Electronic Supplementary Material (ESI) for Green Chemistry

SUPPORTING INFORMATION

"All water chemistry" for a concise total synthesis of the novel class anti-anginal drug (*RS*), (*R*), and (*S*)-ranolazine

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Contents

General Information:

The glassware to be used in reactions was thoroughly washed and dried in an oven and the experiments were carried out with required precautions. Chemicals and all solvents were commercially available (Aldrich Chemical, Merck AG, Fluka and S-D Fine Chemicals) and used without further purification. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 MHz NMR spectrometer in $CDCl_3$ with residual undeuterated solvent ($CDCl_3$: 7.26/77.0) using Me_3SiCl as an internal standard. Chemical shifts (δ) are given in ppm and *J* values are given in Hz. ^{13}C NMR spectra were fully decoupled and were referenced to the middle peak of the solvent $CDCl_3$ at 77.00 ppm. Splitting pattern were designated as s, singlet; bs, broad singlet; d, doublet; dd, doublet of doublet; t, triplet; m, multiplet. Mass spectra were recorded on a Finnigan MAT-LCQ [for APCI] mass spectrometers. Infra-red (IR) spectra were recorded on Perkin Elmer FT-IR spectrometer in the range 4000-600 cm^{-1} either as neat samples or using KBr for preparing pellets for solid samples. Compounds were routinely checked for their purity on the silica gel GF-254 and visualized under UV at wavelength 254 nm. Melting points were measured with Gupta scientific melting point apparatus and were uncorrected. Evaporation of solvents was performed at reduced pressure, using a rotary evaporator. Microwave reactions performed using CEM Discover microwave system. Unless otherwise mentioned the word 'water' implies the use of 'tap water' in the reaction.

Preparation of Pure water

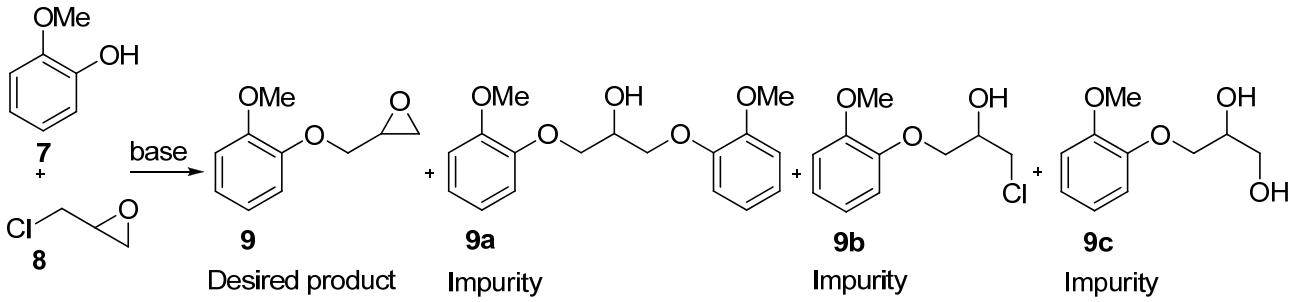
Pure water (15 MΩ-cm resistivity at 25 °C): The pure water was prepared by subjecting the tap water for reverse osmosis and ionic/organic removal by passing through pre-packed cartridge.

Preparation of Ultrapure water

Ultrapure water (18.2 MΩ-cm resistivity at 25 °C): The ultrapure water was prepared by subjecting the pure water for UV treatment (185/254 nm UV Lamp), deionization by passing through deionization cartridge followed by ultra membrane filtration (0.01um) under pressures up to 145 psi (10 bar). Ultrapure water (UPW) is generally considered to be ≥ 18.2 MΩ-cm resistivity at 25ºC, low ppt in metals, less than 50 ppt in inorganic anions and ammonia, less than 0.2 ppb in organic anions, and below 1 ppb total organic carbon (TOC) and silica (dissolved and colloidal).

The impurities generated during the synthesis of ranolazine (1):

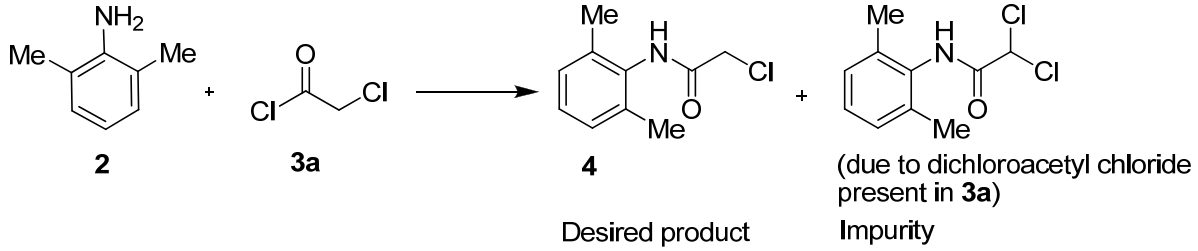
1. Impurities generated during the synthesis of the intermediate 9 by the reaction of 2-methoxyphenol (7) with epichlorohydrine (8).[a]



References:[a]

1. Aalla, S.; Gilla, G.; Anumula, R. R.; Kurella, S.; Padi, P. R.; Vummenthala, P. R. *Org. Process. Res. Dev.* 2012, *16*, 748.
2. Giridhar. T.; Srinivasulu, G.; Srinivasa, R. K. PCT Int. Appl. 2010023687 A2, March 4, 2010.
3. Anumula, R. R.; Gilla, G.; Aalla, S.; Madivada, L. R.; Macherla, P.; Kurella, S.; Charagondla, K.; Kasula, R.; Mandadapu, R. R.; Charagondla, K.; Vakamulla, M.; Bhavanipurapu, D. P. J. PCT Int. Appl. 2010025370 A2, March 4, 2010.
4. Athukuri,V. S.; Swamy, S.; Narani, C.; Khunt, M. D.; Pradhan, N. S. PCT Int. Appl. 2010043976 A2, April 22, 2010.
5. Sexana, R.; Srinivasan, C. V.; Wadawa, L. PCT Int. Appl. 2008047388 A2, April 24, 2008.

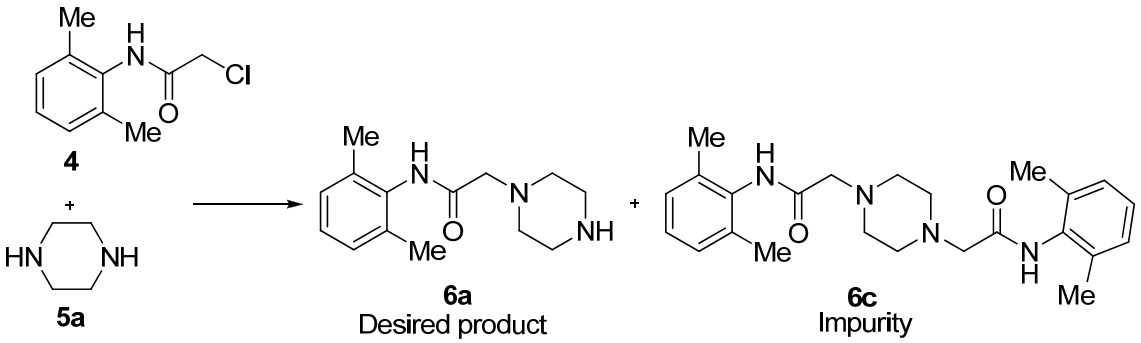
2. Impurities generated during the synthesis of the intermediate 4 by the reaction of 2,6-dimethylaniline (2) with chloroacetyl chloride (3a).[b]



References:[b]

1. Aalla, S.; Gilla, G.; Anumula, R. R.; Kurella, S.; Padi, P. R.; Vummenthala, P. R. *Org. Process. Res. Dev.* 2012, *16*, 748.
2. Giridhar. T.; Srinivasulu, G.; Srinivasa, R. K. PCT Int. Appl. 2010023687 A2, March 4, 2010.
3. Anumula, R. R.; Gilla, G.; Aalla, S.; Madivada, L. R.; Macherla, P.; Kurella, S.; Charagondla, K.; Kasula, R.; Mandadapu, R. R.; Charagondla, K.; Vakamulla, M.; Bhavanipurapu, D. P. J. PCT Int. Appl. 2010025370 A2, March 4, 2010.

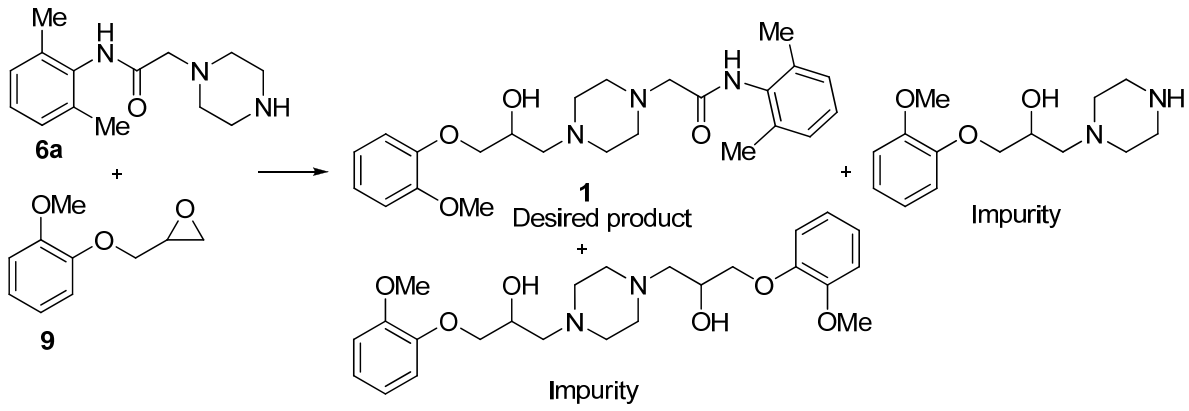
3. Impurities generated during the synthesis of *N*-(2,6-dimethylphenyl)-2-(piperazin-1-yl)acetamide (6a) by the reaction of piperazine (5a) with 4.[c]



References:[c]

1. Aalla, S.; Gilla, G.; Anumula, R. R.; Kurella, S.; Padi, P. R.; Vummenthala, P. R. *Org. Process. Res. Dev.* 2012, *16*, 748.
2. Giridhar. T.; Srinivasulu, G.; Srinivasa, R. K. PCT Int. Appl. 2010023687 A2, March 4, 2010.
3. Anumula, R. R.; Gilla, G.; Aalla, S.; Madivada, L. R.; Macherla, P.; Kurella, S.; Charagondla, K.; Kasula, R.; Mandadapu, R. R.; Charagondla, K.; Vakamulla, M.; Bhavanipurapu, D. P. J. PCT Int. Appl. 2010025370 A2, March 4, 2010.
4. Athukuri,V. S.; Swamy, S.; Narani, C.; Khunt, M. D.; Pradhan, N. S. PCT Int. Appl. 2010043976 A2, April 22, 2010.
5. Sexana, R.; Srinivasan, C. V.; Wadawa, L. PCT Int. Appl. 2008047388 A2, April 24, 2008.
6. Guillaume, M. J. M. A.; Cuypers, J. L. J.; Vervest, I. J. M.; Leurs, S. M. H.; De Smaele, D. PCT Int. Appl. 2004/000824 A1, December 31, 2003.

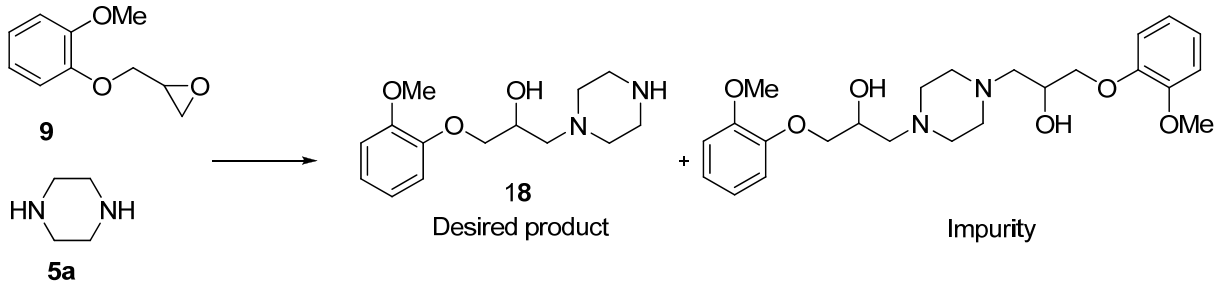
4. Impurities generated during the synthesis of ranolazine (1) by the reaction of 6 with 9[d]



References:[d]

1. Aalla, S.; Gilla, G.; Anumula, R. R.; Kurella, S.; Padi, P. R.; Vummenthala, P. R. *Org. Process. Res. Dev.* 2012, *16*, 748.

5. Impurities generated during the synthesis of 18 by the reaction of 9 with 5a[e]

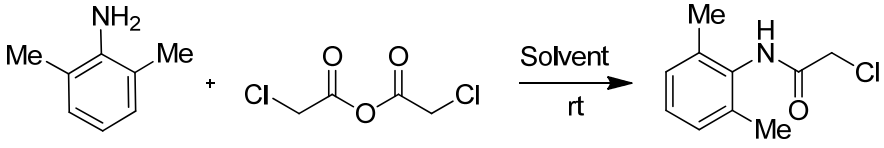


References:[e]

1. 3. Anumula, R. R.; Gilla, G.; Aalla, S.; Madivada, L. R.; Macherla, P.; Kurella, S.; Charagondla, K.; Kasula, R.; Mandadapu, R. R.; Charagondla, K.; Vakamulla, M.; Bhavanipurapu, D. P. J. US Pat 0151258 A1, 2011

Optimization Study

Table 1: Optimization of amount of solvent during *N*-acylation of 2,6-dimethylaniline (2) with chloroacetic anhydride (3b)[a]

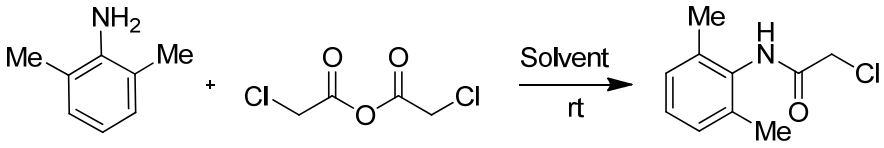


2 **3b** **4**

Entry	Solvent	Amount of solvent (mL)	Time (h)	Yield (%)[b]
1	Water	0.1	2	62
2	Water	0.5	2	94
3	Water	1	2	94
4	TFE	0.1 (1 mmol)	0.5	75
5	TFE	0.3 (3 mmol)	0.5	95
6	TFE	1	0.5	94
7	HFIP	0.17 (1 mmol)	0.5	85
8	HFIP	0.34 (2 mmol)	0.5	95
9	HFIP	1	0.5	95

[a]Reaction of 2,6-dimethyl aniline (**2**) (1 mmol) with chloroacetic anhydride (**3b**) (1 mmol, 1 equiv) in different amount of solvent at rt (~35 °C). [b]Isolated yield of **4**.

Table 2: Optimization of time during *N*-acylation of 2 with 3b[a]



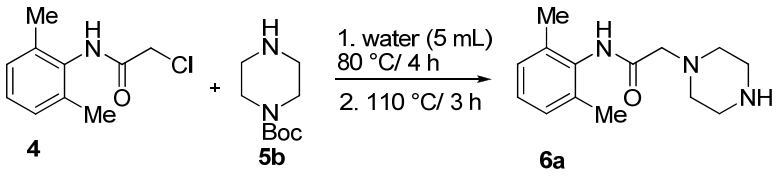
2 **3b** **4**

Entry	Solvent	Amount of solvent (mL)	Time (h)	Yield (%)[b]
1	Water	0.5	1	62
2	Water	0.5	1.5	88
3	Water	0.5	2	94
4	Water	0.5	2.5	94
5	TFE	0.3 (3 mmol)	10 min	59

6	TFE	0.3 (3 mmol)	20 min	80
7	TFE	0.3 (3 mmol)	30 min	95
8	HFIP	0.34 (2 mmol)	10 min	75
9	HFIP	0.34 (2 mmol)	20 min	95
10	HFIP	0.34 (2 mmol)	30 min	95

[a]Reaction of **2** (1 mmol) with **3b** (1 mmol, 1 equiv) in solvent at rt (~35 °C) for different intervals of time. [b]Isolated yield of **4**.

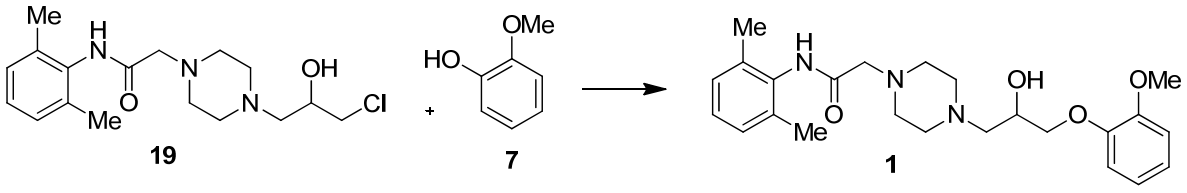
Table 3: Influence of solvent on tandem *N*-alkylation of 4 with *N*-Boc-piperazine 5b and *N*-Boc deprotection for one-pot synthesis of *N*-(2,6-dimethylphenyl)-2-(piperazin-1-yl)acetamide (6a) from 4.[a]



Entry	Solvent (5 mL)	Yield (%)[b]
1	Pure water	94
2	EtOH	trace[c,d]

[a]Reaction of **4** (1 mmol) with *N*-Boc-piperazine (**5b**) (1 mmol, 1 equiv) in solvent (5 mL) at 80 °C for 4 h followed by increase the reaction temperature to 110 °C and continue the stirring for further 3h. [b]Isolated yield of **6a**. [c]Reaction was performed under reflux condition.[c]**6a** was formed 12 % after 8 h.

Table 4: *O*-alkylation of 19 with 7: Synthesis of ranolazine (1)[a]

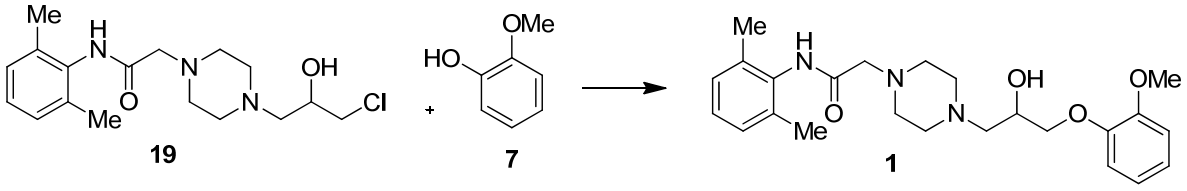


Entry	Base (1.5 equiv)	Catalyst (10 mol%)	Temp (°C)	Time (h)	Yield (%)[b]
1	None	--	rt	10	0
2	None	--	100	10	0
3	None	SDOSS	100	10	0
4	None	TBAB	100	10	0

5	None	Spam	100	10	0
6	None	Triton	100	10	0
7	K_2CO_3	--	rt	10	--
8	K_2CO_3	--	60	5	75
9	K_2CO_3	--	90	5	90
10	CS_2CO_3	--	rt	10	--
11	CS_2CO_3	--	60	5	78
12	CS_2CO_3	--	90	5	91
13	None	--	100/MW	30 min	0
14	None	SDOSS	100/MW	30 min	0
15	None	TBAB	100/MW	30 min	0
16	K_2CO_3	--	90/MW	30 min	91

[a]Reaction of **19** (1 mmol) with **7** (1 mmol, 1 equiv) in water (1 mL) under different conditions. [b]Isolated yield of **1**.

Table 5: Optimization of amount of base during *O*-alkylation of 19 with 7[a]



Entry	K_2CO_3 (equiv)	Yield (%)[b]
1	1	80
2	1.2	86
3	1.5	93
4	2	93

[a]Reaction of **19** (1 mmol) with **7** (1 mmol, 1 equiv) in presence of various amounts of base in water (2 mL). [b]Isolated yield of **1**.

Table 6: Optimization of amount of 5a for the synthesis of 6a[a]

Entry	Piperazine (equiv)	Yield (%)[b]	
		6a	**6c**
1	1	70	14
2	1.2	81	10
3	1.5	88	5
4	2	89	5

[a]Reaction of **4** (1 mmol) with various equivalents of **5a** in presence of 10 mol% TBAI in water (1 mL) at 60 °C for 3 h. [b]Isolated yield.

Table 7: Optimization of catalyst amount during the reaction of 4 with 5a[a]

Entry	TBAI (mol%)	Yield (%)[b]	
		6a	**6c**
1	2.5	21	--
2	5	55	trace
3	10	88	5
4	20	87	5

[a]Reaction of **4** (1 mmol) with **5a** (1 mmol, 1.5 equiv) in presence of different concentrations of TBAI in water (1 mL) at 60 °C for 3 h. [b]Isolated yield.

Table 8: Optimization of temperature during the reaction of 4 with 5a[a]

Entry	Temp (°C)	Yield (%)[b]	
		6a	**6c**
1	rt	--	--
2	60	87	5
3	90	75	12

[a]Reaction of **4** (1 mmol) with **5a** (1 mmol, 1.5 equiv.) in presence of 10 mol% of TBAI in water (1 mL) at different temperatures for 3 h. [b]Isolated yield.

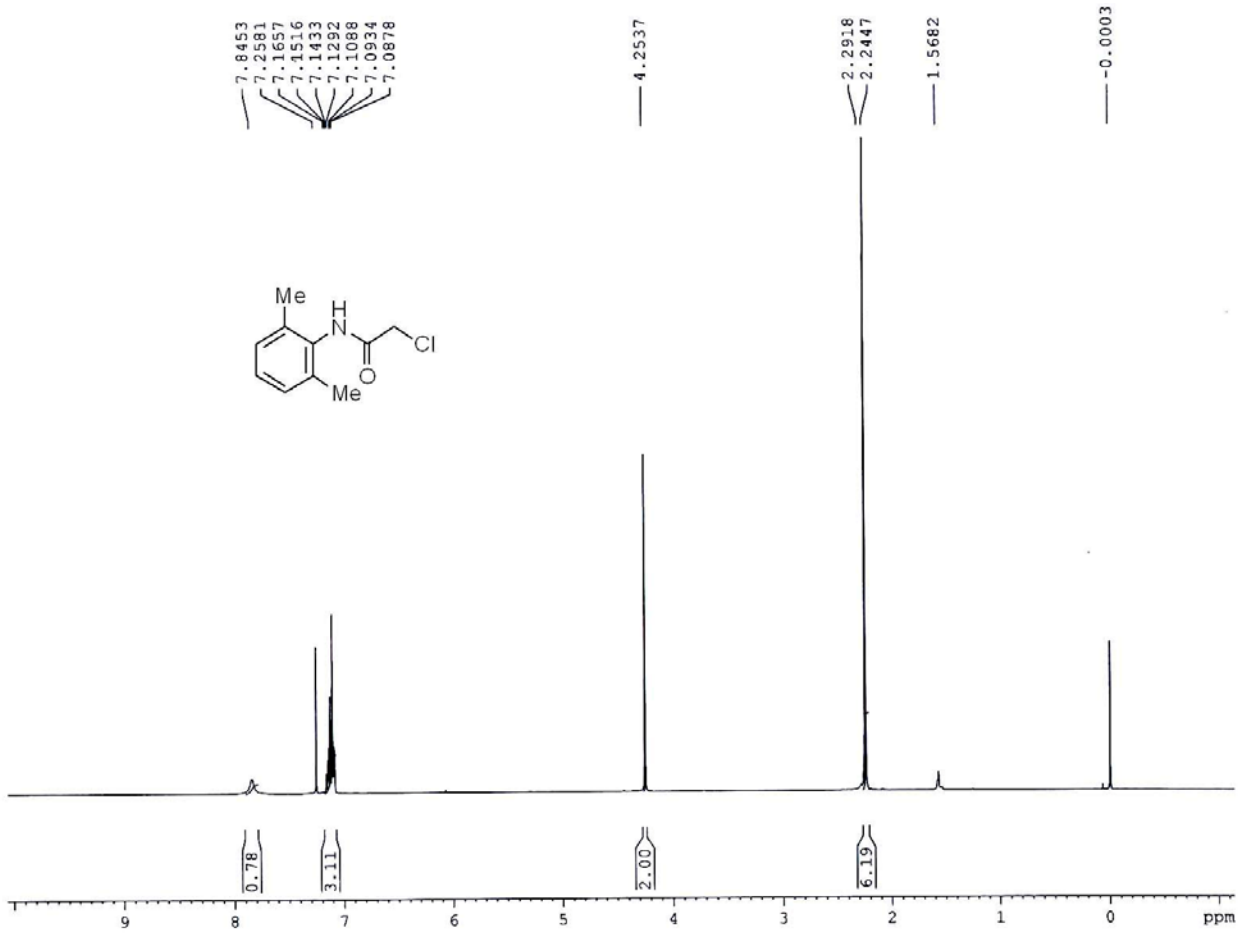
Table 9: Optimization of time during the reaction of 4 with 5a[a]

Entry	Time (h)	Yield of 6a (%)[b]
1	1	62
2	2	75
3	3	88
4	4	88

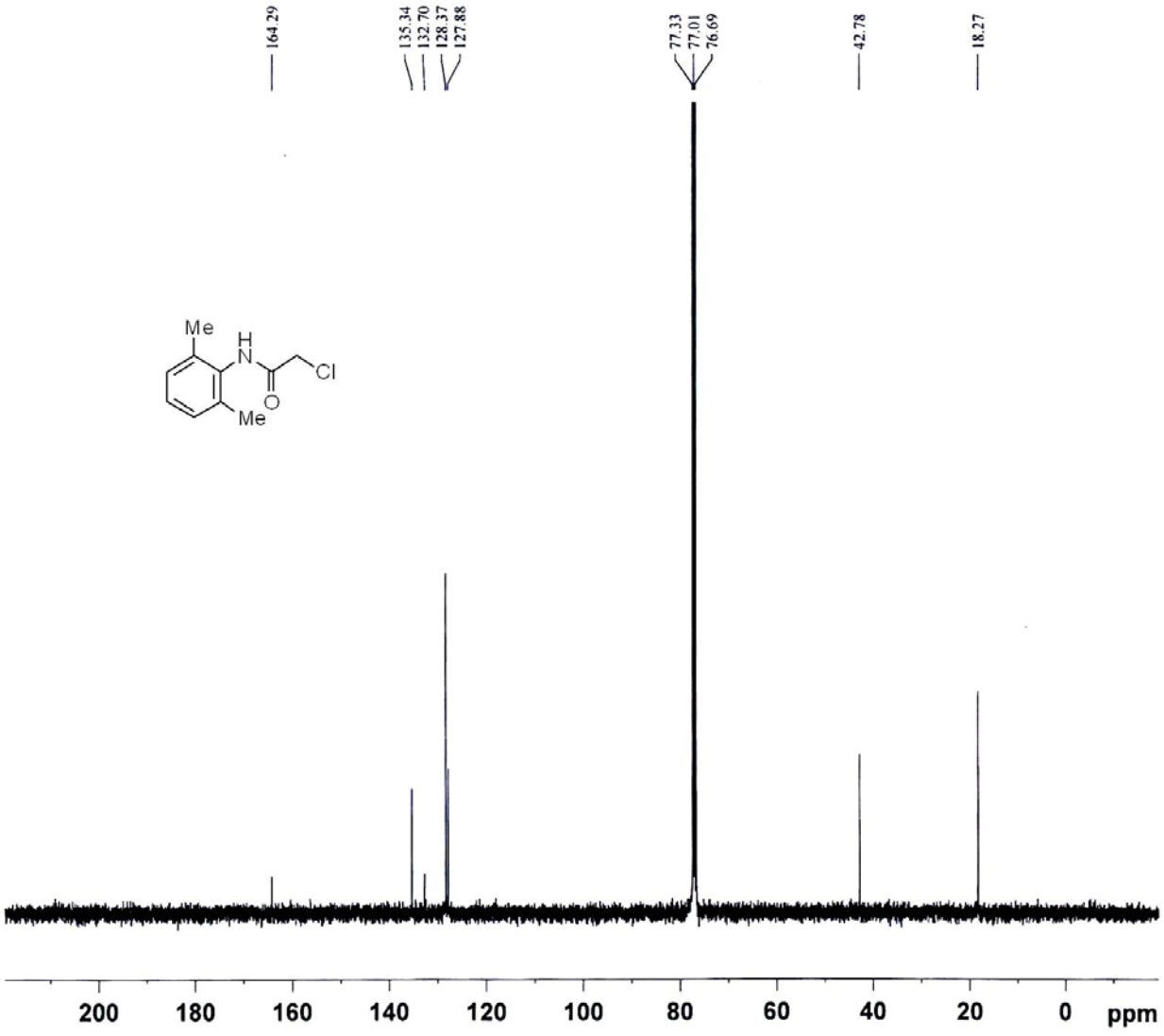
[a]Reaction of **4** (1 mmol) with **5a** (1 mmol, 1.5 equiv) in presence of different concentrations of TBAI in water (1 mL) at 60 °C at different intervals of time. [b]Isolated yield of **6a**.

Scanned NMR spectra

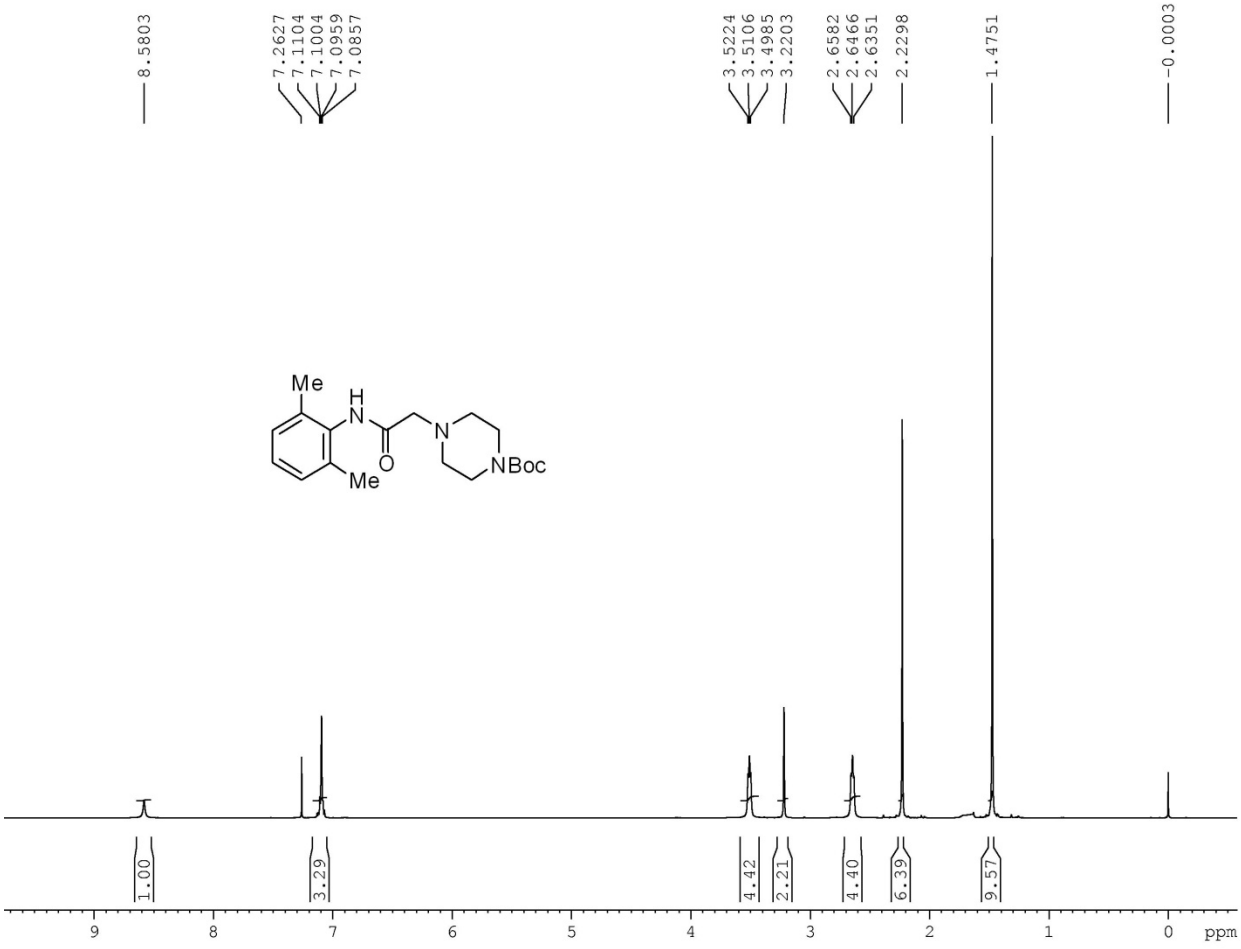
^{1}H NMR of 2-chloro-*N*-(2,6-dimethylphenyl)acetamide (4)



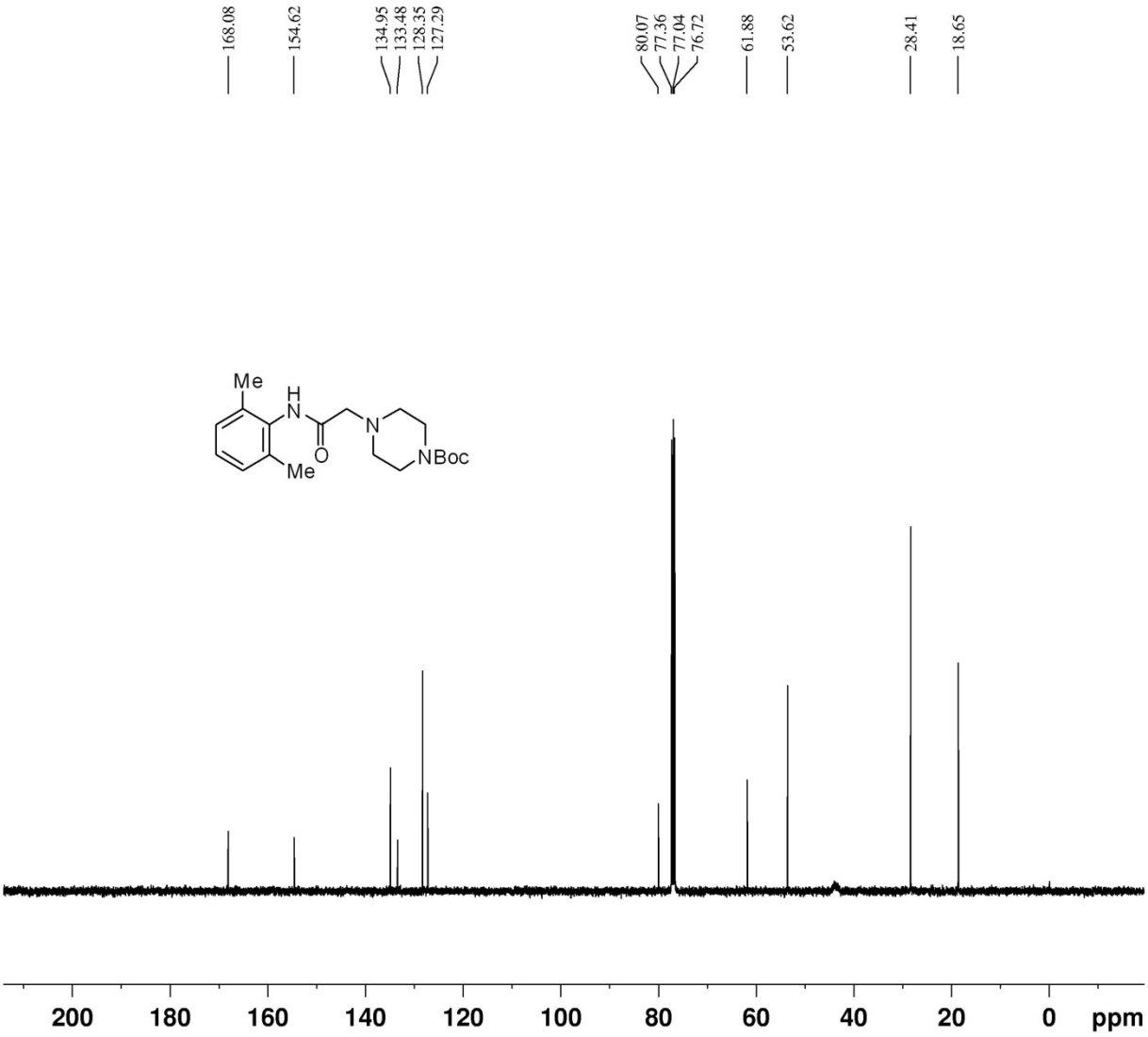
^{13}C NMR of 2-chloro-*N*-(2,6-dimethylphenyl)acetamide (4)



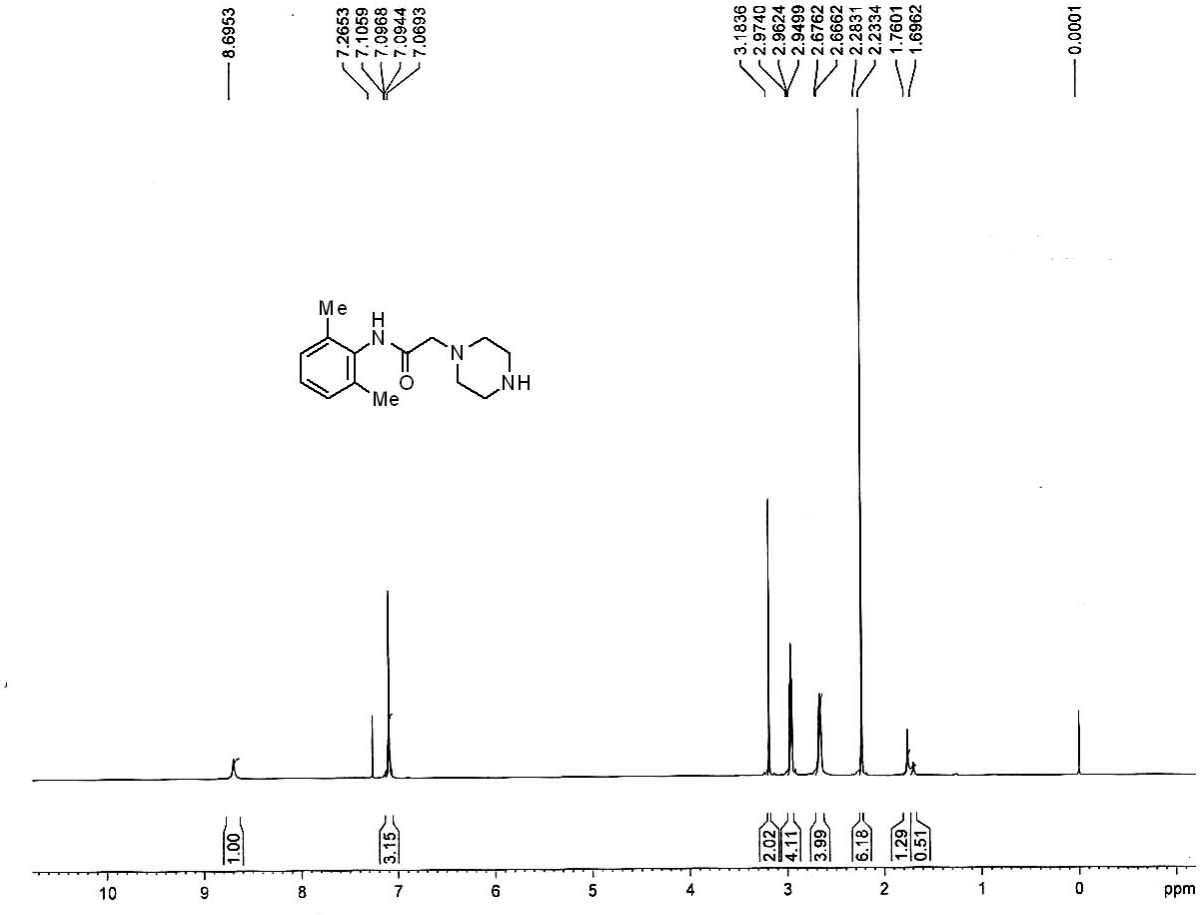
^{1}H NMR of *tert*-butyl 4-(2-(2,6-dimethylphenylamino)-2-oxoethyl)piperazine-1-carboxylate (6b)



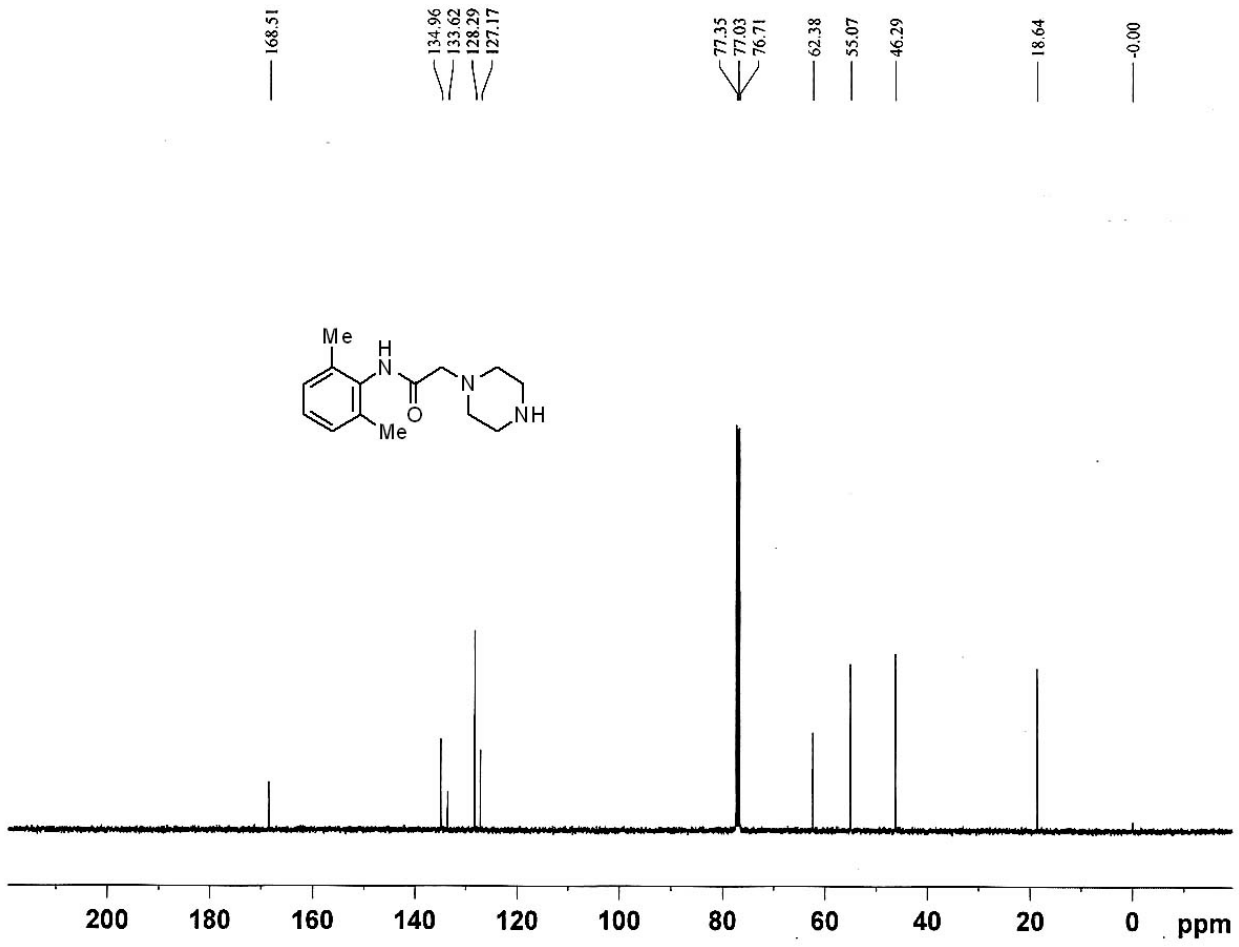
^{13}C NMR of *tert*-butyl 4-(2-(2,6-dimethylphenylamino)-2-oxoethyl)piperazine-1-carboxylate (6b)



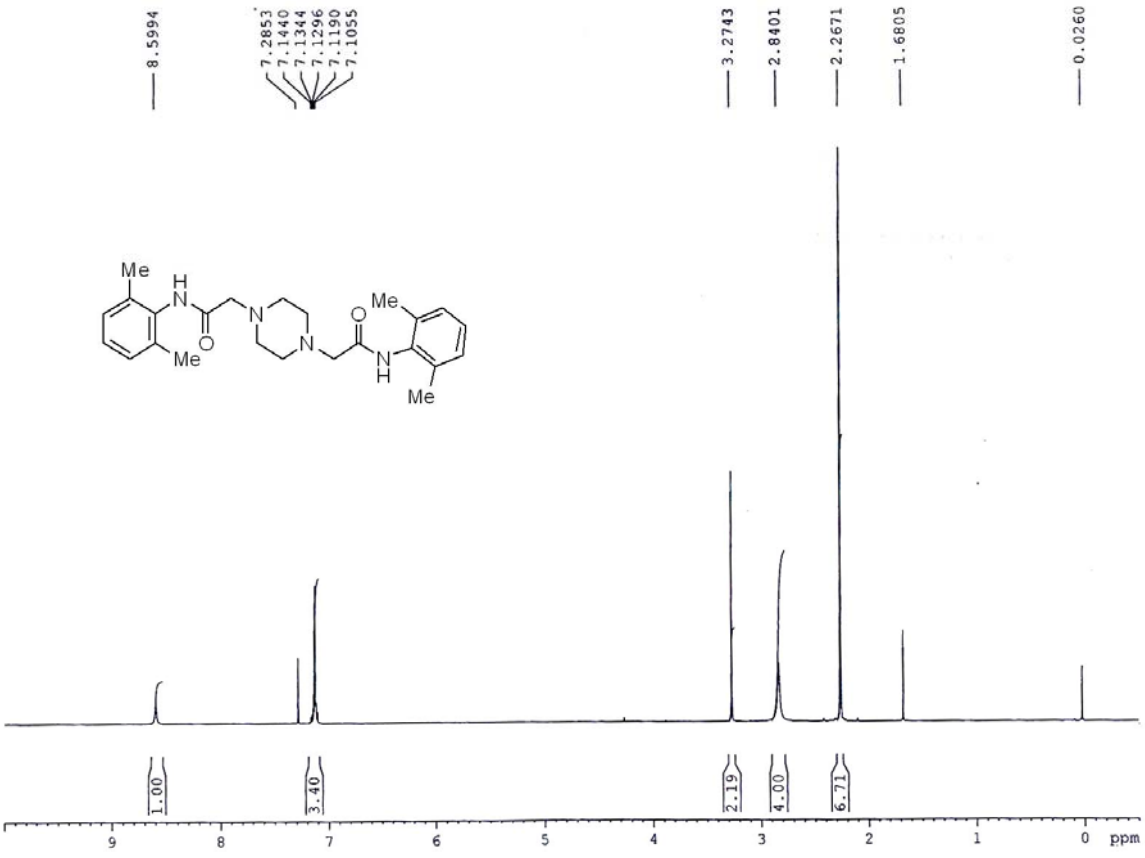
^{1}H NMR of *N*-(2,6-dimethylphenyl)-2-(piperazin-1-yl)acetamide (6a)



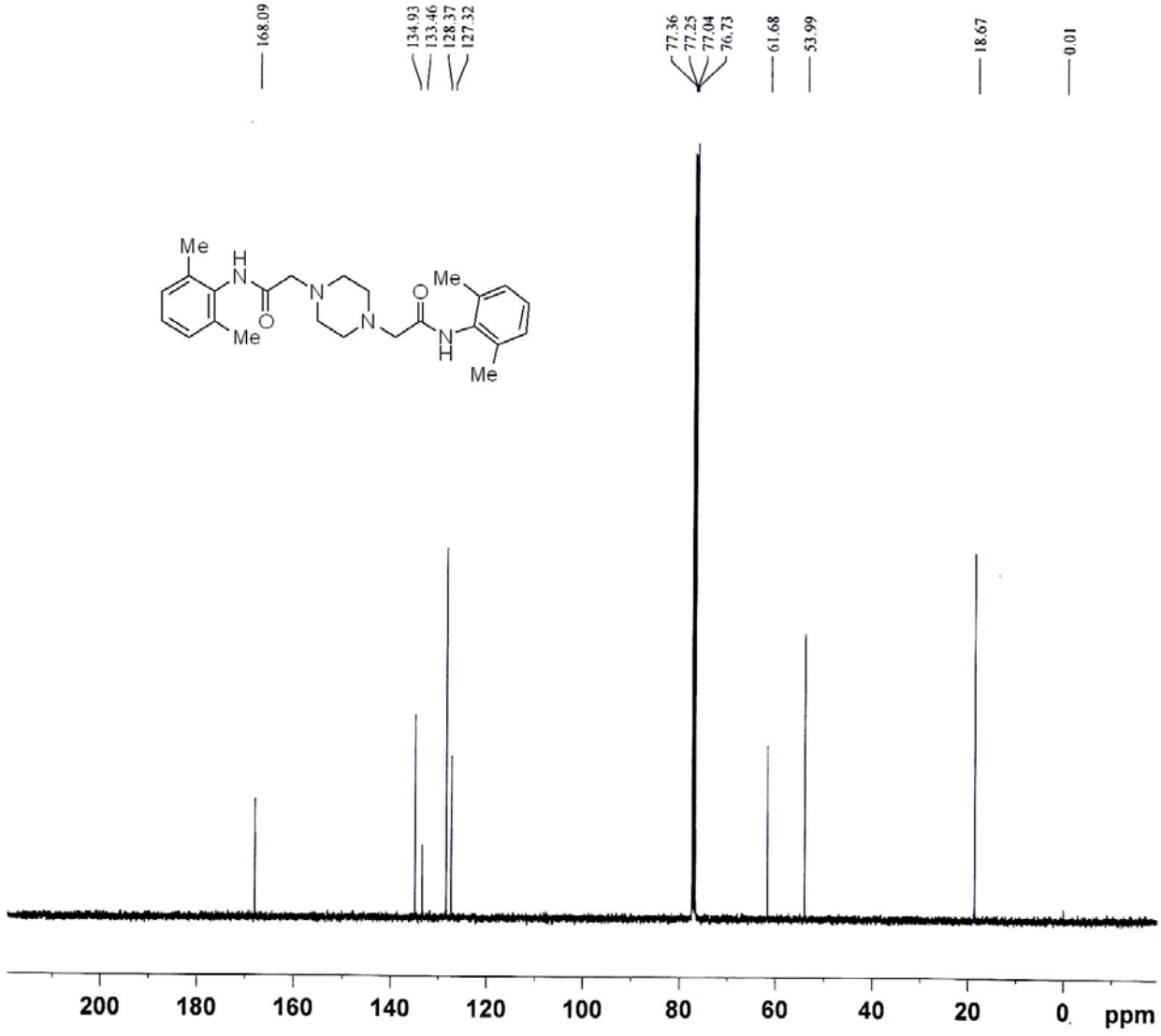
^{13}C NMR of *N*-(2,6-dimethylphenyl)-2-(piperazin-1-yl)acetamide (6a)



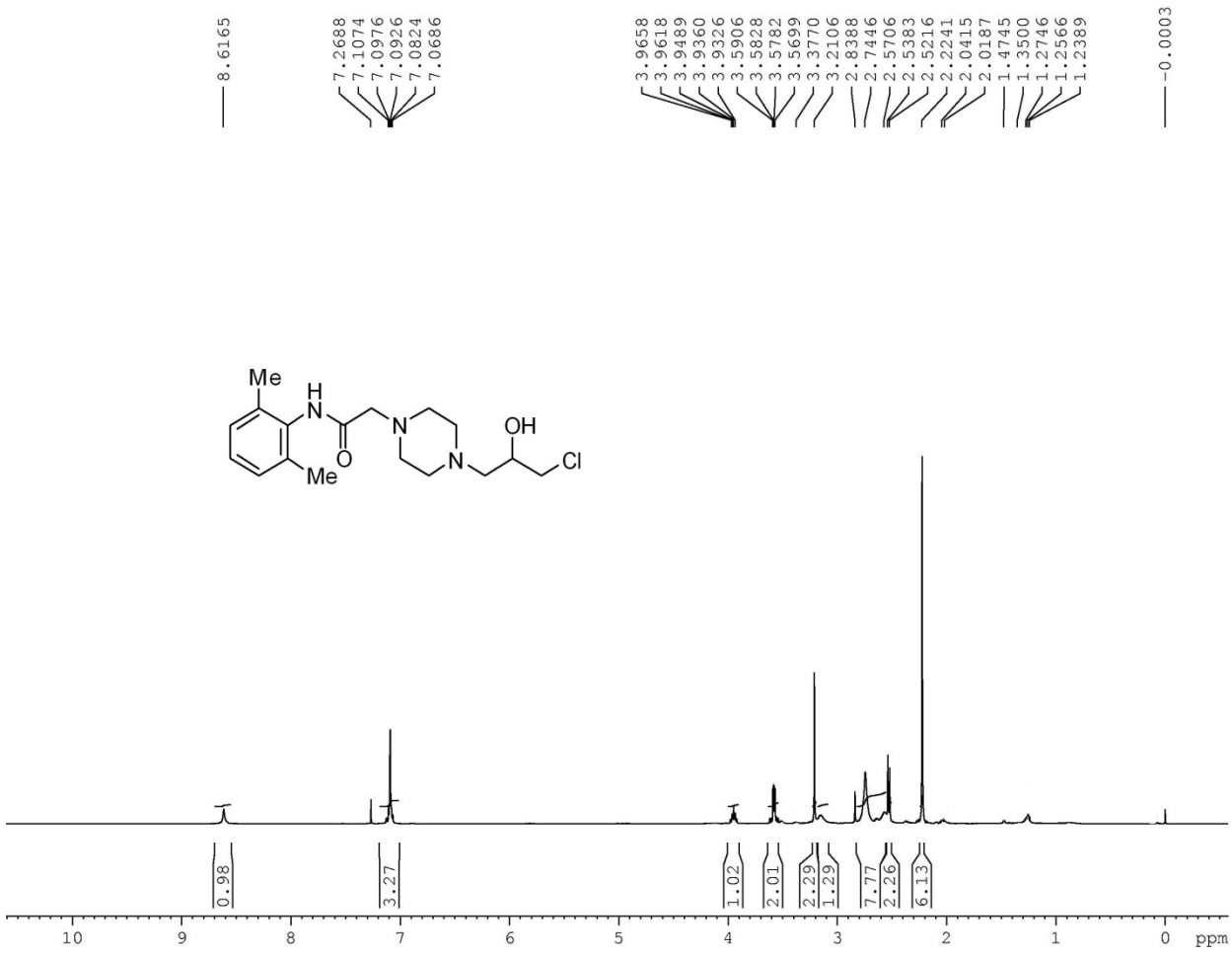
^{1}H NMR of 2,2'-(piperazine-1,4-diyl)bis(*N*-(2,6-dimethylphenyl)acetamide) (6c)



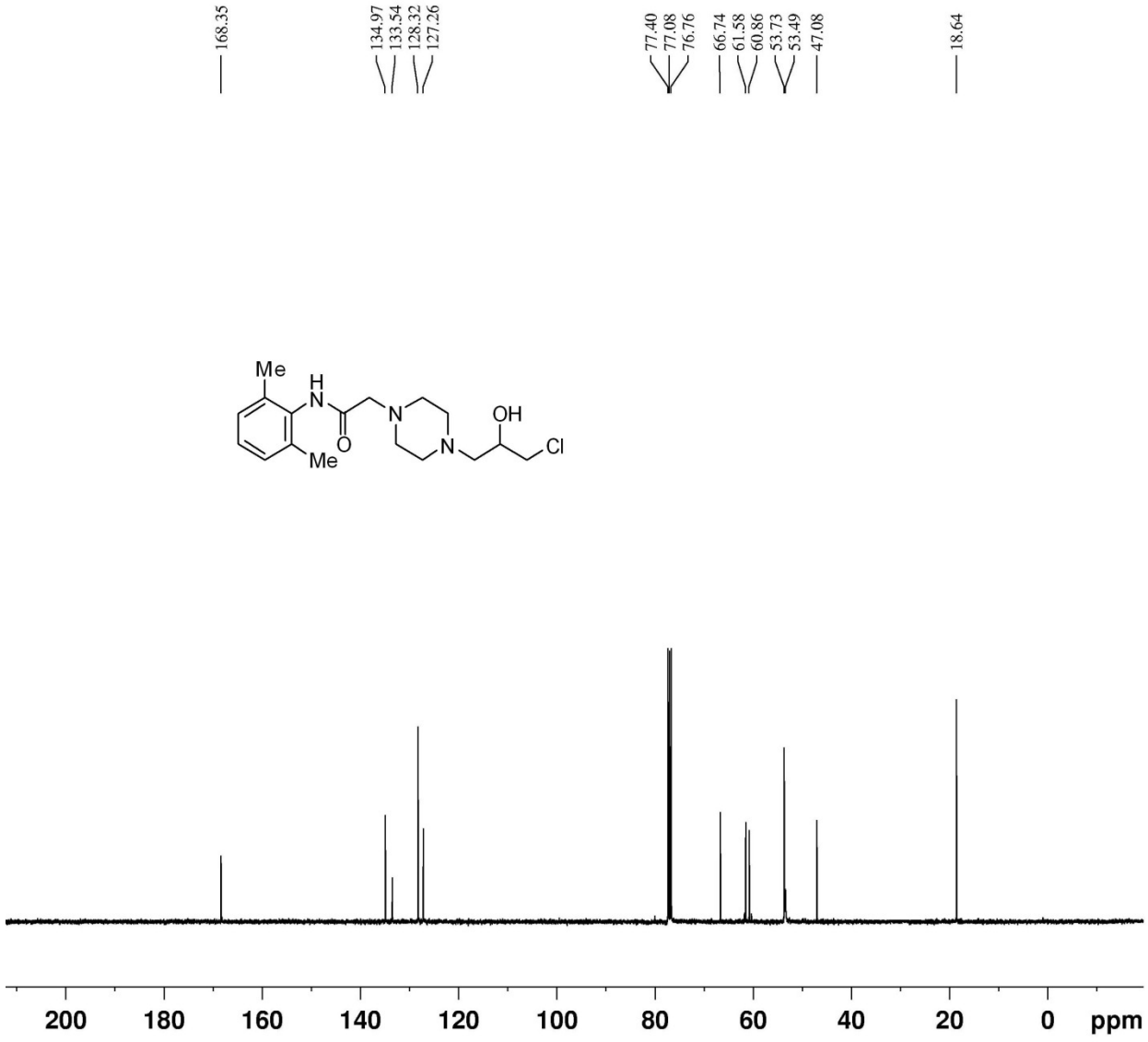
^{13}C NMR of 2,2'-(piperazine-1,4-diyl)bis(*N*-(2,6-dimethylphenyl)acetamide) (6c)



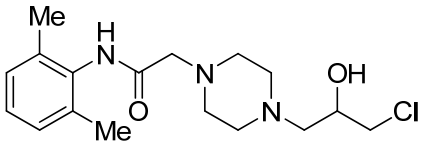
^{1}H NMR of (*RS*)-2-(4-(3-chloro-2-hydroxypropyl)piperazin-1-yl)-*N*-(2,6-dimethylphenyl)acetamide (19)



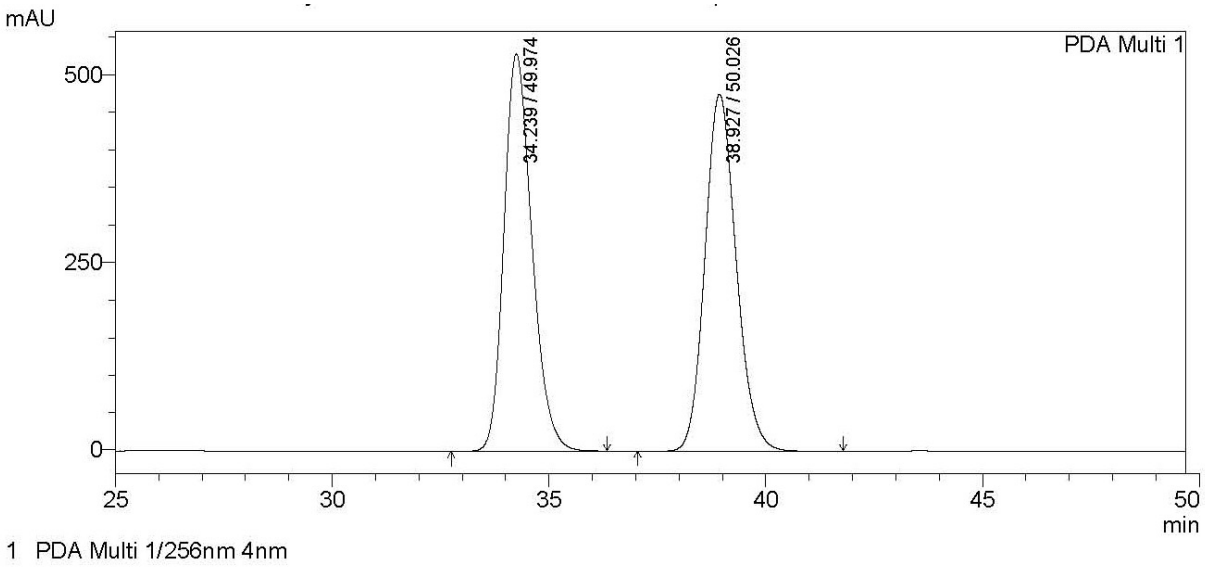
^{13}C NMR of (*RS*)-2-(4-(3-chloro-2-hydroxypropyl)piperazin-1-yl)-*N*-(2,6-dimethylphenyl)acetamide (19)



HPLC profile of (*RS*)- 2-(4-(3-chloro-2-hydroxypropyl)piperazin-1-yl)-*N*-(2,6-dimethylphenyl)acetamide on Chiral Column (19)



(*RS*)- 2-(4-(3-chloro-2-hydroxypropyl)piperazin-1-yl)-N-(2,6-dimethylphenyl)acetamide



PeakTable

PDA Ch1 256nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	34.239	23823099	529069	49.974	52.655
2	38.927	23847870	475710	50.026	47.345
Total		47670969	1004779	100.000	100.000

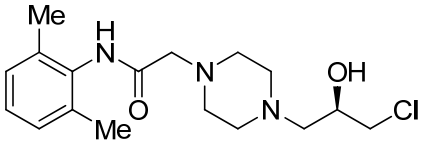
Eluent: Hexane-^{i}Propanol-Diethylamine (80:20: 0.1)

Flow Rate: 0.7 mL/min

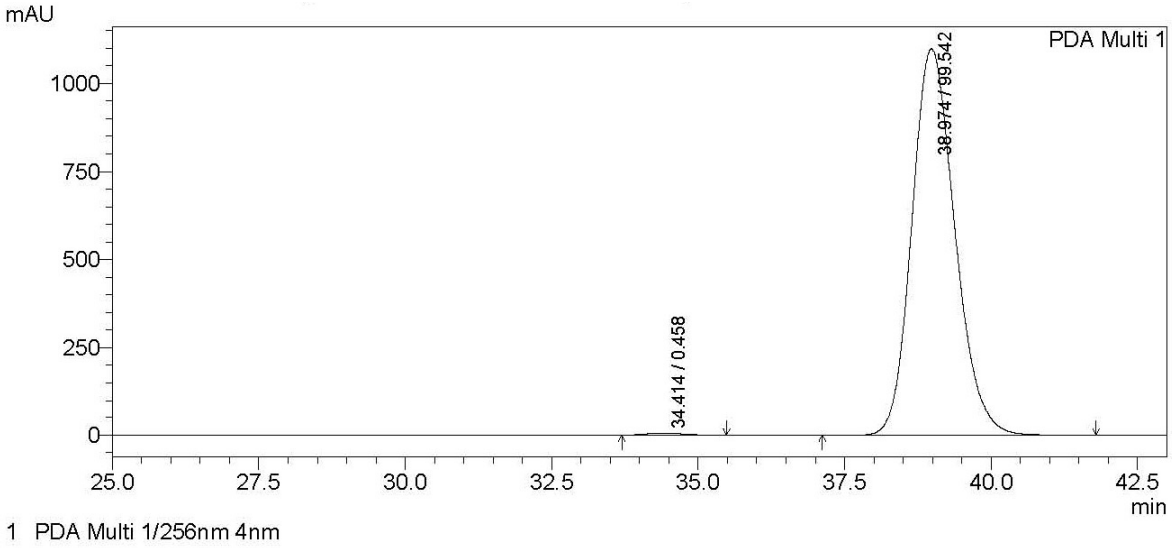
Chiral Column: AD-H

UV Detector Wavelength: 256 nm

HPLC profile of (*R*)- 2-(4-(3-chloro-2-hydroxypropyl)piperazin-1-yl)-N-(2,6-dimethylphenyl)acetamide (*R*-19) on Chiral Column



(*R*)- 2-(4-(3-chloro-2-hydroxypropyl)piperazin-1-yl)-N-(2,6-dimethylphenyl)acetamide



PeakTable

PDA Ch1 256nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
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2	38.974	56114071	1099243	99.542	99.452
Total		56372232	1105302	100.000	100.000

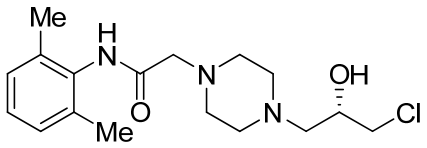
Eluent: Hexane-^{i}Propanol-Diethylamine (80:20: 0.1)

Flow Rate: 0.7 mL/min

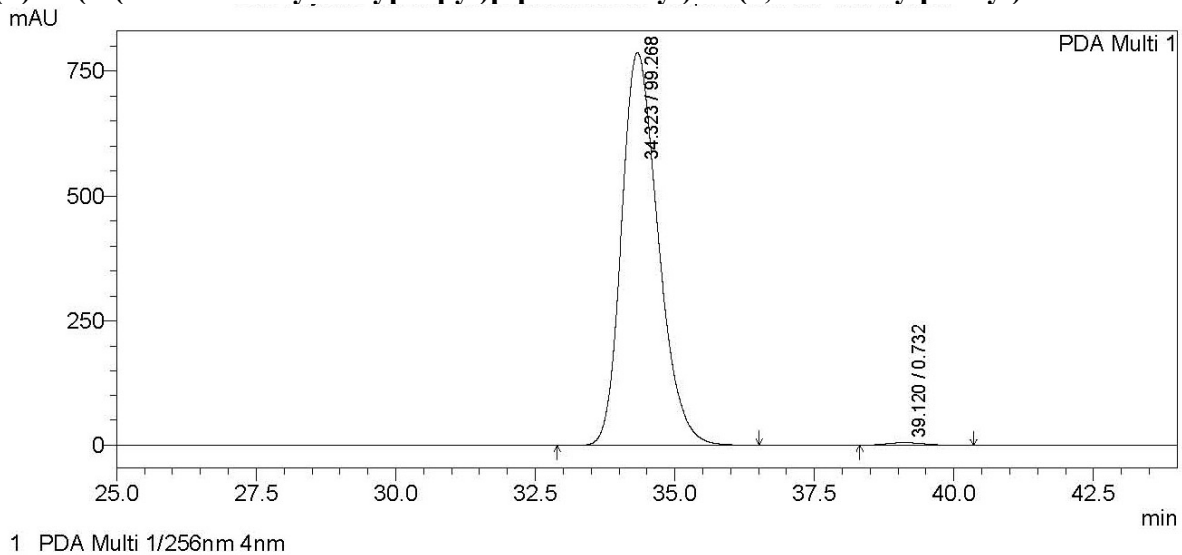
Chiral Column: AD-H

UV Detector Wavelength: 256 nm

HPLC profile of (*S*)- 2-(4-(3-chloro-2-hydroxypropyl)piperazin-1-yl)-N-(2,6-dimethylphenyl)acetamide (*S*-19) on Chiral Column



(*S*)- 2-(4-(3-chloro-2-hydroxypropyl)piperazin-1-yl)-N-(2,6-dimethylphenyl)acetamide



1 PDA Multi 1/256nm 4nm

PeakTable

PDA Ch1 256nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	34.323	35993515	786746	99.268	99.303
2	39.120	265594	5520	0.732	0.697
Total		36259109	792266	100.000	100.000

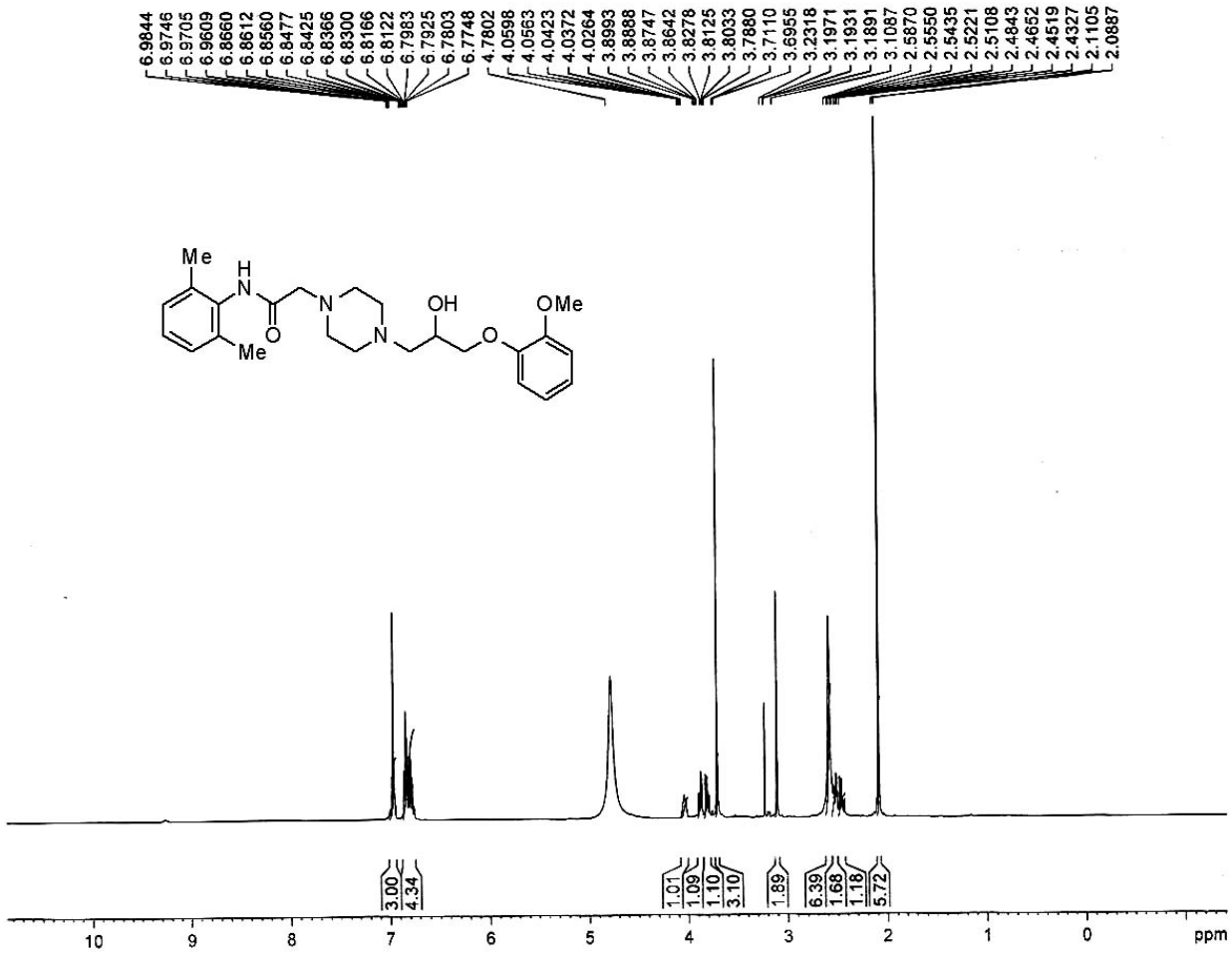
Eluent: Hexane-^{i}Propanol-Diethylamine (80:20: 0.1)

Flow Rate: 0.7 mL/min

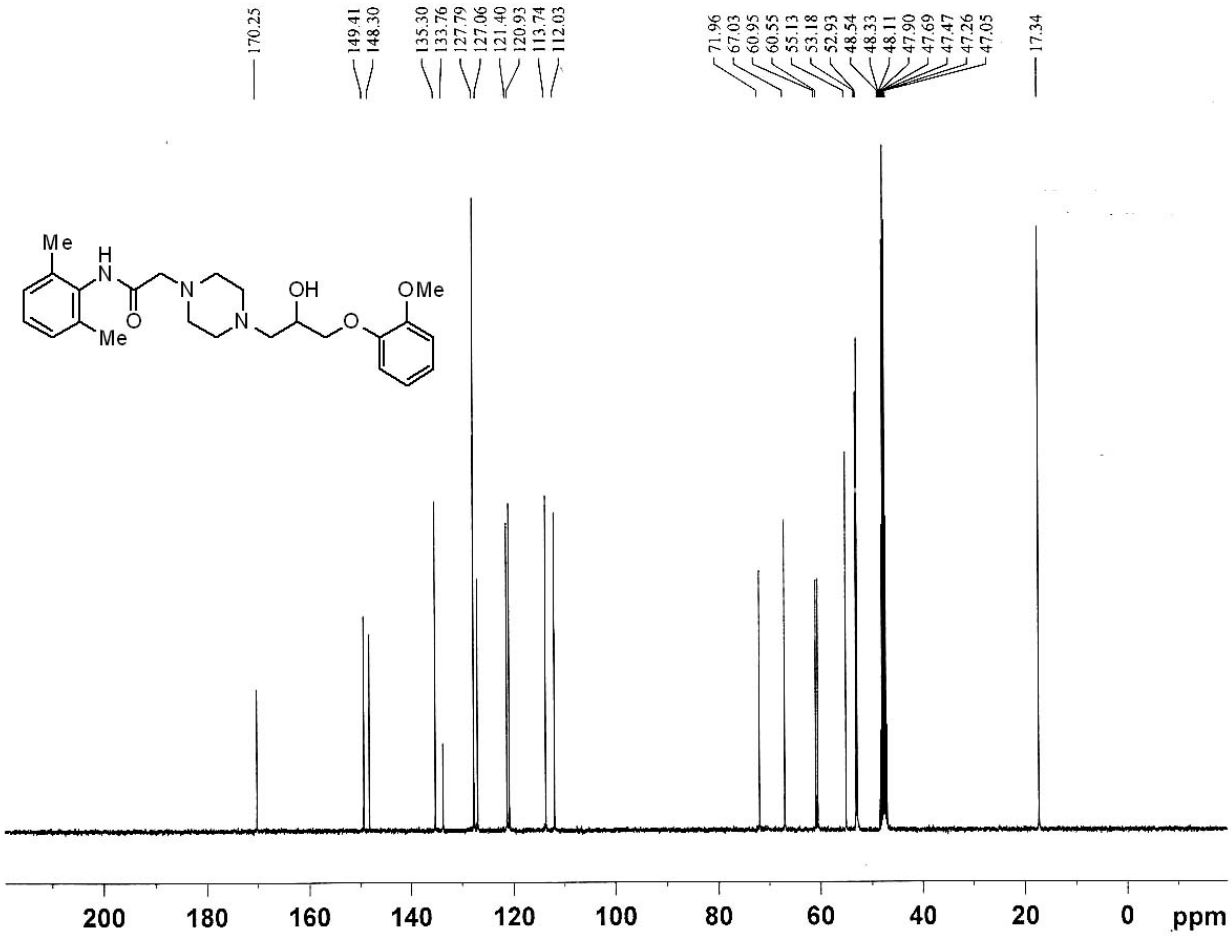
Chiral Column: AD-H

UV Detector Wavelength: 256 nm

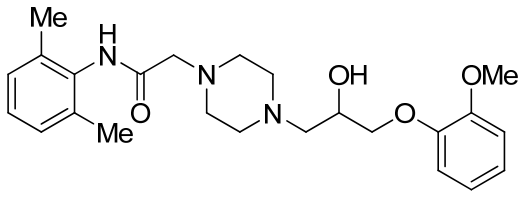
^{1}H NMR of Ranolazine (1)



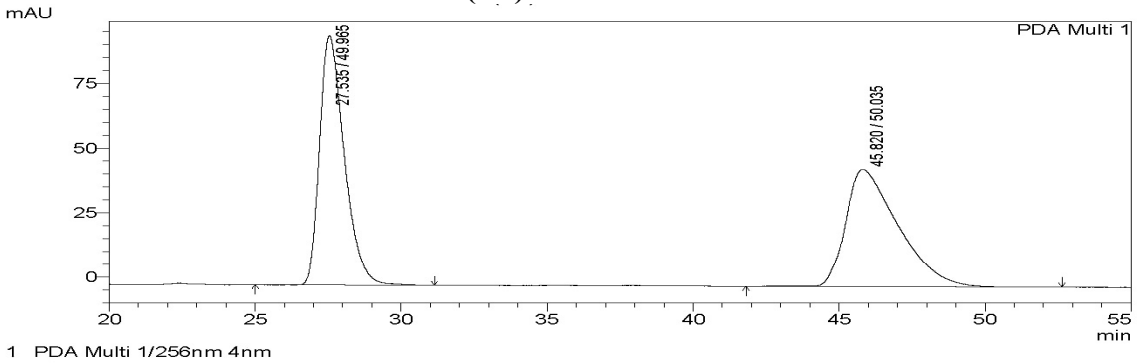
^{13}C NMR of Ranolazine (1)



HPLC profile of (*RS*)-Ranolazine (*RS*-1) on Chiral Column



(*RS*)-Ranolazine



PeakTable

PDA Ch1 256nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	27.535	5689701	96439	49.965	67.942
2	45.820	5697704	45504	50.035	32.058
Total		11387405	141944	100.000	100.000

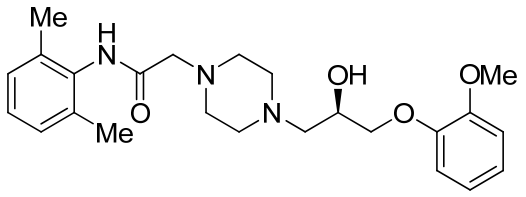
Eluent: Hexane-^{i}Propanol-Diethylamine (70:30: 0.1)

Flow Rate: 0.8 mL/min

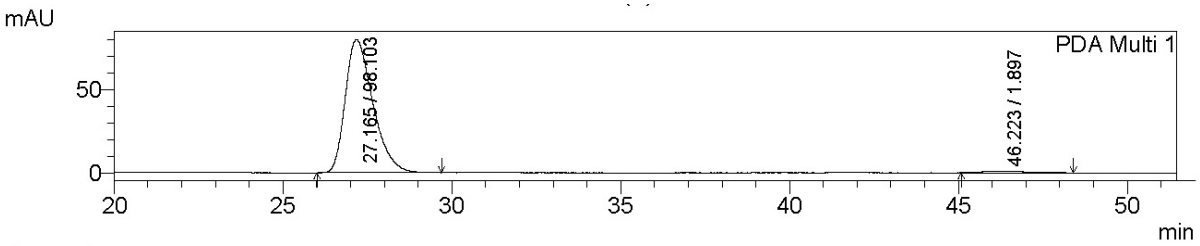
Chiral Column: AD-H

UV Detector Wavelength: 256 nm

HPLC profile of (*R*)-Ranolazine (*R*-1) on Chiral Column



(*R*)-Ranolazine



1 PDA Multi 1/256nm 4nm

PeakTable

PDA Ch1 256nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	27.165	4538761	79859	98.103	98.756
2	46.223	87748	1006	1.897	1.244
Total		4626509	80865	100.000	100.000

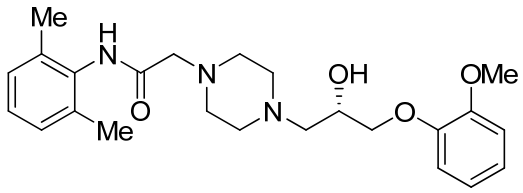
Eluent: Hexane-^{i}Propanol-Diethylamine (70:30: 0.1)

Flow Rate: 0.8 mL/min

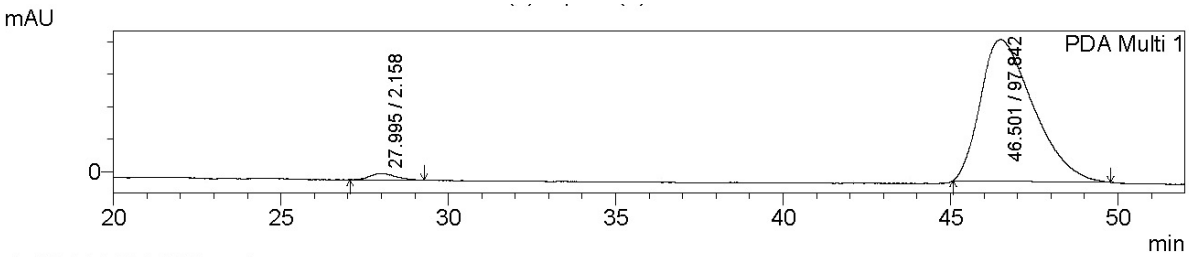
Chiral Column: AD-H

UV Detector Wavelength: 256 nm

HPLC profile of (*S*)-Ranolazine (*S*-1) on Chiral Column



(*S*)-Ranolazine



1 PDA Multi 1/256nm 4nm

PeakTable

PDA Ch1 256nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	27.995	52861	995	2.158	4.352
2	46.501	2396698	21871	97.842	95.648
Total		2449559	22867	100.000	100.000

Eluent: Hexane-^{i}Propanol-Diethylamine (70:30: 0.1)

Flow Rate: 0.8 mL/min

Chiral Column: AD-H

UV Detector Wavelength: 256 nm