

Supporting information

Computational study and in vitro evaluation of the anti-proliferative activity of novel naproxen derivatives

Table S1. The HOMO energies (E_{HOMO}), LUMO energies (E_{LUMO}), HOMO-LUMO energy gaps (E_g) in eV and global reactivity descriptors of **a-e** obtained at B3LYP/6-31+G** levels of theory.

Parameters	a	b	c	d	e
E_{HOMO}	-5.60	-5.65	-5.55	-5.68	-5.77
E_{LUMO}	-2.74	-2.91	-2.59	-2.59	-3.64
E_{gap}	2.86	2.74	2.96	3.09	2.13
χ	-4.17	-4.28	-4.07	-4.11	-4.71
H	1.43	1.37	1.48	1.57	1.06
ω	6.08	6.68	5.60	5.38	10.39
S	0.35	0.36	0.34	0.32	0.47
μ	4.17	4.28	4.07	4.11	4.70
ω_i	1.46	1.56	1.37	1.31	2.21
IP	5.60	5.65	5.55	5.68	5.77

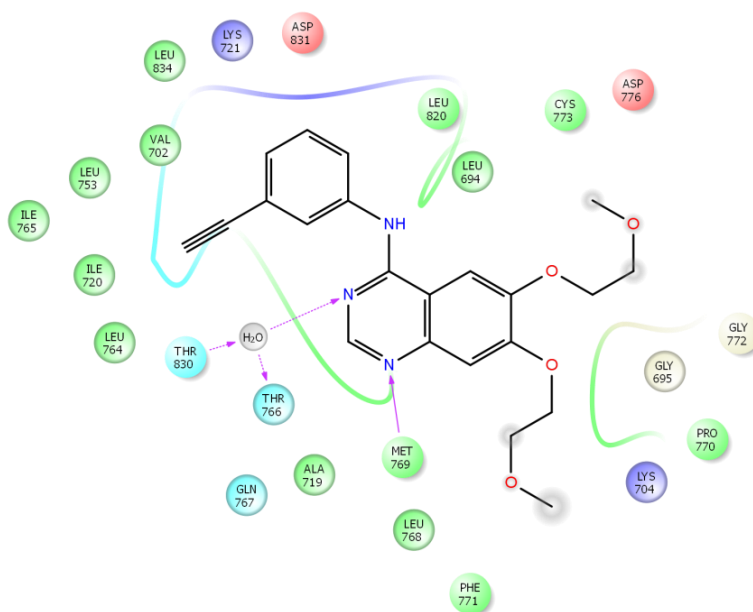


Fig. S1. 2D interactions of native ligand; erlotinib into the active site of EGFR.

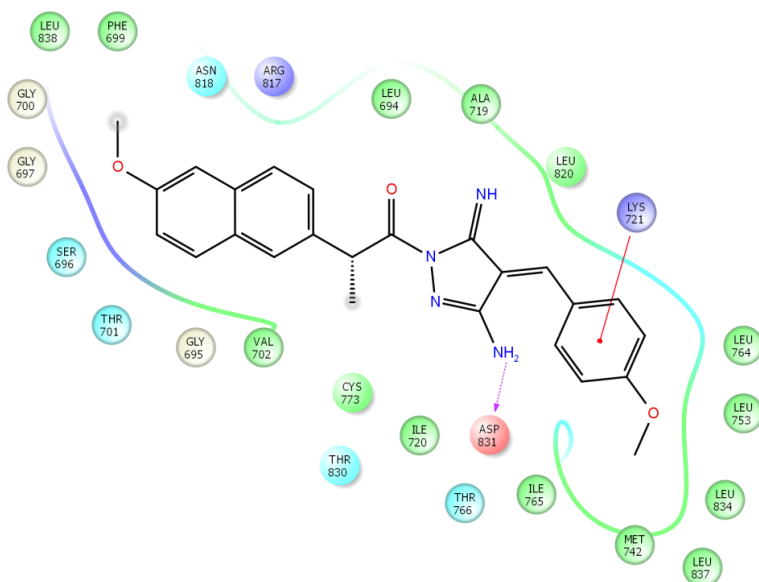


Fig. S2. 2D interactions of **c** with the active site.

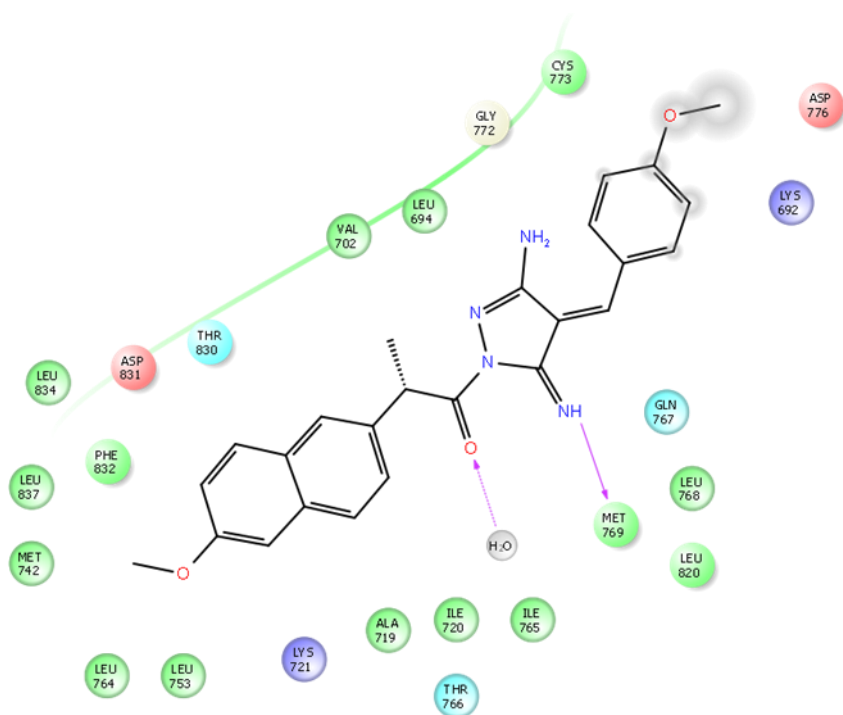


Fig. S2a. 2D interactions of **c** into the active site of EGFR according to quantum docking.

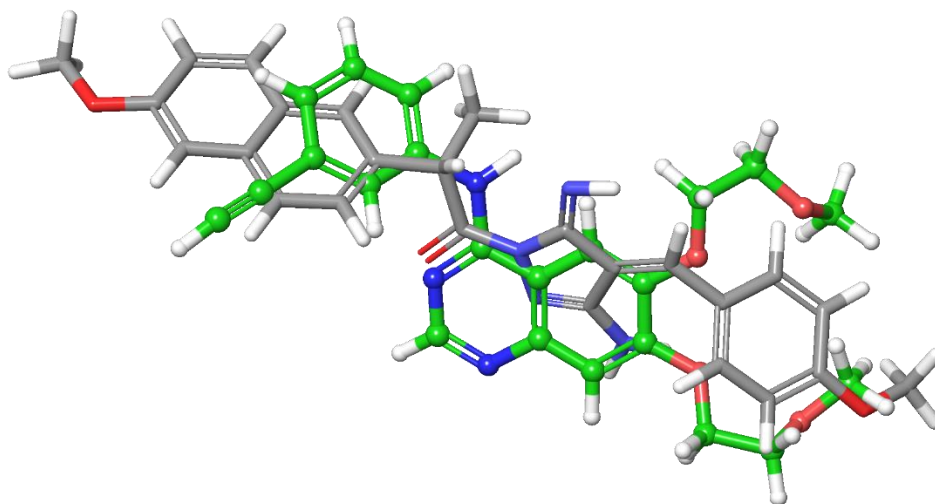


Fig. S2b. Superimposing of compound c and erlotinib in the active site according to quantum docking (erlotinib is green and compound c is gray).

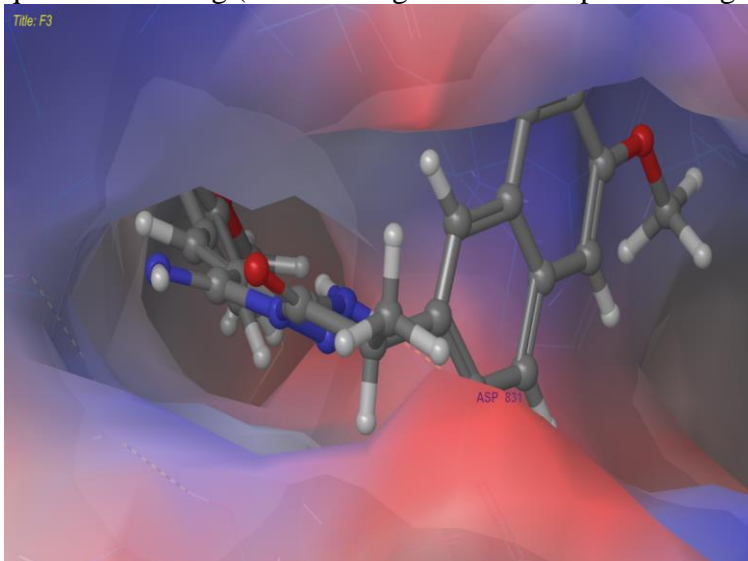


Fig. S3. Electrostatic interactions of c with EGFR binding pocket.

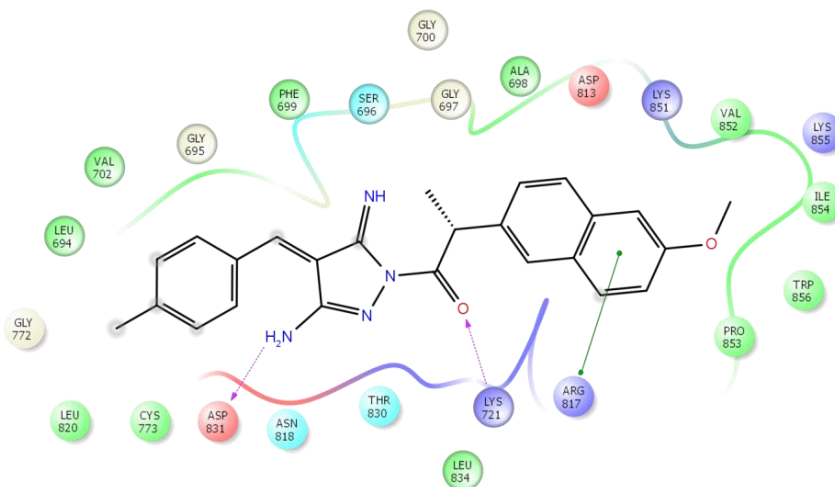


Fig. S4. 2D interactions of d with the active site.

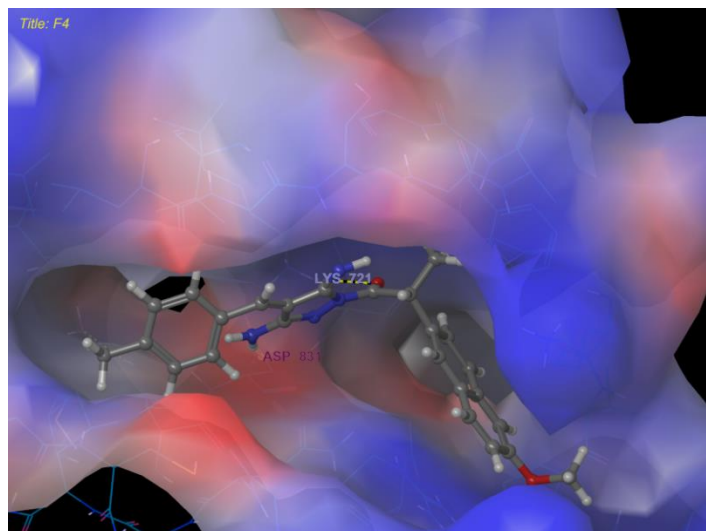


Fig. S5. Electrostatic interactions of **d** with EGFR binding pocket.

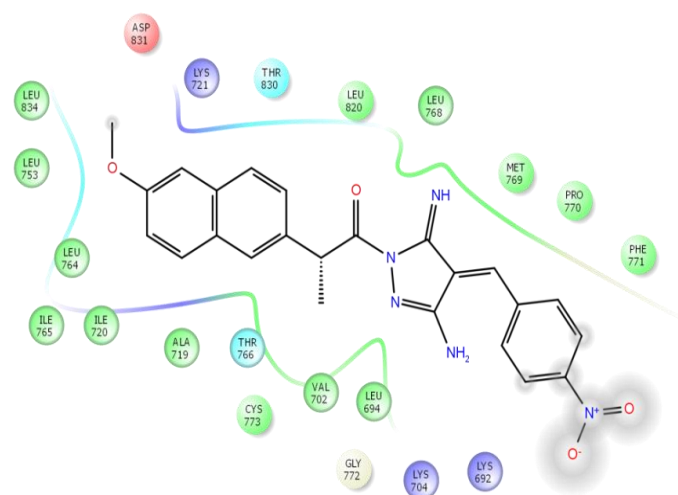


Fig. S6. 2D interactions of **e** with the active site.

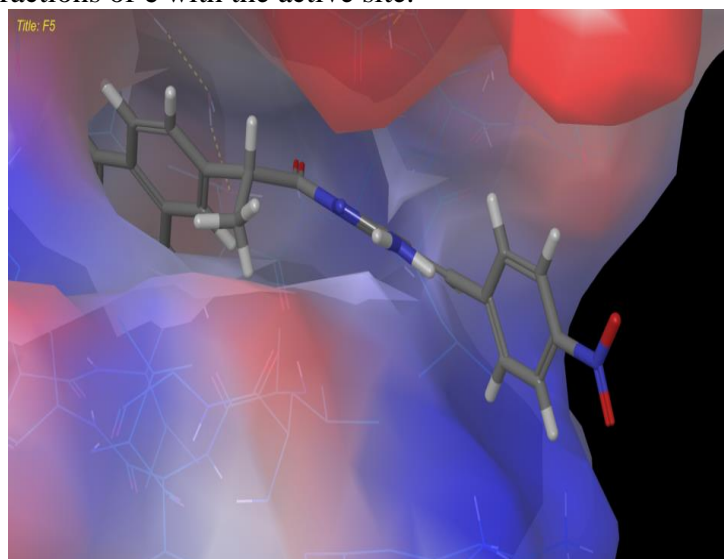


Fig. S7. Electrostatic interactions of **e** with EGFR binding pocket.

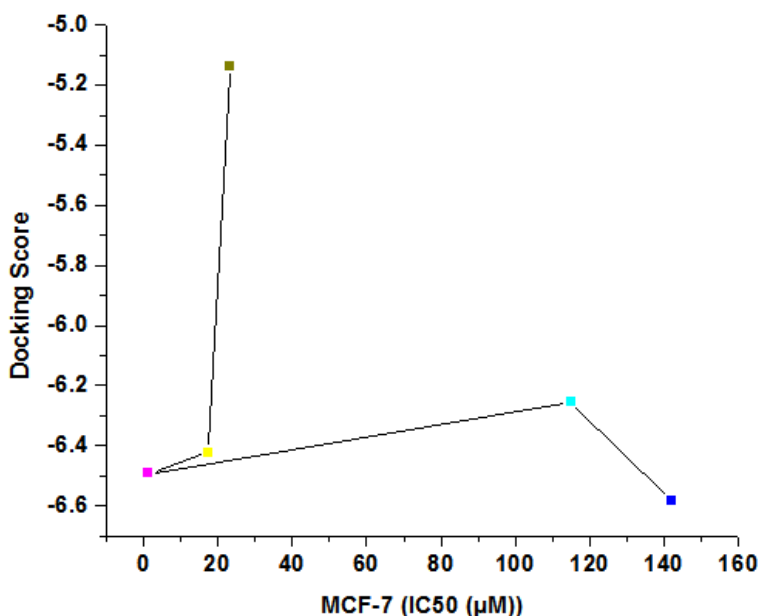


Fig. S8. The Experimental MCF-7 Vs docking score.

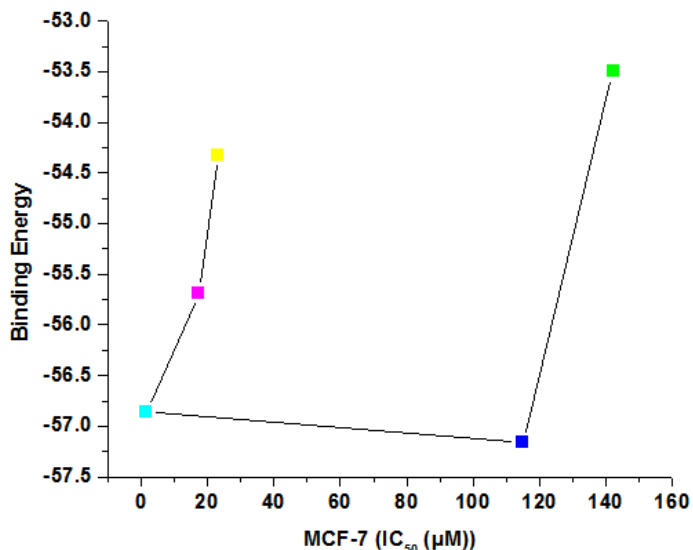


Fig. S9. The Experimental MCF-7 Vs binding energy.

Computational details

Mulliken electronegativity (χ) was calculated from as:

$$\chi = (E_{\text{HOMO}} + E_{\text{LUMO}})/2 \quad (1)$$

The hardness (η) was computed by using eq. 2:

$$\eta = (E_{\text{LUMO}} - E_{\text{HOMO}})/2 \quad (2)$$

Electrophilicity (ω) was calculated as:

$$\omega = (E_{\text{HOMO}} + E_{\text{LUMO}}/2)^2/2\eta \quad (3)$$

Softness (S) was calculated as:

$$S = 1/2\eta \quad (4)$$

Electrophilicity index (ω_i) was calculated by using eq. 5:

$$\omega_i = \mu^2/2\eta \quad (5)$$

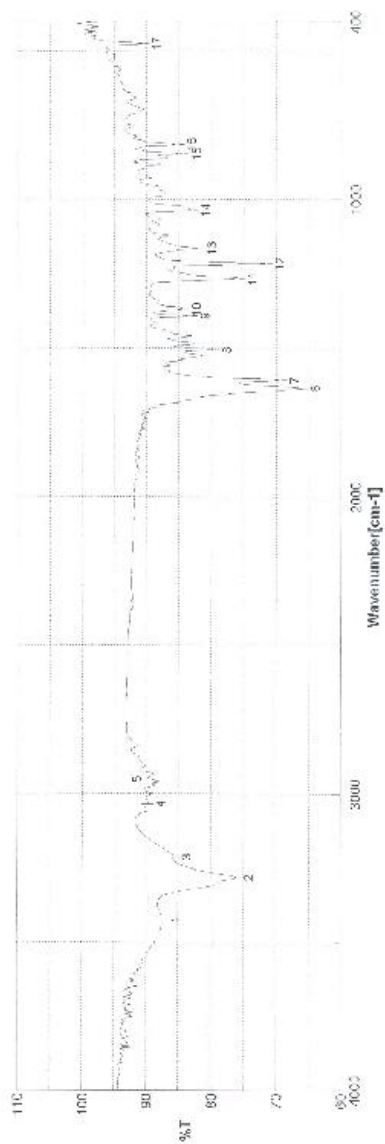
Chemical potential (μ) was calculated as:

$$\mu = -(E_{\text{HOMO}} + E_{\text{LUMO}})/2 \quad (6)$$

Ionization potentials (IP) have been calculated as under:

In vitro cytotoxic screening

Cytotoxic activity of the new compounds and doxorubicin was evaluated using Sulphorhodamine B (SRB) assay method [1, 2]. Human colon cancer cells (HCT 116), Human hepatic carcinoma (HepG2) and Human breast cancer cells (MCF-7) were maintained in RPMI media supplemented with 100 µg/mL streptomycin, 100 units/ml penicillin and 10% heat-inactivated fetal bovine serum in a humidified, 5% (v/v) CO₂ atmosphere at 37 °C. Exponentially growing cells were detached from dishes using 0.25% trypsin–EDTA and plated in 96-well plates at 1000 cells/well. After 24 hours of incubation, cells were exposed to various concentrations of tested compounds for 48 hours. At the end of treatment time, cells were fixed with TCA (10%) for 1h at 4°C, washed several times with distilled water, stained with 0.4% SRB solution for 10 min in a dark place and washed with 1% glacial acetic acid. After drying overnight, Tris–HCl was used to dissolve the SRB-stained cells and the color intensity was measured at 570 nm using microplate reader (Anthos Zenyth-200RT, Cambridge, England). Doxorubicin was used as a positive control.



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Sample Name
Comment

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Rep. CON (101) /

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Scanning Speed
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2	1706.87	1655.17	1604.2	1553.5
3	1585.37	1533.93	1482.97	1431.93
4	1214.92	1162.37	1110.81	1059.26
5	1044.77	992.25	940.69	888.63

No.	Wavenumber (cm⁻¹)	Wavenumber (cm⁻¹)	Wavenumber (cm⁻¹)	Wavenumber (cm⁻¹)
6	814.77	762.71	710.65	658.59
7	644.40	592.34	540.28	488.22
8	474.40	422.28	370.22	318.16
9	304.40	252.34	200.28	148.22
10	178.17	126.11	74.05	21.99
11	158.54	106.48	54.42	2.36
12	138.91	86.85	34.79	12.73
13	119.28	67.22	15.16	0.10
14	100.65	47.59	-5.47	-10.64
15	81.02	27.96	-25.84	-30.99
16	61.39	8.33	-41.21	-51.24
17	41.76	-12.34	-51.56	-61.59

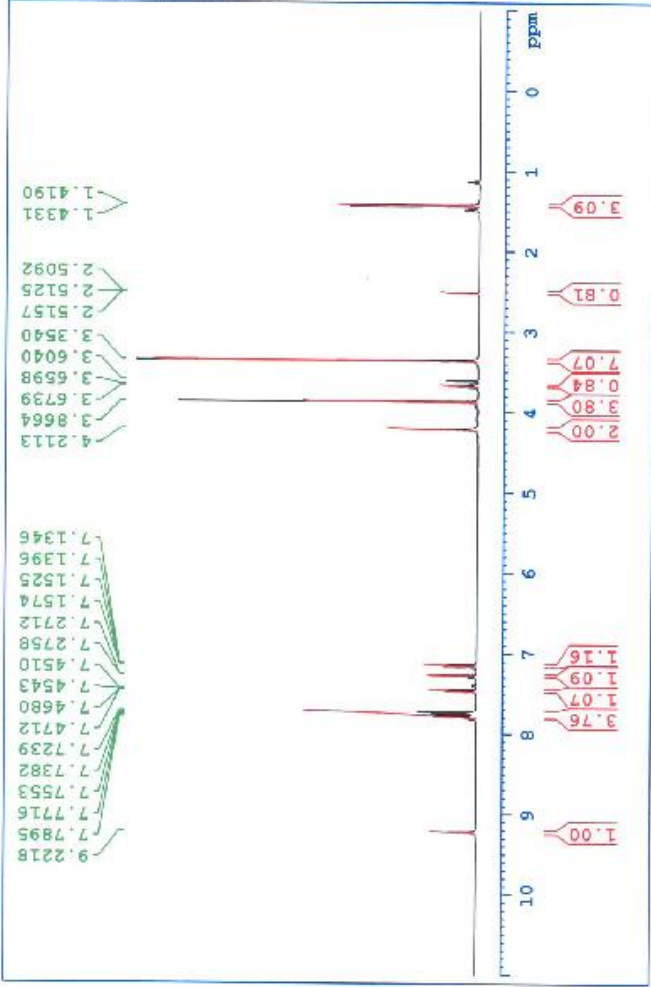
The FTIR spectra of compound (III)



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¹H (AGS-NH)



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PROCNO: 2
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F3: 1
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RG2: 327.5
RG3: 327.5
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NUC2: 13C
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PC: 1.50000000 s
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PE: 0.01000000 s
PR: 1.50000000 s
PS: 1.50000000 s
PT: 1.50000000 s
RF1: 500.136101 MHz
RF2: 500.136101 MHz
RF3: 500.136101 MHz
SOLVENT: CDCl₃
INSTRUM: spect
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RG3: 327.5
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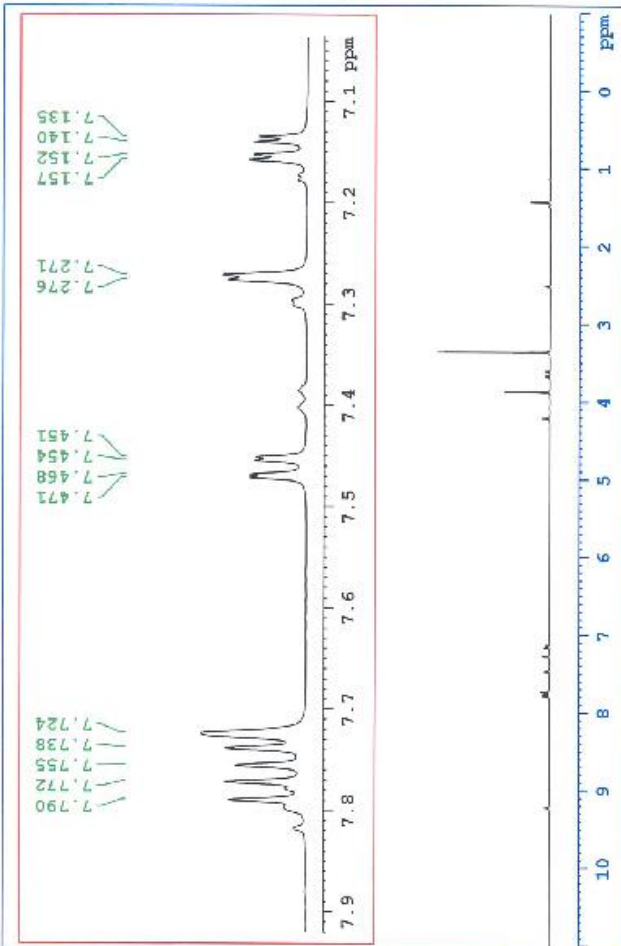


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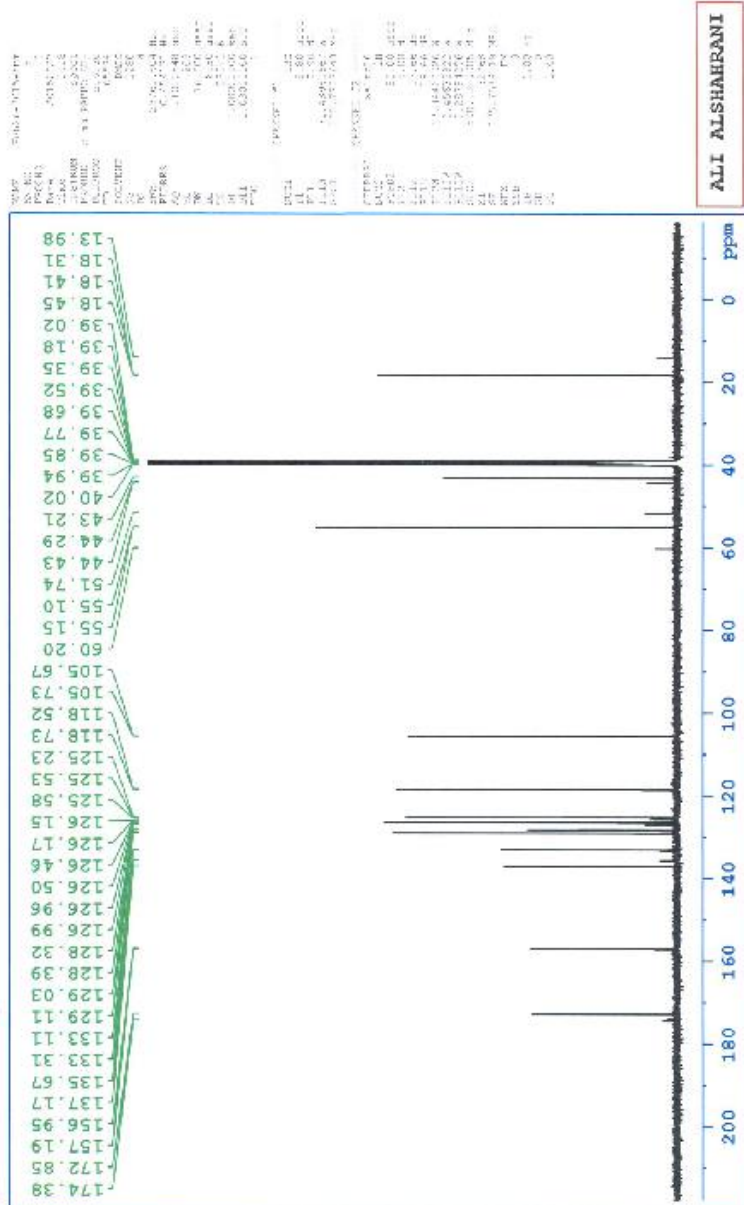
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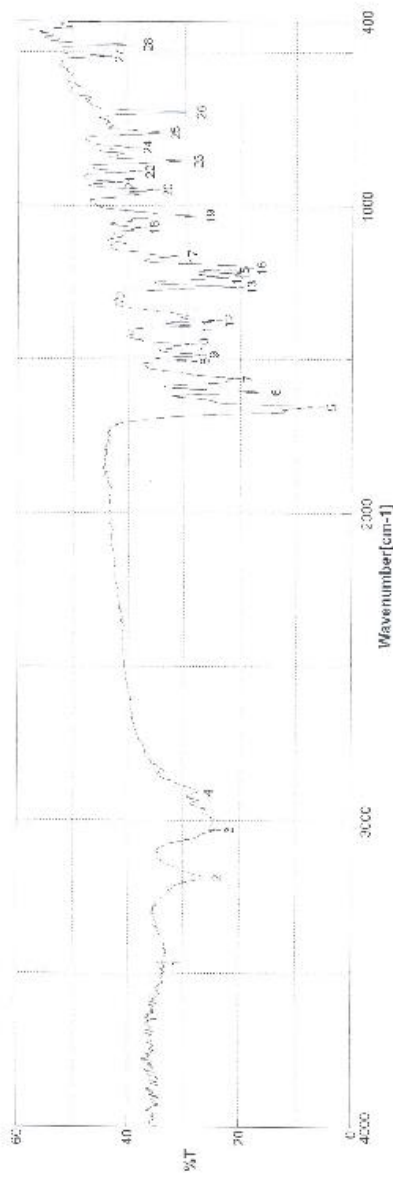


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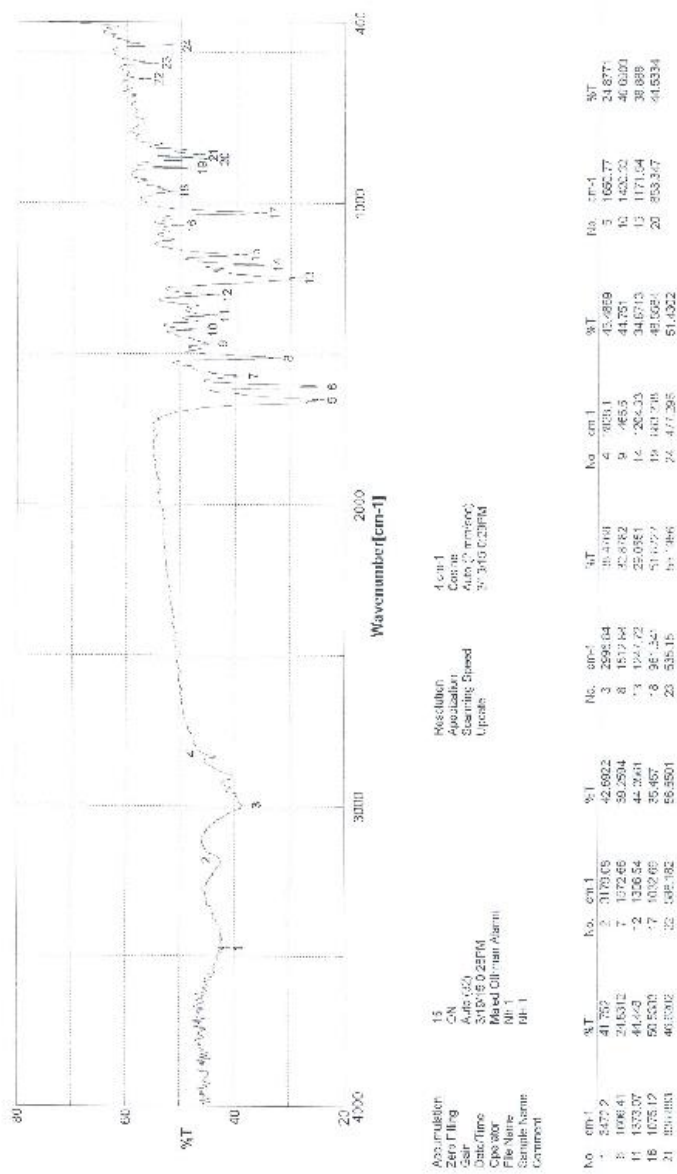
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The NMR spectra of compound (III)

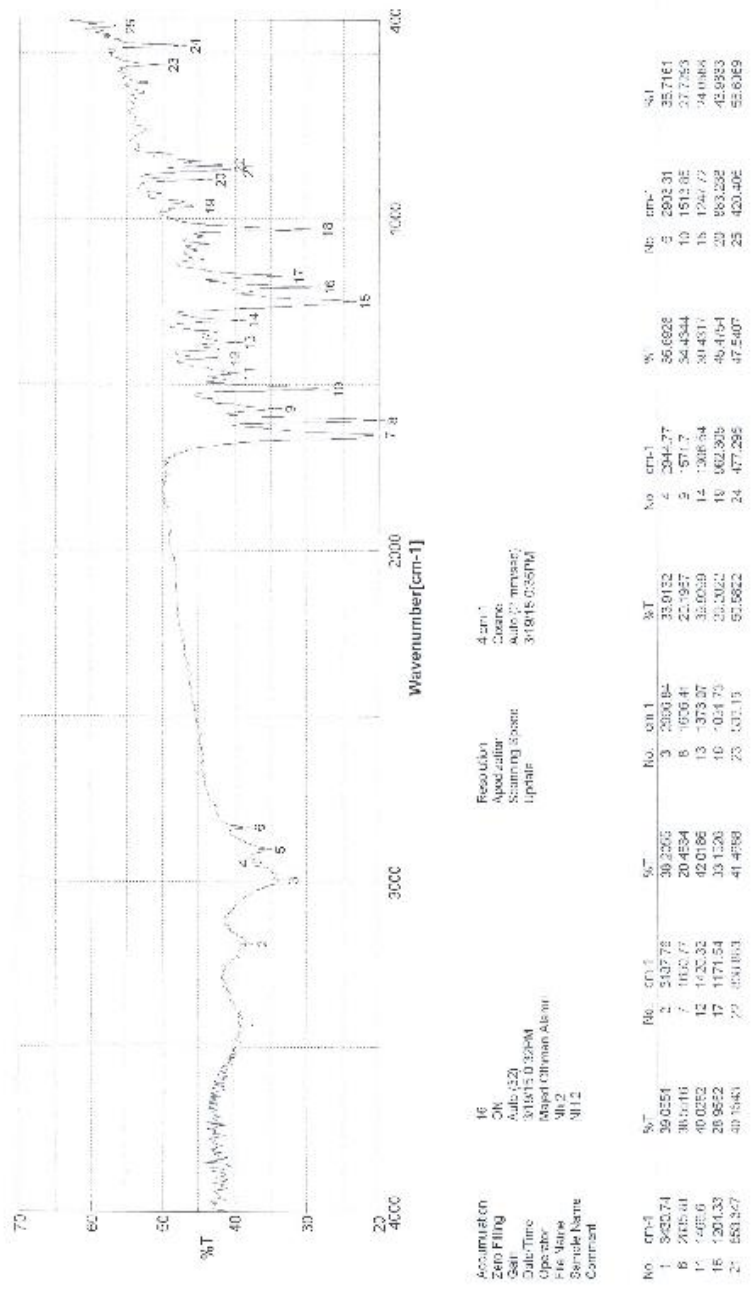


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Operator				Sample Speed							
Intr Name				NH 5							
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6	1605.45	16.0668	7	1561.08	24.1535	9	1525.17	10	1451.17	20.8176	
11	1367.39	24.4467	12	1374.03	24.5014	13	1295.07	15	1215.79	21.8128	
16	1272.4	18.7984	17	1194.04	31.0107	18	1070.3	20	850.005	35.6326	
21	823.735	42.3084	22	808.068	38.6616	23	554.371	24	761.744	34.1450	
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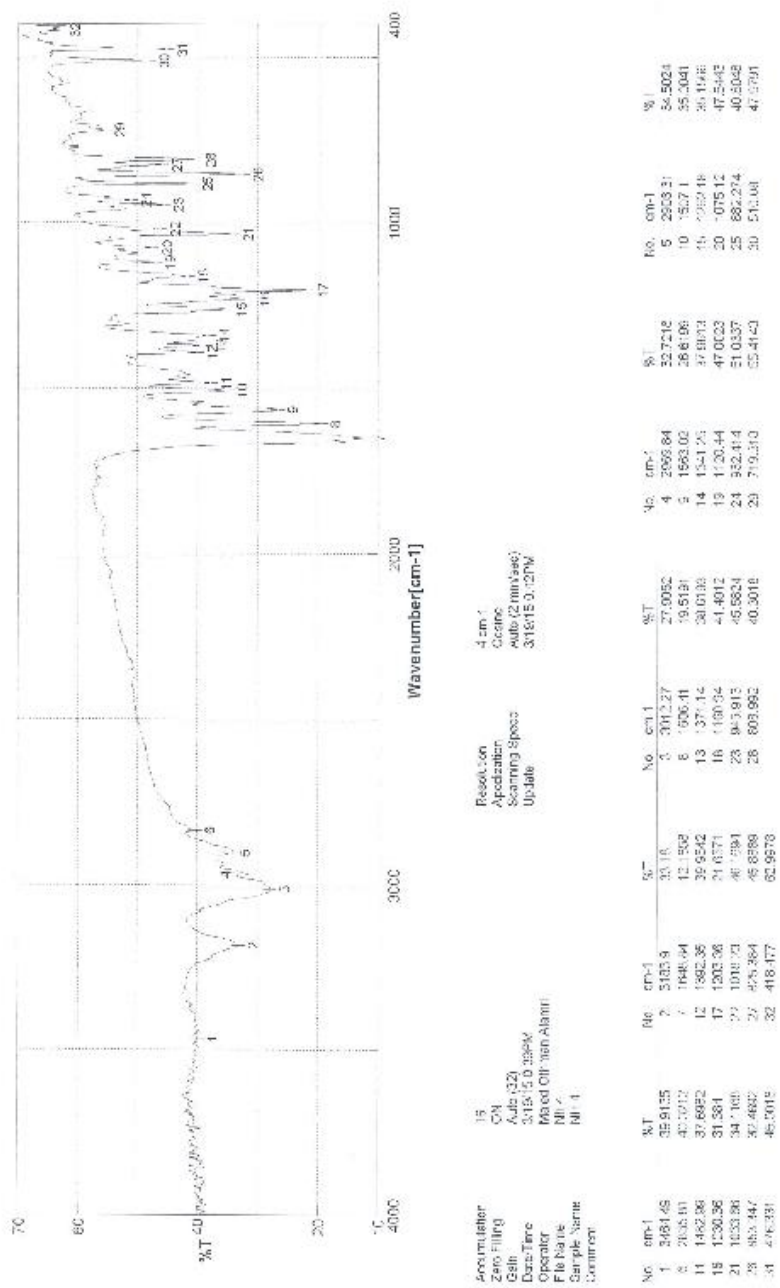
The FTIR spectra of the studied naproxen derivative (a)



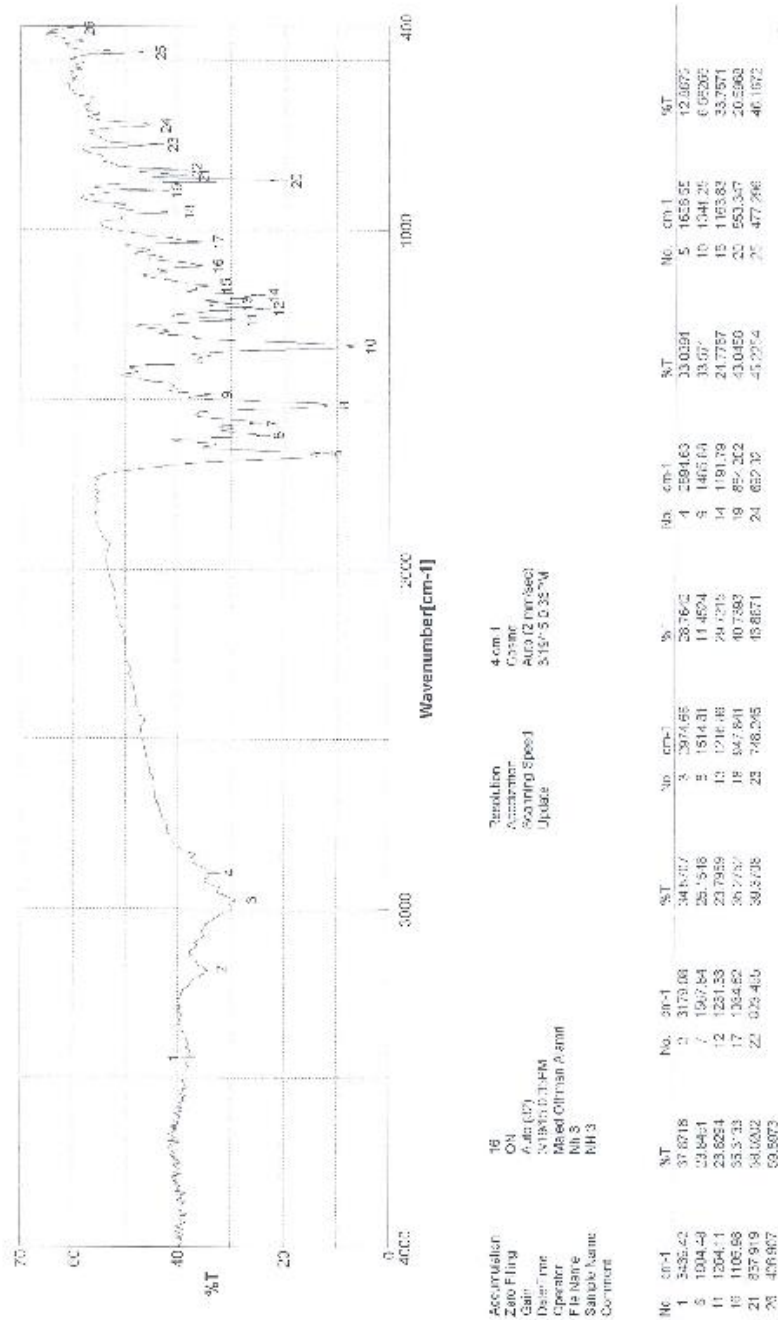
The FTIR spectra of the studied naproxen derivative (b)



The FTIR spectra of the studied naproxen derivative (c)



The FTIR spectra of the studied naproxen derivative (d)



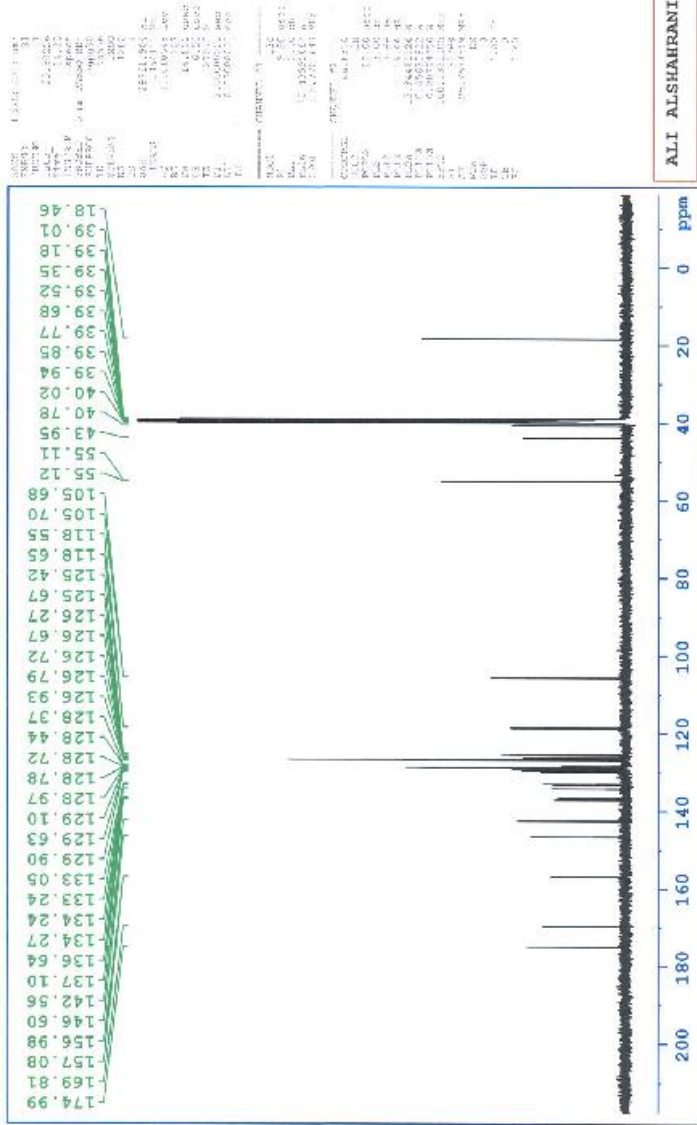
The FTIR spectra of the studied naproxen derivative (e)



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¹³C (AGS-NH5)



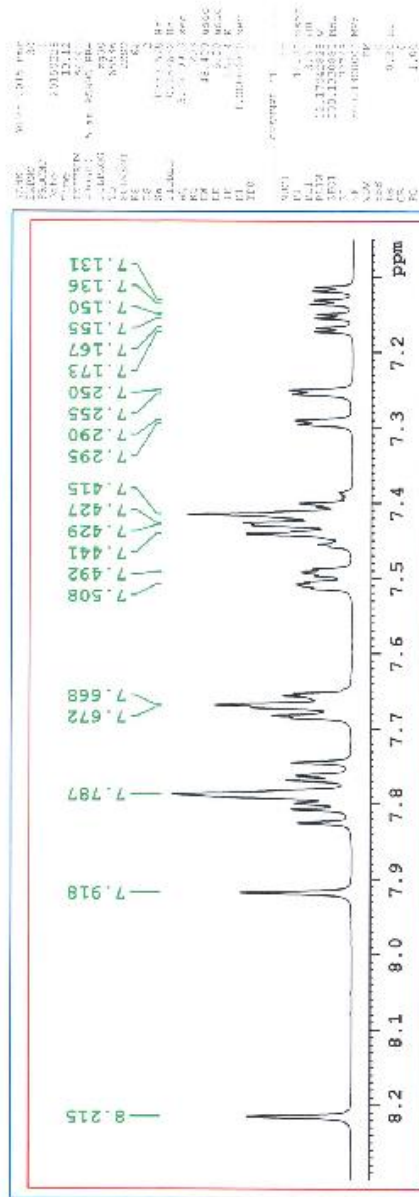
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¹H (ACS-NH5)



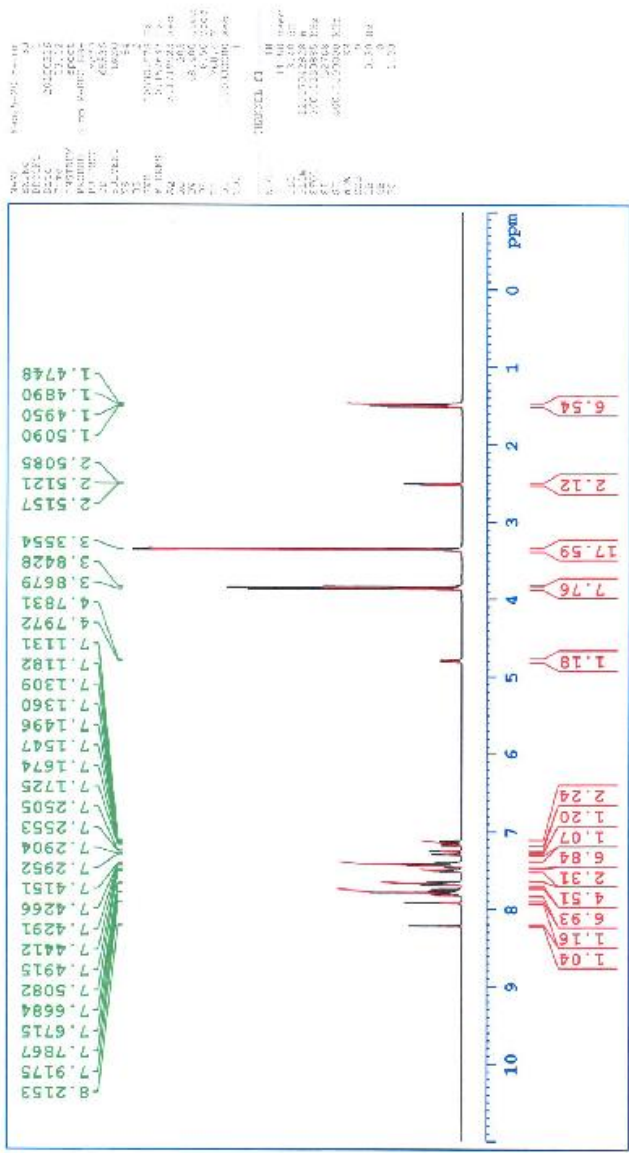
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¹H (AGS-NMS)



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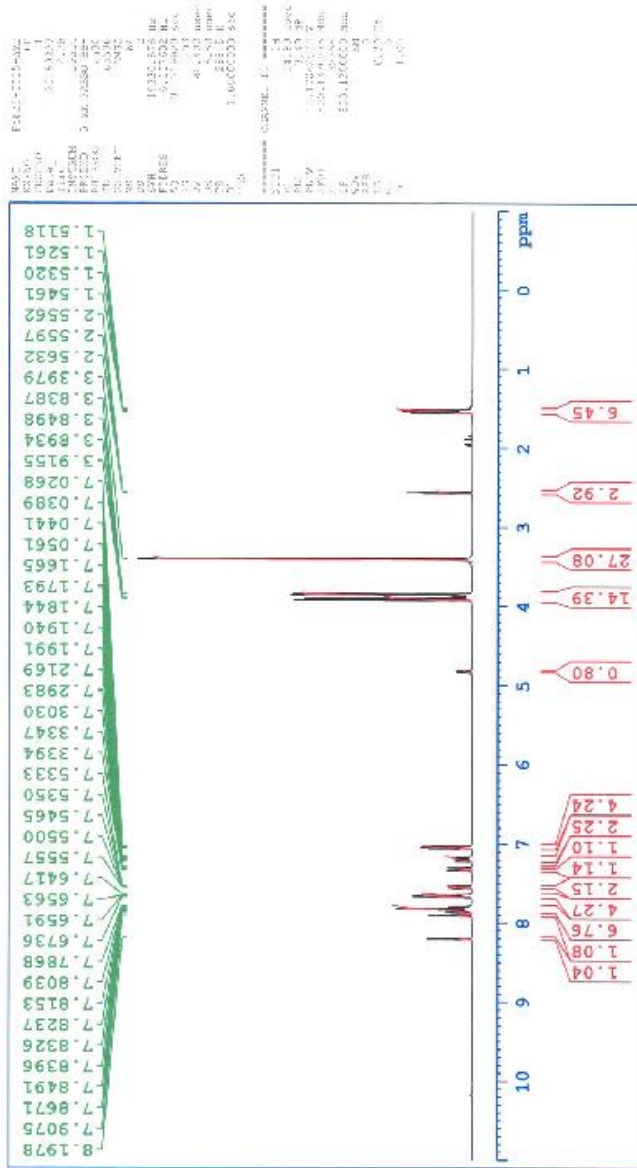
The NMR spectra of the studied naproxen derivative (a)



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¹H (AGS-NH1)



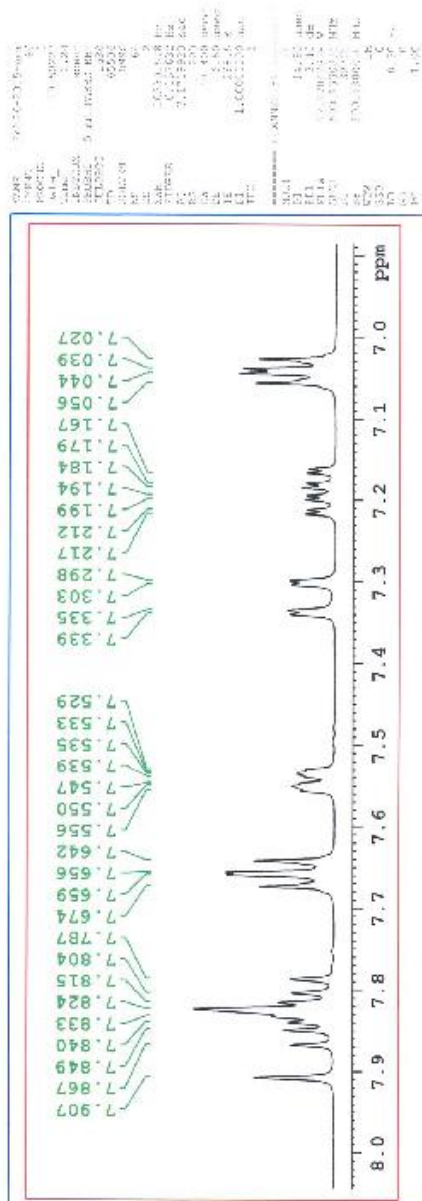
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¹H (AGS-NH1)



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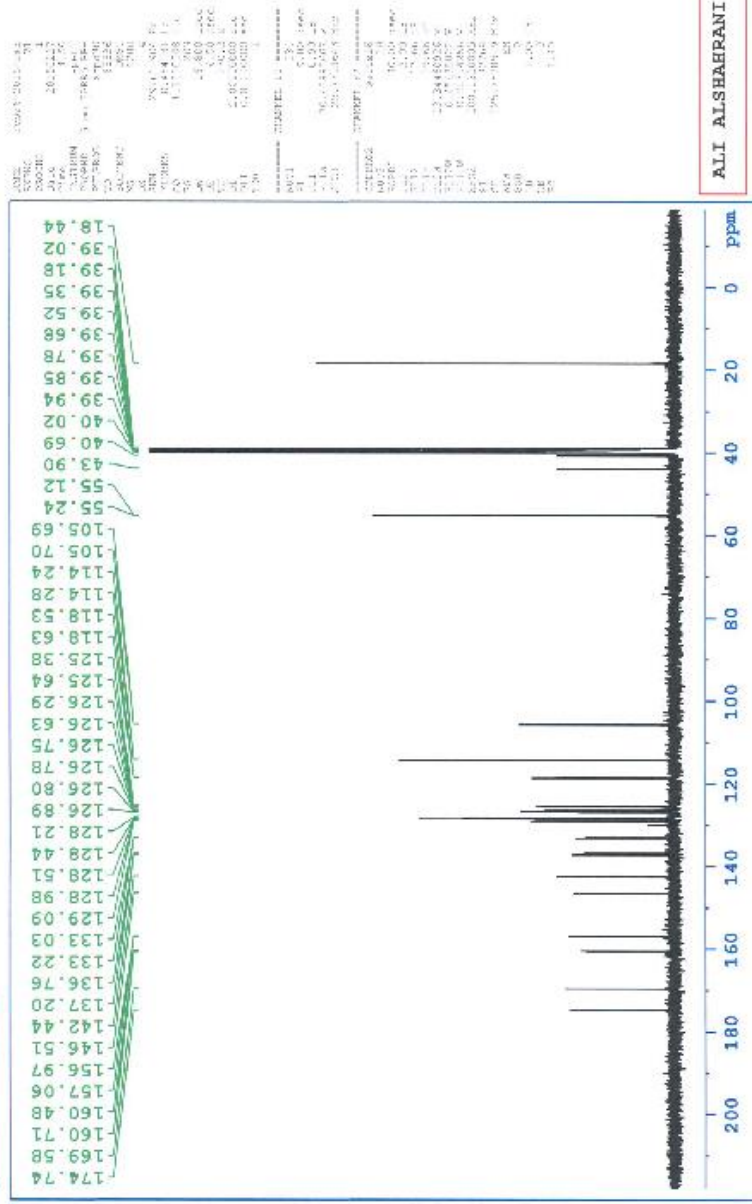
The NMR spectra of the studied naproxen derivative (b)



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13C (AGS-NH2)



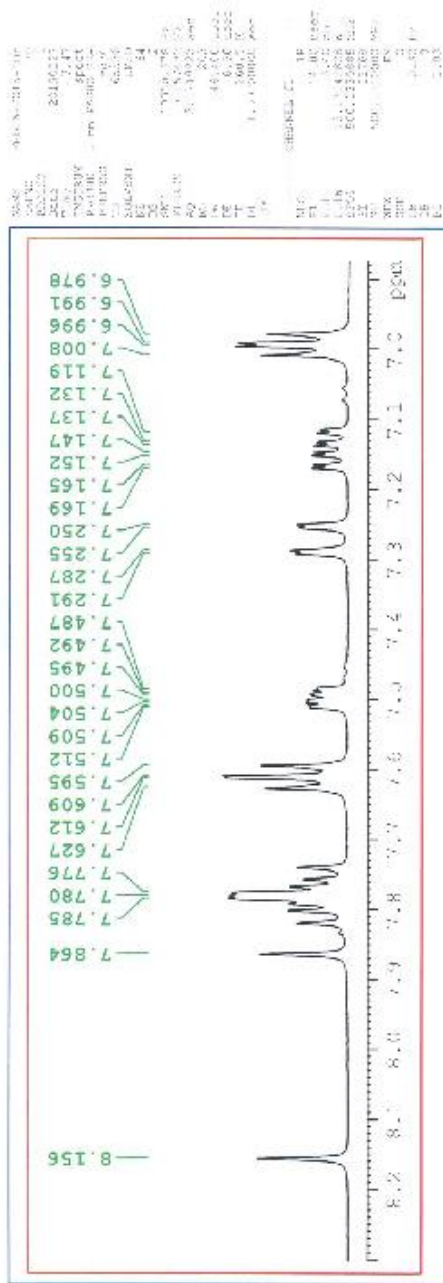
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¹H (AGS-NH2)



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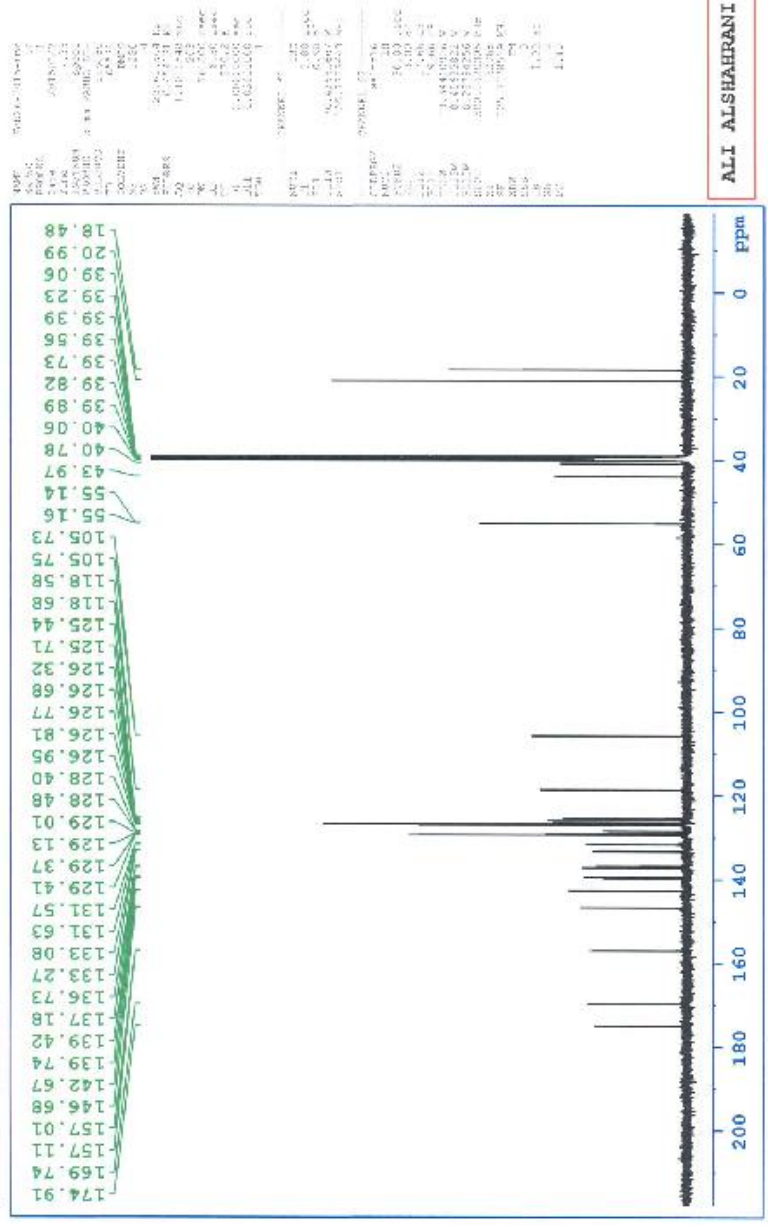
The NMR spectra of the studied naproxen derivative (c)



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1.3C (AGS-NB4)



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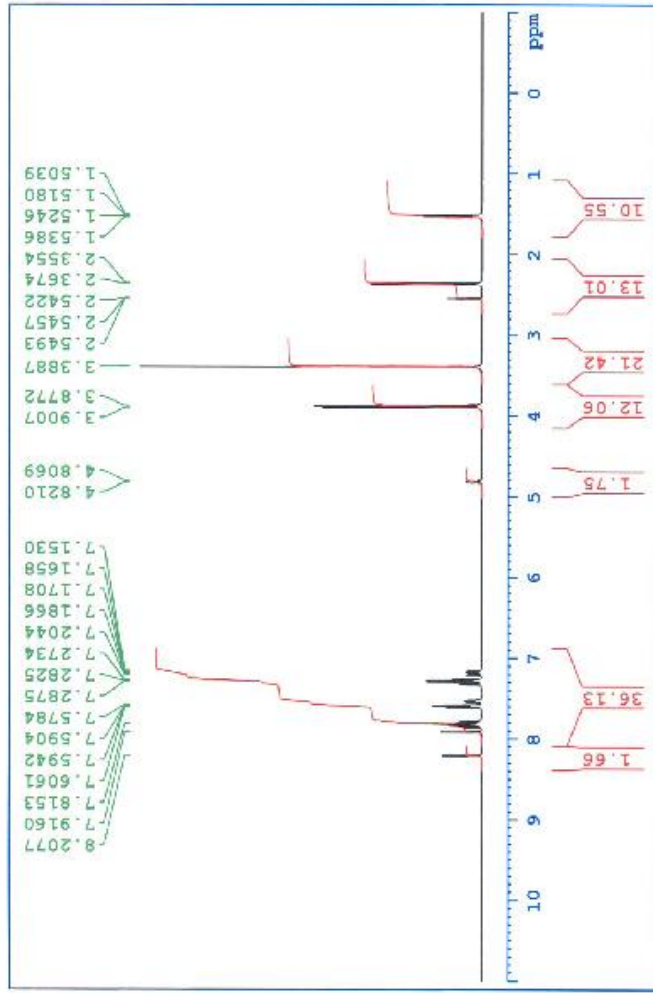


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¹H (AGS-NH4)

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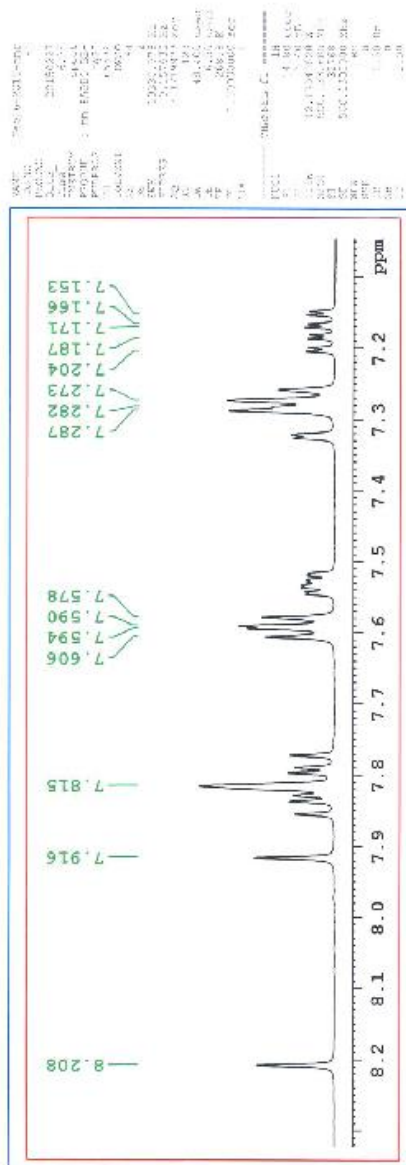
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¹H (ACS-NH4)



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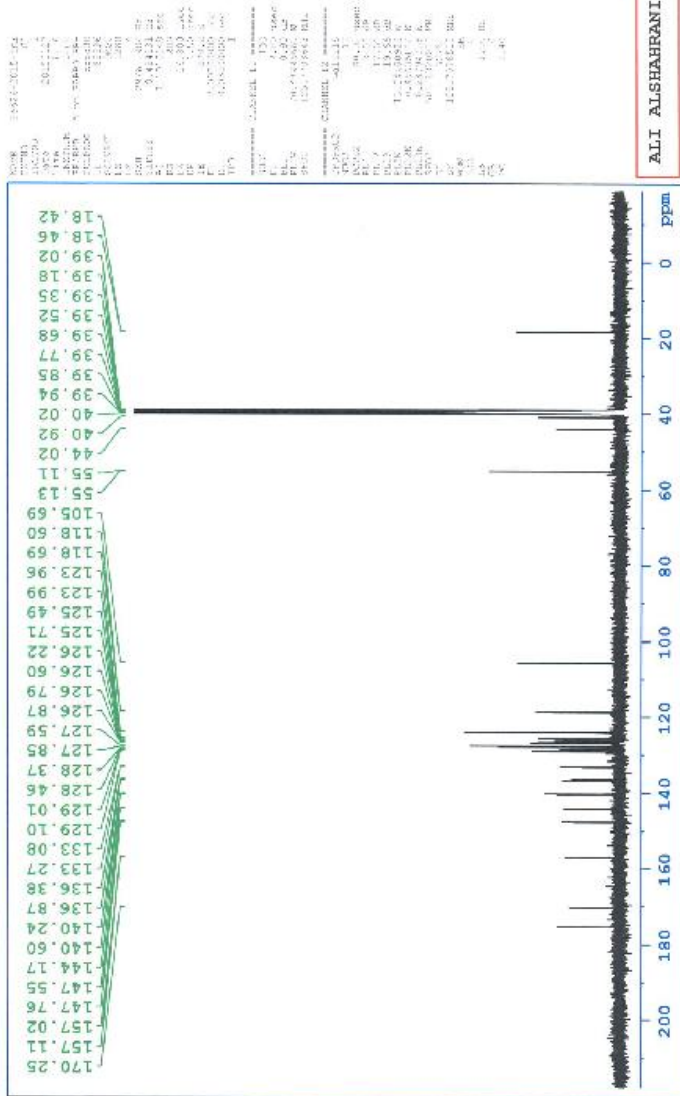
The NMR spectra of the studied naproxen derivative (d)



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¹³C (AGS-NH3)

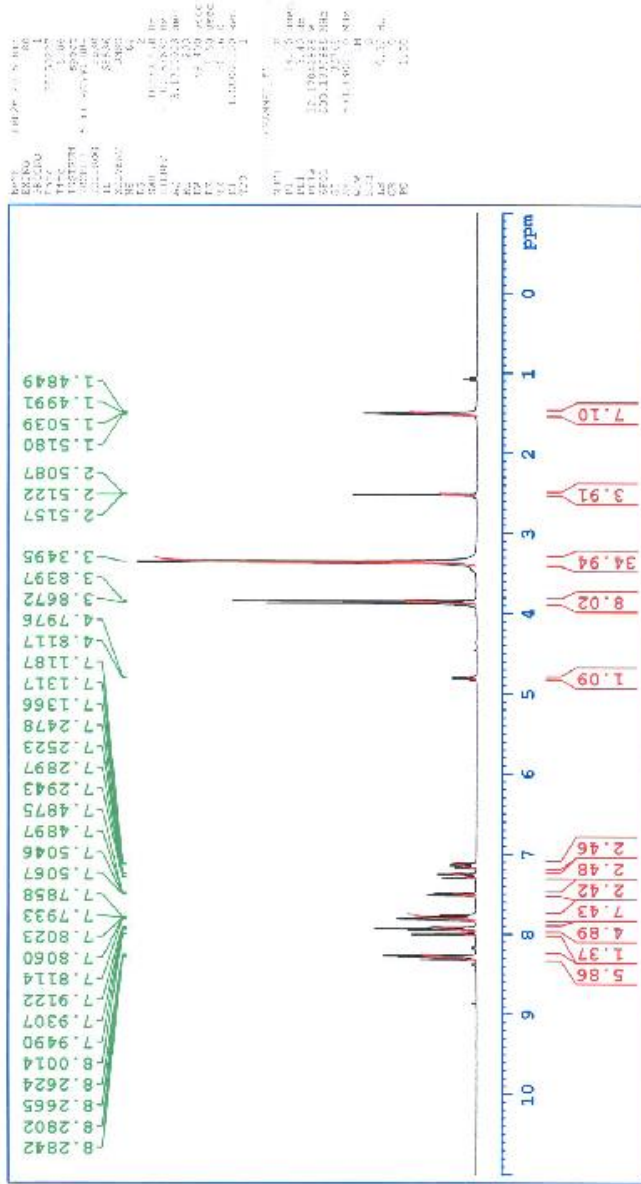




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¹H (AGS-NH3)



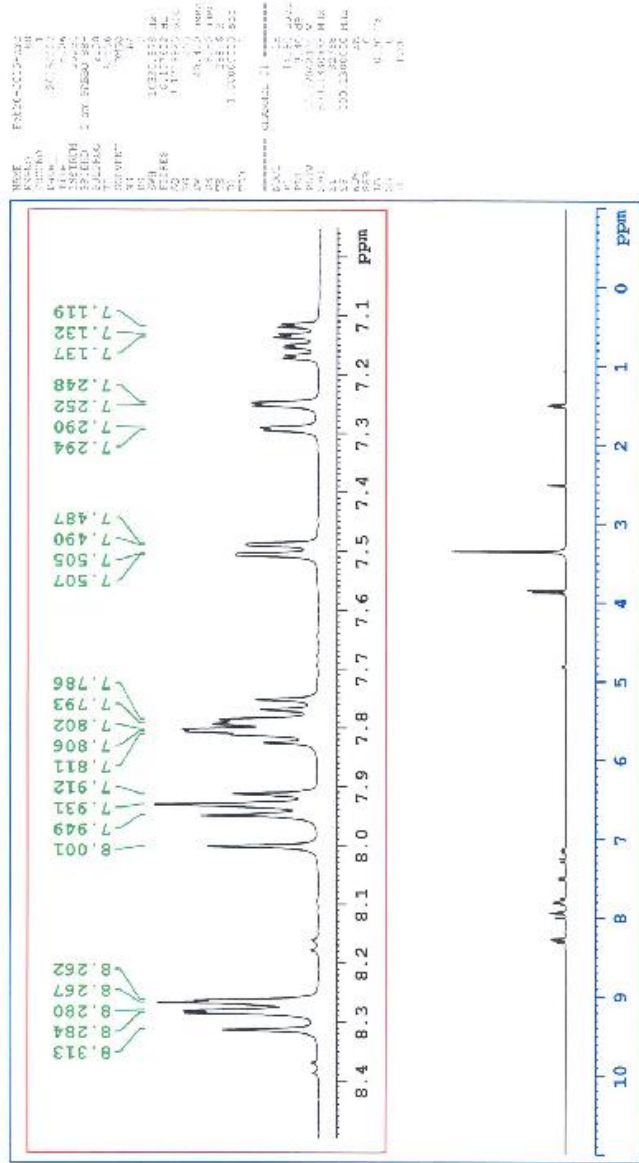
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¹H (AGS-NH3)



ALI ALSHARANI

The NMR spectra of the studied naproxen derivative (e)

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