CHAPTER 3

LITERATURE SURVEY

Cancer is one of the most dreadful diseases in the world. Despite immense advances in the field of basic and clinical research which have resulted in higher cure rates for a number of malignancies, cancer remains the second leading cause of death in developing as well as developed countries. Although chemotherapy is the mainstay of cancer therapy, the use of available chemotherapeutics is often limited mainly due to undesirable side effects and it clearly underscores the need of developing novel chemotherapeutic agents for more effective cancer treatments [43]. Among the wide range of compounds tested as potential anticancer agents, sulfonamides comprise an important class of therapeutic agents that are known to exhibit a broad spectrum of biological activities [30-36, 44-46]. A number of sulfonamides have also been screened particularly for their antitumor activity. There are variety of mechanisms, such as disruption of microtubule assembly, cell cycle arrest in the G1 phase, functional suppression of the transcriptional activator NF-Y, angiogenesis and carbonic anhydrase inhibition for the anticancer activity of sulfonamide compounds.

3.1 SULFONAMIDES AS ANTICANCER MOLECULES

Ali Md and coworkers [47] studied that disruption of the phosphatidylinositol 3-kinase/AKT signaling pathway can lead to apoptosis in cancer cells. Previously these authors have identified a lead sulfonamide that selectively bound to the pleckstrin homology (PH) domain of AKT and induced apoptosis, when present at low micromolar concentrations. To examine the effects of structural modification, a set of sulfonamides (Compounds 57-60; Figure 3.1) related to the lead compound was designed, synthesized and tested for binding to the
expressed pH domain of AKT using a surface Plasmon resonance-based competitive binding assay. Cellular activity was determined by means of an assay for pAKT production and a cell killing assay using BxPC-3 cells. The most active compounds in the set are lipophilic and possess an aliphatic chain of the proper length. Results were interpreted with the aid of computational modeling. This was the first paper dealt with the Structure-Activity Relationship (SAR) study of a large family of AKT pH domain inhibitors. This study is useful to design compounds for the next generation of inhibitors of AKT pH domain function.

Sleeb and co-workers [48] have synthesized ABT-737 and ABT-263 (Compounds 61, 62; Figure 3.2) as potent inhibitors of the BH3 antiapoptotic proteins, Bcl-xL and Bcl-2. This class of putative anticancer agents invariantly contains an acylsulfonamide core.

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**Figure 3.1 AKT pH Domain Inhibitors**

**Figure 3.2 ABT-737 and ABT-263 as Potent Inhibitors**
These compounds exhibit submicromolar mechanism-based activity in human small-cell lung carcinoma cell lines in the presence of 10% human serum. This is the first successful demonstration of a quinazoline sulfonamide core serving as an effective benzoysulfonamide bioisostere. Additionally, these novel quinazolines comprise only the second known class of Bcl-2 family protein inhibitors to induce mechanism-based cell death.

Bernd and coworkers [49] have studied the inhibitors (Compounds 63, 64; Figure 3.3) of hypoxia-inducible factor 1 (HIF-1) representing promising anticancer therapeutics. They have identified a series of potent toluidine sulfonamide HIF-1 inhibitors. However, the series was threatened by a potential liability to inhibit CYP2C9 which could cause dangerous drug-drug interactions when being coadministered with other drugs. They used structure-activity data from the PubChem database to develop a topomer CoMFA model that guided the design of novel sulfonamides with high selectivity for HIF-1 over CYP2C9 inhibition.

Alferd and coworkers [50] have studied a series of sulfonamide compounds (Compounds 65-67; Figure 3.4) that are glucuronidase inhibitors. The glucuronidase inhibitors include phenoxy thiophene sulfonamides. The compounds such as, pyridine sulfonyls, benzene sulfonyls, thiophene sulfonyls, thiazole sulfonyls, thiophene carbonyls and thiazole carbonyls are also studied by the authors. These authors have also reported the composition of one or more of such compounds for inhibiting glucuronidase and use of these compounds as a co-drug along with the anticancer drug CPT-11.
Kamal and co-workers [51] synthesized a series of anilino substituted pyrimidine sulfonamides and evaluated for their anticancer activity. The sulfonamides showed promising activity with IC$_{50}$ values ranging from 5.6 to 12.3 mM. The authors have also studied the detailed biological aspects of some of the promising compounds on the K562 cell lines. Interestingly, the compounds induced G1 cell cycle arrest and down regulation of G1 phase cell cycle regulatory proteins such as cyclin D1 and CDK4. These compounds also exhibited inhibition of NF-kB as well as its downstream target gene Akt1 and the phosphorylated form of AKT ser 474 proteins. The authors advocate that one of the representative compound (Compound 68; Figure 3.5) could be considered as the potential lead for the development as a new anticancer agent.

Hala [52] has reported the synthesis of some novel [1,3,5]triazine derivatives (Compounds 69-71; Figure 3.6) bearing a substituted sulfonamide moiety. All the newly synthesized compounds were evaluated for their in vitro
anticancer activity against the breast cancer cell line, MCF7. Most of the screened compounds showed interesting cytotoxic activities compared with the reference drug doxorubicin.

Figure 3.6 Cytotoxic Novel Sulfonamides

The anticancer activity of the Pyrimidinyl and 1,3,5-triazinyl benzimidazole sulfonamides is well documented [53]. Piperazine and 1,3,5-triazinyl benzimidazole sulfonamides (Compounds 72, 73; Figure 3.7) are used as agents or drugs for cancer therapy, either alone or in combination with radiation and/or other anticancer drugs.

Figure 3.7 Anticancer Novel Sulfonamides

Rodriguez and Novalbos [54] have studied the utility of 4-(5,5-dimethyl-3-oxo-cyclohex-1-enylamino)benzenesulfonamide in the synthesis of novel
4-(quinolin-1-yl) benzenesulfonamide derivatives. These compounds were evaluated for their \textit{in vitro} anticancer activity compared with the reference drug doxorubicin.

Reddy and coworkers [55] have patented the synthetic process and the anticancer activity of the following sulfonamide compound of the type (Compound 74; Figure 3.8), where Ar$^1$ is substituted aromatic compounds, Ar$^2$ is aromatic or hetero aromatic group, D is the nitrile group, G is primary or the secondary amino groups and S is the sulfonyl group in the core structure.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure3.8.png}
\caption{Antiproliferative Agents}
\end{figure}

The following compound of the type (Compound 75; Figure 3.9) containing sulfonamide functional group at R$^1$ exhibited anticancer property mediated by an mTOR kinase or one or more PI3K enzyme [56].

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure3.9.png}
\caption{mTOR Kinase Inhibitor}
\end{figure}

An efficient synthesis of ABT-263 and piperizin-1-yl derivative, novel inhibitors of antiapoptotic Bcl-2 proteins (Compounds 76, 77; Figure 3.10) was reported by Wang and coworkers [57, 58]. The compounds were synthesized through the intermediates of 4-(4-[[2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-enyl[methyl]piperazin-1-yl]benzoic acid and 4-fluoro-3-[[trifluoromethyl]sulfonyl] benzenesulfonamide and tested for anticancer activity. These authors advocate that their work may lay foundation for a new process development in anticancer drug discovery.
Seikwan and coworkers [59] have reported the synthesis of novel Histone Deacetylase (HDAC) sulfonamide inhibitors. The key synthetic strategies involve N-sulfonylation of L-proline benzyl ester hydrochloride and coupling reaction of N-sulfonyl chloride with amines. It was found that several compounds showed good cellular potency. The most potent compounds (Compounds 78, 79; Figure 3.11) exhibited an IC$_{50}$ value of 2.8 µM in vitro.

Kawai and co-workers [60] have developed a series of novel sulfonamide molecules for inhibition of MetAP2, a novel approach toward antiangiogenesis and anticancer therapy using Affinity Selection/Mass Spectrometry (ASMS) employing MetAP2 loaded with Mn$^{2+}$ as the active site metal. The micromolar hits were quickly improved to potent nanomolar inhibitors by chemical modifications guided by insights from X-ray crystallography.

Reddy and Reddy [61] have observed that compounds of the type (Compound 80; Figure 3.12) possess anticancer properties.
Kenneth and coworkers [62] have reported the compounds (Compounds 81, 82; Figure 3.13) having methionine aminopeptidase-2 inhibitory (MetAP2) activity. The authors also described the pharmaceutical compositions of the compounds, methods of treatment using the compounds, methods of inhibiting angiogenesis and methods of treating cancer.

Reddy and coworkers [63] have reported the synthesis of coumarin 3-(N-aryl) sulfonamides by Knoevenagel condensation of anilinosulfonylacetic acids with suitable salicylaldehydes and by the reaction of methyl anilinosulfonylacetates with substituted salicylaldehydes in the presence of a catalytic amount of a base. All the compounds tested for antiproliferative activity in different cancer cell lines have shown $\text{GI}_{50}$ values less than 100 $\mu$M.

Alessandro and coworkers [64] have reported that sulfonamides inhibit the catalytic activity of carbonic anhydrase enzymes participating in the regulation of acid-base balance and ion transport in many tissues. Carbonic anhydrase IX (CA IX), a transmembrane isoform with predominant association with tumors and limited distribution in normal tissues, is strongly overexpressed by hypoxia.
Hypoxia increases the catalytic performance of CA IX contributing to microenvironmental acidosis, which influences cancer progression and treatment outcome. CA IX represents a target for detection and therapy of hypoxic tumors. Sulfonamide CA IX selective inhibitors accumulate only in hypoxic cells containing CA IX, reversing acidification mediated by this enzyme. The design of fluorescent sulfonamides that preferentially inhibit the activity of CA IX, showing reduced penetration through the plasma membranes and binding to hypoxic cells expressing CA IX was reported by these authors. These inhibitors represent promising candidates for developing anticancer therapies based on tumor-associated CA isozyme inhibition and offer interesting tools for imaging and further investigation of hypoxic tumors.

Garaj and co-workers [65] have reported the synthesis of a library of sulfonamides incorporating triazinyl moieties of the following type (Compound 83; Figure 3.14). These compounds were tested for the inhibition of three physiologically relevant carbonic anhydrase isozymes, the cytosolic hCA I and II and the transmembrane tumor associated hCA IX.

![Figure 3.14 Triazine Sulfonamide](image)

It has been observed that the overdosing of the anticancer agent viz., 7-ethyl-10-[4-(1-piperidino)-1-piperidino]carbonyloxy-camptothecin (irinotecan; CPT-11) results in delayed diarrhea. This is caused due to the bacterial mediated hydrolysis of the glucoronide conjugate of the active metabolite 7-ethyl-10-hydroxy camptothecin (SN-38) or the direct conversion of CPT-11 to SN-38 by carboxylesterases (CE) in small intestine. In an attempt to ameliorate this toxicity, Randy and co-workers [66] have designed and synthesized sulfonamide derivatives (Compounds 84, 85; Figure 3.15) which are regarded as lead compounds for the
development of effective and selective carboxylesterases inhibitors for clinical applications.

There are varieties of mechanisms for the anticancer activity of the sulfonamide compounds and the most prominent one is the inhibition of carbonic anhydrase isozymes. The synthesis of some novel quinoline and pyrimido[4,5-b]quinoline derivatives (Compounds 86-88; Figure 3.15) bearing a sulfonamide moiety as possible anticancer agents was reported by Mostafa et al. [67, 68]. All the newly synthesized compounds were evaluated for their in vitro anticancer activity against breast cancer cell line, MCF7. Most of the screened compounds showed interesting cytotoxic activities compared with the used reference drugs. In addition, docking of the synthesized compounds into carbonic anhydrase isozyme II (CA II) active site was performed in order to predict the affinity and the orientation of these compounds at the isozyme active site.

Supuran and coworkers [69-71] have reported carbonic anhydrases as targets for medicinal chemistry. These authors have synthesized sulfonamides /sulfamates/ sulfamides (Compounds 89-97; Figure 3.15) possessing the general formula RXSO2NH2 and studied their anticancer property.

These authors have also prepared novel sulfonamide inhibitors of zinc enzyme carbonic anhydrase by the reaction of aromatic or heterocyclic sulfonamides (Compounds 98-101; Figure 3.15) containing amino, imino, or hydrazino moieties with N, N-dialkylthiocarbamates in the presence of oxidizing agents (sodium hypochlorite or iodine). The N, N-dialkylthiocarbamylsulfenamido-sulfonamides synthesized in this way behaved as strong inhibitors of human CA I and CA II (hCA I and hCA II) and bovine CA IV (bCA IV). The authors claim that optimization of these derivatives from the SAR point of view might lead to the development of effective novel type of anticancer agents.
3.2 BIOLOGICAL IMPORTANCE OF AMINES

The biological significance of four amines taken in the present research work, such as Phenylethylamine, 2-(3,4-Dimethoxyphenyl)-N-methylethanamine, 1-((4-Chloro-phenyl)(phenyl)methyl)piperazine and N-(5-Bromo-2-chlorobenzyl) cyclopropanamine are discussed below:
3.2.1 Phenylethylamine

Phenethylamine (PEA) [Compound 102; Figure 3.16] is a natural monoamine alkaloid, trace amine, and psychoactive drug with stimulant effects. In the mammalian central nervous system, phenethylamine is believed to function as a neuromodulator or neurotransmitter. It is biosynthesized from the amino acid phenylalanine by enzymatic decarboxylation. Besides mammals, phenethylamine is found in many other organisms and foods such as chocolate, especially after microbial fermentation. It is sold as a dietary supplement for purported mood and weight loss-related therapeutic benefits. However, orally ingested phenethylamine is usually inactive on account of extensive first-pass metabolism by monoamine oxidase (MAO) into phenyl acetic acid, preventing significant concentrations from reaching the brain [72,73].

![Figure 3.16 Structure of 2-Phenylethylamine](image)

The group of phenethylamine derivatives are referred to as the phenethylamines. Substituted phenethylamines, substituted amphetamines and substituted methylenedioxyphenethylamines are a series of broad and diverse classes of compounds derived from phenethylamine that include stimulants, psychedelics, entactogens, anorectics, bronchodilators, decongestants and antidepressants.

Phenethylamine, similarly to amphetamine, acts as a releasing agent of norepinephrine and dopamine [74-76]. For this reason, it has been called the “body's endogenous amphetamine”. However when taken orally, it is rapidly metabolized [77]. Low concentrations of endogenous phenethylamine are found in those suffering from attention-deficit hyperactivity disorder (ADHD) [78] and often in clinical depression, when the levels are elevated in schizophrenia [79].
3.2.1.1 PEA Treatment for Restoring the Well-Being

Depression is an illness very much like diabetes. In diabetes, there is a relative deficiency of insulin and it is treated by administering insulin. An even closer analogy is hypothyroidism. Thyroid hormones sustain bodily energy. Their deficit produces a characteristic syndrome that includes depression in the adult and mental retardation in the child.

Mild as well as severe forms of depression may have a simple cause and a simple cure. The brain hormone, phenylethylamine [80-84], promotes energy and elevates mood. A deficiency in PEA renders the person weak, tired, sluggish and depressed. Taking PEA rapidly restores the well-being. PEA is by no means a panacea that controls all depressions, but it may deserve to be used as the first treatment to try because it acts fast, and it can be used for long periods of time without fear of harmful consequences such as weight gain, sexual inhibition and other common side effects of antidepressant drugs. PEA is a natural and physiological treatment for depression.

The clinical observations indicate that 60% of depressed patients have a reduction in PEA metabolism. PEA can be taken by mouth. However, PEA is rapidly destroyed in the body. To prevent its rapid destruction, it must be protected by the simultaneous administration of low doses of selegiline (Eldepryl), a medication used in elderly people to slow down the progress of Parkinson’s disease.

3.2.1.2 Advantages of PEA Treatment

PEA controls depression in 60% of depressed persons, the same percentage as all major antidepressants such as Prozac, but less toxic. Although there are many treatments for depression, PEA treatment has four advantages over other treatments. PEA acts very rapidly, in a matter of hours or days, instead of weeks. A rapid treatment for depression would be an extremely useful tool to reduce disability, to shorten medical treatment and to prevent suicide. The important fact is
that, PEA is very effective in bipolar patients, as this illness represents a high risk for suicide.

3.2.1.3 Phenylethylamine as Sulfonamide Drugs

N-Phenylethyl-benzenesulfonamide derivatives had been reported for the treatment of inflammatory diseases in a mammalian patient, e.g., human, such as asthma, Alzheimer’s disease, atherosclerosis, AIDS, dementia, diabetes, inflammatory bowel disease, rheumatoid arthritis, tumor metastasis and myocardial ischemia [85-87]. In the most recent patent [88], two sulfonamide derivatives of phenylethylamine were synthesized and checked for their anti-inflammatory and anti-coagulatory properties.

3.2.2 2-(3,4-Dimethoxyphenyl)-N-methylethanamine

The compound, 2-(3,4-dimethoxyphenyl)-N-methylethanamine (Compound 103; Figure 3.20) is the key intermediate of Verapamil. Verapamil (Compound 104; Figure 3.17) is a calcium ion influx inhibitor (slow-channel blocker or calcium ion antagonist) available for oral administration. Verapamil (Diversely Substituted Xanthones) have been studied for anti cancer activity [89].

![Figure 3.17 Structures of 2-(3,4-Dimethoxyphenyl)-N-methylethanamine and Verapamil](image)

Kumar and coworkers [90] have reported the synthesis and antimalarial activity of benzene and isoquinoline sulfonamide derivatives (Compounds 105-107; Figure 3.18). These antimalarial compounds have been synthesized from 2-(3,4-dimethoxyphenyl)-N-methylethanamine.
Koichiro and coworkers [91] have reported the antibacterial activity of a number of compounds of the type (Compound 108; Figure 3.19) having the sulfonamide structure.

Thorarensen et al. [92] have reported that the molecule of the type (Compound 109; Figure 3.19) having sulfonamide functional groups X-Y-R₄ possesses antibacterial property.

Grammenos and coworkers [93] reported the antibacterial and antifungal activities of the sulfonamide compounds of the following type (Compound 110; Figure 3.20) where R₂, R₃, R⁴ and R⁵ represent dialkoxy/dimethoxy functional groups and R¹ could be an alkyl/methyl functional group.
3.2.3 1-((4-Chlorophenyl)(phenyl)methyl)piperazine

The compound, viz., 1-((4-chlorophenyl)(phenyl)methyl)piperazine (Compound 111; Figure 3.21) is a key intermediate of Cetirizine hydrochloride. The Cetirizine [94], an antihistamine is a major metabolite of hydroxyzine, and a racemic selective H₁ receptor inverse agonist used in the treatment of allergies, hay fever, angioedema and urticaria.

3.2.3.1 Rhinovirus infection

Cetirizine contains L- and D-stereoisomers. Chemically, levocetirizine is the active L-enantiomer of cetirizine. In a recent study of airway epithelial cells, the following was observed: Levocetirizine inhibits the production of intercellular adhesion molecule ICAM-1 and secretion of interleukin (IL)-6 and IL-8, which may have beneficial effects on the pathophysiologic changes related to human rhinovirus (HRV) infection. Levocetirizine treatment inhibited the HRV-induced increase in ICAM-1 mRNA and protein levels, as well as the HRV-induced expression of IL-6 and IL-8 mRNA and protein levels [95].
3.2.3.2 **Kimura's disease**

Cetirizine (Compound 112; Figure 3.22) is an effective agent in treating the symptoms of Kimura's disease [96], which mostly occurs in young Asian men, affecting the lymph nodes and soft tissue of the head and neck in the form of tumor-like lesions. Cetirizine's properties of being effective both in the treatment of pruritus (itching) and as an anti-inflammatory agent make it suitable for the treatment of the pruritus associated with these lesions.

![Figure 3.22 Structure of Cetirizine](image)

He-Ping Li [97] had studied that the compounds containing piperazine are widely used in pharmaceutical industry. Especially, some substituted piperazine compounds have distinctive anticancer activity [98-103].

3.2.3.3 **1-((4-Chlorophenyl)(phenyl)methyl)piperazine sulfonamide drugs**

Many papers and patents [104-106] have been published with the compounds containing piperazine. They were reported to be very active against infections and showed very good biological activity in different therapeutic areas.

1-[(4-Chloro-phenyl)-phenyl-methyl]-4-(toluene-4-sulfonyl)-piperazine was synthesized [108] in 2002 and was used for a “Asymmetric synthesis of cetirizine dihydrochloride”. It was also reported in the patent [107, 108] that this compound was used for preparation of substantially optically pure levorotatory and dextrorotatory enantiomers of cetirizine.
1-[(4-Chloro-phenyl)-phenyl-methyl]-piperazine-sulfonamide derivatives were not tested for anticancer activity, even though cetirizine hydrochloride shows very good activity against infections.

3.2.4  \textit{N-(5-Bromo-2-chlorobenzyl)cyclopropanamine}

The compound, \textit{N-(5-bromo-2-chlorobenzyl)cyclopropanamine} (Compound 113; Figure 3.23) is the key intermediate of one of the new chemical entity, whose biological activity is Renin inhibition [109,110]. Renin is an enzyme that plays a major role in the Renin-Angiotensin System, a regulatory system in the body, which is responsible to maintain homeostasis of blood pressure.

![Figure 3.23 Structure of N-(5-Bromo-2-chlorobenzyl)cyclopropanamine](image)

The enzyme belongs to the family of aspartic proteases and is responsible for the conversion of inactive angiotensinogen to angiotensin I (Ang I). Angiotensin I by itself is inactive. However, when acted upon by angiotensin converting enzyme (ACE), it gets converted to angiotensin II, which is active and is responsible for most of the pressor effects. Conversion of angiotensinogen to angiotensin I is the rate determining step of the system. The catalytic role played by renin is thus crucial in mediating blood pressure by the Renin-Angiotensin System.

\textit{N-(5-bromo-2-chlorobenzyl)cyclopropanamine} [111,112] is also used as the intermediate for the preparation of a cardiovascular drug.
3.3 BIOLOGICAL IMPORTANCE OF AROMATIC SULFONYL CHLORIDES

3.3.1 Benzenesulfonyl chloride

![Structure of Benzenesulfonyl chloride](image)

Benzenesulfonyl chloride is a basic moiety of all aromatic sulfonyl chlorides. Jakob Avi et al. [113] have carried out the research work on potential new antiepileptic drugs (AEDs). These authors have tested a series of tetramethylecyclopropanecarboxamide derivatives containing benzene ring for antiepileptic activity by Murine Maximal Electroshock (MES) and subcutaneous pentylenetetrazole (scMet) seizure tests. The most potent compound emerged from this study was N-(2, 2, 3, 3-tetramethylecyclopropanecarboxamide)-p-phenyl-sulfonamide (21), possessing an ED$_{50}$ value of 26 mg/kg in the rat-MES test and a remarkable PI (PI = TD$_{50}$/ED$_{50}$) value above 19.

Wang and coworkers [114] developed ABT-263, a new Bcl-2 inhibitor. The key intermediates of the inhibitor are 4-(4-{[2-(4-chlorophenyl)-5,5-dimethylcyclohex-1-enyl] methyl}piperazin-1-yl)benzoic acid and 4-fluoro-3-[(trifluoromethyl)sulfonyl] benzenesulfonamide.

Kashaw and Mishra [115] have reported that substituted imidazolidinone benzenesulfonamides were found to have high affinity for β$_3$-adrenergic receptors of adiposites tissue. In order to establish an exact relationship between β$_3$-adrenergic receptor agonistic activity and various quantifying parameters, these compounds were subjected to quantitative structure-activity relationship (QSAR) analysis.
Francesco and coworkers [116] have carried out the reaction between 4-carboxy-benzenesulfonamide or 4-chloro-3-sulfamoyl benzoic acid with carboxy-protected amino acids/dipeptides, or aromatic/heterocyclic sulfonamides/mercaptans to form the corresponding benzene-carboxamide derivatives. These compounds were tested as inhibitors of three carbonic anhydrase (CA) isozymes, such as CA I, II and IV. Some of the new derivatives showed affinity in the low nanomolar range for isozymes CA II and IV, involved in aqueous humor secretion within the eye, and were tested as topically acting anti-glaucoma agents, in normotensive and glaucomatous rabbits. Good *in vivo* activity and prolonged duration of action has been observed for some of these derivatives, as compared to the clinically used drugs dorzolamide and brinzolamide. Some of the 4-chloro-3-sulfamoyl benzenecarboxamides showed higher affinity for CA I than for the sulfonamide isozyme CA II.

### 3.3.2 4-Methylbenzene-1-sulfonyl chloride

![Structure of 4-Methylbenzene sulfonyl chloride](image)

**Figure 3.25 Structure of 4-Methylbenzene sulfonyl chloride**

The compound viz., 4-methylbenzene sulfonyl chloride (Compound 115; Figure 3.25) is also a basic moiety of aromatic sulfonyl chloride derivatives. This has been used in many sulfá-drugs [117].

Kumar and coworkers [90] have studied the antimalarial activity of methylbenzene and isoquinoline sulfonamide derivatives. (Compounds 116 – 121; Figure 3.26)
3.3.3 2, 4-Dichlorobenzene-1-sulfonyl chloride

![Chemical Structure](image)

Figure 3.26 Antimalarial Sulfonamide Derivatives

The following sulfonamide derivative (Compound 123; Figure 3.28) has been reported [118] as modulators of PPARγ activity. It is used in methods of treating and/or preventing conditions such as osteoporosis, Alzheimer's disease, psoriasis and acne, and cancer.
The following sulfonamide compound coded as P1736 (Compound 124; Figure 3.29) was screened for the treatment of metabolic disorders related to insulin resistance or hyperglycemia [119].

Naphthalene sulfonyl chlorides have received great attention in recent days. The biological activities of the following compounds (Compounds 127, 128; Figure 3.31) have been well documented [120]:
Hidaka et al. [121] have reported the synthesis of sulfonamides from naphthalene sulfonyl chlorides (Compounds 129, 130; Figure 3.32). These compounds were studied for Calmodulin Antagonists. In a patent [122] titled as “Guanidine derivatives as inhibitors of cell adhesion,” naphthalene sulfonyl chloride were used as the intermediates for the synthesis of biociacl active compounds.

In the most recent Patent [123] titled as “1-(Arylsulfonyl)-4-(Piperizin-yl)-1h-Bezimidazoles as 5-Hydroxytryptamie-6 Ligands”, these intermediates were used to prepare new drugs.
3.3.5 4-Bromo-3-(chlorosulfonyl)-5-methylbenzoic Acid

![Structure of 4-Bromo-3-(chlorosulfonyl)-5-methylbenzoic acid](image)

Figure 3.34 Structure of 4-Bromo-3-(chlorosulfonyl)-5-methylbenzoic acid

4-Bromo-3-(chlorosulfonyl)-5-methylbenzoic acid have been used for the synthesis [124] of potent Inhibitors of α-Ketoacyl-acyl Carrier Protein Synthase III.

In the patent [125] titled as “Fused Tricyclic Compounds as Inhibitors of Tumor Necrosis Factor-Alpha,” the 4-Bromo-3-(chlorosulfonyl)-5-methylbenzoic acid is used for the synthesis of many tumor inhibiting compounds.

3.3.6 Quinoline-8-sulfonyl chloride

![Structure of Quinoline-8-sulfonyl chloride](image)

Figure 3.35 Structure of Quinoline-8-sulfonyl chloride

Quinoline derived molecules are shown to exhibit anticancer property [126]. The antimalerial [127] and antibacterial activities of quinoline compounds have also been well document [128, 129].