



## Synthesis of Some Oxazine Compounds Derived from TDI and Schiff Bases

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### Abstract

It is known from ongoing research on heterocyclic compounds that these compounds are used as drug and drug carriers, According to FDI reports that these compounds forms 90% drug for cancer and 75% drugs for different diseases. It was also known from our studies on oxazine compounds that this type of heterocyclic compounds had versatile application in medicine. In this study, new 3,1-Benzoxazine compounds (S7-12) were prepared by cyclization reaction of some 2-(benzylidene-amino) benzoic acids (S1-6) with Toluene diisocyanate (TDI) under reflux conditions in chloroform. The structure of the synthesized compounds were confirmed by IR, <sup>1</sup>HNMR spectral studies.

**Keywords:** Oxazine Compounds; Insects; Fungi; <sup>1</sup>HNMR

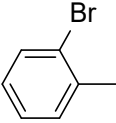
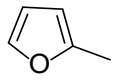
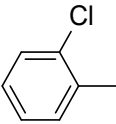
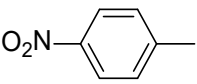
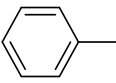
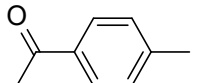
### Introduction

It is well established that Oxazine compounds are quite useful and effective in pharmaceutical and other medical areas, These compounds prove to have anti-bacterial [1,2], anti-plasmodia [3], anti-cancer [4], anti-depressant [5], ant-toxicity [6], and anti-neoplastic effects [7]. The oxazine compounds are considered to be a significant type of heterocyclic compounds toward drug and drug discovery programs. The first time that the oxazine compounds were synthesized was in the year of 1944 by Holly and Cope using the traditional Mannich condensation of phenol, formaldehyde and amines [8]. Other researchers are currently interested in the synthesis using other methods such as solvent-free synthesis [9-11], hetero Diels-alder reaction [12], Some researchers have used induced condensation reaction for the synthetic reaction of this type of compounds [13,14] and cyclization reaction with chalcones [2]. Many vital and significant factors, such as reactant structures, sol-

vent-effect [15], reaction temperature [16], and reaction duration time [17] play a decisive role in the synthesis process and have an impact on the properties of these types of compounds. Moreover, all the previous studies of this type of compounds are very valuable in the chemistry of natural products owing to the formation of acetal-glycoside in a plant [18], which acts as a plant's own factor of resistance against insects, pests, fungi and microbic diseases [19]. In accordance with the above-mentioned importance of this type of compounds, we have chosen, for this research, cyclization reaction as a method of preparation new oxazine derivatives from Schiff bases and isocyanates for the synthesis of series of these new oxazine compounds in our drug discovery program.

### Experimental

All melting points were uncorrected using thermal SMP30 UK melting point apparatus. IR spectra were recorded using Alpha

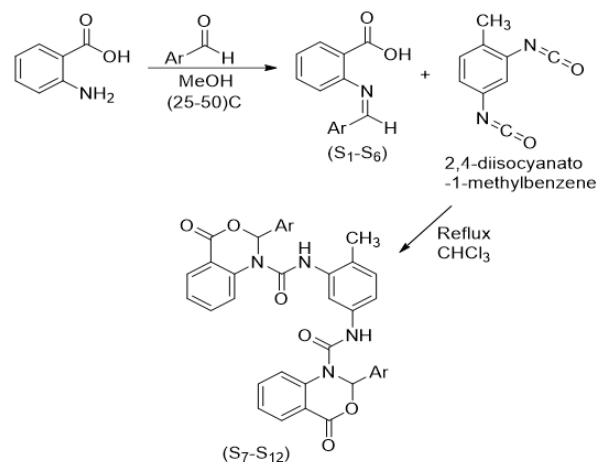
Comp. No.	Ar.	Molecular Formula	M.Wt gm/mol	M.P. (C)	Yield %	Colour
S <sub>1</sub>		C <sub>14</sub> H <sub>10</sub> BrNO <sub>2</sub>	304	95-97	75	Brown
S <sub>2</sub>		C <sub>12</sub> H <sub>9</sub> NO <sub>2</sub>	215	142-144	93	purple
S <sub>3</sub>		C <sub>14</sub> H <sub>10</sub> ClNO <sub>2</sub>	259	75-77	96	Brown
S <sub>4</sub>		C <sub>14</sub> H <sub>10</sub> N <sub>2</sub> O <sub>4</sub>	270	131-132	96	Brown
S <sub>5</sub>		C <sub>14</sub> H <sub>11</sub> NO <sub>2</sub>	225	67-68	97	purple
S <sub>6</sub>		C <sub>15</sub> H <sub>13</sub> NO <sub>3</sub>	255	141-143	70	brown

**Table 1:** Physical properties of compounds (s<sub>1-6</sub>).

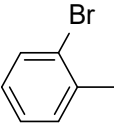
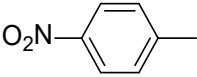
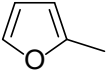
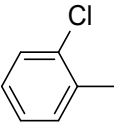
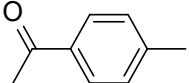
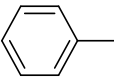
(ATR) instrument. <sup>1</sup>HNMR spectra were recorded using Varian Agilent 499.53MHZ instrument, DMSO as internal solvent. All chemical were supplied by sigma –Aldrich, BHD and Fluka companies.

#### General procedure for the synthesis of 2-carboxy arylidine aniline (s<sub>1-6</sub>) [20]

A mixture of (1 mmol) of an anthranilic acid and (1.2 mmol) of an aryl aldehyde in methanol was stirred for about 1 h. at room temperature. The solvent was removed under reduced pressure to give crude product which was washed with n-hexane and recrystallized from ethanol to afford the Schiff bases (S<sub>1-6</sub>) as pure compounds. Physical properties were listed in table 1.



**Scheme 1:** The synthetic pathway for the synthesis of compounds (S1-12).

Comp. No.	Ar.	Molecular Formula	M.Wt gm/mol	M.P. (°C)	Yield %	Color
S <sub>7</sub>		C <sub>37</sub> H <sub>26</sub> Br <sub>2</sub> N <sub>4</sub> O <sub>6</sub>	782.5	219 dec.	65	white
S <sub>8</sub>		C <sub>37</sub> H <sub>26</sub> N <sub>6</sub> O <sub>10</sub>	714.6	258-260	97	yellow
S <sub>9</sub>		C <sub>33</sub> H <sub>24</sub> N <sub>4</sub> O <sub>6</sub>	604	101-102	93	orange
S <sub>10</sub>		C <sub>37</sub> H <sub>26</sub> Cl <sub>2</sub> N <sub>4</sub> O <sub>6</sub>	693.5	97-98	71	brown
S <sub>11</sub>		C <sub>39</sub> H <sub>32</sub> N <sub>4</sub> O <sub>8</sub>	648	154-155	95	white
S <sub>12</sub>		C <sub>37</sub> H <sub>28</sub> N <sub>4</sub> O <sub>6</sub>	624.6	197-99	75	orange

**Table 2:** Physical properties of compounds (S<sub>7-12</sub>).

### General procedure for the preparation Bis[(2-Aryl-6H-1,2-dihydro-6-oxo[2,1-e](1,3) benzoxazine-1,1'-yl)]-2,4-diamido-toluene [21]

To a solution of (1.5 mmol) of Schiff bases (S<sub>1-6</sub>) and (2.5 mmol, 2.0 gm) of toluene diisocyanate in 1 ml of Chloroform the reaction mixture was refluxed for (3.0h). After the removal of the solvent under reduced pressure, the precipitate was washed with 2 ml of *n*-hexane (three times) and filtered to remove any traces of toluene Diisocyanate. The final product was washed with 10% NaHCO<sub>3</sub> and water then dried. The physical properties of the synthesized compounds were illustrated in table 2.

## Results and Discussion

### 2-carboxy arylidine aniline (s<sub>1-6</sub>)

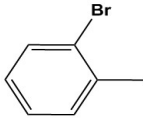
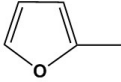
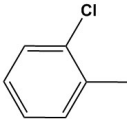
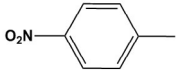
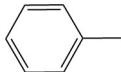
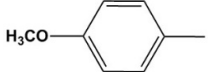
These compounds were synthesized using similar procedure [20] and were characterized by IR as shown in table 3. The fol-

lowing main absorption bands ( $\nu_{\max}$  cm<sup>-1</sup>) at (1585-1654) for C=N, (1402-1626) for C=C, C=C Aromatic, (1619-1718) for C=O while O-H appeared at (3328-3424) other stretching absorptions can be seen in the following Table. The NMR spectral data were indicated in table 4.

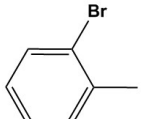
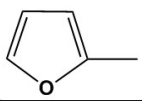
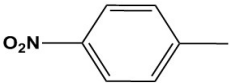
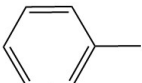
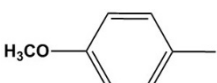
### Bis[(2-Aryl-6H-1,2-dihydro-6-oxo[2,1-e](1,3) benzoxazine-1,1'-yl)]-2,4-diamidotoluene

These compounds were synthesized by cyclization of Schiff bases with toluene diisocyanate using similar procedure<sup>(21)</sup> and were characterized by IR and showed the following main absorption bands ( $\nu_{\max}$  cm<sup>-1</sup>) at (1216-1260) for C-N, (1023-115) for C-O-C, (1446-1661) for C=C, C=C. (1661-1770) for C=O While N-H at (3248-3327) other band were shown in table 5.

The NMR spectra were discussed in details as shown in the following table 6.

Comp. No.	Ar.	IR $\nu$ $\text{cm}^{-1}$				
		C=C Ar.	C=N	C=O	O-H	Others
S <sub>1</sub>		1402,1495	1588	1653	3369	.....
S <sub>2</sub>		1404,1579	1609	1651	3373	.....
S <sub>3</sub>		1464,1513	1585	1619	3424	C-Cl/657
S <sub>4</sub>		1496,1569	1623	1654	3372	N-O sym/1311 Assy/1443
S <sub>5</sub>		1448,1573	1612	1663	3358	.....
S <sub>6</sub>		1466,1626	1654	1718	3328	C-O/1084

**Table 3:** IR spectral data for compounds (S<sub>1-6</sub>).

Comp.No.	R	<sup>1</sup> HNMR (PPM) DMSO-d <sub>6</sub>
S <sub>1</sub>		7.2-7.4 (d, 1 <sup>st</sup> , 2 <sup>nd</sup> , 3 <sup>rd</sup> , 14 <sup>th</sup> , 15 <sup>th</sup> -H); 7.60-7.62 (d, 16 <sup>th</sup> -H) 7.71-7.72 (d for 13 <sup>th</sup> -H) 7.88-7.89 (d, 6 <sup>th</sup> S -H) 8.62 (s, 1H) CH = N; 10.2 (S, 1H) OH
S <sub>2</sub>		6.9-6.92 (d, 14 <sup>th</sup> -H) 7.0-7.01 (d, 13 <sup>th</sup> -H) 7.26-7.33 (m, 1 <sup>st</sup> , 2 <sup>nd</sup> , 3 <sup>rd</sup> -H) 7.60-7.61 (s, 15 <sup>th</sup> -H) 7.86-7.88 (m, 6 <sup>th</sup> -H); 8.37 (S, 1H) CH=N; 9.5- 9.6 (S, 1H) OH
S <sub>3</sub>		7.26-7.34 (d, 1 <sup>st</sup> , 2 <sup>nd</sup> , 3 <sup>rd</sup> , 14 <sup>th</sup> , 16 <sup>th</sup> , -H) 7.86-7.89 (AB q for 13 <sup>th</sup> , 17 <sup>th</sup> -H) 8.16-8.19 (6 <sup>th</sup> -H); 8.71 (S, 1H) CH=N; 9.5 (S, 1H) OH
S <sub>4</sub>		7.26-7.38 (m, ph-H) 7.39-7.7 (d, 1 <sup>st</sup> 2 <sup>nd</sup> 3 <sup>rd</sup> -H) 7.89 (6 <sup>th</sup> -H); 8.6 (S, 1H) CH=N, 10.82 (S, 1H) OH
S <sub>5</sub>		3.78 (S, 3H) CH <sub>3</sub> ; 6.95 -6.98 (14 <sup>th</sup> 16 <sup>th</sup> -H) 7.26-7.34 (1 <sup>st</sup> , 2 <sup>nd</sup> , 3 <sup>rd</sup> -H) 7.71-7.74 (ABq, 13 <sup>th</sup> , 17 <sup>th</sup> -H) 7.78-7.789 (6 <sup>th</sup> -H) 8.70 (S, 1H) CH=N, 10.02 (S, 1H) OH

**Table 4:** <sup>1</sup>HNMR data for compounds (S<sub>1-6</sub>).

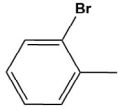
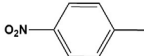

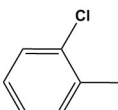
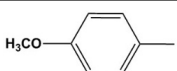
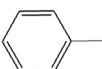
Comp. No.	Ar.	IR $\nu$ $\text{cm}^{-1}$					
		N-H	C=O	C-O-C	C-N	C=C Ar.	Others
S <sub>7</sub>		3327	1776	1023,1266	1260	1467,1573	C-Br/635
S <sub>8</sub>		3282	1765	1062,1150	1266	1446,1603	N-O sym/1380 Assy/1526
S <sub>9</sub>		3292	1767	1041,1154	1216	1447,1661	.....
S <sub>10</sub>		3267	1704	1071,1101	1219	1454,1495	C-Cl/633
S <sub>11</sub>		3294	1661	1044,1145	1292	1448,1605	.....
S <sub>12</sub>		3248	1770	1029,1098	1239	1467,1610	.....

Table 5: IR spectral data for compounds (S<sub>7-12</sub>).

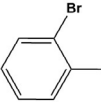
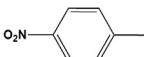
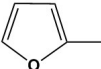
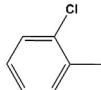
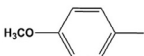
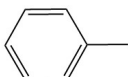
Comp. No.	R	<sup>1</sup> HNMR (PPM) DMSO-d <sub>6</sub>
S <sub>7</sub>		2.47 (S, 3H) CH <sub>3</sub> ; 7.27-8.13 (m, 18H, 5Ar-H and CH), 7.8 (S, 2H) 2NH
S <sub>8</sub>		2.34 (S, 3H) CH <sub>3</sub> ; 7.14-8.18 (m, 19H, 5Ar-H and CH)
S <sub>9</sub>		2.22 (S, 3H) CH <sub>3</sub> ; 6.4 -7.98 (m, 17H) 3Ar -H, 2furfuryl ring and CH); 7.74 (S, 2H) NH
S <sub>10</sub>		2.46 (S, 3H) CH <sub>3</sub> ; 7.14 -7.74 (m, 19H, 5Ar-H and CH); 7.99 (S, 2H) 2NH
S <sub>11</sub>		2.446 (S, 3H) CH <sub>3</sub> ; 3.77 (S, 3H) OCH <sub>3</sub> ; 6.89-7.74 (m, 19H, 5Ar-H and CH); 7.98 (S, 2H) 2NH
S <sub>12</sub>		2.54 (S, 3H) CH <sub>3</sub> ; 7.14 -7.75 (M, 21H, 5Ar-H and CH) 7.99 (S, 2H) 2NH

Table 6: <sup>1</sup>HNMR data for compounds (S<sub>7-12</sub>).

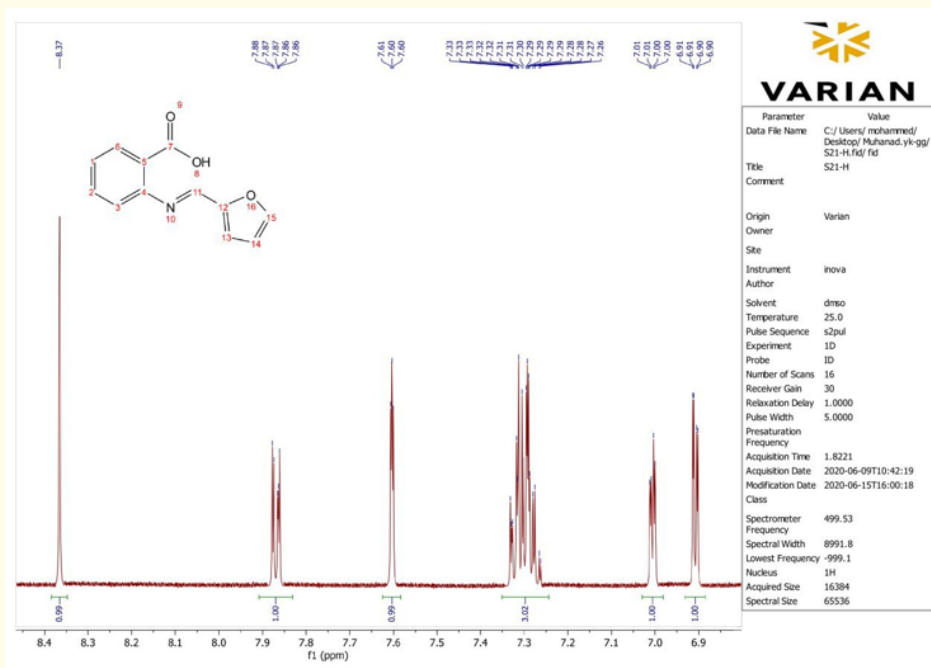


Figure 1: <sup>1</sup>H NMR of compound (S2).

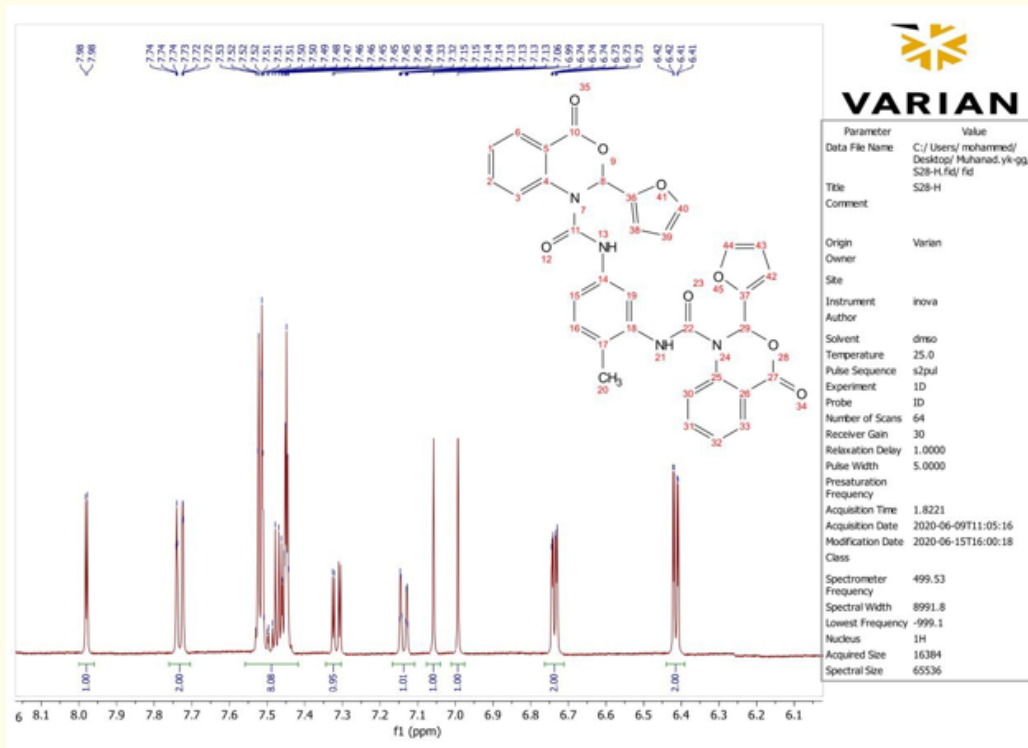


Figure 2: <sup>1</sup>H NMR of compound (S9) aromatic region.

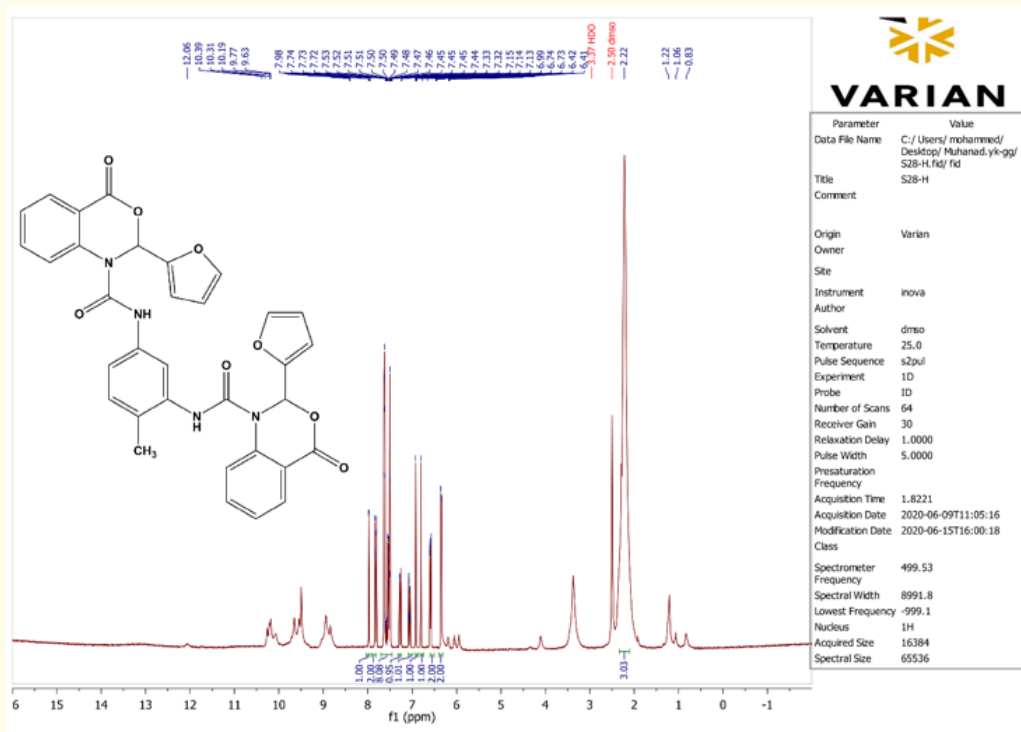


Figure 3:  $^1\text{H}$ NMR of compound ( $S_9$ ).

## Conclusion

We conclude from the above study that Oxazine compounds were successively synthesized from the reaction of the corresponding schiff based of anthranilic acid schiff base with TDI according to the given spectral data. These compound will be studied for their biological activity based on our drug discovery program in our upcoming paper.

## Acknowledgement

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