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Characterization and anti-microbial evaluation of newly synthesized imidazole derivatives

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Abstract: An efficient and practical synthesis of imidazolyl derivatives(B1-B5) were achieved through thiocyanation of aniline derivatives followed by the reaction with ethylene diamine in the presence of carbondisulphide. All the synthesized compounds were characterized on the basis of elemental analysis, IR , ^{1}H-NMR, ^{13}C-NMR spectra. The synthesized compounds were screened for their *in vitro* activity against *Staphylococcus aureus*, *Bacillus Subtilis*, *Escherichia Coli*, *Pseudomonas aeruginosa*, *Candida Albicans*, *Aspergillus Niger*. All the compounds were found to possess significant activities.
Keywords: Imidazole , thiocyanation, ethylene diamine, *in vitro* activity.

Introduction

In recent years, interest has been devoted to the preparation and evaluation of biological activity of various nitrogen heterocyclic compounds / derivatives for their growing potential importance in various pharmaceutical industries. Several heterocyclic nuclei such as imidazoles , pyrimidine , thiazole, triazole, pyrrazole nuclei have contributed significantly towards the development. Considerable interest has been focused on the imidazole structure, which is known to possess a broad spectrum of biological activities [1], such as antimicrobial [2-5], antitumor [6,7], anti-HIV [8], anticonvulsant [9], antitubercular [10], antiprotozoal [11] and anti-inflammatory [12].Therefore in the present study, some new imidazole compounds were synthesized by treating thiocyano-aniline derivatives with ethylene diamine and carbondisulphide.

Experimental

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 a Bruker AC-400 spectrometer using TMS as an internal standard. Elemental analysis was performed on a Perkin-Elmer analyzer.

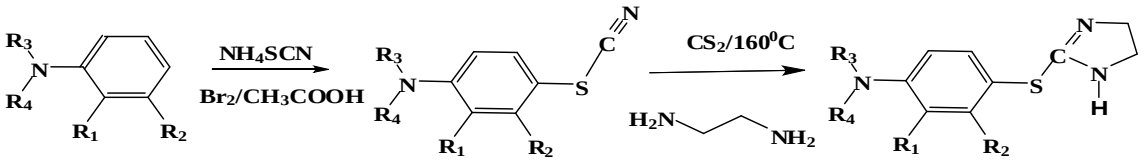
Synthesis of thiocyanate (A1-A5)

The substituted/unsubstituted aniline (0.5 mol) was dissolved in acetic acid (125 ml) and the solution was added to the solution of ammonium thiocyanate (1.05 mol) in glacial acetic acid (250 ml).This solution was cooled to 10-20º C. To this well stirred solution, a solution of bromine (25.7 ml, 0.5 mol) in acetic acid (250 ml) was added dropwise for thirty minutes, and the temperature was maintained below 20ºC.

After the addition of bromine, it was kept at room temperature for ten minutes, and then it was diluted with equal amount of water. The solid material was filtered, washed, dried and recrystallized from ethanol.

Synthesis of imidazoles (B1-B5)

A mixture of thiocyanate A1-A5 (1.0 mol), ethylene diamine (1.0 mol) and carbon disulphide (0.1 mol) was heated in an oil bath at 160° C for 6 hours. The resultant product was cooled and then recrystallised from ethanol.



A1-A5 B1-B5

	R1	R2	R3	R4
A1,B1	-NO_2	-H	-H	-H
A2,B2	-COOH	-H	-H	-H
A3,B3	-H	-NO_2	-H	-H
A4,B4	-H	-COOH	-H	-H
A5,B5	-H	-H	-C_2H_5	-C_2H_5

Table 1 Analytical data of thiocyanate (A1-A5)

Thiocyanate	Yld (%)	M. Pt (° C)	Molecular formula	Elemental Analysis (%) Reported (Calculated)					M wt
				C	H	N	O	S	
A1	76	115-116	$C_7H_5SN_3O_2$	43.18(43.07)	2.51(2.58)	21.29(21.53)	16.32(16.39)	16.39(16.43)	195
A2	62	218-219	$C_8H_6SN_2O_2$	49.41(49.47)	3.08(3.11)	14.38(14.42)	16.40(16.48)	16.45(16.50)	194
A3	97	139-140	$C_8H_6SN_2O_2$	49.42(49.47)	3.05(3.11)	14.35(14.42)	16.39(16.48)	15.90(16.05)	194
A4	75	85-86	$C_{11}H_{14}N2S$	63.99(64.04)	6.80(6.84)	13.47(13.58)	_	15.48(15.54)	206
A5	80	91-92	$C_7H_5SN_3O_2$	43.01(43.07)	2.40(2.58)	21.29(21.35)	16.42(16.39)	16.38(16.43)	195

IR data for the compounds A1-A5

A1 (2-nitro-4-thiocyanatoaniline) - $\nu_{C\equiv N}$: 2170 cm^{-1}
A2 (5-amino-2-thiocyanatobenzoicacid) - $\nu_{C\equiv N}$: 2150 cm^{-1}
A3 (2-amino-5-thiocyanatobenzoicacid) - $\nu_{C\equiv N}$: 2155 cm^{-1}
A4 (N,N-diethyl-4-thiocyanatoaniline) - $\nu_{C\equiv N}$: 2210 cm^{-1}
A5 (3-nitro-4-thiocyanatoaniline) - $\nu_{C\equiv N}$: 2257 cm^{-1}

Table 2 Analytical data of Imidazole (B1-B5)

Imidazole	Yld (%)	M. Pt (° C)	Molecular formula	Elemental Analysis (%) Reported (Calculated)					M wt
				C	H	N	O	S	
B1	83	193-194	$C9H_{10}SN_4O_2$	45.33(45.37)	4.20(4.23)	23.55(23.51)	13.41(13.43)	13.45(13.46)	238
B2	73	262-263	$C_{10}H_{11}SN_3O_2$	50.65(50.62)	4.69(4.67)	17.65(17.71)	13.47(13.49)	13.52(13.51)	237
B3	60	236-237	$C_{10}H_{11}SN_3O_2$	50.61(50.62)	4.63(4.67)	17.73(17.71)	13.45(13.49)	13.50(13.51)	237
B4	71	205-206	$C_{13}H_{19}N_3S$	62.59(62.61)	7.65(7.68)	16.83(16.85)	_	12.82(12.86)	249
B5	64	251-252	$C_9H_{10}SN_4O_2$	45.34(45.37)	4.21(4.23)	23.48(23.51)	13.41(13.43)	13.43(13.46)	238

Compound B1(4-(4,5-dihydro-1*H*-imidazol-2-ylthio)-2-nitroaniline): IR(KBr) cm^{-1} : 3277(NH_2), 1630(C=N str), 2885(NH). ^{1}H-NMR : δ 7.9 (Ar-H, multiplet),δ 3.4 (Ar-NH_2 , singlet). ^{13}C-NMR : δ 183 (Ar-C).

CompoundB2(2-amino-5-(4,5-dihydro -1*H*-imidazol-2-ylthio) benzoicacid) : IR(KBr) cm^{-1} : 3529(NH_2), 1511 (C=Nstr), 3246(NH), 2570(OH str) . ^{1}H-NMR : δ 7.9 (Ar-H, multiplet), δ 9.9 (-COOH , singlet). ^{13}C-NMR : δ 183 (COOH).

Compound B3 (5-amino-2-(4,5-dihydro-1*H*-imidazol-2-ylthio)benzoic acid): IR(KBr) cm^{-1} : 3366 (NH2) , 1601 (C=N str) ,3247 (NH), 2369(OH str), 744 (C=C bending) .^{1}H-NMR : δ 6.5 – 8.0 (Ar-H, multiplet),δ 3.8 (Ar-NH_2 , singlet).^{13}C-NMR : δ 137 (Ar-C) , δ 152 (C=N).

Compound B4(4-(4,5-dihydro-1*H*-imidazol-2-ylthio)-*N*,*N*-diethylaniline): IR(KBr) cm^{-1} : 3311(NH_2), 1622(C=N str), 3089(aromatic) , 729(C=C). ^{1}H-NMR : δ 6.5 – 7.9 (Ar-H, multiplet), δ 1.1 (C_2H_5, singlet). ^{13}C-NMR : δ 118-126 (Ar-C) .

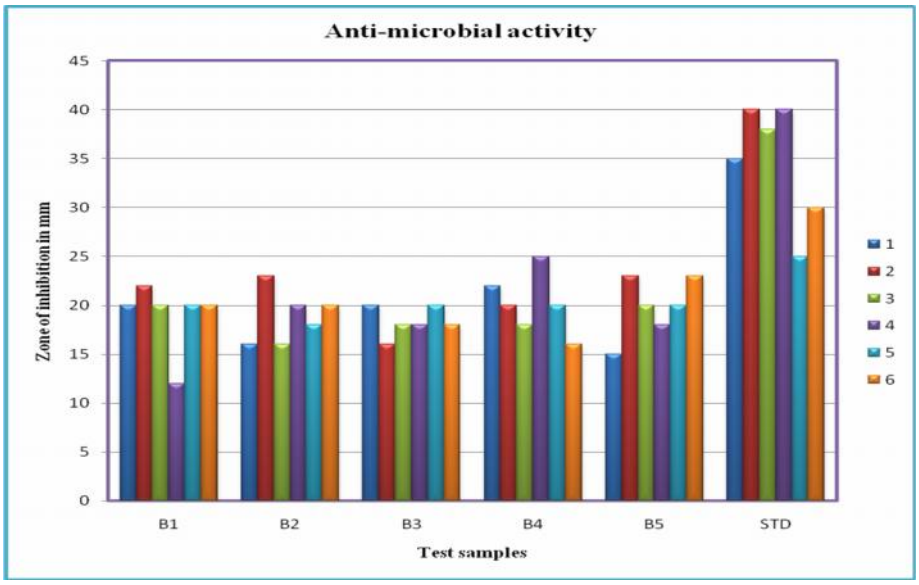
Compound B5(4-(4,5-dihydro-1*H*-imidazol-2-ylthio)-3-nitroaniline):
IR(KBr) cm^{-1} : 3441(NH_2), 1463(NO_2), 1631(C=N str) .^{1}H NMR : δ6.5-8.5 (Ar-H, multiplet),δ 2.4 (Ar-NH_2 , singlet). ^{13}C-NMR : δ 109-148 (Ar-C) , δ 159 (C=N).

Anti-microbial Activity

The anti-microbial activity for the sample was carried out by Disc Diffusion Technique[13]. The test microorganisms were obtained from National Chemical Laboratory NCL),Pune and maintained by periodical subculturing on nutrient agar and sabouraud dextrose agar medium for bacteria and fungi respectively. The effects produced by the sample were compared with the effect produced by the positive control (Reference standard ciprofloxacin 5 µg/disc for bacteria; Nystatin 100 units/disc for fungi).

Table 3: Anti-microbial activity of the compounds B1-B5

S.No	Name of the microorganisms	Zone of Inhibition in mm					
		B1	B2	B3	B4	B5	Std
1.	Staphylococcus aureus	20	16	20	22	15	35
2.	Bacillus Subtilis	22	23	16	20	23	40
3.	Escherichia Coli	20	16	18	18	20	38
4.	Pseudomonas aeruginosa	12	20	18	25	18	40
5.	Candida Albicans	20	18	20	20	20	25
6.	Aspergillus Niger	20	20	18	16	23	30



1.Staphylococcus aureus **2.**Bacillus Subtilis **3.**Escherichia Coli
4.Pseudomonas aeruginosa **5.**Candida Albicans **6.**Aspergillus Niger

Discussion

Compound A1-A5 were synthesized in good yield by the reaction of aniline derivatives with ammonium thiocyanate and Br_2/CH_3COOH under ice-cold condition. Compounds A1-A5 on reaction with ethylene diamine in the presence of carbondisulphide afforded compounds B1-B5. The purity and homogeneity of all the synthesized compounds were confirmed by their sharp melting points (uncorrected) and column chromatography. The chemical structures were confirmed by IR, ^{1}H-NMR and ^{13}C_NMR techniques. The NH_2 stretching frequencies for all the derivatives were found to be at the range of 3277-3529 cm^{-1}.The presence of NH stretching was confirmed by the peaks at 2885-3247 cm^{-1}. Also ^{1}H-NMR spectra were useful for identifying protons. The peaks at the frequency range 6.2 – 8.5 confirms the aromatic protons and 2.4-3.8 confirms the NH_2 protons.

The compound B4 shows good activity and compounds B2 and B5 show moderate activity in anti-microbial study.

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