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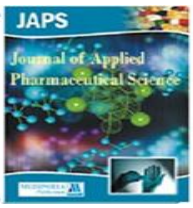

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Synthesis and Antimicrobial Activities of New Indolyl -Pyrimidine Derivatives

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ABSTRACT

The purpose of research was to synthesize a series of new indolyl-pyrimidine-5-carbonitriles **2-5** from compound **1**.The reaction of **2a** with ethylcyanoacetate and aromatic aldehydes in presences of excess ammonium acetate gives **6 a-c** while condensation with aromatic aldehydes produces chalcones **7a-c** via the Claisen condensation .Structure of the synthesized compounds was confirmed by means of their IR,^{1}H-NMR spectral data and elemental analysis .The antimicrobial testing of the synthesized compounds were evaluated. Some of the prepared compounds, 2-(1H-indol-3-yl)-4, 6-dioxo-6, 11-dihydro-4H-pyrimido [2, 1-b] quinazoline-3-carbonitrile **3** and 2-hydrazino-4-(1H-indol-3-yl)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile **4** showed high antibacterial activity. Melting points of the synthesized compounds were determined by open end capillary tube method in Boetius melting point microscope and are uncorrected. The purity of the compounds was checked using precoated TLC plates (Merck 60 F254) using chloroform: methanol (3:1) solvent system. The structures of the compounds were characterized by Beckman Infrared Spectrophotometer PU9712 using KBr discs . The structures of the compounds were elucidated by ^{1}H NMR (Proton Nuclear Magnetic Resonance) . The molecular weights of compound were determined by SSQ7000 mass spectrometer at 70 eV.^{1}H NMR spectra were recorded on JoelEX270MHz spectrometer using TMS as internal standard. All the new compounds gave satisfactory analytical results (within 0.4 of the theoretical values). All the synthesized compounds (1-7) were purified by successive recrystallization . The purity of the synthesized compounds was checked by performing TLC. The structures of the synthesized compounds were determined on the basis of their FTIR and ^{1}HNMR data. In accordance with the data obtained from antimicrobial activity, most of the synthesized compounds have shown moderate activity against the tested bacteria while compounds 2-(1H-indol-3-yl)-4, 6-dioxo-6, 11-dihydro-4H-pyrimido [2, 1-b]quinazoline-3-carbonitrile (**3**) and 2-hydrazino-4-(1H-indol-3-yl)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile (**4**) showed high antibacterial acivity. Only compounds **1**,**3**,**4**,**7a**,**7 b** and **7c** are active against *C.albicans.*

Key words: Synthesis, Indole, pyrimidine, antimicrobial activity.

INTRODUCTION

Pyrimidines are an important class of organic compounds, some of whish show significant biological activities such as antitumor (Cocco, et.al 2006),antimicrobial (Patel, et.al 2003) and cardiovascular agent (Shanker, et.al 1985). In addition , 2-thiouracils have certain biological activities as antibacterial(Wyrzykiewicz E ,et.al 1993),antifungal ,antiprotozoal and antiviral activity (Ram, et.al 1987). Also some 2-thiouracil derivatives have cytotoxic activity (Fathalla, et.al 2002) in addition to antithyroid activity (Harold, et.al 1951).Besides it has been reported that indole exhibit anti-inflammatory (Panda,et.al 2008) , antimicrobial (Lather, et.al 2003) and antifungal activities (Gadaginamath, et.al 1999; Renukadevi, et.al 1999). On the basis of the diverse medicinal uses and biological activities of pyrimidines, thiouracils and indole, we

synthesized here a series of indolyl-2-thiopyrimidines to evaluate their antibacterial and antifungal activities.

EXPERIMENTAL

All melting points are uncorrected and were determined by open end capillary tube method in Boetius melting point microscope.IR spectra were recorded on a Beckman Infrared Spectrophotometer PU9712 using KBr discs .^{1}H-NMR spectra were recorded on JoelEX270MHz spectrometer using TMS as internal standard .Mass spectra were recorded on SSQ7000 mass spectrometer at 70 eV. The physical and spectral data of all the synthesized compounds is presented
in Table 1.

Table 1. Physical and elemental analysis of the prepared compounds 1-7 .

Comp. No.	M.P.° C	Yeild %	Mol.Formula \Mol.weight	Elemental * analysis f (cald) %		
				C	H	N
1	195-198	80	$C_{13}H_8N_4OS$ 268.29	58.32 58.20	3.20 3.01	20.73 20.88
2a	110-2	80	$C_{21}H_{14}N_4O_2S$ 386.42	65.32 65.27	3.80 3.65	14.58 14.50
2b	100-102	74	$C_{20}H_{14}N_4OS$ 358.41	67.21 67.02	3.90 3.94	15.55 15.63
2c	90-92	73	$C_{20}H_{12}N_4O_3S$ 388.39	61.79 61.85	3.05 3.11	14.35 14.43
3	190-192	80	$C_{20}H_{11}N_5O_2$ 353.33	68.08 67.99	3.10 3.14	20.05 19.82
4	282-285	70	$C_{13}H_{10}N_6O$ 266.26	58.57 58.64	3.90 3.79	31.62. 31.56
5a	182-182	50	$C_{20}H_{13}FN_6O$ 372.35	64.45 64.51	3.62 3.52	22.65 22.57
5b	210-213	52	$C_{20}H_{13}BrN_6O$ 433.26	55.52 55.44	3.12 3.02	19.48 19.40
5c	220-223	56	$C_{20}H_{13}ClN_6O$ 388.80	61.65 61.78	3.49 3.37	21.76 21.61
5d	190-192	65	$C_{23}H_{20}N_6O_4$ 444.44	62.25 62.16	4.60 4.54	19.10 18.91
6a	180-183	60	$C_{31}H_{18}N_6O_2S$ 538.57	69.05 69.13	3.50 3.37	15.74 15.60
6b	100-102	62	$C_{32}H_{20}N_6O_3S$ 568.60	67.75 67.59	3.69 3.55	14.85 14.78
6c	120-122	65	$C_{33}H_{23}N_7O_2S$ 581.64	68.23 68.14	4.10 3.99	16.94 16.86
7a	180-182	50	$C_{28}H_{18}N_4O_2S$ 474.53	70.72 70.87	3.95 3.82	11.90 11.81
7b	160-162	52	$C_{29}H_{20}N_4O_3S$ 504.55	69.15 69.03	4.15 4.00	11.17 11.10
7c	190-192	55	$C_{30}H_{23}N_5O_2S$ 517.60	69.55 69.61	4.55 4.48	13.66 13.53

*C, H and N Are within the limit of ± 0.3%

General procedure for the synthesis of 6-(1H-indol-3-yl)-4-oxo-2-thioxo-1, 2, 3, 4-tetrahydro pyrimidine-5-carbonitrile (1).

A mixture of ethylcyanoacetate (0.01 mol), thiourea (0.01 mol), indole-3-carboxaldehyde (0.01 mol) and 25 ml sodium ethoxide / ethanol were stirred for 1 h at room temperature. The reaction mixture poured into ice/ HCl, the produced solid was filtered off, dried and recrystallized from DMF / Water to give compound **1** (Table1).

IR (KBr cm-1): 3300 (NH), 3170(Ar-H), 2230 (CN), 1690(-C=O thiouracil), 1630, 1450 (C=C),1275 (-C=S).

^{1}H-NMR (DMSO 1δ ppm): 6.6 -7.5(5H ,m,Ar-H),10,10.5,11.2 (3H,s , 3NH, D_2O exchangeable).

General procedure for the synthesis of 4-(1H-indol-3-yl)-2-[substituted (phenyl) thio]-6-oxo-1, 6-dihydropyrimidine-5-carbonitriles (2 a - c).

A solution of the appropriate amine (0.01 mol) in hydrochloric acid (3 ml) and water (15 ml) was rapidly cooled below 0° and diazotized by the addition of sodium nitrite (0.01 mol) in water (5 ml) under vigorous stirring. After an hour, the diazonium salt was added to a well cooled, stirred mixture of pyrimidine derivative **1** (0.01 mol) in 10% aqueous NaOH (10 ml) containing excess sodium acetate. The mixture was kept at room temperature for 2 d. The precipitate was filtered off ,washed with water, dried and recrystallized from DMF / Water ,to give **2a-c** (Table1).

2-[(4-acetylphenyl) thio]-6-(1H-indol-3-yl)-4-oxo-1, 2,3,4-tetrahydropyrimidine-5-carbonitrile (2a) :

IR (KBr cm-1): 3420 (NH), 3150(Ar-H), 2220 (CN), 1690(-C=O thiouracil), 1630,1445 (C=C).

^{1}H-NMR (DMSO 1δ ppm): 2.5 (3H, s,$COCH_3$), 7-8.5 (9H ,m,Ar-H),10, 11 (2H ,s ,2 NH,D_2O exchangeable).

4-(1H-indol-3-yl)-2-[(2-methylphenyl)thio]-6-oxo-1,6-dihydropyrimidine-5-carbonitrile (2 b):

IR (KBr cm-1): 3260 (NH),3140(Ar-H), 2225 (CN),1677(-C=O thiouracil), 1650,1440 (C=C).

^{1}H-NMR (DMSO 1δ ppm): 2 (3H , s ,CH_3) , 7.2- 8.3 (9H ,m,Ar -H),10.5, 11.2 (2H ,s,2NH, D_2Oexchangeable).

2-{[5-cyano-4-(1H-indol-3-yl)-6-oxo-1,6-dihydropyrimidin-2-yl]thio}benzoic acid (2c):

IR (KBr cm-1): 3250 (NH), 3108(Ar-H), 2230 (CN), 1680(-C=O thiouracil), 1640,1460 (C=C).

^{1}H-NMR (DMSO 1δ ppm): 7 - 8.5(9H ,m ,Ar-H), 10,11(2H,s ,2 NH , D_2O exchangeable),11.5 (1H,s,COOH , D_2O exchangeable) .

General procedure for the synthesis of 2-(1H-indol-3-yl)-4,6-dioxo-6,11-dihydro-4H-pyrimido[2,1-*b*]quinazoline-3-carbonitrile (3).

A mixture of **1** (0.01 mol) and anthranilic acid (0.01mol) in sodium ethoxide was heated under reflux for 8 h. The reaction mixture was cooled and then poured on ice / water acidified with HCl. The produced solid was filtered off, dried and crystallized from DMF / water to give compound 3 (Table1).

IR (KBr cm-1): 3197 (NH), 3160(Ar-H), 2225 (CN), 1718,1690 (2C=O thiouracil),1650, 1450 (C=C).

^{1}H-NMR (DMSO 1δ ppm): 6.6-8.5 (9H , m , Ar-H), 4,10.5 (2H ,s , 2NH, ,D_2O exchangeable).

General procedure for the synthesis of 2-hydrazino-4-(1H-indol-3-yl)-6-oxo-1,6-dihydro pyrimidine-5-carbonitrile (4).

A mixture of **1** (0.005 mol) and hydrazine hydrate (0.005mol,99%) in 30 ml methanol was refluxed for 30 h ,then cooled and poured on ice/water. The produced precipitate was filtered off, dried and crystallized from methanol to give compound **4** (Table1).

IR (KBr cm-1): 3300 (NH), 3160(Ar-H), 2240 (CN), 1680 (C=O thiouracil), 1650, 1450 (C=C).

^{1}H-NMR (DMSO 1δ ppm): 7.5- 8.5 (5H ,m ,Ar-H), 3.1, 6.1, 10.2 (4H,s,NH_2 **,**2NH ,D_2O exchangeable).

General procedure for the synthesis of 2-[(2*E*)-2-substituted (benzylidene)hydrazino]-4-(1H-indol-3-yl)-6-oxo-1,6-dihydropyrimidine-5-carbonitriles (5 a - d) .

A mixture of **4** (0.001 mol) and appropriate aldehyde (0.001 mol) in 30 ml methanol was heated under reflux for 6-8 h, and then cooled. The produced solid was filtered off, dried and crystallized from DMF/ water, to give compounds **5a-d** (Table1)**.**

2-[(2E)-2-(4-fluorobenzylidene)hydrazino]-4-(1H-indol-3-yl)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile (5a):

IR (KBr cm-1): 3300 (NH),3150 (Ar-H),2220 (CN) ,1670 (C=O thiouracil), 1660, 1430 (C=C) .

^{1}H-NMR (DMSO 1δ ppm): 6.9 (1H,s,CH=N-) , 7-8.9 (9H ,m ,Ar-H), 6.7,10, 10.7 (3H,s,3NH ,D_2Oexchangeable).

2-[(2E)-2-(4-bromobenzylidene)hydrazino]-4-(1H-indol-3-yl)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile (5b) :

IR (KBr cm-1): 3150 (NH), 3170 (Ar-H), 2225 (CN), 1680 (C=O thiouracil), 1650, 1450 (C=C) .

^{1}H-NMR (DMSO 1δ ppm): 6.9 (1H,s,CH=N-),7.2-8.5 (9H ,m,Ar- H), 6.7,10.2, 10.9 (3H,s,3NH ,D_2Oexchangeable).

2-[(2E)-2-(4-chlorobenzylidene)hydrazino]-4-(1H-indol-3-yl)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile (5c):

IR (KBr cm-1): 3360 (NH), 3200 (Ar-H), 2230 (CN),1675 (C=O thiouracil), 1640, 1420 (C=C).

^{1}H-NMR (DMSO 1δ ppm): 6.9 (1H,s,CH=N-) , 7-8.2 (9H ,m ,Ar-H), 6.7,10.5, 10.9 (3H,s,3NH ,D_2O exchangeable).

4-(1H-indol-3-yl)-2-[(2E)-2-(3,4,5-trimethoxybenzylidene) hydrazino]-6-oxo-1,6-dihydropyrimidine-5-carbonitrile (5d) :

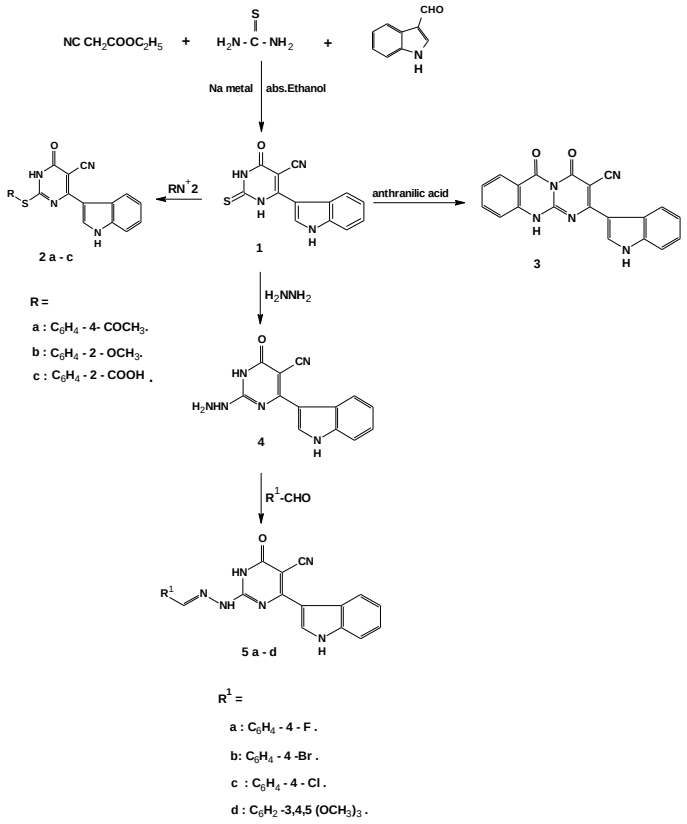
IR (KBr cm-1): 3380 (NH),3190 (Ar-H),2228 (CN) ,1670 (C=O thiouracil), 1650, 1450 (C=C).

^{1}H-NMR (DMSO 1δ ppm): 3.3-3.8 (9H , s ,3OCH_3) , 6.8(1H,s, CH=N-) ,7.2- 8.8 (7H, m ,Ar-H),6.7, 10.5, 11.2 (2H ,s,2NH, ,D_2O exchangeable).

General procedure for the synthesis of 2-[4-(5-Cyano-6-oxo-4-substituted phenyl-1,6-dihydro-pyridin-2-yl)-phenylsulfanyl]-4-(1H-indol-3-yl)-6-oxo-1,6-dihydro-pyrimidine-5-carbonitriles (6 a - c).

A mixture of **2a** (0.001mole), the appropriate aldehyde (0.001 mole), excess ammonium acetate (6.1g, 0.08 mole) and ethyl cyanoacetate (0.001mole) in 40 ml absolute ethanol was

Scheme 1 Synthetic route for the synthesis of 1-5.



refluxed for 6 hours. The reaction mixture was cooled and the produced solid was filtered, dried and crystallized from DMF/Water, to give compounds **6 a-c** (Table1).

2-[4-(5-Cyano-6-oxo-4-phenyl-1,6-dihydro-pyridin-2-yl)-phenylsulfanyl]-6-(1H-indol-3-yl)-4-oxo-1,2,3,4-tetrahydro-pyrimidine-5-carbonitrile(6a) :

IR (KBr cm-1): 3220- 3000 (NH) ,3250 (Ar-H), 2215, 2220 (2CN) , 1680 (C=O thiouracil),1650 (C=O pyridine) ,1445,1630(C=C) .

^{1}H-NMR (DMSO 1δ ppm): 6.5-9.3 (14H ,m ,Ar-H), 10, 10.5 , 11(3H ,s ,3NH, D_2O exchangeab).

2-{4-[5-Cyano-6-oxo-4-(2-methoxy-phenyl)-1,6-dihydro-pyridin-2-yl]-phenylsulfanyl}-6-(1H-indol-3-yl)-4-oxo-1,2,3,4-tetrahydro-pyrimidine-5-carbonitrile (6b):

IR (KBr cm-1): 3300- 3000 (NH) , 3350 (Ar-H), 2215, 2220 (2CN) , 1680 (C=O thiouracil),1655 (C=O pyridine) ,1430, 1620(C=C) .

^{1}H-NMR (DMSO 1δ ppm): 3.7 (3H , s,OCH_3) , 6.7- 9 (13H ,m ,Ar-H)10 , 10.5, 11.2 (3H ,s, 3NH,, D_2Oexchangeable).

2-{4-[5-Cyano--4-(4-Dimethylamino-phenyl)- 6-oxo -1,6-dihydro-pyridin-2-yl]-phenylsulfanyl}-6-(1H-indol-3-yl)-4-oxo-1,2,3,4-tetrahydro-pyrimidine-5- carbonitrile (6c):

IR (KBr cm-1): 3325- 3000 (NH) ,3340 (Ar-H), 2215,

2220 (2CN) , 1680 (C=O thiouracil),1660 (C=O pyridine) ,1450,1650(C=C) .

^{1}H-NMR (DMSO 1δ ppm): 3 (6H, s ,$N(CH_3)_2$) , 7.3 - 9.4(13H ,m ,Ar-H), 10, 10.5 ,11(3H,s ,3 NH , D_2O exchangeable).

General procedure for the synthesis of 4-(1H-Indol-3-yl)-6-oxo-2-[4-(3-substituted phenyl-acryloyl)-phenylsulfanyl]- 1,2,3,4-tetrahydro-pyrimidine-5-carbonitriles (7 a - c).

A mixture of **2a** (0.005 mol) and the appropriate aldehyde (0.005mol) in 50 ml 10 % ethanolic NaOH solution was stirred at room temperature for 24 h then refluxed for 1 h . The solution was cooled, poured on ice/water acidified with dil.HCl .The produced Precipitate was filtered off, dried and crystallized from DMF/ water to give compounds **7 a-d** (Table1).

6-(1H-Indol-3-yl)-4-oxo-2-[4-(3-phenyl-acryloyl)-phenylsulfanyl] -1,2,3,4-tetrahydro-pyrimidine-5-carbonitrile (7a) :

IR (KBr cm-1): 2840- 3026 (NH), 3220(Ar-H), 2225 (CN), 1685 (C=O of thiouracil).

^{1}H-NMR (DMSO 1δ ppm): 6.7- 9 (14H ,m,Ar-H),7.2 ,7.3 (2H,dd ,-CH=CH-),10.5,11(2H ,s, 2NH,D_2O exchangeable).

6-(1H-Indol-3-yl)-2-{4-[3-(4-methoxy-phenyl)-acryloyl]-phenylsulfanyl}-4-oxo-1,2,3,4-tetrahydro-pyrimidine-5-carbonitrile (7b) :

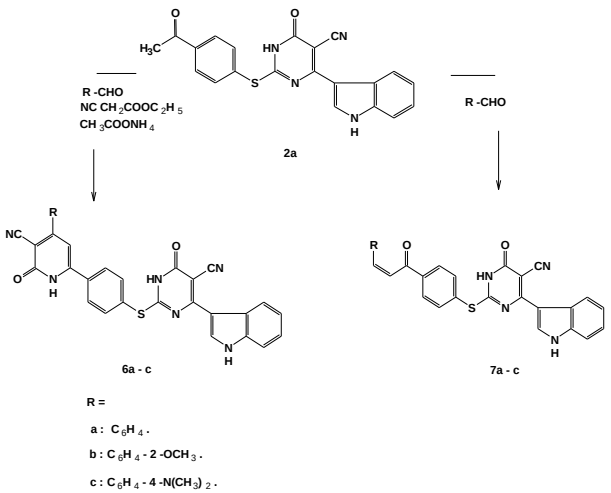
IR (KBr cm-1): 2840- 3130 (NH), 3220(Ar-H), 2220 (CN), 1680 (C=O of thiouracil).

^{1}H-NMR (DMSO 1δ ppm):3.7(3H,s,OCH_3) ,6.8-9 (13H,m ,Ar-H),7.1 ,7.2 (2H ,dd ,-CH=CH-),10.5 , 11.2 (2H,s,2NH, D_2Oexchangeable).

2-{4-[3-(4-Dimethylamino-phenyl)-acryloyl]-phenylsulfanyl}-6-(1H-indol-3-yl)-4-oxo-1,2,3,4-tetrahydro-pyrimidine-5-carbonitrile (7c):

IR (KBr cm-1): 2840- 3200 (NH), 3220(Ar-H), 2230 (CN), 1675 (C=O of thiouracil).

^{1}H-NMR (DMSO 1δ ppm): 3 (6H,s ,$N(CH_3)_2$),6.5-9(13H,m, Ar-H), 6.9 ,7.1 (2H ,dd , -CH=CH-),10, 10.5 (3H,s ,3 NH,D_2O exchangeable).



Scheme :2 Synthetic route for the synthesis of 6 a- d and 7 a- d.

Antimicrobial Activity

The antimicrobial screening of all the newly synthesized compounds were determined by Disc diffusion method in nutrient agar and Mueller Hinton agar (MHA) . The bacterial strains used were *Bacillus subtilis*, Staphylococcus *aureus* for gram positive; Escherichia *coli* for gram negative and for fungal strain, *Aspergillus flavus* and *Candida albicans*. The compounds were dissolved in Dimethylsulfoxide (DMSO) to yield 2, 0 µg / ml. The antimicrobial activity results of the compounds **1-7** were presented in table (2).

Table 2. Antimicrobial activity of the compounds 1-7.

Compd.	Antibacterial activity			antifungal	activity
	Zone of inhibition in mm				
	S.aureus	*B.Subtilis*	*E.Coli*	*C.albicans*	*A.flavus*
1	14	12	14	14	-
2a	-	-	-	-	-
2b	-	-	-	-	-
2c	-	-	-	-	-
3	18	16	16	16	-
4	19	17	18	18	-
5 a	16	12	14	-	-
5b	15	12	14	-	-
5c	16	12	14	-	-
5d	14	12	14	-	-
6 a	16	14	16	-	-
6b	15	13	15	-	-
6c	15	13	15	-	-
7 a	17	15	14	13	-
7b	16	14	13	14	-
7c	16	13	12	15	-
Penicillin	20	15	12	-	-
Fluconazole	-	-	-	17	15

Zone of inhibition expressed in mm .The disc diffusion method was followed. Penicillin and fluconazole were used as standards. The concentration of the drug used is2,0 µg / ml in DMSO.

RESULTS AND DISCUSSION

The structures of the synthesized compounds were determined on the basis of their FTIR and ^{1}HNMR data. In IR spectra ,the disappearance of C=S band and detection of (2 C=O) bands at 1718 and 1690 cm^{-1} are evidence for ring closure of pyrimido quinazoline **3** . The IR spectra of the synthesized compounds (6a to 6c) shows the presence of N-H bands in the region of 3000 -3300 cm^{-1},(2CN) bands at 2220 and 2215 cm^{-1} and (2C=O) absorption band at 1680 and 1650 cm^{-1}. In the 1H NMR spectra, all protons were seen according to the expected chemical shift and integral values. The N-H protons of 2-hdrazinopyrimidine **4** were seen in the range of 3.1-10.2 ppm.

Aromatic protons of compounds (6 a to 6 c) were seen in the range of 6.5 -9.5 ppm. The $COCH_3$ protons were not seen in 6a-c and 7 a-c compounds.

In accordance with the data obtained from antimicrobial activity, most of the synthesized compounds have shown moderate activity against the tested bacteria while compounds 2-(1H-indol-3-yl)-4, 6-dioxo-6, 11-dihydro-4H-pyrimido [2, 1-b]quinazoline-3-carbonitrile (**3**) and 2-hydrazino-4-(1H-indol-3-yl)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile (**4**) showed high antibacterial

activity. Only compounds **1**,**3**,**4**,**7 a**,**7 b** and **7c** are active against *C.albicans.*

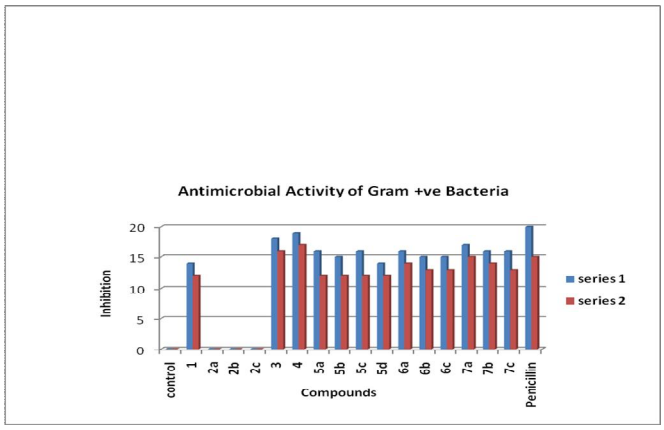


Fig. 1: Antibacterial activity (Gram +ve) of synthesized compounds .

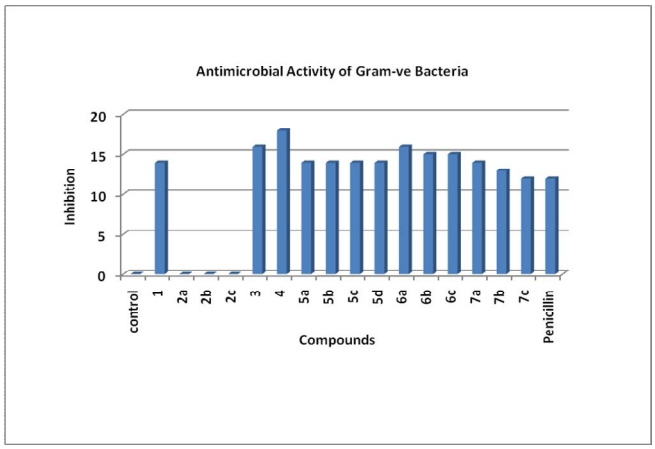


Fig. 2: Antibacterial activity (Gram-ve) of synthesized compounds .

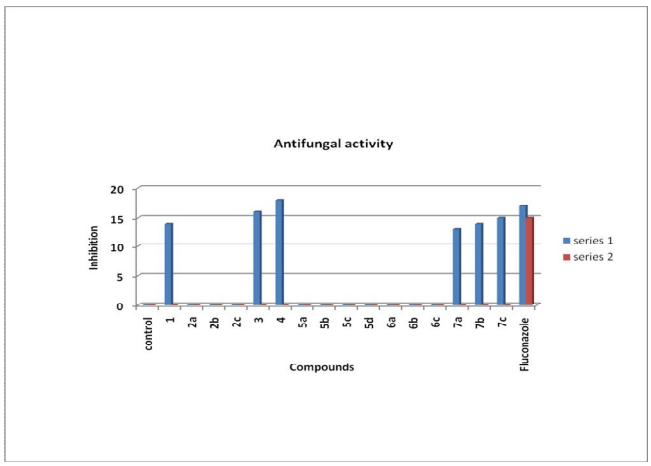


Fig. 3: Antifungal activity) of synthesized compounds

CONCLUSION

Antibacterial and antifungal activity of the synthesized derivatives (1-7) was done in comparison with penicillin and fluconazole as standard to reveal the potency of synthesized derivatives. Most of compounds showed moderate activity against the tested bacteria while compounds 2-(1H-indol-3-yl)-4, 6-dioxo-6, 11-dihydro-4H-pyrimido [2, 1-b]quinazoline-3-carbonitrile (**3**) and 2-hydrazino-4-(1H-indol-3-yl)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile (**4**) showed high antibacterial acivity and the activity is comparble with the standaerd drug penicillin but s-alkylated pyrimidines **2 a-c** are inactive.

Generally ,All compounds are inactive against *C.albicans* except compounds **1**,**3**,**4**,**7 a**,**7 b** and **7c**. Also all are inactive against *A.flavus* .

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