SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL EVALUATION OF PYRIMIDINES AND TETRAZOLES

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ABSTRACT

Tetrazole and Pyrimidine compounds are very useful compounds with well-known biological activities. Whereas these compounds are important components of several pharmacological active moieties. Certain tetrazoles possess Antibacterial, Antifungal, Anthelmintic, Antineoplastic, Antioxidant, Antibiotic, and so on. Whereas pyrimidines possess antibacterial, antifungal and anticonvulsant, analgesic, anti-inflammatory, anthelmintic, sedative, hypnotic, antispasmodic, local anesthetic, and Antitubercular, antihistaminic, antioxidant, and anticancer activities.

In the present study antibacterial and anti-fungal activity of tetrazole and pyrimidine has been described through the synthesis and characterization of 14 compounds. The prepared compounds were subjected to physical evaluation studies such as melting point, TLC, and percentage yield.

In this study, the synthesized compound was based on the substitution of different aromatic aldehydes at Step 3 for tetrazole and Step 4 for pyrimidine. Among those only five have shown significant gram-positive and gram-negative activity against E.coli and Penicillium notatum that indicates stronger anti-fungal and antibacterial effects.

So the present study highlights the importance of tetrazole and pyrimidine derivatives that has various heterocycle moiety features and may serve as a lead molecule for further modification to obtain clinical useful novel entities.

KEYWORDS

Tetrazole, pyrimidine, aromatic, aldehydes, derivatives, antibacterial, antifungal

INTRODUCTION

Chemistry is the science of the composition, structure, properties, and reactions of matter, especially of atomic and molecular systems. Life itself is full of chemistry; i.e., life is the reflection of a series of continuous biochemical processes. Right from the composition of the cell to the whole organism, the presence of chemistry is conspicuous. A chemical synthesis begins with the selection of compounds that are known as reagents or reactants. Various reaction types can be applied to these to synthesize the product or an intermediate product. This requires mixing the compounds in a reaction vessel such as a chemical reactor or a simple round-bottom flask. Many reactions require some form of the work-up procedure before the final product is isolated. The amount of product in a chemical synthesis is the reaction yield. Typically, chemical yields are expressed as a weight in grams or as a percentage of the total theoretical quantity of product that could be produced. A side reaction is an unwanted chemical reaction taking place that diminishes the yield of the desired product.

1. TETRAZOLES

STRUCTURE:

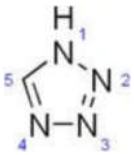


Fig: 1

Tetrazoles are a class of synthetic organic heterocycliccompound[4], consisting of a 5-member ring of four nitrogen and one carbon atom (plus hydrogens). The simplest is tetrazole itself, CN_4H_2.

The majority of tetrazoles are crystalline solids. There is considerable variation in thermal stability; derivatives that melt above 150^0c do so with decomposition, while 5-aryl amino tetrazole does not melt at 300^0c. In general, most tetrazoles are acids and

often yield explosive salts. Tetrazoles are generally soluble in polar solvents and insoluble in nonpolar solvents, 1H-tetrazoles have good solubility in water. Unsubstituted tetrazole and C substituted
1-H tetrazoles show amphoteric properties, they are weak NH-acids and readily form salts with strong mineral acids.

Tetrazole and its derivatives enter electrophilic and nucleophilic substitution reactions generally on the 5 ring position. Thermal destruction of the tetrazole cycle usually takes place at 150-200oc. The tetrazoles in general can be looked upon as gas generators, useful where instantaneous or progressive pressure effects are required.

2 PYRIMIDINES

STRUCTURE:

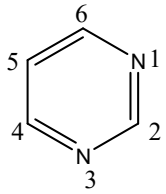


Fig : 2

Pyrimidine is a heterocyclic aromatic organic compound similar to benzene and pyridine, containing two nitrogen atoms at positions 1 and 3 of the six-member ring.

Three nucleobases found in nucleic acids, cytosine (C), thymine (T), and uracil (U), are pyrimidine derivatives.

MATERIALS & METHODOLOGY

TETRAZOLE

Scheme- 1: The present work involves the reaction of Aminoguanidine bicarbonate with nitric acid and diazotized with sodium nitrite to form Guanylazide which on reflux with sodium bicarbonate to give 5-amino tetrazole. Then 5-amino tetrazole on acetylation with acetyl chloride gives 5-acetyl tetrazole which on reaction with different aromatic aldehydes gives respective title compounds i.e 3 derivatives were synthesized by Scheme 1

Scheme-2 It involves the reaction of Aminoguanidine bicarbonate with nitric acid and diazotized with sodium nitrite to form Guanylazide which on reflux with sodium bicarbonate to give 5-amino tetrazole. Then 5-amino tetrazole reacts with different aryl aldehydes to form Schiff's base which on reaction with thioglycolic acid gives respective title compounds i.e. 5 derivatives were synthesized by Scheme 2.

SCHEME1

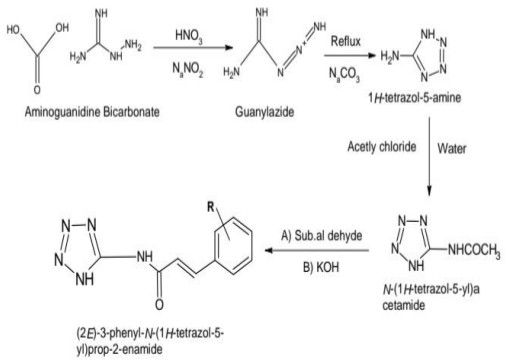


Fig:3

TZ-1 (E)-3-(3-chlorophenyl)-N-(1H-tetrazol-5-yl)acrylamide .**Colour and appearance:** pale yellow solid Solubility: soluble in chloroform **Reaction time:** 24hrs **Recrystallization solvent:** Ethanol **Solvent system: Ethyl acetate:** Methanol(8:2).

Identification and characterization: **IR (KBr):** Cm^{-1}= 1585.86 (N-H; Str), 1280.71(C-N; Str), 1676 (C=O; Str), 1676(C=C; Str), 681.54(C-Cl; Str) **HNMR :** ppm= 7.46 (d, 1H, COCH=), 7.2 (s, 1H, Ar-CH), 8.05 (d, 1H, CH), 8.0 (s,
1H, NH)

TZ-2 (E)-N-(1H-tetrazol-5-yl)cinnamamide. **Colour and appearance:** yellow solid **Solubility:** soluble in chloroform. **Reaction time: 24hrs Recrystallization solvent:** Ethanol **Solvent system:** Ethyl acetate: Methanol(8:2) **Identification and characterization: IR (KBr):** Cm^{-1}= 1603.10 (N=N; Str), 1569.38(N-H; Bend), 1664.52(C=O; Str), 1603.10,1569.38(C=C; Str)**HNMR:** ppm= 1.8 (s, 3H, CH_3), 2.58(d, 1H, COCH=), 7.28 (m, 3H, Ar- CH), 8.02 (d,1H, CH) **C13:**ppm= 29.69 (CH_3), 76.68 (Ar-C=), 76.99 (Ar-C=), 77.31 (Ar-C=), 126.69 (Ar-C=),129.19 (Ar-C=), 130.26 (Ar-C=), 144.59 (-C=), 172.29 (C=O)

TZ-3 (2*E*)-3-[4-(dimethylamino)phenyl]-*N*-(1*H*-tetrazol-5-yl)prop-2-enamide .**Colour and appearance:** pale yellow solid **Solubility:** soluble in chloroform **IUPAC name:** (E)-3-(4-(dimethylamino) phenyl)-N-(1H-tetrazol-5 yl)acrylamide **Reaction time: 24hrs. Recrystallization solvent:** Ethanol .**Solvent system:** Ethyl acetate: Methanol (8:2)

SCHEME -2

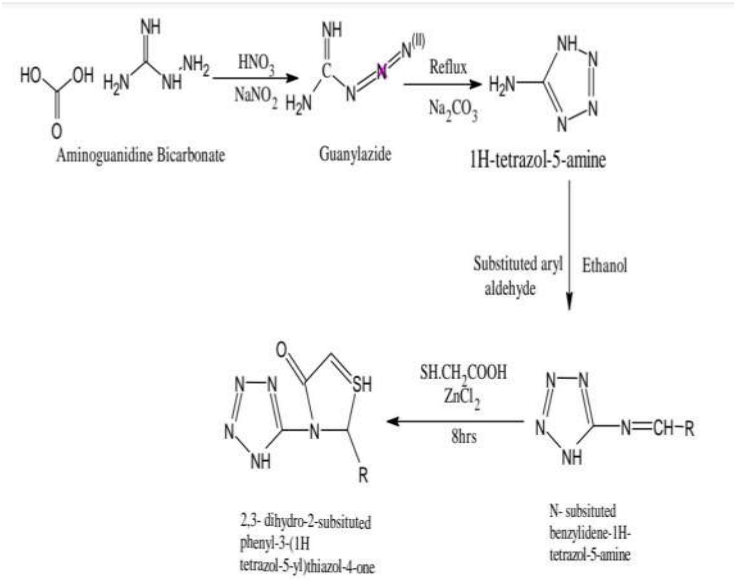


Fig:4

TZ-4

2-(4-bromophenyl)-3-(1*H*-tetrazol-5-yl)-2,3-dihy dro-4*H*-1λ4,3-thiazol-4-one

Colour and appearance: pale yellow .**Solubility:** soluble in ethanol HNMR: ppm= 2.85 (s, 6H, NH), 6.54(d, 2H, Ar- CH), 6.84 (s, 1H, COCH=), 7.12(d, 2H, Ar- CH), 7.55 (s, 1H, CH) **Reaction time:** 8hrs .**Recrystallization solvent:** chloroform **Solvent system:** Ethyl acetate:

Methanol (8:2) Identification and characterization**: IR (KBr):** Cm-1= 1648.36(N=N; Str), 3356.99(N-H; Str), 1044.79(C-N; Str), 1153.97(C=S; Str), 1648.38(C=O; Str), 1648.36(C=N;Str), 747.19(C-Br; Str) **HNMR :**ppm= 4.9 (s, 1H, CH), 6.95(d, 2H, Ar- CH), 7.31(d, 2H, Ar- CH)

TZ-5 2-(4-chlorophenyl)-3-(1*H*-tetrazol-5-yl)-2,3-dihyd ro-4*H*-1λ4,3-thiazol-4-one **Colour and appearance:** pale yellow **Solubility:** soluble in ethanol **Reaction time: 8hrs Recrystallization solvent:** chloroform **Solvent system:** Ethyl acetate: Methanol (8:2) **Identification and characterization: IR (KBr):** Cm-1= 1648.05(N=N;Str), 3357.41(N-H; Str), 1284.52(C-N; Str), 1648.05(C=N;Str), 663.70(C-S, Str), 747.74(C-Cl;Str), 1648.05(C=O;Str) HNMR :ppm= 4.9 (s, 1H, CH), 7.0(d, 2H, Ar- CH), 7.15(d, 2H, Ar- CH)
MASS: m/z 296(M-)

TZ-6 2-(4-methylphenyl)-3-(1*H*-tetrazol-5-yl)-2,3-di hydro-4*H*-1λ4,3-thiazol-4-one **Colour and appearance: white Solubility:** soluble in chloroform **Reaction time: 8hrs Recrystallization solvent:** ethanol **Solvent system:** Ethyl acetate: Methanol (8:2) **Identification and characterization: IR (KBr):** Cm-1= 1556.31(N=N;Str), 3356.22(N-H; Str), 1046.30(C-N; Str), 1079.43(C=S; Str), 1647.73(C=O, Str), 747.69(C-H, Bend), 1647.73(C=N; Str)
HNMR :ppm= 2.35 (s, 1H, CH3), 4.9(d, 1H, CH), 7.15(d, 4H, Ar- CH)

TZ-7 2-(4-fluorophenyl)-2,3-dihydro-3-(1H-tetrazol-5-yl)thiazol-4-one **Colour and appearance:** pale yellow **Solubility:** soluble in chloroform **Reaction time: 8hrs Recrystallization solvent:** ethanol **Solvent system:** Ethyl acetate: Methanol (8:2) **Identification and characterization: IR (KBr):** Cm-1= 3357.8(N-H; Str), 1081.00(C-N; Str), 1649.35(C=N; Str), 603.81(C-S; Str), 1046.11(C-F; Str), 1649.35, 1556.69(C=C, Str),1752.49(C=O, Str), 1155.30(C=S; Str)
HNMR :ppm= 4.9 (s, 1H, CH), 6.85(d, 2H,Ar- CH), 7.04(d, 4H, Ar- CH)
TZ-8 2-phenyl-3-(1*H*-tetrazol-5-yl)-2,3-dihydro-4 *H*-1λ4,3-thiazol-4-one **Colour and appearance: white Solubility:** soluble in methanol **Reaction time: 8hrs Recrystallization solvent:** ethanol **Solvent system:** Ethyl acetate: Methanol (8:2)
Scheme III :

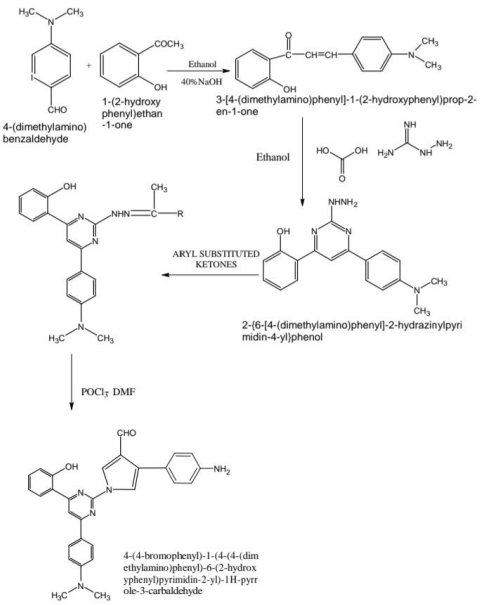


Fig :5

PYR-1 1-(4-(4-(dimethylamino) phenyl)-6-(2-hydroxyphenyl) pyrimidin-2-yl)-4- (4-nitrophenyl)-1H-pyrrole-3-carbaldehyde **Colour and appearance:** orange **Solubility:** soluble in ethanol **.Reaction time: 3hrs . Recrystallization solvent:** chloroform **Solvent system:** Ethyl acetate: Methanol (8:2) **Identification and characterization: IR (KBr):** Cm^{-1}= 3057.19(C-H;Str), 1666.16(C=N;Str), **HNMR :** ppm= 1.3(s, 6H, -N-CH_3), 2.0 (s,1H, OH), 2.89(d, 2H,Ar- CH), 3.4(d,1H,Ar- CH), 3.9-4.0(m, 1H, Ar- CH, 2H, CH), 5.73 (m, 1H, Ar- CH), 6.72(m, 3H, Ar- CH), 8.0(d, 2H,Ar- CH), 10.9(s, 1H,O=CH) 1576.82,1500.21(C=C,Str), 749.77(C-H;Bend), 1180.50 (C-N;Str),1328.21(C-O;Str), 1129.21(O-H;Bend), 2885.72(methyl;Str)

PYR-2 4-(4-bromophenyl)-1-(4-(4- (dimethylamino)phenyl)-6-(2- hydroxyphenyl)pyrimidin- 2-yl)-1H-pyrrole-3-carbaldehyde**Colour and appearance:** yellow **Solubility:** soluble in ethanol **Reaction time: 3hrs Recrystallization solvent:** chloroform **Solvent system:** Ethyl acetate: Methanol (8:2) **Identification and characterization: IR (KBr):** Cm^{-1}=2999.77(C-H;Str),
HNMR: ppm= 1.25(s,6H, -N-CH_3), 1.82(s, 1H, OH), 2.89(d, 2H, Ar- CH), 3.36(d, 1H, Ar-CH), 3.92 (m, 1H, Ar-), 5.72 (m, 1H, Ar-CH), 6.7(m, 5H, Ar-CH), 7.46 (s, 1H, CH), 10.98 (s,1H, O=CH) **MASS:** m/z 573(M+) 1570.00,15518.96,1481.89(C=C;Str),757.10(C-H;Bend), 1164.53(C-N;Bend), 1236.58(O-H;Bend), 1408.59(C-O;Str), 2887.59(C-H;Str), 1307.91(C-H;Bend), 757.10(C-Br;Str).

PYR-3 4-(4-bromophenyl)-1-(4-(4-(dimethylamino)phenyl)-6-(2- hydroxyphenyl)pyrimidin-2-yl)-1H-pyrrole-3-carbaldehyde **Colour and appearance:** orange **Solubility:** soluble in ethanol **Reaction time: 3hrs .Recrystallization solvent:** chloroform.**Solvent system:** Ethyl acetate: Methanol (8:2) **Identification and characterization: IR (KBr):** Cm^{-1}=2982.63(C-H;Str), 1569.41,1515.91,1478.60(C=C;Str), **HNMR :**^{C13}:ppm= 40.14(Ter-N), 111.61(Ar-CH), 112.77(C-H), 117.28(Ar- CH), 117.89(Ar-CH), 119.15(Ar CH),119.20(Ar-CH), 124.64(C-H),126.55(CH), 127.78(Ar-CH), 128.57(Ar-CH), 131.22(Ar-CH),135.88(-C=), 150.04(C-H), 154.27(-C=), 161.57(Ar-CH), 164.73(-C=) 739.33(C-H;Bend),1230.74(O-H;Bend),1413.02(C-O;Str),2891.11(C H;Str),1341.39(C-H;Bend)

SCHEME-4

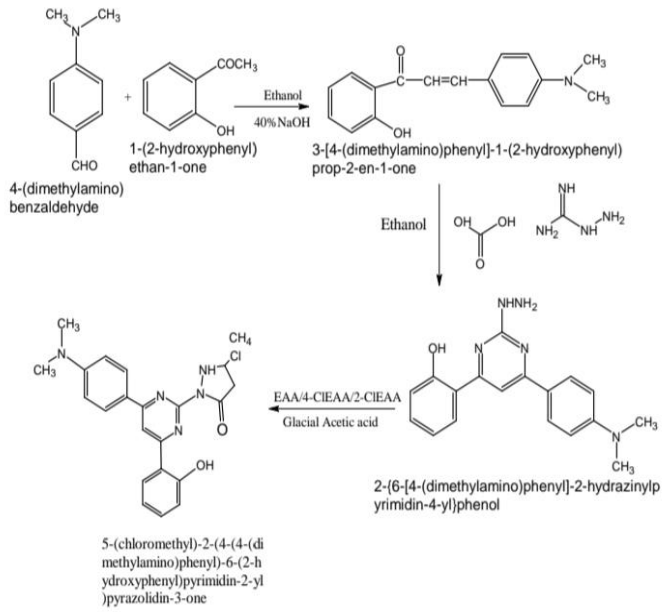


Fig:6

PYR-42-(4-(4-(dimethylamino)phenyl)-6-(2hydroxyphenyl)pyrimidin-2-yl)-5-methylpyrazolidin-3-one **Reaction time: 3hrs Colour and appearance:** yellow **Solubility:** soluble in chloroform **Reaction time: 3hrs Recrystallization solvent:** ethanol **Solvent system:** Ethyl acetate: Methanol (8:2) **Identification and characterization: IR (KBr):** Cm-1= 1686.84(C=N;Str), 2919.78(C-H;Str), 1341.57(C-H;Bend), 1610.5,1567.05,1515.91,1475.59(C=C;Str), 743.39(C-H; Bend), 1153.68(C-N;Str),1367.57(C-O;Str),1194.92(OH;Be

PYR-5 4-chloro-2-(4-(4-(dimethylamino)phenyl)-6-(2hydroxyphenyl)pyrimidin- 2-yl)-5-methylpyrazolidin-3-one **Colour and appearance:** pale yellow

Solubility: soluble in chloroform **Reaction time: 3hrs Recrystallization solvent:** ethanol **Solvent system:** Ethyl acetate: Methanol (8:2) **Identification and characterization: IR (KBr):** Cm-1= 1671.85(C=N;Str), 2791.88(C-H;Str), 1341.14(C-H;Bend), 1610.11,1566.69,1515.45,1479.36(C=C;Str), 744.52(C-H; Bend), 1151.43(CN;Str), 1366.16(C-O;Str), 1193.13(OH;Bend), 809.58(C-Cl, Str**) HNMR** :ppm= 1.25(d, 3H, CH), 1.92(s, 1H, NH), 2.56(s, 6H, -N-CH_3), 2.863.05(m, 1H, CH), 3.92(d, 1H, OH), 6.74(d, 2H,Ar-CH), 6.92 (d, 1H, Ar-CH),7.05 (m,1H, Ar-CH),7.48(m, 1H, Ar-CH), 7.83-7.85(m,3H,Ar-CH), 7.9(s, 1H, CH)

PYR-6 5-(chloromethyl)-2-(4-(4(dimethylamino)phenyl)-6-(2- hydroxyphenyl)pyrimidin-2-yl)pyrazolidin-3-one **Colour and appearance:** pale yellow **Solubility:** soluble in chloroform **Reaction time: 3hrs Recrystallization solvent:** ethanol **Solvent system:** Ethyl acetate: Methanol (8:2) **Identification and characterization:**

HNMR : ppm= 1.25(s, 1H, NH), 3.12(s, 6H,30N), 3.49(m, 1H,CH), 5.3(s,1H,OH), 3.95,3.98(m,2H, -CH_2), 6.7(d, 2H, Ar-CH), 6.9(d, 1H, Ar-CH), 7.18(m,1H, Ar-CH), 7.30(m,1H,Ar-CH), 7.91(m, 3H, Ar-CH),10.97(s,1H,-CH=)

C13:ppm= 21.58(CH_3), 39.05(Ter-N), 42.09(C-H), 59.25(CH_2), 98.90(CH_2),114.94(Ar-C-H) 116.14(Ar-C-H), 118.15(C-H), 127.46(Ar-CH), 130.16(Ar-C-H), 151.19(C-H), 154.54(C-H), 160.49(-C=), 163.58(-C=), 164.18(C=O)

RESULTS AND DISCUSSION

ANTIBACTERIAL ACTIVITY OF THE SYNTHESIZED COMPOUNDS:

S.No	Compound Code	Gm +Ve				Gm –Ve	
		S.aureus		*B. Pimilis*		*E.Coli*	
		50 µg/ml	100 µg/ml	50 µg/ml	100 µg/ml	50 µg/ml	100 µg/ml
1	TZ-1	_	10	_	_	10	12
2	TZ-2	12	17	14	18	17	19
3	TZ-3	_	_	_	_	10	13
4	TZ-4	_	_	_	10	_	_
5	TZ-5	_	_	_	10	_	_

6	TZ-6	_	_	11	12	_	_
7	TZ-7	11	_	12	14	16	18
8	TZ-8	_	17	17	18	11	12
9	PYR-1	_	11	_	_	13	16
10	PYR-2	10	12	_	_	_	_
11	PYR-3	10	11	14	10	12	15
12	PYR-4	_	12	_	_	_	_
13	PYR-5	_	_	10	11	_	_
14	PYR-6	_	14	_	_	15	_
Control	Ethanol	_		_		_	
Standard	Streptomycin (100 µg/ml)	18		20		20	

ANTIBACTERIAL STUDIES OF THE SYNTHESIZED COMPOUNDS:

Antibacterial activity of TZ-2

Compound showed remarkable activity when compared with standard.

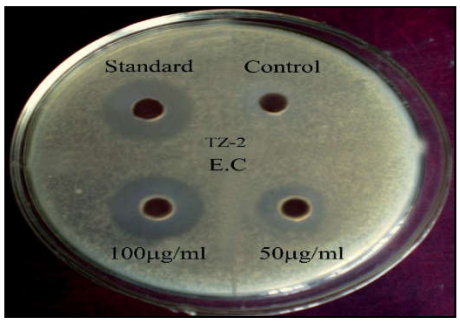


Fig:7 Zone of inhibition of Escherichia coli

Zone of inhibition of Bacillus pimilis **Zone of inhibition of S.Aureus**

Figure: 8 ANTI BACTERIAL STUDIES OF TZ-2

Antibacterial activity of PYR-3

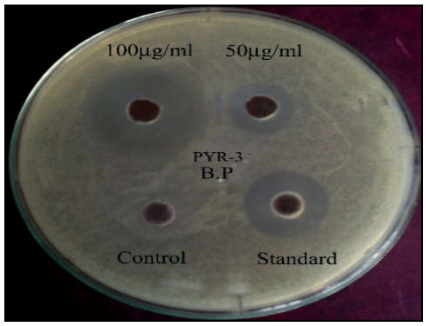
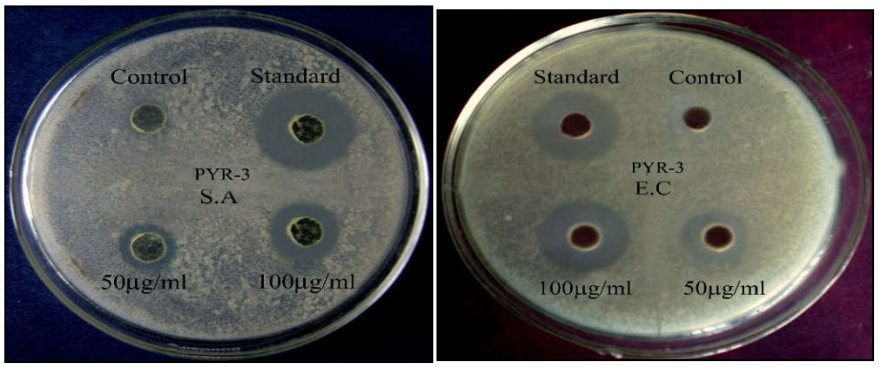


Fig:9 Zone of inhibition of *Bacillus pimilis*



Zone of inhibition of *S.Aureus*Zone of inhibition of *Escherichia coli*

Figure: 10 ANTI BACTERIAL ACTIVITY OF PYR-3

TZ-2 and PYR-3 are effective against both Gram +*ve*and Gram –*ve* ,TZ-4 and TZ-5 is found have moderate activity against both Gram +*ve*and Gram –*ve*and TZ-3and PYR-1 showed activity against E.coli. Other compound every having insignificant activity when compared to standard Streptomycin.

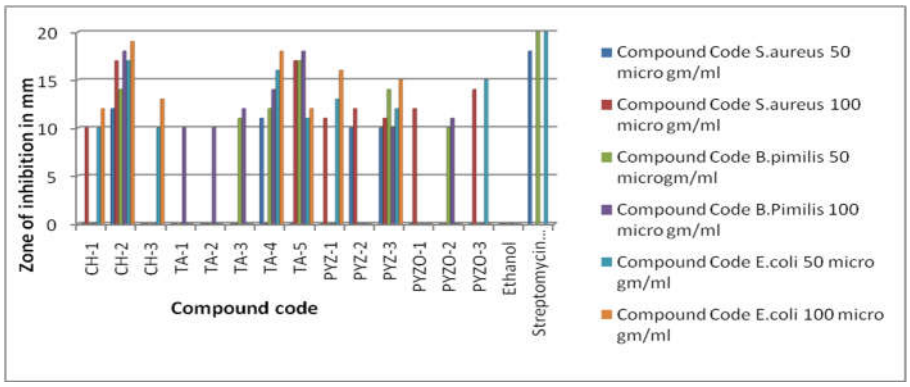


Figure:11 Antibacterial activities of synthesized compounds

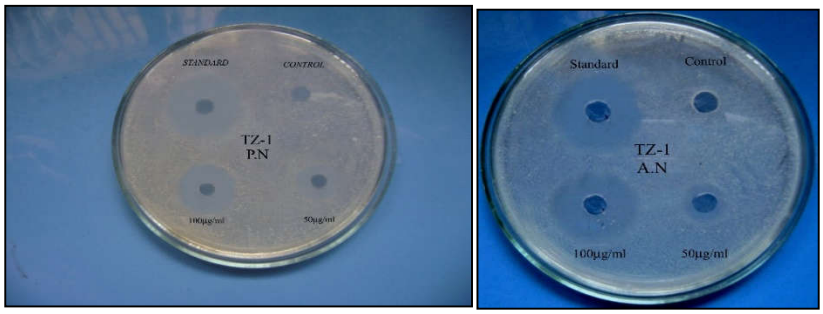
ANTIFUNGAL ACTIVITY OF THE SYNTHESIZED COMPOUNDS:

S.NO	COMPOUND CODE	*Aspergillus niger*		*Penicillumnotatum*	
		50 µg/ml	100 µg/ml	50 µg/ml	100µg/ml
1	TZ-1	15	17	12	20
2	TZ-2	–	–	–	–
3	TZ-3	–	–	14	16
4	TZ-4	11	–	–	–
5	TZ-5	–	–	11	13
6	TZ-6	–	–	9	11
7	TZ-7	–	–	17	19
8	TZ-8	12	–	11	13
9	PYR-1	8	10	13	17
10	PYR-2	–	–	9	11
11	PYR-3	–	–	8	13
12	PYR-4	–	10	–	11

Antifungal activity of the synthesized compounds

13	PYR-5	–	–	9	11
14	PYR-6	12	14	8	10
Control	Ethanol				
Standard	MICONAZOLE NITRATE(50µg/ml)	23		20	

ANTIFUNGAL STUDIES OF THE SYNTHESIZED COMPOUNDS



Zone of inhibition of *P.notatum*Zone of inhibition of *A.niger*

Figure: 12 ANTI FUNGAL ACTIVITY OF TZ-1

Zone of inhibition of*A.niger*Zone of inhibition of *P.notatum*

Figure:13 ANTI FUNGAL ACTIVITY OF PYR-1

TZ-1 and PYR-1 and PYR-6 are effective against both organisms, *TZssss*-4 and TZ-5 is found have moderate activity *and* TZ-4, TZ-6 and PYR-3&5 showed activity against *pencilliumnotatum*. Other compound every having insignificant activity when compared to standard Streptomycin

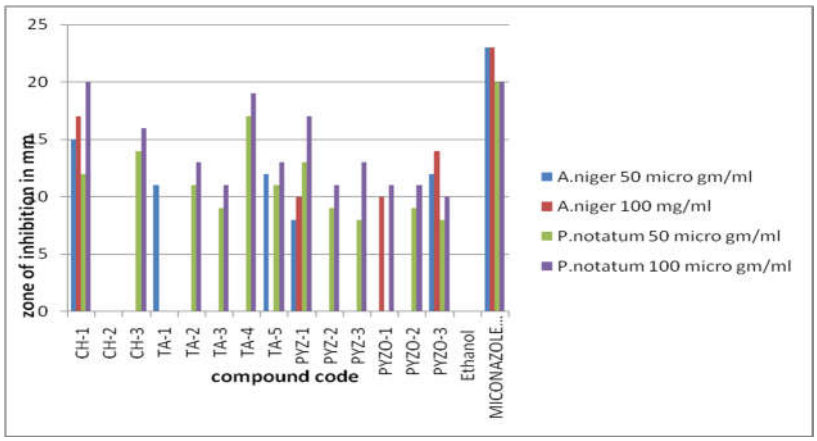


Fig:14 Antifungal activities of synthesized compounds

CONCLUSION

TETRAZOLES AND PYRIMIDINES:

• Several biological activities of tetrazole and pyrimidine derivatives like antibacterial, antifungal, Antitubercular, antidepressant activity, anti-cancer, anti-inflammatory, and antihypertensive are current trends of Tetrazoles and pyrimidine research.

• Materials and methodology deals with schemes and synthesis**.** 5-amino tetrazoles are prepared from Aminoguanidine bicarbonate and further derivatives are synthesized. 5-Amino tetrazole reacts with acetyl chloride to form 5-acetyl tetrazole which further reacts with different aldehydes to form chalcones. 5-Amino tetrazole reacts with different aldehydes to form Schiff-base, to this thioglycolic acid is reacted thereby it formed tetrazole containing thiazole nucleus derivatives.

• O-hydroxy acetophenone reacts with an aromatic aldehyde in presence of sodium hydroxide and ethanol to form Chalcones. Chalcones then reacted with aminoguanidine bicarbonate to form pyrimidine containing molecule and further derivatives are synthesized

• the results of synthesized compounds and their biological evaluation.TZ-2 is effective against both Gram +*ve* and Gram –*ve* , TZ-4 and TZ-5 is found to have moderate activity against both Gram +*ve*

PYR-3is effective against both Gram +*ve* and Gram –*ve,* TZ-4 and TZ-5 are found to have moderate activity against both Gram +*ve* and Gram –*ve,* and PYR-1showed activity against E.coli. Other compounds are having insignificant activity when compared to standard Streptomycin. And few compounds are screened for anti-fungal activity at concentrations of 50 and 100µg/ml. PYR-1 shows moderate activity on both *Penicillium notatum and Aspergillus niger* compared with standard miconazole nitrate.

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