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Synthesis and characterization of some new (1,3-Oxazepine) derivative from 6-methyl 2-thiouracil and study their biological activity

Khalid M. Mohammad[1], Mohammad R. Ahmed[2] , Mahmoud H. Mahmoud[1]
[1] *Department of Chemistry, College of Education College of pure science , Tikrit University, Iraq*
[2] *Department of Chemistry, College of Science , University of Baghdad , Baghdad , Iraq*

Abstract
This research includes synthesis of new heterocyclic containing (1,3-oxazepine) derivatives of 6- methyl 2-thiouracil. The preparation process started by the reaction of 6- methyl 2-thiouracil with ethyl chloroacete to give ethyl 2-((4-hydroxy-6-methylpyrimidin-2-yl) thio) acetate (1). Compound (1) reacted with hydrazine hydrate to give 2-((4-hydroxy-6-methylpyrimidin-2-yl)thio) aceto hydrazide (2). That reacted with various substituted benzaldehydes in the presence of glacial acetic acid as catalyst in absolute ethanol to obtain new Schiff bases derivatives (3-11). The new 1,3-oxazepine derivatives [12-38] were obtained from treatment of each new Schiff bases derivatives (3-11) with each (phthalic anhydride ,maleic anhydride and succinic anhydride) respectively. Newly synthesized compounds were identified via spectral methods; their [FT-IR and some of them by ^{1}H-NMR, ^{13}C-NMR] and measurements of some of its physical properties. Furthermore some of the new compounds were screened for their antimicrobial activity against four strains of bacteria –ve (Escherichia coli and klibsialla) and +ve (Bacillus and Staphylococcus aureus). Most of the tested compounds show significant antibacterial activity.

Keywords: 6- methyl 2- thiouracil, shichff bases, 1,3 oxazepin derivative, antibacterial.

1-Introduction
The development of simple synthesis route to widely used organic compounds ring, using readily available reagents is one of the main objective of organic synthesis, Nitrogen heterocycles are of a special interest because they constitute an important class of natural and non-natural products, many of which exhibit useful biological activities, one–pot efficient synthesis of heterocyclic derivatives, may permit the development of novel therapies for the treatment of epilepsy, pain and other neurodegen disorder.[1]

The literature indicated that Pyrimidine's are important component of nucleic acids and they have been used as building blocks in pharmaceuticals and possesses a broad range of biological activity like thiouracil for the synthesis of antiviral, antineoplastic, antibacterial and antifungal agents. [2-4] Similarly, the related thiouracil derivatives are potential therapeutics as antiviral, anticancer and antimicrobial agents.[5-7] For example S- alkylation products have been recently reported as a novel antibacterial cytotoxic agents.[8-9] Thiouracil derivatives are associated with a number of biological activities. Also, it was with great interest that specifically functionalized S- are alkylated thiouracil may possess specific biological properties including inhibition of bacterial. [10] Schiff bases bearing aryl groups or heterocyclic residues possess excellent biological activities are considered compounds for prepared from thiouracil derivatives have an impact effective in stimulating the high efficiency of the thyroid gland in overlap with the synthesis of thyroxin as a thionamide anti-thyroid drug for the treatment of hyperthyroidism. [11-13]

Oxazepine (benzodiazepine) derivative introduced in 1965 for use in relief of the psychoneuroses characterized by anxiety and tension. Oxazepine compounds have medical and biological important and they have medicinal and pharmaceutical application Among the wide Chemical derivatives are a hetero polymer which have activity and effectiveness against cancer they also have effective against fungi and bacteria, found that some oxazepine derivatives are considered a medical drug against the disease.[14-17]

2-Experimental
2.1- Materials and Instruments
Chemicals used in this work are supplied from BDH, Fluka, Merck and Sigma Aldrich companies and used without further purification. Melting points were uncorrected and registered via digital Stuart scientific SMP3 melting point device. FTIR spectra of the compounds in the (4000-600) cm^{-1} spectral range were recorded on SHIMAZU FTIR-8400 Fourier transform Infrared spectrophotometer using KBr discs. ^{1}HNMR and ^{13}CNMR spectra were recorded on 23ar 500MHz instrument using TMS as internal reference and DMSO-d^{6} as a solvent. The rotary evaporator was used to evaporate the solvents.

2. 3- General Procedures
2. 3. 1- Synthesis of ethyl 2-((4-hydroxy-6-methylpyrimidin-2-yl) thio) acetate (1). [18]

A mixture of 6- methyl 2-thiouracil (2 g, 0.014 mol), dimethyl formamide (DMF) (30ml) and triethyl amine (2ml) was cold at room temperature with stirring for (10 mint). Ethyl chloroacete (1.50ml. 0.014mol) was added dropwise and the reaction mixture was stirred for (2h.). Then, it was heated at (70- 80) C^{0} for (8 h.) The reaction mixture was poured into ice water. The solid product was filtered off, washed with sodium bicarbonate (5%) then, with water. The obtained product was recrystallized from ether. As white crystals, yield 75% m.p (123- 125) C^{0}. Physical properties of the product IR data see table -1.

2.3.2- Synthesis of 2-((4-hydroxy-6-methylpyrimidin -2-yl) thio) acetohydrazide (2).[19]

Compound (1) (1g, 0.004mol) was dissolved in absolute ethanol. (20ml) and hydrazine hydrate (99%, 2ml) was added to the mixture with stirring. The reaction mixture was refluxed for (5-7 h.). The resulting solution was cooled, filtered and recrystallized from ethanol. As off white crystals, yield 60% m.p (238- 240) C^0. Physical properties of the product IR data see table -1.

2.3.3- Synthesis of Schiff bases N'-(argiomethylene)-2- ((4- hydroxyl - 6 – methylpyrimidin – 2 - yl) thio) acetohydrazide (3- 11). [20-21]

A mixture of compound (2) (2.14 gm., 0.01 mol), aromatic aldehydes (0.01mol) in absolute ethanol (25) ml and (3-5) drops of glacial acetic acid was refluxed in water bath for about (5-6 h.). The excess solvent was concentrated under reduced pressure.The crude product was dried, recrystallized from chloroform (**scheme 1**).The Physical properties of compounds (3- 11) IR data see Table -2.

2. 3. 4- Synthesis of (R)-N-(3-argio-1, 5-dioxo-1, 5-dihydrobenzo[e] [1,3] oxazepin – 4 (3H)-yl) – 2 - ((4-hydroxy-6-methylpyrimidin-2-yl) thio)acetamide (12, 21, 30). [22-24]

A mixture of imine compound (0.0008mol) (Schiff bases) and (0.0008mol) of (phthalic anhydride, maleic anhydride and succinic anhydride) in (25ml) Tetrahydrofuran (THF) was refluxed for (14- 16 h.) with stirring. The solvent was removed under reduced pressure. The crude product was recrystallized from chloroform (**scheme 1**). The Physical properties of compounds (12-30) IR data in table-3.

Table 1- Physical properties and FTIR spectral data cm^{-1} of the synthesized compounds (1, 2).

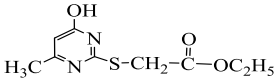
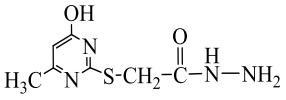
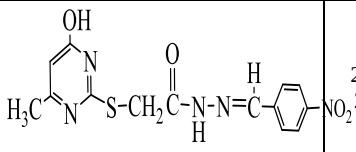
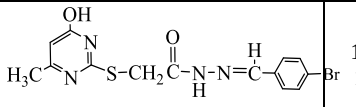
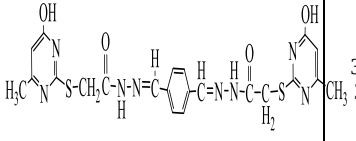
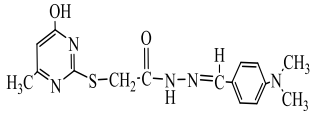
Com. No.	Physical Properties				Major FTIR Absorption cm^{-1}				
	Structures	M.P °C	Yield %	Color	ν (C-H) arom.	ν (C-H) aliph.	ν(C=O)	ν(C=N)	Others
1		123-125	75	White	3002	2927	1739	1645	ν(O-H) 3454 δ(CH_3)1361, 1467
2		238-240	60	Off White	3055	2947	1658	1631	ν(NH_2) asy. 3332, Sy. 3259 ν(O-H) 3429

Table 2-Physical properties and FTIR spectral data cm-1 of the synthesized compounds (3- 11).

Com. No.	Physical Properties				Major FTIR Absorption cm^{-1}				
	Structures	M.P °C	Yield %	Color	ν(C-H) Arom.	ν(C-H) Aliph.	ν(C=O)	ν(C=N)	Others
3		280-282	90	Orange	3103	2908	1674	1643	ν(NO_2) asy. 1510, sy. 1320 ν(O-H) 3431
4		190-192	90	Yellow	3086	2841	1662	1604	ν(C-Br) 810
5		340-342	88	Yellow	3033	2867	1670	1589	ν(O-H) 3450
6		158-160	85	Yellow	3116	2921	1664	1606	ν(C-N) 1363 ν(O-H) 3411

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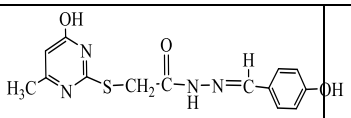
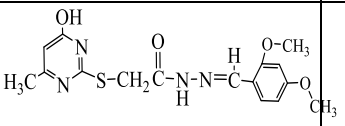
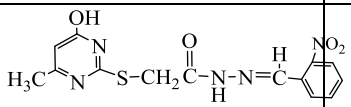
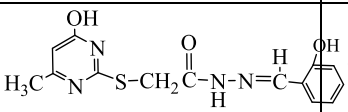
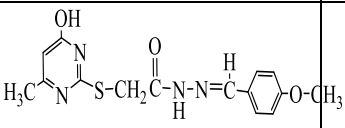
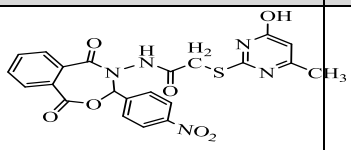
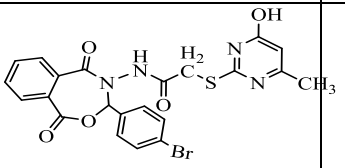
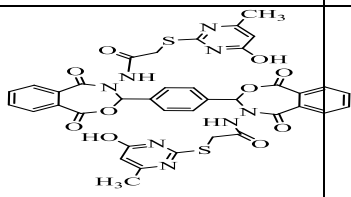
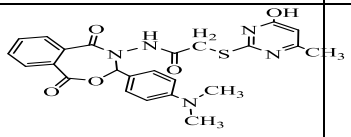
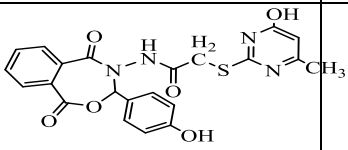
7		113-115	80	Off white	3102	2819	1666	1604	ν(O-H) 3190 (C-S-C)1242 1276
8		140-142	90	Off white	3039	2943	1662	1604	C-O-C1111, 1207 δ(CH_3) 1357, 1454
9		130-132	87	Yellow	3097	2962	1643	1589	ν(NO_2) asy. 1523, sym. 1354
10		210-212	85	Off white	3047	2858	1670	1610	ν(O-H) 3375 oop(OH) 752
11		188-190	90	Yellow	3006	2933	1666	1604	ν(O-H) 3423 ν(C=C) 1514

Table 3-Physical properties and FTIR spectral data cm^{-1} of the synthesized compounds (12- 38).

Com. No.	Physical Properties				Major FTIR Absorption cm^{-1}				
	Structures	M.P °C	Yield %	Color	ν (C-H) arom.	ν (C-H) aliph.	ν(C=O)	ν(C=N)	Others
12		120-125	75	Red	3031	29 25	1710 Lacton 1668 amide	Uracil 1637	ν(C=C) 1591, 1465 ν(O-H) 3454
13		228-230	68	Red	3012	28 81	1712 Lacton 1658 amide	1635	νC-(C=O)-O,1180 ν(C-N) 1238
14		170-172	71	Deep Yellow	3060	29 25	1697 Lacton 1668 amide	1627	δ(CH_3) 1363, 1471 ν(C=C) 1404, 1512 νC-(C=O)-O)1132
15		198-200	66	Red	3065	29 23	1712 Lacton 1656 amide	1635	ν(N-H) 3232 ν(C-N) 1342, 1362
16		193-195	80	White	3074	29 04	1701 Lacton 1658 amide	1604	ν(O-H) 3178 ν(C-O) 1222

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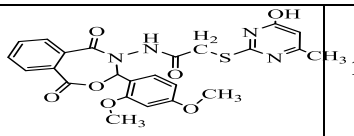
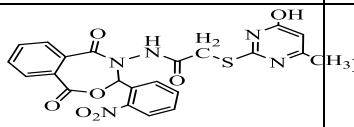
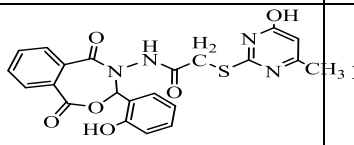
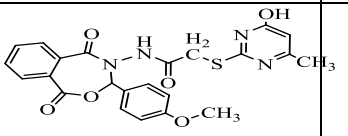
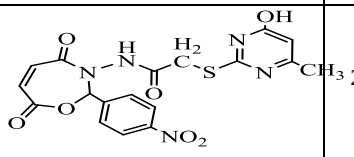
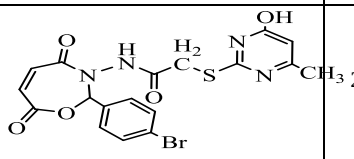
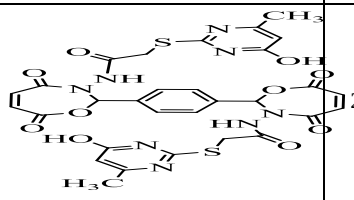
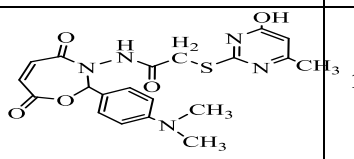
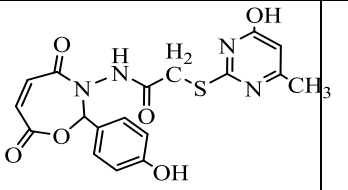
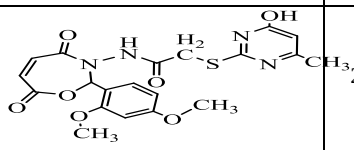
17		158-160	85	Off white	3025	29 25	1710 Lacton 1658 amide	1625	ν(O-H) 3193 ν(C-O) 1282
18		175-177	82	Yellow	3024	29 58	1699 Lacton 1681 amide	1643	ν(NO_2)asy. 1523, sym. 1353
19		195-197	85	Off white	3004	29 29	1716 Lacton 1697 amide	1622	ν(C=C) 1598 Oop(OH) 757
20		170-172	80	White	3089	29 74	1689	1600	(C-O-C) asy. 1255, sym. 1066
21		258-260	88	Orange	3070	29 37	1703 Lacton 1674 amide	1641	ν(NO_2) asy. 1510, Sym. 1336
22		200-202	75	Red	3089	29 25	1708 Lacton	1595	ν(C=C) 1658 ν(O-H) 3460
23		240-242	66	Yellow	3028	29 54	1699 Lacton 1662 amide	1629	δ(CH_3) 1334, 1438 ν(C=C) 1488, 1558 ν(C-(C=O)-O) 1224
24		160-162	60	Red	3020	29 58	1703 Lacton 1652 amide	1595	ν(N-H) 3396 ν(C-N) 1338,1367
25		190-192	70	White	3028	29 66	1701 Lacton 1656 amide	1641	ν(O-H) 3419 ν(C-O) 1269 ν(C=C) 1622
26		215-217	74	Off white	3093	29 39	1703 Lacton 1668 amide	1620	ν(O-H) 3415 ν(C-O) 1278

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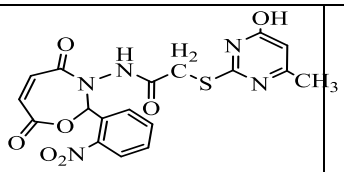
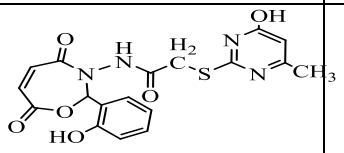
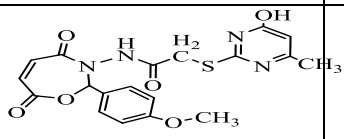
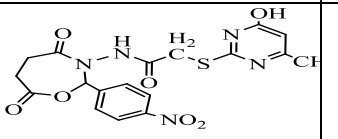
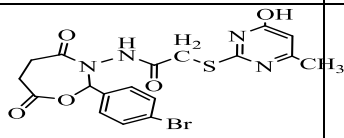
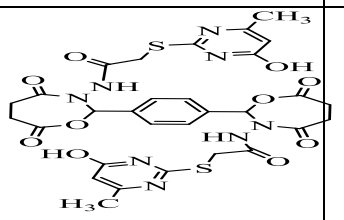
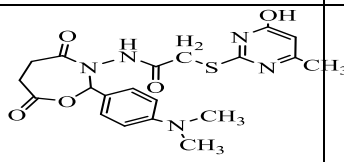
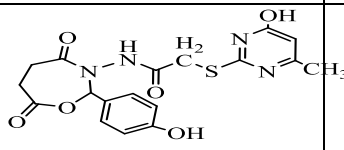
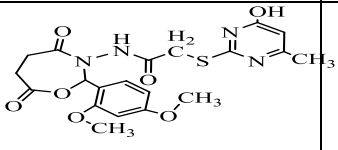
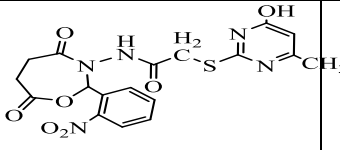
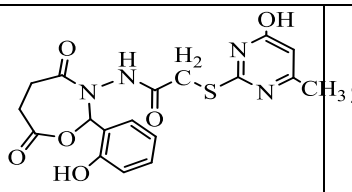
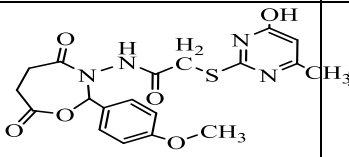
27		118-120	80	Yellow	3033	2925	1714 Lacton 1703 amide	1645	ν(NO_2)asy. 1519, sy.1346
28		185-187	72	Off White	3039	2948	1699 Lacton 1641 amide	1596	ν(C-O) 1265 oop(OH) 763
29		180-182	77	Off White	3079	2958	1704 Lacton 1662 amide	1643	ν(C=C) 1600 ν(O-H) 3423
30		300D	65	Brown	3065	2925	1649	1610	ν(O-H) 3458
31		218-220	75	Yellow	3086	2983	1701 Lacton 1645 amide	1602	νC-(C=O)-O)1186 oop(Br) 634
32		100-102	67	Yellow	3116	2906	1681 Lacton 1641 amide	1573	ν(C-C) 1027 ν(C-(C=O) –O)1107 δ(CH_3) 1342,1425
33		210-212	78	Red	3003	2929	1701 Lacton 1647 amide	1600	ν(N-H) 3161 ν(C-N) 1334,1367
34		203-205	76	Off white	3028	2931	1701 Lacton 1639 amide	1608	ν(O-H) 3461 ν(C-O) 1236
35		200-202	78	Yellow	3022	2947	1697 Lacton 1637 amide	1620	ν(C=C) 1508,1419 ν(C-O) 1207
36		188-190	88	Yellow	3035	2927	1699 Lacton 1645 amide	1591	ν(NO_2)asy. 1523, Sy.1350

37		240-242	80	Deep Yellow	3060	29 31	1677, 1625	1602	ν(N-H) 3355 ν(O-H) 3230 ν(C-O-C) 1199
38		220-222	77	Off White	3097	29 31	1710 Lacton 1635 amide	1612	ν(C-O-C) 1178 δ(CH_3) 1332, 1491

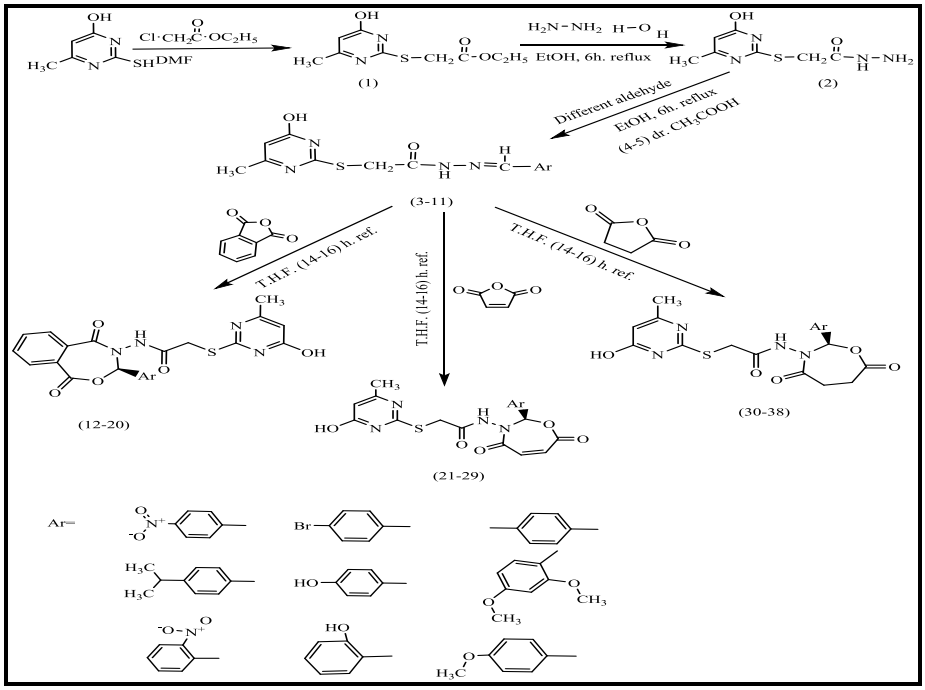
3- Anti-bactrial activity test [25]

The test was performed according to the disk diffusion method. The cup plate method using nutrient agar medium was employed in studying the antimicrobial activity of the prepared oxazepines against four strains of bacteria some of the synthesized compounds were tested against two strain –ve bacteria (Escherichia coli and klibsialla) and two strain gram +ve (Bacillus and Staphylococcus aureus). DMSO was used as sample solution, sample size of all compounds was fixed at (0.1 ml) and the used concentration for all tested compounds was 100 µg/mL. Using a sterilized crok borer cups were scooped out of agar medium contained in a petridish which was previously inoculated with the microorganisms. The test compound solution (0.1 ml) was added in the cups and the petridishes were subsequently incubated at 37^0C for 48 hrs. DMSO as a control.

Zones of inhibition produced by each compound were measured in mm and the results are listed in Table (5).

4-Results and Discussion

The synthetic sequences for preparation of series of new N- dihydrobenzo [1,3] oxazepin) -2-((4-hydroxy-6-methylpyrimidin-2-yl)thio) acetamide as in **scheme -1**.



scheme -1.

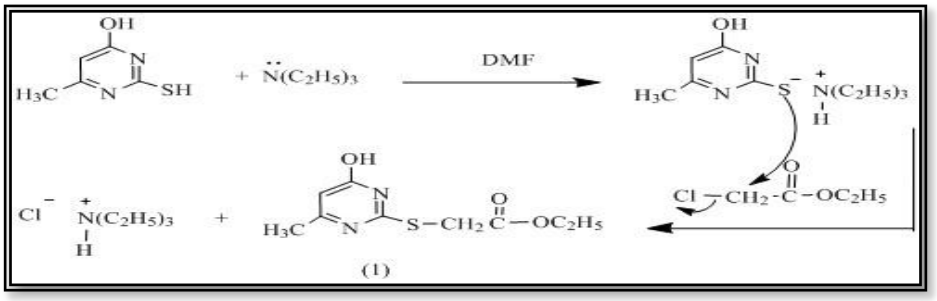
4-1- Synthesis and Characterization

Current study reports the devoted towards the research and development of highly efficient heterocyclic molecules of new the seven-membered heterocyclic 1, 3-Oxazepine derivatives were synthesized by different substituent basing on thiouracil ring. The key intermediate used in the synthesis of the desired Oxazepine (12- 38) was compounds new Schiff bases (3-11). It's were synthesized by a multi-step reaction sequence, starting from 6-methyl 2- thiouracil which introduced in reaction with ethyl chloroacetate in the first step producing uracil thioester (1). Reaction of compound (1) with hydrazine hydrate 99% under reflux

conditions gave the corresponding acetohydrazide (2) which on treatment with condensed with various aromatic aldehydes in ethanol in the presence of glacial acetic acid as catalyst to yield the Schiff bases (3-11). Were introduced in reaction with different cyclic anhydrides including phthalic, succinic and maleic anhydride, producing the new target heterocyclic ring derivatives (12-20), (21-29) and (30-38). The synthetic route of the new compounds is outlined in Scheme (1).

FT-IR, ^{1}HNMR and ^{13}CNMR spectra of the prepared compounds were recorded and found in full agreement with the proposed structures.

As indicated in the Scheme (1) synthesis of compound (3) involved three steps the first one was performed by a nucleopilic attack of (SH) group in 6-methyl 2-thiouracil on α-carbon in ethyl chloroacetate because the halo group is good leaving group and sulfur compounds are a good nucleophile thus, the reaction is a typical of the substitution nucleophilic reaction (SN2) of the thiol group followed by elimination of HCl molecule , where the halo group could be replaced easily in this reaction to get good yield producing uracil 2- thioester (1) according to the mechanism in scheme (2). [26- 27].



Scheme 2- Mechanism of the prepared compound (1)

The structure of compound (1) was confirmed by physical properties which are listed in Table (1). The FTIR spectrum showed appearance of clear absorption band at (1739cm^{-1}) due to ν (C=O) ester indicating success of ester formation and also the disappearance of a ν(S-H) at(2550-2600) cm^{-1} while ν(C-H) for aliphatic at (2927, 2808) cm^{-1}. Bands at (1145, 1296 cm^{-1}) 1654, (1195, 1150) cm^{-1}, 713, and 1396 cm^{-1} due to ν (C-O) ester, ν (C=N), ν (C-N), ν (C-S), and δ (OH) respectively. Figure-1.

^{1}HNMR spectrum of compound (1) showed triplet signal at δ = (1.21) ppm belong to (-CH_2-C$\underline{H}_3$) protons, singlet signal at δ = (2.09) ppm belong to (-C$\underline{H}_3$) thiouracil protons, singlet signal at δ = (3.96) ppm belong to (-S-C$\underline{H}_2$-) protons, quartet signal at δ = (4.17) ppm belongs to (-O-C$\underline{H}_2$-) protons, singlet signal at δ = (5.99) ppm belong to (=C-$\underline{H}$) Thiouracil proton and singlet signal at δ = (2. 13) ppm belong to (-C$\underline{H}_3$) protons. The proton (-O$\underline{H}$) appearance singlet signal at δ = (12.51) ppm. Figure-2 and listed in table-5. ^{13}C-NMR spectrum data of this compound (1) figure-9 and listed in table-6.

In the second step compound [1] was introduced in nucleophilic substitution reaction with hydrazine hydrate leading to replace an ethoxy group with hydrazino (NH-NH2) group producing the corresponding acetohydrazide (2).

The FTIR spectrum of this compound (2) showed disappearance of ν (C=O) ester band and appearance of clear absorption bands at (3332- 3259) cm^{-1} due to the asymmetric and symmetric stretching vibrations of ν (NH-NH2) indicating success of acetohydrazide Formation. Other bands appeared at 1658, 1631, 690 and 3429 cm^{-1} due to ν (C=O) amide, ν (C=N), ν (C-S) and ν (-OH) respectively is listed in table (1). ^{1}HNMR spectrum of compound (2) showed a singlet signal at δ = (4.51) ppm due to (-N$\underline{H}_2$) protons, δ = (3.31) ppm due to (S-C$\underline{H}_2$) protons, δ = (2.02) ppm belong to (-C$\underline{H}_3$) thiouracil protons, singlet signal at δ = (5.36) ppm due to (=C-$\underline{H}$) thiouracil ring proton , singlet signal at δ= (8.78) ppm due to (N$\underline{H}$-NH_2) amide proton and singlet signal at δ= (12.03) ppm due to(-O$\underline{H}$).Table-5. ^{13}C-NMR spectrum data of this compound (2) were listed in table-6.

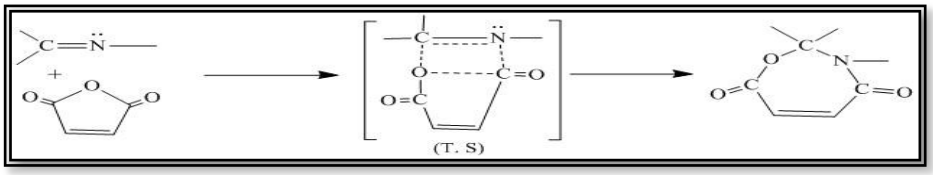
In the third step the compound [2] was introduced in reaction with various aromatic aldehydes were condensed in absolute ethanol under reflux conditions.The reaction proceed through nucleophilic attack of amino group in the compound [2] on electron-deficient carbonyl group in aromatic aldehyde in the presence of a few drops of the catalyst glacial acetic acid, and abstraction of water molecule to produce the desired new Schiff-bases derivatives in a good yield (Scheme-1) (3-11).

The formation of Schiff bases (3-11) were indicated by the presence in its FTIR-spectrra of the azomethine ν (CH=N) stretching band at (1589-1610) cm^{-1}, other absorption bands appeared at (3190- 3434), (1643-1674) and 696 cm^{-1}due to ν (OH), ν (C=O) amide and ν(C-S) respectively. All the spectrial data show disappearance the absorption of the ν (NH_2) stretching band indicating success of formation reaction as shown in table (2).The figure (3) belongs to compound (11) of some them.

It is known that cyclization of schiff bases can be introduced successfully in reaction with many reagents through active imine groups.The synthesis of new seven-membered heterocyclic compounds by

using a pericyclic reaction between new imines as two-membered components, with cyclic anhydrides are (phthalic anhydride, maleic anhydride and succinic anhydride) as five-membered components.
Pericyclic reactions involve bond changes in a circle of atoms. In Pericyclic reactions, bonds are made or broken in a concerted cyclic transition state (T.S).This means that there are no intermediates formed in the course of the reaction. [28]

Process based on principle of conservation of molecular orbital symmetry between the reaction components during the reaction proceeding which is leading to a cyclic transition state corresponds with the arrangement of participating orbitals.Concerted reaction means that breaking and formation of bonds occur simultaneously via a single transition state and there is no intermediate in the process. The mechanism of the pericyclic reaction for the synthesis 1, 3-oxazepine ring shown in scheme (3).[29].



Scheme-3 Approximate transition state geometry for maleic anhydride addition to imine group

Cyclization of compounds (3-11) in THF with (phthalic anhydride, maleic anhydride and succinic anhydride) to obtain oxazepine derivatives [12-38] respectively by scheme-1.Which identified via FTIR spectra, which shows results in table-3. All the spectral data showed clear absorption bands at (1681-1751 cm^{-1}) attributed to the υ (C=O) for lactone and υ (C=O) lactam groups in oxazepine ring bands at (1625-1697) cm^{-1}. The strong absorption broad bands at (3230- 3461 cm^{-1}) for υ (O-H) group which overlap with absorption υ(N-H) group, on the other hand the υ(C=N) inside thiouracil ring showed absorption at (1573- 1643 cm^{-1}). Other bands appeared at (1134-1278) cm^{-1} due to υ [C-(C=O)-O], the υ (C=C) aromatic of benzene ring at (1406-1521) cm^{-1}, the weak absorption band at (634- 702) cm^{-1} duo to υ (C-S) and the two The two weak absorption bands at (1367, 1483) cm^{-1} due to the δ (C-H) aliphatic of methyl group. As shown in figure (5, 7).
The ^{1}HNMR spectrum of compound (15) showed singlet signal at δ= (2.06) ppm due to (-C<u>H</u>$_3$) protons, singlet signal at δ= (2.99) ppm due to (N-(C<u>H</u>$_3$)$_2$) protons, singlet signal at δ= (4.23)ppm due to (S-C<u>H</u>$_2$) protons, singlet signal at δ=(5.43) ppm due to (=C-<u>H</u>) thiouracil ring proton, multi signals at δ=(6.68- 8.02)ppm due to aromatic rings protons, singlet signal at δ=(8.31)ppm due to (-N-C<u>H</u>-O) oxazepine ring proton, besides to these a singlet signals appears at δ=(10.87) ppm , δ=(12.83)ppm due to (C=O)N-<u>H</u>) amide proton and (-O<u>H</u>) proton, figure -4 and listed in table-5. ^{13}C-NMR spectral data of this compound (15) were listed in table-6.
^{1}HNMR spectrum of compound (18) showed singlet signal at δ= (2.07) ppm due to (-C<u>H</u>$_3$) protons, singlet signal at δ= (4.21)ppm due to (S-C<u>H</u>$_2$) protons, singlet signal at δ=(5.53)ppm due to (=C-<u>H</u>) thiouracil ring proton, singlet signal at δ=(8.45)ppm due to (-N-C<u>H</u>-O) oxazepine ring proton, multi signals at δ=(6.79- 7.99)ppm due to aromatic rings protons, besides to these a singlet signals appears at δ=(8.71)ppm, δ=(12.60)ppm due to (C=O)N<u>H</u>) amide proton and (-O<u>H</u>) proton, table-5. ^{13}C-NMR spectrum data of compound (17) were listed in table-6 and figure-10.
The ^{1}HNMR spectrum for compound (24) showed singlet signal at δ= (2.07) ppm due to (-C<u>H</u>$_3$) protons, singlet signals at δ= (2.92, 3.57) ppm due to (-N-(C<u>H</u>$_3$)$_2$) protons, singlet signal at δ= (4.07)ppm due to (S-C<u>H</u>$_2$) protons, singlet signal at δ=(5.50)ppm due to (=C-<u>H</u>) thiouracil ring proton, singlet signal at δ=(6.19, 6.66)ppm due to (<u>H</u>-C=C-<u>H</u>) oxazepine ring protons, multi signals at δ=(6.93-7.95)ppm due to aromatic ring protons, singlet signal at δ=(8.15)ppm due to (-N-C<u>H</u>-) oxazepine ring proton, besides to these a singlet signals appears at δ=(9.63)ppm, δ= (11.57)ppm due to (C=O)N<u>H</u>) amide proton and (-O<u>H</u>) proton, table-5.
The product is also identified by the ^{1}HNMR spectrum of compound (26) which shows singlet signal at δ= (2.07) ppm due to (-C<u>H</u>$_3$) protons, singlet signal at δ= (3.77) ppm due to2(O-C<u>H</u>$_3$) protons, singlet signal at δ=(4.05)ppm due to (S-C<u>H</u>$_2$) protons, singlet signal at δ=(5.50)ppm due to (=C-<u>H</u>) thiouracil ring proton, singlet signal at δ=(6.24, 6.45)ppm due to (<u>H</u>-C=C-<u>H</u>) oxazepine ring protons, signals at δ=(6.68-7.67)ppm due to aromatic rings protons, singlet signal at δ=(8.13)ppm due to (N-C<u>H</u>-O) oxazepine ring proton, besides to these a singlet signals appears at δ=(8.34)ppm , δ= (12.21)ppm due to (C=O)N<u>H</u>) amide proton and (-O<u>H</u>) proton, figure-6 and listed in table-5. ^{13}C-NMR spectral data of these compounds (22, 26) were listed in table-6.
The ^{1}HNMR spectrum for compound (33) showed singlet signal at δ= (2.06) ppm due to (-C<u>H</u>$_3$) protons, singlet signal at δ= (2.42, 2.51) ppm due to (-C<u>H</u>$_2$ -C<u>H</u>$_2$-) oxazepine ring protons, singlet signal at δ=(2.96)ppm due to (N-(C<u>H</u>$_3$)$_2$) protons ,singlet signal at δ= (3.36)ppm due to (-S-C<u>H</u>$_2$) protons, singlet signal at δ=(5.46)ppm due to (=C-<u>H</u>) thiouracil ring proton, multi signals at δ=(6.70-7.69)ppm due to aromatic ring protons, singlet signal at δ=(8.05)ppm due to (-N-C<u>H</u>-O) oxazepine ring

proton, besides to these a singlet signals appears at δ=(8.50)ppm , δ= (11.96)ppm due to (C=O)NH) amide proton and (-OH) proton,table-5. ^{13}C-NMR spectral data of this compound (33) were listed in table-6.

^{1}HNMR spectrum of compound (37) showed showed singlet signal at δ= (2.04) ppm due to (-CH_3) protons, singlet signal at δ= (2.41, 2.62) ppm due to (-CH_2 -CH_2-) oxazepine ring protons, singlet signal at δ= (3.96)ppm due to (S-CH_2) protons, singlet signal at δ=(5.46)ppm due to (=C-H) thiouracil ring proton, signals at δ=(6.77-7.72)ppm due to aromatic rings protons, singlet signal at δ=(8.02)ppm due to (-N-CH-O) oxazepine ring proton, besides to these a singlet signals appears at δ=(9.88, 11.96)ppm, δ= (11.68)ppm due to 2(-OH) protons and (C=O)NH) proton. See figure-8 and table-5. ^{13}C-NMR spectrum data of compound (37) were listed in table-6 and figure-11.

4.2- Anti-bacterial activity

The results of antibacterial activity are listed in table-4. Antimicrobial activity of the synthesized oxazepin were examined against four strains of bacteria each test compound was dissolved in DMSO to prepare stock solution from stock solution different concentration (50,100,150) ppm of each test compound were prepared. The results referred to, that all synthetic compounds possess weak, moderate and strong activity against certain types of bacteria; it indicated that compounds (20, 37) exhibited very good activity against, S.aureus, Bacillus and E.coli, Klebsialla pneumonia. Compounds (13, 25, 31) are also highly active against *Bacillus* ,Staph. Aureus, Klibsialla while the compounds (2, 26) possess weak activity against types of bacteria. The rest of oxazepin were found to be moderately active against the tested organisms.

Table 4- Inhibition zones of antimicrobial activity for prepared compounds in mm

Com. No.	Conc.	Gram positive bacteria		Gram negative bacteria	
		Bacillus	Staph. Aureus	E. coli	Klibsialla
2	150	10	-	-	11
	100		-		-
	50	-	-	-	-
13	150	15	12	10	-
	100	10	11	10	-
	50	-	-	-	-
20	150	18	15	-	18
	100	15	12	-	14
	50	-	-	-	-
25	150	12	-	-	-
	100			14	-
	50	-	-	-	12
26	150	-	12	-	-
	100	-	-	12	-
	50	-	-	-	12
31	150	14	-	-	15
	100	10	-	-	14
	50	-	-	-	10
37	150	17	16	37	-
	100	12	13	14	-
	50	-	-	-	14
DMSO	150	-	-	-	-

Table-5 ^{1}H-NMR spectral data (δ ppm) for some synthesized compounds

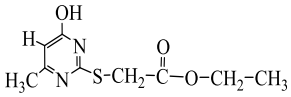
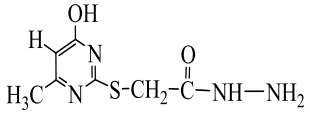
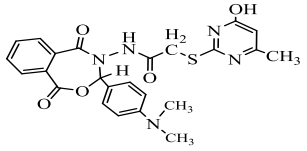
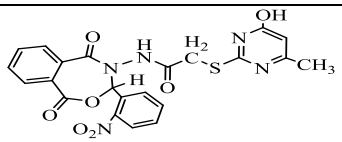
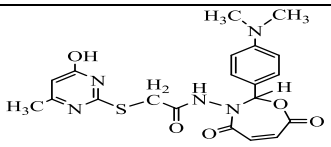
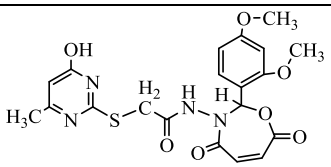
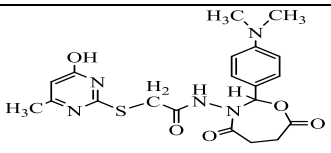
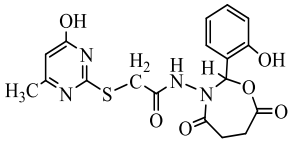
Com No	Structures	Chemical Shift (δ ppm)	No. of Protons	Group
1		1.21	3	-CH_2-CH_3
		2.09	3	-CH_3
		3.96	2	-S-CH_2-
		4.17	2	-O-CH_2-
		5.99	1	-C=H
		12.51	1	-O-H
2		2.02	3	-CH_3
		3.36	2	-S-CH_2-
		4.51	2	-NH_2
		5.36	1	-C=H
		8.78	1	-NH-NH_2
		12.03	1	-OH
15		2.06	3	-CH_3
		2.99	6	-N-(CH_3)2
		4.23	2	-S-CH_2-
		5.43	1	=C-H
		6.68- 8.02	8	Aro.Protons
		8.31	1	-N-CH-
		10.87	1	(C=O)NH-
		12.83	1	-OH
18		2.07	3	-CH_3
		4.21	2	-S-CH_2-
		5.53	1	=C-H
		6.79- 7.99	8	Aro.Protons
		8.45	1	-N-CH-
		8.71	1	(C=O)NH-
		12.60	1	-OH
24		2.07	3	-CH_3
		2.92, 3.57	6	-N-$(CH_3)_2$
		4.07	2	-S-CH_2-
		5.50	1	=C-H
		6.19, 6.66	2	HC=CH
		6.93- 7.95	4	Aro.Protons
		8.15	1	-N-CH-
		9.63	1	(C=O)NH-
		11.57	1	-OH
26		2.07	3	-CH_3
		3.77	6	2(-O-CH_3)
		4.05	2	-S-CH_2-
		5.50	1	=C-H
		6.24, 6.45	2	HC=CH
		6.63- 7.42	3	Aro.Protons
		8.12	1	-N-CH-
		8.34	1	(C=O)NH-
		12.21	1	-OH
33		2.06	3	-CH_3
		2.42, 2.51	4	-CH_2-CH_2-
		2.96	6	-N-$(CH_3)_2$
		3.36	2	-S-CH_2-
		5.46	1	=C-H
		6.70- 7.69	4	Aro.Protons
		8.02	1	-N-CH-
		8.50	1	(C=O)NH-
		11.96	1	-OH
37		2.04	3	-CH_3
		2.41, 2.62	4	-CH_2-CH_2-
		3.96	2	-S-CH_2-
		5.46	1	=C-H
		6.77- 7.72	4	Aro.Protons
		8.02	1	-N-CH-
		11.68	1	(C=O)NH-
		9.88, 11.96	2	2(-OH)

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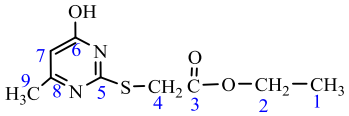
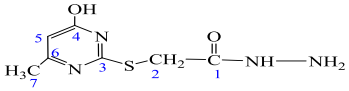
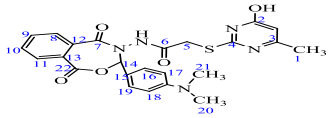
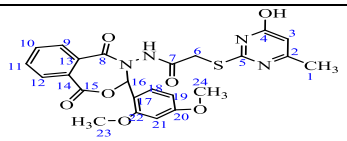
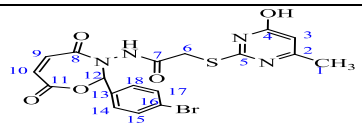
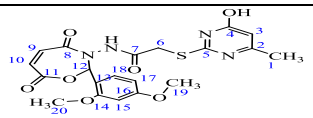
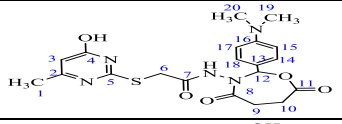
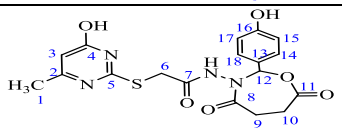
Table -6 ^{13}C-NMR spectral data (ppm) for selected compounds.

Com. No	Structure	^{13}CNMR Spectral data(δppm)
1		14.01 (C1); 60.92 (C2); 170.91 (C3); 32.30 (C4); 106.21-168.56 (C-5, 6, 7, 8); 23.05 (C9).
2		170.01 (C1); 40.08 (C2); 99. 80-157.o5 (C3,4,5,6) 23.38 (C7).
15		22.97 (C1,20,21); 101.16- 145.18 (C2,3, 4,5,8,9,10 ,11,12,13,14,15,16,17,18,19,20,21); 151.16-168.51 (C6,7,22).
17		22.97-61.09 (C1,6,23,24); 97.73- 167.54 (C2,3,4,5,9, 10,11,12,13,14,16,17,18,19,20,21,22) ; 168.04-188.92 (C7,8,15).
22		22.42-100.75 (C1,6,12); 111.98- 162.98 (C2,3,4,5,9, 10,13,14,15,16, 17,18) ; 166.77-189.74 (C7,8,11).
26		25.43-67.53 (C1,6,19,20); 97.75- 158.76 (C2,3,4,5,9, 10,13,14,15,16,17,18) ; 162.16-166.74 (C7,8,11).
33		22.97- 71.91 (C1, 6,9,10,19,20); 82.02- 164.29 (C2, 3, 4,5, 12,13,14,15,16,17,18) ; 173.39-190.02 (C7,8,11).
34		22.72- 66. 98 (C1, 6,9,10); 96.11- 162.39 (C2,3,4,5, 12, 13,14,15,16, 17,18) ; 163.78-173.75 (C7,8,11).

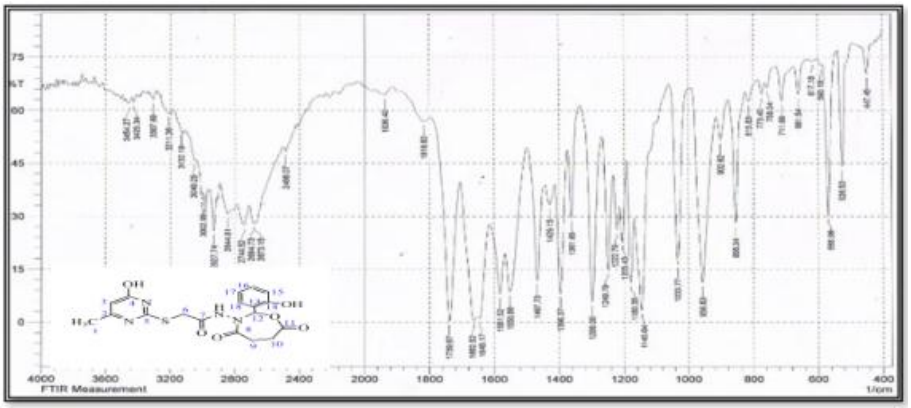


Figure -1 FT-IR spectrum of compound (1)

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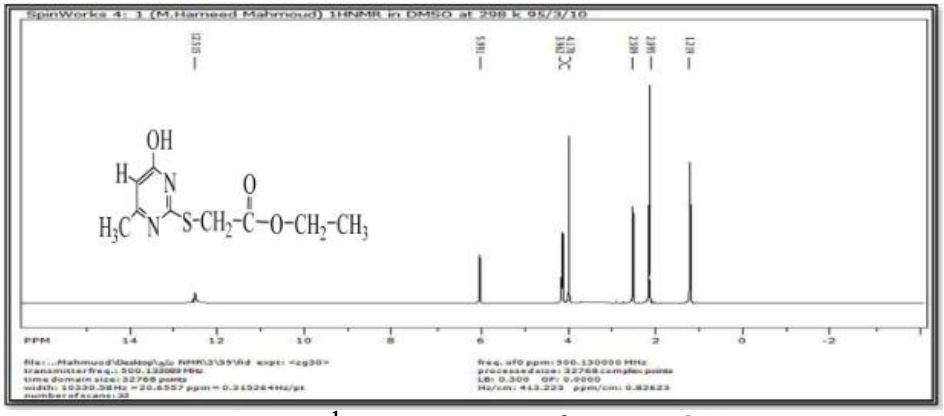

Figure 2 - ^{1}HNMR spectrum of compound (1)

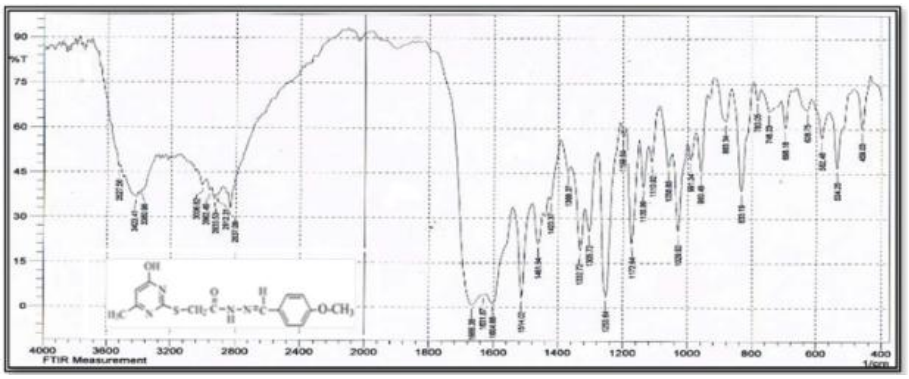

Figure -3 FT-IR spectrum of compound (11)

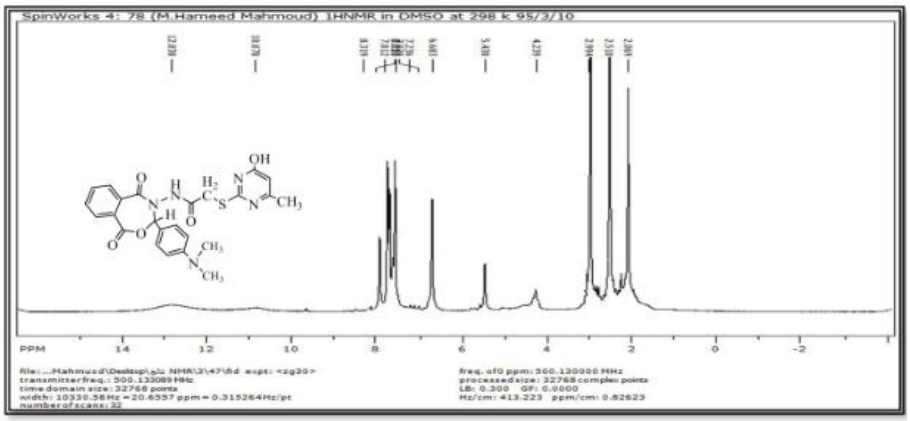

Figure 4 - ^{1}HNMR spectrum of compound (15)

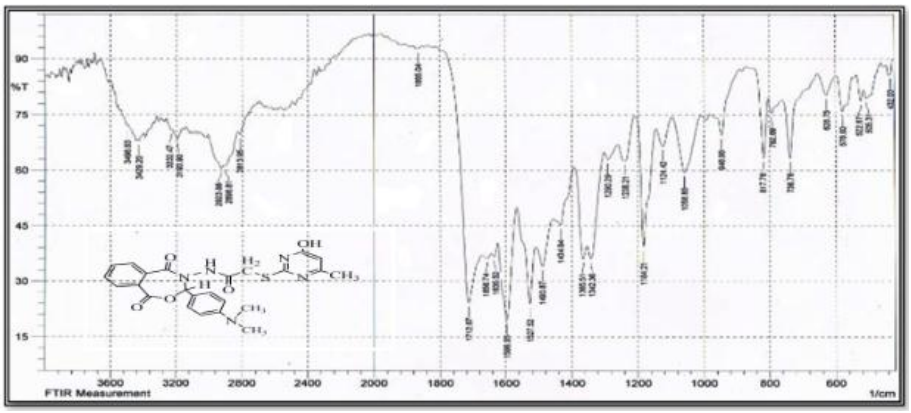

Figure 5 - FTIR spectrum of compound (15)

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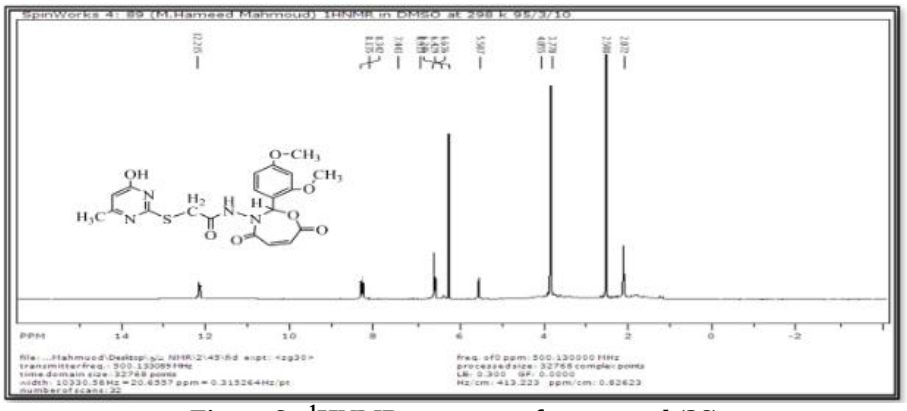

Figure 6 - ^{1}HNMR spectrum of compound (26)

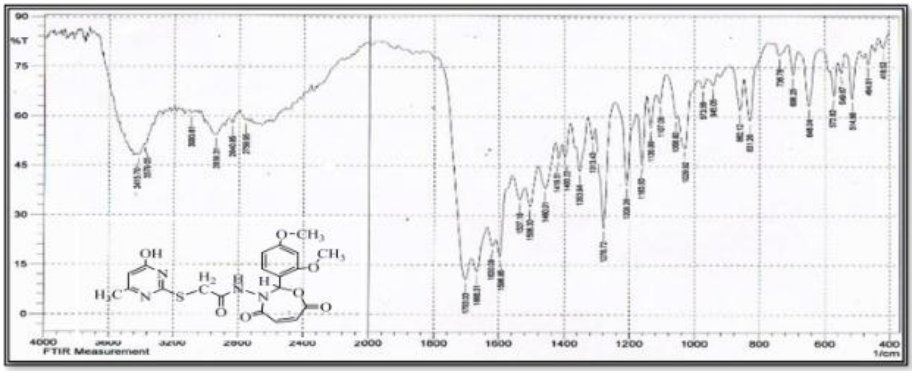

Figure 7 - FTIR spectrum of compound (26)

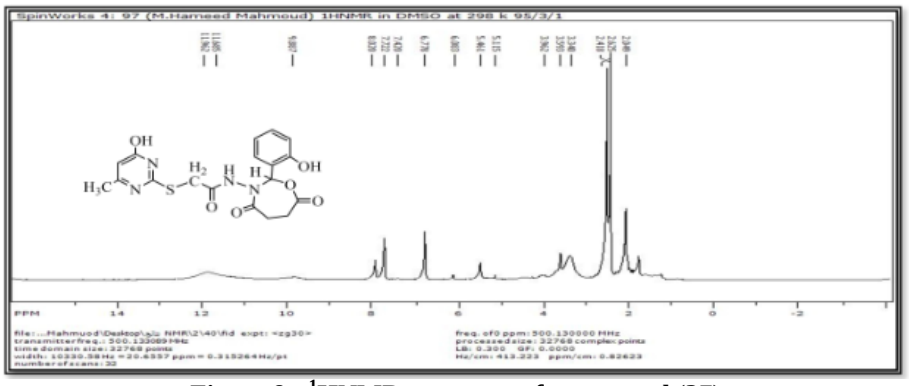

Figure 8 - ^{1}HNMR spectrum of compound (37)

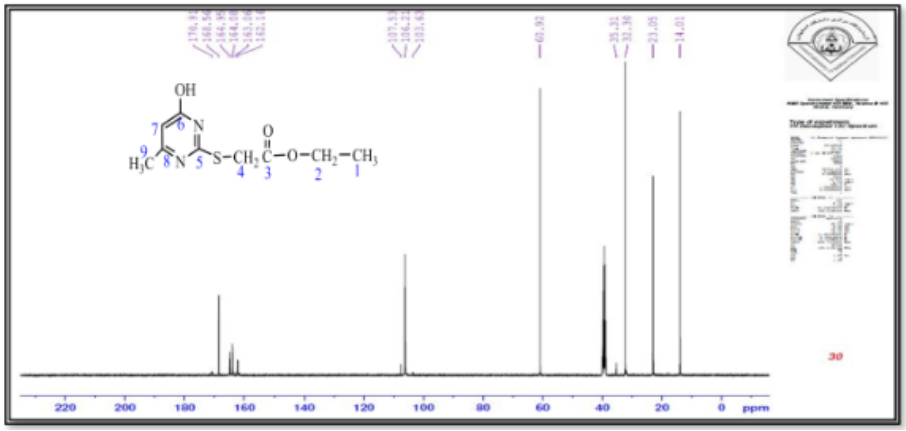

Figure 9- ^{13}C-NMR spectrum of compound (1)

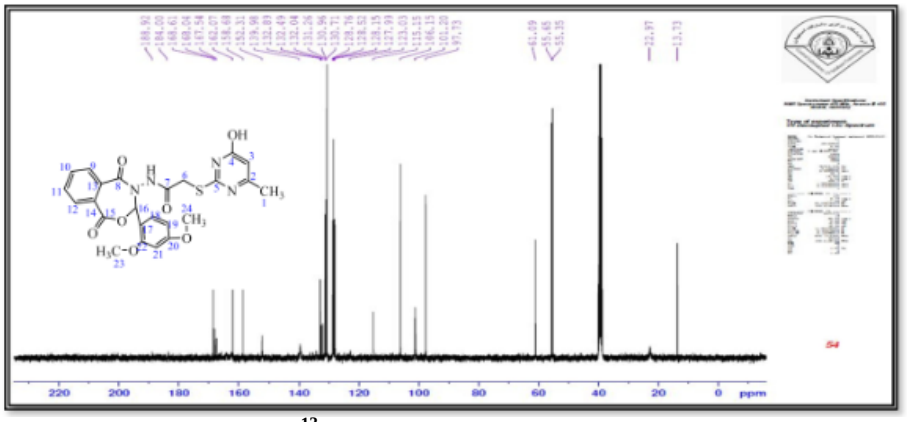

Figure 10- ^{13}C-NMR spectrum of compound (17)

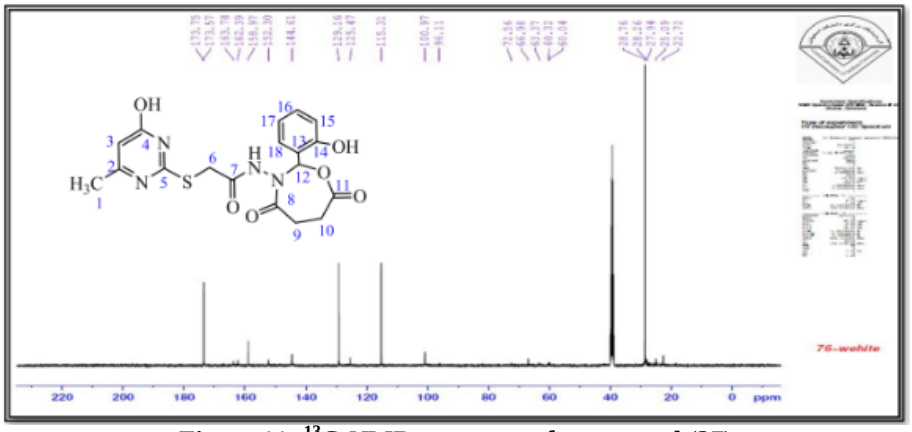

Figure 11- ^{13}C-NMR spectrum of compound (37)

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تحضير وتشخيص بعض المركبات الجديدة (1, 3- أوكسازيبين) المشتقة من 6- مثيل 2- ثايوبوراسيل ودراسة فعاليتها البايلوجية

خالد مطني محمد[1] ، محمد رفعت احمد[2] ، محمود حميد محمود[1]

[1]قسم الكيمياء ، كلية التربية للعلوم الصرفة ، جامعة تكريت ، تكريت ، العراق

[2]قسم الكيمياء ، كلية العلوم ، جامعة بغداد ، بغداد ، العراق

الملخص

تضمن هذا البحث تحضير مشتقات جديدة غير متجانسة الحلقة (3,1- أوكسازيبين) ل 6- مثيل 2- ثايوبوراسيل. وقد بدأت عملية التحضير بتفاعل 6- مثيل 2- ثايوبوراسيل مع أثيل كلورو أستيت مكونا 2((4-هيدروكسي 6- مثيل بايرمدين 2- يل) ثايو) أستيت (1). المركب (1) فوعل مع الهيدرازين المائي ليعطي مشتق 2((4-هيدروكسي 6- مثيل بايرمدين 2- يل) أسيتو) هيدرازايد (2).الذي تمت مفاعلته مع البنزالديهايدات المختلفة بوجود حامض الخليك الثلجي في الايثانول المطلق للحصول على مشتقات جديدة لقواعد شيف(3-11). تم الحصول على مشتقات 3,1- أوكسازيبين الجديدة (12-38) من معاملة مشتقات قواعد شيف المحضرة مع كل من (أنهيدريد الفثاليك, أنهدريد الماليك و أنهدريد السكسنيك) على التوالي. وقد تم اثبات تراكيب المركبات الجديدة المحضرة بواسطة الطرق الطيفية [FT-IR وبعض منها بواسطة ^{1}H-NMR, ^{13}C-NMR] وقياس بعض خصائصهاالفيزيائية. فضلا عن ذلك تمت دراسة تأثر بعض المركبات المحضرة ضد اربعة أنواع من البكتريا.