Synthesis and Characterization of New ethyl -2-(5-benzoxazol-2-ylamine-1H-tetrazol-1-yl) Acetate Derivatives

Nisreen Kais Abood
Science College, University of Al-Mustansiriya /Baghdad.
Email :serein_82@yahoo.com

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ABSTRACT

The present research work describes the synthesis of new heterocyclic compounds. The 2-Hydrazino benzoxazole pre-prepared was reacted with sodium nitrite and CuCN and afford the 2-cyano amine benzoxazole(1).Compound(1) react with sodium azide and ammonium chloride in DMF afford the 1-H-tetrazole-5-amino benzoxazole(2) ,ethyl chloroacetate react with compound (2) to give ethyl -2-(5-benzoxazol-2-ylamine)-1H-tetrazol-1-yl) acetate compound (3).Treatment (3)with thiourea or urea afforded compounds (4,5),p-bromo phenacyl bromide react with compounds (4,5) afforded (6,7),treatment (3) with hydrazine hydrate to afforded 2-(5-benzoxazol-2-ylamino)1-H-tetrazol-1yl) acetohydrazide compound (8) . Azomethines (9, 10) were prepared through reaction of compound (8) with aromatic aldehyde, then (9,10) converted to thaizolidinone derivatives (11,12) after treatment with $HSCH_2COOH$. Reaction of compound (8) with phenyl iso thiocyanate and ethyl chloro acetate afforded compounds (13, 14) respectively. All compounds were confirmed by their melting point, FT-IR spectrum,[1] HNMR spectrum for some them.

Keywords: Tetrazole , Benzoxazole, Thiozolidinone.

INTRODUCTION

Derivatives of benzoxazole have long been known for their varied pharmacological properties such as anti-inflammatory inhibitory[1] ,antioxidant, antitumor, antihistaminic [2] and hetero cyclic compounds display a broad spectrum biological activates 5-Subtituted 1,2,3,4-tetrazole are five member aromatic heterocyclic compound[3],containing 4-nitrogen atoms.5-substuted 1,2,3,4-tetrazole [4] are reported to possess antibacterial [5],antifungal [6],antiviral [7] ,analgesic [8],anti-inflammatory[9] , antiulcer[10] and antihypertensive activities[11] . On the other hand, the substituted tetrazole have long been known for their pharmaceutical activity as stimulants or depressants on the central nervous system [12] and are reported to show oral anti diabetic, anti-thrombotic and anti-microbial properties [13]. Thiazoles are important class of natural and synthetic compounds. Thiazole derivatives display a wide range of biological activities such as, cardiotonic, fungicidal sedative, anaesthetic, bactericidal and anti-inflammatory [13]. The synthesis of thiazole derivatives is important for their wide range of pharmaceutical and biological properties [14]. Oxazoles are a common structural motif found in numerous molecules that display antiviral , antifungal, antibacterial, and antiproliferative activities[15].

Experimental

The melting points were determined in open capillary tubes on a Gallen Kamp melting point apparatus and were uncorrected .The FT.IR Spectra of some prepared derivatives were taken on

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2412-0758/University of Technology-Iraq, Baghdad, Iraq

Shimadzu-2N,FTIR-8400 S.^{1}H-NMR Spectra of some prepared derivatives were recorded on a Varian-Mercury 300MHZ Spectrometer, d6-DMSO used as a solvent in^{1}H-NMR Spectra.

Preparation of N-(benzoxazol-2-yl)cyanamide(1):[13]

2-hydrazino benzoxazole (1.49gm ,0.01 mole) was added to a solution of concentrated hydrochloride acid (2.25ml)in water (4ml).The resulting solution is stirred for 10 min. and cooled to 0-5 °C, then a solution of sodium nitrite (0.76g,0.011mole) in water (2.5ml)was added dropwise. After stirred for 10 mints, the mixture was filtered and the filtrated was cooled to was stirring 0c° .A solution of CuCN (1.069g, 0.012mole) in water (2.5 ml) was added dropwise during which the evaluation of nitrogen gas was evaluated .After the addition is completed the mixture was stirred for 20 min, and the resulting solid was recrystllized by ethanol. (Table 1)

Preparation of N-(1-H-tetrazol-5-yl) benzoxazol-2-amine(2): [13]

A mixture of 2-cyano amine benzoxazole (1)(1.59g,0.01mole)and(0.74gm,0.01 mole)ammonium chloride in (10 ml)DMF was refluxed in oil bath at 125°C for 7hrs.The solvent was removed under reduced pressure ,the residue was dissolved in 100ml of water then carefully acidified to (PH 2) using hydrochloric acid then it was cooled to 5°C in ice bath and recrystallized from methanol. (Table 1)

Preparation of ethyl -2-(5-benzoxazol-2-ylamine)-1H-tetrazol-1-yl) acetate (3):[16]

Ethyl chloro acetate (1.1g ,0.01 mol) was add dropwise to stirred solution of compound (2) -1H-tetrazole-5-amine benzoxazole-2-amine (2g, 0.01 mol) and KOH (0.01 mol) in 20 ml absolute ethanol.

The reaction mixture was refluxed for 7 hours, after that filtered the product and recrystallized from chloroform. (Table 1)

Preparation2-(5-benzoxazol-2-ylamino)1-H-tetrazol-1-yl)N-carbamothioyl acetamide (4), 2-(5-benzoxazol-2-ylamino)-1-H-tetrazol-1-yl)N-carbamoyl acetamide (5).[17]

A mixture of ethyl 2-(5-amino-1-H-tetrazol-yl)acetat benzoxazole (2) (1.2 g, 0.005 mole) with (0.005mole) thiourea, urea respectively dissolving in 25ml absolute ethanol and refluxed for 5hrs. After cooling ,the product was filtered, and recrystallized from ethanol. (Table1)

Preparation 2-(5-benzoxazol-2-ylamino)1-H-tetrazol1-yl)N-4(N-bromo phenyl)thiazol-2-yl)acetamide(6),2-(5-benzoxazol-2-ylamino)1-H-tetrazol-1-yl)-N-4(N-bromo phenyl) oxazol2-yl)acetamide(7).[17]

A mixture of compounds(4,5) (0.002 mole) and (0.002 mole) of bromo phenacyl bromide were dissolved in 20 ml absolute ethanol ,then refluxed for 8hrs.The mixture was cooled and neutralized with ammonium hydroxide ,the precipitated was filtered off and washed with water and recrystallized from ethyl acetate . (Table 1)

Preparation of 2-(5-benzoxazol-2-ylamino)1-H-tetrazol-1yl) acetohydrazide (8):[18]

Ethyl -2-(5-benzoxazol-2-ylamine)-1H-tetrazol-1-yl) acetate (3) (0.8g, 0.003 mole) with hydrazine hydrate (0.15 g, 0.003mole) in 30ml absolute ethanol, then refluxed for (7-12) hrs. The precipitated solid was collected and recrystallized from ethanol. (Table 1)

Preparation of Schiff bases (9,10):[16]

To a stirring solution of compound(8) (2.7g, 0.01mole)in absolute ethanol (15ml),an appropriated different aldehyde (0.01 mole) was added with drops of acetic acid, and the mixture was refluxed for 6hrs.the mixture was cooled at room temperature and the precipitate was filtered and recrystallized from ethanol.(Table 1)

Preparation of thiazolidenones (11,12):[18]

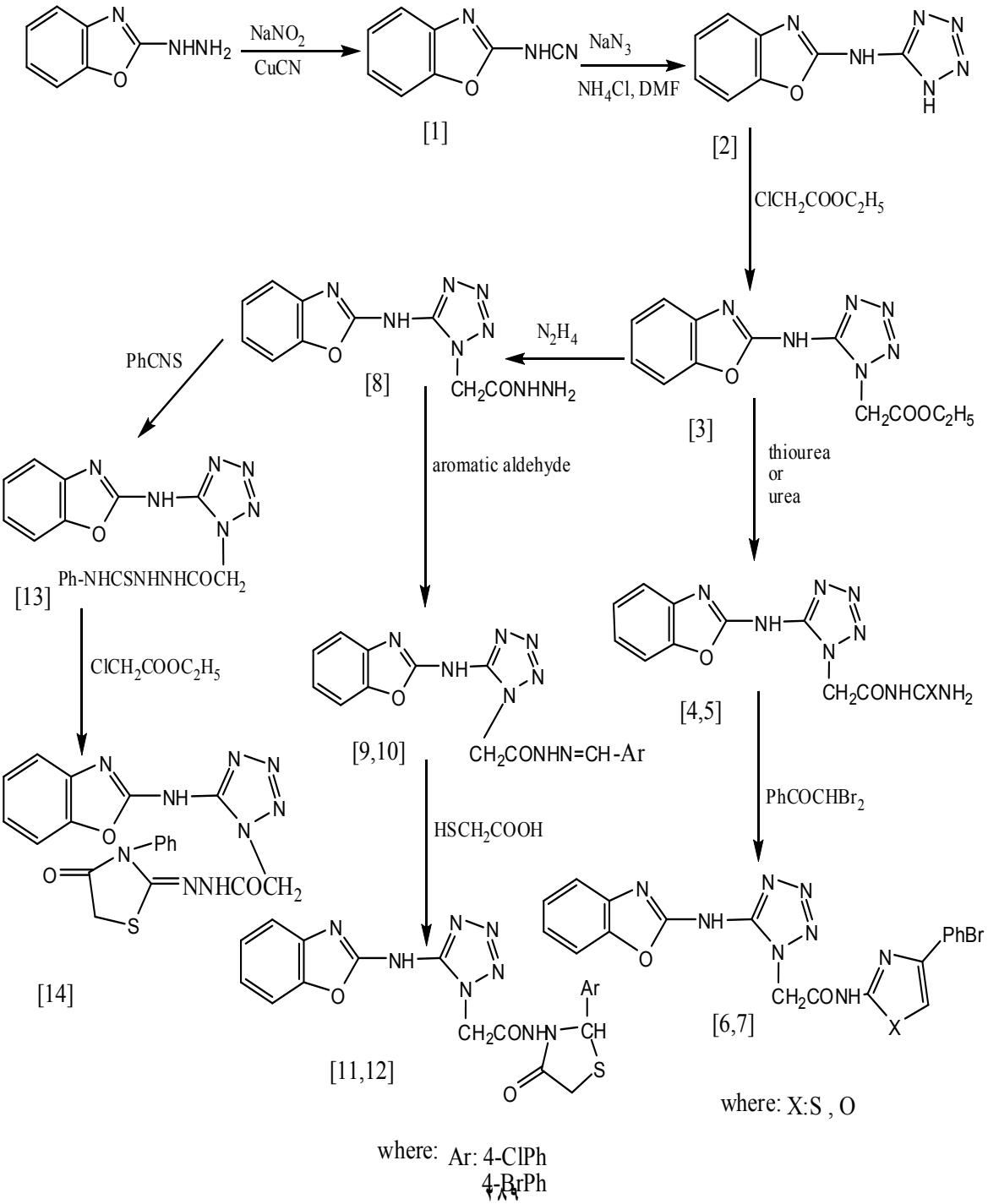
A mixture of compound of Schiff bases (9,10) (0.02 mole) and mercapto acetic acid (0.26 ml,0.04 mole) in dry benzene (30 ml)was refluxed for 10hrs.The mixture was concentrated and recrystallized from methanol. (Table 1)

Preparation 2-(2-(5-benzoxazol-2-ylamino)-1-H-tetrazol-1-yl) acetyl-N-phenyl hydrazine carbothioamide (13).[1]

A mixture of compound (8) (2g, 0.01mole) and phenyl iso thiocyanate (1.31ml, 0.01mole), in absolute ethanol (20 ml) was refluxed for 3hrs. The solid product was filtered and recrystallized from ethanol. (Table 1)

Preparation 2-(5-benzoxazol-20ylamino)1-Htetrazol-1-yl)-N(4-oxo-3phenyl thiazolidin2-ylidene)acetohydrazide(14).[1]

Ethyl chloro acetate (0.49, 0.004mole) was added dropwise to astirring solution of compound(13) (2g, 0.004mole) and anhydrous sodium acetate(0.004mole)in (20 ml) absolute ethanol .The reaction mixture was refluxed for 6hrs. The solid product was filtered and recrystallized from ethanol. (Table 1**)**



Scheme (1):Synthesis New Compoundes (1-14)

DISCUSSION

New N-(1-H-tetrazol-5-yl)benzoxazol-2-amine derivatives containing fused heterocyclic moiety were prepared following the reaction sequence depicted in scheme**(1).**2-Hydrazino benzoxazole pre-prepared was reacted with sodium nitrite and CuCN to gave the N-(benzoxazol-2-yl) cyanamide 1.The FT-IR spectra show the disappearance the NH_2 and appearance the stretching band 2162cm^{-1} of (C≡N) (table 1).Treatment compound 1 with sodium azide and ammonium chloride in DMF Afforded Compound 2.The FT-IR Spectra Show The Disappearance Of (C≡N) And Appearance The Tetrazole Ring 1180cm^{-1} ,1286cm^{-1}(N-N=N) Table1, ^{1}H-NMR(DMSO_D_6) Ppm Of Compound **(2)** :4.0(S,1H,N<u>H</u>),7.3-7.7 CH Aromatic Protons Table 2. Condensation Compound 2 With Ethyl Chloro Acetate To Form Ethyl -2-(5-Benzoxazol-2-Ylamine)-1H-Tetrazol-1-Yl) Acetate **(3)**. The FT-IR Spectra Show The Appearance Carbonyl Of Ester C=O 1739 Cm^{-1} (Table 1), ^{1}H-NMR(DMSO_D_6)Ppm Of Compound **(3)**: 4.0 (S, 1H ,NH), 4.12(S,2H,C<u>H</u>$_2$),5.42(S,2H,C<u>H</u>$_2$CH$_3$),1.19(T,3H,CH$_2$C<u>H</u>$_3$),6.6-7.7CH Aromatic Protons Table2,Then Condensation Compound **(3)** With Thiourea Or Urea To Afford Compound**(4,5),**The FT-IR Spectra Show Disappearance Carbonyl Of Ester And Appearance The CONH Stretching Band At (1683,1678)Cm^{-1} Respectively (Table 1),^{1}H-NMR(DMSO_D_6) Ppm Of Compound **(4)**: 4.0(S,1H, NH),8.0 (S,1H, N<u>h</u>sec .Amide), 9.5 (S,2H,N<u>H</u>$_2$amine),5.6(S,2H,C<u>H</u>$_2$ Methylene) 7.3-7.9 CH Aromatic Protons Table 2.Reaction Compound **(4,5)** With Bromo Phenacyl Bromide Afforded Compound **(6,7),**FT-IR Spectra Show The Appearance Carbonyl Of Amide (1672,1681)Cm^{-1} (Table 1).Condensation Ethyl-2-(5-Benzoxazol-2-Ylamine)-1H-Tetrazol-1-Yl) Acetate with Hydrazine Hydrat To Formed2-(5benzoxazol 2-Ylamino)1- Htetrazol-1yl) Aceto Hydrazide **(8)**, FT-IR Spectra Show The Disappearance Carbonyl Of Ester And Appearance Carbonyl Of Amide CONH 1675cm^{-1} Table 1^{1}H-NMR (DMSO _D_6)Ppm Of Compound **8**: 4.22(D,2H,NHN<u>H</u>$_2$) ,9.08(S,1H,N<u>H</u>NH$_2$),4.0 (S,1H,CN<u>H</u>),7.3-7.7 CH Aromatic Protons Table 2 . Condensation Hydrazide 8 With Aryl Schiff Bases 9,10 In Absolute Ethanol ,The Formation Of These Schiff Bases Was Indicated By The Presence In Their FT-IR Spectra Which Show Azomethine CH=N Stretching At (1623-1628)Cm^{-1},Treatment Of Schiff Bases **(9,10)** With Mercaptoacetic Acid In Dry Benzene Gave Thiazolidenone Derivatives**(11,12)** Structure Of These Compounds Were Confirmed By The Presence Of C=O Stretching Band At (1720-1718) Cm^{-1}due To Thiazolidinone Ring(Table 1).Treatment Compound **(8)** With Phenyl Isothiocyanate Afforded The Corresponding Thiosemicarbazide **(13)**.The FT-IR Spectra Show The Appearance C=S Stretching Band At 1272cm^{-1} And NH Stretching Band At 3296cm^{-1} Table 1, ^{1}H-NMR(DMSO_D_6) Ppm Of Compound **13** :4.0 (S,1H,CN<u>H</u>),5,6(S,2H,C<u>H</u>$_2$methylen),10.08(S,1H,N<u>H</u>NH), 2.0 (D,1H ,NH N<u>H</u>) ,12.5(S,1H,N<u>h</u>ph),7.3-7.7 Charomatic Protons Table 2. Refluxing Of Compound **(13)** With Ethyl Chloro Acetate Afforded 4-Thioazolidone Derivatives **(14)** Which Was Confirmed By The Presence Of C=O Stretching Band At 1695 Cm^{-1} And C=N Stretching Band 1634cm^{-1} (Table 1), ^{1}H-NMR(DMSO_D_6) Ppm Of Compound **14**:4.1(S,1H,NH),10.58(S,1H,NH Hydrazid) ,4.16(S,2H,S-C<u>H</u>$_2$),5.6(S,2H,C<u>H</u>$_2$ Methylene),7.3-7.7 CH Aromatic Protons (Table 2).

Table (1): Physical Prpoperties and Spectral Data Of Compounds.

NO	formula	M.P. C°	Yield %	Color	Recrystallizion Solvent	Infrared data cm^{-1}
1	$C_8H_5N_3O$	230-232	70	Brown	Ethanol	3267NH, 2162 C≡N, 3091 C-H arom. ,1157 C-O-C
2	$C_8H_6N_6O$	250-252	65	Brown	Methanol	3221 NH,1286(N-N=N-),1180 tetrazol ring ,3009 C-H arom.,1585 C=Car.
3	$C_{12}H_{12}N_6O_3$	223-225	66	White	Chloroform	1739 C=O ester,2931 CH alph.,3066 C-H arom.,1605C=N,1581C=Carom.
4	$C_{11}H_{10}N_8O_2S$	166-168	60	White	Ethanol	1678 C=ONH,2924 C-H aliph ,3039 C-Harom.,3412-3398N-H_2,1182 tetrazol ring
5	$C_{11}H_{10}N_8O_3$	190-192	55	White	Ethanol	1683C=ONH,2987 C-H aliph.,3062C-H arom.,3248 N-H_2,1180 tetrazol ring.
6	$C_{19}H_{13}BrN_8O_2S$	210-212	60	Yellow	Ethyl acetate	1681 C=O amide ,2978 C-H aliph.,3045 C-H arom. ,1649 C=N, 1597 C=C.
7	$C_{19}H_{13}BrN_8O_3$	222-224	65	Brown	Ethyl acetate	1672 C=O amide, 2931-2810 C-H aliph.,3021C-H arom., 1638 C=N.1554 C=C.
8	$C_{10}H_{10}N_8O_2$	198-200	70	White	Ethanol	1675 C=Oamide ,3321-3221 N-H_2 ,2981C-H aliph. 3091 C-H arom.,1182 tetrazole ring,1550 C=C , 1630 C=N.
9	$C_{17}H_{13}ClN_8O_2$	165-167	75	Orange	Ethanol	3308 N-H,3026 C-H arom.,1628 CH=N ,1006 C-Cl
10	$C_{17}H_{13}BrN_8O_2$	178-180	77	Orange	Ethanol	3184 N-H,3024 C-H arom.,1623 CH=N ,1049 C-Br
11	$C_{19}H_{15}ClN_8O_3S$	214-216	65	Dark yellow	Methanol	3290 N-H, 3093 C-H arom.,2895 C-H aliph.,1720 C=O, 1016 C-Cl.
12	$C_{18}H_{15}BrN_8O_3S$	224-226	60	Yellow	Methanol	3311 N-H, 3020 C-H arom., 2909 C-H aliph., 1718 C=O,1034 C-Br, 1631 C=N.
13	$C_{17}H_{15}N_9O_2S$	200-202	60	Brown	Ethanol	3296-3180N-H,3080 C-H arom., 1272 C=S.
14	$C_{19}H_{15}N_9O_3S$	220-222	65	Brown	Ethanol	1695C=O,3210N-H,2920 C-H aliph. 1634 C=N.

Table(2): Chemical Schiff's ^{1}h-Nmr Spectra.

No.	^{1}H-NMR (DMSO_d_6)δ ppm
2	4.0(s,1H,NH),7.3-7.7 CH aromatic protons
3	4.0 (s, 1H ,NH) ,4.12(s,2H,CH_2),5.42(s,2H,CH_2CH_3),1.19 (t,3H,CH_2CH_3) ,6.6-7.7CH aromatic protons
4	4.0(s,1H, NH),8.0 (s,1H, NH .amide), 9.5 (s,2H,NH_2amine), 5.6 (s,2H,CH_2 methylen) 7.3-7.9 CH aromatic protons
8	4.22(d,2H,NHNH_2),9.08(s,1H,NHNH_2),4.0 (s,1H,CNH),7.3-7.7 CH aromatic protons
13	4.0 (s,1H,CNH),5,6(s,2H,CH_2methylen),10.08(s,1H,NHNH), 2.0 (d,1H ,NH NH) ,12.5(s,1H,NHPh),7.3-7.7 CHaromatic protons
14	4.1(s,1H,NH),10.58(s,1H,NH hydrazid),4.16(s,2H,S-CH_2),5.6 (s,2H,CH_2 methylene),7.3-7.7 CH aromatic protons

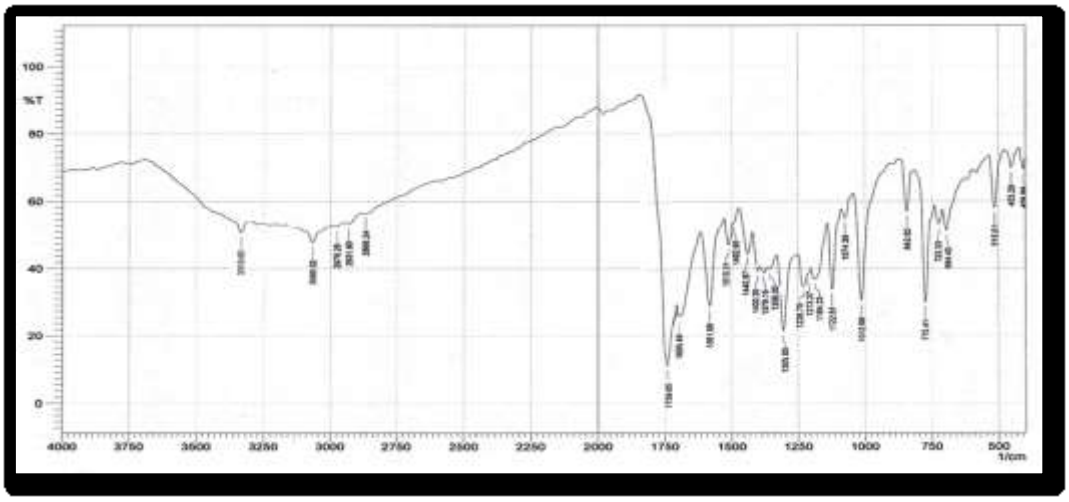
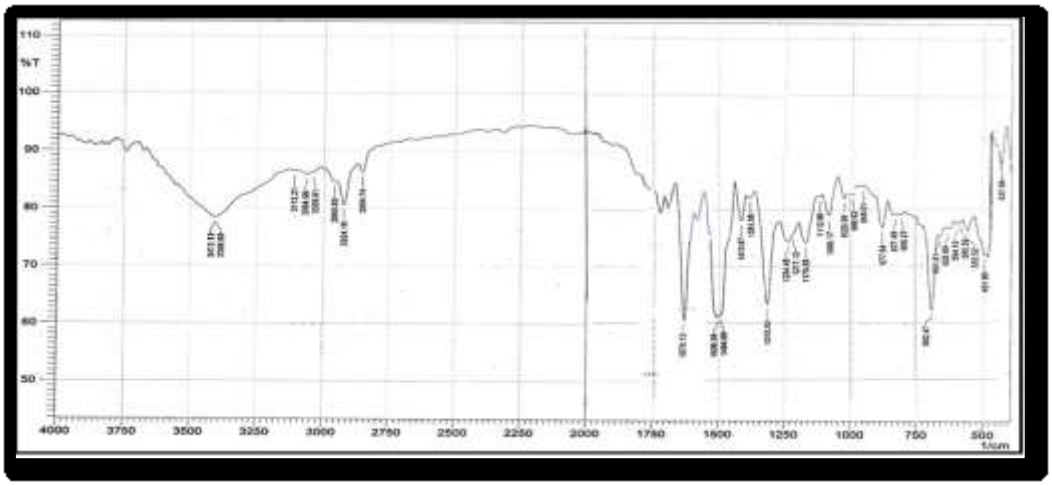


Figure (1):FT-IR Spectrum of compound (3).



Figure(2): ^{1}H-NMR Spectrum of compound(3).

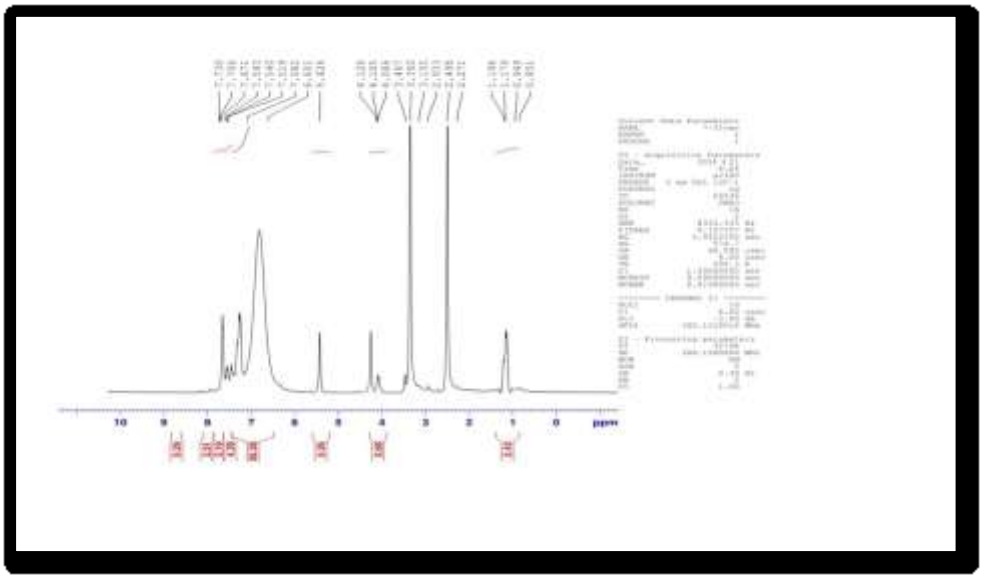


Figure (3): FT-IR Spectrum of compound (4).

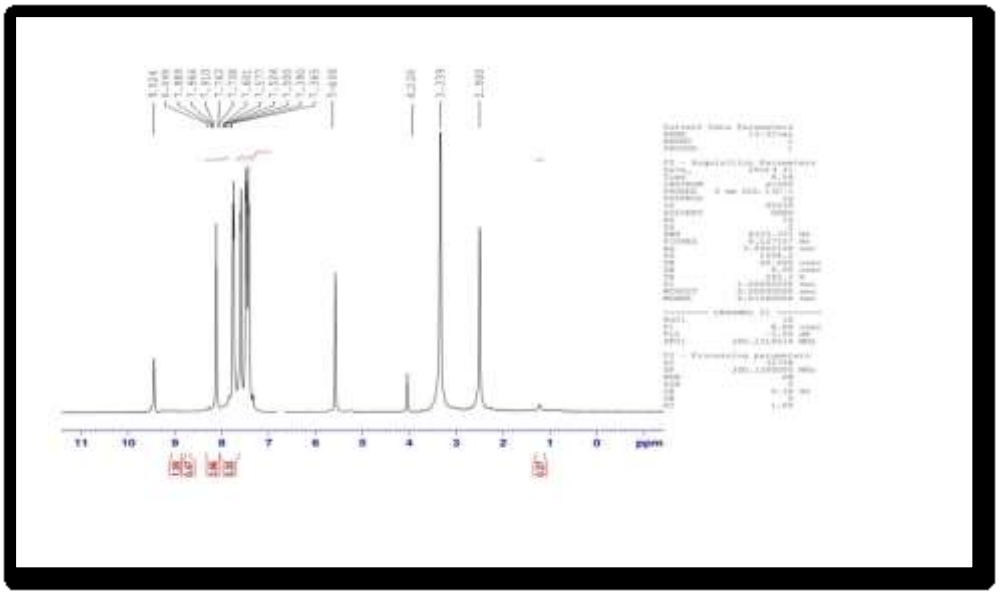


Figure (4): ^{1}H-NMR Spectrum of compound (4)

CONCLUSION

In this work, new compounds tetrazole,azomethines and thiazoldinone derivatives were synthesized from the starting materials 2-hydrazino benzoxazole. These compounds have differents properties such as the colors , melting point ,FT-IR Spectrum and ^{1}H-NMR Spectrum ,were prepared new organic hetrocyclic compounds .

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