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Synthesis and screening of antimicrobial activity of N-(3 cyano - 6phenothazie -10yl-4-phenyl –pyridine -2yl) actamide derivaties

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ABSTRACT

Phenothiazin and its derivatives posses diverse type of biological properties such as antiviral, antiphrastic, antiparkins, etc. They were synthesized by using chalcones of N – acetylphenothiazine. And the structures of these compounds were confirmed by IR, NMR (1H analysis. The newly synthesized compounds were also evaluated for antimicrobial activity against variety of bacterial Strains and some of these compounds have shown significant antibacterial and antifungal activities.

KEYWORDS

Chalcones;
Phenothiazines;
IR;
NMR antibacterial;
Antifungal activities.

INTRODUCTION

Among the variety of heterocyclic that can be explored developing pharmaceutical important molecule such as indole derivative, oxyindole derivative, triazole pyri. Derivative, cyanopynidine derivative plays and important role in medicinal chemistry. Most of the heterocyclic compounds posses broad spectrum of biological activity such as potential cardiovascular drug, antiviral, antidepressant drug, bactericidal, etc.

The existence of thiazole ring system in nature was first demonstrated by Williams[1] et al. In 1935 while working on Vitamin B_1, thiamine. It is also present in the well known class of antibiotics, the penicillins[2] and another antibiotic, 4-oxathiazolidine[3]. Recently an antineoplastic cyclic peptide containing fused oxazole-thiazole units has been isolated from the marine tunicate, Lissoclinum patella[4]. In view of these findings, synthesis of bioactive thiazole derivatives developed during the past few decades.

Various 2-acylamino 5-nitrothiazole preparations in the form of gel are useful in treatment of Trichomonas vaginalis infections[5]. Some thiazole carboxylic acid derivatives have been used against variety of fungus and bacterial infections[6-8]. 2-Aryl 3-acylthaizolidines have been found to show anti-inflammatory, analgesic, tranquilizer and antipyretic activities[9], Sing et al.[10] have also reported anti inflammatory activity of some pyrazolyl-thiazole derivatives. In addition to this, some fluorinated thiazolo [3,2] pyrimidines and imidazothiazoles have also been reported as analgesic and anti inflamatory agents[11,12]. Hayashi[13] et al. have reported insecticidal activity of O,O dimethyl S-[(5-chloro-2 thiazolyl)methyl] phosphorodithioate. 4,5 Bis(d-methoxy phenyl) 2-(trifluoromethyl) thiazole have exhibited antiplatelet activity at very low concentration[14]. 2-(2 Amino 4-thiazolyl methyl) benzothiazoles or benzoxazoles and their pharma-cologically accept-

able salts have been found to inhibit lipoxygenase and are useful as allergy inhibitors[15].

Phenothiazin and its derivatives posses diverse type of biological properties such as antiviral, antiparacitic, antiparkins, etc. In this project we are developing some new derivatives from phenothiazin and screened for their biological activities.

Phenothizine derivateisv are prepared by starting with phenothazine. Intially Acylation of phenothiazin x carried by using phenothazine and acetyl chloride under specific reacto condition, then acyl phenothazine formed subjected to aldol condensation type of reaction to form chalcone of phenothaine. Chalcone of phenothazine is stable and subjected to cyclasition using dimethyl nitril or nalonitrile in dmf as solvent cyclised compound containg

EXPERIMENTAL SCHEME FOR THE REACTION

General procedures

All the melting points were determined on a Cintex melting point apparatus and are uncorrected. The IR – spectra (νmax cm–1) were recorded on Perkin – Elmer783 Spectrophotometer and NMR (1H and 13C) spectra in TFA (Chemical shifts in δ ppm) on Bruker AMX500 MHz using TMS as an internal standard, and mass spectra on Jeol D-300spectrometer. Elemental analysis was performed on Carlo Erba – 1108 analyzer.1) Acylation of phenothiazin2) Aldol condensation reaction3) Reaction malan nitrate:4) Cyclisation:5) For acylation of primary amine group from different acyl chloride finally hydrazone derivative formation.

Phenothiazine

(A) Acylation of phenothiazin

Take 0.01 mole phenothiazin add 10 ml of 2N NaoH stir for 45 min at 30 0c, Then add 0.02 mole acetyl chloride at 0-50C, dropwise stir reaction mixture at room temperature for 3-4 hours. Keep reaction mixture overnight, Solid pricppited out filter and recrystalised form benzene sutiable solvent.. m.p. 197 – 98ºC (reported15 m.p. 198ºC); IR (KBr) cm–1: 1650 (CO), 1450 (C – N), 1580 (C = C of aromaticring); 1H NMR (CDCl3 – d6): δ 7.00 –7.48 (m, 8h, Ar – H), 2.60 (s, 3H, COCH3);

(B) Reaction with different aldehydes

Take 0.1 mole N-acetyl phenothiazin in round bottam flask add 10 ml of methyl alcohol and 0.1 mole benzaldehyde in presence of 2% NaOH reflux for 10-12 hours. Concentrate the solution so as to remove methanol to its half pour into crushed ice extract with suitable solvent evaporate to get product. Recrystrlise from suitable solvent. m.p. 168ºC; IR (KBr) cm–1: 1650 (CO), 1620 (CH = CH), 1575 (C = C aromatic ring) cm-1; 1H NMR (CDCl3 – d6): δ 8.61 (d,1H, = CH – Ar), 7.00 – 7.67 (m, 12H, Ar – H), 6.71 (d, 1H, COCH =)

(C) Reaction malan nitrate

Take 0.1 mole of chalcon in chloroform as solvent in round bottom flask above add malano nitrile and ammonium acetate dissolve in ethyl alcohol and reflux for 6 hours and cool pour in ice containing conc. HCl solution. to get white participate of product. m.p. 197ºC; 1H NMR (DMSO – d6): δ 8.41 (s, 2H, NH2, D2O exchangeable), 7.00 – 8.00 (m, 13H, Ar – H).

(D) Cyclisation

Take 0.1 mole of product of step 3 in toluene in anhydrous and 0.1using AlCl3 as lewis acid and acetyl nitrile reflux for 8 hour at temperature 1500C to 1600C, cool pour in ice cold water, filter and dry. Recrystazie fro m benzene . M.p. 213ºC; 1H NMR (DMSO – d6): δ 3.72 (s, 3H,OCH3), 8.19 (s, 2H, NH2, D2O exchangeable), 7.00 – 8.10 (m, 12H, Ar – H).

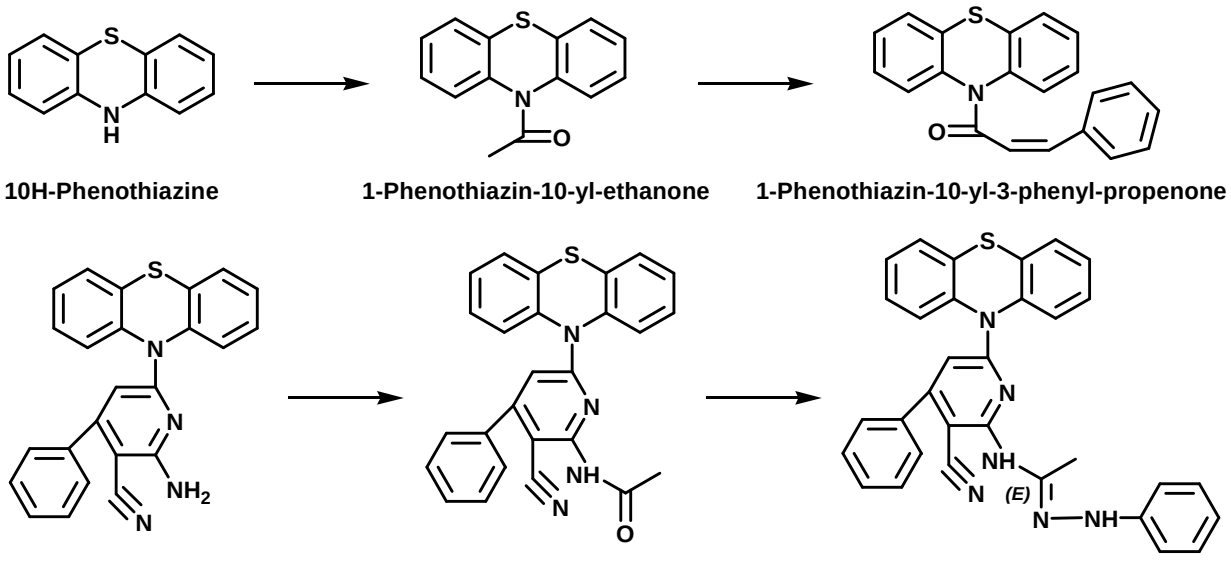
(E) Preparation of amide derivative

Preparation of amide derivative take 0.1 mole of intermediate 4 to the solution of toluene 0.2 mole add acetyl chloride and stir for 3 hours at 400C, cool and pour ice cold water, filter and dry recytalize from ethanol. M.p. 237 ºC; 1H NMR (DMSO – d6): δ 3.11 [s, 6H, N(CH3)2], 8.49 (s, 2H, NH2, D2O exchangeable),7.00 – 8.10 (m, 12H, Ar – H). 13C NMR : 40.3 [N(CH3)2], 59.6 (OCH3), 115.9 (- CN), 130 – 140(Ar – C), 152.9 (C5, >C = N), 178.9 (C2, N – C – N);

(F) Preparation of hydrazine derivative

Take 0.1 mole of intermidate 5 in 10ml acetonitrile as solvent in round bottam flask add 0.2 ml of hydrazine hydrochloride stirred at room temperature for one hour then heat at 400C for 2 hours, cool, filter in ice

and dry. Recrystallize from ethanol. M.p. 254 ºC; 1H NMR (DMSO – d6): δ 3.77 (s, 3H,OCH3); 8.46 (s, 2H, NH2, D2O exchangeable), 7.00 – 8.00 (m, 11H, Ar – H), 10.77 (s, 1H, OH, D2O exchangeable);



Reagents **Step 1 NaoH, acetyl chloride, strring at room temp.**
Step 2 Methyl alcohol, benzaldehyde, NaoH,
Step 3 Malonitrile, etylalcohol, ammonium acetate
Step 4 Toulene, acetonitrile, lewis acid
Step 5 Acetyl chloride
Step 6 Phenyl hydrazine

Scheme 1

TABLE 1 : Observation

Aldehyde	Physical constant in ^{0}C				
	I-I	I-II	I-III	I-IV	I-V
Benzaldehyde	198	160	207	197	210
3-nitrobenzaldehyde	205	190	230	207	217
P-hydroxy benzaldehyde	210	170	225	205	205
4-chlorobenzaldehyde	230	175	235	210	225
Anisaldehyde	240	180	238	212	220

TABLE 2 : Antibacterial activity of phenothazine derivative

Bacterial	Benzaldehyde	3-nitrobenzaldehyde	P-hydroxy benzaldehyde	Ciprofloxacin	Cloxacillin
G (+)	**In mm**	**In mm**	**In mm**	**In mm**	**In mm**
1. Staphylococcus Epidermidis	19	8	12	10	10
2. Staphylococcus oureus	17	12	12	8	11
3. Bacillus paludi	18	17	14	11	11
4. Bacillus subtilis	14	16	11	10	11
G (-)					
1. Escherichia Coli	13	10	14	7.5	5.5
2. Pseudomonus aeruginosa	14	12	13	6	5.5
3. Shigella flaxinely	13	12	12.5	5.5	8
4. Enterobacter aer genes	12	14	11	6	7

TABLE 3 : Antifungal activity of phenothazine derivative

Fungus	Benzaldehyde	3-nitrobenzaldehyde	P-hydroxy benzaldehyde	Penicil	Tetrax
1. Candida albicans	15	16	7	15	14
2. Aspergillus Fumigatus	16	18	12	11	4
3. Aspergillus niger	15	12	09	09	5

CONCLUSION

A new series of antimicrobial agents was designed and by visualizing the antimicrobial data itcould be observed that compounds of the series showed activity ranging from 15µgm/mL to20 µgm/mL. The standard

drugs used for comparision were Ciprofloxacin, Cloxacillin andGentamycin. By visualizing the antimicrobial data it could be observed that some of thecompounds possess significant activity.

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