PART-IV: STUDIES ON AMINOPYRIMIDINES

INTRODUCTION

2-Aminopyrimidine is the most significant member of all the diazine as this ring system occurs widely in living organisms. Pyridine is the parent of the series of molecules that is significant in pharmaceutical, fertilizers, pesticides and industrial chemistry. Among extensive variety of pyridines, 3-cyanopyridines acquired a special attention due to their wide range of therapeutic activities. Gabriel and Colman first reported it in year 1899 which represents one of the most active classes of molecule having a wide spectrum of biological activities.

![Aminopyrimidine Structure](image)

Attention in the synthesis of multi cyclic pyridine containing molecules has increased in modern years because of their biological and pharmacological activities. Many amino pyrimidines play dynamic role in many biological actions. Pyrimidine is considered to be a resonance hybrid of the charged and uncharged canonical structures. Its resonance energy has been found to be less than benzene or pyridine. Some of the physiologically as well as therapeutically important pyrimidine derivatives are as under: e.g., cytosine, bedmethrin (II), blasticidin (III).

![Pyrimidine Derivatives](image)
SYNTHETIC ASPECT:

A very important general method for preparing pyrimidines (IV) is the condensation between a three carbon compounds of the type YCH₂Z, where Y and Z = COR, CO₂R, CN, and compounds having the amidine structure R(C=NH)NH₂, where R = R (an amidine), OH (urea), SH or SR (thiourea or its S-derivatives), NH₂ (guanidine); the condensation is carried out in the presence of sodium hydroxide or sodium ethoxide. This general reaction may be illustrated by the condensation of acetamidine with ethylacetoacetate to form 4-hydroxy-2,6-dimethylpyrimidine.

Pyrimidines (V) can also be prepared by cycloaddition reaction of 1,3,5-triazines, which act as electron deficient dienes.

Rasaki¹ prepared 2-aminopyrimidine by the reaction of chalcone epoxides with guanidine carbonate in xylene.

Abd-El-gail and E. Amr² prepared aminopyrimidines by the reaction of chalcones with guanidine hydrochloride in the presence of NaOH.
Wang Jinjun\(^3\) has prepared some new benzo[c]pyrano [4, 3-\(d\)] pyrimidine derivatives (VI).

**MECHANISM:**

The general reaction mechanism for synthesis of 2-aminopyrimidine under alkaline medium is as under:
THERAPEUTIC IMPORTANCE:

Pyrimidine derivatives have confirmed to be of great prominence in exhibiting and enhancing the therapeutic and biological activities such as:

1. Anticonvulsant\textsuperscript{4}
2. Antiviral\textsuperscript{5,7}
3. Anthelmintic\textsuperscript{8}
4. Antihistamine\textsuperscript{9-10}
5. Anti-HIV\textsuperscript{11-12}
6. Antithyroid\textsuperscript{13-14}
7. Antitumor\textsuperscript{15-17}
8. Antimalarial\textsuperscript{18-20}
9. Antihypertensive\textsuperscript{21-23}
10. Antitubercular\textsuperscript{24}
11. Cardiovascular\textsuperscript{25-27}
12. Antiinflammatory\textsuperscript{28-30}
13. Diuretic\textsuperscript{31}
14. Antimicrobial\textsuperscript{32-35}
15. Antispasmodic\textsuperscript{36}
16. Platelet aggregation inhibitor\textsuperscript{37-38}
17. Antineoplastic\textsuperscript{39-40}

Viney Lather et al.\textsuperscript{41} have proposed to predict the anti-HIV activity of Dihydro-(alkylthio)-(naphthylmethyl)-oxopyrimidines. These models are proficient of providing lead structures for development of potent but safe anti-HIV agents (VII).
Abou El otooh et al.\textsuperscript{42} prepared thiopyrimidine derivatives (VIII) which showed anticancer activity.

H. S. Joshi et al.\textsuperscript{43} has synthesized some new pyrimidines as antitubercular and antimicrobial agents (IX).

Maria T. Cocco et al.\textsuperscript{44} have synthesized pyrimidine derivatives (X) and reported their antitumoral activity.
Hisaki Masakatsu et al.\textsuperscript{45} have synthesized some aminopyrimidines which are useful in the treatment of rotaviral diseases. Robson C. et al.\textsuperscript{46} have prepared aminopyrimidine derivatives as antifungal agents in P9P and MRP over expressive tumor cell lines. Leanne M. et al.\textsuperscript{47} have prepared aminopyrimidines and reported them as antiviral agent.

Amjad Ali et al.\textsuperscript{48} have designed and synthesized pyrimidine derivatives (XI) as newer antibacterial agents with inhibitor activity against DNA polymerase-II.

\begin{center}
\includegraphics[width=0.5\textwidth]{molecule.png}
\end{center}

Considering to the diversified activities exhibited and in continuation of our work on the synthesis of biologically active heterocyclic compounds, the synthesis and biological screening of pyrimidine derivatives have been carried out described as under.

\section*{SECTION–I: SYNTHESIS AND BIOLOGICAL EVALUATION OF N-[4-(2-AMINO-6-ARYL-PYRIMIDIN-4-YL)PHENYL] CYCLOPROPAANE CARBOXAMIDE.}
SECTION–I

SYNTHESIS AND BIOLOGICAL EVALUATION OF N-[4-(2-AMINO-6-ARYL-PYRIMIDIN-4-YL)PHENYL]CYCLOPROPANE CARBOXAMIDE.

In the previous years, great evidence has been accumulated to demonstrate the efficiency of Pyrimidinone. N-[4-(2-Amino-6-aryl-pyrimidin-4-yl)phenyl]cyclopropane carboxamide of type (VII) have been prepared by the condensation of N-[4-(3-Aryl-acryloyl)phenyl]cyclopropane carboxamide of type-(I) with guanidine hydrochloride in presence of catalytic amount of KOH as shown below.

The structure elucidation of synthesized compounds has been done on the basis of Elemental analysis, Infrared and $^1$H Nuclear Magnetic Resonance spectroscopy and further supported by Mass spectrometry. Purity of all compounds has been checked by thin layer chromatography. All the compounds have been evaluated for their in vitro biological assay like antibacterial activity towards Gram positive and Gram negative bacterial strains and antifungal activity towards A.niger at a concentration of 40 μg. The biological activities of synthesized compounds were compared with standard drugs.
REACTION SCHEME

Type-I  \[ R = \text{Aryl} \]

Type-VII  \[ R = \text{Aryl} \]
IR SPECTRAL STUDIES OF N-[4-{2-AMINO-6-(4-METHOXYPHENYL) PYRIMIDIN-4-YL]PHENYL}CYCLOPROPANE CARBOXAMIDE.

Instrument: Bruker Benchtop Infrared; Frequency range: 4000-400cm\(^{-1}\)(KBr disc)

<table>
<thead>
<tr>
<th>Type</th>
<th>Vibration Mode</th>
<th>Frequency in cm(^{-1})</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkane</td>
<td>C-H str.(asym)</td>
<td>2920</td>
<td>2990-2830</td>
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<td></td>
<td>C-H str.(sym)</td>
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<td>2880-2860</td>
</tr>
<tr>
<td></td>
<td>C-H def.(sym)</td>
<td>1362</td>
<td>1390-1360</td>
</tr>
<tr>
<td>Aromatic</td>
<td>C-H i.p (def)</td>
<td>1235</td>
<td>1300-1100</td>
</tr>
<tr>
<td></td>
<td>C=C str.</td>
<td>1572</td>
<td>1600-1450</td>
</tr>
<tr>
<td>Pyrimidine</td>
<td>N-H str.</td>
<td>3442</td>
<td>3500-3400</td>
</tr>
<tr>
<td></td>
<td>C=N str.</td>
<td>1600</td>
<td>1650-1550</td>
</tr>
<tr>
<td></td>
<td>C-N str.</td>
<td>1174</td>
<td>1220-1020</td>
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<tr>
<td>Ar.amine</td>
<td>N-H str.</td>
<td>3298</td>
<td>3350-3250</td>
</tr>
<tr>
<td>Amide</td>
<td>C=O</td>
<td>1656</td>
<td>1680-1630</td>
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</table>
NMR SPECTRAL STUDIES OF N-(4-[2-AMINO-6-(4-METHOXYPHENYL)PYRIMIDIN-4-YL]PHENYL)CYCLOPROPANE CARBOXAMIDE.

Internal standard: TMS; Solvent: DMSO; Instrument: BRUKER Spectrometer (400MHz)

<table>
<thead>
<tr>
<th>No.</th>
<th>Chemical shift (δ ppm)</th>
<th>Multiplicity</th>
<th>No. of Protons</th>
<th>Assignment of proton(s)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.83-1.83</td>
<td>m</td>
<td>5 H</td>
<td>10,11,12</td>
<td>A</td>
</tr>
<tr>
<td>2</td>
<td>3.84</td>
<td>s</td>
<td>3 H</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>7.04-8.20</td>
<td>m</td>
<td>9 H</td>
<td>1,2,4,5,14,15,17,18,20</td>
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</tr>
<tr>
<td>4</td>
<td>6.63</td>
<td>s</td>
<td>2 H</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>10.44</td>
<td>s</td>
<td>1 H</td>
<td>7</td>
<td></td>
</tr>
</tbody>
</table>

Total No. of protons 20 H
MASS SPECTRAL STUDIES OF N-[4-[2-AMINO-6-(4-METHOXYPHENYL) PYRIMIDIN-4-YL]PHENYL]CYCLOPROPANE CARBOXAMIDE.
MASS FRAGMENTATION

m/z = 360
(Base Peak)

m/z = 292

m/z = 277

m/z = 202

m/z = 292

m/z = 161

m/z = 120

m/z = 79

m/z = 69

m/z = 41

m/z = 111

m/z = 43

m/z = 92

m/z = 41
EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL EVALUATION OF N-[4-(2-AMINO-6-ARYL-PYRIMIDIN-4-YL)PHENYL]CYCLOPROPANE CARBOXAMIDE.

(A) Synthesis of N-[4-{3-(4-Methoxyphenyl)acryloyl}phenyl]cyclopropane carboxamide.

See, Part-I, Section-I (B).

(B) Synthesis of N-[4-{2-Amino-6-(4-methoxyphenyl)pyrimidin-4-yl}phenyl]cyclopropane carboxamide.

A mixture of N-[4-{3-(4-Methoxyphenyl)acryloyl}phenyl]cyclopropane carboxamide 0.5 gm (0.01 mol) and guanidine hydrochloride 0.15 gm (0.01 mol) was dissolved in methanol using KOH as catalyst. The whole reaction mass was refluxed for 10 hrs. The reaction mixture was poured into crushed ice. Solid separated was filtered and recrystallized from ethanol. Yield 80.12%, M.P. 187°C. Elemental Analysis Calculated for C_{21}H_{20}N_{4}O_{2}; Requires: C-69.98%; H-5.59%; N-15.55%; O-8.88%; Found: C-69.93%, H-5.55, N-15.54%; O-8.90%. Similarly, other N-[4-(2-Amino-6-aryl-pyrimidin-4-yl)phenyl]cyclopropane carboxamide were prepared. The physical data are recorded in Table No.7.

(C) Biological evaluation of N-[4-(2-Amino-6-aryl-pyrimidin-4-yl)phenyl]cyclopropane carboxamide.

Antimicrobial testing was carried out as described in Part-I, Section-I (C). The zone of inhibition of tested compounds is recorded in Graphical Chart No. 7.
CONCLUSION

Antibacterial activity

The antimicrobial screening data indicated that among aminopyrimidine derivatives tested compounds 7b, 7c, 7g, 7j and 7k showed excellent growth inhibition against *B. subtilis*. However, the compounds 7a, 7d, 7h and 7i were shown significant activity against *E. coli*. The compounds 7c, 7e, 7g, 7i and 7j showed greater degree of antibacterial activity against *S. aureus*. However, the compounds 7b, 7d, 7i and 7j exhibited good to excellent activity against *P. aeruginosa*. The remaining aminopyrimidine derivatives possess moderate to mild activity against all four bacterial species.

Antifungal activity

The screening data indicated that among aminopyrimidine derivatives tested compounds 7b, 7f and 7g showed good to moderate activity against *A. niger*. All other compounds exhibit mild to moderate antifungal activity against *A. niger*. 
TABLE NO. 7: PHYSICAL CONSTANTS OF N-[4-(2-AMINO-6-ARYL-PYRIMIDIN-4-YL)PHENYL]CYCLOPROPANE CARBOXAMIDE.

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>R</th>
<th>Molecular Formula</th>
<th>Molecular Weight</th>
<th>M.P. (°C)</th>
<th>% Yield</th>
<th>Nitrogen %</th>
</tr>
</thead>
<tbody>
<tr>
<td>7a</td>
<td>-C₆H₅</td>
<td>C₂₀H₁₈N₄O</td>
<td>330.38</td>
<td>156</td>
<td>78.32</td>
<td>16.94</td>
</tr>
<tr>
<td>7b</td>
<td>-4-CH₃-C₆H₄</td>
<td>C₂₁H₃₀N₄O₂</td>
<td>360.41</td>
<td>187</td>
<td>80.12</td>
<td>15.54</td>
</tr>
<tr>
<td>7c</td>
<td>-4-N(CH₃)₂C₆H₄</td>
<td>C₂₂H₂₃N₄O</td>
<td>373.45</td>
<td>158</td>
<td>79.21</td>
<td>18.71</td>
</tr>
<tr>
<td>7d</td>
<td>-C₆H₂O</td>
<td>C₁₈H₁₆N₄O₂</td>
<td>320.35</td>
<td>185</td>
<td>77.89</td>
<td>17.46</td>
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<tr>
<td>7e</td>
<td>-2-Cl-C₆H₄</td>
<td>C₂₀H₁₇ClN₂O</td>
<td>364.83</td>
<td>189</td>
<td>82.56</td>
<td>15.34</td>
</tr>
<tr>
<td>7f</td>
<td>-4-F-C₆H₄</td>
<td>C₂₀H₁₇FN₂O</td>
<td>348.37</td>
<td>147</td>
<td>70.12</td>
<td>16.05</td>
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<tr>
<td>7g</td>
<td>-4-OH-C₆H₄</td>
<td>C₂₀H₁₈N₄O₂</td>
<td>346.38</td>
<td>210</td>
<td>71.13</td>
<td>16.15</td>
</tr>
<tr>
<td>7h</td>
<td>-4-OH-3-OCH₃-C₆H₃</td>
<td>C₂₁H₂₀N₄O₃</td>
<td>376.41</td>
<td>197</td>
<td>74.56</td>
<td>14.86</td>
</tr>
<tr>
<td>7i</td>
<td>-2-OH-C₆H₄</td>
<td>C₂₀H₁₈N₄O₂</td>
<td>346.38</td>
<td>206</td>
<td>70.85</td>
<td>16.14</td>
</tr>
<tr>
<td>7j</td>
<td>-2-NO₂-C₆H₄</td>
<td>C₂₀H₁₇NO₃</td>
<td>375.38</td>
<td>180</td>
<td>78.45</td>
<td>18.66</td>
</tr>
<tr>
<td>7k</td>
<td>-4-Cl-C₆H₄</td>
<td>C₂₀H₁₇ClN₂O</td>
<td>364.83</td>
<td>183</td>
<td>80.19</td>
<td>15.33</td>
</tr>
</tbody>
</table>

Characterization data of the compounds.
GRAPHICAL CHART NO.7: ANTIMICROBIAL ACTIVITY OF N-[4-(2-AMINO-6-ARYL-PYRIMIDIN-4-YL)PHENYL] CYCLOPROPANE CARBOXAMIDE.
REFERENCES:


**GENERAL REFERENCES:**
