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AN EFFICIENT METHOD OF BIO ACTIVE SYNTHESIS OF N-SUBSTITUTED BENZIMIDAZOLE DERIVATIVES

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ABSTRACT

A Heterocycles molecule possesses benzimidazoles scaffold are of great important and interest because they represent an important class of numerous synthetic compounds which have beneficial biological properties. In this article, the synthesis of new N-substituted benzimidazole derivatives 5a-5f described. These compounds were prepared by first designing the N-substituted benzimidazoles (5a-f). The derivative 3a was obtained from the condensation reaction between O-Phenylene diamine and p- chlorobenaldehyde in presence of methane sulfonic acid as a catalyst. All the compounds were evaluated by advanced spectroscopic data (1H NMR, 13C NMR and LCMS) and the structural determination of the novel derivations was calculated by elemental analysis. In the present study, ten hybridized acridine derivatives were synthesized via cyclo condensation and evaluated for their in vitro antifungal Activity antimicrobial activity.

KEYWORDS

O-phenyldiamine, 4-Chlorobenzaldehyde, Methanesufonic acid, Substituted (bromomethyl) benzene, 1-benzyl-2-(4-chlorophenyl)-1H-benzo[d] imidazole and Antifungal activity.

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INTRODUCTON

Organic molecules bearing different heterocyclic ring systems have attracted a great deal of attention in now a day, both in chemical and medicinal research that could be attributed to their different pharmacological applications. Benzimidazoles represent a class of nitrogen heterocyclic which possesses biological and pharmacological activities. Synthetically produced heterocycles designed by organic chemists are used as pharmaceuticals, dyestuff, agrochemicals and are of increasing importance in many other areas including

adhesives, molecular engineering, polymers etc. In biological processes naturally occurring heterocyclic moieties played a vital role. They are broadly found in naturally in plant alkaloids, nucleic acids, and anthocyanin's and flavones as well as in chlorophyll. Additionally several proteins, hormones, vitamin's contain aromatic heterocyclic ring system[1-3]. Heterocycles act as drugs because they have specific chemical reactivity and they provide convenient building blocks to which pharmacologically active substituent can be attached. Thus, we needed the development of innovative methodology for bioactive heterocyclic in synthetic organic and medicinal chemistry with some advantages including its simplicity of operation, greener approach, easy workup procedure, selectivity, higher yields and high-atom economic[4]. Nitrogen heterocyclic compounds are among the most privileged and significant structural components of pharmaceuticals[5,6]. A recent analysis of the nitrogen heterocyclic composition of U.S. FDA (Food and Drug Administration) approved drugs has revealed the relative frequency by which various nitrogen heterocyclic compounds have been incorporated into approved drugs architecture[7]. Nitrogen containing heterocycles are present in vitamins, proteins and nucleic acids. Benzimidazoles a heterocyclic aromatic organic compound. The most prominent compound available in the nature containing benzimidazoles skeleton is Nribosyl dimethyl benzimidazoles, which serves as axial ligands for cobalt in vitamin B12[8]. Benzimidazole moieties are very important class of heterocyclic compounds are that have many applications in pharmaceutical industry. Benzimidazole derivatives have attracted a significant attention in recent years because of their medicinal applications as antiviral, antifungal[9], antihypertensive[10] and anticancer[11], compounds. Apart from therapeutic applications, benzimidazoles formed as intermediates in different organic reactions. In addition to this benzimidazoles are used as fluorescent whitening agent, dyes, organic ligands and functional materials[12-14]. Pharmacologically active molecules such as albendazole/ mebendazole/thiabendazole (anthelmintic), omeprazole (antiulcer), astimizole (antihistaminic) etc. contains the substituted benzimidazoles and display a broad spectrum of potential pharmacological activities. Benzimidazole derivatives also show cytotoxic activity. Substituted benzimidazole derivatives is evaluated by their ability to inhibit gastric H+ /K+ ATPase and by blocking the gastric acid secretion[15.]

MATERIAL AND METHODS

Experimental

All chemicals, reagents and solvents were procured from commercial suppliers. The melting points of the newly synthesized derivatives were recorded on Buchi 535 melting apparatus. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Advance 400 MHz/ Ascend instrument. All NMR spectra were measured in $CDCl_3$-d6 solutions using TMS as an internal standard. All compounds were routinely checked by TLC with Merck silica gel 60F-254 glass plates and the spots were detected under UV light. Elemental analysis for carbon, hydrogen and nitrogen were performed on a PerkinElmer 2400 elemental analyzer. Where analyses are indicated only as symbols of elements, analytical results obtained are within 0.4% of the theoretical value.

General procedure for the synthesis of 2-(4-chlorophenyl)-1H-benzo imidazole (3a)

O-Phenylene diamine (1) (mole) and p-chlorobenaldehyde acid (2a) (1mole) both in stoichiometric proportion were taken in a 50mL RBF and introduced Methanesulfonic acid as a catalyst. The reaction mixture was stirred for 2 hrs at RT. The reaction was monitored by TLC (4:6, ethyl acetate: n-hexane) after the completion of reaction. The reaction mixture was poured into crushed ice. The solution was neutralized with aqueous solution of sodium bi carbonate and product was extracted using ethyl acetate, the combined organic layer was washed using water and organic layer separated. The organic layer was dried on anhydrous sodium bi carbonate and the solvent was removed under reduced pressure with using vacuum pump to get the solid product. All the titled compounds were recrystallized from ethanol.

Yield-89%, m.p. 261-263^{o}C. IR(KBr) ν = 3194 (-NH), ν = 1595 (C=N), ν =1427 (C=C), ν = 1320 (C-N), ν =815Aromatic ring and ν =762 1, 2-disub Aromatic ring cm-11H NMR (CDCl3) 8.214 (m, 2H, Ar-H), 7.614 -7.456 (m, 2H, Ar-H), δ7.254-7.125 (m, 2H, Ar-H), δ10.12ppm (s, 1HN Himidazole). Mass (m/z): 229.14 (M+).

General procedure of 1-benzyl-2-(4-chlorophenyl)-1H-benzo[d] imidazole analogous

Take dry and clean four neck 50mL RBF. The solvent as methylene dichloride poured in RBF.Amixture1-benzyl-2-(4-chlorophenyl)-1H-benzo [d] imidazole and substituted (bromomethyl) benzene is dissolved in methylene dichloride and added the strong base triethylamine above the RBF. When the solution becomes clear, was added and the reaction mixture was refluxed for 5 hours. The reaction was monitored by TLC (3:7, ethyl acetate: n-hexane) after the completion of reaction. The reaction mixture was poured into crushed ice. The solution was neutralized with 2N HCl solution and product was extracted using ethyl acetate, the combined organic layer was washed using water and organic layer separated. The organic layer was dried on anhydrous sodium sulphate and the solvent was removed under reduced pressure with using vacuum pump to get the solid product. All the titled compounds were recrystallized from ethanol.

1-benzyl-2-(4-chlorophenyl)-1H-benzo[d] imidazole (5a)

Palered solid yield-85%, m.p-224-226^{o}C. ^{1}HNMR (400Mz, CDCl3) ppm: 8.096-7.892 (m, 2H, Ar-H), 7.656-7.278 (m, 6H, Ar-H), 7.212-7.096 (m, 5H, Ar-H), 5.126 (s, 2H, -CH2-). ^{13}CNMR (100MHz, CDCl3) ppm: 151.74, 142.56, 126.92, 133.92, 131.23, 129.62, 128.92, 128.45, 127.85, 126.57, 123.25, 120.19, 50.19. LCMS (m/z): 320.21 (M+2); Molecular formulae: $C_{20}H_{15}ClN_2$. Elemental analysis: Calculated: C-75.35., H-4.74, N-8.79. Obtained: C-75.27, H-4.73, N-8.86.

2-(4-chlorophenyl)-1-(4-methoxybenzyl)-1H-benzo[d] imidazole (5b)

Palered solid yield-89%, m.p-255-2757^{o}C. 1HNMR (400Mz, CDCl3) ppm: 8.062-7.951 (m, 2H, Ar-H), 7.625-7.284 (m, 6H, Ar-H), 7.102-6.943 (m, 4H, Ar-H), 5.457 (s, 2H, -CH2-), 3.676 (s, 3H, OCH3), 13CNMR (100MHz, CDCl3) ppm: 155.74, 151.62, 141.76, 136.35, 131.46, 129.51, 129.15, 128.88, 128.36, 128.01, 124.72123.11, 114.62, 56.74. LCMS (m/z): 350.24 (M+2). Molecular formulae: C21H17ClN2O. Elemental Analysis: Calculated: C-72.31, H-4.91, N-8.03. Obtained: C-72.23, H-4.89, N-8.11.

1-(4-chlorobenzyl)-2-(4-chlorophenyl)-1H-benzo[d] imidazole (5c)

Palered solid yield-90%, m.p-256-258^{o}C. 1HNMR (400Mz, $CDCl_3$) ppm: 8.096-7.962 (m, 2H, Ar-H), 7.656-7.296 (m, 6H, Ar-H), 7.210-7.092 (m, 4H, Ar-H), 5.156 (s, 2H, -CH2-), 13CNMR (100MHz, $CDCl_3$) ppm: 152.62, 141.02, 137.32, 133.26, 131.47, 130.62, 129.38, 128.92, 128.51, 128.29, 127.65, 122.72, 119.62, 117.92, 50.82. LCMS (m/z): 354.32 (M+2). Molecular formulae: $C_{20}H_{14}ClN_2$. Elemental Analysis: Calculated: C-68.00, H-3.99, N-7.93. Obtained: C-67.91, H-3.97, N-7.99.

4-((2-(4-chlorophenyl)-1H-benzo [d] imidazol-1-yl) methyl) benzonitrile (5d)

Palered solid yield-86%, m.p-269-271^{o}C. ^{1}HNMR (400Mz, $CDCl_3$) ppm: 8.096-7.921 (m, 2H, Ar-H), 7.684-7.274 (m, 10H, Ar-H), 5.145 (s, 2H, -CH2-), ^{13}CNMR (100MHz, CDCl3) ppm: 152.06, 140.32, 138.46, 135.63, 132.74, 129.66, 129.02, 128.77, 128.39, 128.12, 123.05, 119.26, 118.08, 117.45, 51.02; LCMS (m/z): 345.75 (M+2). Molecular formulae: $C_{21}H_{14}ClN_3$. Elemental Analysis: Calculated: C-73.36, H-4.10, N-12.22. Obtained: C-73.27, H-4.08, N-12.30.

2-(4-chlorophenyl)-1-(4-nitrobenzyl)-1H-benzo[d] imidazole (5e)

Palered solid yield-83%, m.p-245-247^{o}C. 1HNMR (400Mz, $CDCl_3$) ppm: 8.142-7.978 (m, 2H, Ar-H), 7.945-7.271 (m, 10, Ar-H), 5.248 (s, 2H, -CH_2-); 13CNMR (100MHz, CDCl3) ppm: 15108, 140. 56, 136.45, 132.78, 129.78, 129.35, 128.86, 128.54, 128.25, 128.08, 123.45, 119.27, 117.45, 51.78, LCMS (m/z): 365.24(M+2). Molecular formulae: $C_{20}H_{14}N_3ClO_2$ Br. Elemental Analysis: Calculated: C-66.03, H-3.88, N-11.55. Obtained: C-65.95, H-3.86, N-11.63.

Biology

Antifungal Activity Assay

The yeasts are grown sabouraud Dextrose Broth media; the yeasts were incubated for 72 h at 25-27°C. The antifungal activity tests were carried out at pH 7.3 in Sabouraud Dextrose Broth and the 2-fold dilution was applied. A set of tubes containing only inoculated broth were kept as controls. After incubation for 72 h at 25-30°C, the last tube with no yeast growth was recorded to represent minimum inhibitory concentration (MIC), expressed in µg/ml.

RESULTS AND DISCUSSION

Chemistry

The reaction sequences scaffold to various titled analgueous is as shown "Scheme No.1". The N-substituted benzimidazoles analogous were synthesized by incorporating new pharamacophores dues amides linkage position at "1" of the N-substituted benzimidazoles moiety by using a conventional method in which O-phenyldiamine and 4-Chlorobenzaldehydes were taken as a starting material in presence of methanesulphonic acid give the corresponding 2-(4-chlorophenyl)-1H-benzo imidazole and N-substituted benzimidazoles analogous can be obtained from2-(4-chlorophenyl)-1H-benzo imidazole with substituted (4-bromobezene) methane. Titled compounds were identified based on their physical properties i.e., solubility, melting point, thin chromatographic methods (TLC).The spectroscopic methods are submitted in the supplementary material for this article.

The 1HNMR spectra exhibited a peak at 3.678 δppm shown the presence of –OCH3proton, a peak between 8.096-6.874δppm showed aromatic proton, a peak exhibited between 5.245-5.125 δppm represents CH protons.

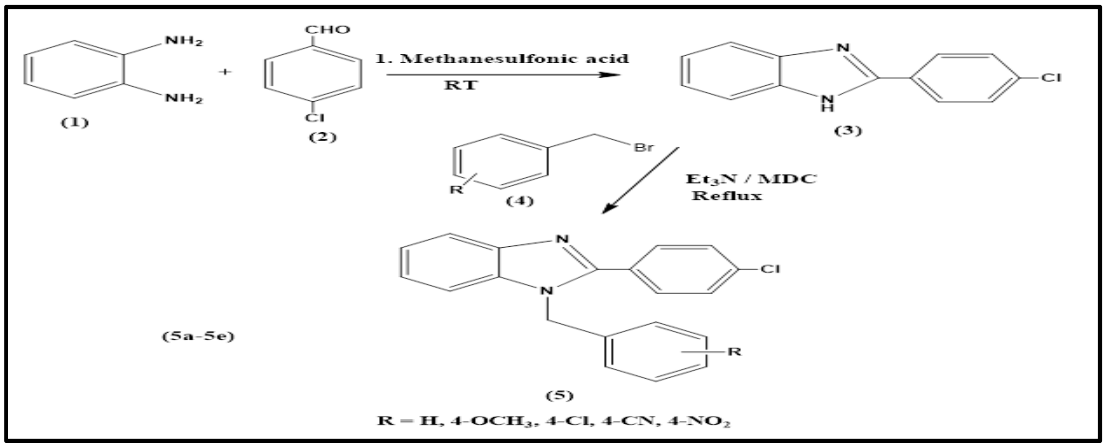
The 13CNMR spectra recorded a peak maximum at 169.5δppm is belongs to the carbonyl group in carboxylic group. The LCMS spectra recorded the molecular weight of halogen compounds represent (M+2) peak. The derivatives "5a-5e" exhibited (M+2) peacks.

Antifungal Activity Assay

The *in vitro* antifungal activity of the compounds was tested by the tube dilution technique (Hausler *et al*, 1991)[16]. Each of the test compounds and standards miconazole and fluconazole were dissolved in 10% DMSO, at concentrations of 100µg/ml. Further dilutions of the compounds and standards in the test medium were performed at the required quantities µg/concentrations. The final concentration was 105CFU/ml. The MICs were defined as the lowest concentration of the compounds that prevented visible growth of the fungus. It was determined that the solvent had no antifungal activity against any ofthe test microorganisms. All the compounds were tested for their *in vitro* growth inhibitory activity against *Aspergillus Niger, C. albicans and Aspergillusfavus* (Table No.1). Compounds 5a, 5b, 5c, 5d and 5e possessed comparable activity to fluconazole against *C. albicans* with a MIC of 12.5µg/ml. None of the compounds was superior to the standards used against any fungus.

Table No.1: Antifungal activity of the synthesized compounds (5a-5e) Zones of inhibition (mm) a of compounds (5a–5e) against tested fungal strains

S.No	Entry	Anti-Fungal Activity		
		Aspergillus Niger	Candida albicans	Aspergillusfavus
1	5a	08	10	10
2	5b	10	09	07
3	5c	12	11	12
4	5d	17	16	14
5	5e	21	22	20
6	Ketonozole	25	25	25
7	DMSO			



Scheme No.1: The reaction sequences scaffold to various titled analgueous

CONCLUSION

To find out this experiment, we prepared the five N-substituted benzimidazoles derivative. The compounds having electron donating groups and electron withdrawing groups including halogen containing derivatives. The percentage of the derivatives acquired electron donating group (90%) compared with electron withdrawing group of the compounds. As shown Scheme No.1, the compound "3" obtained using methane sulfonic acid excellent Bronsted Acid catalyst. The compound "5" prepared using alkali base in neutral non-polar solvent and derivatives of (5a-5e) synthesized by organic base (TEA) in non- polar solvent (DCM).In addition to antifungal activity of these derivatives exhibited different active potential in various bacterial as well as antifungal activity.

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CONFLICT OF INTEREST

We declare that we have no conflict of Interest.

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