



## Synthesis of Some New Oxazine Compounds Derived from Phenols and Schiff Bases

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Received: April 23, 2021

Published: May 06, 2021

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### Abstract

The implication of heterocyclic compounds in most of the drugs used in the market and the timely need for changing drugs due to the drug resistance encourage researchers to synthesize new heterocyclic compounds especially those with oxygen and nitrogen heteroatoms which according to recent FDA reports. They form of 90 percent as anti-tumor agent and about 75 percent of the other diseases. Accordingly in the present research new oxazine compounds have been synthesized from two routes. The first one by grinding technique using formaldehyde, aromatic amines and methanolic ammonia to the synthesis of compounds (A1-5) as a one pot three components reaction system. The second route including the condensation of some aryl aldehydes with anthranilic acid (A6) then the resulting Schiff bases (A7-11) were cyclized using acetic anhydride into the corresponding oxazine compounds (A12-16) This type of reaction including the loss of a molecule of acetic acid molecules from (the solvent)anhydride. The anhydride containing the evolved acetic acid was used several times for some more reaction samples keeping its efficiency during the cyclization process. All the synthesized oxazines were studied using IR,<sup>1</sup> HNMR methods and are discussed.

**Keywords:** Synthesis; Oxazine Compounds; Phenols and Schiff Bases

### Introduction

As it was mentioned above concerning the importance of heterocyclic compounds as drug or co-drug compounds. Researchers always provides the market with new drug discovery research leading into new drug product. Oxazine compounds have proved to be used as drug according the works of many researchers. The synthesis of this type of heterocyclic compounds were achieved from different precursors, Either from anthranilic acid and its derivatives by ring closure either by acetic anhydride [1,2] or by chloro acetyl chloride [3] or succinic anhydride [3] or by alkyl chloro acetate [4] and ethyl ester derivatives [5] for example cyano ethyl ester. There were another methods for the synthesizing of oxazine compounds from other than anthranilic acid [6-11] among these precursors are the amido salicylate [12,13] cyclized by different reagents [14-17] some were cyclized using Vilsmeier-Haack reac-

tion. The cyanate derivative were also cyclized into oxazine [18-21]. It was reported in the literature that cyanate derivatives of anthranilic acid when allowed to react with amino acid esters afforded the quinazoline derivatives and these compounds showed a biological effects in which the water solution of these compounds had HLE and human sputum elastase activities [22,23]. The above work encourage many researchers to develop new synthetic pathways in synthesizing this type of heterocyclic compounds. So Anilkumar. R. has published the synthesis of some oxazine compounds from anthranilic acid. These compounds have showed anti-inflammatory activities [24]. Osman and his co-workers have synthesized oxazine compounds from anthranilic acid containing sulfonic ester moiety, These compounds have been tested against *Bacillus Thuringensis* and *Klebsiella Pneumonia* and showed remarkable activity against these micro organisms [25]. James D. Patronea and his co-workers

have prepared 4-Bromo-2-(3-(N-(3,4-dichlorophenyl) sulfamoyl)-4-methyl benzamido) benzoic which is a derivative of anthranilic acid. This compound was found to be active toward inhibition the Replication of Protein A (RPA) which is specific in distribution of protein-protein interaction that make them as therapeutic cancer target [26]. Guhufran has synthesized aryloxy oxazines from anthranilic acid. She tested these compounds against Gram +ve and Gram -ve bacteria and got excellent screening effects [27,28]. Among the studied oxazines derived from phenols are the work of Zuhail et-al. whom they prepared oxazines and studied their medical applications [29]. In 2014 Mathew and co-workers have prepared cromino oxazine from hydroxyl cromine and 7-hydroxy 4-methyl-2- thio coumarin and screening these compounds against some micro organism *in vivo* and *in vitro* studies [30]. Fadia and here co-workers have synthesized some coumarin compounds from resorcinol and ethyl aceto acetate using pole styrene sulfonic acid Amberlyst-15) as catalyst via Pechmann condensations [31]. Monar and co-workers have synthesized some coumarin derivatives and studied Antioxidant Activity Using ABTS Inhibition, their protective activity against DNA damage induced by the bleomycin-iron complex [32].

Pradeep K., *et al.* have synthesized some 1,3-oxazine compounds, These compounds were used in the synthesis of Cephalandole A an anti-cancer indole type compounds with 80% yield [33]. Dhafer, *et al.* recently have published a review on the synthesis and biological applications of oxazine compounds [34]. Çigdem Özen and co-workers have studied the action of some 1,4-oxazines as DNA strand repairing agent [35]. 84. S. Ondrej and H. Richard have studied poly(oxazine)s of phenolic precursors and the found that this polymer can be used as drug carrier an alternative PEG and poly (N-hydroxypropylmethacrylamide) usually used in the market nowadays [36] in our study we used two different methodologies in the synthesis of oxazine compounds aiming to study there biological effects in our drug discovery program.

## Experimental

All melting points were uncorrected using electro thermal type SMP30 UK melting point apparatus. IR spectra were measured using Alpha (ATR) instrument. <sup>1</sup>HNMR spectra were recorded using Varian Agilent Type 499.53MHZ, DMSO as internal solvent. All chemical were supplied by Sigma- Aldrich and Fluka chemical companies. 7-hydroxy-4-methylcoumarin-8-carbaldehyde was prepared according to the well-known procedure [37]. 2-Chloro-

3-formyl quinolone was also prepared according to the well-established procedure [38].

## Synthesis of oxazine compounds(A1-5)

### General procedure

Following the same published procedure [39] Formaldehyd (0.2 ml), ZrOCl<sub>2</sub>. 8H<sub>2</sub>O, (0.2 mol., 5.8g), Aromatic amine (0.1mol) and Eugenol or 1-Naphtol (0.1 mol) were mixed together in ceramic mortar and pistil. The mixture were grinded for 30 minutes, dichloromethane about 25 mil. was then added. The organic layer was then separated, washed with brine then with water twice and dried over MgSO<sub>4</sub> anhydrous. Evaporation of the solvent affords the crude products of the titled compounds. Crystallization from ethanol gave pure product. The physical properties were listed in Table1.






Comp. No.	Ar.	Formula	M.Wt.	M.P.	Yield	Color
A1		C <sub>15</sub> H <sub>12</sub> N <sub>2</sub> SO	252	90	85	Dark gray
A2		C <sub>18</sub> H <sub>16</sub> NO <sub>2</sub> Br	374	95	60	Yellow
A3		C <sub>19</sub> H <sub>16</sub> N <sub>2</sub> O <sub>4</sub>	340	192	53	Yellow
A4		C <sub>18</sub> H <sub>14</sub> NO <sub>2</sub> Cl	321	175	93	Yellow
A5		C <sub>20</sub> H <sub>12</sub> N <sub>2</sub> O <sub>4</sub>	354	165	70	Dark brown

Table 1: Physical properties of compounds(A1-5).

## Synthesis of 2-carboxy aryldine aniline(A7-11)






### General procedure:

These compounds were synthesized following an elsewhere published procedure [40] with some modification on the method. So Aromatic aldehyde (0.01 mol.), anthranilic acid (0.01 mol.) were mixed together after that methanol (15 ml.) was then added and two drops of glacial acetic acid. The final mixture was refluxed for one hour. And monitored by TLC, solvent was evaporated under reduced pressure. The resulted final product was recrystallized. The physical properties were shown in Table2.






## Synthesis of compounds (A12-16)

The products of the previous method was dissolved in acetic anhydride, then it was refluxed for 3hours. The solvent was removed

under reduced pressure and re used again for the rest of compounds. The final product was recrystallized from methanol. The physical properties of the final compounds were shown in Table 3.

Comp. No.	Ar.	Formula	M.Wt.	M.P.	Yield	Color
A7		C <sub>15</sub> H <sub>13</sub> NO <sub>4</sub>	271	133	75	Light orange
A8		C <sub>15</sub> H <sub>13</sub> NO <sub>3</sub>	255	110	80	White
A9		C <sub>17</sub> H <sub>13</sub> NO <sub>3</sub>	311	185	70	Black
A10		C <sub>17</sub> H <sub>11</sub> N <sub>2</sub> O <sub>2</sub> Cl	292	193	56	Light brown
A11		C <sub>12</sub> H <sub>8</sub> NO <sub>2</sub>	199	210	76	Dark purple

**Table 2:** Physical properties of compounds(A7-11).

Comp. No.	Ar.	Formula	M.Wt.	M.P.	Yield	Color
A12		C <sub>17</sub> H <sub>14</sub> NO <sub>6</sub>	328	140	67	Dark brown
A13		C <sub>17</sub> H <sub>14</sub> NO <sub>4</sub>	296	175	72	White
A14		C <sub>20</sub> H <sub>13</sub> NO <sub>5</sub>	312	155	81	Light brown
A15		C <sub>19</sub> H <sub>12</sub> N <sub>2</sub> O <sub>3</sub> Cl	333	158	65	Dark brown
A16		C <sub>14</sub> H <sub>10</sub> NO <sub>3</sub>	240	97	77	Very dark purple

**Table 3:** Physical properties of compounds(A12-16).

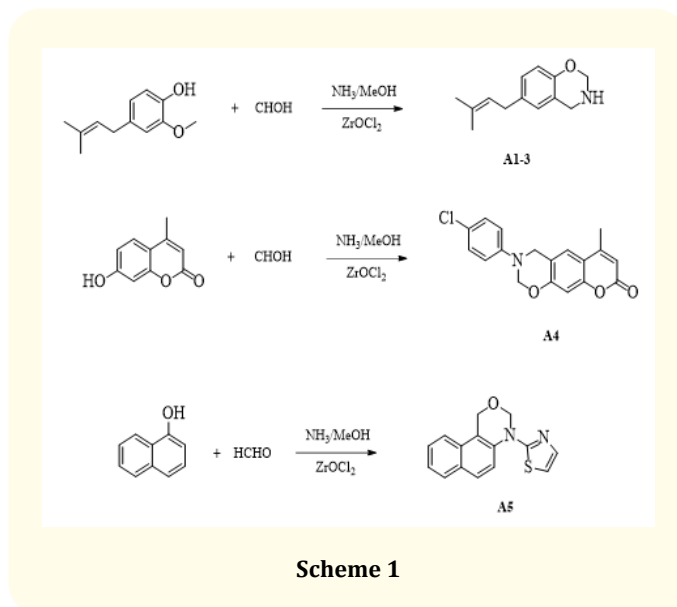
## Results and Discussion

Using grinding technique compounds (A1-5) were prepared Scheme1 and were characterized by the combination of IR and <sup>1</sup>H NMR methods as follows:

N-4-Nitro phenyl-6- [(1-propenyl)-7-methoxy] [3,-e] benzoxazine A1

IR cm<sup>-1</sup>: 1600,1529 for C=C Aromatic, 1262, 1142 C-O-C, 1498, 1230 for asym and sym. stretch for NO<sub>2</sub>, <sup>1</sup>HNMR(ppm); 3.3(d,2H) for eugenol aliphatic protons, 4.7,5 (d,t,2H) alkene protons, 3.78

(s,3H) OCH<sub>3</sub>, 4.9, 6(d of d 4H) AB aromatic., 6.79(s,2H) aromatic, 8.02-8.1(d,2H) AB pro tons near NO<sub>2</sub> group.



N-2-Nitrophenyl-6- [(1-prpppylenyl)-7 methoxy [3,1-e] benzoxazine A2

IR cm<sup>-1</sup>: 1611,1590,1505 for C=C Aromatic,1136, 1197 f or C-O-C, 1440, 1277 for aSym and sym. stretch forNO<sub>2</sub>, <sup>1</sup>HNMR(ppm); 3.3(d,2H) of eugenol,3.7(s,3H) of OCH<sub>3</sub>, 4.6(s,2H) for CH<sub>2</sub>N of Oxazine 4.7(2H) of CH<sub>2</sub> eugenol, 6.7(s,2H) for OCH<sub>2</sub>N of oxazine, 7.1-7.7(m,4H), 7.73(s,d,2H) aromatic protons and ortho protons to the NO<sub>2</sub> group respectively.

N-2-Bromophenyl-6- [91-propenyl-7-mothoxy] [3,1-e]benzoxazine A3

IR cm<sup>-1</sup>: 3011 for C-H, 1617 for C=C, 16051 C=C, 1507 for C=C Aromatic, <sup>1</sup>HNMR(ppm); 3.32 (d,2H) CH<sub>2</sub> of eugenol aliphatic protons, 3.3 (s,3H) OCH<sub>3</sub>, 4.9(t,1H) olefinic proton, 4.7 5and5 (t,2H) for olefinic CH<sub>2</sub> protons.

N-4-Chlorophenyl-6-(3-methyl) [3,1-e] Cumarinyl oxazine A4

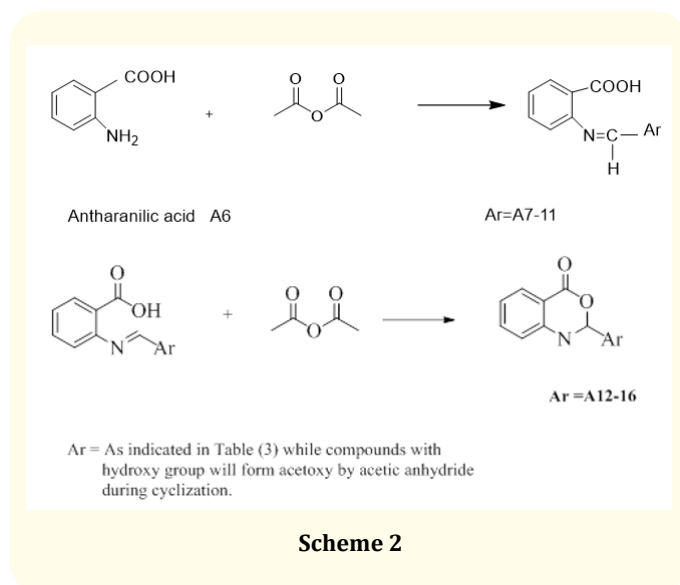
IR cm<sup>-1</sup>:3080 forC-H,1792 for C=O lactone, 1662 for C=C, 1596, 1541 for C=C Aromatic, 1451, 1260 for asym and sym. NO<sub>2</sub>, 1388, 1260 for C-O-C, 1213 for C-N, <sup>1</sup>HNMR(ppm); 2.3 (s,3H) CH<sub>3</sub>, 2.6(s,2H) C<sub>5</sub> of coumarin ring, 4.8(s,2H) C4 oxazine ring, 6.13(s,2H)

C<sub>2</sub> oxazine, 7.13,7.12 (d,2H) A protons Of AB system, 6.8, 7.0(d,2H) of B type protons.

N—Thiazolyl [3,1-e [naphthaoxazine] A5

IR cm<sup>-1</sup>: 3022 for C-H, 1647, 1635 for C=N, 1596, 1577 for C=C aromatic,1318 for C-N, 752 for C-S, <sup>1</sup>HNMR(ppm); 3.35(s,2H) - CH<sub>2</sub>N, 4.92(s,2H) for - OCH<sub>2</sub>, 6.5, 6.8(d,2H) thiazole, 6.88-7-8(m,6H) aromatic.

Schiff bases compounds A7-11, Scheme 2. were characterized by the main IR absorption peaks at 1605 cm<sup>-1</sup> for aromatic, C=C aromatic and at 1330 cm<sup>-1</sup> for C-O.



Compounds A 12-16 as shown above in scheme 2. were characterized as follows :

N-Acetyl-2-(2-methoxy phenyl) [3,1-e] benzoxazine-4-one A12

IR cm<sup>-1</sup>: 1771, C=O lactone 1684 for C=O Amide, 1646 for C=O amide, 1600, 1541 for C=C Aromatic, 776 for C-Cl, <sup>1</sup>HNMR(ppm); 2.1 (s,3H) for CH<sub>3</sub>CO, 2.3(s,3H) for CH<sub>3</sub>COO, 3.8(s,3H) for OCH<sub>3</sub>, 6.9, 7.13, 7.4(d and singlet) 3H of vanillin residue protons, 7.6,7.9 and 7.99(m,4H) aromatic protons of benzoxazine ring.

N-Acetyl-2-(methoxy phenyl-2-yl) [3,1]benzoxazine -4-one A13

IR cm<sup>-1</sup>: 3056 for C-H, 1685 for C=O lactone, 1653 for C=O amide, 1606, 1540 for C=C aromatic, 1143 for C-O, <sup>1</sup>HNMR(ppm); 2.1(s,3H) for CH<sub>3</sub>CON, 2.3(s,3H), 3.17(s,3H) for OCH<sub>3</sub>, 7.1-7.9(m,7H) aromatic, 8.4 (s,1H) C<sub>2</sub> of oxazine ring proton.

N-acetyl-2- [5-methyl-7-acetoxy coumarin-8-yl] [3,1benzoxazine-2-one A14]

- IR cm<sup>-1</sup>: 2926 for C-H, 1792 for C=O lactone, 1746, 1716 for ester, 1696 for C=O amide, 1600, 1540 Aromatic, <sup>1</sup>HNMR(ppm);
- 1.9(s,3H) CH<sub>3</sub>CON, 2.3(s,3H) for - CH<sub>3</sub>, 2.4(s,3H) for CH<sub>3</sub> COO, 6.43(d,1H) C<sub>3</sub> of coumarin proton, 7.1(d,1H) for C<sub>4</sub>, 7.4-8 (m,6H) Aromatic.

N-Acetyl-2-(2-Chloro quinolin-2-yl) [3,1-e] benzoxazine-4-one A15

3056 for C-H, 1733 for ester, 1668 for C=O amide, 1637 for C=N, 1606, 1507 for C=C aromatic, 788 f or C-Cl, <sup>1</sup>HNMR(ppm); 2.1(s,3H) for CH<sub>3</sub>CO, 7.1-8 (m,9H) aromatic, 8.47 (s,1H) for C<sub>2</sub> oxazine ring.

N-Acetyl-2-(2-fury) [3,1]benzoxazine-4-one A16

IR cm<sup>-1</sup>: 2927 for C-H, 1771 for C=O lactone, 1665 for C=O amide, 1490, 1608 for C=C Aromatic, 1339, 1145 for C-O-C, <sup>1</sup>HNMR; 2.2(s,3H) CH<sub>3</sub>CO, 6.6,6.9 (d,2H) furan protons, 7.54(d,1H) furan proton, 7.64-7.9 (m,4H) aromatic, 8.0(s,1H) for oxazine protons.

It is with to note that this work is extension to our previous work [44-46]. So adding new moiety for oxazine ring which is vanillin and nitrogenous residue will might increase the biological effects. We know that vanillin itself known to have antioxidant properties and oxazines also known to have versatile biological applications so making a combination of both may cause to improve the therapeutic impact of this type of compounds.

## Conclusions

In conclusion to the above work it is clear that using one pot three component system and two steps cyclization reaction of anthranilic acid with some aromatic aldehydes resulted into the formation of new oxazine derivatives. The IR and <sup>1</sup>HNMR studies of the above studied compounds revealed it formation through their structures confirmations. The other step of study will be their biological study which is our next goal.

## Acknowledgement

The authors would like to thank the Ministry of higher and research, university of Mosul and dean of our college for providing the facilities to do this work which is part of Asmaa thesis.

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**Volume 2 Issue 6 June 2021**

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