SUPPORTING INFORMATION

Protecting group-free concise synthesis of (*RS*)/(*S*)-lubeluzole

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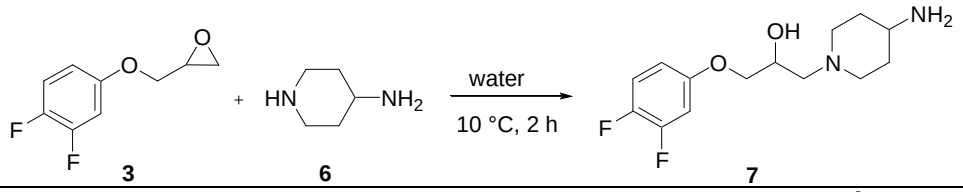
General Information:

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 and used without further purification. The microwave reactions were carried out using CEM Discover System (Model No. 908010, Serial No. DU8952) with 7 mL sealed reaction vessels containing magnetic stir bar. The ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz NMR spectrometer in $CDCl_3$ with residual undeuterated solvent ($CHCl_3$: 7.26/77.0) using TMS 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 under APCI mode of ionisation. Accurate mass measurements were performed on a Q-TOF instrument calibrated internal with sodium formate. Infra-red (IR) spectra were recorded in the range 4000-600 cm^{-1} either as neat for liquid or KBr pellets for solid samples. Purity compounds were checked on the silica gel GF-254 under UV at 254 nm. Melting points were measured using melting point apparatus and were uncorrected. Evaporation of solvents was performed at reduced pressure, using a rotary vacuum evaporator.

Optimization Study:

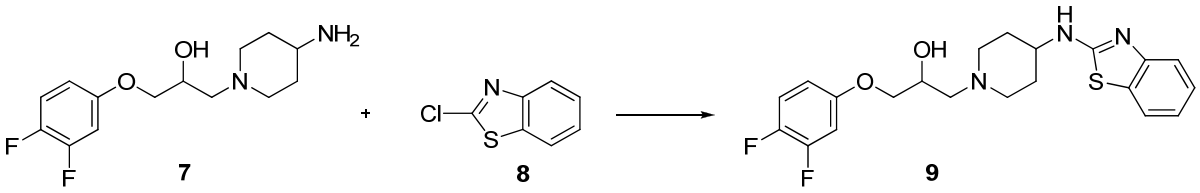
Optimization of amount of water during the epoxide ring opening of 2-((3,4-difluorophenoxy)methyl)oxirane (3) with 4-aminopiperidine (6) to form 7:



Entry	Water	Time (h)	Yield (%)[b]
1	5 eq (0.09 mL)	2	20
2	10 eq (0.18 mL)	2	45
2	15 eq (0.27 mL)	2	75
3	20 eq (0.36 mL)	2	90
5	1 mL	2	90

[a]**3** (186 mg, 1 mmol) was treated with **6** (100 mg, 1 mmol, 1 equiv) in various amount of water at 10 °C for 2 h. [b]GCMS yield of **7**.

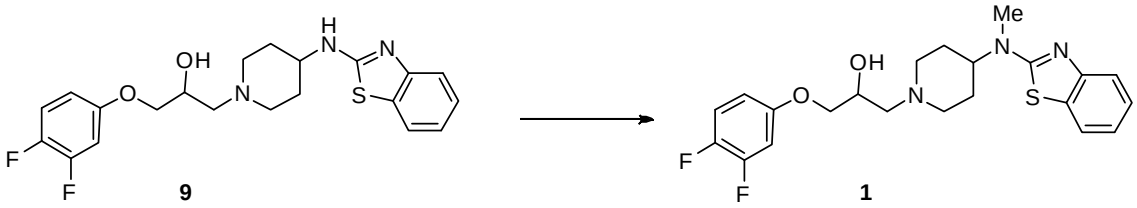
Optimization of amount of water during the *N*-arylation of 7 with 8 to form 9:



Entry	Water	Time (h)	Yield (%)[b]
1	5 eq (0.09 mL)	10	55
2	20 eq (0.18 mL)	10	76
3	55 eq (0.5 mL)	10	90
5	1 mL	10	91

[a]**7** (186 mg, 1 mmol) was treated with **8** (100 mg, 1 mmol, 1 equiv) in various amount of water at 110 °C for 10 h. [b]Isolated yield of **9**.

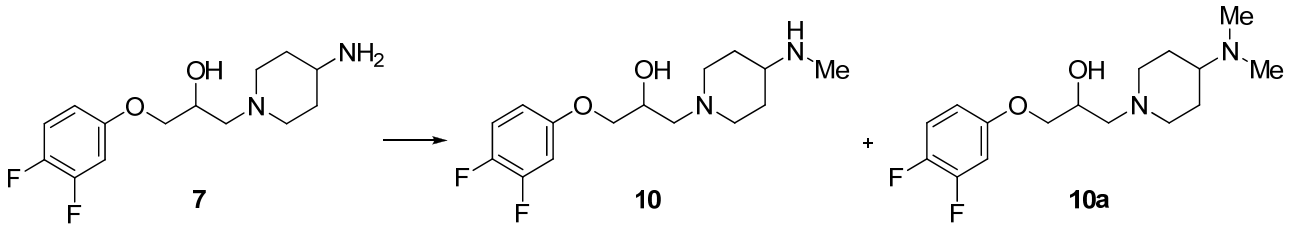
N-Methylation of 1-(4-(benzothiazol-2-ylamino)piperidin-1-yl)-3-(3,4-difluorophenoxy)propan-2-ol (9) to form lubeluzole (1):



Entry	Solvent (1 mL)	Methylating agent	Base (1 equiv)	Time (h)	Yield (%)[b]
1	Water	MeI	none	24	0
2	MeCN	MeI	none	24	0
3	DCM	MeI	none	24	0
4	1,4-Dioxane	MeI	none	24	0
5	Toluene	MeI	none	24	0
6	MeOH	MeI	none	24	0
7	EtOH	MeI	none	24	0
8	Water	MeI	K_2CO_3	4	10
9	DCM	MeI	K_2CO_3	4	15
10	MeCN	MeI	K_2CO_3	4	13
11	Water	MeI	Cs_2CO_3	4	10
12	MeCN	MeI	Cs_2CO_3	4	12
13	Water	Me_2SO_4	$LiOH.H_20$	3	20
14	THF	Me_2SO_4	$LiOH.H_20$	3	25
15	THF	Me_2SO_4	NaH (1.3eq.)	5	30
16	THF	MeI	NaH (1.3eq.)	5	70
17	Water	DMC (100 °C)/MW	none	30 min	0
18	Water	DMDC (100 °C)/MW	none	30 min	0
19	THF	DMC (100 °C)/MW	none	30 min	0

[a]**9** (419 mg, 1 mmol) was treated with the methylating agent (1.2 mmol, 1.2 equiv) at rt. [b]Isolated yield of **1**.

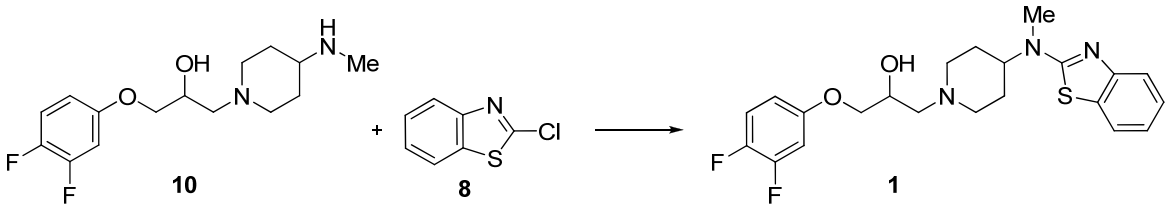
Selective *N*-Monomethylation of 1-(4-aminopiperidin-1-yl)-3-(3,4-difluorophenoxy)propan-2-ol (7) to form 10:



Entry	Solvent	Methylating Agent	Temp (°C)	Yield (%)[b] 10	10a
1	THF	Me_2SO_4	70	0	48
2	Water	Me_2SO_4	rt	0	40
3	Water	MeI	rt	10	35
4	Water/1eq. $NaHCO_3$	MeI	rt	5	43
5	Water	MeI	5	16	25
6	Water/1eq. $NaHCO_3$	MeI	5	10	35
7	DCM	MeI	5	0	30
8	Toluene	MeI	5	7	28
9	1,4-Dioxane	MeI	5	10	25
10	THF	MeI	5	12	27
11	MeOH	MeI	5	0	35
12	EtOH	MeI	5	0	40
13	^{i}PrOH	MeI	5	0	38
14	^{t}BuOH	MeI	5	0	40
15	EtOH	$(CH_2O)_n/NaBH_4$	reflux	55	10
16	EtOH	$(CH_2O)_n/NaBH_4$/ $Ti(O^iPr)$	reflux	75	10
17	Water	$(CH_2O)_n/NaBH_4$/ $Ti(O^iPr)$	90	18	10
18	EtOH	$(CH_2O)_n/NaCNBH_3$ $Ti(O^iPr)$	reflux	75	11
19	water	DMC/MW	100 °C	5	0

[a]**7** (286 mg, 1 mmol) was treated with the methylating agent (1 mmol, 1 equiv) in the respecive solvent (2 mL) for 5 h. [b]GCMS yield.

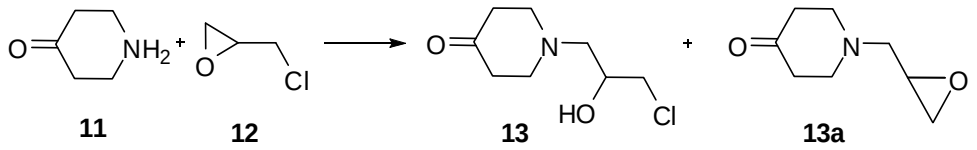
Influence of reaction medium during the base/metal-free *N*-arylation of 10 with 8 to form 1:



Entry	Solvent	Temp (°C)	Time (h)	Yield (%)[b]
1	Water	rt	24	0
2	Water	60	24	0
3	Water	reflux	12	65
4	Water/MW	120	30 min	84
5	DCM	reflux	12	0
6	MeCN	reflux	12	0
7	Toluene	reflux	12	10
8	THF	reflux	12	0
9	$MeNO_2$	110	12	12
10	1,4-Dioxane	reflux	12	10
11	MeOH	reflux	12	0
12	EtOH	reflux	12	trace
13	TFE	reflux	12	15
14	DMF/MW	120	30 min	65
15	1,4-dioxane/MW	120	30 min	60
16	Toluene/MW	120	30 min	54
17	Neat/MW	120	30 min	51
18	Neat	110	30 min	10

[a]**10** (300 mg, 1 mmol) was treated with **8** (168 mg, 1 mmol, 1 equiv) in the respective solvent (1 mL) under indicated condition. [b]Isolated yield of **1**.

Influence of solvent on the epoxide ring opening of epichlorohydrine (11) with 4-piperidone (12) to form 13:

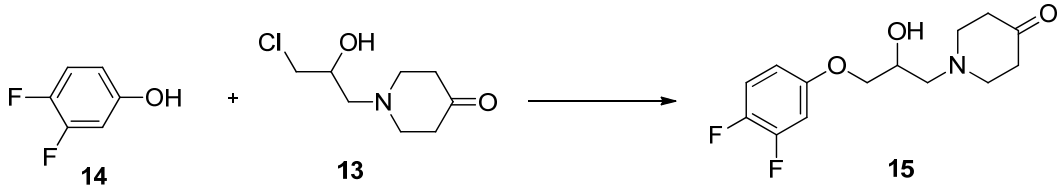


11 **12** **13** **13a**

Entry	Solvent	Yield (%)[b]
1	**Water**	**96**
2	MeOH	32
3	EtOH	28
4	^{i}PrOH	25
5	^{t}BuOH	27
6	TFE	82[c]
7	1,4-Dioxane	trace
8	THF	trace
9	MeCN	trace
10	DMF	trace
11	Toluene	trace
12	$MeNO_2$	trace

[a]**11** (92 mg, 1 mmol) was treated with **12** (99 mg, 1 mmol, 1 equiv) in different solvents (1 mL) at rt for 1 h. [b]Isolated yield of **13**. [c]The side product **13a** arising through substitution of the chlorine was formed in 13% yield.

Optimization of *O*-alkylation of 3,4-difluorophenol (14) with 13 to form 15:



14 **13** **15**

Entry	Base (1.5 equiv)	Surfactant (20 mol%)	temp (°C)	time (h)	Yield (%)[b]
1	None	SDOSS	rt	10	0
2	None	SDOSS	reflux	10	0
3	None	TBAI	reflux	10	0
4	K_2CO_3	--	rt	10	0
5	K_2CO_3	--	60	5	78
6	K_2CO_3	--	80	5	95
7	Cs_2CO_3	--	rt	10	--
8	Cs_2CO_3	--	60	5	80

9	Cs_2CO_3	--	80	5	95
10	K_2CO_3	--	100	0.5	93

[a]**14** (130 mg, 1 mmol) was treated with **13** (191 mg, 1 mmol, 1 equiv) in water (1 mL). [b]Isolated yield of **15**.

Optimization of amount of base during the reaction of 14 with 13[a]

Entry	**K_2CO_3 (equiv)**	**Yield (%)[b]**
1	1	82
2	1.5	95
3	2	95

[a]**14** (130 mg, 1 mmol) was treated with **13** (191 mg, 1 mmol) in the presence of K_2CO_3 in water (1 mL). [b]Isolated yield of **15**.

Experimental Procedure

Typical experimental procedure for the synthesis of 2-((3,4-difluorophenoxy)methyl)oxirane (3): The mixture of 3,4-difluorophenol (**14**) (2.6 g, 20 mmol), epichlorohydrine (**11**) (2.76 g, 30 mmol, 1.5 equiv) and K_2CO_3 (5.56 g, 50 mmol, 2 equiv) in acetonitrile (50 mL) was stirred magnetically under reflux condition (14 h, TLC). The reaction mixture was filtered off and concentrated under rotary vacuum evaporation. The crude product was adsorbed on silica gel (230-400, 5 g) and purified by flash chromatography (hexane-EtOAc, 95:5) to obtain analytically pure **3** (3.05 g, 82 %); Brown oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.05 (q, *J* = 9.16 Hz, 1H), 6.77-6.72 (m, 1H), 6.64-6.60 (m, 1H), 4.21 (dd, *J* = 2.8, 10.8 Hz, 1H), 3.87 (dd, *J* = 5.88, 11.0 Hz, 1H),3.35-3.31 (m, 1H), 2.91 (t, *J* = 4.44 Hz, 1H), 2.74 (dd, *J* = 2.64, 4.80 Hz, 1H); MS (APCI) m/z 187.1 $(M+H)^+$.[1]

Typical experimental procedure for the 1-(4-aminopiperidin-1-yl)-3-(3,4-difluorophenoxy)propan-2-ol (7): The mixture of **3** (1.86 g, 10 mmol), 4-aminopiperidine (**6**) (1.0 g, 10 mmol, 1 equiv) in water (4 mL) was stirred magnetically at 10 °C. After completion of reaction (1 h, TLC), the reaction mixture was extracted with EtOAc (2 × 10 mL). The combined EtOAc extracts were dried ($MgSO_4$), and concentrated under rotary vacuum evaporation. The crude product was adsorbed on silica gel (230-400, 2.5 g) and purified by flash chromatography (hexane-EtOAc, 5: 95) to obtain analytically pure **7** (2.54 g, 89 %); Brown liquid; IR (Neat) *v*: 3390, 3331, 3290, 2995, 2854, 1601, 1228, 1125 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.09-7.01 (m, 1H, Ar-*H*), 6.78-6.72 (m, 1H, Ar-*H*), 6.64-6.61 (m, 1H, Ar-*H*), 4.04-4.01 (m, 1H, C*H*), 3.92-3.88 (m, 2H, C*H*$_2$), 2.98-2.88 (m, 1H, C*H*$_2$), 2.87-2.82 (m, 1H, C*H*$_2$), 2.79-2.69 (m, 1H, C*H*$_2$), 2.55-2.44 (m, 2H, C*H*), 2.43-2.35 (m, 2H, C*H*$_2$), 2.10-1.97 (m, 1H, C*H*$_2$), 1.84-1.81 (m, 1H, C*H*$_2$), 1.47-1.33 (m, 2H, C*H*$_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 155.0 (d, *J* = 9 Hz), 150.4 (dd, *J* = 14 & 246 Hz), 145.1 (dd, *J* = 12 & 239 Hz), 117.1 (d, *J* = 19 Hz), 109.8, 104.24 (d, *J* = 20 Hz), 71.2, 65.5, 60.2, 53.9, 51.4, 48.4; HRMS (ESI) m/z calcd for $C_{14}H_{20}F_2N_2NaO_2$ [M + Na^+], 309.3074; Found 309.1100.

Typical experimental procedure for the 1-(4-(benzothiazol-2-ylamino)piperidin-1-yl)-3-(3,4-difluorophenoxy)propan-2-ol (9): The mixture of **7** (0.85 g, 3 mmol), 2-chlorobenzthiazole (**8**) (0.50 g, 3 mmol, 1 equiv) in water (8 mL) was stirred magnetically under at 110 °C (oil-bath) for 10 h (TLC). The reaction mixture cooled to room temperature and treated with $NaHCO_3$ till the effervescence ceases and extracted with EtOAc (2 × 5 mL). The combined EtOAc extracts were dried ($MgSO_4$), and concentrated under rotary vacuum evaporation. The crude product was adsorbed on silica gel (230-400, 500 mg) and purified by flash chromatography (hexane-EtOAc, 90:10) to obtain analytically pure **9** (1.14 g, 91%). IR (Neat) *v*: 3389, 3012, 2975, 2850, 1605, 1215, 1045 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.58 (d, *J* = 7.88 Hz, 1H, Ar-*H*), 7.53 7.05 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.32-7.27 (m, 1H, Ar-*H*), 7.11-7.02 (m, 2H, Ar-*H*), 6.78-6.73 (m, 1H, Ar-*H*), 6.64-6.60 (m, 1H, Ar-*H*), 5.15 (brs, 1H, O*H*), 4.10-4.04 (m, 1H, C*H*), 3.96-3.90 (m, 2H, CH_2), 3.75 (brs, 1H, N*H*), 3.03-3.00 (m, 1H, C*H*), 2.86-2.83 (m, 1H, C*H*), 2.73-2.50 (m, 3H, C*H*), 2.29-2.20 (m, 1H, C*H*), 2.20-2.17 (m, 1H, C*H*), 1.67-1.58 (m, 1H, C*H*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 168.6, 155.1 (d, *J* = 9 Hz), 152.9, 150.4 (dd, *J* = 14 & 247 Hz), 145.2 (dd, *J* = 12 & 239 Hz), 130.4, 125.9, 120.9, 120.5, 118.7, 117.1 (d, *J* = 18 Hz), 109.9, 104.3 (d, *J* = 21 Hz), 71.2, 65.8, 60.2, 57.8, 54.8, 51.8; HRMS (ESI) m/z calcd for $C_{21}H_{24}F_2N_3O_2S$ [M + H^+], 420.1557; Found 420.1559.

Typical experimental procedure for the synthesis of 1-(4-(benzothiazol-2-ylamino)piperidin-1-yl)-3-(3,4-difluorophenoxy)propan-2-ol (9) under microwave condition (The microwave reactions was carried out using CEM Discover System (Model No. 908010, Serial No. DU8952) with 7 mL sealed reaction vessel): The mixture of **7** (0.28 g, 1 mmol), **8** (0.17 g, 1 mmol, 1 equiv) in water (2 mL) was placed in the microwave reaction vessel (7 mL) containing the magnetic stir bar. The microwave is programmed using the ramp-to-temperature method to heat to 110 °C over 5 min period and then held at this temperature for 30 min. The solution was then allowed to cool for 20 min or until it is below 50 °C before removal from microwave unit. The resultant reaction mixture was cooled to room temperature, treated with $NaHCO_3$ till the effervescence ceases and extracted with EtOAc (2 × 5 mL). The combined EtOAc extracts were dried ($MgSO_4$), and concentrated under rotary vacuum evaporation. The crude product was adsorbed on silica gel (230-400, 250 mg) and purified by flash chromatography (hexane-EtOAc, 90:10) to obtain analytically pure 1-(4-(benzothiazol-2-ylamino)piperidin-1-yl)-3-(3,4-difluorophenoxy)propan-2-ol (0.37 g, 88%).

Typical experimental procedure for the synthesis of Lubeluzole (1) through *N*-methylation of 9: The mixture of **9** (0.49 g, 1 mmol), methyliodide (0.17 g, 1.2 mmol, 1.2 equiv) and NaH (0.03 g, 1.3 mmol, 1.3 equiv) in THF (2 mL) was stirred magnetically under at rt for 5 h. To the reaction mixture EtOAc (3 mL) was added and concentrated under rotary vacuum evaporation. The crude product was adsorbed on silica gel (230-400, 250 mg) and purified by flash chromatography (hexane-EtOAc, 80:20) to obtain analytically pure **1** (0.3 g, 70%); mp = 231-233 °C; IR (Neat) *v*: 3385, 3009, 2985, 2855, 1603, 1218, 1115, 1052 cm^{-1};^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.61-7.55 (m, 2H), 7.31-7.27 (m, 1H), 7.10-7.03 (m, 2H), 6.79-6.74 (m, 1H), 6.64-6.62 (m, 1H), 4.15-4.10 (m, 1H), 4.09-4.06 (m, 1H), 3.96-3.90 (m, 2H), 3.24 (brs, 1H), 3.14-3.12 (m, 1H), 3.07 (s, 3H), 3.00-2.97 (m, 1H), 2.62-2.49 (m, 3H), 2.26-2.20 (m, 1H), 1.97-1.94 (m, 1H), 1.92-1.86 (m, 3H). MS (APCI) m/z: 434.2 ($M+H^+$).[1]

Typical experimental procedure for the synthesis of 1-(3,4-difluorophenoxy)-3-(4-(methylamino)piperidin-1-yl)propan-2-ol (10): The mixture of **7** (0.85 g, 3 mmol), paraformeldehyde (2 equiv) and titanium(IV) isopropaoxide (6 mmol, 2 equiv) in EtOH (4 mL) was stirred magnetically under reflux condition. After completion of reaction (3 h, TLC), cool the reaction mixture to 20 °C followed by addition of $NaBH_4$ (4.5 mml, 1.5 equiv) and continue the stirring for further 2 h. The crude reaction mixture was concentrated under rotary vacuum evaporation and added EtoAc (10 mL), adsorbed on silica gel (230-400, 2.5 g) and purified by flash chromatography (hexane-EtOAc, 10: 90) to obtain analytically pure **10** (0.67 g, 75 %); Brown viscous liquid; IR (Neat) *v*: 3395, 3290, 2985, 1601, 1225, 1125, 1055 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.24-7.17 (m, 1H, Ar-*H*), 6.95-6.92 (m, 1H, Ar-*H*), 6.82-6.78 (m, 1H, Ar-*H*), 4.43-4.39 (m, 1H, C*H*), 4.06-4.000 (m, 2H, CH_2), 3.70-3. 67 (m, 2H, CH_2), 3.70-3.32 (m, 1H, C*H*), 3.24-3.23 (m, 2H, CH_2), 3.08-3.04 (m, 2H, CH_2), 2.78 (s, 3H, CH_3), 2.67 (brs, 1H, O*H or* N*H*), 2.38-2.36 (m, 2H, CH_2), 2.04-1.97 (m, 2H, CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 155.1 (d, *J* = 9 Hz), 150.2 (dd, *J* = 14 & 244 Hz), 145.0 (dd, *J* = 13 & 237 Hz), 117.1 (d, *J* = 19 Hz), 110.1 (q, *J* = 3Hz), 104.1 (d, *J* = 20 Hz), 70.7, 64.5, 58.6, 53.3, 51.61, 50.4, 29.6; HRMS (ESI) m/z calcd for $C_{15}H_{23}F_2N_2O_2$ [M + H^+], 301.1728; Found 301.1728.

Typical experimental procedure for the synthesis of lubeluzole (1) through *N*-arylation of 10 with 8: The mixture of **10** (0.3 g, 1 mmol) and **8** (0.17 g, 1 mmol, 1 equiv) in water (2 mL) was stirred magnetically under at 110 °C (oil-bath) for 12 h (TLC). The reaction mixture cooled

to room temperature and treated with $NaHCO_3$ till the effervescence ceases and extracted with EtOAc (2 × 5 mL). The combined EtOAc extracts were dried ($MgSO_4$), and concentrated under rotary vacuum evaporation. The crude product was adsorbed on silica gel (230-400, 250 mg) and purified by flash chromatography (hexane-EtOAc, 80:20) to obtain analytically pure **1** (0.28 g, 64%).[1]

Typical experimental procedure for the synthesis of 1 through *N*-arylation of 10 with 8 under microwave condition: The mixture of **10** (0.3 g, 1 mmol) and **8** (0.17 g, 1 mmol, 1 equiv) in water (2 mL) was stirred magnetically under microwave 120 °C for 30 min (TLC). The reaction mixture cooled to room temperature and treated with $NaHCO_3$ till the effervescence ceases and extracted with EtOAc (2 × 5 mL). The combined EtOAc extracts were dried ($MgSO_4$), and concentrated under rotary vacuum evaporation. The crude product was adsorbed on silica gel (230-400, 250 mg) and purified by flash chromatography (hexane-EtOAc, 80:20) to obtain analytically pure **1** (0.36 g, 84%).[1]

Typical experimental procedure for the synthesis of 1-(3-chloro-2-hydroxypropyl)piperidin-4-one (13): The mixture of 4-piperidone (**12**) (0.49 g, 5 mmol) and **11** (0.46 g, 5 mmol, 1 equiv) in 5 mL water was stirred magnetically at rt for 1 h (TLC). The reaction mixture was extracted with EtOAc (2 × 5 mL). The combined EtOAc extracts were dried ($MgSO_4$), and concentrated under rotary vacuum evaporation. The crude product was adsorbed on silica gel (230-400, 500 mg) and purified by column chromatography (hexane-EtOAc, 90:10) to obtain analytically pure **13** (0.91 g, 96%). Colourless liquid; IR (Neat) *v*: 3389, 3010, 2953, 1711, 1600, 1245, 1121 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 4.36-3.92 (m, 1H, C<u>*H*</u>), 3.56-3.34 (m, 2H, C<u>*H*₂</u>), 3.08-2.74 (m, 4H, C<u>*H*₂</u>), 2.58-2.27 (m, 4H, C<u>*H*₂</u>), 2.09-1.91 (m, 2H, C<u>*H*₂</u>); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 208.0, 67.4, 59.9, 53.5, 47.1, 41.1; HRMS (ESI) m/z calcd for $C_8H_{15}ClNO_2$ [M + H^+], 192.0791; Found 192.0793.

Typical experimental procedure for the synthesis of 1-(3-(3,4-difluorophenoxy)-2-hydroxypropyl)piperidin-4-one (15) form 1-(3-chloro-2-hydroxypropyl)piperidin-4-one (13): The mixture of **13** (0.19 g, 1 mmol) and **8** (0.13 g, 1 mmol, 1 equiv) and continue the stirring at 90 °C for 5 h (TLC). The reaction mixture was cooled to rt and neutralize with $NaHCO_3$ (till the effervescence ceases) and extracted with EtOAc (2 × 2 mL). The combined

EtOAc extracts were dried ($MgSO_4$), and concentrated under rotary vacuum evaporation. The crude product was adsorbed on silica gel (230-400, 500 mg) and purified by flash chromatography (hexane-EtOAc, 60:40) to obtain analytically pure **15** (0.27 g, 95%). Brown semi solid; IR (Neat) *v*: 3385, 3005, 2945, 2856, 1710, 1601, 1250, 1115 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.10-7.03 (m, 1H, Ar-*H*), 6.78-6.74 (m, 1H, Ar-*H*), 6.64-6.62 (m, 1H, Ar-*H*), 4.12-4.11 (m, 1H, C*H*), 4.01-3.91 (m, 2H, CH_2), 3.51 (brs, 1H, O*H*), 2.99-2.97 (m, 2H, CH_2), 2.83-2.80 (m, 2H, CH_2), 2.70-2.64 (m, 2H, CH_2), 2.49 (s, 4H, CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 208.3, 154.9 (dd, *J* = 2 & 8 Hz), 150.4 (dd, *J* = 13 & 246 Hz), 145.1 (dd, *J* = 13 & 239 Hz), 117.2 (d, *J* = 19 Hz), 109.8 (q, *J* = 3 Hz), 104.2 (d, *J* = 24 Hz), 70.0 ,66.2, 59.2, 53.3, 41.0; HRMS (ESI) m/z calcd for $C_{14}H_{18}F_2NO_3$ [M + H^+], 286.1255; Found 286.1258.

Typical experimental procedure for the one pot synthesis of 15: The mixture of **12** (0.19 g, 2 mmol) and **11** (0.18 g, 2 mmol, 1 equiv) in 2 mL water was stirred magnetically at rt for 1 h (TLC) followed by addition of **8** (0.26 g, 2 mmol, 1 equiv) and continue stirring at 90 °C for further 5 h (TLC). The reaction mixture was cooled to rt and neutralize with $NaHCO_3$ (till the effervescence ceases) and extracted with EtOAc (2 × 4 mL). The combined EtOAc extracts were dried ($MgSO_4$), and concentrated under rotary vacuum evaporation. The crude product was adsorbed on silica gel (230-400, 500 mg) and purified by flash chromatography (hexane-EtOAc, 60:40) to obtain analytically pure **15** (0.48 g, 85%).

Typical experimental procedure for the synthesis of 10 from 15: The mixture of **15** (0.28 g, 1 mmol), methylamine hydrochloride (0.13 g, 2 mmol, 2 equiv), titanium(IV) isopropaoxide (2 mmol, 2 equiv) and Et_3N (0.2 g, 2 mmol, 2 equiv) in EtOH (4 mL) was stirred magnetically at room temperature for 8 h followed by addition of $NaBH_4$ (1.5 mmol, 1.5 equiv) and continue the stirring for further 8 h. The reaction mixture was filtered off to remove the catalyst and concentrated the filtrate under rotary vacuum evaporation. The crude product was adsorbed on silica gel (230-400, 250 mg) and purified by flash chromatography (hexane-EtOAc, 10: 90) to obtain analytically pure **10** (0.26 g, 87 %).

Typical experimental procedure for the (*S*)-15: The mixture of **12** (0.29 g, 3 mmol) and (*S*)-**11** (0.27 g, 3 mmol, 1 equiv) in 3 mL water was stirred magnetically at rt for 1 h (TLC) followed by addition of **14** (0.39 g, 3 mmol, 1 equiv) and continue stirring at 90 °C for further 5 h (TLC). The reaction mixture was cooled to rt and neutralize with $NaHCO_3$ (till the effervescence ceases) and

extracted with EtOAc (2 × 6 mL). The combined EtOAc extracts were dried ($MgSO_4$), and concentrated under rotary vacuum evaporation. The crude product was adsorbed on silica gel (230-400, 500 mg) and purified by flash chromatography (hexane-EtOAc, 60:40) to obtain analytically pure (*S*)-**15** (0.72 g, 84%); $[\alpha]_D$: -15.2 (c =1, DCM).

Typical experimental procedure for the synthesis of *S*-10 from *S*-15: The mixture of *S*-**15** (0.28 g, 1 mmol), methylamine hydrochloride (0.13 g, 2 mmol, 2 equiv), titanium(IV) isopropaoxide (2 mmol, 2 equiv) and Et_3N (0.2 g, 2 mmol, 2 equiv) in EtOH (4 mL) was stirred magnetically at room temperature for 8 h followed by addition of $NaBH_4$ (1.5 mmol, 1.5 equiv) and continue the stirring for further 8 h. The reaction mixture was filtered off to remove the catalyst and concentrated the filtrate under rotary vacuum evaporation. The crude product was adsorbed on silica gel (230-400, 250 mg) and purified by flash chromatography (hexane-EtOAc, 10: 90) to obtain analytically pure **10** (264 mg, 88 %). $[\alpha]_D$: - 12.5 (c =1, DCM).

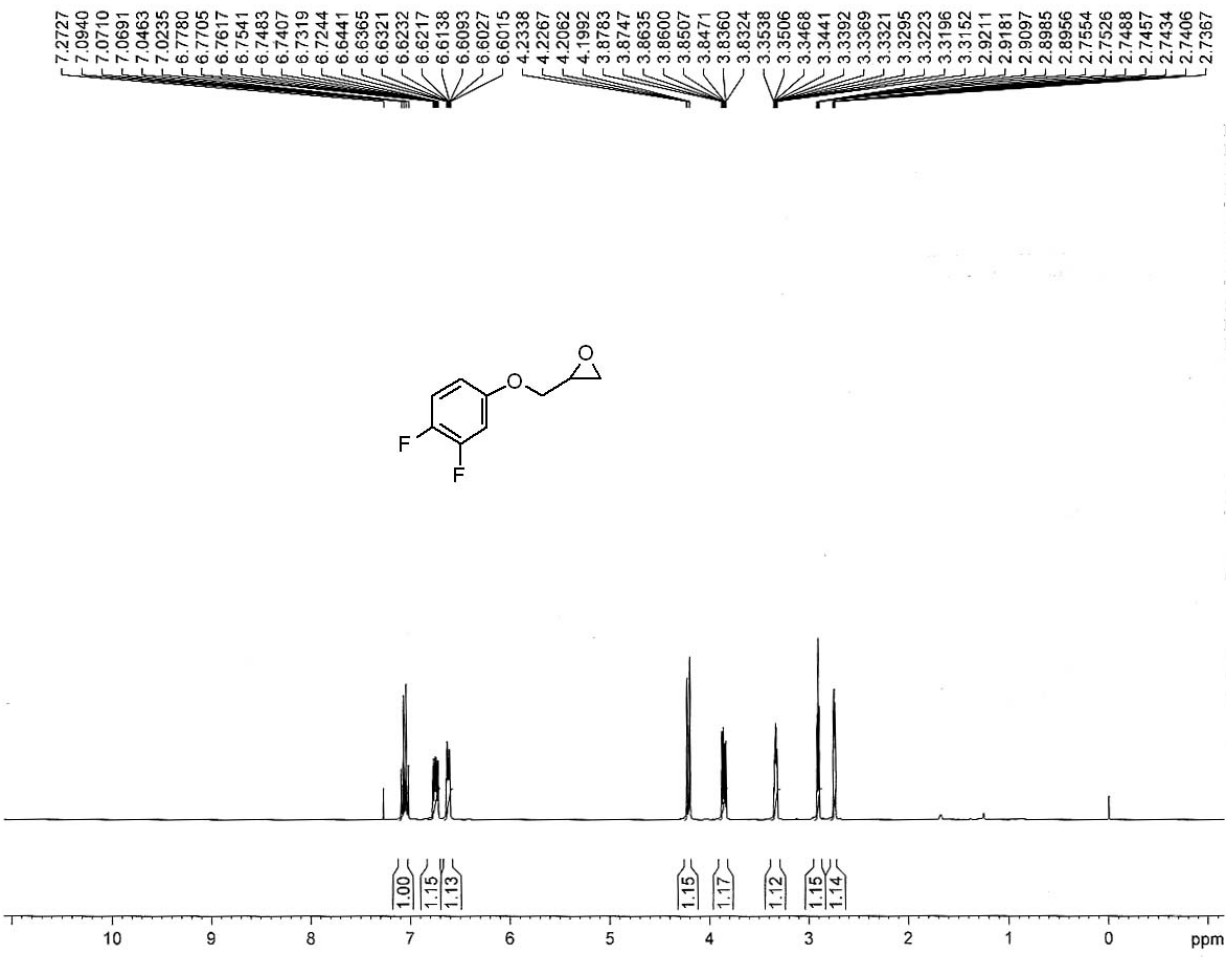
Typical experimental procedure for the synthesis of (*S*)-1: The mixture of (*S*)-**10** (0.3 g, 1 mmol) and **8** (0.16 g, 1 mmol, 1 equiv) in water (2 mL) was stirred magnetically under at 120 °C under microwave for 30 min (TLC). The reaction mixture cooled to room temperature and treated with $NaHCO_3$ till the effervescence ceases and extracted with EtOAc (2 × 3 mL). The combined EtOAc extracts were dried ($MgSO_4$), and concentrated under rotary vacuum evaporation. The crude product was adsorbed on silica gel (230-400, 250 mg) and purified by flash chromatography (hexane-EtOAc, 80:20) to obtain analytically pure (*S*)-**1** (0.36 g, 83%). $[\alpha]_D$: -11.7 (c =1, $CHCl_3$) [lit.[1] $[\alpha]_D$: -11.4 (c =1, $CHCl_3$)].

References

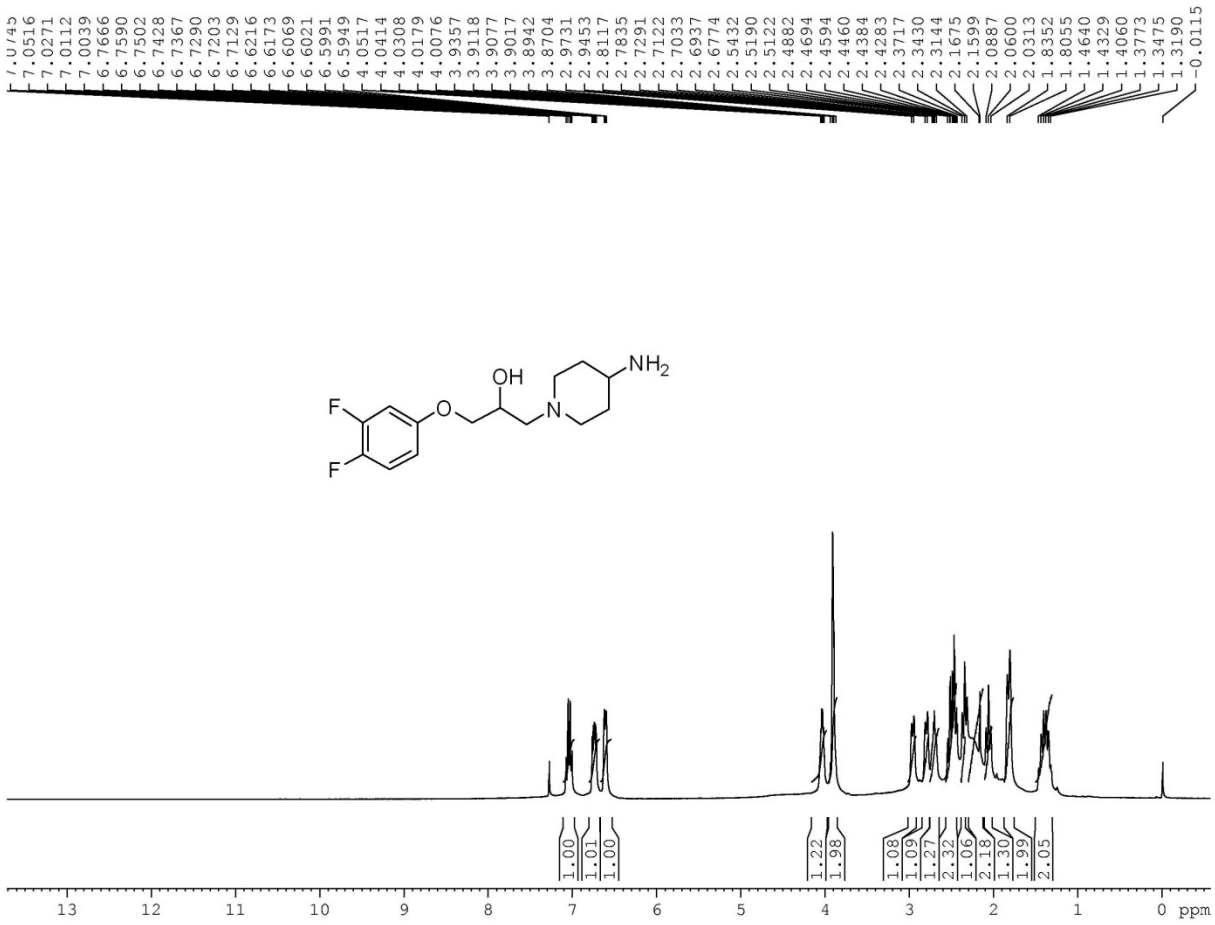
1. Bruno, C.; Carocci, A.; Catalano, A.; Cavalluzzi, M. M.; Corbo, F.; Franchini, C.; Lentini, G.; Tortorella, V. *Chirality* 2006, *18*, 227.

Scanned NMR spectra

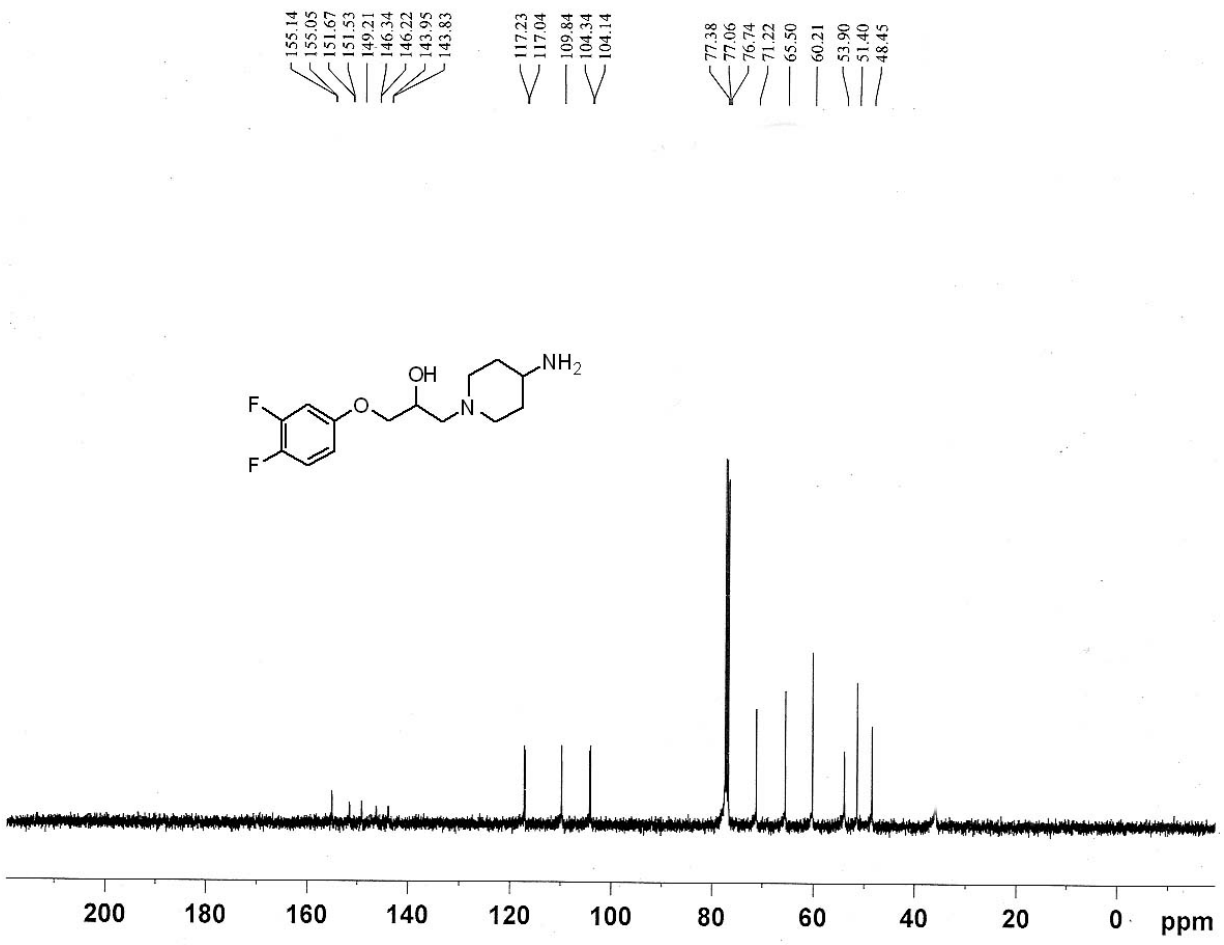
^{1}H NMR of 2-((3,4-difluorophenoxy)methyl)oxirane (3)



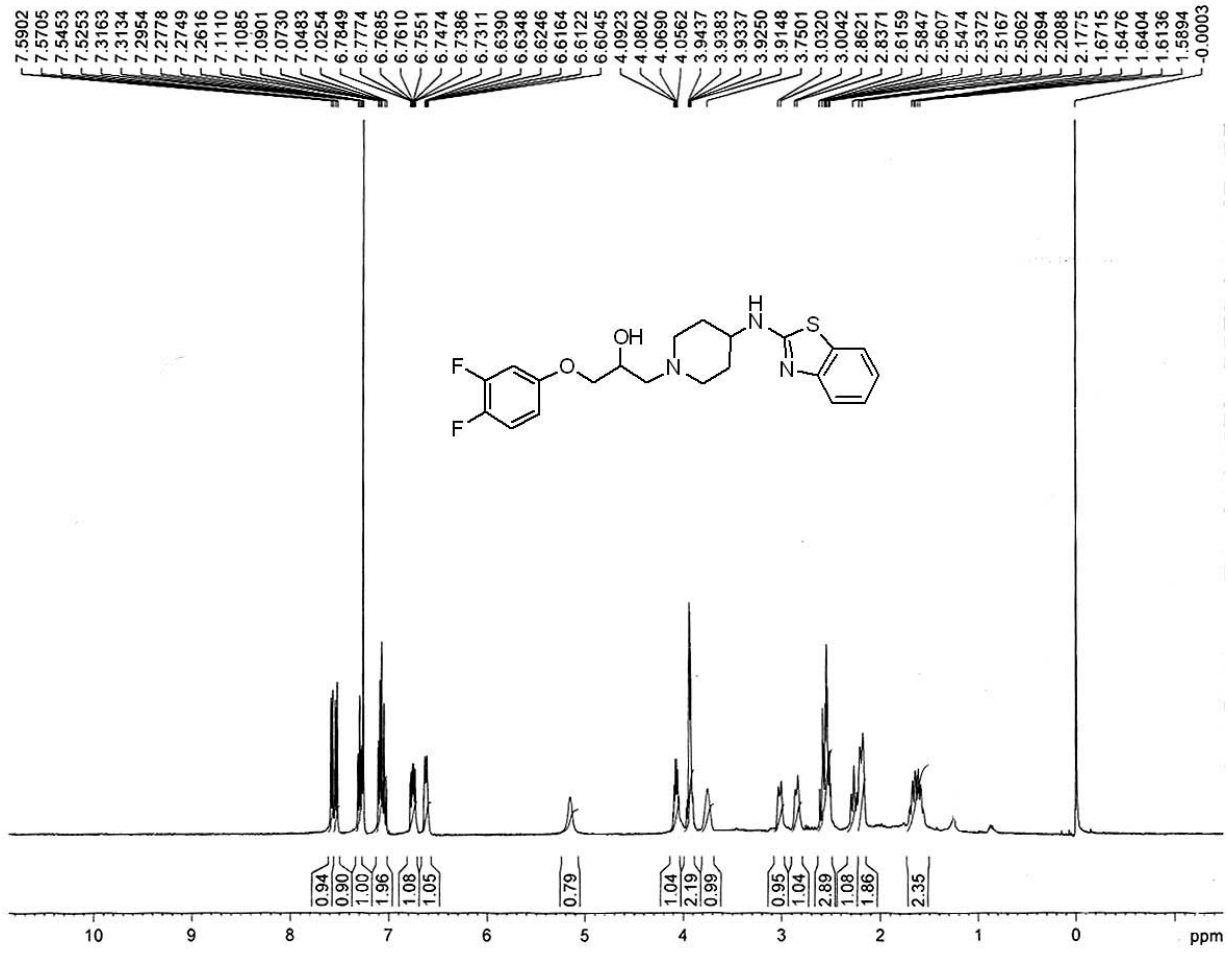
^{1}H NMR of 1-(4-aminopiperidin-1-yl)-3-(3,4-difluorophenoxy)propan-2-ol (7)



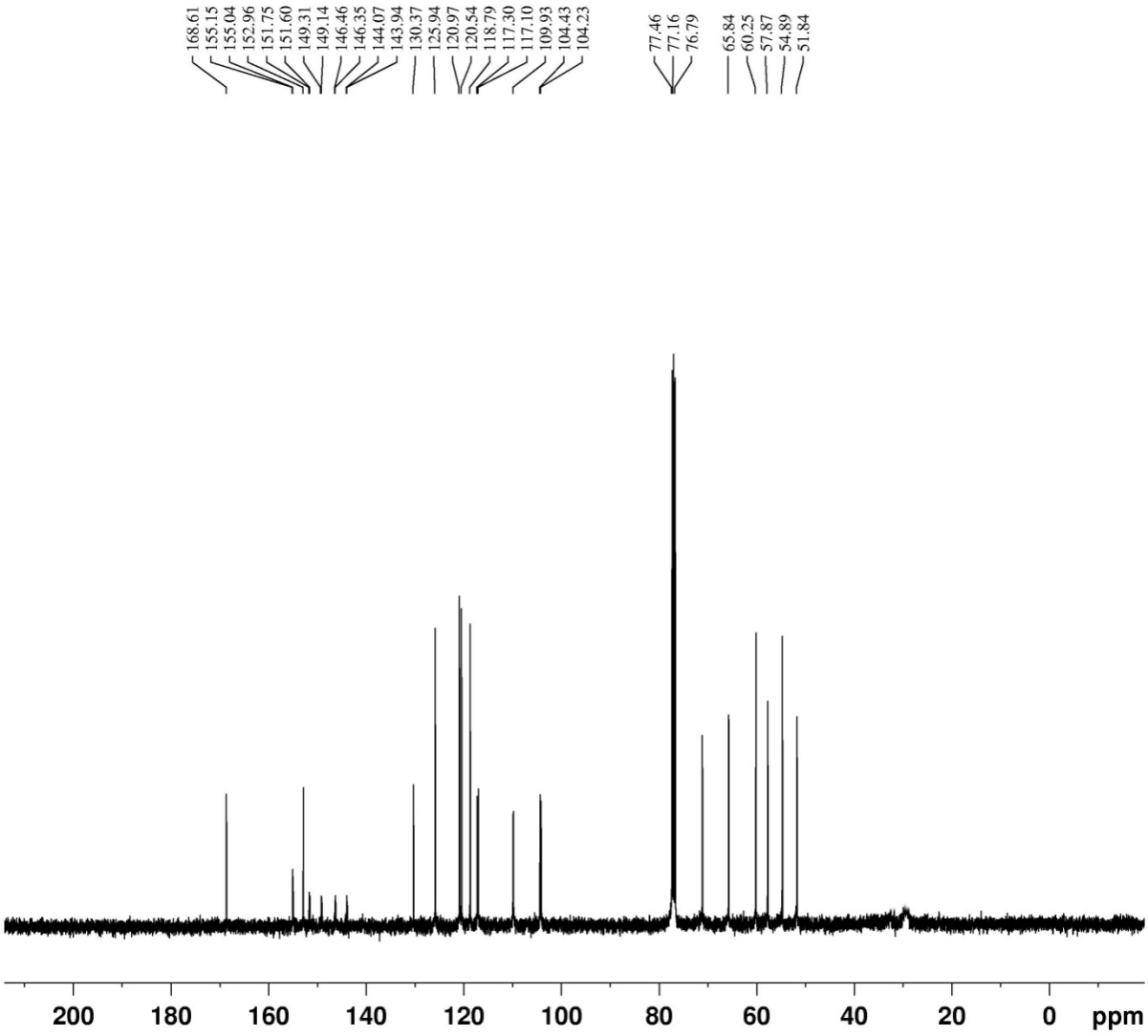
^{13}C NMR of 1-(4-aminopiperidin-1-yl)-3-(3,4-difluorophenoxy)propan-2-ol (7)



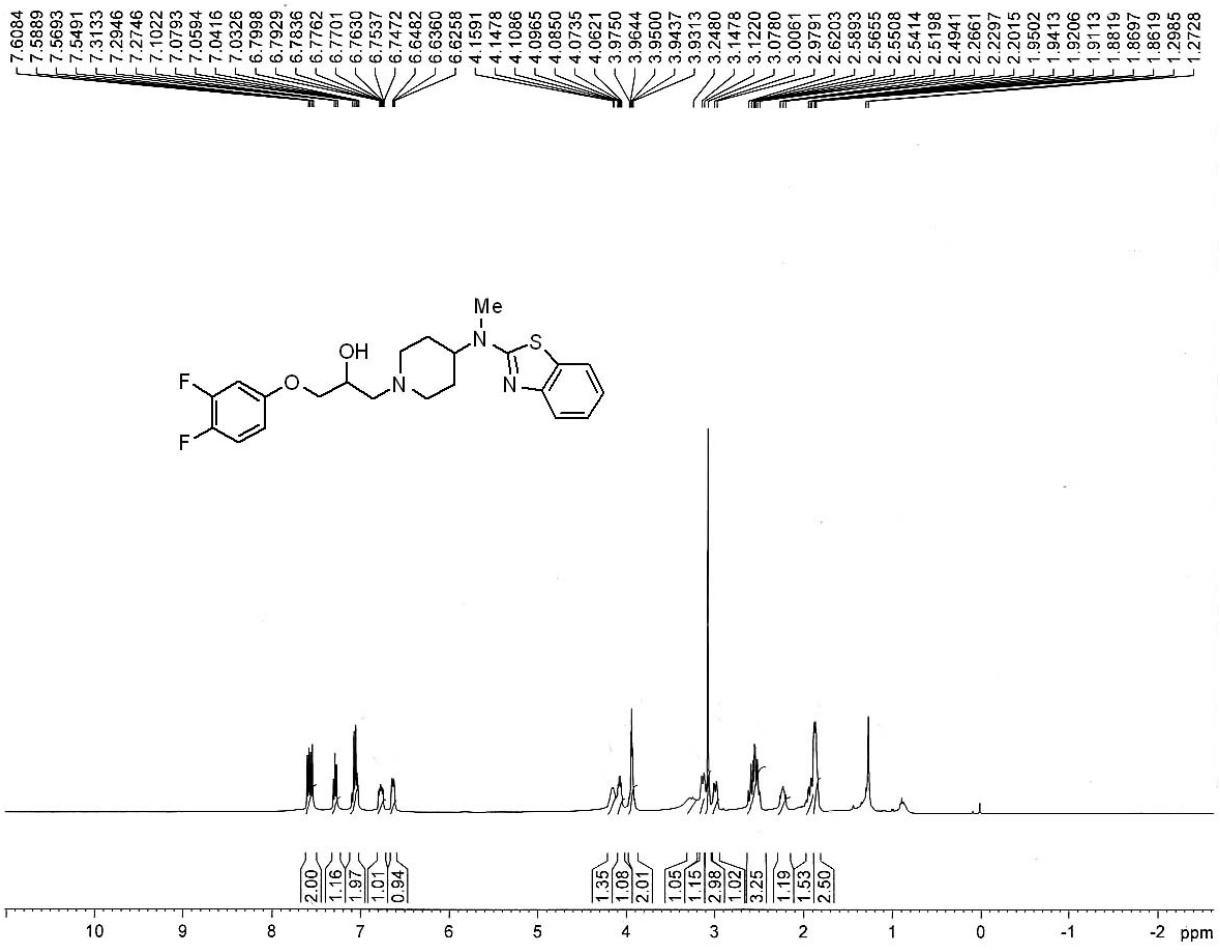
^{1}H NMR of 1-(4-(benzothiazol-2-ylamino)piperidin-1-yl)-3-(3,4-difluorophenoxy)propan-2-ol (9)



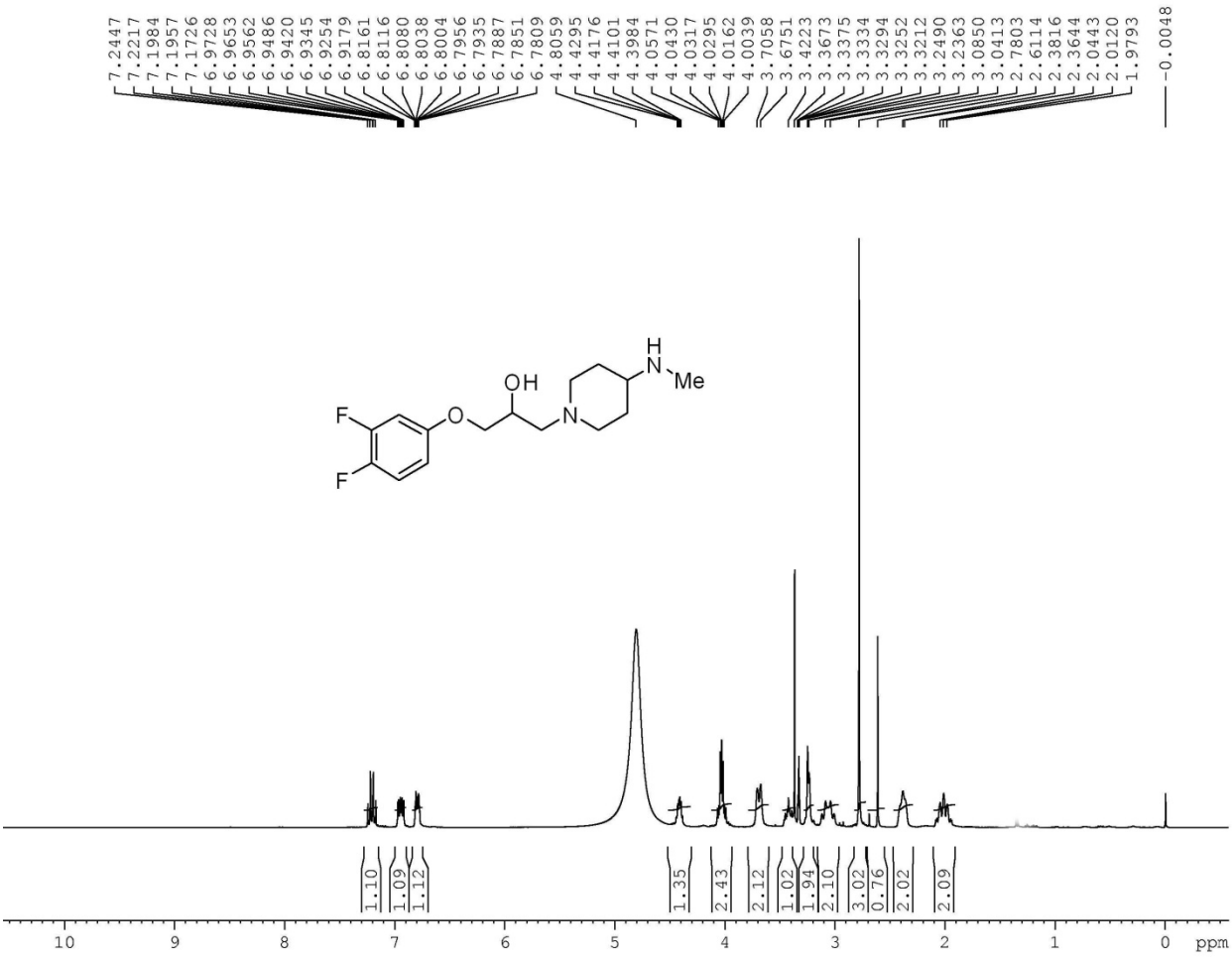
^{13}C NMR of 1-(4-(benzothiazol-2-ylamino)piperidin-1-yl)-3-(3,4-difluorophenoxy)propan-2-ol (9)



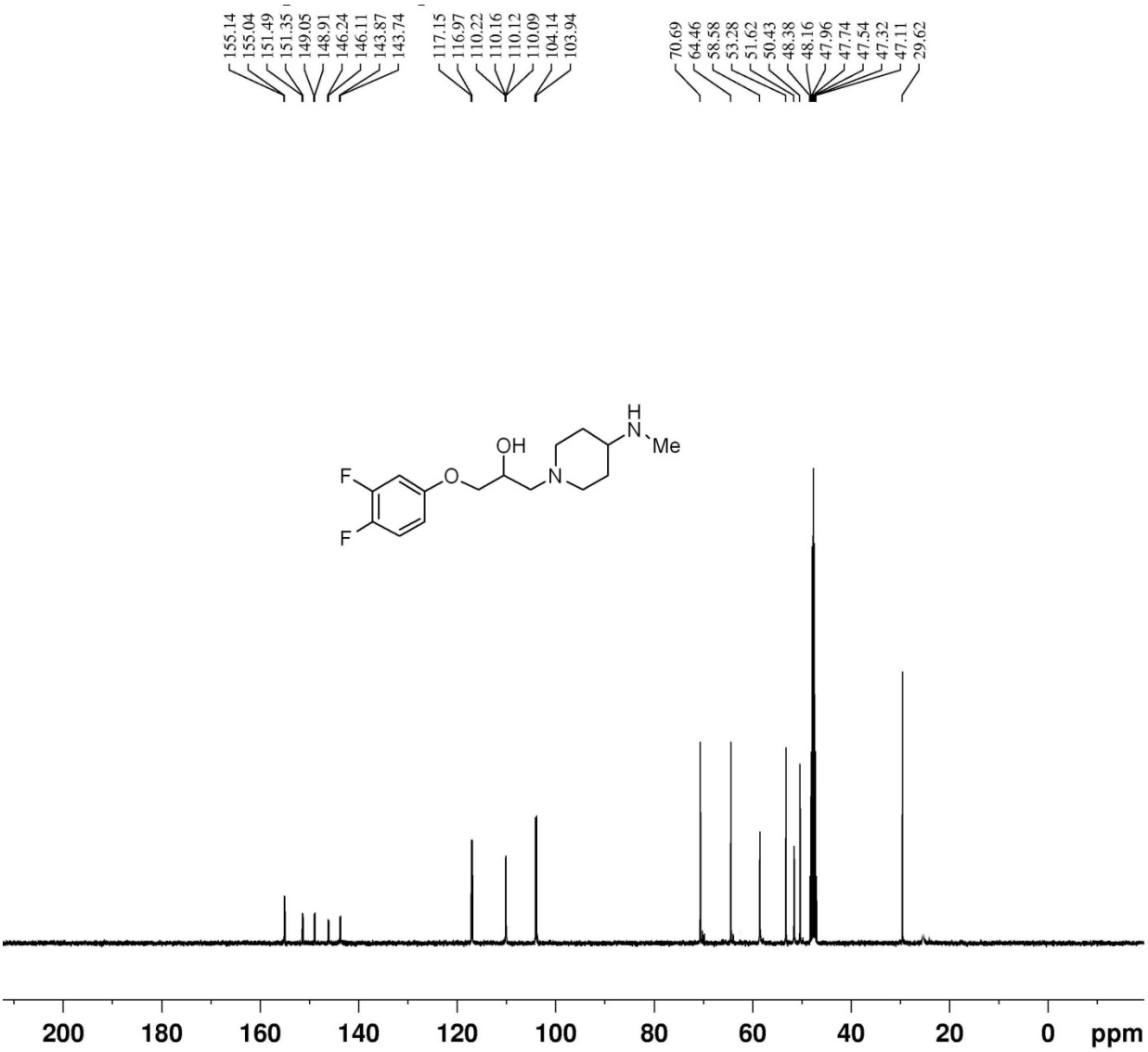
^{1}H NMR of lubeluzole (1)



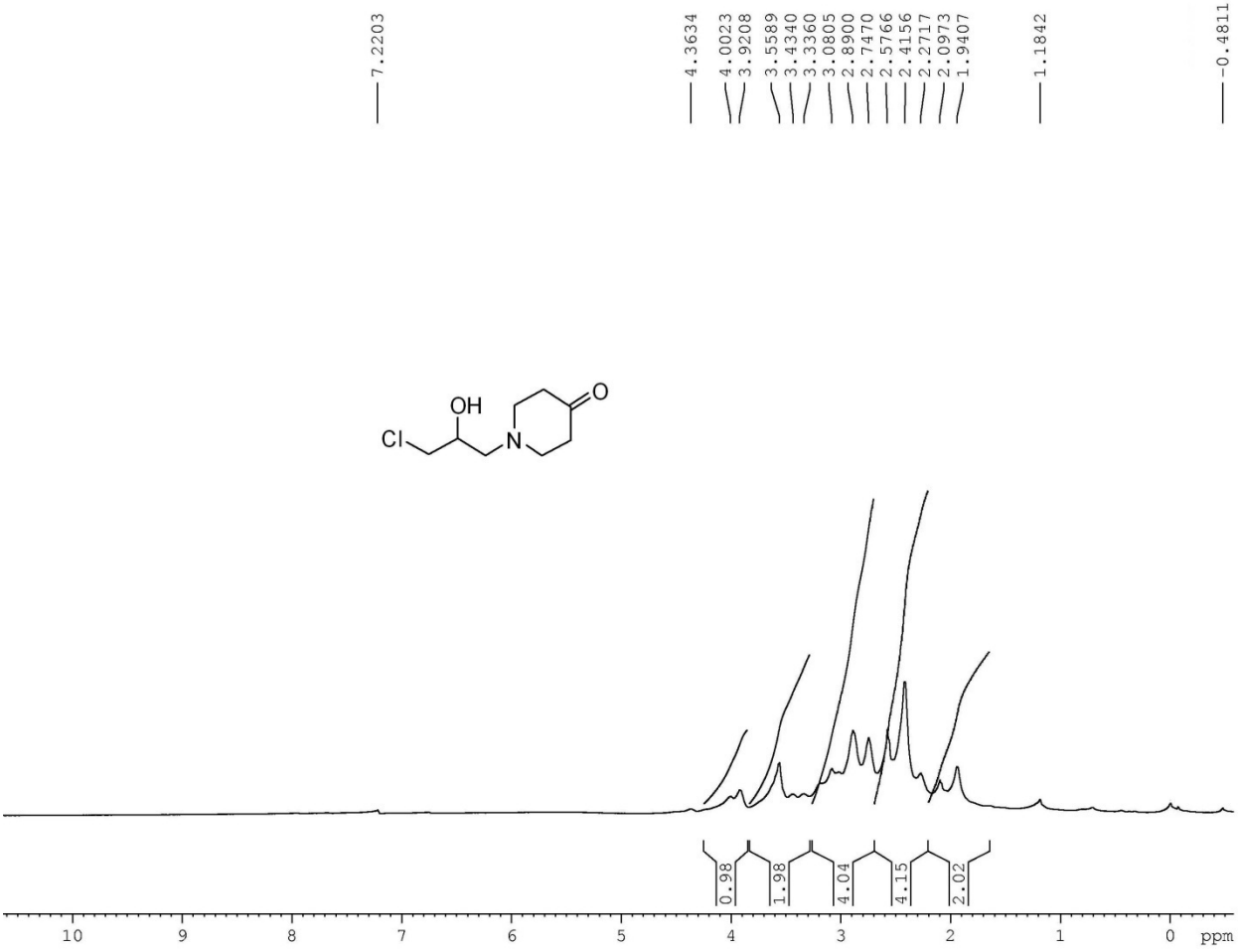
^{1}H NMR of 1-(3,4-difluorophenoxy)-3-(4-(methylamino)piperidin-1-yl)propan-2-ol (10)



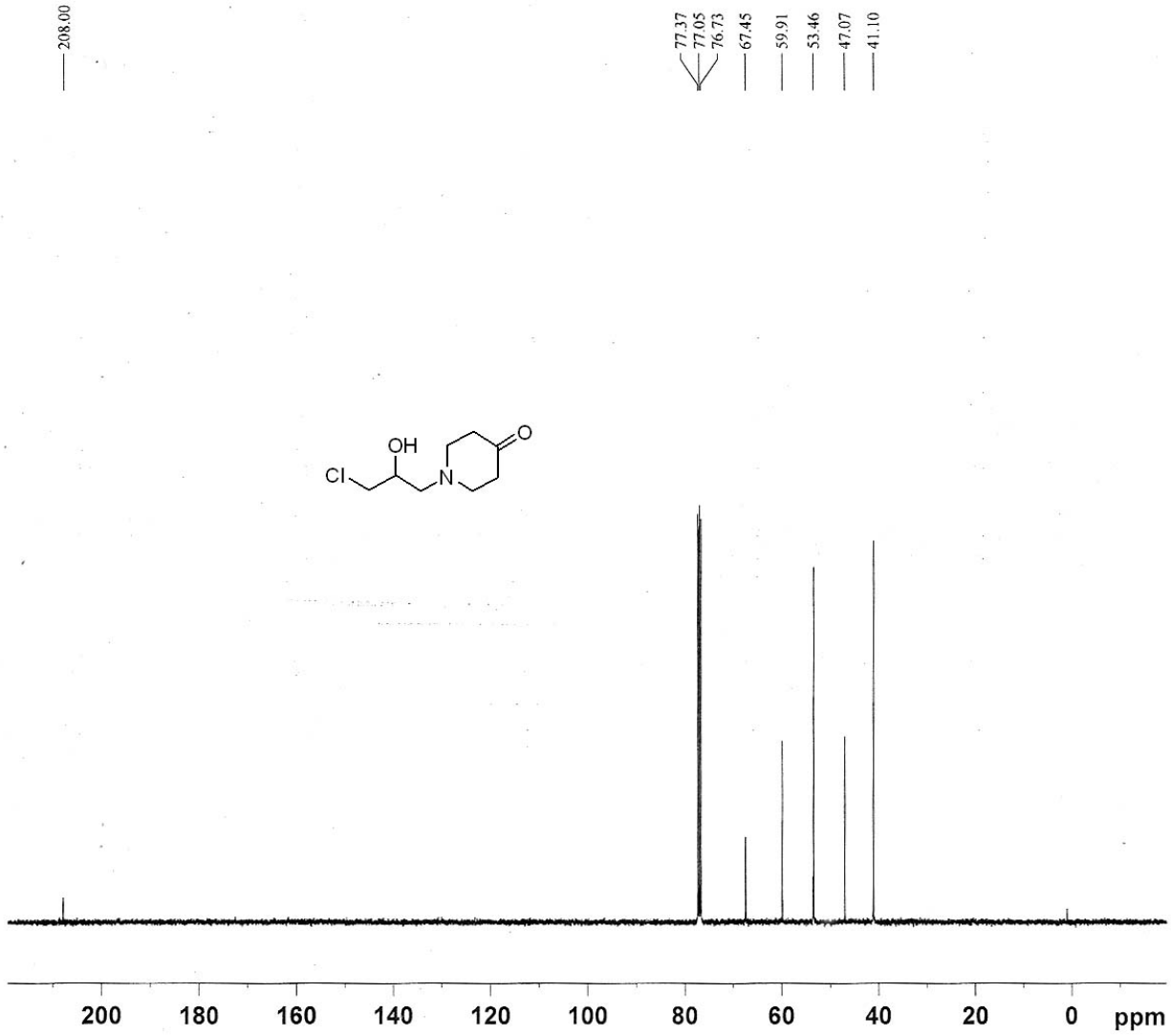
^{13}C NMR of 1-(3,4-difluorophenoxy)-3-(4-(methylamino)piperidin-1-yl)propan-2-ol (10)



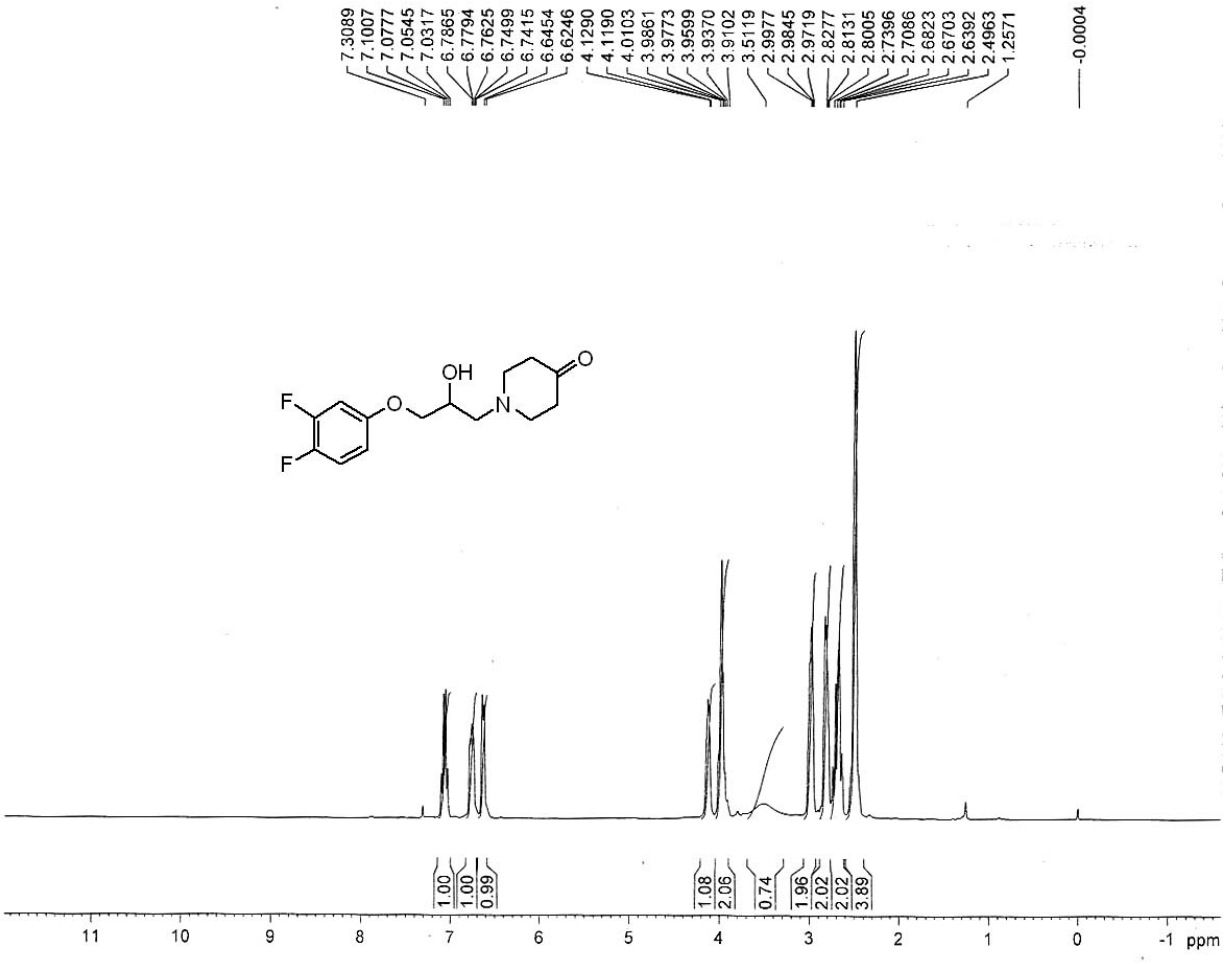
^{1}H NMR of 1-(3-chloro-2-hydroxypropyl)piperidin-4-one (13)



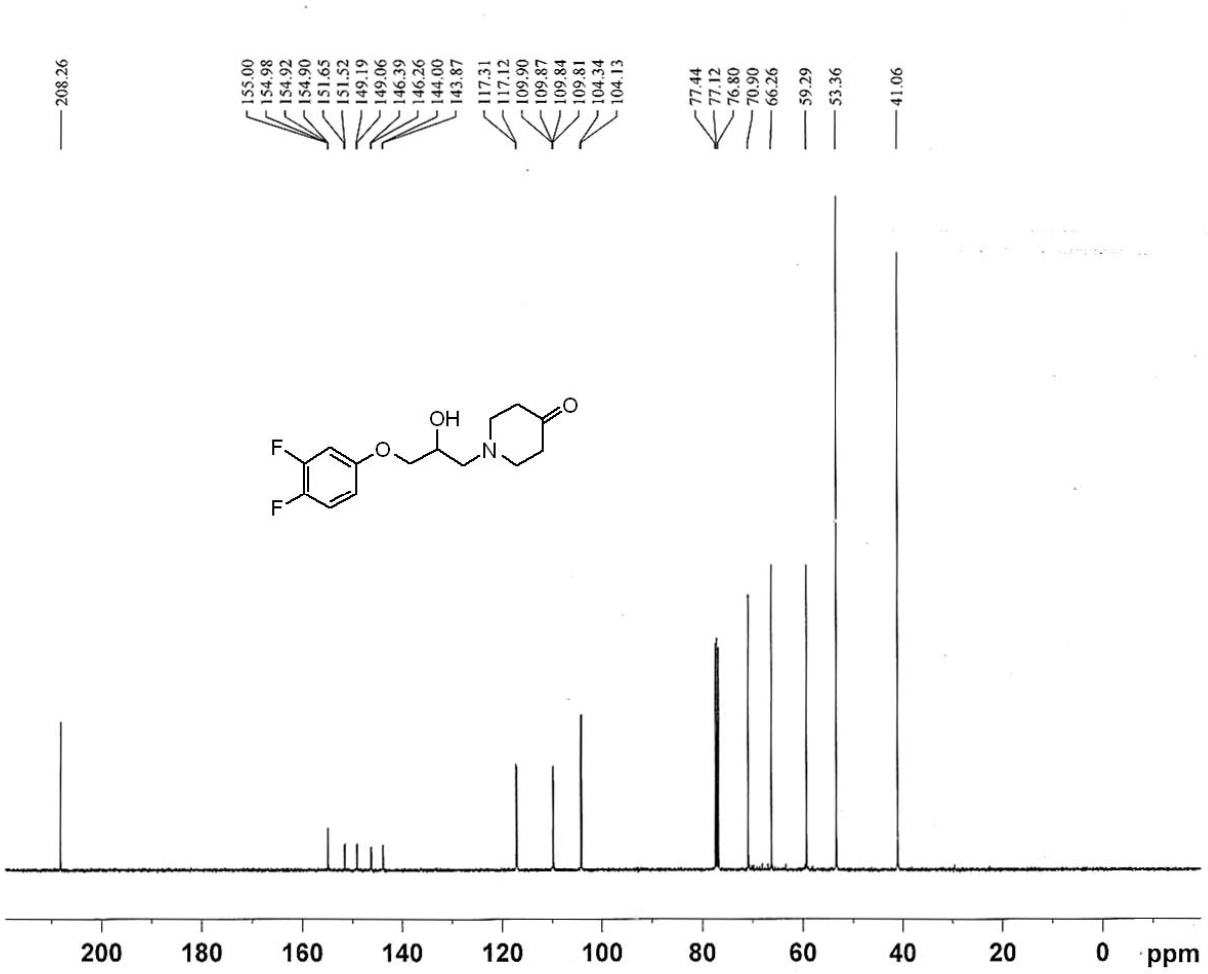
^{13}C NMR of 1-(3-chloro-2-hydroxypropyl)piperidin-4-one (13)



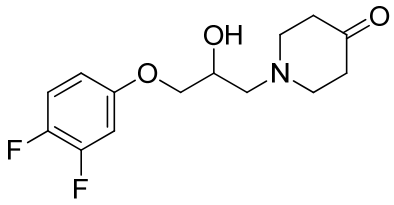
^{1}H NMR of 1-(3-(3,4-difluorophenoxy)-2-hydroxypropyl)piperidin-4-one (15)



^{13}C NMR of 1-(3-(3,4-difluorophenoxy)-2-hydroxypropyl)piperidin-4-one (15)

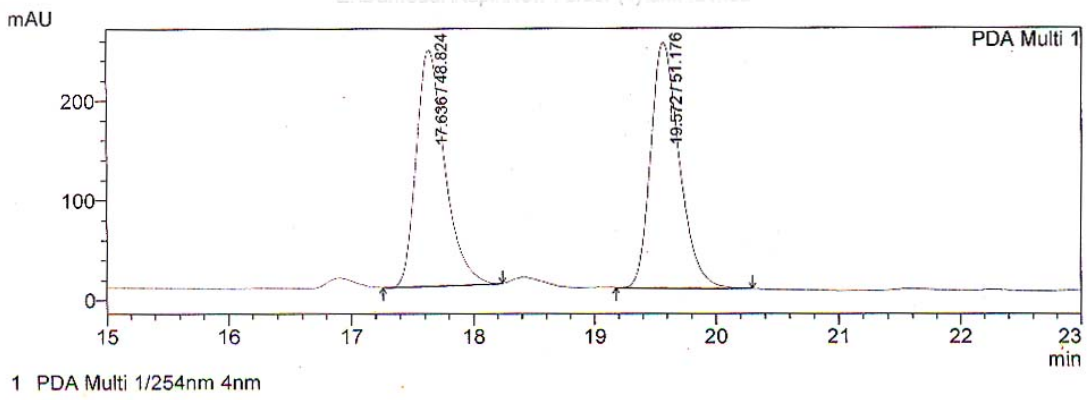


HPLC profile of (*RS*)- 1-(3-(3,4-difluorophenoxy)-2-hydroxypropyl)piperidin-4-one (15) on Chiral Column



(*RS*)- 1-(3-(3,4-difluorophenoxy)-2-hydroxypropyl)piperidin-4-one

<Chromatogram>



PeakTable

PDA Ch1 254nm 4nm

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2	19.572	4036593	245689	51.176	50.895
Total		7887683	482737	100.000	100.000

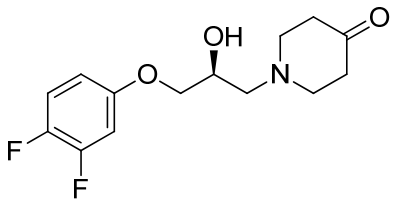
Eluent: Hexane-^{i}Propanol-Diethylamine (90:10: 0.1)

Flow Rate: 1 mL/min

Chiral Column: AD-H

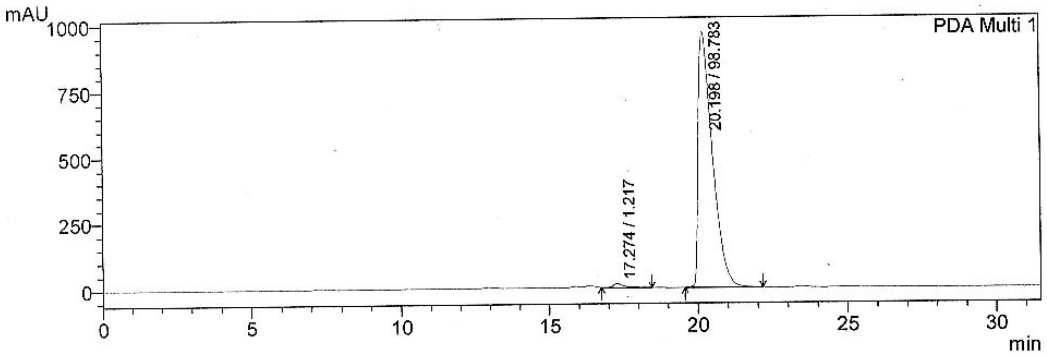
UV Detector Wavelength: 254 nm

HPLC profile of (*S*)- 1-(3-(3,4-difluorophenoxy)-2-hydroxypropyl)piperidin-4-one (*S*-15) on Chiral Column



(*S*)- 1-(3-(3,4-difluorophenoxy)-2-hydroxypropyl)piperidin-4-one

<Chromatogram>



1 PDA Multi 1/254nm 4nm

PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
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2	20.198	31884645	964366	98.783	98.413
Total		32277518	979918	100.000	100.000

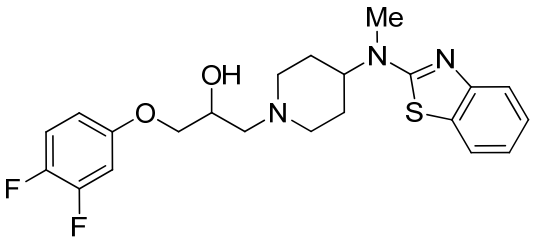
Eluent: Hexane-^{i}Propanol-Diethylamine (90:10: 0.1)

Flow Rate: 1 mL/min

Chiral Column: AD-H

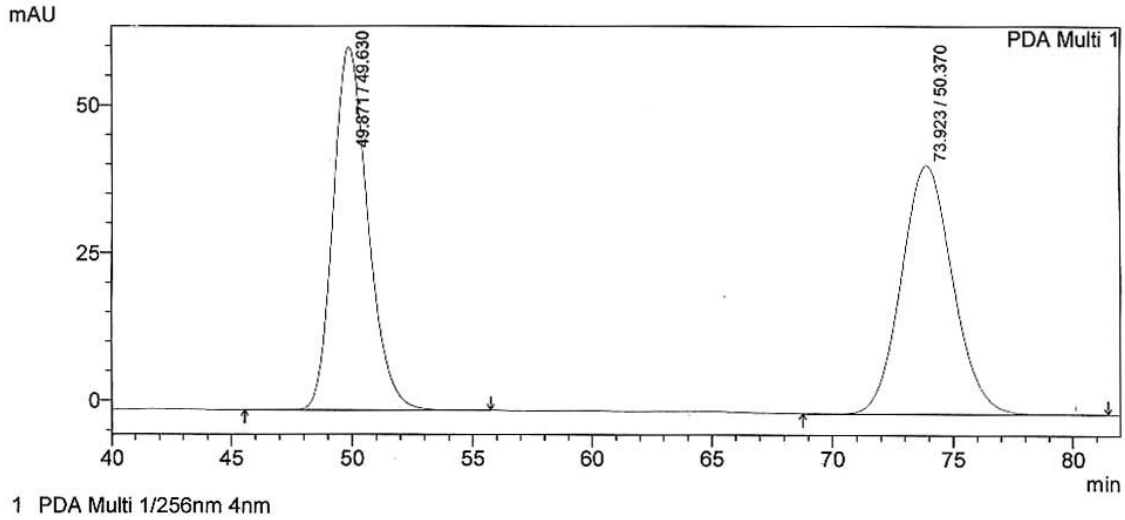
UV Detector Wavelength: 254 nm

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



(*RS*)-Lubeluzole

<Chromatogram>



PeakTable

PDA Ch1 256nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
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2	73.923	6231594	41988	50.370	40.613
Total		12371717	103386	100.000	100.000

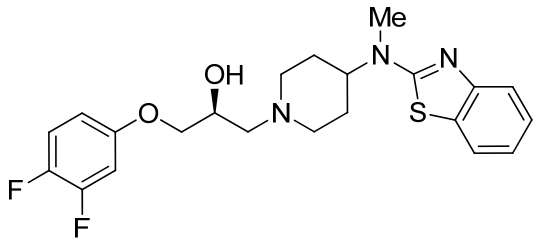
Eluent: Hexane-^{i}Propanol-Diethylamine (83:17: 0.1)

Flow Rate: 0.8 mL/min

Chiral Column: AD-H

UV Detector Wavelength: 256 nm

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



(*S*)-Lubeluzole

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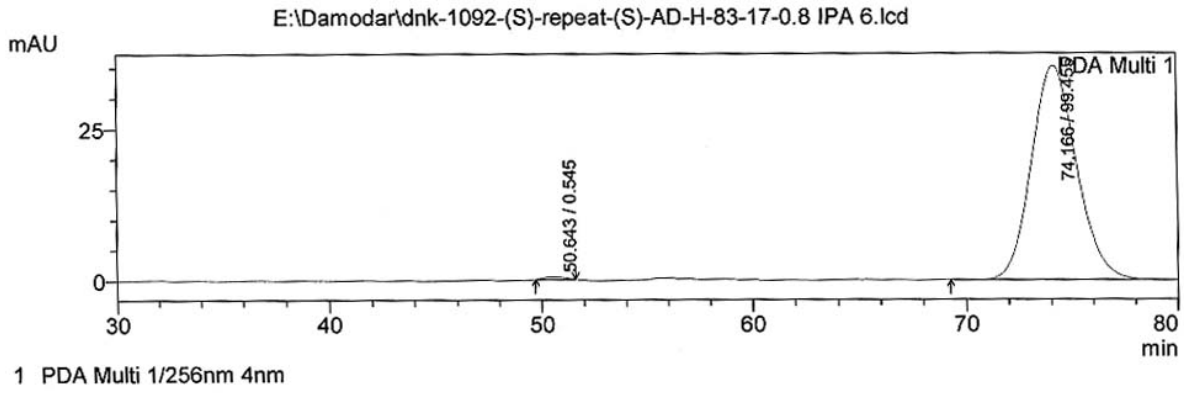

PeakTable

PDA Ch1 256nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
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Total		5229593	35604	100.000	100.000

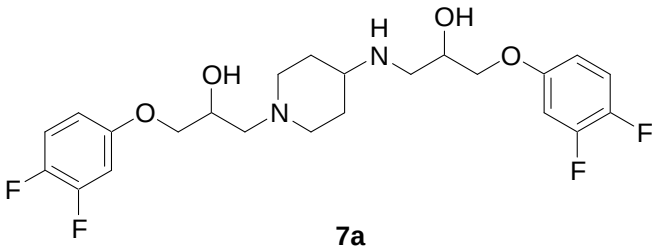
Eluent: Hexane-^{i}Propanol-Diethylamine (83:17: 0.1)

Flow Rate: 0.8 mL/min

Chiral Column: AD-H

UV Detector Wavelength: 256 nm

Structure, IUPAC name, and mass-spectrometry-based identification and estimation of this side product 7a



7a

1-(3,4-Difluoro-phenoxy)-3-{4-[3-(3,4-difluoro-phenoxy)-2-hydroxy-propylamino]-piperidin-1-yl}-propan-2-ol

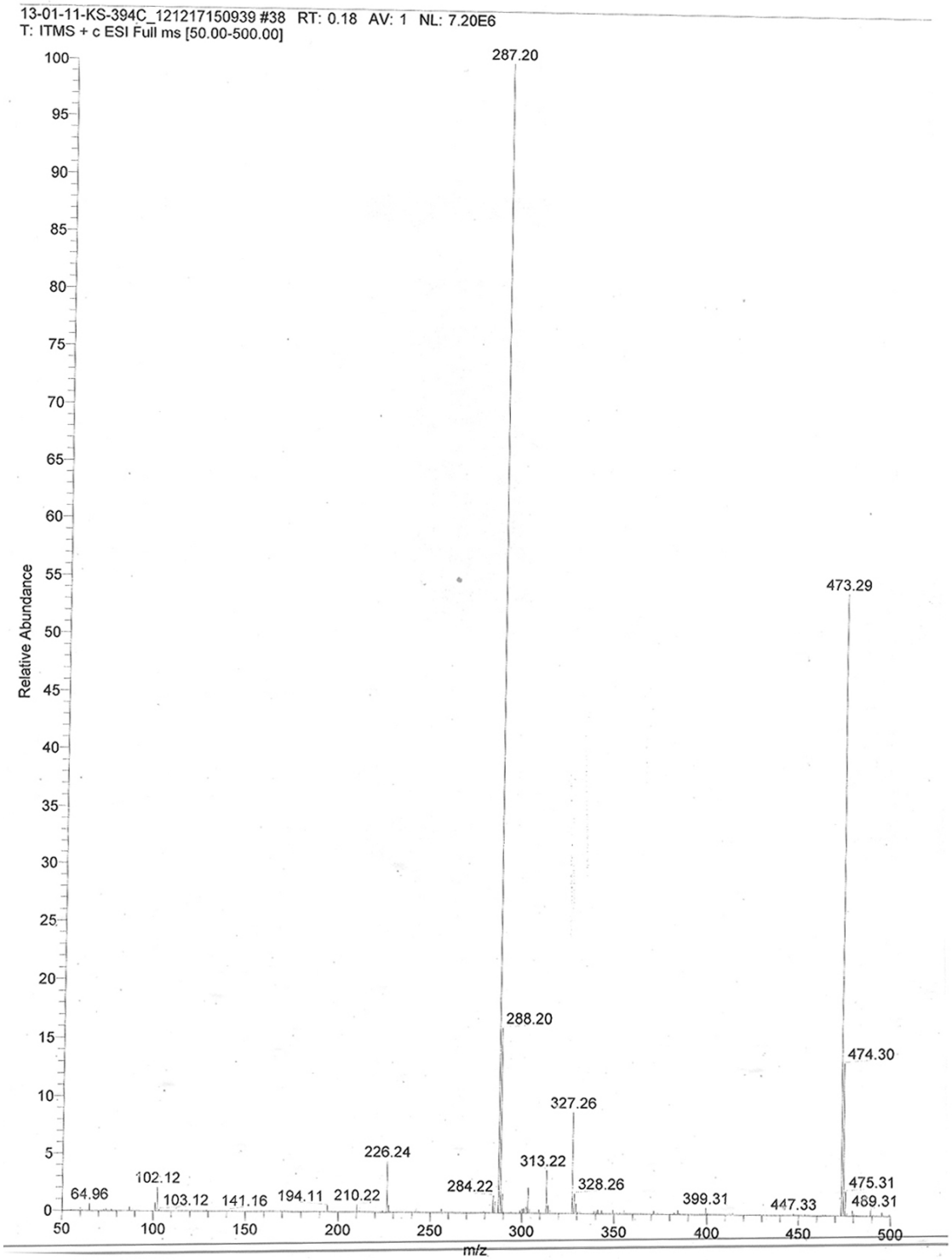
The APCI and ESI MS analyses of the product isolated during the reaction of **3** and **6** under various conditions (table 1) revealed the formation of **7a** as the side product which would arise out of reaction of the initially formed **7** with the starting glycidyl ether **3**. All the attempts to isolate the side product **7a** were unsuccessful. The observed ratio of conversion to **7a** (table 1, footnotes d and e) was estimated based on the "ion-current" measurement of the mass peak 473.29 $[M + H]^+$ (corresponding to 7a) and the mass peak 287.20 $[M + H]^+$ (corresponding to **7**) by subjecting the crude reaction mixture to the (+ve) ESI-MS analyses.

Typical Experimental Procedure for determination Ion current using +pESIMS: The mixture of **3** (1.86 g, 10 mmol), **6** (1.0 g, 10 mmol, 1 equiv) in TFE (4 mL) was stirred magnetically at 10 °C. After completion of reaction (2 h, TLC), an aliquot portion (20 µL) of the reaction mixture were taken out by micro pipette and dissolved in MeOH (1 mL). From the resultant solution an aliquot amount (10 µL) was subjected to +ve ESI MS in advance Thermo Scientific LTQ-XL mass spectrometer.

The abundance of characteristics species for the model reaction

Ion @		Ratio
m/z of 287.20	m/z of 473.29	
1264586700	645024435	1.96

+ve ESI MS Spectra of reaction mixture



"Ion current" measurement of mass peak 473.29 $[M + H]^+$ (corresponding to 7a) and the mass peak 287.20 $[M + H]^+$ (corresponding to 7) by +ve ESI MS