Synthesis of Some New Heterocyclic Fused Rings Compounds Based on 5-Aryl-1,3,4-Oxadiazole

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Abstract

The work includes synthesis and characterization of some new heterocyclic compounds, as flow: The compound (3) (5-(4-chlorophenyl) -2-hydrazinyl-1,3,4-oxadiazole was synthesized by using two methods; the first method includes the direct reaction between hydrazine hydrate 80% and 5-(4-chlorophenyl)-2- (ethylthio) 1,3,4-oxadiazole (1), the second method involves converting 5-(4-chlorophenyl)-1,3,4-oxadiazol-2-amine (2) to diazonium salt then reducing this salt to compound (3) by stannous chloride. Compound (3) was used as starting material for synthesizing several fused heterocyclic compounds. The compound 6-(4-chlorophenyl)[1,2.4] triazolo [3,4,b][1,3,4] oxadiazole-3-(2H) thione (compound 4) was synthesized from the reaction of compound (3) with carbon disulfide in presence of potassium hydroxide. Compound 6-(4-chlorophenyl)-[1,2,4] triazolo [3,4-b][1,3,4] oxadiazole-3-amine (5) was synthesized from treatment of compound (3) with cyanogen bromide at room temperature in the presence of sodium hydrogen carbonate. Direct reaction between acetic acid and compound (3) in $POCl_3$ affords 6-(4-chlorophenyl)-3-methyl-[1,2,4] triazolo [3,4,b][1,3,4] oxadiazole (compound 6). Five new fused rings derivatives (12-16) [6-(4-chlorophenyl)-3-(aryl)-[1,2,4] triazolo[3,4-b][1,3,4]oxadiazol] were synthesized by two steps. The first step was synthesized by corresponding Schiff bases (7-11) from reaction compound (3) with five aryl aldehyde. These Schiff bases were used as substrate to synthesize compounds (12-16) by treating these compounds with bromine in glacial acetic acid in dry sodium acetate.The synthesized compounds were characterized by FTIR,H-NMR,C-NMR and CHNS analysis.

Keywords:, 1,3,4-Oxadiazole, Triazole.

Introduction

Heterocycles and their derivatives are one of the most important species in organic chemistry. These are considered an interesting material due to their diverse biological activity. A large number of medications includes heterocycle in their chemical structure. In recent years, the oxadiazole ring and triazole ring occupied the importance of extensive scientific research. The 1,3,4-oxadiazoles and their derivatives known with their wide biological activity for instant, Anticancer [1], Anti-inflammatory. [2, 3].,Anti-urease[4], Antibacterial[5], Anti-fungal. [6] and Anti-allergic[7]. Furthermore the oxadiazoles derivatives exhibited interested physical properties such as electrochemical properties [8, 9], electro-optical properties[10], Luminescence property [11, 12] and photophysical properties[13]. In other hand, the triazole derivatives as well display intensive biological activity for instant, analgesic activities[14], antioxidant [15], antitumor activity[16], anticancer[17], urea's inhibition activity[18], antifungal [19] and anti-tuberculosis[20].It is well known in medicinal chemistry, that combining two different pharmacophores in same structure enhances the biological activities for the resulting compound [21-23]. According to this fact, incorporation of two different heterocyclic had significant attention. Synthesis and biological activity of fused heterocyclic also occupied paramount in scientific research. Recently, researchers strengthened attention to synthesis and biological activity of fused heterocyclic. Survey of literatures discloses that s-triazolo [3,4-b]-1,3,4-thiadiazole rings, have received significant attention at the recent years for their pharmacological properties. For instant, antifungal activity[24], antibacterial activities[25], anti-HIV-1 activity [26], antimicrobial activity[27], anticancer activity[28], antioxidant and anti-inflammatory activity [29].In this research, we will present synthesized new fused oxadiazole –triazole as promising bioactive compounds**.**

Experimental

The FTIR spectra were discovered by FTIR 600, CHNS analysis was recorded by EURO EA 3000 , NMR ready60,60MHz spectrometer at Central Service Laboratory/ College of Education for Pure Sciences (Ibn Al-Haitham), University of Baghdad, NMR Ultra shield 300 MHz, Bruker, Switzerland (University of Al-albayt / Jordon), $CDCl_3$ and DMSO-d_6 were used as the solvent. The chemicals and solvent which consumed for synthesizing target compounds were brand Sigma-Aldrich, Fisher and Merck. Uncorrected open capillary tube was used to distinguish the melting point by MEL-TEMP II instrumental. Purities of compounds were checked with a thin layer chromatography (Silica gel TLC) plate's brand Merck.The spot located by iodine vapors or UV lights.

1-Synthesis of 5-(4-chlorophenyl)-2-hydrazinyl-1,3,4-oxadiazole(3)

The product was obtained from two methods:

Method A

5-(4-chlorophenyl)-2-hydrazinyl-1,3,4-oxadiazole was synthesized by refluxing a mixture of 5-(4-chlorophenyl)-2-(ethylthio)1,3,4-oxadiazole (5 g , 20 mmol) and excess of hydrazine hydrate 80% (10mL) in ethanol for 48 hrs. The progress of reaction was monitored by T.L.C using ethyl acetate: hexane (3:1) as eluent. Upon cooling the precipitate was separated and collected by filtration. The crud product was washed with toluene to afford bulbous shine dishes crystals. Yield 48 %; M.P. 163-165°C;.FTIR (KBr, cm^{-1}); 3309,3222,3153 (NH_2,NH) 3016 (CH_{Ar})1657, 1612 (C=N) 1558, 1489 (C=C) 1095 (C-O-C); ^{1}H-NMR (DMSO-d_6,300 MHz,ppm): 4.47 (bs, 2H, NH_2) 7.485 (d,2H, H_{Ar} *J*=8.3) 7.795 (d, 2H, H_{Ar} *J*=8.3) 9.81 (s, 1H,

NH); ^{13}C-NMR (DMSO d_6 .75MHz, δppm): 120.93 (1C,C1), 128.15 (2C, C2), 129.59 (2C, C3), 137.28 (1C, C4) 153.65 , 154.14 (2C, C=N).

Method B

To the mixture of 5-(4-chlorophenyl)-1,3,4-oxadiazol-2-amine (1.95 g 10 mmol) and 4N hydrochloric acid (15mL) cooled in an ice-bath , an aqueous solution of $NaNO_2$ (1.38 g, 20 mmol) in 3mL distilled water was added slowly. After cooling to 0 ºC, a mixture of $SnCl_2$ (2.84g, 15 mmol) and conc. HCl (10 mL) was added drop wise within 20 minute. After 4hrs, the reaction mixture was filtered. The residues were dissolved in aqueous KOH (25%) extracted with ether (3 × 25 mL). The combined organic layer was dried. The volatiles were removed to give corresponding hydrazine. Yield 62% .

2-Synthesis of 6-(4-chlorophenyl)[1,2.4] triazolo [3,4,b][1,3,4] oxadiazole-3-(2H) thione(4)

Excess of carbon disulfide (0.5g, 6.5mmol) in one portion was added to a mixture of 5-(4-chlorophenyl)-2-hydrazinyl-1,3,4-oxadiazole (0.52 g, 2.47mmol) potassium hydroxide (0.14g, 2.5mmol) in absolute ethanol (8 mL), was added at ambient temperatures. The mixture was heated under refluxed for 24hr. The solvent was removed under vacuum. Distilled water (16 mL) was added to the residue and stirred for another 15 minutes, then it was filtered and the filtrate was acidified with 5% hydrochloric acid and finally re-filters. The white precipitate was washed with water, recrystallized with ethanol then purified by column chromatography using hexane: ethyl acetate (3:1) as eluent to afford white precipitate. Yield 57 % (0.35g); M.p. 172-173 °C. FTIR (KBr, cm^{-1}); 3290 (NH) 3105 (CH_{Ar}) 1658 (C=N) 1599, 1485 (C=C) 1294 (C=S) 1093 (C-O-C); ^{1}H-NMR (DMSO-d_6,300 MHz,δppm); 7.525 (d,2H, H_{Ar} *J*=9) 7.835 (d, 2H, H_{Ar} *J*=9) 9.85 (bs, 1H, NH); ^{13}C-NMR (DMSO-d_6,75 MHz, δppm): 110.89 (1C , C1) 113.98 (2C, C2) 116.52 (2C, C3) 137.24 (1C, C4) 155.09, 155.65 (2C, C=N) 181.91 (1C, C=S).

3-Synthesis of 6-(4-chlorophenyl)-[1,2,4]triazolo[3,4-b][1,3,4]oxadiazole-3-amine (5)

A solution of 5-(4-chlorophenyl)-2-hydrazinyl-(1,3,4) oxadiazole (0.5g, 2.3mmol) in (10 mL) methanol and sodium bicarbonate (0.2 g, 2.3mmol) was stirred in 50 mL round bottom flask, then (0.25 g, 2.3mmol) cyanogen bromide was added. The mixture was left reflexing for 24hrs.After that (15 mL) cold water was added to the mixture. The precipitate was collected and dried.The precipitate was crystallized from methanol to obtain purple amorphous. Yield 70% (0.39g); M.p. 148°C;.FTIR (KBr, cm^{-1}); 3255 (NH_2), 3118 (CH_{Ar}), 1658 (C=N), 1599, 1485 (C=C) 1090 (C-O-C); ^{1}H-NMR (DMSO-d_6,300 MHz, δppm): 7.31 (bs, 2H, NH2) 7.6 (d,2H, H_{Ar} *J*=6) 7.8 (d, 2H, H $_{Ar}$ *J*=12). ^{13}C-NMR (DMSO-d_6, 75 MHz, δppm): 122.65 (1C, C1) 127.69 (2C, C2) 129.61 (2C, C3) 134.12 (1C, C4) 159.82, 160 14, 162.61 (3C, C=N) .

4-Synthesis of 6-(4-chlorophenyl)-3-methyl-[1,2,4] triazolo [3,4 ,b][1,3,4] oxadiazo- le(6).

A mixture of acetic acid (0.14 mL) and 5-(4-chlorophenyl)-2-hydrazinyl-1,3,4-oxadiazole (0.5 g,2.3mmol) in 50 mL round flask , excess of phosphorus oxychloride (4 mL) was added in a few portions at room temperature .The mixture was stirred and refluxed for 3 hrs in a water bath at 90°C.After cooling the mixture was poured into crushed ice (25mL) and stirred for 15 minutes. Sodium hydroxide was added in few portions until the pH was adjusted to 7-8.The precipitate was filtered, washed with water and dried. The crude product was purified

from column chromatography to afford brown amorphous. Yield 54% (0.3 g); M.p. 80-85°C;.FTIR (KBr, /cm^{-1}) : 3080 (CH_{Ar}) 2929,2854 (CH_{aliph}),1647 (C=N) 1589, 1479 (C=C) 1090 (C-O-C); ^{1}H-NMR ($CDCl_3$,60 MHz, δ,ppm): 2.58 (s, 3H,CH_3) 7.44 (d,2H, H_{Ar} *J*=8.4) 7.95 (d, 2H, H_{Ar} *J*=8.4).

General synthesis of 2-(4-chlorophenyl)-5-(2-(aryl) hydrazinyl-1,3,4-oxadiazole (7-11).

Aryl aldehyde (2.3mmol) was added gradually to suspension of 5-(4-chlorophenyl)-2-hydrazinyl-1,3,4-oxadiazole (0.5g,2.3mmol) in 10mL acetic acid: ethanol (1:1). After the addition, the mixture was refluxed for 24hrs.Upon cooling, the precipitate was filtered and washed with cold water and crystallized from methanol.

5- 2-(2-(4-chlorobenzyildene) hydrazinyl)-5-(4-chlorophenyl)-1,3,4-oxadiazole(7).

The crude product was crystallized from methanol to obtain light brown precipitate. Yield 86% (0.68 g) :M.p .235-240 °C, FTIR (K Br / cm^{-1}): 3132 (NH) 1651, 1601 (CH=N& C=N) 1558, 1489 (C=C) 1095 (C-O-C); ^{1}H-NMR (DMSO-d_6,300MHz, δ, ppm): 7.52-7.96 (m,8H,H_{Ar}) 8.45 (s,1H,$CH=N_{minor}$) 8.72 (s, 1H,$CH=N_{major}$) 12 (s, 1H, NH).

6- 2-(4-chlorophenyl)-5(2-(4-methoxybenzylidene)hydrazinyl)-1,3,4-oxadiazole (8).

The crude product was recrystallized from methanol to obtain off white precipitate. Yield 79% (0.61g) :M.p .184-187 °C, FTIR (KBr, cm^{-1}): 3286 (NH) 3078 (CH_{Ar}) 2968,2933 (CH_{aliph}) 1662,1604 (CH=N,C=N) 1543 ,1452 (C=C) 1254 (C-O) 1099 (C-O-C); ^{1}H-NMR (DMSO-d_6,300 MHz, δ,ppm):3.77 (s,3H,CH_3) 6.985 (d, 2H, H_{Ar} *J*=9) 7.565 (d, 2H, H_{Ar} *J*=9) 7.635 (d, 2H, H_{Ar} *J*=9) 7.885 (d, 2H, H_{Ar} *J*=9) 8.35 (s, 1H, CH=N) 11.74 (s, 1H, NH).

7- 2-(4-chlorophenyl)-5-(2-(methylbenzylidene) hydrazinyl)-1,3,4-oxadiazole(9).

The crude product was recrystallized from methanol to obtain off white precipitate. Yield 75% (0.55g):M.p.206-209 °C, FTIR (K Br, cm^{-1}): 3192 (NH) 3018 (CH_{Ar}) 2924,2848 (CH_{aliph}) 1645,1601 (CH=N,C=N) 1564,1485 (C=C) 1093 (C-O-C); ^{1}H-NMR (DMSO-d_6,300MHz,δ,ppm): 2.35 (s,3H,CH_3) 7.29-7.95 (m, 8H ,CH_{Ar}) 8.41 (s, 1H,CH=N) 11.85 (s, 1H, NH).

8- 2-(4-chlorophenyl)-5-(2-(3-nitrobenzylidene) hydrazinyl)-1,3, 4 – oxadiazole (10).

The crude product was recrystallized from methanol to obtain light brown precipitate. Yield 90% (0.73g) :M.p.215-219°C;FTIR (KBr,cm^{-1}): 3222 (NH) 3062 (CH_{Ar}) 1658, 1601 (CH=N,C=N) 1535,1485 (C=C) 1404, 1342 ($C-NO_2$) 1082 (C-O-C); ^{1}H-NMR ($CDCl_3$, 60 MHz, δ, ppm): 7.09-7.81 (m,8H,H_{Ar}) 8.44 (s, 1H,CH=N) 12.11 (s, 1H, NH).

9- 2-(4-chlorophenyl)-5(2-(4-bromobenzylidene) hydrazinyl)-1,3,4-oxadiazole (11).

The crude product was recrystallized from methanol to obtain yellow precipitate. Yield 88% (0.78g): M.p.220-227°C,FTIR (KBr, cm^{-1}): 3209 (NH) 3032 (CH_{Ar}) 1628 (C=N) 1552, 1479 (C=C) 1090 (C-O-C); ^{1}H-NMR ($CDCl_3$,60 MHz, δ,ppm): 7.23-7.89 (m,8H,H_{Ar}) 8.56 (s, 1H,CH=N) 9.27 (s, 1H, NH).

General synthesis of 6-(4-chlorophenyl)-3-(aryl)-[1,2,4] triazolo[3,4-b][1,3,4] oxadi -azol(12-16).

2-(4-chlorophenyl)-5-(2-(aryl) hydrazinyl -1,3,4-oxadiazole (0.4mmol) in 4 mL glacial acetic acid and anhydrous sodium acetate(0.8mmol) in 50 mL round bottom flask, bromine (0.45mmol in 1mL AcOH) was added drop wise at ambient temperature with vigorous stirring. The mixture was refluxed at 90-100 °C for 24hs. Upon cooling, the mixture was poured into 25mL ice water. The resulting precipitate was collected and washed with distilled water, dried and purified by recrystallized with ethanol.

10- 3,6-bis(4-chlorophenyl)-[1,2,4] triazolo [3,4-b] [1,3,4] oxadiazole(12).

Crude material was recrystallized from ethanol to obtain light brown solid. Yield 51% (0.067g) ; M.p. 242-244°C ; FTIR. (KBr, cm^{-1}) 3086 (CH_{Ar}) 1604 (C=N) 1543, 1475 (C=C) 1090 (C-O-C); ^{1}H-NMR (DMSO-d_6, 300 MHz, δ, ppm): 7.725 (d, 4H, H_{Ar} *J*=9) 8.165 (d, 4H, H_{Ar} *J*=9). ^{13}C-NMR (DMSO-d_6,75 MHz, ppm): 117.18 (1C , C1) 125.77 (2C, C2) 129.73 (2C, C3) 135.73 (1C, C4) 154 82,162.41,162.45(3C=N).

11-6-(4-chlorophenyl)-3-(4-methoxyphenyl)- [1,2,4]triazolo[3,4,b][1,3,4]oxadiazol- e(13).

The solid product was recrystallized from ethanol light brown precipitate. Yield 49% (0.063 g); M.p. 236-238 °C; FTIR (KBr, cm^{-1}): 3084 (CH_{Ar}) 2922,2854 (CH_{aliph}) 1606 (C=N) 1549,1475 (C=C) 1273 (C-O) 1084 (C-O-C); ^{1}H-NMR(DMSO-d_6, 300 MHz, ppm): 3.83 (s,3H,OCH_3) 6.67 (d, 2H, H_{Ar} ,*J* =6) 7.08 (d, 2H, , H_{Ar} ,*J*=6) 7.51 (d, 2H, H_{Ar}, *J*=6) 7.92 (d, 2H, , H_{Ar} *J*=6) ,^{13}C-NMR (DMSO-d_6,75 MHz, δ,ppm): 55.80 (1C , C12) 114.48 (2C, C9) 123.45 (2C, C2) 125.15, (1C,C1),125.67 (1C,C8) 129.32 (2C, C3) 130,75 (2C, C10) 137.07 (1C, C4) 150.1, 152.53,153.11(3C,C5,C6,C7) 155.46(1C,C11).

12- 6-(4-chlorophenyl)-3-(4-tolyl)-[1,2,4]triazolo[3,4-b] [1 ,3 , 4]- oxadiazole(14)

The product was recrystallized from ethanol to obtain off white crystals. Yield 48%(0.059 g); M.p. 200-208°C; FTIR.(KBr, cm^{-1}): 3051 (CH_{Ar}) 2979,2918 (CH_{aliph}.) 1606 (C=N)1549,1479 (C=C) 1082 (C-O-C); ^{1}H-NMR (DMSO-d_6,60 MHz, δ,ppm): 2.37 (s, 3H, CH3) 7.32-8.17(m,8H,CH_{Ar}).

13- 6-(4-chlorophenyl)-3-(3-nitrophenyl)-[1,2,4] triazolo [3.4- b][1,3,4]oxadiazole (15).

The crude product was recrystallized from ethanol to give light brown precipitate. Yield 56% (0.076g); M.p. 210 °C. FTIR (KBr,cm^{-1}):3080 (CH_{Ar}) 1604 (C=N) 1529, 1479 (C=C) 1090 (C-O-C); ^{1}H-NMR (DMSO-d_6, 60 MHz, δ,ppm): 6.87-7.85 (m,8H, CH_{Ar}).

14- 3-(4-bromophenyl)-6-(4-chlorophenyl)[-1,2,4] triazolo [3,4-b] [1,3,4]oxadiazo- le(16).

The solid precipitate was recrystallized from ethanol to give brown precipitate. Yield 50% (0.074 g); M.p. 135 °C; FTIR (KBr, cm^{-1}): 3045 (CH_{Ar}) 1601 (C=N) 1525, 1485 (C=C) 1093 (C-O-C); ^{1}H-NMR (DMSO-d_6, 60 MHz,δ,ppm): 7.63-795 (m, 8H, H_{Ar}).

Result and discussion

5-(4-chlorophenyl)-2-hydrazinyl-1,3,4-oxa-diazole(3) was synthesized by two methods; the first method was by heating the compounds (1) with hydrazine hydrate in ethanol for 48hrs, the second method was achieved from reaction of compound 2 in 4N hydrochloric acid with sodium nitrite at 0 ºC then with $SnCl_2$. The second method granted reasonable yield (62%) while, the first method granted lower yield (48%). However, synthesized compound 3 was relied upon the first method. The general synthesis route demonstrated in Scheme (1).This resulting compound was characterized by FTIR, ^{1}H-NMR,^{13}C-NMR spectrum besides to CHNS analysis. The FTIR spectrum exhibited new signals at 3309, 3222 and 3153 cm^{-1} which are attributed to existence of NH_2 and NH group. The peaks at 3016, 1657, 1612 and 1558,1489 cm^{-1} belonged to CH aromatic, imine group (C=N) and C=C respectively. The ^{1}H-NMR spectra showed disappearing protons of alkyl group from the starting material (first method) and displayed new broad peaks at 4.47 ppm , 9.81 ppm which are attributed to NH_2 and NH respectively as depicted in Figure (1).The ^{13}C-NMR of compound 3 exhibited 6 signals, four of them attributed to1,4-substituted phenyl ring, and the other two carbon was appropriate with existence of oxadiazole ring, as depicted in Figure (2). The peaks at 120.93ppm fit with carbon attached the oxadiazole ring C1 .The two peaks at 128.15ppm and 129.59ppm corresponding to C2and C3 respectively. The peak at 137.28 ppm attributed to C4 which is attached with chlorine atom. The proposed mechanism for first method described in the following scheme(3).The mechanism of converting aromatic diazonium salt to their corresponded hydrazine in the presence of stannous chloride was already known as reduction of aromatic diazonium chloride with $SnCl_2$ [30]. Compound 3 have been utilized as starting material to formation fused newly oxadiazole-triazole ring. Compound 4 successfully synthesized from reaction of compound 3 with CS_2 in the presence of potassium hydroxide in ethanol. The resulting compound characterized from their FTIR, ^{1}H -NMR, ^{13}C-NMR spectra and CHNS analysis Table (1). Disappearing the NH_2 from FTIR spectrum demonstrated the first evidence for successful cyclization of 5-(4-chlorophenyl) -2-hydrazinyl-1,3,4-oxadiazole with CS_2. Furthermore, the FTIR spectrum exhibited the NH signal at 3290 cm^{-1} and shifting in value of C=N peak due to formed endo-exo imine [31]. The signal at 1294 cm^{-1} which can be attributed to C=S showed that the thione tautomer was predominated than the thiol tautomer. The disappearing of NH_2 from ^{1}H-NMR spectrum enhances the evidences of formation the newly fused oxadiazole-triazol ring. The aromatic protons appeared as two doublets; 7.525ppm (d, 2H, H_{Ar} J=9Hz) 7.835ppm (d, 2H, H_{Ar} ,J=9Hz). The ^{13}C-NMR showed clear shifting into high field for C2 and C3 at 113.98 and 116.52ppm. Moreover, shifting into law filed in value of two C=N group (155.65 and 155.09 ppm). The characteristic peak at 181.91 ppm attributed to C=S identify the thione tautomer. New fused heterocyclic was formed from reaction the 5-(4-chlorophenyl) -2-hydrazinyl-1, 3, 4-oxadiazole with cyanogen bromide in the presence of sodium bicarbonate as a scavenger. The target compound characterized by FTIR, ^{1}H-NMR and ^{13}C-NMR . The Disappearance of NH signal from FTIR spectrum and shifting the NH_2 signal from 3309 cm^{-1} to 3255 cm^{-1} endue first evidence of successful the cyclization. Moreover, all expected signals were appeared such as 3118cm^{-1} for CH aromatic, 1658 cm^{-1} for C=N and 1599,1485 cm^{-1} for C=C. The ^{1}H-NMR spectra exhibited fade the NH peak and shift value of NH_2 from 4.47 ppm to 7.31ppm confirmed the proposed structure and clarified that the NH_2 attached aromatic ring. The^{1}H-NMR displayed two doublet peaks at 7.6ppm and 7.8ppm for four protons H2 and H3 respectively belonged to 4-chlorophenyl attached fused rings as depicted in Figure (3). The ^{13}C-NMR spectra showed four peaks 122.65, 127.69 ,129.61ppm and 134.12ppm for C1, C2, C3 andC4 respectively attributed to 4-chlorophenyl attached with fused rings as depicted in Figure(4).The proposed mechanism Scheme(4) suggested that the amine group attacked the CN group without losing bromide ion and the hybridization of carbon convert from sp to sp^2 as well as at the next step the hybridization of carbon converts from sp^2 to sp^3. These

suggested steps could be convinced because migrating leaving group from sp^3 was more acceptable than sp^2 and sp; which is known to be inefficient when compared to a leaving group on sp^3 hybridized carbon [32]. Furthermore, the mechanism of nucleophile addition at 2-chloro or 2-bromo nitrogen heterocyclic such as pyridine, imidazole, Benzimidazole, and pyrrole included convert the Sp^2 carbon to Sp^3 before losing hydrogen chloride or hydrogen bromide[33]. Compound 6 was synthesized from reaction of compound 3 with acetic acid in the presence of Phosphorus oxychloride as dehydrating agent. The pure compound characterized by FTIR, ^{1}H-NMR and CHN analysis. The FTIR spectrum displayed disappearing both of NH and NH_2 peaks as well new peaks of CH aliphatic was appeared at 2929,2854 cm^{-1}. The aromatic CH appeared at 3080 cm^{-1} and C=N appeared at 1647 cm^{-1}.The ^{1}H-NMR spectrum exhibited characteristic singlet peak for three protons at 2.58 ppm which is attributed to CH_3 group attached aromatic ring. This peak was fair evidence for successful cyclization. Moreover the ^{1}H-NMR spectrum showed the aromatic protons as two doublet peaks; 7.44ppm integrated for two protons with *J*=8.4Hz attributed to H2 and 7.95ppm for two proton of H3 with *J* =8.4 Hz. as depicted in Figure(5). Five new Schiff basses (7-11) were synthesized from reaction substituted benzaldehyde with 5-(4-chlorophenyl) -2-hydrazinyl-1,3,4-oxadiazole. The new compounds were synthesized to be intermediate compounds for next step to synthesize 3-aryl fused 1,2,4-triazolo-1,3,4-oxadiazole 12-16 .The synthesized compounds were characterized by FTIR, ^{1}H-NMR and CHN analysis. The FTIR spectra of compounds 7-11 showed the disappearance of the peak of NH_2 at 3309 cm^{-1}. The FTIR spectrum of compound 7 showed the NH peak at 3132$cm^{-1}$and 1651,1601cm^{-1} attributed to endo-exo and conjugated C=N and CH=N [31].The ^{1}H-NMR spectrum of the compound 7 exhibited eight protons appeared as multiplied peak at (7.52-7.96) ppm. Interested two peaks at 8.72 ppm (s, $CH=N_{major}$) and 8.45 ppm (s, $CH=N_{minor}$) with integration of one proton attributed to existence of two geometrical isomer E and Z [34, 35]. Moreover, the ^{1}H-NMR displayed the NH peak at 12.00 ppm. The FTIR spectrum of compound 8 showed the peak of NH at 3286cm^{-1} as well showed the aromatic CH at 3078cm^{-1} and the aliphatic CH at 2968, 2933cm^{-1}. The C=N and CH=N appeared at 1662, 1604cm^{-1} respectively and C=C appeared at 1543 and 1452cm^{-1} besides to 1254 cm^{-1} which is attributed to C-O. The ^{1}H-NMR spectrum of this compound showed the following peaks at 3.77(s, 3H, OCH_3) 6.985(d, 2H, H_{Ar}, *J*=9) 7.565(d, 2H, H_{Ar}, *J*=9) 7.635(d, 2H, H_{Ar}, *J*=9) 7.885(d, 2H H_{Ar} *J*=9) 8.35 (s, 1H, CH=N) 11.74 (s, 1H, NH). Compound 9 displayed the peak of NH at 3192cm^{-1} and the CH aromatic and aliphatic at 3018 and 2924, 2848cm^{-1}respectively. Although the signal of C=N and CH=N appeared at 1645, 1601cm^{-1}, the ^{I}H-NMR spectrum of the compound confirm the existence of CH=N at 8.41 ppm. Furthermore, the H-NMR spectrum exhibited the three protons of *para* methyl at 2.35ppm and the aromatic protons appeared as multiplied, integrated for eight protons. The peak of NH group appeared at 11.85 ppm. The FTIR spectrum of compound 10 exhibited the NH peak at 3222 cm^{-1}, while the aromatic CH appeared at 3062 cm^{-1}. The peak of C=N group appeared at, 1658 and 1601cm^{-1} (for exo-endo).The peaks of C=C group were appeared at 1535 and 1485 cm^{-1}.The ^{1}H-NMR spectrum of this compound showed the eight aromatic protons as multiplied at range (7.09-7.81) ppm. The proton of imine group appeared at 8.44 ppm and the proton of NH appeared at 12.11ppm. The FTIR spectrum of compound 11 showed the essential peaks at 3209, 3032, 1628, 1552 and 1479 cm^{-1} for NH, Aromatic CH, imine group and C=C respectively. The ^{1}H-NMR spectrum of this compound exhibited characteristic peaks of aromatic rings as multiples at 7.23-7.89 ppm. The proton of Schiff base was appeared at 8.56 ppm as singlet peak also singlet peak attributed to NH appeared at 9.27 ppm. Newly synthesized compounds (12-16) were synthesized from reacting 2-(4-chlorophenyl)-5-(2-(substituted benzylidene) hydrazinyl)-1,3,4-oxadiazole (7-11) with bromine in glacial acetic acid in the presence of anhydrous sodium acetate. Interchanging the bromine with proton of imine group have been extensively investigated by Chattaway and Walker [36] and many researcher reported similar investigation in the literatures.[37, 38]

According to this fact a new proposed mechanism has been suggested as depicted in Scheme (5).The newly synthesized compounds were characterized by FTIR ^{1}H-NMR and CHN analysis. Moreover, compound 12 and 13 were characterized by ^{13}C-NMR. Disappearance the peak of NH from FTIR spectra as well the shifting in value of C=N were the first evidence of successful cyclization The ^{1}H-NMR spectra displayed disappearing the proton of CH=N group at (8.72-8.35) ppm as well the proton of NH group at (12.11-9.27) ppm. These indications were good evidences for successful cyclization reaction. The ^{1}H-NMR spectrum of compound 12 showed there is no signals for the NH group and the CH=N. Two doublet peaks integrated for four protons for each one were appeared at 7.725 ppm *J*=9 Hz and 8.165ppm *J*=9 Hz as this could be attributed to this compound possess two groups of 4-chlorophenyl substituted at position 3 and 6 for the fused oxadiazole-triazole ring. The carbon one of 4-chlorophenyl for first substituent attached with carbon of oxadiazole ring, while carbon one of 4-chlorophenyl for second substituent attached with carbon of triazole as shown in Figure (6).This rapprochement in electronic environment which is directly relates to the magnetic environment of the carbon one of the 4-chlorophenyl group. This small difference in electronic environment might reduce the effect of magnetic environment for C2. Furthermore, the electronic environment of H3 is the same. For that, the protons of two groups of 4-chlorophenyl appeared at the same position at ^{1}H-NMR spectrum as depicted in Figure (7). The ^{13}C-NMR spectrum supported these results.as depicted in Figure (8).The ^{13}C-NMR showed four signals for two 4-chlorophenyl rings at 135.78, 129.73, 125.77 and 117.18 ppm assigned to C4,C3,C2 and C1 respectively. Moreover, the spectrum exhibited three signals at 154.82, 162.41 and 162.45 assigned to three C=N group. The ^{1}H-NMR of compound 13 showed the three protons of methoxy group at 3.83 ppm and the aromatic CH was appeared as four doublets each one integrated for two protons as depicted in Figure (9).The ^{13}C-NMR of this compound exhibited the carbon of methoxy group(C12) at 55.80 ppm. The two carbons of aromatic CH for the 4-chlorophenyl group appeared at 123.45 and 129.32 ppm for C2 and C3. The C4 which attached with chloride appeared at 137.07ppm. The two (CH) carbons of the 4-methoxyphenyl appeared at 114.48 and 130.75 ppm for C9 and C10 of 4-methoxyphenyl group. The quaternary carbons of 4-chlorophenyl and 4-methoxyphenyl attached with fused oxadiazole-triazole(C1,C8) appeared at 125.15 and 125.67ppm. Furthermore, four peaks appeared at 150.10, 152.53, 153.11, and 155.46 ppm which is attributed to three carbons of fused cyclic(C5,C6,C7) and (C11) attached with 4-methoxy group, as shown in Figure (10).The distinguish between these carbons as well as with two carbons (C1 &C8) of both aryl attached with fused heterocyclic rings are impossible without 2D NMR (HMBC) which was not available to us.^{1}H-NMR spectrum of compound 14 showed the three protons of 4-methyl at 2.37 while the eight protons appeared at multiplied peaks (See the Appendix). As well as the ^{1}H-NMR spectra of compound 15 and compound 16 showed multiplied peaks for eight protons

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Table (1): physical properties and CHNS analysis of copounds (3-16)

Com No	M.P	Yield%	theoretical	practical
3	163-165	48,62	C-45.62 H-3.35 N-26.6	C-45.97 H-4.222 N-26.16
4	172-173	57	C-42.78 H-1.99 N-22.17 S-12.69	C-43.29 H-2.53 N-22.87 S-13.01
5	148	71	C-45.88 H-2.57 N-29.72	C-46.3 H-2.445 N-29.03
6	80-85	54	C-51.17 H-3.01 N-23.88	C-51.55 H-3.759 N-23.36
7	235-240	86	C-54.07 H-3.03 N-16.82	C-54.59 H-3.62 N-16.24
8	184-187	79	C-58.45 H-3.99 N-17.04	C-58.473 H-4.471 N-16.39
9	206-210	75	C-61.44 H-4.19 N-17.91	C-60.95 H-4.977- N-17.42
10	215-219	90	C-52.41 H-2.93 N-20.37	C-52.78 H-3.404 N-19.73
11	220-227	88	C-47.71 H-2.67 N-14.84	C-47.36 H-2.918 N-14.58
12	242-244	51	C-54.40 H-2.43 N-16.92	C-54.89 H-2.942 N-16.42
13	236-238	49	C-58.82 H-3.39 N-17.15	C-59.25 H-4.01 N-16.67
14	200-208	48	C-61.84 H-3.57 N-18.03	C-62.29 H-4.22 N-17.4
15	210	56	C-52.72 H-2.36 N-20.50	C-53.2 H-2.675 N-19.84
16	135	50	C-47.97 H-2.15 N-14.92	C-48.52 H-2.54 N-14.46-

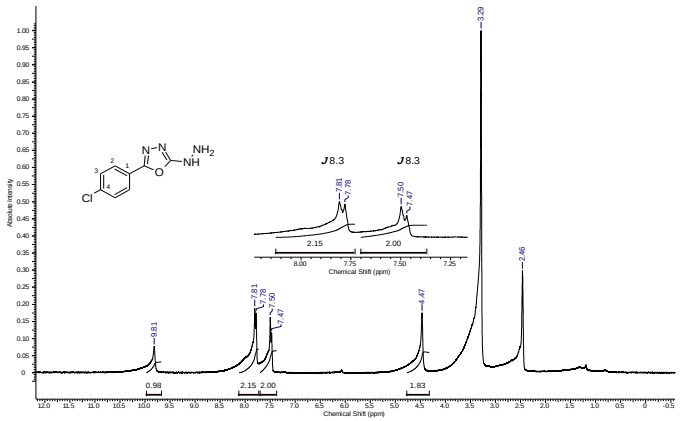


Figure (1):^{1}H-NMR (300 MHz, DMSO-d_6) of compound 3.

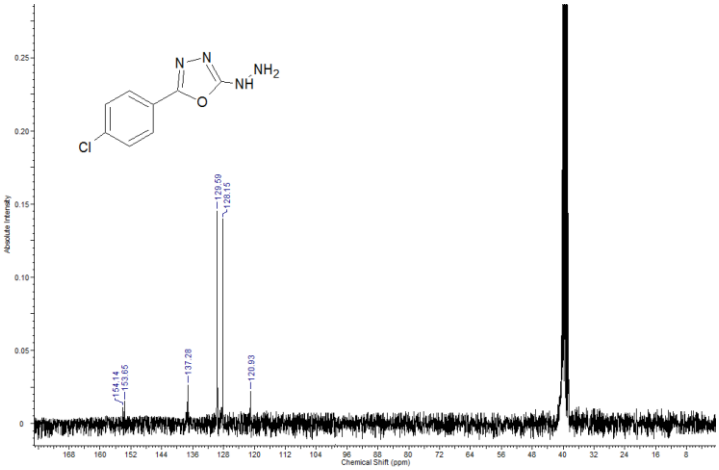


Figure (2):^{13}C-NMR (75MHz, DMSOd_6) of compound 3.

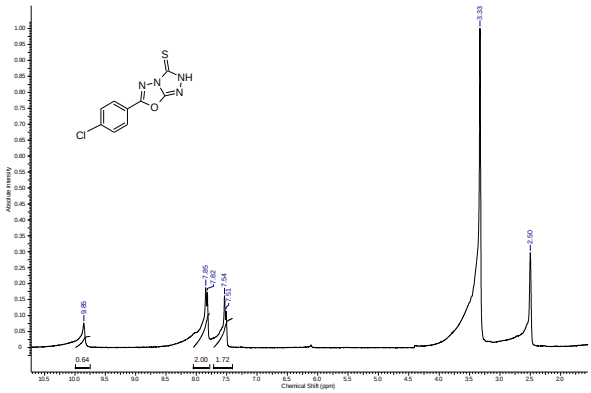


Figure (3):^{1}H-NMR (300MHz,DMSO d_6) of compound 4

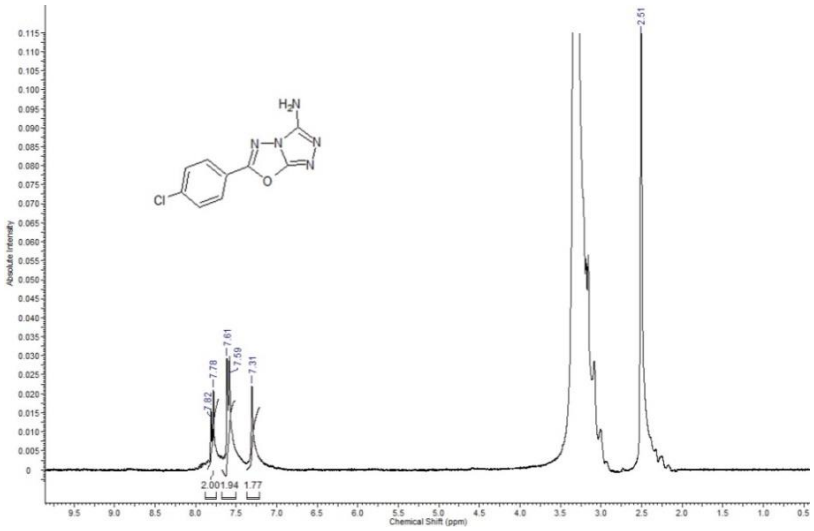
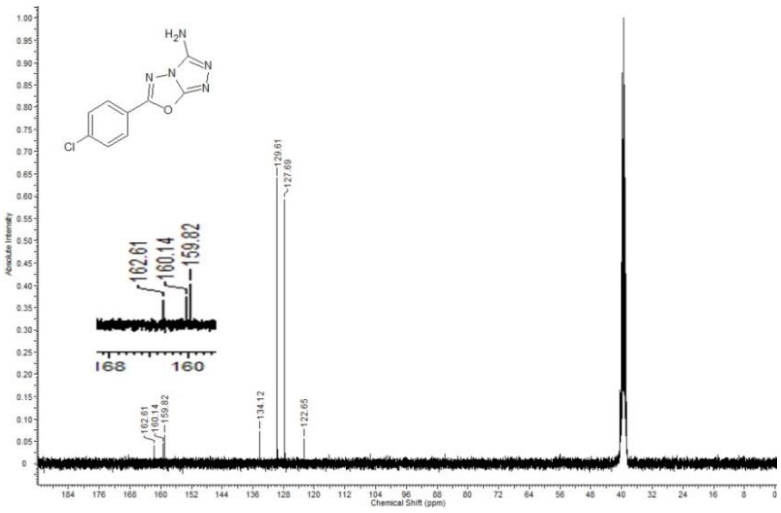


Figure (4): ^{1}H-NMR (300MHz,DMSOd_6) of compound 5



Figure(5): ^{13}C-NMR (75MHz, DMSO d_6) of compound 5

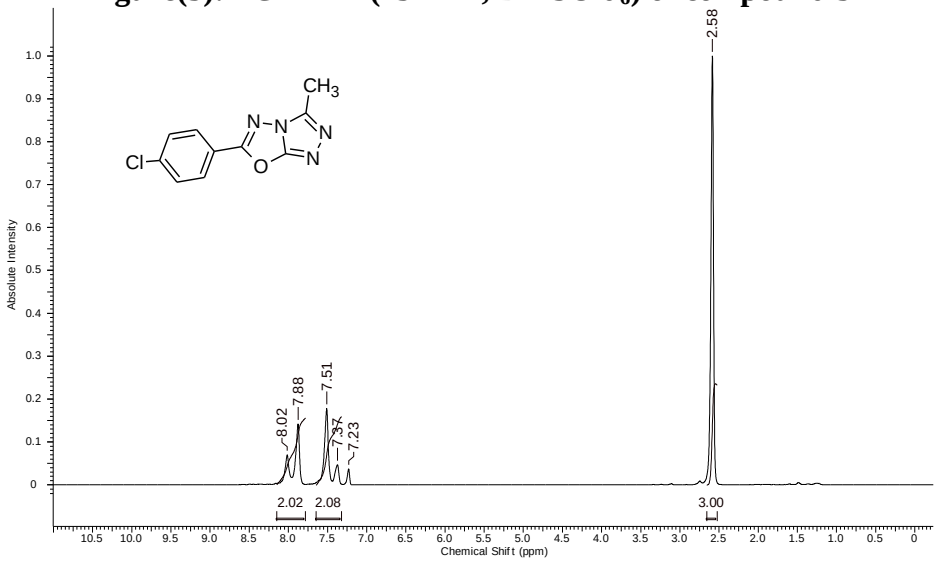


Figure (6): ^{1}H-NMR (60MHz,$CDCl_3$) of compound 6

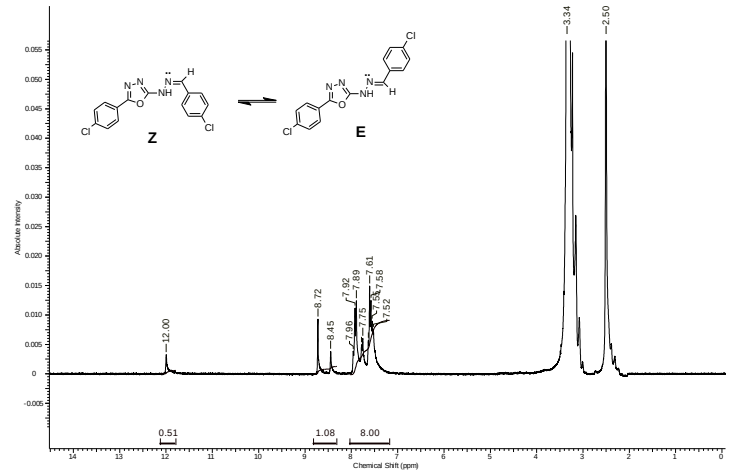


Figure (7): ^{1}H-NMR (300MHz, DMSO d_6) of compound 7

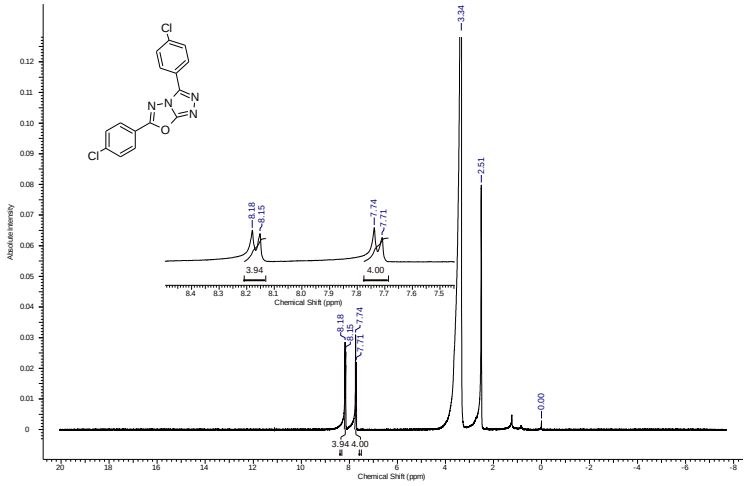


Figure (8): ^{1}H-NMR (300MHz, DMSO d_6) of compound 12

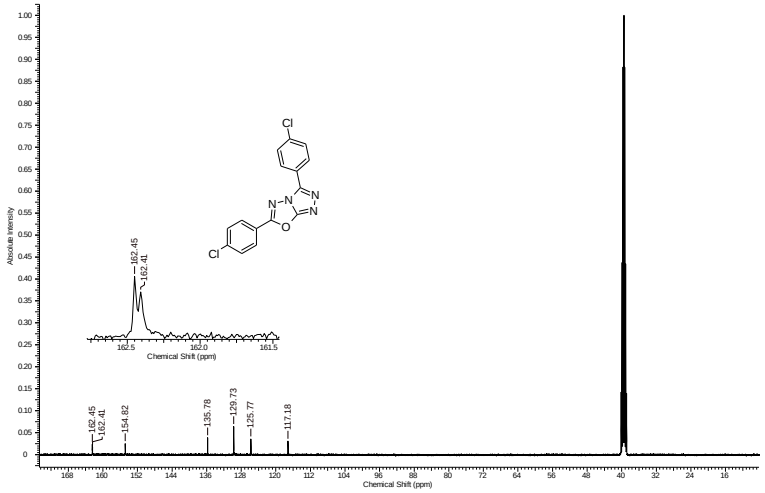


Figure (9):^{13}C-NMR (75 MHz, DMSO-d_6) of compound 12

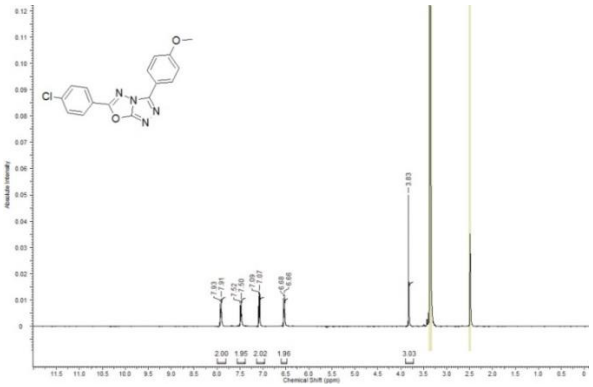


Figure (10):^{1}H-NMR (300 MHz, DMSO-d_6) of compound 13

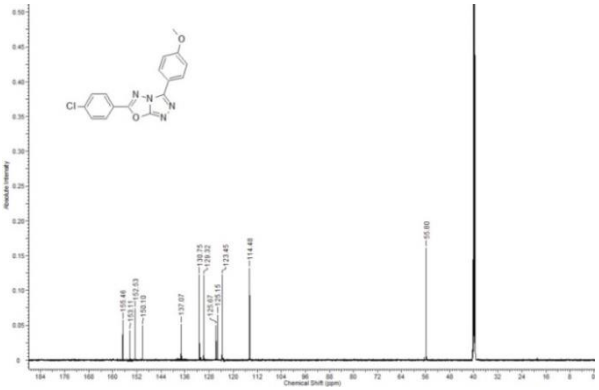


Figure (11):^{13}C-NMR (75 MHz, DMSO-d_6) of compound 13

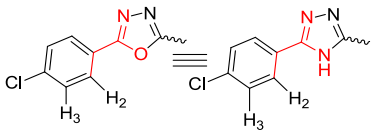
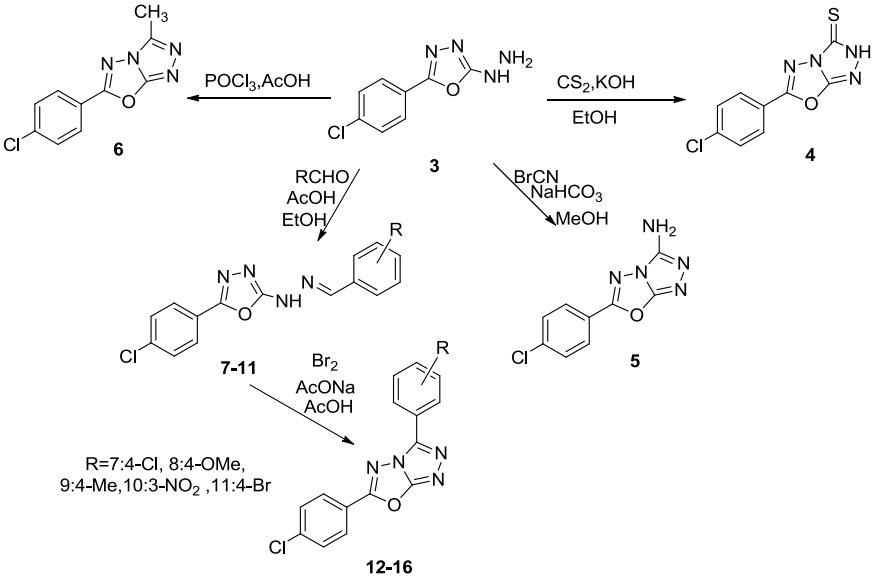
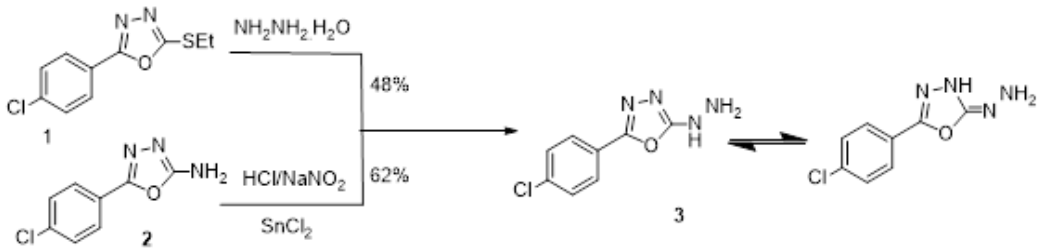


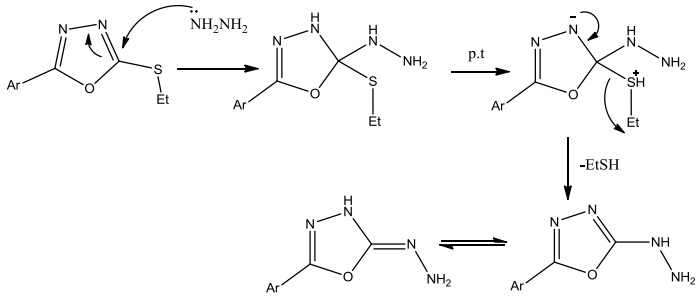
Figure (12): The effect of oxadiazole-triazole ring at H2 and H3



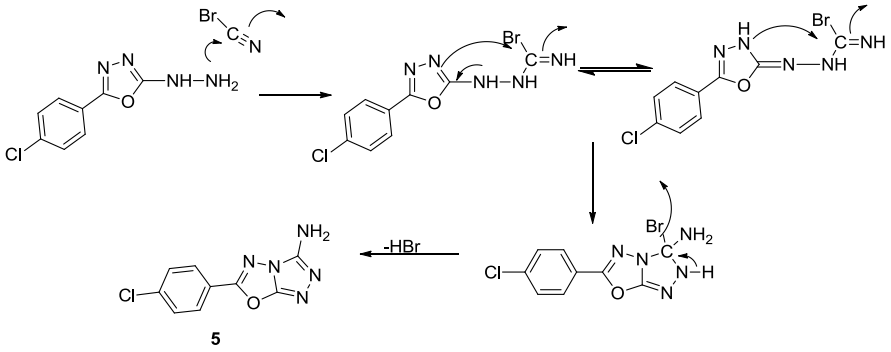
Scheme (1): The scheme for prepared compounds



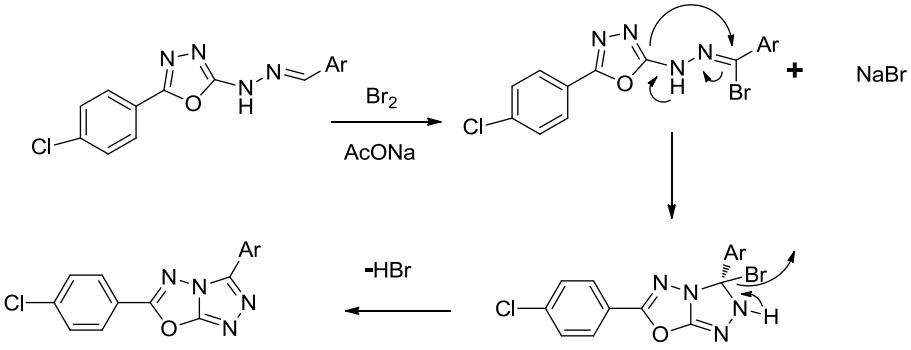
Scheme (2): Synthetic route of formation compound 3.



Scheme (3): Suggested mechanism of formation 5-aryl -2-hydrazinyl-1,3,4-oxadiazole(3).



Scheme (4): Suggested mechanism of formation compound 5



Scheme (5): proposed mechanism of formation compounds 12-16