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Science

Synthesis and Characterization of 1,2-disubstituted -3-(pyrimidine-2-yl)-2,3-dihydro-1H-1,3-diazepine-4,7-dione

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Abstract

1,2-disubstituted-3-(pyrimidine-2-yl)-2,3-dihydro-1H-1,3-diazepine-4,7-dione were prepared from 2-amino pyrimidine via few steps were found to be useful synthesis for fully unsaturated monocyclic seven-membered heterocyclic ring.

In this work the Schiff bases (1-3) was prepared from condensation 2-amino pyimidine with ketones and aldehydes, and then converted into 1,3-oxazepine derivatives(4-6) from maleic anhydride in dry dioxane. Treatment of (4-6) with different amines compounds (hydrazine, 4-amino antipyrine, thiosemicarbazide, and 2-aminothiazole) gave the corresponding 1,3-diazepine derivatives (7-18).

Characterization of 1, 3-diazepine derivatives determined by physical properties and chemical structure confirmed by ^{1} HNMR and FTIR techniques.

Keywords: 1,3-diazepine, 1,3-oxazepine, heterocyclic ring system, seven- membered heterocyclic compounds.

Introduction

Schiff bases have wildly reported to be biologically versatile compounds having antifungal, herbicidal and plant growth regulating properties [1, 2].

The 7-membered heterocyclic ring system: 1, 3-oxazepine has already been reported in the literature. Irradiation of 4-phenyl-2-oxa-3-azabicyclo [3.2.0] hepta-3, 6-diene in n-hexane gave 2-phenyl-1, 3-oxazpeine in 80% yield [3- 8].

Many of the benzodiazepines and their oxides show interesting sedatives, muscle relaxant, and anticonvulsant properties in animals [9].

The discovery of the central nervous system activity (CNS) of the 1,4-benzodiazepine, several clinically useful drugs have been found which contain a heterocyclic moiety fused onto the seven-membered ring [10],also use (pyrido\thieno)-[f]-oxazepin-5-one derivatives in the treatment of neurological diseases and psychiatric disorders which are responsive to enhancement of synaptic responses mediated by AMPA receptors in the central nervous system[11].Many members of the diazepine family are widely used as anticonvulsants, antianxiolitics, analgesics, sedatives, antidepressives and hypnotic agents. Benzodiazepine derivatives are used as dyes for acrylicfibers.In addition; benzodiazepines are valuable intermediates for the synthesis of fused ring compounds such as triazolo-, oxadiazolo-, oxazino-, and furanobenzo-diazepines [12].

In the present work, the synthesis and characterization of new 1,2-substituted-3-(pyrimidine-2-yl)-2,3-dihydro-1H-1,3-diazepine-4,7-dione were carried out few steps of preparing started by 2-amino pyrimidine.

Experimental

Melting points were determined on Gallen kamp melting point apparatus and were uncorrected.

The IR spectra were measured as (KBr disc were recorded with Shimadzu - FTIR 8300 spectrophotometer.

The H^{1}NMR spectra were recorded on a *Brüker ACF* 300 Spectrometer operating at 300 MH_Z in DMSO-d_6.

Synthesis of 2, 2-disubstituted imine-N-pyrimidine-2-yl [13].(1-3)

To stirring solution of 2-amino pyrimidine (0.01 moles) in absolute ethanol (15 mL) appropriate aldehyde or ketone (0.01 mole) was added, mixture was refluxed for (3 hr.) and cooled to room temperature the precipitate was filtered and recrystallized from ethanol. Other

derivates were prepared by the same method, (See Table (1)).

[The[1] HNMR spectrum of compound (1) show the following :(DMSO-d6, TMS, 300MHz);] (Fig.(1)),
δppm = 8.21-8.20(d, 3H, arom.H); 6.60-6.51(dd, 4H, arom.H); 2.07(s, 3H, CH_3).

Synthesis of 2-disbsubtituted-3-(pyrimidine-2-yl)-1, 3-dihydro-1, 3-oxazepine-4, 7-dione [14].(4-6):

A mixture of (0.01 mole) an azomethine derivative and (0.01 mole) of maleic anhydride in (10 ml) of dry dioxane. The reaction mixture was refluxed for (2 hrs.) the solvent was then removed by filteration and the resulting solid was recrystallized from anhydrous THF. (See Table (1)).

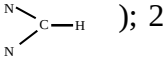
[The[1]HNMR spectrum of compound (6) show the following : (DMSO-d6, TMS, 300MHz);] (Fig.(2)), δppm=8.83-8.79 (d,3H, arom. H) ; 8.65-8.51 (d,2H,CH=CH) ;8.20-6.57(dd, 4H, arom.H);6.03(s,1H, ); 3.86(s, 3H, 0CH_3).

Reaction of amine derivatives with 2-disbsubtituted-3-(pyrimidine-2-yl)-1, 3-dihydro-1, 3-oxazepine-4, 7-dione [15],(7-18):

To a mixture of (0.005 mole) of compound (4) oxazepine suspended in (5 ml) of dry pyridine was added an excess (0.01 mole) of hydrazine. After 10 min of stirring the mixture at room temperature clear solution is obtained. The solution was refluxed for 1 hr., then left to cool to room temperature, and the separation crystalline solid was filtered and recrystallized from benzene.

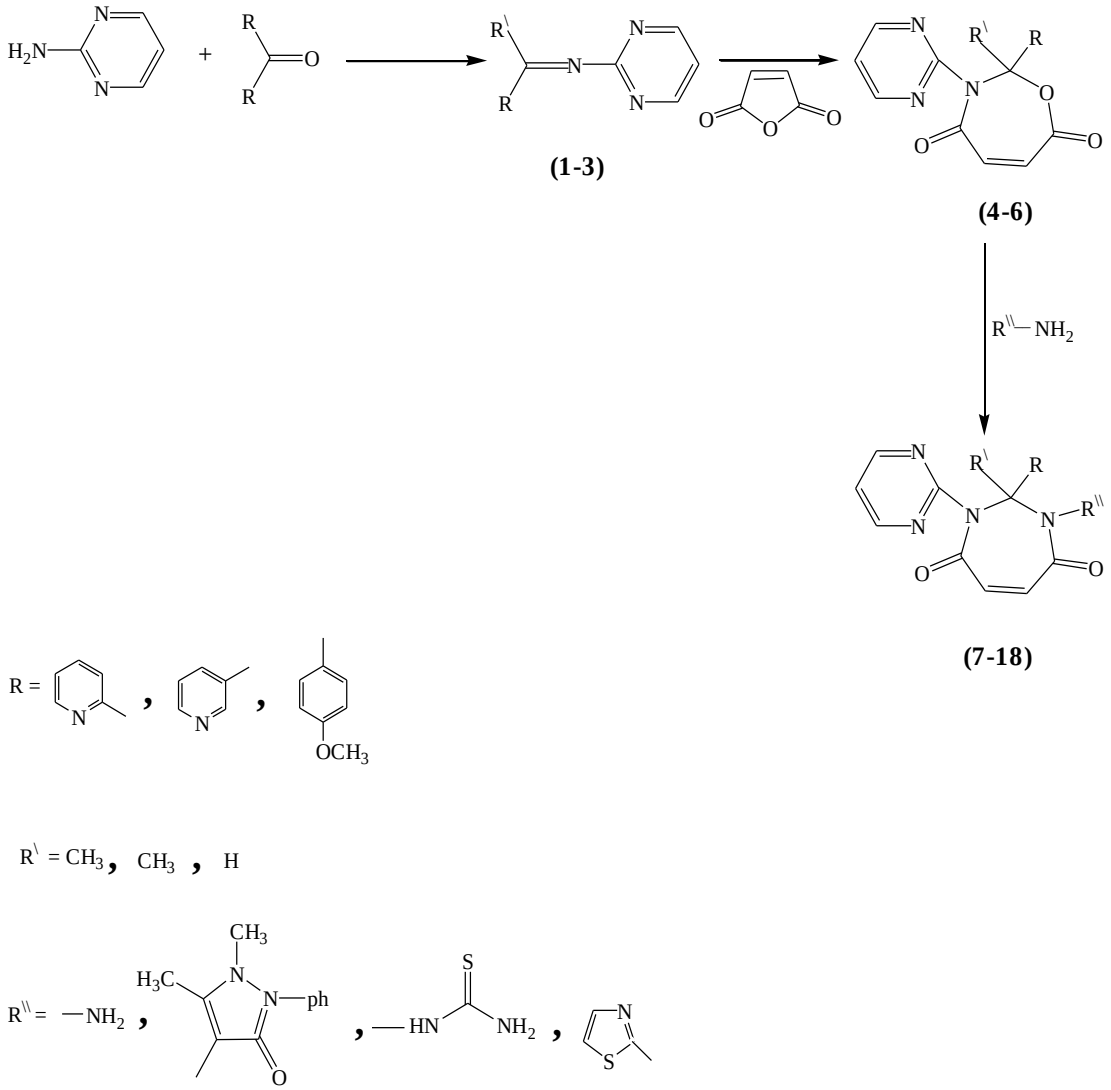
Several other derivatives was prepared following the same procedure, (See Table (1)).

[The[1]HNMR spectrum of compound (8) show the following: (DMSOd6, TMS, 300MHz);] (Fig.(3)), δppm=7.75-7.64 (d,3H, arom.H) ;7.26-7.09 (d,4H,arom.H); 9.86(s,2H, NH_2);7.39-7.34 (d,2H,CH=CH) ;1.22 (s,H,CH_3).

[The[1] HNMR spectrum of compound (12) show the following : (DMSOd6, TMS, 300MHz);] (Fig.(4)), δppm=8.21-8.20 (d,3H, arom.H); 7.52-7.38 (dd,4H,arom.H);7.02-7.00 (s,5H,arom.H); 7.77-7.75(d,2H,CH=CH) ; 3.80 (s,3H,0CH_3); 3.14(s,1H, ); 2.08(s,3H, CH_3).

[The[1] HNMR spectrum of compound (13) show the following : (DMSOd6, TMS,300MHz);] (Fig.(5)), δppm = 7.77-7.66 (d,3H,arom.H) ;7.27-7.22 (d,4H, arom.H); 7.40-7.25(d, 2H, CH=CH); 9.75(s, 3H, NH, NH_2); 1.23(s,H, CH_3).

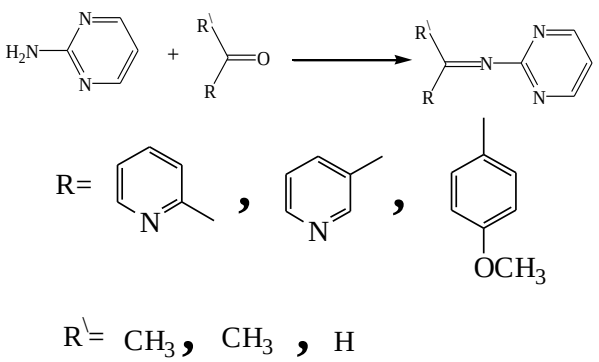
Scheme (1) shows the preparation steps of ١,٢-disubstituted-٣-(pyrimidine-2-yl)-2,3-dihydro-1H-1,3-diazepine-4,7-dione derivatives.



Scheme (1).

Resulting and Discussion

Schiff bases are prepared by condensation of 2-amino pyrimidine with aromatic aldehydes and ketones to give the azomethine compounds and identified by m.p.(see Table (1)), FTIR and ^{1}HNMR compounds (1-3).



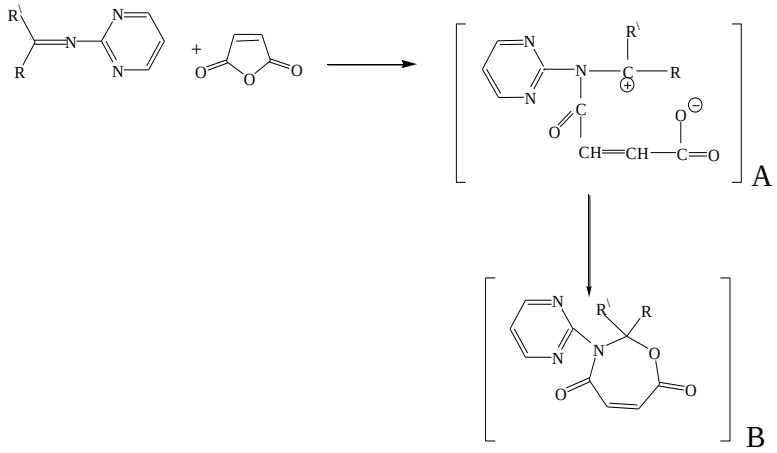
The reaction is followed by disappearance of (C=O) absorption band at (1690-1720) cm^{-1} with disappearance of NH_2 absorption bands of amino pyrimidine and appearance of (C=N) absorption band at (1645-1649) cm^{-1} (see Table (2)). Derivatives of oxazepine are prepared by reaction of maleic anhydride with Schiff bases derivatives (compounds 4-6). It was noted disappearance of the azomethine (C=N) absorption band and appearance of the (C=O) absorption band at (1670-1730) cm^{-1}.

The compounds of oxazepine derivatives are identified by m.p. (see Table (1)), and the important absorptions of FTIR of compounds (4-6) as showing in Table (3) and ^{1}HNMR.

The reaction of maleic anhydride with various Schiff bases is a type of a cyclo addition reaction.

Cyclo addition is a ring formation that results from the addition of л bonds to other σ or л with formation of a new σ bond.

The reaction is initiation by attack of the azomethine nitrogen at one of the two carbonyl groups of maleic anhydride yield the dipolar intermediate (A) which collapses to the natural species (B) which may be attributed to the fact that the combined (C=O) of the lactone and the (C=O) of the lactam in 7-membered ring.



It was demonstrated that the basic hydrolysis of 2,3-dihydro-1,3-oxazepine-4,7-diones is unsuccessful due to immediate reclosure on acidification to the original cyclic structure as evidenced by the fact that both the original 1,3-oxazepine-4,7-dione and assumed hydrolysis product have the same m.p, FTIR, and ^{1}HMNR[16].

Finally, preparation compounds (7-18) from reacted of compounds (4-6) with various amines compounds are identified by their m.p. (see table 1), and the important absorptions of FTIR of compounds (7-18) as showing in Table (4), and ^{1}HNMR.

It is important to note that the two absorption bands at (1800-1920) cm^{-1} and (1640-1780) cm^{-1} in the FTIR spectrum of pure maleic anhydride has disappear, when the anhydride became part of the 7-membered ring of the compounds (4-6), In addition, the nitrogen atom carry hydrogen, closure through elimination of water molecular to the cyclic structure and FTIR spectrum showed carbonyl group (C=O) stretching band at (1640-1660) cm^{-1},as showing below.

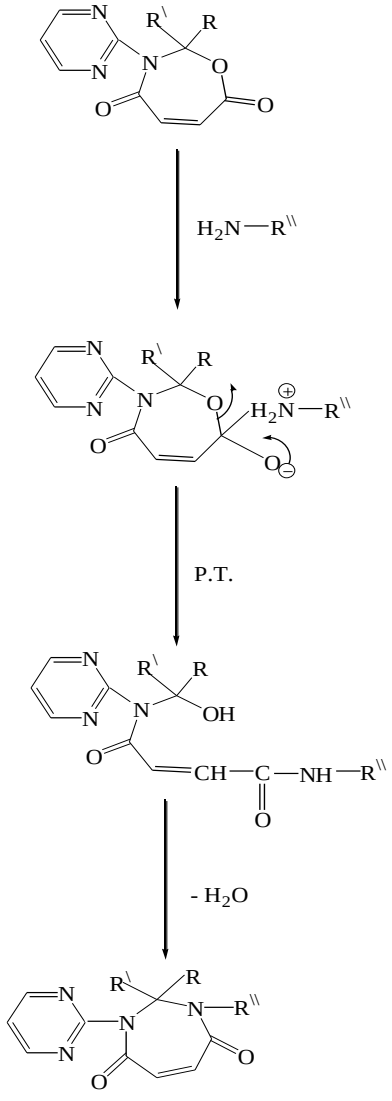


Table (1)
Physical properties of compounds (1-18).

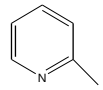
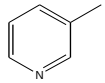
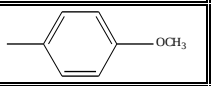
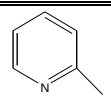
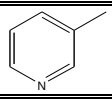
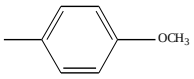
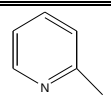
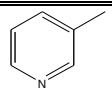
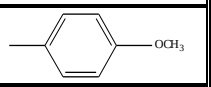
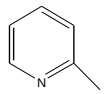
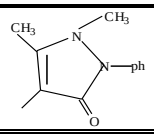
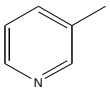
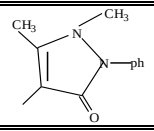
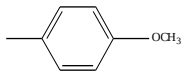
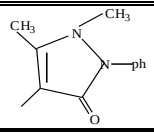
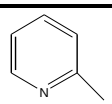
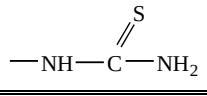
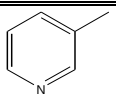
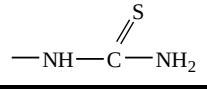
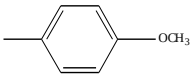
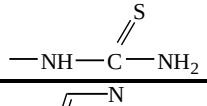
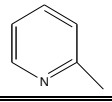
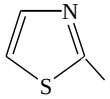
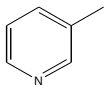
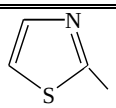
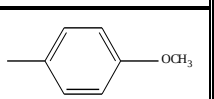
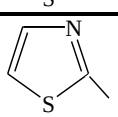
Comp.no.	*R*	*R*	*R*	*M.P.◦C*	*Yield %*	*Molecular formal*
1		CH_3	___	115-117	72	$C_{11}H_{10}N_4$
2		CH_3	___	119-121	86	$C_{11}H_{10}N_4$
3		H	___	146-148	75	$C_{12}H_{11}ON_3$
4		CH_3	___	230-232	67	$C_{15}H_{12}O_3N_4$
5		CH_3	___	149-150	63	$C_{15}H_{12}O_3N_4$
6		H	___	205-207	55	$C_{16}H_{13}O_4N_3$
7		CH_3	$-NH_2$	115-117	60	$C_{15}H_{14}N_6O_2$
8		CH_3	$-NH_2$	102-104	61	$C_{15}H_{14}N_6O_2$
9		H	$-NH_2$	d. 160	65	$C_{16}H_{15}N_5O_3$
10		CH_3		225-226	75	$C_{26}H_{23}N_7O_3$
11		CH_3		215-217	78	$C_{26}H_{23}N_7O_3$
12		H		158-160	80	$C_{27}H_{24}N_6O_4$
13		CH_3		210-212	67	$C_{16}H_{15}N_7O_2S$
14		CH_3		202-204	72	$C_{16}H_{15}N_7O_2S$
15		H		205-207	55	$C_{17}H_{16}N_6O_3S$
16		CH_3		229-231	50	$C_{18}H_{14}N_6O_2S$
17		CH_3		275-276	45	$C_{18}H_{14}N_6O_2S$
18		H		251-253	47	$C_{19}H_{15}N_5O_3S$

Table (2)
The major FTIR absorption (cm^{-1}) of compounds (1-3).

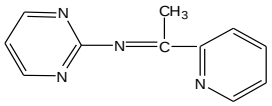
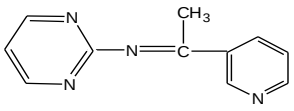
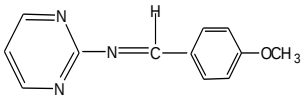
Comp. no.	*Structure*	*υ C-H aromatic cm^{-1}*	*υ C-H aliphatic cm^{-1}*	*υ C=N cm^{-1}*	*υ C=C aromatic cm^{-1}*
1		3166	2956	1649	1630-1525
2		3166.9	2958	1649	1635-1540
3		3170	2960	1645	1580-1520

Table (3)
The major FTIR absorption (cm^{-1}) of compounds (4-6).

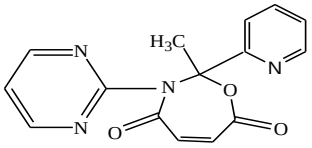
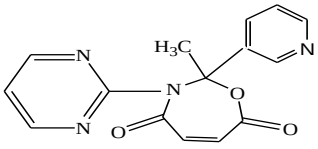
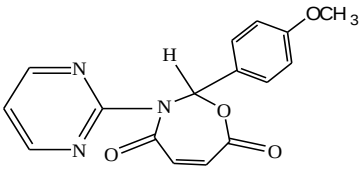
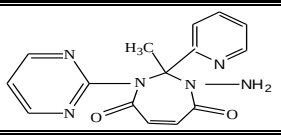
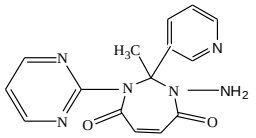
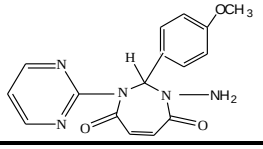
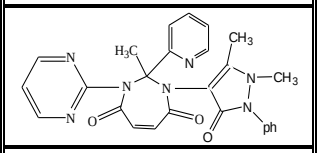
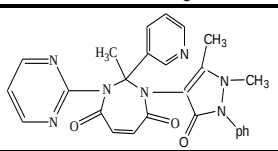
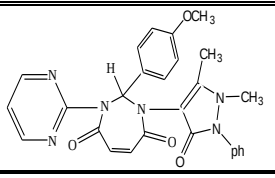
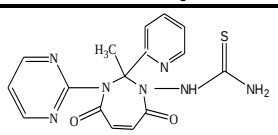
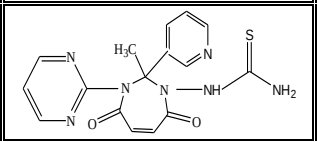
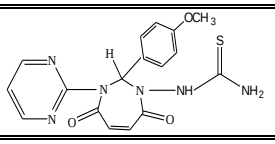
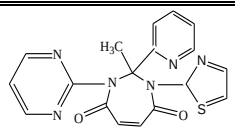
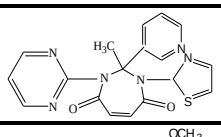
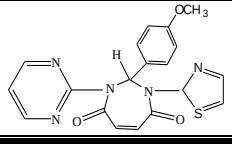
Comp. no.	*Structure*	*υ C–H aromatic cm^{-1}*	*=CH olefinic cm^{-1}*	*υ C=O cm^{-1}*	*υ C–O Lactone cm^{-1}*	*Y C=C Aromatic cm^{-1}*
4		3093	3155	1730	1250	1560
5		3084	3150	1697	1255	1560
6		3014	3130	1670	1245	1580

Table (4)
The major FTIR absorption (cm^{-1}) of compounds (7-18).

Comp. no.	*structure*	*NH_2,NH cm^{-1}*	*υ C-H aromatic cm^{-1}*	*υ C-H aliphatic cm^{-1}*	*υ C=O cm^{-1}*	*υ C=C aromatic cm^{-1}*
7		3300,3280	3080	2931	1660	1560
8		3380,3282	3060	2935	1631	1565
9		3411,3332	3093	2935	1655	1585
10		–	3070	2922	1654	1593
11		–	3085	2922	1652	1590
12		–	3060	2929	1645	1587
13		(3390,3280) NH_2, 3180 NH	3095	2923	1631	1539
14		(3395,3285) NH_2,3184 NH	3080	2924	1655	1585
15		(3400,3295) NH_2,3192 NH	3085	2923	1655	1595
16		–	3060	2922	1650	1530
17		–	3050	2923	1635	1554
18		–	3070	2945	1640	1550

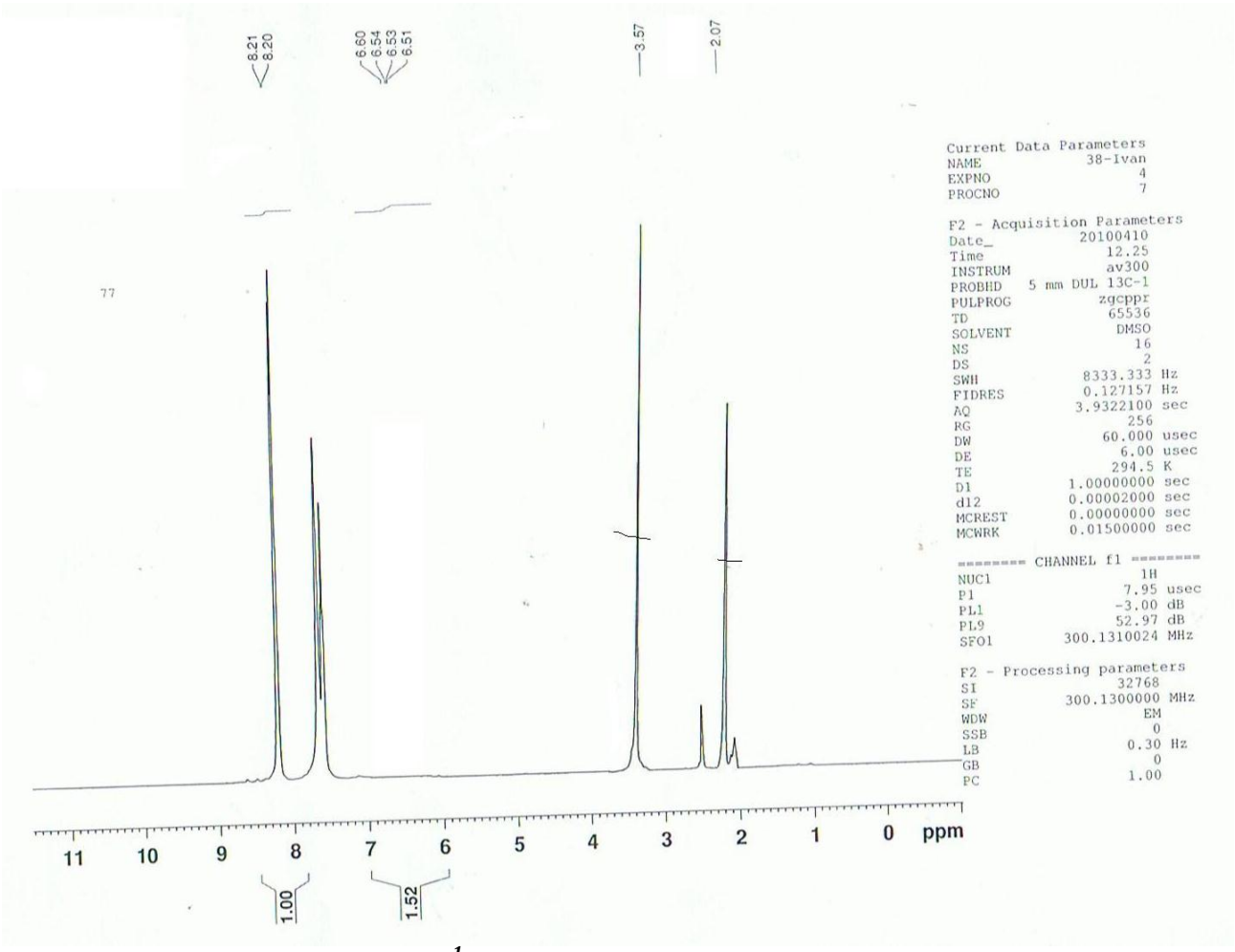


Fig. (1) ^{1}HNMR spectrum of compound 1.

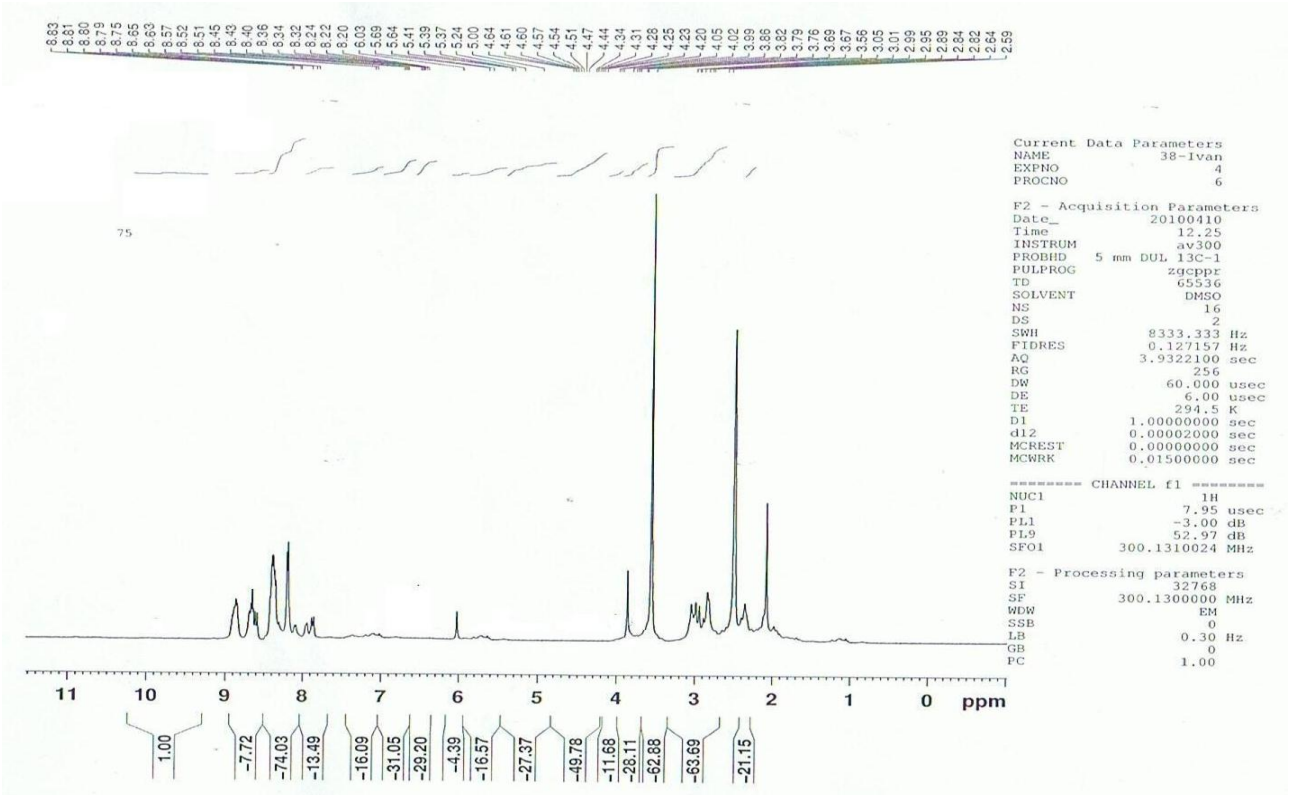


Fig.(2) ^{1}HNMR spectrum of compound 6.

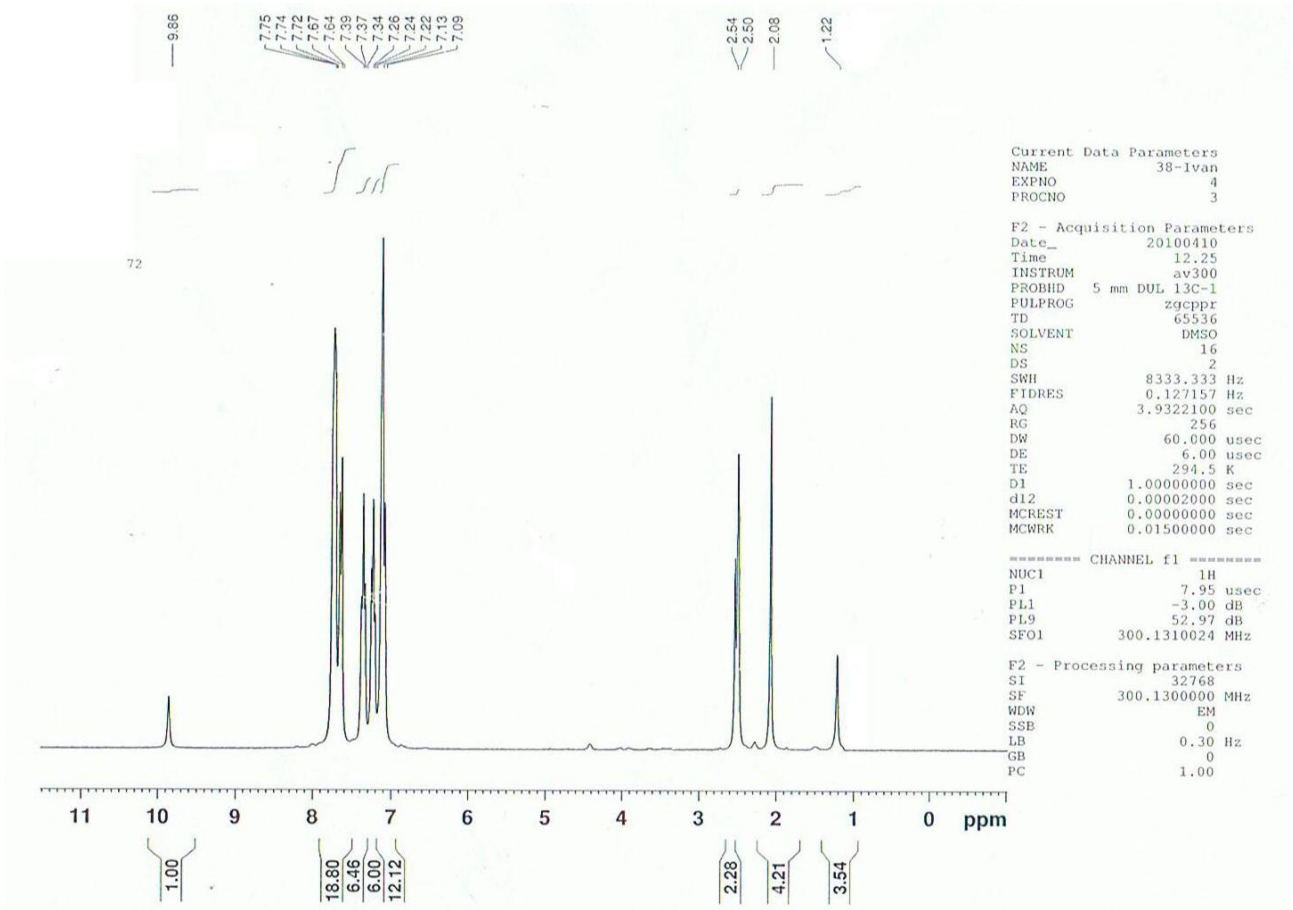


Fig.(3) ^{1}HNMR spectrum of compound 8.

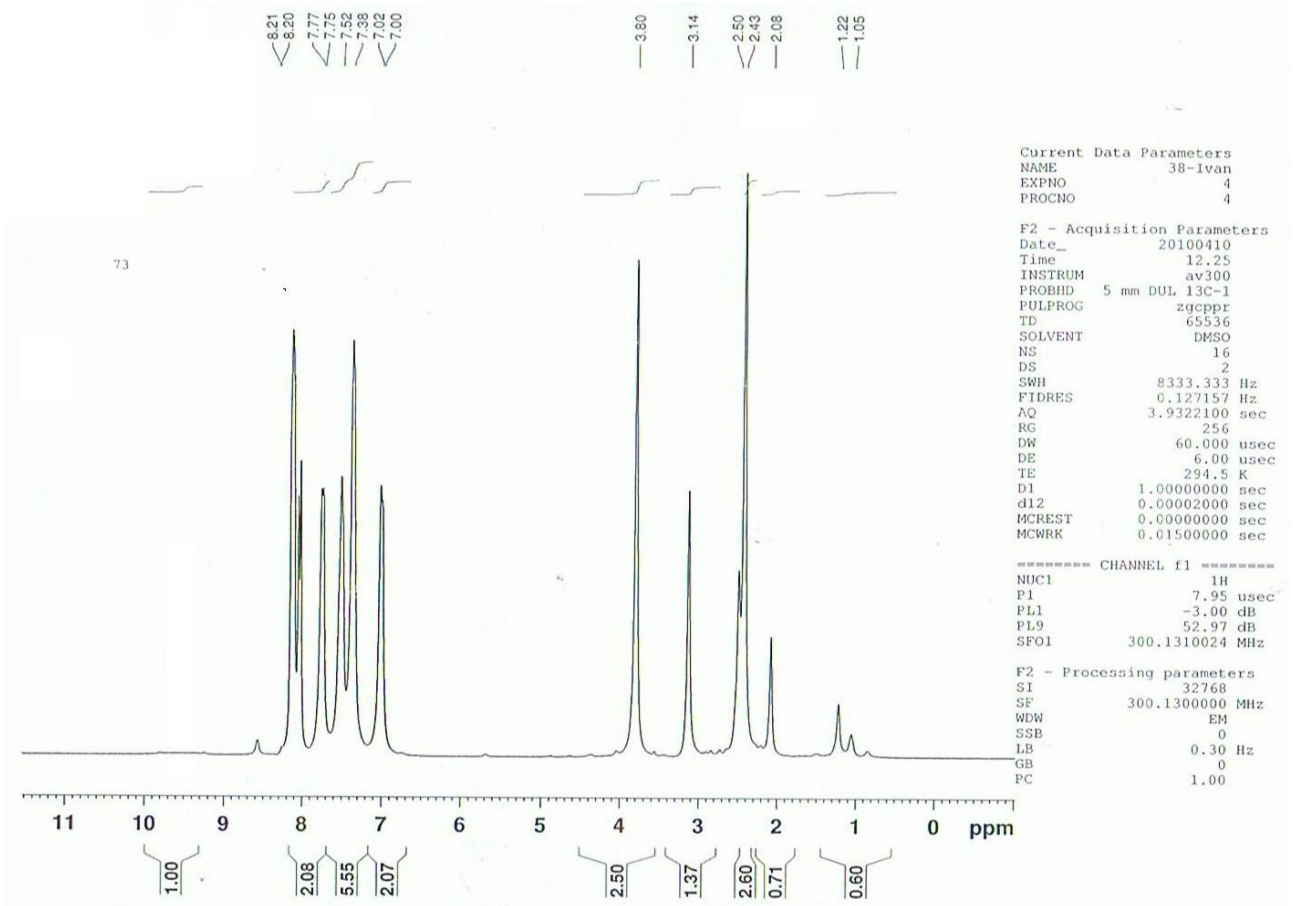


Fig.(4) ^{1}HNMR spectrum of compound 12.

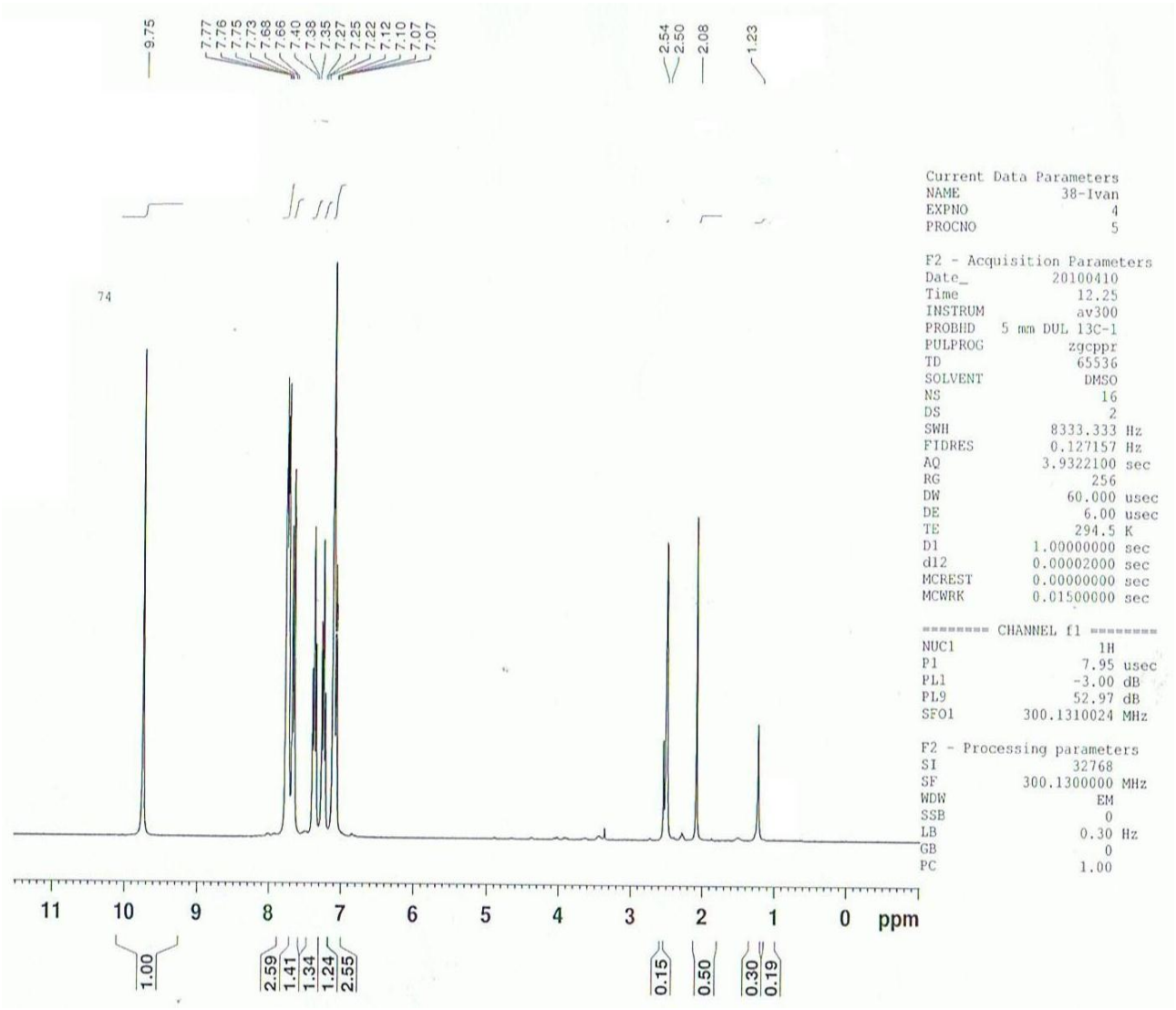


Fig.(5) [1]HNMR spectrum of compound 13.

Conclusions

In this paper, synthesis new seven-member heterocyclic ring systems (oxazepine and diazepine derivatives) which involve direct addition of maleic anhydride with the (C=N) double bond of Schiff bases, prepared derivatives structures were confirmed by physical properties and spectroscopic techniques.

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الخلاصة

٢,١-ثنائي التعويض-٣-(برمدين-٢- يل)-٣,٢-داي هايدرو-H١-١و٣-دايزبين-٧,٤-دايون حضر من تكاثف ٢-امينو برمدين بواسطة خطوات قليلة التي وجد بأنها مفيدة لتخليق مركبات حلقية سباعية غير متجانسة.

في هذا البحث حضرت قواعد شيف (١-٣) وذلك بمفاعله ٢- امينو برمدين مع بعض الكيتونات و الالديهايدات. وحولت الى مشتقات ٣,١- اوكسازيبين (٤-٦) بمفاعلت قواعد شف مع انهدريد الماليك في الدايوكسان الجاف،ومن ثم تم معاملتها مع مركبات امينيه مختلفة (هيدرازين،٢-أمينو أنتي بايرين، ثايوسميكاربازايد،٢-أمينو ثايازول) الى ١,٣-دايزبين القابلة (٧-١٨).وتم تحديد الخواص الفيزيائية لها،والتركيب الكيميائي بتقنيات الاشعة تحت الحمراء والرنين النووي المغناطيسي.