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Synthesis of some new pyrazole nucleus fused 2-thioxo-4-thiazolidinone derivatives and evaluation of their antimicrobial activities

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ABSTRACT

Novel 5-((3-(4-substituted phenyl)-1-phenyl-1H-pyrazol-4-yl) methylene-2-thioxothiazolidin-4-one) derivatives based on 2-thioxothiazolidin-4-one were synthesized in good yields using a simplified experimental conditions. The structure of synthesized compounds was established with the help of common physico-chemical analysis and various spectroscopic techniques like FT-IR, mass and ^{1}H NMR. The results of characterization are in good agreement with the proposed structures of all the synthesized compounds. Further, the antimicrobial (antibacterial, antimycobacterial and antifungal) activities of all the synthesized derivatives were carried out against various strains like, *Escherichia Coli* (MTCC 443), *Pseudomonas Aeruginosa* (MTCC 1688), *Staphylococcus Aureus* (MTCC 96), *Streptococcus Pyogenes* (MTCC 442), highly virulent *Mycobacterium Tuberculosis* H_{37}Rv *Candida Albicans* (MTCC 227), *Aspergillus Niger* (MTCC 282) and *Aspergillus Clavatus* (MTCC 1323) by serial broth dilution method. The results of antimicrobial screening showed that all the compounds possess mild to very good activity towards selected strains.

Keywords: *2-Thioxo-4-thiazolidinone, 1-phenyl-3-(p-substituted phenyl)-1H-pyrazole-4-carbaldehyde, antibacterial activity, antifungal activity, antimycobacterial activity.*

1. INTRODUCTION

Among the class of thiazolidones, 2-thioxothiazolidin-4-ones have been found to be important in structurally as well as pharmacologically due to the presence of =N–C–S linkage which imparts biological activity to the structure [1]. Presently available thiazolidones, rhodanine and N-methyl rhodanine are reported to have significant anti-tubercular and anti-tumor activity [2-6] and are also useful in the treatment of diabetic complications [7-8]. These drugs are also under clinical trials as a potential antimicrobial, and antifungal drugs [9-13].

In recent years, several 4-functionally substituted *N*-aryl pyrazole derivatives have been identified as antimicrobial [14], anti-inflammatory [15], anti-tubercular [16], antitumor [17], antidepressant and anticonvulsant [18], anti-angiogenic activity [19], anti-proliferative [20] as well as possessing antiviral activities [21].

Looking to the aforementioned importance of 2-thioxothiazolidin-4-ones derivatives, we intended to synthesize novel entity such as 5-((1-phenyl-3-(*p*-substituted phenyl)-1*H*-pyrazol-4-yl) methylene)-2-thioxothiazolidin-4-ones (3a–h) using 2-thioxothiazolidin-4-one and 1-phenyl-3-(*p*-substituted phenyl)-1*H*-pyrazole-4-carb aldehyde (2a-h).

2. EXPERIMENTAL SECTION

2.1. General. The melting points of the products were determined by open capillary method using Mettler Toledo FP 62 melting point apparatus (Metter Toledo-Switzerland) and were used without correction. The FT-IR spectra were recorded on a Perkin Elmer Spectrum GX FT-IR System (USA) using KBr pellets. ^{1}H spectra were recorded on 200 MHz Bruker Avance DPX NMR spectrometer using DMSO-d^6 as a solvent and TMS as an internal standard. The mass spectra were recorded on a Shimadzu QP2010 spectrometer (equipped with a direct inlet probe) operated at 70 eV. Elemental analysis was carried out on Perkin Elmer CHNS (O) analyser (PE- 2400 Series II-USA). Purity of the desired compounds were checked by analytical TLC on a silica gel GF 254 plate using ethyl acetate/ methanol (8:92) as a solvent system.

2.2. Biological assay.

2.2.1. Antibacterial activity. The newly synthesized compounds were screened for their antibacterial activity against gram positive bacteria Staphylococcus aureus (MTCC-96) and *Streptococcus Pyogenes* (MTCC-442) and gram negative *Escherichia Coli* (MTCC-443) and *Pseudomonas Aeruginosa* (MTCC-1688). Thiazole inhibits protein synthesis in bacteria by binding to the complex formed between 23S rRNA and ribosomal protein L_{11}, thereby restricting the action of GTP dependent elongation factors. Antibacterial activity was carried out by serial broth dilution method. The standard strains used for the antimicrobial activity was procured from the Institute of Microbial Technology, Chandigarh. The compounds (3a–h) were screened for their antibacterial activity in triplicate against *E. Coli, S. Aureus, P. Aeruginosa and S. Pyogenes* at different concentrations of 1000, 500, 200, 100, 50, 25, 12.5 µg/ml as shown in (Table 1). The growths of bacterial cultures were monitored after 24 and 48 h. The lowest concentration, which showed no growth after spot subculture was considered as MIC for each drug. The highest

dilution showing at least 99% inhibition is taken as MIC. The test mixture should contain 10^8 cells/ml. The standard drug used was 'ampicillin' for evaluating antibacterial activity and it showed 100, 100, 250 and 100 µg/ml MIC against *E. Coli, P. Aeruginosa, S. Aureus* and *S. Pyogenes*, respectively.

2.2.2. Antifungal activity. Same compounds were tested for antifungal activity in triplicate against *Candida Albicans, Aspergillus Niger* and *Aspergillus Clavatus* at various concentrations of 1000, 500, 200 and 100 µg/ml as shown in (Table 1). The results were recorded in the form of primary and secondary screening. The synthesized compounds were diluted at 1000 µg/ml concentration, as a stock solution. The synthesized compounds which were found to be active in this primary screening were further tested in a second set of dilution against all microorganisms. The lowest concentration, which showed no growth after spot subculture was considered as MIC for each drug. The highest dilution showing at least 99% inhibition is taken as MIC and the test mixture was found to contain 10^8 spores/ml. ''Griseofulvin'' was used as a standard drug for antifungal activity and it recorded 500, 100 and 100 µg/ml MIC for *C. Albicans, A. Niger* and *A. Clavatus* respectively.

2.2.3. Antimycobacterial. The screening of antimycobacterial activity of novel synthesized compound was carried out in vitro against a highly virulent $H_{37}Rv$ strain of Mycobacterium tuberculosis. Antimycobacterial activity was performed as per the LJ Medium (conventional method). The media were incubated for four weeks. The screening was performed in triplicate at 250 µg/ml concentration of compound. ''Isoniazid'' was used as a standard drug for antimycobacterial activity, which showed 0.2 µg/ml MIC against $H_{37}Rv$ M. Tuberculosis strains. The data are as shown in (Table 1).

2.3 General synthesis.

2.3.1. General procedure for the synthesis of 5-((1-phenyl-3-(p substituted-phenyl)-1H-pyrazol-4-yl)methylene)-2-thioxothiazolidin-4-one (3a-h). To the solution of 2-thioxo-4-thiazolidinones (1) (10 mM) in ethanol, fused sodium acetate (10 mM) and 1-phenyl-3-(*p* substituted phenyl)-1*H*-pyrazole-4-carbaldehyde (2a-h) (10 mM) was added. The reaction mixture was heated under reflux for 6 hrs. A bright yellow crystalline product was formed and the excess solvent was removed at reduced pressure. Crude product was several times washed with water, isolated by filtration and re-crystallized from ethanol to yield compounds (3a-h.).

2.4. Physical and spectral data.

2.4.1. 5-((1,3-diphenyl-1H-pyrazol-4-yl)methylene-2-thioxothiazolidin-4-one) (3a). Yield 65%; Yellow crystalline solid; mp 270-272 ºC; IR (KBr, cm^{-1}) ν: 3418 (NH- Stretching), 3132, 3013 (Ar-H stretching, pyrazole –H stretching), 1691 (C=O stretching), 1594, 1500, 1441 (C=N, C=C, aromatic ring), 666 (C-S-C linkage), 1309 ((C=S stretching); ^{1}H NMR (DMSO-d^6) δ (ppm): 8.75 (s,1H, -C=CH group in pyrazole ring), 8.31-7.41 (m, 12H, Ar-H, C-NH, -C=CH); MS: m/z: 363 (M^+), 276, 215, 173, 140; Anal. Calcd. for $C_{19}H_{13}N_3OS_2$ (363.5) (%): C, 62.79; H, 3.61; N, 11.56; S, 17.64;. Found: C, 62.87; H, 3.78; N, 11.69; S, 17.52.

2.4.2. 5-((1-phenyl-3-p-tolyl-1H-pyrazol-4-yl)methylene-2-thioxothiazolidin-4-one) (3b). Yield 72%; Yellow crystalline solid; mp 276-278 ºC; IR (KBr, cm^{-1}) ν: 3447 (NH- Stretching), 3136, 3024 (Ar-H stretching, pyrazole –H stretching), 1690 (C=O stretching), 1589, 1528, 1440 (C=N, C=C, aromatic ring) 673 (C-S-C linkage), 1307 ((C=S stretching); ^{1}H NMR (DMSO) δ (ppm): 8.72 (s,1H, -C=CH group in pyrazole ring), 8.33-7.36 (m, 11H, Ar-H, C-NH, -C=CH), 2.40 (s,3H, Ar-CH_3); MS: m/z: 377 (M^+), 290,257,172,128; Anal. Calcd. for $C_{20}H_{15}N_3OS_2$ (377.5) (%): C, 63.64; H, 4.01; N, 11.13; S, 16.99;. Found: C, 63.72; H, 4.21; N, 11.24; S, 17.09.

2.4.3. 5-((3-(4-hydroxyphenyl)-1-phenyl-1H-pyrazol-4-yl) methylene-2-thioxothiazolidin-4-one) (3c). Yield 79%; Yellow crystalline solid; Decomposition; IR (KBr, cm^{-1}) ν: 3401 (NH-Stretching), 3151 (Ar-H stretching, pyrazole –H stretching), 1692 (C=O stretching), 1592, 1524, 1405 (C=N, C=C, aromatic ring), 676 (C-S-C linkage), 1325 ((C=S stretching); ^{1}H NMR (DMSO-d^6) δ (ppm): 8.69 (s,1H, -C=CH group in pyrazole ring), 8.02-7.33 (m, 11H, Ar-H, C-NH, -C=CH); MS: m/z: 379 (M^+), 292,231,156,129; Anal. Calcd. for $C_{19}H_{13}N_3O_2S_2$ (379.5) (%): C, 60.14; H, 3.45; N, 11.07; S, 16.90; Found: C, 60.11; H, 3.31; N, 11.23; S, 16.96.

2.4.4. 5-((3-(4-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl) methylene-2-thioxothiazolidin-4-one) (3d). Yield 78%; Yellow crystalline solid; mp >300 ºC; IR (KBr, cm^{-1}) ν: 3417 (NH-Stretching), 3168, 3076 (Ar-H stretching, pyrazole –H stretching), 1693 (C=O stretching), 1607, 1531, 1421 (C=N, C=C, aromatic ring), 685 (C-S-C linkage), 1306 ((C=S stretching); ^{1}H NMR (DMSO-d^6) δ (ppm): 8.81 (s,1H, -C=CH group in pyrazole ring), 8.49-7.41 (m, 11H, Ar-H, C-NH, -C=CH); MS: m/z: 408 (M^+), 321, 275, 172, 128; Anal. Calcd. for $C_{19}H_{12}N_4O_3S_2$ (408.5) (%): C, 55.87; H, 2.96; N, 13.72; S, 15.70;. Found: C, 55.72; H, 2.83; N, 13.63; S, 15.81.

2.4.5. 5-((3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl) methylene-2-thioxothiazolidin-4-one) (3e). Yield 76%; Yellow crystalline solid; mp >300 ºC; IR (KBr, cm^{-1}) ν: 3432 (NH-Stretching), 3133, 3018 (Ar-H stretching, pyrazole –H stretching), 1691 (C=O stretching), 1597, 1508, 1437 (C=N, C=C, aromatic ring), 668 (C-S-C linkage), 1311 ((C=S stretching); ^{1}H NMR (DMSO-d^6) δ (ppm): 8.73 (s,1H, -C=CH group in pyrazole ring), 8.05-7.36 (m, 11H, Ar-H, C-NH, -C=CH); MS: m/z: 381 (M^+), 294,233,191,147; Anal. Calcd. for $C_{19}H_{12}FN_3OS_2$ (381.4) (%): C, 59.83; H, 3.17; N, 11.02; S, 16.81;. Found: C, 59.65; H, 3.22; N, 11.31; S, 16.69.

2.4.6. 5-((3-(4-bromophenyl)-1-phenyl-1H-pyrazol-4-yl) methylene-2-thioxothiazolidin-4-one) (3f). Yield 67%; Yellow crystalline solid; mp 286-288 ºC; IR (KBr, cm^{-1}) ν: 3417 (NH-Stretching), 3134, 3018 (Ar-H stretching, pyrazole –H stretching), 1689 (C=O stretching), 1589, 1526, 1432 (C=C, C=N, aromatic ring) 1062 (C-S-C linkage), 955 ((C=S stretching); ^{1}H NMR (DMSO-d^6) δ (ppm): 8.72 (s,1H, -C=CH group in pyrazole ring), 8.05-7.35 (m, 11H, Ar-H, C-NH, -C=CH); MS: m/z: 442 (M^+), 443,441,356,275,231,171; Anal. Calcd. for $C_{19}H_{12}BrN_3OS_2$

(442.4) (%): C, 51.59; H, 2.73; N, 9.50; S, 14.50;. Found: C, 51.71; H, 2.83; N, 9.62; S, 14.57.

2.4.7. 5-((3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl) methylene-2-thioxothiazolidin-4-one) (3g). Yield 71%; Yellow crystalline solid; mp 254-256 ºC; IR (KBr, cm^{-1}) ν: 3435 (NH-Stretching), 3135, 3050 (Ar-H stretching, pyrazole –H stretching), 1690 (C=O stretching), 1592, 1530, 1441 (C=N, C=C, aromatic ring), 675 (C-S-C linkage), 1307 ((C=S stretching); ^{1}H NMR (DMSO-d^6) δ (ppm): 8.73 (s,1H, -C=CH group in pyrazole ring), 8.05-7.36 (m, 11H, Ar-H, C-NH, -C=CH); MS: m/z: 397 (M^+), 310,275,231,172,155; Anal. Calcd. for $C_{19}H_{12}ClN_3OS_2$ (397.9) (%): C, 57.35; H, 3.04; N, 10.56; S, 16.12;. Found: C, 57.61; H, 3.29; N, 10.48; S, 16.29.

2.4.8. 5-((3-(4-methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl) methylene-2-thioxothiazolidin-4-one) (3h). Yield 70%; Yellow crystalline solid; mp 254-256 ºC; IR (KBr, cm^{-1}) ν: 3432 (NH-Stretching), 3134, 3002 (Ar-H stretching, pyrazole –H stretching), 1690 (C=O stretching), 1590, 1523, 1441 (C=N, C=C, aromatic ring), 674 (C-S-C linkage), 1306 ((C=S stretching); ^{1}H NMR (DMSO-d^6) δ (ppm): 8.67 (s,1H, -C=CH group in pyrazole ring), 8.04-7.10 (m, 11H, Ar-H, C-NH, -C=CH), 3.48 (s,3H, Ar-OCH_3); MS: m/z: 393 (M^+), 306,263,229,153; Anal. Calcd. for $C_{20}H_{15}N_3O_2S_2$ (393.5) (%): C, 61.05; H, 3.84; N, 10.68; S, 16.30;. Found: C, 61.17; H, 3.79; N, 10.53; S, 16.41.

3. RESULTS SECTION

3.1. Chemistry. 2-thioxothiazolidin-4-one (1) were usually synthesized from the reaction of carbon disulfide, ammonia, and monochloroacetic acid [22-23] and 1-phenyl-3-(*p*-substituted phenyl)-1*H*-pyrazole-4-carbaldehyde (2a-h) were synthesized from *p*-substituted acetophenone, phenyl hydrazine, phosphorous oxychloride and formaldehyde according to Vilsmeier–Haack reaction. Substituted acetophenone was reacted with phenyl hydrazine to produce hydrazones, which further reacted with formylating solution (Dimethyl formamide and phosphorous-oxychloride solution) to produce 1-phenyl-3-(*p*-substituted phenyl)-1H-pyrazole-4-carbaldehyde [24]. The final compounds *5-((1-phenyl-3-(p substituted phenyl)-1H-pyrazol-4-yl) methylene)-2-thioxothiazolidin-4-one* ***(3a-h)*** were synthesized by the reaction of 2-thioxo-4-thiazolidinones (1) with suitable 1-phenyl-3-(*p* substituted phenyl)-1*H*-pyrazole-4-carbaldehyde (2a-h) (**Scheme 1).** All the synthesized compounds were characterized by FT-IR, MMR and Mass spectroscopy. The IR spectra of synthesized compounds (3a-h) assigned as per further. The band observed around 1300-1350 cm^{-1} is attributed to C=S stretching vibration of thiazole ring. Bands at around 666-695 cm^{-1} is attributed to –C-S-C- stretching vibration of thiazolidinone moiety and 1570-1610 cm^{-1} is attributed to C=N stretching vibration of pyrazole moiety. Strong signal in the region 1680-1730 cm^{-1} is assigned to -C=O stretching of thiazolidinone ring. ^{1}H-NMR and Mass spectral data of compound (3a-h) are shown in "Materials and method" section. Chemical shift δ at 8.9-8.7 ppm is due to the presence of -C=CH group in pyrazole ring. The entire compounds were analyzed satisfactorily for C, H and N analysis. Both analytical and spectral data (FT-IR, ^{1}H-NMR, GC-MS) of all the synthesized compounds were in full agreement with the proposed structure. It was concluded that the pyrazole nucleus in 2-(5-methylbenzo[d]thiazol-2-ylimino) thiazolidin-4-one (1) improved their antimicrobial activity. Most of the compounds were found to be active against tested micro-organism. A series of *5-((1-phenyl-3-(p substituted phenyl)-1H-pyrazol-4-yl) methylene)-2-thioxothiazolidin-4-one* (3a-h) exhibited excellent to moderate activities.

3.2. Antimicrobial evaluation. Drug discovery is very important and novel science. Discovery of new novel entities as high selective antimicrobial drugs is in demand nowadays. Drugs discovery is a long term process which required excellent scientific approach. It needs ideal planning and technically designed effort. Antimicrobial activity of synthesized compound was performed against four different bacterial strains like, *E. Coli, P. aeruginosa, S. aureus* and *S. Pyogenes* and three different fungi like, *C. Albicans, A. Niger* and *A. Clavatus*. "Ampicillin", "Griseofulvin" and "Isoniazid" were used as positive control for bacteria, fungi and virus respectively and solvent control was used to know the activity of solvent.

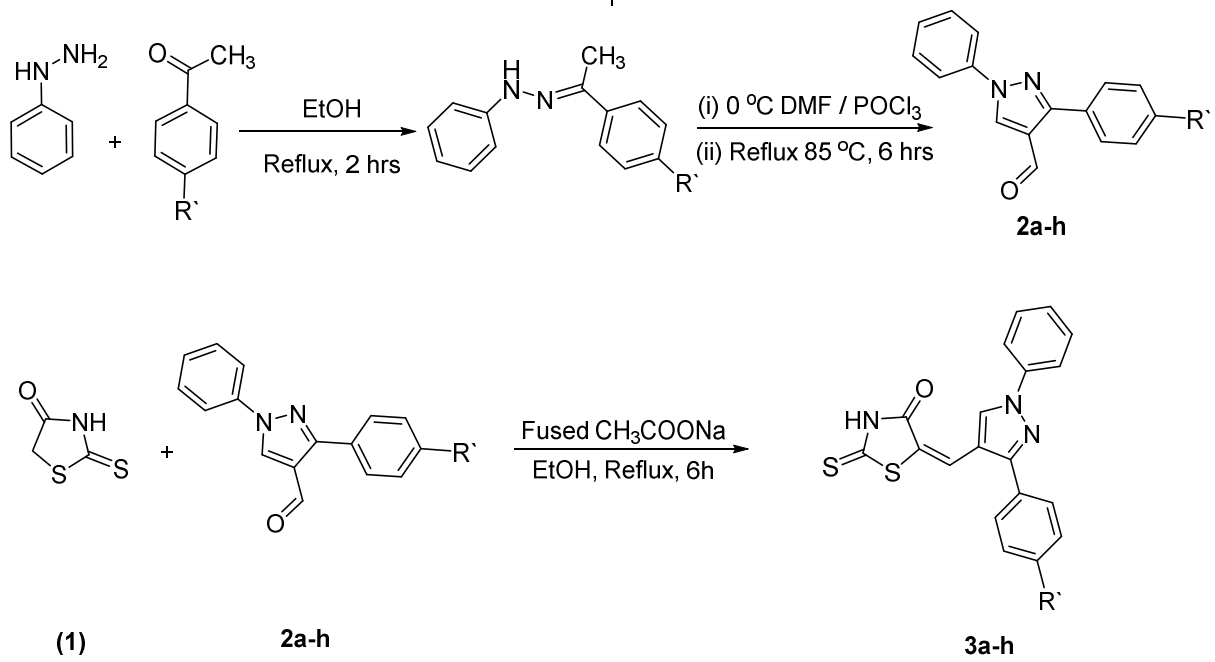
3.2.1. Antibacterial activity. The results of antibacterial screening of newly synthesized compounds are presented in Table 1**.** For the antibacterial activity, we have taken four different bacterial strains like, *E. Coli, P. Aeruginosa, S. Aureus and S. Pyogenes*. For, *E.coli*, compounds 3d and 3f possess good activity as compared to the standard drug ampicillin, while compounds 3b, 3c and 3h possess comparatively moderate activity as compared to the standard drug ampicillin For, *P. Aeruginosa*, compounds 3f and 3g possess good activity as compared to the standard drug ampicillin, while compounds 3b, 3c and 3h possess comparatively moderate activity as compared to the standard drug ampicillin For, *S. Aureus*, compounds 3g and 3h posses excellent activity and compounds 3b and 3c possess good activity as compared to the standard drug ampicillin, while compounds 3a, 3d, 3e and 3f possess comparatively moderate activity as compared to the standard drug ampicillin. For, *S. Pyogenes*, compound 3b, 3g and 3h possess good activity as compared to the standard drug ampicillin, while compounds 3c possesses moderate activity as compared to the standard drug ampicillin.

3.2.2. Antifungal activity. Antifungal screening of data of newly synthesized compounds are as per Table 1**.** For the antifungal activity, three different fungal strains like *C. Albicans, A. Niger and A. Clavatus* are selected. For, *C. Albicans,* compounds 3b and 3d possess excellent activity as compared to the standard drug Griseofulvin, while compound 3c and 3g possess good activity as compared to the standard drug Griseofulvin. For, *A. Niger and A. Clavatus,* compound 3b possesses moderate activity as compared to the standard drug Griseofulvin, while others possess poor activity as compared to the standard drug Griseofulvin.

3.2.3. Antimycobacterial activity. The results of antimycobacterial screening of newly synthesized compounds are presented in Table

1. Highly virulent $H_{37}RV$ strain of *Mycobacterium tuberculosis* was selected for antimycobacterial activity screening. Compounds 3d, 3e and 3g possess good antimycobacterial activity. Compounds 3b and 3f possesses moderate antimycobacterial activity and other compounds possess poor antimycobacterial activity.

3.2.4. Statistical analysis. The standard deviation value is expressed in terms of ±SD. On basis of the calculated value by using ANOVA method, it has been observed that the differences below 0.0001 level ($p \leq 0.0001$) are considered as statistically significant.



	3a	3b	3c	3d	3e	3f	3g	3h
R'	**-H**	**-CH_3**	**-OH**	**-NO_2**	**-F**	**-Br**	**-Cl**	**-OCH_3**

Scheme 1. Schematic diagram of synthesis *5-((1-phenyl-3-(p substituted phenyl)-1H-pyrazol-4-yl) methylene)-2-thioxothiazolidin-4-one (3a-h).*

Table 1. Antibacterial, antifungal and antimycobacterial screening chart for compound *5-((1-phenyl-3-(p substituted phenyl)-1H-pyrazol-4-yl) methylene)-2-thioxothiazolidin-4-one (3a-h).*

Compound Code	-Ar	Minimum inhibitory concentration (MIC) µg/ml ± SD				Minimum inhibitory concentration (MIC) in µg/ml ± SD			Inhibition in %
		EC	*PA*	*SA*	*SP*	*CA*	*AN*	*AC*	*MT*
3a	-H	500 ± 4.32*	250 ± 5.10*	500 ± 4.74*	500 ± 2.11*	1000 ± 2.16*	500 ± 1.41*	500 ± 2.39*	27 ± 2.90*
3b	-CH_3	250 ± 1.82*	500 ± 3.65*	250 ± 3.83*	125 ± 3.15*	250 ± 2.90*	200 ± 4.61*	200 ± 4.07*	62 ± 1.97*
3c	-OH	200 ± 4.17*	250 ± 4.51*	250 ± 0.92*	200 ± 1.77*	500 ± 6.17*	1000 ± 4.23*	1000 ± 2.78*	43 ± 2.67*
3d	-NO_2	100 ± 2.32*	200 ± 1.68*	500 ± 1.86*	500 ± 3.33*	250 ± 4.23*	500 ± 3.76*	1000 ± 5.86*	74 ± 4.53*
3e	-F	500 ± 6.82*	200 ± 2.65*	500 ± 3.96*	500 ± 2.47*	1000 ± 1.32*	1000 ± 4.21*	1000 ± 2.86*	89 ± 0.59*
3f	-Br	125 ± 3.19*	100 ± 2.07*	500 ± 2.15*	500 ± 2.54*	1000 ± 2.62*	1000 ± 2.58*	1000 ± 4.74*	53 ± 1.48*
3g	-Cl	500 ± 1.02*	125 ± 1.59*	100 ± 5.77*	125 ± 4.78*	500 ± 2.38*	1000 ± 1.04*	1000 ± 4.01*	83 ± 3.71*
3h	-OCH_3	200 ± 5.55*	250 ± 1.02*	100 ± 4.03*	125 ± 5.02*	1000 ± 3.21*	1000 ± 1.95*	1000 ± 4.55*	32 ± 4.79*
Standard Drugs	Ampicillin	100 ± 1.43*	100 ± 2.08*	250 ± 2.10*	100 ± 0.81*	–	–	–	–
	Griseofulvin	–	–	–	–	500 ± 1.21*	100 ± 1.62*	100 ± 0.95*	
	Isoniazid								99 ± 1.01*

EC = E. Coli = P. Aeruginosa, SA = S. Aureus, SP = S. Pyogenes, CA = C. Albicans, AN = A. Niger, AC = A. Clavatus, MT = M. Tuberculosis
SD = Standard deviation. *$p \leq 0.0001$. **a** = Maximum % inhibition of *M. Tuberculosis* at 250 µg/ml concentration of synthesized compounds.
b = 99% inhibition of *M. Tuberculosis* at 0.2 µg/ml concentration of Isoniazid

4. CONCLUSIONS

Some Novel compounds of Rhodanine using pyrazole aldehydes were synthesized. Both analytical and spectral data (FT-IR, ^{1}H-NMR, GC-MS) of all the synthesized compounds were in full agreement with the proposed structure. After comparing the antimicrobial and antimycobacterial screening results of compounds (3a-h), it was concluded that the pyrazole derivatives in 2-thioxothiazolidin-4-one (rhodanine) improved their antimicrobial activity and also -NO_2, -Cl, -Br, F and -OCH_3 substitution in the R′ group of the pyrazole derivatives was found to enhance their potency, especially in compound (3a-h).

5. REFERENCES

[1] Brown F. C., 4-Thiazolidinones, *Chemical Review,* 61, 463-521, **1961**.

[2] Li W., Zhai X., Zhong Z., Li G., Pu Y., Gong P., Design, Synthesis and Evaluation of Novel Rhodanine-containing Sorafenib Analogs as Potential Antitumor Agents, *Archiv der Pharmazie,* 344, 349-357, **2011**.

[3] Kawakami M., Koya K., Ukai T., Tatsuta N., Ikegawa A., Ogawa K., Shishido T., Chen L. B., Synthesis and evaluation of novel rhodacyanine dyes that exhibit antitumor activity, *Journal of Medicinal Chemistry*, 40, 3151-3160, **1997**.

[4] Kawakami M., Koya K., Ukai T., Chen L. B., Structure-activity of novel rhodacyanine dyes as antitumor agents, *Journal of Medicinal Chemistry,* 41, 130-142, **1998**.

[5] Yang F., Peng S., Li Y., Su L., Peng Y., Wu J., Chen H., Liu M., Yi Z., Chen Y., A hybrid of thiazolidinone with the hydroxamate scaffold for developing novel histone deacetylase inhibitors with antitumor activities, *Organic & Biomolecular Chemistry*, 14, 1727-1735, **2016.**

[6] Havrylyuk D., Zimenkovsky B., Vasylenko O., Gzella A., Lesyk R., Synthesis of new 4-thiazolidinone-, pyrazoline-, and isatin-based conjugates with promising antitumor activity, *Journal of Medicinal Chemistry*, 55, 8630-8641, **2012**.

[7] Firk S. D., Firake B. M., Chaudhari R.Y., Patil V. R., Synthetic and pharmacological evaluation of some pyridine containing thiazolidinones, *Asian Journal of Chemistry*, 2, 157-161, **2009**.

[8] Ahmad S., Yadav K. K., Narang U., Bhattacharya S., Singh S. J., Chauhan S. M. S., Synthesis, properties and singlet oxygen generation of thiazolidinone double bond linked porphyrin at meso and β-position, *RSC Advance*, 6, 36090-36095, **2016**.

[9] Habib N. S., Ridal S. M., Badaweyl E. A. M., Fahmyl H. T. Y., Ghozlan H. A., Synthesis and antimicrobial activity of rhodanine derivatives, *European Journal of Medicinal Chemistry*, 32, 759-762, **1997**.

[10] Liu J. C., Zheng C. J., Wang M. X., Li Y. R., Ma L. X., Synthesis and evaluation of the antimicrobial activities of 3-((5-phenyl-1,3,4-oxadiazol-2-yl)methyl)-2-thioxothiazolidin-4-one derivatives, *European Journal of Medicinal Chemistry*, 74, 405-410, **2014**.

[11] Inamori Y., Okamoto Y., Takegawa Y., Tsujibo H., Sakagami Y., Insecticidal and antifungal activities of aminorhodanine derivatives, *Bioscience, Biotechnology, and Biochemistry,* 62, 1025-1027, **1998**.

[12] Sortino M., Delgado P., JuÃ¡rez S., Quiroga J., AbonÃa R., Synthesis and antifungal activity of (Z)-5-arylidenerhodanines, *Bioorganic and Medicinal Chemistry*, 15, 484-494, **2007.**

[13] Siddiqui I. R., Singh P. K., Singh J., Facile synthesis and fungicidal activity of novel 4,4'-bis [2"-(5'"-substituted rhodanin-3'"-yl)thiazol-4"-yl]bibenzyls, *Indian journal of chemistry, Sect B*., , 44, 2102-2106, **2005**.

[14] Darwish E. S., Abdel Fattah A. M., Attaby F. A., Al-Shayea O. N., Synthesis and antimicrobial evaluation of some novel thiazole, pyridone, pyrazole, chromene, hydrazone derivatives bearing a biologically active sulfonamide moiety, *International Journal of Molecular Science,*15, 1237-1254, **2014**.

[15] Tonk R. K., Bawa S., Chawla G., Deora G. S., Kumar S., Rathore V., Mulakayala N., Rajaram A., Kalle A. M., Afza, O., Synthesis and pharmacological evaluation of pyrazolo[4,3-c]cinnoline derivatives as potential anti-inflammatory and antibacterial agents, *European Journal of Medicinal Chemistry*, 57, 176-184, **2012**.

[16] Harikrishna N., Isloor A. M., Ananda K., Obaid A., Kun H., Synthesis and antitubercular and antimicrobial activity of 1′-(4-chlorophenyl)pyrazole containing 3,5-disubstituted pyrazoline derivatives, *New Journal of Chemistry*, 40, 73-76, **2016**.

[17] Hou J., Wan S., Wang G., Zhang T., Li Z., Tian Y., Yu Y., Zhang J., Design, synthesis, anti-tumor activity, and molecular modeling of quinazoline and pyrido[2,3-d]pyrimidine derivatives targeting epidermal growth factor receptor, *European Journal of Medicinal Chemistry*, 118, 276-289, **2016**.

[18] Abdel-Aziz M., Abuo-Rahma G. D., Hassan A. A., Synthesis of novel pyrazole derivatives and evaluation of their antidepressant and anticonvulsant activities, European Journal of Medicinal Chemistry, 44, 3480-3487, **2009**.

[19] Christodoulou M. S., Liekens S., Kasiotis K. M., Haroutounian S. A., Novel pyrazole derivatives: synthesis and evaluation of anti-angiogenic activity, *Bioorganic and. Medicinal Chemistry*, 18, 4338-4350, **2010**.

[20] Cankara Pirol S., Çaliskan B., Durmaz I., Atalay R., Banoglu E., Synthesis and preliminary mechanistic evaluation of 5-(p-tolyl)-1-(quinolin-2-yl) pyrazole-3-carboxylic acid amides with potent antiproliferative activity on human cancer cell lines, *European Journal of Medicinal Chemistry*, 87, 140-149, **2014**.

[21] Rashad A. E., Hegab M. I., Abdel-Megeid R. E., Micky J. A., Abdel-Megeid F. M., Synthesis and antiviral evaluation of some new pyrazole and fused pyrazolopyrimidine derivatives, *Bioorganic and Medicinal Chemistry*, 16, 7102-7106, **2008**.

[22] Ramkumar K., Yarovenko V. N., Nikitina A. S., Zavarzin I. V., Krayushkin M. M., Kovalenko L. V., Esqueda A., Odde, S., Neamat N., Design, synthesis and structure-activity studies of rhodanine derivatives as HIV-1 integrase inhibitors, *Molecules*, 15, 3958-3992, **2010**.

[23] Dzurilla M., Demjanova E., Synthesis of thiohydantoin and rhodanine derivatives from 4-substituted cinnamoyl isothiocyanates, *Chemicke Zvesti*, 28, 693, **1974**.

[24] Abdel-Wahab B. F., Khidre R. E., Farahat A .A., Pyrazole-3(4)-carbaldehyde: synthesis, reactions and biological activity, *Arkivoc*, 1, 196-245, **2011**.

6. ACKNOWLEDGEMENTS

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Supplementary information

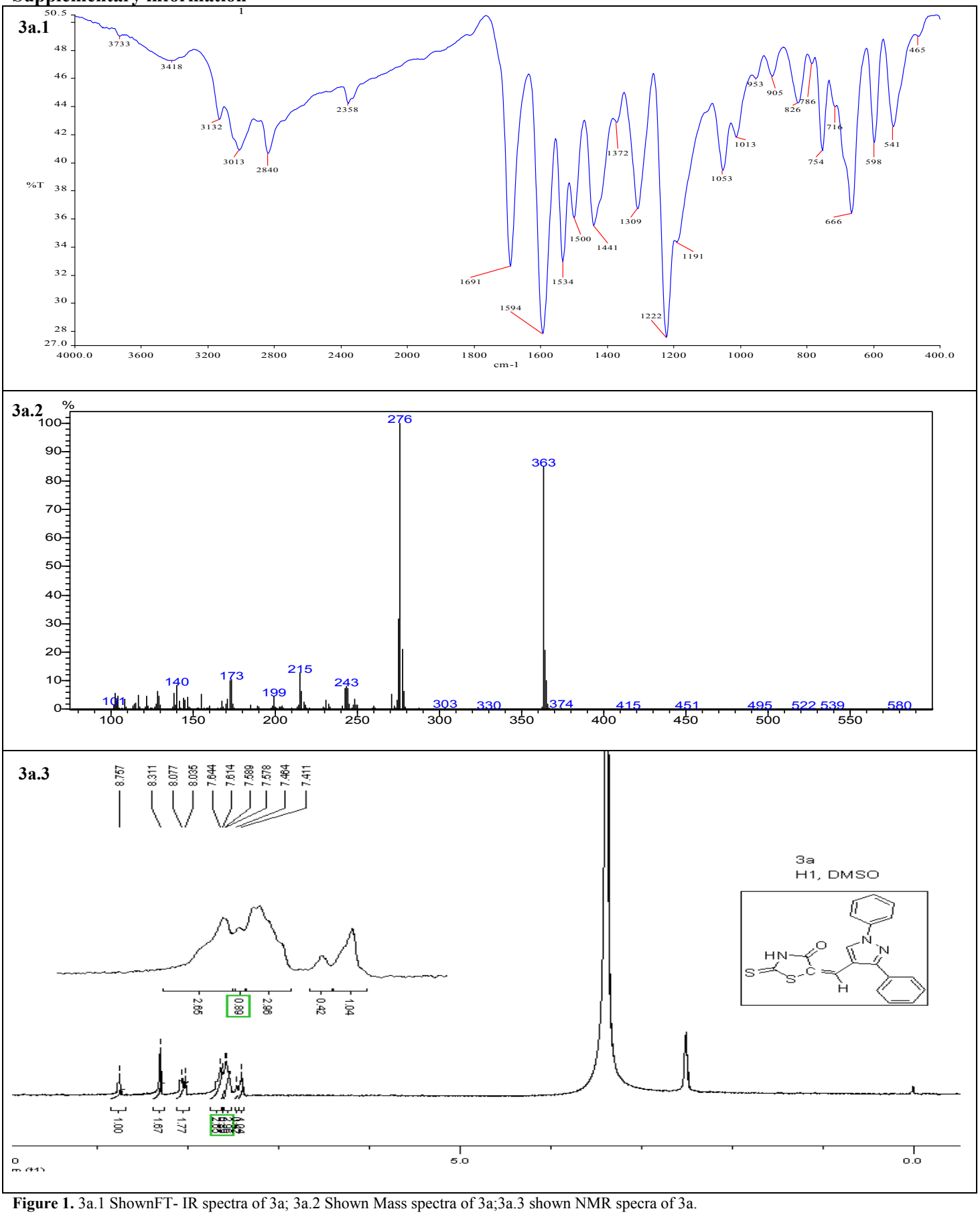

Figure 1. 3a.1 ShownFT- IR spectra of 3a; 3a.2 Shown Mass spectra of 3a;3a.3 shown NMR specra of 3a.

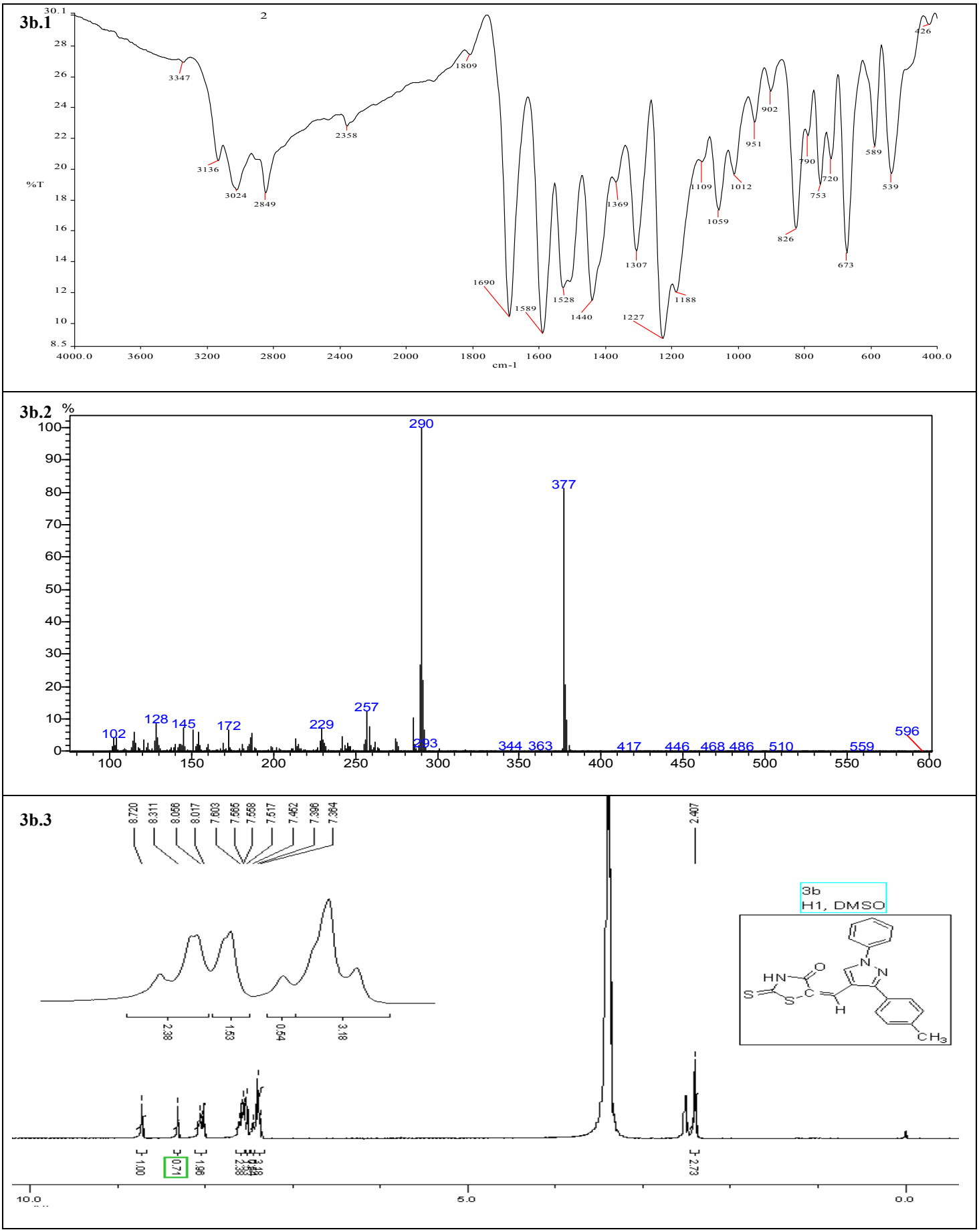

Figure 2. 3b.1 Shown FT- IR spectra of 3b; 3b.2 Shown Mass spectra of 3b; 3b.3 shown NMR specra of 3b.

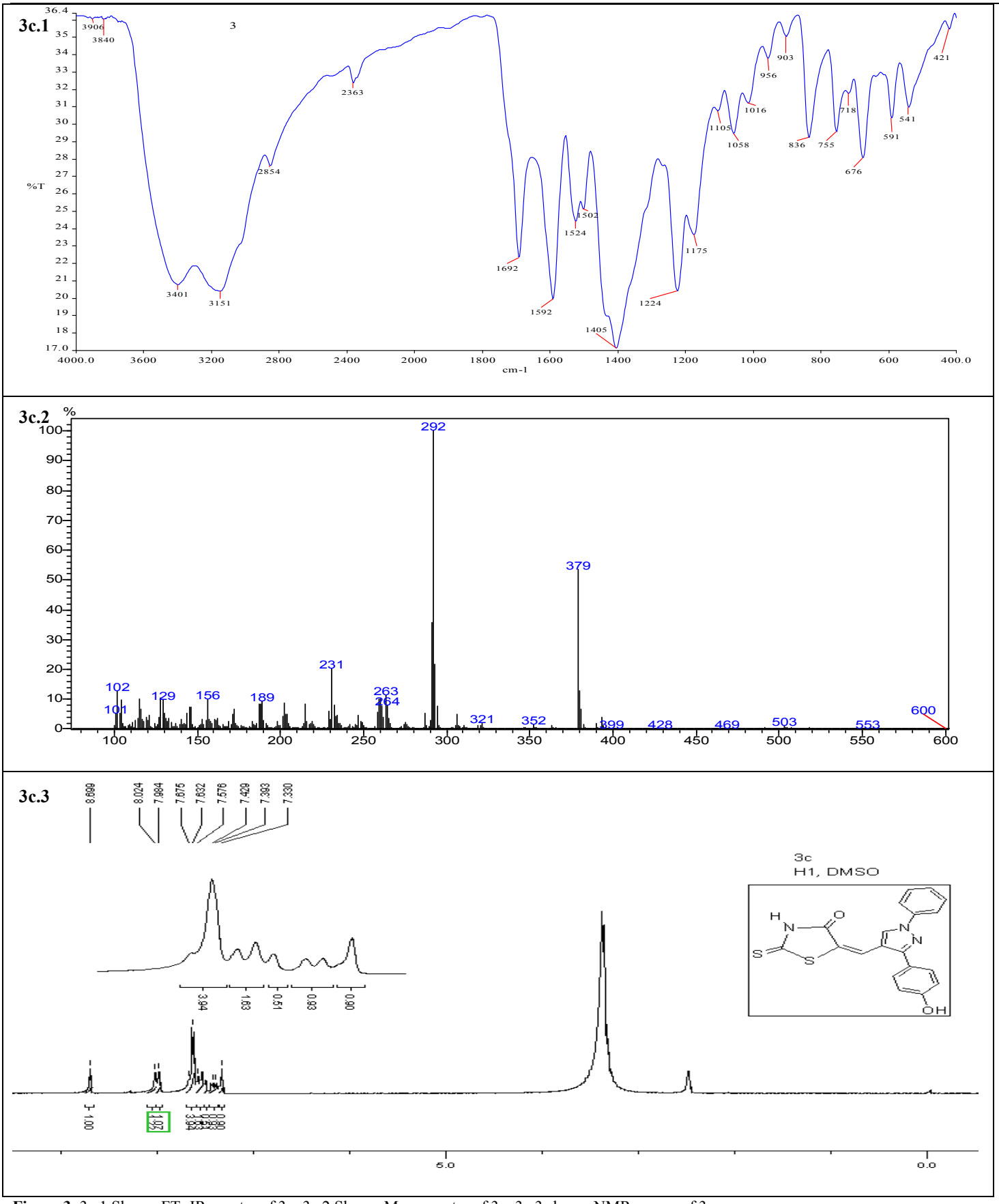

Figure 3. 3c.1 Shown FT- IR spectra of 3c; 3c.2 Shown Mass spectra of 3c; 3c.3 shown NMR specra of 3c.

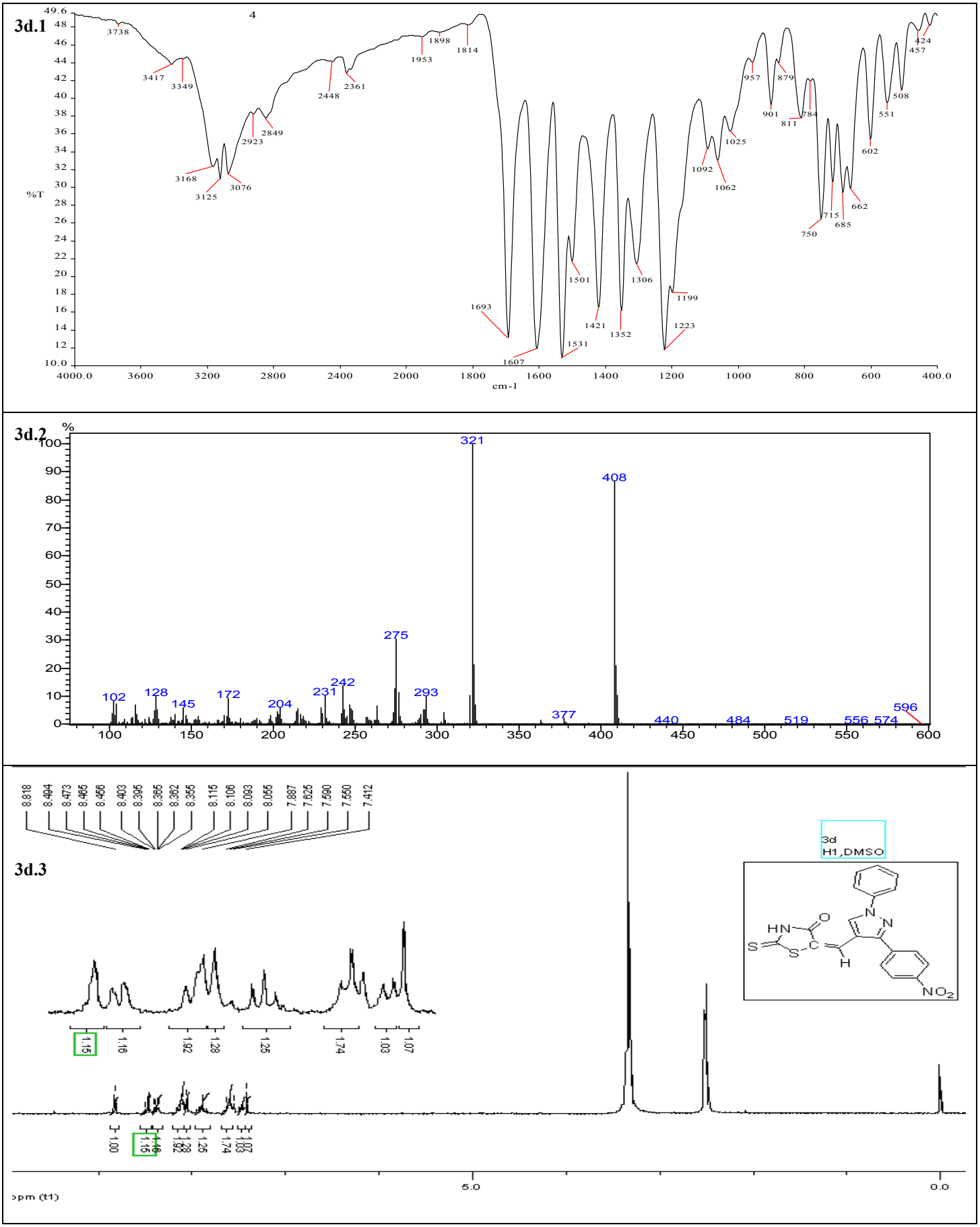

Figure 4. 3d.1 Shown FT- IR spectra of 3d; 3d.2 Shown Mass spectra of 3d; 3d.3 shown NMR specra of 3d.

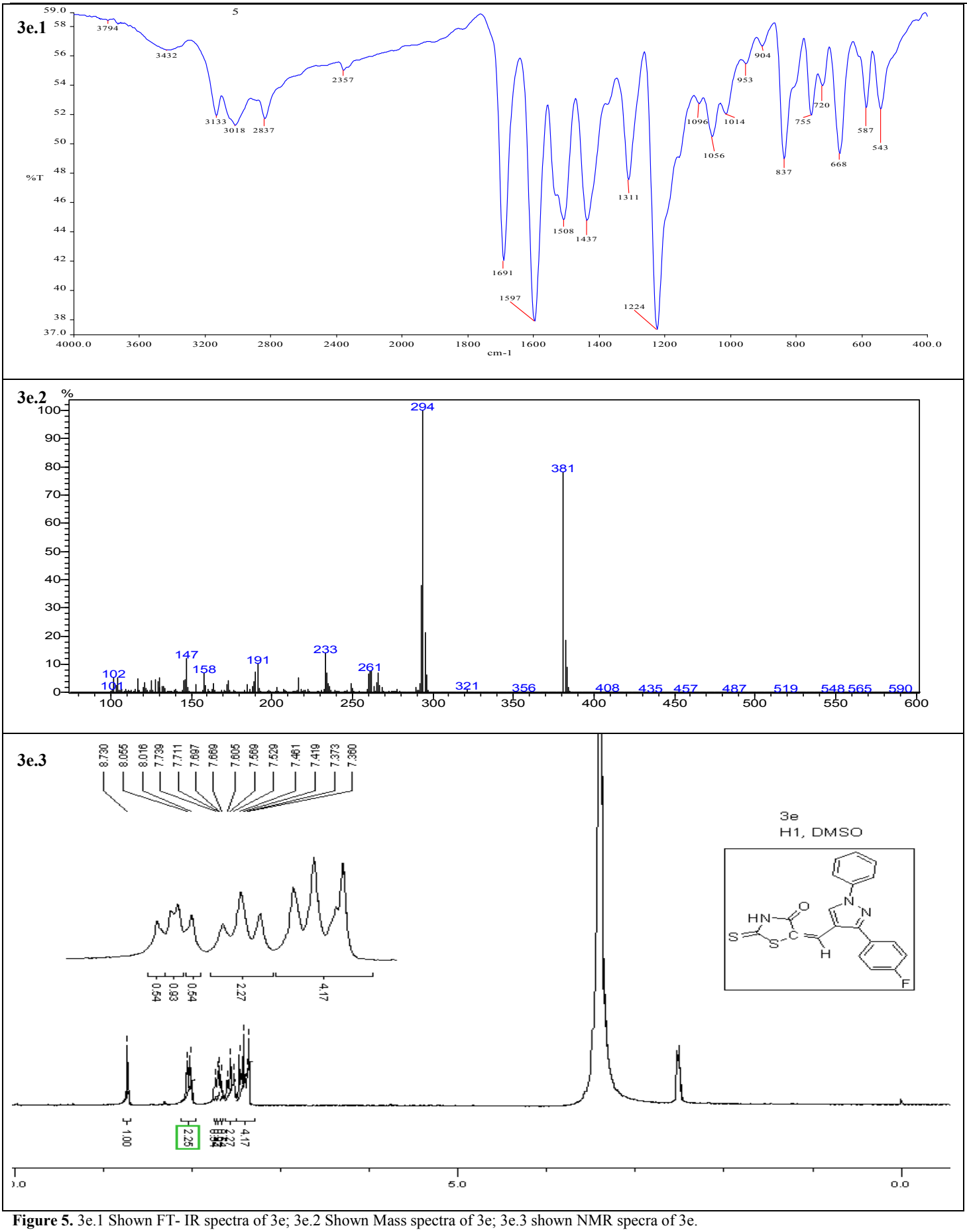

Figure 5. 3e.1 Shown FT- IR spectra of 3e; 3e.2 Shown Mass spectra of 3e; 3e.3 shown NMR specra of 3e.

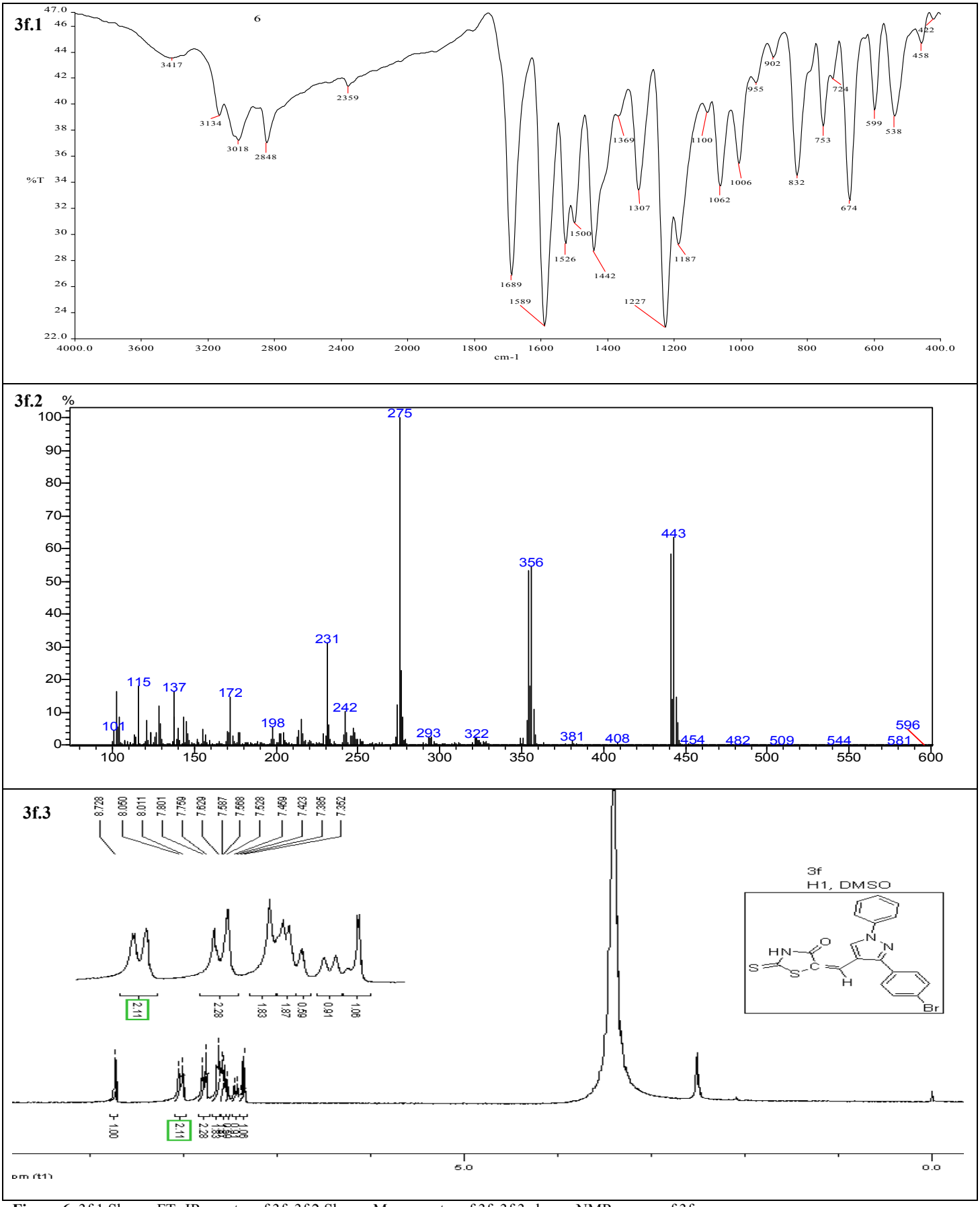

Figure 6. 3f.1 Shown FT- IR spectra of 3f; 3f.2 Shown Mass spectra of 3f; 3f.3 shown NMR specra of 3f.

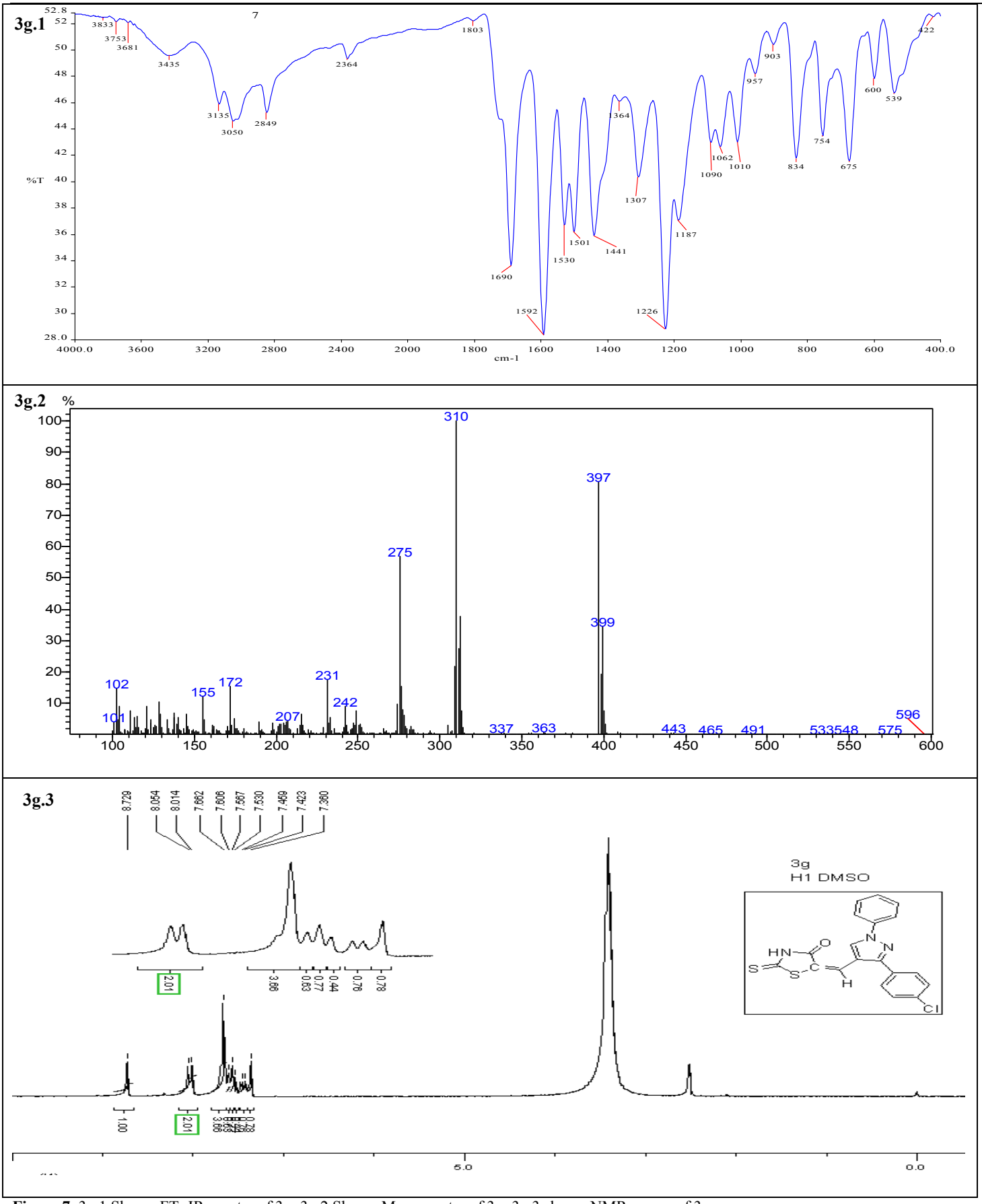

Figure 7. 3g.1 Shown FT- IR spectra of 3g; 3g.2 Shown Mass spectra of 3g; 3g.3 shown NMR specra of 3g.

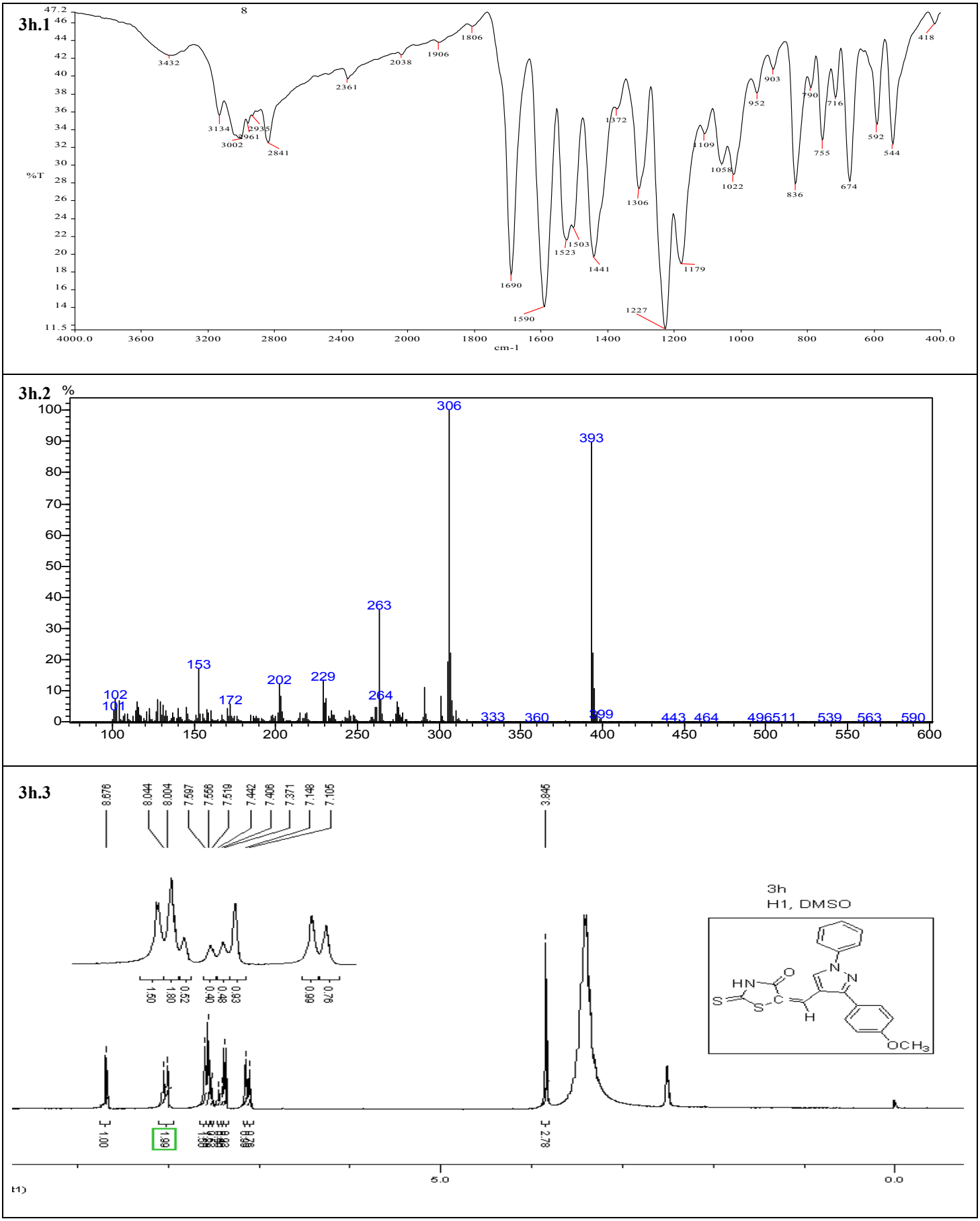

Figure 8. 3h.1 Sown FT- IR spectra of 3h; 3h.2 Shown Mass spectra of 3h; 3h.3 shown NMR specra of 3h.