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Synthesis and characterization of some new derivatives from 6-methyl 2-thiouracil

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Abstract: *This research, involved synthesis of a series of new compound containing different derivatives. The synthesis involved treatment of 6- methyl 2-thiouracil with chloroacetyl chloride to give 1- chloroacetyl 6-methyl 2-thiouracil (1) .The product was treat with hydrazine hydrate to give 2- (aceto hydrazide) thiouracil (2), and with phenyl hydrazine to give phenyl hydrazide thiouracil (13). The new derivatives (3-12, 14- 23) were synthesized by reaction of the hydazide and phenyl hydrazide derivatives (2, 13) with different aromatic aldehydes in the presence of glacial acetic acid. The structure of all the prepared compounds confirmation were proved using (FT- IR), (^1H –NMR) and in addition to melting point.*

Keywords - *6- methyl 2- thiouracil, Schiff bases, 1- chloroacetyl thioracl, phenyl hydrazide derivative.*

I. INTRODUCTION

The literature indicated that Pyrimidine's are important component of nucleic acids and they have been used as building blocks in pharmaceuticals and possesses broad range of biological activity like thiouracil for the synthesis of antiviral, antineoplastic, antibacterial and antifungal agents. [1-3] Similarly, the related thiouracil derivatives are potential therapeutics as antiviral, anticancer and antimicrobial agents.[4-6] For example S- alkylation products have been recently reported as a novel antibacterial cytotoxic agents.[7-8] Thiouracil derivatives are associated with number of biological activities. Also, it was of great interest that specifically functionalized S- are alkylated thiouracil may possess specific biological properties including inhibition of bacterial. [9] Schiff bases are considered compounds for prepared from thiouracil derivatives have an impact effective in stimulating the high efficiency of the thyroid gland in overlap with synthesis of thyroxin as a thionamide anti-thyroid drug for the treatment of hyperthyroidism. [10]

II. EXPERIMENTAL

2.1. Chemicals

All the chemical compounds used with high purity were obtained from BDH, Sigma Aldrich, and Fluka and used as received.

2.2. Instruments

The instruments used in this study are: ^{1}H-NMR spectrum was recorded on Burker 300 MHz instrument using DMSO- d^5 as solvent and TMS as internal reference. The FT-IR spectrum in the range (4000-200) cm^{-1} was recorded as KBr disc on a Shimadzu FT- IR 8300 spectrophotometer. The rotary evaporator was used to evaporate the solvents. .

2.3. General Procedures

2.3.1. Synthesis of 1- chloroacetyl 6-methyl thiouracil (1). [11]

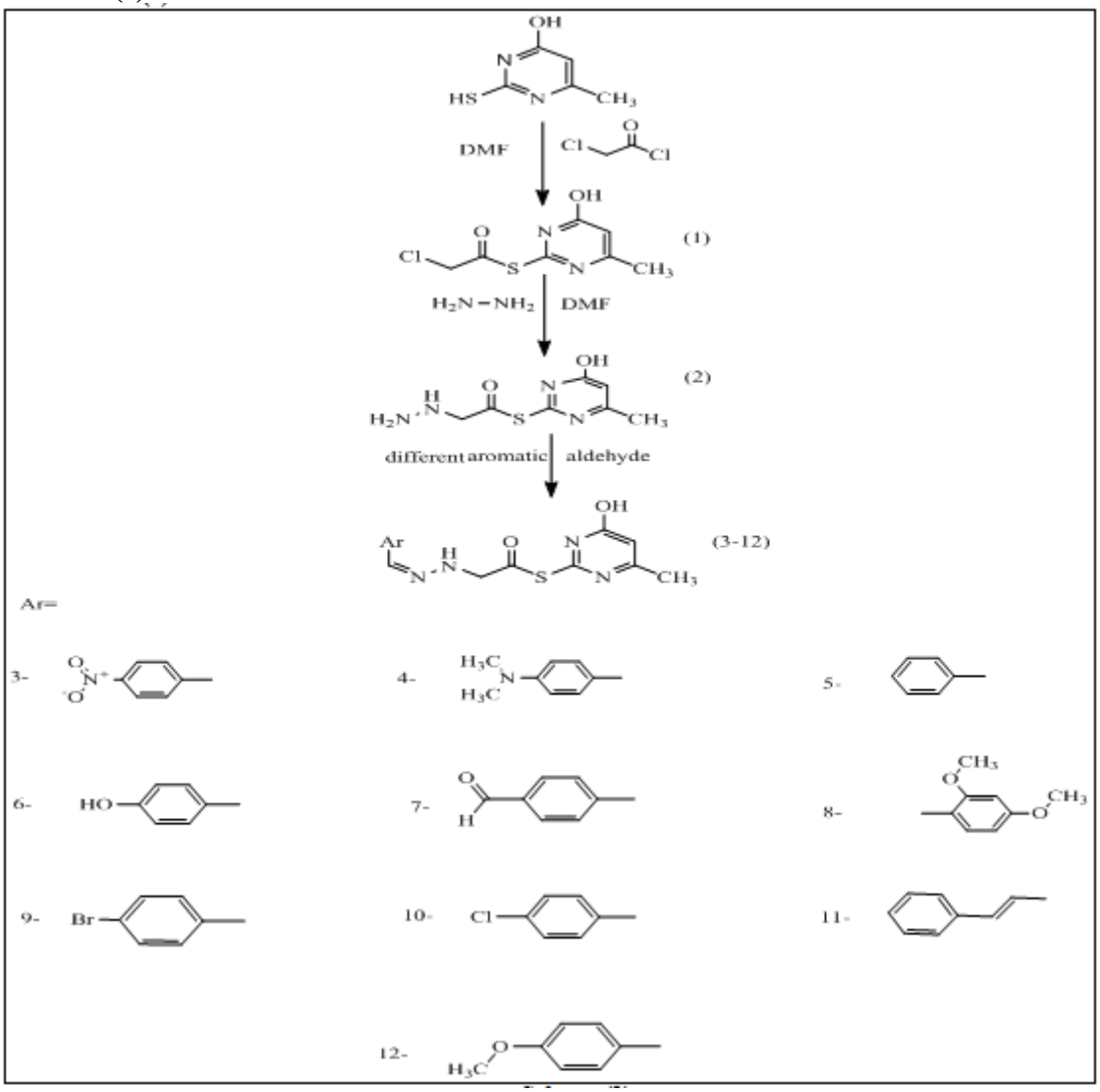
To equimolar of mixture of 6- methyl 2-thiouracil (14.21 gm., 0.1 mol.) in the presence of traces quantities of anhydrous potassium carbonate in dry DMF as solvent (75) ml, chloroacetyl chloride (8ml, 0.1mol) was added drop wise with constant stirring at 0 to 5 ^{0}C .The stirring was continued for about 1-2 hrs. in the same cooling condition and then for overnight at room temperature. After completion of reaction, the reaction mixture was poured into cold water with constant stirring. The resulted precipitate was filtrate and washed with bicarbonate sodium (5%), and water distillation. Dried and recrystallized processes were made using methanol. The physical properties of compound (1) are listed in Table (1).

2.3.2. Synthesis of 2- (aceto hydrazide) 6-methyl thiouracil (2). [12]

A mixture of 1- chloroacetyl 6-methyl thiouracil (1) (21.8gm, 0.1mol) and hydrazine hydrate 99% (6.4ml, 0.2 mol.) in (50) ml dry DMF were stirred at room temperature for about (6) hrs. The resulted precipitate was filtrated to collect the product. The solid precipitate was dried and recrystallized from ethanol. The properties of compound (2) are listed in Table (1).

2.3.3. Synthesis of Schiff bases of 2- (N-substituted 6- methyl thiouracil) benzylidine acetohyrazide (3- 12). [13]

Equimolar quantities of 2- (Aceto hydrazide) 6-methyl thiouracil (2) (2.14 gm., 0.01 mol.) and aromatic aldehydes (0.01mol) in (25) ml of methanol and (3-5) drops of glacial acetic acid were refluxed in water bath for about (5-6) hrs. The solvent was removed under reduced pressure to collect the product. The obtained solid product was recrystallized from chloroform: methanol (scheme 1). The properties of compounds (3- 12) are listed in Table (1).



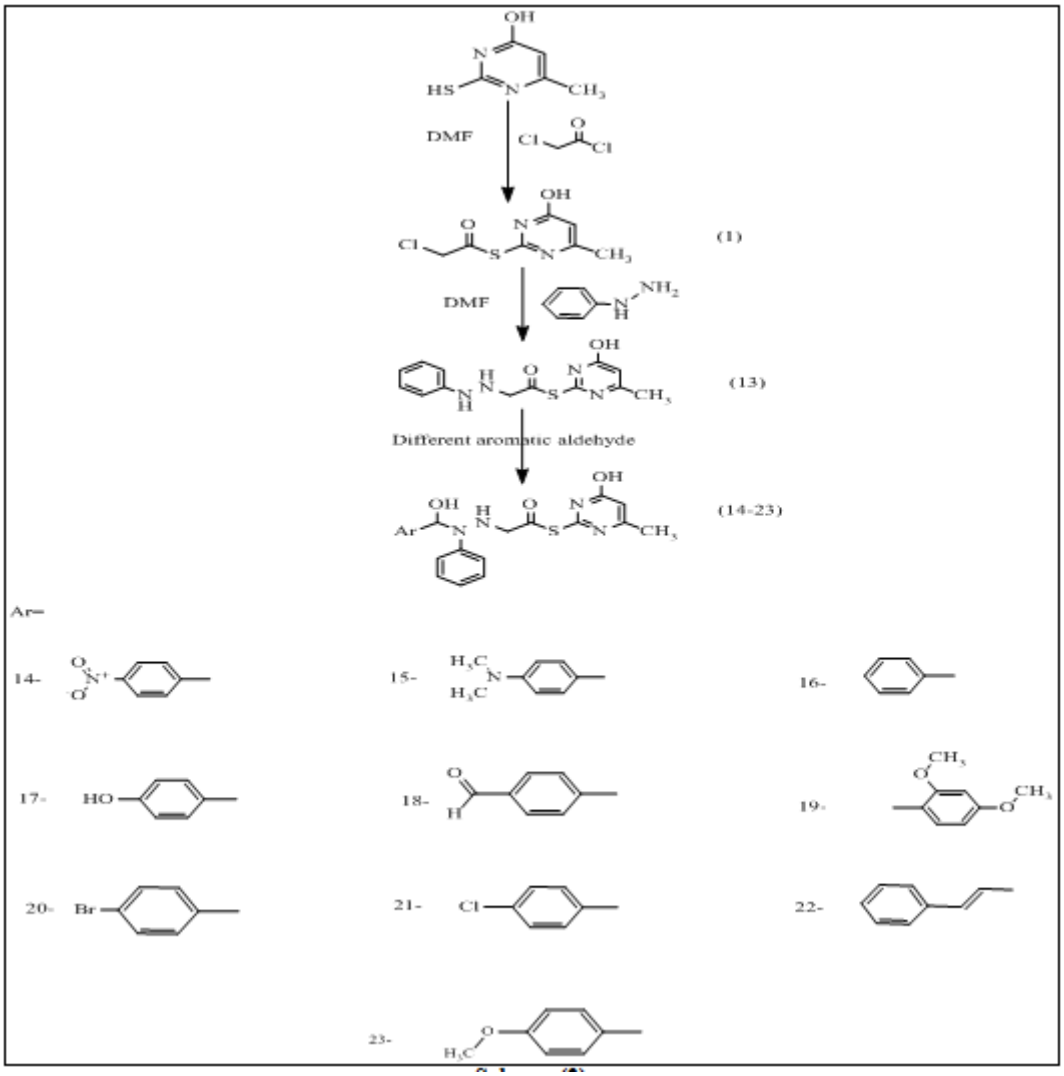
Scheme (1)

2.3.4. Synthesis of 1- (Phenyl hydrazine 6-methyl thiouracil) (13). [14]

A mixture of compound (1) (2.18 gm., 0.01 mol.) and phenyl hydrazine (1 ml, 0.01mol) in dry DMF (20) ml was refluxed for about (6) hrs. The solvent was removed under reduced pressure and the residue to offer the product .The solid was collected and recrystallized from chloroform: methanol. The properties of compound (13) are listed in Table (1).

2.3.5. Synthesis of 1-[α - (Arylidine hydrazino) acetyl] 6-methyl thiouracil (14-23). [15]

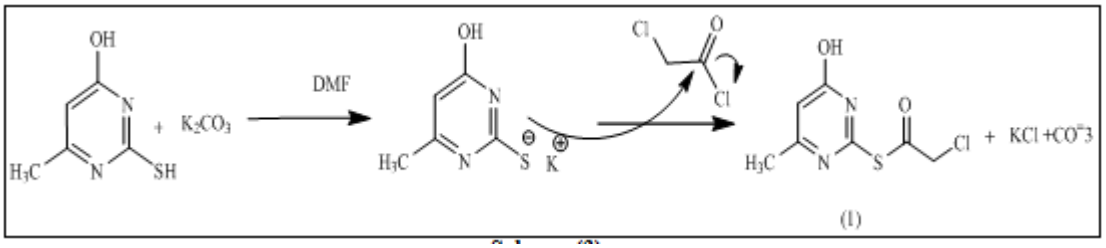
An equimolar quantities of compound (13) (0.29gm, 0.001 mol.) and suitable aromatic aldehydes (0.001mol) in (25) ml of methanol containing few drops of acetic acid were refluxed in water bath for about (6) hrs. The solvent was removed under reduced pressure to offer the product. The solid was collided and recrystallized from chloroform: methanol (scheme 2). The properties of compounds (14-23) are listed in Table (1).



Scheme (2)

III. RESULTS AND DISCUSSION

New thiouracil derivatives were prepared following the reaction sequence depicted in schemes (1&2) and FT-IR spectrum Table (2). The reaction and selective S - alkylation 6- methyl 2-thiouracil with Chloroacetyl chloride in alkali media (K_2CO_3) was used to prepare the starting material for the synthesis of targeted compounds is 1- Chloroacetyl 6-methyl thiouracil (1) carried out by stirring at room temperature dry DMF because the halo group in chloroacetyl chlorid is good leaving group and sulfur compounds are a good nucleophile thus, the reaction is a typical of the nucleophilic substitution reaction of the thiol group, where the halo group could be replaced easily n this reaction to get good yield according to the mechanism in scheme (3) [16].



Scheme (3)

The FT- IR spectrum of compound (1) showed the appearance of absorption bands at (2935, 2891) cm^{-1} due to aliphatic ν(C-H) with the disappearance of (S-H) stretching band at (2550-2650) cm^{-1}. The spectrum also

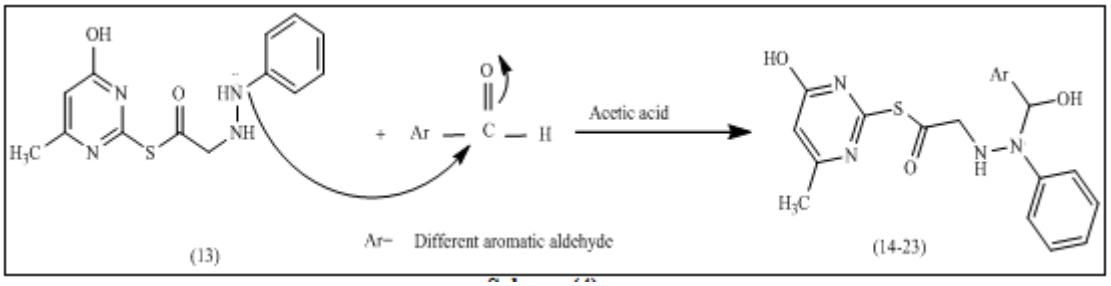
shows absorption sharp band at (1676) cm^{-1} due to ν(C=O) while absorption band due to ν (C-Cl) at (595) cm^{-1}. Other bands are shown in Table (2).
^{1}H-NMR spectrum of compound (1) showed singlet signals at δ= (12.50) due to the phenolic (O-H) proton and singlet signals at δ= (3. 74) due to methyl group protons (-CH_3) in addition to methylene group (-CH_2) appearance singlet signals at δ= (5.90). ^{1}H-NMR spectral data of compound (1) is shown in Figure (5).
The reaction of 2- chloroacetyl thiouracil(1) with hydrazine hydrate 99% yielded 2-(aceto hydrazide) thioracil (2).The halo group in(1) is a good leaving group because of its very high electronegativity, and the reaction condition very easy with very good yield.
The FT-IR spectrum of compound (2) showed the appearance of characteristic absorption bands at (3398, 3205) cm^{-1} belong to ν (NH_2) asymmetric (asym) and symmetric (sym), characteristic absorption band at (1697) cm^{-1} belong to ν(C=O), as shown in Table (2).

^{1}H-NMR spectrum of compound (2) showed broad hump at δ= (3.40- 4.21) ppm due to three protons of the hydrazine moiety, multi signals at δ= (3.78) ppm due to (--CH_2) methylene protons and singlet signals at δ= (5.49) ppm due to aromatic proton for thiouracil. ^{1}H-NMR spectral data of compound (2) is shown in figure (6).

Condensation hydrazide (2) with aryl aldehydes in methanol gave Schiff bases (3-12). The formation of these Schiff bases was indicated by the presence in their FT-IR spectra of the azomethine (CH=N) stretching and appearance of band sym and asym at ν (1645-1577) cm^{-1} which is confirmed through the disappearance of absorption bands of (NH_2) group at (3398, 3205) cm^{-1} other bands are shown in table (2). While ^{1}H-NMR spectra of the compound (7) showed second signal at δ= (3.75) ppm due to (-CH_2) protons of the methylene group, singlet signal at δ= (12.15) ppm due to (O-H) proton of the phenolic group, multi signals at δ= (7.96 – 8.84) ppm due to aromatic protons and singlet signal at δ= (2.73) ppm due to protons of the methyl (-CH_3) group. ^{1}H-NMR spectral data of compound (7) is shown in Figure (7).
^{1}H-NMR spectrum of the compound (8) showed singlet signal with very strong hump at δ= (3.91) ppm due to substituted methoxy (O-CH_3) protons groups, multi signals at δ= (6.94- 8.08) ppm due to aromatic protons, second signal at δ= (4.0) ppm due to (-CH_2) proton and singlet signal at δ= (12.15) ppm due to (O-H) hydroxyl proton hydroxyl. ^{1}H-NMR spectral data of compound (8) is shown in Figure (8).

The compound (13) was prepared from the refluxing of compound (1) with phenyl hydrazine which was found a suitable Chiron for this synthetic approach to give the expected phenyl hydrazide (13), as shown in Scheme (2). The structure of compound (13) was confirmed by the presence of band at (3440) cm^{-1} due to ν (N-H). The spectrum also showed characteristics' aromatic band at (3024) cm^{-1} belong to ν (C-H), and band at (1676) cm^{-1} due to ν(C=O).
^{1}H-NMR spectrum of compound (13) showed multi signals at range δ= (6.81- 7.27) ppm due to aromatic protons, singlet signal at δ= (5.68) ppm due to proton (=C-H) for thiouracil and second signal at δ= (7.31- 7.84) ppm due to protons (N-H). ^{1}H-NMR spectral data of compound (13) is shown in Figure (9).

The new derivatives (14-23) were obtained through the reaction of phenyl hydrazineo acetal thiouracil (13) with different aromatic aldehydes, as presented in Scheme (2). The nucleophilic attack of amino group in compound (13) involved the carbonyl group in different aromatic aldehyde according to mechanism in Scheme (4) [17].



Scheme (4)

The FT-IR spectrum for derivatives (14- 23) showed strong stretching broad band at (3300- 3500) cm^{-1} due to ν (O-H), (3114- 3440) cm^{-1} ν (N-H), (3068) cm^{-1} ν (C-H) aromatic and (1666 – 1753) cm^{-1} for ν (C=O). These bands and others are shown in Table (2).
^{1}H-NMR spectrum of compound (15) showed singlet signal at δ= (3.2) ppm due to (-CH_3) protons, multi signal at range δ= (6.71- 7.27) ppm due aromatic protons, singlet signal at δ= (5.13) ppm due to (O-H) proton and

singlet signal at δ= (7.5) ppm due to (N-H) proton. ^{1}H-NMR spectral data of compound (15) is shown in Figure (10).

Table (1): The nomenclatures and physical properties of compounds (1-23).

No.	Nomenclature	Structure	Chemical formula (M.wt.)	Yield %	Color	M.p. ^{0}C
1	S-(4-hydroxy-6-methylpyrimidin-2-yl) 2-chloroethanethioate		$C_7H_7ClN_2O_5S$ 218.66	70	Yellow	260- 262
2	S-(4-hydroxy-6-methylpyrimidin-2-yl) 2-hydrazinylethanethioate		$C_7H_{10}N_4O_2S$ 214.24	50	Off white	238-240
3	S-(4-hydroxy-6-methylpyrimidin-2-yl) (E)-2-(2-(4-nitrobenzylidene)hydrazinyl)ethanethioate		$C_{14}H_{13}N_5O_4S$ 347.35	80	Orange	182-184
4	S-(4-hydroxy-6-methylpyrimidin-2-yl) (E)-2-(2-(4-(dimethylamino)benzylidene)hydrazinyl)ethanethioate		$C_{16}H_{19}N_5O_2S$ 345.42	80	Orange	185-187
5	S-(4-hydroxy-6-methylpyrimidin-2-yl) (E)-2-(2-benzylidenehydrazinyl)ethanethioate		$C_{14}H_{14}N_4O_2S$ 302.08	65	White yellowish	222-224
6	S-(4-hydroxy-6-methylpyrimidin-2-yl) (E)-2-(2-(4-hydroxybenzylidene)hydrazinyl)ethanethioate		$C_{14}H_{14}N_4O_2S$ 318.35	85	Yellow	215-217
7	S-(4-hydroxy-6-methylpyrimidin-2-yl) (E)-2-(2-(4-formylbenzylidene)hydrazinyl)ethanethioate		$C_{15}H_{14}N_4O_3S$ 330.36	90	Yellow	277-279

8	S-(4-hydroxy-6-methylpyrimidin-2-yl) (Z)-2-(2-(2,4-dimethoxybenzylidene)hydrazinyl)ethanethioate		$C_{14}H_{18}N_4O_4S$ 362.40	80	White	180-182
9	S-(4-hydroxy-6-methylpyrimidin-2-yl) (E)-2-(2-(4-bromobenzylidene)hydrazinyl)ethanethioate		C14H13BrN4O$_2$S 381.25	73	Yellow	185-187
10	S-(4-hydroxy-6-methylpyrimidin-2-yl) (E)-2-(2-(4-chlorobenzylidene)hydrazinyl)ethanethioate		$C_{14}H_{13}ClN_4O_2S$ 336.79	87	White	242-244
11	S-(4-hydroxy-6-methylpyrimidin-2-yl) 2-(2-((1Z,2E)-3-phenylallylidene)hydrazinyl)ethanethioate		$C_{16}H_{16}N_4O_2S$ 328.39	70	yellow dark	220-222
12	S-(4-hydroxy-6-methylpyrimidin-2-yl) (Z)-2-(2-(4-methoxybenzylidene)hydrazinyl)ethanethioate		$C_{15}H_{16}N_4O_3S$ 332.09	80	Yellow	165-167
13	S-(4-hydroxy-6-methylpyrimidin-2-yl) 2-(2-phenylhydrazinyl)ethanethioate		$C_{13}H_{14}N_4O_2S$ 290.34	65	Brown	245-247
14	S-(4-hydroxy-6-methylpyrimidin-2-yl) 2-(1-(hydroxy(4-nitrophenyl)methyl)-2-phenylhydrazinyl)ethanethioate		$C_{20}H_{19}N_5O_5S$ 441.46	66	Yellow	180-182

15	S-(4-hydroxy-6-methylpyrimidin-2-yl) 2-(1-((4-(dimethylamino)phenyl)(hydroxy)methyl)-2-phenylhydrazinyl)ethanethioate		$C_{22}H_{25}N_5O_3S$ 439.53	78	yellow pale	200-202
16	S-(4-hydroxy-6-methylpyrimidin-2-yl) 2-(1-(hydroxy(phenyl)methyl)-2-phenylhydrazinyl)ethanethioate		$C_{20}H_{20}N_4O_3S$ 396.47	75	Brown	158-160
17	S-(4-hydroxy-6-methylpyrimidin-2-yl) 2-(1-(hydroxy(4-hydroxyphenyl)methyl)-2-phenylhydrazinyl)ethanethioate		$C_{20}H_{20}N_4O_4S$ 412.46	85	yellow pale	195-197
18	S-(4-hydroxy-6-methylpyrimidin-2-yl) 2-(1-((4-formylphenyl)(hydroxy)methyl)-2-phenylhydrazinyl)ethanethioate		$C_{21}H_{20}N_4O_4S$ 424.48	80	Yellow	267-269
19	S-(4-hydroxy-6-methylpyrimidin-2-yl) 2-(1-((2,4-dimethoxyphenyl)(hydroxy)methyl)-2-phenylhydrazinyl)ethanethioate		$C_{22}H_{24}N_4O_5S$ 456.52	80	White yellowish	220-222
20	S-(4-hydroxy-6-methylpyrimidin-2-yl) 2-(1-((4-bromophenyl)(hydroxy)methyl)-2-phenylhydrazinyl)ethanethioate		$C_{20}H_{19}BrN_4O_3S$ 475.36	84	Yellow	170-172

21	S-(4-hydroxy-6-methylpyrimidin-2-yl) 2-(1-((4-chlorophenyl)(hydroxy)methyl)-2-phenylhydrazinyl)ethanethioate		$C_{20}H_{19}ClN_4O_3S$ 430.91	88	Yellow	202-204
22	S-(4-hydroxy-6-methylpyrimidin-2-yl) (E)-2-(1-(1-hydroxy-3-phenylallyl)-2-phenylhydrazinyl)ethanethioate		C22H22N4O3S 422.35	65	Yellow pale	188-190
23	S-(4-hydroxy-6-methylpyrimidin-2-yl) 2-(1-(hydroxy(4-methoxyphenyl)methyl)-2-phenylhydrazinyl)ethanethioate		$C_{22}H_{22}N_4O_3S$ 422.14	68	Yellow	167-169

Table (2): FT-IR spectral data of compounds (1-23).

Comp. NO.	ν(C-H)$_{aliph.}$	ν(C-H)$_{Ar.}$	ν(N-H)	ν(O-H)	ν(C=O)	ν(C=N)	Other Bands
1	2935	3006	-	3463	1676	1635	ν C-Cl (595)
2	2951	3016	3113	3398	1697	1643	**ν** NH_2 asym.(3205)
3	2927	3004	3406	3469	1703	1635	**ν** NO_2 (1558)
4	2933	3026	3110	3411	1674	1602	**ν** C-N (1166-1197)
5	2887	3024	3110	3396	1699	1637	**ν** C = C (1558)

6	2933	3087	3118	3423	1639	1600	p- position for OH (838)
7	2933	3018	3116	3338	1676	1627	νC=O aldehyde (1699)
8	2983	3089	3114	3517	1672	1618	σ C-O-C (1290)
9	2925	3012	3116	3269	1676	1600	P - position for Br (729)
10	2933	3004	3419	3566	1699	1635	P - position for Cl (595)
11	2891	3022	3355	3421	1674	1635	ν C= C (1558)
12	2889	3006	3479	3537	1697	1635	σ C-O-C (1250)
13	2933	3024	3440	3504	1676	1637	ν $C=C_{Ar}$ (1419)
14	2871	3066	3205	3431	1712	1604	ν NO_2 (1527)
15	2889	3120	3415	3444	1701	1602	ν C-N (1240-1257)
16	2939	3020	3407	3481	1753	1637	σ CH_3 (1421)
17	2937	3031	3415	3433	1666	1645	ν $C=C_{Ar}$ (1600)
18	2866	3031	3316	3409	1695	1637	ν $C\text{-}H_{aldehyde}$ (2808)
19	2925	3024	3446	3471	1668	1602	σ C-O-C (1263-1284)
20	2935	3006	3442	3537	1672	1641	P - position for Br(811)
21	2947	3089	3400	3480	1685	1639	ν $C=C_{Ar}$ (1500)
22	2939	3062	3251	3500	1674	1639	ν $C=C_{Ar}$ (1558)
23	2929	3068	3114	3452	1699	1608	σ C-O-C (1240-1261)

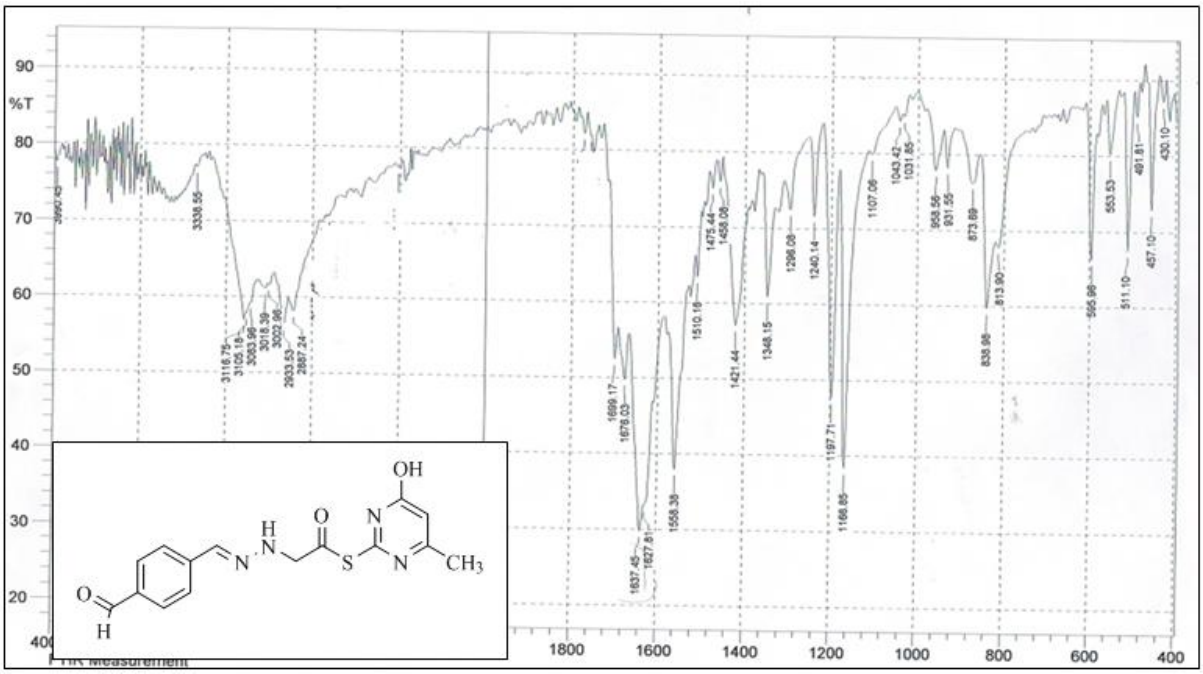


Figure (1): FT-IR spectrum of compound (7)

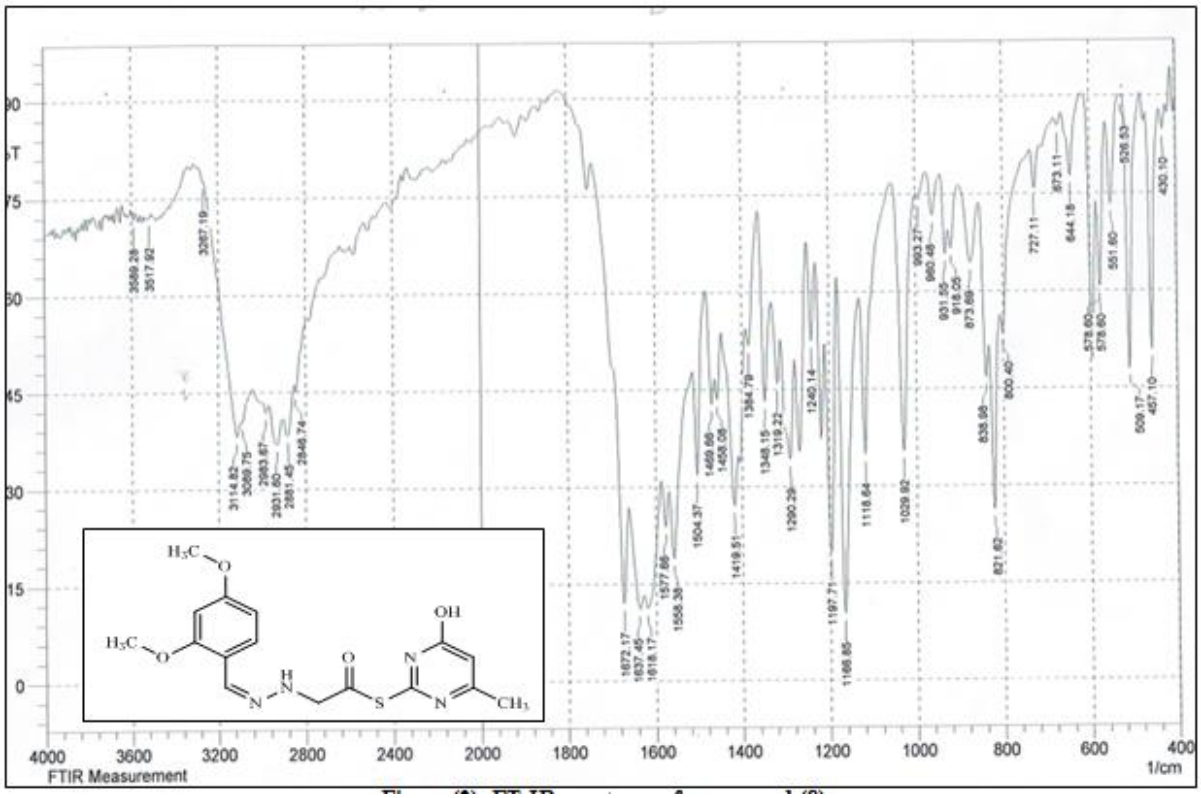


Figure (2): FT-IR spectrum of compound (8)

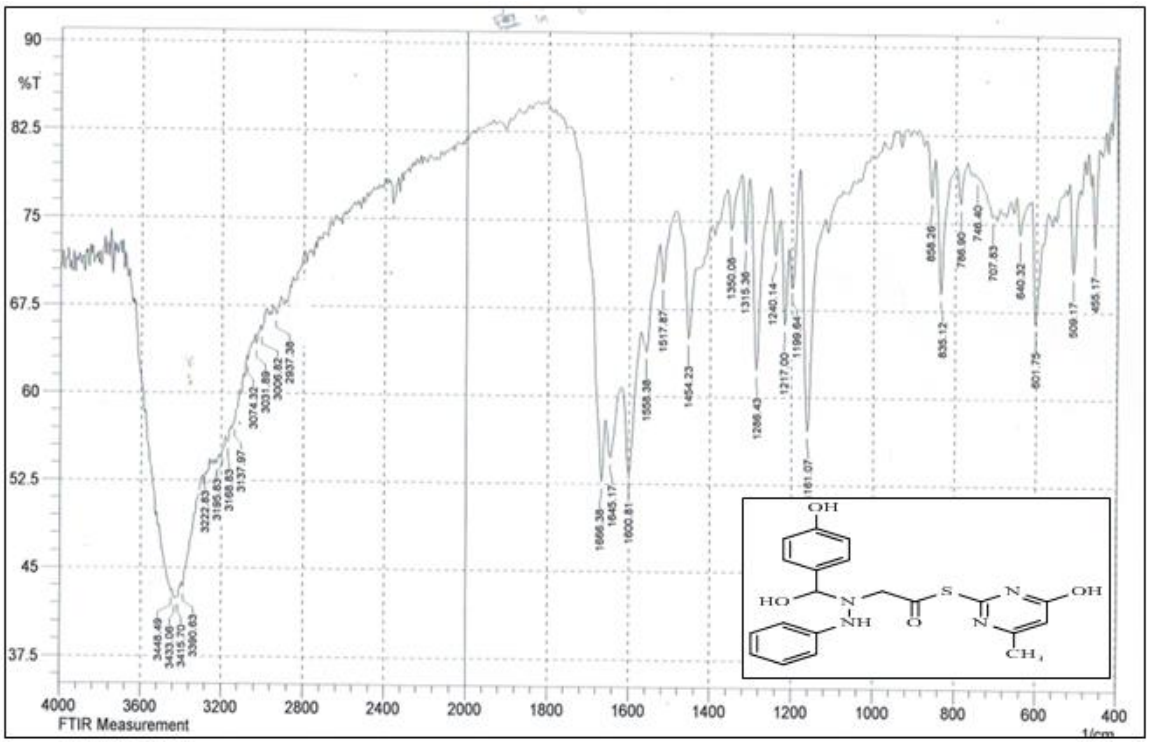


Figure (3): FT-IR Spectrum of Compound (17)

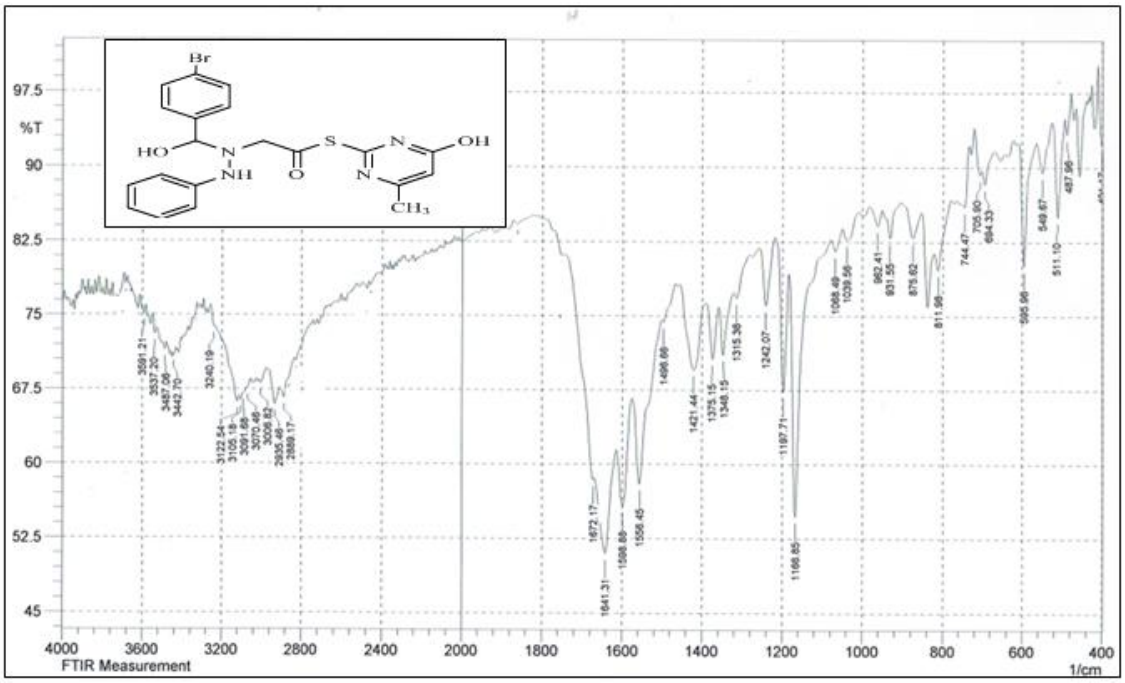


Figure (4): FT-IR Spectrum of Compound (20)

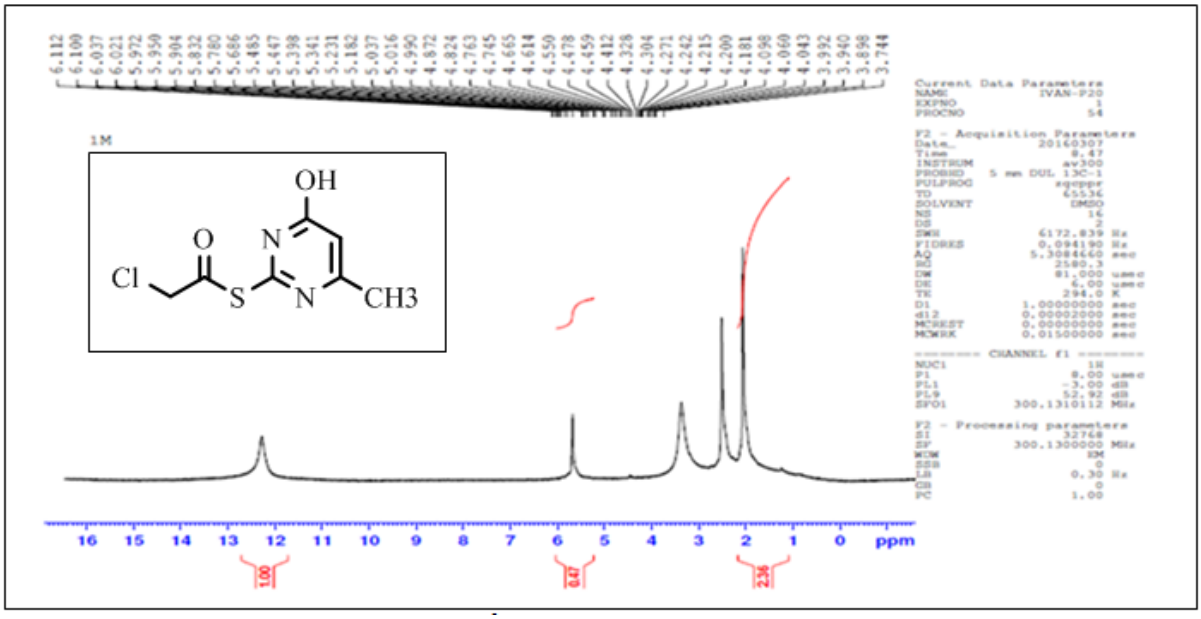


Figure (5): 1H-NMR Spectrum of Compound (1)

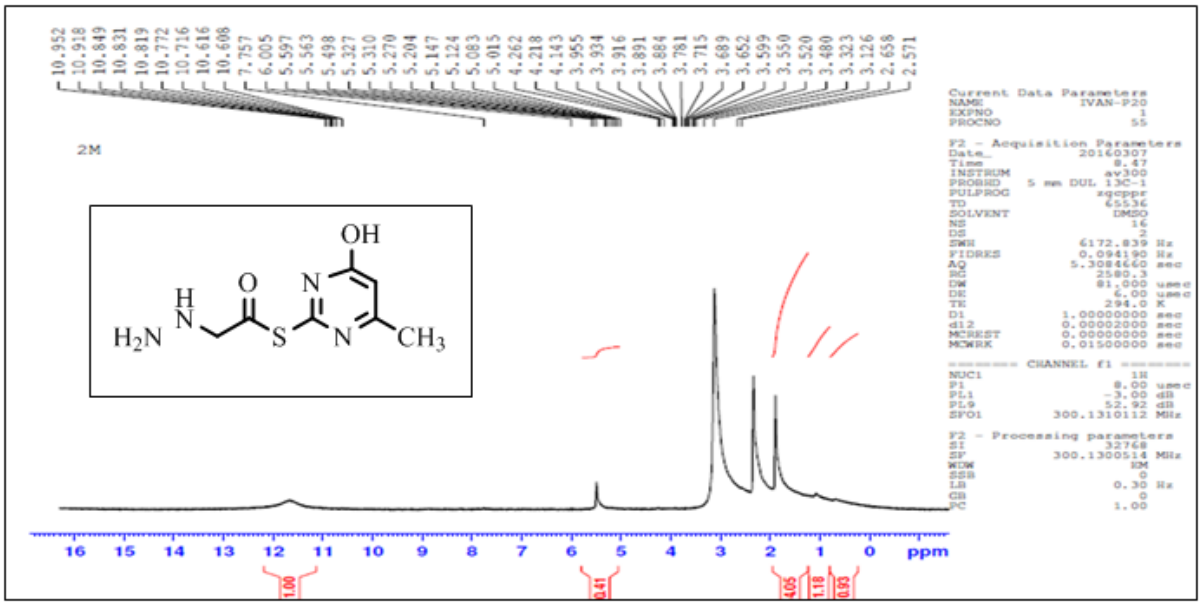


Figure (6): 1H-NMR Spectrum of Compound (2)

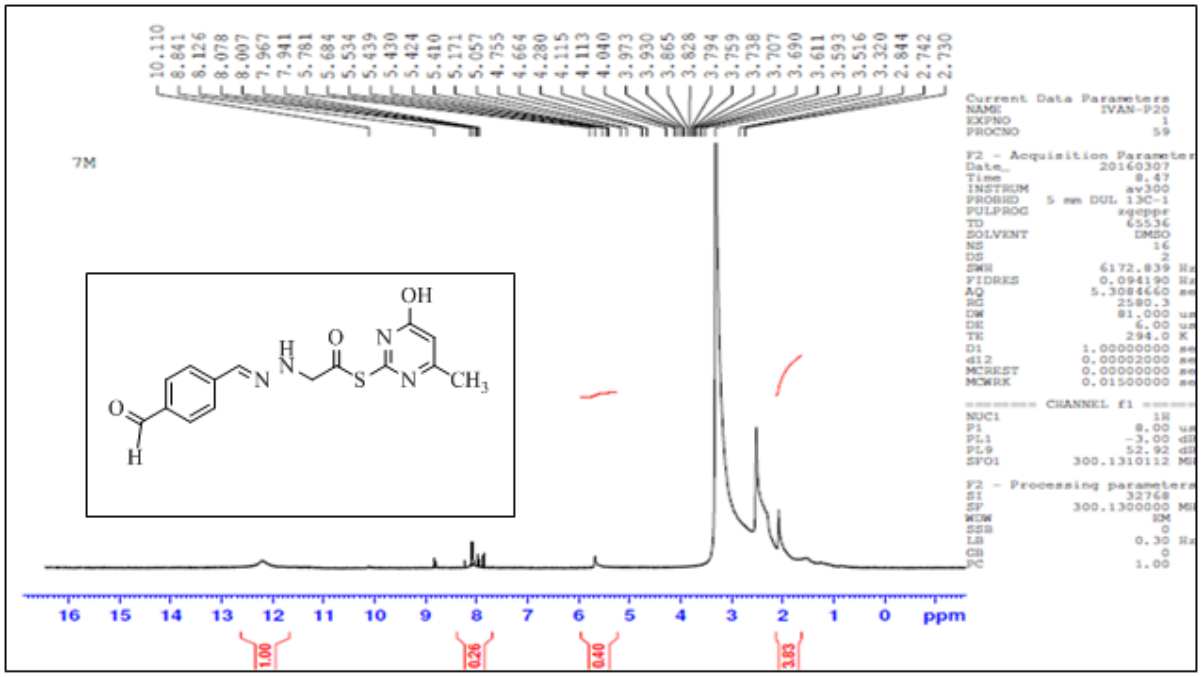


Figure (7): 1H-NMR Spectrum of Compound (7)

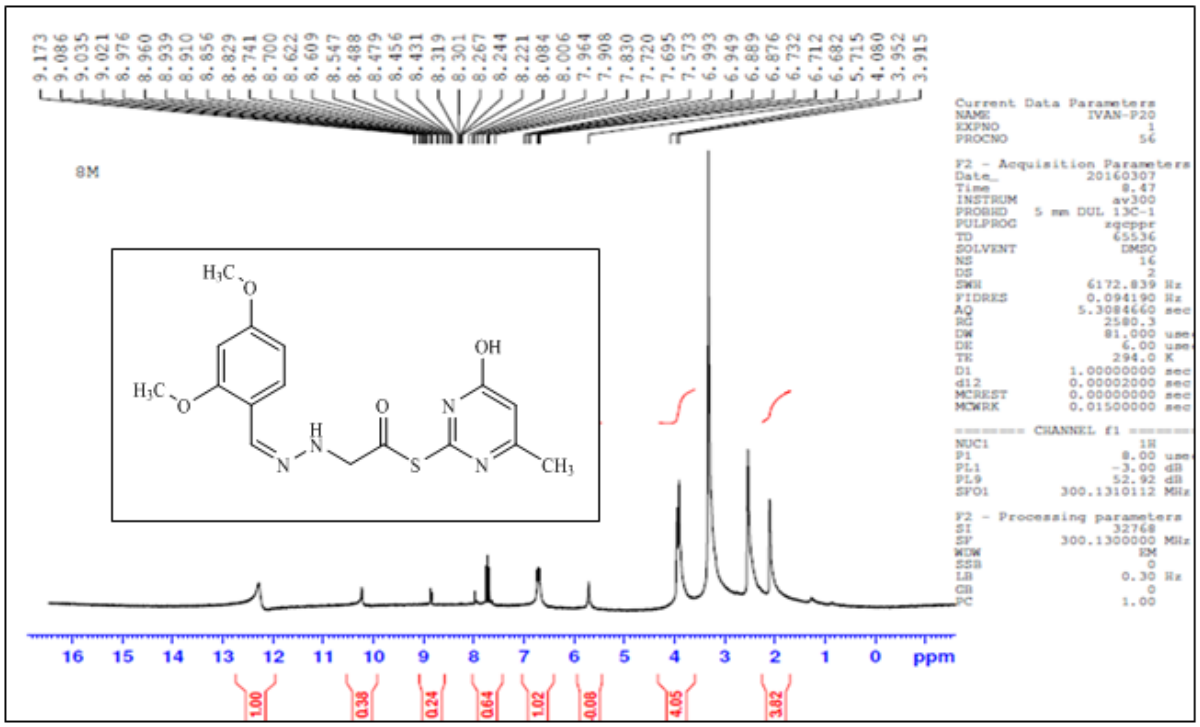


Figure (8): 1H-NMR Spectrum of Compound (8)

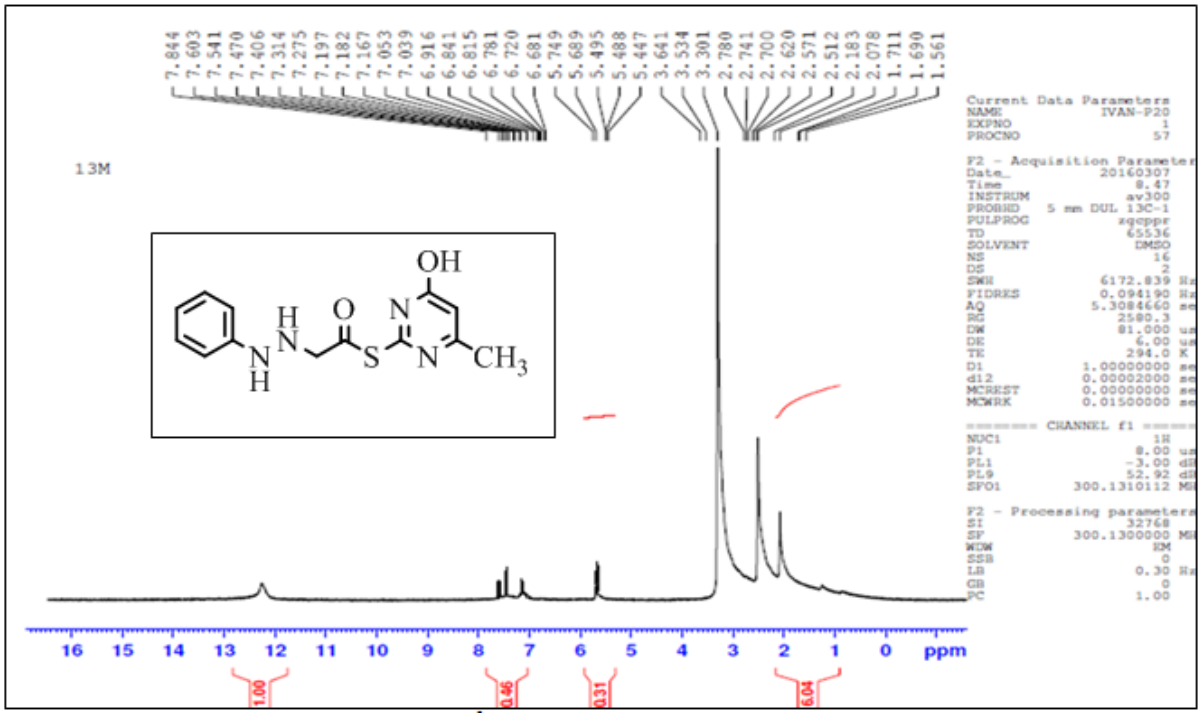


Figure (9): 1H-NMR Spectrum of Compound (13)

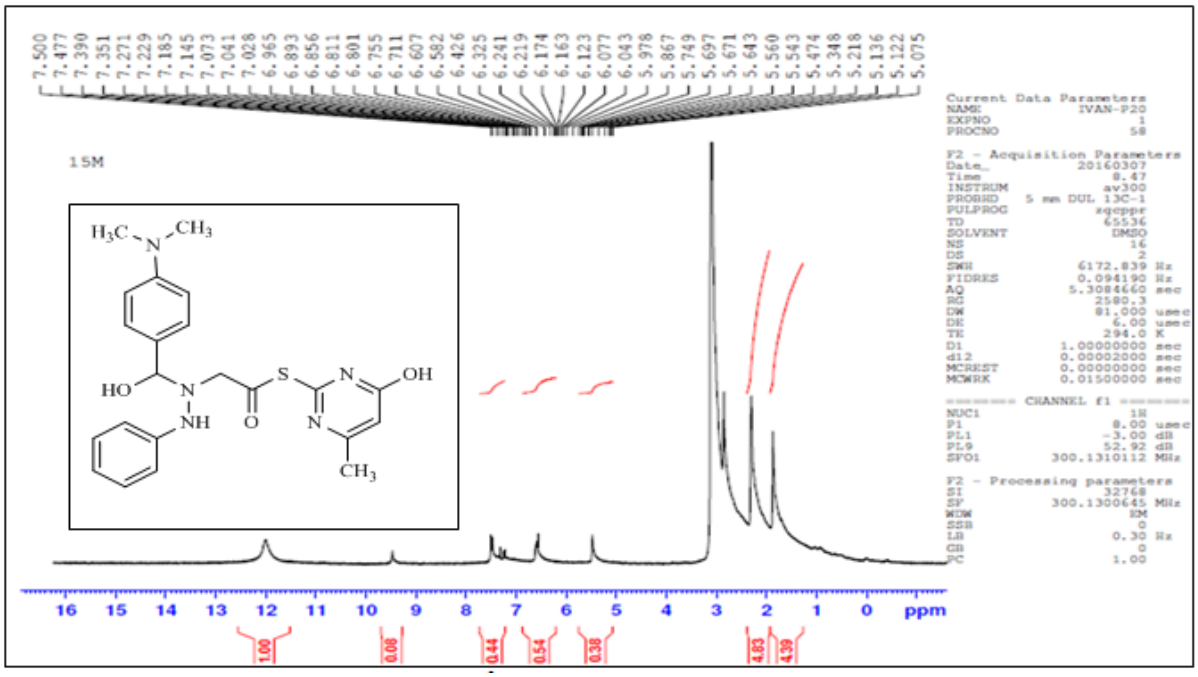


Figure (10): 1H-NMR Spectrum of Compound (15)

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