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Synthesis of *N*-Alkylated Derivatives of Imidazole as Antibacterial Agents

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Abstract—*N*-Alkylation of imidazole, 2-methylimidazole and 2-methyl-4-nitroimidazole have been carried out to achieve effective antibacterial agents. The products were then investigated for antibacterial activity against *Escherichia coil, Staphylococcus aureus* and *Pseudomonas aeruginosa*. Antibacterial effects of 1-alkylimidazole derivatives increase as the number of carbons in alkyl chain increases up to nine carbons. Also substitution of 2-methyl and 2-methyl-4-nitro groups on imidazole ring increases the antibacterial activity.

Introduction

N-Substituted imidazoles exhibit a variety of valuable pharmacological properties such as antiparasitic,[1] antifungal,[2] and antimicrobial[3] activity. It has been reported that *N*-alkylimidazoles with the most simple structure posses inhibitory effects on microsomal oxidation,[4] cytotoxic[5] and antifungal[2] activity. The length of the alkyl chain on the imidazole ring is of importance for biological activity, as 1-alkylimidazoles require a hydrocarbon chain of appropriate length, generally 12 carbons to illustrate antifungal and cytotoxic activity[2,5] and 10 for inhibition of microsomal oxidation.[4] We would like to report the synthesis of the title compounds as possible effective antibacterial agents. In our pervious study, we described that 1-alkylimidazole derivatives posses antifungal activity and this activity increases as the number of carbons in alkyl chain increases up to 12 carbons.[6,7]

In this study, antibacterial effects of these compounds were investigated to achieve the relationship between the length of the alkyl chain and antibacterial activity. Also we synthesized 1-alkylated products from 2-methylimidazole and 2-methyl-4-nitroimidazole to show how these substitutions affect the antibacterial properties of these compounds.

Chemistry

Usually 1-alkylatedimidazoles have been purified by vacuum distillation, and as these compounds have very high bp, even at a very low pressure, high temperature is required, especially for analogues with long alkyl chains,[4] which may lead to decomposition of the compounds. We have purified the crude products by flash chromatography instead of vacuum distillation.

Different azole compounds were reacted with appropriate alkylbromides in an alkaline media, at reflux temperature and in the presence of tetraethylammonium iodide (TEAI) or tetrabuthylammonium bromide (TBAB) as phase transfer catalysts (PTC) or triethylamine by methods A, B, or C (Scheme 1). Unsubstituted imidazoles produce alkylated products in high yield by method A, but substituted analogues work well by method B and C. The results are shown in Table 1.

Biological Assays

The compounds were investigated for antibacterial activity against *Staphylococcus aureus, Pseudomanas*

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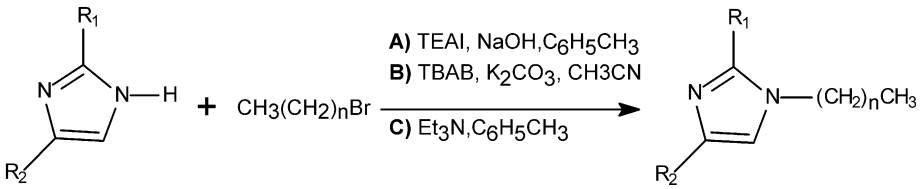

Scheme 1.

Table 1. Synthesis of alkylimidazole derivatives

Compd	R_1	R_2	Method	*n*	Chemical name of product	Yield (%)
1	H	H	A	1	1-Ethylimidazole	61.16
2	H	H	A	2	1-Propylimidazole	63.6
3	H	H	A	3	1-Butylimidazole	68.6
4	H	H	A	4	1-Pentylimidazole	69
5	H	H	A	5	1-Hexylimidazole	68.4
6	H	H	A	6	1-Heptylimidazole	64.8
7	H	H	A	7	1-Octylimidazole	64
8	H	H	A	8	1-Nonylimidazole	67
9	H	H	A	9	1-Decylimidazole	63
10	H	H	A	10	1-Undecylimidazole	67
11	H	H	A	11	1-Dodecylimidazole	70
12	H	H	A	12	1-Tridecylimidazole	65
13	H	H	A	13	1-Tetradecylimidazole	63
14	H	H	A	15	1-Hexadecylimidazole	69
15	H	H	A	17	1-Octadecylimidazole	69
16	CH_3	H	A	5	1-Hexyl-2-methylimidazole	68
17	CH_3	H	C	8	1-Nonyl-2-methylimidazole	72
18	CH_3	H	C	9	1-Decyl-2-methylimidazole	72
19	CH_3	H	A	11	1-Dodecyl-2-methylimidazole	70
20	CH_3	NO_2	B	3	1-Butyl-2-methyl-4-nitroimidazole	70
21	CH_3	NO_2	B	5	1-Hexyl-2-methyl-4-nitroimidazole	69
22	CH_3	NO_2	B	7	1-Octyl-2-methyl-4-nitroimidazole	73

Table 2. MIC and MBC (μg/mL) values for activity of compounds against bacteria

Compd	Chemical name	*S. aureus*		*P. aeruginosa*		*E. coli*	
		MIC	MBC	MIC	MBC	MIC	MBC
1	1-Ethylimidazole	480	960	960	1920	480	960
2	1-Propylimidazole	44	198	550	1100	110	220
3	1-Butylimidazole	87	174	248	496	99	198
4	1-Pentylimidazole	69	138	138	276	97	193
5	1-Hexylimidazole	46	91	122	243	91	182
6	1-Heptylimidazole	33	66	83	166	50	100
7	1-Octylimidazole	27	45	54	108	45	90
8	1-Nonylimidazole	10	19	39	78	19	39
9	1-Decylimidazole	208	416	416	832	208	416
10	1-Undecylimidazole	1110	2220	2220	4440	1110	2220
11	1-Dodecylimidazole	14,160	15,340	16,520	17,700	14,160	15,340
12	1-Tridecylimidazole	17,500	18,750	20,000	21,250	18,750	20,000
13	1-Tetradecylimidazole	19,800	21,120	23,760	25,080	21,120	22,440
16	1-Hexyl-2-methylimidazole	25	50			25	50
19	1-Dodecyl-2-methylimidazole	17,500	18,750			17,500	18,750
20	1-Butyl-2-methyl-4-nitroimidazole	17	33			18	37
22	1-Octyl-2-methyl-4-nitroimidazole	24	48			31	60
23	Gentamycin (10 μg/disk)	2	4	8	12	64	128

aeruginosa and *Escherichia coli* using disk diffusion method. In this method, microbes are streaked onto 15×100 mm Petri dishes containing Mueller Hinton agar and sterilized disks (6 mm in diameter) for each dilution.[8,9] Gentamycin standard disk (10 μg) and the solvent of compounds (hexane) were used as positive and negative blanks respectively. The data are presented in Table 2.

Conclusion

A series of analogues of alkylimidazole have been prepared. Several analogues showed significant in vitro activity against *E. coil, S. aureus* and *P. aeruginosa*. Antibacterial activity of 1-alkylimidazoles increases as the number of carbons in alkyl chain rises up to nine and then again decreases. So 1-nonylimidazole, **8** with

lowest MIC and MBC is the most effective compound, although for antifungal activity the most effective compound was 1-dodecylimidazole.[6,7] The comparison of MIC and MBC between compounds **5** and **16** shows that substitution with a methyl group at 2 position of imidazole ring increases the antibacterial activity in compounds with medium alkyl chain, this comparison between compounds **11** and **19** shows that this substitution decreases the activity in compounds with long alkyl chain. The same comparison between compounds **3** and **20**, **7** and **22** reveals that substitution of a methyl group at the 2-position and a nitro group at 4 position simultaneously increases the antibacterial activity in both compounds with medium and long alkyl chain. However increase in biological activity in 2-methyl-4-nitro analogues is more significant than 2-methyl analogues.

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