Chapter-IV

Studies on Pyrido thieno pyrimidine derivatives

**Introduction**

Thienopyrimidines are a class of fused heterocycles, which are common sources for the development of new potential therapeutic agents. There are three isomeric thienopyrimidines corresponding to the three possible types of annulations of thiophene to the pyrimidine ring: thieno[2,3-d]pyrimidine, thieno[3,4-d]pyrimidine, and thieno[3,2-d]pyrimidine.

![Diagram of thienopyrimidines]

The three isomeric thienopyrimidines

The formation of novel fused heterocycles is an important for heterocyclic chemists from various points of view for the development of living things. Furthermore, many condensed heterocyclic systems especially, when linked to a pyrimidine ring have attracted attention in the past few years as they are found in variety of natural products (e.g., purines, pyrrolopyrimidines, pyridopyrimidines, pteridines). Among these heterocycles, the thienopyrimidine class is also of interest because some derivatives such as Tiprinast has been shown to clinically effective antiallergic\cite{1-7}. In addition, antianaphilactic, antineoplastic\cite{8}, antiatherosclerotic\cite{9}, antibacterial\cite{10-17}, antidepressive\cite{18-19}, antidiabetic\cite{20}, antihypertensive\cite{21-24}, antihistaminic\cite{25-26}, analgesic, anti-inflammatory\cite{27-44}, antiviral\cite{45-46}, spasmyloytic\cite{47}, antipyretic\cite{48-50}, anticonvulsant\cite{51}, fungicida\cite{52}, antiplatelet\cite{53-55} and other Central Nervous System (CNS) affecting\cite{56} activities have been reported for certain thienopyrimidine derivatives.

**Biologically active thienopyrimidine**

Biologically active thienopyrimidine derivatives are shown with their appropriate structure.
Studies on Pyrido thieno pyrimidine derivatives

Antiallergic

DHFR inhibitory

Antihypertensive

Antihistaminic

Antiinflammatory

GnRH antagonist
Studies on Pyrido thieno pyrimidine derivatives

5HT\textsubscript{3}-receptor ligand\textsuperscript{[59]}  Melanin-concentration hormone receptor 1 antagonist\textsuperscript{[60]}

Antiatherosclerotic  Antibacterial

Adenosine A\textsubscript{3A} receptor antagonist\textsuperscript{[61]}  PI3 kinase p110(alfa) inhibitor\textsuperscript{[62]}  PDE4 inhibitor\textsuperscript{[63]}
The similarity between the physicochemical properties of benzene and thiophene is striking. For example, the boiling point of benzene is 81.1°C and the one of thiophenes is 84.4°C (at 760 mm Hg) and therefore, thiophene and benzene are well known examples of bioisosterism. The change of a benzene moiety into a thiophene often results in superior pharmacodynamic, pharmacokinetic or toxicological properties. For example, the thiophene analogue of piroxicam (a non-steroid anti-inflammatory agent used in arthritis patients) has the same biological activity, with the same mechanism of action as piroxicam and even displayed a longer plasma half-life than piroxicam \[^{64}\]. Thiophene isosteres of mianserin (a tetracyclic antidepressive agent) also act as serotonin receptor (5-HT) antagonists \[^{65}\].

Thiophene isosteres of piroxicam and mianserin are shown in the figure 4.1.

![Figure 4.1](image-url)

The exchange of a phenyl ring by a thiophene ring in bicyclic derivatives can generate three regioisomers. For example, Blair and coworkers\[^{66}\] described the replacement of the phenyl ring of \(N,N\)-dimethyltryptamine by a thiophene moiety, giving rise to three isomers: thieno[3,2-b]pyrrole, thieno[2,3-b]pyrrole and thieno[3,4-b]pyrrole as shown in figure 4.2. Biological evaluation demonstrated that both thieno[3,2-b]pyrrole and thieno[2,3-b]pyrrole showed similar activity as the parent indole analogue, whereas
Studies on Pyrido thieno pyrimidine derivatives

thieno[3,4-b]pyrrole show less activity.

As a logical consequence of thiophene – phenyl isosterism, thienopyrimidines can be considered as bioisosteres of quinazolines, which are extensively described in scientific and patent literature as displaying a plethora of biological activities. The synthesis of thienopyrimidine derivatives as potential surrogates for the quinazoline core structure has therefore, become a routine strategy in modern drug design and development. Thienopyrimidines as isosteres of quinazolines are shown here.

Thienopyrimidines can also be considered as structural analogues of five-membered heterocycles such as purines and thiazolopyrimidines. As interesting anti-HIV activity was discovered within the thiazolo[5,4-d]pyrimidine series, whereas the thiazolo[4,5-d]pyrimidines lack antiretroviral activity. The structures of purines and thiazolopyrimidines are shown in the following figure 4.3.
Reported synthetic strategies

Synthetic approaches towards thienopyrimidines can be divided into two main groups according to the type of starting material. Either, the synthesis starts from a pyrimidine derivative and a thiophene ring is then constructed or a thiophene analogue is used as starting material followed by the formation of a pyrimidine ring.

Retrosynthetic analysis of thienopyrimidines

Synthesis of thienopyrimidines from a thiophene moiety

The synthesis of thienopyrimidines from a thiophene moiety, an appropriately substituted aminothiophene serves as the starting material. 2-aminothiophene derivatives, which are the starting materials for thieno[2,3-d]pyrimidines, can be easily synthesized by Gewald reaction\(^{[67]}\). The first step of this multi-component reaction is the Knoevenagel-Cope condensation of carbonyl compound (ketone or aldehyde) with an activated nitrile (α-cyanoester), yielding an α,β-unsaturated nitrile. This intermediate is then thiolated at the methylene group by elemental sulfur followed by an intramolecular cyclization yielding a polysubstituted-2-aminothiophene, which is illustrated in the following scheme.

\[
\begin{align*}
\text{R} & \quad \text{O} \\
\text{R}^1 & \quad \text{NC} \\
\text{R}^2 & \quad \text{OR} \\
\text{OR} & \quad \text{N} \\
\text{S} & \quad \text{H} \\
\end{align*}
\]

The Thorpe-Ziegler reaction is one of the most efficient methods for the synthesis of 5-membered heterocycles containing an amino group at position 3\(^{[68]}\). 3-aminothiophene derivatives are useful building blocks for the construction of thieno[3,2-d]pyrimidines and thieno[3,4-d]pyrimidines. The alkylthio olefin intermediates, generated by the reaction of \textit{vic}-cyanodimethylaminoethylenes or \textit{vic}-bromocynanoethylenes or cyanoacetylenes\(^{[69]}\) with mercapto compounds of general formula HSCH\(_2\)Y (Y is an electron withdrawing group) in the presence of base, undergo a Thorpe-Ziegler
cyclization yielding polysubstituted 3-aminothiophenes as shown in the following scheme.

<table>
<thead>
<tr>
<th>A : thiphene ring</th>
<th>X=CO$_2$Et or CN</th>
<th>Y=O or S</th>
<th>X=CN, Z=NH</th>
<th>X=CO$_2$Et, Z=O</th>
</tr>
</thead>
</table>

The construction of a pyrimidine ring system from a 2 or 3-amino-thiophene derivative follows the same reaction sequence. One of the most popular approaches to construct the pyrimidine ring is via the synthesis of thienylureas or thienylthioureas. In a first step, the amino group of the thiophene moiety is converted into a urea by treatment with an isocyanate, potassium cyanate hydrochloride, or chlorosulfonyl isocyanate and into a thiourea by reaction with an isothiocyanate, thiophosgene and an amine. The resulting thienylureas and thienylthioureas readily undergo an intramolecular cyclization upon treatment with bases or acids to yield thienopyrimidines as shown here.

The synthesis of thienopyrimidin-4(3H)-ones are well studied and can be categorized into 4 groups according to the functional groups on the thiophene moiety and the structures of the intermediates as illustrated in scheme 4.1.

(1) Thienopyrimidinones can be prepared via cyclization of diamides intermediates, which are generated from vic-aminocarbamoylthiophenes by reaction with acylating agents such as orthoesters, acid anhydrides and acid chlorides, formic acid and diethyl oxalate.
Studies on Pyrido thieno pyrimidine derivatives

(2) Alternatively, the synthesis of thienopyrimidinones can be achieved from vic-
aminoalkoxycarbonylthiophenes. Amidine intermediates, formed by the reaction of thiophenes with amides \[^{79}\] , nitriles under acidic conditions \[^{80}\] , orthoesters and amines \[^{81}\] , undergo an intra-molecular cyclization to yield thienopyrimidinones.

(3) A third procedure is based on the recyclization of thieno-oxazinones, which are generated by reaction of vic-aminocarboxylic acids or esters with acid chlorides or orthoesters \[^{82}\] . The recyclization proceeds through the diamide intermediate which is generated upon treatment with amines \[^{83}\] .

(4) Vic-aminocyanothiophenes also serve as valuable starting materials for the synthesis of thienopyrimidinones. Initially, the thieno-oxazinimine intermediates are generated by the acylation of the amino group and then recyclization in the presence of an acid occurs to afford thienopyrimidinones \[^{84}\] .

**Synthesis of thienopyrimidines from a pyrimidine moiety**

Due to the poor availability of appropriately substituted pyrimidines, the synthesis of thienopyrimidines from pyrimidines is much less described in literature. In general,
Studies on Pyrido thieno pyrimidine derivatives

Thieno[2,3-d]pyrimidines and thieno[3,2-d]pyrimidines can be obtained by the intramolecular cyclization of pyrimidine. This pyrimidine derivative can be obtained by the substitution of the mercaptoacetic acid residue for the chlorine \(^{[85]}\). Alkylation of pyrimidinethiones with a chloroacetic acid derivative \(^{[86]}\) is also a possibility depending on the substituent of the pyrimidine ring (X) and of mercapto side chain (Y). Thienopyrimidines with a different substitution pattern on the thiophene moiety can be synthesized. When X = CO\(_2\)R, 5-hydroxythienopyrimidines (which exist predominantly as the oxo form) are formed. In case of X= CN, the Thorpe-Ziegler reaction affords amino substituted pyrimidines. When X and Y are a ketone or an aldehyde, the Claisen-Schmidt condensation yield R substituted thienopyrimidines as shown below.

Alternatively, thienopyrimidines can be prepared by the reaction of vic-chloroalkynylpyrimidines with sodium sulfide \(^{[87]}\). The alkynylpyrimidines are obtained via a Sonogashira reaction as shown below.

\[
\begin{array}{c}
\text{B} \quad \text{X} \\
\text{S} \\
\text{Cl}
\end{array}
\xrightarrow{\text{NaSH}}
\begin{array}{c}
\text{B} \\
\text{Y}
\end{array}
\rightarrow
\begin{array}{c}
\text{B} \\
\text{Z} \\
\text{Y}
\end{array}
\]

X=CO\(_2\)R, Z=OH
X=CN, Z=NH\(_2\)
X=CO\(_R\), Z=R

Sigmatropic rearrangement is a useful method to construct 5-membered nitrogen and sulfur containing heterocycles \(^{[88]}\). The thio-claisen rearrangement of propargylic sulfides yields thienopyrimidines via an allene intermediate followed by tautomerization followed by ring closer yielding the thiophene analogue as shown in following scheme 4.2\([a,b]\)\(^{[89]}\). Another approach of sigmatropic rearrangement involves the oxidation of sulfide to sulfoxide. The sulfoxide undergoes an initial [2,3] sigmatropic rearrangement to generate
the allene intermediate, which then undergoes a Claisen-like [3,3] rearrangement through
the S-O bond, followed by tautomerization to produce intermediate. An intramolecular
Michael type addition followed by aromatization gives access to the desired
thienopyrimidines.

Scheme 4.2a

Thieno[3,4-d]pyrimidines can also be prepared from pyrimidines by thiolation with
elemental sulfur of the methyl group in vic-cyanomethylpyrimidines, followed by the
cyclization of intermediate thiols\(^ {[90]} \) as shown below.

Scheme 4.2b

Alternatively, thieno[3,4-d]pyrimidine-2,4(1H,3H)-dione can also be prepared from 5-
(hydroxymethyl)-2,6-dioxo-1,2,3,6-tetrahydropyrimidine-4-carbaldehyde with BF\(_3\)/Et\(_2\)O
Studies on Pyrido thieno pyrimidine derivatives

in thioacetic acid involving the conversion of the hydroxyl group into a thioester, followed by cyclization\textsuperscript{[91]} as shown here.

**Synthesis of thieno[2,3-d]pyrimidine analogues**

Within the isomeric thieno[3,2-d]pyrimidine series, a versatile starting material has been described in literature\textsuperscript{[92]}. 6-Bromo-4-chloro-thieno[3,2-d]pyrimidine can be regioselectively functionalized at positions 4 and 6. Palladium-catalyzed cross-coupling reactions occur exclusively at position 6, whereas the reaction with amines results in displacement of the chlorine at position 4. Therefore, it was envisioned that the corresponding 6-bromo-4-chloro-2-substituted-thieno [2,3-d]pyrimidine could similarly act as a versatile building block for the introduction of various substituents at position 4 and 6 to build up thieno[2,3-d]pyrimidine libraries.
6-Bromo-2-chloro-thieno[2,3-d]pyrimidine 4 was synthesized from commercially available methyl 2-aminothiophene-3-carboxylate 1 by a procedure similar to the one described for the preparation of thieno[3,2-d]pyrimidine analogues\(^{[86]}\) as described in scheme 4.4.

Standard reaction conditions for Suzuki coupling of compounds 4 and 5 with 4-fluorophenylboronic acid yielded the desired compounds 6a and 6b, respectively. The remaining chlorine atom was displaced by 2-(4-chlorophenoxy)-1-(piperazin-1-yl)ethanone under mild conditions yielding compounds 7a and 7b. For the introduction of anilino moiety at position 4, more vigorous conditions were needed due to the poor nucleophilicity of the aniline nitrogen.
Although 6-bromo-4-chloro-thieno[2,3-d]pyrimidine is a versatile building block, due to synthetic difficulties (such as low yields and the formation of side products), another synthetic route was explored. Since we are mainly interested in thieno[2,3-d]pyrimidines with a 4-fluorophenyl group at position 6, a thiophene derivative substituted with a 4-fluorophenyl group at position 5 would be a valuable starting material. 2-(4-Fluorophenyl) acetaldehyde 10 was prepared by oxidation of 2-(4-fluorophenyl)ethanol 9 with Pyridinium Chloro Chromate (PCC) in moderate yield. The condensation of aldehyde 10 with ethyl cyanoacetate in the presence of a base and elemental sulfur (Gewald reaction) furnished ethyl 2-amino-5-(4-fluorophenyl)thiophene-3-carboxylate 11. Reaction of compound 11 with several nitriles under acidic conditions or with chloroformamidine hydrochloride provided thieno[2,3-d]pyrimidine analogues 12 as shown in scheme 4.5.

![Scheme 4.5](image)

**Synthesis of thieno pyrimidines derivatives:**

Recently, Pokhodylo N T et al. synthesized pyrido[3’,2’:4,5]thieno[2,3-e] [1,2,3]triazolo[1,5-a]pyrimidine from cyanopyridine as illustrated below.
BASF have synthesized several 3-substituted pyrido[3’,4’:4,5]Thieno[2,3-d] pyrimidine derivatives as novel Serotonin reuptake inhibitors. (US patent 6159981) as described below.

Joan T et. al. discloses the synthesis of several pyrido thieno pyrimidine as potent and selective inhibitors of phosphodiesterase 4 (PDE4) and are useful in the treatment, prevention or suppression of pathological conditions, diseases and disorders known to be
susceptible of being improve by inhibition of PDE4 as shown in the following reaction scheme 4.6.

![Scheme 4.6](image)

Bhuiyan et. al.\cite{96} have synthesized several thienopyrimidine derivatives for antimicrobial evaluation shown in following reaction scheme. The starting materials ethyl 2-amino-4,5,6,7-tetrahydrobenzothiophen-3-carboxylate was prepared by condensation of cyclohexanone, elemental sulphure and ethyl cyanoacetate.
Peinador et al.\textsuperscript{[97]} synthesized pyridothienopyrimidine of biological interest. The starting compound for the aza-wittig/heterocumulene mediated annulation was prepared from the easily available 3-cyanopyridine-2(1\textit{H})-thione. Reaction of 3-cyanopyridine-2(1\textit{H})-thione with 2-chloroacetonitrile and subsequent base-promoted intramolecular ring formation yielded the 3-aminothieno[2,3-b]pyridine 2-carbonitrile as described below.
Dave et al. synthesized several pyrido[3',2':4,5]thieno[3,2-d]pyrimidin-4(3H)-ones. When substituted 2-carbethoxy-3-aminothieno[2,3-b]pyridines were refluxed for several hrs with various isothiocyanates in pyridine, pyrido[3',2':4,5]thieno[3,2-d]pyrimidin-4(3H)-ones was obtained, which was methylated at position-2 by dimethyl sulphate in basic medium as described here.

Hossain et al. synthesized antimicrobial active thienopyrimidines. The 2-amino-4,5-dimethylthiophene-3-carbonitrile was prepared from 2-butanone by reacting with malononitrile and sulphure as shown below.
Fatma E M El-Baih et al.\textsuperscript{100} prepared the thienopyrimidinone derivatives by cyclization of the corresponding amino ester with formamide. Nucleophilic aromatic substitution with POCl\textsubscript{3} was carried out on thienopyrimidinone derivatives to yield the 4-chlorothienopyrimidine derivative. Further substitution with an aromatic amine was carried out on this chloro derivative to yield the 4-anilino derivative as shown below.

The reaction of the amino ester with phenylisothiocyanate in boiling absolute ethanol gave the corresponding thiourea derivative when thiourea derivative was allowed to react with hydrazine hydrate, giving 3-amino-7-methyl-2-phenylamino-5,6,7,8-tetrahydro-3\textit{H}-pyrido[4',3':4,5]thieno[2,3-\textit{d}]pyrimidin-4-one\textsuperscript{101}.
Recently, Agathe Begouin et al.\textsuperscript{[102]} described the “one-pot” palladium-catalyzed cross-coupling/cyclization reaction of substituted thiophenes with 2-aminopyridine derivatives or 1-aminoisoquinoline. Tetra- and pentacyclic compounds were obtained as described here.

\[
\text{Imidoformates were prepared by treating substituted thiophene with triethylorthoformate in refluxing temperature. Reactions of imidoformates with hydrazine hydrate yielded the thienopyrimidine. The thienopyrimidine were further converted into triazolopyrimidine derivatives by treatment with triethylorthoesters in dimethylformamide}^{[103]} \text{ as shown below.}
\]

Ahmed M M et al.\textsuperscript{[104]} report the synthesis of some new thienopyridones and thienopyrimidines starting with 3-amino-2-(4-bromobenzoyl)-4-cyano-5-phenylamino thiophene and 2-acetyl-3-amino-4-cyano-5-phenylaminothiophene, which were prepared
Studies on Pyrido thieno pyrimidine derivatives

via ketene N,S-acetal. On reaction of malononitrile with phenyl isothiocyanate in the presence of potassium hydroxide afford the potassium salt of ketene N,S-acetal. Ketene N,S-acetal was allowed to react with p-bromophenacyl bromide or chloroacetone to afford the S-alkylated derivatives, which underwent cyclization in presence of sodium ethoxide to yield the starting materials 3-amino-2-(4-bromobenzoyl)-4-cyano-5-phenylaminothiophene and 2-acetyl-3-amino-4-cyano-5-phenylamino thiophene, respectively. On reaction of 3-amino-2-(4-bromobenzoyl)-4-cyano-5-phenyl amino thiophene and 2-acetyl-3-amino-4-cyano-5-phenylamino thiophene with formamide and formic acid under refluxing temperature afforded the corresponding thieno[3,2-d]pyridine derivatives as described in the scheme 4.7.

![Scheme 4.7](image)

The reaction between 4-aryl-6-(benzoimidazol-2-yl)-2-mercaptopyridine-3-carbonitrile and active halomethylene compounds in boiling ethanol in the presence of sodium ethoxide affords 3-amino-4-aryl-6-(1H-benzoimidazol-2-yl)thieno[2,3-b]pyridines. Condensation of 3-amino-4-aryl-6-(1H-benzoimidazol-2-yl)thieno[2,3-b]pyridines with formamide afforded 4-aryl-2-(1H-benzoimidazol-2-yl)-7H-pyrido[2,3:4',5']thieno[3,2-d]pyrimidin-8-one^{105} as shown below.
3,5-Bis(4-chlorobenzylidene)-1-ethylpiperidin-4-one reacted with cyanothioacetamide in refluxing ethanol containing drops of Et$_3$N to give pyridinethione derivatives, which is reacted with 2-chloro-N-arylacetamide derivatives in refluxing sodium ethoxide solution to yield the 2-(N-aryl)-carboxamidomethyl-thienopyridine derivatives. Fusion of 2-(N-aryl)-carboxamidomethyl-thienopyridine derivatives with an excess of benzoyl chloride gave pyridothieno[3,2-d]pyrimidin-4-one derivative$^{[106]}$ as described in the scheme 4.8.
Present work

It was decided to focus synthetic efforts towards thieno[2,3-d]pyrimidine analogues in order to further explore the structure-activity relationship of these compounds with respect to their anti-HIV activity. In continuation of our interest for the development of new and simple methods for the synthesis of polyfunctional substituted heterocyclic with anticipated biological activity.

In this chapter, we have synthesized various new 7,9-dimethyl-8-substituted pyrido[3',2':4,5]thieno[3,2-d]pyrimidin-4-amine by base-induced alkylation of pentane-2,4-dione in methanol to yield corresponding 3-substituted pentane-2,4-dione, which upon condensation with cyanothioacetamide gave corresponding 5-substituted 2-mercapto-4,6-dimethyl-nicotinonitrile 2a-2h. 5-substituted 2-mercapto-4,6-dimethyl-nicotinonitrile 2a-2h when treated with Chloroacetonitrile gave 5-substituted-3-amino-4,6-dimethylthieno[2,3-b]pyridine-2-carbonitrile 3a-3h followed by condensation with formamide in toluene at 110 °C yielded the target compounds 4a-4h. The proposed reaction scheme is shown below, which indicates the preparation of analogous pyrido(thieno)pyrimidine derivatives.

![Scheme 4.9](image-url)
Studies on Pyrido thieno pyrimidine derivatives

1) Compound 1a, R = Allyl.
2) Compound 1b, R = Ethyl.
3) Compound 1c, R = Benzyl.
4) Compound 1d, R = Methyl.
5) Compound 1e, R = Propyl.
6) Compound 1f, R = Butyl.
7) Compound 1g, R = p-Methylbenzyl.
8) Compound 1h, R = p-Methoxybenzyl.

**Experimental section**

**General procedure for the synthesis of substituted pentane-2,4-dione 1a-1h**

Sodium hydroxide (11 mmol) was dissolved in 3 volume of methanol at room temperature and then chilled to 0°C. To resultant mixture, acetyl acetone (10 mmol) was added over a period of 30 minutes at 0-5°C. Allowed the reaction mixture to come to room temperature and added alkyl bromide (11 mmol) over a period of 30 minutes. Resultant mixture was refluxed for 1-3 hr and then allowed to stir at room temperature overnight. The reaction mixture was filtered and concentrated; residue obtained was purified by column chromatography to yield compound 1a-1h.

**Compound 1a:** 3-allylpentane-2,4-dione, yield 58% m.p.156-158°C. \(^1\)H-NMR (CDCl\(_3\), 300MHz) : 2.19(s, 6H), 2.62(d, 2H), 3.31(t, 1H), 4.85(dd, J=16.7Hz, 1H), 5.03(dd, J=10.3Hz, 1H), 5.70(m, 1H) \(\delta\) ppm.

**Compound 1b:** 3-ethylpentane-2,4-dione, yield 55.2% m.p.165-169 °C. \(^1\)H-NMR (CDCl\(_3\), 300MHz) : 0.98(t, 3H), 1.95(m, 2H), 2.16(s, 6H), 3.25(t, 1H), \(\delta\)ppm.

**Compound 1c:** 3-benzylpentane-2,4-dione, yield 54.5% m.p.149-151°C. \(^1\)H-NMR (CDCl\(_3\), 300MHz) : 2.20(s, 6H), 3.10(d, 2H), 3.65(t, 1H), 7.12-7.21(m, 5H) \(\delta\)ppm.

**Compound 1d:** 3-methylpentane-2,4-dione, yield 60% m.p.143-145 °C. \(^1\)H-NMR (CDCl\(_3\), 300MHz) : 1.36(d, 3H), 2.11(s, 6H), 3.40(q, 1H)\(\delta\)ppm.

**Compound 1e:** 3-propylpentane-2,4-dione, yield 60.4% m.p.162-164 °C. \(^1\)H-NMR (CDCl\(_3\), 300MHz) : 0.97(t, 3H) 1.35m, 2H), 1.82(m, 2H), 2.11(s, 6H), 3.22(t, 1H) \(\delta\)ppm.

**Compound 1f:** 3-butylpentane-2, 4-dione, yield 58% m.p.169-172 °C. \(^1\)H-NMR (CDCl\(_3\), 300MHz) : 0.98(t, 3H) 1.30(m, 2H), 1.35(m, 2H), 1.85(m,
Studies on Pyrido thieno pyrimidine derivatives

Compound 1g: 3-(4-methylbenzyl)pentane-2,4-dione, yield 61% m.p.158-163°C. 
\(^1\)H-NMR (CDCl\(_3\), 300MHz) : 2.30(s, 3H), 2.15(s, 6H), 3.10(d, 2H), 3.65(t, 1H), 7.02(d, 2H), 7.04(d, 2H) \(\delta\)ppm.

Compound 1h: 3-(4-methoxybenzyl)pentane-2,4-dione, yield 64% m.p.144-146°C. \(^1\)H-NMR (CDCl\(_3\), 300MHz) : 2.14 (s, 6H), 3.75(s, 3H), 3.04(d, 2H), 3.70(t, 1H), 6.76(d, 2H), 7.05(d, 2H) \(\delta\)ppm.

General procedure for the synthesis of 5-substituted 2-mercapto-4,6-dimethylnicotinonitrile 2a-h. To the solution of compound 1a-1h (10mmol) in ethanol (5vol) was added cyanothio acetamide (10 mmol) followed by triethylamine (0.5mmol) and then the reaction mixture were refluxed for 30 minutes with stirring. TLC showed disappearance of compound 1a-1h. The reaction mixture was allowed to cool to room temperature and then chilled to 0°C. Solid was filtered and washed with chilled ethanol. Crude solid was purified by column chromatography to yield compound 2a-2h.

Compound 2a: 5-allyl-2-mercapto-4,6-dimethylnicotinonitrile, yield 60% m.p. 139-141 °C. \(^1\)H-NMR (CDCl\(_3\), 300MHz) : 2.48(s, 3H), 2.49(s, 3H), 3.27(m, 2H), 4.86(d, \(J=16.8\)Hz, 1H), 5.12(d, \(J=10.2\)Hz, 1H), 5.80(m, 1H) \(\delta\)ppm.

Compound 2b: 5-ethyl-2-mercapto-4,6-dimethylnicotinonitrile, yield 56% m.p.134-136 °C \(^1\)H-NMR CDCl\(_3\), 300MHz : 1.30(t, 3H), 2.80(q, 2H), 2.47(s, 3H), 2.48(s, 3H) \(\delta\)ppm.

Compound 2c: 5-benzyl-2-mercapto-4,6-dimethylnicotinonitrile, yield 54.7% m.p.129-133 °C. \(^1\)H-NMR (CDCl\(_3\), 300MHz) : 2.48(s, 3H), 2.49(s, 3H), 3.85(s, 2H), 7.08-7.16(br,5H) \(\delta\)ppm.

Compound 2d: 2-mercapto-4,5,6-trimethylnicotinonitrile, yield 58% m.p.131-133 °C. \(^1\)H-NMR (CDCl\(_3\), 300MHz) : 2.42(s, 3H), 2.43(s, 3H), 2.45(s, 3H) \(\delta\)ppm.

Compound 2e: 2-mercapto-4,6-dimethyl-5-propynicotinonitrile, yield 64%, m.p.138-139 °C. \(^1\)H-NMR (CDCl\(_3\), 300MHz) : 1.01(t, 3H), 1.70(m, 2H), 2.47(s, 3H), 2.48(s, 3H), 2.65(t, 2H,) \(\delta\)ppm.
Studies on Pyrido thieno pyrimidine derivatives

Compound 2f: 5-butyl-2-mercapto-4,6-dimethylnicotinonitrile, yield 57.5% m.p. 142-144 °C. ¹H-NMR (CDCl₃, 300MHz) : 1.00(t, 3H), 1.38(m, 2H), 1.62(m, 2H), 2.63(s, 3H), 2.46(s, 3H), 2.48(t, 2H) δppm.

Compound 2g: 5-(4-methylbenzyl)-2-mercapto-4,6-dimethylnicotinonitrile, yield 59% m.p. 152-153 °C. ¹H-NMR (CDCl₃, 300MHz) : 2.38(s, 3H), 2.40(s, 3H), 2.52(s, 3H), 3.65(s, 2H), 6.98-7.01(bs, 4H) δppm.

Compound 2h: 5-(4-methoxybenzyl)-2-mercapto-4,6-dimethylnicotinonitrile, yield 62.3% m.p. 142-145 °C. ¹H-NMR (CDCl₃, 300MHz) : 2.45(s, 3H), 2.50(s, 3H), 3.60(s, 3H), 3.59(s, 2H), 6.70(d, J=7.1Hz, 2H), 7.01(d, J=7.1Hz, 2H) δppm.

General procedure for the synthesis of 5-substituted-3-amino-4,6-dimethylthieno[2,3-b]pyridine-2-carbonitrile 3a-h

To a solution of compound 2a–2h (10mmol) in methanol (25ml) was added NaOMe (11mmol) followed by chloroacetonitrile (11mmol). The reaction mixture was refluxed for 5 hr and allowed to concentrate then water was added to the residue and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, filtered and concentrated to give crude compound 3a-3h, which was purified by column chromatography to give purified compound 3a-3h.

Compound 3a: 5-allyl-3-amino-4,6-dimethylthieno[2,3-b]pyridine-2-carbonitrile
yield 54% m.p. 128-131 °C. ¹H-NMR (CDCl₃, 300MHz) : 2.60(s, 3H), 2.67(s, 3H), 3.49(m, 2H), 4.77(dd, J₁=17.0Hz, J₂=2.1Hz, 1H), 4.89(bs, 2H), 5.07(dd, J₁=9.9Hz, J₂=1.8Hz, 1H), 5.93(m, 1H) δppm.

Compound 3b: 3-amino-5-ethyl-4,6-dimethylthieno[2,3-b]pyridine-2-carbonitrile
yield 53.6% m.p. 136-138 °C. ¹H-NMR (CDCl₃, 300MHz) : 0.99(t, 3H), 2.45(q, 2H), 2.53(s, 3H), 2.58(s, 3H), 4.71(bs, 2H) δppm.

Compound 3c: 3-amino-5-benzyl-4,6-dimethylthieno[2,3-b]pyridine-2-carbonitrile
yield 56% m.p. 145-147 °C. ¹H-NMR (CDCl₃, 300MHz) : 2.60(s, 3H), 2.65(s, 3H), 4.00(s, 2H), 4.83(bs, 2H), 7.00-7.14(m, 5H) δppm.
Studies on Pyrido thieno pyrimidine derivatives

Compound 3d: 3-amino-4,5,6-trimethylthieno[2,3-b]pyridine-2-carbonitrile, yield 58.2% m.p.134-136 °C. \(^1\)H-NMR (CDCl\(_3\), 300MHz) : 2.40(s, 3H), 2.45(s, 3H), 2.49(s, 3H), 4.65(bs, 2H) \(\delta\)ppm.

Compound 3e: 3-amino-4,6-dimethyl-5-propylthieno[2,3-b]pyridine-2-carbonitrile, yield 58% m.p. 131-133 °C. \(^1\)H-NMR (CDCl\(_3\), 300MHz) : 1.00(t, 3H), 1.70(m, 2H), 2.55(s, 3H), 2.59(t,2H), 2.60(s, 3H), 4.73(bs, 2H) \(\delta\)ppm.

Compound 3f: 3-amino-5-butyl-4,6-dimethylthieno[2,3-b]pyridine-2-carbonitrile, yield 59% m.p. 137-139°C. \(^1\)H-NMR (CDCl\(_3\), 300MHz) : 1.10(t, 3H), 1.38(m, 2H), 1.65(m, 2H), 2.40(t, 2H), 2.51(s, 3H), 2.60(s, 3H), 4.84(bs, 2H) \(\delta\)ppm.

Compound 3g: 3-amino-4,6-dimethyl-5-p-tolylthieno[2,3-b]pyridine-2-carbonitrile, yield 58% m.p.138-139°C. \(^1\)H-NMR (CDCl\(_3\), 300MHz) : 2.30(s, 3H), 2.60(s, 3H), 2.67(s, 3H), 3.90(s, 2H), 4.86(bs, 2H),7.00-7.10(br, 4H) \(\delta\)ppm.

Compound 3h: 3-amino-5-(4-methoxyphenyl)-4,6-dimethylthieno[2,3-b]pyridine-2-carbonitrile, yield 63.5% m.p.145-148°C. \(^1\)H-NMR (CDCl\(_3\), 300MHz) : 2.61(s, 3H), 2.68(s, 3H), 3.80(s, 3H), 4.1(s, 2H), 4.84(bs, 2H),6.80(d, \(J=7.3Hz\), 2H),7.10(d, \(J=7.4Hz\), 2H) \(\delta\)ppm.

General procedure for the synthesis of 5-substituted-3-amino-4,6-dimethylthieno[2,3-b]pyridine-2-carbonitrile 4a-h

To a solution of compound 3a–3h (10mmol) in toluene (20ml) was added to the formamide (11mmol). The reaction mixture was refluxed for 4hr. The reaction mixture was poured on to ice, aqueous layer was extracted with ethyl acetate washed with brine, dried over sodium sulfate, filtered and concentrated to give crude compound 4a-4h, which upon purification by column chromatography to gave compound 4a-4h.

Characterization of the synthesized compound 4a-4h using NMR spectroscopy

\(^1\)H-NMR spectrum of final product were carried out in CDCl\(_3\) or DMSO-d6 solvent against TMS as reference on Bruker Avance-300MHz instrument and the respective data were summarize accordingly.
Studies on Pyrido thieno pyrimidine derivatives

$^1$H-NMR spectrum of compound 4a: There are total 14 protons with 8 different types of protons in the structure. The proton of pyrimidine ring appeared around 8.45 δppm as singlet. This data is of suggestive that a basic skeleton of 7,9-dimethyl-8-prop-2-en-1-yl pyrido[3',2':4,5]thieno [3,2-d]pyrimidin-4-amine is present.

Figure-4.1 $^1$H-NMR of the compound 7,9-dimethyl-8-prop-2-en-1-yl pyrido[3',2':4,5]
thieno [3,2-d]pyrimidin-4-amine (4a) is shown here.

Table-4.1 Assignment of the $^1$H-NMR chemical shifts to the different protons of compound 4a is given here.

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Chemical shift</th>
<th>Multiplicity</th>
<th>Proton assignment</th>
<th>No. of protons</th>
</tr>
</thead>
<tbody>
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</tr>
<tr>
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<td>Singlet</td>
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</tr>
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<td>Proton of allyl moiety</td>
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</tr>
<tr>
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<td>Multiplet</td>
<td>Proton of allyl moiety</td>
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</tr>
<tr>
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<td>Singlet</td>
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<tr>
<td>8</td>
<td>8.45</td>
<td>Singlet</td>
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</tr>
</tbody>
</table>
Studies on Pyrido thieno pyrimidine derivatives

$^1$H-NMR spectrum of compound 4b: There are total 14 protons with 6 different types of protons in the structure. The proton of pyrimidine ring appeared around 8.50 $\delta$ppm as singlet. This data is of suggestive that a basic skeleton of 8-ethyl-7,9-dimethyl pyrido[3',2':4,5]thieno[3,2-d] pyrimidin-4-amine is present.

**Figure-4.2** $^1$H-NMR of the compound 8-ethyl-7,9-dimethylpyrido[3',2':4,5]thieno[3,2-d] pyrimidin-4-amine (4b) is shown here.

![4b](image)

**Table-4.2** Assignment of the $^1$H-NMR chemical shifts to the different protons of compound 4b is given here.

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Chemical shift</th>
<th>Multiplicity</th>
<th>Proton assignment</th>
<th>No. of protons</th>
</tr>
</thead>
<tbody>
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<td>Methyl of ethyl moiety</td>
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<tr>
<td>2</td>
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<td>Singlet</td>
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<td>5</td>
<td>6.70</td>
<td>Singlet</td>
<td>Proton of NH$_2$</td>
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</tr>
<tr>
<td>6</td>
<td>8.50</td>
<td>Singlet</td>
<td>Proton of pyrimidine</td>
<td>1</td>
</tr>
</tbody>
</table>
**1H-NMR spectrum of compound 4c:** There are total 16 protons with 6 different types of protons in the structure. The proton of pyrimidine ring appeared around 8.60 δ ppm as singlet. This data is of suggestive that a basic skeleton of 8-benzyl-7,9-dimethyl pyrido[3',2':4,5]thieno[3,2-d] pyrimidin-4-amine is present.

**Figure-4.3** 1H-NMR of the compound 8-benzyl-7,9-dimethylpyrido[3',2':4,5]thieno[3,2-d] pyrimidin-4-amine (4c) is shown here.

**Table-4.3** Assignment of the 1H-NMR chemical shifts to the different protons of compound 4c is given here.

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Chemical shift</th>
<th>Multiplicity</th>
<th>Proton assignment</th>
<th>No. of protons</th>
</tr>
</thead>
<tbody>
<tr>
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</tr>
<tr>
<td>3</td>
<td>3.75</td>
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<td>Proton of methylene</td>
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</tr>
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<td>4</td>
<td>7.21</td>
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<td>Proton of phenyl ring</td>
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</tr>
<tr>
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<td>Singlet</td>
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</tr>
<tr>
<td>6</td>
<td>8.60</td>
<td>Singlet</td>
<td>Proton of pyrimidine</td>
<td>1</td>
</tr>
</tbody>
</table>
Studies on Pyrido thieno pyrimidine derivatives

$^{1}$H-NMR spectrum of compound 4d: There are total 12 protons with 5 different types of protons in the structure. The proton of pyrimidine ring appeared around 8.55 $\delta$ppm as singlet. This data is of suggestive that a basic skeleton of 7,8,9-trimethyl pyrido[3',2':4,5]thieno[3,2-d] pyrimidin-4-amine is present.

Figure-4.4 $^{1}$H-NMR of the compound 7,8,9-trimethylpyrido[3',2':4,5]thieno[3,2-d] pyrimidin-4-amine (4d) is shown here.

Table-4.4 Assignment of the $^{1}$H-NMR chemical shifts to the different protons of compound 4d is given here.

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Chemical shift</th>
<th>Multiplicity</th>
<th>Proton assignment</th>
<th>No. of protons</th>
</tr>
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<tbody>
<tr>
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<td>3</td>
</tr>
<tr>
<td>3</td>
<td>2.80</td>
<td>Singlet</td>
<td>Methyl of pyridine ring</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>7.60</td>
<td>Singlet</td>
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<tr>
<td>5</td>
<td>8.55</td>
<td>Singlet</td>
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</tbody>
</table>
Studies on Pyrido thieno pyrimidine derivatives

**Figure-4.5** $^{13}$C-NMR of the compound 7,8,9-trimethylpyrido[3',2';4,5]thieno[3,2-d]pyrimidin-4-amine (4d) is shown here.

**Table-4.5** Assignment of the $^{13}$C-NMR chemical shifts to the different Carbons of compound 4d is given here.

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Chemical shift</th>
<th>Carbon assignment</th>
<th>No. of Carbons</th>
</tr>
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<tbody>
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<td>1</td>
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<td>17.5</td>
<td>Carbon of methyl group</td>
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</tr>
<tr>
<td>3</td>
<td>22.1</td>
<td>Carbon of methyl group</td>
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</tr>
<tr>
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<td>10</td>
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<td>12</td>
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</tbody>
</table>
Studies on Pyrido thieno pyrimidine derivatives

$^1$H-NMR spectrum of compound 4e: There are total 16 protons with 7 different types of protons in the structure. The proton of pyrimidine ring appeared around 8.48 δ ppm as singlet. This data is suggestive that a basic skeleton of 7,9-dimethyl-8-propylpyrido[3',2':4,5]thieno[3,2-d] pyrimidin-4-amine is present.

**Figure-4.6** $^1$H-NMR of the compound 7,9-dimethyl-8-propylpyrido[3',2':4,5]thieno[3,2-d] pyrimidin-4-amine (4e) is shown here.

![Compound 4e](image)

**Table-4.6** Assignment of the $^1$H-NMR chemical shifts to the different protons of compound 4e is given here.

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Chemical shift</th>
<th>Multiplicity</th>
<th>Proton assignment</th>
<th>No. of protons</th>
</tr>
</thead>
<tbody>
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<td>Triplet</td>
<td>Methyl of propyl moiety</td>
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</tr>
<tr>
<td>2</td>
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<td>Multiplet</td>
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</tr>
<tr>
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<td>Singlet</td>
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<td>Singlet</td>
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</tbody>
</table>
Studies on Pyrido thieno pyrimidine derivatives

$^1$H-NMR spectrum of compound 4f: There are total 18 protons with 7 different types of protons in the structure. The proton of pyrimidine ring appeared around 8.01 $\delta$ppm as singlet. This data is of suggestive that a basic skeleton of 8-butyl-7,9-dimethyl pyrido[3’,2’:4,5]thieno[3,2-d]pyrimidin-4-amine is present.

**Figure-4.7** $^1$H-NMR of the compound 8-butyl-7,9-dimethylpyrido[3’,2’:4,5]thieno[3,2-d]pyrimidin-4-amine (4f) is shown here.

![Image of 4f molecule and NMR spectrum]

**Table-4.7** Assignment of the $^1$H-NMR chemical shifts to the different protons of compound 4f is given here.

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Chemical shift</th>
<th>Multiplicity</th>
<th>Proton assignment</th>
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</thead>
<tbody>
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<td>Triplet</td>
<td>Proton of methylene</td>
<td>2</td>
</tr>
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<td>8.01</td>
<td>Singlet</td>
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</tbody>
</table>
Studies on Pyrido thieno pyrimidine derivatives

$^1$H-NMR spectrum of compound 4g: There are total 18 protons with 8 different types of protons in the structure. The proton of pyrimidine ring appeared around 8.56 $\delta$ppm as singlet. This data is of suggestive that a basic skeleton of 7,9-dimethyl-8-(4-methylbenzyl)pyrido [3',2':4,5]thieno[3,2-d]pyrimidin-4-amine is present.

Figure-4.8 $^1$H-NMR of the compound 7,9-dimethyl-8-(4-methylbenzyl) pyrido [3',2':4,5]thieno[3,2-d]pyrimidin-4-amine (4g) is shown here.

Table-4.8 Assignment of the $^1$H-NMR chemical shifts to the different protons of compound 4g is given here.

<table>
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<th>Sr. No.</th>
<th>Chemical shift</th>
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<th>Proton assignment</th>
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<tbody>
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</table>
Studies on Pyrido thieno pyrimidine derivatives

$^1$H-NMR spectrum of compound 4h: There are total 18 protons with 8 different types of protons in the structure. The proton of pyrimidine ring appeared around 8.55 $\delta$ppm as singlet. This data is of suggestive that a basic skeleton of 8-(4-methoxybenzyl)-7,9-dimethylpyrido [3',2':4,5]thieno[3,2-d]pyrimidin-4-amine is present.

Figure-4.9  $^1$H-NMR of the compound 8-(4-methoxybenzyl)-7,9-dimethylpyrido [3',2':4,5]thieno[3,2-d]pyrimidin-4-amine (4h) is shown here.

Table-4.9 Assignment of the $^1$H-NMR chemical shifts to the different protons of compound 4h is given here

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Chemical shift</th>
<th>Multiplicity</th>
<th>Proton assignment</th>
<th>No. of protons</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.20</td>
<td>Singlet</td>
<td>Methyl of pyridine ring</td>
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References

5. Eggenweiler H M & Eiermann V, patent no.*DE 10063223*.
15. Sauter R & Maier R, patent no.*DE2039662*.
16. Laliberte R, patent no.*US 3644357*.
29. Thomae K, patent no. GB 1048986.
30. Sauter F, patent no. DE 2104435.
31. Sauter F, patent no. DE 2264222.
Studies on Pyrido thieno pyrimidine derivatives

Studies on Pyrido thieno pyrimidine derivatives


Studies on Pyrido thieno pyrimidine derivatives

94. BASF Aktiengesellschaft, Germany, patent no. US patent 6159981.
97. Carlos peinador, Maria J. Moreira & Jose M. Quintela. Tetrahedron. 50(22), 1994, 6705.


102. Agathe Begouin, Stephanie Hesse & Gilbert Kirsch, *ARKVOC* 7, **2008**, 84.


