Synthesis & spectroscopic studies of some Oxazepeines & Benzooxazepine derivatives

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Abstract

The present work includes synthesis, characterization and investigation of a new compounds of [1,3] oxazepines and [1,3] benzooxxazepine which were prepared from pyrimidine -2- thione Schiff-bases (compounds 5-12) with maleic or phthalic anhydride. The chemical structures of the synthesized oxazepine products (compounds 13- 28) were confirmed on the bases of physical & spectroscopic FTIR, NMR (^{1}H & ^{13}CMR) data.

تحضير ودراسة طيفية لبعض مشتقات الاوكسازيين والبنزاوكسازيين

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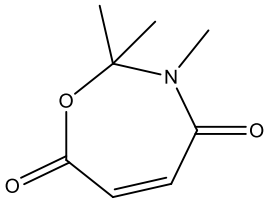
الخلاصة

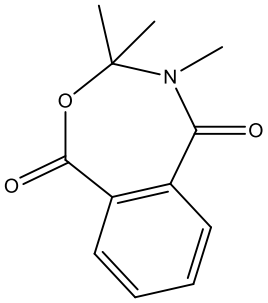
تتضمن الدراسة الحالية تحضير ،تشخيص مركبات جديدة من (1،3) أوكسازيين و (1،3) بنزاوكسازيين المحضرة من تفاعل قواعد شيف لمشتقات البريمدين -2- ثايون (المركبات 5-12) مع حامض الماليك أو حامض الفيثاليك انهيدريد. النواتج الصيغ التركيبية لاوكسازيين المحضرة (المركبات 13-28)، تم التأكيد من صحتها من خلال الاعتماد على الخصائص الفيزيائية والطيفية (الاشعة تحت الحمراء والرنين النووي المغناطيسي (البروتون والكاربون -13).

Introduction

Oxazepines (1) & benzoxazepines (2) are seven membered unsaturated heterocylic that contains two heteroatoms (Nitrogen & Oxygen) [1,2], these compounds were prepared from different precursors, mainly Schiff-bases react with phthalic anhydrides [3] or maleic anhydride [4] to give the corresponding oxazepine products by cycloaddition reactions.



I- Oxazepine



2- Benzoxazepine

Fig. (1):- Chemical structures (1) Oxazepine & (2) Benzoxazepine

Benzoxazepine derivatives have documented consistent advances in the design of novel anticonvulsant agents, benzoxazepine derivatives have been found to posses potent wide spectrum biological activities like anticonvulsant, antidepressant, CNS depressant, antipsychotic and neuroleptic.[1-4]. Oxazepine derivatives are formed to exhibit a vast varieties of biological activities like antimicrobial agents [5&6], CNS depressants (hypnotics, skeletal muscle relaxants, antiepileptics) [7]. The aim of this work was designated to synthesize new [1,3] oxazepine and [1,3] benzoxazpine derivatives.

Experimental

Materials

All reagents were purchased from commercial sources and used without further purification, the employed chemicals and their supplier from BDH &Fluka companies.

Instruments

a- All melting points were uncorrected and determined by the Electro-thermal IA 9100 melting point apparatus. All reactions were monitored by TLC using pre-coated Aluminum sheet silica gel Merck 60 F 254 and were visualized by iodine vapor and detected the spots using UV lamp and purification using micro column with silica gel.

b- The infra-red (IR) spectra were recorded using potassium bromide disc technique on Bruker optics Co.; Alpha P, IR Spectrophotometer. c- The proton nuclear magnetic resonance (^{1}H NMR) & Carbon -13 nuclear resonance (^{13}C NMR) spectra were performed on Bruker 400MHz Spectrophotometer using tetramethylsilane (TMS) as internal standard. Chemical shift values (δ) are given using parts per million scale (ppm) in (Bangor, UK).

Synthesis of 5-bromo-2-mercapto-6-(4-methoxyphenyl)pyrimidin-4yl one compound 3. [8]

Mix (1mmole) of ansialdyhde, bromoethylacetate and thiourea was

dissolved in absolute ethanol and (3mmole) of potassium carbonate was added & the reaction was continue for 2h, and the reaction was monitored using TLC (Methanol: Ether)(80:20 V/V %) until complete the reaction. Then, the solvent was reduced and pour into ice, the yellow powder was filtered and crystallized from ethanol the m.p. was 268-270 ºC and percentage yield 90%.

Synthesis of 5-bromo -2-hydrazine -6-(4-methoxyphenyl)pyrimidin-4 one. Compound 4. [9]

A (5mmole) of 80%hydrazine hydrate was mixed with (1 mmole) of compound 3 in absolute ethanol, the mixture was refluxed for 4h the reaction was monitored using TLC (n-Butanol: Ether) (50: 50 V/V %). The mixture was cold until yellow precipitate was formed. The ppt was filtered and crystallized from absolute ethanol. The m.p. was 145-147 ºC and percentage yield=67%.

Synthesis of 5-bromo-6-(4-methoxyphenyl)2-[2-(substituted benzylidene) hydrazinyl]pyrimidin-4-one. (compounds 5-12)[8]

A compound 4 (1mmole) and glacial acetic acid was dissolved in absolute ethanol and was added the mixture with (1 mmole) substituted aldehydes (freely distill or crystallize), reflux 2-4 h, concentrated the solvent, and pour into ice, the ppt was filtered and crystallized to the corresponding Schiff base products. The physical properties were listed in Table 1.

Synthesis of 3-[5-bromo-4(4-methoxyphenyl)-6- oxo-1,6dihydropyrimidin-2-yl amino] -2—(4-subsituted phenyl) 2,3dihydro[1,3]oxazepine 4,7dione. (Compounds 13-28). [10,11]

A mixture of (0.002mole) the substituted Schiff- bases and (0.01 mole) of maleic anhydride or phthalic anhydride was dissolved in absolute ethanol and refluxed for 4h. The solvent until precipitate product, crystallized from dioxane. The physical properties were listed in Tables 2&3.

Table (1):- Physical properties of substituted Schiff- bases (compounds 5-12).

Comp. No.	X	Molecular formula	Colour	m.p ºC	% yield
5	4-NO_2	$C_{18}H_{14}BrN_5O_4$	yellow	289-291	85
6	3-NO_2	$C_{18}H_{14}BrN_5O_4$	yellow	180-182	80
7	2,6- $(Cl)_2$	$C_{18}H_{13}BrCl_2N_4O_2$	Pale yellow	151-152	84
8	3-OH-4-OCH_3	$C_{19}H_{17}BrN_4O_4$	gray	137-139	80
9	4-OCH_3	$C_{19}H_{17}BrN_4O_3$	yellow	108-110	74
10	H	$C_{18}H_{15}BrN_4O_2$	white	202-204	75

11	4-Cl	$C_{18}H_{14}BrClN_4O_2$	gray	228-231	78
12	4-OH	$C_{18}H_{15}BrN_4O_3$	yellow	211-213	88

Table (2):- Physical properties of the [1,3] oxazepine derivatives (compounds 13-20).

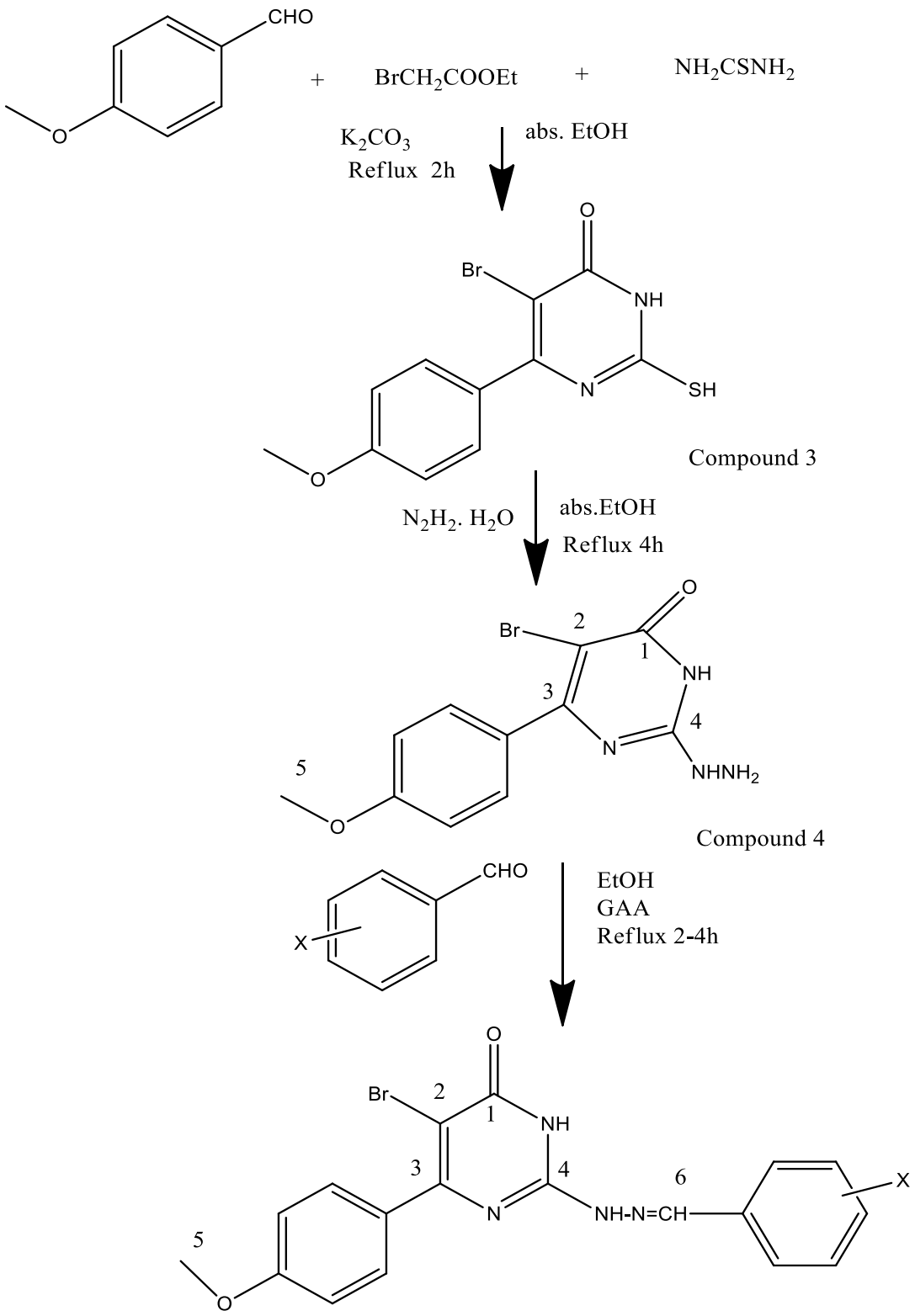
Comp. No.	X	Molecular formula	Colour	m.p ° C	% yield
13	4-NO_2	$C_{22}H_{16}BrN_5O_7$	Pale yellow	129-131	80
14	3-NO_2	$C_{22}H_{16}BrN_5O_7$	yellow	140-142	75
15	2,6-$(Cl)_2$	$C_{22}H_{15}BrCl_2N_4O_5$	Pale yellow	157-159	85
16	3-OH –4-OCH_3	$C_{23}H_{19}BrN_4O_7$	Brown	211-213	82
17	4-OCH_3	$C_{23}H_{19}BrN_4O_6$	yellow	170-172	84
18	H	$C_{22}H_{17}BrN_4O_5$	Brown	195-198	80
19	4-Cl	$C_{22}H_{16}BrClN_4O_5$	yellow	161-163	74
20	4-OH	$C_{22}H_{17}BrN_4O_6$	yellow	128-130	80

Table (3):- Physical properties of the [1,3]benzoxazepine derivatives (compounds 21- 28).

Comp. No.	X	Molecular formula	Colour	m.p ° C	% yield
21	4-NO_2	$C_{26}H_{18}BrN_5O_7$	white	205-206	86
22	3-NO_2	$C_{26}H_{18}BrN_5O_7$	white	241-243	75
23	2,6-$(Cl)_2$	$C_{26}H_{17}BrCl_2N_4O_5$	yellow	168-170	75
24	3-OH –4-OCH_3	$C_{27}H_{21}BrN_4O_7$	Brown	212-214	82
25	4-OCH_3	$C_{27}H_{21}BrN_4O_6$	yellow	171-173	80
26	H	$C_{26}H_{19}BrN_4O_5$	Brown	176-178	78
27	4-Cl	$C_{26}H_{18}BrClN_4O_5$	Brown	188-190	77
28	4-OH	$C_{26}H_{19}BrN_4O_6$	yellow	302-304	72

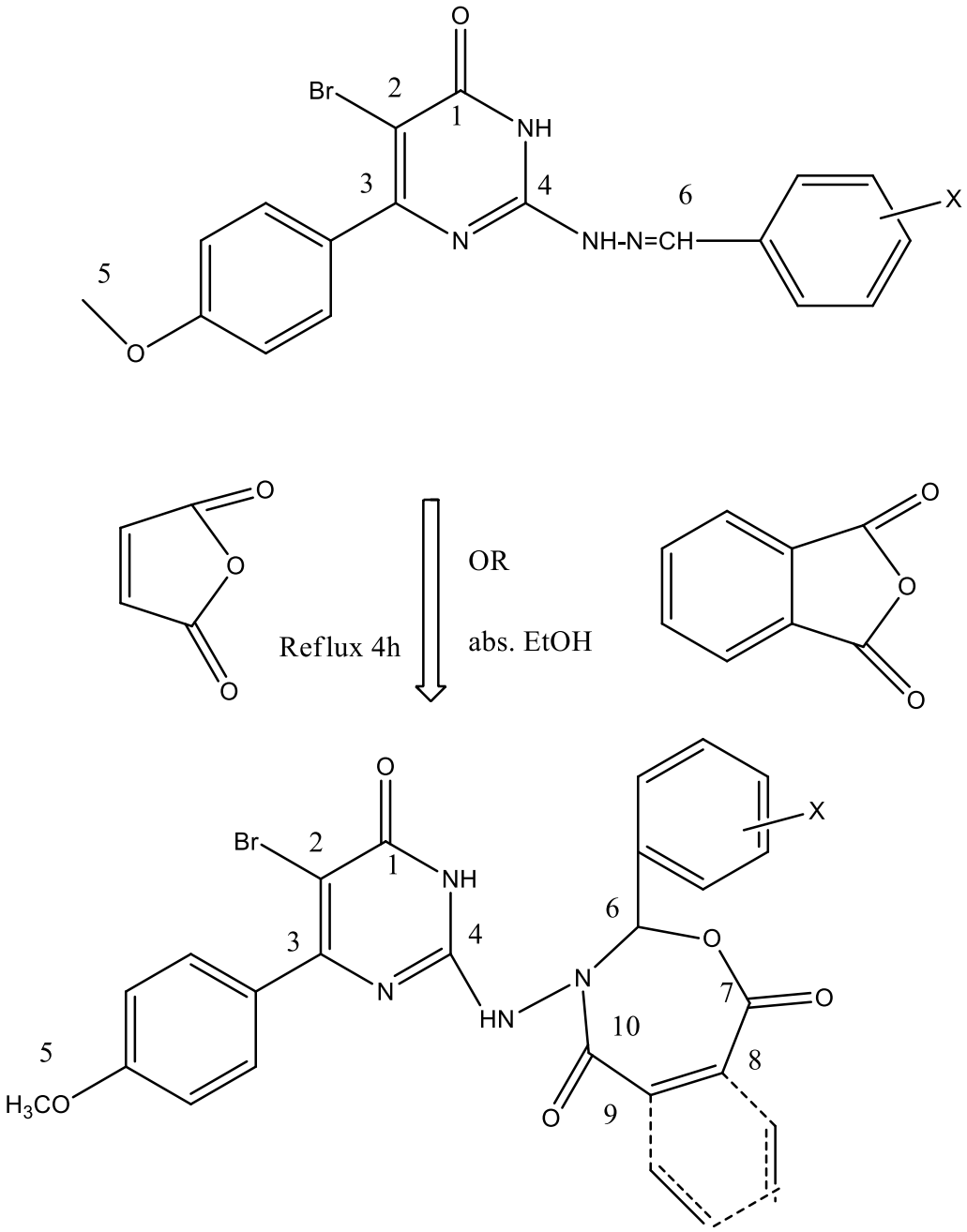
Results & Discussion

The heterocyclic ring 5-bromo-2-mercapto-6-(4-methoxyphenyl)pyrimidin-4yl one compound 3 was synthesized as shown in scheme 1.



X= 4-NO_2, 3-NO_2, -2,6 $(CI)_2$, 3-OH4-OCH_3, 4-OCH_3, H, 4-CI, 4-OH

Scheme (1):- Route of the synthesis of Schiff-bases.



X= 4-NO_2, 3-NO_2, -2,6 $(CI)_2$, 3-OH4-OCH_3, 4-OCH_3, H, 4-CI, 4-OH

Scheme (2):- Route of the synthesis of [1,3] ozazepine - & [1,3] benzoxazepine (----) ring derivatives (compounds 13-28).

The ir spectrum was showed the following peaks υ $_{cm-1}$: 3195(NH); 3085 (CH) aromatic ; 2956-2838 (CH) aliphatic, 1667 (C=O)amide, 1175 (C=S), there is keto-enol (thione-thiol) tautomerism. The second step for the reaction was substituted - SH group by- $NHNH_2$ and the formation of hydrazine derivative (compound 4). The ir spectrum shown the following υ $_{cm-1}$: 3373& 3216 (NH & NH_2); 3063(CH) aromatic ; 2957-2838(CH) aliphatic; 1669 (CONH) amide; 1600 (C=N); 1507(C=C). The ^{1}H & ^{13}C NMR data were listed in Table 4 (Scheme 1).

Table (4):- ^{1}H&^{13}C NMR of compound 4

Position	^{1}H NMR δ(ppm)	^{13}C NMR δ(ppm)
1	-	161.79
2	-	110.55
3	-	
4	-	144.14
5	3.83 (s,3H) OCH_3	56.02
Amine	6.48 (m,2H) NH_2 6.95 (m,1H) NH	
Benzene Ring	7.04-7.48 (dd,4H) ph	115.24, 128.41, 129.84,160.89

The formation of new Schiff bases (5-12) from compound 4 with substituted benzaldehydes in absolute ethanol using glacial acetic acid (GAA) as catalyst, the structures of the products were confirmed on the basis of their spectral method (FTIR, ^{1}H &^{13}CNMR). The ir spectra shows the following characteristic bands υ_{cm-1}:- 3370- 3243 (OH); 3188-3195 (NH); 2958- 2940 (CH), 1667- 1670 (C=O); 1598-1600 (C=N) indicate the imine formation.[12]. The ^{1}H NMR spectra of the synthetic Schiff bases were showed the following characteristic chemical shifts were appeared δ (ppm) : 3.82(s,3H) OCH_3; 3.92(m,1H) NH, 7.47-6-07)(m, nH) depend upon the two phenyl groups. 7.47(m,1H) CH=N. Also, the ^{13} C NMR spectra for the synthetic compounds showed the following chemical shifts δ(ppm): 56.03 (OCH_3); 110.55 (C-Br); 115.24-144.14 two phenyl groups, 145.97(C=N) cyclic; 158.32 (C=C); 160.89 (C=N) imine group; 161.79(C=O). The reaction between the new Schiff bases and maleic anhydride or phthalic anhydride by cyclic addition reaction produce a seven membered heterocylic ring [1,3] oxazepine or [1,3] benzoxazpine, dione derivatives.[13]. The ir spectra shows the following characteristic bands υ_{cm-1}: 3243-3195 (NH); 3057-3055(CH) aromatic, 2999- 2875 (CH) aliphatic, 1707 – 1673 (CONH) lactam, 1778-1765 (OCO) lactone, 1609-1559 (C=N). Other additional groups shows 3384-3369 (OH) phenolic, 1396-1365 (NO_2) aromatic nitro group [10,11], the ir spectra can't give indication to differentiate between oxazepine & benzoxazepine derivatives.[14]. The nuclear magnetic resonance investigation for the oxazepine and benzoxazepine derivatives are fixed in Table 5.

Table (5):- ^{1}H &^{13}C NMR of the new oxazepine & benzoxazepine derivatives.

Poistion	^{1}H NMR δ(ppm) Oxazepine	Benzoxazepin	^{13}C NMR δ(ppm) Oxazepine	Benzoxazepine
1	-	-	163.91 C=O	160.89 C=O
2	-	-	115.24 C-Br	110.55 C-Br
3	-	-	147.91 =C	149.48 =C
4	-	-	145.41 =C	149.18 =C
5	3.83(s, 3H) OCH_3	3.82(s,3H) OCH_3	56.03 OCH_3	56.78 OCH_3
6	8.05 (s,1H) CH	7.43 (s,1H)CH	110.55 CH Benzoxazepine	109.12 CH Benzoxazepine
7	-	-	163.43 C=O Lactone	161.79 C=O Lactone
8	6.62(d,1H) CH=	-	127.56 =C	Mixed with ph
9	7.06 (d,1H) CH=	-	124-12 =C	Mixed with ph
10	-	-	160.89 C=O Lactam ring	166.39 C=O Lactam bond
	1.65 (m,1H) NH	2.98(m,1H)NH	144.14127.56 aromatic	159.43-115.24 aromatic carbon
Benzene Ring	7.52- 7.14(dd,4H) ph	8.02-6.75 (m,nH) three (ph)		
Benzene Ring	8.21-7.56 (m, nH) X-ph n=3,4,5			

In conclusion, the complex structures of both oxazepine and benzoxazepine pyrimidine derivatives will needed further chemical studies such as docking with different enzymes, mass spectra, CHN analysis, .. as well as biological studies such as CNS depressant activity, anti-cancer, antimicrobial etc.

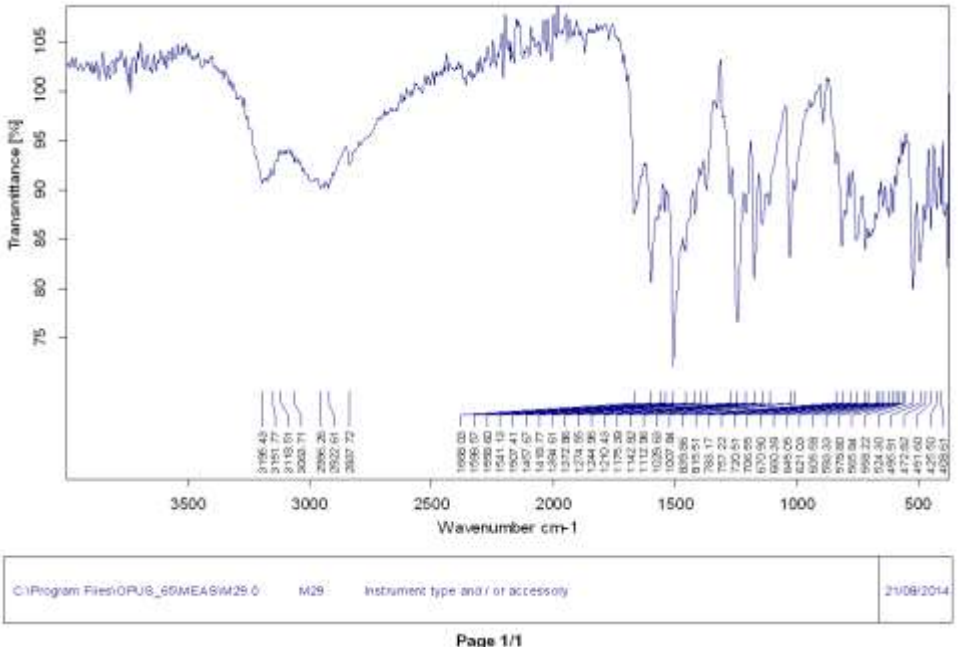


Figure (1):- FTIR spectrum of compound 5-bromo-2-hydrazinyl-6-(4-methoxyphenyl)pyrimidin-4(3H)-one.

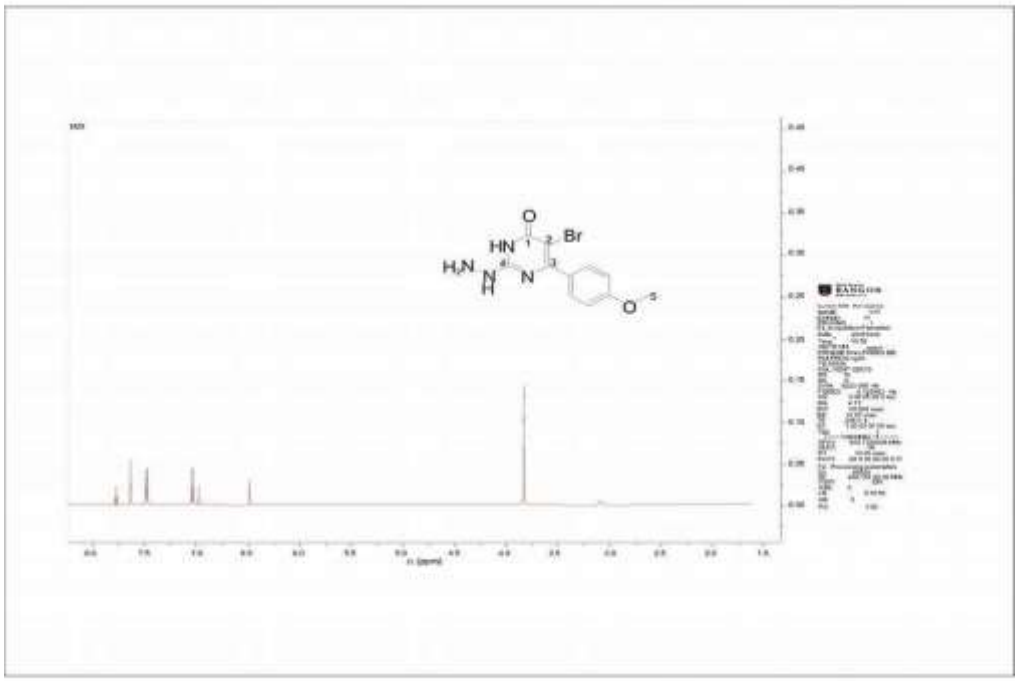


Figure (2):- ^{1}H-NMR spectrum of compound 5-bromo-2-hydrazinyl-6-(4-methoxyphenyl)pyrimidin-4(3H)-one.

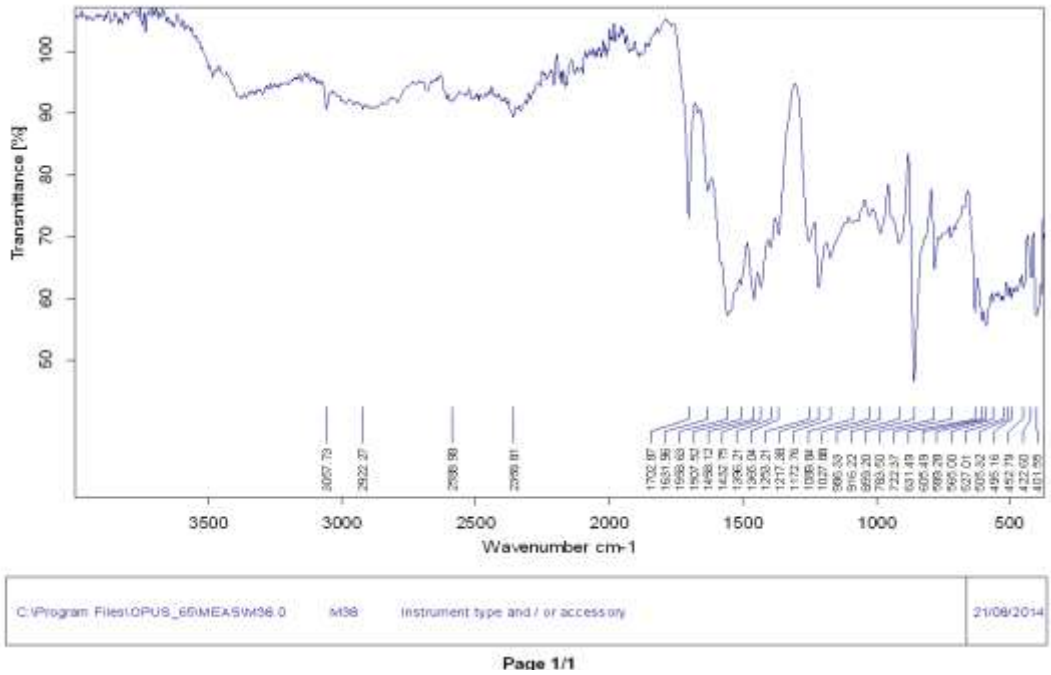


Figure (3):- FTIR spectrum of compound 3-(5-bromo-4-(4-methoxyphenyl)-6-oxo-1,6-dihydropyrimidin-2- ylamino)-2-(4-nitrophenyl)-2,3-dihydro-1,3oxazepine-4,7-dione.

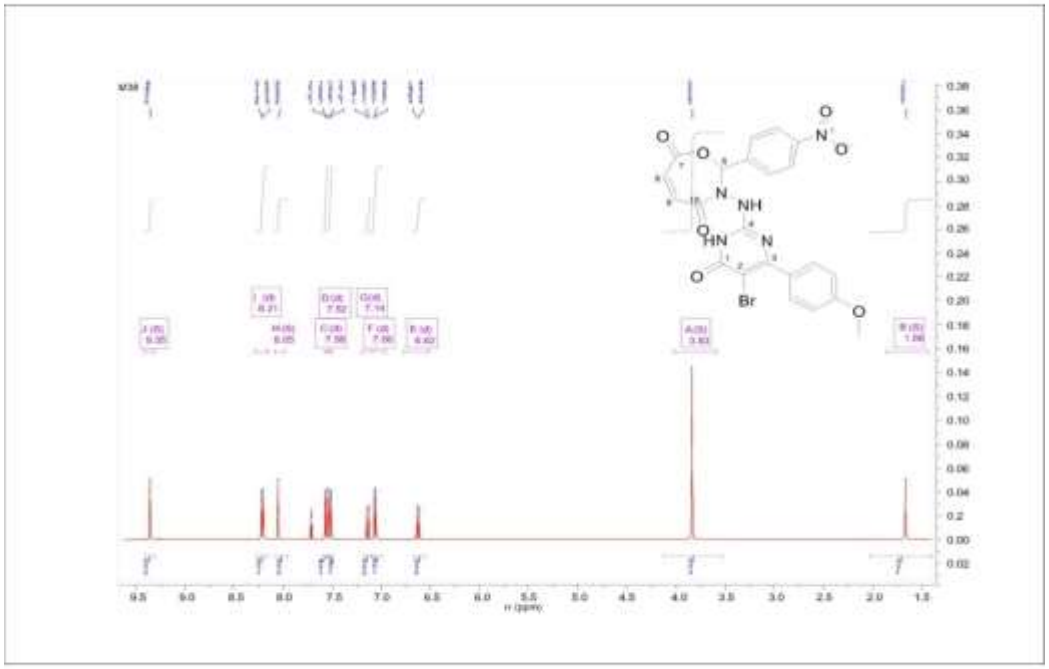


Figure (4):- ^{1}H-NMR spectrum of compound 3-(5-bromo-4-(4-methoxyphenyl)-6-oxo-1,6-dihydropyrimidin-2-ylamino)-2-(4-nitrophenyl)-2,3-dihydro-1,3oxazepine-4,7-dione.

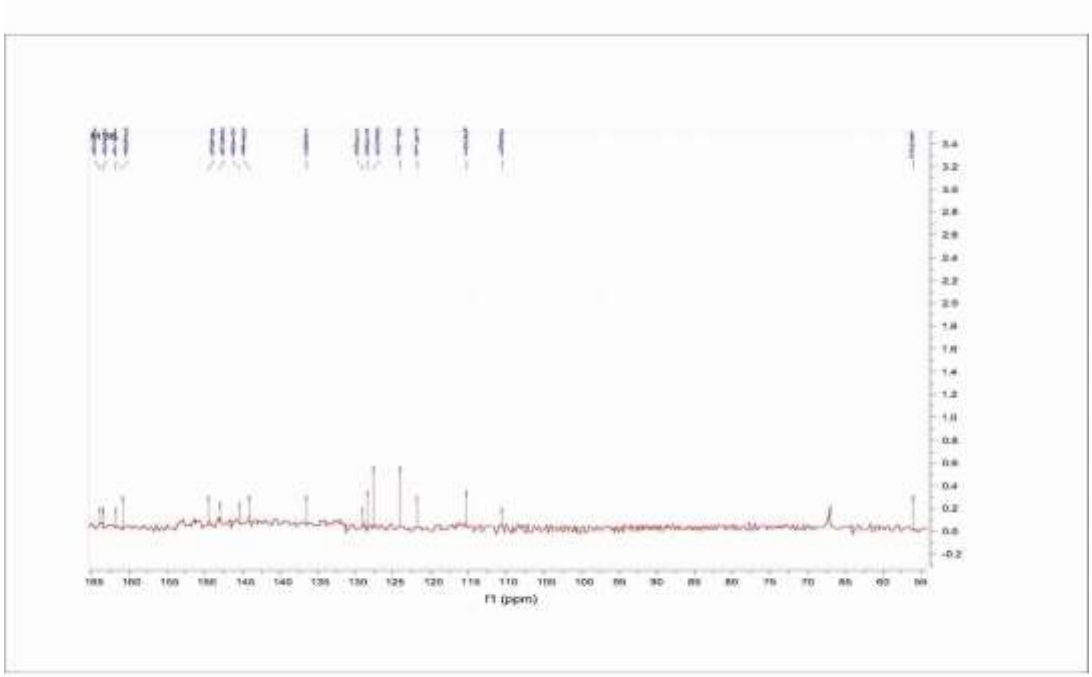


Figure (5):- ^{13}C-NMRspectrum of compound 3-(5-bromo-4-(4-methoxyphenyl)-6-oxo-1,6-dihydropyrimidin-2-ylamino)-2-(4-nitrophenyl)-2,3-dihydro-1,3oxazepine-4,7-dione.

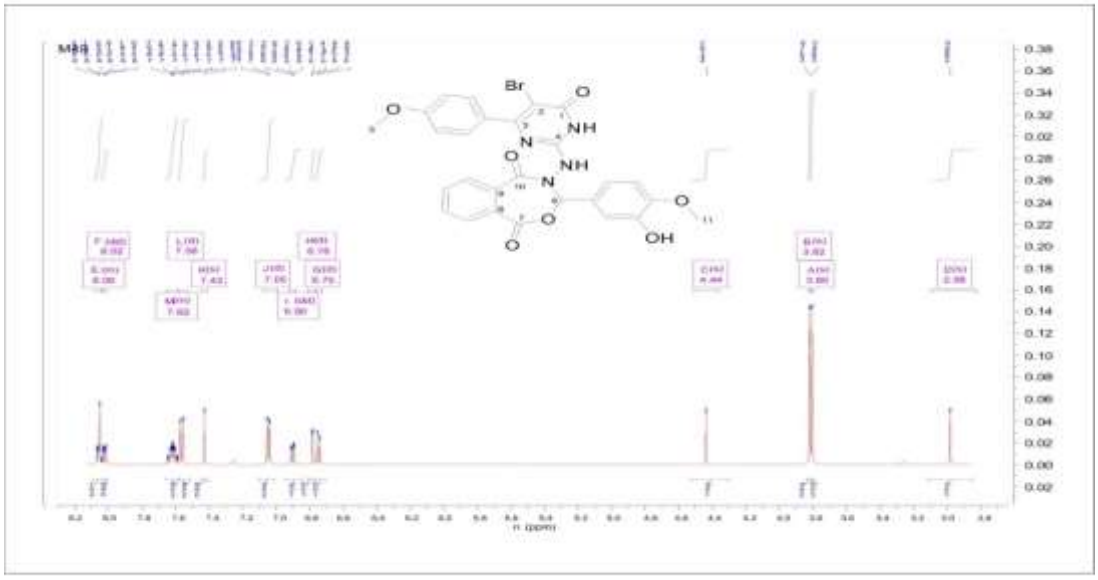


Figure 6: ^{1}H-NMR spectrum of compound 4-(5-bromo-4-(4-methoxyphenyl)-6-oxo1,6-dihydropyrimidin-2-ylamino)-3-(3-hydroxy-4-methoxyphenyl)-3,4-dihydrobenzo [*e*][1,3]oxazepine-1,5-dione

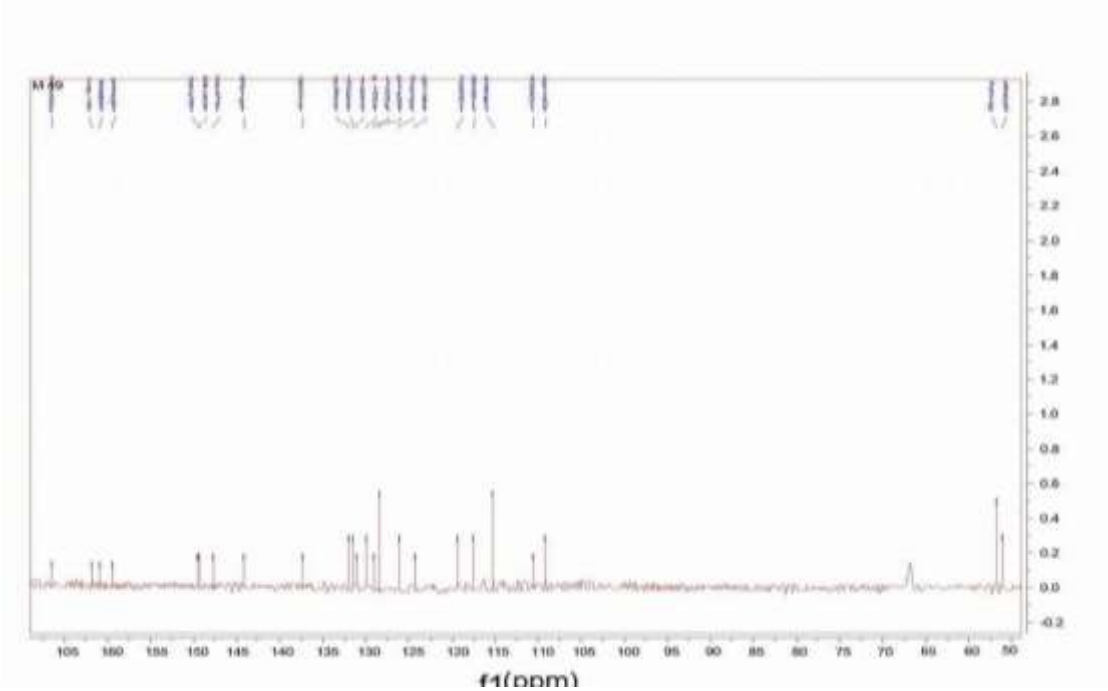


Figure (7):- ^{13}C-NMR spectrum of compound 4-(5-bromo-4-(4-methoxyphenyl)-6-oxo1,6-dihydropyrimidin-2-ylamino)-3-(3-hydroxy-4-methoxyphenyl)-3,4-dihydrobenzo [*e*][1,3]oxazepine-1,5-dione.

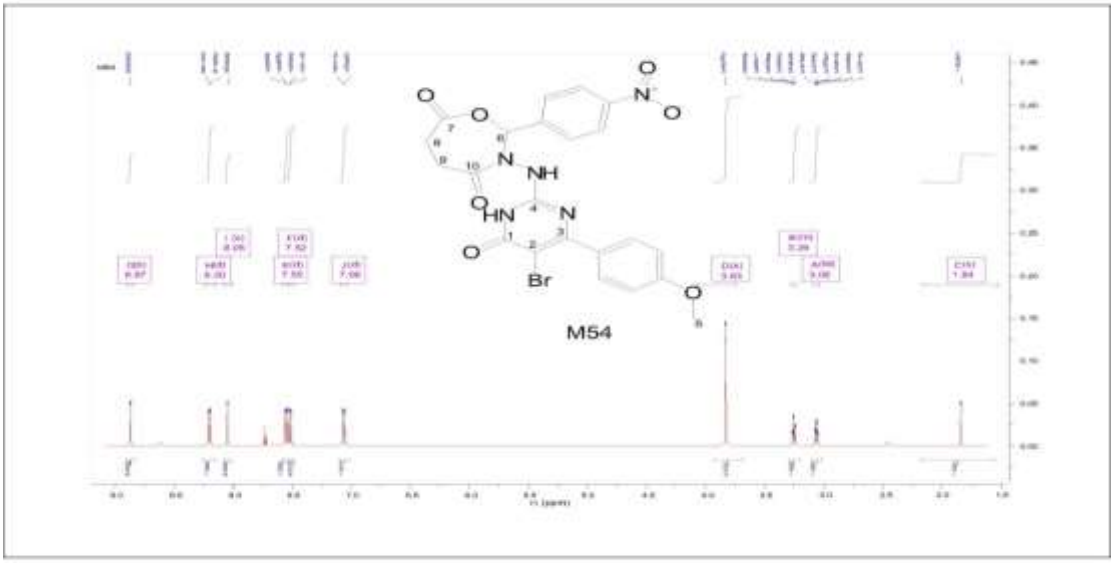


Figure (8):- ^{1}H-NMR spectrum of compound 3-(5-bromo-4-(4-methoxyphenyl)-6-oxo1,6-dihydropyrimidin-2-ylamino)-2-(4-nitrophenyl)-1,3- oxazepane-4,7-dione.

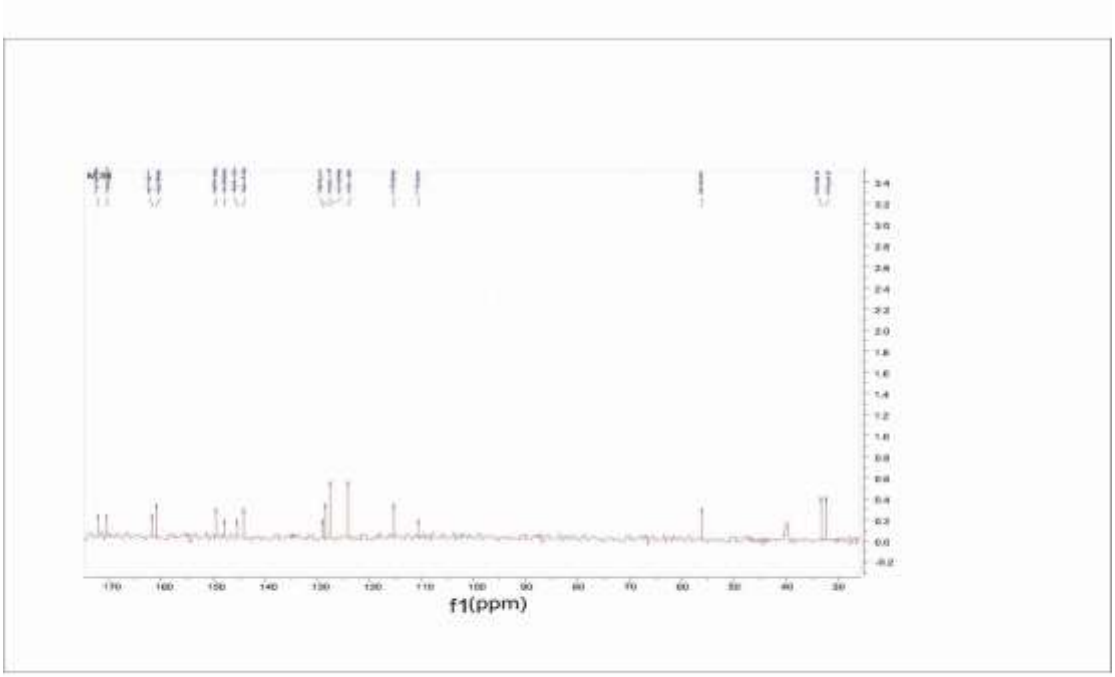


Figure (9):- ^{13}C-NMR spectrum of compound 3-(5-bromo-4-(4-methoxyphenyl)-6-oxo1,6-dihydropyrimidin-2-ylamino)-2-(4-nitrophenyl)-1,3- oxazepane-4,7-dione.

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