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Synthesis of some benzothiazolyl and imidazole derivatives and evaluation of antibacterial activities

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ABSTRACT

Some benzothiazolyl(s) and imidazole(s) derivatives were synthesized starting from simple precursors. These synthetic products were evaluated for potential anti-microbial activities.

Keywords: benzothiazolyl, imidazole, synthesis, antibacterial activity, nitrogen heterocyclic compounds.

INTRODUCTION

In recent years, interest has been devoted to the preparation and evaluation of biological activity of various nitrogen heterocyclic compounds/derivatives for of their growing potential importance

in various pharmaceutical industries. For example, histidine being the part of the human DNA sequence has been widely used as a nucleus for the construction of many important drugs. Several heterocyclic nuclei such as imidazoles, pyrimidine, thiazole, triazole, pyrrazole nuclei have contributed significantly towards the development. Imidazole derivatives have been reported as catalyst in phosphodiester hydrolysis [1], in exhibiting antitubercular activity [2], as potent inhibitors of rat testicular [3] and as hemeoxygenase inhibitors [4]. Imidazole and Imidazolium containing polymers are also finding extensive applications in biological sciences as well as materials sciences [5]. Similarly benzothiazole derivatives have also been reported as potential antitumor agents [6,7], antimicrobial agents [8], and as plant growth regulators [9,10].

A short review of available literatures shows novel application of nitrogen heterocycles on human chronic myelogenous leukemia K562 cells [11]. Interestingly, the synthesized compound induced a biphasic alteration in mitochondrial membrane potential of K562 cells where a dramatic elevation of Ca^{2+} was also observed. This study showed that compound might be a potential chemopreventive agent for chronic myelogenous leukemia. Similarly a series of heterocycle-fused 1,2,3-triazoles prepared in a one-pot reaction at room temperature was evaluated *in vitro* against a panel of human tumour cell lines [12]. Here, 1,3-Oxazoheterocycle fused 1,2,3-triazole compounds were found to be more potent against the tumour cell lines.

Quite recently, biological activity of nitrogen hetero cycles for a series of polysubstituted and fused heterocycles derivatives of acylthiourea was tested against influenza virus [13,14] and acylthiourea derivatives were found to be the most potential candidate for future development as selective inhibitors of influenza virus. Similarly, new pyrrolo[2,3-*d*] pyrimidines with heteroaryl substitution through sulfur linker were synthesized incorporating putative pharmacophoric moieties like benzimidazole and benzothiazole as heteroaryl groups [15]. Cytotoxic effect of all these compounds was carried out on HCT116 colon cancer cell lines where the compounds with

nitrobenzimidazole and pyrimidyl heterocycles attached via sulfur linkage were found to be the most potent drugs with IC_{50} values nearly equal to17.6 μM..

Therefore, in our search for biologically active nitrogen heterocycle, we here in, reporting the synthesis and biological activity of some newly synthesized benzothiazolyl and imidozolyl derivatives. The synthesized compounds were evaluated for their antibacterial activity against gram (+) and gram (-) bacteria. The organic compounds are projected as potential anti-bacterial candidate for further commercial exploitation.

EXPERIMENTAL SECTION

Materials and methods

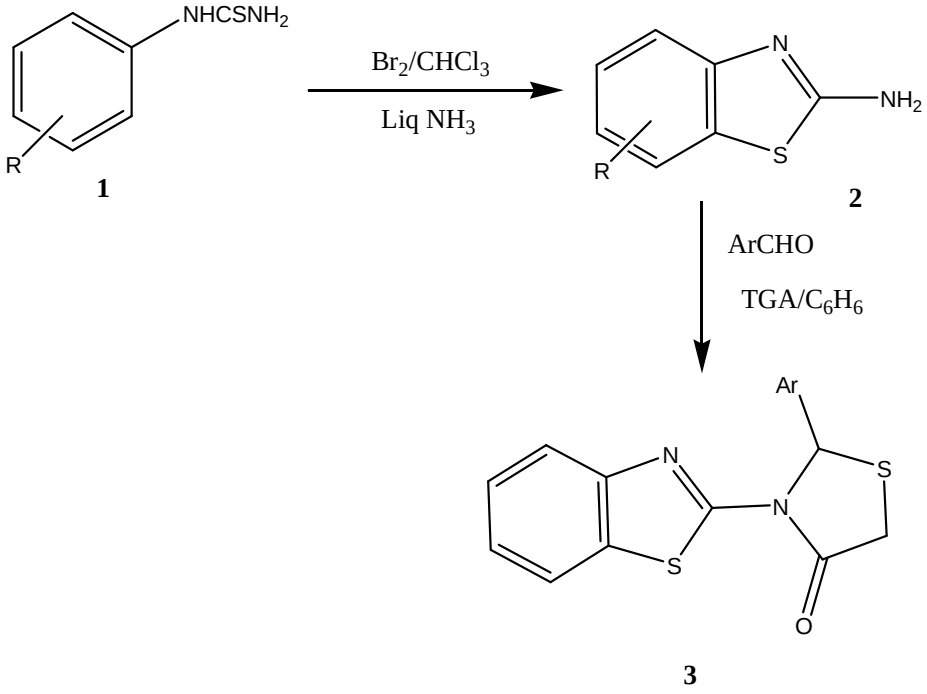
All the chemicals were purchased from Merck. Solid organic compounds were used as such whereas liquid chemicals distilled and then used. Melting points were determined in open capillary tubes and uncorrected values were recorded. NMR spectra of the compounds were taken on a Bruker DRX 300 spectrometer using DMSO-d_6/$CDCl_3$ as solvent and TMS as internal standard.

Antibacterial activity assay: evaluation of minimum inhibitory concentration (MIC)

The antibacterial activity was evaluated by disc-diffusion method. Nutrient agar media was taken in a pre-sterilized petri-dish and the microorganisms were grown. The disc (7 mm) was saturated with 20 μl of 5 mg/ml solution of organic compound, allowed to dry and was introduced on the upper layer of the seeded agar plate and incubated at 37 ^{0}C for 24 hrs. The diameters of zone of inhibition (mm) were recorded and the experiment was done in triplicate and the mean values are presented and compared with standard drug Gentamycin. The minimum inhibitory concentration (MIC) (μg/ml) of the different extracts and fractions was also determined according to standard method [16].

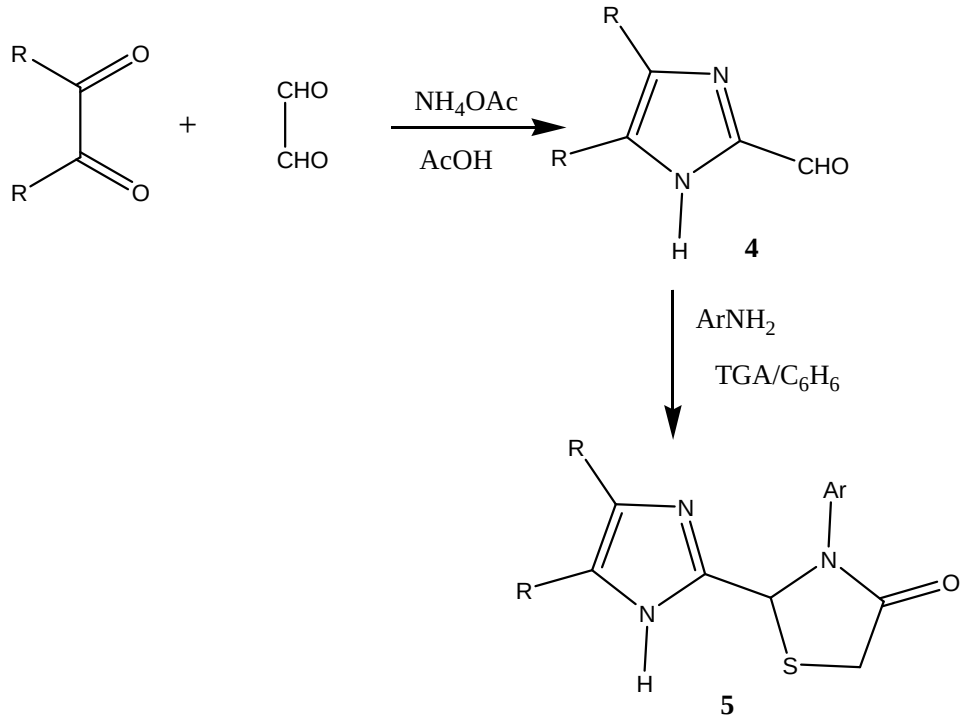
Synthesis

(i)Phenyl thiourea and substituted phenyl thiourea on condensation with bromine (Br_2) in $CHCl_3$ form 2-amino benzothiazolyl hydrobromide which subsequently on saturation with liquid ammonia yield 2-amino benzothiazolyl derivative **(2)** in excellent yield. These synthetic 2-amino benzothiazolyl derivative on further condensation with aromatic aldehydes followed by its treatment with thioglycolic acid vide azeotropic method afforded the benzothiazolyl thiazolidinone derivatives **(3) (Scheme-1**) in appreciably good yield.



(**Scheme-1**)

(ii)Similarly, 1,2-Diketones on condensation with glyoxal in ammonium acetate and acetic acid medium afforded 4,5-disubstituted-1H-imidazole-2-aldehyde in appreciably good yield. These synthetic aldehydes were condensed with aromatic amines to afford corresponding schiff's bases, which in turn condense with thioglycolic acid (TGA) to give the thiazolidinone derivatives (**5**) in appreciably good yield (**Scheme-2**).



(**Scheme-2**)

RESULTS AND DISCUSSION

The structures of all the synthetic compounds were established on the basis of obtained analytical and spectral measurement data. The spectral results for compound 3 and 5 (R = CH_3, Ar = C_6H_5) are furnished below:

Compound: 3. ^{1}H NMR (300MHz in DMSO-d_6, TMS at 0ppm): δ 2.6(t, 2H, CH_2); 7.5 (m, 2H, ArH); 7.9(m, 2H, ArH); ^{13}C NMR (300MHz in DMSO-d_6, TMS at 0 ppm): 121-126, 135.2, 154.5, 172.

Compound 5. ^{1}H NMR (300MHz in $CDCl_3$, TMS at 0ppm): δ 2.6(2H, CH_2); 7.35(m, 1H, ArH); 7.46(m, 1H, ArH); ^{13}C NMR (300MHz in $CDCl_3$, TMS at 0ppm): 43.1, 59.1, 121-126.

Interestingly, all thiazolidinone derivatives exhibited significant methylene peak at 2.6δ with TMS as standard. Further, the analytical data of condensation of derivatives of 3-(4-substituted) benzo [d] thiazol-2-yl)- 2-Aryl- thiazolidin-4-one (3: Scheme-1) is furnished in Table-1 and analytical data of condensation of derivatives of 3-Aryl- 2- (4,5-disubstituted-1H-imidazol-2-yl)- thiazolidin-4-one (5: Scheme-2) is furnished in Table-2.

Table-1: Analytical data of condensation of derivatives of 3-(4-substituted) benzo [d] thiazol-2-yl)- 2-Aryl-thiazolidin-4-one (3: Scheme-1)

S. No.	R	Ar	m.p (^{0}C)	Yield (%)	Calculated (%)			Found (%)		
					C	H	N	C	H	N
a	CH_3	C_6H_5	105	43	62.55	4.32	8.58	62.54	4.30	8.56
b	CH_3	*p*-ClC_6H_4	liquid							
c	CH_3	p-$OCH_3C_6H_4$	60	84	60.65	4.52	7.86	60.61	4.50	7.83
d	CH_3	*o*-$NH_2C_6H_4$	liquid							
e	Br	C_6H_5	98	65	47.30	2.98	10.34	47.27	2.95	10.31
f	Br	*p*-ClC_6H_4	80	42	48.46	3.11	6.65	48.43	3.10	6.61
g	Br	p-$OCH_3C_6H_4$	106	46	45.14	2.37	6.58	45.16	2.36	6.60

Table-2: Analytical data of condensation of derivatives of 3-Aryl- 2- (4,5-disubstituted-1H-imidazol-2-yl)-thiazolidin-4-one (5: Scheme-2)

S. No.	Ar	color	m.p (^{0}C)	Yield (%)	Calculated (%)			Found (%)		
					C	H	N	C	H	N
a	C_6H_5	white	215	66	61.51	5.53	15.37	61.49	5.52	15.38
b	m-ClC_6H_4	Brown	240	50	54.63	4.58	13.65	54.61	4.61	13.62
c	p-BrC_6H_4	Brownish pink	205	66	47.74	4.01	11.93	47.73	4.00	11.92
d	2-NH_2-Pyrimidine	white	190	76	56.91	5.14	20.42	56.86	5.16	20.40
e	4-Cl-2-NO_2-Aniline	red	100	75	47.66	3.71	15.88	47.65	3.72	15.86
f	1-Naphthyl amine	pink	80	80	66.85	5.30	12.99	66.83	5.28	12.96
g	o-phenylene diamine	Black	217	75	56.39	5.16	17.93	56.35	5.06	17.90

To ascertain the therapeutic value, the application of synthesized thiazolidinone derivatives were screened for their potential biological activity against gram (+) *Bacillus cereus* and *Staphylococus aureus* and gram (–) bacteria such as *E.coli.* The findings towards inhibition of microorganisms were correlated with a standard drug (Table-3).

Table 3: Antibacterial activity of Compound 3 and 5 (R = CH_3 and Ar = C_6H_5)

Bacteria	Minimum inhibitory concentration (µg / ml)		
	Compound 3	Compound 5	Gentamycin
Gram (+)			
Bacillus cereus	4.11	10.7	6.25
Staphylococus aureus	12.5	11.3	24.8
Gram (-)			
Escherichia coli	3.75	5.11	6.25

It has been observed that most of them observe signification growth inhibition almost comparable with the standard drug Gentamycin. However, when the substituent is bromine they

exhibit inhibition more than that of the standard employed in both bacteria and fungi. The observed result allows us to conclude that the compounds exhibited good antimicrobial activities and can be further developed for application as effective antimicrobial agent.

CONCLUSION

In this investigation, benzothiazolyl and imidazole derivatives were prepared using a simple, general reaction scheme. By variation of alkyl and aromatic groups, a series of new compounds were prepared and characterized. The potential antimicrobial activities of organic compounds were evaluated against standard drug. The scope of the present investigation provides an opportunity for adopting a simple general scheme of reaction procedure for the synthesis of nitrogen heterocycles that can be used for development of new potential drug molecule.

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