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Synthesis, Characterization of Organic Derivatives Containing Heterocyclic Rings and Evaluation Their Antibacterial Activity

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Abstract: *Schiff bases (Sh1-Sh3) have been synthesized (p-aminophenol) was condensed with different aromatic aldehyde in ethanol inthe presence of glacial acetic acid as catalyst. These Schiff bases on treatment with monochloroacetyl choride gave 3-chloro-1-(4-hydroxyphenyl)-4-(substituted)azetidin-2-one(Az4-Az6), with **α**-mercaptoacetic acid gave 3-(4-hydroxyphenyl)-2-(substituted)thiazolidin-4-one (Th7-Th9) and with anthranilic acid gave 3-(4-hydroxyphenyl)-2(substituted)-2,3-dihydroquinazolin-4(1H)-one (Qu10-Qu12). The purity of the derivatives was confirmed by TLC. The some compoundsidentify by (FT-IR and ^{1}H, ^{13}C-NMR) data. Some of derivatives were evaluated activity against several microbesto determine ability to inhibit bacterial in some heterocyclic structures.*

Keyword: *Schiff base, heterocyclic, azetidine-2-one, thiazolidine-4-one, quinazoline-4-one.*

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I. Introduction

Some Schiff bases bearing aryl groups[1], or heterocyclic residues containing nitrogen and sulfur in the core structure possess excellent biological activities[2, 3], which has attracted many researcher's attention in recent year. Four, five and six member heterocyclic compounds have attracted the attention of pharmaceutical community over the years due to their therapeutic values because of analysis of drugs shows that 68% of them are heterocycles [4, 5]. Azetidinones, thiazolidinones and quinazolinones and their derivatives have been studied extensively for various biological activities and clinical applications such as antibacterial, antimicrobial, anti-inflammatory, antituberculer, antioxidant, anticancer, antiviral, analgesic, and anticonvulsant [6-14].
In this paper synthesized heterocyclic derivatives containing azetidinone, thiazolidinoneand quinazolinone rings because these derivatives have many applications in medicine and industry and have antimicrobial activity.

II. Experimental Part

1.1 Material and Methods

1.1.1 Instruments

A Gallen Kamp melting point apparatus was used to measure melting points. Shimadzu FTIR-8300 spectrophotometer as KBr disc, result are given in cm^{-1} and Bruker spectro spin ultrashield magnets 400 MHz instrument, using DMSO-d_6 and $CHCl_3$-d_1 as solvent and TMS as internal reference used to identification the organic inhibitor.

1.1.2 Chemical

All starting chemical compounds were obtained from Fluka, Aldrich and BDH.

1.2 General procedure for synthesis of Schiff base and its derivatives:

1.2.1 Synthesis of Schiff bases [15] (Sh1-Sh3)

Schiff bases were prepared from the reaction of p-amino phenol (0.01 mole) with different aromatic aldehyde (0.01 mole), in 25 ml C_2H_5OH absolute and few drops of glacialCH_3COOH. This mixture was refluxed for 5-7hrs. The mixture was poured in ice water with stirring and filtration, and then recrystallized from absolute ethanol. Physical properties are listed in Table (1).

1.2.2 Synthesis of 3-chloro-1-(4-hydroxyphenyl)-4-(substituted) azetidin-2-one [16] (Az4-Az6)

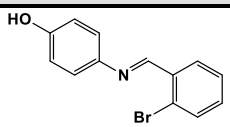
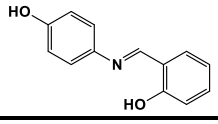
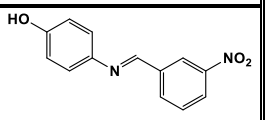
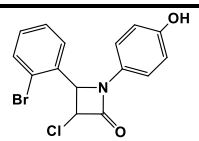
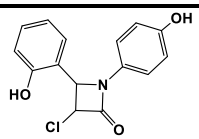
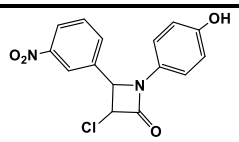
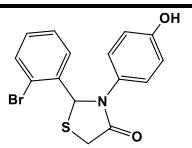
A solution of Schiff base (Sh1-Sh3) (0.002 mol) in DMF (25 ml) was quantify poured into the mixture of monochloroacetyl chloride (0.004 mol, 0.34 ml) and Et_3N (0.004 mol, 0.56 ml) in DMF (20 ml) which was well mixing at 0-5ºC., then the reaction mixture was refluxed for (10-12) hrs. and kept at room temperature in the sealed containers for 2 days. The solid product was obtained by pouring the mixture into the ice, filtered and washed using distilled water. Then the product was dried and recrystallized by water and ethanol. Physical properties are listed in Table (1).

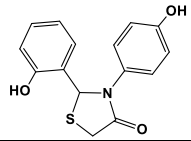
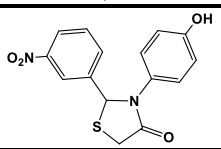
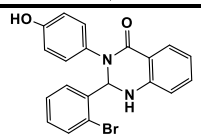
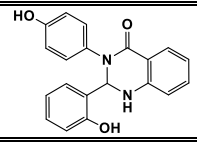
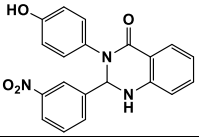
1.2.3 Synthesis of 3-(4-hydroxyphenyl)-2-(substituted)thiazolidin-4-one [17] (Th7-Th9)
To a mixture of Schiff bases (0.002 mol) and α-mercaptoacetic acid (0.01 mol) dissolved in DMF (25 ml), anhydrous $ZnCl_2$ (0.0016 mol) was added and refluxed for 8-10 hrs. The reaction mixture was then poured into crushed ice, filtered and washed with water, dried and recrystallized using absolute ethanol. Physical properties are listed in Table (1).

1.2.4 Synthesis of 3-(4-hydroxyphenyl)-2(substituted)-2,3-dihydroquinazolin-4(1H)-one [18] (Qu10-Qu12)
Schiff bases (0.01mol) in DMF was added to solution of (anthranilic acid) (0.01mol). The solution was heated under reflux temperature for 12 hrs., The reaction mixture was then poured into crushed ice, filtered and washed with water, dried and recrystallized using absolute ethanol. Physical properties are listed in Table (1).

1.3 Biological Activity [19]
The biological activity test was conducted using a method called (disk diffusion method). Some of newly synthesized derivatives were tested against a standard strain of pathogenic microorganism including Gram-positive (***Staphylococcus aurous*** and ***Bacillus***) and two strain gram negative bacteria (***Escherichia coli*** and ***pseudomonas***). Whattman filter paper no.1 with diameter 5mm was sterilized for 15 min. using autoclave device at 121° C. The impregnate process of sterile disks was conducted by different compounds (800µg/disk). The surface of agar plates was uniformly inoculated by 100 µL of tested microorganism. Then, the impregnated disk were incubated for 1 hour at 5°C in order to obtain excellent diffusion and later on were placed in an incubator for 24 hours at 37°C. The results have shown that the synthesized derivatives have formed inhibition zones and tabulated in Table (3).

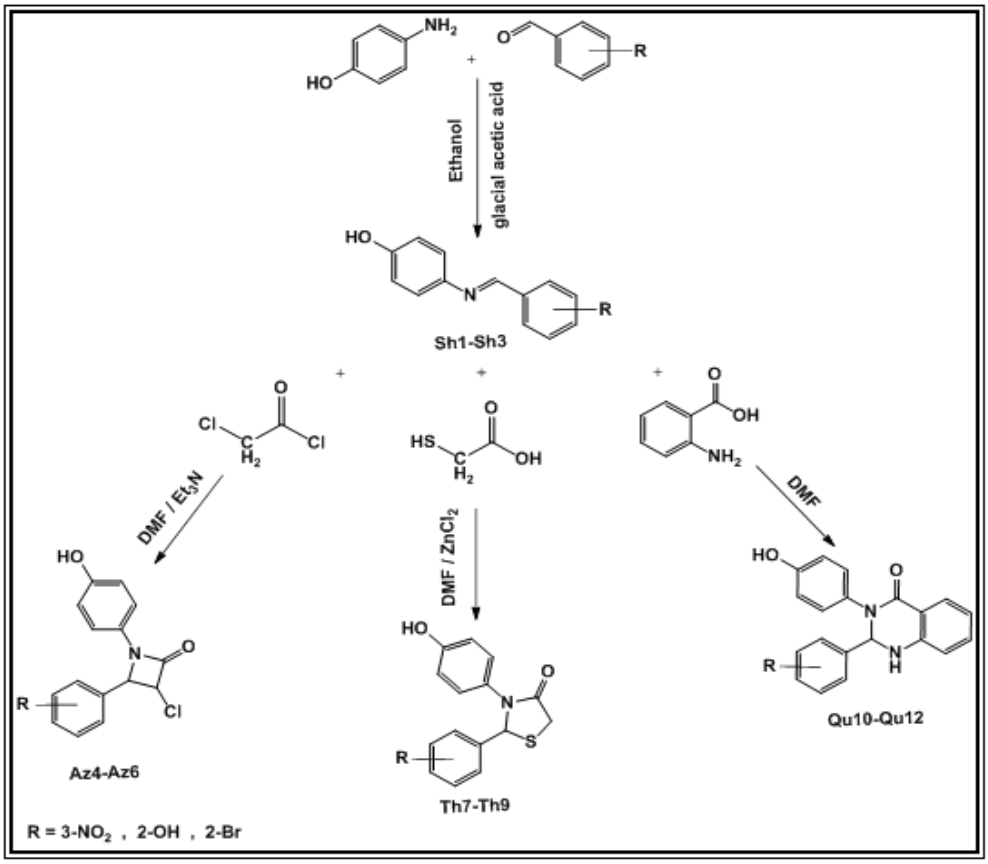
Table 1: Some physical properties and spectral data of synthesized derivatives

Comp. code.	Comp. structure	Melting point °C	Yield %	Color	Major FTIR Absorptions cm^{-1}				
					νO-H	νC-H arom.	νC-H Aliph.	νC=O	Other bands
Sh1		160-162	82	Pink	3568	3053	2930 2812	--	νC=N 1612
Sh2		138-140	84	Green-yellow	3400	3018	2891 2823	--	νC=N 1614
Sh3		158-160	81	Brown	3555	3008	2910 2840	--	νC=N 1620 νC-NO2 1529,1350
Az4		113-115	45	Black	3448	3041	2929	1662	
Az5		98-100	43	Brown	3431	3033	2931 2870	1643	
Az6		108-110	40	Pale-brown	3444	3025	2924 2862	1637	νC-NO2 1527,1354
Th7		260 dec.	72	Black	3480	3033	2920 2840	1745	

Th8		340 dec.	60	Deep-brown	3423	3015	2926 2856	1743	
Th9		338 dec.	56	Black	3346	3010	2930 2820	1750	νC-NO2 1527,1354
Qu10		190-192	50	Brown	3577	3037	--	1656	νN-H 3343
Qu11		199-201	57	Pale-brown	3587	3030	--	1627	νN-H 3290
Qu12		170-172	65	Brown	3460	3020	--	1631	νN-H 3260 νC-NO2 1527,1354

III. Result And Discussion

Scheme (1) showed synthesized different organic compounds contained available heterocyclic rings from Schiff base derivatives. All the derivatives characterization by FTIR and some of derivatives by ^{1}H-NMR and ^{13}C-NMR.



Scheme 1: diagram of synthesized heterocyclic derivatives

The derivatives (Sh1-Sh3) prepared from reaction different aromatic aldehyde with p-amino phenol in presence gly.CH_3COOH, characterized in the first by reaction of them with 2, 4-dinitro phenyl hydrazine to yield negative test, this reaction show disappearance the carbonyl group. FTIR spectral data of these derivatives list in Table (1) show disappearance absorption band of υ NH_2 and appearance bands at (1620-1614) cm^{-1} due to azo methane group [20].

The heterocyclic compounds that contain azetidine-2-one ring (Az4-Az6) synthesized from reaction between chloroacetylchloride and (Sh1-Sh3) derivatives in presence Et_3N, the FTIR showed disappearance absorption band of azo methane group and appearance bands to carbonyl group, ^{1}H-NMR and ^{13}C-NMR for some the derivatives show appear the chemical shift to (CH proton , carbon) in azetidine-2-one ring and (CH proton, carbon) fused with chlorine [21], ^{1}H-NMR spectrum for compound (Az4) appear signals δ 4.81 ppm (d,1H,-N-C<u>H</u>.Ar); δ 6.32 ppm (d, 1H, -C<u>H</u>-Cl); δ 6.4-7.9 ppm (m, 8H, Ar-<u>H</u>) and δ 10.2 ppm (s,1H, -O<u>H</u>) while derivative (Az6) show signals δ 4.93 ppm (d,1H,-N-C<u>H</u>.Ar); δ 6.21 ppm (d, 1H, -C<u>H</u>-Cl); δ 6.6-8.4 ppm (m, 8H, Ar-<u>H</u>) and δ 10.15 ppm (s,1H, -O<u>H</u>). ^{13}C-NMR spectrum for (Az4) and (Az6) show signals listed in Table (2).

Thiazolidine-4-one derivatives (Th7-Th9) prepared from adding mercapto acetic acid to Schiff base derivatives with anhydrous zinc chloride, table (1) showed the FTIR spectral data for these derivatives, the spectrum of FTIR show disappearance (–N=CH-) group and appear the absorption bands at (1750-1743) cm^{-1} due to carbonyl group ,^{1}H-NMR and ^{13}C-NMR used to characterization for some of the derivatives show appear signals due to methylene and carbonyl groups in thiazolidinone ring[21], ^{1}H-NMR spectrum for derivative (Th7) appear signals 3.55 ppm (s, 2H, -CO-C<u>H</u>$_2$-S-); δ 5.32 ppm (s,1H,-N-C<u>H</u>.S-); δ 6.95-7.7 ppm (m, 8H, Ar-<u>H</u>) and δ 10.4 ppm (s,1H, -O<u>H</u>) while derivative (Th8) show signals 3.34 ppm (s, 2H, -CO-C<u>H</u>$_2$-S-); δ 5.51 ppm (s,1H,-N-C<u>H</u>.S-); δ 6.8-7.9 ppm (m, 8H, Ar-<u>H</u>) and δ 10.1 ppm (s,1H, -O<u>H</u>). ^{13}C-NMR spectrum show signals δ 40.5, 39.6 and 169.26, 172.6 due to methylene and carbonyl groups respectively and other signals listed in Table (2)

Quinazolinone derivatives (Qu10-Qu12) prepared from reaction (Sh1-Sh3) with anthranilic acid, these derivatives characterized by FTIR and showed appearance absorption bands at (3343-3260) cm^{-1} due to υ(NH) and (1656-1627) cm^{-1} due to carbonyl group for amide II and disappearance bands azomethane group, ^{1}H-NMR spectrum for derivative (Qu10) appear signals 6.92 ppm (d, 1H, -NH qinazoline ring); δ 8.25 ppm (s,1H,-N-C<u>H</u>.NH-); δ 7.10-7.92 ppm (m, 12H, Ar-<u>H</u>) and δ 10.4 ppm (s,1H, -O<u>H</u>). ^{13}C-NMR spectrum for (Qu10) show signals due to (-CH-) and (C=O) quinazoline ring listed in Table (2).

Some of these derivatives used to determine the antibacterial activity against two strains each of gram positive (***Staphylococcus aurous*** and***Bacillus***) and two strain gram negative bacteria (***Escherichiacoli***and***pseudomonas***) and the activity was determined by measuring the zone inhibition and the result are given in Table (3).

Table 2: ^{13}C-NMR spectral data for some synthesized derivatives

Comp. code	(^{13}C-NMR signals (400 MHz, $CHCl_3$-d_1, δ-H (ppm))
Az4	56.20 (-N-C<u>H</u>- lactam), 49.01(-H<u>C</u>-Cl lactam), 116.4-155.3 (12 Carbon aromatic ring), 171.52 (C=O β-lactam).
Az6	59.90 (-N-C<u>H</u>- lactam), 51.32(-H<u>C</u>-Cl lactam), 115.72-157.21 (12 Carbon aromatic ring),169.27 (C=O β-lactam).
Th7	61.50 (-N-C<u>H</u>- thiazolidinone ring), 40.5 (-C<u>H</u>$_2$-S- thiazolidinone ring), 116.5-161.23 (12 Carbon aromatic ring),169.26 (C=O thiazolidinone ring).
Th8	62.20 (-N-C<u>H</u>- thiazolidinone ring), 39.6 (-C<u>H</u>$_2$-S- thiazolidinone ring), 114.2-160.15 (12 Carbon aromatic ring),172.65 (C=O thiazolidinone ring).
Qu10	92.10 (-N-C<u>H</u>-N-quinazoline ring), 173.24C=O quinazoline ring), 113.71-165.11 (Carbon aromatic ring).

Table 3: antibacterial activity of some synthesized derivatives

Comp. code	*Staphylococcus aurous*	*Bacillus*	*Escherichiacoli*	*pseudomonas*
Az4	+	-	+	-
Az6	++	+	-	++
Th7	+	-	+++	+
Th8	++	+	-	+++
Qu10	+++	++	+	+++

Key the symbol: (-) no inhibition, (+) 3-5 mm inhibition zone, (++) 6-8 mm inhibition zone, (+++) 9-12 mm inhibition zone,

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