Chapter II

SYNTHESIS OF POTENTIAL NEMATODICIDAL AND CESTODICIDAL AGENTS
1. INTRODUCTION:

In 1947, when Stoll\textsuperscript{1} presented a world-wide survey of various helminth infestations in man, it was found that the number of subjects suffering from different intestinal helminths was nearly 2000 million\textsuperscript{*}. This may be attributed probably due to lack of suitable drugs and inadequate knowledge of various aspects of the disease at that time. Since then, more than three decades have passed but the number of cases with intestinal nematode and cestode infections does not seem to have declined despite several measures taken to eliminate helminthiasis from masses. It is estimated that more than 2500 million people suffer from different forms of intestinal nematode infections\textsuperscript{2,3} while more than 870 million people carry the cestode parasites\textsuperscript{2,4}.

Although the poor sanitary habits, lack of prophylaxis and prevalence of proper natural conditions for development of helminth juveniles are the main criterions for the overwhelming increase in the incidence of intestinal helminthiasis, the non-availability of an ideal anthelmintic to masses is also an important factor. An ideal anthelmintic

\textsuperscript{*}Values indicate sum of the patients infected with different nematode and cestode parasites.
for intestinal helminthiasis should be safe and have broader spectrum of activity which could be used effectively to eradicate both nematodes and cestodes, if co-existing, from the gastrointestinal tract. Such type of an anthelmintic would certainly play a vital role in the treatment of such diseases because of the high concurrence of multiple helminth infections in several tropical and sub-tropical regions of the world.

Since last fifteen years, a good progress has been made in the chemotherapy of intestinal helminthiasis. In addition, a more detailed study has been carried out directed towards the biochemistry of the helminth parasites, host-parasite relationships and mode of action of several known anthelmintics. This has greatly helped in providing better treatment of this disease in humans. The evolution of powerful anthelmintics derived from benzimidazoles, arylisothiocyanates and imidazolines has successfully eliminated several bottle-necks (such as toxicity and selective action of classical drugs) in the chemotherapy of man and domestic animals. However, the final answer to the problem has not yet been achieved. It is in this context that the pursuit to find better chemotherapeutic agents for the treatment of intestinal helminthiasis still continues.
2. **BASIS OF WORK:**

One of the most remarkable achievements in the modern chemotherapy of helminthiasis has been the recognition of benzimidazole nucleus as a useful pharmacophore for the synthesis of potent antinematode drugs. This has resulted in the discovery of a series of benzimidazole anthelmintics possessing powerful activity against different helminth parasites in man and animals.

2-Phenylbenzimidazole (1, phenzidole) is the first member of this series which has been used to treat animal helminthiasis in early 60's in combination with phenothiazine. Substitution of the phenyl residue in phenzidole by a 4-thiazolyl moiety gave thiabendazole (2) which proved to be a highly successful drug in the treatment of hookworm infections, creeping eruption and also showed antiinflammatory activity. The discovery of this broad spectrum anthelmintic stimulated research in the benzimidazole anthelmintics in various laboratories of the world. The efforts resulted in the synthesis of cambendazole (3), another congener of thiabendazole, with potent anthelmintic action, carrying a 4-thiazolyl and 1-propoxycarbonylamino function at 2 and 5-positions respectively of benzimidazole ring.
The substitution of aryl and heteroaryl group by a carbalkoxyamino function at 2-position of benzimidazole proved to be highly fruitful as several compounds (4-11) were shown to possess high cure rates against various human and animal helminth infections. The most active compounds of this series are mebendazole (5) and fenbendazole (7) which showed great promise in chemotherapy of human and animal intestinal nematodes.

Some of arylisothiocyanates such as phenylisothiocyanate (12) and 1,4-phenylenedisothiocyanate (13, bitoscanate) are highly effective in eliminating hookworm infestations from different hosts including humans.

Several diaryl sulfides and sulfones have also been shown to exhibit high cestodicidal activity from this laboratory. The most active compounds of this series are 1,4-diisothiocyanatodiphenyl sulfide (14) and sulfone (15).

Although several drugs have emerged possessing high activity against different human and animal helminth parasites, none can be an ideal as most of them either possess low therapeutic indices or if safe do not eliminate all the gastrointestinal nematodes and cestodes since mixed helminth infection is a common and concurrent
1. (Phenzidole)

2. $R = H$ (Thiabendazole)

3. $R = NHCOOCH_3$, (Cambendazole)

4. $R = Bu^R$, (Porbendazole)

5. $R = CO\text{Ph}$ (Mebendazole)

6. $R = O\text{Pr}$, (Oxibendazole)

7. $R = S\text{Ph}$, (Fenbendazole)

8. $R = S\text{OPh}$ (Oxfendazole)

9. $R = SP\text{r}$, (Albendazole)

10. $R = COC_6H_4F(P)$ (Flubendazole)

11. $R = CO\bigtriangleup$ (Ciclobendazole)

12. $R = H$

13. $R = NCS$ (Bitecanate)

14. $X = S$

15. $X = SO_2$

16. $R = \text{Different substituents}$

17. $R = CF_3$, $R^1 = H$

18. $R = H$,

19. $R^1 = \text{Substituted phenyl}$

20. $R^1 = NO_2$

21. $X = S, SO_2$
problem in several developing countries of the world. Hence, the need to develop new compounds possessing all the requirements of an ideal drug can not be overlooked.

Keeping in view, the versatality of benzimidazole nucleus in building molecules with wide-spectrum of biological activity, it was considered rational to synthesize various N-heteroarylbenzimidazoles and benzthiazoles of the type I, II* with an aim to enhance the biological profile of benzimidazoles as also to map out the minimal structural requirements for optimal activity. The synthesis of I and II was also supported by the fact that several 5(6)-acyl, aroylamino, 5-substituted phenyl and 2-trifluoromethylbenzimidazoles (16–19)12–17 show

\[ \text{I, } R = \text{CH}_3, \text{H} \]
\[ X = \text{NH, S} \]
\[ R^1 = \text{CH}_3, \text{H}, \text{NHCOOBt, SH} \]
\[ R^2 = \text{NCS, NHCOCH}_3, \text{NHC} \]

All the prototype molecules have been denoted in Roman numbers while the de facto compounds synthesized are given in Arabic numbers.
marked anthelmintic activity (Scheme 1-3)*.

The powerful anthelmintic activity exhibited by several alkyl 5(6)-substituted benzimidazole-2-carbamates (4-11)\(^3\), some of which even used to treat human helminthiasis, is thought to be due to an appropriate substituent at 5(6)-position and carbamate moiety at 2-position of benzimidazole ring. Maintaining these minimal structural requirements it was considered of interest to synthesize a series of 2,2'-benzimidazoles of the type III with different substituents at 2,2'-positions. This work was carried out to study the role of benzimidazole ring as a carrier molecule in yielding high biological activity and also to establish the structure-activity relationship in 2,5-disubstituted benzimidazoles (Scheme 4-11).

\[
\begin{align*}
\text{III, } R &= \text{H, CH}_3, \text{NHCOCOCH}_3, \text{NHCOCOEt} \\
X &= \text{S, SO}_2, \text{CO, CH}_2, \text{O}, \\
&\quad \text{SCH}_2\text{CH}_2\text{S}, \text{CON}\begin{array}{c}
\text{NCO}
\end{array}
\end{align*}
\]

Although, a large number of 2-arylbenzimidazoles such as phenzidole\(^7\), thiabendazole\(^8\), cambendazole\(^8\), HCE-33258 (20)\(^18\) have been shown to exhibit powerful anthelmintic action in human and animals, a detailed study

*Discussed in Sec.3.
directed towards exploring the biological potential of various 2-arylbenzimidazoles is still lacking. Hence, it was proposed to synthesize a series of 5(6)-phenyl-2-substituted arylbenzimidazoles and their cyclic analogs of the type IV, V (Scheme 12).

\[
\text{IV, } R = 2{-\text{NH}_2}, 4{-\text{NH}_2}, 4{-\text{NCS}} \\
4{-\text{HCOOEt}}, 4{-\text{HCOOCH}_3}
\]

\[
\text{V, } X = 0, S
\]

The demonstration of high cestodicidal activity\textsuperscript{11} of 4,4'-diisothiocyanatodiphenyl sulfide (14) and 4,4'-diisothiocyanatodiphenyl sulfone (15\textsuperscript{11}) has established a definite role of sulfide and sulfone linkage in helminth chemotherapy. This fact was further supported by introduction of fenbendazole (7\textsuperscript{8}) as a broad spectrum anthelmintic and 2-arylthio and sulfono benzimidazoles (21\textsuperscript{1}) reported by earlier workers in this laboratory with high cestodicidal activity\textsuperscript{19}. These observations led us to synthesize various substituted diaryl sulfides and sulfones and their related compounds of the type VI where one of the aryls of 14 and 15 has been replaced by more versatile benzimidazole pharmacophore and to
evaluate their biological activities (Scheme 13 and 14).

\[
\begin{align*}
&\text{VI, } R = \text{H, CH}_3, \text{NHCOOCH}_3, \text{NHCOOEt} \\
&X = S, \text{SO}_2, O \\
&R^1 = \text{NHAC, NH}_2, \text{NCS}
\end{align*}
\]

Synthesis of higher homolog of fenbendazole (7)\(^8\) and its oxygen analog was also undertaken in order to evaluate the change in its biological activity by introduction of a CH\(_2\) unit at 5-position of benzimidazole ring (VII) (Scheme 15).

\[
\begin{align*}
&\text{VII, } R = \text{CH}_3, \text{C}_2\text{H}_5, X = O, S
\end{align*}
\]

The high cestodicidal activity of 14 and 15 prompted us for a further probe in this direction. Hence, few more diisothiocyanatodiaryl sulfides and sulfones of the type VIII were prepared and evaluated for their cestodicidal activity where the distance between two arylthio and sulfono functions is increased by introduction of two or three CH\(_2\) units. Some other active pharmacophores such
as 1,4-dicarbonylpiperazine and 1-carbonylpiperazine have also been introduced between two phenyl rings (VIII) and the change in activity was studied (Scheme 16, and 20).

\[
\text{VIII, } R = \text{NHAc, NH}_2, \text{NO}_2, \text{NCS} \\
X = \text{S(CH}_2)_n\text{S, SO}_2\text{(CH}_2)_n\text{SO}_2, n = 2, 3
\]

\[
\text{CON}, \text{CON}\text{NCO}
\]

Despite 1,4-phenylenediisothiocyanate (13, bitoscanate) has been used to treat various hookworm infections\textsuperscript{10}, it has some serious side effects and is also toxic to animals. Hence its clinical acceptibility is still doubtful and conflicting views have been reported\textsuperscript{20}. This led us to carry out some structural changes in the parent molecule by introduction of either piperazine or benzimidazole residues, which are accepted pharmacophores in antinematode drugs, on either side of isothiocyanato function. This is in conjunction with the facts that some of the arylthioureas and ureas show marked anthelmintic activity\textsuperscript{21,22}. Thus, the compounds of the types IX-XI were synthesized and screened for their antihookworm activity (Scheme 17 and 18).
During the reaction of thiocarboxamides, thioamide and thioureas with thiophosgene, the unusual desulphurization of these compounds was observed which was studied in detail by converting a number of thiocarboxamides, thioamide and thioureas into their corresponding carboxamides, amide and ureas. The mechanism of desulphurization has also been discussed (Scheme 19).
3. CHEMISTRY:

3.1 Synthesis of 2-substituted 5(6)-N-heteroarylbenzimidazoles

Benzimidazole (22) and 2-methylbenzimidazole (23), obtained by reaction of o-phenylenediamine with formic and acetic acids, were nitrated using HNO₃-H₂SO₄ mixture to give 5(6)-nitrobenzimidazole (24) and 2-methyl-5(6)-nitrobenzimidazole (25). Catalytic hydrogenation of 24 and 25 using Raney-nickel in a Parr hydrogenator afforded the respective 5(6)-aminobenzimidazoles (26 and 27), which were condensed with 2,4-dinitrochlorobenzene in ethanol in presence of triethylamine to yield 5(6)-(2,4-dinitrophenyl)aminobenzimidazole (28) and 2-methyl-5(6)-(2,4-dinitrophenyl)aminobenzimidazole (29) respectively. Hydrogenation of 28 and 29 in presence of Raney-nickel catalyst gave the corresponding 5(6)-(2,4-diaminophenyl)aminobenzimidazoles (30 and 31). Better yields of 30 and 31 were obtained by reducing 28 and 29 with hydrazine-hydrate and Raney-nickel in ethanol-THF mixture. Cyclization of 30 and 31 with formic and acetic acids resulted in formation of 2-substituted-5(6)-(2,5-disubstituted-1-benzimidazolyl)benzimidazoles (32-35) (Scheme 1).
Scheme 1

22, \( R = H \)
23, \( R = CH_3 \)
24, \( R = H \)
25, \( R = CH_3 \)
26, \( R = H \)
27, \( R = CH_3 \)
28, \( R = H \)
29, \( R = CH_3 \)
30, \( R = H \)
31, \( R = CH_3 \)
32, \( R = R^1 = H \)
33, \( R = H, R^1 = CH_3 \)
34, \( R = CH_3, R^1 = H \)
35, \( R = R^1 = CH_3 \)
3.2 Synthesis of 2-substituted 6-N-heteroarylbenzthiazoles

Nitration of benzthiazole\(^{26}\) and 2-methylbenzthiazole\(^{27}\) with \(\text{HNO}_3-\text{H}_2\text{SO}_4\) mixture gave 6-nitrobenzthiazole (36) and 2-methyl-6-nitrobenzthiazole (37) respectively. Reduction of 36 with \(\text{SnCl}_2-\text{HCl}\) gave 6-aminobenzthiazole (38)\(^{28}\). However 6-amino-2-methylbenzthiazole (39) could not be prepared by literature method\(^{27}\) but it was obtained in good yield by reduction of 37 with hydrazine-hydrate and Raney-nickel. Reaction of 38 and 39 with 2,4-dinitrochlorobenzene in ethanol in presence of triethylamine gave good yields of 6-(2,4-dinitrophenyl)aminobenzthiazole (40) and 2-methyl-6-(2,4-dinitrophenyl)aminobenzthiazole (41), which were reduced smoothly using freshly washed Raney-nickel and hydrazine-hydrate in ethanol-THF mixture to yield the corresponding 2-substituted-6-(2,4-diaminophenyl)aminobenzthiazoles (42 and 43). Treatment of 42 and 43 with thiophosgene in acetone afforded 2-substituted-6-(2-mercapto-5-isothiocyanato-1-benzimidazolyl)benzthiazoles (44 and 45). The cyclization of 42 and 43 was carried out by treating with formic and acetic acids to yield directly 2-substituted-6-(2,5-disubstituted-1-benzimidazolyl)benzthiazoles (47-50). A similar cyclization of 43 with 1,3-dicarboxy-5-methylisothiourea in ethanol gave 2-methyl-6-[2-carboxyamino-5-(N,N'-dicarboxyguanidino)-1-benzimidazolyl]benzthiazole (46) in poor yield (Scheme 2).
Scheme 2
Reaction of 39 with 2-nitrobenzoyl chloride in presence of triethylamine afforded 2-methyl-6′-(2-nitrobenzoyl)aminobenzthiazole (51) which was reduced using Raney-nickel and hydrogen in a Parr hydrogenator to give 2-methyl-6′-(2-aminobenzoyl)aminobenzthiazole (52). Reaction of 52 with thiophosgene in acetic acid-HCl-chloroform mixture afforded the isothiocyanate 53 in poor yield which was converted thermally into 2-methyl-6′-(2-thioxo-4-oxo-3-quinazolinyl)benzthiazole (54). The latter was also prepared by reaction of 52 with one mole of thiophosgene (Scheme 3).

3.3 Synthesis of 2,2'-substituted-5,5'-dibenzimidazolyl derivatives

m-Chloroacetanilide (55), obtained by acetylation of m-chloroaniline using AcOH-Ac₂O, was nitrated with acetic acid-nitric acid mixture to give 5-chloro-2-nitroacetanilide (56). Reaction of 56 with sodium sulfide in ethanol yielded the deacetylated sulfide 3,3′-diamino-4,4′-dinitrodiphenyl sulfide (57). Its structure was confirmed by NMR of its acetyl derivative 3,3′-diacetamido-4,4′-dinitrodiphenyl sulfide (58) obtained by acetylation of 57 with AcOH-Ac₂O mixture. Reduction of 57 with ferrous sulphate-ammonia in acetone gave 3,3′,4,4′-tetraaminodiphenyl sulfide (59). Since this amino (59) was highly susceptible to aerial oxidation it was immediately treated with formic
Scheme 3
and acetic acids at their refluxing temperatures to afford the corresponding dibenzimidazoles (60-61). Reaction of 59 with 1,3-dicarbalkoxy-S-methylisothioureas in ethanol gave 2,2'-dicarbalkoxyamino-5,5'-dibenzimidazolyl sulfides (62 and 63) (Scheme 4).

4,4'-Dichlorodiphenyl sulfone (64) was nitrated with HN03-H2SO4 to afford 4,4'-dichloro-3,3'-dinitrodiphenyl sulfone (65)30 which was treated with ammonia in DMSO to give 4,4'-diamino-3,3'-dinitrodiphenyl sulfone (66)31. The positional isomer of 66, 3,3'-diamino-4,4'-dinitrodiphenyl sulfone (67) was obtained in poor yield by direct oxidation of 27 using KMnO4 in 80% aqueous acetic acid. Reduction of 66 or 67 with hydrazine-hydrate and Raney-nickel in ethanol-THF mixture gave 3,3',4,4'-tetra-amidodiphenyl sulfone (68) which was allowed to react with formic and acetic acids to afford the 5,5'-dibenzimidazolyl sulfone (69) and 2,2'-dimethyl-5,5'-dibenzimidazolyl sulfone (70) respectively. Cyclization of 68 with 1,3-dicarbalkoxy-S-methylisothioureas in refluxing ethanol gave 2,2'-dicarbalkoxyamino-5,5'-dibenzimidazolyl sulfones (71 and 72) (Scheme 5).

4-Acetamidobenzoic acid (73), obtained by reduction and subsequent acetylation of 4-nitrobenzoic acid, was nitrated using fuming nitric acid to give 4-acetamido-3-nitrobenzoic acid (74)32. The hydrolysis of 74 in
Scheme 4
\[
\begin{align*}
\text{NaNO}_3 & \quad \text{H}_2\text{SO}_4 \\
\rightarrow & \quad \text{NH}_3/\text{DMSO} \\
\end{align*}
\]

\[
\begin{align*}
\text{N}_2\text{H}_4\cdot\text{H}_2\text{O} & \quad \text{Ra-Ni} \\
\rightarrow & \quad \text{Cyclization} \\
\end{align*}
\]

\[
\begin{align*}
\text{64} & \quad \text{65} \\
\text{66}, \ R = \text{NO}_2, \ R' = \text{NH}_2 \\
\text{67}, \ R = \text{NH}_2, \ R' = \text{NO}_2 \\
\text{69}, \ R = \text{H} \\
\text{70}, \ R = \text{CH}_3 \\
\text{71}, \ R = \text{NHCOOCH}_3 \\
\text{72}, \ R = \text{NHCOOCH}_2\text{H}_5 \\
\end{align*}
\]

Scheme 5
concentrated HCl yielded 4-amino-3-nitrobenzoic acid (75)\textsuperscript{32}, which was reduced with Raney-nickel and H\textsubscript{2} in a paar hydrogenator to give 3,4-diaminobenzoic acid (76)\textsuperscript{33}. Reaction of 1,3-dicarbalkoxy-S-methylisothioureas with 76 afforded the corresponding 2-carbalkoxyaminobenzimidazole-5(6)-carboxylic acids (77 and 78).

Attempts to prepare 2,2'-dicarbalkoxyamino-5,5'-dibenzimidazolyl ketone (81 and 82) by Friedel-Crafts aroylation of alkyl benzimidazole-2-carbamates (72 and 73)\textsuperscript{33a}, obtained by cyclization of o-phenylenediamine with 1,3-dicarbalkoxy-S-methylisothioureas, with 77 and 78 did not work because of their poor solubility in different organic solvents. (Scheme 6).

In an alternative approach to prepare 81 and 82, 4,4'-dichlorobenzophenone (83), prepared from 4-chlorobenzoylchloride and chlorobenzene in CS\textsubscript{2} in presence of AlCl\textsubscript{3}\textsuperscript{34}, was nitrated using H\textsubscript{2}SO\textsubscript{4}-HNO\textsubscript{3} to yield 3,3'-dinitro-4,4'-dichlorobenzophenone (84)\textsuperscript{35}. Amination of 84 in DMSO at 140°C with ammonia gas afforded the corresponding 4,4'-diamino-3,3'-dinitrobenzophenone (85)\textsuperscript{36} which was catalytically hydrogenated using Raney-nickel to give 3,3',4,4'-tetra-aminobenzophenone (86)\textsuperscript{37}. Reaction of 86 with 1,3-dicarbalkoxy-S-methylisothioureas in refluxing ethanol yielded the title compounds (81 and 82) in good yields. The Wolff-Kishner reduction of 85 using
Scheme 6
hydrazine-hydrate and potassium hydroxide in steel bomb 
at $170^\circ C$ directly yielded the $3,3',4,4'$-tetra-aminodiphenyl-
methane (87) which was cyclized with 1,3-dicarbalkoxy-S-
methylisothioureas in ethanol to give $2,2'$-dicarbalkoxy-
amino-5,5'-dibenzimidazolylmethanes (90 and 91). Treatment 
of 86 and 87 with formic and glacial acetic acids afforded 
the corresponding 5,5'-dibenzimidazolyl ketones (88 and 
89) and methanes (92 and 93) (Scheme 7).

Acetylation of 4-acetamidophenol (94) using pyridine-
acetic anhydride gave 4-acetoxyacetanilide (95), which 
was nitrated using fuming nitric acid to give 4-acetoxy-2-
nitroacetanilide (96). Selective hydrolysis of 96 with 
aqueous KOH gave 3-nitro-4-acetamidophenol (97) which 
when treated with 5-chloro-2-nitroaniline (98) and 5-chloro-
2-nitroacetanilide (56) could not yield 99 and 100 under 
different experimental conditions. In another attempt, 
4-acetamidophenol (94) was treated with 5-chloro-2-nitro-
acetanilide (56) to give 5-(4-acetamidophenoxy)-2-nitro-
acetanilide (101). Nitration of 101 under different 
experimental conditions also did not yield the required 
intermediate 100 which could have led to the formation of 
the compounds of the type III ($X=0$). (Scheme 8).

4,4'-Dinitrodiphenyl ether (102), prepared from 
4-nitrophenol and 1-chloro-4-nitrobenzene in presence of 
KOH in dry DMF, was reduced with hydrazine-hydrate and
\[
\begin{align*}
    &\text{Cl} \quad \text{Cl} \\
\text{83} &\xrightarrow{\text{NO}_2} \text{Cl} \quad \text{Cl} \\
\text{84} &\xrightarrow{\text{NH}_3} \\
\text{86} &\xrightarrow{\text{Ra-Ni}} \text{H}_2 \\
\text{85} &\xrightarrow{\text{Cyclization}} \\
\text{87} &\xrightarrow{\text{Wolff-Kishner Redn}} \\
\end{align*}
\]

**Scheme 7**

81, \( R = \text{NHCOOCH}_3, \ X = \text{CO} \)
82, \( R = \text{NHCOOC}_2\text{H}_5, \ X = \text{CO} \)
83, \( R = \text{H}, \ X = \text{CO} \)
84, \( R = \text{CH}_3, \ X = \text{CO} \)
85, \( R = \text{NHCOOCH}_3, \ X = \text{CH}_2 \)
86, \( R = \text{NHCOOC}_2\text{H}_5, \ X = \text{CH}_2 \)
87, \( R = \text{H}, \ X = \text{CH}_2 \)
88, \( R = \text{CH}_3, \ X = \text{CH}_2 \)
Scheme 8
Raney-nickel to give 4,4'-diaminodiphenyl ether (103). Acetylation of 103 with acetic anhydride gave 4,4'-diacetamidodiphenyl ether (104) which was nitrated using acetic acid-nitric acid mixture to yield 4,4'-diacetamido-3,3'-dinitrodiphenyl ether (105) in good yield. Hydrolysis of 105 by 50% HCl or 10% aqueous KOH gave 4,4'-diamino-3,3'-dinitrodiphenyl ether (106) which was conveniently reduced with freshly washed Raney-nickel and hydrazine-hydrate to afford 3,3',4,4'-tetra-aminodiphenyl ether (107). Treatment of 107 with 1,3-dicarbalkoxy-S-methylisothioureas yielded the title compounds 2,2'-dicarbalkoxyamino-5,5'-dibenzimidazolyl oxides (110 and 111). Further reaction of 96 with 98% formic and glacial acetic acids yielded the corresponding dibenzimidazoles (108 and 109) (Scheme 9).

Reaction of 1,2-ethanediethiol with 56 in presence of KOH did not afford the desired compound 113 which would have yielded 1,2-di-(3-amino-4-nitrophenylthio)ethane (112) on deacetylation. The latter compound was prepared conveniently by treating 98 with 1,2-ethanediethiol which was reduced with 10% Pd/C in large excess of ethanol under high pressure of H₂ in a Paar hydrogenator to give very poor yield of the tetra-amine 114. Treatment of 114 with 1,3-dicarbalkoxy-S-methylisothioureas in refluxing ethanol gave 1,2-di-(2-carbalkoxyaminobenzimidazolyl-5(6)-thio)ethanes (115 and 116) (Scheme 10).
Scheme 9

81
Scheme 10
4-Chloro-3-nitrobenzoyl chloride (117), obtained by treatment of 4-chloro-3-nitrobenzoic acid with SOCl₂, was reacted with anhydrous piperazine to get 1,4-di-(4-chloro-3-nitrobenzoyl)piperazine (119). Treatment of 119 with ammonia in DMSO gave very poor yield of the diamine 121 which was prepared in better yields by treating anhydrous piperazine with 4-acetamido-3-nitrobenzoyl chloride (118) in dry benzene to get 1,4-di-(4-acetamido-3-nitrobenzoyl)piperazine (120). The selective hydrolysis of 120 with aqueous KOH in ethanol at room temperature gave 1,4-di-(4-amino-3-nitrobenzoyl)piperazine (121). Reduction of 121 using Raney-nickel and hydrogen in THF or ethanol at 3.5 kg/cm² pressure in a Paar hydrogenator afforded 1,4-di-(3,4-diaminobenzoyl)piperazine (122) which reacted with 1,3-dicarbalkoxy-S-methylisothioureas in ethanol to yield the corresponding 1,4-di-(2-carbalkoxyaminobenzimidazolyl-5(6)-carbonyl)piperazines (123 and 124) (Scheme 11).

3.4 Synthesis of 2,5(6)-diarylbenzimidazoles and their cyclic analogs

4-Amino-3-nitrobiphenyl (125)⁴⁰, obtained by subsequent nitration, reduction, acetylation, nitration and hydrolysis of biphenyl, was reduced with hydrazine-hydrate and Raney-nickel in ethanol-THF mixture to give 3,4-diaminobiphenyl (126)⁴¹. Treatment of 126 with 1,3-dicarbethoxy-S-methylisothiourea afforded ethyl 5(6)-phenyl-
Scheme 11

117, $R = \text{Cl}$

118, $R = \text{NHAc}$

119, $R = \text{Cl}$

120, $R = \text{NHAc}$

121

122

123, $R = \text{NHCOOCH}_3$

124, $R = \text{NHCOOC}_2\text{H}_5$
benzimidazole-2-carbamate (127). When 125 was treated with different benzoyl chlorides in refluxing dry benzene the corresponding 4-(arylamino)-3-nitrobiphenyls (128-130) were obtained. Reduction of 128-130 with hydrazine-hydrate and Raney-nickel gave 3-amino-4-(arylamino)biphenyls (131-133) which were subjected to acid catalysed cyclization in ethanol to give the corresponding 2-substituted benzimidazoles (134-136)\(^\text{42}\). Treatment of 136 with thiophosgene in acetone yielded 2-(4-isothiocyanatophenyl)-5(6)-phenylbenzimidazole hydrochloride (139). Similarly, reaction of 136 with ethyl and methyl chloroformates afforded 2-(4-carbalkoxyaminophenyl)-5(6)-phenylbenzimidazoles (140 and 141). Treatment of 135 with alkyl chloroformates or potassium ethyl xanthate yielded the cyclic products 9-phenylbenzimidazo[1,2-c]quinazolin-6-one and 6-thione (137 and 138). When 135 was allowed to react with methyl and ethyl chloroformate in acetone it yielded a mixture of 137 and 114. The structure of 137 and 138 was confirmed by their mass and \(^{13}\text{C-}\text{NMR}\) spectra. 137 and 138 had their \text{M}^+ at m/z 311 and 327 which corresponds to the cyclic products. The \(^{13}\text{C-}\text{NMR}\) spectrum of 137 in DMSO-d\(_6\) showed the chemical shift of C-9 at 135.31 6 which was in agreement with the calculated value (136,1 6) if structure 137 is taken into account. Had the cyclization occurred through the other nitrogen to yield its positional isomer 10-phenylbenzimidazo
[1,2-\text{c}]\text{quinazolin-6-one}, the calculated value for C-10 would have been at \( \delta 130.0 \). The calculation is based on the effect of various groups present in 5-phenylbenzimidazole fused with a quinazolin-nucleus\textsuperscript{43,44}. The structure of 137 was further supported by the fact that \( ^{13}\text{C-NMR} \) of 5(6)-\text{phenylbenzimidazole} and 2-(2-aminophenyl)-5(6)-phenylbenzimidazole (135) showed the absorption for 5(6)-carbon at \( \delta 133.14 \) and 132.98 respectively.

Treatment of 133 with two moles of thiophosgene in presence of triethylamine yielded 1-(4-isothiocyanatobenzoyl)-2-mercapto-5-phenylbenzimidazole (145). When 132 was allowed to react with two moles of thiophosgene under similar experimental conditions, it yielded only 144 out of three possible products 142, 144 and 146. The structure was supported by its IR and mass spectra. The IR spectra of 144 and 145 had sharp bands at 1640 and 1635 cm\(^{-1}\) corresponding to C=N absorption of the benzimidazole ring. The high carbonyl absorption at 1680 and 1710 cm\(^{-1}\) in 144 and 145 also supported the formation of these compounds\textsuperscript{45} thus excluding the possibility of the presence of 146 in the isolated product. The mass spectra of both the compounds had \( \text{M}^+ \) at m/z 387 and clearly indicated the loss of a thiol group (32) from the (\( \text{M}^+-161 \)) at m/z 194 in 144 and from molecular ion at m/z 355 in 145 which is not possible in uncyclized products.
The reaction of 132 with one mole of thiophosgene resulted in the formation of only 1-(2-aminobenzoyl)-2-mercaptop-5-phenylbenzimidazole (143) along with the small amount of corresponding isothiocyanate 144. The structure of 143 was confirmed by its mass (M⁺ at m/z 345), and IR absorption (1690 cm⁻¹ for NCON-C₆H₄-2-NH₂)⁴⁵. Furthermore, isolation of 144 from the reaction mixture can only be accounted by formation of 143 as intermediate (Scheme 12).

3.5 Synthesis of 2-substituted 5(6)-(4-substitutedphenoxy, phenylthio and sulfono)benzimidazoles

Reaction of 4-acetamidothiophenol with 5-chloro-2-nitroacetanilide (6) and 5-chloro-2-nitroaniline (98) in presence of KOH in n-propanol gave excellent yields of 5-(4-acetamidophenylthio)-2-nitroaniline (147) and 5-(4-acetamidophenylthio)-2-nitroacetanilide (148) respectively. Alternatively, 147 was also prepared by selective hydrolysis of 148 with aqueous KOH. Reduction of 147 with hydrazinc-hydrate and Raney-nickel in THF- ethanol mixture afforded 4-(4-acetamidophenylthio)-o-phenylenediamine (149) which was condensed with 1,3-dicarbalkoxy-S-methylisothiouracil in refluxing ethanol to afford alkyl 5(6)-(4-acetamidophenylthio)benzimidazole-2-carbamates (150 and 151) in good yields. 149 was also treated with formic and glacial acetic acids to give the corresponding benzimidazole (152) and 2-methylbenzimidazole (153). Selective hydrolysis of amido function
Scheme 12 (Contd.)
Scheme 12
in 15.0 and 15.1 with 10% HCl afforded the alkyl 5(6)-(4-aminophenylthio)benzimidazole-2-carbamates (15.4 and 15.5). A similar hydrolysis of 15.2 and 15.3 using concentrated HCl yielded the corresponding amines (15.6 and 15.7). However, when 15.0 and 15.1 were refluxed in 50% HCl for a longer period, complete hydrolysis of the compounds took place giving rise to 2-amino-5(6)-(4-aminophenylthio)benzimidazole (15.8).

Oxidation of 15.0-15.3 was carried out using 80% aqueous acetic acid and KMnO₄ at room temperature to yield their corresponding sulfones (15.9-16.2) of which 15.9 and 16.0 were selectively hydrolysed with 10% HCl to yield alkyl 5(6)-(4-aminophenylsulfonyl)benzimidazole-2-carbamates (16.3 and 16.4). Similarly, 16.1 and 16.2 were hydrolysed with 50% HCl to give 5(6)-(4-aminophenylsulfonyl)benzimidazole (16.6) and 2-methyl-5(6)-(4-aminophenylsulfonyl)benzimidazole (16.7) while hydrolysis of 15.9 or 16.0 in 50% HCl yielded 2-amino-5(6)-(4-aminophenylsulfonyl)benzimidazole (16.5). The amines 15.4, 15.5, 16.3 and 16.4 were allowed to react with thiophosgene in presence of triethylamine in large volume of acetone (due to their poor solubility in acetone) to afford their corresponding isothiocyanates 16.8, 16.9, 17.2 and 17.3 respectively. Treatment of thiophosgene with 15.7, 15.8, 16.6 and 16.7 in acetone and triethylamine also yielded the desired isothiocyanates 17.0, 17.1, 17.4 and 17.5 (Scheme 13).
Scheme 1 (Contd.)
159, \( R = \text{NHCOOCH}_3 \)
160, \( R = \text{NHCOOC}_2\text{H}_5 \)
161, \( R = \text{H} \)
162, \( R = \text{CH}_3 \)

\[ 150-153 \xrightarrow{\text{KMnO}_4} \]

\[ 150-157 \xrightarrow{\text{CS}_2\text{Cl}_2} \]

163, \( R = \text{NHCOOCH}_3 \)
164, \( R = \text{NHCOOC}_2\text{H}_5 \)
165, \( R = \text{NH}_2 \)
166, \( R = \text{H} \)
167, \( R = \text{CH}_3 \)

\[ 154-157 \]

168, \( R = \text{NHCOOCH}_3, X = \text{S} \)
169, \( R = \text{NHCOOC}_2\text{H}_5, X = \text{S} \)
170, \( R = \text{H}, X = \text{S} \)
171, \( R = \text{CH}_3, X = \text{S} \)
172, \( R = \text{NHCOOCH}_3, X = \text{SO}_2 \)
173, \( R = \text{NHCOOC}_2\text{H}_5, X = \text{SO}_2 \)
174, \( R = \text{H}, X = \text{SO}_2 \)
175, \( R = \text{CH}_3, X = \text{SO}_2 \)

**Scheme 13**
Reaction of 4-acetamidophenol (94) and 5-chloro-2-nitroaniline (98) in presence of KOH in dry DMF yielded 5-(4-acetamidophenoxy)-2-nitroaniline (176) in 44% yield. 176 was reduced with hydrazine-hydrate and Raney-nickel in THF-ethanol mixture to give 4-(4-acetamidophenoxy)-2-phenylenediamine (177) which was not isolated and was used as such in further reactions. Reaction of 177 with 1,3-dicarbalkoxy-5-methylisothioureas in refluxing ethanol gave alkyl 5(6)-(4-acetamidophenoxy)benzimidazole-2-carbamates (178 and 179) which were hydrolysed selectively with 10% HCl to give the corresponding amines (180 and 181). Reaction of 177 with formic and glacial acetic acids yielded 5(6)-(4-acetamidophenoxy)benzimidazole (182) and 2-methyl-5(6)-(4-acetamidophenoxy)benzimidazole (183) respectively which were isolated as their hydrochlorides. Hydrolysis of 182 and 183 in concentrated HCl afforded the corresponding amines 184 and 185 as their hydrochlorides which were basified with aqueous ammonia to give the free bases. The amines 180, 181, 184, 185 were treated with thiophosgene in acetone in presence of two moles of triethylamine to give their corresponding 5(6)-(4-isothiocyanatophenoxy)benzimidazoles (186-189) (Scheme 14).
Scheme 14
3.6 Synthesis of 5(6)-thiophenoxy and phenoxyethyl benzimidazole-2-carbamates

4-Chloro-3-nitrobenzaldehyde (190), prepared by nitration of 4-chlorobenzaldehyde in KN03-H2SO4, was reduced with sodium borohydride in methanol to give 4-chloro-3-nitrobenzyl alcohol (191). Treatment of 191 with ammonia in steel bomb at 150°C gave the corresponding amino compound 192 which could not be converted to its bromide or chloride by action of PBr3 or thionyl chloride. However, when 191 was treated with PBr3 in dry benzene it gave 4-chloro-3-nitrobenzyl bromide (194) in good yield which was treated with phenol and thiophenol in presence of K2CO3 in acetone to give 2-nitro-4-(phenoxy) and 2-nitro-4-(thiophenoxy)methylchlorobenzene (195 and 196). When 194 was allowed to react with one mole of thiophenol in ethanol in presence of KOH it yielded a mixture of 196 and 2-thiophenoxy-5-thiophenoxymethylnitrobenzene (197) in poor yields. However, better yield of 197 was obtained when two moles of thiophenol was reacted with one mole of 194 in ethanolic potassium hydroxide. Reaction of 195 with aqueous ammonia solution in THF at 150°C in a steel bomb gave 2-nitro-4-phenoxyethylaniline (198). Similarly 196 was treated with aqueous ammonia in THF at 150°C in steel bomb to yield the amine 199 which could not be isolated. However, 199 was obtained when ethanol was
taken as solvent in place of THF in the above reaction. Attempts to reduce \( \text{198} \) with hydrazine-hydrate and Raney-nickel, Raney-nickel and \( H_2 \) or \( \text{FeSO}_4\cdot\text{NH}_3 \) were unsuccessful as it always gave a complex mixture of the products. In contrary, \( \text{199} \) was reduced smoothly with \( \text{FeSO}_4\cdot\text{NH}_3 \) in acetone to give the required diamine \( \text{200} \) in good yield which was treated with 1,3-dicarbalkoxy-S-methylisothioureas in refluxing ethanol to afford alkyl 5(6)-thiophenoxy-methylbenzimidazole-2-carbamates (201 and 202)* (Scheme 15).

3.7 Synthesis of 1,2-disubstituted ethanes and 1,3-disubstituted propanes

Reaction of 4-acetamidothiophenol with 1,2-dibromoethane and 1,3-dibromopropane in presence of KOH yielded 1,2-di-(4-acetamidophenylthio)ethane (203) and 1,3-di-(4-acetamidophenylthio)propane (204) which were oxidized with KMnO₄ in 80% aqueous acetic acid to give the corresponding sulfones (205 and 206). Hydrolysis of 203, 205 and 206 with concentrated HCl gave respective 1,2-di-(4-aminophenylthio) and 1,2-di-(4-aminophenyl-sulfono)ethanes (207 and 208) and 1,3-di-(4-aminophenyl-sulfono)propane (209) respectively. Treatment of 207-209 with thiophosgene in 50% aqueous acetic acid or 10% HCl

*During the course of our investigation Haugwitz et al. 49 reported the synthesis and biological activity of compound 201 with no data.
Scheme 15
afforded the corresponding 1,2-di-(4-isothiocyanato-
phenylthio) and 1,2-di-(4-isothiocyanato-phenylsulfone)
ethanes (210 and 211) and 1,3-di-(4-isothiocyanato-
phenylsulfone)propane (212). Nitration of 205 and 206 under
different experimental conditions failed to yield the
required dinitro compound 213 and hence, dibenzimidazoles
of the type III (X=S02-(CH2)n-S02, n = 2,3) could not be
prepared (Scheme 16).

3.8 Synthesis of substituted thiocarboxamides,
carboxamides and thioureas

Substituted phenylisothiocyanates (219-223)
were prepared by treatment of the corresponding anilines
(214-218) with thiophosgene in acetone or 10% HCl.
Reaction of 4-substituted piperazines with 219-222
yielded the corresponding substituted phenyl-4-substituted-
1-piperazinylthiocarboxamides (227-238) in good yields.
Attempts to reduce 227-238 by Raney-nickel and H2,
hydrazine-hydrate and Raney-nickel, sodium dithionite
Zn-CH3COOH or Sn-HCl were unsuccessful. However,
227-232 were successfully reduced with FeSO4-NH3 using
large volume of aqueous ammonia (as they are poorly
soluble even in hot aqueous ammonia). The reactions of
amines (239-244), obtained by FeSO4-NH3 reduction, with
one mole of thiophosgene in acetone led to an unusual
desulphurization of thiocarboxamides to their corresponding
Scheme 16
carboxamides along with formation of isothiocyanates which were isolated in poor yields. A similar reaction of 232-244 with two moles of thiophosgene yielded the 4-isothiocyanatophenyl-4-substituted-1-piperazinylcarboxamides (245-250) in good yield and no corresponding thio analogs could be isolated. The 4-isothiocyanatophenyl-4-substituted-1-piperazinylthiocarboxamides (224-226) were prepared by reaction of one mole of 4-substituted piperazines on 1,4-phenylenediisothiocyanate (223) in acetone under high dilution at room temperature and the product purified by crystallization or by column chromatography (Scheme 17).

Reaction of 2-aminobenzimidazole (251) with 4-nitrophenylisothiocyanate (219) and 2-chloro-4-nitrophenylisothiocyanate (220) in refluxing ethyl acetate gave N-(4-nitrophenyl)-N'-(2-benzimidazolyl)thiourea (252) and N-(2-chloro-4-nitrophenyl)-N'-(2-benzimidazolyl)thiourea (253). The FeSO₄-NH₃ reduction of 252 gave the required N-(4-aminophenyl)-N'-(2-benzimidazolyl)thiourea (254) which was treated with two moles of thiophosgene to yield N-(4-isothiocyanatophenyl)-N'-(2-benzimidazolyl)urea (255). Similar reaction of 4-aminacetanilide with 219 and 220 gave the N-(4-acetamidophenyl)-N'-(4-nitrophenyl)thiourea (256) and N-(4-acetamidophenyl)-N'-(2-chloro-4-nitrophenyl)thiourea (257) respectively (Scheme 18).
Scheme 17
Scheme 18
Keeping in view the ability of thiophosgene to desulphurize thioureas and thiocarboxamides, the reaction was extended to thioamide also, and its conversion to corresponding amide was demonstrated. Thus, a number of thioureas, thiocarboxamides (258-264) and thioamide (265), when reacted with thiophosgene in acetone at room temperature gave the corresponding ureas and carboxamides (267-273) and amide (274). The thioureas and the thiocarboxamides (258-264) were prepared by reaction of phenyl and alkyl isothiocyanates with corresponding amines. The products obtained after thiophosgene treatment were compared (mixed m.p., Co-IR and Co-TLC) with the ureas and carboxamides prepared directly from phenyl or alkyl isocyanates with amines and acetamide obtained by reaction of acetic anhydride with benzylamine (267-274).

A probable mechanism of desulphurization involves the initial attack of sulphur of thioureas, thiocarboxamides or thioamide (258-265) at thiophosgene resulting in the formation of an activated complex which on synchronous loss of carbondisulfide affords the chloro intermediate (266). Alternatively, 266 may also be obtained by nucleophilic reaction of the chloride ion on the activated complex. Simultaneous reaction of water with 266 yields the corresponding oxygen analogs (267-274). The intermediacy of 266 was further supported by converting it
into corresponding substituted amidine (275) by action of N-methylpiperazine in dry acetone (Scheme 19).

3.9 Synthesis of 1,4-disubstituted piperazines

Reaction of anhydrous piperazine with 1-chloro-4-nitrobenzene in presence of K₂SO₃ in acetone in steel bomb at 150°C gave 1-(4-nitrophenyl)piperazine (276) and no 1,4-di-(4-nitrophenyl)piperazine (277) could be isolated. When 276 was allowed to react with 4-nitrobenzoyl chloride in dry benzene in presence of triethylamine, it yielded 1-(4-nitrobenzoyl)-4-(4-nitrophenyl)piperazine (278) which was reduced with FeSO₄·NH₃ to give the corresponding diamine (279). Treatment of 279 with thiophosgene in acetone in presence of triethylamine gave 1-(4-isothiocyanatobenzoyl)-4-(4-isothiocyanatophenyl)piperazine (280). Similarly, anhydrous piperazine reacted with two moles of 4-nitrobenzoyl chloride to yield 1,4-di-(4-nitrobenzoyl) piperazine (281). Reduction of 281 with Raney-nickel and H₂ in a Paar hydrogenator afforded 1,4-di-(4-aminobenzoyl) piperazine (282). The synthesis of 1,4-di-(4-isothiocyanatobenzoyl)piperazine (283) was achieved by reaction of 282 with thiophosgene in 10% HCl-CHCl₃ mixture (Scheme 20).
R - NH - C - R¹ \xrightarrow{\text{CSCl₂, } -\text{HCl}} \framebox{
\begin{align*}
\text{R - N} & \overset{\text{Cl}}{\rightarrow} \text{Cl} \\
& \text{or} \\
& \text{R - N} = \overset{\text{Cl}}{\text{C = S}} \\
& \overset{\text{Cl}}{\text{R¹}} \\
\end{align*}
}\ \\
\begin{align*}
258, \ R = \text{Ph}, \ R¹ = \text{NHCH₂Ph} \\
259, \ R = \text{Ph}, \ R¹ = \text{NHC₆H₄Cl(m)} \\
260, \ R = \text{Ph}, \ R¹ = \text{NHC₆H₁₁} \\
261, \ R = \text{Ph}, \ R¹ = \text{NEt₂} \\
262, \ R = \text{Ph}, \ R¹ = \text{N} \\
263, \ R = \text{Ph}, \ R¹ = \text{N} \\
264, \ R = \text{Et}, \ R¹ = \text{N} \\
265, \ R = \text{CH₂Ph}, \ R¹ = \text{CH₃} \\
\end{align*}
\ \\
R - NH - C - R¹ \xrightarrow{\text{H₂O, } -\text{HCl}} \framebox{
\begin{align*}
\text{R - N} & \overset{\text{Cl}}{\rightarrow} \text{C} \\
& \overset{\text{R¹}}{\rightarrow} \\
\end{align*}
}\ \\
\begin{align*}
266, \ R = \text{Ph} \\
260, \ R = \text{Ph} \\
\end{align*}
\ \\
\text{Scheme 19}
Scheme 20

\[ \text{HN} \text{NH} \xrightarrow{\text{Cl-} \text{NO}_2} \text{O}_2\text{N} \text{NR} \]

\[ 276, \ R = \text{H} \]

\[ 277, \ R = \text{C}_6\text{H}_4\text{NO}_2 \ (4) \]

\[ \text{Reduction} \]

\[ \text{HN} \text{NH} \xrightarrow{\text{CSCl}_2} \text{HN} \text{NH} \]

\[ 281 \]

\[ \text{HN} \text{NH} \xrightarrow{\text{CSCl}_2} \text{HN} \text{NH} \]

\[ 282, \ R = \text{NH}_2 \]

\[ 283, \ R = \text{NCS} \]
The structures of all the compounds were routinely checked by IR recorded on Perkin-Elmer 157 and 177 infracord spectrophotometers. The NMR spectra were obtained on Varian A60-D and EM-360L (60 MHz) or R-32 (90 MHz) spectrometers using TMS as internal reference. Mass spectra were taken on Jeol JMS-D300 (~70 ev) instrument. The purity of all the compounds was checked on silica - gel G-plates and spots were located by I₂ vapours, KMnO₄ (2%) spray or Dragendorff's reagent spray. Melting points were taken in sulphuric acid bath and are uncorrected.

Benzimidazole (22) and 2-methylbenzimidazole (23)

These compounds were prepared by treating o-phenylene diamine (13.5 g, 0.125 mol) with formic acid and glacial acetic acid respectively.

22, yield 12 g (81.6%), m.p.171° (lit. 23 m.p.171-2°)

23, yield 9.9 g (60%), m.p.176° (lit. 23 m.p.176°)

2-Methyl-5(6)-nitrobenzimidazole (25)

Conc. nitric acid (13.3 ml, d=1.4) was added dropwise to ice-cooled mixture of 23 (11 g, 0.83 mol) in H₂SO₄ (10 ml, d=1.84) during 30 minutes. The reaction mixture was poured on crushed ice and product isolated, yield
12.5 g (85%), m.p.217° (lit.24 m.p.219°).

Similarly 5(6)-nitrobenzimidazole (24) was prepared by nitration of 22 in 90% yield, m.p.207-20° (lit.24 m.p. 203°).

5(6)-Aminobenzimidazole (26)

A mixture of 24 (10 g, 0.061 mol) and Raney-nickel (about 1.5 g) in ethanol (200 ml) was shaken with hydrogen at 3.5 kg/cm² in a paar hydrogenator for 12 hr. The catalyst was filtered out, solvent removed from filtrate and the product was purified as its hydrochloride, yield 4.9 g (60%), m.p.288° (lit.25 m.p.290°).

Using the above method 27 was obtained as its hydrochloride by reduction of 25, yield 62%, m.p.298° (lit.25 m.p.298-9°).

5(6)-(2,4-Dinitrophenyl)aminobenzimidazole (28)

A mixture of 26 (4 g, 0.03 mol), 1-chloro-2,4-dinitrobenzene (6.1 g, 0.03 mol) and triethylamine (4.4 ml, 0.03 mol) in 95% ethanol (50 ml) was refluxed for 14 hr. The reaction mixture was cooled and the separated solid filtered, washed successively with cold ethanol (3x10 ml), water (15 ml) and dried, yield 6.27 g (70%), m.p.141°.

IR(KBr) cm⁻¹ : 1330, 1580 (NO₂), 1610 (Arom).
NMR(DMSO-d₆)δ : 6.88-7.6 (m, 4H, Ar-Η), 8.05 (dd, 1H, Ar-Η, p to NO₂, J=2 & 9Hz), 8.1 (s, 1H,
N=CH-N), 8.75 (d, 1H, Ar-H, o to both NO₂, J=3Hz).

Analysis for : C₁₄H₁₁N₅O₄ (313)
Calcd. : C, 54.12; H, 3.85; N, 22.10%
Found : C, 65.64; H, 5.12; N, 29.68%.

Similarly 29 was prepared by reaction of 27 with 1-chloro-2,4-dinitrobenzene in ethanol, yield 70%, m.p. >300°.

IR(KBr) cm⁻¹ : 3200-3400 (NH₂).

Analysis for : C₁₅H₁₅N₅ (239)
Calcd. : C, 65.27; H, 5.44; N, 29.29
Found : C, 65.64; H, 5.12; N, 29.68%.
Under similar reaction condition compound 31 was prepared by reduction of 29 with Raney-nickel and H₂, yield 70%, m.p. >300°.

IR(KBr) cm⁻¹ : 3200-3300(NH,NH₂).
Analysis for C₁₄H₁₅N₅ (253)
Calcd. : C, 66.40; H, 5.91; N, 27.66
Found : C, 66.68; H, 6.22; N, 27.34%.

5(6)-(5-Formamido-1-benzimidazolyl)benzimidazole (32)

A solution of 30 (1.0 g, 0.0041 mol) was refluxed in 98% formic acid (15 ml) for 8 hr. The reaction mixture was cooled and neutralized with dilute sodium hydroxide solution. The solid, thus obtained, was filtered, washed with water, dried and purified over silica gel column using ethyl acetate-benzene (9:1) mixture as eluant, yield 0.74 g (65%), m.p. >300°.

IR(KBr) cm⁻¹ : 1660 (CO).
Mass at m/z : 277 (M⁺)
Analysis for C₁₅H₁₁N₅O (277)
Calcd. : C, 64.98; H, 3.97; N, 25.27
Found : C, 65.35; H, 4.21; N, 25.56%.

Using the similar method 34 was prepared in 62% yield by treating 31 with formic acid.
5(6)-(5-Acetamido-2-methyl-1-benzimidazolyl)benzimidazole (33)

A solution of 30 (1.2 g, 0.005 mol) in glacial acetic acid (15 ml) was refluxed for 8 hr. The reaction mixture was cooled and neutralized with dilute NaOH solution. The solid, thus separated, was filtered, washed with water, dried and purified over silica gel column using ethyl acetate as eluant, yield 1.0 g (66%), m.p. >300°.

IR(KBr) cm⁻¹ : 1680 (CO).
NMR(TFA) δ : 2.02 (s, 3H, COCH₃), 2.42 (s, 3H, C-CH₃), 6.9-8.0 (m, 6H, Ar-H),
Mass at m/z : 305 (M⁺)
Analysis for Calcd. Found
C₁₇H₁₅N₅O (305) : C, 66.88; H, 4.91; N, 22.95
C, 66.73; H, 5.25; N, 23.21%.

Similar procedure was employed for the preparation of 35 by reaction of 31 with glacial acetic acid.

6-Nitrobenzthiazole (36)

This compound was prepared by the nitration of benzthiazole (13.5 g, 0.1 mol) in HNO₃ (10.7 ml, d=1.5) and H₂SO₄ (21.5 ml, d=1.84) at 10°, yield 9.0 g (50%), m.p. 173° (lit. 26 m.p. 174°).

Similarly 37 was obtained by nitration of 2-methyl-
benzthiazole, yield 80%, m.p. 164-5° (lit. 27 m.p. 165°).

6-Aminobenzthiazole (38)

This was prepared by reduction of 36 (5.0 g, 0.027 mol) in methanol (50 ml) using SnCl₂ (25 g) in concentrated HCl (50 ml), yield 3.6 g (86.5%), m.p. 83° (lit. 28, m.p. 84-5°).

6-Amino-2-methylbenzthiazole (39)

A solution of hydrazine-hydrate (20.6 g, 0.4 mol) in ethanol (30 ml) was added dropwise to refluxing mixture of 37 (10.0 g, 0.05 mol) and Raney-nickel (~1 g) in ethanol (50 ml). Refluxing was continued for 30 minutes and the reaction mixture filtered in hot. The solvent was removed in vacuo and the resulting solid was crystallized from ethanol, yield 7.0 g (83%), m.p. 119-121° (lit. 27 m.p. 122°).

IR(KBr) cm⁻¹: 3200, 3300 (NH₂).

NMR(CDCl₃) δ: 2.92 (s, 3H, C-CH₃), 7.95 (d, 1H, Ar-H, m to NH₂, J=9Hz), 8.28 (dd, 1H, Ar-H, p to -S-, J=3 & 9Hz), 8.7 (d, 1H, Ar-H, o to -S-, J=3Hz)

Analysis for: C₈H₆N₂O₂S (194)
Calcd.: C, 49.48; H, 3.09
Found: C, 49.12; H, 2.74%.
A solution of 38 (2.5 g, 0.016 mol), 1-chloro-2,4-dinitrobenzene (3.36 g, 0.016 mol) and triethylamine (1.5 g, 0.016 mol) in ethanol (40 ml) was refluxed for 15 hr. The reaction mixture was cooled and the separated pure product was filtered, washed with ethanol (3x20 ml) and dried, yield 4.02 g (80.5%), m.p. 201°.

IR(KBr) cm⁻¹ : 1315, 1580 (NO₂), 1605 (Arom), 3230 (NH).  
Mass at m/z : 316 (M⁺)

NMR(DMSO-d₆) δ : 7.08 (d, 1H, Ar-H, m to NO₂, J=9Hz),  
7.48 (dd, 1H, Ar-H, p to -S-, J=1.5 × 8.5Hz), 8.06 (d, 1H, Ar-H, o to -S-, J=1.5Hz), 8.11 (d, 1H, Ar-H, m to -S-, J=6Hz), 8.16 (dd, 1H, Ar-H, p to NO₂, J=2.0 × 6.5Hz), 8.8 (d, 1H, Ar-H, o to NO₂, J=2.5Hz), 9.3 (s, 1H, S-CH=N).

Analysis for : C₁₉H₁₈N₄O₄S (316)  
Calcd. : C, 49.46; H, 2.80  
Found : C, 49.72; H, 2.52%.

Similarly compound 41 was prepared by reaction of 32 with 1-chloro-2,4-dinitrobenzene in refluxing ethanol, yield 85.5%, m.p. 181°.

IR(KBr) cm⁻¹ : 1335, 1585 (NO₂), 1620 (Arom), 3280 (NH).  
NMR(DMSO-d₆) δ : 2.8 (s, 3H, C-CH₃), 7.16 (d, 1H, Ar-H, m to NO₂, J=9Hz), 7.4 (dd, 1H, Ar-H,
\[
\begin{align*}
\text{114} & \\
& \text{p to } -S-, J=2.5 \text{ & 9Hz), 7.88 (m, 2H, Ar-H, o \& m to } -S-, 8.15 (dd, 1H, Ar-H, p \text{ to NO}_2, J=3 \text{ & 9Hz}, 9.0 (d, 1H, Ar-H, o \text{ to NO}_2, J=2.7Hz)} \\
\text{Analysis for } C_{14}H_{10}N_4O_4S (330) \\
\text{Calcd. : C, 50.90; H, 3.03} \\
\text{Found : C, 50.80; H, 3.36\%} \\
\end{align*}
\]

6-(2,4-Diaminophenyl)aminobenzthiazole (42)

To a warm mixture of 40 (2.5 g, 0.008 mol) and Raney-nickel (0.3 g) in THF (15 ml) and ethanol (15 ml) was added dropwise a solution of hydrazine-hydrate (6.6 g, 0.0133 mol) in ethanol (15 ml). When the yellow colour of the solution disappeared, the catalyst was filtered off and the product obtained on removal of solvent, was crystallised from ethanol, yield 1.56 g (78\%), m.p. 120°.

IR(KBr) cm\(^{-1}\) : 3150-3300 (NH\(_2\)).

Compound 43 was also obtained by reduction of 41 with hydrazine-hydrate and Raney-nickel in 75\%. Yield m.p. 146°.

IR(KBr) cm\(^{-1}\) : 3200-3350 (NH\(_2\)).

6-(2-Thioxo-5-isothiocyanato-1-benzimidazolyl)benzthiazole (44)

Thiophosgene (0.48 ml, 0.0062 mol) in acetone (50 ml) was added dropwise to a stirred solution of 42
(0.8 g, 0.0031 mol) in acetone (100 ml). Stirring was continued for 4 hr and then reaction mixture refluxed for 2 hr. The separated solid was filtered and the mother liquor was concentrated to get a further crop of product. The combined solid product was crystallized from acetone, yield 0.55 g (54%), m.p. 245-46°.

IR(KBr) cm⁻¹ : 2040 (NCS).
Analysis for \( \text{C}_{15}\text{H}_8\text{N}_4\text{S}_3 \) (340)
Calcd. : C, 52.94; H, 2.35
Found : C, 52.62; H, 2.72%.

In similar manner compound 45 was prepared from 43 and thiophosgene in acetone.

2-Methyl-6-[2-carbethoxyamino-5-(N,N'-dicarbethoxyguanidino)-1-benzimidazolyl]benzthiazole (46)

A solution of 1,3-dicarbethoxy-S-methylisothiourea (0.87 g, 0.0036 mol) in ethanol (30 ml) was added to the solution of 43 (0.5 g, 0.0018 mol) in ethanol (10 ml) and the reaction mixture refluxed for 15 hr. The solvent was removed in vacuo and the resulting solid purified on a silica gel column using 10% ethyl acetate in benzene as eluant, yield 0.42 g (42%), m.p. 98-100°.

IR(KBr) cm⁻¹ : 1720 (C=O).
NMR(TFA) δ : 0.75-1.10 [m, 9H, \( \text{CH}_2\text{CH}_3 \)], 2.66 (s, 3H, S-\( \text{CH}_3 \)), 3.8-4.1 [m, 6H \( \text{CH}_2\text{CH}_3 \)], 6.8-7.5 (m, 6H, Ar-H)
Analysis for  : C_{25}H_{27}N_{7}O_{6}S (546)
Calcd. : C, 54.07; H, 4.88
Found : C, 54.41; H, 4.76%.

6-[5-Formamido-l-benzimidazolyl]benzthiazole (47)

A solution of 42 (0.6 g, 0.0023 mol) in 98% formic acid (30 ml) was refluxed for 8 hr. The reaction mixture was cooled and neutralized with 30% aqueous ammonia. The separated solid was filtered off, dried and subjected to charcoal treatment. It was further purified on a silica gel column using 15% ethyl acetate in benzene as eluant, yield 0.38 g (55%), m.p. 235-36°.

IR(KBr) cm\(^{-1}\) : 1650 (CO), 3250 (NH).
Mass at m/z : 294 (M\(^+\))
Analysis for : C_{15}H_{10}N_{4}OS (294)
Calcd. : C, 61.22; H, 3.40
Found : C, 60.86; H, 3.15%.

Compound 49 was prepared similarly from 43 in refluxing 98% formic acid.

6-(5-Acetamido-2-methyl-l-benzimidazolyl)benzthiazole (48)

A solution of 42 (0.6 g, 0.0023 mol) in glacial acetic acid (20 ml) was refluxed for 8 hr. The product was worked-up as above and purified on a silica gel column using benzene as eluant, yield 0.46 g (62%), m.p. 241°.

IR(KBr) cm\(^{-1}\) : 1675 (CO), 3250 (NH).
117

NMR(DMSO-d$_6$) $\delta$: 1.95 (s, 3H, COOH), 2.32 (s, 3H, C-CH$_3$), 6.9 (d, 1H, Ar-H, m to NHAc, J=9Hz), 7.2 (d, 1H, Ar-H, m to -S-, J=9Hz), 7.52 (dd, 1H, Ar-H, p to -S-, J=3 & 9Hz), 7.84 (d, 1H, Ar-H, o to -S-, J=2.5Hz), 8.22 (dd, 2H, Ar-H, o to NHAc, J=3 & 9Hz), 9.38 (s, 1H, N=CH-S)

**Analysis for**: C$_{17}$H$_{14}$N$_4$O$_8$ (322)

Calcd.: C, 63.35; H, 4.34

Found: C, 63.72; H, 4.42%

Similarly 50 was prepared from 43 and glacial acetic acid.

2-Methyl-6-(2-nitrobenzoyl)aminobenzthiazole (51)

A solution of 2-nitrobenzoyl chloride (1.12 g, 0.0061 mol) in dry benzene (25 ml) was added dropwise to a stirred solution of 39 (1.0 g, 0.0061 mol) in dry benzene (30 ml) and triethylamine (0.61 g, 0.0061 mol) at room temperature. Stirring was continued for 8 hr. The separated solid was filtered and washed with water (2x10 ml) to remove triethylamine hydrochloride. The product was dried and crystallized from ethanol, yield 1.3 g (72%), m.p. 198°.

IR(KBr) cm$^{-1}$: 1340, 1520 (NO$_2$), 1640 (C=O), 3400 (NH).

NMR(DMSO-d$_6$) $\delta$: 2.75 (s, 3H, CH$_3$), 7.6-8.25 (m, 6H, Ar-H), 8.5 (d, 1H, Ar-H, -S-C=CH-, J=2Hz).
2-Methyl-6-(2-aminobenzoyl)aminobenzthiazole (52)

A mixture of 51 (1.0 g, 0.0032 mol) and Raney-nickel (~ 0.2 g) in ethanol (50 ml) was hydrogenated at 2.5 kg/cm² pressure in a Paar hydrogenator for 6 hr. The product was worked-up as usual and crystallized from ethanol, yield 0.72 g (79%), m.p. 170°.

IR(KBr) cm⁻¹ : 1620 (CO), 3270, 3340 (NH₂).
Mass at m/z : 283 (M⁺)

NMR(DMSO-d₆) δ : 2.76 (s, 3H, C-CH₃), 6.31 (bs, 2H, NH₂), 6.5-7.8 (m, 6H, Ar-H), 8.5 (d, 1H, S-C=CH, J=2Hz)

Analysis for : C₁₅H₁₁N₃0₂S (283)
Calcd. : C, 63.60; H, 4.52
Found : C, 63.48; H, 4.32%.

2-Methyl-6-(2-isothiocyanatobenzoyl)aminobenzthiazole (53)

A solution of thiophosgene (0.054 ml, 0.0007 mol) in chloroform (10 ml) was added dropwise to a stirred solution of 52 (0.2 g, 0.0007 mol) in glacial acetic acid (4 ml) and 10% HCl (5 ml) at room temperature. Stirring was continued for 1 hr. The chloroform layer was washed with water, dried (Na₂SO₄) and concentrated to get a solid
which was washed with pet. ether, yield 0.08 g (38%), m.p. 185°.

IR(KBr) cm⁻¹: 1660 (CO), 2090 (NCS).

2-Methyl-6-(2-thioxo-4-oxo-3-quinazolinyl)benzthiazole (54)

A solution of thiophosgene (0.13 ml, 0.0015 mol) in acetone (20 ml) was added dropwise to a stirred solution of 53 (0.5 g, 0.0018 mol) in acetone (50 ml) at room temperature. Stirring was continued for 6 hr and the solid separated was filtered and crystallized from ethanol, yield 0.35 g (63%), m.p. >300°.

IR(KBr) cm⁻¹: 1680 (CO), 3400 (NH).

Mass at m/z: 325 (M⁺)

Analysis for C₁₆H₁₁N₂O₂S₂ (325)
Calcd.: C, 58.00; H, 3.32
Found: C, 58.35; H, 3.56%.

5-Chloro-2-nitroacetanilide (55)

m-Chloroacetanilide 55 (64.0 g, 0.38 mol) was nitrated by concentrated HNO₃ (27.5 ml, d=1.5) in acetic acid-acetic anhydride mixture, yield 44 g (58.6%), m.p. 117-18° (lit.29 m.p. 117-18°).

3,3'-Diamino-4,4'-dinitrodiphenyl sulfide (57)

A solution of sodium sulfide (5.6 g, 0.024 mol) in 50% aqueous ethanol (20 ml) was added dropwise to a stirred solution of 56 (10.0 g, 0.046 mol) in ethanol (60 ml) and
the reaction mixture was refluxed for 12 hr on a water bath. The solid which came out on cooling the reaction mixture was filtered, washed with 50% aqueous ethanol, dried and purified by column chromatography using silica gel and benzene-ethylacetate (2:1) as eluant, yield 3.6 g (38.5%), m.p. 195°.

IR(KBr) cm⁻¹ : 1300, 1550 (NO₂), 1600 (Arom), 3280, 3400 (NH₂).

Mass at m/z : 306 (M⁺)

NMR(CDCl₃ + DMSO-d₆) δ : 6.37 (dd, 2H, Ar-H, δ to NH₂, J=2.5 & 8Hz), 6.87 (d, 2H, Ar-H, δ to NH₂, J=3Hz), 7.2 (s, 4H, 2xNH₂), 7.82 (d, 2H, Ar-H, δ to NO₂, J=9Hz)

Analysis for
Calcd.: C, 47.05; H, 3.26; N, 18.30
Found: C, 47.50; H, 3.48; N, 17.95%

3,3'-Diacetamido-4,4'-dinitrodiphenyl sulfide (58)

A mixture of 57 (1.0 g, 0.0032 mol) in acetic anhydride (2 ml) and glacial acetic acid (10 ml) was refluxed for 4 hr. The reaction mixture was cooled, the separated solid was filtered, washed successively with 10% NaHCO₃ solution and water. Another crop was obtained on dilution of filtrate with water. The combined product was recrystallised from acetone, yield 1.0 g (80%), m.p. 175°.
IR (KBr) cm⁻¹: 1320, 1580 (NO₂), 1600 (Arom), 1700 (CO), 3300 (NH).

NMR (CDCl₃ + DMSO-d₆) δ:
- 2.1 (s, 6H, 2xCOCH₃), 7.05 (dd, 2H, Ar-H, j=2 & 9Hz), 7.92 (d, 2H, Ar-H, o to NO₂, j=9Hz), 8.14 (d, 2H, Ar-H, o to NHAc, j=3Hz)

Analysis for: C₆H₁₄N₄O₈S (390)
- Calcd.: C, 49.23; H, 3.59
- Found: C, 49.50; H, 3.86%

3,3',4,4'-Tetra-aminodiphenyl sulfide (52)

A hot solution of 57 (1.4 g, 0.0032 mol) in acetone (20 ml) and aqueous ammonia (25 ml) was mixed with hot solution of FeSO₄ (7.0 g) in water (20 ml) and aqueous ammonia solution (30 ml) and the reaction mixture heated on water bath for 30 minutes. Then product was extracted with ethyl acetate (5x20 ml), combined extracts dried (Na₂SO₄) and solvent removed in vacuo to get crude product, yield 0.6 g (75%). This was used as such in further steps.

5,5'-Dibenzimidazolyl sulphide (60)

A solution of 59 (0.6 g, 0.0023 mol) in 98% formic acid was refluxed for 5 hr on water bath. The reaction mixture was cooled, neutralized with aqueous ammonia solution, extracted with methylene chloride (2x30 ml), dried (Na₂SO₄) and solvent removed in vacuo. The residual solid was further purified by charcoal treatment, yield
0.45 g (70%), m.p. 260-2°C.

IR (KBr) cm⁻¹: 1605 (Arom), 3350 (NH).

Mass at m/z: 266 (M⁺)

Analysis for: C₁₄H₁₀N₄S (266)

Calcd.: C, 63.15; H, 3.75

Found: C, 63.50; H, 4.10%.

Similarly 61 was prepared by treating 59 with refluxing acetic acid.

2,2'-Dicarbomethoxyamino-5,5'-dibenzimidazolyl
sulphide (62)

A solution of 59 (0.5 g, 0.002 mol) and 1,3-dicarbo-
methoxy-S-methylisothiourea (0.85 g, 0.0042 mol) in ethanol (50 ml) was refluxed overnight. The reaction mixture was cooled. The separated solid was filtered, washed with ethanol (3x20 ml), water (3x20 ml) and dried. The product was then crystallized from acetic acid-water, yield 0.53 g (64%), m.p. > 280°C.

IR (KBr) cm⁻¹: 1600 (Arom), 1710 (CO), 2700–
2800 (C-H), 3300 (NH).

NMR (TFA) δ: 3.6 (s, 6H, 2x0CH₃), 7.1-7.2 (m, 6H,
Ar-H)

Analysis for: C₁₈H₁₆N₆O₄S (412)

Calcd.: C, 52.42; H, 3.88; N, 20.38

Found: C, 52.80; H, 3.52; N, 20.72%. 
Similarly 63 was prepared by reaction of 59 with 1,3-di-carbethoxy-S-methylisothiourea in refluxing ethanol.

4,4'-Dichloro-3,3'-dinitrodiphenyl sulfone (65)

This was obtained by nitration of 4,4'-dichlorodiphenyl sulfone 64 (6.0 g, 0.021 mol) using H₂SO₄-HNO₃ mixture at 60°. The product isolated by pouring it into water, yield 6.7 g (86%), m.p. 201° (lit. 201-202°).

4,4'-Diamino-3,3'-dinitrodiphenyl sulfone (66)

Ammonia gas was passed in a solution of 65 (5.0 g, 0.013 mol) in DMSO at 140° for 5 hr. The reaction mixture cooled and diluted with water. The separated solid was filtered, washed with water and dried, yield 3.52 g (80%), m.p. 286° (lit. 287°).

3,3'-Diamino-4,4'-dinitrodiphenyl sulfone (67)

To a hot solution of 3,3'-diamino-4,4'-dinitrodiphenyl sulfide 57 (0.5 g, 0.0016 mol) in 80% aqueous acetic acid (250 ml) was added KMnO₄ (0.5 g) in small portions during 30 minutes with constant stirring. Stirring was continued for 5 hr at room temperature and excess KMnO₄ was decomposed with H₂O₂ solution in cold. Then the reaction mixture was diluted with water (250 ml). The separated solid was filtered, washed with water (3x20 ml) and dried, yield 0.2 g (36.36%), m.p. 276-8°.
IR(KBr) cm$^{-1}$: 1150 (SO$_2$), 1320, 1560 (NO$_2$), 1620 (Arom), 3300, 3400 (NH$_2$).

Mass at m/z: 338 (M$^+$)

NMR(DMSO-d$_6$) $\delta$: 6.9 (dd, 2H, Ar-H, p to NH$_2$, J=2.5 & 9Hz), 7.65 (d, 2H, Ar-H, o to NH$_2$, J=2.5Hz), 8.16 (d, 2H, Ar-H, o to NO$_2$, J=9Hz).

Analysis for $C_{12}H_10N_4O_6S$ (338)
Calcd.: C, 42.60; H, 2.95; N, 16.56

Found: C, 43.04; H, 3.16; N, 16.28%.

3,3',4,4'-Tetra-aminodiphenyl sulfone (68)

To a warm solution of 66 (5.0 g, 0.015 mol) in THF-ethanol (1:1, 200 ml) and Raney-nickel ($\sim$ 1.5 g), was added dropwise a solution of hydrazine-hydrate (5.75 ml, 0.12 mol) in ethanol (25 ml) during 30 minutes. After addition was complete, the reaction mixture was refluxed for 3 hr on a water bath. The catalyst was filtered and the product was worked up as usual and purified by acid-base treatment, yield 2.9 g (72%), m.p.148-52$^\circ$.

IR(KBr) cm$^{-1}$: 1125 (SO$_2$), 1620 (Arom), 3200-3350 (NH$_2$).

5,5'-Dibenzimidazolyl sulphone (69)

A solution of 68 (1.0 g, 0.0036 mol) in 98% formic acid (20 ml) was heated for 5 hr on a water bath. The
reaction mixture was cooled, neutralized with 30% aqueous ammonia solution. The separated solid was filtered, washed with water (3x20 ml), dried and purified over a silica gel column using ethyl acetate as eluant, yield 0.76 g (71%), m.p. >300°.

IR(KBr) cm⁻¹: 1145 (SO₂), 1620 (Arom), 3400 (NH).
Mass at m/z: 298 (M⁺)
NMR(DMSO-d₆) δ: 7.65 (bs, 6H, Ar-H), 8.2 (s, 2H, 2xN=CH-N).

Similarly 70 was prepared from 68 and acetic acid.

2,2'-Dicarbomethoxy amino-5,5'-dibenzimidazolyl sulphone (71)

A solution of 68 (1.0 g, 0.0036 mol) and 1,3-dicarbomethoxy-S-methylisothiourea (1.5 g, 0.0072 mol) in ethanol (30 ml) was refluxed for 15 hr. The reaction mixture was worked-up as usual and recrystallized from acetic acid-water, yield 0.98 g (61.8%), m.p. > 280°.

IR(KBr) cm⁻¹: 1715 (CO), 2700-2900 (C-H), 3350 (NH).
NMR(TFA) δ: 3.6 (bs, 6H, 2xOCH₃), 7.5-7.8 (m, 6H, Ar-H)
Analysis for: C₁₈H₁₆N₆O₆S (444)
Calcd.: C, 48.64; H, 3.60; N, 18.91
Found: C, 48.28; H, 4.06; N, 19.32%

Similarly compound 72 was prepared from 68 and 1,3-dicarbethoxy-S-methylisothiourea in refluxing ethanol.
4-Acetamido-3-nitrobenzoic acid (74)

This compound was prepared by nitration of 4-acetamidobenzoic acid (50 g, 0.27 mol) with HNO₃, (200 ml, d=1.5), yield 52 g (87%), m.p. 220° (lit. m.p. 221°).

4-Amino-3-nitrobenzoic acid (75)

Hydrolysis of 74 (10.0 g, 0.044 mol) in concentrated HCl (30 ml) gave the required product, yield 6.15 g (76%), m.p. 282-83° (lit. m.p. 284°).

3,4-Diaminobenzoic acid (76)

Catalytic hydrogenation of 75 (1.0 g, 0.0054 mol) using Raney-nickel (about 200 mg) in ethanol and H₂ at 3 kg/cm² pressure in a Paar hydrogenator gave the product by usual work-up, yield 0.6 g (72.3%), m.p. 215-16° (lit. m.p. 215-18°).

2-Carbethoxyaminobenzimidazole-5(6)-carboxylic acid (78)

A mixture of 76 (1.0 g, 0.0065 mol) and 1,3-dicarbethoxy-S-methylisothiourea (1.53 g, 0.0065 mol) in ethanol (30 ml) was refluxed for 12 hr. The product was worked-up as usual and recrystallised from acetic acid-water, yield 1.0 g (62.5%), m.p. >280°.

IR(KBr) cm⁻¹ : 1595 (Ar ν), 1700 (C=O), 2800-2900 (C-H), 3350 (NH).
NMR(TFA) δ: 1.0 (t, 3H, CH₂CH₃, J=7Hz), 4.08 (q, 2H, CH₂CH₂, J=7Hz), 7.2-8.05 (m, 3H, Ar-H)

Analysis for Calcd.: C, 53.01; H, 4.41
Found: C, 53.42; H, 4.68%

Similarly, compound 77 was prepared from 76 and 1,3-dicarbomethoxy-S-methylisothiourea in refluxing ethanol, yield (56%), m.p. 300°.

IR(KBr) cm⁻¹: 1600 (Arom), 1720 (CO), 2600-2700 (C-H), 3350 (NH).

NMR(TFA) δ: 3.52 (s, 3H, OCH₃), 7.2-8.2 (m, 3H, Ar-H).

Analysis for Calcd.: C₁₀H₉N₃O₄
Found: C, 51.06; H, 3.82

C, 50.60; H, 4.12%

4,4'-Dichlorobenzophenene (83)

4-Chlorobenzoyl chloride (6.0 g, 0.0034 mol) was treated with chlorobenzene (3.8 g, 0.033 mol) in presence of AlCl₃ (10.0 g) in dry CS₂ (50 ml), yield 4.6 g (54.8%), m.p.145° (lit.34 m.p.144-146°).

4,4'-Dichloro-3,3'-dinitrobenzophenone (84)

This compound was prepared by nitration of 83 (6.0 g, 0.023 mol) in H₂SO₄ (24 ml, d=1.84) and HNO₃ (24 ml, d=1.42) at 60°. The product was worked up in usual manner and
crystallized from ethanol, yield 6.75 g (82.8%), m.p. 144-5° (lit. 35 m.p. 146.5°).

4,4'-Diamino-3,3'-dinitrobenzophenone (85)

NH₃ gas was bubbled to a solution of 84 (1.1 g, 0.0032 mol) in DMSO (20 ml) at 140° for 4 hr. The product was isolated on dilution with water, yield 0.9 g (92.7%), m.p. 121° (lit. m.p. 121°).

IR(KBr) cm⁻¹ : 1320, 1530 (NO₂), 1600 (Arom), 1625, (CO), 3380, 3500 (NH₂).

NMR(DMSO-d₆) δ : 7.05 (d, 2H, Ar-Η, 0 to NH₂, J=9Hz), 7.7 (dd, 2H, Ar-Η, P to NO₂, J=2 & 9Hz), 8.26 (d, 2H, Ar-Η, 0 to NO₂, J=2Hz).

3,3',4,4'-Tetra-aminobenzophenone (86)

A mixture of 85 (3.02 g, 0.01 mol) and Raney-nickel (about 0.5 g) in ethanol (100 ml) was shaken with H₂ at 3.5 kg/cm² in a Paar hydrogenator for 16 hr and product worked-up in usual manner, yield 2.0 g (82.6%), m.p. 217° (lit. 37 m.p. 217°).

IR(KBr) cm⁻¹ : 1625 (CO), 3320-3380 (NH₂).

NMR(DMSO-d₆) δ : 6.46 (d, 2H, Ar-Η, J=9Hz), 6.75 (dd, 2H, Ar-Η, J=2 & 9Hz), 6.9 (d, 2H, Ar-Η, J=2Hz).
2,2'-Dicarbomethoxyamino-5,5'-dibenzimidazolyl ketone (81)

A solution of 86 (0.5 g, 0.002 mol) and 1,3-dicarbomethoxy-S-methylisothiourea (0.86 g, 0.0041 mol) in ethanol (20 ml) was refluxed for 12 hr. The product was isolated in usual manner and recrystallised from acetic acid-water, yield 0.55 g (65.5%), m.p. > 280°.

IR(KBr) cm⁻¹: 1590 (Arom), 1630, 1705 (CO), 2700-2900 (C-H), 3300 (NH).

NMR(TFA) δ: 3.62 (s, 6H, 2xOCH₃), 7.4-7.85 (m, 6H, Ar-H)

Analysis for C₁⁹H₁₆N₆O₅ (408)
Calcld.: C, 55.88; H, 3.92
Found:  C, 56.30; H, 3.65%.

Similarly 82 was prepared from 86 and 1,3-dicarbethoxy-S-methylisothiourea in ethanol.

5,5'-Dibenzimidazolyl ketone (88)

A solution of 86 (0.5 g, 0.002 mol) in 98% formic acid (15 ml) was heated for 3 hr on a water bath. The reaction mixture was cooled, neutralized with aqueous ammonia solution. The solid thus separated was filtered, washed with water, dried, yield 0.4 g (74%), m.p. 280°.

IR(KBr) cm⁻¹: 1620 (Arom), 1645 (CO).

Mass at m/z: 262 (M⁺)

NMR(DMSO-d₆) δ: 7.5-8.5 (m, 8H, Ar-H & N=CH-N).
Analysis for: C_{19}H_{10}N_{4}O (262)

Calcd.: C, 68.70; H, 3.81

Found: C, 68.32; H, 4.12%.

Similarly 89 was prepared from 86 and glacial acetic acid.

3,3',4,4'-Tetra-aminodiphenyl methane (87)

A mixture of 85 (3.0 g, 0.01 mol), 99% hydrazine-hydrate (3 ml, 0.08 mol) and KOH (3 g) was heated in steel bomb at 170° for 24 hr. The reaction mixture was cooled, the separated pure solid (1.2 g) was filtered, washed with water and dried. The filtrate was extracted with ethyl acetate (3x20 ml), washed with water (3x20 ml), dried (Na$_2$SO$_4$) and solvent removed in vacuo. The product crystallised from ethanol, yield 1.45 g (64%), m.p.136° (lit. 37 m.p. 137°).

IR(KBr) cm$^{-1}$: 1600 (Arom), 3300-3500 (NH$_2$).

NMR(CDCl$_3$ + DMSO-d$_6$) $\delta$ Ar-H).

2,2'-Dicarbomethoxy amino-5,5'-dibenzimidazolylmethane (90)

A solution of 87 (0.8 g, 0.0035 mol) and 1,3-dicarbomethoxy-S-methylisothiourea (1.45 g, 0.0070 mol) in ethanol (30 ml) was refluxed for 15 hr. The product was isolated in usual manner and recrystallised from acetic acid-water, yield 0.86 g (62.7%), m.p. >300°.
IR(KBr) cm$^{-1}$: 1710 (C=O), 2600-2950 (C-H)

NMR(TFA) δ: 3.6 (s, 6H, 2xOCH$_3$), 3.86 (s, 2H, -CH$_2$-), 6.96-7.15 (m, 6H, Ar-H)

Analysis for Calcd.: C$_{19}$H$_{18}$N$_6$O$_4$ (394)

Calcd.: C, 57.86; H, 4.56

Found: C, 58.22; H, 4.34%.

In similar manner 91 was prepared by treating 87 with 1,3-dicarboxy-S-methylisothiourea in refluxing ethanol.

5,5′-Dibenzimidazolylmethane (92)

87 (0.4 g, 0.0017 mol) was heated in 98% formic acid for 2 hr on water bath. The product was worked-up as usual and finally crystallized from water, yield 0.30 g (70%), m.p.120-2°.

IR(KBr) cm$^{-1}$: 1600 (Arom), 3100-3350 (NH).

NMR(DMSO-d$_6$) δ: 4.1 (s, 2H, CH$_2$), 6.9-7.6 (m, 6H, Ar-H), 8.12 (s, 2H, 2xN=CH-N)

Analysis for Calcd.: C$_{15}$H$_{12}$N$_4$ (248)

Calcd.: C, 72.58; H, 4.83

Found: C, 72.42; H, 5.12%.

Using the above method, 93 was prepared by refluxing 87 in glacial acetic acid.
4-Acetoxyacetanilide (95)

This compound was prepared by acetylation of 4-acetamidophenol 94 (15 g, 0.1 mol) by acetic anhydride in glacial acetic acid using literature method, yield 15.44 g (80%), m.p.148-52° (lit. m.p.151-4°).

4-Acetoxy-2-nitroacetanilide (96)

Nitration of 95 (10.0 g, 0.051 mol) in HNO₃ (10 ml, d=1.5) was done under cooling and stirring. The reaction mixture was poured on ice and product filtered, dried and recrystallized from 50% aqueous ethanol, yield 7.8 g (64%), m.p.142-4° (lit. m.p.145-46°).

4-Acetamido-3-nitrophenol (97)

To a hot suspension of 96 (1.0 g, 0.00 42 mol) in ethanol (10 ml) was added 10% aqueous solution of KOH (0.25 g) and mixture heated for 15 minutes on water bath. Solvent removed and the residue acidified with dilute HCl. The crystals separated on cooling, were filtered, washed and dried, yield 0.70 g (85.3%), m.p.218° (lit. m.p.218-20°).

5-(4-Acetamidophenoxy)-2-nitroacetanilide (101)

A solution of potassium-4-acetamidophenoxy (0.5 g, 0.0031 mol) and 5-chloro-2-nitroacetanilide (56) (0.67 g, 0.0031 mol) in dry DMF (30 ml) was refluxed for
24 hr. The reaction mixture was cooled, diluted with water (100 ml) and extracted with ethyl acetate (3x25 ml). The combined extract was dried (Na$_2$SO$_4$), solvent removed \textit{in vacuo} and the residue crystallised from ethanol, yield 0.48 g (48\%), m.p.178°.

IR(KBr) cm$^{-1}$ : 1320, 1520 (NO$_2$), 1600 (Arom), 1660, 1700 (C=O), 3250 (NH).

NMR(DMSO-d$_6$) $\delta$ : 2.06 (s, 6H, 2xCOCH$_3$), 6.8 (dd, 1H, Ar-H, p to NHAc, $J$=2.5 & 9Hz), 7.06 (d, 2H, Ar-H, m to NHAc, $J$=9Hz), 7.42 (d, 1H, Ar-H, o to NHAc (m to NO$_2$), $J$=2Hz), 7.68 (d, 2H, Ar-H, o to NHAc, $J$=9Hz), 8.0 (d, 1H, Ar-H, o to NO$_2$, $J$=9Hz), 10.0 (s, 1H, NHCO)

Analysis for C$_{16}$H$_{15}$N$_3$O$_5$ (329)
Calcd. : C, 58.05; H, 4.55
Found : C, 58.42; H, 4.35%.

4,4'-Dinitrodiphenyl ether (102)

A mixture of potassium 4-nitrophenoxide (20.0 g, 0.113 mol) and 1-chloro-4-nitrobenzene (17.8 g, 0.113 mol) was refluxed in dry DMF (50 ml) for 40 hr and worked-up as usual, yield 12.5 g (42.6\%), m.p.142° (lit.39 m.p. 142-3°).
4,4'-Diaminodiphenyl ether (103)

This was obtained by reduction of 102 (10.0 g, 0.038 mol) by hydrazine hydrate and Raney-nickel by the method as described for 32, yield 5.5 g (72.3%), m.p. 185-6° (lit.39 m.p. 186-7°).

4,4'-Diacetamidodiphenyl ether (104)

Acetylation of 103 (2.0 g, 0.01 mol) by acetic anhydride in an usual manner gave 2.2 g of the product, yield 77.4%, m.p. 222°.

IR(KBr) cm\(^{-1}\) : 1660 (CO), 3280 (NH).

NMR(DMSO-d\(_6\)) \(\delta\) : 2.0 (s, 6H, 2xCOCH\(_3\)), 6.8 (d, 4H, Ar-H, m to NHAc, J=9Hz), 7.45 (d, 4H, Ar-H, o to NHAc, J=9Hz), 9.76 (s, 2H, 2xNCO)

Analysis for \(\text{C}_{16}\text{H}_{14}\text{N}_{2}\text{O}_3\) (284)
Calcd. : C, 57.60; H, 5.63
Found : C, 57.25; H, 5.46%.

4,4'-Diacetamido-3,3'-dinitrodiphenyl ether (105)

To an ice cooled (10°) solution of 104 (5.0 g, 0.017 mol) in glacial acetic acid (30 ml) was added dropwise fuming HNO\(_3\) (6.24 ml, d=1.5) during 20-30 minutes with stirring. The stirring was continued for 2 hr during cooling and then the mixture poured on crushed ice. The solid separated was filtered, washed with water (3x30 ml), dried and recrystallized from ethanol, yield.
5.4 g (82.1%), m.p. 212°.

IR (KBr) cm⁻¹: 1320, 1500 (NO₂), 1670 (CO), 3240 (NH).

NMR (CDCl₃) δ: 2.2 (s, 6H, 2×COCH₃), 7.18 (dd, 2H, Ar-H, p to NO₂, J=3 & 9Hz), 7.65 (d, 2H, Ar-H, o to NO₂, J=3Hz), 8.65 (d, 2H, Ar-H, m to NO₂, J=9Hz).

Analysis for C₁₂H₁₀N₄O₅: Calcd.: C, 51.33; H, 3.74; N, 14.97; Found: C, 51.56; H, 3.28; N, 15.32%.

4,4'-Diamino-3,3'-dinitrodiphenyl ether (106)

105 (4.0 g, 0.0106 mol) was refluxed in 50% HCl (50 ml) for 5 hr. The reaction mixture was cooled, neutralized with aqueous ammonia and the separated solid was filtered, washed with water (3x20 ml) and dried. The product was recrystallized from ethanol, yield 2.8 g (90%), m.p. 176°.

IR (KBr) cm⁻¹: 1320, 1510 (NO₂), 1600 (Arom), 3360, 3500 (NH₂).

NMR (CDCl₃) δ: 5.85 (hump, 4H, 2×NH₂), 6.65 (d, 2H, Ar-H, o to NH₂, J=9Hz), 7.0 (dd, 2H, Ar-H, p to NO₂, J=3 & 9Hz), 7.51 (d, 2H, Ar-H, m to NO₂, J=3Hz).

Analysis for C₁₂H₁₀N₄O₅: Calcd.: C, 49.65; H, 3.44; N, 19.31; Found: C, 49.26; H, 3.82; N, 19.68%.
3,3',4,4'-Tetra-aminodiphenyl ether (107)

To a warm solution of 106 (1.0 g, 0.0034 mol) in ethanol-THF (1:1, 30 ml) and Raney-nickel (0.2 g) was added dropwise hydrazine-hydrate (1.37 g, 0.0272 mol) in ethanol (10 ml). After the addition was complete, the reaction mixture was heated till it was colourless. The catalyst was filtered off, washed with ethanol and solvent removed to get oily product, yield 0.6 g (76%). This was not purified and used as such for next step.

2,2'-Dicarbomethoxyamino-5,5'-dibenzimidazolyl oxide (110)

A mixture of 107 (0.6 g, 0.0026 mol) and 1,3-dicarbomethoxy-S-methylisothioura (1.74 g, 0.0052 mol) in ethanol (30 ml) was refluxed for 12-15 hr. The product was worked-up as usual and recrystallized from DMSO, yield 0.63 g (62%), m.p. >300°.

IR(KBr) cm⁻¹ : 1600 (Arom), 1710 (CO), 2700-2900 (C-H), 3350 (NH).

NMR(TFA) δ : 3.58 (s, 6H, 2x0CH₂), 6.7-7.2 (m, 6H, Ar-H)

Analysis for C₁₈H₁₆N₆O₅ : 396
Calcd. : C, 52.02; H, 4.04.
Found : C, 51.68; H, 4.44%. 
In similar manner compound 111 was prepared from 107 and 1,3-di-carbethoxy-3-methylisothiourea in ethanol while 108 and 109 were obtained by refluxing 107 in formic and acetic acids respectively.

1,2-Di-(3-amino-4-nitrophenylthio)ethane (112)

A solution of ethanedithiol (1.96 ml, 0.017 mol) and KOH (1.94 g, 0.034 mol) in ethanol (20 ml) was stirred at room temperature for 30 minutes. To this stirred solution, was added a solution of 5-chloro-2-nitroaniline 98 (6.0 g, 0.034 mol) in ethanol (25 ml). The reaction mixture was refluxed for 2 hr on a water bath. The separated solid was filtered after cooling the reaction mixture, washed with ethanol (3x20 ml) and water (3x20 ml) and dried, yield 3.0 g (46.5%), m.p. 265-6° (d).

IR(KBr) cm⁻¹ : 1320, 1560 (NO₂), 1620 (Arom), 3350, 3475 (NH₂).

NMR(DMSO-d₆) δ : 3.28 (s, 4H, S-(CH₂)₂-S), 6.45 (dd, 2H, Ar-H, 2 to NH₂, J=3 & 9Hz), 6.84 (d, 2H, Ar-H, 2 to NH₂, J=3Hz), 7.34 (s, 4H, 2xNH₂ exchangeable in D₂O), 7.79 (d, 2H, Ar-H, 2 to NO₂, J=9Hz).

1,2-Di-(3,4-diaminophenylthio)ethane (114)

A suspension of 112 (1.0 g, 0.0027 mol) and 10% Pd/C (∼ 200 mg) in ethanol (200 ml) was shaken in Paar hydrogenator at 3.5 kg/cm² pressure for 10 hr. The catalyst
was filtered and washed with ethanol (2x10 ml). Solvent was removed from filtrate in vacuo to get crude tetrabaine which was crystallised from ethanol, yield 0.2 g (24%), m.p. 115°.

\[ \text{IR(KBr) cm}^{-1} : 1605 \text{ (Arom)}, 3200, 3300 \text{ (NH}_2\text{).} \]

Mass at m/z : 306 (M$^+$).

1,2-Di-(2-carbomethoxyaminobenzimidazole-5(6)-thio)ethane (115)

A solution of 114 (0.4 g, 0.0013 mol) and 1,3-dicarbomethoxy-S-methylisothiourea (0.54 g, 0.0026 mol) in ethanol (25 ml) was refluxed for 15 hr. The compound was isolated as usual, yield 0.35 g (57.3%), m.p. > 280°.

\[ \text{IR(KBr) cm}^{-1} : 1600 \text{ (Arom)}, 1715 \text{ (CO)}, 2700-2900 \text{ (C-H), 3340 \text{(NH).}} \]

\[ \text{NMR(TFA) } \delta : 2.72 \text{ (s, 4H, S-(OH)}_2 \text{S), 3.58 \text{ (s, 6H, 2xOCH}_3 \text{), 7.08-7.22 \text{ (m, 6H, Ar-H).}} \]

Analysis for $C_{20}H_{20}N_6O_4S_2$ (472)

Calcd. : C, 50.84; H, 4.23

Found : C, 51.22; H, 4.64%.

Similarly 116 was prepared from 114 and 1,3-dicarbethoxy-S-methylisothiourea in refluxing ethanol.
4-Chloro-3-nitrobenzoyl chloride (117) and 4-acetamido-3-nitrobenzoyl chloride (118)

These were prepared by refluxing 4-chloro-3-nitrobenzoic acid and 4-acetamido-3-nitrobenzoic acid with thionyl chloride in dry benzene in 70 and 72% yields. The acid chlorides were used as such in next step.

1,4-Di-(4-chloro-3-nitrobenzoyl)piperazine (119)

A solution of anhydrous piperazine (0.5 g, 0.0058 mol) in dry benzene (20 ml) was added dropwise to a stirred solution of 4-chloro-3-nitrobenzoyl chloride 117 (2.56 g, 0.0116 mol) in dry benzene (100 ml). Stirring was continued for 5 hr at room temperature. The separated solid was filtered, washed with benzene (3x10 ml), water (5x10 ml) and dried, yield 2.2 g (83.6%), m.p. 224°.

IR(KBr) cm⁻¹ : 1340, 1535 (NO₂), 1640 (NCO), 2670, 2920 (C-H).

NMR(DMSO-d₆) δ : 3.47 (s, 8H, 4xN-CH₂), 7.6-7.8 (m, 4H, Ar-H, m & p to NO₂), 8.0 (d, 2H, Ar-H, o to NO₂, J=3Hz)

Analysis for C₁₈H₁₄N₄O₆Cl₂ (453)
Calcd. : C, 47.68; H, 3.09
Found : C, 47.56; H, 3.15%.

Similarly 120 was prepared from 4-acetamido-3-nitrobenzoyl chloride (118) and anhydrous piperazine in dry benzene, yield 88.1%, m.p. 250°.
140

IR(KBr) cm⁻¹: 1360, 1540 (NO₂), 1650 (NCO), 1670 (NHCO), 2700, 2950 (C-H), 3300 (NH).

NMR(TFA) δ: 2.02 (s, 6H, 2xCOCH₃), 3.6 (s, 8H, N-(CH₂)₄), 7.2-8.25 (m, 6H, Ar-H)

Analysis for C₂₂H₂₂N₆O₈ (498)
Calcd.: C, 53.01; H, 4.41
Found: C, 52.65; H, 4.86%.

1,4-Di-(4-amino-3-nitrobenzoyl)piperazine (121)

To a stirred suspension of 120 (4.6 g, 0.0092 mol) in ethanol (100 ml) was added dropwise at room temperature a 10% aqueous solution of KOH in small fractions till all the compound went into the solution. Stirring continued for 5 hr at room temperature, the separated solid was filtered, washed with ethanol (3x20 ml), water (3x20 ml), dried and crystallised from DMSO-water, yield 2.4 g (62.8%), m.p. 280° (d).

IR(KBr) cm⁻¹: 1350, 1520 (NO₂), 1600 (Arom), 1640 (-NCO).

NMR(DMSO-d₆) δ: 3.55 (s, 8H, N-(CH₂)₄), 6.98 (d, 2H, Ar-H, m to NO₂, J=8Hz), 7.42 (dd, 2H, Ar-H, p to NO₂, J=2 & 9Hz), 7.5-7.7 (bs, 4H, 2xNH₂), 7.95 (d, 2H, Ar-H, o to NO₂, J=2Hz)

Analysis for C₁₈H₁₈N₆O₆ (414)
Calcd.: C, 52.17; H, 4.34
Found: C, 52.53; H, 4.68%.
1,4-Di-(3,4-diaminobenzoyl)piperazine (122)

A suspension of 121 (1.0 g, 0.0024 mol) in ethanol-THF (1:1, 200 ml) and Raney-nickel (0.3 g) was shaken on a Paar hydrogenator at 3.5 kg/cm² pressure for 12 hr. The catalyst was filtered off and washed with hot alcohol-THF (3x25 ml). The filtrate was concentrated and the residue crystallized from ethanol, yield 0.45 g (53%), m.p. 266-7°.

IR(KBr) cm⁻¹ : 1590 (Arom), 1620 (CO), 3180, 3240 (NH₂).
Mass at m/z : 354 (M⁺).

1,4-Di-(2-carbomethoxyaminobenzimidazolyl-5(6)-carbonyl)piperazine (123)

A solution of 122 (0.3 g, 0.008 mol) and 1,3-dicarbomethoxy-S-methylisothiourea (0.35 g, 0.0017 mol) in ethanol (25 ml) was refluxed for 15 hr. The reaction mixture was cooled, the solid thus separated was filtered, washed with water (3x10 ml), ethanol (3x10 ml) and dried, yield 0.18 g (41%), m.p. >280°.

IR(KBr) cm⁻¹ : 1720 (CO), 2750-2950 (C-H), 3460 (NH).
NMR(TFA) δ : 3.35 (hump, 8H, N-(CH₄)4), 3.6 (s, 6H, 2xOCH₃), 7.0-7.5 (m, 6H, Ar-H)
Analysis for C₂₄H₂₄N₈O₆ (520)
Calcd. : C, 55.38; H, 4.61; N, 21.53
Found : C, 54.95; H, 4.88; N, 21.32%.
In similar manner 124 was prepared from 101 and 1,3-dicarbethoxy-3-methylisothiourea.

4-Amino-3-nitrobiphenyl (125)

4-Acetamido-3-nitrobiphenyl (25.6 g, 0.1 mol) was suspended in boiling ethanol (100 ml) and potassium hydroxide (12.8 g) in water (12 ml) was added. The reaction mixture was heated on water bath for 25 minutes and cooled. Crystals separated after 10 minutes which were filtered and purified by washing with 30% aqueous ethanol, yield 18.5 g (86.4%), m.p.168° (lit.40 m.p.167-9°).

3,4-Diaminobiphenyl (126)

This was prepared by reduction of 125 using hydrazine-hydrate and Raney-nickel and worked-up as usual, yield 65%, m.p.103° (lit.41 m.p.102°-103°).

Ethyl 5(6)-phenylbenzimidazole-2-carbamate (127)

A mixture of 126 (1.0 g, 0.0054 mol) and 1,3-dicarbethoxy-3-methylisothiourea (1.26 g, 0.006 mol) in ethanol (50 ml) was refluxed for 12 hr. The reaction mixture was cooled and product isolated as usual and crystallized from acetic acid-water, yield 0.9 g (60%), m.p.220°.

IR(KBr) cm⁻¹ : 1700 (C=O), 2700-2900 (C-H), 3400 (NH).
NMR (TFA) $\delta$ : 1.0 (t, 3H, $CH_2CH_3$, $J=8$ Hz), 4.0 (q, $2H$, $CH_2CH_3$, $J=8$ Hz), 6.8-7.3 (m, 8H, Ar-$H$).

**Analysis for** : $C_{16}H_{15}N_2O_2$ (281)

Calcd. : C, 68.37; H, 5.33

Found : C, 68.56; H, 5.66%.

**4-(Benzoyl)amino-3-nitrobiphenyl (128)**

A solution of benzoyl chloride (0.77 g, 0.0055 mol) in dry benzene (20 ml) was added dropwise to a refluxing solution of 125 (1.0 g, 0.0046 mol) in dry benzene (30 ml) and refluxing continued for 12 hr. The reaction mixture was cooled and successively washed with water (3x20 ml) and 10% NaHCO$_3$ solution (3x20 ml). The organic layer was dried (Na$_2$SO$_4$) and solvent removed in vacuo to get a solid mass which was crystallized from benzene, yield 1.2 g (81%), m.p. 140$^\circ$.

IR (KBr) cm$^{-1}$ : 1320, 1580 (NO$_2$), 1680 (CO).

NMR (DMSO-$d_6$) $\delta$ : 7.25-7.95 (m, 12H, Ar-$H$), 8.18 (d, 1H, Ar-$H$, o to NO$_2$, $J=2$ Hz)

**Analysis for** : $C_{19}H_{14}N_2O_3$ (318)

Calcd. : C, 71.69; H, 4.46

Found : C, 72.00; H, 4.42%.

Similarly, compounds 129 and 130 were prepared by treating 125 with corresponding acid chlorides in dry benzene.
129, yield 75%, m.p. 151°.

IR(KBr) cm⁻¹ : 1320, 1520 (NO₂), 1685 (CO).
NMR(DMSO-d₆) δ : 7.32-8.0 (m, 11H, Ar-H), 8.12 (d, 1H, PhC=CH-C-NO₂, J=2Hz)
Analysis for : C₁₉H₁₃N₃O₅ (363)
Calcd. : C, 62.90; H, 3.57
Found : C, 63.32; H, 3.83%.

130, yield 76%, m.p. 244°.

IR(KBr) cm⁻¹ : 1340, 1520 (NO₂), 1680 (CO)
Analysis for : C₁₉H₁₃N₃O₅ (363)
Calcd. : C, 62.90; H, 3.57
Found : C, 62.78; H, 3.68%.

3-Amino-4-(benzoyl)aminobiphenyl (131)

To a warm mixture of 128 (1.0 g, 0.0031 mol) and Raney-nickel (∼ 0.2 g) in ethanol-THF (2:1, 50 ml), a solution of hydrazine-hydrate (1.25 g, 0.0248 mol) in ethanol (20 ml) was added dropwise and refluxing continued for 1 hr. Catalyst was filtered off and mother liquor was concentrated to get a solid which was crystallized from ethanol, yield 0.65 g (72%), m.p. 198-200°.

IR(KBr) cm⁻¹ : 1635 (CO), 3200-3400 (NH,NH₂).
Analysis for : C₁₉H₁₆N₂O (288)
Calcd. : C, 79.13; H, 5.55
Found : C, 79.43; H, 5.28%.
In similar manner 132 and 133 were prepared by reducing 129 and 130 with hydrazine-hydrate and Raney-nickel in ethanol-THF mixture.

132, yield 64%, m.p. 188°.

IR(KBr) cm⁻¹ : 1620 (C=O), 3200-3300 (NH,NH₂)
Analysis for : C₁₉H₁₇N₃O (303)
Calcd. : C, 75.24; H, 5.61
Found : C, 75.62; H, 5.78%.

133, yield 68%, m.p. 228°.

IR(KBr) cm⁻¹ : 1625 (C=O), 3200-3300 (NH,NH₂)
Analysis for : C₁₉H₁₇N₃O (303)
Calcd. : C, 75.24; H, 5.61
Found : C, 75.38; H, 5.46%.

2,5(6)-Diphenylbenzimidazole (134)

A solution of 131 (1.0 g, 0.0034 mol) in ethanol (10 ml) and concentrated hydrochloric acid (20 ml) was refluxed for 8 hr. The reaction mixture was cooled, the separated solid was filtered and basified with aqueous ammonia solution. The aqueous layer was extracted with ethyl acetate (2x30 ml), dried (Na₂SO₄) and solvent removed in vacuo to get pure product, yield 0.58 g (62%), m.p. 195° (lit. 42 m.p. 197-8°).

IR(KBr) cm⁻¹ : 1620 (Arom).
Mass at m/z: 270 (M^+)
Analysis for C_{19}H_{14}N_{2}
Calcd.: C, 84.10; H, 5.18
Found: C, 83.68; H, 5.53%.

Compounds 135 and 136 were prepared similarly from 132 and 133.

135, yield 63%, m.p. 215°.
IR(KBr) cm\(^{-1}\): 1605 (Arom), 3150-3420 (NH,NH\(_2\)).
Mass at m/z: 285 (M^+)
Analysis for C_{19}H_{15}N_{3} (285)
Calcd.: C, 80.00; H, 5.26
Found: C, 80.32; H, 5.48%.

136, yield 58%, m.p. 227-8°.
IR(KBr) cm\(^{-1}\): 1600 (Arom), 3200-3400 (NH,NH\(_2\)).
Mass at m/z: 285 (M^+)
Analysis for C_{19}H_{15}N_{3} (285)
Calcd.: C, 80.00; H, 5.26
Found: C, 80.24; H, 5.12%.

2-(4-Isothiocyanatophenyl)-5(6)-phenylbenzimidazole-
hydrochloride (139)

A solution of thiophosgene (0.27 ml, 0.0035 mol) in dry acetone (10 ml) was added dropwise to a stirred solution of 135 (1.0 g, 0.0035 mol) in dry acetone.
(35 ml) at room temperature. The stirring was continued for 8 hr, the separated hydrochloride was filtered, washed with ethyl acetate (3x10 ml) and dried, yield 0.78 g (65%), m.p. 295-8°.

IR(KBr) cm⁻¹: 1605 (Arom), 1630 (C=N), 2050 (NCS), 2600-2900 (salt),

Analysis for: C₁₀H₁₃N₂S.HCl (363.5)
Calcd.: C, 66.24; H, 3.85
Found: C, 66.38; H, 3.62%.

2-(4-Carbomethoxyaminophenyl)-5(6)-phenylbenzimidazole(141)

Methyl chloroformate (0.4 g, 0.0042 mol) was added to a solution of 136 (1.0 g, 0.0035 mol) in pyridine (20 ml) and the reaction mixture heated at 100° for 1 hr. The reaction mixture was cooled and diluted with water (100 ml). The separated solid was filtered, washed with water, dried and crystallized from ethanol, yield 1.0 g (85%), m.p. 210°.

IR(KBr) cm⁻¹: 1600 (Arom), 1710 (CO), 3320 (NH).
NMR(TFA) δ: 3.5 (s, 3H, OCH₃), 6.8-7.6 (m, 12H, Ar-H)

Analysis for: C₂₁H₁₇N₂O₂ (343)
Calcd.: C, 73.46; H, 4.95
Found: C, 73.72; H, 5.22%.

Similarly 140 was prepared from 136 and ethyl chloroformate, yield 80%, m.p. 255°.
IR(KBr) cm$^{-1}$: 1600 (Arom), 1700 (C=O), 3300-3400 (NH).

NMR(D$_2$O-d$_6$) $\delta$: 1.2 (t, 3H, CH$_2$CH$_3$, J=7Hz), 4.1 (q, 2H, CH$_2$CH$_3$, J=7Hz), 7.2-8.3 (m, 12H, Ar-H)

Analysis for Galcd. Found: C, 73.94; H, 5.32
   Calcd. : C, 74.35; H, 5.12%

9-Phenylbenzimidazo[1,2-c]quinazolin-6-one (137)

A mixture of 135 (1.0 g, 0.0035 mol) and ethyl chloroformate (0.38 g, 0.0035 mol) in pyridine (20 ml) was refluxed for 2 hr. The reaction mixture was cooled and diluted with water. The separated solid was filtered, washed thoroughly with water, dried and crystallized from DMSO, yield 0.83 g (75%), m.p. 296°.

IR(KBr) cm$^{-1}$: 1620 (C=N), 1710 (C=O)

Mass at m/z: 311 (M$^+$)

Analysis for: C$_{22}$H$_{19}$N$_3$O$_2$ (357)
   Calcd.: C, 73.94; H, 5.32
   Found: C, 74.35; H, 5.12%

Under identical reaction condition, 9-phenylbenzimidazo[1,2-c]quinazoline-6-thione (138) was prepared by reaction of 135 with potassium ethyl xanthate in pyridine, yield 72%, m.p. 255-6°.

IR(KBr) cm$^{-1}$: 1160 (C=S), 1630 (C=O).
Mass at m/z : 327 (M$^+$)
Analysis for : C$_{20}$H$_{13}$N$_3$S (327)
Calcd. : C, 73.39; H, 3.91
Found : C, 73.52; H, 4.26%.

1-(2-Aminobenzoyl)-2-mercapto-5-phenylbenzimidazole (143)

Thiophosgene (0.13 ml, 0.0016 mol) in acetone (20 ml) was added dropwise to a stirred solution of 132 (0.5 g, 0.0016 mol) in dry acetone (30 ml) and triethylamine (0.32 ml, 0.0032 mol) dropwise at room temperature. The stirring was continued for 5 hr and the solid separated was filtered, washed with acetone (3x10 ml), dried and crystallized from DMSO-water, yield 0.24 g (45%), m.p. 275°.

IR(KBr) cm$^{-1}$ : 1690 (C=O), 3200-3400 (NH$_2$).
Mass at m/z : 345 (M$^+$)
Analysis for : C$_{20}$H$_{15}$N$_3$O$_8$ (345)
Calcd. : C, 69.56; H, 4.34
Found : C, 70.04; H, 4.15%.

15% of 144 was also obtained from mother liquor.

l-(4-Isothiocyanatobenzoyl)-2-mercapto-5-phenylbenzimidazole (145)

To a stirred solution of 133 (0.5 g, 0.0016 mol) in dry acetone (30 ml) and triethylamine (0.65 ml, 0.0065 mol), a solution of thiophosgene (0.25 ml, 0.0032 mol) in
dry acetone (30 ml) was added dropwise at room temperature. Stirring was continued for 10 hr. Solvent was removed in vacuo and the residue crystallized from benzene, yield 0.41 g (65%), m.p. 195°.

IR(KBr) cm⁻¹ : 1680 (CONH), 2060 (NCS).
Mass at m/z : 387 (M⁺), base peak 162.
Analysis for : C₂₁H₁₃N₃O₂S₂ (387)
Calcd. : C, 65.11; H, 3.35
Found : C, 65.38; H, 3.25%.

Similarly 144 was prepared from 132 and two moles of thiophosgene and purified by column chromatography using silica gel column and ethyl acetate-benzene (1:4) as eluant, yield 50%, m.p. 255-260°.

IR(KBr) cm⁻¹ : 1710 (CO), 2080 (NCS)
Mass at m/z : 387 (M⁺), base peak 329
Analysis for : C₂₁H₁₃N₃O₂S₂ (387)
Calcd. : C, 65.11; H, 3.35
Found : C, 65.23; H, 3.50%.

5-(4-Acetamidophenylthio)-2-nitroacetanilide (148)

To a solution of 4-acetamidothiophenol (5.0 g, 0.03 mol) in n-propanol (30 ml), 10% aqueous solution of KOH (1.66 g, 0.03 mol) was added at room temperature and stirring was continued for 30 minutes. To this was added a solution of 5-chloro-2-nitroacetanilide 56 (6.42 g, 0.03 mol) in n-propanol (20 ml). The reaction mixture
was refluxed for 5 hr, cooled and the crystallized solid filtered, washed successively with n-propanol (2x10 ml) and water (3x10 ml) and dried, yield 7.8 g (75.5%), m.p. 196°.

IR(KBr) cm⁻¹ : 1300, 1570 (NO₂), 1600 (Arom), 1660, 1705 (CO), 3280 (NH).

NMR(DMSO-d₆) δ : 2.02 (s, 3H, COCH₃), 2.08 (s, 3H, COCH₃ o to NO₂), 6.86 (dd, 1H, Ar-H, p to NHAc, J=3 & 9Hz), 7.4-7.95 (m, 6H, Ar-H), 10.2 (hump, 1H, NHCO).

Analysis for C₁₆H₁₅N₃O₄S (345)
Calcd. : C, 55.65; H, 4.34
Found : C, 55.95; H, 4.10%.

Similarly 147 was prepared from 4-acetamidothiophenol and 5-chloro-2-nitroaniline (98) in n-propanol.

147 was also prepared by selective hydrolysis of 148 described below.

5-(4-Acetamidophenylthio)-2-nitroaniline (147)

To a suspension of 148 (10.0 g, 0.029 mol) in boiling ethanol (50 ml) was added a solution of KOH (2.0 g) in water (10 ml). The reaction mixture was heated for 5 minutes on a water bath and left at room temperature. The product crystallized after cooling which was filtered, washed with 50% aqueous ethanol and dried, yield 6.2 g.
m.p.176-7°.

IR(KBr) cm⁻¹ : 1300, 1560 (NO₂), 1600 (Arom), 1650 (C=O), 3260, 3340, 3470 (NH,NH₂).

NMR(DMSO-d₆) δ : 2.1 (s, 3H, COCH₃), 6.25 (dd, 1H, Ar-H, p to NH₂, J=2.9Hz), 6.55 (d, 1H, Ar-H, o to NH₂, J=2Hz), 7.45 (d, 2H, Ar-H, m to NHAc, J=9Hz), 7.78 (d, 2H, Ar-H, o to NHAc, J=9Hz), 7.84 (d, 1H, Ar-H, o to NO₂, J=9Hz), 10.2 (hump, 1H,NHC=O).

Analysis for C₁₄H₁₃N₃S (303)

Calcd. : C, 55.44; H, 4.29; N, 13.86

Found : C, 55.12; H, 4.65; N, 14.24%.

5-(4-Acetamidophenylthio)-o-phenylenediamine (149)

To a warm mixture of 147 (6.06 g, 0.02 mol) and Raney-nickel (~ 0.8 g) in ethanol-THF (1:1, 50 ml), was added dropwise hydrazine-hydrate in ethanol (8.0 g, 0.16 mol) with occasional shaking. When solution became colourless the catalyst was filtered off, washed with ethanol (3x10 ml) and the filtrate was evaporated in vacuo to get crude diamine, yield 3.8 g (78.1%). This product was as such used in next step.

Ethyl 5(6)-(4-acetamidophenylthio)benzimidazole-2-carbamate (151)

A mixture of 149 (9.0 g, 0.033 mol) and 1,3-dicarbethoxy-S-methylisothiourea (7.7 g, 0.0034 mol) in ethanol
(150 ml) was refluxed for 16 hr. The reaction mixture was cooled and the separated solid was filtered, washed with ethanol, dried and recrystallized from acetic acid-water, yield 8.69 g (70.4%), m.p. 235-6°.

IR(KBr) cm⁻¹  : 1650 (COCH₃), 1700 (NHCOO), 2700-2800 (C-H), 3400 (NH).

NMR(TFA) δ  : 0.98 (t, 3H, CH₂CH₃, J=8Hz), 2.0 (s, 3H, COCH₃), 3.98 (q, 2H, CH₂CH₃, J=8Hz), 6.8-7.1 (m, 7H, Ar-H).

Analysis for : C₁₈H₁₈N₄O₃S (370)

Calcd. : C, 58.37; H, 4.86; N, 15.13

Found : C, 58.68; H, 4.44; N, 15.46%.

Using similar experimental condition 150 was also prepared from 149 and 1,3-dicarbomethoxy-3-methylisothiourea in refluxing ethanol.

5(6)-(4-Acetamidophenylthio)-2-methylbenzimidazole (153)

A solution of 149 (7.5 g, 0.027 mol) in glacial acetic acid (40 ml) was refluxed overnight. The reaction mixture was cooled and the crystallized salt of the product was filtered, washed with benzene and treated with aqueous ammonia to give free base (3.7 g). Another crop of pure product (2.8 g) was obtained from the mother liquor on neutralization with 30% aqueous ammonia solution, total yield 6.5 g (79.7%), m.p. 258-60°.
IR(KBr) cm$^{-1}$: 1680 (CO), 3250 (NH).

NMR(TFA) $\delta$:
- 2.08 (s, 3H, COCH$_3$), 2.49 (s, 3H, C-CH$_3$), 6.9-7.25 (m, 7H, Ar-H)

Analysis for $C_{16}H_{15}N_3O$S (297)
- Calcd.: C, 64.64; H, 5.05
- Found: C, 64.26; H, 5.44%

Compound 152 was prepared similarly from 149 and formic acid.

5(6)-(4-Acetamidophenylsulfono)-2-methylbenzimidazole (162)

$\text{KMnO}_4$ (4.0 g) was added to a stirred solution of 153 (4.0 g, 0.013 mol) in 80% aqueous acetic acid (250 ml) during 30 minutes at room temperature. Stirring was continued for further 5 hr and then excess of $\text{KMnO}_4$ was decomposed by careful addition of 30% $\text{H}_2\text{O}_2$ solution during cooling. When the reaction mixture became colourless, it was diluted with large amount of water. The solid separated after 30 minutes was filtered, washed with water and dried to get pure compound, yield 3.4 g (77.2%), m.p. >280°.

IR(KBr) cm$^{-1}$: 1155 (SO$_2$), 1690 (CO), 3200-3400 (NH),

NMR(DMSO-d$_6$) $\delta$:
- 2.03 (s, 3H, COCH$_3$), 2.48 (s, 3H, C-CH$_3$), 7.5-7.9 (m, 7H, Ar-H)

Analysis for $C_{16}H_{15}N_3O_3S$ (329)
- Calcd.: C, 58.35; H, 4.55
- Found: C, 58.72; H, 4.92%
Similarly compounds 159-161 were prepared by oxidation of 150-152 respectively.

5(6)-(4-Aminophenylsulfono)-2-methylbenzimidazole (167)

A solution of 162 (1.0 g, 0.003 mol) in concentrated HCl (20 ml) was refluxed for 12 hr. The reaction mixture was cooled, and the separated hydrochloride filtered, washed with benzene (3x10 ml), dried and neutralized with 30% aqueous ammonia solution to get a pure free base, yield 0.65 g (74.7%), m.p. 130°.

IR (KBr) cm⁻¹: 1140 (S=O₂), 3100-3400 (NH₂NH₂).

NMR (DMSO-d₆) δ: 2.48 (s, 3H, C-CH₃), 5.96 (s, 2H, NH₂),
6.53 (d, 2H, Ar-H, o to NH₂, J=9Hz),
7.35-7.95 (m, 5H, Ar-H).

Analysis for C₁₄H₁₃N₃O₂S (287)

Calcd.: C, 58.53; H, 4.52

Found: C, 58.22; H, 4.12%.

Similarly 156, 157 and 166 were obtained by hydrolysis of 152, 153 and 161 with concentrated HCl.

Ethyl 5(6)-(4-aminophenylsulfono)benzimidazole-2-carbamate (164)

A solution of 160 (1.0 g, 0.0025 mol) in 10% HCl (50 ml) was heated on water bath for 30 minutes. The reaction mixture was cooled in ice and neutralized with 30% aqueous ammonia solution. The separated solid was filtered,
washed with water and dried. It was purified by acid-base treatment, yield 0.76 g (85.3%), m.p. 250°.

\[ \text{IR(KBr) cm}^{-1} : 1140 \text{ (SO}_2\text{)}, 1715 \text{ (NHCOO)}, 2750-2950 \text{ (C-H),} \\
3100-3350 \text{ (NH,NH}_2\text{).} \]

\[ \text{NMR(TFA) } \delta : 0.98 \text{ (t, 3H, CH}_2\text{-CH}_3\text{, J=7Hz), 4.0 } \text{(q, 2H,} \\
\text{CH}_2\text{-CH}_3\text{, J=7Hz), 7.1-8.9 } \text{(m, 7H, Ar-H).} \]

Analysis for \( \text{C}_{16}\text{H}_{16}\text{N}_4\text{O}_4\text{S} \) (360)

Calcd. : C, 53.33; H, 4.44

Found : C, 53.74; H, 4.82%.

Similarly 154, 155 and 163 were prepared from 150, 151 and 152 respectively in 10% HCl.

When 150, 151, 153 and 160 were refluxed in concentrated HCl for 24-30 hr complete hydrolysis took place giving rise to compounds 158 and 165 respectively.

5(6)-(4-Isothiocyanatophenylsulfono)-2-methylbenzimidazole (175)

Thiophosgene (0.14 ml, 0.0018 mol) in acetone (15 ml) was added dropwise to a stirred solution of 167 (0.5 g, 0.0017 mol) in acetone (120 ml) at room temperature. The stirring was continued for 6 hr. The solvent was removed in vacuo and the solid obtained was washed with water (3x10 ml) and hexane (3x10 ml) to get 175, yield 0.38 g (66.6%), m.p. 220-22°.

\[ \text{IR(KBr) cm}^{-1} : 1150 \text{ (SO}_2\text{), 2050 (NCS).} \]
NMR(TFA) δ : 2.56 (s, 3H, C-CH₃), 6.9-8.1 (m, 7H, Ar-H)

Analysis for : C₁₅H₁₁N₂O₂S₂ (329)
Calcd. : C, 54.71; H, 3.34
Found : C, 54.84; H, 3.08%.

Similarly compounds 168-174 were prepared from 154, 155, 157, 158, 163, 164 and 166 in large amount of acetone due to their poor solubility.

5-(4-Acetamidophenoxy)-2-nitroaniline (176)

A solution of potassium 4-acetamidophenoxide 94 (15.0 g, 0.079 mol) and 5-chloro-2-nitroaniline 98 (13.7 g, 0.0079 mol) in dry DMF (50 ml) was refluxed for 24 hr. The reaction mixture was cooled, diluted with water (250 ml) and extracted with ethyl acetate (3x50 ml). The combined extracts were dried (Na₂SO₄) and solvent was removed in vacuo. The residue was crystallized from aqueous ethanol to get 8.2 g product. The filtrate was chromatographed over silica gel column using benzene and 20% ethyl acetate-benzene as eluant to get 1.8 g more product and starting material, total yield 10.0 g (44%), m.p. 218°.

IR(KBr) cm⁻¹ : 1360, 1510 (NO₂), 1620 (Arom), 1680 (CO), 3330, 3460 (NH, NH₂).

NMR(CDCl₃ + DMSO-d₆) δ : 2.03 (s, 3H, COCH₃), 6.02-6.2 (m, 2H, Ar-H, o and p to NH₂), 6.86 (d, 2H,
Ar-H, m to NHAc, J=9Hz), 7.07 (s, 2H, NH$_2$), 7.52 (d, 2H, Ar-H, o to NHAc, J=9Hz), 7.85 (d, 1H, Ar-H, o to NO$_2$, J=9Hz), 9.59 (s, 1H, NH)

Analysis for C$_{14}$H$_3$N$_3$O$_4$ (287)
Calcd. : C, 58.53; H, 4.52
Found : C, 58.21; H, 4.62%

4-(4-Acetamidophenoxy)-o-phenylenediamine (177)

To a warm solution of 176 (10.0 g, 0.034 mol) in ethanol-THF (1:1, 100 ml) and Raney-nickel (1.5 g) was added dropwise with stirring a solution of hydrazine-hydrate (14 g, 0.28 mol) in ethanol (20 ml). The stirring and heating was continued for few minutes and the product isolated as usual, yield 6.8 g (76%). This was not purified and used in further reactions.

Methyl 5(6)-(4-acetamidophenoxy)benzimidazole-2-carbamate (178)

A mixture of 177 (2.0 g, 0.0076 mol) and 1,3-dicarbomethoxy-S-methylisothiourea (1.68 g, 0.008 mol) in ethanol (50 ml) was refluxed for 15 hr. The reaction mixture was worked-up in usual manner and the product recrystallised from acetic acid-water, yield 2.2 g (83.3%), m.p. >280°.
IR(KBr) cm^{-1} : 1600 (Arom.), 1670, 1710 (CO),
2700-2800 (C-H), 3310 (NH).

NMR(TFA) δ : 2.07 (s, 3H, COCH₃), 3.57 (s, 3H,
OCH₃), 6.6-7.2 (m, 7H, Ar-H)

Analysis for Calcd.: 1600 (Arom.),
2700-2800 (C-H), 3310 (NH).

In similar manner compound 179 was prepared from 177
and 1,3-dicarbethoxy-S-methylisothiourea in refluxing
ethanol.

Methyl 5(6)-(4-aminophenoxy)benzimidazole-2-carbamate (180)

A solution of 178 (0.5 g, 0.0014 mol) in 10% HCl
(50 ml) was heated on water bath for 30 minutes. The
reaction mixture was cooled, neutralized with aqueous
ammonia solution. The solid thus separated was filtered,
washed with water (3x10 ml) and dried, yield 0.36 g
(83.7%), m.p. 285°.

IR(KBr) cm^{-1} : 1600 (Arom), 1720 (CO), 2650-
2800 (C-H), 3250-3320 (NH,NH₂)

NMR(TFA) δ : 3.58 (s, 3H, OCH₃), 6.7-7.2 (m, 7H,
Ar-H)

Analysis for Calcd.: C, 60.40; H, 4.69

Found : C, 60.72; H, 4.24%.
In similar way 181 was prepared by hydrolysing 179 in 10% HCl for 30 minutes.

5(6)-(4-Acetamidophenoxy)benzimidazole (182)

A solution of 177 (1.0 g, 0.0038 mol) in 98% formic acid was heated for 2 hr on a water bath. The reaction mixture was cooled and neutralized with aqueous ammonia solution. The separated solid was filtered, washed with water, dried and purified by acid base treatment, yield 0.55 g (63.1%), m.p. 80-2°.

IR(KBr) cm$^{-1}$ : 1640 (CO), 3100-3200 (NH).

NMR(DMSO-d$_6$) δ : 2.02 (s, 3H, COCH$_3$), 6.76-7.6 (m, 7H, Ar-H), 8.13 (s, 1H, N=CH-N)

Analysis for C$_{15}$H$_{13}$N$_3$O$_2$ (267)

Calcd. : C, 67.41; H, 4.86

Found : C, 67.15; H, 5.28%.

Compound 183 was prepared similarly from 177 and glacial acetic acid.

5(6)-(4-Aminophenoxy)benzimidazole dihydrochloride (184)

182 (0.5 g, 0.0018 mol) in concentrated HCl (20 ml) was refluxed for 4 hr. The reaction mixture was cooled and the separated hydrochloride was filtered, washed with dry ether and dried, yield 0.4 g (71.4%), m.p. 240-2°.
IR(KBr) cm\(^{-1}\)(HCl): 1600 (Arom), 2500-2850 (salt).

NMR(D\(_2\)O)(HCl) \(\delta\) : 7.15-7.9 (m, 7H, Ar-H), 9.22 (s, 1H, N=CH-N)

Analysis for \(C_{13}H_{13}Cl_2N_3O\) (298)

Calcd. : C, 52.34; H, 4.36

Found : C, 52.68; H, 4.86%.

Similarly 185 was prepared by hydrolysis of 183 in concentrated HCl.

Methyl 5(6)-(4-isothiocyanatophenoxy)benzimidazole-2-carbamate (186)

A solution of thiophosgene (0.13 ml, 0.0016 mol) in acetone (20 ml) was added dropwise to a stirred solution of 180 (0.5 g, 0.0016 mol) in acetone (100 ml) at room temperature. Stirring was continued for 5 hr at same temperature and then the solvent removed in vacuo. The product was precipitated while washing with water. The solid thus obtained, was purified by filtration through silica gel column using chloroform as eluant, yield 0.46 g (80.7%), m.p. 220\(^{\circ}\).

IR(KBr) cm\(^{-1}\) : 1720 (C=O), 2100 (NCS), 3380 (NH).

NMR(TFA) \(\delta\) : 3.6 (s, 3H, OCH\(_3\)), 6.6-7.3 (m, 7H, Ar-H)
Analysis for \( \text{C}_{16}\text{H}_{12}\text{N}_{4}\text{O}_{3}\text{S} \) (340)

Calcd. : C, 56.47; H, 3.52

Found : C, 56.82; H, 3.12%.

Similarly 187-189 were prepared by treating thiophosgene with their respective amines 181, 184 and 185.

4-Chloro-3-nitrobenzaldehyde (190)

4-Chlorobenzaldehyde (50 g, 0.35 mol) was added gradually to a stirred mixture of \( \text{KNO}_{3} \) (27.5 g) in \( \text{H}_{2}\text{SO}_{4} \) (300 ml) at 15-20°. The mixture was heated at 70° for 30 minutes. The reaction mixture was cooled and poured on ice. The solid, thus obtained, was filtered, washed with water, dried and recrystallized from chloroform-hexane, yield 26.4 g (40%), m.p.64° (lit. 47 m.p.64.5-65°).

4-Chloro-3-nitrobenzyl alcohol (191)

Sodium borohydride (2.24 g) was added in small portions to an ice cooled, stirred solution of 190 (24.0 g, 0.128 mol) in methanol (100 ml). The reaction mixture was stirred for 3 hr and solvent removed in vacuo. The residue was taken in benzene (100 ml) and washed with water (5x20 ml), dried (\( \text{Na}_{2}\text{SO}_{4} \)) and concentrated. The resulting solid was recrystallized from chloroform-hexane, yield 14.0 g (57.8%), m.p.64° (lit. 48 m.p.64-65°).
4-Amino-3-nitrobenzyl alcohol (192)

A mixture of 191 (1.0 g, 0.0053 mol), ethanol (10 ml) and aqueous ammonia (20 ml, d=0.88) was heated in steel bomb at 140-50° for 20 hr. The reaction mixture was cooled, solvent removed in vacuo and extracted with ethyl acetate (3x20 ml). The combined extracts were dried (Na$_2$SO$_4$), concentrated and the crude product was purified by column chromatography using silica gel column and chloroform as eluant, yield 0.58 g (65.1%), m.p. 108°.

IR(KBr) cm$^{-1}$: 1340, 1520 (N$_2$O), 3320, 3450 (NH$_2$,OH).

Mass at m/z : 168 (M$^+$)

NMR(DMSO-d$_6$) δ : 4.32 (s, 2H, CH$_2$OH), 6.9 (d, 1H, Ar-H, o to NH$_2$, J=9Hz), 7.2-7.32 (m, 3H, Ar-H and NH$_2$), 7.82 (d, 1H, Ar-H, o to NO$_2$, J=2Hz)

Analysis for : C$_7$H$_5$N$_2$O$_3$ (168)
Calcd. : C, 50.0; H, 4.76; N, 16.66
Found : C, 49.52; H, 4.95; N, 16.24%

4-Chloro-3-nitrobenzyl bromide (194)

To a stirred and cooled solution of 191 (25.0 g, 0.13 mol) in dry benzene (350 ml) was added dropwise PBr$_3$ (14.4 ml) in dry benzene (80 ml). Stirring was continued for 4-5 hr at room temperature. The reaction mixture was
poured in 500 ml cold water. The benzene layer was separated, washed with water, dried (Na₂SO₄) and concentrated to get an oil, which was purified using silica gel column and hexane as eluant, yield 30 g (89%).

IR(neat) cm⁻¹: 1350, 1540 (NO₂).

NMR(CDCl₃) δ: 4.35 (s, 2H, CH₂Br), 7.38 (s, 2H, Ar-H, m and p to NO₂), 7.75 (d, 1H, Ar-H, o to NO₂, J=2Hz)

Analysis for C₇H₅BrClNO₂ (250.5)
Calcd.: C, 33.53; H, 1.99
Found: C, 33.14; H, 2.41%

2-Nitro-4-phenoxy methyl chlorobenzene (195)

A mixture of 194 (10.0 g, 0.039 mol), phenol (3.8 g, 0.04 mol) and K₂CO₃ (6.5 g) in dry acetone (200 ml) was refluxed with constant stirring for 16 hr. The reaction mixture was cooled, solvent was removed in vacuo and the residue taken in benzene. The solution was washed successively with water, 10% NaOH solution and water, dried (Na₂SO₄) and concentrated to get an oil which was chromatographed over silica gel column in hexane, yield 8.8 g (83.5%).

IR(neat) cm⁻¹: 1360, 1540 (NO₂), 1605 (Arom).
NMR (CDCl₃) δ: 4.96 (s, 2H, OCH₂), 6.75-7.45 (m, 7H, Ar-H, OCH₃ and m and p to NO₂), 7.8 (d, 1H, Ar-H, o to NO₂, J=2Hz)

Analysis for C₃H₁₅NO₃Cl (263.5)
Calcd.: C, 59.20; H, 3.79
Found: C, 58.78; H, 3.38%

Similarly, 196 was prepared from 194 and thiophenol, as an oil, yield 85%.

IR (neat) cm⁻¹: 1340, 1540 (NO₂).
Mass at m/z: 279 and 281 (M⁺)
NMR (CCl₄) δ: 3.94 (s, 2H, S-CH₂), 7.12 (s, 5H, SC₆H₅), 7.25 (s, 2H, Ar-H, m and p to NO₂), 7.52 (d, 1H, Ar-H, o to NO₂, J=2Hz)

Analysis for C₁₃H₁₀ClNO₂S (279.5)
Calcd.: C, 55.81; H, 3.57
Found: C, 56.25; H, 3.22%

2-Thiophenoxy-5-thiophenoxy methylnitrobenzene (197)

Reaction of 194 with 2 moles of thiophenol in presence of KOH in refluxing ethanol yielded the product which was purified by column chromatography using silica gel column and hexane as eluant, yield 68%, m.p. 86-70°.

IR (KBr) cm⁻¹: 1340, 1520 (NO₂).
Mass at m/z: 353 (M⁺)
NMR(CHCl₃) δ : 3.92 (s, 2H, -S-CH₂), 6.62 (d, 1H, Ar-H, m to NO₂, J=9Hz), 7.13 (s, 6H, Ar-H, CH₂SC₆H₅ and p to NO₂), 7.36 (s, 5H, SC₆H₅), 7.95 (d, 1H, Ar-H, o to NO₂, J=2.5 Hz)

Analysis for : C₁₉H₁₅NO₂S₂ (353)
Calcd. : C, 64.58; H, 4.24; N, 3.96
Found : C, 64.42; H, 4.54; N, 4.42%.

2-Nitro-4-phenoxymethylaniline (198)

A mixture of 195 (1.0 g, 0.0037 mol), aqueous ammonia solution (20 ml, d=0.88) and ethanol (20 ml) was heated in steel bomb for 20 hr at 150 °C. The solvent was removed in vacuo and residue extracted with ethyl acetate (3x30 ml). The combined extracts were dried (Na₂SO₄) and concentrated. The product was purified on silica gel column using hexane-benzene (1:1) as eluant, yield 0.35 g (38%), m.p.112 °C.

IR(KBr) cm⁻¹ : 1340, 1560 (NO₂), 3310, 3450 (NH₂).

Mass at m/z : 244 (M⁺)

NMR(DMSO-d₆) δ : 4.89 (s, 2H, OCH₂), 6.84-7.37 (m, 9H, Ar-H & NH₂), 7.97 (d, 1H, Ar-H, o to NO₂, J=2.5Hz)

Analysis for : C₁₃H₁₂N₂O₃ (244)
Calcd. : C, 63.93; H, 4.91; N, 11.67
Found : C, 64.35; H, 5.26; N, 11.42%.
Similarly 199 was prepared from 197 and NH$_3$ in THF-aqueous ammonia in steel bomb at 150°. Yield (37.7%), m.p. 84-5°.

IR(KBr) cm$^{-1}$: 1340, 1560 (NO$_2$), 3340, 3480 (NH$_2$).

Mass at m/z: 250 (M$^+$)

NMR(DMSO-d$_6$) $\delta$: 4.06 (s, 2H, S-CH$_2$), 6.87 (d, 1H, Ar-H, o to NH$_2$, J=9Hz), 7.1-7.4 (m, 8H, Ar-H & NH$_2$), 7.81 (d, 1H, Ar-H, o to NO$_2$, J=2.5Hz).

Analysis for: C$_{13}$H$_{12}$N$_2$O$_2$S (260)

Calcd.: C, 63.92; H, 4.91; N, 11.47

Found: C, 64.12; H, 5.28; N, 11.20%.

4-Thiophenoxymethyl-o-phenylenediamine (200)

A hot solution of FeSO$_4$ (4.0 g) in aqueous ammonia (25 ml) was added to a hot solution of 199 (0.5 g, 0.002 mol) in acetone (20 ml) and aqueous ammonia solution (25 ml). The reaction mixture was heated for 30 minutes on water bath and the product worked-up as usual, yield 0.35 g (79.5%). This product was used as such in further steps.

Methyl 5(6)-thiophenoxymethylbenzimidazole-2-carbamate (201)

A mixture of 200 (0.35 g, 0.0015 mol) and 1,3-dicarbomethoxy-S-methylisothiourea (0.5 g, 0.002 mol) in ethanol (25 ml) was refluxed for 15 hr. Usual work-up of
the reaction mixture gave the product which was recrystallized from ethanol or acetic acid-water, yield 0.4 g (85%), m.p. 200°.

IR(KBr) cm\(^{-1}\) : 1600 (Arom), 1710 (CO), 3300 (NH).
Mass at m/z : 313 (M\(^+\))
NMR(TFA) \(\delta\) : 3.54 (s, 3H, OCH\(_3\)), 3.71 (s, 2H, S\(\text{CH}_2\)), 6.73 (s, 5H, Ar-H, S-C\(_6\)H\(_5\)), 6.95 (d, 3H, Ar-H benimidazole)

Analysis for : C\(_{16}\)H\(_{15}\)N\(_3\)O\(_2\)S (313)
Calcd. : C, 61.34; H, 4.79; N, 13.41
Found : C, 61.52; H, 4.58; N, 13.28%

Similarly, compound 202 was prepared from 200 and 1,3-dicarbethoxy-S-methylisothiourea, yield 75%, m.p. 250°.

IR(KBr) cm\(^{-1}\) : 1600 (Arom), 1700 (CO), 2700-2900 (C-H), 3300 (NH).
Mass at m/z : 327 (M\(^+\))
Analysis for : C\(_{17}\)H\(_{17}\)N\(_3\)O\(_2\)S (327)
Calcd. : C, 62.38; H, 5.19; N, 12.84
Found : C, 62.80; H, 5.56; N, 13.12%

1,2-Di-(4-acetamidophenylthio)ethane (203)

A mixture of 4-acetamidothiophenol (24 5.0 g, 0.03 mol) and KOH (1.67 g, 0.03 mol) in ethanol (50 ml) was stirred at room temperature for 30 minutes. To this
solution was added, a solution of dibromoethane (1.3 ml, 0.014 mol) in ethanol (10 ml) dropwise with stirring. Stirring was continued and reaction mixture heated for 30 minutes. The separated solid was filtered off, washed with ethanol (3x10 ml), water (3x10 ml) and dried, yield 4.5 g (84.8%), m.p. 268°.

\[
\text{IR (KBr) cm}^{-1} : 1600 (\text{Arom}), 1670 (\text{CO}), 3300 (\text{NH}).
\]

\[
\text{NMR (DMSO-d}_6) \delta : 2.02 (s, 6H, 2xCOCH}_2), 2.98 (s, 4H, S(CH}_2)_2S), 7.15 (d, 4H, Ar-H, o to S, J=9Hz), 7.50 (d, 4H, Ar-H, o to NHAc, J=9Hz), 10.0 (s, 2H, 2xNH, D}_2O exchangeable)
\]

\[
\text{Analysis for } \text{C}_{18}\text{H}_{20}\text{N}_2\text{O}_2\text{S}_2 \text{ (360)}
\]

\[
\text{Calcd. : C, 60.00; H, 5.55; N, 7.77}
\]

\[
\text{Found : C, 60.38; H, 5.38; N, 8.12%}
\]

Similarly 204 was prepared from 94 and 1,3-dibromo-propane in presence of KOH in ethanol and purified by filtration through silica gel column using benzene as eluant, yield 80%, m.p. 120-21°.

\[
\text{IR (KBr) cm}^{-1} : 1600 (\text{Arom}), 1660 (\text{CO}), 3300 (\text{NH}).
\]

\[
\text{NMR (CDCl}_3 + \text{DMSO-d}_6) \delta : 1.77 (t, 2H, C=CH}_2-C, J=6Hz), 2.02 (s, 6H, 2xCOCH}_2), 2.87 (t, 4H, S(CH}_2)_2, J=6Hz), 7.13 (d, 4H, Ar-H, m to NHAc, J=9Hz), 7.42 (d, 4H, Ar-H, o to NHAc, J=9Hz), 9.4 (s, 2H, 2xNHCO)
\]
Analysis for: \( \text{C}_{19}\text{H}_{22}\text{N}_{2}\text{O}_{2}\text{S}_{2} \) (374)

Calcd.: C, 69.62; H, 5.88

Found: C, 70.04; H, 6.28%.

1,2-Di-(4-acetamidophenylsulfono)ethane (205)

To a suspension of 203 (5.0 g, 0.013 mol) in acetic acid-water (8:2, 250 ml), \( \text{KMnO}_{4} \) (10 g) was added in three portions at 30 minutes interval with stirring at room temperature. The stirring was continued for 4 hr. The reaction mixture was cooled, the excess \( \text{KMnO}_{4} \) was decomposed using \( \text{H}_{2}\text{O}_{2} \) solution. It was diluted with water (500 ml). The separated pure solid was filtered, washed with water several times and dried, yield 4.2 g (71.18%), m.p. 282°.

\[ \text{IR(KBr) cm}^{-1} : 1160 \text{ (SO}_{2} \text{)}, 1600 \text{ (Arom)}, 1680 \text{ (CO)}, 3300 \text{ (NH)}. \]

\[ \text{NMR(DMSO-d}_{6}\text{)} \delta : 2.03 \text{ (s, 6H, 2XCOCH}_{3}\text{)}, 3.4 \text{ (s, 4H, SO}_{2}(\text{CH}_{2})_{2}\text{SO}_{2}), 7.67 \text{ (s, 8H, Ar-H)}. \]

Analysis for: \( \text{C}_{18}\text{H}_{20}\text{N}_{2}\text{O}_{6}\text{S}_{2} \) (424)

Calcd.: C, 50.46; H, 4.67; N, 6.54

Found: C, 50.86; H, 4.25; N, 6.80%.

Similarly 206 was prepared by oxidizing 204 with \( \text{KMnO}_{4} \) in 80% aqueous acetic acid.

Yield 64.5%, m.p. 238°.

\[ \text{IR(KBr) cm}^{-1} : 1140 \text{ (SO}_{2} \text{)}, 1590 \text{ (Arom)}, 1690 \text{ (CO)}, 3250 \text{ (NH)}. \]
Mass at m/z : 438 (M$^+$)

NMR(CDCl$_3$ + DMSO-d$_6$) $\delta$

- 1.7-1.9 (m, 2H, C-CH$_2$), 2.1 (s, 6H, 2xCOCH$_3$),
- 3.14 (t, 4H, 2xSO$_2$CH$_2$, J=6Hz),
- 7.55 (d, 4H, Ar-H, m to NHAc, J=9Hz),
- 7.78 (d, 4H, Ar-H, o to NHAc, J=9Hz),
- 10.05 (s, 2H, 2xNH$_3$)

Analysis for

Calcd. : C, 52.05; H, 5.02

Found : C, 52.48; H, 5.35%

1,2-Di-(4-aminophenylthio)ethane (207)

A solution of 203 (0.5 g, 0.0013 mol) in concentrated HCl (25 ml) was refluxed overnight. The reaction mixture was cooled, neutralized with aqueous ammonia solution. The separated amine was filtered, washed with water and dried, yield 0.25 g (65.7%), m.p. 100$^\circ$.

IR(KBr) cm$^{-1}$ : 1600 (Arom), 3320-3430 (NH$_2$).

NMR(CDCl$_3$ + DMSO-d$_6$) $\delta$

- 2.7 (s, 4H, S(CH$_2$)$_2$S), 4.55 (bs, 4H, 2xNH$_2$),
- 6.42 (d, 4H, Ar-H, o to NH$_2$, J=9Hz),
- 6.94 (d, 4H, Ar-H, m to NH$_2$, J=9Hz).

Analysis for

Calcd. : C, 60.43; H, 5.75; N, 10.71

Found : C, 60.82; H, 5.32; N, 10.38%.

Similarly 208 and 209 were prepared from 205 and 206
by refluxing it with concentrated HCl.

208, yield 72%, m.p. >300°.

IR(KBr) cm⁻¹: 1160 (SO₂), 3380, 3480 (NH₂).
NMR(DMSO-d₆) δ: 3.21 (s, 4H, SO₂(CH₂)₂SO₂), 6.15 (s, 4H, 2xNH₂), 6.56 (d, 4H, Ar-H, o to NH₂, J=9Hz), 7.36 (d, 4H, Ar-H, m to NH₂, J=9Hz)

Analysis for C₁₄H₁₆N₂O₄S₂ (340)
Calcd.: C, 49.41; H, 4.70; N, 8.23
Found: C, 49.80; H, 5.20; N, 8.58%.

209 (2HCl), yield 70%, m.p. 255°.

IR(KBr) cm⁻¹: 1150 (SO₂), 2550-2820 (Salt).
NMR(TFA) δ: 1.7-2.2 (m, 2H, C-CH₂-C), 2.9-3.4 (m, 4H, 2xSO₂CH₂), 7.3-7.9 (m, 8H, Ar-H)

1,2-Di(4-isothiocyanatophenylthio)ethane (210)

Thiophosgene (0.22 ml, 0.0028 mol) was added to a stirred solution of 207 dihydrochloride (0.5 g, 0.0014 mol) in 50% aqueous acetic acid. The stirring was continued for 3 hr at room temperature. The separated solid was filtered, washed with water and dried, yield 0.28 g (55%), m.p. 280°.
IR (KBr) cm$^{-1}$: 2100 (NCS).
Mass at m/z: 360 (M$^+$)
Analysis for: C$_{16}$H$_{12}$N$_2$S$_4$ (360)
  Calcd.: C, 53.33; H, 3.33
  Found: C, 53.68; H, 3.22%.

Similarly 211 and 212 were prepared from 208 and 209 and thiophosgene in 50% aqueous acetic acid and 10% HCl respectively.

211, yield 62%, m.p. $>$280$^\circ$.
IR (KBr) cm$^{-1}$: 1140 (S=O$_2$), 1580 (Arom), 2100 (NCS).
Mass at m/z: 424 (M$^+$)
Analysis for: C$_{16}$H$_{12}$N$_2$O$_4$S$_4$ (424)
  Calcd.: C, 45.28; H, 3.77
  Found: C, 45.58; H, 3.56%.

212, yield 55%, m.p. 178-80$^\circ$.
IR (KBr) cm$^{-1}$: 1140 (S=O$_2$), 1590 (Arom), 2100 (NCS).
Mass at m/z: 438 (M$^+$)
Analysis for: C$_{17}$H$_{14}$N$_2$O$_4$S$_4$ (438)
  Calcd.: C, 46.57; H, 3.19
  Found: C, 46.68; H, 3.48%.

General Method for preparing aryl isothiocyanates (219-223)
Various aryl isothiocyanates (219-223) were prepared by the method as described for 2-chloro-4-nitrophenyl...
isothiocyanate (220) from their respectively amines (214-218).

Thiophosgene (8.9 ml, 0.116 mol) in acetone (50 ml) was added dropwise to a stirred solution of 215 (20 g, 0.1158 mol) in acetone (250 ml) during 30 minutes at room temperature. The stirring was continued for 3-4 hr, solvent was removed in vacuo and the resulting solid was crystallized from hexane, yield 20.5 g (85.6%), m.p. 102-4°.

IR(KBr) cm⁻¹: 1340, 1530 (NO₂), 2040 (NCS).

NMR(CDCl₃) δ: 7.25 (d, 1H, Ar-H, m to NO₂, J=8.5Hz), 8.02 (dd, 1H, Ar-H, p to chloro, J=3 & 8.5Hz), 8.17 (d, 1H, Ar-H, o to chloro, J=3Hz).

Analysis for C₇H₆ClN₂O₂S (214.5)
Calcd.: C, 39.42; H, 1.74
Found : C, 39.10; H, 1.40%.

N-(4-Isothiocyanatophenyl)-1-methyl-4-piperazinylthiocarboxamide (224)

A solution of N-methylpiperazine (0.57 ml, 0.0052 mol) in acetone (100 ml) was added dropwise to a stirred solution of 223 (1.0 g, 0.0052 mol) in acetone (300 ml) during 1 hr. Stirring was continued for 4 hr at room temperature. The solvent was removed from the reaction mixture and the solid thus obtained was
recrystallized from chloroform, yield 1.2 g (79.8%), m.p. 190-3°.

IR(KBr) cm\(^{-1}\) : 2070 (NCS), 2800, 2900 (C-H), 3150 (NH).

NMR(DMSO-d\(_6\)) \(\delta\) : 2.31 (s, 3H, N-CH\(_3\)), 2.51 (t, 4H, N(CH\(_2\))\(_2\), J=5Hz), 3.55-3.75 (hump, 1H, NH), 3.97 (t, 4H, CSN(CH\(_2\))\(_2\), J=5Hz), 7.12-7.34 (m, 4H, Ar-H)

Analysis for \(\text{C}_{13}\text{H}_{16}\text{N}_{4}\text{S}_{2}\) (292)
Calcd. : C, 53.42; H, 5.47
Found : C, 53.76; H, 5.28%.

Similarly compounds 225 and 226 were prepared by reaction of 223 with corresponding piperazines.

\(\text{N-(4-Nitrophenyl)-1-methyl-4-piperazinylthiocarboxamide (227)}\)

A solution of \(\text{N-methylpiperazine (5 ml, 0.045 mol)}\) in benzene (20 ml) was added dropwise to a stirred solution of 219 (8.0 g, 0.044 mol) in benzene (50 ml) at room temperature. Stirring was continued for 3 hr, the product isolated as above and crystallized from chloroform-hexane, yield 10.2 g (81.6%), m.p. 100-102°.

IR(KBr) cm\(^{-1}\) : 1325, 1540 (NO\(_2\)), 2800, 2900 (C-H), 3150 (NH).

NMR(DMSO-d\(_6\)) \(\delta\) : 2.33 (s, 3H, N-CH\(_3\)), 2.50 (t, 4H, N(CH\(_2\))\(_2\), J=5Hz), 2.7-2.93 (hump, 1H, NH),
Analysis for Calcd. Found

4.00 (t, 4H, CON(CH₂)₂, J=5Hz), 8.00 (d, 2H, Ar-H, m to NO₂, J=9Hz), 8.10 (d, 2H, Ar-H, o to NO₂, J=9Hz).

C₁₂H₁₆N₄O₂S (280)
C, 51.42; H, 5.71
C, 51.14; H, 5.36%

In similar manner compounds 228-235 were prepared by treating 219-221 with the corresponding piperazines.

N-(4-Acetylaminophenyl)-1-methyl-4-piperazinylthiocarboxamide (236)

A solution of N-methylpiperazine (0.57 ml, 0.0052 mol) in acetone (50 ml) was added dropwise to a stirred solution of 222 (1.0 g, 0.0052 mol) and the reaction mixture was refluxed for 3 hr. The separated solid was filtered and recrystallized from acetone, yield 1.1 g (72.5%), m.p. 212°.

IR(KBr) cm⁻¹

1670 (CO), 2700-2800 (C-H), 3200 (NH).

NMR(CDCl₃ + DMSO-d₆) δ

2.02 (s, 3H, COCH₃), 2.23 (s, 3H, N-CH₃), 2.34-2.5 (m, 4H, CH₃-N(CH₂)₂), 3.83 (t, 4H, CON(CH₂)₂, J=5.5Hz), 7.03 (d, 2H, Ar-H, o to NHAc, J=9Hz), 7.40 (d, 2H, Ar-H, m to NHAc, J=9Hz), 9.25 (s, 2H, 2xNH)
Analysis for \( \text{C}_{14}\text{H}_{20}\text{N}_{4}\text{O}_{3} \) (292)

Calcd. : C, 54.10; H, 6.81; N, 15.41

Found : C, 53.68; H, 6.42; N, 15.82%.

Compounds 237 and 238 were prepared similarly from 222 and the corresponding piperazines.

N-(4-Amino-2-chlorophenyl)-1-methyl-4-piperazinylthiocarboxamide (239)

A hot solution of \( \text{FeSO}_4 \) (28 g) in ammonia (100 ml, \( d=0.88 \)) and water (100 ml) was added to a hot solution of 230 (4.0 g, 0.0127 mol) in aqueous ammonia (250 ml, \( d=0.88 \)). The reaction mixture was heated on water bath for 30 minutes and worked-up in usual manner. The resulting solid was recrystallized from ethyl acetate, yield 2.45 g (73%), m.p. 180-5°.

\[
\begin{align*}
\text{IR(KBr)} \text{ cm}^{-1} & : 2780, 2900 (\text{C-H}), 3150, 3250 (\text{NH}_2). \\
\text{NMR(CDCl}_3 + \text{DMSO-d}_6) \delta & : 2.27 (s, 3H, N-CH\text{\textsubscript{3}}), 2.42 (t, 4H, CH\text{\textsubscript{3}}-N(\text{CH}_2)\text{\textsubscript{2}}, J=5.5\text{Hz}), 3.94 (t, 4H, GS\text{\textsubscript{2}}(\text{CH}_2)\text{\textsubscript{2}}, J=5.5\text{Hz}), 6.52 (dd, 1H, Ar-H, p to chloro, J=2.5 & 8\text{Hz}), 6.7 (d, 1H, Ar-H, o to chloro, J=2.5\text{Hz}), 7.0 (d, 1H, Ar-H, m to chloro, J=8\text{Hz})
\end{align*}
\]

Analysis for \( \text{C}_{12}\text{H}_{17}\text{ClN}_{4}\text{S} \) (284.5)

Calcd. : C, 50.51; H, 5.97; N, 19.68

Found : C, 50.25; H, 6.35; N, 20.10%.
Similarly compounds 240-244 were prepared by reduction of the corresponding nitro compounds.

\[ N-(4\text{-isothiocyanatophenyl})-1\text{-phenyl}-4\text{-piperazinyl carboxamide (250)} \]

A solution of thiophosgene (0.50 ml, 0.0064 mol) in acetone (50 ml) was added dropwise to a stirred solution of 244 (1.0 g, 0.0032 mol) in acetone (100 ml) during 30 minutes and the reaction mixture stirred at room temperature for 3 hr. Solvent was removed in vacuo and the residual solid was crystallized from chloroform-pet. ether, yield 0.71 g (65%), m.p. 182-4\(^\circ\).

\( \text{IR(KBr) cm}^{-1} \) : 1635 (C=O), 2050 (NCS), 2700, 2800 (C-H), 3250 (NH).

\( \text{NMR(CDCl}_3+\text{DMSO-d}_6) \delta \) : 3.2 (t, 4H, ArN(CH\(_2\))\(_2\), J=5Hz), 3.74 (t, 4H, CON(CH\(_2\))\(_2\), J=5Hz), 6.8-7.6 (m, 9H, Ar-H), 8.55 (s, 1H, NH)

Analysis for \( \text{C}_{18}\text{H}_{18}\text{N}_4\text{O}_8 \) (338): Calcd. C, 63.90; H, 5.32

Found: C, 64.25; H, 5.76%.

Compounds 245-249 were prepared similarly from their respective amines 239-243 and thiophosgene.

\[ N-(2\text{-benzimidazolyl})-N'-(4\text{-nitrophenyl})\text{thiourea (252)} \]

A mixture of 2-aminobenzimidazole (251, 1.0 g, 0.0075 mol) and 219 (1.35 g, 0.0075 mol) in ethylacetate
(30 ml) was refluxed for 4 hr on a water bath. The reaction mixture was left overnight at room temperature and the crystallized yellow needles were filtered, washed with cold ethyl acetate (2x10 ml) and dried, yield 1.78 g (76%), m.p. 243-4°.

IR(KBr) cm⁻¹: 1315, 1540 (NO₂), 3250 (NH).

Analysis for C₁₄H₁₁N₅O₂S (313)
Calcd.: C, 53.60; H, 3.51
Found: C, 53.26; H, 3.91%.

Similarly compound 253 was prepared by reaction of 2-aminobenzimidazole (251) and 220, yield 75.5%, m.p. 218°.

IR(KBr) cm⁻¹: 1305, 1560 (NO₂), 3250 (NH).

Analysis for C₁₄H₁₀C₁N₅O₂S (347.5)
Calcd.: C, 48.34; H, 2.88
Found: C, 48.72; H, 3.20%.

N-(2-Benzimidazolyl)-N'-(4-aminophenyl)thiourea (254)

A hot solution of FeSO₄ (7.0 g) in aqueous ammonia (50 ml, d=0.88) and water (50 ml) was added to a hot solution of 252 (1.0 g, 0.0032 mol) in ammonia (100 ml, d=0.88). The reaction mixture was heated on water bath for 30 minutes and worked-up as usual, yield 0.55 g (62%), m.p. 86°.

IR(KBr) cm⁻¹: 3200, 3350 (NH₂).
N-(2-Benzimidazolyl)-N'-(4-isothiocyanatophenyl)urea. HCl (295)

A solution of thiophosgene (0.27 ml, 0.0035 mol) in acetone (20 ml) was added dropwise to a stirred solution of 254 (0.5 g, 0.0017 mol) in acetone (50 ml) at room temperature and the product isolated as usual as its hydrochloride, yield 0.4 g (65%), m.p. 256-59°.

IR(KBr) cm⁻¹: 1625 (CO), 2040 (NCS), 3350 (NH).

N-(2-Chloro-4-nitrophenyl)-N'-(4-acetylaminophenyl) thiourea (257)

A solution of 4-aminoacetanilide (0.7 g, 0.0046 mol) in acetone (20 ml) was added dropwise to a refluxing solution of 220 (1.0 g, 0.0046 mol) in acetone (30 ml). Refluxing was continued for 4 hr on a water bath. The solvent was removed in vacuo and the residual solid crystallized from acetone, yield 1.1 g (65%), m.p. 218°.

IR(KBr) cm⁻¹: 1330, 1500 (NO₂), 1655 (CO), 3220 (NH).

NMR(CDCl₃ + DMSO-d₆) δ: 2.05 (s, 3H, COCH₃), 7.42 (d, 2H, Ar-H, J=9 Hz), 7.62 (d, 2H, Ar-H
Analysis for 256:

Calcd.: C, 49.30; H, 3.59

Found:  C, 48.92; H, 3.92%.

Similarly 256 was prepared from 219 and 4-aminoacetanilide in 78% yield, m.p. 105°C.

IR(KBr) cm⁻¹: 1300, 1500 (NO₂), 1655 (CO), 3200 (NH).

NMR(CDCCl₃ + DMSO-d₆) δ:

2.1 (s, 3H, COCH₃), 7.35 (d, 2H, Ar-H, o to NHAc, J=9Hz), 7.58 (d, 2H, Ar-H, m to NHAc, J=9Hz), 7.86 (d, 2H, Ar-H, m to NO₂, J=9Hz), 8.12 (d, 2H, Ar-H, o to NO₂, J=9Hz)

Analysis for 261:

Calcd.: C, 54.54; H, 4.24

Found:  C, 54.25; H, 4.58%.

The thioureas (258-260)⁵⁰-⁵², thiocarboxamide (264)⁵³ and thioamide (265)⁵⁴ were prepared by literature methods in good yields.

N-Phenyldiethylamino thiocarboxamide (261)

To a stirred solution of phenyl isothiocyanate (1.35 g, 0.01 mol) in benzene (20 ml) was added dropwise a solution of diethylamine (0.73 g, 0.01 mol) at room
temperature. Stirring was continued for 3 hr at same temperature and then heated on water bath for 10 minutes. The solvent was removed in vacuo to get viscous oil, yield 1.8 g (89%).

IR(neat) cm⁻¹ : 1340, 1530 (NO₂).

NMR(CDCl₃) δ : 1.08 (t, 3H, CH₂CH₃, J=8Hz), 3.52 (q, 2H, CH₂CH₃, J=8Hz), 7.1 (s, 5H, Ar-H)

Analysis for C₁₁H₁₆N₂S (208)
Calcd. : C, 65.00; H, 7.69
Found : C, 64.68; H, 7.28%.

Similarly 26₂ and 26₃ were prepared by action of piperidine and N-methylpiperazine on phenyl isothiocyanate in benzene.

The General method of desulphurization is illustrated by preparation of 26₇ from 2₅₈ and thiophosgene:

A solution of 2₅₈ (1.21 g, 0.005 mol) in acetone (40 ml) was added dropwise during 30 minutes to a stirred solution of thiophosgene (0.44 ml, 0.005 mol) in acetone (15 ml) at room temperature. The reaction mixture was stirred for 2 hr and solvent removed. The residue crystallized from benzene, yield 0.85 g (75%), m.p. 166-67° (lit. 55 m.p. 167-8°).

Similarly other ureas and carboxamides (2₅₉-2₆₄) and amide 2₆₅ were prepared from their respective thio analogs (m.p., yield given).
All the ureas and carboxamides (267-273) were prepared by reaction of the corresponding isocyanates and amines. The amide 274 was obtained by action of acetic anhydride on benzylamine.

1-Methyl-4-[(N-phenyl-N'-cyclohexyl)amidino]piperazine (275)

To a stirred solution of 271 (1.0 g, 0.0042 mol) and triethylamine (0.86 g, 0.0084 mol) in dry acetone (25 ml) was added dropwise a solution of thiophosgene (0.36 ml, 0.0042 mol) when addition was complete, N-methylpiperazone (0.42 g, 0.0042 mol) in dry acetone (10 ml) was added dropwise with constant stirring. Stirring was continued for 2 hr at room temperature and solvent removed in vacuo. The product was chromatographed over silica gel column using benzene as eluant, yield 0.26 g (20.3%), m.p. 240°.

IR(KBr) cm⁻¹ : 1630 (C=N), 2680, 2740, 2950 (C-H), 3320 (NH).

Analysis for C₁₈H₂₈N₄ (300)

Calcd. : C, 72.00; H, 9.30
Found : C, 72.40; H, 8.95%.
N-(4-Nitrophenyl)piperazine (276)

A mixture of anhydrous piperazine (5.0 g, 0.058 mol), 4-chloronitrobenzene (18.3 g, 0.116 mol) and potassium carbonate (8.1 g, 0.058 mol) in dry acetone (100 ml) was heated in steel bomb for 15 hr at 120-30°. The reaction mixture was cooled, potassium carbonate filtered out and solvent was removed in vacuo. The crude product was chromatographed over silica gel column using ethyl acetate and 10% methanol in ethyl acetate as eluant. The unreacted 4-chloro nitrobenzene (5 g) was recovered, yield 6.5 g (54.1%), m.p. 125°.

IR(KBr) cm⁻¹: 1300, 1580 (NO₂), 2800, 2900 (C-H), 3300 (NH).

Mass at m/z: 207 (M⁺)

NMR(CDCl₃ + DMSO-d₆) δ: 1.7 (bs, 1H, NH), 2.9 (t, 4H, Ar-N(CH₂)₂, J=6Hz), 3.27 (t, 4H, Ar-N(CH₂)₂, J=6Hz), 6.64 (d, 2H, Ar-H, m to NO₂, J=9Hz), 7.93 (d, 2H, Ar-H, o to NO₂, J=9Hz)

Analysis for C₁₀H₁₃N₃O₂ (207)
Calcd.: C, 57.97; H, 6.28
Found: C, 58.42; H, 6.68%.

1-(4-Nitrobenzoyl)-4-(4-nitrophenyl)piperazine (278)

To a solution of 276 (0.5 g, 0.0024 mol) in dry
benzene (30 ml) was added dropwise at room temperature a solution of 4-nitrobenzoyl chloride (0.5 g, 0.0026 mol) in dry benzene (20 ml) with constant stirring. Stirring was continued for 2 hr at room temperature and then reaction mixture was refluxed for 3 hr. It was then cooled and washed successively with 5% NaHCO₃ solution (3x20 ml), water (3x20 ml) and dried (Na₂SO₄). The solvent was removed in vacuo and the residue crystallized from ethanol, yield 0.6 g, (70%), m.p. 174-5°.

IR(KBr) cm⁻¹: 1320, 1520 (N₂), 1600 (Arom), 1635 (CO).

NMR(CDCl₃ + DMSO-d₆) δ: 3.5 (bs, 4H, ArN(CH₂)₂), 3.65 (bs, 4H, ArCON(CH₂)₂), 6.82 (d, 2H, Ar-H, 0 to N(CH₂)₂, J=9Hz), 7.6 (d, 2H, Ar-H, 0 to NO₂, J=9Hz), 8.0 (d, 2H, Ar-H, 0 to NO₂, J=8.5Hz), 8.2 (d, 2H, Ar-H, m to NO₂, J=9Hz)

Analysis for: C₁₇H₁₆N₄O₅ (356)
Calcd.: C, 57.30; H, 4.38
Found: C, 57.75; H, 4.66%.

1-(4-Aminobenzoyl)-4-(4-aminophenyl)piperazine (279)

To a hot solution of 278 (0.5 g, 0.0014 mol) in acetone (30 ml) and aqueous ammonia solution (30 ml) was added a hot solution of ferrous sulfate (4 g) in water
(20 ml) and aqueous ammonia solution (30 ml, d=0.88). The reaction mixture was heated at water bath for 30 minutes and reaction worked-up as usual. The product was recrystallized from benzene, yield 0.2 g (50%), m.p.126-7°.

IR(KBr) cm\(^{-1}\): 1585 (Arom), 1620 (NCO), 3300, 3400 (NH\(_2\)).

Mass at m/z : 296 (M\(^+\))

NMR(CDCl\(_3\) + DMSO-d\(_6\)) \(\delta\): 2.92 (t, 4H, ArN(CH\(_2\))\(_2\), J=6Hz), 3.65 (t, 4H, ArCON(CH\(_2\))\(_2\), J=6Hz), 6.4-6.72 (m, 6H, Ar-H), 7.14 (d, 2H, Ar-H, o to NCO, J=9Hz)

Analysis for Calcd. : C, 68.91; H, 6.75

Found : C, 69.38; H, 6.45%.

1-(4-Isothiocyanatobenzoyl)-4-(4-isothiocyanatophenyl)piperazine (280)

Thiophosgene (0.25 ml, 0.0032 mol) in acetone (20 ml) was added dropwise to a stirred solution of 279 (0.5 g, 0.0016 mol) in acetone (20 ml) at room temperature. The stirring was continued for 4 hr. The separated hydrochloride was filtered, washed with acetone (3x10 ml) and dried. Free base was obtained by treatment with triethylamine, yield 0.42 g (65.6%), m.p.125°.

IR(KBr) cm\(^{-1}\): 1635 (CO), 2100 (NCS).
NMR(DMSO-d$_6$) $\delta$ : 3.15-3.30 (m, 4H, N(CH$_2$)$_2$), 3.45-3.62 (m, 4H, CON(CH$_2$)$_2$), 6.86-7.8 (m, 8H, Ar-H).

Analysis for : C$_{19}$H$_{16}$N$_4$O$_2$S$_2$ (380)
Calcd. : C, 60.00; H, 4.21
Found : C, 60.32; H, 4.10%.

1,4-Di-(4-nitrobenzoyl)piperazine (281)

To a stirred solution of 4-nitrobenzoyl chloride (4.5 g, 0.0242 mol) and triethylamine (2.35 g, 0.0232 mol) in dry benzene (50 ml), was added dropwise a solution of anhydrous piperazine (1.0 g, 0.012 mol) in dry benzene at room temperature during 30 minutes. Stirring was continued for 5 hr at room temperature and the solid separated was filtered, washed with 5% NaHCO$_3$ solution (5x20 ml) and water (3x20 ml) and dried, yield 4.0 g (89.4%), m.p. $>$300°.

IR(KBr) cm$^{-1}$ : 1350, 1510 (NO$_2$), 1630 (CO), 2650, 2720, 2900 (C-H).

Mass at m/z : 384 (M$^+$)

Analysis for : C$_{18}$H$_{16}$N$_4$O$_5$ (384)
Calcd. : C, 56.25; N, 4.16
Found : C, 56.62; H, 3.84%.
1,4-Di-(4-aminobenzoyl)piperazine (282)

A suspension of 281 (1.0 g, 0.0026 mol) and Raney-nickel (~ 0.2 g) in ethanol-THF mixture (1:1, 100 ml) was hydrogenated in a Paar hydrogenator at 3.5 kg/cm$^2$ of hydrogen for 6 hr and the product worked-up as usual which was recrystallised from ethanol, yield 0.58 g (69%), m.p. 250$^\circ$.

IR(KBr) cm$^{-1}$: 1590 (Arom), 1620 (CO), 3300, 3420 (NH$_2$).
Mass at m/z : 324 (M$^+$)
NMR(DMSO-$d_6$) $\delta$ : 3.52 [s, 8H, N(CH$_2$)$_4$], 5.5 (s, 4H, 2xNH$_2$), 6.52 (d, 4H, Ar-H, o to NH$_2$, J=9Hz), 7.2 (d, 4H, Ar-H, m to NH$_2$, J=9Hz)

Analysis for : C$_{16}$H$_{20}$N$_4$O$_2$ (324)
Calcd. : C, 66.66; H, 6.17
Found : C, 67.12; H, 5.92%.

1,4-Di-(4-Isothiocyanatobenzoyl)piperazine (283)

A solution of thiophosgene (0.24 ml, 0.0031 mol) in chloroform (30 ml) was added dropwise to a stirred solution of 282 (0.5 g, 0.0015 mol) in 10% aqueous hydrochloric acid (30 ml) at room temperature during 30 minutes. Stirring was continued for 4 hr at room temperature and the chloroform layer was separated from aqueous layer. It was washed with water (3x10 ml), dried
(Na₂SO₄) and the solvent removed in vacuo. The residual solid was triturated with hexane to get a pure product, yield 0.36 g (57.1%), m.p. 220°.

IR(KBr) cm⁻¹: 1625 (C=O), 2100 (N=S)
Mass at m/z: 408 (M⁺)
NMR(CDCl₃ + DMSO-d₆): 3.55 [s, 8H, N(CH₂)₄], 7.22-7.7 (m, 8H, Ar-H).

Analysis for C₂O₆H₁₆N₄O₂S₂ (408)
Calcd.: C, 58.82; H, 3.92
Found: C, 58.46; H, 4.26%.
### Table 1

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>R</th>
<th>X</th>
<th>R'</th>
<th>Molecular formula (Mol. Wt.)</th>
<th>M.p. °C</th>
<th>Yield %</th>
<th>Analysis (%)</th>
<th>Spectral data</th>
</tr>
</thead>
<tbody>
<tr>
<td>34</td>
<td>CH₃</td>
<td>NH</td>
<td>H</td>
<td>C₁₆H₁₃N₅O (291)</td>
<td>&gt;300</td>
<td>65</td>
<td>Calc. Found</td>
<td>IR(KBr) cm⁻¹: 1665 (CO). NMR(TFA)δ: 2.65 (s, 3H, C-CH₃), 7.2-8.70 (m, 7H, Ar-H &amp; N=CH-N).</td>
</tr>
<tr>
<td>35</td>
<td>CH₃</td>
<td>NH</td>
<td>CH₃</td>
<td>C₁₈H₁₇N₅O (319)</td>
<td>88-90</td>
<td>50</td>
<td>Calc. Found</td>
<td>IR(KBr) cm⁻¹: 1665 (CO). NMR(TFA)δ: 2.08 (s, 3H, COCH₃), 2.48 (s, 3H, N=C(N-)-CH₃), 2.7 (s, 3H, N=C(NH)-CH₃), 6.95-7.95 (m, 6H, Ar-H).</td>
</tr>
<tr>
<td>45</td>
<td>CH₃</td>
<td>S</td>
<td>SH</td>
<td>C₁₆H₁₀N₄S₃ (354)</td>
<td>&gt;300</td>
<td>60</td>
<td>Calc. Found</td>
<td>IR(KBr) cm⁻¹: 2100 (NCS).</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>---</td>
<td>-------</td>
<td>-------</td>
<td>-------</td>
<td>-------</td>
<td>-------</td>
<td>-------</td>
<td>-------</td>
<td>-------</td>
</tr>
<tr>
<td>42</td>
<td>CH$_3$</td>
<td>S</td>
<td>H</td>
<td>C$<em>{16}$H$</em>{12}$N$_4$OS</td>
<td>108-9</td>
<td>65</td>
<td>C: 62.33</td>
<td>62.68</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(308)</td>
<td></td>
<td></td>
<td>H: 3.89</td>
<td>3.56</td>
</tr>
<tr>
<td>50</td>
<td>CH$_3$</td>
<td>S</td>
<td>CH$_3$</td>
<td>C$<em>{18}$H$</em>{16}$N$_4$OS</td>
<td>218-20</td>
<td>62</td>
<td>C: 64.28</td>
<td>63.81</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(336)</td>
<td></td>
<td></td>
<td>H: 4.78</td>
<td>4.38</td>
</tr>
</tbody>
</table>

*R$^2$ = NHCOR$^1$ in all compounds except 45 where R$^2$ = NCS
Table 2

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>R</th>
<th>X</th>
<th>Molecular formula</th>
<th>m.p. °C</th>
<th>Yield %</th>
<th>Analysis (%)</th>
<th>Spectral data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>(Mol.Wt.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>61</td>
<td>CH₃</td>
<td>S</td>
<td>C₁₆H₁₄N₄S</td>
<td>155</td>
<td>67</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(294)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IR(KBr) cm⁻¹: 1600 (Arom), 2800-2900 (C-H), 3400(NH).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NMR(DMSO-d₆): 2.47 (s, 6H, 2xC-CH₃), 6.8-7.4 (m, 6H, Ar-H).</td>
</tr>
<tr>
<td>63</td>
<td>NHCOOC₂H₅</td>
<td>S</td>
<td>C₂₀H₂₀N₆O₄S</td>
<td>280</td>
<td>62</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(440)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IR(KBr) cm⁻¹: 1600 (Arom), 1705 (CO), 2700-2800 (C-H), 3340 (NH).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NMR(DMSO-d₆): 1.3 (t, 3H, CH₂CH₃, J=6Hz), 4.22 (q, 192</td>
</tr>
<tr>
<td>No.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>70</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CH₃</td>
<td>SO₂</td>
<td>C₁₆H₁₄N₄O₂S</td>
<td>195-7</td>
<td>64</td>
<td>C: 58.89</td>
<td>59.27</td>
<td>H: 4.29</td>
</tr>
<tr>
<td>72</td>
<td>NHCOC₂H₅</td>
<td>SO₂</td>
<td>C₂₀H₂₀N₆O₆S</td>
<td>280</td>
<td>58</td>
<td>C: 50.85</td>
<td>51.32</td>
</tr>
</tbody>
</table>

2H, CH₂CH₃, J=6Hz),
6.9-7.5 (m, 6H, Ar-H).
IR(KBr) cm⁻¹: 1160 (SO₂),
1610 (Arom), 3200-3300 (NH).
NMR(DMSO-d₆)δ: 2.42 (s, 6H, 2xO-CH₃), 7.5 (s, 4H, Ar-H), 7.92 (d, 2H, Ar-H, J=2Hz).

IR(KBr) cm⁻¹: 1140 (SO₂),
1500 (Arom), 1730 (CO), 2780-2850 (C-H),
3380 (NH).
NMR(DMSO-d₆)δ: 1.2 (t, 6H, 2xCH₂CH₃, J=6Hz), 4.25 (q, 4H, 2xCH₂CH₃, J=6Hz), 7.6 (s, 4H, Ar-H), 7.95 (d, 2H, Ar-H, J=2Hz).
<p>| | | | | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>82</td>
<td>NHCOOC₂H₅</td>
<td>C₂₁H₂₀N₆O₅</td>
<td>&gt;280</td>
<td>64</td>
<td>C: 57.80 58.18</td>
<td>H: 4.59 4.76</td>
<td>N: 19.27 19.55</td>
<td>IR(KBr)cm⁻¹: 1600 (Arom), 1640, 1720 (CO), 2700-3000 (C-H), 3350 (NH). NMR(TFA)δ: 0.8-1.2 (m, 6H, 2xCH₂CH₃), 3.9-4.3 (m, 4H, 2xCH₂CH₃), 7.2-8.0 (m, 6H, Ar-H).</td>
</tr>
<tr>
<td>89</td>
<td>CH₃</td>
<td>CO</td>
<td>C₁₇H₁₄N₄O</td>
<td>108-10</td>
<td>52</td>
<td>C: 70.34 70.72</td>
<td>H: 4.83 5.25</td>
<td>N: 19.31 19.48</td>
</tr>
</tbody>
</table>
| 91  | NHCOOC₂H₅ | CH₂ | C₂₁H₂₂N₆O₄ | >280 | 60 | C: 59.71 59.48 | H: 5.21 5.68 | IR(KBr)cm⁻¹: 1590 (Arom), 1710 (CO), 2650-2900 (C-H), 3300 (NH). NMR(TFA)δ: 1.0 (t, 6H, 2xCH₂CH₃, J=8Hz), 3.82 (s, }
| 103 | H   | 0   | C_{14}H_{10}N_4O | 135-6 | 68  | C: 67.20 | 67.45 | IR(KBr) cm\(^{-1}\): 1600 (Ar-\(\text{O}\)) | Mass at m/z 250 (M\(^{+}\)) | NMR(DMSO-\(d_6\))\(\delta\): 6.8-7.8 (\(\text{m, 6H, Ar-\(\text{H}\)}\)), 8.3 (s, 2H, 2x N=CH-NH). |
| 109 | CH₃ | 0   | C_{16}H_{14}N_4O | 115-7 | 54  | C: 69.06 | 68.68 | IR(KBr) cm\(^{-1}\): 1600 (Ar-\(\text{O}\)) | Mass at m/z 278 (M\(^{+}\)) |

2H, ArCH₂-Ar, 4.04 (q, 4H, 2xCH₂CH₃, J=3Hz), 6.9-7.3 (\(\text{m, 6H, Ar-\(\text{H}\)}\)).

IR(KBr) cm\(^{-1}\): 1620 (Arom), 3400-3000 (NH)

Mass at m/z 276 (M\(^{+}\))

NMR(TFA)\(\delta\): 2.5 (s, 6H, 2x C-CH₃), 3.92 (s, 2H, ArCH₂ Ar), 7.0-7.5 (\(\text{m, 6H, Ar-\(\text{H}\)}\)).

IR(KBr) cm\(^{-1}\): 1600 (Arom), 3100 (NH).

Mass at m/z 250 (M\(^{+}\))
<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>111</td>
<td>NHC00C₂H₅</td>
<td>0</td>
<td>C₂H₂ON₆O₅</td>
<td>&gt;280</td>
<td>60</td>
<td>C: 56.60</td>
<td>56.80</td>
<td>IR(KBr)cm⁻¹: 1600 (Arom), 1700 (CO), 2700-2950 (C-H), 3320 (NH).</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>H: 4.72</td>
<td>4.40</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N: 19.81</td>
<td>20.25</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NMR(TFA)δ: 0.98 (t, 6H, 2xCH₂CH₃, J=7Hz), 4.0 (q, 4H, 2xCH₂CH₃, J=7Hz), 6.75-8.25 (m, 6H, Ar-H).</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>116</td>
<td>NHC00C₂H₅</td>
<td>8CH₂CH₂S</td>
<td>C₂H₂ON₆O₄S₂</td>
<td>&gt;280</td>
<td>58</td>
<td>C: 52.80</td>
<td>53.16</td>
<td>IR(KBr)cm⁻¹: 1600(Arom), 1705 (CO), 2700-3000 (C-H), 3360 (NH).</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>H: 4.80</td>
<td>4.42</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N: 16.80</td>
<td>17.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NMR(TFA)δ: 0.98 (t, 6H, 2xCH₂CH₃, J=7Hz), 2.72 (s, 2H, S(CH₂)₂S), 4.02 (q, 4H, 2xCH₂CH₃, J=7Hz), 7.0-7.2 (m, 6H, Ar-H).</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| 124 | \( \text{NHCOOC}_2\text{H}_5 \) | \( \text{CON} \) | \( \text{CO} \) | \( \text{C}_{26}\text{H}_{28}\text{N}_8\text{O}_6 \) | \( >280 \) | 45 | C: 53.93 | 54.16 | IR(KBr) cm\(^{-1}\): 1600 (Arom), 1720 (C=O), 2750-2950 (C-H), 3380 (NH).

NMR(TFA)\( \delta \): 1.02 (t, 6H, 2\( x\text{CH}_2\text{CH}_3\), J=7Hz), 3.4-3.6 (m, 8H, 4\( x\text{NCH}_2\)), 4.0 (q, 4H, 2\( x\text{CH}_2\text{CH}_3\), J=7Hz), 6.9-7.6 (m, 6H, Ar-\( \text{H} \)). |
Table 3

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>R</th>
<th>R¹</th>
<th>X</th>
<th>Molecular formula (Mol. Wt.)</th>
<th>m.p. °C</th>
<th>Yield %</th>
<th>Analysis %</th>
<th>Spectral data</th>
</tr>
</thead>
<tbody>
<tr>
<td>150</td>
<td>NHCOOCH₃</td>
<td>NHAc</td>
<td>S</td>
<td>C₁₇H₁₆N₄O₃S</td>
<td>280</td>
<td>68.5</td>
<td>C: 57.30</td>
<td>IR: 1660, 1710 (CO), 3300-3400 (NH).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>H: 4.77</td>
<td>NMR (TFA): 2.02 (s, 3H, COCH₃), 3.56 (s, 3H, OCH₃), 6.85-7.2 (m, 7H, Ar-H)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N: 15.73</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>15.28</td>
<td></td>
</tr>
<tr>
<td>152</td>
<td>H</td>
<td>NHAc</td>
<td>S</td>
<td>C₁₅H₁₃N₃O₃S</td>
<td>160</td>
<td>72.5</td>
<td>C: 63.60</td>
<td>IR: 1660 (CO), 3100-3250 (NH).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>H: 4.59</td>
<td>NMR (DMSO-d₆): 2.02 (s, 3H, COCH₃), 7.0-7.55 (m, 7H, Ar-H), 8.06 (s, 1H, N=CH-N).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N: 14.87</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>15.30</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---------</td>
<td>------</td>
<td>------</td>
<td>-------</td>
<td>-------</td>
</tr>
<tr>
<td>154</td>
<td>NHCOOCH₃</td>
<td>NH₂</td>
<td>S</td>
<td>C₁₅H₁₄N₄O₂S</td>
<td>220-22</td>
<td>80</td>
<td>C: 57.34</td>
<td>57.68</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(314)</td>
<td></td>
<td></td>
<td>H: 4.45</td>
<td>4.22</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>155</td>
<td>NHCOOC₂H₅</td>
<td>NH₂</td>
<td>S</td>
<td>C₁₆H₁₆N₄O₂S</td>
<td>246</td>
<td>79.5</td>
<td>C: 58.53</td>
<td>58.21</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(328)</td>
<td></td>
<td></td>
<td>H: 4.87</td>
<td>5.21</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>156</td>
<td>H</td>
<td>NH₂</td>
<td>S</td>
<td>C₁₃H₁₁N₃S</td>
<td>135</td>
<td>64</td>
<td>C: 64.73</td>
<td>64.38</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(241)</td>
<td></td>
<td></td>
<td>H: 4.56</td>
<td>4.82</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>157</td>
<td>CH₃</td>
<td>NH₂</td>
<td>S</td>
<td>C₁₄H₁₃N₃S</td>
<td>80</td>
<td>66.6</td>
<td>C: 65.88</td>
<td>66.26</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(255)</td>
<td></td>
<td></td>
<td>H: 5.09</td>
<td>5.50</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>-----</td>
<td>---------</td>
<td>--------</td>
<td>--------</td>
<td>---------</td>
<td>---------</td>
<td>----</td>
<td>------</td>
<td>------</td>
</tr>
<tr>
<td>165</td>
<td>NH₂</td>
<td>NH₂</td>
<td>SO₂</td>
<td>C₁₃H₁₂N₄SO₂</td>
<td>250</td>
<td>85.3</td>
<td>C: 52.35</td>
<td>52.68</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(298)</td>
<td></td>
<td></td>
<td>H: 4.03</td>
<td>4.25</td>
</tr>
<tr>
<td>166</td>
<td>H</td>
<td>NH₂</td>
<td>SO₂</td>
<td>C₁₃H₁₁N₃O₂S</td>
<td>274</td>
<td>71</td>
<td>C: 57.14</td>
<td>57.47</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(273)</td>
<td></td>
<td></td>
<td>H: 4.03</td>
<td>4.45</td>
</tr>
<tr>
<td>168</td>
<td>NHCOOCH₃</td>
<td>NCS</td>
<td>S</td>
<td>C₁₆H₁₂N₄O₂S₂</td>
<td>230-32</td>
<td>72</td>
<td>C: 53.93</td>
<td>54.38</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(356)</td>
<td></td>
<td></td>
<td>H: 3.37</td>
<td>3.65</td>
</tr>
<tr>
<td>169</td>
<td>NHCOOC₂H₅</td>
<td>NCS</td>
<td>S</td>
<td>C₁₇H₁₄N₄O₂S₂</td>
<td>222</td>
<td>74</td>
<td>C: 55.13</td>
<td>55.28</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(370)</td>
<td></td>
<td></td>
<td>H: 3.78</td>
<td>4.12</td>
</tr>
</tbody>
</table>

NMR(DMSO-d₆): 6.02 (s, 2H, NH₂), 6.6 (d, 2H, Ar-H), 7.48-8.4 (m, 6H, Ar-H & N=CH-N).

NMR(TFA): 3.75 (s, 3H, OCH₃), 7.0-7.65 (m, 7H, Ar-H).
<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>170</td>
<td>H</td>
<td>NCS</td>
<td>S</td>
<td>( \text{C}_4 \text{H}_9 \text{N}_3 \text{S}_2 )</td>
<td>190-91</td>
<td>62</td>
<td>C: 59.36</td>
<td>59.25</td>
<td>H: 3.18</td>
<td>3.62</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(283)</td>
<td></td>
<td></td>
<td>N: 14.84</td>
<td>15.18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>171</td>
<td>CH(_3)</td>
<td>NCS</td>
<td>S</td>
<td>( \text{C}<em>5 \text{H}</em>{11} \text{N}_3 \text{S}_2 )</td>
<td>196-8</td>
<td>64.4</td>
<td>C: 60.40</td>
<td>60.52</td>
<td>H: 3.70</td>
<td>3.82</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(297)</td>
<td></td>
<td></td>
<td>N: 14.14</td>
<td>14.40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>172</td>
<td>NHCOOC(_2)CH(_3)</td>
<td>NCS</td>
<td>SO(_2)</td>
<td>( \text{C}<em>{16} \text{H}</em>{12} \text{N}_4 \text{O}_4 \text{S}_2 &gt; 280 )</td>
<td>65.3</td>
<td>C: 49.48</td>
<td>49.28</td>
<td>H: 3.09</td>
<td>3.44</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(388)</td>
<td></td>
<td></td>
<td>N: 14.17</td>
<td>14.40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>173</td>
<td>NHCOOC(_2)CH(_3)</td>
<td>NCS</td>
<td>SO(_2)</td>
<td>( \text{C}<em>{17} \text{H}</em>{14} \text{N}_4 \text{O}_4 \text{S}_2 &gt; 280 )</td>
<td>68</td>
<td>C: 50.75</td>
<td>50.62</td>
<td>H: 3.48</td>
<td>3.65</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(402)</td>
<td></td>
<td></td>
<td>N: 14.17</td>
<td>14.40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>174</td>
<td>H</td>
<td>NCS</td>
<td>SO(_2)</td>
<td>( \text{C}_4 \text{H}_9 \text{N}_3 \text{O}_2 \text{S}_2 )</td>
<td>148-9</td>
<td>62.5</td>
<td>C: 53.33</td>
<td>53.14</td>
<td>H: 2.86</td>
<td>3.08</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(315)</td>
<td></td>
<td></td>
<td>N: 14.17</td>
<td>14.40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>178</td>
<td>NHCOOC(_2)CH(_3)</td>
<td>NH(_2)c</td>
<td>O</td>
<td>( \text{C}<em>{18} \text{H}</em>{18} \text{N}_4 \text{O}_4 )</td>
<td>&gt; 280</td>
<td>78</td>
<td>C: 61.02</td>
<td>60.56</td>
<td>H: 5.08</td>
<td>4.72</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(354)</td>
<td></td>
<td></td>
<td>N: 15.82</td>
<td>15.48</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

IR: 2080 (NCS), 3050-3100 (NH).

IR: 2100 (NCS), 3400 (NH).

NMR (TFA) 2.5 (s, 3H, C-CH\(_3\)), 6.5-7.5 (m, 7H, Ar-H).

IR: 1140 (SO\(_2\)), 1720 (C=O), 2030 (NCS), 3360 (NH).

NMR (TFA) 3.58 (s, 3H, CH\(_2\)CH\(_3\)), 6.85-7.9 (m, 7H, Ar-H).

IR: 1150 (SO\(_2\)), 1720 (C=O), 2080 (NCS), 3400 (NH).

NMR (TFA) 1.0 (t, 3H, CH\(_2\)CH\(_3\)), J=6Hz), 4.02 (q, 2H, CH\(_2\)CH\(_3\)), J=6Hz), 6.9-7.9 (m, 7H, Ar-H).

IR: 1160 (SO\(_2\)), 2080 (NCS).

IR: 1650, 1700 (C=O), 3330 (NH).

NMR (TFA) 1.0 (t, 3H, CH\(_2\)CH\(_3\)), J=7Hz), 2.08 (s, 3H, COCH\(_3\)).
<p>| | | | | | | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>181</td>
<td>NHCOOC₂H₅ NH₂</td>
<td>0</td>
<td>C₁₂H₁₆N₄O₃</td>
<td>&gt;280</td>
<td>76</td>
<td>C: 61.54</td>
<td>61.32</td>
<td>H: 5.13</td>
<td>5.62</td>
<td>N: 17.95</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>IR: 1710 (CO), 3460 (NH).</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>NMR(TFA) 1.0 (t, 3H, CH₂CH₃, J=7Hz), 4.04 (q, 2H, CH₂CH₃, J=7Hz), 6.5-7.25 (m, 7H, Ar- H).</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>183</td>
<td>CH₃</td>
<td>NH₄⁺</td>
<td>0</td>
<td>C₁₆H₁₆N₃O₂</td>
<td>205-6</td>
<td>66.6</td>
<td>C: 68.33</td>
<td>68.62</td>
<td>H: 5.34</td>
<td>5.48</td>
</tr>
<tr>
<td></td>
<td>IR: 1660 (CO), 3280 (NH).</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>NMR(TFA) 2.1 (s, 3H, COCH₃), 2.5 (s, 3H, C-CH₃), 6.75-7.3 (m, 7H, Ar- H).</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>185</td>
<td>CH₃</td>
<td>NH₂</td>
<td>0</td>
<td>C₁₄H₁₅N₃O</td>
<td>65-7</td>
<td>64.5</td>
<td>C: 70.29</td>
<td>70.12</td>
<td>H: 5.44</td>
<td>5.34</td>
</tr>
<tr>
<td></td>
<td>IR: 3400 (NH₂).</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>NMR(TFA) 2.5 (s, 3H, C-CH₃), 6.7-7.35 (m, 7H, Ar- H).</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>187</td>
<td>NHCOOC₂H₅ NCS</td>
<td>0</td>
<td>C₁₇H₁₄N₄O₃S</td>
<td>212</td>
<td>72.5</td>
<td>C: 57.63</td>
<td>57.96</td>
<td>H: 3.95</td>
<td>3.62</td>
<td>N: 15.82</td>
</tr>
<tr>
<td></td>
<td>IR: 1700 (CO), 2100 (NCS), 3350 (NH).</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>NMR(TFA) 1.0 (t, 3H, CH₂CH₃, J=7Hz), 4.04 (q, 2H, CH₂CH₃, J=7Hz), 6.5-7.3 (m, 7H, Ar- H).</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>188</td>
<td>H</td>
<td>NCS</td>
<td>0</td>
<td>C\textsubscript{14}H\textsubscript{9}N\textsubscript{3}O\textsubscript{8}</td>
<td>178-9</td>
<td>63.5</td>
<td>C: 62.90</td>
<td>63.16</td>
<td>IR: 2100 (NCS), 3400 (NH).</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(267)</td>
<td></td>
<td></td>
<td>H: 3.37</td>
<td>3.72</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N: 15.73</td>
<td>15.88</td>
<td></td>
<td></td>
</tr>
<tr>
<td>189</td>
<td>CH\textsubscript{3}</td>
<td>NCS</td>
<td>0</td>
<td>C\textsubscript{15}H\textsubscript{11}N\textsubscript{3}O\textsubscript{8}</td>
<td>215-6</td>
<td>58.0</td>
<td>C: 64.06</td>
<td>64.44</td>
<td>IR: 2080 (NCS), 3400 (NH).</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(281)</td>
<td></td>
<td></td>
<td>H: 3.91</td>
<td>4.28</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N: 14.95</td>
<td>15.24</td>
<td>NMR (TFA) 2.5 (s, 3H, C-CH\textsubscript{3}),  6.5-7.3 (m, 7H, Ar-H).</td>
<td></td>
</tr>
</tbody>
</table>
Table 4: Physical Data of Compounds

![Chemical Structure]

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>R</th>
<th>R^1</th>
<th>R^2</th>
<th>X</th>
<th>Molecular formula</th>
<th>m.p. (°C)</th>
<th>Yield (%)</th>
<th>Analysis (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(Mol. Wt.)</td>
<td></td>
<td></td>
<td>Calcd. Found</td>
</tr>
<tr>
<td>225</td>
<td>4-NOS</td>
<td>H</td>
<td>CH₂Ph</td>
<td>S</td>
<td>C₁₉H₂₀N₄S₂</td>
<td>170-74</td>
<td>70.5</td>
<td>61.96  62.35</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(358)</td>
<td></td>
<td></td>
<td>5.43   5.08</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>15.22  15.46</td>
</tr>
<tr>
<td>226</td>
<td>4-NJS</td>
<td>H</td>
<td>COOC₂H₅</td>
<td>S</td>
<td>C₁₅H₁₈N₄O₂S₂</td>
<td>110-15</td>
<td>67.0</td>
<td>51.43  51.65</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(350)</td>
<td></td>
<td></td>
<td>5.14   5.46</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>16.00  16.32</td>
</tr>
<tr>
<td>228</td>
<td>4-N₂O₂</td>
<td>H</td>
<td>CH₂Ph</td>
<td>S</td>
<td>C₁₈H₂₀N₄O₂S</td>
<td>145</td>
<td>82.6</td>
<td>60.67  60.82</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(356)</td>
<td></td>
<td></td>
<td>5.62   5.46</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>15.73  15.52</td>
</tr>
<tr>
<td>229</td>
<td>4-N₂O₂</td>
<td>H</td>
<td>Ph</td>
<td>S</td>
<td>C₁₇H₁₈N₄O₂S</td>
<td>167-8</td>
<td>75.6</td>
<td>59.65  59.52</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(342)</td>
<td></td>
<td></td>
<td>5.26   5.64</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>16.37  16.24</td>
</tr>
<tr>
<td>230</td>
<td>4-N₂O₂</td>
<td>Cl</td>
<td>CH₃</td>
<td>S</td>
<td>C₁₂H₁₅ClN₄O₂S</td>
<td>126</td>
<td>77.0</td>
<td>45.79  46.12</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(314.5)</td>
<td></td>
<td></td>
<td>4.77   4.85</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>17.16  17.38</td>
</tr>
<tr>
<td>231</td>
<td>4-N₂O₂</td>
<td>Cl</td>
<td>CH₂Ph</td>
<td>S</td>
<td>C₁₈H₁₉ClN₄O₂S</td>
<td>136-8</td>
<td>77.1</td>
<td>55.31  55.68</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(390.5)</td>
<td></td>
<td></td>
<td>4.86   4.66</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>14.34  14.18</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>---</td>
<td>-------</td>
<td>--------</td>
<td>---</td>
<td>-------</td>
<td>---------------------------------</td>
<td>------</td>
<td>------</td>
<td>-------</td>
</tr>
<tr>
<td>232</td>
<td>4-NO₂</td>
<td>Cl</td>
<td>Ph</td>
<td>S</td>
<td>C₁₇H₁₇ClN₄O₂S (376.5)</td>
<td>172-4</td>
<td>73.1</td>
<td>C: 54.18</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>H: 4.51</td>
<td>4.10</td>
<td>H: 14.87</td>
</tr>
<tr>
<td>233</td>
<td>3-NO₂</td>
<td>H</td>
<td>CH₃</td>
<td>S</td>
<td>C₁₂H₁₆N₄O₂S (280)</td>
<td>135</td>
<td>87.2</td>
<td>C: 51.43</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>H: 5.71</td>
<td>5.26</td>
<td>H: 20.00</td>
</tr>
<tr>
<td>234</td>
<td>3-NO₂</td>
<td>H</td>
<td>CH₂Ph</td>
<td>S</td>
<td>C₁₈H₂₀N₄O₂S (356)</td>
<td>95</td>
<td>86</td>
<td>C: 50.67</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>H: 5.62</td>
<td>5.85</td>
<td>H: 15.73</td>
</tr>
<tr>
<td>235</td>
<td>3-NO₂</td>
<td>H</td>
<td>Ph</td>
<td>S</td>
<td>C₁₇H₁₈N₄O₂S (342)</td>
<td>162-5</td>
<td>74.0</td>
<td>C: 59.65</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>H: 5.25</td>
<td>5.52</td>
<td>H: 16.37</td>
</tr>
<tr>
<td>237</td>
<td>4-NHAc</td>
<td>H</td>
<td>CH₂Ph</td>
<td>S</td>
<td>C₂₀H₂₄N₄O₄S (368)</td>
<td>200-202</td>
<td>68</td>
<td>C: 65.22</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>H: 6.52</td>
<td>6.76</td>
<td>H: 15.22</td>
</tr>
<tr>
<td>238</td>
<td>4-NHAc</td>
<td>H</td>
<td>COOBt</td>
<td>S</td>
<td>C₁₆H₂₂N₄O₃S (350)</td>
<td>156</td>
<td>70.5</td>
<td>C: 54.86</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>H: 6.28</td>
<td>6.35</td>
<td>H: 16.03</td>
</tr>
<tr>
<td>240</td>
<td>4-NH₂</td>
<td>Cl</td>
<td>CH₂Ph</td>
<td>S</td>
<td>C₁₈H₂₁ClN₄S (360.5)</td>
<td>171-2</td>
<td>70.3</td>
<td>C: 59.92</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>H: 5.82</td>
<td>5.62</td>
<td>H: 15.53</td>
</tr>
<tr>
<td>241</td>
<td>4-NH₂</td>
<td>Cl</td>
<td>Ph</td>
<td>S</td>
<td>C₁₇H₁₉ClN₄S (336.5)</td>
<td>240-42</td>
<td>66.6</td>
<td>C: 60.62</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>H: 5.65</td>
<td>5.42</td>
<td>H: 16.64</td>
</tr>
<tr>
<td></td>
<td>4-NH₂</td>
<td>H</td>
<td>CH₃</td>
<td>S</td>
<td>C₁₂H₁₅N₄S (250)</td>
<td>100-103</td>
<td>75.0</td>
<td>C:</td>
</tr>
<tr>
<td>---</td>
<td>-------</td>
<td>-----</td>
<td>------</td>
<td>-----</td>
<td>-----------------</td>
<td>---------</td>
<td>-----</td>
<td>----</td>
</tr>
<tr>
<td></td>
<td>4-NH₂</td>
<td>H</td>
<td>CH₂Ph</td>
<td>S</td>
<td>C₁₈H₂₂N₄S (326)</td>
<td>160</td>
<td>68.0</td>
<td>C:</td>
</tr>
<tr>
<td></td>
<td>4-NH₂</td>
<td>H</td>
<td>Ph</td>
<td>S</td>
<td>C₁₇H₂₀N₄S (312)</td>
<td>240</td>
<td>55.0</td>
<td>C:</td>
</tr>
<tr>
<td></td>
<td>4-NCS</td>
<td>Cl</td>
<td>CH₃</td>
<td>0</td>
<td>C₁₃H₁₅ClN₄OS.HCl (347)</td>
<td>212-4</td>
<td>71.0</td>
<td>C:</td>
</tr>
<tr>
<td></td>
<td>4-NCS</td>
<td>Cl</td>
<td>CH₂Ph</td>
<td>0</td>
<td>C₁₉H₁₉ClN₄OS.HCl (423)</td>
<td>195-8</td>
<td>69.0</td>
<td>C:</td>
</tr>
<tr>
<td></td>
<td>4-NCS</td>
<td>Cl</td>
<td>Ph</td>
<td>0</td>
<td>C₁₈H₁₇ClN₄OS (372.5)</td>
<td>190</td>
<td>64.2</td>
<td>C:</td>
</tr>
<tr>
<td></td>
<td>4-NCS</td>
<td>H</td>
<td>CH₃</td>
<td>0</td>
<td>C₁₃H₁₆N₄OS.HCl (312.5)</td>
<td>217-8</td>
<td>67.3</td>
<td>C:</td>
</tr>
<tr>
<td></td>
<td>4-NCS</td>
<td>H</td>
<td>CH₂Ph</td>
<td>0</td>
<td>C₁₉H₂₀N₄OS.HCl (388.5)</td>
<td>230-34</td>
<td>66.6</td>
<td>C:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>H:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N:</td>
</tr>
</tbody>
</table>
### Table 4 - Spectral Data

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>IR: KBr in cm(^{-1}), NMR ppm ((\delta))</th>
</tr>
</thead>
<tbody>
<tr>
<td>225</td>
<td>IR: 2100 (NCS), 2800, 2900 (C-H), 3150-3400 (NH).&lt;br&gt;<strong>NMR(CDCl(_3)):</strong> 2.5 (t, 4H, N(CH(_{2}))(_2), J=5Hz), 3.52 (s, 2H, CH(_2)C(_6)H(<em>5)), 3.85 (t, 4H, CSN(CH(</em>{2}))(_2), J=5Hz), 7.1-7.4 (m, 9H, Ar-H).</td>
</tr>
<tr>
<td>226</td>
<td>IR: 1700 (CO), 2080 (NCS), 2850-2960 (C-H), 3150 (NH).&lt;br&gt;<strong>NMR(CDCl(_3) + DMSO-d(_6)):</strong> 1.18 (t, 3H, CH(_2)CH(<em>3), J=7Hz), 3.44 (t, 4H, CON(CH(</em>{2}))(<em>2), J=5Hz), 3.86 (t, 4H, CSN(CH(</em>{2}))(_2), J=5Hz), 4.02 (q, 2H, CH(_2)CH(_3), J=7Hz), 7.0-7.3 (m, 4H, Ar-H).</td>
</tr>
<tr>
<td>228</td>
<td>IR: 1340, 1540 (NO(<em>2)), 1600 (Arom), 2800, 2900 (C-H), 3300 (NH).&lt;br&gt;<strong>NMR(CDCl(_3)):</strong> 2.51 (t, 4H, N(CH(</em>{2}))(_2), J=5.5Hz), 3.42 (s, 2H, CH(_2)C(_6)H(<em>5)), 3.76 (t, 4H, CSN(CH(</em>{2}))(_2), J=5.5Hz), 7.09 (d, 2H, Ar-H, m to NO(_2), J=9Hz), 7.16 (s, 5H, Ar-H, CH(_2)C(_6)H(_5)), 7.95 (d, 2H, Ar-H, m to NO(_2), J=9Hz).</td>
</tr>
<tr>
<td>229</td>
<td>IR: 1340, 1500 (NO(<em>2)), 1600 (Arom).&lt;br&gt;<strong>NMR(CDCl(_3)+DMSO-d(_6)):</strong> 3.18 (t, 4H, N(CH(</em>{2}))(<em>2), J=5.5Hz), 3.98 (t, 4H, CSN(CH(</em>{2}))(_2), J=5.5Hz), 7.15 (s, 5H, Ar-H, N-C(_6)H(_5)), 7.42 (d, 2H, Ar-H, m to NO(_2), J=9Hz), 7.95 (d, 2H, Ar-H, m to NO(_2), J=9Hz).</td>
</tr>
</tbody>
</table>
230. IR: 1300, 1510 (NO₂), 2800 (C-H), 3240 (NH).
NMR(CDCl₃) 2.34 (s, 3H, N-CH₃), 2.55 (t, 4H, N(CH₂)₂, J=5Hz), 3.98 (t, 4H, 
CSN(CH₂)₂, J=5Hz), 8.10-8.34 (m, 3H, Ar-H).

231. IR: 1340, 1500 (NO₂), 2780, 2880 (C-H), 3200 (NH).
NMR(CDCl₃) 2.48 (t, 4H, N(CH₂)₂, J=5Hz), 3.47 (s, 2H, CH₂C₆H₅), 3.87 (t, 4H, 
CSN(CH₂)₂, J=5Hz), 7.18 (s, 5H, CH₂C₆H₅), 7.94 (s, 2H, Ar-H), 8.1 (s, 1H, Ar-H).

232. IR: 1300, 1500 (NO₂), 1590 (Arom), 2780, 2850, 2930 (C-H), 3050 (NH).
NMR(CDCl₃ + DMSO-d₆) 3.18 (t, 4H, N(CH₂)₂, J=5Hz), 4.04 (t, 4H, CSN(CH₂)₂, J=5Hz), 
6.52-7.18 (m, 5H, Ar-H, N-C₆H₅), 7.46 (d, 1H, Ar-H, m to NO₂, J=9Hz), 7.88 (dd, 
1H, Ar-H, p to chloro, J=3 & 9Hz), 8.03 (d, 1H, Ar-H, o to chloro, J=3Hz).

233. IR: 1345, 1545 (NO₂), 1610 (Arom), 2800-2900 (C-H), 3150 (NH).
NMR(CDCl₃) 2.35 (s, 3H, N-CH₃), 2.55 (t, 4H, N(CH₂)₂, J=5Hz), 4.1 (t, 4H, CSN(CH₂)₂, 
J=5Hz), 7.06-8.5 (m, 4H, Ar-H).

234. IR: 1310, 1500 (NO₂), 1600 (Arom), 2800 (C-H), 3310 (NH).
NMR(CDCl₃) 2.56 (t, 4H, N(CH₂)₂, J=5Hz), 3.6 (s, 2H, CH₂C₆H₅), 4.05 (t, 4H, 
CSN(CH₂)₂, J=5Hz), 7.3-8.5 (m, 9H, Ar-H).
IR: 1320, 1520 (NO₂), 1595 (Arom), 2780, 2860, 2950 (C-H), 3080 (NH).
NMR(CDCl₃) 3.54 (t, 4H, N(CH₂)₂, J=5.5Hz), 4.22 (t, 4H, CSN(CH₂)₂, J=5.5Hz),
6.82-8.68 (m, 9H, Ar-H), 10.00 (hump, 1H, NH, D₂O exchangeable).

IR: 1670 (CO), 2800-2900 (C-H), 3280 (NH).
NMR(CDCl₃ + DMSO-d₆) 2.0 (s, 3H, COCH₃), 2.5 (t, 4H, N(CH₂)₂, J=5Hz), 3.5 (s,
2H, CH₂C₆H₅), 3.95 (t, 4H, CSN(CH₂)₂, J=5Hz), 7.1-7.55 (m, 9H, Ar-H).

IR: 1665, 1690 (CO), 2870, 2920, 2980 (C-H), 3300 (NH).
NMR(CDCl₃ + DMSO-d₆) 1.25 (t, 3H, CH₂CH₃, J=7Hz), 2.08 (s, 3H, COCH₃), 3.56
(t, 4H, N(CH₂)₂, J=5Hz), 3.92 (t, 4H, CSN(CH₂)₂, J=5Hz), 4.14 (q, 2H, CH₂-CH₃,
J=7Hz), 7.17 (d, 2H, Ar-H, m to NHAc, J=9Hz), 7.53 (d, 2H, Ar-H, o to NHAc,
J=9Hz), 9.52 (hump, 1H, NH, D₂O exchangeable).

IR: 1620 (Arom), 2780, 2880 (C-H), 3150, 3260 (NH₂).
NMR(CDCl₃) 2.52 (t, 4H, N(CH₂)₂, J=5.5Hz), 3.54 (s, 2H, CH₂C₆H₅), 3.88 (t, 4H,
CSN(CH₂)₂, J=5.5Hz), 6.54 (dd, 1H, Ar-H, o to NH₂, J=2.5 & 9Hz), 6.68 (d, 1H,
Ar-H, o to chloro, J=2.5Hz), 7.24 (d, 1H, Ar-H, m to chloro, J=6Hz), 9.3
(s, 5H, Ar-H, CH₂C₆H₅).
IR: 1590 (Arom), 2800, 2880 (C-H), 3150, 3250 (NH₂).
NMR(CDCl₃ + DMSO-d₆) 3.25 (t, 4H, N(CH₂)₂, J=5.5Hz), 4.12 (t, 4H, CSN(CH₂)₂, J=5.5Hz), 6.5-7.5 (m, 8H, Ar-H), 8.3 (bs, 2H, NH₂, D₂O exchangeable).

IR: 1600 (Arom), 2790, 2880 (C-H), 3100, 3280, 3350 (NH,NH₂).
NMR(CDCl₃) 2.35 (t, 4H, N(CH₂)₂, J=5Hz), 3.4 (s, 2H, CH₂C₆H₅), 3.68 (t, 4H, N(CH₂)₂, J=5Hz), 6.45 (d, 2H, Ar-H, o to NH₂, J=9Hz), 6.77 (d, 2H, Ar-H, m to NH₂, J=9Hz), 7.15 (s, 5H, Ar-H, CH₂C₆H₅).

IR: 1620 (Arom), 2800-2900 (C-H), 3200, 3300, 3380 (NH,NH₂).
NMR(DMSO-d₆) 3.2 (t, 4H, N(CH₂)₂, J=5Hz), 4.06 (t, 4H, CSN(CH₂)₂, J=5Hz), 6.52 (d, 2H, Ar-H, o to NH₂, J=9Hz), 6.72-7.24 (m, 7H, Ar-H).

IR: 1640 (CO), 2060 (NCS), 2500-2680 (HCl salt), 2900 (C-H), 3220 (NH).
NMR(CDCl₃ + DMSO-d₆) 2.82 (s, 3H, NCH₃), 3.25 (t, 4H, N(CH₂)₂, J=5.5Hz), 4.0 (t, 4H, CON(CH₂)₂, J=5.5Hz), 7.02-7.8 (m, 3H, Ar-H), 8.2 (s, 1H, NH, D₂O exchangeable).
| 246 | IR: 1645 (CO), 2080 (NCS), 2400-2600 (HCl salt), 2870 (C-H), 3380 (NH).  
NMR(CDCl\textsubscript{3}) 3.25 (t, 4H, N(CH\textsubscript{2})\textsubscript{2}, J=5Hz), 4.1-4.4 (m, 6H, CON(CH\textsubscript{2})\textsubscript{2} & N-CH\textsubscript{2}C\textsubscript{6}H\textsubscript{5}), 6.7-7.8 (m, 8H, Ar-H). |
| 247 | IR: 1640 (CO), 2100 (NCS), 3360 (NH).  
NMR(CDCl\textsubscript{3}) 3.55 (t, 4H, N(CH\textsubscript{2})\textsubscript{2}, J=5Hz), 4.48 (t, 4H, CON(CH\textsubscript{2})\textsubscript{2}, J=5Hz), 6.8-7.8 (m, 8H, Ar-H). |
| 248 | IR: 1590 (Arom), 1630 (CO), 2100 (NCS), 2500-2660 (HCl salt), 2900 (C-H), 3250 (NH).  
NMR(CDCl\textsubscript{3} + DMSO-d\textsubscript{6}) 2.82 (s, 3H, N-CH\textsubscript{3}), 3.15-3.45 (m, 4H, N-CH\textsubscript{2}C\textsubscript{6}H\textsubscript{5}), 3.8-4.15 (m, 4H, CON(CH\textsubscript{2})\textsubscript{2}), 7.08 (d, 2H, Ar-H, J=9Hz), 7.64 (d, 2H, Ar-H, J=9Hz), 9.15 (s, 1H, NH, D\textsubscript{2}O exchangeable). |
| 249 | IR: 1640 (CO), 2050 (NCS), 2400-2600 (HCl) 2870 (C-H), 3300 (NH).  
NMR(CDCl\textsubscript{3}) 2.70-4.10 (m, 4H, N(CH\textsubscript{2})\textsubscript{2}), 3.50-3.88 (m, 4H, CON(CH\textsubscript{2})\textsubscript{2}), 3.98 (s, 2H, NCH\textsubscript{2}C\textsubscript{6}H\textsubscript{5}), 6.9-7.55 (m, 9H, Ar-H), 8.84 (s, 1H, NH). |
Table 5: Physical Data of Compounds

\[
\begin{align*}
\text{Compd. No.} & \quad \text{R} & \quad \text{X} & \quad \text{m.p.} & \quad \text{Yield} & \quad \text{Molecular formula} & \quad \text{Analysis (\%)} \\
262 & \text{N} & \text{S} & 140 & 95 & C_{12}H_{16}N_{2}S \quad (220) & \text{C:} & 65.45 \quad 65.30 \\
 & \text{N Me} & \text{S} & 102-3 & 96 & C_{12}H_{17}N_{2}S \quad (235) & \text{C:} & 61.27 \quad 61.45 \\
263 & \text{N} & \text{S} & 85 & 95 & C_{11}H_{16}N_{2}O \quad (192) & \text{C:} & 58.75 \quad 58.42 \\
270 & \text{N} & \text{O} & 132 & 90 & C_{12}H_{16}N_{2}O \quad (204) & \text{C:} & 70.58 \quad 70.28 \\
 & \text{N Me} & \text{O} & 167-9 & 93 & C_{12}H_{17}N_{3}O \quad (219) & \text{C:} & 65.75 \quad 66.20 \\
\end{align*}
\]

Analysis (%)

\[
\begin{align*}
\text{Calcd.} & \quad \text{Found} \\
\text{H:} & \quad 7.27 \quad 7.56 \\
\text{N:} & \quad 12.72 \quad 12.50 \\
\text{H:} & \quad 7.23 \quad 7.52 \\
\text{N:} & \quad 17.87 \quad 18.25 \\
\text{H:} & \quad 8.33 \quad 8.72 \\
\text{N:} & \quad 14.58 \quad 14.24 \\
\text{H:} & \quad 7.84 \quad 8.28 \\
\text{N:} & \quad 15.72 \quad 14.10 \\
\text{H:} & \quad 7.76 \quad 7.42 \\
\text{N:} & \quad 19.17 \quad 18.90
\end{align*}
\]
<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>IR: KBr in cm$^{-1}$, NMR ppm ($\delta$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>262</td>
<td>1590 (Arom), 2820, 2900, 3000 (C=H), 3200 (NH).&lt;br&gt;NMR(CDCl$_3$) 1.52 (s, 6H, (C-CH$_2$)$_3$), 3.64 (s, 4H, N(CH$_2$)$_2$), 6.9-7.2 (m, 5H, Ar-H).</td>
</tr>
<tr>
<td>263</td>
<td>1600 (Arom), 2800, 2920 (C=H), 3200 (NH).&lt;br&gt;NMR(CDCl$_3$) 2.18 (s, 3H, N-CH$_3$), 2.26 (t, 4H, N(CH$_2$)$_2$, J=5Hz), 3.66 (t, 4H, CON(CH$_2$)$_2$, J=5Hz), 6.8-7.2 (m, 5H, Ar-H).</td>
</tr>
<tr>
<td>270</td>
<td>1600 (Arom), 1640 (CO), 2900-2980 (C=H), 3280 (NH).&lt;br&gt;NMR(CDCl$_3$) 1.02 (t, 6H, 2xCH$_2$CH$_3$, J=7Hz), 3.2 (q, 4H, 2xCH$_2$CH$_3$, J=7Hz), 6.8-7.32 (m, 5H, Ar-H).</td>
</tr>
<tr>
<td>271</td>
<td>1590 (Arom), 1620 (CO), 2820, 2900 (C=H), 3240 (NH).&lt;br&gt;NMR(CDCl$_3$) 1.5 (s, 6H, (C-CH$_2$)$_3$), 3.3 (s, 4H, N(CH$_2$)$_2$), 6.84-7.3 (m, 5H, Ar-H).</td>
</tr>
<tr>
<td>272</td>
<td>1600 (Arom), 1630 (CO), 2780, 2910 (C=H), 3260 (NH).&lt;br&gt;NMR(CDCl$_3$) 2.2 (s, 3H, N-CH$_3$), 2.28 (t, 4H, N(CH$_2$)$_2$, J=5Hz), 3.38 (t, 4H, CON(CH$_2$)$_2$, J=5Hz), 6.8-7.28 (m, 5H, Ar-H).</td>
</tr>
</tbody>
</table>
5. **BIOLOGICAL ACTIVITY:**

Most of the compounds were evaluated for their anthelmintic and antimicrobial activities in the Divisions of Parasitology and Fermentation Technology of this Institute.

5.1 **Anthelmintic Testing:**

5.1.1 **Antihookworm Testing:**

The compounds were tested for their antihookworm activity against experimental infections of *Nippostrongylus brasiliensis* in rats, *Nematodiroides dubius* in mice and *Ancylostoma ceylanicum* in hamsters by standard methods with slight modifications to suit local conditions.

**Methodology:**

Young male rats weighing 25–40 g (University of Freiburg strain) were inoculated subcutaneously or orally with 500 infective larvae of *N. brasiliensis*. Only those rats showing eggs in their stool on 8th day, were used for screening. An oral dose of the compound was given in a single or multiple dose on the day 9 post injection. The animals were starved over night prior to administration of drugs. This was done to ensure closure contact of the given chemotherapeutic agents with the parasites in absence of food material. Initially a single dose of 250 mg/kg of the compounds was used. The
compounds, insoluble in water, were made into fine suspension with tween 80. For each compound, 3 infected animals were used and a group of 3 animals was kept as untreated control. All the experimental and controlled rats were starved overnight before they were sacrificed on the day 3 post treatment. The total number of worms present in the intestine of a rat was counted on autopsy. The therapeutic efficacy of the compounds was assessed by comparing average number of the worms recovered from the treated group to that from the control group. If $N$ is the average number of worms found in control group of animals and $n$ is the average number of worms found in the treated group of animals, then the % deparasitization was calculated by the formula $\frac{N-n}{N} \times 100$.

A similar method was adopted when the screening was carried out against *Nematospiroides dubius* in mice and *Ancylostoma ceylanicum* in hamsters.

**Results and discussion:**

The compounds were initially tested for their antihookworm activity against *Nematospiroides dubius* in mice and *Nippostrongylus brasiliensis* in rats but none of them showed any noteworthy activity up to an oral dose of 250 mg/kg given for three days except 229 and 230 which showed 62-70% reduction of worms at dose of 250 mg/kg x 3 days. At a lower dose-schedule, compound 231 was found to
be effective in removing 60% of the worms at a dose of 100 mg/kg given orally for 3 days. The antihookworm testing of compounds carried out against *Ancylostoma ceylanicum* showed several compounds to possess high activity. Thus, compounds 62, 63, 72, 90, 110, 111, 127 and 168 cleared 100% of the *A. ceylanicum* worms from hamsters at an oral dose of 12.5-250 mg/kg given once or thrice daily for 3 days. The best compounds of the series are 110 and 168 which cleared 100% worms at a single oral dose of 12.5 mg/kg. Compounds 169 and 211 showed moderate activity and caused only 61.5 and 83.5% reduction in worm load at single oral dose of 250 mg/kg and 50 mg/kg respectively. Rest of the compounds were inactive up to 250 mg/kg given for 3 days. The anthelmintic testing results of the compounds are summarised in Table 6.

The antihookworm testing results would clearly indicate to the fact that a benzimidazole nucleus substituted with a 2-carboxyamino function is an essential requirement for biological activity. This was evident from the fact that none of the benzthiazole derivatives of the type I, II showed any order of anthelmintic activity. However, the presence of a suitable pharmacophore at 5(6)-position of methyl benzimidazole-2-carbamate has a key role in altering (enhancement or lowering) of the biological activity. Thus, introduction of a heterocyclic
Table 6: Efficacy of compounds against *Ancylostoma ceylanicum* infection in hamsters.

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>Name</th>
<th>Dose mg/kg</th>
<th>% clearance of worms</th>
</tr>
</thead>
<tbody>
<tr>
<td>62</td>
<td>2,2'-Dicarboxyamino-5,5'-dibenzimidazolyl sulphide</td>
<td>50x1</td>
<td>100*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>25x1</td>
<td>64-100</td>
</tr>
<tr>
<td>53</td>
<td>2,2'-Dicarboxyamino-5,5'-dibenzimidazolyl sulphide</td>
<td>100x3</td>
<td>90</td>
</tr>
<tr>
<td>72</td>
<td>2,2'-Dicarboxyamino-5,5'-dibenzimidazolyl sulphide</td>
<td>250x3</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>250x2</td>
<td>50-90</td>
</tr>
<tr>
<td>90</td>
<td>2,2'-Dicarboxyamino-5,5'-dibenzimidazolylmethane</td>
<td>100x1</td>
<td>93.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50x1</td>
<td></td>
</tr>
<tr>
<td>110</td>
<td>2,2'-Dicarboxyamino-5,5'-dibenzimidazolyl oxide</td>
<td>25x1</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12.5x1</td>
<td>94-100</td>
</tr>
<tr>
<td>111</td>
<td>2,2'-Dicarboxyamino-5,5'-dibenzimidazolyl oxide</td>
<td>50x1</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>25x1</td>
<td>77</td>
</tr>
<tr>
<td>127</td>
<td>Ethyl 5(6)-phenylbenzimidazole-2-carbamate</td>
<td>50x3</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>25x3</td>
<td>87-100</td>
</tr>
<tr>
<td>168</td>
<td>Methyl 5(6)-(4-isothiocyanato-phenylthio)benzimidazole-2-carbamate</td>
<td>12.5x1</td>
<td>100</td>
</tr>
<tr>
<td>169</td>
<td>Ethyl 5(6)-(4-isothiocyanato-phenylthio)benzimidazole-2-carbamate</td>
<td>250x1</td>
<td>61.5</td>
</tr>
<tr>
<td>211</td>
<td>1,2-Di-(4-isothiocyanato-phenylsulfonyl)ethane</td>
<td>50x1</td>
<td>83.3</td>
</tr>
</tbody>
</table>

*All the experiments showing 100% clearance of worms by a particular compound, were repeated twice or thrice using 3 animals per experimental group and 3 were used as controls.*
system such as a benzimidazole at the 5(6)-position of a benzimidazole ring gives rise to compounds devoid of any antihookworm or anticestode activity. Furthermore, incorporation of the benzimidazole ring in polynuclear heterocyclics such as I may generally lead to lowering or loss of activity. The best results are obtained when an appropriately substituted pharmacophore such as phenyl or benzimidazole ring are linked at the 5(6)-position of alkyl benzimidazole-2-carbamate via a heteroatom like sulphur or oxygen. Attempts to replace these heteroatoms by other groups like SO₂, CO, CH₂, S-CH₂-CH₂S-or piperazine in the dibenzimidazoles (III) leads to compounds having moderate to poor antinematode activity. The conclusions drawn from this study is in the close resemblance with the earlier studies describing the high anthelmintic activity and the molecular frame-work displayed by a series of benzimidazole anthelmintics 1-11.

5.12 Cestodicidal Testing:

The cestodicidal testing of all the compounds was carried out against experimental infection of *Hymenolepis nana* in rats using the technique of Steward with slight modifications.

**Methodology:**

Newly weaned male rats of University of Freiburg strain were infected by feeding them with 200 viable ova
of *H. nana*. On day 15, after incubation of viable ova, rats which were found positive of *H. nana* ova in their stool were treated after being starved overnight. Initially a single oral dose of 250 mg/kg of the compound was given orally to 3 animals and 3 were kept as control. All the animals including controls were again starved overnight before being sacrificed on day 3 post treatment. The small intestine of individual animal was removed separately, washed and the worms collected and scored. Compounds removing 100% of the worms along with their scoleces were considered active in this test.

**Results and Discussions:**

Most of the compounds were also tested for their anticestode activity against *H. nana* when some of the compounds showed high activity against the above tapeworms in rats and mice. Thus, compounds 62, 90, 91, 110, 111, 168, 169, 187 and 210 caused 100% elimination of worms along with their scoleces from rats and mice at single oral dose of 30-250 mg/kg. Poor activity was shown by compound 172 which removed 50% of the worms at a single oral dose of 250 mg/kg from rats. The best compounds of the series are 62 which cleared 100% of *H. nana* worms from rats at single oral dose of 70 mg/kg and 168 which caused 100% reduction in worm load at a single oral dose of 30 mg/kg. However, 62 and 168 eliminated 100 and 80%
worms respectively from mice at single oral dose of 100 mg/kg. Praziquantel was used as standard drug which removed 100% of the H. nana worms along with scolices at a single dose of 5 mg/kg given orally. Rest of the compounds were found to be inactive up to an oral dose of 250 mg/kg. The detail results of the cestodicidal activity is summarized in Table 7.

The fact, that a number of benzimidazole anthelmintics such as mebendazole and fenbendazole exhibit marked activity against different cestodes, led us to evaluate their cestodicidal activity against a common human tapeworm, H. nana (dwarf tapeworm). The testing results showed that the structural parameters required for biological activity in methyl benzimidazole-2-carbamates is complementary to those needed for antihookworm activity described in Sec. 5.11.

5.2 Antimicrobial Activity:

Most of the compounds were also evaluated for their in vitro growth inhibitory activity against different strains of bacteria and fungi and results are summarized in Table 8. The bacteria and fungi were maintained on nutrient and Sabouraud's agar slants respectively and testing was done using the two fold serial dilution technique by dissolving the compounds in ethanol. The bacteria used were Staphylococcus aureus (gram positive,
Table 7: Efficacy of compounds against *Hymenolepis nana* infections in rats.

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>Name</th>
<th>Dose mg/kg</th>
<th>% clearance of worms</th>
</tr>
</thead>
<tbody>
<tr>
<td>62</td>
<td>2,2'-Dicarbomethoxyamino-5,5'-dibenzimidazolyl sulphide</td>
<td>70x1</td>
<td>100a</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100x1</td>
<td>100a</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50x1</td>
<td>60a</td>
</tr>
<tr>
<td>20</td>
<td>2,2'-Dicarbomethoxyamino-5,5'-dibenzimidazolymethane</td>
<td>250x1</td>
<td>100</td>
</tr>
<tr>
<td>91</td>
<td>2,2'-Dicarbethoxyamino-5,5'-dibenzimidazolymethane</td>
<td>250x1</td>
<td>100</td>
</tr>
<tr>
<td>110</td>
<td>2,2'-Dicarbomethoxyamino-5,5'-dibenzimidazolyl oxide</td>
<td>250x1</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100x1</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50x1</td>
<td>66</td>
</tr>
<tr>
<td>111</td>
<td>2,2'-Dicarbethoxyamino-5,5'-dibenzimidazolyl oxide</td>
<td>250x1</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100x1</td>
<td>60</td>
</tr>
<tr>
<td>168</td>
<td>Methyl 5(6)-(4-isothiocyanato-phenylthio)benzimidazole-2-carbamate</td>
<td>30x1</td>
<td>100a</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100x1</td>
<td>80a</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50x1</td>
<td>55.5a</td>
</tr>
<tr>
<td>169</td>
<td>Ethyl 5(6)-(4-isothiocyanato-phenylthio)benzimidazole-2-carbamate</td>
<td>250x1</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100x1</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50x1</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td></td>
<td>25x1</td>
<td>33</td>
</tr>
<tr>
<td>172</td>
<td>Methyl 5(6)-(4-isothiocyanato-phenylsulphono)benzimidazole-2-carbamate</td>
<td>250x1</td>
<td>50</td>
</tr>
<tr>
<td>187</td>
<td>Ethyl 5(6)-(4-isothiocyanato-phenoxy)benzimidazole-2-carbamate</td>
<td>250x1</td>
<td>100</td>
</tr>
<tr>
<td>210</td>
<td>1,2-Di-(4-isothiocyanato-phenylthio)ethane</td>
<td>250x1</td>
<td>100</td>
</tr>
</tbody>
</table>

a, in mice.
resistant to 2500 units of penicillin/ml), Streptococcus faecalis, Salmonella typhi (gram negative), Escherichia coli, Agrobacterium tumefaciens, Klebsiella pneumoniae, Pseudomonas aeruginosa and Proteus vulgaris, while the fungi used were Candida albicans, Trichophyton mentagrophytes, Cryptococcus neoformans, Microsporum canis, Aspergillus niger, Aspergillus fumigatus and Sporotrichum schenckii. Tetracycline and amphotericin B were used as standard drugs in antibacterial and antifungal testings respectively.

5.21 Antibacterial Assay:

All the bacteria were maintained on nutrient agar slants. Testing was done in nutrient broth. After inoculation with a loopful of culture from the slant, the seeded broth were incubated at 37±1°C for 24 hr. The two fold serial dilution technique was applied. A set of tubes containing only inoculated broth was kept as controls. After incubation for 24 hr, the last tube with no growth of the microorganism was taken to represent the minimum inhibitory concentration (MIC, expressed in µg/ml). A compound inhibiting the growth of microbe in a concentration of 25 µg/ml was considered to be active.

5.22 Antifungal Assay:

All the fungi were maintained on Sabouraud's agar slants and the compounds were tested in Sabouraud's broth. Loopfuls of the fungal culture (C. albicans and
C. neoformans) from the slants were inoculated into the broth and the respective inoculated broths were used for testing after incubation for 24 hr at 28±1°C. In the case of small fungi, small pieces of mycelia were introduced into conical flask containing 50 ml of the broth. The flasks were then incubated with shaking for 24-48 hr and the clear broths were taken out of the flasks. The compounds were tested by serial dilution technique as described in antibacterial assay. The compounds which inhibited the growth of fungus at 25 μg/ml concentration, was considered to be active.

5.23 Results:

The compounds were tested against various strains of bacteria and found to be inactive except 215 which inhibited the growth of Streptococcus faecalis and Klebsiella pneumoniae at minimum inhibitory concentrations (MIC) of 25 and 25 μg/ml and 242 which inhibited the growth of above microbes at MIC's of 25 and 50 μg/ml respectively. The growth of rest of the strains remained unaffected by either of the compounds tested.

In antifungal testing the best compound of the series was 214 which inhibited the growth of all the fungi used at the MIC's of 3.125-12.5 μg/ml. However, 215 caused the inhibition of C. albicans, T. mentagrophytes and A. fumigatus at MIC's of 6.25, 6.25 and 100 μg/ml. Rest of the compounds inhibited the growth at higher concentrations and results are summarized in Table 8.
Table 8: *In vitro* antifungal activity of the compounds

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>Minimum inhibitory concentration (MIC) in μg/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><em>C. albicans</em></td>
</tr>
<tr>
<td>130</td>
<td>&gt;100</td>
</tr>
<tr>
<td>131</td>
<td>&gt;100</td>
</tr>
<tr>
<td>132</td>
<td>&gt;100</td>
</tr>
<tr>
<td>134</td>
<td>100</td>
</tr>
<tr>
<td>145</td>
<td>&gt;100</td>
</tr>
<tr>
<td>214</td>
<td>3.125</td>
</tr>
<tr>
<td>215</td>
<td>6.25</td>
</tr>
<tr>
<td>220</td>
<td>25</td>
</tr>
<tr>
<td>221</td>
<td>25</td>
</tr>
<tr>
<td>222</td>
<td>100</td>
</tr>
<tr>
<td>225</td>
<td>100</td>
</tr>
<tr>
<td>232</td>
<td>25</td>
</tr>
<tr>
<td>241</td>
<td>50</td>
</tr>
<tr>
<td>244</td>
<td>&gt;100</td>
</tr>
<tr>
<td>245</td>
<td>100</td>
</tr>
</tbody>
</table>
6. REFERENCES:


60. J. S. Steward, Parasitology, 45, 231 (1955).