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Original Reserach Article

Synthesis, characterization and antimicrobial activity of novel tetrazoles clubbed with pyrimidine

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ABSTRACT

An attempt was made to synthesize pyrimidine tetrazole derivatives of pharmaceutical interest by oxidative cyclization of chalcones with adequate yield and purity, prompted by the diversity of their wider usage and the fact that they are an integral part of genetic content. The present work involves the reaction of 5-(2,6-dimethylphenyl)-1H-tetrazole with acetic anhydride to yield 1-[5-(2,6-dimethylphenyl)-1H-tetrazol-1-yl] ethanone (1) and which then treated with different aromatic aldehydes in presence of alkaline medium to chalcones (2a-f). Reaction of chalcones (2a-f) with urea and thiourea to produce 5-[5-(2,6-dimethylphenyl)-1H-tetrazol-1-yl]-4-(substituted aryl) pyrimidin-2-ol (3a-f) and 5-[5-(2,6-dimethylphenyl)-1H-tetrazol-1-yl]-4-(substituted aryl) pyrimidin-2-thiol (4a-f) respectively. All compounds were characterized by infrared spectroscopy (IR), ^{1}H nuclear magnetic resonance (NMR), and mass spectrometry (MS) to prove the structure and assessed in vitro for their efficacy as antibacterial and antifungal activity against four bacteria. The compounds 3c, 3d and 3f and compounds 4c, 4d and 4f possess very good activity against *S. aureus* and E. coli and the compounds 3e, 3c and 3a and compounds 4e,4b and 4c possess very good activity against fungi *Candida albicans* and *Aspergillus niger*.

1. Introduction

Since they are a diverse group of natural and synthetic products, many of which have biological applications, nitrogen-containing heterocycles are extremely important. Pyrimidine, which is present in DNA and RNA, has a variety of pharmacological properties, including bactericide, fungicide, vermicide, insecticide, anticancer, and antiviral.[1] Some pyrimidine derivatives reported as Anti-HIV-1 agents,[2] antileishmanial,[3] Anti-inflammatory,[4] Anticancer,[5] antimicrobial Antimalarial.[6] To date, a wide range of pyrimidine and pyrimidine-fused heterocyclic compounds have been documented to have anticancer activity through a variety of mechanisms and targets.[7–9] Pyrimidine derivatives[10,11] have played a significant role in the evolution of heterocyclic chemistry and have been widely used as pharmacophores and synthons in organic chemistry. A considerable amount of research effort has been centered on these nuclei due to their flexible chemotherapeutic significance. There has been significant progress in this area since the discovery of many synthetic and semi-synthetic antibacterial sulfa products, nitrofuranes, penicillins, cephalosporins, tetracyclines, macrolides, oxazolidinones, and antifungal agents such as fluconazole, ketoconazole, and miconazole, as well as amphotericin B. Despite advancements in antibacterial and antifungal therapies, most antimicrobial drugs still have a long way to go. Antibiotic overuse has

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resulted in the emergence of multidrug-resistant microbial pathogens.[12] Pyrimidine based heterocycles are potential bioactive molecules and exhibit antimicrobial,[13,14] anti-inflammatory,[11] antioxidant,[15] anticancer,[16] antihypertensive[17] and anticonvulsant.[18] Tetrazole has a great importance as it is bioactive molecules and exhibit antimicrobial,[19] anti-bacterial[20] anti-inflammatory[21], antioxidant,[22] anticancer[23] ant tubercular,[24] anti-fungal,[24] antihypertensive[25], anticonvulsant[26] and also act as enzyme inhibitors. Inspired from these facts, in present work an attempt is being made to synthesize pyrimidine's containing tetrazole and evaluate for antimicrobial activity which has not been reported yet. Hence the present work deals with the reaction of 1-[5-(2,6-dimethylphenyl)-1H-tetrazol-1-yl] ethanone (1) with different aromatic aldehydes in presence of alkaline medium to form (2E)-1-[5-(2,6-dimethylphenyl)- 1H-tetrazol-1-yl]-3-(substituted aryl)prop-2-en-1-one (2a-f). Reaction of (2a-f) with urea and thiourea to produce 5-[5-(2,6-dimethylphenyl)-1H-tetrazol-1-yl]-4-(substituted aryl)pyrimidin-2-ol (3a-f) and 5-[5-(2,6-dimethylphenyl)-1H-tetrazol-1-yl]- 4-(substituted aryl) pyrimidin-2-thiol (4a-f) respectively. The structure of all the various synthesized compounds were assigned on the basis of IR, ^{1}H NMR spectral data and elemental analysis. These compounds were screened for their antimicrobial activity.

2. Materials and Methods

Melting points were determined with open capillary. FT-IR spectra were recorded on a Jasco model 4010 spectrophotometer,^{1}H NMR spectra were recorded in DMSO on a Varian mercury FT-NMR model YH- 300 instrument using TMS as internal standard. Mass spectra were recorded on GC-MS auto tune EI instrument.

2.1. Synthetic procedur

2.1.1. General procedure for the preparation (2E)-1-[5-(2,6-dimethylphenyl)-1H-tetrazol-1-yl]-3-(substituted aryl) prop-2-en-1-one derivatives [2a-f]

A solution of 5-(2,6-dimethylphenyl)-1H-tetrazole (8.5g,0.05 moles) and heterocyclic aldehydes (0.05 mole) in ethanol (12 ml) was cooled to 5 to 10^{o}C in an ice bath. The cooled solution was treated with drop wise addition of aqueous sodium hydroxide (5 ml, 50%). The reaction mixture was magnetically stirred for 30 min and then left over night. The resulting dark solution was diluted with ice water and carefully acidified using diluted hydrochloric acid. The tetrazole analogues of chalcone which crystallized were collected by filtration after washing with sodium bicarbonate and water. It was further purified by crystallization from ethanol.

2.1.2. Synthesis of 5-[5-(2,6-dimethylphenyl)-1H-tetrazol-1-yl]-4- (substituted ary) pyrimidin-2-ol derivatives [3a-f]

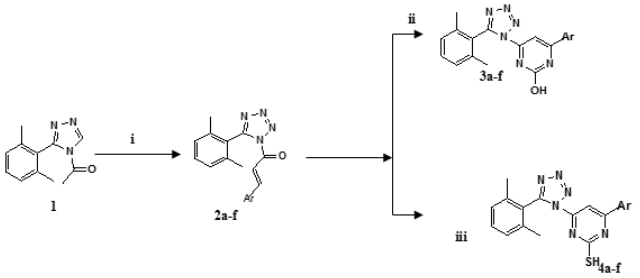
To a solution of 2E)-1-[5-(2,6-dimethylphenyl)-1H-tetrazol-1-yl]- 3-(substituted aryl)prop-2-en-1-one derivatives (2a-f), (0.01mole) in anhydrous ethanol (50 mL), urea (0.01 mole)and aqueous sodium hydroxide (0.01 mole). The reaction mixture was refluxed for 5 hrs and poured into ice cold water the product obtained was filtered, washed with water and crystallized from aqueous ethanol. The purity of the compound was established by TLC using a mixture of hexane and ethyl acetate (7:3) as a mobile phase.

2.1.3. Synthesis of 5-[5-(2,6-dimethylphenyl)-1H-tetrazol-1-yl]-4- (substituted aryl) pyrimidin-2-thiol derivatives [4a-f]

To a solution of 2E)-1-[5-(2,6-dimethylphenyl)-1H-tetrazol-1-yl]-3- (substituted aryl) prop-2-en-1-one derivatives (2a-f), (0.01mole) in anhydrous ethanol (50 mL), thiourea (0.01 mole) and aqueous sodium hydroxide (0.01 mole). The reaction mixture was refluxed for 5 hrs and poured into ice cold water the product obtained was filtered, washed with water and crystallized from aqueous ethanol. The purity of the compound was established by TLC using a mixture of hexane and ethyl acetate (6:4) as a mobile phase.

2.2. Antibacterial and antifungal activity

All the newly synthesized compounds were screened for antimicrobial activity against both gram positive S. aureus and gram negative *E.coli* bacteria and antifungal activity against *C. albicans* and *A. niger* according to cup plate method[13] at a concentration 100ug/0.1ml respectively. Streptomycin and clotrimazole were used as standard for comparison of antibacterial and antifungal activity[14] Indian Pharmacopoeia[15]. Solvent dimethyl sulphoxide (DMSO) was used as control. The results of screening are given inTable 2.



2.3. Synthesis and spectral characterization

A series of 5-[5-(2,6-dimethylphenyl)-1H-tetrazol-1-yl]-4-(substituted aryl) pyrimidin-2-ol (3a-f) and 5-[5-(2,6-dimethylphenyl)-1H-tetrazol-1-yl]-4-(substituted aryl)

Table 1: eagents and conditions:i) Ar-CHO/ EtOH, ii) Urea/Aq. NaOH, iii) Thiourea/Aq. NaOH

Comp no	R	Mole. Formula	MW	% Yield	M.P.^{0} C	R_f .	Found (Calcd) %		
							C	H	N
3a	Fig1	$C_{17}H_{15}N_70$	333	72	164	0.64	61.20 (61.25)	4.50 (4.54)	29.39 (29.41)
3b	Fig2	$C_{17}H_{14}N_60_2$	334	62	172	0.65	61.04 (61.07)	4.20 (4.22)	25.12 (25.14)
3c	Fig3	$C_{18}H_{16}N_60_2$	348	65	174	0.73	62.01 (62.06)	4.60 (4.63)	24.08 (24.12)
3d	Fig4	$C_{18}H_{16}N_60S$	364	60	166	0.68	59.29 (59.32)	4.38 (4.43)	23.04 (23.06)
3e	Fig5	$C_{18}H_{16}N_60S$	364	64	164	0.65	59.29 (59.32)	4.38 (4.43)	23.04 (23.06)
3f	Fig6	$C_{18}H_{15}N_70$	345	74	150	0.75	62.57 (62.60)	4.33 (4.38)	28.36 (28.39)
4a	Fig7	$C_{17}H_{14}N_7S$	348	72	166	0.62	58.41 (58.44)	4.29 (4.33)	28.03 (28.06)
4b	Fig8	$C_{17}H_{16}N_6OS$	350	66	180	0.66	58.22 (58.27)	4.00 (4.03)	23.95 (23.98)
4c	Fig9	$C_{18}H_{16}N_60S$	364	68	178	0.72	59.26 (59.32)	4.41 (4.43)	23.05 (23.06)
4d	Fig10	$C_{18}H_{16}N_6S_2$	380	65	166	0.68	56.80 (56.82)	4.20 (4.24)	22.06 (22.09)
4e	Fig11	$C_{18}H_{16}N_6S_2$	380	64	168	0.58	56.76 (56.82)	4.22 (4.24)	25.04 (22.09)
4f	Fig12	$C_{18}H_{15}N_7S$	361	72	185	0.75	59.77 (59.82)	4.14 (4.18)	27.10 (27.13)

Table 2: Antibacterial and antifungal data of pyrimidine

Comp.	Zone of inhibition in mm at 100 μg/0.1ml			
	S. aureus	E. coli	C. albicans	A. niger
3a	14	12	20	18
3b	15	13	20	16
3c	18	16	21	15
3d	16	14	18	13
3e	18	15	21	22
3f	20	18	16	12
4a	16	13	15	13
4b	16	14	20	16
4c	18	17	20	14
4d	16	15	18	12

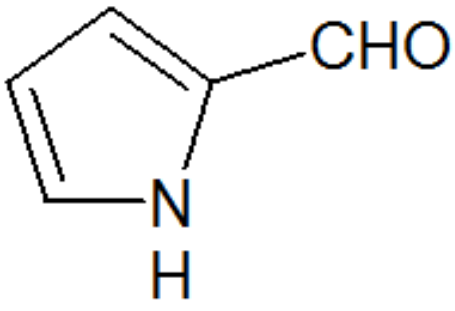


Fig. 1: Table1+R+Show 3a

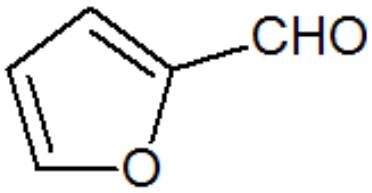


Fig. 2: Table1+R+Show 3b

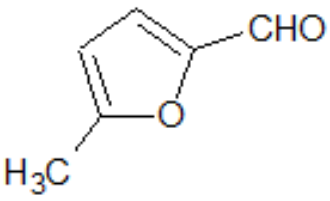


Fig. 3: Table1+R+Show 3c

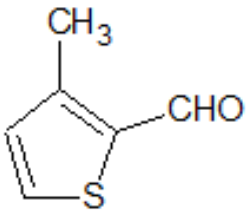


Fig. 4: Table1+R+Show 3d

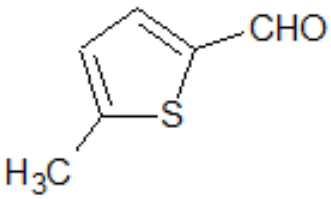


Fig. 5: Table1+R+Show 3e

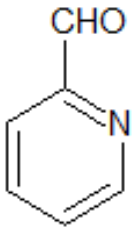


Fig. 6: Table1+R+Show 3f

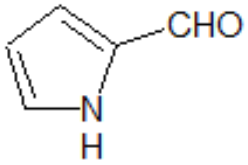


Fig. 7: Table1+R+Show 4a

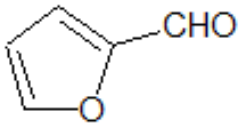


Fig. 8: Table1+R+Show 4b

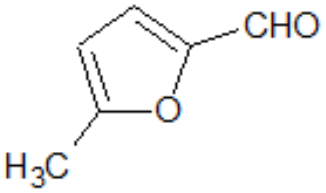


Fig. 9: Table1+R+Show 4c

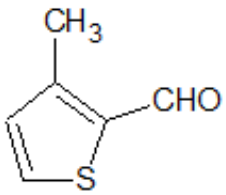


Fig. 10: Table1+R+Show 4d

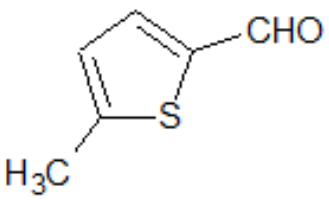


Fig. 11: Table1+R+Show 4e

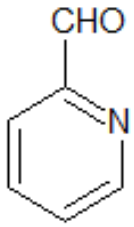


Fig. 12: Table1+R+Show 4f

pyrimidin-2-thiol (4a-f) were synthesized from chalcones of 5-(2,6-dimethylphenyl)-1H-tetrazole. All synthesis steps are presented in scheme 1. The IR spectra shows 1542 (C=N), 1445(C=C) providing the strong evidence for pyrimidine ring. ^{1}H NMR spectrum shows 7.10-7.58 ppm for aromatic protons and 9.7 ppm for OH protons and 13.4 for SH protons were observed at expected signals.

2.3.1. 3a:5-[5-(2,6-dimethylphenyl)-1H-tetrazol-1-yl]-4-(1H-pyrrol-2-yl)pyrimidin-2-ol

IR: 3745 (OH), 3050 (Ar-CH), 1540(C=N), 1435(C=C), 1286(N-N=N-),1120 and 1145(Tetrazole ring),.^{1}H NMR: 2.35 (d, 6H, CH_3), 6.5-6.8 (d,1H,CH=CH) 7.30 -8.40 (m ,8H, Ar-H), 9.5 (1H, Ar- OH), Mass spectrum (m/z) molecular ion peak at 332 and isotopic peak at 333.

2.3.2. 3b: 5-[5-(2,6-dimethylphenyl)-1H-tetrazol-1-yl]-4-(furan-2-yl)pyrimidin-2-ol:
IR: 3744 (OH), 3054 (Ar-CH), 1538 (C=N), 1436(C=C), 1280 (N-N=N-),1120 and 1145(Tetrazole ring) , 780(C-Cl).,^{1}H NMR: 2.35 (d, 6H, CH_3), 6.5-6.8 (d,1H,CH=CH) 7.30 -8.40 (m ,7H, Ar-H), 9.5 (1H, Ar- OH), Mass spectrum (m/z) molecular ion peak at 334 and and isotopic peak at 315.

2.3.3. 3c: 5-[5-(2,6-dimethylphenyl)-1H-tetrazol-1-yl]-4-(5-methylfuran-2-yl)pyrimidin-2-ol:
IR: 3742 (OH), 3056 (Ar-CH), 1536 (C=N), 1432(C=C), 1282(N-N=N-),1245(-OCH3) ,1120 and 1145(Tetrazole ring) ,^{1}H NMR: 2.35 (d, 9H, CH_3), 6.5-6.8 (d,1H,CH=CH) 7.30 -8.40 (m ,7H, Ar-H), 9.5 (1H, Ar- OH),, Mass spectrum (m/z) molecular ion peak at 348.

2.3.4. 3d: 5-[5-(2,6-dimethylphenyl)-1H-tetrazol-1-yl]-4-(5-methylthiophen-2-yl)pyrimidin-2-ol
IR: 3740 (OH), 3058 (Ar-CH), 1546 (-NO2),1530(C=N), 1441(C=C), 1278 (N-N=N-),1120 and 1145(Tetrazole ring) ,^{1}H NMR: 2.35 (d, 9H, CH_3), 6.5-6.8 (d,1H,CH=CH) 7.30 -8.40 (m ,7H, Ar-H), 9.5 (1H, Ar- OH),, Mass spectrum (m/z) molecular ion peak at 364.

*2.3.5. 3e:5-[5-(2,6-dimethylphenyl)-1**H**-tetrazol-1-yl]-4-(3-methylthiophen-2-yl)pyrimidin-2-ol*

IR: 3735 (OH), 3054 (Ar-CH), 1544(C=N), 1435(C=C), 1331(-N(CH3)2,1284 (N-N=N-),1120 and 1145(Tetrazole ring) ,^{1}H NMR: 2.35 (d, 9H, CH_3), 6.5-6.8 (d,1H,CH=CH) 7.30 -8.40 (m,7H, Ar-H), 9.5 (1H, Ar- OH), Mass spectrum (m/z) molecular ion peak at 364.

2.3.6. 3f: 5-[5-(2,6-dimethylphenyl)-1H-tetrazol-1-yl]-4-(pyridin-2-yl)pyrimidin-2-ol
IR: 3741 (OH), 3052 (Ar-CH), 1544 (C=N), 1436(C=C), 1355(CH3),1284 (N-N=N-),1120 and 1145(Tetrazole ring),^{1}H NMR: 2.35 (d, 6H, CH_3), 6.5-6.8 (d,1H,CH=CH) 7.30 -8.40 (m ,9H, Ar-H), 9.5 (1H, Ar- OH), Mass spectrum (m/z) molecular ion peak at 345.

2.3.7. 4a:5-[5-(2,6-dimethylphenyl)-1H-tetrazol-1-yl]-4-(1H-pyrrol-2-yl)pyrimidin-2-thiol
IR:3055 (Ar-CH), 1538(C=N), 1436(C=C), 1288 (N-N=N-), 1120 and 1145 (Tetrazole ring) ,^{1}H NMR: 2.35 (d, 6H, CH_3), 6.5-6.8 (d,1H,CH=CH) 7.30 -8.40 (m ,8H, Ar-H), 13.6 (s, 1H, SH), Mass spectrum (m/z) molecular ion peak at 348.

2.3.8. 4b: 5-[5-(2,6-dimethylphenyl)-1H-tetrazol-1-yl]-4-(furan-2-yl)pyrimidin2-thiol
IR: 3050 (Ar-CH), 1535(C=N), 1436(C=C), 1286(N-N=N-),1120 and 1145 (Tetrazole ring), 780 (C-Cl).,^{1}H NMR: 2.35 (d, 8H, CH_3), 6.5-6.8 (d,1H,CH=CH) 7.30 -8.40 (m, 8H, Ar-H), 13.6 (s, 1H, SH), Mass spectrum (m/z) molecular ion peak at 350.

2.3.9. 4c:5-[5-(2,6-dimethylphenyl)-1H-tetrazol-1-yl]-4-(5-methylfuran-2-yl)pyrimidin-2-thiol
IR: 3052 (Ar-CH), 1544(C=N), 1448(C=C), 1286(N-N=N-),1245(-OCH3), 1120 and 1145(Tetrazole ring) ,^{1}H NMR: 2.35 (d, 9H, CH_3), 6.5-6.8 (d,1H,CH=CH) 7.30 -8.40 (m ,7H, Ar-H), 13.6 (s, 1H, SH), Mass spectrum (m/z) molecular ion peak at 364.

2.3.10. 4d:45-[5-(2,6-dimethylphenyl)-1H-tetrazol-1-yl]-4-(5-methylthiophen-2-yl)pyrimidin-2-thiol
IR: 3058 (Ar-CH), 1543(C=N), 1560(-NO2),1442(C=C), 1286(N-N=N-), 1120 and 1145(Tetrazole ring),^{1}H NMR: 2.35 (d, 9H, CH_3), 6.5-6.8 (d,1H,CH=CH) 7.30 -8.40 (m ,7H, Ar-H), 13.6 (s, 1H, SH), Mass spectrum (m/z) molecular ion peak at 380.

2.3.11. 4e:5-[5-(2,6-dimethylphenyl)-1H-tetrazol-1-yl]-4-(3-methylthiophen-2-yl)pyrimidin-2-thiol
IR:3050 (Ar-CH), 1542(C=N), 1442(C=C), 1331(-N(CH3)2,1286(N-N=N-), 1120 and 1145 (Tetrazole

ring),^{1}H NMR: 2.35 (d, 9H, CH_3), 6.5-6.8 (d,1H,CH=CH) 7.30 -8.40 (m,7H, Ar-H), 13.6 (s, 1H, SH), Mass spectrum (m/z) molecular ion peak at 380 and isotopic peak at 381.

2.3.12. 4f:5-[5-(2,6-dimethylphenyl)-1H-tetrazol-1-yl]-4-(pyridin-2-yl)pyrimidin-2-thiol

IR: 3051(Ar-CH), 1540(C=N), 1442(C=C), 1355(CH3),1286(N-N=N-),1120 and 1145(Tetrazole ring),^{1}H NMR: 2.35 (d, 9H, CH_3), 6.5-6.8 (d,1H,CH=CH) 7.30 -8.40 (m, 9H, Ar-H), 13.6 (s, 1H, SH), Mass spectrum (m/z) molecular ion peak at 361.

3. Results and Discussion

The reaction of 5-(2,6-dimethylphenyl)-1H-tetrazole with acetic anhydride to yield 1-[5-(2,6-dimethylphenyl)-1H-tetrazol-1-yl] ethanone (1) and which then treated with different aromatic aldehydes in presence of alkaline medium to form(2E)-1-[5-(2,6-dimethylphenyl)-1H-tetrazol-1-yl]-3-(substituted aryl) prop-2- en-1-one (2a-f). Reaction of (2a-f) with urea and thiourea to produce 5-[5-(2,6-dimethylphenyl)-1H-tetrazol-1-yl]-4-(substituted aryl) pyrimidin-2-ol (3a-f) and 5-[5-(2,6-dimethylphenyl)-1H-tetrazol-1-yl]-4-(substituted aryl)pyrimidin-2-thiol (4a-f) respectively. The FT-IR spectra of (3a-f) and (4a-f) showed the absence of peak of keto groups and the new peaks which appeared at 3510 cm^{-1} due to OH group. This signifies the keto enol tautomeric in synthesized compounds. Some spectral data are listed in Table 2. The FT-IR absorption bands disappearance at (1610-1650) cm^{-1} is give good evidence for the success step of reaction. These absorption bands due to (NH) amine group stretching frequency is at 3450 cm^{-1}. Also FT-IR spectra of tetrazole showed clear absorption bands at 1286(N-N=N-),1120 and 1145 (Tetrazole ring). The NMR spectra of all the synthesized compounds were determined and the chemical shift values of H^1 NMR shows at 2.35 (d, 9H, CH_3), 6.5-6.8 (d,1H, CH=CH) 7.30 -8.40 (m, 9H, Ar-H), 9.5 (1H, Ar- OH), 13.6 (s, 1H, SH),. This values indicates the presence of all protons which conforms the structure of the synthesized compounds.

3.1. Antibacterial and antifungal activity

The antibacterial activity was evaluated by zone of inhibition method at 100 μg/0.1ml concentration. The results of antibacterial were compared with standard drug ciprofloxacin. Most of the synthesized compounds showed antibacterial activity against the tested Bacteria. It is evident that most of the compounds are very weakly active and few are moderately active against *S. aureus* and *E. coli* but compounds 3c, 3d and 3f and compounds 4c, 4d and 4f possess very good activity against *S. aureus* and *E. coli* at concentration of 100ug/0.1ml.

Similarly, the results of preliminary antifungal bioassays were compared with standard drug clotrimazole. Most of the synthesized compounds showed antifungal activity against the tested fungi. It is evident that the compounds 3e, 3c and 3a and compounds 4e,4b and 4c possess very good activity against fungi *Candida albicans* and *Aspergillus niger* at concentration of 100ug/0.1mL.Compound 3d and 4f showed moderate activity all bacteria and fungi tested

4. Conclusion

Tetrazole and Pyrimidine an important group of heterocyclic compounds reported to have different biological activities and hence the present studies were undertaken in order to synthesize Tetrazole clubbed with pyrimidines in order to potentiate the combined therapeutic effect of both heterocyclic compounds. So all the synthesized compounds were investigated them for their antibacterial and antifungal activity. Compounds with thiopene, furan and pyrrole substituents on pyrimidine clubbed with Tetrazole exhibited significant antibacterial and antifungal activity when compared with control. The compounds with pyrimidines substituents groups showed significant activity when compared to standard drug ciprofloxacin and clotrimazole respectively.

5. Source of Funding

None.

6. Conflict of Interest

None.

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