Life on earth depends on the chemical element carbon, which is present in every living thing. The element carbon forms a vast number of compounds. Organic chemistry arose from the eighteenth-century belief that organic compounds could be formed only by living systems. Organic chemistry focuses on carbon and following movement of the electrons in carbon chains and rings, and also how electrons are shared with other carbon atoms and hetero atoms. Organic chemistry is primarily concerned with the properties of covalent bonds and non-metallic elements, though ions and metals do play critical roles in some reactions [1].

The study of heterocycles is an evergreen field in the branch of organic chemistry and always attracts the attention of scientists working not only in the area of natural products but also in the synthetic organic chemistry. Commonly majority of the published work in organic chemistry involves at least one heterocyclic ring. Moreover, in providing us with a wealth of fascinating molecular arrays, over half of which posses heterocyclic constitution, nature presents a most cogent argument for developing an appreciation for this area [2]. Heterocyclic chemistry is a vast and expanding area of chemistry because of the obvious applications of compounds derived from heterocyclic rings in pharmacy, medicine, agriculture and other fields. The chemistry of heterocyclic compounds is as relevant as that of aliphatic or aromatic compounds. Their study is of great interest both from the theoretical as well as practical standpoint.

A cyclic organic compound containing all carbon atoms in ring formation is referred to as a carbolic compound. If, at least one atom other than carbon forms a part of the ring system then it is designated as a heterocyclic compound [3-5]. Nitrogen, oxygen and sulfur are the most common hetero atoms, but heterocyclic rings containing other hetero atoms are also widely known. An enormous number of heterocyclic compounds are known and this number is increasing rapidly. Accordingly, the literature on the subject is very vast. Heterocyclic compounds may be classified into aliphatic and aromatic heterocyclic compounds. The aliphatic heterocycles are the cyclic analogues of amines, ethers, thioethers, amides etc. The aromatic heterocyclic compounds in contrast are those which have a heteroatom in
the ring and behave in a manner similar to benzene in some of their properties. A heterocyclic ring may comprise of three or more atoms which may be saturated or unsaturated. Also, the ring may contain more than one heteroatom, which may be similar or dissimilar.

Moreover, many useful drugs have emerged from the successful investigations carried out in this branch. Besides, spectacular advances have been made to furtherance the knowledge of relationship between chemical structure and biological activity. In fact, this tendency is reflected by the voluminous data available in literature on heterocyclic chemistry. Thus, the successful applications in various fields ensure a limitless scope for the development of structurally novel compounds of this type with a wide range of physico-chemical and biological properties.

**HYDANTOIN**

One of the main objectives of organic and medicinal chemistry is the design, synthesis and production of molecules having value as human therapeutic agents. During the past decade, combinatorial chemistry has provided access to chemical libraries based on privileged structures, with heterocyclic structures receiving special attention as they belong to a class of compounds with proven utility in medicinal chemistry. There are numerous biologically active molecules with five membered rings, containing two hetero atoms.

Hydantoin nucleus is a common five membered ring containing a reactive cyclic urea core. Hydantoin which is also known as glycolylurea, is a heterocyclic organic compound that can be thought of as a cyclic "double-condensation reaction" product of glycolic acid and urea. It is similar to that of imidazolidine except that the molecule of hydantoin has carbonyl groups at 2 and 4 positions in the ring. Imidazolidine is the hydrogen-saturated analogue of imidazole. In a more general sense, hydantoins can refer to chemical compounds that have substituent groups bonded to a hydantoin (1) ring skeletal structure.
Hydantoin was first isolated in 1861 by Adolf von Baeyer in the course of his study of uric acid. He obtained it by hydrogenation of Allantoin, hence the name. Urech in 1873 [6] synthesized the derivative 5-methylhydantoin from alanine sulfate and potassium cyanate in what is now known as the Urech hydantoin synthesis.

![Chemical structure of hydantoin]

The Bucherer–Bergs reaction is the chemical reaction of carbonyl compounds (aldehydes or ketones) or cyanohydrins with ammonium carbonate and potassium cyanide to give hydantoins [7].

![Chemical reaction of Bucherer–Bergs]]

One of the challenges of medicinal chemistry is the enhancement of the affinity of a given ligand for its target by decreasing its degrees of freedom and thereby reducing the cost in entropy. Another difficult task is the promotion of the structural diversity which can be achieved by the attachment of pharmacophoric groups to the rigidified molecule. An example of such a process includes di- and tri substituted hydantoins (2), which have been widely used in biological screenings resulting in numerous pharmaceutical applications [8-10].
Hydantoin derivatives have attracted much interest in drug discovery because of their wide range of therapeutic properties [11]. This five-membered rigid heterocycle, with four possible points of diversity, represents a significant molecular scaffold in combinatorial chemistry.

From the early days [12] of combinatorial chemistry to recent years, numerous solid-phase syntheses (SPS) of hydantoins have been reported using natural and unnatural acyclic α-amino acids as starting building blocks [13, 14].

Hydantoin moiety constitutes an attractive pharmacological scaffold present in several drugs [15]. This small and rigid heterocyclic backbone, could act on various pharmacological targets. Especially, hydantoin nucleus could be found in a broad range of biologically active compounds displaying neuroprotective, antiarrhythmic, anticonvulsant, antihypertensive, anti-inflammatory, analgesic, antidiabetic, antiandrogen, antibacterial, antiviral, antifungal, or diuretic activities as well as herbicidal or fungicidal properties [16-24]. Various alkaloid compounds from marine organisms or bacteria contain also an hydantoin moiety. Moreover, hydantoin is the key intermediates during the synthesis of optically pure natural and unnatural amino acids especially those involved on metabotropic ligands [25-27].

**Biological significance of Hydantoin**

**Anticonvulsant activity**

The anticonvulsants (also commonly known as antiepileptic drugs) are a diverse group of pharmaceuticals used in the treatment of epileptic seizures. The goal of an anticonvulsant is to suppress the rapid and excessive firing of neurons that start a seizure. Failing this, an effective anticonvulsant would prevent the spread of the seizure within the brain and offer protection against possible excitotoxic effects that may result in brain damage. Some studies have cited that anticonvulsants themselves are linked to lower IQ in children [28]. However, these adverse effects must be balanced against the significant risk epileptic form seizures pose to children and the distinct possibility of death and devastating neurological sequel secondary to seizures. Anticonvulsants are more accurately called antiepileptic drugs (AEDs), and are sometimes referred to as antiseizure drugs. While the term anticonvulsant' is a
fair description of AEDs, the use of this term tends to lead to confusion between epilepsy and non-epileptic convulsions. In epilepsy, an area of the cortex is typically hyper-irritable. This condition can often be confirmed by completing an electroencephalogram (EEG). Antiepileptic drugs function to help reduce this area of irritability and thus prevent epileptiform seizures.

Phenytoin sodium is a commonly used antiepileptic. Phenytoin acts to suppress the abnormal brain activity seen in seizure by reducing electrical conductance among brain cells by stabilizing the inactive state of voltage-gated sodium channels [29]. Aside from seizures, it is an option in the treatment of trigeminal neuralgia in the event that carbamazepine or other first-line treatment seems inappropriate. It is sometimes considered a class 1b antiarrhythmic. In contrast to the earlier accidental discovery of the antiseizure properties of bromide and phenobarbital, phenytoin was the product of a search among nonsedative structural relatives of phenobarbital for agents capable of suppressing electroshock convulsions in laboratory animals [30].

Ethotoin is an anticonvulsant drug used in the treatment of epilepsy. It is a hydantoin, similar to phenytoin. Ethotoin lacks phenytoin's side effects of gingival hyperplasia and hirsutism, however it is less effective. Mephenytoin is a hydantoin, used as an anticonvulsant. It was introduced approximately 10 years after phenytoin, in the late 1940s. The significant metabolite of mephenytoin is nirvanol (5-ethyl-5-phenylhydantoin), which was the first hydantoin (briefly used as a hypnotic). However, nirvanol is quite toxic and mephenytoin was only considered after other less toxic anticonvulsants had failed. It can cause potentially fatal blood dyscrasia in 1% of patients. Fosphenytoin is a water-soluble phenytoin prodrug used only in hospitals for the treatment of epileptic seizures. On 18 November 2004, Sicor received a tentative approval letter from the United States Food and Drug Administration for a generic version of fosphenytoin [31].

**Antiarrhythmic activity**

Azimilide (3) is a new chlorophenylfuranyl compound (structurally unrelated to the methanesulfonanilide class III antiarrhythmic agents-used to control abnormal heart rhythms) shown to be efficacious in a model of sudden cardiac death [32] and
after myocardial infarction [33]. The agents from this heterogeneous group have an
effect on the repolarization, they prolong the duration of the action potential and the
refractory period. Also, they slow down the spontaneous discharge frequency of
automatic pacemakers by depressing the slope of diastolic depolarization. They shift
the threshold towards zero or hyperpolarize the membrane potential. Although each
agent has its own properties and will have thus a different function.

![Chemical structure of a drug]

The allantois (4), an amniote embryonic excretory organ in which it
concentrates during development in most mammals except humans and higher apes,
it is a product of oxidation of uric acid by purine catabolism. After birth, it is the
predominant means by which nitrogenous waste is excreted in the urine of these
animals [34]. In humans and higher apes, the metabolic pathway for conversion of
uric acid to allantoin is not present, so the former is excreted. Recombinant
rasburicase is sometimes used as a drug to catalyze this metabolic conversion in
patients. In fish, allantoin is broken down further (into ammonia) before excretion
[35]. Allantoin is a major metabolic intermediate in many other organisms including
plants and bacteria.

![Chemical structure of allantoin]

**Chemical disinfection**

Antimicrobial interventions are a crucial step for food industries to ensure
that their products are safe before reaching consumers. Hot water treatment has been
found to be effective against pathogens as well as spoilage bacteria, whereas the use
of chlorinated water has shown little or no effect. The disadvantage of hot water
treatment is the high-water-volume use and high cost of maintaining such a high
temperature [36]. 1,3-Dibromo-5,5-dimethylhydantoin (DBDMH; C₅H₆Br₂N₂O₂), or
Bromitize, and other organohalamine derivatives have been widely used as disinfectants for water treatment and for treating industrial or commercial water-cooling systems. These halogenated hydantoin derivatives have shown considerable efficacy against several species of microorganisms. In aqueous solution, DBDMH hydrolyzes to hypobromous acid, an active antimicrobial agent, and dimethylhydantoin [37].

1,3-Dichloro-5,5-dimethylhydantoin (DDH) (5) belongs to the family of imidazolone compounds. This compound shows low solubility in water, but ppm levels are enough to serve as a good disinfectant and bactericide because it slowly decomposes to produce free chlorine in water. After this process, the remaining compound (5,5-dimethylhydantoin) can be rapidly decomposed into ammonia and carbon dioxide by light, oxygen and microorganisms without leaving any environmentally polluting residues. It is used as a chemical disinfectant used for recreational water and drinking water purification [38, 39].

Anaesthesia

Dantrolene sodium (6), a skeletal-muscle relaxant, inhibits excitation-contraction (E-C) coupling in skeletal muscle without affecting either neuromuscular transmission or the electrical properties of the sarcolemma. Some investigators reported that dantrolene sodium has a direct inhibitory action on Ca\(^{2+}\) release from the sarcoplasmic reticulum (SR) [40]. Dantrolene sodium is widely used in the treatment of chronic skeletal-muscle spasticity and malignant hyperthermia, which is known to be caused by abnormal Ca\(^{2+}\) release from the SR. In contrast, some investigators reported dantrolene sodium has almost no cardiovascular effects \textit{in vivo} [41, 42]. In the presence of malignant hyperthermia, the direct cardiac effects of dantrolene are masked, and the effects on skeletal muscles and the resultant effects on the cardiovascular system are of much more interest than are the direct effects of dantrolene on the cardiovascular system. Recently, Meissner and Morgan reported
that dantrolene sodium exerts a direct inhibitory effect on SR Ca\(^{2+}\) release in cardiac muscle, an effect that might be useful in pathophysiologic conditions in which there is altered intracellular Ca\(^{2+}\) homeostasis [43].

Fragrances and preservatives

An antimicrobial is predominantly used as a preservative in cosmetic products, protecting them from the bacteria, yeast and molds known to cause spoilage. It can be found in virtually every type of personal care products such as facial moisturizer/lotion, sunscreen, anti-aging treatment, cleanser, styling gel, foundation, shampoo/conditioner, eye cream, deodorant and mouthwash. Diazolidinyl urea (7) is an antimicrobial preservative used in cosmetics. It is chemically related to imidazolidinyl urea which is used in the same way. Diazolidinyl urea acts as a formaldehyde releaser. It is used in many cosmetics, skin care products, shampoos and conditioners, as well as a wide range of products including bubble baths, baby wipes and household detergents. Diazolidinyl urea is found in the commercially available preservative Germaben. Commercial diazolidinyl urea is a mixture of different formaldehyde addition products including polymers [44].
For a long time, heterocycles have constituted one of the largest areas of research in medicinal Chemistry. Heterocyclic compounds are of particular importance as they are associated with a wide variety of physiological activities with wide variety of heterocyclic systems known today. The nitrogen heterocycles are of great importance as they are present in nucleic acids, vitamins, proteins and other biologically important molecular systems. Among different nitrogen heterocycles, the imidazopyridines ring systems are very important since several of its derivatives have been found to be medicinally useful. Imidazopyridines are prominent among polynitrogen containing heterocycles that exhibit a plethora of biological properties, especially as inhibitors of benzodiazepine receptors. Alpidem, hypnotic drug Zolpidem and antiulcer drug Zolimidine.

Imidazopyridine derivatives are also known for their anticancer, antiviral, antiparasitic and anti-HIV properties. Their effects on neuroactive steroids, their role as NO synthase and GABAA inhibitors and as L-Dopa and Dopamine prodrugs have been documented recently. With increase in the incidence of multi drug–resistant to Gram-positive and Gram-negative bacteria it becomes imperative to continuously search for small molecules as anti-infective agents. Imidazopyridines fit this requirement well since they have demonstrated a diverse set of biological activities that include antibacterial, antiamoebic, antiviral, antifungal, anthelmintic, antiHIV, antihistaminic, antiulcer, cardiotonic, antihypertensive and neuroleptic agents. Their observed activity depends upon the functional group attached to the moiety. The imidazole antifungals such as clotrimazole, miconazole and ketoconazole showed good optical activity, but were only of limited value for systematic administration. But triazole derivatives are the other major chemical group of antifungal azole derivatives. The triazoles (fluconazole and itraconazole) possess a broad spectrum of antifungal activity and reduced toxicity when compared with the imidazole antifungals. Metronidazole and related N-1 substituted 5-nitroimidazoles like ornidazole, secnidazole and tinidazole are widely used in the treatment of diseases caused by protozoa and anaerobic bacteria [45, 46].

Imidazole was first reported in 1858, although various imidazole derivatives had been discovered as early as the 1840s. It is synthesized by glyoxal and
formaldehyde in ammonia to form imidazole (or glyoxaline, as it was originally named) [47]. This synthesis, while producing relatively low yields, is still used for creating C-substituted imidazoles. Imidazole can be synthesized by numerous methods besides the Debus method. Many of these syntheses can also be applied to different substituted imidazoles and imidazole derivatives by varying the functional groups on the reactants.

Pyridine was discovered in 1849 by the Scottish chemist Thomas Anderson as one of the constituents of bone oil. Pyridine was undoubtedly prepared by early alchemists by heating animal bones and other organic matter, [48] but the earliest documented reference is attributed to the Scottish scientist Thomas Anderson [49]. In 1849, Anderson examined the contents of the oil obtained through high-temperature heating of animal bones [50]. Many electrophilic substitutions on pyridine either do not proceed or proceed only partially; however, the heteroaromatic character can be activated by electron-donating functionalization. Common alkylations and acylations, such as Friedel–Crafts alkylation or acylation, usually fail for pyridine because they only lead to the addition at the nitrogen atom. Substitutions usually occur at the 3-position which is the most electron-rich carbon atom in the ring and is therefore more susceptible to an electrophilic addition.

In contrast to benzene, pyridine efficiently supports several nucleophilic substitutions, and is regarded as a good nucleophile. The reason for this is relatively lower electron density of the carbon atoms of the ring. These reactions include substitutions with elimination of a hydride ion and elimination-additions with formation of an intermediate aryne configuration are usually proceeding at 2- or 4-position. Many nucleophilic substitutions occur easier not with bare pyridine, but with pyridine modified with bromine, chlorine, fluorine or sulfonic acid fragments which then become a leaving group. So, fluorine is the best leaving group for the substitution with organolithium compounds. The nucleophilic attack compounds may be alkoxides, thiolates, amines, and ammonia (at elevated pressures) [51]. The hydride ion is generally a poor leaving group and occurs only in a few heterocyclic reactions. They include the Chichibabin reaction which yields pyridine derivatives aminated at the 2-position. Here sodium amide is used as the nucleophile yielding 2-
aminopyridine. The hydride ion released in this reaction combines with a proton of an available amino group forming a hydrogen molecule [52].

**Biological significance of imidazopyridines**

**GABA\(_A\) receptor agonists**

The imidazopyridines are a class of drugs defined by their chemical structure. They are generally GABA\(_A\) receptor agonists, however recently proton pump inhibitors in this class have been developed as well. Imidazopyridines include: Zolpidem (Ambien), Alpidem, Saripidem, Necopidem.

Alpidem is an anxiolytic drug from the imidazopyridine family, related to the better known sleeping medication zolpidem. Unlike zolpidem however, alpidem does not produce sedative effects at normal doses and is instead used specifically for the treatment of anxiety [53, 54]. Alpidem was known to act selectively on the \(\alpha-3\) receptor subtype and to a lesser extent at the \(\alpha-1\) subtype, of the benzodiazepine receptor [55, 56]. However, the chemical structure of alpidem is not related to that of the benzodiazepines and alpidem is thus sometimes referred to as a nonbenzodiazepine [57].

Zolpidem is a prescription medication used for the treatment of insomnia and some brain disorders. It is a short-acting nonbenzodiazepine hypnotic of the imidazopyridine class that potentiates gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter, by binding to GABA\(_A\) receptors at the same location as benzodiazepines [58]. Its hypnotic effects are similar to those of the benzodiazepine class of drugs, but it is molecularly distinct from the classical benzodiazepine molecule and is classified as an imidazopyridine. Flumazenil, a benzodiazepine receptor antagonist, which is used for benzodiazepine overdose, can also reverse zolpidem's sedative/hypnotic and memory-impairing effects [59, 60].

Saripidem is a sedative and anxiolytic drug in the imidazopyridine family, which is related to the better known drugs zolpidem and alpidem. Saripidem has a similar pharmacological profile to the benzodiazepine family of drugs including sedative and anxiolytic properties but its chemical structure is quite different from that of the benzodiazepine drugs and aripipram is described as a nonbenzodiazepine.
The mechanism of action by which saripidem produces its sedative and anxiolytic effects is by modulating the benzodiazepine binding site on GABA<sub>A</sub> receptors, however unlike many older GABA<sub>A</sub> agonists. Necopidem is a drug in the imidazopyridine family, which is related to the better known drugs zolpidem and alpidem. It has sedative and anxiolytic effects [61].

![Chemical structures of Alpidem, Zolpidem, Saripidem, and Necopidem](image)

**Antagonist**

Telcagepant (8) was an investigational drug for the acute treatment and prevention of migraine. In the acute treatment of migraine, it was found to have equal potency to rizatriptan [62] and zolmitriptan [63] in two Phase III clinical trials. The calcitonin gene-related peptide (CGRP) is a strong vasodilator primarily found in nervous tissue. Since vasodilation in the brain is thought to be involved in the development of migraine and CGRP levels are increased during migraine attacks, this peptide may be an important target for potential new antimigraine drugs. Telcagepant acts as a calcitonin gene-related peptide receptor (CRLR) antagonist and blocks this peptide. It is believed to constrict dilated blood vessels within the brain.
Peptic ulcer

Tenatoprazole (rINN, also benatoprazole), discovered in Japan, is a proton pump inhibitor indicated for the treatment of reflux oesophagitis and peptic ulcer. It is an imidazopyridine derivative and has an imidazopyridine ring in place of the benzimidazole moiety found in other proton pump inhibitors. It is activated slowly and its inhibition is said to be resistant to reversal. Tenatoprazole (9) has an extended plasma half-life which makes it more effective in the treatment of nocturnal acid breakthrough than esomeprazole [64]. Antacid preparations such as tenatoprazole by suppressing acid mediated break down of proteins, leads to an elevated risk of developing food or drug allergies. Tenatoprazole is a prodrug of the proton pump inhibitor (PPI) class, which is converted to the active sulfonamide or sulfenic acid by acid in the secretory canaliculus of the stimulated parietal cell of the stomach. This active species binds to luminally accessible cysteines of the gastric H+, K+ -ATPase resulting in disulfide formation and acid secretion inhibition.

Pentosidine (10) is a biomarker for advanced glycation end products, or AGEs. It is a well characterized and easily detected member of this large class of compounds. AGEs are biochemicals formed continuously under normal circumstances, but more rapidly under a variety of stresses, especially oxidative stress and hyperglycemia. They serve as markers of stress and act as toxins themselves. Pentosidine is typical of the class, except that it fluoresces, which allows it to be seen and measured easily. It is formed in a reaction of the amino acids with the Maillard reaction products of ribose [65]. Although it is present only in trace
concentrations among tissue proteins, it is useful for assessing cumulative damage to proteins—advanced glycation end products by non-enzymatic browning reactions with carbohydrates [66-68].

Sedative

Indiplon is a nonbenzodiazepine, hypnotic sedative was developed in 2 formulations - an immediate release product for sleep onset and a modified-release version for sleep maintenance. Indiplon works by enhancing the action of the inhibitory neurotransmitter GABA, like most other nonbenzodiazepine sedatives. It is primarily binds to the α1 subunits of the GABA_A receptors in the brain [69].

Panadiplon is an anxiolytic drug with a novel chemical structure that is not closely related to other drugs of this type. It has a similar pharmacological profile to the benzodiazepine family of drugs, but with mainly anxiolytic properties and relatively little sedative or amnestic effect, and so it is classified as a nonbenzodiazepine anxiolytic [70]. Panadiplon acts as a high-affinity GABA_A receptor partial agonist [71], but despite showing a useful effects profile of a potent anxiolytic with little sedative effects. It was discontinued from clinical development for use in humans after showing evidence of liver damage in both animals and human trials [72, 73]. Panadiplon however continues to be used in animal research, mainly as a subtype-selective reference drug to compare other GABA_A agonists [74].

Zaleplon is a sedative/hypnotic, mainly used for insomnia. It is a nonbenzodiazepine hypnotic from the pyrazolopyrimidine class [75]. In terms of adverse effects zaleplon appears to offer little improvement compared to both benzodiazepines and other non-benzodiazepine Z-drugs [76, 77]. Zaleplon and Zolpidem both are agonists at the GABA_A α1 subunit. It is also available as a white capsule tablet with no identifying markings. It is also prescribed for anxiety. Zaleplon is effective in the treatment of insomnia where difficulty in falling asleep is
the primary complaint. Zaleplon is also effective in the treatment of middle of the night insomnia without causing residual hangover effects [78, 79].

![Indiplon, Panadiplon, and Zaleplon structures]

**Psychoactive drugs**

The non-benzodiazepines, also called benzodiazepine-like drugs, are a class of psychoactive drugs pharmacologically resembling the benzodiazepines, with similar benefits, side effects and risks, despite having dissimilar or entirely different chemical structures [80, 81]. The nonbenzodiazepines are positive allosteric modulators of the GABA-A receptor. Like the benzodiazepines, they exert their effects by binding to and activating the benzodiazepine site of the receptor complex. Nonbenzodiazepines have demonstrated efficacy in treating sleep disorders. There is some limited evidence that suggests the tolerance to nonbenzodiazepines is slower to develop than with benzodiazepines. The first three nonbenzodiazepine drugs are zopiclone, zolpidem and zaleplon. These three drugs are sedatives, used exclusively for the treatment of mild insomnia. They are safer than the older barbiturates especially in over dosage and they may, when compared to the benzodiazepines, have less of a tendency to induce physical dependence and addiction, although these issues can still become a problem. Long term use is not recommended as tolerance and addiction can occur [82-84].

![Zopiclone and Zaleplon structures]
INDOLES

Medicinal chemistry is the discipline concerned with determining the influence of chemical structure on biological activity and in the practice of medicinal chemistry developed from an empirical one involving organic synthesis of new compound based largely on the modification of structure and then identifies their biological activity. Medicinal chemistry concerns with the discovery, development, interpretation and the identification of mechanism of action of biologically active compounds at the molecular level. Various biologically active synthetic compounds have five-membered nitrogen-containing heterocyclic ring in their structures. An important aspect of medicinal chemistry has been to establish a relationship between chemical structure and pharmacological activity [85]. It has been established that half of the therapeutic agents consists of heterocyclic compounds. The heterocyclic ring comprises of very core of the active moiety or the pharmacophore [86].

Indole is an aromatic heterocyclic organic compound. It has a bicyclic structure, consisting of a six-membered benzene ring fused to a five-membered nitrogen-containing pyrole ring. Indole is a popular component of fragrances and the precursor to many pharmaceuticals. Indole containing compounds are best known for their medicinal properties in the pharmaceutical industry. Although to a lesser degree, the indole motif nevertheless appears in many significant products across the entire chemical industry. The structure of indole was not correctly assigned until 1869 by Adolf von Baeyer; its derivatives have had a prominent role in commerce for centuries. In modern times, analogs based on indole are significant players in a diverse array of markets such as dyes, plastics, agriculture, vitamin supplements, over-the-counter drugs, flavor enhancers and perfumery.

Indole chemistry began to develop with the study of the dye indigo. Indigo can be converted to isatin and then to oxindole. Then in 1866, Adolf von Baeyer reduced oxindole to indole using zinc dust [87]. In 1869, he proposed a formula for indole [88]. Certain indole derivatives were important dyestuffs until the end of the 19th century. In the 1930s, interest in indole intensified when it became known that the indole nucleus is present in many important alkaloids, as well as in tryptophan and auxins, and it remains an active area of research today [89].
Indole is a major constituent of coal-tar, and the 220–260 °C distillation fractions are the main industrial source of the material. Indole and its derivatives can also be synthesized by a variety of methods [90-92]. The main industrial routes start from aniline. Illustrative of such large-scale syntheses, indole (and substituted derivatives) forms via vapor-phase reaction of aniline with ethylene glycol in the presence of catalysts:

\[
\text{R}_3^b \quad \text{HO-CH}_2 \quad \text{Catalyst} \quad 200-500 \degree \text{C} \quad \text{R}_3^b
\]

In general, reactions are conducted between 200 and 500 °C. Yields can be as high as 60%. Other precursors to indole include formyltoluidine, 2-ethylaniline, and 2-(2-nitrophenyl)ethanol, all of which undergo cyclizations [93]. Many other methods have been developed that are applicable for its synthesis.

The Fischer indole synthesis is a chemical reaction that produces the aromatic heterocycle indole from a (substituted) phenylhydrazine and an aldehyde or ketone under acidic conditions [94, 95]. The reaction was discovered in 1883 by Hermann Emil Fischer. Today antimigraine drugs of the triptan class are often synthesized by this method.

\[
\text{NH}_2 \quad + \quad \text{R}_1 \quad \text{O} \quad \text{R}_2 \quad \text{acid} \quad \text{R}_1 \quad \text{R}_2
\]

The choice of acid catalyst is very important. Bronsted acids such as HCl, H\textsubscript{2}SO\textsubscript{4}, polyphosphoric acid and \(p\)-toluenesulfonic acid have been used successfully. Lewis acids such as boron trifluoride, zinc chloride, iron chloride, and aluminium chloride are also useful catalysts. Indole undergoes electrophilic substitution mainly on position 3 of the nucleus when the hydrogen on the indole nitrogen atom is substituted or when a strong magnesium base is used. This is because indole nitrogen is the most reactive towards reactions with electrophiles followed by position 3 of the indole nucleus. When both positions 1 and 3 of the indole nucleus are occupied by substituents other than hydrogen, position 2 is the most reactive one [96].
Biological significance of indoles

Cancer activity: PKC inhibitors

The protein kinase C (PKC) family of serine/threonine kinases consists of at least 11 isoforms that are involved in cell proliferation, cell differentiation, gene transcription, tumorigenesis, and angiogenesis. PKC over expression has been linked to several types of cancer such as breast, colon, renal cell, hepatocellular, non-small cell lung and prostate cancer. Therefore, PKC inhibitors may have potential for the treatment of various cancers.

The first-generation of PKC inhibitors include staurosporine (11), a natural product originally isolated in 1977 from bacterium Streptomyces staurosporeus. Staurosporine was the first of over 50 alkaloids to be isolated with this type of bis-indole core structure. However, staurosporine inhibits PKC isoforms non-selectively and this lack of specificity precludes its clinical use due to toxicity concerns. Nevertheless, staurosporine has become a valuable research tool to induce apoptosis. In addition, staurosporine serves as a versatile starting material for the synthesis of novel semisynthetic analogs [97, 98].

Enzastaurin: PKCb Inhibitor

The protein kinase Cb isoform (PKCb) is implicated in several cancer types and is presumably involved in VEGF-induced tumor development and angiogenesis.
Enzastaurin (12) is an acyclic bisindolylmaleimide that potently and selectively inhibits the PKCb isoform. It demonstrated anticancer activity in various preclinical cancer models and in clinical studies involving advanced cancer patients. Enzastaurin is currently being evaluated in a Phase III clinical trial for maintenance therapy for diffuse large B-cell lymphoma and also in several Phase II studies for hematologic malignancies and glioblastoma [99].

Hormone

The natural product melatonin is found in animals and also in insects, microbes and some plants. Melatonin (13) is mainly produced by the pineal gland in animals but it is synthesized throughout the body and readily passes through the blood–brain barrier. A diversity of biological responses is produced by the interaction of melatonin with its widespread receptors in body and central nervous system. In addition to the well-documented role in regulating mammalian circadian rhythms, melatonin receptors are involved in modulating the immune system and bone growth among other processes. The additional powerful antioxidant properties of melatonin are a potential bonus to those taking it for other reasons [100-102].

Tryptophan

L-Tryptophan (14) is produced industrially by fermentation. It is an important growing amino acid feed additive and its market that exceeded worldwide. Its history as a dietary supplement is more sullied, although the toxicity concerns
that were raised in 1989 and led to a ban in its use as a dietary supplement for several years may not have been justified [103].

L-Tryptophan is one of the essential amino acids in animals. In addition, it is the biosynthetic precursor to other important molecules such as serotonin (thus, melatonin) and niacin. Until 1989, L-Tryptophan was sold singly over-the-counter and as a constituent in dietary supplements combinations. One of several effects that ingesting L-tryptophan has on the body is an increase in serotonin levels. Partly because of this, L-tryptophan supplements commonly were used to treat premenstrual syndrome, as a sleep aid and as a natural antidepressant.

Tryptophan is a routine constituent of most protein-based foods or dietary proteins. It is particularly plentiful in chocolate, oats, dried dates, milk, yogurt, cottage cheese, red meat, eggs, fish, poultry, sesame, chickpeas, sunflower seeds, pumpkin seeds, spirulina, bananas, and peanuts. Despite popular belief that turkey meat has a particularly high amount of tryptophan, the amount of tryptophan in turkey is typical of most poultry. There is also a myth that plant protein lacks tryptophan; in fact, tryptophan is present in most types of legumes, though relatively low in cereal [104].

Agriculture

Natural products containing the indole subunit are found throughout the animal, fungal, microbial and plant kingdoms. The purposes to which the producing organisms put these varied structures often are a mystery. However, many of these components have provided an invaluable basis for research programs targeting diseases or other commercial enterprises. When successful, the vast majority of the marketed products bear little resemblance to the initial lead. Auxins are one of the five major classes of plant-produced hormones that affect plant growth including bud formation and root initiation. Indole-3-acetic acid (15) is the most common
auxin found in plants. Although the small amounts produced internally have the desired effects, auxins are toxic to plants in larger amounts. The nefarious weed-control products 2,4-D and 2,4,5-T target the auxin receptor but bear little resemblance to the natural ligand. Other man-made auxins such as 1-naphthaleneacetic acid and indole-3-butyric acid are used, not to kill weeds, but to stimulate root production in cuttings taken from the parent plant [105].

The four naturally occurring (endogenous) auxins are IAA, 4-chloroindole-3-acetic acid (16), phenylacetic acid and indole-3-butyric acid; only these four were found to be isolated by plants. However, most of the knowledge described so far in auxin biology and as described in the article below, apply basically to IAA; the other three endogenous auxins seems to have rather marginal importance for intact plants in natural environments. Apart from endogenous auxins, scientists and manufacturers have developed many synthetic compounds with auxinic activity [106, 107].

Animal Health

Many of the same indoles in human medicine could have parallel application in animal health and indeed, some are used in both arenas. Both livestock and domestic pets may benefit, if only indirectly, from the huge research efforts of the pharmaceutical industry to develop pharmaceutical products. A number of pharmaceutical agents for humans are restricted in livestock or precluded altogether in order to reduce the risk of these drugs entering our food chain from this source.

Over five hundred drugs are registered for animal use, not including different formulations and combination products. The list includes some unusual compounds, such as nitrofurans, arsenic derivatives and toluene (used as a dewormer). Only a handful of drugs on this list contain the indole core. Some are easily recognizable drugs from human medicine while others are only used in animals. Several of these
latter are well known indole alkaloids. The two veterinary drugs Carprofen (17) and Etodolac (18) are better known as Rimadyl and Lodine, the nonsteroidal anti-inflammatory drugs approved for human use. They are especially useful for treating dogs with osteoarthritis, hip dysplasia, and other joint diseases [108].

![Chemical structures of Carprofen (17) and Etodolac (18).]

**Laryngeal papillomatosis**

Animal studies have indicated that indole-3-carbinol (I3C) primarily is a pro-drug. In the acid environment of the stomach, I3C is converted into several self-condensation products and one or more of these appear to be responsible for the intriguing biological activities ascribed to I3C. 3,3′-Diindolylmethane (19) or DIM is a compound derived from the digestion of indole-3-carbinol, found in cruciferous vegetables such as broccoli, Brussels sprouts, cabbage and kale. The reputation of Brassica vegetables as healthy foods rests in part on the activities of diindolylmethane.

Some *in vitro* studies indicate that the cyclic trimer is a strong estrogen receptor agonist, suggesting that further research is warranted on the potential anticancer effects of indole. The potential of DIM as an anticancer agent that is predicted by *in vitro* assays has been reinforced by *in vivo* experiments. In animal models, DIM has shown efficacy in a similar range of carcinomas as I3C including prostate, breast, pancreatic, and colon cancers. DIM induces apoptosis of cancer cells directly by several mechanisms and enhances the effectiveness of some cancer drugs. It also has antiproliferative effects in some cancer cell lines and exhibits protective activity against invasion of normal cells. There are several clinical trials underway to investigate DIM as a cancer treatment therapy [109-111].

![Chemical structure of 3,3′-Diindolylmethane (19).]
Scope of this work

The role of the drug discovery has been changed significantly over the past 50 years - workflows have been reinvented while the goals remain to find and test novel molecules that can reach and act on disease targets. There is a constant and continuous interest in the field of drug discovery. Therefore, it was thought worthwhile to synthesize some novel biodynamic potent molecules.

The author has carried out the synthesis and characterization of the newly synthesized hydantoin, imidazopyridine and difluoroindole derivatives. The modern techniques such as elemental analysis, FT-IR, \(^1\)H NMR, \(^{13}\)C NMR and mass spectrometer were utilized for their characterization. The newly synthesized molecules were screened for pharmacological evaluation. Specifically, the research objectives are:

1. Synthesis and characterization of novel 8-amino-3-[2-(4-fluorophenoxy)ethyl]-1,3-diazaspiro [4.5]decane-2,4-dione derivatives and evaluate pharmacological activity of the synthesized compounds.

2. Synthesis and characterization of 3-[(2,4-dioxo-1,3,8-triazaspiro[4.6]undec-3-yl)methyl]benzonitrile derivatives by elemental analysis, FT-IR, \(^1\)H NMR and mass spectra.

3. Synthesis and characterization of some novel 1'-[2-(difluoromethoxy)benzyl]-2'\(^H\),5'\(^H\)-spiro[8-azabicyclo[3.2.1]octane-3,4'-imidazolidine]-2',5'-diones derivatives and evaluate their anticonvulsant activity.

4. Synthesis and characterization of novel imidazo[4,5-c]pyridine derivatives and to evaluate the antimicrobial and antioxidant activity. The antimycobacterial activity of the synthesized compounds is evaluated against *Mycobacterium tuberculosis*.

5. Synthesis of 4,4-difluoro-8-(propan-2-yl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-\(b\)]indole derivatives. The synthesized molecules were screened for anti-amnesic activity.
Antimicrobial activity of the newly synthesized compounds was evaluated against bacteria *Staphylococcus aureus* and *Escherichia coli* and two fungi namely *Aspergillus niger* and *Aspergillus flavus* by disk diffusion method.

The antioxidant activity of the newly synthesized compounds was performed using DPPH method. The anti-amnesic effect of difluoroindole derivatives was evaluated against scopolamine induced memory loss and in vitro acetylcholinesterase inhibition activity using rat brain homogenate.

The anticonvulsant activity of the newly synthesized compounds was carried out using different experimental methods such as Maximal Electroshock Seizure Model (MES), Behavioural test and CNS depressant study. The neurotoxicity of the compounds was measured in mice by rotorod test.

The in vitro antimycobacterial activity of the imidazopyridine derivatives was studied against *Mycobacterium tuberculosis* H37Rv. The cytotoxicity studies in a mammalian Vero cell line and In vivo activity against *M. tuberculosis* in mice were also included.
REFERENCES


