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An Efficient and Solvent Free Synthesis of N-Aryl 2, 3-Dihydro-4H Naphtho-[2, 1-E] 1, 3-Oxazines

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***Abstract* – Oxazine compounds have proved to have many pharmaceutical applications and most of these compounds now a days are used as drugs. For the importance of this class of heterocyclic compounds we are here investigate the synthesis of new derivatives of 1,3-oxazines using solvent free one pot three component system in a drug discovery program, so starting from β-Naphthol, formaldehyde and aromatic amines in presence of zarconyl chloride as catalyst. Compounds 1-9 were synthesized, Benzo 1,3 diazines(10-14) were also synthesized from their corresponding 1,3 oxazines. These compounds were characterized by IR, some representative by ^{1}HNMR and were discussed.**

***Keywords* – Aryl, 1, 3-Naphthoxazines, Solvent Free and Synthesis.**

I. Introduction

Due to their importance in biological applications oxazines have drew attention of many researchers to investigate this type of hetrocyclic compounds. These researchers have succeeded to prepare different types of oxazines using different methodologies [1-10] most of the starting material is anthranilic acid or its derivatives with aldehydes , isocyanate , acetic anhydride or with oxazolones [11]. Some other researchers used phenal, amine and aldehydes to the synthesis of these oxazine compounds [12]. Other researchers used chalcones for the synthesis of this type of compounds [13, 14] or from 2-Iodoaryl Azides and Amines [15]. Among the studied reactions of oxazine compounds were opening and reclosing of the oxazine ring which is the other way for the synthesis of new oxazine derivatives [16]. The research work on studying the biological activities of some oxazine compounds revealed that most of these compounds have several pharmacological applications for using these compounds as drugs [17-19]. In addition the latest studies on oxazine compounds showed the ability to stop the cancer cell growth and repairing the DNA strands [20] and according to the above facts we studied the synthesis of some new compounds using green technique for this synthesis. These new compounds will be our goal for studying their biological activities in our ongoing drug discovery program.

II. Experimental

All melting points were uncorrected using electro thermal SMP30 UK melting point apparatus. IR spectra were recorded using Alpha (ATR) instrument. ^{1}HNMR spectra were recorded using Varian Agilant (USA) 300 MHz instrument, DMSO as solvent. All chemical were supplied by sigma-Aldrich, BDH and Fluka companies. Compounds 10a, b were synthesized following the some published procedure [21].

2.1. *General Procedure for the Synthesis of Naphthaoxazine Compounds (1-9)*

Formaldehyde (0.2 mol.), Zarconyl chloride ($ZrOCL_2$, $8H_2O$) (0.2mol.), 2-naphthol (0.1 mol.) and aromatic amine (0.1 mol.). This mixture was grind by porcelain mortar for 30 min, after that dichloromethane (CH_2CL_2) was then added. The organic layer was then separated and washed twice with brine then with water. The

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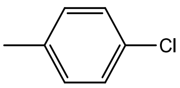
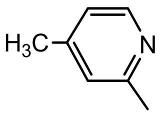
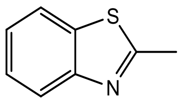
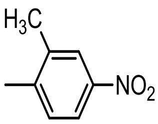
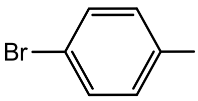
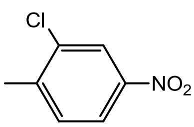
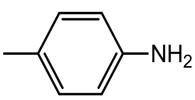
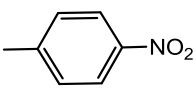
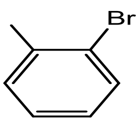
organic layer was separated. Evaporation of the solvent by rotary evaporator afforded a crude product which was recrystallized from minimum amount of methanol. Physical properties were listed in the following Table (1).

Table 1. Physical properties of compounds (1-9).

Comp. No.	Ar.	Molecular Formula	M. Wt.	M.P. (°C)	Yield (%)	Colour
1.	 4-chlorophenyl	$C_{18}H_{14}ClNO$	295.76	98-100	73	Yellow
2.	 4-methyl-2-pyridinyl	$C_{18}H_{16}N_2O$	276.33	115-118	37	Brown
3.	 2-benzothiazolyl	$C_{19}H_{14}N_2OS$	318.39	109-114	83	Dark Brown
4.	 2-methyl-4-nitroaphenyl	$C_{19}H_{16}N_2O_3$	320.34	158-164	33	Orange
5.	 4-bromophenyl	$C_{18}H_{14}BrNO$	340.21	113-117	79	Brown
6.	 2-chloro-4-nitrophenyl	$C_{18}H_{13}ClN_2O_3$	340.76	151-153	59	Yellow
7.	 4-amino phenyl	$C_{18}H_{16}N_2O$	276.33	218-222	67	Brown
8.	 4-nitro phenyl	$C_{18}H_{14}N_2O_3$	306.32	160-164	43	Yellow
9.	 2-bromo phenyl	$C_{18}H_{14}BrNO$	340.21	340.21	70	Orange oil

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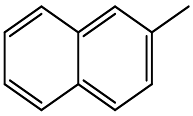
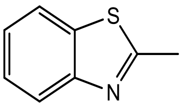
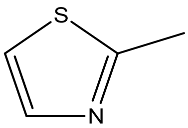
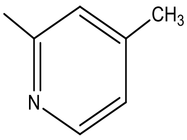
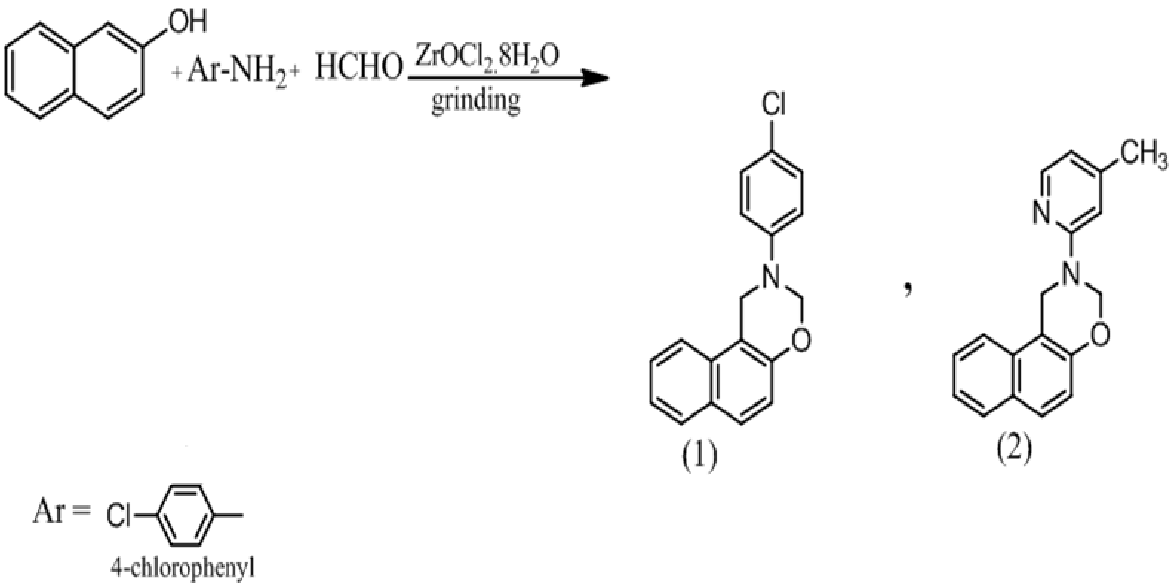
2.2. *General Procedure for the Preparation of N-Substituted 2-Methyl, Aryl Benzo-1, 3-Diazine-4-One (11-24)*

Compound 10a or 10b (0.1 mol),aromatic or aliphatic amine(0.1 mol), this mixture was refluxed for 6h., cooled. The whole mixture was then powered on cold water (50 ml) with stirring. The precipitate was filtered off and dried then crystallized from benzene. The physical properties for the synthesized compound were illustrated in Table (2).

Table 2. Physical properties of compounds (10-13).

Comp. No.	Ar	Molecular Formula	M. Wt.	M.P. (°C)	Yield (%)	Colour
10.	 2-naphthayl	$C_{21}H_{17}NO$	299.37	86-92	83	Brown
11.	 2-benzothiazolyl	$C_{18}H_{14}N_2OS$	306.38	193-196	92	White
12.	 2-thiazolyl	$C_{14}H_{12}N_2OS$	256.32	171-173	89	Yellowish White
13.	 4-methyl-2- pyridinyl	$C_{17}H_{16}N_2O$	264.32	154-157	90	White



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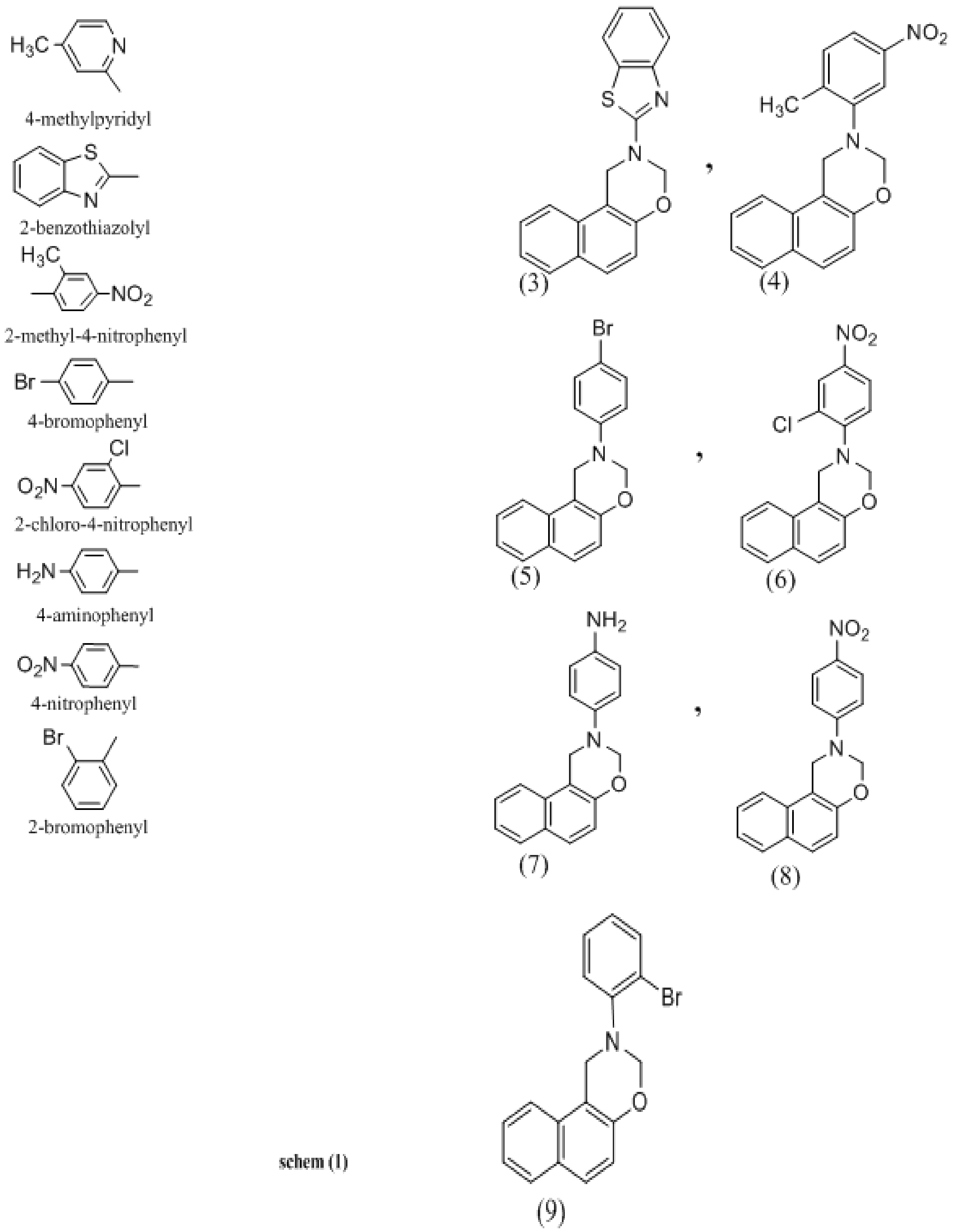
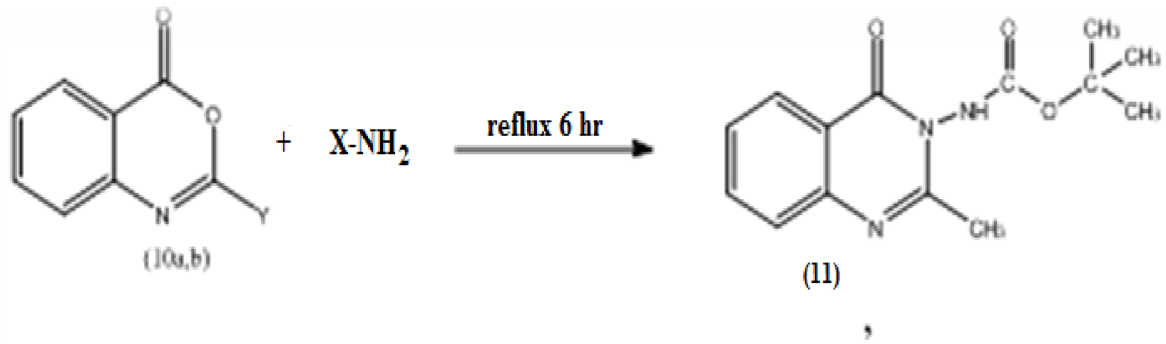


schem (1)



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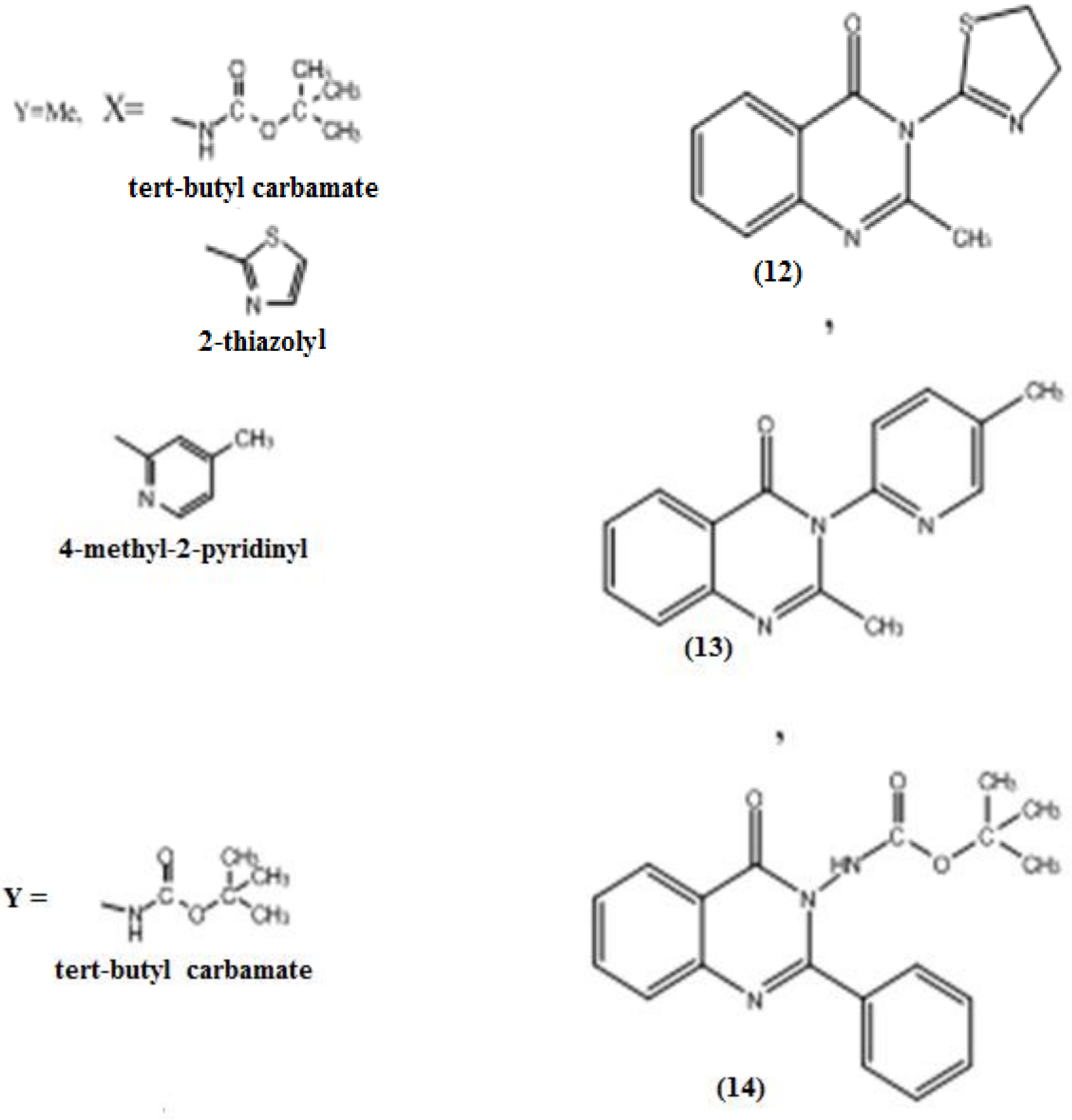

Schem (2)

III. Results and Discussion

It is worth to state here that power sonic 405 micro processes-controlled bench-top ultra-sonic cleaner was used for ultrasonic chemical condensation affording nearly the same yield within the same given time which is another green technique for the synthesis of these compounds. As it was mentioned in the experimental part. Compounds 10a, b were prepared and showed the same melting points, for 10a was found; 79-81 published: 81-82 ^{o}C, while for 10b it was found 120^{0}C the published one at 121-122^{0}C with identical IR data [21].

3.1. *N-Aryl 2, 4H(1, 2E) (1, 3) Napha Oxazine Compounds (1-9)*

These compounds were synthesized using similar procedure [22] and were characterized by IR and showed the following main absorption bands (υ_{max} cm-1) : 3020-3092 for CH , sharp bands at (1654- 1624) for C = N, 1589 -1454 for C = C, C = c Aromatic. While C = N appeared at 1390-1328, C-O-C at 1250-1022 other band were illustrated in Table (3).

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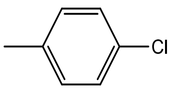
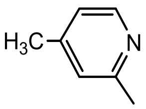
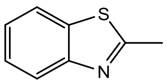
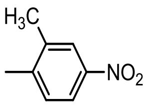
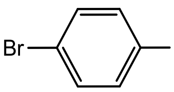
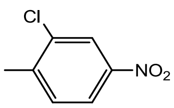
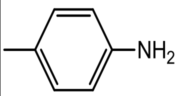
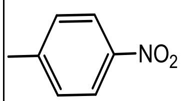
Table 3. IR spectral data for compounds (1-8).

Comp. No.	**Ar.**	**IR υ cm^{-1} (neet)**					
		Ar. C-H	**C = N**	**Ar .C = C, C— — —C**	**C-N**	**C-O-C**	**Others**
1.	 4-chlorophenyl	3059	-----	1588,1482	1366	1220,1094	C-Cl 736
2.	 4-methyl-2-pyridinyl	3048	1628	1586 1505,1454	1328	1204,1157	C-H alph 2910
3.	 2-benzothiazolyl	3020	1654	1572,1462	1381	1256,1066	C-S 749
4.	 2-methyl-4-nitroaphenyl	3051	-----	1588 1508,1464	1390	1215,1046	N-O sym1259 asym1508
5.	 4-bromophenyl	3061	-----	1586 1551,1478	1368	1219,1064	C-Br 486
6.	 2-chloro-4-nitrophenyl	3092	-----	1587 1503,1461	1329	1225,1022	N-O sym1273 asym1503
7.	 4-amino phenyl	3054	-----	1549 1510,1468	1375	1222,1059	$N-H_2$ 3278 3364
8.	 4-nitro phenyl	3063	-----	1589 1502,1481	1323	1235,1060	NOsym1268 asym1589

[1]HNMR for individual compounds were as follow :

3.1.1. *Compound (1)*

In which the aryl group is p-Chloro phenyl see figure (1). The Aromatic protons were 6 types as follows: 7.99, 7.83, 7.7.81ppm. for carbon 8 of naphthyl ring,7.71,7.7ppm. for proton 5. The this ring, 7.54, 7.40ppm for proons 6, 7 while protons 4, 3 appeared at 7.12, 7.11 and 7.054, 7.02ppm.

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Phenyl protons appeared as AB (q) at, 6.79, 6.78 ppm. CH_2 protons of the oxazine ring between oxygen and nitrogen appeared at 5.54 , 5.5ppm. and the other CH_2 protons appeared at 4.96 ,4.77 ppm. protons of naphthyl ring protons appeared as two triplet signals which can be easily differentiated from other protons.

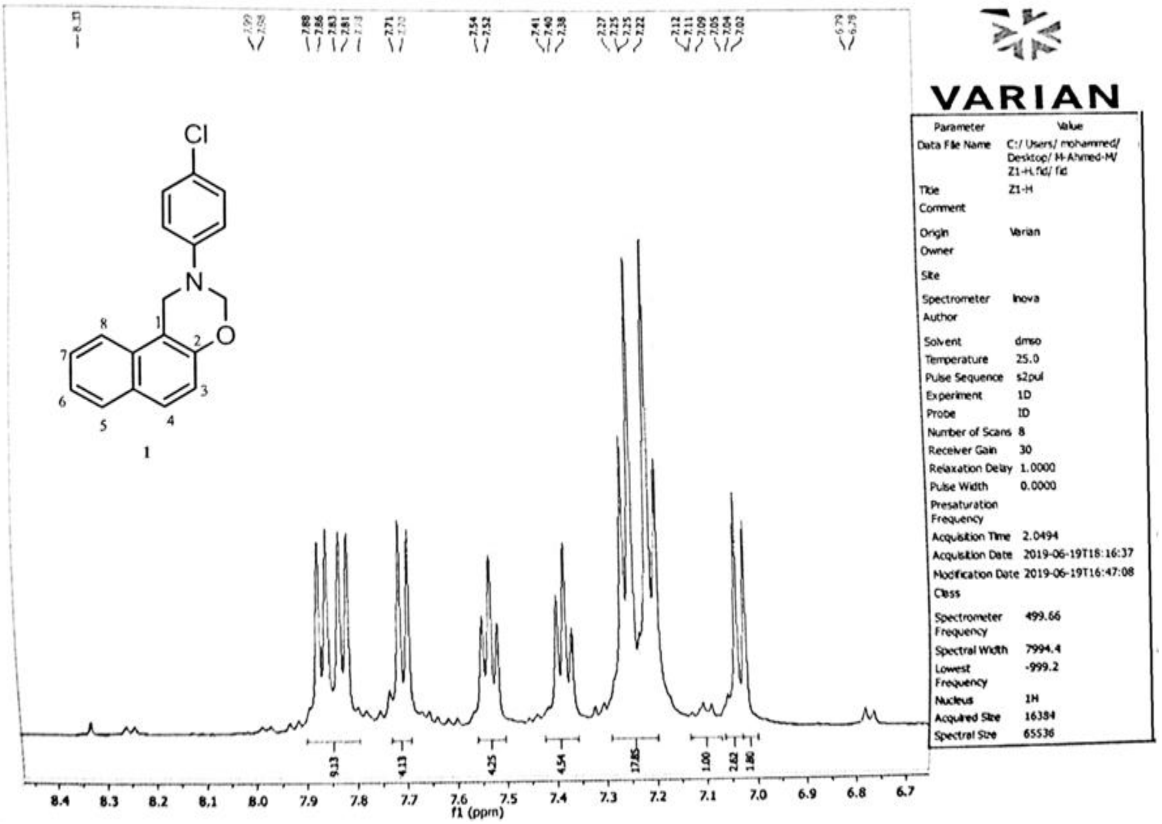

Fig. 1. [1]HNMR spectrum of compound (1).

3.1.2. *Compound (2), Ar is (4-Methyl-2-pyridyl)*

This compound also showed 6 signals for the aromatic protons resonated at 8.1, 8.0, 7.5, 7.4, 6.85 ppm, for 8, 5, 6, 7, 3, 4 protons while the phenyl protons appeared at 7.9, 7.89 ppm. for AB like system, 7.53, 7.52 ppm. for the rest protons nearly equivalents oxazine protons, CH_2 resonated at 5.7, 5.68 ppm. for protons 4, 3 respectively.

3.1.3. *Compound (6) Ar is (2-Bromo phenyl)*

Protons NMR chart for this compound also showed the following signals : 8.0, 8.02, 7.5, 7.45 , 7.65, 6 .91 ppm. for naphthyl ring protons of 8, 5 protons, 6, 7 and 3, 4 protons respectively for oxazine ring protons 6.1, 5.05 ppm while the phenyl ring protons 7.61 ortho to carbon bearing Br substituent, 6.67, 7.21, 6.65 ppm. for the next protons the value of 6.65 ppm. is for proton of the ring adjacent to the nitrogen attachment.

3.1.4. *Compound (8) where Ar is (p-Amino phenyl)*

This compound showed the following resonating signals : 8.1, 8.02 , 7.54 , 7.4 , 7.64 , 6.9 ppm. for 8, 5, 6, 7 and 4, 3 protons respectively. Oxazine protons showed two signals (with and opposite side of ring plane) at 6.1, 6.05 ppm. for CH_2 between N, O atoms and near N atom respectively. The phenyl protons appeared as two types of protons ; near nitrogen oxazine attachment at 6.1, 6.05 ppm, near NH_2 on both sides 6.45, 6.46 ppm. while the phenyl NH_2 protons resonated at 5.5.

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3.1.5. *Compound (9) where Ar is (O-Methyl, P-Nitro phenyl)*

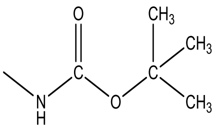
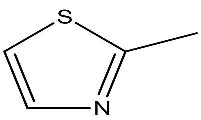
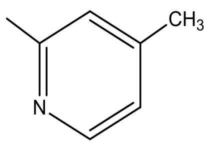
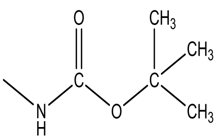
This compound was also gave 3 types of protons of the NMR spectra of naphthyl ring protons resonating at 8.1, 8.02, 7.54, 7.41, 7.65, 6.91 ppm. for 8, 7, 6, 5 and 3, 4 protons . The oxazine ring protons were resonating at 5.0, 6 ppm . for CH_2 near N atom and between N, O atoms respectively.

Phenyl ring protons of two types resonating at 7.89, 7.87 ppm. near NO_2 group, 6.0 ppm. near nitrogen attachment of the oxazine ring , CH_2 of oxazine near nitrogen 5.0 ppm, 6.1 ppm. for the CH_2 protons of the oxazine between N, O atoms while the protons of the phenyl ring appeared at 2.1 ppm.

3.2. *N-substituted, Methyl or phenyl Benzoxazine - 4 - One Compounds (11-14)*

The detail of IR data for these compounds were shown in Table (4).

Table 4. IR data for compounds (11-14).

Comp. No.	**X**	**IR υ cm^{-1} (neet)**						
Y		**N-H**	**Ar C-H**	**Alph C-H**	**C = O**	**C = N**	**Ar C = C, C— — —C**	**C-N Others**
11. CH$_3$	 *tert*-butyl carbamate	3233	3011	2977	1740	1668	1569 1506, 1435	1266 C-O 1151
12. CH$_3$	 2-thiazolyl	3279	3130	2924	1741	1689	1637 1512, 1445	1257
13. CH$_3$	 4-methyl-2- pyridinyl	3271	3031	2810	1671	1585	1585, 1500, 1428	1289
14. -Ph	 *tert*-butyl carbamate	3326	3067	2977	1742	1639	1590 1507, 1436	1233 C-O 1153

The NMR spectra of some selected samples were characterized by the following resonating signals :

3.2.1. *Compound (11) 2-Mrthyl –N-t-butyl -4-Oxo Benzo -1, 3 – Diazino Carbamate*

The benzene ring protons were found at 8.12, ppm. for carbon 5 proton, 7.65, for carbon 8 proton. The other protons of this ring were resonated at 7.86, 7.65, 7.61 ppm for protons at carbon ,7, 6 respectively, protons of the t-Butyl group appeared at 1.48ppm, 3.16 ppm forCH_3 NH at 10ppm. as can be seen in figure (2) below.

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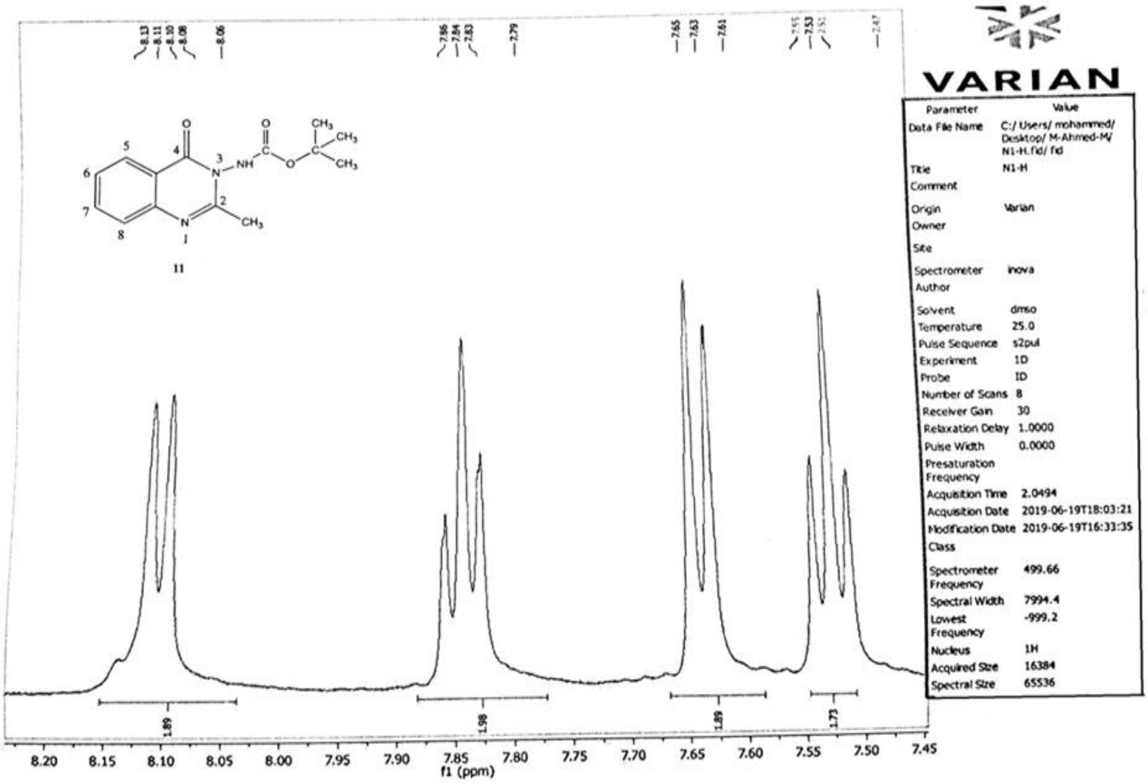

Fig. 2. ^{1}HNMR spectrum of compound (11).

3.2.2. *Compound (12) N-2 Thiozolyl-4 Benzo-1, 3-Diazine-4-One*

Benzene ring protons appeared at 8.4, 8.0, 7.62 ppm assigned to protons 2, 5, 8 and at, 7.7, 7.6ppm. for protons 7, 6 respectively. The thiozolyl protons appeared at 7.2 (near nitrogen proton), the other at 6.7 ppm, 3.18ppm. for CH_3 of Diazine ring protons and 2.35ppm. for pyridyl protons.

IV. Conclusions

We conclude from the above study that all the synthesized compounds were a really oxazine compounds. The study revealed that structure elucidation using the spectral data IR and NMR for the green techniques used for their synthesis that these compounds have an oxazine structure. The screening effects of the synthesized compounds will be studded and their results will be our next paper.

Acknowledgment

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