Synthesis and Biological Study of Gabapentin Mutual Prodrug with Different Antioxidants

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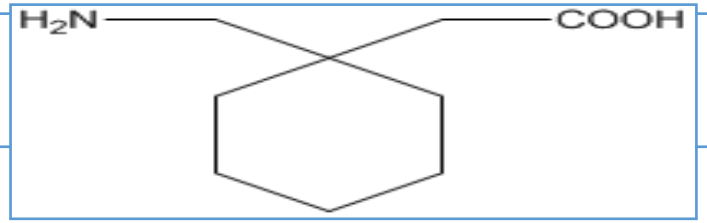
Gabapentin



- Considered as an *artificial amino acid* due to the presence of basic amino group (NH2) and acidic group (COOH) which is responsible for the GI irritation and other gastrointestinal problem's .

Gabapentin is an anticonvulsant drug that was synthesized as structural analog of neurotransmitter γ-aminobutyric acid (GABA); The chemical structure of gabapentin is derived by addition of a cyclohexyl group to the backbone of (GABA).

it was proved by Food and Drug Administered (FDA) in 1993 for treatment.

It is eliminated from the systemic circulation by renal excretion as unchanged drug. Gabapentin is not appreciably metabolized in humans. Gabapentin elimination half-life is 5 to 7 hours

Gabapentin is not protein-bound. A high volume of distribution indicates greater concentration in tissue than in plasma. It is not metabolized and does not induce hepatic enzymes or inhibit metabolism of other antiepileptic drugs.

Gabapentin interacts with a high-affinity binding site in brain membranes, which has recently been identified as an auxiliary subunit of voltage-sensitive Ca 2+ channels. However, the functional correlate of gabapentin binding is unclear and remains under study. Gabapentin crosses several lipid membrane barriers via system L amino acid transporters.

Gabapentin is used to:

- Prevent and control partial seizures.
- Relieve nerve pain following shingles in adults. Shingles is a painful rash that develops many years after you've had chickenpox. The virus that causes chickenpox stays dormant in a portion of your .

serious side effects of gabapentin

- **Changes in mood or behavior.**
- **Signs of an allergic reaction.**

- **Signs of liver abnormalities: Yellowing of your skin or whites of your eyes, dark urine, light-colored stools, vomiting, unusual bleeding or bruising.**
- **Signs of kidney abnormalities: Trouble urinating, a change in how much urine is passed, blood in your urine, or weight gain and swelling of legs and feet from retaining fluid.**
- **Other concerning abnormalities: Change in color of your skin to a bluish color on your lips, nail beds, fingers, or toes along with severe fatigue or weakness and unexpected muscle pain.**

Common side effects of gabapentin include:

Feeling tired.

Dizziness.

Headache.

Nausea and vomiting.

Fever.

Difficulty speaking.

Recurring infections.

Memory loss.

Weight gain.

Movement problems: i,e : jerky movements.

Eye problems: unusual eye movements, double vision.

Antioxidant

Free radical *oxidative stress* has been implicated in the pathogenesis of a variety of human diseases. *Natural antioxidant defenses* have been found to be defective in many of the same diseases. This has led to suggestions that oxidative damage and therefore disease progression may be retarded by supplementing natural antioxidant defenses.

Oxidation reactions produce free radicals, which start chain reactions. When the chain reaction occurs in a cell, it can cause damage or death. Antioxidants terminate these chain reactions by removing free radical intermediates, and inhibit other oxidation reactions. They do this by being oxidized themselves, so antioxidants are often reducing agents

Two principle mechanisms of action:

The first is a chain-breaking mechanism by which the primary antioxidants donate electrons to the free radicals present in the system, example lipid radicals

The second mechanism involves removal of ROS (reactive oxygen species) and RNS (reactive nitrogen species) initiator by quenching chain initiator catalyst .Chain reactions of free radicals· Hydroperoxide which exist in trace quantities prior to oxidation reaction, break down to yield radicals in equation (4) which abstract a hydrogen atom from another molecule and become a hydro-peroxide producing further radicals·.The antioxidants added to it ,will neutralize the free radicals by donating one of their own electrons ending the reactions in equation (1) and (3) of termination step. These occur generally in the body

- Initiation stage

(1) $RH \rightarrow R^{\cdot} + H^{\cdot}$ (2) $R^{\cdot} \rightarrow R^{\cdot} + O_2 \rightarrow ROO^{\cdot}$ (3) $2ROOH \rightarrow ROO^{\cdot} + RO^{\cdot} + H_2O$

- Propagation stage

1) $R^{\cdot} + O2 \rightarrow ROO^{\cdot}$ 2) $ROO^{\cdot} + RH \rightarrow ROOH + R^{\cdot}$ 3) $RO^{\cdot} + RH \rightarrow ROH + R^{\cdot}$

- Termination stage 1)$R^{\cdot} + R^{\cdot} \rightarrow R - R$ 2) $R^{\cdot} + ROO^{\cdot} \rightarrow ROOR$

3)$ROO^{\cdot} + ROO^{\cdot} \rightarrow ROOR + O2$ 4)Antioxidants + O2→oxidized Antioxidants

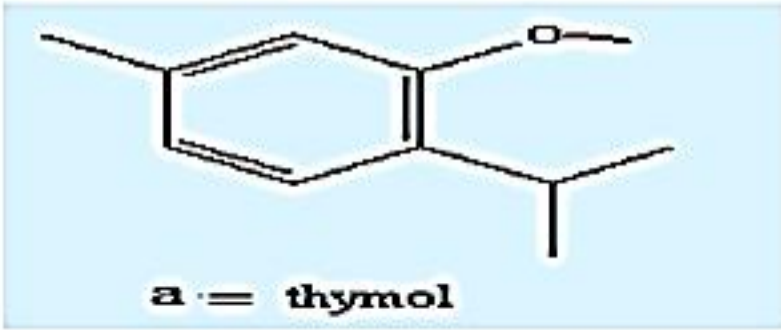
Strategy of the work

Step 1

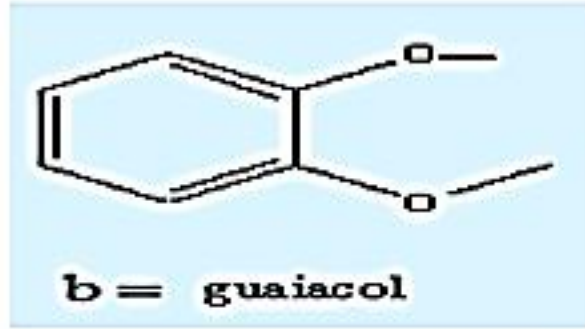
Step 2

Step 3

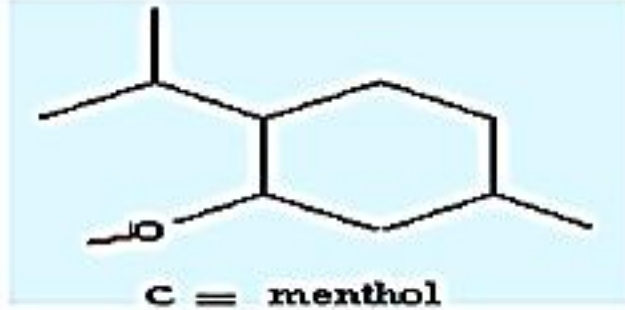
- **Synthesis of mutual prodrugs (gabapentin-antioxidant)**



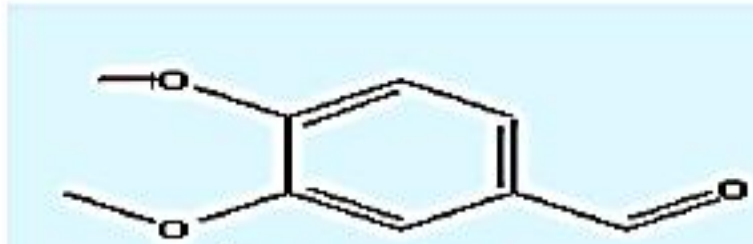
a = thymol



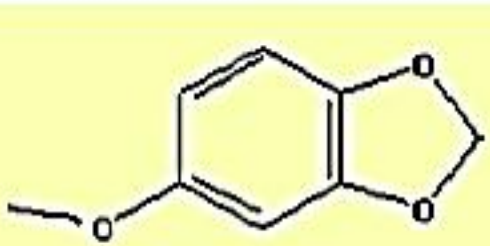
b = guaiacol



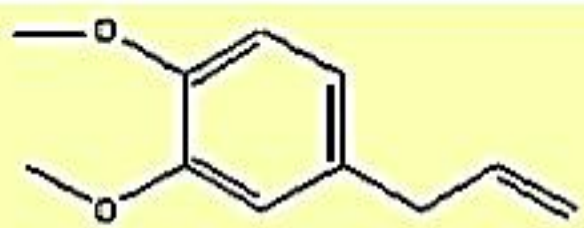
c = menthol



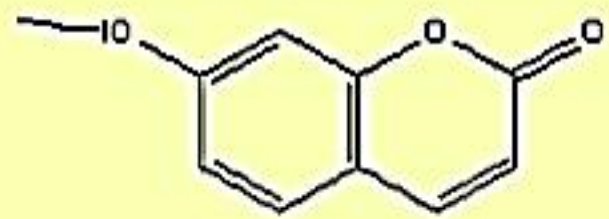
d = vanillin



e = sesamol

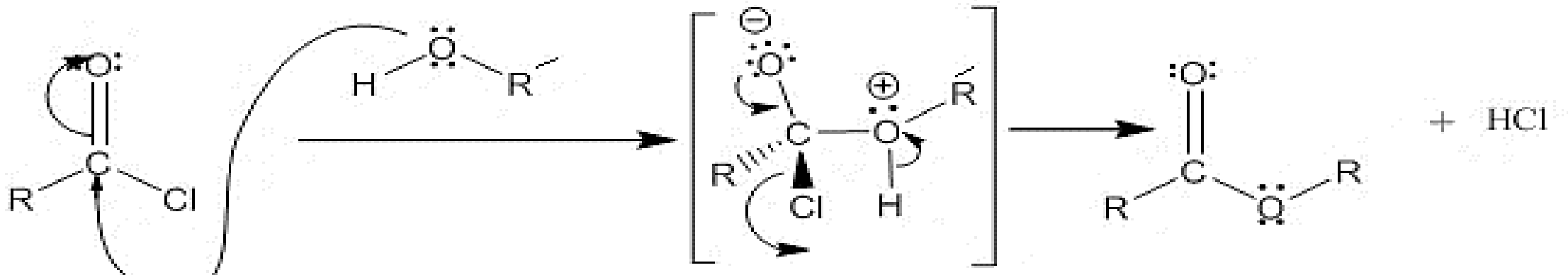


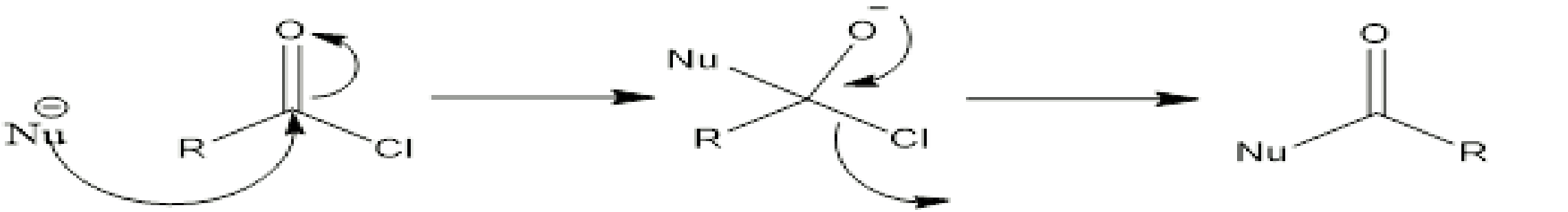
f = eugenol



g = Umbelliferon

mechanism of ester formation





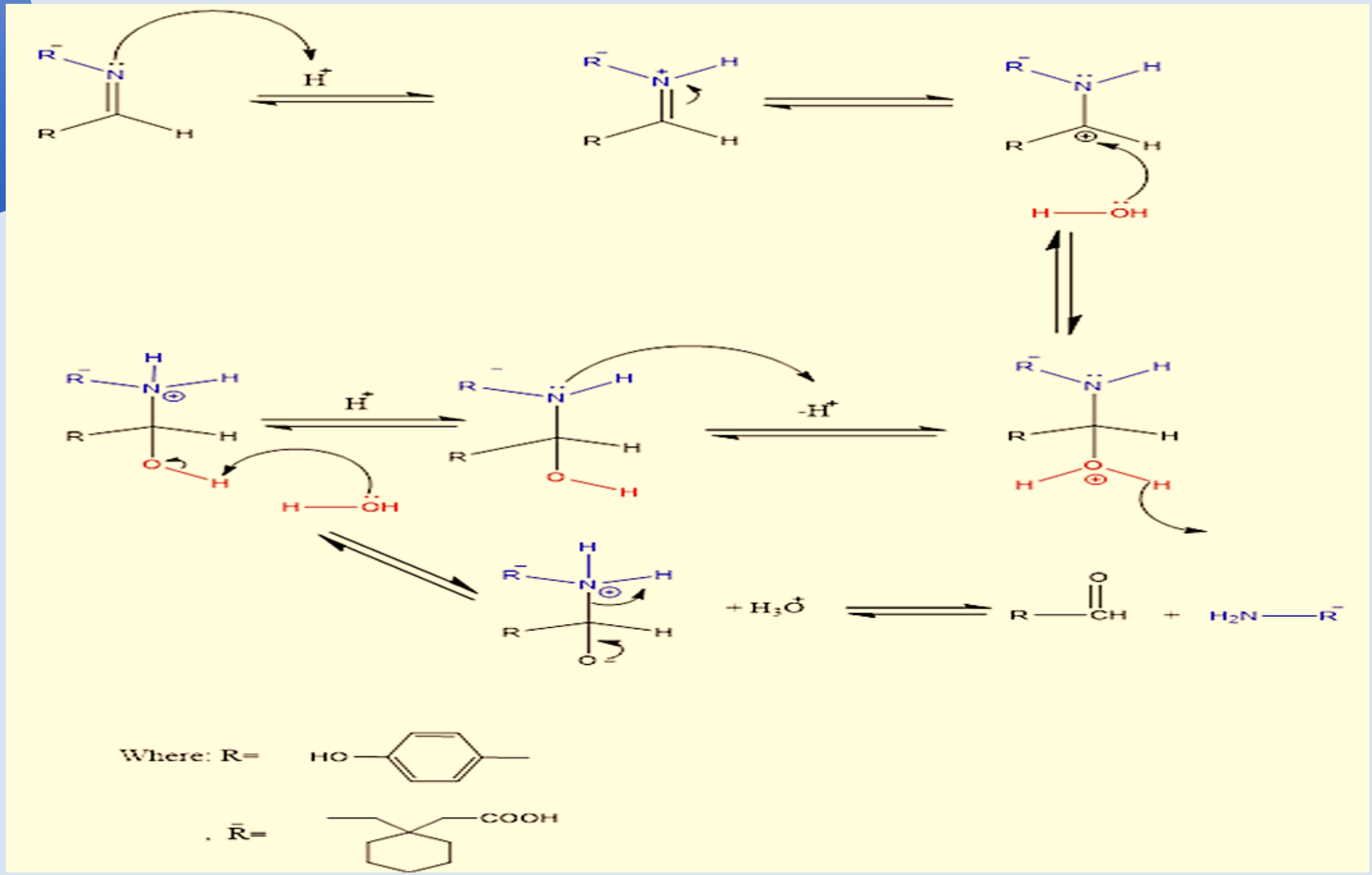
Trigonal plannar

Tetrahedral
(intermediate)

Trigonal plannar

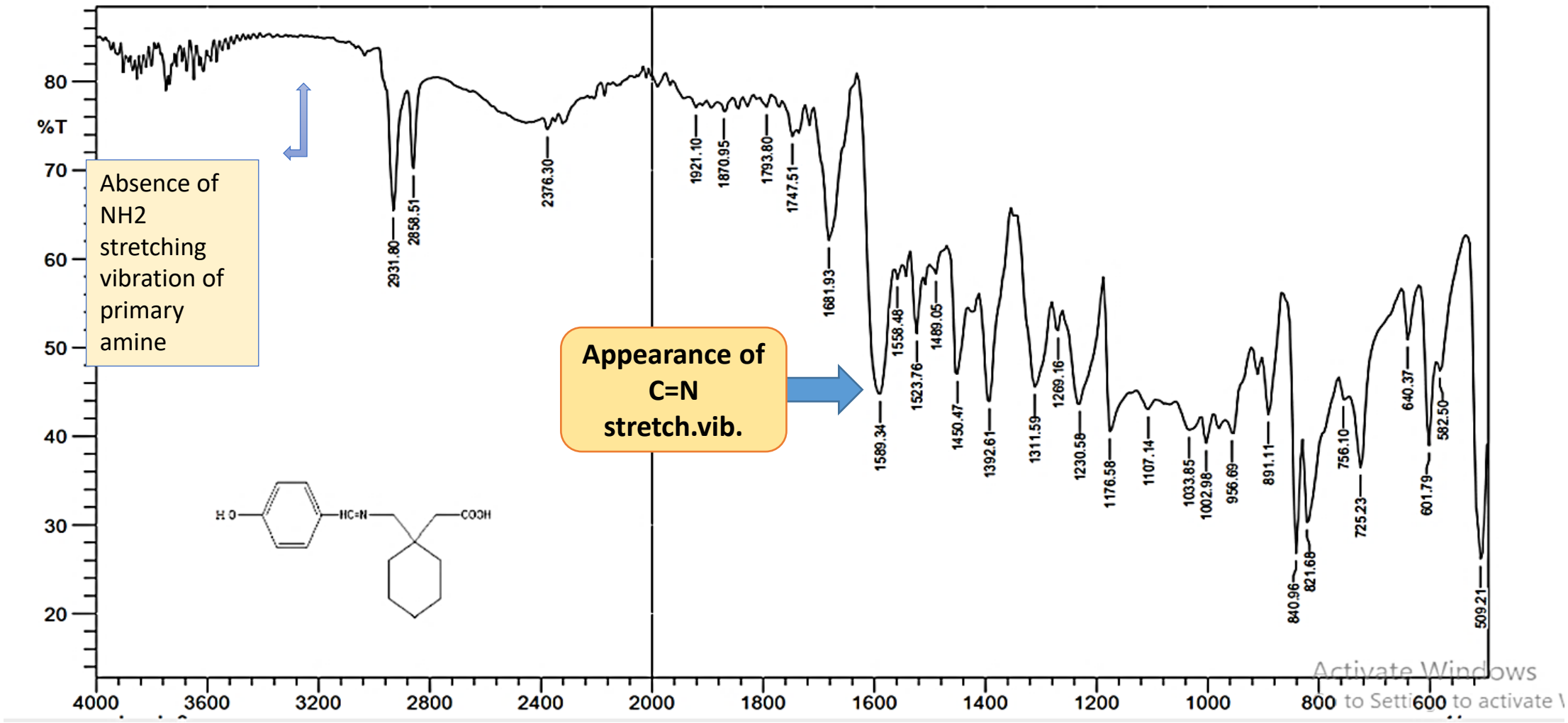
Where Nu= nucleophile
R = CH_2Cl

Mechanism of Schiff Base Hydrolysis

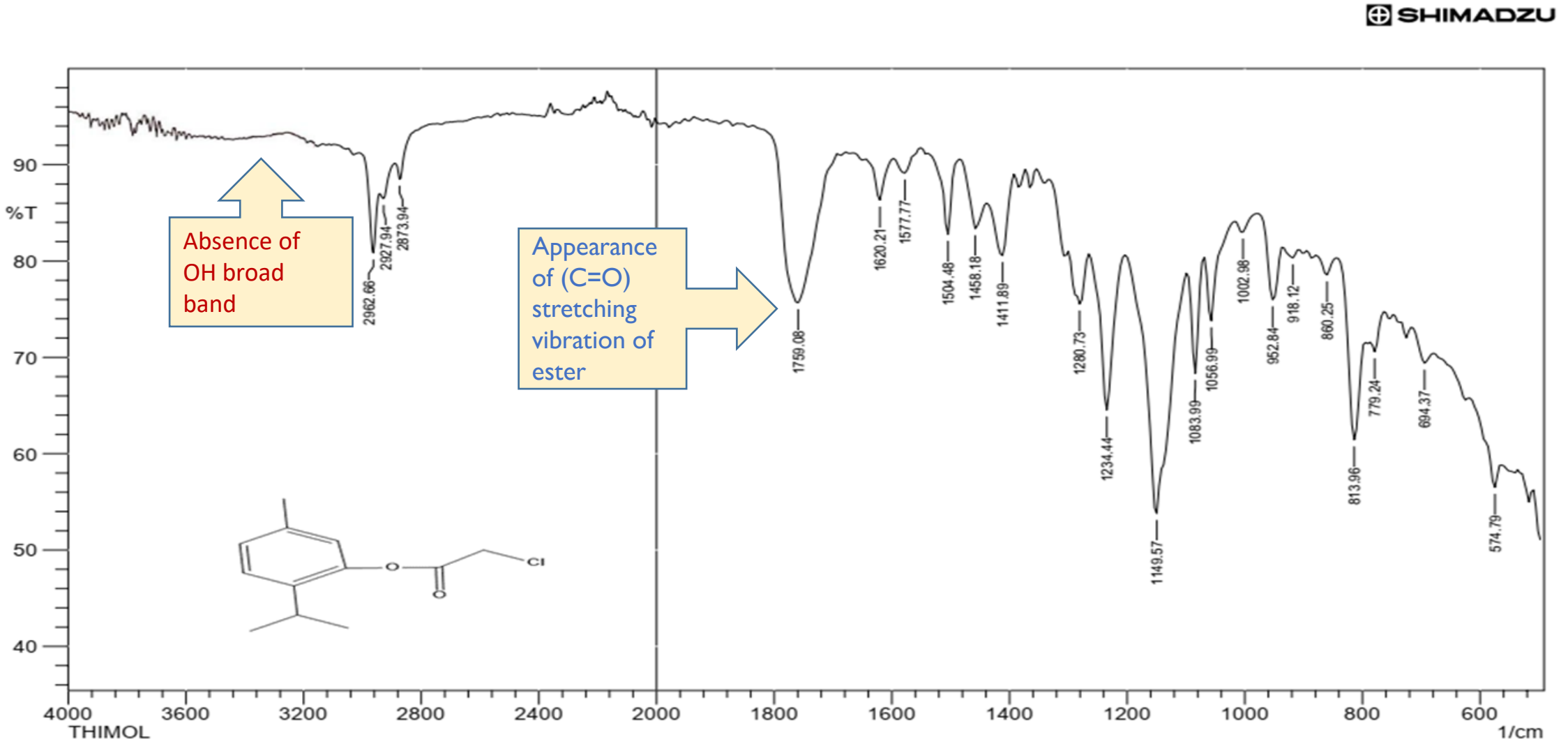


physical appearance, percent yield, melting point and R_f values of the intermediate and target compounds.

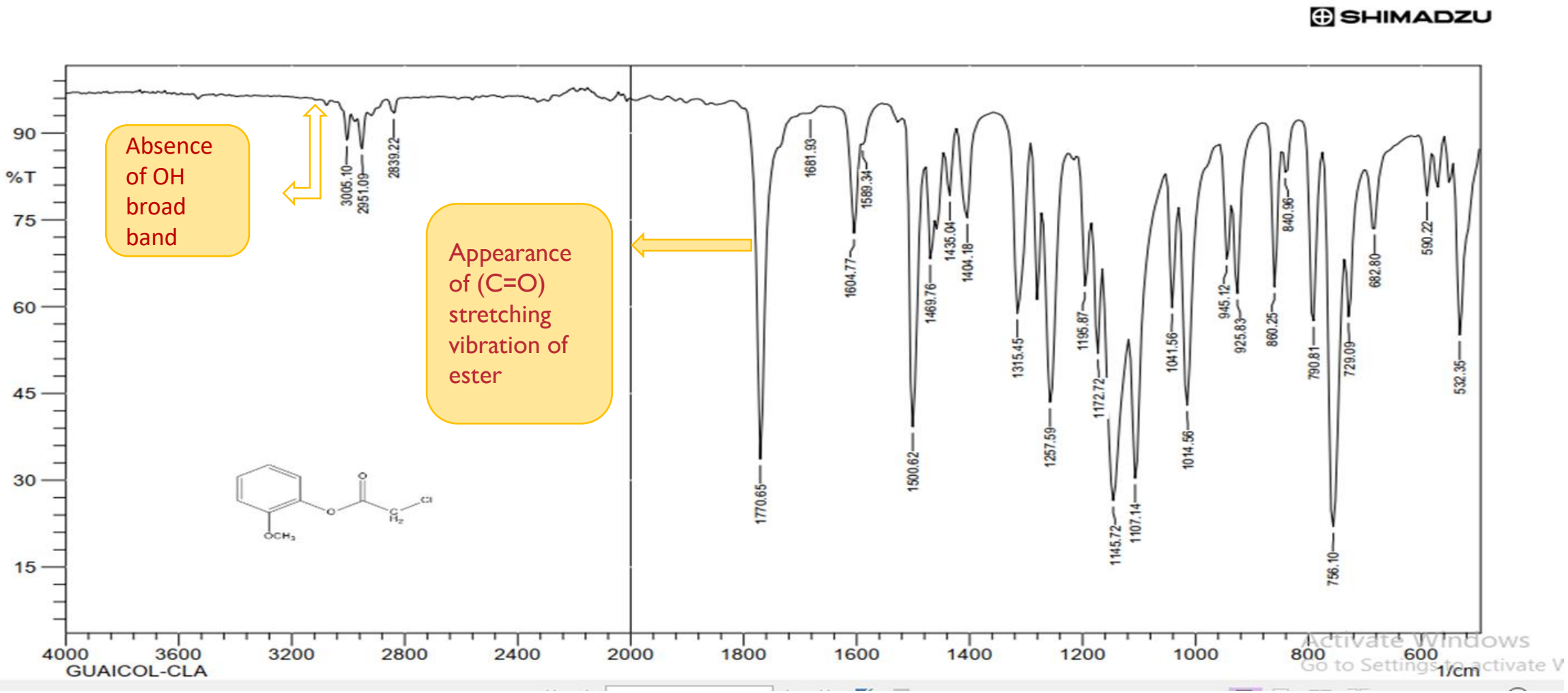
Final and intermediate compounds	Molecular formula	Molecular weight	Description	% yield	Melting point cº	*R_f value
1	$C_{16}H_{21}NO_3$	275.35	Off-white powder	86	195-198	0.93
2a	$C_{12}H_{15}ClO_2$	226.70	Burgundy color oily liquid	72	------	0.91
2b	$C_9H_9ClO_3$	200.62	White crystals	69	58	0.96
2c	$C_{12}H_{21}ClO_2$	232.75	Yellow oily liquid	80	------	0.73
2d	$C_{10}H_9ClO_4$	228.63	Sandy-brown crystals	65	63-65	0.75
2e	$C_9H_7ClO_4$	214.60	Pale –yellow oily liquid	50	-------	0.88
2f	$C_{12}H_{13}ClO_3$	240.68	Violate-brown crystals	54	53-55	0.76
2g	$C_{11}H_7ClO_4$	238.62	Off-white flakes	42	162	0.62
3a	$C_{24}H_{39}NO_6$	437.58	Burgundy color crystals	45	110-115	0.93
3b	$C_{21}H_{33}NO_7$	411.50	Orange crystals	62	115	0.91
3c	$C_{24}H_{45}NO_6$	443.63	Yellow oily liquid	71	-------	0.78
3d	$C_{22}H_{33}NO_8$	439.51	Pinky-orange crystals	73	60	0.56
3e	$C_{28}H_{35}NO_9$	529.59	Brown reddish paste	53	--------	0.79
3f	$C_{31}H_{41}NO_8$	555.67	Maroon color crystals	67	--------	0.83
3g	$C_{23}H_{31}NO_8$	449.50	Blaze –orange crystals	65	75	0.52



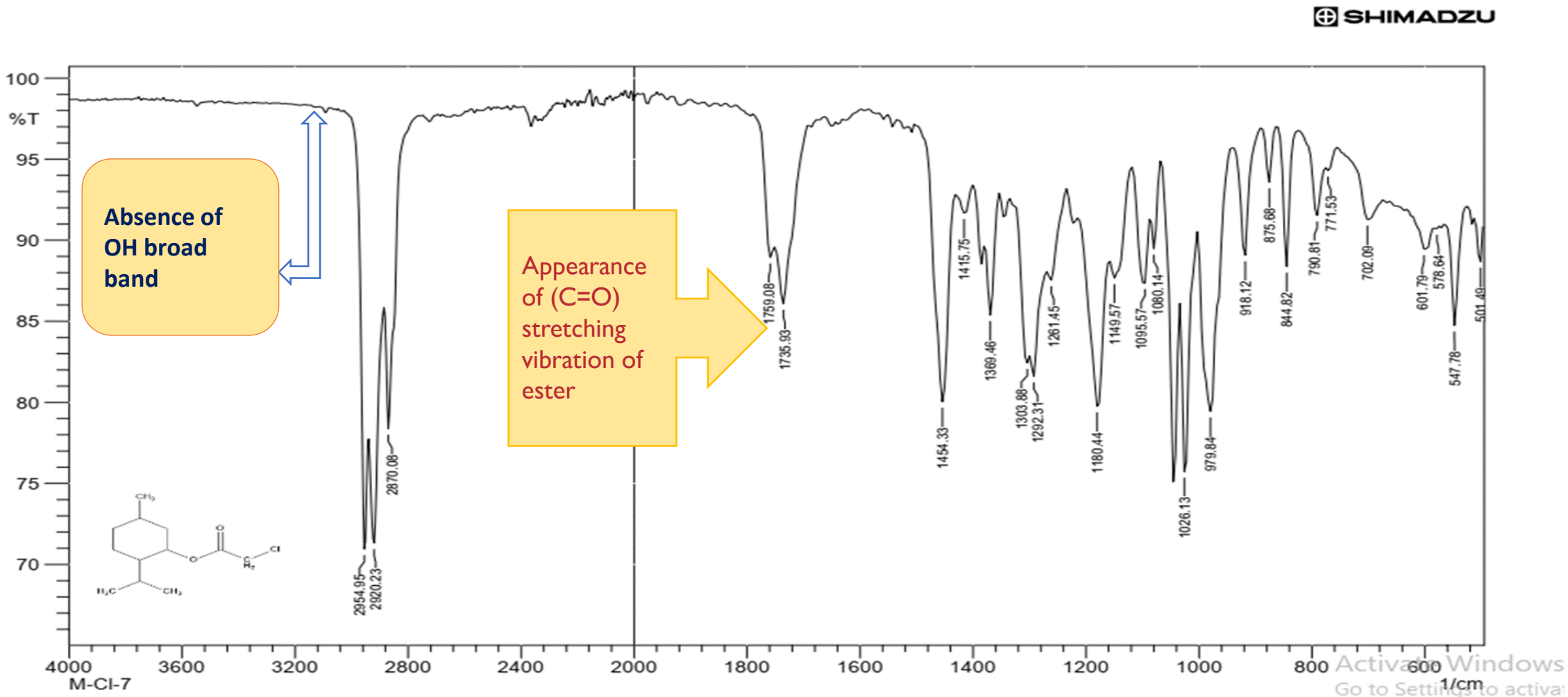
I.R spectrum of Cpd.1 gabapentin-schiff base



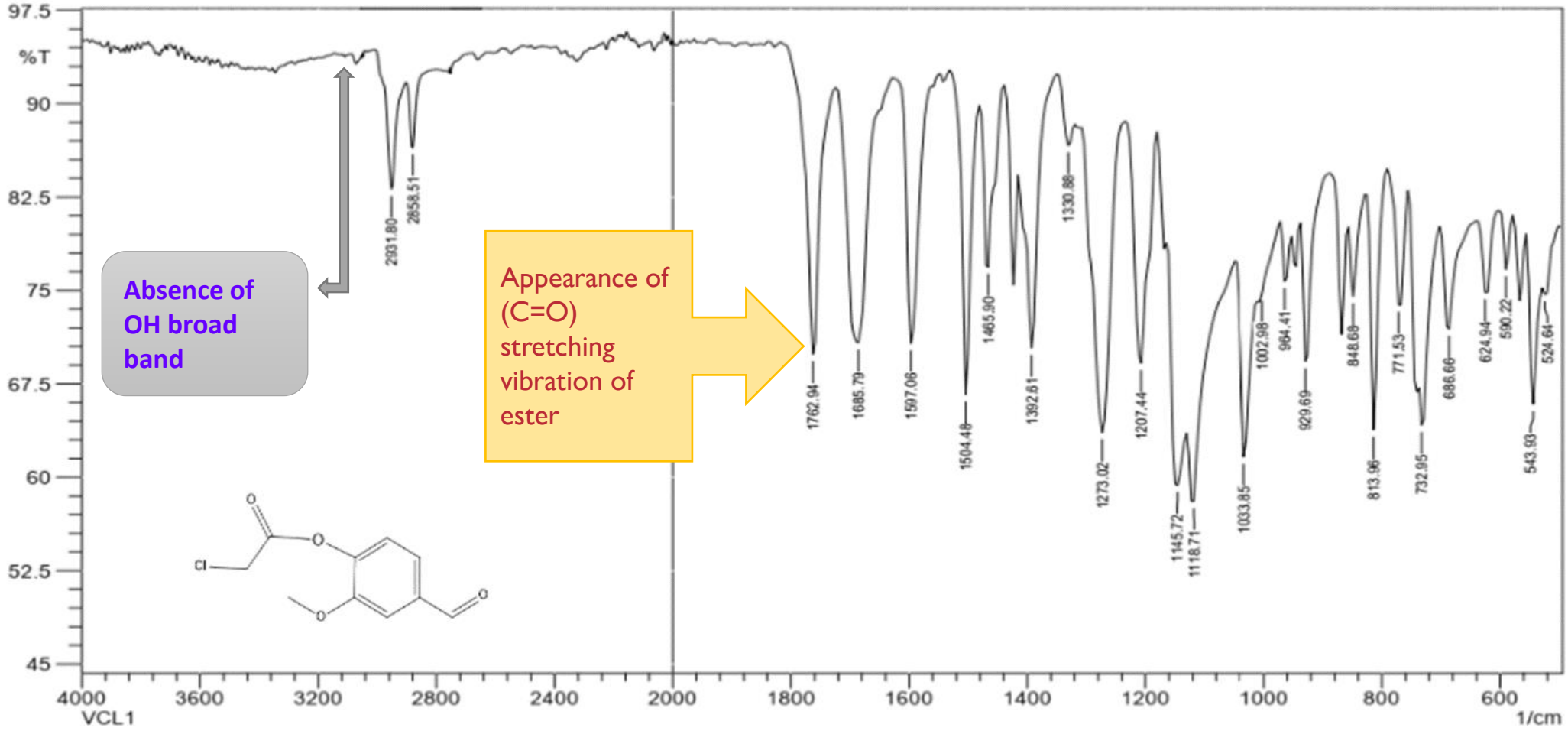
I.R spectrum of Cpd.2a



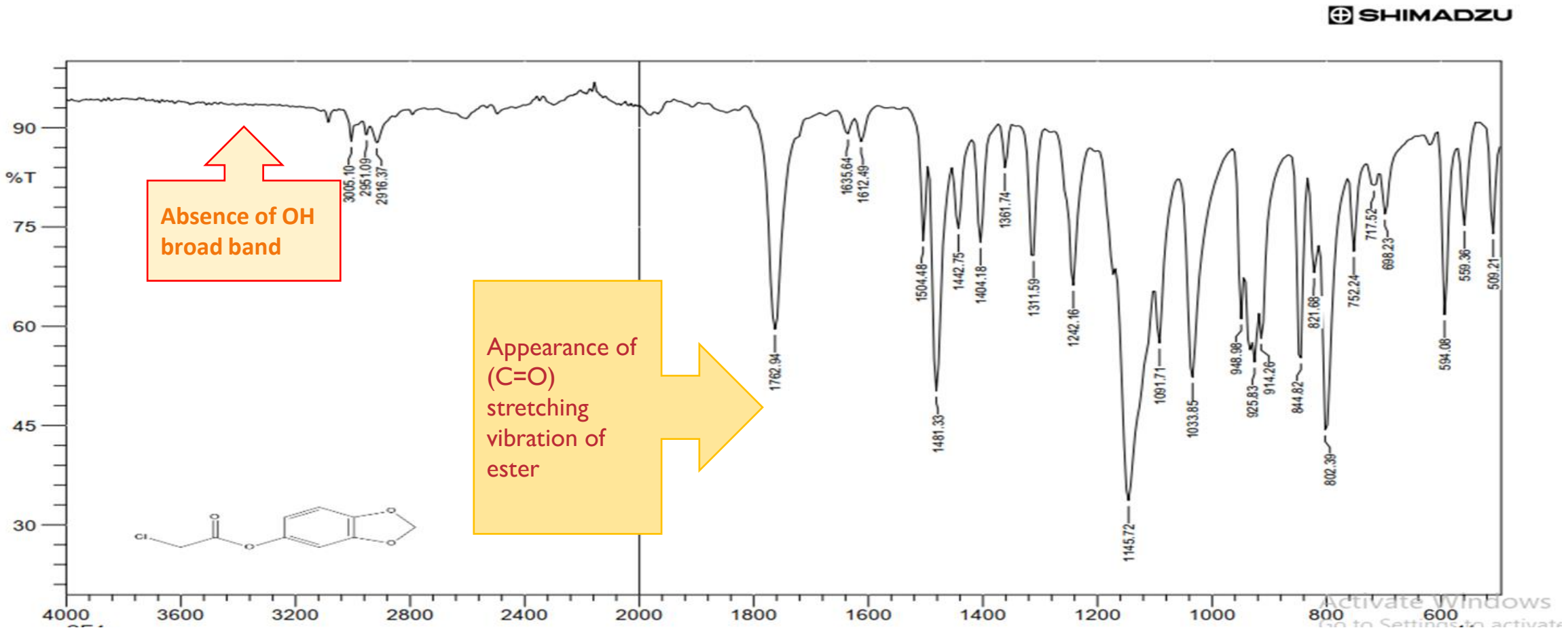
I.R spectrum of Cpd.2b



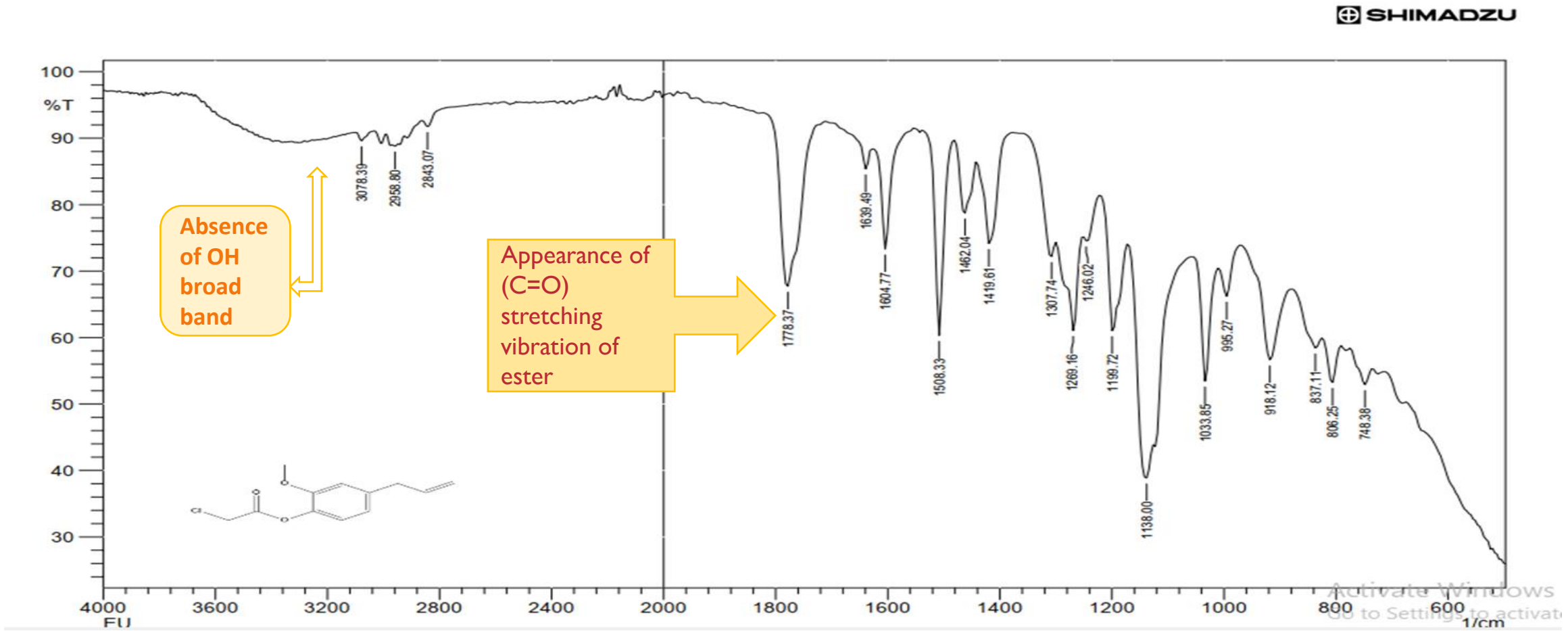
I.R spectrum of Cpd.2c



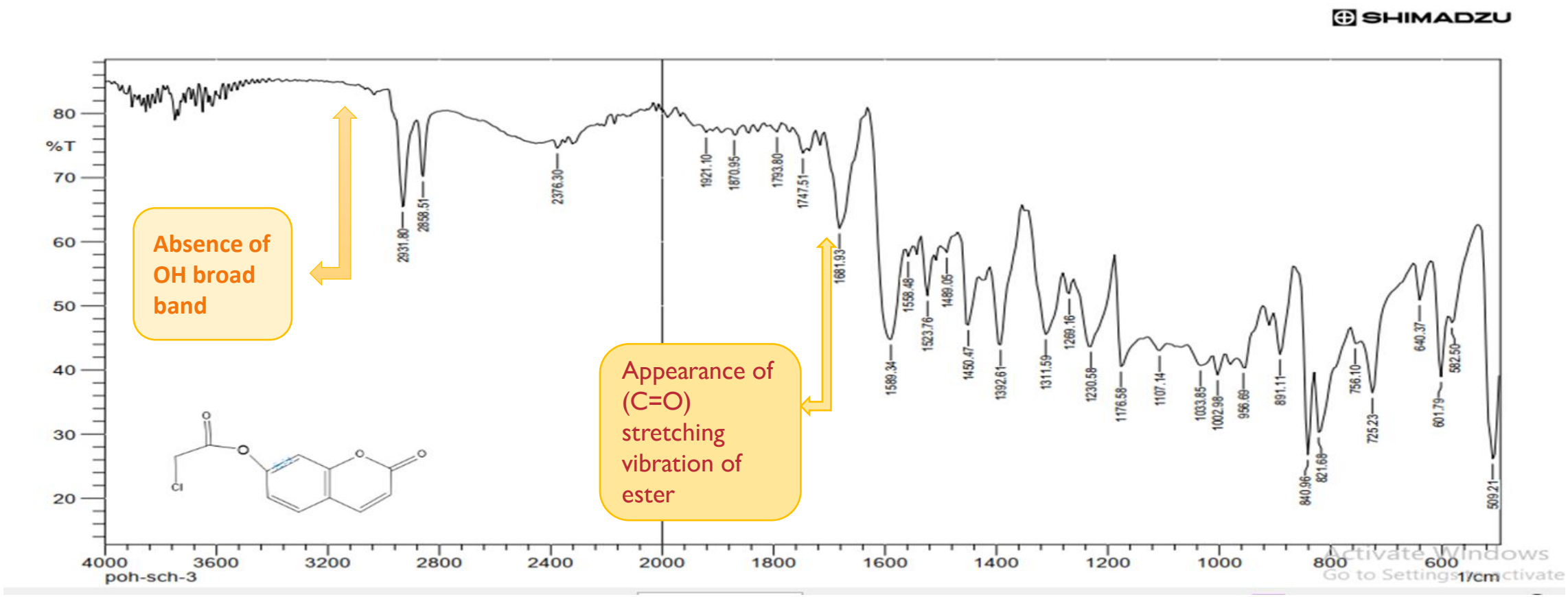
I.R spectrum of Cpd.2d



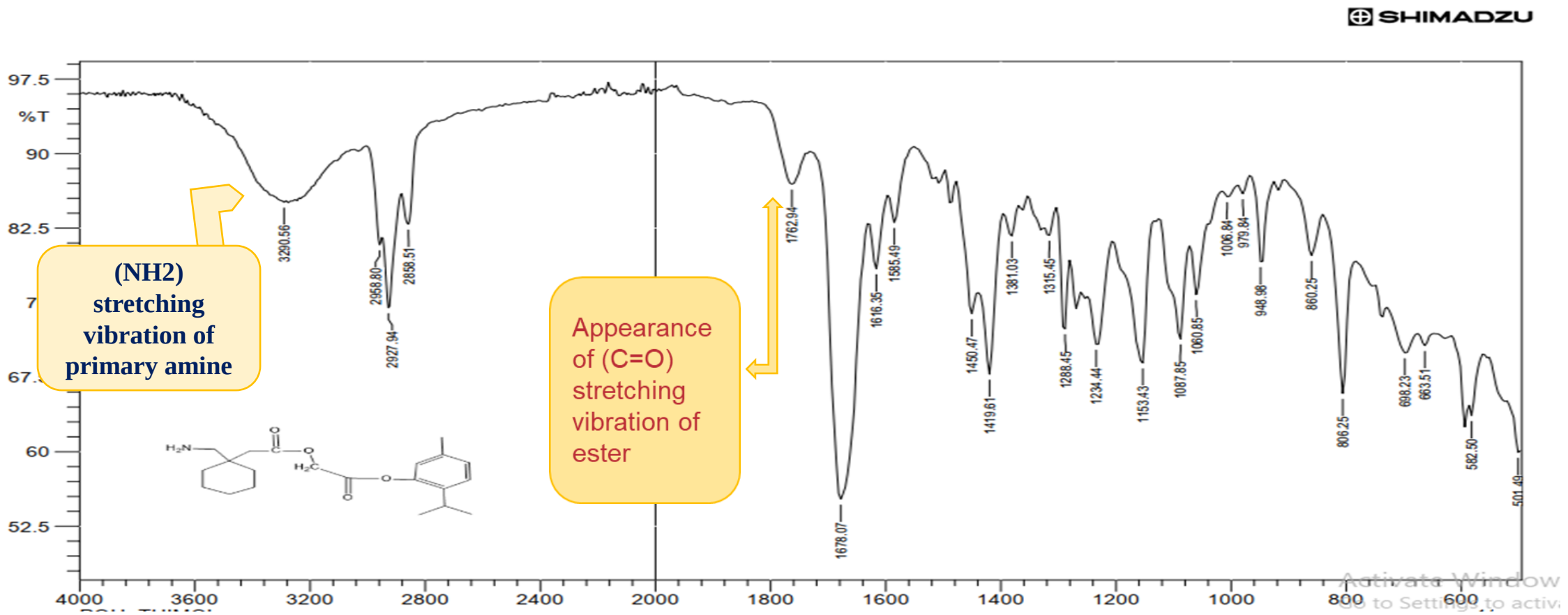
I.R spectrum of Cpd.2e



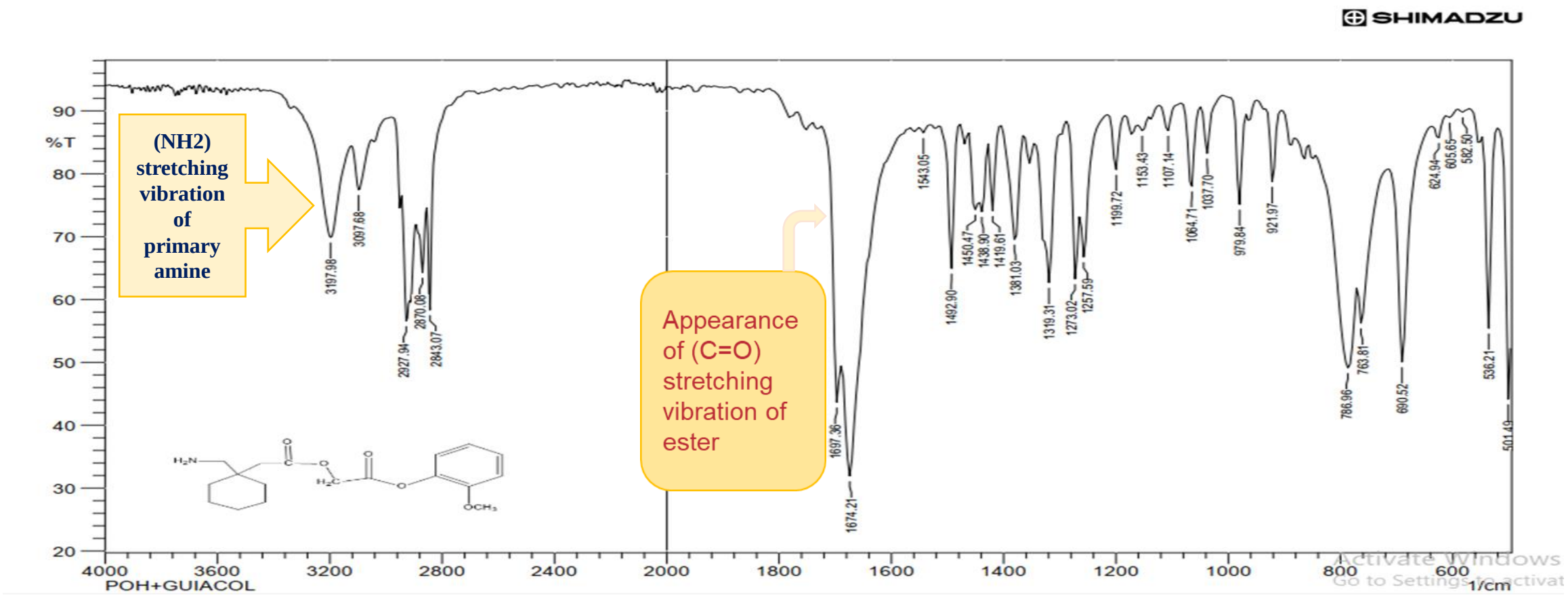
I.R spectrum of Cpd.2f



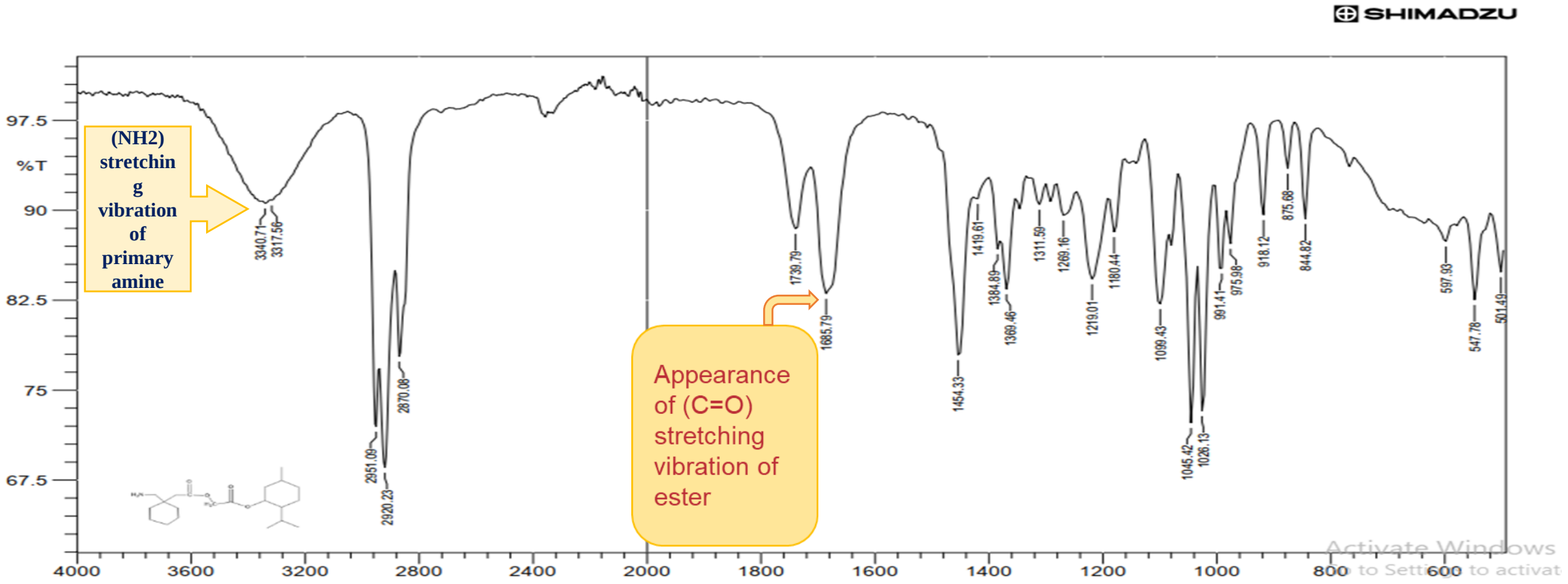
I.R spectrum of Cpd.2g



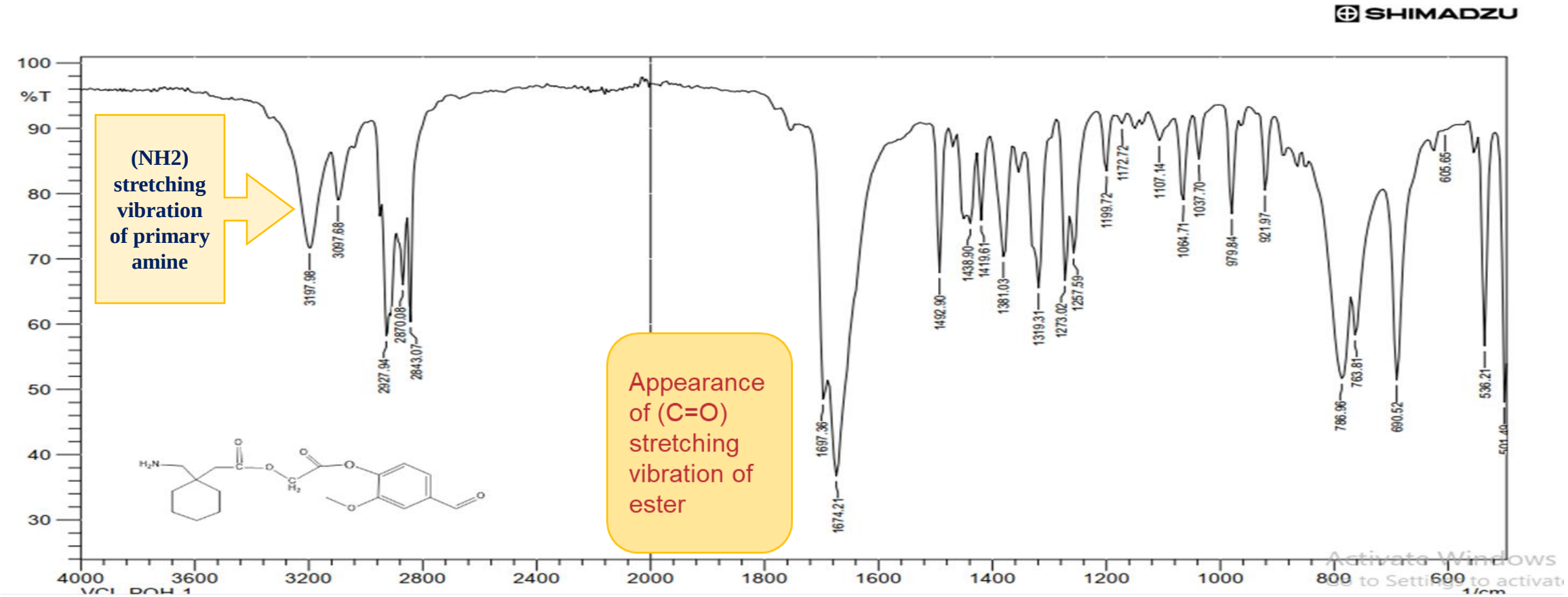
I.R spectrum of Cpd.3a



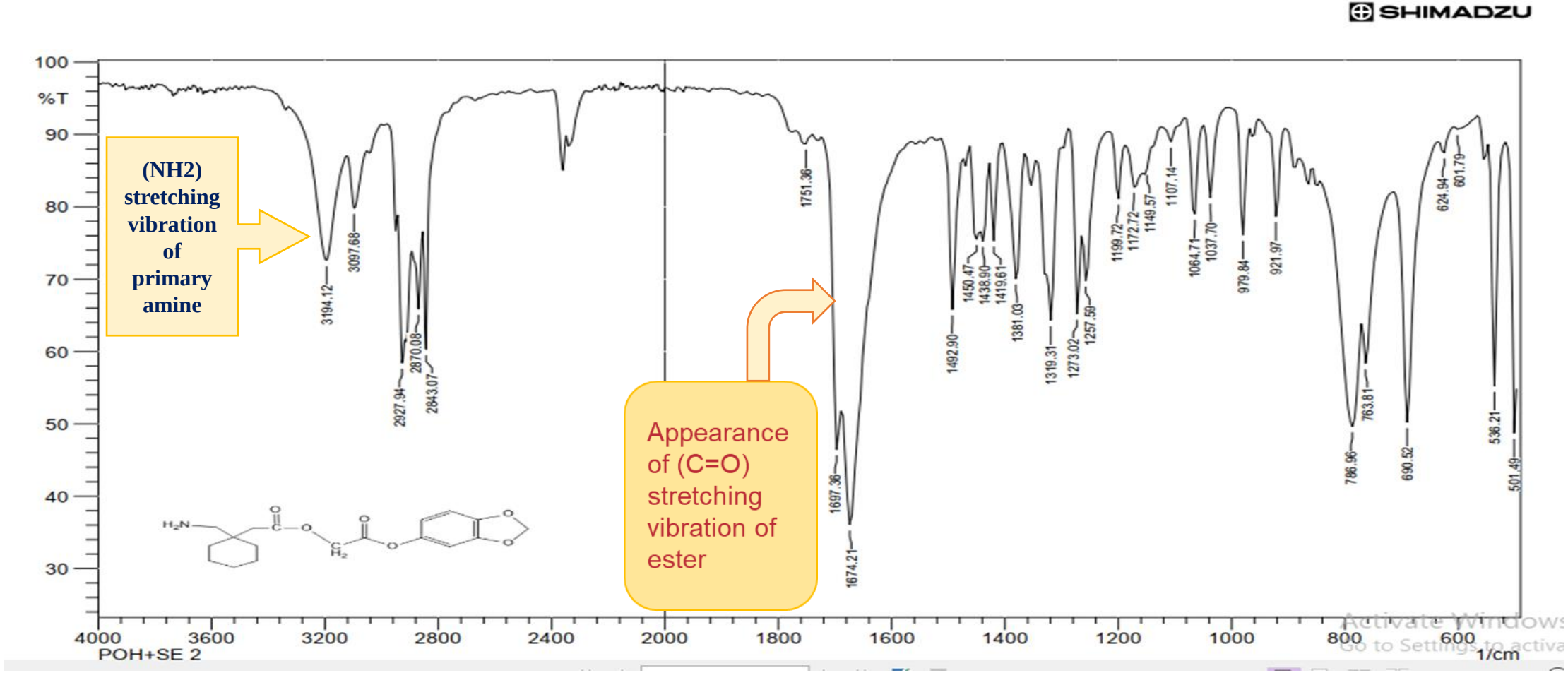
I.R spectrum of Cpd.3b



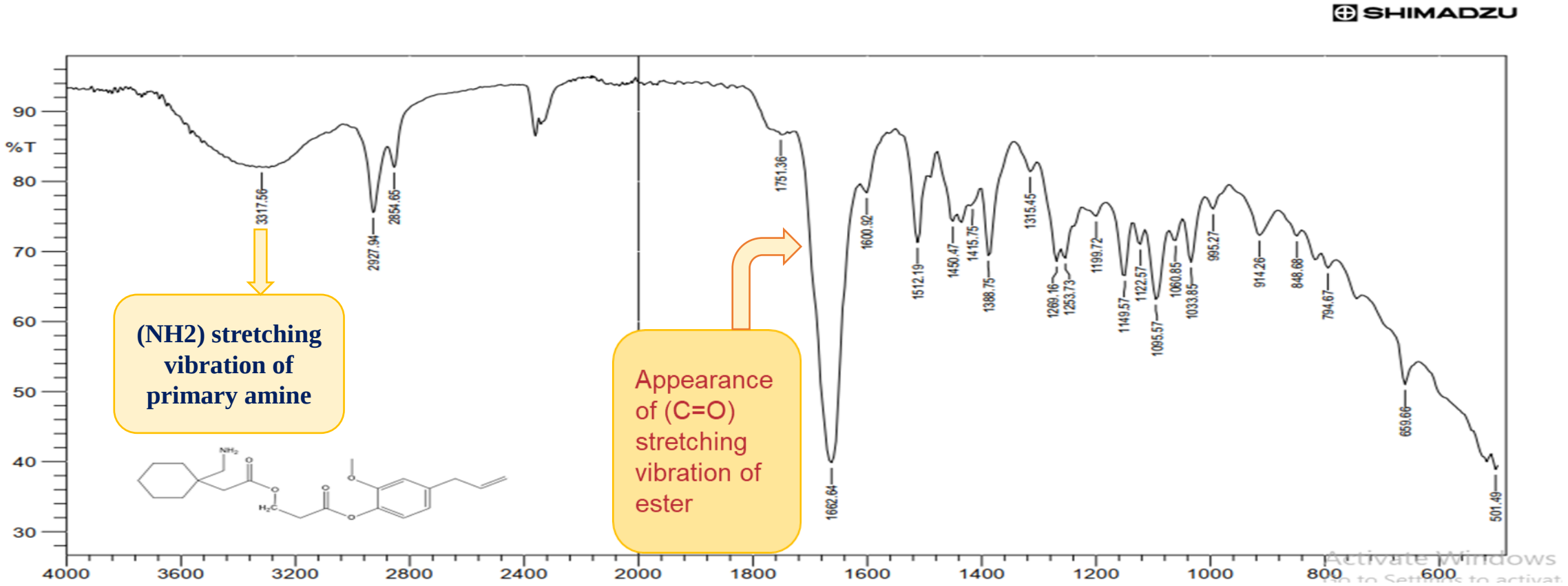
I.R spectrum of Cpd.3c



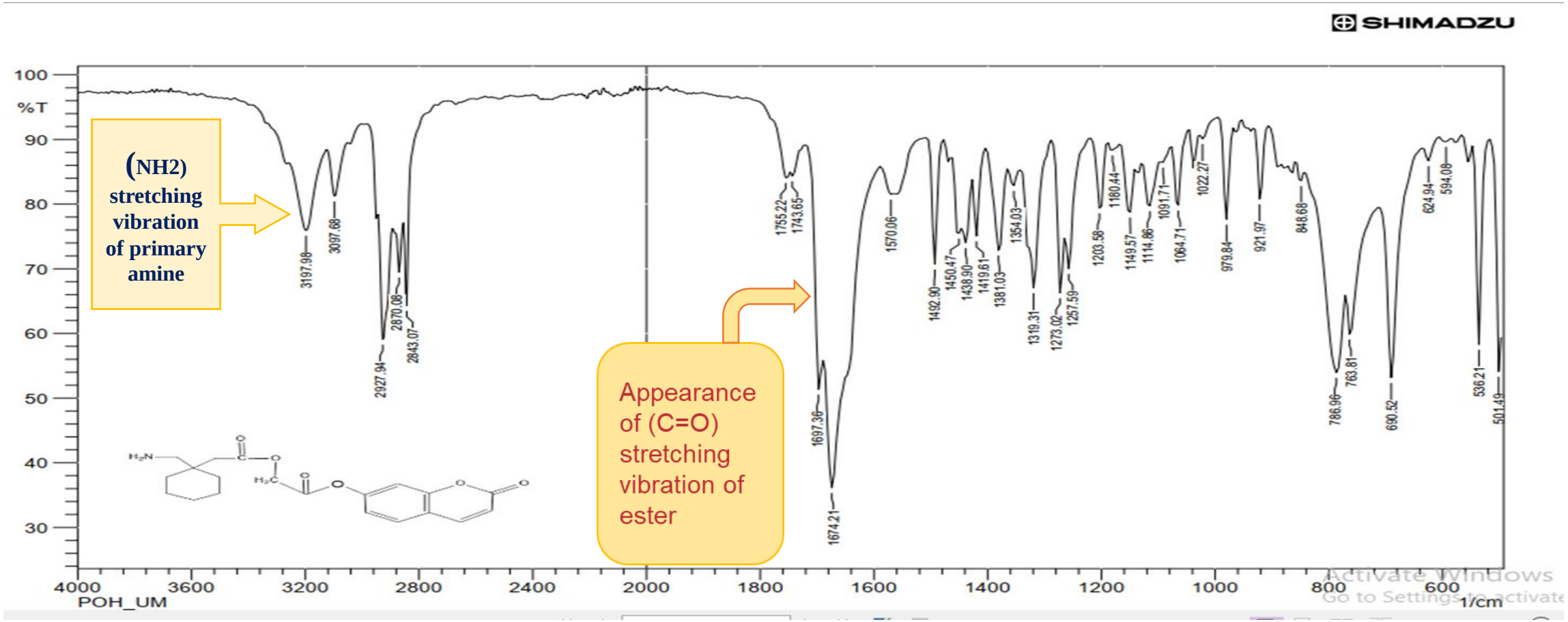
I.R spectrum of Cpd.3d



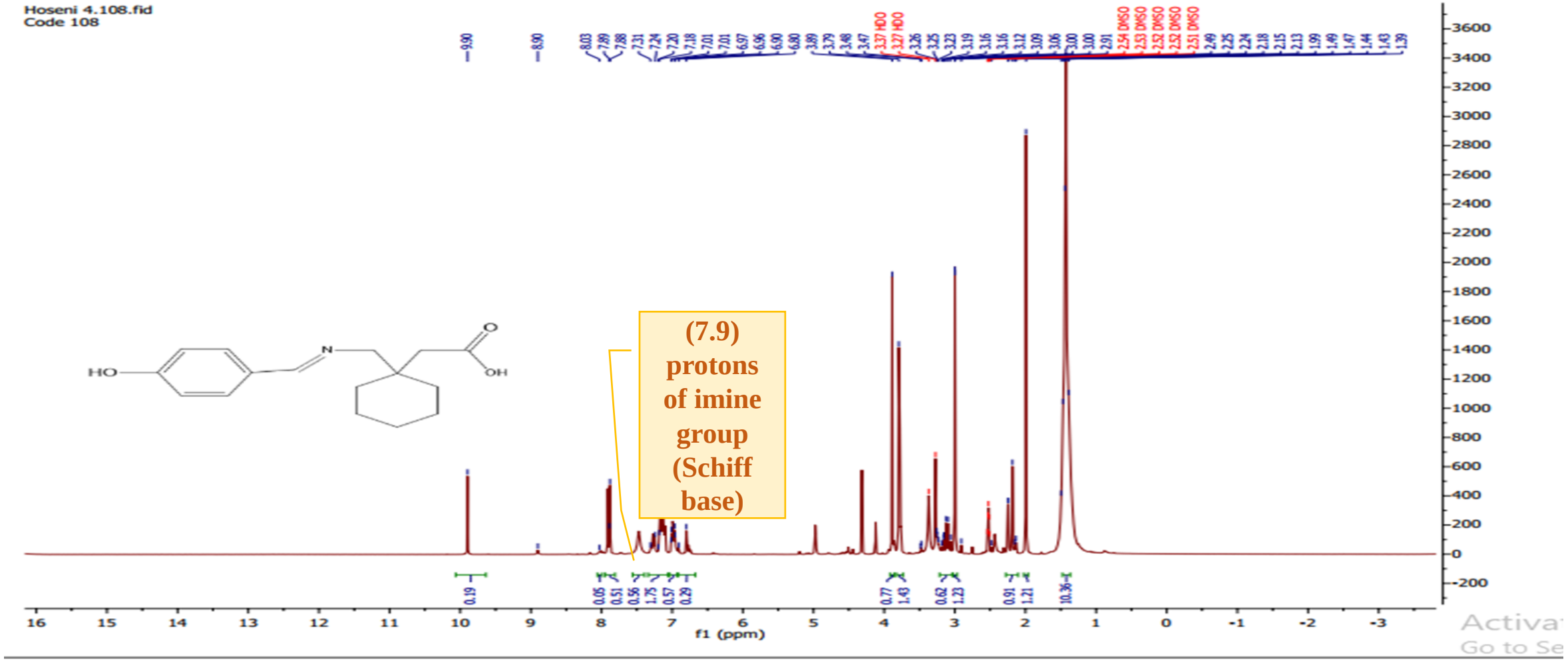
I.R spectrum of Cpd.3e



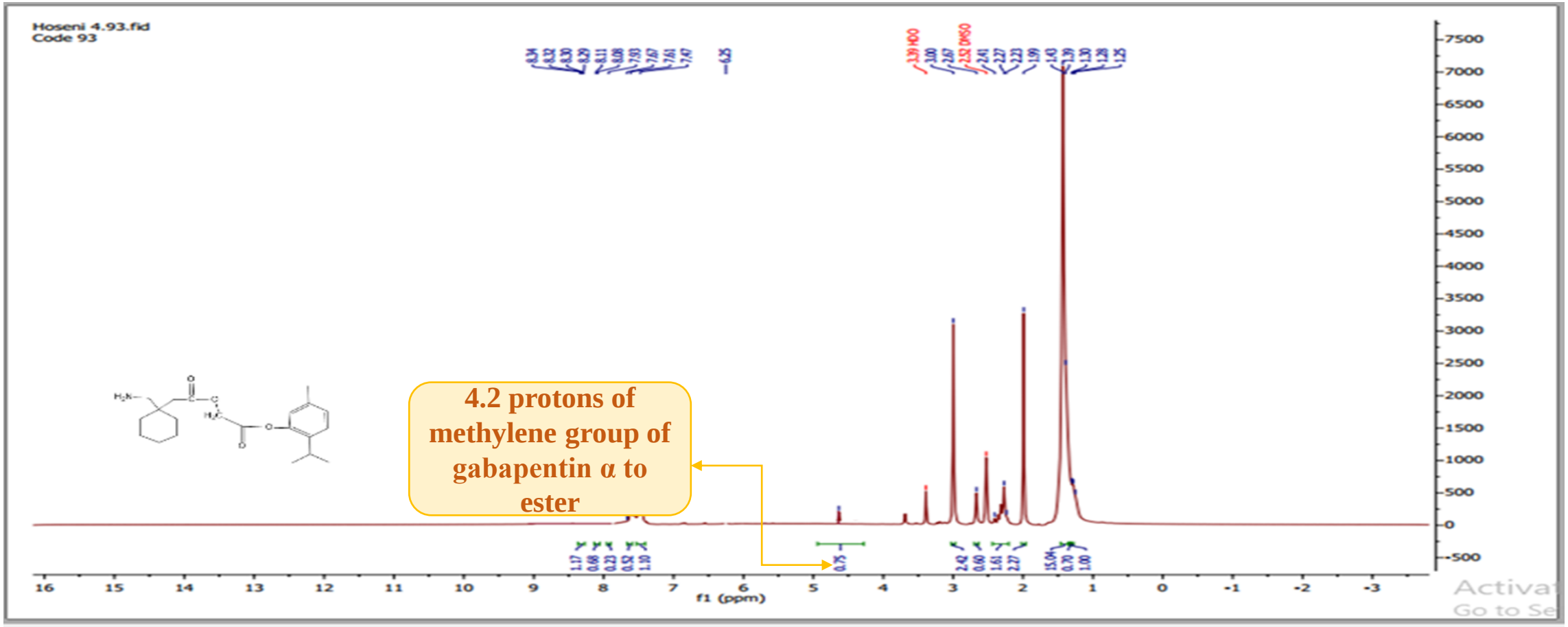
I.R spectrum of Cpd.3f



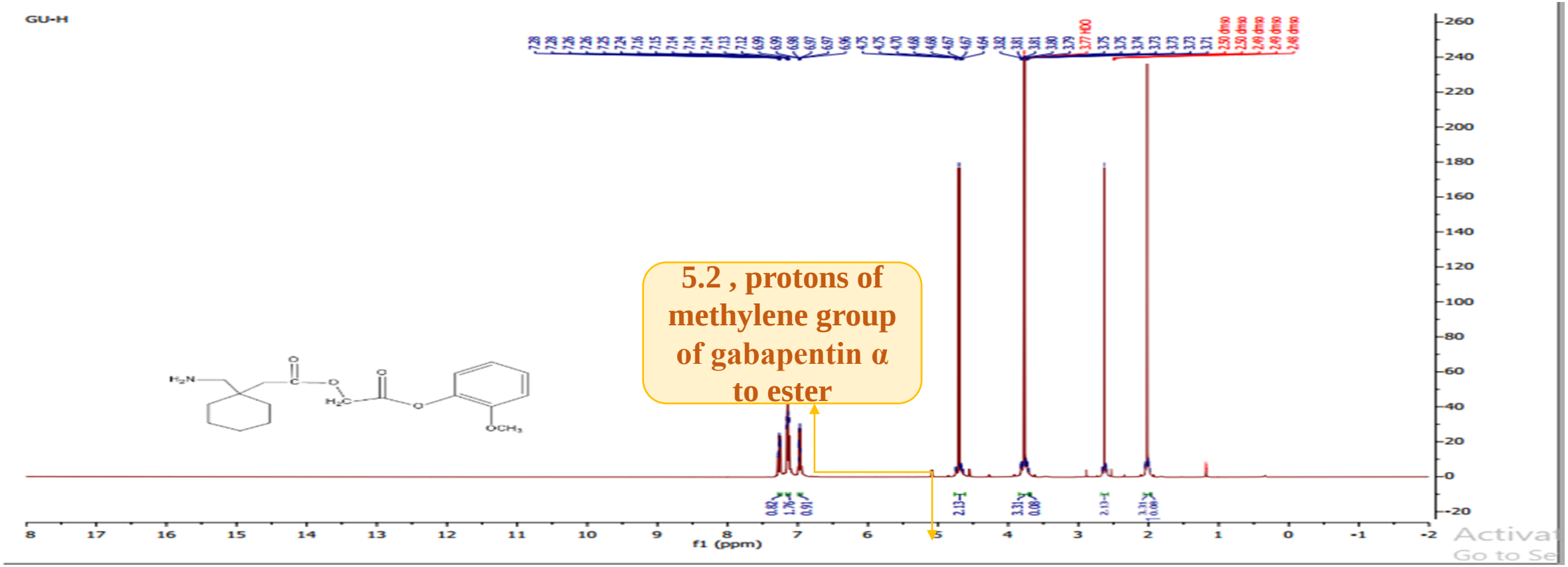
I.R spectrum of Cpd.3g



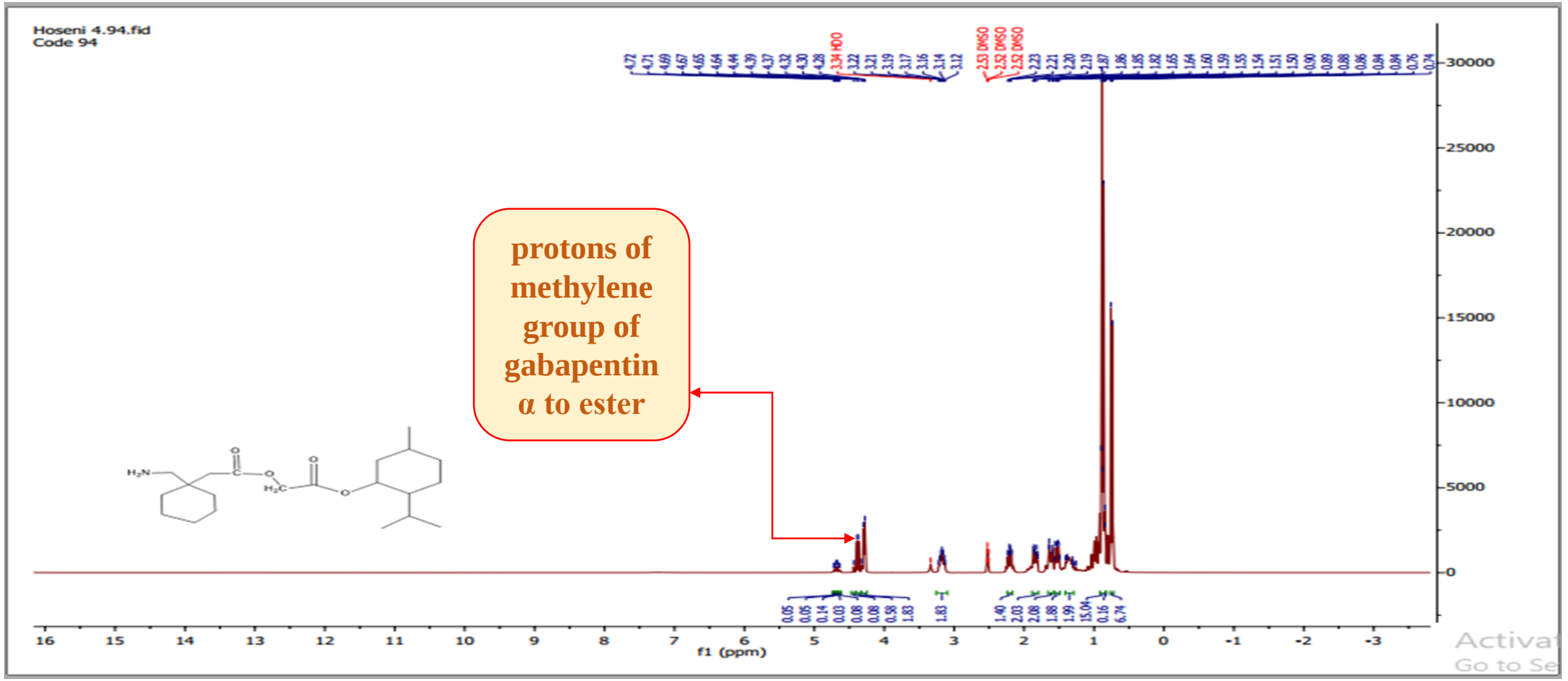
^{1}H -NMR spectrum of compound 1



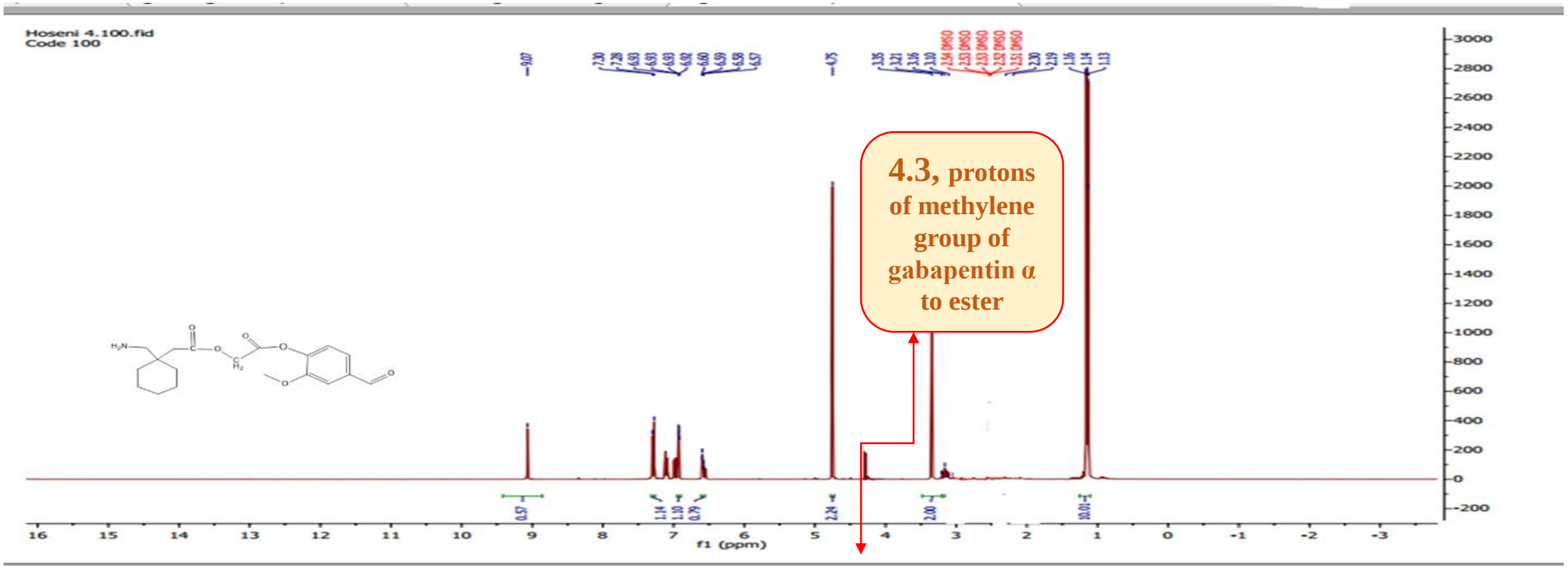
^{1}H -NMR spectrum of compound 3a



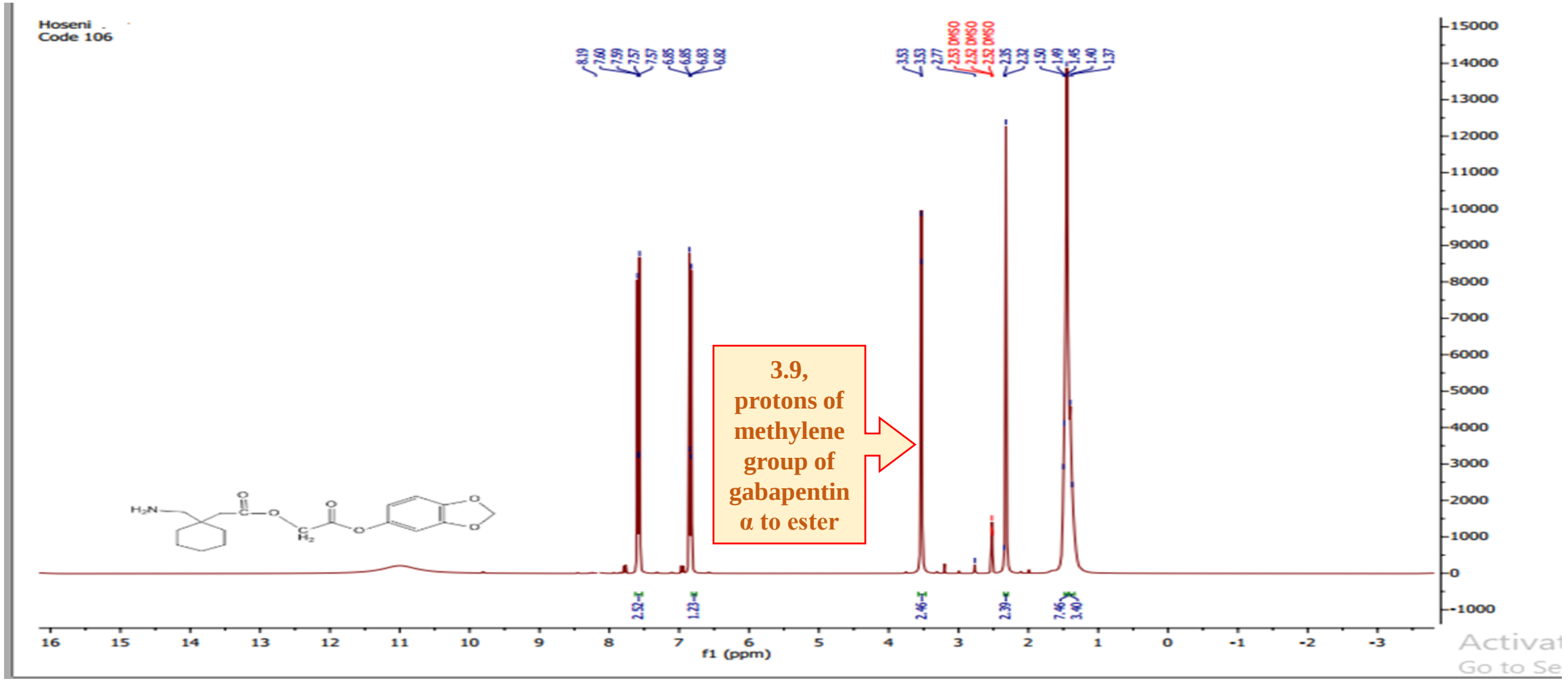
^{1}H -NMR spectrum of compound 3b



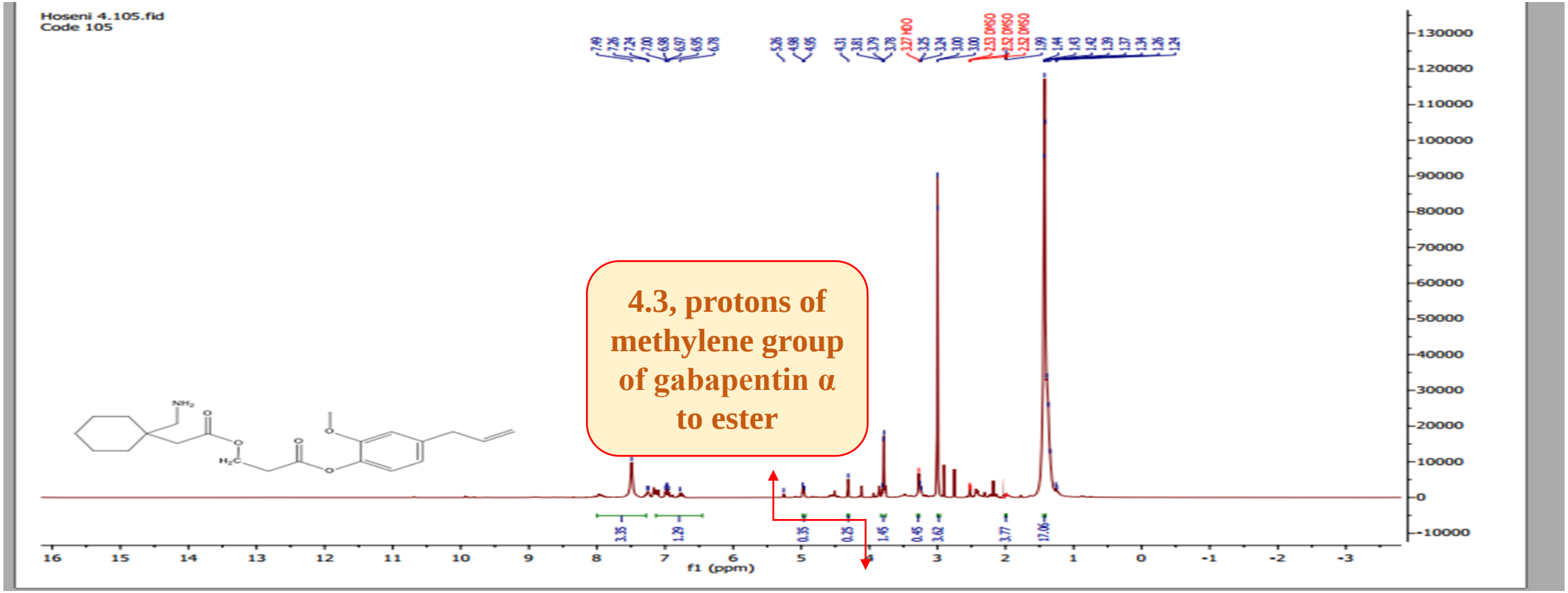
^{1}H -NMR spectrum of compound 3c



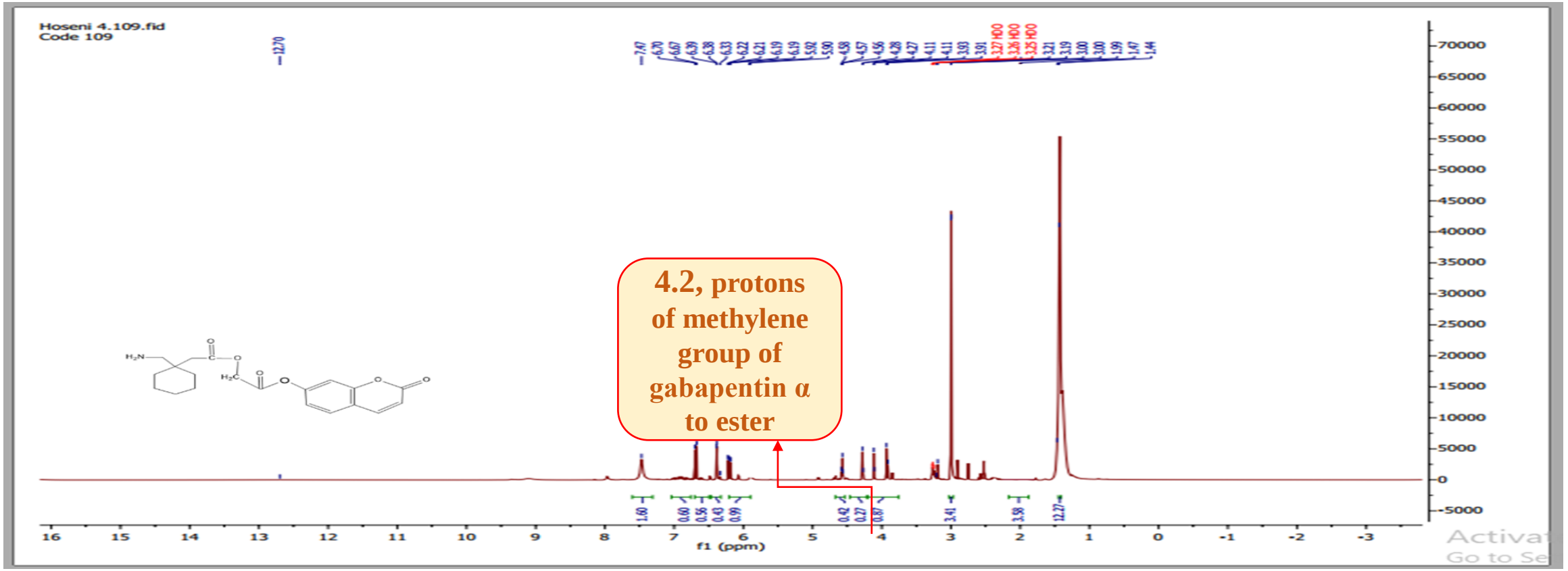
^{1}H -NMR spectrum of compound 3d



^{1}H -NMR spectrum of compound 3e



^{1}H -NMR spectrum of compound 3f



^{1}H -NMR spectrum of compound 3g

Antibacterial activity of gabapentin derivatives

Compound Name	Conc. µg/ml	Staph aureus.	Strep. pneumoniae	klebsilla pneumoniae	E.coli
		Gram Positive		Gram. Negative	
		Zone of inhibition			
Amoxicillin	10^3	1.5	Zero	zero	zero
ciprofloxacin	10^3	3	3.5	3	zero
nitrofurantoin	10^3	2	1.5	1	1.5
DMSO	Control & solvent	zero	Zero	zero	zero
3a	10^3	3	2.5	1.8	2
3b	10^3	1	1.2	zero	1.7
3c	10^3	1.5	1.3	1.3	1.3
3d	10^3	1.2	1.2	1.3	zero
3e	10^3	1.3	1.5	zero	zero
3f	10^3	1.5	1.2	1.5	1.5
3g	10^3	1	1.3	zero	zero

Antifungal activity of gabapentin derivatives

Compound name	Conc.µg/ml	Candida albicans / zone of inhibition
Clotrimazole	10^3	2.5
Nystatin	10^3	Zero
DMSO	10^3	Zero
3a	10^3	2
3b	10^3	Zero
3c	10^3	1.5
3d	10^3	1.3
3e	10^3	zero
3f	10^3	1.5
3g	10^3	1

Anti-inflammatory activity of control, standard (gabapentin) and gabapentin-antioxidants derivatives (3A-3G) on egg-white induced paw edema in rat hand paw

Time	0 min	30 min	60 min	120 min	180 min	240 min	300 min	LSD
control	C4.61±0.19	B5.93±0.17a	A6.63±0.16c	A6.96±0.19a	A6.55±0.22a	B5.91±0.14a	B5.50±0.11a	0.504
standard	E4.76±0.16	DE5.18±0.20bc	B6.16±0.22d	A6.75±0.12a	BC5.96±0.06bcd	CD5.55±0.03bc	D5.21±0.09ab	0.4215
A	D4.70±0.16	CD5.08±0.15c	A6.66±0.23bc	A6.31±0.13bc	B5.70±0.17de	BC5.45±0.13bcd	CD4.98±0.18bc	0.4922
B	E4.63±0.21	D5.38±0.16bc	A7.23±0.12a	B6.80±0.07a	C6.10±0.13bcd	D5.51±0.04bcd	E4.91±0.12bc	0.3868
C	E4.70±0.18	BC5.70±0.22ab	A7.03±0.17abc	A6.65±0.19ab	B6.06±0.18bcd	CD5.50±0.16bcd	DE5.11±0.18ab	0.5408
D	D4.83±0.17	C5.31±0.19bc	A7.30±0.11a	A6.93±0.13a	B6.26±0.16ab	C5.65±0.16ab	CD5.23±0.17ab	0.467
E	E4.63±0.21	D5.11±0.16c	A7.11±0.13ab	B6.63±0.06ab	C5.81±0.08cde	D5.28±0.06cd	E4.66±0.13c	0.3818
F	E4.60±0.22	CD5.13±0.20c	A6.76±0.09bc	B5.96±0.13c	C5.45±0.14e	CD5.16±0.15d	DE4.66±0.21c	0.5013
G	E4.86±0.14	D5.53±0.20abc	A7.31±0.14a	B6.73±0.05a	C6.16±0.09abc	D5.65±0.12ab	E5.08±0.14abc	0.4004
LSD	0.5353 NS	0.5399	0.465	0.3776	0.4271	0.3577	0.4481	

Conclusions

1. Synthetic procedure for the designed target compounds was achieved successfully .

2. Identification and characterization of the synthesized compound were achieved by using FT-IR spectroscopy, ^{1}H-NMR spectroscopy, melting points and R_f values.

3. Preliminary antimicrobial activity study revealed that the synthesized final compounds (3a)demonstrate significant antibacterial &antifungal activity.

4. Preliminary study of anti-inflammatory activity showed gabapentin – antioxidant conjugated derivatives (3a, 3e and 3f) have more potent effect to gabapentin alone while gabapentin with anti-oxidant (guaicol and umbiliferon) showed comparable inhibition in paw hand thickness of the rat, vanillin and menthol gabapentin derivatives showed poor reduction in paw thickness.


thank you