CHAPTER - II
REVIEW OF LITERATURE

The search for chemical structures which exhibit physiological activity was an innovative field of organic research. Observations of interesting biological activity of heterocyclic compounds opened new pathway for the synthesis of new heterocycles.

In the past years, the literature had been enriched with progressive findings about the synthesis and pharmacological action of heterocycles. A variety of reports regarding synthetic and various potent activity of piperidone derivatives, thiosemicarbazones, 1,3,4-thiadiazoles, and spiro compounds have been presented. Synthesis and biological activities some reported nitrogen and sulphur containing heterocyclic compounds were reviewed in this chapter.

Spiro Compounds

Horsfiline an oxindole alkaloid containing a spiro nucleus has been isolated by Bodo and Co workers\textsuperscript{16}

\[
\begin{align*}
\text{MeO} & \quad \text{Me} \\
\text{MeO} & \quad \text{Me} \\
\text{NH} & \quad \text{O} \\
\end{align*}
\]

from Horsfieldia Superba, a tree from Malasia, the extracts of which commonly employed in local medicine

Vidari, etal.\textsuperscript{17} reported the anti tumour activity in human cancer cell lines of the following compounds

\begin{align*}
\text{I a} & \quad R_1 = \text{OH} ; R_2 = R_3 = \text{H} & \quad \text{I c} & \quad R_1 = R_2 = \text{OH} ; R_3 = \text{H} \\
\text{I b} & \quad R_1 = R_2 = R_3 = \text{H} & \quad \text{I d} & \quad R_1 = R_3 = \text{OH} ; R_2 = \text{H} \\
\end{align*}

Each of these compounds contains a unit of tri cyclic trioxa spiroketal.
The alkaloids containing a spiro [indole-pyrrolidine] nucleus are cell-cycle-specific cytostatic agents that arrest mitosis and metaphase by acting as spindle poisons. They are also found to be useful in cancer chemotherapy.\textsuperscript{18}

Hydantocidin, which contains a unique spiro nucleoside structure, possesses potent herbicidal and plant-growth regulatory activity.\textsuperscript{19}

The aza spiro compounds are reported\textsuperscript{20} to be tachykinin antagonists

\[ R_1 = \text{OH, alkyl, PhCO, CN, halo, NH}_2 \]
\[ R_2 = \text{H, alkyl, alkoxy, halo, etc,} \]
\[ R_3 = \text{H, alkyl, cycloalkyl, alkoxy, halo NH}_2, \text{alkylthio, carbamoyl, acyl} \]
\[ R_4 = \text{H, alkyl, alkoxy, halo,CF}_3,\text{OCF}_3, \text{NO}_2,\text{CN,alkylthio, carboxy etc,} \]
\[ R_5 = \text{H, alkyl, CF}_3, \text{halo , etc,} \]
\[ R_6 = \text{H, acyl, carboxy, carbamoyl, phenyl ,etc,} \]
R₇ and R₈ = H, alkyl, alkoxy halo, carboxy, alkoxy methyl, carbamoyl etc, and are of particular use in the treatment of depression, anxiety, pain, inflammation, migraine, emesis or postherpetic neuralgia.

Interesting biological activities have been found in the piperidine alkaloids, (G)-pandamarine and (K)-pandamarilactone, which contain an azaspiro[4.5]-decane structural unit are isolated from Pandanus sp.²¹

![Chemical structure of the piperidine alkaloids](image)

Pinnaic acid (I) and tauropinnaic acid (II), isolated from Pinna muricata, are found to exhibit inhibitory activity against a cytosolic 85 kD phospholipase (cPLA₂).²²

![Chemical structure of Pinnaic acid and Tauropinnaic acid](image)

I R=OH, II R=NHCH₂CH₂SO₃H

Halichlorine (III), isolated from the marine sponge Halichondria okadi, is an inhibitor of the vascular cell adhesion molecule.²³

![Chemical structure of Halichlorine](image)
Pujari et al.\textsuperscript{24,25} have synthesised spiro tetrazine compounds by taking the 3-aryl/alkyl-indan-1-one and thiocarbohydrazide as the synthon components

\[ \text{R} \rightarrow \text{Me, Ph, m/p-Cl-} \text{C}_6\text{H}_4, \text{m/p-HO-} \text{C}_6\text{H}_4, \text{p-MeO-} \text{C}_6\text{H}_4. \]

Spiro cyclic quinuclidines containing spirofused indoles are important

\[ \text{R} = \text{H, C}_3\text{H}_9, \text{C}_6\text{H}_5, \text{i-Pr, 4,4- diethoxy butyl} \]

\[ n = 0,1 \quad m = 1,2 \]

for muscarinic receptor binding.\textsuperscript{26} Substituted quinuclidines exhibit selective muscarinic receptor binding properties.\textsuperscript{27} Some spiroheterocycles, benzopyrans, are aldose reductase

\[ X = 0, \text{CO} \]

inhibitors, which are found to be useful as antidiabetics.\textsuperscript{28}
Hanbiao Yang et al\textsuperscript{39}, reported the synthesis of some novel 1- and 5-substituted 3,9-diazaspiro [5,5] undecanes. The key step involved was Michael addition of lithium enolate to a tetra substituted olefin acceptor.

\[
\begin{array}{c}
\text{NH} \quad \text{NH} \\
\text{H} \quad \text{H}
\end{array}
\quad \begin{array}{c}
\text{NH} \quad \text{NH} \\
\text{O}
\end{array}
\]

3,5- Diazaspiro [5,5] undecane and undecan-2-one

Several spiro [chroman-2,4'-piperidin]-4-one\textsuperscript{30} derivatives have been designed, synthesized and evaluated for in vitro acetyl - CoA Carboxylase (ACC) Inhibitory activity. Several compounds have shown Acc inhibitory activity in low nanomolar range.

Ji-Feng Liu et al\textsuperscript{31} performed novel and expeditious microwave assisted three component reactions for the synthesis of spiro imidazolin-4-ones. The efficiency and utility of the methods have been demonstrated by quickly accessing the anti hypertensive drug irbesartan.

\[
\begin{array}{c}
\text{O} \\
\text{NH} \\
\text{R'} 000H + R 2 NHBoc
\end{array}
\]

\[
\begin{array}{c}
\text{Oxononium ion-mediated synthesis of 4-substituted spiro-isoxalines was reported by Eric McClendon and others}\textsuperscript{32}.
\end{array}
\]
A rapid and efficient strategy for the preparation of spiro-pyridones and spiro quinolone using sequential Pd(O)/C- catalyzed allylation and ring closing metathesis was described by Laura Kersten and co-workers\textsuperscript{33}.

Ji-beng Merg et al\textsuperscript{34} have designed and synthesised a series of novel heterocycles containing spiro oxazines and studied their photochromic properties under flash photolysins and their life time of the photomerocyanine form in various solutions and polymers.

Myoung-Seon Gong et al\textsuperscript{35} have synthesised novel spiro [fluorene - 7,9' benzo fluorene] based blue host material, 2-(10-phenylanthracene)-spiro fluorene - 7-9'-benzofluorene through the suzuki reaction.
An efficient synthetic method for chiral (isoxazole-isoxazoline) ligands, based on a spiro [4,5] decane framework has been developed by Hiroaki Sasai & others\textsuperscript{36}.

Ashok and Shravani\textsuperscript{37} have reported One-pot synthesis of novel spiro 2, 3, 7, 8-tetrahydro-benzo [1, 2-b; 5, 4-b]-dipyran-4, 6-dione and 2, 3, 8, 9 -tetrahydro-benzo [1,2-6' 4,3-b] dipyr - 4,10-dione derivatives.

Damytro, Oleksandr and Igo\textsuperscript{v38} designed a library of isomeric glutamic acid analogs based on the spiro [3,3]-heptane skeleton and synthesised two members. The stereo chemistry of the synthesized amino acids was determined using $^1$H-$^1$H-Nosey of their diastereomeric derivative.
Laszlo Somsak et al.\textsuperscript{39} have described 2-naphthyl substituted glucopyranosylidene-spiro-oxathiazole prepared following a novel design principle as the best known glucose analogue phosphorylase 6 (K, 160nM).

Nadezhde N. Koles and co-workers\textsuperscript{40} have obtained a series of new tetraaza spiro \([5,5]\) undec-4-one-2, 7, 9, 1 tetraones by reaction of 5-(2-aryl ethylidene-2-oxo)-1,3-dimethylpyrimidine-2,4,6-trione with ureas.

Andreas Palmer and co-workers\textsuperscript{41} prepared asymmetric and symmetric spiro (imidazo [1,2-a] pyrano [2,3-c] pyridine-9-idenes using a cross-metathesis reaction and an acid-catalyzed cyclopolymerisation as key steps.
Perumal et al. have reported an efficient one-pot synthesis of spiro dihydrofuran fluorene and spiro-2-hydroxy tetrahydrofuran fluorene derivatives via [3+2] oxidative cycloaddition mediated by CAN.

The synthesis of spiro (thiadiazoline-piperidine) derivatives by cyclization of thiosemicarbazones of piperidine derivatives was described by Balasubramaniam S., Ramalingam C. and Kabilan S.
The compounds were characterized by IR, $^1$H NMR, $^{13}$C NMR & Mass spectra.

Padmavathi V. and co-workers reported the synthesis of new class of spiro pyrimidinetriones, thioxopyrimidinediones, pyrazolidinediones, and isoxazolidinediones from dihedron pyridine/pyran/thiopyran dicarboxylates.

The mass spectral behaviour of some new spiro heterocyclic compounds where studied by Padmavathi V. and Bhaskar Reddy D.

Madhukar S. Chande and Niranjan M. Paingankar made a new approach to the chemistry of spiro hetero cycles. Interaction of α, α-dibromodiethylmalonate with 4-substituted thiosemicarbazide in the presence of a base afforded 2, 2'-dialkyl/arylimino-octahydro -6, 6'-spiro-bi(1, 3, 4-thiadiazines)-5, 5'-diones.
Jarosaw Romanski et al.\textsuperscript{47} reported the reaction of pentacyclo-undecane-8-thione with diazomethane and 2-diazopropane which afforded 1, 3, 4-thiadiazoline.

Novel spiroannulated 3-Benzofuranones were synthesised by Manfred Braun et al.\textsuperscript{48}. They studied the inhibition of the human peptidyl prolylisis/trans Isomerase pin 1 with these compounds.

\begin{center}
\begin{tikzpicture}
\node at (0,0) {\includegraphics[width=0.4\textwidth]{image1}};
\end{tikzpicture}
\end{center}

$R = H, \text{OCH}_3$

Roberto Ballini\textsuperscript{49} and co-workers reported nitroalkanes as central reagents in the synthesis of spiroketals, via nitroaldol, Michael reaction & Nef reaction. They have reported the formation of 1, 6-Dioxaspiro(4,4)nonanes.

\begin{center}
\begin{tikzpicture}
\node at (0,0) {\includegraphics[width=0.4\textwidth]{image2}};
\end{tikzpicture}
\end{center}

1, 6-Dioxaspiro (4,5)decane al 1, 6-dioxaspiro(4,6)undecane and several other spiro compounds.

Synthesis of 6-Methoxy-1-oxaspiro(4,5)deca-6,9-diene-8-one\textsuperscript{50} was reported by Guy L. Plourde and Benjamin B. Fischer.

\begin{center}
\begin{tikzpicture}
\node at (0,0) {\includegraphics[width=0.2\textwidth]{image3}};
\end{tikzpicture}
\end{center}
Diastereoselective spiro annulation\textsuperscript{51} of phenolic substrates producing (+) 2-t-butyl-6-methoxy-1-oxaspiro(4,5)deca-6, 9-diene-8-one was reported by Plourde et al.

\[ \text{O} \]
\[ \begin{array}{c}
9 \\
8 \\
7 \\
6 \\
5 \\
4 \\
3 \\
2 \\
\text{Me} \\
\text{t-butyl}
\end{array} \]

\(^{13}\text{C} \) NMR (CDCl\textsubscript{3}) of the compound was reported as follows.
26.0 (26.2, t-butyl CH\textsubscript{3}), 27.6 (C\textsubscript{3}), 29.8 (t-butyl C) 36.8 (C\textsubscript{4}), 55.7 (OCH\textsubscript{3}), 78.2 (C\textsubscript{5}), 89.5 (C\textsubscript{2})

Padmavathi V. and co-workers have proved 4-piperidones\textsuperscript{52} as synthons for spiro-heterocycles. The compounds were characterised by IR, \(^{1}\text{H} \) NMR and \(^{13}\text{C} \) NMR.

Michael adducts\textsuperscript{53} acting as synthons for a new class of 1, 4-dispirocyclohexane derivatives were reported by Padmavathi V. et al.

The compounds were characterised by IR, \(^{1}\text{H} \) NMR and \(^{13}\text{C} \) NMR.
A simple, clean and efficient method for the synthesis of spiro\textsuperscript{54} (indoline-3, 9-xanthene)trione derivatives and spiro(acenaphthene-1,9-xanthene)\textsuperscript{1}, 2, 8'(2'H, 5'H)trione by condensation reaction of dimedone and isatins or acenaphthene in aquas media was reported by Somayeh Ahadi et al.

Raviraj et al\textsuperscript{55} have synthesized and studied the activity of spiro(indolo-1, 5-benzodiacepines) from 3-acetyl coumarines as possible antianxiety agents.

Martino et al\textsuperscript{56} have done an extensive synthesis and characterization of 2, 4-substituted thiadiazolines from several ketones. The compounds were characterized by \textsuperscript{1}H NMR and \textsuperscript{13}C NMR.

Some spiro\textsuperscript{57} [piperidine-4, 2\textsuperscript{1} (1\textsuperscript{H}-quinazolines)-4\textsuperscript{3} (3\textsuperscript{1}H)-ones and spiro [piperidine-4, 5\textsuperscript{1} (6\textsuperscript{1}H)-(1, 2, 4)triazolo(1, 5-c) quinozolines were synthesized and evaluated as ligands of the nociception receptor by Carlo Mustazza et al.
Palani K. and co-workers\textsuperscript{58} studied the crystal structure of 1-N-Methyl (2, 2')spiroacenaphthene-1\textsuperscript{1}-one[3, 2']spirocyclohexane-1\textsuperscript{1}4-(p-methylphenyl) pyrrolidine.

Attia M.S. et al\textsuperscript{59} studied and discussed the effect of complexation with lanthanide metal ions on the photochromism of [1, 3, 3-trimethyl-5\textsuperscript{1}-hydroxy-6\textsuperscript{1}-formylindoline-spiro2, 2(2H)chromene]in different media.

Total synthesis of biologically important axane sesquiterpenes and axenol was accomplished through a readily available spiro-[4, 5]-decane via. claisen rearrangement was reported by Atsuo Nakazaki et al\textsuperscript{60}.

Crystal structure of 1-N-methyl-2[1\textsuperscript{1}-N(p-methoxyphenyl)-3\textsuperscript{1}-phenyl-azetidin-2\textsuperscript{1}-one]-3(p-methoxy benzoyl)spiro[4,4\textsuperscript{1}]oxindole-pyrrolidine was reported by Sundari Bhaskaran and co-workers\textsuperscript{61}.

Hidemitsu Nishida et al\textsuperscript{62} reported the synthesis and evaluation of 1-aryl sulphonly-3-piperizone derivatives as Factor Xa Inhibitors. A series of new derivatives containing spiro[5H-oxozolo][3, 2-a]pyrazine-2(3H)4\textsuperscript{1}-piperidin]-one skeleton was given by them.

Microwave activation\textsuperscript{63} coupled with dry media technique as a green chemistry procedure had been applied to synthesis of a series of new spiro [1, 5]benzothiazepin-2,3\textsuperscript{1}[3\textsuperscript{1}H]Indol-2[1\textsuperscript{1}H]-one. The authors have reported antifungal, antitubercular screening of the title compound.
Singh et al$^{64}$ synthesised a series of isatin-based spiro azetidinones and screened for their anticonvulsant activity.

Preparation$^{65}$ of chiral spiro compounds of the thiadiazoline types starting from natural terpenones such as fenchone, camphor and menthone was described by Beatriz N. Brousse et al, via., the formation of thiosemicarbazones.

Synthesis of spirocyclics$^{66}$ via. ring-closing metathesis was reported by Sambasivarao Kothe and Manivannan E.
Somogy and co-workers have synthesized racemic 3-acetyl-5-aminospiro[1, 3, 4-thiadiazoline-2, 4'-thioflavons from thioflavanone thiosemicarbazone by cyclisation under acetylating conditions. The isomers were reported to be separated by HPLC and stereo chemistry studied by X-ray diffraction analysis, $^1$H, $^{13}$C, $^{15}$N NMR measurements as well as MOPAC QM calculations.

Structural characterization and anti-oxidant activity of aromatic and 3-aryl sydnonyl substituted hydrazine-thiazoles and hydrazino-thiazolines were reported by Mei-Hsiu Shih and co-workers. They synthesized a series of aromatic ring substituted hydrazino-thiazole derivatives from aromatic or heterocyclic thiosemicarbazones using 2-chloro acetoacetate and 2-bromoacetophenones as cyclising agent. The ORTEP drawings of the compounds provide strong evidence of the structure of aromatic thiazole derivatives.

Michael and Rosemary described a general procedure for the synthesis of functionalised spiro ketals from lactones. Addition of lithium acetylide of cis-1-methoxy-1-buten-3-yne to lactone followed by hydration of the acetylene of hydrolysis of the enol ether and cyclisation gave excellent yields of spiro ketals.

Design and synthesis of spiro heterocycles by ring-closing metathesis was reported by Kotha and Deb. The authors have synthesized spiro heterocycles from disubstituted barbituric acid.
Some novel spiro piperidenyl 1, 2, 4-triazolidin-3-thiones have been synthesised and studied for their antibacterial activity against Staphylococcus aureus, bacillus subtilis, E.coli and pseudomonas aureginosa and antifungal activity against Candida Albicans.

1, 3, 4-Thiadiazoles and 1, 3, 4-Thiadiazolines.

Heterocycles bearing 1, 3, 4-thiadiazole moieties constitute the core structure of a number of pharmacologically and biologically active interesting compounds. The efficacy of 1, 3, 4-thiadiazoles is due to the virtue of the toxophoric N=C-S grouping.

In the medicinal field one of the best known drug based on 1, 3, 4-thiadiazole was acetazolamide (acetazola) a carbonic anhydrase inhibitor launched in 1954. Its usage were many including the treatment of glaucoma, epilepsy and congestive cardiac failure.

Rawat and Srivatsava reported the synthesis and antifungal activity of phenothiazino thiadiazoles and their azetidinones as given in scheme.
Synthesis of 1, 2, 4-thiatrizolo-thiadiazoles\textsuperscript{71} and its 2-oxoaazetidines as antimicrobial, anticonvulsant and anti-inflammatory agents were reported by Srivastava et al.

Man-Lin Li and co-workers\textsuperscript{72} synthesized and studied the bioactivity of 2, 5-bismercapto-1, 3, 4-thiadiazole derivatives.
AAF Wasly et al. reported various heterocycles derived from 2-amino-5-[6-(dibenzotheiene-4-yl)-4,5-dihydropyridazin-3-yloxymethyl]-1,3,4-thiadiazole.

Synthesis and fungicidal activities of some 3-aryloxymethyl-6-substituted-1, 2, 4-triazolo[3, 4-b][1, 3, 4]-thiadiazole was reported by Q Bano and others.

Synthesis of some new 5-[2-{1, 2, 3-benzotriazole}-1-yl-methyl]-1-[4-substitutedaryl-3'chboro-2'oxazetidine]-amino-1, 3, 4-thiadiazole and their antifungal, antibacterial activities were reported by Shukla and Srivastava.
Green synthesis\textsuperscript{75} of substituted imidazothiadiazoles using ionic liquids was given by Kidwai and Rastogi.

Tai-Bao-Wei and co-workers\textsuperscript{4} reported microwave promoted efficient synthesis of 2, 5-disubstituted 1, 3, 4-thiadiazoles.

S. K. Narmada et al\textsuperscript{76} reported Conventional and Ultrasound mediated synthesis of some thiadiazoles, triazoles and oxodiazoles.

Newer and simpler synthetic methods\textsuperscript{77} of some alkoxyphthalimide derivatives of benzotriazolythiadiazoles and benzotriazolythiadiazolines were described by Swati Ojha and others. The compounds were characterized by IR, \textsuperscript{1}H NMR and Mass spectra.

S. M. Mohammad and co-workers\textsuperscript{78} reported synthesis and mass spectral fragmentation patterns of some thiazoles and imidazoline derivatives.
Synthesis\textsuperscript{79} and fungicidal, and bacteriocidal activity of some thiazole derivatives were discussed by Arun Kumar Pandy and others.

Sanmati K. Jain and P. Mishra\textsuperscript{5} reported the preparation and Evaluation of some 1, 3, 4-thiazoles as diuretic agents. The compounds were characterized by\textsuperscript{13}C NMR and Mass spectra.

Microwave assisted synthesis\textsuperscript{80} and biological activity of 3-alkyl/aryl-6-(1-chloro-3, 4-dihydronaphth-2yl)-5, 6-dihydro-s-triazolo[3, 4-b][1, 3, 4]-thiadiazoles was discussed by Poonam et al.

Carbazolyl-thiazol-2-oxo-azetidines were reported as antimicrobial anticonvulsant and anti-inflammatory agents by S. K. Srivastava et al.\textsuperscript{81}.
K. Mogilaiah et al\textsuperscript{82} reported chloramine-T mediated synthesis of 1, 8 naphthyridinyl-1, 3, 4-oxodiazoles.

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{Ph} & \quad \text{Ph} \\
\text{Ph} & \quad \text{Ph}
\end{align*}
\]

A rapid one-pot synthesis\textsuperscript{83} of 5-substituted-2-mercapto-1, 3, 4-thiadiazole using microwave was reported by Mazaahir Kidwai and Kumar Ranjan Bhushan.

\[
\begin{align*}
R-C-NH_2 & \quad \text{(i) } N_2H_4 \\
R-C-NH_2 & \quad \text{(ii) } CS_2 \\
R-C-NH_2 & \quad \text{(iii) } MW
\end{align*}
\]

Otilia Tintilie and co-workers\textsuperscript{84} have discussed the synthesis of new 1, 3, 4-thiadiazole and 1, 2, 4-triazole compounds containing a D, L methionine moiety by intramolecular cyclisation of 1, 4-disubstituted thiosemicarbazide in acid and alkaline media. They have also reported that the synthesized compounds exhibited promising activities against Bacillus antracis and Bacillus cereus.
Synthesis of N-(4-acetyl-5-aryl-4, 5-dihydro-1, 3, 4-thiadiazol-2-yl)-N-benzothiazol-2-yl-acetamide and their potency as a new class of Schistosomicidal agent was discussed by Mona A. Mahran and others.  

Nadia Adil Salih reported synthesis and characterization of novel azole heterocycles based on 2, 5-disubstituted thiadiazoles.

Synthesis of 2-acylamino, 2-aroylamino and ethoxycarbonylamino-1, 3, 4-thiadiazoles as antitumor agents was reported by Kemal Sancak et al.
A series of 5-[2-(phenylthio)-phenyl]-1, 3, 4-oxodiazole-1, 3, 4-thiadiazole and 1, 2, 4-triazole derivatives were synthesized and compounds were evaluated in vivo for their anticonvulsant muscle relaxant activities using PT2 and rotated test by Ali Almasired et al.

Foroumadi A. and co-workers synthesized and studied the anticonvulsant activity of novel 2-amino-3-[4-chloro-2(2-chlorophenoxy)-phenyl]-1, 3, 4-thiadiazole derivative and found the unsubstituted amino group was inactive in both PT2 and MES tests.

![Thiadiazole derivative](image)

Synthesis, antitubercular activity and QSAR study of some novel 2-(nitroaryl)-5-(nitrobenzyl, sulfinyl and sulfonyl)-1, 3, 4-thiadiazole derivatives was reported by Foroumadi A. and co-workers.

A route to methyl pyrrolo[2, 3, d][1, 2, 3]-thiadiazole-6-carboxylate as potential plank activators and inducers of systemic acquired resistance was reported Martin Turner et al. A synthetic strategy based on cyclisation of the thiazole ring system using thionylchloride via., Hurd-Mori protocol as key step was developed.
Condensation\textsuperscript{92} 3-(substituted-phenyl)-4-amino-5-mercapto-1, 2, 4-triazole and alkyl/alkoxy/halide substituted carbonyl chloride in presence of phosphoryl chloride yielded 3-(substituted phenyl)-1, 2, 4-triazolo-6-(substituted phenyl)-[3, 4-b][1, 3, 4]-thiadiazole. The structure had been established by chemical analysis and spectral data.

Synthesis\textsuperscript{93} and antibacterial activity of 2\textsuperscript{1}-aryl-3-(4\textsuperscript{1}-trifluoromethylphenyl)-4-oxo-thiadiazolines were reported by Anjani Solankee and others. The synthesized compounds were characterized on the basis of elemental analysis and spectral data.

Sheela V. Nair\textsuperscript{94} had reported the oxidation of 1-alkylthioureas leading to the formation of 3-alkylimino-4-alkyl-5-imino-Δ2-1, 2, 4-thiadiazolines. The compounds were characterized by chemical and spectral studies.

Sheela V. Nair\textsuperscript{95} had reported the oxidation of binary mixtures of 1, 3-dialkylthiourea and thiourea leading to the formation of 3-amino-4-alkyl-5-alkylimino-Δ2-1, 2, 4-thiadiazolines.

\textbf{Thiosemicarbazones:}

Thiosemicarbazones were important compounds because of their antibacterial, anti-inflammatory, antituberculosis, hypoglycemic and plant
growth regulative activities. They were found to be active against influenza, protozoa, small pox and certain kinds of tumour.

A.K. Parekh and K. K. Desai\textsuperscript{13} synthesized the following thiosemicarbazone.

\[
\begin{align*}
\text{Ar} & \quad \text{NH} \quad \text{C(S)} \quad \text{NH} \quad \text{N} = \text{C} \quad \text{O} \quad \text{CH} \quad (\text{CH}_2)_2 \\
\text{HO} & 
\end{align*}
\]

The antibacterial screening showed that it possesses good activity against gram positive and moderate activity against gram negative bacteria.

N. Fuji et al\textsuperscript{96} reported thiosemicarbazone derivatives of aromatic aldehyde, and propiophenones, 3, 4-dichlorophenyl and 3-trifluoromethylphenyl as potent inhibitors of malarial parasite proteases.

\[
\begin{align*}
\text{Cl} & \quad \text{N} \quad \text{C} \quad \text{NH}_2 \\
\text{Br} & \quad \text{N} \quad \text{C} \quad \text{NH}_2 \\
\end{align*}
\]

Sab and Daniels\textsuperscript{97} reported the synthesis of a large number of thiosemicarbazones of phenylaceto, diphenylaceto, 3-hydroxy-1-naphthaldehyde and they were found to inhibit the growth of Mycobacterium tuberculosis var. hominis H3TRV.

Synthesis and inhibitory effect\textsuperscript{98} of thiosemicarbazone derivatives of aryl ketones and terpenones and their inhibitory effect on Junin Virus replication in vitro was reported by Cybele C. Garcia et al.
Warren Levinson and co-workers\textsuperscript{99} discussed the inhibition of RNA-dependent DNA polymerase of Rous Sarcoma virus by N-methyl isatin-\(\beta\)-thiosemicarbazone but not by semicarbazide.

Rebecca Brown et al\textsuperscript{100} have studied the biological activity groups of some pyrazole, thiosemicarbazone and substituted thiazones. The authors have screened the compounds for growth inhibition against Bacillus Subtilis and Pseudomonas Fluorescens and found that the thiosemicarbazones showed pronounced growth inhibition activity.

Varma and Nobles\textsuperscript{101} synthesised isatin-N-Mannich base of the following structure.

Kupinic et al\textsuperscript{102} reported the synthesis of a congenic series of isatin-N-Mannich base of the type where \(R^1=N\) NHCOCH\(_3\), NNHCSNH\(_2\).
compound showed strong inhibition against gram positive bacterium Micrococcus Flarus.

\[
R_3 - \text{[Structure]} - R^2
\]

Where \( R^2 = O, \text{NNHCOCH}_3, \text{NNHCSNH}_2 \)

D. L. Klayman, and others\textsuperscript{103} reported a series of N4, N4-disubstituted-2-acetylpyridine thiosemicarbazone as effective antimalarial agent against Plasmodium Berghei.

N-substituted-2-acetylpyridine\textsuperscript{104} thiosemicarbazones were found to be a new class of potential antimalarial agents by D. L. Klayman and others.

Three thiosemicarbazones\textsuperscript{105} derived from 3-azabicyclo[3, 2, 2]nonane were found to be most effective against Plasmodium Berghei in the mouse by D. L. Klayman and co-workers.

Twenty seven 2-acetylpyridinethiosemicarbazones\textsuperscript{106} and analogs were tested antitrypanosomal activity against Trypanosoma Rhodesiense by R. A. Casiro Junior, D. L. Klayman and others. Twenty four of the twenty seven compounds were tested exhibited activities comparable to that found for the antitrypanosomal agent ethidium bromide.

J. P. Scovill et al\textsuperscript{107} showed that the complexes of Cu(II), Ni(II), Fe(III) and Mn(II) with 2-acetylpyridinethiosemicarbazones and relative compounds exhibited reduced antimalarial activities in mice infected with plasmodium Berghei: However antileukemic properties were enhanced by coordination with the metals.
Teitz et al\textsuperscript{108} studied the selective suppression of \textit{V.alb} coded protein(P\textsubscript{120}) on oncogene product associated with tyrosine kinase activity by N-methyl-isatin-4\textsuperscript{1}-4\textsuperscript{1}-diethyl thiosemicarbazone and N-allyl-isatin-4\textsuperscript{1}-4\textsuperscript{1}, diallyl thiosemicarbazone. These compounds selectively suppressed \textit{V. alb} oncogene as well as molovey mumine lukeamic virus.

Teitz et al\textsuperscript{109} have shown the HIV inhibition by N-methyl isatin-\textit{β}-4\textsuperscript{1}-4\textsuperscript{1}-diethylthiosemicarbazone and N-allyl-\textit{β}-4\textsuperscript{1}-4\textsuperscript{1}-diallylthiosemicarbazones. They inhibit HIV by their action on reverse transcriphase and viral structural proteins.

Methisazone\textsuperscript{110}(N-methyl isatin-3-thiosemicarbazone) was found to be an effective compound against variola and vaccunia viruses.

Synthesis and anticonvulsant\textsuperscript{111} of some new thiosemicarbazones and 4-thiazolidine derivatives bearing an isatin moiety was reported N. Karali and A. Gursoy.

N. Karali et al\textsuperscript{112} synthesized a series of 3-thiosemicarbazino-2-indolinones.
S. N. Pandeya et al. reported the synthesis and antimicrobial activity of 1-[N, N-dimethylaminoethy1]-5-bromo isatin (1-(4-parachlorophenyl)-thiazole-2-yl)-thiosemicarbazone. Antimicrobial activity was tested against 28 pathogenic bacteria and fungi and anti-HIV against HIV-1 in MT-4 cells.

S. N. Pandeya group reported the synthesis of N-(6-chlorobenzthiazol-2-yl)-thiosemicarbazide-schiff’s base of isatin and its N-Mannich bases and antimicrobial activity of the above compounds against 25 pathogenic bacteria.

A new photochromic compound 1, 3-diphenyl-4(4-fluo)benzal-5-pyrazolone-4-ethylthiosemicarbazone was synthesized by direct condensation of 1, 3-diphenyl-5-pyrazolone with N4-ethylthiosemicarbazide. The photochromic properties were studied using time-dependent fluorescence emission spectra by Hui Chai et al.

The molecular structures of two salicylaldehyde thiosemicarbazone derivatives namely salicylaldehyde-4-phenyl-thiosemicarbazide and 4-methoxysalicylaldehyde-4-phenyl-thiosemicarbazide, both of potential pharmacological interest were found to exist in the keto form by M. Rubcic et al.

Preparation in excellent yields of cyclobutylbenzofuran-2-yl and naphthofuran-2-ylketones, corresponding ketoximes and thiosemicarbazones and derivatives of ketoximes and thiozoles derived from thiosemicarbazones were described by Murat Koca and others. Two of the synthesized compounds

\[
R = H, - COCH_3; R' = H, Br; R^2 = CH_3, C_2H_5, C_6H_5
\]

were identified as: 

\[
\begin{align*}
N-NH-CSNHR^2 \\
R = H, - COCH_3; R' = H, Br; R^2 = CH_3, C_2H_5, C_6H_5
\end{align*}
\]
were tested against eight different microorganisms and found to be active against some of the species studied.

Fused-N-(di)-arylamino-pyrrol-2, 3-diones\textsuperscript{118} were reacted with diphenyl ketene, thiosemicarbazide or 1, 2-diaminobenzene to afford the 3-diphenyl-methylene-pyrrolones, thiosemicarbazones or quinoxalines derivatives respectively by the authors Gert Kolienz and others.

Haleem and others\textsuperscript{119} prepared hydrazones, semi and/or thiosemicarbazones of 2-substituted and unsubstituted 4-(4-acetylanilino)-5, 6, 7, 8-tetrahydrobenzo(b)thieno [2, 3-dipyrimidine] derivatives. They were converted into corresponding Chalcones and the compounds were tested for their antimicrobial activity against Candida Albicans and other gram positive and gram negative bacteria.

\[
\text{NH} - \text{C} = \text{N} - \text{NH} - \text{CS} - \text{NHR}
\]

Brousse and others\textsuperscript{120} studied antibacterial and antifungal activity of some thiosemicarbazones and 1, 3, 4-thiadiazolines against various microorganisms such as Bacillus Subtilis, Micrococcus Luteus, Listeria monocytogenes, Pseudomonas aeruginosa, Staphylococcus aureus, Candida Albicans.

Reaction of bromoacetyl\textsuperscript{121}-substituted azulenes with thioamides, thioureas and thiosemicarbazones was reported by Hiromi Takao and co-authors.

Sun, Liu and Xie\textsuperscript{122} prepared three new thiosemicarbazones by condensation reaction of 2-bromo-1-arylethones with thiosemicarbazide.
These thiosemicarbazone structures were confirmed by IR, $^1$H NMR, Mass Spectra and elemental analysis.

Mylonas and Mamalis$^{123}$ reported the synthesis and antitumor activity of new thiosemicarbazones of 2-acetyl imidazo[4, 5, b]-pyridine. These compounds were tested against prostate cancer.

A joint experimental and computational study$^{124}$ of oxidative cyclisation of aldehyde thiosemicarbazones induced by potassium Ferricyanide and Tris(p-bromophenyl)-aminohexachloroantimonate was investigated by Paolo, Michaelangelo and Renato.

The electrochemical behaviour$^{125}$ of substituted thiosemicarbazones of the type

\[
\text{R} = \text{C}_6\text{H}_9, \text{p} - \text{cl} - \text{C}_9\text{H}_4, \text{p} - \text{OCH}_3 - \text{C}_6\text{H}_4, \text{C}_4\text{H}_5\text{S}, \text{C}_4\text{H}_4\text{O}
\]

had been investigated by Refacy, Hassan and Shehata. The cyclic voltammetric data indicates that if donor groups present, they increased the height of the oxidative peaks and led to decay of cathodic peaks.

Tritylisothiocyanate resin$^{126}$ is a useful precursor of the tritylthiosemicarbazide. This resin could be employed in the solid phase synthesis of a variety of isatin-β-thiosemicarbazones and their Mannich derivatives.
A series of thiosemicarbazone derivatives of 2-hydroxy-8-R-tricyclo-[7, 3, 1, 0]-trideca-[3-One] were synthesized and their chelating behaviour towards Co(II), Ni(II) and Cu(II) have been investigated by elemental analysis, molar conductivity measurements, UV-Vis, IR, ESR and thermal studies. The antimicrobial activity of thiosemicarbazones towards Acinetobacter Boumanic, E.Coli and Staphylococcus were determined.

A series of p-substituted N-Mannich bases of isatin-3-thiosemicarbazones were found to show antiviral and tuberculositic activity. Methisazone is an effective compound against Varilo and Vaccinic viruses.

\[ \text{Piperidones:} \]

Two dimensional NMR spectral studies of some 2, 6-diarylpiperidin-4-ones were reported by K. Pandiarajan and others they reported the influence of electronic and conformational effects on chemical shifts and coupling constants.

R. Vijayalakshmi et al have given the competing A\(^{1,3}\) strain and ph-ph diaxial repulsion in oximes and semicarbazones of N-nitroso-r-2, c-6-diphenylpiperidin-4-one.

An efficient synthesis of cis-2, 6 diaryl-1-Me-4-piperidones in DME was reported by Veerappan Vijayabaskar and others.
Electron impact mass spectrometry\textsuperscript{132} of some cis and trans-4, 6-diaryl-2-piperidones was reported by Suriyaprakash Rao and B. Bharathi.

A study of the conformations\textsuperscript{133} of ethyl and isopropyl groups in some 2, 6-diphenyl-3-alkyl-1-heterocyclohexane derivatives using NMR Spectra were made by K. Pandiarajan and P. Tamilselvi.

\[
\begin{array}{c}
\text{R}_1 \\
\text{N} \\
\text{Ph} \\
\text{Ph} \\
\text{R} \\
\end{array}
\]

K. Pandiarajan et al\textsuperscript{134} discussed the conformational studies of some piperidin-4-ones using PMR spectroscopy.

\[
\begin{array}{c}
\text{N - NH - CO -} \\
\text{Ar} \\
\text{X} \\
\text{Ar} \\
\end{array}
\]

\[X = \text{NH, S}\]

A. Manimakali and co-workers\textsuperscript{135} reported NMR Spectral studies of N-aroylhydrazones of substituted 4-piperidones and its thio counter part.

A series of 1-[2-(1H-benzimidazon-1-yl)-acetyl]-2, 6-diaryl piperidin-4-ones were synthesized under mild conditions in good yields by G. Aridoss et al\textsuperscript{136}. The authors have studied the structure and conformations of the compounds using \textsuperscript{1}H, \textsuperscript{13}C NMR, two dimensional(NOESY and HSQC)NMR studies. The antimicrobial activities of the compounds were also reported by them.
A. Manimakali and co-workers\textsuperscript{137} reported the synthesis of a series of \textit{t}(3)-benzyl-\textit{r}(2), \textit{c}(6)-diarylpiperidin-4-ones. They have tested the compounds for their in vitro antibacterial and antifungal activities.

A series of N-(N-methylpiperizinoacetyl)-2, 6-diarylpiperidin-4-ones\textsuperscript{138} were synthesized by base catalysed nucleophilic substitution of N-chloroacetyl-2, 6-diarylpiperidin-4-ones obtained from corresponding 2, 6-diaryl piperidin-4-ones with N-methylpiperizine. These new compounds were characterized by one and two dimensional NMR Spectra. All the compounds were screened for their antibacterial, antifungal, analgesic and antipyretic activities.

A new array of novel\textsuperscript{139} N-morpholino-acetyl-2, 6-diarylpiperidin-4-ones were synthesized and their in vitro activity against staphylococcus aureus, E.Coli, Pseudomonas aeruginosa and S. Typhi and antifungal activities against Candida Albicans, A.Niger, Aspergillus flavus were evaluated by Aridoss and others.
A new series of 2, 6-diary1-3-methyl-4-piperidones\textsuperscript{15} was synthesized by Mannich reaction of ethylmethylketone, substituted aromatic aldehydes and ammonium acetate.

Oximes or thiosemicarbazone derivatives\textsuperscript{15} were synthesized and confirmed by IR, $^1$H, $^{13}$C NMR and Mass Spectral data. They were tested for antifungal activity against A. Niger and Candida Albicans.

\[
\text{CHO} + \text{OHC CH, COONH,} \xrightarrow{\text{NH}_{2}\text{HNCSNH}_2} \text{OCH, COC,H,} \xrightarrow{\text{R,} = \text{H, OCH,} \text{R,} = \text{H, CH, OCN, N(CH,)}, \text{R,} = \text{H, OCH,} \text{R,} = \text{cl, OH}}
\]

Conformational studies of substituted piperidones was discussed by Pandiarajan and Christopher\textsuperscript{140} using $^{13}$C & $^1$H NMR studies.
Mass Spectral Studies

Sun, Zhang and Zhang\textsuperscript{141} reported the mass spectral studies on condensed heterocycle compounds.
Patil et al.\textsuperscript{142}, discussed the mass spectral fragmentation of substituted Indones.
Mass spectrometric studies of some spiro heterocyclic compounds were discussed by Padmavathi and Reddy\textsuperscript{143}.

\begin{align*}
1 \; X &= \text{CO} \quad ; \; \text{Ar} = \text{C}_6\text{H}_4-\text{OCH}_3 \; (P) \\
4 \; X &= \text{SO}_2 \quad ; \; \text{Ar} = \text{C}_6\text{H}_5
\end{align*}
Younus and others\textsuperscript{144} reported the mass spectral fragmentation of thiosemicarbazones of some typical aliphatic, alicyclic and aromatic aldehydes and ketones, using high resolution mass spectrometry supplemented by deuterium labeling.

\begin{align*}
\text{N} \rightarrow \text{N} \rightarrow \text{C} \rightarrow \text{NH}_2 & \\
\text{a-cleavage} & \\
\text{CH}_2 & \\
\text{N} \rightarrow \text{N} \rightarrow \text{C} \rightarrow \text{NH}_2 & \\
\text{0.1'} & 3 & \\
\text{N} \rightarrow \text{C} \rightarrow \text{H} & \\
\text{H} & \\
\text{p', m/e 128} & \\
\text{CH} & \\
\text{p, m/e 128} & \\
\text{CH}_2 & \\
\text{CH} & \\
\text{CH} & \\
\text{CH}_2 & \\
\text{CH} & \\
\text{CH} & \\
\text{CH}_2 & \\
\text{q, m/e 115} & \\
\end{align*}

Aldous and Bowie\textsuperscript{145} reported the skeletal rearrangement fragments in the mass spectra of 3,5-diphenylisoxazole and 3,5 diphenyl pyrazole.
Compernolle et al\textsuperscript{146} have discussed the mass spectral structure elucidation of substituted 4-oxazolidinones and 2,4-Azetidindiones.

\[ \text{Diagram showing mass spectral structure elucidation} \]

\[ \text{Formula:} \quad m/e\ 169 \quad m/e\ 127 \quad m/e\ 112 \]