RESEARCH ARTICLE

Synthesis, Characterization, and Biological Activity of New Heterocyclic Compounds Derivatives from Thiazole Derivative

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ABSTRACT

This study involves the synthesis of new heterocycle compounds in many steps. The first is to react between 2-Amino-5-nitrothiazole with salicylaldehyde at 0°C and acid media to form azo derivative,[1] then react (1) with 4-hydroxyacetophenone to get chalcone derivative (2). Third step involve react (2) with (hydrazine hydrate, phenylhydrazine, 2,4-dinitrophenylhydrazine, hydroxylamine hydrochloride, urea, thiourea, ethyl cyanoacetate, malononitrile, guanidine) to form pyrazole derivatives,[3-5] isoxazole derivative,[6] oxazine derivative,[7] thiazine derivative,[8] pyridine derivatives.[9-11] All these compounds were diagnosed by FT-IR spectrum, ^{1}H-NMR, ^{13}C-NMR, CHN, subsequent Rf -TLC reaction, and measurement liquefaction point. Then we studied the biological action for eleven compounds towards two kinds of microorganisms.

Keywords: Isoxazole, Pyrazole, Pyridine, Oxazine, Thiazine, Thiazole.

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1. INTRODUCTION

Heterocycle compounds are very important and classified. They were used in main domains such as Dyeing, pharmaceutical industry, agriculture, medicine, etc. For that, I synthesized many types from there.[1,2] Pyrazoles are heterocycle compounds of a five-member with two nitrogen atoms and three adjacent carbons. Pyrazole byproducts have acceptable pharmacological impacts or possible biological actions, such as fungicidal activities, antitumor, antimicrobial, herbicidal, veridical, and insecticidal activity.[3-5]

Isoxazole is a five-member oxygen-nitrogen-containing heterocyclic compound with a broad spectrum of pharmacological activities like anticancer, anti-inflammatory, anti-tubercular, anti-hypertensive, and anti-bacterial anti-fungal, and anti-HIV.[6-9] Oxazines are six-members heterocyclic compounds containing one oxygen and one nitrogen its also have valuable biological properties like antipyretic, analgesic, anti-leukemic, antimalarial, anticonvulsant, antimicrobial activities, and anti-inflammatory.[10-12]

Thiazines are very important heterocyclic compounds. It has very active biological properties. some thiazine derivatives are cannabinoid receptor agonists, anti hypotensive, anti-tubercular,[3] anti-bacterial[4] agents. Furthermore, it could be employed for gastrointestinal disorders[5] or to prevent diabetes.[6] antioxidants,[7] analgesics, anti-inflammatory agents,[8] or calcium channel modulators.[13-15] Many heterocyclic compounds have pyridine rings and are used in the pharmacological field, for example, anticancer, antiviral, anti-fungal, anti-bacterial activities, antimicrobial, anti-HlV, and anticonvulsant.[16-18]

EXPERIMENTAL

Materials and Instrumental Analysis

All compounds are equipped by BDH, Aldrich, and sigma chemical companies. Fourier Transform Infrared Spectroscopy (FTIR) Spectra (4000-400cm^{-1}) in KBr disk is registered on a Shimadzu FTIR-8400S Fourier-transform. The liquefaction point was defined using Stuart, UK. ^{1}H-NMR and ^{13}C-NMR spectra are gained with a model Bruker AM(400MHz) spectrometer for utilizing DMSO-d6 solvent in a suitable deuterated solution. Primary analysis (CHNS) was achieved employing a CHN EA-99 mth tool. The purity of all compounds evaluated by thin film chromatography (TLC) utilizing Whatman 250 m silica gel plates as the stationary stage and methanol as developing solvent.

Preparation of 2-hydroxy-5-((5-nitrothiazol-2-yl)diazenyl) benzaldehyde.compound (1)[19]

synthesized compound (1) Mixed 2-amino-5-nitro thiazole (1.45gm,0.01mol) in 40 mL distilled water with 4 mL HCl. The solution is diazotized with (0.75 gm, 0.01 mol)in 20 mL distilled water sodium nitrate ($NaNO_2$) was cooled and supplemented slowly with a solution of 2-amino-5-nitro thiazole. The resulted reaction blend is moved for 25 minutes, made a brown solution. The resulted diazonium chloride solution was supplemented slowly with the cooling conditions and continuously moving at 0-5°C. The solvent of salicylaldehyde (0.01 mol) melted in 50 mL ethanol. The color of the reaction mass was altered from brown to red color. The reaction blend was moved for additional

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2 hours at 0–5ºC in ice-bath. After completing the reaction, the reaction blend was supplemented with ice cold water 200 mL stirring. The crude produce is isolated by filtration, flushed with distilled water then desiccated. The solids gained were recrystallized with ethanol to obtain red crystals.

Preparation of 3-(2-hydroxy-5-((5-nitrothiazol-2-yl) diazenyl)phenyl)-1-(4-hydroxyphenyl) prop -2-en-1-one. compound (2)[20]

chalcone is made according to the hot concentration (0.1 mole) derivatives p-hydroxy acetophenone and (0.1 mole) compound (1) are solved in least quantity of ethanol, 55 mL of 50% potassium hydroxide is supplemented to the solvent mentioned above. The flask is heated at 50ºC for 20 hours. The solvent is acidified by cold 6 N HCl solvent (congored), crystal-like objects isolated, purified, and flushed with water. It is recrystallized from ethanol.

Preparation of (3-5) Compounds[20]

In a 100 mL round bottom flask a blend of(0.01 mole) of Chalcone derivative (2) and (0.01 mole) (hydrazine hydrate, phenylhydrazine and 2,4-dinitrophenyl hydrazine) in 50 ml of Ethanol absolute. with continuous stirring at 72ºC for (7–12) h, the solvent was then removed, and the resulting solid was recrystallized from ethanol to get (3,4 and 5) respectively.

Synthesis of (E)-2-(3-(4-hydroxyphenyl)isoxazol-5-yl)-4-((5-nitrothiazol-2-yl)diazenyl) phenol compound (6)[20]

In a 100 mL round bottom flask a mixture of (0.001 mole) of Chalcone derivative (2) and (0.001mole) (hydroxylamine hydrochloride) in (50 ml) of Ethanol absolute, after that add (0.025mole) from ammoniumacetat with continuous stirring at 72ºC for 8 hours, the solution is detached, and the resulted solid is recrystallized from ethanol (Scheme 1).

Synthesis of 2-(2-amino-4-(4-hydroxyphenyl)-6H-1,3-oxazin-6-yl)-4-((5-nitrothiazol-2-yl) diazenyl) phenol compound (7) [21]

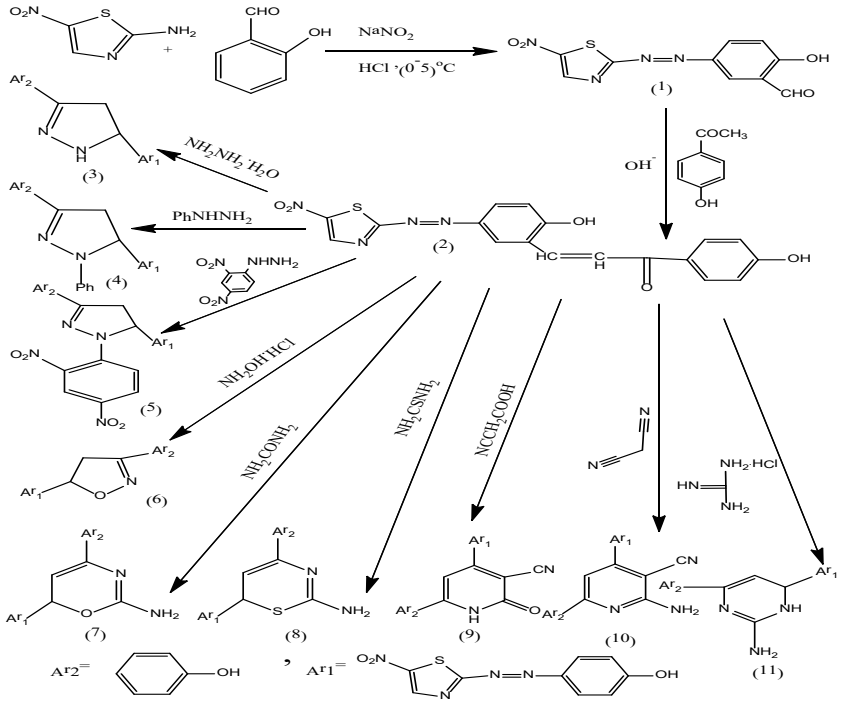
A mixture of the same moles (0.02 mol) for Chalcone derivative (2) and urea are melted in ethanolic sodium hydroxide 10 mL is moved for about 5 hours with a magnetic stirrer. Then transferred into 400 mL of cold water with constant moving for 1 hour and maintained in a fridge for 42 hours. The sediment gained is filtered and flushed, then recrystallized.

Preparation of 2-(2-amino-4-(4-hydroxyphenyl)-6H-1,3-thiazin-6-yl)-4-((5-nitrothiazol-2-yl) diazenyl)phenol compound (8) [22]

A mixture of chalcone derivative (2) 0.02 mol, thiourea (0.02 mol) are melted in ethanolic NaOH 25 mL is moved for 4 hours by a magnetic stirrer, then emptied into 300 mL of cold water with continuous moving for one hour. After that, it is preserved in a refrigerator for 24 hours. The isolated solid was filtered, flushed and recrystallized from ethanol. TLC observed the completion of the reaction.

Preparation 6-(2-hydroxy-5-((5-nitrothiazol-2-yl) diazenyl)phenyl)-4-(4-hydroxyphenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile compound (9)[23]

A blend of same moles (2 mmol) derivative (2) and ethylcyanoacetate and ammonium acetate (0.3 g, 4 mmol) in absolute ethanol (30 mL) is refluxed for 7 hours, then refrigerating, the produce is gathered through purification,



Scheme 1: Synthesis of compounds (1-11)

flushed with ethanol, desiccated and crystallized from the suitable solution to yield the complex (9).

Synthesis of 2-amino-4-(2-hydroxy-5-((5-nitrothiazol-2-yl) diazenyl)phenyl)-6-(4-hydroxy phenyl) nicotinonitrile compound (10)[23]

A blend of the same moles (2 mmol) derivative (2) and malononitrile also ammonium acetate (0.3 g, 4 mmol) in absolute ethanol (30 ml) was refluxed for (8) hours. It is then cooled, the new yield is gathered by filtration, flushed with ethanol, desiccated, and crystallized from the appropriate solvent to yield compound (Scheme 1).[10]

Synthesis of 2-(2-amino-6-(4-hydroxyphenyl)-3,4-dihydropyrimidin-4-yl)-4-((5-nitrothiazol-2-yl)diazenyl) phenol compound (11)[23]

A solvent of complexes (2) (2 mmol), sodium acetate (0.2 g in 1 mL water) in 30 mL ethanol, guanidine hydrochloride (0.2 g, 2 mmol) is supplemented. The reaction blend was refluxed for 9 hours. It is then cooled, the solid objects are shaped and gathered by filtration, desiccated, and crystallized from the suitable solvent to yield the compound.[11]

RESULT AND DISCUSSION

2-hydroxy-5-((5-nitrothiazol-2-yl)diazenyl)benzaldehyde compound (1)

The infrared spectrum information of derivative (1) reveal absorption at (1735) cm^{-1} for (C=O), (1458) cm^{-1}(-N=N-),(3409) cm^{-1} (OH) for phenol, and display band at (3139) for (N-H) for imidazol and vanishing band for NH_2 at (3379-3325)cm^{-1}**.** The ^{1}H-NMR(DMSO) spectrum data of derivative (1) display δ:6.7-8.9(m, 4H, Ar-H), 9.11 (m, 1H, OH),13.8 (m, 1H,CH) Ald. The^{13}C-NMR(DMSO) spectrum data reveal δ:196 (C10), 167(C1),163(C2),159(C4),154(C7), 101-151(C-ar) (Figure 1).

3-(2-hydroxy-5-((5-nitrothiazol-2-yl)diazenyl)phenyl)-1-(4-hydroxyphenyl)prop-2-en-1-one compound (2)

The infrared spectrum data of derivative (2) reveal absorption at (1730) cm^{-1} for (C=O), (1442) cm^{-1} (-N=N-), (3393) cm^{-1} two groups of (OH) for phenol. The ^{1}H-NMR (DMSO) spectrum data of complex (2) reveal δ:6.5–7.7 (m, 8H, Ar-H), (9.5,5.4) (m, 2H, OH), 3.4,3,7 (d,2H,CH=CH). The ^{13}C-NMR (DMSO) spectrum data of derivative (2) display δ:196 (C7), 175(C16), 130 (C4,C11), 127(C14), 115-125(C-ar) (Figure 3).

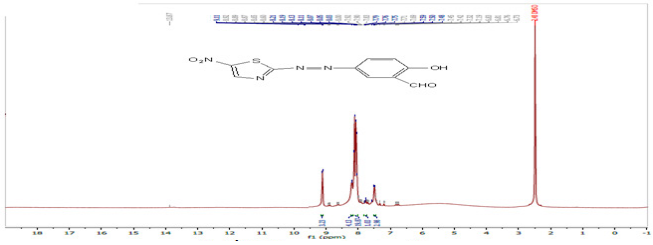


Figure 1: ^{1}H NMR compound spectrum (1)

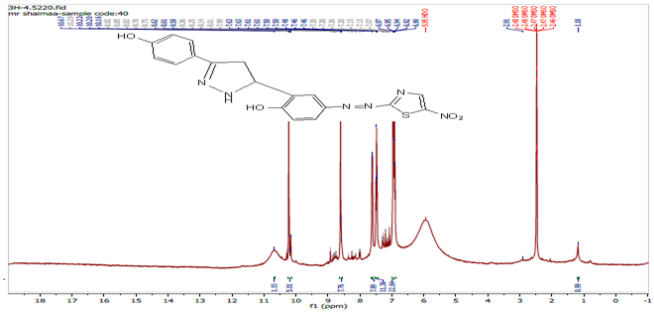


Figure 3: ^{1}H NMR compound spectrum (3)

2-(3-(4-hydroxyphenyl)-4,5-dihydro-1H-pyrazol-5-yl)-4-((5-nitrothiazol-2-yl)diazenyl)phenol compound (3)

The infrared spectrum data of derivative (3) reveal absorption at (1455) cm^{-1}(-N=N-),(3304) cm^{-1} (OH) for phenol, and display band at (3189) for (N-H)for imidazol. The ^{1}H-NMR(DMSO) spectrum data of complex (3) denote δ:6.9–8.9(m, 9H, Ar-H), 10.1,5.9 (S, **2**H, OH) 10.6 (s,1H,NH), 1.8(d,2H,CH_2), 2.9(t,1H,CH). The ^{13}C-NMR(DMSO) spectrum data reveal δ:160 (C16), 145(C18), 143 (C4,C11), 136(C7), 134(C12) 117-129 (C-ar). (Figure 3)

2-(3-(4-hydroxyphenyl)-1-phenyl-4,5-dihydro-1H-pyrazol-5-yl)-4-((5-nitrothiazol-2-yl)diazenyl) phenol compound (4)

The infrared spectrum data of derivative (4) denote absorption at (1735) cm^{-1} for (C=O),(1458) cm^{-1}(-N=N-)**,** (3409) cm^{-1} (OH) for phenol, and reveal band at (3139) for (N-H)for imidazole and vanishing band for NH_2 at (3379–3325)cm^{-1}**.** The ^{1}H-NMR (DMSO) spectrum data of derivative (4) reveal δ:6.7–7.8 (m, 14H, Ar-H), 8.4,5.3 (S, 1H, OH),1.9 (d,2H,CH2), 3.4(t,1H,CH). The^{13}C-NMR(DMSO) spectrum data display δ:164 (C16), 24(C8), 26(C9), 115-144(C-ar) (Figure 4).

2-(1-(2,4-dinitrophenyl)-3-(4-hydroxyphenyl)-4,5-dihydro-1H-pyrazol-5-yl)-4-((5-nitrothiazol-2-yl)diazenyl) phenol compound (5)

The infrared spectrum data of derivative (5) reveal absorption at (1735) cm^{-1} for (C=O),(1458) cm^{-1}(-N=N-),(3409) cm^{-1}

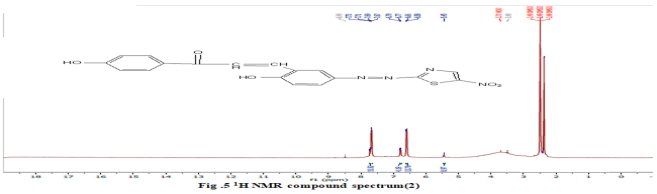


Figure 2: ^{1}H NMR compound spectrum (2)

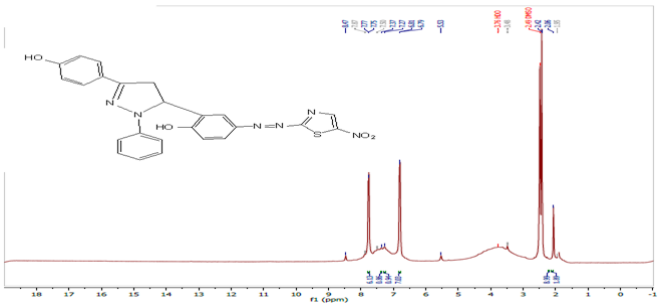


Figure 4: ^{1}H NMR compound spectrum (4)

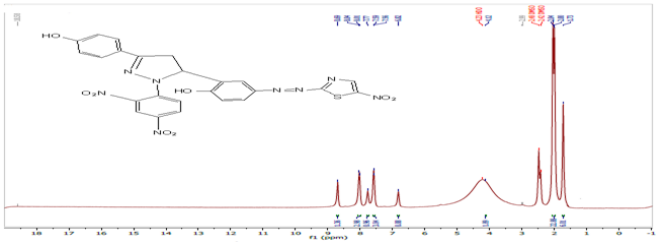


Figure 5: ^{1}H NMR compound spectrum (5)

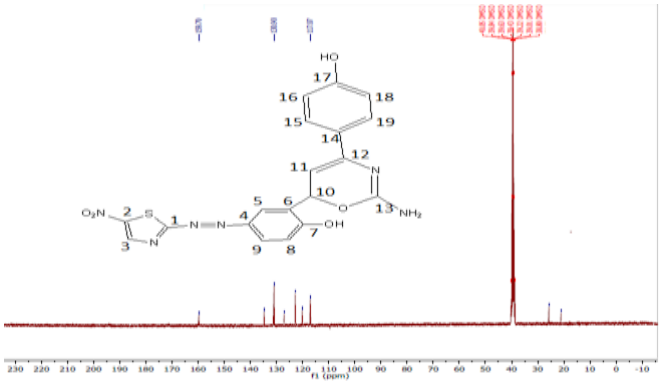


Figure 7: ^{13}C NMR compound spectrum (7)

(OH) for phenol,and display band at (3139) for (N-H)for imidazole and Vanishing band for NH_2 at (3379–3325)cm^{-1}**.** The^{1}H-NMR(DMSO) spectrum data of derivative (5) denote δ:6.8–8(m, 11H, Ar-H), 8.4,4.4 (s, 2H, OH),1.7 (d, 2H,CH_2), 2.9 (t, `H,CH). The ^{13}C-NMR (DMSO) spectrum data reveal δ:174 (C17), 23(C8),25(C9), 163(C19), 157(C7),134(C7), 130(C9),115-129(C-ar) (Figure 5).

(E)-2-(3-(4-hydroxyphenyl)isoxazol-5-yl)-4-((5-nitrothiazol-2-yl)diazenyl)phenol compound (6)

The infrared spectrum data of derivative (6) reveal absorption at (1735) cm^{-1} for (C=O),(1458) cm^{-1}(-N=N-),(3409) cm^{-1} (OH) for phenol, and display band at (3139) for (N-H) for imidazole and Vanishing band for NH_2 at (3379–3325) cm^{-1}. The ^{1}H-NMR (DMSO) spectrum data of derivative(6) denote δ:6.8–8.4 (m, 8H, Ar-H), 10.7,5.4 (s, 2H, OH),2.06 (t, 1H,CH), 1.9 (d,2H,CH_2). The ^{13}C-NMR(DMSO) spectrum data denote δ:158 (C7,C16), 15(C11), 22(C10), 169(C1), 111-132 (C-ar) (Figure 6).

2-(2-amino-4-(4-hydroxyphenyl)-6H-1,3-oxazin-6-yl)-4-((5-nitrothiazol-2-yl)diazenyl) phenol compound (7)

This complex is attained as red solid product 85%,R_f =0.3, M.P (152)°C. The infrared spectrum data of complex (7) reveal absorption at (1735) cm^{-1} for (C=O),(1458) cm^{-1} (-N=N-), (3409) cm^{-1} (OH) for phenol,and display band at (3139) for (N-H)for imidazole and Vanishing band for NH_2 at (3379-3325)cm^{-1}**.** The ^{1}H-NMR(DMSO) spectrum data of complex (7) denote δ: δ:6.5–8.01(m, 8H, Ar-H), 8.6, 5.5 (S, 2H, OH),3.5 (s, 2H,NH_2), 0.9(d,1H,CH), 1.7(d,1H,CH-O). The^{13}C-NMR (DMSO) spectrum data reveal δ:159 (C1), 10(C19),11(C22),135(C13), 115-130(C-ar) (Figure 7).

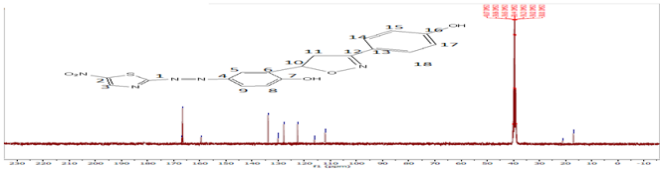


Figure 6: ^{13}C NMR compound spectrum (6)

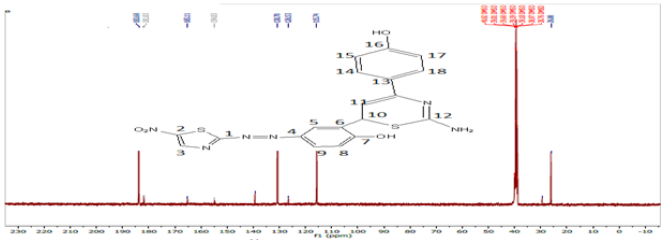


Figure 8: ^{13}C NMR compound spectrum (8)

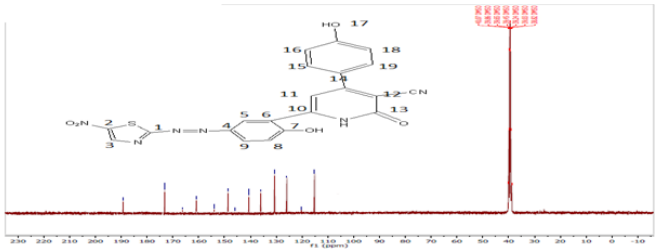


Figure 9: ^{13}C NMR compound spectrum (9)

2-(2-amino-4-(4-hydroxyphenyl)-6H-1,3-thiazin-6-yl)-4-((5-nitrothiazol-2-yl)diazenyl) phenol compound (8)

The infrared spectrum data of derivative (8) reveal absorption at (1735) cm^{-1} for (C=O),(1458) cm^{-1}(-N=N-)**,**(3409) cm^{-1} (OH) for phenol, and display band at (3139) for (N-H)for imidazole and Vanishing band for NH_2 at (3379–3325) cm^{-1}**.** The ^{1}H-NMR (DMSO) spectrum data of derivative (8) denote δ:6–7.4 (m, 8H, Ar-H), 9.6, 5.4 (S, 2H, OH), 4.3 (s, 2H,NH_2), 1.12(d,1H,CH), 1.59 (1H, CH-S). The ^{13}C-NMR (DMSO) spectrum data display δ:183(C1), 26(C10), 29(C11), 181(C12), 165(C16,C7), 115-135(C-ar) (Figure 8).

6-(2-hydroxy-5-((5-nitrothiazol-2-yl)diazenyl)phenyl)-4-(4-hydroxyphenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile compound (9)

The infrared spectrum data of derivative (9) display absorption at (1735) cm^{-1} for (C=O), (1458) cm^{-1} (-N=N-), (3409) cm^{-1} (OH) for phenol, and reveal band at (3139) for (N-H)for imidazole and Vanishing band for NH_2 at (3379–3325) cm^{-1}**.** The ^{1}H-NMR (DMSO) spectrum data of derivative (9) display δ:6.8–7.9(m, 8H, Ar-H), 9.03, 5.4 (s, 2H, OH), 4.3 (s, 1H,CH) 10.5(s,1H,NH). The ^{13}C-NMR (DMSO) spectrum data display δ:188(C13), 173(C12, 162(C1),149(C7,C17),106-140(C-ar) (Figure 1).

2-amino-4-(2-hydroxy-5-((5-nitrothiazol-2-yl)diazenyl) phenyl)-6-(4-hydroxyphenyl) nicotinonitrile compound (10)

The infrared spectrum data of derivative (10) display absorption at (1735) cm^{-1} for (C=O),(1458) cm^{-1}(-N=N-), (3409) cm^{-1} (OH) for phenol,and show band at (3139) for (N-H) for

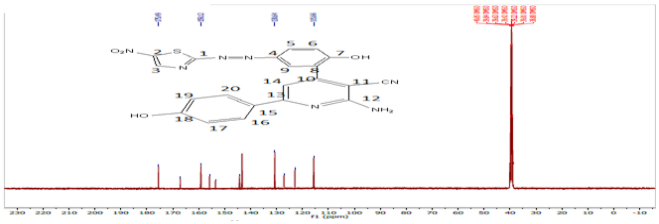


Figure 10: ^{13}C NMR compound spectrum (10)

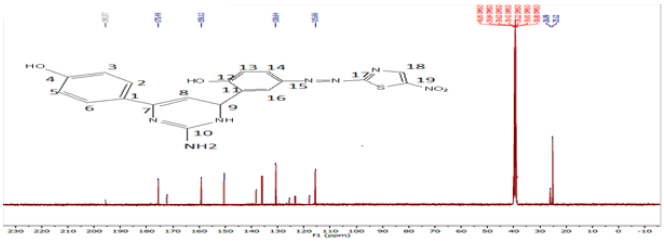


Figure 11: ^{13}C NMR compound spectrum (11)

Table 1: The physical properties and analytical data of derivatives (1-11)

Compound	*Color*	*m.p °C*	*Yield%*	*R_f*	*Molecular formula (Mol.wt)*	*Found (calc.)% C*	*H*	*N*
1	Brown	200	78	0.4	$C_{10}H_6N_4O_4S$ (278.24)	(43.17) 43.23	(2.17) 2.20	(20.14) 20.01
2	Brown	105	80	0.3	$C_{18}H_{12}N_4O_5S$ (396.38)	(54.54) 54.38	(3.05) 3.25	(14.13) 14.11
3	Yellow	226	79	0.3	$C_{18}H_{14}N_6O_4S$ (410.41)	(52.68) 52.77	(3.44) 3.46	(20.48) 20.51
4	Brown	131	73	0.3	$C_{24}H_{18}N_6O_4S$ (486.50)	(59.25) 59.59	(3.73) 3.29	(17.27) 17.42
5	Yellow	126	77	0.3	$C_{24}H_{16}N_8O_8S$ (576.50)	(50.00) 50.21	(2.80) 2.38	(19.44) 19.53
6	Brown	190	81	0.3	$C_{18}H_{13}N_5O_5S$ (411.39)	(52.55) 52.51	(3.19) 3.65	(17.02) 17.18
7	Red	152	85	0.3	$C_{19}H_{14}N_6O_5S$ (438.42)	(52.05) 52.09	(3.22) 3.26	(19.17) 19.21
8	Orange	200	80	0.3	$C_{19}H_{14}N_6O_4S_2$ (454.48)	(50.21) 50.26	(3.10) 3.11	(18.49) 18.48
9	Red	198	79	0.3	$C_{21}H_{12}N_6O_5S$ (460.42)	(54.78) 54.82	(2.63) 2.60	(18.25) 18.29
10	Black	244	71	0.3	$C_{21}H_{13}N_7O_4S$ (459.44)	(54.90) 54.89	(2.85) 2.82	(21.34) 21.39
11	brown	98	73		$C_{19}H_{15}N_7O_4S$ (437.43)	(52.17) 52.47	(3.46) 2.98	(22.41) 22.41

imidazole and Vanishing band for NH_2 at (3379–3325) cm^{-1}**.** The ^{1}H-NMR(DMSO) spectrum data of complex (10) reveal δ:6.5–8.9 (m, 4H, Ar-H), 9.4 (m, 1H, OH), 11.4 (m, 1H,CH) Ald. The ^{13}C-NMR(DMSO) spectrum data display δ:175(C1), 166(C11),159(C12),143(C7,C18),105-129(C-ar) (Figure 10).

2-(2-amino-6-(4-hydroxyphenyl)-3,4-dihydropyrimidin-4-yl)-4-((5-nitrothiazol-2-yl)diazenyl) phenol compound (11)

The infrared spectrum data of derivative (11) display absorption at (1735) cm^{-1} for (C=O),(1458) cm^{-1}(-N=N-)**,**(3409) cm^{-1} (OH) for phenol, and display band at (3139) for (N-H) for imidazole and Vanishing band for NH_2 at (3379-3325) cm^{-1}**.** The ^{1}H-NMR(DMSO) spectrum data of derivative (4) reveal δ:6.7–7.8(m, 9H, Ar-H), 10.01,5.4 (s, 2H, OH),1.2 (d, 1H,CH), 1.6(d,1H,C=CH), 3(s,1H,CH). The ^{13}C-NMR(DMSO) spectrum data display δ:195(C10), 25(C9),175(C17),170 (C7,C18),159(C19), 150(C15),111-135(C-ar) (Figure 11).

Table 2: Reveal Biological action of derivatives (1-11)

Compounds No.	*Kind of bacteria*	
	E. coli	*Staph. aureus*
1	+	-
2	-	++
3	+	-
4	+	-
5	++	+++
6	++	+
7	+++	++
8	++	++
9	+	+
10	-	+
11	+++	+

- The negative sambal (-) refer to No inhibition (inactive) but positive sambal (+) refer to (5–10) mm (slightly active),well (++) shamble refer to (11-20) mm (reasonably active) and (+++) sambal refer to (more than 20) mm (Good action).

CONCLUSION

Aftercare synthesized derivatives display important anti-bacterial action against to kind of bacteria *Escherichia coli* and *staphylococcus aurous*, the compounds that appeared very good activity are (5) against (staphylococcus aurous) on the other hand, compound (11,7) display efficient action against (*Escherichia coli*), the outcomes of the anti-bacterial action were displayed in table 2 showinmg the results of anti-bacterial

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