CHAPTER - II

BISHETEROCYCLES

INTRODUCTION
Literature survey revealed that when one biodynamic heterocyclic system was coupled with another, a molecule with enhanced biological activities was produced. In view of these reports, under present investigation, it was planned to prepare various bridged bis-heterocycles wherein biologically interesting indole moiety has been linked to different heterocycles such as oxadiazole, triazole, pyrrole, tetrazole, triazine and quinazoline with a scope of obtaining variety of heterocycles endowed with enhanced biological activities

1,3,4-Oxadiazoles

Five membered heterocycles with two carbon atoms, two nitrogen atoms and one oxygen atom are called oxadiazoles. Depending upon the orientation of the nitrogen atoms they are described as 1,2,3-, 1,2,4-, 1,2,5- and 1,3,4-oxadiazoles 80-83.

\[
\begin{align*}
\text{1,3,4-Oxadiazoles} & \\
\text{80} & \quad \text{81} & \quad \text{82} & \quad \text{83}
\end{align*}
\]

The 1,3,4-oxadiazole is thermally stable aromatic nucleus with many uses as biologically active ingredients in medicine and agriculture, as dye stuff, UV absorbing and fluorescent materials, heat resistant polymers and scintillators. The 1,3,4-oxadiazoles have been shown to possess muscle relaxant, tranquilizing and antitubercular\textsuperscript{127,128}, leprostatic and tuberculostatic\textsuperscript{129} hypoglycemic\textsuperscript{130,131}, herbicidal\textsuperscript{132}, antiviral\textsuperscript{133}, amoebicidal\textsuperscript{134} and insecticidal\textsuperscript{135} activities. Some 1,3,4-oxadiazoles have been patented as dyestuffs particularly in anthraquinone vat dyes\textsuperscript{136} and azo dyes\textsuperscript{37}. Various substituted 1,3,4-oxadiazoles 84 prepared by Buguet et al\textsuperscript{138} were shown to possess analgesic, antiinflammatory, anticonvulsant, tranquilizing, muscle relaxant, hypotensive, bronchodilator, diuretic, antiulcer, antiarrhythmic, antiemetic anticholinergic and antidepressant properties.
2-(Dialkoxyphosphinylthiomethyl)-5-alkoxycarbonyl-1,3,4-oxadiazole 85 were reported\textsuperscript{139} to be effective against house-flies and cockroaches.

\begin{equation}
\mathrm{H}_2\mathrm{C}_2\mathrm{OOC} \quad \mathrm{O} \quad \mathrm{CH}_2\mathrm{S} \quad \mathrm{P} \quad \mathrm{R}
\end{equation}

\begin{align*}
R &= (\mathrm{OCH}_3)_2, \ (\mathrm{OC}_2\mathrm{H}_5)_2
\end{align*}

Ramlingam and coworkers\textsuperscript{140} have synthesised 2,5-disubstituted-1,3,4-oxadiazoles 86 and evaluated their antiinflammatory, CNS depressant and antihypertensive activities.

\begin{align*}
R = \mathrm{NH}_2, \mathrm{SH}; \ R_1, R_3, R_4 = \mathrm{H}, \mathrm{CH}_3; \ R_2 = \mathrm{H}, \mathrm{Cl}
\end{align*}

Symmetrical 2,5-disubstituted-1,3,4-oxadiazoles 87 synthesised by Sharma and coworkers\textsuperscript{141} were screened for CNS depressant and anticonvulsant activities.
An U.S. patent\textsuperscript{142} described the synthesis and psychotropic activity of 1-(3-chlorophenyl)-4-(1,3,4-oxadiazol-2-yl)alkylpiperazine 88.

\[
\begin{array}{c}
\text{\raisebox{.5em}{\includegraphics[width=.3\textwidth]{88.png}}}
\end{array}
\]

\[R = \text{C}_{1-4}\text{-Alkyl, CF}_3, \text{C}_2\text{F}_5; n = 3, 4.\]

Recently, Hiremath and coworkers\textsuperscript{143} have synthesized several 1,3,4-oxadiazolyl indole derivatives 89 and screened them for their antimicrobial activity, oxytocic activity and catatonic activity.

\[
\begin{array}{c}
\text{\raisebox{.5em}{\includegraphics[width=.3\textwidth]{89.png}}}
\end{array}
\]

\[R_1 = \text{C}_6\text{H}_5, \text{C}_6\text{H}_4\text{-Cl} (p), \text{C}_6\text{H}_4\text{-CH}_3 (o), \text{C}_6\text{H}_4\text{-CH}_3(p)\]

L. J. Street and coworkers\textsuperscript{144} have synthesised several 5-(oxadiazolyl) tryptamines 90 and reported their 5-HT\textsubscript{1D} receptor activity.

\[
\begin{array}{c}
\text{\raisebox{.5em}{\includegraphics[width=.3\textwidth]{90.png}}}
\end{array}
\]

\[n = 0, 1, 2 \text{ or } 3; R = \text{Me or C}_2\text{H}_5; R_1 = \text{H or Me}\]
The length of linking chain (n), and the amine substituents are explored and revealed a large binding pocket in the 5HT₁D receptor domain.

Antibacterial and CNS depressant activities were exhibited by 2-alkyl-3-substituted indole derivatives of 1,3,4-oxadiazoles. Gadaginamath and associates have reported the synthesis and antimicrobial activity of (oxadiazolyl)phenyl-furymethoxyindole 91.

![Chemical structure of 91](image)

Ebeid and associates have synthesised the type 92 and their amino derivatives. They were found to possess analgesic antipyretic and antiinflammatory activities.

![Chemical structure of 92](image)

Omar et al have prepared the following oxadiazole derivatives 93 and screened for their antiinflammatory activity.

![Chemical structure of 93](image)

R= m-pyridyl, R¹ = ethyl, R = m-pyridyl, R¹ = phenyl, R = p-pyridyl, R¹ = ethyl, R = quinolinyl, R¹ = cyclohexyl
R= (CH₃)₂CHCH₂C₆H₄CH(CH₃)₂ and R¹ = cyclohexyl.
Oxadiazole derivatives 94 showed insecticidal and fungicidal activities.\[146\]

\[\begin{align*}
\text{Cl-}\quad \text{Cl} \\
\text{N} \quad \text{N} \\
\text{R} \\
\end{align*}\]

94

Mandour et al\[147\] have reported the synthesis of oxadiazoles 95 as antimicrobial, antiaflatoxigenic agents.

\[\begin{align*}
\text{R} \\
\text{CH} = \text{CH} \\
\text{O} \\
\text{R}_1 \\
\end{align*}\]

95

\[X = \text{NH, S, O ; R = NO}_2; \text{Et}_2\text{NSO}_2, \text{piperidinosulfonyl, morpholinosulfonyl, R}^1 = \text{SH, NH}_2\]

Gadaginamath and et al\[148\] have synthesised cis-3,6-bis [4-(5-mercapto-1,3,4-oxadiazol-2-ylmethoxy)benzyl] piperazine-2, 5-dione 96.

\[\begin{align*}
\text{H} \\
\text{N} \\
\text{O} \\
\text{H}_2\text{C-O-} \\
\text{N} \\
\text{CH}_2 \\
\text{O-CH}_2 \\
\text{N} \\
\end{align*}\]

96

Zhang and associates\[149\] have reported the synthesis and larvicidal activity of 5-aryloxadiazole 97.
Schoenafinger and et al.\textsuperscript{150} reported the synthesis of 3-phenyl-5-alkoxy-1,3,4-oxadiazol-2-one 97 and as its inhibitor of hormone sensitive lipase.

\[
\begin{align*}
R_1 &= \text{(Substituted) alkyl, cycloalkyl;} \\
R_2-R_5 &= \text{H, halo, alkyl,} \\
&\hspace{1cm}\text{alkoxy, (substituted) PhCH}_2\text{O, aryloxy, aryl, cycloalkyl.}
\end{align*}
\]

Miyazaki and et al.\textsuperscript{152} showed (E)-1-(5-tert-butyl-1,3,4-oxadiazol-2yl)-3-methyl-2-(methoxyimino)-butan-1-one 99 as elastase inhibitor.

Dhiman and coworker\textsuperscript{152} synthesised pyrazolyloxadiazole 100 and screened them for antimicrobial activity.
Mogilaiah and associates\textsuperscript{153} have reported the synthesis and antimicrobial activity of naphthyridinyl-1,3,4-oxadiazole 101.

![Chemical structure of 101]

R= benzyl, styryl, phenyl.

Chen-Hangson et al\textsuperscript{154} showed the fungicidal activity of 2-alkythio-5-pyrazolyl-1,3,4-oxadiazole 102.

![Chemical structure of 102]

Srivastava and associates\textsuperscript{155} reported the fungitoxicity of 2-amino-[5-(substitutedphenoxy)methyl]-1,3,4-oxadiazoles 103 against \textit{Aspergillus niger} and \textit{Helminthosporium oryzae}. 

44
Berghot M. A.\textsuperscript{156} have reported the synthesis and antibacterial activity of oxadiazolylidiazepam \textbf{104}.

Krasovskii and et al\textsuperscript{157} have synthesised 5-aryl-1,3,4-oxadiazol-2-thione \textbf{105} as antibacterial agent.

Shah and Bhat\textsuperscript{158} have reported the synthesis, antimicrobial and anticancer activities of oxadiazole \textbf{106}. 

\begin{align*}
R_1 &= R_2 = \text{H, Cl, Me}; R_3 = \text{H, Me} \\
\text{Berghot M. A.}^\text{156} &\text{ have reported the synthesis and antibacterial activity of oxadiazolylidiazepam} \textbf{104}. \\
\text{Krasovskii and et al}^\text{157} &\text{ have synthesised 5-aryl-1,3,4-oxadiazol-2-thione} \textbf{105} \text{ as antibacterial agent.} \\
\text{Shah and Bhat}^\text{158} &\text{ have reported the synthesis, antimicrobial and anticancer activities of oxadiazole} \textbf{106}. 
\end{align*}
Dogan and associates\textsuperscript{159} have synthesised and studied anti-
convulsant activity of 2-(3-acetyloxy-2-naphthyl)-4-acetyl-5-substituted-1,3,4-
oxadiazoline \textbf{107}.

\begin{center}
\begin{align*}
\text{N} & \text{N-CO-CH}_3 \\
\text{O} & \text{R} \\
\text{O} & \text{C-CH}_3 \\
\end{align*}
\end{center}

\textbf{107}

Qian et al\textsuperscript{160} have reported the insecticidal activity of 2-(2,4-dichloro-
5-fluorophenyl-5-(fluorophenoxymethyl)-1,3,4-oxadiazole \textbf{108}.

\begin{center}
\begin{align*}
\text{Cl} & \text{N} \text{N} \\
\text{Cl} & \text{O} \\
\text{CH}_2 \text{O} & \text{F} \\
\end{align*}
\end{center}

\textbf{108}

Satyanarayana Rao and associates\textsuperscript{161} have reported the biological 
activity of 2-(4-pyridyl)-4-arylaminomethyl-1,3,4-oxadiazoline-5-thione \textbf{109}.

\begin{center}
\begin{align*}
\text{N} & \text{N-CH}_2 \text{NH} \\
\text{O} & \text{S} \\
\text{N} & \text{O} \\
\text{N} & \text{C} \\
\end{align*}
\end{center}

\textbf{109}

Vaidya et al\textsuperscript{162} have reported the synthesis, analgesic and anthelmintic 
activities of 1,3,4-oxadiazolyl-aminonaphtho[2,1-b]furans \textbf{110}.

46
Rai and associates\textsuperscript{163} reported the synthesis and antimicrobial activity of 2,5-disubstituted 1,3,4-oxadiazoles \textbf{111}.

![Image of 111]

Parekh and et al\textsuperscript{164} reported the synthesis and antitubercular activity of 2-aryl-5-[2-(benzimidazol-2-yl)phenyl]-1, 3, 4-oxadiazole \textbf{112}.

![Image of 112]

R= aryl, haloaryl etc.

Singh et al\textsuperscript{165} reported chloramine-T mediated synthesis and antimicrobial activity of 2-benzothiazolyl-5-aryl-1,3,4-oxadiazole \textbf{113}.

![Image of 110]
Shah and coworkers\textsuperscript{166} have reported the synthesis and antimicrobial activity of 2-aryl-5-\(p\)(nicotinamidophenyl)-1,3,4-oxadiazole 114.

Joshi et al\textsuperscript{167} reported the synthesis of 2-aryl-5-(5,7-diiodo-8-quinolox)-1,3,4-oxadiazole 115.

Dubey and associates\textsuperscript{168} have reported the synthesis and antifungal activity of 5-(3,5-diphenylpyrazol-4-yloxymethyl)-2-(4-oxo-2-substituted-phenyl-3-thiazolidinyl)-1,3,4-oxadiazole 116.
1,3,4-oxadiazoles were prepared by different methods\textsuperscript{169} and out of them the methods framed by Hoggarth,\textsuperscript{170} Anisworth\textsuperscript{171}, Silberg and Cosa\textsuperscript{172} have been adopted in the present investigation.

**Triazoles:**

Triazoles are five-membered heterocycles with three nitrogen and two carbon atoms. The two possible combinations of these atoms account for vicinal triazole (1,2,3-triazoles) and symmetrical triazoles (1,2,4-triazoles).

**1,2,3-Triazoles**

\[
\begin{align*}
\text{1H-1,2,3-triazole} & \leftrightarrow \text{2H-1,2,3-triazole} \\
117
\end{align*}
\]

**1,2,4-Triazoles**

\[
\begin{align*}
\text{1H-1,2,4-triazole} & \leftrightarrow \text{4H-1,2,4-triazole} \\
118
\end{align*}
\]
3-Amino-1,2,4-triazole was the first symmetrical triazole to be manufactured on large scale for the use as neutral herbicide and defoliant of cotton. Simple 1,2,4-triazoles exhibited wide spectrum of biological activities such as inhibition of cholinesterase; interference with mitosis and reversible denaturation of serum proteins. Several alkyl and aryl derivatives of mercaptotriazole were also reported to be active against bacteria and fungi.

Medne et al. have studied the tuberculostatic activity of triazoles and reported that tuberculostatic activity of these compounds increased with the increase in the magnitude of the total planar surface area of the molecule, whereas decrease in the basicity of amino derivatives of triazoles reduced the tuberculostatic activity. Tuberculostatic activity of triazoles was also decreased appreciably when the hydrogen atom of the amino group was replaced by alkyl group.

Burch and Smith reported that 5-(5-nitro-2-furyl)-3-alkyl-1,2,4-triazoles exhibited broad antibacterial activity in vitro against both Gram positive and Gram negative bacteria. It was noted that lengthening of the carbon chain at position-3 in triazoles caused a decrease in activity.

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Akerblom and Campbell prepared a series of 5-(5-nitro-2-furyl)-1,2,4-triazoles and evaluated them for their urinary tract antibacterial activity. Most of the compounds have showed higher antibacterial activities than nitrofurantoin especially against Gram negative bacteria.
Fauran and associates\textsuperscript{180} studied anticholinergic bronchodilatory, antidepressive, analgesic, antihypotensive, vasodilatory, antiinflammatory, cardiac stimulatory, diuretic and antihypertensive properties of triazole methanols, \textbf{122}.

A few 5-mercapto-4-amino-1,2,4-triazoles \textbf{123} displayed bactericidal, herbicidal, antispasmodial and diuretic activities\textsuperscript{161}.

A series of 3-substituted-4-amino-5-mercapto-1,2,4-triazoles\textsuperscript{182} \textbf{124} were synthesised and tested for their antimicrobial, analgesic and antiinflammatory activities. All these compounds displayed low toxicity [LD\textsubscript{50}>800 mg /kg] and antimicrobial activity. Some of them showed antiinflammatory activity.
Several 4-amino-1,2,4-triazolin-5-thione derivatives 125 were reported to be good pharmaceutical agrochemicals and photographic coupler intermediates.\textsuperscript{183}

\begin{equation}
\text{R} = \text{alkyl, alkenyl, cycloalkyl, aryl, heteroaryl}
\end{equation}

Goswami et al.\textsuperscript{184} synthesized 3-(2,4-dichlorophenyl)-4-amino-1,2,4-triazole-5-thiol 126 and other 5-thiotriazoles 127 and 128 and they were screened \textit{in vitro} for antibacterial against \textit{Bacillus subtilis}, \textit{Bacillus cereus}, \textit{Escherichia coli} and \textit{Pseudomonas solanarium}. The 4-amino triazole 125 showed the highest inhibitory effect against all the test organisms.

\begin{equation}
\text{R} = (\text{Un})\text{substituted phenyl}
\end{equation}
Hiremath et al. synthesized 3-(1,2,4-triazolyl)aminoindoles 129 and evaluated their antimicrobial activities.

Kadry and coworkers prepared a series of 5-triazolylindole derivatives 130 and reported their antiinflammatory activities.

Miller has reported that 5-aryl-4-alkyl-3H-1,2,4-triazole-3-thione of the type 131 is useful as memory enhancer.
Meenakshi et al\textsuperscript{188} have synthesized and evaluated the indolyl-1,2,4-triazoles of the type 132 \textit{in vitro} for their ability to exhibit monoamine oxidase, \textit{in vivo} for their anticonvulsant and analgesic activities in rats.

\begin{center}
\includegraphics[width=0.8\textwidth]{131.png}
\end{center}

R\textsubscript{1} = H, Ph

Recently, Ratnakar and associates\textsuperscript{189} have synthesised and reported antimicrobial activities of 5-heteroaryl-3-thio-4-amino-1,2,4-triazoles of the type 133.

\begin{center}
\includegraphics[width=0.8\textwidth]{132.png}
\end{center}

R = 4-methylcoumarin-7-yl-oxyethyl, 4-pyridyl, benzoxazol-2-y1thiomethy1, etc. R\textsubscript{1} = H, Me, Et, Ac

El-diwani and coworkers\textsuperscript{190} have synthesised the 1,2,4-triazole derivative of the type 134 and reported their anticonvulsant and analgesic activities.
activities. They have found that 134 (R = Et) are more active than the anticonvulsant drug diphenylhydantion.

Matassa et al\textsuperscript{191} have prepared indolyl-1,2,4-triazole derivatives of the type 135 and reported their 5-HT\textsubscript{1} like receptor activity and it was also found that they were useful in the treatment of migraine and associated disorders.

Ashiskumar and William\textsuperscript{192} have prepared triazoles of the type 136 which possess farnesyl-transferase inhibiting property.
Feng and associates\textsuperscript{193} have synthesised 1-[2-(benzylmethylamino)-2-(2,4-dichlorophenyl)ethyl]-1H-1,2,4-triazoles 137 and screened them for antifungal activity.

\begin{center}
\includegraphics[width=0.5\textwidth]{137.png}
\end{center}

R = H, 4-F, 4-CN

Atsushi et al\textsuperscript{194} have reported the synthesis and fungicidal activity of triazolylmethylcyclopentyl ethers 138.

\begin{center}
\includegraphics[width=0.5\textwidth]{138.png}
\end{center}

R\textsubscript{2}, R\textsubscript{3} = H, alkyl, R\textsubscript{1} = alkyl.

Sharma\textsuperscript{195} has synthesised and patented 1-substituted-(4-aminophenyl)-triazoles 139 as antiinflammatory agents.
$R_1, R_2 = \text{same or different, CF}_3, \text{halo, CN, (Un)branched C}_{1,8}-\text{alkyl, (Un)branched C}_{1,8}-\text{alkenyl, C}_{3,8}-\text{cycloalkyl optionally substituted with OH, CN, OMe, C}_{1,4}-\text{alkoxyalkyl, C}_{1,8}-\text{alkylthio, C}_{1,8}-\text{dialkylamino}, L = NH \text{C(O), NHCO(O)O, R}_3 = \text{C}_{1,8}-\text{alkyl, C}_{1,8}-\text{alkoxy.}}$

Song Bao et al\textsuperscript{196} have constructed phosphorodithioate containing 1,2,4-triazole moiety \textsuperscript{140}.

\begin{center}
\includegraphics{140}
\end{center}

$R_1 = \text{Me, Et, i-Pr}$

$R_2 = \text{Me, Et, i-pr, 4-Cl C}_6\text{H}_4, 4-\text{CH}_3\text{C}_6\text{H}_4$.

Kiraz and associates\textsuperscript{197} have synthesised some 3-thioxo/alkylthio-1,2,4-triazoles with substituted thiourea as possible antimycobacterial agents \textsuperscript{141, 142}.

\begin{center}
\includegraphics{141}
\end{center}
Wadodkar et al. have synthesised pyrazolyltriazoles of the type \[ \text{143} \]
and screened them for antimicrobial activity against *S. aureus*, *S. typhi* and *S. dysenteriae*.

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

142

Zappala-Maria and associates have synthesised 5-amino-pyrazolo[4,3-e]1,2,4-triazolo [1,5-c ]pyrimidines \[ \text{144} \] as adenosine A\text{_{2a}} receptor antagonist, which are useful in the treatment of Parkinson disease.

\[
\begin{array}{c}
\text{R}_2 \\
\text{R}_1 \\
\text{R}_3 \\
\text{NH} \\
\text{NH}_2 \\
\text{SH} \\
\text{N} \\
\text{N} \\
\text{N} \\
\text{N} \\
\end{array}
\]

143

\[
\begin{array}{c}
\text{NH}_2 \\
\text{Z} - Y - X - N \\
\end{array}
\]

144

\[ X = \text{COCH}_2, \text{alkylene}, Y = \text{O, S, CH}_2\text{S}, (\text{CH}_2)_2\text{NH}, \text{etc}; Z = \text{(Un) substituted Ph, phenylalkyl, heteroaryl, etc} \text{ Z and Y together are substituted piperidinyl or phenyl}. \text{R = (Un) substituted Ph, heteroaryl.} \]
Dobosz et al. have prepared bistriazoles of the type 145 and studied their effects on central nervous system.

\[
\text{HN}\text{-N} \text{-NH}
\]
\[
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{N} \\
\text{H} \\
\text{CH}_2 \\
\text{N} \text{-NH}
\end{array}
\]

145

Camden and associates have showed the use of 1H-1,2,4-triazoles 146 in the treatment of cancer, and viral infection.

\[
\begin{array}{c}
\text{N} \\
\text{N} \\
\text{H}
\end{array}
\]

146

Faming et al. have synthesised triazolyl propanols 147 as antifungal agents.

\[
\begin{array}{c}
\text{N} \\
\text{N} \\
\text{CH}_2 \\
\text{OH} \\
\text{CH}_2 \\
\text{N} \\
\text{CH}_2 \\
\text{N} \\
\text{H}
\end{array}
\]

147

\[R = \text{H}, 2-\text{F}, 3-\text{F}, 3-\text{Br}, 3-\text{CH}_3, 4-\text{F}, 4-\text{Cl}, 4-\text{Br}, 4-\text{NO}_2, 4-\text{CN}, 4-\text{Et.}\]

Berghot has reported the synthesis and antibacterial activity of diazepam containing triazole moiety 148.
Yoshiro et al.\textsuperscript{204} have synthesised some optically active antifungal triazoles of the type 149.

Liu and coworkers\textsuperscript{205} reported the synthesis of \textit{l-}(\textit{lH}-1,2,4-triazol-1-\textit{yl})-3-\textit{piperazinopropan-2-ol} 150, as antifungal agents.

Shimada and associates\textsuperscript{206} have synthesised \textit{[1,2,4]triazolo[1,5-c]} pyrimidine 151 as adenosine A\textsubscript{2A} receptor antagonists.

X = H, alkyl; M = H, OH, COOR; Ar = (un) substituted piperazino.
Kawanishi and coworker\textsuperscript{207} have synthesised sulfoximine containing triazole 152 as a potent antifungal agent.

Mahajanshetti and Khazi\textsuperscript{208} have reported the synthesis and antibacterial activity of 2-alkyl-6,6-dimethyl-8-oxo-5,6,7,8-tetrahydro-s-triazolo[3,2-b]-benzothiazoles 153.

Kilpatrick and Ian Charles\textsuperscript{209} synthesised 1,2,4-triazolo[1,5-a]pyrimidines 154 possessing antiobesity activity.
R₁ = H, C₁₋₆-alkyl R₂, R₃, C₁₋₆-alkylthio, C₁₋₆-alkoxy,
R₄ R₅ = H, C₁₋₆-alkyl, R₆, R₇, R₈ = H, halo, OH, mercapto C₁₋₆-alkanoyl.

Synthesis of 1, 2, 4-triazoles:

Several methods are available for the synthesis of various triazoles. In the present investigation, method due to Reid and Heindel was adopted.

Pyrroles:

Pyrrole 155 is a five membered ring system with one nitrogen atom and four carbon atoms which occurs in bone oil, ccal tar and products derived from proteins. It is one of the most ubiquitous heterocycles in the plant and animal kingdom because of its participation as a subunit of chlorophyll and the haem. Biosynthetically related vitamin B₁₂ is a tetrapyrrole. A number of antibiotics are also derivatives of pyrrole. The indole ring system, in which pyrrole is fused to benzene ring, is widespread in nature and it is also present in the tryptophan, serotonin, many alkaloids and indigo.

Several compounds containing pyrrole nucleus have been used as antitumors, analgesics, antiinflammatory and antiallergic and...
photographic emulsion\textsuperscript{216} agents. The derivatives of 2,5-dimethylpyrroles are also known to exhibit antiulcer\textsuperscript{217} and hypotensive activities.

A Japanese patent\textsuperscript{218} has reported the synthesis of pyrrole derivative of the type 156, 157 and their usefulness as one of the components of rice and paddy microbicide compositions.

![Chemical structure of 156](image1)

![Chemical structure of 157](image2)

De Micheli and coworkers\textsuperscript{219} have reported synthesis of aminopropionyl pyrrole derivatives which showed central nervous system stimulant activity.

Genda and associates\textsuperscript{220} have synthesised 3-phenyl-4-cyanopyrroles which are used as intermediates for medicines and agrochemicals. Massa et al\textsuperscript{221} have described the synthesis and pharmacological activity of arylthiophenacetic acids containing a pyrrole group. These compounds have exhibited greater analgesic activity than indomethacin and their antiinflammatory activity was found to be less than that of indomethacin.

An European patent\textsuperscript{222} described the preparation of (pyrrolealkenyl) mevalonates 158 and their hypolimpemic and antiatherosclerotic properties.

![Chemical structure of 158](image3)

![Chemical structure of 159](image4)
Toja and associates\textsuperscript{223} have reported the synthesis of 1-benzenesulphonyl-5-butoxy-1,5-dihydropyrrol-2-one 159 and it was found to be better memory enhancer than the known memory enhancer piracetan at 50 mg/kg orally (5.4 times as active as piracetan in mice).

An U.S. patent\textsuperscript{214} has described the synthesis of 1,5-disubstituted pyrrolidin-2-ones 160 which were used in treating memory dysfunction characterized by decreased cholinergic function.

\[
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{R}_1 \\
\text{R}_2 \\
\text{R}_3 \\
\end{array}
\]

160

\begin{align*}
R_1 &= \text{alkoxycarbonyl, } \text{CH}_2\text{OH, } \text{CONR}_3\text{R}_4 \\
R_2 &= \text{CH}_2-\text{CH} = \text{CH}_2, \text{C}_6\text{H}_5-\text{CH}_2, \text{CH}_2-\text{C} = \text{CH}, \text{CH}_2-\text{C} = \text{C-CH}_3 \\
R_3, R_4 &= \text{H, aralkyl,}
\end{align*}

Taniguchi and coworkers\textsuperscript{225} prepared 5-tridecylpyrrol-3-carboxylic acids 161 and these pyrrole derivatives reduced serum triglycerides and cholesterol by 46\% and 70\% respectively when administered 30 mg/kg/day orally for eight days in rats.

\[
\begin{array}{c}
\text{R}_1 \\
\text{R}_3 \\
\text{N} \\
\text{COOR}_2 \\
\text{R}_2 \\
\end{array}
\]

161

\begin{align*}
R_1, R_3 &= \text{H, C}_{5.25} \text{ alkyl or alkenyl} \\
R_2 &= \text{H, C}_6\text{H}_5 \text{ (un)substituted C}_{1.10} \text{ alkyl}
\end{align*}

Tamato and associates\textsuperscript{225} reported the synthesis of 1-acyl-2-((1-hydroalkyl)pyrrolindines and (N-acylpyrrolidinyl)acetates and these compounds were useful as psychonaleptic agents. Preparation of pyrrole
aldehyde derivatives and their application in treating brain disorders were also reported in the literature\textsuperscript{227}. The 2,5-dimethylpyrroles\textsuperscript{162} were prepared by Lambellin and coworkers\textsuperscript{225} and these were used as analgesic, antiphlogistics and antipyretics.

\[ R = \text{Substituted phenyl, } \text{CH}_2\text{CH}_2\text{C}_6\text{H}_5, \text{cyclohexyl and 2-pyridyl} \\
R_1 = \text{CH}_2\text{COOH and CH} \ (\text{CH}_3) \text{ COOH.} \]

A German patent described\textsuperscript{229} the synthesis of 2,5-dimethylpyrroles of the type 163 which were useful as antihypertensive, antiarrhythmics and also as drug for all the treatment of angina pectoris.

\[ R = \text{NHCH} (\text{CH}_3)_2, \text{NHC(CH}_3)_3, \text{morpholino.} \]

Vollenberg and Beckmann\textsuperscript{230} prepared several 2,5-dimethylpyrroles 164 which exhibited anticholesteremic activity.

\[ R = \text{Cl, NO}_2, \text{F, Br, I} \]
The pyrrolesulfonamide 165 was prepared by Budzinski\textsuperscript{231} and it
displayed herbicidal activity at 0.4 kg/ha pre or post emergence.

Hussain and Srivastava 165 synthesised a number of N-aryloxy-(or thio)
acetamide-2,5-dimethylpyrroles 166 and studied their hypoglycemic and CNS
activities. Some of these compounds were found to be CNS stimulants and
relatively nontoxic in albino mice.

\[
\begin{array}{c}
\text{CH}_3 \\
\text{NH} \quad \text{COCH}_2 \quad \text{X} \quad \text{Ar} \\
\text{CH}_3 \\
\end{array}
\]

166

\(\text{Ar} = \text{p-tolyl, o-tolyl, p-chlorophenyl, 2,4-dichlorophenyl, p-nitrophenyl,}
\text{p-acetamidophenyl, } \alpha \text{ or } \beta\text{-napthyl, } X = \text{O, S}\)

Several 2,5-dimethylpyrroles 167 were prepared and tested for their
antiinflammatory activities by Ramalingam et al\textsuperscript{233,234}. All these pyrroles bearing
3-pentadecylphenyl (3-PDP) were devoid of toxicity and showed significant
antiinflammatory activity. Similar results were also observed with 1-\(\alpha\)-(3'-
pentadecylaryloxy)isobutaramido-2,5-dimethylpyrroles.
Murthy et al.\textsuperscript{235} have prepared pyrroles of the type \textbf{168} possessing antiviral and antineoplastic activity.

\begin{align*}
\text{R, R}_2, R_3 &= \text{H, Cl} \quad \text{R}_1 = \text{CH}_3, C_{15}H_{31} \\
\end{align*}

Aydogan Feray\textsuperscript{235} has synthesised derivatives of pyrroles \textbf{169} and reported their antimicrobial and tuberculostatic activities.

\begin{align*}
\text{R}_1 &= \text{H, Me, Et, CH}_2\text{Ph, COMe} \quad \text{R}_2 = \text{H, C}_1\text{.}_2\text{-alkyl, CH}_2\text{Ph, 2-tetrahydropyranyl} \\
\text{R}_3 &= \text{H, C}_1\text{.}_4\text{-alkyl, Ph, R}_{16} = \text{R}_{17} = \text{H, m = 1}-5. \\
\end{align*}

Green Jeremy et al.\textsuperscript{237} have reported the synthesis of 4-(1H-pyrazol-3-yl)-1H-pyrrole-2-carboxylic acid derivative \textbf{170} as inhibitors of ERK useful for treating disease states in mammals that are alleviated by a protein kinase
inhibitor. Particularly diseases such as cancer, inflammatory disorders and cardiovascular disease.

\[ \text{R}_2 = \text{H}, \text{CN}, \text{halo}; \text{R}_1 = \text{Halo, T= a bond linker group q = CO, R}_4 = \text{NHCH}_2\text{Ph} \]

Tang Peng and associates\textsuperscript{238} have synthesised pyrrolylactoneindolinone 171 as antineoplastic agents.

\[ \text{Biava et al}^{239} \text{ have prepared pyrrole derivatives of the type 172 and reported their antimycobacterial activity.} \]

\[ \text{172} \]

\[ X = Y = \text{Cl, } Z = \text{H, Me} \]
Przewosmy and coworkers\textsuperscript{240} have prepared 1,5-dihydropyrrol-2-ones \textsuperscript{173} as pain killer.

\[ \text{\( R_1 = H, R_2 = R_3 = \text{H, F, Cl, Br, CF}_3 R_4 = \text{H, OH, R}_5 \text{ and } R_6 = \text{H, OH.} \)} \]

Waly\textsuperscript{241} has prepared 4,6,7,8,-Tetrahydropyrrolo[2,3-d]azepine\textsuperscript{174} with interesting pharmacological properties.

Eskova et al\textsuperscript{242} have prepared pyrroles of the type \textsuperscript{175} possessing photosensitising property.
The derivatives of 2,5-dimethylpyrroles were also known to exhibit antisecretory\textsuperscript{243} and antulcer\textsuperscript{244}, nematocidal\textsuperscript{245} activities and some of these were also used as antioxidants and cosmetic materials\textsuperscript{246}.

Several methods for the synthesis of pyrrole derivatives are known\textsuperscript{247} and in the present investigation, we have adopted the Paal-Knorr\textsuperscript{248} synthesis.

**Tetrazoles**:

Five membered heterocycles with four nitrogen atoms and one carbon atom are called tetrazoles. Tetrazole itself is an aromatic azapyrrole nucleus which may exist in the following tautomeric forms.

\begin{align*}
\text{N} & \text{N} \\
\text{N} & \text{N} \\
\text{H} & \text{N}
\end{align*}

Tetrazoles\textsuperscript{249,250} possess metabolically stable acidic functions having comparable acidity as that of corresponding carboxylic acids. Hence, biological activity observed in various substituted carboxylic acids might also be expected in the corresponding tetrazole compounds with longer duration of activity. Retention of activity by tetrazole analogues of known carboxylic acid counterparts was observed in the antiinflammatory\textsuperscript{251}, hypocholesterolemic\textsuperscript{252}, antiinfective\textsuperscript{253} and antiallergic\textsuperscript{254} areas. In contrast, tetrazole analogues of active estrogenic acids\textsuperscript{255}, and antiarrhythmic agents\textsuperscript{256} displayed loss or considerable decrease of biological activity.

The active research in the area of tetrazoles began since the application of L-substituted-5-aminotetrazole for clinical purposes. Gross and Featherstone\textsuperscript{257} described central nervous stimulatory effect of 1-(or 5-)alkyl-5-(or 1)-aminophenyl tetrazoles. Inserting CH\textsubscript{2} between amino group and the ring decreased the stimulant action and increased the hypnotic and anaesthetic action, the optical structural factors\textsuperscript{258} for central nervous stimulation activity
appeared to be the presence of a large alkyl or phenylalkyl group in the 1-position and a small group on the 5-amino function. The 5-amino-1-phenyl tetrazole was found to be effective in patients with rheumatoid arthritis. Further, it was clinically investigated as an antiinflammatory agents\textsuperscript{259}.

With a hope of finding lipolysis inhibitory activity, a series of pyridyltetrazoles\textsuperscript{260} were prepared. These compounds were screened for their ability to inhibit the norepinephrine induced release of free fatty acids (FFA) from isolated rat adipose tissue and also for their ability to depress the fasting plasma FFA levels in the dog. The most active lipolysis inhibitor was 5-(3-pyridyl)tetrazole 177.

\[
\begin{array}{c}
\text{R} = 4, 5, 6-\text{CH}_3, 4-\text{CF}_3, 5-\text{F, 2, 6- OCH}_3, 2, 6-\text{SCH}_3, 6-\text{SO}_2\text{CH}_3, 5-6-\text{NH}_2, 6-\text{NH-CO-CH}_3, 5-\text{COOH, 2-OH, H.} \\
\end{array}
\]

A number of 3-(1H-tetrazol-5-yl)chromones 178 were synthesised and they displayed antiallergic activity. In the rat passive cutaneous anaphylaxis test, all these compounds were found active when administered orally in rats.

\[
\begin{array}{c}
\text{R = H, 6-CH}_3, 6-\text{C}_2\text{H}_5, 6-\text{n-propyl, 6-isopropyl, 6-n-butyl, 6-OH,}} \\
6, 8-(\text{CH}_3)_2, 6, 7-(\text{OCOCH}_3)_2, 6, 7-(\text{OH})_2.
\end{array}
\]
Hayao and coworkers\textsuperscript{262} synthesised several 5-dialkylaminoalkyl-tetrazoles and evaluated their antihypertensive activity. Aries\textsuperscript{263} reported the synthesis of aralkyltetrazoles \textbf{179} with analgesic, anticonvulsive, antipyretic, antiinflammatory and antirheumatic activities.

\[
\begin{array}{c}
\text{R} \\
| \text{X} \text{CH}_2, \text{CH} (\text{CH}_3)_2; \text{R} = \text{isobutyl, cyclohexyl, phenyl}
\end{array}
\]

A German patent\textsuperscript{264} has claimed the preparation of 5-(2-phenylamino-3-pyridyl)tetrazoles \textbf{180} and also their use in human therapy especially as antinflammatory agents, analgesics and anaesthetic.

\[
\begin{array}{c}
\text{R} = \text{methyl, ethyl, n-propyl, n-butyl, phenyl, o-, m-, p-tolyl,} \\
\text{o-}, \text{p-} \text{anisyl, p-ethoxyphenyl.}
\end{array}
\]

2-Substituted-5-phenyltetrazoles \textbf{181} prepared by Kishore et al\textsuperscript{265} were tested for their antiinflammatory activity. Some of these compounds also exhibited antiproteolytic activity.

\[
\begin{array}{c}
\text{R} = \text{methyl, ethyl, n-propyl, n-butyl, phenyl, o-, m-, p-tolyl,} \\
o-}, \text{p-} \text{anisyl, p-ethoxyphenyl.}
\end{array}
\]
Synthesis of a series of tetrazolylthiosemicarbazides with possible antiproteolytic activity was reported. In an attempt to develop relatively less toxic and more potent antiinflammatory agent than the presently available ones, a few indanyltetrazoles were synthesised and screened for their antiinflammatory activity. Two of them viz., (n=1) and (n=1) showed antiinflammatory potency close to that of phenylbutazone in both acute and chronic animal test models, these compounds possessed high LD$_{50}$ and high therapeutic index and appreciable analgesic and antipyretic activity.

\[ \text{182} \]

\( \text{a}; X = Y = H, \text{b}; X = \text{OCH}_3, Y = H, X = Y = \text{OCH}_3, n = 0,1. \)

Roderick and associates have reported the synthesis of tetrazolyl benzopyrans which are used in the treatment of disease associated with the altered tone or motility of smooth muscle i.e., smooth muscle relaxant.

\[ \text{183} \]

\( R_2 = \text{H, alkyl}; X = \text{O, NH, S}, R_3 = \text{OH}, R_4 = \text{hydroxyphenyl}. \)

Istvan and coworkers have synthesised several tetrazolyl pyrimidinones derivatives which were found useful as antiallergic and antiulcer agents.
R = H, C1-6 alkyl, C1-6 aryl, halo, OH, R2 = H, C1-6 alkyl
when R = H, R1 = H, C1-6 alkyl or halogen.

3-Tetrazolyl-(benzylamino)-2-phenylpiperidine derivatives 185 were prepared as neurokinin antagonists by Giblin and Sharratt.185

\[
\begin{align*}
\text{184} & \\
R = H, C_{1-6} \text{ alkyl, } C_{1-6} \text{ aryl, halo, } OH, R_2 = H, C_{1-6} \text{ alkyl} \\
\text{when } R = H, R_1 = H, C_{1-6} \text{ alkyl or halogen.}
\end{align*}
\]

A new parental cephalosporin containing tetrazole moiety 186 showed high order of antibacterial activity \textit{in vitro} and \textit{in vivo} against a broad spectrum of clinical isolates. In mouse infection studies using bacterial pathogens, compound 186 also showed protective activity comparable to that of cefazolin and superior to that of cephalothin.

\[
\begin{align*}
\text{185} & \\
R_1 = \text{ alkoxy } R_3 = H, \text{ halo; } R_4, R_5 = H, \text{ Halo, alkyl, alkoxy, CF}_3
\end{align*}
\]

\[
\text{186}
\]
Nohara and coworkers\textsuperscript{272} reported the synthesis of tetrazolylchromone \textbf{187} with antiallergic property and it was found suitable for treating hayfever as well as asthma.

\[ \text{187} \]

McManus and Herbs\textsuperscript{273} prepared tetrazole analogue \textbf{188a} of the natural plant auxin, 3-indolyl acetic acid in which the carboxylic acid was replaced by acidic tetrazole moiety.

\[ \text{188a} \]

A series of 1-substituted 3-(5-tetrazolylalkyl)indoles \textbf{188b}, tetrazole analogues of indomethacin were prepared\textsuperscript{251b} and some of these compounds showed antiinflammatory activity when tested orally in rats.
Indolecarboxamidotetrazoles\textsuperscript{112} tetrazolylpyranoindol-4-one\textsuperscript{274} possessing potent antiallergic activity have been also reported in the literature.

Connor et al\textsuperscript{275} have synthesised some novel benzothiophene, benzo-furan and naphthalene carboxamidotetrazole as potential antiallergenic agents\textsuperscript{189}. Benzothiophenes have also inhibited respiratory burst of human neutrophils. This activity distinguishes, the benzothiophenes from the corresponding benzo-furans, naphthalenes and indoles.

\begin{equation}
\begin{array}{c}
\text{188b}
\end{array}
\end{equation}

n = 0, 1, 2; R\textsubscript{1} = R\textsubscript{2} = H, CH\textsubscript{3}, R\textsubscript{3} = H, OCH\textsubscript{3}, OCH\textsubscript{2}CH\textsubscript{3}, OH, NO\textsubscript{2}, Cl, Br, R\textsubscript{5} = H, Cl, OCH\textsubscript{3}, R\textsubscript{6} = H, F, Cl, CF\textsubscript{3}, OCH\textsubscript{3}. R\textsubscript{7} = H, Cl, Br, CH\textsubscript{3}, CF\textsubscript{3}, OCH\textsubscript{3}, SCH\textsubscript{3}, OCF\textsubscript{3}.

Indolecarboxamidotetrazoles\textsuperscript{112} tetrazolylpyranoindol-4-one\textsuperscript{274} possessing potent antiallergic activity have been also reported in the literature.

Connor et al\textsuperscript{275} have synthesised some novel benzothiophene, benzo-furan and naphthalene carboxamidotetrazole as potential antiallergenic agents\textsuperscript{189}. Benzothiophenes have also inhibited respiratory burst of human neutrophils. This activity distinguishes, the benzothiophenes from the corresponding benzo-furans, naphthalenes and indoles.
Bellioti et al. have prepared tetrazole derivative 190 and reported its pharmacological properties such as anxiolytic, antiepileptic, and analgesic.

Fedynk and associates have reported the hypotensive activity of tetrazole derivative 191.
Takeuchi and coworkers\textsuperscript{278} have synthesised \textit{l}-(3,4-dihydroxyphenyl)-
\textit{lH}-tetrazole 192 as tyrosine phosphatase inhibitor.

Ohnari et al\textsuperscript{279} have synthesised carbamoyltetrazolinones 193 and
reported their herbicidal and fungicidal activities.

Boie, and Heinemann\textsuperscript{250} have reported the pesticidal and fungicidal
activities of tetrazole derivatives 194.
Chan et al\textsuperscript{281} have prepared tetrazoles of the type \textbf{195} as thyroid receptor ligands.

\begin{center}
\begin{picture}(120,80)
\put(10,40){\includegraphics[width=12cm]{195.png}}
\end{picture}
\end{center}

\textbf{195}

$W = \text{O, S, SO, SO}_2 \text{CH}_2, \text{CF}_2 \text{CO, CH(OH)}, (\text{Un}) \text{Substituted NH.}$

$X = \text{O, CH}_2, \text{CH}_2-\text{CH}_2, \text{S, SO, SO}_2 \text{R}_1, \text{R}_2, \text{R}_3, \text{R}_5 = \text{H, halo,}$

$\text{C}_{1-8} \text{ alkyl, C}_{2-12} \text{ alkenyl, C}_{2-12} \text{ alkynyl, halo, cyano.} R_4 = \text{H, (un)}$

$\text{substituted C}_{1-12} \text{ alkyl, R}_5 = \text{OH, C}_{1-6} \text{ alkoxy.}$

Odingo and coworkers\textsuperscript{262} have synthesised 3-tetrazolylpyrrolidines \textbf{196} as specific phosphodiesterase inhibitors.

\begin{center}
\begin{picture}(120,80)
\put(10,40){\includegraphics[width=12cm]{196.png}}
\end{picture}
\end{center}

\textbf{196}

Hironari and associates\textsuperscript{283} have prepared carbamoyltetrazolinones \textbf{197} as herbicides.

\begin{center}
\begin{picture}(120,80)
\put(10,40){\includegraphics[width=12cm]{197.png}}
\end{picture}
\end{center}

\textbf{197}

$R_1 = \text{substituted C}_{1-6} \text{ alkyl, C}_{1-6} \text{ alkoxy, C}_{2-6} \text{ alkynlyoxy}$

$R_2, R_3 = \text{H, C}_{1-6} \text{ alkyl, C}_{3-6} \text{ cycloalkyl, C}_{2-4} \text{ alkenyl C}_{2-4} \text{ alkynyl,}$

$\text{C}_{1-4} \text{ haloalkyl.}$
Sugimoto and Atsushi\textsuperscript{284} have reported the antidiabetic property of tetrazole derivatives \textsuperscript{198}.

\[
\begin{align*}
\text{\textsuperscript{198}} \\
R_1=\text{alkyl}, \ Y=\text{CO}_2, \ \text{SC}_2, \ n=3,7
\end{align*}
\]

Several methods of synthesizing tetrazoles have been reported\textsuperscript{285} and in the present work, the method due to Finnegan et al\textsuperscript{286} has been employed.

**Triazaines:**

Six-membered aromatic ring containing three nitrogen atoms are known as triazines, with three possible arrangements of nitrogen atoms in the ring as seen in 1,2,3-triazines, \textsuperscript{199} 1,2,4-triazines \textsuperscript{200}, and 1,3,5-triazines\textsuperscript{201}. 1,3,5-triazines \textsuperscript{201} are sometimes referred to as sym (symmetrical) isomer, 1,2,4-triazines \textsuperscript{200} as the asym (asymmetrical) isomer (often present in fused systems) are referred to as the vic (vicinal isomers).

\[
\begin{align*}
\text{\textsuperscript{199}} & \quad \text{\textsuperscript{200}} & \quad \text{\textsuperscript{201}}
\end{align*}
\]

Of the three parent triazines, only 1,3,5-triazine is known, 1,2,3-triazine was not prepared until 1960 and there were no proven examples of monocyclic 1,2,3-triazines\textsuperscript{287}.

The facility with which electrophilic substitution occurs in $\pi$-deficient heterocyclic species generally decreases on increasing the number of hetero atoms in the ring and for this reason, the triazines would be expected to be extremely inert. The only reported attempts at substitution of 1,3,5-triazines by
electrophiles relate to halogenation reaction\textsuperscript{287} Triazines are easily hydrolyzed almost instantly by dilute acids to formic acid and ammonia.

The valuable high explosive RDX or cyclonite is 1,3,5-trinitrohexahydro 1,3,5-triazine \textsuperscript{202} and is obtained by nitrating hexamethylene tetramine\textsuperscript{288}.

\begin{center}
\text{\begin{tikzpicture}[scale=0.5]
    \node[svg] (schema) {
        \begin{tikzpicture}
            \draw[blue, thick] (0,0) -- (1,0);
            \draw[blue, thick] (0,0) -- (0,1);
            \draw[blue, thick] (1,0) -- (0,1);
            \draw[blue, thick] (1,0) -- (1,1);
            \draw[blue, thick] (1,1) -- (1,2);
            \draw[blue, thick] (1,2) -- (0,2);
            \draw[blue, thick] (0,2) -- (0,1);
            \draw[blue, thick] (0,1) -- (0,0);
            \draw[blue, thick] (0,1) -- (1,2);
            \draw[blue, thick] (0,2) -- (1,1);
        \end{tikzpicture}
    }
\end{tikzpicture}}
\end{center}

\textbf{202}

The drug "paludrine" also called "proguanil" \textsuperscript{203} is widely used as antimalarial agent. It has however, been shown that paludrine itself has no action on the malarial parasite, but it is converted into active agent, a triazine \textsuperscript{204} by the host\textsuperscript{288}.

\begin{center}
\text{\begin{tikzpicture}[scale=0.5]
    \node[svg] (schema) {
        \begin{tikzpicture}
            \draw[blue, thick] (0,0) -- (1,0);
            \draw[blue, thick] (0,0) -- (0,1);
            \draw[blue, thick] (1,0) -- (0,1);
            \draw[blue, thick] (1,0) -- (1,1);
            \draw[blue, thick] (1,1) -- (1,2);
            \draw[blue, thick] (1,2) -- (0,2);
            \draw[blue, thick] (0,2) -- (0,1);
            \draw[blue, thick] (0,1) -- (0,0);
            \draw[blue, thick] (0,1) -- (1,2);
            \draw[blue, thick] (0,2) -- (1,1);
        \end{tikzpicture}
    }
\end{tikzpicture}}
\end{center}

\textbf{203}

\begin{center}
\text{\begin{tikzpicture}[scale=0.5]
    \node[svg] (schema) {
        \begin{tikzpicture}
            \draw[blue, thick] (0,0) -- (1,0);
            \draw[blue, thick] (0,0) -- (0,1);
            \draw[blue, thick] (1,0) -- (0,1);
            \draw[blue, thick] (1,0) -- (1,1);
            \draw[blue, thick] (1,1) -- (1,2);
            \draw[blue, thick] (1,2) -- (0,2);
            \draw[blue, thick] (0,2) -- (0,1);
            \draw[blue, thick] (0,1) -- (0,0);
            \draw[blue, thick] (0,1) -- (1,2);
            \draw[blue, thick] (0,2) -- (1,1);
        \end{tikzpicture}
    }
\end{center}

\textbf{204}

Tsujikava et al\textsuperscript{289} have synthesised different 1,3,5-triazine derivatives \textsuperscript{205} and reported their anticonvulsant activities.

\begin{center}
\text{\begin{tikzpicture}[scale=0.5]
    \node[svg] (schema) {
        \begin{tikzpicture}
            \node[rectangle, draw] (n1) at (0,0) {R_1};
            \node[rectangle, draw] (n2) at (1,0) {R_2};
            \node[rectangle, draw] (n3) at (0,1) {R};
            \draw[blue, thick] (n1) -- (n2);
            \draw[blue, thick] (n1) -- (n3);
            \draw[blue, thick] (n2) -- (n3);
        \end{tikzpicture}
    }
\end{center}

\textbf{205}

Unsymmetrical triazines of the type triazino[5,6-b]indol-3-amines \textsuperscript{206} are considered as potential drug for treating common cold infections caused by
rhinoviruses and strong \textit{in vitro} activity is observed against many rhinoviruses\cite{290,293}.

\begin{center}
\includegraphics[width=0.5\textwidth]{chart1.png}
\end{center}

\begin{align*}
R = H, \text{NH}_2 \quad R_1 = H, \text{Cl} \quad R_2 = \text{CH}_2, \text{CH}_2\text{OH, CH}_2\text{C(}\text{CH}_3)2\text{-OH,C(}\text{CH}_3)2\text{-CH}_2\text{OH}
\end{align*}

Triethylenemelamine [2,4,6-tris(1-aziridinyl)1,3,5-triazine-TEM] \textit{207} is the first alkylating agent as antineoplastic drug but are of limited clinical interest today \textit{204}.

\begin{center}
\includegraphics[width=0.2\textwidth]{chart2.png}
\end{center}

Hiroshi et al\textit{295} have synthesised 2,4-diamino-6-(2,5-dichlorophenyl)-1,3,5-triazine \textit{208} which is used for treating diseases of the liver, kidney, colon and rectum.

\begin{center}
\includegraphics[width=0.2\textwidth]{chart3.png}
\end{center}
2-Chloro-4-ethylamino-6-isopropylamino-1,3,5-triazine [ATREX-Ciba-Geigy, etc] 209, a selective herbicide is used in season-long weed control in corn, sorghum and certain other crops. It is also used at higher rates of application for non selective weed control in non cropped areas.

Morpholinyl substituted [1,2,4-triazolo-(1,5-a)]-triazines 210 and 211 and their analogues are used as adenosine antagonists.

Tadahide et al. prepared the following types of compound 212 which are used as UV absorbers in cosmetics.
Webb and coworkers\textsuperscript{299} have reported the following type of compound 213 which are useful for treating disorders related to hypertension of CRF, such as depression, anxiety, substance abuse, feeding disorder, epilepsy etc.

\[
\begin{array}{c}
\begin{array}{c}
\text{A} \\
\hline
\end{array} \\
\begin{array}{c}
\text{R} \\
\hline
\end{array} \\
\begin{array}{c}
\text{R_1} \\
\hline
\end{array} \\
\begin{array}{c}
\text{R_2} \\
\hline
\end{array} \\
\begin{array}{c}
\text{N} \\
\hline
\end{array} \\
\begin{array}{c}
\text{N} \\
\hline
\end{array} \\
\begin{array}{c}
\text{NR_1R_2} \\
\hline
\end{array}
\end{array}
\]

213

R = C\textsubscript{1-6} alkyl, NH\textsubscript{2}, R\textsubscript{1} = H, C\textsubscript{1-6} alkyl, C\textsubscript{3-alkenyl}, R\textsubscript{1}R\textsubscript{2} = pyrrolidinyl, morpholinyl, piperidinyl, R\textsubscript{4} = (unsubstituted) Ph, A = C or O.

Richard et al\textsuperscript{300} have prepared following compounds 214 which are useful as UV filters and are used in cosmetics for protecting skin and hair against UV radiation.

\[
\begin{array}{c}
\begin{array}{c}
\text{R_1} \\
\hline
\end{array} \\
\begin{array}{c}
\text{R} \\
\hline
\end{array}
\end{array}
\]

214

R = benzothiazolylphenylamine, R\textsubscript{1} = halo etc.

Kawaikiyoshi and associates\textsuperscript{301} have prepared triazinylbenzimidazole derivatives 215 and reported their fungicidal activities.

\[
\begin{array}{c}
\begin{array}{c}
\text{X} \\
\hline
\end{array} \\
\begin{array}{c}
\text{R_1} \\
\hline
\end{array} \\
\begin{array}{c}
\text{R_2} \\
\hline
\end{array}
\end{array}
\]

215

R\textsubscript{1}, R\textsubscript{2} = Halo, alkyl, alkenyl, X = Halo, nitro, cyano, Y = Halo, nitro, cyano, alkyl.
Formylaminotriazines 216 were synthesised by Riebel and associates\textsuperscript{302} as herbicides.

\[
\begin{align*}
\text{A} &= (\text{substituted}) \text{(o-interrupted) alkylene}, \\
\text{Z} &= (\text{substituted}) \text{cyclopentyl, cyclohexyl, phenyl, naphthyl, tetralinyl, decaliny}, \\
&\quad \text{ldanyl, indenyl, furyl, benzfuryl, thienyl, quinolyl, quinoxaliny}, \\
&\quad \text{pyridaziny}, \text{R} = \text{H, CN, halo, (substituted) alkyl, alkoxy, alkylcarbonyl, alkoxycarbonyl,}
\end{align*}
\]

Ueda\textsuperscript{303} has reported the herbicidal activity of triazine derivatives 217.

Kevin and co-workers\textsuperscript{304} have synthesised the triazines 218 as cytokine, especially TNF-\(\alpha\) inhibitors.
Gerard et al.\textsuperscript{305} have reported the synthesis of dihydro-1,3,5-triazine amines 219 and 220 which are used in the treatment of pathologies related to insulin-resistance syndrome.

Wolfgang and associates\textsuperscript{306} have synthesised 4,6-disubstituted-2-amino-1,3,5-triazine 221 as plant growth regulator.

Rosu and coworkers\textsuperscript{307} have reported the herbicidal activity of triazine derivatives 222.
Several methods of synthesizing triazines are reported\textsuperscript{308} and in the present investigation, the method due to Ram et al\textsuperscript{309} has been employed.

\textbf{Quinazolines:}

Quinazoline\textsuperscript{310,311}, or 1,3-diazanaphthalene is represented by structure \textbf{223}.

\begin{center}
\textbf{223}
\end{center}

The quinazoline nucleus occurs in association with other heterocyclic systems in a number of alkaloids but knowledge of quinazolines has been gained mainly from synthetic chemistry, rather than the study of natural products. Several alkaloids containing quinazoline nucleus have been described. Among them are vasicine (peganine) \textbf{224}, rutecarpine \textbf{225} and evodiamine \textbf{226}. Perhaps, the most interesting quinazoline alkaloid is febrifugine \textbf{227} a substance of high antimalarial activity, but of such high toxicity as to preclude its practical use.
Quinazolines have gained importance because of antimalarial activity. Quinazoline derivatives prepared as antimalarial drugs include group of 3-(dialkylaminoalkyl)-4-quinazolines, 2,4-dimethyl-7-(1-hydroxy-3-dimethylaminopropyl)quinazoline, 2-(dialkylaminoalkylamino)4-quinazalones and a series of 2-amino-4-hydroxy and 2,4-diamino-5,6,7,8-tetrahydroquinazolines.

Shenoy et al have prepared 7-nitro-2-methyl-4(3H)-quinazoline 228 and reported its antitubercular activity.

R = substituted ph, (aryloxy)methyl.
Raghuram and associates\textsuperscript{318}, have reported the synthesis of 6-alkylbenzimidazo[1,2-c]quinazolines 229 as bronchodilators.

\[
\text{NR'}R^2=\text{NMe}_2, \text{NEt}_2, \text{1-morpholino, 1-pyrrolidiny, 1-piperidino, 1-piperazinyl.}
\]

Algarsamy and coworkers\textsuperscript{319} have synthesised quinazolin-4(3H)-ones 230 as analgesic, antiinflammatory and antibacterial agents.

Rodney et al\textsuperscript{320} have prepared quinazolin-2-ones 231, 232 as HIV-reverse transcriptase inhibitors.

Rubin and associates\textsuperscript{321} have synthesised N-hydroxyquinazoline 233 possessing leukotriene and histamine inhibiting activity for the treatment of asthma and allergy.
Though oxygen heterocycles are used as potent anticoagulants, it is not surprising that 4-aminoquinazoles are also used as anticoagulants.

Ewing et al\textsuperscript{322} reported the anticoagulant activity of 4-aminoquinazole derivative of the type 234.

Apfel Christian and coworkers\textsuperscript{323} have synthesised 2-oxo-1,4-dihydro-2H-quinazolines 235 as potent selective peptide \textit{Deformylase} inhibitor.

Garg and associates\textsuperscript{324} have prepared quinazoline-4(3H)-ones of the type 236, 237 and reported their antiamoebic activity.
Present Work: Part A

Synthesis of 1,3,4-oxadiazolylmethoxyindoles
Alagarsamy et al\textsuperscript{325} have synthesised 2-mercapto-3-(substituted methyl-amino)quinazolin-4(3H)-ones 238 and reported their antihistaminic activity.

There are several methods available for synthesising quinazoline derivatives\textsuperscript{327} and in the present investigation, we have employed the method of Bogert et al\textsuperscript{328}. 

\begin{align*}
\text{R}_1 = \text{H, Br, NO}_2, \text{Ar} = \text{(Un)substituted phenyl, Ar}_1 = \text{substituted phenyl.}
\end{align*}
In the light of wide spectrum of biological activities associated with 1,3,4-oxadiazoles\textsuperscript{127-167}, it was thought of considerable interest to undertake the synthesis of indole derivatives carrying the bioactive 1,3,4-oxadiazole at position-5 linked through methoxy bridge.

During the present investigation 5-hydroxyindole-3-ester 243 prepared by adopting Nenitzescu reaction\textsuperscript{329} was reacted with methyl chloroacetate in refluxing dry acetone in presence of anhydrous potassium carbonate to get the required 1-cyclohexyl-3-ethoxycarbonyl-5-methoxycarbonyl-methoxy-2-methylindole 244. When this indole diester 244 was heated with excess of hydrazine hydrate (99\%) in boiling ethanol, produced exclusively monocarbohydrazide 1-cyclohexyl-3-ethoxycarbonyl-2-methylindol-5-yloxy-acetic acid hydrazide 245. It was observed that the C3-carbethoxy carbonyl group in this diester 244 did not react with hydrazine hydrate under above reaction conditions and only C-5 ester of indole diester 244 chemoselectively reacted with hydrazine hydrate to yield only above indole monocarbohydrazide 245 but not the expected indole dicarbohydrazide 246.

Further, an additional support to the above observation was adduced from the following experiment. When 1-cyclohexyl-3-ethoxycarbonyl-5-methoxy-2-methylindole A was heated at reflux with hydrazine hydrate in ethanol, only starting material A was obtained.

\[ \text{A} \xrightarrow{\text{N}_2\text{H}_4\cdot\text{H}_2\text{O, Ethanol}} \text{B} \]
Scheme – 1
The observed resistance of C3-carbethoxy group of compound 244 towards the nucleophilic attack of hydrazine hydrate may be due to the canonical form of this compound 244b wherein the C3-carbethoxy carbonyl has reduced double bond character.

In another investigation, 1-p-acetanilido-3-acetyl-5-hydroxy-2-methylindole 254a prepared by adopting the method of Grinev et al. was reacted with methyl iodide in refluxing dry acetone in presence of anhydrous K$_2$CO$_3$ to yield 1-p-N-methylacetanilido-3-acetyl-5-methoxy-2-methylindole 255 wherein both C5-hydroxyl and amide NH groups of the above hydroxyindole 254 were methylated.

Further, when this 5-hydroxyindole 254a was reacted with methyl chloroacetate in refluxing dry acetone, in presence of anhydrous K$_2$CO$_3$, it was observed that only C5-hydroxyl group reacted with methyl chloroacetate, revealing the chemoselective reaction of C5-hydroxyl towards methyl chloroacetate over that of amide NH and produced only 1-p-acetanilido-3-acetyl-5-methoxy carbonylmethoxy-2-methylindole 257 in good yield instead of the expected indole diester 256 [scheme-2]. This monoester 257 was heated at reflux with hydrazine hydrate in ethanol to obtain the desired 1-p-acetanilido-3-acetyl-5-(1,3,4-oxadiazol-2yl)methoxy-2-methylindole 260 [Scheme-2].
1-Cyclohexyl-3-ethoxycarbonyl-2-methylindol-5-yloxyacetic acid hydrazide 245 was reacted separately with triethyl orthoformate, carbon disulphide and alcoholic potassium hydroxide to obtain the desired 1-cyclohexyl-3-ethoxycarbonyl-5-(1,3,4-oxadiazol-2-yl)methoxy-2-methylindole 247 and 1-cyclohexyl-3-ethoxycarbonyl-5-(5-mercapto-1,3,4-oxadiazol-2-yl)methoxy-2-methylindole 249 respectively [Scheme-1].

1-Cyclohexyl-3-ethoxycarbonyl-5-hydroxy-2-methylindole 243 obtained by adopting Nenitzescu reaction\textsuperscript{329} exhibited broad stretching band at 3240 cm\textsuperscript{-1} due to C5-hydroxyl group and a strong stretching band at 1659 cm\textsuperscript{-1} assigned to C3-ester carbonyl group in its IR spectrum (Fig-1). The \textsuperscript{1}H NMR spectrum of 243 (Fig-2) displayed a triplet (J=7.1 Hz) at 1.34 δ due to C3-ester methyl. A multiplet from 1.4-2.5 δ was assigned to ten protons of cyclohexane. A singlet at 2.72 δ was attributed to C2-methyl and a multiplet at 3.36 δ was assigned to C1-proton of cyclohexane. A quartet (J = 7.1 Hz) at 4.25 δ was assigned to C3-ester methylene. A doublet of doublet (J = 8.5 Hz and 2.5 Hz) at 6.62 δ was ascribed to C6-proton while a doublet (J = 2.5 Hz) at 7.38 δ was accounted for C4-proton. Another doublet (J = 8.5 Hz) at 7.50 δ was attributed to C7-proton. A singlet at 8.92 δ was assigned to C5-OH which disappeared on D\textsubscript{2}O exchange.

The 5-hydroxyindole 243 was treated with methyl chloroacetate in presence of anhydrous potassium carbonate and potassium iodide in dry acetone to yield the desired 1-cyclohexyl-3-ethoxycarbonyl-5-methoxy carbonylmethoxy-2-methylindole 244 which exhibited stretching bands at 1764/1739 and 1689 cm\textsuperscript{-1} due to C5-ester and C3-ester carbonyl groups respectively in its IR spectrum (Fig-3). The \textsuperscript{1}H NMR spectrum of 244 (Fig-4) exhibited a multiplet from 1.24-2.48 for ten protons of cyclohexane. A triplet (J = 7.2 Hz) at 1.44 δ was assigned to C3-ester methyl. The C2-methyl protons appeared at 2.79 δ as singlet and another singlet observed at 3.81 δ was due to C5-ester methyl. A multiplet at 4.25 δ was accounted for C1-proton of
cyclohexane. A quartet ($J = 7.2$ Hz) at 4.36 δ was attributed to C$_3$-ester methylene group while a singlet at 4.70 δ was assigned to C$_5$-O-CH$_2$ protons. A doublet of doublet ($J = 8.5$ Hz and 2.5 Hz) at 6.88 δ was attributed to C$_6$-proton and C$_7$-proton resonated as doublet ($J = 8.5$ Hz) at 7.45 δ. A doublet ($J = 2.5$ Hz) at 7.63 δ was accounted for C$_4$-proton.

The mass spectrum (Fig-5) of compound 244 showed a molecular ion base peak M$^+$ at m/z (%) 373(100) and a peak due to M+1 at m/z (%) 374(18). The fragment F$_1$ was produced from M$^+$ at m/z (%) 357(6) by the loss of CH$_3$ and H while fragment F$_2$ was generated from M$^+$ at m/z (%) 328 (12) after the loss of OC$_2$H$_5$. The fragment F$_3$ was found at m/z (%) 300(18) due to the loss of COOEt from M$^+$ and fragment F$_4$ was generated at m/z(%) 291(8) from M$^+$ after the loss of C$_6$H$_{10}$ from M$^+$. The fragment F$_5$ produced from M$^+$ by the loss of C$_6$H$_{10}$ and C$_3$H$_5$O$_2$ was found at m/z (%) 218 (38) while fragment F$_6$ was observed at m/z (%) 172(16) due to the loss of C$_6$H$_{11}$, C$_3$H$_5$O$_2$, OC$_2$H$_5$ and H from M$^+$. The F$_7$ fragment was found at m/z (%) 156(18) from M$^+$ due to the loss of C$_6$H$_{11}$, C$_3$H$_5$O$_3$, OC$_2$H$_5$ and H. The fragment F$_8$ was generated from M$^+$ at m/z (%) 116(6) after the loss of C$_6$H$_{10}$, C$_3$H$_4$O$_3$, C$_2$H$_4$, CO$_2$, CH$_3$ from M$^+$. [Scheme-3].

Compound 244 was reacted with hydrazine hydrate in refluxing ethanol to yield exclusively 1-cyclohexyl-3-ethoxycarbonyl-2-methylindol-5-yloxy acetic acid hydrazide 245 and IR spectrum (Fig-6) of this sample 245 exhibited broad stretching band around 3320 cm$^{-1}$ due to amine/amide NH while strong stretching bands at 1683 cm$^{-1}$ and 1673 cm$^{-1}$ were attributed to C$_5$-amide and C$_3$-ester carbonyls.

The $^1$H NMR spectrum of 245 (Fig-7) displayed a multiplet from 1.29 to 2.40 δ due to ten protons of cyclohexane. A triplet ($J = 7.2$ Hz) at 1.44 δ was attributed to C$_3$-ester methyl while a singlet at 2.79 δ was accounted for C$_2$-methyl protons. A broad singlet at 3.94 δ was assigned to C$_5$-amide NH$_2$ which vanished on D$_2$O exchange.
Scheme -3

F7
m/z (%) 156 (18)

F6
m/z (%) 172 (16)

F5
m/z (%) 218 (38)

C₆H₁₈OC₂H₅

F8
m/z (%) 116 (6)

C₆H₁₄OC₂H₅

F1
m/z (%) 357 (6)

F2
m/z (%) 328 (12)

F3
m/z (%) 300 (18)

F4
m/z (%) 291 (8)
A multiplet at 4.26 δ was due to C1-proton of cyclohexane. A quartet (J=7.2 Hz) at 4.36 δ was assigned to C3-ester methylene protons while singlet at 4.64 δ was accounted for C5-OCH2 protons. The C6-proton resonated at 6.81 δ as doublet of doublet (J=8.5 Hz and 2.5 Hz) and the C7-proton appeared at 7.45 δ as doublet (J=8.5 Hz). The C4-proton was observed as doublet (J=2.5 Hz) at 7.66 δ. Amide NH showed a broad singlet at 7.84 δ which disappeared on D2O exchange.

The carbohydrazide 245 was heated at reflux with excess of triethyl orthoformate to yield the desired 1-cyclohexyl-3-ethoxycarbonyl-5-(1,3,4-oxadiazol-2-yl)methoxy-2-methylindole 247. In the IR spectrum (Fig-8) of 247, a strong stretching band observed at 1665 cm⁻¹ was assigned to C3-ester carbonyl. However stretching bands due to NH2 and amide NH were absent in this IR spectrum which confirmed the formation of oxadiazole 247. ¹H NMR spectrum of 247 (Fig-9) displayed multiplet from 1.20 to 2.40 δ due to ten protons of cyclohexane. A triplet (J=7.1 Hz) at 1.45 δ was assigned to C3-ester methyl while singlet at 2.79 δ was accounted for C2-methyl protons. The C1-proton of cyclohexane resonated as multiplet at 4.20 δ and a quartet (J=7.1 Hz) at 4.36 δ was attributed to C3-ester methylene. Singlet at 5.37 δ was accounted for C5-OCH2 protons and this downfield shift of C5-OCH2 signal is due to the deshielding effect of oxadiazole ring. A doublet of doublet (J=8.5 Hz, 2.5 Hz) observed at 6.91 δ was accounted for C6-proton but the C7-proton resonated as doublet (J=8.5 Hz) at 7.45 δ. A doublet (J=2.5 Hz) at 7.79 δ was attributed to C4-proton and singlet at 8.45 δ was accounted for C5-proton of oxadiazole.

The carbohydrazide 245 was reacted at reflux with carbon disulfide and ethanolic potassium hydroxide to yield the desired 1-cyclohexyl-3-ethoxycarbonyl-5-(5-mercapto-1,3,4-oxadiazol-2-yl)methoxy-2-methylindole 248. IR spectrum (Fig-10) of 248 displayed stretching bands at 3133/3098 cm⁻¹ of NH and a strong stretching band at 1640 cm⁻¹ due to C3-ester carbonyl. The
strong stretching band observed at 1152 cm\textsuperscript{-1} due to C=S indicated the predominant existence of this compound in the thione form. The \textsuperscript{1}H NMR spectrum (Fig-11) of 248 exhibited a multiplet from 1.32 to 2.40 δ due to ten protons of cyclohexane. A triplet (J=7 Hz) at 1.43 δ was accounted for C\textsubscript{3}-ester methyl protons and C\textsubscript{2}-methyl protons resonated as singlet at 2.79 δ. A multiplet at 4.26 δ was attributed to C\textsubscript{1}-proton of cyclohexane. A quartet (J=7Hz) at 4.34 δ was assigned to C\textsubscript{3}-ester methylene protons while downfield singlet at 5.12 δ was due to C\textsubscript{5}-O-CH\textsubscript{2} protons indicating the formation of mercapto oxadiazole. A doublet of doublet (J=8.1 Hz and 2.5 Hz) at 6.86 δ was accounted for C\textsubscript{6}-proton and a doublet (J=8.1Hz) at 7.49 δ was assigned to C\textsubscript{7}-proton. Another doublet (J=2.5 Hz) at 7.70 δ was attributed to C\textsubscript{4}-proton.

The mass spectrum of 248 (Fig-12) displayed a molecular ion peak at m/z (%) 415(7.8) and a peak due to M+1 was found at m/z (%) 416(2). The F\textsubscript{1} fragment at m/z (%) 400(5) was produced by the loss of CH\textsubscript{3} while F\textsubscript{2} at m/z (%) 399(7) was generated from M\textsuperscript{*} by the loss of CH\textsubscript{4}. F\textsubscript{3} fragment at m/z (%) 383 (5) resulted due to the loss of sulphur from M\textsuperscript{*}. Fragments F\textsubscript{4} and F\textsubscript{5} observed at m/z (%) 370(10) and m/z (%) 359(10.9) were generated after the loss of OC\textsubscript{2}H\textsubscript{5} and cyclobutane (C\textsubscript{4}H\textsubscript{5}) respectively from molecular ion M\textsuperscript{*}. Fragments F\textsubscript{6} and F\textsubscript{7} were generated from M\textsuperscript{*} at m/z (%) 340(8) and m/z (%) 300(95) due to the loss of COOC\textsubscript{2}H\textsubscript{5}, 2H and C\textsubscript{6}H\textsubscript{10}N\textsubscript{2}OS respectively. Peaks due to F\textsubscript{6}, F\textsubscript{9} and F\textsubscript{10} fragments found at m/z (%) 219(38.3), m/z (%) 190(27.6) and m/z (%) 174(19.6) were produced from M\textsuperscript{*} by the loss of C\textsubscript{6}H\textsubscript{10}N\textsubscript{2}OS, C\textsubscript{6}H\textsubscript{9}, C\textsubscript{3}H\textsubscript{3}N\textsubscript{2}OS, C\textsubscript{6}H\textsubscript{10}, C\textsubscript{2}H\textsubscript{4} and C\textsubscript{3}H\textsubscript{3}N\textsubscript{2}OS, C\textsubscript{6}H\textsubscript{10}, C\textsubscript{2}H\textsubscript{5}, CH\textsubscript{3} respectively [Scheme-4].

Further, the carbohydrizade 245 was reacted separately with allylisothiocyanate and p-chlorophenylisothiocyanate in boiling ethanol to obtain the required 1-cyclohexyl-3-ethoxycarbonyl-5-yloxymethylcarboallylthiosemicarbazide 249 and 1-cyclohexyl-3-ethoxycarbonyl-5-yloxymethylcarbo-p-chlorophenylthiosemicarbazide 250 respectively.
Scheme - 4

F9
m/z (%) 190 (27.6)

F8
m/z (%) 219 (38.3)

F7
m/z (%) 300 (95)

F10
m/z (%) 174 (19.6)

F1
m/z (%) 400 (6)

F2
m/z (%) 399 (7)

F3
m/z (%) 383 (8.5)

F4
m/z (%) 370 (7.5)

F5
m/z (%) 359 (14.6)

F6
m/z (%) 340 (8)

F11
m/z (%) 399 (7)

F12
m/z (%) 383 (8.5)

F13
m/z (%) 370 (7.5)
The IR spectrum (Fig-13) of 249 showed stretching band at 3431 cm\(^{-1}\) and 3172 cm\(^{-1}\) due to amide and thioamide NH. Strong stretching bands at 1686 cm\(^{-1}\) and 1660 cm\(^{-1}\) were assigned to C\(_3\)-ester and C\(_5\)-amide carbonyls. The band at 1189 cm\(^{-1}\) was due to C=S function. \(^1\)H NMR spectrum (Fig-14) of 249 exhibited a multiplet from 1.25 to 2.40 \(\delta\) due to ten protons of cyclohexane while a triplet (\(J=7.1\) Hz) at 1.43 \(\delta\) was assigned to C\(_3\)-ester methyl protons and a singlet at 2.76 \(\delta\) was attributed to C\(_2\)-methyl protons. A triplet at 4.15 \(\delta\) was assigned to two methylene protons of allyl group. A multiplet at 4.29 \(\delta\) was accounted for C\(_1\)-proton of cyclohexane. A quartet (\(J=7.1\) Hz) at 4.36 \(\delta\) was assigned to C\(_3\)-ester methylene protons and singlet at 4.72 \(\delta\) was accounted for C\(_3\)-O-CH\(_2\) protons. A multiplet from 5.05 to 5.13 \(\delta\) was assigned to two vinyl protons of allyl group while another multiplet from 5.69-5.82 \(\delta\) was characterized for methine proton of allyl group. A broad singlet at 6.61 \(\delta\) was assigned to NH which disappeared on D\(_2\)O exchange. A doublet of doublet (\(J=8.2\) Hz and 2.5 Hz) at 6.87 \(\delta\) was accounted for C\(_6\)-proton while C\(_7\)-proton appeared as doublet (\(J=8.2\) Hz) at 7.46 \(\delta\). A doublet (\(J=2.5\) Hz) at 7.70 \(\delta\) was accounted for C\(_4\)-proton. Thioamide NH appeared as broad singlet at 8.26 \(\delta\) while amide NH showed broad singlet at 8.91 \(\delta\) and both these peaks vanished on D\(_2\)O exchange.

The IR spectrum (Fig-15) of \(p\)-chloro phenylthiosemicarbazide 250 exhibited a stretching bands at 3450 cm\(^{-1}\) and 3295 cm\(^{-1}\) due to amide and thioamide NH. Strong stretching bands at 1696 cm\(^{-1}\) and 1671 cm\(^{-1}\) were assigned to C\(_3\)-ester and C\(_5\)-amide carbonyls. A strong band at 1195 cm\(^{-1}\) was assigned to C=S stretching. \(^1\)H NMR spectrum (Fig-16) of this compound 250 displayed a multiplet from 1.31 to 2.30 \(\delta\) due to ten protons of cyclohexane. A triplet (\(J=7.1\) Hz) at 1.45 \(\delta\) was accounted for C\(_3\)-ester methyl protons while C\(_1\)-proton of cyclohexane appeared as a multiplet at 4.25 \(\delta\) the C\(_3\)-ester methylene protons resonated as quartet (\(J=7.1\) Hz) at 4.32 \(\delta\) and singlet at 4.69 \(\delta\) was accounted for C\(_5\)-O-CH\(_2\) protons. A doublet of doublet
(J=8.5 Hz & 2.5 Hz) at 6.93 δ was assigned to C₆-proton while C₇-proton appeared as doublet (J=8.5 Hz) at 7.25 δ. A multiplet ranging from 7.41 to 7.49 δ was due to four aromatic protons of p-chlorophenyl. A broad singlet at 7.46 δ was assigned to NH that disappeared on D₂O exchange. A doublet (J=2.5 Hz) at 7.71 δ was due to C₄-proton. Two broad singlets at 9.20 δ and 10.0 δ were attributed to amide NH and thioamide NH respectively and they vanished on D₂O exchange.

The thiosemicarbazides 249 and 250 were oxidatively cyclised with iodine and potassium iodide in ethanolic 1% sodium hydroxide to get the desired 1-cyclohexyl-3-ethoxycarbonyl-5-(5-allylamino-1,3,4-oxadiazol-2-yl)-methoxy-2-methylindole 251 and 1-cyclohexyl-3-ethoxycarbonyl-5-[5-p-chloroanilino-1,3,4-oxadiazol-2-yl]methoxy-2-methylindole 252 respectively. The IR spectrum (Fig-17) of compound 251 displayed stretching bands at 3158 cm⁻¹ and 1654 cm⁻¹ due to NH and C₃-ester carbonyl respectively. The ¹H NMR spectrum (Fig-18) of this sample 251 showed a multiplet ranging from 1.30 to 2.4 δ corresponding to ten protons of cyclohexane. A triplet (J=7.2 Hz) at 1.42 δ was accounted for C₃-ester methyl protons while singlet at 2.78 δ was attributed to C₂-methyl protons. A doublet at 4.13 δ was assigned to two protons of allyl methylene and multiplet centered at 4.24 δ was related to C₁-proton of cyclohexane while quartet (J=7.2 Hz) at 4.35 δ was accounted for C₃-ester methylene protons. A downfield singlet at 4.72 δ was assigned to two protons of C₅-O-CH₂ group confirming the heterocyclisation. A multiplet centered at 5.08 δ was accounted for two vinyl protons of allyl group while another multiplet at 5.73 δ was assigned to methine proton of allyl group. A doublet of doublet (J=8.5 Hz and 3 Hz) at 6.87 δ was related to C₆-proton and C₇-proton appeared as doublet (J=8.5 Hz) at 7.46 δ. Another doublet (J= 2.5 Hz) at 7.69 δ was attributed to C₄-proton while broad singlet at 8.47 δ was characteristic of NH which disappeared on D₂O exchange.
The IR spectrum (Fig-19) of 252 displayed stretching bands at 3425 cm\(^{-1}\) and 1652 cm\(^{-1}\) due to NH and C\(_3\)-ester carbonyl respectively. \(^1\)H NMR spectrum (Fig-20) of this compound 252 exhibited a multiplet from 1.34 to 2.4 \(\delta\) due to ten protons of cyclohexane. A triplet (J=7.0 Hz) at 1.43 \(\delta\) was assigned to C\(_3\)-ester methyl protons while singlet at 2.77 \(\delta\) was accounted for C\(_2\)-methyl protons. A multiplet at 4.24 \(\delta\) was related to C\(_1\)-proton of cyclohexane. The C\(_3\)-ester methylene protons resonated as quartet (J=7.0 Hz) at 4.37 \(\delta\) while singlet at 4.96 \(\delta\) was pertaining to C\(_3\)-O-CH\(_2\)-protons. A doublet of doublet (J=8.5 Hz and 2.5 Hz) at 6.64 \(\delta\) was assigned to C\(_5\)-proton and doublet (J=8.5 Hz) at 6.87 \(\delta\) was accounted for C\(_7\)-proton. The C\(_4\)-proton resonated as doublet (J=2.5 Hz) at 7.64 \(\delta\) and broad singlet at 7.72 \(\delta\) was attributed to NH which vanished on D\(_2\)O exchange. A multiplet ranging from 7.26 \(\delta\) - 7.68 \(\delta\) was assigned to four aromatic protons of p-chlorophenyl.

The IR spectrum (Fig-21) of 1-p-\(\beta\)-acetanilido-3-acetyl-5-hydroxy-2-methylindole 254a displayed broad stretching bands at 3240 cm\(^{-1}\) and 3178 cm\(^{-1}\) due to amide NH and hydroxyl groups respectively. Two sharp stretching bands observed at 1671 cm\(^{-1}\) and 1652 cm\(^{-1}\) were corresponding to anilido carbonyl and C\(_3\)-acetyl functions respectively. \(^1\)H NMR spectrum (Fig-22) of 254a exhibited singlets at 2.52 \(\delta\) and 2.19 \(\delta\) pertaining to C\(_3\)-acetyl methyl and anilido methyl protons while another singlet observed at 2.64 \(\delta\) was attributed to C\(_2\)-methyl protons. A doublet of doublet (J=8.5 Hz and 2.5 Hz) at 6.71 \(\delta\) was assigned to C\(_5\)-proton. A doublet (J=8.5 Hz) at 6.81 \(\delta\) was accounted for C\(_7\)-proton while C\(_4\)-proton resonated as doublet (J=2.5 Hz) at 7.52 \(\delta\). The two ortho protons and two meta protons of acetanilido group appeared as doublets (J=8.5 Hz) at 7.21 \(\delta\) and 7.80 \(\delta\) respectively. A broad singlet at 9.63 \(\delta\) was attributed to amide NH which vanished on D\(_2\)O exchange.

The IR spectrum (Fig-23) of 1-p-N-methylacetanilido-3-acetyl-5-methoxy-2-methylindole 255 exhibited sharp stretching bands at 1684 cm\(^{-1}\) and 1616 cm\(^{-1}\) due to amide and C\(_3\)-acetyl carbonyls respectively. \(^1\)H NMR
spectrum (Fig-24) of 255 displayed singlets at 2.55 δ and 2.67 δ due to C3-acetyl methyl and C2-methyl protons respectively. Six protons of methyl and acetyl methyl on N resonated as singlet at 3.05 δ while methoxy protons resonated as singlet at 3.89 δ. A multiplet ranging from 6.76 to 7.62 δ was attributed to seven aromatic protons.

IR spectrum (Fig-25) of 1-p-acetanilido-3-acetyl-5-methoxycarbonyl-methoxy-2-methylindole 257 displayed a stretching band at 3357 cm\(^{-1}\) due to amide NH while strong stretching bands at 1733 cm\(^{-1}\), 1690 cm\(^{-1}\) and 1622 cm\(^{-1}\) were assigned to C5-ester carbonyl, amide carbonyl and C3-acetyl carbonyls respectively. \(^1\)H NMR spectrum (Fig-26) of sample 257 showed singlet at 2.17 δ and 2.46 δ related to amide methyl and C3-acetyl protons respectively. The C2-methyl protons showed singlet at 2.58 δ while C5-ester methyl protons resonated at 3.75 δ as singlet. Singlet due to C5-O-CH\(_2\) protons appeared at 4.66 δ. A doublet of doublet (J=8.5 Hz and 2.5 Hz) pertaining to C6-proton was found at 6.81 δ while C7-proton resonated as doublet (J= 8.5 Hz) at 7.31 δ. Four aromatic protons of 1-p-acetanilide function displayed two doublets (J=8.5 Hz) at 7.16 δ and 7.65 δ. A doublet (J=2.5 Hz) at 7.63 δ was assigned to C4-proton and broad singlet at 7.57 δ was attributed to amide NH which disappeared on D\(_2\)O exchange.

The IR spectrum (Fig-27) of 1-p-acetanilido-3-acetyl-2-methylindol-5-yloxyacetic acid hydrazide 258 exhibited stretching bands at 3319 cm\(^{-1}\) and 3276 cm\(^{-1}\) due to NH\(_2\)/NH functions. Strong stretching bands at 1694 cm\(^{-1}\), 1671 cm\(^{-1}\) and 1630 cm\(^{-1}\) were assigned to C5-amide carbonyl, C1-amide carbonyl and C3-acetyl carbonyl groups respectively. \(^1\)H NMR spectrum (Fig-28) of this compound displayed singlet at 2.18 δ and 2.48 δ pertaining to amide methyl and C3-acetyl methyl protons respectively. The C2-methyl protons appeared as singlet at 2.60 δ while a broad singlet at 4.3 δ was attributed to C5-amide NH\(_2\) which disappeared on D\(_2\)O exchange. A singlet observed at 4.53 δ was due to C5-O-CH\(_2\) protons. A singlet at 6.88 δ was
assigned to C₆- and C₇-protons who seemed to have attained magnetic 
equivalence. A doublet (J= 8.5 Hz) at 7.35 δ and 7.83 δ were related to four 
aromatic protons of 1-p-acetanilido group. A doublet (J=2.5 Hz) at 7.65 δ was 
accounted for C₄-proton. Singlet at 9.35 δ was due to 1-anilido NH while 
singlet observed at 10.25 δ corresponded to C₃-amide NH and both of them 
vanished on D₂O exchange.

The IR spectrum (Fig-29) of 1-p-acetanilido-3-acetyl-5-(1,3,4-
oxadiazol-2-yl)methoxy-2-methylindole 260 displayed a stretching band at 
3320 cm⁻¹ due to amide NH while 1-anilido carbonyl and C₃-acetyl carbonyl 
stretching bands were observed at 1696 cm⁻¹ and 1634 cm⁻¹ respectively. 
¹H NMR spectrum (Fig-30) of this sample 260 showed singlet at 2.118 δ due to 
amide methyl protons. The C₃-acetyl methyl and C₂-methyl protons displayed 
overlapping singlet at 2.50 δ while another singlet at and 5.50 δ was attributed 
to C₅-O-CH₂ protons and this downfield shift of C₅-O-CH₂ singlet has 
confirmed the formation of oxadiazole ring. A multiplet ranging from 6.65 to 
7.84 δ was accounted for seven aromatic protons. A singlet at 9.32 δ was 
attributed to C₅-oxadiazole proton while broad singlet at 10.28 δ was assigned 
to amide NH which disappeared on D₂O exchange.

Proton decoupled ¹³C NMR spectrum (Fig-31) of 260 displayed a peak 
at 14.03 δ due to C₂-methyl carbon and a peak at 24.27 δ due to anilido methyl 
carbon. The signal at 31.48 δ was assigned to C₃-acetyl methyl carbon and 
C₅-methylene carbon resonated at 60.54 δ. The signal at 105.1 δ and 106.1 δ 
were assigned to C₇ and C₆ of indole nucleus while junction carbon C[b] was 
found at 111.4 δ and the signal of C₃ was observed at 112.3 δ. Signal at 114.5 δ 
was attributed to C₃' and C₅' of anilido ring while the signal of C₂' and C₆' of the 
same ring was observed at 120.4 δ. The peak junction carbon C[a] was found at 
126.7 δ and peak at 128.7 δ was assigned to C₂ of indole nucleus. The signal 
C₄' of anilido ring was observed at 130.24 δ while peak due to C₄ resonated at 
133.32 δ. The peak at 140.12 δ was assigned to C₅ of indole nucleus and signal

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due to $C_1'$ of anilido ring was observed at $145.5 \, \delta$. The peak at $153 \, \delta$ was assigned to $C_2$ of oxadiazole ring while $C_5$ of indole moiety resonated at $155.3 \, \delta$. The peak due to $C_5$ of oxadiazole ring was found at $162.8 \, \delta$ while anilido carbonyl carbon resonated at $168.9 \, \delta$. The signal due to $C_3$ carbonyl carbon was observed at $193.5 \, \delta$. 
Present Work: Part B

Synthesis of 1,2,4-triazolylmethoxyindoles
In view of wide spectrum of biological activities associated with 1,2,4-triazoles\textsuperscript{176-208} and also in continuation of our studies on bridged bisheterocycles and chemoselectivity of indole dicarboxylates towards hydrazine hydrate, we thought of linking 1,2,4-triazole to C\textsubscript{5}-position of biologically active indole moiety through methoxy bridge leading to the synthesis of hitherto unknown 1,2,4-triazolylmethoxyindoles with enhanced biological activities.

Under the present investigation, the required starting material 1-substituted-3-ethoxycarbonyl/acetyl-5-hydroxy-2-methylindoles \textsuperscript{243} and \textsuperscript{254} were prepared by Nenitzescu reaction\textsuperscript{329}. These 5-hydroxyindoles \textsuperscript{243} and \textsuperscript{254} were reacted with methyl chloroacetate in presence of anhydrous potassium carbonate to give 1-substituted-3-ethoxycarbonyl/acetyl-5-methoxycarbonyl-methoxy-2-methylindoles \textsuperscript{244} and \textsuperscript{257}. When these diesters \textsuperscript{244} and \textsuperscript{257} were reacted with excess of hydrazine hydrate (99\%) in boiling ethanol produced exclusively the monocarbohydrazides 1-substituted-3-ethoxycarbonyl/acetyl-2-methylindol-5-yloxyacetic acid hydrazides \textsuperscript{245} and \textsuperscript{258} instead of the expected indoledicarbohydrazides \textsuperscript{246} and \textsuperscript{259} revealing the chemoselectivity of C\textsubscript{5}-ester group over that of C\textsubscript{3}-ester/acetyl towards the nucleophilic attack of hydrazine hydrate. The C\textsubscript{3}-ester/acetyl group remained intact.

The carbohydrazide \textsuperscript{245} was reacted separately with carbon disulphide and alcoholic potassium hydroxide followed by reaction with hydrazine hydrate (99\%), potassium thiocyanate and hydrochloric acid followed by refluxing the salt in 4\% sodium hydroxide to afford 1-cyclohexyl-3-ethoxycarbonyl-5-(4-amino-5-mercapto-1,2,4-triazol-3-yl)methoxy-2-methylindole \textsuperscript{261} and 1-cyclohexyl-3-ethoxycarbonyl-5-(4H-5-mercapto-1,2,4-triazol-3-yl)methoxy-2-methylindole \textsuperscript{262} respectively.
Scheme – 6

1. CS₂/KOH
2. N₂H₄·H₂O

Pyridine
Ethanol

K₂CO₃, KI

dry acetone

Δ
The IR spectrum (Fig-32) of 261 displayed stretching bands at 3410 cm\(^{-1}\) and 3129 cm\(^{-1}\) due to NH/NH\(_2\) while a strong stretching band at 1647 cm\(^{-1}\) was assigned to C\(_3\)-ester carbonyl. The presence of strong band at 1185 cm\(^{-1}\) indicated that this compound 261 existed predominantly in thione form. \(^1\)H NMR spectrum (Fig-33) of this sample displayed a multiplet at 1.25-2.40 \(\delta\) due to ten protons of cyclohexane. A triplet (\(J=7.1\) Hz) at 1.44 \(\delta\) belonged to C\(_3\)-ester methyl while a singlet at 2.79 \(\delta\) corresponded to C\(_2\)-methyl. A broad singlet at 3.0 \(\delta\) was accounted for NH\(_2\) group which disappeared on D\(_2\)O exchange. The C\(_1\)-proton of cyclohexane resonated at 4.26 \(\delta\) as multiplet and quartet (\(J=7.2\) Hz) at 4.36 \(\delta\) was attributed to C\(_1\)-ester methylene protons. Downfield singlet at 5.09 \(\delta\) corresponded to C\(_5\)-O-CH\(_2\) group while doublet of doublet (\(J=8.5\) Hz and 2.5 Hz) at 6.88 \(\delta\) was assigned to C\(_6\)-proton. The C\(_7\)-proton resonated as doublet (\(J=8.5\) Hz) at 7.50 \(\delta\) but doublet (\(J=2.5\) Hz) at 7.78 \(\delta\) was attributed to C\(_4\)-proton. A broad singlet at 13.64 \(\delta\) was related to NH which vanished on D\(_2\)O exchange.

The IR spectrum (Fig-34) of 262 exhibited a stretching band at 3425 cm\(^{-1}\) due to NH and a strong stretching band at 1694 cm\(^{-1}\) was assigned to C\(_3\)-ester carbonyl. \(^1\)H NMR spectrum (Fig-35) of 262 displayed multiplet from 1.20 to 2.4 \(\delta\) due to ten protons of cyclohexane. A triplet (\(J=7.1\) Hz) at 1.43 \(\delta\) was accounted for C\(_3\)-ester methyl while singlet at 2.79 \(\delta\) belonged to C\(_2\)-methyl. A multiplet at 4.28 \(\delta\) was assigned to C\(_1\)-proton of cyclohexane. Quartet (\(J=7.1\) Hz) at 4.35 \(\delta\) was characteristic of C\(_3\)-ester methylene and singlet at 4.72 \(\delta\) was attributed to C\(_5\)-O-CH\(_2\) group. The C\(_6\)-proton resonated at 6.88 \(\delta\) as doublet of doublet (\(J=8.5\) Hz and 2.5 Hz) while doublet (\(J=8.5\) Hz) at 7.45 \(\delta\) was accounted for C\(_7\)-proton. The C\(_4\)-proton resonated as doublet (\(J=2.5\) Hz) at 7.69 \(\delta\) but broad singlet at 8.97 \(\delta\) was assigned to NH which vanished on D\(_2\)O exchange.

The mass spectrum (Fig-36) of 262 gave molecular ion peak M\(^+\) at m/z (%) 414 (12.8) and a peak due to M+1 was observed at m/z (%) 415 (3.9). The loss of CH\(_4\) from M\(^+\) produced F\(_1\) fragment at m/z (%) 398 (15.8) and F\(_2\)
fragment obtained after the loss of 'S' from M* gave signal at m/z (%) 382 (4). The C3H5 was lost from M* to yield F3 fragment at m/z (%) 373 (3.1) while the loss of C4H8 from M* generated peak of F4 fragment at m/z (%) 358 (14.2). The signal of F5 fragment at m/z (%) 340 (13.4) was secured by the loss of COOC2H5 and H. The loss of C3H4N3S from M* provided a base peak fragment F6 at m/z (%) 300 (100). Fragment F7 was produced after the loss of C3H4N3S and C6H10 from M* to give peak at m/z (%) 218 (75.5) while peak at m/z (%) 190 (32.1) was due to fragment F8 resulted by the loss of C3H4N3S, C6H10 and C2H4 from M*. The signal of fragment F9 found at m/z (%) 174 (24.9) was produced by the loss of C3H4N3S, C6H10, C2H4 and CH4 from M* [Scheme-7].

Thiosemicarbazides 249 and 250 on heating with 4% sodium hydroxide solution underwent cyclodehydration to secure the desired 1-cyclohexyl-3-ethoxycarbonyl-5-(4-allyl-5-mercapto-1,2,4-triazol-3-yl)methoxy-2-methylindole 263 and 1-cyclohexyl-3-ethoxycarbonyl-5-(4-p-chlorophenyl-5-mercapto-1,2,4-triazol-3-yl)methoxy-2-methylindole 264 respectively.

The IR spectrum (Fig-37) of 263 exhibited a stretching band at 3178 cm⁻¹ and 1695 cm⁻¹ due to NH and C₂-ester carbonyl respectively. ¹H NMR spectrum (Fig-38) of 263 displayed a multiplet from 1.20 to 2.4 8 due to ten protons of cyclohexane while a triplet (J=7.1 Hz) at 1.45 8 belonged to C₃-ester methyl. Singlet at 2.79 8 corresponded to C₂-methyl and a multiplet at 4.25 8 was accounted for C₁-proton of cyclohexane. A quartet (J = 7.1 Hz) at 4.41 8 was attributed to C₃-ester methylene protons. A doublet at 4.84 8 was accounted for two allyl methylene protons. Singlet at 5.12 8 was assigned to C₅-O-CH₂ group and this downfield shift has indicated the formation of mercapto triazole ring. Multiplet from 5.21 to 5.29 8 was accounted for two vinyl methylene protons and another multiplet centered at 5.93 8 was related to vinyl methine proton. Doublet of doublet (J=8.5 Hz and 2.5 Hz) at 6.83 8 corresponded to C₆-proton while C₇-proton appeared as doublet (J=8.5 Hz) at 7.46 8. The C₄-proton resonated at 7.77 8 as doublet (J = 2.5 Hz) and broad singlet at 10.66 8 was assigned to NH which vanished on D₂O exchange.
Scheme - 7

F9
m / z (%)
174 (24.9)

F8
m / z (%)
190 (32.1)

F7
m / z (%)
218 (55)

F1
m / z (%)
398 (15.8)

F2
m / z (%)
382 (2.5)

F3
m / z (%)
373 (3.1)

F4
m / z (%)
358 (14.2)

F6
m / z (%)
300 (100)

F5
m / z (%)
340 (13.4)
The mass spectrum (Fig-39) of 263 displayed a molecular ion peak \( M^+ \) at \( m/z \) (%) 454 (22) and \( M+1 \) at \( m/z \) (%) 455 (6) while \( M+2 \) was observed at \( m/z \) (%) 456 (2). The \( F_1 \) fragment generated from \( M^+ \) after the loss of sulphur showed a singlet at \( m/z \) (%) 422 (4). \( F_2 \) fragment produced after the loss of \( \text{OC}_2\text{H}_5 \) from \( M^+ \) gave signal at \( m/z \) (%) 409 (6) while peak of \( F_3 \) fragment was seen at \( m/z \) (%) 382(14) by the loss of \( \text{COOC}_2\text{H}_5 \) from \( M^+ \). The \( F_4 \) fragment displayed signal at \( m/z \) (%) 300 (74) by the loss of \( \text{C}_8\text{H}_8\text{N}_3\text{S} \) from \( M^+ \). \( F_5 \) fragment peak was found at \( m/z \) (%) 288 (44) due to the loss of \( \text{C}_8\text{H}_8\text{N}_3\text{S} \) and \( \text{COOC}_2\text{H}_5 \) from \( M^+ \). The signal of \( F_6 \) fragment was observed at \( m/z \) (%) 218(32) after the loss \( \text{C}_8\text{H}_8\text{N}_3\text{S} \) and \( \text{C}_8\text{H}_{10} \) from \( M^+ \). And fragment \( F_7 \) signal was found at \( m/z \) (%) 174 (10) by the loss of \( \text{C}_8\text{H}_8\text{N}_3\text{S}, \text{OC}_2\text{H}_5 \) and \( \text{C}_8\text{H}_9 \). \( F_8 \) fragment peak was produced from \( M^+ \) at \( m/z \) (%) 154 (12) after the loss of \( \text{C}_{10}\text{H}_{22}\text{NO}_3 \) and \( F_9 \) fragment signal was observed at \( m/z \) (%) 146 (34) by losing \( \text{C}_8\text{H}_8\text{N}_3\text{S}, \text{C}_8\text{H}_{10} \) and \( \text{COOC}_2\text{H}_5 \). \( F_{10} \) fragment peak was generated from \( M^+ \) at \( m/z \) (%) 118 (12) due to the loss of \( \text{C}_8\text{H}_8\text{N}_3\text{S}, \text{COOC}_2\text{H}_5, \text{C}_8\text{H}_{10} \) and CO [Scheme-8].

The IR spectrum (Fig-40) of 264 displayed stretching bands at 3154 cm\(^{-1}\) and 1659 cm\(^{-1}\) due to NH and \( \text{C}_3\)-ester carbonyl respectively. A strong band at 1196 cm\(^{-1}\) was assigned to C=S group indicating the predominant existence of this compound in thione form. \(^1\text{H} \) NMR spectrum (Fig-41) of 264 showed a multiplet ranging from 1.25 to 2.4 \( \delta \) due to ten protons of cyclohexane. A triplet (\( J=7 \) Hz) at 1.44 \( \delta \) was accounted for \( \text{C}_3\)-ester methyl and singlet at 2.78 \( \delta \) corresponded to \( \text{C}_2\)-methyl protons. A multiplet centered at 4.24 \( \delta \) was characterized for \( \text{C}_1\)-proton of cyclohexane. A quartet (\( J=7 \) Hz) at 4.39 \( \delta \) was assigned to \( \text{C}_3\)-ester methylene protons while \( \text{C}_3\)-O-CH\(_2\) protons resonated as singlet at 4.95 \( \delta \) and this downfield shift has confirmed the formation of triazole ring. A multiplet from 6.63 to 7.69 \( \delta \) was attributed to seven aromatic protons. A broad singlet at 10.81 \( \delta \) was accounted for NH which disappeared on D\(_2\)O exchange.

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Present Work: Part C

Synthesis of 2,5-dimethylpyrrol-1-yl-aminocarbonylmethoxyindoles
1-p-Acetanilido-3-acetyl-2-methylindol-5-yloxyacetic acid hydrazide 258 was reacted with carbon disulphide and alcoholic potassium hydroxide to produce the desired 1-p-acetanilido-3-acetyl-5-(4-amino-5-mercapto-1,2,4-triazol-3-yl)methoxy-2-methylindole 265 which displayed in its IR spectrum (Fig-42) stretching bands at 3314 cm⁻¹ and 3258 cm⁻¹ due to NH/NH₂ functions while amide and C₃-acetyl carbonyls showed strong stretching bands at 1690 cm⁻¹ and 1634 cm⁻¹ respectively. Strong band at 1171 cm⁻¹ was assigned to C=S group indicating that this compound 265 existed predominately in thione form. ¹H NMR spectrum (Fig-43) of this sample 265 displayed singlet at 2.11 δ due to amide methyl and two overlapping singlets at 2.50 δ were assigned to C₃-acetyl and C₂-methyl protons. Broad singlet at 4.5 δ corresponded to amine NH₂ group which vanished on D₂O exchange. A downfield singlet at 5.16 δ belonged to C₅-O-CH₂ group and this downfield shift confirmed the formation of triazole ring. Multiplet from 6.89 to 7.82 δ was assigned to seven aromatic protons. Broad singlet at 10.24 δ was accounted for amide NH which disappeared on D₂O exchange. Another broad singlet at 13.81 δ belonged to NH (triazole) which vanished on D₂O exchange.
In the light of wide varieties of biological activities associated with 2,5-dimethylpyrroles213-246, we were very much encouraged to undertake the synthesis of pyrrolylindoles with enhanced biological properties.

The convenient starting material for the synthesis of pyrrolylindoles was indol-5-yloxyacetic acid hydrazides 245 and 258 which were obtained by the nucleophilic reaction of hydrazine hydrate (99%) with the indole esters 244 and 257.

1-Cyclohexyl-3-ethoxycarbonyl-2-methylindol-5-yloxyacetic acid hydrazide 245 was reacted with acetonyl acetone in boiling ethanol to secure the desired 1-cyclohexyl-3-ethoxycarbonyl-5-(2,5-dimethylpyrrol-1-yl)aminocarbonylmethoxy-2-methylindole 266 and its IR spectrum (Fig-44) displayed stretching bands at 3258 cm\(^{-1}\) due to C5-amine NH while C5-amine carbonyl and C3-ester carbonyl exhibited strong bands at 1698 cm\(^{-1}\) and 1671 cm\(^{-1}\) respectively.

\(^1\)H NMR spectrum (Fig-45) of this sample 266 showed a multiplet from 1.25 to 2.4 \(\delta\) corresponding to ten protons of cyclohexane. A triplet (\(J=7.1\) Hz) at 1.48 \(\delta\) was assigned to C2-ester methyl group while singlet at 2.09 \(\delta\) corresponded to two methyls of pyrrole (C'2 and C'5-CH\(_3\)). Another singlet at 2.83 \(\delta\) belonged to C2-methyl. Multiplet centered at 4.26 \(\delta\) was attributed to C1-proton of cyclohexane and quartet (\(J=7.1\) Hz) at 4.37 \(\delta\) was accounted for C3-ester methylene. Two singlets at 4.85 \(\delta\) and 5.82 \(\delta\) were attributed to C5-O-CH\(_2\) group and C'3, C'4 protons of pyrrole respectively. A doublet of doublet (\(J=8.5\) Hz and 2.5 Hz) at 6.90 \(\delta\) represented C6-proton while C7-proton appeared as doublet (\(J=8.5\) Hz) at 7.53 \(\delta\). The C4-proton resonated as doublet (\(J=2.5\) Hz) at 7.78 \(\delta\). Broad singlet at 8.74 \(\delta\) was assigned to C5-amine NH which disappeared on D\(_2\)O exchange.
Scheme-10

\[
\begin{align*}
\text{Scheme-10} & \\
\begin{array}{c}
\text{A}n_2h_4.h:o \\
\text{----- Pyridine} \\
y^ \text{Ethanol} \\
\text{O O} \\
\text{CRCO-CR-CR-CO-CH} \\
gl. \text{AcOH} \\
\text{Ethanol} \\
\text{O} \\
\text{HN} \\
\text{NH}, \\
120
\end{array}
\end{align*}
\]
The proton decoupled $^{13}$C NMR spectrum (Fig-46) of 266 compound displayed overlapping signals at $11.5 \delta$ due to C$_3$-ester methyl and 2,5-dimethyls of pyrrole while C$_2$-methyl carbon peak appeared at $15.09 \delta$. The cyclohexyl carbons resonated at 25.81 $\delta$, 26.73 $\delta$ and 56.56 $\delta$ due to C$_3$, C$_4$, C$_2$ and C$_1$ carbons respectively. The C$_3$-ester methylene carbon resonated at 59.91 $\delta$ and signal at 68.23 $\delta$ was assigned to C$_5$-O-methylene carbon. The C$_7$ of indole ring resonated at 104.38 $\delta$ while peaks of C$_6$ and C$_4$ were observed as overlapping singlet at 104.66 $\delta$. The peak at 105.90 $\delta$ was attributed to C$_3$ and C$_4$ of pyrrole. The junction carbon [b] of indole ring resonated at 111.12 $\delta$ while signals due to C$_2$ and C$_3$ of pyrrole nucleus appeared at 128 $\delta$. The peak of C$_2$ of indole ring was observed at 128.85 $\delta$ and peak at 131.18 $\delta$ was accounted for junction carbon [a] of indole nucleus. The peak of C$_3$ of indole ring resonated at 146.09 $\delta$ and peak of C$_5$ of indole was found at 152.75 $\delta$. The peaks of carbonyl carbons of C$_5$ amide and C$_3$ ester groups were found at 166 $\delta$ and 168 $\delta$ respectively.

Mass spectrum (Fig-47) of 266 displayed a molecular ion base peak M$^+$ at m/z (%) 451 (100) and a peak due to M+1 at m/z (%) 452 (28). F$_1$ fragment peak was produced from M$^+$ at m/z (%) 423 (1) after the loss of C$_2$H$_4$ and F$_2$ fragment signal was generated at m/z (%) 406 (10) from M$^+$ by losing OC$_2$H$_5$. The peak of F$_3$ fragment was obtained at m/z (%) 368 (1) by the loss of C$_6$H$_{11}$ from M$^+$ while F$_4$ fragment peak was observed at m/z (%) 358 (26) due to the loss of C$_6$H$_2$N from M$^+$. F$_5$ fragment gave a peak at m/z (%) 314 (10) by the loss of C$_7$H$_9$N$_2$O from M$^+$ and F$_6$ fragment signal was produced from M$^+$ at m/z (%) 300 (14) by the loss of C$_8$H$_{11}$NO. F$_7$ fragment peak was secured at m/z (%) 174 (6) from M$^+$ due to the loss of C$_8$H$_{16}$NO, OC$_2$H$_5$ and C$_6$H$_{10}$ while F$_8$ fragment signal was generated at m/z (%) 137 (30) from M$^+$ by the loss of C$_{10}$H$_{24}$NO$_3$. The signals of fragments F$_9$ and F$_{10}$ were produced at m/z (%) 109 (18) and m/z (%) 94 (20) after the loss of C$_{20}$H$_{24}$N$_2$O$_4$ and C$_{20}$H$_{28}$N$_2$O$_4$ from M$^+$ respectively [Scheme-11].
Scheme - 11

$\text{F10}$

$\text{m/z (\%)}$ 94 (20)

$\text{F9}$

$\text{m/z (\%)}$ 109 (18)

$\text{F8}$

$\text{m/z (\%)}$ 127 (30)

$\text{F7}$

$\text{m/z (\%)}$ 174 (6)

$\text{F6}$

$\text{m/z (\%)}$ 300 (14)

$\text{F5}$

$\text{m/z (\%)}$ 451 (100)

$\text{F4}$

$\text{m/z (\%)}$ 314 (10)

$\text{F3}$

$\text{m/z (\%)}$ 358 (26)

$\text{F2}$

$\text{m/z (\%)}$ 406 (10)

$\text{F1}$

$\text{m/z (\%)}$ 423 (2)
1-p-Acetanilido-3-acetyl-2-methylindol-5-yloxyacetic acid hydrazide 258 in ethanol was heated at reflux with acetonyl acetone to secure the required 1-p-acetanilido-3-acetyl-5-(2,5-dimethylpyrrol-1-yl)aminocarbonylethoxy-2-methylindole 267. The IR spectrum (Fig-48) of 267 showed stretching bands at 3431 cm⁻¹ and 3314 cm⁻¹ due to C₅-amide and anilido NH. The stretching bands at 1690 cm⁻¹, 1680 cm⁻¹ 1628 cm⁻¹ were assigned to C₅-amide and C₁-anilide and C₃-acetyl carbonyls respectively. ¹H NMR spectrum (Fig-49) of this sample 267 exhibited singlets at 2.11 δ and 1.96 δ due to anilido methyl and C₂ and C₃-methyl protons of pyrrole respectively. The C₃-acetyl methyl protons resonated as singlet at 2.50 δ while C₂-methyl appeared as singlet at 2.59 δ. Singlet at 4.82 δ belonged to C₅-O-CH₂ group and another singlet at 5.64 δ corresponded to C'₃- and C'₄- protons of pyrrole. An overlapping singlet at 6.92 δ was assigned to C₆- and C₇-protons who seemed to be magnetically equivalent. Doublets (J = 9 Hz) at 7.36 δ and 7.84 δ were assigned to C'₃, C'₅ and C'₂, C'₆ protons of 1-acetanilide group. Another doublet (J = 2.5 Hz) at 7.84 δ was accounted for C₄-proton. Two broad singlets at 10.27 δ and 11.03 δ corresponded to acetanilide NH and C₅-amide NH respectively and they disappeared on D₂O exchange.
Present Work: Part D

Synthesis of 1,2,3,4-tetrazolylmethoxyindoles
In the light of wide spectrum of biological activities associated with tetrazoles \(^{257-284}\), it was thought of considerable interest to undertake the synthesis of indole derivatives carrying the bioactive tetrazole moiety at position-5 linked through methoxy bridge.

In the present investigation, 1-\(\beta\)-acetanilido-3-acetyl-5-hydroxy-2-methylindole \(254\) was reacted with chloroacetonitrile in dry acetone in presence of anhydrous potassium carbonate and catalytic amount of potassium iodide to yield the desired 1-\(\beta\)-acetanilido-3-acetyl-2-methylindol-5-yloxy-acetonitrile \(268f\) [Scheme-12] and its IR spectrum (Fig-50) exhibited band at 3357 cm\(^{-1}\) due to amide NH while strong stretching bands at 1672 cm\(^{-1}\) and 1630 cm\(^{-1}\) were assigned to anilido acetyl and C\(_3\)-acetyl carbonyls respectively. Stretching band at 2190 cm\(^{-1}\) belonged to CN group. \(^1\)H NMR spectrum (Fig-51) of \(268f\) displayed singlet at 2.50 \(\delta\) and 2.10 \(\delta\) due to C\(_3\)-acetyl methyl and amide methyl protons respectively. Another singlet at 2.60 \(\delta\) was accounted for C\(_2\)-methyl and two protons of C\(_5\)-O-CH\(_2\)CN group resonated as singlet at 5.20 \(\delta\). An overlapping singlet at 6.92 \(\delta\) corresponded to C\(_6\)- and C\(_7\)- protons which seemed to be magnetically equivalent. Multiplet ranging from 7.20-8.00 \(\delta\) corresponded to five aromatic protons. Broad singlet at 10.28 \(\delta\) belonged to NH which disappeared on D\(_2\)O exchange.
Scheme – 12

254a

$\text{Cl-CH$_2$-CN}$

$\text{K$_2$CO$_3$, KI}$

dry acetone, $\Delta$

268f

$\text{NaN$_3$, NH$_3$Cl}$

LiCl, dry DMF

269

HN-CO-CH$_3$

125
This indolyl nitrile 268 was reacted with sodium azide, ammonium chloride in presence of catalytic amount of lithium chloride in dry dimethyl formamide to get the desired 1-p-acetanilido-3-acetyl-5-(1,2,3,4-tetrazol-5-yl)methoxy-2-methylindole 269. IR spectrum (Fig-52) of this sample 269 displayed a broad stretching band at 3420 cm\(^{-1}\) due to amide NH and tetrazole NH. Strong stretching bands observed at 1672 cm\(^{-1}\) and 1618 cm\(^{-1}\) were assigned to amide carbonyl and C\(_3\)-acetyl carbonyls respectively. Stretching band at 1300 cm\(^{-1}\) was assigned to N=N=N group while tetrazole skeletal vibrations were found in range of 1000 cm\(^{-1}\) to 1100 cm\(^{-1}\) which were in conformity with earlier reports\(^{331}\).

\(^1\)H NMR spectrum (Fig-53) of 269 exhibited singlets at 2.55 \(\delta\) and 2.11 \(\delta\) due to C\(_3\)-acetyl methyl and anilido methyl protons respectively. Singlet at 2.60 \(\delta\) was related to C\(_2\)-methyl. Downfield singlet at 5.51 \(\delta\) was attributed to C\(_5\)-O-CH\(_2\) group which indicated the formation of tetrazole ring. Multiplet ranging from 6.62 \(\delta\) to 7.9 \(\delta\) correspond to seven aromatic proton. Broad singlets at 9.1 \(\delta\) and 10.28 \(\delta\) were assigned to amide NH and tetrazole NH respectively and they vanished on D\(_2\)O exchange.

The proton decoupled \(^13\)C NMR spectrum (Fig-54) of 269 showed C\(_2\)-methyl carbon signal at 15 \(\delta\) and anilido methyl carbon peak was observed at 24 \(\delta\). The peak at 32 \(\delta\) was related to C\(_3\)-methyl while deshielded C\(_5\)-methylenes signal was observed at 66 \(\delta\) the C\(_7\) of indole nucleus was found at 105 \(\delta\) and peak due to C\(_6\) was observed at 106 \(\delta\). The C\(_3\)' and C\(_5\)' of anilido carbons resonated at 115 \(\delta\) and peak due to C\(_2\)' and C\(_6\)' anilido carbons was found at 121 \(\delta\). The signal of C\(_4\) of indole nucleus was observed at 113 \(\delta\) while the ring junction [b] carbon resonated at 112 \(\delta\). Peak of ring junction [a] carbon was observed at 127 \(\delta\). The signal of C\(_4\)' of anilido ring was found at 133 \(\delta\) while the peak at 153 \(\delta\) was assigned to C\(_5\) of indole nucleus. The peak of C\(_1\)' of anilido ring was observed at 146 \(\delta\). The peak of C\(_5\)' of tetrazole was seen at 171 \(\delta\) while the peak pertaining to anilido carbonyl was found at 172 \(\delta\). The C\(_3\)-carbonyl carbon resonated at 196.5 \(\delta\).
Present Work: Part E

Synthesis of 1,3,5-triazin-6-ylmethoxyindoles
In light of wide spectrum of biological activities associated with 1,3,5-triazines\textsuperscript{288-307}, it was thought of considerable interest to undertake the synthesis of hitherto unknown indole derivatives carrying the biodyanamic triazine nucleus at position-5 linked through methoxy bridge.

The starting materials for the synthesis of triazinylmethoxyindoles 270a-e were indol-5-yloxyacetonitriles 268a-e which were conveniently prepared by reacting 5-hydroxyindole 243a-e with chloroacetonitrile in dry acetone in presence of anhydrous potassium carbonate. The triazines 270a-e were prepared by heating these nitriles 268a-e with dicyanodiimide in isopropyl alcohol and methanol [Scheme-13].

1-Cyclohexyl-3-ethoxycarbonyl-5-hydroxy-2-methylindole 243a was reacted with chloroacetonitrile in presence of anhydrous potassium carbonate in refluxing dry acetone to obtain the required 1-cyclohexyl-3-ethoxycarbonyl-2-methylindol-5-yloxyacetonitrile 268a. IR spectrum (Fig-55) of 268a showed a C$_3$-ester carbonyl stretching band at 1674 cm$^{-1}$ and broad band due to C$_5$-OH was found absent. $^1$H NMR spectrum (Fig-56) of this sample 268a displayed multiplet from 1.2 to 2.4 $\delta$ due to ten protons of cyclohexane. Triplet ($J = 7.1$ Hz) at 1.46 $\delta$ was accounted for C$_3$-ester methyl while C$_2$-methyl protons resonated as singlet at 2.8 $\delta$. A multiplet centered at 4.25 $\delta$ was assigned to C$_1$-proton of cyclohexane and two protons of C$_5$-O-CH$_2$CN appeared as singlet at 4.81 $\delta$. Doublet of doublet ($J = 8.5$ Hz and 2.5 Hz) at 6.89 $\delta$ belonged to C$_6$-proton while C$_7$-proton resonated as doublet ($J = 8.5$ Hz) at 7.47 $\delta$. Another doublet ($J = 2.5$ Hz) at 7.80 $\delta$ was attributed to C$_4$-proton.

1-Cyclohexyl-3-ethoxycarbonyl-2-methylindol-5-yloxyacetonitrile 268a was heated at reflux with dicyanodiimide and KOH in a mixture of methanol and isopropanol to yield the desired 1-cyclohexyl-3-ethoxycarbonyl-5-(2,4-diamino-1,3,5-triazin-6-yl)methoxy-2-methylindole 270a, in good yield. IR spectrum (Fig-57) of 270a exhibited stretching bands at 3549 cm$^{-1}$ and 3326 cm$^{-1}$ due to amine group.
Scheme-13

$$\begin{array}{c}
\text{HO} & \text{Cl-CH}_2\text{-CN} & \text{R}_1 \text{CH}_3 \\
\text{R}_1 & & \\
\text{K}_2\text{CO}_3, \text{KI} & \text{dry acetone} & \Delta \\
\end{array}$$

$$\begin{array}{c}
\text{243a-e} & \text{268a-e} & \text{270a-e} \\
\end{array}$$

<table>
<thead>
<tr>
<th>$R_1$</th>
<th>$R$</th>
</tr>
</thead>
<tbody>
<tr>
<td>a -C_6H_{11}</td>
<td>-COOEt</td>
</tr>
<tr>
<td>b -C_6H_5</td>
<td>-COCH_3</td>
</tr>
<tr>
<td>c -C_6H_4OCH_3-p</td>
<td>-COCH_3</td>
</tr>
<tr>
<td>d -C_6H_4CH_3-p</td>
<td>-COCH_3</td>
</tr>
<tr>
<td>e -C_6H_4Cl-p</td>
<td>-COCH_3</td>
</tr>
</tbody>
</table>
A sharp band at 1678 cm\(^{-1}\) was related to C\(_3\)-ester carbonyl. \(^1\)H NMR spectrum (Fig-58) of 270a showed multiplet from 1.27 to 2.49 \(\delta\) due to ten protons of cyclohexane. Triplet (\(J = 7.0\) Hz) at 1.29 \(\delta\) was assigned to C\(_3\)-ester methyl and singlet at 2.74 \(\delta\) was attributed to C\(_2\)-methyl protons. Multiplet centered at 4.22 \(\delta\) was assigned to C\(_1\)-proton of cyclohexane. Quartet (\(J = 7.0\) Hz) at 4.25 \(\delta\) was accounted for C\(_3\)-ester methylene protons and singlet at 4.72 \(\delta\) belonged to C\(_5\)-O-CH\(_2\) protons. Broad singlet at 6.75 \(\delta\) overlapping the signal of C\(_6\)-proton was assigned to protons of two amine group. Doublet of doublet (\(J = 8.5\) Hz and 2.5 Hz) at 6.78 \(\delta\) was attributed to C\(_6\)-proton while C\(_4\)-proton appeared as doublet (\(J = 2.5\) Hz) at 7.44 \(\delta\). A doublet (\(J = 8.5\) Hz) at 7.6 \(\delta\) was attributed to C\(_7\)-proton.

The proton decoupled \(^{13}\)C NMR spectrum (Fig-59) of this sample showed a signal at 12.5 \(\delta\) due to ester methyl carbon and the C\(_2\)-methyl carbon resonated at 14.8 \(\delta\). The cyclohexyl carbons exhibited signals at 25 \(\delta\), 26 \(\delta\), 30.7 \(\delta\), 55 \(\delta\) due to C\(_3\), C\(_4\), C\(_2\) and C\(_1\)-carbons respectively. The peak due to O-CH\(_2\) carbon resonated at 59 \(\delta\) while peak of C\(_3\)-ester methylene carbon appeared at 70 \(\delta\). The C\(_7\) of indole nucleus resonated at 102.8 \(\delta\) and peak of C\(_6\) appeared at 104.8 \(\delta\). Signal of junction carbon [b] was observed at 111.5 \(\delta\) and peak of C\(_2\) appeared at 127.9 \(\delta\). Peak of another junction carbon [a] was found at 129.8 \(\delta\) and peak of C\(_3\) appeared at 145.7 \(\delta\) while that of C\(_5\)-resonated at 153.9 \(\delta\). The peak of triazine carbons C\(_3\) and C\(_5\) were observed at 165.7 \(\delta\) where as C\(_1\) of triazine resonated at 167.2 \(\delta\). The signal of C\(_3\)-carbonyl carbon was found at 174 \(\delta\).

Mass spectrum (Fig-60) of 270a gave molecular ion peak M\(^+\) at m/z (%) 424(100) which is a base peak and a peak due to M+1 was observed at m/z (%) 425 (28.3). Fragment F\(_1\) signal was generated by the loss of CH\(_3\) from M\(^+\) at m/z (%) 409 (6.1) and fragment F\(_2\) peak was obtained after the loss of C\(_3\)H\(_2\)O (ethanol) from M\(^+\) at m/z (%) 378 (8.6). The F\(_3\) fragment peak at m/z (%)
342(7) was due to the loss of C₆H₁₀ from M⁺. The COOC₂H₅ was lost from M⁺ to yield the signal of fragment F₄ at m/z (%) 351 (6.5). The loss of C₄H₆N₅ from M⁺ afforded F₅ fragment signal at m/z (%) 300 (57.8) while F₆ fragment peak was obtained due to the loss of C₄H₆N₅ and QH₁₀ from M⁺ at m/z (%) 218 (42.4). The F₇ fragment signal was generated at m/z (%) 189 (15.8) from M⁺ by the loss of C₆H₁₀, C₄H₆N₅ and C₂H₅. Fragment F₈ peak was obtained from M⁺ at m/z (%) 173 (11.6) by the loss of C₆H₁₀, C₄H₆N₅ and C₂H₅O [Scheme-14].
Present Work: Part F

Synthesis of 4(3H)-oxoquinazolin-3-ylaminocarbonylmethoxyindoles
In view of wide spectrum of biological activities associated with quinazoles\textsuperscript{312-326} we embarked upon the synthesis of new quinazolylindoles wherein quinazoline moiety was linked to biohydramic indole nucleus at position-5 through aminocarbonylmethoxy bridge.

In the present investigation, 1-\textit{p}-acetanilido-3-acetyl-2-methylindol-5-yloxyacetic acid hydrazide 258 was reacted with 1,3-benzoxazine in refluxing acetic acid to secure the desired 1-\textit{p}-acetanilido-3-acetyl-5-(2-phenyl-4(3H)-oxoquinazolin-3-yl)aminocarbonylmethoxy-2-methylindole 271.

IR spectrum (Fig-61) of this compound 271 showed a broad stretching band at 3283 cm\textsuperscript{-1} due to C\textsubscript{2}-amide and C\textsubscript{1}-anilido NH. Sharp stretching bands at 1658 cm\textsuperscript{-1} and 1634cm\textsuperscript{-1} were associated with quinazole amide and C\textsubscript{3}-acetyl carbonyls. \textsuperscript{1}H NMR spectrum (Fig-62) of this sample 271 displayed singlets at 2.11 \(\delta\) and 2.50 \(\delta\) due to amide methyl and C\textsubscript{3}-acetyl protons respectively. The C\textsubscript{2}-methyl protons resonated as singlet at 2.58 \(\delta\) while protons of C\textsubscript{5}-O-CH\textsubscript{2} group showed singlet at 4.63 \(\delta\). Multiplet ranging from 6.24 to 8.21 \(\delta\) corresponded to sixteen aromatic protons. Singlet at 10.30 \(\delta\) was attributed to anilide NH which disappeared on D\textsubscript{2}O exchange and C\textsubscript{3}-amide NH appeared as broad peak at 12.85 \(\delta\) which vanished on D\textsubscript{2}O exchange.
Scheme-15

HN-CO-CI^  

271

HN-CO-CH_3

257

HN-CO-CH_3

259

HN-CO-CH_3

258

HN-CO-CH_3

254

HN-CO-CH_3

257

HN-CO-CH_3

259
The proton decoupled $^{13}$C NMR spectrum (Fig-63) displayed a signal at 13.7 $\delta$ due to C$_2$-methyl carbon and signal at 24 $\delta$ was assigned to C$_3$-acetyl methyl while peak at 31.2 $\delta$ was related to anilido methyl carbon. The C$_5$-amide methylene carbon resonated at 61 $\delta$. The C$_7$ of indole ring was found at 105 $\delta$ while C$_6$ was observed at 106 $\delta$. C$_2'$, C$_6'$ of anilide moiety resonated at 111 $\delta$ and junction [b] carbon of indole ring observed at 112 $\delta$. The C$_4$ of indole ring resonated at 113 $\delta$ and C$_3'$ and C$_5'$ of anilide ring was observed at 120 $\delta$ while the junction [a] carbon of indole ring was found at 135 $\delta$. The C$_4'$ of anilide ring resonated at 140 $\delta$ while C$_1'$ of anilide ring was found at 145 $\delta$. The peak at 151.5 $\delta$ was accounted for C$_5$ of indole nucleus and signal due to C$_2$ of quinazoline ring was observed at 154 $\delta$. The carbonyls due to C$_5$ amide and anilido nucleus resonated at 165 $\delta$ and 167 $\delta$. The signal pertaining to C$_3$-acetyl carbonyl was found at 194 $\delta$. 

134
Fig. 1: IR Spectrum
Fig. 2: $^1$H NMR Spectrum
DMSO-$d_6$

on $D_2O$ exchange
Fig. 4: 'H NMR Spectrum 
CDCl₃
Fig. 6: IR Spectrum

Wavenumbers (cm$^{-1}$)

Chemical structure of the compound

1115.25
1020.04
1446.79
1409.72
1530.17
1633.74
3060.30
2977.72
2856.36
Fig. 9: 1H NMR Spectrum
CDCl₃
Fig. 10: IR Spectrum

Wavenumbers (cm⁻¹)
Fig-13 : IR Spectrum
Fig-14: $^1$H NMR Spectrum

CDCl$_3$

on D$_2$O exchange
Fig-16: $^1$H NMR Spectrum
CDCl$_3$+DMSO-d$_6$

on D$_2$O exchange
Fig. 17: IR Spectrum
Fig-18: "H NMR Spectrum
CDCl₃

on D₂O exchange
Fig-20: 1H NMR Spectrum
CDCl₃
Fig-21: IR Spectrum

Wavenumbers (cm$^{-1}$)

2960, 2920
1600
3082
3062
1631
1614
1544
1454
1426
1372
1320
1247
1164
1100
965
765
657
500
400
300
200
100
0

% Transmission

0 10 20 30 40 50 60 70 80 90 100

Chemical Structure
Fig-22: $^1$H NMR Spectrum
DMSO-$d_6$ on D$_2$O exchange
Fig. 25: IR Spectrum
Fig-26: $^1$H NMR Spectrum
$^{CDCl_3}$

on D$_2$O exchange
Fig. 30: $^1$H NMR Spectrum
DMSO-$d_6$

on D$_2$O exchange
Fig. 31: $^{13}$C NMR Spectrum
DMSO-d$_6$
Fig. 33: \(^1\)H NMR Spectrum
\(\text{CDCl}_3\)

on D\(_2\)O exchange
Fig. 38: $^1$H NMR Spectrum
CDCl$_3$

on D$_2$O exchange
Fig-39: Mass Spectrum

EI
Fig-43: $^1$H NMR Spectrum
DMSO-d$_6$

on D$_2$O exchange

$\text{HN-CO-CH}_3$
Fig. 45: $^1$H NMR Spectrum
CDCl$_3$

on D$_2$O exchange
Fig. 46: $^{13}$C NMR Spectrum
CDCl$_3$
Fig. 48: IR Spectrum

[Diagram showing IR spectrum with various peaks labeled with frequencies.]
Fig. 49: $^1$H NMR Spectrum  
DMSO-d$_6$
Fig. 50: IR Spectrum

Wavenumbers (cm$^{-1}$)

- 3000
- 3500
- 4000
- 4500
- 5000
- 5500
- 6000
- 6500
- 7000
- 7500
- 8000
- 8500
- 9000
- 9500
- 10000

Temperature (%)
Fig. 51: 'H NMR Spectrum
DMSO-d$_6$

on D$_2$O exchange
Fig. 52: IR Spectrum

Wavenumbers (cm⁻¹)

1783
1738
1672
1632
1514
1224
Fig-53: $^1$H NMR Spectrum
DMSO-$d_6$

on D$_2$O exchange
Fig-56: \(^1\)H NMR Spectrum
CDCl\(_3\)
Fig. 57: IR Spectrum
Fig. 58: 1H NMR Spectrum
DMSO-d$_6$

[Chemical structure and NMR spectrum diagram]
Fig-59: $^{13}$C NMR Spectrum
DMSO-d$_6$
Fig. 60: Mass Spectrum

H

NH₂
Fig-62: H NMR Spectrum
DMSO-d6
\[ \text{ppm} \]
on D₂O exchange
HN-CO-CH₃

chemical shifts: 0.29 P, 6.00 P, 6.19 P, 6.38 P, 7.50 P, 7.87 P
Fig-63: $^{13}$C NMR Spectrum
DMSO-$d_6$
Experimental
**p-Benzoquinone : 241**

Hydroquinone (100g) in water (1:1) was heated to 50°C on a water bath till a clear solution was obtained. The solution was cooled to 20°C and sulphuric acid (50mL, 5N) was added slowly in small portions. Potassium bromate (55g) was carefully added, in small lots to the mixture while heating the flask to 60°C on a water bath. The formation of a greenish black precipitate of quinhydrone was the indication of beginning of the reaction. Heating was stopped as the temperature rose to 75°C and the reaction was considered to be complete as soon as the black colour of reaction mixture changed to bright yellow colour of p-benzoquinine. The reaction mixture was heated to 80°C till p-benzoquinone dissolved and then cooled to 0°C. The separated solid (p-benzoquinone) was filtered washed with cold water, air dried and recrystallised from benzene as bright orange-yellowish needles m.p. 116-17°C yield : 80g, 75%.

**Ethyl 3-cyclohexylaminocrotonate : 242**

Cyclohexyl amine (37.1g, 0.375mol) was added with stirring to ethyl acetoacetate (4g, 0.423 mol) at such a rate that the temperature remained at 40-45°C. The addition required one hour and stirring was continued for additional 2 hours at 40-45°C. The mixture was set aside overnight at room temperature, extracted with ether and ethereal solution was dried over anhydrous sodium sulphate to get ethyl 3-cyclohexylaminocrotonate 242 as pale yellow oil and directly used for next stage (indolisation).

**N-(4-Acetamidophenyl)acetylacetoneimine : 253**

To a solution of p-acetamidoaniline (10g, 0.006mol) in ether (50mL) was added acetyl acetone (6g, 0.06mol) in dropwise with constant magnetic stirring at 40-45°C during 30 minutes. The separated solid on cooling to room
temperature was recrystallised from ethanol as pale brown prisms, m.p. 135-6°C (Lit.\textsuperscript{330} m.p. 138°C), yield : 85%.

1-Cyclohexyl-3-ethoxycarbonyl-5-hydroxy-2-methylindole : 243

\[ \text{p-Benzoquinone (27.5g, 0.25mol) in acetone (100mL) was mixed with a solution of ethyl 3-cyclohexylaminotonate (52.75g, 0.25mol). The mixture was refluxed for 1.5 hours on a water bath. Solvent was removed under reduced pressure and residual mass was treated with alcohol (200mL) and kept overnight. The separated solid was filtered and recrystallised from ethanol as pale brownish crystals, m.p. 275.6°C (Lit\textsuperscript{329a,b} 273.4°C), yield : 40\%}. \]

Anal. Calcd. for C\textsubscript{18}H\textsubscript{23}N\textsubscript{O\textsubscript{3}}: C, 71.62; H, 7.69; N, 4.64. Found : C, 71.84; H, 7.42; N, 4.52%.

1-p-Acetanilido-3-acetyl-5-hydroxy-2-methylindole : 254

\[ \text{p-Benzquinone (27.5g, 0.25mol) in acetone (100mL) was mixed with a solution of N-(p-acetamidophenyl)acetyl acetoneimine (58g, 0.25mol). The mixture was refluxed for 1.5 hours on a water bath. Solvent was removed under reduced pressure and residual mass was treated with alcohol (200mL) and kept overnight. The separated solid was filtered and recrystallised from ethanol as white granules m. p. 270.1°C (Lit\textsuperscript{330} 272°C), yield : 44\%}. \]

Anal. Calcd. for C\textsubscript{19}H\textsubscript{18}N\textsubscript{2}O\textsubscript{3}: C, 70. 79; H, 5.62 ; N; 8.69. Found : C, 70. 92; H, 5.36; N, 8.62%.

1-Cyclohexyl-3-ethoxycarbonyl-5-methoxycarbonylmethoxy-2 methylindole: 244

To the 5-hydroxyindole 243 (9g, 0.03mol) in dry acetone (200mL) was added methyl chloroacetate (6.48g, 0.06mol), anhydrous potassium carbonate (8g) and potassium iodide (0.1g). The mixture was heated at reflux for 50 hours. It was filtered hot and the solvent was removed under reduced pressure.
The residue was recrystallised from ethanol as white needles, m.p. 140-1°C, yield: 95%.

Anal. Calcd for $C_{21}H_{27}NO_5$: C, 67.54; H, 7.23; N, 3.75. Found: C, 67.76; H, 7.31; N, 3.42%.

1-$p$-Acetanilido-3-acetyl-5-methoxycarbonylmethoxy-2-methylindole: 257

This compound 257 was prepared as per the procedure depicted for compound 244 and recrystallised as pale yellow needles from ethanol, m.p. 261-2°C, yield: 82%.

Anal. Calcd for $C_{22}H_{22}N_2O_5$: C, 66.90; H, 5.62; N, 7.10. Found: C, 66.81; H, 5.75; N, 7.18%.

1-Cyclohexyl-3-ethoxycarbonyl-2-methylindol-5-yloxyacetic acid hydrazide: 245

A mixture of 5-methoxycarbonylmethoxyindole 244 (7.46g, 0.02mol) in ethanol (200mL), hydrazine hydrate (99%) (1g, 0.02mol) and pyridine (2 drops) was heated on a boiling water bath for 20 hours and concentrated to half volume and left overnight. The separated solid was filtered, washed with little ethanol and recrystallised from ethanol as white flowery crystals m.p. 110-11°C, yield: 55%.

Anal. Calcd for $C_{20}H_{27}N_3O_4$: C, 64.32; H, 7.28; N, 11.25. Found: C, 64.46; H, 7.32; N, 11.46%.

1-$p$-Acetanilido-3-acetyl-2-methylindol-5-yloxy acetic acid hydrazide: 258

This carbohydrazide 258 was prepared according to the procedure given for compound 245 and recrystallised from ethanol as white flowers m.p. 256-7°C, yield: 46%. Anal. Calcd for $C_{21}H_{22}N_4O_4$: C, 63.94; H, 5.62; N, 14.20. Found: C, 63.54; H, 5.67; N, 14.58%.
1-Cyclohexyl-3-ethoxycarbonyl-5-(5-mercapto-1,3,4-oxadiazol-2-yl)-methoxy-2-methylindole: 248

A mixture of carbohyrazide 254 (0.55g, 0.0015mol) in ethanol (20mL), potassium hydroxide (0.16g, 0.003mol) dissolved in water (3mL) and carbon disulphide (0.34g, 0.0045mol) was heated under reflux until the evolution of H₂S ceased (about 25 hours). The reaction mixture was cooled to room temperature and poured into ice cold water (100mL). It was then neutralized with dilute hydrochloric acid. The precipitated solid was filtered, washed with water and dried product was recrystallised from ethanol as white granules, m.p.235-6°C, yield : 48%.

Anal. Calcd for C₂₁H₂₅N₃O₄S: C, 60.70; H, 6.06; N, 10.11. Found: C, 60. 84; H, 6.28; N, 10.36%.

1-Cyclohexyl-3-ethoxycarbonyl-2-methylindol-5-yloxymethylcarboallyl-thiosemicarbazide : 249

To a solution of carbohydrazide 245 (1.8g, 0.005mol) in ethanol (50mL) was added allylisothiocyanate (0.49g, 0.005mol) with stirring. The mixture was heated under reflux for 4 hours and part of the solvent was evaporated. The solid that separated on cooling to room temperature was filtered, washed with ethanol and recrystallised from ethanol as pale yellow crystals, m.p. 151-2°C, yield : 73%.

Anal. Calcd for C₂₄H₃₂N₄O₄S: C, 60.70; H, 6.06; N, 10.11. Found: C, 60. 84; H, 6.28; N, 10.36%.

1-Cyclohexyl-3-ethoxycarbonyl-2-methylindol-5-yloxymethylcarbo-/>-chlorophenyIthiosemicarbazide: 250

A mixture of carbohydrazide 245 (1.8g, 0.005mol) and p-chlorophenylisothiocyanate (2.5g, 0.015mol) in ethanol (50mL) was refluxed for 8-10 hours. The solvent was removed under suction and the separated solid
was filtered, washed with ethanol, dried and recrystallised from ethanol as yellow flakes m.p. 139-40°C, yield : 58%.

Anal. Calcd for C_{27}H_{31}N_{4}O_{4}ClS : C, 59.71; H, 5.75; N, 10.31; C, 59.63; H, 5.50; N, 10.65%.

1-Cyclohexyl-3-ethoxycarbonyl-5-(5-allylamino-1,3,4-oxadiazol-2-yl)-methoxy-2-methylindole: 251

To the solution of allylthiosemicarbazide 249 (0.7g, 0.0015mol) in ethanol (15mL) was added NaOH solution (1mL, 4%) with cooling and shaking. A solution of iodine in potassium iodide (aq. 5%) was added gradually to it with shaking till the colour of iodine persisted at room temperature. The contents were heated at reflux on a boiling water bath and more iodine solution was added, till the iodine colour persisted. The heating was continued for 4 hours and the volume of the solution was concentrated under reduced pressure. The residue was cooled and poured into ice cold water. This solution was filtered and acidified with dilute acetic acid (10%) to liberate free oxadiazolylindole. This was filtered washed with water, then with little ethanol and recrystallised from ethanol as brown crystals, m.p. 251-2°C, yield : 42%.

Anal. Calcd for C_{24}H_{30}N_{4}O_{4}: C, 65.73; H, 6.89; N, 12.77. Found: C, 65.83; H, 6.76; N, 12.88%.

1-Cyclohexyl-3-ethoxycarbonyl-5-(5-p-chloroanilino-1,3,4-oxadiazol-2-yl)methoxy-2-methylindole: 252

A solution of p-chlorophenylthiosemicarbazide 250 (0.8g, 0.0015mol) in ethanol (15mL) was added NaOH (1mL, 4%) with cooling and shaking. A solution of iodine in potassium iodide (aq. 5%) was added gradually to it with shaking till the colour of iodine persisted at room temperature. The contents were heated at reflux and more iodine solution was added, till the colour of iodine persisted. The reflux was continued for 6 hours and the volume of solution was concentrated under reduced pressure. The residue was cooled and...
poured into ice cold water (100mL). This solution was filtered and acidified with dilute acetic acid (10%) to liberate free oxadiazolylindole. This was filtered, washed with cold ethanol and recrystallised from ethanol as brown flakes, m.p. 236-7°C, yield: 56%.

Anal. Calcd for C_{27}H_{29}N_4O_4Cl: C, 63.71; H, 5.74; N, 11.00. Found: C, 63.53; H, 5.82; N, 11.43%.

1-p-N-methylacetanilido-3-acetyl-5-methoxy-2-methylindole: 255.

To the solution 5-hydroxyindole 254 (1g, 0.003mol) in dry acetone (25mL) were added methyl iodide (0.8g, 0.006mol) and anhydrous potassium carbonate (2g) and potassium iodide (0.1g). The mixture was heated at reflux for 45 hours and filtered hot. The solvent was removed under reduced pressure and residue was recrystallised from ethanol as dark brown flakes, m.p. 232-3°C, yield: 77%.

Anal. Calcd for C_{21}H_{22}N_2O_3: C, 71.97; H, 6.32; N, 7.99. Found: C, 71.66; H, 6.48; N, 7.33%.

1-Cyclohexyl-3-ethoxycarbonyl-5-(4-amino-5-mercapto-1,2,4-triazol-3-yl)-methoxy-2-methylindole: 261

To an ice cold solution of potassium hydroxide (0.16g, 0.003mol) in dry ethanol (25mL) was added indole carbohydrazide 245 (0.7g, 0.002mol) and carbon disulphide (0.3g, 0.004mol) with stirring. The reaction mixture was stirred further at room temperature for 20 hours. This mixture was then diluted with dry ether and dried to secure the potassium salt of indol-5-yloxy acetic dithiocarbazinic acid in quantitative yield. This was used in the next step without further purification. The potassium salt was heated with stirring on a boiling water bath with hydrazine hydrate (0.1mL) till the evolution of H_2S ceased (about 5-6 hours). The reaction mixture was poured into ice cold water (20mL) and acidified with glacial acetic acid. The precipitated triazolyl indole
was filtered, dried and recrystallised from ethanol as pale yellow needles, m.p. 188-9°C, yield: 48%.

Anal. Calcd for C_{21}H_{27}N_{5}O_{3}S: C, 58.71; H, 6.33; N, 16.30. Found: C, 58.62; H, 6.45; N, 16.48%.

1-p-Acetanilido-3-acetyl-5-(4-amino-5-mercapto-1,2,4-triazol-3-yl)-methoxy-2-methylindole: 265

This compound 265 was prepared as per the procedure depicted for compound 261. It was recrystallised as yellow needles from ethanol m.p. 221-2°C, yield: 53%.

Anal. Calcd for C_{22}H_{22}N_{6}O_{3}S: C, 58.64; H, 4.92; N, 18.65. Found: C, 58.73; H, 4.56; N, 18.44%.

1-Cyclohexyl-3-ethoxycarbonyl-5-(4H-5-mercapto-1,2,4-triazol-3-yl)-methoxy-2-methylindole: 262.

To a solution of carbohydrazide 245 (0.7g, 0.002mol) in methanol (25mL) was added KCNS (0.29g, 0.003mol) and concentrated hydrochloric acid (3mL). The reaction mixture was refluxed on a water bath for 4 hours and the solvent was removed under pressure. The residue was triturated with water and pH was adjusted to 6 with aq. NH₃. The solid that separated was filtered, washed with water, dried and recrystallised from ethanol to obtain thiosemicarbazide. A suspension of thiosemicarbazide in aq. solution of NaOH (10% 5mL) was gently refluxed for 4 hours. The reaction mixture was cooled, filtered and filtrate acidified (pH 5), the separated solid was filtered washed, dried and recrystallised from dioxan-ethanol as white granules, m.p. 210-11°C, yield: 51%.

Anal. Calcd for C_{21}H_{26}N_{4}O_{3}S: C, 60.84; H, 6.32; N, 13.51. Found: C, 60.73; H, 6.48; N, 13.68%.
1-Cyclohexyl-3-ethoxycarbonyl-5-(4-allyl-5-mercapto-1,2,4-triazol-3-yl) methoxy-2-methylindole: 263.

The suspension of allylthiosemicarbazide 249 (0.7g, 0.0015mol) in sodium hydroxide (4%, 10mL) was gently warmed on water bath for about 1 hour. The reaction mixture after cooling to room temperature was poured into crushed ice (20g) and acidified carefully with dilute acetic acid. The precipitate thus obtained was filtered, washed with water, dried and recrystallised from ethanol as white flakes, m.p. 263-4°C, yield: 65%.

Anal. Calcd for C_{24}H_{30}N_{4}O_{3}S: C, 36.40; H, 6.65; N, 12.32. Found: C, 63.42; H, 6.31; N, 12.57%.

1-Cyclohexyl-3-ethoxycarbonyl-5-(4-p-chlorphenyl-5-mercapto-1,2,4-triazol-3-yl) methoxy-2-methylindole: 264

This compound 264 was obtained from the thiosemicarbazide by using the procedure depicted for compound 263 and it was recrystallised from ethanol as white flakes, m.p. 247-8°C, yield: 57%.

Anal. Calcd for C_{27}H_{29}N_{4}O_{3}S: C, 61.76; H, 5.56; N, 10.67. Found: C, 61.32; H, 5.84; N, 10.43%.

1-Cyclohexyl-3-ethoxycarbonyl-5-(1,3,4-oxadiazol-2-yl)methoxy-2-methylindole: 247.

A solution of triethyl orthoformate and carbohydrazide 245 (0.7g, 0.02mol) was refluxed for 12 hours. The excess of triethyl orthoformate was removed under reduced pressure and the solid obtained was recrystallised from ethanol as yellow flakes, m.p. 152-3°C, yield: 77%.

Anal. Calcd for C_{21}H_{25}N_{3}O_{4}: C, 65.77; H, 6.57; N, 10.96. Found: C, 65.32; H, 6.02; N, 10.43%.
1-p-Acetanilido-3-acetyl-5-(1,3,4-oxadiazol-2-yl)methoxy-2-methylindole: 260

This compound 260 was prepared from carbohydrazide 258 as per the procedure given for compound 247 and it was recrystallised from ethanol as yellow needles, m.p. 170-1°C, yield : 45%.

Anal. Calcd for C_{22}H_{20}N_{4}O_{4}: C, 65.33; H, 4.98; N, 13.85. Found: C, 65.15; H, 4.36; N, 13.23%.

1-Cychexyl-3-ethoxycarbonyl-5-(2,5-dimethylpyrrol-1-yl)aminocarbonylmethoxy-2-methylindole: 266

To a suspension of carbohydrazide 245 (0.37g, 0.001 mol) in ethanol (10mL) was added acetonyl acetone (0.22g, 0.002mol) and glacial acetic acid (1mL) and the reaction mixture was heated on a boiling water bath for 4 hours. The reaction mixture was concentrated to half of original volume and poured into crushed ice (50g). The separated solid was filtered, washed with water, dried and recrystallised from ethanol as pinkish brown flakes, m.p. 171-2°C, yield 88%.

Anal. Calcd for C_{26}H_{33}N_{3}O_{4}: C, 69.15; H, 7.36; N, 9.30. Found: C, 69.42; H, 7.84; N, 9.05%.

1-p-Acetanilido-3-acetyl-5-(2,5-dimethylpyrrol-1-yl)aminocarbonylmethoxy-2-methylindole: 267

This compound 267 was prepared from carbohydrazide 258 according to the procedure depicted for compound 266 and it was recrystallised from ethanol as brown flakes, m.p. 274-5°C, yield : 62%.

Anal. Calcd for C_{27}H_{28}N_{4}O_{4}: C, 68.62; H, 5.97; N, 11.85. Found: C, 68.88; H, 5.22; N, 11.36%.
**1-Substituted-3-acetyl-2-methylindol-5-yloxyacetonitriles : 268a-f**

To the 5-hydroxyindole 254a-f (0.005 mol) in dry acetone (100 mL) were added chloroacetonitrile (0.52 g, 0.01 mol), anhydrous potassium carbonate (3 g) and potassium iodide (0.1 g). The reaction mixture was heated at reflux for 50 hours and filtered hot. The solvent was removed under reduced pressure and the residue was recrystallised from suitable solvent [Table-1].

**1-p-Acetanilido-3-acetyl-5-(1,2,3,4-tetrazol-5-yl)methoxy-2-methylindole : 269**

A mixture of 1-p-acetanilido-3-acetyl-2-methylindole-5-yloxyacetonitrile 268f (1 g, 0.003 mol) in dry dimethylformamide, (10 mL), sodium azide (0.58 g, 0.009 mol) ammonium chloride (0.47 g, 0.009 mol) and lithium chloride (0.1 g) was heated in an oil bath with stirring at 125-30°C for 24 hours. It was then filtered to remove the inorganic salts and the solvent was removed under reduced pressure. The residue was dissolved in water and filtered to remove the suspended particles, if any. The filtrate was cooled and acidified to pH 2 with dilute hydrochloric acid. The separated solid was filtered, washed with water dried and recrystallised from methanol as brown flakes, m.p. 261-2°C, yield : 42%.


**1-Substitued-3-ethoxycarbonyl/acetyl-5-(2,4-diamino-1,3,5-triazin-6-yl)methoxy-2-methylindoles : 270a-e**

A mixture of indol-5-yloxyacetonitriles 268a-e (0.001 mol), dicyanodi-imide (0.1 g, 0.00125 mol) and potassium hydroxide (1.2 g, 0.022 mol) in methanol (6 mL) and isopropanol (50 mL) was refluxed for 8 hours. The reaction mixture was cooled and filtered. The separated solid was recrystallised from suitable solvent [Table -2].
1-\(p\)-Acetanilido-3-acetyl-5-(2-phenyl-4(3H)-oxoquinazolin-3-yl)amino-carbonylmethoxy-2-methylindole : 271

The solution of 1-\(p\)-acetanilido-3-acetyl-2-methylindol-5-yloxyacetic acid hydrazide 258 (0.5g, 0.013mol) and 1,3-\(\beta\)enoxazine (0.27g, 0.013mol) in acetic acid was heated at reflux for 12 hours. The solvent was removed under reduced pressure and residue was thoroughly washed with water till neutral to pH, dried and recrystallised from ethanol as brown flakes, m.p. 213-4°C, yield : 36%.

Anal. Calcd for C\(_{35}\)H\(_{29}\)N\(_5\)O\(_5\) : C, 70.10, H, 4.87, N, 11.68. Found : C, 70.56; H, 4.14; N, 11.21%. 

145
Table-1

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<th>Compd.</th>
<th>R</th>
<th>R¹</th>
<th>m.p. °C</th>
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<th>Nature (Solvent)</th>
<th>Molecular formula</th>
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Table-2