CHAPTER FOUR

4.0 STUDIES ON THE SYNTHESIS OF CONDENSED PYRIMIDINES FROM 0-AMINONITRILES BY THE REACTION WITH NITRILES UNDER ACIDIC CONDITIONS

2-SUBSTITUTED-7,9-DIMETHYL-4-CHLOROPYRIDO(3',2':4,5)THIENO(3,2-d)PYRIMIDINES

AND

2-SUBSTITUTED-4-CHLORO/AND 4-AMINOBENZO(3,2-d)PYRIMIDINES
4.1 INTRODUCTION

4.1.1 THE IMIDOYL HALIDES

Reaction of nitriles in the presence of dry HCl gas has been developed into a general and facile method for the one-pot synthesis of condensed pyrimidines in this laboratory. This reaction has been exploited to prepare more than 300 condensed pyrimidines.\textsuperscript{464-466} Nitriles have played a major role in the synthesis of a variety of open-chain and heterocyclic compounds. The polar C≡N group of the nitriles is prone to electrophilic attack at the nitrogen and nucleophilic attack at the carbon. The interaction of a nitrile 597 with an acid or its complexation with a Lewis acid leads to the formation of a species 598 possessing greater electrophilicity and, therefore, many of the reactions of nitriles with nucleophilic reagents are acid catalysed.\textsuperscript{467}

\[
\begin{align*}
R-\text{C}≡\text{N} & \quad \text{A} \quad \longrightarrow \quad R-\text{C}≡\text{N}\text{A} \quad \longrightarrow \quad R-\text{C}≡\text{N}\text{A} \\
597 & \quad \text{598}
\end{align*}
\]

Halogen acids are particularly effective in promoting the reactions of nitriles with a variety of nucleophilic species. Nitriles react with halogen acids to yield unstable and nonisolable adducts of varying compositions, such as RCN-HX, 2RCN-HX, 2RCN-nHX. The protonation of the nitriles yields the nitrilium ion 599 which combines with a halide ion to form imidoyl halide 600 (Scheme 63). The imidoyl halide 600 thus formed is sufficiently basic to react with another molecule of halogen acid to yield the imidoyl halide hydrohalide salt 601. In this reversible
reaction, the formation of imidoyl halide salt 601 is frequently slow and is favoured by high concentration of hydrogen halide.  

\[ R-CN + HX \rightarrow R-CN\textsuperscript{+} \quad (598) \]  

\[ \text{R-CN\textsuperscript{+} + HX} \rightarrow R-CN\textsuperscript{+} \text{X} \quad (600) \]  

\[ R-CN\textsuperscript{+} \text{X} \rightarrow R-CN\textsuperscript{+} \text{X} \quad (601) \]  

**Scheme 63**  

Though only a few reactions of the isolated nitrile-halogen acid adducts have been studied, nitrilium salt 599, imidoyl halide 600 and imidoyl halide hydrohalide 601 have been proposed as the transient intermediates in a variety of reactions of nitriles with nucleophiles in presence of halogen acids, such as Pinner synthesis, Gatterman synthesis, Houben Hoesch synthesis and Stephen synthesis.  

4.1.2 Synthesis of Condensed Pyrimidines through the Reaction of Nitriles with o-Aminocarbonyl compounds:  

The intramolecular condensation of a nitrile with a substrate possessing electrophilic and nucleophilic centers often leads to the direct formation of an aza-heterocycle by the incorporation of C=N of the nitriles (Scheme 64).
The enhanced reactivity of nitriles towards nucleophiles in presence of acids, particularly halogen acids, is known. However, utilization of the enhanced reactivity of nitriles in the presence of acids for the synthesis of condensed pyrimidines through the reaction with \(\alpha\)-aminocarbonyl compounds has, hitherto, remained unexplored.

With a view to exploit this increased reactivity of nitriles in the presence of acids for the synthesis of condensed pyrimidines, a variety of nitriles have been reacted with \(\alpha\)-aminocarbonyl compounds in this laboratory. This approach has led to the development of a facile one-pot synthesis of condensed pyrimidines of general applicability.

Thus, a variety of \(\alpha\)-aminoketones 602, \(\alpha\)-aminonitriles 603, \(\alpha\)-aminoesters 604 and \(\alpha\)-aminoamides 605 have been reacted with nitriles to obtain the 4-substituted condensed pyrimidines 606-608, respectively (Scheme 65).
Scheme 65

602 + \text{N} R \rightarrow 606

603 + \text{N} R \rightarrow 607

604 \text{R}^2 = \text{OR}^1
605 \text{R}^2 = \text{NHR}^1

609 + \text{N} R \rightarrow 615

610 + \text{N} R \rightarrow 616
Anthranilic acid esters 609 and o-aminoesters of thiophene 610 and 611 benzothiophene 612 pyrido-thiophene 613 and isothiazole 614 have been found to react with a variety of aliphatic, aromatic and heterocyclic nitriles in the presence of dry hydrogen chloride gas to yield the corresponding condensed 4-oxopyrimidines 615-620 (Scheme 66). 464, 465, 482-484

Functionalized acetonitriles, such as chloroacetonitrile, dichloro-acetonitrile, trichloroacetonitrile, aryloxyacetonitrile, arylthioacetonitrile, arylsulfonylacetonitrile and arylsulfonylaminoacetonitriles have been condensed with o-aminoesters of benzene and thiophene to obtain the

Scheme 66
corresponding 2-substitutedmethylene condensed pyrimidin-4-ones 621.

\[
R = \text{ClCH}_2, \text{Cl}_2\text{CH}, \text{Cl}_3\text{C}, \\
\text{ArOCH}_2, \text{ArSCH}_2, \text{ArSOCH}_2, \\
\text{ArSO}_2\text{NHCH}_2;
\]
\[
X = \text{S}, R^1, R^2 = -(\text{CH}_2)_4, R^1 = R^2 = \text{CH}_3; \\
X = -\text{CH}=\text{CH}^-, R^1 = R^2 = \text{H}
\]

Attempts to demonstrate the intermediacy of such o-functionalised amidines by their isolation, in general, have not met with success in the condensations involving nitriles and o-aminocarbonyl substrates, like o-aminoesters, o-aminonitriles and o-aminoketones of benzene, thiophene, furan and pyrrole.

However, under controlled conditions, stable amidine intermediates 623 have been isolated in the reaction of thiophene o-aminonitriles 622 with nitriles under acidic conditions.

Thus, a stream of dry HCl was passed through a solution of thiophene o-aminonamide, and excess of acetonitrile, for 5-6 hr, at a temperature of 5-10 °C.

On pouring the mixture into ice water and adjusting the pH to 7 with dil. ammonium hydroxide solution, the solid obtained was filtered, dried under vacuum, and recrystallized with dichloromethane and n-hexane.
Further, amidine 625 has also been isolated as intermediate in the reaction of pyrrole \( \alpha \)-aminonitrile 624 with the excess of acetonitrile, in this laboratory.\(^{486}\)

\[
\begin{array}{c}
\text{C}_6\text{H}_5 \\
\text{C}_6\text{H}_5 \\
\text{C}_6\text{H}_5 \\
\text{C}_6\text{H}_5 \\
\end{array}
\text{N} \\
\text{C} \\
\text{C} = \text{N} \\
\text{C} \\
\text{C}_6\text{H}_5
\]

\[624\]

\[
\begin{array}{c}
\text{C}_6\text{H}_5 \\
\text{C}_6\text{H}_5 \\
\text{C}_6\text{H}_5 \\
\text{C}_6\text{H}_5 \\
\end{array}
\text{N} \\
\text{C} \\
\text{R} = \text{NH}_2, \text{CH}_3 \\
\text{C}_6\text{H}_5 \\
\text{C}_6\text{H}_5
\]

\[625\]

Recently, Eger and co-workers\(^{487}\) have also reported isolation of amidine intermediates 627 similar to 625 in the reaction of pyrrole \( \alpha \)-aminonitrile 626 with acetonitrile under the influence of dry HCl gas. These amidines have been thermally cyclized to the condensed 4-aminopyrimidine 628 in presence of alcoholic ammonia.

This reaction has been exploited for the synthesis of known drugs used in therapy of their CNS activity. Thus, amidine 629a and 629b on refluxing in absolute ethanol cyclise to give methanqualone 630a and meclaqualone 630b, respectively, in good yields.
4.1.3 Condensed-Aminopyrimidines

Extension of this reaction to the condensation of nitriles 597 with the substrate o-aminonitrile 631 results in the formation of condensed 4-aminopyrimidines 632.

Earlier, 4-amino-2-methylquinazoline 634 has been obtained in low yields (24%) through the condensation of anthranilonitrile 633 with acetonitrile in the presence of ammonia in methanol at 210 °C.

However, in presence of dry HCl, the condensation of anthranilonitrile 633 with acetonitrile and phenylacetonitrile has yielded the 4-aminoquinazolines 634 at room temperature. Similar reaction of thiophene o-aminonitrile 635 with acetonitrile, phenylacetonitrile, benzonitrile and ethyl cyanoacetate yield the corresponding 4-aminothieno(2,3-d)pyrimidines 636 (Scheme 67).
However, in some of the reactions of nitriles with \( \alpha \)-aminonitrile substrate the product formed was condensed 4-chloropyrimidine 637 instead of the expected condensed 4-aminopyrimidine 632.\(^{489,466}\)

Preliminary studies in this laboratory have indicated that the nature of nitrile plays an important role in determining course of the reaction. For example, nitriles, such as acetonitrile, yielded exclusively fused 4-aminopyrimidines 632 while chloroacetonitrile leads to the formation of condensed 4-chloropyrimidines 637. Since the electron withdrawing nature of
chlorine in chloroacetonitrile appeared to influence the course of the reaction, an attempt was made to investigate the product distribution in the reactions of a series of substituted acetonitriles, arylcyanides and other nitriles possessing various electron withdrawing functions.\textsuperscript{466,490}

![Chemical structures](image)

The readily accessible anthranilonitrile 638 thiophene \(\alpha\)-aminonitriles 639a, 639b and furan \(\alpha\)-aminonitrile 640 were selected as substrates. The condensation between these substrates and variously substituted nitriles was conducted in dioxane, under carefully controlled conditions employing anhydrous hydrogen chloride gas as the catalyst.

An examination of the overall results obtained with the substituted acetonitriles employed appears to substantiate the expectation that the electron withdrawing ability of the substituent on the \(\text{C}=\text{N}\) group of the nitrile does affect the course of the reaction.\textsuperscript{464,466}

The possibility of a formation of 4-chloropyrimidines 637 from 4-aminopyrimidines 632 under the reaction conditions employed for the condensation has been excluded by passing excess of dry hydrogen chloride gas through the solution of the 4-aminopyrimidine in dioxane; workup of the reaction mixture yielded the unreacted starting material. Therefore, the chloro- and aminopyrimidine formation occurs probably by different reaction pathways. It appears reasonable to assume that under the reaction conditions employed, the \(\text{C}=\text{N}\) groups of both the substrate and the reactant
are activated by protonation or by the formation of hydrogen chloride adducts. The initial condensation between the two components or their activated forms might be expected to result in the formation of amidine hydrochloride 641 or its hydrochloride adduct 642 (Scheme 68).

![Scheme 68](image)

All attempts to demonstrate the formation of such amidine intermediates by their isolation under carefully controlled conditions did not meet with success. Only fused pyrimidines could be isolated. However, amidine intermediates have been isolated in the condensations of certain thiophene o-aminonitrile with cyanamide under acidic conditions.487

The general procedure employed by the earlier workers involves the bubbling of excess of dry hydrogen chloride through a mixture of o-aminocarbonyl substrate and nitrile in a suitable solvent like dioxane. The duration of the passage of dry HCl ranges from 4–24 hrs. Thus, the total time involved in the reaction may vary from 8–36 hr.
With a view to optimise this one-pot reaction for the synthesis of condensed pyrimidines, a concentrated solution of dry hydrogen chloride was prepared in dioxane (6-8 M). Due to nonavailability of dry hydrogen chloride cylinders in this country, the hydrogen chloride gas is generated by dropping concentrated sulphuric acid through a dropping funnel into a slurry of sodium chloride and concentrated hydrochloric acid, contained in a generator. The HCl gas thus generated is passed through concentrated sulphuric acid to remove any moisture associated with the gas.\(^{491}\)

The HCl dioxane solution has been prepared in this laboratory by passing the dry HCl was bubbled into cooled dry dioxane. Dioxane is chosen for the purpose as it has a good capacity to absorb the HCl gas. the solvent is neutral, stable in acidic media and is miscible with water. The gas was passed for a duration of 3 hr. This solution of dry HCl in dioxane was then standardised by titrating it against a standard solution of sodium carbonate using methyl orange as the indicator. The molarity of this solution was generally found to range between 6-8 M. The calculated molar concentration was used to determine the volume of this solution equivalent to different molar concentrations of HCl. The HCl dioxane solution was stored in a tightly stoppered bottle in cool conditions.

For conducting this study, 2-amino-3-cyano-4,5,6,7-tetrahydrobenzo-(b)thiophene 643 was selected as the substrate and chloroacetonitrile as the condensing nitrile. Earlier workers have reported exclusive formation of 4-chloropyrimidine 644 without a trace of 4-aminopyrimidine 645 by passing dry HCl for a period of 6 hr. It was sought to determine the effect of duration of HCl passage on the yield of 4-chloropyrimidine.
When dry HCl was bubbled for a duration of 3 hr through a solution of 2-amino-3-cyanotetrahydrobenzo(b)thiophene 643 and chloroacetonitrile in dioxane, a mixture of 4-aminotetrahydrobenzo(b)thieno(2,3-d)pyrimidine 645 and 4-chloropyrimidine 644, is obtained. When isolated, the yield of the two products were found to be nearly equal (40% and 41%, respectively).

Earlier workers have overlooked the importance of duration of HCl gas passage and its effect on the course of reaction.

However, when dry HCl gas was passed for nearly 24 hr the yield of 4-chloropyrimidine 644 was found to increase to 74% while the yield of 4-aminopyrimidine, 645, was negligible.

Therefore, it appeared important to study the effect of HCl concentration on the course of reaction.

4.1.4 Nucleophilic displacement reaction of 4-chloro fused pyrimidines

4-Chloropyrimidines undergo facile nucleophilic displacement with amines to give 4-substituted amino pyrimidines 647. Manhas and his
co-workers have studied nucleophilic reactions of 4-chlorothieno(2,3-d)pyrimidines 646.  

![Chemical Structure](image)

Various substituted thieno(2,3-d)pyrimidines I-V have been screened for pharmacological activities, especially anti-inflammatory and analgesic activities in mice. Thieno(2,3-d)pyrimidin-2-mercaptoacetic acid II and its ethyl ester derivatives have been patented for their anti-inflammatory, analgesic and blood sugar lowering properties. Similarly, derivatives III has been found to inhibit the rise in blood sugar levels. Recently Boehm et al. have demonstrated blood platelet aggregation inhibiting properties of arylaminosubstituted thieno(2,3-d)pyrimidine V.
Table XXII A Pharmacology of 4-Substituted thieno(2,3-d)pyrimidines

<table>
<thead>
<tr>
<th>Compd No.</th>
<th>R&lt;sub&gt;1&lt;/sub&gt;</th>
<th>R&lt;sub&gt;2&lt;/sub&gt;</th>
<th>R&lt;sub&gt;3&lt;/sub&gt;</th>
<th>R&lt;sub&gt;4&lt;/sub&gt;</th>
<th>Pharmacological Activity&lt;sup&gt;*&lt;/sup&gt;</th>
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</thead>
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<tr>
<td>I</td>
<td>Me</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;COOH</td>
<td>H</td>
<td>NH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Anti-inflammatory and Analgesic&lt;sup&gt;541&lt;/sup&gt;</td>
</tr>
<tr>
<td>II</td>
<td>H</td>
<td>H</td>
<td>SCH&lt;sub&gt;2&lt;/sub&gt;COOEt</td>
<td>OH</td>
<td>Anti-inflammatory Analgesic, Blood sugar lowering&lt;sup&gt;542&lt;/sup&gt;</td>
</tr>
<tr>
<td>III</td>
<td>Me</td>
<td>H</td>
<td>-N&lt;sub&gt;2&lt;/sub&gt;</td>
<td>NH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Inhibite the rise in blood sugar level&lt;sup&gt;542&lt;/sup&gt;</td>
</tr>
<tr>
<td>IV</td>
<td>H</td>
<td>H</td>
<td>C&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;COOH</td>
<td>Ph</td>
<td>Anticholesterolimic activity&lt;sup&gt;542&lt;/sup&gt;</td>
</tr>
<tr>
<td>V</td>
<td>H&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;-&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;Cl</td>
<td>-N&lt;sub&gt;2&lt;/sub&gt;</td>
<td>H&lt;sub&gt;3&lt;/sub&gt;C</td>
<td>Blood platelet aggregation inhibiting&lt;sup&gt;543&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

<sup>*</sup> Reference No.
4.2 PRESENT WORK

The hydrogen chloride catalysed reaction of nitriles with o-aminonitrile substrate 630 generally results in the formation of 4-aminopyrimidine 632 as the product. However, this is not true in all the cases. In some of the reactions the product formed is 4-chloropyrimidine 637 instead of the expected 4-aminopyrimidine 632.

Recently, 2-amino-3-cyano substrates like furan-, benzene-, thiophene o-aminonitriles have been condensed in this laboratory with a variety of substituted nitriles under the influence of HCl gas. The product formed is either 4-chloropyrimidine 637, 4-aminopyrimidine 632 or a mixture of the two, in varying proportions.

An examination of the overall results obtained from these acid catalysed nitrile reactions indicates that the electron withdrawing ability of the substituent on nitrile plays an important role in determining the course of the reaction.

With a view to explore the scope, limitations and generality of this facile hydrogen catalysed condensation, the reaction was extended to
include 2-cyano-3-amino substrates such as 3-amino-2-cyano-4,6-dimethylthieno(2,3-b)pyridine 648 and 3-amino-2-benzofurancarbonitrile 649.

Recently, preliminary results on the condensation of 2-cyano-3-amino-substrates 648 and 649 with nitriles has indicated that the formation of 4-chloropyrimidine 650 and 4-aminopyrimidine 651 depends not only on the reaction of nitriles but also on the nature of the substrate employed.495,496

Therefore, a detailed study was undertaken essentially to delineate the factors influencing the course of reaction. This in turn may help to explain the mechanism of the nitrile reaction.
4.2.1 RESULTS AND DISCUSSION

4.2.1.1 Reaction of nitriles with 3-amino-2-cyano-4,6-dimethylthieno(2,3-b)pyridine under acidic conditions

Passing a stream of dry hydrogen chloride gas through a mixture of 3-amino-2-cyano-4,6-dimethylthieno(2,3-b)pyridine and acetonitrile in dioxane for 12-14 hr, followed by usual work-up gave a single product which recrystallized from petroleum ether to yield 71% of colourless crystals with melting point 154-55 °C.

![Scheme 69](image)

IR spectrum of the product formed was devoid of any absorption above 3000 cm\(^{-1}\). The C\(_{\text{N}}\)N peak at 2200 cm\(^{-1}\) was found to be absent. The expected D\(_2\)O washable two proton singlet was also absent in the \(^1\)H-NMR spectrum, thereby confirming the absence of amino group. Instead of the expected 4-aminopyrimidine 652, the product was found to be 4-chloropyrimidine and...
received confirmation from its mass spectrum showing an intense mass peak at 263 accompanied by a prominent M+2 peak at 265. Loss of $^{35}$Cl and $^{37}$Cl gave rise to base peak at 228 and 226, respectively.

Based on the spectral data and the satisfactory microanalysis the product was assigned structure as 2,7,9-trimethyl-4-chloropyrido-(3',2':4,5)thieno(3,2-d)pyrimidine 653 (Scheme 69).

The expected 2,7,9-trimethyl-4-aminopyrido(3',2':4,5)thieno(3,2-d)pyrimidine 652 was not present even in traces. In fact all our attempts to synthesize this 4-amino fused pyrimidine 652 even by controlling the molar concentration of HCl failed.

Similarly, chloroacetonitrile when condensed with thieno(2,3-b)pyridine 648 substrate in dioxane under the influence of dry hydrogen chloride gas gave a single product. Recrystallized from petrooleum ether to obtain 68% colourless product with melting point 156-57 °C (140-42 °C). IR spectrum of the product was found to be devoid of any absorption above 3000 cm$^{-1}$. Downfield two proton singlet at $\delta$ 4.2 showed the presence of methylene proton and signal around $\delta$ 7.1 corresponding to aromatic proton characterized the $^1$H-NMR spectrum of the product. Mass spectrum (Scheme 70), confirmed the formation of 7,9-trimethyl-2-chloromethyl-4-chloropyrido(3',2':4,5)thieno(3,2-d)pyrimidine 654.
Likewise, when dry HCl gas was bubbled through a mixture of dichloroacetonitrile and thieno(2,3-b)pyridine 648 in dioxane, only one product 655 was obtained. Recrystallized from petroleum ether to afford 75% colourless crystals which melted at 163-64 °C.
The product obtained exhibits two proton singlets in the δ 7.1-7.3 region of 1H-NMR spectrum. Based on its elemental analysis and spectral data, the product confirmed as 655.

Finally, all the 4-chloropyrimidines 653-656 synthesized are characterized by satisfactory microanalysis (Table XXVII).

Surprisingly, other nitriles like benzonitrile, phenylacetonitrile, ethyl cyanoformate, ethyl cyanoacetate and p-nitrobenzonitrile failed to react with the substrate thiieno(2,3-b)pyridine 648 and only the unreacted starting material was obtained from the reaction mixture.

4.2.1.2 Reaction of nitrile with Benzofurancarbonitrile under acidic conditions:

A stream of dry hydrogen chloride gas was passed through a mixture of 3-amino-2-benzofurancarbonitrile 649 and excess of acetonitrile for 8-10 hr. Product isolated was found to be a mixture of two compounds. This mixture was separated by extraction with hot n-hexane. The residue remaining behind was recrystallized from ethanol-chloroform with a melting point 209-11 °C. Evaporation of the n-hexane afforded a crystalline compound which melts at 113-14 °C.
Lower melting point compound has no absorption above 3000 cm\(^{-1}\) indicating thereby absence of free N\(_2\)H\(_2\) group. A three proton singlet at \(\delta 2.4\) corresponds to methyl group and a multiplet for aryl protons in the region \(\delta 7.3-7.7\) characterised the \(^1\)H-NMR spectra. Mass spectrum showed an intense molecular ion (M\(^+\) \(^{35}\)Cl) peak along with prominent (M\(^+\) \(^{37}\)Cl) peak. Base peaks are observed due to loss of \(^{35}\)Cl and \(^{37}\)Cl (Scheme 74).

The spectral data and the satisfactory microanalysis confirmed that the lower melting point compound has a structure of 4-chloro-2-methylbenzofuro(3,2-d)pyrimidine 657.

The higher melting point product exhibits two strong absorption bands around 3500 cm\(^{-1}\) and 3140 cm\(^{-1}\) due to asymmetric and symmetric N-H stretching vibrations. D\(_2\)O washable two proton singlet at \(\delta 2.55\) indicated the presence of NH\(_2\) group, three proton singlet at \(\delta 2.4\) was observed for CH\(_3\) group. Aryl protons appear as a multiplet in the \(\delta 7.3-7.6\) region of \(^1\)H-NMR spectrum. Mass spectrum showed intense molecular ion (M\(^+\)) peak at 199 and other peaks are observed due to loss of CH\(_3\)\(^+\), NH\(_2\)\(^+\), H\(^+\)H\(_2\)CN, H\(^+\), and CH\(_3\)CN (Scheme 75).
Thus, spectral data and the satisfactory microanalysis confirmed that the higher melting point compound has a structure of 4-amino-2-methylbenzofuro(3,2-d)pyrimidine 658.

When dry HCl gas was passed through a mixture of 3-amino-2-benzofurancarbonitrile 649 and excess of acetonitrile for 24 hr, only 4-chloropyrimidine 657 was obtained, in 68% yield. 4-Aminopyrimidine 658 was not detected even in traces.

On the other hand, when 3-amino-2-benzofurancarbonitrile 649 and excess of acetonitrile was reacted in presence of 0.04M HCl, only 4-aminopyrimidine 658 was obtained, exclusively, in 55% of yield.

Further, dry hydrogen chloride gas when bubbled for 7-8 hr through a mixture of 3-amino-2-benzofurancarbonitrile 649 substrate and nitrile such as chloroacetonitrile, dichloroacetonitrile, acrylonitrile, benzylcyanide, p-nitrobenzylcyanide or p-chlorophenylthioacetonitrile, a mixture of the corresponding 2-substituted 4-chloro and 4-aminobenzofuro(3,2-d)pyrimidines 659-675 in varying proportions were obtained as mentioned in Table XXVIII.
However, reaction of 3-amino-2-benzofurancarbonitrile 649 with benzonitrile, methylthiocyanate, ethyl cyanoformate, ethyl cyanoacetate and phenylthiocyanate in dioxane afforded only the corresponding 4-aminobenzofuro(3,2-d)pyrimidines 659, 660, 667, 668 and 675, respectively in yields ranging from 40-58%.

659, \( R = \text{C}_6\text{H}_5 \)
660, \( R = \text{CH}_3\text{S} \)
667, \( R = \text{COOEt} \)
668, \( R = \text{CH}_2\text{COOEt} \)
675, \( R = \text{SC}_6\text{H}_5 \)
Structures of all the 4-chloro and 4-aminopyrimidines are based on the spectral data and satisfactory microanalysis (Table XXVIII). Physical and spectral properties have been discussed in section 4.2.3.2.

4.2.1.3 Conclusion of 'Nitrile Reaction' of 3-Amino-2-cyano substrates under acidic conditions

Condensation of 3-amino-2-cyano-4,6-dimethylthieno(2,3-b)pyridine 648 with acetonitrile results in the formation of 2,7,9-trimethyl-4-chloropyrido(3',2':4,5)thieno(3,2-d)pyrimidine 653, exclusively, even though dry HCl gas was passed for only 5-6 hr.

Similarly, 4-chloro-2-methylbenzofuro(3,2-d)pyrimidine was obtained, exclusively, when dry HCl gas was passed through a mixture of 3-amino-2-benzofurancarbonitrile 649 and acetonitrile in dioxane for 18-20 hr.

Thieno(2,3-b)pyridine 648 substrate reacted with only a limited number of nitriles to form 2-substituted 4-chloropyrido(3,2-d)pyrimidine 654-656 in the presence of dry HCl gas. Whereas, 3-amino-2-benzofurancarbonitrile 649 was condensed with various aliphatic and aryl nitriles in presence of dry HCl gas to afford the 4-chloro and 4-amino-2-substituted benzofuro(3,2-d)pyrimidines in varying proportions.

Moreover, all our attempts have failed to obtain directly 4-aminopyrido(3,2-d)pyrimidine 652 from thieno(2,3-b)pyridine 648 substrate under acidic conditions.
3-Amino-2-benzofurancarbonitrile 649 substrate yielded 4-aminobenzofuro(3,2-d)pyrimidines 659, 660, 667, 668, 675, exclusively, with certain nitriles such as benzonitrile, methylthiocyanate, ethyl cyanoformate, ethyl cyanoacetate, and phenylthiocyanate, respectively under acidic conditions.

This new data thereby underlining that the substrate plays an important role in acid catalysed nitrile reaction. Apparently, electrophilicity of C=N group in position 2 appears to differ quantitatively in comparison to C=N group at C-3.

Though the nitrile reaction is acid catalysed, the formation of condensed 4-amino and 4-chloropyrimidines in a reaction of 3-amino-2-cyano substrates with nitriles is dependent upon the concentration of HCl. For example, the exclusive formation of 4-aminobenzofuro(3,2-d)pyrimidine 658 was achieved in a reaction of 3-amino-2-benzofurancarbonitrile 649 with acetonitrile in presence of 0.04M HCl in dioxane. On the other hand dry HCl
when passed for a duration of 7-8 hr through the reaction mixture resulted in the formation of a mixture of condensed 4-chloro-657 and 4-aminopyrimidine 658 in varying proportions. At the same time, passage of dry HCl for about 18-20 hr resulted in exclusive formation of 4-chloropyrimidine 657 (Scheme 71).

Scheme 71

Results obtained with the substrates 3-amino-2-cyano-4,6-dimethylthieno(2,3-b)pyridine 648 and 3-amino-2-benzofurancarbonitrile 649 are in total variance with the earlier reports on the 'Nitrile Reaction' with 2-amino-3-cyano substrates.464,465 The present results indicate that apart from the nature of the nitrile, other factors, such as the nature of
substrate and concentration of HCl also play an important role in the product distribution to yield 4-chloro, 4-amino or a mixture of both 4-amino and 4-chloro in this novel condensed pyrimidine synthesis.

4.2.2 REACTION MECHANISM OF ACID CATALYSED NITRILE REACTIONS

Formation of 4-chloro and 4-aminopyrimidines presumably proceeds through the transient o-cyanoamidine intermediates, in view of the demonstrated isolability of 2-amidinothiophene-3-carboxanilides in the reaction of 2-aminothiophene-3-carboxanilides with nitriles, and also the cyclization of acyclic analogs of o-cyanoamidines, namely the N-(cyanovinyl)amidines to 4-chloropyrimidines in the presence of hydrogen chloride under essentially the same conditions from this laboratory.

It is suggested that the cyano groups of both the reactants get activated under the reaction conditions employed via the protonation and formation of their HCl adducts (Scheme 72).

The initial condensation of 3-amino-2-cyano substrates 648, 649 and nitrile should presumably lead to the formation of the hydrochloride of amidine intermediate or its adduct with one more molecule of HCl. The formation of 4-chloropyrimidine can occur either by path B or path C and that of 4-aminopyrimidine can occur by path A.

The Path B involves the nucleophilic attack of the amidine nitrogen at the imidoyl halide carbon and the subsequent loss of ammonium chloride from position 4. Path C involves the nucleophilic attack from the imidoyl halide nitrogen at the amidine carbon, which is exactly reverse of Path B,
and subsequent loss of ammonium chloride from position 2, ultimately leading to the formation of 4-chloropyrimidine.

Scheme 72
4.2.3 PHYSICAL AND SPECTRAL PROPERTIES

4.2.3.1 7,9-Dimethyl-4-chloropyrido(3',2':4,5)thieno(3,2-d)pyrimidines

All the pyrido(3',2':4,5)thieno(3,2-d)pyrimidines 653-656 synthesized are colourless crystalline compounds with a melting point range of 132-158 °C. These condensed 4-chloropyrimidines are freely soluble in almost solvents like benzene, ethanol, chloroform except petereoleum ether. (Table XXVII).

IR spectra of 4-chloropyrido(3',2':4,5)thieno(3,2-d)pyrimidines 653-656 are characterized by absence of absorption bands in the 3500-3100 region of N-H stretching.

$^1$H-NMR spectra of compounds 653, 654 and 655 exhibit singlet corresponding to six protons around δ 2.5 indicating thereby the presence of two methyl groups at C-7 and C-9 positions whereas proton of C-6 position in the region δ 7.1-7.4. Compound 653 shows three proton singlet at δ 2.8 for ²C-CH₃, 654 shows two proton singlet at δ 4.2 for ²C-CH₂Cl. Compound 655 shows one proton singlet around δ 7.0 corresponding to ²C-CHCl₂.

A prominent molecular ion (M⁺) peak is also the base peak at m/z=263 and 298 in the mass spectra of pyridothieno(3,2-d)pyrimidines 653 and 654 respectively. Cations 653a and 654a are observed due to the loss of Cl⁻ free radical from the molecular ion (M⁺).
Loss of a neutral molecule 2-chlorodiazetidine with simultaneous loss of H' radical from the molecular ion \((M^+)\) gives rise to cation type b, which is also the characteristic peak of these compounds.

Loss of Cl' radical and neutral molecule CH3CN forms a radical cation type c, the fragment ion further loses neutral molecule CH3CN to give cation type d.

Other losses characteristic of these compounds are CH3', CH3C≡CH, -ClCN to yield fragment ions e, f, g, respectively, from the molecular ion (Scheme 73).
Scheme 73

653  \( R = \text{CH}_3 \)  \( m/z = 263 \)
654  \( R = \text{CH}_2\text{Cl} \)  \( m/z = 298 \)

- **CH\(_3\)**
- **CH\(_2^\circ\)**
- **CH\(_3\)**
- **CH\(_3\)**
- **CH\(_3\)**
- **CH\(_3\)**

**Scheme 73**
4.2.3.2 2-Substituted benzofuro(3,2-d)pyrimidines

The condensed 4-chloro and 4-aminopyrimidines synthesized in the present study are colourless to pale yellow crystalline solids. 4-Chloropyrimidines are highly soluble in almost all the organic solvents, while the 4-amino- analogues exhibit only a moderate solubility in solvents, like benzene, chloroform and ethanol. In general, condensed 4-chloropyrimidines being less polar melt at lower temperature than the condensed 4-aminopyrimidines.

4-Chloropyrimidines are devoid of any NH stretching absorption bands in the 3500-3100 cm\(^{-1}\) region of IR spectra. 4-Amino- analogues exhibit at least two strong absorption bands around 3500 cm\(^{-1}\) and 3140 cm\(^{-1}\) due to asymmetric and symmetric N-H stretching vibrations. The 2-carbethoxy-methylbenzofuropyrimidine \(668\) and 2-carbethoxybenzofuropyrimidine \(667\) show strong C=O stretching absorption bands at around 1740 cm\(^{-1}\).

\(^1\)H-NMR spectra of 4-chloropyrimidines \(657\), \(663\) and \(671\) in CDCl\(_3\) exhibit four aryl protons as a multiplet in the region \(\delta 7.2-7.8\). Compound \(657\) shows three-proton singlet at \(\delta 2.4\) for \(^2\)C-CH\(_3\); \(663\) shows two-proton singlet at \(\delta 4.4\) for \(^2\)C-p-ClC\(_6\)H\(_4\)SCH\(_2\) whereas \(671\) shows two-proton singlet at \(\delta 4.85\) for \(^2\)C-CH\(_2\)Cl.

In the \(^1\)H-NMR spectra of the condensed 4-aminopyrimidines \(658\), \(664\), \(667\), \(672\) and \(673\) amino protons appear as singlet in the \(\delta 2.5-2.7\) region. These signals are washable with deuterium oxide. Compounds \(658\) and \(667\) show singlet of three protons of methyl group about \(\delta 2.4\). Methylene protons of compounds \(672\) exhibit a singlet in the \(\delta 3.5-4.8\) region whereas
methylene group of 2-carbethoxybenzofuropyrimidine 667 occurs as quartet at δ 4.4. Compound 674 shows one proton of CHCl₂ group as singlet at δ 7.1. Aryl protons appear as a multiplet in the δ 7.3-7.7 region.

Mass spectral fragmentation pattern of a few condensed benzofuropyrimidines was studied under electron impact. The mass spectra of 4-chlorobenzofuropyrimidines 657, 663, and 671 exhibit intense molecular ion (M⁺) peaks at m/z 218, 360 and 252, respectively. The loss of Cl⁻ (m/z = 35) from the molecular ion (M⁺) appears to be a major pathway of the decomposition of these 4-chlorobenzofuropyrimidines. The cations thus formed can be formulated as 657a, 663b and 671c, respectively.

Ejection of substituted nitriles (RCN) from 657a, 663b and 671c yielded common cation of type A.

Similarly, loss of cyanogen chloride (ClCN) from the molecular ion (M⁺) to yield neutral molecule of type B.

Other moderately intense peaks observed are due to loss of R', and 2-chlorodiazetidine from the molecular ion (M⁺) as shown in Scheme 74.
Moreover Compound 663 and 671 show base peak at m/z=217 due to loss of 
\( p-\text{ClC}_6\text{H}_4\text{S}^- \) and Cl\(^-\) from the molecular ion (M\(^+\)) and form cation of type 663f and 671f, respectively.
Mass spectra of 4-aminobenzofuropyrimidines 658, 667, 672 and 674 show intense molecular ion (M⁺) peaks at m/z = 199, 257, 233 and 292 respectively. The loss of H⁺ radical from the molecular ion (M⁺) is quite
common and peaks of the formulations 658a, 667a, 672a, and 674a are observed in the corresponding spectra. The fragmentation pathways are depicted in Scheme 75.

2-Carbethoxybenzofuropyrimidine 667 shows loss of $'\text{OC}_2\text{H}_5$ radical from the molecular ion ($M^+$) and forms fragment ion 667f ($m/z=212$). This daughter ion 667f leads to common fragment ion 667e by the loss of CO.
4.2.4 Synthesis of 4-Substitutedamino-2,7,9-trimethylpyrido(3',2':4,5)thieno(3,2-d)pyrimidines

2,7,9-Trimethyl-4-chloropyrido(3',2':4,5)thieno(3,2-d)pyrimidine 653 and N-methylpiperazine in benzene was refluxed on a water bath for 12-14 hr. The reaction mixture was then cooled and filtered and excess benzene was removed from filtrate under vacuo. Recrystallized from petroleum ether to yield white crystals of the product which melts at 142-43 °C.

IR spectrum of aminated product shows weak C-H stretching vibrations at 2920 and 2800 cm⁻¹. ¹H-NMR spectrum in CDCl₃ shows three singlets at δ 2.5, δ 2.8 and δ 3.2 for 2C-CH₃, 7C-CH₃ + 9C-CH₃ and >N-CH₃, respectively. Two triplets about δ 2.7 and δ 4.2 for 8 protons of cyclic methylene probably due to 4-(N-methylpiperazino) group. One proton at C-6 position is observed in the δ 7.1-7.4 region. Mass spectrum of this aminated product shows intense molecular ion peak at m/z = 327 (Scheme 76).

Spectral data and satisfactory microanalysis confirmed the structure of aminated product as 2,7,9-trimethyl-4-(N-methylpiperazino)pyrido(3',2':4,5)thieno(3,2-d)pyrimidine 676.
The reaction was extended to condense other amines such as piperidine, morpholine, diethylamine, isopropylamine, hexylamine and p-anisidine with 2,7,9-trimethyl-4-chloropyrido(3',2':4,5)thieno(3,2-d)pyrimidine 653 in presence of benzene or dimethylformamide to obtain 2,7,9-trimethyl-4-piperidino-677, 4-morpholino-678, 4-(N-diethyl)-679, 4-isopropyl-680, 4-hexylimino-681 and 4-(p-anisidino)pyrido(3',2':4,5)thieno(3,2-d)pyrimidine 682, respectively, in yields ranging from 62-71%.

\[
\begin{align*}
\text{NR}_2^3 = & \quad \text{677,} & \quad \text{680,} \\
& \quad \text{678,} & \quad \text{681,} \\
& \quad \text{679,} & \quad \text{682,}
\end{align*}
\]

All the 4-substituted aminopyrido(3',2':4,5)thieno(3,2-d)pyrimidine 676-682 are crystalline solid products and melting point ranging from 92-220 °C. Recrystallized from petroleum ether except 682 from ethanol-chloroform and compounds 676-682 give satisfactory microanalysis (Table XXIX).

IR spectra of 680 and 681 show N-H stretching band around 3260 cm\(^{-1}\) whereas 682 shows N-H stretching band at 3200 cm\(^{-1}\). C-H stretching
\[ NR_2^3 = 676, -\text{N}_2\text{N}-\text{CH}_3, \text{m/z}=327(M^+) \; 677, -\text{N}_2\text{N}, \text{m/z}=312(M^+) \; 678, -\text{N}_2\text{O}, \text{m/z}=314(M^+) \; 679, -\text{N}_2\text{C}_2\text{H}_5, \text{m/z}=300(M^+) \;
680, -\text{NH-CH}_2\text{CH}_3, \text{m/z}=285(M^+) \; 681, -\text{NH-hexyl}, \text{m/z}=328(M^+) \; 682, -\text{NH}, \text{m/z}=350(M^+) \]

\[ (\text{Scheme 76}) \]
vibration band is observed at about 2960 and 2800 cm\(^{-1}\). Mass spectra of 676-682 exhibit intense molecular ion (M\(^+\)) peak. Other peaks observed are due to loss of \(\text{NR}_2^3, \text{CH}_3\) as shown in Scheme 76.

5.2.5 Synthesis of 4-Substitutedamino-2-methylbenzofuro(3,2-d)pyrimidines

2-Methyl-4-chlorobenzofuro(3,2-d)pyrimidine 657 was reacted with substituted amines such as N-methylpiperazine, piperidine, morpholine, diethylamine, isopropylamine, hexylamine and p-anisidine in benzene to afford 4-(N-methylpiperazino) 683, 4-piperidino- 684, 4-morpholino- 685, 4-(N-diethyl)- 686, 4-isopropyl- 687, 4-hexylimino 688, and 4-(p-anisidino)-2-methylbenzofuro(3,2-d)pyrimidine 689, respectively, in yields ranging from 58-78\% (Table XXX).

![Chemical Structure](image)

\[\text{NR}_2^3 = 683, \quad 684, \quad 685, \quad 686, \quad 687, \quad 688, \quad 689, \quad \text{NH-phenyl} \]

Compounds 683-689 are soluble in solvents like benzene, ethanol, chloroform, dichloromethane therefore recrystallized from petroleum ether.
Compound 689 was only exception which recrystallized from ethanol-chloroform because of its lower solubility. Melting point ranging from 91-199 °C. 4-Aminated products 683-689 give satisfactory microanalysis (Table XXX).

IR spectra of 687-688 and 689 show N-H stretching band around 3200 cm⁻¹. Whereas weak C-H stretching vibration band is observed around 2940 and 2800 cm⁻¹.

¹H-NMR spectrum of 683 in CDCl₃ shows two singlet at δ 2.35 and δ 2.6 for ²C-CH₃ and >N-CH₃, respectively. Two triplet at δ 2.4 and δ 4.05 for four cyclic methylene groups of 4-((N-methylpiperazino)-.

Mass spectrum of 683 exhibits intense molecular ion (M⁺) peak at m/z = 282. Fragmentation pathways are shown in Scheme 77.
4.3 PHARMACOLOGICAL SCREENING OF 4-SUBSTITUTEDAMINO 2,7,9-TRIMETHYL-
PYRIDO(3',2': 4,5)THIENO(3,2-d)PYRIMIDINES

A series of 4-substitutedamino thieno(3,2-d)pyrimidines was studied for biological activity with a special emphasis on their effects on cardiovascular system. These compounds were found to possess specific $\beta_1$-adrenoreceptor antagonistic activity when tested on dog heart (Table XXIIIB).

Of these, 4-piperazinopyrido(3',2':4,5)thieno(3,2-d)pyrimidine 676 (LM-2616) was selected for detailed study.

![Chemical structure](image)

676, LM-2616

The compound 676 melts at 140-142 °C, and is soluble in benzene, chloroform and methanol. Compound 676 (LM-2616) has exhibited $\beta_1$-adrenoreceptor antagonistic activity, local anaesthetic activity comparable to lignocaine and highly significant anticonvulsant activity against electric shock and 6-mercaptopropionic acid.

Pharmacological Screening

When tested on dogs, LM-2616 per se did not produce any effect on blood pressure and heart rate. However, the compound (3mg/kg) inhibited
adrenaline-induced increase in heart rate. Similarly, the compound inhibited isoprenaline induced positive chronotropic effect.

The specificity of LM-2616 on \( \beta_1 \)-adrenoreceptor was confirmed through other preparations. On isolated frog heart the compound antagonised adrenaline induced increase in heart rate.

These results provide an evidence that the compound LM-2616 possesses \( \beta_1 \)-adrenoreceptor antagonistic activity. What is more interesting was that on the same heart preparation, adrenaline induced increase in force of contraction was rather potentiated by LM-2616.

The potentiation of isoprenaline induced positive inotropic effect in guinea pig heart preparations suggested that the activity of LM-2616 (30 \( \mu \text{g/kg} \)) related to \( \beta_2 \)-adrenoreceptor.

Further, isoprenaline (3 \( \mu \text{g} \)) induced vasodilation in frog blood vessels was found to be potentiated by the compound LM-2616 (100 \( \mu \text{g} \)), whereas adrenaline induced vasoconstriction was not affected.

Even on guinea pig tracheal chain, the compound (9.15\( \times 10^{-5} \)) potentiated isoprenaline (4.04\( \times 10^{-9} \) to 1.21\( \times 10^{-6} \)) induced relaxation.

Lastly, the compound (3.06\( \times 10^{-9} \) to 9.17\( \times 10^{-5} \)) was found to produce \textit{per se} and dose dependent relaxation of rat uterus, blocked by propranolol (3.38\( \times 10^{-6} \)) but not by practolol (3.75\( \times 10^{-7} \)).

All these results provide a clear evidence for \( \beta_2 \)-adrenoreceptor agonistic activity of the compound 676, LM-2616.
Table: XXII B

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>Code No.</th>
<th>R</th>
<th>M.P. °C</th>
<th>Dose mg/kg</th>
<th>Change in Heart Rate (b/m)</th>
<th>Change in B.P. mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ADR</td>
<td>Comp.</td>
</tr>
<tr>
<td>676 LM-2616</td>
<td></td>
<td></td>
<td>140-142</td>
<td>3</td>
<td>+20</td>
<td>+12*</td>
</tr>
<tr>
<td>678 LM-2617</td>
<td></td>
<td></td>
<td>154-156</td>
<td>3</td>
<td>+08</td>
<td>+16</td>
</tr>
<tr>
<td>677 LM-2618</td>
<td></td>
<td></td>
<td>112-114</td>
<td>3</td>
<td>+18</td>
<td>+26**</td>
</tr>
<tr>
<td>680 LM-2619</td>
<td></td>
<td></td>
<td>160-162</td>
<td>3</td>
<td>+18</td>
<td>-12*</td>
</tr>
<tr>
<td>682 LM-2620</td>
<td>218-220</td>
<td></td>
<td></td>
<td>3</td>
<td>+14</td>
<td>+16</td>
</tr>
</tbody>
</table>

Inference:
1. (LM-2616) $\beta_1$-adrenoreceptor antagonist + $\beta_2$-adrenoreceptor agonist
2. (LM-2617) Not effective
3. (LM-2618) $\beta_1$-adrenoreceptor antagonist + $\beta_2$-adrenoreceptor agonist
4. (LM-2619) $\beta_1 + \beta_2$ adrenoreceptor antagonist?
5. (LM-2620) Slight $\beta_1$-adrenoreceptor agonist?
In addition to the effects on β-adrenoreceptors, the compound was found to possess local anaesthetic activity as assessed by infiltration anaesthesia in guinea pig and surface anaesthesia in rabbits (Table XXIII & XXIV).

**INFLTRATION ANAESTHESIA**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose in mg</th>
<th>Onset in min</th>
<th>Duration in min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lignocaine</td>
<td>3</td>
<td>5</td>
<td>55 ± 2.9</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>5</td>
<td>81.6 ± 4.41</td>
</tr>
<tr>
<td>LM-2616</td>
<td>3</td>
<td>5</td>
<td>61.7 ± 4.4</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>5</td>
<td>58.75 ± 7.7*</td>
</tr>
</tbody>
</table>

Table XXIII: The table shows the effect of compound LM-2616 on infiltration anaesthesia as compared with lignocaine.

**SURFACE ANAESTHESIA**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose in mg</th>
<th>Onset in min</th>
<th>Duration in min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lignocaine</td>
<td>2</td>
<td>3</td>
<td>20 ± 4.1</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>3</td>
<td>25 ± 3.2</td>
</tr>
<tr>
<td>LM-2616</td>
<td>2</td>
<td>4</td>
<td>25 ± 5.14</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>4</td>
<td>50 ± 2.03</td>
</tr>
</tbody>
</table>

Table XXIV: The table shows the effect of compound LM-2616 on surface anaesthesia as compared with lignocaine.

The local anaesthetic activity of **LM-2616** when tested by these two models was found to be comparable to Lignocaine.

**LM-2616** was also found to exhibit anticonvulsant activity against electrical induced and chemically induced convulsants (Table XXV).
Table XXV: ANTICONVULSANT ACTIVITY

Maximal Electric shock method with Chemical Convulsants-

Strichnine 1 mg/kg S.C. - Prolongs convulsion onset but does not prevent death
6-Mercaptopropionic acid 15 mg/kg S.C. - 45 mg/kg, I.P.

Protection against convulsion induced by electrical shock and 6-mercaptopropionic acid was highly significant. On the other hand, compound was less effective against strychnine induced convulsions (Table: XXVI). The mechanism of anti-convulsant activity is under study.

Table XXVI: Comparison of activity with Diazepam & Phenobarbitone Sodium

<table>
<thead>
<tr>
<th></th>
<th>Strychnine induced convulsion 1 mg/kg, S.C.</th>
<th>6-Mercaptopropionic acid induced convulsion 15 mg/kg, S.C.</th>
</tr>
</thead>
<tbody>
<tr>
<td>LM-2616 (45 mg/kg) I.P.</td>
<td>33% Protection</td>
<td>66% Protection</td>
</tr>
<tr>
<td>Phenobarbitone (50 mg/kg)</td>
<td>66% Protection</td>
<td>40% Protection</td>
</tr>
<tr>
<td>Diazepam (10 mg/kg)</td>
<td>70% Protection</td>
<td>10% Protection</td>
</tr>
</tbody>
</table>

In conclusion, our data suggests that the compound 676, LM-2616 possesses $\beta_1$-adrenoreceptor antagonistic and $\beta_2$-adrenoreceptor agonistic activity.

Further studies are in progress to explore the potentialities of LM-2616 as anti-arrhythemic agent.
Table XXVII

2,4-Disubstituted-7,9-dimethylpyrido(3',2':4,5)thieno(3,2-d)pyrimidines

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Compd No.</th>
<th>R</th>
<th>Mp°C</th>
<th>Yield (%)</th>
<th>Recrystallization solvent[a]</th>
<th>Formula</th>
<th>Microanalysis (%)</th>
<th>Found/(Calcd.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>653</td>
<td>CH₃</td>
<td>154-55</td>
<td>71</td>
<td>P.E.</td>
<td>C₁₂H₁₀N₂ClS</td>
<td>(263.73)</td>
<td>54.75 (54.64)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3.98 (3.82)</td>
</tr>
<tr>
<td>654</td>
<td>CH₂Cl</td>
<td>156-57</td>
<td>68</td>
<td>P.E.</td>
<td>C₁₂H₉N₂Cl₂S</td>
<td>(298.18)</td>
<td>48.33 (48.33)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>3.07 (3.04)</td>
</tr>
<tr>
<td>655</td>
<td>CHCl₂</td>
<td>163-64</td>
<td>75</td>
<td>P.E.</td>
<td>C₁₂H₈N₂Cl₃S</td>
<td>(332.63)</td>
<td>43.38 (43.32)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.41 (2.42)</td>
</tr>
<tr>
<td>656</td>
<td>CH₂CH₂Cl</td>
<td>132-34</td>
<td>65</td>
<td>P.E.</td>
<td>C₁₃H₁₁N₂Cl₂S</td>
<td>(312.21)</td>
<td></td>
</tr>
</tbody>
</table>

[a] P.E. = Petroleum Ether
Table XXVIII
2,4-Disubstitutedbenzofuro(3,2-d)pyrimidines

<table>
<thead>
<tr>
<th>Compd No.</th>
<th>R</th>
<th>X</th>
<th>Mp °C</th>
<th>Yield (%)</th>
<th>Recrystallization solvent[a]</th>
<th>Formula</th>
<th>Microanalysis(%) Found/(Calcd.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>657</td>
<td>CH₃</td>
<td>Cl</td>
<td>113-14</td>
<td>65</td>
<td>P.E.</td>
<td>C₁₁H₇N₂ClO</td>
<td>60.63 (60.42) 3.53 (3.22)</td>
</tr>
<tr>
<td>658</td>
<td>CH₃</td>
<td>NH₂</td>
<td>209-10</td>
<td>10</td>
<td>C+E</td>
<td>C₁₁H₉N₃O</td>
<td>66.51 (66.32) 4.38 (4.55)</td>
</tr>
<tr>
<td>659</td>
<td>C₆H₅</td>
<td>NH₂</td>
<td>292-93</td>
<td>62</td>
<td>C+E</td>
<td>C₁₆H₁₁N₃O</td>
<td>73.43 (73.54) 4.16 (4.24)</td>
</tr>
<tr>
<td>660</td>
<td>CH₃S</td>
<td>NH₂</td>
<td>215-17</td>
<td>55</td>
<td>C+E</td>
<td>C₁₁H₈N₉O₃S</td>
<td>56.91 (57.12) 3.8 (3.92)</td>
</tr>
<tr>
<td>661</td>
<td>CH₂C₆H₅</td>
<td>Cl</td>
<td>110-11</td>
<td>40</td>
<td>P.E.</td>
<td>C₁₇H₁₁N₂ClO</td>
<td>69.30 (69.27) 3.72 (3.76)</td>
</tr>
<tr>
<td>662</td>
<td>CH₂C₆H₅</td>
<td>NH₂</td>
<td>243-44</td>
<td>42</td>
<td>C+E</td>
<td>C₁₇H₁₂N₃O</td>
<td>74.36 (74.16) 4.75 (4.75)</td>
</tr>
<tr>
<td>663</td>
<td>CH₂S</td>
<td>Cl</td>
<td>125-26</td>
<td>40</td>
<td>P.E.</td>
<td>C₁₇H₁₀N₂Cl₂O₃S</td>
<td>56.30 (56.51) 3.02 (2.79)</td>
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</table>

*a* solvent details not provided.
<table>
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<tr>
<th>Compd No.</th>
<th>R</th>
<th>X</th>
<th>Mp °C</th>
<th>Yield (%)</th>
<th>Recrystallization solvent[a]</th>
<th>Formula</th>
<th>Microanalysis(%)</th>
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<tr>
<td>664</td>
<td>CH₂S</td>
<td>NH₂</td>
<td>240-42</td>
<td>38</td>
<td>C+E</td>
<td>C₁₇H₁₂N₃ClO₅</td>
<td>59.36 3.49</td>
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<td>(341.80)</td>
<td>(59.73) (3.54)</td>
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<tr>
<td>665</td>
<td>CH₂</td>
<td>Cl</td>
<td>139-40</td>
<td>28</td>
<td>P.E.</td>
<td>C₁₇H₁₀N₃ClO₃</td>
<td>60.15 2.58</td>
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<td>(339.72)</td>
<td>(60.09) (2.96)</td>
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<tr>
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<td>CH₂</td>
<td>NH₂</td>
<td>234-35</td>
<td>42</td>
<td>C+E</td>
<td>C₁₇H₁₁N₄O₃</td>
<td>63.43 3.61</td>
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<td>(320.30)</td>
<td>(63.74) (3.77)</td>
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<tr>
<td>667</td>
<td>COOEt</td>
<td>NH₂</td>
<td>218-20</td>
<td>58</td>
<td>C+E</td>
<td>C₁₃H₁₄N₃O₃</td>
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<td>(60.69) (4.31)</td>
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<td>668</td>
<td>CH₂COOEt</td>
<td>NH₂</td>
<td>302-04</td>
<td>48</td>
<td>C+E</td>
<td>C₁₄H₁₃N₃O₃</td>
<td>61.80 4.78</td>
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<td>(271.26)</td>
<td>(61.98) (4.82)</td>
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<tr>
<td>669</td>
<td>CH₂CH₂Cl</td>
<td>Cl</td>
<td>84-85</td>
<td>28</td>
<td>P.E.</td>
<td>C₁₂H₁₀N₂Cl₂O</td>
<td>54.10 3.04</td>
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<td></td>
<td>(267.11)</td>
<td>(53.95) (3.01)</td>
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<tr>
<td>670</td>
<td>CH₂CH₂Cl</td>
<td>NH₂</td>
<td>&gt;300</td>
<td>35</td>
<td>C+E</td>
<td>C₁₂H₁₀N₃ClO</td>
<td>58.25 4.09</td>
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<td>(247.67)</td>
<td>(58.19) (4.06)</td>
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<tr>
<td>671</td>
<td>CH₂Cl</td>
<td>Cl</td>
<td>155-56</td>
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<td>P.E.</td>
<td>C₁₁H₈N₂Cl₂O</td>
<td>52.57 2.26</td>
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<td>(253.08)</td>
<td>(52.20) (2.38)</td>
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<td>672</td>
<td>CH₂Cl</td>
<td>NH₂</td>
<td>236-37</td>
<td>26</td>
<td>C+E</td>
<td>C₁₁H₈N₃ClO</td>
<td>56.34 3.76</td>
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<td>(56.54) (3.45)</td>
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<tr>
<td>Compd No.</td>
<td>R</td>
<td>X</td>
<td>Mp °C</td>
<td>Yield (%)</td>
<td>Recrystallization solvent</td>
<td>Formula</td>
<td>Microanalysis(% C H)</td>
</tr>
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<td>-----------</td>
<td>----</td>
<td>----</td>
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<td>-----------</td>
<td>---------------------------</td>
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<tr>
<td>673</td>
<td>CHCl₂</td>
<td>Cl</td>
<td>162-64</td>
<td>40</td>
<td>P.E.</td>
<td>C₁₁H₅N₃Cl₃O</td>
<td>44.15       1.92 (301.54) (43.81) (1.67)</td>
</tr>
<tr>
<td>674</td>
<td>CHCl₂</td>
<td>NH₂</td>
<td>250-52</td>
<td>28</td>
<td>C+E</td>
<td>C₁₁H₇N₃Cl₄O</td>
<td>49.13       2.60 (268.09) (49.27) (2.63)</td>
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<tr>
<td>675</td>
<td>SC₆H₅</td>
<td>NH₂</td>
<td>303-05</td>
<td>51</td>
<td>C+E</td>
<td>C₁₅H₁₁N₂Os</td>
<td>65.43       3.73 (293.33) (65.50) (3.78)</td>
</tr>
</tbody>
</table>

[a] B = Benzene, C = Chloroform; E = Ethanol, P.E. = Petroleum Ether
### Table XXIX

2,7,9-Trimethyl-4-substituted pyrido(3',2':4,5)thieno(3,2-d)pyrimidines

<table>
<thead>
<tr>
<th>Compd No.</th>
<th>X</th>
<th>Mp °C</th>
<th>Yield (%)</th>
<th>Recrystallization solvent[a]</th>
<th>Formula</th>
<th>Microanalysis(%) Found/(Calcd.)</th>
<th>C</th>
<th>H</th>
</tr>
</thead>
<tbody>
<tr>
<td>676</td>
<td>-N(\text{CH}_3)</td>
<td>142-43</td>
<td>65</td>
<td>P.E.</td>
<td>C(<em>{17})H(</em>{21})N(_5)S</td>
<td>62.19 6.52</td>
<td>(327.44) (62.35) (6.46)</td>
<td></td>
</tr>
<tr>
<td>677</td>
<td>-N</td>
<td>112-13</td>
<td>68</td>
<td>P.E.</td>
<td>C(<em>{17})H(</em>{20})N(_4)S</td>
<td>65.63 7.01</td>
<td>(312.42) (65.35) (6.45)</td>
<td></td>
</tr>
<tr>
<td>678</td>
<td>-O</td>
<td>162-64</td>
<td>71</td>
<td>P.E.+B</td>
<td>C(<em>{18})H(</em>{18})N(_4)OS</td>
<td>61.12 6.20</td>
<td>(314.39) (61.12) (5.76)</td>
<td></td>
</tr>
<tr>
<td>679</td>
<td>-C(_2)H(_5)</td>
<td>135-36</td>
<td>64</td>
<td>P.E.</td>
<td>C(<em>{16})H(</em>{20})N(_4)S</td>
<td>63.40 6.81</td>
<td>(300.41) (63.96) (6.71)</td>
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<tr>
<td>680</td>
<td>-NH-(\text{CH}_3)</td>
<td>165-66</td>
<td>70</td>
<td>P.E.</td>
<td>C(<em>{15})H(</em>{17})N(_4)S</td>
<td>63.26 6.01</td>
<td>(285.38) (63.12) (6.00)</td>
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<tr>
<td>681</td>
<td>-NH-Hexyl</td>
<td>92-93</td>
<td>66</td>
<td>P.E.</td>
<td>C(<em>{18})H(</em>{26})N(_4)S</td>
<td>65.93 7.45</td>
<td>(328.46) (65.81) (7.36)</td>
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<tr>
<td>682</td>
<td>-NH (\text{OCH}_3)</td>
<td>218-20</td>
<td>62</td>
<td>P.E.+B</td>
<td>C(<em>{19})H(</em>{18})N(_4)OS</td>
<td>64.99 4.97</td>
<td>(350.42) (65.11) (5.17)</td>
<td></td>
</tr>
</tbody>
</table>

[a] B = Benzene; P.E. = Petroleum Ether
Table XXX

2-Methyl-4-substituted benzofuro(3,2-d)pyrimidines

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Compd No.</th>
<th>X</th>
<th>Mp °C</th>
<th>Yield (%)</th>
<th>Recrystallization solvent[a]</th>
<th>Formula</th>
<th>Microanalysis(%) Found/(Calcd.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>683</td>
<td>-N=N-CH₃</td>
<td>141-42</td>
<td>72</td>
<td>P.E.</td>
<td>C₁₅H₁₈N₄O</td>
<td>67.91 (68.06) 6.30 (6.42)</td>
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<td></td>
<td>(282.33)</td>
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</tr>
<tr>
<td>684</td>
<td>-N</td>
<td>110-12</td>
<td>56</td>
<td>P.E.</td>
<td>C₁₅H₁₇N₃O</td>
<td>71.82 (71.88) 6.42 (6.41)</td>
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<td>(267.32)</td>
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</tr>
<tr>
<td>685</td>
<td>-O</td>
<td>132-34</td>
<td>78</td>
<td>P.E.</td>
<td>C₁₅H₁₆N₃O</td>
<td>71.33 (71.12) 6.02 (5.96)</td>
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<td>(253.29)</td>
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</tr>
<tr>
<td>686</td>
<td>N=C₂H₅</td>
<td>128-30</td>
<td>58</td>
<td>P.E.</td>
<td>C₁₅H₁₇N₃O</td>
<td>70.69 (70.56) 6.84 (6.71)</td>
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<td></td>
<td>C₂H₅</td>
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<td>(255.31)</td>
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</tr>
<tr>
<td>687</td>
<td>-NH-CH₂CH₃</td>
<td>136-37</td>
<td>71</td>
<td>P.E.</td>
<td>C₁₄H₁₅N₃O</td>
<td>69.81 (69.68) 6.30 (6.26)</td>
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<tr>
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<td></td>
<td></td>
<td>(241.28)</td>
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</tr>
<tr>
<td>688</td>
<td>-NH-Hexyl</td>
<td>91-92</td>
<td>68</td>
<td>P.E.</td>
<td>C₁₇H₂₁N₃O</td>
<td>72.13 (72.05) 7.43 (7.47)</td>
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<td></td>
<td></td>
<td>(283.36)</td>
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</tr>
<tr>
<td>689</td>
<td>-NH</td>
<td>198-99</td>
<td>75</td>
<td>P.E.+B</td>
<td>C₁₈H₁₅N₃O₂</td>
<td>70.90 (70.80) 5.08 (4.95)</td>
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<tr>
<td></td>
<td>OCH₃</td>
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<td>(305.32)</td>
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</tbody>
</table>

[a]  B = Benzene;  P.E. = Petroleum Ether
**EXPERIMENTAL SECTION 4.4**

2,7,9-Trimethyl-4-chloropyrido(3',2':4,5)thieno(3,2-d)pyrimidine 653

A stream of dry hydrogen chloride gas was passed through a solution of 3-amino-2-cyano-4,6-dimethylthieno(2,3-b)pyridine\(^{497}\) (0.01M, 2.03g) in 25 ml acetonitrile for 12-14 hr. The reaction mixture was then heated on water bath for 4-5 hr. The product obtained was cooled, poured into ice-cold water, filtered, washed with water and dried. Recrystallized from petroleum ether to afford 71% colourless crystals of the title compound 653, mp 154-56 °C (Lit.\(^{496}\) 154-55 °C).

Microanalysis: \(\text{C}_{12}\text{H}_{10}\text{N}_{3}\text{Cl}_{1}\text{S}\) Requires C, 54.64; H, 3.82% (263.73) Found C, 54.75; H, 3.98%

IR(KBr) cm\(^{-1}\): 1590, 1560, 1495, 1410, 1350, 1300, 1245, 1200, 1050, 910, 860, 820, 790

\(^{1}\text{H}-\text{NMR}(\text{CDCl}_3)\Delta ppm:\) 2.5(s, 6H, 2\text{CH}_3); 2.8(s, 3H, \text{C-CH}_3); 7.1-7.4(m, 1H, 6\text{C-Ar-H})

MS m/z: 263(M\(^+\), 35\text{Cl}), 228, 213, 187, 172, 146, 131, 116, 114, 113, 102, 91, 77, 69, 51, 39, 28

2-Chloromethyl-4-chloro-7,9-dimethylpyrido(3',2':4,5)thieno(3,2-d)pyrimidine 654

A stream of dry hydrogen chloride gas was passed through a solution of 3-amino-2-cyano-4,6-dimethylthieno(2,3-b)pyridine\(^{497}\) (0.01M, 2.03g) and chloroacetonitrile (0.015M, 1.13g) in 20 ml dioxane for 12-14 hr. Reaction

* Refer Experimental Section 1.3, p.107
mixture was further treated according to the procedure described for compound 653. Recrystallized from petroleum ether to afford 68% colourless crystals of the title compound 654, mp 156-57 °C.

Microanalysis : \( \text{C}_{12}\text{H}_9\text{N}_3\text{Cl}_2\text{S} \) Requires C, 48.33; H, 3.04% (298.18) Found C, 48.33; H, 3.07%

IR(KBr)cm\(^{-1}\) : 1590, 1550, 1480, 1430, 1400, 1380, 1350, 1300, 1260, 1240, 1050, 920, 810, 720

\(^1\)H-NMR(CHCl_3)δppm : 2.5(s, 6H, 2XCH_3); 4.2(s, 2H, CH_2); 7.1-7.3(m, 1H, 6C-Ar-H)

MS m/z : 301(M+ 37Cl), 297(M+ 35Cl), 264, 262, 213, 187, 172

2-Dichloromethyl-4-chloro-7,9-dimethylpyrido(3',2':4,5)thieno(3,2-d)pyrimidine 655

A stream of dry hydrogen chloride gas was passed through a solution of 3-amino-2-cyano-4,6-dimethylthieno(2,3-b)pyridine\(^{497}\) (0.01M, 2.03g) and dichloroacetonitrile (0.015M, 1.13g) in 20 ml dioxane for 12-14 hr. Reaction mixture was further treated according to the procedure described for compound 653. Recrystallized from petroleum ether to afford 75% colourless crystals of the title compound 655, mp 163-64 °C.

Microanalysis : \( \text{C}_{12}\text{H}_9\text{N}_3\text{Cl}_3\text{S} \) Requires C, 43.32; H, 2.42% (332.63) Found C, 43.38; H, 2.41%

IR(KBr)cm\(^{-1}\) : 1590, 1500, 1440, 1390, 1380, 1240, 1200, 1080, 930, 880, 830, 740

\(^1\)H-NMR(CHCl_3)δppm : 2.5(s, 6H, 2XCH_3); 7.1-7.4(m, 2H, 2C-CHCl_2+6C-ArH)
2-Chloroethyl-4-chloro-7,9-dimethylpyrido(3',2':4,5)thieno(3,2-d)pyrimidine
656

A stream of dry hydrogen chloride gas was passed through a solution of 3-amino-2-cyano-4,6-dimethylthieno(2,3-b)pyridine\(^\text{497}\) (0.01M, 2.03g) and acrylonitrile (0.02M, 1.06g) in 20 ml dioxane for 12-14 hr. Reaction mixture was further treated according to the procedure described for compound 653. Recrystallized from petroleum ether to afford 65% colourless crystals of the title compound 656, mp 132-34 °C.

\[\text{IR(\text{KBr})cm}^{-1} : 1590, 1560, 1500, 1440, 1390, 1300, 1160, 1060, 920, 820\]

Reaction of 3-amino-2-benzofurancarbonitrile with acetonitrile in the presence of dry hydrogen chloride gas 657, 658

A stream of dry hydrogen chloride gas was passed through a mixture of 3-amino-2-benzofurancarbonitrile\(^\text{498}\) (0.02M, 3.2g) and 25 ml acetonitrile for 7-8 hr. Reaction mixture was then heated on a water bath for 4-5 hr, cooled, poured into ice water, filtered, washed with water and dried. The filtrate obtained was treated separately. The residue on recrystallization from petroleum ether yielded 65% colourless crystals of 2-methyl-4-chlorobenzofuro(3,2-d)pyrimidine 657, mp 113-14 °C.

An exclusive formation of 2-methyl-4-chlorobenzofuro(3,2-d)pyrimidine 657 was observed when a stream of dry hydrogen chloride gas passed for 18-20 hr through a mixture of 3-amino-2-benzofurancarbonitrile\(^\text{498}\) (0.02M, 3.2g) and 25 ml acetonitrile. After usual work-up only one compound was isolated. Recrystallization from petroleum ether yielded 68% crystals of
compound 657, mp 113-14 °C.

Microanalysis : \( \text{C}_{11}\text{H}_{7}\text{N}_{2}\text{C}_{10} \) Requires C, 60.42; H, 3.22%

(218.63) Found C, 60.63; H, 3.53%

IR(KBr) cm\(^{-1}\) : 1660, 1580, 1540, 1100, 750

\(^1\text{H}-\text{NMR(CDC}_3\text{)} \text{sppm} : 2.4(\text{s, 3H, CH}_3); 7.3-7.6(\text{m, 4H, Ar-H})

MS m/z : 218(\text{M}^+ \text{ Cl}), 183, 168, 140

The acidic aqueous mother liquor obtained after filtration of 2-methyl-4-chlorobenzofuro(3,2-d)pyrimidine 657, was treated with 10% ammonium hydroxide solution (pH=7-8). The crystalline product separated was filtered, washed with water and dried. Recrystallization from ethanol-chloroform yielded 10% fine crystals of 2-methyl-4-aminobenzofuro(3,2-d)pyrimidine 658, mp 209-10 °C.

An exclusive formation of 2-methyl-4-aminobenzofuro(3,2-d)pyrimidine 658 was observed when 3-Amino-2-benzofurancarbonitrile \(^{498}\) (0.01M, 1.6g) was reacted with acetonitrile (0.02M, 0.82g) in presence of 5.7 ml 7M HCl-dioxane solution (0.04M HCl). The contents were stirred for 30 min. The reaction mixture was allowed to stand 2 hr at the ice-bath temperature (5-10 °C), heated for 1 hr and then poured into ice-water. The solid obtained after basification (pH=8-8.5) with dilute ammonium hydroxide solution was filtered, washed with water and dried. Recrystallized from ethanol-chloroform to afford 1.1g (55.2%) of a crystalline product 658, mp 208-21 °C.

Microanalysis : \( \text{C}_{11}\text{H}_{9}\text{N}_{2}\text{O} \) Requires C, 66.32; H, 4.55%

(199.20) Found C, 66.51; H, 4.38%
2-Phenyl-4-aminobenzofuro(3,2-d)pyrimidine 659

A stream of dry hydrogen chloride gas was passed through a mixture of 3-amino-2-benzofurancarbonitrile** (0.02M, 3.2g) and benzonitrile (0.04M, 4.12g) in 30 ml dioxane for 7-8 hr. The reaction mixture was then heated on water bath for 4-5 hr, cooled and poured into ice cooled water. Neutralized with 10% ammonium hydroxide solution to separate crystalline product. TLC confirmed that product was not a mixture. Recrystallization from ethanol-chloroform yielded 62% fine crystals of the title compound 659, mp 292-93 °C.

Microanalysis : \(\text{C}_{15}\text{H}_{11}\text{N}_{3}\)O Requires C, 73.54%; H, 4.24% (261.27) Found C, 73.43%; H, 4.16%  

IR(KBr)\(\text{cm}^{-1}\) : 3420, 3350, 3140(NH), 1640, 1620, 1560, 1500, 1480, 1440, 1380, 1340, 1210, 1100, 910, 890, 740

2-Methylthio-4-aminobenzofuro(3,2-d)pyrimidine 660

A stream of dry hydrogen chloride gas was passed through a mixture of 3-amino-2-benzofurancarbonitrile** (0.01M, 1.6g) and methylthiocyanate (0.015M, 1.09g) in 20 ml dioxane for 7-8 hr. Reaction mixture was further treated according to the procedure described for compound 659. Recrystallized from ethanol-chloroform to afford 55% fine crystals of the
title compound 660, mp 215-17 °C.

Microanalysis : C_{11}H_{9}N_{3}OS Requires C, 57.12; H, 3.92%
(231.26) Found C, 56.91; H, 3.80%

IR(KBr)cm⁻¹ : 3420, 3300, 3120(NH), 1650, 1610, 1490, 1460,
1380, 1340, 1210, 1100, 890, 750

Reaction of 3-amino-2-benzofurancarbonitrile with benzylcyanide in the presence of dry hydrogen chloride gas 661, 662

A stream of dry hydrogen chloride gas was passed through a mixture 3-amino-2-benzofurancarbonitrile (0.01M, 1.6g) and benzylcyanide (0.04M, 4.68g) in 20 ml dioxane for 7-8 hr. Reaction mixture was further treated according to the procedure described for compound 657. Recrystallized from petroleum ether to yield 40% colourless crystals of the 2-benzyl-4-chlorobenzofuro(3,2-d)pyrimidine 661, mp 110-11 °C.

Microanalysis : C_{17}H_{13}N_{3}O Requires C, 69.27; H, 3.76%
(294.73) Found C, 69.30; H, 3.72%

IR(KBr)cm⁻¹ : 1625, 1580, 1540, 725, 650

The acidic aqueous mother liquor obtained after filtration of 2-benzyl-4-chlorobenzofuro(3,2-d)pyrimidine 661, was treated with 10% ammonium hydroxide solution (pH=7-8) to separate crystalline product. After usual work-up, recrystallization from ethanol-chloroform afforded 42% fine crystals of 2-benzyl-4-aminobenzofuro(3,2-d)pyrimidine 662, mp 243-244 °C.

Microanalysis : C_{17}H_{13}N_{3}O Requires C, 74.16; H, 4.75%
(275.29) Found C, 74.36; H, 4.75%
Reaction of 3-amino-2-benzofurancarbonitrile with p-chlorobenzylthiocyanide in the presence of dry hydrogen chloride gas 663, 664

A stream of dry hydrogen chloride gas was passed through a mixture 3-amino-2-benzofurancarbonitrile\(^{698}\) (0.01M, 1.6g) and p-chlorobenzylthiocyanide (0.015M, 2.75g) in 20 ml dioxane for 7-8 hr. Reaction mixture was further treated according to the procedure described for compound 657. Recrystallized from petroleum ether to afford 40% colourless crystals of 2-(p-chlorobenzylthio)-4-chlorobenzofuro(3,2-d)pyrimidine 663, mp 125-26 °C.

Microanalysis : \(\text{C}_{17}\text{H}_{10}\text{N}_{2}\text{Cl}_{2}\text{O}\text{S}\) Requires C, 56.51; H, 2.79%
(361.24) Found C, 56.30; H, 3.02%

IR(KBr) cm\(^{-1}\) : 1630, 1580, 1550, 1480, 1380, 1200, 1080, 800, 750
\(^1\text{H}-\text{NMR(CDC}_3\text{)} \delta \text{ppm} : 4.4\text{ (s, 2H, CH}_2\text{)}; 7.2-7.8\text{ (m, 8H, Ar-H)}

The acidic aqueous mother liquor obtained after filtration of 2-(p-chlorobenzylthio)-4-chlorobenzofuro(3,2-d)pyrimidine 663, was treated with 10% ammonium hydroxide to separate crystalline product. After usual work-up, recrystallization from ethanol-chloroform yielded 38% fine crystals of 2-(p-chlorobenzylthio)-4-aminobenzofuro(3,2-d)pyrimidine 664, mp 240-42 °C.

Microanalysis : \(\text{C}_{17}\text{H}_{12}\text{N}_{3}\text{ClO}\text{S}\) Requires C, 59.73; H, 3.54%
(341.80) Found C, 59.36; H, 3.49%
Reaction of 3-amino-2-benzofurancarbonitrile with p-nitrobenzylcyanide in the reaction of dry hydrogen chloride gas 665, 666

A stream of dry hydrogen chloride gas was passed through a mixture 3-amino-2-benzofurancarbonitrile (0.01M, 1.6g) and p-nitrobenzylcyanide (0.015M, 2.43g) in 20 ml dioxane for 7-8 hr. Reaction mixture was further treated according to the procedure described for compound 657. Recrystallized from petroleum ether to afford 28% colourless crystals of 2-(p-nitrobenzyl)-4-chlorobenzofuro(3,2-d)pyrimidine 665, mp 139-40 °C.

Microanalysis: \[ \text{C}_17\text{H}_7\text{N}_3\text{Cl}_2 \] Requires C, 60.09; H, 2.96% 
(339.72) Found C, 60.15; H, 2.58%

IR(KBr) cm\(^{-1}\): 1600, 1520, 1350, 1110, 1080, 860, 840, 740

The acidic aqueous mother liquor obtained after filtration of 2-(p-nitrobenzyl)-4-chlorobenzofuro(3,2-d)pyrimidine 665 was treated with 10% ammonium hydroxide to separate crystalline product. After usual work-up, recrystallization from ethanol-chloroform yielded 42% fine crystals of 2-(p-nitrobenzyl)-4-aminobenzofuro(3,2-d)pyrimidine 666, mp 234-35 °C.

Microanalysis: \[ \text{C}_17\text{H}_12\text{N}_4\text{O}_3 \] Requires C, 63.74; H, 3.77% 
(320.30) Found C, 63.43; H, 3.61%

IR(KBr) cm\(^{-1}\): 3410, 3320(NH), 1660, 1540, 1360, 1300, 860, 700
2- Carbethoxy-4-aminobenzofuro(3,2-d)pyrimidine 667

A stream of dry hydrogen chloride gas was passed through a mixture of 3-aminobenzofurancarbonitrile (0.01M, 1.6g) and carbethoxynitrile (0.015M, 1.48g) in 20 ml dioxane for 7-8 hr. Reaction mixture was further treated according to the procedure described for compound 659. Recrystallized from ethanol-chloroform to afford 58% fine crystals of the title compound 667, mp 218-20 °C.

Microanalysis: \( C_{13}H_{11}N_{3}O_3 \) Requires C, 60.69; H, 4.31%

(257.24) Found C, 60.73; H, 4.01%

IR(KBr)cm\(^{-1}\): 3500, 3180(NH), 1740, 1680, 1400, 1260, 1200, 1100, 750

\(^1\text{H}-\text{NMR(DMSO-d}_6\) ppm: 2.7 (br, 2H, NH\(_2\)); 4.75 (s, 2H, CH\(_2\)); 7.5-7.9 (m, 4H, Ar-H)

MS m/z: 257(M\(^+\)), 212, 184, 168

2-Ethylacetate-4-aminobenzofuro(3,2-d)pyrimidine 668

A stream of dry hydrogen chloride gas was passed through a mixture of 3-aminobenzofurancarbonitrile (0.01M, 1.6g) and ethyl cyanoacetate (0.015M, 1.69g) in 20 ml dioxane for 7-8 hr. Reaction mixture was further treated according to the procedure described for compound 659. Recrystallized from ethanol-chloroform to afford 48% fine crystals of the title compound 668, mp 302-04 °C.

Microanalysis: \( C_{13}H_{13}N_{3}O_3 \) Requires C, 61.98; H, 4.82%

(271.26) Found C, 61.80; H, 4.78%

IR(KBr)cm\(^{-1}\): 3500, 3180(NH), 1740, 1690, 1420, 1280, 1200, 1100, 750
Reaction of 3-amino-2-benzofurancarbonitrile with acrylonitrile in the presence of dry hydrogen chloride gas: 669, 670

A stream of dry hydrogen chloride gas was passed through a mixture of 3-amino-2-benzofurancarbonitrile (0.01M, 1.6g) and acrylonitrile (0.02M, 1.06g) in 20 ml dioxane for 7-8 hr. Reaction mixture was further treated according to the procedure described for compound 657. Recrystallized from petroleum ether to yield 28% colourless crystals of 2-chloroethyl-4-chlorobenzofuro(3,2-d)pyrimidine 669, mp 84-85 °C.

Microanalysis: \( \text{C}_{12}\text{H}_8\text{N}_2\text{Cl}_2\text{O} \) Requires C, 53.95%; H, 3.01%

(267.11) Found C, 54.10%; H, 3.04%

IR(KBr)cm\(^{-1}\): 1625, 1580, 1550, 1450, 1380, 1360, 1200, 1090, 880, 760

The acidic aqueous mother liquor obtained after filtration of 2-chloroethyl-4-chlorobenzofuro(3,2-d)pyrimidine 669, was treated with 10% ammonium hydroxide solution (pH=7-8) to separate crystalline product. After usual work-up, recrystallization from ethanol-chloroform afforded 35% fine crystals of 2-chloroethyl-4-aminobenzofuro(3,2-d)pyrimidine 670, mp >300 °C.

Microanalysis: \( \text{C}_{12}\text{H}_{10}\text{N}_3\text{Cl}_2 \) Requires C, 58.19%; H, 4.06%

(247.67) Found C, 58.25%; H, 4.09%

IR(KBr)cm\(^{-1}\): 3450(NH), 1660, 1630, 1550, 1440, 1390, 1200, 1095, 1040, 960, 920, 825, 750
Reaction of 3-amino-2-benzofurancarbonitrile with chloroacetonitrile in the presence of dry hydrogen chloride gas: 671, 672

A stream of dry hydrogen chloride gas was passed through a mixture of 3-amino-2-benzofurancarbonitrile (0.01M, 1.6g) and chloroacetonitrile (0.015M, 1.13g) in 20 ml dioxane for 7-8 hr. Reaction mixture was further treated according to the procedure described for compound 657. Recrystallized from petroleum ether to yield 33% colourless crystals of the 2-chloromethyl-4-chlorobenzofuro(3,2-d)pyrimidine 671, mp 155-56 °C.

Microanalysis: \( \text{C}_{14}\text{H}_6\text{N}_2\text{Cl}_2\text{O} \) Requires C, 52.20; H, 2.38% 
(253.08) Found C, 52.57; H, 2.26%

\( \text{IR(KBr)} \text{cm}^{-1} \): 1630, 1580, 1550, 1450, 1410, 1390, 1260, 1240, 1200, 1150, 1090, 890, 760

\( \text{^1H-NMR} (\text{CDCl}_3) \delta \text{ppm} : \) 4.85 (s, 2H, CH\text{2}); 7.5-7.7 (m, 4H, Ar-H)

MS \( m/z \): 252(M\text{+}^{35}\text{Cl}), 217, 182, 168, 139, 129, 115, 88, 76

The acidic aqueous mother liquor obtained after filtration of 2-chloromethyl-4-chlorobenzofuro(3,2-d)pyrimidine 671, was treated with 10% ammonium hydroxide solution (pH=7-8) to separate crystalline product. After usual work-up, recrystallization from ethanol-chloroform afforded 26% fine crystals of 2-chloromethyl-4-aminochlorobenzofuro(3,2-d)pyrimidine 672, mp 236-37 °C.

Microanalysis: \( \text{C}_{14}\text{H}_6\text{N}_2\text{Cl} \) Requires C, 56.54; H, 3.45% 
(233.64) Found C, 56.34; H, 3.76%

\( \text{IR(KBr)} \text{cm}^{-1} \): 3460, 3320, 3100(NH), 1660, 1610, 1560, 1460, 1280, 1200, 1100, 890, 750
\[ ^1H-NMR(DMSO-d_6) \delta ppm: \quad 2.7 \text{ (br, 2H, NH-)}; \quad 4.75 \text{ (s, 2H, CHa)}; \quad 7.5-7.9 \text{ (m, 4H, Ar-H)} \]

MS m/z : 233(M^+ {^{35}Cl}), 198, 168, 172, 139, 138, 129, 128, 115, 114, 102, 88, 76

Reaction of 3-amino-2-benzofurancarbonitrile with dichloroacetonitrile in the presence of dry hydrogen chloride gas: 673, 674

A stream of dry hydrogen chloride gas was passed through a mixture of 3-amino-2-benzofurancarbonitrile (0.01M, 1.6g) and dichloroacetonitrile (0.015M, 1.65g) in 20 ml dioxane for 7-8 hr. Reaction mixture was further treated according to the procedure described for compound 657. Recrystallized from petroleum ether to yield 40% colourless crystals of 2-dichloromethyl-4-chlorobenzofuro(3,2-d)pyrimidine 673, mp 162-64 °C.

Microanalysis : C_{11}H_5N_3Cl_3O Requires C, 43.81%; H, 1.67%
(301.54) Found C, 44.15%; H, 1.92%

IR(KBr) cm^{-1} : 1625, 1580, 1540, 1380, 1260, 1140, 1280, 925, 880, 760, 695, 660, 640

The acidic aqueous mother liquor obtained after filtration of 2-dichloromethyl-4-chlorobenzofuro(3,2-d)pyrimidine 673, was treated with 10% ammonium hydroxide solution (pH=7-8) to separate crystalline product. After usual work-up, recrystallization from ethanol-chloroform afforded 28% fine crystals of 2-dichloromethyl-4-aminobenzofuro(3,2-d)pyrimidine 674, mp 250-52 °C.
Microanalysis : $C_{11}H_7N_3Cl_2O$ Requires C, 49.27; H, 2.63%
(268.09) Found C, 49.13; H, 2.60%
$^1$H-NMR(DMSO-d$_6$)δppm: 2.52 (br, 2H, NH$_2$); 7.0 (s, 1H, CH); 7.3-7.7 (m, 4H, Ar-H)
MS m/z : 267(M$^+$ $^{35}$Cl), 232, 197, 184, 168, 138, 128, 115

2-Phenylthio-4-aminobenzofuro(3,2-d)pyrimidine 675

A stream of dry hydrogen chloride gas was passed through a mixture of 3-amino-2-benzofurancarbonitrile (0.01M, 1.6g) and phenylthiocyanate (0.015M, 2.02g) in 20 ml dioxane for 7-8 hr. Reaction mixture was further treated according to the procedure described for compound 659. Recrystallized from ethanol-chloroform to afford 51% fine crystals of the title compound 675, mp 303-05 °C.

Microanalysis : $C_{15}H_{11}N_3O$ Requires C, 65.50; H, 3.78%
(293.33) Found C, 65.43; H, 3.73%
IR(KBr)cm$^{-1}$ : 3480, 3400(NH), 1650, 1620, 1560, 1460, 1340, 1210, 1100, 750
2,7,9-Trimethyl-4-(N-methylpiperazino)pyrido(3',2':4,5)thieno(3,2-d)pyrimidine 676

A suspension of 2,7,9-trimethyl-4-chloropyrido(3',2':4,5)thieno(3,2-d)pyrimidine (0.01M, 2.6g) and N-methylpiperazine (0.04M, 4.40g) in 30 ml benzene was refluxed on water bath for 12-14 hr. The reaction mixture was cooled and filtered to remove hydrochloride salt. Excess benzene was removed under vacuo. Residue obtained was washed with water and dried. Recrystallization from petroleum ether yielded 65% white crystals of the title compound 676, mp 142-43°C.

Microanalysis : \( \text{C}_{17}\text{H}_{21}\text{N}_{5}\text{S} \) Requires C, 62.35; H, 6.46%

\( 327.44 \) Found C, 62.19; H, 6.52%

\(^1\text{H}-\text{NMR}(\text{CDCl}_3)\delta \text{ppm} : 2.5 (s, 3\text{H}, 2\text{C}-\text{CH}_3); 2.8 (s, 6\text{H}, 7\text{C}-\text{CH}_3 + 9\text{C}-\text{CH}_3); 3.2 (s, 3\text{H}, >\text{N}-\text{CH}_3); 2.7, 4.2 (2t, 8\text{H}, 4\text{XCH}_2); 7.1-7.4 (m, 1\text{H}, 6\text{C-Ar-H})

\( \text{MS m/z} : 327(\text{M}^+), 228, 213 \)

2,7,9-Trimethyl-4-(piperidino)pyrido(3',2':4,5)thieno(3,2-d)pyrimidine 677

A suspension of 2,7,9-trimethyl-4-chloropyrido(3',2':4,5)thieno(3,2-d)pyrimidine (0.01M, 2.6g) and piperidine (0.04M, 3.4g) in 20 ml benzene was refluxed on water bath for 10-12 hr. Work-up the reaction mixture according to the procedure described for compound 676. Recrystallized from petroleum ether to yield 68% white crystals of the title compound 677, mp 112-13°C.

Microanalysis : \( \text{C}_{17}\text{H}_{20}\text{N}_{4}\text{S} \) Requires C, 65.35; H, 6.45%

\( 312.42 \) Found C, 65.63; H, 7.01%

\( \text{MS m/z} : 313(\text{M}^+), 312(\text{M}^+), 311, 284, 283, 228, 213, 187 \)
A suspension of 2,7,9-trimethyl-4-chloropyrido(3',2':4,5)thieno(3,2-d)pyrimidine (0.01M, 2.6g) and morpholine (0.04M, 3.48g) in 20 ml benzene was refluxed on water bath for 10-12 hr. Work-up the reaction mixture according to the procedure described for compound 676. Recrystallized from petroleum ether to yield 71% white crystals of the title compound 678, mp 162-64 °C.

Microanalysis: C_{16}H_{16}N_{4}O_{S} Requires C, 61.12; H, 5.76%. (314.39) Found C, 61.12; H, 6.20%. MS m/z: 314(M^+), 228, 213

A suspension of 2,7,9-trimethyl-4-chloropyrido(3',2':4,5)thieno(3,2-d)pyrimidine (0.01M, 2.6g) and diethylamine (0.04M, 2.92g) in 30 ml benzene was refluxed on water bath for 10-12 hr. Work-up the reaction mixture according to the procedure described for compound 676. Recrystallized from petroleum ether to afford 64% white crystals of the title compound 679, mp 135-36 °C.

Microanalysis: C_{16}H_{20}N_{4}S Requires C, 63.96; H, 6.71%. (300.41) Found C, 63.40; H, 6.81%. MS m/z: 300(M^+), 228, 213

A suspension of 2,7,9-trimethyl-4-chloropyrido(3',2':4,5)thieno(3,2-d)pyrimidine (0.01M, 2.6g) and isopropylamine (0.04M, 2.3g) in 25 ml
Dimethylformamide was refluxed on oil bath for 4 hr. The reaction mixture was cooled, poured into ice-cold water, filtered, washed with water and dried. Recrystallized from petroleum ether to yield 70% white crystals of the title compound 680, mp 165-66 °C.

Microanalysis: \( \text{C}_{15}\text{H}_{17}\text{N}_4\text{S} \) Requires C, 63.12; H, 6.00%  
(285.38) Found C, 63.26; H, 6.01%

MS m/z: 287(M+2), 286(M+1), 285(M⁺), 275, 274, 273, 272, 259, 257, 242, 228, 213, 178

2,7,9-Trimethyl-4-(hexylimino)pyrido(3',2':4,5)thieno(3,2-d)pyrimidine 681

A suspension of 2,7,9-trimethyl-4-chloropyrido(3',2':4,5)thieno(3,2-d)pyrimidine (0.01M, 2.6g) and hexylamine (0.04M, 4.04g) in 30 ml benzene was refluxed on water bath for 10-12 hr. Work-up the reaction mixture according to the procedure described for compound 676. Recrystallized from petroleum ether to yield 66% white crystals of the title compound 681, mp 92-93 °C.

Microanalysis: \( \text{C}_{19}\text{H}_{28}\text{N}_4\text{S} \) Requires C, 65.81; H, 7.36%  
(328.46) Found C, 65.93; H, 7.45%

MS m/z: 329(M+1), 328(M⁺), 228, 213, 187

2,7,9-Trimethyl-4-(p-anisidino)pyrido(3',2':4,5)thieno(3,2-d)pyrimidine 682

A suspension of 2,7,9-trimethyl-4-chloropyrido(3',2':4,5)thieno(3,2-d)pyrimidine (0.01M, 2.6g) and p-anisidine (0.04M, 4.9g) in 25 ml dimethylformamide was refluxed on oil bath for 6 hr. Work-up the reaction mixture according to the procedure described for compound 680.
Recrystallized from petroleum ether-benzene to afford 62% fine crystals of the title compound 682, mp 218-20 °C.

Microanalysis : \[ \text{C}_{19}\text{H}_{18}\text{N}_4\text{O}_5 \] Requires C, 65.11; H, 5.17%
(350.42) Found C, 64.99; H, 4.97%

MS m/z : 351(M+1), 350(M^+), 336, 335, 228, 213

2-Methyl-4-(N-methylpiperazino)benzofuro(3,2-d)pyrimidine 683

A suspension of 2-methyl-4-chlorobenzofuro(3,2-d)pyrimidine (0.01M, 2.18g) and N-methylpiperazine (0.04M, 4.40g) in 30 ml benzene was refluxed on water bath for 10-12 hr. Work-up the reaction mixture according to the procedure described for compound 676. Recrystallized from petroleum ether to afford 72% white crystals of the title compound 683, mp 141-42 °C.

Microanalysis : \[ \text{C}_{18}\text{H}_{18}\text{N}_4\text{O}_5 \] Requires C, 68.06; H, 6.42%
(282.33) Found C, 67.91; H, 6.30%

\[ ^1\text{H-NMR(CDCl}_3\text{)}\delta \text{ppm} \]
2.35 (s, 3H, \( ^2\text{C-CH}_3 \)); 2.6 (s, 3H, \( >\text{N-CH}_3 \)); 2.4, 4.05 (t, 8H, 4CH2); 7.3-7.6 (m, 4H, Ar-H)

MS m/z : 282(M^+), 267, 238, 226, 225, 224, 213, 212, 183, 168

2-Methyl-4-(piperidino)benzofuro(3,2-d)pyrimidine 684

A suspension of 2-methyl-4-chlorobenzofuro(3,2-d)pyrimidine (0.01M, 2.18g) and piperidine (0.04M, 3.4g) in 25 ml benzene was refluxed on water bath for 10-12 hr. Work-up the reaction mixture according to the procedure described for compound 676. Recrystallized from petroleum ether to afford 56% white crystals of the title compound 684, mp 110-12 °C.
2-Methyl-4-(morpholino)benzofuro(3,2-d)pyrimidine 685

A suspension of 2-methyl-4-chlorobenzofuro(3,2-d)pyrimidine (0.01M, 2.18g) and morpholine (0.04M, 3.48g) in 30 ml benzene was refluxed on water bath for 10-12 hr. Work-up the reaction mixture according to the procedure described for compound 676. Recrystallized from petroleum ether to afford 78% white crystals of the title compound 685, mp 132-34 °C.

Microanalysis : \( \text{C}_{16}\text{H}_{17}\text{N}_3\text{O} \) Requires C, 71.88; H, 6.41%
(267.32) Found C, 71.82; H, 6.42%

2-Methyl-4-(N-diethyl)benzofuro(3,2-d)pyrimidine 686

A suspension of 2-methyl-4-chlorobenzofuro(3,2-d)pyrimidine (0.01M, 2.18g) and diethylamine (0.04M, 2.92g) in 30 ml benzene was refluxed on water bath for 10-12 hr. Work-up the reaction mixture according to the procedure described for compound 676. Recrystallized from petroleum ether to yield 58% white crystals of the title compound 686, mp 128-30 °C.

Microanalysis : \( \text{C}_{15}\text{H}_{18}\text{N}_3\text{O} \) Requires C, 71.12; H, 5.96%
(253.29) Found C, 71.33; H, 6.02%

2-Methyl-4-(isopropylimino)benzofuro(3,2-d)pyrimidine 687

A suspension of 2-methyl-4-chlorobenzofuro(3,2-d)pyrimidine (0.01M, 2.18g) and isopropylamine (0.04M, 2.3g) in 25 ml dimethylformamide was refluxed on oil bath for 4 hr. Work-up the reaction mixture according to the procedure described for compound 680. Recrystallized from petroleum
ether to afford 71% fine crystals of the title compound 687, mp 136-37 °C.

Microanalysis : $C_{14}H_{11}N_3O$ Requires C, 69.68; H, 6.26%

(241.28) Found C, 69.81; H, 6.30%

2-Methyl-4-(hexylimino)benzofuro(3,2-d)pyrimidine 688

A suspension of 2-methyl-4-chlorobenzofuro(3,2-d)pyrimidine (0.01M, 2.18g) and hexylamine (0.04M, 4.04g) in 30 ml benzene was refluxed on water bath for 10-12 hr. Work-up the reaction mixture according to the procedure described for compound 676. Recrystallized from petroleum ether to afford 68% white crystals of the title compound 688, mp 91-92 °C.

Microanalysis : $C_{17}H_{21}N_3O$ Requires C, 72.05; H, 7.47%

(283.36) Found C, 72.13; H, 7.43%

2-Methyl-4-(p-anisidino)benzofuro(3,2-d)pyrimidine 689

A suspension of 2-methyl-4-chlorobenzofuro(3,2-d)pyrimidine (0.01M, 2.18g) and p-anisidine (0.04M, 4.9g) in 25 ml dimethylformamide was refluxed on oil bath for 4 hr. Work-up the reaction mixture according to the procedure described for compound 680. Recrystallized from petroleum ether-benzene to yield 75% fine crystals of the title compound 689, mp 198-99 °C.

Microanalysis : $C_{18}H_{16}N_3O_2$ Requires C, 70.80; H, 4.95%

(305.32) Found C, 70.90; H, 5.08%