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Research Paper

Synthesis, Characterization and Anti-Microbial Activity of Novel Pyramidine Derivatives

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Abstract

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. A pyrimidine has many properties in common with pyridine, as the number of nitrogen atoms in the ring increases the ring pi electrons become less energetic and electrophilic aromatic substitution gets more difficult while nucleophilic aromatic substitution gets easier. Chalcones react with aminoguanidine to give intermediate compounds which on further reacts with substituted ketones to give Pyramidine derivatives. A total of 6 compounds were synthesized from one scheme and they were recrystallized by appropriate solvents. They were identified and characterized by various spectral methods. In the present study, all synthesized compounds tested for anti bacterial activity and anti-fungal activity. They shown significant activity when compared with standard drug Streptomycin and Miconazole respectively.

Keywords: Pyramidines, Characterization, Streptomycin, Miconazole, Anti-microbial activity.

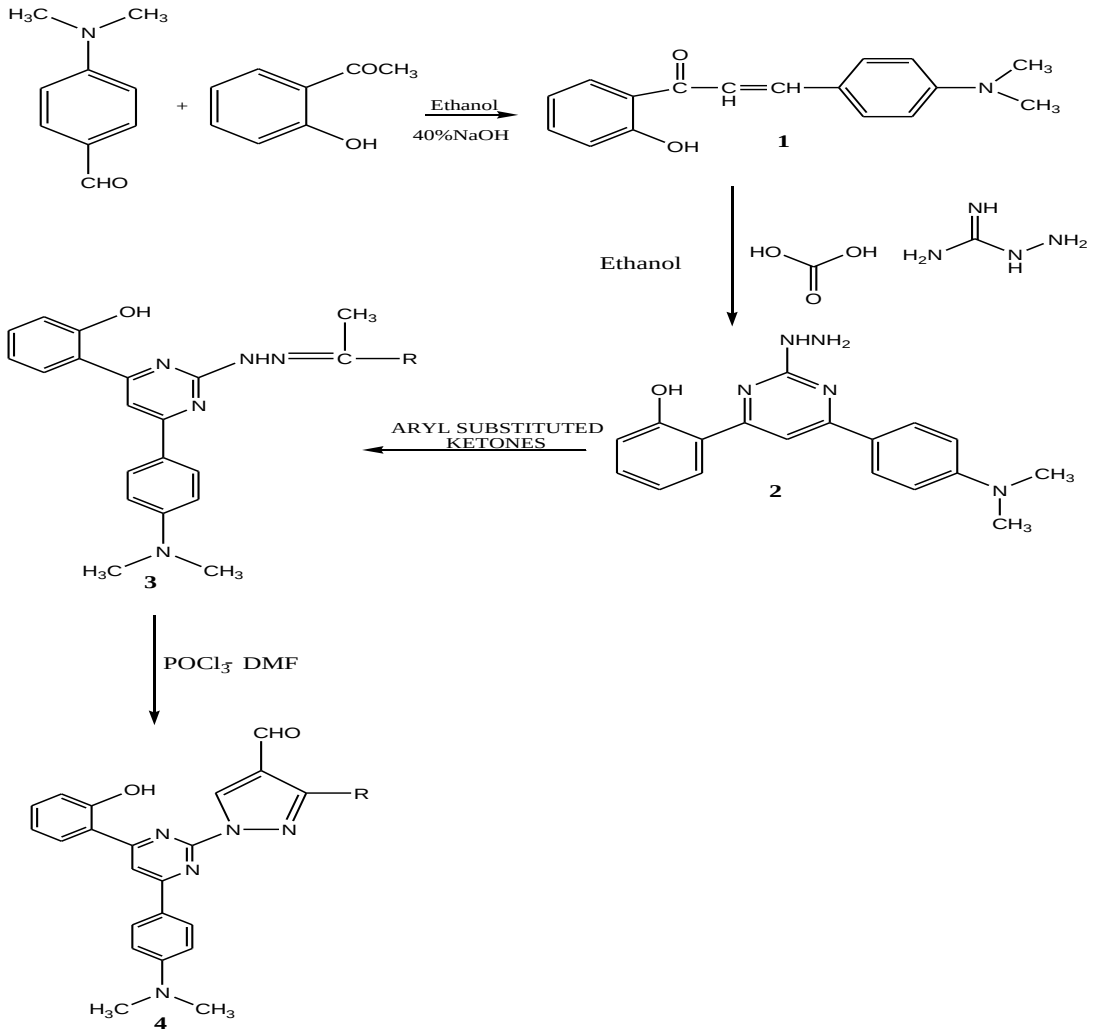
INTRODUCTION

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.[1] Three nucleobases found in nucleic acids, cytosine (C), thymine (T), and uracil (U), are pyrimidine derivatives. A pyrimidine has many properties in common with pyridine,[2] as the number of nitrogen atoms in the ring increases the ring pi electrons become less energetic and electrophilic aromatic substitution gets more difficult while nucleophilic aromatic substitution gets easier[3-4]. Reduction in resonance stabilization of pyrimidines may lead to addition and ring cleavage reactions rather than substitutions.[5-6] Pyrimidine derivatives possess very interesting pharmacological and biological properties and are reported to exhibit variety of biological activities like antibacterial, antifungal and anticonvulsant, analgesic, anti-inflammatory, antihelmentic, sedative, hypnotic, antispasmodic,[7-10] local anaesthetic Antitubercular, antihistaminic, antioxidant and anticancer activity.[11-14]

MATERIALS AND METHODS

Melting points of the synthesized compounds were determined in open capillary tubes and were uncorrected.IR spectra were recorded on BRUKER FT-IR spectrometer using ATR. ^{1}HNMR spectra of the compounds in deuteriated dimethyl sulfoxide and $CDCl_3$ was recorded on Bruker Av 400 spectrometer. Mass spectra were recorded on LCMS QP 5000 Schimadzu.Thin layer Chromatography was performed using pre-coated aluminium plates, coated with silica gel GF_{254}[E.Merck].Ethyl acetate:Methanol in the ratio of 3:2 was used as the eluent. The spots were visualized in the UV/Iodine chamber.

EXPERIMENTAL WORK



SCHEME -1

STEP-1: Synthesis of 5-amino tetrazole (1)

Thiele method

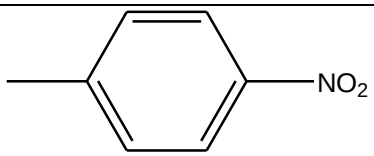
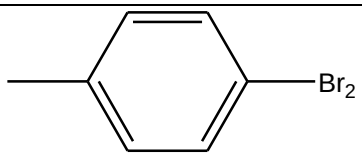
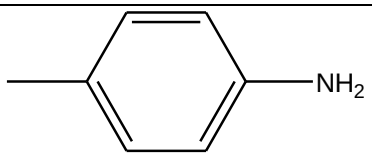
34g (0.25mol) of amino guanidine bicarbonate is added to 217ml of 15% nitric acid (0.561mol), and mixed until evaluation of carbon dioxide is stopped and resulted amino guanidine nitrate is fully dissolved in solution. Yellow transparent solution is diazotised by slow addition of 17.2g sodium nitrite (0.25mol) in 35ml of water. Addition is accompanied by stirring, and temperature during all addition period is kept between 20-25^{0}c by using water bath if needed. After completion of reaction the diazotisation mixture is allowed to sit for 20 min at room temperature. And 29g of sodium carbonate is added (or 46g of sodium bicarbonate). Mixture is then heated on a water bath and refluxed for 4hrs. The solution is then neutralized by 30% sulphuric acid to ph=4, cooled to room temperature and allowed to sit over night. The precipitated crystals of 5-amino tetrazole monohydrate are filtered, washed with cold water and dried. Yield is about 70-74% based on amino guanidine.

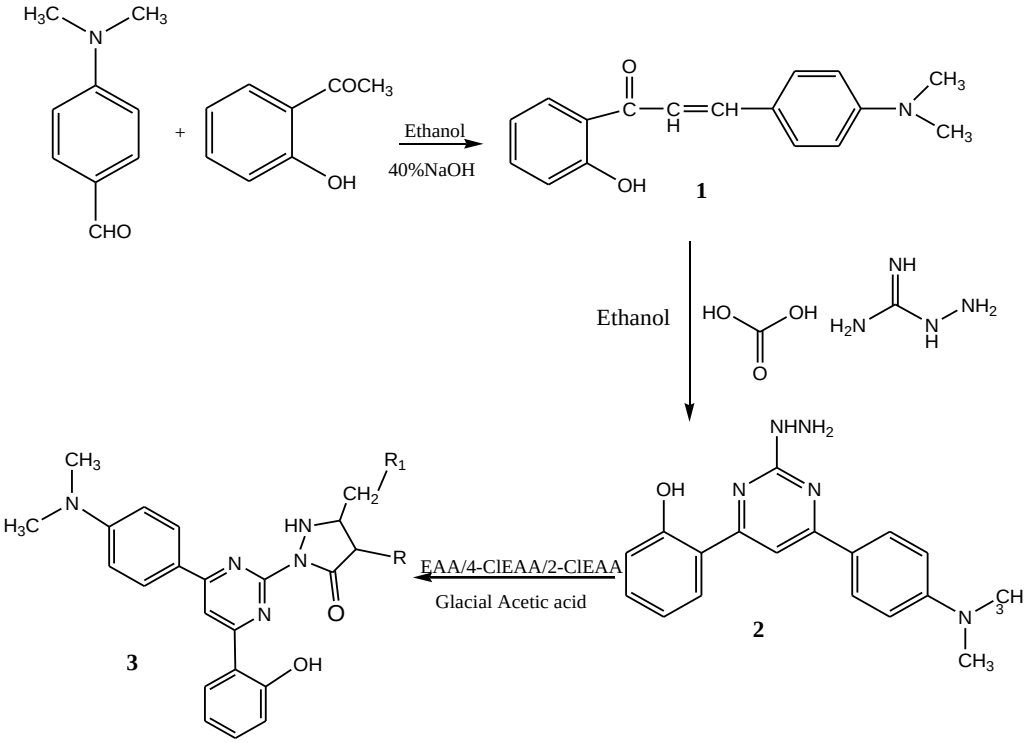
STEP-2: Synthesis of N-Substituted benzylidene-1H-tetrazol-5-amine (2)

To the mixture of (0.01mol) of compound was added (0.01mol) substituted benzaldehydes and 20ml of ethanol taken in RBF and was refluxed on a water bath for 2hrs. The resultant solution was cooled; the solid that separated was filtered and recrystallized from pet ether.

STEP-3: Synthesis of 2,3-dihydro-2-substituted phenyl-3-(1H tetrazoll-5-yl)thiazol-4-one (3)

To mixture of compound, 8ml of ethanol (0.2mol), 0.1g of zinc chloride and 0.4ml (0.004mol) of thioglycolic acid was added and the mixture was refluxed for 8hrs. After that the solid was separated out.

S.NO	CODE	R
1.	PYR-1	
2.	PYR-2	
3.	PYR-3	



S.NO	CODE	R	R_1
1.	PYR-4	-	H
2.	PYR-5	Cl	H
3.	PYR-6	-	Cl

SCHEME-2

RESULTS AND DISCUSSION

A total of **6** compounds were synthesized from two schemes and they were recrystallized by appropriate solvents. They were identified and characterized by various spectral methods. All the compounds were tabulated and characterization data was tabulated in **Tab.1.**

IR (KBr): Cm^{-1}: 3057.19(C-H;Str.), 1666.16(C=N;Str.), 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.)

IR (KBr): Cm^{-1}: 2999.77(C-H;Str.), 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.).

IR (KBr): Cm^{-1}: 2982.63(C-H;Str), 1569.41,1515.91,1478.60(C=C;Str), 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)

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; Bend)

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(C-N; Str.), 1366.16(C-O; Str.), 1193.13(OH; Bend), 809.58(C-Cl, Str.)

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(C-N; Str.), 1366.16(C-O; Str.), 1193.13(OH; Bend), 809.58(C-Cl, Str.)

Table 1: Characterization data of Synthesized compounds.

Compound Code	Mole. Formula	Mole. Weight. (g/mole)	Melting Point (^{0}C)	% Yield
PYR-1	$C_{29}H_{23}N_5O_4$	505.52	230-238	54.24
PYR-2	$C_{29}H_{23}BrN_4O_2$	539.42	194-198	60.36
PYR-3	$C_{29}H_{25}N_5O_2$	475.54	210-216	58
PYR-4	$C_{22}H_{23}N_5O_2$	389.45	154-158	62.12
PYR-5	$C_{22}H_{22}$ Cl N_5O_2	423.9	144-150	53.12
PYR-6	$C_{22}H_{22}$ Cl N_5O_2	423.9	200-208	49.59

Anti-bacterial activity of synthesized compounds

A total of **6** compounds were synthesized from one scheme and they were recrystallized by appropriate solvents. They were identified and characterized by various spectral methods. Synthesized Pyrimidine derivatives were evaluated for Anti-bacterial activity with cup plate method at concentrations of 50µg/ml and 100µg/ml .Standard was taken as streptomycin Control was taken as ethanol. The results were tabulated in **Tab.2.** PYR-3 is effective against both Gram $^{+ve}$ and Gram $^{-ve}$, PYR-1 and PYR-2 are found to have moderate activity against both Gram +*ve* and Gram –*ve* where as PYR-1 showed activity against E.coli. Other compounds having insignificant activity when compared to standard Streptomycin.

Table 2: Anti-bacterial activity of 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.	PYR-1	_	11	_	_	13	16
2.	PYR-2	10	12	_	_	_	_
3.	PYR-3	10	11	14	10	12	15
4.	PYR-4	_	12	_	_	_	_
5.	PYR-5	_	_	10	11	_	_
6.	PYR-6	_	14	_	_	15	_
Control	Ethanol	_		_		_	
Standard	Streptomycin (100 µg/ml)	18		20		20	

(*) significant zone of inhibition Bore size: 8 mm.

Anti-fungal activity of synthesized compounds

PYR-1 and PYR-6 are effective against both organisms was found to have moderate activity and PYR-3& 5 showed activity against *pencillium notatum*. Other compound every having insignificant activity when compared to standard Miconazole.

Table 3: Anti-fungal activity of the synthesized compounds.

S.NO	Compound code	*Aspergillus niger*		*Penicillum notatum*	
		50 µg/ml	100 µg/ml	50 µg/ml	100µg/ml
1.	PYR-1	8	10	13	17
2.	PYR-2	-	-	9	11
3.	PYR-3	-	-	8	13
4.	PYR-4	-	10	-	11
5.	PYR-5	-	-	9	11
6.	PYR-6	12	14	8	10
Control	Ethanol				
Standard	Miconazole (50µg/ml)	23		20	

CONCLUSION

We have described simple and efficient protocol for the synthesis of novel pyramidine derivatives with good yields. The schemes include Chalcones react with aminoguanidine to give intermediate compounds which on further reacts with substituted ketones to give 6 Pyramidine derivatives. A total of **6** compounds were synthesized from one scheme and they were recrystallized by appropriate solvents. They were identified and characterized by various spectral methods. In the present study, all synthesized compounds tested for anti bacterial activity and anti-fungal activity. They shown significant activity when compared with standard drug Streptomycin and Miconazole respectively. Among the synthesized compounds some of the compounds possess moderate to promising activity when compared with standard. All the compounds show dose dependent activity.

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