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SYNTHESIS AND BIOLOGICAL EVALUATION OF SOME PYRIMIDINE-2-ONE DERIVATIVES

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ABSTRACT
Pyrimidine-2-one derivatives (3a-g) were synthesized by reacting the chalcones(1a-g) with urea(2) in presence of potassium hydroxide in ethanol . The chemical structure were confirmed by means of FT-IR, ^{1}H NMR, mass spectra and elemental analysis . The compounds were screened for antimicrobial activity. The antimicrobial activities are attributed to the presence of 4-NO_2 , 4-OH and 4-Cl in phenyl ring at 6 - position of pyrimidine ring of synthesised compounds. In some cases their activities are equal or more potent than the standard drugs.

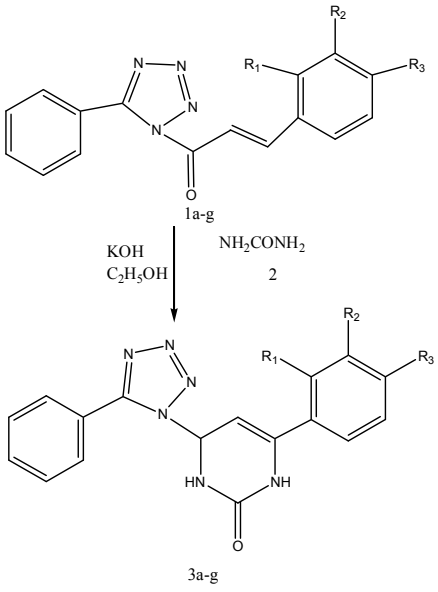
KEY WORDS: Pyrimidine , Tetrazole , Chalcones, Antimicrobial Activity**.**

INTRODUCTION
Heterocyclic ring have played an important role in medicinal chemical serving as key templates central to the development of numerous important therapeutic agents[i]. Pyrimidine derivatives have found application in wide range of medicinal chemistry because of their diverse biological activities , such as antimicrobial[ii], antitumor and antifungal activities,[iii] also these compounds are considered to be important for drugs and agricultural chemical[iv-vi] . Tetrazoles are important functionality with wide ranging application in pharmaceutical and material sciences and appealing ligands in coordination chemistry and this significance led us to synthesize the title compounds.
In the present communication we have reported, the synthesis of a new pyrimidine-2-one derivatives (scheme -1) and evaluated for their antimicrobial activities**.**

EXPERIMENTAL
Melting points were determined in open capillaries and were uncorrected. Reactions were monitored by thin layer chromatography using silica gel-G as adsorbent using benzene : ethylacetate (9:1) as eluent . IR spectra (KBr pellets) were recorded on Shimadzu FT-IR model 8010 spectrophotometer. ^{1}H NMR spectra (DMSO-d6) were taken a Varian mercury spectrometer (model YH-300 FT NMR) using TMS as internal standard and chemical shift are expressed in δ ppm. Mass spectra were taken on Jeol sx-102/PA-6000(EI) spectrometer.

CHEMISTRY
In the present research work chalcone derivatives(1a-g) were reacted with urea 2 in the

presence of potassium hydroxide in ethanol to produce the pyrimidine-2-one derivatives (3a-g). The reaction was carried out in two steps, at first the conjugate addition take place on ß position of carbonyl group and then the nucleophilic attack to carbonyl group followed by dehydration lead to six member ring products [vii-ix].



Synthesis of pyrimidine -2-one derivatives

Compound

3a $R_1 = H$, $R_2 = H$, $R_3 = H$, *3d* $R_1 = H$, $R_2 = H$, $R_3 = OCH_3$ *3g* $R_1 = H$, $R_2 = H$, $R_3 = N(CH_3)_2$
3b $R_1 = H$, $R_2 = H$, $R_3 = Cl$ *3e* $R_1 = H$, $R_2 = H$, $R_3 = OH$
3c $R_1 = H$, $R_2 = H$, $R_3 = Br$ *3f* $R_1 = H$, $R_2 = H$, $R_3 = NO_2$

General procedure for the synthesis of pyrimidine-2-one derivatives

A mixture of chalcone (0.005 mol), urea (0.005) and potassium hydroxide(0.5g) in ethanol(20ml) was refluxed on oil bath at 70-80^{0}C for 6 hours. Then the reaction mixture was left for overnight and then was concentrated under reduced pressure. The residue was filtered , washed with water and recrystallised from ethanol.

6-Phenyl-(5'phenyl-1'H-tetrazole-1'-yl)-3, 4-dihydropyrimidine-2-(1H)-one (3a)

Yield 68%, M.P.125-126^{0}C.FT-IR: 3054(Ar-H),1285(-N-N=N-),1108 and 1138 (Tetrazole ring), 2966 (CH str.) and 1610 (C=N ring stretch),3340(NH str.),1478 (C=C),1682(C=O).^{1}H NMR (DMSO-d_6) δ 4.86(d, 1H, 4-CH),5.15(d,1H,5-CH –C=CH),6.78-6.79(m,10 H, Ar-H),8.85(bs,1H,NH),9.60(bs,1H,NH).Anal for $C_{17}H_{14}N_6O$ Calcd.(found)%;C 64.15(64.14) H 4.40 (4.43) N 26.41(26.40) MS;(m/z)318(m$^+$).

6(4'-Chlorophenyl-(5'phenyl-1'H-tetrazole-1'-yl)-3,4-dihydropyrimidine-2-(1H)-one(3b)

Yield 72%, M.P.148-150^{0}C. FT-IR: 3054(Ar-H),1285(-N-N=N-),1108 and 1138 (Tetrazole ring), 2958 (CH str.) and 1606 (C=N ring stretch),3340(NH str.),1478 (C=C), 1682(C=O),788(C-Cl).^{1}H NMR (DMSO-d_6) δ 4.86(d, 1H, 4-CH),5.15(d,1H,5-CH –C=CH),7.14-7.80(m,9 1 H, Ar-H),8.85(bs,1H,NH),9.60(bs,1H,NH).Anal for $C_{17}H_{13}N_6OCl$ Calcd.(found)%;C 57.95(57.87) H 3.69 (3.71) N 23.86(23.81) MS;(m/z)352(m$^+$).

6(4'-Bromophenyl-(5'phenyl-1'H-tetrazole-1'-yl)-3,4-dihydropyrimidine-2-(1H)-one(3c)

Yield 73%, M.P.145-146^{0}C. FT-IR: 3054(Ar-H),1285(-N-N=N-),1108 and 1138 (Tetrazole ring), 2955 (CH str.) and 1605 (C=N ring stretch),3345(NH str.),1478 (C=C),1682(C=O),

674(C-Br).^{1}H NMR (DMSO-d_6) δ 4.86(d, 1H, 4-CH),5.15(d,1H,5-CH –C=CH),7.14-7.80(m,9 1H, Ar-H),8.85(bs,1H,NH),9.60(bs,1H,NH).Anal for $C_{17}H_{13}N_6OBr$ Calcd.(found)%;C 51.38(51.40) H 3.27 (3.29) N 21.15(21.15) MS;(m/z)397(m^+).

6(4'-Methoxyphenyl-(5'phenyl-1'H-tetrazole-1'-yl)-3,4-dihydropyrimidine-2-(1H)-one(3d)

Yield 68%, M.P.150-151^{0}C. FT-IR: 3054(Ar-H),1285(-N-N=N-),1108 and 1138 (Tetrazole ring), 2968 (CH str.) and 1612 (C=N ring stretch),3336 (NH str.),1479 (C=C),1682(C=O), 1251(-OCH_3). ^{1}H NMR (DMSO-d_6) δ 3.6(s 3H-OCH_3) 4.86(d, 1H, 4-CH),5.15(d,1H,5-CH),6.79-7.80(m,9 1H, Ar-H),8.83(bs,1H,NH),9.60(bs,1H,NH).Anal for $C_{18}H_{16}N_6O_2$ Calcd.(found)%;C 65.06(65.02) H 4.81 (4.85) N 25.30(25.29) MS;(m/z)332(m^+).

6(4'-Hydroxyphenyl-(5'phenyl-1'H-tetrazole-1'-yl)-3,4-dihydropyrimidine-2-(1H)-one(3e)

Yield 62%, M.P.130-132^{0}C. FT-IR: 3054(Ar-H),1285(-N-N=N-),1108 and 1138 (Tetrazole ring), 2958 (CH str.) and 1611 (C=N ring stretch),3342 (NH str.),1478(C=C),1682(C=O), 3412(-OH). ^{1}H NMR (DMSO-d_6) δ 4.86(d, 1H, 4-CH),5.15(d,1H,5-CH),5.35 (1H,s Ar-OH) 7.14-7.80(m,9 1H, Ar-H),8.85(bs,1H,NH),9.60(bs,1H,NH).Anal for $C_{17}H_{14}N_6O_2$ Calcd.(found)%;C 61.07(61.07) H 4.19 (4.22) N 25.14(25.13) MS;(m/z)334(m^+).

6(4'-Nitroxyphenyl-(5'phenyl-1'H-tetrazole-1'-yl)-3,4-dihydropyrimidine-2-(1H)-one(3f)

Yield 64%, M.P.162-163^{0}C. FT-IR: 3054(Ar-H),1285(-N-N=N-),1108 and 1138 (Tetrazole ring), 2958 (CH str.) and 1612 (C=N ring stretch),3345(NH str.), 1478 (C=C),1682(C=O), 1578 (-NO_2).^{1}H NMR (DMSO-d_6) δ 4.86(d, 1H, 4-CH),5.15(d,1H,5-CH), 7.14-7.25(m,9 1H, Ar-H),8.64(bs,1H,NH),9.60(bs,1H,NH). Anal for $C_{17}H_{13}N_7O_3$ Calcd.(found)%; C 56.15(56.15) H 3.58 (3.60) N 26.99(26.98) MS;(m/z)363(m^+).

6(4'-N,N-dimethylphenyl-(5'phenyl-1'H-tetrazole-1'-yl)-3,4-dihydropyrimidine-2-(1H)-one(3g)

Yield 67%, M.P.169-170^{0}C. FT-IR: 3054(Ar-H),1285(-N-N=N-),1106 and 1138 (Tetrazole ring), 2958 (CH str.) and 1610 (C=N ring stretch),3336 (NH str.),1475 (C=C),1680(C=O), 1365(CH_3).^{1}H NMR (DMSO-d_6) δ 2.74 (s, 6H ,$N(CH_3)_2$, 5.00(m, 2H, 4-CH ,5-CH), 7.13-7.21(m,9 1H, Ar-H),8.63(bs,1H,NH),9.60(bs,1H,NH).Anal for $C_{19}H_{19}N_7O$ Calcd.(found)%;C 63.15(63.14) H 5.26 (5.30) N 27.14(27.12) MS;(m/z)361(m^+).

BIOLOGICAL EVALUATION

Evaluation of Antimicrobial Activity:

The in vitro antimicrobial activity of compounds (3a-g) were determined by agar cup plate method , the results of which are summarized in Table -1

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Table- 1 Antibacterial and Antifungal data of compound (3a-g)

	Zone of inhibition in mm							
Compound	S.aures		E.coli		C.albicans		A.niger	
	50 ug	100 ug	50 ug	100ug	50 ug	100 ug	50 ug	100 ug
3a	12	14	11	12	12	14	11	13
3b	16	15	15	17	19	21	14	16
3c	12	15	11	18	20	18	10	12
3d	13	18	10	10	20	22	20	22
3e	13	16	9	12	13	17	10	16
3f	14	16	11	12	14	16	11	13
3g	11	12	10	12	14	18	10	11

Ciprofloxacin	20	24	20	24	-	-	-	-
Griseofulvin	-	-	-	-	20	24	20	24

RESULT AND DISCUSSION

Antimicrobial Activity :

The invitro antimicrobial activity of compounds (3a-g) were determined by agar plate method .The results of which are summarized in table- 1. The antimicrobial data in table -1 clearly showed that the halogen nitrophenyl, dimethylaminophenyl groups is by for the most active substituted phenyl group . The methoxyphenyl group generally confers weak antimicrobial activity. Phenyl substitution are weakly active to inactive among the synthesized compounds . Compounds 3b, 3d & 3e showed good activity against S. aureous and E.coli. The compounds 3a & 3b exhibit promising activity against C. albicans and A. niger. However, the compounds were less active in comparison to Ciprofloxacin and Griseofulvin (standard Durgs).

CONCLUSION

In conclusion, the results of this investigation revealed that the observed increase in antimicrobial activities are attributed to the presence of 4-NO_2 , 4-OH, 4-$N(CH_3)_2$, 4-OCH_3, 4-Cl in phenyl ring at 4- position of pyrimidine ring of synthesized compounds containing tetrazole. It is clear that the comparative evaluation of active compounds will required further studies ; the data reported in this article may be helpful guide for the medicinal chemist who are working in this area.

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