Synthesis of Some New Water Soluble Heterocyclic Compounds Derived from Ethyl (α-D-glucofuranose-3-O-yl) Acetate

Ahmed W. Naser
Department of Chemistry, College of Science, University of Baghdad, Baghdad, Iraq

(Received: 17 / 2 / 2013 ---- Accepted: 22 / 5 / 2013)

Abstract

Derivatives of 1- (*p*-nitrophenyl)- 4- (1,2:5,6-di-O-isopropylidene -α- D-glucofuranose -3- O-yl)- 1,3-butanedione(2)and1,2:5,6-di-O-isopropylidene-α-D-glucofuranose-3-O-yl-acetohydrazide (3) were obtained by reaction of ethyl(1,2:5,6- di-O-isopropylidene-α-D- glucofuranos-3-O-yl) acetate (1) as starting material with p-nitroacetophenone and hydrazine hydrate respectively. The cyclization of (2) with hydrazine hydrate, phenylhydrazine, thiourea and urea gave the corresponding pyrazole (4,5) and pyrimidine (6,7) derivatives. Pyridizine derivatives (8,9) were synthesized by reaction (3) with maleic anhydride and phthalic anhydride in presence acetic acid. Reaction (3) with acetyl acetone afforded pyrazole derivative (10). Hydrolysis of the 1,2 and 5,6-isopropylidene groups for all prepared derivatives (4-10) gave the water soluble compounds (11-17). FT-IR. , elemental analysis and ^{1}H-NMR were used to characterize the target compounds.

Introduction

Heterocyclic compounds have biological and medical use as antibacterial, antifungal[1,2], antimicrobial[3], antitumorand antiflammatory[4-7]. Heterocyclic compounds are found as construction units through several biological molecules, mostly are molecules which contain five or six member ring [8, 9].

Pyridazine derivatives are reported to possess antiasthmatic and analgesic activities on the other hand, substituted pyridazine are often used in medicine field and fungicidal effects [10]. Pyrimidine derivatives play an important role in many biological processes their ring being present in nucleic acids, vitamin coenzymes and uric acid many drugs and chemotherapeutic agents contain pyrimidine ring [11, 12]

Pyrazoles and its derivatives exhibit a wide variety of potentially useful applications including clinical and pharmaceutical [13, 14].

Experimental

All melting points were recorded with electrothermal melting point apparatus and were uncorrected. Thin-layer chromatography was performed glass plats coated with 0.25 mm layer of silica-gel (Fluka). Infrared spectra were recorded on a Shimadzu FT-IR-8400s spectrophotometer.

^{1}H-NMR spectra were recorder on Bruker Ultra Shield, 300 MHz, using DMSO-d6 as a solvent and TMS as internal standard. Elemental analysis was run by Eurovectro, EA3000A, Italy.

Preparation of ethyl(1,2:5,6-di-O-isopropylidene-α-D-glucofuranose-3-O-yl) acetate[15](1)

1,2:5,6-di-O-isopropylidene-α-D-glucofuranose[16] (1.0gm , 3.8 mmol.) was dissolved in DMSO (20 ml) and powdered NaOH pellets (0.16 gm , 4.0 mmol.) were added. The contents were stirred in ice bath for 10 min. then ethyl chloroacetate (o.488 gm , 3.8 mmol. was added dropwise. The reaction mixture allowed to stir for 24 h , gradually warming to room temperature then reaction mixture was poured onto ice-cold water, and the obtained solid was recrystallized from ethanol to give compounds (1). Yield 61%, m.p. 118-120°C, I.R. (KBr) cm^{-1}: 1733(C=O ester).

Preparation of 1-(*p*-nitrophenyl) -4- (1,2:5,6-di-O-isopropylidene -α- D-glucofuranose -3- O-yl) -1,3-butanedione (2)

p-nitroacetophenone (0.24 gm, 1.4 mmol.) was slowly added to the sodium metal (0.05 gm, 2.00 mmol.) in (15 ml) ethanol, then compound (1) (0.5 gm, 1.4 mmol.) was added and the reaction mixture was refluxed for 5h. cooled then acidified with hydrochloric acid. The precipitated solid product was separated and recrystallized from ethanol to give compound (2).

Yield 65%, m.p. 58-60°C, R_f(0.800), I.R. (KBr) cm^{-1}: 2950-2980 CH(CH3)2, 1693, 1604 (2 C=O) ,1525(NO2). Alna. Calcd.: C, 56.8; H, 5.8; N, 3.00. Found: C, 56.3; H, 5.69; N, 2.79

Preparation of Pyrazole Derivatives (4,5)

General procedure:

Equimolar amounts of compound (2) (1.9 mmol.) and hydrazine hydrate or phenyl hydrazine in 4 ml glacial acetic acid were refluxed for 3h. The reaction mixture was cooled and poured onto ice-water then neutralized with sodium bicarbonate solution. The solid that separated out was filtered, dried and recrystallized from ethanol to give compounds (4)and(5a) respectively.

3-(*p*-nitrophenyl)-5-[(1,2:5,6-di-O-isopropylidene-α-D-glucofuranose-3- O-yl) methyl] pyrazole (4)

Yield 45%, m.p. 80°C d., R_f (0.727), I.R. (KBr) cm^{-1}: 3220(NH), C=N (1580). Alna. Calcd.: C, 57.3; H, 5.8; N, 9.1. Found: C, 56.91; H, 4.68; N, 8.89.

^{1}H-NMR (DMSO-d6) δ: 5.1(s, 2H, -OCH2-), 7.0-7.4(m, 6H, Ar-H, pyrazole H4, NH).

1-Phenyl-5-(*p*-nitrophenyl)-3-[(1,2:5,6-di-O-isopropylidene-α-D-glucofuranose-3-O-yl) methyl] pyrazole (5a)

Yield 40%, m.p. 85-87°C, R_f (0.4857), I.R. (KBr) cm^{-1}: 1610(C=N). Alna. Calcd.: C, 62.6; H, 5.8; N, 7.8. Found: C, 62.31; H, 5.62; N, 759.

^{1}H-NMR (DMSO-d6) δ: 5.3(s, 2H, -OCH2-), 7.20-7.7(m, 10H, Ar-H, pyrazole H4).

Preparation of Pyrimidine Derivatives (6,7)

General procedure:

A mixture of compound (2) (0.2 gm, 0.43 mmol.) and thiourea or urea (2.57 mmol.) in absolute ethanol (15 ml) was refluxed for 3h. The reaction mixture was poured onto ice-cold water, and the obtained solid was recrystallized from ethanol to give compounds 6 and 7 respectively.

4-(*p*-nitrophenyl)-6-[(1,2:5,6-di-O-isopropylidene-α-D-glucofuranose-3-O-yl) methyl] -2- thioxo -1-H-pyrimidine (6)

Yield 65%, m.p. 145-147°C, R_f (0.3428), I.R. (KBr) cm^{-1}: 3250(NH),1620(C=N), 1170(C=S). Alna. Calcd.: C, 54.70; H, 5.30; N, 8.3. Found: C, 54.27; H,5.16; N, 8.07.

^{1}H-NMR (DMSO-d6) δ: 5.3(s, 2H, -OCH2-), 7.1-7.5(m, 7H, Ar-H, pyrimidine,H3, H5, NH).

4-(*p*-nitrophenyl)-6-[(1,2:5,6-di-O-isopropylidene-α-D-glucofuranose-3- O-yl) methyl]-1-H-pyrimidine-2-one (7)

Yield 60%, m.p. 78-80°C, R_f (0.764), I.R. (KBr) cm^{-1} 3200 (NH), 1680 (C=O), 1610 (C=N). Alna. Calcd.: C, 56.4; H, 5.5; N, 8.6 Found:C, 55.84; H, 5.26; N, 8.28.^{1}H-NMR (DMSO-d6) δ: 5.2(s, 2H, -OCH2-), 7.3-7.7 (m, 7H, Ar-H, pyrimidine,H3, H5, NH).

Preparation of 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose-3-O-yl-acetohydrazide (3)

A mixture of ethyl(1,2:5,6-di-O-isopropylidene-α-D-glucofuranose-3-O-yl) acetate (0.64 gm., 1.8 mmol.), hydrazine hydrate 5 ml and 15ml absolute ethanol was refluxed for 5h. The reaction mixture was cooled the formed precipitate was filtered, dried and recrystallized from ethanol to give compound (3).

Yield 75%, m.p. 72-74°C, R_f (0.794), I.R. (KBr) cm^{-1}: 3278, 3383(NH-NH2), 2950-2980(CH(CH3)2), 1710(C=O amide). Alna. Calcd.: C, 50.6; H, 7.2; N, 8.4. Found: C, 50.17; H, 7.09; N, 8.19.

Preparation of Pyridizine Derivatives (8,9)

General procedure:

A mixture of compound (3) (1.5 gm, 5 mmol.) and the appropriate acid anhydride, namely, maleic anhydride and phthalic anhydride (5 mmol.) in 10 ml acetic acid was refluxed for 7h. then cooled and added into cursched ice. The precipitate was filtered off and recrystallized from ethanol to give compounds 8 and 9 respectively.

1-[(1,2:5,6-di-O-isopropylidene-α-D-glucofuranose-3-O-yl aceto]-1,2-dihydropyridazine-3,6-dione (8)

Yield 65%, m.p. 190°C dec., R_f (0.1428), I.R. (KBr) cm^{-1}: 3210(NH), 1700(C=O pyridazine ring), 1650(C=O amide). Alna. Calcd.: C, 52.4; H, 5.8; N, 6.8. Found: C, 52.26; H, 5.70; N, 6.59.^{1}H-NMR (DMSO-d6) δ: 5.4(s, 2H, -OCH2-), 6.9 (s, 2H, pyridazine ring).

1-[(1,2:5,6-di-O-isopropylidene-α-D-glucofuranose-3-O-yl) aceto]-1,2-dihydrophthalazine-3,6-dione (9)

Yield 70%, m.p. 210°C dec., R_f (0.1428), I.R. (KBr) cm^{-1}: 3420(NH), 1750(C=O phthalazine ring), 1650(C=O amide). Alna. Calcd.: C, 57.1; H, 5.6; N, 6.10. Found: C, 56.7; H, 5.48; N, 5.71.

^{1}H-NMR (DMSO-d6) δ: 5.22(s, 2H, -OCH2-), 7.4-7.7(m, 4H, Ar-H).

Preparatio of 1-[(1,2:5,6-di-O-isopropylidene-α-D-glucofuranose-3-O-yl) aceto]-3,5-dimethylpyrazole (10)

The mixture of compound (3) (0.3 gm, 1.0 mmol.), acetyl acetone (0.1 gm, 1.0 mmol.) and (10 ml) acetic acid was refluxed for 8h. The formed precipitate after cooling was filtered, dried and recrystallized from ethanol to give compound (10).

Yield 62%, m.p. 187-189°C, R_f (0.441), I.R. (KBr) cm^{-1}: 1697(C=O), 1653(C=N). Alna. Calcd.: C, 57.6; H, 7.1; N, 7.1. Found: C, 57.28; H, 6.83; N, 6.87.

^{1}H-NMR (DMSO-d6) δ: 5.4(s, 2H,-OCH_2-), 6.9(s,1H, pyrazol, H4).

The ^{1}H-NMR spectrum of all the prepared derivatives (4-10) showed the characteristic signals, which were due to the presence of the protons of the sugar moiety: 1.3-1.6(s,12H, isopropylidene groups), 4.7-4.9(d, H1), 3.30-3.9(m, H2, H4, H5, H6).

Preparation of Water Soluble Derivatives (11-17)

To a solution containing (4-10) derivatives (2.1 mmol.) in concentrated acetic acid (5 ml), concentrated sulphuric acid 0.5 ml was added. The reaction mixture was stirred for 24h. at room temperature. The mixture was poured into 20 ml water and neutralized then extracted (3×10) with chloroform. The combined chloroform extracts were dried over $MgSO_4$ and the solvent was evaporated to give compounds (11-17).

3-(*p*-nitrophenyl)-5-(D-glucofuranose-3-O-yl)methyl pyrazole (11)

Yield 60%, m.p. 140°C dec., I.R. (KBr) cm^{-1}: 3350-3470 (OH).

1-Phenyl-5-(*p*-nitrophenyl)-3-(D-glucofuranose-3-O-yl)methylpyrazole (12)

Yield 40%, m.p. 185°C dec., I.R. (KBr) cm^{-1}: 3350-3470 (OH).

4-(*p*-nitrophenyl)-6-(D-glucofuranose-3-O-yl)methyl-2-thioxo-1-pyrimidine(13)

Yield 65%, m.p. 200°C dec., I.R. (KBr) cm^{-1}: 3300-3450 (OH).

4-(*p*-nitrophenyl)-6-(D-glucofuranose-3-O-yl)methyl-1H-pyrimidine-2-one (14)

Yield 60%, m.p. 195°C dec., I.R. (KBr) cm^{-1}: 3350-3470 (OH).

1-[(D-glucofuranose-3-O-yl)aceto]-1,2-dihydropyridazine-3,6-dione (15)

Yield 55%, m.p. 130°C dec., I.R. (KBr) cm^{-1}: 3300-3470 (OH).

1-[(D-glucofuranose-3-O-yl)aceto]-1,2-dihydrophthalazine-3,6-dione (16)

Yield 46%, m.p. 158°C dec., I.R. (KBr) cm^{-1}: 3300-3470 (OH).

1-[(D-glucofuranose-3-O-yl)aceto]-3,5-dimethylpyrazole (17)

Yield 60%, m.p. 172°C dec., I.R. (KBr) cm^{-1}: 3300-3470 (OH).

Results and Discussion

D-glucose has been chosen as a starting material to prepare 1,2: 5, 6- di- O-isopropylidene -α- D-glucofuranose because of it is readily available and comparatively inexpensive compound.

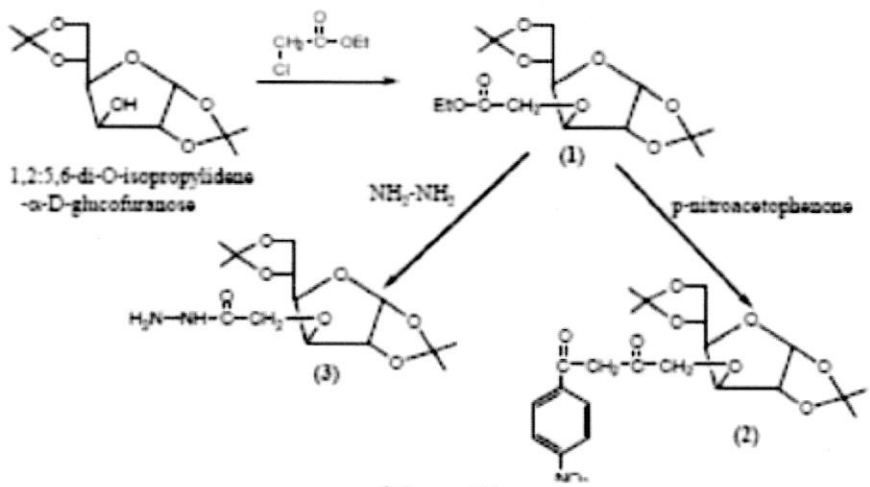
Treatment of the ethyl (1,2:5,6-di-O-isopropylidene-α-D-glucofuranose-3- O-yl)acetate (1) with *p*-nitroacetophenone in presence of sodium metal (Scheme 1) gave the corresponding 1,3-diketone derivative (2). The structure of (2) has been established by I.R. spectrum which showed absorption bands at 1693 cm^{-1} and 1604 cm^{-1} for tautomeric keto-enol forms[17].

Pyrazoles derivatives (4,5) (Scheme 2) were prepared by the reaction of (2) with hydrazine hydrate and phenyl hydrazine in the presence of acetic acid.

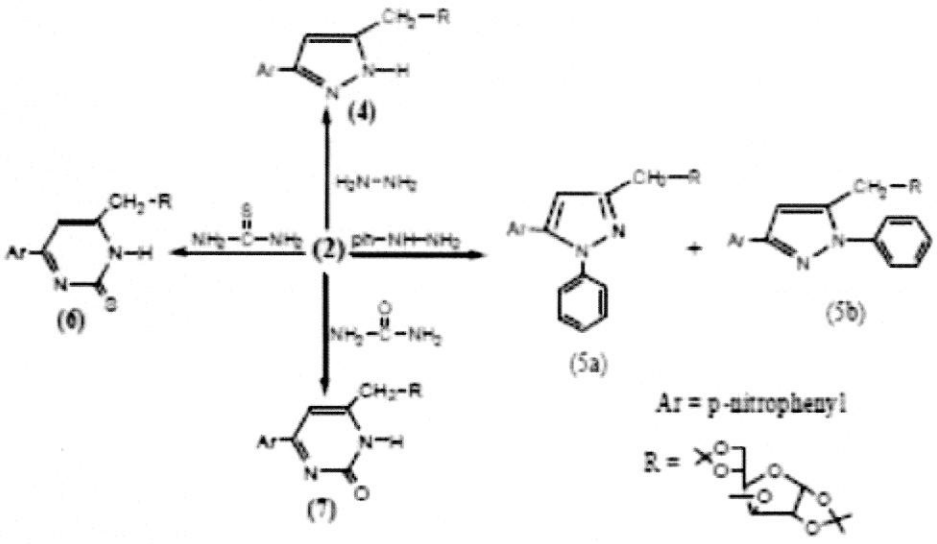
In compound (2), carbonyl group at position (1) is less nucleophilic than carbonyl group at position (3) due to the electron -withdrawing effect of the phenyl group and NH_2 in phenyl hydrazine attacks the C-3 to yield compound (5a).[18] Reaction of (2) with thiourea and urea afforded the corresponding pyrimidine derivatives (6,7). The appearance of C=N, C=O and C=S stretching bands and disappearance absorption band of keto-enol forms are attributed to the formation of the compounds (4-7). The ^{1}HNMR spectrum of these derivatives showed singlet signal at (5.1-5.3) ppm assigned to oxymethyl group. The reaction of hydrazine hydrate with compound (1) (Scheme 1) is one of the most common reaction to synthesis the acid hydrazide (3). The I.R. spectrum of acetohydrazide (3) showed the appearance of the characteristic absorption bands at (3270-3380) cm^{-1} and 1710 cm^{-1} which are due to ($NH-NH_2$) and C=O amide respectively.

Cyclization of (3) (Scheme 3) with maleic anhydride and phthalic anhydride in the presence acetic acid gave the corresponding pyridizine derivatives (8, 9).

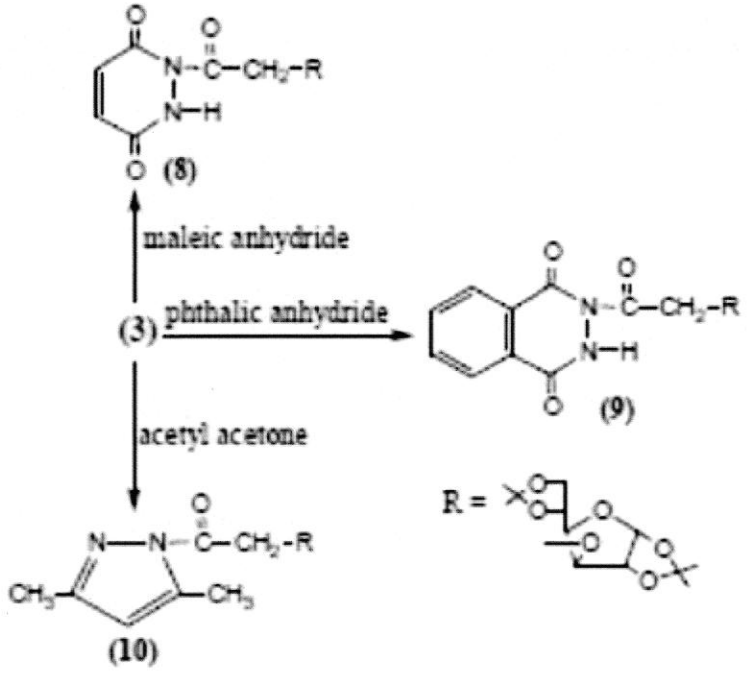
The I.R. and ^{1}H-NMR spectrum of these derivatives showed the presence of NH band at (3200-3420) cm^{-1}, (1750 cm^{-1}, C=O pyridizine ring) and a singlet signal for ($O-CH_2-\overset{O}{\overset{\|}{C}}-$) at (5.2-5.4) ppm. Also cyclization of (3) with acetylaceton afforded the 3,5-dimethyl pyrazol compound (10). The appearance of signals at 2.1 ppm ($2CH_3$) and 5.4 ppm ($O-CH_2-\overset{O}{\overset{\|}{C}}-$) was utilized to confirm the structure of the compound (10). Hydrolysis of the 1,2 and 5,6 isopropylidene groups of (4-10) derivatives using concentrated acetic acid and sulphuric acids gave the water soluble compounds (11-17). The disappearance absorption band at (2950-2980) cm^{-1} which due to isopropylidene groups and the appearance OH stretching band at (3300-3470) cm^{-1} indicates the formation of the (11-17) compounds.



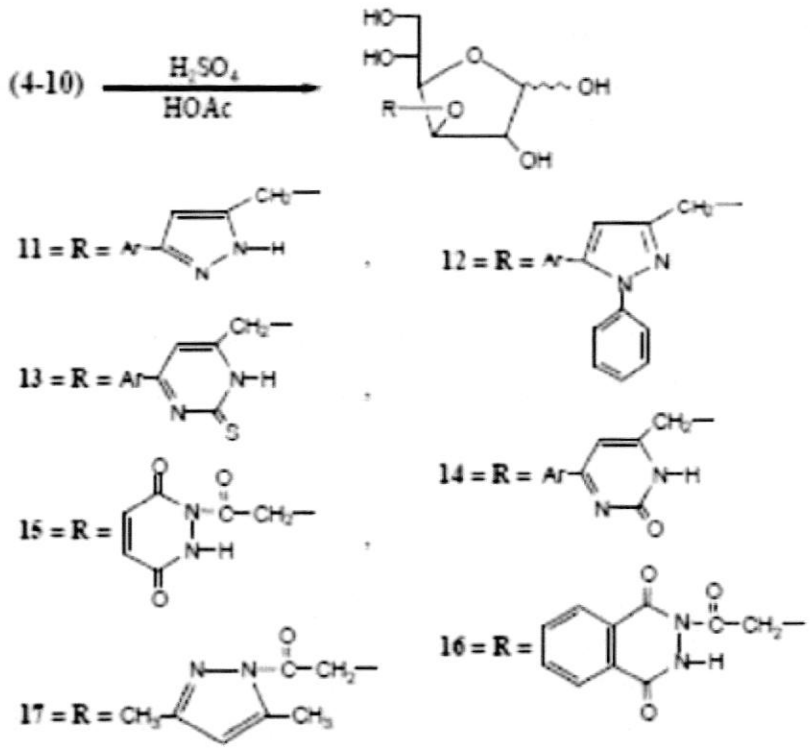
Scheme (1)



Scheme (2)



Scheme (3)



References

1- I. Magdy EL-Zahar, S. Somaia Abd ELKarim and E. Mogedda Haiba (2009), Synthesis and cytotoxic evaluation of some novel 6-(benzofurane-2-yl)-4- (4-fluorophenyl) pyridines,World J. Chem., 4, 2, 18.

2- H. Michel, R. Denis, A. James, E. Cheries, M. Terry and S. Henry (2002), Sordarin oxazepine derivatives as potent antifungal agents, Bio. and Med. Chem., 12, 19, 2757.

3- D. Harish and M. Karavekar (2010), Senthesis of benzofurane derivatives and their evaluation of antimicrobial activity, E. J. Chem., 7, 2, 636.

4- J. Biao, X. Xen-Nan and Y. Gai-Guang (2001), Synthesis and antitumor evaluation of novel monoindoly-4-trifluoro methyl pyridines and bisindoly-4-trifluoromethyl pyridines, Bioorg. Med. Chem. Lett. , 11, 4, 475.

5- V. Beneteau, T., Besson, J.Gullard, S. Leonoce and B. Pfeiffer (1999), Synthesis and in vitro antitumor or evaluation of benzothiazole-2-carbonitrile derivatives, Eur. J. Med. Chem., 34, 12, 1053

6- A. Badawi, H. EL-Sharkawy and D. Ismail (2008), Synthesis, characterization and antitumor activity of four novel sulphonamide compounds, Aust. J. Basic. Appl. Sci., 2, 2, 301.

7- I. Hayakawa, R. Shioya, T. Agatsuma, H. Furukawa and Y. Sugano (2004), Thienopyridine and benzofuran derivatives as potent antitumor agents possessing different structure activity relationships, Bioorg. Med.,Chem., Lett. , 14, 13, 3411.

8- J.Elguero, A. Katritzky, C. Rees and E. Scriven, "Comprehensive Heterocyclic Chemistry" (1996). 2nd ed., Elsevier Oxford, Vol.3, 75.

9- A. Ahmed , M. Muhanned , and Y. Emad (2013) , Synthesis and characterization di five and six heterocyclic rings ,Int. J. Pharm.and Chem. Sci., 2, 1 , 15.

10- F. AL-Assar , K. Zelenin , E. Bezhan and B. Chakchir (2002) , Synthesis and pharmacological activity of 1-hydroxy-1-amino- and 1-hydrazino-substituted-2,3-dihydro-1H-pyrazolo(1,2-b)pyridaazine-5-8-dione, Pharm. Chem.J. , 36, 598.

11- E.Taylor, H. Patel and H. Kumar (1992), Synthesis of pyrazolo 3,4-dipyrimidine analogues of the potent agent , Tetrahedron , 48 , 8089.

12- A. Amr, A. Mohamed, S. Mohamed, N. Abdel-Hafez and G. Hammam (2006), Anticancer activities and of some newly senthized pyridine and pyrimidine derivatives, Bioorg. Med., Chem., 14, 16, 5481.

13- I. Bouabdallah L. Mbarek , A. Zayed , A. Ramadani , I. Zidane and A. Melhaoui (2006) , Anticancer effect of three pyrazole derivatives , Nature Product Research , 20 , 11 , 1024.

14- A. Abadi, A. Eissa and G. Hassan (2003), Synthesis of novel 1,3,4-trisubstituted pyrazole derivatives and their evaluation as antitumor and antiangiogenic agents , Chem. Pharm. Bull. , 51, 7, 8381.

15- R.Saad Jwad, Synthesis of 1-nonyl-4-(6-deoxy-1,2:3,4-di-O- isopropylidene-α-D-galactose-6-yl oxy

methyl) 1H-1,2,3- triazole via clic chemistry (2011), Journal of Al-Nahrain University-Science,14 ,1 , 58
16- N. Falih Al-Ghrary, Synthesis of 3,3-gem-di-C-nitromethyl nucleoside analogues at (C-3) of possible biological activity (2007), Ph.D. thesis, College of Pharmacy, Baghdad University.
17- E. Boshra, Synnthesis of some new heterocyclic compounds with expected potential biological activity (1989), J. Isala. Acad. Sci., 2, 4, 237.
18- F. Gosselin, P. Oshea, R. Webster, R. Tillyer and E. Grabowski, Higly regioselective synthesis of 1-aryl-3,4,5-substituted pyrazoles (2006) , Synlet, 3267.

تحضير بعض المركبات الحلقيه الغير متجانسه الجديده الذائبه في الماء والمشتقه من Ethyl(α-D-glucofuranose-3-O-yl) Acetate

أحمد وحيد ناصر

قسم الكيمياء ، كلية العلوم ، جامعة بغداد ، بغداد ، العراق

(تاريخ الاستلام: 17 / 2 / 2013 ---- تاريخ القبول: 22 / 5 / 2013)

الملخص

حضر المشتقان (2) و(3) من من تفاعل المركب الاساس (1) مع بارا- نايتروفنيل أسيتوفينون والهيدرازين على التوالي. أعطى الغلق الخلقي للمركب (2) مع الهيدرازين و الفنيل هايدرازين و ثايوبوريا والبوريا مشتقات البايرازول (5,4) ومشتقات البيريمدين (7,6) حضرت مشتقات البايردیزین (9,8) ومشتق البايرازول(10) من تفاعل المشتق (3) مع أنهدريد الماليك وأنهدريد الفثاليك بوجود حامض الخليك والأستايل أسيتون على التوالي. أعطى التحلل المائي لمجاميع الايزوبروبلدرين لجميع المشتقات المحضرة (4-10) المركبات الذائية في الماء (11-17). شخصت المركبات المحضره بواسطة مطيافية الأشعة تحت الأحمراء و الرنين النووي المغناطيسي البروتوني والتحليل الدقيق للعناصر