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Research Article

Synthesis and Anti-microbial Activity of some 2-Substituted Benzimidazole Analogs

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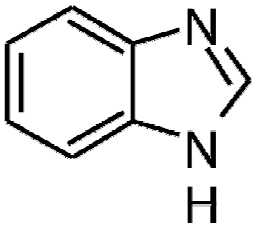
Abstract

Some 2-aminomethyl benzimidazoles derivatives were synthesized by reacting 2-chloromethyl benzimidazole with several amines and the compounds synthesized were identified by IR and NMR spectroscopy. Anti bacterial activity were screened against Staphylococcus aureus, Bacillus subtilis, and Salmonella typhi by zone inhibition method. Most of the compound shows potential anti bacterial activity.

Keywords: Benzimidazole, antimicrobial activity, spectroscopy, zone of inhibition

Introduction



Benzimidazole ring displays an important heterocyclic pharmacophore and privileged scaffold in drug discovery.[1]

This compound carrying different substituent's encompassing adiversified range of biological activities[2-4] include – anticancer, antiviral, antibacterial, antifungal, anthelmintics, antiinflammatory, antihistaminic,antihypertensive etc. Benzimidazole derivatives emerged to be an effective anti microbial agent in the year of 1964.[5] Since then, explorations of the same have already been made in different corner of horizon. The synthesis of novel benzimidazole derivatives remains a main focus of medicinal research. Recent observations suggest that substituted benzimidazoles and heterocycle, which are the structural isosters of nucleotides owing fused heterocyclic nuclei in their structures that allow them to interact easily with the biopolymers, posses potential activity with lower toxicities in the chemotherapeutic approach in man.[6,7] As an outgrowth of our investigation to discover novel antimicrobial agent a new series of 2-substituted benzimidazole analogs were synthesized and antimicrobial activity were evaluated.

Materials and Methods

Materials

Commercially available reagent grade chemicals were used for synthesis. O- Phenyl diamine and napthaldehyde were purchased from Loba Chemie Ind Co., Mumbai, India. Benzaldehyde was purchased from Merck Specialities Pvt Ltd.

Chemistry

General strategy for synthesis of the compounds is illustrated below. 2-cholоromethylbenzimidazole was synthesized by reacting ortho phenylene diamine with chloracetic acid in presence of Conc. HCl. The desired benzimidazole analogs were prepared by refluxing 2chloromethyl benzimidazole with several primary amines in ethyl alcohol. Spectral data (NMR and IR) confirmed the synthesis of new compounds.

Melting point

Melting point was determined by thiele apparatus and was uncorrected.

Thin layer chromatography

All the reactions were monitored by thin layer chromatography. The solvent system was ethyl acetate: n-hexane: methanol in the ratio of 3:2:1(v/v) and the spots were exposed in iodine chamber.

IR spectroscopy

IR spectra were recorded in Press Pellet Technique on SPECTRUM Bx (Ser. no: 78625).

NMR spectroscopy

NMR spectra were taken on BRUKER DPX-300.

Synthesis of 2-chloromethyl benzimidazole

Derivatives of benzimidazoles were synthesized by using o-phenyl diamine as starting material.

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A mixture of 5.43g (0.03 mol) of O–phenyl diamine as starting material.

A mixture of 5.43g (0.03 mol) of O–phenyl diamine dihydrochloride , 20ml of water and 5.4g (0.09 mol) of chloracetic acid was heated and refluxed for 45 min. The cooled reaction mixture was made distinctly basic by the gradual addition of concentrated ammonia solution. The precipitated product was collected, and re-crystallized from 10% aqueous ethanol. Yield: 81.88%, melting point: 142-144ºC.

IR (KBr) cm-1: 3058 (aromatic C-H stretching); 2941 (C-H symmetrical stretching, alkyl); 740 (C-Cl stretching monochloro alkyl); 1276 (C-N stretching).

Synthesis of 2-arylaminomethel benzimidazole (30a-e)

Heat together a mixture of 2.25g (0.015mol) of 2- chloromethyl benzimidazole, 10-15 ml of ethanol and 0.015 moles of different amines under reflux for 4.5h.

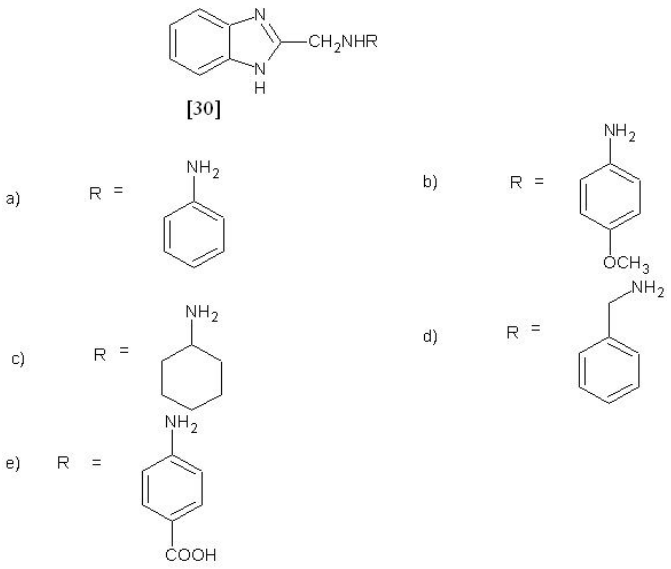

Table 1: Anti-microbial activity of the compounds against *S. aureus* at various concentrations

Compounds	Zone of Inhibition (cm)			
	(5 mg/ ml)	(2.5 mg/ ml)	(1.25 mg/ml)	(0.625 mg/ml)
Standard	+ +	+ +	+ +	+
30a	+ +	+	-	-
30b	+	+	-	-
30c	+ +	+	+	-
30d	+	-	-	-
30e	+ +	+	+	-

Table 2: Anti-microbial activity of the compounds against *B. subtilis* at various concentrations

Compounds	Zone of Inhibition (cm)			
	(5 mg/ ml)	(2.5 mg/ ml)	(1.25 mg/ml)	(0.625 mg/ml)
Standard	+ +	+ +	+ +	+
30a	+ +	+	-	-
30b	+ +	+	+	-
30c	+ +	+	+	-
30d	+	-	-	-
30e	+ +	+	+	-

Table 3: Anti-microbial activity of the compounds against *S. typhi* at various concentrations

Compounds	Zone of Inhibition (cm)			
	(5 mg/ ml)	(2.5 mg/ ml)	(1.25 mg/ml)	(0.625 mg/ml)
Standard	+ +	+ +	+ +	+
30a	+	+	-	-
30b	+	+	-	-
30c	+ +	+	+	-
30d	+ +	+	-	-
30e	+ +	+	+	-

'++' indicates high zone of inhibition, '+' indicates moderate zone of inhibition, '-' indicates no inhibition

After cooling the reaction mixture, it was extracted with chloroform and then chloroform layer was separated. Heating on water bath evaporated the chloroform. Then the product was collected and re-crystallized from ethanol. Yield: 41%, melting point: 212°C - 214°C.

Anti-microbial activity

Anti-microbial activity was studied by zone inhibition method. Tested microorganism stains were *Staphylococcus aureus*, *Bacillus subtilis* and *Salmonella typhyi*. Compounds were dissolved in DMSO. Ciprofloxacin was used as a standard drug.

Results and Discussion

Synthetic studied were carried out on benzimidazole analogs by substitution of different moiety at position 2 of benzimidazole moiety.

30a-e compounds were prepared from 2-chloromethyl benzimidazole (2-chloromethyl benzemidazole were prepared[8] by treating o-phenyldiamine dihydrochloride and chloroacetic acid in presence of water under refluxed condition and then treated with concentrated ammonia) by treating 2-chloromethyl benzimidazole with several amines.

IR spectrum of these compounds shows absorption band at about 3400cm^{-1} for N-H stretching; about 3000cm^{-1} for aromatic C-H stretching; about 2920cm^{-1} for C-H stretching alkyl; about 1280 for C-N stretching secondary amine.

1^{H} NMR spectra of compound N- ((1H-benzo[d] imidazol-2-yl) methyl) cyclohexamine (30c) showed that doublet of 2 proton at δ7.63 and another triplet of 2 proton at δ7.94 assign to the proton of benzimidazole. A singlet of 2 protons at δ3.81 assign to the proton of methylene. A singlet of 1 proton at δ3.012 assign to the proton of NH. A multiplete of 10 protons at δ 1.16-1.14 assign to the proton of cyclohexyle moiety.

Antimicrobial activities of compound 30a-e were carried out by cylinder plate method using nutrient agar media, first five compounds were evaluated against *S. aureus* at concentration 50μg/ml (in DMSO). Most of the compounds showed significant antimicrobial activity against *S. aureus, B. subtilis*, and *S. typhi*. The results of anti-microbial studies are given in the Table -1-3.

References

1. Sharma S, Gangal S, Rauf A. Convenient one-pot synthesis of novel 2-substituted benzimidazoles, tetrahydrobenzimidazole and imidazole and evaluation of their in vitro antibacterial, antifungal activities. E J Med Chem 2009; 44: 1751-1757.

2. Bishop BC, Chelton ETJ, Jones AS. Antibacterial activity of some fluorine- containing benzimidazoles. Biochem Pharmacol 1964; 13:751-754.

3. Hubschwerlen C, Pflieger P, Specklin JL, Gubernator K, Gmuender H,Angehrn P, Kompis I. Pyrimido [1,6-a] benzimidazoles: a new class of DNA gyrase inhibitors. J Med Chem 1992; 35: 1385-92.

4. Sharma S, Gangal S, Rauf A. Convenient one-pot synthesis of novel 2-substituted benzimidazoles, tetrahydrobenzimidazole and imidazole and evaluation of their in vitro antibacterial, antifungal activities. E J Med Chem 2009; 44: 1751-1757.

5. Bishop BC, Chelton ETJ, Jones AS. Antibacterial activity of some fluorine- containing benzimidazoles. Biochem Pharmacol 1964; 13:751-754.

6.Hubschwerlen C, Pflieger P, Specklin JL, Gubernator K, Gmuender H, Angehrn P, Kompis I. Pyrimido [1,6-a] benzimidazoles: a new class of DNA gyrase inhibitors. J Med Chem 1992; 35: 1385-92.

7. Furniss, Hannaford, Smith, Tatchell. Vogels Text Book of Practical Organic Chemistry, 5th ed., Singapore Publishers: Lougmain, 1996, p.