Synthesis of New 5-Ethyl-5-Phenyl Barbituric Acid Derivatives

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(NJC)

(Received on 16/ 10 /2004) (Accepted for publication on 23/3/2005)

Abstract

The reaction of some new Schiff bases (5-ethyl-5-phenyl-1,3-di[N-4-substituted benzilidin hydrazinyl] barbituric acids) with benzoyl chloride or 3,5-dinitrobenzoyl chloride were carried out. Subsequent reactions of these products di[N-(α-chloro(substituted benzyl)-N-benzoyl or 3,5-dinitro benzoyl)-5-ethyl-5-phenyl-1,3-di(acetic acid hydrazinyl) barbituric acids with thiourea afforded thioureas compounds.

The synthesized compounds were confirmed by their IR, UV spectra and C.H.N. analyses data.

الخلاصـة

تعطي تفاعلات قواعد شيف جديدة
(5-ethyl-5-phenyl-1,3-di[N-4-substituted benzilidin hydrazinyl] barbituric acids)
مع كلوريد البنزويل أو كلوريد 5,3–ثنائي نتروالبنزويل مركبات
di[N-(α-chloro-substituted benzyl)-N-benzoyl or 3,5-dinitro benzoyl] -5-ethyl-5-phenyl-1,3-di(acetic acid hydrazinyl) barbituric acids
وتفاعلات المركبات الناتجة مع الثايويوريا يؤدي إلى تكوين مركبات الثايويوريز.

شخصت المركبات المحضرة باستخدام بعض الطرق الطيفية (UV, IR) والتحليل الدقيق للعناصر.

Introduction

Phenobarbital derivatives are interesting series of heterocyclic compounds, which have been shown to be diverse pharmacological properties [(1)] such as antifungal [(2)], antimicrobial [(3)], antipulsive [(4)] and antibacterial [(5,6)]. This paper reports the synthesis of some new

phenobarbital compounds from the reaction of some phenobarbital system containing Schiff bases moiety with benzoyl and 3,5-dinitro benzoyl chlorides. Subsequent reactions of these products with thiourea afforded thioureas compounds.

Experimental

Melting points were recorded on a Gallen-Kamp MFB-600 melting point apparatus. IR spectra were recorded in KBr disc and film on a Pye-Unicam SP3-100 spectrophotometer. UV spectra were recorded on a Hitachi/UV-2000 spectrophotometer using absolute ethanol as solvent. Elemental analyses of some compounds were carried out on C.H.N. analyzer type 1160 (Carlo-Erba).

Preparation of Schiff bases (1-5): -

These compounds were prepared as reported previously [7,8].

Preparation of 5-ethyl-5-phenyl barbituric acid derivatives (6-15) [9]: -

To an appropriate Schiff base (0.0008 mole), benzoyl chloride or 3,5-dinitro benzoyl chloride (0.016 mole) in dry benzene (20 ml) was added. The mixture was refluxed for (6 hrs), cooled, filtered and recrystallized from suitable solvent (Tables 1,2,3,7).

Preparation of isothioureas compounds (16-25) [9]: -

To an appropriate derivatives of (5-16) (0.001 mole) thiourea (0.002 mole) and Na_2CO_3 (0.002 mole) in absolute ethanol (25 ml) were added. The mixture was refluxed for (2-4 hrs), cooled and filtered. The filtrate was poured into crushed ice, the separated solid was collected and recrystallized from appropriate solvent (Tables 4,5,6,7).

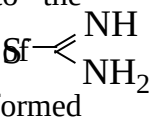
Results and Discussion

Schiff bases (1-5) were prepared by condensation of 5-ethyl-5-phenyl-1,3-di(acetic acid hydrazide) barbituric acids with various aromatic aldehydes (p-ClC_6H_4CHO, p-OHC_6H_4CHO, p-$OCH_3C_6H_4CHO$, o-$NO_2C_6H_4CHO$ and m-$NO_2C_6H_4CHO$). The reaction was followed by the appearance of absorption bands for (υC=N) at (1620-1640 cm^{-1}) in their IR spectra. In the present work the reaction of compounds (1-5) with benzoyl or or 3,5-dinitro benzoyl chlorides and subsequent reactions of above reaction

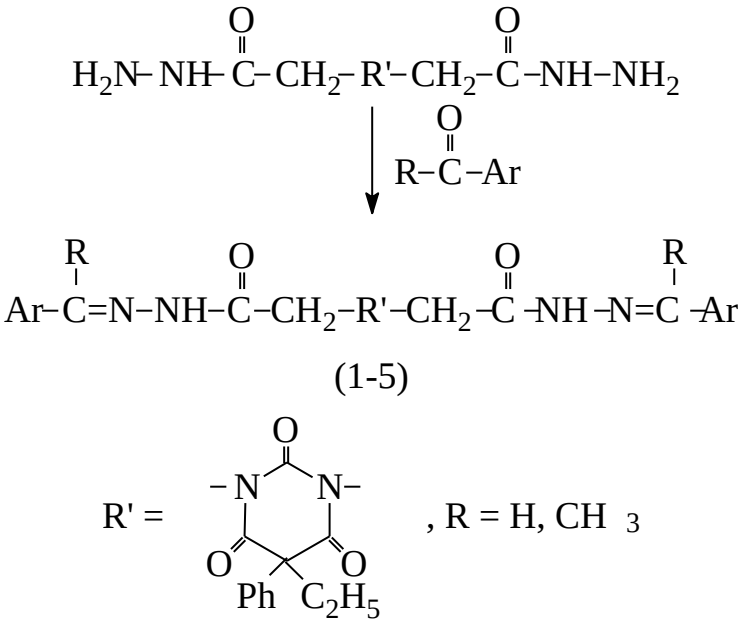
products (6-15) with thiourea were carried out as shown in scheme (1).

However, treatment of Schiff bases with acid halides results in the formation of compounds (6-15) in which two groups (Cl and ArCO) were introduced in the same step of the reaction. This reaction was followed by disappearance of absorption bands at (1620-1640 cm^{-1}) for (υC=N) and appearance of new absorption bands at (1230-1250 cm^{-1}) and (730-750 cm^{-1}) which were attributed to (C-N) and (C-Cl) moieties.

The reaction was followed the attack by the azomethine nitrogen at the carbonyl group of the aroyl chlorides, displacing the chloride as chloride anion and forming the iminium cation. However, iminium cation was unstable, so the Cl^- attacked $-^+N=C$ moiety and afforded more stable covalently bonded compounds (6-15) (Scheme 2).

Moreover, the reactions of acid halides addition products (6-15) with thiourea were afforded thioureas products (16-25). So, heating compounds (6-25) under reflux with thiourea in the presence of Na_2CO_3 for (2-4 hrs) led to the nucleophilic substitution of Cl by S of  and compounds (16-25) were formed through the following mechanism (Scheme 3).

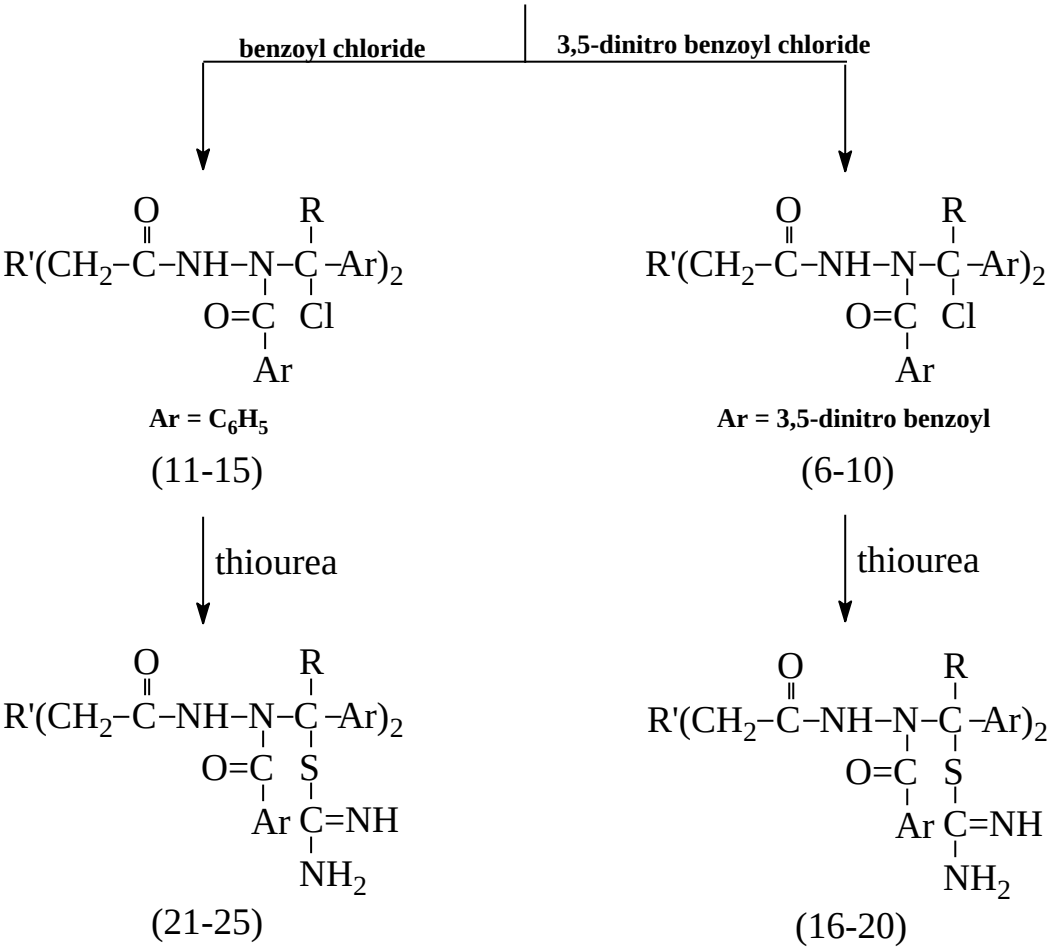
These compounds (16-25) were characterized by their IR spectra. New doublet absorption bands in the region (3200-3450 cm^{-1}) were attributed to (NH_2) and (NH) functional moieties. Other characteristic bands in the region (650-710 cm^{-1}) correlated to (C-S) moiety. Moreover, (δ C-Cl) around (730-750 cm^{-1}) disappeared.



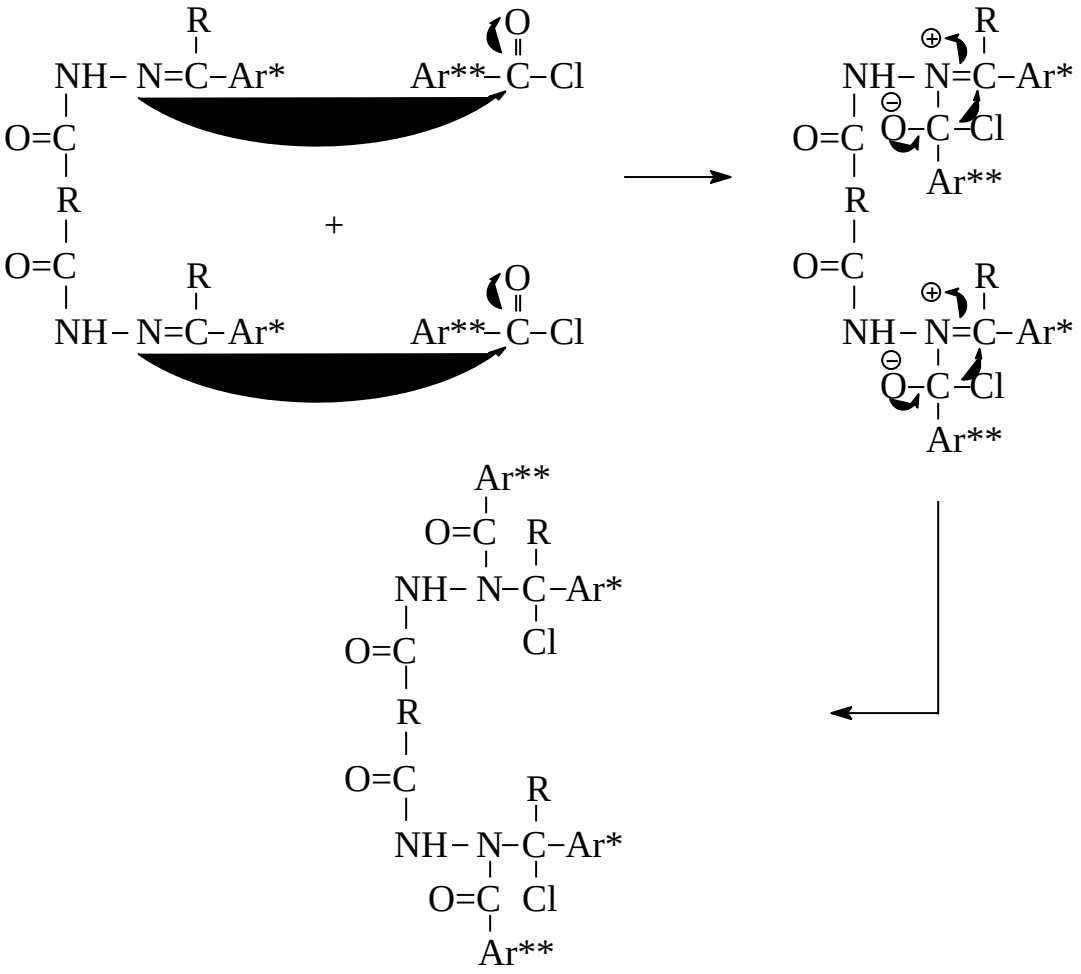
(1-5)

R' = , R = H, CH_3

Ar = o-$NO_2C_6H_4$, p-HOC_6H_4, p-ClC_6H_4, p-$MeOC_6H_4$, m-$NO_2C_6H_4$



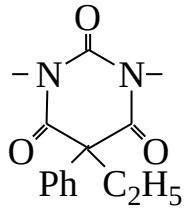
Scheme 1



Ar* = H, R

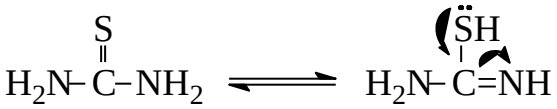
Ar** = (i) 3,5-dinitro benzoyl chloride

(ii) benzoyl chloride

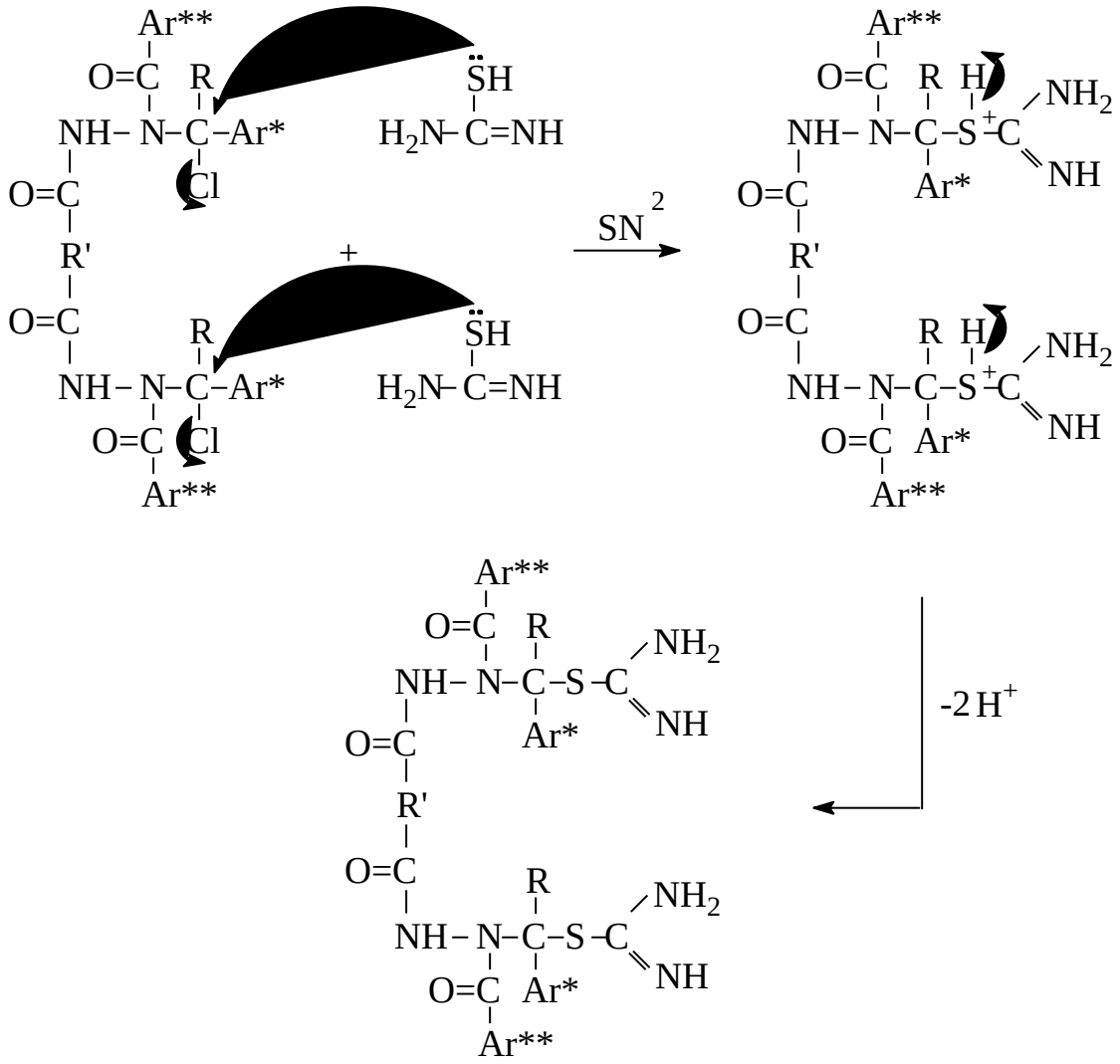
R = 

Scheme 2

(1)



(2)



Ar* = H, R

Ar** = (i) 3,5-dinitro benzoyl chloride

(ii) benzoyl chloride

Scheme 3

Table (1): Some physical properties of compound (6-10)

Comp. No.	Name of compounds	-R	Colour	Yield (%)	m.p. °C	Molecular formula
6	Di[N-(α-chloro(p-chloro benzyl)-N-3,5-dinitro benzoyl)]-5-ethyl-5-phenyl-1,3-di(acetic acid hydrazinyl) barbituric acid		Yellow	39	185-187	$C_{44}H_{32}Cl_4N_{10}O_{15}$
7	Di[N-(α-chloro(p-hydroxy benzyl)-N-3,5-dinitro benzoyl)]-5-ethyl-5-phenyl-1,3-di(acetic acid hydrazinyl) barbituric acid		Yellow	45	172-175	$C_{44}H_{34}Cl_2N_{10}O_{17}$
8	Di[N-(α-chloro(p-methoxy benzyl)-N-3,5-dinitro benzoyl)]-5-ethyl-5-phenyl-1,3-di(acetic acid hydrazinyl) barbituric acid		Brown	50	130-132	$C_{46}H_{38}Cl_2N_{10}O_{17}$
9	Di[N-(α-chloro(2-nitro benzyl)-N-3,5-dinitro benzoyl)]-5-ethyl-5-phenyl-1,3-di(acetic acid hydrazinyl) barbituric acid		Yellow	55	85-87	$C_{44}H_{34}Cl_2N_{12}O_{19}$
10	Di[N-(α-chloro(3-nitro benzyl)-N-3,5-dinitro benzoyl)]-5-ethyl-5-phenyl-1,3-di(acetic acid hydrazinyl) barbituric acid		Yellow	43	165-168	$C_{44}H_{38}Cl_2N_{12}O_{19}$

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Table (2): Some physical properties of compound (11-15)

Comp. No.	Name of compounds	-R	Colour	Yield (%)	m.p. °C	Molecular formula
11	Di[N-(α-chloro(p-hydroxy benzyl)-N-benzoyl)]-5-ethyl-5-phenyl-1,3-di(acetic acid hydrazinyl) barbituric acid		Yellow	35	190-192	$C_{44}H_{38}Cl_2N_6O_9$
12	Di[N-(α-chloro(p- chloro benzyl)-N-benzoyl)]-5-ethyl-5-phenyl-1,3-di(acetic acid hydrazinyl) barbituric acid		Brown	44	119-120	$C_{44}H_{36}Cl_4N_6O_7$
13	Di[N-(α-chloro(p-methoxy benzyl)-N-benzoyl)]-5-ethyl-5-phenyl-1,3-di(acetic acid hydrazinyl) barbituric acid		Red	49	180-182	$C_{46}H_{42}Cl_2N_6O_9$
14	Di[N-(α-chloro(2-nitro benzyl)-N-benzoyl)]-5-ethyl-5-phenyl-1,3-di(acetic acid hydrazinyl) barbituric acid		Orange	30	178-180	$C_{44}H_{36}Cl_2N_8O_{11}$
15	Di[N-(α-chloro(3-nitro benzyl)-N-benzoyl)]-5-ethyl-5-phenyl-1,3-di(acetic acid hydrazinyl) barbituric acid		Yellow	34	138-140	$C_{44}H_{36}Cl_2N_8O_{11}$

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Table (3): UV and IR Spectral data of compounds (6-15)

Comp. No.	UV Spectrum		Characteristic bands of IR spectrum						
	λ_{max} = nm	ε_{max} = $cm^2.gm$	υ(C=O) (cm^{-1})	υ(C-H)$_{aliph.}$ (cm^{-1})	υ(C-H)$_{arom.}$ (cm^{-1})	υ(C-O) (cm^{-1})	υ(C-N) (cm^{-1})	υ(C=C) (cm^{-1})	Others
6	332.0 229.6 210.0	16×10^{-5} 14×10^{-5} 9×10^{-5}	1710 1690	2840-2920	3080	-	1230	1510 1600	υ(NO_2)=(1320-1350)s (1530-1550)as υ(C-Cl)=730
7	320.4 230.4 210.4	29×10^{-5} 19×10^{-5} 11×10^{-5}	1680 1700	2810-2940	3050	1250	1220	1500 1600	υ(OH)=3450 υ(NO_2)=(1420-1540)s (1500-1550)as υ(C-Cl)=740
8	330.4 228.4	28×10^{-5} 25×10^{-5}	1690 1710	2840-2980	3090	1290	1250	1500 1590	υ(NO_2-sub)=750 υ(C-Cl)=740
9	-	-	1710 1680	2900-3000	3080	-	1230	1525 1600	υ(NO_2)=(1420-1550)s (1390-1410)as υ(C-Cl)=730
10	-	-	1700 1690	2890-2950	3070	-	1240	1500 1600	υ(NO_2)=(1430-1500)s (1350-1420)as υ(NH)=3150 υ(C-Cl)=740

Comp. No.	UV Spectrum		Characteristic bands of IR spectrum						
	λ_{max} = nm	ε_{max} = cm^2.gm	υ(C=O) (cm^{-1})	υ(C-H)$_{aliph.}$ (cm^{-1})	υ(C-H)$_{arom.}$ (cm^{-1})	υ(C-O) (cm^{-1})	υ(C-N) (cm^{-1})	υ(C=C) (cm^{-1})	Others
11	330.8 260.8 228.0	15×10^{-5} 10×10^{-5} 5×10^{-5}	1700 1690	2900-3010	3090	1280	1240	1550 1600	υ(OH)=3400 υ(C-Cl)=740
12	306.0 234.4	31×10^{-5} 25×10^{-5}	1690 1700	2890-2990	3080	-	1230	1500 1590	υ(C-Cl)=730
13	-	-	1670 1710	2890-3000	3050	1290	1250	1550 1600	υ(C-Cl)=750
14	-	-	1660 1690	2890-3000	3080	-	1230	1515 1590	υ(NO_2)=(1450-1550)s (1320-1430)as υ(C-Cl)=750
15	268.4 233.6	22×10^{-5} 17×10^{-5}	1690 1700	2870-2950	3070	-	1240	1525 1600	υ(NO_2)=(1450-1530)s (1330-1350)as υ(C-Cl)=740

Table (4): Some physical properties of compound (16-20)

Comp. No.	Name of compounds	-R	Colour	Yield (%)	m.p. °C	Molecular formula
16	Di[N-(p-hydroxy benzyl)-α-isothioureayl-N-3,5-dinitro benzoyl]-5-ethyl-5-phenyl-1,3-di(acetic acid hydrazinyl) barbituric acid		Yellow	35	207-210	$C_{46}H_{38}N_{14}O_{17}S_2$
17	Di[N-(p-chloro benzyl)-α-isothioureayl-N-3,5-dinitro benzoyl]-5-ethyl-5-phenyl-1,3-di(acetic acid hydrazinyl) barbituric acid		Orange	30	180-183	$C_{46}H_{36}Cl_2N_{14}O_{15}S_2$
18	Di[N-(p-methoxy benzyl)-α-isothioureayl-N-3,5-dinitro benzoyl]-5-ethyl-5-phenyl-1,3-di(acetic acid hydrazinyl) barbituric acid		Brown	33	98-100	$C_{48}H_{42}N_{14}O_{17}S_2$
19	Di[N-(2-nitro benzyl)-α-isothioureayl-N-3,5-dinitro benzoyl]-5-ethyl-5-phenyl-1,3-di(acetic acid hydrazinyl) barbituric acid		Light green	35	145-147 dec.	$C_{46}H_{36}N_{16}O_{19}S_2$
20	Di[N-(3-nitro benzyl)-α-isothioureayl-N-3,5-dinitro benzoyl]-5-ethyl-5-phenyl-1,3-di(acetic acid hydrazinyl) barbituric acid		Light brown	30	170-172	$C_{46}H_{46}N_{16}O_{19}S_2$

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Table (5): Some physical properties of compound (21-25)

Comp. No.	Name of compounds	-R	Colour	Yield (%)	m.p. °C	Molecular formula
21	Di[N-(p-hydroxy benzyl)-α-isothioureayl-N-benzoyl]-5-ethyl-1,3-di(acetic acid hydrazinyl) barbituric acid		Yellow	25	207-210 dec.	$C_{46}H_{44}N_{10}O_9S_2$
22	Di[N-(p-chloro benzyl)-α-isothioureayl)-N-benzoyl]-5-ethyl-5-phenyl-1,3-di(acetic acid hydrazinyl) barbituric acid		Brown	27	130-128	$C_{46}H_{42}Cl_2N_{10}O_7S_2$
23	Di[N-(p-methoxy benzyl)-α-isothioureayl-N-benzoyl]-5-ethyl-5-phenyl-1,3-di(acetic acid hydrazinyl) barbituric acid		Yellow	30	180-182	$C_{48}H_{48}N_{10}O_9S_2$
24	Di[N-(2-nitro benzyl)-α-isothioureayl-N-benzoyl]-5-ethyl-5-phenyl-1,3-di(acetic acid hydrazinyl) barbituric acid		Yellow	29	130-132 dec.	$C_{46}H_{42}N_{12}O_{11}S_2$
25	Di[N-(3-nitro benzyl)-α-isothioureayl-N-benzoyl]-5-ethyl-5-phenyl-1,3-di(acetic acid hydrazinyl) barbituric acid		White	25	150-147 dec.	$C_{46}H_{42}N_{12}O_{11}S_2$

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Table (6): UV and IR Spectral data of compounds (16-25)

Comp. No.	UV Spectrum		Characteristic bands of IR spectrum						
	λ_{max} = nm	ε_{max} = $cm^2.gm$	υ(C=O) (cm^{-1})	υ(C-H)$_{aliph.}$ (cm^{-1})	υ(C-H)$_{arom.}$ (cm^{-1})	υ(C-O) (cm^{-1})	υ(C-N) (cm^{-1})	υ(C=C) (cm^{-1})	Others
16	331.6 227.2 206.0	15×10^{-5} 6×10^{-5} 5×10^{-5}	1680 1700	2900-3000	3050	1250	1240	1500 1590	υ(OH)=3500 υ(NH)=3400 υ(NH$_2$)=3200-3300 υ(C-S)=730
17	-	-	1690 1700	2800-2990	3060	-	1230	1500 1590	υ(C-Cl)=740 υ(NH$_2$)=3400-3450 υ(C=N)=1640 υ(C-S)=660
18	-	-	1670 1690	2890-2980	3080	1290	1220	1520 1600	υ(NH$_2$)=3400-3450 υ(NH)=3200 υ(C=N)=1630 υ(C-S)=710
19	-	-	1690 1700	2890-3000	3090	-	1230	1540 1590	υ(N-O)=670 υ(C-N)=1640 υ(C-S)=700
20	-	-	1720 1690	2900-3000	3080	-	1240	1550 1600	υ(NH$_2$)=3220-3300 υ(C=N)=1620 υ(C-S)=720

Comp. No.	UV Spectrum		Characteristic bands of IR spectrum						
	λ_{max} = nm	ε_{max} = $cm^2.gm$	υ(C=O) (cm^{-1})	υ(C-H)$_{aliph.}$ (cm^{-1})	υ(C-H)$_{arom.}$ (cm^{-1})	υ(C-O) (cm^{-1})	υ(C-N) (cm^{-1})	υ(C=C) (cm^{-1})	Others
21	-	-	1680 1700	2900-3000	3080	1270	1230	1500 1590	υ(OH)=3400 υ(NH)=3200 υ(C=N)=1630 υ(C-S)=730 υ(NO_2)=(1450-1500)as (1310-1350)s
22	-	-	1690 1710	2800-2900	3070	-	1220	1550 1575	υ(C-Cl)=750 υ(NH)=3250 υ(C=N)=1640 υ(C-S)=650 υ(NO_2)=(1420-1550)as (1320-1390)s
23	221.6 230.4	19×10^{-5} 15×10^{-5}	1670 1700	2900-3000	3080	1255	1240	1490 1580	υ(NH)=3300 υ(C-S)=710 υ(C=N)=1630
24	-	-	1730 1690	2900-2950	3050	-	1250	1510 1600	υ(NH)=3350 υ(C-S)=730 υ(NO_2)=(1450-1540)as (1390-1400)s υ(C=N)=1630
25	-	-	1720 1690	2900-3000	3060	-	1220	1590 1600	υ(NH)=3400 υ(C-S)=730 υ(NO_2)=(1450-1555)as (1320-1390)s υ(C=N)=1640

Table (7): C.H.N analyses of some prepared compounds

Comp. No.	C.H.N analysis % calculated (found %)		
	C %	H %	N %
6	35.00 (34.80)	2.10 (1.90)	9.20 (9.00)
8	51.40 (51.29)	3.50 (3.44)	13.10 (13.05)
11	6.11 (6.09)	4.40 (4.35)	9.70 (9.63)
16	50.60 (50.49)	3.40 (3.30)	17.90 (17.70)
21	60.50 (60.40)	4.80 (4.69)	15.30 (15.10)

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