PART A
SYNTHESIS OF BASE MODIFIED NUCLEOSIDES
Chapter 2

Synthesis of benzofuropyrimidine analogs
2.1. Introduction

Pyrimidine is a six membered heterocyclic ring, containing two nitrogen atoms at first and third positions. It is a much weaker base than pyridine and soluble in water. Pyrimidine and its derivatives represent one of the most active classes of heterocyclic compounds possessing wide range of biological activities\(^1-^3\). Pyrimidine nucleus occurs in biologically important compounds such as nucleic acids, vitamins, co-enzymes and pharmacologically useful natural products of plant origin, mostly in the form of alkaloids. Some of them were distinguished as analgesic\(^4\), antihypertensive\(^5\), antipyretic\(^6\), antiviral\(^7\) and anti-inflammatory\(^8\), antimalarial and anticancer drugs\(^9\) CNS depressant\(^10\).

The rich chemistry and pharmacological properties connected with pyrimidine ring system led to investigation of several condensed pyrimidines containing various five membered, six membered and seven membered heterocycles containing oxygen, nitrogen and sulphur as hetero atoms. Thus, enormous research work has been carried out concerning pyrimidine and its derivatives. Many of the research papers describe the synthesis, characterization, biological and pharmacological investigation of pyrimidine derivatives. The discussion about the importance and methods of preparation of fused pyrimidine derivatives was felt necessary, which has been summarized in the following pages.

Sasikumar et al., synthesized the tricyclic heterocycles viz., thienopyridine–pyrimidines 1 and thienopyrimidine–pyrimidines 2\(^11\). These compounds were found to inhibit the mGluR1 antagonists orally which belongs to the Group I mGluRs and play a key role in the central sensitization of pain and other neurologic disorders\(^12-15\).
Duval et al., studied the structure activity relationship of newly synthesized thieno[2,3-\textit{d}]pyrimidin-4-one acylhydrazide derivatives 3\textit{a-c}, 4\textit{a-d} as tissue transglutaminase 2 (TGases 2) inhibitor\textsuperscript{16}. The studies revealed that acylhydrazide thioether side chain and thiophene ring fused to pyrimidine are crucial for inhibitory activity of TGases 2 which is isozyme linked to celiac disease\textsuperscript{17}, such as Alzheimer’s\textsuperscript{18} and Huntington’s\textsuperscript{19}.

Wenyan et al., carried out synthesis of fluorine-containing pyrido[4,3-\textit{d}]pyrimidines 5 and investigated them for their herbicidal activity. Some of these compounds have been found to possess a significant herbicidal activity against barnyard grass. They also reported that the introduction of fluorine to the para position of the substituent improved the herbicidal activity\textsuperscript{20}. 

\begin{center}
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\end{center}
Some of the pyrimidine-fused 5,6-dihydrobenzodiazepines 6 have been synthesized via Pictet–Spengler cyclization using various aldehydes in presence of protic acids by Che, et al\textsuperscript{21}.

Zhang et al., reported the synthesis of pyrimidine derivatives 7 via Ytterbium(III) Triflate catalyzed reaction, which are important class of natural and non-natural compounds exhibiting the useful biological activity\textsuperscript{22}.

Sheng et al., synthesized the benzo[4,5]imidazo[1,2-a]pyrimidine derivatives 8 through one pot process. These derivatives have been synthesized via solvent free procedure which was catalyzed by sulfonic acid\textsuperscript{23}.
Holla et al., in their search to find out better antimicrobial agents, synthesized pyrazolo[3,4-d]pyrimidine derivatives 9 connected to quinoline moiety. These were evaluated for antibacterial and antifungal activity. Some of the compounds have been proved to possess potent antimicrobial activity.

The compounds containing furan ring system are known to exhibit wide range of pharmacological activities. In fact many drugs which are used for the treatment of various diseases encompass furan ring in their structure.

Encouraged by this fact many researchers synthesized condensed heterocycles involving pyrimidine, furan, benzofuran and naphthofuran moieties. Some of the interesting research findings are summarized in the following pages.

Sayed et al., synthesized fused pyranosyl-pyrimidine derivatives 10, 11, 12 and tetracyclic pyrimidine derivatives 13, 14 and evaluated these compounds for their antibacterial activity against *Staphylococcus aureus*, *Bacillus subtilis* and *Escherichia coli* by agar diffusion method using Ciprofloxacin as a standard drug. Similarly, screening of antifungal activity was carried out against *Candida albicans* using Ketoconazole as a standard.
Shaker reported the preparation of furo[2,3-d]pyrimidines and furo[3,2-e][1,2,4]triazolo[1,5-c]pyrimidines 15a-b, 16a-b which are important class of heterocyclic compounds in pharmaceutical discovery research. This was achieved by using 2-amino-4,5-bis(4-methoxyphenyl)furan-3-carbonitrile, as a starting material.

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Foloppe et al., in their discovery of Chk1 inhibitors, synthesized some furanopyrimidine derivatives\textsuperscript{17} and investigated them as inhibitors of the Chk1 kinase through crystallographic binding mode studies.

\[\text{Ar} \quad \text{NHR} \quad \text{Ar} \quad \text{N} \]

Mohsen et al., synthesized some derivatives of pyrrolylfuro[2,3-d]pyrimidines \textsuperscript{18}, \textsuperscript{19}, \textsuperscript{20} and pyrrolopyrazinofuro[2,3-d]pyrimidines \textsuperscript{21}, \textsuperscript{22} and selected compounds were screened \textit{in vitro} for their antimicrobial activity against four strains of bacteria Viz., \textit{Bacillus cereus, Escherichia coli, Pseudomonas aeruginosa} and \textit{staphylococcus albus} and six fungal species Viz., \textit{Aspergillus flavus, Aspergillus niger, Candida albicans, Geotrichum candidum, Scopulariopsis brevicaulis} and \textit{Trichophyton rubrum} using the filter paper disc method\textsuperscript{32}.

\[\text{Ph} \quad \text{N} \quad \text{Ph} \quad \text{N} \quad \text{Ph} \quad \text{N} \quad \text{Ph} \quad \text{N} \quad \text{Ph} \quad \text{N} \quad \text{Ph} \]

Realizing the importance of benzofuran and pyrimidine moieties in their molecular frame work, many scientists have directed their research work towards
synthesis of novel compounds in the form of fused benzofuropyrimidine derivatives. Such compounds have been evaluated for many pharmacological activities. Some of the compounds exhibited important biological activities containing benzofuropyrimidine as core structure.

The benzofuropyrimidine derivative 23 exhibited the property of multi targeted tyrosine kinase inhibition by acting as radiosensitizing several GBM cell lines.

![Image of compound 23]

Welsh et al., synthesized benzofuro[3,2-d]pyrimidine derivative 24 and observed that it plays a significant role in enhancement of long-term memory by potentiating the CREB (cAMP response element binding) signaling pathway.

![Image of compound 24]

The series of benzofuropyrimidine derivatives were found to act as modulators of the histamine H4 receptor and one of the example is compound 25.
Chao et al., synthesized benzofuropyrimidine derivatives 26 by reacting 3-halo chromones with amidines through new approach, mediated by CuBr. The reaction takes place via a chemoselective Michael addition-elimination-double intramolecular cyclization sequence.\(^\text{36}\)

\[
\begin{align*}
\text{CuBr, DBU, DMF} & \quad \text{NH}_2, 90^\circ\text{C}, 10\text{ hrs} \\
\end{align*}
\]

Liu et al., reported the preparation of series of benzofuropyrimidine derivatives 27 via chemo/regioselective Suzuki coupling and CuTC-mediated intramolecular cyclization under neutral and relatively mild conditions.\(^\text{37}\)

Synthesis of some 2-thioxo-2,3-dihydro-1H-benzofuro[3,2-d]pyrimidin-4(1H)-one derivatives 28 through both the traditional and new synthetic pathways by using 3-amino-1-benzofuran-2-ethylcarboxylate as a starting material has been reported by Chenko et al.\(^\text{38}\).
Savall et al., synthesized the tricyclic benzofuropyrimidine derivatives 29 and evaluated for the histamine H4 receptor antagonists properties. Some of the derivatives delivered a potent and selective H4 receptor antagonist which have a main role in human inflammatory diseases such as asthma, pruritis and colitis.

Koltun et al., studied the CDC7 inhibitory activity of novel benzofuropyrimidine derivatives 30, 31. The inhibition of CDC7 in tumor cells lines (colon, lung, ovary, breast, leukemia, and prostate) with small molecules results in defective S phase progression that leads to a halt in cell cycle progression and subsequent p53-independent apoptotic cell death and make CDC7 inhibition as an attractive target for cancer therapy. The compound labeled as XL413, in this series, was proved to have potent CDC7 activity.

Therefore, it is thought of to synthesize, new organic molecules encompassing benzo[1,2-c]pyran and pyrimidine ring system and investigate the novel compounds for their antimicrobial and antioxidant properties.

In the present investigation, we focused our interest on the synthesis of various benzofuropyrimidine derivatives and some of the selected compounds were used for construction of nucleosides, which has been discussed in Chapter 3. It was further

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contemplated to evaluate antibacterial, antifungal and antioxidant activity of synthesized compounds which has been described in Chapter 8.

It was contemplated to synthesize four different types of derivatives of benzo[3,2-d]pyrimidines. For systematic presentation of the work carried out, this Chapter has been divided into the following four sections:


Section 2.1

Synthesis of substituted 8-bromo-4-oxo[1]benzofuro [3,2-d]pyrimidines 5, 6 and 7
2.1a. Present work

It was contemplated to synthesize the following three types of derivatives of 8-bromo-4-oxo[1]benzofuro[3,2-d]pyrimidine:

1. 3-Amino-8-bromo[1]benzofuro[3,2-c]pyrimidin-4(3H)-one 5

The synthesis of these derivatives was accomplished by sequence of reactions as depicted in Scheme 2.1a.
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The synthesis of all these three types of derivatives involved a common intermediate i.e. 3-amino-5-bromo-1-benzofuran-2-carboxyhydrazide 3. It was obtained by the following sequence of reactions (Scheme 2.1a).

![Scheme 2.1a](image)

Parameshwarappa et. al., 42 reported the synthesis of ethyl 3-amino-5-bromo-1-benzofuran-2-carboxylate 2, which involved two steps. In the first step, 5-bromo-hydroxybenzonitrile 1 was condensed with ethyl chloroacetate using potassium carbonate as a base and acetone as a solvent to obtain the condensed product i.e. ethyl (4-bromo-2-cyanophenoxy)acetate 1a. The condensed product 1a, was cyclized by treating with potassium carbonate in N,N-dimethylformamide at elevated temperature, to get the desired product ethyl 3-amino-5-bromo-1-benzofuran-2-carboxylate 2. (Scheme 2.1b)

![Scheme 2.1b](image)

However, in the present work, the synthesis ethyl 3-amino-5-bromo-1-benzofuran-2-carboxylate 2, was carried out by a modified procedure involving the
reaction between 5-bromo-hydroxybnezonitinle 1, ethyl chloroacetate and potassium carbonate using N,N-dimethylformamide as a solvent. In this method both condensation and Thorpe-Zeigler cyclization occurred in a single step (Scheme 2.1c).

![Scheme 2.1c](image)

Moreover, in this modified method yield and purity of the product was better than the earlier method and also helpful in saving time.

The structure assigned to compound 2 was established by IR (Figure 2.1a), $^1$H NMR (Figure 2.1b), $^{13}$C NMR (Figure 2.1c) and mass spectral (Figure 2.1d) studies. All the spectra superimposed with the spectra of authentic sample. The mixed melting point of these compounds with the known sample did not show any depression.

To provide final proof to the structure assigned, single X-ray crystal structure of compound 2 was recorded. The details of which are discussed Chapter 6 of this thesis.

The conversion of ethyl 3-amino-5-bromo-1-benzofuran-2-carboxylate 2 into 3-amino-5-bromo-1-benzofuran-2-carbohydrazide 3 was accomplished by reacting compound 2 with excess of hydrazine hydrate (99%) in ethanol at reflux temperature (Scheme 2.1d).

![Scheme 2.1d](image)

The formation of compound 3 was confirmed by recording its IR, $^1$H NMR and mass spectra. The IR spectrum (Figure 2.2a) of hydrazide 3 exhibited absorption bands
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at 3402 cm⁻¹, 3307 cm⁻¹, 3201 cm⁻¹ and 1856 cm⁻¹ due to -NH, -NH₂, =C-H (aromatic) and -C=O stretching frequencies respectively. In ¹H NMR spectrum (Figure 2.2b), one singlet appeared at δ 4.3 due to two protons of -NH-NH₂ group, second singlet at δ 5.9 due to two protons of -NH₂ group at C-3 and third singlet of δ 9.2 due to one proton of -NH-NH₂ group. Three aromatic protons appeared as a singlet at δ 8.1 and two doublets at δ 7.5 and δ 7.3. The mass spectrum (Figure 2.2c) of compound 3 exhibited molecular ion peak at m/z 272 (M)⁺ and at m/z 274 (M+2)⁺ of equal intensity as expected for the compounds containing bromine atom.

The carboxyhydrazide 3, thus obtained was utilized as an intermediate for the synthesis of all the three types of derivatives of 8-bromo-4-oxo[1]benzofuro[3,2-d]pyrimidine i.e. compounds 5, 6, and 7 as described one by one in the following pages:


The synthesis of the desired amino compound 5 was brought about via the formation of ethyl (8-bromo-4-oxo[1]benzofuro[3,2-d]pyrimidine-3(4H)-yl) imidoformate 4. The imidoformate 4 was obtained by reacting 3-amino-1-benzofuran-2-carbonylhydrazide 3 with triethyl orthoformate (Scheme 2.1e).

![Scheme 2.1e](image)

The formation of the compound 4 was established by recording its IR, ¹H NMR and mass spectra. The IR spectrum (Figure 2.3a) exhibited absorption bands at 3090 cm⁻¹, 3030 cm⁻¹, 2988 cm⁻¹ and 2939 cm⁻¹ due the stretching frequencies of -=CH, -=CH₂ and -CH₃ groups. The absorption bands at 1760 cm⁻¹ and 1607 cm⁻¹ were attributed to
to the \(-\text{C}=\text{O}\) and \(-\text{C}=\text{C}\-) groups. The \(^1\text{H}\) NMR spectrum (Figure 2.3b) displayed a singlet at \(\delta 5.0\), a quartet at \(\delta 4.4\) and triplet at 1.4 assignable for \(-\text{N}=\text{CH}-\text{OEt}, -\text{CH}_2\) and \(-\text{CH}_3\) protons. The remaining peaks at \(\delta 7.5\) to \(\delta 8.6\) integrating for four protons were assignable for aromatic protons. The mass spectrum (Figure 2.3c) exhibited molecular ion peak at \(m/z\) 336 (M)\(^+\) and molecular ion isotopic peak at \(m/z\) 338 (M+2)\(^+\) with equal intensity which corresponds to molecular weight. It served as an additional support for the structure assigned to the compound 4.

The overall reaction mechanism involved condensation followed by intramolecular cyclization, with the formation of new C-N bonds and elimination of five molecules of ethanol. The mechanism of this reaction is depicted in Scheme 2.1f.

In this part of the work, our main interest was to synthesize 3-amino-8-bromo[1]benzofuro[3,2-d]pyrimidin-4(3H)one 5. Hence, it was thought of to utilize
imidoformate 4 to realize this synthesis. It was accomplished by treating the compound 4 with excess of hydrazine hydrate (Scheme 2.1g).

The compound 5, with only one nucleophilic centre i.e. \(-\text{NH}_2\) group at third position of pyrimidine moiety, is most suitable compound for ribosylation.

The structure of the compound 5 obtained was established by recording the IR, \(^1\text{H}\) NMR and mass spectra.

The IR spectrum (Figure 2.4a) of compound 5 exhibited absorption at 3307 cm\(^{-1}\) and 1703 cm\(^{-1}\) due to stretching frequencies of \(-\text{NH}_2\) and carbonyl groups respectively. The weak absorption bands observed at 3198 cm\(^{-1}\) and 2962 cm\(^{-1}\) were due to the \(-\text{C-H}\) stretching frequencies and carbonyl overtone bands. In \(^1\text{H}\) NMR spectrum (Figure 2.4b) of the compound 5, the peaks appeared at \(\delta\) 8.5, \(\delta\) 8.2 and \(\delta\) 7.8 were due to the four aromatic protons and the broad peak at \(\delta\) 6.1 integrating for two protons was attributed to \(-\text{NH}_2\) protons. The \(^1\text{H}\) NMR spectrum was conspicuous by the absence of a quartet and triplet due to ethyl protons which were present in its precursor 4. The mass spectrum (Figure 2.4c) also confirmed the structure of this compound 5 by exhibiting the molecular and isotopic ion peaks at m/z 280 (M\(^+\)) and m/z 282 (M+2)\(^+\) with equal intensity as expected.

It was planned to introduce formyl group and methyl keto group, in the above ring system at \(-\text{NH}_2\) functionality attached to pyrimidine moiety, to study the effect of such groups of biological activities. The reaction was brought about by reacting hydrazide 3
with formic acid acetic anhydride respectively, which has been discussed in the following pages:

\[ b) \textbf{Synthesis } N-(8\text{-bromo-4-oxo}[1]\text{benzofuro}[3,2-d]\text{pyrimidin-3(4H)-yl)} \text{formamide } 6 \]

The conversion of carbohydrazide \( 3 \) into \( N-(8\text{-bromo-4-oxo}[1]\text{benzofuro}[3,2-d]\text{pyrimidin-3(4H)-yl})\text{formamide } 6 \) was realized by treating carbohydrazide \( 3 \) with formic acid (Scheme 2.1h).

\[
\begin{array}{c}
\text{Br} \quad \text{NH}_2 \\
\text{O} \\
\text{H}
\end{array}
\quad \xrightarrow{\text{HCOOH, } \Delta} \quad
\begin{array}{c}
\text{Br} \\
\text{NH} \\
\text{O} \\
\text{CHO}
\end{array}
\]

\textbf{Scheme 2.1h}

The mechanism of the above reaction probably involved formation of two C-N bonds, followed intramolecular cyclization with the removal of three molecules of water as shown in the Scheme 2.1i.

\[
\begin{array}{c}
\text{Br} \quad \text{NH}_2 \\
\text{O} \\
\text{H}
\end{array}
\quad \xrightarrow{\text{HCOOH, } \Delta} \quad
\begin{array}{c}
\text{Br} \\
\text{NH} \\
\text{O} \\
\text{CHO}
\end{array}
\]

\textbf{Scheme 2.1i}

The spectral data supported the formation of the compound \( 6 \). The IR spectrum (Figure 2.5a) exhibited two absorption bands at 1703 cm\(^{-1}\) and 1699 cm\(^{-1}\) due stretching frequencies of to ring carbonyl and formyl carbonyl groups respectively.
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The $^1$H NMR spectrum (Figure 2.5b) displayed two singlets; one D$_2$O exchangeable singlet at $\delta$ 8.2 due to –NH proton and another singlet at $\delta$ 11.6 due to aldehydic proton. The four aromatic protons appeared as a multiplet between $\delta$ 7.8 and $\delta$ 8.5. The appearance of molecular ion peak at m/z 310 (M$^+$) along with isotopic peak at m/z 312 (M+2)$^+$ in its mass spectrum (Figure 2.5c) provided an additional evidence for the proposed structure.


Similarly, the introduction of methyl ketone group was achieved by treating hydrazide 3 with acetic anhydride. The product obtained (Scheme 2.1j) was identified as $N$-(8-bromo-2-methyl-4-oxo[1]benzofuro[3,2-d]pyrimidin-3(4H)-yl)acetamide 7 on the basis of spectral studies. The reaction not only resulted in introduction of –COCH$_3$ group but also resulted in introduction of methyl group at C-2 of pyrimidine ring as shown in Scheme 2.1j.

![Scheme 2.1j](image)

Its IR spectrum (Figure 2.6a) showed absorption bands at appropriate frequencies. The compound 7 show absorption bands at 3504 cm$^{-1}$, 3155 cm$^{-1}$ and 2977 cm$^{-1}$ due to stretching frequencies of –NH and –CH$_3$ groups. The broad absorption band appeared at 1719 cm$^{-1}$ is due to carbonyl groups.

The $^1$H NMR spectrum (Figure 2.6b) of the compound 7 exhibited two singlets at $\delta$ 2.1 and $\delta$ 2.4 integrating for three protons each, which were attributed to –COCH$_3$ and -CH$_3$ group. A D$_2$O exchangeable singlet at $\delta$ 11.2 was assigned to –NH proton. The
peaks at δ 8.2 and δ 7.8 integrated for the three protons of the aromatic system. The mass spectrum (Figure 2.6c) also supported the structure of the compound 7 by exhibiting the molecular ion peak at m/z 336 (M)^+ and isotopic molecular ion peak at m/z 338 (M+2)^+ corresponds to the molecular weight of the expected compound.

The probable mechanism of this reaction is similar to that of formylation reaction (Scheme 2.1k).

![Scheme 2.1k](image)

It was thought of to utilize the compound 7 for the synthesis of 3-amino-8-bromo-2-methyl[1]benzofuro[3,2-Δ]pyrimidin-4(3H)-one 8, which could be employed for ribosylation. However, attempts to hydrolysis the compound 7 under different reaction conditions were futile (Scheme 2.11).

![Scheme 2.11](image)
2.1b. Experimental

Melting points were determined with an open capillary melting point apparatus and are uncorrected. Purity of the compounds was checked by TLC on silica gel. The IR spectra were recorded on a Nicolet Impact 410 FT-IR Spectrophotometer, using KBr pellets. $^1$H NMR and $^{13}$C NMR spectra were recorded on a Bruker-400 MHz spectrometer and Bruker-100 MHz respectively in DMSO or CDCl$_3$ using TMS as an internal standard. High-resolution mass spectra (HRMS-ESI) were obtained on a MicroTM Q-TOF Mass Spectrometer. All reagents were AR grade or chemically pure.

Synthesis of ethyl 3-amino-5-bromobenzofuran-2-carboxylate 2:

The mixture of compound 1 (1.98 g, 0.01 mole), ethyl chloroacetate (1 ml, 0.01 mole) and potassium carbonate (2.76 g, 0.02 mole) in DMF (10 ml) was refluxed for 90 min. Potassium carbonate was removed by filtration. Filtrate was added to crushed ice with constant stirring. The solid that separated was filtered, dried and recrystallized from ethanol.

Synthesis of 3-amino-5-bromo-1-benzofuran-2-carbohydrazide 3:

Ethyl 3-amino-5-bromobenzofuran-2-carboxylate 2 (2.84 g, 0.01 mole) and hydrazine hydrate (4 ml, 99%) was taken in round bottomed flask and refluxed in ethanol (20 ml) on a steam bath for about 3 hrs and the progress of the reaction was monitored by TLC. The reaction mixture was cooled thoroughly and colorless solid that separated was collected by filtration. It was recrystallized from ethanol as colorless thin needles.

Synthesis of ethyl (8-bromo-4-oxo[1]benzofuro[3,2-d]pyrimidin-3(4H)-yl) imidoformate 4:
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The mixture of 3-amino-5-bromo-1-benzofuran-2-carbohydrazide 3 (0.5 g) and excess of triethyl orthoformate (5 ml) was refluxed for about 5 hrs. The excess of triethyl orthoformate was removed by vacuum distillation. The solid that separated was filtered and recrystallized from methanol.

Synthesis of 3-amino-8-bromo[1]benzofuro[3,2-d]pyrimidin-4(3H)-one 5:

The mixture of compound 4 (3.36 g, 0.01 mole) and hydrazine hydrate (1 ml, 0.02 mole) refluxed in ethanol (30 ml) for about 2 hrs. The reaction mixture was cooled and solid separated was filtered, washed with cold alcohol and recrystallized from alcohol.

Synthesis of N-(8-bromo-4-oxo[1]benzofuro[3,2-d]pyrimidin-3(4H)-yl)formamide 6:

3-Amino-5-bromo-1-benzofuran-2-carbohydrazide 3 (0.5 g) was refluxed for 1 hr with excess of formic acid (5ml). The reaction mixture was cooled and added to crushed ice with constant stirring. Solid separated was filtered and recrystallized from ethanol.

Synthesis of N-(8-bromo-2-methyl-4-oxo[1]benzofuro[3,2-d]pyrimidin-3(4H)-yl)acetamide 7:

The mixture of 3-amino-5-bromo-1-benzofuran-2-carbohydrazide 3 (0.5 g) and excess of acetic anhydride (5 ml) was refluxed for 1 hr. The excess of acetic anhydride was removed by vacuum distillation. The pasty mass obtained was added to ice cold water with constant stirring. Solid separated was filtered and recrystallized from ethanol.

The various spectra of selected compounds have been reproduced in Figure 2.1a to 2.6c.
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Figure 2.1a: IR spectrum of compound 2

Figure 2.1b: $^1$H NMR spectrum of compound 2
Figure 2.1c: $^{13}$C NMR spectrum of compound 2

Figure 2.1d: Mass spectrum of compound 2
Figure 2.2a: IR spectrum of compound 3

Figure 2.2b: $^1$H NMR spectrum of compound 3

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User Spectra

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<th>Fragmentor Voltage</th>
<th>Collision Energy</th>
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<tr>
<td>175</td>
<td>0</td>
<td>ESI</td>
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$^+\text{ESI Scan (0.475 min) Frag}=175.0\text{V GP-Brhy.d}$

Figure 2.2c: Mass spectrum of compound 3

![Mass spectrum of compound 3](image)

Figure 2.3a: IR spectrum of compound 4

![IR spectrum of compound 4](image)
Figure 2.3b: $^1$H NMR spectrum of compound 4

Figure 2.3c: Mass spectrum of compound 4
Figure 2.4a: IR spectrum of compound 5

Figure 2.4b: $^1$H NMR spectrum of compound 5
**Figure 2.4c: Mass spectrum of compound 5**

**Figure 2.5a: IR spectrum of compound 6**
Figure 2.5b: $^1$H NMR spectrum of compound 6

Figure 2.5c: Mass spectrum of compound 6
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Figure 2.6a: IR spectrum of compound 7

Figure 2.6b: $^1$H NMR spectrum of compound 7
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Figure 2.6c: Mass spectrum of compound 7
Section 2.2

Synthesis of 3-amino-8-bromo[1]benzofuro[3,2-\(d\)]pyrimidine-2,4(1\(H\), 3\(H\))-dione
2.2a. Present work

Uracil is a heterocyclic base associated with both ribonucleic acid and deoxyribonucleic acid.

To mimic uracil ring system in the synthesis of base modified nucleosides, it was thought of to incorporate uracil type of nucleus along with benzofuran. 3-Amino-8-bromo[1]benzofuro[3,2-\(d\)]pyrimidine-2,4(1\(H\), 3\(H\))-dione 12 was found most suitable for connecting ribose moiety at \(-\text{NH}_2\) group. It was planned to utilize ethyl 3-amino-5-bromo-1-benzofuran-2-carboxylate 2 to bring about the synthesis of desired compound 12 involving following sequence of reactions (Scheme 2.2)

Therefore it was planned to synthesize compound 12 in two steps:

**Step 1:** Synthesis of ethyl 5-bromo-3-[(ethoxycarbonyl)amino]-1-benzofuran-2-carboxylate 9 from ethyl 3-amino-5-bromo-1-benzofuran-2-carboxylate 2.

**Step 2:** Reaction of diester 9 with hydrazine hydrate.

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Step 1: Synthesis of ethyl 5-bromo-3-[(ethoxycarbonyl)amino]-1-benzofuran-2-carboxylate 9 from ethyl 3-amino-5-bromo-1-benzofuran-2-carboxylate 2

Synthesis of diester 9 was accomplished by reacting monoester 2 with ethyl chloroformate in presence of weak base, potassium carbonate (Scheme 2.2a). The reaction occurred smoothly and produced the desired compounds in good yield.

\[
\begin{align*}
\text{NH}_2 & \quad \text{COOEt} \\
\text{Br} & \quad \text{ClCOOEt, K}_2\text{CO}_3 \\
\text{Acetone, } \Delta, 6 \text{ hrs} & \quad \text{NH} & \quad \text{COOEt} \\
\text{2} & \quad \text{9}
\end{align*}
\]

Scheme 2.2a

The IR, \(^1\text{H NMR}, \text{C}^13\text{ NMR}\) and mass spectra were recorded to prove the structure diester 9. The structure also confirmed by single crystal X-ray study, which has been discussed in Chapter 7 of this thesis.

The IR spectrum (Figure 2.7a) of compound 9 exhibited the absorption bands at 3322 cm\(^{-1}\), 2983 cm\(^{-1}\) and 2930 cm\(^{-1}\) due to –NH, –CH\(_2\) and –CH\(_3\) group stretching frequencies. The absorption bands at 1707 cm\(^{-1}\) and 1616 cm\(^{-1}\) were attributed to the presence of carbonyl groups in the molecule. The \(^1\text{H NMR}\) spectrum (Figure 2.7b) of this compound exhibited the broad singlet at \(\delta 8.6\) due to –NH proton and the peaks at \(\delta 8.6, \delta 7.5\) and \(\delta 7.3\) were due to three aromatic protons. Two sets of triplet and quartet were observed at \(\delta 1.3, \delta 1.4\) and \(\delta 4.3, \delta 4.4\) due to the protons of –CH\(_2\)-CH\(_3\) group of two ester groups. The \(^13\text{C NMR}\) spectrum (Figure 2.7c) of the compound also supports the structure of compound 9 by displaying the peaks at \(\delta 14.50, \delta 14.58, \delta 61.8\) and \(\delta 62.4\) were due to the pair of –CH\(_2\) and –CH\(_3\) of ethyl ester groups. The remaining peaks at \(\delta 113, \delta 116, \delta 122, \delta 128, \delta 130, \delta 130.4, \delta 132\), and \(\delta 153\) were due to the aromatic carbon atoms and \(\delta 153.3, \delta 161.2\) were due to the two carbonyl groups in the compound.
9. To confirm the structure, the mass spectrum (Figure 2.7d) of the compound 9 was recorded, which showed molecular ion peak and isotopic molecular ion peak with equal intensity at m/z 356 (M\(^+\)) and m/z 358 (M+2\(^+\)) corresponding to molecular weight of the compound.

**Step 2: Reaction of diester 9 with hydrazine hydrate**

In order to obtain 3-amino-8-bromo[1]benzofuro[3,2-(5f]pyrimidine-2,4(1H,3H)-dione 12, the diester 9 was reacted with excess of hydrazine hydrate using ethanol as a solvent and acetic acid as a catalyst for 1 hr. The reaction took place very easily and resulted in the formation of solid product. However, study of spectral data indicated that the product obtained was not the anticipated benzofuropyrimidine derivative 12, but was ethyl [5-bromo-2-(hydrazinocarbonyl)-1-benzofuran-3-yl]carbamate 10 (Scheme 2.2b).

![Scheme 2.2b](image)

The IR spectrum (Figure 2.8a) of the compound 10 exhibited the broad absorption bands at 3280 cm\(^{-1}\), 3067 cm\(^{-1}\) and 2983 cm\(^{-1}\) due to stretching frequencies of \(-\text{NH}, -\text{NH}_2, -\text{CH}_2\) and \(-\text{CH}_3\) groups respectively. The absorption band at 1740 cm\(^{-1}\) was due to the stretching frequency of carbonyl group. The structure of this compound was supported by \(^1\text{H NMR}\) spectrum (Figure 2.8b) which exhibited the broad peaks at \(\delta 9.0, \delta 7.6\) and \(\delta 4.0\) were assignable for the \(-\text{NH}\) of hydrazide group, \(-\text{NH}\) attached to ester group and \(-\text{NH}_2\) group respectively. The peaks at \(\delta 8.6, \delta 7.5, \delta 7.2\) were attributed to
aromatic protons. The quartet at \( \delta 4.3 \) and triplet at \( \delta 1.3 \) were assignable to the ethyl of ester group. The mass spectrum (Figure 2.8c) showed molecular ion peak at \( m/z \) 342 \((M)^+\) and isotopic molecular ion peak at \( m/z \) 344 \((M+2)^+\) with equal intensity corresponding to the molecular weight of the compound 10 confirmed the structure.

This observation, forced us to carry out reaction of compound 9 with hydrazine hydrate under different reaction conditions. The reaction was carried out in ethanol without using catalyst. In this reaction also the well defined solid was obtained. However, even in this case benzofuropyrimidine 12 was not obtained, instead the product was identified as 9-bromo-3,4-dihydro-\(1H\)-[1]benzofuro[3,2-e][1,2,4]triazepine-2,5-dione 11 (Scheme 2.2c).

\[
\begin{align*}
\text{NH}_2\text{NH}_2\text{H}_2\text{O} & \quad \text{EtOH, } \Delta \\
9 & \quad \text{COOEt} \\
\text{Br} & \quad \text{COOEt} \\
\text{NH} & \quad \text{COOEt} \\
\text{Br} & \quad \text{COOEt} \\
11 & \quad \text{NH}_2\text{NH}_2\text{H}_2\text{O}
\end{align*}
\]

Scheme 2.2c

The IR spectrum (Figure 2.9a) of the compound 11 displayed two broad absorption bands at 3300 cm\(^{-1}\), 3200 cm\(^{-1}\) due to two -NH groups, and absorption band at 1674 cm\(^{-1}\) due to carbonyl groups. The \(^1\)H NMR spectrum (Figure 2.9b) exhibited a broad singlet at \( \delta 6.4 \) integrating for three protons of three -NH groups of seven membered ring. The peaks at \( \delta 7.6 \) and \( \delta 8.0 \) were attributed to three aromatic protons.

The synthesis of benzofuropyrimidine derivative 12 was successful only when the reaction between diester 9 was carried out with hydrazine hydrate using 2-butanol as a solvent (Scheme 2.2d).
Identity of compound 12 was established by its IR, $^1$H NMR and mass spectral studies.

The IR spectrum (Figure 2.10a) of the compound 12 showed the absorption bands 3475 cm$^{-1}$, 3337 cm$^{-1}$, 1710 cm$^{-1}$ and 1660 cm$^{-1}$ due to the stretching frequencies of $-\text{NH}$ and $-\text{NH}_2$ carbonyl groups respectively. The $^1$H NMR spectrum (Figure 2.10b) supported the structure of the compound 12 which exhibited the broad singlet peaks at $\delta$ 12.4 and $\delta$ 5.5 assignable for the $-\text{NH}$ and $-\text{NH}_2$ groups. The peaks at $\delta$ 7.7 and $\delta$ 8.1 integrated for three protons of aromatic system.

The mechanism of the formation of the products 11 and 12 is as shown in Scheme 2.2e. The initial step of the mechanism involves the attack of hydrazine hydrate on carbonyl carbon atom of ester group at C-2 of benzofuran nucleus resulting in the formation of compound 10. It further undergoes cyclization via two pathways. In path a, lone pair of electrons on N-1 of hydrazide 10 attacks carbonyl carbon of ester group to give compound 12 where as in the path b, the lone pair of electron on N-2 at attacks carbonyl carbon atom of ester group to produce compound 11.
2.2b. Experimental

Synthesis of ethyl 5-bromo-3-carbethoxyaminobenzofuran-2-carboxylate (9):

The mixture of ethyl 3-amino-5-bromo-2-benzofurancarboxylate 2 (2.84 g, 0.01 mole), anhydrous potassium carbonate (2.76 g, 0.02 mole) and ethyl chloroformate (5 ml, 0.05 mole) in dry acetone (30 ml) was refluxed for about 8 hrs. The reaction mixture was filtered and potassium salts were washed with acetone. The filtrate on removal of acetone furnished the compound 9 as colorless solid. It was recrystallized from aqueous ethanol.

Synthesis of ethyl [5-bromo-2-(hydrazinocarbonyl)-1-benzofuran-3-yl]carbamate (10):

The mixture of ethyl 5-bromo-3-[(ethoxycarbonyl)amino]-1-benzofuran-2-carboxylate 9 (3.56 g, 0.01 mole) hydrazine hydrate (99%) (5 ml, 0.10 mole) and few drops of acetic acid in ethanol was stirred at room temperature for 1 hr. Reaction was monitored by TLC. Then added to crushed ice and solid separated was filtered and dried.
Chapter 2

Synthesis of 9-bromo-3,4-dihydro-1H-[1]benzofuro[3,2-e][1,2,4]triazepine-2,5-dione (11):

The mixture of 5-bromo-3-[(ethoxycarbonyl)amino]-1-benzofuran-2-carboxylate 9 (3.56 g, 0.01 mole), hydrazine hydrate (99%) (1 ml, 0.02 mole) in ethanol (10 ml) was refluxed for about 30-40 min. Reaction was monitored by TLC on cooling the reaction mixture, solid separated which was filtered and dried. Recrystallized from alcohol.


Ethyl 5-bromo-3-carbethoxyaminobenzofuran-2-carboxylate 9 (3.56 g) was refluxed with hydrazine hydrate (99%) (1 ml, 0.02 mole) in 2-butanol (20 ml) was refluxed for about 1 hr. Reaction was monitored by TLC. The product that separated as solid on cooling was filtered and dried and recrystallized from alcohol.

The spectra of synthesized compounds have been depicted in Figure 2.7a to 2.10c.
Figure 2.7a: IR spectrum of compound 9

Figure 2.7b: $^1$H NMR spectrum of compound 9
Figure 2.7c: $^{13}$C NMR spectrum of compound 9

Figure 2.7d: Mass spectrum of compound 9
Figure 2.8a: IR spectrum of compound 10

Figure 2.8b: $^1$H NMR spectrum of compound 10
Chapter 2

Figure 2.8c: Mass spectrum of compound 10

Figure 2.9a: IR spectrum of compound 11
Figure 2.9b: $^1$H NMR spectrum of compound 11

Figure 2.9c: $^{13}$C NMR spectrum of compound 11
Figure 2.9d: Mass spectrum of compound 11

Figure 2.10a: IR spectrum of compound 12
Figure 2.10b: $^1$H NMR spectrum of compound 12

Figure 2.10c: Mass spectrum of compound 12
Section 2.3

Synthesis of 3-amino-8-bromo-2-thioxo-2,3-dihydro[1]benzofuro[3,2-\textit{d}]pyrimidin-4(1\textit{H})-one
2.3a. Present work

The ring system containing both -C=O and -C=S have gained importance owing to their wide range of biological and pharmacological activities. As described in the introduction part, Chenko\(^{38}\) reported the synthesis of compound 28.

\[
\text{\begin{center}
\includegraphics[width=0.5\textwidth]{compound_28.jpg}
\end{center}}
\]

Hence, it was thought interesting to construct pyrimidine nucleus on furan moiety of benzofuran containing -C=O and -C=S functionalities.

To achieve this synthesis, two methodologies came to our mind. First methodology involved reaction of 3-amino-5-bromo-1-benzofuran-2-carboxyhydrazide 3 with thiourea using N, N-dimethyl formamide as a solvent (Scheme 2.3a). This reaction resulted in the formation of desired compound 3-amino-8-bromo-2-thioxo-2,3-dihydro[1]benzofuro[3,2-\textit{d}] pyrimidin-4(1\textit{H})-one 13.

\[
\text{\begin{center}
\includegraphics[width=0.5\textwidth]{scheme_2.3a.png}
\end{center}}
\]

**Scheme 2.3a**

In another methodology compound 3 was reacted with carbon disulphide in presence of potassium hydroxide and ethanol. However, this reaction instead of producing desired compound 13 gave isomeric compound which was identified as 5-(3-amino-5-bromo-1-benzofuran-2-yl)-1,3,4-oxadiazole-2-thiol 14 on the basis of spectral studies (Scheme 2.3b).
Both these compounds displayed molecular ion peaks at m/z 312 (M)$^+$ and isotopic peak at m/z 314 (M+2)$^+$ (Figure 2.11c and Figure 2.12c).

The structural assignment to the compounds 13 and 14 was mainly based upon their IR spectra. The IR spectrum of compound 13 (Figure 2.11a) exhibited predominate absorption bands at 1704 cm$^{-1}$ and 1641 cm$^{-1}$ due to stretching frequencies of -C=O and -C=S of pyrimidine ring. Whereas IR spectrum of compound 14 (Figure 2.12a) displayed only one absorption band at 1641 cm$^{-1}$ which can be attributed to the tautomeric existence of compound 14 as follows:

The $^1$H NMR spectra of these compounds exhibited signals at different chemical shift values. The $^1$H NMR spectrum of compound 13 (Figure 2.11b) displayed a D$_2$O exchangeable singlet at $\delta$ 5.04 due to-NH$_2$ protons, whereas singlet due to -NH appeared at $\delta$ 8.4. The three aromatic protons appeared between $\delta$ 7.4 and $\delta$ 8.2. On the another hand $^1$H NMR spectrum of compound 14 (Figure 2.12b) exhibited a D$_2$O exchangeable singlet at $\delta$ 6.1 due to -NH$_2$ protons of benzofuran ring. The spectrum was conspicuous by appearance of a singlet at downfield at $\delta$ 14.7 due to -SH proton. Aromatic protons resonated at $\delta$ 7.25 to $\delta$ 8.22.
2.3b. Experimental


Compound 3 (2.70 g, 0.01 mole) was refluxed with thiourea (2.28 g, 0.03 mole) in N,N-dimethyl foramide (10 ml) for about 5 hrs. Reaction was monitored by TLC. The reaction mixture was cooled and added to crushed ice and solid separated was filtered, dried and recrystallized fro alcohol.

Synthesis of 5-(3-amino-5-bromo-1-benzofuran-2-yl)-1,3,4-oxadiazole-2-thiol (14):

Compound 3 (2.70 g, 0.01 mole) was dissolved ethanol (20 ml). The solution thus obtained was heated with aqueous potassium hydroxide (10 %, 2 ml) for about 10 min then carbon disulphide (2.4 ml, 0.04 mole) was added and refluxed for 3 hrs. The cooled reaction mixture was poured on to crushed ice with stirring and neutralized with dilute HCl. The product that separated as a solid was collected by filtration and recrystallized from methanol.

The spectra of compounds 13 and 14 are depicted in Figure 2.11a to Figure 2.12c.
Figure 2.11a: IR spectrum of compound 13

Figure 2.11b: $^1$H NMR spectrum of compound 13
Figure 2.11c: Mass spectrum of compound 13

Figure 2.12a: IR spectrum of compound 14
Chapter 2

Figure 2.12b: $^1$H NMR spectrum of compound 14

Figure 2.12c: Mass spectrum of compound 14
Section 2.4

Synthesis of ethyl [(8-bromo-4-oxo-3,4-dihydro[1] benzofuro[3,2-\(d\)pyrimidin-2-yl)sulfanyl]acetate
2.4a. Present work

Ribosylation of modified base 13 could occur at three different sites Viz., at –NH₂, at –NH or at tautomeric –SH.

![Diagram of structures 13 and 13a]

To avoid the ambiguity of ribosylation, it was thought of to protect –SH group. This protection was accomplished by using sequence of reactions as shown in Scheme 2.4.

![Scheme 2.4]

The conversion of ethyl 3-amino-5-bromo-1-benzofuran-2-carboxylate 2 into ethyl 5-bromo-3-[(chloroacetyl)amino]-1-benzofuran-2-carboxylate 15 was straightforward reaction, which was achieved by treating 2 with chloro acetyl chloride and triethyl amine in 1,4-dioxane as shown in Scheme 2.4a.

![Scheme 2.4a]
To confirm the structure assigned to compound 15, the IR, $^1$H NMR and mass spectra were recorded. The IR spectrum (Figure 2.13a) of the compound exhibited absorption bands at 3264 cm$^{-1}$, 3112 cm$^{-1}$, 2995 cm$^{-1}$, 2960 cm$^{-1}$ and 1675 cm$^{-1}$ due to the $-\text{NH}$, $-\text{C-H}$, $-\text{CH}_{2}$, $-\text{CH}_{3}$ and $-\text{C=O}$ stretching frequencies. The $^1$H NMR spectrum (Figure 2.13b) of this compound exhibited a singlet at $\delta$ 10.2, a quartet at $\delta$ 4.5, singlet at $\delta$ 4.2 and a triplet at 1.4 assignable for the $-\text{NH}$, ester $-\text{CH}_{2}$, $-\text{CH}_{2}$ attached to Cl atom and ester $-\text{CH}_{3}$ group respectively. The peaks at $\delta$ 7.3, $\delta$ 7.5 and $\delta$ 8.5 integrating for the three protons were due to the aromatic protons. The mass spectrum (Figure 2.13c) showed the molecular ion peak and isotopic molecular ion peak with equal intensity at m/z 360 (M)$^+$ and m/z 362 (M+2)$^+$ were corresponding to molecular weight of the desired compound 15.

The synthesis of desired modified base i.e., ethyl [(8-bromo-4-oxo-3,4-dihydro[1]benzofuro[3,2-d] pyrimidin-2-yl)sulfanyl]acetate 16 was accomplished by the refluxing the mixture of compound 15 and potassium thiocyanate in ethanol as shown in Scheme 2.4b.

![Scheme 2.4b](image)

The IR spectrum (Figure 2.14a) having the absorption bands at 3237 cm$^{-1}$, 3067 cm$^{-1}$, 2975 cm$^{-1}$, 2819 cm$^{-1}$, 1738 cm$^{-1}$ and 1690 cm$^{-1}$ due to the $-\text{NH}$, $-\text{C-H}$, $-\text{CH}_{2}$, $-\text{CH}_{3}$ and carbonyl stretching frequencies supported the structure assigned to the compound. The $^1$H NMR spectrum (Figure 2.14b) provided additional evidence to the assigned to
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the structure of the compound 16. It exhibited a broad singlet at δ 13.3 for –NH proton, a peaks at δ 7.9 to δ 7.8 integrating for three protons of aromatic system, the quartet at δ 4.1 and triplet at δ 1.2 for the –CH₂ and –CH₃ groups of ethyl ester. The –CH₂ group situated in between ester and the sulphur atom in structure 16 showed a singlet at δ 4.1 and merged with ester methylene group which is having the similar shielding capability.

To confirm the structure, the mass spectrum (Figure 2.14c) of the compound 16 was recorded, which showed molecular ion peak and isotopic molecular ion peak with equal intensity at m/z 384 (M⁺) and m/z 385 (M+2)⁺ corresponding to molecular weight.

The mechanism of formation of the desired product 16 was as shown Scheme 2.4c.
2.4b. Experimental

Synthesis of ethyl 5-bromo-3-[(chloroacetyl)amino]-1-benzofuran-2-carboxylate (15):

A mixture of ethyl 3-amino-5-bromobenzofuran-2-carboxylate 2 (2.84 g, 0.01 mole), chloro acetyl chloride (1.31 ml, 0.01 mole) and triethyl amine (1.35 ml, 0.01 mole) in 1,4-dioxane (20 ml) was refluxed for 2 hrs. The reaction was monitored by TLC. The reaction mixture was cooled, added to crushed ice with constant stirring. The solid separated was filtered, dried and recrystallized from alcohol.


A mixture of compound 15 (3.60 g, 0.01 mole), potassium thiocyanate (1.45 g, 0.015 mole) in ethanol (20 ml) was refluxed for 10 hrs. The reaction mixture was cooled and added to crushed ice with constant stirring and pH=4 was maintained using dilute HCl. The solid separated was filtered, washed with water and dried.

The spectra of compounds 13 and 14 were shown in Figure 2.13a to Figure 2.14c.
Figure 2.13a: IR spectrum of compound 15

Figure 2.13b: $^1$H NMR spectrum of compound 15
Figure 2.13c: Mass spectrum of compound 15

Figure 2.14a: IR spectrum of compound 16
Figure 2.14b: $^1$H NMR spectrum of compound 16

Figure 2.14c: Mass spectrum of compound 16
The physical and analytical data of synthesized compounds is presented in Table 2.

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*Isolated yield
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References


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