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SYNTHESIS CHARACTERIZATION AND BIOLOGICAL ACTIVITY BENZIMIDAZOLE DERIVATIVES

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Abstract:

The reaction of o-phenylenediamine with anthranillic acid yield compound 2-(1H-benzo[d]imidazol-2-yl) aniline (AOP). The compound AOP was cadenced with aromatic acid chlorides in the presences of pyridine to get compound N-(2-(1H-benzo[d]imidazol-2-yl) phenyl) benzamide (AB). Further it to then treated with PCl_5 to get an intermediate compound then reacted with NaN_3 to get compound 2-(2-(5-phenyl-1H-tetrazol-1-yl) phenyl)-1H-benzo[d]imidazole (ABC). The compound was synthesized in good yield and the structures were confirmed by their TLC, IR, ^1H NMR, ^{13}C NMR and Elemental analysis. Their antimicrobial activity against bacteria and fungi were studied. The result showed that all of the compounds have good biological activity.

Key words*:* Anthranillic Acid, *o*-phenylenediamine, PCl_5 & NaN_3

Introduction:

The vast array of structures which organic compound adopt, may contain ring system as a component. When the ring system is made up of carbon and at least one other element, the compound classified is heterocyclic compounds. The main aim of organic chemist is to identify the effects which the presence of such ring system has on the properties of a molecule, to show how the ring can be made, and describe some of the properties and uses of the compounds in organic synthesis, in medicine and in other context. Organic chemistry has its origin in the study of natural products and this still remains its most important role. Many heterocyclic compounds occur naturally and their functions are often fundamental importance to living systems, it is sticking how often heterocyclic compound is found as a key component in biological process[1].

Natural products often occur in very small quantities and therefore difficult to isolate from natural sources. Organic chemists can provide a solution to this problem by devising laboratory synthesis. For example is provided by serotonin, which although widely distributed in nature, occur very small or low concentration. It is derived from tryptophan by enzymatic hydroxylation at C-5 followed by decarboxylation. Chemists can thus make use of these natural products as the starting materials for modified, synthetic drugs, or as the prototypes for the design of total synthetic drugs. Many pharmaceuticals are totally synthetic compounds and a large proportion of these are heterocyclic[2].

We will be familiar with carbocyclic compounds, such as cyclohexane and benzene, which are built from rings of carbon atoms. If one or more of the carbon atoms is replaced by another element, the product is a heterocyclic. Multiple replacements are commonplace, and the elements involved need not be the same. The most common are oxygen sulfur and nitrogen, but many other elements can function in this way including boron, silicon and phosphorus. Chemists have been working with heterocyclic for more than two centuries, and trivial names were often applied long before the structures of the compounds were known for a result, many heterocyclics retain these names for

selection of common five and six member heterocyclic that contain one oxygen, nitrogen and sulfur atom are included. The ring atoms are normally numbered such that the heteroatom carries the lowest number.

In other areas in which organic compounds are widely used, such as the peptides and dyestuffs industries, heterocyclic compounds are also predominant. In laboratory synthesis, the heterocyclic compounds are frequently a source of latent functionality. The ring system can be carried through many stages of a synthetic sequence and they cleaved to produce delicate functional groups, often in a highly stereo selective manner. The pharmaceutical activity of the compounds due to the function of specific groups that occupied the position of that group or atom or bond or stereo chemical orientation. The whole pharmaceutical activity of the compounds has been decided by the above groups. Hence the determination of the structure of a biologically active molecule provides two-fold benefits to pharmacy and medicine. It makes possible research leading to synthesis and modification of the structure. Pharmacological research plays an important role in its contribution to pharmacy and medicine.

Many of heterocyclic compounds show biological as well as the pharmacological activities. Some of the medicinally used compounds are listed below. The following compounds are not used as such is converted into its derivatives. These derivatives are more biological and pharmacologically active. For example benzimidazole is less potent compared to its carbamide, acid chloride and tetrazole derivatives. So only the derivatives of heterocyclic compounds are only used for the pharmaceutical application. From these compounds benzimidazole derivatives are widely used in the pharmaceutical areas so now days may of organic chemist to do research in this area. Hence the recent researchers focus in this area.

Benzimidazole derivatives are very useful intermediates or subunits of the development of pharmaceutical or biological interest[1]. Benzimidazole derivatives are an important class of bioactive molecules in the field of drugs and pharmaceuticals[2]. Benzimidazole derivatives have found the application in diverse therapeutic areas including antiulcers, antihypertensive, antiviral, antifungal, anticancer, anti histaminics[3], antitublercular[4], antiallergic[5.6], antioxident[7,8],antimicrobial activity[9-11] and *in vitro* anti-HIV-1 activity[12] etc.,

A wide variety of Benzimidazole derivatives have been described for their chemotherapeutic importance [13,14]. Oxdiazole compounds have shown biological activity against parasites[15] and bacteria[16,17] and also presence of Mannich base side chains in drug may over come the water insolubility problem through the formation of hydrochlorides. Some heterocyclic moieties such as triazole nucleus are known to posse's antibacterial activity[18], anti fungicidal[19]. Further Schiff base posses anticancer activity[20,21] in animal screening and pyrazole, pyrazolone and alkylpyrazoles have show wide range of pharmaceutical activities[22].

A compound contains Benzimidazole rings and benzene rings have been used extensively or pharmaceutical purpose since 1960. 1-H-benzinidazole rings, which exhibit remarkable basic characteristics due to their nitrogen content, comprise the active substances for several drugs. A number of biological activities have been attributed to these compounds[23].

The development of drug resistance to existing antimicrobial treatment has lent to research for novel more effective antimicrobial and antifungal agents. Literature survey shows that benzimidazole derivatives are play vital role in biological field such as antidiabetic[24], antimicrobial[25], antiviral[26], antispasmodic[27] and anticancer activities[28,29].

Experimental Section:

All the melting point were taken in open capillaries and are uncorrected. IR spectra were recorded in KBr on Schimadzu, ^{1}H NMR and ^{13}C NMR in DMSO-$d_6$on Burker (AC 400 MHz) using TMS as an internal standard.

Synthesis of 2-(6- Bromo-1H-benzoimidaol-2-yl) phenylamine (1)

A mixture of o- Phenylendiamine (0.1mol) and 2-aminobenzoic acid (0.1 mol) was heated on a water bath for 2 1/2 hours. It was cooled and add 10% NaOH was added slowly with constant stirring until just alkaline. The crude product was filtered, washed with cold ice water, decolorized and washed repeatedly and dried well. The product was recrystalized from ethanol.

Synthesis of N-(2-(6-Bromo-1H-benzoimidazol-2-yl) phenyl) benzamide (2)

A mixture of compound (0.01 moles) of **(1)** and equivalent amount of benzoyl chloride (0.01 moles) was refluxed with pyridine (40 ml) for 3 hours. The reaction mixture was cooled, treated with cold ice and neutralized with conc. HCl. The separating solid was filtered and washed with ice cold water. The product was recrystalized from ethanol.

Synthesis of 6- Bromo-2-(2-(5-phenyl-tetrazol-1-yl)-phenyl)-1H-benzoimidazole (3)

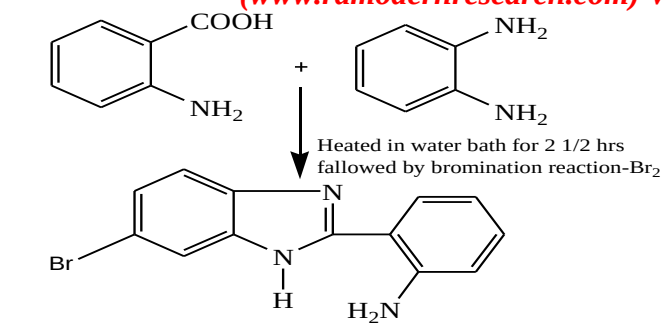
A known amount of compound AB 0.01 mole was taken in a beaker and added a known amount of PCl_5 0.01mol was heated at 100^0C until the evaluation of HCl fumes ceased. The reaction mixtures contain some unreacted $POCl_3$ this was removed by distillation under reduced pressure. The resulting was treated with ice cold solution of known weight of NaN_3 0.02 mol, a known volume of acetone 40 ml, known volume of sodium acetate was added. The reaction mixture was stirred over night. The acetone was removed by distillation under reduced pressure. The resulting mixture was extracted with $CHCl_3$ then the organic layer was separated and evaporated we got product. The product filtered and washed with ice cold water. The product was recrystalized from benzene and pet-ether mixture.

Reaction Scheme:

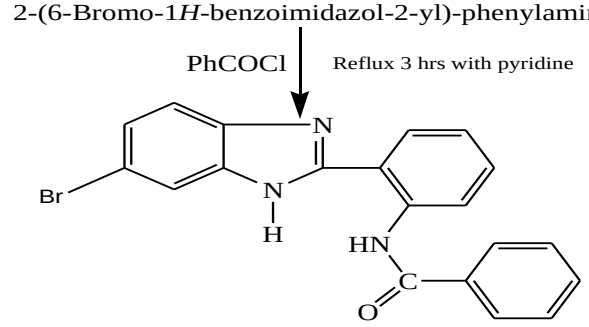
Compound **(1)** mp 108 ^{0}C Yield 74% (Found C, 74.64; H, 5.26; N, 20.09% $C_{13}H_{11}N_3Br$) IR: 3391.23 (N-H stretching for 1^0 amine), 3284.2 (N-H stretching for 2^0 amine), 3040.3 (aromatic C-H stretching), 1636.1 (C=N stretching), 1326.7 (C-N stretching).

Compound **(2)** mp 187 ^{0}C (Found C, 76.64; H, 4.7; N, 13.39; O, 5.09% $C_{20}H_{15}N_3OBr$) IR: 3272.12 (N-H stretching), 3060.4 (aromatic C-H stretching), 1650.25 (C=O stretching), 1587.29 (C=N stretching), 1311.3 (C-N stretching), ^{1}H NMR: δ 7.29-7.88 (13H, m, Ar-H), 8.4 (1H, s, CO-NH), 10.9 (1H, s, imidazole ring NH), ^{13}C NMR: δ 115-128 (18C, Ar-C), 169 (1C, C=O), 150 (1C, C=N).

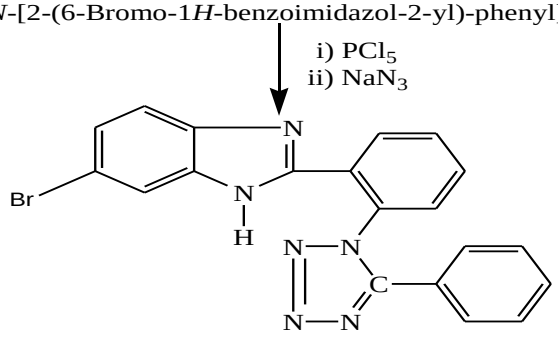
Compound **(3)** mp 236 ^{0}C (Found C, 70.97; H, 4.14; N, 24.80; $C_{20}H_{14}N_6Br$) IR: 3274.3 (N-H stretching), 3059.3 (aromatic C-H stretching), 1658.7 (C=N stretching), 1312.3 (C-N stretching), ^{1}H NMR: δ 7.1-7.91 (13H, m, Ar-H), 10.5 (1H, s, imidazole ring NH), ^{13}C NMR: δ 114-131 (18C, Ar-C), 159 (1C, C=N in tetrazole ring), 150 (1C, C=N).



2-(6-Bromo-1*H*-benzoimidazol-2-yl)-phenylamine



N-[2-(6-Bromo-1*H*-benzoimidazol-2-yl)-phenyl]-benzamide



6-Bromo-2-[2-(5-phenyl-tetrazol-1-yl)-phenyl]-1*H*-benzoimidazole

Antimicrobial Activities:

The antimicrobial activity for the given samples was carried out by Disc Diffusion Technique (Indian Pharmacopoeia 1996, Vol II A-105). The test micro organisms of Gram positive *Staphylococcus aureus* and Gram negative *Escherichia coli* and fungus *Candida albicans, Aspergillus Niger* were obtained from National Chemical Laboratory (NCL) Pune and maintained by periodical sub culturing on Nutrient agar and Sabourad dextrose medium both bacteria and fungus respectively. The effect produced by the sample was compared with the effect produced by the positive control (Reference standard Ciprofloxacin 5µg/discfor bacteria and Fluconazole 10 µg/disc for fungi). The result indicated that compounds were more active against all four organisms with reference to standard. The results are shown in the table I.

Table I – Antimicrobial screening results of the compounds

S. No.	Name of the Microorganism	Diameter zone of inhibition in mm		
		1	2	Std.
1.	*Staphylococcus aureus* (NCIM 2079)	25	32	40
2.	*Escherichia coli* (NCIM 2065)	30	36	40
3.	*Candida albicans* (NICM 3102)	15	17	20
4.	*Aspergillus Niger* (NICM 105)	14	16	20

Conclusion:

The present research work demonstrates an unforced and convenient method for synthesized those compounds are solvent using method for the condensation step proved to be more efficient and friendlier to the environment than the standard procedures. The condensation reaction takes place at relatively high temperatures. This method also simplifies the handling of the reactions and yields benzimidazole derivative. This procedure is simple, non-toxic and low cost. The reactions scheme exhibited good activity and valuable contribution to the existing methodologies. All the biological activities have good inhibition property.

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