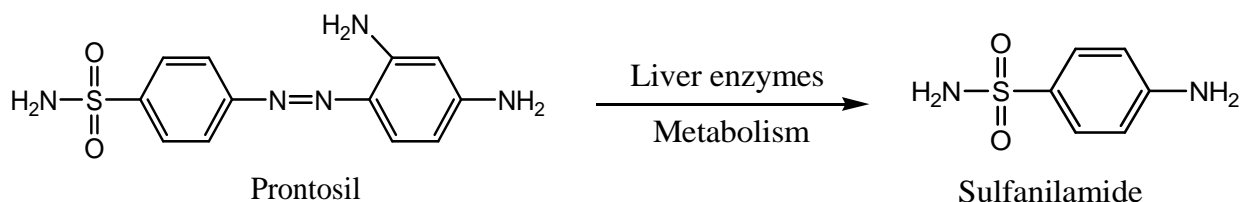


A. Sulfonamides

A.1. Background

Sulfonamide is one of a group of chemotherapeutic agents commonly referred to as Sulfa drugs which were discovered in the 1930's. Exactly in 1935, *Gerhard Domagk* discovered that a red dye, 4'-sulfamyl-2,4-diaminoazo-benzene, which was later named prontosil (**Scheme 1**). Strangely enough, prontosil was inactive against these same hemolytic streptococci in vitro. *Trefouel* made the important observation that the antibacterial activity was not due directly to prontosil, but rather to a metabolite formed in the animal by the reduction of the diazyl bond of the prontosil ^[1]. This metabolite was identified as sulfanilamide in 1939, *Domagk* was awarded the Nobel prize in medicine for his classic discovery of what was termed in 1940 "the only known chemicals capable of curing serious systemic bacterial infections in man in doses allowing a satisfactory margin of safety" ^[2].



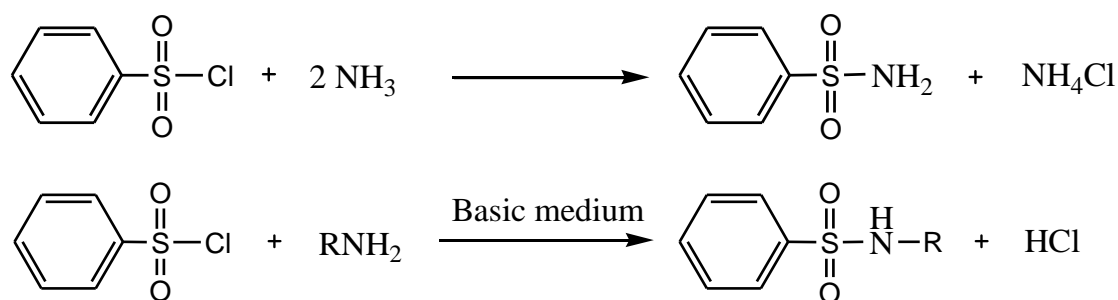
Scheme 1 Structural formulas of Prontosil and its metabolite in human body (Sulfanilamide)

The observation by *Domagk* that the red dye prontosil had a high antibacterial activity, coupled with systematic efforts to identify the active structure, led to the opening of a new chapter in chemotherapy.

Domagk's discovery quickly resulted in the development of a variety of sulfonamides, all of which were essentially substituted sulfanilamides. Sulfa drugs were found to be effective against such grave bacterial infections as meningitis, pneumonia and blood poisoning, and saved thousands of lives in World War II (1939-1945).

A.2. Synthesis of Sulfonamides

The most common method used for preparation of sulfonamides is by the reaction of appropriate sulfonyl halide, either aliphatic or aromatic, with ammonia or amines. Therefore, heterocyclic sulfonamides were similarly prepared through the reaction of heterocyclic sulfonyl halide with ammonia or amines.



Scheme 2. Reaction for synthesis of sulfonamide

The reaction between sulfonyl halide and amines is usually catalyzed by basic catalyst such as sodium carbonate, potassium carbonate, pyridine or triethyl amine.

The sulfonyl chloride method represents the most simple and direct route for the preparation of sulfonamides. This is due to the ease with which the required sulfonyl chlorides are obtained in high yields.

A.2.1. Common Synthesis of Sulfonyl Chloride Derivatives

Chlorosulfonation reactions are widely used in organic (in particular, pharmaceutical) chemistry. Sulfonyl chlorides are intermediates in syntheses of active and dispersible dyes, herbicides, and fungicides. Among six-membered heterocyclic compounds containing two nitrogen atoms, a prominent place is occupied by pyrimidine derivatives used as drugs such as Sulfadimethoxine, Sulfamonomethoxine (sulfa drugs); antitumor agent Fluorouracil; antibiotic Amecytin, etc.

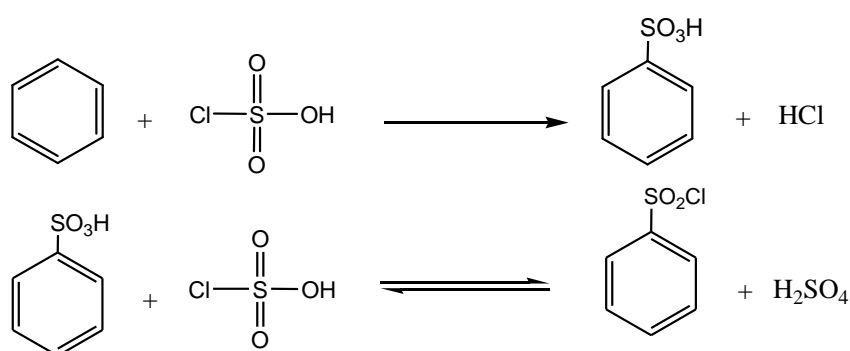
Sulfonyl chlorides are either aliphatic or aromatic. The aliphatic sulfonyl chlorides are in general water insoluble liquids while the aromatic derivatives are in general colourless crystalline solids insoluble in water, except benzene sulfonyl chloride, which is an oily liquid that freezes at 14 °C ^[3].

The desired sulfonyl chlorides are very slowly hydrolyzed in aqueous solution furthermore rapidly by alkali. To suppress the hydrolysis, the reaction mixture was poured onto a 1 : 1 mixture of ice and acetic acid.

There are different methods used successfully for synthesis of sulfonyl chlorides such as:-

i) By chlorosulfonic acid

The best preparation of sulfonyl chloride of most aromatic compounds is achieved ^[3] by treating the desired aromatic compound with excess of chlorosulfonic acid by the direct replacement of hydrogen with the sulfonyl chloride group. This reagent forms the sulfonic acid at first, and then converts it into a sulfonyl chloride by these excess of chlorosulfonic acid. This reaction is showed in (Scheme 3).



Scheme 3. Steps of chlorosulfonylation reaction .

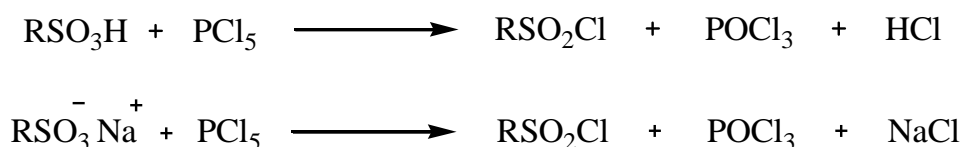
Step 1 goes to complete easily since hydrogen chloride is evolved, driving the reaction towards the right. **Step 2** is an equilibrium reaction. Therefore, a considerable excess of reagent is required to ensure a fair yield of the desired sulfonyl chloride.

There are some notes ^[4] should be taken under consideration:

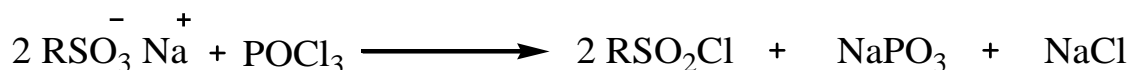
- 1) If less than 50 percent excess of chlorosulfonic acid is taken, the yield of diphenyl sulfone increases at the expense of the sulfonyl chloride.
- 2) The aromatic compound must be added to the acid (not vice versa); otherwise, a larger proportion of sulfone is formed.
- 3) The sulfonyl chloride should be removed from the water as soon as possible; otherwise, the yield falls, owing to hydrolysis forming sulfonic acid, which would promote decomposition of the sulfonyl chloride during its distillation.

ii) By Phosphorus Pentachloride (PCl₅), Phosphoryl Chloride (POCl₃)

Since chlorosulfonic acid has been used for the preparation of sulfonyl chloride, recently, some sulfonyl chlorides have been obtained by the action of phosphorus pentachloride upon sulfonic acid or its sodium salt ^[5].

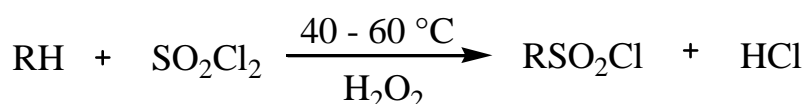


Phosphoryl chloride (POCl_3) can be used giving two moles of sulfonyl chloride product.

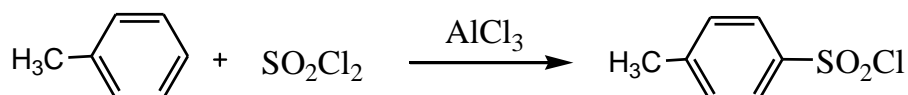


iii) By Sulfuryl Chloride (SO_2Cl_2)

Sulfonyl chloride is prepared by reaction of hydrocarbon with sulfuryl chloride (SO_2Cl_2) in the presence of light or hydrogen peroxide at $40 - 60^\circ\text{C}$ often in high yield ^[3].

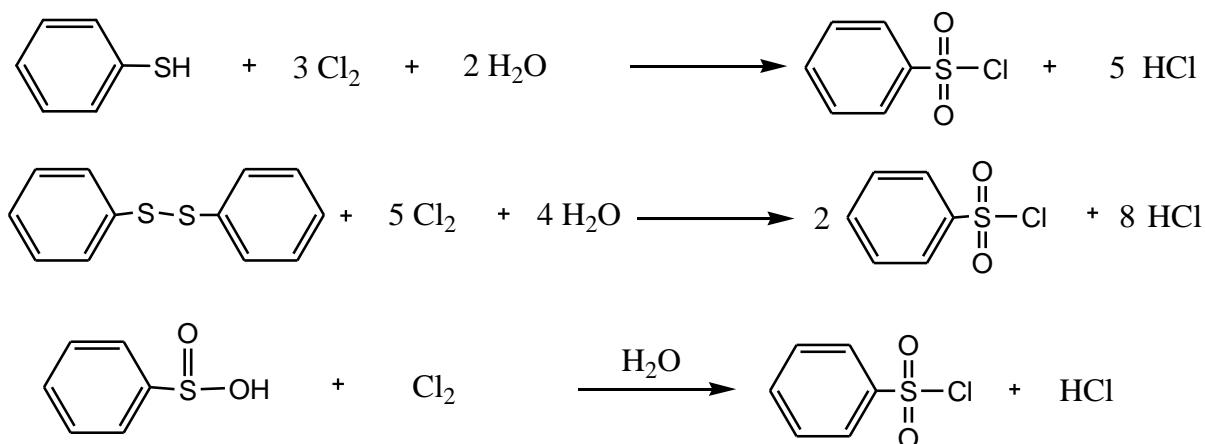


Alternatively, the same reaction may also proceed with aromatic hydrocarbon in the presence of aluminum chloride (AlCl_3)



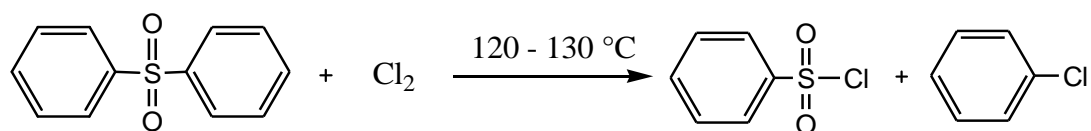
iv) By Action of Chlorine Cl_2

The less used methods for obtaining aromatic sulfonyl chlorides, the only one with practical value is the action of chlorine in water solution upon thiophenols ^[6] and their derivatives, disulfides, or sulfinic acids. These compounds have been converted into sulfonyl chlorides by the action of chlorine in water or acetic acid solution (or suspension).



Scheme 4. Examples for action of chlorine in water to obtain sulfonyl chlorides

Chlorine reacts with sulfones by cleavage of a carbon – sulfur bond and then formation of sulfonyl chloride. Thus, diphenyl sulfone reacts at 120 – 130 °C to give benzene sulfonyl chloride^[7].



Richarfd Langler^[8] studied the synthesis of sulfonyl chloride using chlorine Cl_2 . He realized a good yield of methane sulfonyl chloride from the chlorination of benzyl methyl sulfide in aqueous acetic acid. At this time, we proposed that methane sulfenyl chloride was the principal intermediate in the reaction.

A.3. Antibacterial Activity of Sulfonamides

Sulfonamides remain the most widely used antibacterial agents ^[9, 10] in the world because of their low cost, low toxicity and excellent activity against common bacterial diseases. Sulfa drugs include:

- **Topical sulfonamides:** sulfacetamide, silver sulfadiazine, mafenide and mafenide acetate.
- **Rapidly absorbed and eliminated sulfonamides:** sulfisoxazole diolamine, sulfadiazine and sulfamethoxazole.
- **Hydrophilic sulfonamides:** phthalylsulfacetamide, phthalylsulfathiazole, sulfasalazine and sulfaguanidine.
- **Long lasting sulfonamides:** sulfadoxine.
- **Others:** sulfamazole, sulfamazone, sulfametopirazine, sulfametoxypridazine, sulfametrol and succinylsulfathiazole.

Most of these sulfonamides are still being used in the treatment of pneumonia, meningitis and urinary tract infections. **Table (1)** shows examples of current sulfonamides and their therapeutic use.

Table 1: Examples of Current Therapeutic Use of Sulfonamides

Sulfonamide	Therapeutic Indication
trimethoprim-sulfamethoxazole	Treatment and prophylaxis of pneumonia
pyrimethamine-sulfadiazine	Treatment and prophylaxis of cerebral toxoplasmosis
trimethoprim-sulfamethoxazole	First attack of urinary tract infection
silver sulfadiazine	Prevention and treatment of bacterial infection for burn patients
sodium sulfacetamide	Conjunctivitis and related superficial ocular infections
sulfadoxine and sulfalene in combination with quinine	Chloroquine-resistant malaria

A.3.1. Mechanism of Antibacterial Action

The activity of the sulfa drugs has been extensively studied and can be explained in the following manner. Sulfonamides are typically administered in doses that are bacteriostatic ^[9, 10], meaning they prevent or limit bacterial multiplication. Sulfonamides achieve this bacteriostatic action (i.e., the mechanism of action) by inhibiting the synthesis of folic acid in bacteria. Bacteria synthesize their own folic acid using endogenous compounds and enzymes, Endogenous compounds are those that occur naturally in the biological system, Specifically, sulfonamides inhibit the enzyme dihydropteroate synthase, an enzyme that catalyzes the conversion of p-aminobenzoic acid (PABA) and dihydropteroate diphosphate to dihydropteroic acid, a precursor to folic acid and DNA. Sulfonamides compete with PABA for the “active site” in the dihydropteroate synthase enzyme, and are considered to be “competitive inhibitors” of this enzyme. The structural similarity of the sulfonamides to PABA “tricks” the enzyme into binding with the drug (sulfonamide) instead of the endogenous compound (PABA). The displacement of the PABA by the sulfonamide leads to the formation of a “false” metabolite in the folic acid synthesis, which cannot continue through the synthetic sequence. **(Figure 1)** shows a

comparative illustration between mechanism of synthesis of folic acid in bacteria and mechanism of competitive inhibition of sulfonamides.

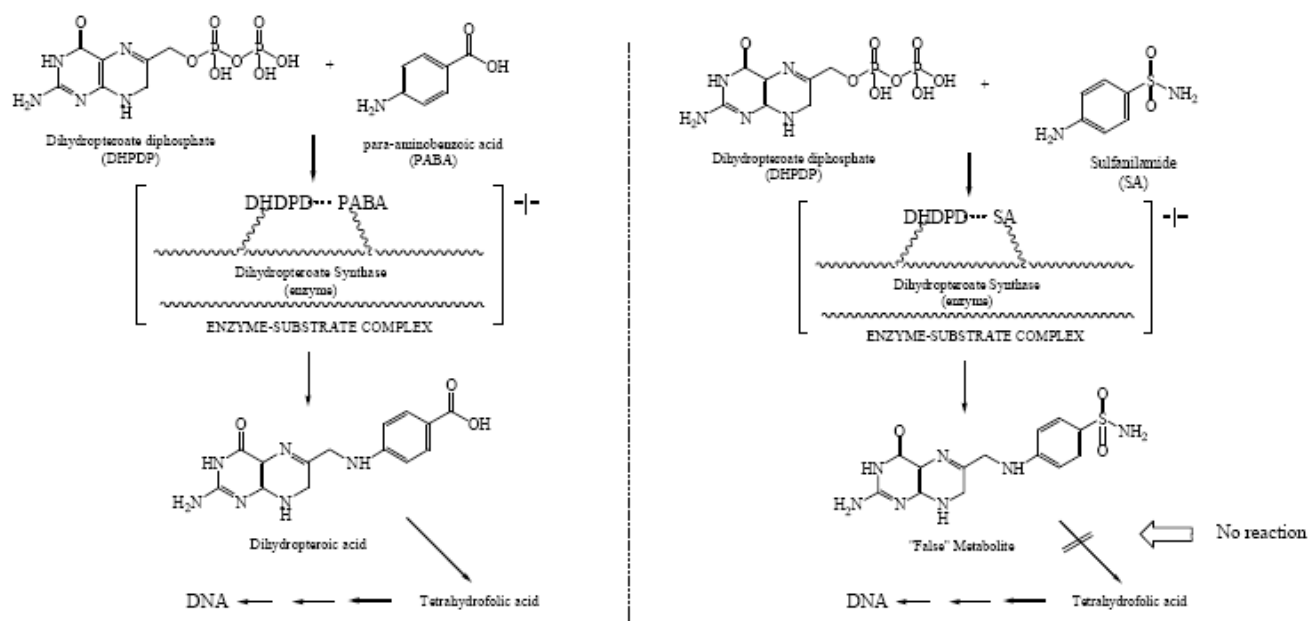


Figure 1. Schematic illustration of the mechanism of action of Sulfanilamide (as sulfonamide)

Folic acid is essential for DNA synthesis, thus lack of folic acid will prevent replication that requires DNA. Humans do not synthesize folic acid. Thus, the hosts of these bacteria needed ready-made folic acid in their diets, and the hosts were unaffected by sulfonamides. This difference between bacteria and animals gave sulfonamides the properties of the magic bullet that would hit the target without harming the host.

Therefore, Sulfonamides act as antimicrobial agents by inhibiting bacterial growth and activity. Some recent classes of sulfonamides and related sulfonyl derivatives disclosed as effective antibacterial agent, *A. M. Badawi et al* ^[11]

synthesized and studied series of cresols disulfonamide derivatives and evaluate their antibacterial activity. Moreover, alkylation of these disulfonamides was performed to investigate new compounds possessing more pharmacological activity. More research lines that progressed to regard different sulfonamides with remarkable antibacterial activity. By **A. M. Badawi**, a series of dihydroxybenzene disulfonamide were prepared and evaluated for antibacterial activity ^[12], another series of acetanilide sulfonyl hydrazides and hydrazones were synthesized and evaluated ^[13]. Most of these compounds exhibit more potent activity against pathogenic bacterial species.

Sulfonamides are used in not only the prevention and treatment of bacterial infections but also in diabetes mellitus, edema, hypertension, and gout.

A.4. Applications of Sulfonamides

Sulfanilamide was the beginning of a great adventure that more substituted aromatic, heterocyclic, and bis-sulfonamide classes that have been synthesized and investigated for their biological activity. These led to important drugs widely used to treat and prevent a multitude of diseases.

The discovery of sulfanilamide leads to the development of all these types of pharmacological agents that have a wide variety of biological actions. From 1950s, more potent high-ceiling diuretics have been developed as well as to the systemic antiglucoma drugs such as Acetazolamide,

Methazolamide, Ethoxzolamide and Dichlorophenamide. Moreover, the antibacterial agent Sulfathiazole, the carbonic anhydrase inhibitor Acetazolamide (clinically used for more than 45 years) ^[14], the widely used diuretic Furosemide, the hypoglycemic agent Glibenclamide, the anticancer sulfonamide Indisulam (in advanced clinical trials), the aspartic HIV protease inhibitor Amprenavir used to treat AIDS and HIV infection and the metalloprotease (MMP) inhibitors of the sulfonyl amino acid hydroxamate type ^[15, 16, 17]. All these classes are shown in **(Figure 2)**

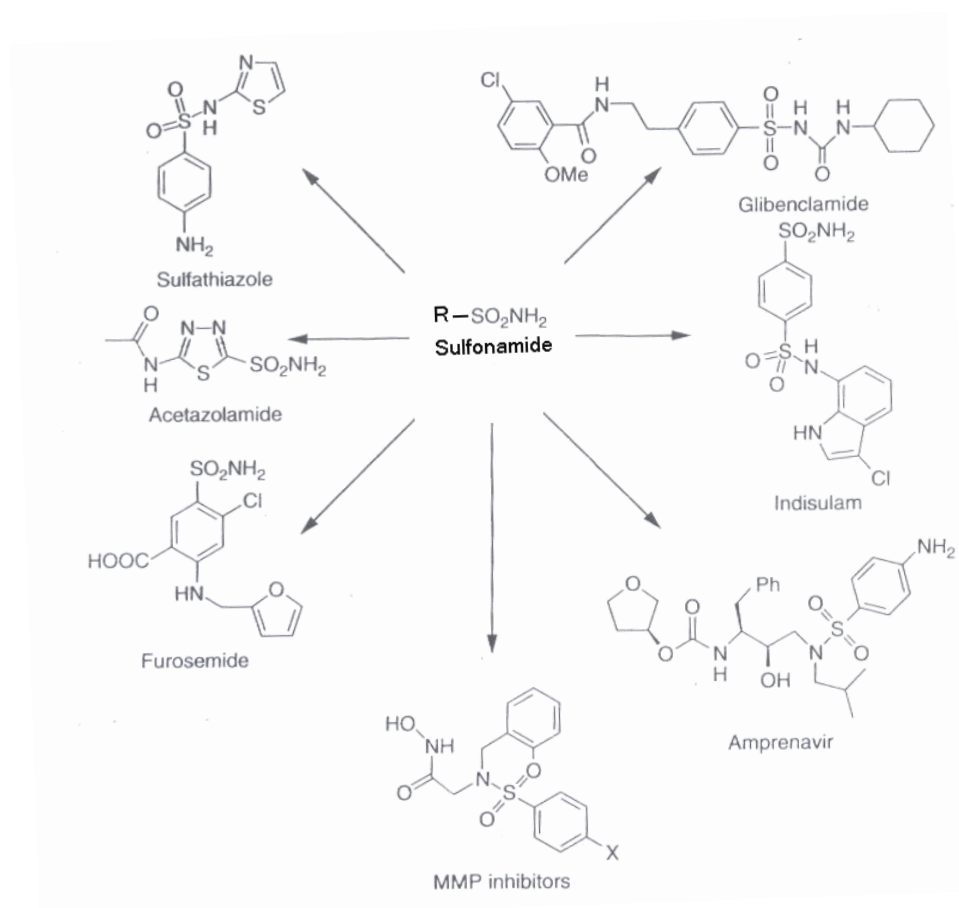


Figure 2. Different sulfonamide derivatives with their pharmacological activity.

Therefore, Sulfonamides represent an important class of medicinally effective molecules and are known to possess wide varieties of biological activities. In addition to antibacterial activity, sulfonamides with different substituted groups are considered also as several types of pharmacological agents ^[18-29, 30]. These activities will be discussed in details as the following:

A.4.1. Anticancer Sulfonamides

Cancer is a disease of cells characterized by the reduction or loss of effectiveness of the normal controlling influences that maintain cellular organization in tissues. Cancer cells have acquired properties that, in simplistic terms, provide them with growth advantages over normal cells; this permits their continuous proliferation not only in their sites of origin but also in other environments. The abnormal behavior of tumor cells leads to damage in the host at a variety of levels; a) locally by pressure effects, b) by destruction of involved tissues, both physically and in terms of normal function, and c) by systemic effects secondary to the localized growth.

As an initiation point in the design of therapy and the understanding of cancer growth, comparisons at different levels have been made of tumor and normal equivalent tissue from which we can summarize the basic features of cancer cells:

- 1- Uncontrolled cell proliferation.
- 2- A lack of cellular differentiation features.
- 3- The ability to invade surrounding tissue.
- 4- The ability to metastasize (establish new focal growth in distant sites).

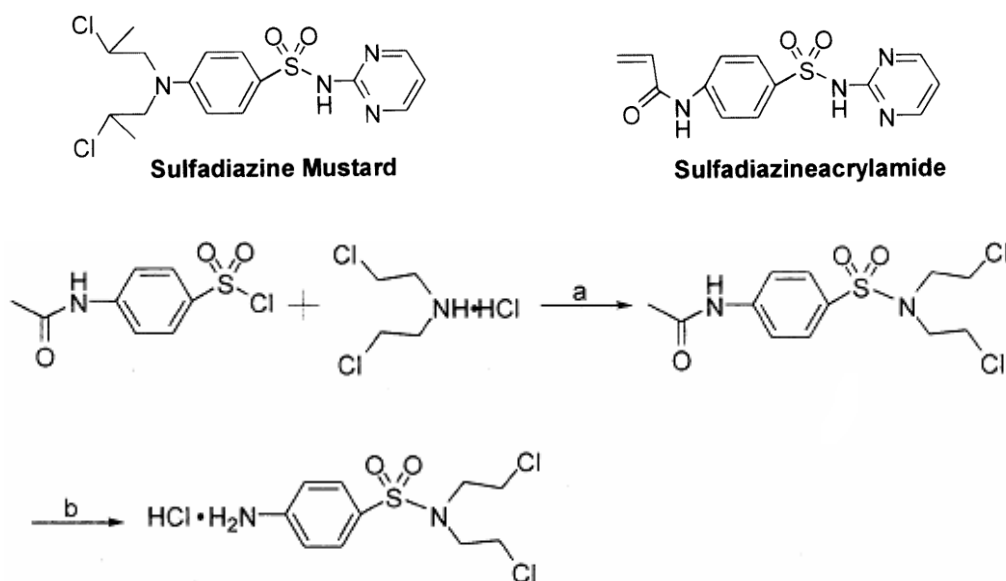
Most causes of cancer (carcinogens) are unknown but the common causes include chemicals such as benzidine dye, most of herbicides and pesticides, some heavy metals such as mercury and some drugs and hormones; radiation such as ionized radiation and ultraviolet light and biological agents such as hepatitis B, C viruses.

Cancer therapy with cytotoxic drugs has made enormous progress since the initial application of chemicals in the late 1940 when *Farber* prescribed Methotrexate to treat childhood leukemia. In the recent years the emphasis has been on the integration of chemotherapy with other treatment modalities; surgery, radiotherapy, and immunotherapy. It is now clear that chemotherapy's most effective role in solid tumors is as an adjuvant to initial therapy by surgical or radiotherapeutic procedures.

Because the most characteristic of tumor tissue is its increase in size by an increase in cell number, chemotherapeutic agents have naturally been selected as antiproliferative. Their ability to impede cell proliferation is, in general, a

function of interference with a critical biochemical component the cell division process.

A large number of structurally novel sulfonamide derivatives have ultimately been studied to show substantial antitumor activity in vitro and in vivo ^[31-37]. Although Sulfonamides have a common chemical motif of aromatic / heterocyclic or amino acid sulfonamide, there are a variety of mechanisms of their antitumor action, such as carbonic anhydrase inhibition ^[38-41], cell cycle perturbation in the G1 phase ^[42, 44], disruption of microtubule assembly and angiogenesis (matrix metalloproteinase, MMP) ^[45] inhibition among others. More researches were established to synthesize sulfonamide derivatives and study their antitumor activity, **Z. Huang et al.** ^[46] obtained a novel kind of antitumor drugs sulfonamide derivatives with low toxicity from parent compound, Sulfapyrazine has been shown to concentrate selectively in the Walker carcinoma growing in rats ^[47]. Therefore, this work aimed to design new antitumor agents by combining sulfadiazine and antitumor agents in one compound. Heretofore, the main work of modified sulfadiazine has been focused on the aromatic amine due to its relatively high reaction activity.

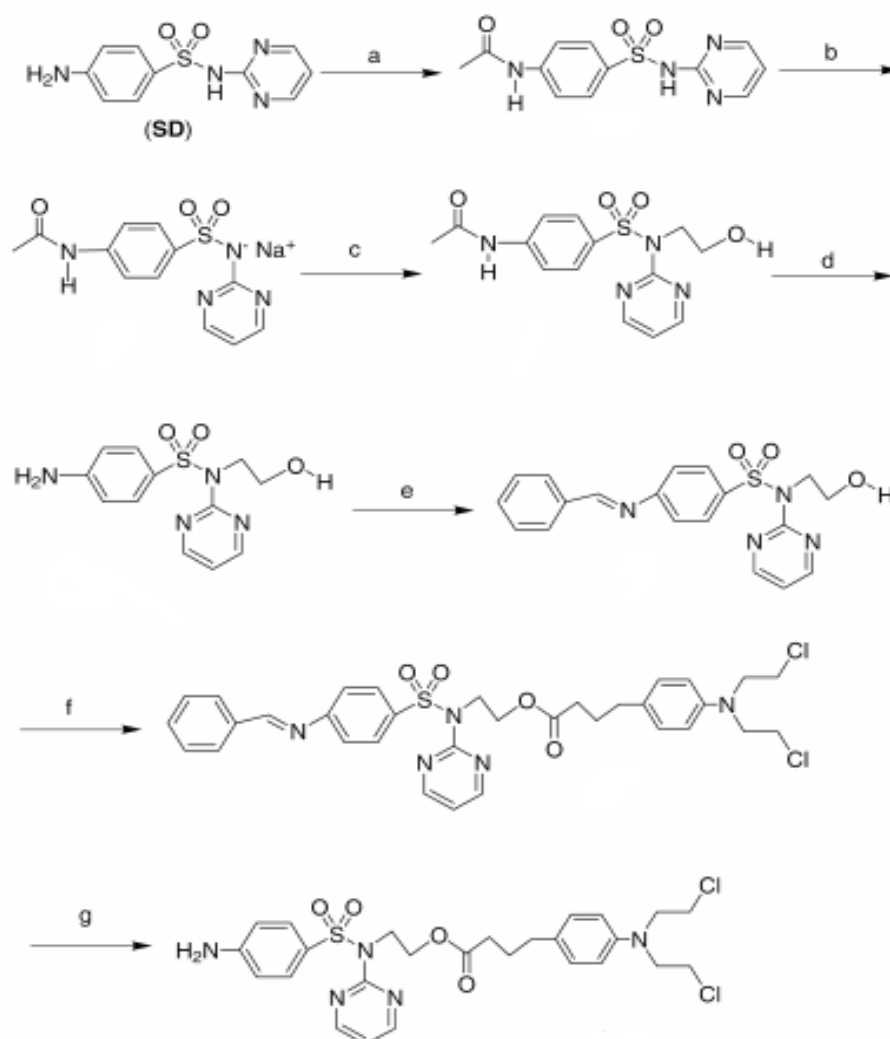


Scheme 5. Reagents and conditions: (**a**) Et_3N (1.2 equivalent), pyridine, 0–40 °C, 3 h; (**b**) HCl (6 M), reflux, 40 min

This compound demonstrates high antitumor activity and is more potent and safer than its mother compound. The concentration of sulfonamides in tumor cells may be related to the basicity of the aromatic amino group and the acidity of the tumor cells. This class of targeting agents may be further developed to form candidate drugs, which may have advantages over the currently available anticancer agents.

Z. Huang et al. ^[48] also obtained 2-[N1-2-Pyrimidyl-aminobenzene-sulfonamido] ethyl-4-bis (2-chloroethyl) amino- phenyl butyrate as potent antitumor agent, in the design of the target compound (**Scheme 6**), they considered two factors. First, instead of the aromatic amine, sulfonamide has been chosen as the reaction site for modification since those modified on the

aromatic amine lost selectivity toward tumor cells. Second, sulfadiazine should be connected with chlorambucil (CBL) in an appropriate way such that both the selectivity of sulfadiazine toward tumor cells and the antitumor activity of CBL are not destroyed.

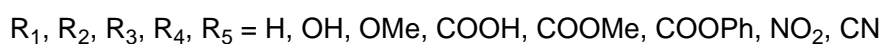
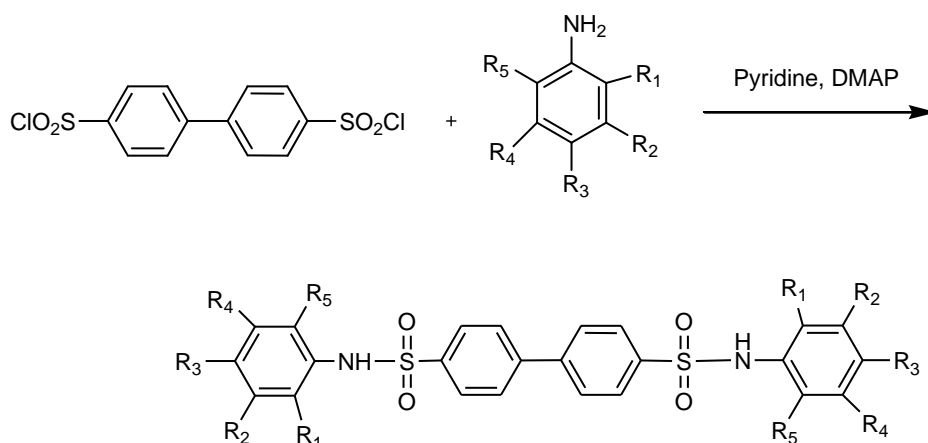


Scheme 6. Reagents and conditions: (a) acetyl chloride, pyridine, 0 °C, 2 h; (b) NaOH (aq, 1.0 equiv); (c) DMF, BrCH₂CH₂OH (1.0 equiv), 80 °C, 8 h; (d) HCl (1.2 M), reflux, 1 h; (e) benzaldehyde, 100 °C, 6 h; (f) chlorambucil (1.0 equiv), DCC (1.1 equiv), pyridine, rt, 48 h; (g) acetone, 365nm UV light, rt, 1 h

To prepare the target compound, it is important to choose an appropriate protective group for the aromatic amine of sulfadiazine because of its relatively high reactivity.

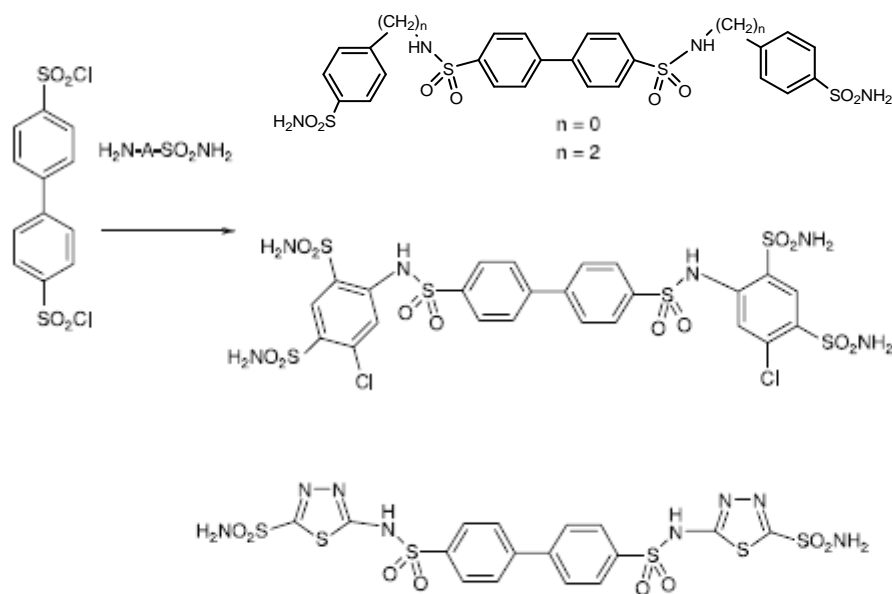
Yokoi and J. Kuromitsu et al ^[49] introduced and profiled novel sulfonamide antitumor agents with cell-based phenotypic screens and array-based gene expression analysis. *L. Novotny et al* ^[50] studied antileukemic activity of sulfonamide conjugates of arabinosyl-cytosine.

A recent series of biphenyl sulfonamides derivatives of (S)-2-(biphenyl-4-sulfonyl-amino)-3-methylbutyric acid were prepared and evaluated for their ability to inhibit matrix metalloproteinase, MMP, as effective tumor cell growth inhibitors which were studied by *Patrick M. O'Brien et al* ^[45]. Another work was concerned with the structure-activity relationships for a series of potent, systemically available as matrix metalloproteinase, MMP, and was studied by *Sellarajah et al* ^[51]. They synthesized series of biphenyl bis-sulfonamide derivatives from the readily available biphenyl-4,4'-disulphonyl chloride and the appropriate amine utilizing DMAP and pyridine and evaluated for the treatment of different types of cancer.



Scheme 7. Series of biphenyl bis-sulfonamide derivatives from biphenyl-4,4'-disulphonyl chloride.

Recently, **A. M. Badawi** ^[52] published a new paper which is more closely related to our work. It is a result of cooperation with **Andrea Scozzafava** and **Claudiu T. Supuran**. It introduced the reaction of biphenyl-4,4'-disulfonyl chloride with aromatic/heterocyclic sulfonamides having a free amino group, and have been tested as inhibitors of the zinc enzyme carbonic anhydrase (CA, EC 4.2.1.1). These sulfonamides are 4-aminobenzenesulfonamide, 4-aminoethyl-benzenesulfonamide, 6-chloro-4-aminobenzene-1,3-disulfonamide and 5-amino-1,3,4-thiadiazole 2-sulfonamide.



Scheme 8. Biphenyl bis-sulfonamide derivatives formed using four sulfonamides having a free amino group.

Furthermore, these compounds were screened for in vitro antiproliferative activity against the human colon cancer cell line HCT116, the human lung cancer cell line H460 and the human breast cancer cell line MCF-7. These disulfonamide derivatives showed a good antiproliferative activity especially against the HCT116 line, with a GI_{50} in the range of 3.92–8.19 mg/mL. The results showed that the first derivative was the most active against the HCT116 cell line and H460 cell lines, with GI_{50} values of 3.29 mg/mL and 10 mg/mL respectively. The 4th derivative had a comparable antiproliferative activity against the human colon cell line, with a GI_{50} value of 3.789 mg/mL.

The other two derivatives showed a relatively less strong antiproliferative activity with GI_{50} value 0.74 mg/mL and 8.19 mg/mL respectively.

A.4.2. Antihypertensive Sulfonamides

In addition to antihypertensive activity of sulfonamides by the well-known diuretic action (releasing more water content of blood therefore reducing its volume), some recent classes of sulfonamides and related sulfonyl derivatives disclosed as effective antihypertensive agent as angiotensin II receptor antagonists. *J. E. Tellet et al* ^[53] introduced more interesting research that a series of 4'-[(imidazol-1-yl)methyl] biphenyl sulfonamides having potent antagonist activity against angiotensin II AT1 receptors. This action is not only for the treatment of hypertension but also for heart failure, and other cardiovascular diseases in a broad patient population.

A.4.3. Antimalarial Sulfonamides

Malaria remains major health problem in tropical and subtropical countries ^[54-55]. The treatment of malaria depends largely on chemotherapeutics and chemoprophylaxis due to the existence of limitations in vaccine development and vector control. Malaria parasite, *Plasmodium falciparum*, the most severe form of malaria, has developed resistance against

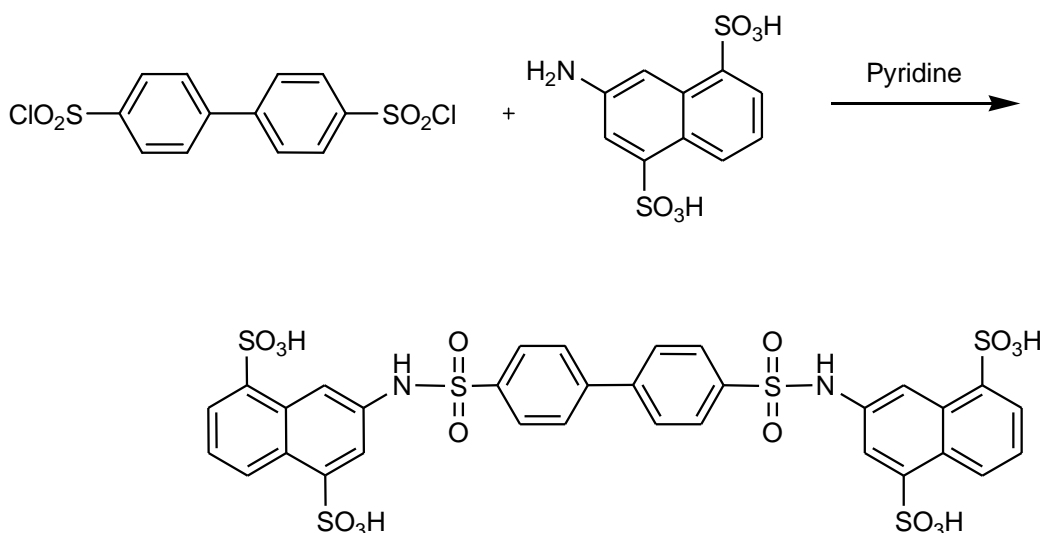
almost all the drugs available ^[56]. The design and development of novel drugs for the comprehensive treatment of malaria is highly necessary and intensive research warrants to eradicate this deadly disease ^[57]. Sulfadoxine and Pyrimethamine is already antimalarial agent that is effective against strains of *Plasmodium falciparum* resistant to chloroquine.

A new series of benzene and isoquinoline sulfonamide derivatives were synthesized and evaluated for antimalarial activity against *Plasmodium falciparum* in vitro by *M. Kumar Parai et al* ^[58]. Antimalarial activity of several benzene sulfonamides was reported ^[59-65].

A.4.4. Antiviral Sulfonamides

More research lines that progressed much in the last time regard different sulfonamides with remarkable antiviral activity. Thus, at least two clinically used HIV protease inhibitors possess sulfonamide moieties in their molecules, whereas a very large number of other derivatives are constantly being synthesized and evaluated in order to obtain compounds with less toxicity or activity against drug-resistant viruses. Several non-nucleoside HIV reverse transcriptase or HIV integrase inhibitors containing sulfonamido groups were also reported.

Study that is more interesting, introduced certain biphenyl bis-sulfonamide of naphthalene sulfonic acid analogues by *Prem Mohan et al.* ^[66] as potential anti-AIDS agent.



Scheme 9. *Biphenyl bis-sulfonamide of naphthalene sulfonic acid analogue*

These compounds have been synthesized and evaluated for their inhibitory effect on HIV-1- and HIV-2- induced cytopathogenicity. This study concludes that all the compounds that achieved complete inhibition of virus-induced cytopathogenicity at concentrations not toxic to host cells were derivatives of 3-aminonaphthalene-1,5-disulfonic acid. These analogues represent new leads for the development of anti-HIV agents. *Zhijian Zhao et al* ^[67] introduced novel indole-3-sulfonamides as potent HIV non-nucleoside reverse transcriptase inhibitors.

The hepatitis C virus (HCV) is a major health problem afflicting millions of people worldwide. Current therapies suffer from low efficacy and several side effects. So, **Robert Rönn et al**^[68] explored new antiviral agents of the acyl sulfonamide functionality as a carboxylic acid replacement in hepatitis C virus protease inhibitors.

A.4.5. Miscellaneous Applications

Sulfonamides have wide variety of biological activities. More recent researches are directed to evaluate antithyroid activity^[69], insulin-releasing antidiabetic^[70], ulcerative colitis can be treated by sulphasalazine (salazopyrin), where mesalazine is joined to a sulphapyridine, and acts as an anti-inflammatory drug in the treatment of rheumatic fever and rheumatoid arthritis^[71-75]. Similarly, dermatitis herpetiformis, a skin disorder, was treated with sulphapyridine and sulphones^[76].

It is well-known that absorption of biomolecules, such as amino acids and proteins, is critical to cellular function. About 75 percent of the solids in the mammalian body are proteins, including enzymes, polypeptides such as cytokines, nucleoproteins, transport proteins, and structural proteins. The principal functional constituents of these proteins, amino acids, polypeptides and isolated amino acids, are also important for cellular metabolic functions.

Moreover, recent series of biphenyl amino acid sulfonamide derivatives of (S)-2-(biphenyl-4-sulfonyl-amino)-3-methylbutyric acid were prepared and evaluated for their ability to inhibit matrix metalloproteinase, MMP, as effective tumor cell growth inhibitors which were studied by **Patrick M. O'Brien et al** ^[45]. With nearly similar idea of our research, reaction of 26 aromatic/heterocyclic sulfonamides containing free amino, imino or hydrazino with series of amino acids, some dipeptides and tripeptides were performed by **Claudiu T. Supuran et al** ^[77] and they evaluate carbonic anhydrase inhibition and antiglucoma activity giving very promising experimental data.

From all of these facts, biphenyl amino acid, dipeptide and tripeptide bis-sulfonamide derivatives have been synthesized and evaluated for surface properties, anti bacterial, antifungal and anticancer activities in our research.

A.4.6. Sulfonamides as Biocides

Sulfonamides are beneficial not only biologically but also in industrial applications. For instance, in oil and gas operations, major problems result from the biogenic formation of hydrogen sulfide (H₂S) in the reservoir. The presence of H₂S results in increased corrosion, iron sulfide formation, higher

operating costs, and reduced revenue and constitutes a serious environmental and health hazard ^[78].

Severe corrosion also can result from the production of acids associated with the growth of certain bacterial biofilms. These bacterial biofilms are often composed of sulfate reducing bacteria, which grow anaerobically in water, often in the presence of oil and natural gases. Once biofilms are established, it is extremely difficult to regain biologic control of the system.

When biofilms are formed on metallic surfaces, they can seriously corrode performance oil production facilities, chemical processing plants, paper mills, ships, and water distribution networks. Microbiologically influenced corrosion (MIC) represents the most serious form of that degradation.

Early detection of microbiologic problems is imperative, and reparative actions must be taken as soon as possible. These measures should include changes in operating methods to prevent degradation of the operating environment. In general, biocides are needed to control the activity of the bacteria in a system.

Some recent literatures, *Schneider et al* ^[79] and *Sprengeler et al* ^[80], studied the biocidal action of some aromatic sulfonamides derivatives which

prove that sulfonamides are used successfully because of achieving some requirements for the biocide action such as:

- Wide bacteria-killing ability and range.
- Noncorrosive property, good inhibiting ability.
- Nontoxic or low-toxicity property that causes no damage to human beings and is within environmental control regulations.
- Good miscibility, with no damage or interference to drilling fluid or its chemical agents.
- Bacteria killing effect that is not affected by environmental adaptation of the bacteria.

Moreover, **B.N. Herbert** ^[81] introduces various compounds known to possess microbiocidal properties including sulfonamide derivatives and some fatty acid salts of alkyl diamines.

A.5. Modification of Sulfonamides

There is required to modify synthesized compounds even if these compounds is potentially effective on the target action for investigation of new compounds possessing more pharmacological activity and to improve efficacy of sulfonamides with lower toxicity and more safety. Sulfonamide molecule can be modified through its active sites. For example, there are two

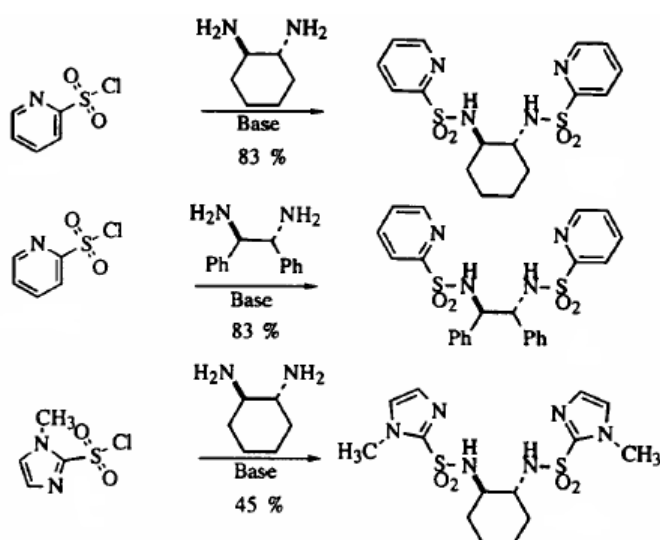
reactive sites for the modification of sulfadiazine, one is the aromatic amine, and the other is sulfonamide. Heretofore, the main work of modified sulfadiazine has been focused on the aromatic amine due to its relatively high reaction activity ^[82-86]. Thus, modification can be made by many methods for example:

A.5.1. Complexation

Heavy metals in traces are essential for all forms of life. They are taken up by the living cells as cations. Heavy metals like copper Cu(II), iron Fe(II), molybdenum Mo(II), cobalt Co(II) and occasionally manganese Mn(II) assist oxidation-reduction equilibrium while those like zinc Zn(II), magnesium Mg(II) and manganese Mn(II) are concerned with hydrolytic processes ^[87]. Most of heavy metals play a vital role as co-factors for many important enzymatic reactions in human body.

However, coordination metal complexes are gaining increasing importance in the design of respiratory, slow release and long acting drugs. Metal ions are therefore known to accelerate drug actions. The efficacies of some therapeutic agents are known to increase upon coordination ^[88]. Some metal complexes are known to exhibit remarkable antitumor, antiviral and special biological activities ^[87].

It is evident that the sulfonamides behave as bidentate ligands through the N_{-sulphamido} and the N_{-heterocyclic} atoms ^[89-92]. *Claudiu T. Supuran et al* synthesized coordination compounds of Co(II), Ni(II), Cu(II), Zn(II), and Cd(II) with 1,3,4-thiadiazole-2,5-disulfonamide ^[93] as ligand which were characterized by FT-IR and UV spectroscopy, although the ligand possesses very weak such properties, the metal complexes of sulfonamides behave as very strong Carbonic Anhydrase inhibitors, and their mechanism of action has also been explained as being due to a dual inhibition, by means of sulfonamide anions and metal ions, formed by dissociation of the complexes in dilute solutions during the enzymatic assay. *S. Diltz et al.* ^[94] developed an efficient method to synthesize modular tetradentate sulfonamide based ligands that are shown in **Scheme 10**



Scheme 10. The used ligands contain pyridine and imidazole groups to form tetradentate sulfonamide based complexes.

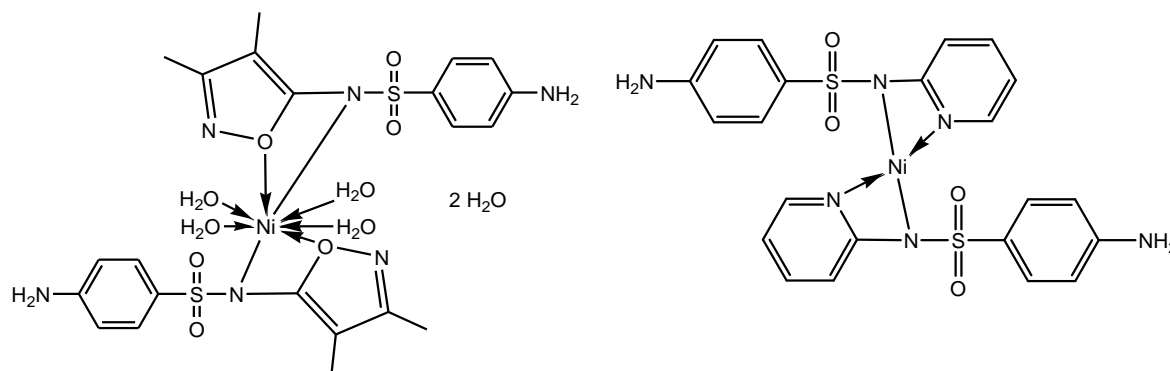
These compounds containing aromatic nitrogen atoms have extensive and well-documented coordination chemistry. The resulting sulfonamido complexes exhibit enhanced Lewis acidity. Additionally, the sulfonamide linkers are remarkably stable, being resistant to hydrolyzing, oxidizing and reducing conditions ^[95]. **Claudiu T. Supuran et al** ^[93] also explored the coordination chemistry of sulfonamide CA inhibitors, in addition to their pharmacological applications ^[96-100]. Furthermore, synthesis, characterization and biological studies of Schiff base-derived sulfonamides and their Co (II), Cu (II), Ni (II) and Zn (II) complexes have been studied by **Chohan ZH** and screened for in-vitro antibacterial activity and antifungal activity ^[101].

More metal complexes of these sulfa drugs have been extensively studied ^[102-112]. For instance, Ag-sulfadiazine has proved to be an effective topical antimicrobial agent, of significance in burn therapy, better than the free ligand or than AgNO₃ ^[113]. Moreover, several Cu(II), Ce(III), Bi(III), Cd(II) and Hg(II) sulfonamide complexes have shown antibacterial activity ^[114-116]. Specially, a series of copper complexes with heterocyclic sulfonamides was studied and a plausible explanation of their activities was presented ^[117]. Nine different Cu^{II}(sulf)₂ derivatives were prepared from Cu(II) and sulfonamides (sulfH = sulfadiazine, sulfadimethoxine, sulfadimidine, sulfamerazine, sulfamethoxydiazine, sulfamethoxypyridazine,

sulfapyridine, sulfathiazole and sulfisomidine) in alkaline solution ^[118]. Zn^{II} , Cd^{II} and Hg^{II} complexes of sulfa drugs, such as sulfathiazole, sulfadiazine, sulfamerazine and sulfamethazine, were prepared and characterized by analytical and spectroscopic data ^[119].

The synthesis, structural characterization and antibacterial activity of $[\text{Ni}(\text{sulfisoxazole})_2(\text{H}_2\text{O})_4] \cdot 2\text{H}_2\text{O}$ and $[\text{Ni}(\text{sulfapyridine})_2]$ were studied and compared with similar previously reported copper complexes by **M. H. Torre** ^[120]. $[\text{Cu}(\text{sulfisoxazole})_2(\text{H}_2\text{O})_4] \cdot 2\text{H}_2\text{O}$ was more active than the free ligand. This research presented different antibacterial behavior against *Staphylococcus aureus* and *Escherichia coli*. Their structures are shown in

Scheme 11



Scheme 11. Chemical structure of $[\text{Ni}(\text{sulfisoxazole})_2(\text{H}_2\text{O})_4] \cdot 2\text{H}_2\text{O}$ and $[\text{Ni}(\text{sulfapyridine})_2]$ complexes.

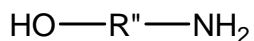
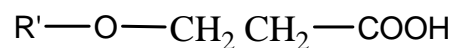
The synthesis, characterization and comparative biological study of a series of antibacterial copper complexes with heterocyclic sulfonamides were studied by **E. Kremer et al** ^[121]. The results showed that the complexes with

five-membered heterocyclic rings were more active than the free sulfonamides while the pyrimidine, pyridine and pyridazine complexes had similar or less activity than the free ligands.

In our research, copper and cobalt complexes of bis (2-aminophenyl) biphenyl-4,4'-disulfonamide were synthesized and evaluated for surface properties, anti bacterial, antifungal and anticancer activities.

A.5.2. Amine Acid Saltation

Amine salts are useful as surface active agents ^[122-123] in aqueous and non-aqueous systems. They are also important in the pharmaceutical ^[124], cosmetic and agrochemical industries. The salt form of organic amine compound enables easy storage and handling. Consequently, most of available drugs in the market are in salt form to improve their chemical and physical stability, pH and solubility of organic amine in water and other solvents particularly when carboxylic acid is used, eliminate the possibility of contamination by impurities, degradation and structural transformation of the final product. *Jams A. Krogh et al* ^[122] introduced novel amine ether acid salt surfactants capable of use in a wide variety of applications shown in **Scheme 12**.

Amines**Acid**

Where:

R' comprises C₁ - C₁₆ alkyl group

R'' comprises C₂ - C₆ alkyl group

R''' comprises C₁ - C₂₀ alkyl group

Scheme 12. Chemical formulas of amine ether acid salt surfactants constituents

The processes by which organic amine acid salt are produced include an exothermic neutralization reaction of a strong acid ^[125], such as hydrochloric acid, sulphuric acid, nitric acid, or acetic acid with amine or the reaction of an organic acid in solvent with amine, followed by the addition of antisolvent to induce crystallization of the organic amine acid salt compound. Alternatively, the solvent may be stripped off to leave the organic amine acid salt compound as residual.

Another process by which amine acid salts are produced includes use of solvent in which amine, acid and acid salt of amine have significantly different solubilities. The exothermic neutralization reaction is carried out in the presence of a strong acid in the solvent.

Each of these processes has serious shortcomings, which affect the properties of the organic amine acid salt product. For example, because the exothermic neutralization reaction is a direct reaction between acid and base, it is difficult to control the rate of the reaction. Consequently, crystal size and shape cannot be easily controlled.

Additionally, the use of excess acid in the exothermic neutralization reaction can lead to contamination of the amine acid salt by various side reaction and / or degradation or structural transformation of the final amine salt compound due to the presence of residual acid.

Seo Hong Yoo ^[126] studied amine acid salt compounds and the process of production and mentioned many factors that affect the exothermic neutralization reaction and the resulted amine acid salts such as:

i) The Selection of Solvent

The solvent used in the present process may be selected on the basis of its polarity, solvation and the solubilities therein of the free amine, carboxylic acid compounds and the amine acid salt product of the reaction. The two reactants should be soluble. In contrast, the solvent should not be a good solvent for the amine acid salt product of the reaction, in that the amine acid salt product should precipitate in the solvent over time. For example, it will

be readily recognized by those of skill in the art that many free amine compounds are readily soluble in hydroxyl solvents.

Solvent may also be selected on the basis of the desired crystalline form of the amine acid salt product. It is known that many amine acid salt compounds may have two or more polymorphic structures. The polarity of the solvent affects the polymorphic form of the crystalline product, therefore, depending upon which polymorph of the product is desired, and either low or high polarity solvent may be selected. Low polarity solvents include, for example, mixtures of tetrahydrofuran and ethyl acetate (1:1 v/v), ethanol, and ethyl acetate (1:1 v/v). High polarity solvents include, for example, hydroxyl solvents such as ethanol, isopropanol and methanol that was used in the production of diamine dicarboxylic acid salts.

ii) The Reaction Temperature

The temperature at which the reaction is carried out can be varied to increase or decrease the rate of the reaction. Generally, the reaction is carried out at a temperature in the range of from about ambient temperature to about 40°C. However, because the reactants are less active in our work, the exothermic neutralization reaction is carried out at elevated temperature without detrimental effect upon the integrity of the product. Thus, if desired,

the present process can be performed at elevated temperature of up to about the boiling point of the used solvent.

iii) Molar Concentration Adjustment

The desired amine acid salt product is achieved by adjusting the molar amount of the reactants. This is based on number of amino groups in the start which is determine the amount of used carboxylic acid so, diacid diamine salt is produced by the present process by adjusting the molar amounts of amine and carboxylic acid to 1:2 .

A.5.2.1. Benefits of Amine Acid Saltation

Solubility is one of the key determinations of the bioavailability of a pharmaceutical agent. The dissolution of pharmaceutical agents in a pharmaceutically acceptable medium is the most preferred manner of the formulation to deliver therapeutic agents to their targets ^[127].

Many attempts have been made to improve the solubility of insoluble compounds. From these approaches is the modification of crystal habit of a compound, complexation with other agents or solubalization of a compound using surfactants.

Moreover, there are methods to enhance the solubility of our compounds by contacting the amine compound with fatty acid forming amine salt ^[128].

John G. Augustine et al ^[129] introduced in their invention a method of enhancing the solubility of insoluble compounds based on that any combination of an acid and a base can effectively form salt and initiates the formation of micelles. This method provides many advantages over methods of solubilization conventionally known in the art. For example, it eliminates or reduces the need of toxic solvents such as dimethylformamide and DMSO in the formulation of human-used products, and provide an easy and convenient way to solubilize a compound, while providing a safer resulting formulations, by eliminating many harmful additives currently used for the solubilization of a compound such as carrier agents which exhibit various clinical side effects, especially in children and newborns, and is believed to cause hypersensitivity reactions and the resulting micellar solution can be used with no need in high concentrations to achieve a desired effect of used compounds. In addition, fatty acid salt mixtures provide other advantages in clinical settings, such as promoting an increase in drug permeability by penetration of cell wall.

From all of these facts, a series of long chain fatty acid salts of bis (2-aminophenyl) biphenyl-4,4'-disulfonamide have been synthesized and evaluated for expected anticancer, antibacterial, antifungal activities and surface properties in our research.

A.5.2.2. Using Bioactive Molecules in Amine Acid Saltation

It is well-known that absorption of biomolecules, such as amino acids and proteins, is critical to cellular function. The principal functional constituents of these proteins, amino acids ^[130], polypeptides and isolated amino acids, are also important for cellular metabolic functions. The amino acid glutamine, for example, serves important functions in metabolism, including transport of carbon and nitrogen between tissues. It is a precursor for hepatic and renal gluconeogenesis, as well as urea synthesis in the liver and ammonia production in the kidney. A number of cell types, particularly the cells of the intestinal mucosa, also utilize large amounts of glutamine as their major source of respiratory fuel.

Dietary glutamine supplementation has been proposed for the treatment of patients recovering from surgery or suffering from sepsis, inflammation, burns, or trauma.

Glutamine supplementation can be beneficial for cancer therapy for both its direct and indirect results. Glutamine supplementation has been shown to increase glutathione release from the gut in Fisher-344 rats ^[131] when given in conjunction with either radiation or chemotherapy; glutamine has been demonstrated to increase selectivity of either therapy for tumor cells ^[132]. In one study, tumor growth in rats receiving glutamine, either by gavage or as a

food additive, decreased by 40 % within three weeks ^[133]. In a separate study, tumor volume loss in rats receiving methotrexate was nearly doubled when glutamine was added to the diet ^[134]. Decreased tumor growth in glutamine-supplemented rats has been correlated with greater natural killer cell activity, presumably due to glutathione-mediated suppression of prostaglandin E2 (PGE2) synthesis

Effectiveness supplementation with certain amino acids is further limited to varying degrees by the low aqueous solubility and limited cellular uptake of some amino acids. Glutamine, for example, exhibits a low solubility in water (48 g/l at 30° C., 26 g/l at 18° C., 18 g/l at 0° C) and a lower chemical stability in aqueous solution (11 day at 22-24° C).

Transport of small molecules into various cell types is controlled by alternate transport systems, making it more difficult to devise methods for increasing cellular uptake into particular cell types. Despite the need for methods to enhance the uptake of amino acids and other small molecules, methods for increasing initial direct absorption of amino acids, peptides and other compounds into cells such as epithelial cells, the type of cells initially responsible for initial uptake of many bioactive compounds, has not been described. Therefore, a containing need exists for methods to increase cellular uptake of bioactive compounds into mammalian cells.

Several proteins are known to promote or inhibit cancer cell proliferation, or alternatively apoptosis (programmed cell death). The inventors have discovered that administration of glutamine increases the levels of pro-apoptotic proteins, and decreases the levels of proteins that are anti-apoptotic or promote cancer cell proliferation

From all of these facts, glutamine acid salt of bis (2-aminophenyl) biphenyl-4,4'-disulfonamide have been synthesized and evaluated for expected anticancer, anti-bacterial, antifungal activities and surface properties in our research.

As we mentioned, amine salts are useful as surface active agents ^[122-123]. Moreover, they are classified as cationic surfactant. Therefore, the best way to explain what about cationic surfactants is to introduce the surfactants in details.

B. Sulfonamides as Surface Active Agents:

B.1. Background:-

The good start of an introduction to such a subject would be to back up just a little, explain some terms used in the industry, and define the origin of surface-active agents. Surfactants are low to moderate molecular weight compounds which contain one hydrophobic part, which is generally readily soluble in oil but sparingly soluble or insoluble in water, and one hydrophilic (or polar) part, which is sparingly soluble or insoluble in oil but readily soluble in water (**Figure 3**). Due to this double nature of surfactant molecules, these experience suboptimal conditions when dissolved molecularly in aqueous solution. If the hydrophobic segment is very large, the surfactant will not be water-soluble, whereas for smaller hydrophobic moieties, the surfactant is soluble, but the contact between the hydrophobic block and the aqueous medium nevertheless energetically less favorable than the water-water contacts.



Figure 3. *Schematic illustration of a surfactant molecule*

It is obviously necessary to understand the causes of the behavior of matter at the interfaces and the variables that affect this behavior in order to predict and control the properties of these systems.

B.2. General Structural Features and Behavior of Surfactants

The molecules at a surface have higher potential energies than those in the interior. This is because they interact more strongly with the molecules in the interior of the substance than they do with the widely spaced gas molecules above it. Work is therefore required to bring a molecule from the interior to the surface.

Surfactants have a characteristic molecular structure consisting of a structural group that has very little attraction for the solvent, known as a lyophobic group, together with a group that has strong attraction for the solvent, called the lyophilic group. This is known as an amphipathic structure. When a molecule with an amphipathic structure is dissolved in a solvent, the lyophobic group may distort the structure of the solvent, increasing the free energy of the system. When that occurs, the system responds in some fashion in order to minimize contact between the lyophobic group and the solvent. In the case of a surfactant dissolved in aqueous

medium, the lyophobic (hydrophobic group) distorts the structure of the water (by breaking hydrogen bonds between the water molecules and by structuring the water near the hydrophobic group).

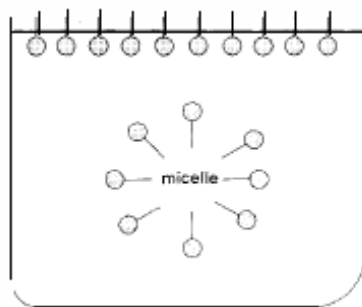


Figure 4. *Schematic representation of surfactant molecules at surface and surfactant micelle in bulk liquid.*

As a result of this distortion, some of the surfactant molecules are expelled to the interfaces of the system, with their hydrophobic groups oriented to minimize contact with the water molecules. The surface of the water becomes covered with a single layer of surfactant molecules with their hydrophobic groups oriented predominantly toward the air (**Figure 4**).

Since air molecules are essentially nonpolar in nature, as are the hydrophobic groups, this decrease in the dissimilarity of the two phases contacting each other at the surface results in a decrease in the surface tension of the water. On the other hand, the presence of the lyophilic (hydrophilic) group prevents the surfactant from being expelled completely from the solvent as a separate phase, since that would require dehydration of the

hydrophilic group. The amphipathic structure of the surfactant therefore causes not only concentration of the surfactant at the surface and reduction of the surface tension of the water, but also orientation of the molecule at the surface with its hydrophilic group in the aqueous phase and its hydrophobic group oriented away from it.

The chemical structures of groupings suitable as the lyophobic and lyophilic portions of the surfactant molecule vary with the nature of the solvent and the conditions of use. In a highly polar solvent such as water, the lyophobic group may be a hydrocarbon or fluorocarbon or siloxane chain of proper length, whereas in a less polar solvent only some of these may be suitable (e.g., fluorocarbon or siloxane chains in polypropylene glycol). In a polar solvent such as water, ionic or highly polar groups may act as lyophilic groups, whereas in a nonpolar solvent such as heptane they may act as lyophobic groups. On the other hand, the hydrophilic group is polar and may be either ionic or nonionic.

As the temperature and use conditions (e.g., presence of electrolyte or organic additives) vary, modifications in the structure of the lyophobic and lyophilic groups may become necessary to maintain surface activity at a suitable level. Thus, for surface activity in a particular system the surfactant

molecule must have a chemical structure that is amphipathic in that solvent under the conditions of use.

B.2.1. Micelles formation and cmc:

Since surfactant molecules have both hydrophilic and hydrophobic parts, the most attractive place for them in water is at the surface where the forces of both attraction and repulsion to water can be satisfied.

.In aqueous solution, dilute concentrations of surfactant act much as normal electrolytes, but at higher concentrations very different behaviour results. This behaviour is explained in terms of the formation of organized aggregates of large numbers of molecules called micelles when the surfactant interact to satisfy natural forces of attraction and repulsion between molecules.

Micelles consist of hydrophobic interior regions, where hydrophobic tails interact with one another. These hydrophobic regions are surrounded by the hydrophilic regions where the heads of the surfactant molecules interact with aqueous medium water. Thus, the formation of micelles in aqueous solution is generally viewed as a compromise between the tendency for alkyl chains to avoid energetically unfavourable contacts with water, and the desire for polar parts to maintain contact with the aqueous environment (**Figure 5**).

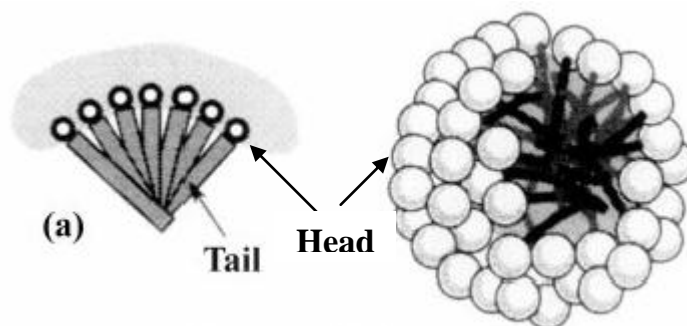


Figure 5. Schematic representation of the structure of an aqueous micelle with two regions (Hiemenz and Rajagopalan et al, New York)

At very low concentration in water, surfactant molecules are unassociated, but at a specific, higher, surfactant concentration, known as the critical micelle concentration (cmc), molecular aggregates termed micelles are formed and the surface tension of water undergoes a precipitous decrease, and the detergency of the mixture increases dramatically at the cmc. The cmc is a property of the surfactant and several other factors, since micellization is opposed by thermal and electrostatic forces. A low cmc is favoured by increasing the molecular mass of the lipophilic part of the molecule, lowering the temperature (usually), and adding electrolyte.

B.3. Classification of Surfactants:-

Surfactants are classified according to the nature of hydrophilic group (their polar head groups) as the following:

- **Anionic Surfactant:** refer to surfactants with a negatively charged head group
- **Cationic Surfactants:** contain polar head groups with a positive charge
- **Nonionic Surfactants:** refer to uncharged surfactants
- **Zwitterionic Surfactants (amphoteric):** that contain both a negatively charged and a positively charged group charge depends on pH of the medium. (Figure 6).

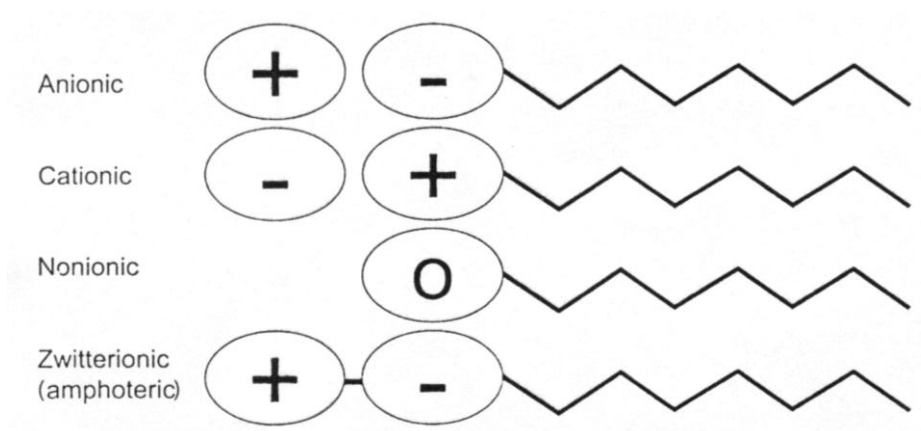
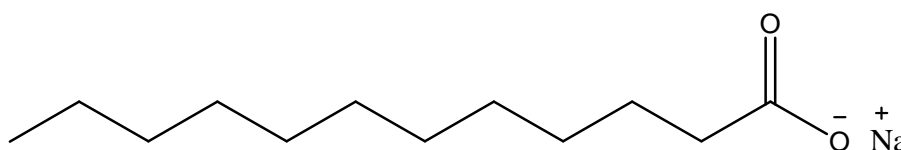


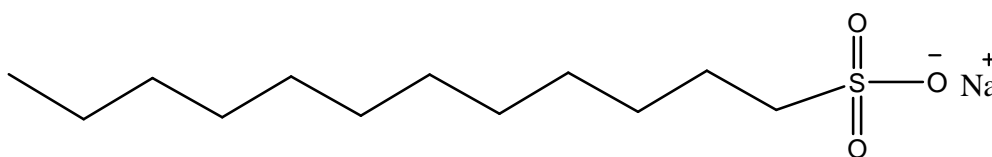
Figure 6. Schematic illustration of the various types of surfactants

B.3.1. Anionic Surfactants

An anionic surface-active agent is the reaction product of an organic compound such as a high molecular weight acid or alcohol with an inorganic compound such as sodium hydroxide or sulfuric acid, yielding a product wherein the organic part of the molecule, or the water-insoluble part of the molecule, has a negative charge and the water-soluble part of the molecule wherein the sodium ion has a positive charge. For example, soap is an anionic and has the following structure.



Also, the reaction product of a long-chain alcohol and sulfuric acid, and thus neutralized with sodium hydroxide has the following structure.



The anionics have the advantage of being high and stable foaming agents; however, they do have the disadvantage of being sensitive to minerals and the presence of minerals in water (water hardness) or pH changes. Examples of such surfactants include:

i) Fatty acid salts ("Carboxylates "):

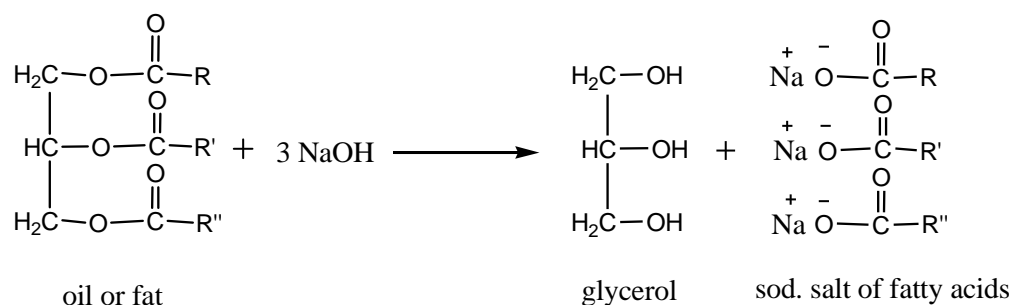
Most carboxylate surfactants are soaps. Soaps are alkali metal salts of fatty acids. Fatty acids are carboxylic acids derived from or contained in animal or vegetable fats or oils. They contain linear hydrocarbon groups and may be either saturated or unsaturated. The most important fatty acids used for manufacturing of surfactants are as follows:

- **Stearic acid** : $C_{17}H_{35}COOH$ (saturated); solid at room temperature;
- **Palmitic acid** : $C_{16}H_{33}COOH$ (saturated); solid at room temperature;
- **Lauric acid** : $C_{11}H_{21}COOH$ (saturated); solid at room temperature;
- **Oleic acid** : $C_{17}H_{33}COOH$ (unsaturated at C9-C10); liquid at room temperature

Those with less than 10 carbons are too soluble in water to have good surface activity. Those with more than 20 carbons in a linear configuration are too insoluble in water to use in aqueous medium.

Sodium is the most common cation in soap. However, potassium and ammonium are less common. Soaps are effective as cleaning agents in aqueous medium. Since soaps are relatively weak acids, the free acid is liberated in acidic medium. The free acids are insoluble in water. Therefore, soaps are only effective in alkaline medium. Soaps can be made by neutralization of free fatty acids by alkali metals hydroxides or by alkaline hydrolysis (saponification) of fats and oils (**Scheme 13**). Fats and oils belong

to the lipid family. The chemistry of oils as used in making soaps is identical to that of fats. Fats are solid. Oils are liquid.



Scheme 13. *Alkaline hydrolysis of fats and oils forming fatty acid salt (saponification reaction).*

Generally, lipids with more saturated content are more firm and have higher melting temperatures than those with unsaturated hydrocarbon groups. Fats are esters of the trihydric alcohol, glycerol. Fatty acids are produced by alkaline hydrolysis (saponification) of fats. The soap (fatty acid solid) thus formed is separate from the glycerol byproduct by neutralization of the alkali or addition of salt to precipitate the soap.

ii) Sulfonates:

The sulfonate group is an effective solubilizing group when attached to an alkyl, aryl, or alkylaryl hydrophobe.

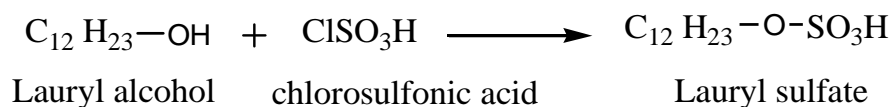
Since the sulfonate group is a strong acid, the sulfonate surfactants are soluble and effective in acidic as well as in alkaline medium. The calcium

and magnesium salts are soluble in water, so sulfonate surfactants are not greatly affected by hard water. The sodium salt sulfonate surfactants are soluble and effective even in the presence of electrolytes such as sodium chloride and sodium sulfate.

Since the sulfonate surfactants are resistant to hydrolysis by both hot acid and alkali, since sulfonation is relatively inexpensive, they are found in high-volume products. Sulfonate surfactants include alkyl sulfonates, alkyl benzene sulfonates, lignin sulfonates, naphthalene sulfonates and petroleum sulfonates.

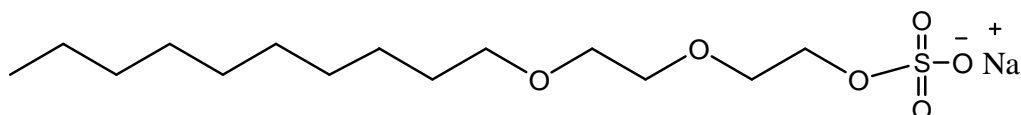
iii) Sulfates:

Various fatty alcohols can be reacted with chlorosulfonic acid or sulfur trioxide to produce their sulfuric acid esters. The properties of these surfactants depend on the alcohol chain length as well as the polar group and are often mixtures or blends comprised of several alcohols of different lengths (**Scheme 14**).



Scheme 14. *Reaction of fatty alcohols with chlorosulfonic acid to produce Sulfate surfactant*

Straight chain alkyl ether sulfates are advantageous. These sulfates are more water soluble, more electrolyte resistant and forming foam more resistant to water hardness and protein soil as shown:



These surfactants are sulfates rather than sulfonates like those described above. Because of the presence of an additional oxygen atom, the sulfates are more hydrophilic than the sulfonates. However, the sulfate group is less stable to hydrolysis than is the sulfonate group.

The sodium salt is most common although salts with diethanolamine, triethanol-amine or ammonia are used in cosmetics and shampoos. Sodium lauryl sulfate is an excellent foaming agent. Foaming properties are enhanced when some unsulfated fatty alcohol is retained in the product.

iv) Phosphate esters:

Phosphate esters of fatty alcohols are useful surfactants. Resistance of phosphate surfactants to acid and hardness ions is poor. Because of these limitations and their relatively high cost, phosphate surfactants are mainly specialty products. Since phosphate surfactants are excellent emulsifiers

under strongly alkaline conditions, they are effective for scouring of oil and wax from textile materials.

B.3.2. Cationic Surfactants

Here the water-insoluble part of the molecule has a positive charge and the water-soluble part of the molecule is negatively charged, thus giving it the name of a cationic surface-active agent. Cationic surfactants are frequently based on amine-containing polar head-groups (**Figure 7**). Due to their charged nature, the properties of cationic surfactants, e.g., surface activity or structure formation, are generally strongly dependent on the salt concentration, and on the valancy of anions present.

Cationic surfactants are frequently used as antibacterial agents, corrosion inhibitors, fuel and lubricating oil additives, germicides and hair conditioners. Cationic surface active agents are characterized by a structural balance between the hydrophobic residue (e.g., paraffinic chains, alkyl substituted benzene or naphthalene ring) and positively charged hydrophilic groups (e.g., quaternary ammonium, sulfonium, arsonium, phosphonium or iodonium). The field of non nitrogen "onium" chemistry has been extensively grown. Cationic surface active agents can be classified into several classes as listed below.

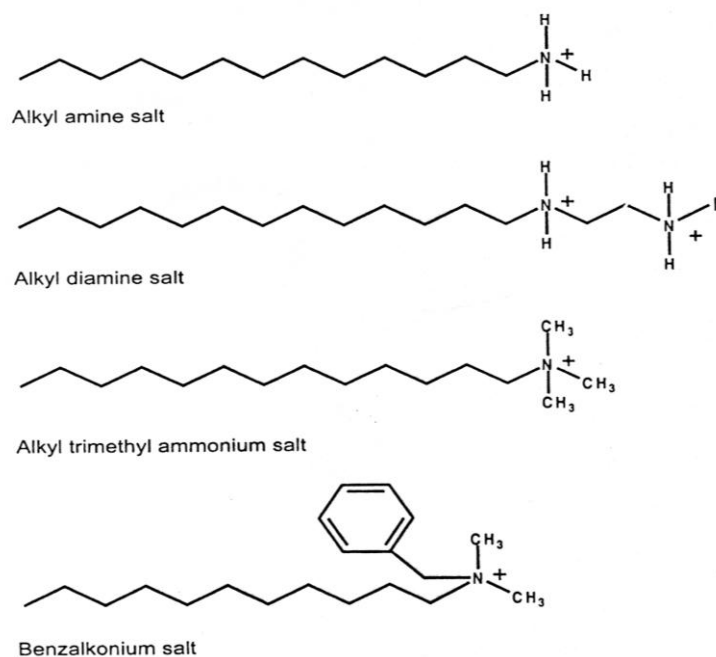


Figure 7. Chemical structure of some commonly used cationic surfactants

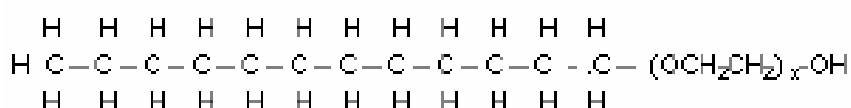
Cationic surface-active agents reduce surface tension and are used as wetting agents in acid media. However, a disadvantage of a cationic surface-active agent is that they have no detergent action when formulated into an alkaline solution.

B.3.3. Nonionic Surfactant:

Surfactants with an uncharged polar head group are often based on oligo (ethylene oxide)-containing polar head groups while the hydrocarbon group is the hydrophobic part (**Figure 8**).

Due to the uncharged nature of the latter, they are not affected by water hardness or pH changes as the anionic and cationic surfactants but instead

quite sensitive to temperature. The critical micelle concentration for such surfactants is generally much lower than that of the corresponding charged surfactants, and partly due to this, such surfactants are generally less irritant and better tolerated than the anionic and cationic surfactants. This class of surfactants possess excellent soil removal and grease emulsification properties and are accompanied normally with low foamability. An example of the chemical structure of a nonionic surface-active agent is shown below in the reaction product of lauryl alcohol and ethylene oxide.



Nonionic surfactants, like most ethylene oxide derivatives, exhibit inverse solubility characteristics and may precipitate with increase in temperature of their solutions. This sometimes precludes their use in high temperature applications but can be an advantage in that elevation of the temperature can be used to destroy activity of the surfactant if desired. The temperature at which precipitation occurs is called the “cloud point” of the surfactant.

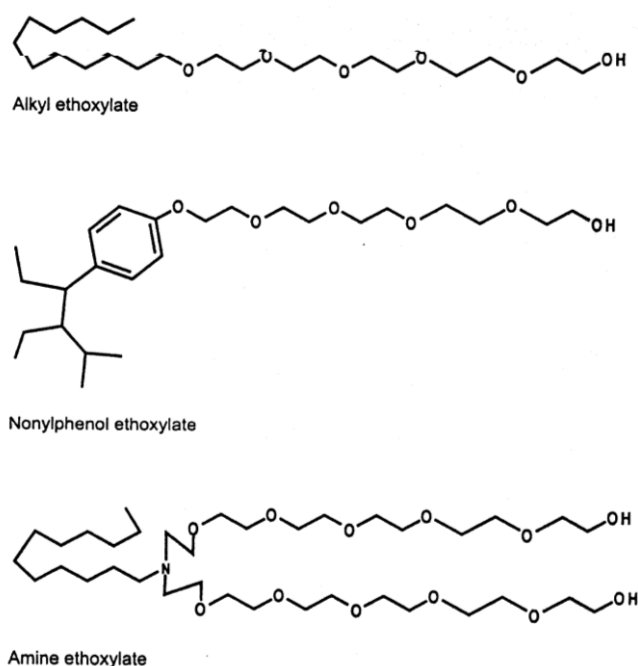


Figure 8. Chemical structure of some commonly used nonionic surfactants

The properties of a nonionic surfactant can be tailored somewhat for a particular use by controlling the relative amounts of hydrophilic and hydrophobic character. The relative amounts of hydrophilic and hydrophobic character may be expressed as the hydrophile-lipophile balance (HLB) of the surfactant.

i) Alkylphenol Ethoxylates:

Various alkylphenols are used as the hydrophobic portion of many surface-active agents. The alkylphenols most commonly used for the preparation of surface-active agents are the nonyloctyl-, dodecyl-, and

dinonylphenol. In some cases, amylphenol is used as a hydrophobic group for surface-active agents as well as phenol itself.

ii) Alcohol Ethoxylates:

The three types of alcohols most commonly used for ethoxylation are primary alcohols from natural sources. Branched chain alcohols are also ethoxylates but are being phased out due to their biologically hard character.

The primary and secondary alcohol ethoxylates have become very popular during the last decade simply because they are more biodegradable than the alkylphenol ethoxylates. Branched chain alcohol ethoxylates such as tridecyl alcohol ethylene oxide adducts are biologically hard and are used only where biodegradability is of minor concern and the excellent wetting properties of these products are required.

The surface tension (or interfacial tension if the interface is not a surface) determines the tendency for surfaces to establish contact with one another. Therefore, surface tension is responsible for the shape of a droplet of liquid. If the surface tension is high, the molecules in the liquid are greatly attracted to one another and not so much to the surrounding air.

B.3.4. Zwitterionic Surfactants

This type of surfactants is less common than anionic, cationic, and non-ionic ones. Frequently, the polar head group consists of a quaternary amine group and a sulfonic or carboxyl group, (**Figure 9**) Due to the zwitterionic nature of the polar head group, they are soluble and effective in the presence of high concentrations of electrolytes, acids and alkalies so, the surfactant charge changes with pH, so that it is cationic at low pH and anionic at high pH. Due to the often low irritating properties of such surfactants, they are commonly used in personal care products.

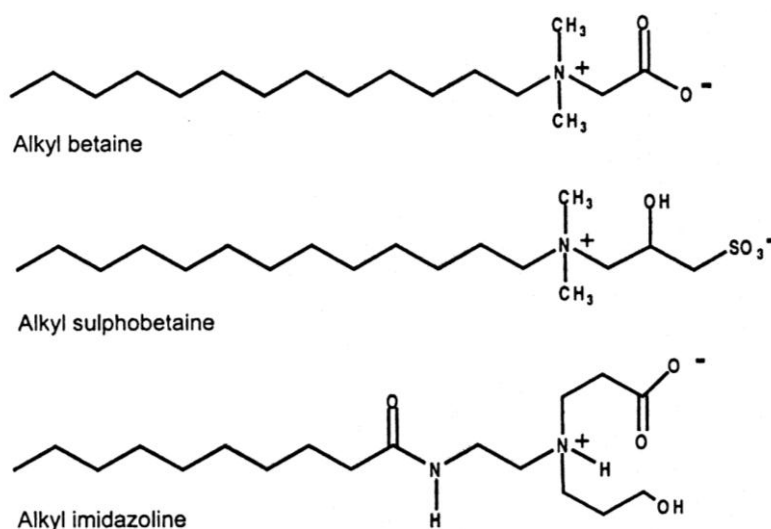


Figure 9. Chemical structure of some typical zwitterionic surfactants