RESEARCH ARTICLE

Synthesis and Characterization of Some New Heterocyclic Derivatives and Studying of their Biological Activity (Anti-Bacteria)

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ABSTRACT

Introduction: In this work synthesis, many kinds of heterocyclic derivatives by many steps, the first we preparation 1-(4-((1H-imidazol_2-yl-) diazenyl) phenyl) ethan-1_one. (1) by coupling of diazonium salt of p-amino acetophenone with imidazole in alkaline alcoholic media, the second step include react (1) with 2_amino_6_methylpyrimidin _4_ol in acid medium to get Schiff base derivatives(2)the last step include react(2) with (sodium azide, thioglycolic acid, glycine, alanine, Tryptophan, (2 aminobenzoic acid), (2-mercaptobenzoic acid) to give (tetrazole(3), thiazolidine(4), imidazolidine(5-7), Thiazinie(8), Quinazoline (9) derivatives, respectively. All these derivatives Characterization by FTIR, 1HNMR, 13C-NMR, After that we studied the biological activity for all derivatives for all derivatives studied the anticancer for (2).

Keywords: Azo, Imidazolidine, Quinazoline, Schiff bases, Tetrazole, Thiazinie, Thiazolidine.

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INTRODUCTION

The azo compound is consists of (–N=N–) group in their structure, connected with aromatic ring and Heterocyclic system.[1] its formed by conjugation reaction between a diazonium salt and a conjugation agent.[2] Azo, have applications such as inhibition of DNA RNA, dyes, nitrogen fixation, antibacterial.[3]

Schiff bases or azomethine (C=N) Consisting of from condensation an amino compound and carbonyl compound.[4] Schiff base derivatives exhibit biological activities such as significant exhibit antidepressant and cardiac stimulant, anticonvulsant antitumor activity, Candida albicans growth-inhibitory anti.[5,6] All Heterocyclic Tetrazole we synthesis have a high biological activity such as five-membered.[7] It has versatile applications in various medicinal chemistry, synthetic chemistry.[8] Thiazolidinones (are unsaturated ring five-membered).[9] Thiazolidines are heterocyclic compounds that have biological activity and semiconductor properties. The thiazolidine ring consists of nitrogen and sulfur atoms. Thiazolidine compounds are known to exhibit interesting and pharmacological activity. Specifically, they are applied, such as antiseizure, fungicida ic anti bacterial, antitubercular, antifungal, antiamoebic, diabetic and, *anticonvulsant, hypoglycemic* and *non-narcotic analgesic*.[10,11] Imidazolidine are compound five-member heterocyclic contain nitrogen, carbon, and oxygen atoms in their ring structure.[12] Imidazolidines are a well-known type of organic compound of excess interest due to their numerous pharmaceutical applications such as, hypotension, anticarcinogenic, or antibacterial.[13] Quinazolines and quinazolinones are kinds of fused heterocycles that are of appreciable interest because of the diverse arear of their biological properties.[14] Activities of quinazoline derivatives, involve, anti-cancer anti-inflammation, analgesia, anti-virus, anti-spam, anti-bacterial, anti-cytotoxin.[15] Thiazines are an important kind of heterocycles contain one atom nitrogen, one sulfur, and Oxygen.[16]

EXPERIMENTAL

FTIR Spectra (400-4000 cm^{-1}) in KBr disk was recorded on a SHIMADZU FTIR-8400S Fourier transform. Melting points were measured using Stuart, UK ^{13}C-NMR and ^{1}HNMR were recorded on Fourier transformation Bruker spectrometer operating at (400MHz) with (DMSO-d6) measurements were made at Department of Chemistry, Esfahan University, Iran

Synthesis Azo Derivative

A diazonium solution was prepared by dissolve (1.36g, 0.01 mol) of p-amino acetophenone in (60 mL) water and (4N) concentrated HCl. This solution was cooled to 0°C, treated with (1.00 g, 0.01 mol) $NaNO_2$ in (20mL) of water were added gradually with stirring for 20 min at (0–5)°C to complete the diazotization. The mixture of diazonium chloride was then slowly added into the solution of (1.35 g, 0.01 mol) imidazole with 50mL of ethanol, which was dissolved in (5% NaOH) (130 mL) at (0–5)°C. The mixture was keep cooled in the ice

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bath and stirred continuously for 1 hour, followed by adjusting the pH of the solution to pH=5. The precipitate formed was filtered, recrystallized from ethanol, washed with water then dried in air.

Synthesis Schiff bases Derivative

A mixture of equimolar quantities (1.00mol) from(1) and (0.570g) from(2-amin 6- methyl pyrimidin- 4-ol) and (3 drops) of glacial acetic acid was refluxed for 7-hour in 30 ml of ethanol. The reaction mixture was cooled and kept for (24 hs). The crystals found was filtered, dried and recrystallized from ethanol

Synthesis tetrazol*e* Derivative

Compounds of (2) (0.0031mole) were dissolved in (20mL) dioxane and mixed with (0.0031 mole) sodium azide. These mixtures were refluxed for (32) h at T = 55 0C. The Crystals found was filtered, dried, and recrystallized from ethanol.

Synthesis thiazolidine Derivatives

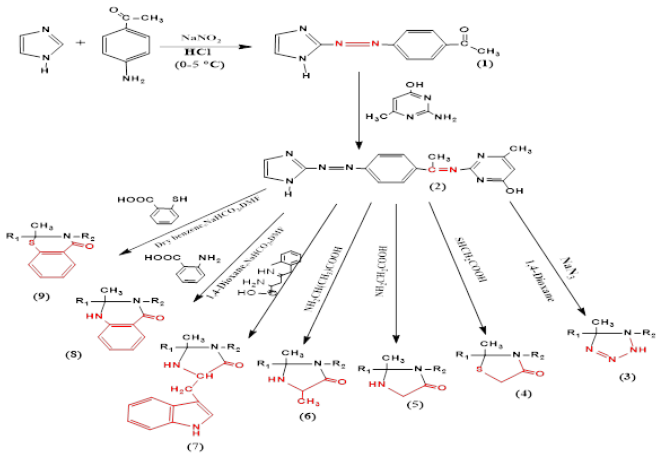
Thioglycolic acid (0.0031 mol) in 1, 4- dioxane (20 mL) was added to (0.0031 mol) of Schiff bases (2). Then added to the mixture (0.5 g m) anhydrous zinc chloride with stirring, then the mixture was refluxed for 16 hours. The reaction mixture was cooled and kept for (30 hs). Crystals found were filtered, dried, and recrystallized from ethanol**.**

Synthesis Thiazinie Derivatives

A mixture of Schiff bases (2) (0.0031 mol) dissolved in THF (15mL) and (alanine, glycine, Tryptophan) (0.002mol) was dissolved in THF(15mL) and refluxed for 48 hs. The reaction was then cooled and recrystallized from absolute ethanol.[9]

Synthesis Quinazolin Derivatives

A solution (0.425) g, 0.0031 mL) of dissolved (2-amino benzoic acid) was added hours in a 20mL) (1, 4-Dioxan) to (1.00 g, 0.0013 mol) of the Derivative 2 with 3 mL DMF water bath and at 101°C with reaction Using thin-layer chromatography (TLC) and using the mobile phase(methanol -benzene)(1:4)(v-v). The solvent a was evaporated under pressure, and a 10% solution added (NaHCO3) and then filtration and re-crystallization with a mixture of (benzene: dioxin) by (2:1). phase (methanol -benzene)(1:4)(v-v). The solvent a was evaporated under pressure, and a 10% solution added(NaHCO3) and then filtration and re-crystallization with a mixture of (benzene: dioxin) by (2:1).



Scheme 1: Synthesis of some heterocyclic compounds derivatives

Synthesis Thiazinie Derivatives

The mixture (1.00 g, 0.0031 m) of the Derivative (2) was mixed with (0.477 g, 0.0031 m) of (2-mercapto benzoic acid) in (22 mL) of dry benzene and (3 ml)of DMF (5 drops) of ((triethyl amine), followed by an escalation (46 h) at 50 °C with control. Interaction by thin-layer chromatography (TLC) and using mobile phases (benzene Methanol) and by(1: 4) (v: v) and then steaming the solvent under pressure a the addition of (10%) solution(NaHCO3) and the filtrate and re-crystallize by(1, 4-Dioxan).

RESULT AND DISCUSSION

1- *Compound* (1):1-(4-((1H-imidazol-2-yl) diazeny l) phenyl) ethan-1-one).

The ^{1}H- NMR (DMSO) spectrum data of compound (1) show δ:8- (m, 4H, Ar-H), 2.6 (S, 3H, CH_3), 9.19 (S, 1H, NH imidazol ring), 8.15 (S, 2H, CH imidazol ring). The ^{13}C- NMR (DMSO) spectrum data of compound (1) show δ: 27.6 (C_{11}), 197.5 (C_{10}), 159.9 (C_2, C_3), 124.22 (C_1), 150.3 (C_8), 140 (C_5, $C_{4)}$, 130.1 (C_7, C_6), 130.21 (C_9). See Figures 1 and 2.

2- *Compound* 2-((1-(4-((1H-imidazol-2 yl)diazenyl)phenyl -)ethylidene)amino)-6-methylpyrimidin-4-ol)

The ^{1}H NMR (DMSO)spectrum data of compound 2 show δ: 8.17 (m, 4H, Ar-H), 2 (S, 3H, CH_3), 2.67 (S, 1H NH imidazol

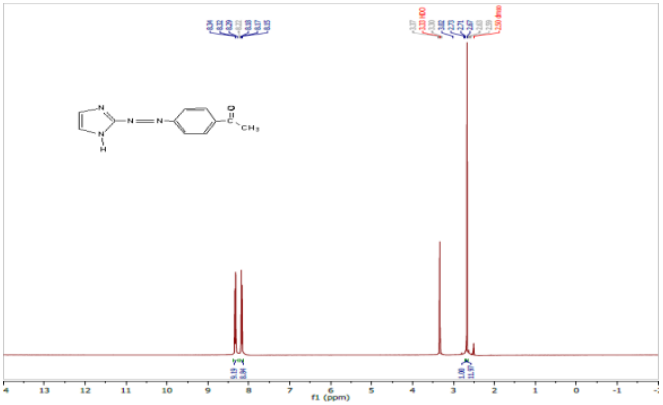


Figure 1: ^{1}H NMR spectrum of compound (1)

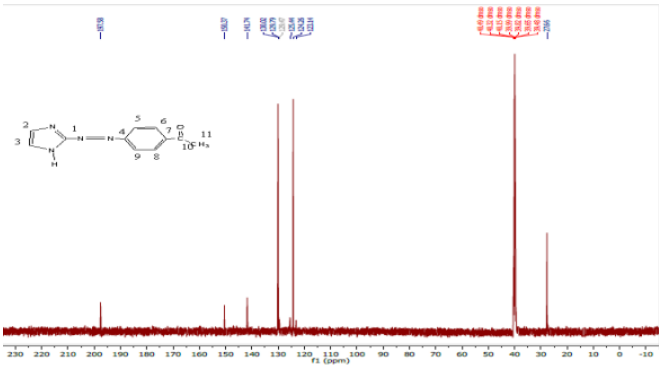


Figure 2: ^{13}C-NMR spectrum of compound (1)

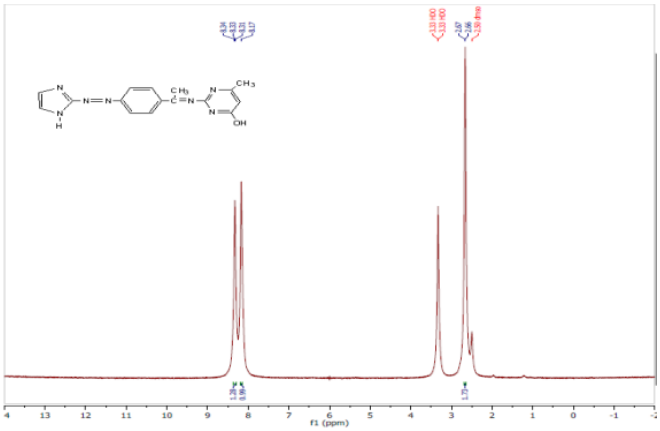


Figure 3: ^{1}HNMR spectrum of compound (2)

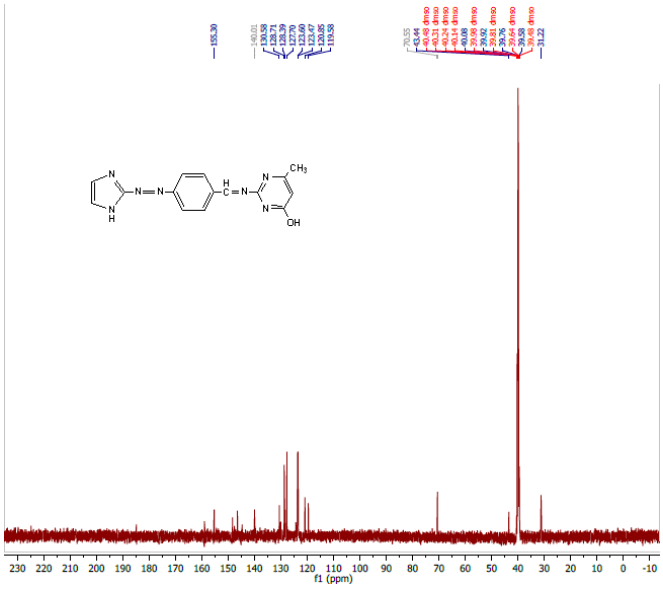


Figure 4: ^{13}C-NMRspectrum of compound (2)

ring), 8.34 (S, 3H, CH_3), 2.66 pyrimidin ring. The ^{13}C-NMR (DMSO) spectrum data of compound (2) show δ: 22.96 (C_{11}), 24 (C_{16}), 124.2 (C_2, C_3), 140.9 (C_1), 149.3 (C_8), 140 (C_5, C_4), 127.68 (C_7, C_6), 130.03 (C_9). Caromatic (100-163). See Figures 3 and 4.

3- *Compound* 6-methylpyrimidin-4-ol compound with 1, 5-dimethyl-2, 5-dihydro-1H-tetrazole and 2-(p-tolyldiazenyl)-1H-imidazole

The ^{1}H- NMR (DMSO)spectrum data of compound (3) show δ: 6.53-8.34 (m, 4H, Ar-H), 2(S, 3H, CH_3), 1.698, (S, 1H NH imidazol ring), 10.79., (S, 3H, CH_3), 2.67 pyrimidin ring, 5.39 (S, 1H OH), 3.35(S, 1H NH) . The^{13} C-NMR (DMSO) spectrum data of`compound (2) show δ: 23.94 (C_{11}), 39.92 (C_{16}), 124.2 (C_2, C_3), 140.9(C_1,), 149.3 , 155 (C_5, C_4), 100.59 (C_7, C_6), 159.87 (C_9, C_8)Caromatic.(100-1). See Figures 5 and 6.

4- 6-methylpyrimidin -4-ol compound with 2, 3-dimethyl-4-methylenethiazolidine and 2-(P-tolyldiazenyl)1H-

The ^{1}H -NMR (DMSO)spectrum data of compound (4) show δ: 6.88-8.33 (m, 4H, Ar-H), 2(S, 3H, CH_3), 2.03, (S, 1H NH imidazol ring)8.34, (S, 3H, CH_3), 2.66 pyrimidin ring, 5.50 (S, 1H OH) . The ^{13}C-NMR (DMSO) spectrum data of compound (2) show δ: 27.66 (C_{11}), 40.02 (C_{16}), 124.26 (C_2, C_3), 141.9(C_1), 149.3 , 130 (C_5, C_4), 131 (C_7, C_6), 197.58 (C_{10}), C aromatic.($_{142\text{-}150.37}$). See Figures 7 and 8.

5- 2-(4-((1H-imidazol-2-yl)diazenyl)phenyl)-3-(4-hydroxy-6-methylpyrimidin-2-yl)-2-methylimidazolidin -4-one.

The ^{1}H NMR (DMSO)spectrum data of compound 5 show δ: 6.88-8.33 (m, 4H, Ar-H), 2(S, 3H, CH_3), 2.03, (S, 1H NH

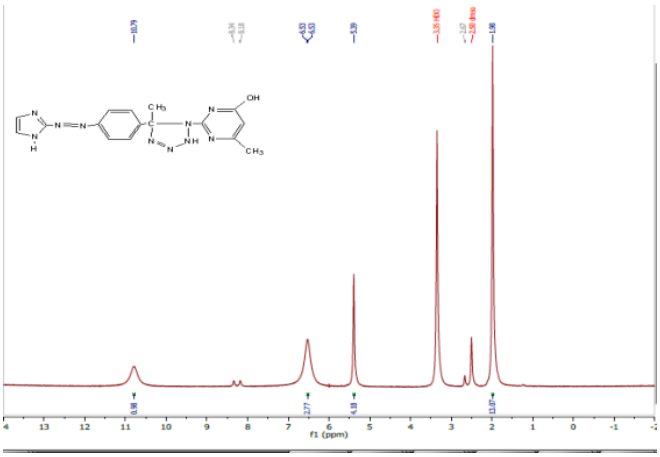


Figure 5: ^{1}H NMR spectrum of compound (3)

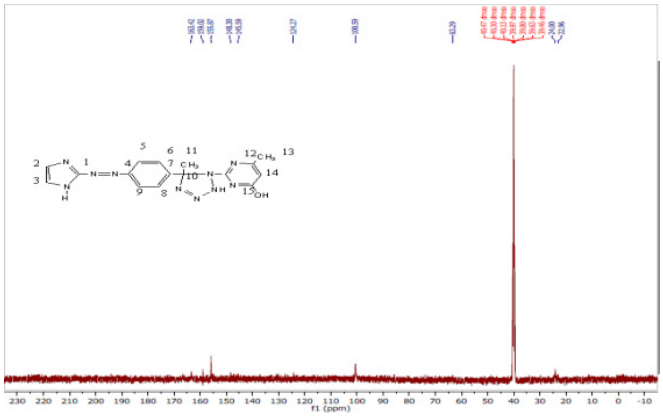


Figure 6: ^{13}C-NMR spectrum of compound(3)

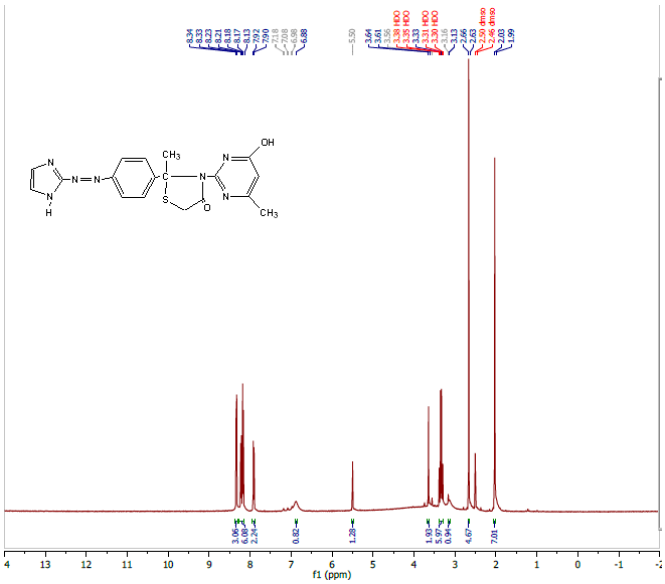


Figure 7: 1H- NMR spectrum of compound (4)

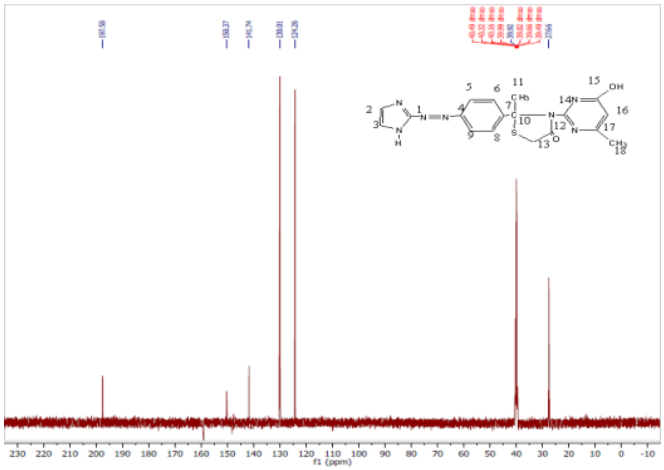


Figure 8: ^{13}C-NMRspectrumof compound(4)

imidazol ring)8.34, (S, 3H, CH_3), 2.66 pyrimidin ring, 5.50 (S, 1H OH) . The ^{13}C-NMR (DMSO) spectrum data of compound 2 show δ: 27.66 (C_{11}), 23.32 (C_{16}), 124.26 (C_2, C_3), 141.9(C_1,), 149.3 , 130 (C_5, C_4), 131 (C_7, C_6), 197.58 (C_{10}), 40.02(C_{10}) C aromatic.($_{142\text{-}150.37}$). See Figures 9 and 10.

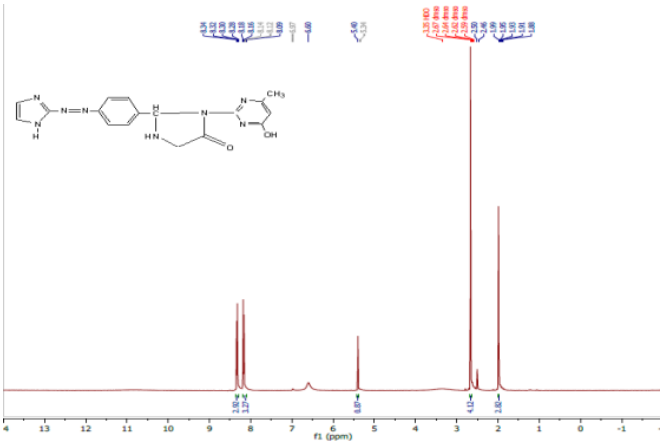


Figure 9: ^{1}H NMR spectrum of compound (5)

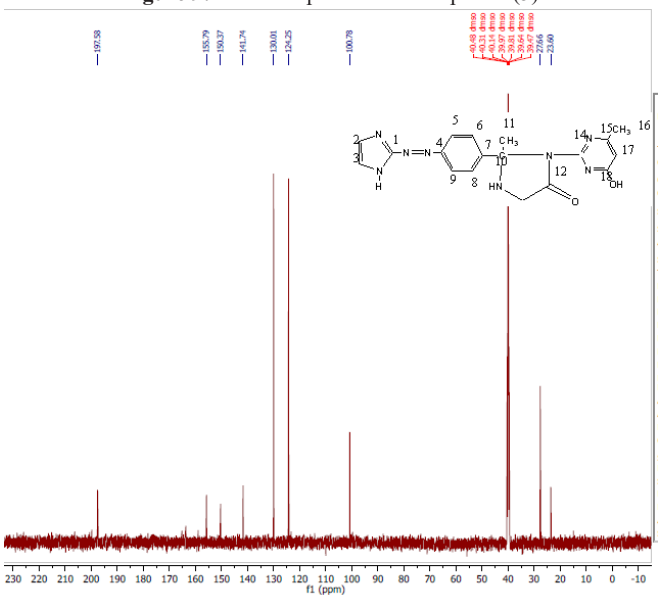


Figure 10: ^{13}C-NMRspectrum of compound (5)

6- 2-(4-((1H-imidazol-2-yl)diazenyl)phenyl)-3-(4-hydroxy-6-methylpyrimidin-2-yl)2, 5-dimethylimidazolidin-4-one.

The ^{1}H NMR (DMSO)spectrum data of compound (6) show δ: 8-8.39 (m, 4H, Ar-H), 1.22(S, 3H, CH_3), 8.40 (S, 1H NH imidazol ring), 2.64(S, 3H, CH_3) 2.66 pyrimidin ring, 3.28 (S, 1H OH), 3.37cm-for(S, 1H (N-H). The ^{13}C-NMR (DMSO) spectrum data of compound (6) show δ: 29.14 (C_{11}), 34.03 (C_{19}), 41.15 (C_{14}) 124.27 (C_2, C_3), 128.7($C_{1,}$) , 130.02 (C_5, C_4), 147.08 (C_7, C_6), 171.06. (C_{13}), C aromatic.($_{101.23\text{-}150.14}$). See Figure 11 and 12.

7-Compound 2-((1H-indol-3-yl)methyl)4-((4- hydroxy-6-methylpyrimidin-2-yl)amino)-5, 5- dimethylpyrrolidin-3-one compound with 2-(phenyldiazenyl)-1H-imidazole. See Figure 13 and 14.

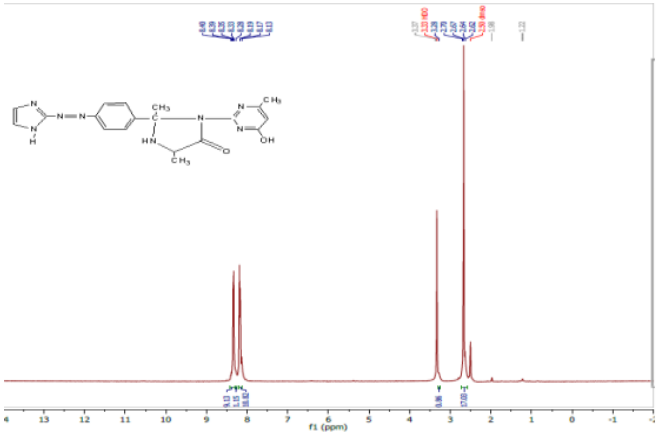


Figure 11: ^{1}H-NMR spectrum of compound (6)

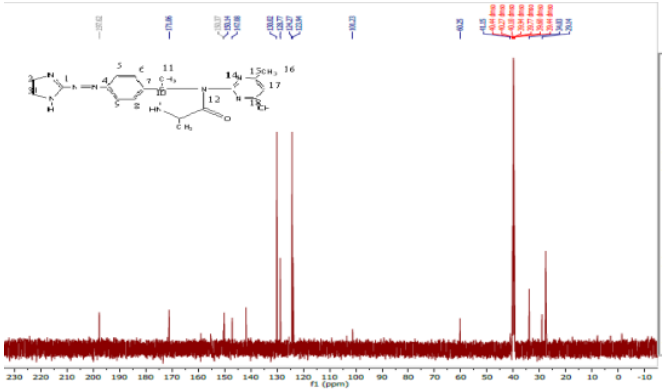


Figure 12: ^{13}C-NMRspectrum of compound (7)

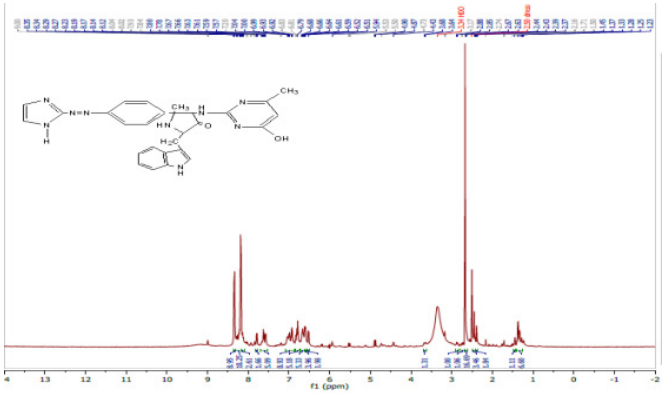


Figure 13: ^{1}H NMR spectrum of compound (7)

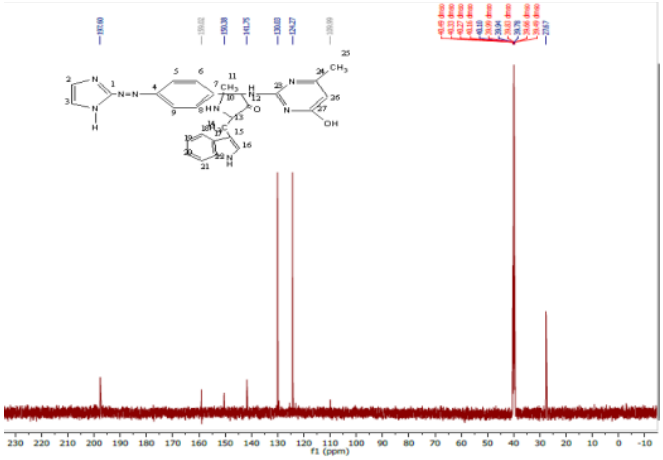


Figure 14: ^{13}C-NMR spectrum of compound (7)

8- dihydroquinazolin-4(1H)-one 2-(4-((1H-imidazol-2-yl) diazenyl)phenyl)-3-(4-hydroxy-6-methylpyrimidin-2-yl)-2-methyl-2, 3-dihydroquinazolin-4(1H)-one

The ^{1}H NMR (DMSO)spectrum data of compound (8) show δ: 6.-8.35 (m, 4H, Ar-H), 2(S, 3H, CH_3)1.98, (S, ^{1}H NH imidazol ring)8.47, (S, 3H, CH_3), 3.40 pyrimidin ring, 5.35(S, 1H OH), 4.73cm- for (S, 1H, N-H)5.29. The ^{13}C-NMR (DMSO) spectrum

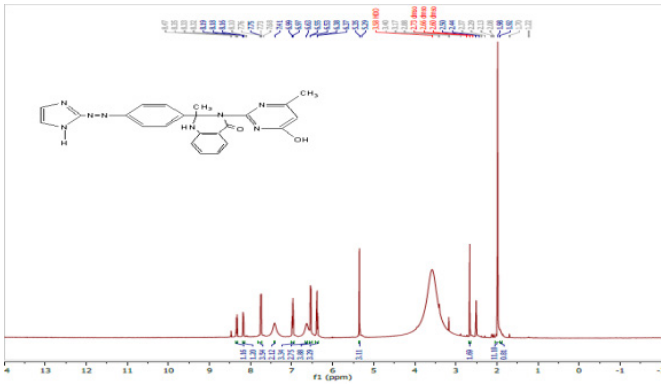


Figure 15: ^{1}H- NMR spectrum of compound (8)

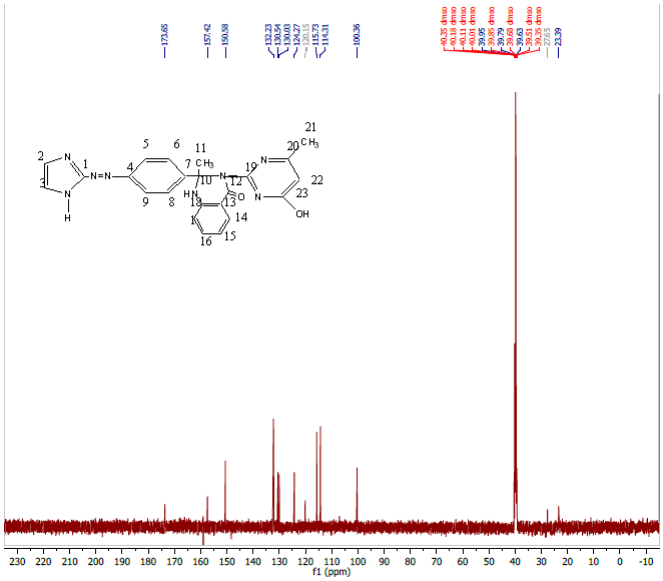


Figure 16: ^{13}C-NMRspectrum of compound (8)

data of compound (2) show δ: 23.39 (C_{11}), 40.10 (C_{21}), 39.95 cm- for (C_{14}) 124.27 (C_2, C_3), 132.73(C_1,), 100.36, 157.02 (C_5, C_4), 173.65 (C_{12}), C aromatic.($_{100\text{-}157.37}$). See Figure 15 and 16.

9- 2-yl)diazenyl)phenyl)-3-(4-hydroxy-6-methylpyrimidin-2-yl)-2-methyl-2, 3-dihydro-4H-benzo[e][1, 3]thiazin-4-one

The ^{1}H-NMR (DMSO)spectrum data of compound (9) show δ: 7.-8.17 (m, 4H, Ar-H), 2(S, 3H, CH3)1.99, (S, 1H NH imidazol

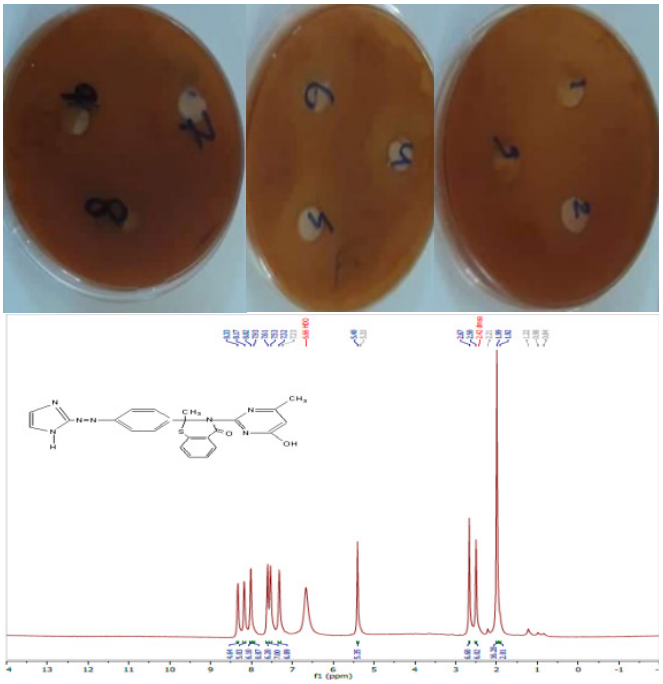


Figure 17: ^{1}H NMR spectrum of compound (9)

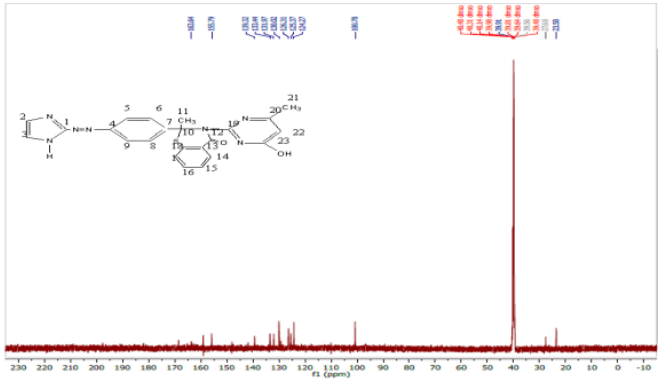


Figure 18: ^{13}C-NMR spectrum of compound (9)

Figure 19: Shows the effect of prepared compounds (1-9) on *E. col*

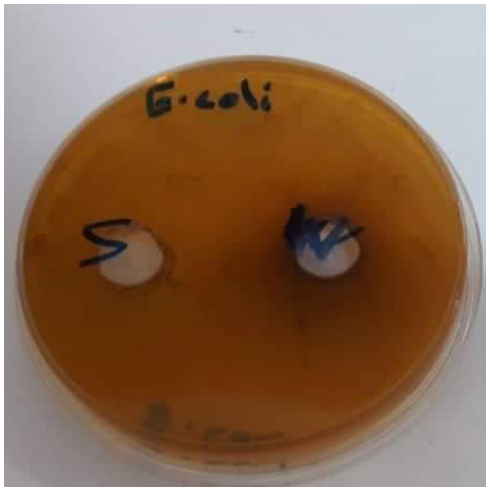


Figure 20: Shows the antibiotic effect on *E. col***i**

ring) 8.33, (S, 3H, CH_3), 2.67 pyrimidin ring, 5.40(S, 1H OH) . The[13] C-NMR (DMSO) spectrum data of compound (9) show δ: 23.58 (C_{11}), 27.10 (C_{20}), 40.91, (C_{14}) 124.27 (C_2, C_3), 131.73(C_1,), 100.36, 155.02 (C_5, C_4), 163.64 (C_{12}), C aromatic.($_{100\text{-}157.37}$). See Figures 17 and 18.

BIOLOGICAL ACTIVITY

From the above studies, it can be concluded that the synthesized compounds exhibit significant antibacterial activity against

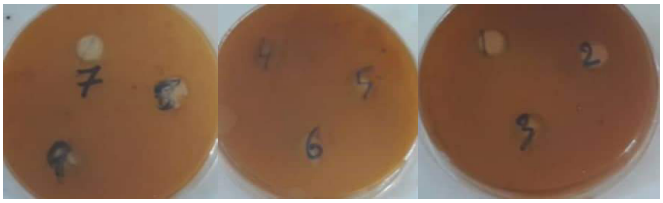


Figure 21: Shows the effect of prepared compounds (1-9) on *Strepto Coccus*

Table 1: Show biological activity for compounds (1-9)

Compounds No.	*E. coli*	*Staph. Aureus*	*Compounds No*	*E. coli*	*Staph. Aureus*
1	+++	++	6	+	+
2	+++	+++	7	+	+
3	+++	+++	8	_	+
4	++	_	9	_	_
5	++	_			

= No inhibition = inactive, + = (5–10) mm = slightly active, ++ = (11–20) mm = moderately active, +++ = (more than 24) mm = Good

Table 2: Physical and analytical data of compounds (1-9)

Comp.	*Name of compound*	*M.F*	*M.W*	*M.p (°C)*	R_f	*Color*	*Yield %*
1	1-(4-((1H-imidazol-2-yl) diazeny l) phenyl) ethan-1-one	$C_{11}H_{10}N_4O_4$	214.23	170-172	--------	Light orange powder	78
3	6-methylpyrimidin-4-ol compound with 1, 5-dimethyl-2, 5-dihydro-1H-tetrazole and 2-(p-tolyldiazenyl)-1H-imidazole	$C_{16}H_{16}N_{10}O$	364.37	115-117	0.49	yellow powder	77
4	6-methylpyrimidin-4-ol compound with 2, 3-dimethyl-4-methylenethiazolidine and 2-(p-tolyldiazenyl)-1H-imidazole	$C_{11}H_{10}N_4O_4$	214.23	170-172	0.50	Light orange powder	78
5	2-(4-((1H-imidazol-2-yl) diazenyl)phenyl)-3-(4-hydroxy-6-methylpyrimidin-2-yl)-2-methylimidazolidin-4-one	$C_{24}H1_9N_7$	405.47	177-178	0.45	Dark orange powder	77
6	2-(4-((1H-imidazol-2-yl) diazenyl)phenyl)-3-(4-hydroxy-6-methylpyrimidin-2-yl)-2, 5-dimethylimidazolidin-4-one	$C_{20}H_{21}N_7O_2$	490.13	180-182	0.50	Dark orange powder	89
7	2-(4-((1H-imidazol-2-yl)diazenyl) phenyl)-5-((1H-indol-3-yl)methyl)-3-(4-hydroxy-6-methylpyrimidin-2-yl)-2-methylimidazolidin-4-one	$C_{29}H_{31}N_9O_2$	489.13	128-135	0.50	Powder yellow dark	88
8	2-(4-((1H-imidazol-2-yl) diazenyl)phenyl)-3-(4-hydroxy-6-methylpyrimidin-2-yl)-2-methyl-2, 3-dihydroquinazolin-4(1H)-one	$C_{24}H_{21}N_7O_2$	481.13	190-200	0.41	Light brown powder	79
9	2-(4-((1H-imidazol-2-yl) diazenyl)phenyl)-3-(4-hydroxy-6-methylpyrimidin-2-yl)-2-methyl-2, 3-dihydro-4H-benzo[e][1, 3]thiazin-4-one	$C_{24}H_{20}N_6O_2S$	456.52	220-225	0.49	Brown powder	83

bacteria Staphylococcus aureus and Escherichia coli, the compounds that appeared good activity are (1, 2, 3, 6, 7, 8) against (staphylococcus aurous) on the other hand, compounds (1, 2, 3, 4, 5, 6, 7) show good activity against (Escherichia coli), the results of the antibacterial activity are shown in

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