Synthesis of New Heterocyclic Compounds Derived from 4-Amino Antipyrine

Redha I. Al-Bayati

College of Science-Mustansiriyah University

Iyad S. Hameed Mustafa K. Toema

College of Education-Tikrit University

(NJC)

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Abstract

In this work, isondoline -1,3-dione derivatives [2-5] were prepared from the corresponding anhydrides and 4-amino antipyrine [1].Derivatives[6-11] containing urea and thioureamoieties at position [4]were prepared from 4-amino antipyrine[1] and an appropriatearyl or alkyliso or (isothio)cyanates and then converted into pyrimidine derivatives [12-15].

Treatment of compound [1] with formic acid or acetic acid give the amide derivatives [16 and 17], which upon refluxing of compound [16]) with hydrazine hydrate in ethanol yielded the corresponding 2,3-dimethyl-1-phenyl-2,4-dihydro-1*H*-pyrazolo[4,3,e][1,2,4]-triazine [18].

Reacting compound [1] with acetyl acetone in boiling ethanol for 6hrs, leads to 4-amino antipyrine derivative [19]. The azomethines[20-22] were prepared from the corresponding aryl aldehydes and compound [1].

الخلاصة

حضرت في هذه الدراسة مشتقات ازندولين 3،1 داي اون isondoline -1,3-dione (2-5) من خلال الانهدريدات مع 4- امينو انتي بايرين 4-amino antipyrine [1] ومشتقاتها [6-11] المحتوية على اليوريا والثايوريا في الموقع [4] والتي حضرت من 4- امينو انتي بايرن [1]، والتي حولت بعد مفاعلتها بالالكلة او آيزثايوسيانات (isothio)cyanates الى مشتقات بيريميدنية]12-15[عومل المركب [1] مع حامض الفورميك

او حامض الخليك ليعطي مشتقات اميدية [16 و17]، والتي يحصل عليها من التصعيد للمركب [16] مع الهايدرازين المائي في الكحول ليعطي نتيجة مطابقة الى 3،2-ثنائي مثيل 1- فنيل-4،2 –ثنائي هيدرو-1 H – بايرازول [4,2,1][e,3,4] تراي ازين [18]، مفاعلة المركب [1] مع استيل اسيتون في اثيانول فعلي لمدة 6 ساعات، يقود لمشتقات 4- امينوانتي بايرن [19]، حضرت ايزومثينات [20-22]azomethines من الالديهايدات والمركب [1].

Introduction

The development of simple synthetic routes to widely used organic compounds sing readily available reagents is one of the main objectives of organic synthesis, Nitrogen heterocycles are of special interest because of their constitute on important class of natural and non natural products.

4-amino antipyrine derivatives are interesting series of heterocyclic compounds, which have been shown to be diverse biological properties such as anti inflammatory[1], analgesic[2], bactericidal[3], antifungal[4].

They has been considerable interest in the development of preparative methods for the production of pyrimidines, this seems to be because pyrimidines represent one of the most active classes of compounds possessing a wide spectrum of biological activities[5].

Various 1,2,4-triazines and its derivatives are well known to possess an array of physiological activities such as anticancer muscle relaxant, anti-inflammatory and antihypertensive activities and are widely used in pharmaceuticals[6].

Some Schiff bases bearing aryl groups or heterocyclic residues posses excellent biological activities, they have been reported to be used as analgesic, anthelmintic and plant growth regular[7].

In this work new derivatives of 4-amino antipyrine were synthesized.

Materials and Methods

Melting points were determined on Gallen-Kamp melting point apparatus, the U.V spectra were performed on Hitachi-2000 spectrophotometer, IR-Spectra wer recorded on a shimadzu FT-IR 8300 spectrometer as KBr disc, ^{1}H and ^{13}C-NMR spectra were recorded at 300 MHz in DMSO-d6 on Bruker-Ultra Shield spectrometer, the chemical Shift are reported in (ppm), and in δ values, with TMS as standard, MS spectra were obtained on Shimadzu QP 5050A.

4-amino antipyrine[1]

This compound was supplied from BDH company, a cream to pale, yellow powder, m.p. (107-109^{o}c).

Synthesis of 2-(4-antipyrineyl-5-isoindoline-1,3-diones [2-5][8], General Procedure

A mixture of compound [1] (0.0024mole) and an appropriate acid

anhydride (0.0024mole) was heated at 185°c in oil bath for 15 min, then cooled and poured on crushed ice. This solid product was filtered off and dried. The physical properties at table1 and the spectral data at table 7.

^{1}H-NMR (DMSO-d6, δ) ppm, of compound (2): 2.2 and 3.2 (m, 6*H*, $2CH_3$), 7.56-7.36 (m, 5*H*, N-C_6H_5), 8.26-8 (S, 4*H*, C_6H_4).

^{13}C-NMR (DMSO-d6, δ) ppm, of compound (2): 10.8 and 35.5 (H_3C-C, H_3C-N) respectively, aromatic carbones (pyrazole), 99.37, 123.3, 124.1 and 125.1.

Phthaliccarbons : 127.8, 129.5, 130.8 and 135.8 also, 154.4 (C-NO_2), 137.1-144.9 (C=C) pyrazole, 160, 162.6 and 165.3 (3C, C=O).

MS : m/z of compound [3] = 331.3, 255.8, 212.1 and 191.8.

Synthesis of 1-(4-antipyrinyl-3-alkyl urea or (thiourea). [6-11][9]. General Procedure

A mixture of compound [1] (0.0049 mole) and (0.0049 mole) of an aproperiateiso or isothiocyanate in ethano (15ml) was refluxed for (7-14 hrs), the white solid products was filtered off and recrystallized from ethanol. The physical properties at table2 and the spectral data at table 8.

^{1}H-NMR (DMSO-d6, δ) p..m : of compound (6): 2.1 and 3.02 (m, 6*H*, $2CH_3$), 7.51-7.26 (m, 8*H*, $2C_6H_4$) 8.79 and 6.95 (NH–C(=O)–NH).

^{13}C-NMR (DMSO-d6, δ)p.p.m: of compound (6): 11.7 and 36.6 (2C, H_3C-C, H_3C-N) respectively, 108.7 – 140.3 aromatic carons, 152.1 (C=C) pyrazole, 154, 162.6 (2C, C=O).

Synthesis of 1-(4-antipyrinyl-3-alkyl urea or (thiourea). [6-11][9]. General Procedure

MS : m/z of compound (9) : 372.3, 312.2, 29, 203.2

Synthesis of1-(4-antiyrinyl -3-alkyl pyrimidine-2,4,6-(1*H*,2*H*,3*H*)trion. [12-15][10]. General Procedure

Diethyl malonate or malonic acid (0.0015 mole) was added to solution of compounds [6-9] (o.oo15 mole) in dry benzene and the mixture was refluxed for (8hrs). the solid products were collected and dried then recrystalized from ether. The physical properties at tables 3 and 4, and the spectral data at table 9.

^{1}H-NMR (DMSO-d6, δ) p.p.m of compound (12): 2.2 and 3 (m, 6*H*, $2CH^3$), 7.2-7.5 (m, 6*H*, $2C_6H_5$) 6.94 (S, 2*H*, CH_2), 8.87 tautomeric proton.

^{13}C-NMR (DMSO-d6, δ) p.p.m : 11.7 and 36.64 (2C, H_3C-C, H_3C-N) respectively, 108.7-140.4 aromatic carbons, 152.2 (C=C) pyrazole, 154, 162.6 (C=O).

Synthesis of N-(4-antipyrinyl amide). Compounds [16 and 17][11].

A mixture of compound [1] and formic acid or acetic acid (10ml) was refluxed for (3hrs) then cooled and evaporated of excess acids. The solid products was filtered off and dried then recrystalized from ethanol. Tables (5 and 10).

^{1}H-NMR (DMSO-d6, δ) p.p.m of compound (16): 2.1 and 3 (m, 6*H*, $2CH_3$), 2.2 (S, NH, tautomeric proton),

7.28-7.51 (m, 3*H*, C_6H_5), 8.2 (S, ), 9.28 (S, 1*H*, tautomeric proton).

^{13}C-NMR (DMSO-d6, δ) p.p.m of compound (16) 11.8 and 36.1 (2C, H_3C-C, H_3C-N) respectively, 106.7-135.3 aromatic carbons, 152.12 (C=C) pyrazole 162, 165 (S, amide and pyrazole) respectively.

MS : m/z of compound [17] : 245.2, 203.2, 216.2 and 230.2.

Synthesis of 2,3-dimethyl-1-phenyl-2,4-dihydro-1*H*-pyrazolo[4,3-e][1,2,4] triazine[18][(12)].

A mixture of compound [16] (0.002 mole) and hydrazine hydrate (0.01 mole) in ethanol (30ml) was refluxed for (3hrs). the solid product was filtered off, washed with chloroform then dried to give yellow oily product, yield 58%. The general data of compound [18] were given at table (11).

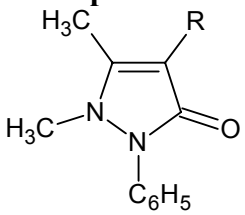
Synthesis of 4-((*E*)-(*E*)-4-amino antipyrinyl pent-3-en-2-ylidene)amino antipyrine (19)[(13)].

Acetyl aceton (0.0045 mole) was added to a solution of compound [1] (0.0098 mole) in abs. ethanol (25ml) and refluxed for (6hrs). The solid product was collected, filtered then recrystallized by using suitable solvent.

Synthesis of 4-(3-benzylidene amino antipyrine). [20-22][(14)] Schiff bases

Equimolar amounts of compound [1] (0.01 mole) and aromatic aldehyde (0.01 mole) in abs. ethanol was refluxed for (4-5hrs), and then cooled to room temp. The solid product was filtered off and recrystalized from ethanol. The physical properties at table 6 and the spectral data at table 11.

Table -1: physical Properties of Compounds [2-5]



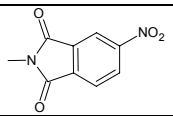
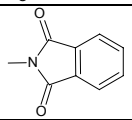
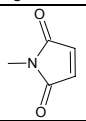
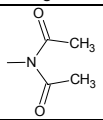
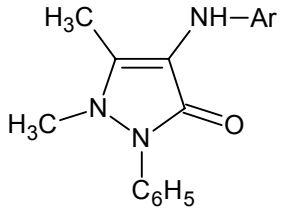
Comp.	-R	m.p°c	Yield%	Purification Solvent	Structural Formula
2		212-214	91	$CHCl_3$	$C_{19}H_{14}N_4O_5$
3		204-206	93	$CHCl_3$	$C_{10}H_{15}N_3O_3$
4		186-188	88	$CHCl_3$	$C_{15}H_{13}N_3O_3$
5		183-185	93	$ChCl_3$	$C_{15}H_{17}N_3O_3$

Table -2 : Physical Properties of Compound [6-11]



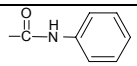
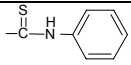
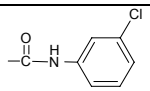
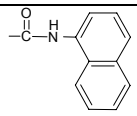
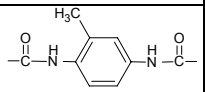
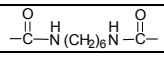
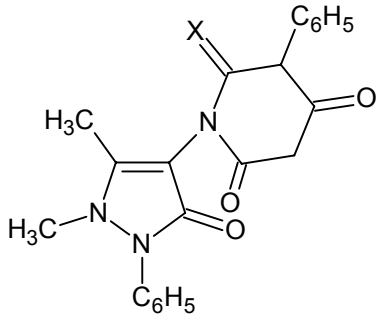
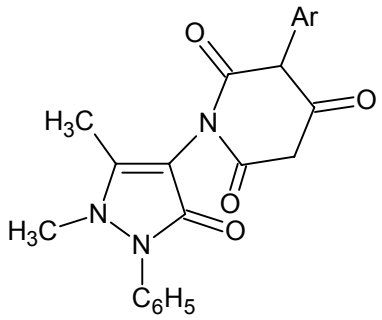
Comp.	-Ar	Reaction Time	m.p°c	Yield %	Purification Solvent	Structural Formula
6		7	248-250	77	EtOH-H_2O	$C_{18}H_{18}N_4O_2$
7		7	190-192	83	EtOH-H_2O	$C_{18}H_{18}N_4O_5$
8		7	225-227	76	EtOH-H_2O	$C_{18}H_{17}N_4O_2Cl$
9		7	221-223	85	EtOH-H_2O	$C_{22}H_{20}N_4O_2$
10		14	276-278	75	EtOH-H_2O	$C_{31}H_{32}N_8O_4$
11		14	249-251	66	EtOH-H_2O	$C_{25}H_{28}N_8O_4$

Table -3 : Physical Properties of Compounds [12 & 13]



Comp.	X	m.p.°c	Yield%	Purification Solvent	Structural Formula
12	O	232-234	79	Ether-H_2O	$C_{21}H_{18}N_4O_4$
13	S	204-206	58	Ether-H_2O	$C_{21}H_{18}N_4O_3S$

Table -4 : Physical Properties of Compounds [14& 15]



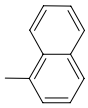
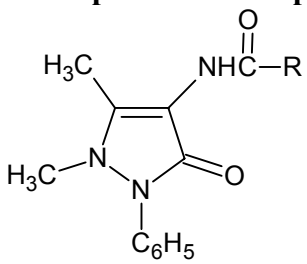
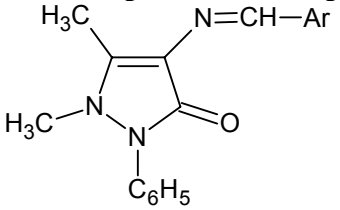
Comp.	-Ar	m.p.°c	Yield%	Purification Solvent	Structural Formula
14		210-212	69	Ether-H_2O	$C_{25}H_{18}N_4O_4$
15		218-220	66	Ether-H_2O	$C_{21}H_{17}N_4O_4Cl$

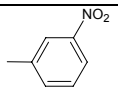
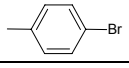
Table -5 : Physical Properties of Compounds [16 & 17]



Comp.	-R	m.p.°c	Yield%	Purification Solvent	Structural Formula
16	-H	188-190	89	EtOH	$C_{12}H_{13}N_3O_2$
17	$-CH_3$	252-254	78	Ethyl acetate	$C_{13}H_{16}N_4O_2$

Table -6 : Physical Properties of Compounds [20-22]



Comp.	-Ar	m.p.°c	Yield%	Purification Solvent	Structural Formula
20		183-185	74	EtOH-H_2O	$C_{18}H_{16}N_4O_3$
21		192-194	79	EtOH-H_2O	$C_{18}H_{17}N_3O_2$
22		178-180	71	EtOH-H_2O	$C_{18}H_{16}N_3OBr$

Results and Discussion

The new antipyrine derivatives were prepared following the reaction sequences depicted in scheme (1).

The reaction between compound [1] and an appropriate anhydride using fusion method afforded the corresponding 5-isondoline-1,3-diones [2-5] in a good yields. The IR spectra showed the (C=O) stretching absorptions near 1734, 1668 and 1647 cm^{-1} combined with the disappearance of the $–NH_2$ stretching bands.

Condensation of compound [1] with alkyl or aryl iso (isothio) cyanates in absolute ethanol gave the antipyrine derivatives [6-11] containing urea and thiourea moieties. The formation of these derivatives [6-11] was indicated by the presence in their IR spectra of the –NH and C=O at 3226-3286 cm^{-1} and 1699cm^{-1} respectively, combined with disappearance of the NH_2 stretching band.

Ring closure of moieties ($-NH\overset{X}{\overset{\|}{C}}-NH-$) (X= O, S) with diethyl malonate or malonic acid afforded the corresponding pyrimidine derivatives [12-15], which displayed two bands at 1708 cm^{-1} and 3307cm^{-1} for the C=O and tautomeric OH respectively.

Refluxing compound [1] with formic acid and acetic acid for three hoursafforded amide derivatives [16 & 17], which displayed bands at 3230 cm^{-1}, 3196 cm^{-1}, and 1685 cm^{-1} for the tautomeric (OH) $-N=\overset{HO}{\overset{|}{C}}$, NH and C=O stretching bands respectively.

Moreover, pyrazolotriazine derivative [18] was obtained from the raction of compound [16] with hydrazine under reflux in ethanol solution. The absorption bands at 3273 and 1591 in the IR spectrum are due to –NH and C=N stretching respectively.

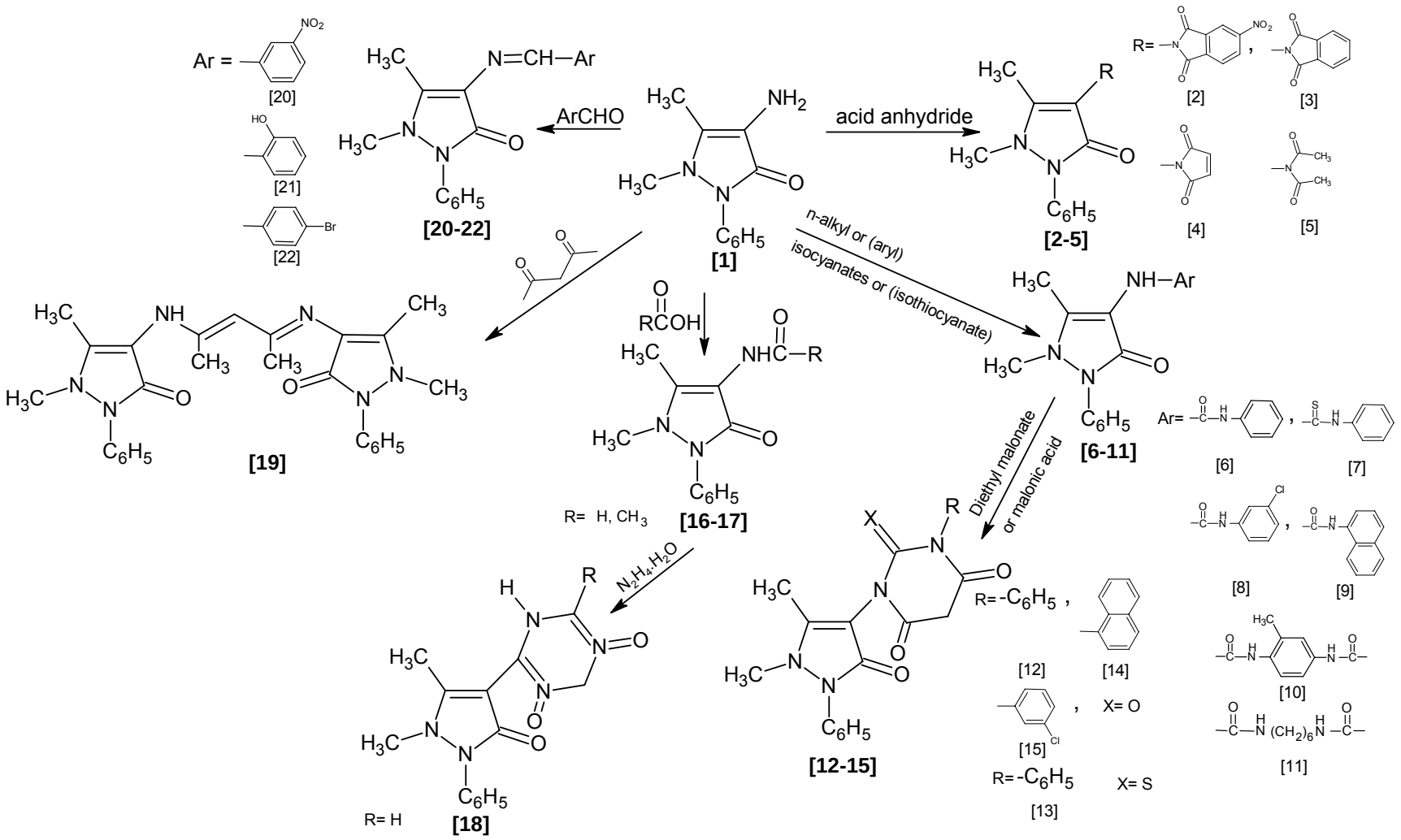
On the other hand, the reaction of compound [1] with acetyl acetone in refluxing ethanol for 3 hrs, afforded derivative [19] as indicated by the strong band at 1610cm^{-1} for (C=N) stretching band and 3385 cm^{-1} for the NH stretching respectively.

Finally, condensation of compound [1] with aryl aldehydes in absolute ethanol gave the Schiff bases [20-22], the formation of these bases was indicated by the presence in their IR spectra of the azomethine (HC=N) stretching band at 1593-1614cm^{-1} combined with the disappearance of the NH_2stretching band.

^{1}H-NMR of compounds [2, 6, 12, 16] showed new multiplate signals due to new aromatic protons of compounds [2, 6, 12], while compound [16] have tautomeric form; so new single signal will be formed.

^{13}C-NMR of compounds [2, 6, 12 and 16] appear new multiple signals were attributed to new aromatic carbons, also, new signals of (C=O) belong to anhydride, pyrimidine and acet amide derivatives.

The mass spectra of compounds [3, 9and 17] were consistent with the proposed structures.


Ar =
[20]
[21]
[22]
ArCHO
[20-22]
[1]
acid anhydride
[2-5]
R=
[2]
[3]
[4]
[5]
n-alkyl or (aryl)
isocyanates or (isothiocyanate)
[6-11]
Ar=
[6]
[7]
[8]
[9]
[10]
[11]
Diethyl malonate
or malonic acid
[12-15]
R= -C6H5
X= O
X= S
[12]
[13]
[14]
[15]
RCOOH
[16-17]
R= H, CH3
N2H4.H2O
[18]
R= H
[19]

Scheme -1-

Table -7 : Some Spectral Data of Compounds (2-5)

Comp.	U.V (EtOH)		Characteristic Bands of FT-IR Spectra (cm^{-1}, KBr Disc)				
	λ_{max}(nm)	ϵ_{max} ($l.mol^{-1}.cm^{-1}$)	υ(C=O) anhydride	υ(C=O) pyrazol	υ(C-H) aromatic	υ(C-H) aliphatic	Other υ
2	267 224	1484 3135	1668 1734	1647	3066	2926	$-NO_2$ 1496 C=C 1550
3	367 267	2330 727	1676 1718	1653	3070	2920 (sym) 2795 (asym)	C=C 1560
4	271	2027	1658 1720	1643	3072	2935 (sym) 2810 (asym)	C=C 1546
5	275.5 222.9 204.9	1172 1193 2127	1644 1724	1653	3032	2933 (sym) 2790 (asym)	C=C 1610

Table -8 : Some Spectral Data of Compounds (6-11)

Comp.	U.V (EtOH)		Characteristic Bands of FT-IR Spectra (cm^{-1}, KBr Disc)						
	λ_{max}(nm)	ϵ_{max} ($l.mol^{-1}.cm^{-1}$)	υ(N-H)	υ(C=O) amide	υ(C=O) ring	υ(C-H) aromatic	υ(C-H) al. sum asym	υ(C=C)	Other υ
6	275.4 241.7 205.3	1083 2513 2731	3280	1699	1643	3150	2955 2860	1600	-OH* 3400
7	276.8 272.6 211.3	3327 2217 3471	3271	-	1637	3057	2900 2830	1560	C=S 1325
8	275.7 245.1 208.5	828 1882 2748	3232	1714	1645	3054	2920 2845	1610	C-Cl 690 -OH* 3445
9	275.4 241.7	1083 2513	3251	1670	1635	3010	2900 2870	1616	-OH* 3398
10	275.4 234.1 204.4	1029 2312 2273	3286	1668	1638	3032	2922 2816	1570	-OH* 3414
11	276.4 247.6 231.6	262.4 2408 2279	3275	1674	1647	3041	2935 2880	1591	-OH* 3410

* = Tautomeric

Table -9 : Some Spectral Data of Compounds (12-15)

Comp.	U.V (EtOH)		Characteristic Bands of FT-IR Spectra (cm^{-1}, KBr Disc)					
	λ_{max}(nm)	ϵ_{max} ($l.mol^{-1}.cm^{-1}$)	pyrimidine υ(C=O) (C-OH)	υ(C=O) ring	υ(C-H) aromatic	υ(C-H) sum al. asym	υ(C=C)	Other υ
12	275.5 241.6 206.6	1325 3068 3055	1708 3307	1637	3030	2950 2895	1541	C-N 1303
13	275.4 241.7 205.7	1083 2513 2731	1676 3273	1635	3095	2960 2890	1566	C=S 1294
14	232.2 225.7	2360 2533	1670 3280	1637	3041	2922 2860	1560	C-N 1311
15	243.5 224.2	3112 2752	1714 3230	1637	3057	2920 2880	1593	C-Cl 775

Table -10 : Some Spectral Data of Compounds (16-17)

Comp.	U.V (EtOH)		Characteristic Bands of FT-IR Spectra (cm^{-1}, KBr Disc)					
	λ_{max}(nm)	ϵ_{max} ($l.mol^{-1}.cm^{-1}$)	υ(N-H) (C-OH)	υ(C=O) amide	υ(C=O) ring	υ(C=O) aromatic	υ(C-H) sum al. asym	υ(C=C)
16	275.8 221.8	1881 2012	3230 3196	1685	1635	3012	2930 2879	1589
17	244.4	1677	3032 3203	1683	1647	3034	2922 2876	1624

* Tautomeric

Table -11 : Some Spectral Data of Compounds (18-22)

Comp.	U.V (EtOH)		Characteristic Bands of FT-IR Spectra (cm^{-1}, KBr Disc)						
	λ_{max}(nm)	ϵ_{max} ($l.mol^{-1}.cm^{-1}$)	υ(N-H) Triazine	υ(C=O) ring	υ(C-H) aromatic	υ(C-H) sym al. asym	υ(C-H) aromatic	υ(C=C)	Other υ
18	232.2 228.6	1087 1676	3273	-	3100	2966 2910	1591	1514	C-N 1294
19	270.6 239.6	1940 1807	3285	1638	3034	2916 2864	1610	1496	C-N 1210
20	373.2 367.7	1630 2160	-	1653	3082	2960 2893	1614	1560	$-NO_2$ 1540
21	371.2 362.5	1636 2210	-	1643	3076	2980 2850	1610	1565	-OH 3410
22	362.9 348.7	1666 2150	-	1647	3055	2939 2890	1593	1570	C-Br 760

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