Journal of Education and Science
Vol. 29, No.3, 2020, pp. 218-226
ISSN 1812-125X
http://edusj.mosuljournals.com

تحضير ودراسة بعض المعوضات الملتحمة لـ1،3،4–ثيادايازول و 1،2،4–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

DOI: 10.33899/edusj.2020.166251

الاستلام	القبول
2013/12/09	2014/05/08

الخلاصة

حُضِّرَ في هذا البحث عدد من مركبات 4,2,1–ترايازول وعدد من المركبات ثنائية الحلقة الملتحمة، حُضِّرَ حامض 2–(4– كلوروفينوكسي) الخليك (Q_1) 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_2 وQ_2)، تم تحويل الاسترين الناتجين الى هيدرازيد الحامض (S_3 وQ_3) من خلال تفاعلهما مع الهيدرازين المائي في الايثانول.

تم تحويل مركبي الهيدرازيد المحضران الى ملح البوتاسيوم (Q_4 وS_4) من خلال تفاعلهما مع ثنائي كبريتيد الكربون في محلول هيدروكسيد البوتاسيوم وأعطى الملحان الناتجان عند تفاعلهما مع الهيدرازين المائي معوضي 4–أمينو– 4,2,1–ترايازول (Q_5 وS_5).

حُوِّلَ معوضي الترايازول (Q_5 وS_5) الى مركبات حلقية ملتحمة (Q_6 و S_6)، (Q_9 و S_9)، (Q_{10} و S_{10}) عند تفاعلهما مع ثنائي كبريتيد الكربون في البيريدين، اليوريا، حامض كلوروالخليك على التوالي. بينما اعطى تفاعل معوضي الترايازول (Q_5 وS_5) مع آيزوثايوسيانات الفنيل معوضي الثايوسميكاربازيد (Q_7 وS_7) حيث أعطت المعوضات 4,2,1–ثيادايازول ملتحمة عند معاملتها بالحرارة. شُخِّصَتْ التراكيب المحضرة بالطرائق الفيزيائية والطيفية.

الكلمات المفتاحية : ثيوسيميكاربازيد، 1،3،4 –ثيادايازول، 1،2،4–ترايازول

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
mudr1973@yahoo.com

DOI: 10.33899/edusj.2020.166251

Received 09/ 12/ 2013 **Accepted** 08/ 05 / 2014

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_1) was synthesis from corresponding substituted phenol by its reaction with chloroacetic acid in sodium hydroxide solution, the acids (Q_1 and S_1) esterified with methanol and sulfuric acid to give esters (Q_2 and S_2) which converted to acid hydrazides (Q_3 and S_3) by their reaction with hydrazine hydrate in ethanol.

The acid hydrazides (Q_3 and S_3) were treated with carbon disulfide in potassium hydroxide solution to give potassium salts (Q_4 and S_4) the formed salts were treated with hydrazine hydrate to give substituted 4-amino-1,2,4-triazoles (Q_5 and S_5).

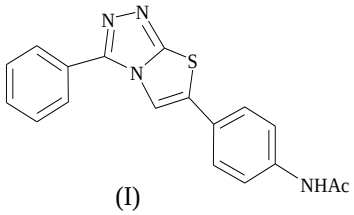
4-Amino-1,2,4-Triazole (Q_5 and S_5) were converted to (Q_6 and S_6), (Q_9 and S_9) and (Q_{10} and S_{10}) by treating with CS_2 in pyridine, urea and chloroacetic acid. While reaction of 4-amino-1,2,4-triazole (Q_5 and S_5) with phenyl isothiocyanate gave thiosemicarbazide derivatives (Q_7 and S_7) that converted to *N*-phenyl substituted 1,2,4-triazole (Q_8 and S_8).

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.

Introduction:

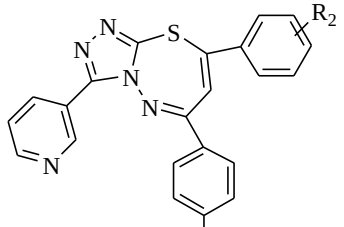
In the last few decades, the chemistry of heterocycles containing 1,2,4-triazole moiety was reported to show a wide spectrum of biological activity as antibacterial, against *B. subtilis,S. aureus, P. aeruginosa* and *E. coli.* [1,2] like compound (I) that prepared by reaction of *N*-acetyl-p-amino benzoic acid and 4-amino-5-phenyl-4H-1,2,4-triazole-3-thiol in $POCl_3$.



(I)

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].

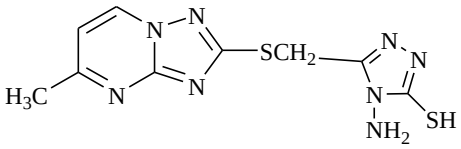


(II)

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) isothiourea 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_1) [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. 154-155ºC (Lit. 154-155 ºC) yield % (65%).

Methyl- 2-(substituted phenoxy)acetate(Q_2,S_2)[19]:

In (250 ml) dry round bottom flask, a mixture of (Q_1 or S_1) (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 ºC). Tables (1,2,3 and 4).

2-(Substituted phenoxy) acetohydrazide (Q_3,S_3)[20].

A mixture of methyl ester (Q_2 or S_2) (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_4,S_4) [21]

To a cold solution of (Q_3,S_3) (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_4,S_4). Tables (1,2,3 and 4).

4-Amino-5-(substituted phenoxymethyl)-4H-1, 2, 4-triazole-3-thiol (Q_5,S_5) [22]

To compounds (Q_4,S_4) 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 phenoxymethyl)-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazolo-6(5H)-thione (Q_6,S_6) [23]

A mixture of compounds (Q_5 or S_5) (0.01 mol), dry pyridine (20 ml) and carbon disulphide (0.01 mol), wasrefluxed for (3 hour). The mixture was cooled and poured into

a beaker containing ice-water. A solid product (Q_6 or S_6) was obtained by filtering the and purifyied by recrystallized it from ethanol. Tables (1,2,3 and 4).

2-{[4-amino-5-(substituted phenoxymethyl)-4H-1, 2, 4-triazole-3-yl]thio}-N-phenyl hydrazine carbothio amide (Q_7,S_7) [19]:

product was filtered and purified by recrystallized from ethanol.

A mixture of (Q_5 or S_5) (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 phenoxymethyl)-[1,2,4] triazolo [3,4-b][1,3,4] thiadiazol-6-amine (Q_8,S_8) [19]:

Thiosemicarbazide (Q_7,S_7) 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 phenoxymethyl)-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazolo-6(5H)-one (Q_9,S_9)[19]:

A mixture of (Q_5 or S_5) (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_9 or S_9) was purified by recrystallization from ethanol. Tables (1,2,3 and 4).

3-(Substituted phenoxymethyl)-5H-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazin-6(7H)-one (Q_{10} and S_{10}) [19]:

A mixture of (Q_5 or S_5) (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_3-Q_{10})

Comp. No.	m.p. ºC	Yield %	Color	Molecular Formula
Q_1	154-155	63	white	$C_8H_7ClO_3$
Q_2	oily	87	brown	$C_9H_9ClO_3$
Q_3	153-155	90	white	$C_8H_9ClN_2O_2$
Q_4	270-275	86	Dark brown	$C_9H_8ClKN_2O_2S_2$
Q_5	116-118	85	Pale brown	$C_9H_9ClN_4OS$
Q_6	146-148	18	white	$C_{10}H_7ClN_4OS_2$
Q_7	118-120	60	Brown	$C_{16}H_{16}ClN_7OS_2$
Q_8	180-182	87	Pale brown	$C_{16}H_{12}ClN_5OS$
Q_9	150-152	43	White	$C_{10}H_7ClN_4O_2S$
Q_{10}	120-122	16	Pale brown	$C_{11}H_9ClN_4O_2S$

Table 2: physical data of compounds (S_3-S_{10})

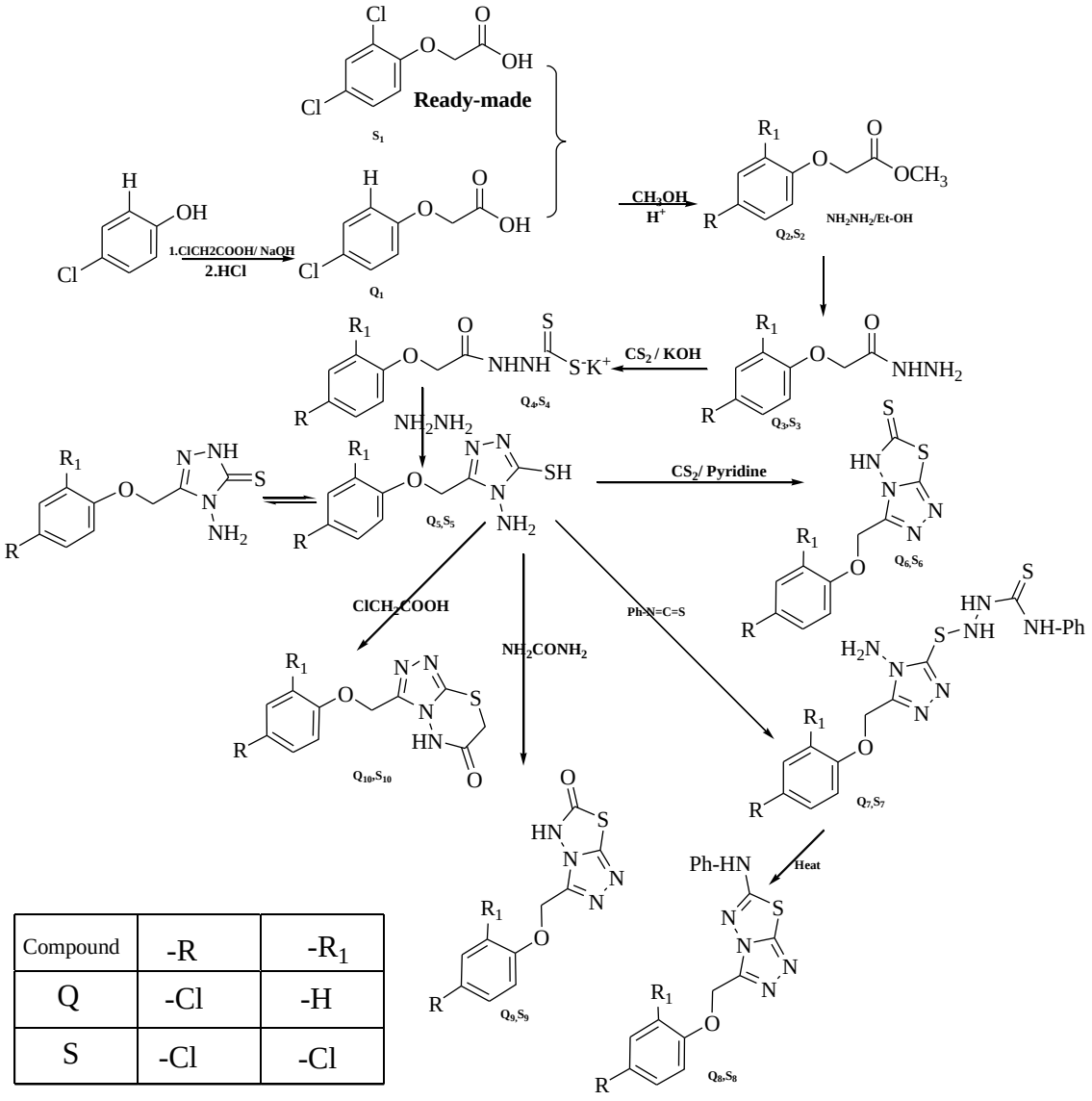
Comp. No.	m.p. ºC	Yield %	Color	Molecular Formula
S_1	Ready-made			
S_2	oily	65	colorless	$C_9H_8Cl_2O_3$
S_3	152-154	54	White	$C_8H_8Cl_2N_2O_2$
S_4	320 dec.	95	White	$C_9H_7Cl_2KN_2O_2S_2$
S_5	146-148	35	Pale brown	$C_9H_8Cl_2N_4OS$
S_6	168-170	14	Grey	$C_{10}H_6Cl_2N_4OS_2$
S_7	156-158	55	Grey	$C_{16}H_{15}Cl_2N_7OS_2$
S_8	158-160	53	white	$C_{16}H_{11}Cl_2N_5OS$
S_9	156-158	10	Dark brown	$C_{10}H_6Cl_2N_4O_2S$
S_{10}	118-120	21	Pale yellow	$C_{11}H_8Cl_2N_4O_2S$

Table 3: Ultra Violet and Infrared spectrum data of compounds (Q_3-Q_{10})

Comp. No.	U.V λ *max.*	*v cm^{-1}*								
		C=C aromatic	C-Cl aromatic	N-H	O=C—N	O=C—O	C=N	C=S	C-S-C	C-O-C
Q_1	236	1583	707	---	---	1707	---	---	645	1104
2	256	1595	722	---	---	1760	---	---	642	1129
Q_3	285	1541	798	3310	1671	---	---	---	592	1071
Q_4	290	1493	708	3419	1663	---	---	1252	665	1054
Q_5	294	1589	732	3442	---	---	1667	1249	675	1022
Q_6	312	1522	699	3447	---	---	1660	1242	635	1076
Q_7	299	1549	695	3312	---	---	1682	1240	631	1095
Q_8	305	1552	741	3436	---	---	1604	---	683	1087
Q_9	317	1579	699	3160	1618	---	1618	---	617	1061
Q_{10}	314	1556	736	3444	1667	---	1660	---	606	1024

Table 4: Ultra Violet and Infrared spectrum data of compounds (S_3-S_{10})

Comp. No.	U.V λ *max.*	*v cm^{-1}*								
		C=C aromatic	C-Cl aromatic	N-H	O=C—N	O=C—O	C=N	C=S	C-S-C	C-O-C
S_1	253	1585	720	---	---	1736	---	---	643	1093
S_2	240	1586	719	---	---	1760	---	---	595	1051
S_3	327	1576	729	3318	1671	---	---	---	650	1074
S_4	292	1482	703	3336	1663	---	---	1266	620	1046
S_5	291	1540	737	3315	---	---	1635	1290	616	1080
S_6	293	1576	714	3397	1655	---	1655	1266	608	1043
S_7	318	1543	658	3316	1605	---	1601	1252	577	1061
S_8	322	1480	746	3316	---	---	1605	---	603	1105
S_9	293	1541	694	3311	1606	---	1616	---	604	1079
S_{10}	294	1575	711	3375	1605	---	1604	---	618	1067



Compound	-R	-R_1
Q	-Cl	-H
S	-Cl	-Cl

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 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-trazoles (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 cm^{-1} for (S compounds) (C=N) ,1240-1252 cm^{-1} of (Q compounds) and 1252-1290 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 cm^{-1} for (C=N) and 1242-1266 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 cm^{-1} (C=N) , 1240-1252 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 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 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).

References:

1. K. Parmer, P. Sarju, Rinku, P. and P. Rikha, Res.J.Chem.Sci., 1(1),(2011)18-24.
2. K. V. Singh, M. K. Bhardwaj, V. K. Singh, and Savita, International Journal of Current Research in Applied Chemistry & Chemical Engineering, 4, (2020) 41-45.
3. D.S. Bele and I. Singhvi, Asian Journal of Biochemical and Pharmaceutical Research, 1(2),(2011)88-101.
4. A.S. Geetha, R. Vijayaraj, T.R. Kumar and R.S. Anand, International Journal of Research in Pharmaceutical and Biomedical Sciences., 2(1),(2011)155-159.
5. N. Upmanyu, S. Kumar, M.D. Kharya, K. Shah, and P. Mishra, Acta Poloniae Pharmaceutica Drug Research., 68(2),(2011)213-221.
6. J.W .Dhore, G.B. Petha, S.P. Waghi, and G.D. Thorat, Scholar Research Library. 3 (1),(2011) 407-414.
7. H. E. Hashem, A. E. E. Amr, E. S. Nossier, E. A. Elsayed and E. M. Azmy, Molecules 25 (2766), (2020), 1-18.
8. V.K. Tirlapur and T. Tadmalle, Der Pharmacia Sinica, 2 (1),(2011)135-141.
9. Z. M. Liu, Q. Chen, C.N. Chen, H.Y. Tu and G.F. Yang , Molecules, 13,(2008)1353-1360.
10. S. Jubie, P. Sikdar, S. Antony, R. Kalirajan, B. Goramma, S. Gomathy and K. Elango, Pak. J. Pharm. Sci., 24 (2),(2011) 109-112.
11. S. M. Gomha, H. M. Abdel-aziz, T. Z. Abolibda, S. A. Hassan and M. M. Abdalla, J. Heterocycl. Chem., (2020), 1-10.
12. A.S Geetha, R. Vijayaraj, T.R. Kumar, and R.S. Anand, International Journal of Research in Pharmaceutical and Biomedical Sciences, 2(1),(2011) 155-159.
13. A. A. Karigar, M. Himaja, M.V. Sunil, K.J. Parathap and S.S. Mukesha , IRJP, 2 (1), .(2011) 153-158.
14. G. Mishra, A.K. Singh and K. Jyoti, Int. J. ChemTech Res.3 (3),(2011) 1380-1393.
15. A.A. Aly,* , A. A. Hassan, M. M. Makhlouf and S. Bräse, Molecules 25 (3036), (2020), 1-54.
16. T. Beresneva and E. Abele. Heterocyclic Letters, 1 (1),(2011) 73-78.
17. S. Valiulienė and A. Rutavičius. Chemija, 12 (1),(2001) 84-88.
18. Smith,T.V. and Waldron, N.M., "Vogel's Elementary Practical Organic Chemistry Preparation"3rd Ed., Longman group Ltd., London, p 316 (1980).

19. Al-naimi, K.H Yousif., Ph.D. Thesis, College of Education, University of Mosul (2000). (In Arabic).
20. Abdel-Aziz, H.A.; Elsaman, T.; Attia, M.I. and Alanazi, A.M., Molecules, 18, 2084-2095 (2013).
21. S. Hussain, Sharma, J. and M. Amir, E-Journal of Chemistry,5(4),(2008) 963-968.
22. K. A. Ali, J. Sharma and M. Amir, Acta Poloniae Pharmaceutica-Drug Research, 68(2),(2011) 237-247.
23. G. Omprakash, Y. Anjaneyulu, N.S. Subramanian, M. Ramadevi, V.R.M. Gupta and G. Vijayalakshmi, RJPBCS, 2(1),(2011) 410-418.