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SYNTHESIS, CHARACTERIZATION AND PHARMACOLOGICAL STUDIES OF BIOLOGICALLY ACTIVE BENZOTHIAZOLE DERIVATIVES

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ABSTRACT

A series of some benzothiazole was synthesized and evaluated for antimicrobial activity. The reaction of aniline compounds with ammonium thiocyante and HCl yielded 1 phenylthiourea. The title compounds were synthesized by treating 1-phenylthiourea with bromine in glacial acetic acid. Their structures were confirmed by IR, ^{1}H-NMR and ^{13}C-NMR spectral techniques. Docking study was done to find the binding capacity of the synthesized compounds with the protein molecule COX-2

Key Words: Benzothiazole, pharmacological activity, Docking.

INTRODUCTION

Benzothiazole is a heterocyclic compound consisting of benzene ring fused with imidazole ring. The chemistry and pharmacology of benzothiazole have been of great interest to medicinal chemistry [1], because its derivatives possessed various biological activities [2] such as anticancer [3-5], antihypertensive [6], antimicrobial [7-9] etc. Moreover benzothaizole is the important intermediate in organic reaction [10]. In the present study is it planned to synthesize benzothiazole compounds and characterize these compounds by IR, ^{1}H NMR and ^{13}C NMR spectral analysis. Since these compounds contain highly biological active benzothiazole nucleus, it is also aimed at carrying out anti-microbial activity. It is further planned to carry out the docking study to find the binding capacity of the synthesized compounds with the protein molecule COX-2.

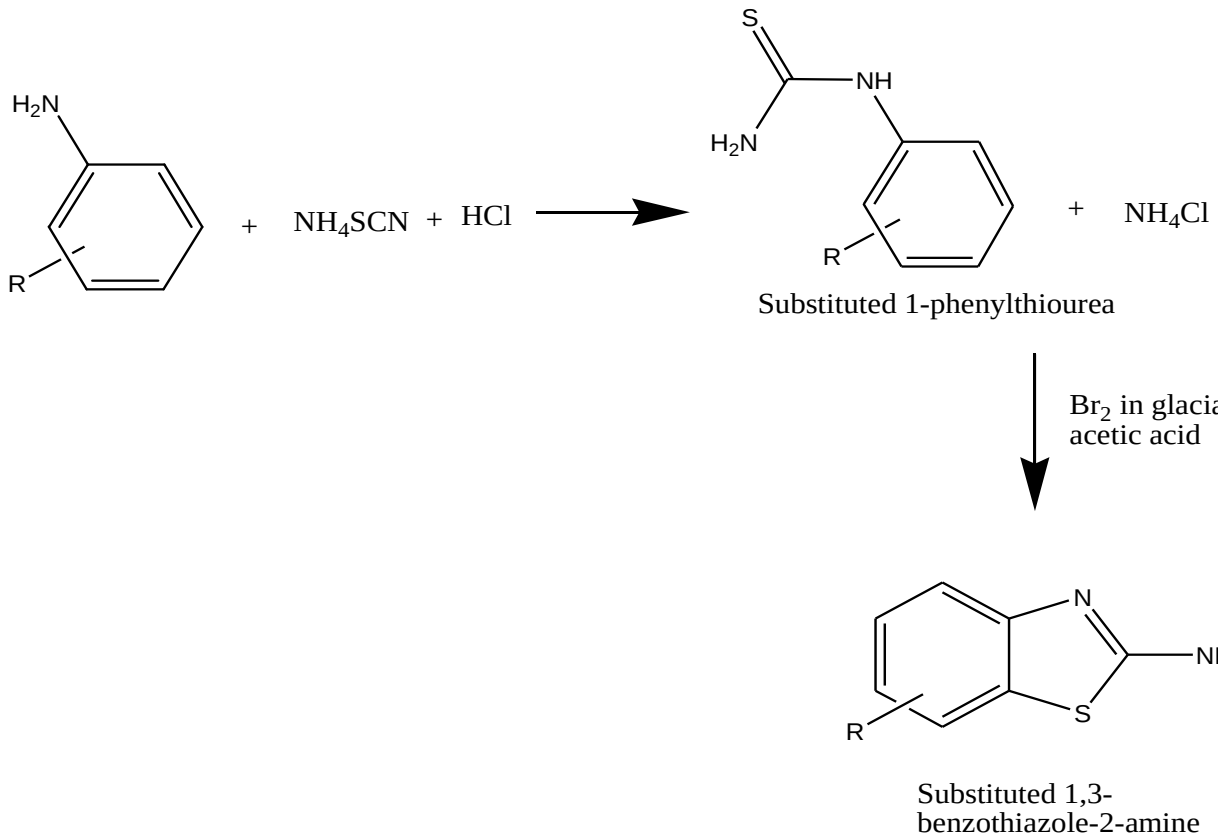
EXPERIMENTAL SECTION

All melting points were taken in open capillaries and are uncorrected.IR spectra were recorded in KBr on Shimadzu spectrometer. ^{1}H-NMR and ^{13}C-NMR in DMSO-d6 on Bruker AC-400 spectrometer using MeOD as an internal standard. The microorganisms for anti-microbial activity were obtained from National Chemical Laboratory, Pune.

General procedure for the synthesis of benzothiaole

Procedure:

Substituted / unsubstituted aniline (0.02mol) and ammonium thiocyanate (0.02mol) were dissolved in ethanol containing 2ml of con. Hydrochloric acid. To this bromine in glacial acetic acid (2.7ml, 0.05mol) was added and the reaction mixture was refluxed for 2hours. Then, it was cooled in ice-water. The precipitate obtained was stirred well, filtered, washed with cold water and dried. The crude product was recrystallized from rectified spirit (scheme-1)



R

A- $2NO_2$

B- $3NO_3$

C- COOH

D- COOH

Table 1 Analytical data ofbenzothiazole compounds(A-D)

Compound	%yield	M.pt	Molecular Formula	Moleculr Weight
A	72	125°C	$C_7H_5N_3O_2S$	195.20
B	37	123°C	$C_8H_6N_2O_2S$	194.21
C	72	128°C	$C_7H_5N_3O_2S$	195.21
D	75	145°C	$C_8H_6N_2O_2S$	194.21

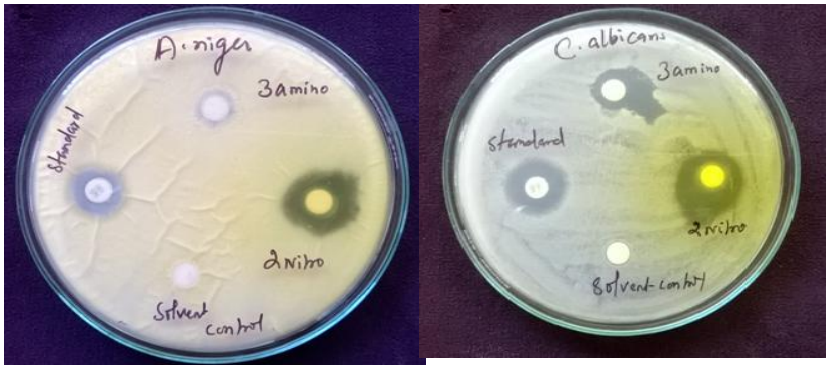
IR SPECTRAL DATA (A-D)

Compound A: 5-nitrobenzo(d)thiazole-2-amine :IR KBr(cm^{-1}):1501(C-C $_{str}$), 1626(C=C $_{str}$),1250(C=N-C $_{str}$,), 2200(C-S $_{str}$),3482(C-NH_{2str}),1250(C-H_{str}),1550(C-NO_2 $_{str}$)^{1}H NMR:δ 7.3(aromatic proton),2.503(NH_2)proton.^{13}C NMR : δ39.96(Ar-C), δ133.42(C-NO_2). Compound B: 6-nitrobenzo(d)thiazole-2-amine : IR KBr(cm^{-1}):1528(C-C $_{str}$), 1538(C=C $_{str}$),1349(C=N-C $_{str}$,), 2050(C-S $_{str}$),3471(C-NH_{2str}),1090(C-H_{str}),1349(C-NO_2 $_{str}$)^{1}H NMR: δ7.6 (aromatic proton), δ2.5(NH_2)proton.^{13}C NMR : δ39.71(Ar-C), δ132.41(C-NO_2). Compound C: 2-aminobenzo(d)thaizole-5-carboxlicacid : IR KBr(cm^{-1}):1596(C-C $_{str}$), 1640(C=C $_{str}$),1311(C=N-C $_{str}$,), 2030(C-S $_{str}$),3408(C-NH_{2str}),1276(C-H_{str}),1700(COOH $_{str}$)2928(OH_{str})^{1}H NMR: δ7.8(aromatic proton), δ4.3(NH_2)proton, δ12.4(O-H)proton.^{13}C NMR: δ39.65(Ar-C), δ138.42(COOH) Compound D: 2-aminobenzo(d)thaizole-5-carboxlicacid : IR KBr(cm^{-1}):1630(C-C $_{str}$), 1570(C=C $_{str}$),1307(C=N-C $_{str}$,), 2100(C-S $_{str}$),3631(C-NH_{2str}),1340(C-H_{str}),1700(COOH $_{str}$)2920(OH_{str})^{1}H NMR: δ7.6(aromatic proton), δ2.499(NH_2)proton, δ9.950(O-H)proton.^{13}C NMR: δ39.76(Ar-C), δ139.72(COOH)

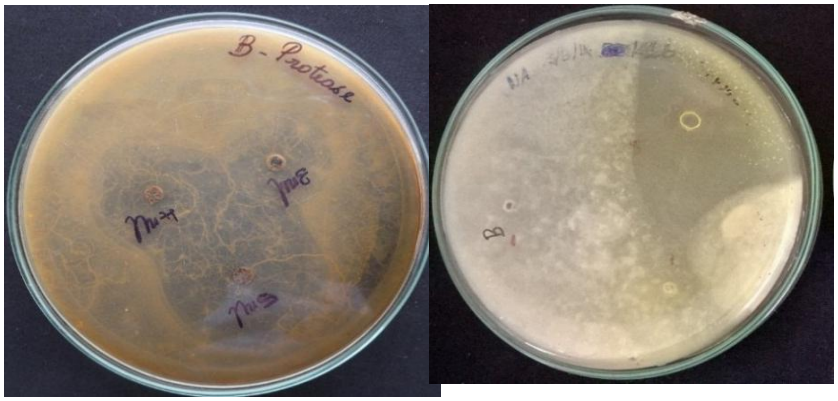
Antimicrobial study

The purified compounds A,B,C, and D were tested for their antimicrobial activity against Staphylococcus aureus, Escherichia coli, Aspergillus niger, Candida albicans , Proteus, Enterobacter, and Klebsiella. The results suggest that the synthesized compound A,B, and D exhibit higher antimicrobial activity against Staphylococcus aureus, Proteus,Aspergillus niger. [11]

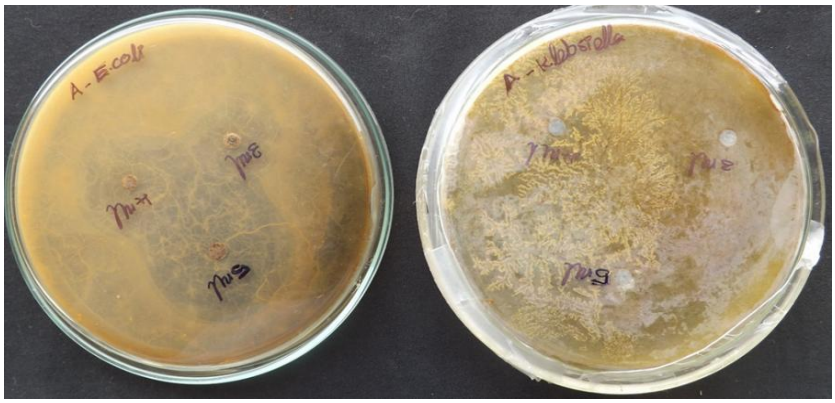
"Fig.1"Staphylococcus aureus &E.coli



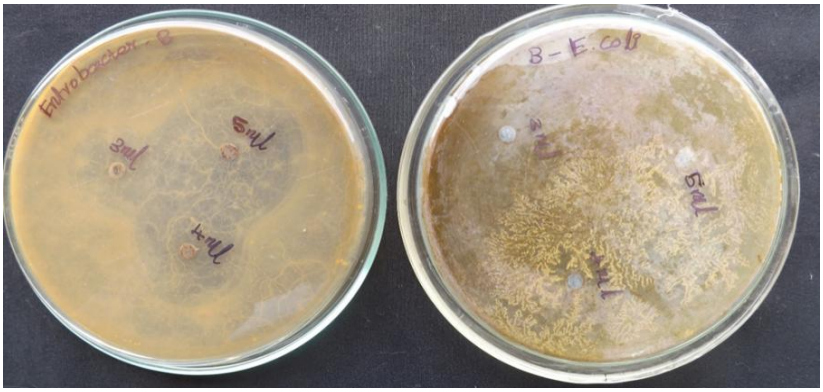
"Fig.2"Aspergillus niger&Candida albicans



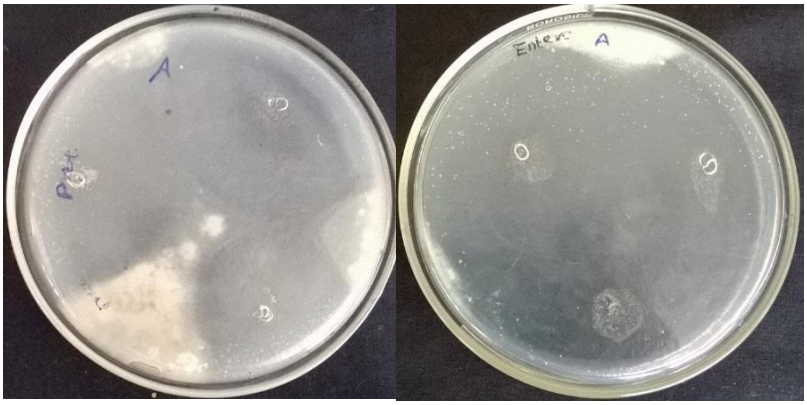
"Fig.3" Proteus &Enterobacter



"Fig.4" E.coli & Klebsiella



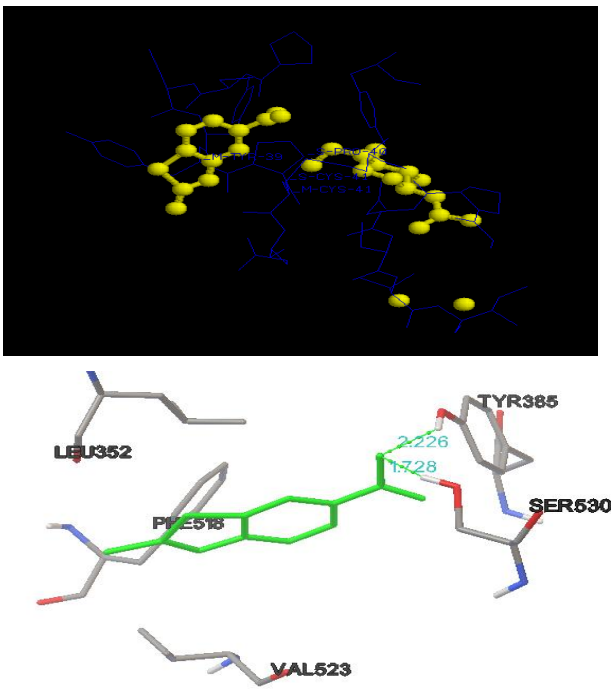
"Fig.5"Enterobacter & E.coli



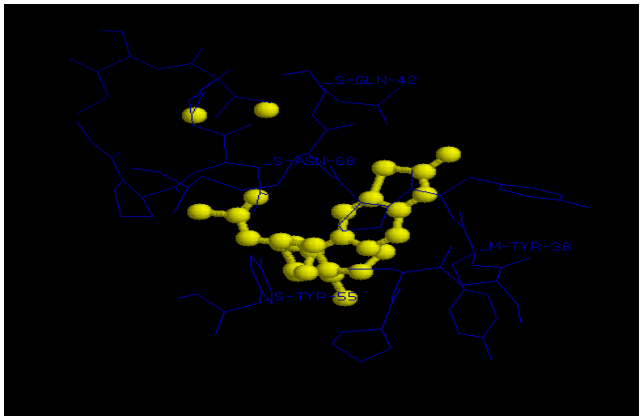
"Fig.6" Proteus & Enterobacter

Molecular Docking

The molecular docking studies of synthesized compounds with Cox-2 was done. Compound: A&B The amino acid residues SER530 and TYR 385 were involved in interactions with 6-nitro-benzothiazol-2-ylamine in the active site of cyclooxygenase-2. The length of hydrogen bonds formed 2.226 Å,1.728 and Å 5.709 Å. TheIC_{50} value of this compound have 20 (µm) and low docking score (-5)[12-14]. Compounds: C&D The amino acid residues LEU352 and ARG120were involved in interactions with 2-Amino-benzothiazole-5-carboxylic acid the active site of cyclooxygenase-2. The length of hydrogen bond formed 2.076 Å, 2.22 Å,1.932Å and 1.987 Å. The IC_{50} values of this compound have 29 (µm) and low docking score (-6)[15]



"Fig.7"



"Fig.8"

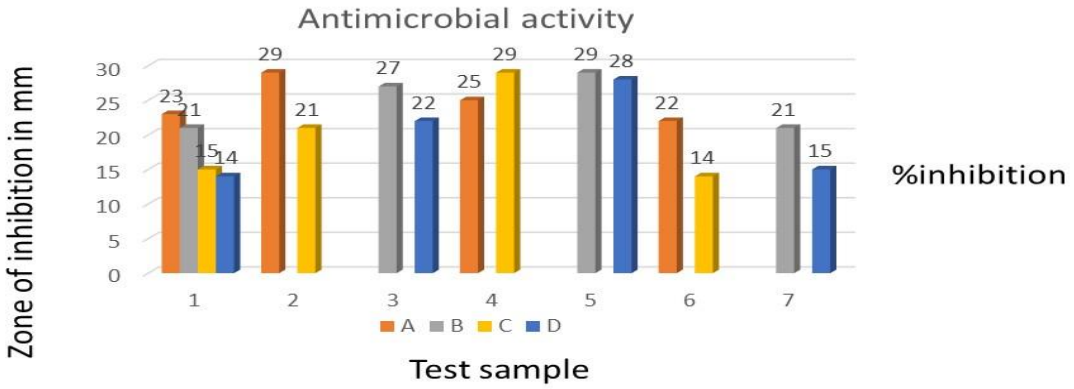
Interaction of compounds A, B, C&D with the binding site

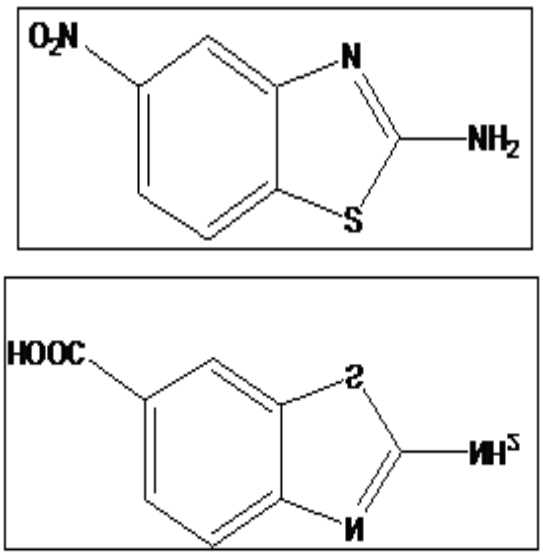
RESULTS AND DISCUSSION

The anti-microbial activity for the given sample was carried out by disc diffusion technique.The test microorganisms of Staphylococcus aureus, E.coli, Aspergillus niger,Candida albicans, Proteus, Enterobacter, Klebsiella were obtained from National Chemical Laboratory(NLC) Pune and maintained by periodical sub culturing on nutrient agar medium for bacteria. The effect produced by the sample was compared with the effect produced by the positive control(reference standard ciprofloxacin 5 µg/disc.[16-20]

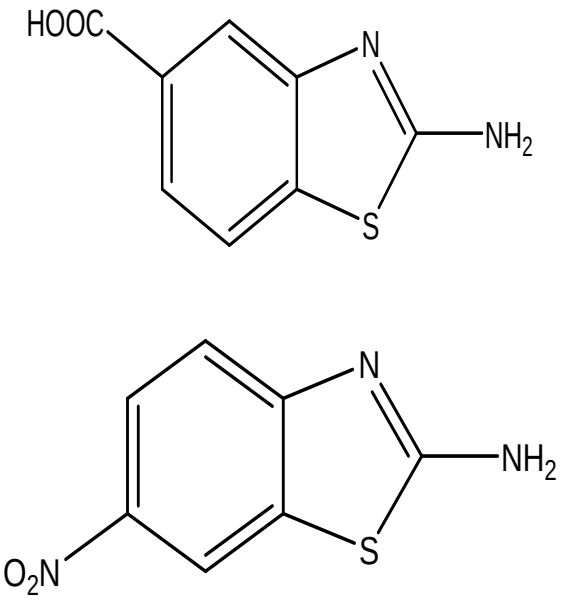
Table 2The obtained results are tabulated as follows:

S.No	Name of the Microorganisms	zone of inhibition in mm				
		A	B	C	D	Std
1	E.coli	23	21	15	14	38
2	Proteus	29	-	21	-	30
3	Aspergillus niger	-	27	-	22	30
4	Enterobacter	25	-	29	-	32
5	Staphylococcus aureus	-	29	-	28	35
6	Klebsiella	22	-	14	-	26
7	Candida albicans	-	21		15	25


Antimicrobial activity
Zone of inhibition in mm
30
25
20
15
10
5
0
23
21
15
14
29
21
27
22
25
29
29
28
22
14
21
15
1
2
3
4
5
6
7
A B C D
Test sample
%inhibition


O2N
N
NH2
S
HOOC
2
NH2
N

"Fig.9"


HOOC
N
NH2
S
N
NH2
O2N
S

"Fig.10"

DISCUSSION

The benzothiazole(A-D) were synthesized in good yield by the reaction of aniline derivatives with ammonium thiocyanate and Br2/CH3COOH under ice-cold condition.The purity of all the synthesized compounds were confirmed by their sharp melting points (uncorrected) and column chromatography. The chemical structures were confirmed by IR, 1H-NMR and 13C_NMR techniques.Antimicrobial activity against Staphylococcus aureus, E.coli, Aspergillus niger, Candida albicans, Proteus, Enterobacter, Klebsiellawas studied for the synthesized compounds. The aromatic (Ar-H) stretching frequencies for all thederivatives were found to be at the range of 2900-3100 cm-1.The presence of NH stretching was confirmed by the peaks at 3100-3550 cm-1. Also 1H-NMR spectra were useful for identifying protons. The peaks at the frequency range 7.3– 7.8 confirm the aromatic protons and 2.4-4.3 confirms the NH2 protons. From the microbiological studies, the antimicrobial activity of A,B and C compounds was found to be the highest among the other compounds [19-25].

CONCLUSION

The present investigation is focused on the synthesis, characterization and biological activities of a series of compounds from substituted aniline. The findings are furnished below:

1. Four compounds were prepared from substituted aniline by the scheme-1.
2. All the compounds synthesized by the investigator, were characterized by infrared data.
3. The IR spectra of the four compounds provide the expected frequencies.
4. The 1H NMR and 13C NMR spectra of the four compounds provides signals.
5. A study of the anti-microbial activity was carried out and the results are given.

Molecular Docking study was also made and the results are shown.

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