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Journal of Chemical and Pharmaceutical Research

J. Chem. Pharm. Res., 2010, 2(3):691-698

ISSN No: 0975-7384
CODEN(USA): JCPRC5

Synthesis and antimicrobial activity of some novel 2-amino thiazole derivatives

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ABSTRACT

A series of 2-aminothiazoles derivatives have been synthesized and tested for in vitro antibacterial and antifungal activity on different microorganisms. Syntheses have been carried out following simple methodology in excellent isolated yields. The structure and purity of the original compounds were confirmed by IR, NMR, and elemental analysis. All compounds were tested for antibacterial and antifungal activity against Bacillus subtilus (+ve), E. coli (-ve), albicans (+ve) and Aspergillus niger (-ve) on concentration of 50 and 100µg/ml by Disk-diffusion method. These preliminary results indicate that some of compounds are exhibiting good activity.

Key words: Thiazole, 2-Chloro-N-(thiazol-2-yl) acetamide, Antimicrobial activity.

INTRODUCTION

The rapidly expanding population of immunocompromised patient results in a corresponding increase of diseases cause by bacteria, fungi and other yeast. Infection caused by these microorganisms pose a serious challenge to the medical community and highlight the importance and urgent need for new, more potent and selective non-traditional antimicrobial agent. The incidence of bacterial infections has increased dramatically in recent years [1]. The widespread use of antibacterial and antifungal drugs and their resistance against bacterial and fungal infections has led to serious health hazards. The resistance of wide spectrum antibacterial agents has prompted discovery and modification towards new antifungal and antibacterial drugs [2, 3].

Thiazole derivatives are an important class of heterocyclic compounds. They occupy an important position in medicinal chemistry, presenting a wide range of bioactivities. As medicines, many of them display including antibacterial & antifungal [1, 2], anti-HIV [3], hypertension [4], anti-inflammatory [5], anticancer [6], anti-convulsant [7], antidepressant and tubercular activities [8]. Thiazoles and their derivatives have attracted continuing interest over the years because of their varied biological activities. Thiazole, particularly the 2-amino thiazole nucleus have been incorporated into a wide variety of therapeutically interesting candidates.

Recent studies have shown the synthesis of some new thiazole candidates as adenosine receptor antagonists and more recently 2-aminothiazole analogues reported as potential neuroprotective agents for the treatment of neurological diseases and modulators of transcriptional repression for treatment of Huntington's disease.

Prompted by the observed biological activities of the above mentioned derivatives and in continuation of our ongoing studies on novel biologically active molecules, we have designed and synthesized some novel 2-aminothiazoles derivatives as potential antibacterial agents.

EXPERIMENTAL SECTION

Antibacterial activity: [9, 10]
The synthesized compounds were evaluated for the in-vitro antibacterial activity against microorganism strains *Bacillus subtilus* (MTCC-441), *E.coli (*NCTC 10418*)* by Cup-plate agar diffusion method using nutrient agar.

Antifungal activity: [9, 10]
The compounds were also tested for the in-vitro antifungal activity against C*andida albicans* (ATCC10231), *Aspergillus Niger* by cup plate method at 50µg/ml and 100µg/ml**.** concentration of test compounds by Cup-plate agar diffusion method using Sabouraud-Dextrose agar.

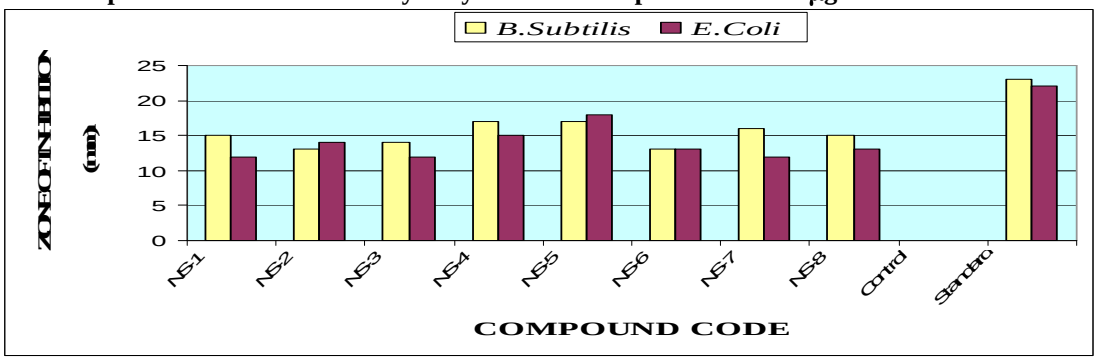
The observed data on the antimicrobial activity of the compounds and control drugs are given in Table 1&2. And graph 1&2

Table No. 1-Antibacterial activity data of synthesized compounds

S. No.	Compounds Code.	Zone of inhibition in mm			
		B. Subtilis (NCIM 2439)		*E. coli (NCIM 2831)*	
		50 µg/ml.	**100 µg/ml.**	**50 µg/ml.**	**100 µg/ml.**
1.	NS-1	15	16	12	14
2.	NS-2	13	14	14	15
3.	NS-3	14	16	12	13
4.	NS-4	17	18	15	17
5.	NS-5	17	20	18	21
6.	NS-6	13	15	13	14
7.	NS-7	16	18	12	15
8.	NS-8	15	17	13	14
9.	Control	-	-	-	-
10.	Standard	**23**	**25**	**22**	**25**

[Control Drug- DMSO, Standard Drug- Ampicillin]

Graph 1: Antibacterial activity of synthesized compounds with 50µg/ml concentration



Graph 2: Antibacterial activity of synthesized compounds with 100µg/ml concentration

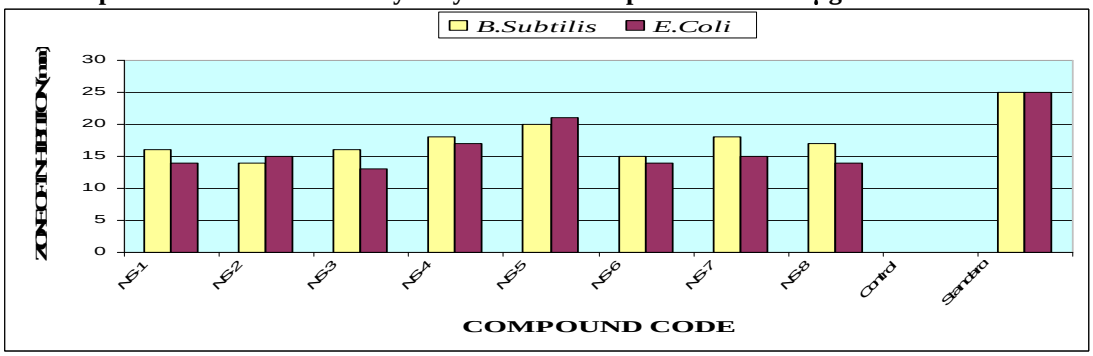
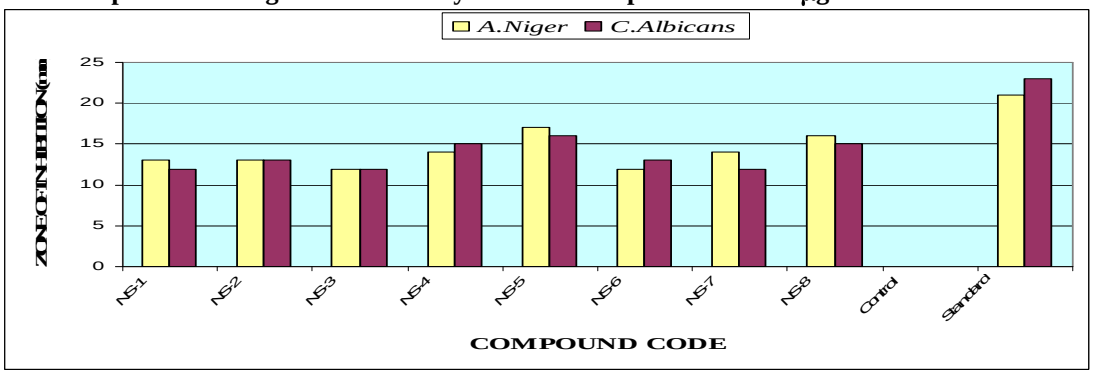


Table No-2- Antifungal activity data of synthesized Compounds

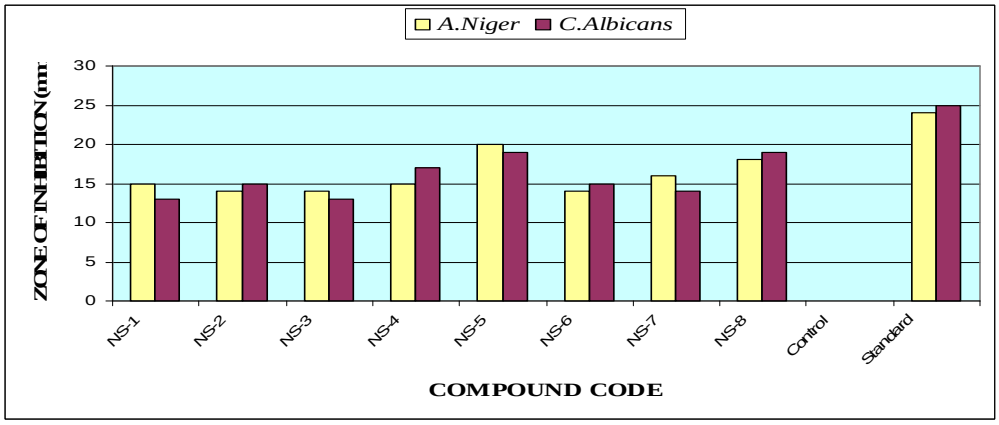
S.No S.No.	Compounds Code.	Zone of inhibition in mm			
		A. Niger		*C. albicans*	
		50µg/ml.	**100 µg/ml.**	**50µg/ml.**	**100 µg/ml.**
1.	NS-1	13	15	12	13
2.	NS-2	13	14	13	15
3.	NS-3	12	14	12	13
4.	NS-4	14	15	15	17
5.	NS-5	17	20	16	19
6.	NS-6	12	14	13	15
7.	NS-7	14	16	12	14
8.	NS-8	18	20	19	21
9.	Control	-	-	-	-
10.	Standard	**21**	**24**	**23**	**25**

[Control Drug- DMSO, Standard Drug- Fluconazole]

Graph 3: Antifungal activities of synthesized compounds with 50µg/ml concentration



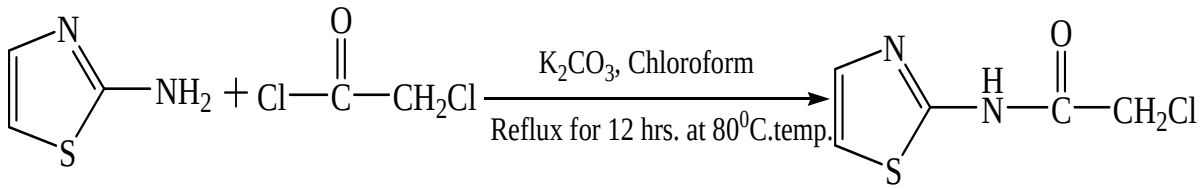
Graph 4: Antifungal activities of synthesized compounds with 100µg/ml concentration



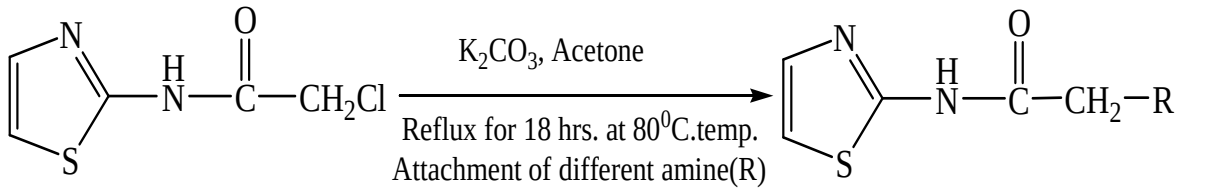
Melting Points were determined in open capillary method and are uncorrected. IR spectra were recorded on Perkinelmer FTIR-spectrophotometer using KBr disc method. The 1H-NMR spectra were recorded on sophisticated multinuclear FT-NMR spectrometer model Avance-II (Bruker) using dimethylsulphoxide-d6 as solvent and tetramethylsilane as internal standard.

Synthetic Scheme

STEP-1:



STEP-2:

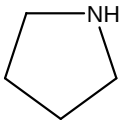
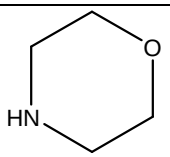
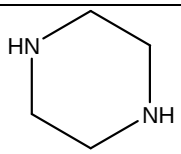
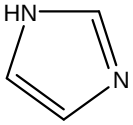
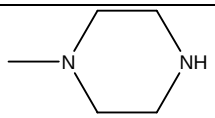
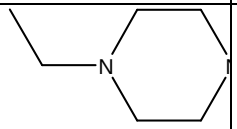
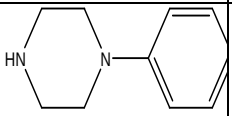
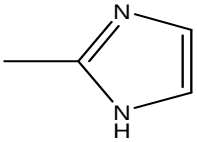


Procedure for synthesis: [11-13]

Procedure for the synthesis of intermediate Compound 2-Chloro-N-(thiazol-2yl) acetamide (NS)

Accurately weighed, 10.0gm (0.1mole) 2-Amino thiazole was dissolved in 75ml of chloroform in a 500ml two neck round bottom flask. To this solution 13.82gm (0.1mol) of anhydrous potassium carbonate was added and placed on water bath for reflux. A dropping funnel was fitted to the RBF and in the dropping funnel a solution of 8.06ml (0.1mol) of chloroacetylchloride in chloroform was taken. A very slow dropwise addition of chloroacetylchloride solution was done. The reaction mixture was refluxed in a water bath at 80^0C for 12 hours. After 12 hours, Excess of solvent and chloroacetyl chlorides was removed by distillation under residue pressure and the residue was washed with aqueous sodium bicarbonate (5%w/v, 30ml) and subsequently with cold water (50ml). The crude product was dried and on recrystallisation from ethanol afforded white crystalline solid 2-Chloro-N-(thiazol-2yl) acetamide.

Table No.3: Physical Constant of Different Synthesized Compound

S.NO.	Code	R	Molecular Formula	Melting point* (±2°C)	% Yield	$^{\bullet}R_f$ Value
1.	NS-1	 Pyrrolidine	$C_9H_{13}N_3OS$	125	65	0.64
2.	NS-2	 Morpholine	$C_9H_{13}N_3O_2S$	105	50	0.52
3.	NS-3	 Piperazine	$C_9H_{14}N_4OS$	118	47	0.60
4.	NS-4	 Imidazole	$C_8H_8N_4OS$	155	52	0.57
5.	NS-5	 n-methylpiperazine	$C_{10}H_{16}N_4OS$	180	48	0.51
6.	N NS-6	 N-Ethylpiperazine	$C_{11}H_{18}N_4OS$	200	50	0.59
7.	NS-7	 N-Phenylpiperazine	$C_{15}H_{18}N_4OS$	170	52	0.55
8.	NS-8	 2-Methylimidazole	$C_9H_{10}N_4OS$	130	42	0.53

Spectral data of intermediate Compound:
Obtained as white crystals, Yield 85.0%; mp 172ºC, IR (KBr, cm^{-1}) : 3315(N-H str.), 2900-3052(Aliphatic &ArC-H str.), 1680(C=O str), 1560(C=C str.), 745(N-Cl str.), 617(ArC-S str.); The ^{1}HNMR(δ, ppm): (DMSO-*d6*, 250 MHz): 7-8 (1H,ArN-CH), 6-7 (1H,ArS-CH), 12.42 (1H,Ar-NH), 4.36(2H,C=O-CH_2),

General procedure for the synthesis of 2-Substituted-N-(thiazol-2-yl)acetamide derivatives (NS 1-8)
A mixture of 2-Chloro-N-(thiazol-2yl) acetamide (NS) (0.006mol) with different amines and K2CO3 (0.012mol) in acetone (100 mL) was refluxed for 15-20 hrs. After 16 Hrs, The solvent was removed by vacuum distillation and the residue was treated with sodium bicarbonate (5%w/v) to remove acid impurities. The residue was washed with water, dried and on recrystallisation from ethanol afforded 2- Substituted - N- (thiazol-2-yl) acetamide derivatives (NS1-8)

Spectral data of different derivatives:
Synthesis of 2-(Pyrrolidin-1-yl)-N-(thiazol-2-yl) acetamide (NS-1)
Yield 65.0%; mp 125ºC, IR (KBr, cm^{-1}) : 3372(N-H str.), 2951-3020(Aliphatic &ArC-H str.), 1677 (C=O str), 1572(C=C str.), 1326.46(C-N str.),622(ArC-S str.);The ^{1}HNMR(δ, ppm): (DMSO-*d6*, 250 MHz): 7-8 (1H,ArN-CH), 6-7 (1H,ArS-CH), 8.47 (1H,Ar-NH), 3.27(2H,C=O-CH_2), 2.32(4H, -CH_2).

Synthesis of 2-Morpholino-N-(thiazol-2-yl) acetamide (NS-2)
Yield 50.0%; mp 105ºC, IR (KBr, cm^{-1}) : 3492(N-H str.), 2912-2955(Aliphatic &ArC-H str.), 1694 (C=O str), 1577(C=C str.), 1331(C-N str.),629(ArC-S str.); The ^{1}HNMR(δ, ppm): (DMSO-*d6*, 250 MHz): 7-8 (1H,ArN-CH), 6-7 (1H,ArS-CH), 8.77 (1H,Ar-NH), 3.37(2H,C=O-CH_2), 3.84(4H, -CH_2).

Synthesis of 2-(Piperazin-1-yl)-N-(thiazol-2-yl) acetamide (NS-3)
Yield 47.0%; mp 118ºC, IR (KBr, cm^{-1}) : 3397(N-H str.), 2949-3050(Aliphatic &ArC-H str.), 1691 (C=O str), 1570(C=C str.), 1329(C-N str.),623(ArC-S str.); The ^{1}HNMR(δ, ppm): (DMSO-*d6*, 250 MHz): 7-8 (1H,ArN-CH), 6-7 (1H,ArS-CH), 12.14 (1H,Ar-NH), 4.18 (-NH in piperazine), 3.30(2H,C=O-CH_2), 2-3(4H, -CH_2).
Synthesis of 2-(1H-Imidazol-1-yl)-N-(thiazol-2-yl) acetamide (NS-4)
Yield 52.0%; mp 155ºC, IR (KBr, cm^{-1}) : 3489(N-H str.), 2905-3039(Aliphatic &ArC-H str.), 1696 (C=O str), 1578(C=C str.), 1333(C-N str.),631(ArC-S str.); The ^{1}HNMR(δ, ppm): (DMSO-*d6*, 250 MHz): 7-8 (1H,ArN-CH), 6-7 (1H,ArS-CH), 8.48 (1H,Ar-NH), 6-8 (imidazole ring), 4.83(2H,C=O-CH_2), 2-3(4H, -CH_2)

Synthesis of 2-(4-Methylpiperazin-1-yl)-N-(thiazol-2-yl) acetamide (NS-5)
Yield 42.0%; mp 130ºC, IR (KBr, cm^{-1}) : 3403(N-H str.), 2955-2959(Aliphatic &ArC-H str.), 1696 (C=O str), 1578(C=C str.), 1332(C-N str.),683(ArC-S str.); The ^{1}HNMR(δ, ppm): (DMSO-*d6*, 250 MHz): 7-8 (1H,ArN-CH), 6-7 (1H,ArS-CH), 12.06 (1H,Ar-NH), 3.97(2H,C=O-CH_2), 2-3(8H, -CH_2), 2.49 (-CH_3 attached to piperazine ring).

Synthesis of 2-(4-Ethylpiperazin-1-yl)-N-(thiazol-2-yl) acetamide (NS-6)
Yield 50.0%; mp 200ºC, IR (KBr, cm^{-1}) : 3380(N-H str.), 2952-3180(Aliphatic &ArC-H str.), 1694(C=O str), 1576(C=C str.), 1330(C-N str.),627(ArC-S str.); The ^{1}HNMR(δ, ppm): (DMSO-*d6*, 250 MHz): 7-8 (1H,ArN-CH), 6-7 (1H,ArS-CH), 12.47 (1H,Ar-NH), 3.97(2H,C=O-CH_2), 2-3(8H, -CH_2), 2-3 (2H,-CH_2 attached to piperazine ring).

Synthesis of 2-(4-Phenylpiperazin-1-yl)-N-(thiazol-2-yl) acetamide (NS-7)
Yield 52.0%; mp 170ºC, IR (KBr, cm^{-1}) : 3385(N-H str.), 2953-3065(Aliphatic &ArC-H str.), 1690(C=O str), 1575(C=C str.), 1328(C-N str.),625(ArC-S str.); The ^{1}HNMR(δ, ppm): (DMSO-*d6*, 250 MHz): 7-8 (1H,ArN-CH), 6-7 (1H,ArS-CH), 12.14 (1H,Ar-NH), 3.31(2H,C=O-CH_2), 2-3(8H, -CH_2), 6-8 (5H, phenyl ring attached to piperazine ring).

Synthesis of 2-(2-Methyl-1H-imidazol-1-yl)-N-(thiazol-2-yl) acetamide (NS-8)
Yield 52.0%; mp 170ºC, IR (KBr, cm^{-1}) : 3292(N-H str.), 2915-3049(Aliphatic &ArC-H str.), 1687(C=O str), 1592(C=C str.), 1331(C-N str.),635(ArC-S str.); The ^{1}HNMR(δ, ppm): (DMSO-*d6*, 250 MHz): 7-8 (1H,ArN-CH), 6-7 (1H,ArS-CH), 8.13 (1H,Ar-NH), 4.61 (2H,C=O-CH_2), 6-7 (2H, imidazole ring), 2.48 (3H, -CH_3 attached to imidazole ring).

RESULTS AND DISCUSSION

Literature review reveal that thiazole derivatives could be used as a template for the development and designing of more potent therapeutic agents through modification or derivatization. These finding suggested that derivatives of thiazole possess different type of biological activities including antibacterial, antifungal, anti-inflammatory, antidepressant, antipsychotics and antipyretic activity[14-17].

Thus eight different derivatives of 2-aminothiazole were synthesized. The synthesis of 2-chloro-N-(thiazol-2-yl) acetamide (NS) was accomplished by reacting 2-amino thiazole and chloroacetylchloride in the presence of potassium carbonate in chloroform. The 2-chloro-N-(thiazol-2-yl) acetamide (NS)was reacted with various substituted amines in the presence of K_2CO_3 in acetone afforded various derivatives viz, NS-1, NS-2, NS-3, NS-4, NS-5, NS-6, NS-7& NS-8.Yields obtained from 42% to 65%. The structures of these compounds were established on the basis of IR spectral analysis and **^{1}**H-NMR spectral studies.

The purity and homogeneity of all compounds were confirmed by their sharp meltig point and TLC. All the above result positively confirmed the formation of the synthesized compounds and hence correctness of the anticipated structures drawn for synthesized compounds. All the synthesized compounds have been tested for antibacterial and antifungal activities by Disk-diffusion method. The compounds showed mild to good antibacterial activity and antifungal activity.

CONCLUSION

Present study reports synthesis of novel 2-aminothiazole derivatives viz, NS-1, NS-2, NS-3, NS-4, NS-5, NS-6, NS-7 and NS-8 which are synthesized according to scheme and the identity of the compounds were confirmed on the basis of their sharp m.p., TLC, IR and ^{1}H-NMR data.

All the synthesized compounds have been tested for antibacterial and antifungal activities by Disk-diffusion method. These compounds showed mild to good antibacterial activity and antifungal activity. The compound NS-5 showed potent antibacterial activity and compound NS-8 showed potent antifungal activity.

Acknowledgement
Author thanks to Dr.A.K.Wahi, Dean, Moradabad Educational Trust Group of Institutions, Faculty of Pharmacy, MIT Campus, Moradabad for his immense support in completing our

research. Authors also thanks to Mr.Vivek Yadav, Chairman, Sir Madanlal Group of Institution, Etawah, Uttar Pradesh, India.

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