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Imidazole : Having Versatile Biological Activities

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ABSTRACT

Imidazole and its derivatives are one of the most vital and universal heterocycles in medicinal chemistry. Owing to their special structural features, these compounds exhibit a widespread spectrum of significant pharmacological or biological activities, and are widely researched and applied by pharmaceutical companies for drug discovery. We synthesized, evaluated for their antibacterial and antifungal activities. All the target compounds showed strong antifungal and antibacterial activity. These results strongly suggest that some of the compounds produced in this work have value for development as Antimicrobial agents.

Keywords : Antibacterial Agents, Antifungal Agents, Imidazole, Drug

I. INTRODUCTION

Imidazole ring, which is widely found in natural products and medical molecules, is one of the most prominent, five-membered, nitrogen-containing, heterocyclic scaffolds. Furthermore, imidazole-based heterocyclic compounds, which possess a vital position in medicinal chemistry, have been playing a central role in the treatment of numerous types of diseases, and new derivatives for medicinal use are being energetically developed worldwide[1-2]Imidazole application in solar cells[3]Tang et al. reported the synthesis of 2,4,5-trisubstited NH-imidazoles in moderate to good yield[4] Nitriles have also been used as reagents in metal free reactions for the formation of substituted imidazoles in which two-bonds of the heterocycle are formed. Harisha et al. recently reported the reaction of α-azidoenones with substituted nitriles to form tri-substituted NH-imidazoles [5] Recently, Nikolaenkova reported the synthesis of 2-carboxylate substituted imidazoles from oxime-hydroxlyamines[6]. Strelnikova et al. reported the synthesis of 5-sulphonamidoimidazoles from the reaction of two different heterocyclic starting materials in the presence of a rhodium catalyst [7]A number of recent methods for the synthesis of imidazoles in which three of the heterocycle bonds are formed have been reported. For example, imidamides were reacted with carboxylic acids in the presence of a copper catalyst to form imidazoles. [8] The reaction of excess amine

with enones has been shown to afford trisubstitued imidazoles. For examples, Salfeena et al. recently reported the copper-catalyzed reaction of amines with enones gave imidazoles with substitution at the 1, 2 and 4 positions in poor to moderate yield. [9]Heravi et al.[10] formulat heterogeneous catalyst using nickel chloride supported acidic alumina ($NiCl_2$6.H_2O/Al_2O_3).The authors explored the catalytic performance of this heterogeneous catalyst in preparing 2,4,5-trisubstituted imidazole derivatives.Kiumars et al. [11] have described a simple rapid procedure for the synthesis of 2,4,5- trisubstituted and 1,2,4,5-tetrasubstituted imidazoles through one-pot condensation reaction.Nikoorfar et al.[12] have reported the synthesis of 2,4,5-trisubstituted imidazoles by using ZnO nano rods as a reusable heterogeneous catalyst.

Chitosan, as a partially deacetylated derivative of chitin, is a linear polysaccharide consisting of b-(1,4)-linked D-glucosamine residues with variable randomly located N-acetyl-glucosamine groups on it. [13] As a natural polymer, polyaminosaccharide chitosan has attracted considerable attention due to its unique properties such as biological renewability, biodegradability, non-antigenicity and biocompatibility. It also has several chemical, medicinal and industrial applications. [14] The history of chitosan dates back to the 19th century, when Rouget [15] discussed the deacetylated forms of the parent chitin natural polymer in 1859. During the past 20 years, a substantial amount of work has been reported on chitosan and its potential use in various bioapplications. Chitosan is derived from naturally occurring sources, which is the exoskeleton of insects, crustaceans and fungi that has been shown to be biocompatible and biodegradable[16]The source of chitosan is a naturally occuring polymer, the chitin that is the second most abundant polysaccharide in nature, cellulose being the most abundant. Chitin is found in the exoskeleton of crustacea, insects, and some fungi[17].The main commercial sources of chitin are the shell waste of shrimps, lobsters, krills and crabs. In the world several millions tons of chitin are harvested annually and hence this biopolymer represents a cheap and readily available source. Chitosan is obtained by the thermochemical deacetylation of chitin in the presence of alkali and naturally it occurs only in certain fungi (Mucoraceae) [18]The attached side groups on chitosan provide versatile materials with specific functionality, alter biological properties or modify physical properties[19].

Slassi et.al.synthesized A new Schiff base by condensation of 2-Hydroxy-5-(p-tolyldiazenyl) benzaldehyde and N(-3-aminopropyl)imidazole, was assessed for its in vitro antibacterial activities against four pathogenic strains: Staphylococcus aureus, Pseudomonas putida, Klebsiella pneumoniae and Escherichia coli exhibited encouraging antibacterial activities comparing to other reported Schiff bases. [20] In the present work, synthesized Imidazole were assayed for antimicrobial activities, against selected strains.

II. METHODS AND MATERIAL

All the chemical of analytical grade. Benzil, 3-methoxy-4-methylbenzaldehyde, Ammonium Acetate(Sigma-Aldrich) were purchased from Sigma-Aldrich and used without further purification. IR Spectra recorded on Perkin Elmer Spectrometer in range 4000-400 cm-1 KBr pellets. Room Temperature magnetic moments by Guoy's method in B.M.Electronic Spectra using DMSO on Varian Carry 5000 Spectrometer. Molar Conductance measurements in dry DMSO having 1×10-3 concentration on Systronics conductivity bridge at room temperature. Elemental analysis (C, H, N) were carried out by using perkin Elmer 2400 elemental analyzer

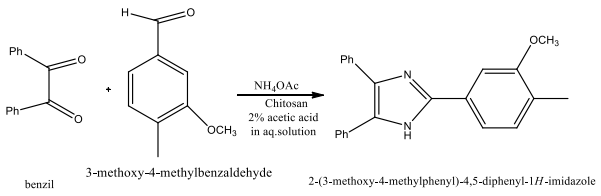
Antimicrobial Activity

2-(3-methoxy-4-methylphenyl)-4,5-diphenyl-1H-imidazole was evaluated in vitro their antibacterial activity against two Gram-Positive bacteria,viz, *B. Subtilis*; *S. aureus,* Two fungal strains *A. niger* and *F. oxysporum* by Kirby-Bauer disc diffusion method[21].The experimental value compare with standard drug value Miconazole for the Antifungal activity and Ciprofloxacin for the antibacterial activity.

Synthesis of 2-(3-methoxy-4-methylphenyl)-4,5-diphenyl-1H-imidazole

3-methoxy-4-methylbenzaldehyde (0.30g, 2 mmol), benzil (0.42 g, 2 mmol) and ammonium acetate (0.32 g, 4.2 mmol) were added in a round-bottom flask with 0.09g of chitosan in 2% aq.acetic acid solution[22]. The reaction mixture was stirred a room temperature for 5 min.Then reaction mixture was heated at 65-70^{o}C for 4 hr . The reaction was allowed to cool to room temperature. The resulting precipitate was collected by filtration and washed with cold ethanol to afford the product. The crude product was purified by recrystallization from ethanol (Scheme.1).

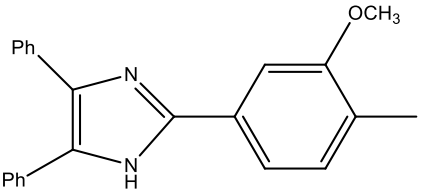
Scheme 1.Synthesis of Substitute imidazole



III.RESULTS AND DISCUSSION

2-(3-chloro-4-methylphenyl)-4,5-diphenyl-1H-imidazole is prepared (Table.1).Imidazole is stable at room temperature in solid state. The Imidazole is soluble in organic solvent DMSO, DMF, The solid imidazole products, which separated out, were filtered, washed with water and dried. The crude products, thus isolated, were pure (single spot on TLC). After completion of the reactions, solid mass was filtered and the filtrate having chitosan catalyst was reused in the next run as such without any further treatment. Recycled chitosan catalyst was reused for 15 times. Acetic acid was used in this reaction only for homogenizing the chitosan catalyst and itself did not work as catalyst which has already been studied in experiment.

Table 1 : Proposed Structures of Subtituted Imidazole



2-(3-methoxy-4-methylphenyl)-4,5-diphenyl-1H-imidazole

Chacterization of 2-(3-methoxy-4-methylphenyl)-4,5-diphenyl-1H-imidazole

Faint yellow Solid; $C_{23}H_{20}N_2O$; M.P.:140^{o}C;Yield:92%; IR(KBr Cm^{-1}): 686,1215,1655,2468,2872,3427, 2935;^{1}H NMR (400 MHZ.DMSO d_6) δ ppm: δ 2.12(s,3H), δ 3.36(s,3H), 7.12–7.36 (m,10H), 12.96 (s,1H); 7.20 (s,1H), 8.06 (d,1H), 7.12(d,1H),, ^{13}C NMR($CDCl_3$/DMSO-d_6, 400 MHz) δ 20.6, 56.4,124.5-138.6,110.3-164.2,129.6 178.2; $C_{23}H_{20}N_2O$: calcd C, 81.15; H, 5.92; N, 8.23;Found C, 80.25; H, 4.98; N, 8.59.

IR Spectra of 2-(3-methoxy-4-methylphenyl)-4,5-diphenyl-1H-imidazole show peak at 3427 Cm^{-1} for imidazole ring nitrogen atom confirms the formation of Imidazole, peak at 686 Cm^{-1} due to C-Cl stretching in imidazole ring. Peak at 2935 cm^{-1} is an absorption band due to C-H vibrations in the side-chain methyl group of methylbenzene, Also different peak at 1215,1665,2468,2872 Cm^{-1} also suggest substituted imidazole compound is formed[23].^{1}H NMR Peak at δ 3.36 for s for 3H of methoxy group and peak at δ 2.12 for s for 3H of methyl group attached to aromatic ring, Aromatic ring peak observed in between range of δ 7.12-8.06. δ 7.12–7.36 is m,for 10H of two phenyl ring proton. δ 12.96 is for 1H attached to nitrogen atom

confirms the formation of imidazole. ^{13}C-NMR spectra of imidazole show peak at δ 56.4 for methoxy carbon and peak at δ 20.6 for methyl carbon attached to benzene ring, Aromatic carbon in benzene show peak in range between δ124.5-138.6 and imidazole ring carbon show peak in between range δ 110.3-178.2[24].Mass Spectra of Substituted imidazole shows peak at m/z 341.40 [M+H,100%], which is M+H peak at 100% intensity this peak support to the structure of the Imidazole. [25].

Antimicrobial Activity

2-(3-methoxy-4-methylphenyl)-4,5-diphenyl-1H-imidazole were examined for antimicrobial activity against different bacteria, namely, B. subtilus, S. aureus, and Fungal species A. niger and F.Oxysporum. Imidazole derivatives evidenced that the compounds have emerged as potent antibacterial and antifungal agents with moderate activity compared to the standards.(Table 2.) [26].

Table 2. Antimicrobial activity of Imidazole

Compounds	**Antibacterial Activity**		**Antifungal Activity**	
	S.aureus	***B.subtilis***	***A.niger***	***F.oxysporum***
	Diameter of inhibition Zone in mm	Diameter of inhibition Zone in mm	Diameter of inhibition Zone in mm	Diameter of inhibition Zone in mm
	500 ppm	500 ppm	500 ppm	500 ppm
S.Imidazole	23	26	27	22
Ciprofloxacin (Standard)	34	33	----	----
Miconazole (Standard)	----	----	31	27

IV. CONCLUSION

Different derivatives of benzaldehyde produced an excellent yield of imidazole-containing products in a short reaction time under optimized reaction conditions. Green Catalyst Chitosan was recycled and reused with a minimum loss of its catalytic activity, useful for industrial purposes. Green Catalyst Chitosan is a cost-efective and potential green catalyst in organic synthesis, which can contribute to the development of catalytic processes and reducing the environmental impact. The prepared Substituted imidazoles revealed high antibacterial and antifungal activities and can be useful in many biomedical applications.

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