Synthesis of novelN-{5-(2,2-Dimethylisopropylidenyl)thio-1,3,4-thiadiazolyl}-N-acetyl-amino-(4-(N-Dimethylamino)benzyl –amino Barbituric Acid

Fadhel Omran Essa , Kaudhm Jwad AL-Hmdani, Abbas Ali Drea

Babylon university . College of Science/ Chemistry Department

Babylon university . College of Medicine/ Chemistry Department

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Abstract

5-amino-1,3,4-thiadiazole-2-thiol (1) was reacted with4-(N-dimethylamino) benzaldehyde in refluxing ethanol to give Schiff base 5-{[4-(dimethylamino)benzylidene]amino}-1,3,4-thiadiazole-2-thiol (2) .Compound (2) was reacted with Acetylchloridein dry benzene to give*N*-{chloro[4-(dimethylamino)phenyl]methyl}-*N*-(5-mercapto-1,3,4-thiadiazol-2-yl)acetamide(3)

the reaction of compound (3) with quindinehydrochloridin ethanol to gave N-{5-mercapto(1,3,4-thiadiazol-2-yl) }-amino-N-acetyl -4-(N-dimethyl amino benzyl) guanidine (4)

Compound(4)was reacted with dimethylmalonate in ethanol to afford N-{ 5-mercapto (1,3,4-thiadiazol-2yl)}-amino-N-acetyl -4-(N-dimethylaminobenzyl) aminobarbituric acid (5), these compounds were reacted with 2,2-dimethyl-4-[(phenylsulfonyl)methyl]-1,3-dioxolane in dioxane to give N-{5-(2,2-Dimethylisopropylidenyl)thio-1,3,4-thiadiazolyl}-amino-N-acetyl -(4-(N-Dimethylamino)benzyl –amino barbituric Acid(6)

The prepared compounds were identified by elemental analysis and spectroscopic methods :FT-IR,UV-visible and ^{1}HNMR for compounds (4-6)

تحضر المركب N-{5- (2,2-ثنائي مثيل ازوبروبريلدينيل) ثايو-4,3,1-ثاياديازوليل-N-استيل- امينو- 4- (N-ثنائي مثيل امينو) بنزيل - امينو حامض باربيتيوريك

فاضل [1] عمران عيسى . كاظم جواد الحمداني عباس [1] علي الدريع

جامعة بابل . كلية العلوم / قسم الكيمياء

جامعة بابل . كلية الطب / قسم الكيمياء

مفتاح البحث : حامض الباربيتيوريك ، ثاياديازول

الخلاصة

يتضمن البحث تحضير مشتق حامض الباربيوتريك والذي يحتوي على الحلقة الا روماتية غير المتجانسة 4,3,1- ثاياديازول . من خلال تفاعل المركب 2-امينو 5- مركبتو 4,3,1- ثاياديازول مع المركب 4-ثنائي المثيل امينو بنزالديهايد ليعطي مشتق قاعدة شيف 5-(4-ثنائي مثيل امينو بنزيليدين) امينو-4,3,1-ثاياديازول - 2-ثايول (2)،تم مفاعلةهذا المركب مع كلوريد الاستيل ليعطيالمركبN-{ كلورو(4-ثنائي مثيل امينو –فنيل – مثيل}–N-(5-مركبتو-4,3,1-ثاياديازول-2-يل)-استياميد (3) تمت اضافة مركب الكواندين هيدروكلوريد بوجود خلات الصوديوم فاعطى المركب N–{(5–مركبتو (4,3,1-ثاياديازول-2- يل) -N-استيل –امينو-4- (N-ثنائي مثيل امينو بنزيل)كواندين (4)وبتفاعل هذا المركب مع ثنائي مثيل مالونيت في الايثانول اعطي المركبN–{5 –مركبتو (4,3,1-ثاياديازول-2- يل) } -N-استيل –امينو-4- (N-ثنائي مثيل امينو بنزيل) امينو حامض باربيتيوريك (5)تم تفاعل المركب(5) مع 2,2-ثنائي ميثل 4-{(فنيل سلفونيل) ميثل}-3,1- داياكسولان في الدايوكسان ليعطي المركبN-{5- (2,2-ثنائي ايزوبروبيليد ينيل) ثايو-

4,3,1- ثاياديازوليل- N- استيل –امينو -4-(N-ثنائي مثيل امينو بنزيل) امينو حامض باربيتيوريك (6) .تم تشخيص المركبات المحضرة عن طريق تحليل العناصر وكذلك بطيف الاشعة تحت الحمراء وطيف الاشعة فوق البنفسجية - المرئية وكذلك شخصت المركبات(4-6) بطيف الرنين النووي المغناطيسي .

Introduction

Thiadiazole and its derivatives represent a very important class of organic compounds for their interesting uses in many areas[1-4].They can be used as antimicrobial agent ,some thiadiazole compound have reported to exhibit antifungal , anti-microbial , fungicidal,amebicidal[5-7], some compounds have been found to exhibit muscle relaxant properties[8] ,high antibacterial activity[9,10], used as multi- functional ligands[11,12].

Barbituric acid derivativesare used in many areas[13-15] ,as antispasmodic ,some have been reported to exhibit antifungal and antimicrobial properties[16] ,antifungal activity,

also it has been found to be an excellent fungicidal bactericidal , Also barbituric acid derivatives are well known to possess antibacterial, [17] sedatives, [18] herbicides, [19] fungicides [20] and antiviral agents. [21]

Materials and Methods

All chemicals used are supplied from Fluka and Merck companies and used without any further purification. Infrared spectra were performed using a Shimadzu (FT-IR) - 8400S spectrophotometer in the range (4000-400cm^{-1}).Spectra were recoded as potassium bromide discs .

The electronic spectra of the compounds were obtained using a (UV-Visible) spectrophotometer type spectrophotometer type Shimadzu, (160A) in the range (200-700) nm using quartz cell of (1.0)cm length with concentration (10^{-3}) mole $L^{-1}$of samples in acetone at 25Ć, elemental analysis (C.H.N.S.) was carried out with: European Elemental Analyzer Italia Measurements were made at Chemistry Department, Al– Al-Bayt University, Jordan and melting points were obtained using an electrothermal apparatus Stuart melting point. ^{1}H.NMR spectra were recorded on Fourier Transform Varian spectrometer, operating at 300 MHz with tetramethylsilane as internal standard in DMSO, Measurements were made at Chemistry Department, Al-Bayt University, Jordan.

Experimental

1- Preparation of 2-amino- 5-mercapto -1,3,4- thiadiazole (1)

Amixture of thiosemicarbazide(2.0g,0.02mol)of and anhydrous sodiumcarbonate (2.33g,0.02mol) was dissolved in of absolute ethanol (25 mL)to this solution of carbon disulhide(3.2g,0.04mol) was added,the resulting mixture was heated under reflux for (8 h) , and the reaction mixture was then allowed to cooldown to room temperature ,most of solvent was removed under reduced pressure and the residue was dissolved in distilled water (20 mL),after which it was carefully acidified with cold concentrated hydrochloric acid to give pale yellow precipitate .The crude product was filtered and washed with cold water distilled and recrystallized from ethanol distilled water to give the desired product(1.6g ,55%) as yellow needles.M. p of (233-235) Ć, [22]

2- Preparation of (5-(4-Dimethylamino)benzylidene)amino-1,3,4-thiadiazole-2-thiol (2)A mixture of compound (1) (0.5g,0.006mol) ,absolute ethanol and the

appropriate aldehyde (0.56gm,0.006mol) in acidic medium was refluxed in water bath for (4h) and the reaction mixture was then allowed to cool at room temperature and the precipitate was filtered ,dried and recrystallized from ethanol (50%) to give red crystals with yield of 75% . M.p(259-260.5) Ć

3- Preparation of *N*-{chloro[4-(dimethylamino)phenyl]methyl}-*N*-(5-mercapto-1,3,4-thiadiazol-2-yl)acetamide (3)

Compound (0.5,0.0019mol) was dissolved in dry benzene5mL to this solution Acetylchloride(0.147gm,0.0019mol)was added,the resulting mixture was heated under reflux for 2h and the reaction mixture was then allowed to cool down to room temperature, filtered , dried and recrystallized from ethanol +acetone ,to give red crystals with yield of 65%.methanol +Benzene 2:3 R_f=0.8M .p of(230-232)

4-Preparation ofN-{5-mercapto(1,3,4-thiadiazol-2-yl) }-N-acetyl-amino-4-(N-dimethylaminobenzyl) guanidine(4)

The mixture of sodium acetate (0.096g,0.0011mol) and quanidine hydrochloride (0.0248g,0.00029mol) in absolute ethanol(15mL)was added , after the compounds (3) (0.1g,0.00029mol).After stirring for (2h) at 60 Ć , the TLC showed that the reaction was complete (benzene-:methanol,2:3) and the resulting mixture was filtered then solvent was evaporated ,the combined residue was washed with $NaHCO_3$ solution and recrystallized in ethanol give 70% yellow crystals , methanol +Benzene 2:3 R_f=0.9 .M .p 230-232 Ċ

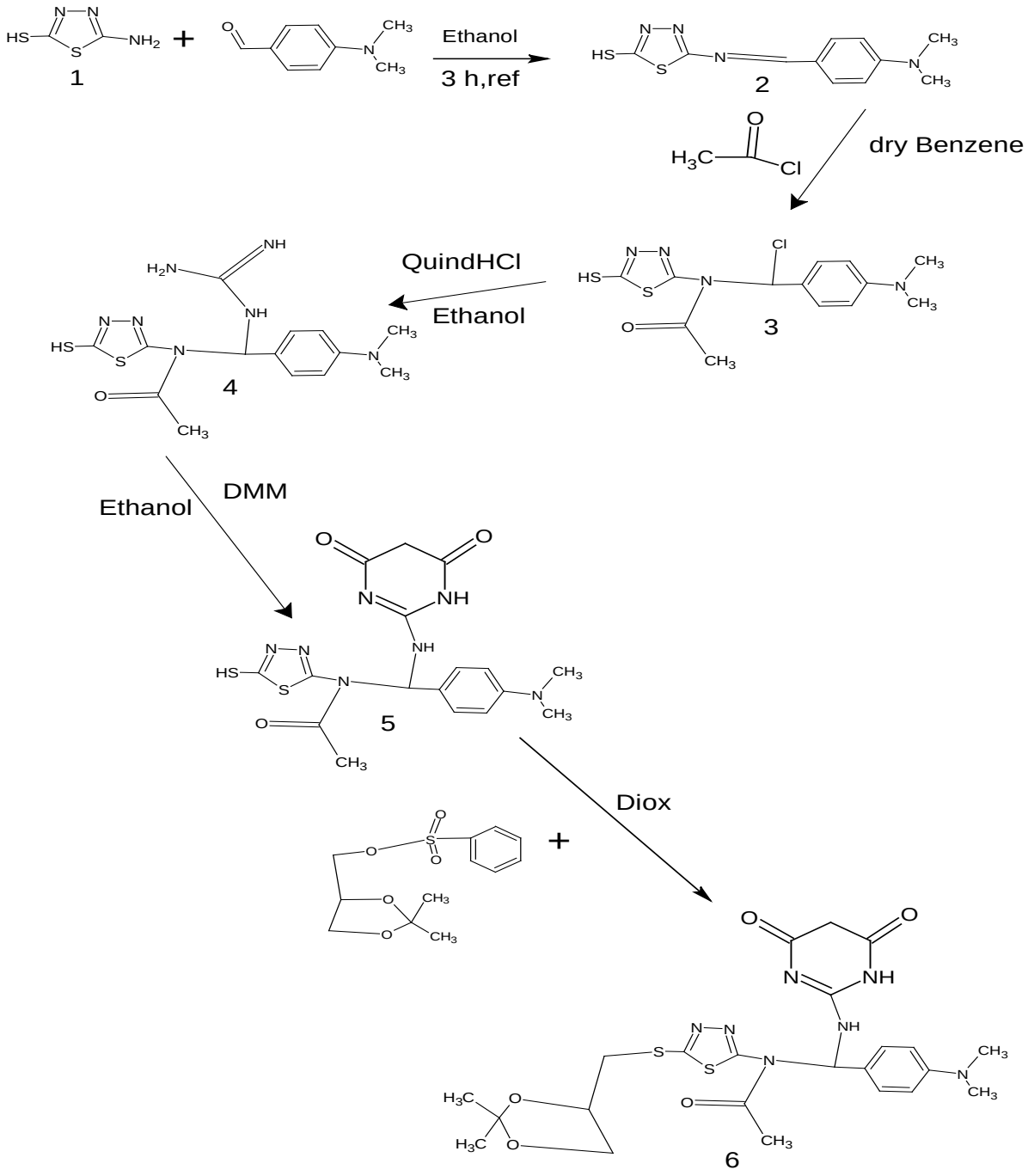
5- Preparation of N- {5-mercapto(1,3,4- thiadiazol-2-yl)-N-acetly-amino -4-(N-dimethylaminobenzyl) amino Barbituric Acid(5)

To the solution of sodium methoxide 0.00053mol of sodium metal dissolved in absolute methanol (20mL)), then of dimethyl malonate(0.00027mol) was added ,followed by a solution of compound(4) (0.27mmol), the mixture was shacked well,fit a calcium chloride guard-tube to the top of the condenser and the mixture was reflux for (8h) in an oil bath heated to 110 Ć .

Then the solutionwas left to cool to room temperature ,then distilled water 20 mL was added followed with hydrochloride ,red crystals were formed and filtered , yield 60%, methanol +Benzene 2:3 .R_f=0.8 m.p 220-222 Ć

6- preparation of N-{5-((2,2-dimethyl-1,3-dioxolan-4-yl)methylene)thio-1,3,4-thiadiazol-2-yl}N-acetyl-amino(4-(N-dimethylaminobenzyl)amino Barbituric Acid (6)

The mixture of compound (5) (0.1g,0.00023mol) and sodium carbonate (0.024g,0.00023mol) in dry dioxan (15mL)was added ,after stirring for 20min, then(0.063g,0.00023mol)2,2-dimethyl-4-[(phenylsulfonyl)methyl]-1,3-dioxolane was added ,after the reflux for 3hours ,then the solvent was evaporated and then extracted by ethyl acetate (50 mL): water (30mL) three time, organic layer was dried with $MgSO_4$ to give syrup product and evaporated where materials syrup is formedyield 54% , methanol +Benzene 2:3 R_f=0.71



Scheme 1.Synthesis of compounds(2-6)

Results and Discussion

Synthesis and Characterization of 2-amino-5-mercapto-1,3,4-thiadiazol

Compound (1) was synthesized as a starting material through the reaction of thiosemicarbazide with carbon disulphide in the presence of anh.sodium carbonate in abs. ethanol followed by concentrated. HCl

The structure of the compound (1) was confirmed by IR Spectrum showing two bands at 3338 cm^{-1} and 3257 cm^{-1} due to asym. and sym. stretching vibrations of ν NH_2 group respectively. ν NH tautomer form stretching revealed absorbing band at 3103 cm^{-1},The absorption at 1604 cm^{-1} was due to ν C=N stretching. The sharp bands at 1546 and 1475 are due to the ν N-H bending and ν N-N stretching vibration respectively. SH showed weak absorption at 2499 cm^{-1}, but the stretching band is characteristically weak and may go undetected in the spectra of dilute solution or thin film. Absorption at 1288, 1172 are due to ν C=S and NCS stretching respectively; absorption of ν SH and ν C=S indicated thiol- thionetautomerism). ν C-S showed absorption at 675, 615 cm^{-1}., other informative bands and some of physical properties are listed in table(1-2).

*Synthesis and Characterization*of (5-(4-Dimethylamino)benzylidene)amino-1,3,4-thiadiazole-2-thiol Compound (2) was synthesized as a starting material through the reaction of compound (1) with 4-dimethylamino benzaldehyde in absolute ethanol in the presence of a few drops of acetic acid

The FT-IR spectrum of compound (2) showed the following characteristic absorption bands :ν (C=N)at 1612 $cm^{-1}$and disappearance of the bands at 3338 cm^{-1} and 3257 cm^{-1} stretching vibrations of ν NH_2 group and absence of the band at 1674 $cm^{-1}$to (C=O) aldehyde, other informative bands and some of physical properties are listed in table(1-2).

Synthesis and Characterization of N-{chloro[4-(dimethylamino)phenyl]methyl}-*N*-(5-mercapto-1,3,4-thiadiazol-2-yl)acetamide (3)

On following the reactions of compound(2) withacetylchloridein dry benzene .FT.IR spectrum of compound (3)showed of band carbonyl amide group at (1695) cm^{-1},and absorption band at (779) $cm^{-1}$to group of the C-Cl , other informative bands and some of physical properties are listed in table (1-2)

Synthesis and Characterization of N-{5-mercapto(1,3,4-thiadiazol-2-yl) }-N-acetyl-amino-4-(N-dimethylaminobenzyl) guanidine (4)

Reaction of compound (3) with quinidinehydrochloride in presence sodium acetate in absolute ethanol to give compound (4) is indicated by FT-IR spectrum revealing band at 3336 cm^{-1}, 3207 cm^{-1} as a doublet for ν (NH_2), while bands at 3115 cm^{-1} and 3107

cm^{-1} were attributed to –NH str. (tautomeric form). Bands at 2906 cm^{-1} for C-H aliphatic, band carbonyl amide1 group at (1664) cm^{-1} , Bands at 1614cm^{-1} for ν (C=N), 1560 cm^{-1} for (NH bend), 1425 cm^{-1} ν (N-N str.), 1363 cm^{-1} ν (C-N bend.), 1082 cm^{-1}, 1039m^{-1} due to the intermolecular hydrogen banded of –NH,and absence absorption band at 779 $cm^{-1}$to group of the C-Cl , other informative bands and some of physical properties are listed in table (1-2).The confirmation of the product structure was proved by ^{1}H-NMR spectrum revealing bands in table(3)

Synthesis and Characterizations of N- {5-mercapto(1,3,4- thiadiazol-2-yl)-N-acetly-amino -4-(N-dimethylaminobenzyl) amino Barbituric Acid(5) Compound (5) .This compound was prepared by the reaction of sodium ethoxide with DMM and compound (4), the confirmation of the product structure was proved by FT-IR spectrum revealing band at3283 cm^{-1} ν (NHcycl-bar), 3184 cm^{-} ν (NH),band carbonyl amide 3 1753 cm^{-1} =N-C=O,1733cm^{-1}ν(C=O Amide2), band carbonyl amide1 group at (1664) $cm^{-1}$and 1644 (C=Nstr ,cyclo,bar), absence absorption band at 3336 $cm^{-1}$to group of the NH_2, other informative bands and some of physical properties are listed in table (1-2).The confirmation of the product structure was proved by ^{1}HNMR spectrum revealing bands in table(3).figure(1) shows the FT-IR spectra and figure (2) shows the ^{1}HNMR of compound (5)

Synthesis and Characterizations of N-{5-((2,2-dimethyl-1,3-dioxolan-4-yl)methylene)thio-1,3,4-thiadiazol-2-yl}N-acetyl-amino(4-(N-dimethylaminobenzyl)amino Barbituric Acid (6)

Compound (6) on following the reactions of compound (5) with 2,2-dimethyl-1,3-dioxaolan-4-yl-methylbenzenesulfonate in dioxane , the confirmation of the product structure was proved by FT-IR spectrum revealing bands at 3174 (NHasstr), note that there are three bands at (2987,2937,2891) cm^{-1} as evidence of isopropylidine groups in compound (6) ,1749 ,1732 cm^{-1}ν(C=O str ,cyclo, Amide3,Amide2) at 1681 cm^{-1}(C=O,Cyclo amide1) , other informative bands and some of physical properties are listed in table (1-2).^{1}HNMR spectrum revealing bands in table(3),the confirmation of the product structure was prove by figure(3) which shows the FT-IR spectra andfigure (4) shows the ^{1}HNMR of compound (6)) ,

Table (1) Physical properties for prepared compounds (1-6**)**

No .of Compounds	Molecular Formula	Solvent Purifications	Yield% Color	M.p Ć	Calculated(Found)%				max(nm) Ethanolג
					C	H	N	S	
1	$C_2H_4N_3S_2$	Water	67% yellow needles	233-235					255 333
2	$C_{11}H_{12}N_4S_2$	Ethanol+Acetone	80% Red	258-260					278 430
3	$C_{13}H_{15}N_4S_2ClO$	Ethanol	80% pink	230-232	45.61 45.52	4.38 4.40	16.37 16.41	18.71 19.10	302 429
4	$C_{14}H_{19}N_7S_2O$	Ethanol	84%yellow	239-241	46.02 46.13	5.20 5.12	26.84 26.45	17.53 17.32	302 430
5	$C_{17}H_{19}N_7S_2O_3$	Ethanol	55% pale yellow	220-222	52.98 53.02	4.93 5.12	25.45 25.40	16.62 17.I2	278 444
6	$C_{28}H_{31}N_7S_2O_5$	Ethanol	50%brown	Syrup	50.45 49.98	5.30 5.76	17.91 18.11	11.70 11.34	276 338

Table(2) :Characteristic FT -IR absorptions of compounds (1-6)

No .of. Comp	Band cm^{-1}	Interpretation
1	3338-3257	N-H stretching vibration of primary amines ($-NH_2$),asym, sym,respectively

	3103	N-H stretching v N-H(tautomeric) with SH in thiadiazole
	2620	S-H stretching v of thiol
	1604	C=N Stretching v of thiadiazole ring
	1556	N-H bending
	1058	C=S stretching v gives that compound can exist in two tautomeric form ,thiol form and thione form
2	3088	C-H stretching vibration of aromatic ring
	3010	=C-H str v of Schiff base
	2958	CH stretching vibration of CH_3
	2620	S-H str v of thiol
	1624	C=N Schiff base+ thiadiazole ring
	1550	N-H bending
	1068	C=S stretching vibration
	821	Para-sub-aromatic ring
3	3084	C-H stretching vibration of aromatic ring
	2953	CH stretching vibration of CH_3
	1695	C=O stretching vibration carbonyl amide 1
	1591	C=N Stretching vibration ofthiadiazole ring
	1533	C=C stretching vibration of aromatic ring
	779	C-Cl stretching vibration
4	3332-3284	N-H stretching v primary amines ($-NH_2$),asym, sym,respectively
	3267-3107	N-H stretching v secondary amines (-NH),asym, sym,respectively
	2930	CH stretching vibration of CH_3
	1664	C=O stretching vibration carbonyl amide 1
	1614	C=N stretching vibration in quinidine
	1585	N-H bending
	1534	H- Aromatic ring
	1039	C=S stretching v gives that compound can exist in two tautomeric form ,thiol form and thione form
	810	Para-sub-aromatic ring
5	3283	N-H stretching vibration cycl,bar
	3211	N-H stretching vibration

	3097	C-H str v of aromatic ring
	2895	CH2 stretching vibration
	1753	=N-C=O stretching vibration (Amide3)
	1733	C=O stretching vibration (Amide2)
	1664	C=O stretching vibration (Amide1)
6	3335	N-H stretching vibration
	3066	C-H str v of aromatic ring
	2985-2935	C-H stretching vibration (Isopropylidine)
	2895	CH2 stretching vibration
	1747	=N-C=O stretching vibration (Amide3)
	1732	C=O stretching vibration (Amide2)
	1681	C=O stretching vibration (Amide1)
	1597	C=N Stretching vibration of thiadiazole ring
	1531	C=C stretching vibration aromatic ring

Table(3) : ^{1}H-NMR spectral data of the synthesized compounds (4-6)

Compound No.	δ in ppm
4	8.35(1H,s,=NH),7.8-6.9(4H,d,Ar),4.8(1H,S,CH),4.6(2H,s,NH_2), 3.35(6H,s,2CH_3),2.5(3H,s,CH_3)
5	8.4(1H,s,-NH),7.8-7.6(4H,d,Ar),4.6 (1H,S,CH),4.0(2H,s,CH_2),3.10(6H,s,2CH_3),2.5(3H,s,CH_3)
6	8.0(1H,s,-NH),7.9-7.6(4H,d,Ar),4.6 (1H,S,CH),4.15(2H,s,CH_2),3.6(6H,s,2CH_3),2.5(3H,s,CH_3),4.17(1H,m,CH),3.1(2H,d,CH_2),3.6(2H,m,CH_2) ,1.6(6H,s,2CH_3)

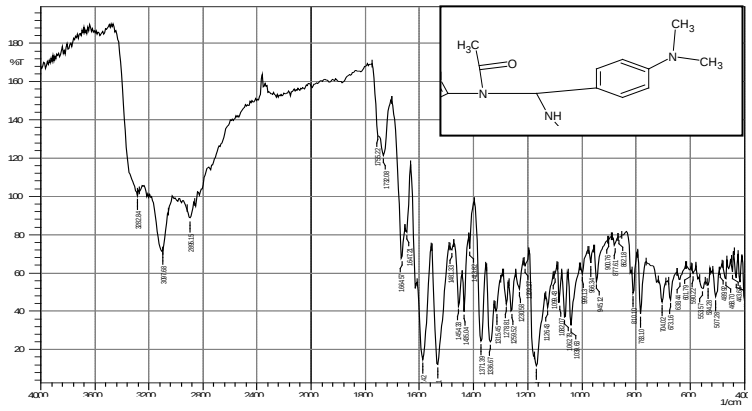
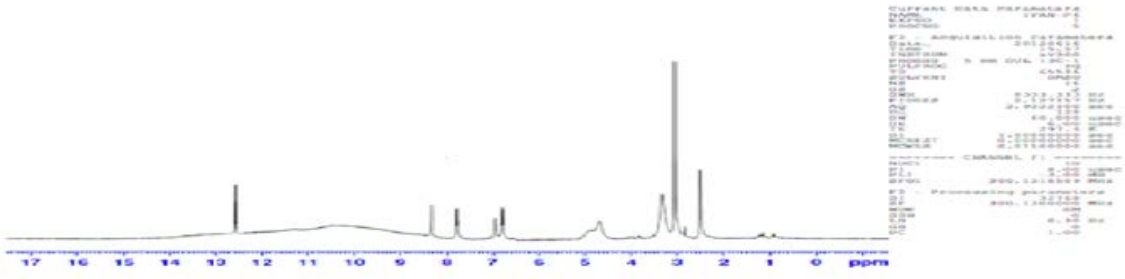
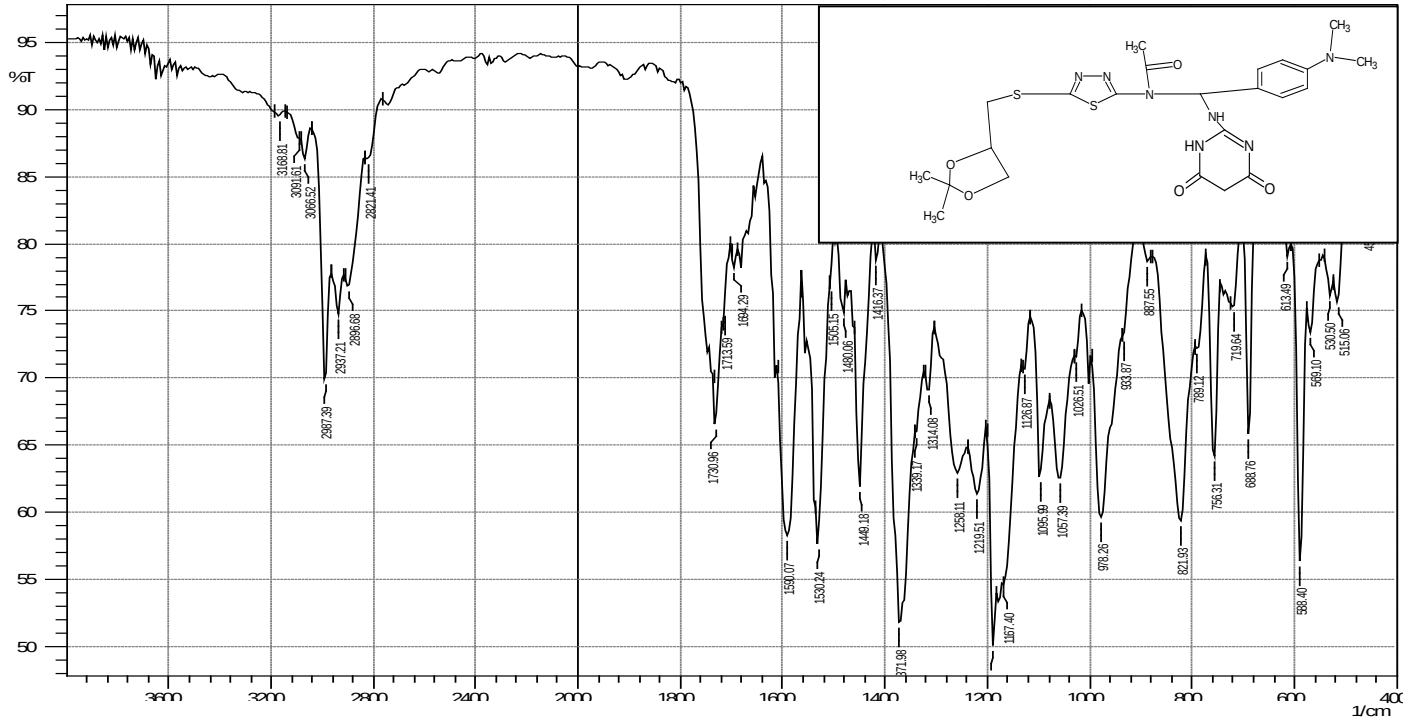


Fig.1.FT-IR spectrum for compound(5)





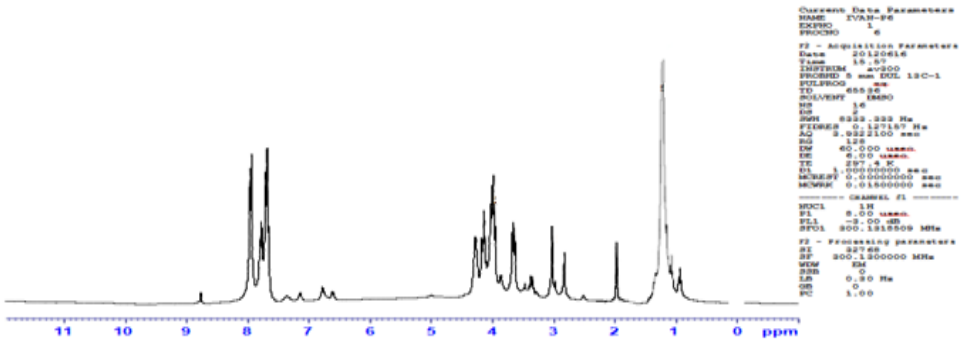


Fig.4.[1]HNMR spectrum for compound(6)

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