Opioid receptor modulators with a cinnamyl group

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Supporting Information

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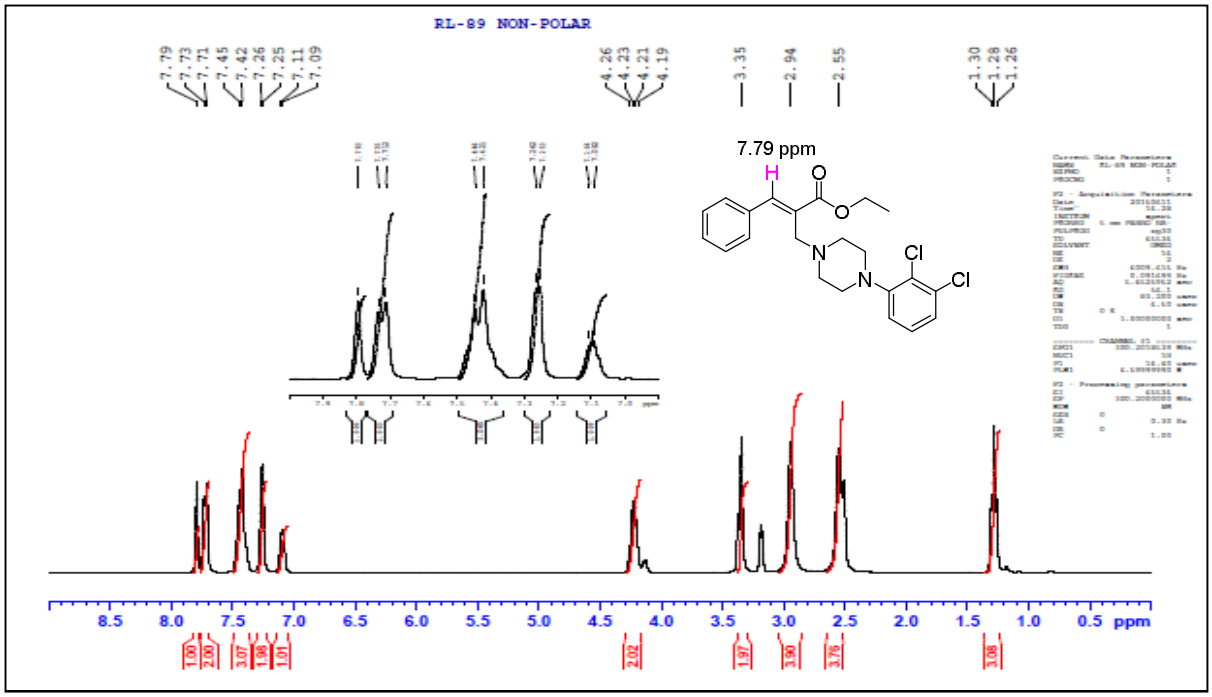
Table 3. List of all possible interactions of the docked protein structures along with the Binding Energies. AutoDock4[Morris, G M, Huey R, Lindstrom W, Sanner M F, Belew R K, Goodsell D S and Olson A J. Autodock4 and AutoDockTools4: automated docking with selective receptor flexiblity. Journal ofComputational Chemistry. 2009; 16: 2785-91] was used for docking of protein-ligand complex.

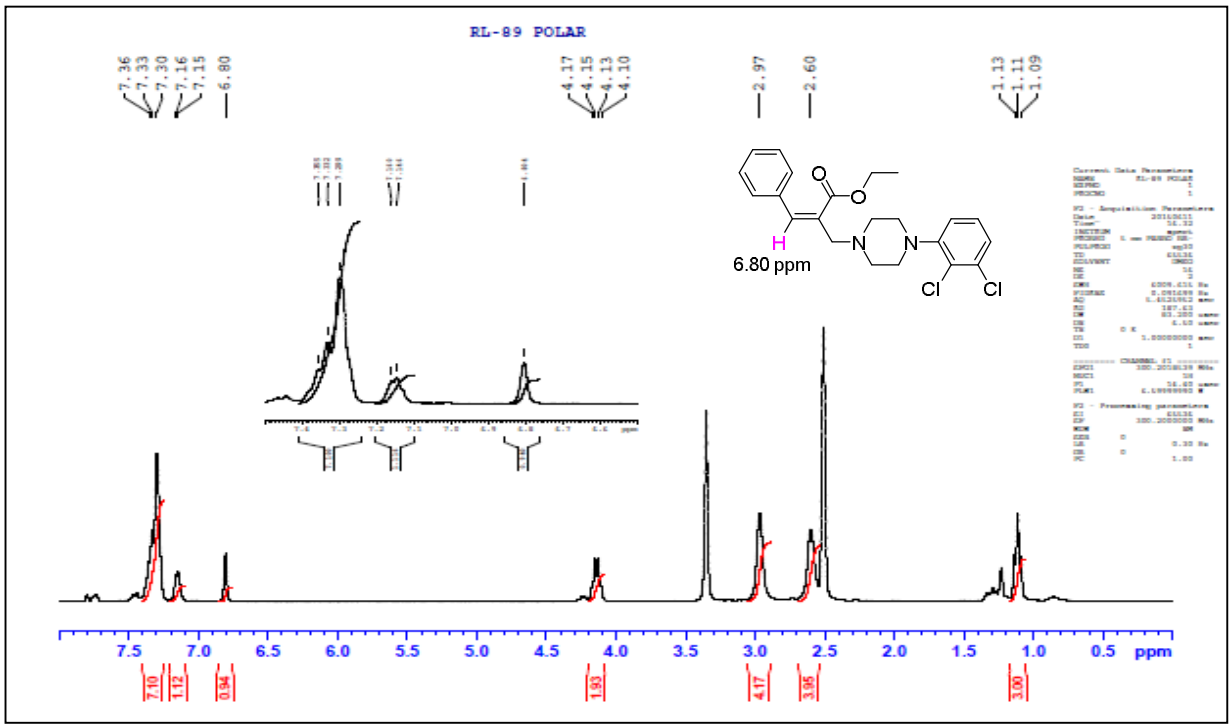
Protein Complex	**Interactions**				**Energy (kcal/mol)**
	Hydrogen	**Hydrophobic**	**π Stacking**	**Salt Bridge**	
μ-opioid receptor-Dehydro alvimopan (28f) (MOR)	His 297	Tyr 148, Lys 233, Val 236, Phe 237, Trp 293, Ile 296, Val 300, Ile 301, Ile 322, Tyr 326	-	Asp147, Lys 233	-8.87
κ-opioid receptor-18b (KOR)	Gln 115, Tyr 312	Val 108, Val 118, Trp 124, Lys 227, Val 230, Ile 294, Ile 316, Tyr 320	Tyr 139	Asp 138	-9.08
μ-opioid receptor-Alvimopan (1) (MOR)	Tyr 148, Asn 150, Lys 233	Asn 150, Met 151, Lys 233, Val 236, Val 300, Ile 322, Tyr 326	Trp 293	Asp 147	-9.38

Geometric discussion of *E* and *Z*-isomers

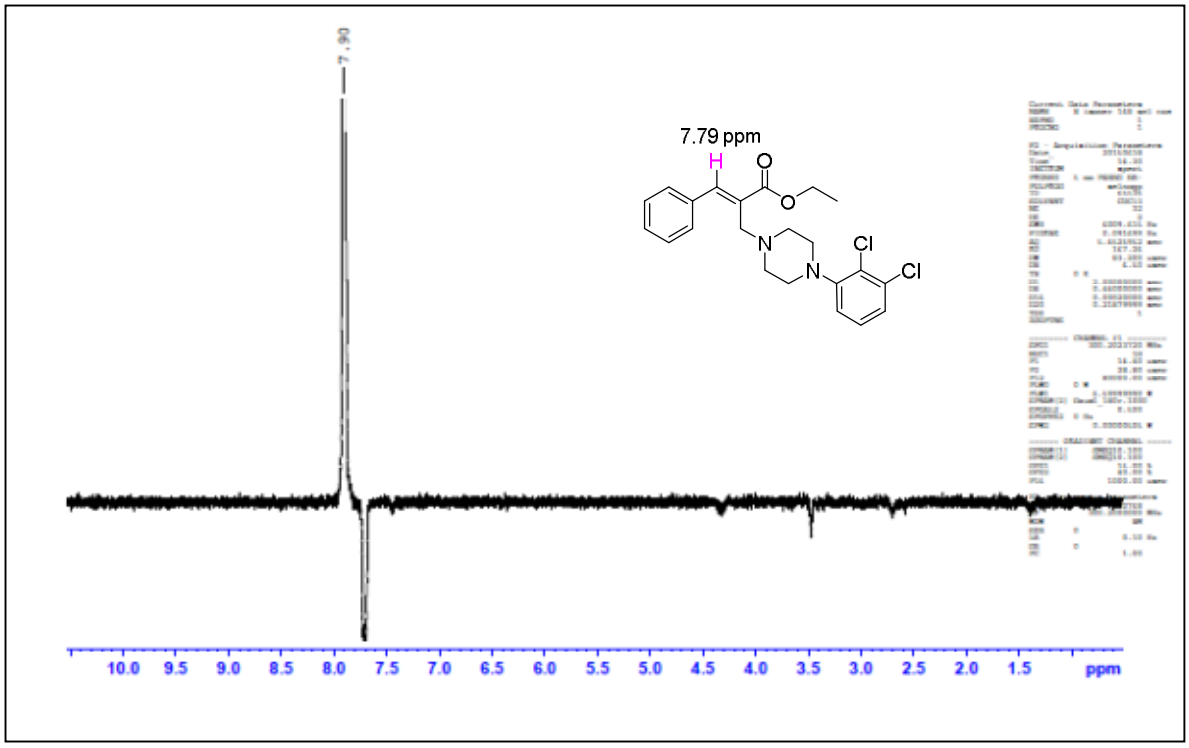
The retention of *E*-geometry during displacement of bromine was demonstrated as follows in the case of **10b.** When the reaction was conducted at 70^{o} C two products were formed; one was **10b** and the other was the *Z*-isomer. This was demonstrated by NOESY studies in the proton NMR. In the 300 MHz ^{1}H NMR spectrum of **10b** (DMSO-d_6) the benzylidene proton was seen as a singlet at 7.79 ppm. In the ^{1}H-^{1}H NOESY spectrum of **10b** there was a strong interaction between aromatic proton with piperazine protons, aromatic proton with allylic $–CH_2$ protons and weak interaction between benzylidene proton and $–CH_2$ and $–CH_3$ ester protons but none with the allylic methylene. In the 300 MHz ^{1}H NMR spectrum of *Z*-isomer the benzylidene proton was seen as a singlet at 6.79 ppm. In the ^{1}H-^{1}H NOESY spectrum of *Z*-isomer the benzylidene proton had interaction with allylic $–CH_2$ protons.



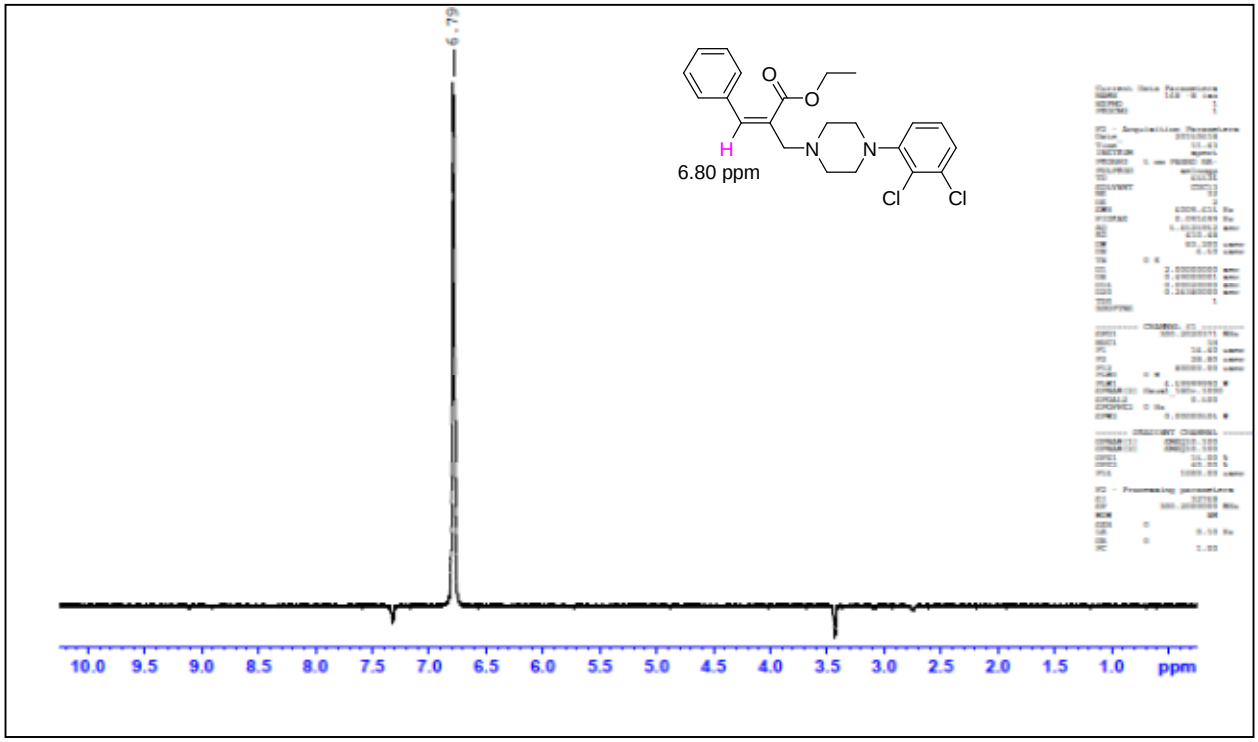
^{1}H NMR Spectra of Ethyl (*E*)-2-((4-(2,3-dichlorophenyl)piperazin-1-yl)methyl)-3-phenylacrylate **(10b)**



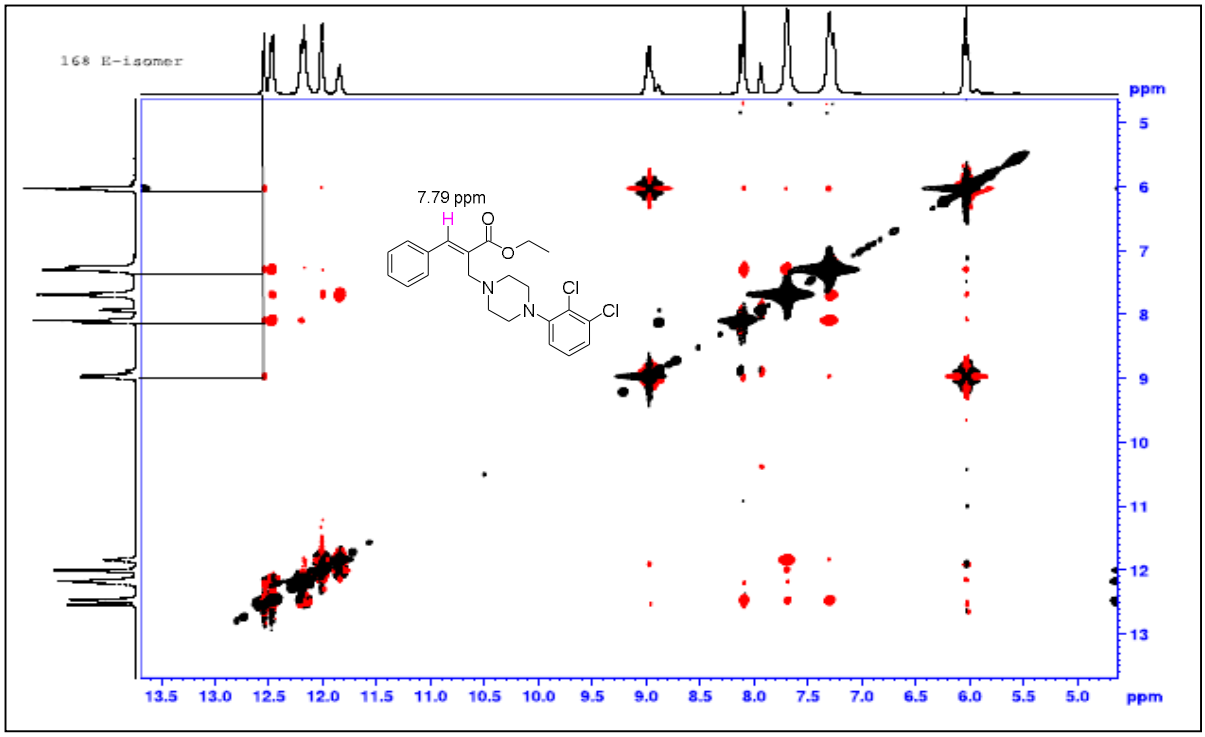
^{1}H NMR Spectra of Ethyl (*E*)-2-((4-(2,3-dichlorophenyl)piperazin-1-yl)methyl)-3-phenylacrylate **(Z-isomer)**



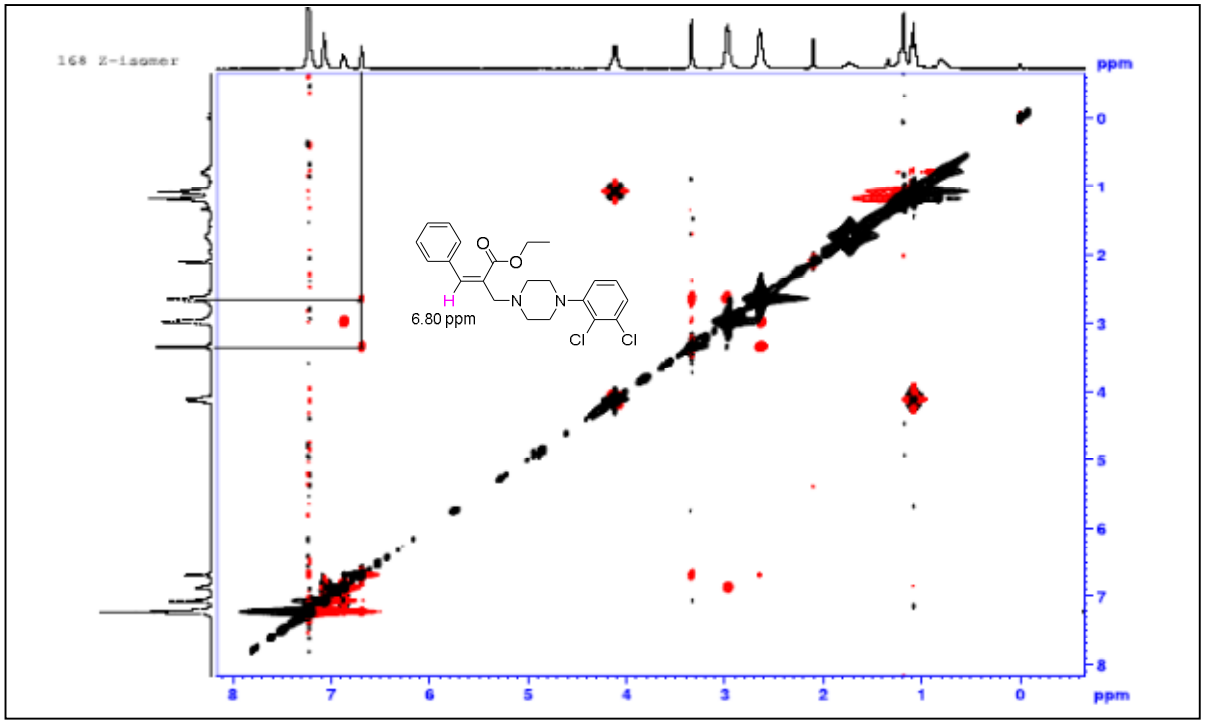
NOE NMR Spectra of Ethyl (*E*)-2-((4-(2,3-dichlorophenyl)piperazin-1-yl)methyl)-3-phenylacrylate **(10b)**



NOE NMR Spectra of Ethyl (*E*)-2-((4-(2,3-dichlorophenyl)piperazin-1-yl)methyl)-3-phenylacrylate **(Z-isomer)**

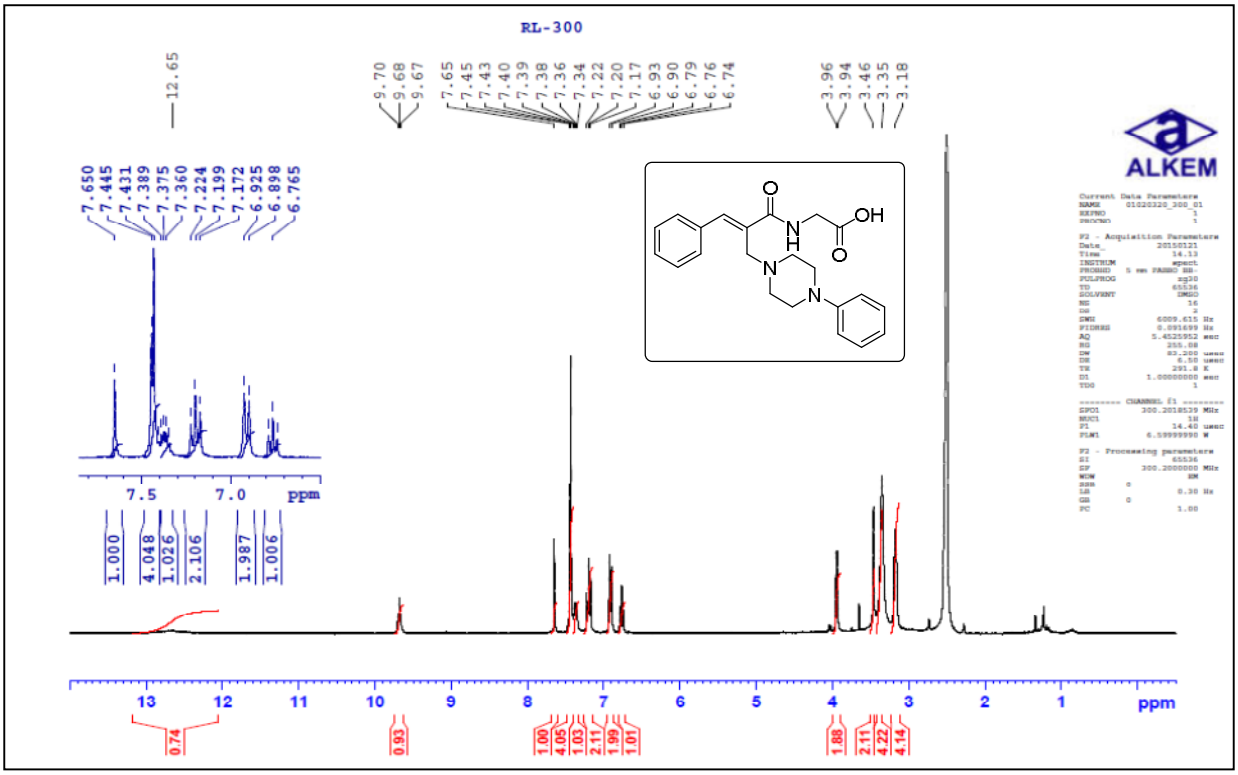


NOESY NMR Spectra of Ethyl (*E*)-2-((4-(2,3-dichlorophenyl)piperazin-1-yl)methyl)-3-phenylacrylate **(10b)**



NOESY NMR Ethyl (*E*)-2-((4-(2,3-dichlorophenyl)piperazin-1-yl)methyl)-3-phenylacrylate **(Z-isomer)**

^{1}H, ^{13}C NMR and Mass Spectra's:



^{1}H NMR spectrum of (*E*)-(3-phenyl-2-((4-phenylpiperazin-1-yl)methyl)acryloyl)Glycine **(13a)**

Sample Information

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Sample ID : RL-300
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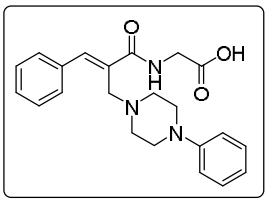
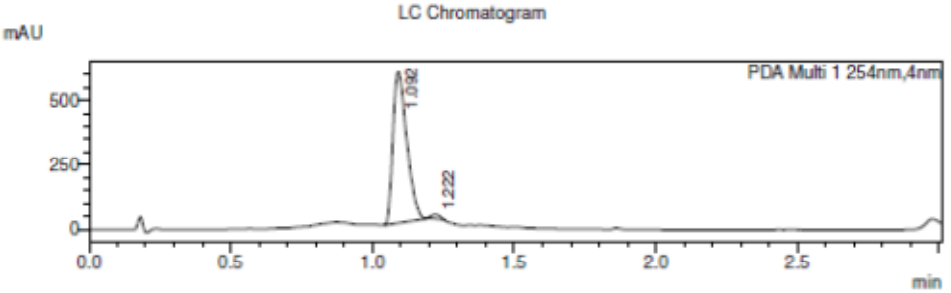
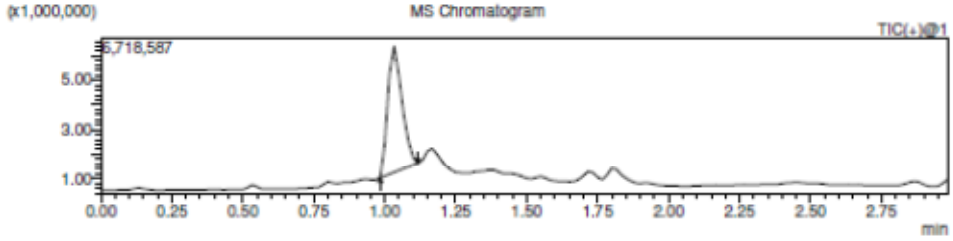
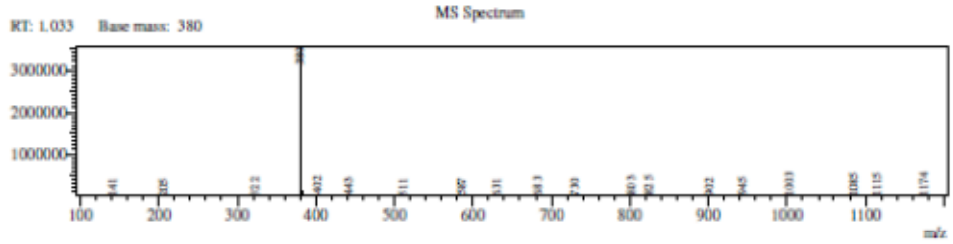
Method Filename : Alkem_LCMS_3min.lcm
Batch Filename : 26062015.lcb
Vial # : 1-7
Injection Volume : 3 uL
Date Acquired : 25-06-2015 15:07:12
Method Info :Mobile Phase : A: 0.1% Formic acid ; B: Acetonitrile
Column : Ascentis Express 50X2.1mm ; 2.7um
%B 5 100 100 5 5
Time 0.2 1.5 2.25 2.75 3



Chromatogram







Peak Table

PDA Ch1 254nm

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1	1.092	98.312
2	1.222	1.688
Total		100.000

MASS Peak Table TIC

Peak#	Ret. Time	Peak m/z
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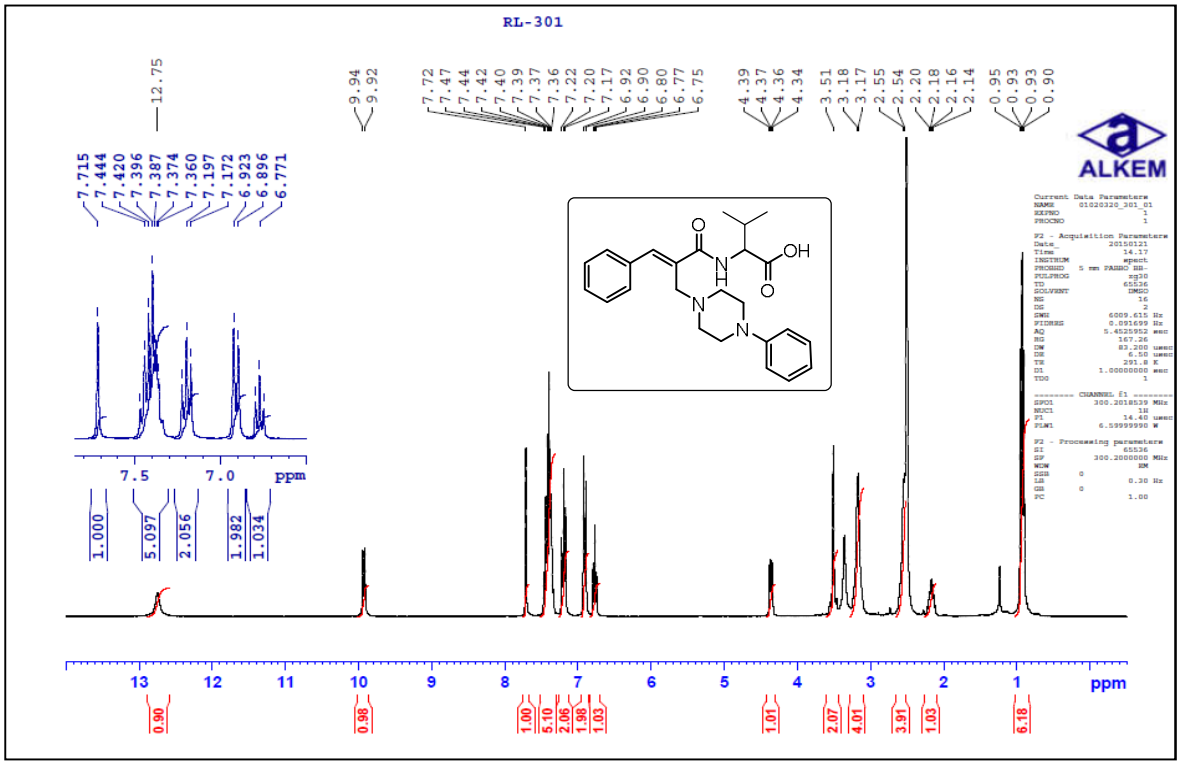
Total		

Mass spectrum of (*E*)-(3-phenyl-2-((4-phenylpiperazin-1-yl)methyl)acryloyl)Glycine **(13a)**



^{1}H NMR spectrum of (*E*)-(3-phenyl-2-((4-phenylpiperazin-1-yl)methyl)acryloyl)valine **(13b)**

Sample Information

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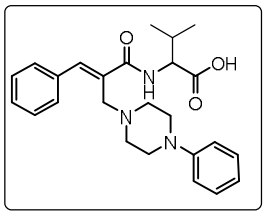
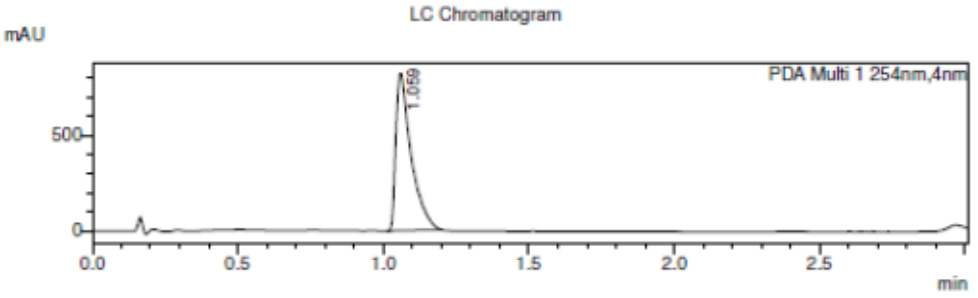
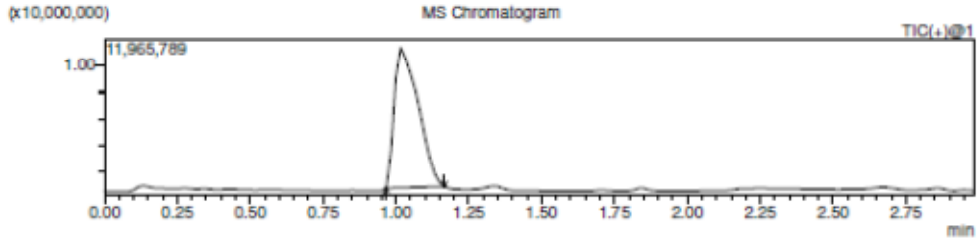
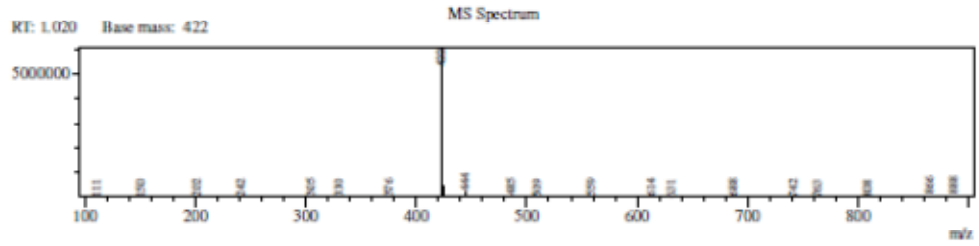
Sample ID : 01020320_301_01
Data Filename : 210115024.lcd
Method Filename : Alkem_LCMS_3min.lcm
Batch Filename : 21012015.lcb
Vial # : 1-20
Injection Volume : 3 uL
Date Acquired : 21-01-2015 15:21:22
Method Info :Mobile Phase : A: 10mM NH4OAC; B: Acetonitrile
Column : Ascentis Express 50X2.1mm ; 2.7um
%B 5 100 100 5 5
Time 0.2 1.5 2.25 2.75 3



Chromatogram







Peak Table

PDA Ch1 254nm

Peak#	Ret. Time	Area%
1	1.059	100.000
Total		100.000

MASS Peak Table TIC

Peak#	Ret. Time	Peak m/z
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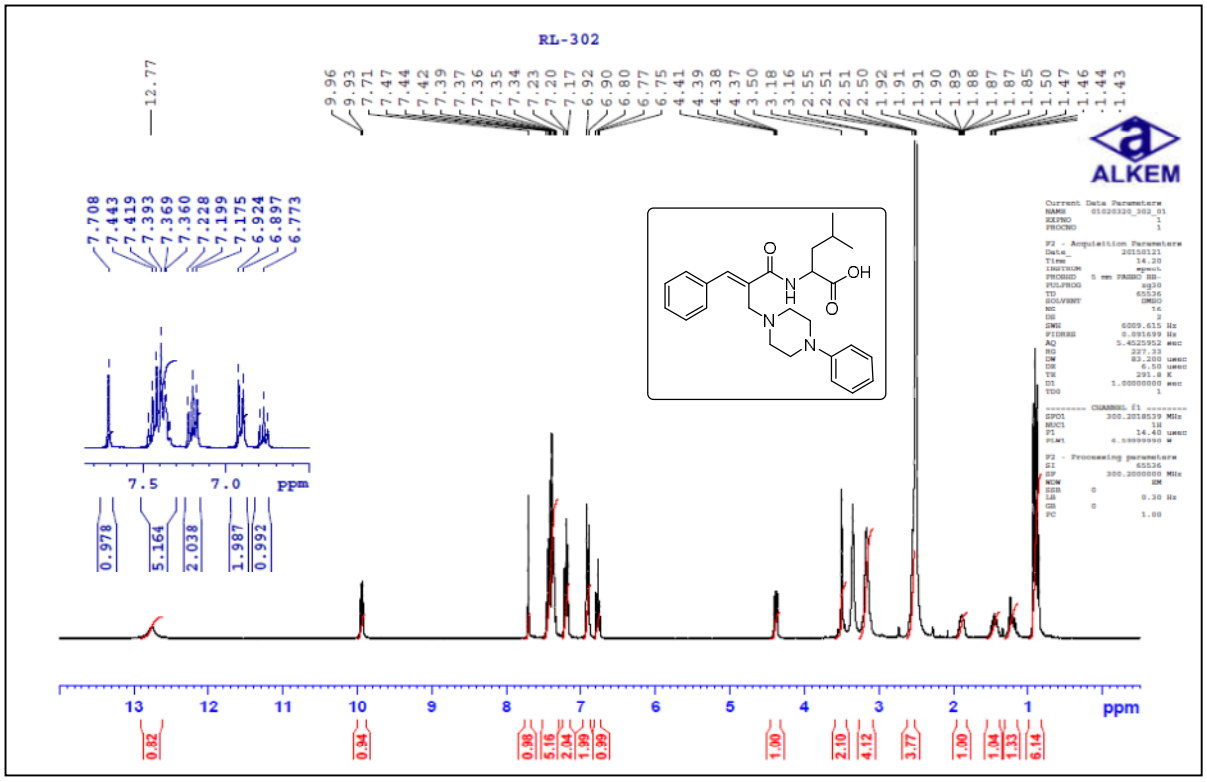
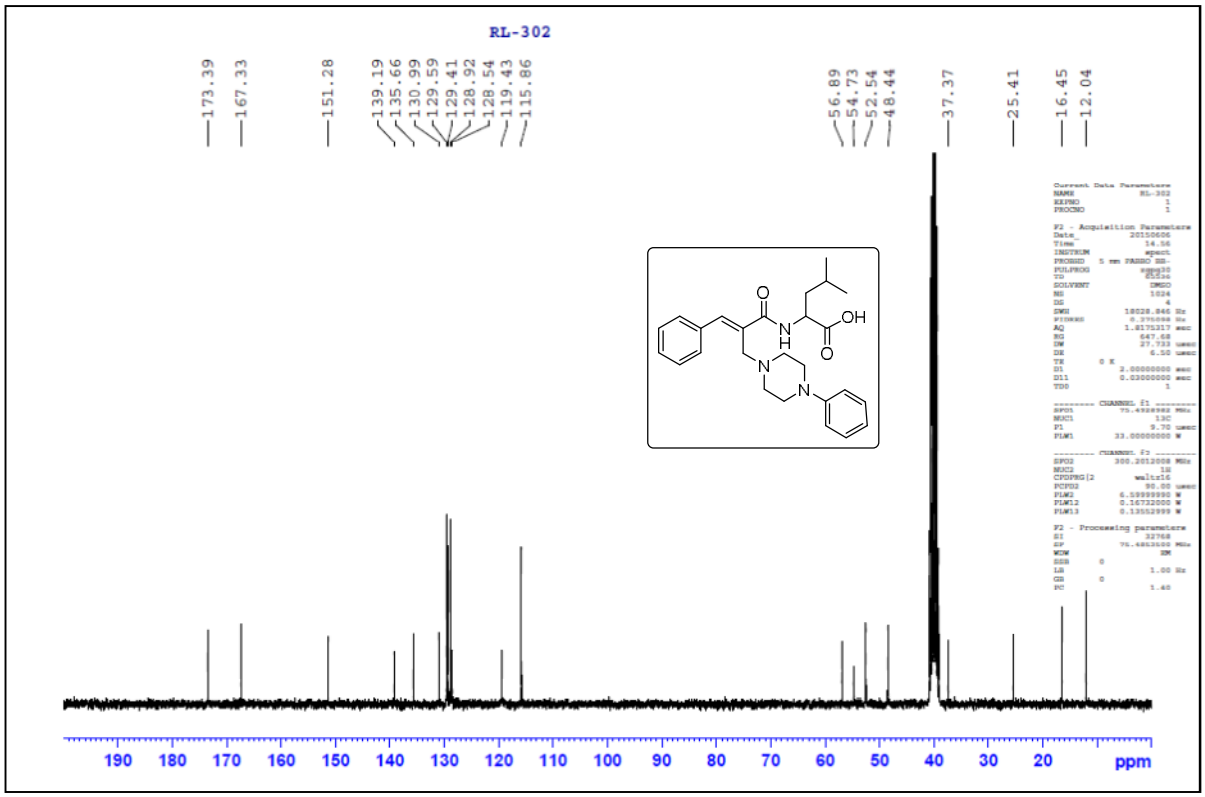
Total		

Mass spectrum (*E*)-(3-phenyl-2-((4-phenylpiperazin-1-yl)methyl)acryloyl)valine **(13b)**





^{1}H and ^{13}C NMR spectra of (*E*)-(3-phenyl-2-((4-phenylpiperazin-1-yl)methyl)acryloyl)leucine **(13c)**

Sample Information

Sample Name	: 01020320_302_01
Sample ID	: 01020320_302_01
Data Filename	: 210115025.lcd
Method Filename	: Alkem_LCMS_3min.lcm
Batch Filename	: 21012015.lcb
Vial #	: 1-21
Injection Volume	: 3 uL
Date Acquired	: 21-01-2015 15:25:01
Method Info	:Mobile Phase : A: 10mM NH4OAC; B: Acetonitrile
	Column : Ascentis Express 50X2.1mm ; 2.7um
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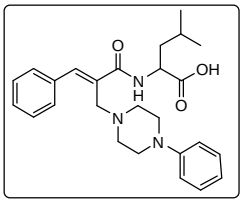
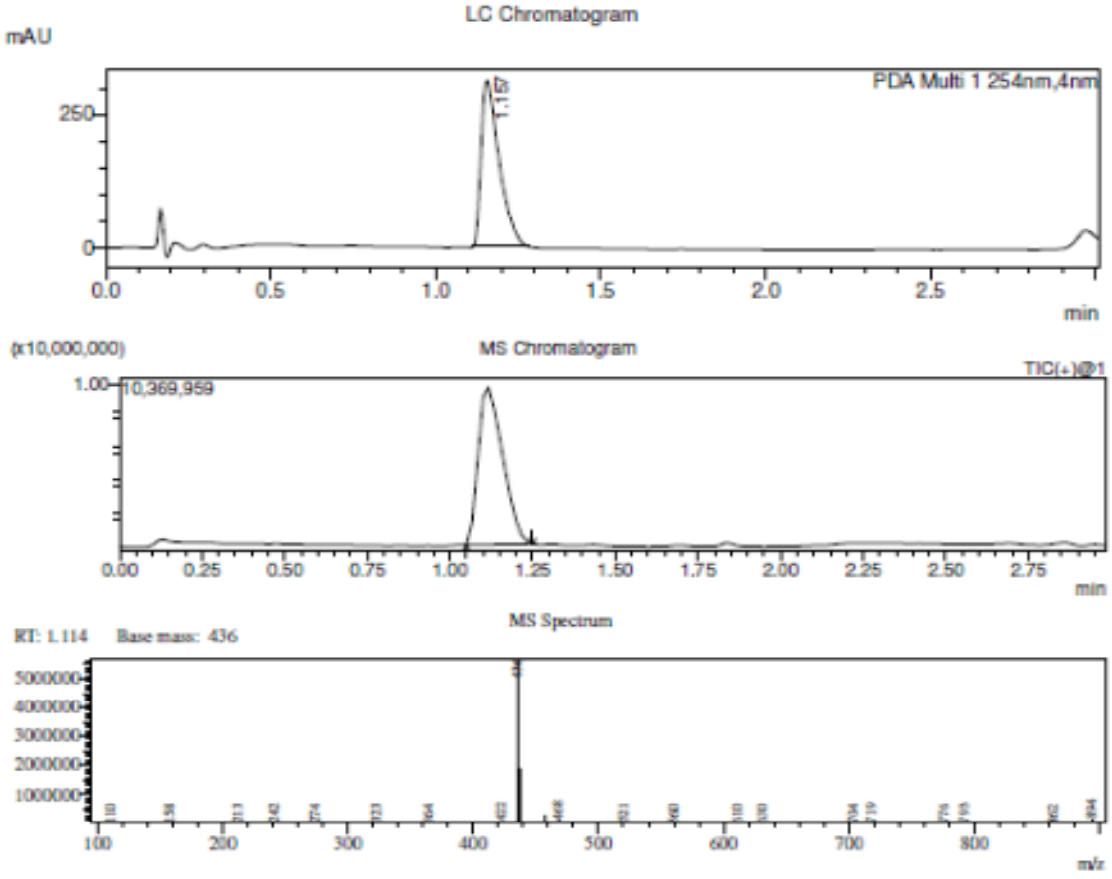
	Time 0.2 1.5 2.25 2.75 3



Chromatogram



Peak Table

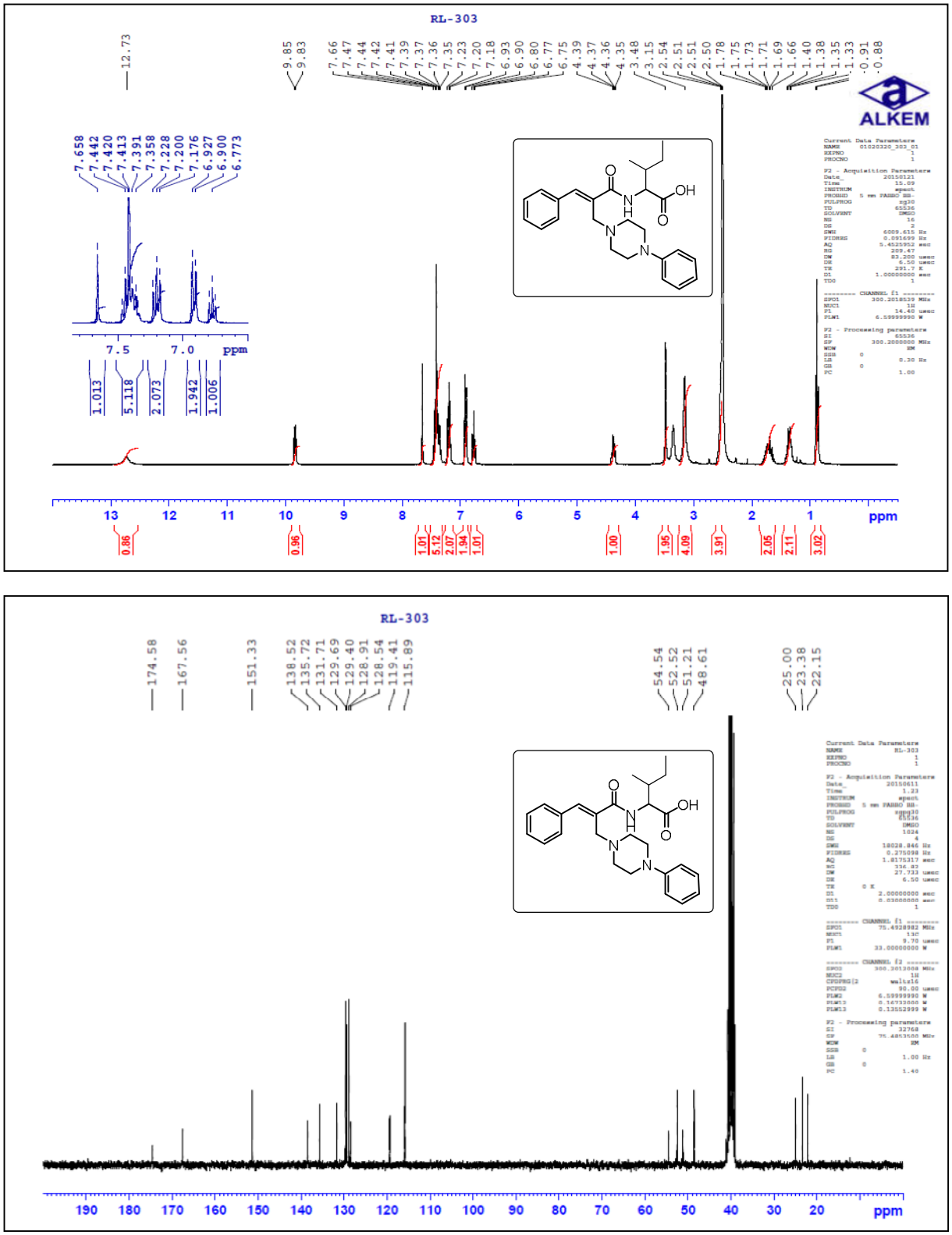
PDA Ch1 254nm

Peak#	Ret. Time	Area%
1	1.157	100.000
Total		100.000

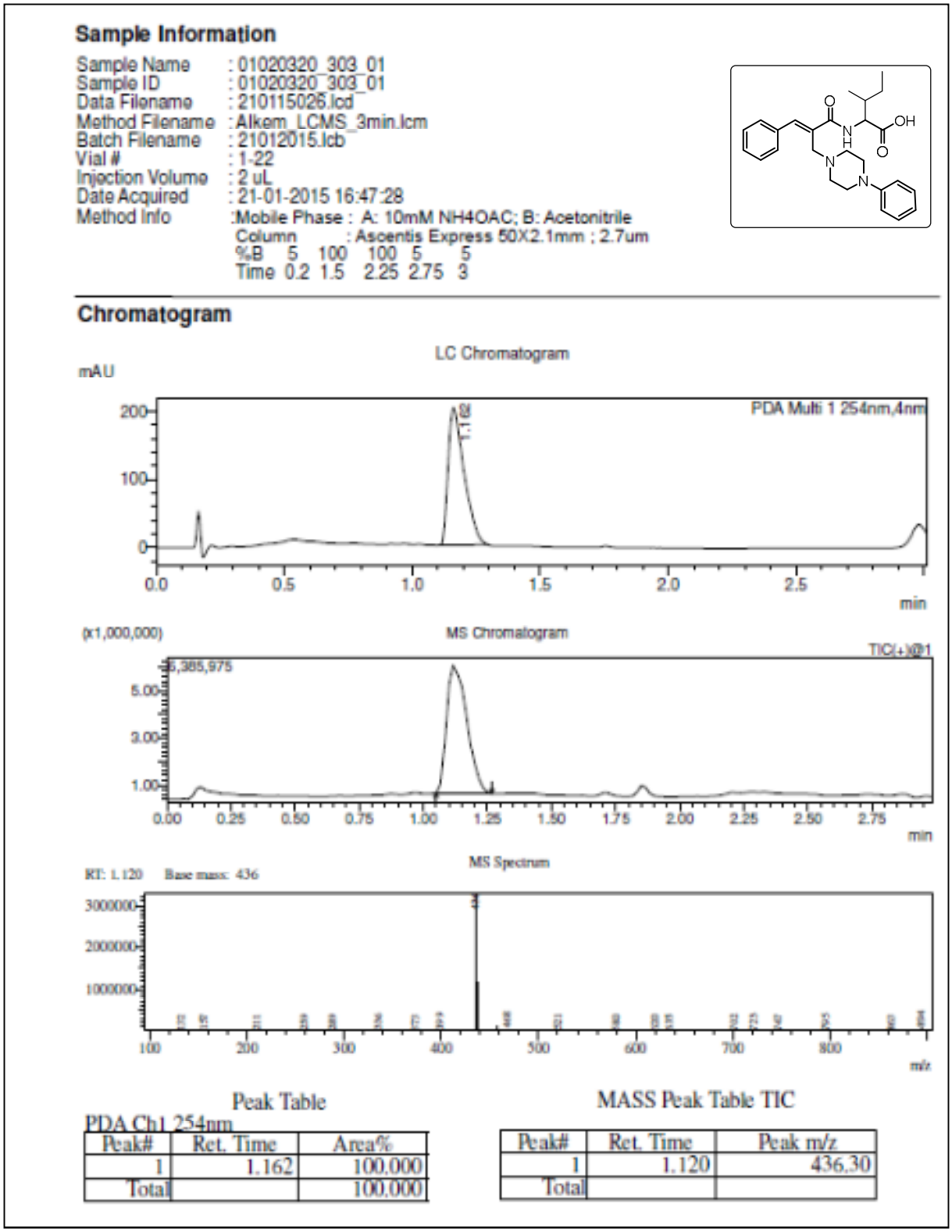
MASS Peak Table TIC

Peak#	Ret. Time	Peak m/z
1	1.114	436.25
Total		

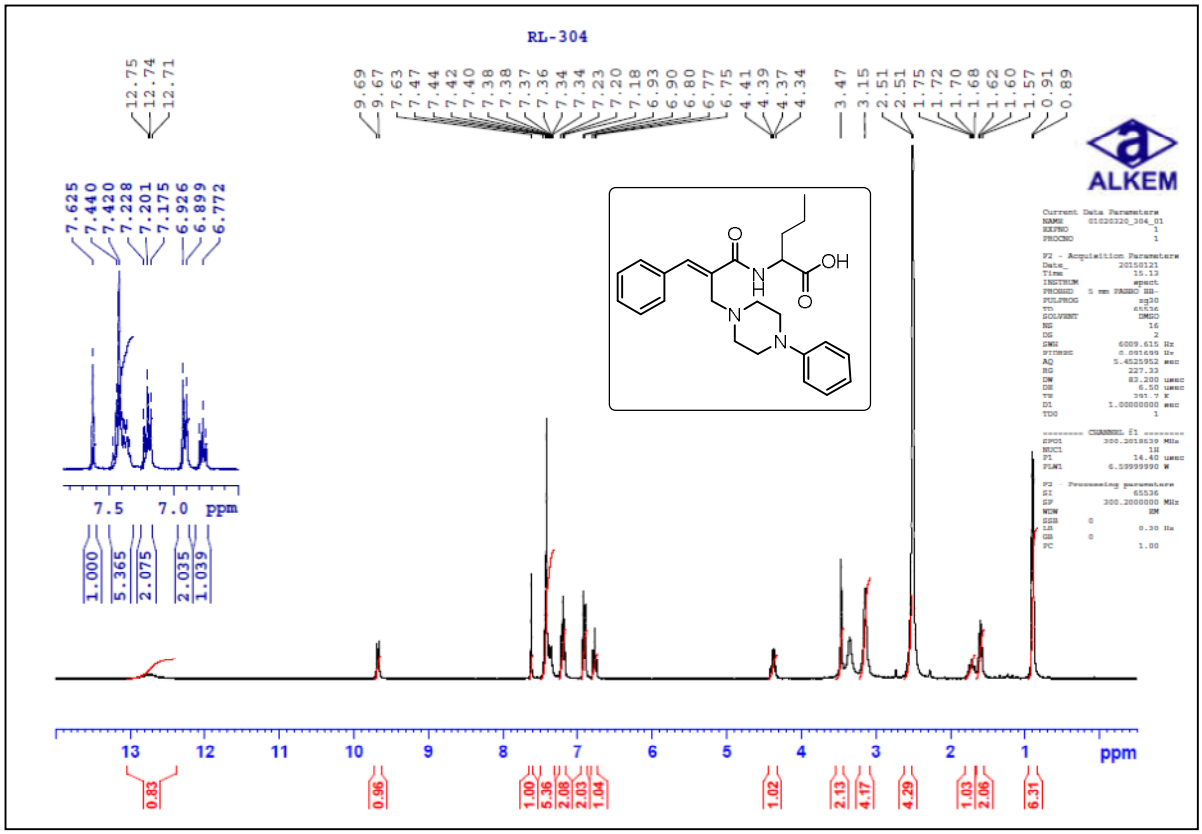
Mass spectrum of (*E*)-(3-phenyl-2-((4-phenylpiperazin-1-yl)methyl)acryloyl)leucine **(13c)**

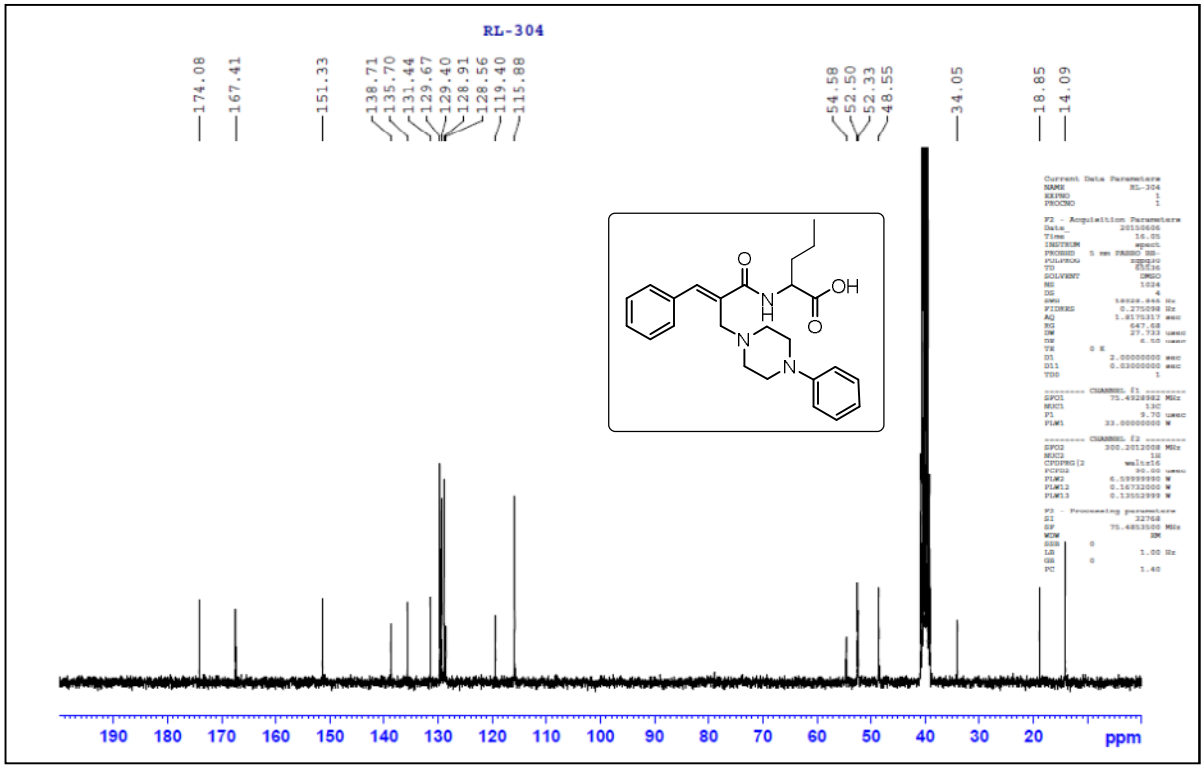


[1]H and [13]C NMR spectra of (*E*)-3-methyl-2-(3-phenyl-2-((4-phenylpiperazin-1-yl)methyl) acrylamido)pentanoic acid **(13d)**



Mass spectra of (*E*)-3-methyl-2-(3-phenyl-2-((4-phenylpiperazin-1-yl)methyl) acrylamido) pentanoic acid **(13d)**





^{1}H and ^{13}C NMR spectra of (*E*)-2-(3-phenyl-2-((4-phenylpiperazin-1-yl)methyl)acrylamido) pentanoic acid **(13e)**

Sample Information

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Sample ID : 01020320_304_01
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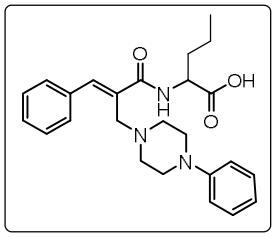
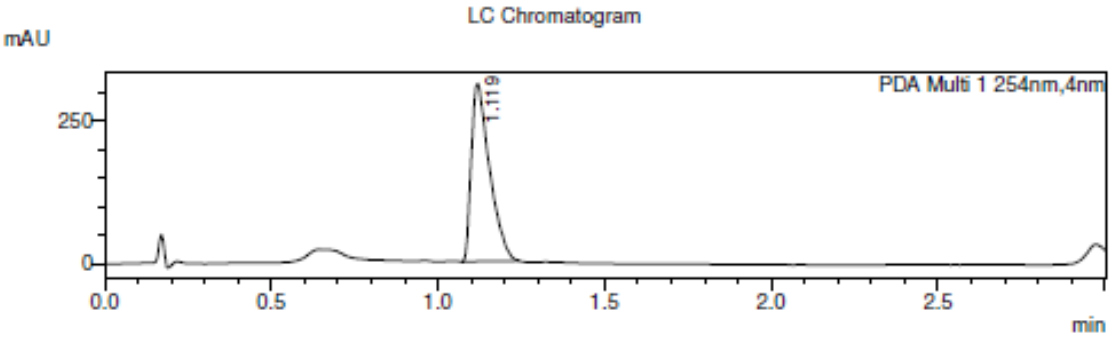
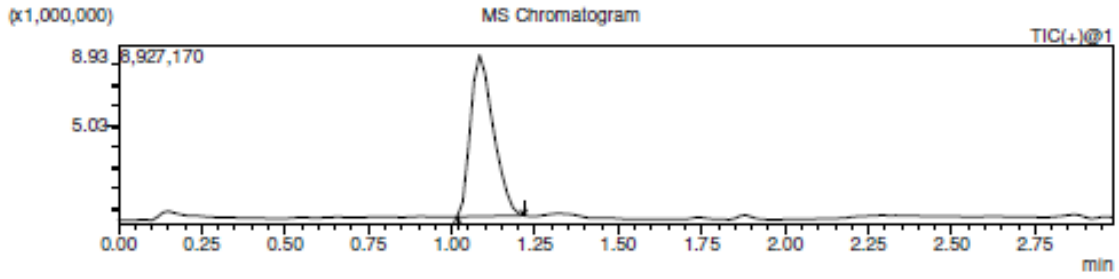
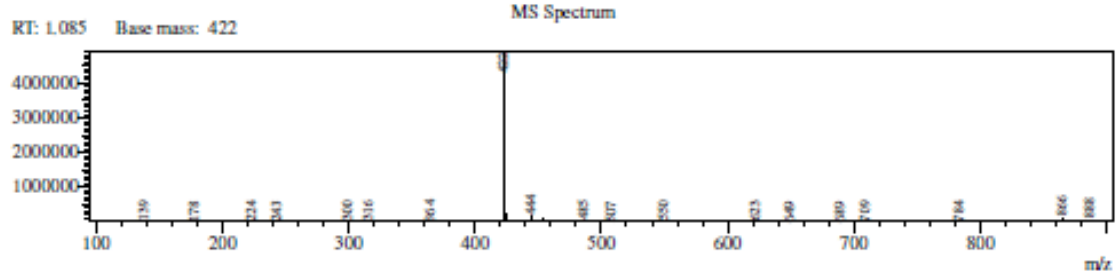
Batch Filename : 21012015.lcb
Vial # : 1-23
Injection Volume : 2 uL
Date Acquired : 21-01-2015 16:54:16
Method Info :Mobile Phase : A: 10mM NH4OAC; B: Acetonitrile
Column : Ascentis Express 50X2.1mm ; 2.7um
%B 5 100 100 5 5
Time 0.2 1.5 2.25 2.75 3



Chromatogram







Peak Table

PDA Ch1 254nm

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Total		100.000

MASS Peak Table TIC

Peak#	Ret. Time	Peak m/z
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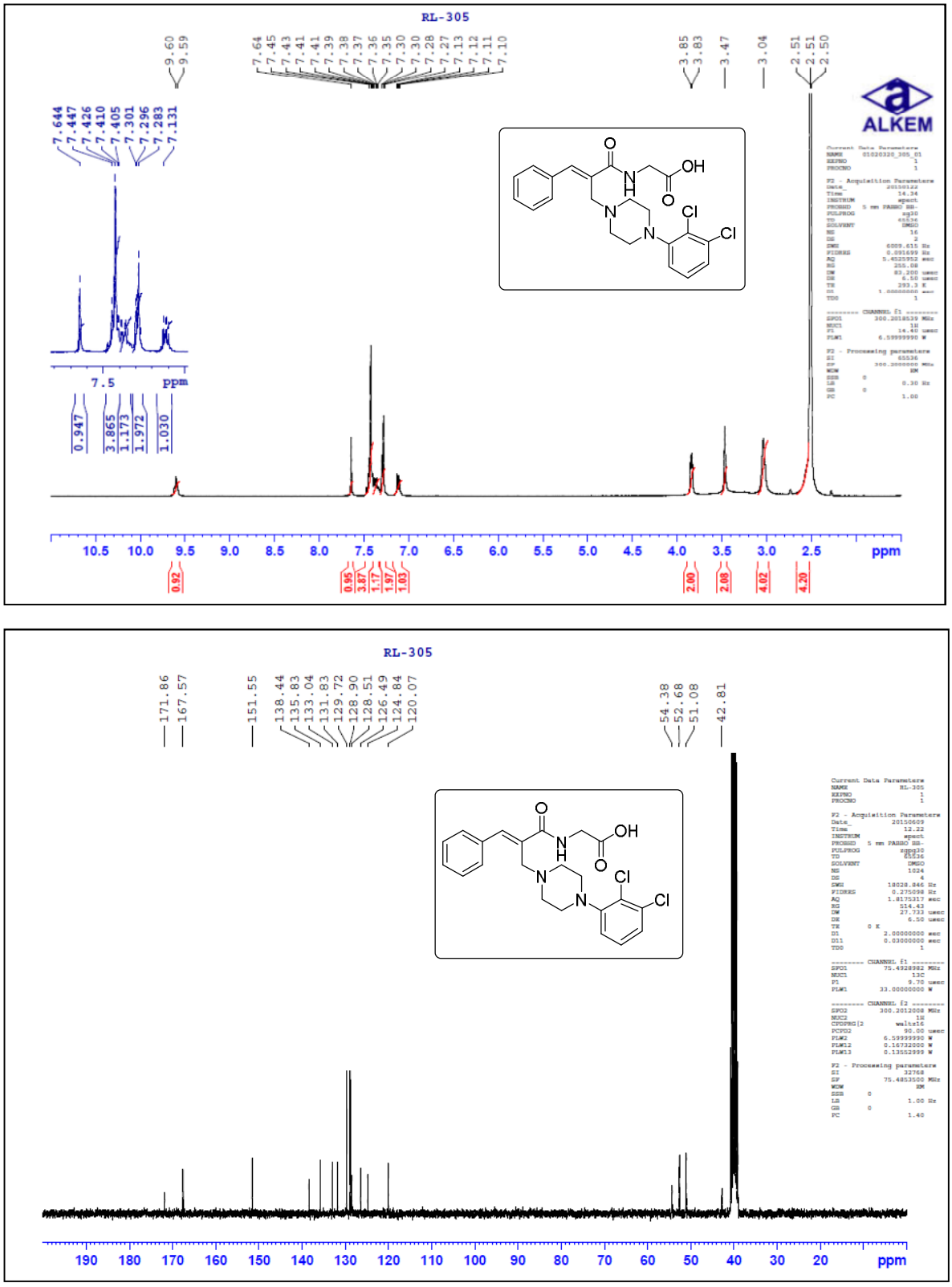
Total		

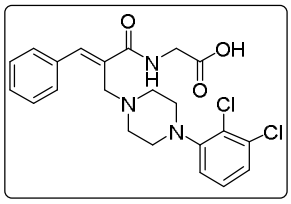
Mass spectra of (*E*)-2-(3-phenyl-2-((4-phenylpiperazin-1-yl)methyl)acrylamido) pentanoicacid **(13e)**



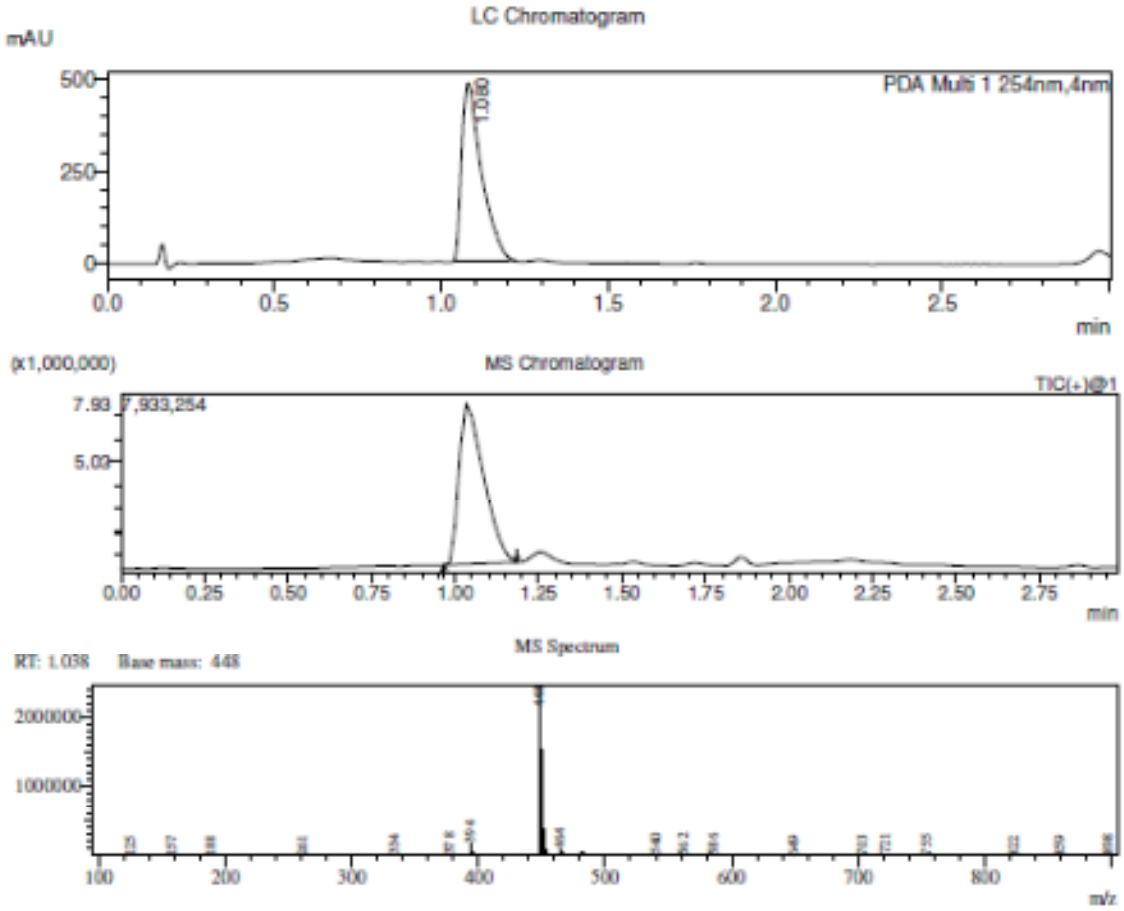
^{1}H and ^{13}C NMR spectra of (*E*)-(2-((4-(2,3-dichlorophenyl)piperazin-1-yl)methyl)-3-phenylacryloyl)glycine **(13f)**

Sample Information

Sample Name	: 01020320_305_01
Sample ID	: 01020320_305_01
Data Filename	: 230115025.lcd
Method Filename	: Alkem_LCMS_3min.lcm
Batch Filename	: 23012015.lcb
Vial #	: 1-21
Injection Volume	: 3 uL
Date Acquired	: 22-01-2015 16:52:08
Method Info	:Mobile Phase : A: 10mM NH4OAC; B: Acetonitrile
	Column : Ascentis Express 50X2.1mm ; 2.7um
	%B 5 100 100 5 5
	Time 0.2 1.5 2.25 2.75 3



Chromatogram



Peak Table

PDA Ch1 254nm

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Total		100.000

MASS Peak Table TIC

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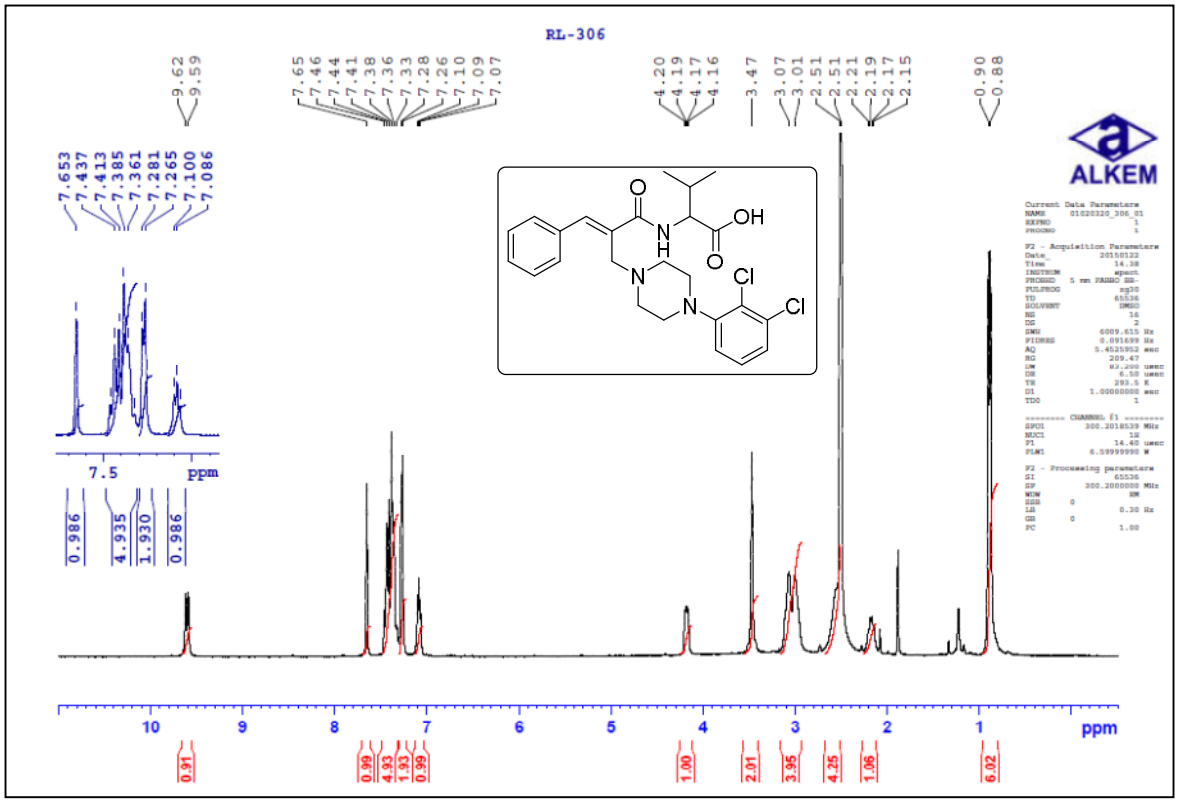
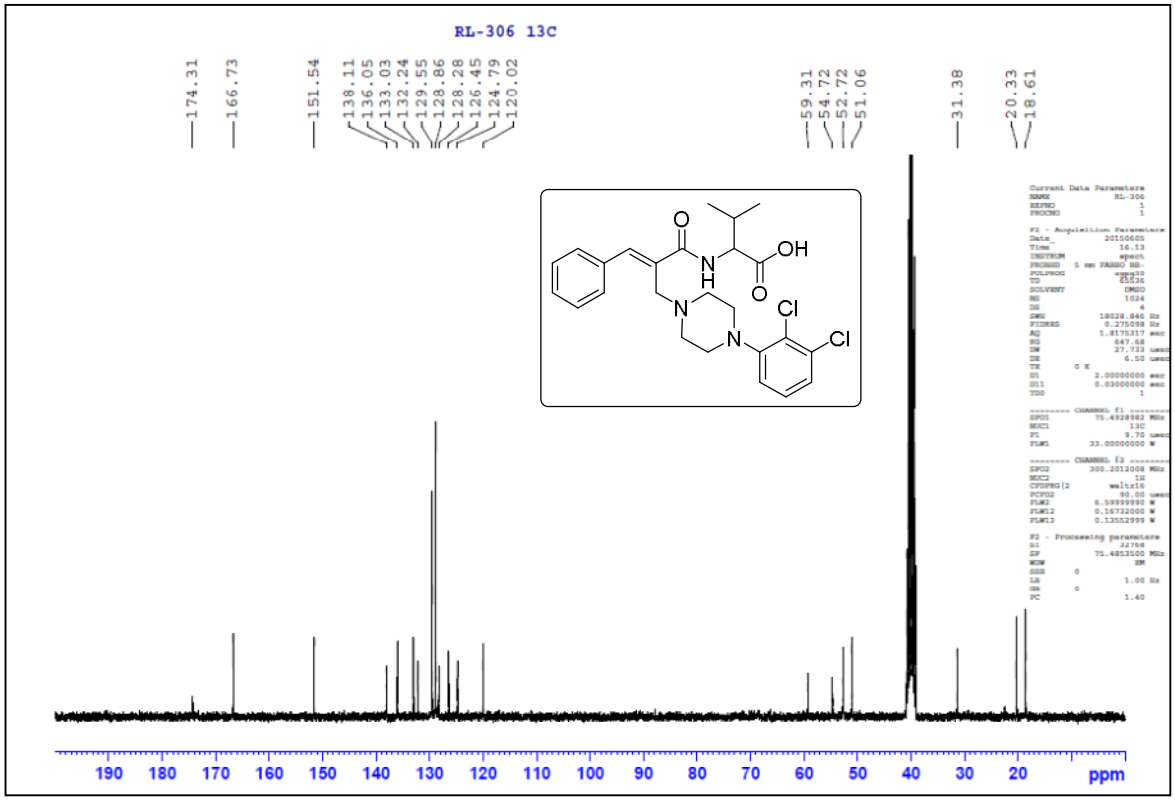
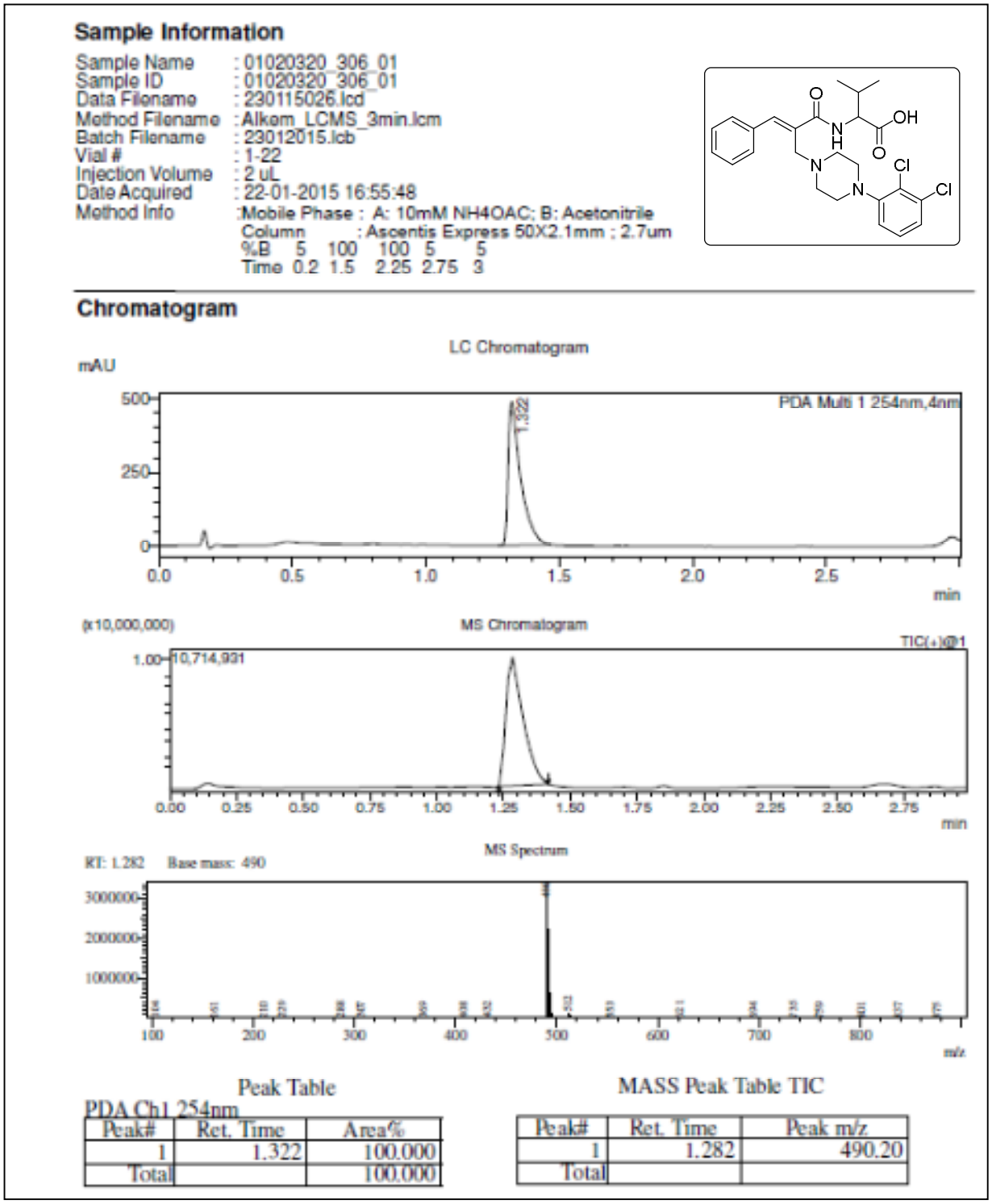
Total		

Mass spectra of (*E*)-(2-((4-(2,3-dichlorophenyl)piperazin-1-yl)methyl)-3-phenylacryloyl)glycine **(13f)**

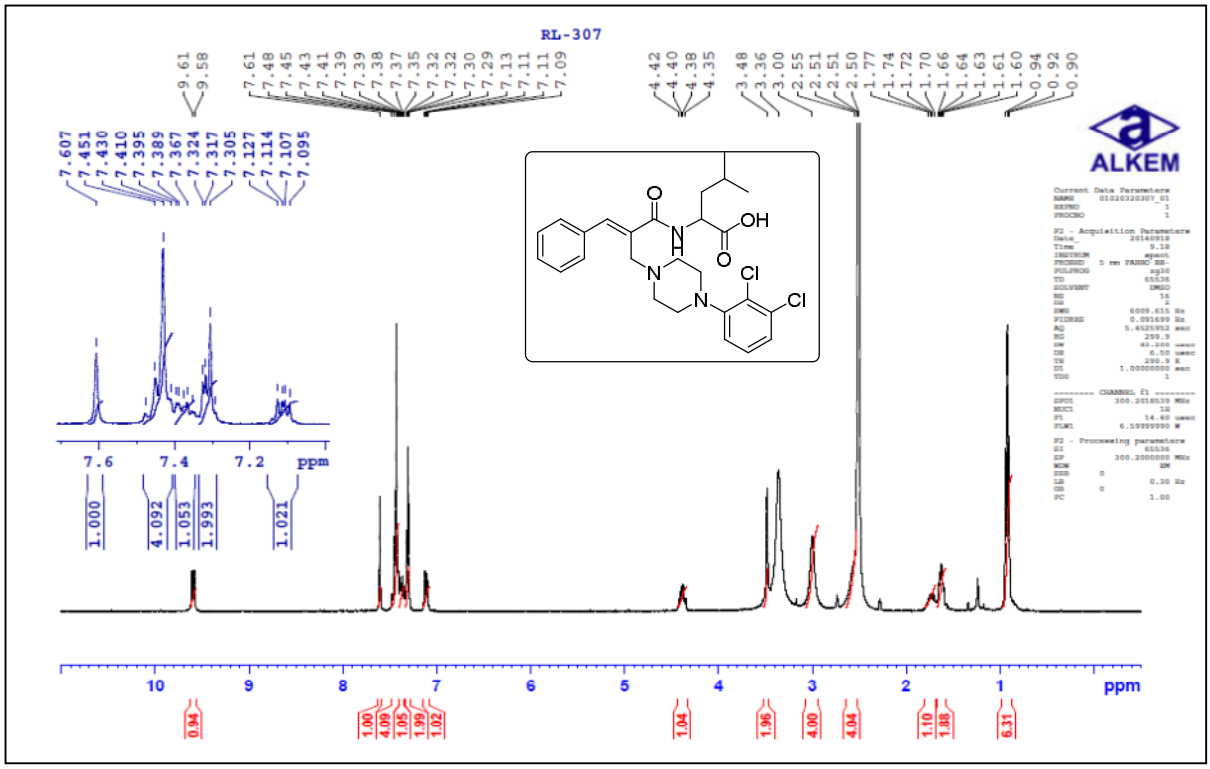


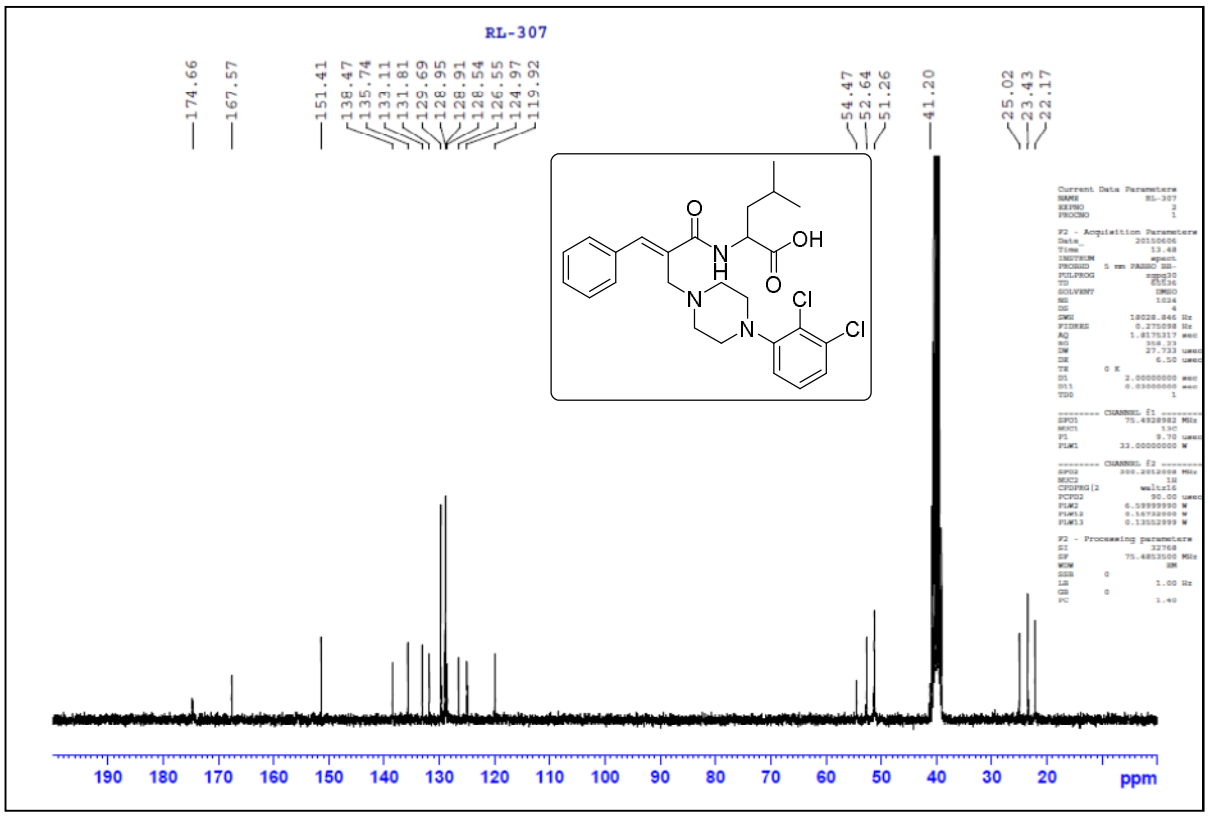


^{1}H and ^{13}C NMR spectra of (*E*)-(2-((4-(2,3-dichlorophenyl)piperazin-1-yl)methyl)-3-phenylacryloyl)valine **(13g)**

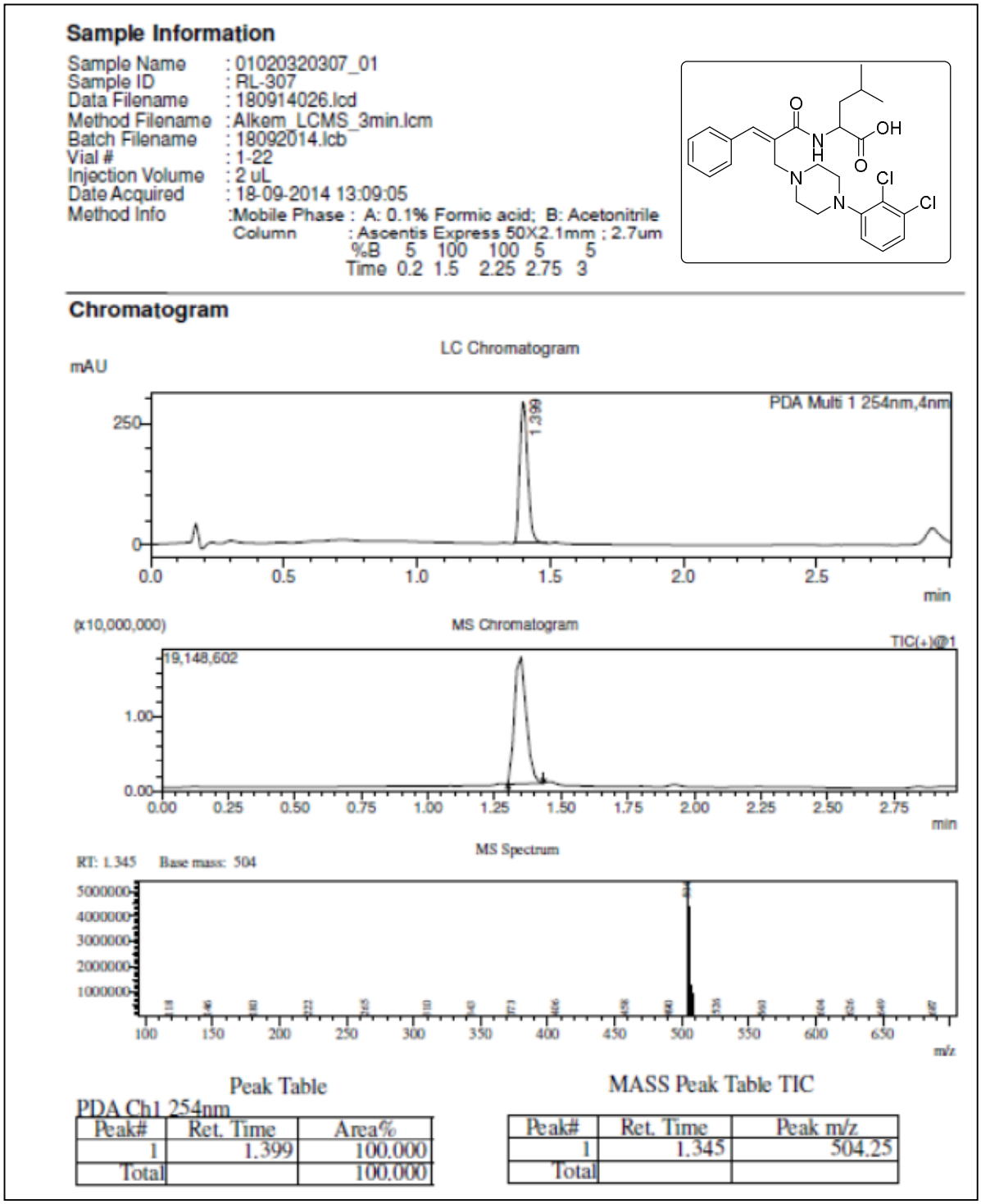


Mass spectra of (*E*)-(2-((4-(2,3-dichlorophenyl)piperazin-1-yl)methyl)-3-phenylacryloyl)valine **(13g)**

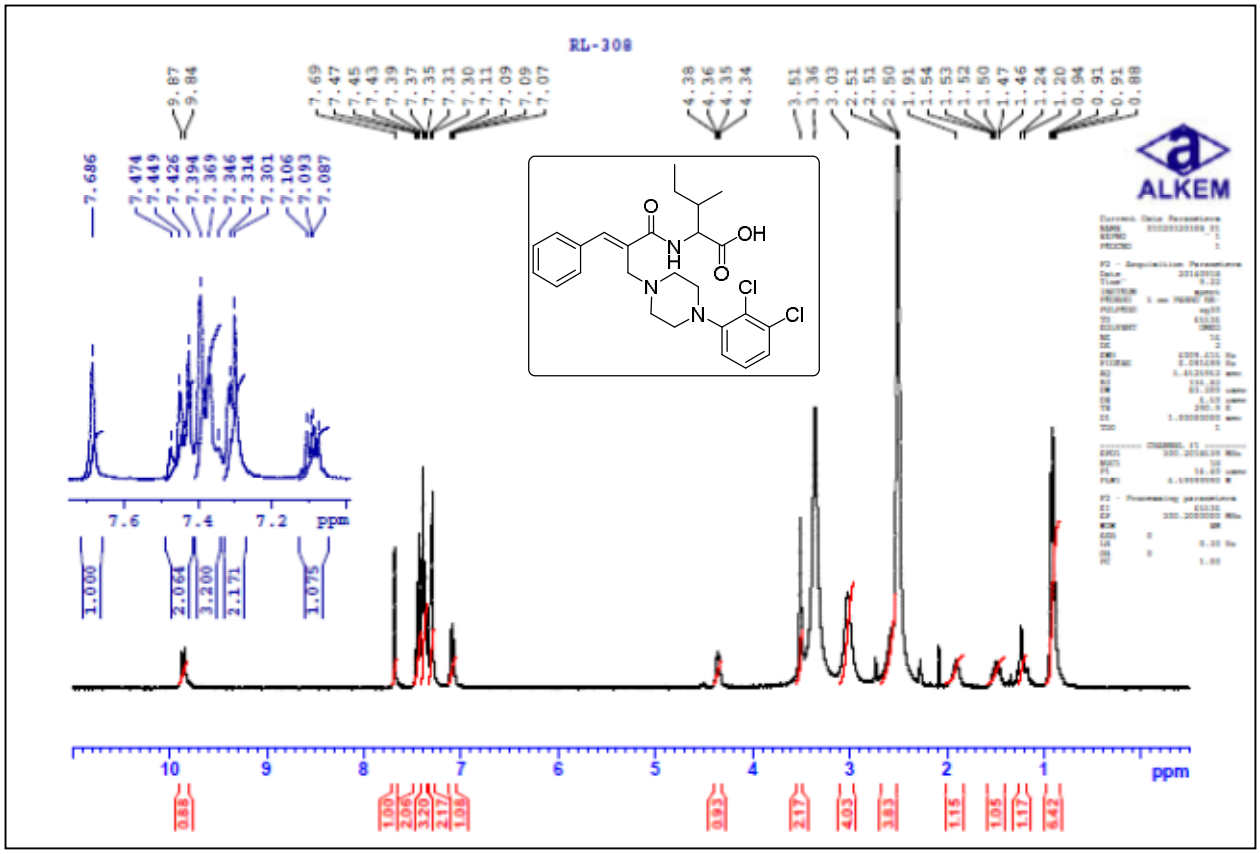




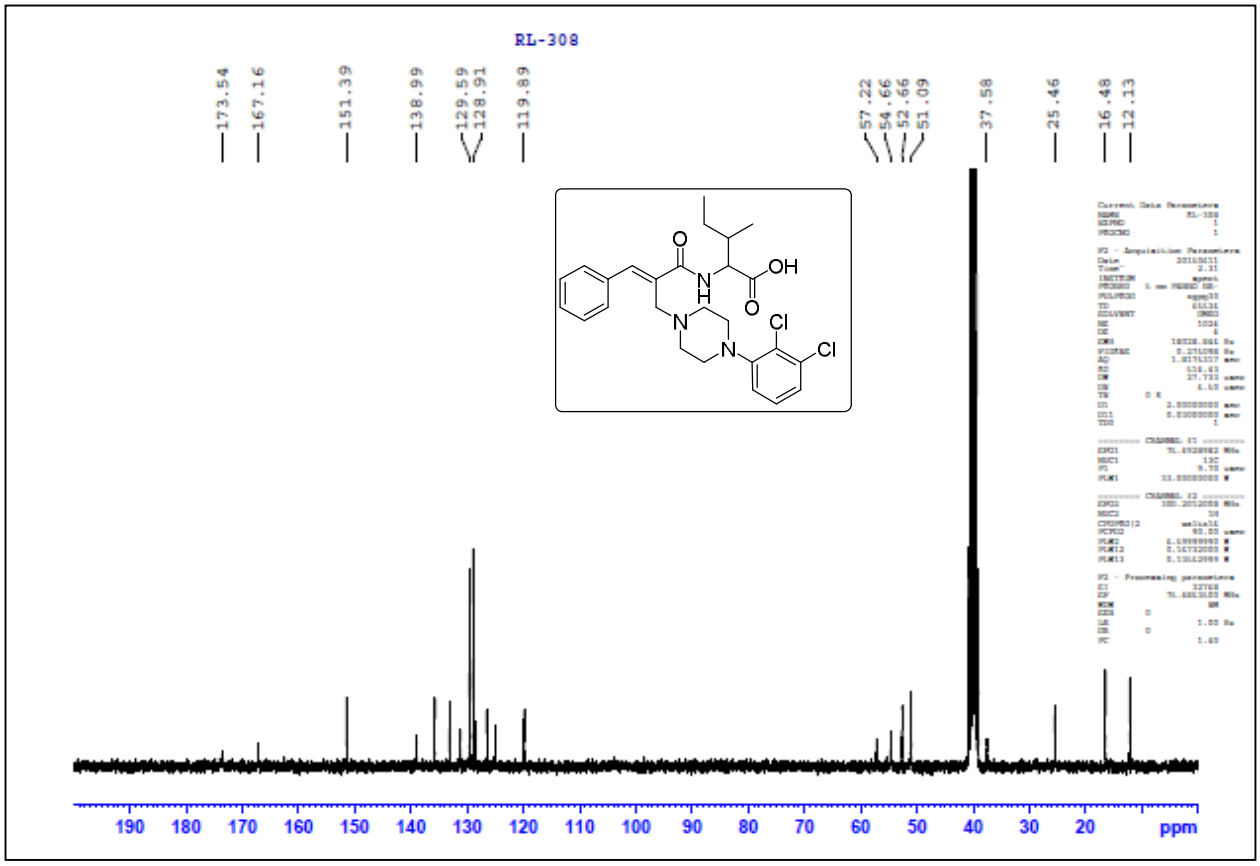
^{1}H and ^{13}C NMR spectra of (*E*)-(2-((4-(2,3-dichlorophenyl)piperazin-1-yl)methyl)-3-phenylacryloyl)leucine **(13h)**



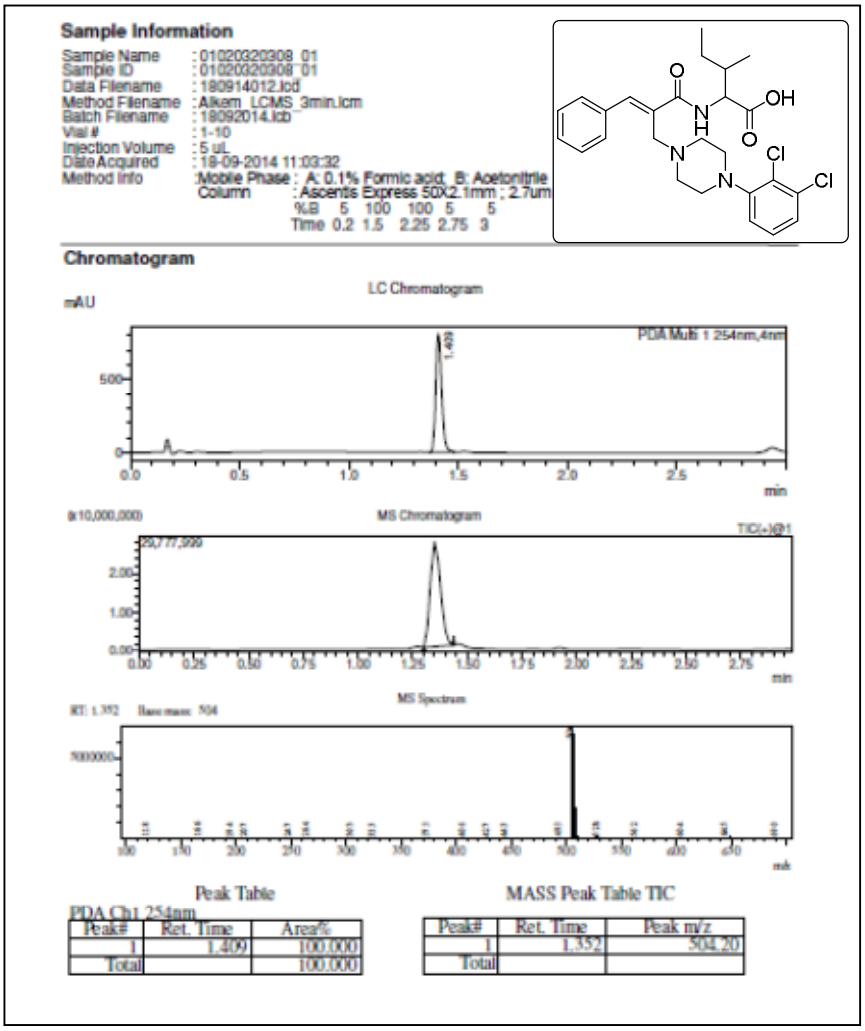
Mass spectra of (*E*)-(2-((4-(2,3-dichlorophenyl)piperazin-1-yl)methyl)-3-phenylacryloyl)leucine **(13h)**



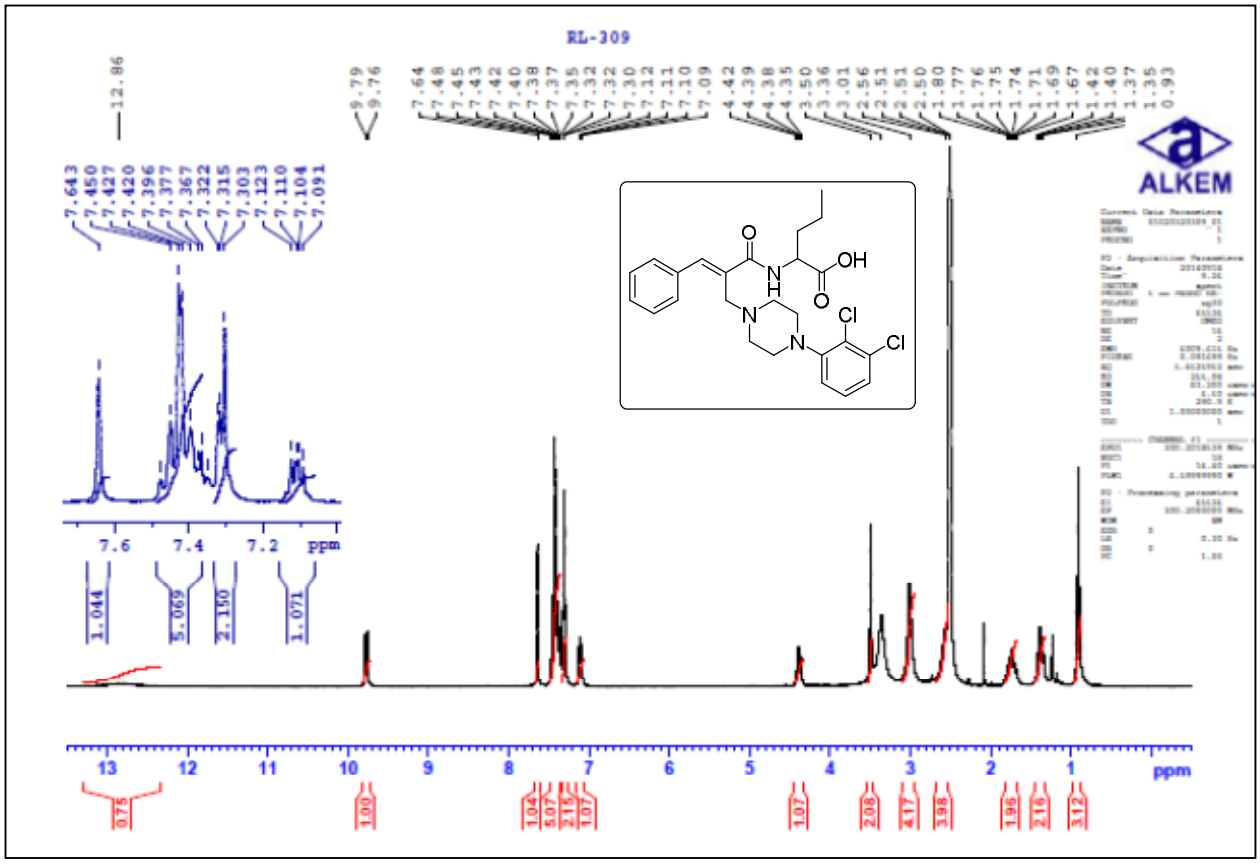
^{1}H NMR spectra of (*E*)-2-(2-((4-(2,3-dichlorophenyl)piperazin-1-yl)methyl)-3-phenylacrylamido)-3-methyl pentanoicacid **(13i)**



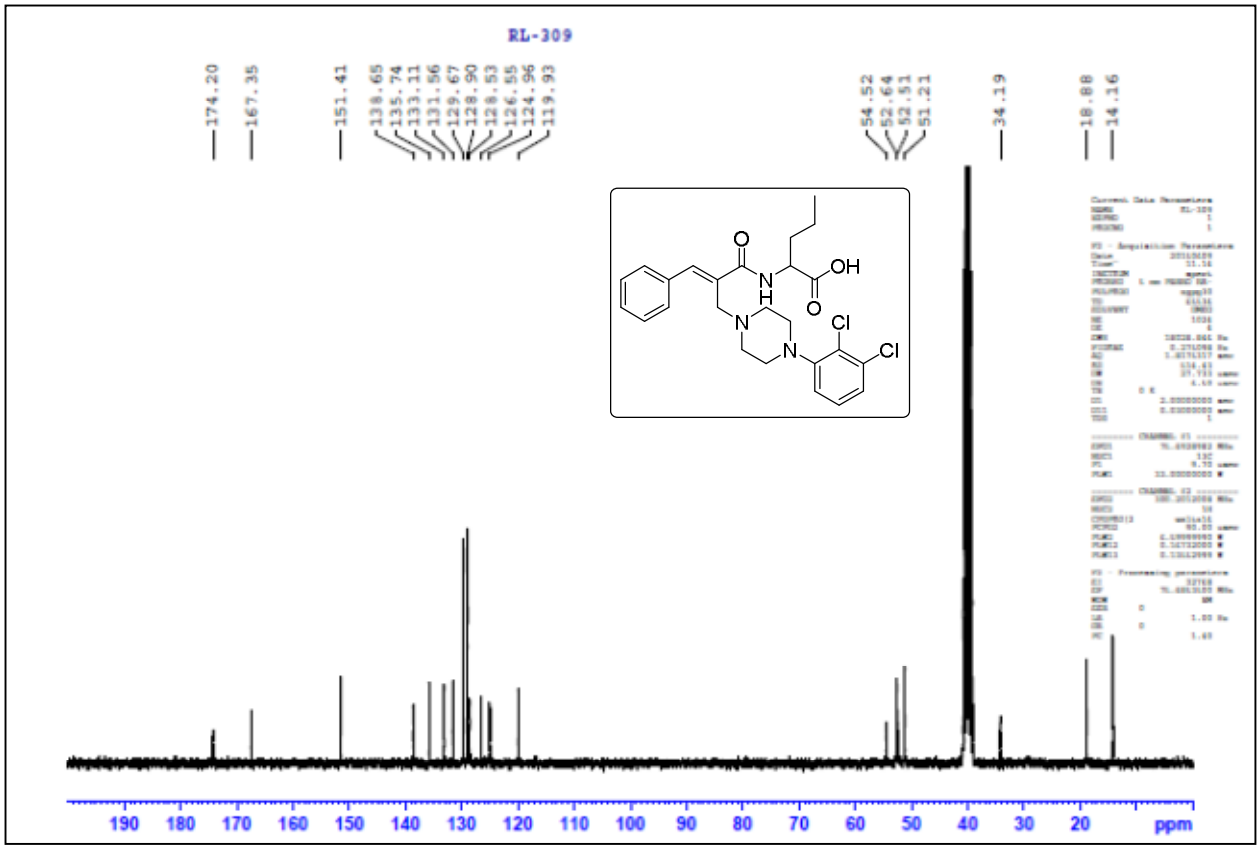
^{13}C NMR spectra of (*E*)-2-(2-((4-(2,3-dichlorophenyl)piperazin-1-yl)methyl)-3-phenylacrylamido)-3-methyl pentanoicacid **(13i)**



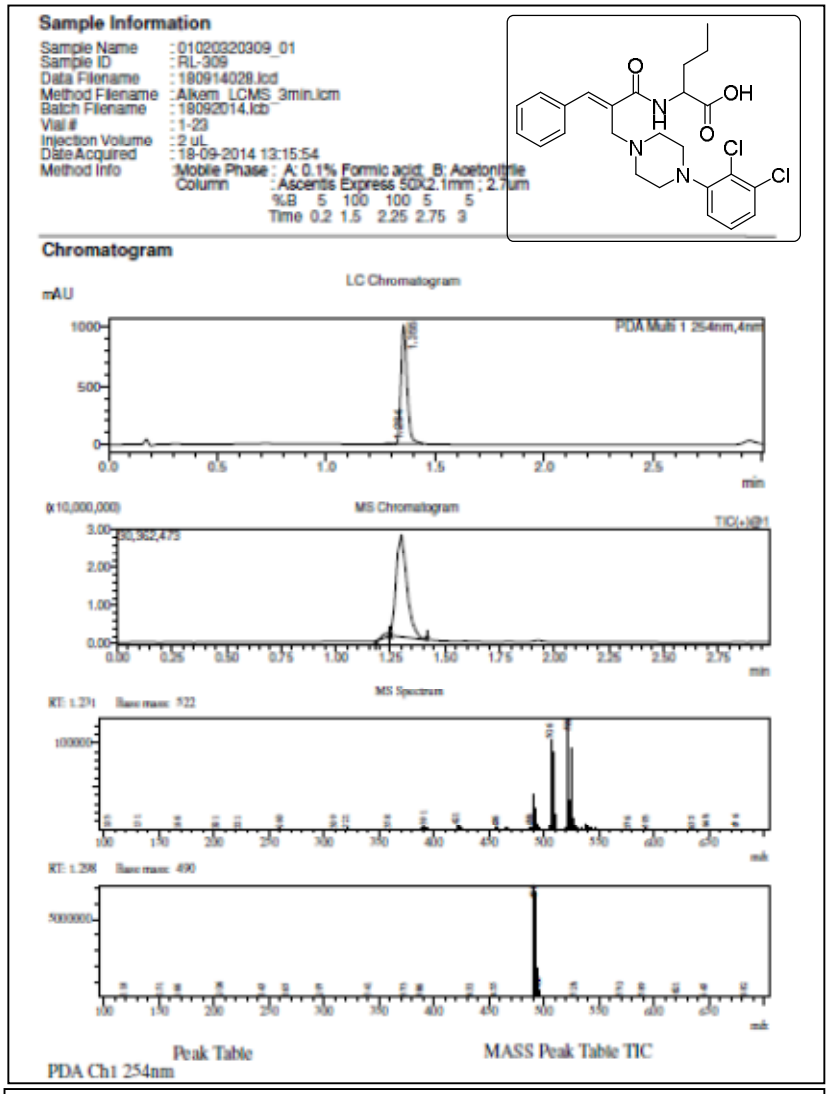
Mass spectra of (*E*)-2-(2-((4-(2,3-dichlorophenyl)piperazin-1-yl)methyl)-3-phenylacrylamido)-3-methyl pentanoicacid **(13i)**



^{1}H NMR spectra of (*E*)-2-(2-((4-(2,3-dichlorophenyl)piperazin-1-yl)methyl)-3-phenylacrylamido) pentanoic acid **(13j)**



^{13}C NMR spectra of (*E*)-2-(2-((4-(2,3-dichlorophenyl)piperazin-1-yl)methyl)-3-phenylacrylamido) pentanoic acid **(13j)**



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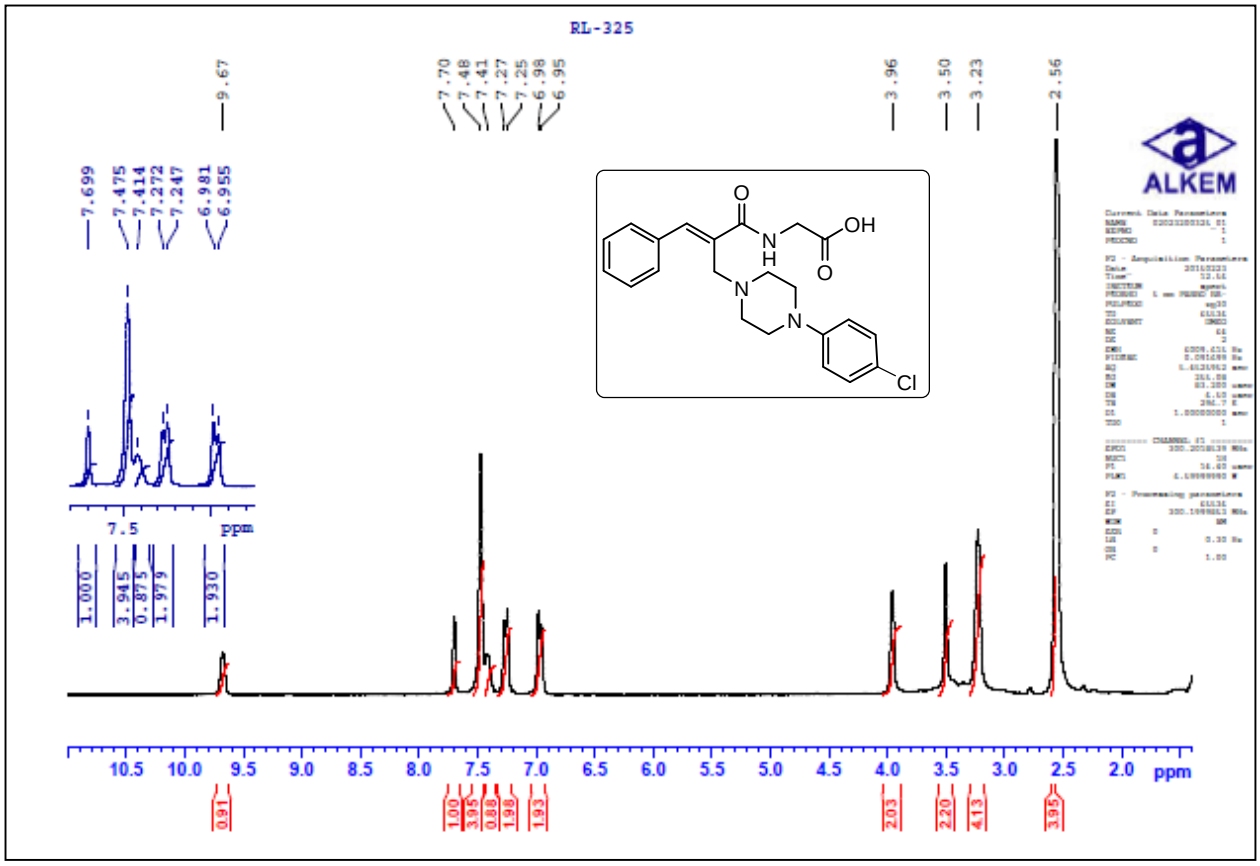
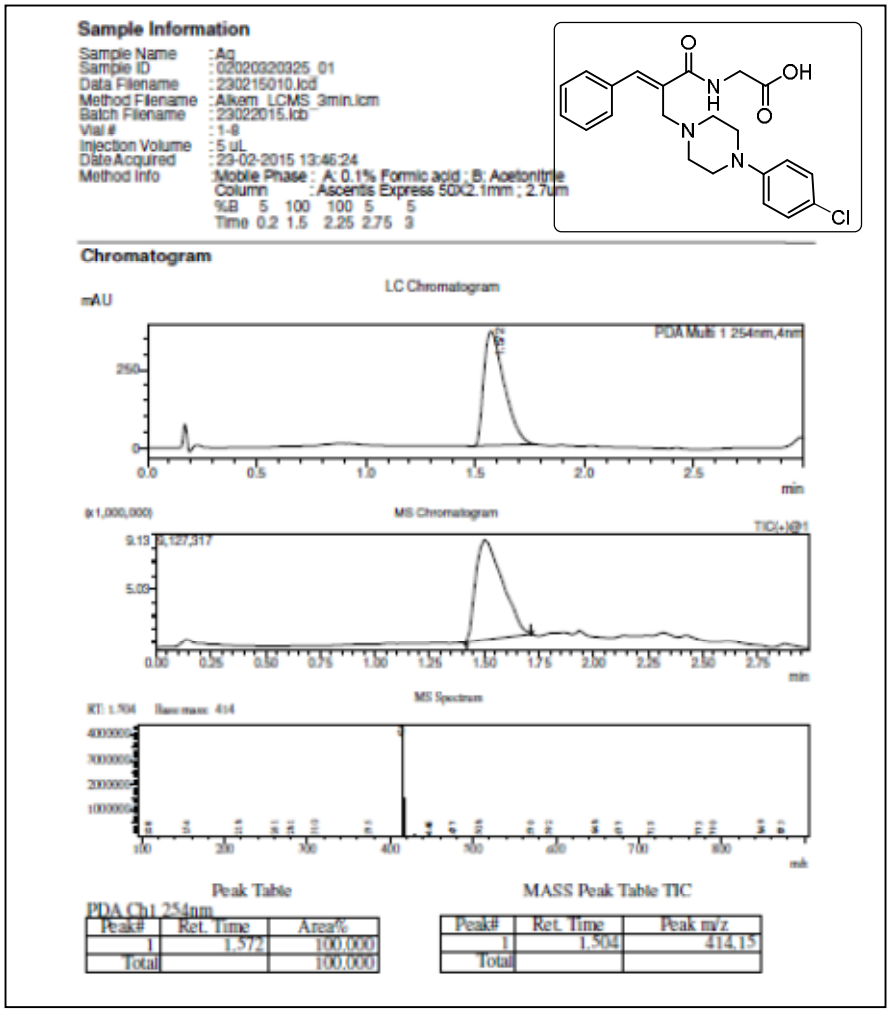
2	1.355	99.239
Total		100.000

Peak#	Ret. Time	Peak m/z
1	1.231	522.25
2	1.298	490.20
Total		

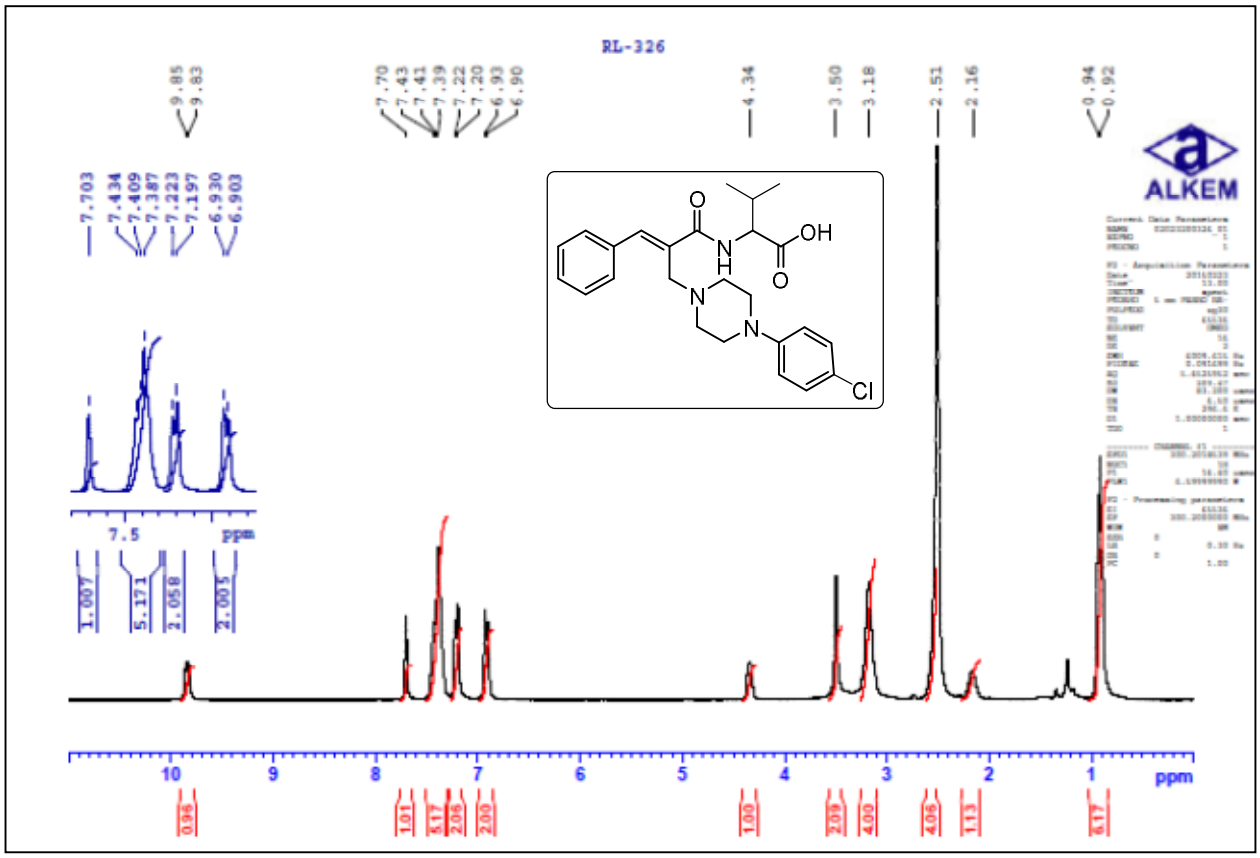
Mass spectra of (*E*)-2-(2-((4-(2,3-dichlorophenyl)piperazin-1-yl)methyl)-3-phenylacrylamido) pentanoic acid **(13j)**



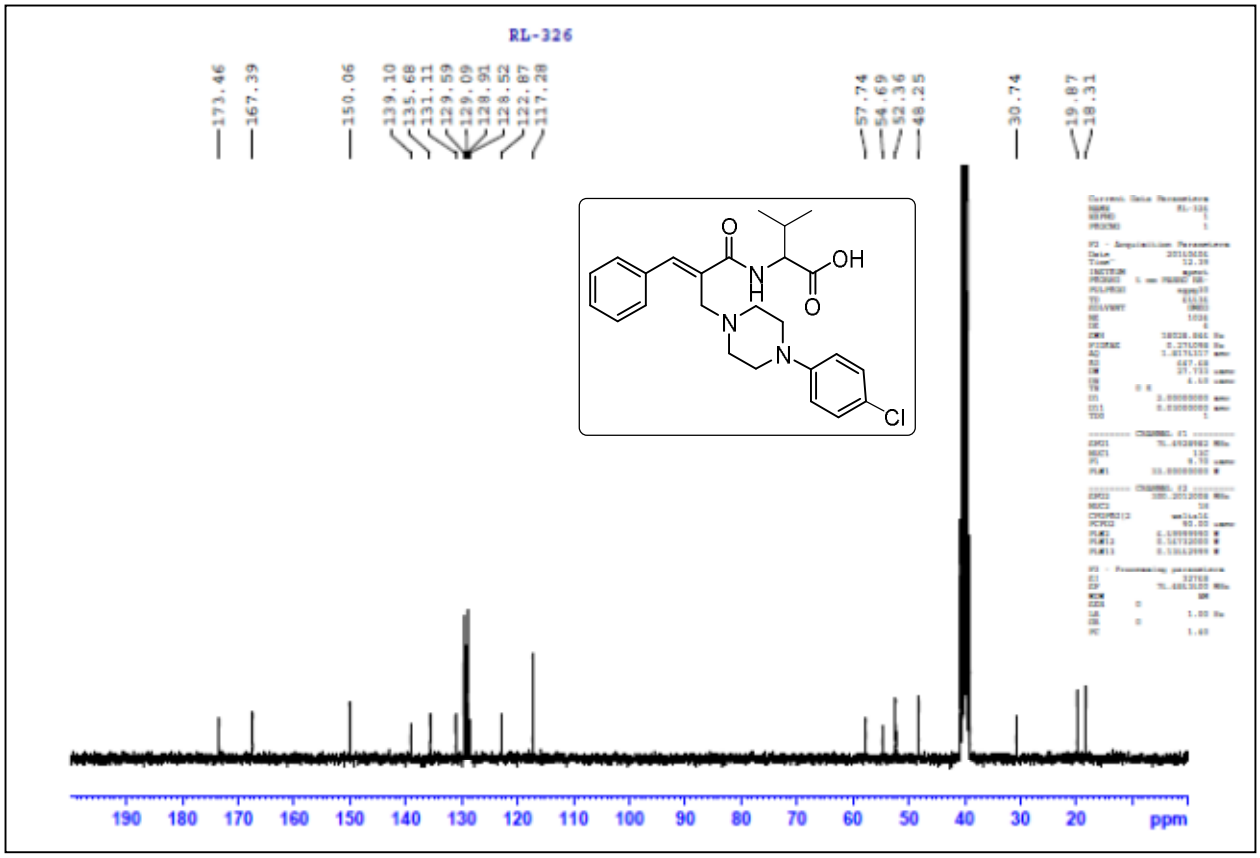
^{1}H NMR spectra of (*E*)-(2-((4-(4-chlorophenyl)piperazin-1-yl)methyl)-3-phenylacryloyl)glycine **(13k)**



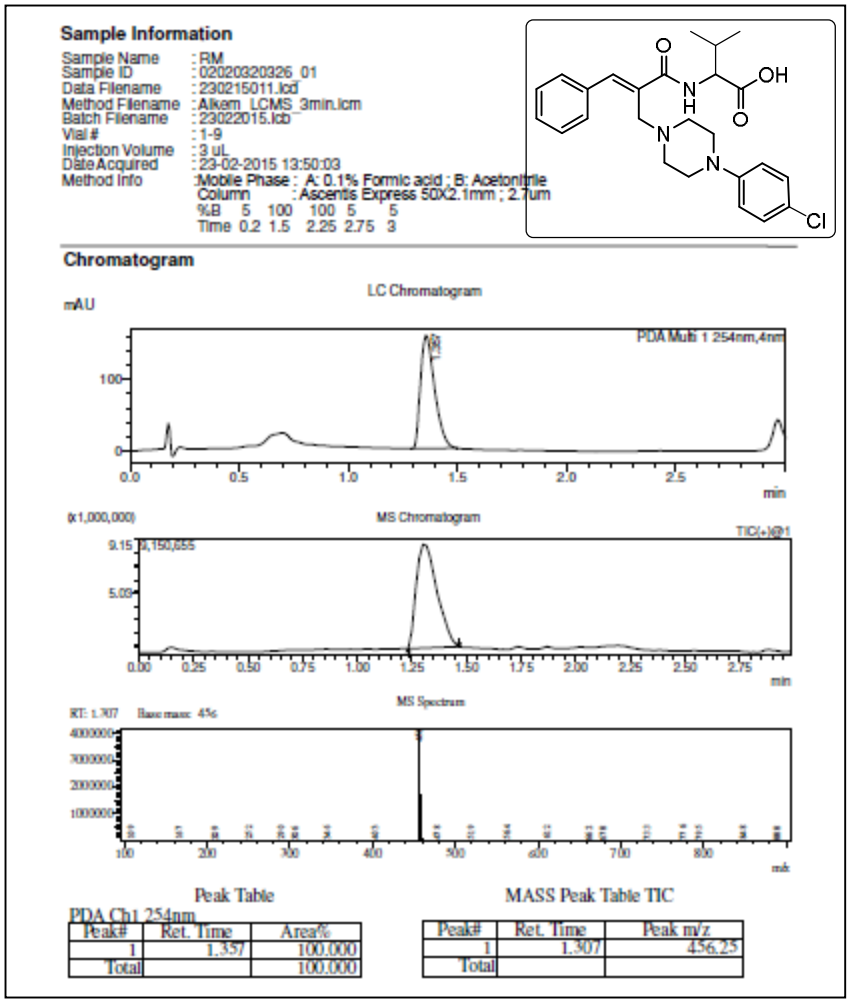
Mass spectra of (*E*)-(2-((4-(4-chlorophenyl)piperazin-1-yl)methyl)-3-phenylacryloyl)glycine **(13k)**



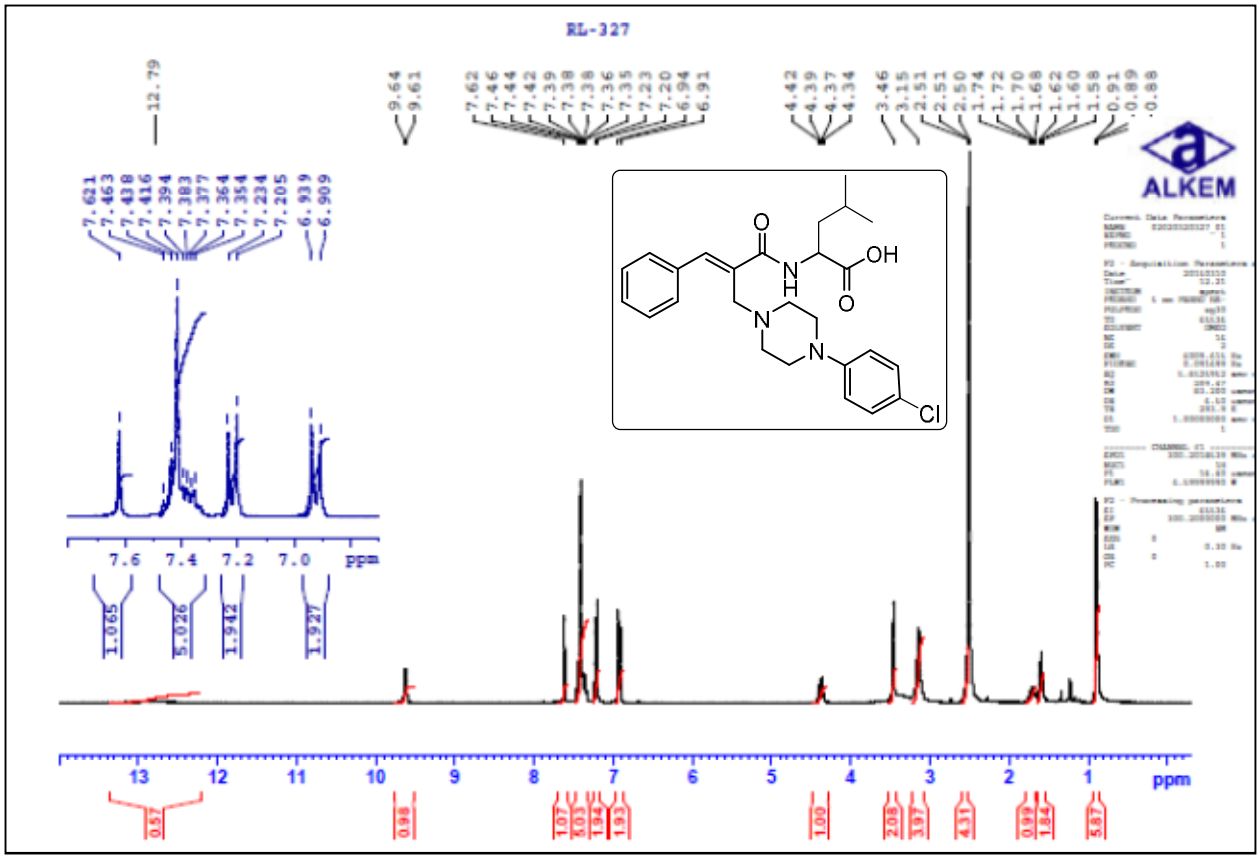
[1]H NMR spectra of (E)-(2-((4-(4-chlorophenyl)piperazin-1-yl)methyl)-3-phenylacryloyl)valine **(13l)**



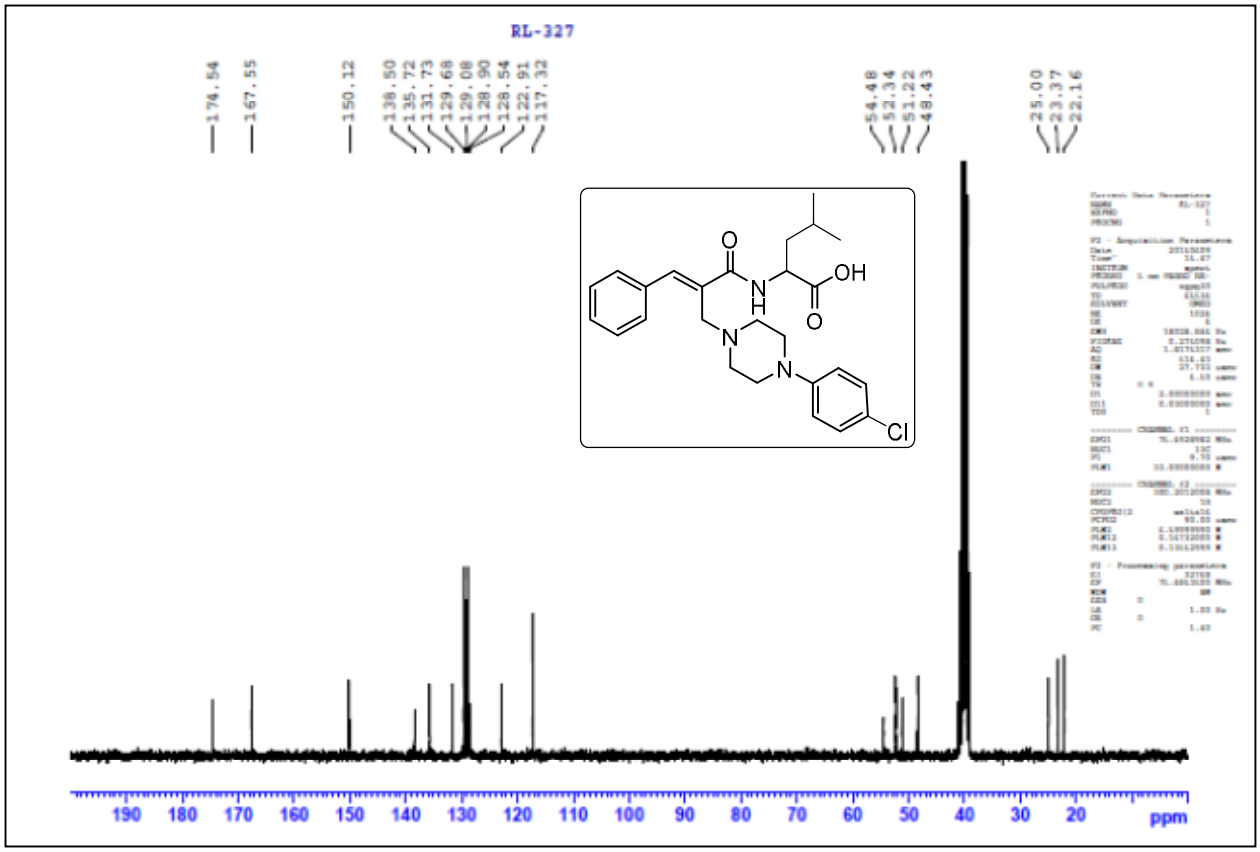
^{13}C NMR spectra of (E)-(2-((4-(4-chlorophenyl)piperazin-1-yl)methyl)-3-phenylacryloyl)valine **(13l)**



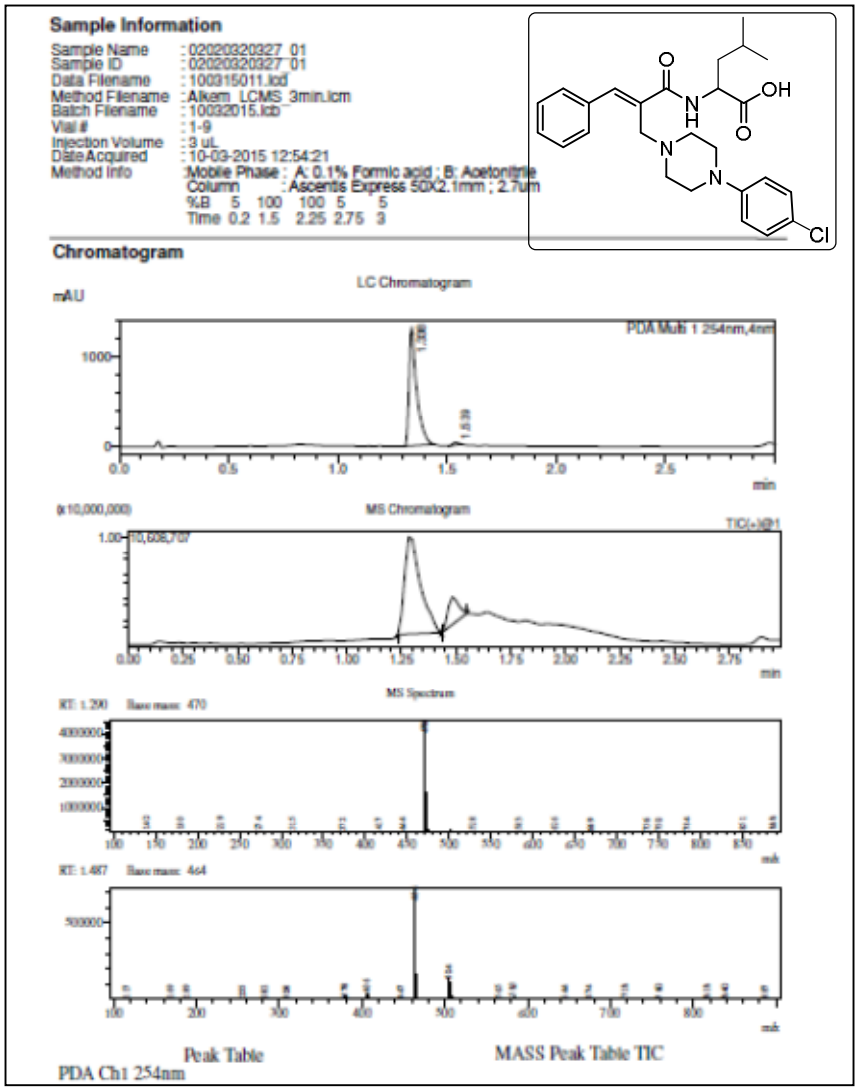
Mass spectra of (E)-(2-((4-(4-chlorophenyl)piperazin-1-yl)methyl)-3-phenylacryloyl)valine **(13l)**



^{1}H NMR spectra of (E)-(2-((4-(4-chlorophenyl)piperazin-1-yl)methyl)-3-phenylacryloyl)leucine **(13m)**



^{13}C NMR spectra of (E)-(2-((4-(4-chlorophenyl)piperazin-1-yl)methyl)-3-phenylacryloyl)leucine **(13m)**



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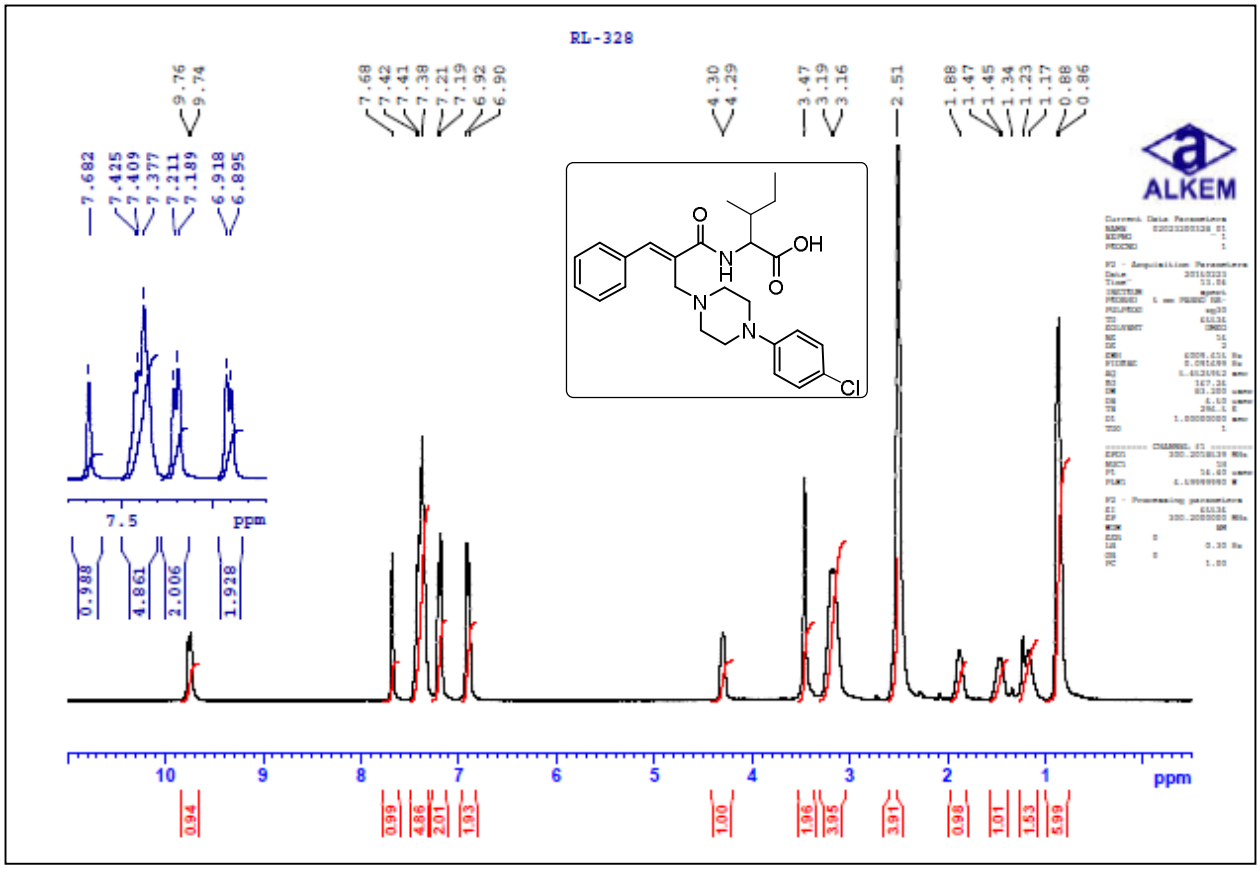
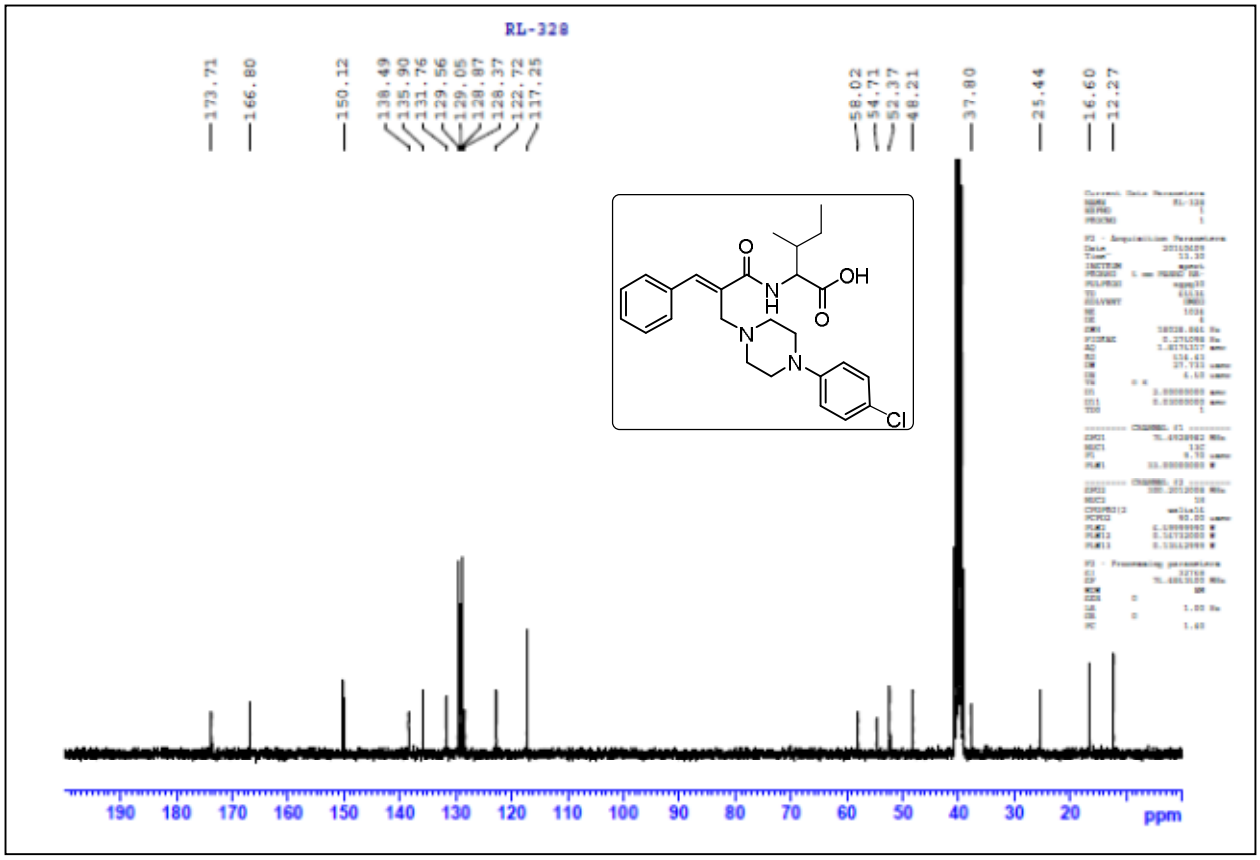
2	1.539	1.475
Total		100.000

Peak#	Ret. Time	Peak m/z
1	1.290	470.20
2	1.487	464.15
Total		

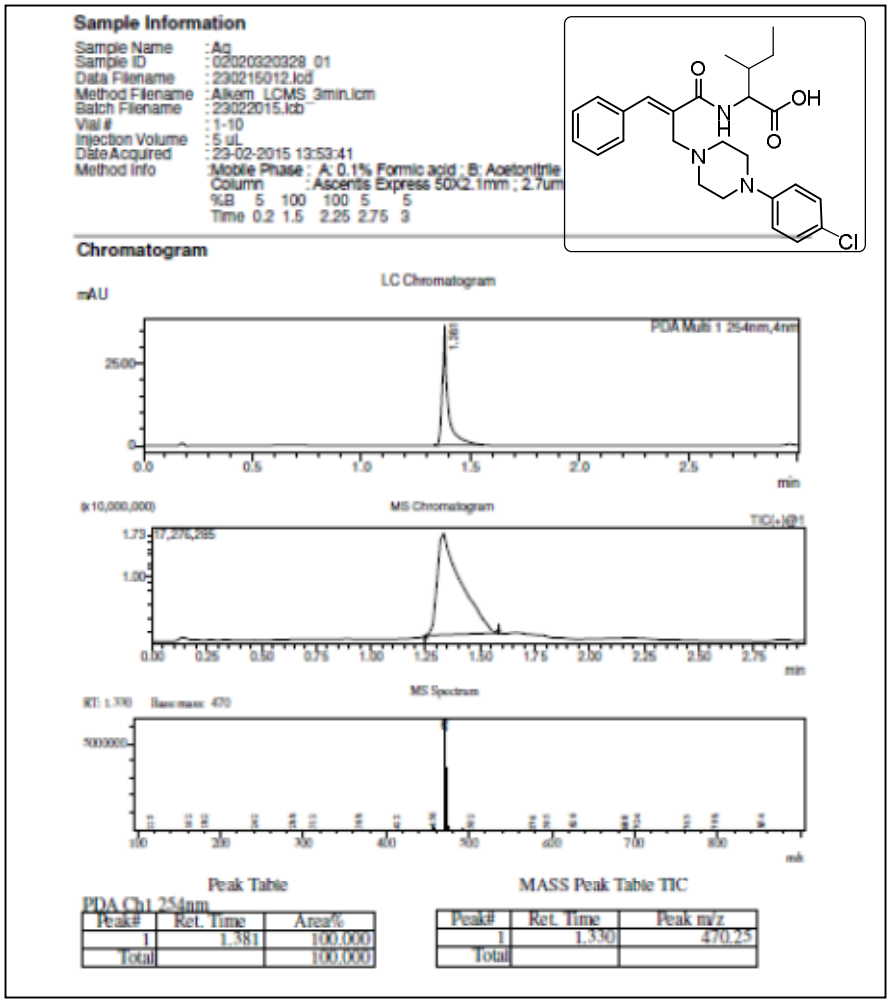
Mass spectra of (E)-(2-((4-(4-chlorophenyl)piperazin-1-yl)methyl)-3-phenylacryloyl)leucine **(13m)**



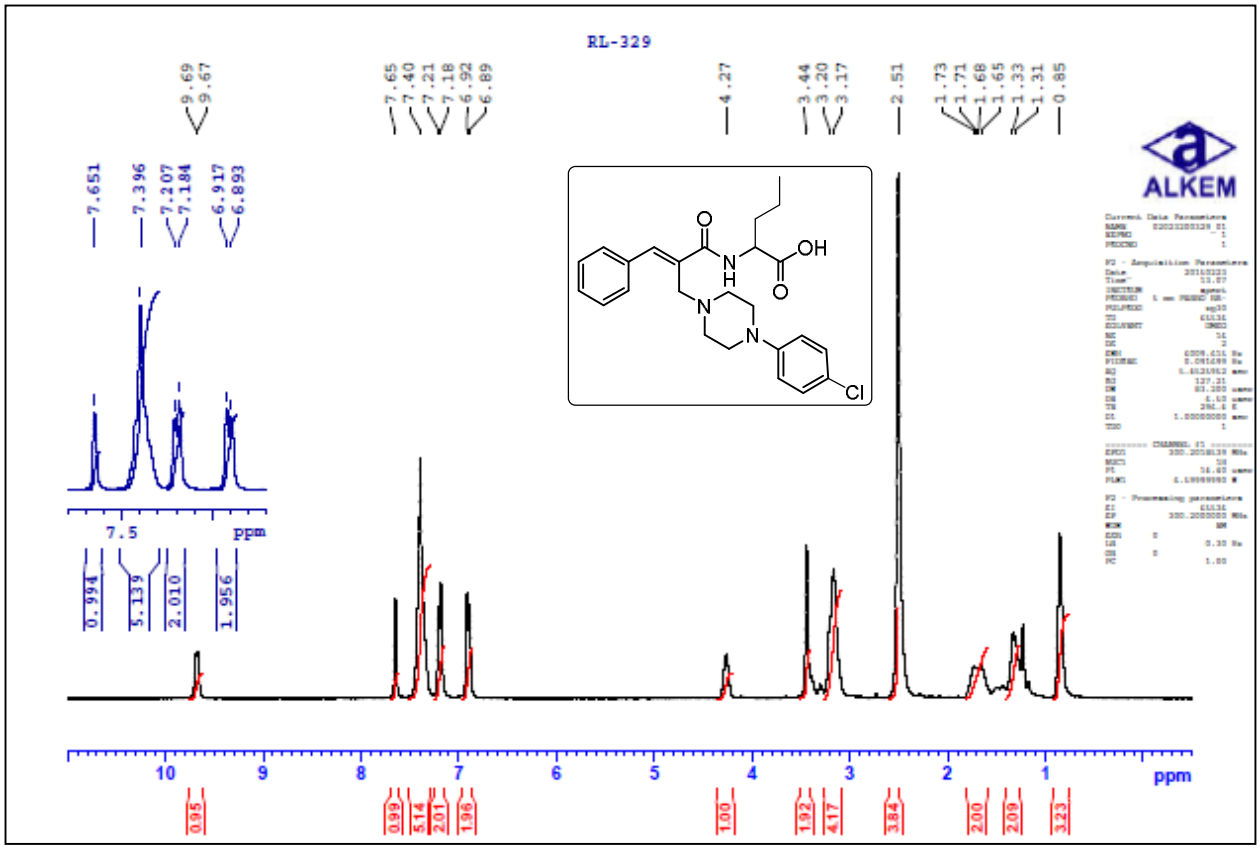
^{1}H NMR spectra of (E)-2-(2-((4-(4-chlorophenyl)piperazin-1-yl)methyl)-3-phenylacrylamido)-3-methylpentanoic acid **(13n)**



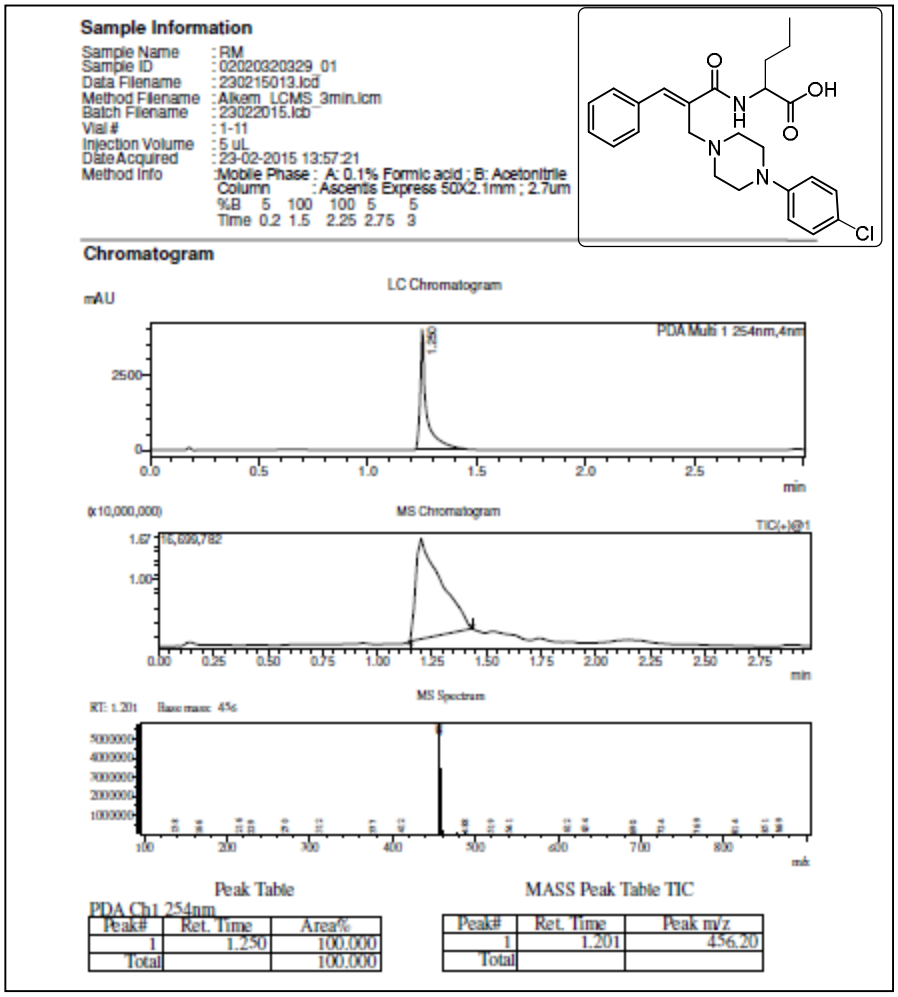
^{13}C NMR spectra of (E)-2-(2-((4-(4-chlorophenyl)piperazin-1-yl)methyl)-3-phenylacrylamido)-3-methylpentanoic acid **(13n)**



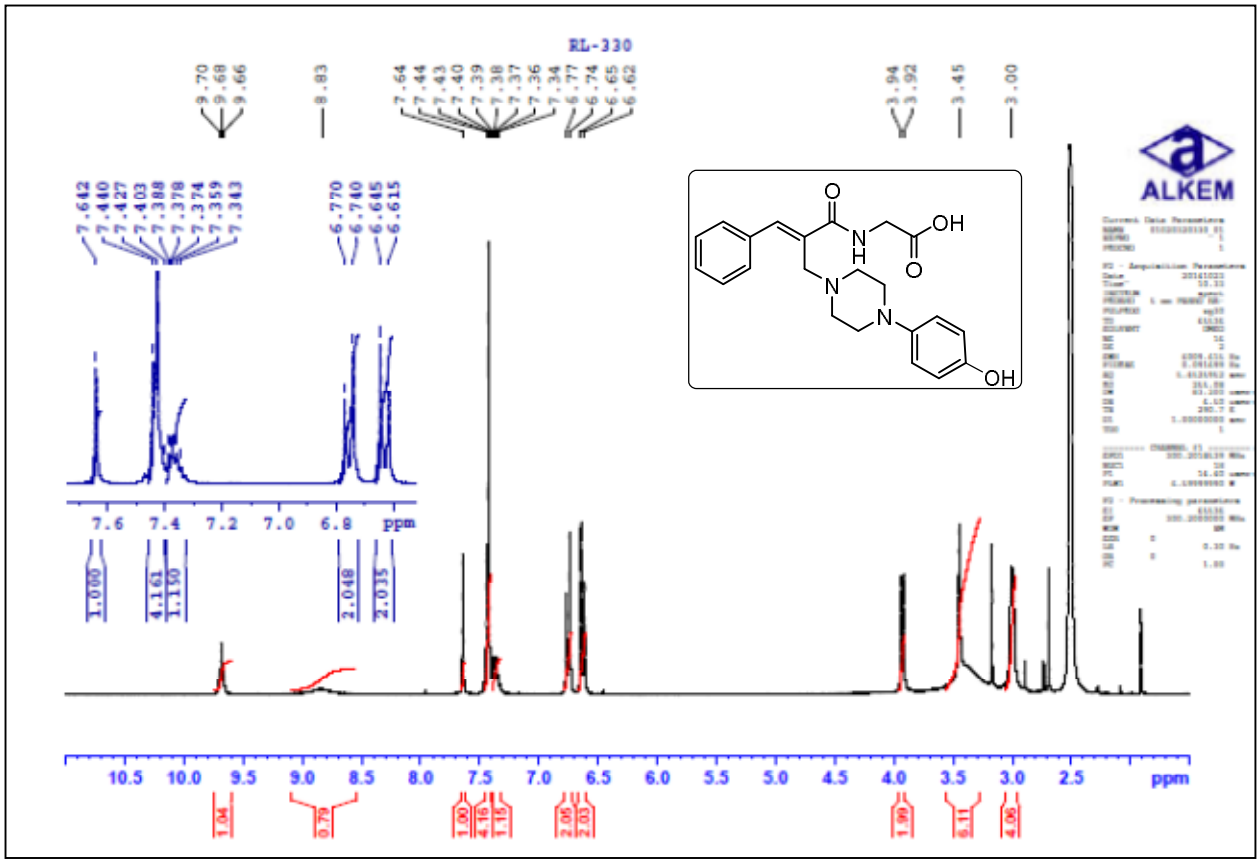
Mass spectra of (E)-2-(2-((4-(4-chlorophenyl)piperazin-1-yl)methyl)-3-phenylacrylamido)-3-methylpentanoic acid **(13n)**



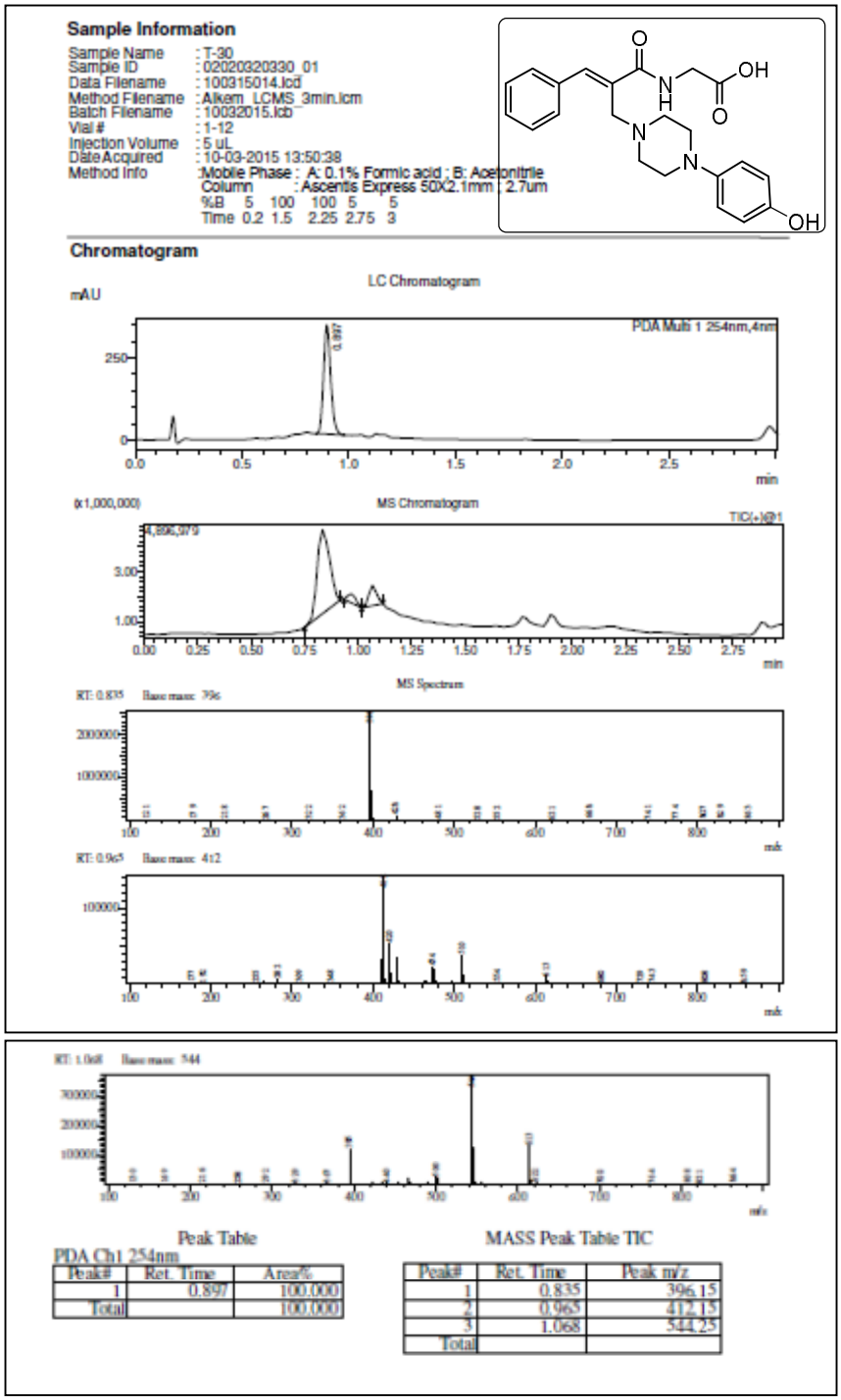
^{1}H NMR spectra of (E)-2-(2-((4-(4-chlorophenyl)piperazin-1-yl)methyl)-3-phenylacrylamido)pentanoic acid **(13o)**



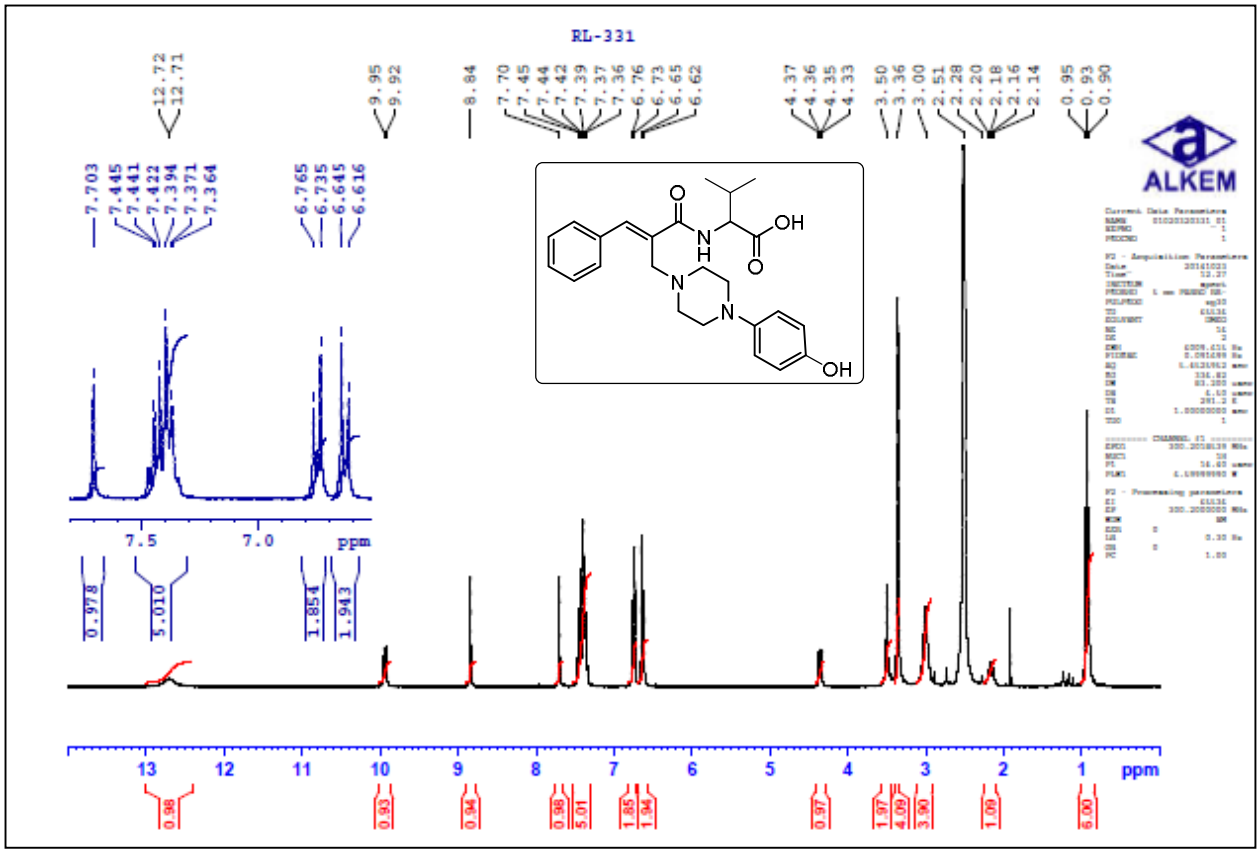
Mass spectra of (E)-2-(2-((4-(4-chlorophenyl)piperazin-1-yl)methyl)-3-phenylacrylamido)pentanoic acid **(13o)**



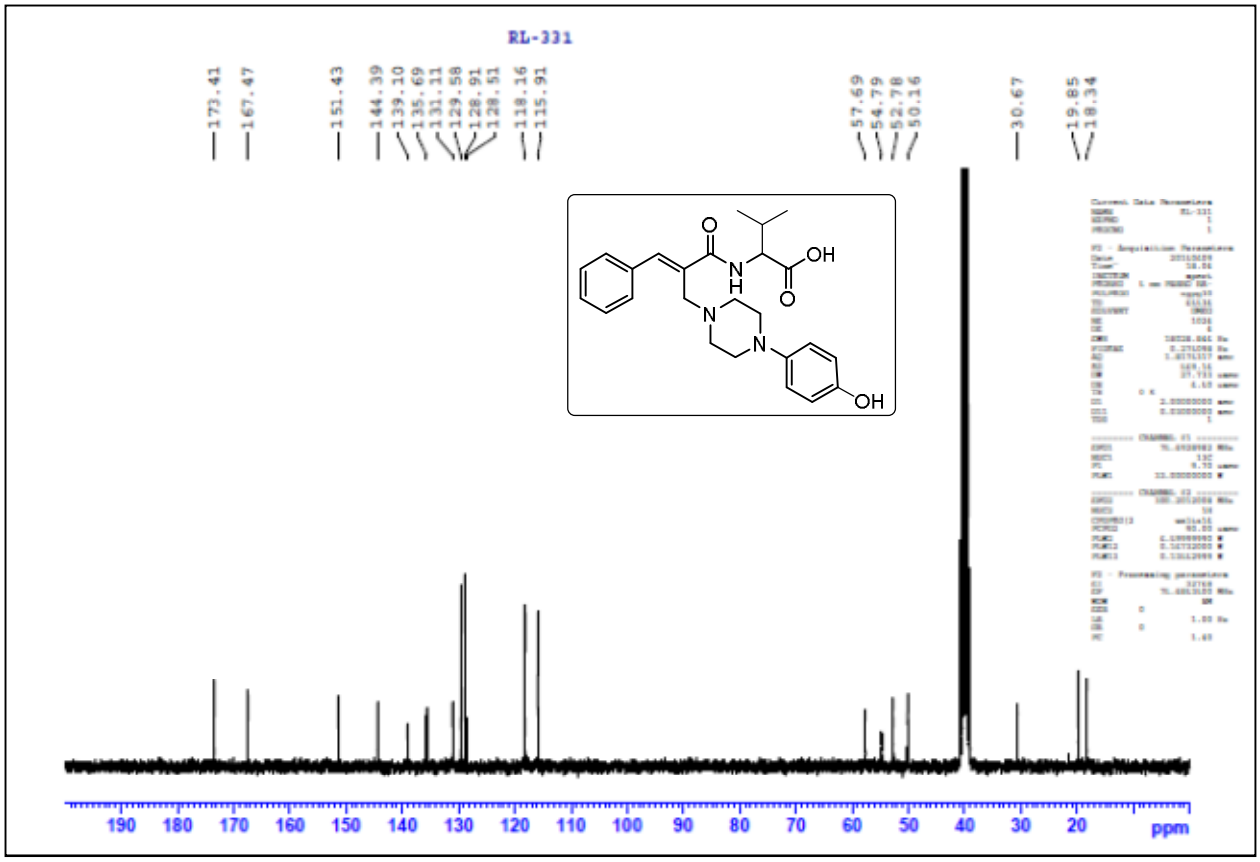
^{1}H NMR spectra of (E)-(2-((4-(4-hydroxyphenyl)piperazin-1-yl)methyl)-3-phenylacryloyl)glycine **(13p)**



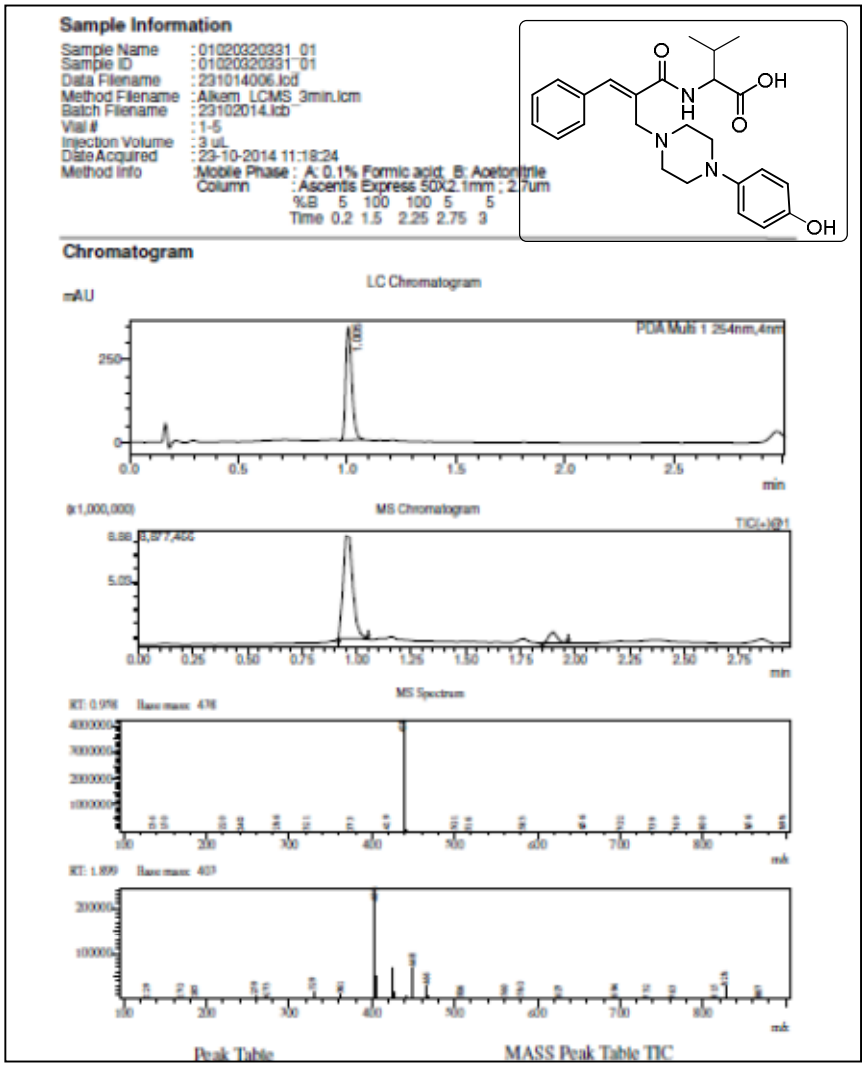
Mass spectra of (E)-(2-((4-(4-hydroxyphenyl)piperazin-1-yl)methyl)-3-phenylacryloyl)glycine **(13p)**



^{1}H NMR spectra of (E)-(2-((4-(4-hydroxyphenyl)piperazin-1-yl)methyl)-3-phenylacryloyl)valine **(13q)**



^{13}C NMR spectra of (E)-(2-((4-(4-hydroxyphenyl)piperazin-1-yl)methyl)-3-phenylacryloyl)valine **(13q)**



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Total		100.000

Peak#	Ret. Time	Peak m/z
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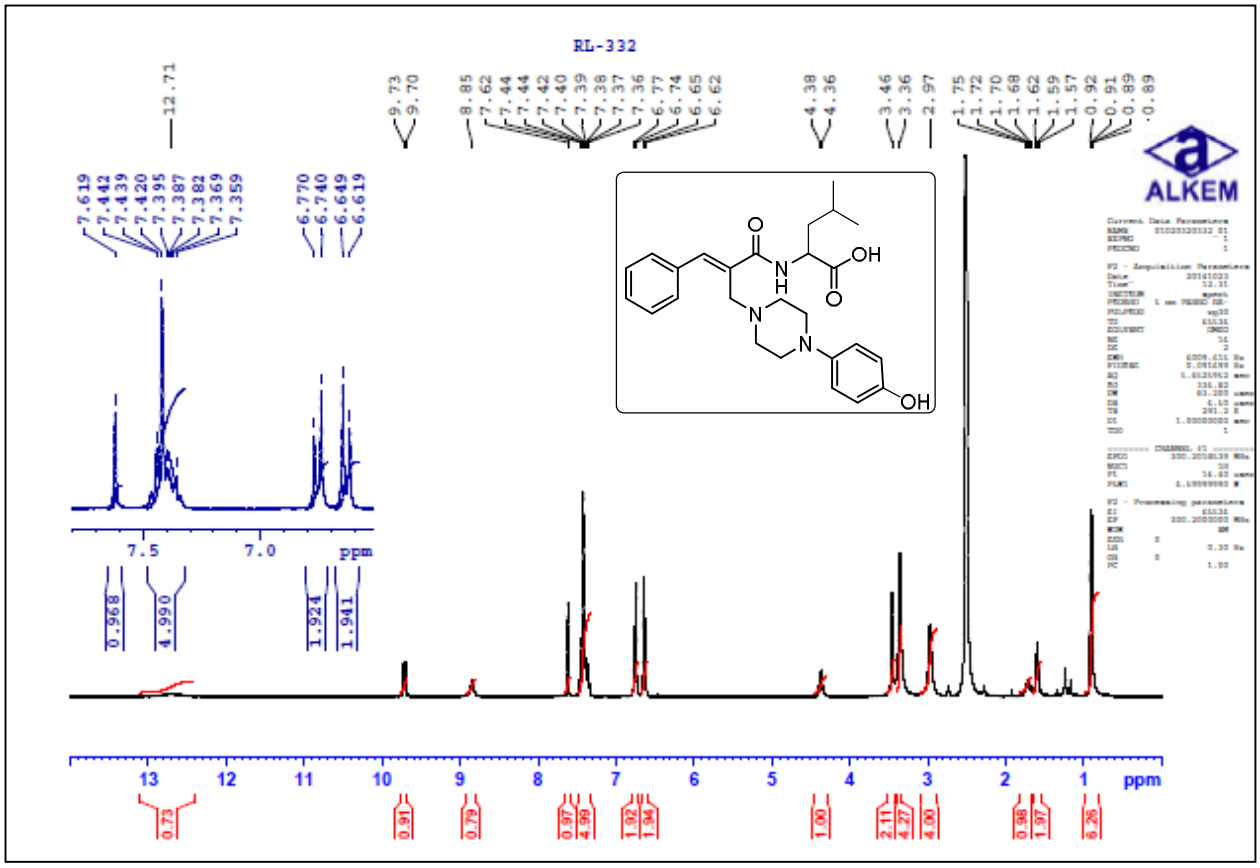
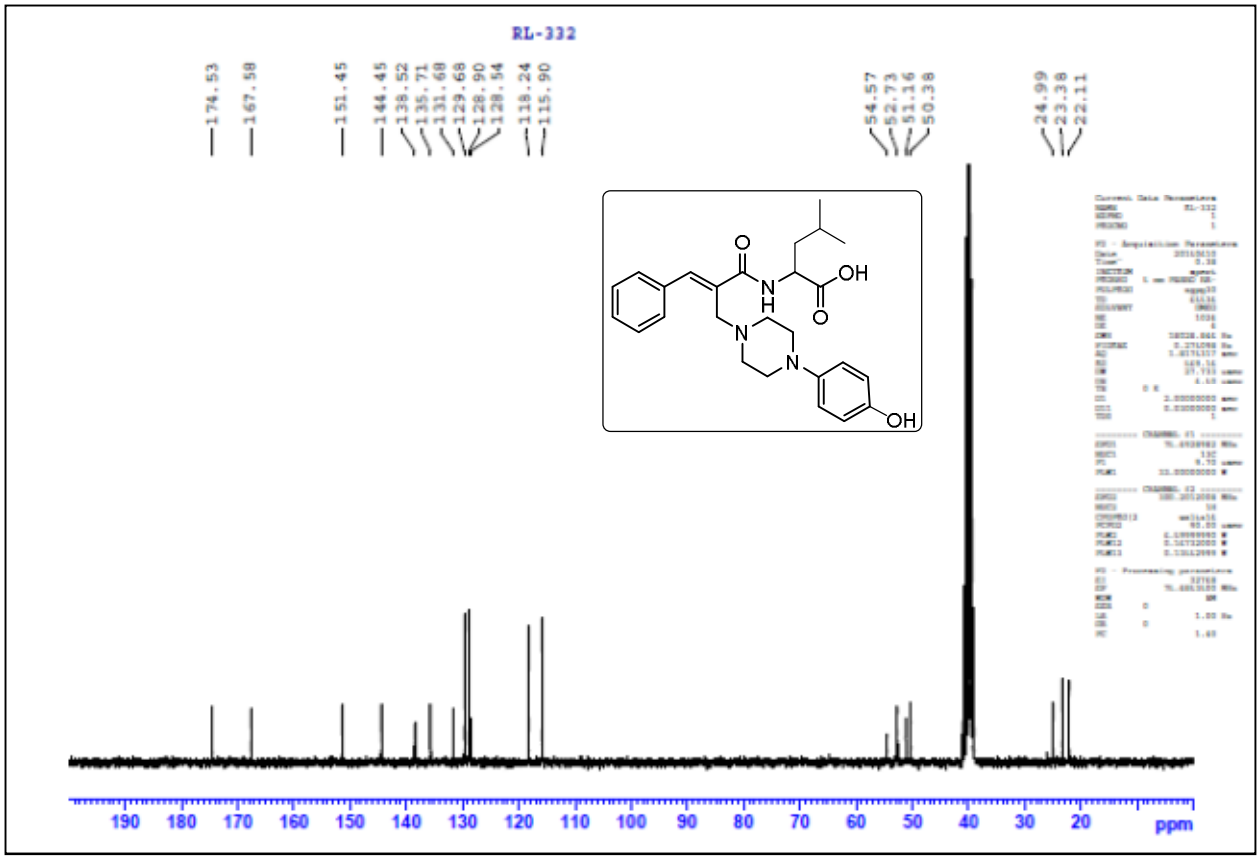
2	1.899	403.20
Total		

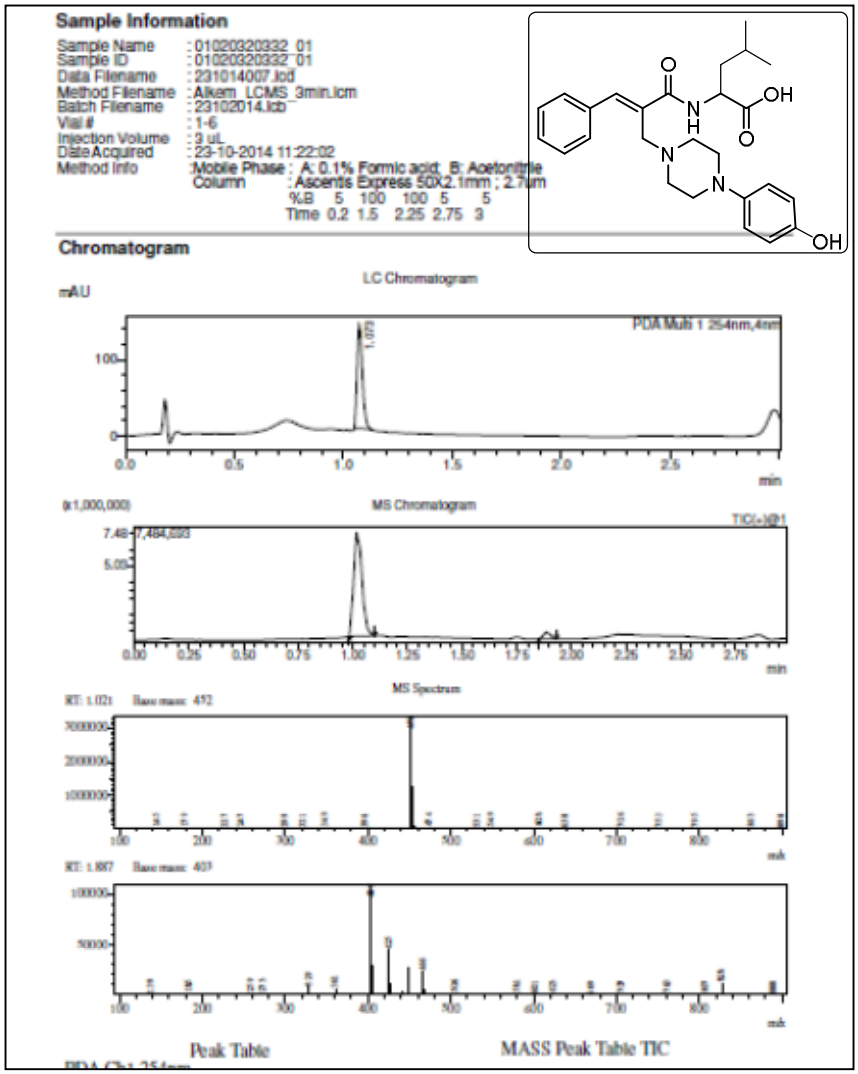
Mass spectra of (E)-(2-((4-(4-hydroxyphenyl)piperazin-1-yl)methyl)-3-phenylacryloyl)valine **(13q)**



^{1}H NMR spectra of (E)-(2-((4-(4-hydroxyphenyl)piperazin-1-yl)methyl)-3-phenylacryloyl) leucine **(13r)**



^{13}C NMR spectra of (E)-(2-((4-(4-hydroxyphenyl)piperazin-1-yl)methyl)-3-phenylacryloyl) leucine **(13r)**



Peak#	Ret. Time	Area%
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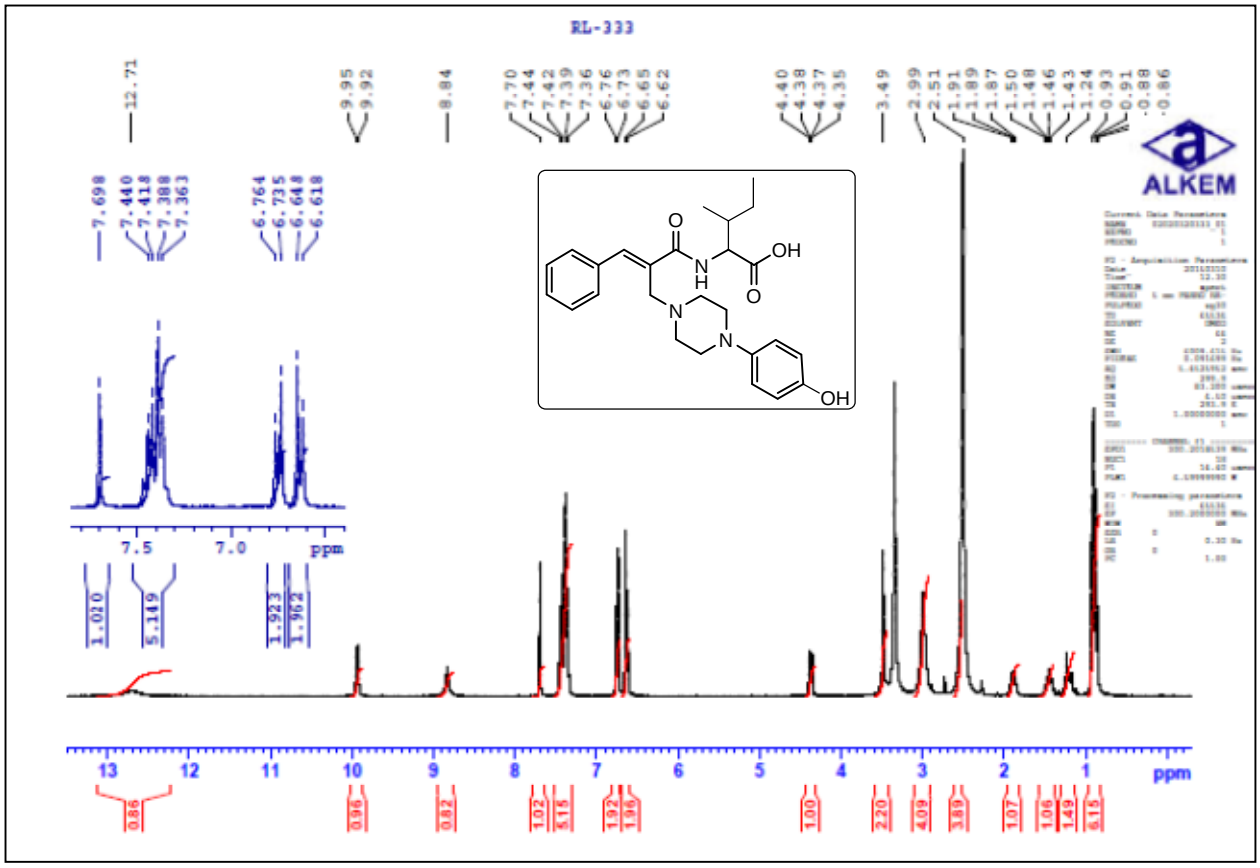
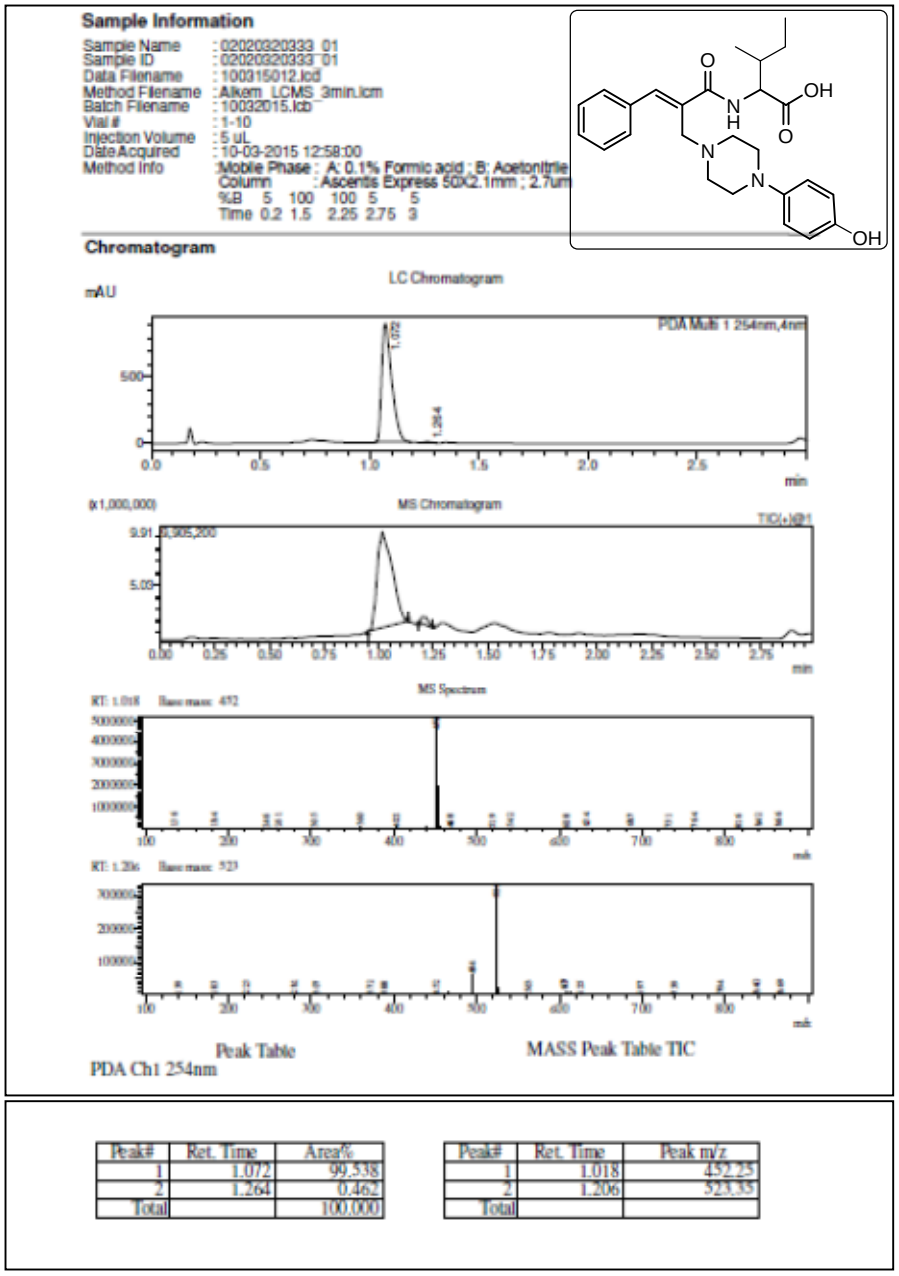
Total		100.000

Peak#	Ret. Time	Peak m/z
1	1.021	452.30
2	1.887	403.25
Total		

^{13}C NMR spectra of (E)-(2-((4-(4-hydroxyphenyl)piperazin-1-yl)methyl)-3-phenylacryloyl) leucine **(13r)**



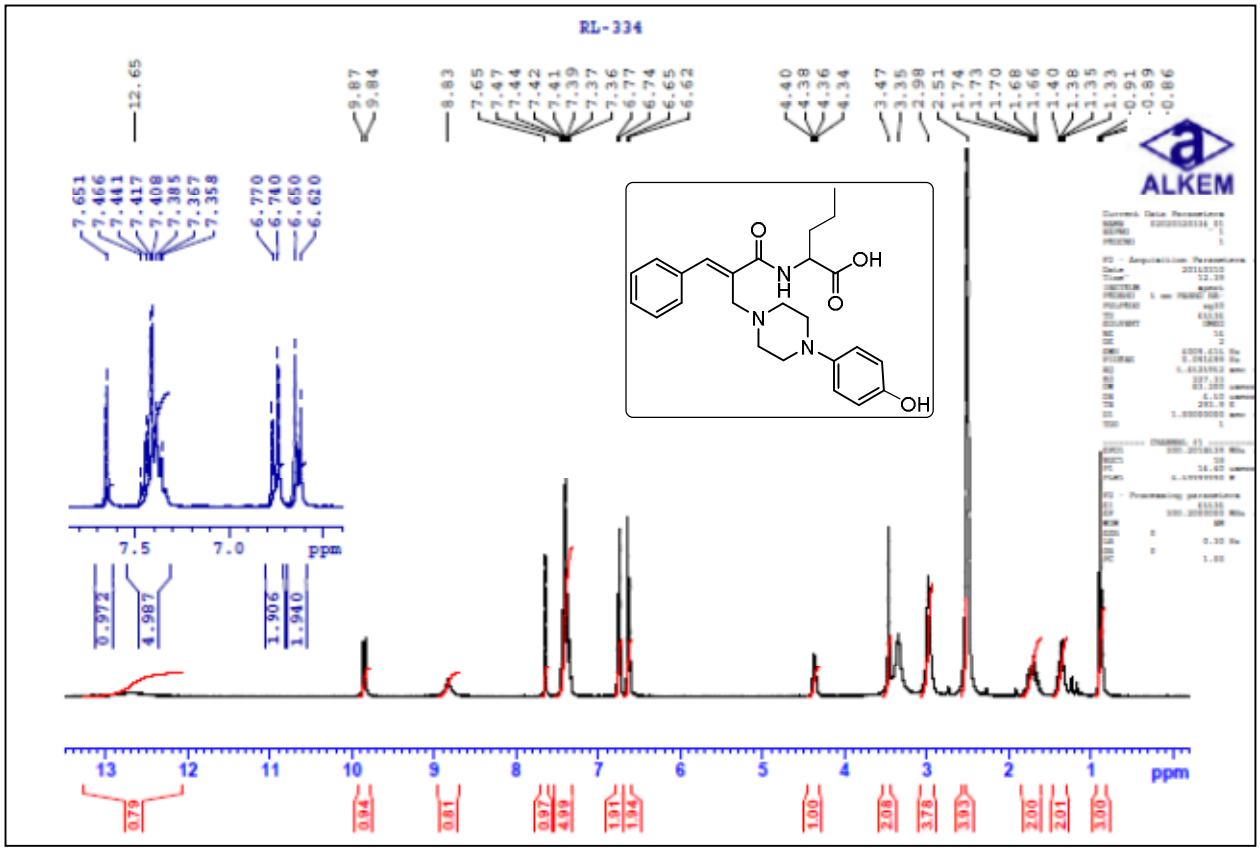
^{1}H NMR spectra of (E)-2-(2-((4-(4-hydroxyphenyl)piperazin-1-yl)methyl)-3-phenylacrylamido)-3-methylpentanoic acid **(13s)**



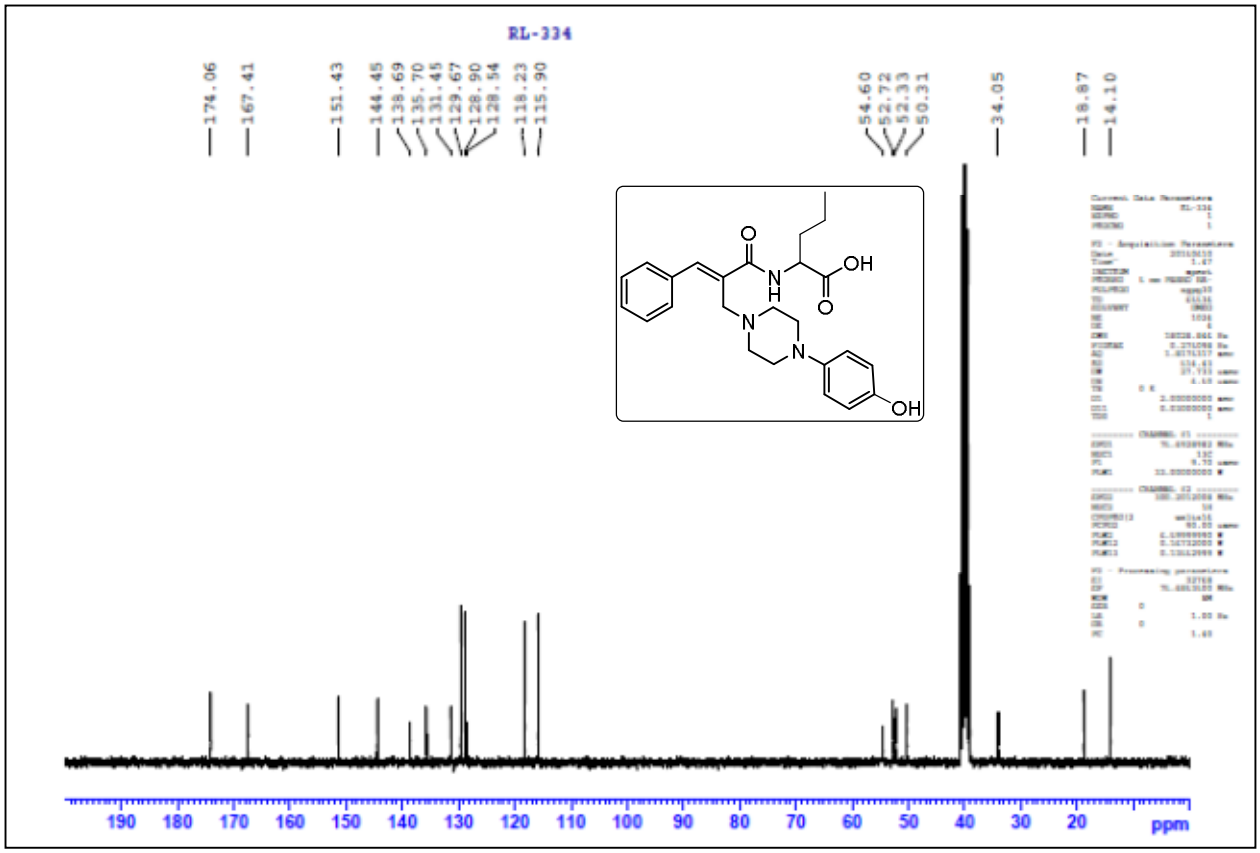
Peak#	Ret. Time	Area%
1	1.072	99.538
2	1.264	0.462
Total		100.000

Peak#	Ret. Time	Peak m/z
1	1.018	452.25
2	1.206	523.35
Total		

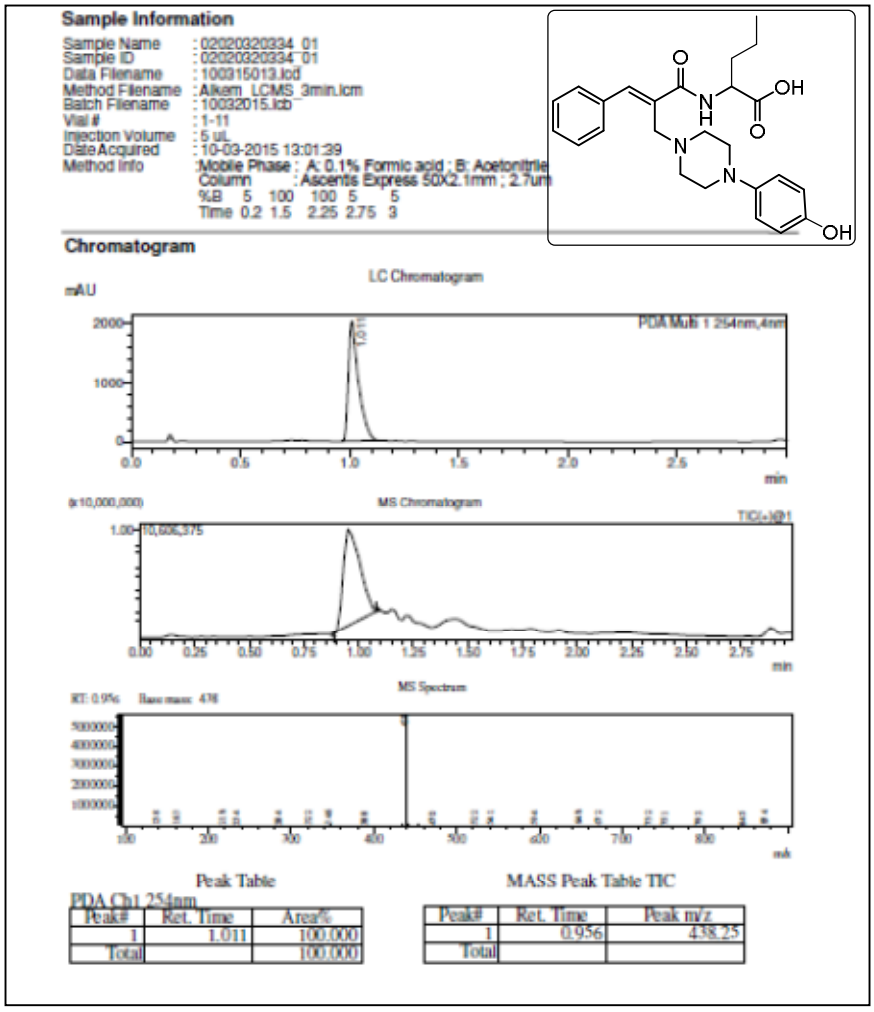
Mass spectra of (E)-2-(2-((4-(4-hydroxyphenyl)piperazin-1-yl)methyl)-3-phenylacrylamido)-3-methylpentanoic acid **(13s)**



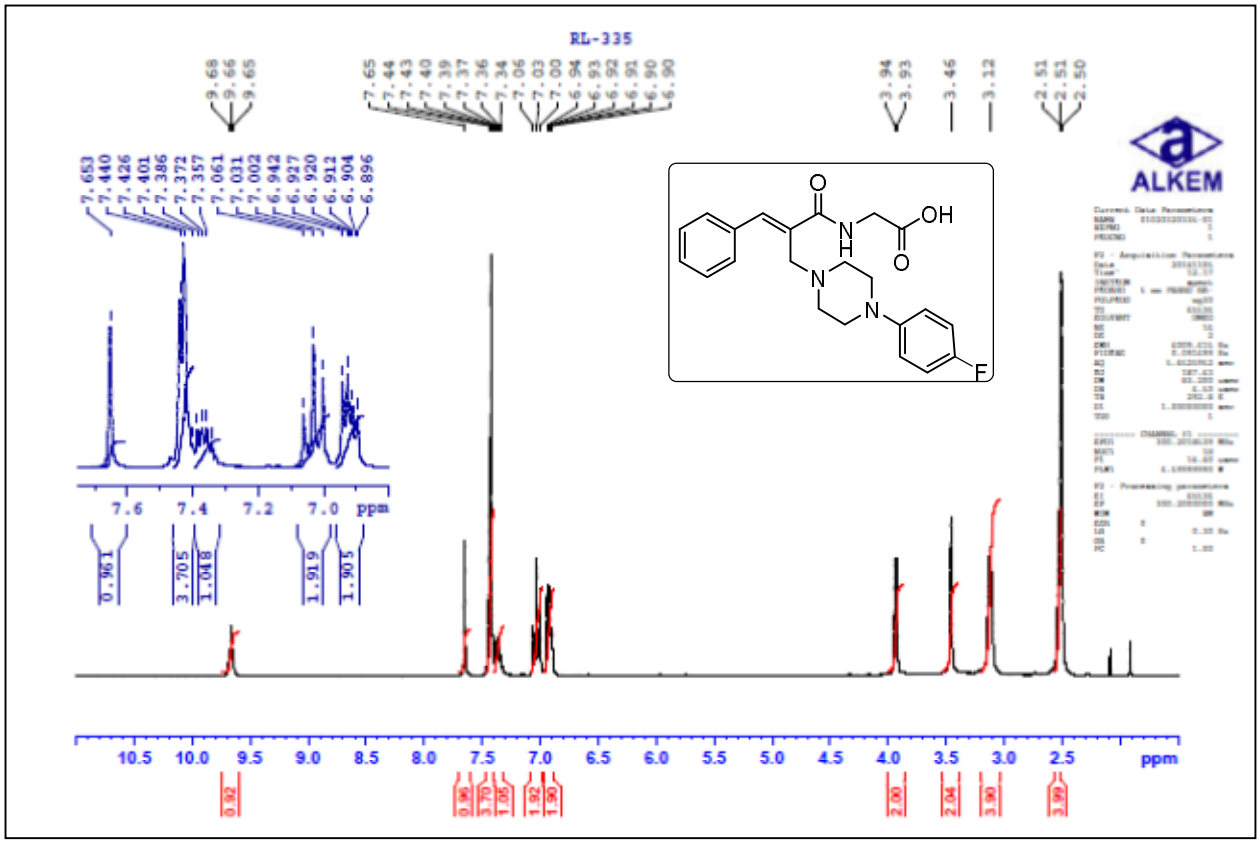
^{1}H NMR spectra of (E)-2-(2-((4-(4-hydroxyphenyl)piperazin-1-yl)methyl)-3-phenylacrylamido) pentanoic acid **(13t)**



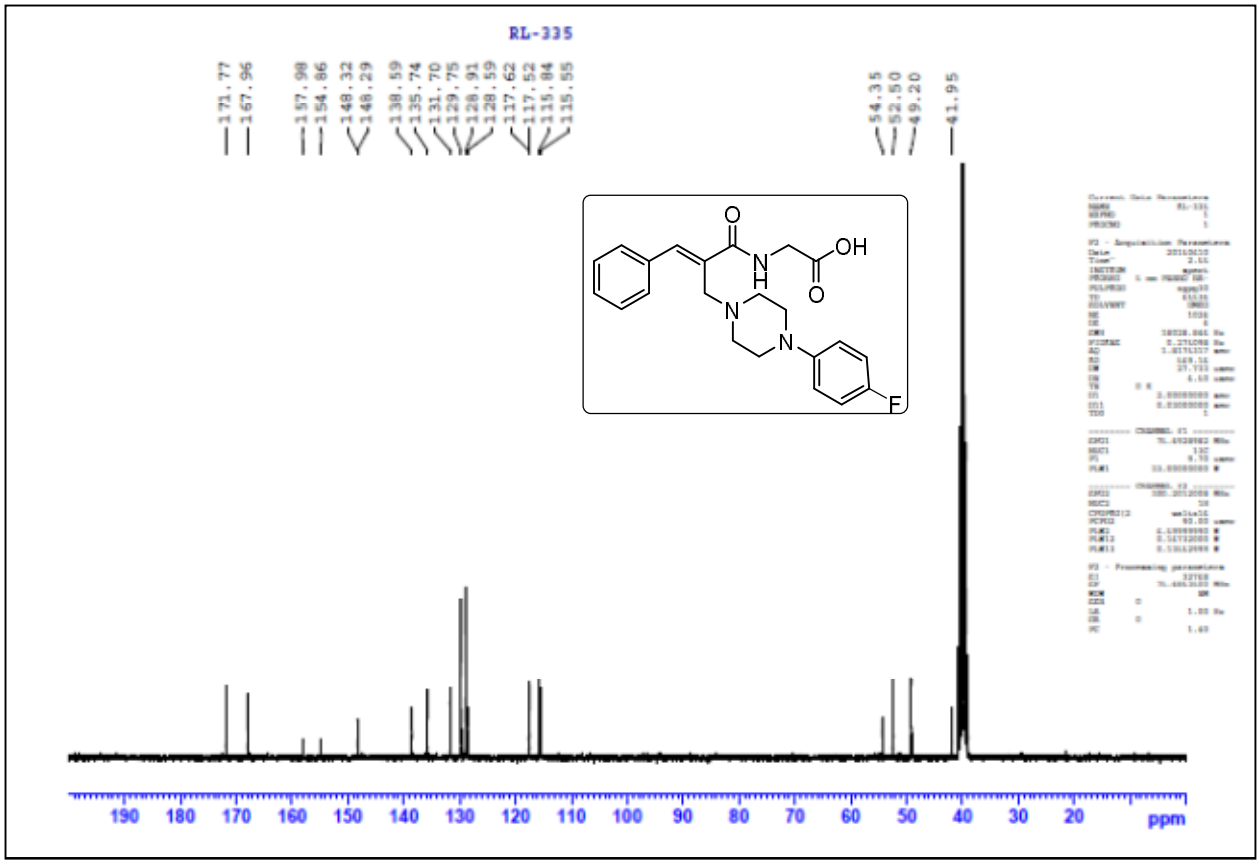
^{13}C NMR spectra of (E)-2-(2-((4-(4-hydroxyphenyl)piperazin-1-yl)methyl)-3-phenylacrylamido) pentanoic acid **(13t)**



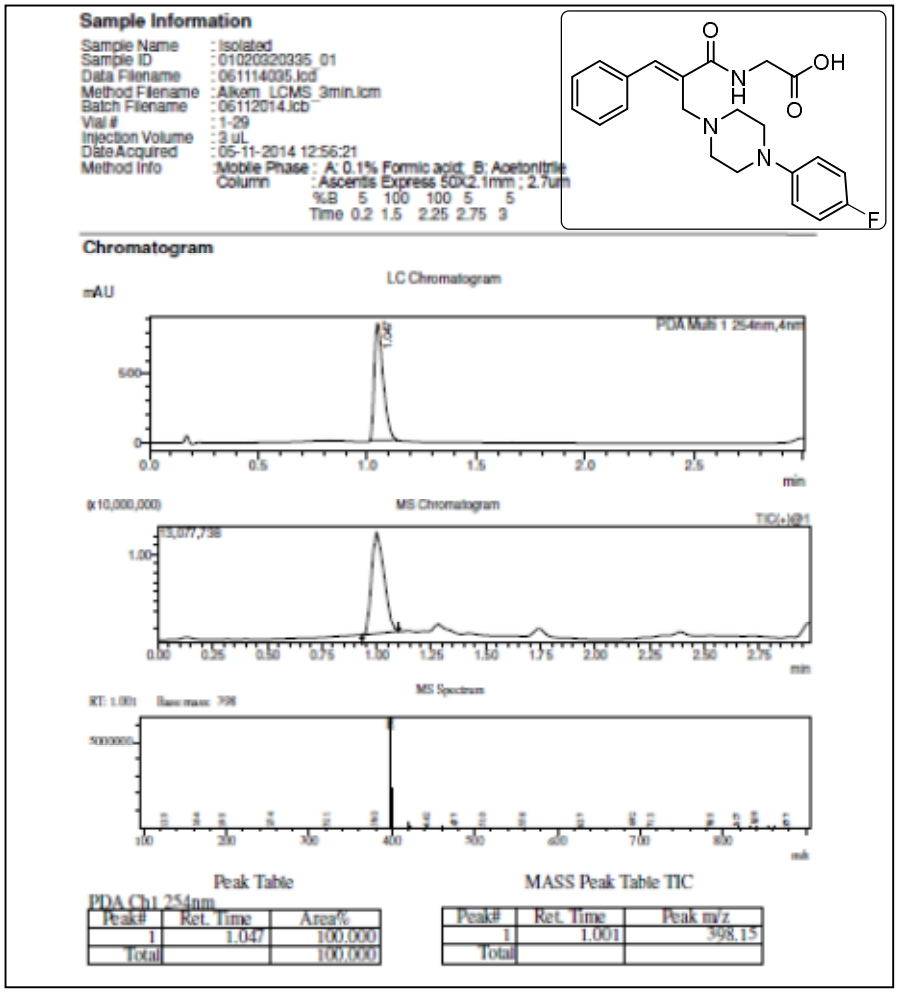
Mass spectra of (E)-2-(2-((4-(4-hydroxyphenyl)piperazin-1-yl)methyl)-3-phenylacrylamido) pentanoic acid **(13t)**



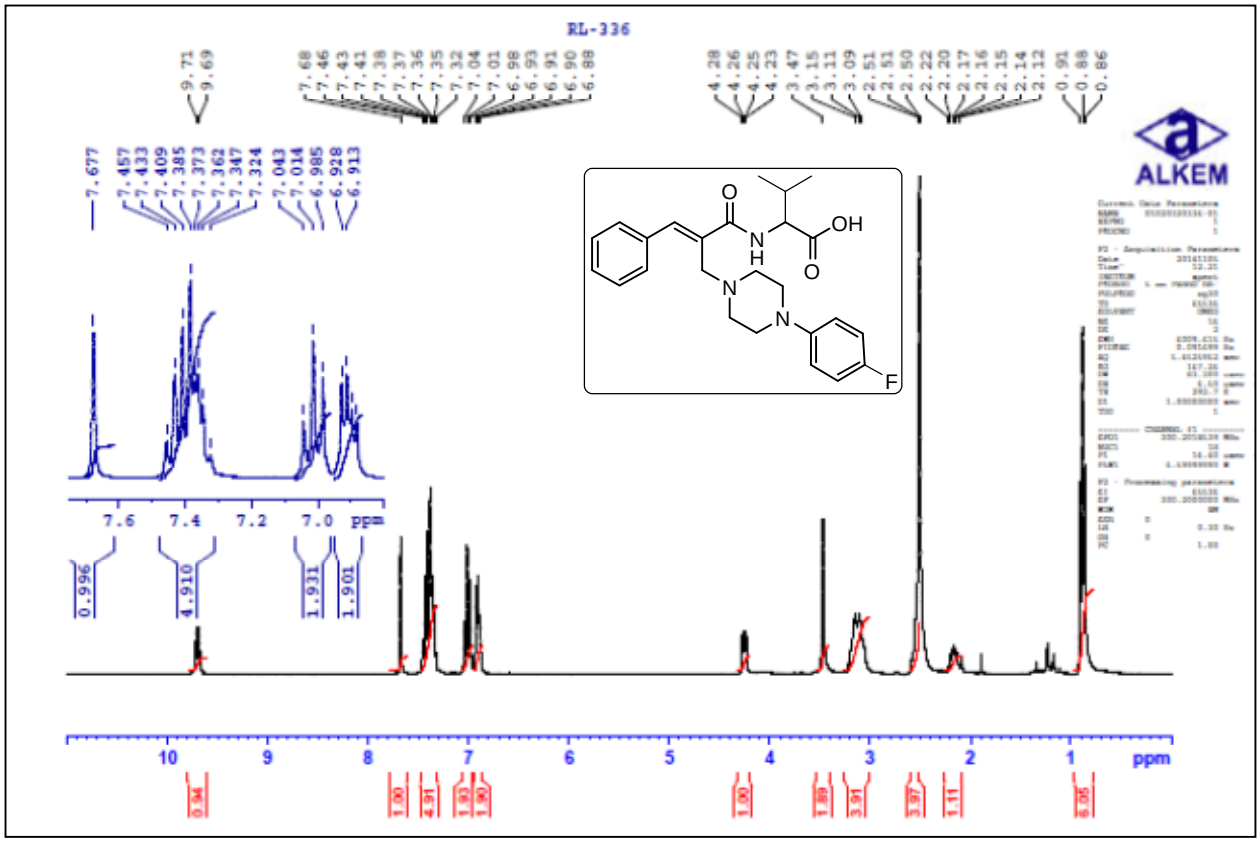
^{1}H NMR spectra of (E)-(2-((4-(4-fluorophenyl)piperazin-1-yl)methyl)-3-phenylacryloyl)glycine **(13u)**



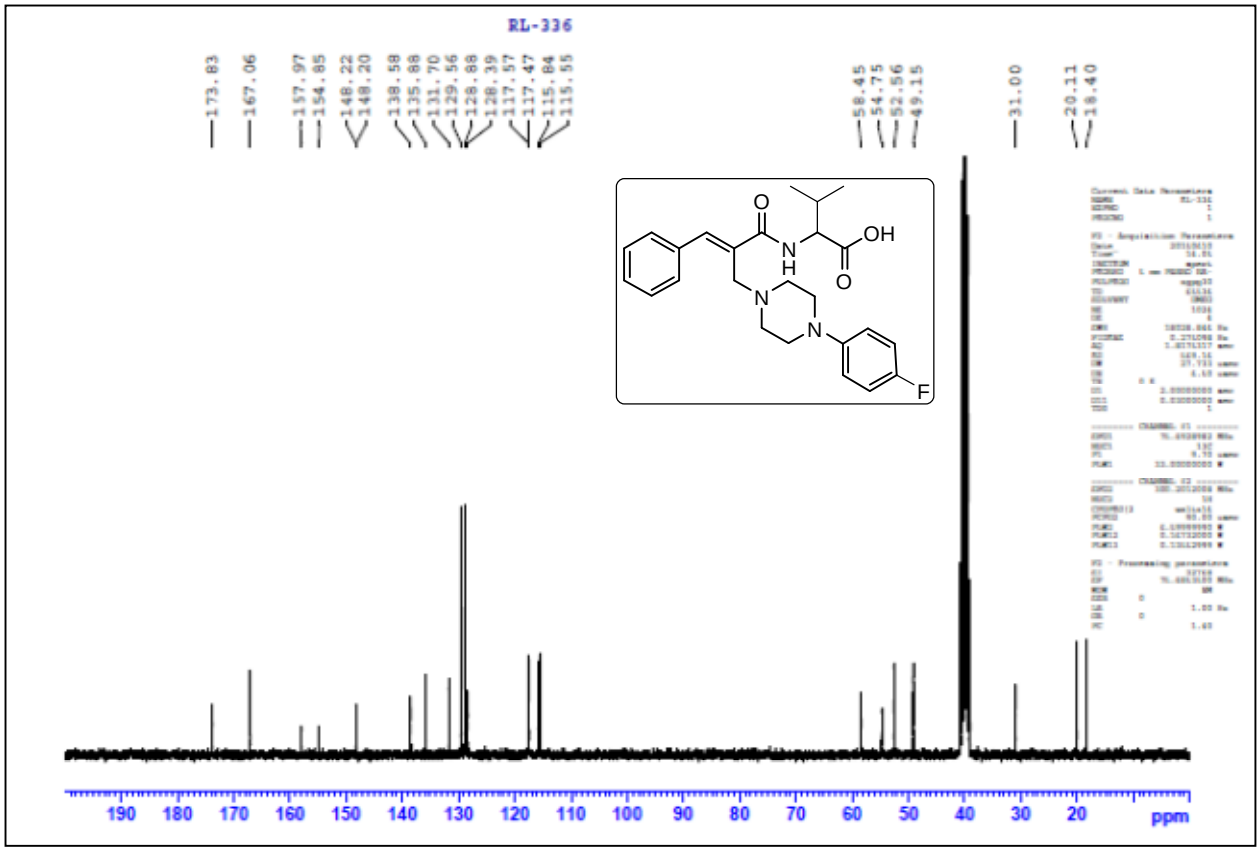
^{13}C NMR spectra of (E)-(2-((4-(4-fluorophenyl)piperazin-1-yl)methyl)-3-phenylacryloyl)glycine **(13u)**



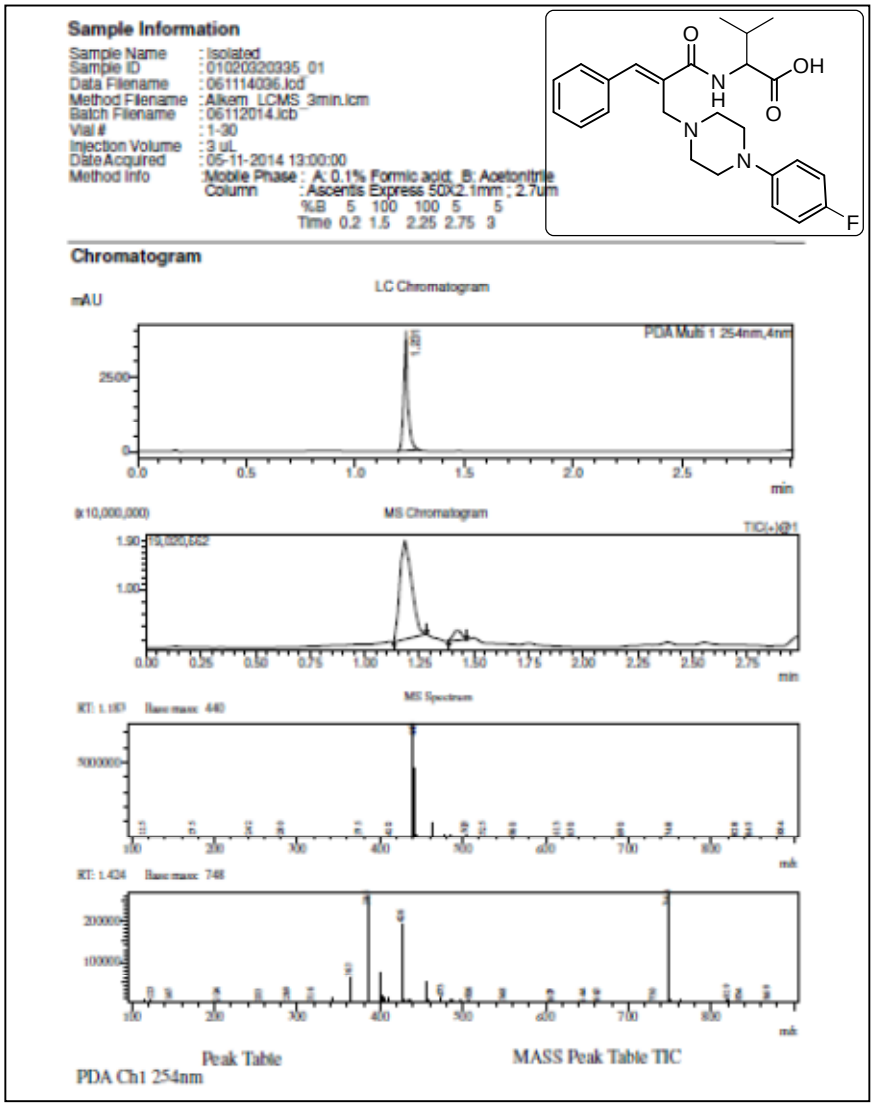
Mass spectra of (E)-(2-((4-(4-fluorophenyl)piperazin-1-yl)methyl)-3-phenylacryloyl)glycine **(13u)**



^{1}H NMR spectra of (E)-(2-((4-(4-fluorophenyl)piperazin-1-yl)methyl)-3-phenylacryloyl)valine **(13v)**



^{13}C NMR spectra of (E)-(2-((4-(4-fluorophenyl)piperazin-1-yl)methyl)-3-phenylacryloyl)valine **(13v)**



Peak#	Ret. Time	Area%
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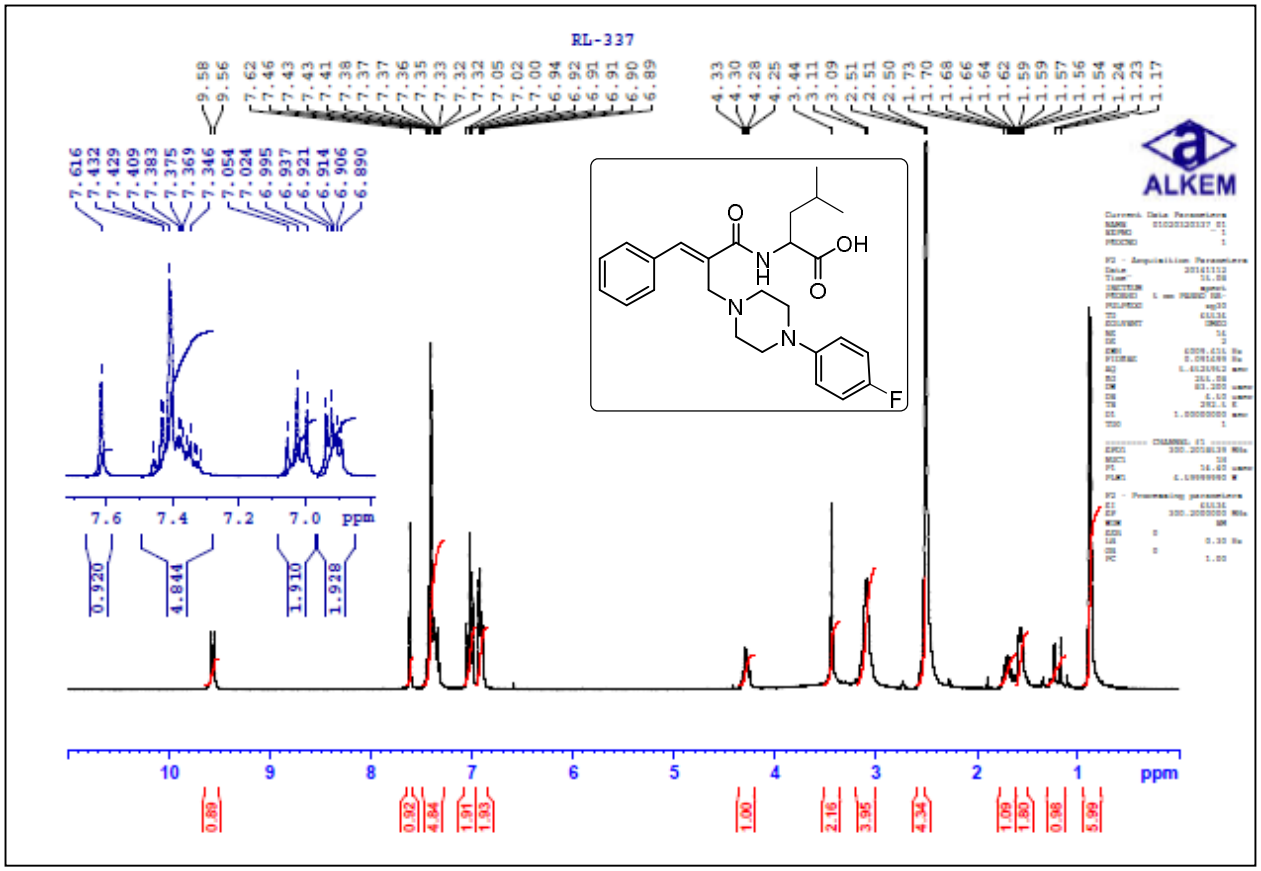
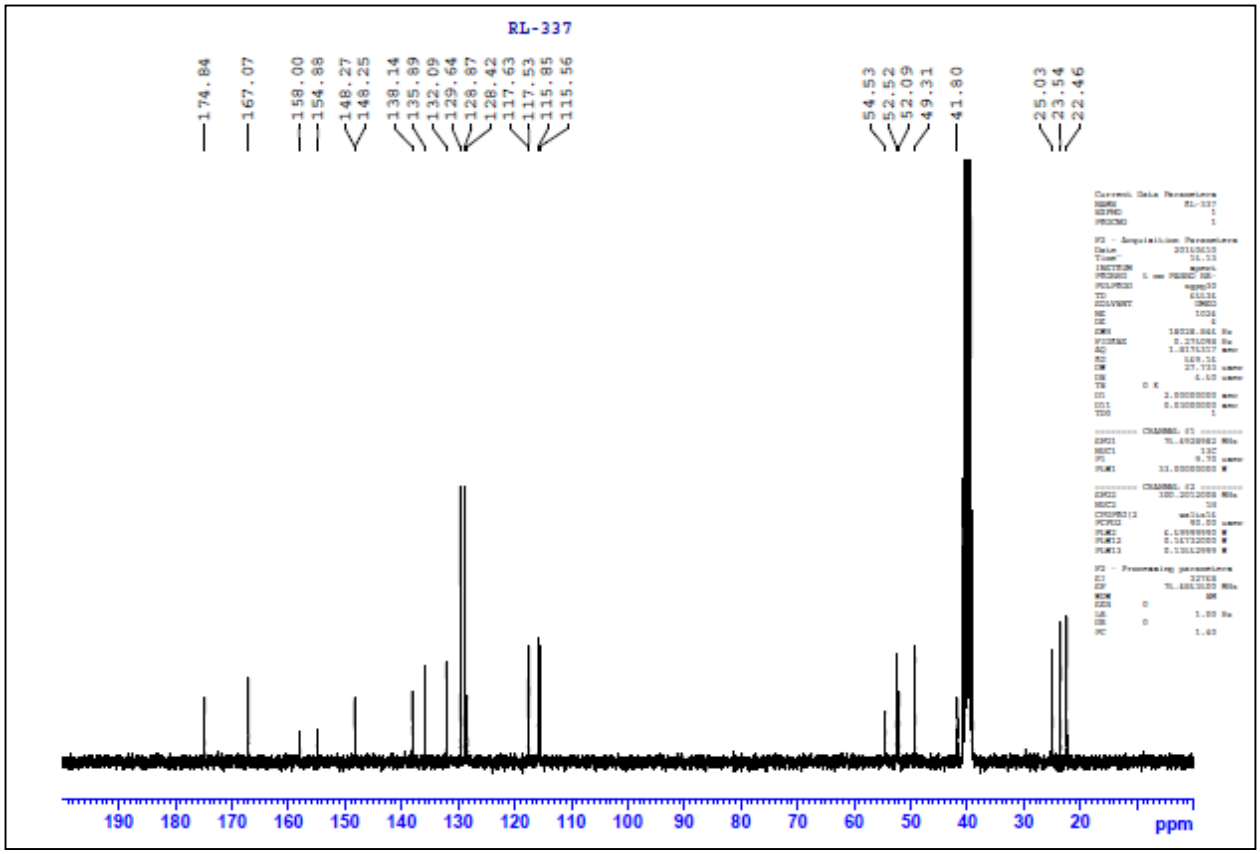
Total		100.000

Peak#	Ret. Time	Peak m/z
1	1.183	440.20
2	1.424	747.50
Total		

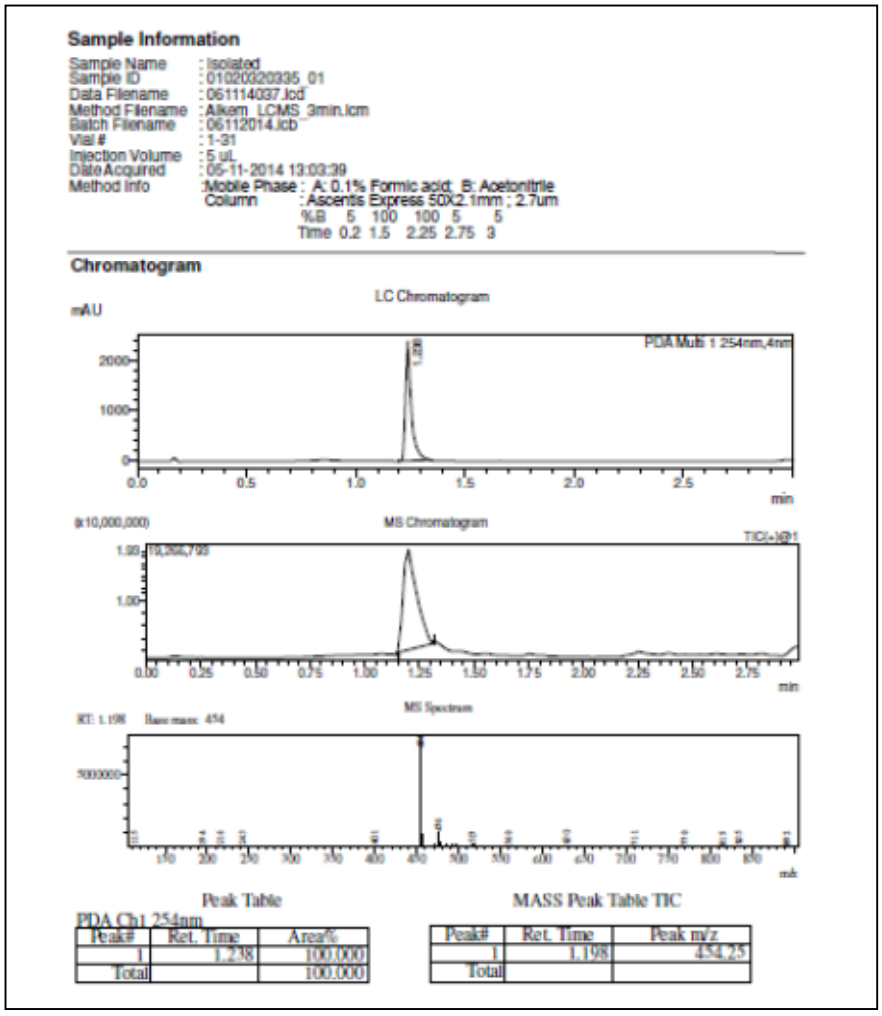
Mass spectra of (E)-(2-((4-(4-fluorophenyl)piperazin-1-yl)methyl)-3-phenylacryloyl)valine **(13v)**



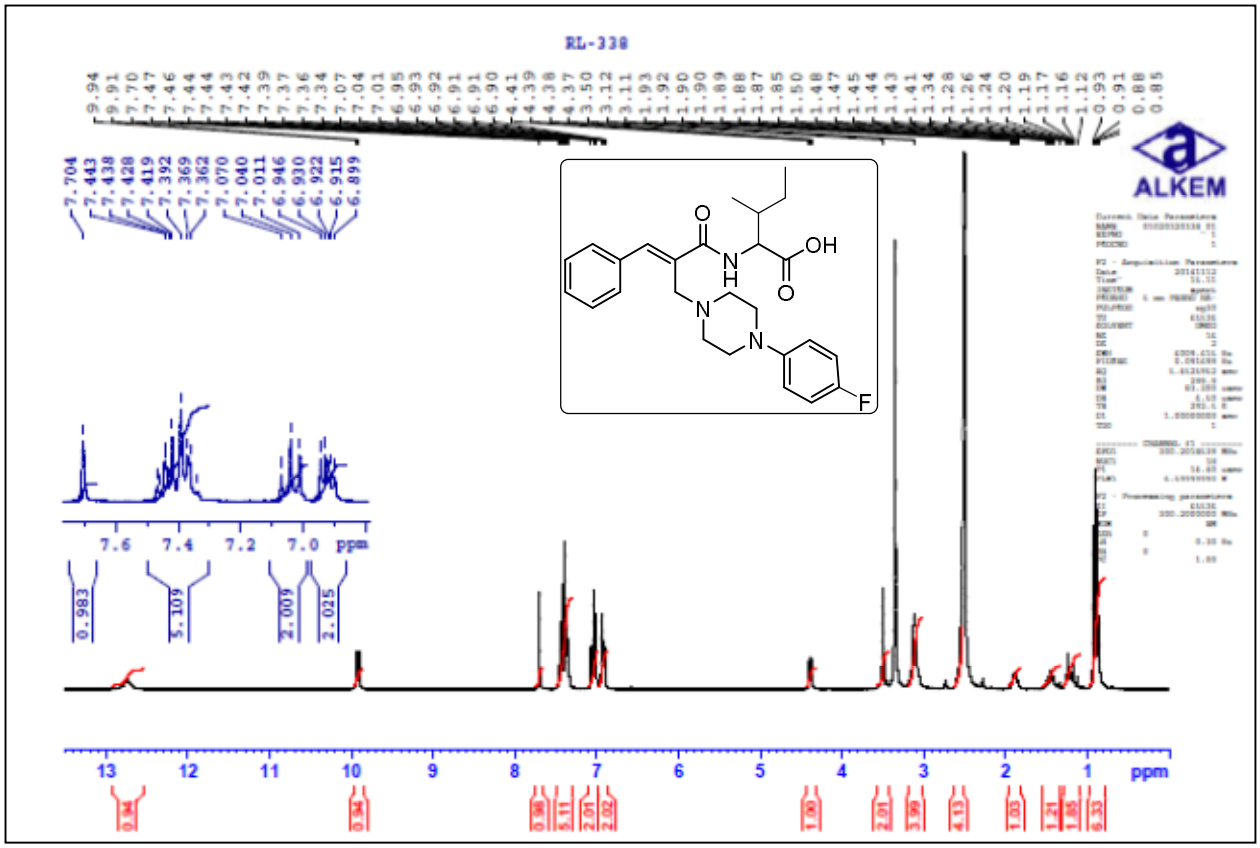
^{1}H NMR spectra of (E)-(2-((4-(4-fluorophenyl)piperazin-1-yl)methyl)-3-phenylacryloyl)leucine **(13w)**



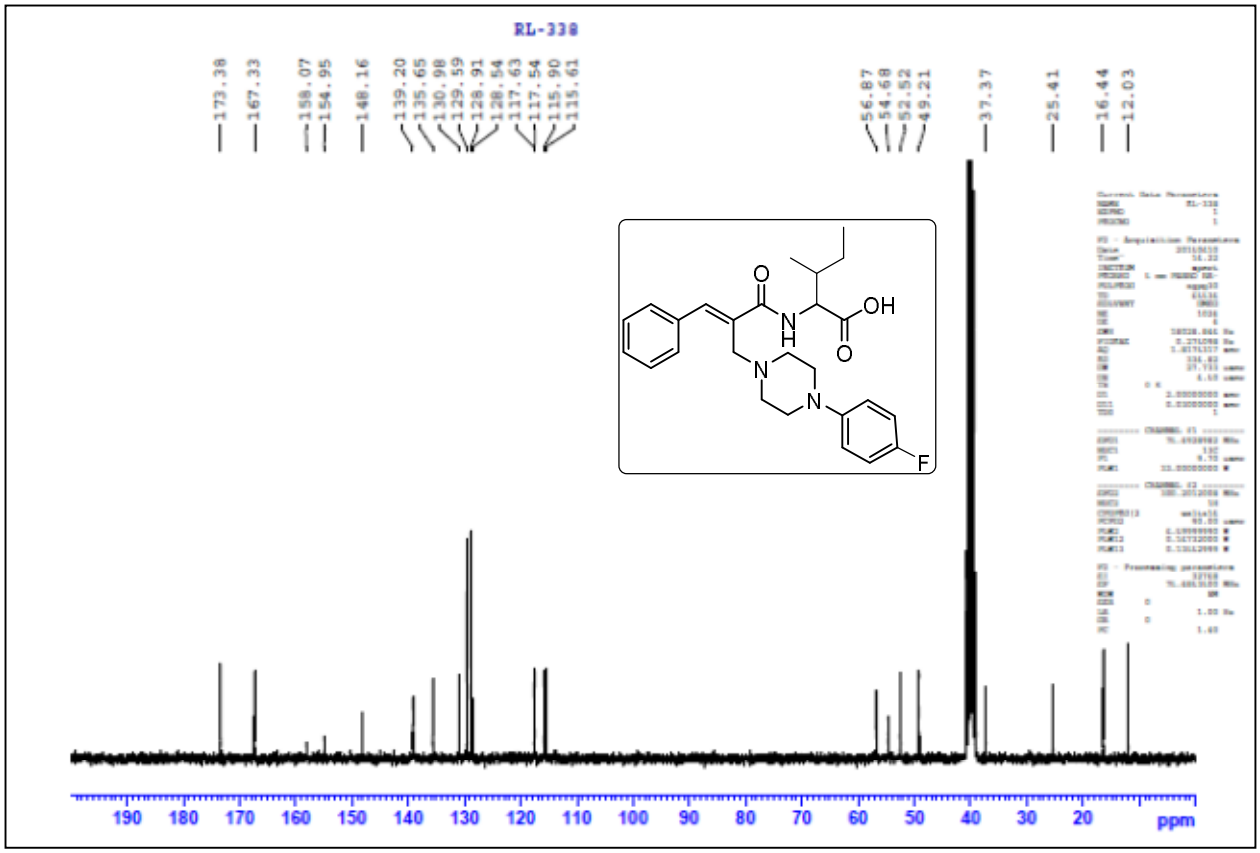
^{13}C NMR spectra of (E)-(2-((4-(4-fluorophenyl)piperazin-1-yl)methyl)-3-phenylacryloyl)leucine **(13w)**



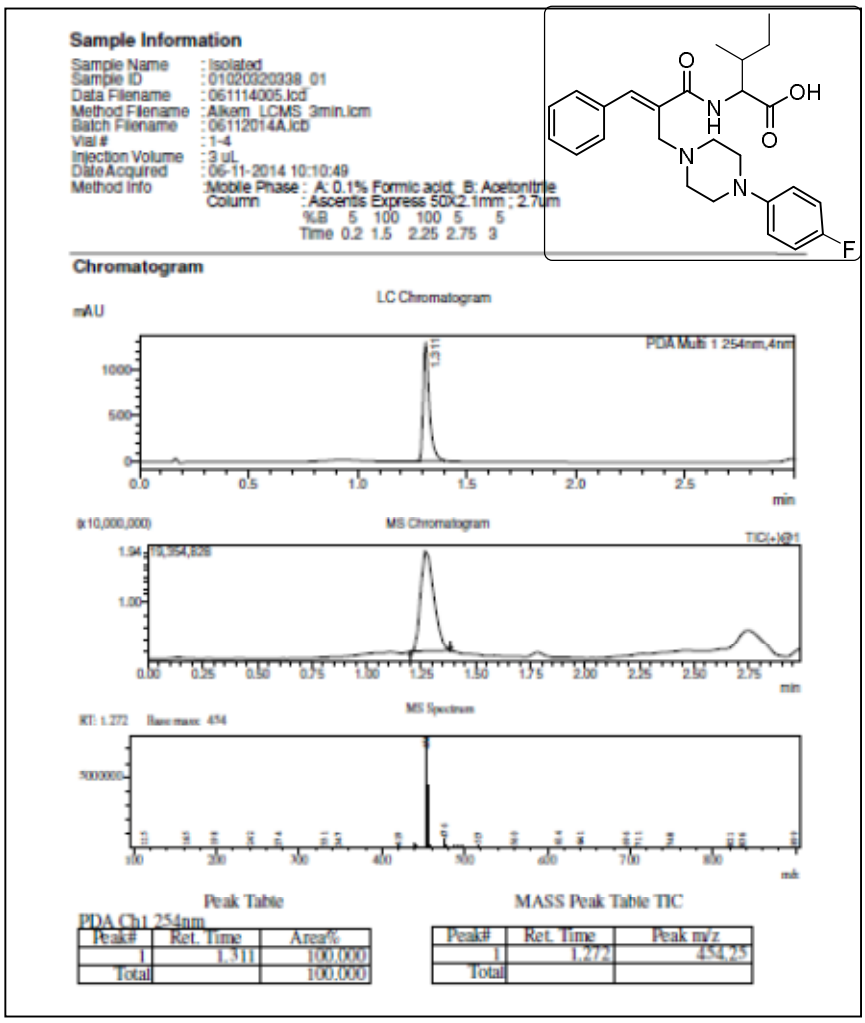
Mass spectra of (E)-(2-((4-(4-fluorophenyl)piperazin-1-yl)methyl)-3-phenylacryloyl)leucine **(13w)**



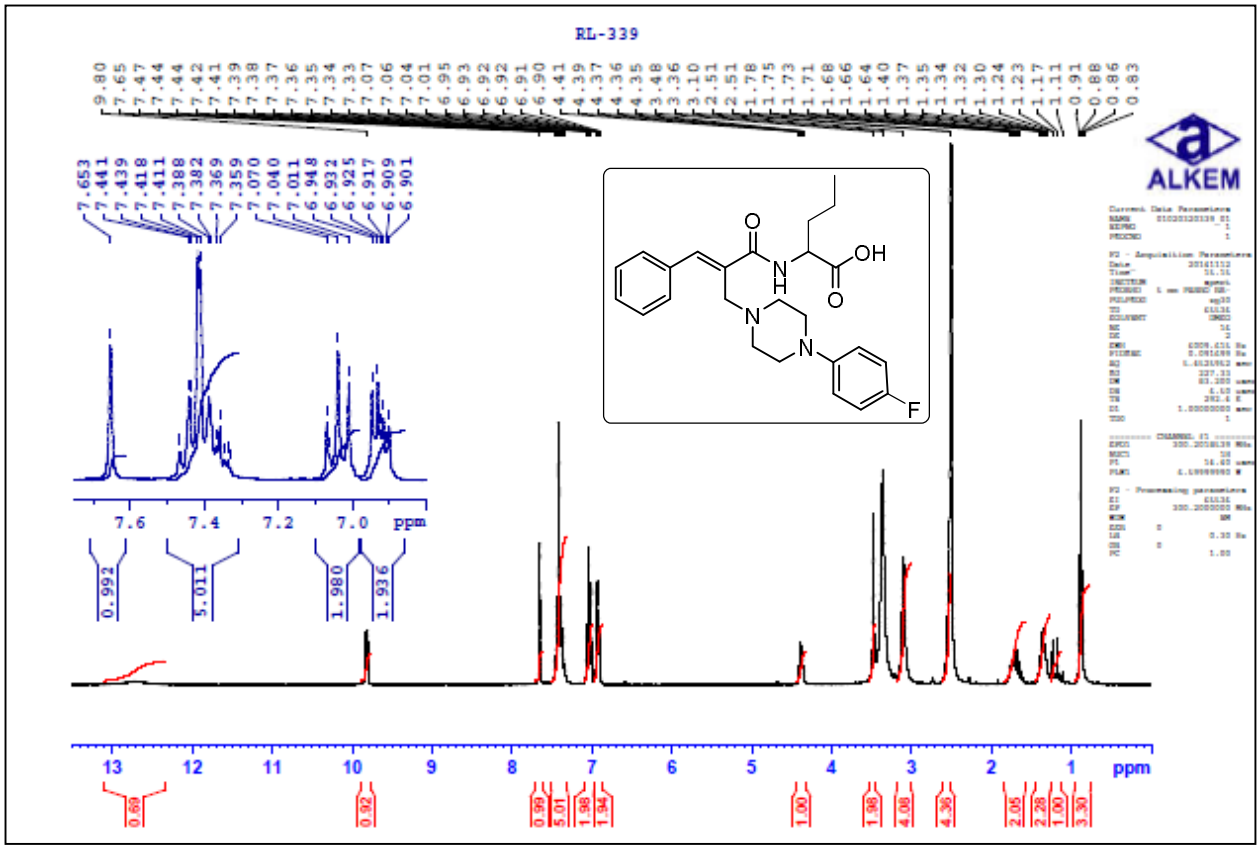
^{1}H NMR spectra of (E)-2-(2-((4-(4-fluorophenyl)piperazin-1-yl)methyl)-3-phenylacrylamido)-3-methylpentanoic acid **(13x)**



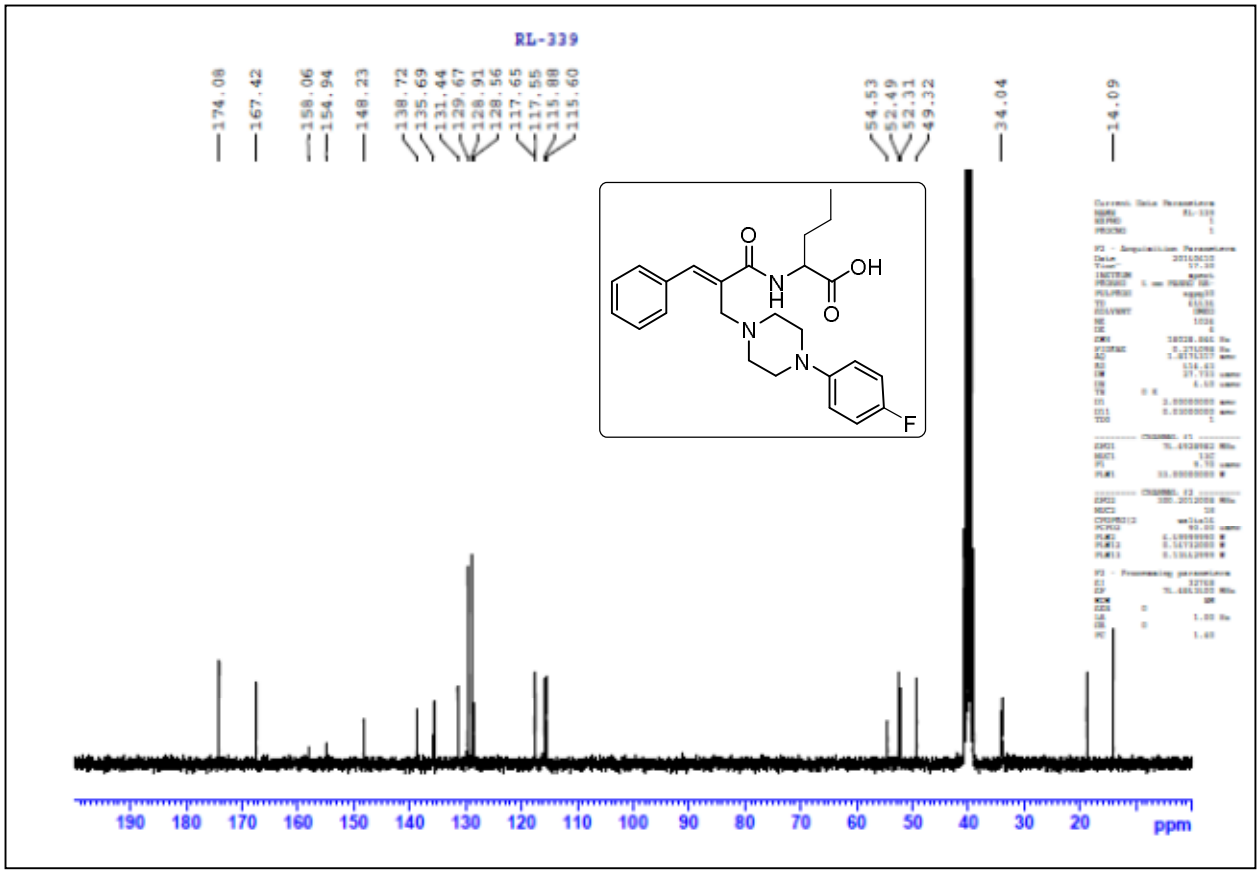
^{13}C NMR spectra of (E)-2-(2-((4-(4-fluorophenyl)piperazin-1-yl)methyl)-3-phenylacrylamido)-3-methylpentanoic acid **(13x)**



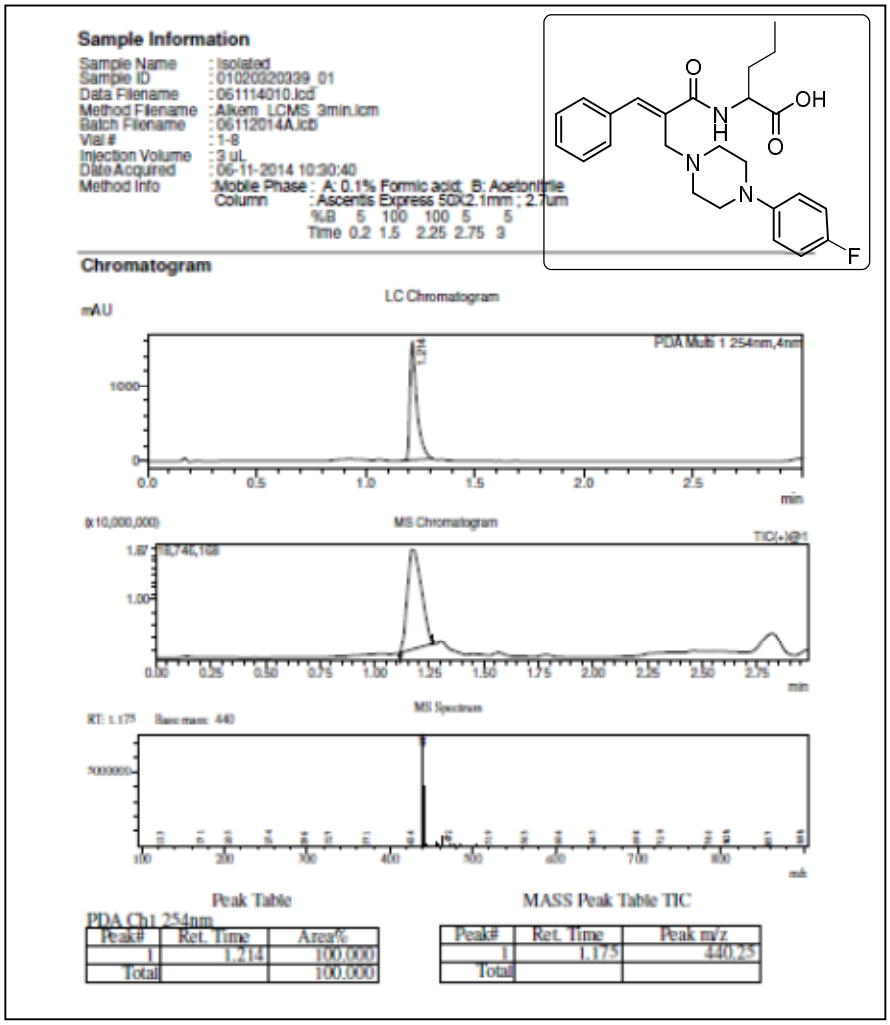
Mass spectra of (E)-2-(2-((4-(4-fluorophenyl)piperazin-1-yl)methyl)-3-phenylacrylamido)-3-methylpentanoic acid **(13x)**



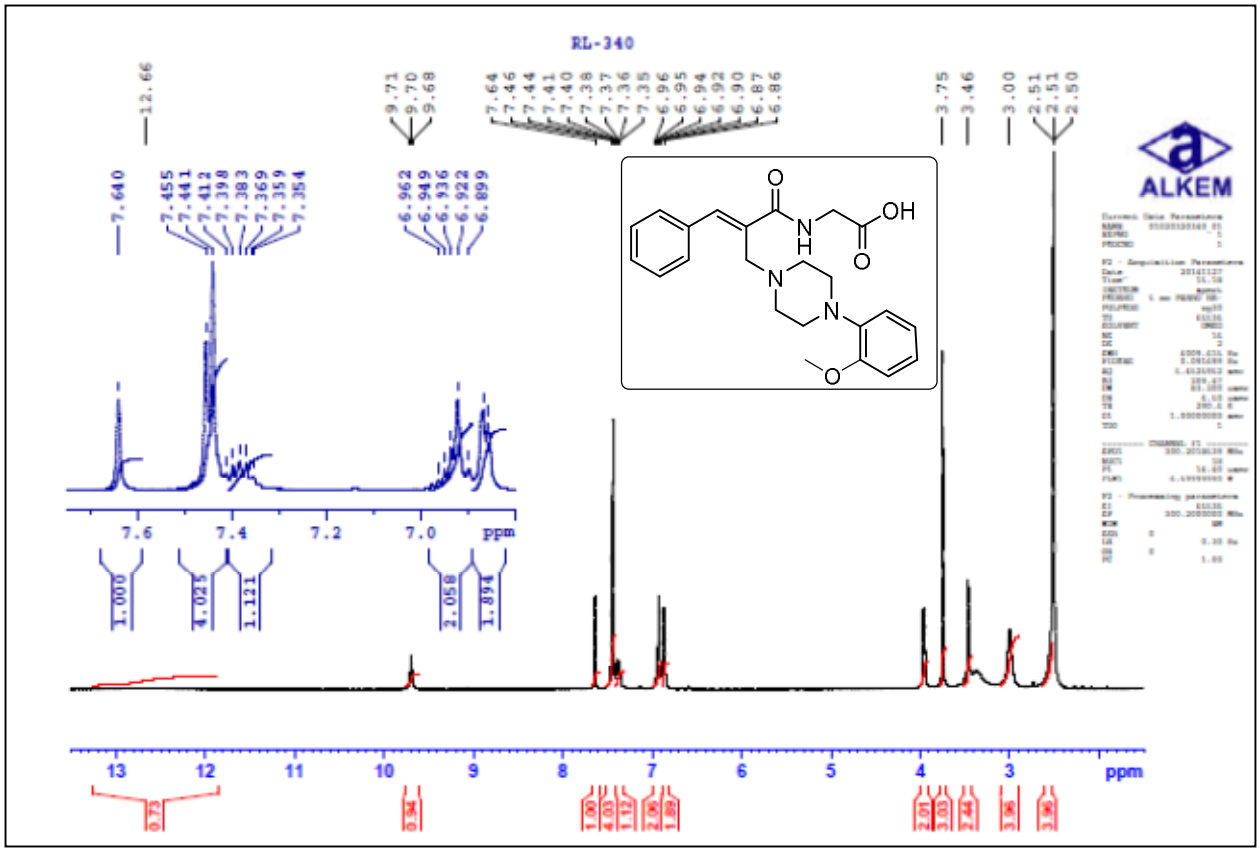
^{1}H NMR spectra of (E)-2-(2-((4-(4-fluorophenyl)piperazin-1-yl)methyl)-3-phenylacrylamido) pentanoic acid **(13y)**



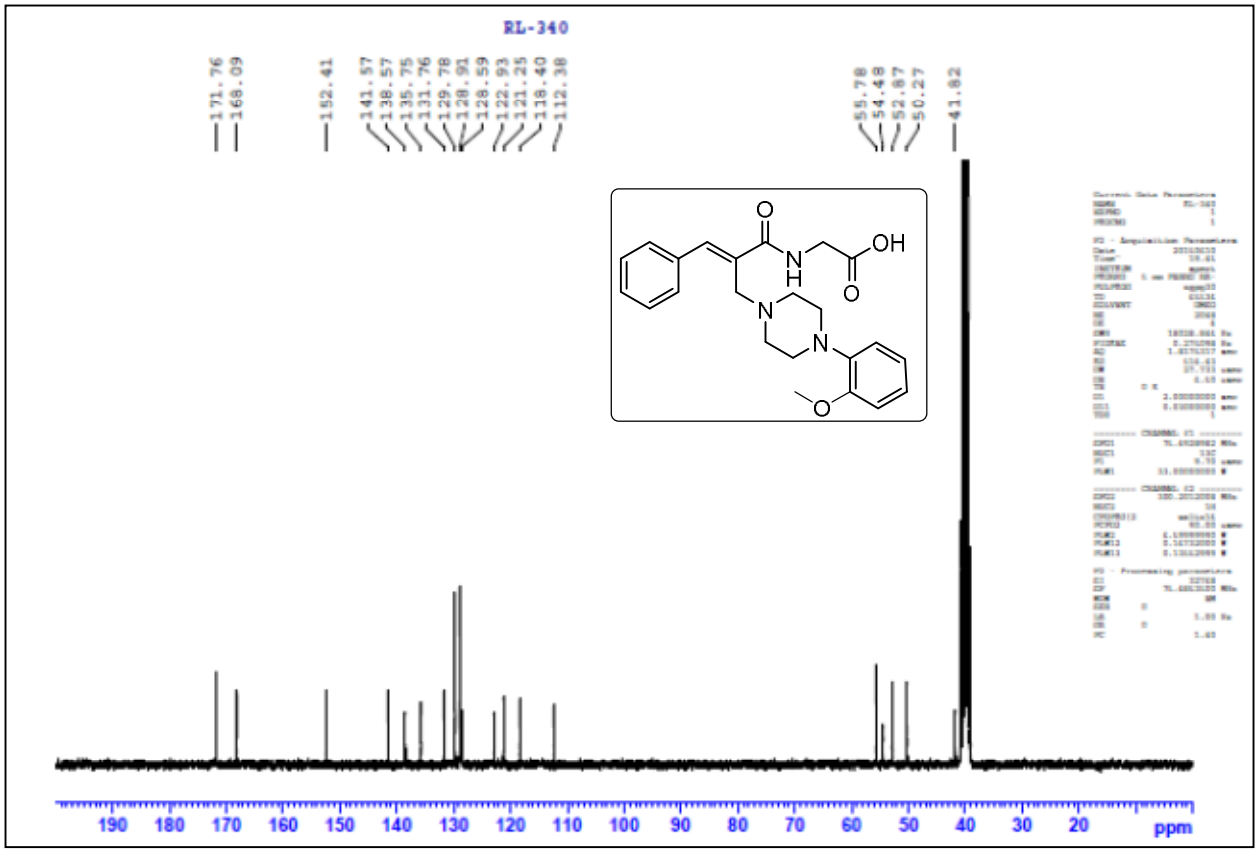
^{13}C NMR spectra of (E)-2-(2-((4-(4-fluorophenyl)piperazin-1-yl)methyl)-3-phenylacrylamido) pentanoic acid **(13y)**



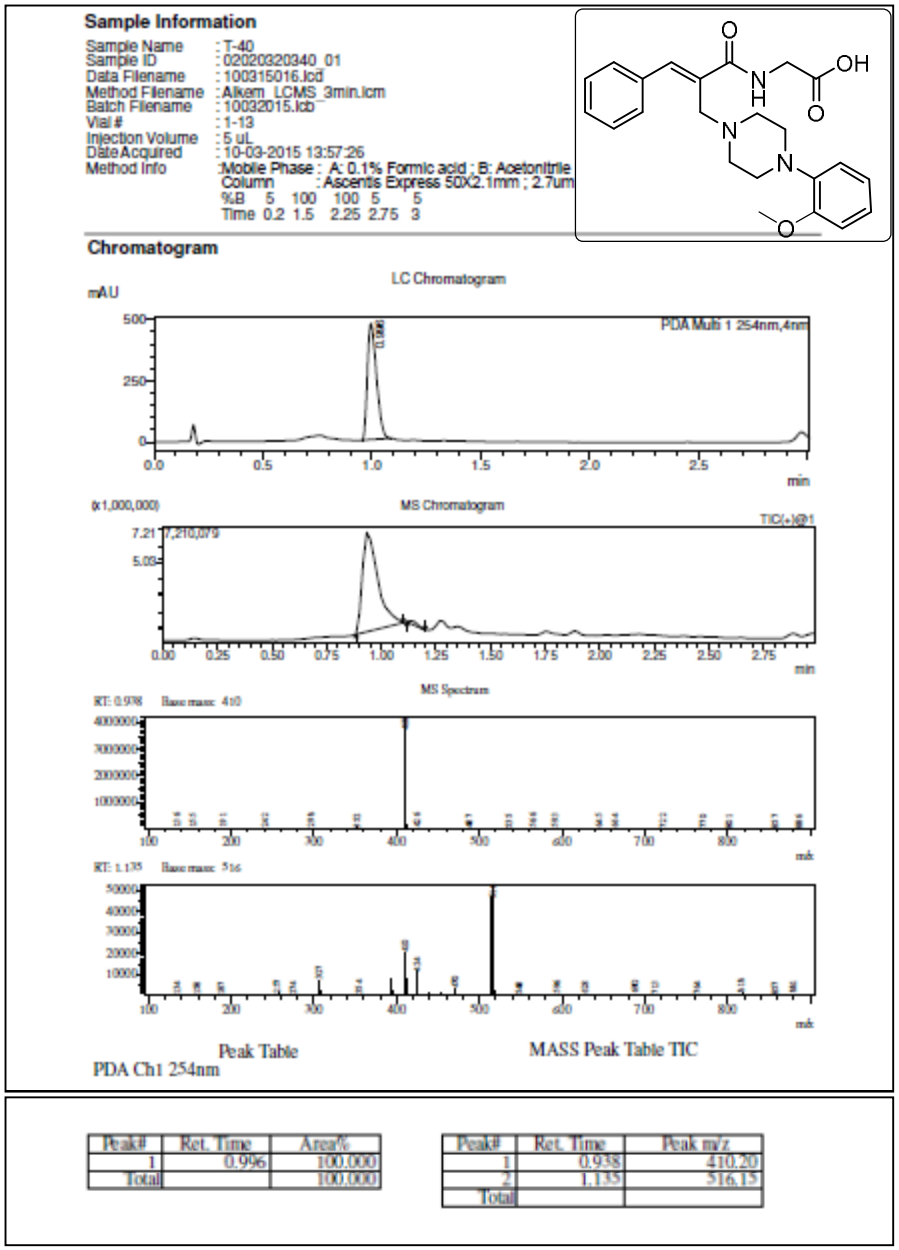
Mass spectra of (E)-2-(2-((4-(4-fluorophenyl)piperazin-1-yl)methyl)-3-phenylacrylamido) pentanoic acid **(13y)**



[1]H NMR spectra of (E)-(2-((4-(2-methoxyphenyl)piperazin-1-yl)methyl)-3-phenylacryloyl) glycine **(13z)**



^{13}C NMR spectra of (E)-(2-((4-(2-methoxyphenyl)piperazin-1-yl)methyl)-3-phenylacryloyl) glycine **(13z)**



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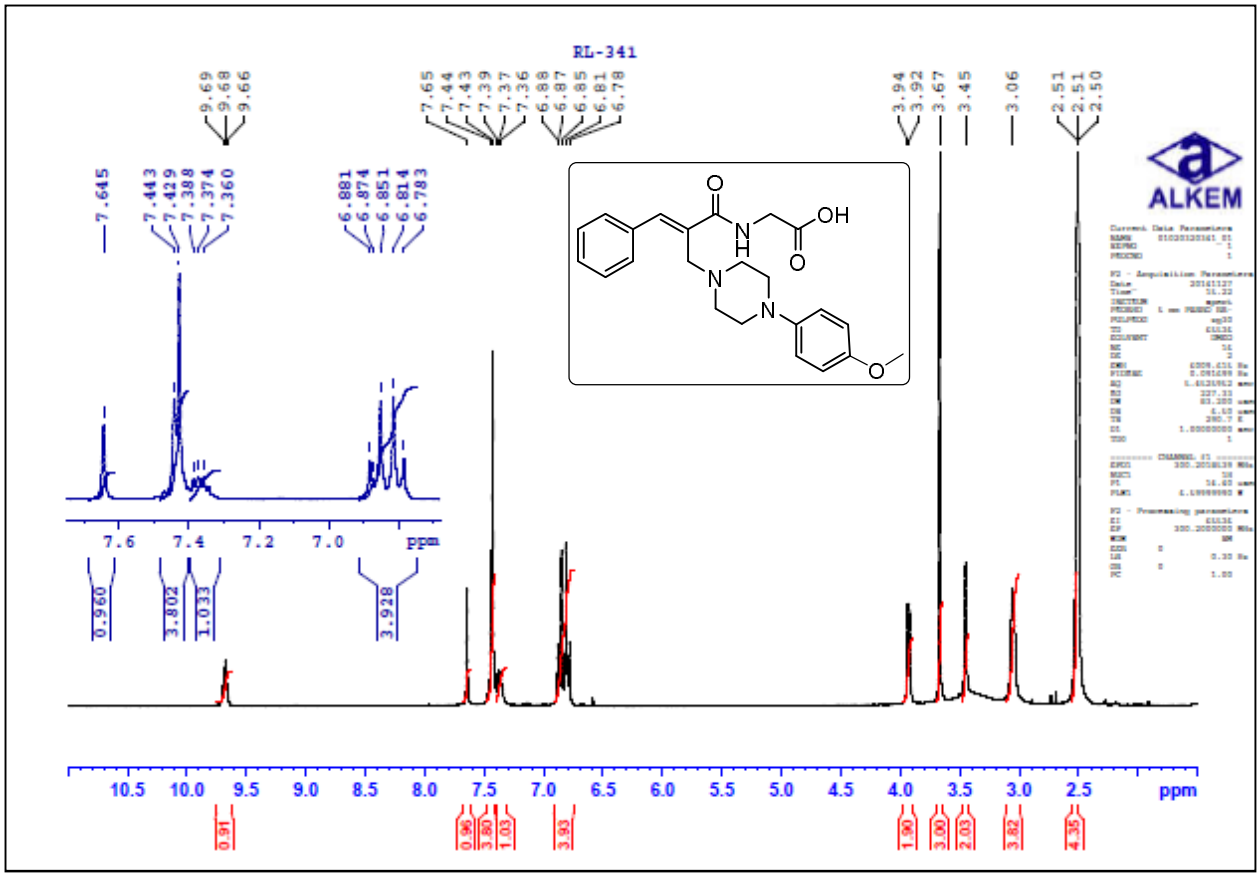
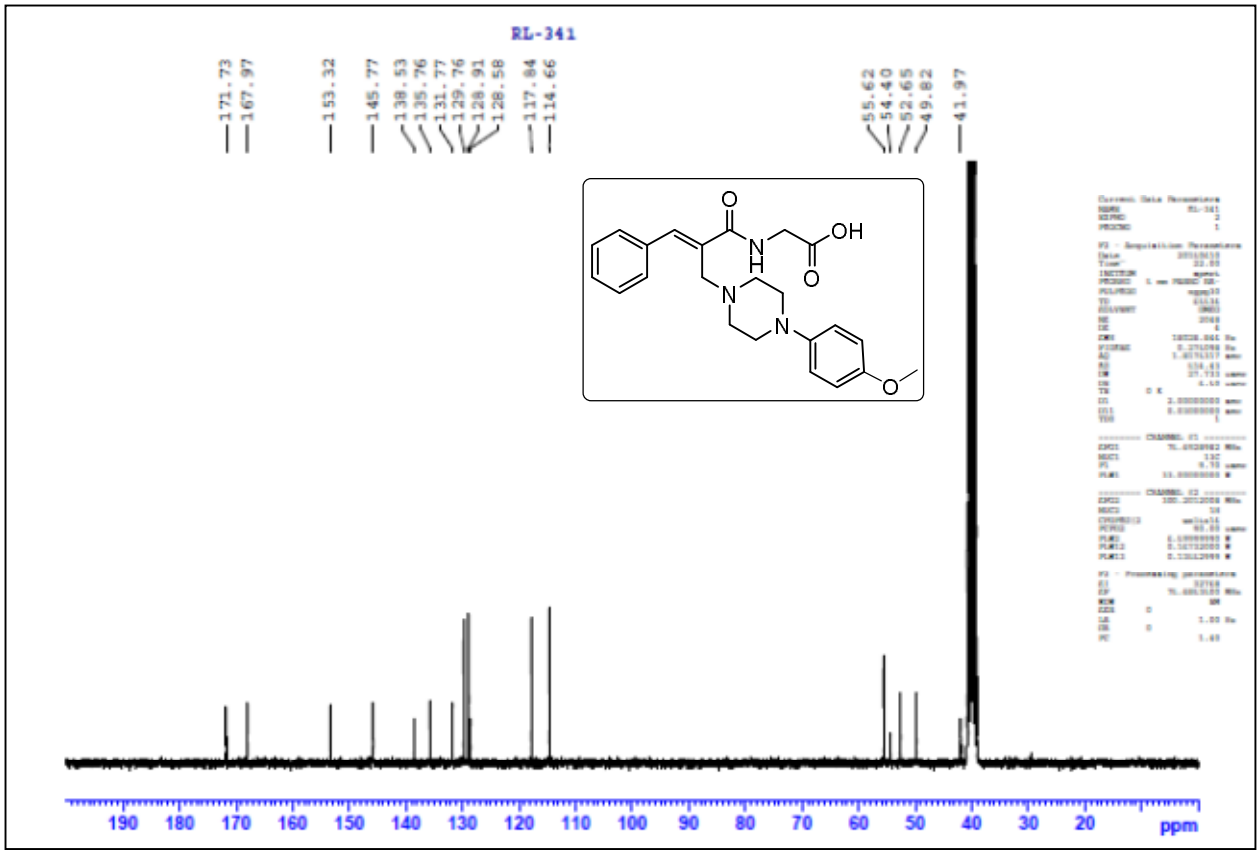
Total		100.000

Peak#	Ret. Time	Peak m/z
1	0.938	410.20
2	1.135	516.15
Total		

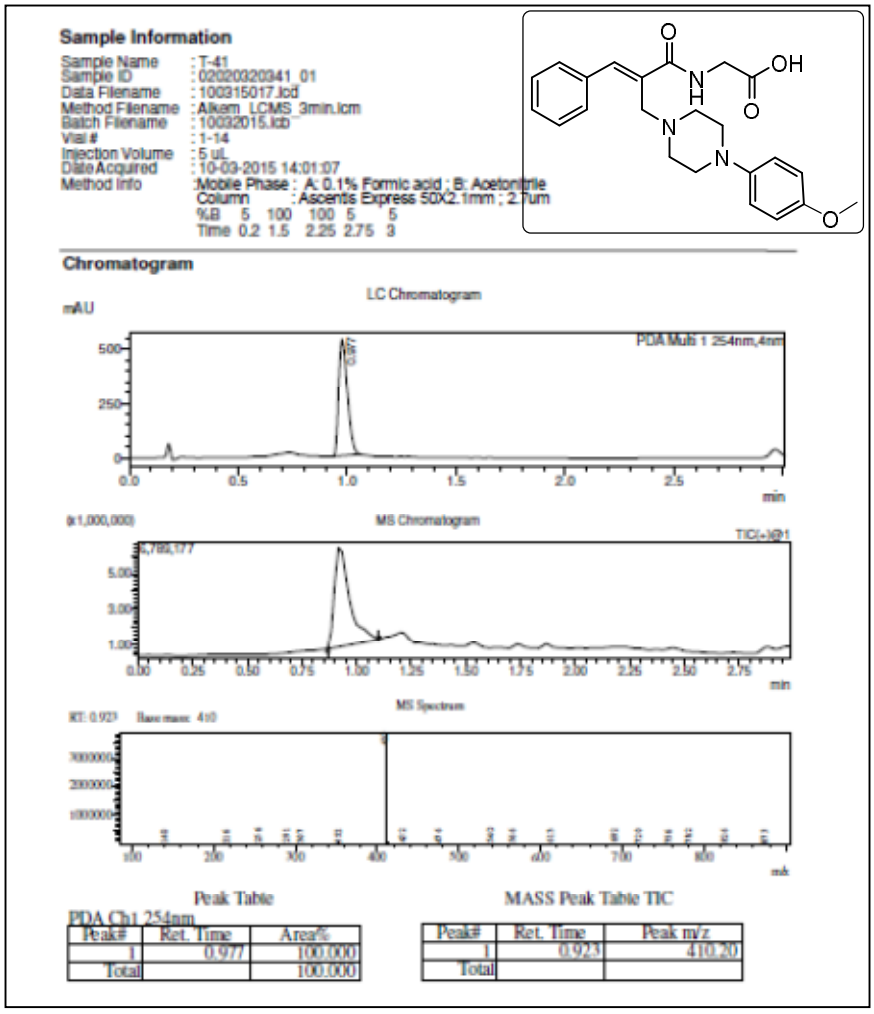
Mass spectra of (E)-(2-((4-(2-methoxyphenyl)piperazin-1-yl)methyl)-3-phenylacryloyl) glycine **(13z)**



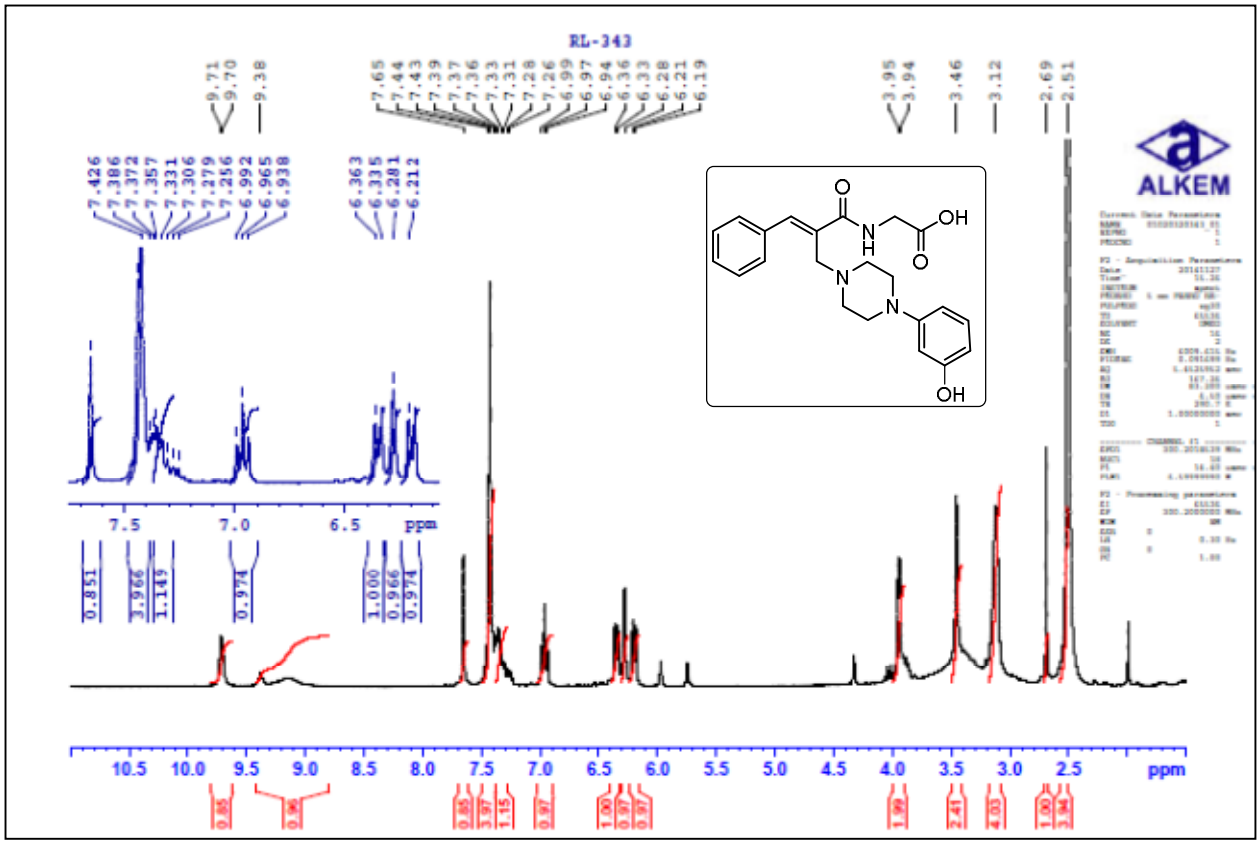
^{1}H NMR spectra of (E)-(2-((4-(4-methoxyphenyl)piperazin-1-yl)methyl)-3-phenylacryloyl) glycine **(13aa)**



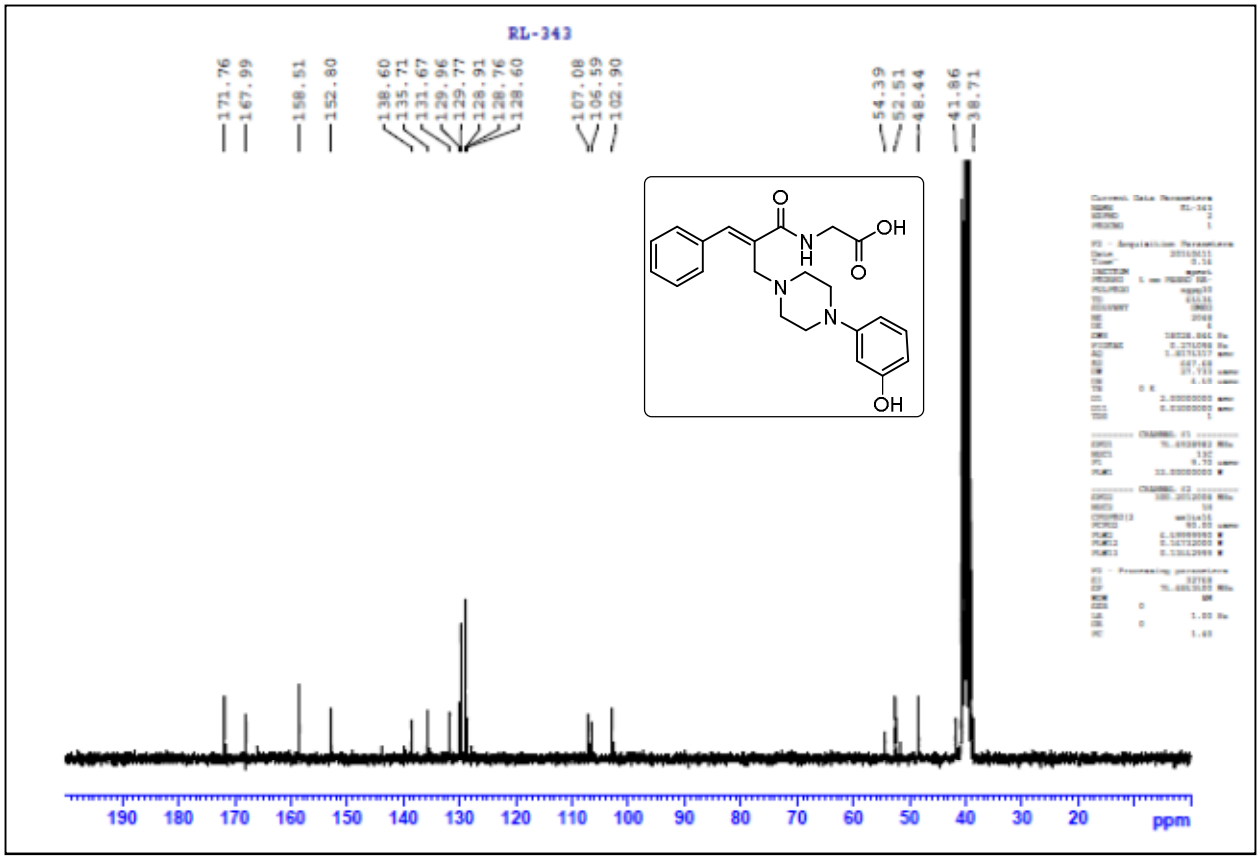
^{13}C NMR spectra of (E)-(2-((4-(4-methoxyphenyl)piperazin-1-yl)methyl)-3-phenylacryloyl) glycine **(13aa)**



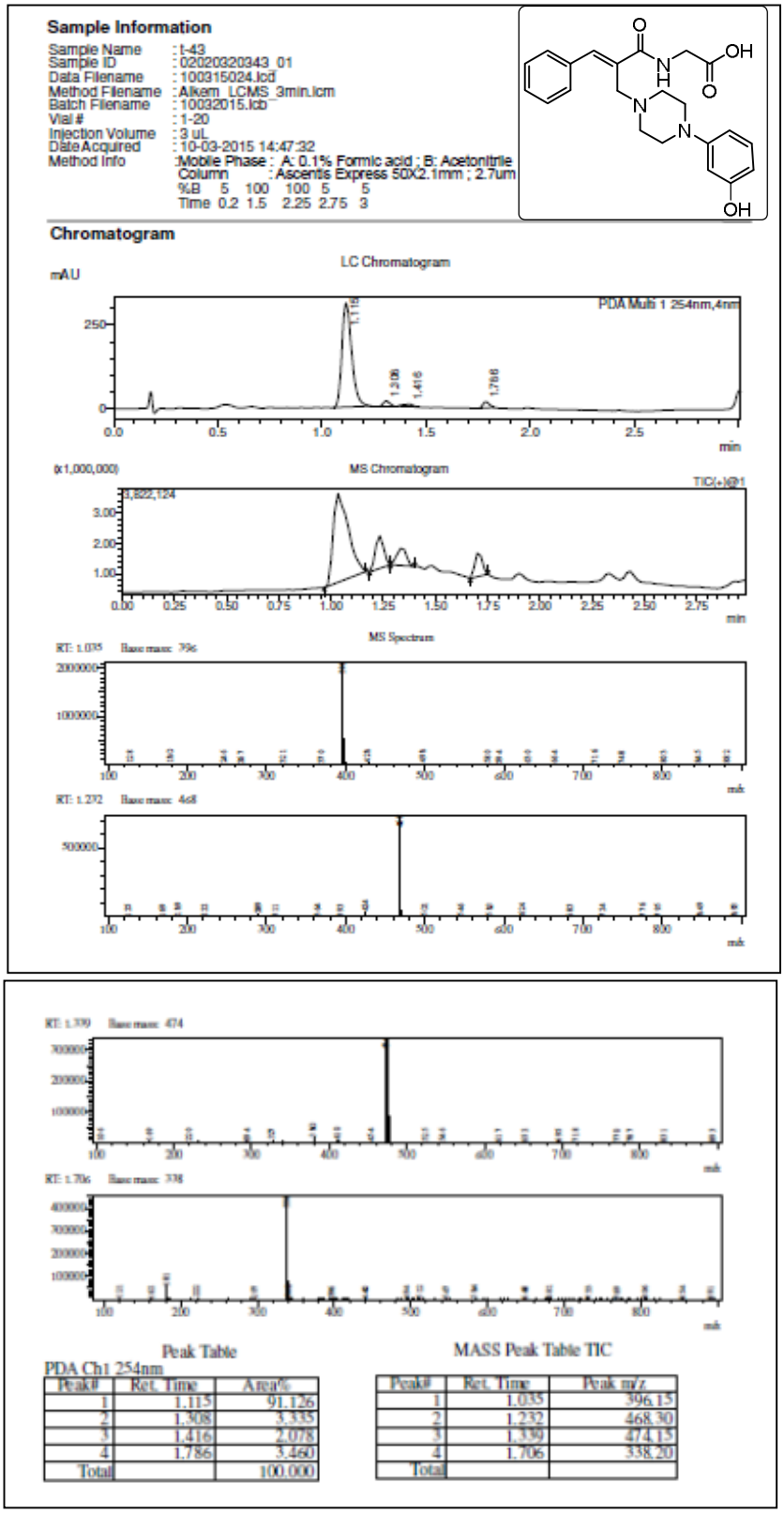
Mass spectra of (E)-(2-((4-(4-methoxyphenyl)piperazin-1-yl)methyl)-3-phenylacryloyl) glycine **(13aa)**



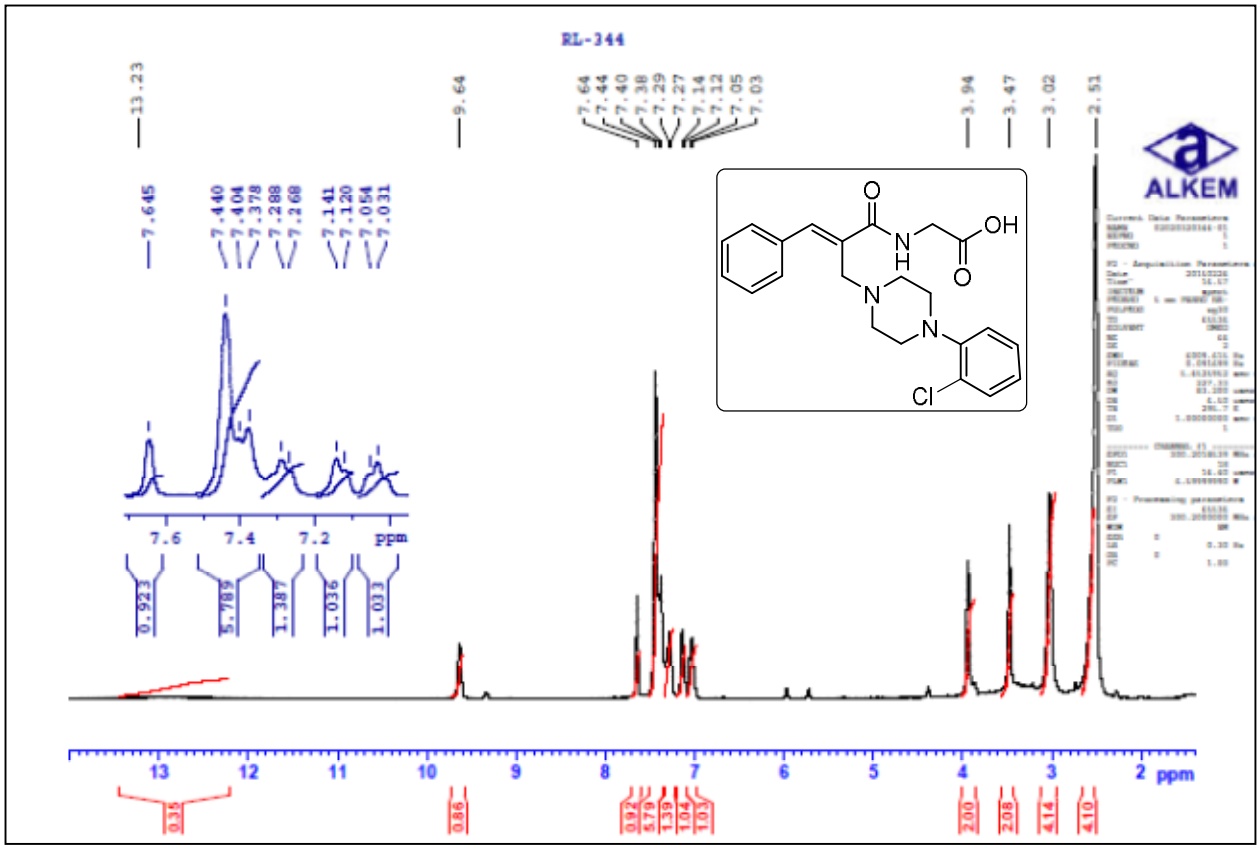
^{1}H NMR spectra of (E)-(2-((4-(3-hydroxyphenyl)piperazin-1-yl)methyl)-3-phenylacryloyl) glycine **(13ab)**



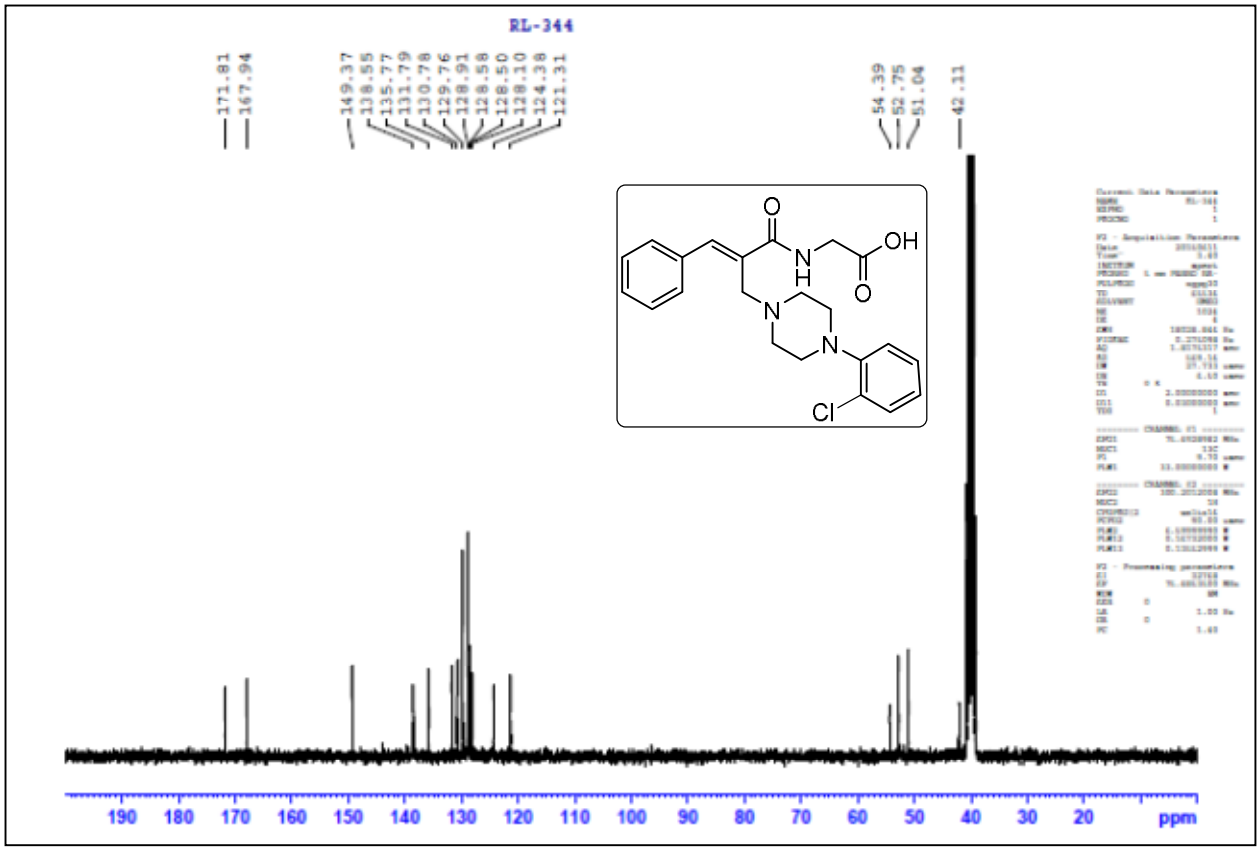
^{13}C NMR spectra of (E)-(2-((4-(3-hydroxyphenyl)piperazin-1-yl)methyl)-3-phenylacryloyl) glycine **(13ab)**



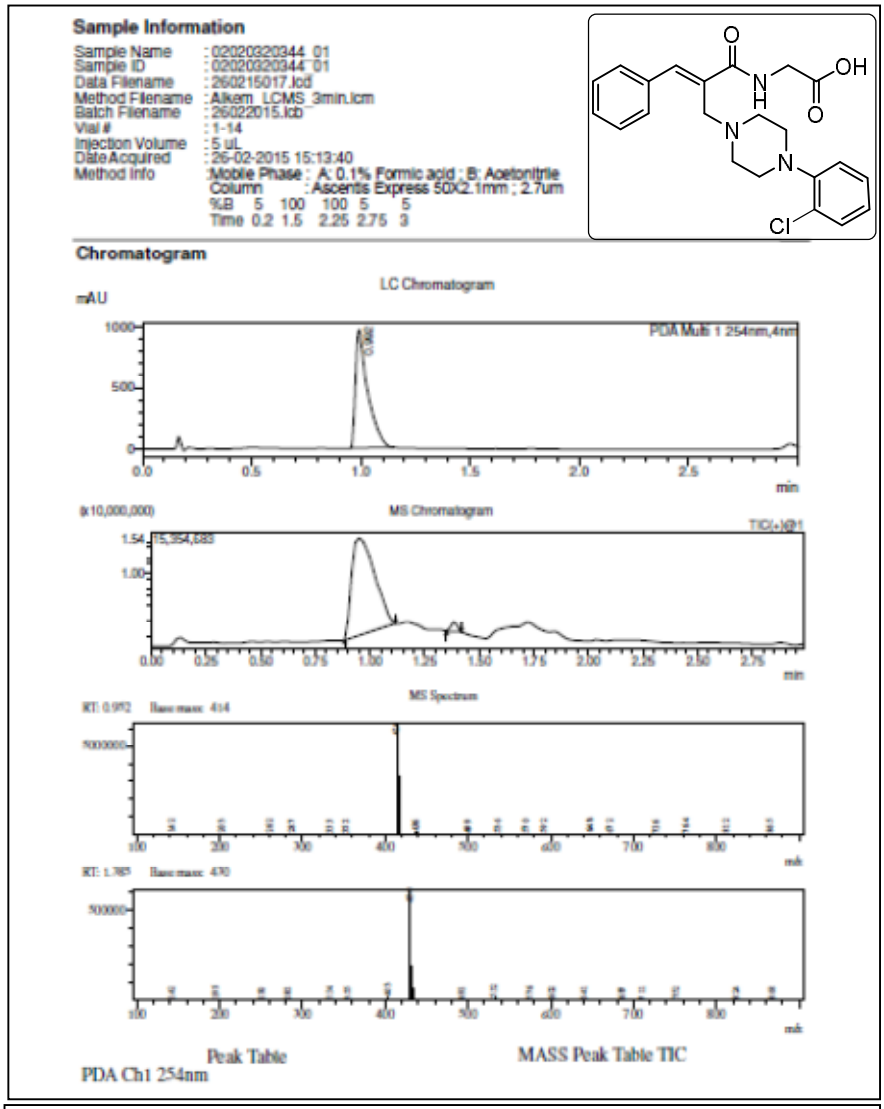
Mass spectra of (E)-(2-((4-(3-hydroxyphenyl)piperazin-1-yl)methyl)-3-phenylacryloyl)glycine **(13ab)**



^{1}H NMR spectra of (E)-(2-((4-(2-chlorophenyl)piperazin-1-yl)methyl)-3-phenylacryloyl)glycine **(13ac)**



^{13}C NMR spectra of (E)-(2-((4-(2-chlorophenyl)piperazin-1-yl)methyl)-3-phenylacryloyl)glycine **(13ac)**



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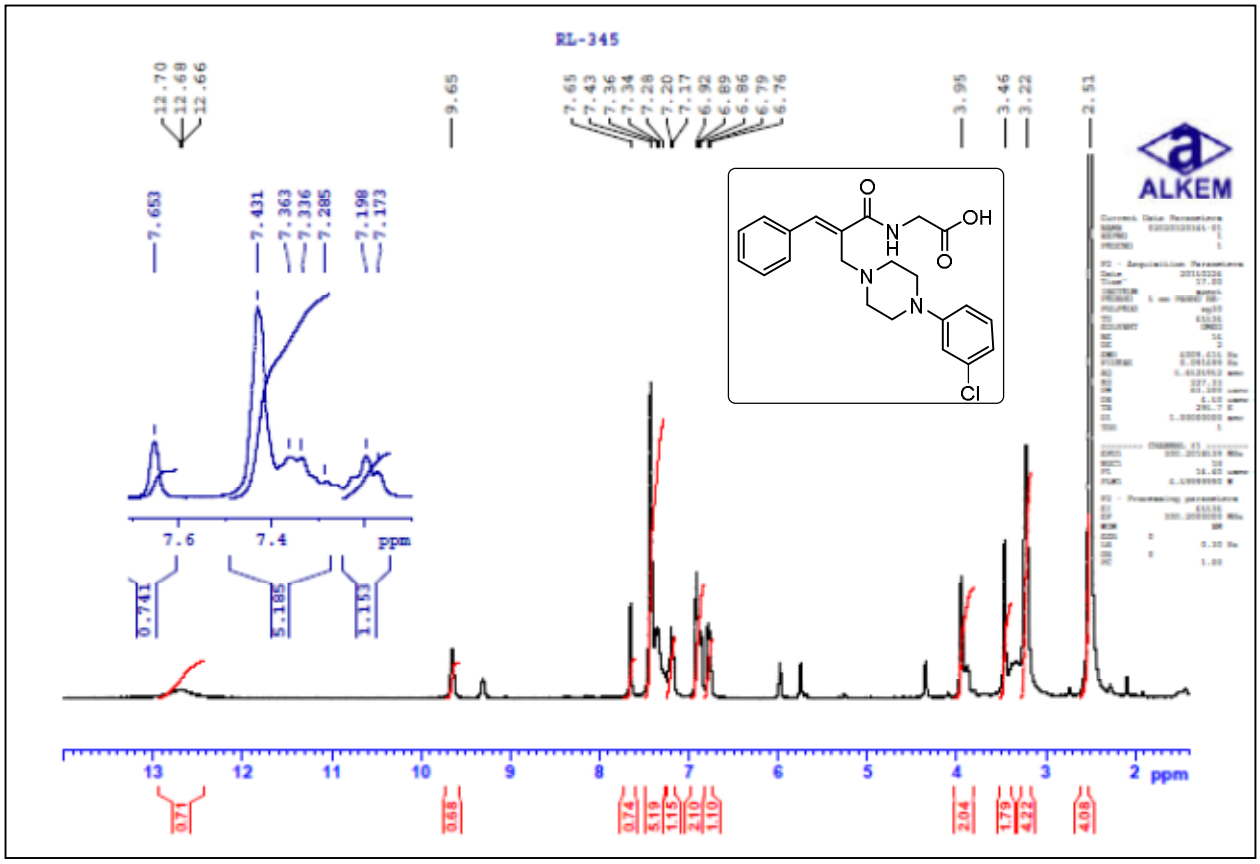
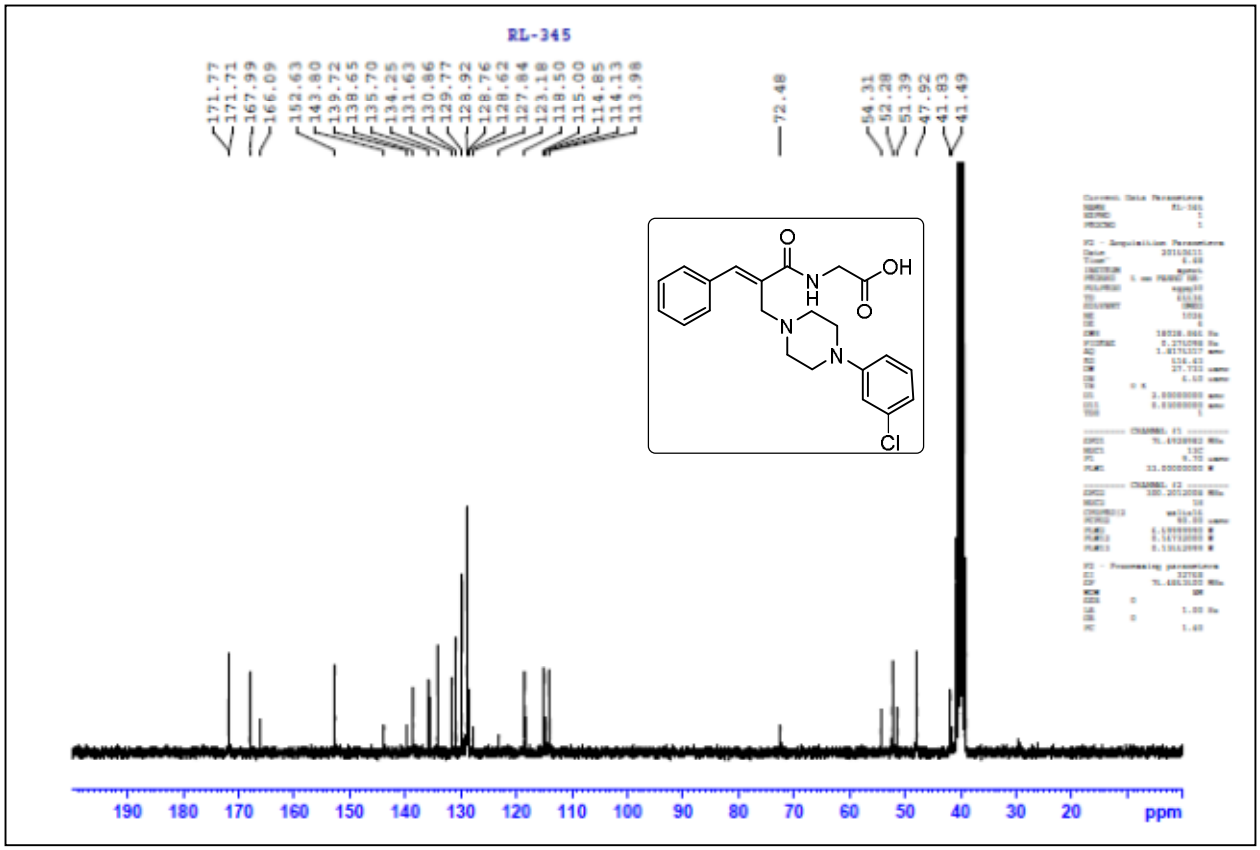
Total		100.000

Peak#	Ret. Time	Peak m/z
1	0.952	414.15
2	1.385	430.15
Total		

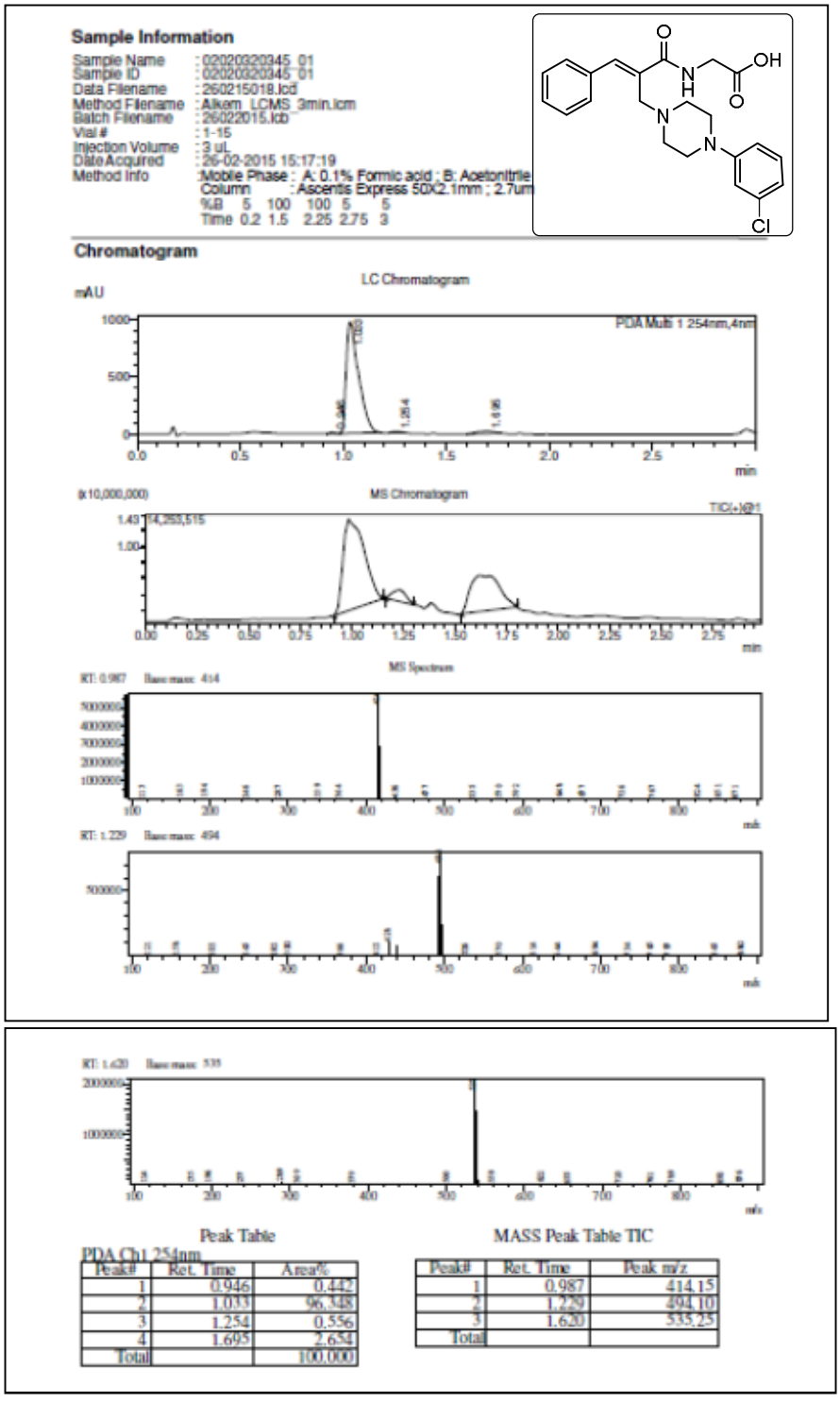
Mass spectra of (E)-(2-((4-(2-chlorophenyl)piperazin-1-yl)methyl)-3-phenylacryloyl)glycine **(13ac)**



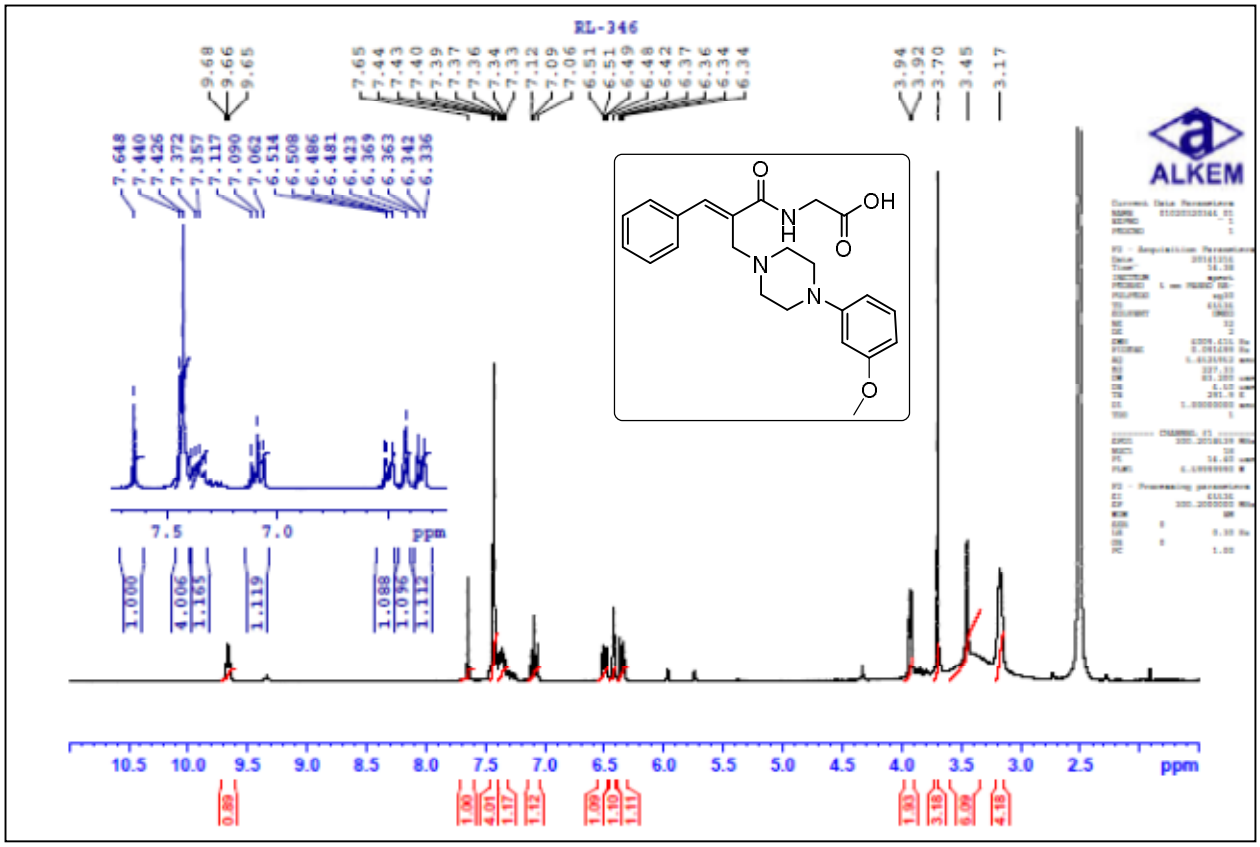
[1]H NMR spectra of (E)-(2-((4-(3-chlorophenyl)piperazin-1-yl)methyl)-3-phenylacryloyl)glycine **(13ad)**



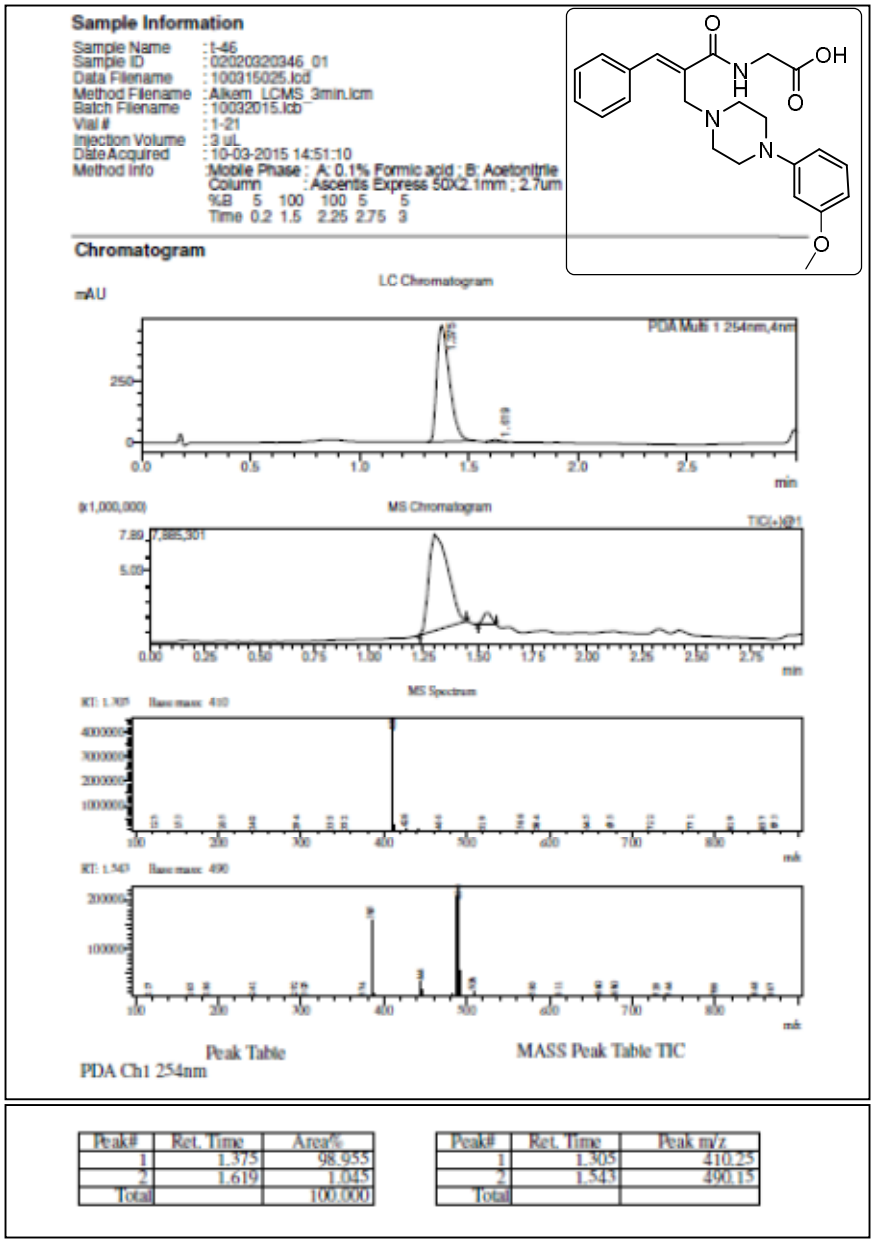
^{13}C NMR spectra of (E)-(2-((4-(3-chlorophenyl)piperazin-1-yl)methyl)-3-phenylacryloyl)glycine **(13ad)**



Mass spectra of (E)-(2-((4-(3-chlorophenyl)piperazin-1-yl)methyl)-3-phenylacryloyl)glycine **(13ad)**



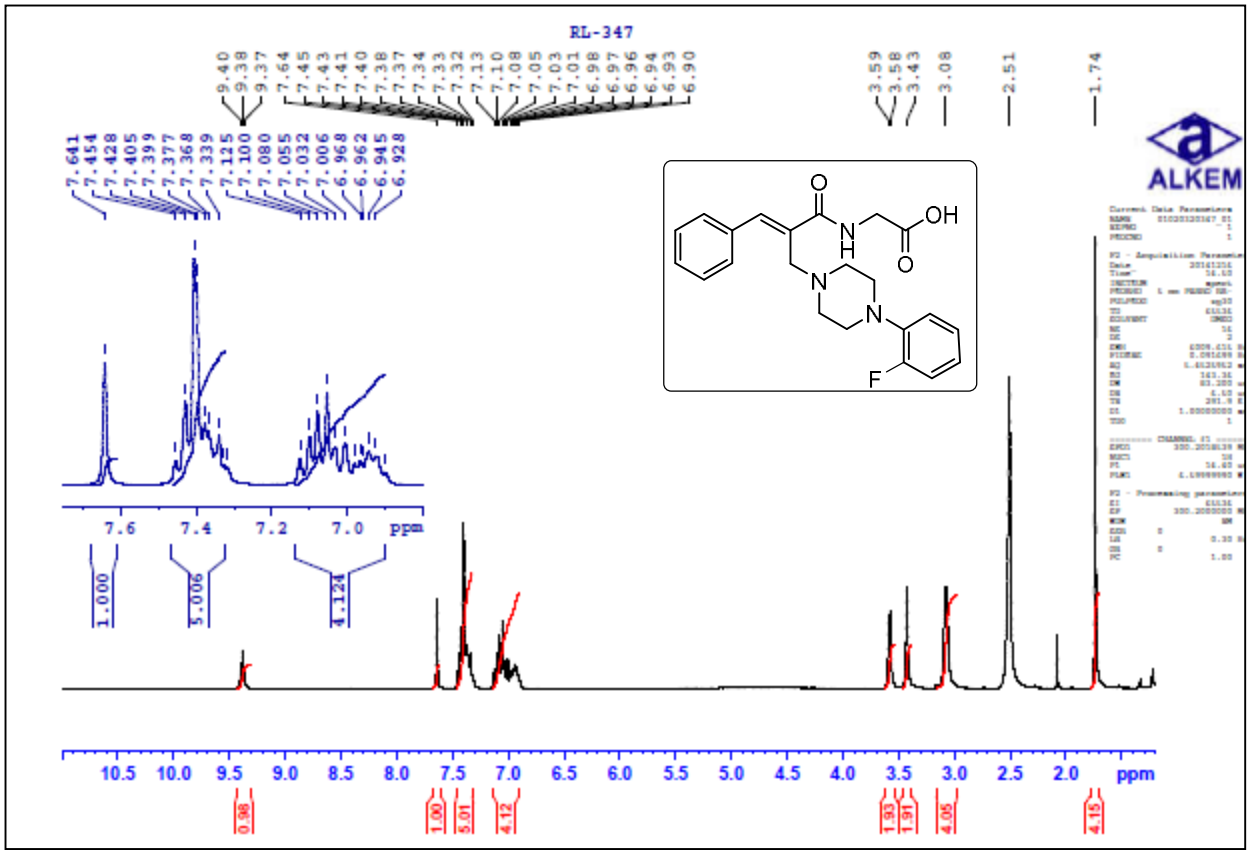
^{1}H NMR spectra of (E)-(2-((4-(3-methoxyphenyl)piperazin-1-yl)methyl)-3-phenylacryloyl)glycine **(13ae)**



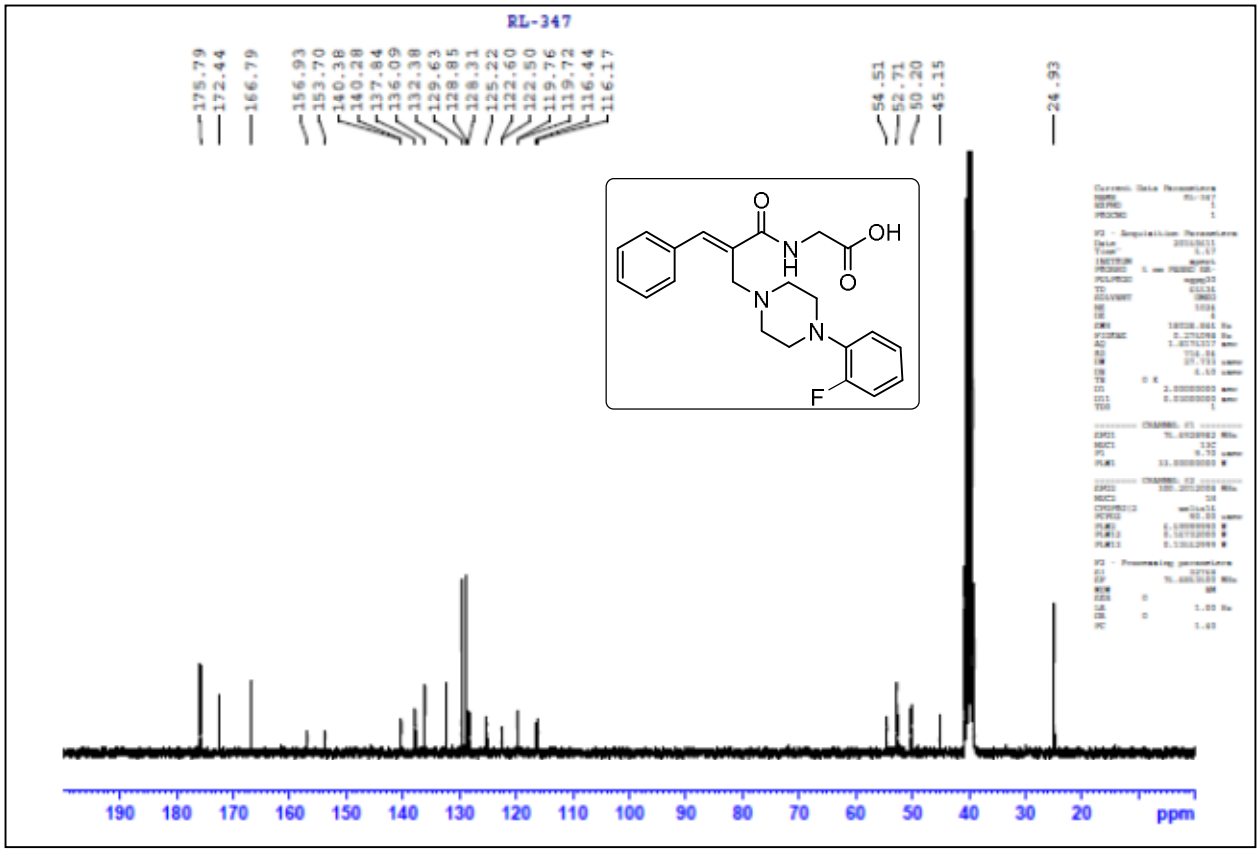
Peak#	Ret. Time	Area%
1	1.375	98.955
2	1.619	1.045
Total		100.000

Peak#	Ret. Time	Peak m/z
1	1.305	410.25
2	1.543	490.15
Total		

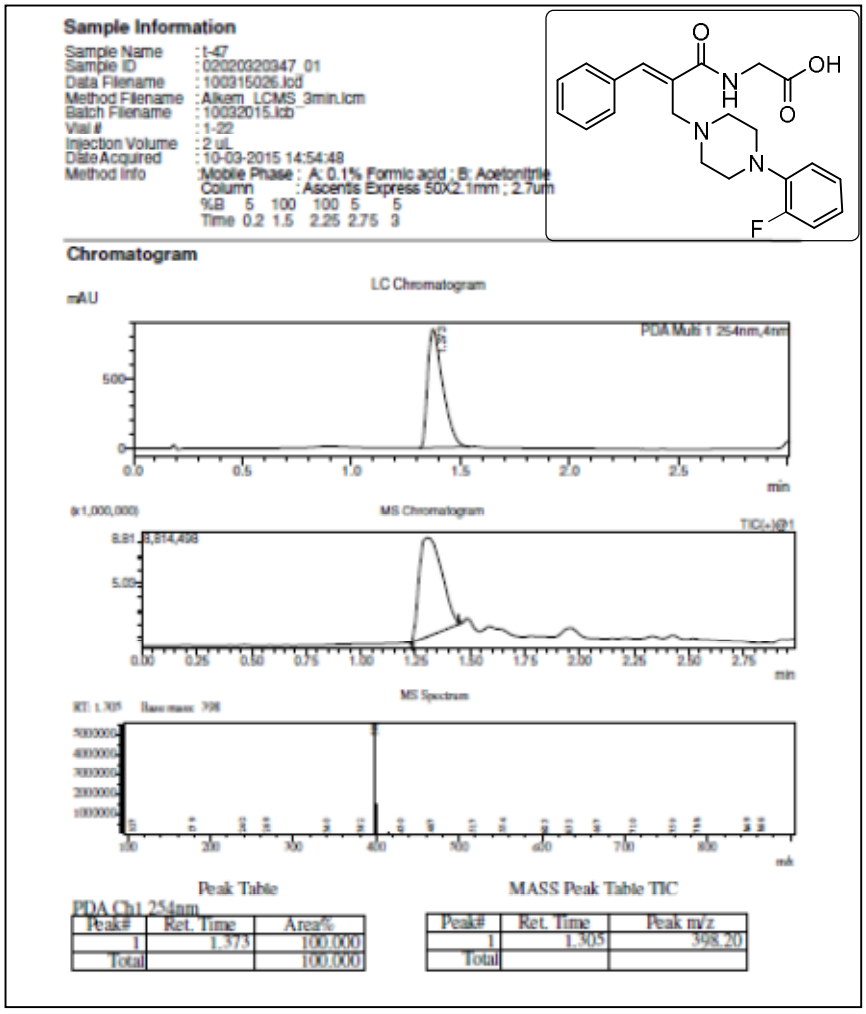
Mass spectra of (E)-(2-((4-(3-methoxyphenyl)piperazin-1-yl)methyl)-3-phenylacryloyl)glycine **(13ae)**



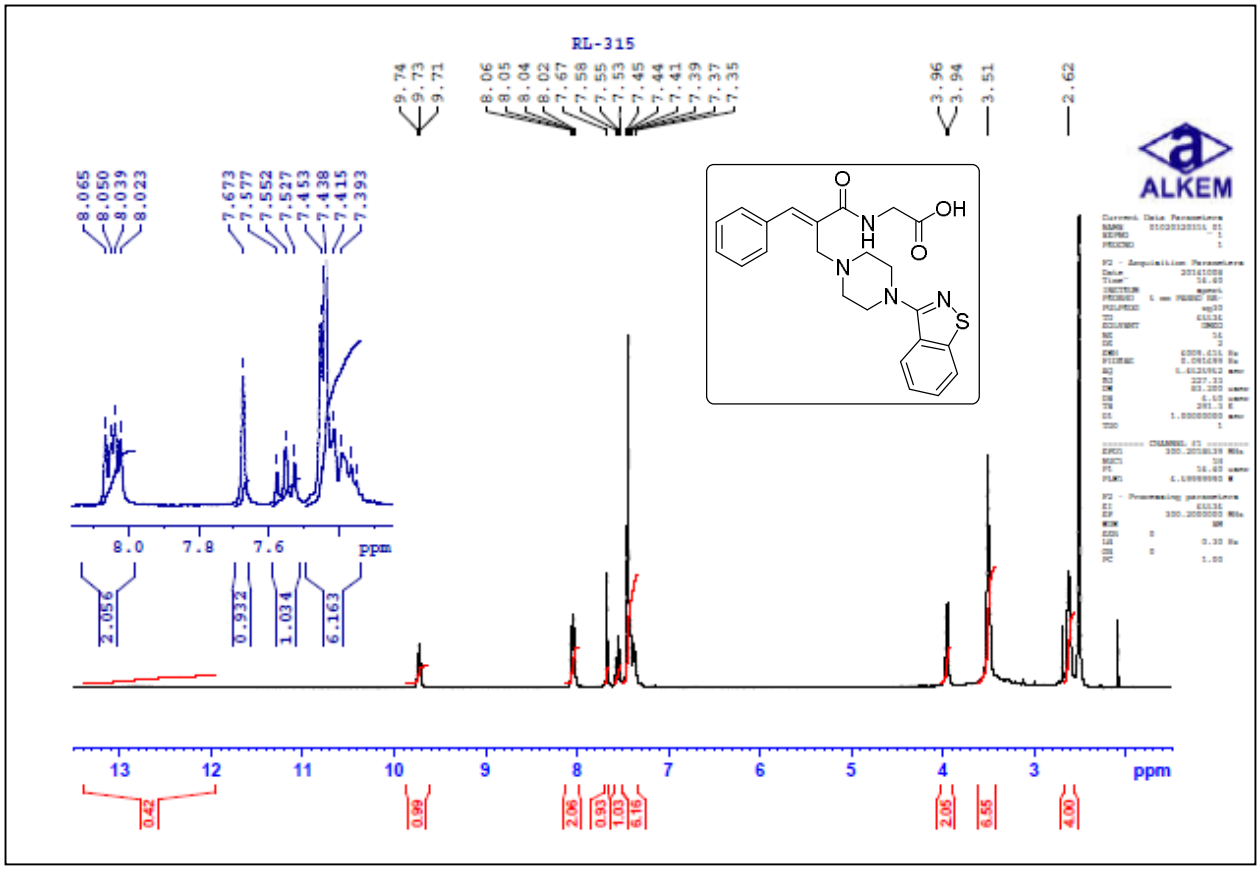
[1]H NMR spectra of (E)-(2-((4-(2-fluorophenyl)piperazin-1-yl)methyl)-3-phenylacryloyl)glycine **(13af)**



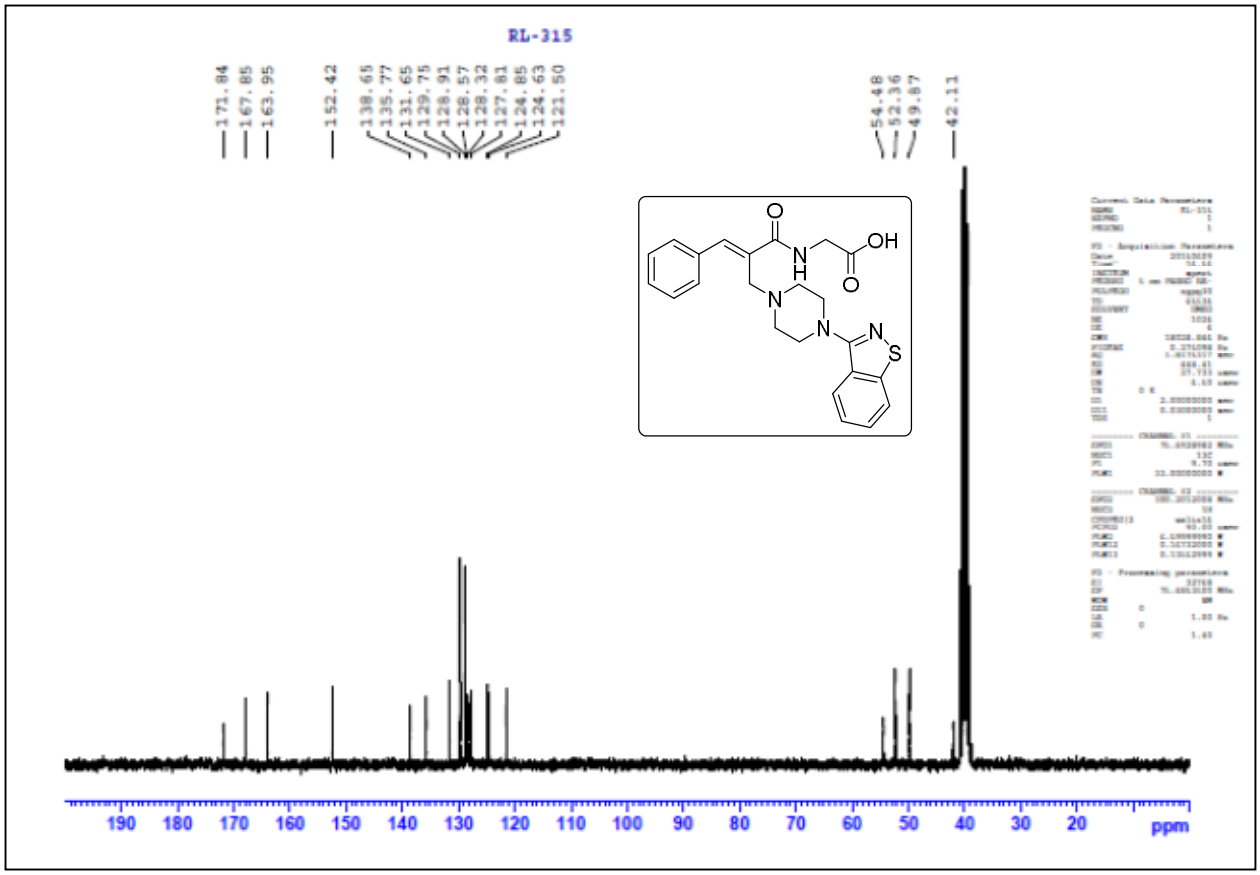
^{13}C NMR spectra of (E)-(2-((4-(2-fluorophenyl)piperazin-1-yl)methyl)-3-phenylacryloyl)glycine **(13af)**



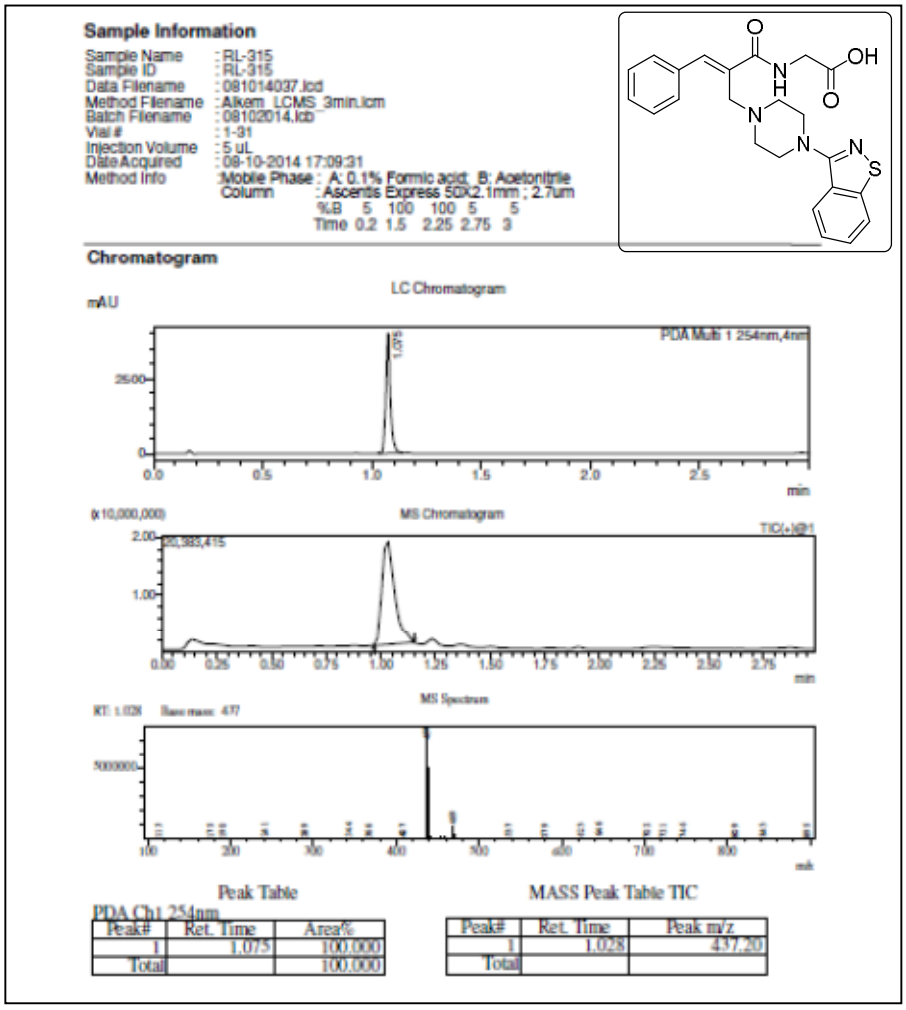
Mass spectra of (E)-(2-((4-(2-fluorophenyl)piperazin-1-yl)methyl)-3-phenylacryloyl)glycine **(13af)**



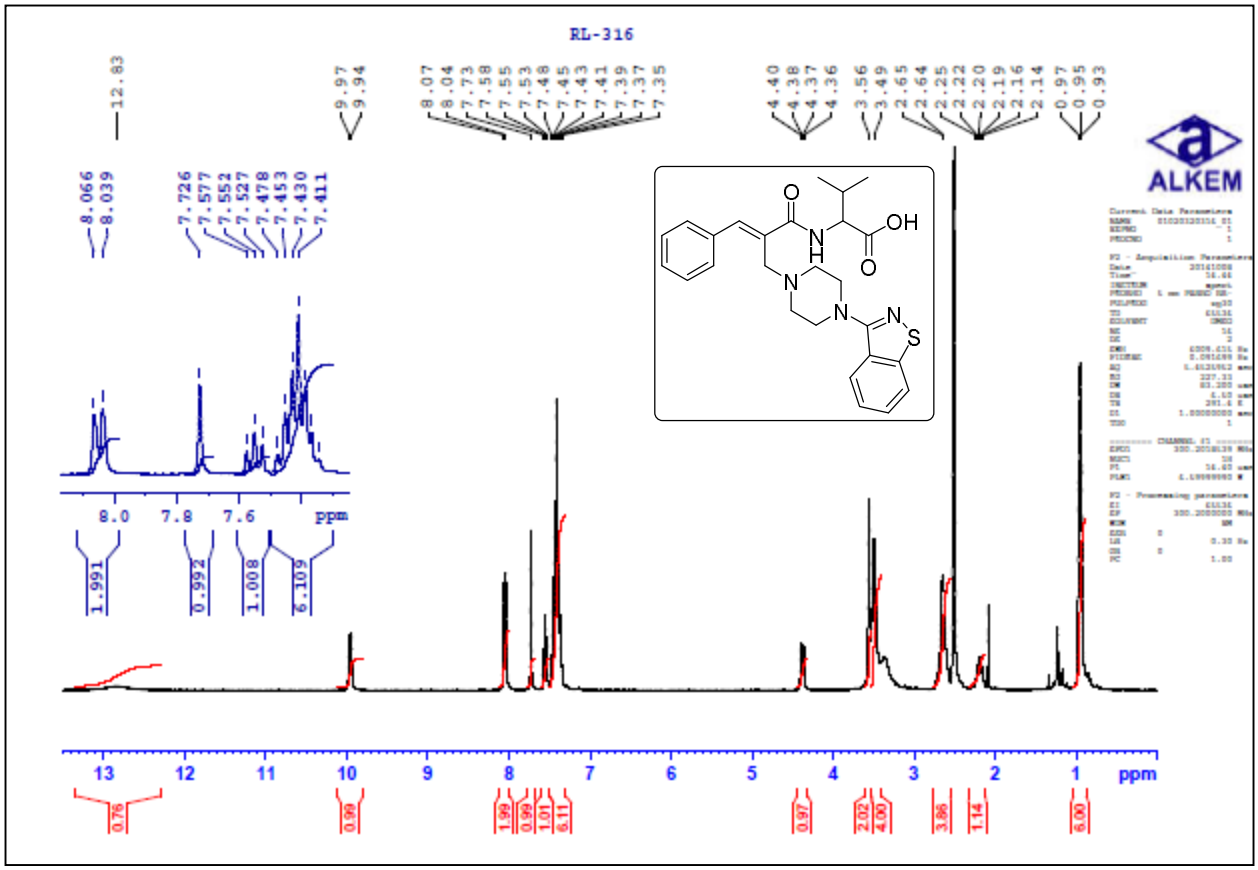
^{1}H NMR spectra of (E)-(2-((4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)methyl)-3-phenylacryloyl) glycine **(18a)**



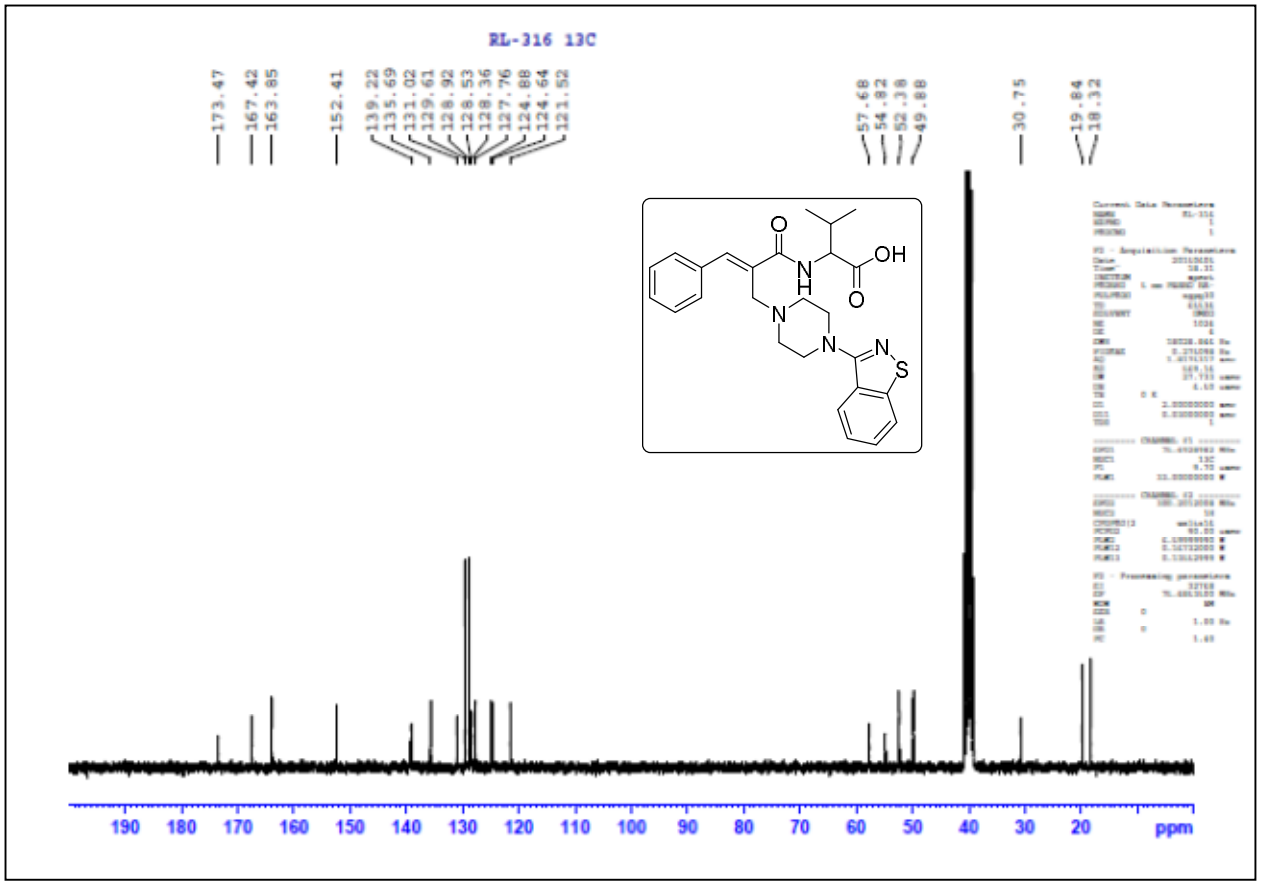
^{13}C NMR spectra of (E)-(2-((4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)methyl)-3-phenylacryloyl) glycine **(18a)**



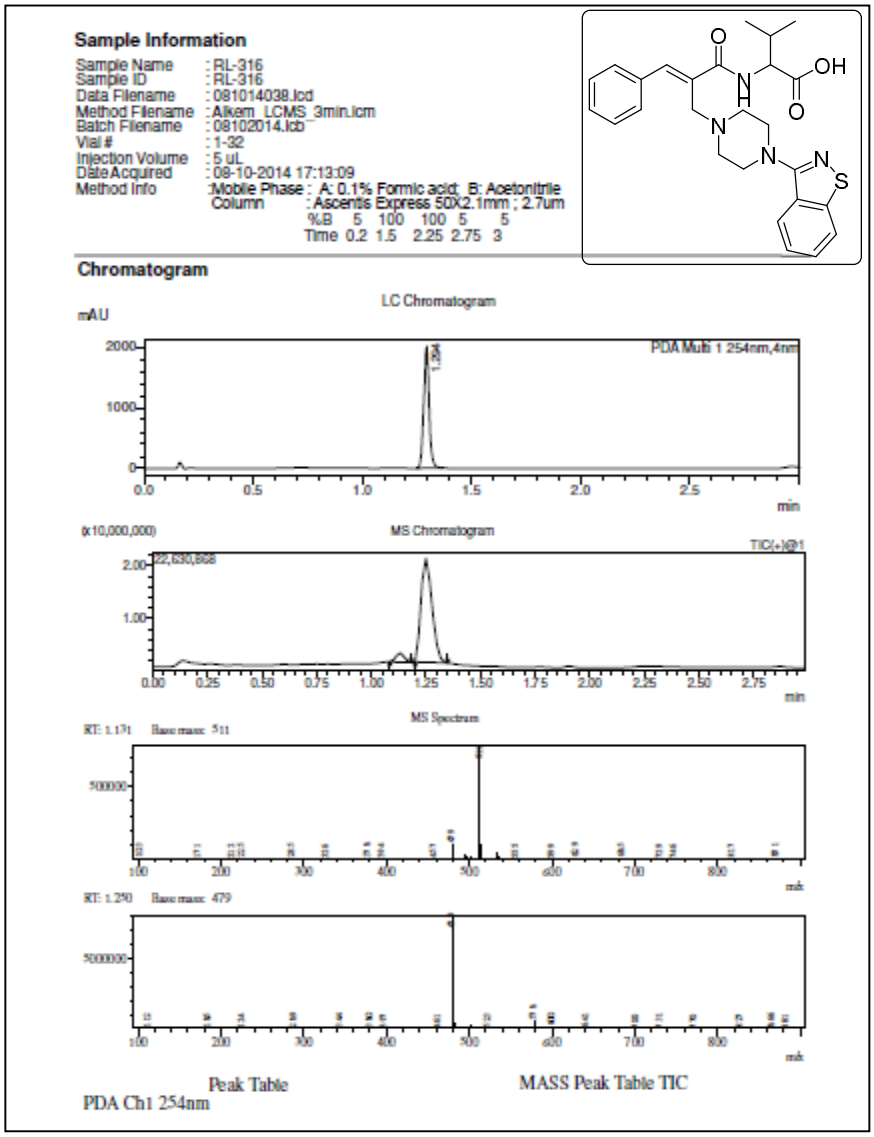
Mass spectra of (E)-(2-((4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)methyl)-3-phenylacryloyl) glycine **(18a)**



^{1}H NMR spectra of (E)-(2-((4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)methyl)-3-phenylacryloyl)valine **(18b)**



^{13}C NMR spectra of (E)-(2-((4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)methyl)-3-phenylacryloyl)valine **(18b)**



Peak#	Ret. Time	Area%
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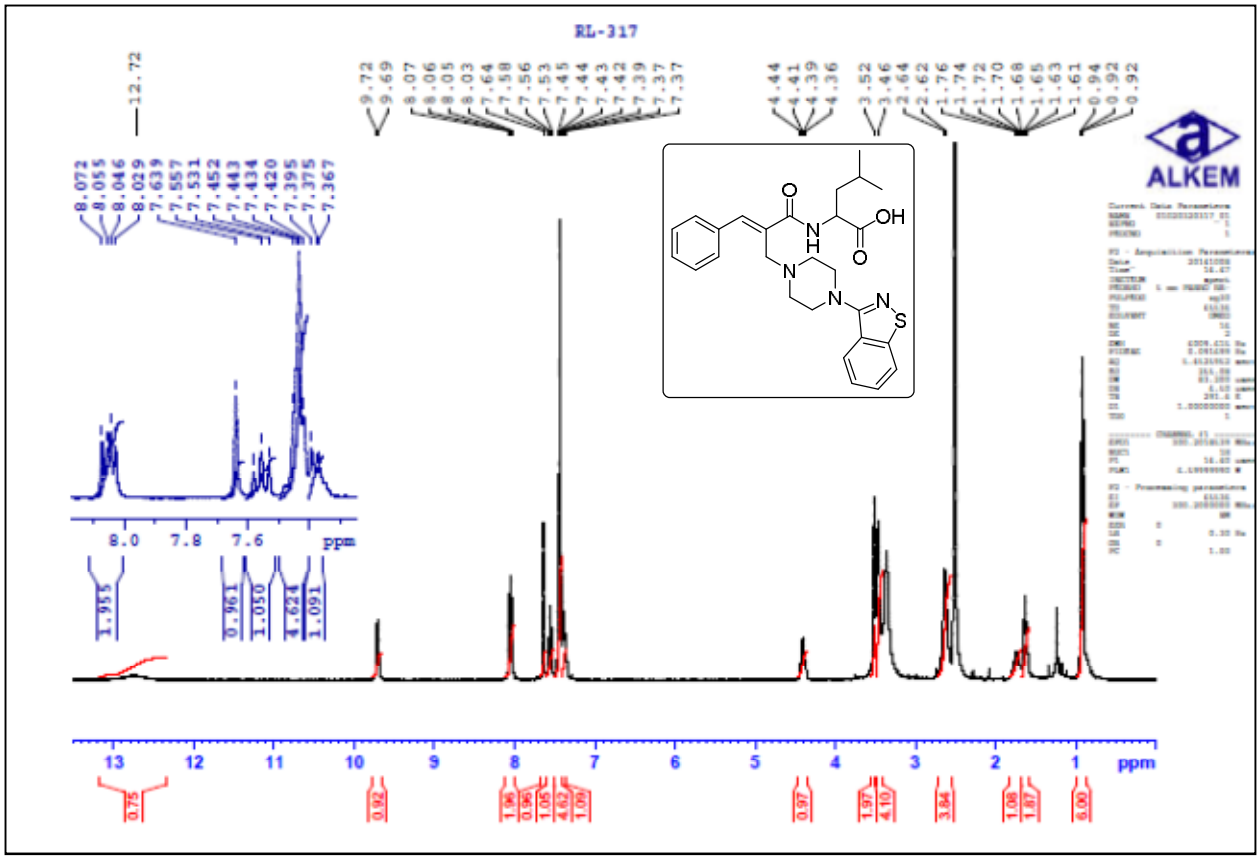
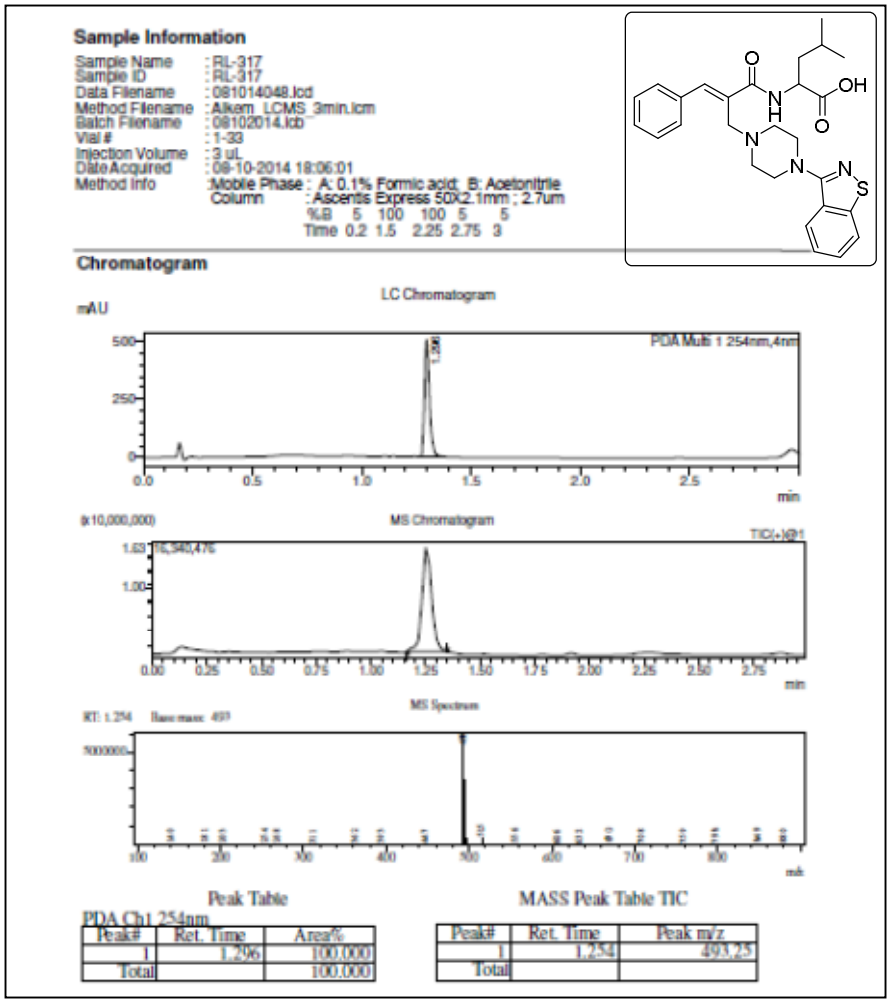
Total		100.000

Peak#	Ret. Time	Peak m/z
1	1.131	511.30
2	1.250	479.30
Total		

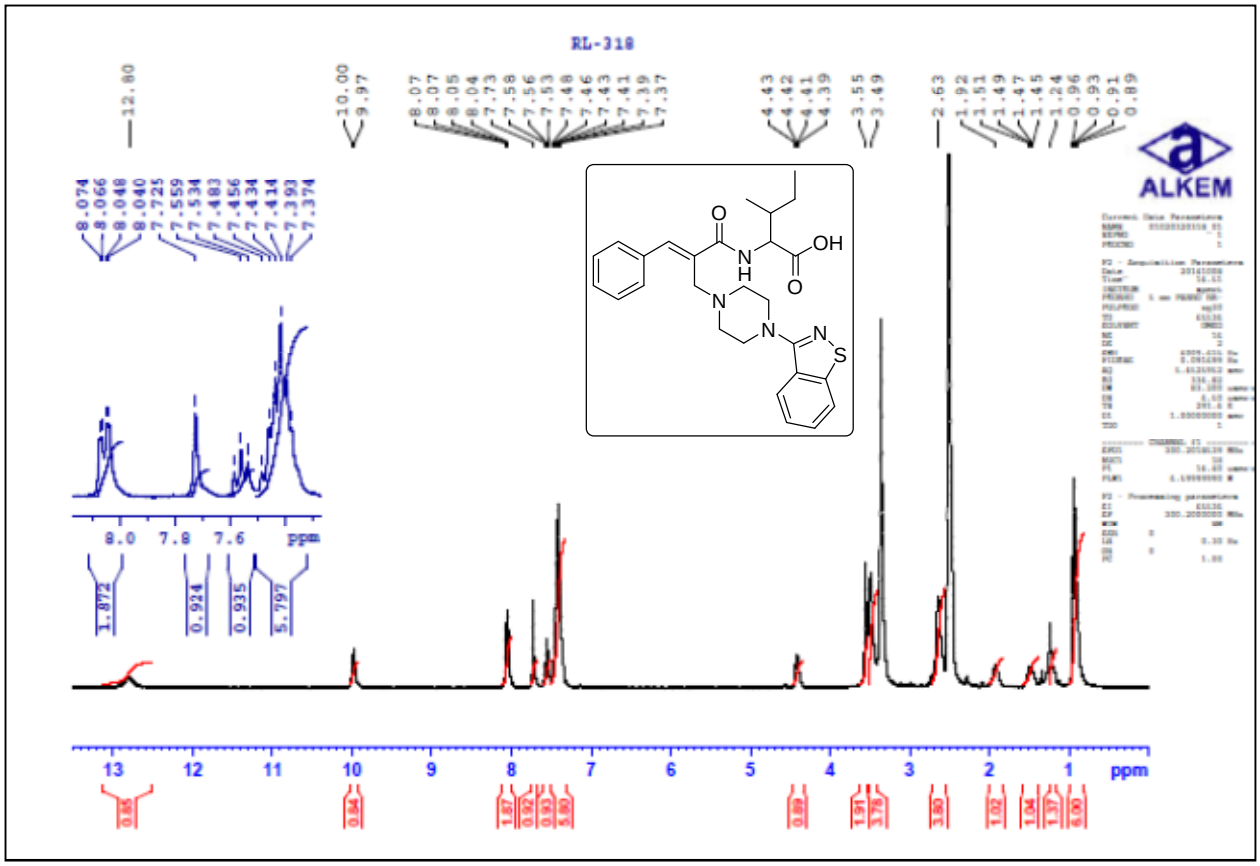
Mass spectra of (E)-(2-((4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)methyl)-3-phenylacryloyl) valine **(18b)**



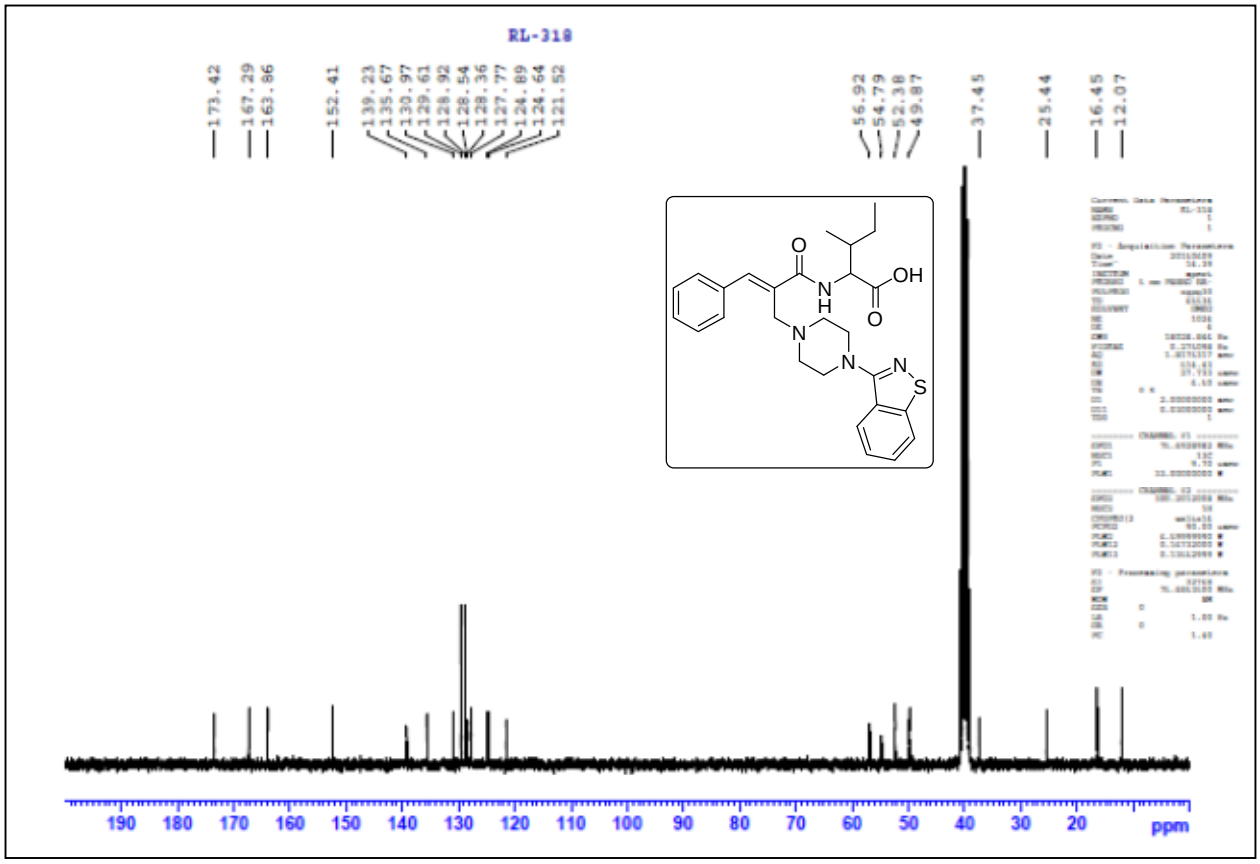
^{1}H NMR spectra of (E)-(2-((4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)methyl)-3-phenylacryloyl)leucine **(18c)**



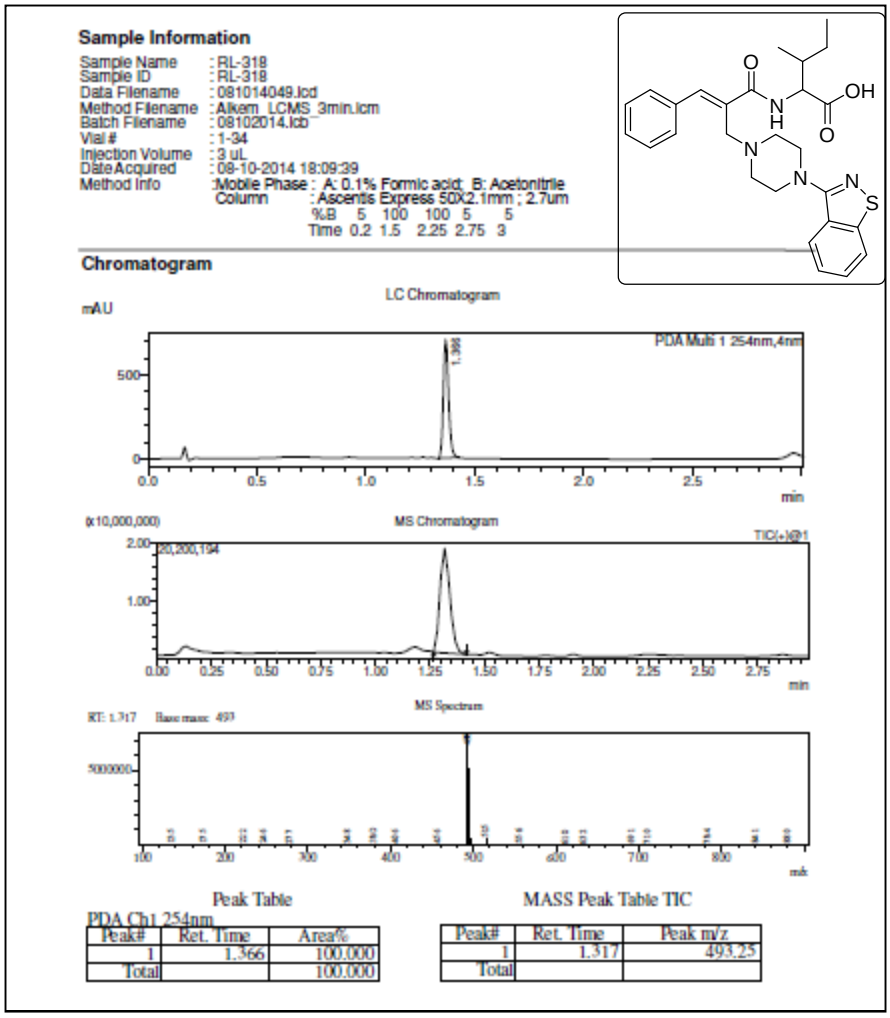
Mass spectra of (E)-(2-((4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)methyl)-3-phenylacryloyl)leucine **(18c)**



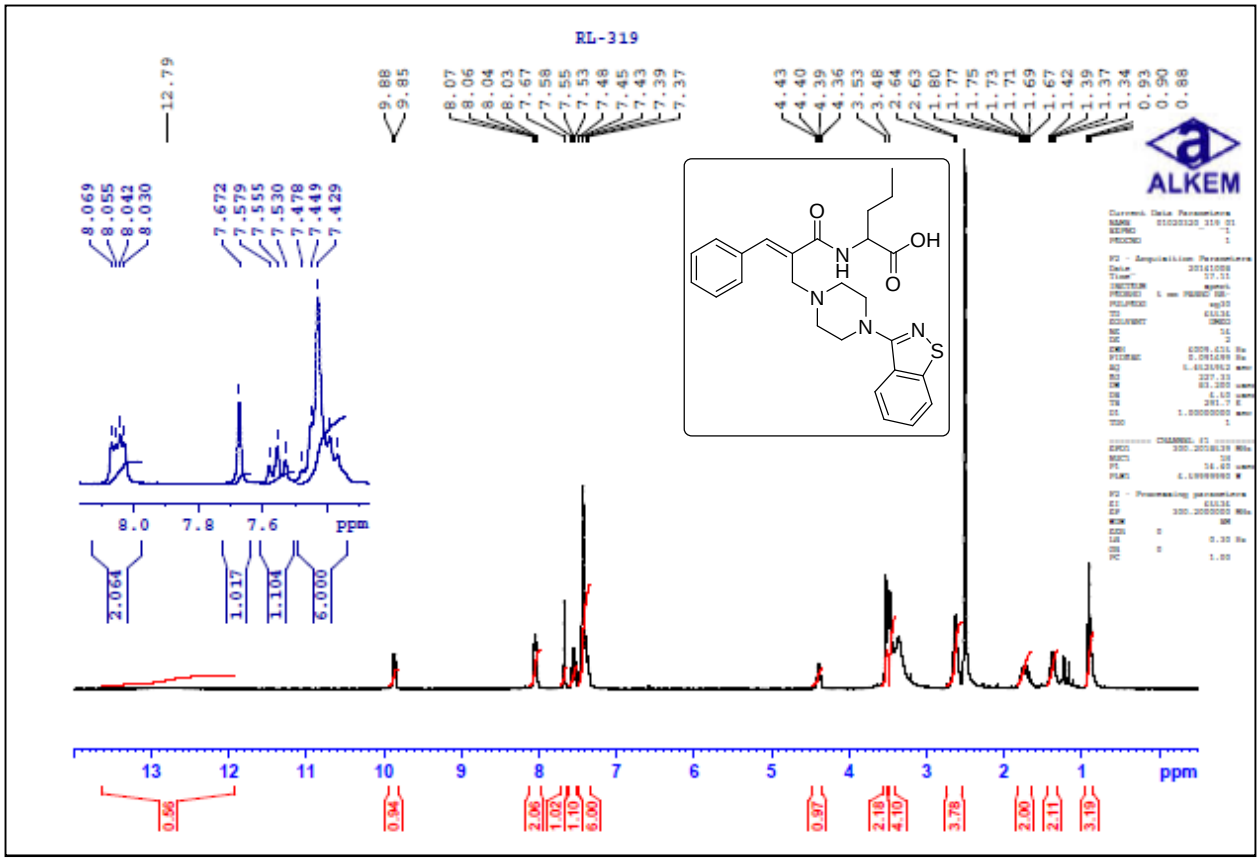
^{1}H NMR spectra of (E)-2-(2-((4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)methyl)-3-phenylacrylamido)-3-methylpentanoic acid **(18d)**



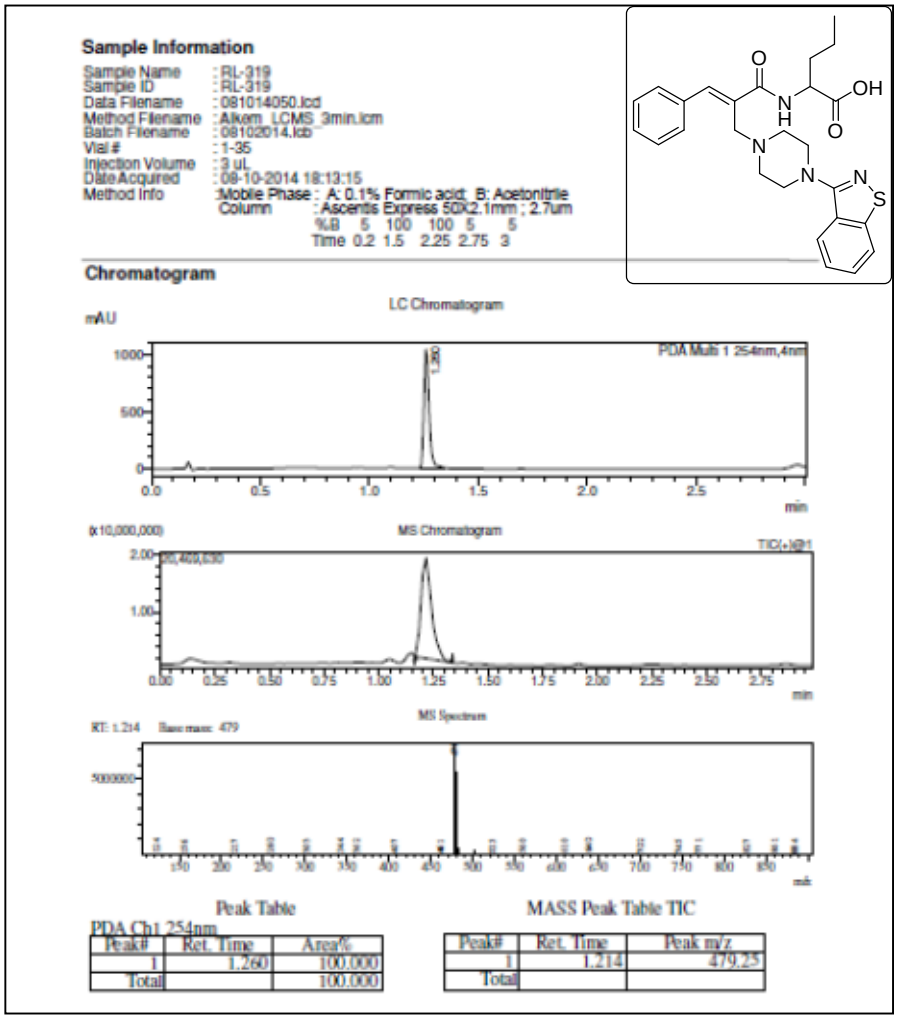
^{13}C NMR spectra of (E)-2-(2-((4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)methyl)-3-phenylacrylamido)-3-methylpentanoic acid **(18d)**



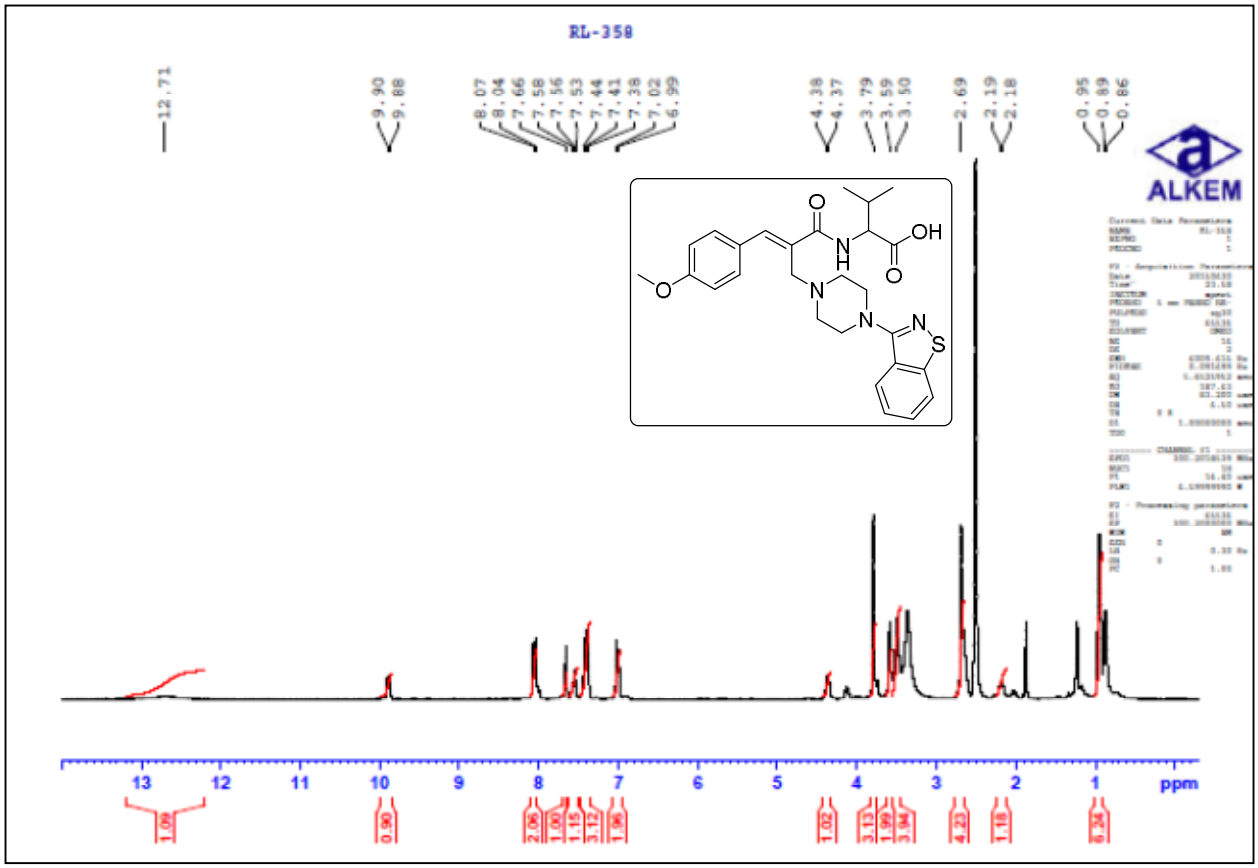
Mass spectra of (E)-2-(2-((4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)methyl)-3-phenylacrylamido)-3-methylpentanoic acid **(18d)**



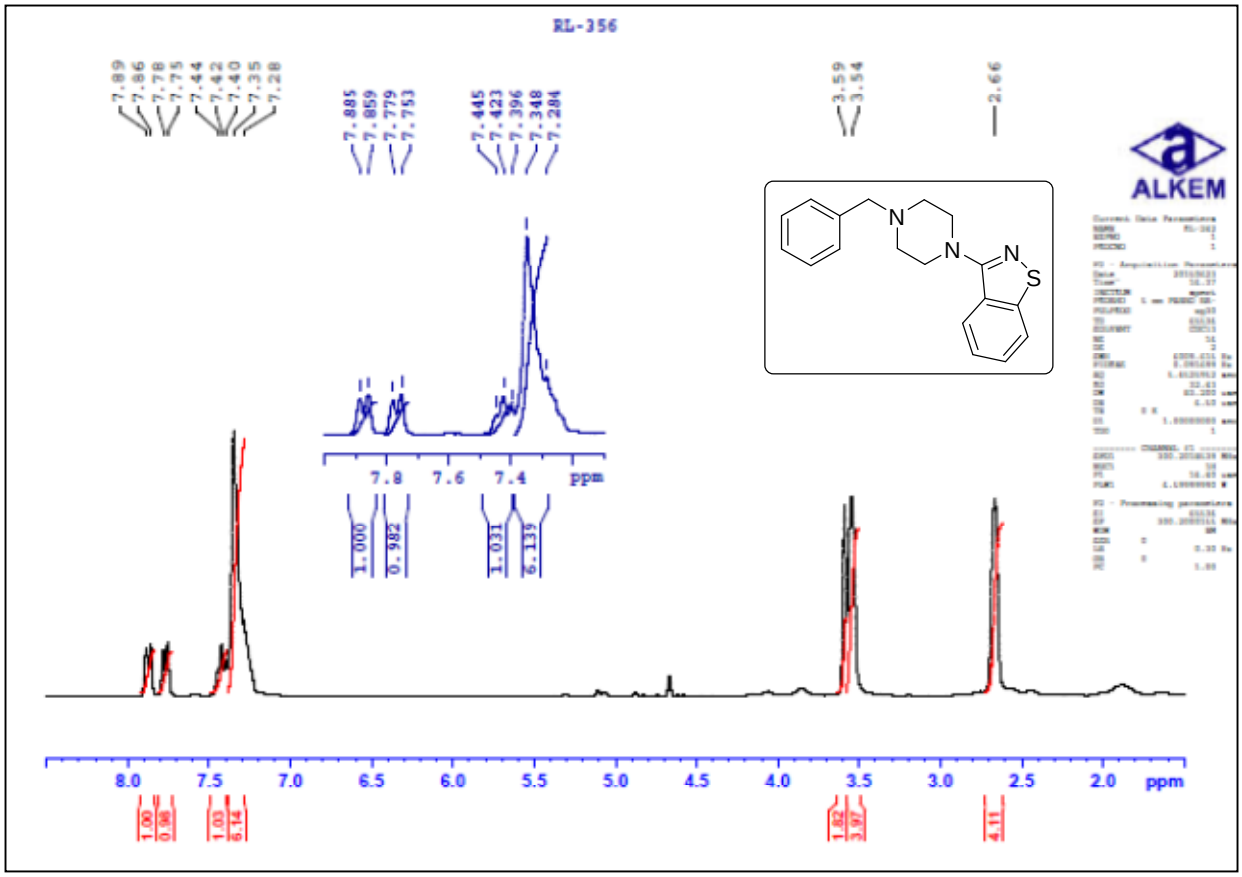
^{1}H NMR spectra of (E)-2-(2-((4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)methyl)-3-phenylacrylamido)pentanoic acid **(18e)**



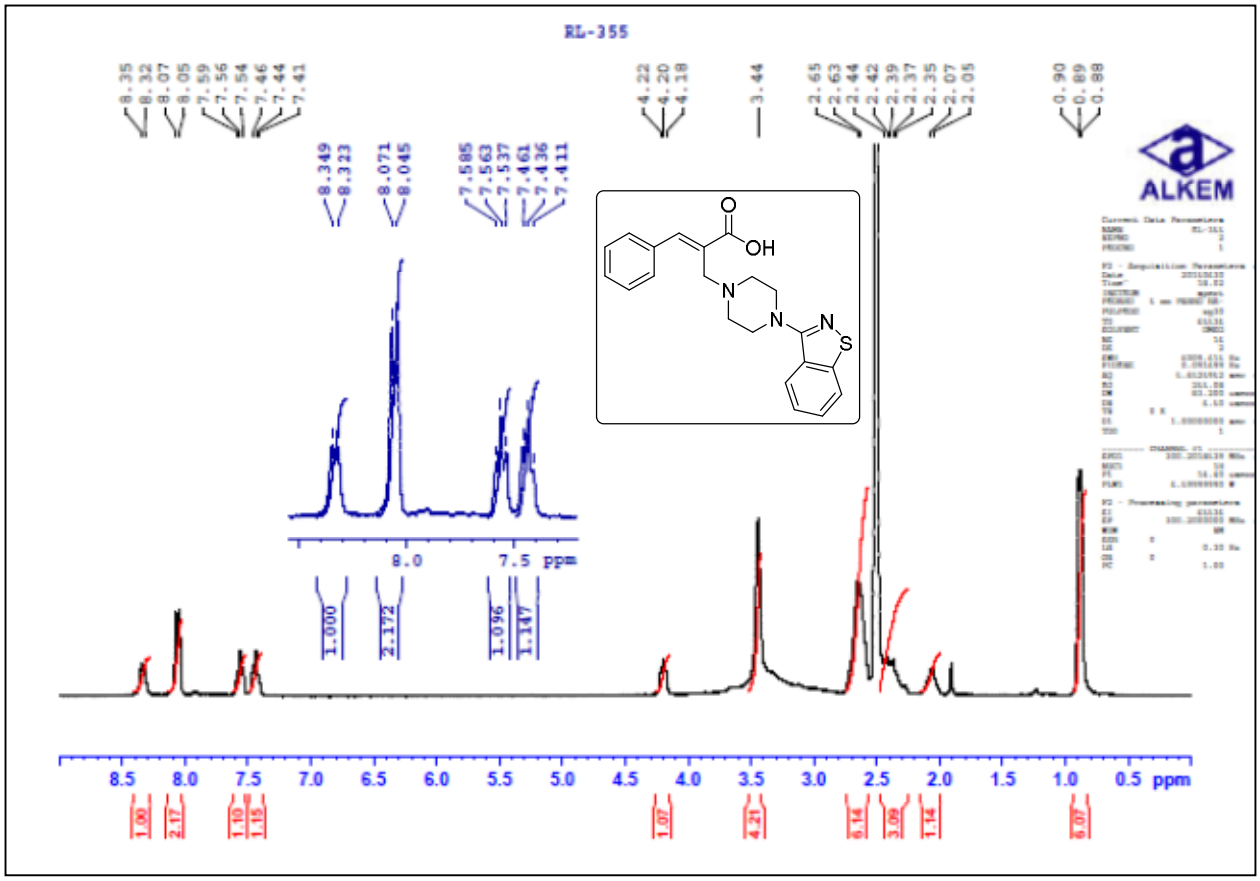
Mass spectra of (E)-2-(2-((4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)methyl)-3-phenylacrylamido)pentanoic acid **(18e)**



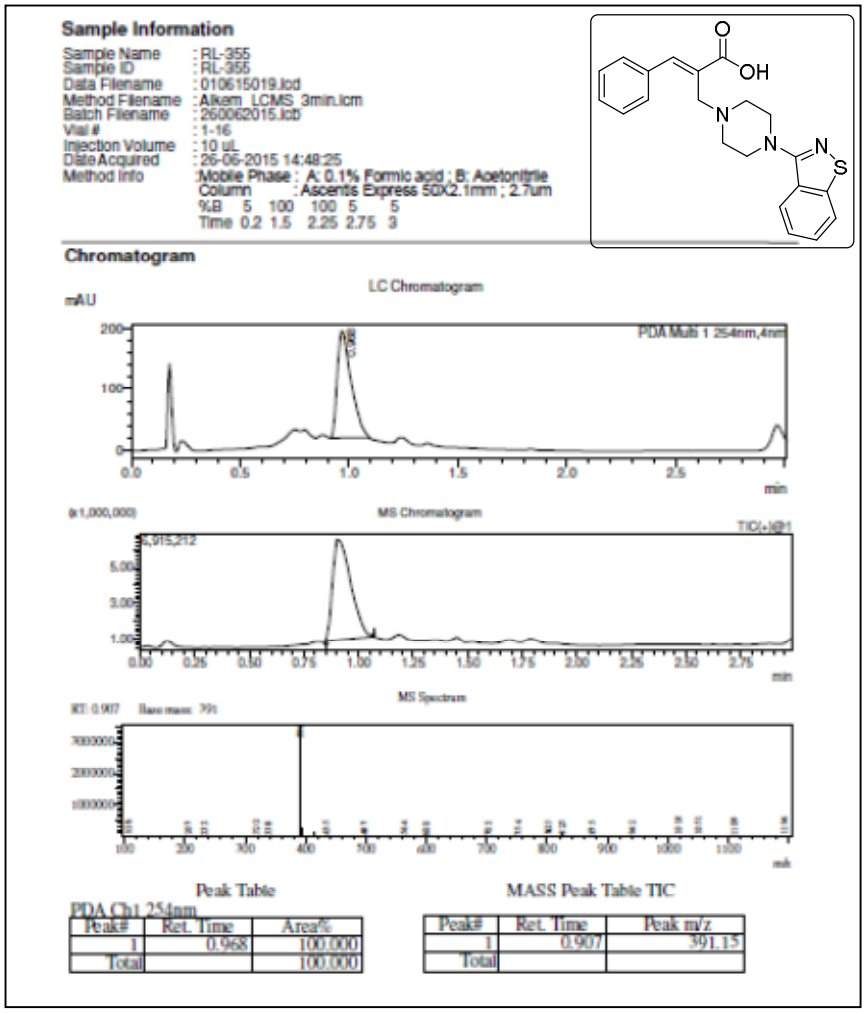
^{1}H NMR spectra of (E)-(2-((4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)methyl)-3-(4-methoxyphenyl)acryloyl)valine **(18f)**



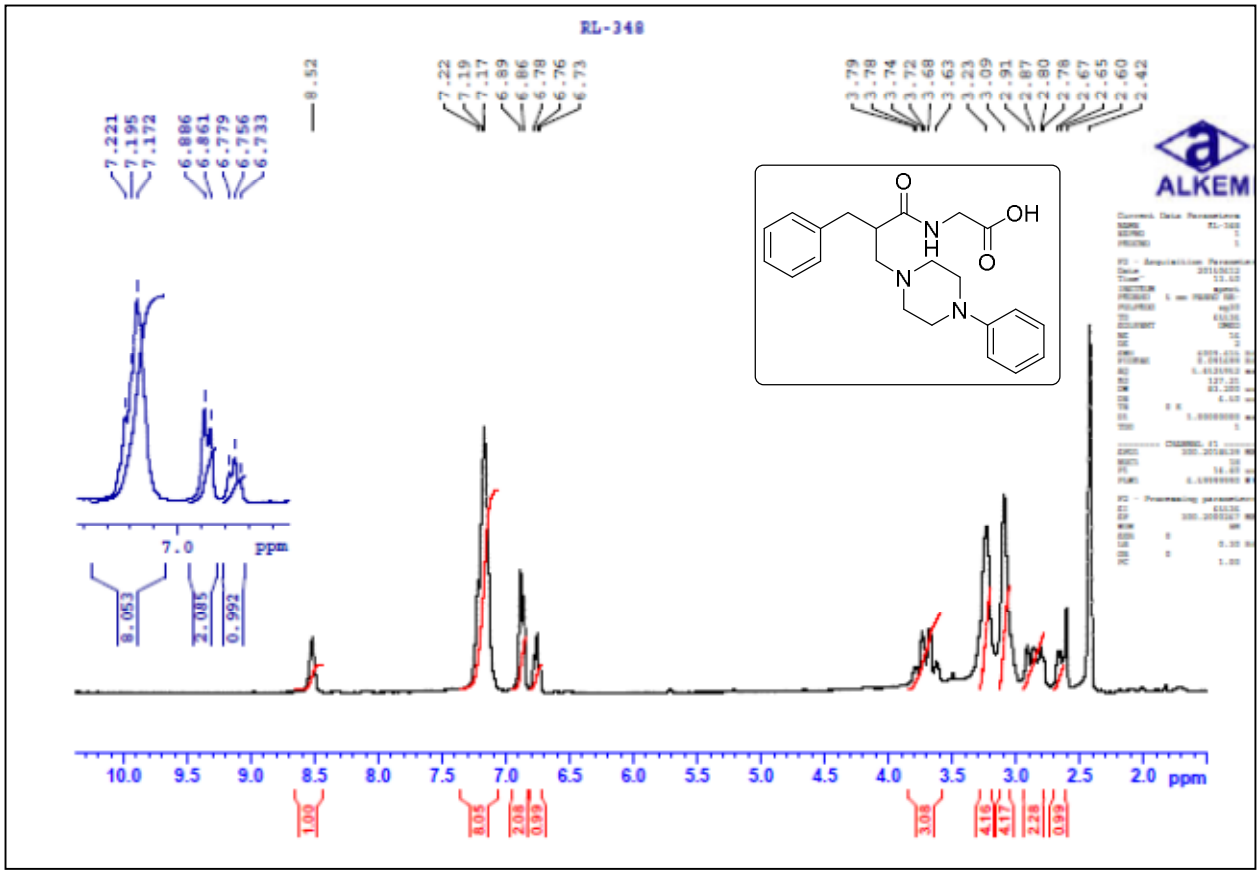
[1]H NMR spectra of 3-(4-benzylpiperazin-1-yl)benzo[d]isothiazole **(19a)**



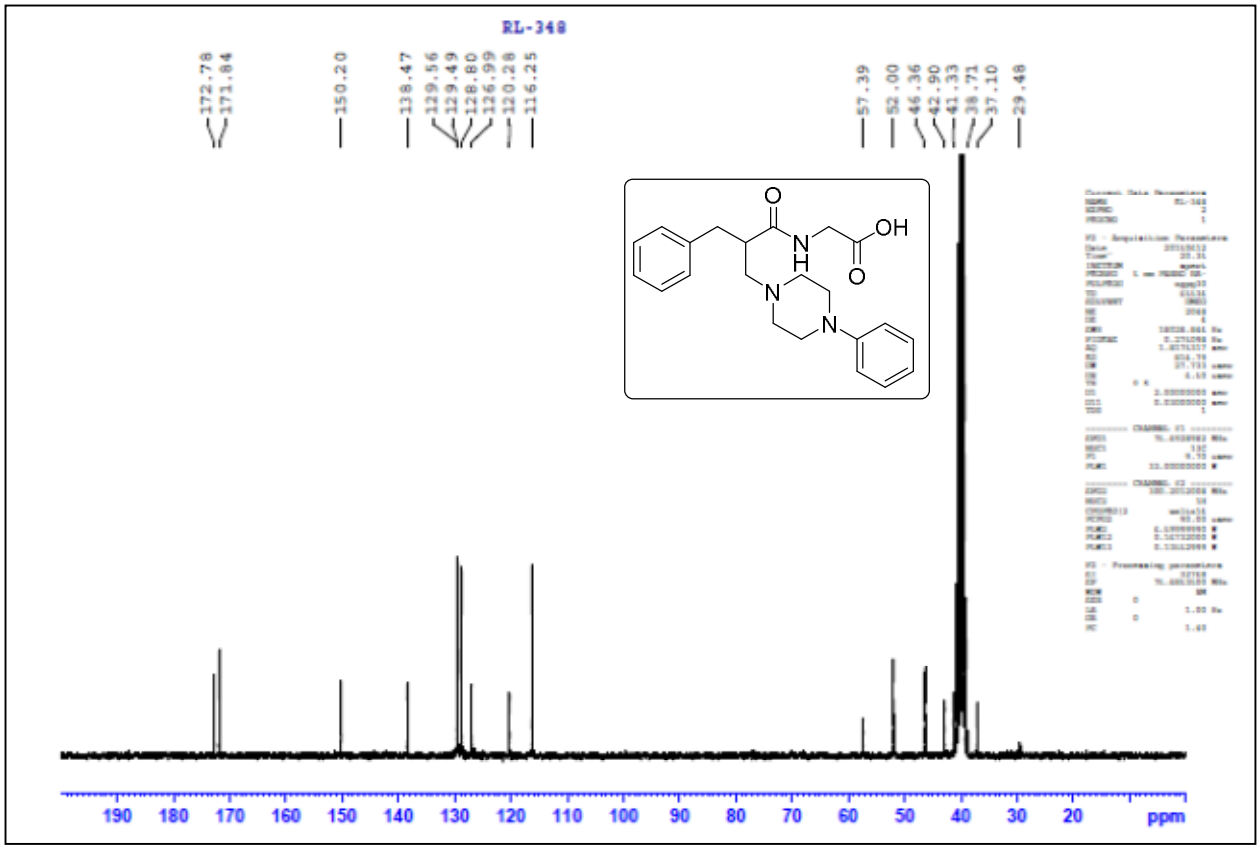
^{1}H NMR spectra of (3-(4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)propanoyl)valine **(19b)**



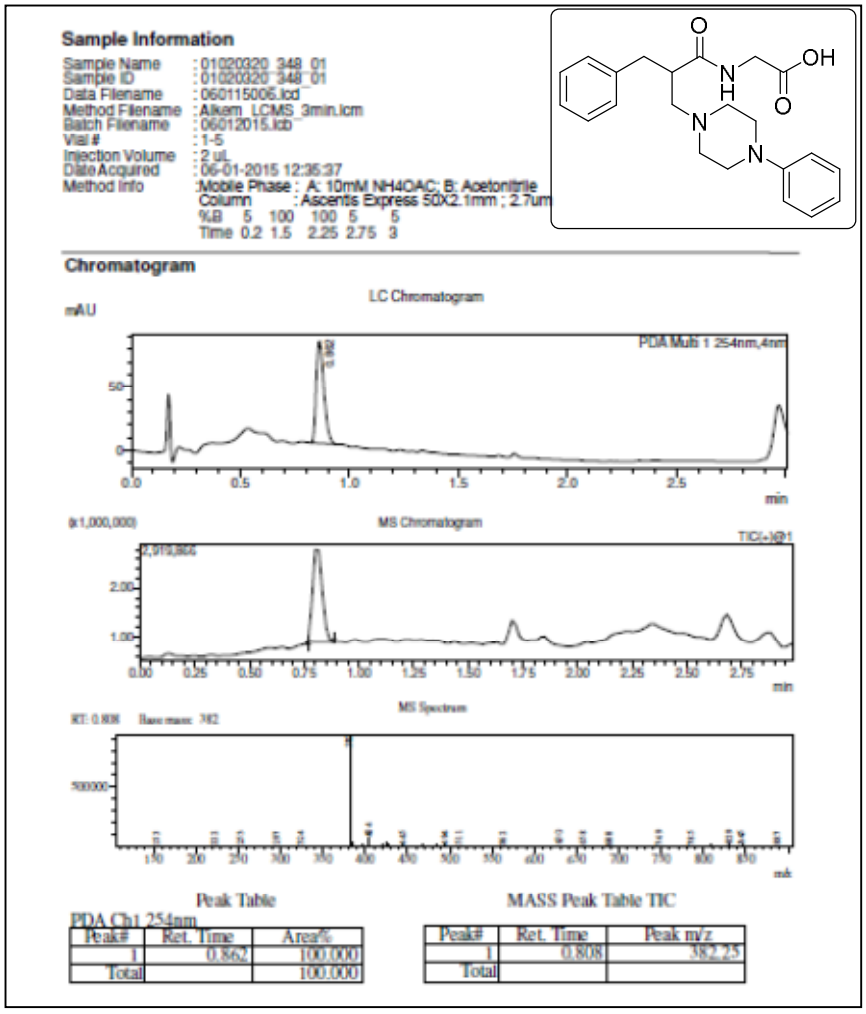
Mass spectra of (3-(4-(benzo[d]isothiazol-3-yl)piperazin-1-yl)propanoyl)valine **(19b)**



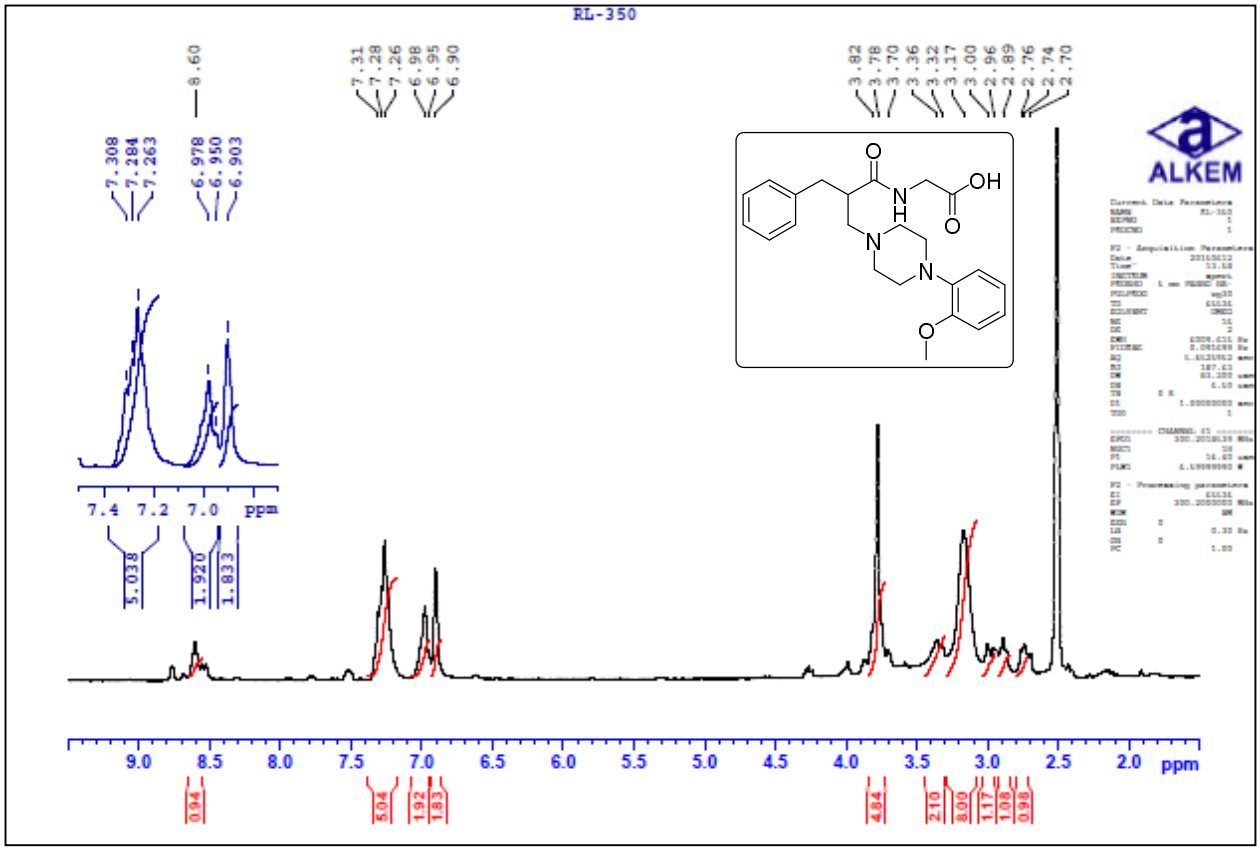
^{1}H NMR spectra of (2-benzyl-3-(4-phenylpiperazin-1-yl)propanoyl)glycine **(23a)**



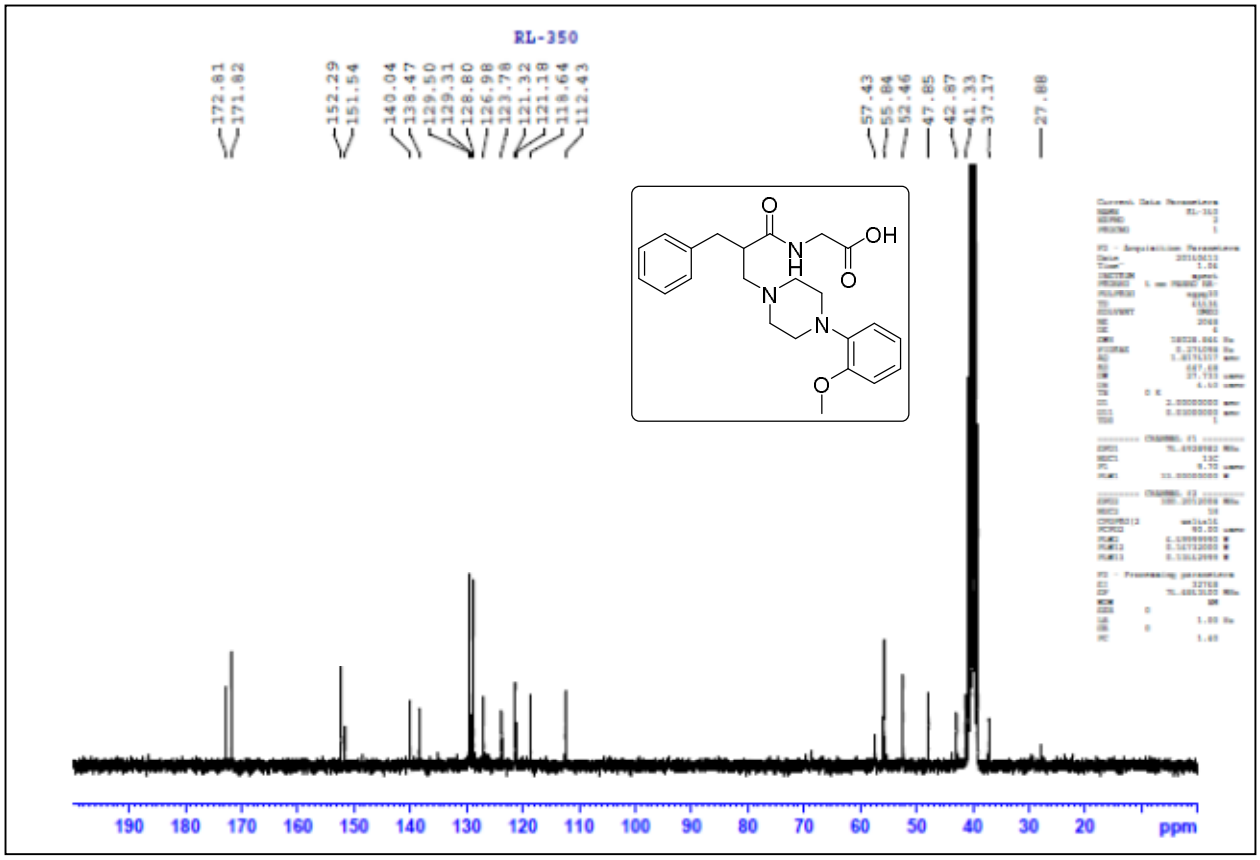
^{13}C NMR spectra of (2-benzyl-3-(4-phenylpiperazin-1-yl)propanoyl)glycine **(23a)**



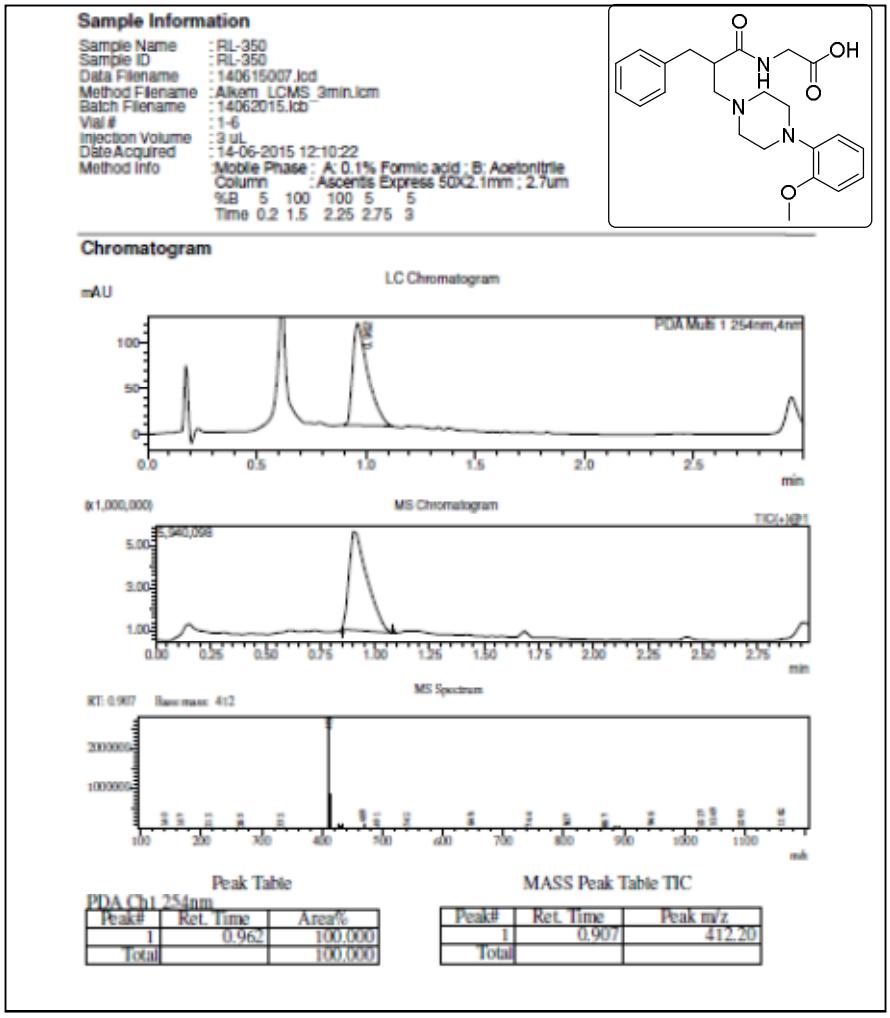
Mass spectra of (2-benzyl-3-(4-phenylpiperazin-1-yl)propanoyl)glycine **(23a)**



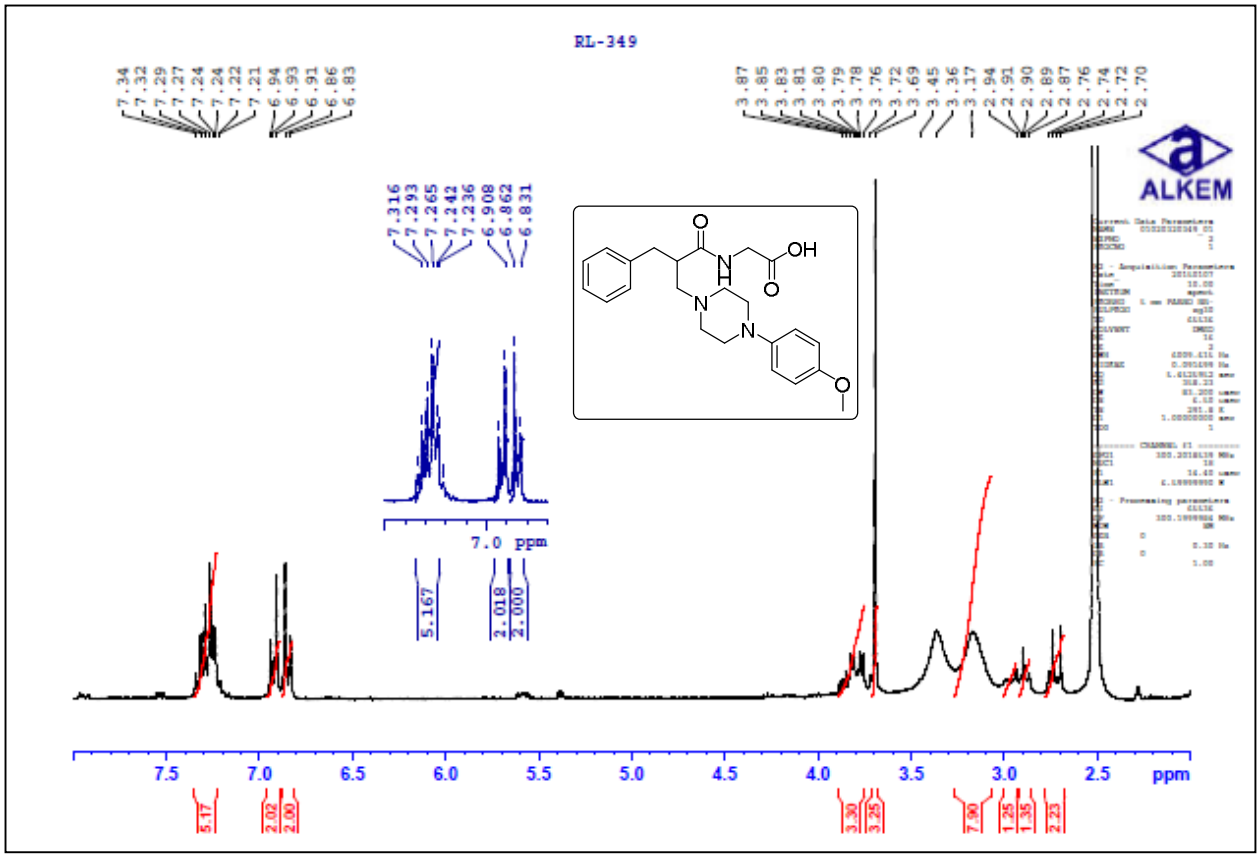
^{1}H NMR spectra of (2-benzyl-3-(4-(2-methoxyphenyl)piperazin-1-yl)propanoyl)glycine **(23f)**



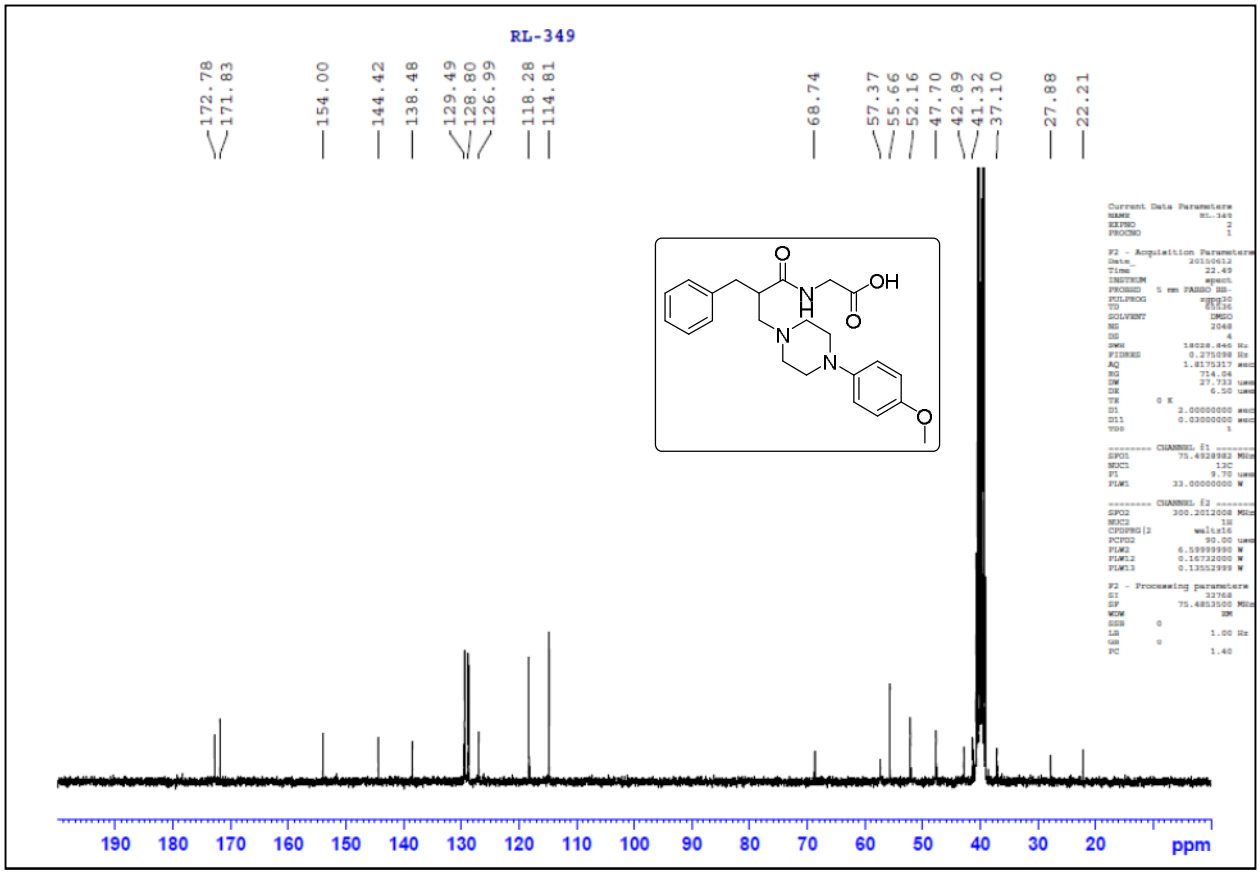
^{13}C NMR spectra of (2-benzyl-3-(4-(2-methoxyphenyl)piperazin-1-yl)propanoyl)glycine **(23f)**



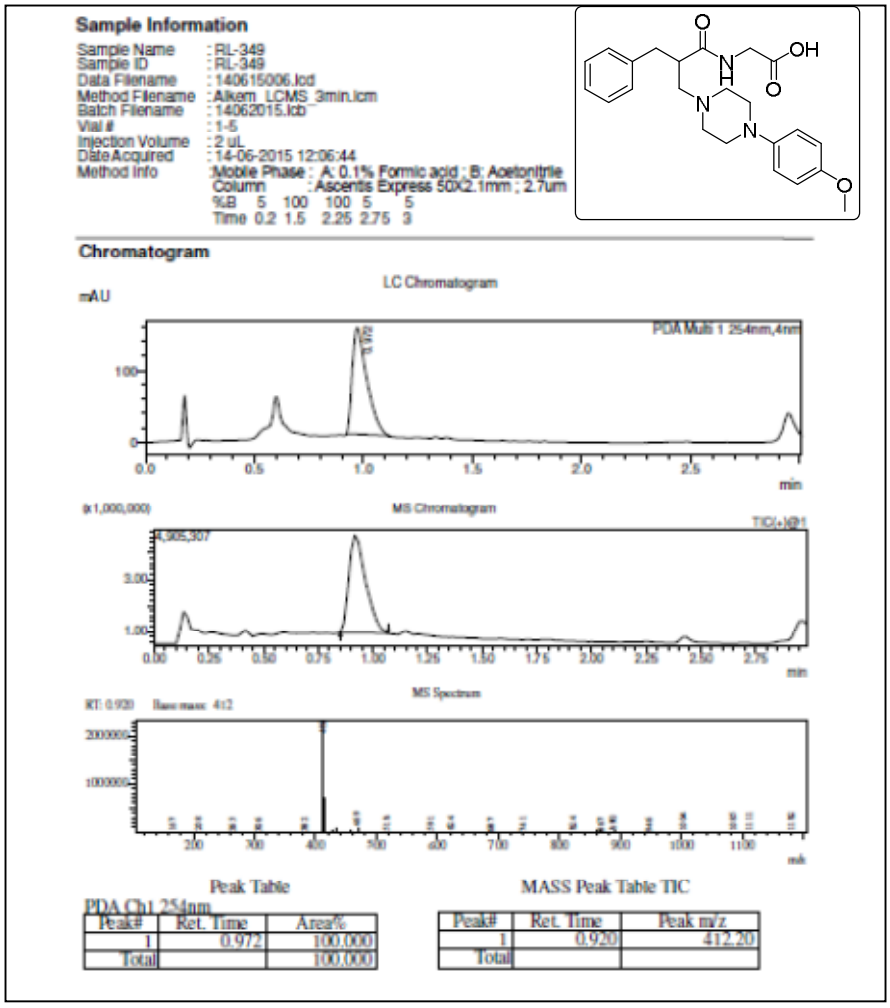
Mass spectra of (2-benzyl-3-(4-(2-methoxyphenyl)piperazin-1-yl)propanoyl)glycine **(23f)**



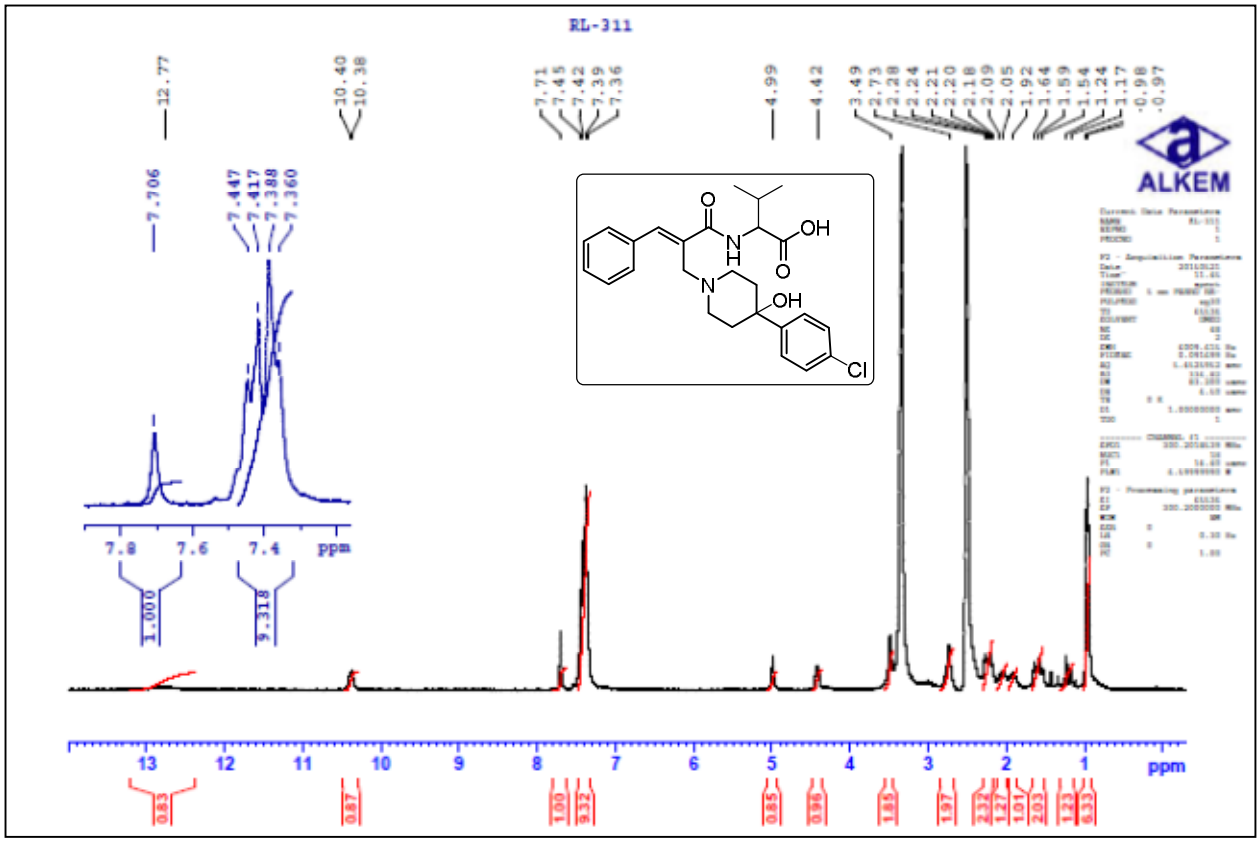
^{1}H NMR spectra of (2-benzyl-3-(4-(4-methoxyphenyl)piperazin-1-yl)propanoyl)glycine **(23g)**



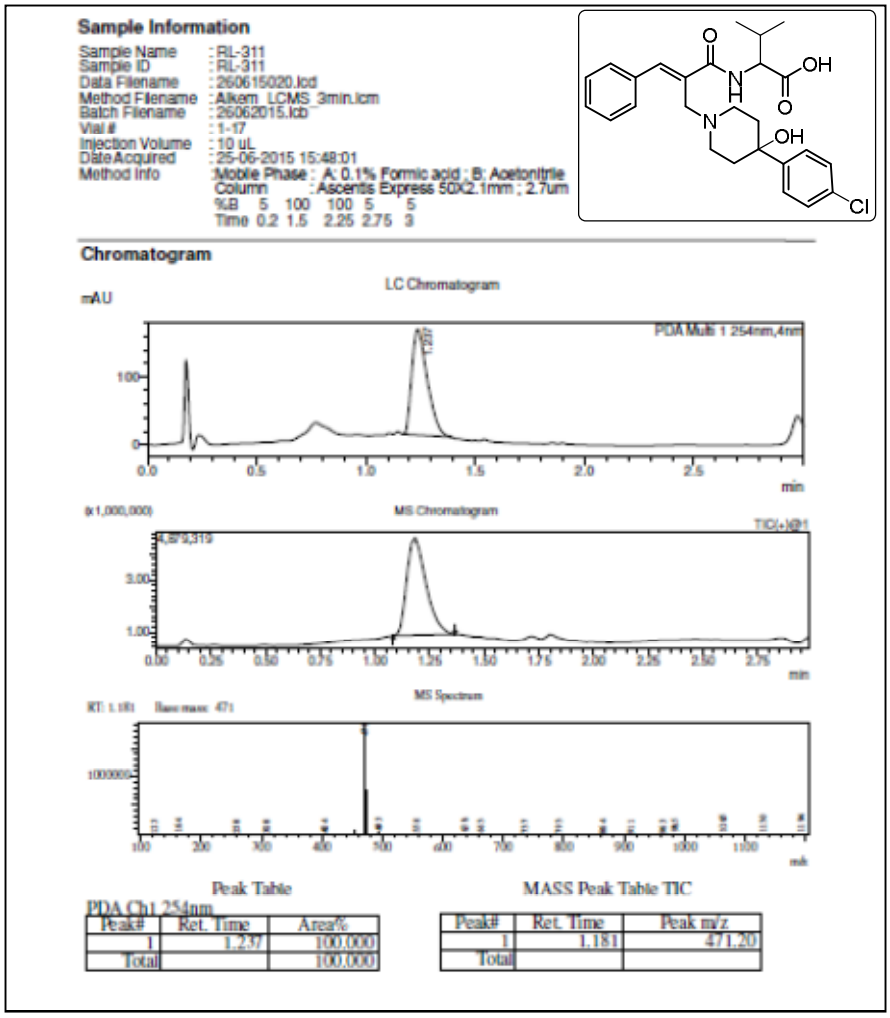
^{13}C NMR spectra of (2-benzyl-3-(4-(4-methoxyphenyl)piperazin-1-yl)propanoyl)glycine **(23g)**



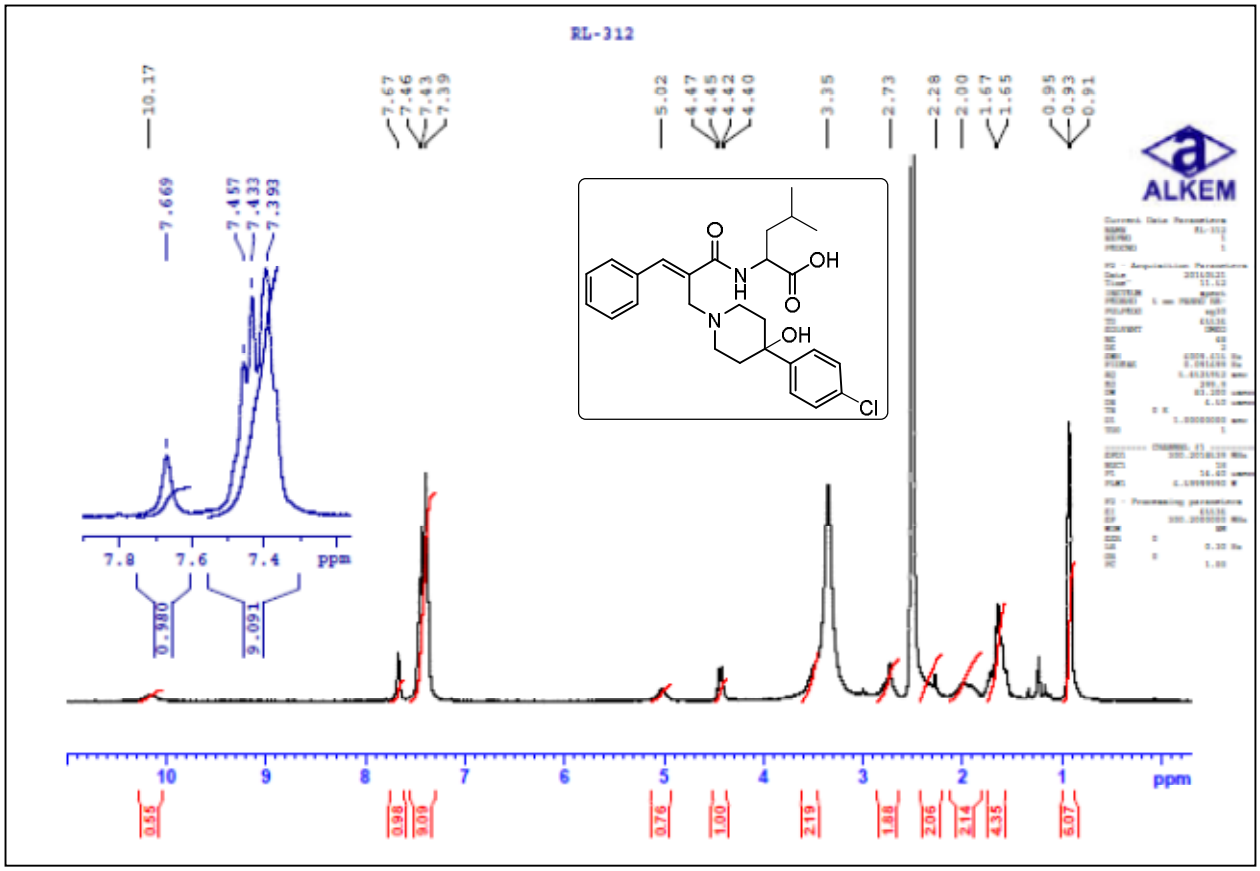
Mass spectra of (2-benzyl-3-(4-(4-methoxyphenyl)piperazin-1-yl)propanoyl)glycine **(23g)**



^{1}H NMR spectra of (E)-(2-((4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl)methyl)-3-phenylacryloyl)valine **(28b)**

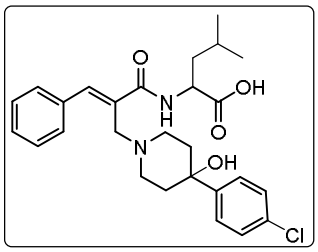


Mass spectra of (E)-(2-((4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl)methyl)-3-phenylacryloyl)valine **(28b)**



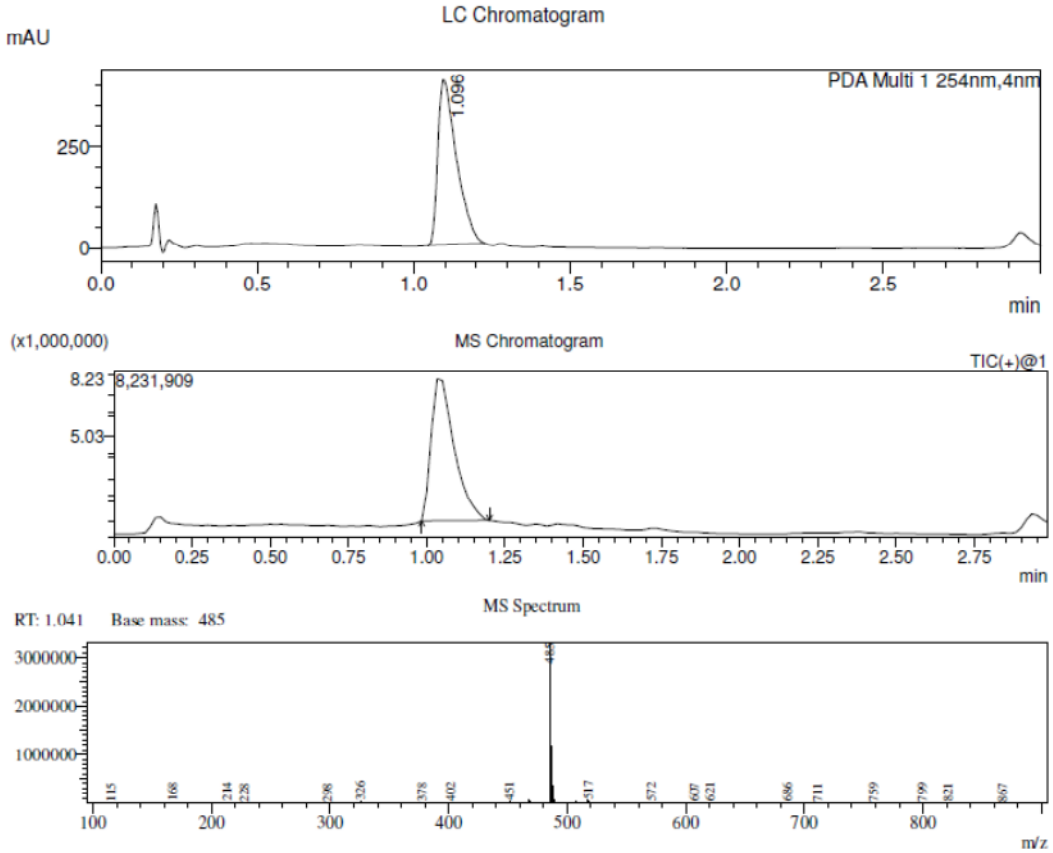
^{1}H NMR spectra of (E)-(2-((4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl)methyl)-3-phenylacryloyl)leucine **(28c)**

Sample Information



Sample Name	: RL-312
Sample ID	: RL-312
Data Filename	: 230515034.lcd
Method Filename	: Alkem_LCMS_3min.lcm
Batch Filename	: 23052015.lcb
Vial #	: 1-28
Injection Volume	: 3 uL
Date Acquired	: 25-05-2015 17:06:02
Method Info	:Mobile Phase : A: 0.1% Formic acid ; B: Acetonitrile
	Column : Ascentis Express 50X2.1mm ; 2.7um
	%B 5 100 100 5 5
	Time 0.2 1.5 2.25 2.75 3

Chromatogram



Peak Table

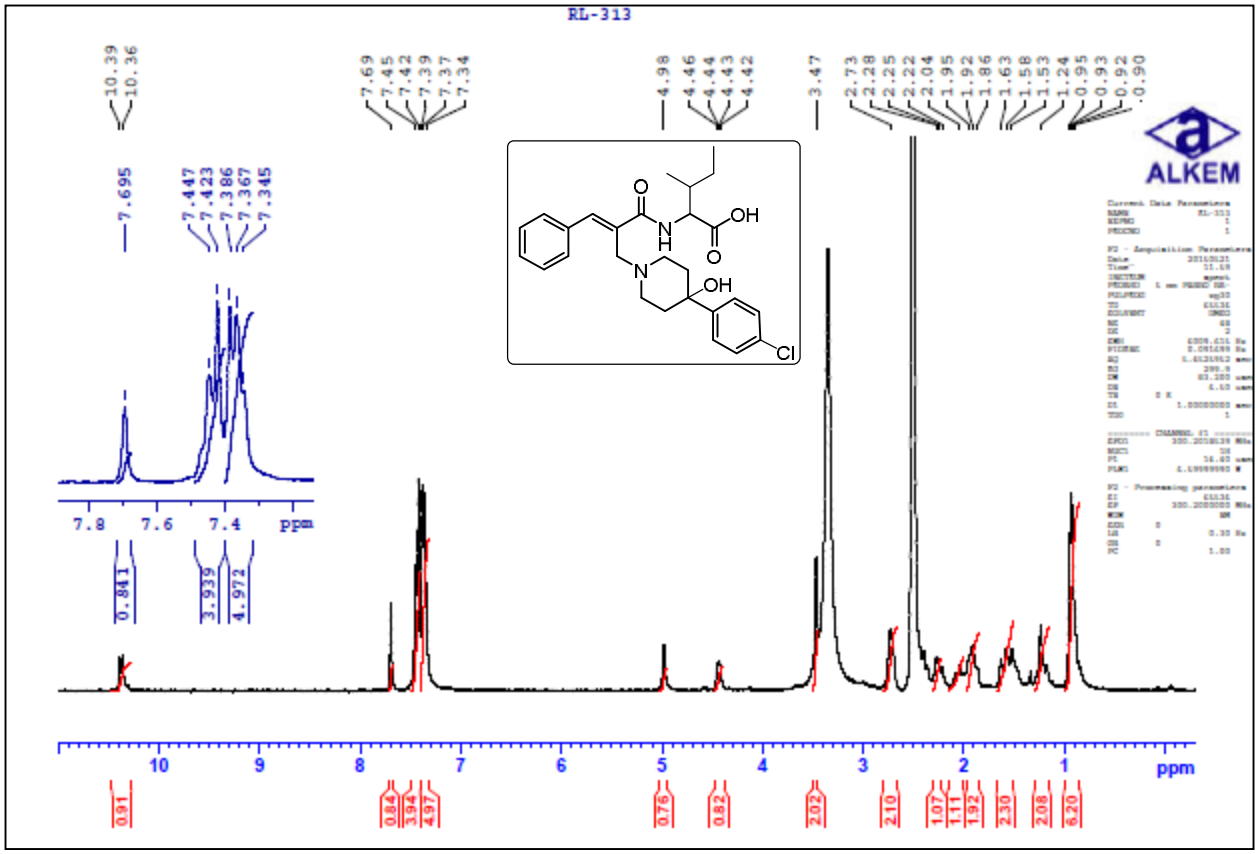
PDA Ch1 254nm

Peak#	Ret. Time	Area%
1	1.096	100.000
Total		100.000

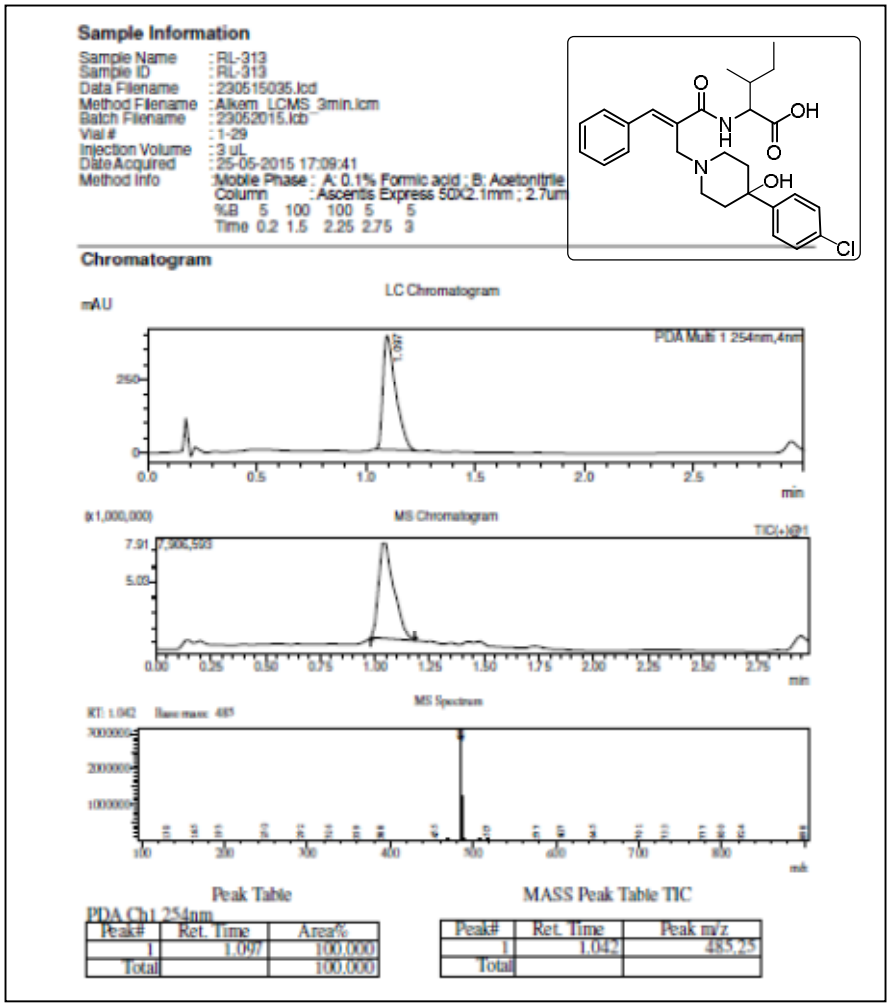
MASS Peak Table TIC

Peak#	Ret. Time	Peak m/z
1	1.041	485.25
Total		

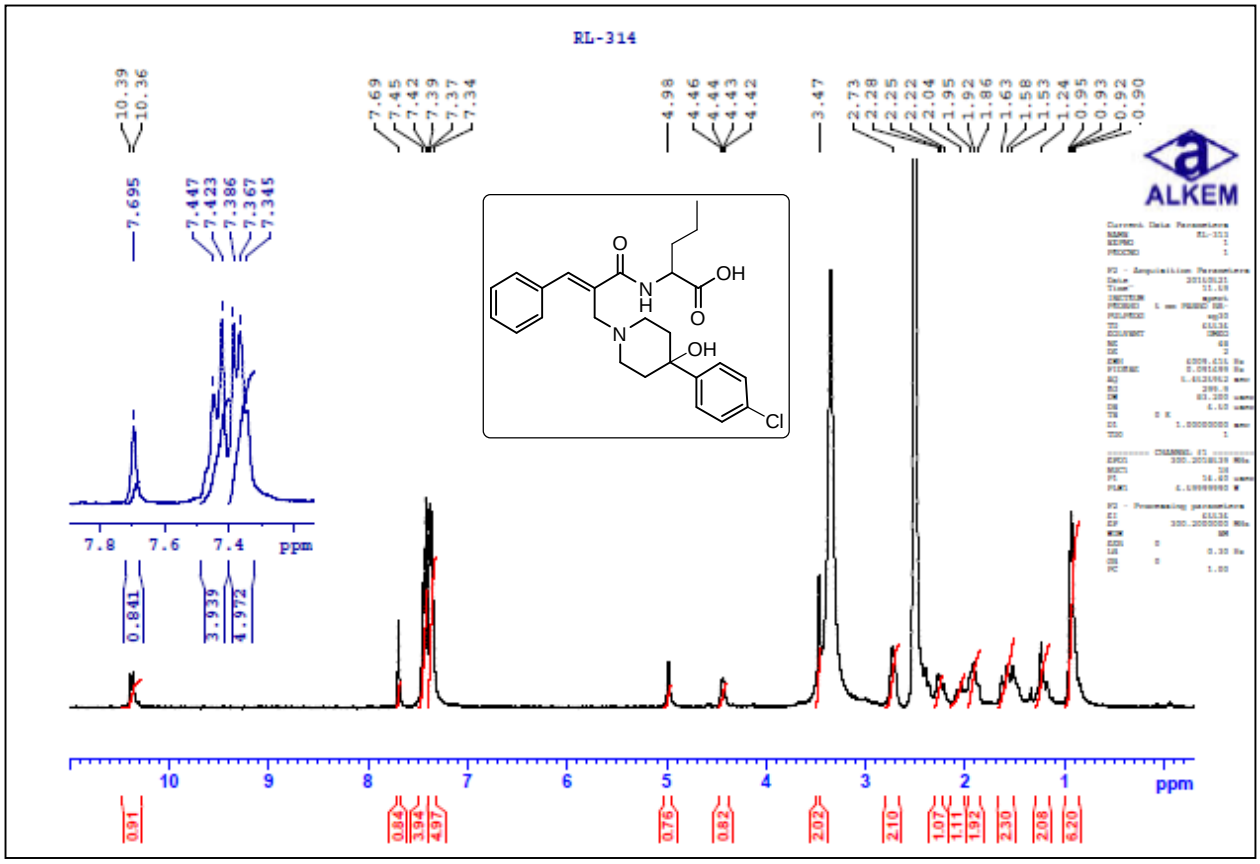
Mass spectra of (E)-(2-((4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl)methyl)-3-phenylacryloyl)leucine **(28c)**



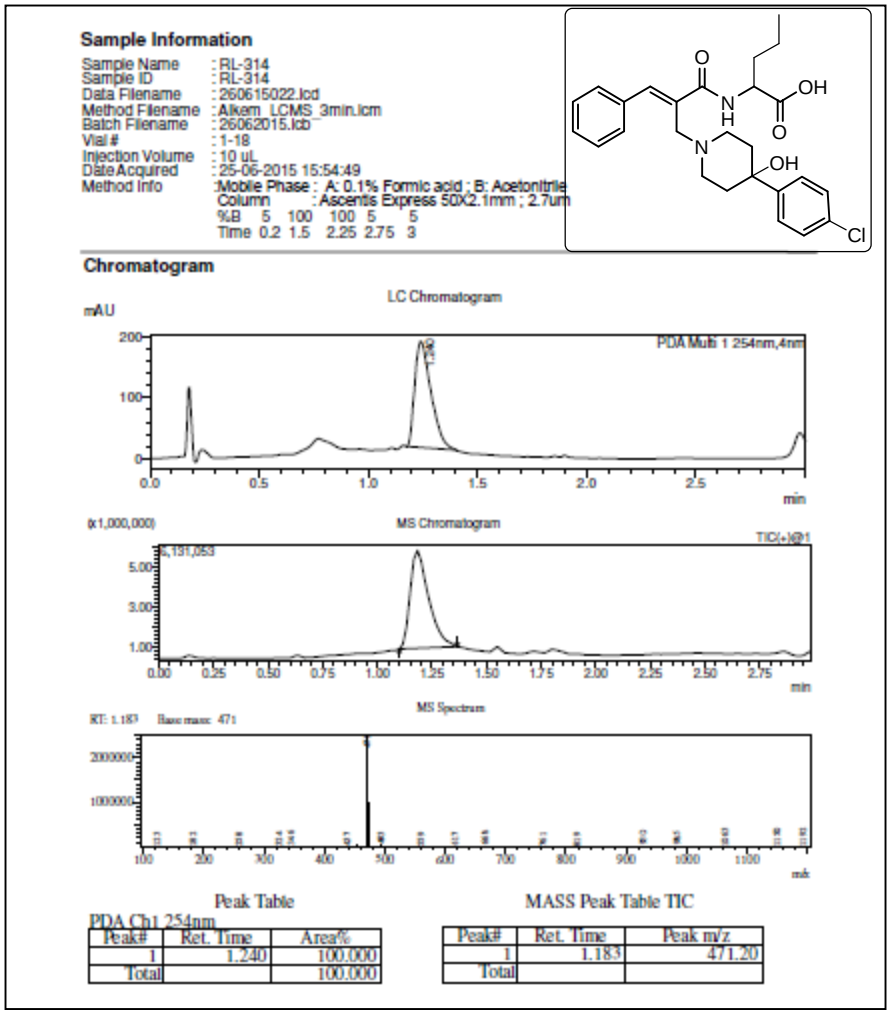
^{1}H NMR spectra of (E)-2-(2-((4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl)methyl)-3-phenylacrylamido)-3-methylpentanoic acid **(28d)**



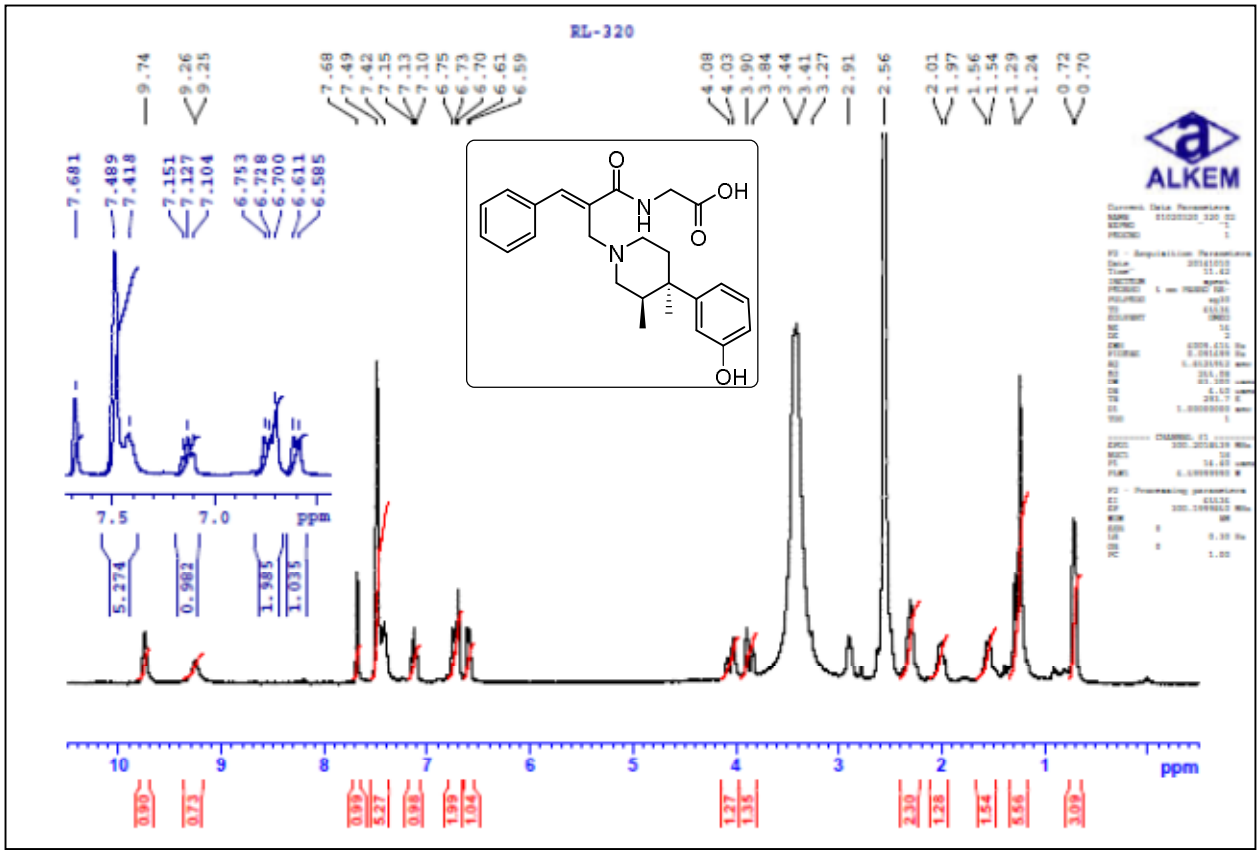
Mass spectra of (E)-2-(2-((4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl)methyl)-3-phenylacrylamido)-3-methylpentanoic acid **(28d)**



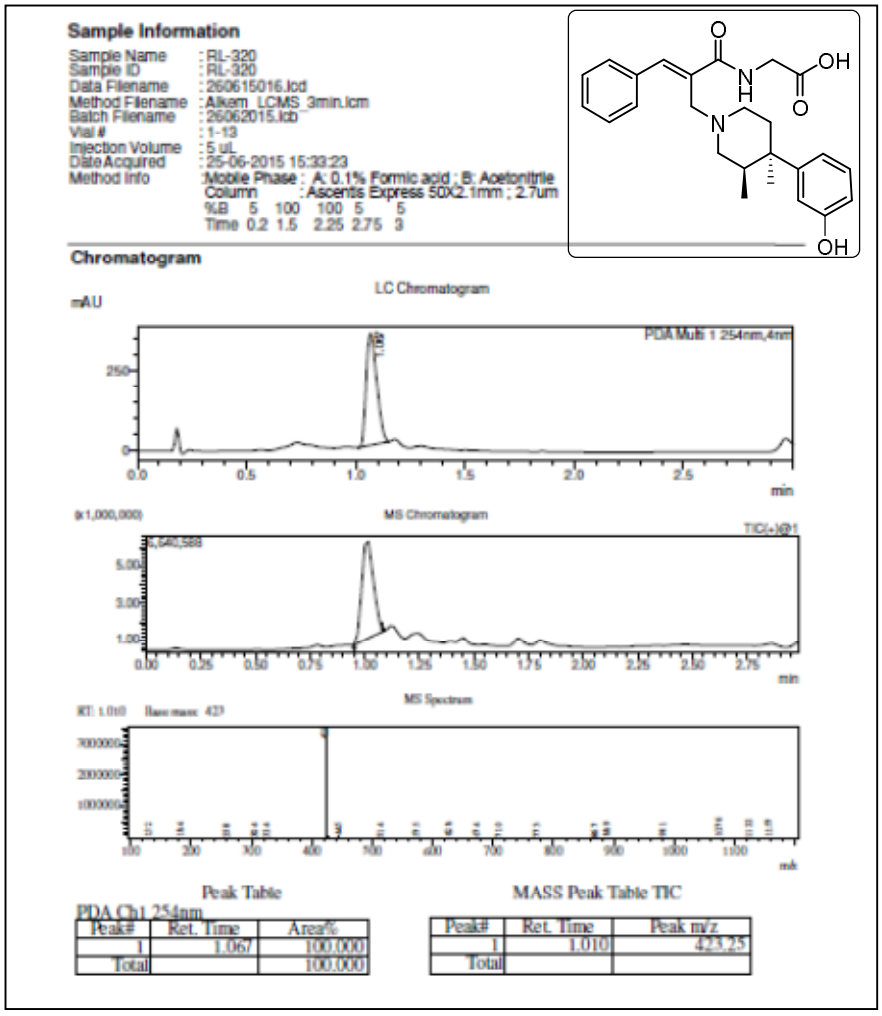
^{1}H NMR spectra of (E)-2-(2-((4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl)methyl)-3-phenylacrylamido)pentanoic acid **(28e)**



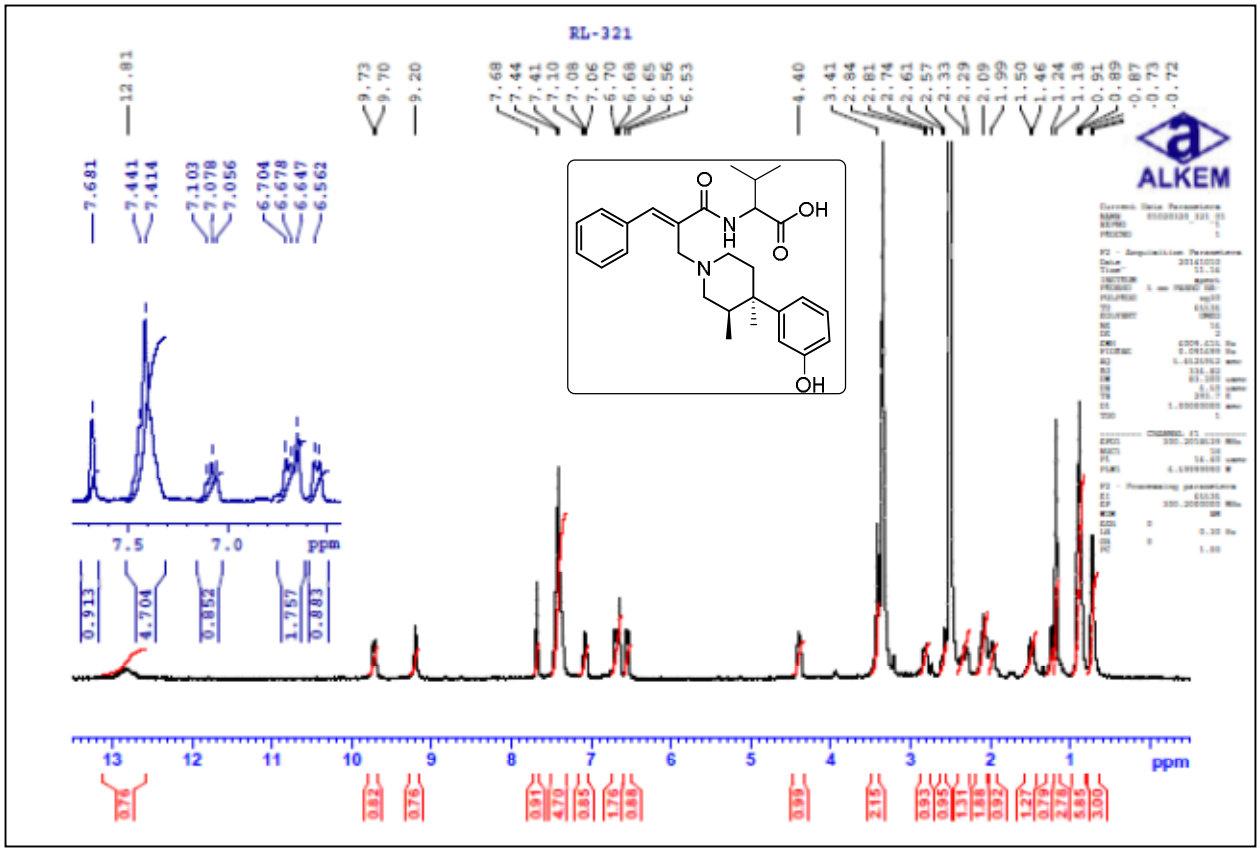
Mass spectra of (E)-2-(2-((4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl)methyl)-3-phenylacrylamido)pentanoic acid **(28e)**



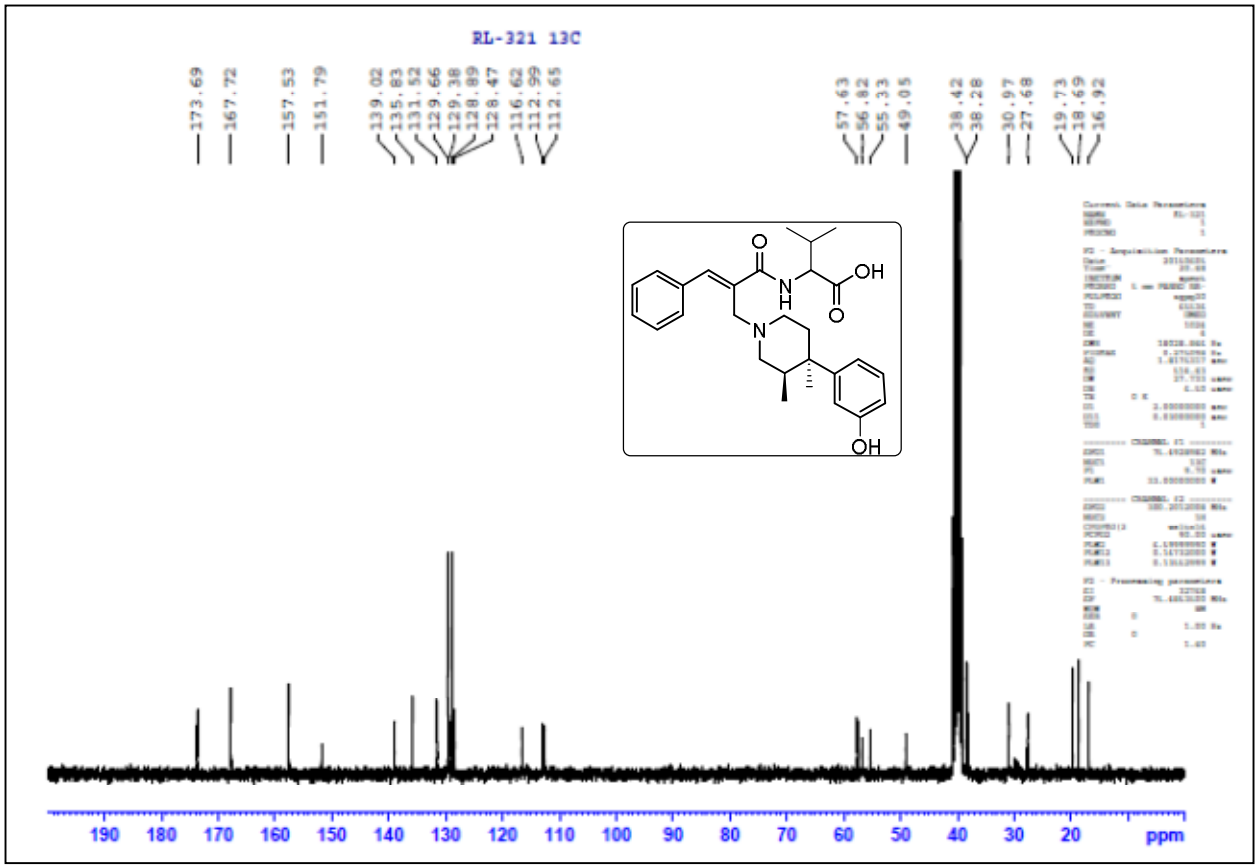
^{1}H NMR spectra of ((E)-2-(((3R,4R)-4-(3-hydroxyphenyl)-3,4-dimethylpiperidin-1-yl)methyl)-3-phenylacryloyl)glycine **(28f)**



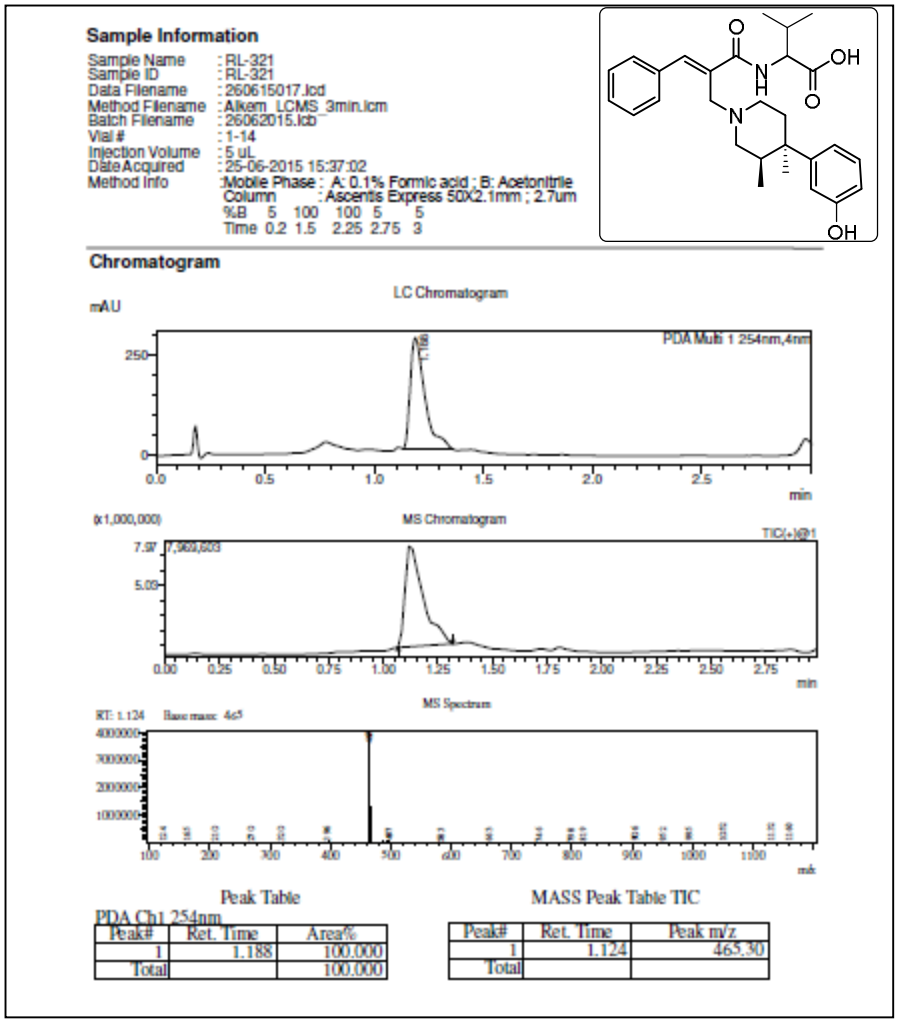
Mass spectra of ((E)-2-(((3R,4R)-4-(3-hydroxyphenyl)-3,4-dimethylpiperidin-1-yl)methyl)-3-phenylacryloyl)glycine **(28f)**



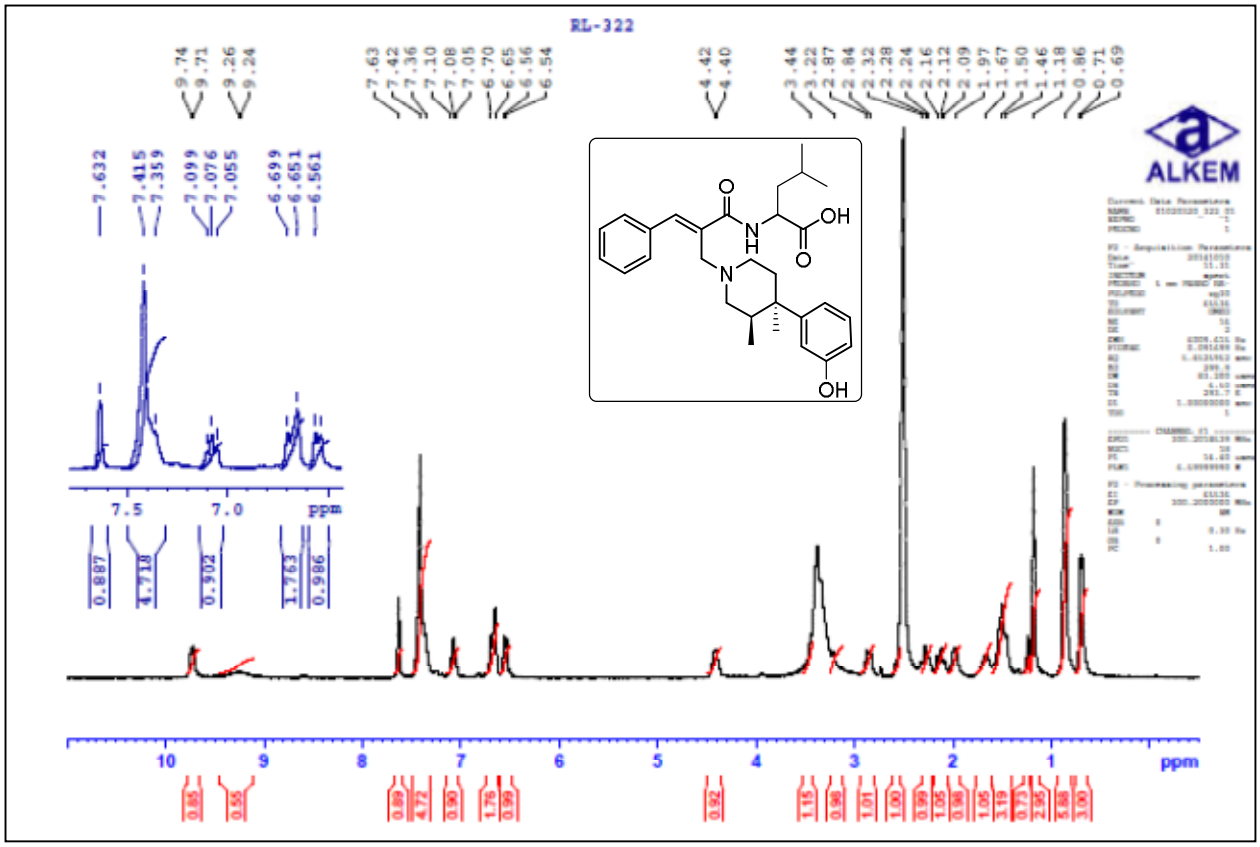
^{1}H NMR spectra of ((E)-2-(((3R,4R)-4-(3-hydroxyphenyl)-3,4-dimethylpiperidin-1-yl)methyl)-3-phenylacryloyl)valine **(28g)**



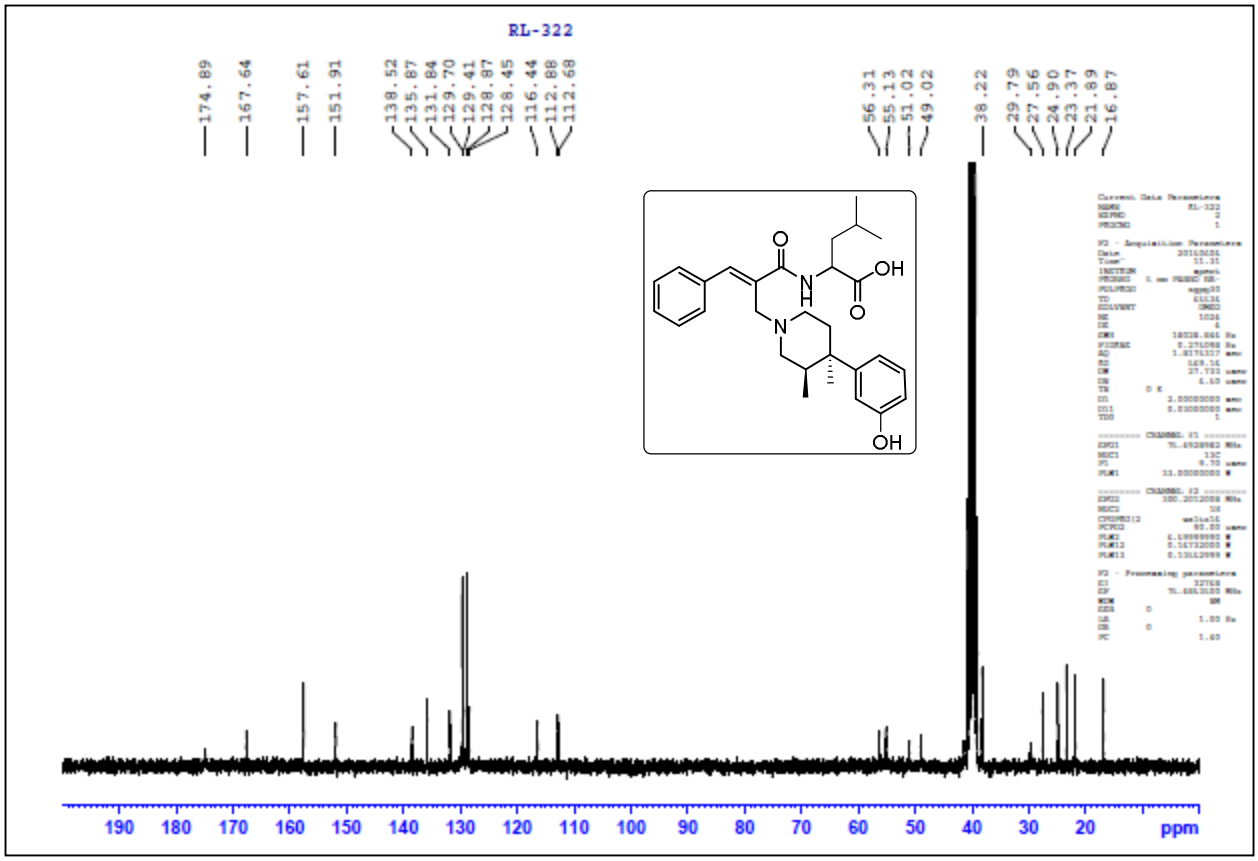
^{13}C NMR spectra of ((E)-2-(((3R,4R)-4-(3-hydroxyphenyl)-3,4-dimethylpiperidin-1-yl)methyl)-3-phenylacryloyl)valine **(28g)**



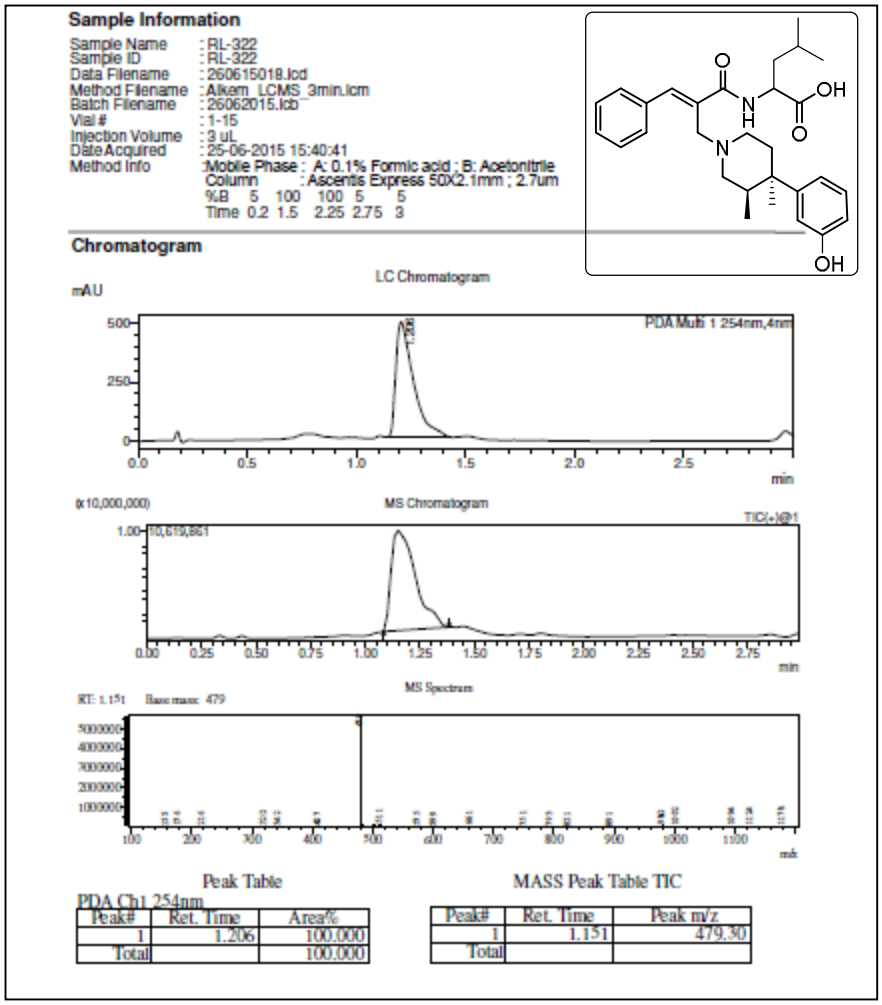
Mass spectra of ((E)-2-(((3R,4R)-4-(3-hydroxyphenyl)-3,4-dimethylpiperidin-1-yl)methyl)-3-phenylacryloyl)valine **(28g)**



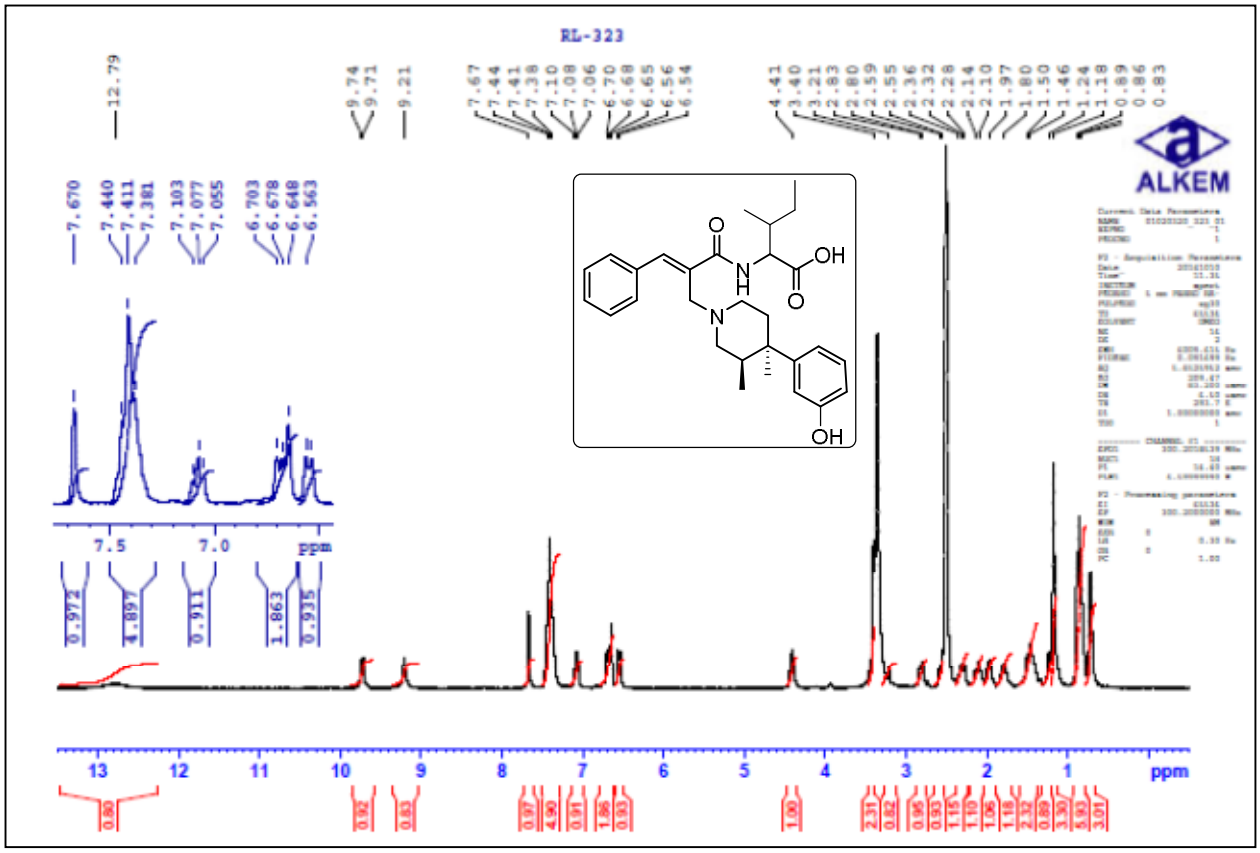
^{1}H NMR spectra of ((E)-2-(((3R,4R)-4-(3-hydroxyphenyl)-3,4-dimethylpiperidin-1-yl)methyl)-3-phenylacryloyl)leucine **(28h)**



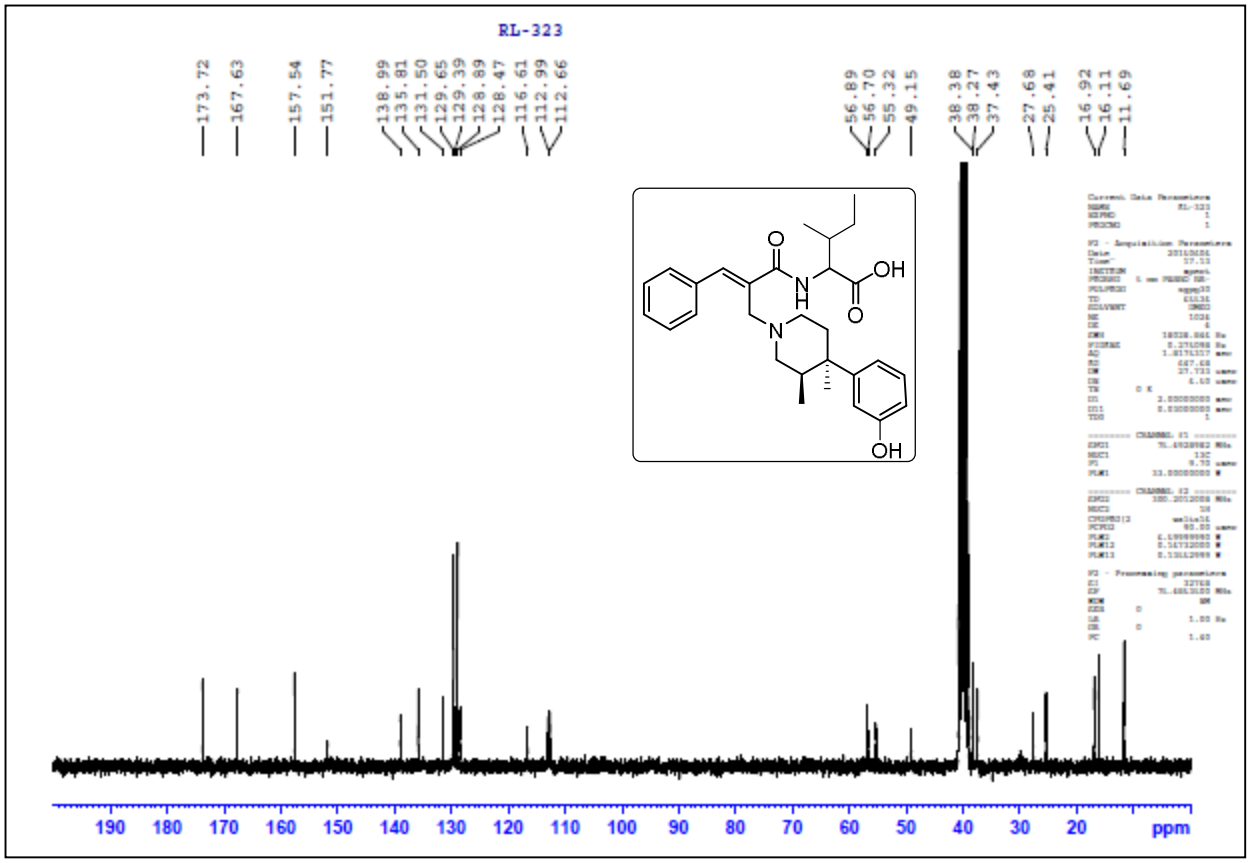
^{13}C NMR spectra of ((E)-2-(((3R,4R)-4-(3-hydroxyphenyl)-3,4-dimethylpiperidin-1-yl)methyl)-3-phenylacryloyl)leucine **(28h)**



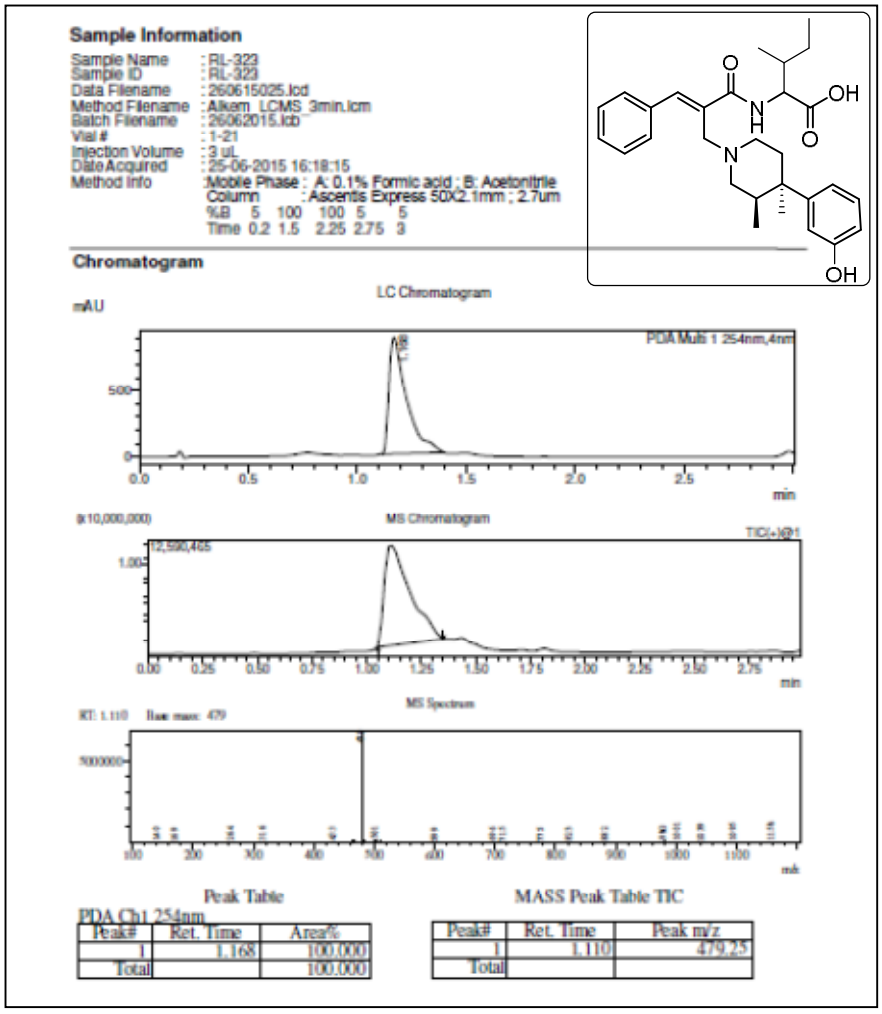
Mass spectra of ((E)-2-(((3R,4R)-4-(3-hydroxyphenyl)-3,4-dimethylpiperidin-1-yl)methyl)-3-phenylacryloyl)leucine **(28h)**



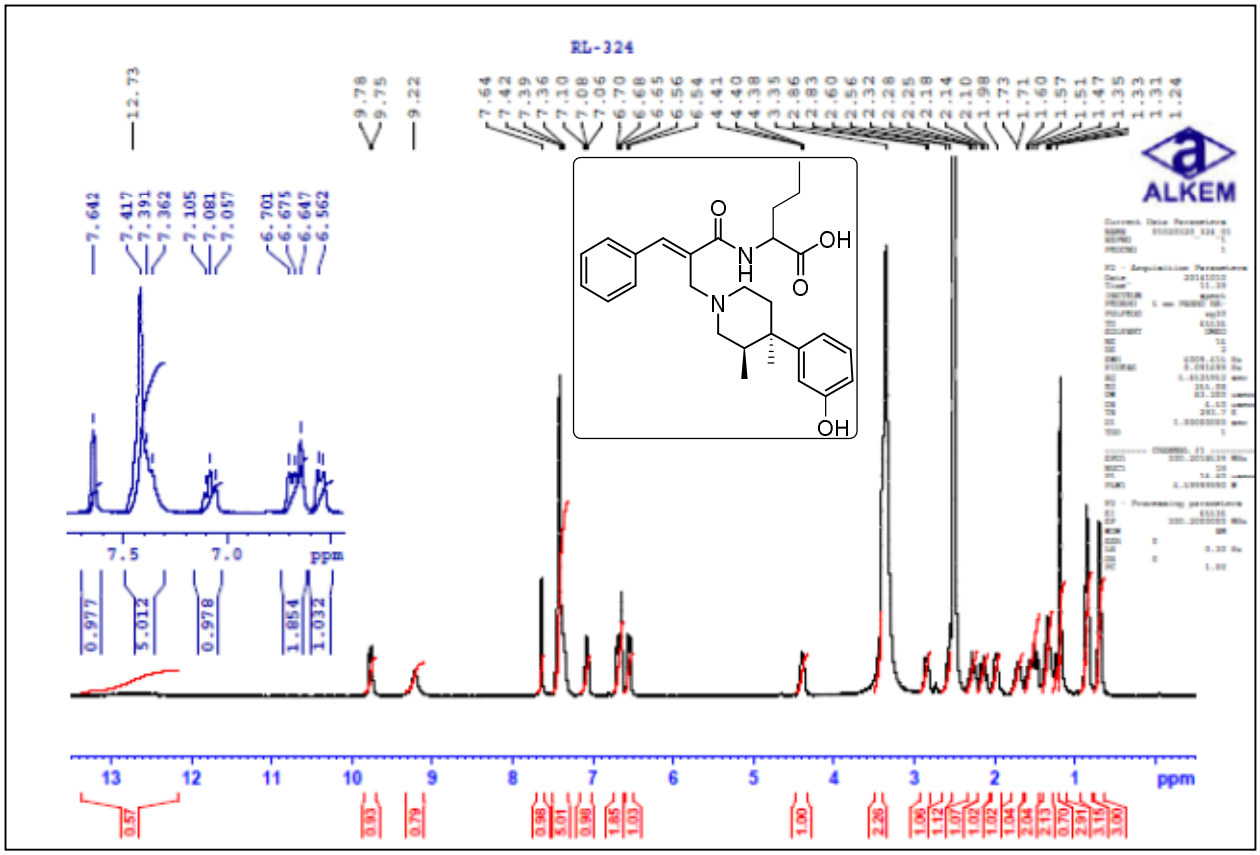
^{1}H NMR spectra of 2-((E)-2-(((3R,4R)-4-(3-hydroxyphenyl)-3,4-dimethylpiperidin-1-yl)methyl)-3-phenylacrylamido)-3-methylpentanoic acid **(28i)**



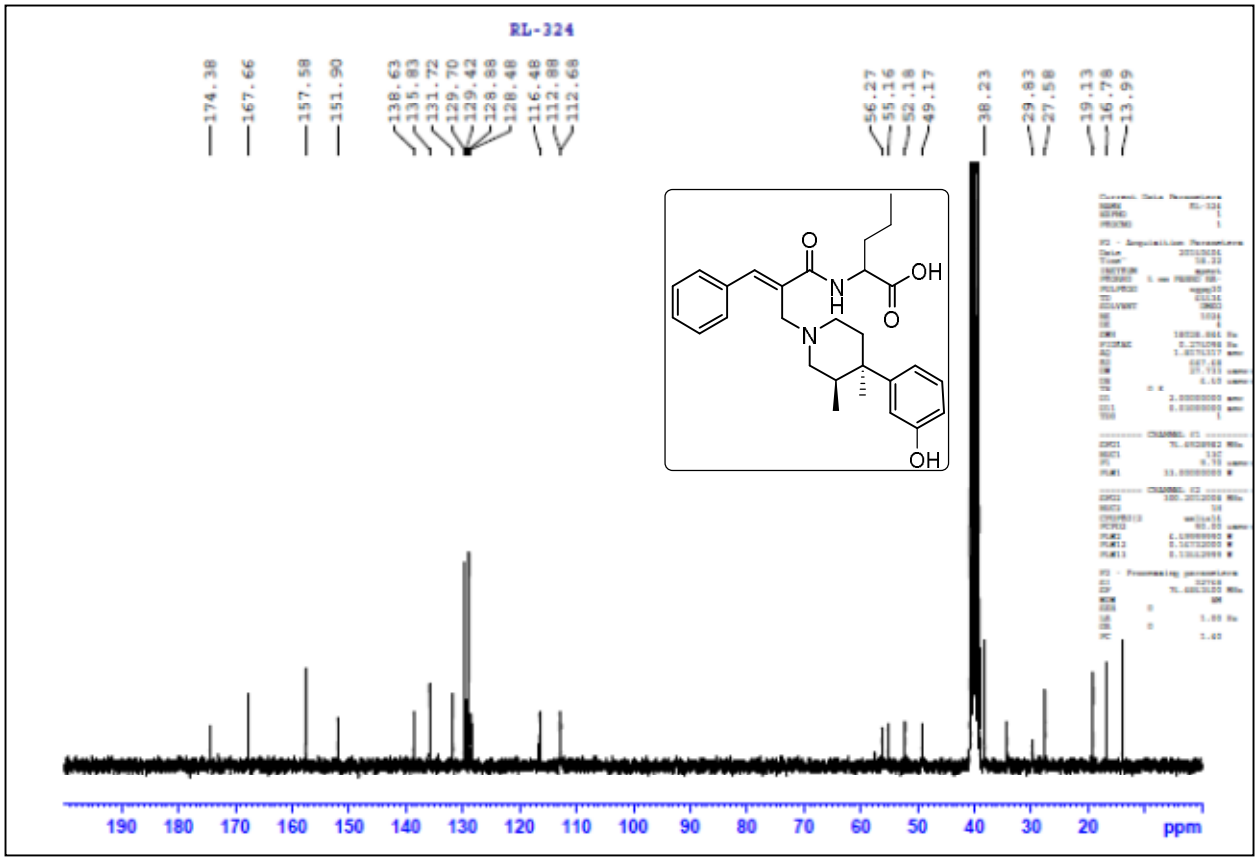
^{13}C NMR spectra of 2-((E)-2-(((3R,4R)-4-(3-hydroxyphenyl)-3,4-dimethylpiperidin-1-yl)methyl)-3-phenylacrylamido)-3-methylpentanoic acid **(28i)**



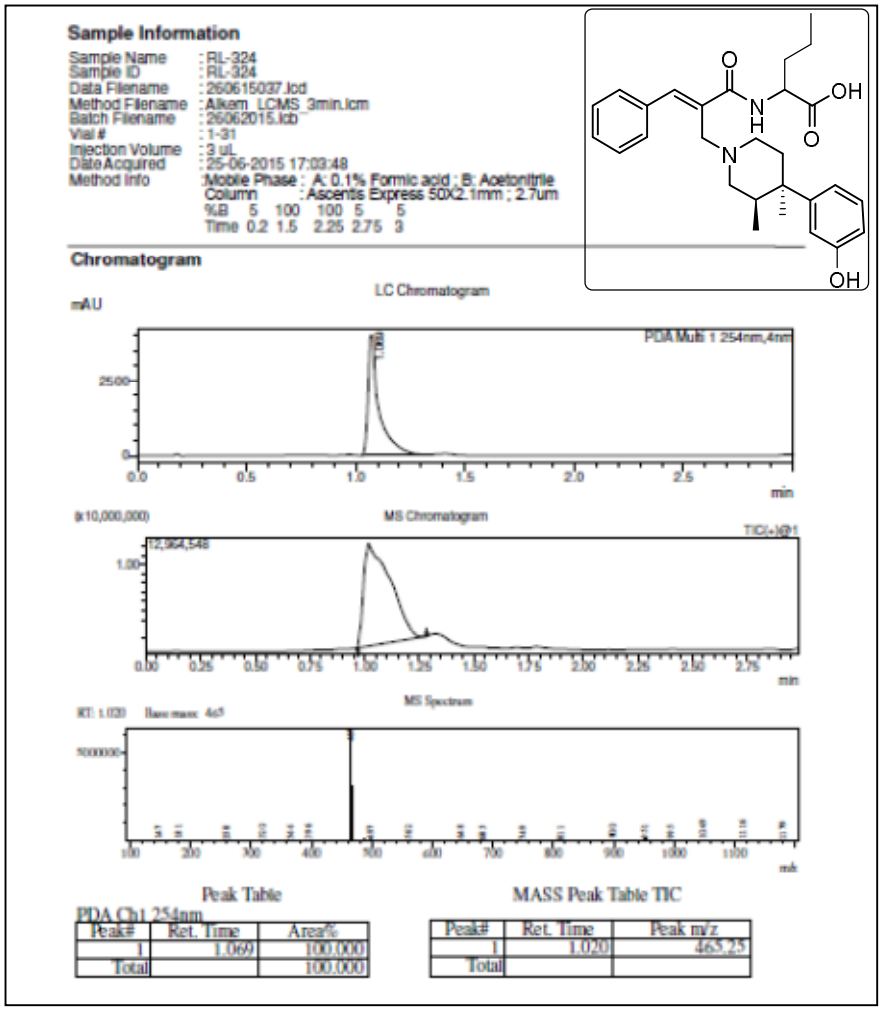
Mass spectra of 2-((E)-2-(((3R,4R)-4-(3-hydroxyphenyl)-3,4-dimethylpiperidin-1-yl)methyl)-3-phenylacrylamido)-3-methylpentanoic acid **(28i)**



^{1}H NMR spectra of 2-((E)-2-(((3R,4R)-4-(3-hydroxyphenyl)-3,4-dimethylpiperidin-1-yl)methyl)-3-phenylacrylamido)pentanoic acid **(28j)**



^{13}C NMR spectra of 2-((E)-2-(((3R,4R)-4-(3-hydroxyphenyl)-3,4-dimethylpiperidin-1-yl)methyl)-3-phenylacrylamido)pentanoic acid **(28j)**



Mass spectra of 2-((E)-2-(((3R,4R)-4-(3-hydroxyphenyl)-3,4-dimethylpiperidin-1-yl)methyl)-3-phenylacrylamido)pentanoic acid **(28j)**