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SYNTHESIS, STRUCTURAL CHARACTERIZATION AND ANTIBACTERIAL EVALUATION OF SOME NEW 2-PYRAZOLINE DERIVATIVES

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ABSTRACT

The title compounds were synthesized by condensation of ethyl acetoacetate, urea and substituted benzaldehydes resulting pyrimidinones and in treating with hydrazine hydrate gave pyrimidinone hyrazides which by condensation with 2- nephthyl chalcones by Micheal addition (1,4) afforded the titled compounds 6-Methyl-5-(5-2-naphthyl)-3-aryl-2,3-dihydro-1-H-pyrazole-1-carbonyl-4-aryl- 3,4-dihydro pyrimidin-2-(1H)-ones or pyrazoline derivatives (1-35). The spectral data and some physical properties were used to support the structure of new products. (UV, IR, ^{1}H-NMR, ^{13}C-NMR), the suggested mechanism of the product formation was supported by theoretical calculations of AM1 modeling model. The antibacterial activity of some prepared compounds were tested through its inhibition effects on two kinds of bacteria.

KEYWORDS: 2-naphthyl chalcone, pyrimidinones, 2-pyrazolines, anti-bacterial activity.

INTRODUCTION

Pyrazoline is unsaturated compound containing three carbon atoms and two nitrogens at adjacent positions and its a reductive product for pyrazole which in continuous reduction turn into pyrazolidine. Pyrazole and pyrazolidine are bases stronger than pyrazole, and on the depend on the double bond position, there are three possible formulas for pyrazoline structures which are in equilibrium with each other 1- pyrazoline, 2- pyrazoline and 3-pyrazoline.[1] The 2-pyrazoline derivatives were prepared and their biological activity was detected against H5N1 viruses, antitrypanosomal and leukemia[2] other prepared derivatives

showed activity as antidepressant, anticovnlsant compared with drugs like phenytionin, imipramine[3] and against *Mycobacterium tuberculosis* H37*Rv*[4], hypotensive, anti-cancer and antifungal[5-8], antiamoebic[9,10], antimicrobial[11,12], antioxidant[13], anticonvulsant[14], antidiabetic[15], antibacterial[16] and analgesic.[17]

2-pyrazoline derivatives were prepared by using phenyl hydrazine and chalcone derivatives using $CeCl_3.7H_2O$[18] and by using DABCO, pyrazoline turned to pyrazole.[19]

EXPERIMENTAL

Melting points were determined by Stuart SMP11 - melting point apparatus, Ultra violent spectra were determined by UV PG+ 92, Fourier-Transform Infrared Spectra were recorded by FT-IR Nicolet 100 thrmo scientific using KBr-disk, Nuclear Magnetic Resonance ^{1}H-NMR, ^{13}C-NMR spectra were registeredat 400 MHz Varian spectrometer (Selçuk University / Turkey) using TMS as an internal standard and $CDCl_3$ as solvent. Theoretical study of heat of formation (H.F) and steric energy (S.E) was achieved by using AM1 (Austin - Model 1) to explain the effect of different groups (electron donating or drawing) on the reaction.

Experimental method

General method for the Synthesis of pyrazoline[20]

(1 mmole) of 2-naphthyl chalcones[21] and (2 mmole) of pyrimidinone hydrazides[22] were dissolved in (15 ml) of ethanol in the presence of 1 ml of 4% NaOH (alc.), mixture was refluxed for (1.5 - 4) hrs., solid precipitate was filtered, dried then recrystallized from ethanol.

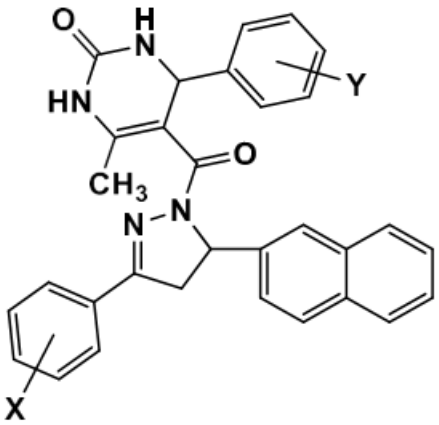


Table 1: Some physical properties for prepared pyrazoline compounds (1-35).

Comp. No.	X	Y	m.p (°C)	Yield %	Colour
1	H	H	197 – 198	89	white
2	H	3-OCH_3	172 – 174	72	creamy white
3	H	4-OCH_3	198 – 200	56	white
4	H	4-$N(CH_3)_2$	171 – 173	75	creamy white
5	H	4-Br	201 – 203	80	yellow
6	H	4-NO_2	181 – 183	66	white
7	H	2-Cl	204 – 206	73	white
8	4-OCH_3	H	194 – 196	63	dark yellow
9	4-OCH_3	3-OCH_3	180 – 182	71	white
10	4-OCH_3	4-OCH_3	173- -175	65	white
11	4-OCH_3	4-$N(CH_3)_2$	199 – 200	51	yellow
12	4-OCH_3	4-Br	189 – 191	48	pale yellow
13	4-OCH_3	4-NO_2	177 – 179	71	white
14	4-OCH_3	3-Cl	179 – 180	64	white
15	4-Br	H	186 – 188	52	pale yellow
16	4-Br	3-OCH_3	169 – 170	79	white
17	4-Br	4-OCH_3	202 – 204	81	creamy
18	4-Br	4-$N(CH_3)_2$	203 – 205	75	dark yellow
19	4-Br	4-Br	178 – 180	66	yellow
20	4-Br	4-NO_2	172 – 174	70	creamy
21	4-Br	2-Cl	186 – 188	86	white
22	4-$N(CH_3)_2$	H	205 – 206	88	orange
23	4-$N(CH_3)_2$	3-OCH_3	214 – 216	85	white
24	4-$N(CH_3)_2$	4-OCH_3	195 – 197	70	pale yellow
25	4-$N(CH_3)_2$	4-$N(CH_3)_2$	185 – 187	82	dark yellow
26	4-$N(CH_3)_2$	4-Br	210 – 212	63	pale yellow
27	4-$N(CH_3)_2$	4-NO_2	202 – 204	71	shine yellow
28	4-$N(CH_3)_2$	2-Cl	200 – 201	64	white
29	4-NO_2	H	184 – 186	70	pale yellow
30	4-NO_2	3-OCH_3	203 – 205	65	white
31	4-NO_2	4-OCH_3	196 – 198	74	yellow
32	4-NO_2	4-$N(CH_3)_2$	210 – 213	60	yellow
33	4-NO_2	4-Br	206 – 208	71	yellow
34	4-NO_2	4-NO_2	187 – 190	66	creamy
35	4-NO_2	2-Cl	175 – 177	53	white

Biological activity

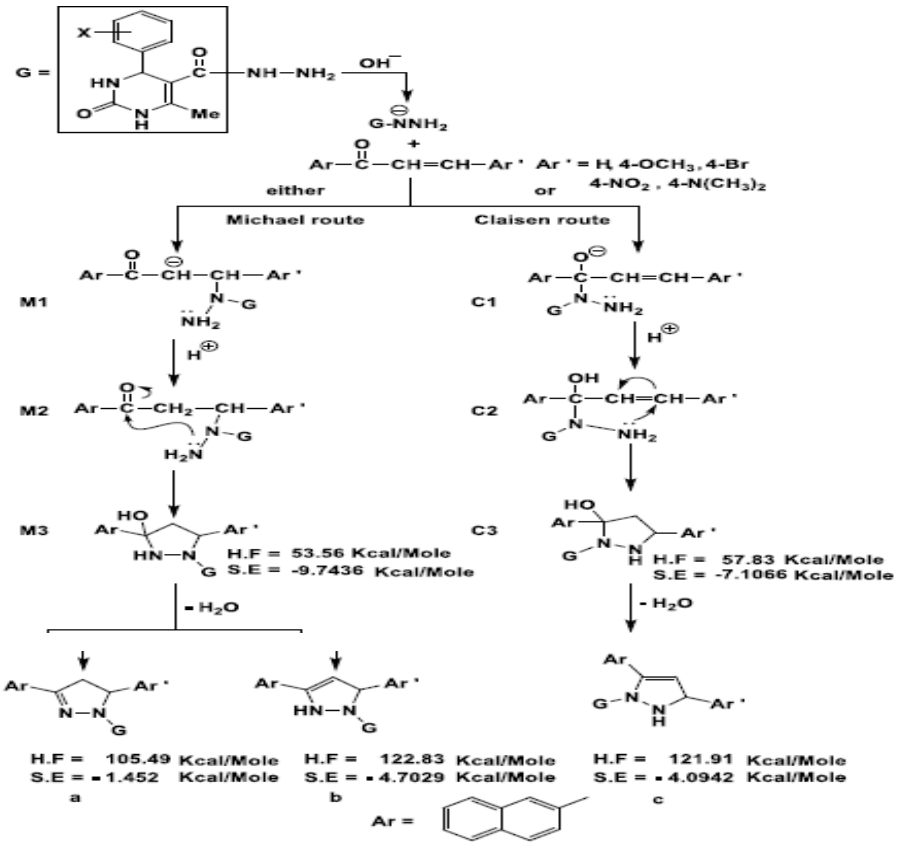
Source of microorganism: ***Staphylococcus aureus*** (Gram +ve) and ***Escherichia Coli***) Gram -ve was used as micro organism for present investigation. The synthesized pyrazoline derivatives were screend for their invitro antibacterial activity against ***Escherichia Coli (E. coli) Staphylococcus aureus (Staph)*** bacterial strains at a concentration (12.5 mg/ml, 100 mg/ml) by well diffusion method.[23] A standard drugs (tetracycline and ciprofloxacin) was

used for comparison. Approximately (20 ml) of freshly prepared liquid agar medium was poured into each Petri dish and then the Petri dishes were dried in an incubator at (37^0C) for duration of (1h) an L-shaped spreader was used to spread the standardized culture of micro organism on each petri dish. Cups of approximately (6 mm) diameter were made in petri dishes using sterile cork borer and were labeled, a solvent control was also tested to see the effect of control on the growth of the microbes. Dimethyl sulfoxide (DMSO) was used to prepare the solutions of synthesized compounds and ciprofloxacin and tetracycline (12.5 mg/ml, 100 mg/ml). The prepared solution were added to each cup in petri dishes and were kept aside in an aseptic area for (1h) to allow diffusion of the drug / sample, followed by incubation at (37°C) for (24 h). The diameter of the zone of inhibition (in mm) was measured and the results are shown in (Table 6).

RESULT AND DISCUSSION

4-Aryl-6-methyl-3,4-dihydro-5 (1H)-pyrimidin-5-yl-(B-naphthyl)-5-aryl-2- pyrazolin-1-yl ketone (1-35)

Compounds were prepared by the reaction between chalcones and pyrimidinone hydrazides in the presence of ethanol as solvent, and the suggested mechanism is as following:-



Scheme 1: Shows pyrazoline formation mechanism.

The IR spectrum[24] of (15) showed many distinguished absorption bands at υ (1647) cm^{-1} belongs to amidic carbonyl group (C=O), υ (1583) related to pyrazoline ring double bond (C=C), υ (1627) cm^{-1} belongs to (C=N), υ (1463) cm^{-1}, (3244) cm^{-1} and (2980) cm^{-1} belongs to aromatic (C…C), (N-H) and aliphatic (C-H) respectively see (Table 2). The UV spectrum of (15) exhibited a blue shift to a longer wave length at maximum absorption (λ max = 276) nm due to removal of conjugation see (Table 2). The ^{1}H-NMR spectrum[23] of (15) showed a doublet signal at (3.952) ppm belongs to (-CH_2) group protons, triplet signal at (5.107) ppm for (-CH) group of protons of pyrazoline a singlet signal watched at (9.100) ppm for (N-H) group, a multiple of signal noticed for benzene ring protons at a range of (7.164 - 8.116) ppm and a singlet signal for the protons of substituted methyl group see (Table 3).^{13}C-NMR for comp. (15) showed a signal for pyrazoline (CH_2) group C_4, C_3 at 40.090 ppm, 153.0 ppm respectively and a signal was shown for (-CH) C_5 and (CH_3) C_{15} at (39.957) ppm and (54.384) ppm consecutively and a signal for carbonyl group (C_{14}) at (165.9) ppm, aromatic rings carbons showed a shift at range of (99-132) ppm as shown in (Table 4).

Table 2: Some of the spectral data for pyrazoline (1-35).

comp. no.	X	Y	IR υ cm^{-1} (KBr)							UV λ max (nm)
			NH	C=O	C=N	C=C aliphatic	C⋯C aromatic	C-H aliphatic	others	
1	H	H	3240	1667	1603	1511	1456	2890	–	264 316
2	H	3-OCH3	3246	1687	1649	1597	1494	2850	C-O-C 1118 1255	226 276
3	H	4-OCH3	3244	1647	1620	1598	1465	2941	C-O-C 1140 1290	242 318
4	H	4-N(CH3)2	3242	1651	1618	1560	1458	2978	–	220 280
5	H	4-Br	3242	1647	1608	1573	1460	2956	C-Br 510	228 276
6	H	4-NO2	3236	1645	1699	1595	1463	2987	N⋯O 1348 1519	222 268
7	H	4-Cl	3228	1641	1629	1591	1494	2980	C-Cl 761	240 310
8	4-OCH3	H	3242	1654	1625	1597	1496	2978	C-O-C 1249 1126	240 280
9	4-OCH3	3-OCH3	3242	1647	1620	1598	1463	2980	C-O-C 1150 1290	238 276

10	**4-OCH3**	**4-OCH3**	3242	1651	1620	1598	1467	2981	C-O-C 1255 1140	262 298
11	**4-OCH3**	**4-N(CH3)2**	3242	1649	1618	1525	1448	2978	C-O-C 1224 1145	238 278
12	**4-OCH3**	**4-Br**	3240	1647	1612	1571	1460	2956	C-O-C 1147 1250 C-Br 570	226 280
13	**4-OCH3**	**4-NO2**	3242	1653	1625	1598	1467	2910	N⋯O 1345 1520 C-O-C 1286 1145	245 262
14	**4-OCH3**	**2-Cl**	3226	1639	1610	1595	1456	2978	C-O-C 1298 1143	243 278
15	**4-Br**	**H**	3244	1647	1627	1583	1463	2980	C-Br 514	276 318
16	**4-Br**	**3-OCH3**	3240	1649	1627	1483	1467	2939	C-Br 542	240 264
17	**4-Br**	**3-OCH3**	3244	1647	1610	1598	1463	2980	C-O-C 1273 1145	240 278
18	**4-Br**	**4-N(CH3)2**	3242	1647	1618	1560	1458	2953	C-Br 528	242 276
19	**4-Br**	**4-Br**	3244	1649	1625	1583	1485	2958	C-Br 572	224 320
20	**4-Br**	**4-NO2**	3226	1645	1605	1575	1463	2987	N⋯O 1348 1519	236 268
21	**4-Br**	**2-Cl**	3230	1641	1633	1571	1456	2981	C-Cl 744 C-Br 553	240 278
22	**4-N(CH3)2**	**H**	3244	1649	1624	1577	1463	2958	–	262 280
23	**4-N(CH3)2**	**3-OCH3**	3242	1651	1620	1598	1467	2937	C-O-C 1255 1145	236 278
24	**4-N(CH3)2**	**2-OCH3**	3242	1649	1624	1577	1487	2960	C-O-C 1220 1128	236 276
25	**4-N(CH3)2**	**4-N(CH3)2**	3242	1647	1618	1560	1458	2976	—	240 280
26	**4-N(CH3)2**	**4-Br**	3242	1649	1610	1573	1460	2980	C-Br 520	230 282
27	**4-N(CH3)2**	**4-NO2**	3234	1649	1624	1577	1463	2949	N⋯O 1359 1550	240 268
28	**4-N(CH3)2**	**2-Cl**	3234	1643	1610	1589	1463	2929	C-Cl 761	258 290

29	**4-NO2**	**H**	3244	1647	1627	1598	1463	2978	N⋯O 1367 1516	242 280
30	**4-NO2**	**3-OCH3**	3242	1653	1625	1598	1467	2981	N⋯O 1516 1346 C-O-C 1286 1145	244 318
31	**4-NO2**	**4-OCH3**	3242	1647	1610	1596	1453	2980	C-O-C 1140 1255 N⋯O 1348 1555	242 320
32	**4-NO2**	**4-N(CH3)2**	3240	1649	1625	1598	1467	2939	C-O-C 1145 1286 N⋯O 1380 1516	254 342
33	**4-NO2**	**4-Br**	3200	1660	1625	1595	1460	2850	C-Br 538 N⋯O 1352 1415	242 320
34	**4-NO2**	**4-NO2**	3230	1645	1606	1597	1463	2987	N⋯O 1348 1519	252 320
35	**4-NO2**	**2-Cl**	3200	1660	1625	1597	1460	2947	N⋯O 1348 1516 C-Cl 709	224 316

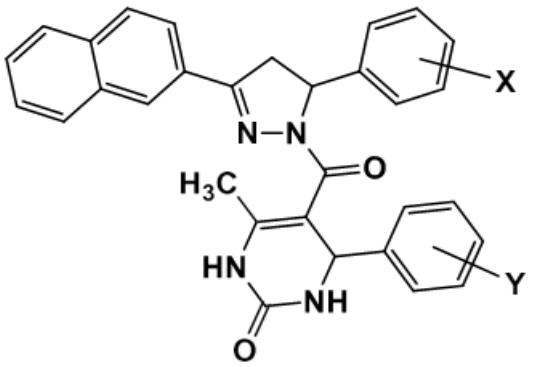


Table 3: ^{1}H-NMR spectra for compounds (1,15,22,24).

Comp. No.	X	Y	Substituted X Y	CH2	CH	NH	CH3	Ar-H
1	**H**	**H**	**—**	3.8,2H,d	5.2,1H,t	9.2,1H,s	2.2,3H,s	7.172-7.983,16H,m
15	**4-Br**	**H**	**—**	3.952,2H,d	5.107,1H,t	9.100,1H,s	2.3,3H,s	8.116-7.164,15H,m
22	**4-N(CH3)2**	**H**	2.9,6H,s	3.919,2H,d	5.234,1H,t	9.323,1H,s	2.458,3H,s	8.195-7.452,15H,m
24	**4-N(CH3)2**	**4-OCH3**	2.2,6H,s	3.964,2H,d	5.127,1H,t	9.191,1H,s	2.477,3H,s	7.736-7.207,15H,m

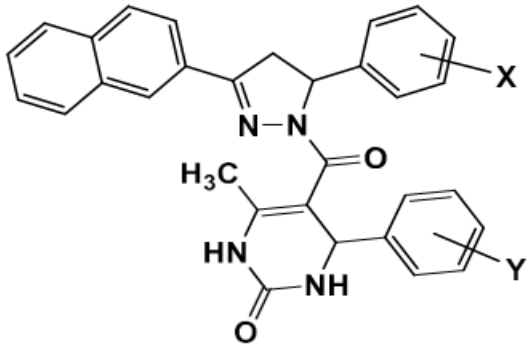


Table 4: ^{13}C-NMR spectra for compounds (1,3,8,15,24,27).

Comp. No.	Substitute X	Substitute Y	Substitutes X C12 Y C13	C4 C3	C15 C5	C14	Ar-H C
1	**H**	**H**	**— —**	40.536 152.614	39.771 59.637	165.767	122, 124, 126, 127, 128.1, 128.8, 128.9, 129, 130, 144, 145, 148
3	**H**	**4-OCH3**	14.590	40.590 152.526	39.827 54.364	165.730	99, 126, 127, 128, 145, 148
8	**4-OCH3**	**H**	14.518 —	40.149 152.592	39.314 54.418	165.770	99, 119, 124, 126, 127, 128, 130, 131, 132, 135, 144, 145, 148, 161
15	**4-Br**	**H**	**— —**	40.090 153.0	39.957 54.384	165.9	99, 123, 124, 126, 127, 128, 129, 130, 131, 132
24	**4-N(CH3)2**	**4-OCH3**	14.5 18.2	40 152.6	39 54	165	99, 126, 126.8, 127, 128, 145, 148
27	**4-N(CH3)2**	**4-NO2**	14.4 —	40 152.2	59 54	165.4	98, 124, 128, 147, 149.8, 152.4

Table 5: H.F (Kcal/mole) & S.E (Kcal/mole) for compounds (1,3,6).

Comp. No.	X	Y	H.F (Kcal/mole)	S.E Kal/mole
1	H	H	106.23377	-12.4042
3	H	4-OCH_3	69.77025	-6.5599
6	H	4-NO_2	112.85985	-12.0577

Biological Activity

From the (Table 6) we obtain that the compounds (4,10) had sensitive activity against ***(E. coli***) in (100 mg/ml) concentration, but in (12.5 mg/ml) don't had activity against (***Staph. Aureus)*** in comparison with control drugs (ciprofloxacin, tetracycline). The compound (15) had moderately sensitive activity in (12.5 mg/ml) against (***E. coli***) the compounds (5,7,10,15,17,19,28,35) had moderately sensitive activity against (***E. coli***) in (100 mg/ml) concentration, and the compounds (1,5,10,17,18,19,20,21,22,25,28,31,33,34,35) had no activity (resistant) against (***E. coli***), (***Staph. Aureus)*** in (12.5 gm/ml) concentration, and the compounds (1,18,22,25,31) had resistant against (***E. coli***) and (***Staph. Aureus)*** in (100 mg/ml) concentration with control drug (ciprofloxacin, tetracycline) in the same concentration.

Table 6: Shows the biological activity of some compounds and the control drugs against some bacteria Inhibitions (zones measured in mm).

	12.5		100	
Comp. No.	***Staph.***	***E. Coli***	***Staph.***	***E. Coli***
1	3	10	5	10
7	16	10	17	14
10	5	10	18	12
15	6	12	7	13
17	10	10	10	14
18	0	4	5	4
19	7	10	9	13
20	10	5	12	5
21	0	10	0	10
22	0	10	0	10
25	0	10	10	11
27	14	11	17	22
28	9	10	10	15
31	5	10	10	20
33	10	9	12	10

	12.5		100	
Comp. No.	***Staph.***	***E. Coli***	***Staph.***	***E. Coli***
34	7	7	11	9
35	10	10	0	12
ciprofloxacin	22	20	21	24
tetracycline	19	20	20	22

R = resistant (R < 11 mm)

MS = moderately sensitive (MS = 12-16 mm) S = sensitive (S > 16 mm).

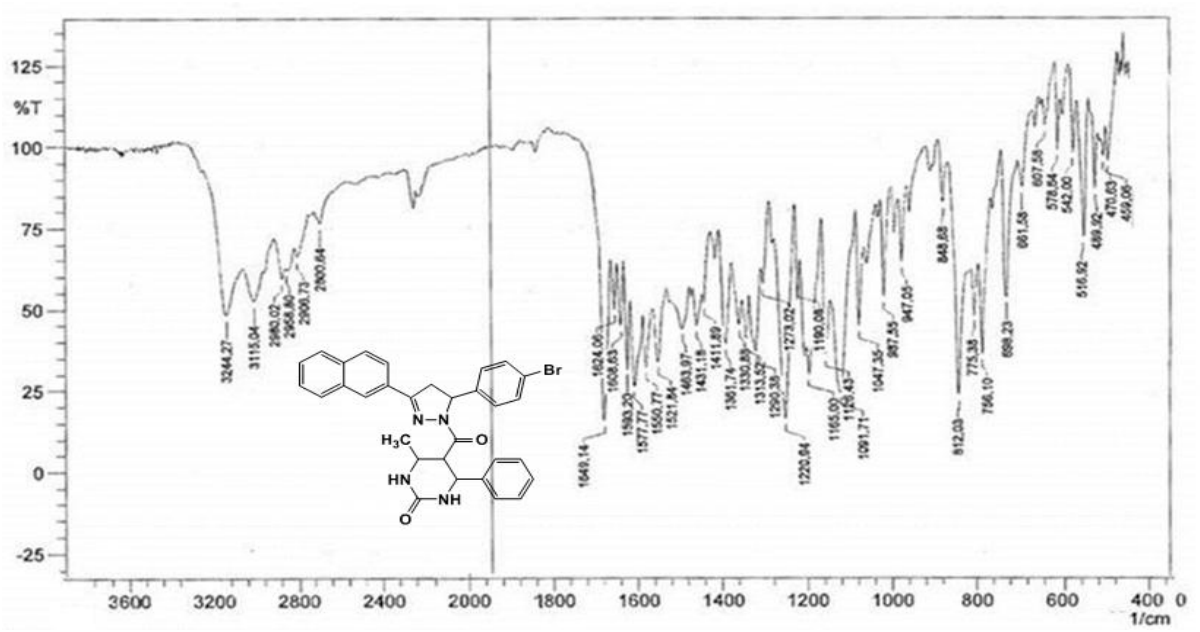


Figure 1: IR spectrum for (15).

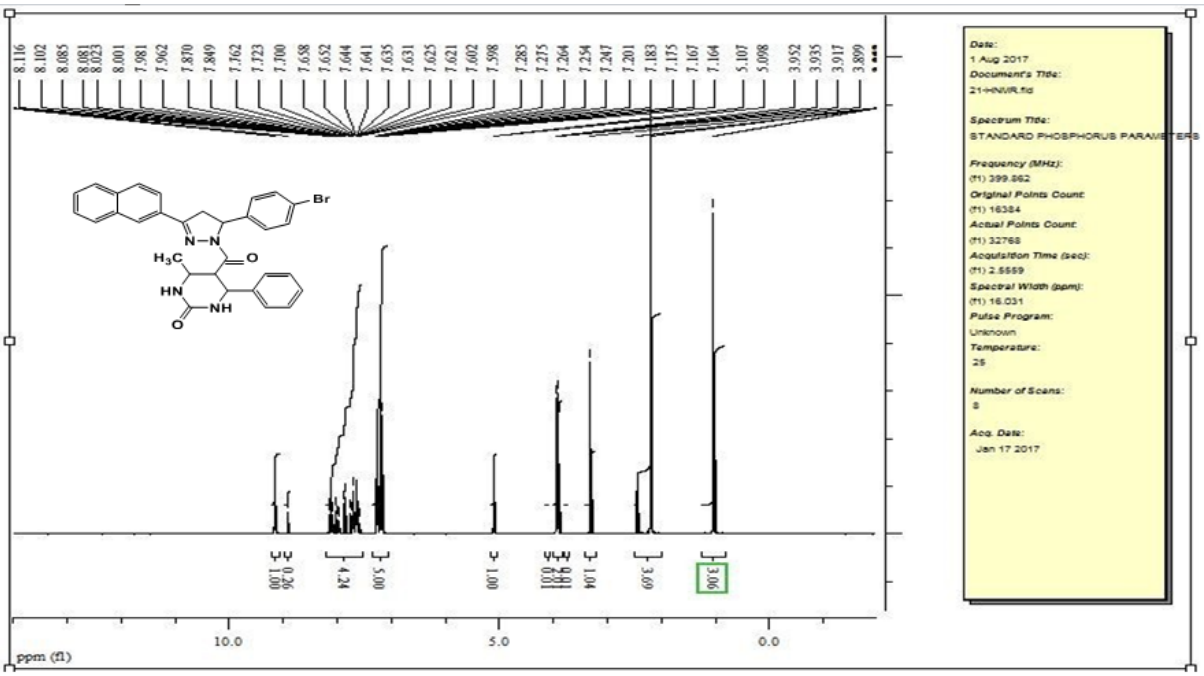


Figure 2: ^{1}H-NMR spectrum for (15).

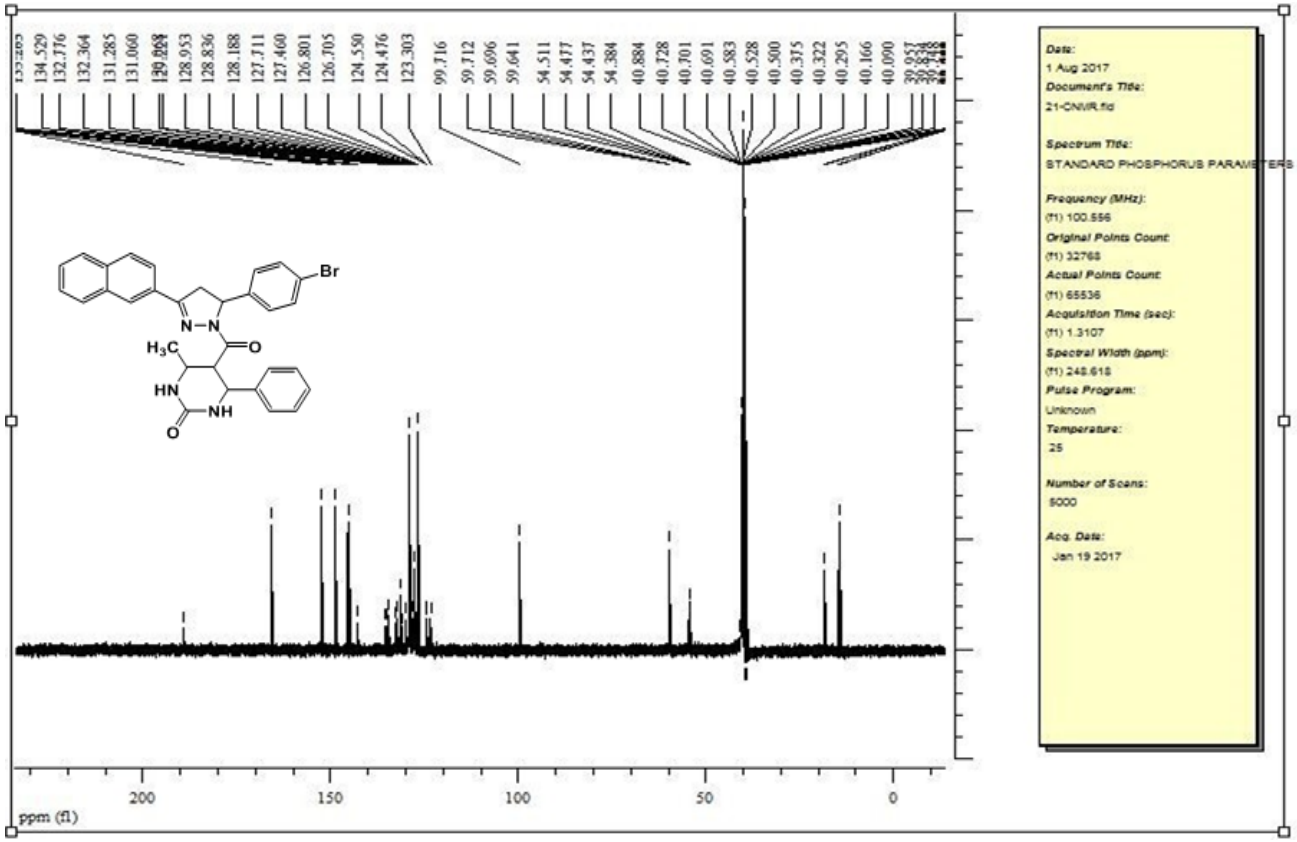


Figure 3: ^{13}C-NMR spectrum for (15).

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