

**One-Pot Synthesis of Azolyl methanesulfonamido Oxadiazoles,
Thiadiazoles and Triazoles as Antimicrobial, Antioxidant, and Anticancer
Agents supported by Molecular Docking Studies**

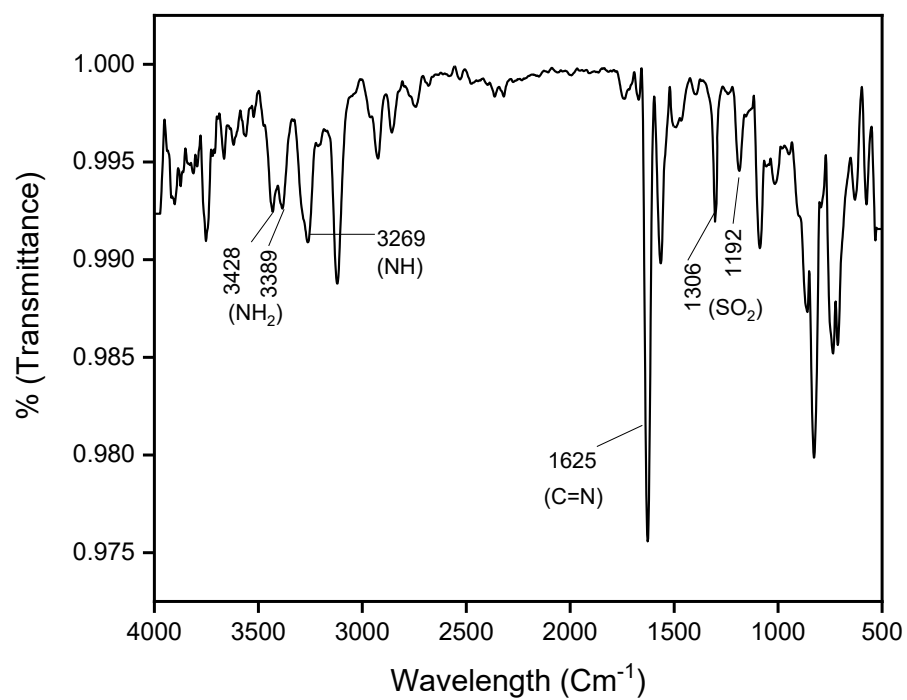
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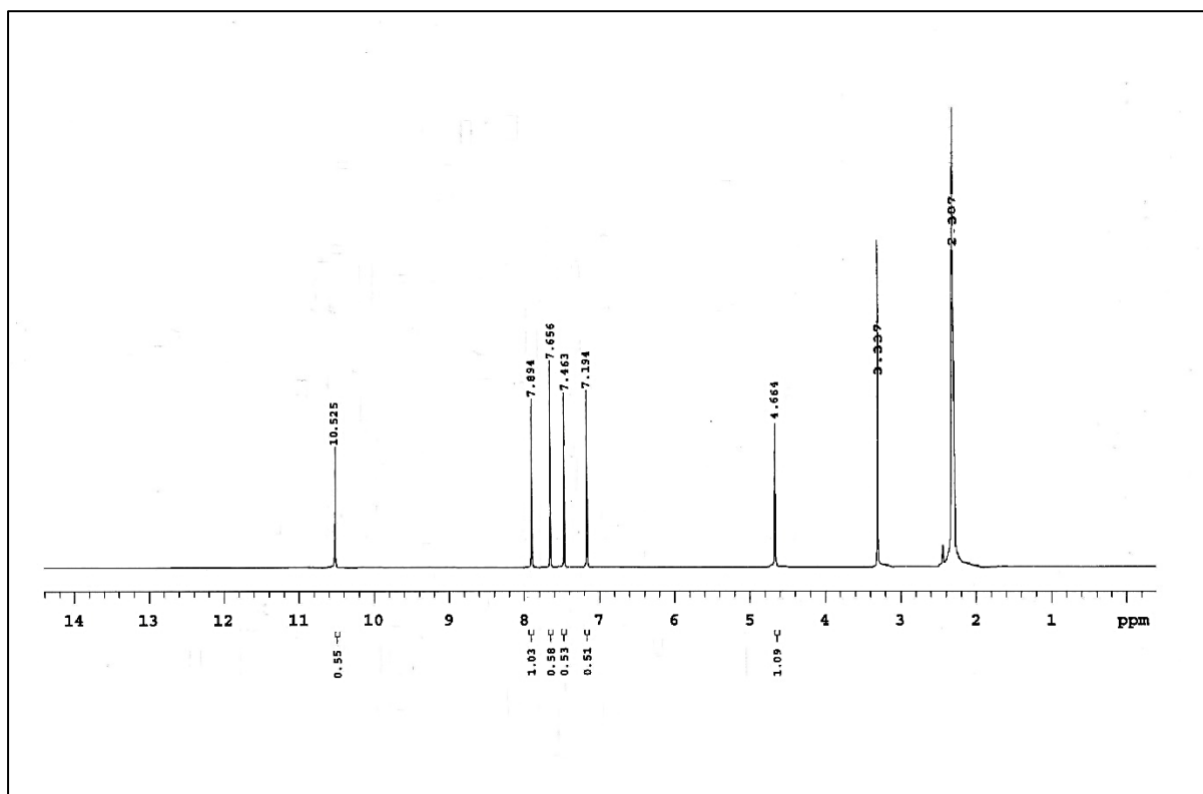
^b Gitam School of Pharmacy, GITAM University, Hyderabad, India.

^c Department of Chemistry, Sogang University, Seoul, South Korea.

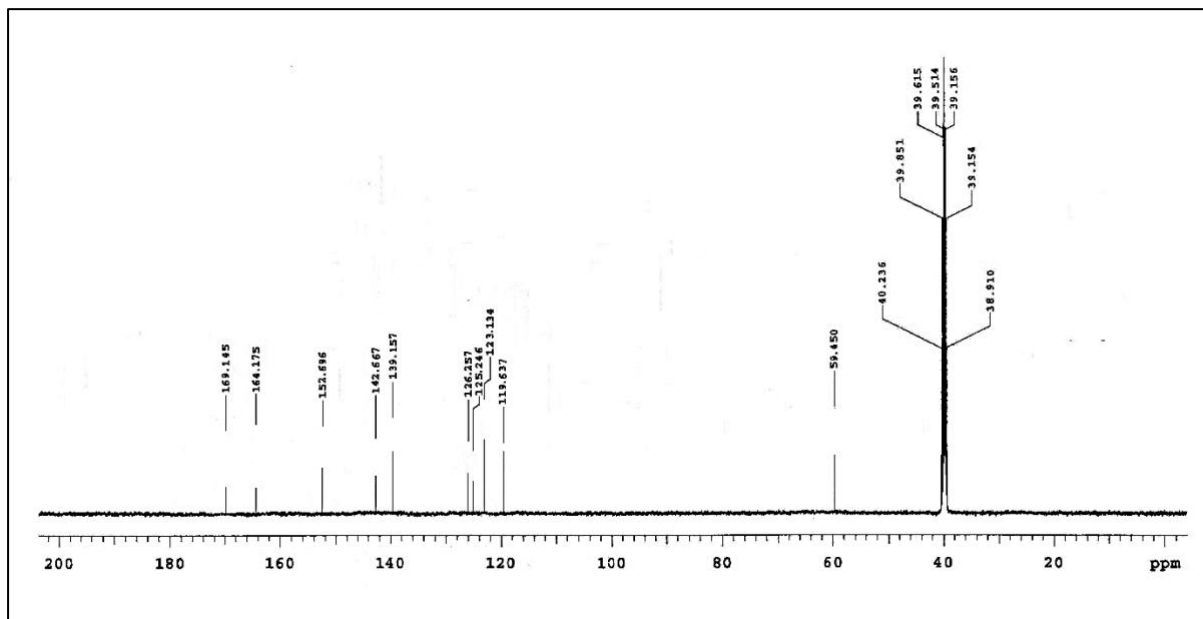
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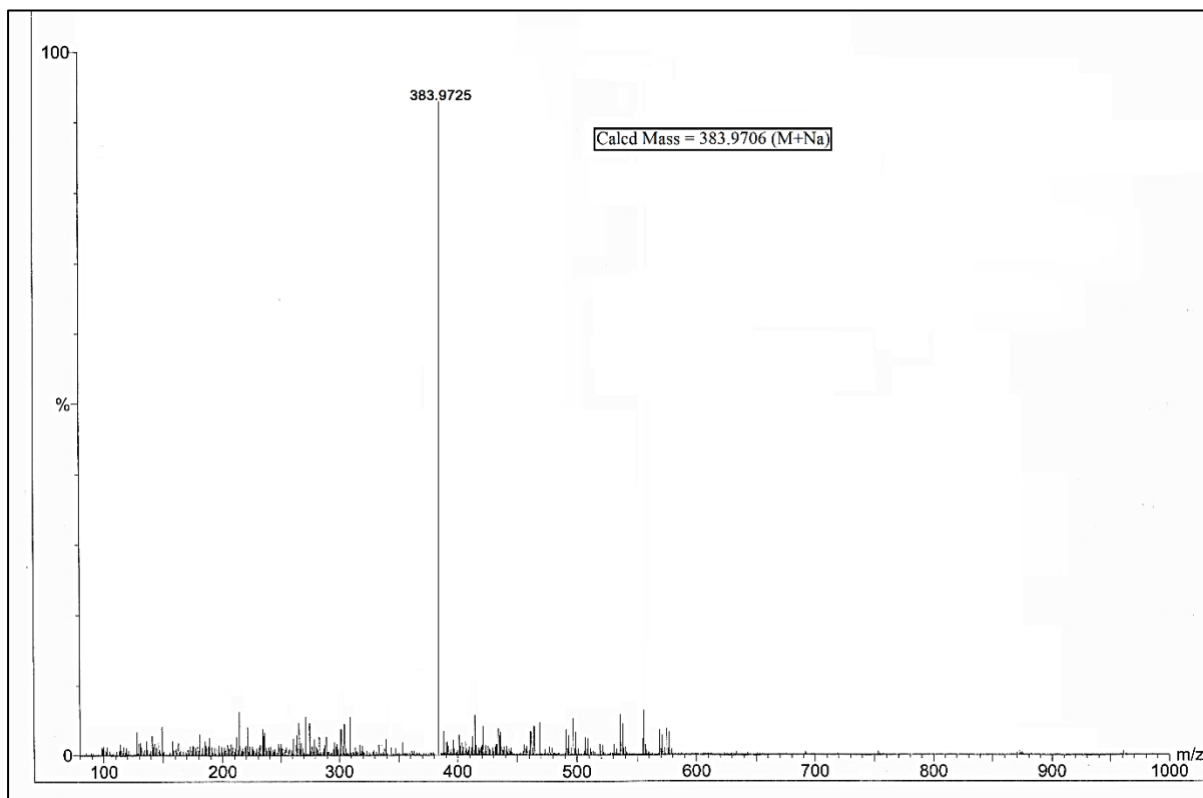
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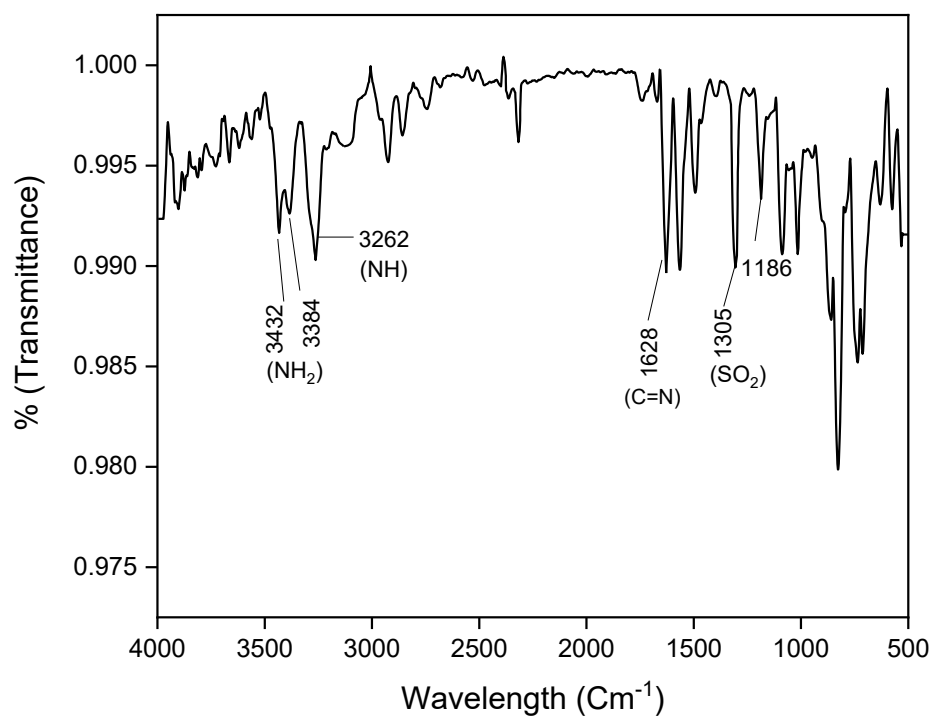
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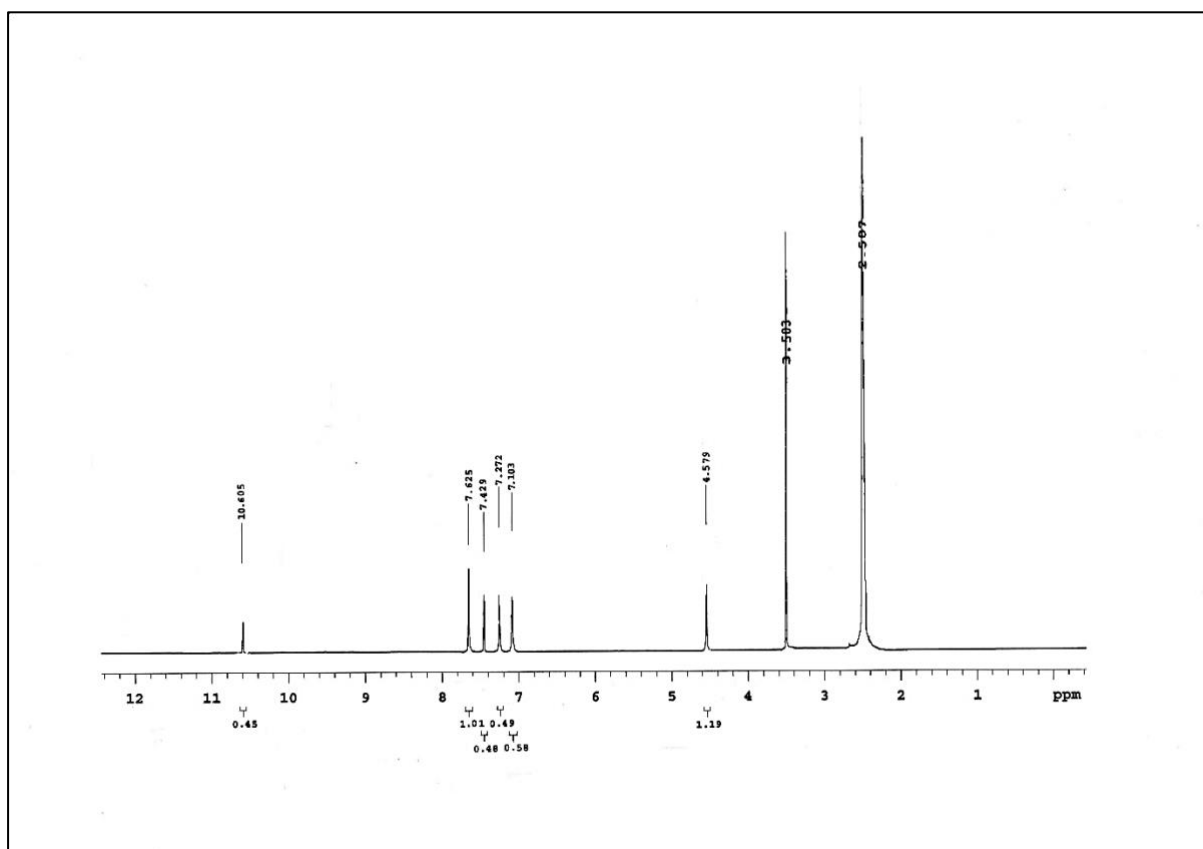
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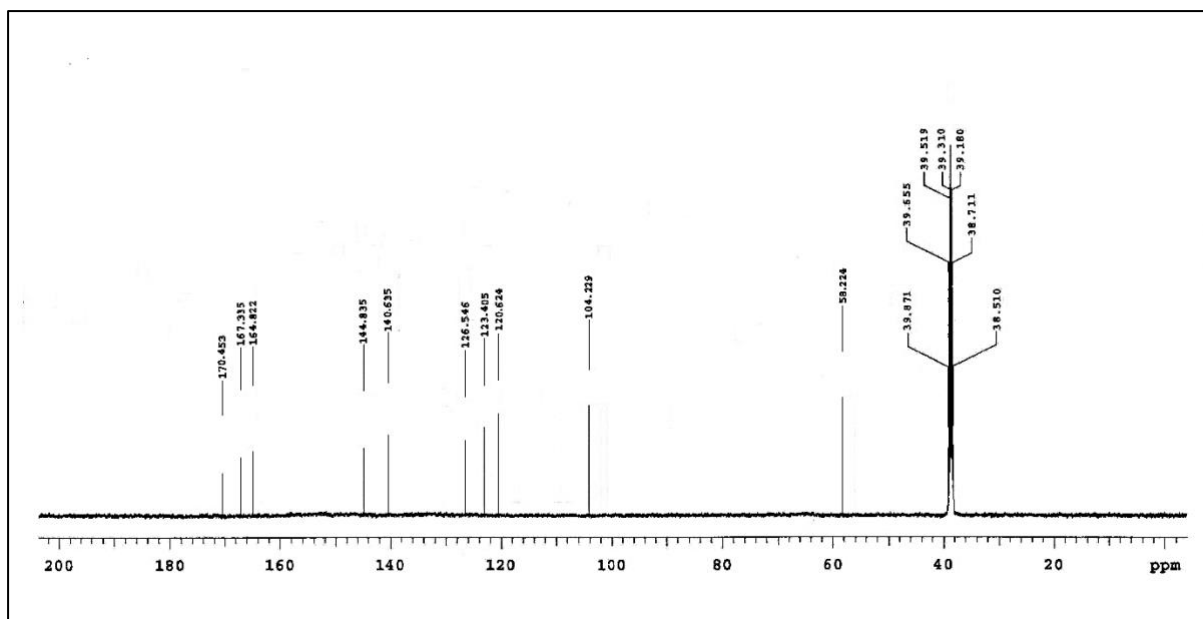
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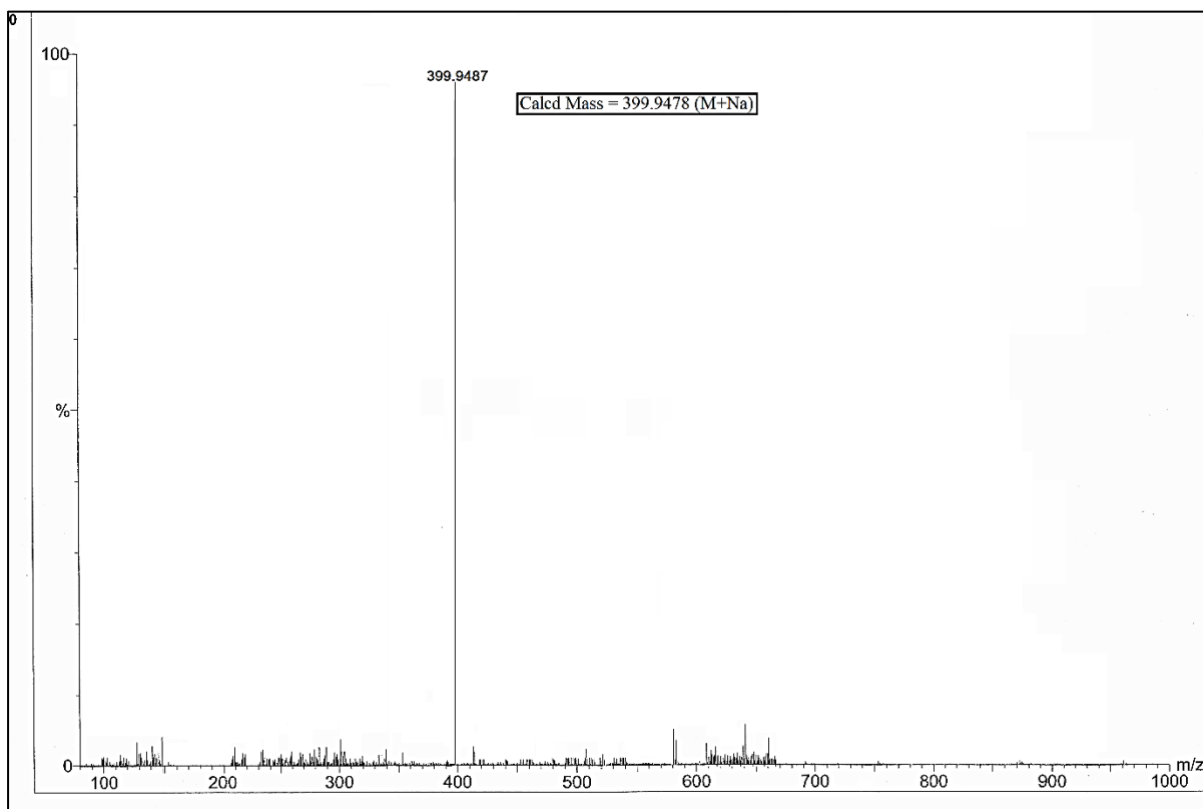
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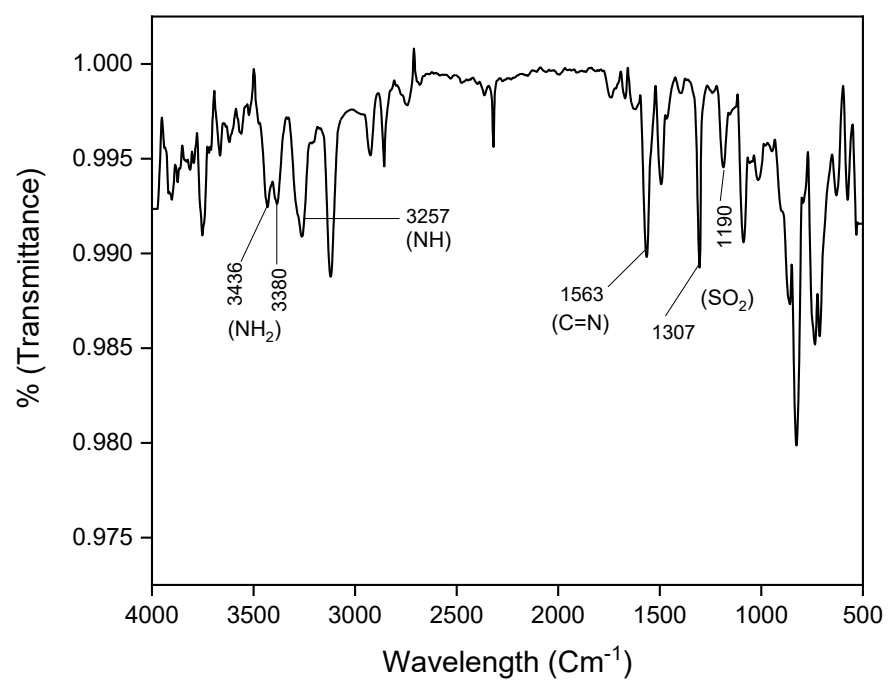
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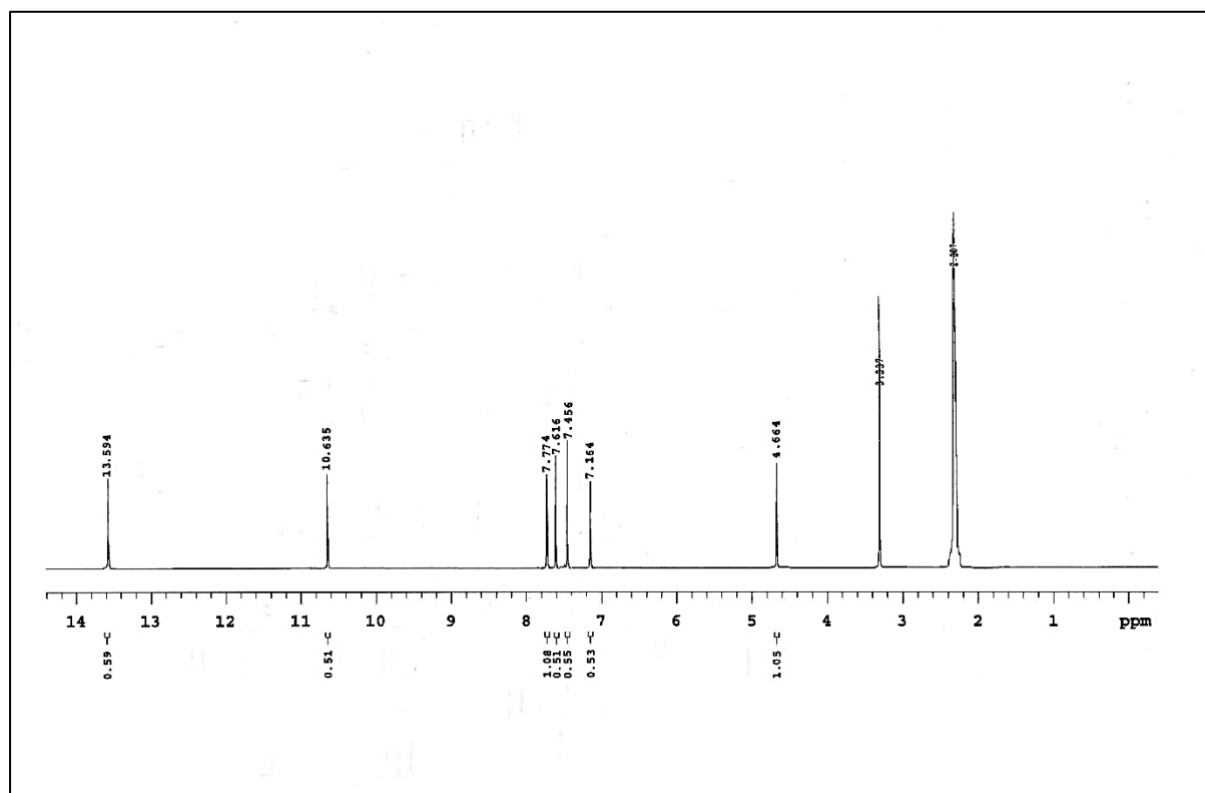
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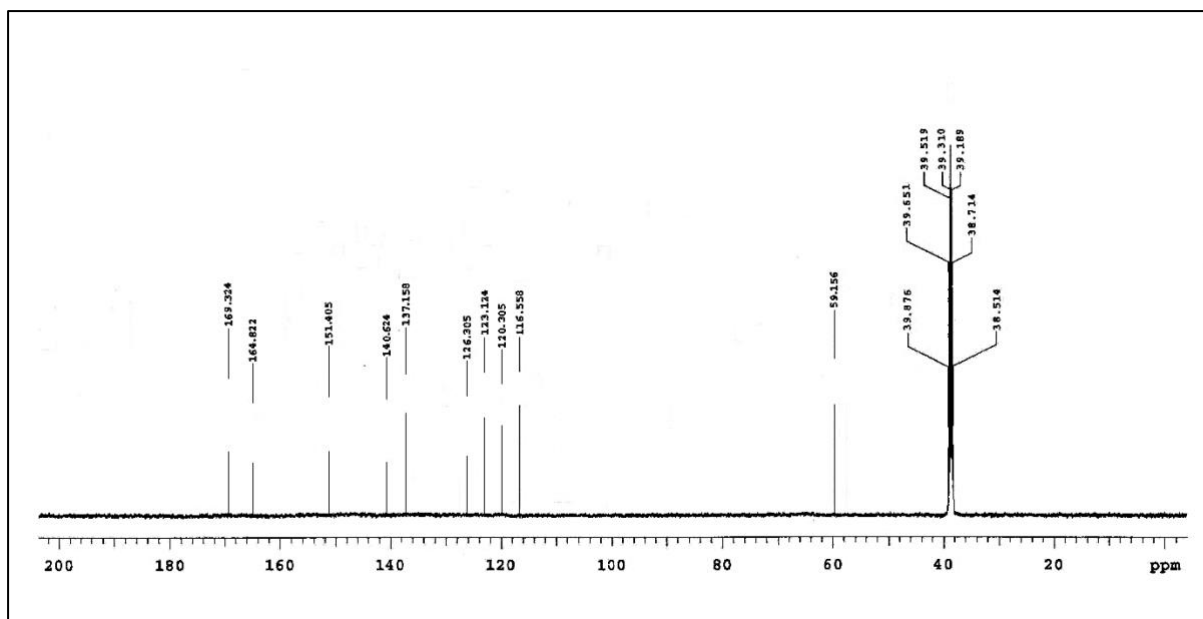
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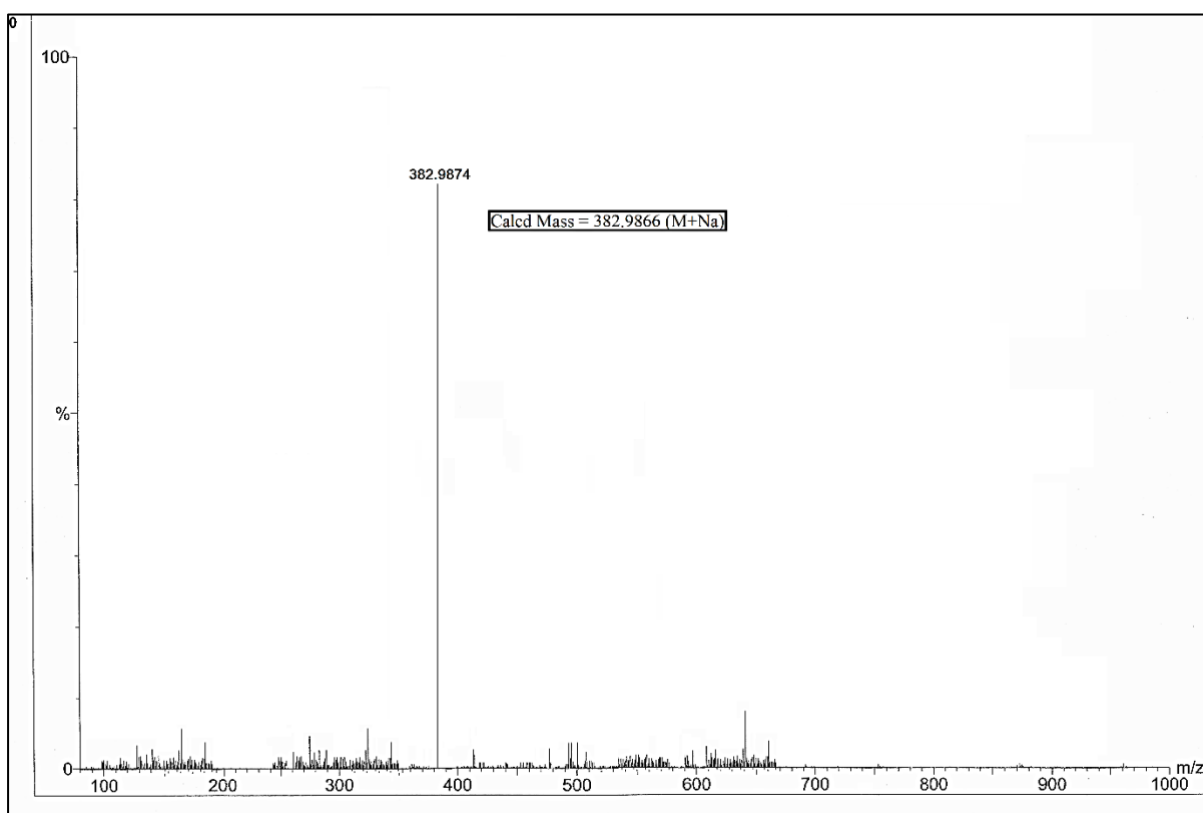
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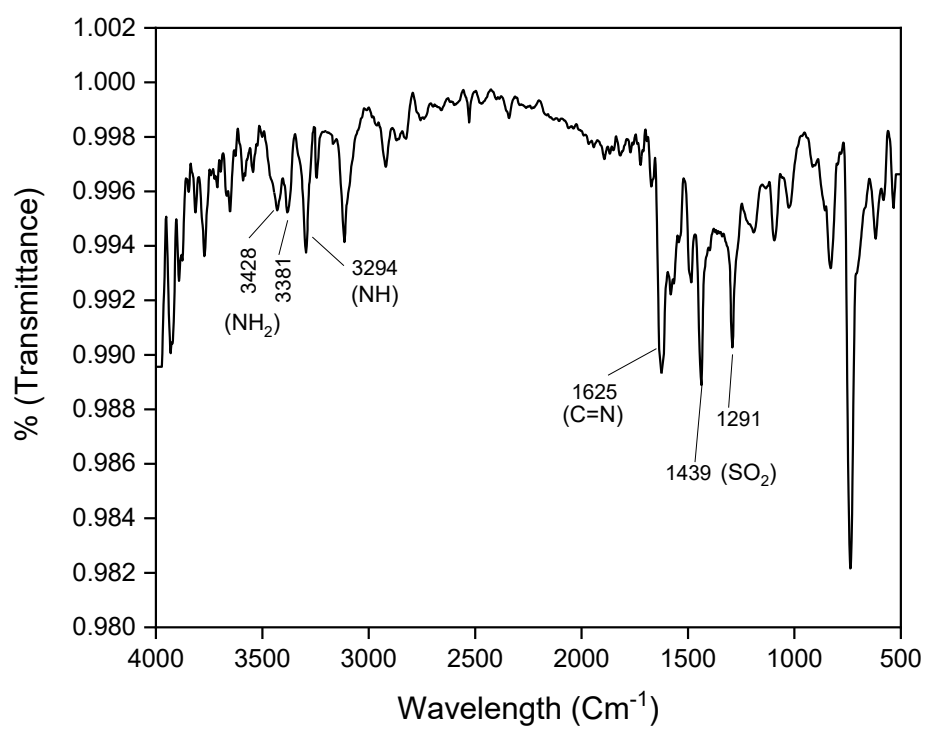
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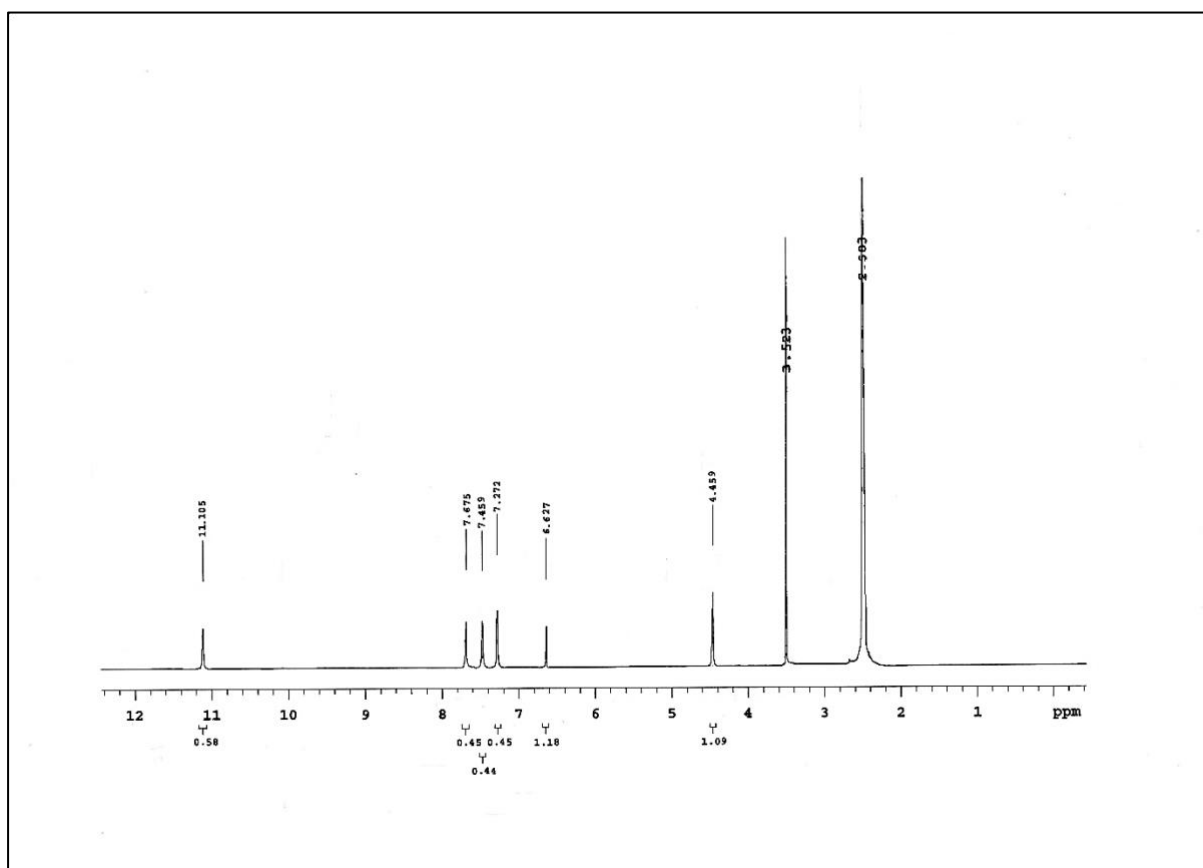
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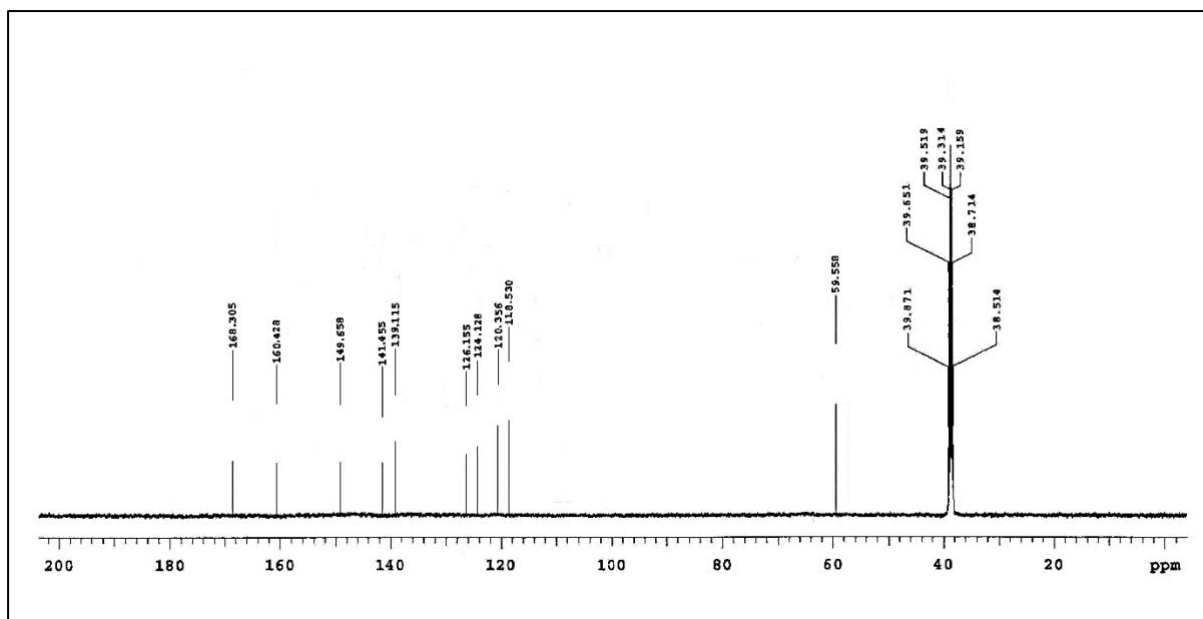
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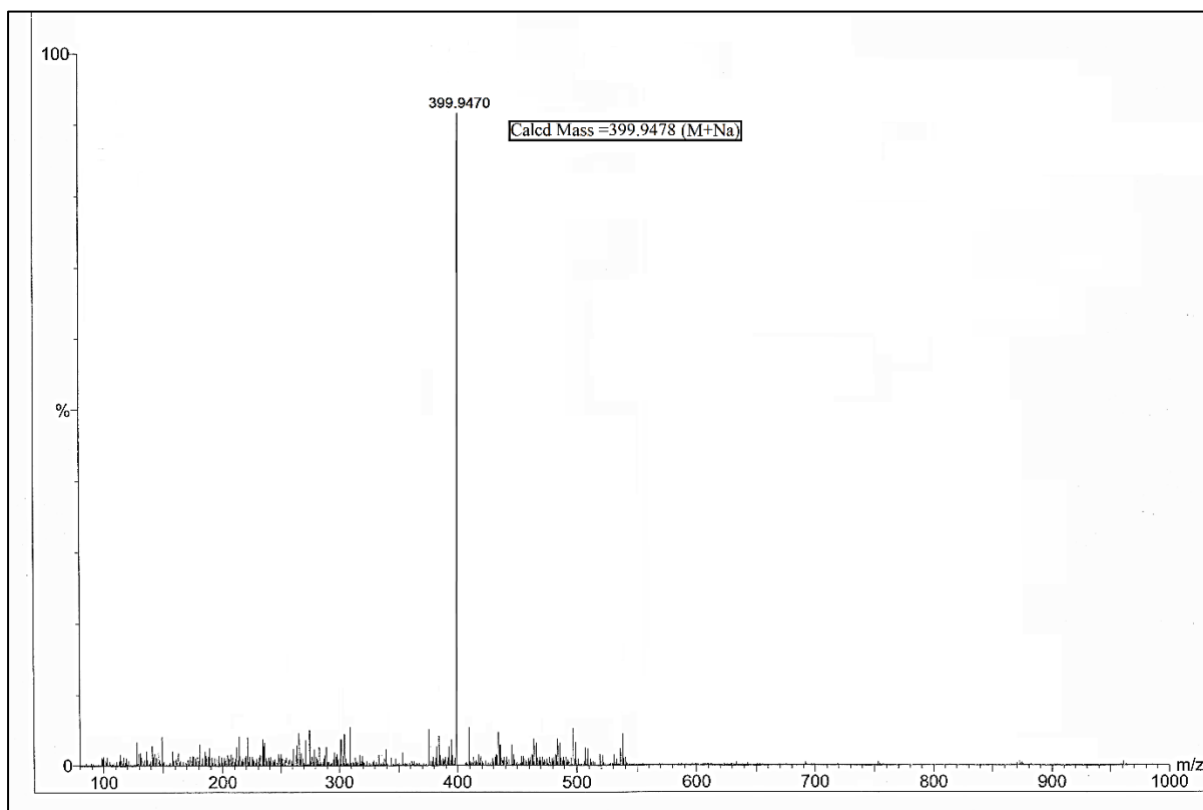
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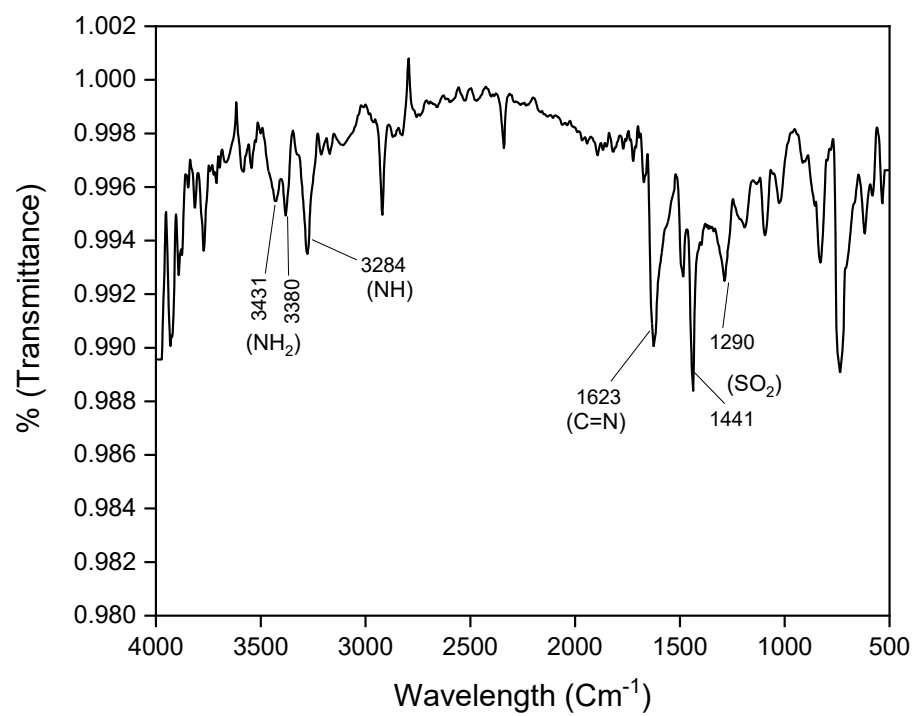
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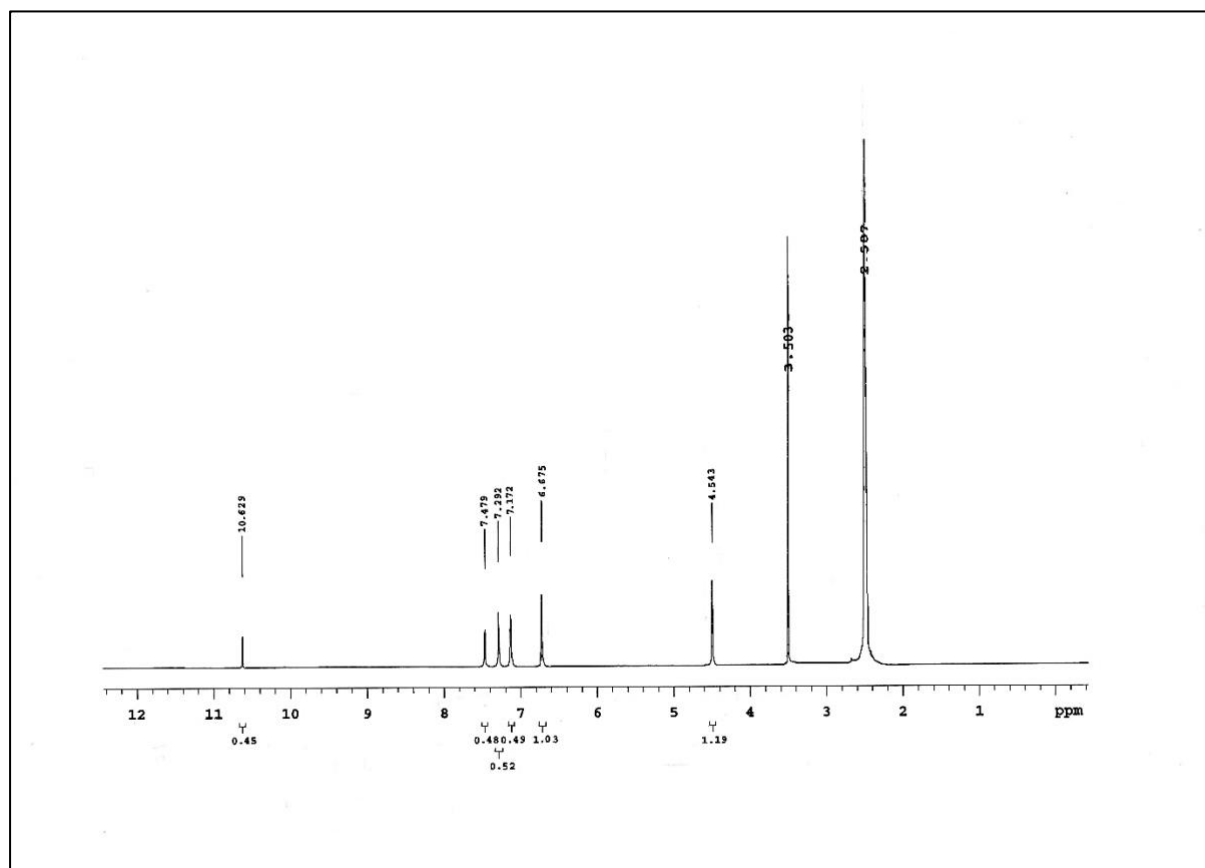
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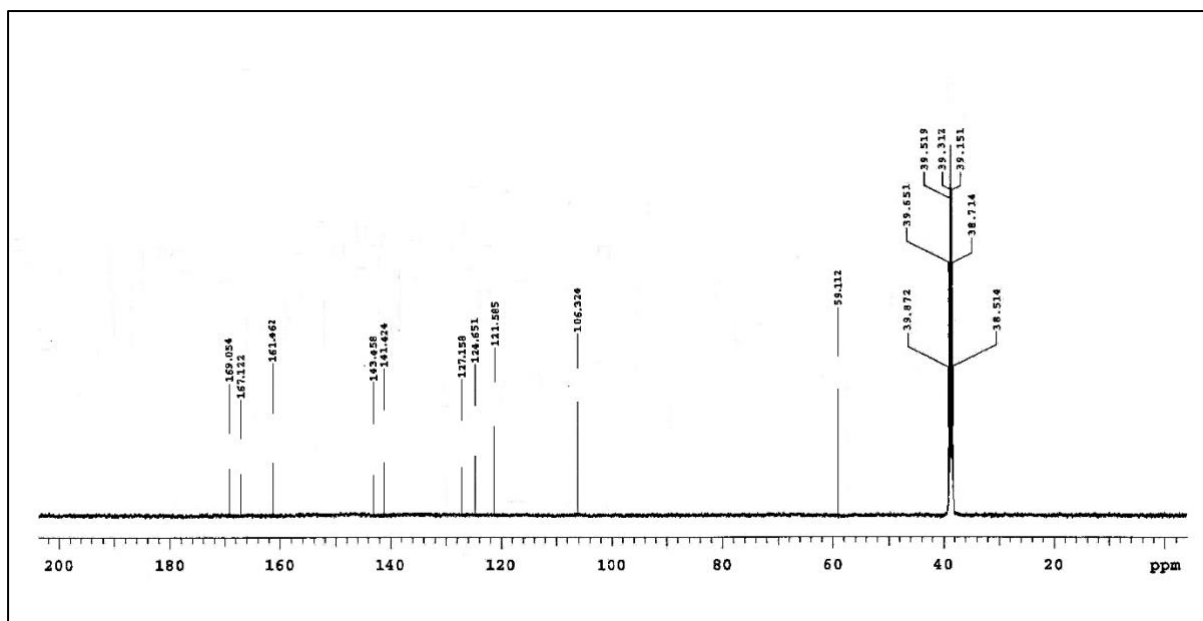
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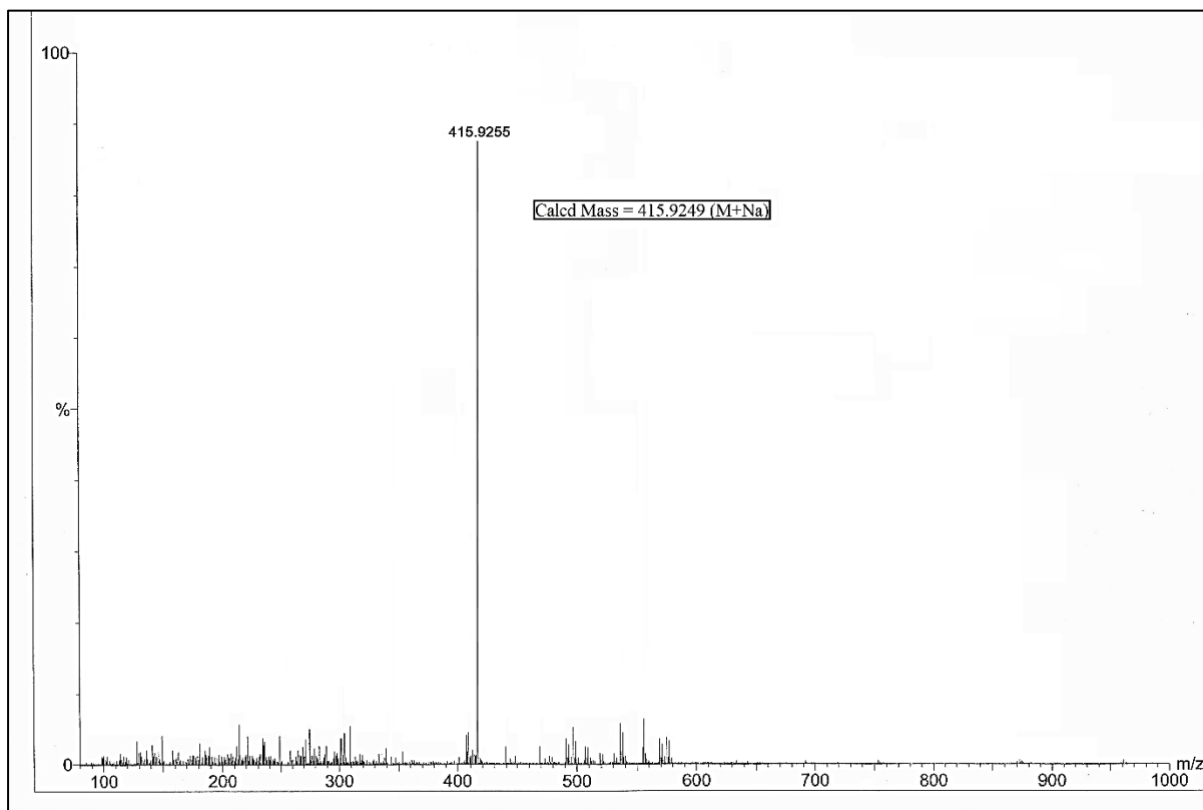
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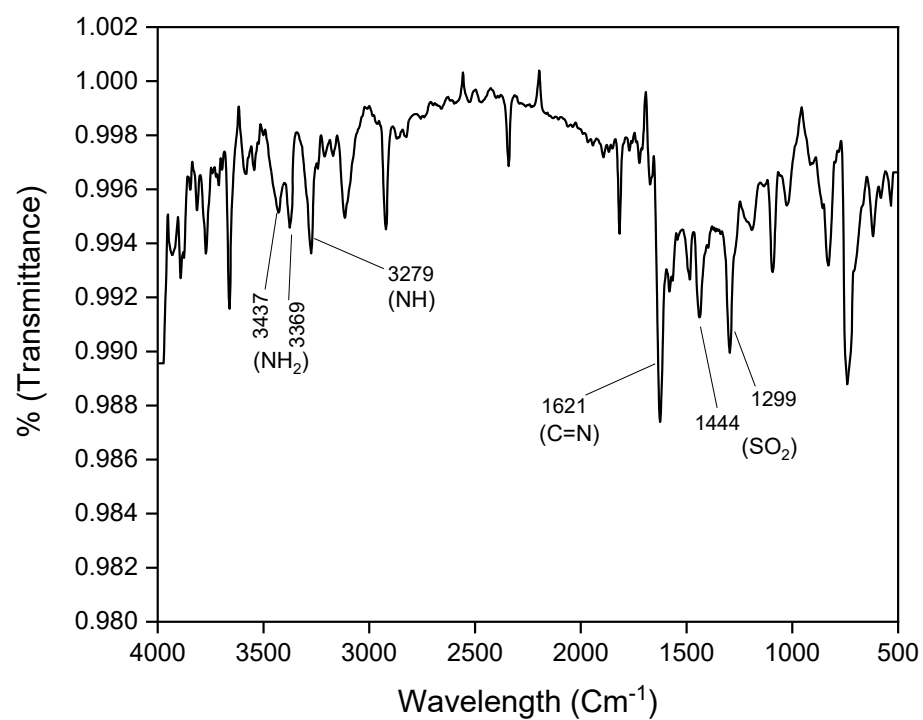
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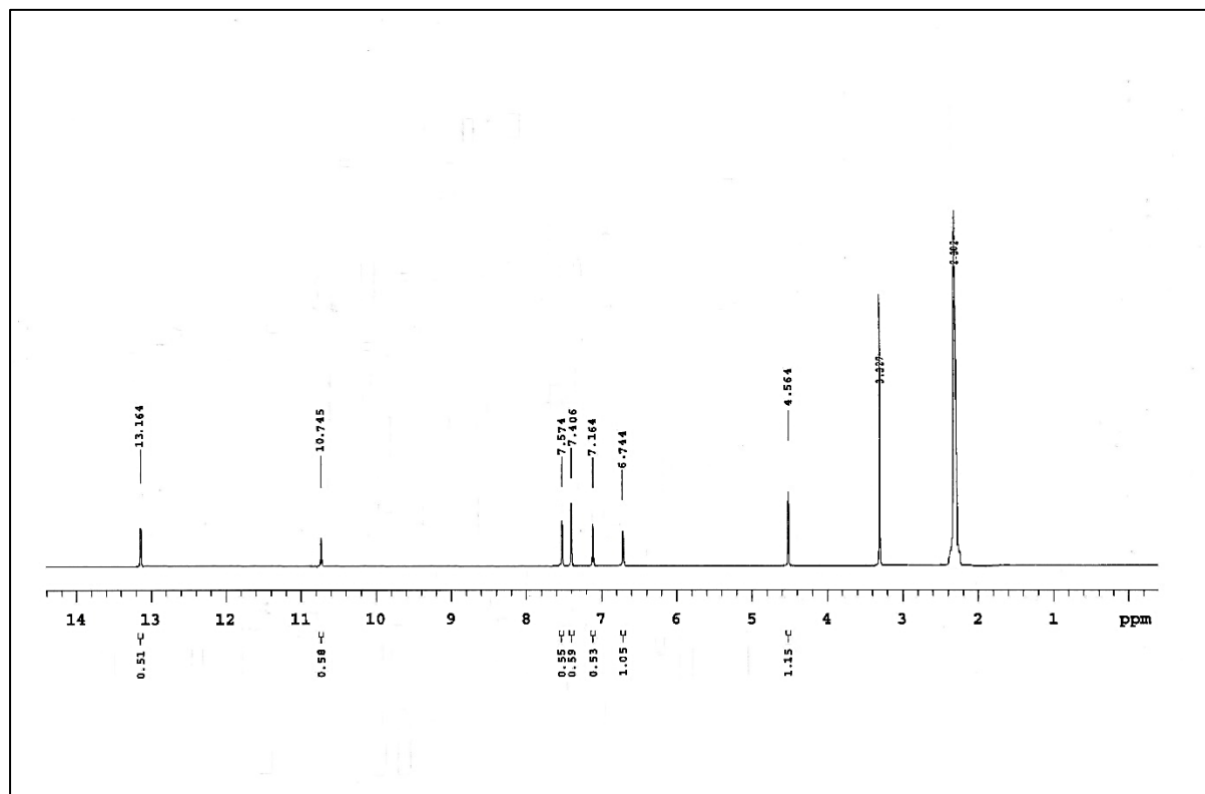
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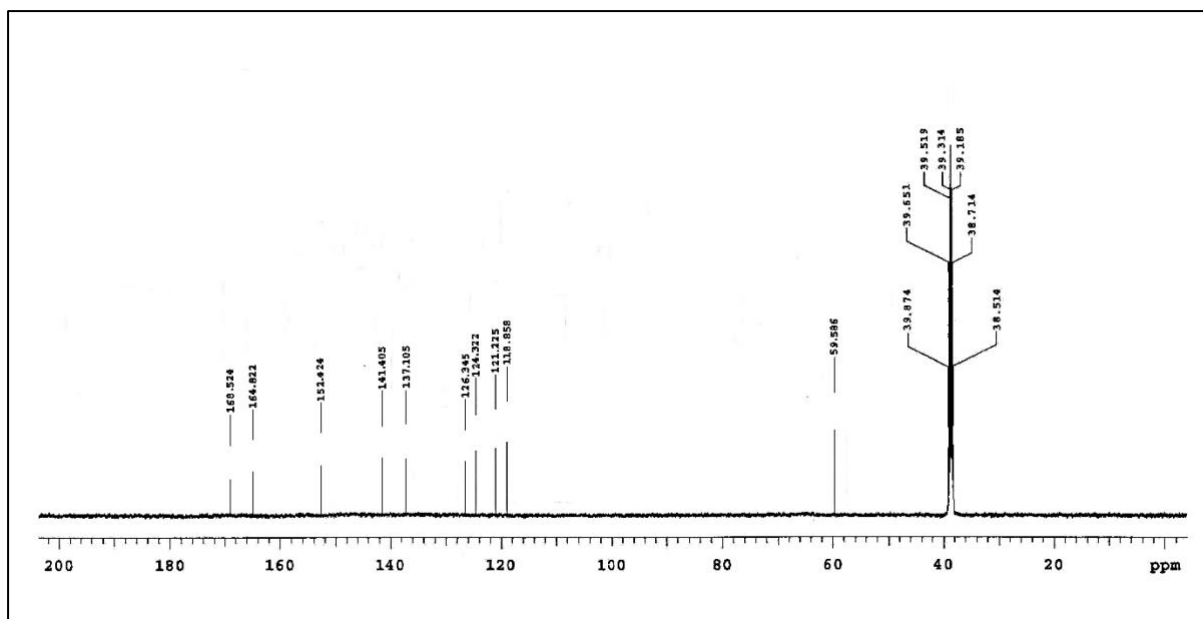
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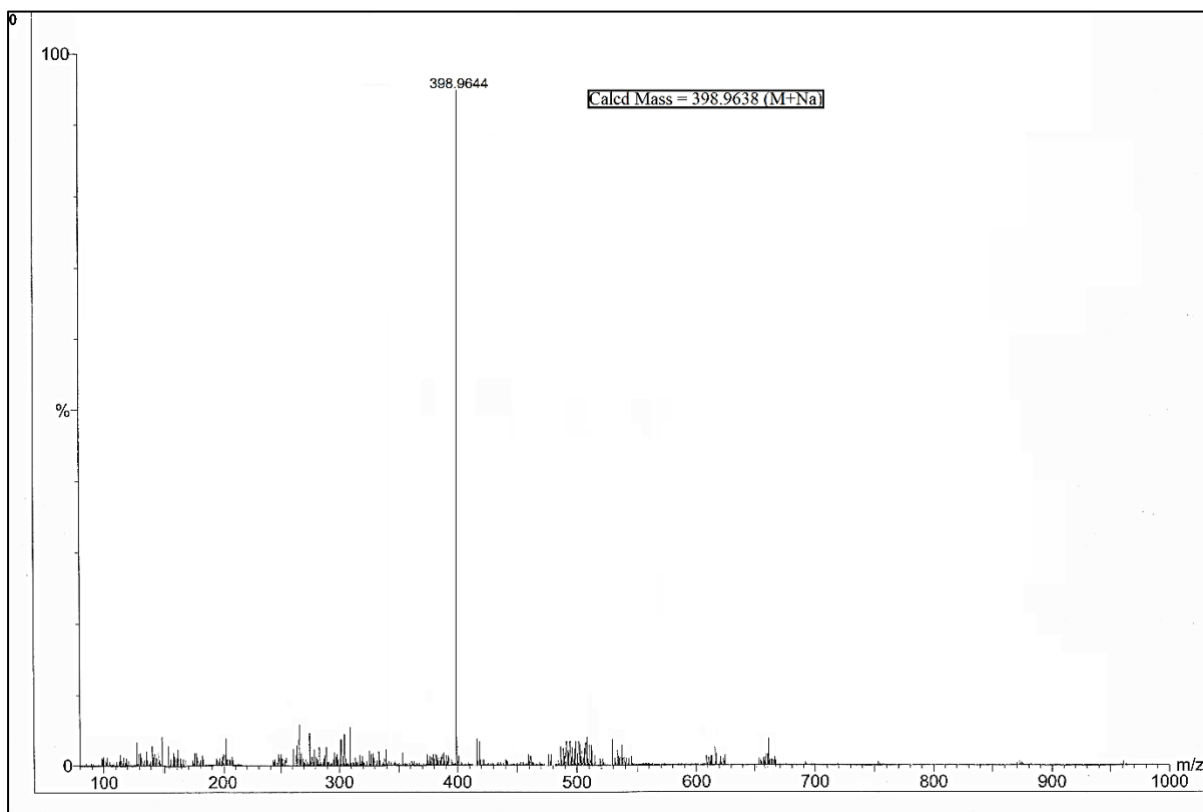
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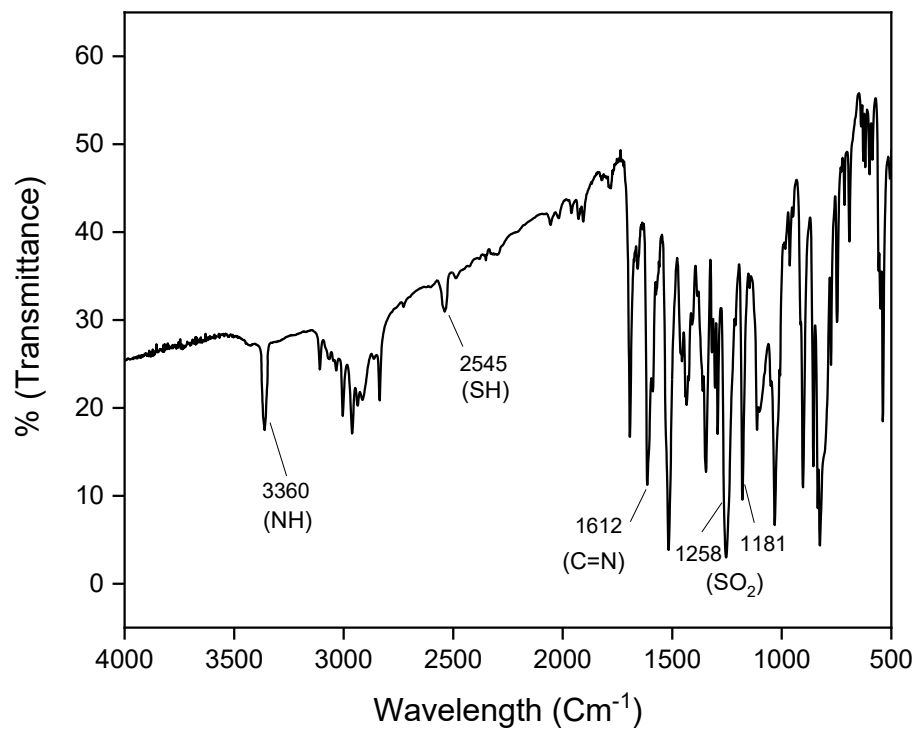
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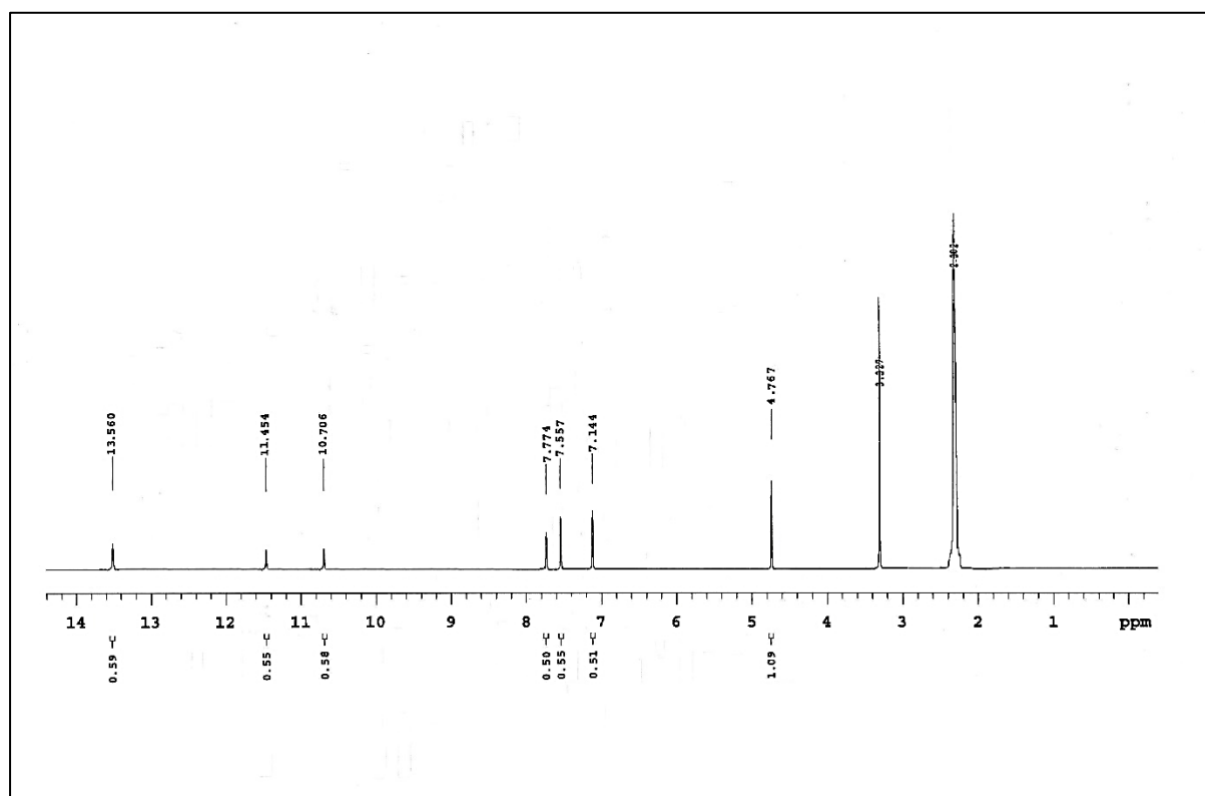
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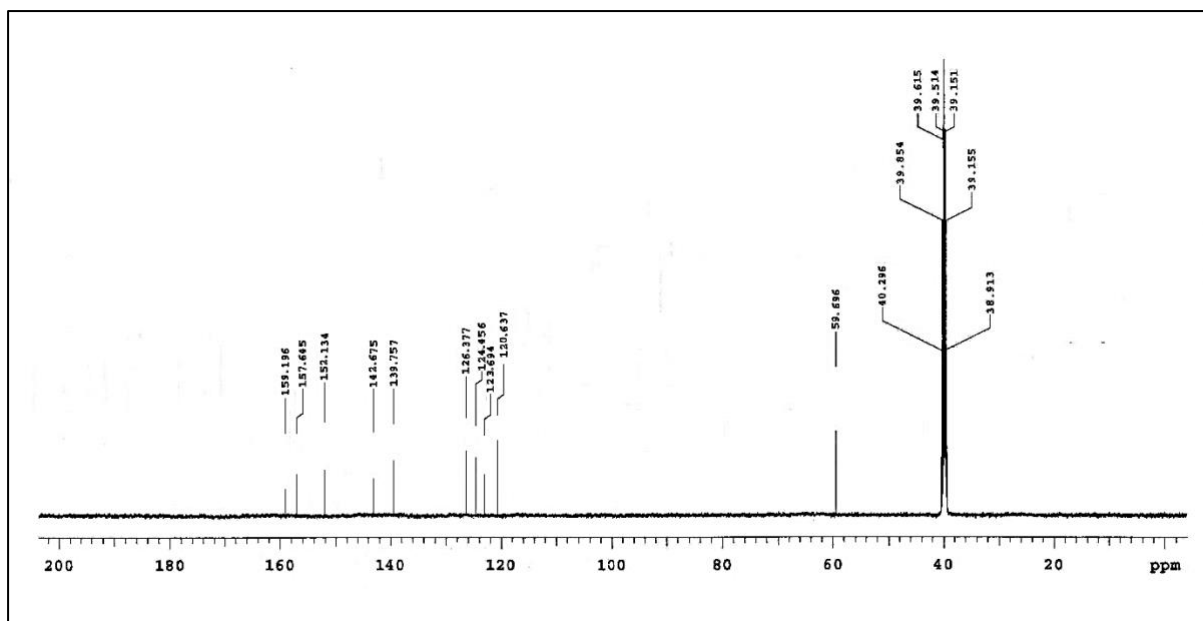
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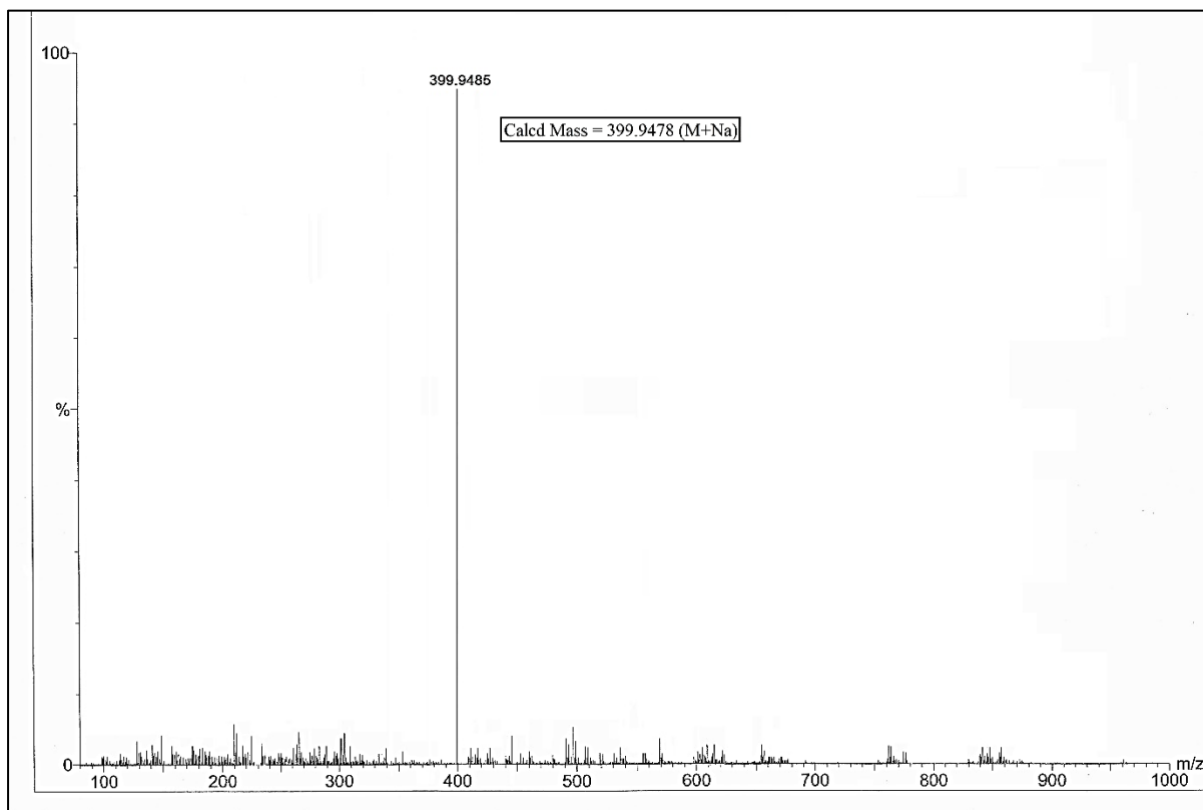
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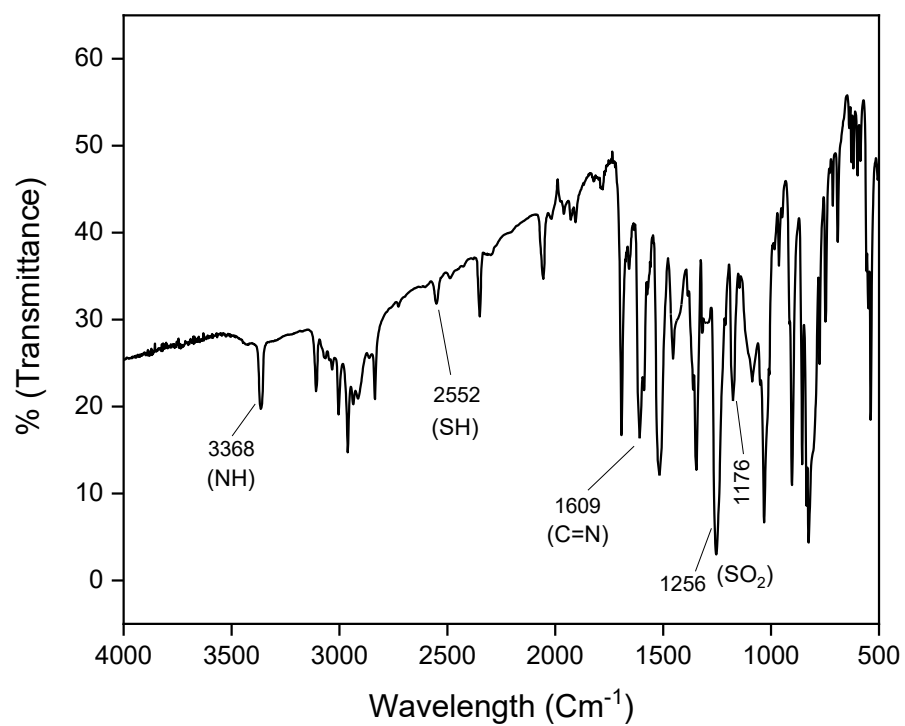
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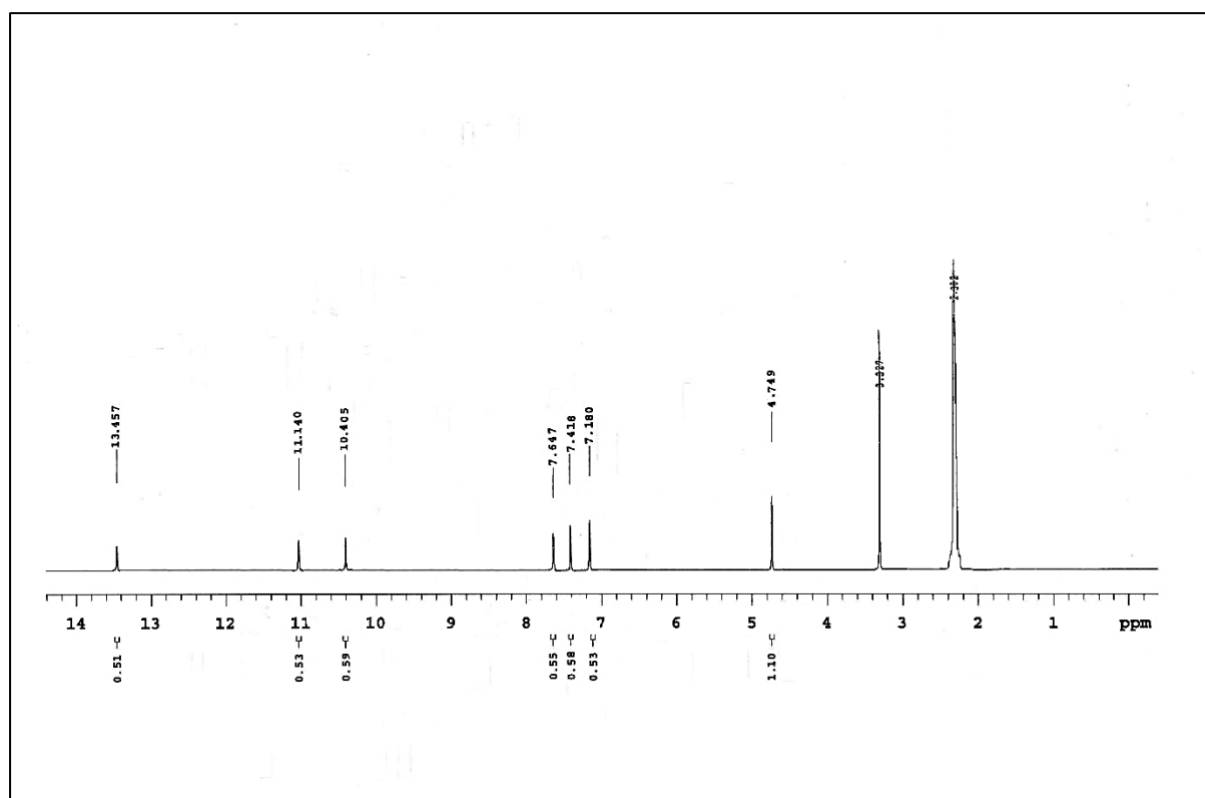
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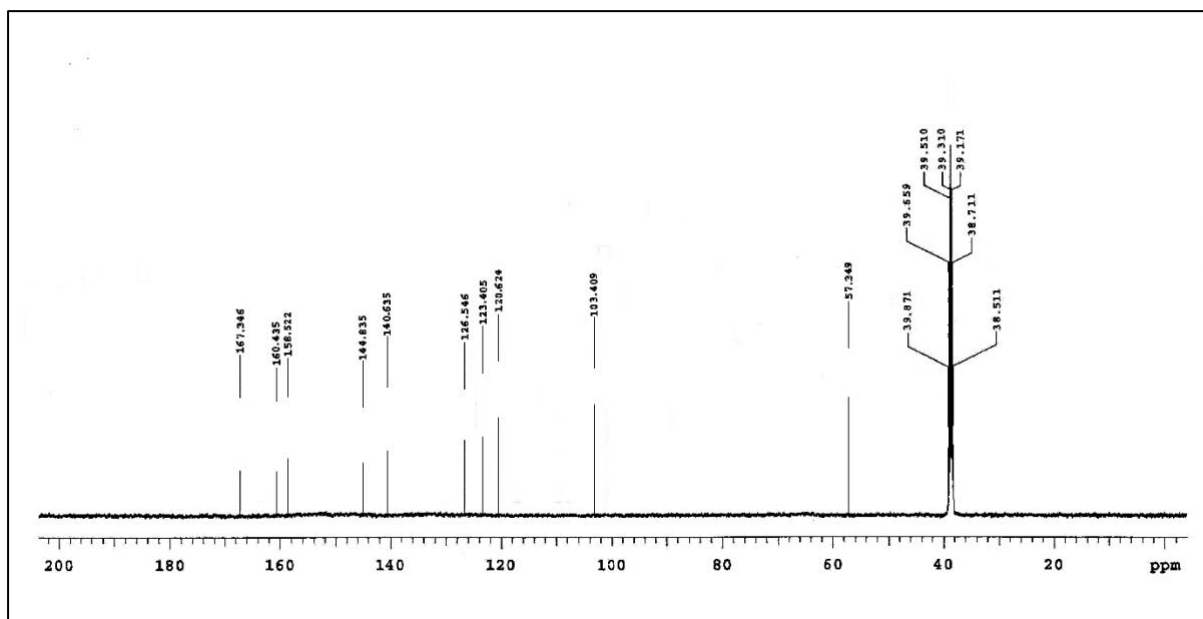
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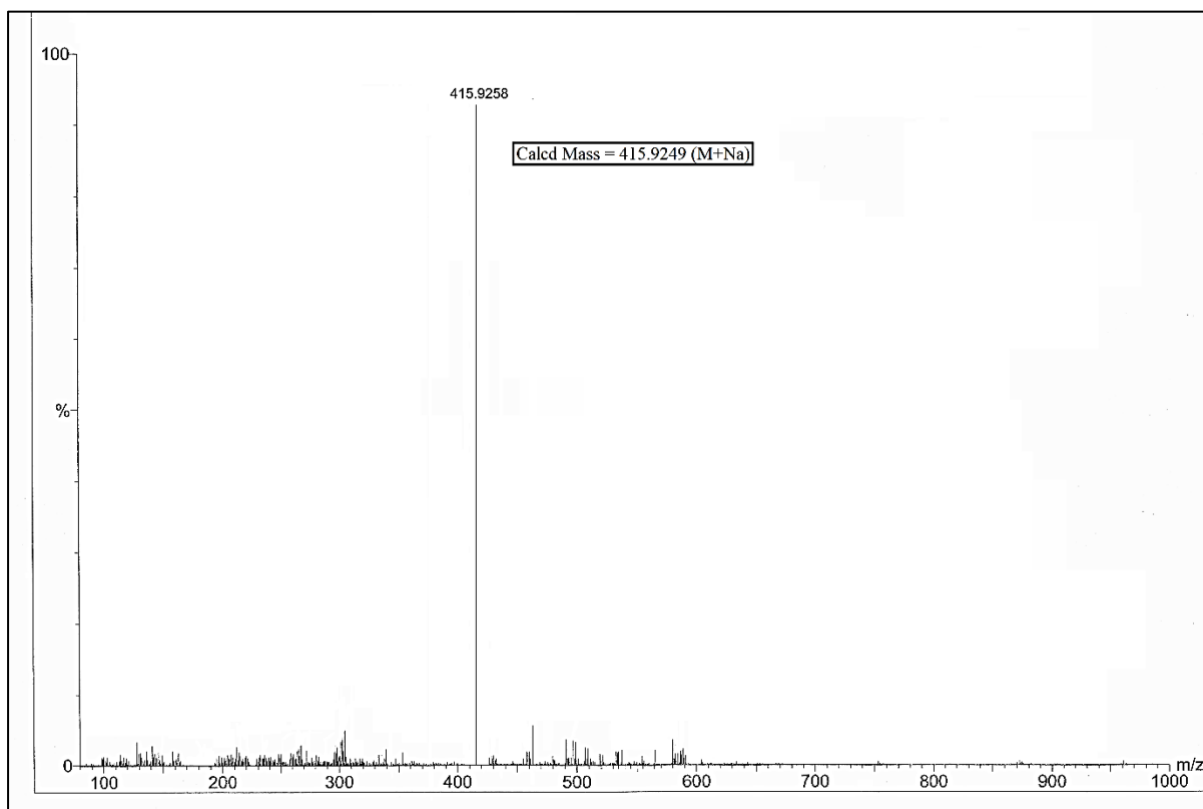
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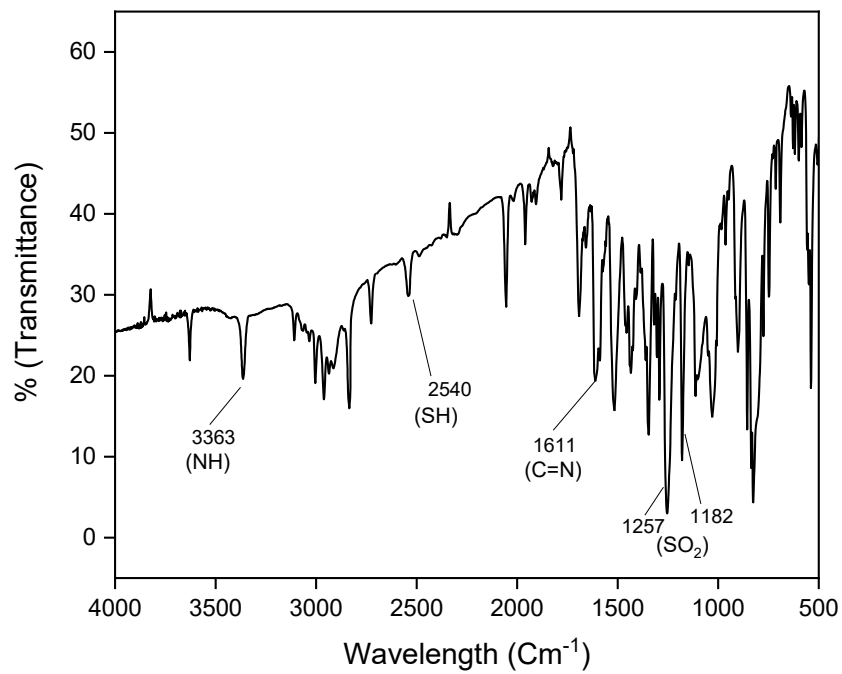
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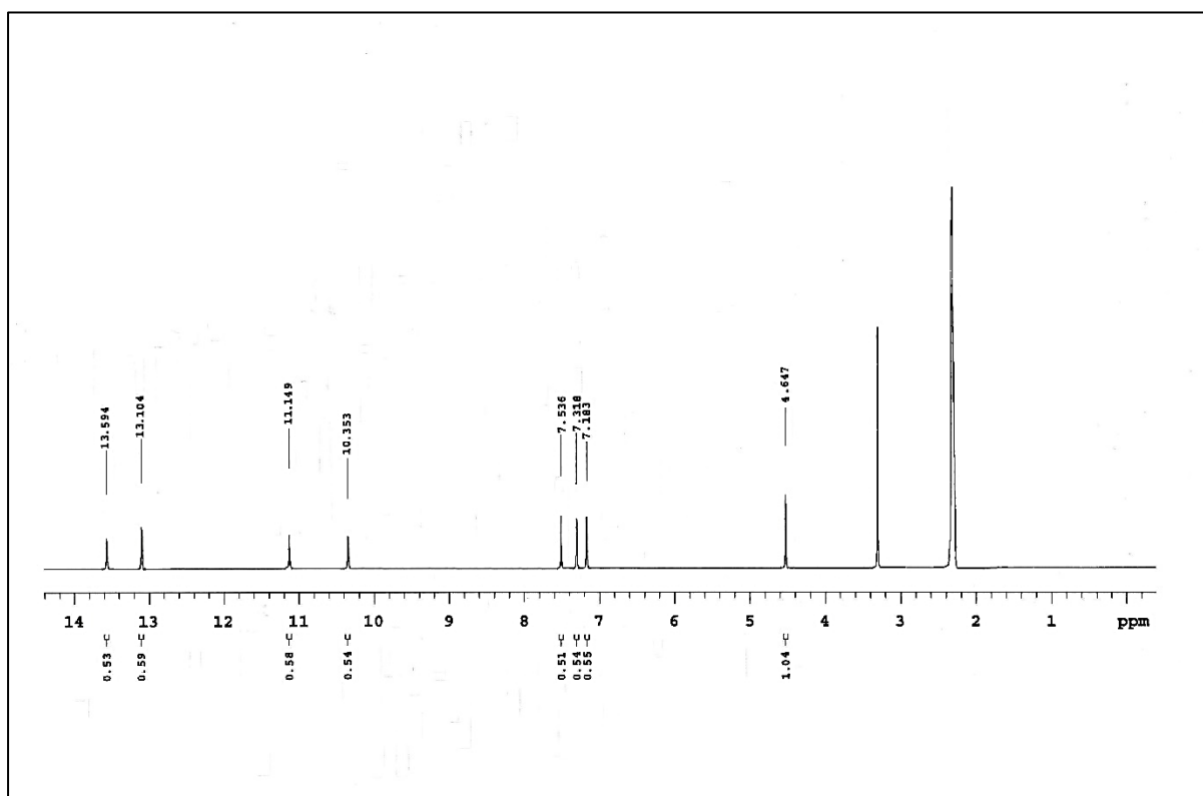
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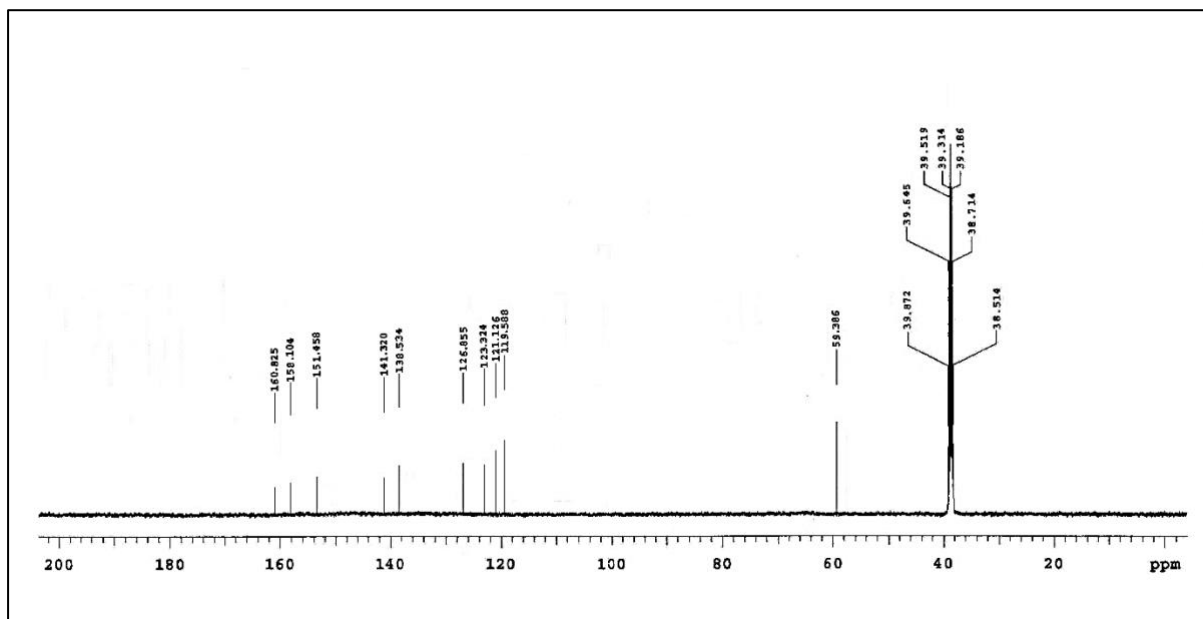
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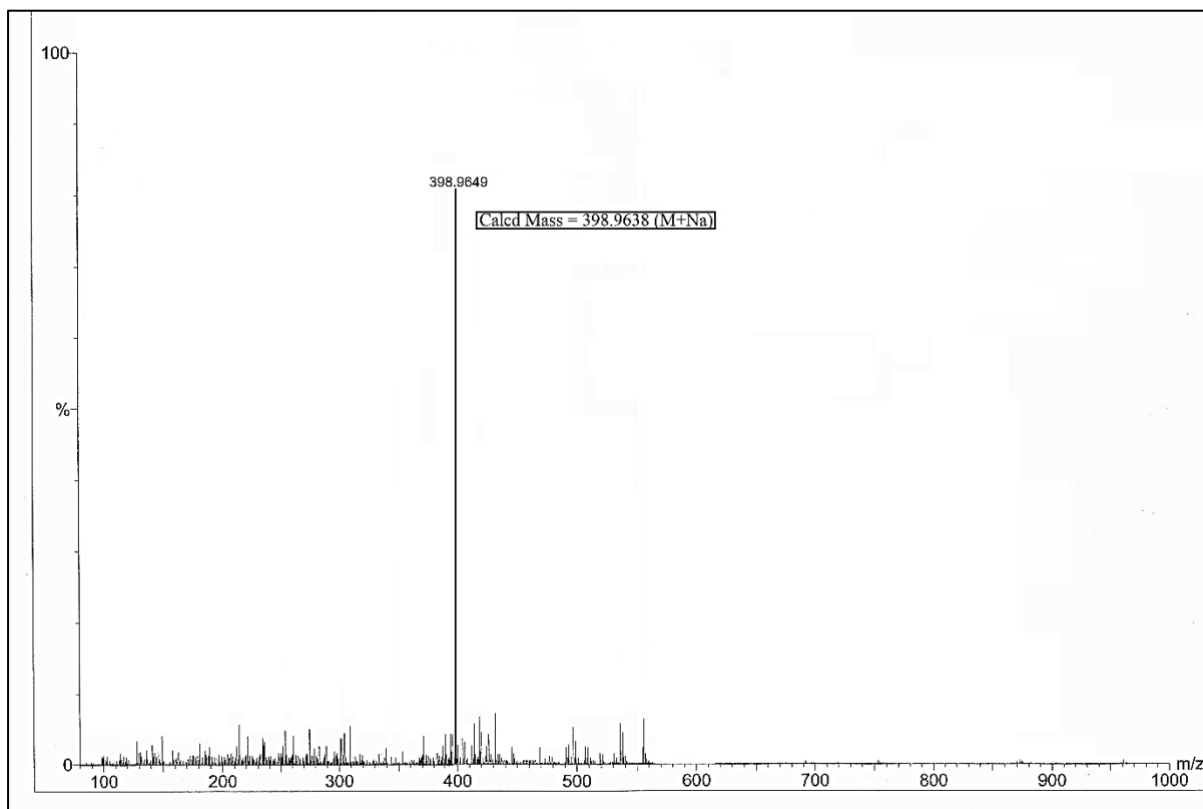
7c ¹HNMR



7c ^{13}C NMR:



7c HRMS:



1-(5-Amino-1,3,4-oxadiazol-2-yl)-N-(4-(4-chlorothiophen-2-yl)oxazol-2-yl)methanesulfonamide (4a).

White solid; *mp*: 138–140 °C; FT-IR (KBr, cm^{-1}): 3428, 3389 (NH_2), 3269 (NH), 1625 ($\text{C}=\text{N}$), 1306, 1192 (SO_2); ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 4.66 (s, 2H, CH_2), 7.19 (s, 1H, $\text{C}_5\text{-H}$), 7.46 (s, 1H, $\text{C}_3\text{-H}$), 7.65 (s, 1H, $\text{C}_5'\text{-H}$), 7.89 (s, 2H, NH_2), 10.52 (br s, 1H, NH-SO_2); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): δ 59.4 (CH_2), 119.6 (C-5), 123.1 (C-3), 125.2 (C-2), 126.2 (C-4), 139.1 (C-5'), 142.6 (C-4'), 152.6 (C-2'), 164.1 (C-5''), 169.1 (C-2''); HRMS (ESI-TOF) *m/z*: $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{10}\text{H}_8\text{ClN}_5\text{NaO}_4\text{S}_2$, 383.9725; found, 383.9725. Anal. calcd for $\text{C}_{10}\text{H}_8\text{ClN}_5\text{O}_4\text{S}_2$ (%): C, 33.20; H, 2.23; N, 19.36; found (%): C, 33.15; H, 2.26; N, 19.44.

1-(5-Amino-1,3,4-oxadiazol-2-yl)-N-(4-(4-chlorothiophen-2-yl)thiazol-2-yl)methanesulfonamide (4b).

White solid; *mp*: 144–146 °C; FT-IR (KBr, cm^{-1}): 3432, 3384 (NH_2), 3262 (NH), 1628 ($\text{C}=\text{N}$), 1305, 1186 (SO_2); ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 4.57 (s, 2H, CH_2), 7.10 (s, 1H, $\text{C}_5\text{-H}$), 7.27 (s, 1H, $\text{C}_3\text{-H}$), 7.42 (s, 1H, $\text{C}_5'\text{-H}$), 7.62 (s, 2H, NH_2), 10.60 (br s, 1H, NH-SO_2); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): δ 58.2 (CH_2), 104.2 (C-5), 120.6 (C-3), 123.4 (C-2), 126.5 (C-4), 140.6 (C-5'), 144.8 (C-4'), 164.8 (C-2'), 167.3 (C-5''), 170.4 (C-2''); HRMS (ESI-TOF) *m/z*: $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{10}\text{H}_8\text{ClN}_5\text{NaO}_3\text{S}_3$, 399.9487; found, 399.9487. Anal. calcd for $\text{C}_{10}\text{H}_8\text{ClN}_5\text{O}_3\text{S}_3$ (%): C, 31.79; H, 2.13; N, 18.54; found (%): C, 31.73; H, 2.17; N, 18.63.

1-(5-Amino-1,3,4-oxadiazol-2-yl)-N-(4-(4-chlorothiophen-2-yl)-1*H*-imidazol-2-yl)methanesulfonamide (4c).

White solid; *mp*: 162–164 °C; FT-IR (KBr, cm^{-1}): 3436, 3380 (NH_2), 3257 (NH), 1563 ($\text{C}=\text{N}$), 1307, 1190 (SO_2); ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 4.66 (s, 2H, CH_2), 7.16 (s, 1H, $\text{C}_5\text{-H}$), 7.45 (s, 1H, $\text{C}_3\text{-H}$), 7.61 (s, 1H, $\text{C}_5'\text{-H}$), 7.77 (s, 2H, NH_2), 10.63 (br s, 1H, NH-SO_2), 13.59 (br s, 1H, NH-imidazole); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): δ 59.1 (CH_2), 116.5 (C-5), 120.3 (C-3), 123.1 (C-2), 126.3 (C-4), 137.1 (C-5'), 140.6 (C-4'), 151.4 (C-2'), 164.8 (C-5''), 169.3 (C-2''); HRMS (ESI-TOF) *m/z*: $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{10}\text{H}_9\text{ClN}_6\text{NaO}_3\text{S}_2$, 382.9874; found, 382.9874. Anal. calcd for $\text{C}_{10}\text{H}_9\text{ClN}_6\text{O}_3\text{S}_2$ (%): C, 33.29; H, 2.51; N, 23.29; found (%): C, 33.36; H, 2.55; N, 23.40.

1-(5-Amino-1,3,4-thiadiazol-2-yl)-N-(4-(4-chlorothiophen-2-yl)oxazol-2-yl)methanesulfonamide (5a).

White solid; *mp*: 146–148 °C; FT-IR (KBr, cm^{-1}): 3428, 3381 (NH_2), 3294 (NH), 1625 ($\text{C}=\text{N}$), 1439, 1291 (SO_2); ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 4.45 (s, 2H, CH_2), 6.62 (s, 1H, $\text{C}_5\text{-H}$), 7.27 (s, 1H, $\text{C}_3\text{-H}$), 7.45 (s, 1H, $\text{C}_5'\text{-H}$), 7.67 (s, 2H, NH_2), 11.10 (br s, 1H, NH-SO_2); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): δ 59.5 (CH_2), 118.5 (C-5), 120.3 (C-3), 124.1 (C-2), 126.1 (C-4), 139.1 (C-5'), 141.4 (C-4'), 149.6 (C-2'), 160.4 (C-5''), 168.3 (C-2''); HRMS (ESI-TOF) *m/z*: $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{10}\text{H}_8\text{ClN}_5\text{NaO}_3\text{S}_3$, 399.9470; found, 399.9470. Anal. calcd for $\text{C}_{10}\text{H}_8\text{ClN}_5\text{O}_3\text{S}_3$ (%): C, 31.79; H, 2.13; N, 18.54; found (%): C, 31.71; H, 2.09; N, 18.62.

1-(5-Amino-1,3,4-thiadiazol-2-yl)-N-(4-(4-chlorothiophen-2-yl)thiazol-2-yl)methanesulfonamide (5b).

White solid; *mp*: 155–157 °C; FT-IR (KBr, cm^{-1}): 3431, 3380 (NH_2), 3284 (NH), 1623 ($\text{C}=\text{N}$), 1441, 1290 (SO_2); ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 4.54 (s, 2H, CH_2), 6.67 (s, 1H, $\text{C}_5\text{-H}$), 7.17 (s, 1H, $\text{C}_3\text{-H}$), 7.29 (s, 1H, $\text{C}_5'\text{-H}$), 7.47 (s, 2H, NH_2), 10.62 (br s, 1H, NH-SO_2); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): δ 59.1 (CH_2), 106.3 (C-5), 121.5 (C-3), 124.6 (C-2), 127.1 (C-4), 141.4 (C-5'), 143.4 (C-4'), 161.4 (C-2'), 167.1 (C-5''), 169.0 (C-2''); HRMS (ESI-TOF) *m/z*: $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{10}\text{H}_8\text{ClN}_5\text{NaO}_2\text{S}_4$, 415.9255; found, 415.9255. Anal. calcd for $\text{C}_{10}\text{H}_8\text{ClN}_5\text{O}_2\text{S}_4$ (%): C, 30.49; H, 2.05; N, 17.78; found (%): C, 30.56; H, 2.08; N, 17.86.

1-(5-Amino-1,3,4-thiadiazol-2-yl)-N-(4-(4-chlorothiophen-2-yl)-1H-imidazol-2-yl)methanesulfonamide (5c).

White solid; *mp*: 171–173 °C; FT-IR (KBr, cm^{-1}): 3437, 3369 (NH_2), 3279 (NH), 1621 ($\text{C}=\text{N}$), 1444, 1299 (SO_2); ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 4.56 (s, 2H, CH_2), 6.74 (s, 1H, $\text{C}_5\text{-H}$), 7.16 (s, 1H, $\text{C}_3\text{-H}$), 7.40 (s, 1H, $\text{C}_5'\text{-H}$), 7.57 (s, 2H, NH_2), 10.74 (br s, 1H, NH-SO_2), 13.16 (br s, 1H, NH-imidazole); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): δ 59.5 (CH_2), 118.8 (C-5), 121.2 (C-3), 124.3 (C-2), 126.3 (C-4), 137.1 (C-5'), 141.4 (C-4'), 152.4 (C-2'), 164.8 (C-5''), 168.5 (C-2''); HRMS (ESI-TOF) *m/z*: $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{10}\text{H}_9\text{ClN}_6\text{NaO}_2\text{S}_3$, 398.9644; found, 398.9644. Anal. calcd for $\text{C}_{10}\text{H}_9\text{ClN}_6\text{O}_2\text{S}_3$ (%): C, 31.87; H, 2.41; N, 22.30; found (%): C, 31.81; H, 2.44; N, 22.42.

N-(4-(4-Chlorothiophen-2-yl)oxazol-2-yl)-1-(5-mercapto-4H-1,2,4-triazol-3-yl)methanesulfonamide (7a).

White solid; *mp*: 163–165 °C; FT-IR (KBr, cm^{-1}): 3360 (NH), 2545 (SH), 1612 ($\text{C}=\text{N}$), 1258, 1181 (SO_2); ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 4.76 (s, 2H, CH_2), 7.14 (s, 1H, $\text{C}_5\text{-H}$), 7.55 (s, 1H, $\text{C}_3\text{-H}$), 7.77 (s, 1H, $\text{C}_5'\text{-H}$), 10.70 (br s, 1H, NH-SO_2), 11.45 (s, 1H, NH-triazole), 13.56 (s, 1H, SH); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): δ 59.6 (CH_2), 120.6 (C-5), 123.6 (C-3), 124.4 (C-2), 126.3 (C-4), 139.7 (C-5'), 142.6 (C-4'), 152.1 (C-2'), 157.6 (C-5''), 159.1 (C-2''); HRMS (ESI-TOF) *m/z*: $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{10}\text{H}_8\text{ClN}_5\text{NaO}_3\text{S}_3$, 399.9485; found, 399.9485. Anal. calcd for $\text{C}_{10}\text{H}_8\text{ClN}_5\text{O}_3\text{S}_3$ (%): C, 31.79; H, 2.13; N, 18.54; found (%): C, 31.85; H, 2.10; N, 18.66.

N-(4-(4-Chlorothiophen-2-yl)thiazol-2-yl)-1-(5-mercapto-4H-1,2,4-triazol-3-yl)methanesulfonamide (7b).

White solid; *mp*: 174–176 °C; FT-IR (KBr, cm^{-1}): 3368 (NH), 2552 (SH), 1609 ($\text{C}=\text{N}$), 1256, 1176 (SO_2); ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 4.74 (s, 2H, CH_2), 7.18 (s, 1H, $\text{C}_5\text{-H}$), 7.41 (s, 1H, $\text{C}_3\text{-H}$), 7.64 (s, 1H, $\text{C}_5'\text{-H}$), 10.40 (br s, 1H, NH-SO_2), 11.14 (s, 1H, NH-triazole), 13.45 (s, 1H, SH); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): δ 57.3 (CH_2), 103.4 (C-5), 120.6 (C-3), 123.4 (C-2), 126.5 (C-4), 140.6 (C-5'), 144.8 (C-4'), 158.5 (C-2'), 160.4 (C-5''), 167.3 (C-2''); HRMS (ESI-TOF) *m/z*: $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{10}\text{H}_8\text{ClN}_5\text{NaO}_2\text{S}_4$, 415.9258; found, 415.9258. Anal. calcd for $\text{C}_{10}\text{H}_8\text{ClN}_5\text{O}_2\text{S}_4$ (%): C, 30.49; H, 2.05; N, 17.78; found (%): C, 30.55; H, 2.02; N, 17.86.

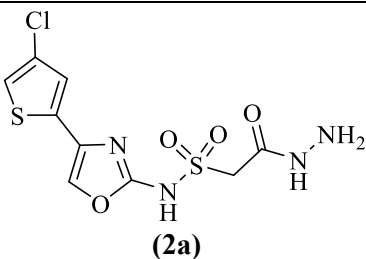
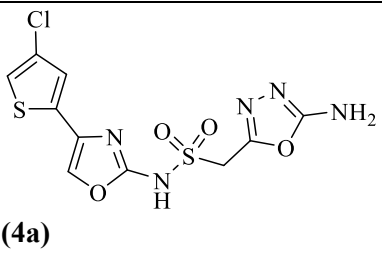
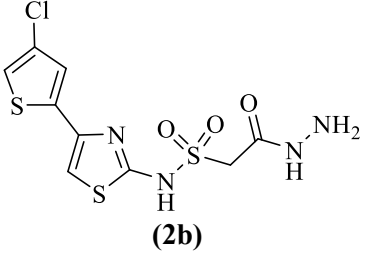
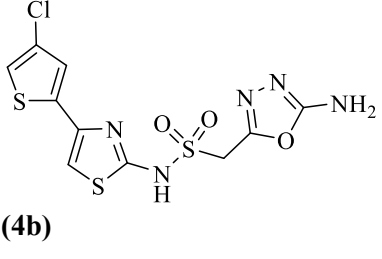
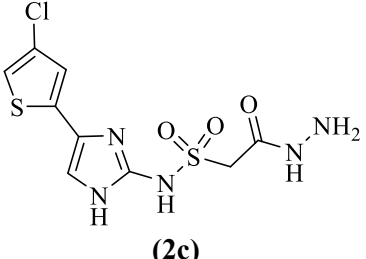
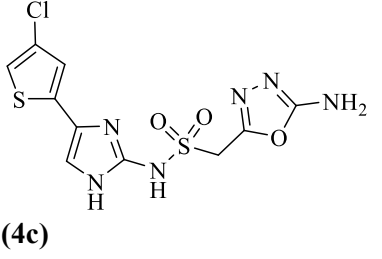
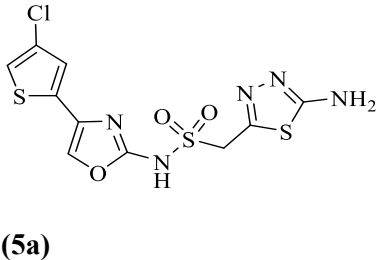
N-(4-(4-Chlorothiophen-2-yl)-1H-imidazol-2-yl)-1-(5-mercapto-4H-1,2,4-triazol-3-yl)methanesulfonamide (7c).

White solid; *mp*: 188–190 °C; FT-IR (KBr, cm^{-1}): 3363 (NH), 2540 (SH), 1611 ($\text{C}=\text{N}$), 1257, 1182 (SO_2); ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 4.64 (s, 2H, CH_2), 7.18 (s, 1H, $\text{C}_5\text{-H}$), 7.31 (s, 1H, $\text{C}_3\text{-H}$), 7.53 (s, 1H, $\text{C}_5'\text{-H}$), 10.35 (br s, 1H, NH-SO_2), 11.14 (s, 1H, NH-triazole), 13.10 (br s, 1H, NH-imidazole), 13.59 (s, 1H, SH); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): δ 59.3 (CH_2), 119.5 (C-5), 121.1 (C-3), 123.3 (C-2), 126.8 (C-4), 138.5 (C-5'), 141.3 (C-4'), 151.4 (C-2'), 158.1 (C-5''), 160.8 (C-2''); HRMS (ESI-TOF) *m/z*: $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{10}\text{H}_9\text{ClN}_6\text{NaO}_2\text{S}_3$, 382.9649; found, 382.9649. Anal. calcd for $\text{C}_{10}\text{H}_9\text{ClN}_6\text{O}_2\text{S}_3$ (%): C, 31.87; H, 2.41; N, 22.30; found (%): C, 31.79; H, 2.45; N, 22.44.

Table S1. Optimization of synthetic yields for azolylmethanesulfonamides under conventional and ultrasonic methods across diverse solvent systems.

S. No.	Solvents	Conventional Method: Time (h)	Conventional Method: Yield (%)	Ultrasonic Method: Time (min)	Ultrasonic Method: Yield (%)
1	1,4-Dioxane	12	07	134	14
2	THF	14	08	154	12
3	EtOH	4.5	63	50	72
4	AcOH	8	40	90	52

Table S2. Preparation of 1,3,4-oxadiazoles, 1,3,4-thiadiazoles and 1,2,4-triazoles from acid hydrazides.

S. No	Acid hydrazides	Products	Yield (%) A/B
1	 (2a)	 (4a)	63/76
2	 (2b)	 (4b)	64/78
3	 (2c)	 (4c)	62/75
4	(2a)	 (5a)	67/78

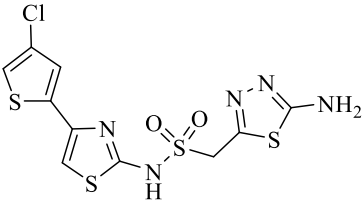
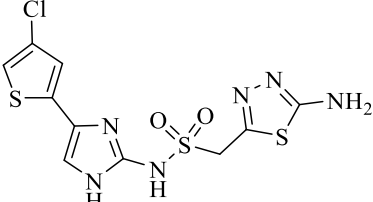
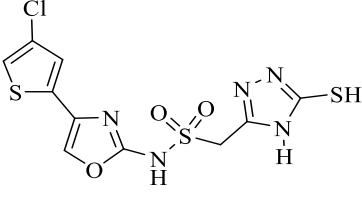
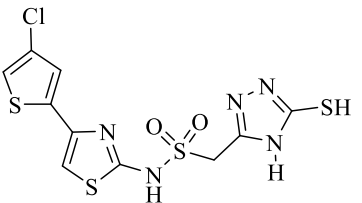
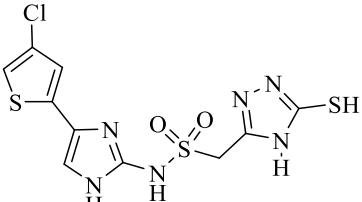
5	(2b)	 (5b)	65/77
6	(2c)	 (5c)	67/78
7	(2a)	 (7a)	62/75
8	(2b)	 (7b)	65/77
9	(2c)	 (7c)	64/74

Table S3. *In vitro* Antibacterial activity of 4a-c, 5a-c, 7a-c.

	Zone of inhibition (mm)															
	Gram-positive bacteria								Gram-negative bacteria							
Compound	<i>Staphylococcus aureus</i>				<i>Bacillus subtilis</i>				<i>Pseudomonas aeruginosa</i>				<i>Klebsiella pneumoniae</i>			
	Concentrations (µg/mL)				Concentrations (µg/mL)				Concentrations (µg/mL)				Concentrations (µg/mL)			
	12.5	25	50	100	12.5	25	50	100	12.5	25	50	100	12.5	25	50	100
4a	33±2	34±1	36±2	39±2	35±2	37±3	39±1	42±2	23±2	25±1	27±2	30±1	27±1	28±1	30±3	33±2
4b	24±1	26±1	27±3	30±2	27±1	29±2	32±2	33±3	14±2	17±2	19±3	20±1	17±3	18±2	20±2	23±1
4c	32±2	34±2	35±3	38±2	32±2	34±1	35±1	37±2	20±3	22±3	25±2	27±2	25±2	27±1	30±3	32±1
5a	34±1	36±2	39±1	42±1	34±3	35±2	37±3	39±1	23±1	25±2	27±2	30±2	29±2	32±1	34±2	37±3
5b	28±1	31±3	33±1	35±2	31±2	33±1	34±1	38±2	18±1	19±2	21±1	24±1	22±2	24±2	28±3	30±2
5c	30±3	32±2	34±2	37±1	30±3	33±1	34±2	38±3	18±3	20±1	22±3	25±3	23±1	26±2	29±1	31±2
7a	26±2	28±1	29±3	33±2	25±1	28±1	29±3	33±1	16±2	18±2	20±3	22±1	20±2	22±3	23±2	26±1
7b	32±2	33±2	35±1	37±2	32±2	33±2	34±3	36±2	20±2	21±3	24±1	27±2	24±1	26±1	28±2	31±2
7c	27±3	30±1	32±2	34±3	24±1	26±1	29±3	31±1	16±1	18±1	19±1	22±2	19±2	22±2	24±3	25±2
Chloramphenicol	28±1	30±2	33±1	35±3	30±2	32±2	34±3	38±2	23±1	25±3	27±1	30±2	36±1	38±2	40±1	42±1
Control (DMSO)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Table S4. *In vitro* Antifungal activity of 4a-c, 5a-c, 7a-c.

	Zone of inhibition (mm)							
Compound	<i>Aspergillus niger</i>				<i>Penicillium chrysogenum</i>			
	Concentrations (µg/mL)				Concentrations (µg/mL)			
	12.5	25	50	100	12.5	25	50	100
4a	33±2	35±3	37±1	40±1	38±2	41±2	43±3	46±2
4b	35±3	37±1	40±1	43±3	36±2	38±1	40±2	43±2
4c	34±1	36±2	41±2	43±3	35±2	37±1	38±1	40±3
5a	21±2	23±1	26±3	29±1	17±2	19±3	22±2	24±3
5b	22±1	25±2	27±3	29±2	19±2	22±1	24±1	26±2
5c	35±2	38±2	42±1	44±2	36±1	38±2	40±2	43±1
7a	18±3	22±2	23±3	25±1	15±3	16±2	18±2	21±1
7b	15±1	18±2	21±2	23±3	12±2	14±1	15±3	18±2
7c	18±2	20±3	23±1	25±2	17±1	19±2	20±2	23±3
Fluconazole	29±1	31±3	33±2	36±3	33±3	35±1	36±2	38±3
Control (DMSO)	-	-	-	-	-	-	-	-

Table S5. Minimum inhibitory concentration (MIC), minimum bactericidal concentration (MBC), and minimum fungicidal concentration (MFC) in µg/mL of target hybrids 4a–c, 5a–c, and 7a–c.

Compound	<i>Staphylococcus aureus</i>	<i>Bacillus subtilis</i>	<i>Pseudomonas aeruginosa</i>	<i>Klebsiella pneumoniae</i>	<i>Aspergillus niger</i>	<i>Penicillium chrysogenum</i>
4a	6.25 (12)	6.25 (12)	12.5 (25)	50 (100)	6.25 (12)	12.5 (25)
4b	25 (100)	25 (100)	100 (–)	200 (–)	6.25 (12)	12.5 (25)
4c	6.25 (12)	12.5 (25)	12.5 (25)	50 (100)	6.25 (12)	12.5 (25)
5a	6.25 (12)	6.25 (12)	12.5 (25)	25 (50)	50 (100)	200 (–)
5b	6.25 (12)	6.25 (12)	25 (50)	200 (–)	50 (100)	200 (–)
5c	6.25 (12)	6.25 (12)	25 (100)	50 (100)	6.25 (12)	12.5 (25)
7a	12.5 (25)	25 (100)	100 (–)	100 (–)	100 (–)	200 (–)
7b	6.25 (12)	12.5 (25)	12.5 (25)	50 (100)	100 (–)	200 (–)
7c	12.5 (25)	50 (200)	100 (–)	200 (–)	100 (–)	200 (–)
Chloramphenicol	6.25	6.25	6.25	12.5	—	—
Fluconazole	—	—	—	—	6.25	12.5

Table S6. *In vitro* antioxidant activity of target hybrids 4a–c, 5a–c, and 7a–c determined via the DPPH radical-scavenging method.

Compound	25 µg/mL (Mean ± SD)	50 µg/mL (Mean ± SD)	75 µg/mL (Mean ± SD)	100 µg/mL (Mean ± SD)	IC ₅₀ (µg mL ⁻¹) (Mean ± SD)
4a	77.62 ± 0.18	78.48 ± 0.65	79.12 ± 0.69	81.52 ± 0.56	16.10 ± 0.68
4b	78.58 ± 0.76	79.29 ± 0.69	82.43 ± 0.28	83.28 ± 0.47	15.90 ± 0.56
4c	76.32 ± 0.45	77.25 ± 0.39	78.09 ± 0.24	79.05 ± 0.28	16.37 ± 0.36
5a	65.62 ± 0.31	66.37 ± 0.62	67.14 ± 0.53	68.14 ± 0.74	19.04 ± 0.55
5b	58.34 ± 0.65	59.57 ± 0.74	60.70 ± 0.76	62.89 ± 0.12	21.42 ± 0.57
5c	72.24 ± 0.28	74.62 ± 0.23	76.25 ± 0.17	78.66 ± 0.61	17.30 ± 0.34
7a	68.16 Ext	69.49 ± 0.49	71.91 Ext	72.72 ± 0.12	18.33 ± 0.27
7b	67.28 ± 0.49	68.27 ± 0.24	69.72 ± 0.53	71.35 ± 0.67	18.57 ± 0.47
7c	70.21 ± 0.46	71.83 ± 0.58	72.24 ± 0.71	73.15 ± 0.63	17.80 ± 0.62
Ascorbic acid	72.67 ± 0.64	74.89 ± 0.17	76.73 ± 0.34	78.38 ± 0.15	17.20 ± 0.32
Blank	—	—	—	—	—

Table S7. *In vitro* antioxidant activity of target hybrids 4a–c, 5a–c, and 7a–c determined via the H₂O₂ radical-scavenging method.

Compound	25 µg/mL (Mean ± SD)	50 µg/mL (Mean ± SD)	75 µg/mL (Mean ± SD)	100 µg/mL (Mean ± SD)	IC ₅₀ (µg mL ⁻¹) (Mean ± SD)
4a	78.28 ± 0.56	79.24 ± 0.42	80.41 ± 0.17	81.55 ± 0.55	15.96 ± 0.44
4b	79.23 ± 0.16	81.56 ± 0.29	83.53 ± 0.39	84.62 ± 0.18	15.77 ± 0.26
4c	77.62 ± 0.18	78.19 ± 0.35	79.44 ± 0.45	80.53 ± 0.65	16.10 ± 0.41
5a	67.36 ± 0.67	68.52 ± 0.24	69.72 ± 0.63	71.16 ± 0.77	18.55 ± 0.56
5b	60.73 ± 0.41	61.67 ± 0.53	62.56 ± 0.21	63.45 ± 0.74	20.58 ± 0.47
5c	74.12 ± 0.54	75.61 ± 0.69	76.14 ± 0.26	78.38 ± 0.69	16.86 ± 0.54
7a	70.33 ± 0.15	71.65 ± 0.59	73.42 ± 0.44	74.25 ± 0.32	17.77 ± 0.38
7b	68.86 ± 0.33	69.25 ± 0.31	70.76 ± 0.83	71.70 Ext	18.15 ± 0.51
7c	73.72 ± 0.27	74.14 ± 0.68	75.79 ± 0.28	76.92 ± 0.75	16.95 Ext
Ascorbic acid	74.56 ± 0.25	76.56 ± 0.62	78.63 ± 0.77	80.82 ± 0.31	16.76 ± 0.49
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Table S8. *In vitro* antioxidant activity of target hybrids 4a–c, 5a–c, and 7a–c determined via the NO radical-scavenging method.

Compound	25 µg/mL (Mean ± SD)	50 µg/mL (Mean ± SD)	75 µg/mL (Mean ± SD)	100 µg/mL (Mean ± SD)	IC ₅₀ (µg mL ⁻¹) (Mean ± SD)
4a	81.55 ± 0.48	82.68 ± 0.14	83.47 ± 0.67	84.44 ± 0.31	15.32 ± 0.39
4b	82.42 ± 0.42	84.16 ± 0.52	85.59 ± 0.44	87.38 ± 0.65	15.16 ± 0.50
4c	79.53 ± 0.22	80.54 ± 0.34	81.56 ± 0.36	82.72 ± 0.63	15.71 ± 0.39
5a	69.52 ± 0.16	70.41 ± 0.13	71.40 ± 0.19	73.92 ± 0.51	17.98 ± 0.25
5b	62.26 ± 0.59	63.43 ± 0.33	65.66 ± 0.64	66.82 ± 0.32	20.07 ± 0.48
5c	77.89 ± 0.46	78.56 ± 0.15	79.90 ± 0.49	80.55 ± 0.62	16.04 ± 0.41
7a	74.27 ± 0.36	75.21 Ext	77.48 ± 0.29	79.78 ± 0.55	16.83 ± 0.40
7b	73.23 ± 0.17	74.39 ± 0.36	75.40 ± 0.27	77.25 ± 0.11	17.06 ± 0.24
7c	76.43 ± 0.35	77.64 ± 0.59	78.41 ± 0.24	79.28 ± 0.33	16.35 ± 0.38
Ascorbic acid	76.86 ± 0.65	78.74 ± 0.51	80.41 ± 0.47	82.25 ± 0.68	16.26 ± 0.59
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Table S9. Molecular docking interaction parameters of target hybrids 4a–c, 5a–c, and 7a–c within the active site of *Staphylococcus aureus* dihydrofolate reductase (PDB ID: 2W9S).

Ligands	Binding Affinity in kcal per mol	Hydrophobic Interactions	H ₂ bond Interactions	No. of H ₂ Bonds	H ₂ Bond distance
4a	-9.4	LEU:20, ILE:14, THR:121, LYS:45, ALA:43, ILE:50, PHE:92	THR:46, GLY:94, GLN:95	4	2.38, 2.14, 2.08
4b	-7.1	GLY:15, ILE:14, LEU:28, ILE:50, LEU:20, ILE:31, LEU:54	SER:49	1	2.32
4c	-8.9	GLY:15, LYS:45, THR:121, THR:96, TYR:98, PHE:92, LEU:20	ASN:18, THR:46	2	2.02, 2.18
5a	-9.4	LEU:20, ILE:14, THR:121, LYS:45, ALA:43, PHE:92, GLY:15, ILE:31	THR:46, GLY:94, GLN:95	3	2.18, 2.29, 2.80
5b	-7.6	LEU:20, ILE:14, LYS:45, ALA:43, PHE:92, GLY:15, ILE:31, ILE:50, GLY:94, LEU:28	ASN:18	1	2.38
5c	-8.6	GLY:15, ILE:14, TYR:98, LEU:20, ALA:43, LYS:45, THR:121	ASN:18, THR:46, GLY:94	3	2.90, 2.53, 2.10
7a	-7.5	VAL:6, ALA:7, PHE:92, TYR:98	THR:46, PHE:92, TYR:98, ALA:7	4	1.97, 2.05, 2.58, 2.56
7b	-8.1	LEU:20, ILE:31, THR:46, GLY:94, PHE:92, THR:121	ASN:18, GLN:95	2	2.11, 2.89

7c	-7.5	ASN:18, GLY:94, TYR:98, LYS:45	THR:46, ILE:14	2	2.31, 2.54
Chloramphenicol	-7.6	ASN:18, GLN:19, LEU:20, ILE:14	ASN:18, GLN:95	2	2.21, 2.42

Table S10. Molecular docking interaction parameters of target hybrids 4a–c, 5a–c, and 7a–c within the active site of pathogenic fungi sterol 14- α demethylase (PDB ID: 6F0E).

Ligands	Binding Affinity in kcal per mol	Hydrophobic Interactions	H ₂ bond Interactions	No. of H ₂ Bonds	H ₂ Bond distance
4a	-8.2	LEU:159, GLU:171, LEU:10, ARG:52	SER:56, ASP:54, VAL:170, ARG:208	4	2.07, 2.19, 2.51, 2.87
4b	-8.3	PRO:18, HIS:168, ASP:20, ASP:117	ARG:119, GLU:171, GLY:210	4	2.11, 2.20, 2.50, 2.56
4c	-8.3	GLY:210, VAL:170, PRO:18, HIS:168, ASP:20, ALA:21, LEU:22	ASP:117, ARG:119, THR:172	3	1.84, 2.32, 2.58
5a	-7.5	ALA:21, PRO:18, VAL:170, ASP:20, ASP:117, GLY:210	ARG:119, THR:172, CYS:17, GLU:171	4	2.08, 2.81, 2.89, 2.90
5b	-7.5	VAL:154, MET:209, ALA:197, ARG:208, TYR:151	GLU:124, SER:201	2	1.97, 2.04
5c	-8.4	ALA:197, VAL:154, TYR:151, VAL:155, ARG:208, MET:209, TYR:205	SER:173, VAL:194, SER:201	2	1.97, 2.10
7a	-6.6	CYS:17, ALA:21, LYS:211	ARG:119	1	2.04
7b	-7.2	SER:173, MET:209, PRO:206, ALA:64	SER:201, TYR:151, TYR:111	3	2.09, 2.36, 2.87
7c	-7.3	SER:201, MET:209, ARG:208, TYR:205	SER:173	1	2.01
fluconazole	-8.2	TYR:151, ARG:208, MET:209	Nil	Nil	Nil

Table S11. Molecular docking interaction parameters of target hybrids 4a–c, 5a–c, and 7a–c within the active site of cytochrome **c** peroxidase (PDB ID: 2X08).

Ligands	Binding Affinity in kcal per mol	Hydrophobic Interactions	H ₂ bond Interactions	No. of H ₂ Bonds	H ₂ Bond distance
4a	-7.4	LEU A:294, LEU A:30, MET A:119	GLN A:117, GLN A:118, GLU A:290, ARG A:31	4	2.01, 2.13, 2.34, 2.53
4b	-7.5	LEU A:30, MET A:119, LEU A:294	GLN A:117, GLU A:118, GLU A:290, ARG A:31	4	2.71, 2.33, 2.42, 2.99
4c	-7.3	LEU A:30 ALA A:27	GLU A:290 GLN A:117 GLU A:118 ARG A:31	4	2.11, 2.17, 2.84, 2.90
5a	-7	ILE A:40 MET A:119 LEU A:30 ALA A:27	ASN A:196 ARG A:31 ASP A:34 GLU A:118 TYR A:39	5	2.11, 2.30, 2.99, 3.21, 2.53
5b	-6.6	LEU A:30 MET A:119	GLN A:117 GLU A:290 ARG A:31	3	2.71, 2.73, 2.89
5c	-7.3	LEU A:294 ALA A:27 MET A:119 ALA A:117 LEU A:30	ARG A:31 GLU A:118 GLU A:290	3	2.01, 2.13, 2.34
7a	-6.9	LEU A:294 MET A:119 LEU A:30	ARG A:31 GLU A:118 GLU A:290	3	2.13, 2.34, 2.98
7b	-6.8	MET A:119 LEU A:30	GLU A:290 ARG A:31 GLU A:118	3	2.56, 2.33, 3.12
7c	-7.1	LEU A:30 MET A:119 ALA A:27	ARG A:31 GLU A:290 GLU A:118	3	2.09, 2.55, 2.67
Ascorbic acid	-5.7	ASP A:146 SER A:185	PRO A:145 ALA A:147 SER A:81	3	2.06, 2.83, 2.88

Table S12. Molecular docking interaction parameters of target hybrids 4a–c, 5a–c, and 7a–c within the catalytic domain of Janus kinase 2 (JAK2; PDB ID: 3KRR).

Ligands	Binding Energy (kcal/mol)	Hydrophobic Interactions	Hydrogen Bond Interactions	Hydrogen Bond Distance (Å ⁰)
4a	-6.8	LEU:855, VAL:863, ALA:880, VAL:911, MET:929, LEU:983, TYR:931	ASP:939	2.32
4b	-8	LEU:855, VAL:863, ALA:880, MET:929, LEU:983, TYR:931, ASN:859	LYS:857, ASP:976	2.18, 2.64
4c	-8.1	LEU:855, VAL:863, ALA:880, MET:929, LEU:983, ASN:859	ASP:976, ASP:994, GLY:993	1.95, 2.26, 2.40, 2.64, 2.82
5a	-7.4	PHE:860, HIS:891, LEU:997	ASP:894, ARG:975, GLY:1014	2.08, 2.18, 2.22, 2.62
5b	-5.7	LYS:999, PTR:1008, VAL:1010, LYS:1011	ASP:894, HIS:891	2.09, 2.16
5c	-8.1	LEU:855, VAL:863, ALA:880, TYR:931, LEU:983, ASN:859, LEU:932	ASP:976, ASP:994, GLY:993	1.81, 2.32, 2.33, 2.81, 2.83
7a	-7.2	LEU:855, VAL:863, ALA:880, VAL:911, LEU:983, MET:929	ARG:980, SER:936	2.34, 2.70
7b	-7.3	LEU:855, VAL:863, ALA:880, TYR:931, LEU:983, MET:929	LYS:857	2.57
7c	-7.5	LEU:855, VAL:863, ALA:880, TYR:931, LEU:983, MET:929, GLY:856	ASP:994, GLY:993	2.23, 2.74
Tamoxifen	-7	LEU:997, LYS:999	PHE:860, LYS:882	2.51, 3.01

Table S13. Molecular docking interaction parameters of target hybrids 4a–c, 5a–c, and 7a–c within the catalytic domain of phosphoinositide-dependent kinase-1 (PDK1; PDB ID: 1Z5M).

Ligands	Binding Energy (kcal/mol)	Hydrophobic Interactions	Hydrogen Bond Interactions	Hydrogen Bond Distance (Å ⁰)
4a	-7.3	LEU:88, GLY:89, VAL:96, ALA:109, TYR:161, ALA:162, GLU:166, LEU:212, ASP:223	SER:94	2.76
4b	-7	LEU:88, VAL:96, GLU:166, CL:698, ASP:223	SER:92, PHE:93	2.04, 2.27
4c	-7.3	GLY:91, VAL:96, GLU:166, ALA:109, LEU:212	GLU:90, LYS:111, GLU:209, ASN:210, ASP:224, GOL:607,	2.40, 2.41, 2.42, 2.55, 2.63, 2.72
5a	-7.7	LEU:88, VAL:96, ALA:109, TYR:161, ALA:162, LEU:212, ASP:223	GLU:209, GLU:166, GOL:607,	1.93, 2.34, 2.65
5b	-7.8	LEU:88, VAL:96, ALA:109, TYR:161, ALA:162, LEU:212, ASP:223, GOL:607	GLY:91, SER:94	2.56, 2.65
5c	-6.6	PHE:184, PRO:356	ARG:183, THR:354	2.40, 2.41
7a	-7.3	LEU:88, ALA:109, TYR:161, ALA:162, LEU:212, ASP:223	SER:94	2.29
7b	-7.8	LEU:88, VAL:96, ALA:109, TYR:161, ALA:162, LEU:212, ASP:223	GLY:91, SER:94, GLY:89	2.50, 2.51, 3.08
7c	-7	TYR: 195, LEU:350, GLN:352	HIS:139, HIS:351, TRP:347, GLU: 348, GLU: 194	1.87, 1.91, 2.12, 2.20, 2.31, 2.34, 2.50
Doxorubicin	-8.7	PHE:93, ASP:223	GLY:91, SER:94, GLY:89, ASP:205	1.92, 2.25, 2.32, 2.50, 2.55

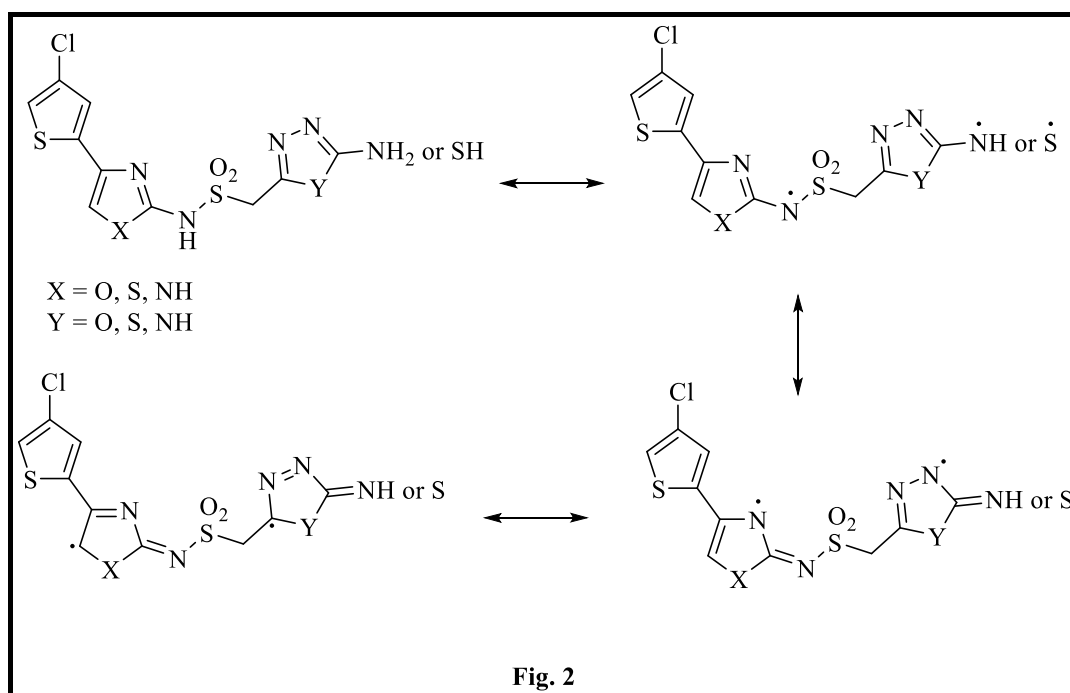
Table S14. Molecular docking interaction parameters of target hybrids 4a–c, 5a–c, and 7a–c within the catalytic domain of human anaplastic lymphoma kinase (ALK; PDB ID: 1M17).

Ligands	Binding Energy (kcal/ mol)	Hydrophobic Interactions	Hydrogen Bond Interactions	Hydrogen Bond Distance (Å ⁰)
4a	-7.1	VAL:702, LYS:721, CYS:773, ARG:817, LEU:820, ASP:831	MET:742, GLU:738, THR:766, THR:830	2.77, 2.85, 2.86, 3.05
4b	-6.8	VAL:702, LYS:721, CYS:773, MET:742, ARG:817	ASP:831	2.54, 2.62
4c	-7.4	LEU:694, VAL:702, ALA:719, LEU:820, ASP:831	LYS:721, GLN:767	2.22, 2.24
5a	-7.2	PHE:699, VAL:702, ALA:719, LYS:721, MET:742	LYS:721, CYS:751	3.69, 2.80
5b	-7	PHE:699, ASP:831, ALA:719, LYS:721, MET:742		
5c	-7.5	LEU:694, VAL:702, ALA:719, LEU:820, ASP:831	THR:766, GLN:767, LYS:721	2.39, 2.43, 2.46
7a	-6.7	PHE:699, VAL:702, ALA:719, ASP:831, MET:742	ASP:831, LYS:721	2.26, 2.52, 2.55
7b	-6.9	LEU:768, LEU:694, VAL:702, ALA:719, LEU:820, ASP:813,	ASP:831, ARG:817	2.02, 2.38, 2.55, 2.67, 2.91
7c	-7.4	LEU:694, VAL:702, ALA:719, LEU:820, ASP:831, MET:769	LYS:721, CYS:751, GLN:767	2.04, 2.16, 2.44, 3.70
Erlotinib	-7.9	PHE:699, VAL:702, ASP:831, GLU:738, THR:766	CYS:751, MET:769	1.92, 3.71

Table S15. Calculated ADMET properties, pharmacokinetic profiles, and drug-likeness parameters of target hybrids 4a–c, 5a–c, and 7a–c evaluated via the SwissADME platform.

Molecule	MW	#Rotatable bonds	#H-bond acceptors	#H-bond donors	MR	TPSA	Log P	Lipinski #violations	Synthetic Accessibility
4a	361.78	5	7	2	79.84	173.76	1.05	0	3.59
4b	377.85	5	6	2	85.45	188.86	1.71	0	3.64
4c	363.82	5	8	4	87.53	171.79	-0.34	0	4.09
5a	377.85	5	6	2	85.45	188.86	1.62	0	3.69
5b	393.92	5	5	2	91.07	203.96	2.18	0	3.76
5c	376.87	5	5	3	87.54	191.51	0.53	0	4.48
7a	377.85	5	6	2	84.78	189.19	2	0	4.37
7b	393.92	5	5	2	90.39	204.29	2.68	0	4.44
7c	379.89	5	7	4	92.46	187.22	0.49	0	4.67

Ascorbic acid	176.12	2	6	4	35.12	107.22	-1.42	0	3.47
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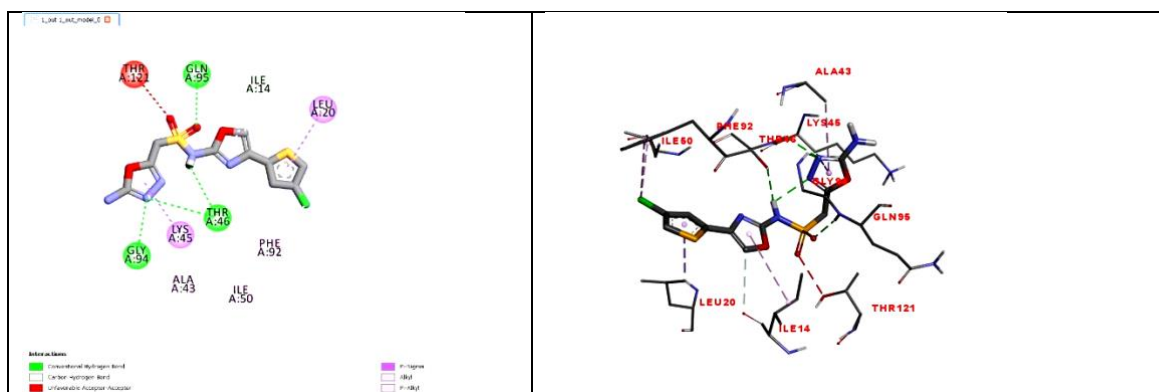


(PDB: 2W9S)

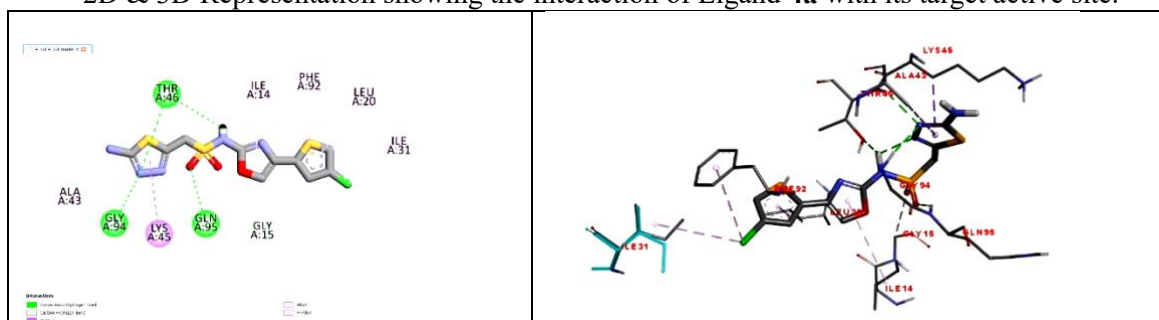


(PDB: 6F0E)

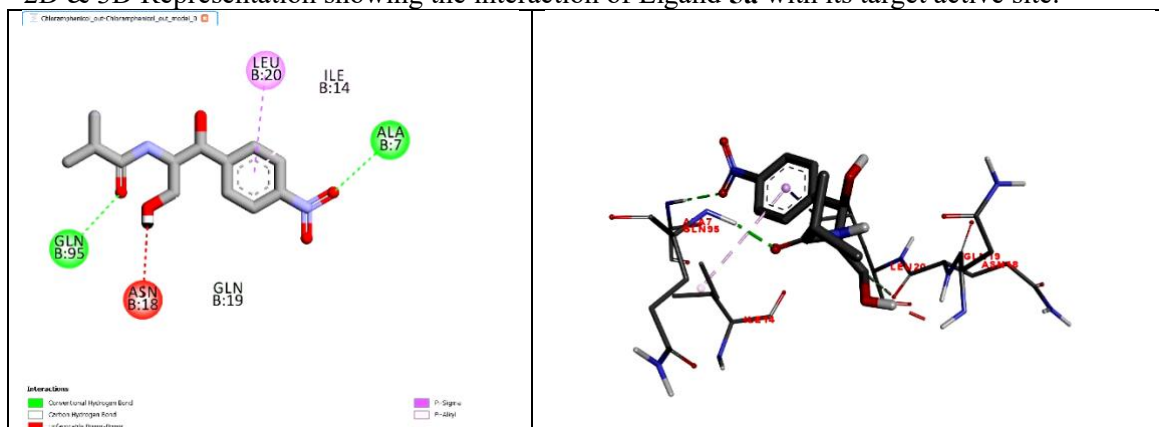
Fig. S2. 3D representation of enzyme from protein data bank used in the virtual screening



2D & 3D Representation showing the interaction of Ligand **4a** with its target active site.

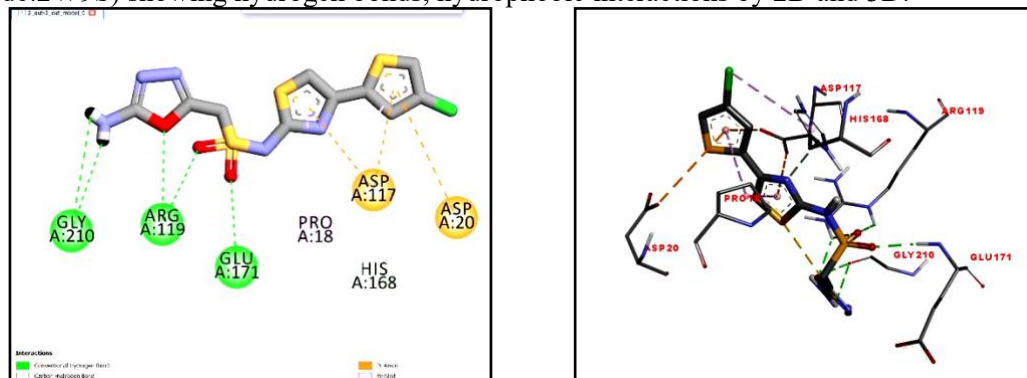


2D & 3D Representation showing the interaction of Ligand **5a** with its target active site.

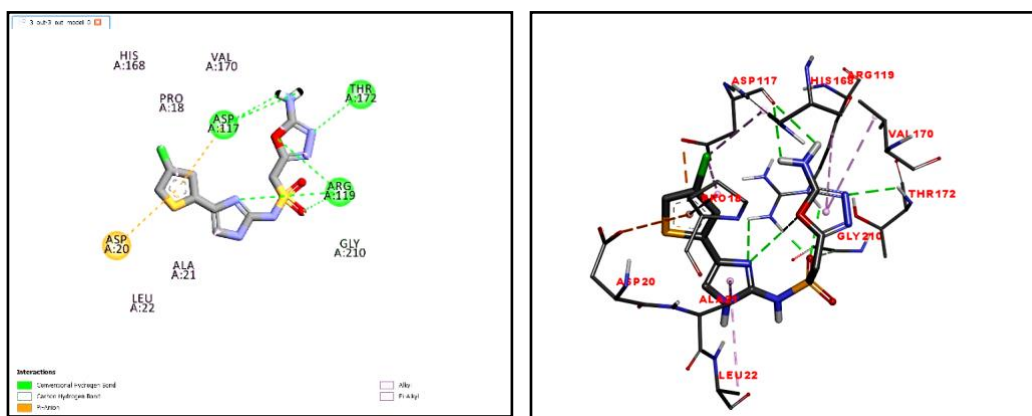


2D & 3D representation showing the interaction of standard drug **Chloramphenicol** with its target active site.

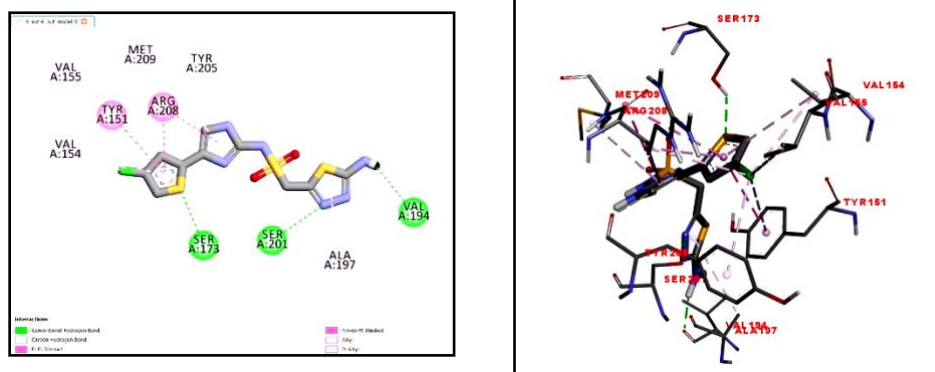
Fig. S3. Docking mode of ligands **4a**, **5a** & standard drug **Chloramphenicol** into target (PDB code:2W9S) showing hydrogen bonds, hydrophobic interactions by 2D and 3D.



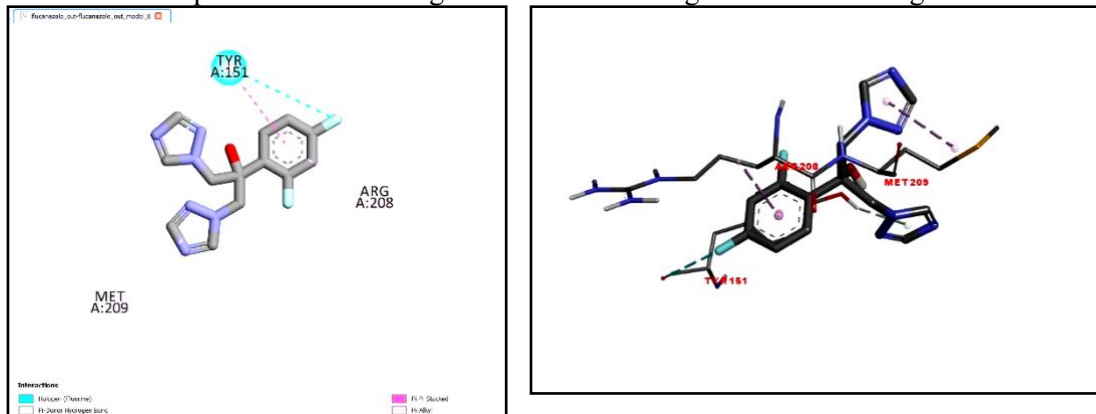
2D & 3D Representation showing the interaction of Ligand **4b** with its target active site.



2D & 3D Representation showing the interaction of Ligand **4c** with its target active site.



2D & 3D Representation showing the interaction of Ligand **5c** with its target active site.



2D & 3D representation showing the interaction of standard drug **Fluconazole** with its target active site.

Fig. S4. The 3D and 2D representation of docking mode of ligands **4b**, **4c**, **5c** & standard drug **fluconazole** into target (PDB code: 6F0E) showing hydrogen bonds, hydrophobic interactions.

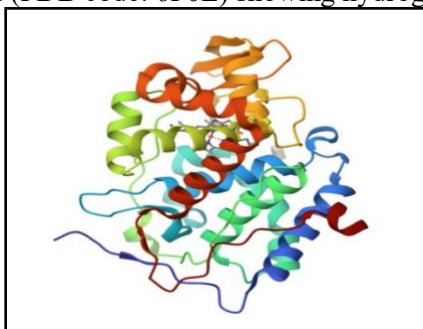
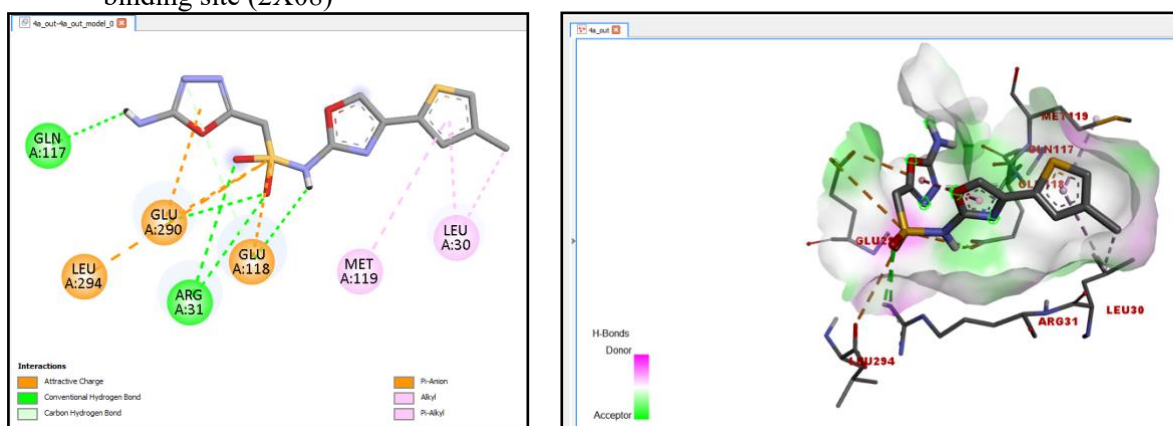
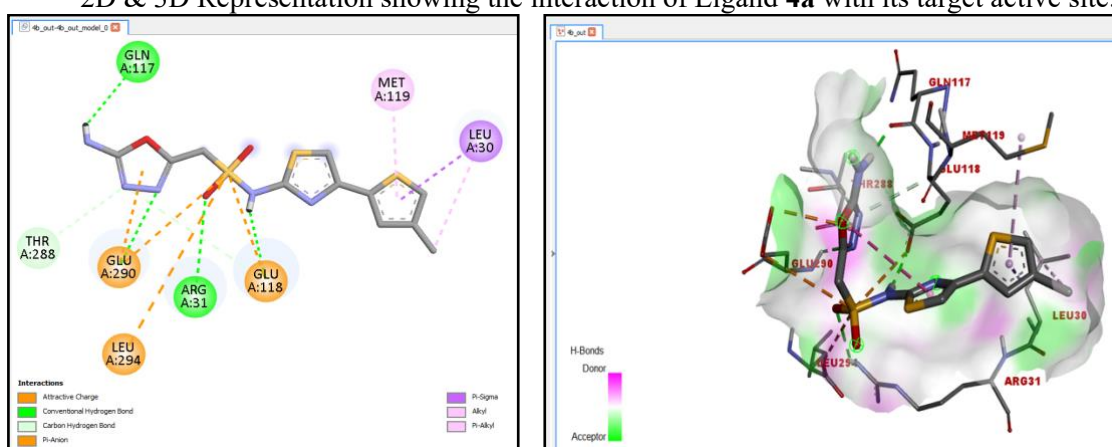


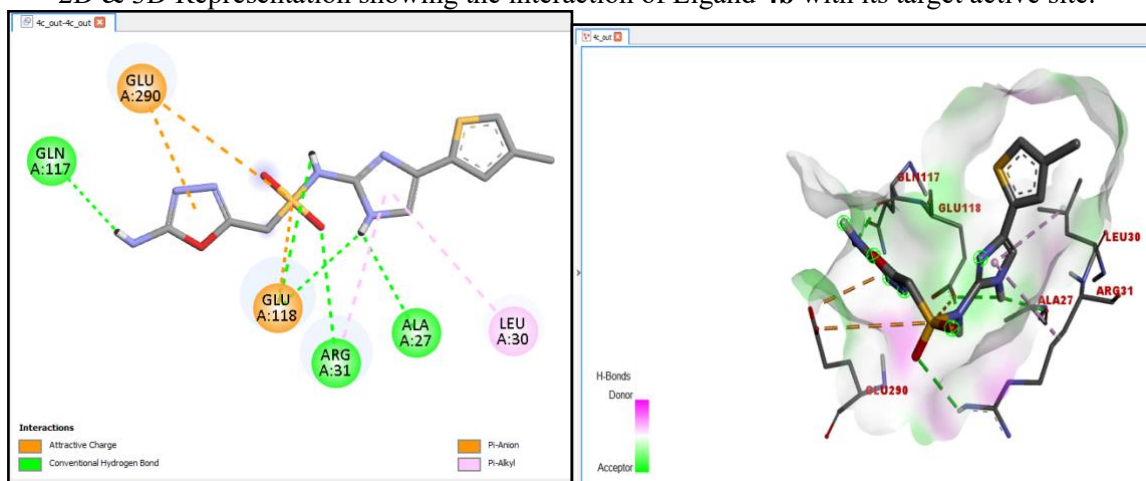
Fig. S5. Target: cytochrome c peroxidase: ascorbate bound to the engineered ascorbate binding site (2X08)



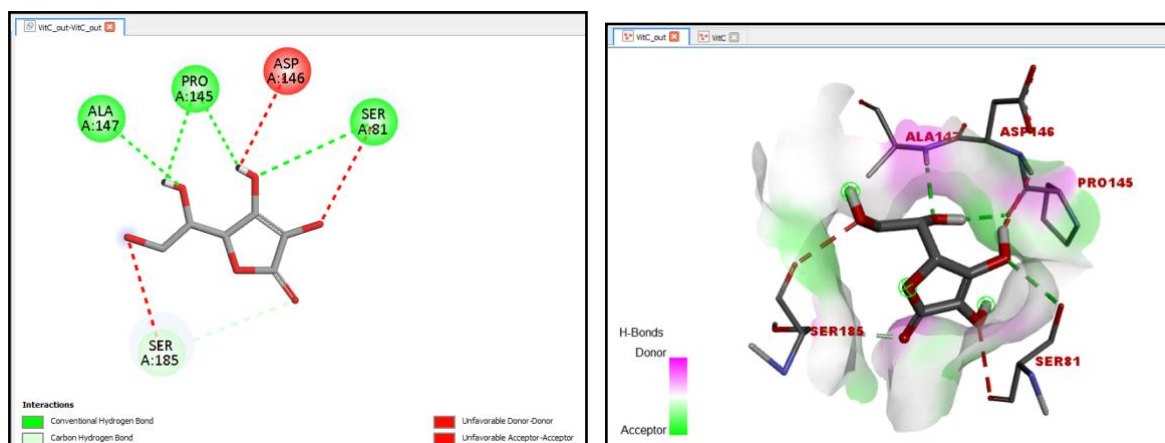
2D & 3D Representation showing the interaction of Ligand **4a** with its target active site.



2D & 3D Representation showing the interaction of Ligand **4b** with its target active site.

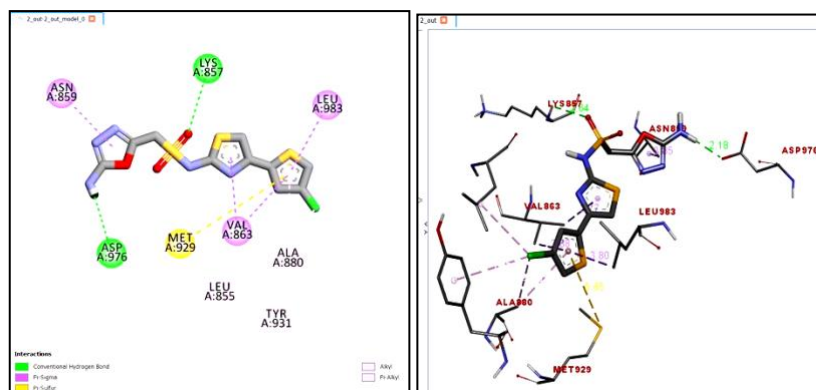


2D & 3D Representation showing the interaction of Ligand **4c** with its target active site.

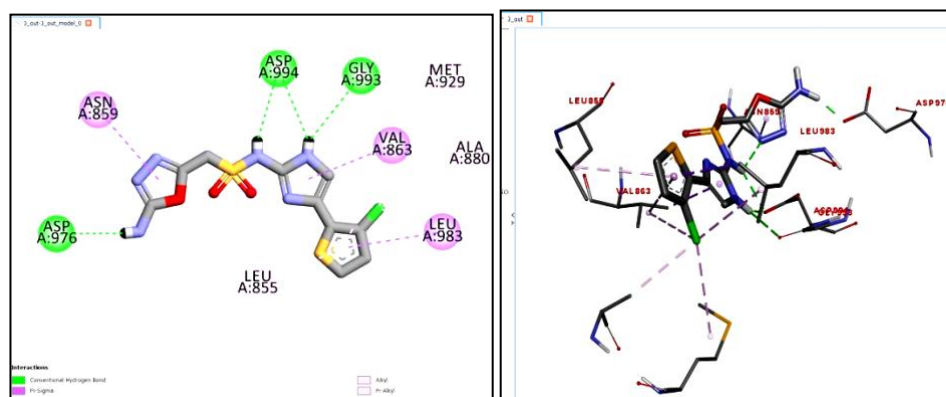


2D & 3D Representation showing the interaction of Ascorbic acid (Vitamin C) with its target active site.

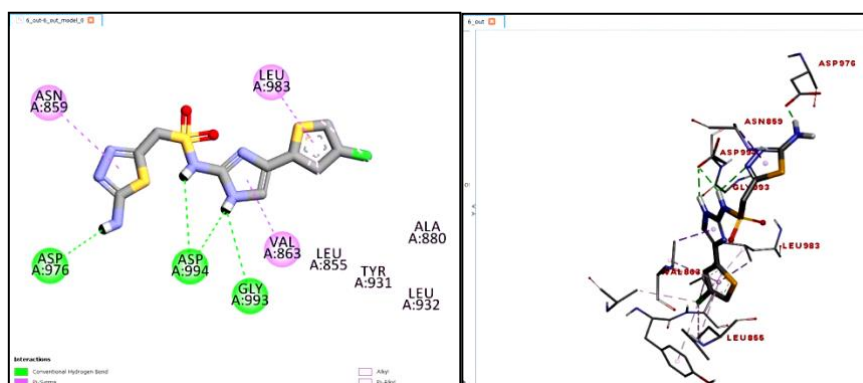
Fig. S6. The 3D and 2D representation of docking mode of ligands **4a**, **4b**, **4c** & standard drug **Ascorbic acid** into target (PDB ID: 2X08) showing hydrogen bonds, hydrophobic interactions.



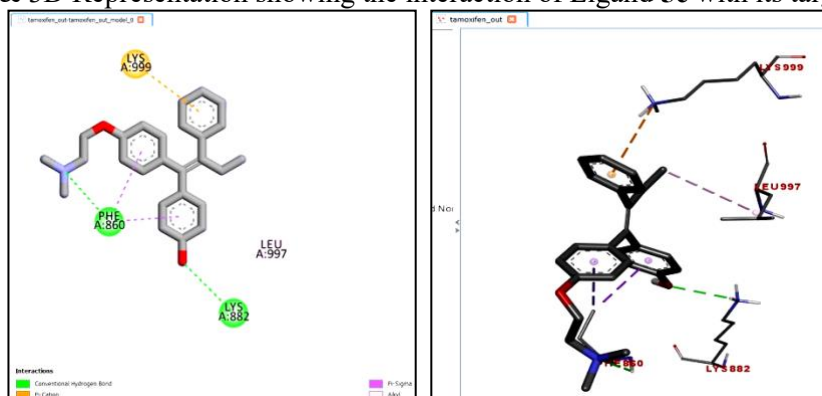
2D & 3D Representation showing the interaction of Ligand **4b** with its target active site.



2D & 3D Representation showing the interaction of Ligand **4c** with its target active site.

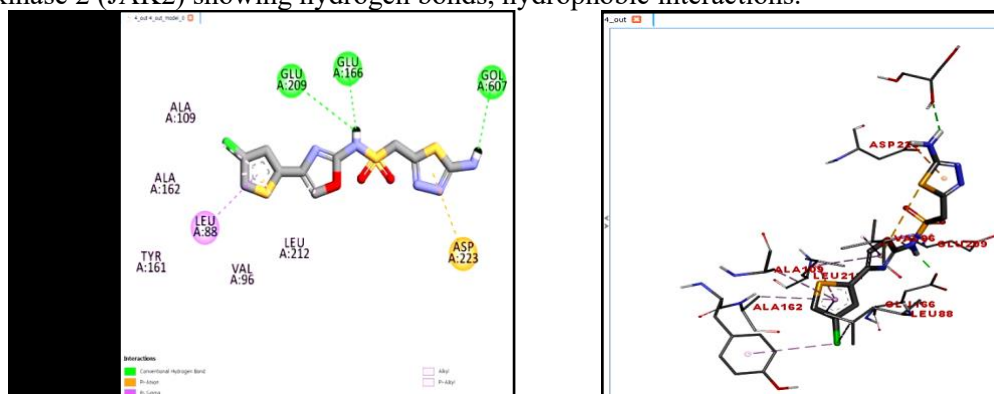


2D & 3D Representation showing the interaction of Ligand **5c** with its target active site.

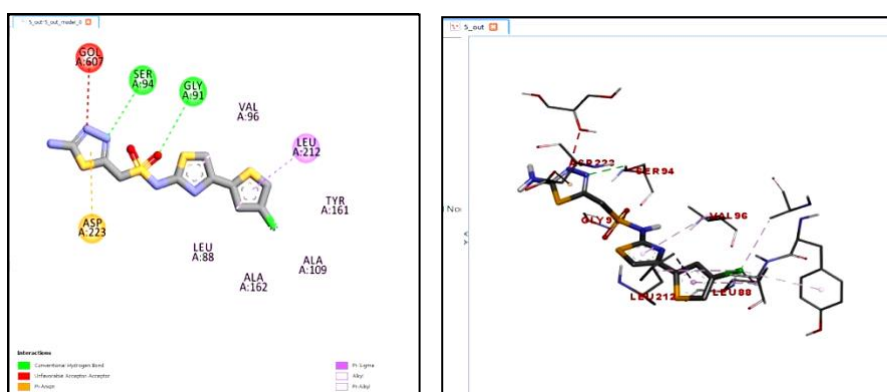


2D & 3D representation showing the interaction of standard drug **Tamoxifen** with its target active site.

Fig. S7. The 3D and 2D docking mode of ligands **4b**, **4c**, **5c** & standard drug **Tamoxifen** into target Janus kinase 2 (JAK2) showing hydrogen bonds, hydrophobic interactions.



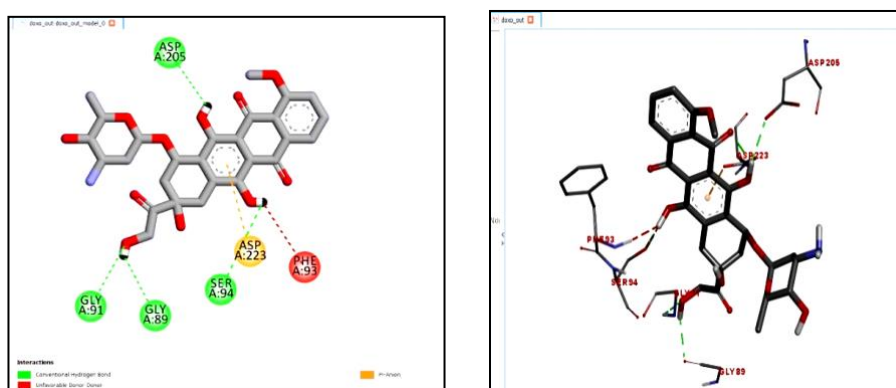
2D & 3D Representation showing the interaction of Ligand **5a** with its target active site.



2D & 3D Representation showing the interaction of Ligand **5b** with its target active site.

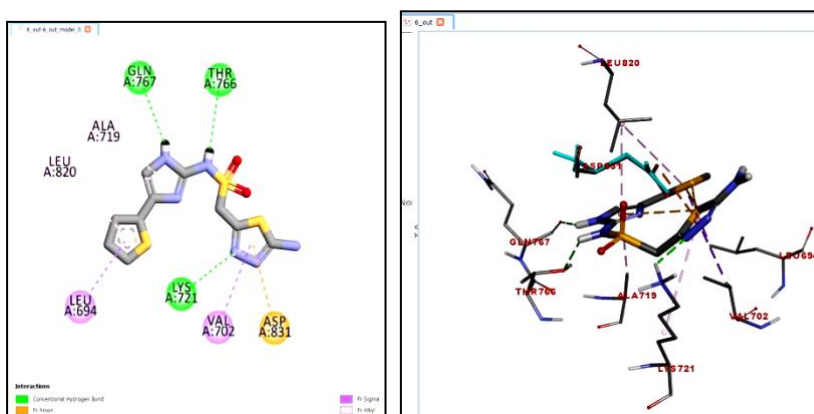


2D & 3D Representation showing the interaction of Ligand **7b** with its target active site.

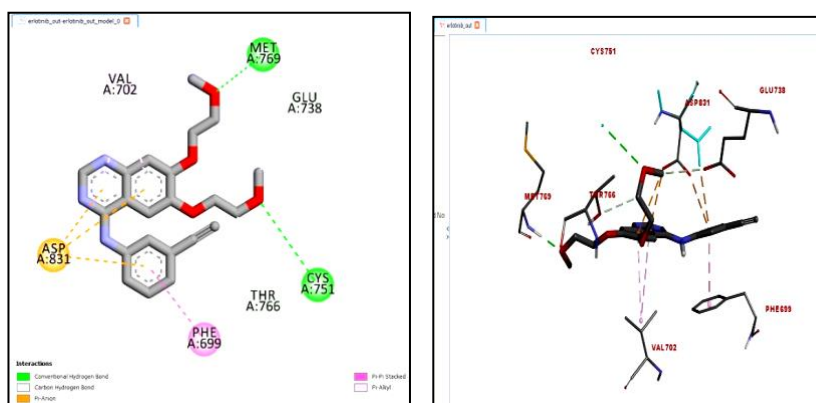


2D & 3D representation showing the interaction of standard drug **Doxorubicin** with its target active site.

Fig. S8. The 3D and 2D docking mode of ligands **5a**, **5b**, **7b** & standard drug **Doxorubicin** into target phosphoinositide-dependent kinase-1 (PDK1) showing hydrogen bonds, hydrophobic interactions.



2D & 3D Representation showing the interaction of Ligand **5c** with its target active site.



2D & 3D representation showing the interaction of standard drug **Erlotinib** with its target active site.

Fig. S9. The 3D and 2D docking mode of ligands **5c** & standard drug **Erlotinib** into target anaplastic lymphoma kinase (ALK) showing hydrogen bonds, hydrophobic interactions.