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Synthesis and Characterization of Some New Oxadiazole,Triazole and Oxazepin Compounds Bearing A quinazoline-4(3H)-one

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Abstract : In the present study ,some new phenylquinazoline derivatives have been prepared starting from reaction of 2-aminobenzoic acid with benzoyl chloride in pyridine afforded the 2-phenyl-4H-benzo[d][1,3]oxazin-4-one(1).Treatment of the latter with glycine yielded 2-(4-oxo-2-phenylquinazoline-3(4H)yl)acetic acid (2).The reaction of compound (2) with thionyl chloride produced 2-(4-oxo-2-phenylquinazoline-3(4H)-yl)acetylchloride(3).Condensation of compound (3) with hydrazine hydrate afforded 2-(4-oxo-2-phenylquinazoline -3(4H)-yl) acetohydrized (4).The reaction of compound (4) with carbon disulfide and potassium hydroxide yielded 3-[(5-mercapto-1,3,4-oxadiazole-2-yl)methyl]-2-phenylquinazoline-4(3H)-one(5).The azomethines (6a-d)were synthesized from the reaction between corresponding aldehydesand acid hydrized(4).Moreover,N-(3-methyl-1,5-dioxobenzo[e][1,3]oxazepin-4(1H,3H,5H)-yl-2-(4-oxo-2-phenylquinazoline -3(4H)-yl)acetamide (7a,b) were synthesized from the cyclic condensationof Schiff bases compounds with phthalic anhydride. Moreover,2-(2-oxo-2-phenylquinazoline-3(4H)-yl)acetyl)-N-phenylhydrazincarbothioamide(8) was synthesized via reaction of compound (4) with phenylisothiocyanate. The treatment of compound (8) with $NaHCO_3$gave 3-((5-mercapto-4-phenyl-4H-1,2,4-triazol-3-yl)-2-phenylquinazoline -4(3H)-one(9). The structure of novel synthesized compounds were assured by physical properties and spectral (FT-IR,^{1}H-NMR and ^{13}C NMR).
Keywords : Oxazin,Oxazepin, Oxadiazole ,Triazole, Phenylquinazoline.

Introduction:

Quinazoline is a bicyclical compound involved pyrimidine system fused at 5,6 with benzene ring that have importance in medical fields[1].Quinazoline analogs are used in pharmaceutical industry, medicine and agriculture for their wide scope of biological activity[2].Also these compounds have been showed various biological activities such as anti-inflammatory, analgesic[1],antioxidant[3],anticancer[4], antidiabetic[5], antituberclar[6]and antifungal activity[7].

Diversity of quinazoline for biological response profile has important considerable in several researchers to explore this skeleton for therapeutic significance[8].

It has been suggested that quinazoline-4(3H)-ones with substitution at position3, has attractive role as anti-microbial agent[9]such as substitutions with phenyl ring moieties, bridged phenyl rings[10], heterocyclic rings and aliphatic systems[11].Thus , their synthesis has been of great interest in the elaboration of biologically active heterocyclic compounds. Novel oxadiazole, triazole and oxazepin bearing a quinazoline -4(3H)-one were synthesized.

Experimental:

A-Materials:

All the chemicals used in this researchwere of analytical grades.

B-Instruments:

Melting points were read using electrothermal melting point apparatus. Infrared spectra were read as KBrdisc on SHIMADZU-FT-IR-8400 spectrometer.$^{1}H,^{13}$ C-NMR spectra was read on Burker 300 MHz instrument using DMSO-d^{6} as a solvent and TMS as internal reference ,measurement were made at Al-Albayt University, Jordan. The progress of the reaction was monitored by TLC using aluminum silica gel plates.

C-Preparation Methods:

1-Synthesis of 2-phenyl-4H-benzo[d][1,3] oxazine -4-one(1):

Benzoyl chloride (0.02mol) was added to a solution of 2-aminobenzoic acid (0.01mol)in (30 ml) pyridine and the mixture was shaken for (5 min) and then kept a side room temp. for further 25 min with occasional shaking. The reaction mixture was treated with 15 ml of 10% $NaHCO_3$, filtered, washed with water, dried and also the crude product was recrystallized from absolute ethanol. Yield (58%),m.p.(118-120)$^{0}C^{12}$.

2-Synthesis of 2-(4-oxo-2-phenylquinazoline-3(4H)yl)acetic acid (2):

A mixture of equimolar amounts (0.001 mol) of 2-phenyl -4H-benzo[d][1,3]oxazine -8-one in presence of glycine with (15 ml)of glacial acetic acid then mixture was refluxed for (3.5-5)hr.A liquate of 25 ml ice cold distilled water was added to the reaction The compound was filtered and dried .Yield (73%),m.p.(168-171)$^{0}C^{13}$.

3-Synthesis of 2-(4-oxo-2-phenylquinazoline-3(4H)-yl)acetyl chloride(3):

A mixture of compound (2) (0.01 mol) and thionyl chloride (10 ml) in dry benzene (5ml) was refluxed for 3hr.The solution was cooled then the excess of thionyl chloride and benzene evaporated under vacuum,the product was purified with yieldof(80%)and m.p. (120-122)$^{0}C^{14}$.

4-Synthesis of 2-(4-oxo-2-phenylquinazoline -3(4H)-yl)acetohydrizede (4):

(0.01 mol) of compound (3) and 80% hydrazine hydrate(0.05 mol)in dry benzene (15 ml) was refluxed for 4h with stirring. After cooling, the benzene and excess hydrazine hydrate were removed under reduce pressure, the residue was washed with ether, then recrystallized from ethanol to provide solid products, yield(88%), m.p.(179-181)0C^{14}.

5-Synthesisof3-((5-mercapto-1,3,4-oxadiazole-2-yl)methyl)-2-phenylquinazoline-4(3H)-one(5) :

To a solution of compound (4) (0.01 mol) in ethanol (20 ml) of KOH (0.015 mol) in (20 ml) was added ,after that (2.5 ml) of CS_2 was added . The mixture was refluxed for 8 hr., concentrated ,then acidified with dilute HCl. The precipitate was collected, washed with water and also recrystallized from ethanol, Yield (86%) ,m.p.(208-210)$^{0}C^{15}$.

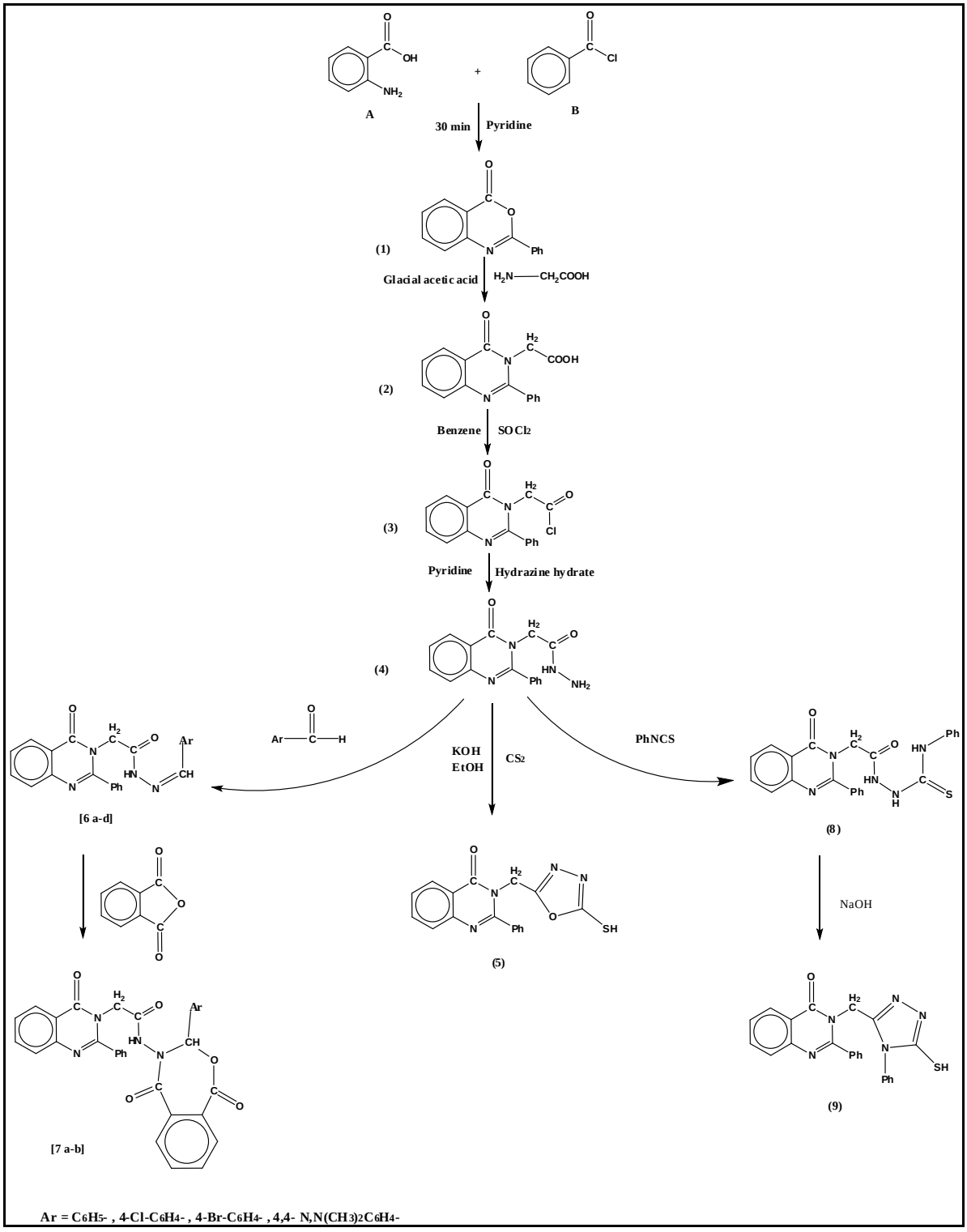
6-General method for synthesis of Schiff's bases compounds(6a-d):

Amixture of equimolar amounts (0.01 mol)of applicable aldehyde and compound(4) in (15 ml) of absolute ethanol. Glacial acetic acid (3drops) were value added to the mixture which was refluxed in water bath for 8hr. Then mixture was cooled at room temp. Results was filtered and dried[15].The yields and some physical properties of these compounds are shown in table1.

7-General method for synthesis of oxazepines compounds(7a,b) :

Amixture of compounds (6a,c)(0.01 mol) and (0.01 mol) of phthalic anhydride was dissolved in (10 ml) of dry benzene and refluxed in a water bath for 8hr .The remaining solution was treated with sodium

bicarbonate to produce compounds (7a,b)as a solid precipitate and recrystallized from ethanol[16]**.** Table(1) represent data for compounds (7a.b).



Scheme-1-

8-Synthesisof2-(2-oxo-2-phenylquinazoline-3(4H)-yl)acetyl-N-phenylhydrazinecarbothioamide(8):

A mixture of compound (4) (0.005 mol) and (0.005 mol) of phenylisothiocyanate was refluxed in ethanol for 6h,then cooled. A white precipitate appeared, that filtered and recrystallized from ethanol with yield(85%) and m.p.(134-136)^{0}C[15].

9-Synthesis of3-((5-mercapto-4-phenyl-4H-1,2,4-triazol-3-yl)-2-phenylquinazoline-4(3H)-one(9):

A solution of compound (8) in (4%) of NaOH was refluxed for 24h.The solution that result was cooled to room temperature and acidified to pH (5-6). Results was filtered ,washed with water and recrystallized from ethanol /water (1:1) to give compound (9) with yield(58%) and m.p.(269-271)^{0}C[15].

Results &Discussion:

Scheme1summarizedthe performed reactions in this work. Compounds (1) and (2)were prepared according to literatures[12,13].The formation of these compounds were indicated by m.p. which agreement with these literatures..

Compound (2) reacted with $SOCl_2$ in benzene (dry) which gave acid chloride compound (3),the reaction was followed by changing the absorption of carbonyl group of acid from1685 cm^{-1} to 1762$cm^{-1}$for a carbonyl of acyl chloride and disappearance of stretching absorption band at 2500 -3210cm^{-1} for OH of acid.

Reaction between (3) and hydrazine hydrate afforded the acid hydrazide compound (4).The FT-IR spectrum showed the NH_2 ,NH stretching absorption near 3205 -3315cm^{-1} and the carbonyl stretching band at 1651cm^{-1}.The ^{1}H-NMR spectrum provide a perfect conformation to the structure formation in which the conformation hydrazide compounds showed new singlet signal at (8.65ppm),(12.20ppm,2H,s,for NH_2.In the^{13}C-NMR spectrum of compound (4) ,the signals of the carbon of carbonyl amid ,cyclic amid and carbon of imine were observed in 168.60,164.98 and 164.50ppm respectively.

The treatment of compound (4) with CS_2inKOH solution resulted 3-[(5-mercapto-1,3,4-oxadiazole -2-yl)methyl]-2-phenylquinazolin -4(3H)-one(5). The FT-IR spectrum of compound (5) showed a peak at 1614 cm^{-1} attributable to the C=N of imine .The carbonyl absorption band was seen at 1660cm^{-1}.Also absence of signals in the region 3205-3315cm^{-1} for NH_2 group. In the ^{1}H-NMR spectrum of this compound two signals related to the CH_2 group, C- S group and NH group of thione were observed between 2.51,3.33 and 10.19 ppm respectively.In the ^{13}C-NMR spectrum of compound (5),C=S group resonated at 164.29ppm, while new signal was seen at 38.66ppmdue to SH group.

Synthesis of four various Schiff bases derivatives of compound (6)was synthasized by the reaction of compound (4) with served aromatic aldehydes in ethanol with acetic acid as a catalytic agent. The ^{1}H and ^{13}C-NMR spectrum of compounds (6a-d) displayed other signals belong to the aromatic ring derived from aldehyde at aromatic region ,while the signal related to NH_2group of hydrzide structure did not appear. The FT-IR spectra of compounds (6a-d) showed a peak at region (1645-1653)cm^{-1} belonging to C=N group. The ^{1}H-NMR spectrum for these compounds showed two sets of signals each belonging to the CH=N group,N-CH_2group of amide were observed between 10.49,2.51 and 7.36 and 8.20 ppm for proton of aromatic ring. The^{13}C-NMR spectra of compounds (6a-d), theC=N signals related to individual cis/trans conformers were seen as two sets between 127.46 and 128.67 ppm.

The compounds (7a,b)were synthesized by the condensation reaction of compounds (6a,b) with phthalic anhydride in dry benzene. The chemical structures and purity of compounds (7a,b) were determined by FT-IR,^{1}H-NMR and ^{13}C-NMR spectroscopic techniques .The FT-IR spectrum of compounds (7a,b)showed a peak at region (1691-1693)cm^{-1} belong to carbonyl of cyclic ester. The carbonyl absorption band of amide was observed at (1656-1681)cm^{-1}.In the ^{1}H-NMR spectrum of compound (7b) represent the following characteristics chemical shifts were appeared ,the singlet signal at 2.98 ppm of -CH_2 group and two singlet signals at 11.83 and 12.09 ppm due to OH group and NH protons in two tautomeric forms. The singlet signal of one proton at 8.61 ppm for CH of cyclic oxazepine. The ^{1}H-NMR spectrum also showed the multiple signal at (6.75-8.58)ppm of aromatic protons for three benzene rings.

The ^{13}C-NMR spectrum of compound (7a), the carbonyl group of cyclic ester resonated at 195.63 ppm ,while (174.74,164.40 and 151.67)ppm due to carbon of carbonyl of amide.

The synthesis of compound (8)was carried out by reaction of compound (4) with phenylisothiocyanate .The FT-IR spectrum of compound(8) showed three peaks at 3151cm^{-1},3216$cm^{-1}$and 3119cm^{-1}due to NH

groups. The formation of this compound(8) was indicated by the presence of the azomethine(C=N), (C=S)and(C=O) stretching band at 1610cm^{-1},1180 cm^{-1},and 1658 cm^{-1} respectively.

The ^{1}H-NMR spectrum provide a perfect confirmation to the structure formation in which the compound (8) showed new singlet signal at (7.20-7.42)ppm,(7.25-7.48)ppm and (8.40-8.84)ppm for aromatic protons,while signals resonating at (9.60)ppm ,(9.75)ppm and (10.20)ppm related to NH of this compound. Moreover,signal resonating at (2.89) ppm due to –CH_2group.

Refluxing of compound (8) with NaOH for (24) hrs and resulting solution was cooled and acidified afforded compound (9) containing triazole -2- yl moiety which disappearance two bands at 1658 cm^{-1} and 1180 cm^{-1} for (C=O)group of amide and (C=S) group respectively ,in addition to the band at 2632 cm^{-1} for the SH stretch.In the ^{1}H-NMR spectrum of compound (9),other signal belong to –SH group appeared at 12.72 ppm (controlled by changing D_2O) while the –NH signals disappeared. These prepared compounds consider interesting in the field of water treatment.[17-22]

Table (1):physicalproperties and spectral data for synthesized compounds

Comp. No.	R	R$^-$	Molecular Formula	M.P. (^{0}C)	Yield (%)	IR(KBr) (cm^{-1})
1			$C_{14}H_9NO_2$	113-115	58	1762 C=O; 1614 C=N 1571 C=C
2			$C_{16}H_{12}N_2O_3$	134-136	73	1685 C=O; 1643 C=O 1608 C=N; 1541C=C
3			$C_{16}H_{11}N_2O_2Cl$	120-122	80	1762 C=O; 1656 C=O 1614C=N; 1598C=C
4			$C_{16}H_{14}N_4O_2$	179-181	88	3205 N-H 1651C=O 1633C=N 1600C=C
5			$C_{17}H_{12}N_4SO_2$	208-210	86	3334 N-H; 1660C=O 1614C=N; 1598C=C
6a	N,N$(CH_3)_2$ C6H4-		$C_{25}H_{23}N_5O_2$	251-253	74	3197 N-H; 1662 C=O 1604C=N; 1595C=C
6b	C6H5-		$C_{23}H_{17}N_4O_2$	160-162	78	3236N-H 1674 C=O 1610C=N 1591C=C
6c	P-BrC6H4-		$C_{23}H_{16}N_4O_2Br$	238-240	76	3329N-H 1651 C=O 1604 C=N 1589 C=C
6d	P-ClC6H4-		$C_{23}H_{16}N_4O_2Cl$	233-235	80	3329 N-H 1653 C=O 1604 C=N 1589 C=C
7a		N,N$(CH_3)_2$ C_6H_4-	$C_{33}H_{27}N_5O_5$	172-173	70	3180 N-H; 1691 C=O 1664 C=O; 1645 C=O 1600 C=N; 1521 C=C
7b		P-BrC_6H_4-	$C_{31}H_{21}N_4O_5Br$	218-220	65	3323 N-H; 1693 C=O 1681 C=O; 1656 C=O 1604 C=N; 1588 C=C
8			$C_{23}H_{19}N_5O_2S$	134-136	85	3216 N-H; 1658 C=O 1610 C=N; 1180 C=S
9			$C_{23}H_{17}N_5OS$	269-271	58	1648 C=O; 1607 C=N 1230 C=S; 2632 S-H

Table (2): ^{13}C-NMR Spectral Data for Compounds

No.	^{13}C-NMR(DMSO-d^{6}δ ppm)
2	38.65,38.92,39.2,39.76,40.04,40.31,119.86,122.94,126.98,128.97,131.52, 132.17,134.28,134.5,141.06,164.68,169.97.
4	38.63,38.92,39.19,39.47,39.75,40.03,40.3,120.43,121.07,123.61,123.03, 127.02,128.22,128.6,128.89,129.08,130.68,131.86,132.65,133.29,134.35, 139.3,147.72,164.5,164.98,168.6.
5	38.66,38.93,39.21,39.49,39.77,40.04,40.34,40.82,44.05,120.17,122.84,126.89,127.62,128.92,132 .05,139.19,151.93,164.29.
6	38.66,38.94,39.22,39.5,39.77,40.05,40.32,90.89,98.24,127.64,128.67.
7	28.23,38.64,38.92,39.19,39.47,39.75,40.03,40.31,41.95,42.29,42.82,43.69,52.62,54.56,57.09,111 .73,120.36,120.73,121.12,123.01,126.97,128.42,128.68,128.92,130.92,132.08,132.33,139.3,145. 46,150.03,151.67,164.4,174.74, 195.63.

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