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Synthesis of Some Heterocyclic Compounds Derived from Ortho-Carboxybenzaldehyde

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Abstract

In this work different heterocyclic compounds derivatives were synthesized using ortho-Carboxybenzaldehyde as a starting material which reacted with different aromatic amines to produce Schiff bases. These Schiff bases introduced in three types of reactions using different reagents (Chloroacetylchloride, Thio acetic acid, Malic anhydride and Phthalic anhydride) to give the target heterocyclic compounds four, five and seven heterocyclic compounds derivatives. The structure of these compounds identified by FT-IR and some of them by ^{1}H-NMR spectra

Keywords: OrthoCarboxybenzaldehyde; Schiff Base; Chloroacetylchloride; Thio acetic acid.

1. Introduction

Schiff bases are considered as a very important class of organic compounds. Which have a wide application in many biological aspects [1]. So, Schiff bases, due to their conjugation with aromatic system give an important group of stabilized imines [2].

In the present work, reaction of aromatic aldehyde and aromatic amines afforded there corresponding Schiff bases which react later with different reagents to give heterocyclic compounds.

four membered ring azitidinones derivatives are an important group of heterocyclic compounds that have a wide range of biological activities it act as anticancer [3], antimicrobial [4], anti-bacterial, anti-fungal [5] and anti-inflammatory [6]. These compound were prepared through the reaction of Schiff bases with chloroacetylchloride.

The second type of the synthesized compounds is thiazolidine derivatives which have a broad spectrim of biological activities [7]. They are prepared by the reaction of Schiff bases with thioglycolic acid.

The third type of the target heterocyclic compounds are the oxazepine derivatives which synthesized through the reaction of Schiff bases with malic anhydride and phthalic anhydride have been found to exhibit biological activities as antibacterial [8] , antifungal [9], antiepileptic [10] and anticancer [11].

2. Experimental

All reagent and compounds are from fluka and BDH. Melting points are measured using open capillary tube on Stuart SMP30 Melting point apparatus and they were uncorrected. The purity of the compounds were confirmed by TLC using silica gel and visualized in iodine. FT-IR spectra, Fourier transform infrared SHIMADZU (8400) in the region between 4000-400 cm^{-1} by using potassium bromide (KBr disc). ^{1}H-NMR spectra was carried out by Bruker ultra-shield 400 MHz origin: Switzerland and are reported in ppm (δ) DMSO-d_6 was used as a solvent with TMS as an internal standard.

2.1. General procedure for the synthesis of Schiff bases (synthesis *of 2-{(z)-[4-substituted phenyl)imino] methyl}benzoic acid 1-6) [12]*

A mixture of ortho carboxybenzaldehyde (1.50 g, 0.01 mole) and substituted amines (0.01 mole) in 20 ml methanol. Two drops of acetic acid was added to the mixture. The mixture was refluxed for 6 hours (monitored by TLC) the solvent system is (4:1) benzene: MeOH, After completion, filtered the hot mixture and the mixture was evaporated to its half volume, then let it overnight. Solid separated, which was filtered off washed with cold water and recrystallized from ethanol. Note the compound 6 use the double of moles of ortho carboxybenzaldehyde. Table 1, Scheme 1

2.2. General procedure for the synthesis of azetidin-2-one compounds (2-[3- chloro-1-(4-substituted phenyl)-2-oxoazetidin-2-yl) benzoic acid 7-12 [13])

To a stirred solution of compound 1-6 (0.001mole) in 20 ml of dry 1,4 dioxane, triethylamine (0.05 ml, 0.001 mole) and chloroacetylchloride (0.1 ml ,0.001 mole) were added slowly drop wise with stirring at 0-20 ºC. The reaction mixture was kept at room temperature for 30 minutes. Then reflux for 8 hrs (monitored by TLC) the solvent system is (4:1) benzene : MeOH**,** the residue obtained after removal

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of solvent under vacuum poured into 50 ml ice-cold water with stirring, solid separated filtered off recrystallized from ethanol. Note the compound 12 use the double of moles of triethylamine and chloroacetyl chloride. Table 2, Scheme 1

2.3. General procedure for the synthesis of **thiazolidine** *derivatives.* **(***2-[3-(4-substituted phenyl)-4-oxo-1,3-thiazolidine-2-yl] benzoic acid 13-18***) [14,15]**

(0.001 mol) of Schiff bases 1-6 in abs-ethanol (20 ml) was added (0.1 ml, 0.001 mole) of thioglycolic acid in presence of anhydrous zinc chloride (0.14 gm, 0.001 mole). The mixture was reflux for 10 hrs (monitored by TLC) the solvent system is (4:1) benzene: MeOH**,** After completion, the mixture poured into crushed ice, then treated with potassium carbonate with stirring to obtain the product, then filtered and recrystallized from ethanol. Note the compound 18 use the double of moles of thioglycolic acid.Table 3, Scheme 1.

2.4. General procedure for the synthesis of 1,3-oxazepine derivatives (***2-[3-(4-substituted phenyl)-4,7-dioxo-2,3,4,7-tetra hydro-1,3-oxazepin-2-yl] benzoic acid 19-30***) [16,17]**

In a round bottom flask placed a mixture of (0.001 mole) of Schiff bases 1-6 and (0.001 mole) of malic anhydride or phthalic anhydride in 20 ml of absolute Ethanol. The reaction mixture was refluxed for 15 hr. (monitored by TLC) the solvent system is (4:1) benzene: MeOH**,** Concentrated the mixture, then cooled. The product obtained, filtered off and recrystallized from ethanol. Note the compound 24 and 30 use the double of moles of malic anhydride and phthalic anhydride respectively. Table 4, Scheme 1

Table 1: physical properties of compounds 1-6

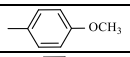
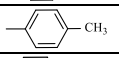
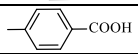
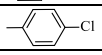
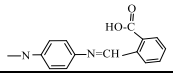
Comp. No.	Ar	M.P (°C)	Yield %	colour
1		131-133	61	silver
2		142-144	75	Brown
3		290-292	99	White
4		170-172	98	White
5		193-195	84	Yellow
6		272-274	96	White

Table 2: physical properties of compounds 7-12

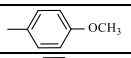
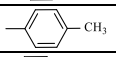
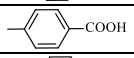
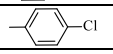
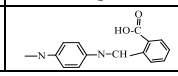
Comp. No.	Ar	M.P (°C)	*Yield %*	colour
7		146-148	58	White
8		86-88	47	Brown
9		203-205	60	White
10		154-156	55	White
11		120-122	41	Brown
12		249-251	59	White

Table 3: physical properties of compounds 13-18

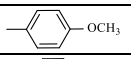
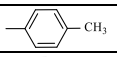
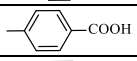
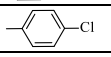
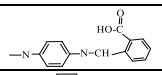
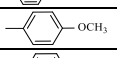
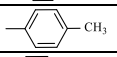
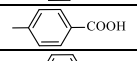
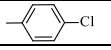
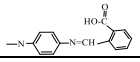
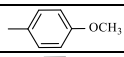
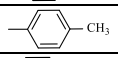
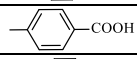
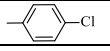
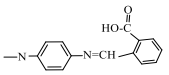
Comp. No.	Ar	M.P (°C)	Yield %	colour
19		172-174	56	Yellow
20		198-200	50	Yellow
21		264-266	49	Brown
22		202-204	60	Yellow
23		160-162	65	Yellow
24		279-281	48	White
25		148-150	49	Yellow
26		194-196	40	White
27		272-273	70	White
28		147-149	63	White
29		219-221	69	Yellow
30		242-244	73	Brown

Table 4: physical properties of compounds 19-30

Comp. No.	Ar	M.P (°C)	Yield %	colour
13		>300	42	Brown
14		106-108	52	Brown
15		155-157	60	White
16		270 dec	64	White
17		103-105	47	White
18		>300	67	White

3. Results And Discussion

Ortho Carboxybenzaldehyde is starting material used for synthesis of different Schiff bases 1-6. This starting material have two functional group, carboxyl group and aldehyde group. These two substituted groups may react to give two different product which depended on the condition of the reaction.[12]

The FT-IR spectra of Schiff bases 1-6 compounds showed an absorption appeared at (1602-1614) cm^{-1} for the new C=N group, and there are an absorption appeared at the rang of (1741-1766) cm^{-1} for the carbonyl of carboxyl group, and the OH group of acid appeared at (3306- 3462) cm^{-1}. We noticed that the aldehydic carbonyl was disappeared. Table 5, Fig.1, Fig.2, Fig.3

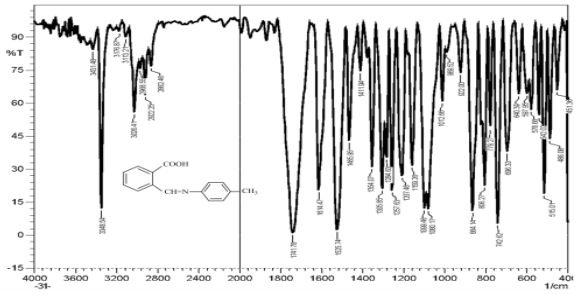


Fig. 1: FT-IR spectrum of compound 1

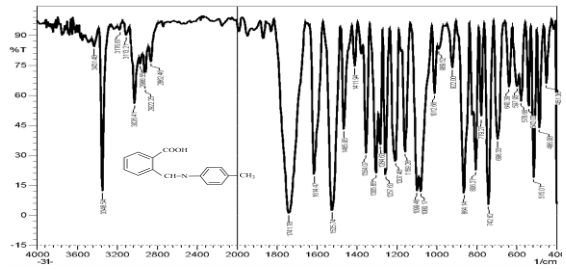


Fig. 2: FT-IR spectrum of compound 2

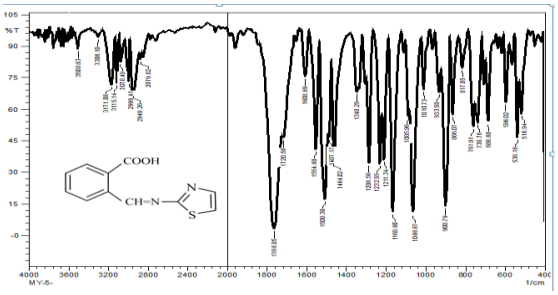


Fig. 3: FT-IR spectrum of compound 5

On the other hand, the ^{1}H-NMR spectra, we take the spectrum of compound 2 as a sample, there is a peak at (2.23) ppm for protons of methyl group, and there is a multiple peak at (6.88-7.69) ppm for aromatic protons, for the proton of CH=N group, we noticed it at (7.90) ppm, and there is another peak at (11.72) ppm for the OH group of carboxyl group, which disappeared when we added deuterated water. Table 9, Fig.12.

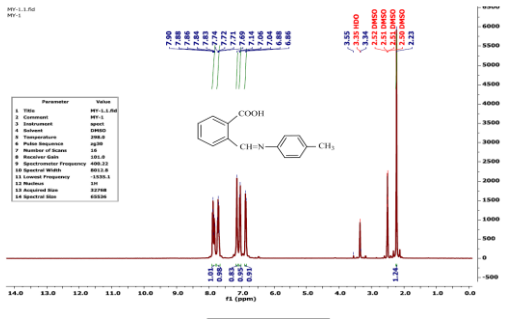


Fig. 12: ^{1}H-NMR spectrum of compound

The azetidine compounds 7-12 which have a four membered ring were elucidated on the bases of their spectral data. The FT-IR spectra showed an absorption at (746-770) cm^{-1} for C-Cl bond and there is absorption at (1314-1338) cm^{-1} for C-N group and There is an absorption at the rang of (1677-1701) cm^{-1} for carbonyl of carboxylic group, and another absorption at the rang of (1757-1774) cm^{-1} for a lactam carbonyl and the OH group of acid appeared at (3271- 3414) cm^{-1}. Table 6, Fig.4 , Fig. 5, Fig.6 .

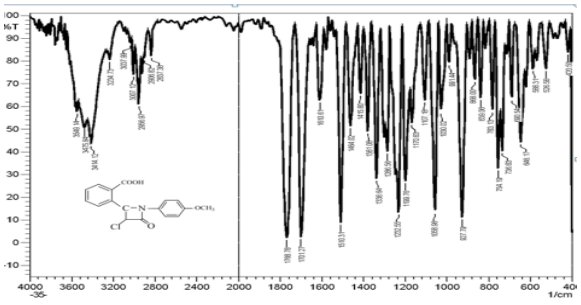


Fig. 4 : FT-IR spectrum of compound 7

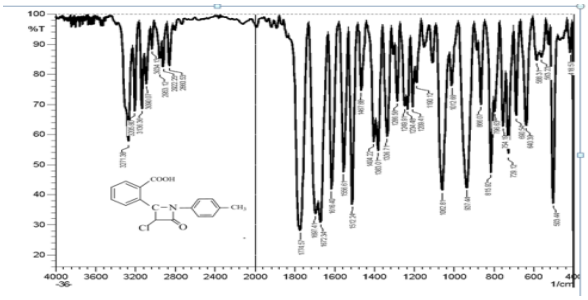


Fig. 5 : FT-IR spectrum of compound 8

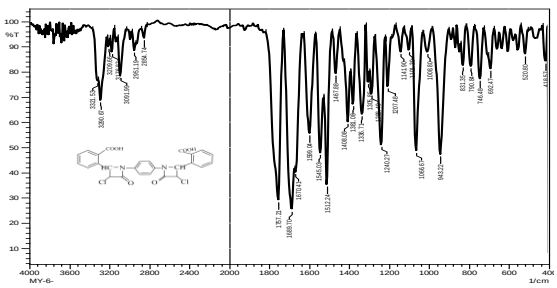


Fig. 6 : FT-IR spectrum of compound 12

For ^{1}H-NMR we take compound 7 as a sample for compounds 7-12. There is an absorption at (3.57) ppm for OCH_3 group and at (4.13) ppm for CH-Cl group, and at (6.76) ppm for CH-N group and for aromatic protons, they appeared at (7.52- 7.86) ppm. The hydroxy of carboxyl group, it appear at (12.74) ppm which disappeared when we added deuterated water. Table 9 Fig. 13

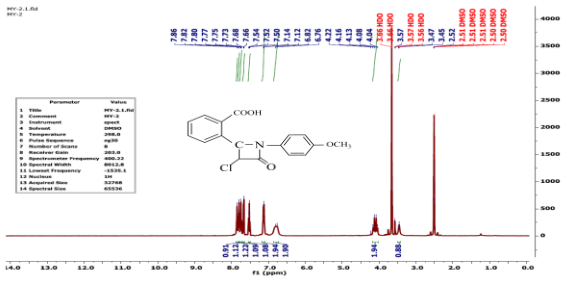


Fig. 13 : ^{1}H-NMR spectrum of compound 7

Thiazolidine derivatives compounds 13-18 which they are five membered rings have the spectral data as shown, FT-IR spectrum showed a new absorption at (704-777) cm^{-1} for C-S group, and another absorption at (1231- 1298) cm^{-1} for C-N group, cyclic carbonyl group, it appeared at (1703-1726) cm^{-1}, and carbonyl for the carboxylic group at (1734- 1770) cm^{-1} and the hydroxyl of carboxylic group appeared at (3279- 3429) cm^{-1}. Table 7, Fig.7, Fig.8

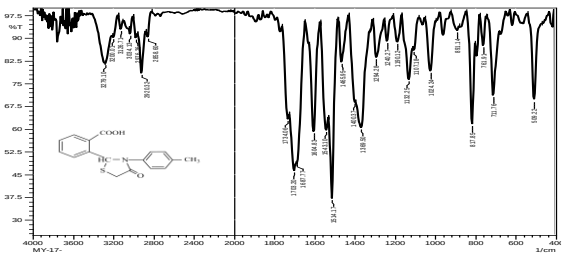


Fig. 7 : FT-IR spectrum of compound 14

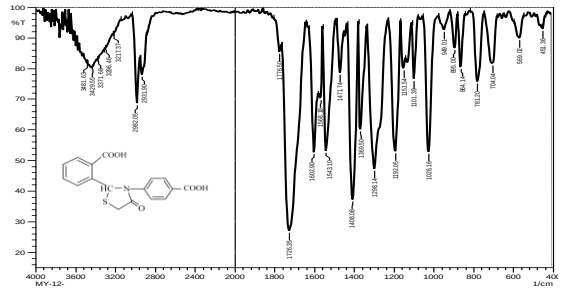
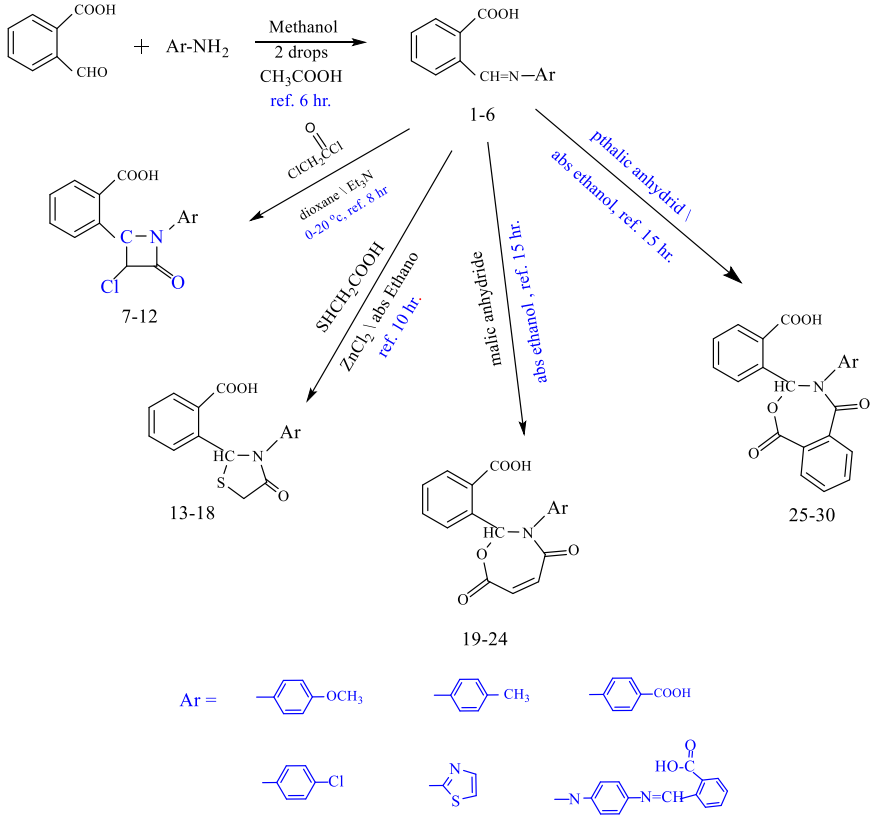


Fig. 8 : FT-IR spectrum of compound 15



Scheme 1: Synthesis of compounds 1-30

For ^{1}H-NMR spectrum, we take compound 15 as a sample for this type of compounds. There is an absorption at (3.98) ppm for S-CH_2 group, and another one at (4.04) ppm for CH-N group, aromatic protons appeared at (7.6-8.10) ppm and hydroxyl for carboxyl group at (10.14) ppm which disappeared when we added deuterated water. Table 9, Fig.14

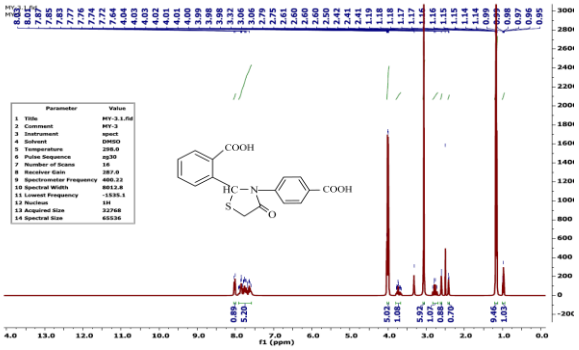


Fig. 14 : ^{1}H-NMR spectrum of compound 15

For 1,3-oxazepine compounds 19-30, which have seven membered rings, have spectral data as shown: FT-IR spectra showed a new band at (1159-1255) cm^{-1} for C-O-C group, and another band at (1651- 1708) cm^{-1} for lactam carbonyl group, another band at (1701-1739) cm^{-1} for carbonyl of carboxylic group, the band of lactone carbonyl group of oxazepine ring appeared at (1732- 1778) cm^{-1}, the last absorption was for hydroxyl of carboxylic group which appeared at (3261- 3456) cm^{-1}. Table 8, Fig.9, Fig.10, Fig.11

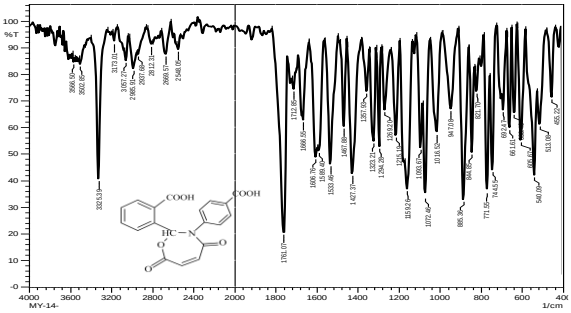


Fig. 9 : FT-IR spectrum of compound 21

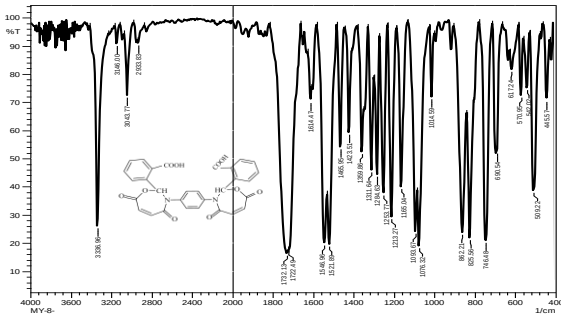


Fig. 10 : FT-IR spectrum of compound 24

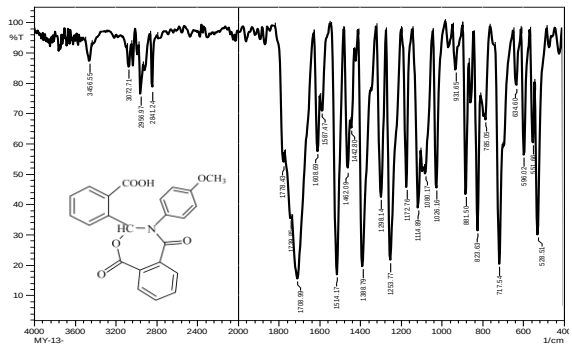


Fig. 11: FT-IR spectrum of compound 25

For ^{1}H-NMR spectrum for these compounds, we take compound 20 and compound 30 as a sample. For compound 20, we showed an absorption at (2.27) ppm for methyl group, and (6.29-6.45) ppm for (=CH) and (7.13-7.15) ppm for (CH=) and aromatic protons appeared at (7.50-7.53) ppm and (10.37) ppm for CH-N group,. The proton of hydroxyl of carboxylic acid appeared at (13.20) ppm. Fig. 15 . And the compound 30 there is an absorption at (4.27) ppm for CH-N, aromatic protons appeared at (6.95-7.98) ppm, and hydroxyl of carboxylic acid appeared at (11.51) ppm which disappeared when we added deuterated water. Table 9 Fig.16.

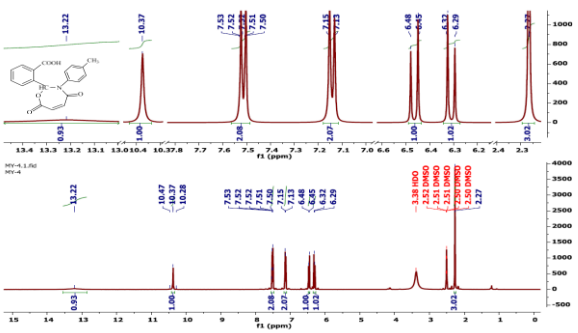


Fig. 15 : ^{1}H-NMR spectrum of compound

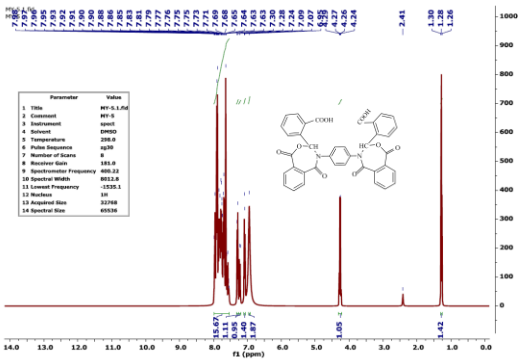


Fig. 16 : ^{1}H-NMR spectrum of compound

Table 5: showed IR spectral data for compounds 1-6

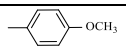
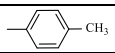
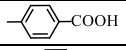
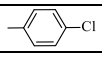
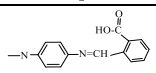
Comp. No.	Ar	IR (KBr) ν cm^{-1}			
		C=N	**C=O** acid	OH acid	Others
1		1608	1745	3462	1155 sym. 125z5 asym. for C-O-C
2		1614	1741	3348	
3		1604	1757	3325	
4		1602	1751	3325	764 for C-Cl
5		1608	1766	3306	686 for C-S
6		1608 1612	1755	3336	

Table 6: showed IR spectral data for compounds 7-12

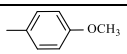
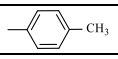
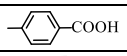
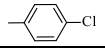
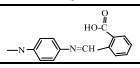
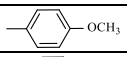
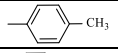
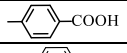
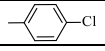
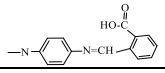
Comp.No	Ar	IR (KBr) ν cm^{-1}				
		C=O acid	C=O lactam	C-Cl	C-N	OH acid
7		1701	1768	754	1338	3414
8		1697	1774	754	1336	3271
9		1687	1770	767	1319	3404
10		1690	1767	756	1330	3400
11		1677	1760	770	1314	3408
12		1689	1757	746	1336	3290

Table 7 showed IR spectral data for compounds 13-18

Comp. No	Ar	IR(KBr) ν cm-^{1}				
		C=O ring	C=O acid	C-S-C	C-N	OH acid
13		1715	1753	743	1231	3290
14		1703	1734	761	1294	3279
15		1726	1776	704	1298	3429
16		1707	1770	754	1284	3403
17		1722	1760	770	1270	3330
18		1703	1765	777	1294	3360

4. Conclusion

In this study we are reported synthesis of different heterocyclic derivatives of azetiden, Thiazolidine and oxaazepin compounds. All these compounds were prepared via the reaction of ortho Carboxybenzaldehyde with different aromatic amines to give Schiff bases, which then reacted with different reagents to give the heterocyclic derivatives mentioned above.

All these compounds were confirmed from the spectral data analysis FT-IR and ^{1}H-NMR.

5. . Conflicts of interest

There are no conflicts to declare.

6. Acknowledgments

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Table 8: showed IR spectral data for compounds 19-30

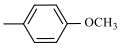
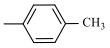
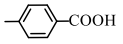
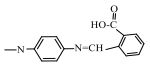
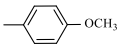
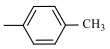
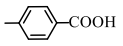
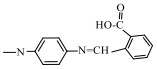
Comp.No	Ar	IR (KBr) ν cm^{-1}				
		C=O lactam	C=O acid	C=O lacton	C-O-C	OH acid
19		1651	1701	1750	1174	3261
20		1667	1724	1735	1159	3320
21		1666	1712	1761	1215	3325
22		1655	1710	1760	1220	3336
23		1656	1725	1764	1165	3340
24		1658	1722	1732	1213	3336
25		1708	1739	1778	1253	3456
26		1660	1720	1745	1172	3320
27		1654	1718	1766	1215	3270
28		1673	1726	1770	1160	3330
29		1665	1730	1774	1220	3420
30		1667	1726	1765	1255	3389

Table 9: showed ^{1}H-NMR spectral data for compounds

Comp. No.	^{1}H-NMR δ (ppm) DMSO-$_6$
2	2.23,s,3H,(CH_3), 6.88-7.69 ,m,8H,(ArH), 7.90,s,1H,(CH=N), 11.72,b.1H,(OH)
7	3.57,s,3H,(OCH_3), 4.13,s,1H,(CH-Cl), 6.76,s,1H,(CH-N), 7.52- 7.86,m,8H,(ArH), 12.74,b.1H,(OH)
15	3.98,s,2H,(S-CH_2), 4.04,s,1H,(CH-N), 7.6-8.10,m,8H,(ArH), 10.14,b.2H,2(OH)
20	2.27,s,3H,(CH_3), 6.29-6.45,d, 1H,(=CH), 7.13-7.15,d, 1H, (CH=), 7.50-7.53, m, 8H,(ArH), 10.37,s,1H,(CH-N), 13.20,b.1H,(OH).
30	4.27,s,2H,(2CH-N), 6.95-7.98,m,20H,(ArH), 11.51,b. ,(OH)

s=singlet,, d= doublet,, b= broad,, m=multiple

7. 7. References

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