CHAPTER–I

Overview on the Chemistry of Benzamide and its derivatives
1.1 INTRODUCTION

Benzamides are identified as important structural unit present in many compounds having potential biological activities, which are extracted from natural sources. For example, molecules, like proteins which play a essential role in almost all biological processes such as enzymatic catalysis (nearly all known enzymes are proteins), transport/storage (haemoglobin), immune protection (antibodies) and mechanical support (collagen). In amide all the three atoms in the O–C–N chain are reactive which makes them a useful moiety in organic compounds and hence become a key part for medicinal chemists. Some of the naturally occurring amides [1] are 1, 2, 3, 4.

![Image of structures 1 and 2]

Some of the medicinally important drugs [1] containing amide moiety are, (3), (4).

![Image of structures 3 and 4]
Benzamide (C₆H₅CONH₂) (5) exhibits an angle of about 15º with the plane of the amide group; this shows that benzamide molecule is not flat [2, 3]. The rotation of the amide group relative to the aromatic ring may result from the repulsion interaction between the hydrogen atoms of the amide group and those of the aromatic ring.

The nitrogen is in $sp^2$ hybridization state and non-bonding electron pair of the nitrogen atom has an almost pure p orbital character. The bond length investigation reveals that the length of C = O bond is 1.26 Å which is greater than the standard length (1.20 Å). The length of the C-N (1.38 Å) bond shows deviation from the standard C-N length (1.47 Å) [4, 5]. In other words the calculated bond length values are intermediate between the double bonds and single bonds. This confirms that the π electrons of the CO bond are combined with the p lone pair of the nitrogen atom [6].
1.2 SYNTHESIS OF BENZAMIDE

The formation of amide bonds were explained by well known classical reaction like Schotten Baumann, Scmidt and Ugi reactions.

**scheme 1.1.**

![Scheme 1.1: General Method of synthesis of Amide](image)

**Scheme 1.1: General Method of synthesis of Amide**

One of the methods frequently used is aminolysis of acid chlorides (18) in the presence of non nucleophilic tertiary amines. [7]. as presented in **scheme 1.2**

![Scheme 1.2: Synthesis of Amides](image)

**Scheme 1.2: Synthesis of Amides**

Another method employed by Aleksandra Filipovska *et al* for synthesis of N-phenylbenzamide (22) is shown in **scheme 1.3** were used [8].
1.3 APPLICATIONS OF BENZAMIDE DERIVATIVES

The comprehensive medicinal chemistry database revealed that the carboxamide group appears in more than 25% of known drugs [9]. Benzamides (23) have been reported to possess in vitro antibacterial activity. These benzamides exhibit optimal antimicrobial activity against *Staphylococcus aureus* [10].

M L Carmellino *et al.* have synthesized the fluoro derivatives of dithiobis(benzamide)(24) which showed antifungal activity [11].
2-Iodobenzamide derivatives (25) were synthesized by D.Raffa et al. and showed antifungal activity against phytopathogenic fungi P.citrophthora, B.cinerea, R.solani and Alternaria species [12].

Benzamides containing diketoacids (26) were designed and synthesized by H.Li et al. and evaluated for HIV activity. Structure activity relationship of these compounds were investigated by increasing the carbon chain between benzene and amide group [13].

G. Nagalakshmi et al have synthesized and further reported that N-[substituted phenyl]-5-methyl-4-oxo-1,3-thiazolidin-3-yl]benzamide (27) exhibited significant anti HIV [14].

A series of N-phenylbenzamide derivatives were synthesized, the synthesized compound (28) was a promising anti-Enterovirus [15].
3,5-dihydroxy-\(N\)-(4-hydroxyphenyl)benzamide (30) showed various radical scavenging activities similar to those of trans-resveratrol (29) [16].

The aromatic ring carrying thiazol-2-ylidene benzamide (31) shows enhanced the anti-HIV activity [17].

A heterocyclic compound containing aromatic systems (32) was synthesized and evaluated for analgesic activity [18].
N-heterocyclic substituted benzamide (33) derivatives are reported to have antihypertensive activity [19].

\[
\text{A} = \left(\text{CH}_2\right)\left(\text{R}_{10}\right)\left(\text{CH}_2\right)^n
\]

Indapamide, 3-(aminosulfonyl)-4-chloro-\(N\)-(2,3-dihydro-2-methyl-1H-indol-1-yl) benzamide (34), is a non-thiazide antihypertensive diuretic agent which contains sulfamoylchlorobenzamide and methylindoline moieties. It has been extensively used for its gentle and continued antihypertensive effect when administered orally at low doses [20].

Angiotensin II (Ang II) is the major component of the rennin–angiotensin system (RAS), which plays an important role in the regulation of blood pressure, fluid and electrolyte homeostasis. This octapeptide mediates its effects through stimulation of two receptor subtypes, the AT1 receptor and the AT2 receptor. The RAS is an established target in the treatment of hypertension and it was recently postulated that some of the positive effects of AT1 receptor
antagonists could be ascribed to a stimulation of the AT2 receptor. Substituted triphenyl analogue of benzamides (35) exhibit high affinity for AT2 and act as agonist AT2 receptor [21] which is receptor subtype of RAS.

![Chemical structure of 35]

Substituted $N$-(anilinocarbonothioyl)benzamide (36) also showed significant inhibition of lipid peroxidation [22].

![Chemical structure of 36]

Substituted-$N$-(5- cyanopyrimidin-4-yl)benzamide (37) exhibited antioxidant property in both Nitric Oxide and DPPH assay [23].

![Chemical structure of 37]
1.4 INTRODUCTION TO BIOLOGICAL ACTIVITIES

**Antimicrobial activity:**

Production of antimicrobial compounds is very important in drug industry. Several types of protein exotoxins, and bacteriocins, which are biologically active peptide moieties with bactericidal mode of action are described [24-29]. From this viewpoint, novel amide derivatives, which plays an extremely important role in therapeutic as well as in medicinal field are being targeted. One of the important categories of medicine is antibiotic, where sulfonamides are used for the treatment of bacterial infections [30], in which the amide moiety may apply their effects by varying the metabolic activity of the attacked pathogenic microorganisms. These categories of medicines on absorption into the system interfere with microbe’s growth or kill them. Penicillin, erythromycin, tetracycline, norfloxacin, etc. come under this category for the treatment of antimicrobials.

**Antioxidant activity**

Scientific verification suggests that antioxidants reduce the risk of chronic diseases including cancer and heart disease. Primary sources of naturally occurring antioxidants are whole grains, fruits and vegetables. Plant sourced food like vitamin C, vitamin E, carotenes, phenolic acids, phytate and phytoestrogens have been accepted as antioxidants. Highly reactive free radicals and oxygen species are present in biological systems. These free radicals may oxidize nucleic acids, proteins, lipids or DNA and can initiate
degenerative disease. Antioxidant compounds like phenolic acids, polyphenols and flavonoids scavenge free radicals such as peroxide, hydroperoxide or lipid peroxyl and thus inhibit the oxidative mechanisms that lead to degenerative diseases. Among types of methods available in the literature the malondialdehyde (MDA) or thiobarbituric acid-reactive-substances (TBARS) [31] assays have been used extensively. Methods that measure the radical scavenging activity of antioxidants against free radicals are 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical, the superoxide anion radical (O$_2^-$), the hydroxyl radical (OH) or the peroxyl radical (ROO).

**ACE inhibition Activity**

Hypertension is illustrated as a quiet killer which increases the occurrence of cardiovascular diseases. Blockers have been widely used since more than four decades for the treatment of hypertension. Human angiotensin II (Ang II) is an important peptide in blood pressure regulation. The wealth of available on literature, and the known effects of amino acid alterations and the availability of receptor assays [32] make Ang II a particularly attractive target to examine new approaches for conformational control. With this background angiotensin converting enzyme inhibition activity is screened for some of the synthesized moieties.
1.5 RESEARCH OBJECTIVE

Pharmacology of heterocyclic compounds containing aromatic structure received great consideration in the past decades for their physiological and therapeutic responses and their growing use in the synthesis. With this scenario and literature the synthesis of benzamide appended heterocycles like pyrazolone, oxazoline, oxadiazole and thiadizole and biological importance of the synthesised compounds was planned.
1.6 Reference:


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