CHAPTER 2

Synthesis and biological evaluation of tetrahydro pyrimidine derivatives

2.1 Introduction

Pyrimidine (1) is a six membered heterocyclic compound consisting of two nitrogen atoms at one and three positions of heterocyclic ring.

![Pyrimidine structure](image)

Generally pyrimidine derivatives such as 2-hydroxy-substituted pyrimidine, 2-mercapto-substituted pyrimidine and 2-amino-substituted pyrimidine are studied. Pyrimidines have been isolated from the nucleic acid hydrolysates. Pyrimidines are among those molecules that make life possible, have been some of the building blocks of DNA and RNA. Several analogues of pyrimidines have been used as compounds that interfere with the synthesis and functioning of nucleic acids e.g. fluorouracil, which has been used in cancer treatment. Also there are some thiouracil derivatives, which produce adverse reduction in susceptible patients and found more potent and less likely to produce side effects and is being widely used. There are several other important groups of pyrimidines with medicinal uses. Pyrimidine ring carrying various substituents may be built up from two or three aliphatic fragments by the principle synthesis or by a variety of other syntheses,
which are complimentary rather than alternative to it. An alternative method of synthesis
is the isomerisation or break down of another heterocyclic such as hydration of purine,
but such methods are rarely used.

![Figure-2.2]

**Figure-2.2**

![Figure-2.3]

**Figure-2.3**

Pyrimidine is best considered as a resonance hybrid to which the uncharged equivalent
Kekule structures 2 and 2a and charged structures 2b and 2g contributes. The self
consistent \( \pi \) (pi) electron densities required for the ground state of pyrimidine are 0.776,
0.825 and 1.103 for positions 2, 4 and 5 respectively\(^\text{12}\).

The first primary production from aliphatic compound was conceded by Frankland et.al.
in 1848. While many distinct primary synthetic methods have been devised\(^\text{1, 3-5, 9, 11, 14, 16,}
17, 20\). Pyrimidine compound also prepare from other heterocyclic compound. Such as
pyrrole\(^\text{2}\), imidazole\(^\text{6}\), isoxazole and oxazole\(^\text{8, 10}\), pyridine\(^\text{18}\), pyrazine\(^\text{19}\), 1, 3, 5 triazine\(^\text{13}\),
oxazine\(^\text{15}\), thiazine\(^\text{21}\) by different processes.
2.2 Synthetic methods for pyrimidines

Various methods for synthesis of pyrimidines which are reported in the literatures are as follows.

a) By the condensation of urea and malonic acid led to formation of Pyrimidine\textsuperscript{24}.

b) By the condensation of malonic ester and urea led to formation of Pyrimidine\textsuperscript{25}.

c) By the condensation of formamidine with phenylazomalononitrile led to formation of 4, 5, 6-triaminopyrimidine\textsuperscript{23}.

d) By the condensation of aromatic aldehydes, β-ketoester or substituted β-ketoester with urea or thiourea led to formation of pyrimidines\textsuperscript{22}.

e) By the condensation of thiourea and substituted β-ketoester in presence of sodium ethoxide led to formation of mercaptopyrimidines\textsuperscript{26}.

f) By the condensation of chalcones with dicyandiamide in presence of piperidine led to formation of pyrimidines\textsuperscript{27}.

g) By thermal or microwave irradiation of thiourea and substituted β-ketoester in presence of dimethylformamide led to formation of substituted tetrahydropyrimidines\textsuperscript{28}.

h) One pot synthesis of aromatic aldehydes, β-ketoester or substituted β-ketoester with urea or thiourea led to formation of substituted dihydropyrimidin-2-ones catalysed by CuCl\textsubscript{2}\textsuperscript{29}.

i) One pot synthesis of aromatic aldehydes, β-ketoester or substituted β-ketoester with urea or thiourea led to development of 3,4-dihydro pyrimidin-2-(1H)-ones/thiones under microwave irradiation\textsuperscript{30}.

j) One pot synthesis of aromatic aldehydes, β-ketoester or substituted β-ketoester with urea or thiourea led to development of dihydropyrimidine 2-(1H)-ones initiated by SnCl\textsubscript{2}\textsuperscript{30}.

k) One pot synthesis of aromatic aldehydes, β-ketoester or substituted β-ketoester with urea or thiourea led to formation of dihydropyrimidine-2-(1H)-ones by ecofriendly and solvent free reaction in microwave by CaCl\textsubscript{2}\textsuperscript{31}.
2.2.1 Mechanism

The reaction mechanism of pyrimidine formation can be depicted as under:

Part: I

\[
\begin{align*}
\text{H} & \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad 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chloro-4-(trifluoromethyl)phenyl)-3-oxobutanamide with removal of proton to produce (d).

The intermediate (d) undergoes intramolecular condensation in presence of acid between oxygen of ketone and amino group of urea or thiourea or N-methyl urea to give the cyclised targeted product (e).

**Part: II**

The reaction mechanism of pyrimidine formation can be depicted as under:

![Reaction Mechanism Diagram]

*Figure-2.5*
This mechanism includes the condensation of Benzaldehydes (a) with keto enol of N-(2-chloro-4-(trifluoromethyl)phenyl)-3-oxobutanamide (b) to form intermediate (c) with some similarities to the aldol condensation. Intermediate (c) undergoes dehydration in presence of acid catalyst to produce arylidine (d). The condensation of arylidine (d) with either urea or thiourea to form hemiaminal intermediate (e). Hemiaminal intermediate (e) undergoes intramolecular condensation in presence of acid between oxygen of ketone and amino group of urea or thiourea or guanidine to give cyclised targeted product (f).

2.3 Pharmacological importance of pyrimidines

Numerous pyrimidines are well known drugs for variety of diseases. They may be placed in four categories viz. barbiturates, sulphonamides, antimicrobials and antitumor agents. Uracil, thymine, alloxan, vicine and divicine, cytosine, chroticacid, willardiline, tetradoxine, becimethrian (3), blasticidine (4), cougerotin, amicetin, bamicetin and plicacetin, phleomicine, blemycin and related families (5).

![Figure-2.6](image)

Derivative of pyrimidine have broad variety of usages. Folic acid and Vitamin B2 also contain Pyrimidine ring system. Pyrimidine ring system having a mercapto group occupy a unique position in medicinal chemistry. These types of derivatives play a crucial task in genetic processes and synthetic drugs.

Some of the therapeutic activities of pyrimidine derivatives can be summarized as follows.
I. Antithyroid
II. Antitumor
III. Antihypertensive
IV. Antiinflammatory
V. Diuretic
VI. Antimalarial
VII. Antispasmodic
VIII. Anticonvulsant
IX. Antineoplastic
X. Anthelmintic
XI. Antimicrobial
XII. Cardiovascular
XIII. Antiviral
XIV. Platelet aggregation inhibitor
XV. Antihistamine
XVI. Anti-HIV
XVII. Antitubercular

The medicinal chemistry is any normal drug discovery. Now synthesis of new method for preparing of nucleic acid is intense focus for medicinal chemistry of oligonucleotides. As a result of this, the range of medicinal chemistry has been delayed extremely, but the genetic data of supporting the conclusions about synthetic strategies have just begun to emerge.

In oligonucleotides, some changes in the sugar, phosphate moiety and conjugates reported. The approach of medicinal chemistry to create better similarity and more selective similarity for RNA/duplex structure, the capacity to cut nucleic acid targets, better nuclease stability. Although extensive development in the oligonucleotides made in the past three years, it is not yet possible to reach the conclusion about the therapeutic ability of the novel modifications. Preliminary data on effects on nuclease stability and
hybridization properties for a few modifications and movement *in vitro* propose that the next creation of oligonucleotides display largely better potencies and selectivity.

### 2.3.1 Modified Pyrimidine (nucleotide)

Huge amount of pyrimidine compound synthesized and incorporated in oligonucleotides. The typical sites of variation are Carbon-2, Carbon-4, Carbon-5 and Carbon-6. These and additional nucleoside analogues include newly systematically evaluation.\(^{(123)}\)

![Pyrimidine Structure](image)

**Sites of pyrimidine Modification**

\(^{(6)}\)

In as much as the C\(_2\) place is occupied in hybridization of Watson-Crick, oligonucleotides containing C\(_2\) alkyl modified pyrimidines have shown unsightly hybridization characters. However, 2-thiothymidine in oligonucleotide is create to hybridize excellent to DNA and, actually still superior to RNA with a thermal melting temperature (\(\Delta T_m\)) value of 1.5°C/modification. In a different study, oligoribonucleotides with 2’-o-methyl-2-thiouridine (8) exhibited a thermal melting temperature (\(\Delta T_m\)) value of +5.5°C/modification when hybridized against RNA resulting from a highly preorganized RNA-like C3’-endo conformation (attributed to the combination of 2-thio modification and 2’-o-Me substituent). Oligonucleotides with this modification also exhibit better hybridization discrimination for the wobble uracil-guanosine (U-G) base pair formation compared to the normal uracil-adenine
(U-A) base pair. This selectivity is a result of H-H bonding is weak and increased steric bulk of the thio-carbonyl functional group.\textsuperscript{121}

![Figure-2.7](image)

Figure-2.7

In contrast, the pyrimidine modifications in 4-position with attractive property have been reported. However, recent studies have shown destabilization in the normal uracil-adenine (U-A) base pair formation and stabilization of the wobble uracil-guanosine (U-G) base pair for 4-thiouridine. 4-OMe derivative of cytosine was exposed to hybridize by collectively purine bases in DNA by means of thermal melting temperature values about the same to that of normal base pairs.

![Figure-2.8](image)

Figure-2.8

The pyrimidine modifications at C5 position including halogenated nucleosides have been reported. Even if the strength of duplexes may be improved by addition of 5-halogenated uracil contain nucleosides, the rare impairing by guanidine, probable to the oligonucleotide strength corrupt and liberate toxic compound. Oligonucleotides contain 5-propynyl-pyrimidine (11,12,13) modification have been exposed to improve the duplex stability thermal melting temperature ($\Delta T_m = 1.6^\circ C$/modification), and support R Nase H
movement. 5-heteroaryl pyrimidine was also exposed toward improve the constancy of duplexes. An extra impressive power was reported for the 2’-deoxycytidine analoges, termed phenoxazine, an improvement of 2-5°C/change, depends on the positioning of the adapted bases.\textsuperscript{111}

![Figure-2.9](image)

As predictable, changes in Carbon-6 place of pyrimidine is extremely dupled destabilizing. Oligonucleotides containing 6-azapirimidines (14) have been shown not only to reduce the thermal melting temperature (Tm) value by 1-2°C / change, also to improve the nuclease stability of oligonucleotides and to carry E. coli R Nase H-induce deradation of RNA.\textsuperscript{124}
2.3.2 Pyrimidine modifications (Non-nucleotide)

The increasing interest in the early 1970s in properties and use of interferon (IFN) together with the difficulty in producing useful amounts of interferon (IFN) led to the search for agents that would induce IFN in the host. Preceded at that time for interferon (IFN) inducers included viruses and bacteria wall constituents and entities of large molecular weight such as thepolynucleotides. There were also several examples of low molecular weight substances such as certain antibiotics and the antiviral agent, tilorone. In 1976, it was reported that 6-methyl pyrimidinone induced circulating levels of interferon (IFN) in some animal species upon oral or intraperitoneal management. Subsequent structure-activity studies yielded a more potent and less toxic 6-phenyl analog called ABPP or bropirimine (figure 1 and Table 1). Bropirimine and related 6-aryl analogs were examined extensively for efficacy in virus and tumor models, along with their immunomodulatory properties and overall pharmacological effects.
As with the polynucleotides, the pyrimidinones exhibited significant activity against interferon (IFN) sensitive viruses such as Semliki Forest virus in vivo. However, in addition, they exhibited prophylactic and therapeutic activity upon either local or
systemic administration to rodents infected with a mixture of DNA viruses, the herpes viruses (HSV-1, HSV-2, CMV and pseudorabies), and when administered intranasally for upper respiratory infections, such as infectious bovine rhinorachitis, influenza A and para influenza-3. Particularly interestion activity was noted with bropirimine on intravaginal administration in protection against HSV-2 intravaginal infection in guinea pigs, an important model for genital herpes in humans. Bropirimine also exhibited activity when given either intraperitoneally or orally to mice infected with Listeria monocytogenes. The efficacy in this model was not abrogated by the addition of anti-interferon (IFN) antibody.

2.4 Pyrimidines as antitumour agents

A number of other pyrimidine antagonists displaying antitumour activity, in which the base is conjugated to a modified sugar ring have been reported. Although D-Arabinofuranosyl uridine (ara-uridine) shows no useful activity, and 5-bromo- and 5-iodo-D-arabinofuranosyl uridine inhibit the growth of sarcoma 180 and L1210 cells in culture. Other thymidine analogues with similar activity include 5-azidomethyl-,5-aminomethyl and 5 hydroxymethyl-2’-deoxyuridine. 3’-Amino-3’-deoxy thymidine and 3’-amino-2’,3’-dideoxycytidine also posses strong activity against L1210 leukaemia. FMAU; 15 is highly active against arabinofuranosyl cytidine (ara-C) resistant L1210 and P815 cell lines both in vitro and in vivo. 2-B-D-Ribofuranosylthiazole4 carboxamide (Tiazofurin; 16) has aroused much interest recently for its activity against solid tumour such as lung carcinoma. It is metabolized to an analogue of NAD in which the thiazole-4-carboxamide moiety replaces the nicotinamide ring. However, it also depresses the synthesis of DNA and RNA, and thus merits inclusion as an antagonist of normal purine and pyrimidine metabolism.
2.5 Pyrimidines as anti-hiv agents

The strategy of designing nucleoside analogs that are selective for viral DNA polymerases is the most well-studied and successful approach to viral chemotherapy, and has led to the discovery of several clinically useful antiviral drugs. This strategy, however, has inherent limitations. Human DNA polymerases also require dNTP’s and the chemical mechanisms of polymerization by the viral and human enzymes are similar. Nucleoside analogs often have significant host toxicity that is probably related to inhibition of host cell DNA synthesis. Nevertheless, these compounds constitute the major class of antiviral drugs, and this approach is likely to yield additional active compounds in the near future. For the long term, however, other strategies may ultimately lead to more selective agent with lower toxicity.

Obviously, the key to design analogue with a lower affinity for the host enzyme than the viral enzyme, which requires that there be structural differences between the enzyme active sites. For reverse transcriptase, the most well studied inhibitor is 3’-azido-3’-deoxythymidine (AZT; 17), which is currently used clinically to treat AIDS.\textsuperscript{132-133}
3’-azido-3’-deoxythymidine (AZT) inhibits HIV reverse transcriptase with an IC50 of 40nM115, but is 100-300 times less active against mammalian DNA polymerase α and DNA polymerase γ. The reason for this selectivity is not clear since 3’-azido-3’-deoxythymidine (AZT) is a chain terminator for mammalian DNA polymerases and inhibits normal cellular DNA synthesis.105 Several other dideoxynucleoside analogs have been shown to be strong inhibitors of HIV imitation in vitro.116,120 In general, these compounds have the same mechanism of action as 3’-azido-3’-deoxythymidine (AZT), that is, intracellular conversion to the triphosphate derivative and subsequent inhibition of HIV reverse transcriptase.

Some of these compounds are simply analogs of the natural 2’-deoxy-nucleoside in which the 3’-OH group has been replaced with a hydrogen, such as 2’,3’-dideoxycytidine(18), 2’,3’-dideoxyadenosine(19) and 2’,3’-dideoxy thymidine(20). Other analogs contain a 2’-3’ double bond, such as 2’3’-didehydro-2’,3’-dideoxythymidine(21). Several related analogs with other modifications to the ribose ring or the heterocyclic base moiety have also been reported to have activity against HIV or HIV reverse transcriptase.117, 118
R. A. Nugent et al.\textsuperscript{125} have synthesized pyrimidine thioethers (22) and evaluated for inhibitory properties against wild-type HIV-1 reverse transcriptase.

COX-2 inhibitor describes in trisubstituted pyrimidine. To discover the value of pyrimidine compound as probable NSAIDs. Aurelio Orjales et al.\textsuperscript{126} have prepared new pyrimidine compound (23) and (24).
F. Manetti et al.\textsuperscript{127} have synthesized novel pyrimidines (25) with nanomolar activity toward recombinant HIV-1 and mutant HIV-1 strains.

D. Rotili et al.\textsuperscript{128} have synthesized 6-substituted-[1-(2,6-difluorophenyl)]-pyrimidinones (26,27) and checked in opposition to endogenous, nontelomeric endo-RT in person differentiate cell systems to consider their anti-proliferative action.
R. Stoorer et al.,\textsuperscript{129} have synthesized 3-substituted uracil derivative (28,29) screened for their ability to reduce the reproduction of bacterial dna polymerase IIC and the increase of gram positive microbes in culture.

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{28_29.png}
\caption{Figure-2.18}
\end{figure}

A. Orjales et al.,\textsuperscript{130} have synthesized novel compound of 2-(4- methyl sulfonyl-phenyl) and 2-(4-sulfamoyl-phenyl) pyrimidines (30) and checked their capacity to reduce (COX-2).

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{30.png}
\caption{Figure-2.19}
\end{figure}

Recently, Y. Miyazaki et al.,\textsuperscript{131} have synthesized 4-NH2-5, 6-furo-2,3-d pyrimidines (31) checked their capacity to reduce GSK-3B.
Pyrimidine derivatives as Anti-Microbial Agents: Mosharef Hossain Bhuiyan, et al [132]. Synthesized some new thienopyrimidine derivatives and the newly prepared product was checked their antibacterial action. Out of all synthesized 12 compounds give the good activity of all bacteria as compared to other derivatives. And that compounds was also screened for their antifungal activities against Macrophomina phaseolina, Fusarium equiseti, Alternaria alternate, and Collectotrichum corchori, good against the fungi. Alternate and C. corchori. Nada M. Abunda, et al[133] synthesized a series of a few novel pyrazole, derivatives and some synthesized compounds were checked for antibacterial activity and antifungal activity. The product was checked for their action against gram positive bacteria and gram negative bacteria. The entire checked product showed important activity against E. coli, S. aureus, and C.
Munawar Ali Munawar, et al [134], synthesized a series of quinolinyl-pyrimidine compounds were checked for the antibacterial activity. The property of recently synthesized quinolinyl-pyrimidine compounds on biological checking was found to be moderately low vigorous than the control.

![Figure-2.22](image)

**Figure-2.22**

Gunwanti Malhotra, et al [135] Synthesized new 4-phenyl-5-[3',5'-diaryl-2 pyrazolin-1-yl]-3,4-dihydro-pyrimidine 2-(1H)-ones synthesized by 1-acetyl pyrazoline, urea and aldehydes in presences of N-bromosuccinamide. Newly synthesized product was characterized by their CHNS analysis. S. Gopalakrishnan, et al [136], synthesized, molecular docking and ADME predution of some pyridine and pyrimidine derivatives as Anticoleoctal cancer drugs. In view of procuring highly potent biodynamic agents and after reviewing recent literature survey on oxo / thioxo / iminopyrimidines for their various methods of synthesis and different pharmacological activities.

![Figure-2.23](image)

**Figure-2.23**
2.6 Current Work

From last 100 years pyrimidine and its derivative were studied because of their biological activity. The 1, 2, 3, 4-tetrahydropyrimidines have biological activity because many pharmacological and medicinal application \textit{viz:} antimicrobial and radio protective.

Now think about the range of biomedical applications and the pharmacological report of these group of compounds, three new series of N-(2-chloro-4-(trifluoromethyl)phenyl)-4-(sub-phenyl)-1, 2, 3, 4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide (ND-101 to 145) are synthesized. The synthesis of (ND-101 to 145) was achieved by acid catalysed cyclocondensation of N-(2-chloro-4-(trifluoromethyl)phenyl)-3-oxobutanamide, substituted urea and Benzaldehydes. The compounds were characterized by IR, NMR and CHN analysis. The synthesize products were perform to different biological activities \textit{viz:}, antimicrobial.
2.6.1 Reaction scheme

\[
\begin{align*}
&\text{Cl} & \text{N-CH}_3 & \text{O} & \text{CHO} \\
+ & \text{R} & \text{Cl} & \text{CF}_3 & \text{CHO} \\
& & & \text{Conc. HCl} & \text{N-CH}_3 & \text{O} & \text{NH}_2 \\
\end{align*}
\]

\[\text{R} = \text{OCH}_3, \text{CH}_3, \text{Cl}, \text{F}, \text{Br}, \ldots \text{etc}\]

\[\text{R}_1 = \text{H}\]

\[\text{X} = \text{O}\]

ND-101 to ND-115

\[
\begin{align*}
&\text{Cl} & \text{N-CH}_3 & \text{O} & \text{CHO} \\
+ & \text{R} & \text{Cl} & \text{CF}_3 & \text{CHO} \\
& & & \text{Conc. HCl} & \text{N-CH}_3 & \text{O} & \text{NH}_2 \\
\end{align*}
\]

\[\text{R} = \text{OCH}_3, \text{CH}_3, \text{Cl}, \text{F}, \text{Br}, \ldots \text{etc}\]

\[\text{R}_1 = \text{H}\]

\[\text{X} = \text{S}\]

ND-116 to ND-130

\[
\begin{align*}
&\text{Cl} & \text{N-CH}_3 & \text{O} & \text{CHO} \\
+ & \text{R} & \text{Cl} & \text{CF}_3 & \text{CHO} \\
& & & \text{Conc. HCl} & \text{N-CH}_3 & \text{O} & \text{NH}_2 \\
\end{align*}
\]

\[\text{R} = \text{OCH}_3, \text{CH}_3, \text{Cl}, \text{F}, \text{Br}, \ldots \text{etc}\]

\[\text{R}_1 = \text{CH}_3\]

\[\text{X} = \text{O}\]

ND-131 to ND-145

Figure-2.24
**Chapter: - 2  Tetrahydro Pyrimidine derivatives**

Table 2.1 **Physical Data Table of Series-1**

<table>
<thead>
<tr>
<th>Code</th>
<th>R&lt;sub&gt;1&lt;/sub&gt;</th>
<th>M.F.</th>
<th>M.W.</th>
<th>M.P.&lt;sup&gt;°&lt;/sup&gt;C</th>
<th>Yield %</th>
<th>R&lt;sub&gt;f1&lt;/sub&gt;</th>
<th>R&lt;sub&gt;f2&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>ND-101</td>
<td>2-OCH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>C&lt;sub&gt;20&lt;/sub&gt;H&lt;sub&gt;17&lt;/sub&gt;ClF&lt;sub&gt;3&lt;/sub&gt;N&lt;sub&gt;3&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;</td>
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TLC Solvent system R<sub>f1</sub>:- Hexane: Ethyl acetate – 6:4,

R<sub>f2</sub>: - Chloroform: methanol – 9:1.
## Table 2.2 Physical Data Table of Series-2

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TLC Solvent system R₁₁:- Hexane: Ethyl acetate – 6:4,  
### Table 2.3 Physical Data Table of Series-3

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TLC Solvent system R<sub>f1</sub>: Hexane: Ethyl acetate – 6:4,  
R<sub>f2</sub>: Chloroform: methanol – 9:1.
2.6.2 Plausible Reaction Mechanism

The reaction mechanism of pyrimidine formation can be depicted as under:

\[ \text{Reaction Mechanism Diagram} \]

\[ \text{Figure-2.25} \]
2.6.3 Experimental

2.6.3.1 Materials and Methods

Product formed was determined by TLC analysis and all the compounds melting point were checked. IR, NMR and elemental analysis were done and reported.

2.6.3.2 Synthesis of N-(2-chloro-4-(trifluoromethyl)phenyl)-3-oxobutanamide

Syntheses of N-(2-chloro-4-(trifluoromethyl)phenyl)-3-oxobutanamide were prepare as per process available in literature [137].

2.6.3.3 General procedure for the synthesis N-(2-chloro-4-(trifluoromethyl)phenyl)-4-(sub-phenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide (ND-101 to 115)

Series No 1 from Urea

N-(2-chloro-4-(trifluoromethyl)phenyl)-3-oxobutanamide, Benzaldehydes, urea derivatives (0.015M) and small quantity of HCl in ethyl alcohol (25ml) were heat to 80-85°C for 10 to 12 hrs. After that cool the reaction mixture to 25-35°C for 20 hrs. Crude product was dissolves in ethyl alcohol and reprecipitated to give desire compound.

2.6.3.3.1 N-(2-chloro-4-(trifluoromethyl) phenyl)-4-(2-methoxyphenyl)-1, 2, 3, 4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide (ND-101)
Practical yield: 68%; Melting point 207°C; Molecular formula: C₂₀H₁₇ClF₃N₃O₃ Carbon: 54.62; Hydrogen: 3.90; Chlorine: 8.06; Fluorine: 12.96; Nitrogen: 9.55; Oxygen: 10.91
Obtained Carbon: 54.42; Hydrogen: 3.81; Chlorine: 8.00; Fluorine: 12.90; Nitrogen: 9.55; Oxygen: 10.91%; IR spectra: 3410 (For -NH), 3070 (For -C-H, of Phenyl ring), 1660 (C=O, amide carbonyl stretching), 1600 (N-H, pyrimidine ring), 1525 (C=C, Phenyl ring stretching), 1344 (For -C-N-C of pyrimidine), 1247 (C-O-C, asymmetrical stretching of OCH₃), 1074 (C-F stretching); Mass: 440; 1H NMR (Solvent: DMSO-d₆) δ ppm: 2.28 (s, 3(H), Hᵢ), 3.72 (s, 3(H), Hᵢi), 5.15 (s, 1(H), Hᵢii), 6.87 (s, 1(H), Hᵢv), 6.97-7.14 (m, 2(H), Hᵥ), 7.28-7.30 (d, 2(H), Hᵥi'v), 7.48-7.50 (d, 2(H), Hᵥii'I), 8.37 (s, 1(H), Hᵥiii), 8.44-8.47 (m, 1(H), Hᵢx), 8.90 (s, 1H, Hᵢ).

2.6.3.3.2 N-[2-chloro-4-(trifluoro methyl) phenyl]-4-(3-chlorophenyl)-1, 2, 3, 4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide (ND-102)

Practical yield: 63%; Melting point: 217°C; Molecular formula: C₁₉H₁₄Cl₂F₃N₃O₂; Carbon: 51.37; Hydrogen: 3.18; Chlorine: 15.96; Fluorine: 12.83; Nitrogen: 9.46;
Oxygen: 7.20; Results: Carbon: 51.12; Hydrogen: 3.02; Chlorine: 15.85; Fluorine, 12.49; Nitrogen, 9.23; Oxygen, 7.12%; MS: \(m/z 445\).

3.6.3.3.3 \(N\)-[(2-chloro-4-(trifluoro methyl) phenyl)-4-(2-fluorophenyl)]-1, 2, 3, 4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide (ND-103)

Practical yield: 59%; Melting point: 202°C Molecular formula: \(C_{19}H_{14}ClF_4N_3O_2\); Carbon: 53.35; Hydrogen: 3.30; Chlorine: 8.29; Fluorine: 17.76; Nitrogen: 9.82; Oxygen, 7.48; Results: Carbon: 53.21; Hydrogen: 3.10; Chlorine: 8.08; Fluorine: 17.12; Nitrogen: 9.71; Oxygen: 7.40%; MS: \(m/z 428\).

2.6.3.3.4 \(N\)-[(2-chloro-4-(trifluoro methyl) phenyl)-4-(3, 4 dimethoxyphenyl)]-1, 2, 3, 4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide (ND-104)

Practical yield: 70%; Melting point 212°C; Molecular formula: \(C_{21}H_{19}ClF_3N_3O_4\); Carbon: 53.68; Hydrogen: 4.08; Chlorine: 7.55; Fluorine: 12.13; Nitrogen: 8.94; Oxygen: 13.62;

2.6.3.3.5 \( N-[(2\text{-chloro}-4-(\text{trifluoro methyl}) \text{ phenyl})-4-(\text{methoxyphenyl})]-1, 2, 3, 4\text{-tetrahydro}-6\text{-methyl}-2\text{-oxopyrimidine-5-carboxamide} \) (ND-105)

Practical yield: 75%; Melting point 205ºC; Molecular formula: \( C_{20}H_{17}ClF_3N_3O_3 \); Carbon: 54.62; Hydrogen: 3.90; Chlorine: 8.06; Fluorine: 12.96; Nitrogen: 9.55; Oxygen: 10.91; Results: Carbon: 54.31; Hydrogen: 3.81; Chlorine: 8.00; Fluorine: 12.24; Nitrogen: 9.41; Oxygen, 10.20%; MS: \( m/z \) 440.

2.6.3.3. \( N-[(2\text{-chloro}-4-(\text{trifluoro methyl}) \text{ phenyl})-4-(\text{chlorophenyl})]-1, 2, 3, 4\text{-tetrahydro}-6\text{-methyl}-2\text{-oxopyrimidine-5-carboxamide} \) (ND-106)

Practical yield: 71%; Melting point 224ºC; Molecular formula: \( C_{19}H_{14}Cl_2F_3N_3O_2 \); Carbon: 51.37; Hydrogen: 3.18; Chlorine: 15.96; Fluorine: 12.83; Nitrogen: 9.46;
Oxygen: 7.20; Results: Carbon: 51.20; Hydrogen: 3.03; Chlorine: 15.56; Fluorine: 12.66; Nitrogen: 9.22; Oxygen: 7.10%; MS: \( m/z \ 445 \);

2.6.3.3.7 \( N\)\[-(2\text{-chloro-4-(trifluoro methyl) phenyl})-4-(4-methylphenyl)\]-1, 2, 3, 4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide (ND-107)

![Chemical structure of ND-107](image)

Practical yield: 69%; Melting point 201°C; Molecular formula: \( C_{20}H_{17}ClF_3N_3O_2 \); Carbon: 56.68; Hydrogen: 4.04; Chlorine: 8.37; Fluorine: 13.45; Nitrogen: 9.91; Oxygen: 7.55; Results: Carbon: 56.24; Hydrogen: 4.00; Chlorine: 8.22; Fluorine: 13.24; Nitrogen: 8.5; Oxygen: 7.35%; MS: \( m/z \ 424 \).

2.6.3.3. \( N\)[-[(2-chloro-4-(trifluoro methyl) phenyl)-4-(4-fluorophenyl)\]-1, 2, 3, 4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide (ND-108)

![Chemical structure of ND-108](image)
Chapter: - 2

Tetrahydro Pyrimidine derivatives

Practical yield: 55%; Melting point 195°C; Molecular formula C_{19}H_{14}ClF_{4}N_{3}O_{2}; Carbon: 53.35; Hydrogen: 3.30; Chlorine: 8.29; Fluorine: 17.76; Nitrogen: 9.82; Oxygen: 7.48; Results: Carbon: 53.09; Hydrogen: 3.12; Chlorine: 8.11; Fluorine: 17.23; Nitrogen: 9.45; Oxygen: 7.24%; MS: m/z 428.

2.6.3.3.9 N-[(2-chloro-4-(trifluoro methyl) phenyl)-4-(2-chlorophenyl)]-1, 2, 3, 4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide (ND-109)

![Chemical structure](image1)

Practical yield: 74%; Melting point 187°C; Molecular formula: C_{19}H_{14}Cl_{2}F_{3}N_{3}O_{2}; Carbon: 51.37; Hydrogen: 3.18; Chlorine: 15.96; Fluorine: 12.83; Nitrogen: 9.46; Oxygen: 7.20; Results: Carbon: 51.20; Hydrogen: 3.03; Chlorine: 15.56; Fluorine: 12.66; Nitrogen: 9.22; Oxygen: 7.10%; MS: m/z 445;

2.6.3.3.10 N-[(2-chloro-4-(trifluoro methyl) phenyl)-4-(3, 4-dichlorophenyl)]-1, 2, 3, 4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide (ND-110)

![Chemical structure](image2)
Practical yield: 75%; Melting point 235°C; Molecular formula: C_{19}H_{13}Cl_{3}F_{3}N_{3}O_{2}; Carbon: 47.67; Hydrogen: 2.74; Chlorine: 22.22; Fluorine: 11.91; Nitrogen: 8.78; Oxygen: 6.68; Results: Carbon: 47.43; Hydrogen: 2.34; Chlorine: 22.01; Fluorine: 11.23; Nitrogen: 8.42; Oxygen: 6.12%; MS: m/z 479.

2.6.3.4.11 N-[(2-chloro-4-(trifluoro methyl) phenyl)-4-(3-methoxyphenyl)]-1, 2, 3, 4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide (ND-111)

Practical yield: 68%; Melting point 207°C; Molecular formula: C_{20}H_{17}ClF_{3}N_{3}O_{3}; Carbon: 54.62; Hydrogen: 3.90; Chlorine: 8.06; Fluorine: 12.96; Nitrogen: 9.55; Oxygen: 10.91 Results: Carbon: 54.42; Hydrogen: 3.81; Chlorine: 8.00; Fluorine: 12.90; Nitrogen: 9.55; Oxygen: 10.91%; MS: m/z 440.

2.6.3.4.12 N – [(2-chloro-4-(trifluoro methyl) phenyl)-4-(2, 4-Dimethylphenyl)]-1, 2, 3, 4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide (ND-112)
Practical yield: 58%; Melting point 233°C; Molecular formula: C_{21}H_{19}ClF_{3}N_{3}O_{2}; Carbon: 57.61; Hydrogen: 4.37; Chlorine: 8.10; Fluorine, 13.02; Nitrogen: 9.60; Oxygen: 7.31; Results: Carbon: 57.33; Hydrogen: 4.22; Chlorine: 8.01; Fluorine: 12.56; Nitrogen: 9.13; Oxygen: 7.21%; MS: m/z 438.

2.6.3.4.13 \(N\-\[(2\text{-chloro-4-}(\text{trifluoro methyl}) \text{phenyl})-4\-\text{(4-bromophenyl)}\]-1, 2, 3, 4-\text{tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide (ND-113)}\)

Practical yield: 68%; melting point: 211°C; Molecular formula: C_{19}H_{14}BrClF_{3}N_{3}O_{2}; Carbon: 46.70; Hydrogen: 2.89; Bromine: 16.35; Chlorine: 7.25; Fluorine: 11.66; Nitrogen: 8.60; Oxygen: 6.55; Results: Carbon: 46.61; Hydrogen: 2.75; Bromine: 16.13; Chlorine: 7.11; Fluorine: 11.22; Nitrogen: 8.21; Oxygen: 6.12%; MS: m/z 489.

2.6.3.4.14 \(N\-\[(2\text{-chloro-4-}(\text{trifluoro methyl}) \text{phenyl})-4\-\text{(3-bromophenyl)}\]-1, 2, 3, 4-\text{tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide (ND-114)}\)

Practical yield: 70%; Melting point 200°C; Molecular formula C_{19}H_{14}BrClF_{3}N_{3}O_{2}; Carbon: 46.70; Hydrogen: 2.89; Bromine: 16.35; Chlorine: 7.25; Fluorine: 11.66;
Nitrogen: 8.60; Oxygen: 6.55; Results: Carbon: 46.61; Hydrogen: 2.75; Bromine: 16.13; Chlorine: 7.11; Fluorine: 11.22; Nitrogen: 8.21; Oxygen: 6.12%; MS: \( m/z \) 489.

**2.6.3.4.15 N-[(2-chloro-4-(trifluoro methyl) phenyl)-4-phenyl]-1, 2, 3, 4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide (ND-115)**

![Chemical Structure of ND-115](image)

Practical yield: 67%; melting point 213°C; Molecular formula: \( C_{19}H_{15}ClF_3N_3O_2 \): Carbon: 55.69; Hydrogen: 3.69; Chlorine: 8.65; Fluorine: 13.91; Nitrogen: 10.25; Oxygen: 7.81; Results: Carbon: 55.46; Hydrogen: 3.41; Chlorine: 8.60; Fluorine: 13.81; Nitrogen: 10.10; Oxygen: 7.58%; MS: \( m/z \) 410.

**Series No 2 from Thiourea**

**2.6.3.3.16 N-[2-chloro-4-(trifluoro methyl) phenyl]-4-(2-methoxyphenyl)-6-methyl-2-thioxo-1, 2, 3, 4-tetrahydro pyrimidine-5-carboxamide (ND-116)**

![Chemical Structure of ND-116](image)

Yield: 68%; Melting point 221°C; Molecular formula \( C_{20}H_{17}ClF_3N_3O_2S \): Carbon: 52.64; Hydrogen: 3.72; Chlorine: 7.78; Fluorine: 12.50; Nitrogen, 9.22; Oxygen, 7.02; Sulphur,
7.03 Results: Carbon: 52.58; Hydrogen: 3.68; Chlorine: 7.62; Fluorine: 12.31; Nitrogen: 9.18; Oxygen: 6.89; Sulphur: 7.03%; MS: \( m/z \) 456. 18 IR: 3240, 3140 (For -NH), 2970 (For -C-H, of phenyl ring), 1690 (For -C=O, of carbonyl), 1520(For -C=S), 1074 (For -C-F).

2.6.3.3.17 4-(3-chlorophenyl)-N-[2-chloro-4-(trifluoro methyl) phenyl]-6-methyl-2-thioxo-1, 2, 3, 4-tetrahydro pyrimidine-5-carboxamide (ND-117)

![Chemical structure of compound 4-(3-chlorophenyl)-N-[2-chloro-4-(trifluoro methyl) phenyl]-6-methyl-2-thioxo-1, 2, 3, 4-tetrahydro pyrimidine-5-carboxamide (ND-117)](image)

Practical yield: 65%; Melting point 213°C; Molecular formula \( \text{C}_{19}\text{H}_{14}\text{Cl}_{3}\text{F}_{3}\text{N}_{3}\text{OS} \): Carbon: 49.53; Hydrogen: 3.04; Chlorine: 15.40; Fluorine: 12.38; Nitrogen: 9.12; Oxygen: 3.48; Sulphur: 6.97; Results: Carbon: 49.58; Hydrogen: 3.06; Chlorine: 15.21; Fluorine: 12.11; Nitrogen: 9.18; Oxygen: 3.12; Sulphur: 6.54%; MS: \( m/z \) 460. IR: 3260, 3130 (For -NH), 2960 (For -C-H of phenyl ring), 1692 (For -C=O carbonyl), 1525(For -C=S), 1078 (For -C-F)

2.6.3.3.18 N-[2-chloro-4-(trifluoro methyl) phenyl]-4-(2-fluorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydro pyrimidine-5-carboxamide (ND-118)

![Chemical structure of compound N-[2-chloro-4-(trifluoro methyl) phenyl]-4-(2-fluorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydro pyrimidine-5-carboxamide (ND-118)](image)
Practical yield: 67%; Melting point 201ºC; Molecular formula $\text{C}_{19}\text{H}_{14}\text{ClF}_4\text{N}_3\text{OS}$: Carbon: 51.36; Hydrogen: 3.15; Chlorine: 7.99; Fluorine: 17.12; Nitrogen: 9.46; Oxygen: 3.60; Sulphur: 7.22; Results: Carbon: 51.46; Hydrogen: 3.19; Chlorine: 7.87; Fluorine: 17.10; Nitrogen: 9.38; Oxygen: 3.43; Sulphur, 7.10 %; MS: $m/z$ 444. IR: 3250, 3145 (For $-\text{NH}$), 2975 (For $-\text{C-H}$ of phenyl ring), 1690 (For $-\text{C}=\text{O}$, carbonyl), 1510(For $-\text{C}=\text{S}$), 1078 (For $-\text{C-F}$).

2.6.3.3.19 $\text{N-}[2\text{-chloro-4-(trifluoro methyl) phenyl}]\text{-4-(3,4-dimethoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydro pyrimidine-5-carboxamide (ND-119)}$

![Chemical structure of ND-119]

Practical yield: 63%; Melting point 204ºC; Molecular formula $\text{C}_{21}\text{H}_{19}\text{ClF}_3\text{N}_3\text{O}_3\text{S}$: Carbon: 51.86; Hydrogen: 3.91; Chlorine: 7.30; Fluorine: 11.73; Nitrogen: 8.46; Oxygen: 9.88; S: 6.60; Results: Carbon: 51.79; Hydrogen: 3.09; Chlorine: 7.22; Fluorine: 11.54; Nitrogen: 9.23; Oxygen: 9.75; Sulphur: 6.42 %; MS: $m/z$ 486 . IR: 3250, 3100 (For $-\text{NH}$), 2980 (For $-\text{C-H}$ of phenyl ring), 1691 (For $-\text{C}=\text{O}$ carbonyl), 1520(For $-\text{C}=\text{S}$), 1080 (For $-\text{C-F}$).

2.6.3.3.20 $\text{N-}[2\text{-chloro-4-(trifluoro methyl) phenyl}]\text{-4-(4-methoxyphenyl)-6-methyl-2-thioxo-1, 2, 3, 4-tetrahydro pyrimidine-5-carboxamide (ND-120)}$
Practical yield: 70%; Melting point 205°C; Molecular formula $C_{20}H_{17}ClF_3N_3O_5S$: Carbon: 52.64; Hydrogen: 3.72; Chlorine: 7.53; Fluorine: 12.23; Nitrogen: 9.21; Oxygen: 6.54; S: 6.54; Results: Carbon: 52.68; Hydrogen: 3.78; Chlorine: 8.00; Fluorine: 12.24; Nitrogen: 9.25; Oxygen: 10.20%; MS: $m/z$ 456. IR: 3245, 3100 (For $-\text{NH}$), 2980 (For $-\text{C-H}$ of phenyl ring), 1692 (For $-\text{C=O}$, carbonyl), 1520(FOR $-\text{C=S}$), 1078 (For $-\text{C-F}$).

2.6.3.3.21 4-(4-chlorophenyl)-N-[2-chloro-4-(trifluoro methyl) phenyl]-6-methyl-2-thioxo-1, 2, 3, 4-tetrahydro pyrimidine-5-carboxamide (ND-121)

Practical yield: 71%; Melting point 220°C; Molecular formula $C_{19}H_{14}ClF_3N_3OS$: Carbon: 49.53; Hydrogen: 3.04; Chlorine: 15.40; Fluorine: 12.38; Nitrogen: 9.12; Oxygen: 3.48; Sulphur: 6.97; Results: Carbon: 49.57; Hydrogen: 3.08; Chlorine: 15.23; Fluorine: 12.24; Nitrogen: 9.17; Oxygen: 3.23; Sulphur: 6.81%; IR cm$^{-1}$: 3363 (For $-\text{NH}$), 3109 (For $-\text{C-H}$, of Phenyl ring), 2955 (C-H, CH$_3$ group stretching), 2871 (C-H, CH$_3$ group stretching), 1666 (C=O, amide carbonyl stretching), 1597 (N-H pyrimidine ring), 1523 (C=C Phenyl ring stretching), 1423 (C-H, CH$_3$ group asymmetrical deformation), 1342 (C-H, CH$_3$ group symmetrical deformation), 1320 (C-N-C pyrimidine ring
stretching), 1269/1246 (C-N, stretching), 1014 (C-F stretching), 677 (C-Cl stretching)
Mass: 460; Proton NMR (Solvent :Dimethyl sulfoxide-\textit{d}_6) \delta ppm: 2.02 (s, 3(H),H_a), 5.43
(s, 1(H),H_b), 6.95-6.98 (d, 1(H),H_c), 7.10 (s, 1(H),H_d), 7.27-7.29 (d, 2(H),H_{ef}), 7.51-7.53
(m, 1(H),H_g), 7.66 (s, 1(H),H_h), 8.19-8.22 (m, 1(H), H_i), 8.81 (s, 1(H),H_j), 8.84
(s, 1(H),H_k), 9.70 (s, 1(H),H_l).

2.6.3.3.22 \textit{N}-[2-chloro-4-(trifluoro methyl) phenyl]-6-methyl-4-(4-methylphenyl)-2-thioxo-1, 2, 3, 4-tetrahydro pyrimidine-5-carboxamide (ND-122)

Practical yield: 66%; Melting point 197ºC; Molecular formula C_{20}H_{17}ClF_3N_3OS: Carbon:
54.56; Hydrogen: 3.86; Chlorine: 8.06; Fluorine: 12.96; Nitrogen: 9.54; Oxygen: 3.64;
Sulphur: 7.29; Results: Carbon: 54.61; Hydrogen: 3.91; Chlorine: 8.00; Fluorine: 12.85;
Nitrogen: 9.47; Oxygen: 3.31; Sulphur: 7.11 %; MS: \textit{m/z} 440. IR: 3260, 3125 (For -NH),
2965 (-C-H, phenyl ring stretching), 1694 (For -C=O, carbonyl), 1515(For -C=S), 1070
(For -C-F).

2.6.3.3.23 \textit{N}-[2-chloro-4-(trifluoro methyl) phenyl]-4-(4-fluorophenyl)-6-methyl-2-thioxo-1, 2, 3, 4-tetrahydro pyrimidine-5-carboxamide (ND-123)
Practical yield: 57%; Melting point 195°C; Molecular formula C_{19}H_{14}ClF_{4}N_{3}OS: Carbon: 51.36; Hydrogen: 3.15; Chlorine: 7.99; Fluorine: 17.12; Nitrogen: 9.46; Oxygen: 3.60; Sulphur: 7.22; Results: Carbon: 51.41; Hydrogen: 3.20; Chlorine: 7.87; Fluorine: 17.01; Nitrogen: 9.51; Oxygen: 3.33; Sulphur: 7.00%; MS: m/z 444. IR: 3220, 3100 (For -NH), 2980 (For -C-H of phenyl ring), 1696 (For -C=O carbonyl), 1510 (For -C=S), 1071 (For -C-F).

2.6.3.3.24 4-(2-chlorophenyl)-N-[2-chloro-4-(trifluoro methyl) phenyl]-6-methyl-2-thioxo-1, 2, 3, 4-tetrahydro pyrimidine-5-carbamide (ND-124)

Practical yield: 69%; Melting point 188°C; Molecular formula C_{19}H_{14}Cl_{2}F_{3}N_{3}OS: Carbon: 49.53; Hydrogen: 3.04; Chlorine: 15.40; Fluorine: 12.38; Nitrogen: 9.12; Oxygen: 3.48; Sulphur: 6.97; Results: Carbon: 49.51; Hydrogen: 3.02; Chlorine: 15.20; Fluorine: 12.21; Nitrogen: 9.13; Oxygen: 3.20; Sulphur: 6.72%; MS: m/z 460; 13 IR: 3250,3100 (For -NH), 2980 (For -C-H of phenyl ring), 1697 (For -C=O carbonyl), 1520(For -C=S),1070 (For -C-F),
2.6.3.3.25 *N*-2-chloro-4-(trifluoro methyl) phenyl]-4-(3, 4-dichlorophenyl)-6-methyl-2-thioxo-1, 2, 3, 4-tetrahydro pyrimidine-5-carboxamide (ND-125)

Practical yield: 72%; Melting point 211°C; Molecular formula C_{19}H_{13}Cl_{3}F_{3}N_{3}O_{3}S: Carbon: 46.08; Hydrogen: 2.62; Chlorine: 21.50; Fluorine: 11.52; Nitrogen: 8.48; Oxygen: 3.23; Sulphur: 6.48; Results: Carbon: 46.11; Hydrogen: 2.69; Chlorine: 21.24; Fluorine: 11.22; Nitrogen: 8.52; Oxygen: 3.11; Sulphur: 6.83%; MS: *m/z* 495. IR: 3240, 3110 (For -NH), 2970 (For -C-H of phenyl ring), 1695 (For -C=O, carbonyl), 1510 (For -C=S), 1075 (For -C-F).

2.6.3.3.26 *N*-2-chloro-4-(trifluoro methyl) phenyl]-4-(3-methoxyphenyl)-6-methyl-2-thioxo-1, 2, 3, 4-tetrahydro pyrimidine-5-carboxamide (ND-126)

Practical yield: 58%; Melting point 186°C; Molecular formula C_{20}H_{17}ClF_{3}N_{3}O_{2}S: Carbon: 52.64; Hydrogen: 3.72; Chlorine: 7.78; Fluorine: 12.50; Nitrogen: 9.21; Oxygen: 7.02; S: 7.03 Results: Carbon: 52.62; Hydrogen: 3.43; Chlorine: 7.61; Fluorine: 12.30; Nitrogen: 9.27; Oxygen: 6.80; Sulphur: 7.00 %; MS: *m/z* 456. IR: 3260, 3120 (For -NH),
2965 (For -C-H of phenyl ring), 1700 (For -C=O, carbonyl), 1505 (For -C=S), 1080 (For -C-F)

2.6.3.3.27 N-[2-chloro-4-(trifluoromethyl) phenyl]-4-(2, 4-dimethylphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (ND-127)

Practical yield: 61%; Melting point 187ºC; Molecular formula C_{21}H_{19}ClF_{3}N_{3}O_{2}S: Carbon: 55.51; Hydrogen: 4.18; Chlorine: 7.81; Fluorine: 12.56; Nitrogen: 9.25; Oxygen: 3.52; Sulphur: 7.06; Results: Carbon: 55.62; Hydrogen: 4.37; Chlorine: 7.75; Fluorine: 12.43; Nitrogen: 9.36; Oxygen: 3.21; Sulphur: 7.00%; MS: m/z 454. IR: 3210, 3160 (For -NH), 2980 (For -C-H of phenyl ring), 1695 (For -C=O carbonyl), 1525(For -C=S), 1080 (For -C-F).

2.6.3.3.28 4-(4-bromophenyl)-N-[2-chloro-4-(trifluoromethyl) phenyl]-6-methyl-2-thioxo-1, 2, 3, 4-tetrahydro pyrimidine-5-carboxamide (ND-128)
Practical yield: 68%; Melting point 205°C; Molecular formula C_{19}H_{14}BrClF_{3}N_{3}OS:
Carbon: 45.17; Hydrogen: 2.77; Bromine: 15.83; Chlorine: 7.02; Fluorine: 11.29;
Nitrogen: 8.32; Oxygen: 3.17; Sulphur: 6.35; Results: Carbon: 45.25; Hydrogen: 2.96;
Bromine, 15.63; Chlorine, 6.94; Fluorine, 11.10; Nitrogen, 8.49; Oxygen, 3.11; Sulphur,
6.21%; MS: m/z 205. IR: 3250, 3130 (For -NH), 2960 (For -C-H of phenyl ring), 1690
(For -C=O carbonyl), 1515(For -C=S), 1070 (For -C-F).

2.6.3.3.29 4-(3-bromophenyl)-N-[2-chloro-4-(trifluoro methyl) phenyl]-6-methyl-2-
thioxo-1, 2, 3, 4-tetrahydro pyrimidine-5-carboxamide: (ND-129)

Practical yield: 70%; Melting point 214°C; Molecular formula C_{19}H_{14}BrClF_{3}N_{3}OS:
Carbon: 45.17; Hydrogen: 2.77; Bromine: 15.83; Chlorine: 7.02; Fluorine: 11.29;
Nitrogen: 8.32; Oxygen: 3.17; S: 6.35; Results: Carbon: 45.31; Hydrogen: 2.89; Bromine:
15.62; Chlorine: 6.91; Fluorine: 11.11; Nitrogen: 8.47; Oxygen: 3.13; Sulphur: 6.12%;
MS: m/z 205. IR: 3240, 3140 (For -NH), 2970 (For -C-H of phenyl ring), 1692 (For -
C=O carbonyl), 1515(For -C=S), 1074 (For -C-F).

2.6.3.3.30 N-[2-chloro-4-(trifluoro methyl) phenyl]-6-methyl-4-phenyl-2-thioxo-1, 2, 3,
4-tetrahydro pyrimidine-5-carboxamide (ND-130)
Practical yield: 64%; Melting point 224ºC; Molecular formula C_{19}H_{15}ClF_{3}N_{3}O_{3}: Carbon: 53.53; Hydrogen: 3.52; Chlorine: 8.33; Nitrogen: 9.86; Oxygen: 3.76; Sulphur: 7.53; Results: Carbon: 53.75; Hydrogen: 3.76; Chlorine: 8.30; Nitrogen: 9.26; Oxygen: 3.75; Sulphur: 7.21%; MS: m/z 426. IR: 3240, 3120 (For -NH), 2975 (For -C-H of phenyl ring), 1696 (For -C=O carbonyl), 1525 (For -C=S), 1075 (For -C-F).

Series No 3 from N-methyl urea

2.6.3.3.31 N-[2-chloro-4-(trifluoro methyl) phenyl]-4-(2-methoxyphenyl)-3,6-dimethyl-2-oxo-1,2,3,4-tetrahydro pyrimidine-5-carboxamide (ND-131)

Practical yield: 68%; Melting point 204ºC; Molecular formula C_{21}H_{19}ClF_{3}N_{3}O_{3}: Carbon: 55.58; Hydrogen: 4.22; Chlorine: 7.81; Fluorine: 12.56; Nitrogen: 9.26; Oxygen: 10.58; Results: Carbon: 55.50; Hydrogen: 4.20; Chlorine: 7.72; Fluorine: 12.34; Nitrogen: 9.18; Oxygen: 10.45%; Mass: 454. IR: 3240, 3140 (For -NH), 2970 (For -C-H of Phenyl ring), 1690 (For -C=O carbonyl), 1074 (For -C-F)

2.6.3.3.32 4-(3-chlorophenyl)-N-[2-chloro-4-(trifluoro methyl) phenyl]-3, 6-dimethyl-2-oxo-1, 2, 3, 4-tetrahydro pyrimidine-5-carboxamide (ND-132)
Practical yield: 63%; Melting point 222°C; Molecular formula C\textsubscript{20}H\textsubscript{16}Cl\textsubscript{2}F\textsubscript{3}N\textsubscript{3}O\textsubscript{2}: Carbon: 52.42; Hydrogen: 3.52; chlorine: 15.47; Fluorine: 12.44; Nitrogen: 9.17; Oxygen: 6.98; Results: Carbon: 52.02; Hydrogen: 3.46; Chlorine: 15.23; Fluorine: 12.13; Nitrogen: 9.08; Oxygen: 6.43%; MS: m/z 458. IR: 3260, 3130 (For -NH), 2960 (For -C-H, of Phenyl ring), 1695 (For C=O, carbonyl), 1078 (For -C-F).

\textbf{2.6.3.3.33 N-[2-chloro-4-(trifluoro methyl) phenyl]-4-(2-fluorophenyl)-3,6-dimethyl-2-oxo-1,2,3,4-tetrahydro pyrimidine-5-carboxamide (ND-133)}

Practical yield: 59%; Melting point 215°C; Molecular formula C\textsubscript{20}H\textsubscript{16}ClF\textsubscript{4}N\textsubscript{3}O\textsubscript{2}: Carbon: 54.37; Hydrogen: 3.65; Chlorine: 8.02; Fluorine: 17.20; Nitrogen: 9.51; Oxygen: 7.24; Results: Carbon: 54.30; Hydrogen: 3.52; Chlorine: 7.89; Fluorine: 17.10; Nitrogen: 9.42; Oxygen: 7.14%; MS: m/z 442. IR: 3255, 3120 (For -NH), 2958 (For -C-H of phenyl ring), 1691 (For C=O, carbonyl), 1078 (For C-F).
2.6.3.3.34 \(N\)-[2-chloro-4-(trifluoro methyl) phenyl]-4-(3, 4-dimethoxyphenyl)-3,6-dimethyl-2-oxo-1, 2, 3, 4-tetrahydro pyrimidine-5-carboxamide (ND-134)

Practical yield: 64%; Melting point 216ºC; Molecular formula \(C_{22}H_{21}ClF_{3}N_{2}O_{4}\): Carbon: 54.61; Hydrogen: 4.37; Chlorine: 7.33; Fluorine: 11.78; Nitrogen: 8.68; Oxygen: 13.23; Results: Carbon: 54.43; Hydrogen: 4.21; Chlorine: 7.24; Fluorine: 11.64; Nitrogen: 8.52; Oxygen: 13.02%; MS: \(m/z\) 484. IR: 3253, 3122 (For -NH), 2952 (For -C-H, of Phenyl ring), 1692 (For C=O, carbonyl), 1078 (For -C-F).

2.6.3.3.35 \(N\)-[2-chloro-4-(trifluoro methyl) phenyl]-4-(4-methoxyphenyl)-3, 6-dimethyl-2-oxo-1, 2, 3, 4-tetrahydro pyrimidine-5-carboxamide (ND-135)

Practical yield: 75%; Melting point 228ºC; Molecular formula \(C_{21}H_{19}ClF_{3}N_{2}O_{3}\): Carbon: 55.58; Hydrogen: 4.22; Chlorine: 7.81; Fluorine: 12.56; Nitrogen: 9.26; Oxygen: 10.58; Results: Carbon: 55.40; Hydrogen: 4.32; Chlorine: 7.75; Fluorine: 12.24; Nitrogen: 9.32; Oxygen: 10.42%; MS: \(m/z\) 454. IR: 3263, 3132 (For -NH), 2952 (For -C-H, of Phenyl ring), 1692 (For C=O, carbonyl), 1078 (For -C-F).
2.6.3.3.36 4-(4-chlorophenyl)-N-[2-chloro-4-(trifluoro methyl) phenyl]-3,6-dimethyl-2-oxo-1,2,3,4-tetrahydro pyrimidine-5-carboxamide (ND-136)

\[
\begin{align*}
\text{Practical yield: } \, 71\%; \, \text{Melting point } & 197^\circ \text{C}; \, \text{Molecular formula } C_{20}H_{16}Cl_2F_3N_3O_2; \, \text{Carbon: } 52.42; \, \text{Hydrogen: } 3.52; \, \text{Chlorine: } 15.47; \, \text{Fluorine: } 12.44; \, \text{Nitrogen: } 9.17; \, \text{Oxygen: } 6.98; \\
\text{Results: Carbon: } & 52.40; \, \text{Hydrogen: } 3.42; \, \text{Chlorine: } 15.25; \, \text{Fluorine: } 12.21; \, \text{Nitrogen: } 9.12; \, \text{Oxygen: } 6.23%; \, \text{IR : } 3315 (\text{ For } -NH) , \, 3070 (\text{ For } -C-H, \, \text{of Phenyl ring}), \, 2923 (\text{C-H, CH}_3 \, \text{group stretching}), \, 2868 (\text{C-H CH}_3 \, \text{group stretching}), \, 1680 (\text{C=O amide stretching}), \, 1600 (\text{N-H, pyrimidine ring}), \, 1529 (\text{C=C, Phenyl ring stretching}), \, 1491 (\text{C-H, CH}_3 \, \text{group asymmetrical deformation}), \, 1404 (\text{C-H, CH}_3 \, \text{group symmetrical deformation}), \, 1344 (\text{C-N-C, pyrimidine ring stretching}), \, 1267 (\text{C-N, stretching}), \, 1062 (\text{C-F stretching}), \, 653 (\text{C-Cl stretching}); \, \text{Mass: } 458; \, ^1H \text{ NMR (Solvent: Dimethyl sulfoxide-}d_6\text{)} \, \delta \text{ppm}: 2.19 (s, 3(H),H_a), \, 3.09 (s, 3(H),H_b), \, 5.33-5.32 (s, 1(H),H_c), \, 7.08-7.10 (d, 1(H),H_d), \, 7.23-7.26 (d, 1(H),H_e), \, 7.32-7.39(m, 3(H),H_{f-h}), \, 7.88-7.90 (m,1(H),H_i), \, 8.43-8.46 (m, 1(H),H_j), \, 8.88-8.89 (d, 1(H),H_k), \, 10.07 (s, 1(H), H_l).
\end{align*}
\]

2.6.3.3.37 N-[2-chloro-4-(trifluoro methyl) phenyl]-3, 6-dimethyl-4-(4-methylphenyl)-2-oxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxamide (ND-137)
Practical yield: 69%; Melting point 201°C; Molecular formula C₂₁H₁₉ClF₃N₃O₂: Carbon: 57.61; Hydrogen: 4.37; Chlorine: 8.10; Fluorine: 13.02; Nitrogen: 9.60; Oxygen: 7.31; Results: Carbon: 57.50; Hydrogen: 4.42; Chlorine: 7.94; Fluorine: 12.89; Nitrogen: 9.52; Oxygen: 7.12%; MS: m/z 438. IR: 3257, 3125 (For -NH), 2955 (For -C-H, of Phenyl ring), 1689 (For C=O, carbonyl), 1069 (For -C-F).

2.6.3.3.38 N-[2-chloro-4-(trifluoro methyl) phenyl]-4-(4-fluorophenyl)-3, 6-dimethyl-2-oxo-1, 2, 3, 4-tetrahydro pyrimidine-5-carboxamide (ND-138)

Practical yield: 55%; Melting point 205°C; Molecular formula C₂₀H₁₆ClF₄N₃O₂: Carbon: 54.37; Hydrogen: 3.65; Chlorine: 8.02; Fluorine: 17.20; Nitrogen, 9.51; Oxygen: 7.24; Results: Carbon: 54.50; Hydrogen: 3.55; Chlorine: 8.00; Fluorine: 17.11; Nitrogen: 9.52; Oxygen: 7.13%; MS: m/z 441. IR: 3252, 3129 (For -NH), 2956 (For -C-H, of Phenyl ring), 1691 (For C=O, carbonyl), 1071 (For -C-F).
2.6.3.3.39 4-(2-chlorophenyl)-N-[2-chloro-4-(trifluoro methyl) phenyl]-3,6-dimethyl-2-oxo-1,2,3,4-tetrahydro pyrimidine-5-carboxamide (ND-139)

Practical yield: 70%; Melting point 189ºC; Molecular formula C_{20}H_{16}Cl_{2}F_{3}N_{3}O_{2}: Carbon: 52.42; Hydrogen: 3.52; Chlorine: 15.47; Fluorine: 12.44; Nitrogen: 9.17; Oxygen: 6.98; Results: Carbon: 52.40; Hydrogen: 3.55; Chlorine: 15.28; Fluorine: 12.23; Nitrogen: 9.12; Oxygen: 6.89%; MS: m/z 458; IR: 3250, 3130 (For -NH), 2951 (For -C-H, of Phenyl ring), 1693 (For -C=O, carbonyl), 1073 (For -C-F).

2.6.3.3.40 N-[2-chloro-4-(trifluoro methyl) phenyl]-4-(3, 4-dichlorophenyl)-3, 6-dimethyl-2-oxo-1, 2, 3, 4-tetrahydro pyrimidine-5-carboxamide (ND-140)

Practical yield: 71%; Melting point 232ºC; Molecular formula C_{20}H_{15}Cl_{3}F_{3}N_{3}O_{2}: Carbon: 48.75; Hydrogen: 3.07; Chlorine: 21.59; Fluorine: 11.57; Nitrogen: 8.53; O: 6.49; Results: Carbon: 48.70; Hydrogen: 3.10; Chlorine: 21.29; Fluorine: 11.34; Nitrogen:
8.52; Oxygen: 6.31%; MS: m/z 493. IR: 3254, 3134 (For -NH), 2954 (For -C-H, of Phenyl ring), 1684 (For -C=O, carbonyl), 1074 (For -C-F).

2.6.3.4.41 N-[2-chloro-4-(trifluoro methyl) phenyl]-4-(3-methoxyphenyl)-3, 6-dimethyl-2-oxo-1, 2, 3, 4-tetrahydro pyrimidine-5-carboxamide (ND-141)

Practical yield: 59%; Melting point 222ºC; Molecular formula C_{21}H_{19}ClF_{3}N_{3}O_{3}: Carbon: 55.58; Hydrogen: 4.22; Chlorine: 7.81; Fluorine: 12.56; Nitrogen: 9.26; Oxygen: 10.58; Results: Carbon: 55.52; Hydrogen: 4.15; Chlorine: 7.29; Fluorine: 12.50; Nitrogen: 9.22; Oxygen: 10.34%; Mass: 454. IR: 3244, 3124 (For -NH), 2944 (For -C-H, of Phenyl ring), 1694 (For -C=O, carbonyl), 1064 (For -C-F).

2.6.3.4.42 N-[2-chloro-4-(trifluoro methyl) phenyl]-4-(2, 4-dimethylphenyl)-3, 6-dimethyl-2-oxo-1, 2, 3, 4-tetrahydro pyrimidine-5-carboxamide (ND-142)

Practical yield: 70%; Melting point 213ºC; Molecular formula C_{22}H_{21}ClF_{3}N_{3}O_{2}: Carbon: 58.48; Hydrogen: 4.68; Chlorine: 7.85; Fluorine: 12.61; Nitrogen: 9.30; Oxygen: 7.08;
Chapter: - 2

Tetrahydro Pyrimidine derivatives

Results: Carbon: 58.52; Hydrogen: 4.65; Chlorine: 7.64; Fluorine: 12.52; Nitrogen: 9.23;
Oxygen: 7.00%; MS: m/z 452. IR: 3248, 3131 (For -NH), 2955 (For -C-H, of Phenyl
ring), 1687 (For -C=O, carbonyl), 1069(For -C-F).

2.6.3.4.43 4-(4-bromophenyl)-N-[2-chloro-4-(trifluoromethyl) phenyl]-3, 6-dimethyl-2-
oxo-1, 2, 3, 4-tetrahydro pyrimidine-5-carboxamide (ND-143)

Practical yield: 67%; Melting point 195ºC; Molecular formula C_{20}H_{16}BrClF_3N_3O_2:
Carbon: 47.78; Hydrogen: 3.21; Bromine: 15.89; Chlorine: 7.05; Fluorine: 11.34;
Nitrogen: 8.36; Oxygen: 6.37; Results: Carbon: 47.60; Hydrogen: 3.22; Bromine: 15.74;
Chlorine: 7.00; Fluorine: 11.25; Nitrogen: 8.33; Oxygen: 6.22%; MS: m/z 503. IR: 3247,
3135 (For -NH), 2957 (For -C-H, of Phenyl ring), 1692 (For -C=O, carbonyl), 1070(For -
C-F).

2.6.3.4.44 4-(3-bromophenyl)-N-[2-chloro-4-(trifluoromethyl) phenyl]-3, 6-dimethyl-2-
oxo-1, 2, 3, 4-tetrahydro pyrimidine-5-carboxamide (ND-144)
Practical yield: 70%; Melting point 216ºC; Molecular formula C_{20}H_{16}BrClF_{3}N_{3}O_{2}:
   Carbon: 47.78; Hydrogen: 3.21; Bromine: 15.89; Chlorine: 7.05; Fluorine: 11.34;
   Nitrogen: 8.36; Oxygen: 6.37; Results: Carbon: 47.70; Hydrogen: 3.15; Bromine: 15.76;
   Chlorine: 7.00; Fluorine: 11.10; Nitrogen: 8.30; Oxygen, 6.23%; MS: \textit{m/z} 503. IR: 3246,
   3134 (For -NH), 2956 (For -C-H, of Phenyl ring), 1683 (For -C=O, carbonyl), 1071(For C-F).

2.6.3.4.45 \textit{N-}[2-chloro-4-(trifluoro methyl) phenyl]-3, 6-dimethyl-2-oxo-4-phenyl-1, 2,
   3, 4-tetrahydro pyrimidine-5-carboxamide (ND-145)

![Chemical structure]

Practical yield: 71%; Melting point 232ºC; Molecular formula C_{20}H_{17}ClF_{3}N_{3}O_{2}: Carbon:
   56.68; Hydrogen: 4.04; Chlorine: 8.37; Fluorine: 13.45; Nitrogen: 9.91; Oxygen: 7.55;
   Results: Carbon: 56.56; Hydrogen: 4.00; Chlorine: 8.13; Fluorine: 13.34; Nitrogen: 9.90;
   Oxygen: 7.23%; MS: \textit{m/z} 424. IR: 3245, 3131 (For -NH), 2951 (For -C-H, of Phenyl ring), 1688 (For -C=O, carbonyl), 1075(For -C-F).

2.7 Spectral discussion

2.7.1 Mass spectral study

Mass analysis was performed on GCMS with DIPT. Systematic fragmentation pattern
   was observed in mass spectral analyses. Base peak was obtained at mol.wt of compound.
   Mass fragmentation pattern for a representative compound of each series is depicted below.
Mass fragmentation pattern for ND-101
Mass fragmentation pattern for ND-121

![Diagram showing mass fragmentation pattern for ND-121]

Figure-2.27
Mass fragmentation pattern for ND-136

Figure-2.28
2.7.2 IR spectral study

IR analysis were done and reported. Various functional groups present in molecule were identified by characteristic frequency obtained for them. For Tetrahydro pyrimidines ND-101 to 145, confirmatory bands for secondary amine and amidic carbonyl groups was at 3450-3200 cm⁻¹ and 1715-1600 cm⁻¹ correspondingly. Another characteristic C-N-C, (pyrimidine ring stretching) was observed at 1360-1300 cm⁻¹, which suggested formation of desired products RHK-101 to 160.

2.7.3 ¹H NMR spectral study

¹H NMR analysis was reported and it’s done in Dimethyl sulfoxide-d6 solution on a bruker Ac 400 MHz instrument. Tetra methyl silane as a standard. Number of protons and their chemical shifts were found to confirm the compound was form. NMR spectra confirmed the structures of tetrahydropyrimidine ND-101 to 145 on the basis of following signals: a singlet for the methane proton of pyrimidine ring at 5.90-4.30 δ ppm, and singlet for N-H of pyrimidine at 7.80-9.60 δ ppm and amide group protons at 9.10-10.32 δ ppm, respectively. The aromatic ring protons and J value were found to be in accordance with substitution pattern on phenyl ring.
IR spectrum of ND – 101

Figure-2.29

Mass spectrum of ND – 101

Figure-2.30
Proton NMR spectra of ND – 101

![Proton NMR spectra of ND – 101](image1)

Expanded proton NMR spectra of ND – 101

![Expanded proton NMR spectra of ND – 101](image2)
IR spectrum of ND – 121

Figure-2.33

Mass spectrum of ND – 121

Figure-2.34
Proton NMR spectra of ND – 121

![NMR Spectra](image)

**Figure-2.35**

Expanded proton NMR spectra of ND – 121

![Expanded NMR Spectra](image)

**Figure-2.36**
IR spectrum of ND – 136

Figure-2.37

Mass spectrum of ND – 136

Figure-2.38
Proton NMR spectra of ND – 136

![NMR spectra](image1)

Figure-2.39

Expanded Proton NMR spectra of ND – 136

![Expanded NMR spectra](image2)

Figure-2.40
2.8 Biological evaluation

2.8.1 Antimicrobial Activity

Activity of compound confirm against bacteria like grampositive and gram negative. In gram positive includes staphylococcus aureus, streptococcus pyogenes and for gram negative Escherichia coli, pseudomonas aeruginosa. For anti fungal activity yeast including candida and asperginosa clavatus is used. Amplicilline and chloramphenicol are used for antibiotic. Reference anti fungal drug fluconazole used for comparization of antifungal activity. Summary of the antimicrobial activity in Table 2.4.

From the result of antifungal data, compounds 3e, 3f were active against C.albicans. while compounds 3c, 3h, 3f, 3n were active against A.clavatus. Further in Antibacterial study shows compounds 3f, 3g, 3o were active against S.aures and compounds 3a, 3c, 3i, 3j shows activity against S.pyrogenes. In case of E.coli compounds 3h, 3i, 3m, 3n, 3o shows good activity while in case of P.aeruginosh compounds 3a, 3e, 3l, 3o shows good activity. Other compounds did not show any hopeful activity against tested bacteria and fungi.

*Minimal Inhibition Concentration [MIC]:-

**Method:** ‘Broth Dilution Method’

**Advantage:**

1. For primary and secondary screening, serial dilutions were prepared.
2. The control tube contain no antibiotic is instantly sub cultured through dispersion a loopful uniformly, proper for the increase of the test organism and plant for store at 36°C during the night.
3. To check accuracy of the drug concentrations is interpret by MIC of control organism
4. MIC record the minimum inhibiting increase of organism.
5. The total expansion of the control tube prior to storage is compare.
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*Tetrahydro Pyrimidine derivatives*

**Methods: primary and secondary screening**

Prepared compound was reducing to 2000 microgram per milliliter use for stock solution. To compare the turbidity for inoculums test strain is adjust to $10^8$.

**First screen:** - Concentration for first screening of all synthesized compound were (1) 1000 microgram per milliliter (2) 500 micrograms per milliliter and (3) 250 microgram per milliliter. If active compound found in first test then all active compound again tested in second test.

**Second screen:** - The compound found active in first test were also diluted to (1) 200 microgram per milliliter (2) 100 microgram per milliliter (3) 50 microgram per milliliter, (4) 25 microgram per milliliter (5) 12.5 microgram per milliliter and (6) 6.250 microgram per milliliter concentrations.

**Reading Result:** - The maximum strength of diluted shows 99.00 % inhibition zone is in use as IC. All the results are fully depend on size of inoculums.

**Table-2.4. Summary of the antimicrobial activity**

<table>
<thead>
<tr>
<th>Compounds No.</th>
<th>Zone of inhibition (in mm)</th>
<th>Antibacterial activity</th>
<th>Antifungal activity</th>
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<td>Gram +ve</td>
<td>Gram -ve</td>
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<td></td>
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<td>S. aureus</td>
<td>S. pyrogenes</td>
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