

## Synthesis and Study of Some fused Substituted 1,3,4-Thiadiazoles and 1,2,4-Triazoles from 4-Chloro- phenoxy acetic acid and 2,4-dichlorophenoxy acetic acid

Mudhar A. Othman

Department of Chemistry, College of Education for girls, University of Mosul, Mosul, Iraq

E-mail: [mudr1973@yahoo.com](mailto:mudr1973@yahoo.com)

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### Abstract:

In this work the synthesis of some substituted 1,2,4-triazoles and five ring system's reported. 2-(4-Chlorophenoxy) acetic acid (S<sub>1</sub>) was synthesis from corresponding substituted phenol by its reaction with chloroacetic acid in sodium hydroxide solution, the acids (Q<sub>1</sub> and S<sub>1</sub>) esterified with methanol and sulfuric acid to give esters (Q<sub>2</sub> and S<sub>2</sub>) which converted to acid hydrazides (Q<sub>3</sub> and S<sub>3</sub>) by their reaction with hydrazine hydrate in ethanol.

The acid hydrazides (Q<sub>3</sub> and S<sub>3</sub>) were treated with carbon disulfide in potassium hydroxide solution to give potassium salts (Q<sub>4</sub> and S<sub>4</sub>) the formed salts were treated with hydrazine hydrate to give substituted 4-amino-1,2,4-triazoles (Q<sub>5</sub> and S<sub>5</sub>).

4-Amino-1,2,4-Triazole (Q<sub>5</sub> and S<sub>5</sub>) were converted to (Q<sub>6</sub> and S<sub>6</sub>), (Q<sub>9</sub> and S<sub>9</sub>) and (Q<sub>10</sub> and S<sub>10</sub>) by treating with CS<sub>2</sub> in pyridine, urea and chloroacetic acid. While reaction of 4-amino-1,2,4-triazole (Q<sub>5</sub> and S<sub>5</sub>) with phenyl isothiocyanate gave thiosemicarbazide derivatives (Q<sub>7</sub> and S<sub>7</sub>) that converted to *N*-phenyl substituted 1,2,4-triazole (Q<sub>8</sub> and S<sub>8</sub>).

The structures of the synthesized compounds were confirmed by physical and spectral data.

**Keywords:** Thiosemicarbazide, 1,3,4-Oxadiazole, 1,3,4-Thiadiazole, 1,2,4-Triazole.

تحضير ودراسة بعض المعوضات الملتحمة لـ 4،3،1-ثيادايازول و 4،2،1-ترايازول من 4-كلورو-فينوكسي حامض الأسيتيك و 4،2-ثنائي كلورو فينوكسي حامض الأسيتيك.

مضر أكرم عثمان

قسم الكيمياء، كلية التربية للبنات، جامعة الموصل، الموصل، العراق

### الخلاصة

حُضِرَ في هذا البحث عدد من مركبات 4،2،1-ترايازول وعدد من المركبات ثنائية الحلقة الملتحمة، حُضِرَ حامض 2-4-كلوروفينوكسي (Q<sub>1</sub>) من معوض الفينول المقابل من خلال تفاعله مع حامض كلوروالخليك في محلول هيدروكسيد

الصوديوم، وتمت أسترة الناتج في الميثانول بوجود حامض الكبريتيك الى مثيل الاسترين (S<sub>2</sub> و Q<sub>2</sub>)، تم تحويل الاسترين الناتجين الى هيدرازيد الحامض (S<sub>3</sub> و Q<sub>3</sub>) من خلال تفاعلها مع الهيدرازين المائي في الايثانول.

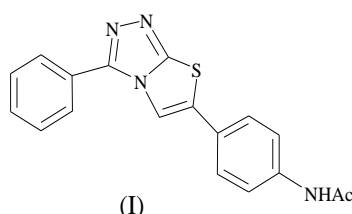
تم تحويل مركبي الهيدرازيد المحضران الى ملح البوتاسيوم (S<sub>4</sub> و Q<sub>4</sub>) من خلال تفاعلها مع ثنائي كبريتيد الكربون في محلول هيدروكسيد البوتاسيوم وأعطى الملحان الناتجان عند تفاعلها مع الهيدرازين المائي معوضي 4-أمينو-4,2,1-ترايازول (S<sub>5</sub> و Q<sub>5</sub>).

حوّل معوضي الترايازول (S<sub>5</sub> و Q<sub>5</sub>) الى مركبات حلقيّة ملتحمة (S<sub>6</sub> و Q<sub>6</sub>)، (S<sub>9</sub> و Q<sub>9</sub>)، (S<sub>10</sub> و Q<sub>10</sub>) عند تفاعلها مع ثنائي كبريتيد الكربون في البيريدين، اليوريا، حامض كلوروالخليك على التوالي. بينما اعطى تفاعل معوضي الترايازول (S<sub>5</sub> و Q<sub>5</sub>) مع آيزوثايوسيانات الفنيل معوضي الثايوسميكاريازيد (S<sub>7</sub> و Q<sub>7</sub>) حيث أعطت المعوضات 4,2,1-ثيادايازول ملتحمة عند معاملتها بالحرارة. شُخِّصَت التراكيب المحضرة بالطرائق الفيزيائية والطيفية.

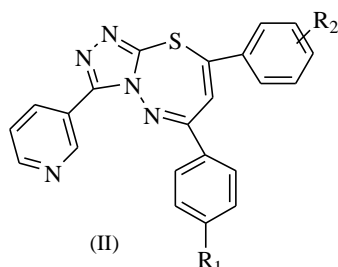
**الكلمات المفتاحية :** ثيوسميكاريازيد، 4,3,1-ثيادايازول، 4,2,1-ترايازول

### Introduction:

In the last few decades, the chemistry of heterocycles containing 1,2,4-triazole moiety was reported to show a wide spectrum of biological activity as antibacterial, against *B. subtilis*, *S. aureus*, *P. aeruginosa* and *E. coli*. [1,2] like compound (I) that prepared by reaction of *N*-acetyl-*p*-amino benzoic acid and 4-amino-5-phenyl-4H-1,2,4-triazole-3-thiol in POCl<sub>3</sub>.



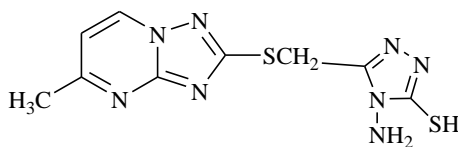
1,2,4-Triazole derivatives are showing very promising and excellent therapeutic effectiveness[3]. Furthermore synthesis of 6-(4-substituted phenyl)-8-(*N*-substituted phenyl)-3-(pyridinyl) [1,2,4] triazolo [3,4-*b*][1,3,4] thiadiazepine (II) by reaction of 4-amino-5-pyridin-3-yl-4H-1,2,4-triazole-3-thiol with chalcone in ethanol[4].



The reaction of potassium-3-(4-nitrobenzoyl) dithiocarbazate with hydrazine hydrate give 4-amino-3-mercapto-5-(4-nitro)phenyl-1,2,4-triazole that used as a nucleus to prepared 4-(substituted ethanoyl) amino-3-mercapto-5-(4-nitro) phenyl-1,2,4-triazoles were synthesized as novel antimicrobial agents starting from 4-nitrobenzoic acid[5].

Condensation of substituted 1,2,4-triazole and isoniazide gives *N*-[(3,5-substituted)-4H-1,2,4-triazole-4yl] isonicotinamide show *in-vitro* antimicrobial activity [6,7].

In another search 4-amino-5-(4-chlorophenyl)-4H-1,2,4-triazole-3-thiol was prepared by reacting of 4-chlorobenzoic acid with carbohydrazide[8]. While Liu[9], *et al* were prepared substituted 1,2,4-triazole by reacting of thioacetohydrazide-5,7-dimethyl-1,2,4-triazolo[1,5-a]pyrimidine potassium hydroxide in carbon disulfide (III).



(III)

The substituted 1,2,4-triazole show antianxietic [10] and antifungal activities[11,12].

Fused substituted 1,3,4-thiadiazole was prepared by dehydration of 1-(4-hydroxy-2-phenylthiazol-3(2H)-yl) isothioureia show antitubercular[13]. Due to the presence of bromophenyl group 1,3,4-thiadiazole with show antiviral activity as compound [14,15].

Novel bicyclic and tricyclic substituted 1,3,4-thiadiazole was prepared by Beresneva T. and Abele E.[16] and the used sodium bromide and acetic acid with 1,3-dichloroacetone produced substituted 1,3,4-thiadiazole like compound under Mannich reaction conditions[17].

## **Experimental:**

### *a. Measurements:*

Melting points were determined in open capillary tubes in a Thomas Hoover melting point apparatus and are uncorrected .

UV-Visible/Shimadzu-1601 and Infrared spectra were recorded on FT-IR , Shimadzu/157.

### *b. Preparations:*

#### *2-(4-chlorophenoxy)acetic acid (Q<sub>1</sub>) [18]:*

A solution of sodium hydroxide (4.5 g/25 ml) was added slowly to mixture of 4-chlorophenol (6.63 g, 0.049 mole) and chloroacetic acid (4.7 g, 0.049 mole). The mixture was heated with stirring for (30 minutes) to evaporate most of the solvent, then water (150 ml) was added and the solution acidified with concentrated hydrochloric acid. The resultant precipitate was filtered and recrystallized from ethanol / water. m.p. 154-155°C (Lit. 154-155 °C) yield % (65%).

#### *Methyl- 2-( substituted phenoxy)acetate(Q<sub>2</sub>,S<sub>2</sub>)[19]:*

In (250 ml) dry round bottom flask, a mixture of (Q<sub>1</sub> or S<sub>1</sub>) (0.001 mol) and absolute methanol (50 ml) were taken. Few drops of conc. Sulfuric acid along with a small porcelain chip were added. The reaction mixture was refluxed for (10 hours) on heating mantle, the mixture then cooled in an ice-bath, added 10% sodium bicarbonate (5 ml). Filtrated by buchner funnel, washed with cold water three times, then oily products were extract with diethylether . b.p. (Lit. [15] 300.5 °C). Tables (1,2,3 and 4).

#### *2-(Substituted phenoxy) acetohydrazide (Q<sub>3</sub>,S<sub>3</sub>)[20].*

A mixture of methyl ester (Q<sub>2</sub> or S<sub>2</sub>) (2.81g, 0.01 mole) and hydrazine hydrate (95%, 2.5 ml, 0.05 mole) in (50 ml) absolute ethanol was refluxed for (3 hours). The mixture was cooled to room temperature then the solvent evaporate under reduced pressure. The precipitate was filtered and recrystallized from ethanol. Tables (1,2,3 and 4).

#### *Potassium salt of thiosemicarbazide derivatives (Q<sub>4</sub>,S<sub>4</sub>) [21]*

To a cold solution of (Q<sub>3</sub>,S<sub>3</sub>) (0.01 mol) in ethanol (25 ml) and potassium hydroxide (0.84 g, 0.015 mol), carbon disulfide (1.14 g, 0.015 mol) was added. The reaction mixture was stirred at room temperature for (8 hours), and the precipitate formed was collected by filtration and washed with dry diethyl ether to give yellow solid of potassium salts (Q<sub>4</sub>,S<sub>4</sub>). Tables (1,2,3 and 4).

*4-Amino-5-( substituted phenoxyethyl)-4H-1, 2, 4-triazole-3-thiol (Q<sub>5</sub>,S<sub>5</sub>) [22]*

To compounds (Q<sub>4</sub>,S<sub>4</sub>) hydrazine hydrate solution (10 ml, 0.2 ml) was added and the contents of the round-bottom flask are refluxed for about one hour. The change in the color of the reaction mixture to one of the degrees of green with the release of hydrogen sulfide gas coincides with obtaining a homogeneous mass of solution. Then the mixture was cooled and diluted by adding (100ml) cold water in batches. The cold mixture was acidified by adding concentrated hydrochloric acid. The solid separated from the solution was filtered, washed with water several times, allowed to dry and recrystallized it from methanol. Tables (1,2,3 and 4).

*3-( Substituted phenoxyethyl)-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazolo-6(5H)-thione (Q<sub>6</sub>,S<sub>6</sub>) [23]*

A mixture of compounds (Q<sub>5</sub> or S<sub>5</sub>) (0.01 mol), dry pyridine (20 ml) and carbon disulphide (0.01 mol), was refluxed for (3 hour). The mixture was cooled and poured into a beaker containing ice-water. A solid product (Q<sub>6</sub> or S<sub>6</sub>) was obtained by filtering the and purified by recrystallized it from ethanol. Tables (1,2,3 and 4).

*2-[[4-amino-5-( substituted phenoxyethyl)-4H-1, 2, 4-triazole-3-yl]thio]-N-phenyl hydrazine carbothio amide (Q<sub>7</sub>,S<sub>7</sub>) [19]:*

product was filtered and purified by recrystallized from ethanol.

A mixture of (Q<sub>5</sub> or S<sub>5</sub>) (0.1 mol), phenyl isothiocyanate (0.1 mol) and powdered of sodium hydroxide (0.8 g) dissolved in DMF (25 ml) was continuous stirred at room temperature for (24 hours). The product was poured into dilute acetic acid (5%, 15 ml). The precipitated product was filtered, leave at room temperature to dry and purified by recrystallized it from 96% ethanol.

*N-phenyl-3-( substituted phenoxyethyl)-[1,2,4] triazolo [3,4-b][1,3,4] thiadiazol-6-amine (Q<sub>8</sub>,S<sub>8</sub>) [19]:*

Thiosemicarbazide (Q<sub>7</sub>,S<sub>7</sub>) derivative was fused in an oil-bath above its melting point. The products was cooled, diluted with ethyl acetate, and filtered. The solid products was purified by recrystallization from ethanol. Tables (1,2,3 and 4).

*3-( Substituted phenoxyethyl)-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazolo-6(5H)-one (Q<sub>9</sub>,S<sub>9</sub>)[19]:*

A mixture of (Q<sub>5</sub> or S<sub>5</sub>) (0.01 mol) and urea (0.13 mol) was heated at (180-190 °C) on sand bath for (6 hours). The reaction mixture were cooled and added to a solution of sodium hydroxide (5%, 20 ml), then filtered and the filtrate acidified with dilute hydrochloric acid. The solid product (Q<sub>9</sub> or S<sub>9</sub>) was purified by recrystallization from ethanol. Tables (1,2,3 and 4).

*3-(Substituted phenoxyethyl)-5H-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazin-6(7H)-one (Q<sub>10</sub> and S<sub>10</sub>) [19]:*

A mixture of (Q<sub>5</sub> or S<sub>5</sub>) ( 0.01 mol), chloroacetic acid (0.94 g, 0.01 mol) and anhydrous sodium acetate (0.82 g, 0.01 mol) in absolute alcohol (50 ml) was heated under reflux for (6 hours) and then cooled in ice. The solid thus separated were filtered, washed thoroughly with water and crystallized from methanol. Tables (1,2,3 and 4).

**Table 1: physical data of compounds (Q<sub>3</sub>-Q<sub>10</sub>)**

Comp. No.	m.p. °C	Yield %	Color	Molecular Formula
Q <sub>1</sub>	154-155	63	white	C <sub>8</sub> H <sub>7</sub> ClO <sub>3</sub>
Q <sub>2</sub>	oily	87	brown	C <sub>9</sub> H <sub>9</sub> ClO <sub>3</sub>
Q <sub>3</sub>	153-155	90	white	C <sub>8</sub> H <sub>9</sub> ClN <sub>2</sub> O <sub>2</sub>
Q <sub>4</sub>	270-275	86	Dark brown	C <sub>9</sub> H <sub>8</sub> ClKN <sub>2</sub> O <sub>2</sub> S <sub>2</sub>
Q <sub>5</sub>	116-118	85	Pale brown	C <sub>9</sub> H <sub>9</sub> ClN <sub>4</sub> OS
Q <sub>6</sub>	146-148	18	white	C <sub>10</sub> H <sub>7</sub> ClN <sub>4</sub> OS <sub>2</sub>
Q <sub>7</sub>	118-120	60	Brown	C <sub>16</sub> H <sub>16</sub> ClN <sub>7</sub> OS <sub>2</sub>
Q <sub>8</sub>	180-182	87	Pale brown	C <sub>16</sub> H <sub>12</sub> ClN <sub>5</sub> OS
Q <sub>9</sub>	150-152	43	White	C <sub>10</sub> H <sub>7</sub> ClN <sub>4</sub> O <sub>2</sub> S
Q <sub>10</sub>	120-122	16	Pale brown	C <sub>11</sub> H <sub>9</sub> ClN <sub>4</sub> O <sub>2</sub> S

**Table 2: physical data of compounds (S<sub>3</sub>-S<sub>10</sub>)**

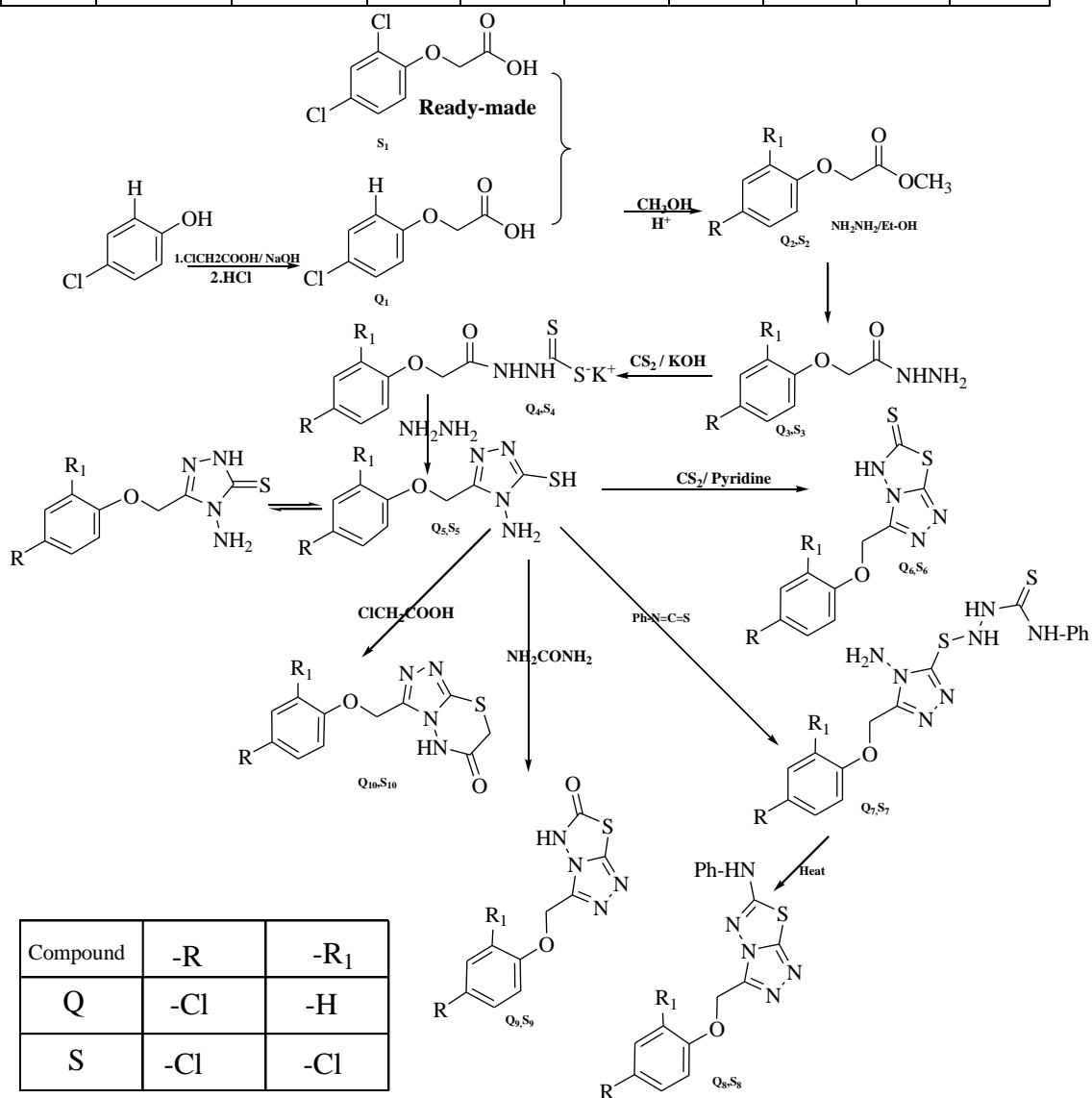
Comp. No.	m.p. °C	Yield %	Color	Molecular Formula
S <sub>1</sub>	Ready-made			
S <sub>2</sub>	oily	65	colorless	C <sub>9</sub> H <sub>8</sub> Cl <sub>2</sub> O <sub>3</sub>
S <sub>3</sub>	152-154	54	White	C <sub>8</sub> H <sub>8</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>2</sub>
S <sub>4</sub>	320 dec.	95	White	C <sub>9</sub> H <sub>7</sub> Cl <sub>2</sub> KN <sub>2</sub> O <sub>2</sub> S <sub>2</sub>
S <sub>5</sub>	146-148	35	Pale brown	C <sub>9</sub> H <sub>8</sub> Cl <sub>2</sub> N <sub>4</sub> OS
S <sub>6</sub>	168-170	14	Grey	C <sub>10</sub> H <sub>6</sub> Cl <sub>2</sub> N <sub>4</sub> OS <sub>2</sub>
S <sub>7</sub>	156-158	55	Grey	C <sub>16</sub> H <sub>15</sub> Cl <sub>2</sub> N <sub>7</sub> OS <sub>2</sub>
S <sub>8</sub>	158-160	53	white	C <sub>16</sub> H <sub>11</sub> Cl <sub>2</sub> N <sub>5</sub> OS
S <sub>9</sub>	156-158	10	Dark brown	C <sub>10</sub> H <sub>6</sub> Cl <sub>2</sub> N <sub>4</sub> O <sub>2</sub> S
S <sub>10</sub>	118-120	21	Pale yellow	C <sub>11</sub> H <sub>8</sub> Cl <sub>2</sub> N <sub>4</sub> O <sub>2</sub> S

**Table 3: Ultra Violet and Infrared spectrum data of compounds (Q<sub>3</sub>-Q<sub>10</sub>)**

Comp. No.	U.V λ max.	ν cm <sup>-1</sup>								
		C=C aromatic	C-Cl aromatic	N-H	$\begin{array}{c} \text{O} \\ \parallel \\ \text{C}-\text{N} \end{array}$	$\begin{array}{c} \text{O} \\ \parallel \\ \text{C}-\text{O} \end{array}$	C=N	C=S	C-S-C	C-O-C
Q <sub>1</sub>	236	1583	707	---	---	1707	---	---	645	1104
Q <sub>2</sub>	256	1595	722	---	---	1760	---	---	642	1129
Q <sub>3</sub>	285	1541	798	3310	1671	---	---	---	592	1071
Q <sub>4</sub>	290	1493	708	3419	1663	---	---	1252	665	1054
Q <sub>5</sub>	294	1589	732	3442	---	---	1667	1249	675	1022
Q <sub>6</sub>	312	1522	699	3447	---	---	1660	1242	635	1076
Q <sub>7</sub>	299	1549	695	3312	---	---	1682	1240	631	1095
Q <sub>8</sub>	305	1552	741	3436	---	---	1604	---	683	1087
Q <sub>9</sub>	317	1579	699	3160	1618	---	1618	---	617	1061
Q <sub>10</sub>	314	1556	736	3444	1667	---	1660	---	606	1024

Table 4: Ultra Violet and Infrared spectrum data of compounds (S<sub>3</sub>-S<sub>10</sub>)

Comp. No.	U.V $\lambda$ max.	$\nu$ $cm^{-1}$								
		C=C aromatic	C-Cl aromatic	N-H	$\begin{matrix} O \\    \\ C-N \end{matrix}$	$\begin{matrix} O \\    \\ C-O \end{matrix}$	C=N	C=S	C-S-C	C-O-C
S <sub>1</sub>	253	1585	720	---	---	1736	---	---	643	1093
S <sub>2</sub>	240	1586	719	---	---	1760	---	---	595	1051
S <sub>3</sub>	327	1576	729	3318	1671	---	---	---	650	1074
S <sub>4</sub>	292	1482	703	3336	1663	---	---	1266	620	1046
S <sub>5</sub>	291	1540	737	3315	---	---	1635	1290	616	1080
S <sub>6</sub>	293	1576	714	3397	1655	---	1655	1266	608	1043
S <sub>7</sub>	318	1543	658	3316	1605	---	1601	1252	577	1061
S <sub>8</sub>	322	1480	746	3316	---	---	1605	---	603	1105
S <sub>9</sub>	293	1541	694	3311	1606	---	1616	---	604	1079
S <sub>10</sub>	294	1575	711	3375	1605	---	1604	---	618	1067



Scheme (1)

### **Results and Discussion:**

In this research the synthesis of new mono and bicyclic five membered ring heterocyclic compounds are reported. 4-Chlorophenol was treated with chloroacetic acid to give 4-chloro phenoxy acetic acid ( $Q_1$ ) which when esterified with another phenoxy acetic acid (2,4-dichloro phenoxy acetic acid  $S_1$ ) to gave methyl ester ( $Q_2, S_2$ ) by their reaction with absolute methanol in presence of sulfuric acid.

The ester then treated with hydrazine hydrate in ethanol to give the corresponding acid hydrazides ( $Q_3, S_3$ ), the I.R spectrum of compounds ( $Q_3, S_3$ ) show absorption at  $1618-1671\text{ cm}^{-1}$  due to (C=O amide). UV-Visible spectrum of ( $Q_3, S_3$ ) show bands at (227-285 nm), The acid hydrazides were converted to 1,2,4-triazoles ( $Q_5, S_5$ ) by their reaction carbon disulfide followed by hydrazine hydrate, the I.R spectrum for compounds ( $Q_5, S_5$ ) showed absorption at  $1604-1682$  for (Q compounds),  $1635-1667\text{ cm}^{-1}$  for (S compounds) (C=N),  $1240-1252\text{ cm}^{-1}$  of (Q compounds) and  $1252-1290\text{ cm}^{-1}$  of (S compounds) (C=S). UV-Visible spectrum of ( $Q_5, S_5$ ) show bands at (292-294 nm) for (Q and S compounds). Substituted 1,2,4-triazoles ( $Q_5, S_5$ ) were treated with carbon disulfide in pyridine or with phenyl isothiocyanate to give triazole-thiadiazole fused ring systems ( $Q_6, S_6$ ) and triazoles ( $Q_7, S_7$ ) which on heating gave fused ring systems ( $Q_8, S_8$ ) while the reaction of ( $Q_5, S_5$ ) with urea or chloroacetic acid gave ( $Q_9, S_9$ ) and ( $Q_{10}, S_{10}$ ) respectively.

The I.R spectrum for compounds ( $Q_6, S_6$ )  $1655-1660\text{ cm}^{-1}$  for (C=N) and  $1242-1266\text{ cm}^{-1}$  for (C=S). UV-Visible spectrum of ( $Q_6, S_6$ ) show bands at (293-312 nm), compounds ( $Q_7, S_7$ )  $1601-1682\text{ cm}^{-1}$  (C=N),  $1240-1252\text{ cm}^{-1}$  for (C=S). UV-Visible spectrum of ( $Q_7, S_7$ ) show bands at (299-318 nm).

Compounds ( $Q_9, S_9$ ) show absorption at  $1616-1618\text{ cm}^{-1}$  for (C=N). UV-Visible spectrum of ( $Q_9, S_9$ ) show bands at (293-317 nm) and compounds ( $Q_{10}, S_{10}$ ) showed absorption at  $1604-1660\text{ cm}^{-1}$  for (C=N). UV-Visible spectrum of ( $Q_{10}, S_{10}$ ) show bands at (294-314 nm), Tables (3 and 4). The physical data for the synthesized compounds showed on tables (1 and 2).

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