Studies on the Syntheses of Possible Antifertility and Anthelmintic Agents

(SUMMARY)

A THESIS SUBMITTED TO THE
ALIGARH MUSLIM UNIVERSITY, ALIGARH
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IN CHEMISTRY

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SUMMARY
SYNTHESES OF POSSIBLE ANTIFERTILITY AGENTS

In India, one of the priority areas of research work in medicinal chemistry relates to the prevention of pregnancy. A chemical agent, capable of preventing pregnancy, has greater acceptability provided it does not prolong the period of menstruation and does not cause unwanted side-effects. Search for structural lead to achieve this objective has resulted in the synthesis and biological evaluation of thousands of aryl-ethylene derivatives. These compounds, though very effective in preventing pregnancy in experimental animals, are not suitable for clinical use. Thereafter no useful structural lead has been identified for the development of a non-steroidal oral contraceptive agent. However, various attempts made to identify possible lead molecules have suggested that exploratory research activities in the area of heterocycles may provide useful lead for achieving this objective. The present study is, therefore, aimed towards identifying simpler heterocycles capable of evoking contraceptive activity. The various molecules identified for the syntheses and biological evaluation are listed below:-
In another approach it was considered of interest to design compounds which may selectively alter the permeability of the decidual cells in uterus and may also interfere with the oxido-reductive processes of the cell biochemistry. Representative prototypes of such compounds are:

Syntheses of compounds belonging to prototypes I-III required substituted aroyl propionic acids as the starting materials. These were prepared by the Friedel-Craft reaction of sodium aromatic substrate with succinic anhydride. Esterification of the substituted aroyl propionic acids so obtained followed by their reduction with sodium borohydride gave a mixture of 4-hydroxy-4-substituted phenyl butyrate and 2-oxo-5-substituted phenyl tetrahydrofurans (Prototype I). These were separated by column chromatography over silica gel. Ring closure of methyl-4-substituted phenyl-4-oxo-butyrate with acetic anhydride and hydrazine hydrate yielded compounds belonging to prototypes II and III respectively.

Synthetic approach towards fourth prototype, namely 4-arylidine-3-methyl-isoxazolone-5- involved the reaction of appropriate aryl aldoximes with methylacetoacetate. One representative compound of this class of compounds
was reduced with sodium borohydride to obtain a stereomeric mixtures of IVa.

**Syntheses of prototypes V and VI** namely 3-substitutedphenyl 2-isoxazolin-5-one and 3-substitutedphenyl-5-methyl isoxazole respectively required starting materials of the type A.

![Chemical structures](image)

These compounds namely 4-acetyl-3-methoxycarbonyl or acetyl-4-substitutedphenyl but-3-ene-2-ones, in principle, can be prepared by the pyridinium chlorochromate (PCC) oxidation of 2,5-dimethyl-3-methoxycarbonyl or acetyl-4-substitutedphenylfurans. Results of the PCC oxidation of these furans indicated that instead of compound A 4-acetoxy-3-methoxycarbonyl or acetyl-4-substitutedphenyl but-3-ene-2-ones (1) were obtained. This oxidation is novel and the products being reactive organic intermediates are of interest for more than one reason. For example, the reaction of the oxidation products with aqueous acid to yield acetophenones may evoke interest for understanding reaction mechanism. This is precisely why an appropriate intermediate has been isolated to delineate the reaction pathway of this reaction. Hydroxylamine reacted smoothly with the PCC oxidation products to furnish compounds belonging to prototypes V and VI. However, the facile loss of COCH₃ group even at milder reaction conditions prevented the preparation of other compounds (R¹ = COCH₃) of the prototype V. Besides the chemical reactivity of the PCC oxidation products, their behaviour under electron impact was also interesting and a careful study of their mass fragmentation pattern has been carried out.

The required starting material for the synthesis of 2,5-dimethyl-3-methoxycarbonyl-4-(3-cyano-2-oxo-1,2,3,4-tetrahydroquinolino) furan (Prototype VII) was obtained by carrying out modified Nef reaction of 1-(p-acetamidophenyl)-2-nitro propene. The resulting compound
namely 2,5-dimethyl-3-methoxycarbonyl-4-(p-acetamidophenyl)furan was subjected to Vilsmier-Haak reaction and the formyl derivative so obtained on oximation gave 2,5-dimethyl-3-methoxycarbonyl-4-(3-aldoximino-2-chloro quinolino) furan. This compound on reaction with SOCl₂ followed by sodium borohydride reduction furnished the desired molecule.

Compounds representing prototype VIII were prepared by reacting substituted aldehydes with methyl-3-amino crotonate in presence of appropriate solvents. In order to change R, two synthetic strategies have been employed. In the first one, appropriately substituted aromatic or heterocyclic aldehydes were prepared and in the second one, appropriate functionalities on the phenyl ring of 2,6-dimethyl-3,5-dimethoxycarbonyl-4-phenyl-1,4-dihydropyridine were simulated for elaborating them to heterocyclic ring systems. Aldehydes such as 4-chloro-3-nitro benzaldehyde, 2-chloro-3-formyl-quinoline and 4-formyl tetrazolo [1,5-a] quinoline have been prepared. The heterocyclic ring systems on the phenyl ring of 2,6-dimethyl-3,5-dimethoxycarbonyl-4-phenyl-1,4-dihydropyridine have been made from appropriate 1,4-dihydropyridine substrate. For example, hydrogenation of 2,6-dimethyl-3,5-dimethoxycarbonyl-4-(4-amino-3-nitrophenyl)-1,4-dihydropyridine gave the expected diamine, which without further purification was reacted with a variety of reagents such as arylaldehydes, sodium nitrite, benzil, CS₂ and phthalic anhydride to yield 2-aryl-5(6)-[4-(2,6-dimethyl-3,5-dimethoxycarbonyl-1,4-dihydropyridyl]-1(3)-substitutedbenzyl benzimidazole, 5(6)-[4-(2,6-dimethyl-3,5-dimethoxycarbonyl-1,4-dihydropyridyl)]benztriazole, 6-[4-(2,6-dimethyl-3,5-dimethoxycarbonyl-1,4-dihydropyridyl)]-2,3-diphenyl quinoxaline, 5(6)-[4-(2,6-dimethyl-3,5-dimethoxycarbonyl-1,4-dihydropyridyl)]-2-mercapto benzimidazole and 10-H-2-[4-(2,6-dimethyl-3,5-dimethoxycarbonyl)-1,4-dihydropyridyl]-
10-oxo-isoindolo [3,2-a] benzimidazole respectively.

**Biological Activity:**

Various compounds synthesised as possible antifertility agents have been screened for their contraceptive efficacy in rats and hamsters. *New leads have been generated* and significant contraceptive activity in 2,6-dimethyl-3,5-dimethoxycarbonyl-4-substituted-1,4-dihydropyridine have been observed.

**SYNTHESSES OF POSSIBLE ANTHELMINTIC AGENTS**

The existing medical facilities in rural areas and the socio-economic structure of the endemic population of India call for the development of a broad-spectrum anthelmintic. In principle, a broad-spectrum anthelmintic agent should possess the ability to enter cestode and nematode parasites irrespective of their tissue locations and should be capable of evoking selective interference with the biochemistry of the parasites. In order to achieve this objective, the identification of the pharmacophore, which should be attached to the lead molecule, is essential. Earlier work on benzimidazole-2-carbamates, carried out in this laboratory, suggested that the orientation of the carbonyl group(s) simulated in the molecular framework of substituents attached to position 5(6) of benzimidazole nucleus greatly influences antinematodal and anticestodal properties. Although a large number of compounds have been synthesised to identify the pharmacophore responsible for wide-spectrum anthelmintic activity, the complete knowledge of desired pharmacophore has not yet been achieved. It was, therefore, considered of interest to extend this exploratory research activity and the synthesis of prototypes IX-XXII (Fig.1) was then undertaken. The design of prototypes XVI and XVII is based on the concept that dihydropyrimidine derivatives may interfere selectively with the redox reactions of the parasite energy metabolism and if found active may serve as lead compounds for drug development work.

The synthetic strategy for prototype IX, namely 4-benzoyl-N-[5(6)-(2-methoxycarbonylamino)benzimidazolyl]pyrrolidin-2-one required 4-benzoyl-N-(4-amino-3-nitrophenyl)-pyrrolidin-2-one as the starting material and this was prepared by reaction of β-benzoylγ-butyrolactone with 2-nitro-p-phenylene diamine. Structural elucidation
(Fig. 1)
of the reaction product called for a model reaction and the one identified for this purpose was concerned with the reaction of β-(p-toluoyl)-γ-butyrolactones with p-anisidine. **Detailed studies on the $^{13}$C and $^{15}$N-NMR spectra of the reaction product in this model reaction helped to identify it as 4-toluoyl-N-(p-methoxyphenyl)-pyrrolidin-2-one. Based on this result, the reaction product of β-benoyl-γ-butyrolactone with 2-nitro-p-phenylene diamine was identified as 4-benzoyl-N-(4-amino-3-nitophenyl)-pyrrolidin-2-one.

**The synthesis of prototype X,** namely β-(2-methoxycarbonyl-amino)-5(6)-benzimidazolyl-acrylic acid, was initiated by reacting 4-acetamido-3-nitro benzaldehyde with malonic acid in presence of catalytic amount of pyridine. The resulting product was hydrolysed under alkaline conditions and the o-nitro aniline derivative so obtained was hydrogenated under controlled conditions to furnish the desired diamine. Reaction of this compound with N,N-dimethoxycarbonyl-S-methylisothiourea yielded the desired prototype X.

**The synthesis of prototype XI,** namely methyl 5(6)-(5-ethoxycarbonyl-6-methyl-3, 4-dihydropyrimidin-4-yl) benzimidazole-2-carbamate required 5-ethoxycarbonyl-6-methyl-2-oxo-4-(4-acetamido-3-nitrophenyl) pyrimidine as the starting material. This was prepared by the acid catalysed reaction of 4-acetamido-3-nitrobenzaldehyde with ethyl-acetoacetate and urea. The pyrimidine so obtained after hydrogenation was cyclised with N,N-dimethoxycarbonyl-S-methylisothiourea to give the required prototype XI.
During the course of present investigation on the preparation of dihydropyrimidines, it was possible to isolate the intermediate formed in the acid catalysed reaction of aromatic aldehyde with \( \beta \)-ketoester in presence of thiourea. It is noteworthy because earlier attempts to isolate the intermediate were unsuccessful.

The preparation of the prototype XII, namely 2-methoxycarbonylamino benzimidazole-5(6)-acetoxime by the direct oximation of methyl-5(6)-acetyl benzimidazole-2-carbamate has revealed that despite the presence of a carbamate moiety, the oximation of carbonyl group was possible.

The synthesis of prototype XIII \((X = \text{NH})\) owes its origin to the observation made during the upscaling studies of the CDRI compound 83/148, a potent anthelmintic agent. It was observed that during the preparation of 2,5-dimethyl-3-methoxycarbonyl-4-(4-amino-3-nitrophenyl) furan, the required intermediate for the preparation of 83/148, invariably a small amount of red compound was formed in the reaction mixture and this was identified as 2,5-dimethyl-3-methoxycarbonyl-4-(4-amino-3-nitrophenyl)pyrrole. The formation of this pyrrole derivative along with the corresponding furan in the Nef reaction of 1-(4-amino-3-nitrophenyl)-2-nitro propene in presence of methylacetoacetate and piperidine suggested that a careful study of this reaction may furnish a reaction condition in which the pyrrole could be obtained as the predominant product.
This prompted to study the Nef reaction in presence of primary, secondary and tertiary amines and the results were monitored by HPLC. The reactions of 2-nitro-1-substitutedphenyl propenes with methylacetoacetate in presence of primary amines gave exclusively N-substituted pyrrole, while the presence of secondary amines furnished a mixture of pyrrole and furan derivatives and the presence of tertiary amine exclusively yielded furan derivatives. The hydrogenation of 2,5-dimethyl-3-methoxycarbonyl-4-(4-amino-3-nitrophenyl)-N-substituted pyrroles and 2,5-dimethyl-3-methoxycarbonyl-4-substituted phenyl-N-(4-amino-3-nitrophenyl)pyrroles followed by the cyclisation of the hydrogenation products with N,N-dimethoxycarbonyl-S-methylisothiourea yielded compounds of prototypes XIII and XIV respectively. The $^{13}$C-NMR spectra of tetrasubstituted furans and tetra or penta-substituted pyrroles and their comparison with spectra computed by a computer on the basis of literature data have yielded useful information.

The synthetic strategy for prototype XV, namely 2,2'-dicarboxymethoxyamino-5,5'-dibenzimidazolyl methanol involved the following sequence of reactions. Nucleophilic displacement of chlorine in 4,4'-dichloro-3,3'-dinitro benzophenone with aqueous ammonia followed by the sodium borohydride reduction of the resulting nitroamine gave the secondary alcohol. Hydrogenation of this compound followed by the cyclisation of the resulting diamine with N,N-dimethoxycarbonyl-S-methylisothiourea furnished the required prototype XV.

Synthesis of prototypes XVI-XVII were initiated by carrying out acid catalysed reaction of aromatic aldehydes with methylacetoacetate in presence of thiourea. Studies on the alkylation of resulting compound, namely 5-ethoxy-carbonyl-6-methyl-4-substitutedphenyl-3,4-dihydropyrimidine-2-thione, gave useful information. Alkylation with
methyl iodide in presence of sodium hydroxide in methanol yielded only S-methyl derivative and the methylation of the same substrate in DMSO gave the dimethylated product namely 1,6-dimethyl-5-ethoxy-carbonyl-2-methylmercapto-4-phenyl-4-(1-H)-pyrimidine. Nucleophilic displacement of methyl mercaptan from S-methyl derivative (mono alkylated product) by N-methyl piperazine furnished XVI. In an another novel alkylation reaction, 5-ethoxycarbonyl-6-methyl-4-substituted-phenyl-3,4-dihydropyrimidin-2-thione was reacted with monochloroacetic acid in presence of BF$_3$-etherate in methanol and this resulted in the formation of prototype XVII.

The synthesis of prototype XVIII, namely 5(6)-N[(2-methylmercapto-6-methyl-4-phenyl pyrimidin-5-yl)methyl]amino benzimidazole-2-carbamate involved the aromatisation of 5-ethoxycarbonyl-2-methylmercapto-6-methyl-4-phenyl-4(1H)-pyrimidine with manganic acetate as the first step of the total synthesis. This was followed by LAH reduction and the resulting compound namely 5-hydroxymethyl-2-methylmercapto-6-methyl-4-phenyl pyrimidine was reacted with PBr$_3$ to obtain the desired bromo derivative. The latter was reacted with 2-nitro-p-phenylene diamine, and the reaction product was then hydrogenated to yield the desired diamine which was then cyclised with N,N-dimethoxycarbonyl-S-methylisothiourea to furnish the required compound of the prototype XVIII.
Syntheses of molecules belonging to prototype XIX, namely methyl-5(6)-[4-(2,6-dimethyl-3,5-dimethoxycarbonyl-1,4-dihydropyridino)]-N-substituted benzimidazole-2-carbamates, were achieved by following sequence of 3-Nitro-4-substitutedamino-chlorobenzaldehyde was reacted with methyl-3-amino crotonate to obtain the corresponding 1,4-dihydropyridine derivative. Nucleophilic displacement of chlorine by amines followed by hydrogenation of the resulting o-nitro aniline derivatives gave the desired o-phenylenediamine derivatives which were then cyclised with N,N-dimethoxycarbonyl-S-methylisothiourea to yield XIX.

The compounds representing prototype XX namely N,N-dimethoxycarbonyl-N-substitutedbenzyl guanidines were prepared by reacting appropriate benzylamines with N,N-dimethoxycarbonyl-S-methylisothiourea.

The synthetic strategy for prototype XXI namely methyl-4(5)-methyl-5(4)-(3,4-methylenedioxyphenyl)-4,5-dihydroimidazole-2-carbamate, involved the reaction of 2-nitro-1-(3,4-methylenedioxyphenyl)propene with hydroxylamine hydrochloride as the first step. The compound so obtained was hydrogenated and the resulting diamine was cyclised with N,N-dimethoxycarbonyl-S-methylisothiourea to yield compounds of the prototype XXI.

The synthetic strategy for the prototype XXII, namely 1,6-biscarbomethoxy-2-methoxycarbonylamino-7-methyl-5-(p-methoxyphenyl)-4,5,6,7-tetrahydro-1,3-diazepine required 3-amino-2-[(p-methoxyphenyl)nitroethyl]crotonate as the starting material. This was prepared by
reacting 2-nitro-1-(p-methoxyphenyl)propene with methyl-3-amino crotonate. This compound was reacted with hydroxylamine to obtain 3-carbomethoxy 5-nitro-2-oximino-(4-p-methoxyphenyl) pentane. Evidence for the assigned structure was obtained from spectroscopic data and from the results of chemical transformations. Similar to the reaction of 1-(p-methoxyphenyl)-propene with methyl-3-amino crotonate, reactions of other 2-nitro-1-substitutedphenyl propenes with the same reactant gave 3-amino-2-[(p-substitutedphenyl)nitroethyl]crotonates, which in turn reacted with hydroxylamine to yield 5-nitro-2-oximino-4-substitutedphenyl pentanes. Oxidation of the latter class of compounds with either monoperphthalic acid or m-chloro perbenzoic acid yielded 3-carbomethoxy-3-hydroxy-5-nitro-4-substitutedphenyl pentan-2-ones. Oximation of these compounds gave 3-carbomethoxy-3-hydroxy-5-nitro-2-oximino-4-substitutedphenyl pentanes. On the basis of Dreiding model the stereochemistry of these diastereomers was assigned as R,R (threo). In order to obtain the prototype molecule, 3-carbomethoxy-4-(p-methoxyphenyl)-5-nitro-2-oximino pentane was hydrogenated and the product without further purification was cyclised with N,N-dimethoxycarbonyl-S-methylisothioureia to yield XXII.

**Biological Activity**

Compounds representing various prototypes were evaluated for their antifilarial activity against *L. carinii*, cestocidal activity against *H. nana* and nematocidal activity against *A. ceylanicum* and *N. brasiliensis* infections. Compounds exhibiting significant anthelmintic activity were screened for their activity against developing stages of parasites. Sensitivity of pharmacophores in "benzimidazole carbamates" for eliciting anthelmintic activity has been discussed and a compound exhibiting specific activity against hook-work has also been identified. Compounds representing prototypes X, XII, XVI, XVII, XVIII, XX and XXII did not exhibit any anthelmintic activity.
Studies on the Syntheses of Possible Antifertility and Anthelmintic Agents

A THESIS SUBMITTED TO THE ALIGARH MUSLIM UNIVERSITY, ALIGARH FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN CHEMISTRY

BY Mohammad Shamim Akhtar M. Phil.

DIVISION OF MEDICINAL CHEMISTRY CENTRAL DRUG RESEARCH INSTITUTE LUCKNOW-226001 FEBRUARY, 1987
TO
MY PARENTS
AND
TEACHERS
CERTIFICATE

This is to certify that the work embodied in this thesis has been carried out by Mr. M. Shamim Akhtar, M.Phil., under our supervision. He has fulfilled the requirements for the degree of Doctor of Philosophy of the Aligarh Muslim University regarding the nature and prescribed period of investigational work. The work included in this thesis unless otherwise stated, is all original.

(M.S. AHMAD)

(A.P. BHADURI)
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(M. Shamim Akhtar)
**LIST OF ABBREVIATIONS**

Unless otherwise stated all arabic numbers in **BOLD** letters refer to compounds discussed in this dissertation.

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<th>Description</th>
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<td>AlCl₃</td>
<td>Aluminium Chloride</td>
</tr>
<tr>
<td>bs</td>
<td>Broad singlet</td>
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<tr>
<td>¹³C-NMR</td>
<td>¹³Carbon nuclear magnetic resonance</td>
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<td>d</td>
<td>Doublet</td>
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<tr>
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PREFACE

In India, the priority areas of research work in medicinal chemistry are two; the first one is concerned with parasitic infections while the second one relates to the prevention of pregnancy. The existing medical facility in villages and the socio-economic structure of the population call for an easy access to a broad-spectrum antiparasitic agent and if a cheap chemoprophylactic is also made available, the diseased and those who are susceptible to the disease would be benefitted and would help in restricting the endemic areas to a manageable situation. Prevention of pregnancy by a chemical agent would be more acceptable to those who are motivated for family welfare if the agent causes minimum physiological insult and if the period of menstruation is not enhanced.

In the light of these concepts the present study has been initiated. Approach for developing an agent to prevent pregnancy, therefore, is concerned with the non-steroidal molecules. The failure of triarylethylenes to provide a non-steroidal remedy has prompted a world wide search for new structural leads. The first part of this dissertation is directed towards this objective. The second part of this dissertation is aimed towards identifying pharmacophores which are responsible for evoking anticestodal and antinematodal activities irrespective of their tissue locations. Care has also been taken to evaluate active compounds for chemoprophylactic activity since this may help to identify the pharmacophore responsible for chemoprophylaxis.

Synthesis of desired prototype molecules is often associated with interesting chemical reactions and a few of the molecules synthesized might also offer an opportunity to enrich the present state of knowledge provided their spectral properties are carefully studied. The present dissertation has taken a note of this situation.
CHAPTER 1

1.1 : NON-STERoidal CONTRAgestational HETEROCYCLES

1.1.1 : Monocyclic heterocycles
1.1.2 : Bicyclic heterocycles
1.1.3 : Polycyclic heterocycles

1.2 : BASIS OF WORK
1.1 NON-STEROIDAL CONTRAGESTATIONAL HETEROCYCLES

Chemical agents which provoke pregnancy failure by creating a situation in which the proper endocrine requirements have been disturbed to cause directly or indirectly antizygotic, blastolytic, balstotoxic or abortifacient activities, are termed as contragestational agents\(^1\). Control of population, a prime need of the present age, may be achieved by these agents but the small and definite incidence of serious side-effects resulting from these agents should be carefully studied since inhibition of pregnancy must lead to minimum physiological insult. The most common type of contragestational agent effective by oral route of administration (oral contraceptives) represent a combination of an estrogen and a progestin since a progestin or an estrogen alone is clinically less acceptable. However, the need for a second generation of oral contraceptives has been realised because agents which do not exhibit any hormonal or antihormonal effect but are capable of evoking selective physiological imbalance in the uterus to cause pregnancy failure would be more acceptable. A desirable choice for designing a such contragestational agents are heterocycles and this has prompted to review the earlier reports of the contragestational efficacy of heterocycles and a brief report of the same is presented here.

1.1.1 Monocyclic heterocycles

The most conspicuous non-hormonal contraceptive agents, developed by Omodei-sale et al.\(^2\), are represented by 3,5-disubstituted-1H-1,2,4-triazoles (1). These inhibit pregnancy in hamsters at a dose of 5 mg/kg P.O. A more effective compound of this series,

\[
\begin{align*}
R &= C_{1-4}\text{-alkyl}; R^1 = H, F, Cl, MeO, EtO, C_{1-4}\text{-alkyl}; \\
R^2 &= H, F, Cl, C_{1-4}\text{-alkyl or alkoxy}; R^2R^3 = OCH_2O
\end{align*}
\]
namely 3-(2-ethylphenyl-5-(3-methoxyphenyl)-1H-1,2,4-triazole (2), developed by Galliani et al., exhibits antifertility effect by acting on the uteroplacental unit (UPU), resulting in resorption or expulsion of the conceptuses. This compound is active whether given orally, subcutaneously, intramuscularly or intravaginally but the requirement of a very high oral dose limits its usefulness. Another derivative of 1 (R = CH₃; R¹, R², R³ = H) also exhibits significant pregnancy terminating activity. The ED₅₀ values are 0.3 mg/kg/day s.c. in hamsters and 2 mg/kg/day s.c. in rats. Instead of three nitrogen atoms in the heterocyclic ring, pyrazole derivative (3) with two nitrogen atoms also exhibits pregnancy terminating activity and the reported ED₅₀ values are 3 mg/kg/day in hamsters and 25 mg/kg/day in rats.

Oral administration of a representative of six-membered heterocycles namely 2', 3', 5'-tri-O-acetyl-6-azurine (4), at a dose of 300 mg/kg on days 8, 9, 10, 11 and 12 of pregnancy in rabbits, have been reported to inhibit pregnancy in all cases while derivatives of 2-(α-(orthosubstituted benzimidoyl) benzyl] pyridine (5) have been found to inhibit ovulation.
1.1.2 Bicyclic Heterocycles

Compared to monocyclic heterocycles, more number of bicyclic heterocycles have been evaluated for their antifertility activity. Of these 3-(2-benzofuranyl)-3-alkyl-2,2-dimethyl proionic acids\(^7\) (6), substituted 2-anilino benzoxazoles\(^8\) (7) and 2-benzoyl-3-phenyl benzothiophene (or benzothiophene oxide) derivatives\(^9\) (8) have shown pregnancy inhibiting activity in rats.

\[ \begin{align*}
R & = \text{H, Me}; R^1 = \text{H, OMe}; \\
R^2 & = \text{Me, Et}; R^3 = R^4 = \text{H}
\end{align*} \]

\[ R = \text{H, alkyl, alkoxy, alkylxox, CO}_2\text{H} \]

\[ \begin{align*}
R, R^1 & = \text{OH, H, alkoxy}; \\
R^2 & = \text{H, Cl, Br, OH, alkoxy}; \\
R^3 & = \text{H, Pyrrolodinoethoxy}; \\
n & = 0, 1
\end{align*} \]

Derivatives of 2-aroyl-3-phenyl benzothiophenes\(^{10}\) (9) at 1 mg/day S.C. and 1,2-diphenyl-1,2,3,4-tetrahydroquinoline\(^{11}\) (10) at 50-100 mg in rats have been reported to prevent pregnancy.
Bicyclic compounds such as indazole derivatives $^{12}$ (11) and 1,2-diphenylindoles $^{13}$ (12) also exhibit contraceptive activity.

A chroman derivative namely 3,4-trans-2,2-dimethyl-3-phenyl-4-[p-(\(\beta\)-pyrrolidinoethoxy)phenyl]-7-methoxycroman $^{14}$ (13) prevents conception at a single oral dose of 1.25 mg/kg in rats and mice and 2.5 mg/kg in dogs and rhesus monkeys immediately postcoitum. It also possesses estrogen, antiestrogen and antiprogestational properties.
The isoquinoline derivative, 1-N-methylpiperazine-2-chloro-4-nitroisoquinoline (14), exhibits anti-implantation activity\textsuperscript{15} in rats at $\geq 50$ mg/kg with maximum activity on days 4, 5 and 6 of pregnancy. Another class of bicyclic nitrogen heterocycles such as 3-[p-(ω-substituted aminoalkoxy)benzoyl]indoles\textsuperscript{16} (15) and α-methylarylamido-β-naphthyl(1-methylamino-2-methylbenzimidazolyl) ethers\textsuperscript{17} (16) possess anti-implantation activity in albino female rats.

A bicyclic sulphur containing heterocycle, 2-Phenyl-3-aryloyl benzothiophenes (17), at 1 mg/kg/day S.C. in rats for 15 days completely inhibits fetus development\textsuperscript{18}.
1.1.3 Polycyclic Heterocycles:

A wider variety of tricyclic and/or polycyclic heterocycles exhibit antifertility activity. Tricyclic nitrogen containing compounds such as 18-24 are reported to be useful contraceptives.

![Chemical Structures](image)

Of the polycyclic oxygen containing heterocycles, benzofurobenzopyranones (25) cause 83.3% inhibition of fetal implantation at 10 mg/kg i.p. in rats and several derivatives of the nitrogen containing heterocycle 26 are luteolytic in rabbits at a dose of 1 mg/day for 14 days.
Several substituted indeno, naphtho and cyclohepta pyrazoles (27) exhibit antifertility activity in rats at a dose of 1-100 mg/day\textsuperscript{22} and triazolisoindole derivatives (28) are postcoital contraceptives in rats. The ED\textsubscript{50} values range between 1-10 mg/kg s.c.\textsuperscript{23}.

\begin{itemize}
  \item \textbf{27}
  \begin{align*}
    \text{R} &= \text{4-pyridyl} \\
    \text{R}^1 &= \text{R}^2 = \text{H}; \\
    \text{n} &= 2
  \end{align*}
  \item \textbf{28}
  \begin{align*}
    \text{R} &= \text{Substitutedphenyl}
  \end{align*}
\end{itemize}

Nitrogen and sulfur containing heterocycles such as thieno [2,3-g] indazoles (29) at 50 mg/day\textsuperscript{24}, 2H[1]-benzothiepino [4,5-C] pyrazoles (30) at 2 mg/day\textsuperscript{25} and methanobenzo [b] thiophenes (31) at 5 mg/kg\textsuperscript{26} exhibit antifertility activity.
Eight membered tricyclic nitrogen containing heterocycle such as dibenzodiazocine\textsuperscript{27} (32) and the angular benzo [4,5] pyrano [2,3-C] pyrroles\textsuperscript{28} (33) with two different heteroatoms are reported to be useful contraceptives.

\[
\begin{align*}
X &= 2,8-\text{Cl}_2; \quad R = 2\text{-thienyl} \\
X &= 2,8-\text{Cl}_2; \quad R = 2\text{-thienyl} \\
R, R^1 &= H, \text{alkyl, alkoxy, OH, halo, acyloxy;} \\
R^2 &= H, \text{alkyl, aralkyl, aminoalkyl}
\end{align*}
\]

Another class of compounds namely pyrazolo [5,1-a] isoquinoline (34; 2 mg/kg/day in hamsters)\textsuperscript{29} and aminoindolobenzodiazepines\textsuperscript{30} (35) have been found to possess contraceptive efficacy.
The contraceptive efficacy of the members of the nitrogen containing tricyclic heterocycles (36-38) are as follows\(^3,4\).

\[
\begin{array}{cccc}
R^1 & R^2 & A & ED_{50} \text{ (mg/kg/day)} \\
\hline
H & C_6H_5 & CH_2-CH_2 & 3.5 & 20 \\
H & C_6H_5 & CH = CH & 1 & 5 \\
H & m-(OCH_3)C_6H_4 & CH = CH & >5 & 25 \\
CH_2OH & C_6H_5 & CH_2-CH_2 & \sim10 & \sim20 \\
CH_3 & C_6H_5 & CH_2-CH_2 & >3 & 20 \\
H & C_6H_5 & CH_2 & 10 & >5
\end{array}
\]

1.2 **BASIS OF WORK**

The text of the preceeding section suggests that heterocycles are capable of terminating pregnancy but the available reports do not project a clear picture about their contraceptive efficacy by oral route of administration and the results of the follow up action in large number of cases have possibly remained unreported. However, the desired details concerning the profile of antifertility activity are available for triazole derivatives and this prompted an earlier effort in this laboratory to ascertain whether the isomeric triazoles (A&B) and the replacement of one of the nitrogen atom in these compounds by other heteroatoms could influence the contraceptive efficacy.
It has been found that isomeric triazoles (A&B) and oxadiazole derivatives (C) exhibit contraceptive activity but their efficacy by oral route of administration is extremely poor \(^{31,32}\).

The present study represents an extension of the work initiated earlier in this laboratory and is directed to explore the contraceptive efficacy of other simpler heterocycles possessing only one phenyl ring. The stress on having a single phenyl ring in the molecular framework of simpler heterocycles is based on the assumption that two phenyl rings in simpler heterocycles at higher doses may lead to oestrogenicity. In view of these considerations, the syntheses and the evaluation of contraceptive efficacy of prototypes I-VI were undertaken.
Another approach in the present study for obtaining second generation contraceptive agents relates to the design of compounds which simulate two distinct type of pharmacophores in their molecular structures; the first one is concerned with its ability to alter membrane permeability while the second one is concerned with its capability to interfere oxido-reduction processes. The choice of these pharmacophores is based on the assumption that compounds capable of eliciting these activities in uterus would lead to inhibition of pregnancy. A situation such as this would generate fresh leads and this approach appears to have not been employed by earlier workers. In the present study two representative class of compounds namely 1,2,3,4-tetrahydroquinoline derivatives (VII) and 1,4-dihydro pyridine derivatives (VIII) have been identified for synthesis and biological evaluation as antifertility agents.

![Chemical structures](image)

**VII**

**VIII**
CHAPTER 2

2.1 Syntheses of 2-oxo-5-substitutedphenyl tetrahydrofurans, 5-Substituted phenyl-2,3-dihydrofuran-2-ones and 6-oxo-3-substitutedphenyl-1,4,5,6-tetrahydro-1H-pyridazines

2.2 Syntheses of 4-Arylidine-3-methyl-4,5-dihydroisoxazolin-2-ones and 4-(3,4-Dimethoxybenzyl)-3-methyl-2,3,4,5-tetrahydroisoxazolin-5-one

2.3 Syntheses of 5-Substitutedphenyl-2-isoxazolin-5-ones and 3-substitutedphenyl-5-methylisoxazoles

2.4 Synthesis of 2,5-Dimethyl-3-methoxycarboxyl-4-(3-cyano-2-oxo-1,2,3,4-tetrahydroquinolinol)furans

2.5 Syntheses of 2,6-Dimethyl-3,5-dimethoxycarbonyl-4-substituted-1,4-dihydropyridines
CHAPTER - 2

2.1 Substituted aroyl propionic acids (1-2) were identified as the starting materials for the syntheses of compounds belonging to prototypes I-III. Benzoyl propionic acid (1) was easily prepared by the Friedel-Craft reaction of benzene with succinic anhydride while 4-(3-nitrophenyl)-4-oxo butyric acid (2) was obtained by the nitration of 1 with fuming nitric acid. Esterification of these acids with dry methanol in presence of BF₃-etherate furnished the methyl esters (3-4) which on reduction with sodium borohydride gave a mixture of 4-hydroxy-4-substituted phenyl butyrates (5-6) and 2-oxo-5-substituted phenyl tetrahydrofurans (7-8; Scheme 1). These were separated by column chromatography over silica gel using chloroform, hexane (1:1) as the eluent. The dehydro derivatives of 7-8, the second prototype of the present study, were obtained by the ring closure of 3-4 with acetic anhydride (9-10; Scheme 1). Similar ring closure of 3-4 with hydrazine hydrate furnished 11-12, the representatives of prototype III (Scheme 1).

2.2 Compounds representing the molecular framework of prototype IV were prepared by reacting appropriate aromatic aldoximes (19-24) with methyl acetoacetate in methanol (Scheme 2). The resulting compounds (25-30) were obtained as non-separable mixture of Z and E isomers. The stereomeric mixture was evident from the PMR spectrum which indicated the presence of two singlets for ethylenic proton at around 8.50 - 9.00 ppm.

One representative compound of prototype IVa was prepared by the sodium borohydride reduction of the benzylidene derivative
a, Dry MeOH/BF$_3$etherate; b, NaBH$_4$/MeOH; c, Ac$_2$O; d, NH$_2$NH$_2$H$_2$O/MeOH

Scheme 1
Substituent $R$ as in 13-18

$\text{a, } \text{NH}_2\text{OH/MeOH}; \text{b, } \text{AcCH}_2\text{CO}_2\text{Me/MeOH}; \text{c, } \text{NaBH}_4/\text{MeOH}$

Scheme 2
in methanol (Scheme 2). The compound 31 so obtained was a mixture of isomers, which could not be separated by preparative TLC or column chromatography.

2.3 A retro-synthetic analysis for obtaining compounds representing prototypes V and VI suggests the preparation of starting materials of the type A (Fig. A), which in turn can be obtained from tetrasubstituted furans (B). Since substantial quantity of tetrasubstituted furans were available in the laboratory, efforts were directed to obtain compounds of the type A from these furans (B). Oxidation of substituted furans (C) have been reported earlier to yield α,β-unsaturated ketones (D; Fig. A)\textsuperscript{33,34}. In the present study it was observed that the oxidation of 3-methoxycarbonyl-2,5-dimethyl-4-substituted phenyl furans (32-36) with pyridinium chlorochromate gave compounds which exhibited sixteen mass units more than the expected mass of α,β-unsaturated ketones (G). The ir spectra of these compounds showed carbonyl bands at around 1660, 1720 and 1760 cm\textsuperscript{-1}. The nmr spectra indicated the presence of two acetyl groups and one methoxy group besides the required aromatic protons. On the basis of these data, three tentative structures E, F or H may be proposed for these oxidation products. Structures E and F were ruled out on the basis of \textsuperscript{13}C-nmr spectra of the oxidation products. The two quaternary carbon atoms of three membered ring in E and the quaternary sp\textsuperscript{3} carbon atom in F are expected to appear between 65-70 ppm but the \textsuperscript{13}C-nmr signals for the two quaternary carbon atoms at around 160 ppm and the absence of any peak between 65-70 ppm supported the structure H (37-41; Scheme 3). Since these compounds were the enol acetates of the desired starting material (A), they were reacted with aqueous acid. Instead of the desired ketones (A; R\textsuperscript{1} = OMe) substituted acetophenones 42-46 were obtained. The possible mechanism by which these compounds (37-41) broke down to substituted acetophenones is described in Scheme 4. The
Fig A
Rv ^C02Me

PCC

CH2Cl2

Rv ^COM

CH2Cl2

Rv ^COM

37-41

Substituent R as in 32-36

32 : R = 3,4-dimethoxyphenyl
33 : R = 3,4-methylenedioxyphenyl
34 : R = 4-methoxyphenyl
35 : R = 4-ethoxy-3-methoxy-phenyl
36 : R = 4-benzyloxy-3-methoxy-phenyl

(Scheme 3)

42-46

47

Substituent R as in 32-36

(Scheme 4)
conversion of 38 on activated surface to 47 provided additional evidence for the proposed mechanism. The stereochemistry of 37-41 has been worked out by comparing PMR spectra of these compounds with the spectra of 57-61 (Table 8, page 54). The downfield shift of the \(-OCOCH_3\) signals in 37-41 is only possible if the acetyl group at C-4 and methoxycarbonyl at C-3 are oriented in a cis geometry.

The reaction of oxidation products (37-41) with hydroxylamine hydrochloride in methanol furnished one of the planned compounds \((R^1 = H)\) of prototype V (Scheme 5). The facile loss of the COCH_3 group even at milder reaction conditions prevented the preparation of other compounds \((R^1 = COCH_3)\) of the prototype V. Additional evidence for the assigned structures (48-51) was obtained by an unambiguous synthesis of one of the representative compound (49) by reacting 47 with hydroxylamine hydrochloride.

\[
\begin{align*}
\text{H}_3\text{CO}_2\text{C} & \text{C} & \text{COCH}_3 \\
\text{R} & \text{OCOCH}_3 \\
\end{align*}
\]

\(\text{a, NH}_2\text{OH/MeOH}

(Scheme 5)

The compounds belonging to prototype VI namely 3-substituted-phenyl-5-methyl isoxazoles (62-65) were prepared by reacting 4-acetoxy-3-acetyl-4-substituted phenyl but-3-ene-2-ones (57-61), obtained by the pyridinium chlorochromate (PCC) oxidation of 3-acetyl-2,5-dimethyl-4-substituted phenyl furans \(^{35}\) (52-56), with hydroxylamine hydrochloride in methanol \(^{36}\) (Scheme 6).
19

[Scheme 6]

52 : R = 3,4-dimethoxyphenyl
53 : R = 3,4-methylenedioxyphenyl
54 : R = 4-methoxyphenyl
55 : R = 4-ethoxy-3-methoxyphenyl
56 : R = 4-benzyloxy-3-methoxyphenyl
57 : R = 3,4-dimethoxyphenyl
58 : R = 3,4-methylenedioxyphenyl
59 : R = 4-methoxyphenyl
60 : R = 4-ethoxy-3-methoxyphenyl
61 : R = 4-benzyloxy-3-methoxyphenyl
62 : R = 3,4-dimethoxy
63 : R = 3,4-methylenedioxy
64 : R = 4-methoxy
65 : R = 4-ethoxy-3-methoxy

a, PCC/CH₂Cl₂; b, NH₂OH/MeOH

(Scheme 6)
This facile loss of two carbon atoms from 4-acetoxy-3-methoxy-carbonyl-4-substituted phenyl but-3-ene-2-ones under acidic and basic conditions provided temptation to study the behaviour of this class of compounds under electron impact. Since this class of compounds is novel, its chemical reactivity and behaviour under electron impact are expected to contribute towards the existing knowledge in this field. Only the results of the mass spectrometric study are described here. The EI and CI behaviour of tetrasubstituted ethylenes (37-40, 57-60) under positive and negative ionization conditions employing techniques such as collisional activation (CA), metastable scan, exact mass measurements and D₂O CI have been studied. The positive ion EI, positive ion CI (CH₄) and negative ion EI spectra of 59 and 39 are shown in Fig.1 and 2. The metastable transitions observed under positive ion EI conditions by high voltage scan are also indicated in the EI spectra of 59 and 39 (Fig.1a and 2a). The molecular ions are not sufficiently stable to give intense M⁺ peaks and they fragment by loss of CH₂CO and CH₃CO. A γ-hydrogen rearrangement followed by the transfer of the acyl group from C₁ to C₂ could lead to a stable (M-CH₂CO) ion (Scheme 7). In the compounds 57-60, the (M-CH₂CO)⁺ ion decomposed by the loss of radicals such as CH₃·, CH₃CH₂·, HO·, CH₃O⁺, CH₃CH₂O⁺ and CH₃CO⁺ while in the compounds 36-39 loss of CH₃CO from M⁺ induce further loss of neutral molecules (CH₃OH and CO) as shown in Scheme 8. A characteristic difference is observed in the precursor ion spectra of the aroyl ion in two groups of compounds (57-60 and 37-40). The major precursor for aroyl ion in 57-60 is the (M-CH₂COCH₃)⁺ ion, while in 37-40 arCO⁺ is formed mainly from (M-CH₂CO-CH₃OH)⁺ ion (Scheme 8). Metastable transitions were also observed for the direct decomposition of the (M-CH₂CO)⁺ ion to ArCO⁺ in all the compounds thus supporting the generation of a carbonyl function on C₁ by the transfer of the acyl group during the loss of CH₂CO from M⁺.

The CA fragmentation pattern of the stable M⁺ resembles the 70 eV EI induced fragmentation of the molecule. However, the relative abundances of the fragment ions are different in the two spectra. This difference is attributable to the difference in the reactivities of the decomposing and non-decomposing M⁺ ions due to their having different structures. The (M-CH₂CO)⁺ ion gives rise to the base peak in the CA spectra, while the most intense
FIG. 2 — Mass spectra of 39(a) positive EI, (b) positive CI (CH₄) and (c) negative EI
(Scheme 7)
Scheme 8
ion in the normal EI spectra is ArCO⁺. This is understandable as the aroyl ion is produced in the source from several precursors such as (M-CH₂CO)⁺, (M-CH₂CO-CH₃)⁺ and (M-CH₂CO-CH₃CO)⁺.

As observed from CI(CH₄) spectra of 57-60 and 37-40, apart from MH⁺ and (M-H)⁺ ions, the major fragment ions arise by the loss of neutral molecules such as CH₂CO, CH₃CO₂H and CH₃O (Scheme 9). The methyl esters 37-40 are characterised by the presence of peaks corresponding to (MH-CH₂CO-CH₃OH)⁺ and (MH-CH₃CO₂H-CH₃OH)⁺. The CI (D₂O) spectra of these compounds show (MD-CH₂CO)⁺ and (MD-CH₃CO₂H)⁺ ions indicating thereby that proton added is not lost in these processes. Moreover, metastable peaks corresponding to these losses are also observed in the CI(D₂O) spectra (Table 1). The retention of D in the elimination ion indicates that a mechanism such as the one shown in scheme 9 operates for loss of acetic acid resulting in a cyclised product. In the methyl esters 37-40 the further fragmentation of this ion results in the loss of CH₃CO.

Yet another noteworthy feature in the CI spectra of these compounds is the presence of (M+43)⁺ ions, presumably due to self-acylation reaction. The acyl ion is produced from the sample itself as a result of which the (M+43)⁺ ion abundance increases when the sample pressure increases or when acetone is used as the reagent for CI. With acetone-d₆ both (M+CH₃CO)⁺ and (M+CD₃CO)⁺ are obtained. The (M+CH₃CO)⁺ ion is found to decompose by the loss of CH₂CO giving rise to MH⁺ ions (Scheme 10b). A metastable peak is seen at m/z 240.5 in CI (acetone, CH₄ or D₂O) spectrum of 59 corresponding to this decomposition.

The CA spectrum of the MH⁺ and CI(CH₄) spectrum of 59 show considerable difference in the relative abundance of the fragment ions (Table 2, Fig.1). Loss of H₂ from MH⁺ (Scheme 10c) leads to the most abundant ion in the CA spectrum, while (MH-CH₂CO)⁺ gives rise to the base peak in its CI(CH₄) spectrum. The (MH-Ar-COCH₃)⁺ ion is very prominent in the CA spectrum showing thereby that the acyl migration is an important process even under CA conditions.

As in the case of positive ion EI spectra, the molecular ions in the negative ion EI spectra are also not very abundant except in 60 and 40. However, in the electron capture spectrum of 59 (run
(Scheme 9)
Table 1: Metastable Peaks Observed in the D₂O CI Spectra of 57, 59, 37 and 39.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Transition</th>
<th>m⁺ obsd</th>
<th>m⁺ Calcd</th>
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<tbody>
<tr>
<td>57</td>
<td>MD⁺ (MD-CH₃CO₂)⁺</td>
<td>199.8</td>
<td>199.7</td>
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<tr>
<td></td>
<td>(m/z 308) m/z 248+60</td>
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<tr>
<td>58</td>
<td>(M+CH₃CO)⁺ MH⁺</td>
<td>240.5</td>
<td>240.5</td>
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<td>(m/z 319) m/z 277+42</td>
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<tr>
<td>59</td>
<td>MD⁺ (MD-CH₂CO)⁺</td>
<td>200.5</td>
<td>200.3</td>
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<td></td>
<td>(m/z 278) m/z 236+42</td>
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<tr>
<td>37</td>
<td>MD⁺ (MD-CH₂CO)⁺</td>
<td>245.5</td>
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<td>(m/z 324) m/z 282+42</td>
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<tr>
<td></td>
<td>MD⁺ (MD-CH₃CO₂H)⁺</td>
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<td></td>
<td>(m/z 324) m/z 264+60</td>
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<tr>
<td></td>
<td>(MD-CH₃CO₂H)⁺ (MD-CH₂CO₂H-CH₃OH)⁺</td>
<td>202.3</td>
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<td></td>
<td>(m/z 264) m/z 231+33</td>
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<tr>
<td>39</td>
<td>MD⁺ (MD-CH₂CO)⁺</td>
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<td>(m/z 294) m/z 252-42</td>
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(Scheme 10)
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<th>m/z</th>
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<th>NCI (CH₄), M⁻ m/z 276</th>
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under Cl(CH₄) conditions) the base peak is due to M⁻. Fragmentation occurs mainly by the loss of CH₃CO⁻, CH₃CO₂H, (CH₃CO₂H⁺H) or (CH₃CO₂H+CH₃) as shown in scheme 11. Similar fragmentation pattern of the M⁻ of 59 is also observed under collisional activation (Table 2). The methyl esters 37-40 fragment less rapidly than 57-60. The presence of acetoxy group in these molecules results in the formation of abundant acetoxy ion, at m/z 59 which gives rise to the base peak in the spectra of 57-60 (M-ArCO)⁻ is a characteristic fragment observed in their spectra. It is interesting to note that the complementary fragment ion, ArCO⁺, gives rise to intense peaks in the positive ion spectra. An acyl group migration from C₁ to C₂ as under positive ion conditions would explain the formation of (M-ArCO)⁻ ion (Scheme 11). This rearrangement ion is also observed under collisional activation of the M⁻ (Table 2).

2.4 The synthesis of prototype VII involves Nef reaction of 2-nitro-1-(p-acetamidophenyl) Propene (66) as the first step. The resulting compound namely 3-methoxy-carbonyl-2,5-dimethyl-4-(p-acetamidophenyl) furan (67) was subjected to vilsmeier-Haak reaction and the formyl derivative (68) so obtained on oximation gave 69 which was then reacted with SOCl₂ to yield 70. Sodium borohydride reduction of 70 in methanol furnished desired compound 71 (Scheme 12).

2.5 Compounds representing prototype VIII (79-86) were prepared by reacting appropriately substituted aldehydes (72-78 and 68) with methyl-3-aminocrotonate in presence of appropriate solvents (Scheme 13). In order to change R in compounds 79-86, two strategies have been employed. In the first one appropriate aldehydes were generated and in the second one, appropriate functionalities on the phenyl ring of 2,6-dimethyl 3,5-dimethoxycarbonyl-4-phenyl-1,4-dihydropyridine were simulated for elaborating them to heterocyclic ring systems.
(Scheme 11)
AcHNC\text{\textsuperscript{66}} \xrightarrow{\text{a}} \text{AcHNC}\text{\textsuperscript{67}}

\begin{align*}
\text{Cl} & \quad \text{H} \\
\text{N} & \quad \text{O} \\
\text{Cl} & \quad \text{N} \\
\text{C} & \quad \text{H} \\
\text{C} & \quad \text{O} \\
\text{Me} & \quad \text{Me}
\end{align*}

\xrightarrow{\text{b}}

\begin{align*}
\text{Cl} & \quad \text{H} \\
\text{N} & \quad \text{O} \\
\text{Cl} & \quad \text{N} \\
\text{C} & \quad \text{H} \\
\text{C} & \quad \text{O} \\
\text{Me} & \quad \text{Me}
\end{align*}

\xrightarrow{\text{c}}

\begin{align*}
\text{Cl} & \quad \text{H} \\
\text{N} & \quad \text{O} \\
\text{Cl} & \quad \text{N} \\
\text{C} & \quad \text{H} \\
\text{C} & \quad \text{O} \\
\text{Me} & \quad \text{Me}
\end{align*}

\xrightarrow{\text{d}}

\begin{align*}
\text{Cl} & \quad \text{H} \\
\text{N} & \quad \text{O} \\
\text{Cl} & \quad \text{N} \\
\text{C} & \quad \text{H} \\
\text{C} & \quad \text{O} \\
\text{Me} & \quad \text{Me}
\end{align*}

\xrightarrow{\text{e}}

\begin{align*}
\text{Cl} & \quad \text{H} \\
\text{N} & \quad \text{O} \\
\text{Cl} & \quad \text{N} \\
\text{C} & \quad \text{H} \\
\text{C} & \quad \text{O} \\
\text{Me} & \quad \text{Me}
\end{align*}

a, CH_3COCH_2CO_2CH_3, Et_3N/MeOH; b, DMF/POCl_3; C, NH_2OH/MeOH;
d, SOCl_2/Benzene; e, NaBH_4/MeOH

(Scheme 12)
R-CHO \[ \rightarrow \]

**72-78 & 68**

72 : R = 4-chloro-3-nitrophenyl
73 : R = 4-acetamidophenyl
74 : R = 4-amino-3-nitrophenyl
75 : R = \[\text{Benzen CHO}\]
76 : R = \[\text{Indole Cl}\]
77 : R = \[\text{OH OH OH OH CH}_2\text{OH OH OH OH CH}_2\text{OH}\]
78 : R = \[\text{Indazole NN NN}\]
79 : R = 4-chloro-3-nitrophenyl
80 : R = 4-acetamidophenyl
81 : R = 4-amino-3-nitrophenyl
82 : R = \[\text{Indole NN NH R}_1^1 R_2^2 \]
R\(^1\) = Me, R\(^2\) = CO\(_2\)Me
83 : R = \[\text{Indole Cl}\]
84 : R = \[\text{OH OH OH OH CH}_2\text{OH OH OH OH CH}_2\text{OH}\]
85 : R = \[\text{Indazole NN NN}\]
86 : R = \[\text{Indazole NN NN}\]

a, Methyl-3-aminocrotonate/appropriate solvent

*(Scheme 13)*
Appropriately substituted aldehydes were prepared as follows:

Nitration of 4-chlorobenzaldehyde with conc. HNO₃ gave 72 while 2-chloro-3-formyl quinoline (76), obtained by vilsmeier-Haak reaction of acetanilide, was reacted with sodium azide to obtain 78 (Scheme 14).

\[
\text{AcH} \text{N} \rightarrow \text{CH} \rightarrow \text{Cl} \rightarrow \text{N=NN}
\]

a, DMF/POCl₃; b, NaN₃

(Scheme 14)

In order to build heterocyclic ring systems on the phenyl ring of 2,6-dimethyl-3,5-dimethoxycarbonyl-4-phenyl-1,4-dihydro pyridine, the compound 81 was hydrogenated in presence of Raney-nickel to obtain the corresponding diamine (90; Scheme 15) and

\[
\text{NH}_2 \text{NO}_2 \rightarrow \text{NH}_2 \text{NH}_2
\]

a, H₂, Raney-Ni/MeOH

(Scheme 15)

the methanolic solution of compound 72 was reacted with aqueous methylamine and aqueous ammonia under pressure to yield 87 and 89 respectively. Reaction of 72 with benzylamine at atmospheric pressure yielded 88 (Scheme 16).
Ring closure in 90 was evoked either by reacting it with substituted benzaldehydes in presence of acetic acid (91-95; Scheme 17) or by reacting it with sodium nitrite in presence of aqueous acetic acid. The latter yielded 96 (Scheme 17). Synthesis of a

(Scheme 16)

(Scheme 17)
compound 97 structurally related to prototype VIII, was achieved by reacting 90 with benzil in presence of methanol (Scheme 18) whereas the reaction of 90 with carbon disulfide yielded 98 (Scheme 18). The tetracyclic heterocycle 99 was obtained by refluxing methanolic solution of 90 with phthalic anhydride (Scheme 18).

\[ a, \text{Benzil/MeOH}; \ b, \text{CS}_2; \ c, \text{Phthalic anhydride/MeOH} \]

(Scheme 18)
CHAPTER 3

3.1 : EXPERIMENTAL

3.2 : Tables

3.3 : BIOLOGICAL ACTIVITY
CHAPTER - 3

EXPERIMENTAL

3.1 The melting points were determined on a sulphuric acid or an electrically heated block and are uncorrected. All the reactions were checked by thin layer chromatography over silica gel G or alumina (basic or neutral) plates using iodine vapours. KMnO₄ spray or Dragendorf's spray as the developing reagent. The structures of all the compounds were routinely checked by IR and PMR Spectroscopy-IR spectra were recorded on Perkin-Elmer 157 infracord and Beckman Acculab-1 grating instruments and values are expressed in cm⁻¹. PMR spectra were recorded on Varion EM 360L or Perkin-Elmer R-32 using TMS as internal reference (Chemical shift in ppm). ¹³C-NMR spectra were recorded on CFT-20 spectrometer operating at 20 MHz, 8192 data points were collected and a sweep width of 5000 Hz was used. Pulse delay of 0.5 sec. was essential for recording the signals of carbonyl carbons. ¹⁵N-NMR spectrum was recorded on a Bruker WM-400 FT NMR spectrometer using formamide as the reference. Mass spectra of these compounds were recorded on Jeol-D 3000 instrument. The second place after the decimal point in the required value of C,H,N analyses have been approximated.

β-Benzoyl propionic acid (1)

This compound was essentially prepared by the method reported earlier.⁴¹a.

β-(3-Nitrobenzoyl) propionic acid (2, Table 3)

To fuming HNO₃ (d; 1.54, 20 ml) held at 0°C was added 1 (5 gm) in portions to prevent the reaction temperature to rise above 8-10°. After complete addition of the compound it was stirred at the same temperature (8-10°) for an additional 1 hr. The reaction mixture was then poured on to crushed ice under stirring. The separated solid was filtered and washed with ice-cold water (≈5°). The compound (2) was dried and recrystallized from minimum ethanol.

Methyl-4-substituted phenyl-4-oxo-butrate (3-4, Table 3)

A solution of 1 or 2 (5 gm) in methanol (20 ml) and BF₃-etherate (0.1 ml) was refluxed for 3 hrs. After completion of the reaction, water was added to the reaction mixture and extracted
with ethylacetate. The organic layer was washed with water three times, dried on anhydrous sodium sulphate and removed under reduced pressure. The residue on trituration with hexane gave the desired compound 3 or 4 which was recrystallised from ethanol.

**Methyl-4-hydroxy-substituted phenyl butyrate (5-6, Table 4) and 2-oxo-5-substituted phenyl tetrahydrofuran (7-8, Table 5)**

To a solution of 3 or 4 (0.01 mole) in methanol (8 ml) was added sodium borohydride (0.02 mole) in portions under cooling (0-5°) and stirring. The reaction was allowed to continue at the same temperature for 20 mts. The reaction mixture was then diluted with water (20 ml) and extracted with chloroform (50 ml). Usual work up of the organic layer yielded a mixture (5-6 and 7-8) which was separated by column chromatography over silica gel using a mixture of chloroform, ethylacetate (80:20) as eluent. The compounds 5-6, obtained as crystalline, solids, which were recrystallised from chloroform-hexane mixture while compounds 7-8 were oils.

**5-Substituted phenyl-2,3-dihydrofuran-2-one (9-10)**

A mixture of 1 or 2 (0.01 mole) and acetic anhydride (0.04 mole) was refluxed for 3.5 hr. After removal of the solvent under reduced pressure, water (20 ml) was added to it and extracted with ethyl acetate. Usual work up yielded dark red solid which was purified by column chromatography over silica gel using chloroform-ethylacetate mixture as the eluent. The compounds 9-10 so obtained were recrystallised from chloroform-hexane mixture.

9: Yield 70%; m.p. 82-83°; M⁺ at m/z 160

IR (KBr): 1800 (CO)
PMMR (CDCl₃): 3.36-3.38 (d, 2H, CH₂), 5.68-5.74 (t, 1H, CH), 7.25-7.63 (m, 5H, Ar-H).

C₁₀H₈O₂: Requires: C, 75.00; H, 5.00
Found: C, 74.62; H, 4.81

10: Yield 65%; m.p. 105°; M⁺ at m/z 205

IR (KBr): 1790 (CO)
PMMR (CDCl₃): 3.44-3.46 (d, 2H, CH₂), 5.91-5.97 (t, 1H, CH), 7.42-8.33 (m, 4H, Ar-H)

C₁₀H₇NO₄: Requires: C, 58.53; H, 3.41; N, 6.82
Found: C, 58.70; H, 3.88, N, 6.60
6-Oxo-3-substituted-phenyl-1,4,5,6-tetrahydro-1H-pyridazine (11-12)

To a solution of 3 or 4 (0.01 mole) in methanol (5 ml) was added hydrazine hydrate (0.02 mole) and stirred at room temperature (25°) for 1.5 hr. Addition of water (10 ml) to the reaction mixture yielded 11 or 12 as solid which was recrystallised from hot methanol.

11 : Yield 65%; m.p. 120-21°; M⁺ at m/z 174
IR (KBr) : 1680 (CO)
PMR (CDCl₃) : 2.40-2.98 (m, 4H, 2xCH₂), 7.20-7.70 (m, 5H, Ar-H), 9.12-9.40 (bs, 1H, NH)
C₁₀H₁₀N₂O : Requires: C, 68.96; H, 5.74; N, 16.09
Found: C, 69.21; H, 5.98; N, 15.84.

12 : Yield 60%; m.p. 160°; M⁺ at m/z 219
IR (KBr) : 1680 (CO)
PMR(CDCl₃+DMSO-d₆) : 2.40-2.60 (t, 2H, CH₂), 2.98-3.19 (t, 2H, CH₂), 7.55-8.21 (m, 5H, Ar-H & NH)
C₁₀H₉N₂O₃ : Requires: C, 54.79; H, 4.10; N, 19.17
Found: C, 54.90; H, 4.45; N, 18.91.

Arylidine-3-methyl-4,5-dihydro-isoxazolin-5-one (25-30, Table 6)

To a solution of the required oxime (19-24; 0.01 mole) in methanol (10 ml) was added methyl acetoacetate (0.02 mole) and refluxed for 3 hr. Solvent was removed under reduced pressure and the residue was triturated with water (20 ml) to yield the required compound (25-30) as solid which was recrystallised from aqueous methanol.

4-(3,4-Dimethoxybenzyl)-3-methyl-2,3,4,5-tetrahydro-isoxazolin-5-one (31)

To a suspension of 26 (2.47 gm, 0.01 mole) in methanol (10 ml) was added NaBH₄ (0.57 gm, 0.015 mole) in portions under stirring and cooling (5-10°). It was stirred at the same temperature for 1.5 hr. Water was added to the reaction mixture and extracted with ethylacetate. Usual work up of the organic layer yielded a residue which on trituration with petroleum benzene furnished 31 as a crystalline solid. This was recrystallised from chloroform-petroleum benzene mixture.
**31**  
Yield 55%; m.p. 130°; M⁺ at m/z 251  
IR (KBr) : 1738 (CO)  
PMR (CDCl₃) : 1.93-1.98 (m, 3H, 3H₃), 3.00-3.90 (m, 10H, CH₂, 2XCH, 2XOCH₃), 6.50-6.98 (m, 4H, Ar-H, NH)  
C₁₃H₁₇NO₄ : Requires: C, 62.15; H, 6.77; N, 5.57  
Found: C, 62.48; H, 6.31; N, 5.81

2,5-Dimethyl-3-methoxycarbonyl-4-substituted ³phenyl furans (32-36), Table 7

To a suspension of appropriate nitrostyrene (0.01 mole) in methanol (10 ml) was added triethylamine (0.02 mole) and methyl acetoacetate (0.02 mole) under stirring and cooling (5-10°). After 15 minutes the reaction mixture was allowed to come to room temperature (25°) and the stirring was continued for 24 hr. Removal of solvent under reduced pressure at 25°C was followed by the addition of water (20 ml) and the reaction mixture was further stirred at room temperature for 1 hr. The separated solid was filtered, washed with water, dried and recrystallised from chloroform-hexane mixture.

4-Acetoxy-3-methoxycarbonyl-4-substituted ³phenyl but-3-ene-2-ones (37-41, Table 8)

To a well stirred solution of tetrasubstituted furan (32-36, 0.01 mole) in dry dichloromethane (50 ml) was added pyridinium chlorochromate (0.04 mole) and the reaction mixture was stirred at room temperature (30°) for 10 hr. It was then diluted with ether and the organic layer was passed through a column of silica gel. The column was finally eluted with chloroform-hexane (1:2) and the usual work up of the organic layer yielded the desired compounds (37-41) as solids except 38 & 39 which were oils. The solid compounds (37, 40 & 41) were recrystallised from chloroform-petroleum benzene.

Substituted acetophenones (42-46)

To a solution of substituted but-3-ene-2-ones (37-41; 0.5 gm) in methanol (1.5 ml) was added aqueous hydrochloric acid (10%, 0.5 ml) and the mixture was refluxed for 2 hr. The solvent was removed and the residue was extracted with chloroform. The usual work up of organic layer gave the required acetophenones (42-46). These were identical in all respects with the authentic acetophenones.
Isolation of methyl piperonoylacetate (47)

A solution of 38 (1 gm) in chloroform (3 ml) was added to a short band of silica gel and left to stand for 48 hr. Thereafter it was eluted with a mixture of hexane-chloroform (1:1). Removal of the solvent furnished oily residue which on trituration with hexane gave 47 as a solid. This was recrystallised from chloroform-hexane mixture, and was found to be identical in all respect with the authentic sample prepared by the method reported earlier.

3-Substituted phenyl-2-isoxazoline-5-ones (48-51, Table 9)

To a solution of substituted but-3-ene-2-ones (37-41; 0.001 mole) in methanol (10 ml) was added hydroxylamine hydrochloride (0.003 mole) and sodium acetate (0.003 mole). This mixture was stirred at room temperature (20°) for 6 hr. Water (10 ml) was then added to the reaction mixture and the separated solid was filtered, washed with water, dried and recrystallised from methanol.

2,5-Dimethyl-3-acetyl-4-substituted phenyl furans (52-56, Table 7)

These were essentially prepared by the method described for compounds 32-36.

4-Acetoxy-3-acetyl-4-substituted phenyl but-3-ene-2-ones (57-61, Table 8)

These compounds were prepared by the method described for compounds 37-41.

3-Substituted phenyl-5-methyl-isoxazole (62-65, Table 10)

The method described for compounds 48-51, was followed to obtain these compounds.

2-Nitro-1-(p-acetamidophenyl) propene (66)

This was essentially prepared by the method reported earlier.

2,5-Dimethyl-3-methoxycarbonyl-4-(p-acetamidophenyl) furan (67)

The method of preparation of these compounds was essentially the one reported for compounds 32-36.
2,5-Dimethyl-3-methoxycarbonyl-4-(2-chloro-3-formyl quinolino) furan (68, Table 11)

To a precooled flask in an ice-bath for 15 minutes was added POCl₃ (15.4 ml, 0.01 mole) and it was allowed to stand at this temperature for another 15 minutes. Dry DMF (6.3 ml, 0.01 mole) was then added under stirring and after 5 minutes the compound 67 (2.87 gm, 0.01 mole) was added. The resulting mixture was heated at 70-74° under stirring for 16 hr. Finally it was poured onto crushed ice, and then separated solid was filtered, washed with water and dried. It was recrystallised from chloroform-hexane mixture.

2,5-Dimethyl-3-methoxycarbonyl-4-(3-aldoximino-2-chloroquinolino) furan (69, Table 11)

A solution of 68 (3.4 gm, 0.01 mole) in methanol (15 ml), hydroxylamine hydrochloride (1.38 gm, 0.02 mole) and sodium acetate (1.64 gm, 0.02 mole) was stirred at room temperature (25°) for 3 hr. Water (20 ml) was then added to the reaction mixture and the precipitated solid was filtered, washed with water, dried and recrystallised from aqueous DMF.

2,5-Dimethyl-3-methoxycarbonyl-4-(2-chloro-3-cyano quinolino) furan (70, Table 11)

To a suspension of 69 (1.79 gm, 0.005 mole) in dry benzene (8 ml) was added SOCl₂ (5.9 ml, 0.025 mole) and the resulting mixture was heated at 90° for 3 hr. Finally it was poured on to crushed ice and the resulting mixture was allowed to come to 90°. After holding it at this temperature for 45 minutes, it was cooled to room temperature (25°) and allowed to stay at this temperature for 6 hr. The separated solid was then filtered, dried and recrystallised from aqueous DMF.

2,5-Dimethyl-3-methoxycarbonyl-4-(3-cyano-2-oxo-1,2,3,4-tetrahydroquinolino) furan (71)

To a suspension of 70 (0.35 gm, 0.001 mole) in methanol (5 ml) was added NaBH₄ (0.15 gm, 0.004 mole) under cooling (5-10°) and stirring. It was then stirred at this temperature for 1.5 hr. Water was added to it and the mixture was extracted with ethyl acetate. Usual work up of the organic layer yielded an oil which
on trituration with petroleum benzene furnished a solid. This was recrystallised from aqueous DMF.

**71**
- **Yield**: 92%; **m.p.**: 145-46°
- **IR (KBr)**: 1675, 1700 (CO), 2200 (CN)
- **PMR (TFA)**: 2.00 (s, 3H, 5-CH$_3$), 2.40 (s, 3H, 2-CH$_3$),
  3.27-3.37 (d, 2H, CH$_2$), 3.69 (s, 3H, CO$_2$CH$_3$),
  3.89-4.07 (t, 1H, CH), 6.74-7.18 (m, 3H, Ar-
  H)

*C$_{18}$H$_{16}$N$_2$O$_4*
- **Requires**: C, 66.66; H, 4.93; N, 8.64
- **Found**: C, 66.51; H, 4.58; N, 8.35.

4-Chloro-3-nitro benzaldehyde (72)

To fuming HNO$_3$ (d; 1.54, 10 ml) held at 0° was added p-chloro benzaldehyde (1.4 gm) in portions so that temperature remains 0-5°. After complete addition of the compound it was stirred at the same temperature (0-5°) for 2 hr. The reaction mixture was poured on crushed ice and the separated solid was filtered, washed with water and dried. It was recrystallised from chloroform-hexane mixture.

4-Amino-3-nitro benzaldehyde (74)

This was prepared by following the method reported in the literature$^{44}$.

2-Chloro-3-formyl quinoline (76)

This compound was prepared by the method reported earlier$^{45}$.

4-Formyl tetrazolo [1,5-a] quinoline (78)

This was prepared by the method reported in the literature$^{45a}$.

2,6-Dimethyl-3,5-dimethoxycarbonyl-4-substituted-1,4-dihydropyridines (79-86, Table 12)

A mixture of the appropriate aldehyde (72-78 & 68, 0.01 mole) and methyl-3-amino crotonate in an appropriate solvent (ethylene glycol for 79-83, 85 and methanol for 84, 86) was heated on water bath for 24 hr. Thereafter water was added to the reaction mixture and stirred at room temperature (25-30°) for 2 hr., the
separated solid was filtered, washed with water and dried. In the case of 84 the work up was different. In this case dry ether was added to the reaction mixture and the solid obtained after trituration was filtered and dried. The compounds 79-83 and 86 were recrystallised from aqueous methanol while 85 was recrystallised from aqueous DMF.

2,6-Dimethyl-3,5-dimethoxycarbonyl-4-substituted phenyl-1,4-dihydropyridines (87-89, Table 12)

A mixture of the compound 79 (0.01 mole) and aqueous methyl amine or aqueous ammonia (0.04 mole) in methanol (20 ml) was heated in steel bomb at 150° for 24 hr. The volume of the reaction mixture was reduced to 10 ml and to this, water (20 ml) was added, and the mixture was allowed to stand at room temperature for 3 hr. The separated solid was filtered, washed with water and dried. These compounds were recrystallised from aqueous methanol.

2,6-Dimethyl-3,5-dimethoxycarbonyl-4-(4-benzylamino-3-nitro phenyl)-1,4-dihydropyridine (88, Table 12)

A mixture of the compound 79 (3.8 gm, 0.01 mole) and benzyl amine (6.3 ml, 0.06 mole) was heated at 110° under stirring for 8 hr. Water was then added to the reaction mixture and extracted with ethyl acetate. Usual work up of the organic layer gave an oil which on trituration with petroleum benzene, yielded a solid. This was recrystallised from chloroform-petroleum benzene mixture.

2,6-Dimethyl-3,5-dimethoxycarbonyl-4-(3,4-diaminophenyl)-1,4-dihydropyridine (90, Table 12)

To a suspension of 81 (1 gm) in methanol (100 ml) was added Raney-Ni (~0.2 gm) and hydrogenated at 2.5 kg/cm³ for 2 hr. The catalyst was filtered off, solvent removed under reduced pressure and the residue triturated with water. The solid so obtained was filtered, dried and recrystallised from aqueous methanol.

2-Aryl-5(6)\{4-(2,6-dimethyl-3,5-dimethoxycarbonyl-1,4-dihydropyrildyl)\}-1(3)-substituted benzyl benzimidazole (91-95, Table 12a).

A mixture of 90 (0.001 mole) and substituted benzaldehyde (0.002 mole) in glacial acetic acid (2 ml) was heated on a water bath for 4 hr. Water was then added to the reaction mixture and
extracted with ethyl acetate. Usual work up of the organic layer yielded a residual mass which on trituration with petroleum benzene furnished 90-95 as solid. These were recrystallised from aqueous methanol.

5(6)-[4-(2,6-Dimethyl-3,5-dimethoxycarbonyl-1,4-dihydropyridyl)] benzotriazole (96)

To a solution of 90 (0.662 gm, 0.002 mole) in acetic acid (2 ml) was added water (2 ml) and to this mixture was added a solution of sodium nitrite (0.414 gm, 0.006 mole) in water (1 ml) under cooling (5-10°) and stirring. It was stirred under cooling for 15 minutes and then it was heated at 80-90° for 1.5 hr. The reaction mixture was poured into crushed ice. The separated solid was filtered, washed with water and dried. It was recrystallised from aqueous methanol.

6-[4-(2,6-Dimethyl-3,5-dimethoxycarbonyl-1,4-dihydropyridyl)] 2,3-diphenyl quinoxaline (97)

A mixture of 90 (0.331 gm, 0.001 mole) and benzil (0.21 gm, 0.001 mole) in methanol (5 ml) was refluxed under stirring for 5 hr. Water was then added to the reaction mixture and the separated solid was filtered, washed with water, dried and recrystallised from aqueous methanol.

97: Yield 65%; m.p. 172-3°; M⁺ at m/z 505
IR (KBr): 1680 (CO)
PMR(CDC₃ + DMSO-d₆): 2.29 (s, 6H, 2xCH₃), 3.51 (s, 6H, 2xCO₂CH₃), 5.10 (s, 1H, CH), 7.15-7.65 (m, 13H, Ar-H), 8.38 (s, 1H, NH)
C₃₁H₂₇N₃O₄: Requires: C, 73.66; H, 5.34; N, 8.31
Found: C, 73.66; H, 5.37; N, 8.66.

5(6)-[4-(2,6-Dimethyl-3,5-dimethoxycarbonyl-1,4-dihydropyridyl)]-2-mercapto benzimidazole (98)

To a solution of 90 (0.331 gm, 0.001 mole) in ethanol (2 ml) and water (2 ml) was added carbon disulfide (2 ml). The reaction mixture was heated under stirring at 60° for 6 hr. Water was then added to it and the separated solid was filtered, washed with water, dried and recrystallised from aqueous DMF.
98  : Yield 70%; m.p. 268-9°; M⁺ at m/z 373
IR (KBr)  : 1660 (CO)

PMR(CDC₁₅+DMSO-d₆): 2.20 (s, 6H, 2xCH₃), 3.50 (s, 6H, 2xCO₂CH₃),
4.85 (s, 1H, CH), 6.69-7.05 (m, 3H, Ar-H).

C₁₈H₁₉N₃O₄S  : Requires: C, 57.90; H, 5.09; N, 11.26
              Found: C, 57.68; H, 4.81; N, 11.58.

10-H-2-[4-(2,6-Dimethyl-3,5-dimethoxycarbonyl)-1,4-dihydropyridyl]-
10-oxo-isoindolo [3,2-a] benzimidazole (99)

A mixture of 90 (0.331 gm, 0.001 mole) and phthalic anhydride (0.148 gm, 0.001 mole) in methanol (5 ml) was refluxed for 10 hr. Water was added to the reaction mixture, the separated solid was filtered, washed with water, dried and recrystallised from aqueous methanol.

99  : Yield 55%; m.p. 225-6°; M⁺ at m/z 443
IR (KBr)  : 1680, 1650 (CO)

PMR(CDC₁₅+DMSO-d₆): 2.22 (s, 6H, 2xCH₃), 3.50 (s, 6H, 2xCO₂CH₃),
4.90 (s, 1H, CH), 7.01-7.80 (m, 8H, Ar-H, NH).

C₂₅H₂₁N₃O₅  : Requires: C, 67.72; H, 4.74; N, 9.48
              Found: C, 67.58; H, 4.92; N, 9.05.
Physical and Analytical data of Compounds, which have not been included in Experimental section, are described under vertical columns and their spectral characteristics have been recorded in horizontal sequence.
Table 3:

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>R</th>
<th>R₁</th>
<th>m.p. °C</th>
<th>Yield %</th>
<th>Mol. Formula</th>
<th>Mol. Wt.</th>
<th>Analysis % Required</th>
<th>Found</th>
</tr>
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<tbody>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>C</td>
<td>H</td>
</tr>
<tr>
<td>1</td>
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</tr>
<tr>
<td>2</td>
<td>NO₂</td>
<td>H</td>
<td>152-53</td>
<td>70</td>
<td>C₁₀H₉NO₅</td>
<td>(223)</td>
<td>53.81</td>
<td>4.03</td>
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<td></td>
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<td></td>
<td></td>
<td>IR(KBr): 1700 &amp; 1720 (CO); PMR(CDC₃+DMSO-d₆): 2.49-2.70 (t, 2H, CH₂), 3.13-3.31 (t, 2H, CH₂), 7.50-8.70 (m, 4H, Ar-H); Mass: M⁺ at m/z 223.</td>
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</tr>
<tr>
<td>3</td>
<td>H</td>
<td>CH₃</td>
<td>91</td>
<td>72</td>
<td>C₁₁H₁₂O₃</td>
<td>(192)</td>
<td>68.75</td>
<td>6.25</td>
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<td></td>
<td>IR(KBr): 1690 &amp; 1725 (CO); PMR(CDC₃): 2.65-2.81 (t, 2H, CH₂), 3.23-3.36 (t, 2H, CH₂), 3.65 (s, 3H, CO₂CH₃), 7.71-8.12 (m, 5H, Ar-H); Mass: M⁺ at m/z 192.</td>
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<tr>
<td>4</td>
<td>NO₂</td>
<td>CH₃</td>
<td>86</td>
<td>70</td>
<td>C₁₁H₁₁NO₅</td>
<td>(237)</td>
<td>55.69</td>
<td>4.64</td>
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<td></td>
<td>IR(KBr): 1690 &amp; 1730 (CO); PMR(CDC₃): 2.70-2.84 (t, 2H, CH₂), 3.25-3.39 (t, 2H, CH₂), 3.67 (s, 3H, CO₂CH₃), 7.48-7.70 (m, 1H, 5Ar-H), 8.10-8.40 (m, 2H, 4 &amp; 6 Ar-H), 8.59-8.62 (bs, 1H, 2Ar-H); Mass: M⁺ at m/z 237.</td>
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**Table 4:**

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<th>Compound No.</th>
<th>R</th>
<th>m.p. °C</th>
<th>Yield %</th>
<th>Mol. Formula</th>
<th>Mol. Wt. (g/mol)</th>
<th>Analysis %</th>
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</thead>
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<tr>
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<td></td>
<td></td>
<td></td>
<td>Required</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C</td>
</tr>
<tr>
<td>5</td>
<td>H</td>
<td>oil</td>
<td>37</td>
<td>C₁₁H₁₄O₃</td>
<td>(194)</td>
<td>68.04</td>
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<tr>
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<td></td>
<td>IR(Neat): 1720 (CO) &amp; 3400 (OH); PMR(CCl₄): 1.82-2.01 (m, 2H, CH₂), 2.30-2.46 (t, 2H, CH₂), 3.61 (s, 3H, CO₂CH₃), 4.61-4.79 (t, 1H, CH), 6.98-8.09 (m, 5H, Ar-H); Mass: M⁺ at m/z 194</td>
</tr>
<tr>
<td>6</td>
<td>NO₂</td>
<td>oil</td>
<td>51</td>
<td>C₁₁H₁₃NO₅</td>
<td>(239)</td>
<td>55.23</td>
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<tr>
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<td></td>
<td>IR(Neat): 1725 (CO) &amp; 3400 (OH); PMR(CDCl₃): 1.84-2.15 (m, 2H, CH₂), 2.31-2.48 (t, 2H, CH₂), 3.59 (s, 3H, CO₂CH₃), 4.70-4.84 (t, 1H, CH), 7.20-8.10 (m, 4H, Ar-H); Mass: M⁺ at m/z 239.</td>
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Table 5:

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<th>m.p. °C</th>
<th>Yield %</th>
<th>Mol. Formula</th>
<th>Mol. Wt.</th>
<th>Analysis %</th>
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<td>C</td>
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<td></td>
<td>N</td>
</tr>
</tbody>
</table>

7  
H  81  61  C_{10}H_{10}O_{2}  
(162)  
74.07  6.17  -  
73.80  6.51  -  

IR(KBr): 1780 (CO); PMR(CDC\textsubscript{3}): 1.65-2.34 (m, 2H, CH\textsubscript{2}), 2.41-2.72 (t, 2H, CH\textsubscript{2}), 6.29-6.70 (m, 1H, CH), 7.81 (bs, 5 H, Ar-H); Mass: M\textsuperscript{+} at m/z 162.

8  
NO\textsubscript{2}  74-75  45  C_{10}H_{9}NO\textsubscript{4}  
(207)  
57.97  4.34  6.76  
58.21  4.60  6.60  

IR(KBr): 1775 (CO); PMR(CDC\textsubscript{3}): 1.71-2.40 (m, 2H, CH\textsubscript{2}), 2.50-2.80 (t, 2H, CH\textsubscript{2}), 6.30-6.70 (t, 1H, CH), 7.32-8.20 (m, 4H, Ar-H); Mass: M\textsuperscript{+} at m/z 207.
Table 6:

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>R</th>
<th>m.p. °C</th>
<th>Yield %</th>
<th>Mol. Formula</th>
<th>Mol. Wt.</th>
<th>Analysis %</th>
<th>Required</th>
<th>Found</th>
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<td>R</td>
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</tr>
<tr>
<td></td>
<td>C</td>
<td>H</td>
<td>N</td>
<td>C</td>
<td>H</td>
<td>N</td>
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</tr>
<tr>
<td>25</td>
<td>H</td>
<td>134-35</td>
<td>62</td>
<td>C₁₁H₉NO₂</td>
<td>(187)</td>
<td>70.58</td>
<td>4.81</td>
<td>7.48</td>
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<td></td>
<td>IR(KBr): 1735 (CO); PMR(CDC₁₃): 2.23 (s, 3H, CH₃), 7.37-7.52 (m, 4H, Ar-H), 8.19-8.40 (m, 2H, Ar-H &amp; CH)</td>
<td></td>
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<tr>
<td>26</td>
<td>3,4-Dimethoxy</td>
<td>151</td>
<td>68</td>
<td>C₁₃H₁₃NO₄</td>
<td>(247)</td>
<td>63.15</td>
<td>5.26</td>
<td>5.66</td>
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<tr>
<td></td>
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<td></td>
<td>IR(KBr): 1738 (CO); PMR(CDC₁₃): 2.20 (s, 3H, CH₃), 3.90 (s, 6H, 2xOCH₃), 6.81-6.91 (d, 1H, 5 Ar-H), Jo = 8Hz, 7.24 (s, 1H, 2Ar-H), 7.49-7.60 (dd, 1H, 6Ar-H, Jo = 9Hz, Jm = 2Hz), 8.61 &amp; 8.63 (2s, 1H, CH); Mass: M⁺ at m/z 247</td>
<td></td>
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</tr>
<tr>
<td>27</td>
<td>4-Hydroxy</td>
<td>277-78</td>
<td>66</td>
<td>C₁₂H₁₁NO₄</td>
<td>(233)</td>
<td>61.80</td>
<td>4.72</td>
<td>6.00</td>
</tr>
</tbody>
</table>
**IR(KBr):** 1730 (CO);  **PMR(CDC\textsubscript{3}+DMSO-d\textsubscript{6}):** 2.20 (s, 3H, CH\textsubscript{3}), 3.80 (s, 3H, OCH\textsubscript{3}), 6.82-6.91 (d, 1H, 5Ar-H, Jo = 9Hz), 7.46 (s, 1H, 2Ar-H), 7.57-7.69 (dd, 1H, 6Ar-H, Jo = 9Hz, Jm = 2Hz), 8.53 & 8.56 (2s, 1H, CH); **Mass:** M\textsuperscript{+} at m/z 233.

<table>
<thead>
<tr>
<th>28</th>
<th>4-Amino 280-81</th>
<th>81</th>
<th>C\textsubscript{11}H\textsubscript{9}N\textsubscript{3}O\textsubscript{4}</th>
<th>53.44</th>
<th>3.64</th>
<th>17.00</th>
<th>53.61</th>
<th>4.01</th>
<th>17.40</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>3-nitro</td>
<td></td>
<td></td>
<td>(247)</td>
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</table>

**IR(KBr):** 1730 (CO); **PMR(DMSO-d\textsubscript{6}):** 2.20 (s, 3H, CH\textsubscript{3}), 6.99-7.08 (d, 1H, 5Ar-H, Jo = 9Hz), 7.78 (s, 1H, 2Ar-H), 8.42-8.54 (dd, 1H, 6Ar-H, Jo = 9Hz, Jm = 2Hz), 9.24 & 9.27 (2s, 1H, CH); **Mass:** M\textsuperscript{+} at m/z 247.

<table>
<thead>
<tr>
<th>29</th>
<th>4-Acetamido</th>
<th>262-63</th>
<th>75</th>
<th>C\textsubscript{13}H\textsubscript{12}N\textsubscript{2}O\textsubscript{3}</th>
<th>63.93</th>
<th>4.91</th>
<th>11.47</th>
<th>64.12</th>
<th>4.80</th>
<th>11.08</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(244)</td>
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</tbody>
</table>

**IR(KBr):** 1720 & 1730 (CO); **PMR(DMSO-d\textsubscript{6}):** 2.30 (s, 3H, CH\textsubscript{3}), 2.45 (s, 3H, NHCOCH\textsubscript{3}), 7.80-8.20 (m, 3H, CH & Ar-H), 8.50-8.85 (m, 2H, Ar-H); **Mass:** M\textsuperscript{+} at m/z 244.

<table>
<thead>
<tr>
<th>30</th>
<th>4-Amino 253-54</th>
<th>70</th>
<th>C\textsubscript{11}H\textsubscript{10}N\textsubscript{2}O\textsubscript{2}</th>
<th>65.34</th>
<th>4.95</th>
<th>13.86</th>
<th>65.11</th>
<th>5.31</th>
<th>13.51</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(202)</td>
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</table>

**IR(KBr):** 1695 (CO); **PMR(DMSO-d\textsubscript{6}):** 2.19 (s, 3H, CH\textsubscript{3}), 6.55-6.73 (m, 2H, 3&5Ar-H), 7.45-7.51 (bs, 1H, CH), 8.21-8.41 (m, 2H, 2&6Ar-H); **Mass:** M\textsuperscript{+} at m/z 202.
Table 7:

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>R</th>
<th>R₁</th>
<th>m.p. °C</th>
<th>Yield %</th>
<th>Mol. Formula</th>
<th>Mol. Wt.</th>
<th>Analysis %</th>
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<tbody>
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<td></td>
<td></td>
<td></td>
<td>C₁₇H₂₀O₅</td>
<td>(304)</td>
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<tr>
<td>35</td>
<td>4-ethoxy</td>
<td>CO₂CH₃</td>
<td>95</td>
<td>62</td>
<td>C₁₇H₂₀O₅</td>
<td>67.10</td>
<td>6.57</td>
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<td>67.41</td>
<td>6.82</td>
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<tr>
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<td>IR(KBr): 1695 (CO); PMR(CDC₃): 1.51-1.66 (t, 3H, CH₃), 2.06 (s, 3H, 5-CH₃), 2.28 (s, 3H, 2-CH₃), 3.61 (s, 3H, CO₂CH₃), 3.83 (s, 3H, OCH₃), 4.10-4.31 (q, 2H, CH₂), 6.69-7.32 (m, 3H, Ar-H); Mass: M⁺ at m/z 304.</td>
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<tr>
<td>36</td>
<td>4-Benzy-</td>
<td>CO₂CH₃</td>
<td>98</td>
<td>59</td>
<td>C₂₂H₂₂O₅</td>
<td>72.13</td>
<td>6.01</td>
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<td>72.41</td>
<td>6.32</td>
</tr>
<tr>
<td></td>
<td>IR(KBr): 1690 (CO); PMR(CDC₃): 2.13 (s, 3H, 5-CH₃), 2.50 (s, 3H, 2-CH₃), 3.59 (s, 3H, CO₂CH₃), 3.80 (s, 3H, OCH₃), 5.09 (s, 2H, OCH₂), 6.57-6.90 (m, 3H, Ar-H), 7.15-7.45 (m, 5H, Ar-H); Mass: M⁺ at m/z 366.</td>
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<tr>
<td>55</td>
<td>4-Ethoxy</td>
<td>COCH₃</td>
<td>90</td>
<td>68</td>
<td>C₁₇H₂₀O₄</td>
<td>70.83</td>
<td>6.94</td>
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<td>70.51</td>
<td>6.71</td>
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<tr>
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<td>IR(KBr): 1690 (CO); PMR(CDC₃): 2.13 (s, 3H, 5-CH₃), 2.50 (s, 3H, 2-CH₃), 3.59 (s, 3H, CO₂CH₃), 3.80 (s, 3H, OCH₃), 5.09 (s, 2H, OCH₂), 6.57-6.90 (m, 3H, Ar-H), 7.15-7.45 (m, 5H, Ar-H); Mass: M⁺ at m/z 366.</td>
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<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
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<tr>
<td>IR(KBr): 1690 (CO); PMR(CDCl$_3$): 1.39-1.54 (t, 3H, CH$_3$), 1.93 (s, 3H, 5-CH$_3$), 2.15 (s, 3H, 2-CH$_3$), 2.50 (s, 3H, COCH$_3$), 3.82 (s, 3H, OCH$_3$), 3.99-4.21 (q, 2H, CH$_2$), 6.67-6.83 (m, 3H, Ar-H); Mass: M$^+$ at m/z 288.</td>
<td></td>
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<tr>
<td>56</td>
<td>4-Benzyl- COCH$_3$</td>
<td>95</td>
<td>50</td>
<td>C$<em>{22}$H$</em>{22}$O$_4$</td>
<td>75.42</td>
<td>6.28</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>loxy</td>
<td></td>
<td></td>
<td>(350)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IR(KBr): 1685 (CO); PMR(CDCl$_3$): 1.90 (s, 3H, 5-CH$_3$), 2.10 (s, 3H, 2-CH$_3$), 2.49 (s, 3H, COCH$_3$), 3.80 (s, 3H, OCH$_3$), 5.10 (s, 2H, OCH$_2$), 6.58-6.92 (m, 3H, Ar-H), 7.15-7.50 (m, 5H, Ar-H); Mass: M$^+$ at m/z 350</td>
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</table>
Table 8:

<table>
<thead>
<tr>
<th>Compd. R</th>
<th>R¹</th>
<th>m.p.</th>
<th>Yield %</th>
<th>Mol. Formula</th>
<th>Mol. Wt.</th>
<th>Analysis %</th>
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<tr>
<td></td>
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<td>37</td>
<td>3,4-Dimethoxy CO₂CH₃</td>
<td>98</td>
<td>70</td>
<td>C₁₆H₁₈O₇</td>
<td>(322)</td>
<td>59.62</td>
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IR(KBr): 1660, 1720 & 1760 (CO); PMR(CDC₁₃): 1.80 (s, 3H, COCH₃), 2.48 (s, 3H, OCOC₂H₃), 3.61 (s, 3H, CO₂CH₃), 3.86 (s, 6H, 2xOCH₃), 6.73-6.83 (d, 1H, 5Ar-H, Jo = 9Hz), 7.32-7.44 (dd, 2H, 2&6 Ar-H, Jo = 9Hz, Jm = 3Hz); ¹³C-nmr(CDC₁₃): 19.03 (q, 1-C), 20.57 (q, OCOC₂H₃), 52.18 (q, 3-CO₂CH₃), 56.09, 56.17 (q, 2xOCH₃), 110.40, 110.66, 124.68 (d, Ar-C), 129.59, 149.28, 154.06 (s, Ar-C), 162.07 (s, 3-C), 164.58 (s, 4-C), 167.52 (s, 3-CO₂CH₃), 189-87 (s, 2C & OCOC₂H₃); Mass: M⁺ at m/z 322

38 3,4-Methylenedioxy CO₂CH₃ Oil | 54 | C₁₅H₁₄O₇ | (306) |

IR(Neat): 1660, 1720 & 1765 (CO); PMR(CC₁₃): 1.80 (s, 3H, COCH₃), 2.42 (s, 3H, OCOC₂H₃), 3.58 (s, 3H, CO₂CH₃), 5.93 (s, 2H, OCH₂O), 6.62-6.73 (d, 1H, 5Ar-H, Jo = 9Hz), 7.20-7.32 (dd, 2H, 2 & 6 Ar-H, Jo = 9Hz, Jm = 3Hz); ¹³C-nmr(CDC₁₃): 18.99 (q, 1-C), 20.52 (q, OCOC₂H₃), 52.14 (q, 3-CO₂CH₃), 108.04, 108.20, 126.31 (d, Ar-C), 102.07 (t, OCH₂O), 131.30, 148.39, 152.48 (s, Ar-C), 162.23 (s, 3-C), 164.44 (s, 4-C), 5
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<td>167.42 (s, CO$_2$CH$_3$), 189.35 (s, 2-C &amp; OCOCH$_3$); <strong>Mass:</strong> M$^+$ at m/z 306</td>
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<td>39</td>
<td>4-Methoxy</td>
<td>CO$_2$CH$_3$ oil</td>
<td>50</td>
<td>C$<em>{15}$H$</em>{16}$O$_6$</td>
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<td>5.47</td>
<td>-</td>
<td>62.00</td>
<td>5.34</td>
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<td>IR(Neat): 1660, 1720 &amp; 1760 (CO); PMR(CCl$_4$): 1.79 (s, 3H, COCH$_3$), 2.45 (s, 3H, OCOCH$_3$), 3.60 (s, 3H, CO$_2$CH$_3$), 3.81 (s, 3H, OCH$_3$), 6.74-6.85 (dd, 2H, 3 &amp; 5 Ar-H), Jo = 9Hz, Jm = 2Hz), 7.66-7.78 (dd, 2H, 2 &amp; 6 Ar-H, Jo = 9Hz, Jm = 2Hz); <strong>Mass:</strong> M$^+$ at m/z 292</td>
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<td>40</td>
<td>4-Ethoxy</td>
<td>3-methoxy</td>
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<td>58</td>
<td>C$<em>{17}$H$</em>{20}$O$_7$</td>
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<td>61.00</td>
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<td>IR(KBr): 1680, 1740 &amp; 1780 (CO); PMR(CDC$_3$): 1.42-1.59 (t, 3H, CH$_3$), 1.88 (s, 3H, COCH$_3$), 2.53 (s, 3H, OCOCH$_3$), 3.68 (s, 3H, CO$_2$CH$_3$), 3.92 (s, 3H, OCH$_3$), 3.98-4.20 (q, 2H, CH$_2$), 6.79-6.89 (d, 1H, 5Ar-H), Jo = 9Hz), 7.37-7.51 (m, 2H, Ar-H); <strong>Mass:</strong> M$^+$ at m/z 336</td>
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<td>IR(Neat): 1660, 1685 &amp; 1760 (CO); PMR(CCl$_4$): 1.79 (s, 3H, COCH$_3$), 2.41 (s, 3H, OCOCH$_3$), 3.59 (s, 3H, CO$_2$CH$_3$), 3.84 (s, 3H, OCH$_3$), 5.12 (s, 2H, OCH$_2$), 6.58-6.95 (m, 3H, Ar-H), 7.12-7.42 (m, 5H, Ar-H); <strong>Mass:</strong> M$^+$ at m/z 398</td>
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57 3,4-Dimethoxy COCH₃ oil 63 C₁₀H₁₈O₆ 62.70 5.88 - 62.50 5.60 -

IR (Neat): 1650, 1690, & 1755 (CO); PMR (CCl₄): 1.74 (s, 3H, COCH₃), 2.05 (s, 3H, 3-COCH₃), 2.36 (s, 3H, OCOCH₃), 3.85 (s, 6H, 2xOCH₃), 6.71-6.81 (d, 1H, J = 9Hz, Jo = 9 Hz, Jm = 3Hz); ¹³C-nmr (CDCl₃): 19.35 (q, 1-C), 20.50 (q, OCOCH₃), 30.44 (q, 3-COCH₃), 56.04, 56.14 (q, 2xOCH₃), 110.51, 124.87 (d, Ar-C), 130-37, 149.41, 154.34 (s, Ar-C), 160.09 (s, 3-C), 167.59 (s, 4-C), 191.63 (s, 3-COCH₃), 195.35 (s, 2-C & OCOCH₃)

58 3,4-Methylenedioxy COCH₃ oil 54 C₁₅H₁₄O₆ 62.06 4.82 - 62.45 4.84 -

IR (Neat): 1640, 1680 & 1745 (CO); PMR (CCl₄): 1.70 (s, 3H, COCH₃), 1.68 (s, 3H, 3-COCH₃), 2.26 (s, 3H, OCOCH₃), 5.95 (s, 2H, OCH₂O), 6.64-6.74 (d, 1H, J = 9Hz, Jo = 9 Hz, Jm = 3Hz); ¹³C-nmr (CDCl₃): 19.35 (q, 1-C), 20.50 (q, OCOCH₃), 30.44 (q, 3-COCH₃), 108.17, 108.50, 126.68 (d, Ar-C), 131.56, 148.66, 152.82 (s, Ar-C), 160.18 (s, 3-C), 167.51 (s, 4-C), 191.88 (s, 3-COCH₃), 195.23 (s, 2-C & OCOCH₃); Mass: M⁺ at m/z 290

59 4-Methoxy COCH₃ oil 50 C₁₅H₁₆O₃ 65.21 5.79 - 65.00 5.88 -

IR (Neat): 1650, 1685 & 1750 (CO); PMR (CCl₄): 1.69 (s, 3H, COCH₃), 1.98 (s, 3H, 3-COCH₃), 2.28 (s, 3H,
OCOCH₃, 3.78 (s, 3H, OCH₃), 6.73-6.86 (dd, 2H, 3 & 5 Ar-H, Jo = 9Hz, Jm = 3Hz), 7.68-7.82 (dd, 2H, 2 & 6 Ar-H, Jo = 9Hz, Jm = 2Hz); ¹³C-nmr(CDC₁₈): 19.34 (q, 1-C), 20.45 (q, OCOCH₃), 30.45 (q, 3-COCH₃), 55.59 (q, OCH₃), 114.20, 114.42, 129.73, 130.55 (d, Ar-C), 131.65, 132.19 (s, Ar-C), 160.03 (s, 3-C), 167.53 (s, 4-C), 192.38 (s, 3-COCH₃), 195.43 (s, 2-C & OCOCH₃); Mass: M⁺ at m/z 276

60 4-Ethoxy 3-methoxy COCH₃ Oil 60 C₁₇H₂₀O₆ 63.75 6.25 - 63.41 6.39 - (320)

IR(Neat): 1650, 1690 & 1760 (CO); PMR(CCl₄): 1.37-1.55 (t, 3H, CH₃), 1.83 (s, 3H, COCH₃), 2.04 (s, 3H, 3-COCH₃), 2.35 (s, 3H, OCOCH₃), 3.91 (s, 4H, OCH₃), 3.97-4.21 (q, 2H, CH₂), 6.81-7.23 (m, 3H, Ar-H); Mass: M⁺ at m/z 320.

61 4-Benzylxy 3-methoxy COCH₃ Oil 52 C₂₂H₂₂O₆ 69.10 5.75 - 70.31 5.99 - (382)

IR(Neat): 1650, 1685 & 1760 (CO); PMR(CCl₄): 1.73 (s, 3H, COCH₃), 2.02 (s, 3H, 3-COCH₃), 2.34 (s, 3H, OCOCH₃), 3.83 (s, 3H, OCH₃), 5.10 (s, 2H, OCH₂O), 6.57-6.90 (m, 3H, Ar-H), 7.11-7.38 (m, 5H, Ar-H); Mass: M⁺ at m/z 382.
Table 9:

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<th>Compound No.</th>
<th>R</th>
<th>m.p. °C</th>
<th>Yield %</th>
<th>Mol. Formula</th>
<th>Mol. Wt.</th>
<th>Analysis %</th>
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IR(KBr): 1790 (CO); PMR(CDC<sub>3</sub>): 3.70 (s, 2H, CH<sub>2</sub>), 3.83 (s, 6H, 2xOCH<sub>3</sub>), 6.90-7.10 (m, 2H, 2xAr-H), 7.28-7.40 (dd, 1H, 6Ar-H), J<sub>o</sub> = 9Hz, J<sub>m</sub> = 2Hz; Mass: M<sup>+</sup> at m/z 221.

IR(KBr): 1785 (CO); PMR(CDC<sub>3</sub>+DMSO-d<sub>6</sub>): 3.86 (s, 2H, CH<sub>2</sub>), 6.00 (s, 2H, OCH<sub>2</sub>O), 6.70-7.50 (m, 3H, Ar-H); Mass: M<sup>+</sup> at m/z 205.

IR(KBr): 1780 (CO); PMR(CDC<sub>3</sub>): 3.70 (s, 2H, CH<sub>2</sub>), 3.83 (s, 6H, 2xOCH<sub>3</sub>), 6.90-7.10 (m, 2H, 2xAr-H), 7.28-7.40 (dd, 1H, 6Ar-H), J<sub>o</sub> = 9Hz, J<sub>m</sub> = 2Hz; Mass: M<sup>+</sup> at m/z 221.
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IR(KBr): 1790 (CO); PMR(CDC$_3$): 3.66 (s, 2H, CH$_2$), 3.76 (s, 3H, OCH$_3$), 6.83-6.96 (dd, 2H, 3&5Ar-H, Jo = 9Hz, Jm = 3Hz), 7.46-7.60 (dd, 2H, 2&6Ar-H, Jo = 9Hz, Jm = 3Hz); Mass: M$^+$ at m/z 191.

51  4-Ethoxy 145-46  65  C$_{12}$H$_{13}$NO$_4$  61.27  5.53  5.95  61.41  5.20  5.81
3-methoxy

IR(KBr): 1790 (CO); PMR(CDC$_3$+DMSO-d$_6$): 1.32-1.48 (t, 3H, CH$_3$), 3.77 (s, 2H, CH$_2$), 3.82 (s, 3H, OCH$_3$), 3.92-4.15 (q, 2H, CH$_2$), 6.64-7.20 (m, 3H, Ar-H); Mass: M$^+$ at m/z 235.
Table 10:

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<th>Compound No.</th>
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<th>Yield %</th>
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PMR(CDC)\textsubscript{3}: 2.26 (s, 3H, CH\textsubscript{3}), 3.83 (s, 6H, 2\times OCH\textsubscript{3}), 6.20 (s, 1H, CH), 6.76-7.36 (m, 3H, Ar-H); \textsuperscript{13}C-nmr(CDC)\textsubscript{3}: 11.45 (q, 5-CH\textsubscript{3}), 56.05 (q, 2\times OCH\textsubscript{3}), 99.12 (d, 4-CH), 160.31 (s, 5-C), 169.62 (s, 3-C), 108.94, 111.51, 119.06, 120.71, 149.42, 150.74 (Ar-C); Mass: M\textsuperscript{+} at m/z 219.

63 3,4-methylenedioxy 97-98 79 C_{11}H_{9}NO_{3} (203)

PMR(CDC)\textsubscript{3}: 2.23 (s, 3H, CH\textsubscript{3}), 5.93 (s, 2H, OCH\textsubscript{2}O), 6.13 (s, 1H, CH), 6.73-7.30 (m, 3H, Ar-H); Mass: M\textsuperscript{+} at m/z 203.

64 4-Methoxy 102-3 81 C_{11}H_{11}NO_{2} (189)

69.84 5.82 7.40 69.61 5.74 7.41
Table 11:

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| 68       | CHO | 168-70  | 50      | C₁₈H₁₄ClNO₄ | 62.88   | 4.07       |
|          |     |         |         |             |         | 4.07       |
|          |     |         |         |              |         | 62.95      |
|          |     |         |         |              |         | 4.44       |
|          |     |         |         |              |         | 4.17       |

IR(KBr): 1680 & 1700 (CO); PMR(CDCl₃): 2.18 (s, 3H, 5-CH₃), 2.53 (s, 3H, 2-CH₃), 3.57 (s, 3H, CO₂CH₃), 7.60-8.06 (m, 4H, Ar-H), 8.61 (s, 1H, CHO); Mass: M⁺ at m/z 343.

| 69       | CH=N=OH | 216-18 | 86      | C₁₈H₁₅ClNO₄ | 60.25   | 4.18       |
|          |         |        |         |             |         | 7.81       |
|          |         |        |         |              |         | 60.34      |
|          |         |        |         |              |         | 4.51       |
|          |         |        |         |              |         | 7.61       |

IR(KBr): 1700 (CO); PMR(TFA): 2.10 (s, 3H, 5-CH₃), 2.48 (s, 3H, 2-CH₃), 3.65 (s, 3H, CO₂CH₃), 7.80-8.21 (m, 4H, Ar-H); Mass: M⁺ at m/z 358.

| 70       | CN    | 176-78 | 68      | C₁₈H₁₃ClNO₃ | 63.43   | 3.81       |
|          |       |        |         |             |         | 8.22       |
|          |       |        |         |              |         | 62.95      |
|          |       |        |         |              |         | 3.51       |
|          |       |        |         |              |         | 8.45       |

IR(KBr): 1740 (CO), 2280 (CN); PMR(TFA): 2.10 (s, 3H, 5-CH₃), 2.43 (s, 3H, 2-CH₃), 3.63 (s, 3H, CO₂CH₃), 7.81-8.21 (m, 4H, Ar-H); Mass: M⁺ at m/z 340.
### Table 12:

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<th>Compound No.</th>
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<th>Yield %</th>
<th>Mol. Formula</th>
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<td></td>
<td>C</td>
<td>H</td>
<td>N</td>
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<tr>
<td>79</td>
<td>4-Chloro 3-nitrophenyl</td>
<td>138-39</td>
<td>60</td>
<td>C_{17}H_{17}CIN_{2}O_{6} (380.5)</td>
<td>53.61</td>
<td>4.46</td>
<td>7.35</td>
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<td>IR(KBr): 1680 (CO); PMR(CDC_{3}): 2.29 (s, 6H, 2xCH_{3}), 3.60 (s, 6H, 2xCO_{2}CH_{3}), 4.99 (s, 1H, CH), 6.09 bs, 1H, NH, 7.28-7.68 (m, 3H, Ar-H) Mass: M^+ at m/z 380.</td>
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<tr>
<td>80</td>
<td>4-Aceto-3-midophenyl</td>
<td>264-65</td>
<td>62</td>
<td>C_{19}H_{22}N_{2}O_{5} (358)</td>
<td>63.68</td>
<td>6.14</td>
<td>7.82</td>
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<td>IR(KBr): 1670 &amp; 1720 (CO); PMR(DMSO-d_{6}): 2.21 (s, 3H, NHCOCH_{3}), 2.49 (s, 6H, 2xCH_{3}), 3.75 (s, 6H, 2xCO_{2}CH_{3}), 5.02 (s, 1H, CH), 7.18-7.29 (dd, 2H, 3a5Ar-H, Jo = 9Hz, Jm = 2Hz), 7.51-7.63 (dd, 2H, 2&amp;6Ar-H, Jo = 9Hz, Jm = 2Hz), 8.98 &amp; 9.91 (2bs, 2H, 2xNH) Mass: M^+ at m/z 358.</td>
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<tr>
<td>81</td>
<td>4-Amino 3-nitrophenyl</td>
<td>231-32</td>
<td>68</td>
<td>C_{17}H_{19}N_{3}O_{6} (361)</td>
<td>56.50</td>
<td>5.26</td>
<td>11.63</td>
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<tr>
<td><strong>IR(KBr):</strong> 1690 (CO); <strong>PMR(CDCl₃+DMSO-d₆):</strong> 2.21 (s, 6H, 2xCH₃), 3.50 (s, 6H, 2xCO₂CH₃), 4.70 (s, 1H, CH), 6.61-6.93 (m, 3H, Ar-H), 7.63-7.73 (bs, 1H, NH), 8.28-8.41 (bs, 2H, NH₂); <strong>Mass:</strong> M⁺ at m/z 361.</td>
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<tr>
<td><img src="image" alt="Structure 82" /></td>
<td>301-2</td>
<td>60</td>
<td>C₂₈H₃₂N₂O₈</td>
<td>64.12</td>
<td>6.10</td>
<td>5.34</td>
<td>64.20</td>
</tr>
<tr>
<td><strong>IR(KBr):</strong> 1670 (CO); <strong>PMR(TFA):</strong> 1.79 (s, 12H, 4xCH₃), 3.69 (s, 12H, 4xCO₂CH₃), 4.90 (s, 2H, 2xCH), 7.12-7.43 (m, 4H, Ar-H); <strong>Mass:</strong> M⁺ at m/z 525.</td>
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<tr>
<td><img src="image" alt="Structure 83" /></td>
<td>220-22</td>
<td>35</td>
<td>C₂₀H₁₉ClN₂O₄</td>
<td>62.09</td>
<td>4.91</td>
<td>7.24</td>
<td>62.41</td>
</tr>
<tr>
<td><strong>IR(KBr):</strong> 1710 (CO); <strong>PMR(TFA):</strong> 2.29 (s, 6H, 2xCH₃), 3.58 (s, 6H, 2xCO₂CH₃), 5.50 (s, 1H, CH), 7.51-8.20 (m, 6H, Ar-H &amp; NH); <strong>Mass:</strong> M⁺ at m/z 386.</td>
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<tr>
<td><img src="image" alt="Structure 84" /></td>
<td>121-22</td>
<td>55</td>
<td>C₁₆H₂₅NO₉</td>
<td>51.20</td>
<td>6.66</td>
<td>3.73</td>
<td>51.51</td>
</tr>
<tr>
<td><strong>IR(KBr):</strong> 1735 (CO) &amp; 3350 (OH); <strong>PMR(D₂O):</strong> (s, 6H, 2xCH₃), 3.93 (s, 6H, 2xCO₂CH₃), 3.94-4.41 (m, 6H, CH &amp; CH₂), 5.29-5.38 (d, 1H, CH); <strong>Mass:</strong> M⁺ at m/z 375.</td>
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<tr>
<td>85</td>
<td>190-92</td>
<td>62</td>
<td>C&lt;sub&gt;20&lt;/sub&gt;H&lt;sub&gt;19&lt;/sub&gt;N&lt;sub&gt;5&lt;/sub&gt;O&lt;sub&gt;4&lt;/sub&gt;</td>
<td>61.06</td>
<td>4.83</td>
<td>17.81</td>
<td>60.70</td>
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<td>(393)</td>
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</tbody>
</table>

**IR(KBr):** 1700 (CO); **PMR(TFA):** 2.30 (s, 6H, 2xCH<sub>3</sub>), 3.58 (s, 6H, 2xCO<sub>2</sub>CH<sub>3</sub>), 5.40 (s, 1H, CH), 7.59-8.21 (m, 6H, Ar-H & NH); **Mass:** M<sup>+</sup> at m/z 393.

| 86 | 220-21 | 65 | C<sub>28</sub>H<sub>27</sub>CIN<sub>2</sub>O<sub>7</sub> | 62.39 | 5.01 | 5.19 | 62.41 | 4.56 | 5.61 |
|   |   |   | (538.5) |   |   |   |   |   |   |

**IR(KBr):** 1700 & 1740 (CO); **PMR(CDCl<sub>3</sub>):** 2.13 (s, 3H, 5-CH<sub>3</sub>), 2.27 (s, 6H, 2xCH<sub>3</sub>), 2.51 (s, 3H, 2-CH<sub>3</sub>), 3.53 (s, 9H, 3xCO<sub>2</sub>CH<sub>3</sub>), 5.40 (s, 1H, CH), 7.31-7.90 (m, 4H, Ar-H)

| 87 | 149-50 | 80 | C<sub>18</sub>H<sub>21</sub>N<sub>3</sub>O<sub>6</sub> | 57.60 | 5.60 | 11.20 | 57.38 | 5.60 | 11.51 |
|   |   |   | (375) |   |   |   |   |   |   |

**IR(KBr):** 1700 (CO); **PMR(CDCl<sub>3</sub>):** 2.27 (s, 6H, 2xCH<sub>3</sub>), 2.88-2.94 (d, 3H, CH<sub>3</sub>), 3.59 (s, 6H, 2xCO<sub>2</sub>CH<sub>3</sub>), 4.80 (s, 1H, CH), 5.98-6.08 (bs, 1H, NH), 7.18-7.39 (m, 3H, Ar-H); **Mass:** M<sup>+</sup> at m/z 375.

<p>| 88 | 206-7 | 63 | C&lt;sub&gt;24&lt;/sub&gt;H&lt;sub&gt;25&lt;/sub&gt;N&lt;sub&gt;3&lt;/sub&gt;O&lt;sub&gt;6&lt;/sub&gt; | 63.85 | 5.54 | 9.31 | 63.51 | 5.41 | 9.56 |
|   |   |   | (451) |   |   |   |   |   |   |</p>
<table>
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<th>10</th>
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<tbody>
<tr>
<td>89</td>
<td>(4-Hydroxy 168-69</td>
<td>41</td>
<td>C_{17}H_{18}N_{2}O_{7}</td>
<td>56.35</td>
<td>4.97</td>
<td>7.73</td>
<td>56.15</td>
<td>4.71</td>
<td>7.95</td>
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<td>90</td>
<td>3,4-Diamino 239-40</td>
<td>72</td>
<td>C_{17}H_{21}N_{3}O_{4}</td>
<td>61.63</td>
<td>6.34</td>
<td>12.68</td>
<td>61.70</td>
<td>6.15</td>
<td>12.89</td>
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</table>

**IR**(KBr): 1700 (CO); **PMR**(CDCl$_3$): 2.24 (s, 6H, 2xCH$_3$), 3.55 (s, 6H, 2xCO$_2$CH$_3$), 4.35-4.41 (d, 2H, CH$_2$), 4.80 (s, 1H, CH), 7.15-7.31 (m, 9H, Ar-H & NH); **Mass**: M$^+$ at m/z 451.

**IR**(KBr): 1690 (CO); **PMR**(CDCl$_3$+DMSO-$d_6$): 2.26 (s, 6H, 2xCH$_3$), 3.53 (s, 6H, 2xCO$_2$CH$_3$), 5.90 (s, 1H, CH), 7.29-7.51 (m, 4H, Ar-H & NH); **Mass**: M$^+$ at m/z 362.

**IR**(KBr): 1710 (CO); **PMR**(TFA): 2.20 (s, 6H, 2xCH$_3$), 3.60 (s, 6H, 2xCO$_2$CH$_3$), 4.99 (s, 1H, CH), 6.55-6.63 (bs, 2H, NH$_2$), 7.31-7.52 (m, 3H, Ar-H), 7.60-7.71 (bs, 2H, NH$_2$); **Mass**: M$^+$ at m/z 331.
Table 12a:

\[
\begin{array}{cccccccccc}
\text{Compound No.} & R & \text{m.p.} & \text{Yield} & \text{Mol. Formula} & \text{Mol. Wt.} & \text{Analysis \%} \\
& & \text{°C} & \text{\%} & \text{Mol. Wt.} & & \text{Required} & \text{Found} \\
\hline
91 & & & & & & & \\
Phenyl 195-96 & 58 & C_{31}H_{29}N_{3}O_4 & 73.37 & 5.71 & 8.28 & 73.49 & 5.33 & 8.61 \\
\hline
92 & 4-Methoxy & 135-36 & 66 & C_{33}H_{33}N_{3}O_6 & 69.84 & 5.82 & 7.40 & 70.12 & 5.58 & 7.34 \\
phenyl & & & & (567) & & & \\
\hline
93 & 3,4-Dimethoxyphenyl & 220-21 & 62 & C_{35}H_{37}N_{3}O_8 & 66.98 & 5.90 & 6.69 & 66.61 & 5.78 & 6.91 & \\
& & & & (627) & & & \\
\end{array}
\]

\[
\begin{array}{cccccccc}
\text{IR(KBr):} & 1680 (CO); & \text{PMR(CDC}_3\text{)} & 2.18 \text{ (s, 6H, 2xCH}_3\text{),} & 3.33 \text{ (s, 6H, 2xCO}_2\text{CH}_3\text{),} & 4.85 \text{ (s, 1H, CH}, & 5.36 \text{ (s, 2H, CH}_2\text{),} & 6.80-7.52 \text{ (m, 13H, Ar-H),} & 8.42 \text{ (s, 1H, NH), Mass: M}^+ \text{ at m/z 507.} \\
\text{IR(KBr):} & 1690 (CO); & \text{PMR(CDC}_3\text{)} & 2.20 \text{ (s, 6H, 2xCH}_3\text{),} & 3.41 & 3.54 \text{ (2s, 6H, 2xCO}_2\text{CH}_3\text{),} & 3.69 & 3.73 \text{ (2s,} & 6H, 2xOCH}_3\text{),} & 4.97 \text{ (s, 1H, CH}, & 5.25 \text{ (s, 2H, CH}_2\text{),} & 6.52-7.75 \text{ (m, 12H, Ar-H & NH).} \\
\end{array}
\]
<table>
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<th>9</th>
<th>10</th>
<th>11</th>
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</thead>
<tbody>
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<td><strong>IR(KBr): 1695 (CO); PMR(CDC$_3$): 2.18 (s, 6H, 2xCH$_3$), 3.50 (s, 6H, 2xCO$_2$CH$_3$), 3.59, 3.68, 3.72 &amp; 3.79 (4s, 12H, 4xOCH$_3$), 5.00 (s, 1H, CH), 5.20 (s, 2H, CH$_2$), 6.50-7.25 (m, 9H, Ar-H), 7.60 (s, 1H, NH)</strong>*</td>
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<tr>
<td><strong>94</strong></td>
<td>4-Hydroxy</td>
<td>130</td>
<td>58</td>
<td>C$<em>{33}$H$</em>{33}$N$_3$O$_8$</td>
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<td>7.01</td>
<td>65.89</td>
<td>5.31</td>
<td>7.46</td>
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<td><strong>IR(KBr): 1685 (CO); PMR(CDC$_3$,DMSO-d$_6$): 2.21 (s, 6H, 2xCH$_3$), 3.40 &amp; 3.50 (2s, 6H, 2xCO$_2$CH$_3$), 3.61 &amp; 3.80 (2s, 6H, 2xOCH$_3$), 4.97 (s, 1H, CH), 5.25 (s, 2H, CH$_2$), 6.35-7.64 (m, 10H, Ar-H &amp; NH)</strong>*</td>
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<td><strong>95</strong></td>
<td>3,4-Methylenedioxy</td>
<td>180-81</td>
<td>53</td>
<td>C$<em>{33}$H$</em>{29}$N$_3$O$_8$</td>
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<td>66.41</td>
<td>4.59</td>
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</table>
3.2 ANTIFERTILITY ACTIVITY OF COMPOUND SYNTHESISED

Almost all the compounds synthesised as possible antifertility agents have been screened for their early abortifacient activity in the Division of Endocrinology of Central Drug Research Institute, Lucknow.

Evaluation of Early Abortifacient Activity Material and Method:

Adult male and female hamsters and rats of proven fertility, maintained under uniform husbandry conditions having a regulated light and dark period were caged for overnight and the vaginal smear was examined following morning. Finding of spermatozoa in smear was considered as day 1 of pregnancy. From days 4-8 of pregnancy in hamster and days 6-10 in rats the compounds were administered subcutaneously.

On day 12 of pregnancy in hamster, animals were laprotomized and examined for implantation/resorption sites. Required area of the resorption sites was fixed in Bovin's fluid for histological examinations. Results have revealed that if compounds were administered before day 4 of pregnancy in hamster or day 6 in rat they were not equally effective as in the post-implantation stage. The results of biological activities of various compounds synthesised are described in Table 13.

RESULTS AND CONCLUSIONS:

Simpler heterocycles possessing only one phenyl ring did not show any remarkable contraceptive efficacy. The present study has also revealed the pregnancy inhibitory effect of compounds belonging to a new class of heterocyclic system namely 2,6-dimethyl-3,5-dimethoxycarbonyl-4-substituted-1,4-dihydropyridine. This new lead is worth exploiting and calls for evaluation of other compounds of this series.
<table>
<thead>
<tr>
<th>Compound No.</th>
<th>Dose (mg/kg)</th>
<th>Treatment (day of pregnancy)</th>
<th>No. of Animals</th>
<th>Pregnancy prevention in % Animals</th>
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<td>4-8</td>
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<td>4-8</td>
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CHAPTER 4

STUDIES ON THE CHEMOTHERAPY OF HELMINTH INFECTIONS:
RETROSPECTS AND PROSPECTS

4.1 : The health hazard of helminth infections in India

4.2 : Development of experimental models

4.3 : Biochemical studies

4.4 : Mode of Action

4.5 : Future development

4.6 : BASIS OF WORK
CHAPTER - 4

"STUDIES ON THE CHEMOTHERAPY OF HELMINTH INFECTIONS: RETROSPECTS AND PROSPECTS"

4.1 Helminthiasis, a group of several diseases caused by the invasion of human body by the roundworms (nematodes), flatworms (trematodes) and tapeworms (cestodes), may be broadly classified as gastrointestinal or enteric helminthiasis, schistosomiasis and filariasis. Of these, filariasis alone affects the health and general well-being of nearly 400 million people in tropical and subtropical regions of the world. Of the 900 million people around the world living in the areas endemic to filariasis, 236 million population belong to India. The picture of endemicity in this country is becoming alarming day by day since 22 million microfilaremic carriers and about 16 million cases with clinicopathological symptoms have been reported. The continuous spread of the disease and protracted suffering and disability caused by the parasites to the infected population have attracted greater attention and priority has been laid for combating helminth infection not only in this country but also by the members of the World Health Organisation.

The enteric or gastrointestinal helminthiasis is also highly prevalent in different parts of the tropical world. In India it is endemic in rural masses and the urban population with low standard of living and poor sanitation. The incidence of ancylostomiasis ranges from 40% in plains to 90% or even more in the area of tea estate and coffee plantation.46,47 The ever growing dimensions of this disease in this country is evident from the recently published statistical figures. In Uttar Pradesh alone 20.1% of rural population is affected by hookworm infection.48

Helminthiasis, in principle, can be controlled by improving personal and public hygiene and in the event of less satisfactory sanitation conditions, chemoprevention is possibly the most attracting approach. Any chemical which may evoke selective toxicity to parasites or is capable of stimulating immunosurveillance mechanism of the host would be of interest for the treatment of the infected population. Present state of art in immunology possibly permits immunodiagnosis but specific immunotherapy of various diseases caused
by helminth infections is not yet possible and this has prompted
to analyse the retrospects and prospects of the chemotherapy of
helminth infections.

4.2 The retrospective analysis of the chemotherapy of helminth
infections reveals the attempts made by earlier workers to develop
suitable experimental models for the evaluation of possible anthel­
mintic agents.

DEVELOPMENT OF EXPERIMENTAL MODELS

A. Filariasis: The search for experimental host-parasite models
has led to investigations on parasites such as Litomosoides carinii
(Vector, Liponyssu bacoti), Dipetalonema viteae \(^49\) (Vector, Orni-
thodorous moubata) and Brugia malayi \(^50,51\) (Vector, Aedes aegypti).
The suitable hosts are cotton rats (Sigmodon hispidus) Masto-
mys natalensis, albino rats and gerbils (Meriones unguiculatus).

The difficulty of breeding, handling and maintenance of
cotton rats, the natural infection for L. carinii, the most commonly used
filarial infection have led to the identification of mostomys as
alternative host \(^52\). Subsequently, mastomys has been found to be
more suitable as a host for D. viteae and B. malayi infections.
The latter can also be infected to cat \(^53\), rhesus monkey and langoor.

B. Intestinal Helminthiasis:

Hookworms and tapeworms are the main targets in intestinal
helminthiasis. Albino rats \(^54\) and golden hamsters as laboratory animals
for N. brasiliensis \(^54,57\) (a trichostrongylid) and Ancylostoma ceylanicum
(hookworm) respectively, have been found to be more suitable but
certain advantages and susceptibility of M. natalensis to N. brasilienis-
sis infection have furnished yet another model for hookworm infection,
for detailed study of infectivity longevity and fecundity of A. ceylan-
cum \(^58\), laboratory rodents have been used. The laboratory models
for tapeworm infections such as Hymenolepis nana \(^59,60\) in mice and
H. diminuta, a natural infection in rodents, have been found to be
satisfactory.

The development of suitable experimental models for the
evaluation of possible anthelmintic agents has provided impetus for
the screening of large number of compounds. However, the need for
the replacement of this empirical approach has been realised much
earlier and in order to provide a scientific rationale for the drug
design, two distinct approaches have been made. The first one is
cconcerned with the studies on the biochemistry of the helminth para-
sites and the second one relates to the understanding of the mode
of action of active compounds discovered during random screening.

4.3 BIOCHEMICAL STUDIES

The anaerobic habitat of most of the intestinal helminths
has provoked studies on glycolysis and the inhibitor for the key
enzymes of the glycolytic pathway in helminth parasites such as
Chandlerella hawkingi, L. carinii and ascarda galli has been search-
ed. Cyanine 863,62 an active inhibitor of these enzymes, has
not developed into a drug because of its toxicity. The biochemistry
of Setaria cervi, the parasite of the Indian water buffalo, has been
studied. A phosphoenol pyruvate (PEP) succinate pathway requiring
a thiol function for the enzyme activity has also been mapped. Adult
and microfilariae of S. cervi are very different in biochemical
compositions. Unlike microfilariae, adults have higher contents of
glycogen and glucose but have lower contents of fructose, lipids,
nucleic acids and phosphorous63. Recent observations emphasize transculticular absorption as an active transport process and inhibition
of this transport can starve the parasite and probably kill it. Pre-
sence of CAMP dependent and independent protein kinases in Brugia mala-
layi and N. brasiliensis64,65 play a regulatory role and the activity
of high molecular weight phosvitin kinase have been inhibited by
suramin and heparin, indicating a relationship between drug action
and inhibition of this enzyme. The parasitic intestinal helminths
such as A. lumbricoides and A. galli protect themselves from proteo-
lytic and other degradative enzymes secreted in the lumen, with
the help of trypsin and chymotrypsin inhibitors. Different organs
of A. galli contain several amino acid metabolising enzymes such as
Histamine ammonia-lyase, threonine dehydratase, glutamate dehydroge-
nase and alanine and aspartate amino transferases of which alanine
and aspartate transaminases have been found most active. Transami-
nases for alanine and aspartate have been reported in S. cervi, L.carinii and D. vittae while arginine and isoleucine transaminases are
also present in S. cervi. The presence of various biogenic amines
in helminth parasites has been verified as adult worms of L. carinii
contains all the four amines tested which are histamine, 5-hydroxytryptamine, dopamine and nor-epinephrine but dopamine is found to be absent in the microfilarial stage which possess higher amine content than adults. S. cervi, N.brasiliensis, A. lumbricoides var. hominis and A. galli contains all the four neuro amines but with varying level of 5-HT and NE in different parasites. The presence of both type A and type B monoamine oxidase (MAO) in A. galli and aliphatic polyamines such as spermidine, spermine as well as putrescine in S. cervi, A. galli, C. digonopora have been shown.

4.4 MODE OF ACTION

Biochemical composition of parasites, the enzymes involved in metabolic reactions as well as susceptibility of the parasites to anthelmintics have been investigated to understand the mode of action of these drugs and to identify target for chemotherapy. Inhibition of cholinesterases, interference with fumarate reductase, inhibition of mitochondrial NADH oxidizing activity, interference with phosphofructokinase and folate metabolism and disruption of cellular integrity are the major target sites for the anthelmintic drugs. Antifilarial drugs have been found to effect the various metabolic activities of the parasites which could either be direct targets of the drug or the secondary effect of their action. The capacity to synthesize glycogen and protein from glucose and valine by adult L. carinii is altered by DEC. It also affects the oxidative and metabolizing enzymes of the host. Consequently administration of DEC to the host has been found to alter its immunological response and to cause adverse reaction in microfilaraemic host. This drug has shown to cause the loss of sheath from L. carinii and the electron microscopic studies have revealed that the cuticle of microfilariae of O. volvulus also undergo changes. Levamisole alters the aerobic glucose metabolism of Brugia pahani and it has been suggested that the effect of this drug on the metabolism of microfilariae are secondary to the observed paralysis. Suramin inhibits the lactate and malate dehydrogenase of O. volvulus. It also inhibits protein kinase of the same organism and circumstantial evidence exists to presume that Suramin might have more than one site of action. Niclosamide, Praziquantel and Mebendazole inhibit glucose uptake by the parasite and an increase in lactate formation indicates a change-over to homolactate fermentation. Proposed mode of actions of drugs containing
benzimidazole-2-carbamate nucleus (Mebendazole, Albendazole, Fenbendazole, Flubendazole, Oxibendazole, Parbendazole, etc.) thiabendazole and cambendazole reveal their actions mainly through inhibitions of microtubule polymerisation and fumerate reductase.

Current evidence is inadequate to determine whether or not DEC is capable of invoking a prophylactic action in the lymphatic filariasis in man. More than thousand compounds have been evaluated as possible new macrofilaricide by the special programme of WHO alone and a few compounds which have been identified for clinical studies are described\(^7\) in fig.a.

The chemotherapeutic agent employed for the treatment of nematode and cestode infections and their structure to activity relationship have been reviewed\(^8\). Of the various chemotherapeutic agents, methyl benzimidazole-2-carbamates occupy a unique position. This is primarily because of their wider spectrum of anthelmintic activity but no attempt appears to have been made to review the present status of benzimidazole anthelmintics for the treatment of various helminth infections for assessing the spectrum of anthelmintic activity. The present status of benzimidazole anthelmintics has, therefore, been presented in table 1a to provide a bird's eye-view of their efficacy.

4.5 The trend of research activities in the area of chemoprevention of helminth infections suggests that in the coming decade, possibly more emphasis would be laid on the development of chemoprophylactics and immuno-regulators. The latter would be more concerned with the development of agents which would enable an immuno-incompetent host to regain its immunocompetence. The classical chemotherapeutic approach may furnish exciting and interesting data on nitro group bearing heterocycles. Development of new lead molecules as GABA agonist is a strong possibility and the detailed understanding of the mode of action of ivermectins would be possibly achieved.

4.6 BASIS OF WORK

The socio-economic problems and inadequate public health facilities of this country call for the development of a broad-spectrum
**Furapyridone:** N-(5-nitro-2-furfurylidone) amino tetrahydro-2(1H) Pyrimidone

**Desmethymisindazole:** 1,2-Propanediol, 3(2-nitro-1H-imidazol-1-yl)

Contd.
Ivermectine (A mixture of Components I and II)

Component I: 5-0-demethyl-22,23-dihydro avermectin Ala

Component II: 5-0-demethyl-25-de(1-methylpropyl)-22,23-dihydro-25-(1-methylethyl) avermectin Ala.

ALBENDAZOLE: \( R = \text{SCH}_3 \)
FENBENDAZOLE: \( R = \text{SC}_6\text{H}_5 \)
OXIBENDAZOLE: \( R = \text{OC}_3\text{H}_7 \)
PARBENDAZOLE: \( R = \text{C}_4\text{H}_9 \)

THIABENDAZOLE: \( R = \text{H} \)
CAMBENDAZOLE: \( R = \text{NH-C-0CH(CH}_3)_2 \)

LEVAMISOLE

PRAZIQUANTEL

Contd.
Suramin (Hexa-sodium 3,3'-Ureylene-bis-8-(3-benzimido-\(p\)-toluido)-1,3,5-naphthalene sulphonate)

DEC (1-Diethylcarbamyl-4-methylpiperazine)

Lodoxamide \(N,N'\)-(2-Chloro-5-Cyano-\(m\)-phenylene)

Mebendazole (Methyl 5-benzoyl-2-benzimidazole carbamate)

Flubendazole (\(p\)-fluorobenzoyl)-2-benzimidazole carbamate

Fig. 4
Table 1: Spectrum of anthelmintic activity of common antinematode and anticestode drugs

<table>
<thead>
<tr>
<th>Drug/Dose</th>
<th>Parasite</th>
<th>Host</th>
<th>Anthelmintic efficacy (%)</th>
<th>Bibliography Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>400 mg (single)</td>
<td><em>Ascaris lumbricoides, Necator americanus, Trichuris trichura</em></td>
<td>Man</td>
<td>93.3</td>
<td>79</td>
</tr>
<tr>
<td>200 mg (single)</td>
<td><em>Strongyloides stercoralis</em></td>
<td>Man</td>
<td>100</td>
<td>79</td>
</tr>
<tr>
<td>400 mg (single)</td>
<td><em>Enterobius Vermicularis</em></td>
<td>Man</td>
<td>100</td>
<td>80</td>
</tr>
<tr>
<td>30 mg/kg (single)</td>
<td><em>Capillaria hepatica</em></td>
<td>Mice</td>
<td>99</td>
<td>81</td>
</tr>
<tr>
<td>800 mg (Multiple)</td>
<td><em>Hymenolepis nana</em></td>
<td>Man</td>
<td>69</td>
<td>82</td>
</tr>
<tr>
<td>10 mg/kg (Multiple)</td>
<td><em>Taenia saginata</em></td>
<td>Man</td>
<td>92</td>
<td></td>
</tr>
<tr>
<td>100 mg/kg (Multiple)</td>
<td><em>Ostertagia ostertagi</em></td>
<td>Calves</td>
<td>99.99</td>
<td></td>
</tr>
<tr>
<td>15 mg/kg (single)</td>
<td><em>Dicrocoelium lanceatum</em></td>
<td>Ewes</td>
<td>94.46</td>
<td></td>
</tr>
<tr>
<td>400 mg (single)</td>
<td><em>Ancylostoma duodenale</em></td>
<td>Man</td>
<td>79</td>
<td></td>
</tr>
<tr>
<td>10 mg/kg (Multiple)</td>
<td><em>Trichuris globulosa</em></td>
<td>Goat</td>
<td>41-50</td>
<td></td>
</tr>
<tr>
<td>15 mg/kg (Multiple)</td>
<td><em>Fasciola hepatica</em></td>
<td>Sheep</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>10 mg/kg (single)</td>
<td><em>Trichinella pseudospiralis</em></td>
<td>Mice</td>
<td>36</td>
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</tr>
<tr>
<td>20 mg/kg</td>
<td>Dicrocoelium dendriticum</td>
<td>Sheep</td>
<td>98.61</td>
<td>90</td>
</tr>
<tr>
<td>(Multiple)</td>
<td></td>
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</tr>
<tr>
<td>5-10 mg/kg</td>
<td>Ascaridia galli,</td>
<td>Fowls</td>
<td>100</td>
<td>91</td>
</tr>
<tr>
<td>(Multiple)</td>
<td>Raillietina tetragona,</td>
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</tr>
<tr>
<td></td>
<td>R. echinobothridia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.5 mg/kg</td>
<td>Cooperia punctata,</td>
<td>Calves</td>
<td>99-100</td>
<td>92</td>
</tr>
<tr>
<td>(Multiple)</td>
<td>Nematodirus spathiger,</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Haemonchus placei,</td>
<td></td>
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<tr>
<td></td>
<td>Trichostrongylus axie,</td>
<td></td>
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<tr>
<td></td>
<td>T. colubriformis,</td>
<td></td>
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<tr>
<td></td>
<td>N. filicollis,</td>
<td></td>
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<tr>
<td></td>
<td>N. helvetianus,</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Desophagostomum radiatum</td>
<td></td>
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</tr>
<tr>
<td>2.5 or 3.8 mg/kg (Multiple)</td>
<td>Haemonchus contortus,</td>
<td>Sheep</td>
<td>~ 99.8</td>
<td>93</td>
</tr>
<tr>
<td></td>
<td>Trichostrongylus colubriformis,</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Gaigeria ovina,</td>
<td></td>
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<tr>
<td></td>
<td>Marshallagia marshalli</td>
<td></td>
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</tr>
<tr>
<td>2.5 mg/kg</td>
<td>Dictyocaulus filaria</td>
<td>Sheep</td>
<td>99</td>
<td>93</td>
</tr>
<tr>
<td>(Multiple)</td>
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<tr>
<td>4.8 mg/kg</td>
<td>Fasciola gigantica</td>
<td>Sheep</td>
<td>63.2</td>
<td>93</td>
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<tr>
<td>(Multiple)</td>
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**FENBENDAZOLE**

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<tr>
<td>50 mg/kg</td>
<td>Trichinella spiralis</td>
<td>Mice</td>
<td>95.1</td>
<td>94</td>
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<tr>
<td>(Multiple)</td>
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<td>7.5 mg/kg</td>
<td>Strongyloides westeri,</td>
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<td>Parascaris equorum</td>
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<tr>
<td>50 mg/kg</td>
<td>Toxocara canis,</td>
<td>Dogs</td>
<td>98-100</td>
<td>96</td>
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<tr>
<td>(Multiple)</td>
<td>Ancylostoma caninum,</td>
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<tr>
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<td>Trichuris vulpis</td>
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<td>10 mg/kg</td>
<td>Ascaris suum</td>
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<td>97</td>
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<td>Cyathostomum,</td>
<td>Donkey</td>
<td>100</td>
<td>98</td>
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<td>Cylicostephanus,</td>
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<td>Cylicocycalus,</td>
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<td>Cylicodontophorus,</td>
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<td></td>
<td>Craterostomum,</td>
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<tr>
<td><strong>10 mg/kg</strong></td>
<td><em>Triodontophorus,</em></td>
<td><strong>Donkey</strong></td>
<td><strong>55.5-100</strong></td>
<td>98</td>
<td></td>
</tr>
<tr>
<td>(Single)</td>
<td><em>Strongylus equinus,</em></td>
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<tr>
<td></td>
<td><em>Oxyuris equi</em></td>
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<tr>
<td></td>
<td><strong>S. vulgaris</strong></td>
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<tr>
<td>- do -</td>
<td><em>Habronema majus</em></td>
<td><strong>Donkey</strong></td>
<td><strong>81.8-100</strong></td>
<td>98</td>
<td></td>
</tr>
<tr>
<td>- do -</td>
<td><em>H. muscae</em></td>
<td><strong>Donkey</strong></td>
<td><strong>47.6-100</strong></td>
<td>&gt;8</td>
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<td><em>Ostertagia ostertagi,</em></td>
<td><strong>Heifer</strong></td>
<td>100</td>
<td>99</td>
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</tr>
<tr>
<td>(Multiple)</td>
<td><em>Cooperia spp.</em></td>
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<tr>
<td></td>
<td><em>Trichostrongylus axei</em></td>
<td><strong>Heifer</strong></td>
<td>90</td>
<td>100</td>
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<tr>
<td></td>
<td><em>Dicrocoelium dendriticum</em></td>
<td><strong>Sheep</strong></td>
<td><strong>99.3-100</strong></td>
<td>101</td>
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<tr>
<td><strong>100 mg/kg</strong></td>
<td><em>Paramphistomum spp.</em></td>
<td><strong>Cattle</strong></td>
<td><strong>87.2</strong></td>
<td>101</td>
<td></td>
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<tr>
<td>(Single)</td>
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<tr>
<td><strong>15 mg/kg</strong></td>
<td><em>Fasciola hepatica</em></td>
<td><strong>Sheep</strong></td>
<td>50</td>
<td>101</td>
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<td>(Multiple)</td>
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<tr>
<td><strong>15 mg/kg</strong></td>
<td><em>Moniezia spp.</em></td>
<td><strong>Sheep</strong></td>
<td>100</td>
<td>101</td>
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<tr>
<td>(Single)</td>
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<tr>
<td><strong>7.5 mg/kg</strong></td>
<td><em>Strongylus edentatus,</em></td>
<td><strong>Ponies</strong></td>
<td>100</td>
<td>102</td>
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</tr>
<tr>
<td>(Multiple)</td>
<td><em>Trichonema spp.</em></td>
<td><strong>99.7</strong></td>
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<tr>
<td><strong>100 mg/kg</strong></td>
<td><em>Toxascaris canis,</em></td>
<td><strong>Dogs</strong></td>
<td>&gt;90</td>
<td>103</td>
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<tr>
<td>(Single)</td>
<td><em>Taenia sp.</em></td>
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<tr>
<td>- do -</td>
<td><em>Dipylidium caninum</em></td>
<td><strong>Dogs</strong></td>
<td>&lt;50</td>
<td>103</td>
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<tr>
<td><strong>20 mg/kg</strong></td>
<td><em>Toxocara mystax,</em></td>
<td><strong>Dogs &amp; Cats</strong></td>
<td>100</td>
<td>104</td>
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</tr>
<tr>
<td>(Multiple)</td>
<td><em>Toxascaris leonina,</em></td>
<td></td>
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<tr>
<td></td>
<td><em>Uncinaria stenocephala</em></td>
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<tr>
<td><strong>35 mg/kg</strong></td>
<td><em>Metastrongylus spp.</em></td>
<td><strong>Pigs</strong></td>
<td><strong>93-100</strong></td>
<td>105</td>
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<tr>
<td>(Multiple)</td>
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<tr>
<td>- do -</td>
<td><em>Globocephalus urosubulatus</em></td>
<td><strong>Pigs</strong></td>
<td><strong>70-100</strong></td>
<td>105</td>
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</tr>
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<td>- do -</td>
<td><em>Trichuris suis</em></td>
<td><strong>Pigs</strong></td>
<td><strong>0-100</strong></td>
<td>105</td>
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<tr>
<td>MEBENDAZOLE</td>
<td>1</td>
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<td>4</td>
<td>5</td>
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<tr>
<td>5 mg/kg</td>
<td>N. dubius</td>
<td>Mice</td>
<td>100</td>
<td>106</td>
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<tr>
<td>(double)</td>
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<tr>
<td>70-100 mg/kg</td>
<td>P. ambiguus</td>
<td>Rabbits</td>
<td>100</td>
<td>107</td>
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<tr>
<td>(single)</td>
<td></td>
<td></td>
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<tr>
<td>10 mg/kg</td>
<td>Ancylostoma caninum</td>
<td>Dog</td>
<td>100</td>
<td>108</td>
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</tr>
<tr>
<td>(Multiple)</td>
<td></td>
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<tr>
<td>5 mg/kg</td>
<td>Trichinella nelsoni</td>
<td>Rats</td>
<td>98</td>
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<td>(Multiple)</td>
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<tr>
<td>50 mg/kg</td>
<td>Dicrocoelium dendriticum</td>
<td>Sheep</td>
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<tr>
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<td>Fasciola hepatica</td>
<td>Sheep</td>
<td>79.4</td>
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<td>1.5 g/10 kg</td>
<td>Dicytocalus filaria</td>
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<td>Ascaris lumbricoides</td>
<td>Man</td>
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<td>0.5 g/kg</td>
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<td>Mice</td>
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<td>119</td>
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<tr>
<td>8.8 mg/kg</td>
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<td>Ponies 99-100</td>
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<td>(Multiple)</td>
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<td>10-100 mg/kg</td>
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<td>Hamsters 99.7-100</td>
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<td>100 mg</td>
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<td><em>Chabertia ovina,</em></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- d0 -</td>
<td></td>
<td>Sheep 90</td>
<td>123</td>
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<tr>
<td>- d0 -</td>
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<td>Sheep 80</td>
<td>123</td>
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<td>100 mg (single)</td>
<td><em>Ternidens deminutus,</em></td>
<td>Man ≈100</td>
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<td><em>Taenia saginata,</em></td>
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<tr>
<td>- d0 -</td>
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<td>Man ≈40</td>
<td>124</td>
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<td>600 mg/kg</td>
<td><em>Ascaris lumbricoides</em></td>
<td>Man 97</td>
<td>125</td>
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</tr>
<tr>
<td>(double)</td>
<td></td>
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</tr>
<tr>
<td>300 mg/kg</td>
<td><em>Trichuris trichiura</em></td>
<td>Man 65.1</td>
<td>125</td>
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<td></td>
</tr>
<tr>
<td>(double)</td>
<td></td>
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<tr>
<td>5 mg/kg</td>
<td>A. cantonensis</td>
<td>Mice 65.1</td>
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<td>D. erinacei</td>
<td>Mice No effect</td>
<td>126</td>
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<td>Hymenolepis nana</td>
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<tr>
<td>50 mg/kg</td>
<td>T. spiralis</td>
<td>Mice 100</td>
<td>126</td>
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<td>(Multiple)</td>
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</tr>
<tr>
<td>1.5 mg/kg</td>
<td>Oesophagostomum dentatum,*</td>
<td>Pigs 100</td>
<td>127</td>
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<tr>
<td>(Multiple)</td>
<td>Ascaris suum,*</td>
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<td>Trichuris suis,*</td>
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<td>Metastrongylus apri</td>
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<tr>
<td>1.5 mg/kg (Multiple)</td>
<td>Strongyloides ransomi</td>
<td>Pigs</td>
<td>88</td>
<td>127</td>
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<tr>
<td>- do -</td>
<td>Stephanurus dentatus</td>
<td>Pigs</td>
<td>85</td>
<td>127</td>
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<tr>
<td>50 mg/Kg (Multiple)</td>
<td>Echinostoma caproni</td>
<td>Mice</td>
<td>100</td>
<td>128</td>
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<tr>
<td>150 mg/kg (Multiple)</td>
<td>G. urosubulatus</td>
<td>Mice</td>
<td>67-100</td>
<td>129</td>
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<tr>
<td>- do -</td>
<td>Capillaria spp.</td>
<td>Mice</td>
<td>25-86</td>
<td>129</td>
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<tr>
<td>150 mg/kg (Multiple)</td>
<td>Litomosoides carinii</td>
<td>Man</td>
<td>99</td>
<td>130</td>
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</tbody>
</table>

**OXYBENDAZOLE**

<p>| 150 mg/kg (Multiple) | L. carinii | Man | 85 | 130 |
| 15 mg/kg (single) Ascaris suum | Pigs | 100 | 131 |
| 40 ppm. in food (20-29 days) oesophagostomum dentatum | Pigs | 66.4 | 131 |
| 10 mg/kg (Multiple) | Strongyloides westeri | Foals | &gt; 99 | 132 |
| 40 mg/kg (Multiple) | Ascardia galli | Chicks | 98.4 | 133 |
| 15 mg/kg (Multiple) | Trichorema | Ponies | 97.7 | 134 |
| - do - | Strongylus vulgaris, S. edentatus, Oxyuris equi | Ponies | 100 | 134 |
| 15 mg/kg (single) | Haemonchus placei, Trichostrongylus axei, Cooperia spp. T. colubriformis, Bunostomum phlebotomum, Oesophagostomum radiatum | Cattle | &gt; 99 | 135 |
| 15 mg/kg (single) | Ostertagia ostertagi | Cattle | 96 | 135 |</p>
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<tbody>
<tr>
<td>15 mg/kg (single)</td>
<td>Trichuris sp.</td>
<td>Cattle</td>
<td>&gt; 80</td>
<td>135</td>
</tr>
<tr>
<td>- do -</td>
<td>Moniezia sp.</td>
<td>Cattle</td>
<td>&gt; 71</td>
<td>135</td>
</tr>
<tr>
<td>7.5 mg/kg (Multiple)</td>
<td>Cooperia oncophora</td>
<td>Cattle</td>
<td>98</td>
<td>136</td>
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<tr>
<td></td>
<td>(Larvae)</td>
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</tr>
<tr>
<td>15 mg/kg (Multiple)</td>
<td>Nematodirus spp.</td>
<td>Cattle</td>
<td>83</td>
<td>136</td>
</tr>
<tr>
<td>- do -</td>
<td>Strongyloides papillosus</td>
<td>Cattle</td>
<td>94</td>
<td>136</td>
</tr>
<tr>
<td>- do -</td>
<td>Capillaria bovis</td>
<td>Cattle</td>
<td>92</td>
<td>136</td>
</tr>
<tr>
<td>- do -</td>
<td>Bunostomum phlebotomum</td>
<td>Cattle</td>
<td>94</td>
<td>136</td>
</tr>
<tr>
<td>40 mg/kg (Multiple)</td>
<td>Trichinella spiralis</td>
<td>Mice</td>
<td>100</td>
<td>137</td>
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<tr>
<td>10 mg/kg (Multiple)</td>
<td>Proboscephalum viviparum,</td>
<td>Ponies</td>
<td>~ 100</td>
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<td>Parascaris equorum</td>
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<td>50 mg/kg (Multiple)</td>
<td>Trichuris trichiura</td>
<td>Man</td>
<td>12</td>
<td>139</td>
</tr>
<tr>
<td>- do -</td>
<td>Ascaris lumbricoides</td>
<td>Man</td>
<td>78</td>
<td>139</td>
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<tr>
<td>- do -</td>
<td>Enterobius vermicularis</td>
<td>Man</td>
<td>83</td>
<td>139</td>
</tr>
<tr>
<td>- do -</td>
<td>Trichostrongylus spp.,</td>
<td>Man</td>
<td>100</td>
<td>139</td>
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<tr>
<td>- do -</td>
<td>Necator americanus</td>
<td>Man</td>
<td>50</td>
<td>139</td>
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<tr>
<td>- do -</td>
<td>Hymenolepis nana</td>
<td>Man</td>
<td>Not effec-</td>
<td>139</td>
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<td></td>
<td></td>
<td>tive</td>
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<td>53 mg/kg</td>
<td>Ostertagia circumcincta</td>
<td>Sheep</td>
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<td>88.0 mg/kg (Multiple)</td>
<td>Ostertagia ostertagi,</td>
<td>Heifer</td>
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<tr>
<td></td>
<td>Cooperia spp.</td>
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<tr>
<td>50 mg/kg (Multiple)</td>
<td>Strongylus vulgaris,</td>
<td>Horses</td>
<td>100</td>
<td>141</td>
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<tr>
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<td>S. edentatus</td>
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<tr>
<td>50 mg/kg</td>
<td>Cylcocyclus nassatus, Cyathostomum coronatum, C. catinatum,</td>
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<td>insignae, Cyathostomum labiatum</td>
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<tr>
<td>50 mg/kg</td>
<td>Draculus medinensis</td>
<td>Man</td>
<td>100</td>
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<tr>
<td>50 mg/kg</td>
<td>Strongylus stercoralis</td>
<td>Man</td>
<td>84</td>
<td>143</td>
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<tr>
<td>300 mg/kg</td>
<td>Dicrocoelium dendriticum</td>
<td>Sheep</td>
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<td>CAMBENDAZOLE</td>
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<tr>
<td>10 mg/kg</td>
<td>Strongyloides westeri</td>
<td>Foals</td>
<td>&gt;99</td>
<td>132</td>
</tr>
<tr>
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<td>Dicrocoelium lanceolatum</td>
<td>Sheep</td>
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<tr>
<td>100 mg/kg</td>
<td>Ancylostoma caninum</td>
<td>Dogs</td>
<td>70.5</td>
<td>146</td>
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<td>95</td>
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<td>Dicrocoelium dendriticum</td>
<td>Ewes</td>
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<tr>
<td></td>
<td>Trichostrongylus axei Chabertia ovina</td>
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<tr>
<td>40 mg/kg</td>
<td>Trichinella spiralis</td>
<td>Mice</td>
<td>100</td>
<td>149</td>
</tr>
<tr>
<td>(Multiple)</td>
<td></td>
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</tr>
<tr>
<td>20 mg/kg</td>
<td>Parascaris equorum, Oxyuris equi</td>
<td>Horses</td>
<td>100</td>
<td>150</td>
</tr>
<tr>
<td></td>
<td>Haemonchus contortus</td>
<td>Zebu</td>
<td>100</td>
<td>151</td>
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<tr>
<td>15 mg/kg</td>
<td>Cooperia pectinata, C. Punctata, Oesophagostatum radiatum</td>
<td>Zebu</td>
<td>100</td>
<td>151</td>
</tr>
<tr>
<td>1 mg/kg</td>
<td>2 mg/kg</td>
<td>3 mg/kg</td>
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<tr>
<td><strong>15 mg/kg</strong></td>
<td>Bunostomum phlebotomum</td>
<td>Zebu</td>
<td>Infective</td>
<td>151</td>
</tr>
<tr>
<td><strong>20 mg/kg</strong></td>
<td>Ostertagia circumcincta, Capillaria longipes, Bunostomum trigoncephalum Cooperia curvicei</td>
<td>Sheep</td>
<td>100</td>
<td>152</td>
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<tr>
<td>- do -</td>
<td>Trichostrongylus vitrinus</td>
<td>Sheep</td>
<td>99.6</td>
<td>152</td>
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<tr>
<td>- do -</td>
<td>Nematodirus pathiger</td>
<td>Sheep</td>
<td>90.7</td>
<td>152</td>
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<tr>
<td><strong>30 mg/kg</strong></td>
<td>Dictyocaulus viviparous</td>
<td>Cattle</td>
<td>99</td>
<td>153</td>
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</tbody>
</table>

**Oxfendazole**

<p>| 7.5 mg/kg | Muellerius capillaris | Goats | 90 | 154 |
| 12.5 mg/kg (single) | Capillaria hepatica | Mice | 99 | 81 |
| <strong>7.5 mg/kg (Multiple)</strong> | Ascaris suum, Oesophagostomum dentatum | Piglets | 100 | 155 |
| - do - | Strongyloides ransomi | Piglets | 80 | 155 |
| - do - | Trichuris suis | Piglets | 60 | 155 |
| <strong>2 mg/kg (Multiple)</strong> | Chabertia ovina | Roe deer &amp; Mufflon | 75-100 | 156 |
| - do - | Dictyocaulus viviparous | - do - | 100 | 156 |
| - do - | Capreocaulus capreoli | - do - | 70.9 | 156 |
| - do - | Muellerius capillaris | - do - | 70.9 | 156 |
| <strong>2.5 mg/kg (Multiple)</strong> | Bunostomum sp. | Cattle | 99.4 | 157 |
| - do - | Haemonchus sp. | Cattle | 96.4 | 157 |
| - do - | Cooperia sp. | Cattle | 98.3 | 157 |
| - do - | Trichostrongylus sp. | Cattle | 99.9 | 157 |
| - do - | Mecistocirrus | Cattle | 100 | 157 |</p>
<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>Species</th>
<th>Host</th>
<th>Dose Range (%)</th>
<th>Reference</th>
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<tr>
<td>4.5 mg/kg</td>
<td>Dictyocaulus filaria</td>
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<td>94-100</td>
<td>111</td>
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<tr>
<td>- do -</td>
<td>Moniezia</td>
<td>Sheep</td>
<td>96-100</td>
<td>111</td>
</tr>
<tr>
<td>1.6 mg/kg (Single)</td>
<td>Trichinella spiralis</td>
<td>Mice</td>
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<td>158</td>
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<tr>
<td>10 mg/kg</td>
<td>Parascaris equorum, Oxyuris equi, Strongyloides vulgaris, S. edentatus, Triodontophorus, Trichostrongylus axei</td>
<td>Ponies</td>
<td>&gt;96</td>
<td>159</td>
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<tr>
<td>3 mg/kg</td>
<td>Hyostrongylus rubidus</td>
<td>Pigs</td>
<td>100</td>
<td>160</td>
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<tr>
<td>2.5 mg/kg</td>
<td>Dictyocaulus viviparus</td>
<td>Calves</td>
<td>100</td>
<td>161</td>
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<tr>
<td>2.5 mg/kg</td>
<td>Ostertagia ostertagi, Cooperia oncophora, C. mosmasteri, C. pectinata, C. punctata, Nematodirus helvetianus, T. longispicularis, Oesophagostomum radiatum</td>
<td>Calves</td>
<td>97-100</td>
<td>162</td>
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<td>1.5-9.0 mg/kg (Multiple)</td>
<td>Ascaris suum</td>
<td>Pigs</td>
<td>99.2-100</td>
<td>163</td>
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<td>9.0 mg/kg (Multiple)</td>
<td>Metastrongylus apri &amp; M. pudendotectus</td>
<td>Pigs</td>
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<td>163</td>
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<td>2.8 mg/kg</td>
<td>Haemonchus contortus</td>
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<td>82</td>
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<tr>
<td>- do -</td>
<td>Cooperia curticei, Buorostomum trigonocephalum</td>
<td>Goats</td>
<td>91.3</td>
<td>164</td>
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**Parbendazole**

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<th>Dose Range (%)</th>
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<tr>
<td>20 mg/kg (Multiple)</td>
<td>Haemonchus contortus, Trichostrongylus colubriformis, Buorostomum trigonocephalum, Strongyloides papillosus, Toxocara canis</td>
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<td>100</td>
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<tr>
<td></td>
<td>Goats</td>
<td>100</td>
<td></td>
<td>165</td>
</tr>
<tr>
<td></td>
<td>Sheep</td>
<td>100</td>
<td></td>
<td>165</td>
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<tr>
<td></td>
<td>Dog</td>
<td>100</td>
<td></td>
<td>165</td>
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<tr>
<td>4 mg/kg (Multiple)</td>
<td>Murshidia falcifera</td>
<td>Elephant</td>
<td>100</td>
<td>165</td>
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<tr>
<td>20 mg/kg</td>
<td>Ascaris vitulorum</td>
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<tr>
<td>(Multiple)</td>
<td>Ancylostoma caninum</td>
<td>Dog</td>
<td>66.1-88.7</td>
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<td></td>
<td>Trichurus globulosa</td>
<td>Goat</td>
<td>51.6</td>
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<tr>
<td>30 mg/Ig</td>
<td>Ostertagia ostertagi</td>
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<tr>
<td>active</td>
<td>Cooperia oncophora</td>
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<td>ingredient</td>
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<tr>
<td>300 mg/kg</td>
<td>Ascaris summ</td>
<td>Boar</td>
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<tr>
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<td>Globocephalus urosubulatus</td>
<td>Boar</td>
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<tr>
<td>41 mg/kg</td>
<td>Ascaridia numidae</td>
<td>Guinea-fowls</td>
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<tr>
<td>(single)</td>
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<tr>
<td>30 mg/kg</td>
<td>Ostertagia circumcincta,</td>
<td>Sheep</td>
<td>94.1-100</td>
<td>169</td>
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<tr>
<td></td>
<td>O. trifurcata, Gaigeria</td>
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<td></td>
<td>pachyscelis, Chabertia</td>
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<tr>
<td></td>
<td>ovina, Nematodirus</td>
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<tr>
<td></td>
<td>spathiger, Oesophagostomum</td>
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<tr>
<td></td>
<td>columbianum</td>
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</table>

**FEBENDAZOLE**

<p>| 1.5 mg/kg  | Dictyocaulus viviparus,        | Roe deer  | 100       | 170       |
| (Multiple) | Haemonchus contortus,          |           |           |           |
|            | Nematodirus spp.               |           |           |           |
| - do -     | Capreocaulus capreoli,         | -do-      | 60.6      | 170       |
|            | Muellerius capillaris          |           |           |           |
| - do -     | Moniezia                       | -do-      | 75        | 170       |
| 50 mg/kg   | Toxocara canis                 | Puppies   | 64        | 171       |
| (Multiple) |                                 |           |           |           |
| - do -     | Ancylostoma caninum            | Puppies   | 88        | 172       |
| 5 mg/kg    | Ostertagia ostertagi           | Calves    | 71.3      | 173       |
| (Multiple) | O. lyrata                      | Calves    | 64.9      | 173       |
| - do -     | Haemonchus placei              | Calves    | 85.9      | 173       |
| - do -     | Nematodirus helvetianus        | Calves    | 96.7      | 173       |
| - do -     | Trichostrongylus colubriformis | Calves    | &lt;99.9     | 173       |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>50 mg/kg (Multiple)</td>
<td>Taenia saginata</td>
<td>Calves 100</td>
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<tr>
<td>200-500 mg/kg (Multiple)</td>
<td>Strongyloides, Parascaris equorum</td>
<td>Horses 98.5-100</td>
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<tr>
<td>3 mg/kg (Multiple)</td>
<td>Ascaris suum</td>
<td>Pigs 100</td>
<td>176</td>
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<tr>
<td>10 mg/kg</td>
<td>Ascaridia galli</td>
<td>Chicken 100</td>
<td>177</td>
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<tr>
<td>100 mg/kg (Multiple)</td>
<td>Syngamus trachea, Capillaria obsignata, Heterakis spp.</td>
<td>Pheasants &lt; 90</td>
<td>178</td>
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<tr>
<td>7.5 mg/kg</td>
<td>Cooperia punctata</td>
<td>Calves 75.4</td>
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<tr>
<td>- do -</td>
<td>Haemonchus</td>
<td>Calves 100</td>
<td>179</td>
<td></td>
<td></td>
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<tr>
<td>- do -</td>
<td>Oesophagostomum radiatum</td>
<td>Calves 100</td>
<td>179</td>
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<td></td>
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<tr>
<td>2.5 mg/kg (single)</td>
<td>Metastrongylus apri</td>
<td>Pigs 97.8</td>
<td>180</td>
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<td></td>
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<tr>
<td>7.5 mg/kg (Multiple)</td>
<td>Moniezia scolices</td>
<td>Calves 91.7</td>
<td>181</td>
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**LEVAMISOLE**

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<tbody>
<tr>
<td>50 mg/kg (Multiple)</td>
<td>A. manlyiensis</td>
<td>Rats 90.77</td>
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<tr>
<td>5 mg/kg (Multiple)</td>
<td>Trichostrongylus axei, Cooperia curticei, Nematodirus spattiger, N. filicollis</td>
<td>Sheep 97.9-99.9</td>
<td>183</td>
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<tr>
<td>3 mg/kg</td>
<td>Ascaris</td>
<td>Children 99.99</td>
<td>184</td>
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<tr>
<td>6 mg/kg</td>
<td>Necator americanus</td>
<td>Children 99.99</td>
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<tr>
<td>8 mg/kg (Multiple)</td>
<td>Ostertagia ostertagi</td>
<td>Calves 99.7</td>
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<tr>
<td>10 mg/kg</td>
<td>Parascaris equorum</td>
<td>Horses 100</td>
<td>186</td>
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<tr>
<td>- do -</td>
<td>Trichonema sp.</td>
<td>Horses 9</td>
<td>186</td>
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<tr>
<td>- do -</td>
<td>Strongylus dentatus</td>
<td>Horses 61</td>
<td>186</td>
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<tr>
<td>8 mg/kg (Multiple)</td>
<td><em>Ostertagia circumcincta</em>, <em>O. trifurcata</em>, <em>Teladorsagia davitiani</em>, <em>Trichostrongylus vitrinus</em>, <em>T. colubriiformis</em>, <em>Nematodirus battus</em></td>
<td>Lambs</td>
<td>100</td>
<td>187</td>
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</tr>
<tr>
<td>10 mg/kg (Multiple)</td>
<td><em>Haemonchus placei</em></td>
<td>Calves</td>
<td>100</td>
<td>188</td>
<td></td>
</tr>
<tr>
<td>- do -</td>
<td><em>Bunostomum phlebotamum</em></td>
<td>Calves</td>
<td>98.5</td>
<td>188</td>
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<tr>
<td>- do -</td>
<td><em>Oesophagostomum radiatum</em></td>
<td>Calves</td>
<td>99.6</td>
<td>188</td>
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<tr>
<td>- do -</td>
<td><em>Dictyocaulus viviparus</em></td>
<td>Calves</td>
<td>90.9</td>
<td>188</td>
<td></td>
</tr>
<tr>
<td>8 mg/kg (Multiple)</td>
<td><em>Ascaris suum</em></td>
<td>Pigs</td>
<td>100</td>
<td>189</td>
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<tr>
<td>- do -</td>
<td><em>Trichuris suis</em></td>
<td>Pigs</td>
<td>91</td>
<td>189</td>
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<tr>
<td>- do -</td>
<td><em>Metastrongylus spp.</em></td>
<td>Pigs</td>
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<tr>
<td>0.6-2.4 mg/kg (Multiple)</td>
<td><em>Auchereria bancrofti</em> (microfilariae)</td>
<td>Man</td>
<td>98.75</td>
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**TETRAMISOLE**

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<td><em>Digestive strongyles</em></td>
<td>Sheep</td>
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<td><em>Dictyocaulus</em></td>
<td>Sheep</td>
<td>97.1</td>
<td>191</td>
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<td><em>Protostrongylus</em></td>
<td>Sheep</td>
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<td>7.5 mg/kg (Multiple)</td>
<td><em>Ascaris suum</em>, <em>Oesophagostomum dentatum</em></td>
<td>Piglets</td>
<td>90-100</td>
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<td>15 mg/kg</td>
<td><em>Haemonchus, chabertia</em></td>
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<td>10-100 mg/kg</td>
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<td>Mice or rats</td>
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<td><em>Nippostrongylus brasiliensis</em></td>
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<tr>
<td>- do -</td>
<td><em>Trichuris muris</em>, <em>Hymenolepis nana</em></td>
<td>- do -</td>
<td>Ineffective</td>
<td>193</td>
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<tr>
<td>20 mg/Kg</td>
<td>Ancylostoma caninum, Toxocara canis, Toxocaris leonina</td>
<td>Dogs</td>
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<tr>
<td>- do -</td>
<td>Trichuris vulpis, Dipylidium caninum, Echinococcus granulosus</td>
<td>Dogs</td>
<td>Infec-tive</td>
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**FEBANTEL**

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<thead>
<tr>
<th>6 mg/kg</th>
<th>Parascaris equorum</th>
<th>Horses</th>
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<tr>
<td>15 mg/kg</td>
<td>Trichinella spiralis</td>
<td>Rats</td>
<td>94.4</td>
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<tr>
<td>10 mg/kg</td>
<td>Haemorchus placei, Trichosontrigus axei, Oesophagostomatium radiatum, Cooperia pectinata, C. oncophora, Nematodirus spathiger</td>
<td>Calves</td>
<td>97-100</td>
<td>197</td>
</tr>
<tr>
<td>(Multiple)</td>
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<tr>
<td>- do -</td>
<td>Ostertagia ostertagi</td>
<td>Calves</td>
<td>93-98</td>
<td>197</td>
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<tr>
<td>- do -</td>
<td>Moniezia benedini</td>
<td>Calves</td>
<td>Nil</td>
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<tr>
<td>5 mg/kg</td>
<td>Hyostrongylus rubidus</td>
<td>Pigs</td>
<td>99</td>
<td>198</td>
</tr>
<tr>
<td>(Multiple)</td>
<td></td>
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<td>Camel</td>
<td>100</td>
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<td>- do -</td>
<td>D. arnfieldi</td>
<td>Zebras</td>
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<td>199</td>
</tr>
<tr>
<td>- do -</td>
<td>Toxocara vitulorum</td>
<td>Buffaloes</td>
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<tr>
<td>5 mg/kg</td>
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<td>Sheep</td>
<td>99</td>
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<tr>
<td>7.5 mg/kg</td>
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<td>Calves</td>
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<tr>
<td>(Multiple)</td>
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**PRAZIQUANTEL**

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<td><em>C. fasciolasis</em></td>
<td>Mice</td>
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<td>- do -</td>
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<td><em>Taenia hydatigena</em></td>
<td>Dogs</td>
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anthelmintic agent. In the light of the presently mapped endemic areas of this country, a compound capable of evoking anticestodal and antinematodal actions would be an adequate coverage for achieving the desired objective.

A rational approach for the development of a wide-spectrum anthelmintic is, therefore, essential. In principle, a broad-spectrum anthelmintic agent should possess the ability to enter cestode and nematode parasites irrespective of their tissue locations and should be capable of binding effectively with parasite tubulins. Yet another approach to achieve the same objective is concerned with the simulation of pharmacophores in the molecular architecture of compounds for providing capability to interfere with more than one target sites of the parasites. Besides microtubule polymerisation, energy and lipid metabolism of the parasites have been identified by WHO as effective alternate target sites for the development of anthelmintic agents. It is, therefore, obvious that a knowledge of pharmacophores is of prime importance. The earlier work of this laboratory concerning the identification of proper pharmacophores relates to changes carried out in five different areas (Fig.3a) of the Mebendazole molecule and the results obtained have suggested that substituents at position 5(6) of methyl benzimidazole-2-carbamates greatly influence antinematodal and anticestodal properties. Minor structural variations in the substituents at position 5(6) has been found to influence the tissue nematocidal activity. In continuation of this work it was considered of interest to synthesize compounds structurally related to prototypes IX-XXII and to evaluate them as broad-spectrum anthelmintic agents. The active compounds could then be evaluated for their ability to bind parasite tubulin and as inhibitors of parasite energy metabolism. The present study has also been extended to obtain compounds structurally related to prototypes XVI & XVII. The design of these two prototype molecules is based on the concept that dihydropyrimidine derivatives may interfere selectively with the redox reactions of the parasite energy metabolism and if found active may serve as lead compounds for drug development work.
(Fig. 3a)
CHAPTER 5

5.1 : Syntheses of 4-Benzoyl-N-[5(6)-(2-methoxycarbonylamino)-benzimidazolyl]pyrrolidin-2-one

5.2 : Syntheses of β-[(2-Methoxycarbonylamino)-5(6)-benzimidazolyl]-acrylic acid, Methyl 5(6)-[5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-4-yl]benzimidazole-2-carbamate and 2-Methoxycarbonylaminobenzimidazole-5(6)-acetoxime

5.3 : Methyl-5(6)-[2,5-dimethyl-3-methoxycarbonyl-N-substituted pyrrolo]-benzimidazole-2-carbamates and Methyl-5(6)-N-[2,5-dimethyl-3-methoxycarbonyl-4-substitutedphenyl]-benzimidazole-2-carbamates

5.4 : Comparative $^{13}$C-NMR study of tetrastituted furans and tetra/pentastituted pyrroles

5.5 : 2,2'-Dicarbomethoxyamino-5,5'-dibenzimidazol-yl-methanol

5.6 : 5-Ethoxycarbonyl-(2-(1-methylpiperazino)-6-phenyl-4(1H)-pyrimidine and 5-Aryl-6-ethoxycarbonyl-7-methyl-3-oxo-2,3-dihydro-5H-thiazolo [3,2-a] pyrimidine

5.7 : Methyl 5(6)-N-[(2-methylmercapto-6-methyl-4-phenyl pyrimidin-5-yl)methyl]aminobenzimidazole-2-carbamate

5.8 : Methyl-5(6)-[4-(2,6-dimethyl-3,5-dimethoxycarbonyl-1,4-dihydropyridinyl)]-N-substituted benzimidazole-2-carbamate and N,N-Dimethoxycarbonyl-N-(substitutedbenzyl)quainidine

5.9 : Methyl-4(5)-methyl-5(4)-[3,4-methyleneoxypyphenyl]-4,5-dihydropyridazole-2-carbamate

5.9a : 1,6-Bis carbomethoxy-2-methoxycarbonylamino-7-methyl-5-(p-methoxyphenyl)-4,5,6,7-tetrahydro-1,3-diazepine
CHAPTER - 5

5.1 The synthesis of prototype IX required appropriately substituted pyrrolidine-2-one derivative as the starting material and for which a model study was considered desirable because substituted butyrolactones after ring opening with primary aromatic amines, in principle, can recyclize to give compounds structurally related to either 99a or 100.

Benzoyl and (p-toluoyl)-γ-butyrolactones (103, 104), required for the model studies, have been prepared by reacting appropriate aroyl propionic acid (101, 102) with formaldehyde and hydrochloric acid. Reactions of 103 and 104 with p-anisidine yielded compounds which were devoid of IR signals for lactone carbonyls. This suggested that the lactone ring had participated in the reaction and the mass spectra of the compounds suggested that the opening of lactone ring must have been followed by a ring closure reaction. In order to eliminate one of the two possible structures (99a and 100), studies on the $^{13}$C-nmr spectra of two compounds (105, 106) were undertaken. The difference in the chemical shifts of methylene carbon attached to the hetero atom in 104 and 105 (Scheme 19) was of a diagnostic value for the structural assignment of the reaction product. The appearance of the methylene carbon attached to the hetero atom in 104 at 69.07 $\delta$ ppm and in 105 at 50.58 $\delta$ ppm indicated that the methylene carbon in the reaction products was not attached to oxygen. This lent support for structure 105 and further support for the assigned structure was obtained from the $^{15}$N signal. The appearance
SCHEME 19

a, HCHO/HCl, b, p-Anisidine, c, H₂/Pd/C, d, 2-Nitro-p-phenylenediamine, e, H₂/Raney-Ni, f, HN=CH₂/CD₂Me. ¹³C-NMR data.
of the $^{15}\text{N}$ signal at $33.689 \delta$ ppm indicated the amide character of the nitrogen. Catalytic hydrogenation of $^{105}$ gave $^{106}$ and the methylene carbon of this compound appeared at $51.27 \delta$ ppm providing further evidence for the attachment of the methylene carbon with the nitrogen atom.

These model studies prompted the synthesis of the ninth prototype molecule namely 4-Benzoyl-N-[5(6)-(2-methoxycarbonylamino) benzimidazolyl] pyrrolidin-2-one ($^{109}$). Reaction of $\beta$-benzoyl-$\gamma$-butyrolactone ($^{103}$) with 2-nitro p-phenylene diamine in presence of triethylamine yielded 4-benzoyl-N-(4-amino-3-nitrophenyl)-pyrrolidin-2-one ($^{108}$; Scheme 19). Catalytic hydrogenation of $^{108}$ in presence of Pd/C followed by the ring closure of the resulting diamine with S-methylisothiouroniumsulphate and methylchloroformate furnished the desired prototype molecule ($^{109}$; Scheme 19).

5.2 Unlike the synthesis of IX, the preparation of compounds relating to prototypes X-XII required the O-nitroaniline derivatives ($^{114}$, $^1D_1$ & $^{123}$) as the starting materials, which after catalytic hydrogenation and ring closure with N,N-dimethoxycarbonyl-S-methylisothiourea could be expected to furnish the desired compound. Reaction of 4-acetamido-3-nitro benzoaldehyde ($^{112}$) with malonic acid
in the presence of catalytic amount of pyridine gave 4-acetamido-3-nitro cinnamic acid (113; Scheme 20). Alkaline hydrolysis of this compound yielded the desired starting material (114; Scheme 20). Preferential hydrogenation of nitro group in 114 was possible in presence of Raney nickel but it failed for the starting material (D).

\[
\begin{align*}
\text{AcHN} & \quad \text{O2N} \\
\text{H} & \quad \text{H2} \\
\text{AcHN} & \quad \text{O2N}
\end{align*}
\]

\[
\begin{align*}
112 & \quad \rightarrow \quad 113 \\
114 & \quad \leftarrow \quad 115
\end{align*}
\]

\[
\begin{align*}
\text{O=CHN} & \quad \text{N=CH} \\
\text{Me} & \quad \text{N-} \\
\text{OMe} & \quad \text{H2}
\end{align*}
\]

\[
\begin{align*}
a, \text{malonic acid, pyridine}/\text{MeOH}; & \quad b, 10\% \text{aq. NaOH}/\text{MeOH}; \\
c, \text{H2, Raney-Ni}/\text{MeOH}; & \quad d, \text{HN=C-NH}_{2}/\text{ClCO}_{2}\text{CH}_{3}
\end{align*}
\]

(Scheme 20)

The reaction of 4-acetamido-3-nitro benzaldehyde (116) with ethylacetoacetate and thiourea under acidic condition gave 5-ethoxycarbonyl-6-methyl-2-oxo-4-(4-acetamido-3-nitrophenyl) pyrimidine (117):

\[
\begin{align*}
\text{O2N} & \quad \text{H} & \quad \text{O2N} \\
\text{AcHN} & \quad \text{AcHN} & \quad \text{EtO2C} \\
\text{H} & \quad \text{H} & \quad \text{Me}
\end{align*}
\]

\[
\begin{align*}
a, \text{CH}_3\text{COCH}_2\text{CO}_2\text{Me}, \text{Urea}; & \quad b, 10\% \text{aq. NaOH}; \\
c, \text{H2, Raney-Ni}/\text{MeOH}; & \quad d, \text{MeS-C=NOCO}_2\text{Me}
\end{align*}
\]

(Scheme 21)
Scheme 21) which on alkaline hydrolysis yielded 118. Hydrogenation of this compound in presence of Raney-Ni furnished the desired diamine. The diamines prepared from 114 and 118 were cyclized by reacting them with N,N-dimethoxycarbonyl-S-methylisothiourea to obtain the desired prototype compounds 115 and 119 respectively. Since the preparation of diamine D was not possible, 5(6)-acetyl benzimidazole-2-carbamate (124), prepared by the method reported earlier, was reacted with hydroxylamine under controlled conditions to furnish 125 (Scheme 22).

\[
\begin{align*}
D_2 & \quad \text{NOH} \quad \text{Me} \\
& \quad \text{H}_2 \text{N} \\
& \quad \text{H}_2 \text{N}

\text{120} & \quad \text{OMe} \quad \text{Me} \\
& \quad \text{H}_2 \text{N} \\
& \quad \text{AcCHN}

\text{122} & \quad \text{O} \quad \text{Me} \\
& \quad \text{AcCHN} \\
& \quad \text{H}_2 \text{N}

\text{123} & \quad \text{O} \quad \text{Me} \\
& \quad \text{H}_2 \text{N} \\
& \quad \text{MeO}_2\text{C}^\text{N} \quad \text{H}

\text{124} & \quad \text{H} \quad \text{Me} \\
& \quad \text{MeO}_2\text{C}^\text{N} \quad \text{H}

\text{125} & \quad \text{H} \quad \text{Me} \\
& \quad \text{MeO}_2\text{C}^\text{N} \quad \text{H}
\end{align*}
\]

a, AC\textsubscript{2}O; B, Fuming \text{HNO\textsubscript{3}}; c, 10\% aq. NaOH/MeOH; d, H\textsubscript{2}, Raney-Ni/MeOH; e, \text{HN}^\text{C}^\text{C}^\text{N}^\text{NH}^2/\text{ClCO}_2\text{CH}_3; f, \text{NH}_2\text{OH}/\text{MeOH}

\text{(Scheme 22)}
5.3 In order to study the effect of NH and NR in place of the oxygen atom in the furan ring of a promising anthelmintic compound 83/148 (CDRI Code number), the synthesis of XIII was undertaken and as an extension of this study compounds representing prototype XIV were also synthesised.

The synthesis of XIII (X=NH) owes its origin to the observation made during the upscaling studies of the compound 83/148. It was observed that during the preparation of 2,5-dimethyl-3-methoxycarbonyl-4-(4-amino-3-nitrophenyl) furan, (the required intermediate for the preparation of 83/148) was invariably associated with a small amount of a red compound formed in the reaction mixture. This was identified as 2,5-dimethyl-3-methoxycarbonyl-4-(4-amino-3-nitrophenyl) pyrrole. The formation of this pyrrole derivative along with the corresponding furan in the reaction of 126 in presence of methylacetoacetate and piperidine suggested that a careful study of this reaction may furnish a reaction condition in which the pyrrole could be obtained as the predominant product. This prompted to study the Nef reaction of 126 in presence of primary, secondary and tertiary amines and the results were monitored by HPLC. The reaction of 126 with methylacetoacetate in presence of primary amines gave N-substituted pyrrole derivatives (132-137; Scheme 23) and the corresponding furan derivatives could not be detected in the reaction mixture. This method has a preparative value and gives better yields of the pyrrole derivatives as compared to the method reported in literature which invariably gave poor yields of 2,5-dimethyl-3-methoxycarbonyl-4-substituted phenyl pyrroles in our hands. The reaction of 126 and methylacetoacetate in presence of secondary amines gave different percentage ratios of 128 and 130.
128 : R = NH₂
129 : R = Cl

128-129

130 : R = NH₂
131 : R = Cl

126 : R = NH₂
127 : R = Cl

148 : R = NH₂
148a : R = OMe

132 : R = n-Bu
133 : R = CH₂Ph
134 : R = 4-anisyl
135 : R = 3,4,5-trimethoxyphenyl
136 : R = 4-amino-3-nitrophenyl
137 : R = (CH₂)₃-N(C₂H₅)₂

a. Piperidine;  b. Primary amine;  c. Triethyl amine;
d. Hydrazine hydrate

(Scheme 23)
MECHANISM OF NEF REACTION IN PRESENCE OF AMINES

a) TERTIARY AMINE

\[
\begin{align*}
R_1 & \quad H \\
\text{H}_3\text{C} & \quad \text{NO}_2 \\
+ & \quad \text{H}_2\text{C} & \quad \text{CO}_2\text{R}_2 \\
\text{H}_3\text{C} & \quad \text{CH}_3 \\
(\text{C}_2\text{H}_5)_3\text{N} & \quad \text{\textit{O}} \\
\text{H}_3\text{C} & \quad \text{C} \text{O}_2\text{R}_2 \\
\text{H}_3\text{C} & \quad \text{CH}_3 \\
\text{N} & \quad \text{\textit{O}} \\
\text{H}_3\text{C} & \quad \text{CH}_3 \\
\text{H}_3\text{C} & \quad \text{O} \quad \text{\textit{N}} \\
\text{138} & \quad \text{139} \\
\text{H}_2\text{O} & \quad \text{-HNO} \\
\text{CONT.} & \quad \text{CONT.}
\end{align*}
\]
(b) SECONDARY AMINE

(i)

\[ \text{amine} + \text{H}_2\text{CO}_2\text{R}_2 \rightarrow \text{amine} + \text{H}_2\text{CO}_2\text{R}_2 \]

\[ \text{amine} + \text{H}_2\text{CO}_2\text{R}_2 \rightarrow \text{amine} + \text{H}_2\text{CO}_2\text{R}_2 \]

\[ \text{amine} + \text{H}_2\text{CO}_2\text{R}_2 \rightarrow \text{amine} + \text{H}_2\text{CO}_2\text{R}_2 \]

\[ \text{amine} + \text{H}_2\text{CO}_2\text{R}_2 \rightarrow \text{amine} + \text{H}_2\text{CO}_2\text{R}_2 \]

\[ \text{amine} + \text{H}_2\text{CO}_2\text{R}_2 \rightarrow \text{amine} + \text{H}_2\text{CO}_2\text{R}_2 \]

\[ \text{amine} + \text{H}_2\text{CO}_2\text{R}_2 \rightarrow \text{amine} + \text{H}_2\text{CO}_2\text{R}_2 \]

\[ \text{amine} + \text{H}_2\text{CO}_2\text{R}_2 \rightarrow \text{amine} + \text{H}_2\text{CO}_2\text{R}_2 \]

Contd.
(c) PRIMARY AMINE

(Scheme 24)
For example in presence of piperidine the percentage ratio of 128 and 130 was 96:4, in morpholine it was 80:20, in N-methyl-piperazine it was 89:11 and in presence of N-phenylpiperazine it was 87:13. Replacement of piperidine with triethylamine in the reaction of 126 and methylacetoacetate gave only 128 and the presence of 130 in the reaction mixture was not detected.

Recent studies on the mechanism of Nef reaction indicate the formation of an intermediate 138 (Scheme 24). It is likely that reaction of 126 and methylacetoacetate in presence of triethylamine also yielded an intermediate structurally similar to 138, which after elimination of H₂O and HNO as suggested by Boberg, yielded the tetrasubstituted furan. In the presence of piperidine the reaction of 126 and methylacetoacetate possibly proceeds in three directions. The formation of intermediates 138 and enamine possibly contribute towards the formation of tetrasubstituted furan. The third pathway might involve the addition of water in 140 which leads to the ring opening and recyclization of the open product to give tetrasubstituted pyrrole (Scheme 24). This pathway possibly becomes more facile in presence of primary amines and therefore leads to exclusively N-substituted pyrrole derivatives. Despite a successful synthesis of N-substituted pyrrole derivatives (132-137), the synthesis of 130 by Nef reaction of 126 in presence of methylacetoacetate and ammonia was not at all promising due to extremely poor yield (~10%). An alternate preparation was, therefore, sought and this prompted the reaction of 126 with 144 (Scheme 25) in different solvents. The yield of the compound 130 has been improved upto 90% by using pyridine as a catalyst and methanol as a solvent.

![Diagram](https://example.com/diagram.png)

\(144 : R = H\)

\(145 : R = CH_3\)

\(130 : R = H\)

\(146 : R = CH_3\)

(Scheme 25)
Based on this observation, attempts were made to prepare 2,5-dimethyl-3-acetyl-4-(4-amino-3-nitrophenyl) pyrrole by reacting 126 with enamine 147. However, it failed to give the desired product. It was, therefore, considered of interest to ascertain the reason which led to the failure of this reaction. One of the logical explanations for the failure of 147 to react with 126, would be the lack of adequate nucleophilicity of the carbon α to the acetyl group. In principle, experimental evidence for the same may be obtained from the chemical shift of carbon atoms since substantial difference in nucleophilicity of the carbon atom α to methoxycarbonyl and acetyl groups in enamines 144 and 147 is bound to make a significant difference in their chemical shifts. This prompted a comparative study of the $^{13}$C-NMR spectra of 144 and 147. As would be expected, the carbon α to the acetyl group in 147 was deshielded by almost 14 ppm. This suggested that the enamine carbon in 147 did not possess adequate nucleophilicity to react with 126. The preliminary data of the $^{13}$C-chemical shift of carbon in enamines 144 and 147 tempted to study the chemical shifts of carbon atoms in tetra and pentasubstituted pyrroles (154-158 and 158a-158b). These pyrrole derivatives may be considered as the E-configuration (Fig.5) of enamanine in a rigid geometry. Since pyrroles exhibit heteroaromatic character while furans failed to do so, the comparative $^{13}$C-NMR study of
tetra or pentasubstituted pyrroles (154-158, 158a, 158b) and tetra substituted furans (a-q) was considered interesting. The tetra-substituted pyrroles (154-158) were prepared by reacting enamine 144 with appropriate nitrostyrene derivatives (149-153; Scheme 26). The details of this study are presented in sec. 5.4.

![Scheme 26](154-158)

The next phase of the studies on Nef reaction was concerned with the reaction of 126 with methylacetoacetate in presence of hydrazine hydrate. Mechanistic considerations of this reaction suggest the formation of 148a but the excess of hydrazine hydrate possibly gave 148 (Scheme 23; page 106). Preparation of compounds belonging to prototype XIV required N-substituted pyrrole derivatives (171-175) as the starting material. These were obtained by the reaction of 166-170 with methylacetoacetate in presence of 2-nitro-£-phenylene diamine (Scheme 27). Hydrogenation of 130, 132-139 and 171-175 in presence of Raney-Ni followed by their cyclisation with N,N-dimethoxy carbonyl-S-methylisothiourea yielded the compounds structurally related to prototypes XIII and XIV respectively (Scheme 26 & Scheme 27).

5.4 Comparative $^{13}$C-NMR study of 144 and pyrrole derivatives 154-158 revealed two interesting features. Despite the fact that pyrrole has a heteroaromatic character, the C-2 in compounds 154-158, which corresponds to carbon d of 144 (Fig.4; page 112), appears as a shielded carbon while C-3 in 154-158 which corresponds to
130, 132-137 $\xrightarrow{a,b}$

![Chemical structure](image)

$^{159}$ : $R = H$
$^{160}$ : $R = CH_3$
$^{161}$ : $R = n-Bu$
$^{162}$ : $R = CH_2Ph$
$^{163}$ : $R = 4-OCH_3$-Phenyl
$^{164}$ : $R = 3,4,5$-trimethoxyphenyl
$^{165}$ : $R = (CH_2)_3N$-$NHCO_2$Me
$^{166}$ : $R = (CH_2)_3N(C_2H_5)_2$

(Scheme 26)

$^{166a}$ : $R = H$
$^{167}$ : $R = 3,4$-dimethoxy
$^{168}$ : $R = 4$-methyl
$^{169}$ : $R = 4$-acetamido
$^{170}$ : $R = 4$-benzoxo-3-methoxy

a, 2-Nitro-$p$-phenylene diamine
b, $H_2$, Raney-Ni/MeOH
c, MeO$_2$CN=C$-$NHCO$_2$Me

$^{171-175}$ Substituent $R$ corresponds to $^{166a-170}$

(Scheme 27)

$^{176-180}$ Substituent $R$ corresponds to $^{166a-170}$
carbon C in 144 (Fig.5; page  ) appears as deshielded carbon. This may be explained by assuming that 144 in solution possibly exists as 144α. This is why the methyl carbon in 144 appears downfield than the methyl carbon attached to position 2 in compounds 154-158.

The comparative study of the 13C-NMR spectra of tetrasubstituted furans and tetra or pentasubstituted pyrroles (Tables A-R) was concerned with the chemical shift of C-2, C-3, C-4 and C-5 in these class of compounds. As would be expected C-2 and C-5 in furans appeared downfield than the corresponding pyrrole derivatives. However, C-3 and C-4 may be expected to show different chemical shift in these two class of compounds, because furan lacks heteroaromaticity while pyrrole possesses the same. Surprisingly the chemical shift of C-3 and C-4 in furans are marginally different from those of pyrroles. This would also explain that effect of substituents on the phenyl ring on C-4 in these class of compounds remains unaltered.

The effect of substituents on C-3, the chemical shifts of C-2 in furans (a-q) indicated that a methoxycarbonyl or an acetyl residue predominantly deshielded C-2 while an amide function led to a shielding of almost 9-10 ppm. In continuation of this study the observed chemical shifts of C-2, C-3, C-4 & C-5 in furans and pyrroles were compared with the theoretical values computed by a computer for representative compounds (Table C).

5.5 The synthesis of next prototype molecule (XV) namely 2,2'-Dicarbomethoxyamino-5,5'-dibenzimidazoylmethanol is based on the presumption that the carbinol of 82/437 (CDRI Code number) in biomembrane may slowly get oxidized to the parent compound which has exhibited significant broad-spectrum anthelmintic activity. In a situation such as this the carbinol may exhibit longer duration of action.
Table A: Chemical shifts of various carbons of Tetrasubstituted Furans

![Chemical structure of furan with substituents](image)

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>R</th>
<th>R&lt;sub&gt;1&lt;/sub&gt;</th>
<th>C-2</th>
<th>C-3</th>
<th>C-4</th>
<th>C-5</th>
<th>2-CH&lt;sub&gt;3&lt;/sub&gt;</th>
<th>5-CH&lt;sub&gt;3&lt;/sub&gt;</th>
<th>Other Carbons</th>
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<td></td>
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<td></td>
<td>132.89, 129.61, 127.25, 126.84, 126.40, 125.97, (Aromatic-C), 164.11.</td>
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<tr>
<td>a</td>
<td>H</td>
<td>CO&lt;sub&gt;3&lt;/sub&gt;CH&lt;sub&gt;3&lt;/sub&gt;</td>
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<td>113.01</td>
<td>121.13</td>
<td>146.82</td>
<td>13.54</td>
<td>11.21</td>
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</tr>
<tr>
<td>b</td>
<td>3,4-methylene-dioxy</td>
<td>CO&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>156.80</td>
<td>112.85</td>
<td>120.61</td>
<td>146.65</td>
<td>13.31</td>
<td>10.93</td>
<td>146.12, 145.64, 126.32, 122.71, 110.11, 107.05, (Aromatic-C), 163.80,</td>
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(Aromatic-C), 163.38, (CO₂CH₃), 50.29 (CO₂CH₃)<sup>2</sup>
(Aromatic-C), 164.45, (CO₂CH₃), 50.87 (CO₂CH₃)<sup>2</sup>
(Aromatic-C), 194.98, (COCH₃), 30.11 (COCH₃)
(Aromatic-C), 194.83, (COCH₃), 30.02 (COCH₃)

100.76 (CH₂O)
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</table>
Table B: Chemical shifts of various carbons of Tetra and Pentasubstituted Pyrroles

![Chemical structure of a pyrrole with substituents](image)

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<tr>
<th>Compound</th>
<th>R</th>
<th>R&lt;sub&gt;1&lt;/sub&gt;</th>
<th>C-2</th>
<th>C-3</th>
<th>C-4</th>
<th>C-5</th>
<th>2-CH&lt;sub&gt;3&lt;/sub&gt;</th>
<th>5-CH&lt;sub&gt;3&lt;/sub&gt;</th>
<th>Other Carbons</th>
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</thead>
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<td>154</td>
<td>H</td>
<td>NH</td>
<td>134.09</td>
<td>110.01</td>
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<td>123.78</td>
<td>13.44</td>
<td>10.94</td>
<td>136.19, 130.21, 127.27, 127.07, 125.70, 114.66, (Aromatic-C), 166.46, (CO&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;3&lt;/sub&gt;), 50.19 (CO&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;3&lt;/sub&gt;)</td>
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<tr>
<td>156</td>
<td>3,4-methylene-dioxy</td>
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<td>133.93</td>
<td>110.83</td>
<td>121.84</td>
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<td>146.64, 145.56, 129.96, 123.41, 109.77, 107.23, (Aromatic-C), 166.39, (CO&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;3&lt;/sub&gt;), 50.17 (CO&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;3&lt;/sub&gt;), 3100.50 (OCH&lt;sub&gt;2&lt;/sub&gt;O)</td>
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<td>123.58</td>
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<td>4-NHCOCH&lt;sub&gt;3&lt;/sub&gt;</td>
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<td>134.09</td>
<td>110.02</td>
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Table C: Chemical shifts of various carbons of tetrasubstituted furans and tetra/pentasubstituted pyroles computed on the basis of literature data by a computer (Bold letters are observed values)

![Structure of compound](https://via.placeholder.com/150)

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<th>Compd. No.</th>
<th>R</th>
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<th>C-2 (± ppm)</th>
<th>C-3 (± ppm)</th>
<th>C-4 (± ppm)</th>
<th>C-5 (± ppm)</th>
<th>2-CH₃</th>
<th>5-CH₃</th>
<th>CO (± ppm)</th>
<th>Other Carbons</th>
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<tbody>
<tr>
<td>A</td>
<td>OCH₃</td>
<td>O</td>
<td>158.5 (±0.0)</td>
<td>115.4 (±0.0)</td>
<td>129.7 (±9.8)</td>
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<td>14.3 (±0.0)</td>
<td>11.7 (±0.8)</td>
<td>165.0 (±0.0)</td>
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<td>Ar-C: 130.5 (±2.2)</td>
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<td>113.01</td>
<td>121.13</td>
<td>146.82</td>
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<tr>
<td>B</td>
<td>N(CH₃)₂</td>
<td>O</td>
<td>156.4 (±4.4)</td>
<td>98.7 (±12.1)</td>
<td>129.7 (±9.8)</td>
<td>148.5 (±6.5)</td>
<td>13.3 (±2.5)</td>
<td>11.7 (±0.8)</td>
<td>162.1 (±0.3)</td>
<td>N(CH₃)₂: 36.9 (±1.1)</td>
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<td>148.48</td>
<td>117.31</td>
<td>119.93</td>
<td>145.55</td>
<td>11.84</td>
<td>11.12</td>
<td>164.71</td>
<td>Ar-C: 130.5 (±2.2)</td>
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<td>(±0.7)</td>
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122
It was also considered desirable to evaluate the carbinol as a chemoprophylactic. The synthesis of 183, reported earlier in this laboratory was slightly modified to obtain a better yield and the main sequence of reactions are described in Scheme 28. The reduction of the carbonyl group in 183 was difficult but large excess of sodium borohydride helped in obtaining 184. Hydrogenation of this compound followed by ring closure with N,N-dimethoxycarbonyl-S-methylisothiourea furnished 185 (Scheme 28).

\[
\begin{align*}
&\text{181} \\
&\text{a. } \text{Cl}_2C\equiv NO_2 \\
&\text{182} \\
&\text{b. } \text{MeOH} \\
&\text{c. } \text{H}_2, \text{MeOH} \\
&\text{d. } \text{MeO}_2C\equiv \text{CO}_2\text{Me} \\
&\text{e. } \text{MeO}_2C\equiv \text{C}-\text{NH}_2 \longrightarrow \text{MeO}_2C\equiv \text{CO}_2\text{Me} \\
&\text{(Scheme 28)}
\end{align*}
\]
As an extension of our exploratory research activities for identifying new molecular structures associated with broad-spectrum anthelmintic activity, the syntheses of prototype XVI-XVII were considered of interest. The starting compounds 192-197 were obtained by Biginelli reaction.

Acid catalysed reaction of aromatic aldehyde with ethylacetoacetate in presence of urea to yield 5-ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2-one (202), commonly known as Biginelli reaction, was reinvestigated by Hinkle and Hey and it was observed that the replacement of urea with thiourea led to the formation of the corresponding 3,4-dihydropyrimidin-2-thione derivatives (192-197; Scheme 29).

Before undertaking the synthesis of dihydropyrimidine prototypes XVI and XVII, model studies on the alkylation of 5-ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2-thione (192), were considered as essential prerequisites. Reaction of 192 with methyl iodide under various experimental conditions was studied. This reaction in presence of sodium hydroxide in methanol yielded 198 (Scheme 29). Earlier workers have prepared this compound by reacting 5-ethoxycarbonyl-2-methylmercapto-4-methylpyrimidine with phenyl magnesium halide and the spectroscopic data of the reaction product reported by them agreed well with that of 198. Reaction of 192 with methyl iodide in presence of soidum hydroxide in DMSO gave 190 (Scheme 29). Demercaptation of 199 with strong acid gave 201 (Scheme 27). The U.V. absorption maxima at 290 nm supported the assigned structure. Finally the reaction of 198 with N-methylpiperazine yielded the prototype molecule 200 (Scheme 29).
$\text{R} \quad \text{CO}_2\text{Me}$

186: $\text{R} = \text{H}$
187: $\text{R} = 3,4\text{-dimethoxy}$
188: $\text{R} = 4\text{-methoxy}$
189: $\text{R} = 3\text{-methyl}$
190: $\text{R} = 4\text{-acetamido}$
191: $\text{R} = 4\text{-nitro}$

Substituent $\text{R}$ corresponds to 186-191

a, $\text{CH}_2\text{I}, \text{NaOH/MeOH}$;  b, $\text{CH}_3\text{I}, \text{NaOH/DMSO}$;  c, $\text{N-methylpiperazine}$;  d, $\text{H}_2\text{SO}_4/\text{MeOH}$

(Scheme 29)
In the light of these observations alkylation of (192-195) with monochloroacetic acid in presence of potassium hydroxide in methanol could be expected to yield the prototype (XVII) molecules 202-205 but the reaction of 192, 194, 195 with monochloroacetic acid in presence of potassium hydroxide yielded 205-208 (Scheme 30) while the reaction of 192-195 with monochloroacetic acid in presence

![Chemical Structure](image)

202 : R = H  
203 : R = 3,4-dimethoxy  
204 : R = 4-OCH₃  
205 : R = 3-CH₃  

a, ClCH₂CO₂H, BF₃·Et₂O/MeOH;  b, ClCH₂CO₂H, NaOH/MeOH

(Scheme 30)

BF₃ etherate yielded 202-205 (Scheme 30). The cyclocondensation of 192-196 with monochloroacetic acid is expected to yield two isomeric bicyclics, 5-Aryl-6-ethoxycarbonyl-7-methyl-3-oxo-2,3-dihydro-5H-thiazolo [3,2-a] pyrimidines (202-205) and 7-Aryl-6-ethoxycarbonyl 5-methyl-3-oxo-2,3-dihydro-7H-thiazolo [3,2-a] pyrimidines. Of these the former could be isolated from the reaction mixture. The structure of 202-205 was supported by their PMR data (Table 24, page 174) which revealed a downfield shift (~0.70 ppm) of the methine proton at position 6. This can only be explained if 3-N is involved in ring closure to form 202-205.

As a next step towards the synthesis of yet another 1,4-dihydropyrimidine derivative, benzaldehyde was reacted with ethyl
trifluoromethylacetoacetate in presence of thiourea. It was interesting to note that instead of 1,4-dihydropyrimidine derivative, the intermediate \textbf{209}, \textbf{210} (Scheme 31) was obtained as a mixture of diastereomers. Isolation of these compounds has a significance because no intermediate appears to have been isolated from the Biginelli reaction\textsuperscript{223}. Ring closure of \textbf{209} with polyphosphoric acid gave \textbf{211} (Scheme 31).

\[ \text{R = H, 4-NHCOCH}_3 \]

\[ \text{R} = \text{H, 4-NHCOCH}_3 \]

\[ \text{R} = \text{H, 4-NHCOCH}_3 \]

\[ \text{R} = \text{4-NHCOCH}_3 \]

\( \text{(Scheme 31)} \)

5.7 In order to evaluate the contribution of pyrimidine moiety appended with benzimidazole-2-carbamate nucleus, the synthesis of prototype XVIII namely methyl 5(6)-N-[(2-methylmercapto-6-methyl-4-phenyl pyrimidin-5-yl)methyl] amino benzimidazole-2-carbamate was undertaken. The synthetic strategy of prototype XVIII involves oxidation of \textbf{198} with manganic acetate to obtain \textbf{212} (Scheme 32) which on reduction with sodium borohydride yielded a mixture of \textbf{213} and \textbf{214} (Scheme 32) which were separated through column chromatography. However, LAH reduction of \textbf{212} did not lead to the
Scheme 32
reduction of pyrimidine ring but gave a mixture of 215 and 216 (Scheme 32) which were also separated through column chromatography. The spectroscopic data of these compounds supported the assigned structures and as an additional evidence 216 was oxidized with pyridinium chlorochromate to yield 217 (Scheme 32). Reaction of 216 with PBr₃ gave 218 which in turn was reacted with 2-nitro-p-phenylenediamine to get 219. Finally hydrogenation of 219 in presence of Raney-Ni as a Catalyst and cyclisation of the resulting diamine with N,N-dimethoxycarbonyl-S-methylisothiourea furnished the prototype molecule 220 (Scheme 32).

5.8 Synthesis of molecules belonging to prototype XIX required 87, 88 and 90 as the starting materials and their synthesis have already been reported in section 2.5. Hydrogenation of 87 or 88 gave the desired diamines which were cyclized with N,N-dimethoxycarbonyl-S-methylisothiourea to obtain the desired benzimidazole carbamates (Scheme 33). The compounds representing prototype XX (227-229) were prepared by reacting appropriate benzylamines with N,N-dimethoxycarbonyl-S-methylisothiourea (Scheme 33).

5.9 The synthetic strategy employed for the prototype XXI involved the reaction of 2-nitro-1-(3,4-methylenedioxyphenyl)-propene with hydroxylamine hydrochloride and as would be expected, a mixture of theo isomers of 1-hydroxylamino-1-(3,4-methylenedioxyphenyl)-2-nitro propane was obtained (230; Scheme 34). Separation of these two isomers by fractional crystallisation or preparative TLC was unsuccessful but the column chromatography of the isomeric mixture over silica gel revealed an interesting feature. It was observed that only one of
\[ \begin{align*}
90 & \xrightarrow{\text{b}} 221 \\
87. R = \text{NHMe} & \quad 222. R = \text{Me} \\
88. R = \text{NHCH}_2\text{Ph} & \quad 223. R = \text{CH}_2\text{Ph} \\
224: R = \text{H} & \quad 227-229 \quad \text{Substituents R as in 224-226} \\
225: R = \text{3,4-methylenedioxy} & \\
226: R = \text{3,4-dimethoxy} & \\
a = \text{H}_2, \text{Raney Ni/MeOH}, \quad b = \text{MeS} & \\
\end{align*} \]

Scheme 33
\[ a, \text{NH}_2\text{OH/MeOH}; \quad b, \text{H}_2/\text{Raney-Ni}; \quad c, \text{MeS=CNCO}_2\text{Me} \]

(Scheme 34)
the two possible diastereomers was obtained in pure state while
the second isomer was possibly involved in a retroreaction leading
to the formation of starting nitropropene. Two possible conclusions
can be drawn from this observation. Firstly, the orientation of the
NHOH and H in one of the diastereomers must be anti to each other
otherwise the elimination of NH$_2$OH would not have occurred. Secondly,
the isomer which was obtained in a pure state must possess NHOH
and H groups in orientation which would not allow the elimination
of NH$_2$OH. In a situation such as this, two possible diastereomers
(230a and 230b) can be envisaged. The diastereomer 230b (R*S*; 
erthro) would be expected to be energetically favoured since the
bulky groups (Ph & NO$_2$) are trans to each other thereby minimising
the gauche interactions. The stereochemistry would also permit hy­
drogen-bonding between NHOH and NO$_2$ and thus becomes the favoured
diastereomer. Hydrogenation of 230 with Raney-Ni led to the formation
of 231 which was cyclized with N,N-dimethoxycarbonyl-S-methyliso­
thiourea to obtain the required prototype molecule 232. The inter­
mediate diamine 231 was not very stable and was therefore charac­
terized as its dihydrochloride. The relative stereochemistry in 232
was ascertained from the decoupled PMR spectrum. A doublet (J =
7Hz) at 3.63 - 3.71 $\delta$ ppm for the methine proton adjacent to methyl
group and a doublet (J = 7 Hz) at 4.23 - 4.31 $\delta$ ppm for CH adjacent
to aryl group supported trans stereochemistry for two protons.
A retrospective analysis of the stereochemistry of 230b, on the basis
of observed relative stereochemistry in 232 also supports the assigned
stereochemistry of 230b.

5.9a A retro-synthetic approach for obtaining prototype XXII re­
vealed methyl-2-substituted-3-amino crotonates (233-236) as starting
materials. These were prepared by reacting 1-aryl-2-nitro ethylene
with methyl-3-amino crotonate. Nucleophilic displacement of NH$_2$
with NHOH group in 233-235 gave 237-239 (Scheme 35). The structural and stereochemical assignments
of these compounds were concerned with three problems. Firstly,
it was essential to ascertain whether the compounds existed as oximes
or as the tautomeric hydroxylamines. In case the compounds were
oximes, the stereochemistry across the -C=N, the second problem
R-NO2 + CO2Me →

\[ \text{233, } R = \text{H} \]
\[ \text{234, } R = 3,4-\text{Dimethoxy} \]
\[ \text{235, } R = 4-\text{Methoxy} \]
\[ \text{236, } R = 4-\text{Nitro} \]

\[ a \]

\[ \text{240-242} \]
\[ \text{237-239} \]
\[ \text{243-246} \]

\[ b \]

\[ e, f \]

\[ \text{247, } R = \text{H} \]
\[ \text{248, } R = 4-\text{Methoxy} \]

\[ a, \text{MeOH}; \ b, \text{NH}_2\text{OH}/\text{MeOH}; \ c, \text{dil. } \text{H}_2\text{SO}_4/\text{MeOH}; \]
\[ d, \text{Mono perphthallic acid or m-CPBA}; \ e, \text{H}_2, \text{Raney-Ni}/\text{MeOH}; \]
\[ f, \text{Me}_2\text{C}=\text{NCO}_2\text{CH}_3 \]
\[ \text{NHCO}_2\text{CH}_3 \]

\[ \text{(Scheme 35)} \]
in the present context, had to be ascertained. Thirdly, the relative stereochemistry across the two asymmetric carbon centres (in case the compounds were oximes) had to be worked out. Indirect evidence for the structure of compounds 237-239 was obtained from the following chemical reactions. Acid hydrolysis of 233-235 furnished the ketones 240-242 which could then be converted into 237-239 by reacting them with hydroxylamine hydrochloride. The direct evidence for the assigned structures of the compounds was obtained from the $^{13}$C-NMR spectrum of one of the representative compound (239). The $^{13}$C signal for $\text{-C}=\text{N}$ at 158.51 δ ppm in the NMR spectrum of 239 and the appearance of the carbon of methyl group at 12.05 δ ppm indicated it to be anti oxime. In order to ascertain the stereochemical purity of compounds 237-239, the multiplicity of the methine proton (CH-CO$_2$Me) was studied. However, this methine proton in these compounds appeared along with the signals of other methine and methylene protons in a 90 MHz PMR spectrum. This prompted to record a 400 MHz PMR spectrum of one of the representative compound (239). The appearance of a neat doublet at 3.72 δ ppm in the PMR spectrum suggested stereochemical homogeneity and indicated stereoselective formation of only one diastereomer. The other minor diastereomer could not be isolated from the reaction mixture and in the absence of this minor diastereomer, the relative stereochemistry of 239 could not be ascertained. Reaction of 233-236 with either monoperphthalic acid or m-chloro perbenzoic acid yielded 243-246. It was interesting to note that the tertiary hydroxyl group in these compounds was not prone to easy elimination reaction and the reaction of 243-244 with hydroxylamine hydrochloride yielded oximes 247-248 without eliminating a molecule of water. The presence of a tertiary hydroxyl group in these compounds was evident from the PMR signal (D$_2$O exchangeable) at 4.0 δ ppm. The stability of the tertiary hydroxy groups in compounds 247-248 suggested that the hydroxyl group was not placed anti to vicinal CH. In the light of this observation the Dreiding models of various rotamers of the two possible diastereomers were studied to ascertain the steric crowding in the molecule. On the basis of Dreiding model the stereochemically most favoured diastereomer (I : $R$ $R$, threo) is described below:
In order to obtain a representative compound of the desired prototype XXII, compound 239 was hydrogenated over Raney-Ni and the resulting solution was reacted with N,N-dimethoxycarbonyl-S-methyl-isothiourea to yield 249. The appearance of one broad singlet and a sharp doublet for the methyl protons in the PMR spectrum (400 MHz) indicated it to be a mixture of stereomers. This was further supported by the appearance of two extremely close peaks in the HPLC spectrum. Preparative HPLC to separate the isomers was not attempted. The possible mechanism of formation of compound 249 is described in scheme 36.
Scheme 36
CHAPTER 6

6.1 : EXPERIMENTAL

6.2 : Tables

6.3 : BIOLOGICAL ACTIVITY
CHAPTER - 6

EXPERIMENTAL

6.1 The melting points were determined on a sulphuric acid bath or an electrically heated block and are uncorrected. All the reactions were checked by thin layer chromatography over silica gel G or alumina (basic or neutral) plates using iodine vapours. KMnO$_4$ spray or Dragendorf's spray as the developing reagent. The structures of all the compounds were routinely checked by IR and PMR Spectroscopy. IR spectra were recorded on Perkin-Elmer 157 infrared and Beckman Acculab-1 grating instruments and values are expressed in cm$^{-1}$. PMR spectra were recorded on varian EM 360L or Perkin-Elmer R-32 using TMS as internal reference (Chemical shift in $\delta$ ppm). $^{13}$C-NMR spectra were recorded on CFT-20 spectrometer operating at 20 MHz, 8192 data points were collected and a sweep width of 5000 Hz was used. Pulse delay of 0.5 sec. was essential for recording the signals of carbonyl carbons. $^{13}$C-NMR spectra were also recorded on a Bruker WM-400 FT NMR spectrometer. Mass spectra of these compounds were recorded on Jeol-D 3000 instrument. The second place after the decimal point in the required value of C,H,N analyses have been approximated.

$\beta$-Aroyl propionic acid (101,102)

These compounds were essentially prepared by the method reported earlier $^{41a}$.

$\beta$-Aroyl-$\gamma$-butyrolactones (103,104)

These compounds were prepared in better yields by modifying the method reported earlier $^{41a}$. The details are as follows:

Formaldehyde (37.41%; 0.30 mole) was added to a stirred solution of $\beta$-aroyl propionic acid (103, 104; 0.27 mole) in NaOH solution (0.5N, 60 ml, 0.30 mole). After stirring at room temperature (25$^\circ$) for 1 hr. the mixture was acidified with conc. HCl (~15 ml) and stirred at room temperature (25$^\circ$) for additional 12 hr. The separated semi solid was triturated with ether to obtain the required compound. The mother liquor was again stirred at room temperature (25$^\circ$) for 4 hr. and the separated solid was filtered. The combined solid product was recrystallised from hot benzene.
**41a**

Yield 82%; m.p. 62-64° (Lit. m.p. 63-65°); M$^+$
at m/z 190

IR (KBr) : 1670 & 1775 (CO)

PMR (CDCl$_3$) : 2.71-2.88 (t, 2H, CH$_2$), 4.25-4.53 (m, 3H, OCH$_2$ & CH), 7.26-7.58 (m, 3H, 3, 4 & 5Ar-H), 7.72-7.90 (m, 2H, 2 & 6Ar-H).

**103**

Yield 80%; m.p. 84-85° (Lit. m.p. 85-87°); M$^+$
at m/z 204

IR (KBr) : 1670 & 1760 (CO)

PMR (CDCl$_3$) : 2.40 (s, 3H, CH$_3$), 2.69-2.82 ((t, 2H, CH$_2$), 4.12-4.58 (m, 3H, OCH$_2$ & CH), 7.20-7.29 (d, 2H, 3 & 5 Ar-H, Jo = 9Hz), 7.73-7.83 (d, 2H, 2 & 6 Ar-H, Jo = 9Hz).

**4-Aroyl-N-(p-methoxyphenyl)-pyrrolidin-2-ones (105 & 107; Table 15)**

**General Procedure:**

To a mixture of **103** or **104** (0.1 mole) and p-anisidine (0.1 mole) in alcohol (6 ml) was added triethylamine (0.2 mole) and refluxed for 8 hr. Water was added to it and extracted with ethyl acetate. Usual work up of organic layer yielded a residue which was treated with ether to obtain a solid. It was recrystallised from a mixture of chloroform-hexane.

**4-(α-Hydroxy-4-methyl) benzyl-N-(p-methoxyphenyl) pyrrolidin-2-one (106)**

A solution of **105** (0.01 mole, 3.0 gm) in methanol (35 ml) was hydrogenated in presence of Pd/c (10%, 0.3 gm) at 2.5 kg/cm$^3$ for 2 hr. The catalyst was filtered off and the filtrate was concentrated under reduced pressure. The residue on tituration with CCl$_4$ furnished a crystalline solid which was recrystallised from hot CCl$_4$.

Yield 90%; m.p. 115-16°; M$^+$ at m/z 311

PMR (CDCl$_3$) : 2.30 (s, 3H, CH$_3$), 2.54-2.72 (m, 2H, CH-CH$_2$), 3.40-3.80 (m, 6H, OCH$_3$), NCH$_2$ & CH), 4.40-4.60 (m, 1H, CHO), 6.70-7.45 (m, 8H, Ar-H).

**4-Benzoyl-N-(4-amino-3-nitrophenyl)-pyrrolidin-2-one (108; Table 15)**

The experimental procedure was essentially same as described for **105** but instead of p-anisidine, 2-nitro-p-phenylene diamine was
used. The compound 108 was recrystallised from ethyl acetate-ether mixture.

**Catalytic hydrogenation of 108**

A solution of 108 (0.65 gm, 0.02 mole) in methanol (30 ml) was hydrogenated at 2.5 kg/cm$^3$ in the presence of Raney-Ni (0.3 gm) for 30 minutes. Catalyst was filtered off and the solvent was removed under reduced pressure. The residue without further purification was utilised for the next step.

4-Benzoyl-N-[5(6)-(2-methoxycarbonylamino) benzimidazolyl] pyrrolidin-2-one (109; Table 15)

Aqueous NaOH solution (25%, 3 ml) was added under stirring to a precooled (10-15°) mixture of S-methylisothiouronium sulphate (0.01 mole) and methylchloroformate (0.02 mole) in water (4 ml) and the pH of the reaction mixture was maintained between 8.0 - 9.0. Glacial acetic acid was then carefully added for readjusting the pH to about 5.0 and to this mixture, was then added the required diamine (mentioned above, 0.01 mole) in methanol (15 ml). This reaction mixture was refluxed for 3 hr, cooled to room temperature and finally diluted with water, the solid so obtained was filtered, washed with water and dried. It was recrystallised from ethanol.

4-Acetamido-3-nitro benzaldehyde (112)

This was prepared by the method reported earlier.

4-Acetamido-3-nitro cinnamic acid (113)

To a mixture of 112 (2 gm, 0.01 mole) and malonic acid (1 gm, 0.01 mole) in ethanol (5 ml) was added pyridine (0.1 ml) and refluxed for 2 hr. The separated solid was filtered, washed with hot ethanol (5 ml), dried and recrystallised from DMF-H$_2$O mixture.

113  : Yield 88%; m.p. 254-5°; M$^+$ at m/z 250
IR(KBr)  : 1620, 1690 (CO)
PMR (DMSO-d$_6$)  : 2.08 (s, 3H, NHCOCH$_3$), 6.50-6.58 (s, 1H, =CH, J = 16Hz), 7.40-8.20 (m, 5H, Ar-H, =CH, & NH)
C$_{11}$H$_{10}$N$_2$O$_5$  : Requires : C, 52.80; H, 4.00; N, 11.20
                   : Found:     C, 52.60; H, 3.80; N, 11.50.
4-Amino-3-nitro cinnamic acid (114)

To a suspension of 113 (2.5 gm, 0.01 mole) in methanol (8 ml) was slowly added aqueous NaOH solution (10%, 2.5 ml) and stirred at room temperature (28°) for 30 minutes. A mixture of water (10 ml) and acetic acid (0.1 ml) was added to the reaction mixture and the separated solid was filtered, washed with water, dried and recrystallised from DMF-H₂O mixture.

**114**

IR (KBr) : Yield 90%; m.p. 206-7°; M⁺ at m/z 208
PMR (DMSO-d₆) : 1690 (CO), 3350 (NH)

Yield 90%; m.p. 206-7°; M⁺ at m/z 208

C₉H₆N₂O₄ : Requires : C, 51.92; H, 3.84; N, 13.46
Found : C, 52.20; H, 3.50; N, 13.11

Catalytic hydrogenation of 114

The experimental procedure was essentially same as described for the reduction of 108 and the resulting diamine was used for the next step without further purification.

**β-[(2-Methoxycarbonylamino)-5(6)-benzimidazolyl]-acrylic acid (115)**

This was prepared by the method described for 109 and recrystallised from DMF-H₂O mixture.

**115**

IR(KBr) : Yield 63%; m.p. > 300°; M⁺ at m/z 261
PMR (DMSO-d₆) : 1665 (CO₂H), 1720 (CO)

Yield 63%; m.p. > 300°; M⁺ at m/z 261

C₁₂H₁₁N₃O₄ : Requires : C, 55.17; H, 4.21; N, 16.09
Found : C, 55.10; H, 4.26; N, 15.80

5-Ethoxycarbonyl-6-methyl-2-oxo-4-(4-acetamido-3-nitrophenyl) pyrimidine (117; Table 16)

This was prepared by the method reported in the literature.

5-Ethoxycarbonyl-6-methyl-2-oxo-4-(4-amino-3-nitrophenyl) pyrimidine (118; Table 16)

This was essentially prepared by the method described for 114 and recrystallised from DMF-H₂O mixture.
Methyl-5(6)-[5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-4-yl] benzimidazole-2-carbamate (119; Table 16)

The method for preparation of 119 was the one reported for 115.

4-Acetamido acetophenone (121)

This was prepared by the method reported earlier 231.

4-Acetamido-3-nitro acetophenone (122)

This compound was prepared by the method reported earlier 231.

4-Amino-3-nitro acetophenone (123)

This was prepared by the method described for 114.

Methyl-5(6)-acyl benzimidazole-2-carbamate (124)

This was also prepared by the method reported in the literature 232.

2-Methoxycarbonylamino benzimidazole-5-(6)-acetoxime (125)

A mixture of hydroxylamine hydrochloride (0.96 gm, 0.015 mole) and sodium acetate (1.36 gm, 0.015 mole) was added to a solution of 124 (2.3 gm, 0.01 mole) in methanol (12 ml). The mixture was refluxed for 5 hr. cooled and diluted with water (10 ml). The solid so obtained was filtered, washed with water, dried and recrystallised from DMF-H2O mixture.

IR (KBr) : 1640 (C = N), 1720 (CO), 3300 (NH)
PMR (DMSO-d6) : 2.22 (s, 3H, CH3), 3.80 (s, 3H, CO2CH3), 7.40-7.70 (m, 3H, Ar-H)

C11H12N2O3 : Requires : C, 53.22; H, 4.83; N, 22.58
Found : C, 53.15; H, 5.31; N, 22.20

2-Nitro-1-(4-substituted phenyl) propene (126, 127)

These compounds were prepared by the method reported earlier 43.

2,5-Dimethyl-3-methoxycarbonyl-4-substituted phenyl furan (128, 129; Table 17) and 2,5-dimethyl-3-methoxycarbonyl-4-substituted phenyl pyrrole (130, 131; Table 17)
Method A:

To a suspension of 126, 127 (0.001 mole) in methanol (10 ml) was added piperidine (0.002 mole) and methylacetoacetate (0.002 mole) under cooling (5-10°) and stirring. It was stirred at room temperature (25°) for 24 hr. Water was added to the reaction mixture and extracted with ethyl acetate. Usual work up of organic layer yielded an oil containing a mixture of 126, 129 and 130, 131 which were separated through column chromatography over silica gel using hexane: Chloroform (80:20) as an eluent. These compounds were recrystallised from chloroform-hexane mixture.

Method B for 128

To a suspension of 126 (1.1 gm, 0.005 mole) in methanol (8 ml) was added triethylamine (1.0 ml, 0.01 mole) and methylacetoacetate (1.1 ml, 0.01 mole) under cooling (5-10°) and stirring. It was then stirred at room temperature (20°) for 24 hr. Water (20 ml) was added to the reaction mixture, the separated solid was filtered, washed with water and dried. It was purified through scoxilation using benzene as a solvent.

Method B for 130

A mixture of 126 (1.1 gm 0.005 mole), methyl-3-amino crotonate (1.15 gm, 0.01 mole) and pyridine (0.1 ml) in methanol (10 ml) was refluxed for 36 hr. Water was added to the reaction mixture and after 4 hr the separated solid was filtered, washed with water and dried.

2,5-Dimethyl-3-methoxycarbonyl-4-substituted phenyl-N-substituted pyrroles (132-137; Table 17)

General Procedure:

A mixture of 126 (0.01 mole), methylacetoacetate (0.02 mole) and primary amines (0.02 mole) in methanol (15 ml) was refluxed for 12-14 hr. Water was added to the reaction mixture, the separated solid was filtered, washed with water and dried. These compounds were recrystallised from chloroform-petroleum benzene mixture.

2,5-Dimethyl-3-methoxycarbonyl-4-(4-amin0-3-nitrophenyl)-N-methyl pyrrole (146; Table 17)

A mixture of 126 (2.2 gm, 0.01 mole) and 145 (2.58 gm,
0.02 mole) in methanol (15 ml) was refluxed for 36 hr. Water was added to the reaction mixture, the separated solid was filtered, washed with water and dried. It was recrystallised from aqueous methanol.

3,6-Dimethyl-4-hydrazinocarbonyl-5-(4-amino-3-nitrophenyl) pyridazine (148)

A mixture of 126 (0.002 mole), methylacetoacetate (0.004 mole) and hydrazine hydrate (0.004 mole) in ethanol (10 ml) was refluxed on a waterbath for 3 hr. The reaction mixture was diluted with water, the separated solid was filtered, dried and recrystallised from ethylacetate-hexane.

\[
\text{IR(KBr)} : \text{Yield 70%; m.p. 170-71°; } M^+ \text{ at m/z 303}
\]

\[
\text{PMR (TFA)} : 1650 (\text{CO})
\]

\[
2.18 \ (s, 6H, 2xCH_3), 7.47-7.61 \ (m, 3H, Ar-H)
\]

\[
C_{13}H_{14}N_6O_3 \ : \text{Requires: C, 51.65; H, 4.63; N, 27.81}
\]

\[
\text{Found : C, 51.45; H, 4.31; N, 27.96}
\]

2-Nitro-1-substituted phenyl propene (149-153)

These compounds were prepared by the method reported earlier.

2,5-Dimethyl-3-methoxycarbonyl-4-substituted phenyl pyroles (154-158; Table 18)

The experimental procedure was essentially same as described for 146.

Catalytic hydrogenation of 130, 132-137

The experimental procedure was essentially same as described for 108.

Methyl 5(6)-[2,5-dimethyl-3-methoxycarbonyl-N-substituted] pyrrolo] benzimidazole-2-carbamates (159-166; Table 19)

To a solution of diamine (mentioned above, 0.01 mole) in methanol (10 ml) was added N,N-dimethoxycarbonyl-S-methylisothiourea (0.01 mole) and catalytic amount of p-TSA and refluxed for 5 hr. Water (20 ml) was added to the reaction mixture, the solid so obtained was filtered, washed with water and dried. These were recrystallised from aqueous methanol.
2-Nitro-1-substituted phenyl propene (166-170)

These were prepared by the method reported earlier.

2,5-Dimethyl-3-methoxycarbonyl-4-substituted phenyl-N-(4-amino-3-nitrophenyl) pyrrole (171-175; Table 20)

These compounds were essentially prepared by the method described for 132-137.

Methyl-5(6)-N-[2,5-dimethyl-3-methoxycarbonyl-4-substituted phenyl] pyrrolo benzimidazole-2-carbamates (176-180; Table 21)

The experimental procedure was same as described for 159-166.

4,4'-Dichloro-3,3'-dinitro benzophenone (182)

This was prepared by the method reported in literature.

4,4'-Diamino-3,3'-dinitro benzophenone (183)

This compound was also prepared by the method reported.

2,2'-[Bis-(4-amino-3-nitrophenyl)]methanol (184)

To a suspension of 183 (3.04 gm, 0.01 mole) in methanol (10 ml) was added sodium borohydride (4.56 gm, 0.12 mole) and refluxed for 4.5 hr. Water was then added to the reaction mixture and pH was adjusted to 7 by adding glacial acetic acid dropwise. The solid so obtained was filtered, washed with water, dried and recrystallised from aqueous DMF.

184: Yield 85%; m.p. 230-32°; M⁺ at m/z 304

PMR (DMSO-d₆): 5.50 (s, 1H, CH), 6.88-6.98 and 7.23-7.31 (m, 6H, Ar-H), 7.70-8.01 (bs, 4H, 2xNH₂)

C₁₃H₁₂N₄O₅: Requires: C, 51.31; H, 3.94; N, 18.42

Found: C, 51.80; H, 4.24; N, 18.51

2,2'-Dicarbomethoxyamino-5,5'-dibenzimidazolylmethanol (185)

This compound was prepared by following the method described for 159-166. It was recrystallised from aqueous DMF.

185: Yield 78%; m.p. > 300°; M⁺ at m/z 410

IR (KBr): 1725 (CO)
1,6-Dimethyl-5-Ethoxycarbonyl-2-methylmercapto-4-phenyl-4-[1H]-pyrimidine (199)

A mixture of 192 (0.01 mole), potassium hydroxide (0.02 mole) and methyl iodide (0.022 mole) in N,N-dimethyl sulfoxide (3 ml) was stirred at room temperature (30°C) for 1 hr. Water (5 ml) was added to the reaction mixture, the separated solid was filtered, washed with water (50 ml) and recrystallised from aqueous methanol. Removal of solvent yielded the compound 200 as an oil.

IR (KBr) : 1680 (CO)
PMR (CDCl₃) : 1.03-1.19 (t, 3H, CH₃), 2.30 (s, 3H, CH₃), 2.43 (s, 3H, S-CH₃), 2.90 (s, 3H, N-CH₃), 3.88-4.10 (q, 2H, CH₂), 5.11 (s, 1H, CH), 7.18 (s, 5H, Ar-H)

Yield 70%; m.p. 160°; M⁺ at m/z 304
C₁₆H₂₀N₂O₂S : Requires: C, 63.15; H, 6.57; N, 9.21
Found: C, 63.00; H, 6.25; N, 8.80

1,6-Dimethyl-5-ethoxycarbonyl-4-phenyl-3,4-dihydropyrimidin-2-one (201)

To a solution of 18 (0.5 g) in methanol (2 ml) was added conc. H₂SO₄ (2 drops) and refluxed on steam bath for 4 hr. Water was added to it and extracted with ethyl acetate. Usual work up yielded a solid which was recrystallised from aqueous methanol.

\[ 201 \]

IR (KBr) : Yield 55%; m.p. 160-61°; M⁺ at m/z 274
PMR (CDCl₃) : 1660, 1690 (CO)
Yield: 1.03-1.20 (t, 3H, CH₃), 2.27 (s, 3H, CH₃),
2.77 (s, 3H, N-CH₃), 3.79-4.11 (q, 2H, CH₂),
5.12 (bs, 1H, CH), 7.21 (m, 5H, Ar-H), 8.50
(bs, 1H, NH)

C₁₅H₁₈N₂O₃ : Requires: C, 65.69; H, 6.56; N, 10.21
Found: C, 65.73; H, 6.81; N, 9.84

5-Aryl-6-ethoxycarbonyl-7-methyl-3-oxo-2,3-dihydro-5H-thiazolo [3,2-a] pyrimidine (202-205; Table 24)

General Procedure:

A mixture of 192-195 (0.01 mole), monochloroacetic acid (0.05 mole) and BF₃ etherate (0.1 ml) in methanol (5 ml) was stirred at room temperature (30°C) for 3.5 hr. Water (10 ml) was then added to the reaction mixture. Extraction with ethyl acetate (10 ml) followed by usual work-up yielded an oil which on trituration with petroleum benzene furnished a solid 202 which was recrystallised from chloroform-hexane mixture, while other compounds 203-205 were obtained as oil.

1-Carboxymethyl-5-ethoxycarbonyl-6-methyl-4-substituted phenyl-3,4-dihydropyrimidin-2-thione (206-208; Table 25)

General Procedure:

A mixture of 192, 194-195 (0.01 mole), monochloroacetic acid (0.05 mole) and potassium hydroxide (0.01 mole) in methanol (5 ml) was refluxed on steam bath for 2 hr. The separated solid was filtered, washed with water (40 ml), dried and recrystallised from methanol.
Ethyl (α-trifluoroacetyl-β-thiourido) substituted phenyl propionate (209, 210)

**General Procedure:**

A mixture of appropriate benzaldehyde (0.01 mole), Ethyl-trifluoromethyl acetoacetate (0.01 mole), thiourea (0.02 mole) in HCl (3.5 ml, 3N in 1:1 methanol : water) was stirred at room temperature (20°C) for 48 hr. The separated solid was filtered, washed with water and dried. It was recrystallised from chloroform-hexane mixture.

5-Ethoxycarbonyl-6-trifluoromethyl-4-phenyl-3,4-dihydropyrimidin-2-thione (211)

0.1 g of 209 was taken in 2 gm of polyphosphoric acid and heated on water bath for 8 hr. water was added and on trituration a solid was obtained which was recrystallised from benzene.

5-Ethoxycarbonyl-2-methylmercapto-6-methyl-4-phenyl pyrimidine (212; Table 26)

A mixture of 198 (5.8 g, 0.02 mole) and manganic acetate (11.8 g, 0.04 mole) in dry benzene (50 ml) was refluxed for 2.5 hr. Manganous acetate was filtered off. Water was added to the filtrate and it was extracted with benzene. Usual work up yielded an oil which was purified through a short band of silica gel using hexane as eluent.

5-Ethoxycarbonyl-2-methylmercapto-6-methyl-4-phenyl-2-(1H)-pyrimidine (213) and 5-Ethoxycarbonyl-2-methoxy-5-methyl-4-phenyl-2-(1H) pyrimidine (214)

To a solution of 212 (5.6 g, 0.02 mole) in methanol (8 ml) was added NaBH₄ (1.5 g, 0.04 mole) under cooling (5-10°C) and stirring. It was stirred at room temperature (20°C) for 1 hr. Water was added to the reaction mixture and extracted with ethyl acetate. Usual work up yielded a mixture of two compounds 213 and 214 which were separated through a column of silica gel using hexane, chloroform as eluent.

5,6-Dimethyl-2-methylmercapto-4-phenyl-pyrimidine (215; Table 26) and 5-Hydroxymethyl-2-methylmercapto-6-methyl-4-phenyl pyrimidine (216; Table 26)
To a suspension of LAH (1.14 g, 0.03 mole) in dry ether (5 ml) was added a solution of 212 (8.7 g, 0.03 mole) in dry ether (20 ml) under cooling (5-10°C) and stirring. It was stirred at the same temperature for 0.5 hr. Ordinary benzene was added followed by addition of water. It was extracted with benzene. Usual work up yielded a mixture of 215 and 216 which were separated through a column of silica gel using hexane, chloroform as eluent.

5-Formyl-2-methylmercapto-6-methyl-4-phenyl pyrimidine (217; Table 26)

To a solution of 216 (2.4 g, 0.01 mole) in dry CH₂Cl₂ (15 ml) was added pyridinium chlorochromate (2.2 g, 0.01 mole). It was stirred at room temperature (25°C) for 40 minutes. Solvent ether was added and eluted with ether through a short band of silica gel. Solvent was removed and on trituration with hexane a crystalline solid obtained was recrystallised from chloroform-hexane mixture.

5-Bromomethyl-2-methylmercapto-6-methyl-4-phenyl pyrimidine (218; Table 26)

To a solution of 216 (2.4 g, 0.01 mole) in dry benzene (10 ml) was added a mixture of PBr₃ (0.95 ml, 0.01 mole) and triethylamine (1.0 ml, 0.01 mole) in dry benzene (5 ml) under cooling (5°C) and stirring. It was stirred at room temperature (25°C) for 1 hr. Water was added and extracted with ethyl acetate. Usual work up yielded a solid which was recrystallised from chloroform-hexane mixture.

5-\[N-(4-Amino-3-nitrophenyl)\]aminomethyl-2-methylmercapto-6-methyl-4-phenyl pyrimidine (219; Table 26)

To a solution of 218 (0.3 gm, 0.001 mole) in dry benzene (5 ml) was added triethylamine (0.1 ml, 0.001 mole) and O-nitro-\(\phi\)-phenylenediamine (0.15 gm, 0.001 mole). It was stirred at room temperature (25°C) for 1 hr. Water was added to it and extracted with ethyl acetate. Usual work up yielded an oil which on trituration with pet. benzene yielded a solid which was recrystallised from chloroform-hexane mixture.

Methyl-5(6)-N-[2-methylmercapto-6-methyl-4-phenyl pyrimidine-5-yl]methyl amino benzimidazole-2-carbamate (220; Table 26)

To a solution of 219 (0.38 gm, 0.001 mole) in methanol (20
ml) was added Raney-Ni (0.1 gm) and hydrogenated at 2.5 kg/cm² for 1 hr. The catalyst was filtered off and the solvent was reduced to 5 ml. N,N-dimethoxycarbonyl-S-methyl isothiourea (0.2 gm, 0.001 mole) was added to it and refluxed for 3.5 hr. Water (20 ml) was added to it, the separated solid was filtered, washed with water and dried. It was recrystallised from chloroform-hexane mixture.

**Methyl-5(6)-(4-(2,6-dimethyl-3,5-dimethoxycarbonyl-1,4-dihydropyridyl)) benzimidazole-2-carbamate (221; Table 27)**

A mixture of 90 (0.331 gm, 0.001 mole), N,N-dimethoxycarbonyl-S-methylisothiourea (0.206 gm, 0.001 mole) and catalytic amount of p-TSA in methanol (5 ml) was refluxed for 4 hr. The reaction mixture was diluted with water, the solid so obtained was filtered, washed with water and dried. It was recrystallised from aqueous methanol.

**Methyl-5(6)-(4-(2,6-dimethyl-3,5-dimethoxycarbonyl-1,4-dihydropyridyl))-N-substituted benzimidazole-2-carbamate (222-223; Table 27)**

The experimental procedure was essentially same as described for 159-166.

**N,N-Dimethoxycarbonyl-N-(substituted benzyl)guanidine (227-229; Table 28)**

The experimental procedure was essentially same as described for 221.

**1-Hydroxylamine-1-(3,4-methylenedioxyphenyl)-2-nitro propane (230)**

To a solution of 1-(3,4-methylenedioxyphenyl)-2-nitro propene (2.07 g, 0.01 mole) in methanol (10 ml) was added hydroxylamine hydrochloride (1.39 g, 0.02 mole) and sodium acetate (1.64 g, 0.02 mole). The reaction mixture was stirred at room temperature (20°C) for 5 hr. Water (20 ml) was added to it, the precipitated solid was filtered, washed with water and dried. It was purified through column chromatography over silica gel using hexane : chloroform (20 : 80) as eluent. The compound was recrystallised from chloroform-hexane mixture.

230 : Yield 82%; m.p. 123-124°C; M⁺ at m/z 240
IR(KBr) : 3000 (NH) & 3320 (OH)
PMR(CDCl₃+DMSO-d₆) : 1.18-1.25 (d, 3H, CH₃, J = 7Hz), 4.20-4.30
1,2-Diamino-1-(3,4-methylenedioxyphenyl)propane (231)

To a suspension of 230 (1.2 g, 0.005 mole) in methanol (20 ml) was added Raney-Ni (~0.5 g) and hydrogenated at 2.5 mg/cm\(^2\) for 2 hr. After removal of the catalyst solvent was reduced to ~10 ml and this was used for the next step as such.

However, for characterisation 231 was isolated as its dihydrochloride.

231: m.p. 101°C; IR (KBr): 3000 (NH)
PMR(D\(_2\)O): 1.31-1.39 (d, 3H, CH\(_3\)), 3.60-3.85 (m, 1H, CH), 4.05-4.17 (m, 1H, CH), 6.19 (s, 2H, OCH\(_2\)O), 7.08-7.21 (m, 3H, Ar-H)

C\(_{10}\)H\(_{12}\)N\(_2\)O\(_5\) : Requires: C, 50.00; H, 5.00; N, 11.66
Found: C, 50.41; H, 4.82; N, 11.40

Methyl-4(5)-methyl-5(4)-[3,4-methylenedioxyphenyl]-4,5-dihydroimidazole-2-carbamate (232)

To a solution of 231 obtained from above in methanol (5 ml) was added N,N-dimethylxycarbonyl-S-methylisothiourea and p-TSA in catalytic amount. The reaction mixture was refluxed for 5 hr. It was cooled to room temperature (20°C) water was added to it, the separated solid was filtered, washed with water and dried. It was recrystallised from aqueous methanol.

232: Yield 68%; m.p. 171°C; M\(^+\) at m/z 277
IR(KBr) : 1700 (CO)
PMR(CDC\(_3\)) : 1.26-1.32 (d, 3H, CH\(_3\), J = 6Hz), 3.42 (s, 3H, NHCO\(_2\)CH\(_3\)), 3.58-3.74 (m, 1H, CH), 4.23-4.31 (d, 1H, CH, J = 7Hz), 5.89 (s, 2H, OCH\(_2\)O), 6.65-6.85 (m, 3H, Ar-H)

C\(_{13}\)H\(_{18}\)N\(_3\)O\(_4\) : Requires: C, 56.31; H, 5.41; N, 15.16
Found: C, 56.12; H, 5.59; N, 15.06

Methyl-3-amino-2[(β -substitutedphenyl)nitroethyl] crotonate (233-236; Table 29)
General Procedure:

To a solution of 1-aryl-2-nitro ethylene (0.01 mole) in methanol (10 ml) was added methyl-3-aminocrotonate (0.02 mole) and stirred at room temperature (20°C) for 8 hr. Water (20 ml) was added, the precipitated solid was filtered, washed with water, dried and recrystallised from chloroform, hexane mixture.

3-Carbomethoxy-5-nitro-2-oximinoo-4-substituted phenyl pentane (237-239; Table 30)

General Procedure:

To a suspension of 233-236 (0.01 mole) in methanol (10 ml) was added hydroxylamine hydrochloride (0.02 mole) and sodium acetate (0.02 mole). It was stirred at room temperature (20°C) for 5 hr. Water (20 ml) was added to the reaction mixture the separated solid was filtered, washed with water, dried and recrystallised from aqueous methanol.

3-Carbomethoxy-5-nitro-4-substituted phenyl pentan-2-one (240-242; Table 30)

General Procedure:

A mixture of the compound 233-235 (1 g) and sulfuric acid (2 drops) in methanol (10 ml) was refluxed on water bath for 6 hr. Water was added to the reaction mixture and extracted with ethyl acetate. Usual work up of organic layer yielded an oil.

3-Carbomethoxy-3-hydroxy-5-nitro-4-substituted phenyl pentan-2-one (243-246; Table 30)

Method A:

To a solution of 233-236 (1 g) in dry CH₂Cl₂ (5 ml) was added etherial solution of monophorphthalic acid (15 ml) and stirred at 20°C for 20 hr. The separated phthalic acid was filtered, solvent was removed and on trituration with petroleum benzene a solid was obtained. It was recrystallised from chloroform-petroleum benzene mixture.

Method B:

To a solution of 233-236 (0.01 mole) in dry CH₂Cl₂ (10 ml) was added m-chloroperbenzoic acid (0.02 mole) and stirred at 20°C for 24 hr. Work up was same as in method A.
3-Carbomethoxy-3-hydroxy-5-nitro-2-oximino-4-substituted phenyl pentane (247-248; Table 30)

The experimental procedure was same as described for 237-239.

1,6-Bis carbomethoxy-2-methoxycarbonylamino-7-methyl-5-p-methoxyphenyl)-4,5,6,7-tetrahydro-1,3-diazepine (249)

This compound was prepared essentially by following the method as for 232 but here refluxing time was 36 hr. The compound was purified through column chromatography over silica gel using hexane : Chloroform (1 : 1) as eluent. It was recrystallised from chloroform, hexane mixture.

249 : Yield 20%; m.p. 139°C; M+ at m/z 407
IR(KBr) : 1730 (CO)
PMR(400 MHz, CDCl₃) : 1.54-1.55 (d, 3H, CH₃), 1.59 (bs, 3H, CH₃), 2.90-3.02 (m, 1H, CH), 3.45 (s, 3H, CO₂CH₃), 3.75 (s, 6H, OCH₃ & NCO₂CH₃), 3.82 (s, 3H, NHCO₂CH₃), 4.59-4.70 (m, 2H, CH₂), 6.86-6.87 (d, 2H, 3 & 5 Ar-H, Jo = 9Hz), 7.19-7.21 (d, 2H, 2 & 6 Ar-H, Jo = 9Hz), 7.27 (s, 1H, NH)

¹³C-NMR(DMSO-d₆) : 18.61 (q, CH₃), 45.64 (d, Ar-CH), 51.78 (q, CO₂CH₃), 54.65 (t, CH₂), 54.92 (q, NCO₂CH₃, NHCO₂CH₃ & OCH₃), 150.01 (s, C=N), 160.95 (s, NCO₂CH₃ & NHCO₂CH₃), 171.84 (s, CO₂CH₃), 113.84, 128.41, 129.44 & 158.39 (Ar=C)

C₁₉H₂₅N₃O₇ : Requires : C, 56.01; H, 6.14; N, 10.31
Found : C, 56.51; H, 6.35; N, 10.65
Physical and Analytical data of Compounds, which have not been included in Experimental section, are described under vertical columns and their spectral characteristics have been recorded in horizontal sequence.
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<td>12.88</td>
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**IR(KBr):** 1680 & 1700 (CO); **PMR(CDCl₃):** 2.40 (s, 3H, CH₃), 2.81-2.90 (d, 2H, CH₂), 3.74 (s, 3H, OCH₃), 3.90-4.20 (m, 3H, N-CH₂ & CH), 6.80-7.90 (m, 8H, Ar-H); **Mass:** M⁺ at m/z 309.

**IR(KBr):** 1680 & 1705 (CO); **PMR(CDCl₃):** 2.79-2.85 (d, 2H, CH₂), 3.70 (s, 3H, OCH₃), 3.90-4.21 (m, 3H, N-CH₂ & CH), 6.75-6.82 (m, 2H, Ar-H), 7.30-7.60 (m, 5H, Ar-H), 7.81-8.00 (m, 2H, Ar-H); **Mass:** M⁺ at m/z 295.
IR(KBr): 1680 (CO); PMR(CDC$_3$ + DMSO-d$_6$): 2.82-2.91 (d, 2H, CH$_2$), 4.00-4.09 (d, 2H, N-CH$_2$), 4.20-4.42 (m, 1H, CH), 6.87-8.08 (m, 10H, Ar-H & NH$_2$); Mass: M$^+$ at m/z 325.

$^{109}$H

$\begin{array}{cccccccccc}
\text{N} & \text{N} & \text{N} \\
\text{H} & \text{H} & \text{CO}_2\text{Me} \\
\end{array}$

>300

44 C$_{20}$H$_{18}$N$_4$O$_4$ 63.42 4.76 14.81 63.45 4.41 14.48

IR(KBr): 1640 & 1720 (CO); PMR(DMSO-d$_6$): 2.40-2.70 (d, 2H, CH$_2$), 3.60-4.58 (m, 6H, CO$_2$CH$_3$, N-CH$_2$ & CH), 6.30-7.62 (m, 8H, Ar-H), 7.85-8.05 (bs, 1H, NH); Mass: M$^+$ at m/z 378.
Table 16:

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<td>C</td>
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<td>117</td>
<td>4-Acetamido 3-nitrophenyl</td>
<td>162-63</td>
<td>80</td>
<td>C₁₆H₁₈N₄O₆ (362)</td>
<td>53.03</td>
<td>4.97</td>
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<td></td>
<td>IR(KBr): 1630 &amp; 1700 (CO); PMR(DMSO-d₆): 0.97-1.11 (t, 3H, CH₃), 2.00 (s, 3H, NHCOCH₃), 2.21 (s, 3H, CH₃), 3.81-4.04 (q, 2H, CH₂), 5.00-5.14 (d, 1H, CH), 7.18-7.68 (m, 5H, Ar-H &amp; NH); Mass: M⁺ at m/z 362.</td>
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<tr>
<td>118</td>
<td>4-Amino 3-nitrophenyl</td>
<td>230-31</td>
<td>90</td>
<td>C₁₆H₁₆N₄O₅ (320)</td>
<td>52.50</td>
<td>5.00</td>
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<td>IR(KBr): 1630 &amp; 1700 (CO); PMR(DMSO-d₆): 1.04-1.19 (t, 3H, CH₃), 2.27 (s, 3H, CH₃), 3.78-4.10 (q, 2H, CH₂), 5.08 (s, 1H, CH), 6.90-7.79 (m, 7H, Ar-H &amp; NH); Mass: M⁺ at m/z 320.</td>
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<tr>
<td>119</td>
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<td>&gt; 300</td>
<td>71</td>
<td>C₁₇H₁₉N₅O₅ (373)</td>
<td>54.69</td>
<td>5.09</td>
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IR(KBr): 1630 & 1720 (CO); PMR(DMSO-d$_6$): 0.96-1.21 (t, 3H, CH$_3$), 2.22 (s, 3H, CH$_3$), 3.69 (s, 3H, NHCO-CH$_3$), 3.80-4.02 (q, 2H, CH$_2$), 5.13-5.18 (bs, 1H, NH), 6.79-7.61 (m, 5H, Ar-H & NH); Mass: M$^+$ at m/z 373.
Table 17:

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<tr>
<td>128</td>
<td>NH₂</td>
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<td>144-45</td>
<td>45</td>
<td>C₁₄H₁₂N₂O₅</td>
<td>(290)</td>
<td>57.93</td>
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<td>IR(KBr): 1710 (CO); PMR(CDCl₃): 2.12 (s, 3H, 5-CH₃), 2.49 (s, 3H, 2-CH₃), 3.60 (s, 3H, CO₂CH₃), 6.65-6.74 (d, 1H, 5 Ar-H, Jm = 9Hz), 7.11-7.23 (dd, 1H, 6Ar-H, Jo = 9Hz, Jm = 2Hz), 7.87-7.89 (d, 1H, 2Ar-H, Jm = 2Hz); Mass: M⁺ at m/z 290.</td>
</tr>
<tr>
<td>129</td>
<td>Cl</td>
<td>O</td>
<td>95-96</td>
<td>27</td>
<td>C₁₄H₁₂ClNO₅</td>
<td>(309.5)</td>
<td>54.28</td>
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<td>IR(KBr): 1700 (CO); PMR(CDCl₃): 2.15 (s, 3H, 5-CH₃), 2.41 (s, 3H, 2-CH₃), 3.61 (s, 3H, CO₂CH₃), 7.33-7.48 (m, 2H, 5 &amp; 6 Ar-H), 7.70-7.72 (d, 1H, 2 Ar-H, Jm = 2Hz); Mass: M⁺ at m/z 309.</td>
</tr>
<tr>
<td>130</td>
<td>NH₂</td>
<td>NH</td>
<td>223-24</td>
<td>90</td>
<td>C₁₄H₁₅N₃O₄</td>
<td>(289)</td>
<td>58.13</td>
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<td>Compound</td>
<td>Functional Groups</td>
<td>Molecular Formula</td>
<td>Molecular Weight</td>
<td>Elemental Analysis</td>
<td>IR (KBr)</td>
<td>PMR (CDCl₃ + DMSO-d₆)</td>
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<tr>
<td><strong>131</strong></td>
<td>Cl NH</td>
<td>C₁₁H₁₃ClN₂O₄</td>
<td>269.16</td>
<td>54.45 4.21 9.07 54.51 4.21 8.69</td>
<td>1700 (CO); 6.69-6.79 (d, 1H, 5Ar-H, J₀ = 9Hz), 7.12-7.24 (dd, 1H, 6Ar-H, J₀ = 9Hz, Jₘ = 2Hz), 7.78-7.80 (d, 1H, 2Ar-H, Jₘ = 2Hz); Mass: M⁺ at m/z 308.5</td>
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<tr>
<td><strong>132</strong></td>
<td>NH₂ N-Bu(n)</td>
<td>C₁₈H₂₃N₃O₄</td>
<td>345</td>
<td>62.60 6.66 12.17 62.91 6.83 11.98</td>
<td>1690 (CO); 0.85-0.99 (t, 3H, CH₃), 1.21-1.75 (m, 4H, 2xCH₂), 2.04 (s, 3H, 5-CH₃), 2.48 (s, 3H, 2-CH₃), 3.53 (s, 3H, CO₂CH₃), 3.66-3.81 (t, 2H, CH₂), 5.95-6.18 (bs, 2H, NH₂), 6.62-6.72 (d, 1H, 5Ar-H, J₀ = 9Hz), 7.11-7.23 (dd, 1H, 6Ar-H, J₀ = 9Hz, Jₘ = 2Hz), 7.83-7.85 (d, 1H, 2Ar-H, Jₘ = 2Hz); Mass: M⁺ at m/z 345</td>
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<tr>
<td><strong>133</strong></td>
<td>NH₂ N-CH₂Ph</td>
<td>C₂₁H₂₁N₃O₄</td>
<td>379</td>
<td>64.94 5.67 10.82 64.92 5.48 10.68</td>
<td>1690 (CO); 6.69-6.79 (d, 1H, 5Ar-H, J₀ = 9Hz), 7.12-7.24 (dd, 1H, 6Ar-H, J₀ = 9Hz, Jₘ = 2Hz), 7.78-7.80 (d, 1H, 2Ar-H, Jₘ = 2Hz); Mass: M⁺ at m/z 345</td>
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(Analysed as hemihydrate)
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<tbody>
<tr>
<td>134</td>
<td>NH₂</td>
<td>N-</td>
<td>O</td>
<td>Me</td>
<td>155-56</td>
<td>50</td>
<td>C₂₁H₂₁N₃O₅</td>
<td>63.79</td>
<td>5.31</td>
<td>10.63</td>
<td>63.71</td>
<td>5.35</td>
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</table>

IR(KBr): 1680 (CO); PMR(CDC₁₃): 2.00 (s, 3H, 5-CH₃), 2.45 (s, 3H, 2-CH₃), 3.59 (s, 3H, CO₂CH₃), 5.06 (s, 2H, CH₂), 6.71-7.38 (m, 7H, Ar-H), 7.91-7.93 (d, 1H, 2Ar-H, Jm = 2Hz); Mass: M⁺ at m/z 379.

| 135 | NH₂ | N- | O | OMe | 65 | C₂₃H₂₅N₃O₇ | 60.65 | 5.49 | 9.23 | 60.29 | 5.31 | 9.10 |

IR(KBr): 1690 (CO); PMR(CDC₁₃): 1.80 (s, 3H, 5-CH₃), 2.20 (s, 3H, 2-CH₃), 3.78 (s, 3H, OCH₃), 6.50-7.40 (m, 6H, Ar-H), 7.88-7.90 (d, 1H, 2Ar-H, Jm = 2Hz); Mass: M⁺ at m/z 395.

IR(NEAT): 1710 (CO); PMR(CDC₁₃): 1.84 (s, 3H, 5-CH₃), 2.21 (s, 3H, 2-CH₃), 3.51 (s, 3H, CO₂CH₃), 3.75 (s, 9H, 3xOCH₃), 6.11 & 6.32 (2bs, 2H, N-Ar-H), 6.59-6.69 (d, 1H, 5Ar-H, J₀ = 9Hz), 7.06-7.18 (dd, 1H, 6Ar-H, J₀ = 9Hz, Jm = 2Hz), 7.78-7.80 (d, 1H, 2Ar-H, Jm = 2Hz); Mass: M⁺ at m/z 455.

| 136 | NH₂ | N- | NH₂ | OMe | 70 | C₂₀H₁₉N₅O₆ | 56.47 | 4.47 | 16.47 | 56.14 | 4.31 | 16.51 |

IR(NEAT): 1700 (CO); PMR(CC₁₄): 1.81 (s, 3H, 5-CH₃), 2.22 (s, 3H, 2-CH₃), 3.53 (s, 3H, CO₂CH₃), 5.80 & 6.33 (2s, 4H, 2xNH₂), 6.50-7.03 (m, 5H, Ar-H), 7.90-7.92 (d, 1H, 2Ar-H, Jm = 2Hz)
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<tr>
<td>137</td>
<td>NH₂</td>
<td>N(CH₂)₃⁻</td>
<td>110</td>
<td>83</td>
<td>C₂₁H₃₀N₄O₄</td>
<td>62.68</td>
<td>7.46</td>
<td>13.93</td>
<td>62.19</td>
<td>7.21</td>
<td>13.61</td>
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<td>N(Et)₂</td>
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<td>(402)</td>
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**IR(KBr):** 1720 (CO); **PMR(CDCl₃):** 0.88-1.10 (t, 6H, 2xCH₃), 2.01-2.58 (m, 14H, 2 & 5-CH₃, N(CH₂)₃CH₂), 3.45-3.67 (m, 5H, N-CH₂ & CO₂CH₃), 7.01-7.35 (m, 3H, Ar-H); **Mass:** M⁺ at m/z 402.

| 146 | NH₂  | N-CH₃ | 162-63 | 70  | C₁₅H₁₇N₃O₄ | 59.40 | 5.61 | 13.86 | 58.98 | 5.87 | 13.76 |
|     |      |       |        |     | (303)                      |

**IR(KBr):** 1700 (CO); **PMR(CDCl₃):** 2.03 (s, 3H, 5-CH₃), 2.45 (s, 3H, 2-CH₃), 3.40 (s, 3H, N-CH₃), 3.50 (s, 3H, CO₂CH₃), 6.79-6.89 (d, 1H, 5Ar-H, J₀ = 9Hz), 7.06-7.18 (dd, 1H, 6Ar-H, J₀ = 9Hz, Jₐm = 2Hz), 7.60-7.62 (d, 1H, 2Ar-H, Jₐm = 2Hz); **Mass:** M⁺ at m/z 303.
Table 18:  

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<tr>
<th>Compd. No.</th>
<th>R</th>
<th>m.p. ºC</th>
<th>Yield %</th>
<th>Mol. Formula</th>
<th>Mol. Wt.</th>
<th>Analysis % Required</th>
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<td>H</td>
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<tr>
<td>154</td>
<td>H</td>
<td>102</td>
<td>58</td>
<td>C_{14}H_{15}NO_{2}</td>
<td>(229)</td>
<td>73.36</td>
<td>6.55</td>
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</table>

IR(KBr): 1670 (CO); PMR(CDCl$_3$): 1.99 (s, 3H, 5-CH$_3$), 2.40 (s, 3H, 2-CH$_3$), 3.51 (s, 3H, CO$_2$CH$_3$), 7.09-7.40 (m, 5H, Ar-H); Mass: M$^+$ at m/z 229.

155 3,4-Dimethoxy  181  45  C$_{16}$H$_{19}$NO$_4$  (289)  66.43  6.57  4.84  66.10  6.18  4.92

IR(KBr): 1670 (CO); PMR(CDCl$_3$): 2.00 (s, 3H, 5-CH$_3$), 2.45 (s, 3H, 2-CH$_3$), 3.71 & 3.79 (2s, 6H, 2xOCH$_3$), 3.51 (s, 3H, CO$_2$CH$_3$), 6.73-6.89 (m, 3H, Ar-H); Mass: M$^+$ at m/z 289.

156 3,4-Methylene dioxy  98  51  C$_{15}$H$_{15}$NO$_4$  (273)  65.93  5.49  5.12  66.30  5.15  4.81

162
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<tr>
<td>157</td>
<td>4-Benzylolxy</td>
<td>160-62</td>
<td>51</td>
<td>C\textsubscript{22}H\textsubscript{23}NO\textsubscript{4}</td>
<td>72.32</td>
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<td>72.51</td>
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<td>3-Methoxy</td>
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<tr>
<td></td>
<td>IR(KBr): 1670 (CO); PMR(CDCl\textsubscript{3}): 1.99 (s, 3H, 5-CH\textsubscript{3}), 2.39 (s, 3H, 2-CH\textsubscript{3}), 3.56 (s, 3H, CO\textsubscript{2}CH\textsubscript{3}), 5.80 (s, 2H, OCH\textsubscript{2}O), 6.56-6.70 (m, 3H, Ar-H); Mass: M\textsuperscript{+} at m/z 273.</td>
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<tr>
<td>158</td>
<td>4-Acetamido</td>
<td>145-46</td>
<td>46</td>
<td>C\textsubscript{16}H\textsubscript{18}N\textsubscript{2}O\textsubscript{3}</td>
<td>67.13</td>
<td>6.29</td>
<td>9.79</td>
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<td>6.51</td>
<td>9.91</td>
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<td>IR(KBr): 1640 &amp; 1660 (CO); PMR(CDCl\textsubscript{3}): 1.97 (s, 3H, NHCOCH\textsubscript{3}), 1.99 (s, 3H, 5-CH\textsubscript{3}), 2.39 (s, 3H, 2-CH\textsubscript{3}), 3.58 (s, 3H, CO\textsubscript{2}CH\textsubscript{3}), 6.73-6.85 (dd, 2H, 3 &amp; 5 Ar-H, Jo = 9Hz, Jm = 3Hz), 7.34-7.45 (dd, 2H, 2 &amp; 6 Ar-H, Jo = 9Hz, Jm = 2Hz); Mass: M\textsuperscript{+} at m/z 286.</td>
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<tr>
<td>159</td>
<td>H</td>
<td>221-22</td>
<td>70</td>
<td>C&lt;sub&gt;17&lt;/sub&gt;H&lt;sub&gt;18&lt;/sub&gt;N&lt;sub&gt;4&lt;/sub&gt;O&lt;sub&gt;4&lt;/sub&gt; (342)</td>
<td>58.14</td>
<td>5.69 15.95 58.62 5.30 15.75</td>
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<tr>
<td>160</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>224</td>
<td>93</td>
<td>C&lt;sub&gt;18&lt;/sub&gt;H&lt;sub&gt;20&lt;/sub&gt;N&lt;sub&gt;4&lt;/sub&gt;O&lt;sub&gt;4&lt;/sub&gt; (356)</td>
<td>60.67</td>
<td>5.61 15.73 60.60 6.00 15.42</td>
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<td>n-Bu</td>
<td>208-9</td>
<td>98</td>
<td>C&lt;sub&gt;21&lt;/sub&gt;H&lt;sub&gt;26&lt;/sub&gt;N&lt;sub&gt;4&lt;/sub&gt;O&lt;sub&gt;6&lt;/sub&gt; (398)</td>
<td>63.31</td>
<td>6.53 14.07 63.10 6.98 14.03</td>
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</table>

Table 19: MeO<sub>2</sub>CHN- 

IR(KBr): 1660 & 1720 (CO); PMR(TFA): 1.91 (s, 3H, 5-CH<sub>3</sub>), 2.34 (s, 3H, 2-CH<sub>3</sub>), 3.63 (s, 3H, CO<sub>2</sub>CH<sub>3</sub>), 3.77 (s, 3H, N-CH<sub>3</sub>), 3.88 (s, 3H, NHCO<sub>2</sub>CH<sub>3</sub>), 7.18-7.70 (m, 3H, Ar-H)
IR(KBr): 1700 & 1730 (CO); PMR(CDC\textsubscript{3}): 0.80-0.96 (t, 3H, CH\textsubscript{3}), 1.13-1.76 (m, 4, 2xCH\textsubscript{2}), 2.06 (s, 3H, 5-CH\textsubscript{3}), 2.50 (s, 3H, 2-CH\textsubscript{3}), 3.45 (s, 3H, CO\textsubscript{2}CH\textsubscript{3}), 3.63-3.74 (t, 2H, N-CH\textsubscript{2}), 3.81 (s, 3H, NHCO\textsubscript{2}CH\textsubscript{3}), 6.89-7.35 (m, 5H, Ar-H & 2xNH); Mass: M\textsuperscript{+} at m/z 398.

162

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<tr>
<th>CH\textsubscript{2}Ph</th>
<th>207-8</th>
<th>85</th>
<th>C\textsubscript{24}H\textsubscript{24}N\textsubscript{4}O\textsubscript{4}</th>
<th>66.66</th>
<th>5.55</th>
<th>12.96</th>
<th>66.80</th>
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IR(KBr): 1700 & 1730 (CO); PMR(TFA): 1.90 (s, 3H, 5-CH\textsubscript{3}), 2.37 (s, 3H, 2-CH\textsubscript{3}), 3.63 (s, 3H, CO\textsubscript{2}CH\textsubscript{3}), 3.89 (s, 3H, NHCO\textsubscript{2}CH\textsubscript{3}), 6.00 (s, 2H, CH\textsubscript{2}), 6.67-6.90 (m, 2H, 2xNH), 7.01-7.50 (m, 8H, Ar-H),

163

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<tr>
<th>4-OCH\textsubscript{3} Phenyl</th>
<th>210-11</th>
<th>61</th>
<th>C\textsubscript{24}H\textsubscript{24}N\textsubscript{4}O\textsubscript{5}</th>
<th>64.28</th>
<th>5.35</th>
<th>12.50</th>
<th>64.30</th>
<th>5.90</th>
<th>12.67</th>
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IR(KBr): 1690 & 1720 (CO); PMR(CDC\textsubscript{3}): 1.80 (s, 3H, 5-CH\textsubscript{3}), 2.21 (s, 3H, 2-CH\textsubscript{3}), 3.49 (s, 3H, CO\textsubscript{2}CH\textsubscript{3}), 3.76 (s, 3H, OCH\textsubscript{3}), 3.83 (s, 3H, NHCO\textsubscript{2}CH\textsubscript{3}), 6.80-7.10 (m, 4H, Ar-H), 7.23-7.41 (m, 3H, Ar-H),

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<th>189-90</th>
<th>83</th>
<th>C\textsubscript{26}H\textsubscript{28}N\textsubscript{4}O\textsubscript{7}</th>
<th>61.41</th>
<th>5.51</th>
<th>11.02</th>
<th>60.90</th>
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IR(KBr): 1700 & 1720 (CO); PMR(CDC\textsubscript{3}): 1.84 (s, 3H, 5-CH\textsubscript{3}), 2.25 (s, 3H, 2-CH\textsubscript{3}), 3.56 (s, 3H, CO\textsubscript{2}CH\textsubscript{3}), 3.77 (s, 9H, 3xOCH\textsubscript{3}), 3.81 (s, 3H, NHCO\textsubscript{2}CH\textsubscript{3}), 6.50-7.11 (m, 3H, Ar-H), 7.50-7.90 (m, 2H, Ar-H).
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<td>165</td>
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<td>115-16</td>
<td>68</td>
<td>C_{26}H_{25}N_{7}O_{6}</td>
<td>58.75</td>
<td>4.70</td>
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IR(KBr): 1670 & 1730 (CO); PMR(CDC\textsubscript{3}): 1.75 (s, 3H, 5-CH\textsubscript{3}), 2.09 (s, 3H, 2-CH\textsubscript{3}), 3.61 (s, 3H, CO\textsubscript{2}CH\textsubscript{3}), 3.81 & 3.83 (2s, 6H, 2xNHCO\textsubscript{2}CH\textsubscript{3}), 6.56-7.22 (m, 6H, Ar-H).

|166|   |   |   |   |   |126-28 | 88 | C_{24}H_{33}N_{5}O_{4} | 63.29 | 7.25 | 15.38 | 63.51 | 7.30 | 15.41 |

IR(KBr): 1720 & 1730 (CO); PMR(CDC\textsubscript{3}): 0.90-1.20 (t, 6H, 2xCH\textsubscript{3}), 2.01-2.60 (m, 14H, 2 & 5-CH\textsubscript{3}, N(CH\textsubscript{2})\textsubscript{3}-CH\textsubscript{2}), 3.36-3.75 (m, 5H, N-CH\textsubscript{2} & CO\textsubscript{2}CH\textsubscript{3}), 3.84 (s, 3H, NHCO\textsubscript{2}CH\textsubscript{3}), 6.95-7.35 (m, 3H, Ar-H)
Table 20:

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<tr>
<td>171</td>
<td>H</td>
<td>185-86</td>
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<td>C_{20}H_{19}N_{3}O_{4}</td>
<td>(365)</td>
<td>65.75</td>
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IR(KBr): 1690 (CO); PMR(CDC\textsubscript{3}): 1.83 (s, 3H, 5-CH\textsubscript{3}), 2.27 (s, 3H, 2-CH\textsubscript{3}), 3.53 (s, 3H, CO\textsubscript{2}CH\textsubscript{3}), 6.12-6.30 (bs, 2H, NH\textsubscript{2}), 6.74-7.29 (m, 8H, Ar-H); Mass: M\textsuperscript{+} at m/z 365.

172 3,4-Dimethoxy 205-6 81 C_{22}H_{23}N_{3}O_{6} (425)

IR(KBr): 1720 (CO); PMR(CDC\textsubscript{3}+DMSO-d\textsubscript{6}): 1.85 (s, 3H, 5-CH\textsubscript{3}), 2.25 (s, 3H, 2-CH\textsubscript{3}), 3.53 (s, 3H, CO\textsubscript{2}CH\textsubscript{3}), 3.77 & 3.80 (2s, 6H, 2xOCH\textsubscript{3}), 7.11-7.95 (m, 6H, Ar-H)

173 4-Methyl 199-200 53 C_{21}H_{21}N_{3}O_{4} (379)

IR(KBr): 1700 (CO); PMR(CDC\textsubscript{3}+DMSO-d\textsubscript{6}): 1.85 (s, 3H, 5-CH\textsubscript{3}), 2.28 (s, 3H, 2-CH\textsubscript{3}), 2.31 (s, 3H, CH\textsubscript{3}), 3.58
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<td>174</td>
<td>4-Acetamido</td>
<td>280-81</td>
<td>67</td>
<td>C\textsubscript{22}H\textsubscript{22}N\textsubscript{4}O\textsubscript{5}</td>
<td>62.55</td>
<td>5.21</td>
<td>13.27</td>
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<td>5.61</td>
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<td>175</td>
<td>4-Benzylaloxy</td>
<td>oil</td>
<td>52</td>
<td>C\textsubscript{28}H\textsubscript{27}N\textsubscript{3}O\textsubscript{6}</td>
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<td>5.38</td>
<td>8.38</td>
<td>67.41</td>
<td>5.21</td>
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**IR(KBr):** 1660 & 1700 (CO); **PMR(TFA):** 1.75 (s, 3H, 5-CH\textsubscript{3}), 2.18 (s, 3H, 2-CH\textsubscript{3}), 2.41 (s, 3H, NHCOCH\textsubscript{3}), 3.64 (s, 3H, CO\textsubscript{2}CH\textsubscript{3}), 7.12-7.35 (m, 4H, Ar-H), 7.42-7.60 (m, 3H, Ar-H)

**IR(Neat):** 1710 (CO); **PMR(CCl\textsubscript{4}):** 1.80 (s, 3H, 5-CH\textsubscript{3}), 2.20 (s, 3H, 2-CH\textsubscript{3}), 3.50 (s, 3H, CO\textsubscript{2}CH\textsubscript{3}), 3.72 (s, 3H, OCH\textsubscript{3}), 4.94 (s, 2H, CH\textsubscript{2}), 6.21-7.35 (m, 11H, Ar-H)
Table 21:

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</table>

176        | H   | 249-50  | 97      | C_{23}H_{22}N_{4}O_{4} | 66.02     | 5.26       |
|            |     |         |         |              |          | 13.39      |
|            |     |         |         |              |          | 65.81      |
|            |     |         |         |              |          | 5.10       |
|            |     |         |         |              |          | 13.51      |

IR(KBr): 1690 & 1720 (CO); PMR(DMSO-d_6): 1.71 (s, 3H, 5-CH_3), 2.12 (s, 3H, 2-CH_3), 3.62 (s, 3H, CO_2CH_3), 3.82 (s, 3H, NHCO_2CH_3), 6.81-7.45 (m, 8H, Ar-H)

177        | 3,4-Dimethoxy | 225   | 48      | C_{25}H_{26}N_{4}O_{6} | 62.76     |
|            |                |       |         |              |          | 5.43       |
|            |                |       |         |              |          | 11.71      |
|            |                |       |         |              |          | 62.50      |
|            |                |       |         |              |          | 5.30       |
|            |                |       |         |              |          | 12.05      |

IR(KBr): 1700 & 1740 (CO); PMR(TFA): 1.70 (s, 3H, 5-CH_3), 2.13 (s, 3H, 2-CH_3), 3.66 (s, 3H, CO_2CH_3), 3.76 (s, 6H, 2xOCH_3), 3.89 (s, 3H, NHCO_2CH_3), 7.25-7.96 (m, 6H, Ar-H)

178        | 4-Methyl       | 260-62| 78      | C_{24}H_{24}N_{4}O_{4} | 66.66     |
<p>|            |                |       |         |              |          | 5.55       |
|            |                |       |         |              |          | 12.96      |
|            |                |       |         |              |          | 66.60      |
|            |                |       |         |              |          | 5.55       |
|            |                |       |         |              |          | 12.81      |</p>
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<tr>
<td>IR(KBr):</td>
<td>1700 &amp; 1740 (CO);</td>
<td>PMR(TFA):</td>
<td>1.79 (s, 3H, 5-CH₃), 2.21 (s, 3H, 2-CH₃), 2.32 (s, 3H, CH₃), 3.70 (s, 3H, CO₂CH₃), 3.84 (s, 3H, NHCO₂CH₃), 6.91-7.82 (m, 7H, Ar-H)</td>
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</table>

| 179 | 4-Acetamido | >300 | 98 | C₂₅H₂₅N₅O₅ | 63.15 | 5.26 | 14.73 | 63.50 | 5.10 | 14.41 |

IR(KBr): 1700 & 1740 (CO); PMR(TFA): 1.70 (s, 3H, 5-CH₃), 2.13 (s, 3H, 2-CH₃), 2.40 (s, 3H, NHCOCH₃), 3.64 (s, 3H, CO₂CH₃), 3.88 (s, 3H, NHCO₂CH₃), 7.13-7.31 (m, 4H, Ar-H), 7.40-7.70 (m, 3H, Ar-H)
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<tr>
<td>192</td>
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<td>199-200</td>
<td>80</td>
<td>C_{14}H_{16}N_{2}O_{2}S</td>
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<td>60.86</td>
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<td>IR(KBr): 1680 (CO); PMR(CDC$_3$+DMSO-d$_6$): 1.05-1.21 (t, 3H, CH$_3$), 2.33 (s, 3H, CH$_3$), 3.90-4.14 (q, 2H, CH$_2$), 5.27-5.30 (d, 1H, CH), 7.21 (s, 5H, Ar-H), 9.07 (bs, 1H, NH), 9.67 (bs, 1H, NH); Mass: M$^+$ at m/z 276.</td>
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<td>193</td>
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<td>149-50</td>
<td>70</td>
<td>C$<em>{16}$H$</em>{20}$N$<em>{2}$O$</em>{4}$S (336)</td>
<td>57.14</td>
<td>5.94</td>
<td>8.33</td>
<td>57.32</td>
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<td>IR(KBr): 1670 (CO); PMR(CDC$_3$): 1.05-1.20 (t, 3H, CH$_3$), 2.30 (s, 3H, CH$_3$), 3.79 (s, 6H, 2xOCH$_3$), 3.82-4.15 (q, 2H, CH$_2$), 5.29 (bs, 1H, CH), 6.75 (bs, 3H, Ar-H); Mass: M$^+$ at m/z 336.</td>
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<td>194</td>
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<td>131-32</td>
<td>68</td>
<td>C$<em>{15}$H$</em>{18}$N$<em>{2}$O$</em>{3}$ (306)</td>
<td>58.82</td>
<td>5.88</td>
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<td>IR(KBr): 1675 (CO); PMR(CDCl₃): 1.01-1.20 (t, 3H, CH₃), 2.26 (s, 3H, CH₃), 3.66 (s, 3H, OCH₃), 3.80-4.16 (q, 2H, CH₂), 5.20 (bs, 1H, CH), 6.66-7.05 (m, 4H, Ar-H), 7.66 &amp; 8.26 (bs, 2H, 2xNH); Mass: M⁺ at m/z 306.</td>
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<td>4-CH₃</td>
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<td>72</td>
<td>C₁₅H₁₈N₂O₂S</td>
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| IR(KBr): 1660 (CO); PMR(CDCl₃): 0.99-1.14 (t, 3H, CH₃), 2.22 & 2.25 (2s, 6H, 2xCH₃), 3.85-4.09 (q, 2H, CH₂), 5.11 (bs, 1H, CH), 6.78-7.15 (m, 4H, Ar-H), 7.80 & 8.40 (2bs, 2H, 2xNH); Mass: M⁺ at m/z 290. |
|     | 4-Acetamido | 190-91 | 78 | C₁₈H₁₉N₃O₃S | 57.65 | 5.70 | 12.61 | 57.41 | 5.61 | 12.30 |
|     | 196  |       |    | (333)         |        |      |      |       |      |    |

| IR(KBr): 1660 (CO); PMR(DMSO-d₆): 1.00-1.15 (t, 3H, CH₃), 2.25 (s, 3H, NHCOCH₃), 2.30 (s, 3H, CH₃), 3.81-4.06 (q, 2H, CH₂), 5.19 (bs, 1H, CH), 7.39-7.50 (dd, 2H, 3 & 5 Ar-H, Jo = 9Hz, Jm = 2Hz), 8.12-8.23 (dd, 2H, 2 & 6 Ar-H, Jo = 9Hz, Jm = 2Hz); Mass: M⁺ at m/z 333. |
|     | 4-NO₂ | 171-72 | 65 | C₁₄H₁₅N₃O₄S | 52.33 | 4.67 | 13.08 | 52.31 | 4.41 | 13.38 |
|     | 197  |       |    | (321)         |        |      |      |       |      |    |

| IR(KBr): 1660 (CO); PMR(CDCl₃): 0.99-1.14 (t, 3H, CH₃), 2.29 (s, 3H, CH₃), 3.85-4.09 (q, 2H, CH₂), 5.26 (bs, 1H, CH), 7.38-7.49 (dd, 2H, 3 & 5 Ar-H, Jo = 9Hz, Jm = 2Hz), 8.09-8.21 (dd, 2H, 2 & 6 Ar-H, Jo = 9Hz, Jm = 2Hz); Mass: M⁺ at m/z 321. |
|     | 172  |       |    |               |        |      |      |       |      |    |
Table 23:

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<td>SCh₃</td>
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<td>75</td>
<td>C₁₅H₁₈N₂O₂S (290)</td>
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<td>41</td>
<td>C₁₉H₂₆N₂O₂ (342)</td>
<td>66.66</td>
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</table>

IR(KBr): 1660 (CO); PMR(CDC₁₃): 1.04-1.20 (t, 3H, CH₃), 2.28 (s, 3H, CH₃), 2.37 (s, 3H, S-CH₃), 3.90-4.13 (q, 2H, CH₂), 5.54 (s, 1H, CH), 7.20 (m, 5H, Ar-H); Mass: M⁺ at m/z 290.

IR(NEAT): 1650 (CO); PMR(CCl₄): 0.99-1.13 (t, 3H, CH₃), 2.00-2.40 (m, 10H, 2xCH₂, CH₃ & NCH₃), 3.10-3.52 (m, 4H, 2xCH₂), 3.69-3.98 (q, 2H, CH₂), 5.17 (s, 1H, CH), 7.00-7.19 (bs, 5H, Ar-H); Mass: M⁺ at m/z 342.
### Table 24:

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<td>202</td>
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<td>108</td>
<td>45</td>
<td>$\text{C}<em>{16}\text{H}</em>{16}\text{N}<em>{2}\text{O}</em>{3}\text{S}$ (316)</td>
<td>60.75</td>
<td>5.06</td>
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**IR (KBr):** 1720 & 1760 (CO); **PMR (CDCl$_3$):** 1.01-1.19 (t, 3H, CH$_3$), 2.43 (s, 3H, CH$_3$), 3.70 (s, 2H, CH$_2$), 3.90-4.13 (q, 2H, CH$_2$), 6.00 (s, 1H, CH), 7.18-7.38 (bs, 5H, Ar-H); **Mass:** M$^+$ at m/z 316.

203 3,4-Dimethoxy oil 42 $\text{C}_{18}\text{H}_{20}\text{N}_{2}\text{O}_{5}$ (376) 57.44 5.31 7.44 57.28 5.45 7.61

**IR (Nujol):** 1720 & 1760 (CO); **PMR (CDCl$_3$):** 1.02-1.18 (t, 2H, CH$_3$), 2.32 (s, 3H, CH$_3$), 3.59 (s, 2H, CH$_2$), 3.65 & 3.69 (2s, 6H, 2xOCH$_3$), 3.83-4.06 (q, 2H, CH$_2$), 5.73 (s, 1H, CH), 6.57-6.74 (m, 3H, Ar-H); **Mass:** M$^+$ at m/z 376.

204 4-OMe oil 40 $\text{C}_{17}\text{H}_{18}\text{N}_{2}\text{O}_{4}$ (346) 58.95 5.20 8.09 58.81 5.48 8.12
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<td>175</td>
<td>101-1.18 (t, 3H, CH₃), 2.34 (s, 3H, CH₃), 3.58 (s, 2H, CH₂), 3.66 (s, 3H, OCH₃), 3.83-4.08 (q, 2H, CH₂), 5.78 (s, 1H, CH), 6.58-6.69 (dd, 2H, 3 &amp; 5 Ar-H), Jₒ = 9Hz, Jₘ = 2Hz), 7.01-7.13 (dd, 2H, 2 &amp; 6 Ar-H), Jₒ = 9Hz, Jₘ = 2Hz); Mass: M⁺ at m/z 346.</td>
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<td>205</td>
<td>3-CH₃</td>
<td>oil</td>
<td>45 C₁₇H₁₈N₂O₃S</td>
<td>61.81</td>
<td>5.45</td>
<td>8.48</td>
<td>61.62</td>
<td>5.31</td>
<td>8.24</td>
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<td>1720 &amp; 1750 (CO); PMR(CCl₄): 0.98-1.13 (t, 3H, CH₃), 2.21 &amp; 2.24 (2s, 6H, 2xCH₃), 3.60 (s, 2H, CH₂), 3.84-4.08 (q, 2H, CH₂), 5.75 (s, 1H, CH), 6.77-7.16 (m, 4H, Ar-H); Mass: M⁺ at m/z 330.</td>
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Table 25:

![Chemical structure](image)

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<td>206</td>
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<td>C_{17}H_{20}N_{2}O_{5}S</td>
<td>57.48 5.38 8.38 57.78 5.41 8.52</td>
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IR(KBr): 1660 & 1720 (CO); PMR(CDC_{3}+DMSO-d_{6}): 1.01-1.18 (t, 3H, CH_{3}), 2.28 (s, 3H, CH_{3}), 3.17 (s, 2H, CH_{2}), 3.87-4.10 (q, 2H, CH_{2}), 5.22-5.24 (d, 1H, CH), 7.23 (m, 5H, Ar-H), 8.92 (bs 1H, NH); Mass: M^{+} at m/z 334.

207 4-OMe 180-81 81 C_{17}H_{20}N_{2}O_{5}S (364)

IR(KBr): 1660 & 1720 (CO); PMR(DMSO-d_{6}): 0.98-1.12 (t, 3H, CH_{3}), 2.21 (s, 3H, CH_{3}), 3.30 (s, 2H, CH_{2}), 3.68 (s, 3H, OCH_{3}), 3.81-4.04 (q, 2H, CH_{2}), 5.05-5.08 (d, H, CH), 6.77-6.88 (dd, 2H, 3 & 5 Ar-H, Jo = 9Hz, Jm = 2Hz), 7.08-7.19 (dd, 2H, 2 & 6 Ar-H, Jo = 9Hz, Jm = 2Hz), 9.06 (bs, 1H, NH); Mass: M^{+} at m/z 364.
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<td><strong>208</strong></td>
<td>4-Acetamido</td>
<td>220-21</td>
<td>75</td>
<td>C\textsubscript{18}H\textsubscript{21}N\textsubscript{3}O\textsubscript{5}S</td>
<td>55.24</td>
<td>5.37</td>
<td>10.74</td>
<td>55.01</td>
<td>5.61</td>
<td>10.29</td>
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IR(KBr): 1660 & 1720 (CO); PMR(DMSO-\textit{d}_6): 0.94-1.10 (t, 3H, CH\textsubscript{3}), 1.95 (s, 3H, CH\textsubscript{3}), 2.21 (s, 3H, NHCOCH\textsubscript{3}), 3.28 (s, 2H, CH\textsubscript{2}), 3.80-4.02 (q, 2H, CH\textsubscript{2}), 5.02 (s, 1H, CH), 6.98-7.09 (dd, 2H, 3 & 5 Ar-H, Jo = 9Hz, Jm = 2Hz), 7.35-7.47 (dd, 2H, 2 & 6 Ar-H, Jo = 9Hz, Jm = 2Hz); Mass: M\textsuperscript{+} at m/z 391.
Table 26:

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<td>212</td>
<td>CO₂C₂H₅</td>
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<td>C₁₅H₁₆N₂O₂S</td>
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<td>(288)</td>
<td>62.50</td>
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<td>IR(Neat):</td>
<td>1640 (CO); PMR(CCl₄): 0.76-1.03 (t, 3H, CH₃), 2.43 &amp; 2.46 (2s, 6H, CH₃ &amp; S-CH₃), 3.80-4.16 (q, 2H, CH₂), 7.06-7.66 (m, 5H, Ar-H); Mass: M⁺ at m/z 288.</td>
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<td>215</td>
<td>CH₃</td>
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<td>C₁₃H₁₄N₂S</td>
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<td>(230)</td>
<td>67.82</td>
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<td>PMR(CDCl₃): 2.10 (s, 3H, CH₃), 2.40 (s, 3H, CH₃), 2.47 (s, 3H, S-CH₃), 7.32-7.50 (m, 5H, Ar-H); Mass: M⁺ at m/z 230.</td>
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<tr>
<td>216</td>
<td>CH₂OH</td>
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<td>25</td>
<td>C₁₃H₁₄N₂OS</td>
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<td>(246)</td>
<td>63.41</td>
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<td><strong>IR(KBr): 3330 (OH); PMR(CDC\textsubscript{3}): 2.52 (s, 3H, CH\textsubscript{3}), 2.59 (s, 3H, S-CH\textsubscript{3}), 4.55 (s, 2H, CH\textsubscript{2}), 7.32-7.65 (m, 5H, Ar-H); Mass: M\textsuperscript{+} at m/z 246.</strong></td>
<td>CHO</td>
<td>120</td>
<td>60</td>
<td>C\textsubscript{13}H\textsubscript{12}N\textsubscript{2}OS</td>
<td>63.93</td>
<td>4.91</td>
<td>11.47</td>
<td>64.21</td>
<td>4.74</td>
<td>11.30</td>
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<td><strong>IR(KBr): 1700 (CO); PMR(CDC\textsubscript{3}): 2.56 (s, 3H, CH\textsubscript{3}), 2.71 (s, 3H, S-CH\textsubscript{3}), 7.30-7.69 (m, 5H, Ar-H), 9.95 (s, 1H, CHO); Mass: M\textsuperscript{+} at m/z 244.</strong></td>
<td>CH\textsubscript{2}Br</td>
<td>118</td>
<td>55</td>
<td>C\textsubscript{13}H\textsubscript{13}BrN\textsubscript{2}S</td>
<td>50.64</td>
<td>4.22</td>
<td>9.09</td>
<td>51.19</td>
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<td><strong>PMR(CDC\textsubscript{3}): 2.58 (s, 3H, CH\textsubscript{3}), 2.64 (s, 3H, S-CH\textsubscript{3}), 4.42 (s, 2H, CH\textsubscript{2}), 7.31-7.70 (m, 5H, Ar-H); Mass: M\textsuperscript{+} at m/z 308.</strong></td>
<td>H\textsubscript{2}CHN-\fbox{\textsubscript{NO\textsubscript{2}}}</td>
<td>223-24</td>
<td>65</td>
<td>C\textsubscript{19}H\textsubscript{19}N\textsubscript{5}O\textsubscript{2}S</td>
<td>59.84</td>
<td>4.98</td>
<td>18.37</td>
<td>60.10</td>
<td>5.31</td>
<td>18.14</td>
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<td><strong>PMR(CDC\textsubscript{3}): 2.52 (s, 6H, 2xCH\textsubscript{3}), 4.08 (s, 2H, CH\textsubscript{2}), 6.63-7.59 (m, 8H, Ar-H); Mass: M\textsuperscript{+} at m/z 381.</strong></td>
<td>H\textsubscript{2}CHN-\fbox{\textsubscript{CO\textsubscript{2}Me}}</td>
<td>200-1</td>
<td>75</td>
<td>C\textsubscript{22}H\textsubscript{22}N\textsubscript{6}O\textsubscript{2}S</td>
<td>60.82</td>
<td>5.06</td>
<td>19.35</td>
<td>61.21</td>
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**IR(KBr):** 1740 (CO);
**PMR(CDC$_3$):** 2.22 (s, 3H, CH$_3$), 2.50 (s, 3H, S-CH$_3$), 3.69 (s, 3H, NHCO$_2$CH$_3$), 4.01 (s, 2H, CH$_2$), 6.51-7.52 (m, 8H, Ar-H)
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<tr>
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<td>57.97</td>
<td>5.31 13.52</td>
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<td>58.31 5.33</td>
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<td>IR(KBr):</td>
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<td>79</td>
<td>90</td>
<td>C_{12}H_{15}N_{3}O_{4} (265)</td>
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<td>IR(KBr): 1720 (CO); PMR(CCl_{4}+CDCl_{3}): 3.53 &amp; 3.63 (2s, 6H, NCO_{2}CH_{3} &amp; NHCO_{2}CH_{3}), 4.43-4.52 (d, 2H, CH_{2}), 7.00-7.30 (m, 5H, Ar-H), 8.30-8.60 (m, 1H, NH); Mass: M^+ at m/z 265.</td>
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<td>C_{13}H_{15}N_{3}O_{6} (309)</td>
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<td>C_{14}H_{19}N_{3}O_{6} (325)</td>
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<td>3,4-Dimethoxy</td>
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<td>IR(KBr): 1730 (CO); PMR(CDCl_{3}): 3.64 &amp; 3.68 (2s, 6H, NCO_{2}CH_{3} &amp; NHCO_{2}CH_{3}), 3.78 (s, 6H, 2xOCH_{3}), 4.43-4.50 (d, 2H, CH_{2}), 6.65-6.89 (m, 3H, Ar-H), 8.35-8.05 (bs, 1H, NH); Mass: M^+ at m/z 225.</td>
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<td>233</td>
<td>H</td>
<td>115</td>
<td>65</td>
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<td>C_{13}H_{16}N_{2}O_{4}</td>
<td>59.09 6.06</td>
<td>10.60 59.33 6.00 10.44</td>
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<td>IR(KBr): 1678 (CO); PMR(CDC\textsubscript{13}): 2.02 (s, 3H, CH\textsubscript{3}), 3.46 (s, 3H, CO\textsubscript{2}CH\textsubscript{3}), 4.47-4.70 (m, 1H, CH), 4.89-5.02 (m, 2H, CH), 7.01-7.20 (bs, 5H, Ar-H); Mass: M\textsuperscript{+} at m/z 264.</td>
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<tr>
<td>234</td>
<td>3,4-Dimethoxy</td>
<td>101-2</td>
<td>87</td>
<td></td>
<td>C_{15}H_{20}N_{2}O_{6}</td>
<td>55.55 6.17</td>
<td>8.64 55.95 5.71 8.41</td>
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<td>IR(KBr): 1680 (CO); PMR(CCl\textsubscript{4} + CDC\textsubscript{13}): 2.09 (s, 3H, CH\textsubscript{3}), 3.58 (s, 3H, CO\textsubscript{2}CH\textsubscript{3}), 3.80 (s, 6H, 2xOCH\textsubscript{3}), 4.41-4.69 (m, 1H, CH), 4.83-5.05 (m, 2H, CH\textsubscript{2}), 6.60-6.73 (m, 3H, Ar-H); Mass: M\textsuperscript{+} at m/z 324.</td>
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<tr>
<td>235</td>
<td>4-OCH\textsubscript{3}</td>
<td>128-30</td>
<td>48</td>
<td></td>
<td>C_{14}H_{18}N_{2}O_{5}</td>
<td>57.14 6.12</td>
<td>9.52 57.31 6.50 9.68</td>
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<td>IR(KBr): 1670 (CO); PMR(CDC\textsubscript{13}): 2.01 (s, 3H, CH\textsubscript{3}), 3.50 (s, 3H, CO\textsubscript{2}CH\textsubscript{3}), 3.68 (s, 3H, OCH\textsubscript{3}), 4.38-4.70 (m, 1H, CH), 4.80-5.02 (m, 2H, CH\textsubscript{2}), 6.63-7.74 (dd, 2H, 3 &amp; 5 Ar-H, Jo = 9Hz, Jm = 2Hz), 6.92-7.03 (dd, 2H, 2 &amp; 5 Ar-H, Jo = 9Hz, Jm = 2Hz); Mass: M\textsuperscript{+} at m/z 249.</td>
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<tr>
<td>236</td>
<td>4-NO₂</td>
<td>135-36</td>
<td>70</td>
<td>C₁₃H₁₅N₃O₆</td>
<td>50.48</td>
<td>4.85</td>
<td>13.59</td>
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IR(KBr): 1670 (CO); PMR(CDCl₃): 2.10 (s, 3H, CH₃), 3.44 (s, 3H, CO₂CH₃), 4.53-4.80 (m, 1H, CH), 4.89-5.09 (m, 2H, CH₂), 7.17-7.28 (dd, 2H, 3 & 5 Ar-H, Jₐ = 9Hz, Jₘ = 2Hz), 7.96-8.07 (dd, 2H, 2 & 6 Ar-H, J₀ = 9 Hz, Jₘ = 2Hz); Mass: M⁺ at m/z 309.
Table 30:

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<th>Compd. No.</th>
<th>R</th>
<th>R₁</th>
<th>X</th>
<th>m.p. °C</th>
<th>Yield %</th>
<th>Mol. Formula</th>
<th>Mol. Wt.</th>
<th>Analysis %</th>
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<td>Found</td>
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<tr>
<td>237</td>
<td>H</td>
<td>H</td>
<td>NOH</td>
<td>158</td>
<td>85</td>
<td>C₁₃H₁₆N₂O₅</td>
<td>(280)</td>
<td>55.71</td>
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<td>IR(KBr): 1730 (CO); PMR(CDC1₃); 1.88 (s, 3H, CH₃), 3.33 (s, 3H, CO₂CH₃), 3.90-4.22 (m, 2H, 2×CH), 4.48-4.54 (d, 2H, CH₂), 7.05-7.29 (m, 5H, Ar-H); Mass: M⁺ at m/z 280.</td>
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<tr>
<td>238</td>
<td>3,4-Di-</td>
<td>methoxy</td>
<td>NOH</td>
<td>100-102</td>
<td>76</td>
<td>C₁₅H₂₀N₂O₇</td>
<td>(340)</td>
<td>52.94</td>
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<td>IR(KBr): 1735 (CO); PMR(CDC1₃); 1.92 (s, 3H, CH₃), 3.41 (s, 3H, CO₂CH₃), 3.77 (s, 6H, 2×OCH₃), 3.99-4.22 (m, 2H, 2×CH), 4.50-4.57 (d, 2H, CH₂), 6.67-6.78 (m, 3H, Ar-H); Mass: M⁺ at m/z 340.</td>
</tr>
<tr>
<td>239</td>
<td>4-Me-</td>
<td>methoxy</td>
<td>NOH</td>
<td>70</td>
<td>96</td>
<td>C₁₄H₁₈N₂O₆</td>
<td>(310)</td>
<td>54.19</td>
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<td>IR(KBr): 1710 (CO); PMR(400 MHz, DMSO-d₆); 1.80 (s, 3H, CH₃), 3.30 (s, 3H, CO₂CH₃), 3.69 (s, 3H, OCH₃), 3.71-3.73 (d, 1H, CH), 3.82-3.95 (m, 1H, CH), 4.69-4.79 (m, 2H, CH₂), 6.78-6.80 (d, 2H, 3 &amp; 5 Ar-H, J₀ = 7.2Hz), 7.19-7.22 (d, 2H, 2 &amp; 6 Ar-H, J₀ = 7.2Hz); ¹³C-NMR(DMSO-d₆); 12.05 (q, CH₃), 42.23 (d, CH), 51.63 (q, CO₂CH₃), 54.54 (d, CHCO₂CH₃), 54.85 (q, OCH₃), 78.16 (t, CH₂), 158.51 (s, C=N), 169.55 (s, CO₂CH₃), 113.66, 129.24, 129.25 &amp; 150.55 (Ar-C); Mass: M⁺ at m/z 310.</td>
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<tr>
<td>240</td>
<td>H</td>
<td>H</td>
<td>O</td>
<td>77</td>
<td>87</td>
<td>C_{13}H_{15}NO_{5}</td>
<td>58.86</td>
<td>5.66</td>
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<tr>
<td>IR(KBr):</td>
<td>1715 &amp; 1730 (CO); PMR(CCl_{4}):</td>
<td>1.89 &amp; 2.11 (2s, 3H, CH_{3}), 3.36 &amp; 3.60 (2s, 3H, CO_{2}CH_{3}), 3.90-4.10 (m, 2H, CH_{2}), 4.51-4.70 (m, 2H, 2xCH), 7.00-7.20 (bs, 5H, Ar-H); Mass: M^{+} at m/z 265.</td>
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<tr>
<td>241</td>
<td>3,4-Di-</td>
<td>H</td>
<td>O</td>
<td>240-41</td>
<td>68</td>
<td>C_{15}H_{19}NO_{7}</td>
<td>55.38</td>
<td>5.84</td>
</tr>
<tr>
<td>IR(KBr):</td>
<td>1710 &amp; 1730 (CO); PMR(CDCl_{3}):</td>
<td>2.01 &amp; 2.24 (2s, 3H, CH_{3}), 3.50 &amp; 3.71 (2s, 3H, CO_{2}CH_{3}), 3.80 (s, 6H, 2xOCH_{3}), 3.98-4.12 (m, 2H, CH_{2}), 4.60-4.79 (m, 2H, 2xCH), 6.58-6.81 (m, 3H, Ar-H); Mass: M^{+} at m/z 325.</td>
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<tr>
<td>242</td>
<td>4-OCH_{3}</td>
<td>H</td>
<td>O</td>
<td>Oil</td>
<td>76</td>
<td>C_{14}H_{17}NO_{6}</td>
<td>56.91</td>
<td>5.76</td>
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<td>IR(Neat):</td>
<td>1720 &amp; 1730 (CO); PMR(CDCl_{3}):</td>
<td>1.97 &amp; 2.19 (2s, 3H, CH_{3}), 3.44 &amp; 3.69 (2s, 6H, CO_{2}CH_{3} &amp; OCH_{3}), 3.89-4.10 (m, 2H, CH_{2}), 4.59-4.74 (m, 2H, 2xCH), 6.68-6.80 (dd, 2H, 3 &amp; 5 Ar-H, Jo = 9Hz, Jm = 2Hz), 6.96-7.09 (dd, 2H, 2 &amp; 6 Ar-H, Jo = 9Hz, Jm = 3Hz); Mass: M^{+} at m/z 295.</td>
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<tr>
<td>243</td>
<td>H</td>
<td>OH</td>
<td>O</td>
<td>94-95</td>
<td>86</td>
<td>C_{13}H_{15}NO_{6}</td>
<td>55.51</td>
<td>5.33</td>
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<tr>
<td>IR(KBr):</td>
<td>1720 (CO); PMR(CDCl_{3}+DMSO-d_{6}):</td>
<td>2.17 (s, 3H, CH_{3}), 3.40 (s, 3H, CO_{2}CH_{3}), 3.70 (s, 1H, OH), 4.34-4.64 (m, 3H, CH &amp; CH_{2}), 7.09-7.30 (m, 5H, Ar-H); Mass: M^{+} at m/z 281.</td>
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<tr>
<td>244</td>
<td>3,4-Di-</td>
<td>OH</td>
<td>O</td>
<td>186-87</td>
<td>81</td>
<td>C_{15}H_{19}NO_{8}</td>
<td>52.78</td>
<td>5.57</td>
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<tr>
<td>IR(KBr):</td>
<td>1720 (CO); PMR(CDCl₃):</td>
<td>2.20 (s, 3H, CH₃), 3.49 (s, 3H, CO₂CH₃), 3.37 (s, 6H, 2xOCH₃), 4.15-4.23 (bs, 1H, OH), 4.22-4.58 (m, 3H, CH &amp; CH₂), 6.58-6.81 (m, 3H, Ar-H); Mass: M⁺ at m/z 341.</td>
<td>245</td>
<td>4-OCH₃</td>
<td>OH</td>
<td>O</td>
<td>139</td>
<td>86</td>
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<td>IR(KBr):</td>
<td>1735 (CO); PMR(CDCl₃):</td>
<td>2.22 (s, 3H, CH₃), 3.50 (s, 3H, CO₂CH₃), 3.68 (s, 3H, OCH₃), 4.22 (s, 1H, OH), 4.38-4.72 (m, 3H, CH &amp; CH₂), 6.63-6.74 (dd, 2H, 3 &amp; 5 Ar-H, Jo = 9Hz, Jm = 2Hz), 7.08-7.19 (dd, 2H, 2 &amp; 6 Ar-H, Jo = 9Hz, Jm = 2Hz); ¹³C-NMR(DMSO-d₆): 25.34 (q, CH₃), 46.19 (d, CH), 52.59 (q, CO₂CH₃), 54.84 (q, OCH₃), 76.62 (t, CH₂), 85.54 (s, COH), 168.62 (s, CO₂CH₃), 204.05 (s, COCH₃), 113.30, 126.90, 130.16 &amp; 158.78 (Ar-C); Mass: M⁺ at m/z 311.</td>
<td>246</td>
<td>4-NO₂</td>
<td>OH</td>
<td>O</td>
<td>122-23</td>
<td>68</td>
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<tr>
<td>IR(KBr):</td>
<td>1720 (CO); PMR(CDCl₃)+DMSO-d₆:</td>
<td>2.19 (s, 3H, CH₃), 3.42 (s, 3H, CO₂CH₃), 4.40-4.71 (m, 3H, CH &amp; CH₂), 7.42-7.53 (dd, 2H, 3 &amp; 5 Ar-H, Jo = 9Hz, Jm = 2Hz), 7.92-8.04 (dd, 2H, 2 &amp; 6 Ar-H, Jo = 9Hz, Jm = 2Hz); Mass: M⁺ at m/z 326.</td>
<td>247</td>
<td>H</td>
<td>OH</td>
<td>NOH</td>
<td>110</td>
<td>85</td>
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<tr>
<td>IR(KBr):</td>
<td>1720 (CO); PMR(CDCl₃)+DMSO-d₆:</td>
<td>1.70 (s, 3H, CH₃), 3.38 (s, 3H, CO₂CH₃), 3.61 (s, 1H, OH), 4.26-4.51 (m, 3H, CH &amp; CH₂), 7.00-7.25 (m, 5H, Ar-H); Mass: M⁺ at m/z 296.</td>
<td>248</td>
<td>4-OMe</td>
<td>OH</td>
<td>NOH</td>
<td>137</td>
<td>95</td>
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</table>
IR(KBr): 1720 (CO); PMR(400 MHz, DMSO-d$_6$): 1.75 (s, 3H, CH$_3$), 3.36 (s, 3H, CO$_2$CH$_3$), 3.58 (s, 3H, OCH$_3$),
4.00 (s, 1H, OH), 4.25-4.35 (dd, 1H, CH-NO$_2$), 4.69-4.80 (t, 1H, CH), 4.95-5.04 (dd, 1H, CH-NO$_2$), 6.76-
6.79 (d, 2H, 3 & 5 Ar-H, Jo = 8.8 Hz), 7.16-7.19 (d, 2H, 2 & 6 Ar-H, Jo = 8.8 Hz); $^{13}$C-NMR(DMSO-d$_6$):
9.97 (q, CH$_3$), 46.03 (d, CH), 52.18 (q, CO$_2$CH$_3$), 54.81 (q, OCH$_3$), 77.41 (t, CH$_2$), 80.89 (s, COH), 158.66
(s, C=NOH), 170.86 (CO$_2$CH$_3$), 113.30, 127.14, 130.30 & 153.50 (Ar-C); Mass: M$^+$ at m/z 326.
6.3 BIOLOGICAL ACTIVITY

The compounds synthesized were tested for their in vivo antifilarial activity against *Litomosoides carinii* in cotton rats, cestocidal activity against *Hymenolepis nana* infection in mice and rats. Nematocidal activity against *Ancylostoma ceylanicum* in hamsters and against *Nippostrongylus brasiliensis* in rats in the division of parasitology of this institute.

METHOD OF ANTHELMINTIC SCREENING

1. Antifilarial screening of Compounds:

   *Litomosoides carinii* infection in cotton rat (*Sigmodon hispidus*) was used as experimental model for the detection of antifilarial activity. The vector of this infection namely *Liponyssus bacoti*, obtained originally from National Institute for Medical Research, Mill Hill, London, was maintained in a room in which temperature (26°) and humidity (90%) were automatically controlled. Culturing of the vector and the propagation of infection to healthy cotton rats were carried out as per the methods of Hawking and Sewell and Sewell and Hawking.

   (a) Preliminary toxicity studies:

   Before administering any compound to infected cotton rats, the preliminary toxicity study of each compound was conducted in mice. This study helped in finding out the maximum tolerated dose (MTD) of the test compound in mice. One fifth of the MTD was used against cotton rat.

   (b) Selection of infected cotton rat:

   Recently infected cotton rat (3 months or so) with progressive rise in peripheral microfilariae and having count of 250 mf or more per 5 cmm of blood were used for screening.

   (c) Testing of Compounds:

   For primary screening two infected cotton rats were used for each compound at any particular dose level study. Suspension of the test compounds were made with 0.1% Tween 80 after grinding it to a fine powder. The pH of all the solutions were finally adjusted to 7.0. Infected cotton rats were injected intraperitoneally 1/5th MTD
in mice for six consecutive days. Tail blood of the animals were examined just before the commencement of treatment and thereafter at weekly interval up to 42nd day. Generally, 5 cmm of blood were taken from the tail every time and smeared on a clean glass slide. The smears were air dried, dehaemoglobinised, fixed in methanol and stained with 5% Gilmis for 1 hr in the usual way. These were then examined under high power magnification of the microscope and the number of microfilariae per cmm of blood counted. Compounds capable of cleaning 90% of the pretreatment circulating microfilariae were considered as the effective microfilaricidal. The animals were sacrificed on 42nd day (counted from the day of commencement of the treatment) and the adult filarial worms were removed from pleural cavity, kept in a petry dish containing normal saline at 37° and incubated at this temperature for 15 minutes. Animals were sacrificed and adult worms were examined for motility, cell adhesion on the surface and changes in different developmental stages of mf in the uterus. If the worms were found dead, the compound was considered as an effective adulticidal.

2. Screening against *Ancylostoma ceylanicum*

(a) Adulticidal activity:

This nematode was obtained from Sarabhai Research Centre, Baroda and each hamsters (weighing 40-60 g) was administered 50 to 60 larvae orally. The larvae were harvested 10-15 day old faecal cultures by the Baermann method. The screening technique was essentially that of Steward with slight modifications, to suit the local conditions. Animals in different groups were administered the compounds (made to suspension with Tween 80) orally in varying doses using three infected animals for each dose; the other three infected and untreated served as controls. The administration of compounds was initiated on day 18-20 of infection either in single or multiple doses on successive days. The experimental and control animals were sacrificed on day three after the last dose, their worms were counted and compared with control group of animals. The efficacy has been expressed in terms of percent worm reduction.

(b) Larvicidal activity:

Golden hamster of either sex weighing 40-60 g were inoculated orally with 60 ± 5 infective larvae (L3) and divided into several
groups, depending on the number of doses, routes of the drug adminis-
tration and the stages of parasites against which the action of the
drug was to be evaluated. L$_3$ of this parasite moults to L$_4$ on the
day 2 and L$_4$ to L$_5$ on day 5$^{234}$. The test compound and the reference
drug were administered on days 1, 3 and 6 post infection (p.i.) so
that effect on L$_3$, L$_4$ and L$_5$ stages respectively could be evaluated.
Treated and untreated hamsters were necropsied on day 20 p.i., when
worms reached maturity in the intestine.. The efficacy was expressed
in terms of absolute worm expulsion from the host and per cent worm
reduction compared to untreated controls$^{235}$.

3. Screening against *Hymenolepis nana*:

(a) Adulticidal activity:

The screening technique followed was essentially that of Ste­
ward$^{232}$ with modifications as described by Gupta et al$^{233}$. The test
compounds were screened in male swiss mice (18-20 g) and male albino
rats (40-45 g). The experimental animals were infected with 20 viable
eggs and 17-20 days after infection, the faeces of the individual ani­
mal was examined for the presence of eggs and those found infected,
were used for screening. The animals were then colour marked, weighed
and divided into groups of three animals, each for different compounds
under test. The compounds synthesized were administered initially
at a dose of 250 mg/kg x 3 (given for three consecutive days). Inso­
luble compounds were made into fine suspension with the help of
Tween 80 (the amount used just to moisten the compound), gumaccacia
or 0.1% agar. The experimental animals received the initial dose of
the test compounds, after they were starved for 6 hr. On day three
post-treatment, the animals did not receive any food for 5-6 hr before
they were sacrificed for assessing their worm burden. The intestine
from each animal was removed, washed with normal saline and examined
for worms and scolices under dissecting microscope. Absolute clearance
of parasite along with scolices from individual mice was taken as
the criterian for assessing the activity. Even, if a single scolex
or worm remained in the intestine, the drug at that dose was consi­
dered in-effective for that particular animal (because the range of
adult worms maturing from a particular inoculum is very wide). The
percentage efficacy of the compound was obtained from the number
of treated animals freed from infection and those which did not res­
pond to the drug treatment.
The compound showing activity at the initial dose level, were pursued further in lower doses till a reasonable activity was retained by the compound.

4. Screening against *Nippostrongylus brasiliensis*:

Young male rats of university of Freiburg strain weighing 25-40 g were used as the host of *N. brasiliensis*. This parasite was originally obtained from Wellcome Laboratory, Bechenham, London. Rats were infected by inoculating 500 infective larvae each (harvested from 6-10 day old copro-cultures) sub-cutaneously.

The screening technique was essentially same as described for *A. ceylanicum* (adulticidal) but in the case of *N. brasiliensis*, the administration of compounds was initiated on day 9 post-infection either in single or multiple doses on successive days.

**Parameters selected for identifying active compounds**

The death of the adult worms was the primary parameter for monitoring the antifilarial activity. The percentage of worm clearance (PWC) was monitored for evaluating compounds against *A. ceylanicum* infection. If PWC was less than 100 at a single dose of 250 mg/kg, the compounds were considered as less active and were not evaluated further. In cases where PWC was less than 50, the compounds were considered as inactive against this infection. For evaluating compounds against *H. nana* infection, the total clearance of scolex was taken into consideration. In cases where scolex was not eliminated (SNE), the compound was considered as inactive and the complete absence of scolex was considered as 100% activity.

**Profile of anthelmintic activity of the various compounds synthesized**

Almost all the compounds were evaluated for their antifilarial activity against *Litomosoides carinii* in cotton rats, nematocidal activity against *Ancylostoma ceylanicum* in hamsters and against *Nippostrongylus brasiliensis* in rats and cestocidal activity against *Hymenolepis nana* in mice and rats. Only the active compounds have been described in tables 31 and 34. Of these two compounds (159 and 185) had been picked up for larvicidal activity and the results are described in tables 32 and 33.
Table 31: Activity of Compounds against *A. ceylanicum* (in hamsters) and *N. brasiliensis* (in rats) infections.

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>A. ceylanicum</th>
<th>N. brasiliensis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dose mg/kg</td>
<td>Activity %</td>
</tr>
<tr>
<td><strong>125</strong></td>
<td>250 x 1 100</td>
<td>250 x 1 0</td>
</tr>
<tr>
<td></td>
<td>50 x 1 0</td>
<td>--</td>
</tr>
<tr>
<td><strong>159</strong></td>
<td>250 x 1 100</td>
<td>250 x 1 100</td>
</tr>
<tr>
<td></td>
<td>100 x 1 100</td>
<td>100 x 1 100</td>
</tr>
<tr>
<td></td>
<td>50 x 1 97.22</td>
<td>50 x 1 97.2</td>
</tr>
<tr>
<td></td>
<td>12.25 x 1 77.78</td>
<td>12.25 x 1 77.7</td>
</tr>
<tr>
<td></td>
<td>6.12 x 1 27.77</td>
<td>6.12 x 1 27.77</td>
</tr>
<tr>
<td><strong>160</strong></td>
<td>250 x 1 80.00</td>
<td>250 x 1 0.0</td>
</tr>
<tr>
<td><strong>177</strong></td>
<td>250 x 1 80.00</td>
<td>250 x 1 0.00</td>
</tr>
<tr>
<td><strong>185</strong></td>
<td>250 x 1 100</td>
<td>250 x 1 100</td>
</tr>
<tr>
<td></td>
<td>100 x 1 100</td>
<td>100 x 1 100</td>
</tr>
<tr>
<td></td>
<td>50 x 1 100</td>
<td>50 x 1 100</td>
</tr>
<tr>
<td></td>
<td>25 x 1 100</td>
<td>25 x 1 100</td>
</tr>
<tr>
<td></td>
<td>12.5 x 1 91</td>
<td>12.5 x 1 91</td>
</tr>
<tr>
<td></td>
<td>6.25 x 1 83.06</td>
<td>6.25 x 1 83</td>
</tr>
<tr>
<td></td>
<td>3.12 x 1 78.46</td>
<td>3.12 x 1 78</td>
</tr>
<tr>
<td><strong>221</strong></td>
<td>250 x 1 100</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>100 x 1 0</td>
<td>--</td>
</tr>
<tr>
<td><strong>232</strong></td>
<td>250 x 1 100</td>
<td>250 x 1 0</td>
</tr>
<tr>
<td></td>
<td>100 x 1 100</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>50 x 1 50</td>
<td>--</td>
</tr>
</tbody>
</table>
Table 32: Efficacy of compound 159 against developing stages of *A. ceylanicum*.

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>Stage</th>
<th>Oral</th>
<th>Intraperitoneal</th>
<th>Control mean (with range)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Animals cured/ treated (No. of expts.)</td>
<td>Percent animals freed from parasites (With range)</td>
<td>Worm recovery mean</td>
</tr>
<tr>
<td>250x1</td>
<td><em>L</em>₃</td>
<td>3/6(2)</td>
<td>50</td>
<td>1.33(0-4) 94</td>
</tr>
<tr>
<td>100x1</td>
<td><em>L</em>₃</td>
<td>0/10(4)</td>
<td>0</td>
<td>7.4(3-10) 74</td>
</tr>
<tr>
<td>50x1</td>
<td><em>L</em>₃</td>
<td>0/3(1)</td>
<td>0</td>
<td>6.66(6-8) 74</td>
</tr>
<tr>
<td>25x1</td>
<td><em>L</em>₃</td>
<td>0/3(1)</td>
<td>0</td>
<td>9.00(8-10) 65</td>
</tr>
<tr>
<td>250x1</td>
<td><em>L</em>₄</td>
<td>6/6(2)</td>
<td>100</td>
<td>Nil</td>
</tr>
<tr>
<td>100x1</td>
<td><em>L</em>₄</td>
<td>4/6(2)</td>
<td>66</td>
<td>0.5(1-2) 97</td>
</tr>
<tr>
<td>250x1</td>
<td><em>L</em>₅</td>
<td>6/6(2)</td>
<td>100</td>
<td>Nil</td>
</tr>
<tr>
<td>100x1</td>
<td><em>L</em>₅</td>
<td>6/6(2)</td>
<td>100</td>
<td>Nil</td>
</tr>
<tr>
<td>50x1</td>
<td><em>L</em>₅</td>
<td>0/6(2)</td>
<td>0</td>
<td>8.5(6-11) 71</td>
</tr>
</tbody>
</table>
Table 32a: Efficacy of compound 83/148 against developing stages of *A. ceylanicum*

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>Stage</th>
<th>Oral†</th>
<th>Intraperitoneal</th>
<th>Control mean (with range)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Animals cured/treated</td>
<td>Percent animals freed from parasites</td>
<td>Percent worm recovery mean (with range)</td>
</tr>
<tr>
<td>100x1</td>
<td>L₃</td>
<td>0/9(3)</td>
<td>0</td>
<td>5.33(2-8)</td>
</tr>
<tr>
<td>50x1</td>
<td>L₃</td>
<td>0/6(2)</td>
<td>0</td>
<td>9.00(3-12)</td>
</tr>
<tr>
<td>25x1</td>
<td>L₃</td>
<td>0/3(1)</td>
<td>0</td>
<td>10.00(7-14)</td>
</tr>
<tr>
<td>100x1</td>
<td>L₄</td>
<td>6/6(2)</td>
<td>100</td>
<td>Nil</td>
</tr>
<tr>
<td>50x1</td>
<td>L₄</td>
<td>0/6(2)</td>
<td>0</td>
<td>7.50(5-10)</td>
</tr>
<tr>
<td>25x1</td>
<td>L₄</td>
<td>0/3(1)</td>
<td>0</td>
<td>7.33(4-10)</td>
</tr>
<tr>
<td>100x1</td>
<td>L₅</td>
<td>6/6(2)</td>
<td>100</td>
<td>Nil</td>
</tr>
<tr>
<td>50x1</td>
<td>L₅</td>
<td>6/6(2)</td>
<td>100</td>
<td>Nil</td>
</tr>
<tr>
<td>25x1</td>
<td>L₅</td>
<td>2/6(2)</td>
<td>33.33</td>
<td>6.67(0-22)</td>
</tr>
</tbody>
</table>
### Table 33: Efficacy of compound 185 against developing stages of A. ceylanicum.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Oral</th>
<th>Intraperitoneal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dose (mg/kg)</td>
<td>Animals treated</td>
</tr>
<tr>
<td></td>
<td>250x1</td>
<td>1-2/(1-2)</td>
</tr>
<tr>
<td></td>
<td>50x1</td>
<td>0/5(2)</td>
</tr>
<tr>
<td></td>
<td>100x1</td>
<td>0/5(2)</td>
</tr>
<tr>
<td></td>
<td>50x1</td>
<td>0/5(1-4)</td>
</tr>
<tr>
<td></td>
<td>100x1</td>
<td>2/5(1-4)</td>
</tr>
<tr>
<td></td>
<td>50x1</td>
<td>5/5(2)</td>
</tr>
</tbody>
</table>
Table 34: Effect of compounds in cotton rat infected with *L. carinii*

<table>
<thead>
<tr>
<th>Compound</th>
<th>Dose (mg/kg)</th>
<th>Percent activity* against mf on day</th>
<th>Percent activity against adult worms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>8th 14th 21st 28th 42nd</td>
<td>O* Q Total</td>
</tr>
<tr>
<td>159</td>
<td>30x5 (i.p.)</td>
<td>-- -4.3 -100 -100 -100</td>
<td>Toxic</td>
</tr>
<tr>
<td>166</td>
<td>30x5 (i.p.)</td>
<td>-23.9 +8.5 -7.5 -20.5 -94.8</td>
<td>Partially active</td>
</tr>
<tr>
<td>185</td>
<td>30x5 (i.p.)</td>
<td>+31.3 -100 -100 -100 -100</td>
<td>100 100 100</td>
</tr>
</tbody>
</table>

*Average value.*
The sensitivity of pharmacophores in benzimidazole-2-carbamates for evoking anthelmintic activity is evident from the results of the biological screening listed in tables 31 and 34. For example, the oxidised form of 185 (CDRI Code No.82/437 page 115) is active as a macrofilaricidal agent by oral route of administration while the alcohol 185 fails to exhibit antifilarial activity by oral route. Yet another striking example of the effect of minor change in the pharmacophore on the profile of anthelmintic activity is obvious from the comparative study of the results of biological screening of compounds 83/148 (prepared earlier in CDRI) and 159. Replacement of the oxygen atom in the furan ring of 83/148 by a nitrogen atom (compound 159) has resulted in the abolition of antifilarial activity. However, only minor differences in the profile of biological activity against developing stages of A. ceylanicum of these compounds have been observed. A comparative study of the anthelmintic activity of 159 and 177 indicates that the orientation of the ester carbonyl, with respect to benzimidazole nucleus and the linkage of the C-5 of the benzimidazole ring significantly influence the profile of biological activity. Similarly in compounds 221 the benzimidazole nucleus is not planar with the 1,4-dihydropyridine residue and this in turn makes the orientation of the ester carbonyl different than the other compounds. Possibly this is one of the contributing factor for the diminished anthelmintic activity. The biological activity of compound 232 is interesting because in this compound the phenyl ring has been dissociated from the benzimidazole ring system and the resulting substituted imidazole-2-carbamate is capable of exhibiting specificity of anthelmintic activity. This molecule, therefore, provides a good base for undertaking lead optimisation studies and should there be a need to develop a specific antihookworm compound, this exercise may prove to be beneficial. The antifilarial activity of 185 is encouraging and calls for undertaking special drug formulation studies to induce oral absorption. The prototypes XVI, XVII, XX and XXII have failed to yield a new lead for developing an anthelmintic agent.
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