CHAPTER 1

A Brief Overview of Synthesis and Pharmacological Activities of Substituted Hydrazones, Sulphonamides and Sulphonates
CHAPTER 1

1. A Brief Overview of Synthesis and Pharmacological Activities of Substituted Hydrazones, Sulphonamides and Sulphonates

1.1 Section-1 A brief review on Substituted Hydrazones

1.1.1 Introduction to substituted hydrazones

This section presents an overview of literature survey on the natural occurrence, medicinal importance, use and synthesis of acyl hydrazones as important tool in organic chemistry. Acyl hydrazones are a very old class of molecules: the first example of N-acylhydrazines was mentioned in 1850, and a number of N-unsubstituted, mono- and disubstituted acylhydrazines are now commercially available. Acyl hydrazones are a versatile class of nitrogen-substituted molecules with a high degree of chemical reactivity, used as precursors and intermediates of many important organic molecules such as heterocycles, pharmaceuticals, polymers, dyestuffs and photographic products. Their use for analytical purposes is well known, and allows the detection of aldehydes, ketones and carboxylic acids. The chemiluminescence of both cyclic and acyclic acyl hydrazones when they undergo oxidation is another interesting and useful property. Acylhydrazones have been
extensively investigated in recent years as they were found to be associated with various biological activities have promising analytical properties and can be used as catalysts.

The cyclic products of acylhydrazones are an important class of heterocyclic compounds with a wide range of biological activities.\(^4\)\(^-\)\(^8\) They are synthesized by simply refluxing acid hydrazide (AH) with various carbonyl compounds in methanol or ethanol. Due to the simplest reaction conditions, diversified chemical libraries may be constructed for discovering potential bioactive molecules. The resulting double bond between C and N of the hydrazones contributes to the formation of geometrical isomers (syn and anti). Geometrical isomerism may have some important role in the bioactivity of the acyl hydrazones hence their studies are very crucial to develop synthetic methods for selective synthesis of a particular isomer.

1.1.2 Chemistry and nomenclature of substituted hydrazones

Compounds of general formula ArCONHN=C(R) Ar’ are known as N-acyl hydrazones. Hydrazones containing an azomethine CH=NNH-hydrogen are obtained from the action of acid hydrazide with aldehyde or ketones either in various solvents or under solvent free conditions. Overall, the acylhydrazone derivatives can exist in four possible forms due to collective effect of configurational stereochemistry E and Z as well as conformational stereoisomers or rotamers i.e antiperiplaner (ap) and syn periplaner conformers (sp).
1.1.3 Medicinal importance

Substituted acyl hydrazones show a variety of biological activity, such as analgesic, anti-inflammatory, anti-microbial, anti-convulsant, anti-platelet, anti-tubercular, anti-viral, schistomiasis and anti-tumoral activities. Isoniazid or isonicotinic acid hydrazide (INH) is the first-line anti-tuberculosis medication in prevention and treatment. It was first discovered in 1912, and later in 1951 it was found to be effective against tuberculosis. Isoniazid also has an anti depressant effect, and it was one of the first antidepressants discovered. It has high in vivo inhibitory activity towards *M.tuberculosis* H37Rv. Hydrazones of 1NH were synthesized which have inhibitory activity in mice infected with various strains of *M. tuberculous*. Hydrazones show less toxicity than hydrazides because of the blockage of –NH₂ group. These findings further support the growing importance of the synthesis of hydrazide-hydrazones compound. Nifuroxazide (INN), 4-hydroxy-*N*-[(5-nitrofuran-2-yl)methylene] benzo hydrazide is an oral hydrazone based nitrofuran antibiotic used to treat colitis and diarrhea. Some of the representative examples are given below.
1.1.3a Anticonvulsant Activity

Epilepsy is a common neurological disorder and a collective term given to a group of syndromes that involve spontaneous, intermittent, abnormal electrical activity in the brain. The pharmacotherapy of epilepsy has been archived during the last decade. Furthermore, although for the last twenty years new antiepileptic drugs have been introduced into clinical practice, the maximal electroshock (MES) test and the subcutaneous pentylenetetrazole (scPTZ) test are the most widely used animal models of epilepsy to characterize the anticonvulsant activity. The biological results revealed that in general, the acetyl hydrazones provided good protection. The biological revealed that in general, the acetyl hydrazones 1 provided good protection against convulsions while the oxamoylhydrazones 2 were significantly less active.

1 2

1.1.3b Antidepressant Activity

Iproniazide, isocarboxazide and nialamide, which are hydrazide derivatives, exert their action by inhibiting the enzyme monoamine oxidase (MAO). Inhibition results in increased levels of nor epinephrine, dopamine, tyramine and serotonin in brain neurons and in various other
tissues. There have been many reports on the antidepressant / MAO-inhibiting the activity of hydrazones derived from substituted hydrazides and reduction products. Ten new arylidenehydrazides\textsuperscript{15} 3-phenyl-2,3-dihydro-1H-indole-2-corboxylic acid benzylidene-hydrazide (3) which were synthesized by reacting 3-Phenyl-5-sulfonamidoindole-2-carboxylic acid hydrazide with various aldehydes, evaluated for their antidepressant activity. 3-Phenyl-5-sulfonamidoindole-2-carboxylic acid 3,4-methylenedioxy / 4-methyl / 4-nitrobenzylidene-hydrazide showed Antidepressant activity\textsuperscript{8,9} at 100 mg/k.

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{3.png}
\caption{3}
\end{figure}

\textbf{1.1.3c Analgesic, Anti-inflammatory and Antiplatelet Activity}

Todeschini and his team has derived the most important anti-inflammatory derivative\textsuperscript{16} 2-(2-formylfuranyl) pyridylhydrazone, it presented 79\% inhibition of pleurisy at a dose of 80.1 $\mu$mol/kg. The results concerning the mechanism of the action of these series of N-heterocyclic derivatives in platelet aggregation that suggests a Ca$^{+2}$ scavenger mechanism, this compound (4) was able to complex Ca$^{+2}$ in \textit{in vitro} experiments at 100 $\mu$m concentration, indicating that these series of
compounds can act as Ca\textsuperscript{2+} scavenger depending on the nature of the aryl moiety present at the imine subunit.

![Diagram](image)

1.1.3d Antiplatelet activity.

Novel tricyclic acylhydrazone derivative\textsuperscript{17} (5) was given by Fraga and his team and evaluated their ability to inhibit platelet aggregation of rabbit platelet-rich plasma induced by platelet-activating factor at 50nM. Benzylidene-4′-bromobenzylidene 3-hydroxy-8-methyl-6-phenylpyrazolo[3,4-b]theino-[2,3-d]pyridine-2-carbohydrazode were evaluated at 10µM, presenting respectively 10.4 and 13.6% of inhibition of the PAF-induced platelet aggregation.

![Diagram](image)

1.1.3e Antimalarial Activity

Walcourt and his co-workers has derived novel aroylhydrazone and thiosemicarbazone iron chelators and tested anti-malarial activity against chloroquine-resistant and sensitive parasites. In these derivatives
the aroylhydrazone chelator 2-hydroxy-1-naphthylaldehyde isonicotinoyl hydrazone\(^\text{18}\) Isonicotinic acid (2-hydroxy-naphthalen-1-ylmethylene)-hydrazide (6) showed greater anti malarial agent activity than desferrioxamine against chloroquine-resistant and sensitive parasites.

![Image of compound 6]

1.1.3f Antimicrobial Activity

A series of Ethyl 2-arylhydrazono-3-oxobutyrate\(^\text{19}\) were synthesized by Kucukguzel and his team in order to determine their antimicrobial properties. Compound 7 showed significant activity against S. aureus whereas the others had no remarkable activity on this strain and compound was found to be more active than the others against Mycobacterium fortuitum at a MIC value of 32 $\mu$g/ml.

![Images of compounds 7 and 8]

1.1.3g Cytotoxic Activity

1-aryloyl-2-(alkenyl/aryl)idene hydrazines\(^\text{20}\) were prepared by Reddy and his team from mefenamic acid moiety which were found to be
cytotoxically active, in which the acid moiety in mefenamic acid was replaced by azomethine group moiety and were tested against human lung adenocarcinoma cell line (A549) \textit{in vitro}, all the compounds showed moderate cytotoxic activities particularly at higher dose. 2-(2,3-Dimethyl-phenylamino)-benzoic acid(2-hydroxy-benzylidene)-hydrazide (10) was found to be the most active.

1.3.1h Analgesic activity

A series of 2-phenoxybenzoic acid and N-phenylanthranilic acid hydrazides\textsuperscript{21} were prepared by Ali Almasirad and his team by taking a mixture of hydrazide and corresponding aldehyde or acetophenone in absolute ethanol and was stirred at room temperature in the presence of hydrochloric acid as a catalyst, most of the synthesized compounds were significantly more potent than mefenamic acid and diclofenac in abdominal constriction and formalin tests.
1.1.3i Selective Agonists for Estrogen-Related Orphan nuclear Receptors

The first small molecule agonists (12) of the estrogen related receptors have been identified by William J. Zuercher and his co-workers. A solid-phase approach was developed using the phenol building block as an anchor point and a solution-phase route was also developed. The compounds synthesized when screened showed activity in the ERRγ FRET assay with an 40-55% increase in coactivator peptide recruitment. The ERRγ activity is highly sensitive to substitution at R1. The optimal substituents were 4- iPr and 4-NEt2.

<table>
<thead>
<tr>
<th>R1</th>
<th>iPr</th>
<th>O\textsuperscript{t}Bu</th>
<th>N-Et\textsubscript{2}</th>
</tr>
</thead>
<tbody>
<tr>
<td>R\textsuperscript{2}</td>
<td>4-OH</td>
<td>4-NH\textsubscript{2}</td>
<td>H</td>
</tr>
<tr>
<td>R\textsuperscript{3}</td>
<td>H</td>
<td>Me</td>
<td></td>
</tr>
</tbody>
</table>
1.1.3j Antimycobacterial activity

Cocco and his team has reacted Isonicotinoylhydrazones further pyridinecarboxaldehydes to give the corresponding pyridymethyleneamino derivatives\(^{(13)}\). The new synthesized hydrazones and their pyridymethyleneamino derivatives were tested for their activity against mycobacteria, Gram +ve and Gram –ve bacteria. The cytotoxicity was also tested. Several compounds showed a good activity against M. tuberculosis H37Rv and some isonicotinoylhydrazones showed a moderate activity against a clinically isolated M. tuberculosis (6.25-50 µg/mL) which was 1NH resistant.

\[
\begin{align*}
\text{R} & \text{O} \\
\text{N} & \text{Py} \\
\text{N} & \text{NH} \\
\text{N} & \text{NH}
\end{align*}
\]

1.1.3k Antitumor activity

Pandey and his team has derived several hydrazones\(^{(24)}\) having antitumoral activity. Some of diphenolic hydrazones showed maximum uterotrophic inhibition of 70%, where as compound (no) exhibited cytotoxicity in the range of 50-70% against MCF-7 and ZR-75-1 human malignant breast cell lines.
1.1.3 Vasodilator activity

A new bioactive compound of the N-acylhydrazone\textsuperscript{25} class, 3,4-methylenedioxybenzoyl-2-thienyl hydrazone (\textbf{15}) named LASSBio-294, was shown to have inotropic and vasodilatory effects. New derivatives of LASSBio-294 were designed by Silva and his team and tested on the contractile responses of rat vascular smooth muscle \textit{in vitro}. Most of the compounds has shown the vasodilator activity.

1.1.4 Synthetic utility: use as intermediates

Although hydrazide hydrazones are pharmacologically active they are also used as intermediates for many important organic heterocyclic molecules possessing wide range of biological activity, as intermediates, coupling products\textsuperscript{26}, N-alkylhydrazides\textsuperscript{27}, 1, 3, 4-oxadiazolines\textsuperscript{28-30}, 2-azetidinones\textsuperscript{31} and 4-thiazolidinones.\textsuperscript{32, 33} N-Acylhydrazones are often crystalline, can be purified by sometimes simple recrystallization but organic chemists have recently focused on their utility as electrophiles in
reactions with nucleophiles to get aza compounds. N-Acylhydrazones can be readily prepared, stored and act as stable imine surrogates in these reactions. N-Acylhydrazones act as good template for metal catalysts which improves stereo chemical control.

N-Acyl hydrazones (16a) give N-acyl (17) and N-alkylhydrazines (18) along with derivatives\textsuperscript{34} according to the following (Scheme 1).

\textbf{Scheme 1}

\[
\begin{align*}
\text{Ar} & \quad \text{O} & \quad \text{N} & \quad \text{H} & \quad \text{N} & \quad \text{R} \\
\text{Ar} & \quad \text{O} & \quad \text{N} & \quad \text{H} & \quad \text{N} & \quad \text{R} \\
\end{align*}
\]

\[
\begin{align*}
\text{Ar} & \quad \text{O} & \quad \text{N} & \quad \text{H} & \quad \text{N} & \quad \text{R} \\
\text{Ar} & \quad \text{O} & \quad \text{N} & \quad \text{H} & \quad \text{N} & \quad \text{R} \\
\end{align*}
\]

N-Acyl hydrazones (16b) give only N-alkylhydrazines (19)\textsuperscript{35} according to the following Scheme 2 by using milder reducing agent sodium borohydride in place of lithium aluminium hydride.

\textbf{Scheme 2}

\[
\begin{align*}
\text{Ar} & \quad \text{O} & \quad \text{N} & \quad \text{H} & \quad \text{N} & \quad \text{Ar} \\
\text{Ar} & \quad \text{O} & \quad \text{N} & \quad \text{H} & \quad \text{N} & \quad \text{Ar} \\
\end{align*}
\]

\[
\begin{align*}
\text{Ar} & \quad \text{O} & \quad \text{N} & \quad \text{H} & \quad \text{N} & \quad \text{Ar} \\
\text{Ar} & \quad \text{O} & \quad \text{N} & \quad \text{H} & \quad \text{N} & \quad \text{Ar} \\
\end{align*}
\]

Many effective compounds, such as iproniazide (20) and isocarboxazide (21), are synthesized by reduction of hydrazide-hydrazones. Iproniazide (20), like INH, is used in the treatment of
tuberculosis. It also displays an antidepressant effect and patients appear to have a better mood during the treatment.

![Iproniazide (20) and Isocarboxazide (21)]

Reductions of N-acylhydrazones to N’-alkyl-N-acylhydrazines have also been accomplished with catalytic hydrogenation, reducing metals and boron, silicon or tin reagents.\(^{36}\)

A variety of N-acylhydrazones can be allylated by tetra allyltin (22) in the presence of a Lewis acid catalyst. This reaction is tolerant to many functional groups, and homoallylic hydrazides (23) were obtained in high yield (Scheme 3).

**Scheme 3**

\[
\begin{align*}
16b + \text{Sn}(\text{CH}_2\text{CH}═\text{CH}_2)_4 & \xrightleftharpoons[\text{MeCN, RT}]{\text{Sc(OTf)}_3} \text{MeCN, RT} \rightarrow HN\text{NHBz} \\
22 & \text{23}
\end{align*}
\]
N-Acylhydrazones (24 and 25) can serve as azadienes in Aza-Diels Alder reactions and can participate in both intra and inter molecular [4+2] cycloaddition at high temperature (Scheme 4)\textsuperscript{37} to produce 26 and 27 respectively.

\textbf{Scheme 4}

\begin{center}
\begin{tikzpicture}
  \node[align=center] (A) at (0,0) {\textbf{24}}; \node[align=center] (B) at (3,0) {\textbf{26}}; \node[align=center] (C) at (0,-1.5) {\textbf{25}}; \node[align=center] (D) at (3,-1.5) {\textbf{27}};
  \draw[->] (A) -- node[above]{1,2-Dichlorobenzene} node[below]{Reflux, 48 h} (B);
  \draw[->] (C) -- node[above]{1,2-Dichlorobenzene} node[below]{Reflux, 48 h} (D);
\end{tikzpicture}
\end{center}

Cyclocondensation of arylidine hydrazones 16b with thioglycolic acid and thiolactic acid in dry benzene gives thiazolidinone derivatives 28 and thiazolidine derivatives respectively\textsuperscript{38, 39} in 60-70\% yield according to (Scheme 5).

\textbf{Scheme 5}

\begin{center}
\begin{tikzpicture}
  \node[align=center] (A) at (0,0) {16b}; \node[align=center] (B) at (3,0) {28};
  \draw[->] (A) -- node[above]{Thiolactic acid} (B);
\end{tikzpicture}
\end{center}
Substituted benzoic acid hydrazones 1b undergo cyclisation with phenoxy acetic acid in presence of thionyl chloride in dry benzene to furnish 3-phenoxy-2-azetidinones (29) (Scheme 6).\(^{40}\)

**Scheme 6**

\[
\begin{align*}
\text{Ar} & \text{N} \text{H} \text{N} \text{Ar} & \xrightarrow{\text{PhOCH}_2\text{COOH}} & \text{Ar} \text{N} \text{N} \text{O} \text{Ph} \\
1b & & & 29
\end{align*}
\]

Substituted 1, 3, 4-oxadiazolines 30 can be synthesized when hydrazones are heated in the presence of acetic anhydride (Scheme 7).\(^{41-43}\)

**Scheme 7**

\[
\begin{align*}
\text{Ar} & \text{N} \text{H} \text{N} \text{Ar} & \xrightarrow{\text{Ac}_2\text{O}} & \text{Ar} \text{N} \text{N} \text{H} \text{COCH}_3 \\
1b & & & 30
\end{align*}
\]

N-Acyl hydrazones (16b) give only N-alkylhydrazines (31)\(^{44}\) according to the following Scheme 8 by using milder reducing agent sodium borohydride in place of lithium aluminium hydride.

**Scheme 8**

\[
\begin{align*}
\text{Ar} & \text{N} \text{H} \text{N} \text{Ar} & \xrightarrow{\text{SBH}} & \text{Ar} \text{N} \text{N} \text{H} \text{Ar} \\
16b & & & 31
\end{align*}
\]
The hydrocyanation of N-acylhydrazones (32) enables a practical access to α-hydrazino acids (33) (Scheme 9). It was reported in 1990 that addition of hydrogen cyanide generated in situ to N-acylhydrazones proceeds efficiently in the presence of a phase transfer catalyst.45

**Scheme 9**

\[
R_1\text{N} = \text{NHCOR}_3 + \text{NaCN} \xrightarrow{\text{PTC, AcOH, H}_2\text{O/hexane}} R_1\text{N} = \text{NHCOR}_3
\]

Hydrazones are better radical acceptors than imines. Friested and Qin reported the diastereoselective reaction of chiral N-acylhydrazones (34) to give 35 with secondary and tertiary alkyl radicals in presence of a stoichiometric amount of zinc chloride as an activator and tributylstannane as a radical mediator (Scheme 10).46

**Scheme 10**

Trichloroacetic acid hydrazones (36), prepared from the condensation of carbonyl derivatives mainly aromatic and α, β-unsaturated aldehydes with trichloroacetic acid hydrazide are easily transformed in 1, 3, 4 oxadiazole (37) derivatives when treated with
potassium carbonate (Scheme 11). There is growing interest in 1, 3, 4-oxadiazole derivatives as they possess broad spectrum biological activity.

**Scheme 11**

\[
\text{Cl}_3\text{C} = \text{N} \rightleftharpoons \text{N} \rightleftharpoons \text{H} \xrightarrow{\text{K}_2\text{CO}_3 \text{ (3 EQV), TEBA (2\% mol)}} \text{Cl}_2\text{H} \xrightarrow{\text{Dioxane, reflux, 2 hr}} \text{O} \rightleftharpoons \text{N} \rightleftharpoons \text{R}
\]

36 37

1.1.5 Synthesis of Substituted hydrazones

The older methods for the synthesis of N-acylhydrazones involve the intermolecular dehydration of suitably substituted acid hydrazide and carbonyl compounds. The conditions for the dehydration are variable. Some of these methods are described below.

All these approaches involve classic organic synthetic methodology and display typical organic reactivity patterns and selectivities. Recently, however, a number of new and potentially quite versatile methods have been developed for the synthesis of substituted N-acylhydrazones.

A number of pyrazole analogues with 1, 3, 4-substitution pattern 38 were synthesized according to the following (Scheme 12) by A. H. Abadi and his co-workers and evaluated for their antitumor and antiangiogenic properties.
1-Phenyl-1H-pyrazole-4-carboxaldehyde (40) was obtained via Vilsmeier-Haack formylation of (39) in 65% yield. Condensation of 40 with phenyl acetic acid afforded the acid (41). The methyl ester of 41 reacted with hydrazide hydrate to obtain carbohydrazide (42) in 68% yields.

It was dissolved in ethanol, different aldehydes were added and at the end of the reaction, the mixture was poured in ice to get the desired carbohydrazides (43) (Scheme 13).
Acyl hydrazone derivaties of 7-hydroxy-2-oxo-2H-chromen-4-yl)-acetic hydrazide (45) was prepared from acid hydrazide 44 according to the Scheme 14.50

Scheme 14

V.K Panday and his co workers synthesized acylhydrazones 47 by refluxing a mixture of acid hydrazide 46 and aromatic aldehydes in glacial acetic acid for few hours. The desired hydrazones 47 were isolated by pouring the crude mixture in cold methanol. The solid was filtered and recrystallised from ethanol (Scheme 15).51

<table>
<thead>
<tr>
<th>R</th>
<th>H</th>
<th>Et</th>
<th>Ph</th>
<th>H</th>
</tr>
</thead>
<tbody>
<tr>
<td>R1</td>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
<td><img src="image3.png" alt="Image" /></td>
<td><img src="image4.png" alt="Image" /></td>
</tr>
</tbody>
</table>
A series of N-aryl hydrazone derivatives of mefenamic acid (49), a known NSAID were synthesized by Ali Almasirad and co-workers. The hydrazide of mefenamic acid (48) was prepared by the following literature method. An equimolar mixture of the hydrazide (48) and aldehydes were dissolved in ethanol and stirred at room temperature for 0.5-1 hr in presence of two drops of conc. HCl. The hydrazones (49) were isolated by removing solvent under reduced pressure, followed by neutralization with 10% aqueous sodium bicarbonate (Scheme 16).

**Scheme 16**

![Scheme 16 Diagram](https://via.placeholder.com/150)

Similarly, 2-phenoxybenzoic acid and N-phenylanthranilic acid hydrazides were synthesized and evaluated for the analgesic activities by treating equimolar mixture of hydrazides and aldehydes or ketones in ethanol in presence of 2 drops of HCl.53

The target compound (52) was prepared by acid catalysed condensation of aldehyde and ketone in high overall yield by synthetic sequence depicted in the Scheme 14. The regioselective condensation of 2-aminopyridine (50) with 2-chloroethylacetoacetate (51) produced
functionalized methyl ester imidazo [1, 2 α] pyridine 52 derivative in 93% yield. Treatment of methanolic solution of the ester with hydrazine hydrate at reflux gave desired acylhydrazine which underwent condensation with aldehydes and ketones in ethanol using hydrochloric acid as catalyst (Scheme 17).54

![Scheme 17](image)

The new N-acylarylhydrazone compounds 56 were obtained in diasteromeric form and the E–form being major one. The base catalysed isomerisation of the double bond of safrole (53) followed by oxidative cleavage, it was converted into methyl ester 54 by treatment with 2.6 eqv of KOH and 1.3 eqv of iodine in methanol. The acylhydrazine intermediate 55 was obtained in 70% yield by treatment of an ethanolic solution of the ester 54 with hydrazine hydrate at reflux for 3.5 hr (Scheme 18).55
Olsson and his co workers reported the discovery and initial SAR of potent and selective nonpeptidic small molecule PAR-2 agonists (proteinase activated receptor). The hydrazide 58 was formed by adding hydrazine in ethyl ester 57 under microwave conditions. Finally the hydrazide 58 was condensed with 3-bromoacetophenone to get desired product 59 (Scheme 19).
A library of 156 acyl hydrazones (62) was designed from commercially available aldehydes and hydrazides. The acyl hydrazones 62 synthesized in deep well plates at 10µmol scale according to Scheme 20. In deep well plates different aldehydes 60 and hydrazides 61 were stirred at room temperature in DMF. 57

**Scheme 20**

1.2 Section B – A brief review on Sulphonamides

1.2.1 Introduction

This section presents an introduction on the medicinal importance, synthesis and use of sulphonamides as synthetic tools in organic chemistry. The sulfonamide functionality is much more widespread in pharmaceuticals than just in an early class of antibiotics. Sulfonamides have been the subject of pharmaceutical interest as a result of their potent biological activities such as antihypertensive agent bosentan, phophodiesterase-5 inhibitor sildenafil and antiviral HIV protease inhibitor amprenavir, anticancer, anti-inflammatory and antiviral gents. 62
1.2.2 Chemistry and nomenclature of sulphonamides

Sulphonamides are the derivatives of sulfonic acids. Sulphonamides are chemically quite stable, these are weak acids compared to carboxylic acid amides. The acidic nature results from the ability of the SO₂ moiety to stabilize the nitrogen anion through resonance. The sulphonamide functional group is –S(=O)₂-NH₂, a sulfonyl group connected to an imine group. The general formula is RSO₂NH₂. Where R is some organic group.

Any sulfonamide can be considered as derived from a sulfonic acid by replacing a hydroxyl group with an amine group. In medicine, the term "sulfonamide" is sometimes used as a synonym for sulfa drug, a derivative or variation of sulfanilamide.

1.2.3 Medicinal importance of sulphonamides

Sulfonamide scaffold is well known for the design of many synthetic compounds with diverse pharmacological properties. The presence of the Benzene ring that allows sulfonamides to partition through bacterial cell walls, Once inside of the bacterial cells, Sulfonamides must be ionizable, and contain both a positive and negative charge on opposite sides of its structure, which further resembles the structure of PABA and results in Binding of Sulfonamides.
1.2.3a Antibacterial activity

Kumar and his team have given the synthesis of some Schiff bases\(^{63}\) of sulfonamides by condensing 4-amino benzene sulfonamide with different aromatic aldehydes in the presence of glacial acetic acid and ethanol at 50-60\(^{0}\)C. The antimicrobial activity of these compounds was evaluated by Agar diffusion method. Several Schiff bases derived from sulphonamide as shown good antibacterial activity.

\[
\begin{align*}
\text{Ar-HC=N} & \\
\text{Ar} & = \text{substituted aldehydes}
\end{align*}
\]

1.2.3b Anti inflammatory activity

Benzenesulfonamide\(^{64}\) derivatives carrying a pyrazole moiety were prepared by Abdel Aal et al which were structurally related to the COX-2 inhibitor celecoxib (Celebrex®) and were found to be potent anti-inflammatory agents with no or less tendency to evoke gastric ulceration. In these derivatives N-Ethyl-2-(3-methyl-5-oxo-4,5-dihydro-pyrazole-1-carbonyl)-benzenesulfonamide (\(64\)) was found to be more active.
1.2.3c Hepatitis C virus NS3 protease inhibitor

Aryl bromide moiety\textsuperscript{65} represents a building block of a class of HCV NS3 protease inhibitors these were prepared by using Mo(CO)\textsubscript{6} as a convenient CO-releasing group from aryl bromides with a primary sulfonamide exemplifying the use of amidocarbonylation method for potential analogue generation. When evaluated in an \textit{in vitro} assay comprising the full-length NS3 protein, N-(4-Methoxy-benzoyl)-4-methyl-benzenesulfonamide ( ) proved to be highly potent inhibitor with \(K_i\) value 85 ± 7nM.

1.2.3d Growth Hormone Secretagogue Receptor

High specific activity sulfur-35-labeled sulfonamide\textsuperscript{66} radioligand (66) has been developed by Dean and his co-workers for the identification of a GH secretagogue receptor. \([^{35}\text{S}]-\text{MK-0677}\) was found to
possess the necessary combination of high selectivity, affinity and specific activity required for utilization as a radioligand in the study of this newly discovered receptor.

1.2.3e Antiglaucoma drugs

A new series of sulfonamide (CA) inhibitors by reacting arylsulfonyl chlorides with aromatic/heterocyclic sulfonamides possessing a free amino/imino/hydroxyl group were given by Andrea and his co-workers. Sulfonamide showed strong affinities toward isozymes I, II, and IV of carbonic anhydrase (CA), and also showed strongly lowered intraocular pressure (IOP) when applied topically, directly into the normotensive/glaucomatous rabbit eye, as 2% water solutions.
1.2.3f Cancer-Associated Carbonic Anhydrases (CAs)

Neoglucoconjugate\textsuperscript{68} a new class of sulfonamide (68) link was designed by Marie and his co-workers to selectively target and inhibit the extracellular domains of the cancer-relevant CA isozymes. The carbohydrate fragment in these compounds is linked to the classical aromatic sulfonamide CA pharmacore to target inhibition of cancer-associated CAs. The CA inhibitors designed were very good CA IX inhibitors and potent CA XII inhibitors.

\[
\begin{array}{|c|c|c|}
\hline
X = & \text{SO}_2 & \text{S} \\
\hline
R = & \text{H} & \text{Ac} \\
\hline
\end{array}
\]

1.2.3g Antimicrobial activity

Iqbal and his team synthesized benzene sulphonamides\textsuperscript{69} bearing 2,5-distubstituted-1,3,4-oxadiazole moiety and tested for antimicrobial and antifungal activity for all the compopunds. Compound 69 exhibited significant antibacterial and antifungal activities due to the presence of a chloro group on position 4 of the phenyl substituent, free SH group at position 5 of the oxadiazole ring, the free \( -\text{NH}_2 \) group of the sulphonamido moiety.
1.2.3h β-Lactamase inhibitors

Eidam and his team has given new sulfonamide boronic acids\textsuperscript{70} (70) derived from the conversion of the canonical \( R_1 \) carboxamide retain substantial inhibition activity against β-lactamases, they also rescued antibiotic resistance when used in combination with third generation antibiotics in bacterial cell cultures. This superficially modest substitution changes the geometry of the inhibitors enough to scramble the SAR observed in the analogue carboxamides.

<table>
<thead>
<tr>
<th>( R )</th>
<th>( \text{CH}_3 )</th>
<th>( \text{Ph} )</th>
<th>Substituted phenyls</th>
</tr>
</thead>
</table>

1.2.3i Protein Kinase Inhibitors

The isoquinoline sulphonamide derivatives (71) given by Hidaka and his team had ability to inhibit protein kinases, Some of the derivatives\textsuperscript{71} exhibited selective inhibition toward a certain protein
kinase. The inhibitors were freely reversible and of the noncompetitive type with respect to the phosphate acceptor. The isoquinolinesulphonamides structurally unrelated to ATP, compete with ATP for free enzyme but do not interact with same enzyme form as does the phosphate acceptor.

1.2.4 Synthesis of sulphonamides

Gopalsamy and his co-workers has prepared diarylsulfone sulfonamides 73, from diarylsulfonyl chlorides 72 and phenylethyl amine in the presence of Et₃N and CH₂Cl₂ at 37°C for 16 hr to yield 82% of diarylsulfone sulfonamides⁷² (Scheme 21).

![Scheme 21](image-url)
A two step synthesis of pentadentate tetraionic based ligands based on sulfonamide, amide and pyridyl groups is reported by Karno and his team. These ligands are easily accessible in good to excellent yield from commercially available materials (Scheme 22).

Scheme 22

Bahrami and his co-workers has given the direct oxidative conversion of thiol derivatives to the corresponding sulfonyl chlorides through oxidative chlorination, using valuable reagent H$_2$O$_2$-SOCl$_2$, this upon reaction with amines to yield sulfonamides in excellent yields (Scheme 23).

Scheme 23

R = alkyl, aryl
A series of novel disulfonamide derivatives 77 were synthesized by Behmadi and his co-workers and characterized by FT-IR, $^1$HNMR and MS techniques. In order to prepare new disulfonamides, at first they have synthesized new diamines containing a pyridine ring 76. Then, they have been reacted with sulfonyl chlorides to give corresponding disulfonamides (Scheme 24). 75

\[ \text{Scheme 24} \]

\[ \text{α-fluorosulfonamides 79 were prepared by Taylor, Yong and Bryan by electrophilic fluorination of tertiary sulfonamides using N-fluorobenzenesulfonylimide as fluorinating agent. First benzene sulfonyl chloride was reacted with secondary amines in the presence of Et$_3$N and cat. DMAP in THF and then fluorination (Scheme 25). 76} \]

\[ \text{Scheme 25} \]
One-Pot synthesis of aromatic and heteroaromatic sulfonamides was given by Pandya and is co-workers, analogues were prepared from aryl and heteroaryl bromides by converting to Grignard reagent using isopropylmagnesium chloride or magnesium bromide and reacting with sulfuryl chloride, sulfur dioxide and an amine to give sulfonamide analogues (Scheme 26).

Deng and Mani has given an environmentally benign synthesis of sulfonamide in water by reacting amino and aminobenzoic acids with sulfonyl chlorides by maintaining the $\text{pH}$ at 8.0 using 1 Mol L$^{-1}$ Na$_2$CO$_3$ in water and to get the yield $\text{pH}$ was adjusted to 2.0 by using Conc. HCl to get 98% yield using 5% Bu$_4$N$^+$Br$^-$ as a phase transfer catalyst as the amines are less soluble in water (Scheme 27).
A series of arene and alkane sulfonamides 83 were prepared by Kataoka by treating the sodium sulfonates with triphenylphosphine dibromide followed by treating with amines in the presence of sulfonyl halides and triethylamine to yield sulfonamides (Scheme 28).79

Scheme 28

\[
\begin{align*}
\text{PhSO}_2\text{Na} & \xrightarrow{\text{Ph}_3\text{P}.\text{Br}_2} \text{PhSO}_2\text{Br} \xrightarrow{\text{R}^1\text{R}^2\text{NH}, \text{Et}_3\text{N}, \text{O}^0, \text{rt}} \text{PhSO}_2\text{NR}^1\text{R}^2 \\
\text{R}^1 &= \text{PhCH}_2, \text{Et}, \text{H} \\
\text{R}^2 &= \text{H}, \text{Et}
\end{align*}
\]

A series of aryl N-aminosulfonamides80 84 was given by Nguyen and his team with palladium-catalyzed three-component coupling of aryl iodides, hydrazines and a crystalline solid DABCO.(SO\textsubscript{2})\textsubscript{2} as a convenient source of sulfur dioxide which is easy to handle and employ only a slight excess of sulfur dioxide (Scheme 29).

Scheme 29

\[
\begin{align*}
\text{Me} + \text{H}_2\text{N}-\text{N} & \xrightarrow{\text{Pd(OAc)}_2, \text{P}^3\text{Bu}_3, 70^\circ\text{C}} \text{Me} \\
(\text{DABCO})_2(\text{SO}_2)_2
\end{align*}
\]

81

Wright and Hallstrom as reported the conversion of heteroaryl thiols to heteroaryl heteroaryl sulfonyl chlorides by using NaOCl, HCl.
and by reacting with excess of benzylamine at \(-5^0\) to \(-25^0\)C to sulfonamides\(^81\) (Scheme 30).

**Scheme 30**

\[
\begin{align*}
\text{Scheme 30} & \\
\text{NaOCl, HCl} & \rightarrow \text{Sulfonamide}
\end{align*}
\]

82

An easy and handy synthesis of sulfonamides 83 directly from sulfonic acids or its sodium salts is reported by Luca and Giacomelli. 2,4,6-Trichloro-[1,3,5]-triazine was added at room temperature to a solution of benzenesulfonic acid sodium salt in acetone dry and 18-crown-6 and the mixture was irradiated to 80°C for few min in sealed tube to yield sulfonamides (Scheme 31). \(^82\)

**Scheme 31**

\[
\begin{align*}
\text{Scheme 31} & \\
\text{1. TCT, 18-crown-6, acetone} & \rightarrow \text{Sulfonamide}
\end{align*}
\]

84 85

A mild and efficient reaction of amine derived sulfonate salts in the presence of cyanuric chloride, triethylamine as base, and anhydrous acetonitrile as solvent at room temperature gives the corresponding sulfonamides 86 in good to excellent yields (Scheme 32). \(^83\)
1.3 Section C – A brief review on Sulphonates

1.3.1 Introduction to sulphonates

Sulfonic esters are used as reagents in organic synthesis, chiefly because the RSO₂O- group is a good leaving group in Sn1, Sn2, E1 and E2 reactions. Methyl triflate, for example, is a strong methylating reagent. They are commonly used to lend water solubility to protein crosslinkers such as N-hydroxysulfosuccinimide (Sulfo-NHS), BS3, Sulfo-SMCC, etc.

1.3.2 Chemistry and nomenclature of sulphonates

Esters with the general formula R¹SO₂OR² are as a category called sulfonic esters, with individual members of the category being named analogously to how ordinary carboxyl esters are named. For example, if the R² group is a methyl group and the R¹ group is a trifluoromethyl group, the resulting compound is methyl trifluoromethane sulfonate.
1.3.3 Synthesis of sulphonates

Enantiopure α-substituted sodium sulfonates without any racemization using polymer bound triazenes based on triazene T2* linker was performed by Vignola and his co-workers in the presence of alkylation resin. Without any purification all products 87 were obtained in good yield and in excellent purities (Scheme 33). 84

![Scheme 33](image)

Alkyl trifluoromethyl sulfonates (triflates) 89 are prepared by taking a solution of phenol 88 and phenyl bis[(trifluoromethyl)sulfonyl] amine in dichloromethane is triethylamine is added keeping in an ice bath, and stirred for 1hr at 0°C and warmed to room temperature and the reaction is stopped by addition of diethyl ether, and the organic layer washed with water (Scheme 34).
To a cooled solution of dry pyridine in alcohol triflic anhydride was added dropwise at a rate to maintain a reaction temperature of 0-20°C and after the addition it was stirred at 0°C for 30 min at room temperature and the volatiles are removed in vacuo, and residue obtained was extracted with ether (Scheme 35) to get the trifluoromethane sulfonates 90 (triflates).87

The triethylamine and alcohol were dissolved in dichloromethane and cooled to 0°C and methane sulfonyl chloride taken in CH₂Cl₂ was added dropwise over 30 min and stirred at room temperature until the reaction was completed it was poured into 0.5 M NaHCO₃ and it was extracted with CH₂Cl₂ and washed with brine to get the methyl sulfonates 91 (mesylates) (Scheme 36).87
The useful protecting group for the construction of sulfonate-containing analogs of nucleosides was found to be isobutyl ester. Synthesis of useful uridine or adenosine 3′-C-methanesulfonate analogs were readily achieved with the isobutyl ester as a protecting group (Scheme 37).

The regioselective 1,3-dipolar cycloaddition of α-bromo-pentafluorophenyl vinyl sulfonate with nitrile oxides has been used to rapidly access a range of 3,5-isoxazoles which could be converted directly to their corresponding sulfonates (Scheme 39).
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