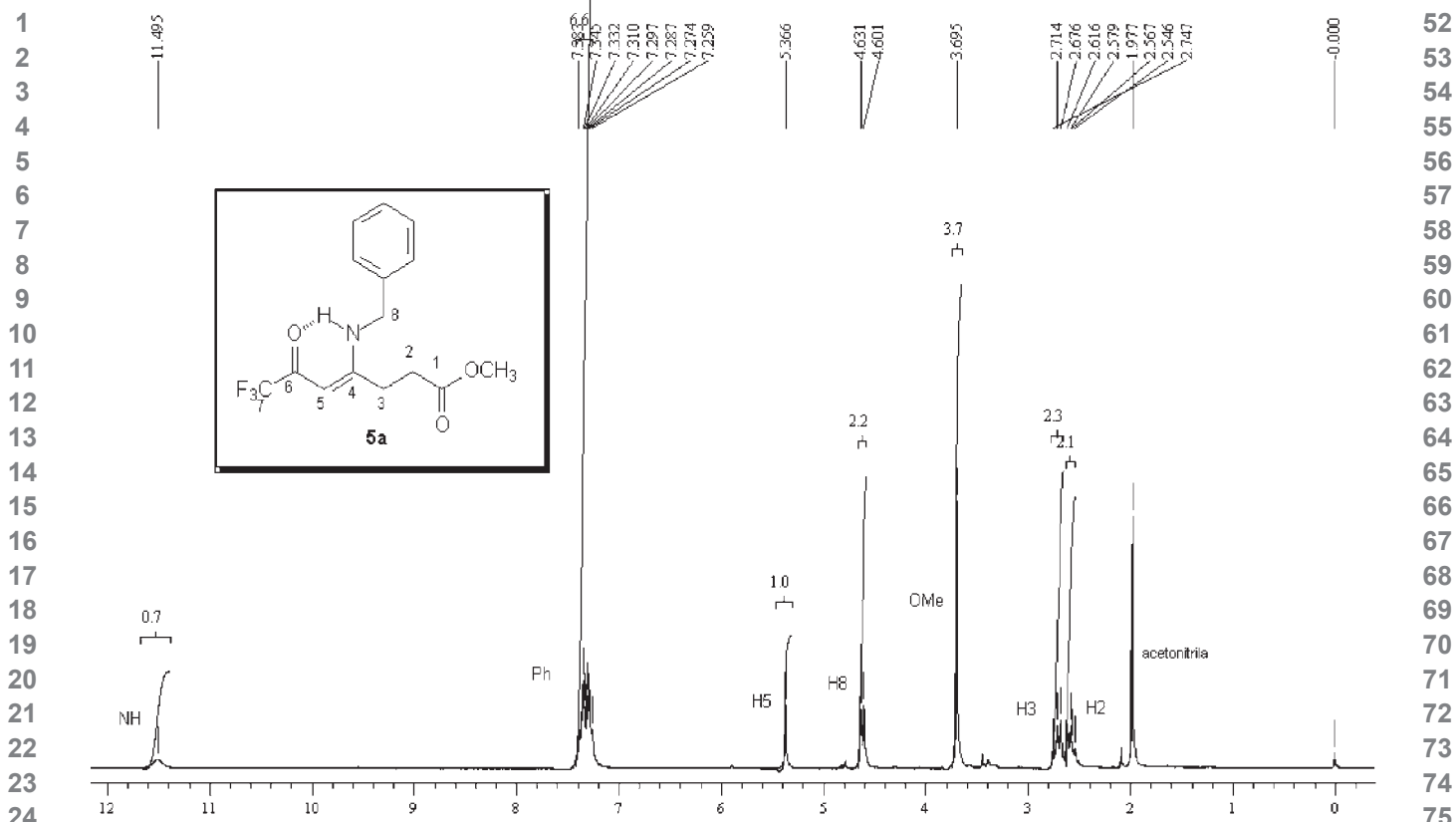
<sup>a</sup> Ratio from integration of the vinylic H and methoxy group signals.

**Table S2.** Reaction conditions for methyl 4-alkyl[aryl]amino-6-oxo-7,7,7-trichloro-4-heptenoates and 1-Alkyl(aryl)-5-(3,3,3-trifluoro-2-oxopropylidene)-pyrrolidin-2-one

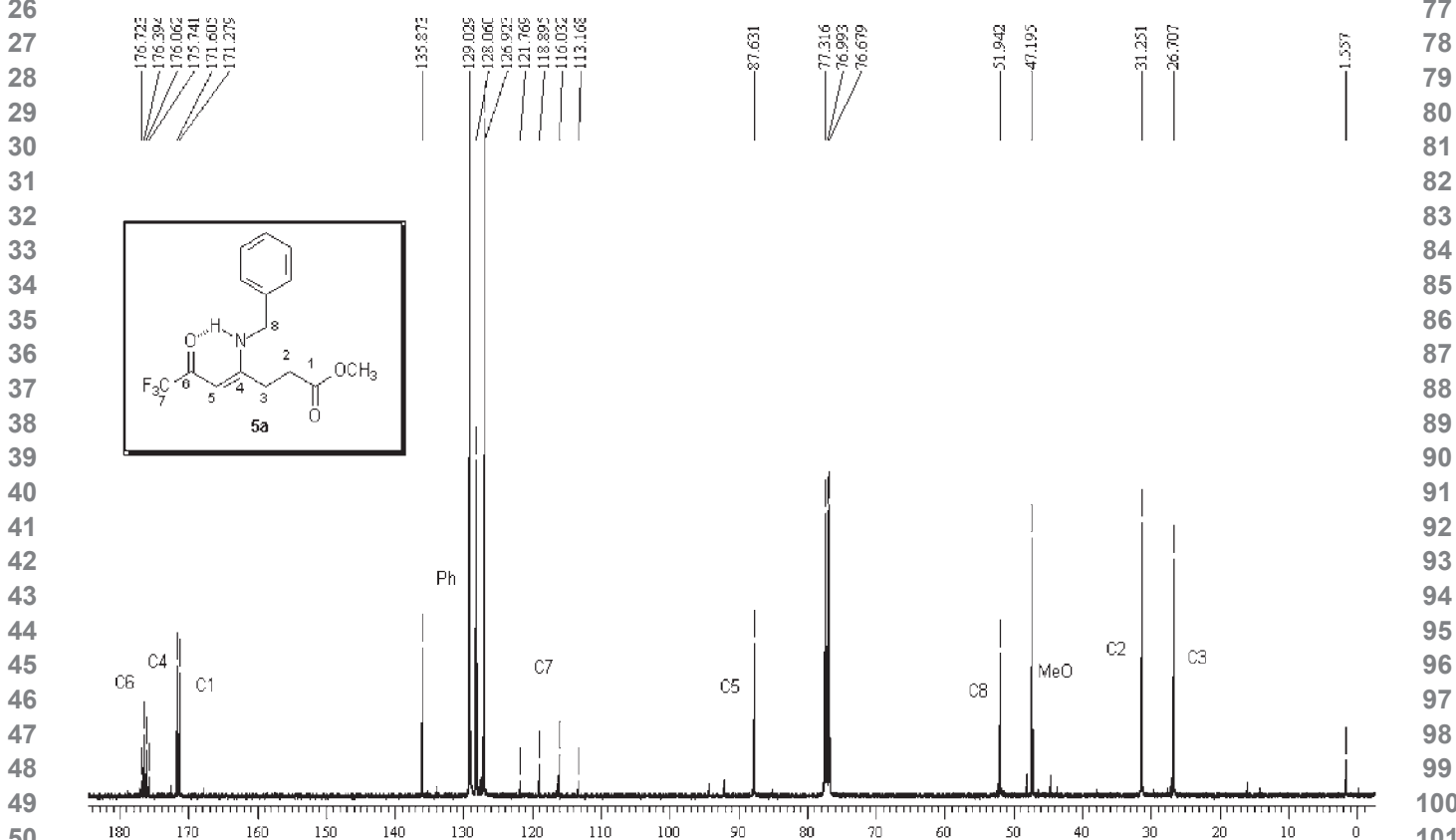
RNH <sub>2</sub>	Solvent	Time (h)	Temperature (°C)	Product (ratio, yield <sup>a</sup> %)
Isopropylamine	CH <sub>2</sub> Cl <sub>2</sub>	2	-5	<b>4a</b> (75)
Isopropylamine	CH <sub>3</sub> CN	2	-5	<b>4a</b> + <b>6a</b> (1:1, 78)
Phenethylamine	CH <sub>2</sub> Cl <sub>2</sub>	4	0	<b>4c</b> (86)
Phenethylamine	CH <sub>3</sub> CN	4	0	<b>4c</b> + <b>6c</b> ( 3:2, 89)
Aniline	CH <sub>2</sub> Cl <sub>2</sub>	6	0 - 25	RNH <sub>2</sub> + <b>2</b> + <b>4d</b> (3:1, 45)
Aniline	MeCN	6	25	<b>4d</b> (87)
Aniline	MeCN	6	85	<b>4d</b> + <b>6d</b> (1:2, 76)
4-methoxyaniline	CH <sub>2</sub> Cl <sub>2</sub>	4	0 - 25	RNH <sub>2</sub> + <b>2</b> + <b>4f</b> (2:1, 49)
4-methoxyaniline	MeCN	6	25	<b>4f</b> (68)
4-bromoaniline	CH <sub>2</sub> Cl <sub>2</sub>	4	0 - 25	<b>4h</b> (89)
4-bromoaniline	MeCN	6	25	<b>4h</b> + <b>6h</b> (87)
4-bromoaniline	MeCN	6	80-85	<b>6h</b> (90)
Ethylenediamine	CH <sub>2</sub> Cl <sub>2</sub>	24	25	<b>6l</b> (86)
Ethylenediamine	CH <sub>3</sub> CN	6	25	<b>6l</b> (85)

<sup>a</sup> Ratio from integration of the vinylic-H signals.

\*e-mail: alexflores@smail.ufsm.br



**Figure S1.**  $^1\text{H}$  NMR spectrum from methyl 4-benzylamino-6-oxo-7,7,7-trifluoro-4-heptenoate (**3b**), 400.13 MHz in  $\text{CDCl}_3$  using TMS as internal standard.



**Figure S2.**  $^{13}\text{C}\{^1\text{H}\}$  NMR spectrum from methyl 4-benzylamino-6-oxo-7,7,7-trifluoro-4-heptenoate (**3b**), 100.62 MHz in  $\text{CDCl}_3$  using TMS as internal standard.



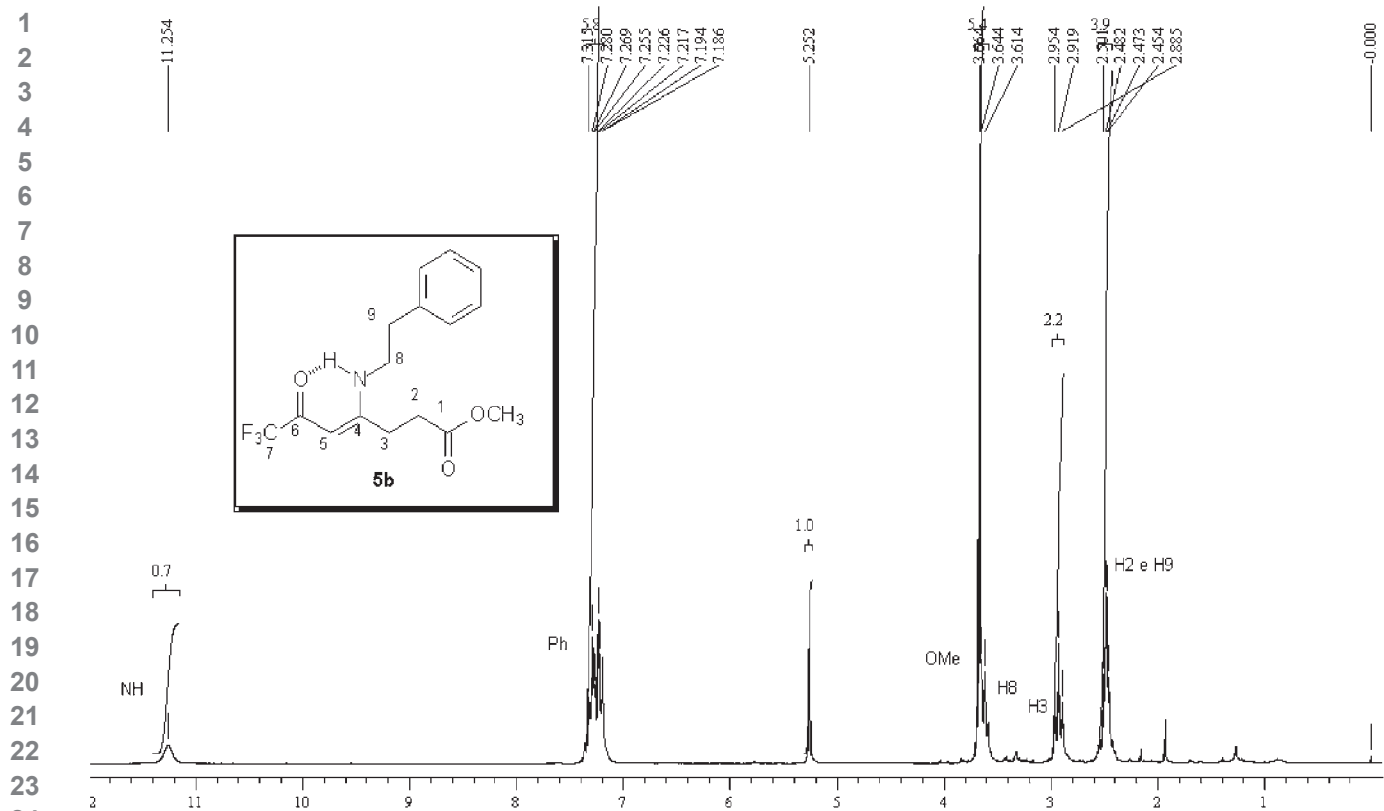


Figure S3.  $^1\text{H}$  NMR spectrum from methyl 6-oxo-4-(2-phenylethyl)amino-7,7,7-trifluoro-4-heptenoate (**3c**), 400.13 MHz in  $\text{CDCl}_3$  using TMS as internal standard.

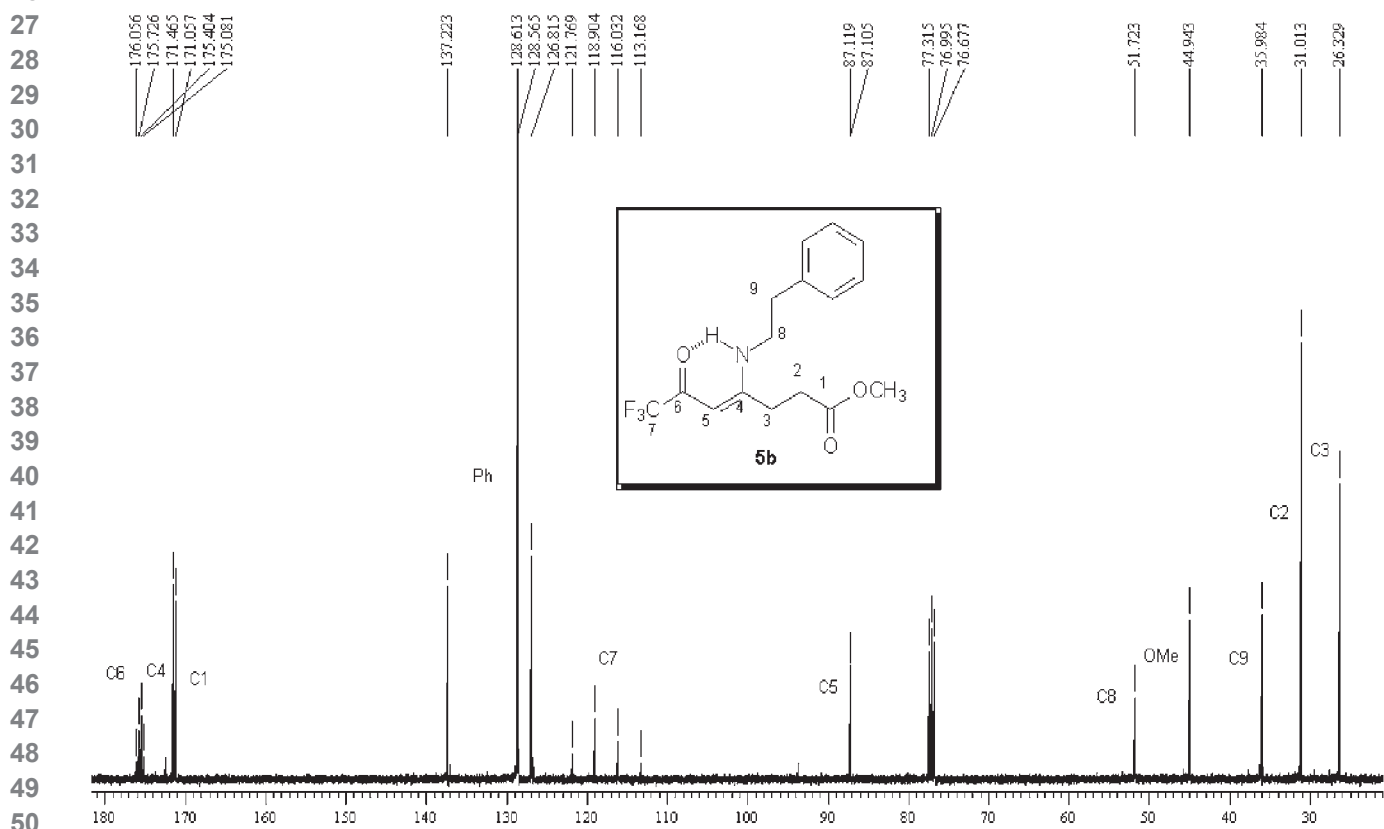
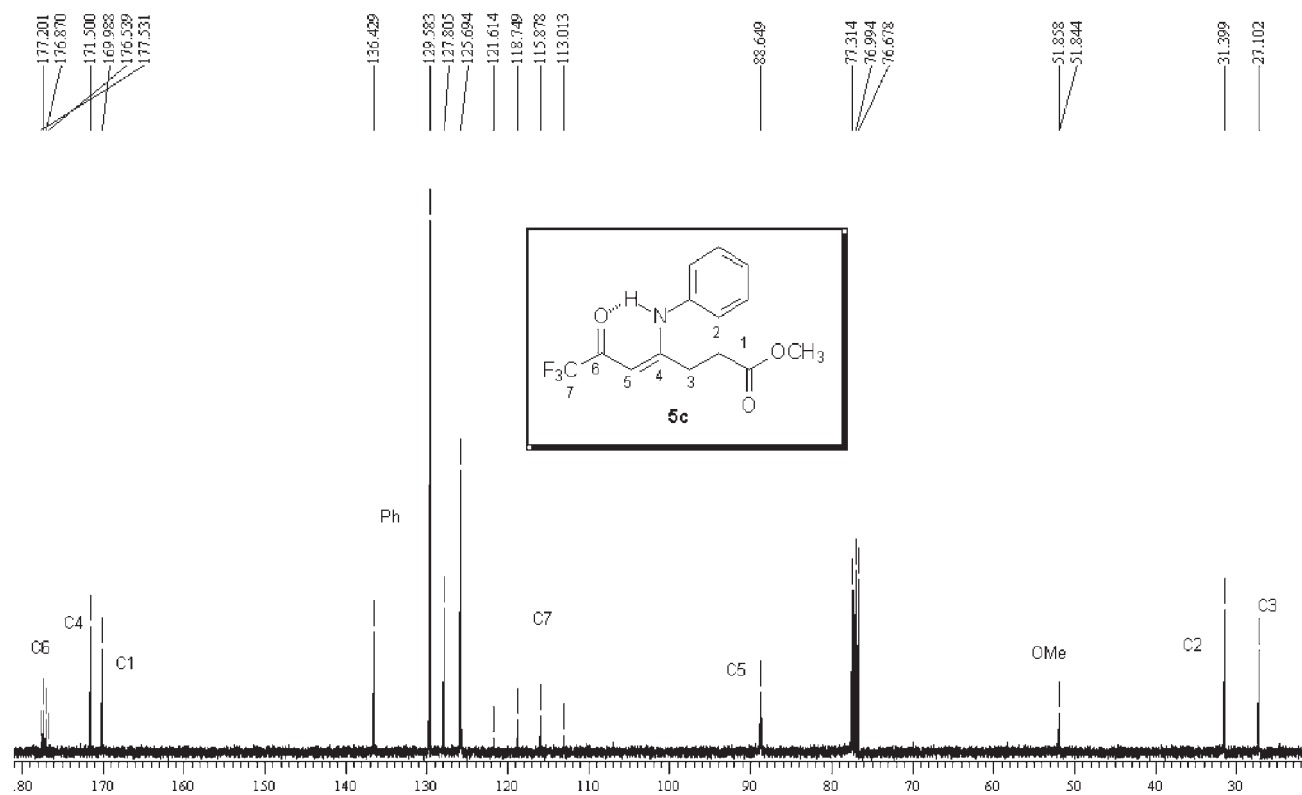
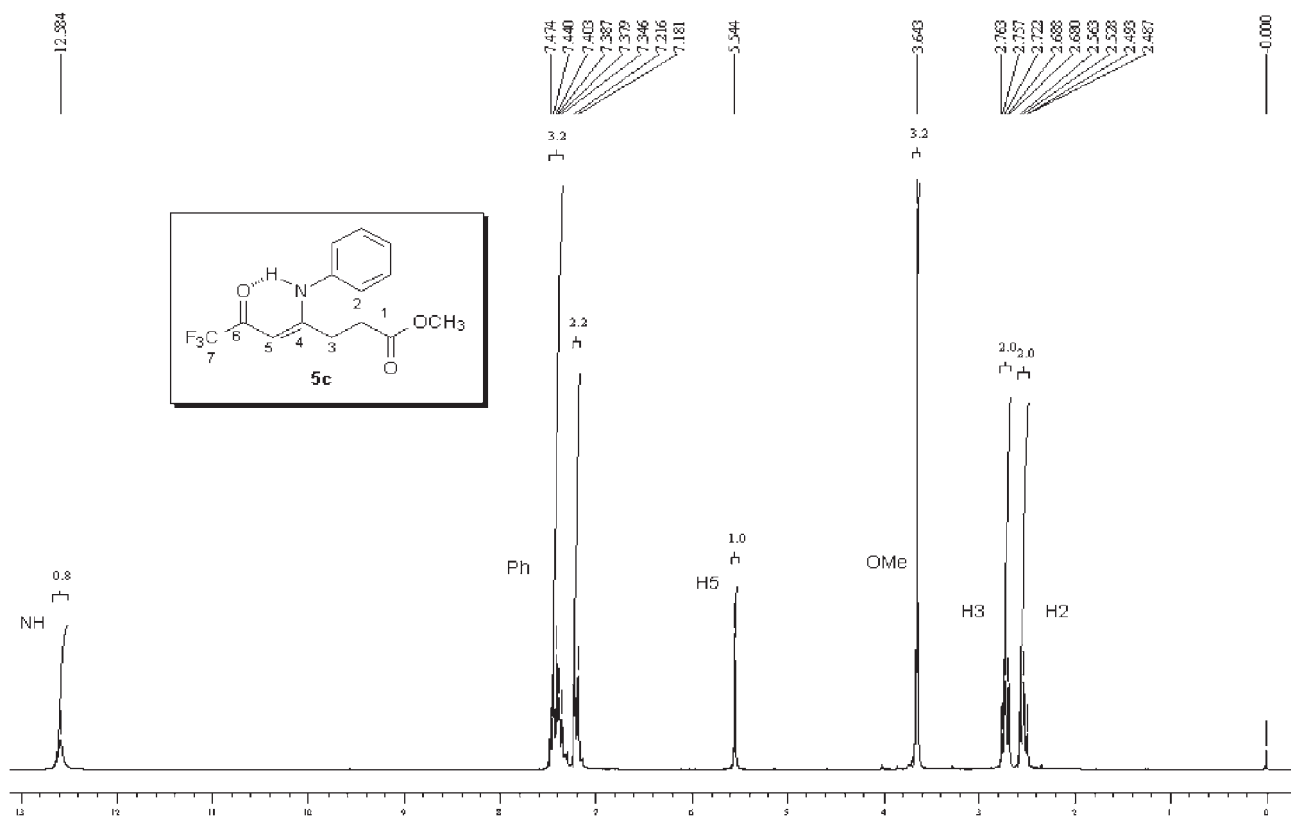
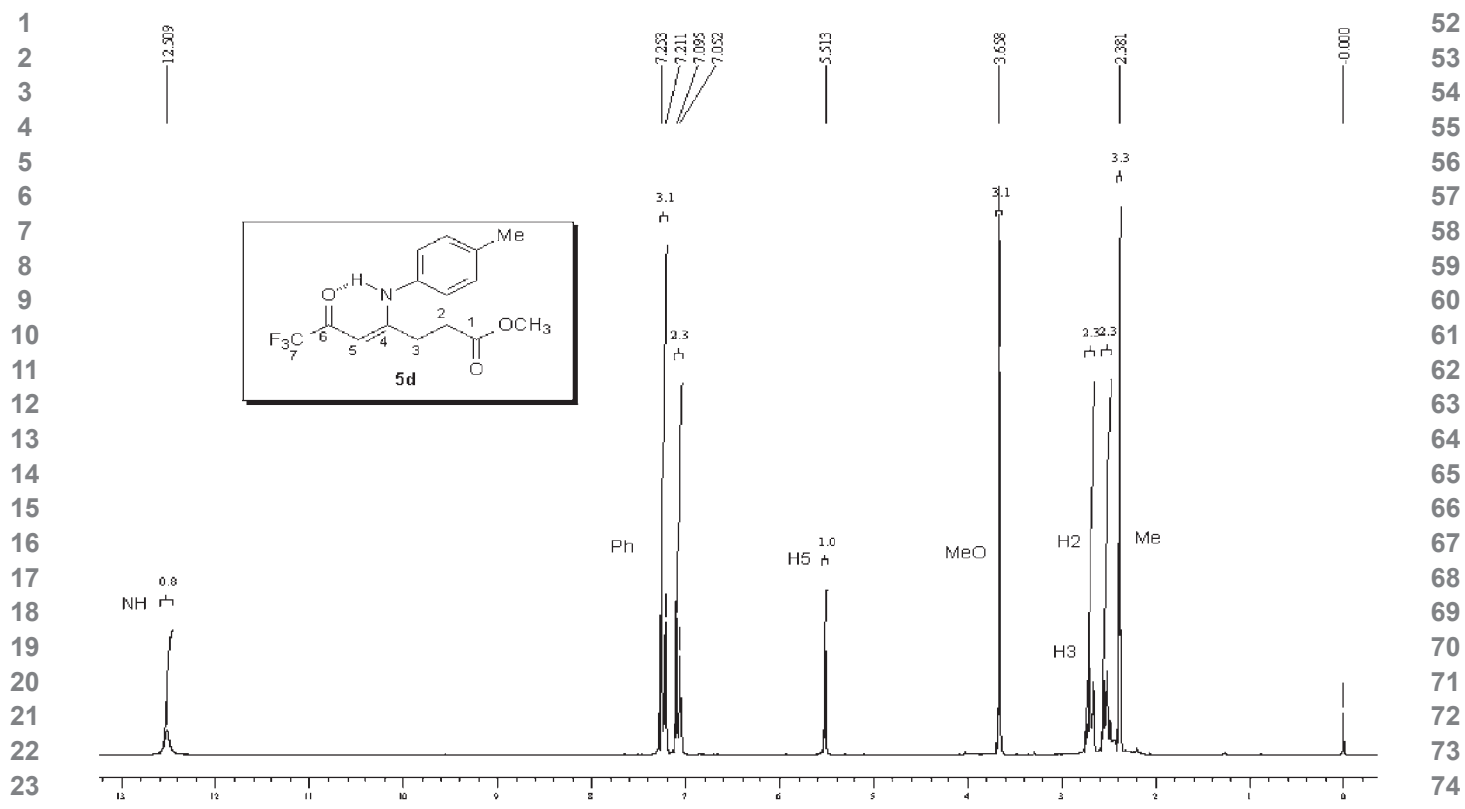
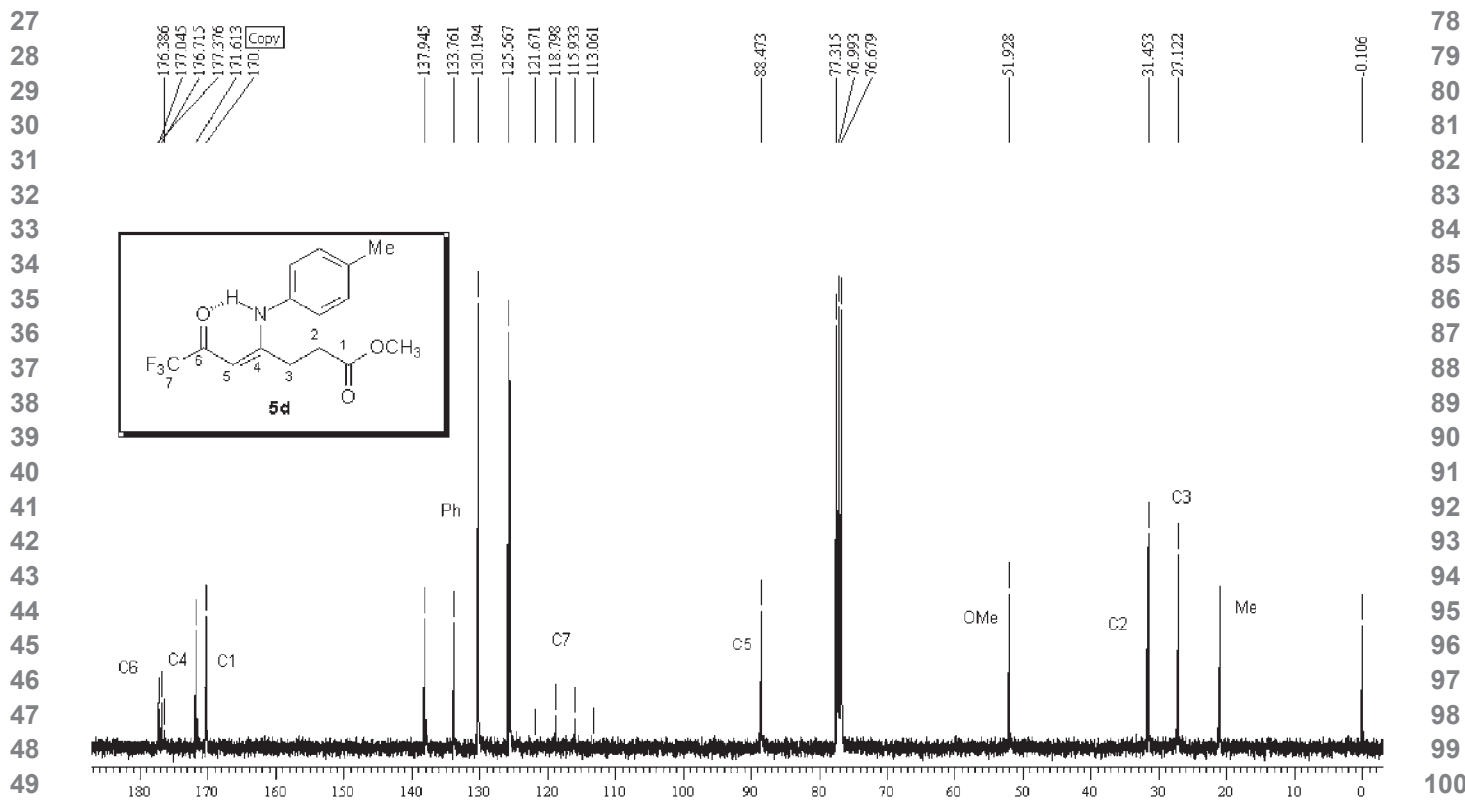


Figure S4.  $^{13}\text{C}$  NMR spectrum from methyl 6-oxo-4-(2-phenylethyl)amino-7,7,7-trifluoro-4-heptenoate (**3c**), 100.62 MHz in  $\text{CDCl}_3$  using TMS as internal standard.



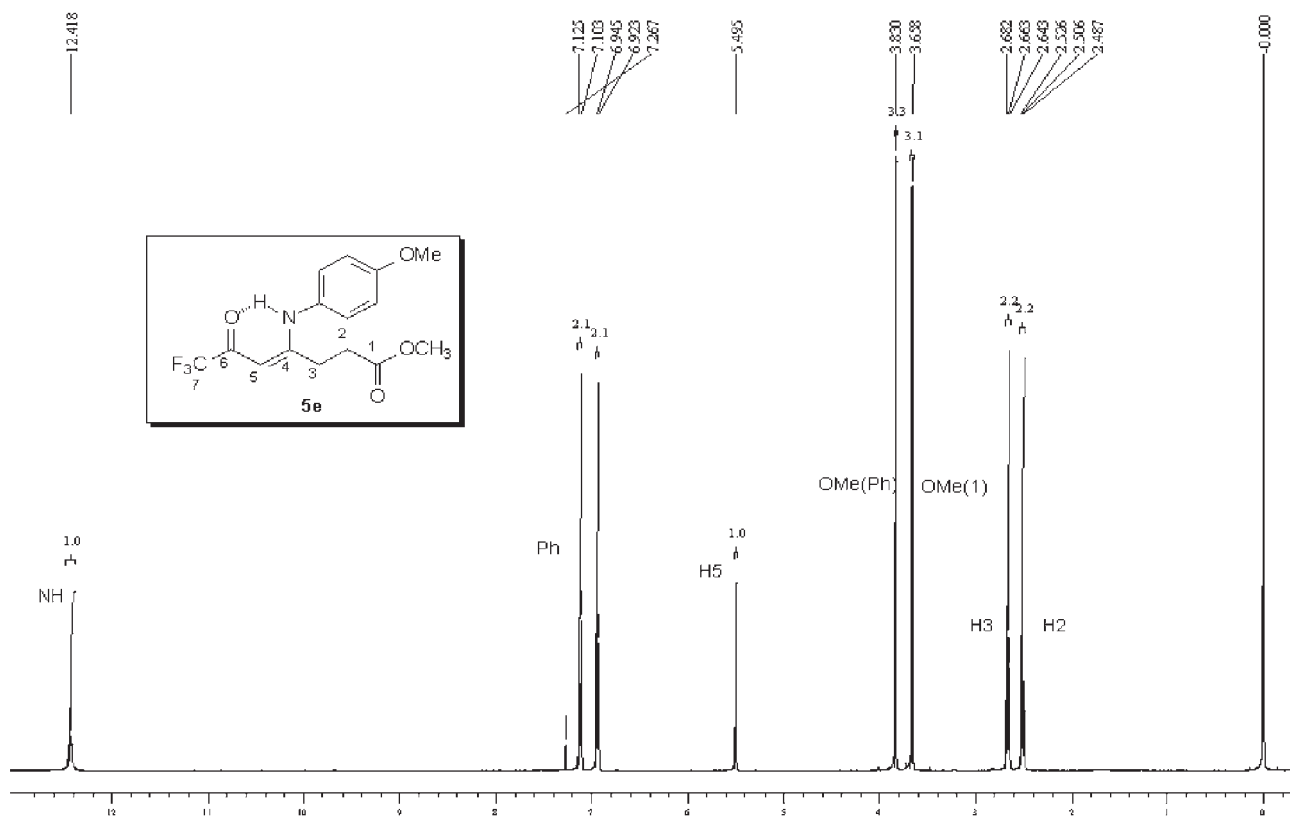


**Figure S7.**  $^1\text{H}$  NMR spectrum from methyl 4-(4-methylphenyl)amino-6-oxo-7,7,7-trifluor-4-heptenoate (**3e**), 400.13 MHz in  $\text{CDCl}_3$  using TMS as internal standard.

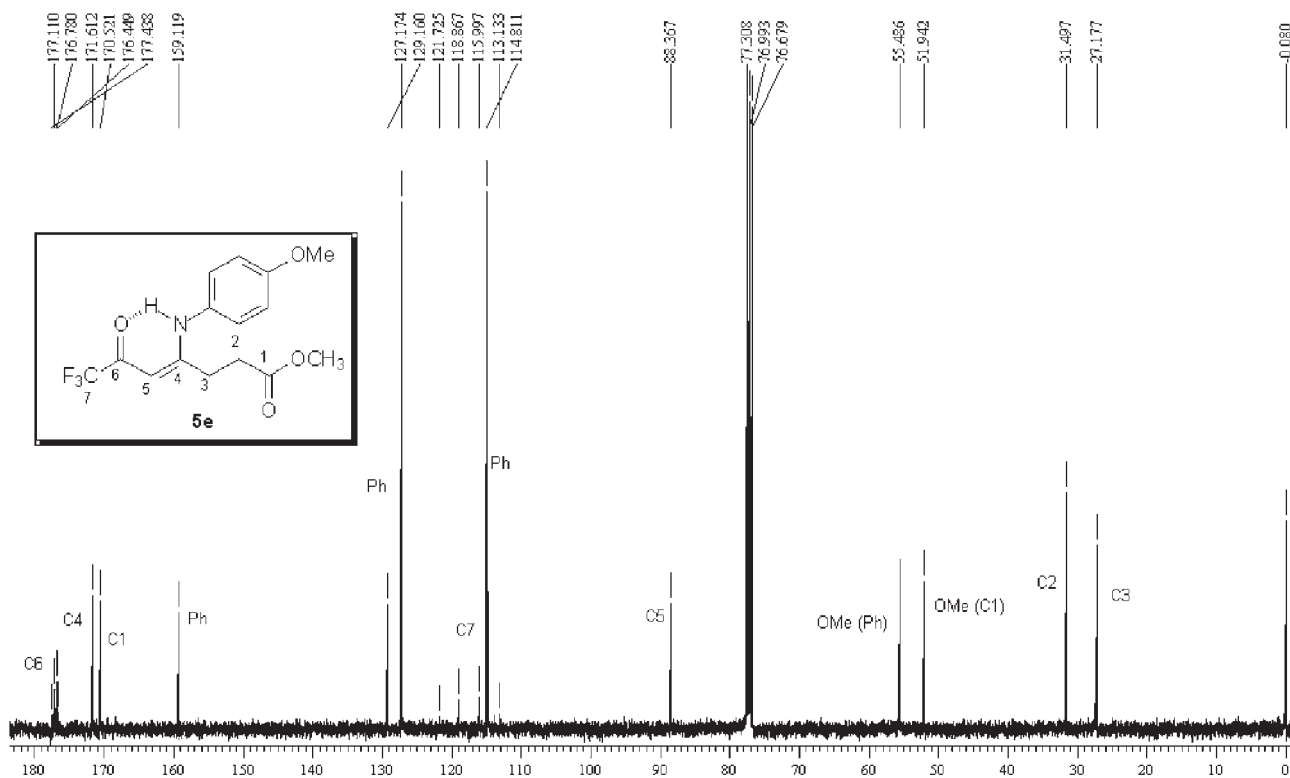


**Figure S8.**  $^{13}\text{C}$  { $^1\text{H}$ } NMR spectrum from methyl 4-(4-methylphenyl)amino-6-oxo-7,7,7-trifluor-4-heptenoate (**3e**), 100.62 MHz in  $\text{CDCl}_3$  using TMS as internal standard.

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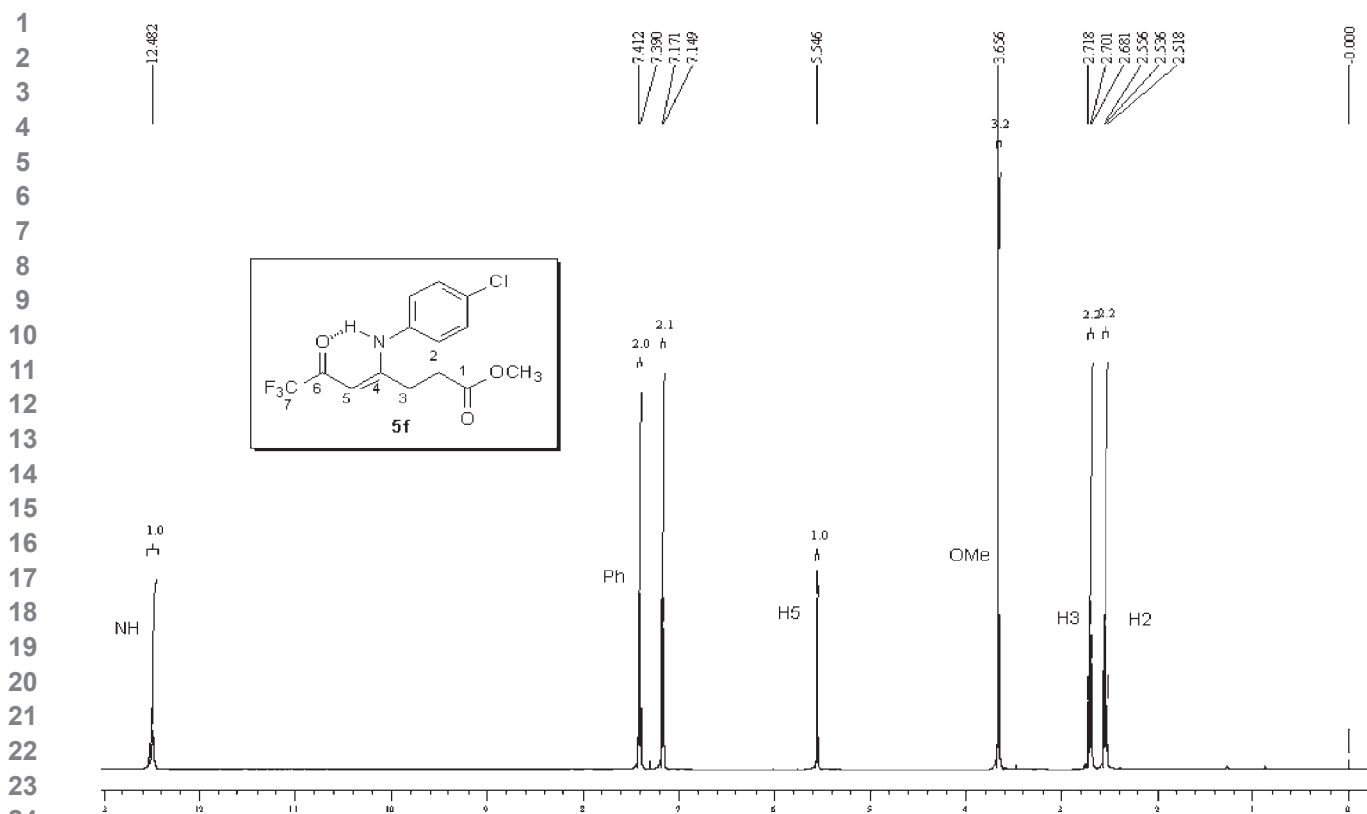


**Figure S9.**  $^1\text{H}$  NMR spectrum from methyl 4-(4-methoxyphenyl)amino-6-oxo-7,7,7-trifluor-4-heptenoate (**3f**), 400.13 MHz in  $\text{CDCl}_3$  using TMS as internal standard.

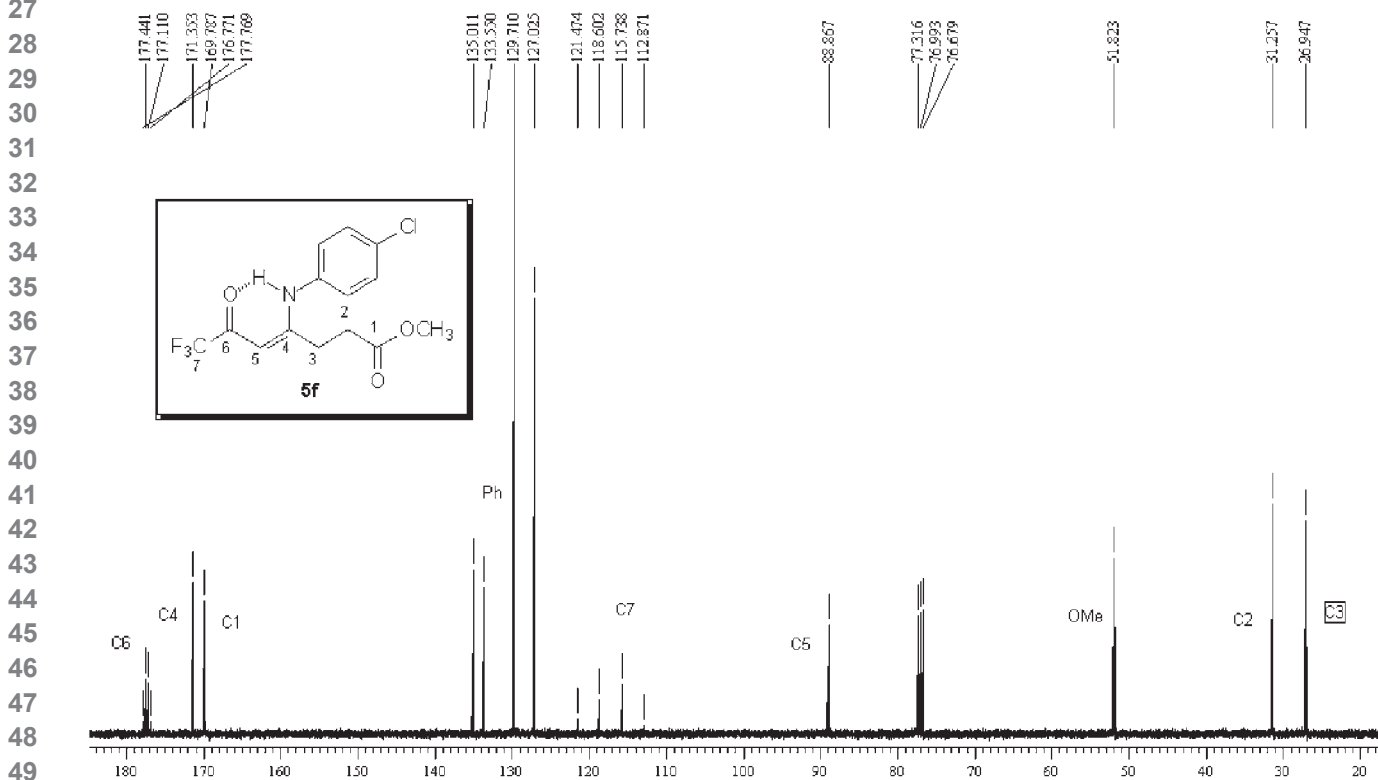


**Figure S10.**  $^{13}\text{C}$  { $^1\text{H}$ } NMR spectrum from methyl 4-(4-methoxyphenyl)amino-6-oxo-7,7,7-trifluor-4-heptenoate (**3f**), 100.62 MHz in  $\text{CDCl}_3$  using TMS as internal standard.

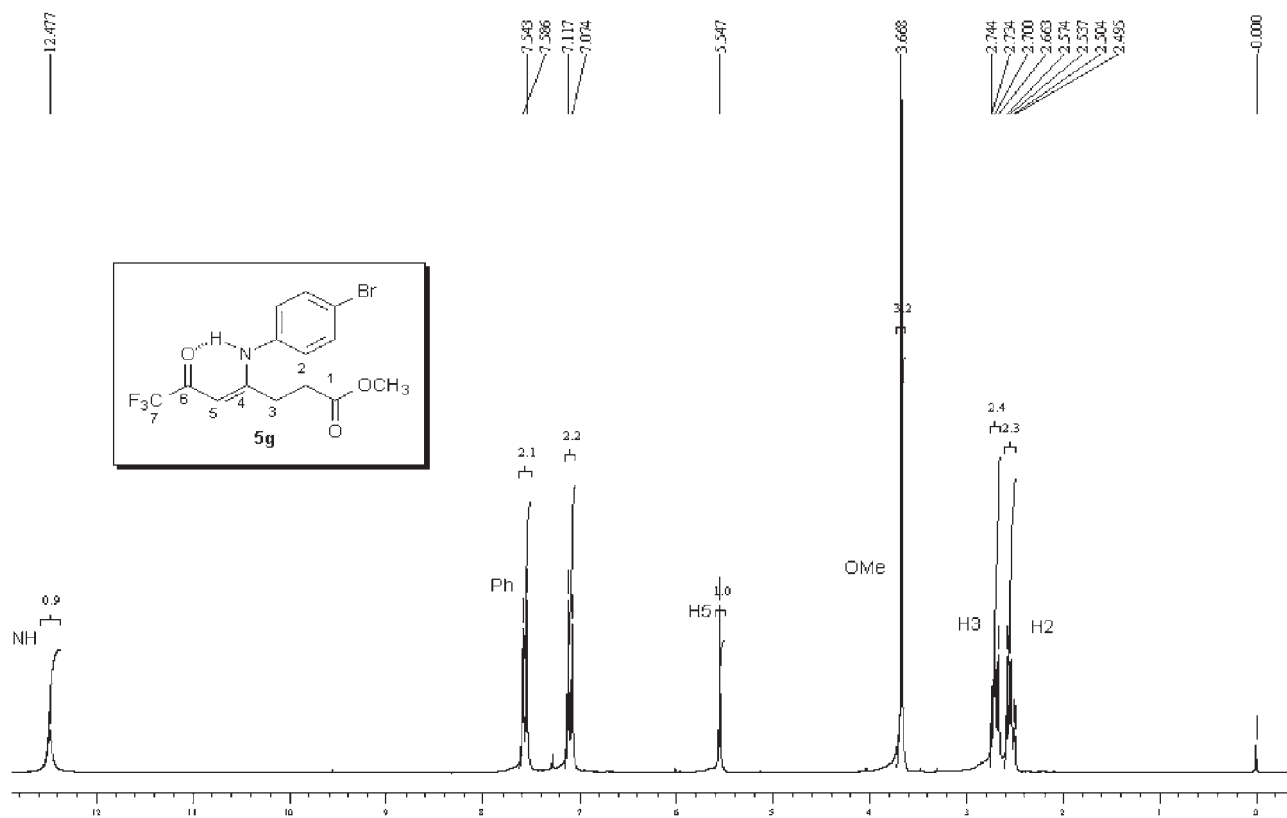




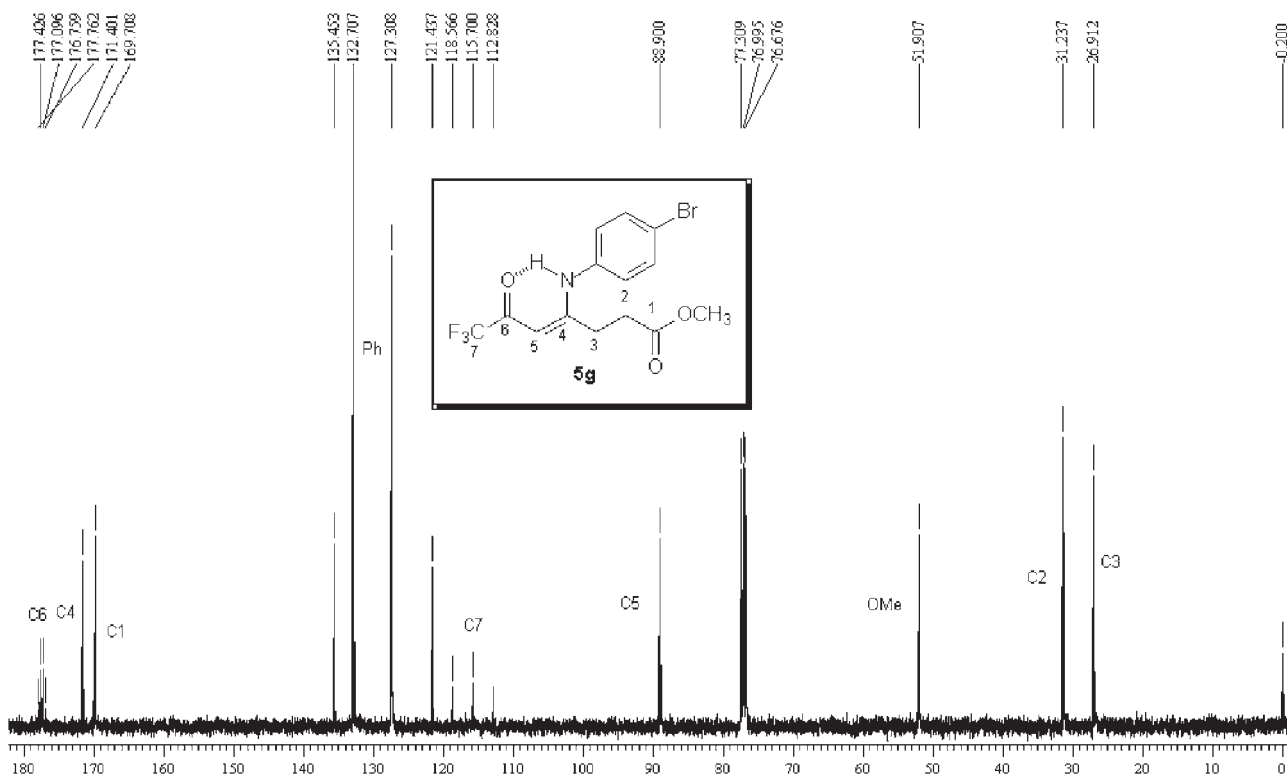
**Figure S11.**  $^1\text{H}$  NMR spectrum from methyl 4-(4-chlorophenyl)amino-6-oxo-7,7,7-trifluoro-4-heptenoate (**3g**), 400.13 MHz in  $\text{CDCl}_3$  using TMS as internal standard.



**Figure S12.**  $^{13}\text{C}$  NMR spectrum from methyl 4-(4-chlorophenyl)amino-6-oxo-7,7,7-trifluoro-4-heptenoate (**3g**), 100.62 MHz in  $\text{CDCl}_3$  using TMS as internal standard.



**Figure S13.**  $^1\text{H}$  NMR spectrum from 4-(4-bromophenyl)amino-6-oxo-7,7,7-trifluoro-4-heptenoate (**3h**), 400.13 MHz in  $\text{CDCl}_3$  using TMS as internal standard.



**Figure S14.**  $^{13}\text{C}\{^1\text{H}\}$  NMR spectrum from 4-(4-bromophenyl)amino-6-oxo-7,7,7-trifluoro-4-heptenoate (**3h**), 100.62 MHz in  $\text{CDCl}_3$  using TMS as internal standard.

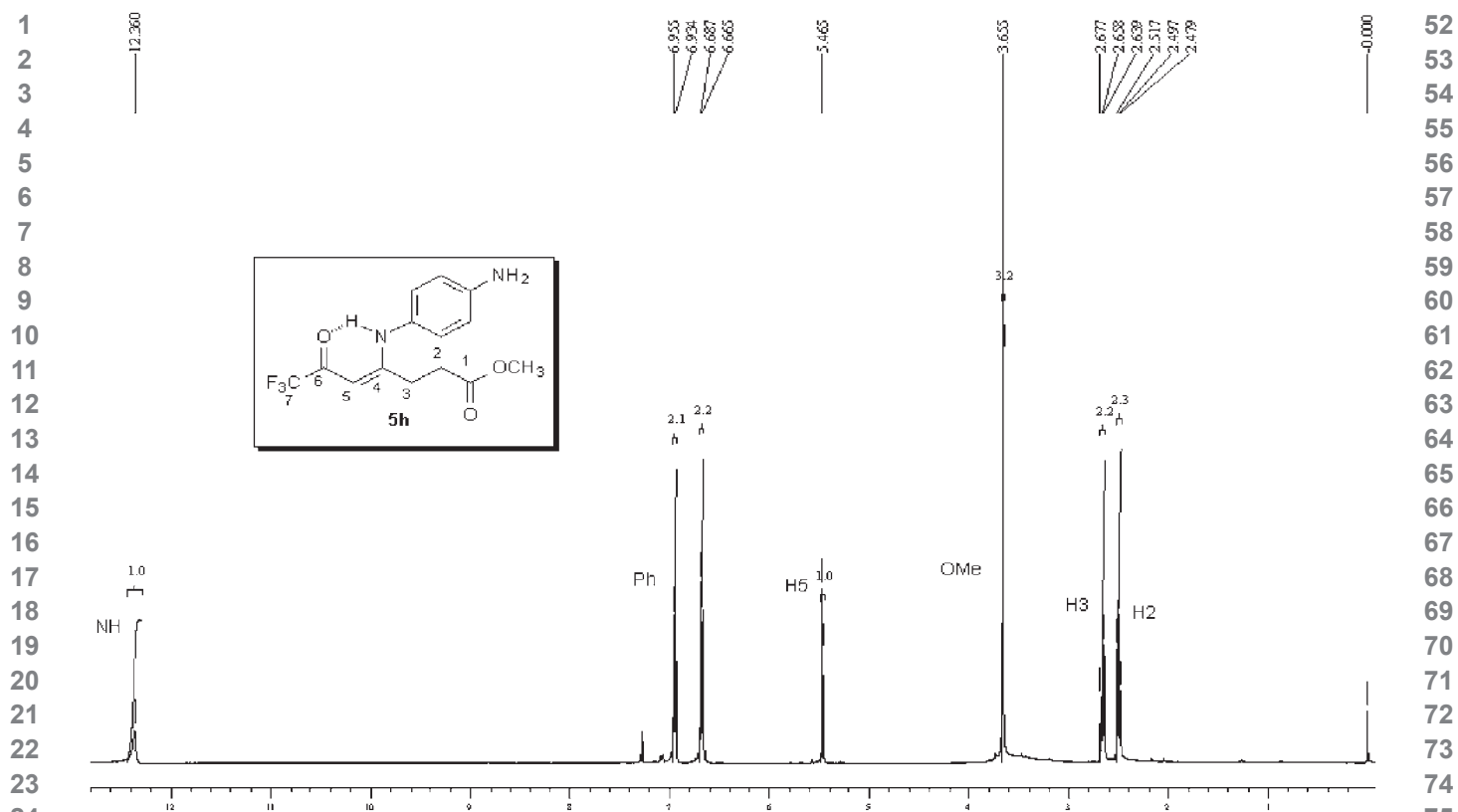


Figure S15. <sup>1</sup>H NMR spectrum from methyl 4-(4-aminophenyl)amino-6-oxo-7,7,7-trifluoro-4-heptenoate (**3k**), 400.13 MHz in CDCl<sub>3</sub> using TMS as internal standard.

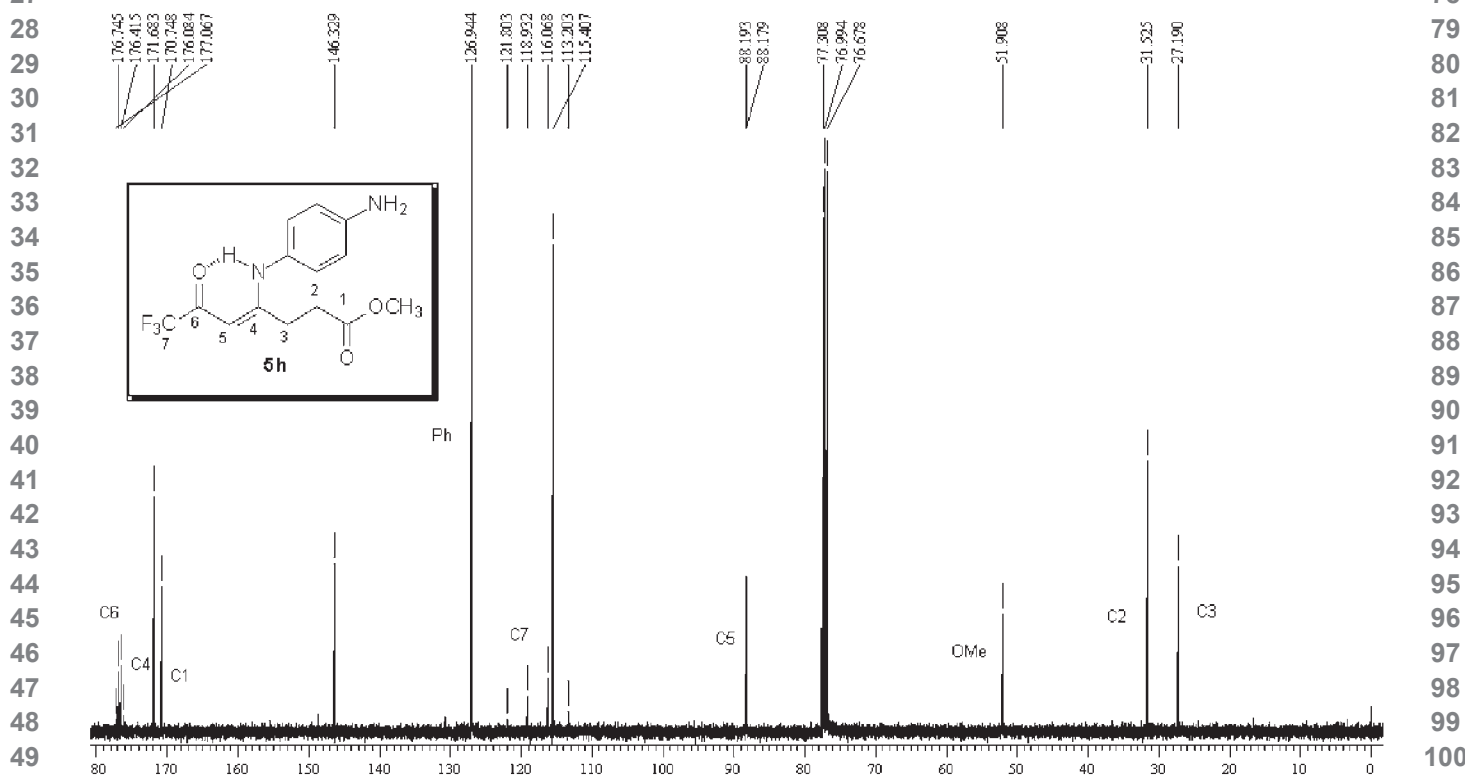
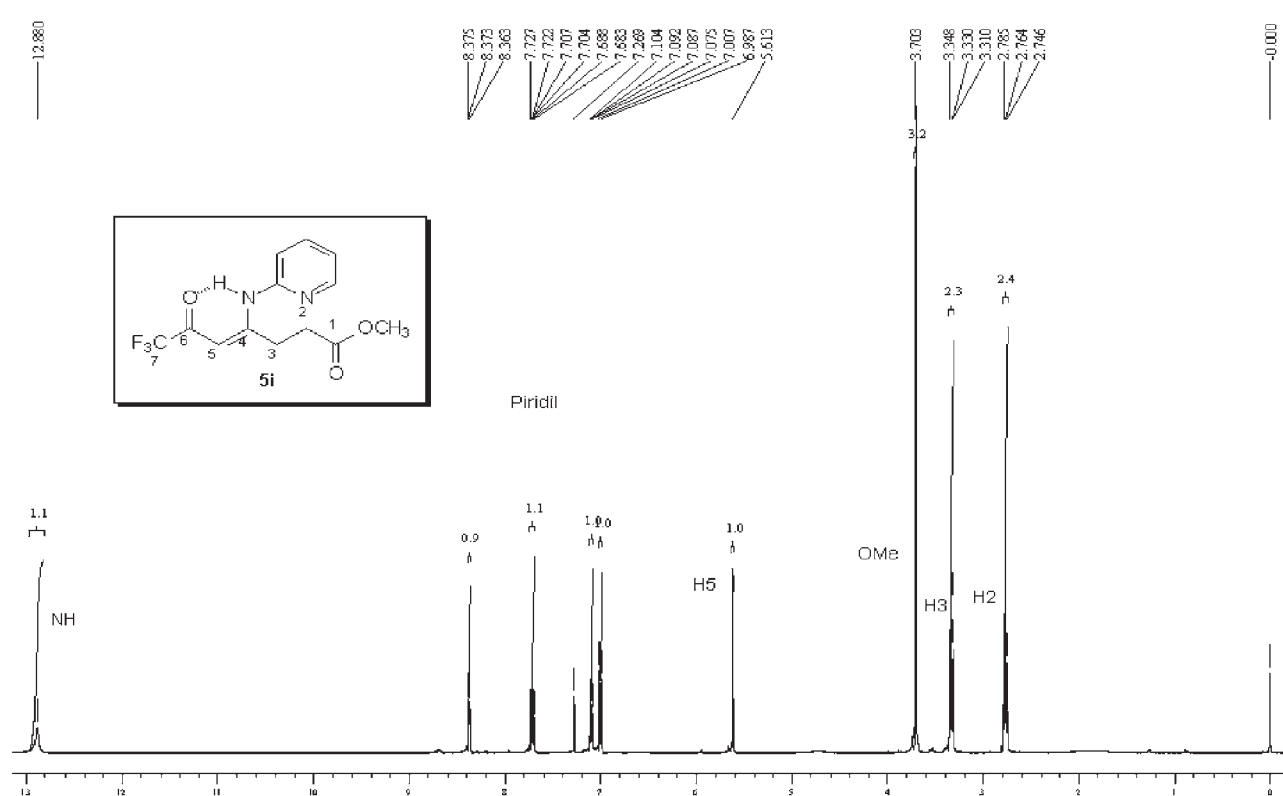
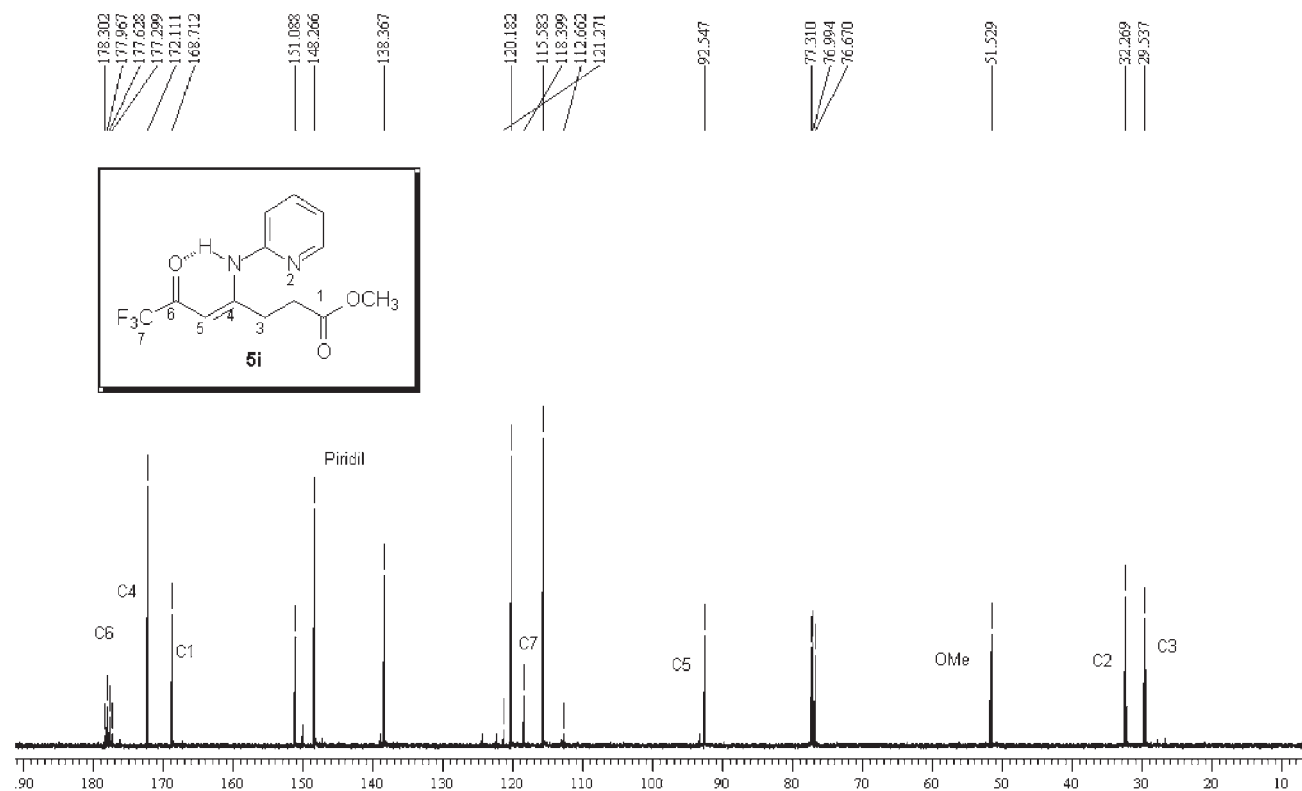


Figure S16. <sup>13</sup>C NMR spectrum from methyl 4-(4-aminophenyl)amino-6-oxo-7,7,7-trifluoro-4-heptenoate (**3k**), 100.62 MHz in CDCl<sub>3</sub> using TMS as internal standard.

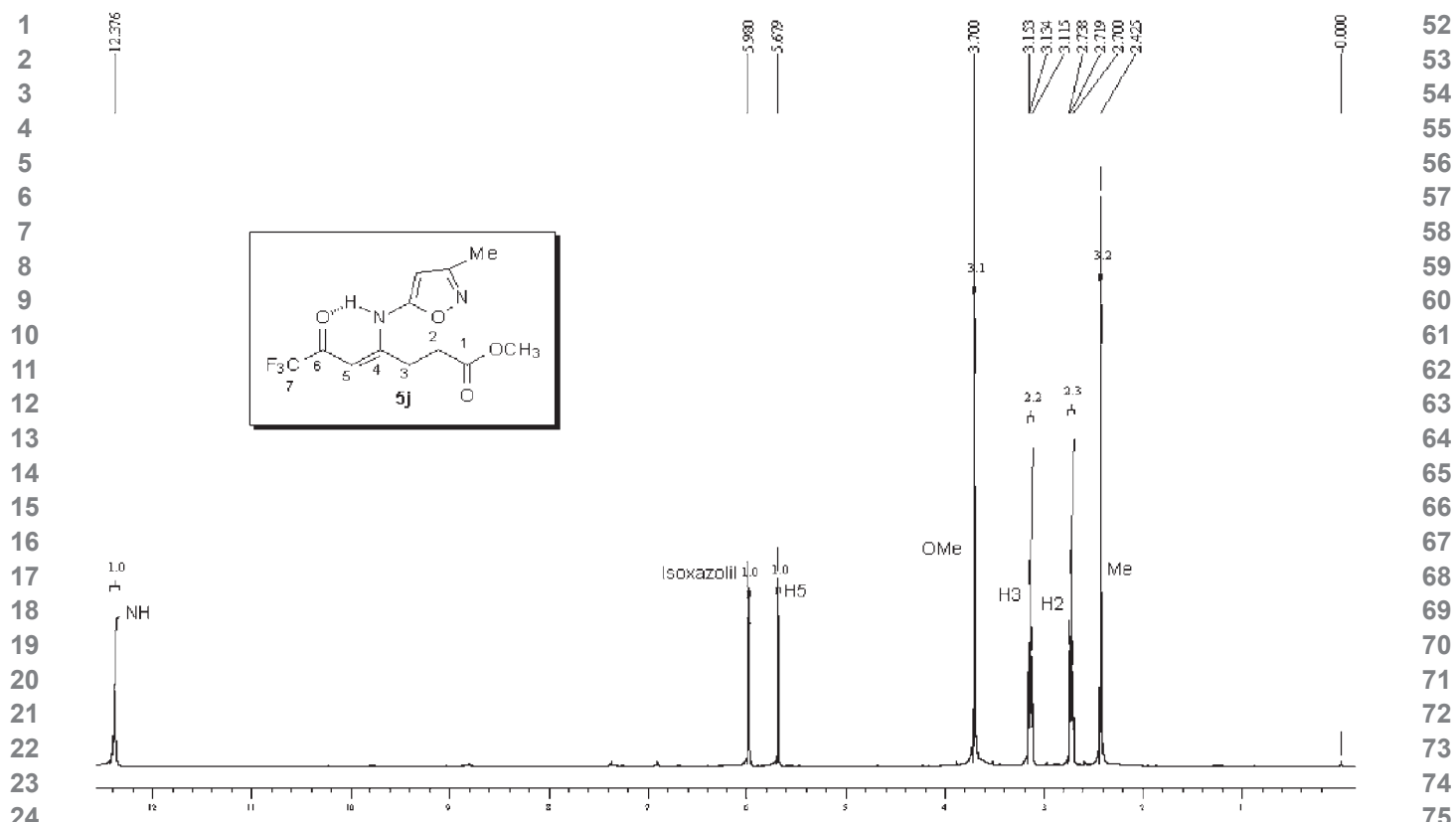


**Figure S17.**  $^1\text{H}$  NMR spectrum from methyl 4-(2-pyridinyl)amino-6-oxo-7,7,7-trifluoro-4-heptenoate (**3j**), 400.13 MHz in  $\text{CDCl}_3$  using TMS as internal standard.

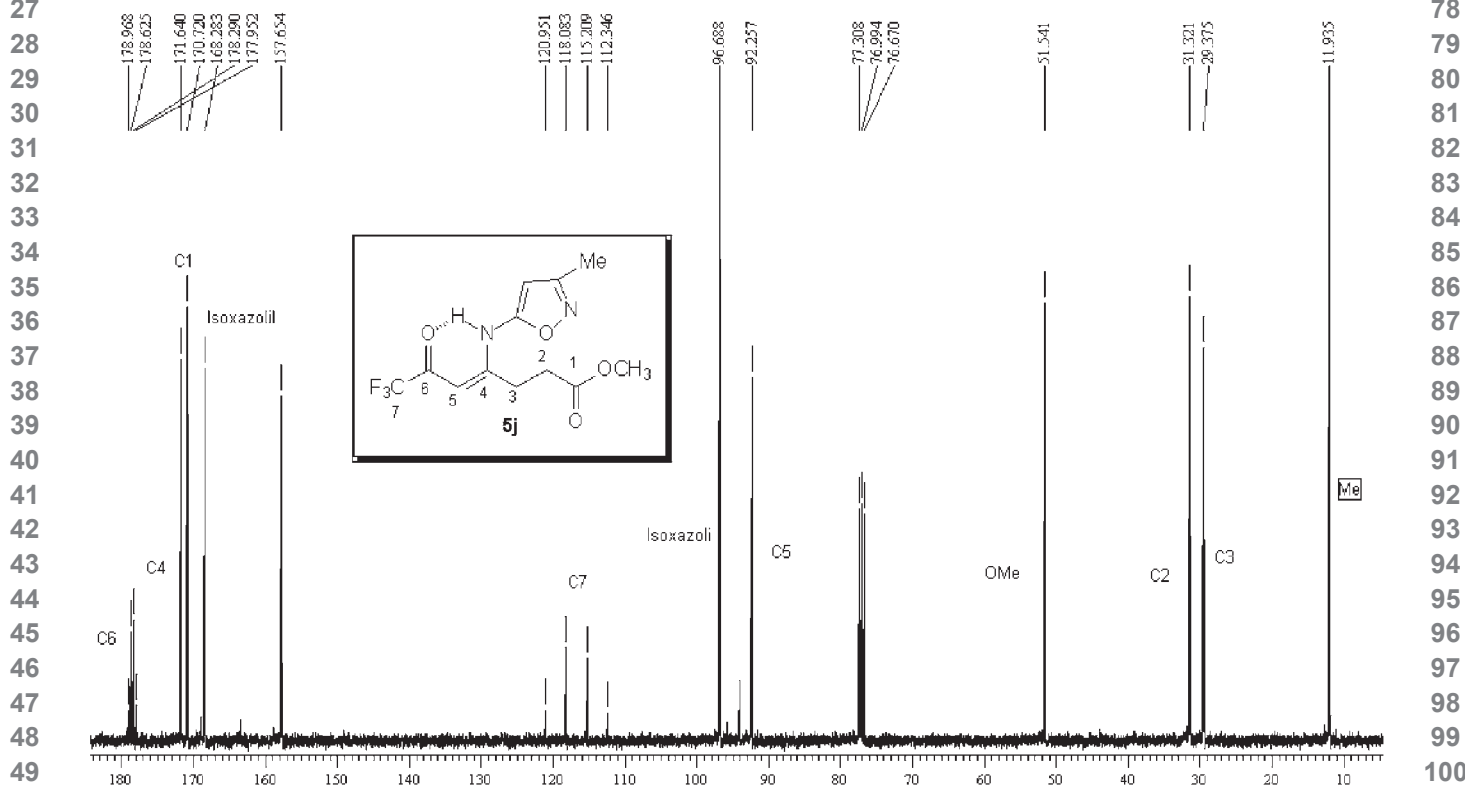


**Figure S18.**  $^{13}\text{C}$  { $^1\text{H}$ } NMR spectrum from methyl 4-(2-pyridinyl)amino-6-oxo-7,7,7-trifluoro-4-heptenoate (**3j**), 100.62 MHz in  $\text{CDCl}_3$  using TMS as internal standard.

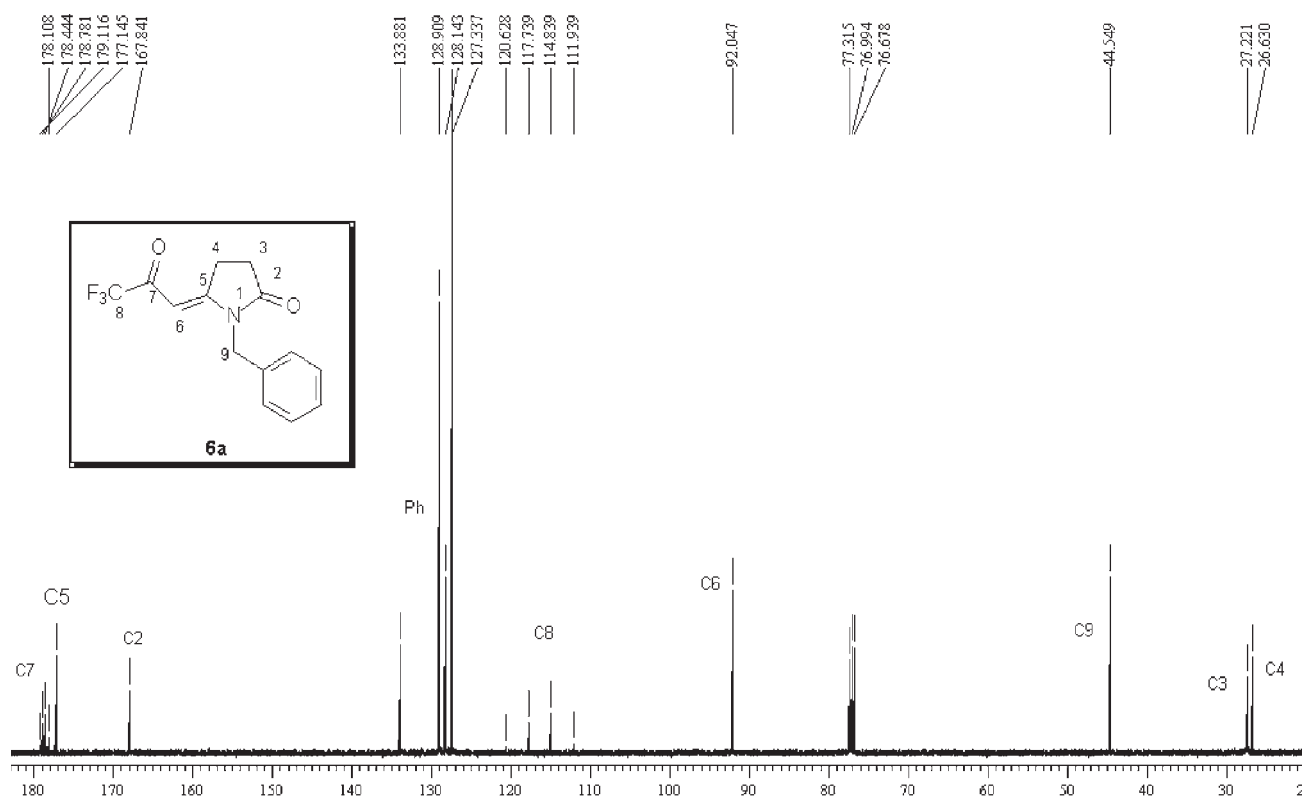
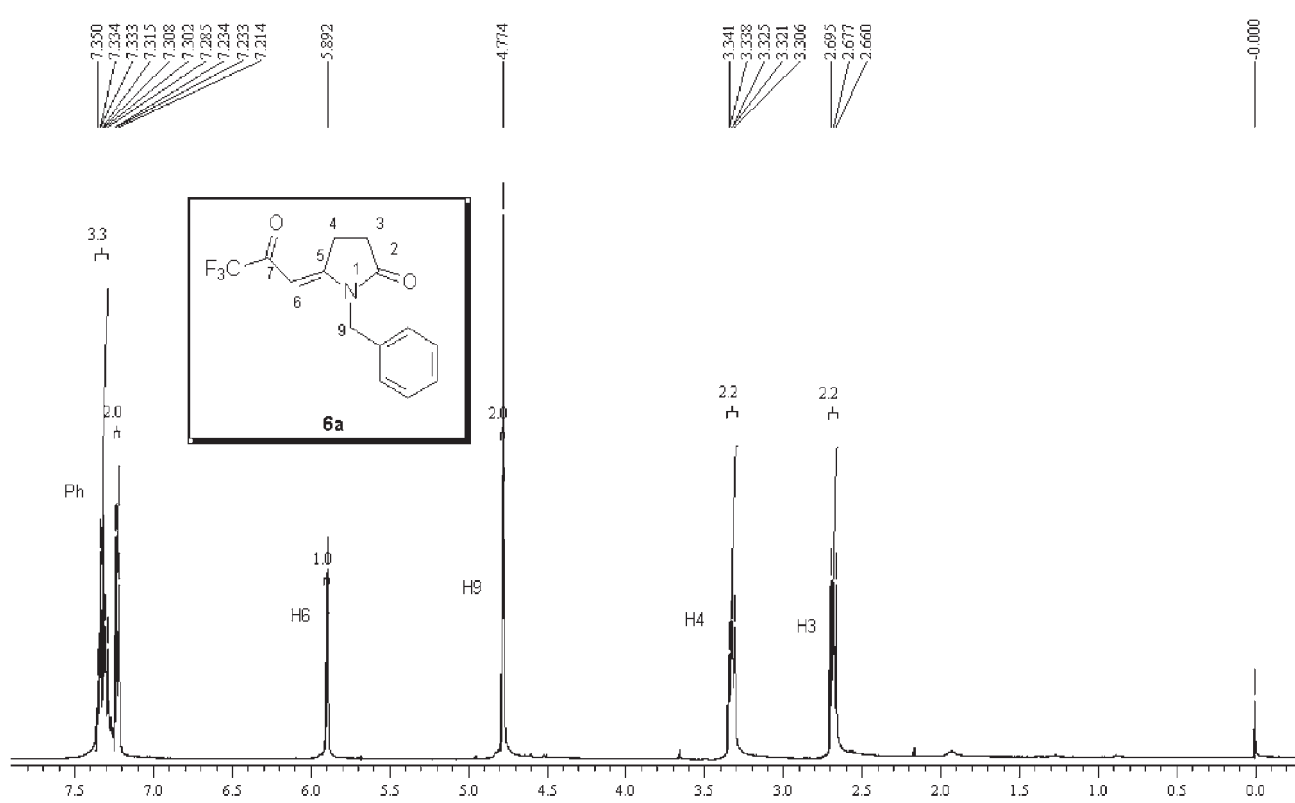




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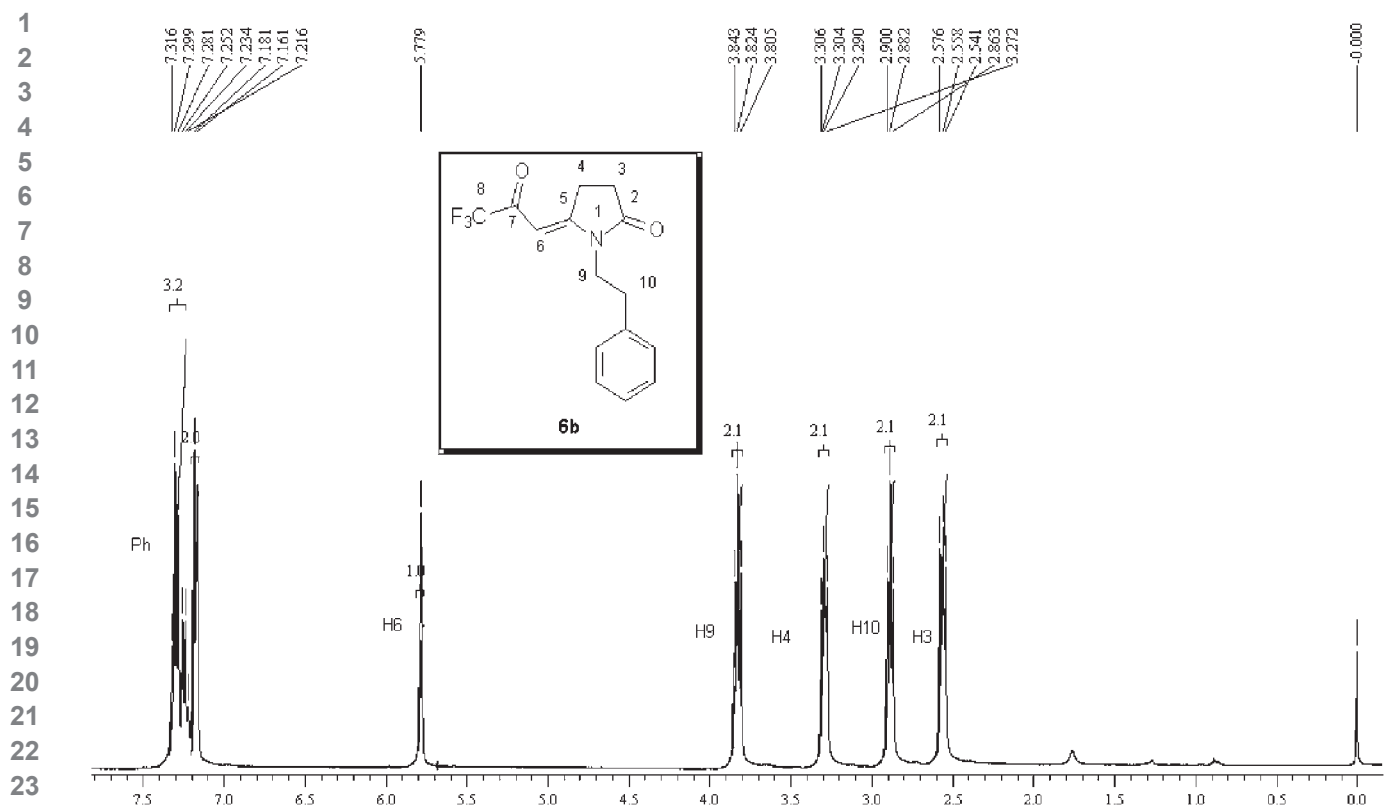


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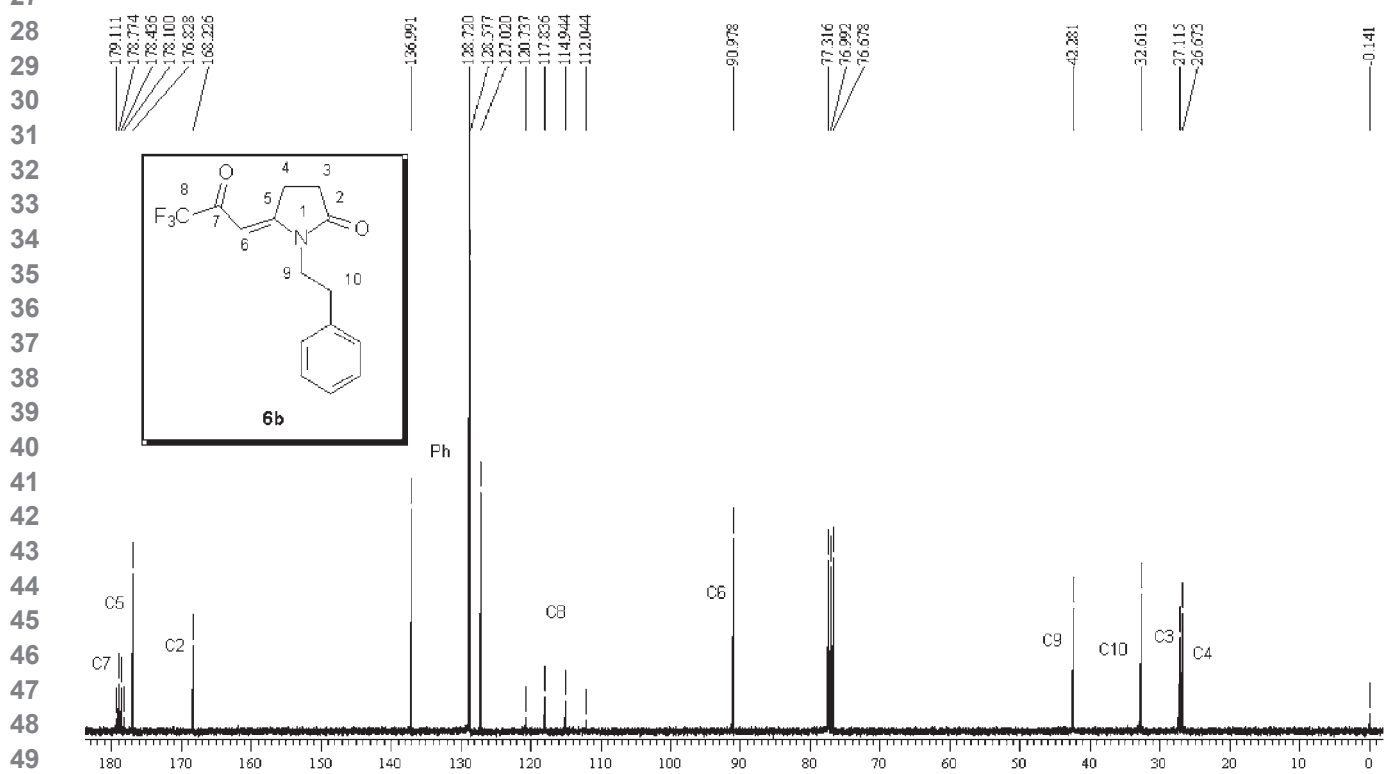


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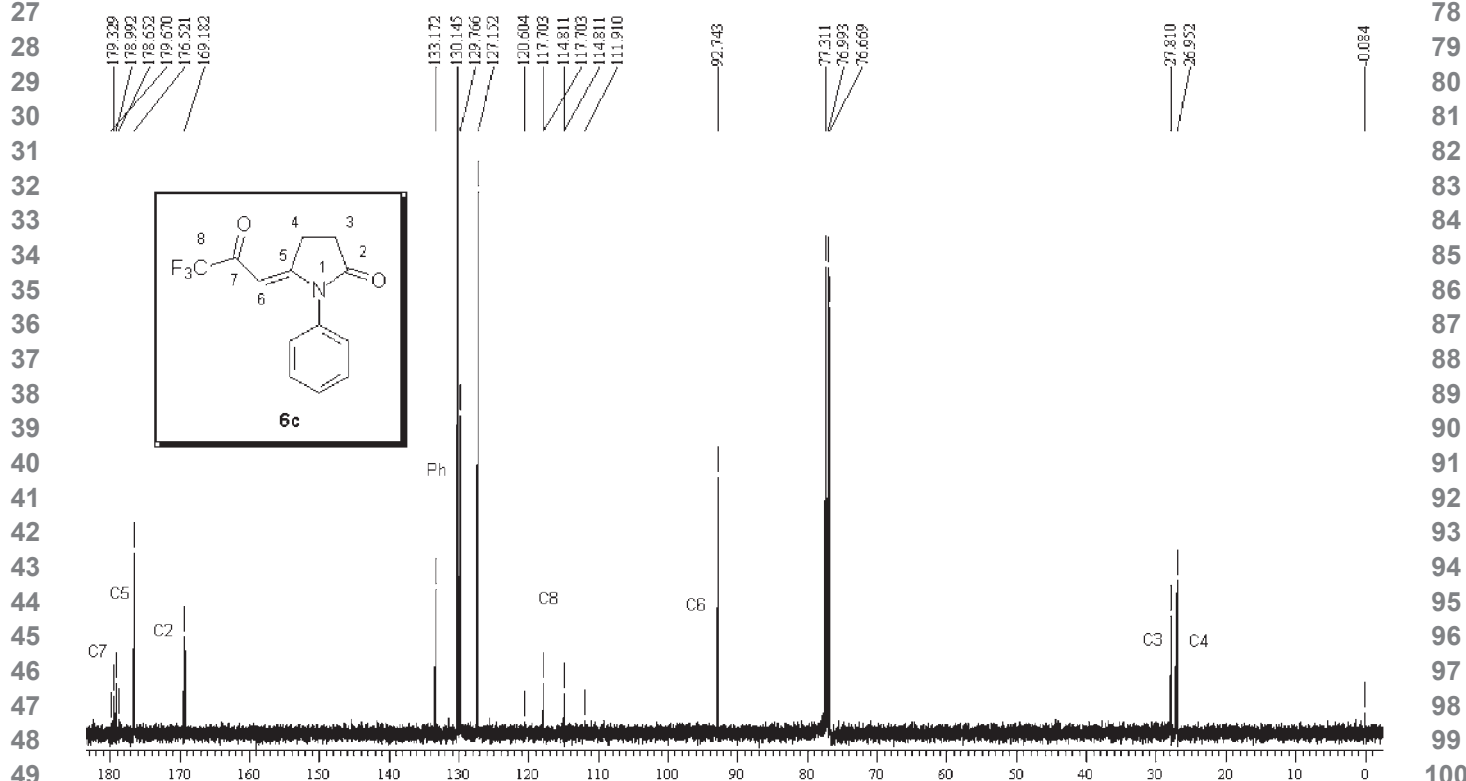
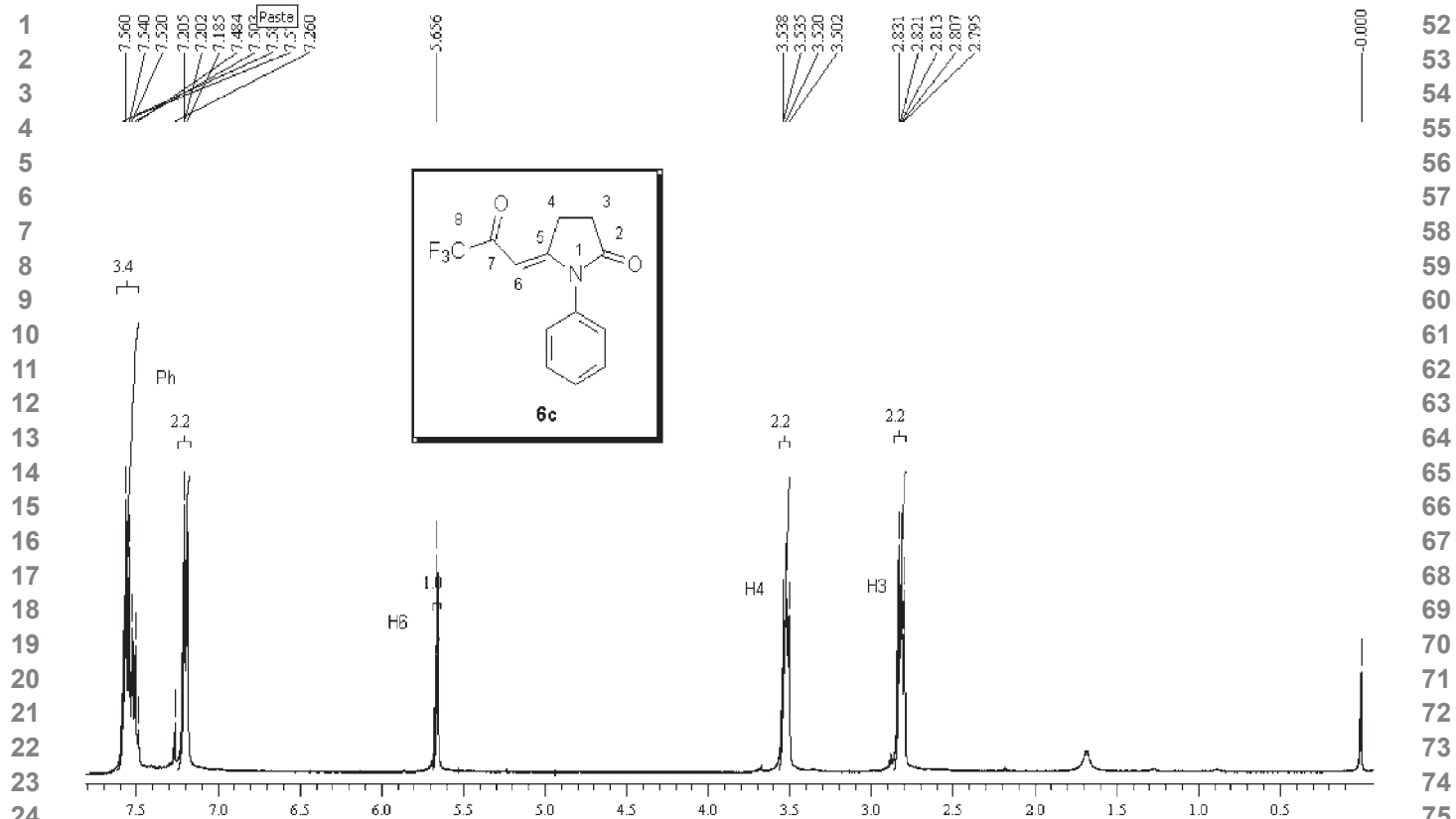
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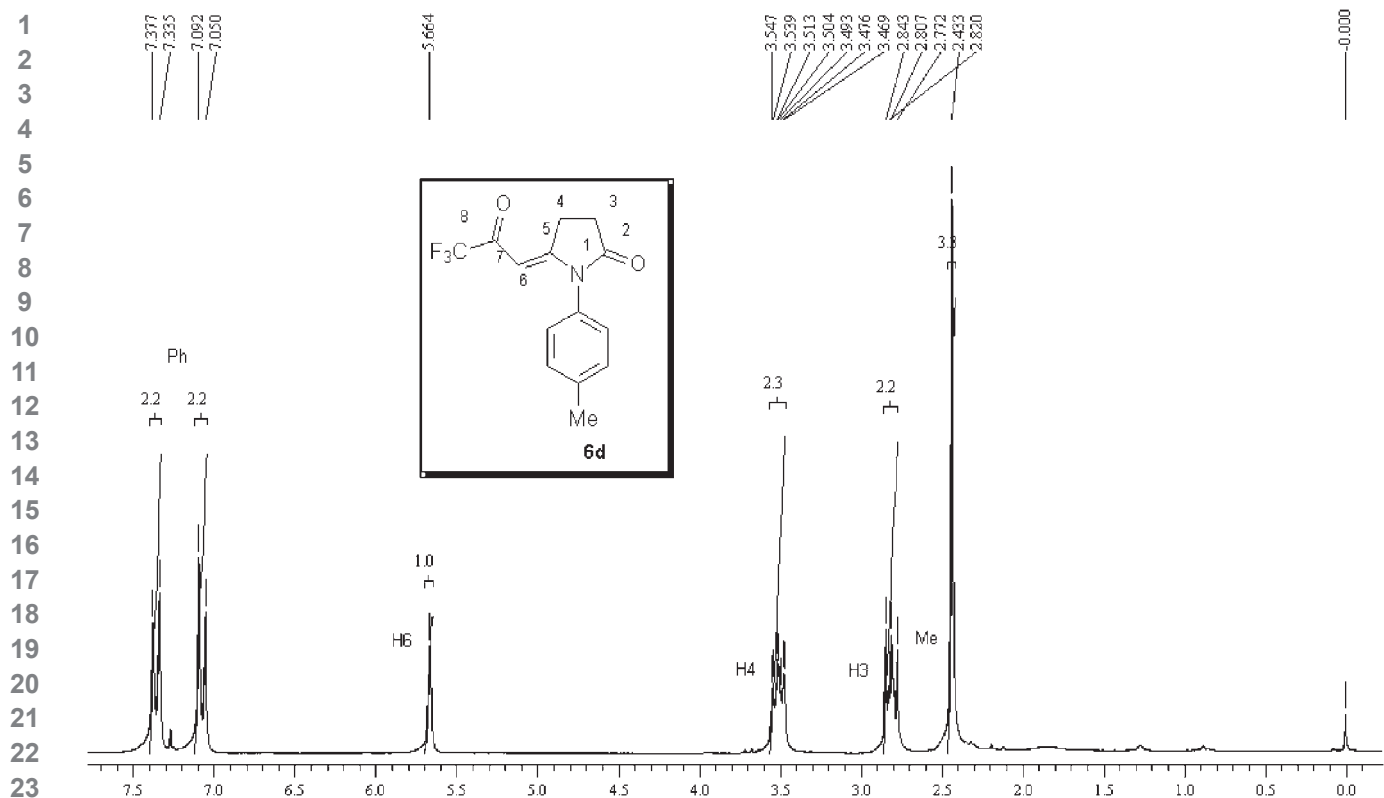


**Figure S23.**  $^1\text{H}$  NMR spectrum from 1-(2-phenylethyl)-5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-2-one (**5c**), 400.13 MHz in  $\text{CDCl}_3$  using TMS as internal standard.

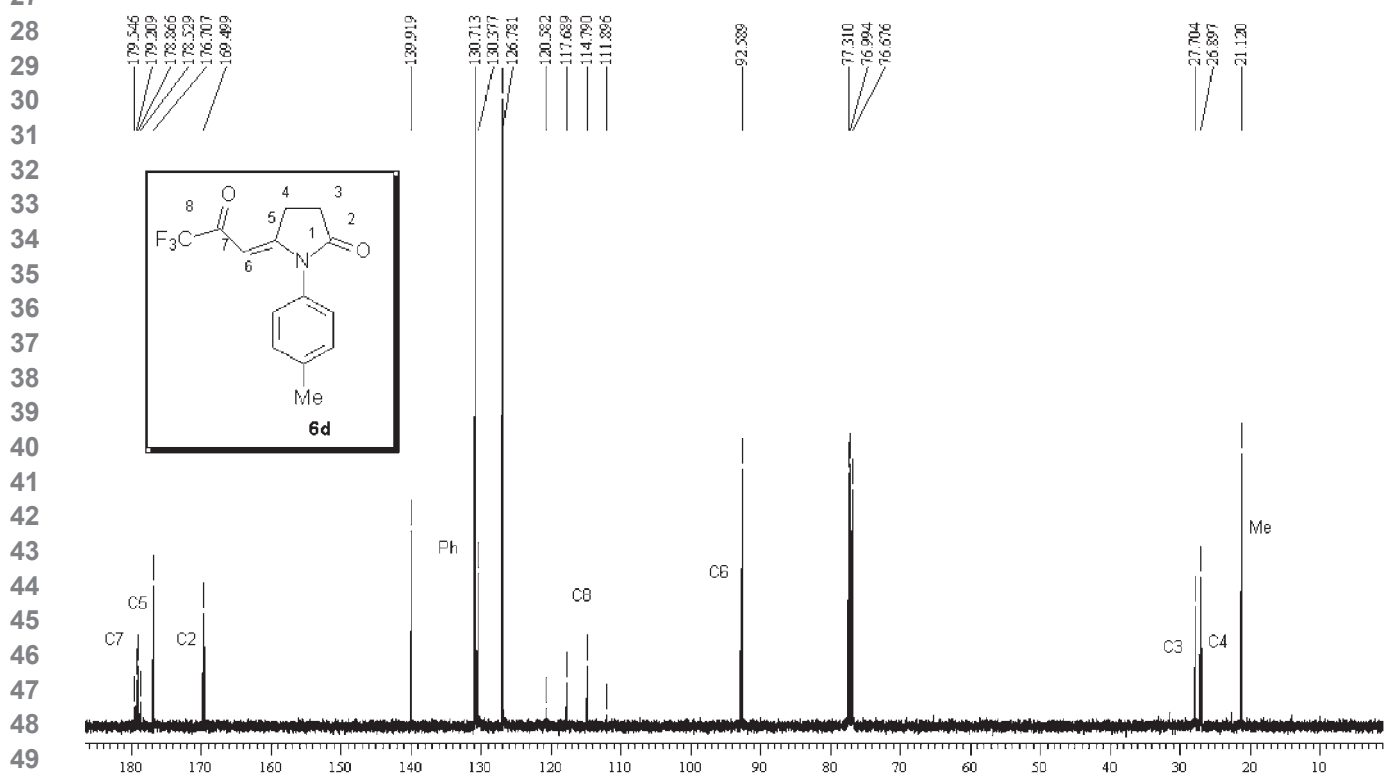


**Figure S24.**  $^{13}\text{C}$  NMR spectrum from 1-(2-phenylethyl)-5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-2-one (**5c**), 100.62 MHz in  $\text{CDCl}_3$  using TMS as internal standard.

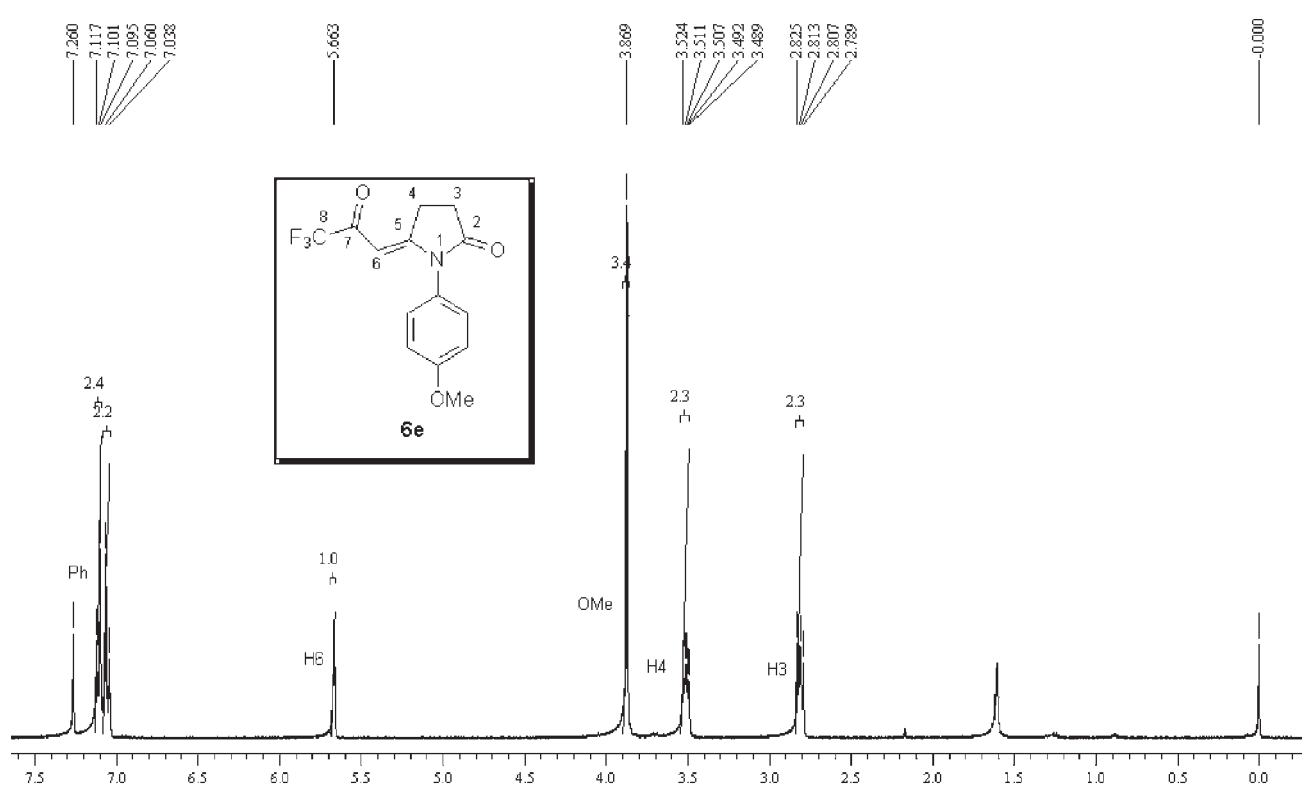




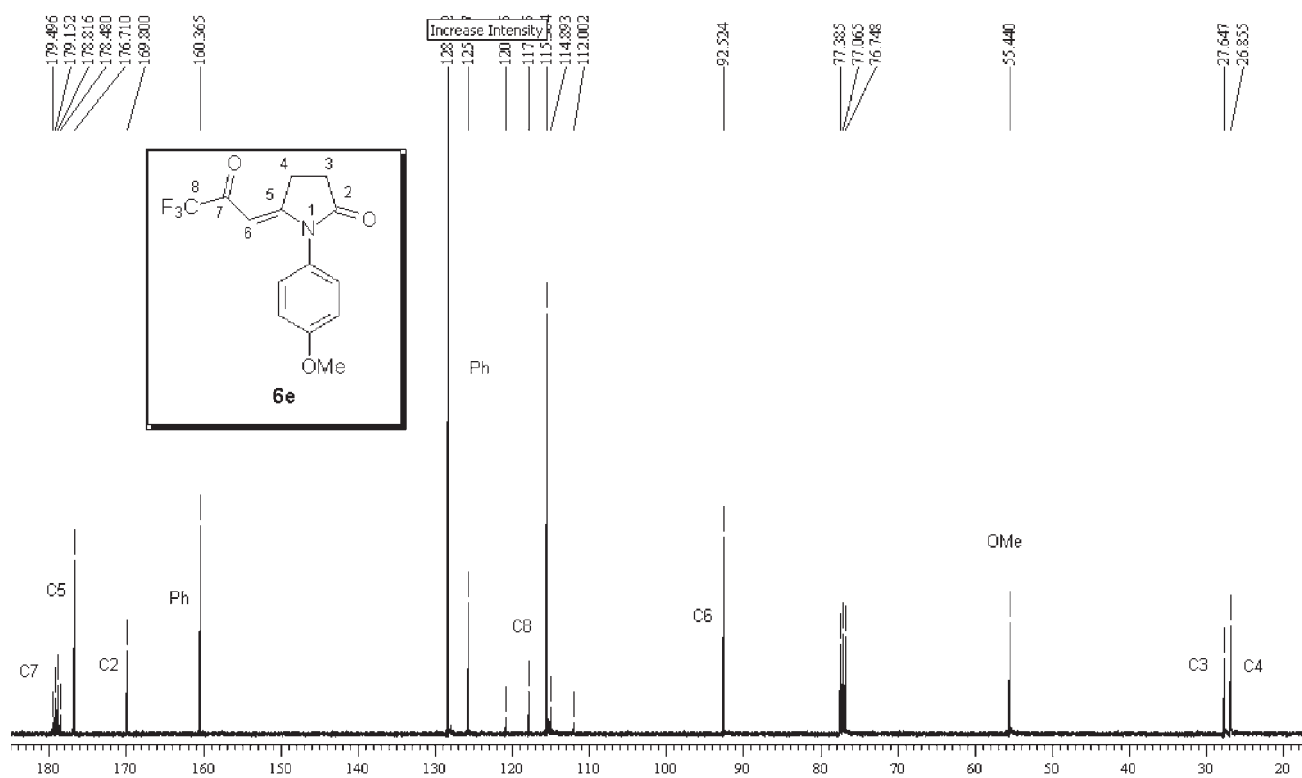
**Figure S27.**  $^1\text{H}$  NMR spectrum from 1-(4-methylphenyl)- 5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-2-one (**5e**), 400.13 MHz in  $\text{CDCl}_3$  using TMS as internal standard.



**Figure S28.**  $^{13}\text{C}$  NMR spectrum from 1-(4-methylphenyl)- 5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-2-one (**5e**), 100.62 MHz in  $\text{CDCl}_3$  using TMS as internal standard.

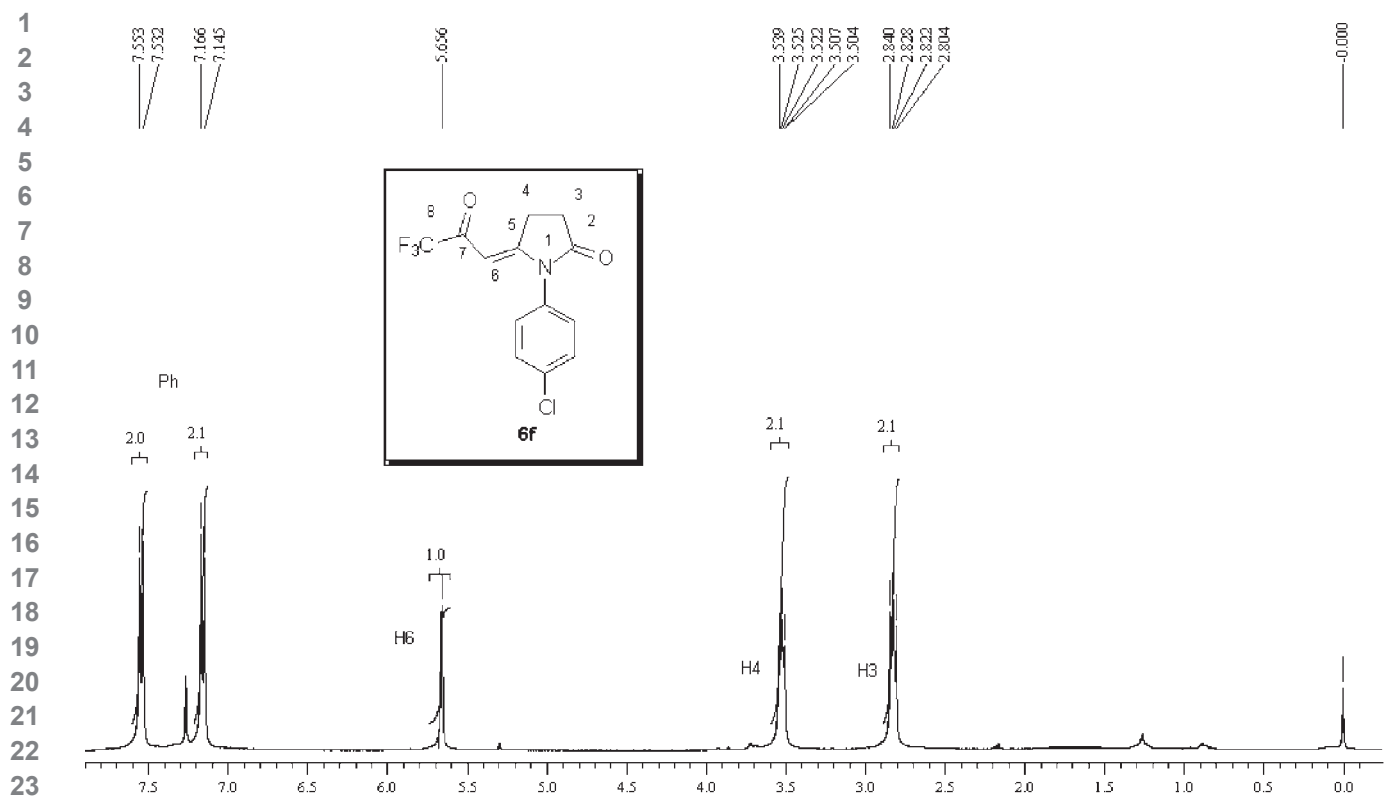


**Figure S29.**  $^1\text{H}$  NMR spectrum from 1-(4-methoxyphenyl)-5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-2-one (**5f**), 400.13 MHz in  $\text{CDCl}_3$  using TMS as internal standard.

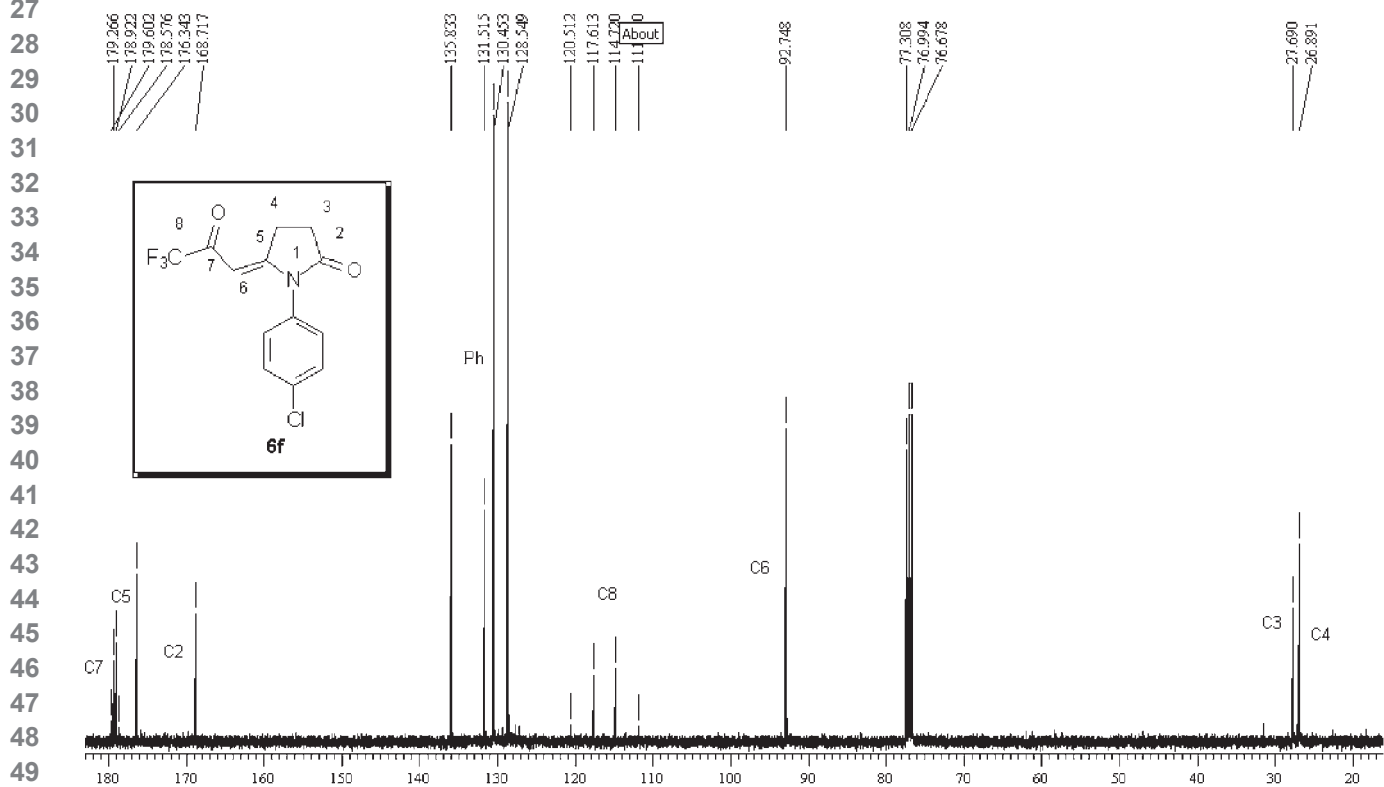


**Figure S30.**  $^{13}\text{C}\{^1\text{H}\}$  NMR spectrum from 1-(4-methoxyphenyl)-5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-2-one (**5f**), 100.62 MHz in  $\text{CDCl}_3$  using TMS as internal standard.

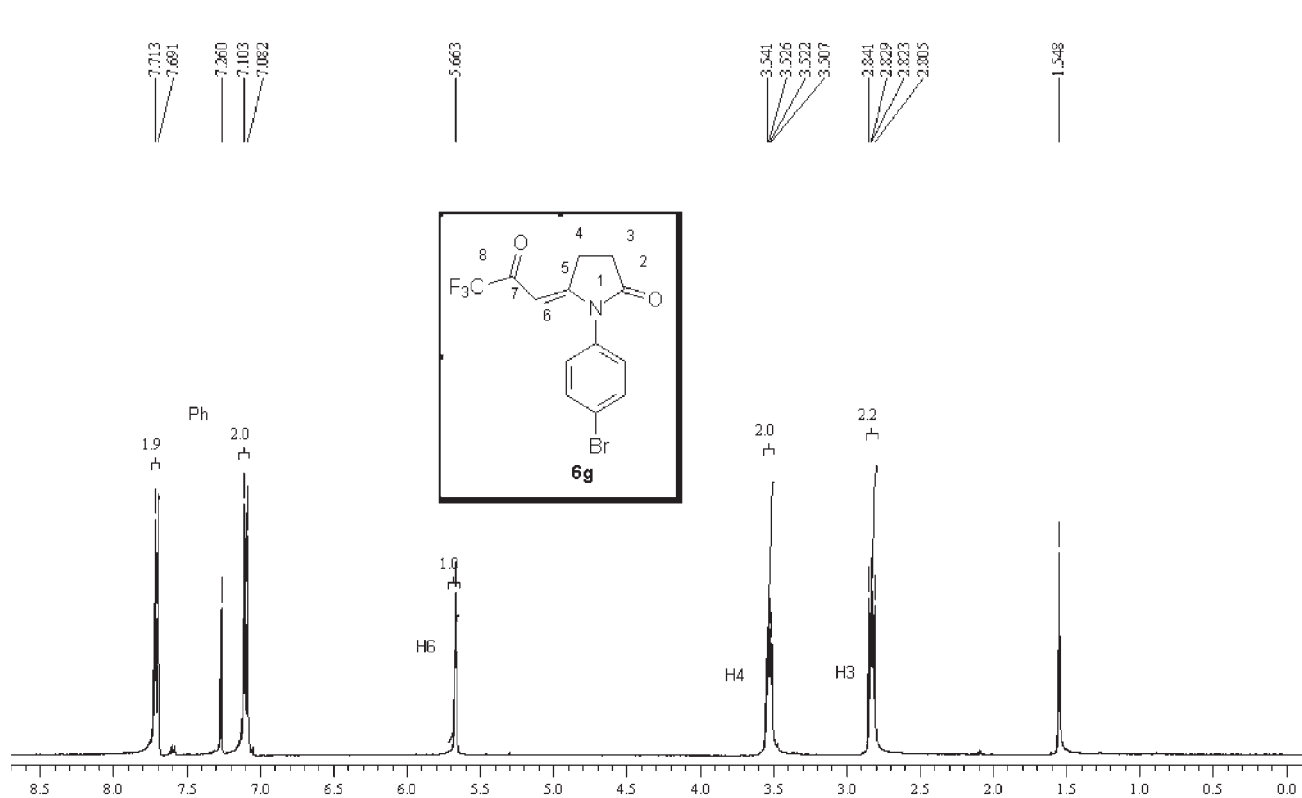




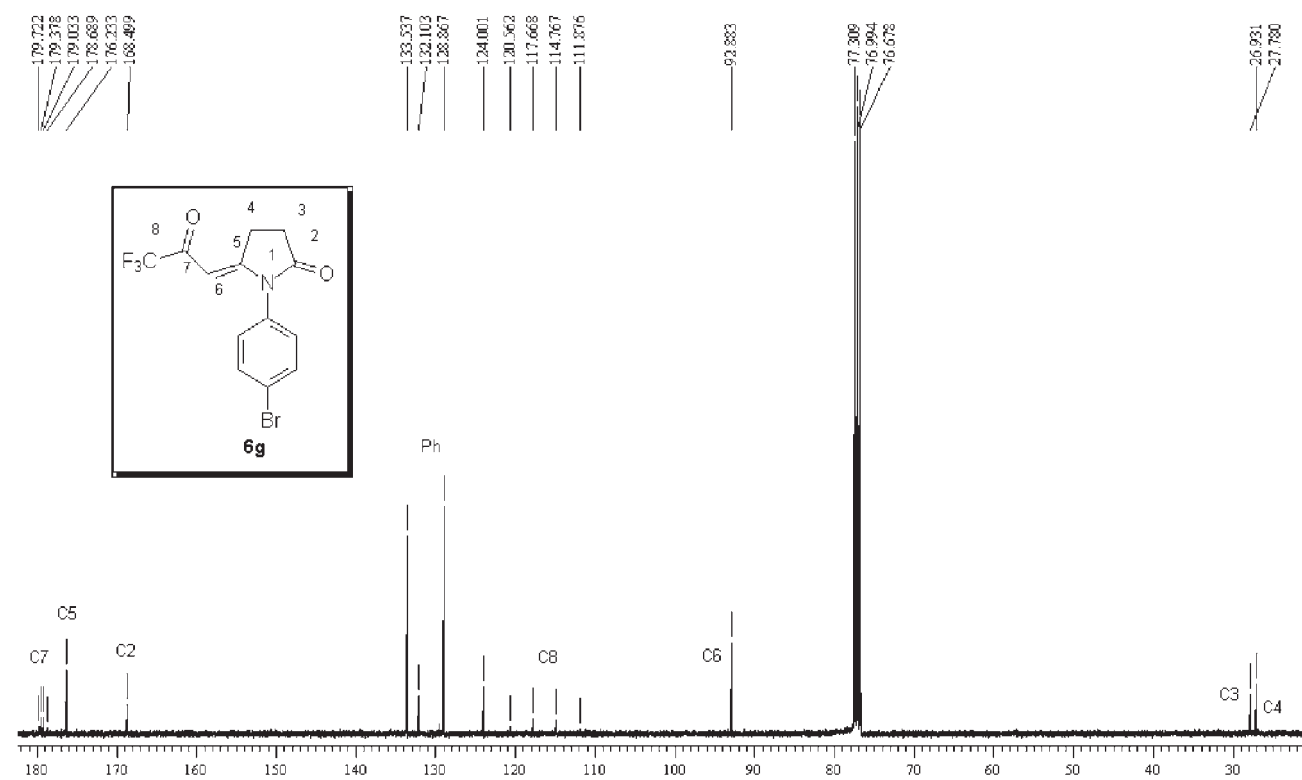
**Figure S31.**  $^1\text{H}$  NMR spectrum from 1-(4-chlorophenyl)-5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-2-one (**5g**), 400.13 MHz in  $\text{CDCl}_3$  using TMS as internal standard.



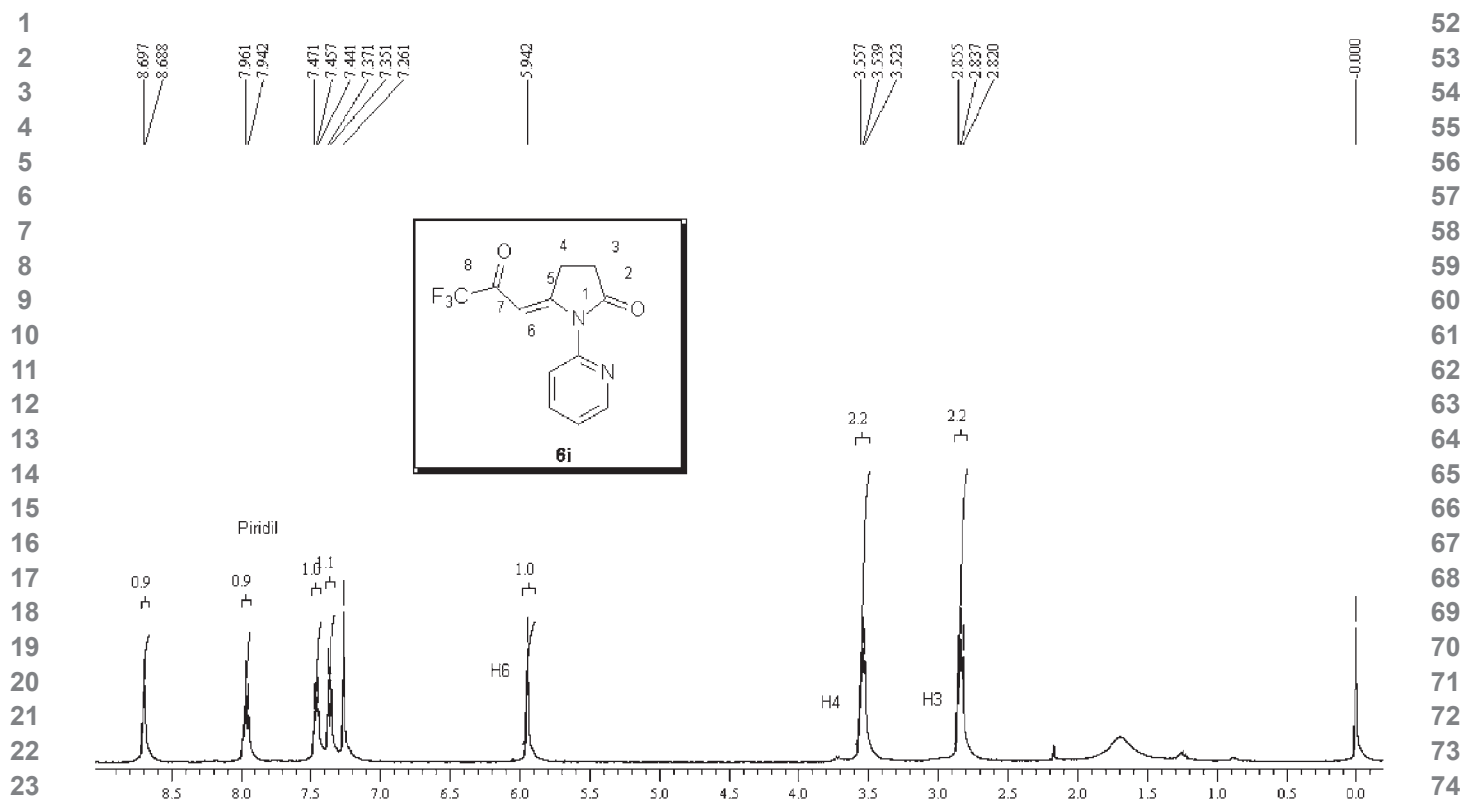
**Figure S32.**  $^{13}\text{C}\{^1\text{H}\}$  NMR spectrum from 1-(4-chlorophenyl)-5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-2-one (**5g**), 100.62 MHz in  $\text{CDCl}_3$  using TMS as internal standard.



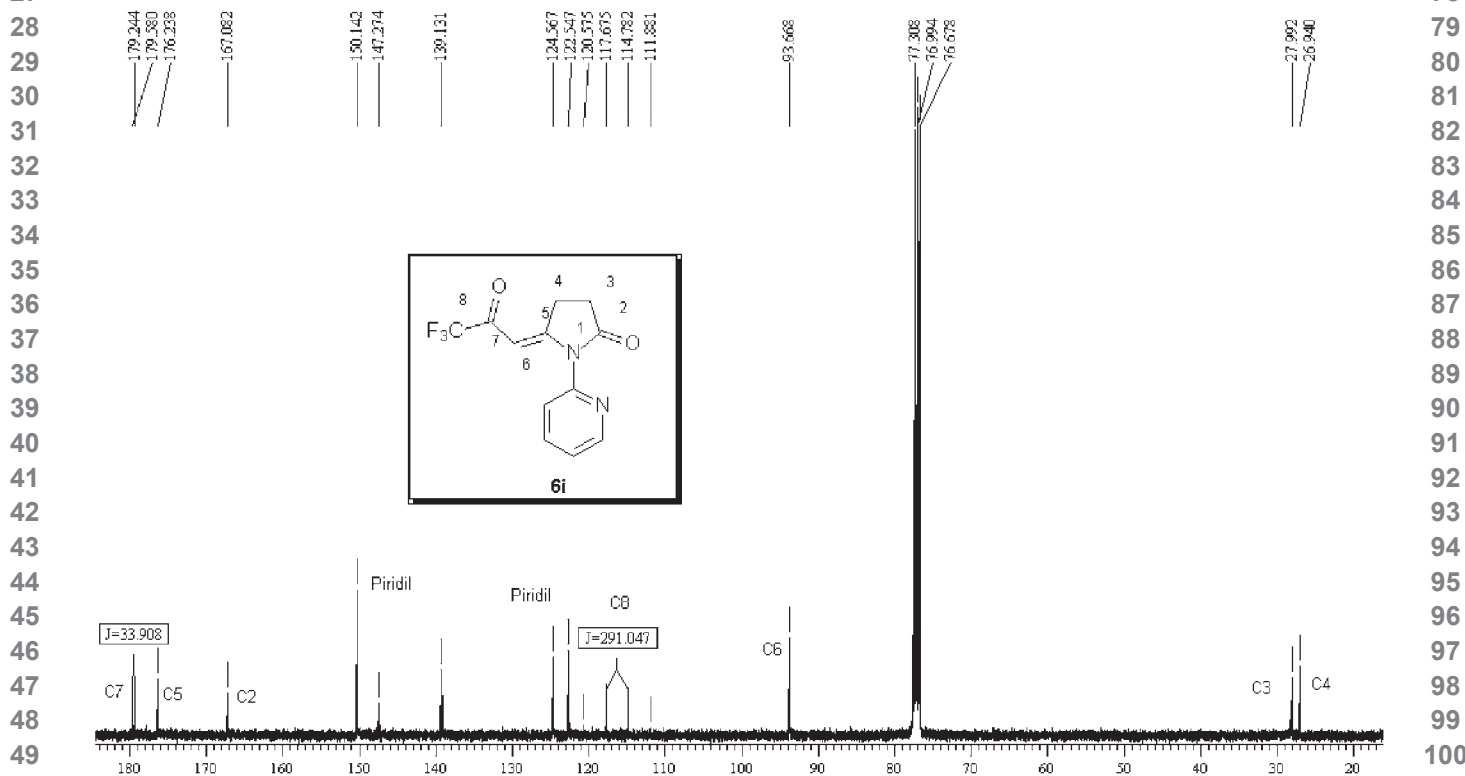
**Figure S33.**  $^1\text{H}$  NMR spectrum from 1-(4-bromophenyl)-5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-2-one (**5h**), 400.13 MHz in  $\text{CDCl}_3$  using TMS as internal standard.



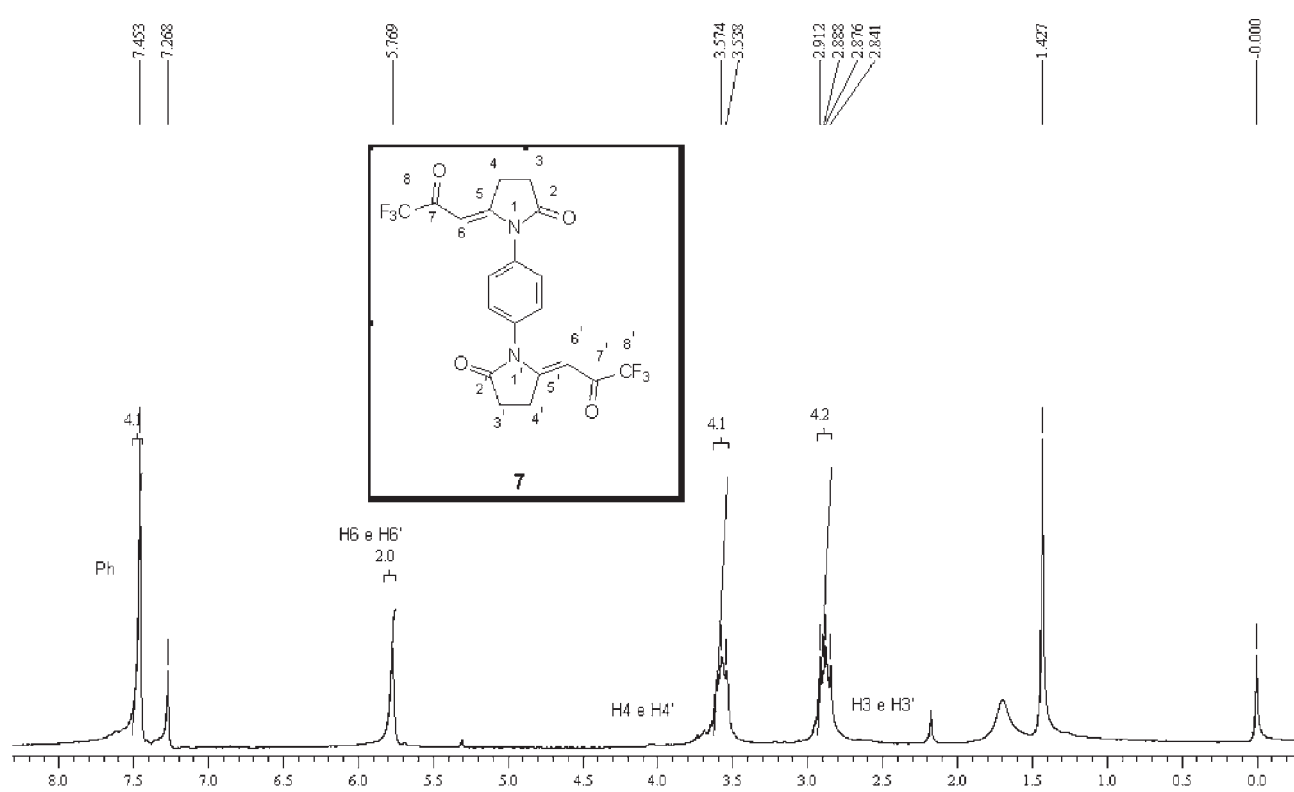
**Figure S34.**  $^{13}\text{C}$  NMR spectrum from 1-(4-bromophenyl)-5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-2-one (**5h**), 100.62 MHz in  $\text{CDCl}_3$  using TMS as internal standard.



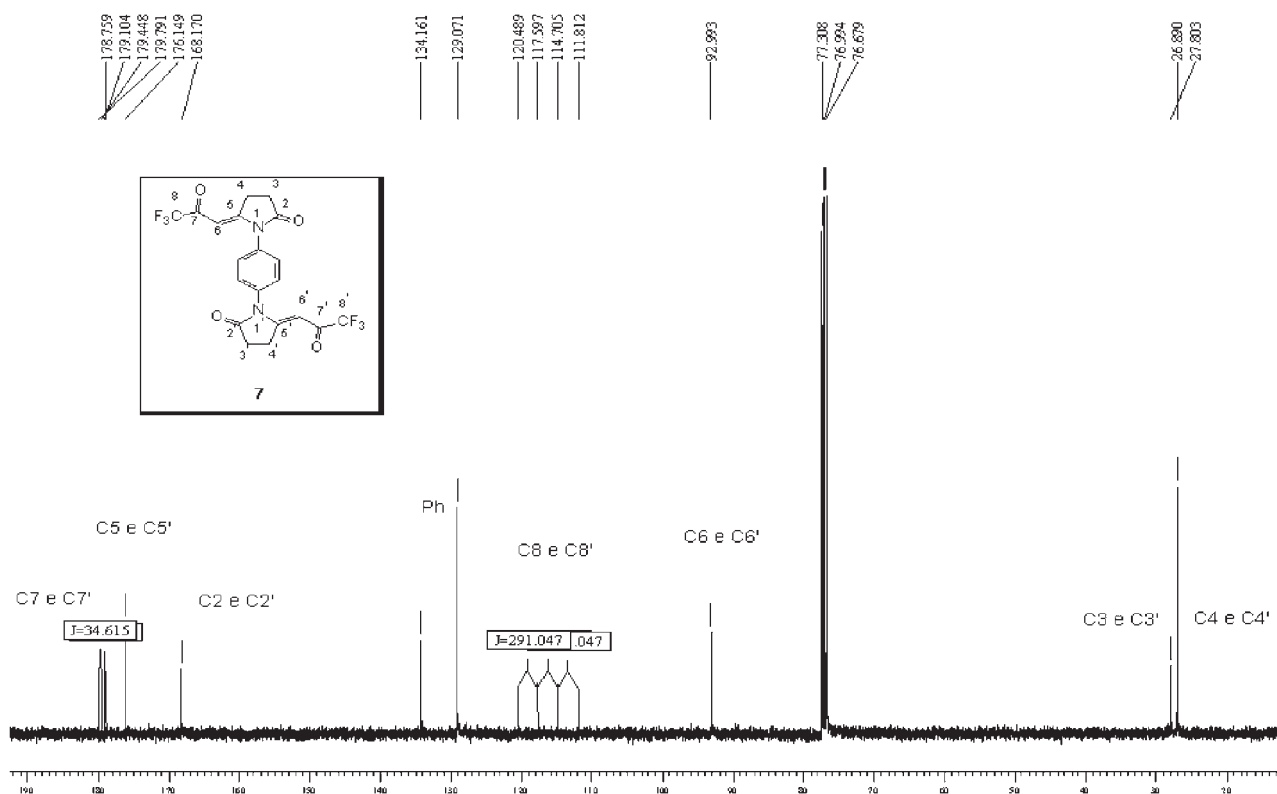
**Figure S35.**  $^1\text{H}$  NMR spectrum from 1-(2-pyridyl)- 5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-2-one (**5j**), 400.13 MHz in  $\text{CDCl}_3$  using TMS as internal standard.



**Figure S36.**  $^{13}\text{C}$  NMR spectrum from 2-oxo-1-(2-pyridyl)- 5-(3,3,3-trifluoro-2-oxo-propylidene)pyrrolidin-2-one (**5j**), 100.62 MHz in  $\text{CDCl}_3$  using TMS as internal standard.



**Figure S37.**  $^1\text{H}$  NMR spectrum from 1,4-(phenylene)bis(5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-2-one) (**5k**), 400.13 MHz in  $\text{CDCl}_3$  using TMS as internal standard.



**Figure S38.**  $^{13}\text{C}\{^1\text{H}\}$  NMR spectrum from 1,4-(phenylene)bis(5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-2-one) (**5k**), 100.62 MHz in  $\text{CDCl}_3$  using TMS as internal standard.