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
ωi	1.46	1.56	1.37	1.31	2.21
IP	5.60	5.65	5.55	5.68	5.77

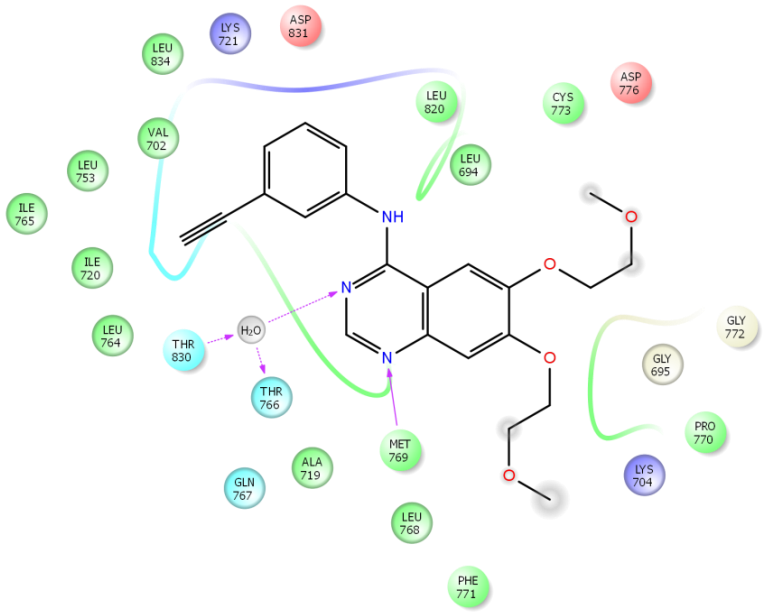


Fig. S1. 2D interactions of native ligand; erlotinib into the active site of EGFR.

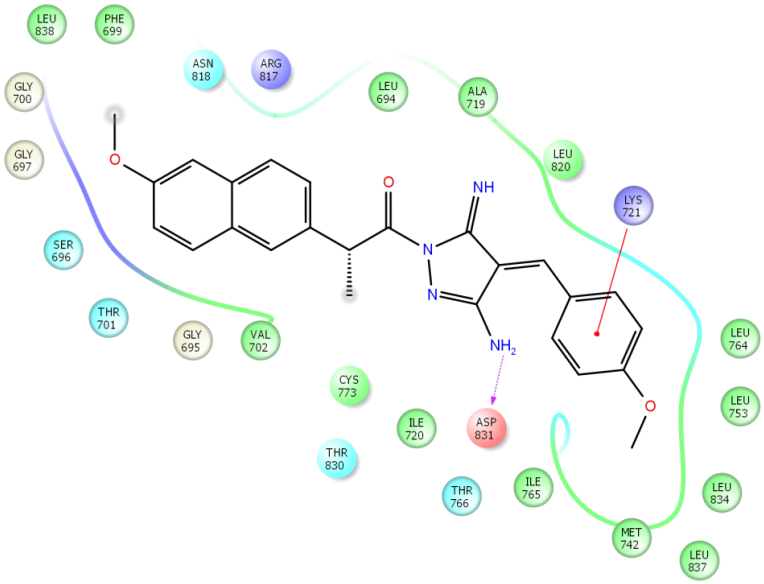


Fig. S2. 2D interactions of **c** with the active site.

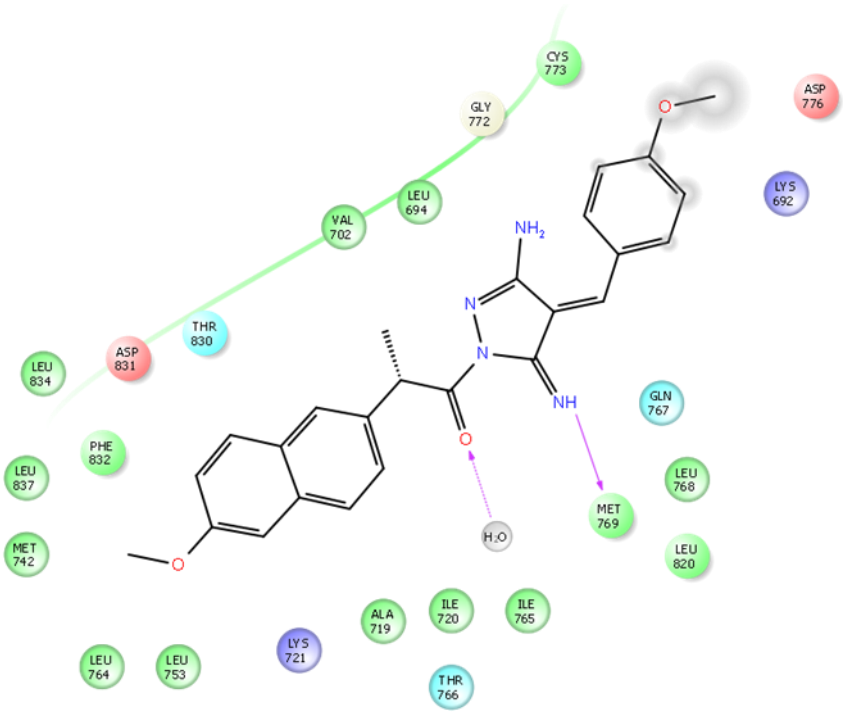


Fig. S2a. 2D interactions of c into the active site of EGFR according to quantum docking.

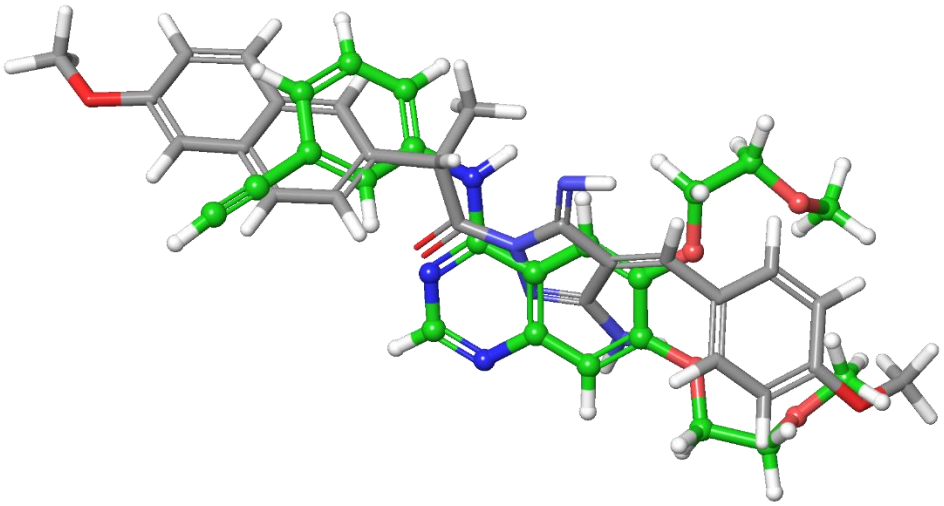


Fig. S2b. Superimposing of compound c and erlotinib in the active site according to quantum docking (erlotinib is green and compound c is gray).

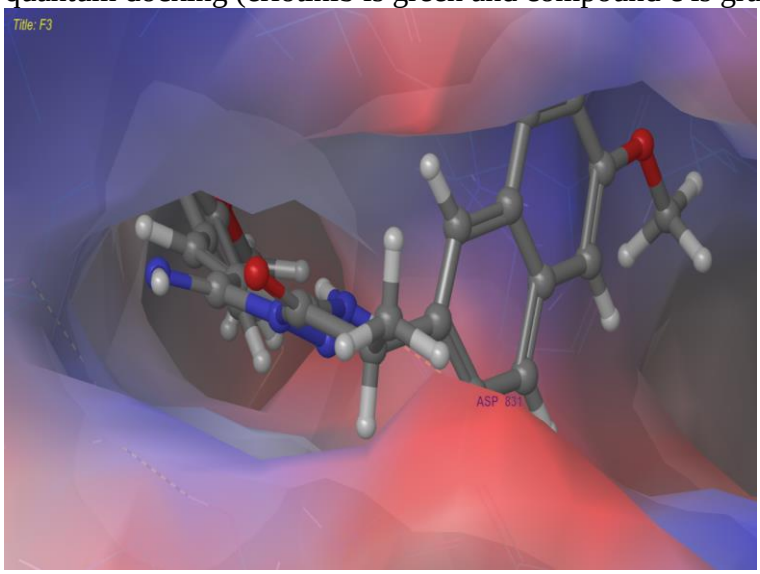


Fig. S3. Electrostatic interactions of **c** with EGFR binding pocket.

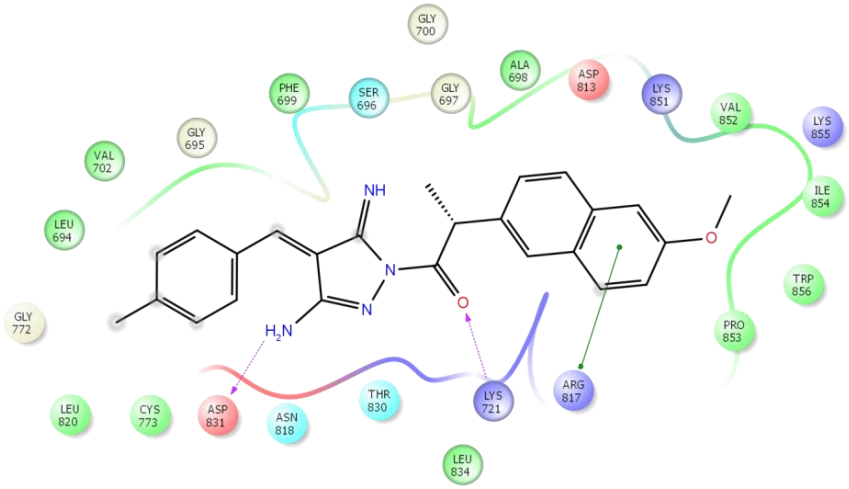


Fig. S4. 2D interactions of **d** with the active site.

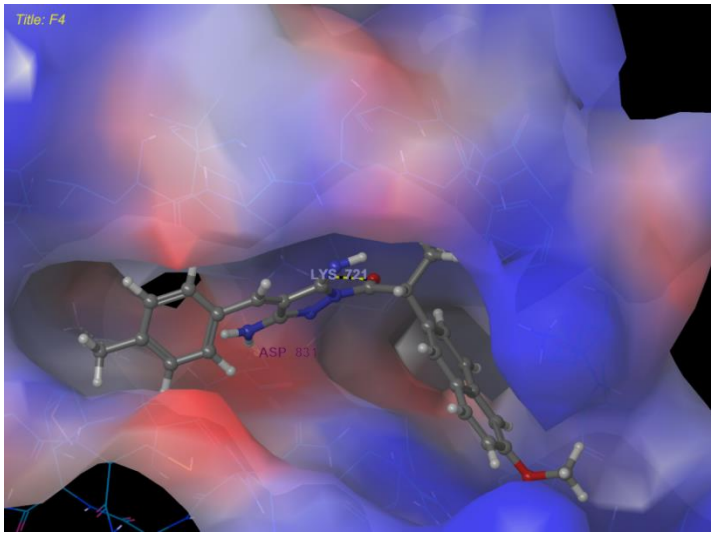


Fig. S5. Electrostatic interactions of **d** with EGFR binding pocket.

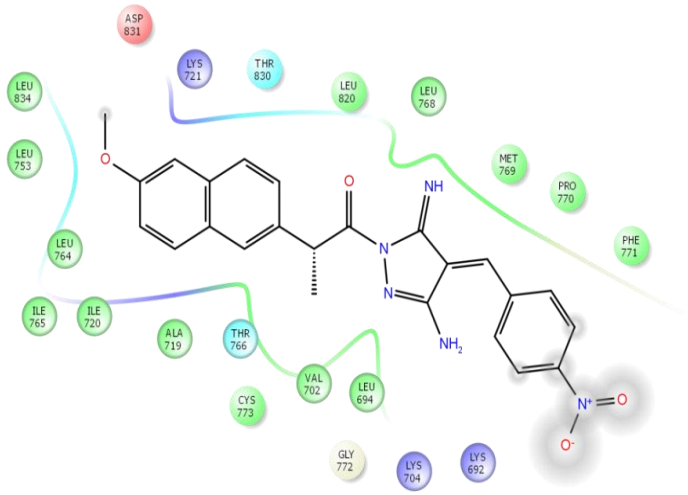


Fig. S6. 2D interactions of **e** with the active site.

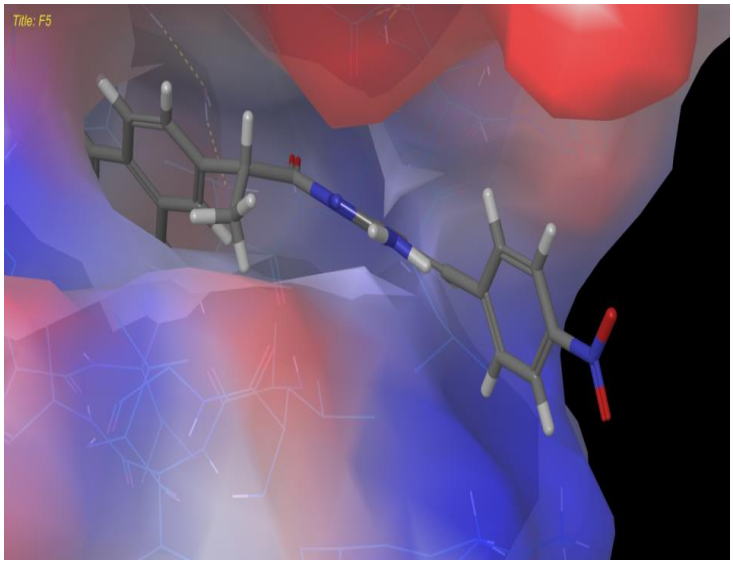


Fig. S7. Electrostatic interactions of **e** with EGFR binding pocket.

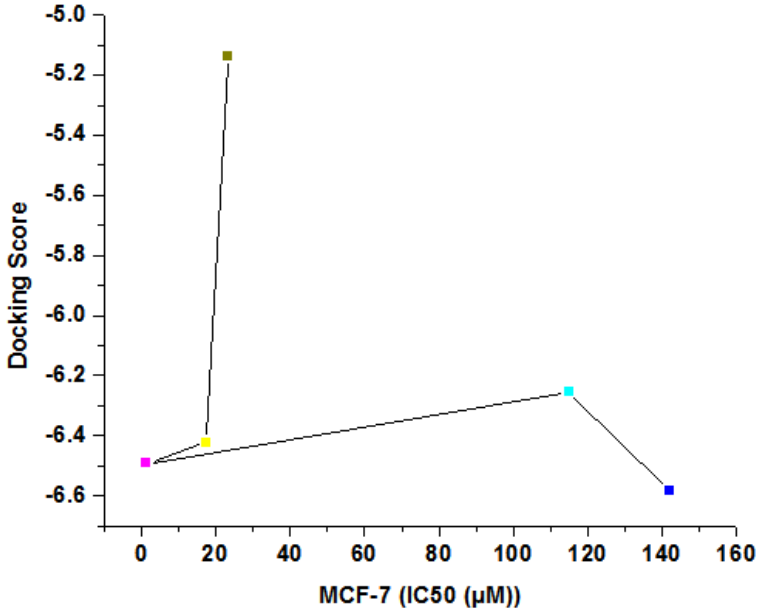


Fig. S8. The Experimental MCF-7 Vs docking score.

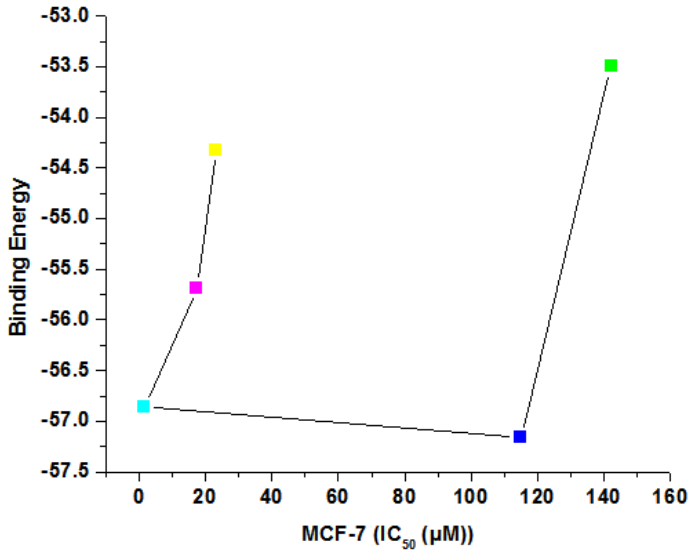


Fig. S9. The Experimental MCF-7 Vs binding energy.

Computational details

Mulliken electronegativity (χ) was calculated from as:

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

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

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

Electrophilicity (ω) was calculated as:

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

Softness (S) was calculated as:

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

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

$\omega i = \mu^2/2\eta$ (5)

Chemical potential (μ) was calculated as:

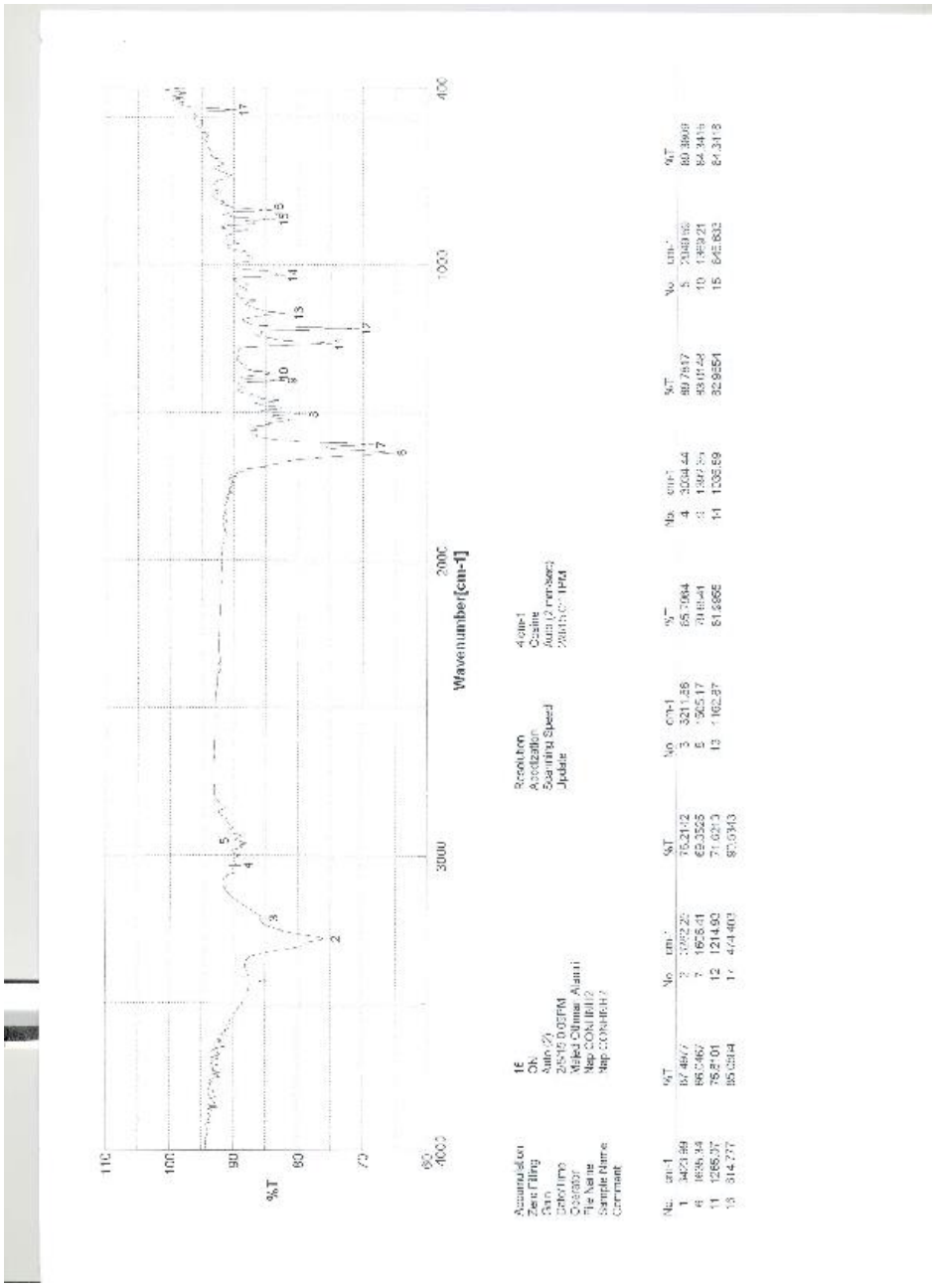
$\mu = -(HOMO + LUMO/2)$ (6)

Ionization potentials (IP) have been calculated as under:

$IP = -E_{HOMO}$ (7)

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) CO_2 atmosphere at 37 ºC. 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.

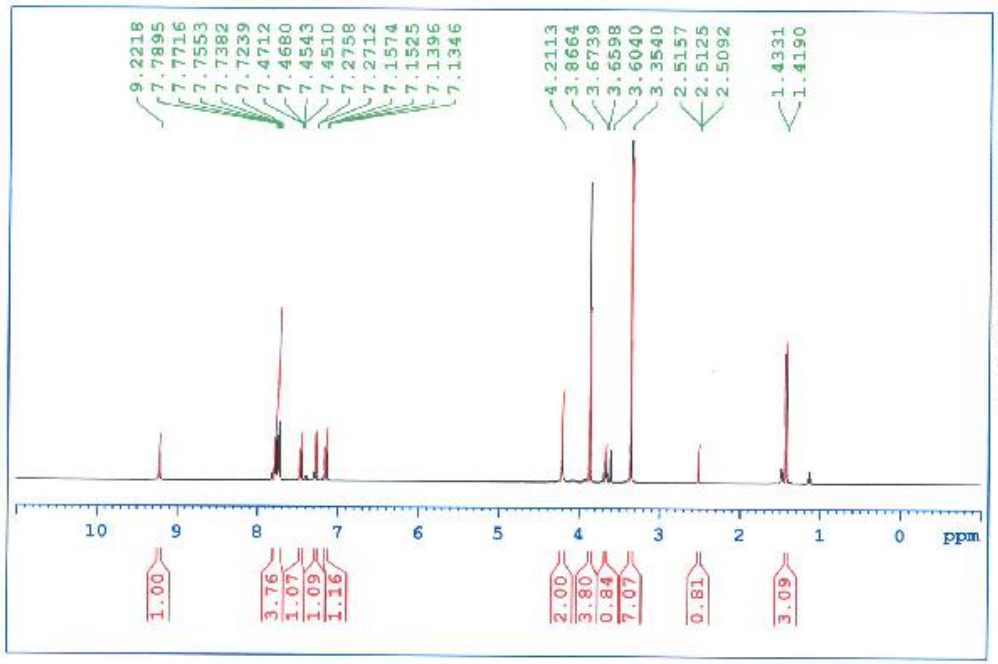


The FTIR spectra of compound (III)

NMR 500 MHz Ultra Shield™

BRUKER

1H (AGS-NH)

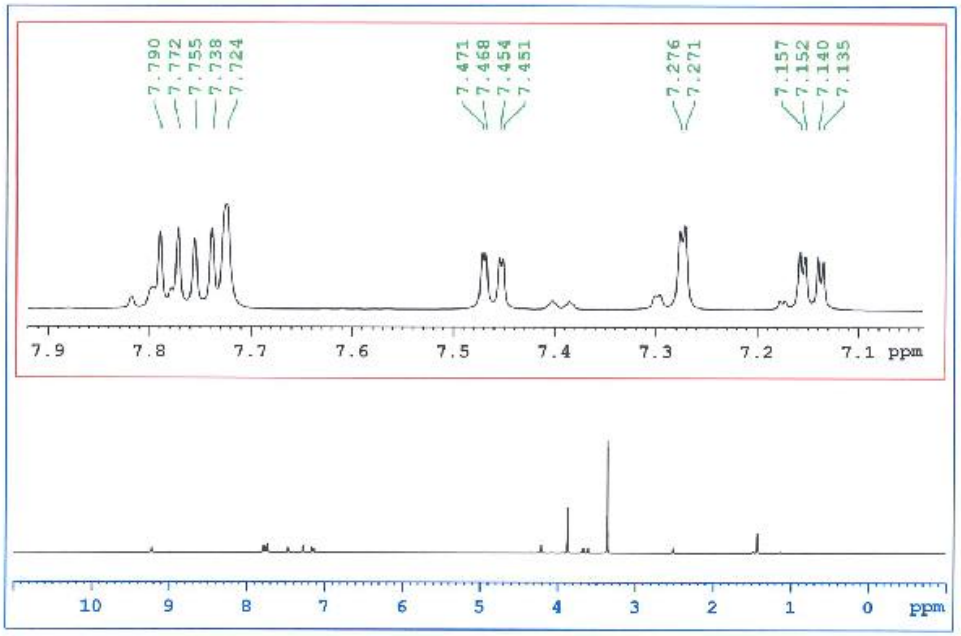


ALI ALSHAHRANI

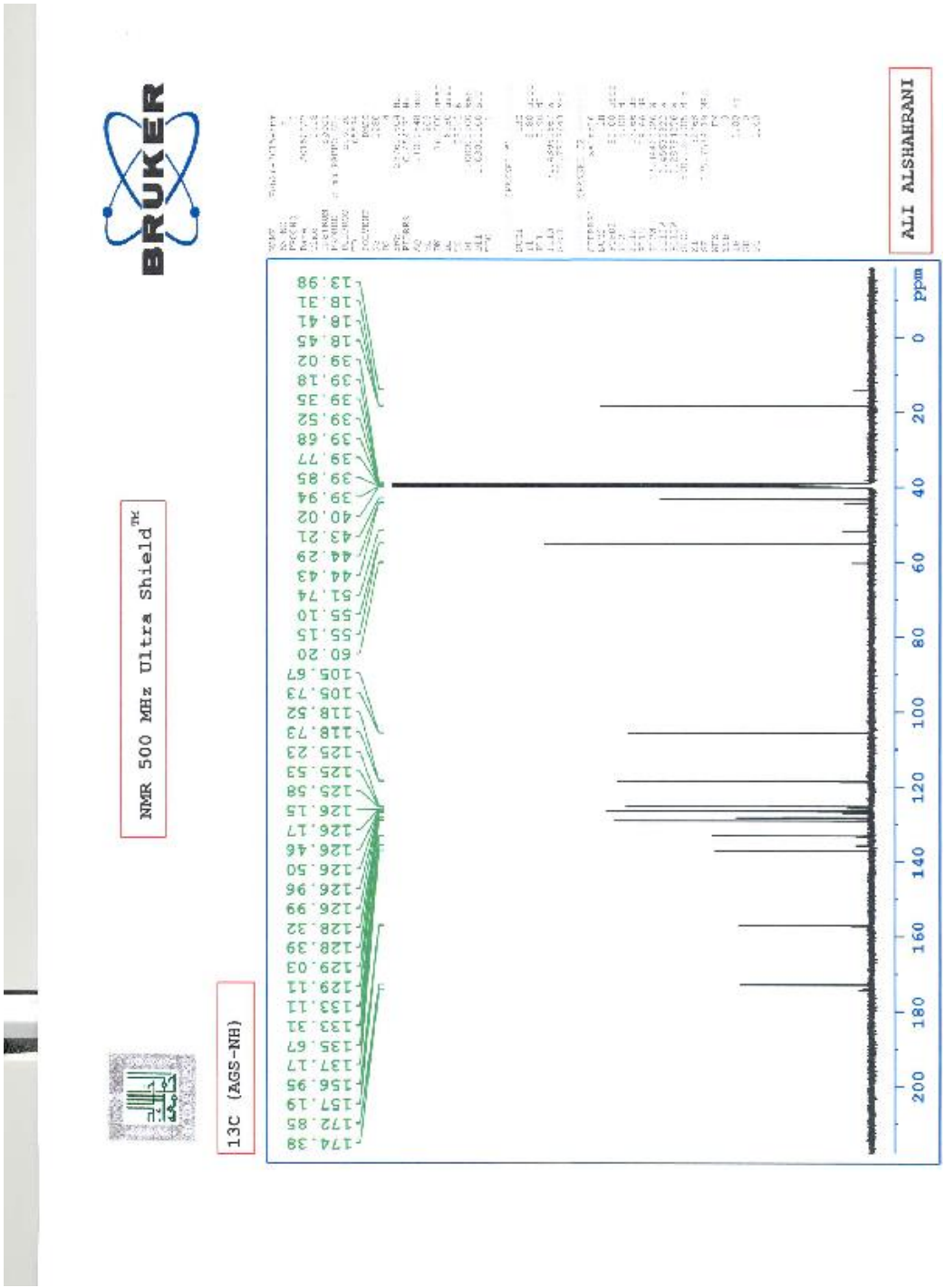
NMR 500 MHz Ultra Shield™

BRUKER

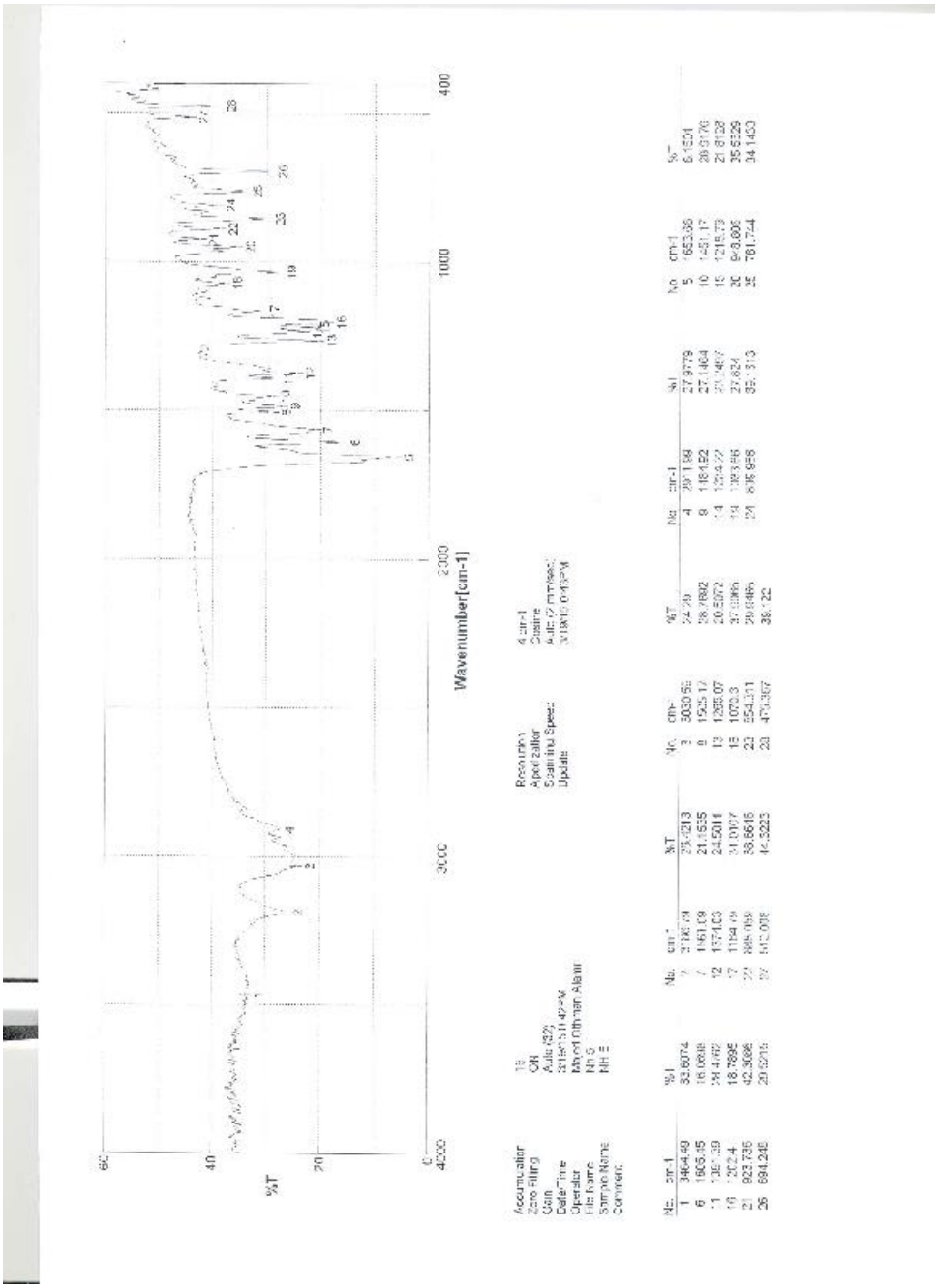
1H (AGS-NH)



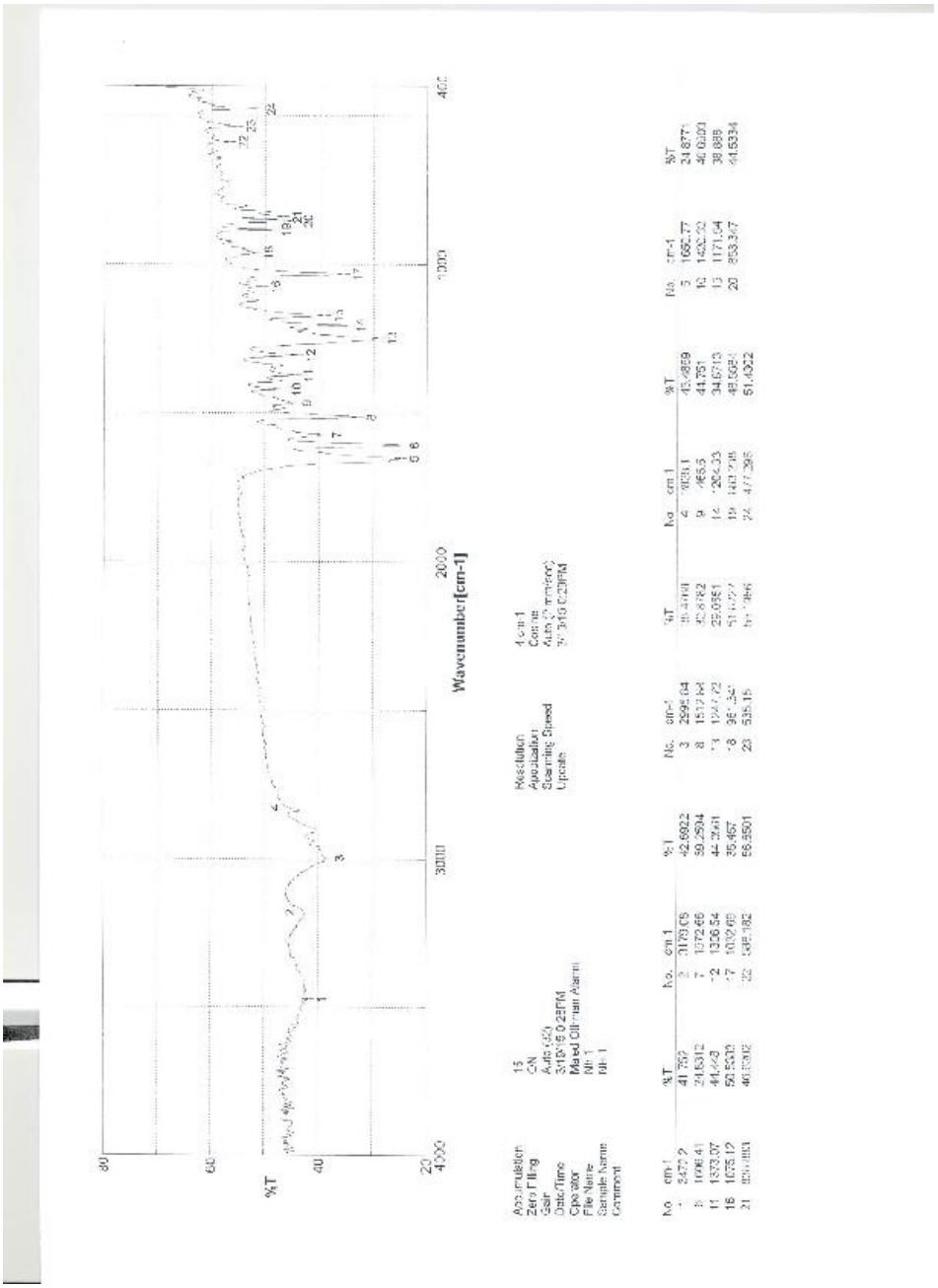
ALI ALSHAHRANI



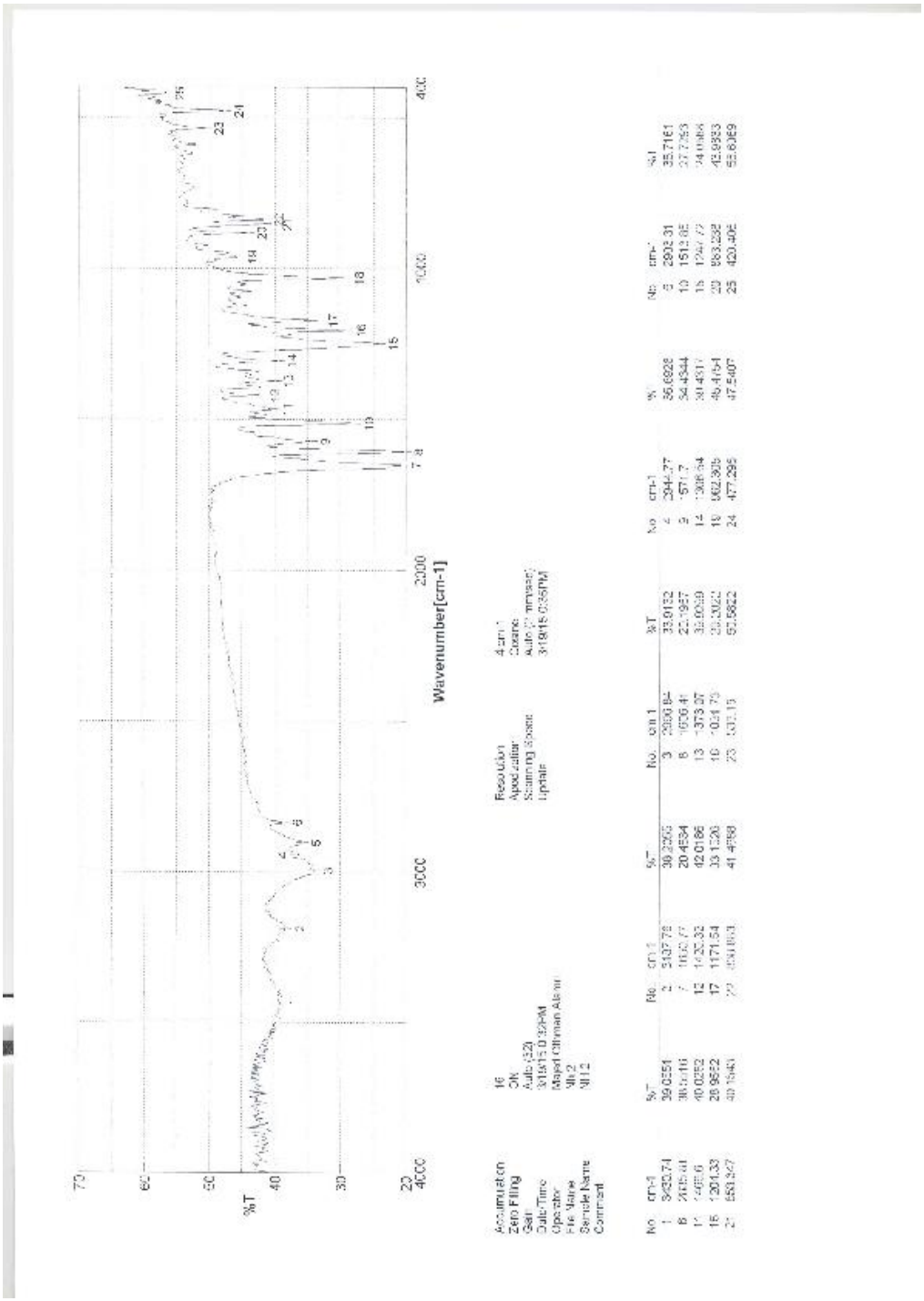
The NMR spectra of compound (III)



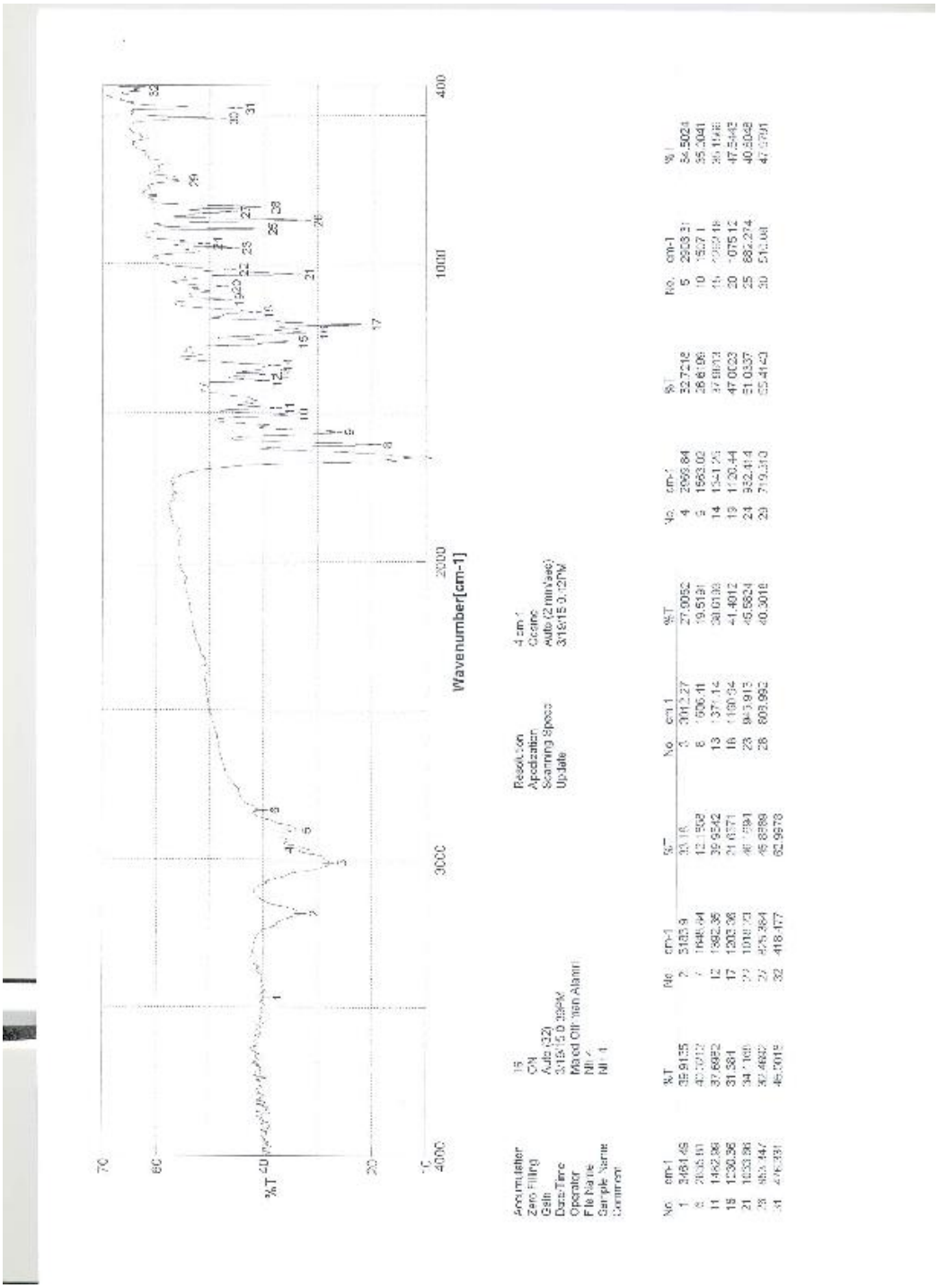
The FTIR spectra of the studied naproxen derivative (a)



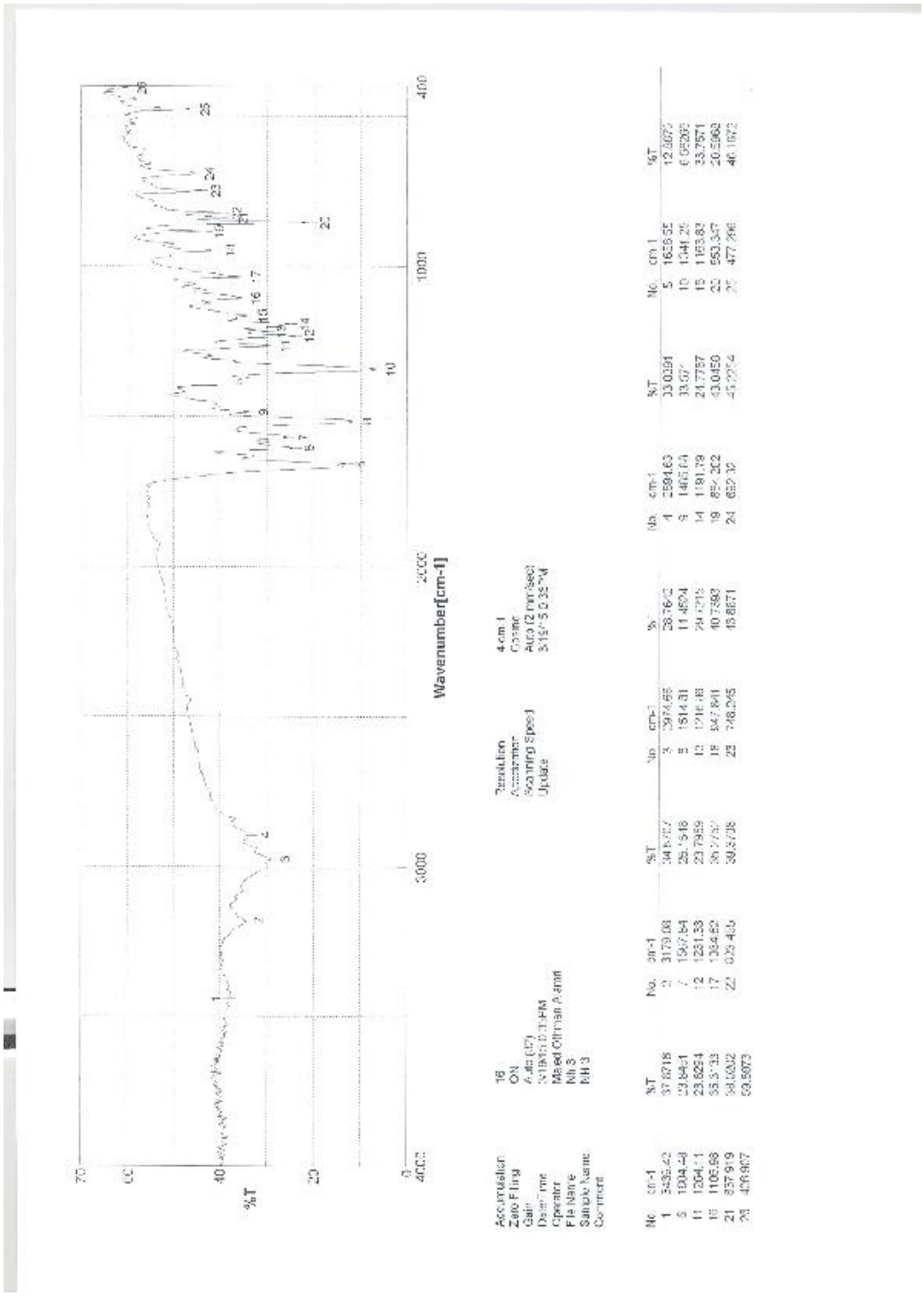
The FTIR spectra of the studied naproxen derivative (b)



The FTIR spectra of the studied naproxen derivative (c)



The FTIR spectra of the studied naproxen derivative (d)

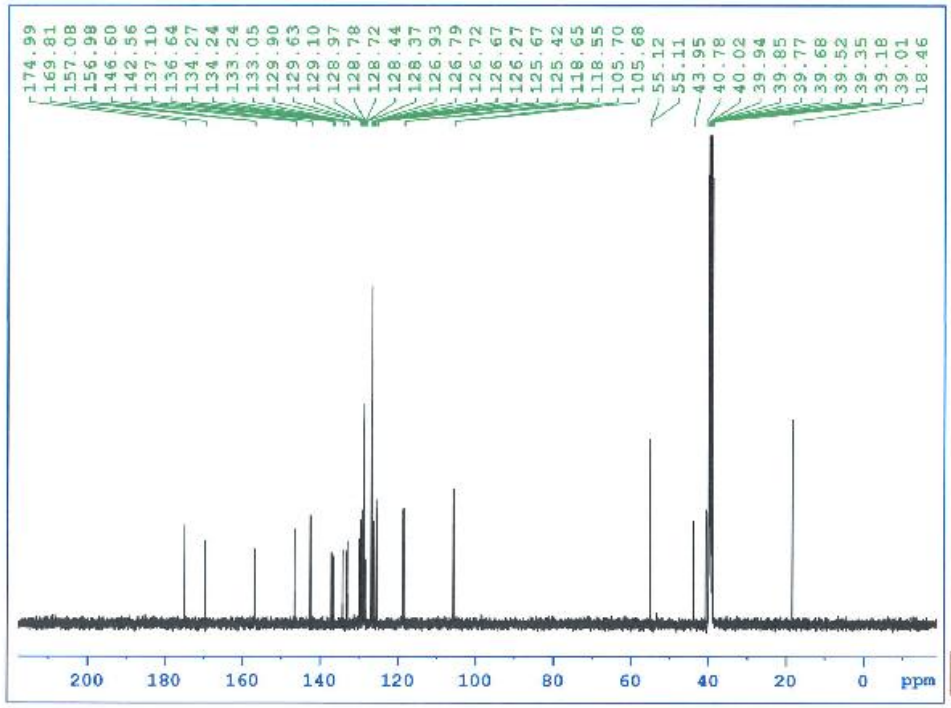


The FTIR spectra of the studied naproxen derivative (e)

NMR 500 MHz Ultra Shield™

BRUKER

13C (AGS-NH5)

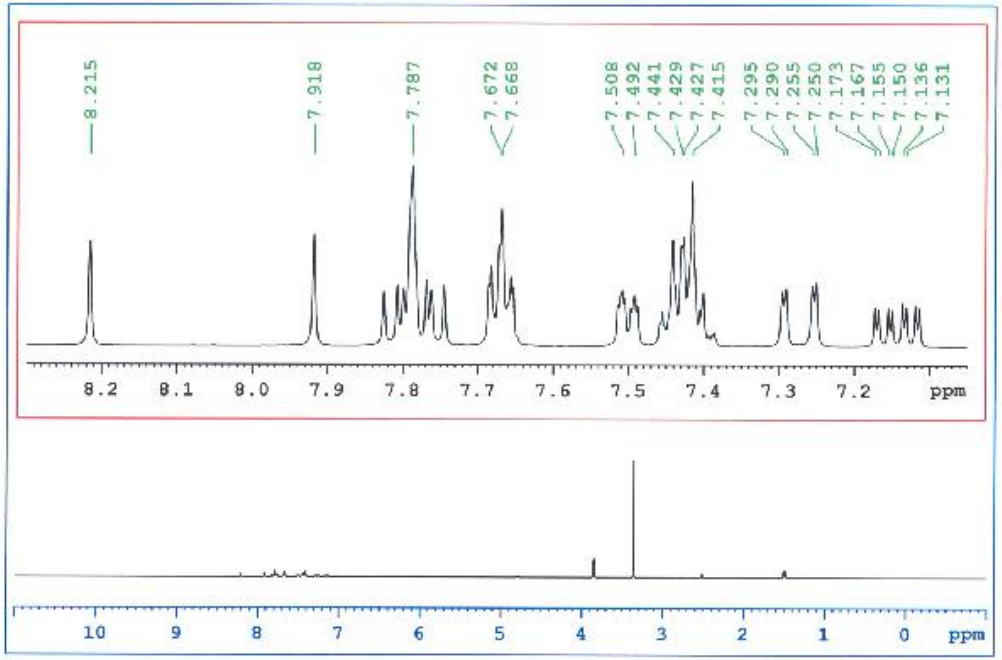


ALI ALSHAHRANI

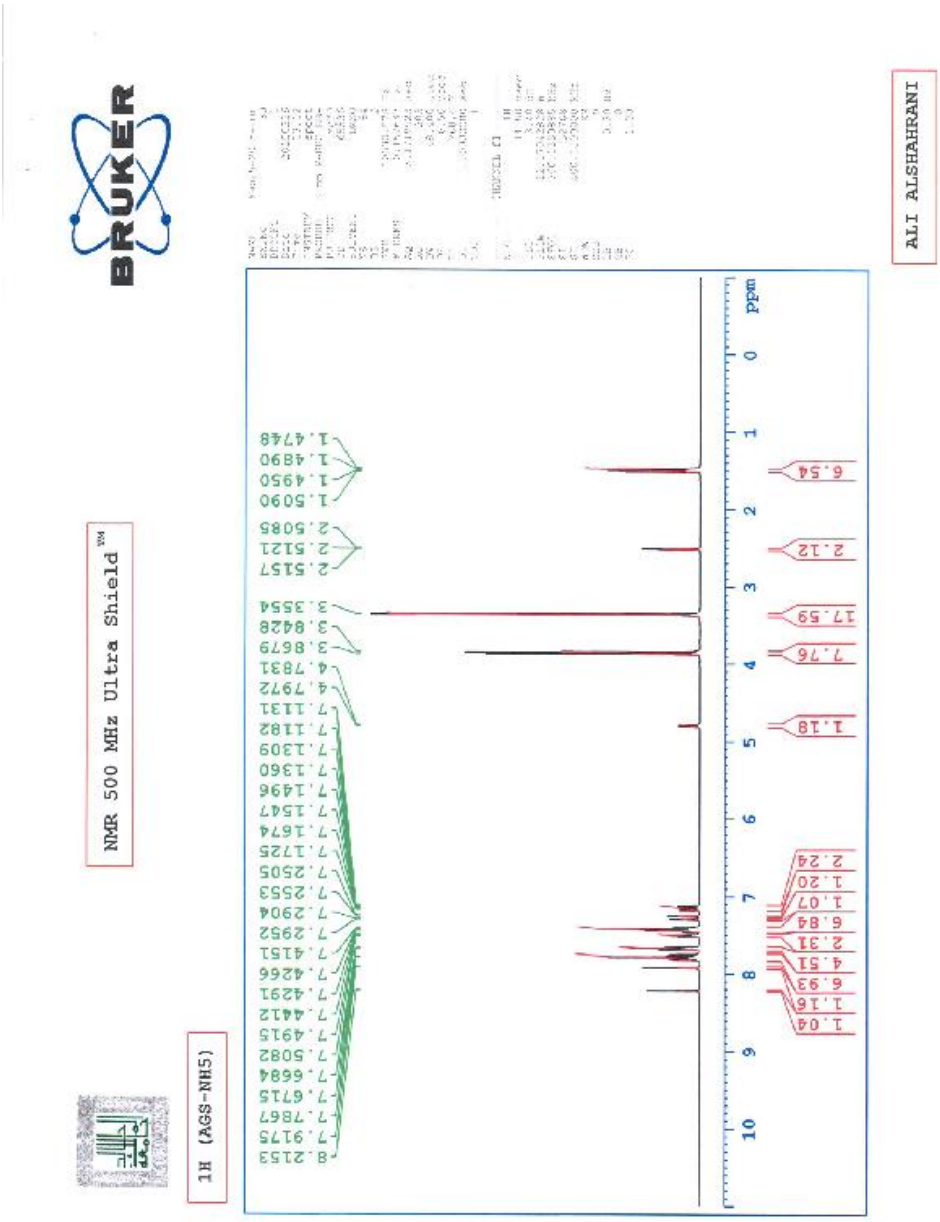
NMR 500 MHz Ultra Shield™

BRUKER

1H (AGS-NH5)



ALI ALSHAHRANI

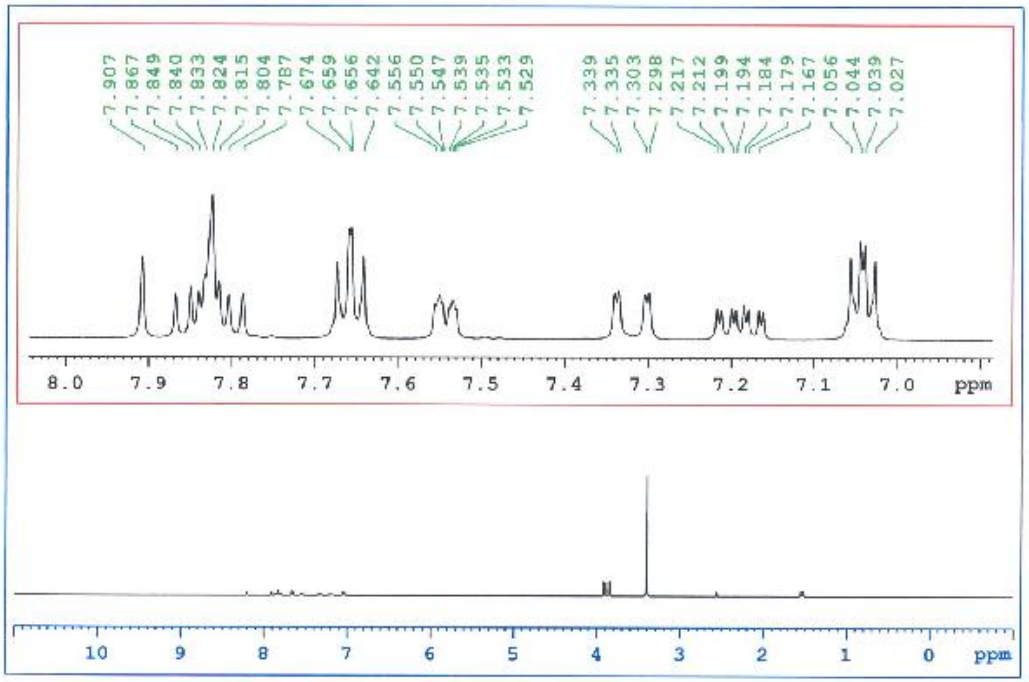


The NMR spectra of the studied naproxen derivative (a)

NMR 500 MHz Ultra Shield™

BRUKER

1H (AGS-NH1)

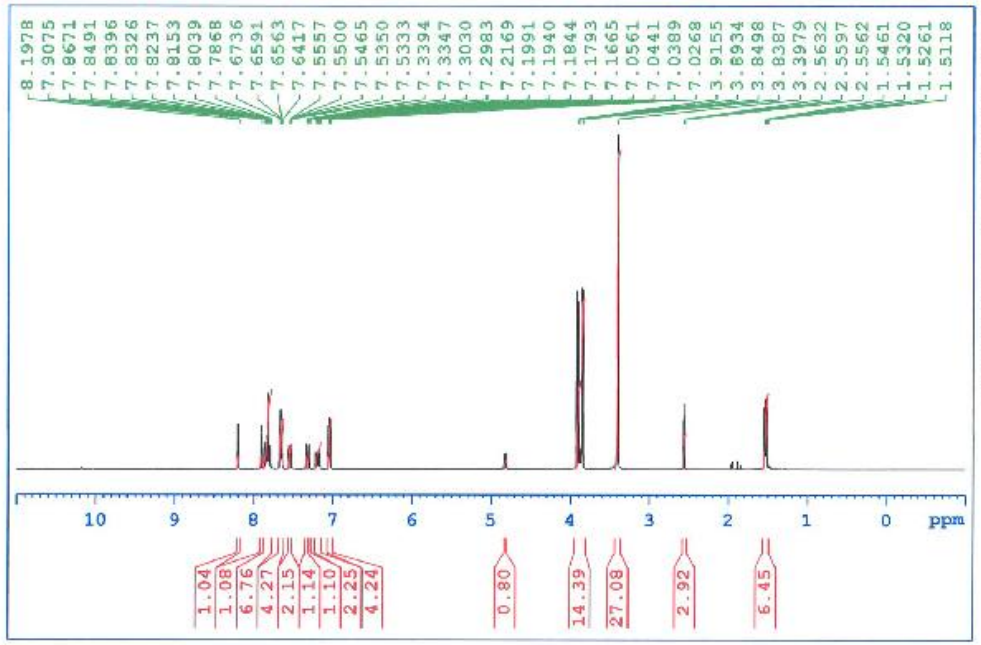


ALI ALSHAHRANI

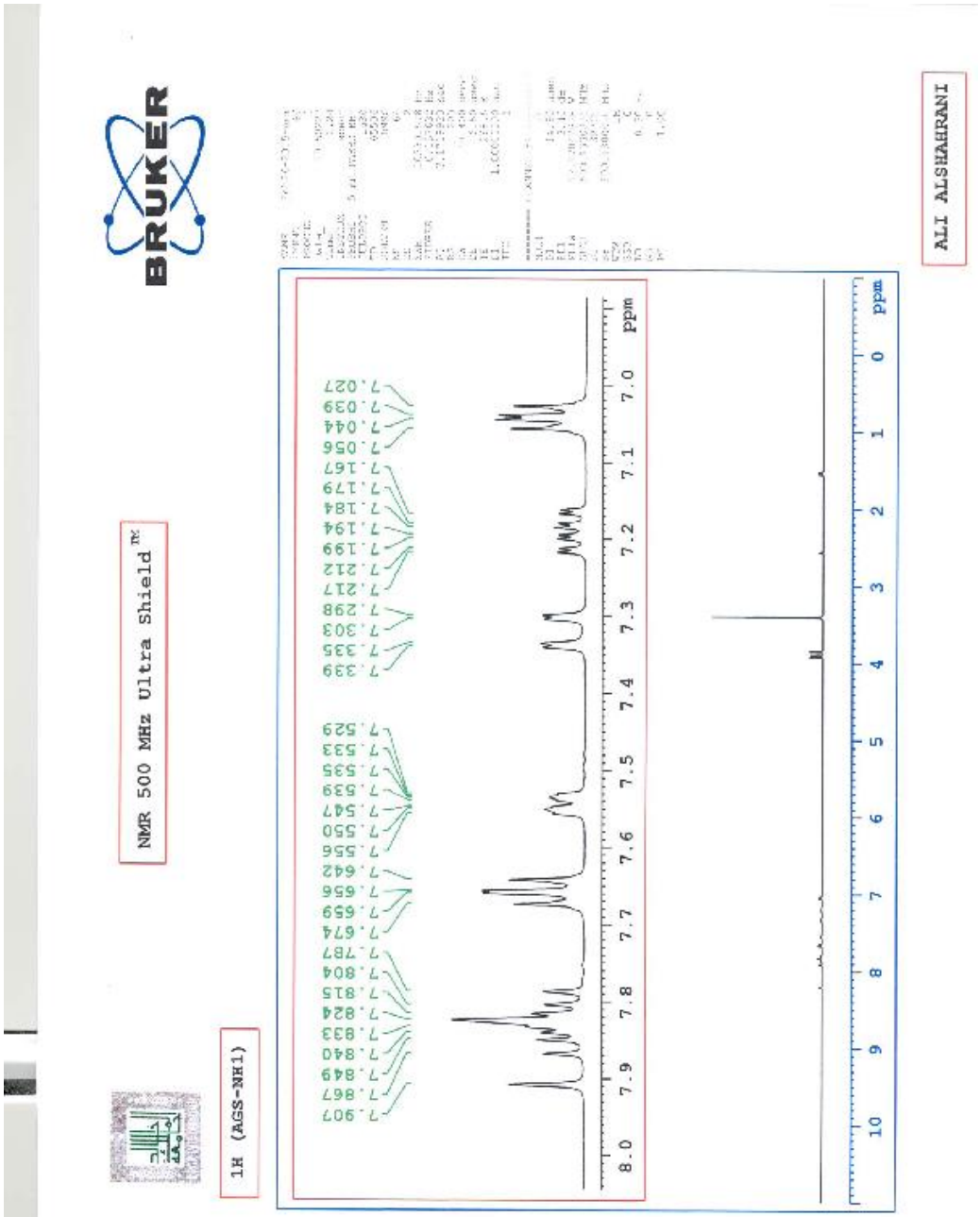
NMR 500 MHz Ultra Shield™

BRUKER

1H (AGS-NH1)



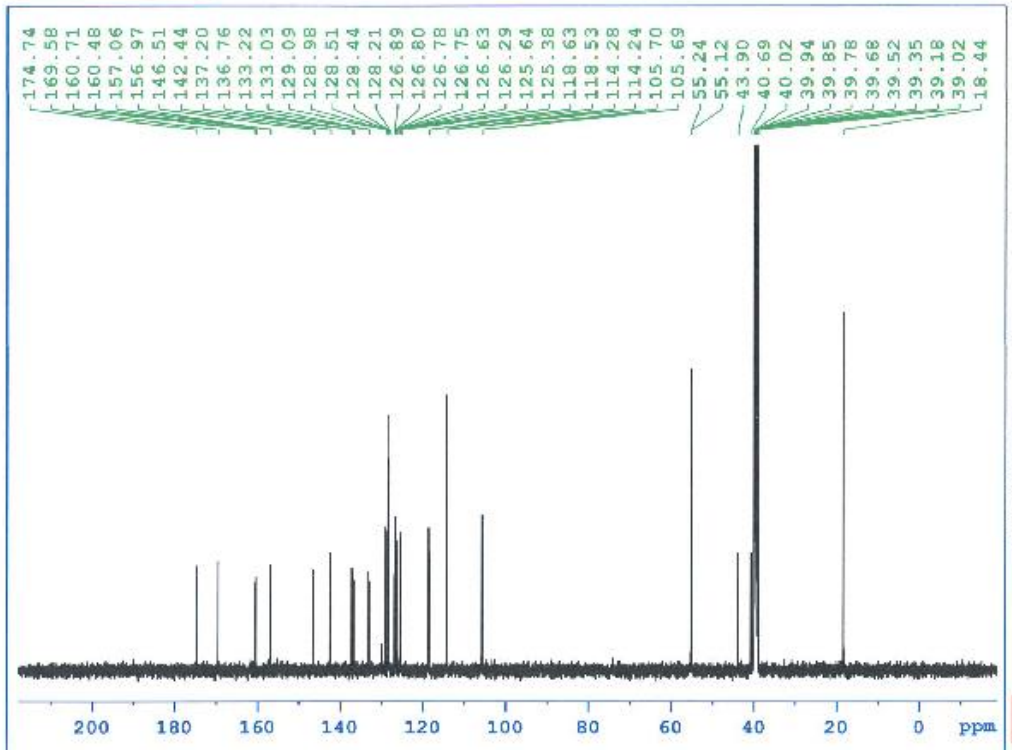
ALI ALSHAHRANI



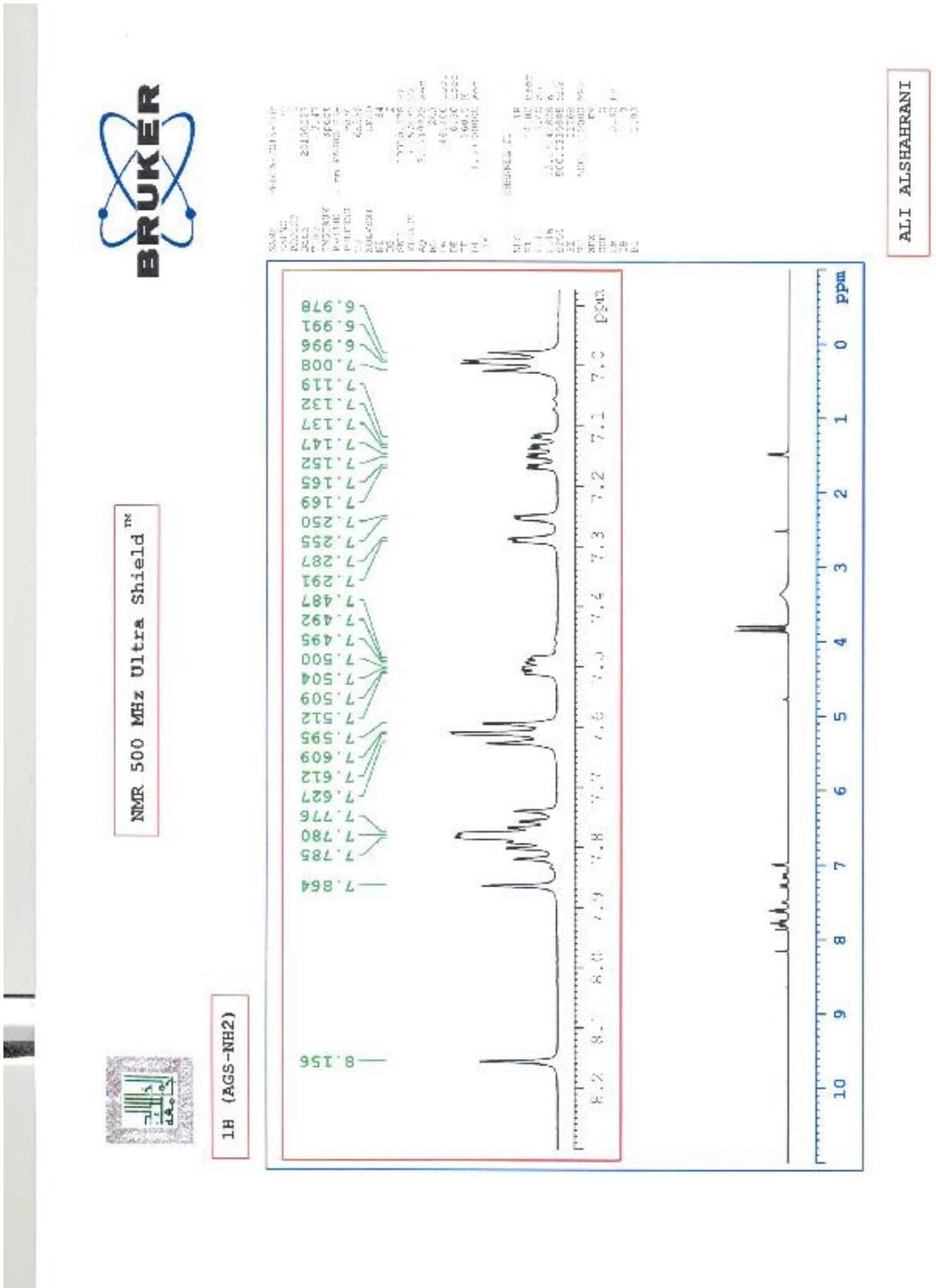
The NMR spectra of the studied naproxen derivative (b)

NMR 500 MHz Ultra Shield™

13C (AGS-NH2)



ALI ALSHAHRANI

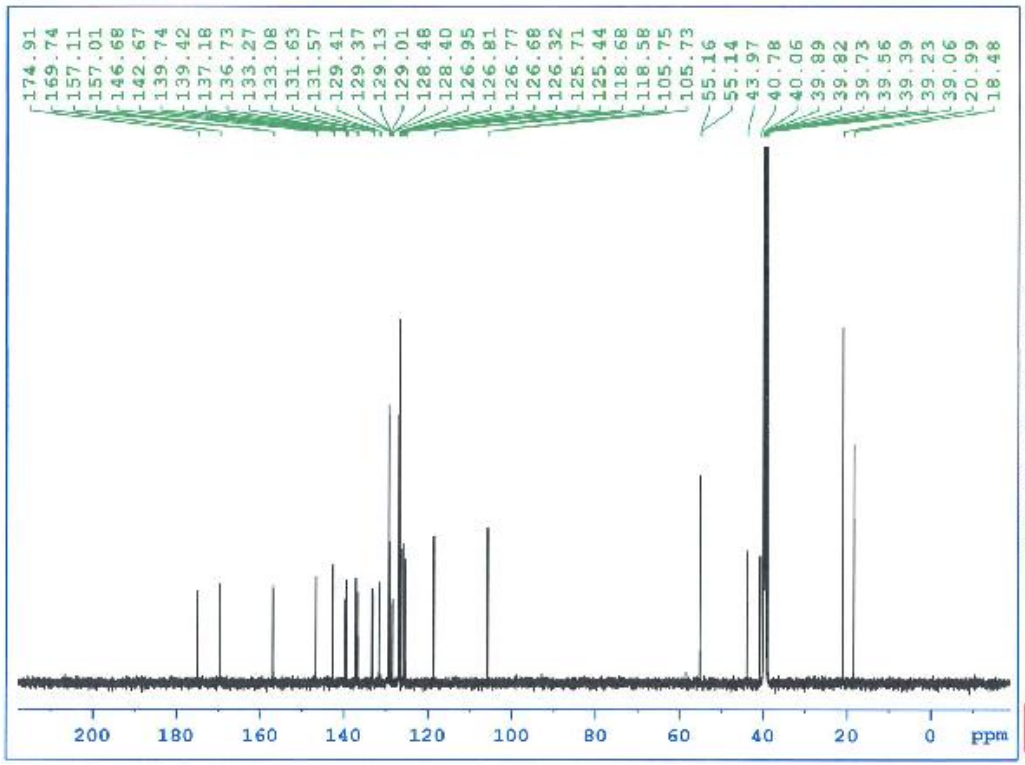


The NMR spectra of the studied naproxen derivative (c)

NMR 500 MHz Ultra Shield™

BRUKER

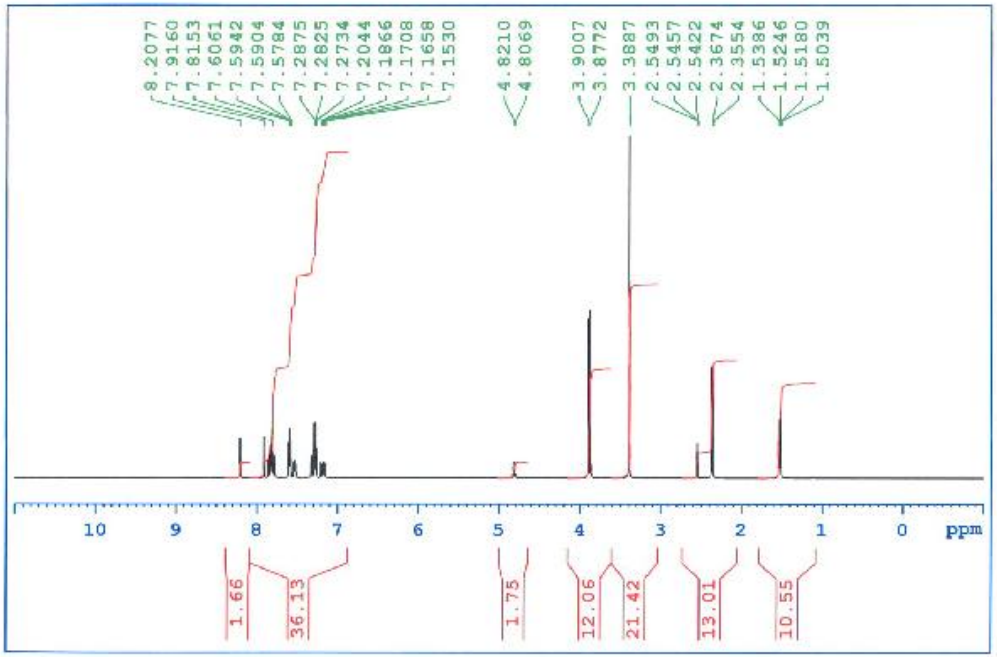
13C (AGS-NB4)



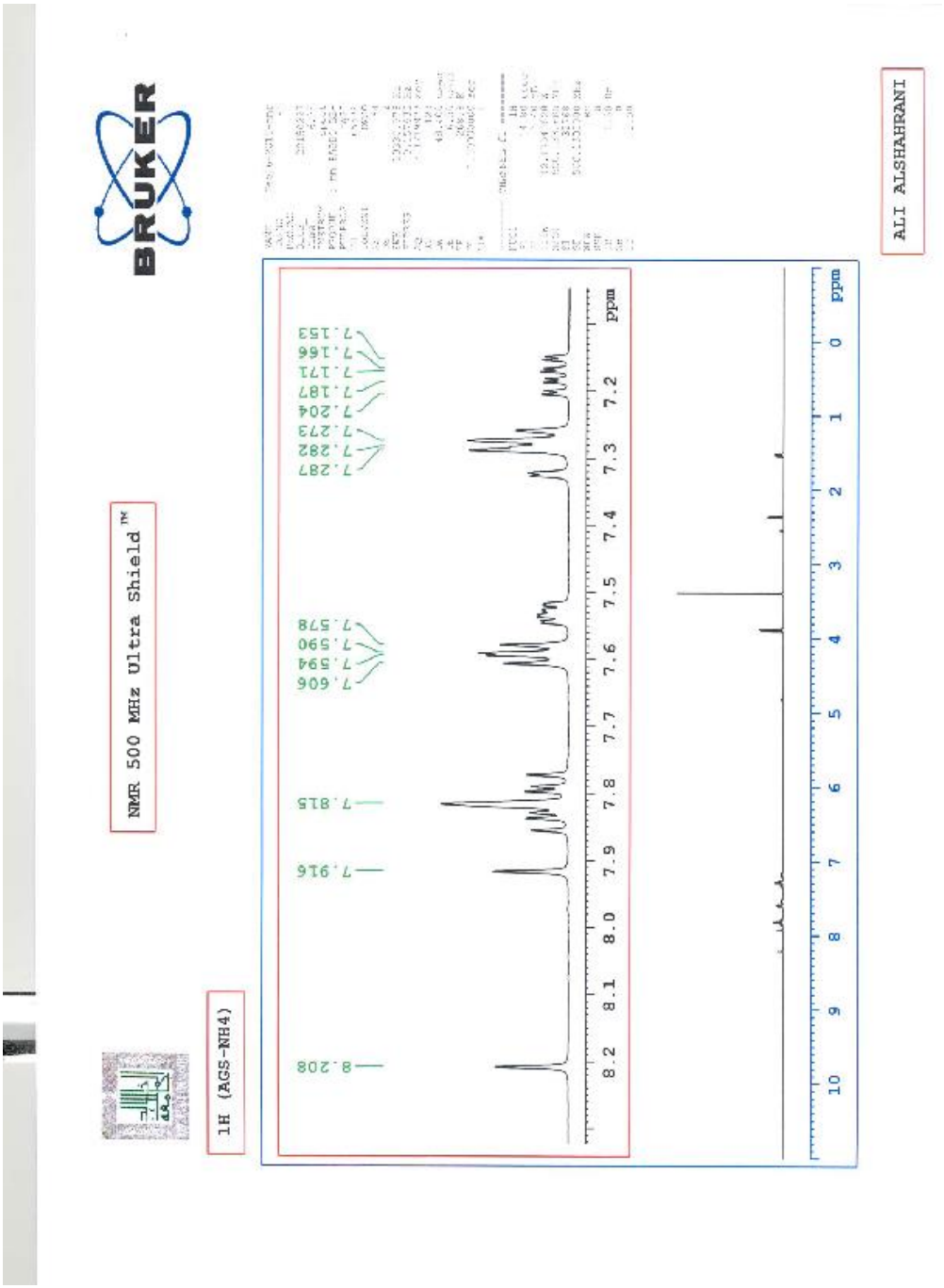
ALI ALSHAHRANI

NMR 500 MHz Ultra Shield™

1H (AGS-NH4)



ALI ALSHAHRANI

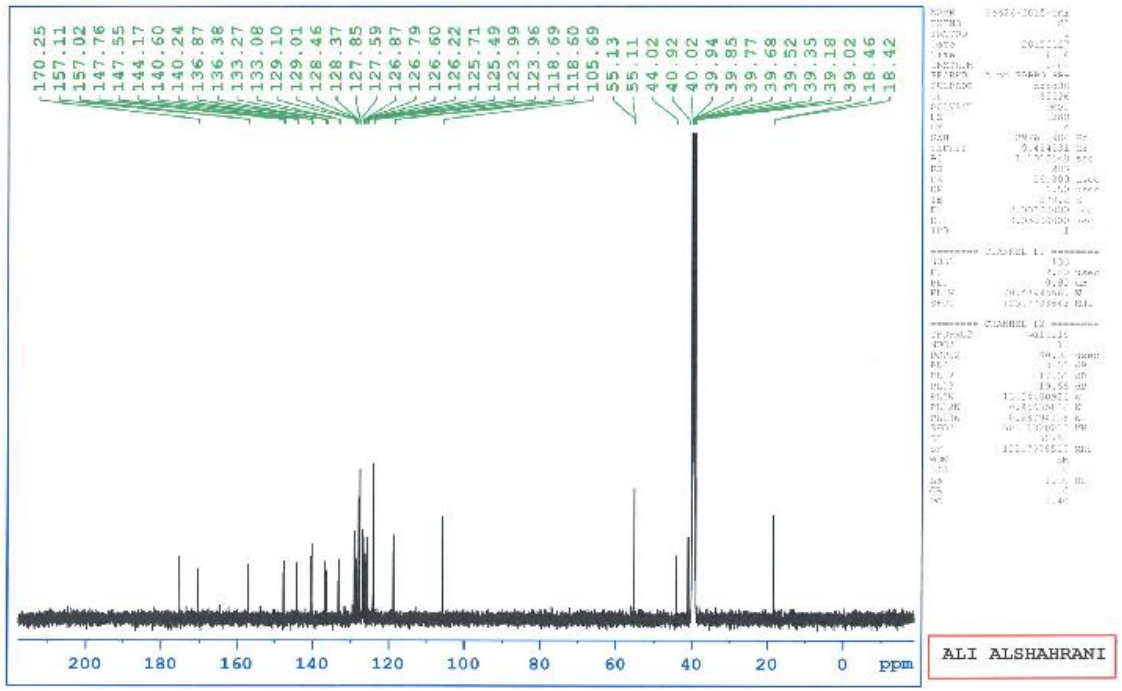


The NMR spectra of the studied naproxen derivative (d)

NMR 500 MHz Ultra Shield™

BRUKER

13C (AGS-NH3)

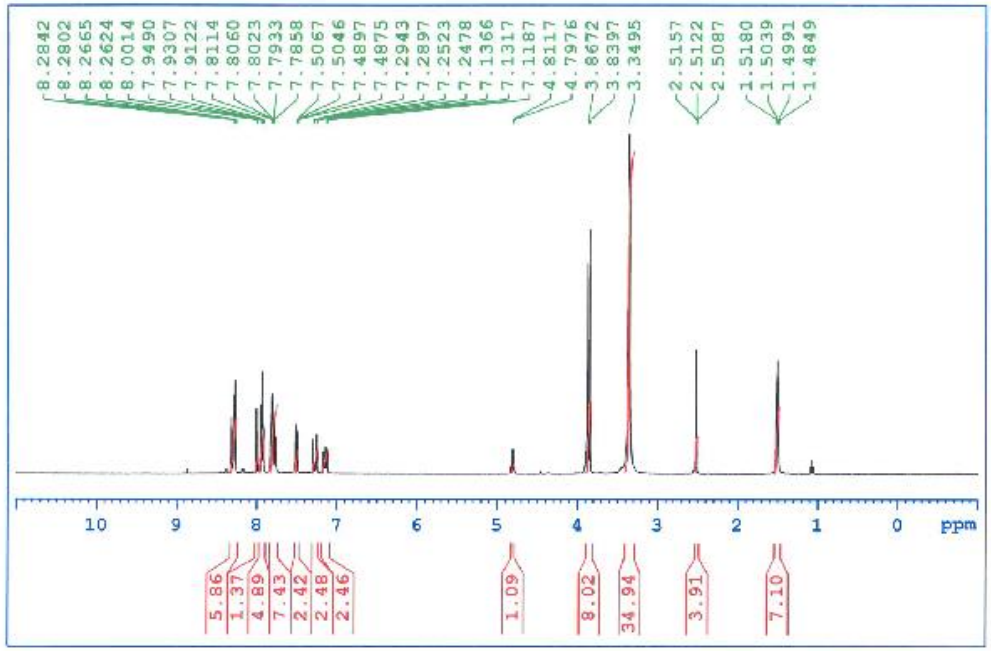


ALI ALSHAHRANI

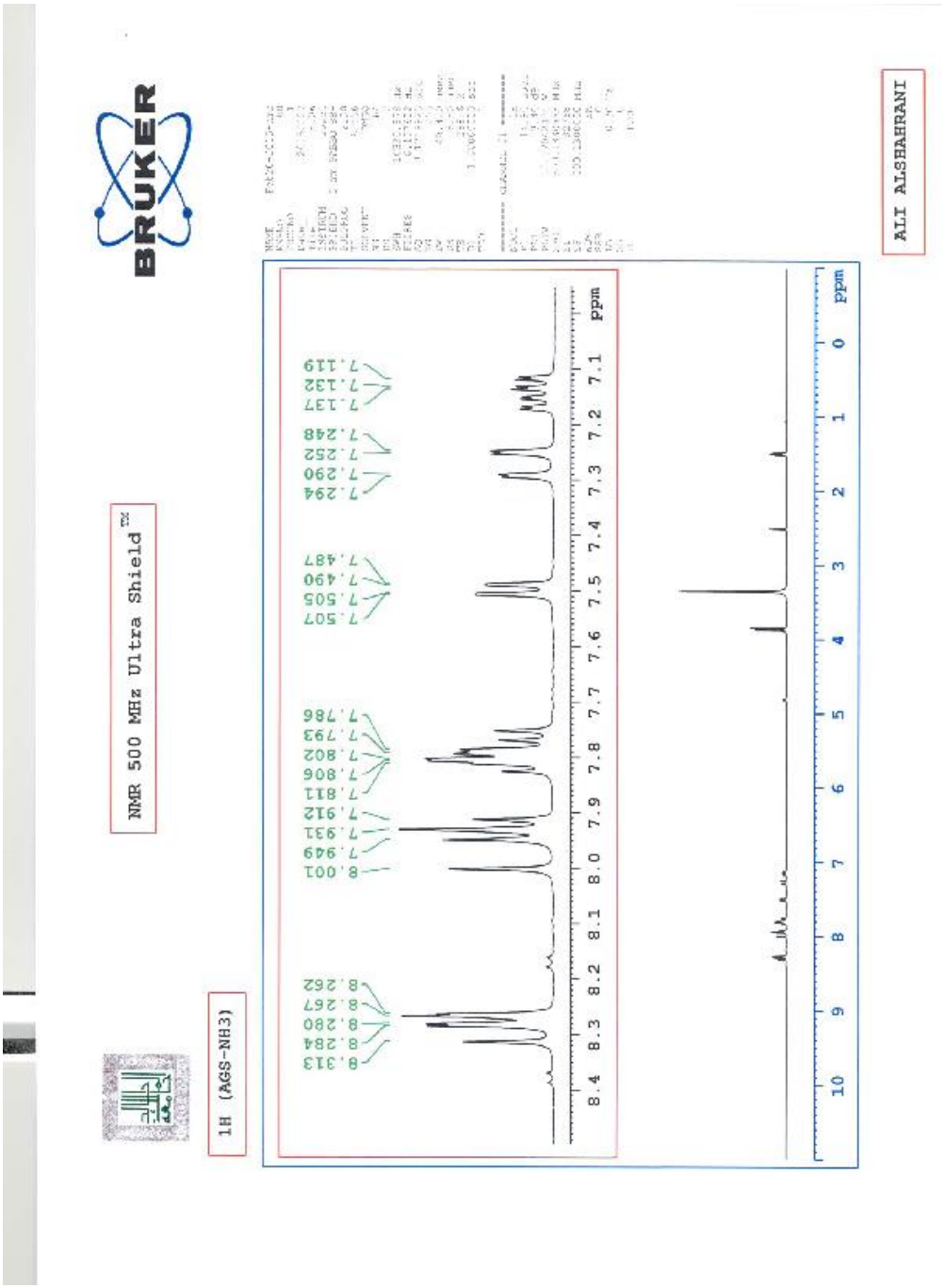
NMR 500 MHz Ultra Shield™

BRUKER

1H (AGS-NH3)



ALI ALSHAHRANI



The NMR spectra of the studied naproxen derivative (e)

[1] P. Skehan, R. Storeng, D. Scudiero, A. Monks, J. McMahon, D. Vistica, J.T. Warren, H. Bokesch, S. Kenney, M.R. Boyd, New colorimetric cytotoxicity assay for anticancer-drug screening, Journal of the National Cancer Institute 82 (1990) 1107-1112.
[2] V. Vichai, K. Kirtikara, Sulforhodamine B colorimetric assay for cytotoxicity screening, Nature protocols 1 (2006) 1112-1116.