Chapter 3: 
Synthesis of Pyrimidine based aniline mustard derivatives

3.1 Introduction of Pyrimidine heterocycles

General Introduction

Pyrimidine scaffold represents an important pharmacophore endowed with a wide range of pharmacological activities according to the specific makeover of the heterocycle. Heterocycles with nitrogen heteroatom are widely distributed in nature and are essential to life, playing a vital role in the function of all living cells. Among these, pyrimidines represent one of the most prevalent heterocycles found in natural products such as amino acid derivatives (willardiine, tingitanine), antibiotics (bacimethrin, sparsomycin, bleomycin), alkaloids (heteromines, crambescins, manzacidins, variolins, meridianins, psammopemmins etc.), vitamins (vitamin B1), and toxins. The first synthetic pyrimidine derivative (alloxan) was obtained as early as 1818, by Brugnatelli, oxidizing uric acid with HNO3. In 1848, a second pyrimidine synthesis was pioneered by Frankland and Kolbe, who heated propionitrile with metallic potassium to give a pure product (2,6-diethyl-5-methyl-4-pyrimidinamine), while in 1878 Grimaux prepared barbituric acid by condensation of malonic acid with urea. The latter procedure has been later named after Pinner who gave the name to the pyrimidine scaffold and was the first to understand the chemical nature of this structure. Pyrimidine nucleus present in rosuvastatin (Figure-3.1), which is member of drug class of statins, used to treat high cholesterol and related condition to prevent cardiovascular diseases.

![Figure 3.1](image-url)
Due to the long-lasting interest in pyrimidine derivatives as potential drugs, the synthetic community has much effort to investigation of new method to build up variety of pyrimidine derivatives. Accordingly, we have described here an overview of the most interesting synthetic strategies recently reported for the generation of highly functionalized pyrimidines.

**A literature review on the biological activity associated with Pyrimidine derivatives**

In medicinal chemistry pyrimidine derivatives have been very well known for their therapeutic applications. Many pyrimidine derivatives have been developed as chemotherapeutic agents. Over the years, the pyrimidine system turned out to be an important pharmacophore endowed with drug like properties and a wide range of pharmacological activities depending on the decoration of the scaffold. A few illustrative examples of pyrimidine derivatives active as inhibitors of HIV, HCV, CDK, CB2, VEGFR and Adenosine A1/A2a/A3 are reported in Figure 3.2.

![Figure 3.2](image_url)

Microbes are causative agents for various types of disease like pneumonia, amoebiasis, typhoid, malaria, common cough and cold various infections and some severe diseases like tuberculosis, influenza, syphilis, and AIDS as well. Various
approaches were made to check the role of pyrimidine moiety as antimicrobial agent from the discovery of molecule to the present scenario.\textsuperscript{20} synthesized 2-{{\{2 (Morpholino)-3-pyridinyl-5-thio\}-2-oxoethyloxadiazolyl}-amino-4-(2,4-dichloro-5-fluorophenyl)\}-6-(aryl)pyrimidines, which exhibit maximum zone of inhibition against \textit{E.coli}, \textit{S. aureus}, \textit{S.typhi} and \textit{B.subtilis} (\textbf{Figure-3.3}).

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{PyrimidineDerivative.png}
\caption{Figure 3.3}
\end{figure}

Mishra et al.\textsuperscript{21} have synthesized various derivatives of pyrimidines. The fungicidal activities of the compound were evaluated against \textit{P. infestans} and \textit{C. falcatus} by the usual agar plate method (\textbf{Figure-3.4}).

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{FungicidalActivity.png}
\caption{Figure 3.4}
\end{figure}

The pyrimidine moiety with some substitution gave promising antitumor activity as there are large numbers of pyrimidine based antimetabolites. Early metabolite prepared was 5-fluorouracil,\textsuperscript{22} a pyrimidine derivative followed by 5-thiouracil which also exhibits some useful antineoplastic activities (\textbf{Figure-3.5}).\textsuperscript{23}

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{AntitumorActivity.png}
\caption{Figure 3.5}
\end{figure}

Palwinder Singh et al.\textsuperscript{21} has reacted 5-benzoyl/5-carbaldehyde/5-(3-phenyl acryloyl)-6-hydroxy-1\textit{H}-pyrimidine-2,4diones with amines provided the corresponding
enamines (Figure-3.6). The investigation for anticancer activity of molecule at 59 human tumor cell lines was done representing leukemia, melanoma and cancer of lung, colon, brain, ovary, breast as well as kidney.

Stephanepedeboscq et al.\textsuperscript{24} has synthesized 4-(2-Methylanilino) benzo[\textit{b}]thieno[2,3-\textit{d}]pyrimidine (1) and 4-(2-Methoxyanilino)benzo[\textit{b}]thieno[2,3-\textit{d}] pyrimidine (2) (Figure-3.7), which showed a similar cytotoxicity to the standard anti- EGFR gefitinib suggesting a blockade of the EGFR pathway by binding to the tyrosine kinase receptor.

Fathalla et al.\textsuperscript{25} has synthesized a series of some new pyrimidine derivatives like 7-(2-methoxyphenyl)-3-methyl-5-thioxo-5, 6-dihydro[1, 2, 4]-triazolo[4,3-\textit{c}] pyrimidine-8-carbo-nitrile via reaction of ethyl cyanoacetate with thiourea and the appropriate aldehydes namely 2-methyl-benzaldehyde and 2-methoxy-benzaldehyde followed reaction with different reagents. All structures were than screened for bacterial activity and anticancer activity (Figure-3.8).
Pyrimidine has a remarkable pharmacological efficiency and therefore an intensive research has been focused on anti-inflammatory activity of Pyrimidine nucleus. Recently two PCT international applications have been filed for 2-thiopyrimidine derivatives possessing potent activity against inflammation and immune disorders. Padama shale et al. have been reported Naphtho[2,1-b]furo[3,2-d]Pyrimidine and Carrageen induced rat paw edema method was employed for evaluating the anti-inflammatory activity. The compounds were given at a dose of 80 mg/kg body weight in albino rats weighing between 150 and 200 g. The oedema was produced by injecting carrageenan solution at the left hind paw (Figure-3.9).

Lee et al. has synthesized some novel pyrimidines derivative having thiazolidinedione. These compounds were evaluated for their glucose and lipid lowering activity using pioglitazone and rosiglitazone as reference compound (Figure-3.10).

Many pyrimidine ring containing drugs have exhibited antihypertensive activity. A quinozoline derivative, prazosin, is a selective α1-adrenergic antagonist. Its related analogues bunazosin, trimazosin and terazosin are potent antihypertensive agents (Figure-3.11).
Ketanserin\textsuperscript{33} has a similar effect and is an antagonist of both $\alpha_1$-adrenergic and serotonin-S2 receptors. A trimaminopyrimidine derivative, minoxidil, whose mechanism of action and therapeutic action are similar to prazosin, has been introduced in therapy for its side effects, in the treatment of alopecia, male baldness etc (Figure-3.12).

\[ \text{Ketanserin} \]

\[ \text{Minoxidil} \]

**Figure 3.12**

Rahaman et al.\textsuperscript{34} has synthesized novel pyrimidines by the condensation of chalcones of 4’-piperazine acetophenone with guanidine HCl (Figure-3.13). It showed significant antihistaminic activity when compared to the reference antihistaminic drug mepiramine.

\[ \text{Figure 3.13} \]

A small library of 20 tri-substituted pyrimidines was synthesized by Anu et al.\textsuperscript{33} evaluated for their *in vitro* anti-malarial and anti-tubercular activities. Out of all screened compound, 16 compounds have shown in-vitro anti-malarial activity against *Plasmodium falciparum* in the range of 0.25-2μg/ml and 8 compounds have shown anti-tubercular activity against *Mycobacterium tuberculosis* at a concentration 12.5 μg/ml (Figure-3.14).

\[ \text{Figure 3.14} \]
3.2 Current research work

Nitrogen mustards have been found to be potential anticancerous agent; pyrimidine derivatives find an important role in life process. Both simple and complex forms of pyrimidine are important as their chemotherapeutic potential has also given a considerable impetus to their study. The early use of barbiturates (hydroxyl pyrimidine derivatives) as soporifics. Widely use of sulphadiazine in clinical practice and antithyroid activity of thiouracil highlight the important pharmacological activity of pyrimidines. These pyrimidines have also close relation with the nucleic acids, enzymes and vitamins, e.g. thymine and cytosine and uracil and cytosine are pyrimidine base constituents of DNA and RNA respectively.

In this chapter, synthesis and characterization of various aniline mustard derivatives (Figure-3.15) containing pyrimidine nucleus are discussed. The chloro-amine coupling of chloropyrimidine and aniline nitrogen mustard was carried out. The constitution of all the synthesized compounds has been characterized by using mass, IR, $^1$H NMR and $^{13}$C NMR spectroscopy. Synthesized compounds were also evaluated for antimicrobial activity, In vitro cytotoxicity study on Prostate cancer cell line PC-3 and Cervical cancer cell line HeLa and Genotoxicity study.

![Figure-3.15](image-url)
3.3 Synthesis of pyrimidine aniline N-mustard:

Scheme-1.1: Synthesis of 2-(bis(methylthio)methylene)-4-methyl-3-oxo-N-arylpentanamide

Substituted ketene dithioacetal were prepared by two step reaction. Here 4-methyl-3-oxo-N-arylpentanamide (Int-1a-m) were synthesized from methyl isobutrylacetate and substituted anilines around 100-120 °C. Pre chilled 4-methyl-3-oxo-N-arylpentanamide (Int-1a-m) were reacted simultaneously with CS$_2$ and methyl iodide in presence of K$_2$CO$_3$ to get 2-(bis(methylthio)methylene)-4-methyl-3-oxo-N-arylpentanamide (Int-2a-m).

Scheme-1.2: Synthesis of 4-isopropoxybenzimidamide

4-isopropoxybenzimidamide was prepared in four steps. Protection of –OH group of 4-hydroxybenzonitrile was done by reaction with isopropyl bromide at 50 °C followed
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by reaction with NaSH and iodomethane in cooling condition respectively yields methyl 4-isopropoxybenzimidothioate. Product was dissolved in ACN and further reaction with ammonium acetate was carried out at R.T. to get 4-isopropoxybenzimidamide.

**Scheme-3.3: 4-((4-(bis(2-chloroethyl)amino)phenyl)amino)-2-imino-6-isopropyl-N-aryl-1,2-dihydropyrimidine-5-carboxamide**

![Scheme-3.3](image)

A modified biginelli approach for the synthesis of pyrimidine was carried out from ketene dithioacetal of various acetoacetanilides and 4-isopropoxybenzimidamide (Scheme-3.3). Here equimolar mixture of 2-(bis(methylthio)methylene)-4-methyl-3-oxo-N-arylpentanamide (Int-2a-m) and 4-isopropoxybenzimidamide were refluxed in Dioxane for 15-20h in presence of K$_2$CO$_3$ afford 2-(4-isopropoxyphenyl)-6-isopropyl-4-(methylthio)-N-phenyl-1,2-dihydropyrimidine-5-carboxamide (Int-3a-o). 2-(4-isopropoxyphenyl)-6-isopropyl-4-(methylthio)-N-phenyl-1,2-dihydropyrimidine-5-carboxamide (Int-3a-o) contains –SCH$_3$ group. The conversion of –SCH$_3$ to –Cl

**Figure-3.18**

<table>
<thead>
<tr>
<th>$R$</th>
<th>$A$= 4-CH$_3$</th>
<th>$F$= 3-Cl4-F</th>
<th>$J$= 2-Cl</th>
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<tr>
<td></td>
<td>$B$= 4-OMe</td>
<td>$G$= 3,4-di Me</td>
<td>$K$= 2-F</td>
</tr>
<tr>
<td></td>
<td>$C$= 4-F</td>
<td>$H$= 2,4-di CH$_3$</td>
<td>$L$= 3-4-di Cl</td>
</tr>
<tr>
<td></td>
<td>$D$= 4-Br</td>
<td>$I$= 4-CF$_3$</td>
<td>$M$= 4-NO$_2$</td>
</tr>
</tbody>
</table>

|     | $E$= 4-Cl   |
was carried out by reaction of Int-3a-o with sulphuryl chloride (SO$_2$Cl$_2$) at 0 °C. In pyrimidine chlorine adjacent to nitrogen is labile and can be easily replaced with any nucleophile. So this nucleophilic substitution reaction of 4-chloro-2-(4-isopropoxyphenyl)-6-isopropyl-N-phenyl-1,2-dihydropyrimidine-5-carboxamide (Int-4a-o) was carried out by aniline nitrogen mustard (synthesized in chapter-2) in refluxing condition.

Table 3.1: Synthesized pyrimidine based aniline nitrogen mustard analogues

<table>
<thead>
<tr>
<th>Code</th>
<th>Molecular Formula</th>
<th>R</th>
<th>Molecular Weight</th>
<th>Melting Point °C</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>JPM-A</td>
<td>C$<em>{33}$H$</em>{39}$Cl$_2$N$_5$O$_2$</td>
<td>4-CH$_3$</td>
<td>620</td>
<td>190-192</td>
<td>74</td>
</tr>
<tr>
<td>JPM-B</td>
<td>C$<em>{34}$H$</em>{39}$Cl$_2$N$_5$O$_3$</td>
<td>4-OMe</td>
<td>636</td>
<td>196-198</td>
<td>62</td>
</tr>
<tr>
<td>JPM-C</td>
<td>C$<em>{33}$H$</em>{39}$Cl$_2$FN$_5$O$_2$</td>
<td>4-F</td>
<td>623</td>
<td>188-190</td>
<td>69</td>
</tr>
<tr>
<td>JPM-D</td>
<td>C$<em>{33}$H$</em>{36}$BrCl$_2$N$_5$O$_2$</td>
<td>4-Br</td>
<td>685</td>
<td>195-197</td>
<td>54</td>
</tr>
<tr>
<td>JPM-E</td>
<td>C$<em>{33}$H$</em>{36}$Cl$_5$N$_5$O$_2$</td>
<td>4-Cl</td>
<td>641</td>
<td>187-189</td>
<td>71</td>
</tr>
<tr>
<td>JPM-F</td>
<td>C$<em>{33}$H$</em>{35}$Cl$_3$FN$_5$O$_2$</td>
<td>3-Cl-4-F</td>
<td>659</td>
<td>173-175</td>
<td>63</td>
</tr>
<tr>
<td>JPM-G</td>
<td>C$<em>{33}$H$</em>{41}$Cl$_2$N$_5$O$_2$</td>
<td>2,3-di Me</td>
<td>634</td>
<td>199-201</td>
<td>68</td>
</tr>
<tr>
<td>JPM-H</td>
<td>C$<em>{33}$H$</em>{41}$Cl$_2$N$_5$O$_2$</td>
<td>2,4-di Me</td>
<td>634</td>
<td>234-236</td>
<td>52</td>
</tr>
<tr>
<td>JPM-I</td>
<td>C$<em>{34}$H$</em>{36}$Cl$_2$FN$_5$O$_2$</td>
<td>4-CF$_3$</td>
<td>674</td>
<td>186-188</td>
<td>63</td>
</tr>
<tr>
<td>JPM-J</td>
<td>C$<em>{33}$H$</em>{36}$Cl$_5$N$_5$O$_2$</td>
<td>2-Cl</td>
<td>641</td>
<td>197-199</td>
<td>61</td>
</tr>
<tr>
<td>JPM-K</td>
<td>C$<em>{33}$H$</em>{36}$Cl$_2$FN$_5$O$_2$</td>
<td>2-F</td>
<td>623</td>
<td>217-219</td>
<td>57</td>
</tr>
<tr>
<td>JPM-L</td>
<td>C$<em>{33}$H$</em>{35}$Cl$_4$N$_5$O$_2$</td>
<td>3,4-di Cl</td>
<td>675</td>
<td>191-193</td>
<td>52</td>
</tr>
<tr>
<td>JPM-M</td>
<td>C$<em>{33}$H$</em>{36}$Cl$_6$N$_5$O$_2$</td>
<td>4-NO$_2$</td>
<td>651</td>
<td>211-213</td>
<td>60</td>
</tr>
</tbody>
</table>

Pyrimidine based aniline nitrogen mustard analogues
3.4 Experimental section

Thin-layer chromatography was accomplished on 0.2-mm precoated plates of silica gel G60 F$^{254}$ (Merck). Visualization was made with UV light (254 and 365nm) or with an iodine vapor. IR spectra were recorded on a FTIR-8400 spectrophotometer using DRS prob. $^1$H (400 MHz), $^{13}$C (100 MHz) NMR spectra were recorded on a Bruker AVANCE II spectrometer in DMSO. Chemical shifts are expressed in $\delta$ ppm downfield from TMS as an internal standard. Mass spectra were determined using direct inlet probe on a GCMS-QP 2010 mass spectrometer (Shimadzu). Solvents were evaporated with a BUCHI rotary evaporator. Melting points were measured in open capillaries and are uncorrected.

General procedure for the synthesis of 2-(bis(methylthio)methylene)-4-methyl-3-oxo-N-arylpentanamide (Int 2a-m).

The mixture of Int-1a-m (3.25 mmol) and K$_2$CO$_3$ (6.5 mmol) in DMF were stirred for 1 hrs at R.T. CS$_2$ (3.25 mmol) was then added at the same temperature and stirred for another 1h. The colour of the reaction mixture turns red. Methyl iodide(6.5 mmol) was added dropwise in cooling condition. Reaction mixture was allowed to stirr for 2-4 h at R.T. and poured on to crushed ice. Separated solid was filtered and washed with water and dried to afford Int-2a-m. This compound was used in next step without further purification.

General procedure for the synthesis of 2-(4-isoproxyphenyl)-6-isopropyl-4-(methylthio)-N-phenyl-1,2-dihydropyrimidine-5-carboxamide(Int 3a-m).

The equimolar mixture of Int 2a-m (5 mmol) and guanidine hydrochloride(5 mmol) were refluxed in Dioxane in presence of K$_2$CO$_3$ (10 mmol) for 24 h. The completion of reaction was confirmed by TLC. After completion of reaction, it was poured in ice water. Separated solid was filtered and washed with water and dried to afford Int 3a-m. Solid product was titurated with diethylether to get analytical pure compounds.

General procedure for the synthesis of 4-chloro-2-(4-isoproxyphenyl)-6-isopropyl-N-phenyl-1,2-dihydropyrimidine-5-carboxamide (Int 4a-m).

Int 3a-m (6 mmol) was suspended in 25 ml MDC and cooled for 0.5 hrs. Then sulphuryl chloride(30 mmol) was added drop wise and allowed to stir for 1h in ice
bath. The completion of reaction was confirmed by TLC. After completion of reaction it was poured in satd NaHCO$_3$ solution. MDC layer was distilled out under vacuum. Solid product present in water was filtered and washed to afford pure compound (Int-4a-m)

General procedure for the synthesis of 4-((4-(bis(2-chloroethyl)amino)phenyl)amino)-2-isoproxy-6-isopropyl-N-phenyl-1,2-dihydropyrimidine-5-carboxamide (JPM A-M).

$N,N$-bis(2-chloroethyl)benzene-1,4-diamine hydrochloride (5 mmol) and Int 4a-m (5mmol) were dissolved in IPA or EtOH. Few drops of con HCl were added in to the reaction mixture and it was refluxed for 2-4 h. Reaction progress was monitored on TLC. After completion of reaction, reaction mixture was cooled in ice-bath. The crystallized solid was filtered and recrystallised from IPA or EtOH to get final compound (JPM A-M)
### 3.5 Spectral data of the synthesized compounds

4-((4-(bis(2-chloroethyl)amino)phenyl)amino)-2-(4-isopropoxyphenyl)-6-isopropyl-N-(p-tolyl)pyrimidine-5-carboxamide (JPM-A):

Light yellow solid; mp 190-192°C; Rf:0.47(6:4 hexane-EtOAc); IR (KBr): 3344, 2837, 1664, 1591, 1510, 1440, 1319, 1002, 744, 690 cm⁻¹; ¹H NMR (δ ppm): 1.32(s, 6H, -CH(CH₃)₂), 1.40(s, 6H, CH(CH₃)₂), 2.37(s, 3H, -CH₃), 3.34(s, 1H, -CH), 3.49(s, 2H, (-CH₂-), 3.67(s, 2H, (-CH₂-)), 3.77(s, 4H, (-CH₂-)), 4.46-4.55(m, 1H, -CH), 6.19-6.20(d, 1H, Ar-H, J=6 Hz), 6.71-6.72(d, 1H, Ar-H, J=4.4Hz), 6.76-6.78(d, 1H, Ar-H, J=7.2Hz), 6.87-6.89(d, 1H, Ar-H, J=6.4 Hz), 7.01-7.02(d, 1H, Ar-H, J=6.0Hz), 7.201-7.208(d, 2H, Ar-H, J=2.8Hz), 7.28(s, 1H, Ar-H), 7.36-7.38(d, 1H, Ar-H, J=7.2Hz), 7.45-7.46(d, 1H, Ar-H, J=5.2), 7.81-7.82(d, 1H, Ar-H, J=4.8Hz), 8.23-8.25(d, 1H, Ar-H, J=7.2), 8.39-8.40(d, 1H, Ar-H, J=5.6), 10.29(s, 1H, -NH-), 10.92(s, 1H, -NH-); ¹³C NMR (δ ppm): 20.23, 20.57, 21.14, 31.33, 41.02, 52.04, 73.99, 111.58, 118.62, 119.84, 126.27, 126.75, 128.64, 130.11, 131.72, 136.59, 138.42, 144.90, 145.46, 145.93, 160.03, 161.35, 168.52 MS (m/z): 619(M⁺), Anal. Calcd for: C₃₄H₃₉Cl₂N₅O₂; C, 65.80; H, 6.33; N, 11.28; Found: C, 65.09; H, 6.18; N, 11.72.

4-((4-(bis(2-chloroethyl)amino)phenyl)amino)-2-(4-isopropoxyphenyl)-6-isopropyl-N-(4-methoxyphenyl)pyrimidine-5-carboxamide (JPM-B):

Light yellow solid; mp 196-198°C; Rf:0.46(6:4 hexane-EtOAc); IR (KBr):3343, 2961, 2838, 1662, 1594, 1508, 1442, 1314, 1001, 743, 691, 662 cm⁻¹; MS (m/z): 635(M⁺); Anal. Calcd for: C₃₄H₃₉Cl₂N₅O₃; C, 64.15; H, 6.17; N, 11.00; Found: C, 64.36; H, 6.09; N, 11.32.

4-((4-(bis(2-chloroethyl)amino)phenyl)amino)-N-(4-fluorophenyl)-2-(4-isopropoxyphenyl)-6-isopropylpyrimidine-5-carboxamide (JPM-C):

Light yellow solid; mp 188-190°C; Rf:0.46(6:4 hexane-EtOAc); IR (KBr):3336, 2968, 2839, 1663, 1592, 1512, 1442, 1319, 1001, 845, 743, 691, 664 cm⁻¹; ¹H NMR (δ ppm): 1.32-1.33(d, 6H, -CH(CH₃)₂), 1.41-1.42(d, 6H, -CH(CH₃)₂), 3.25-3.27(d, 1H, -CH, J=9.1Hz), 3.74(s, 8H, (-CH₂-)), 4.35-4.37(d, 1H, -CH, J=8.4), 6.70-6.72(d, 2H, Ar-H, J=8.7Hz), 6.88-6.90(d, 1H, Ar-H, J=8.2Hz), 7.01-7.03(d, 2H, Ar-H, J=8.1Hz), 7.20-7.21(d, 1H, Ar-H, J=8.4Hz), 7.36-7.38(d, 1H, Ar-H, J=8.7Hz), 7.60-7.61(d, 1H, Ar-H,
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4-((4-(bis(2-chloroethyl)amino)phenyl)amino)-N-(4-bromophenyl)-2-(4-isopropoxyphenyl)-6-isopropylpyrimidine-5-carboxamide (JPM-D):

Light yellow solid; mp 195-197°C; Rf:0.44(6:4 hexane-EtOAc); IR (KBr): 3334, 2967, 2834, 1667, 1595, 1514, 1447, 1317, 1003, 846, 741, 693, 667 cm⁻¹; MS (m/z):685 (M⁺); Anal. Calcd for: C₃₃H₃₆Cl₂F₂N₅O₂; C, 57.82; H, 5.29; N, 10.22; Found: C, 57.34; H, 5.24; N, 10.21.

4-((4-(bis(2-chloroethyl)amino)phenyl)amino)-N-(4-chlorophenyl)-2-(4-isopropoxyphenyl)-6-isopropylpyrimidine-5-carboxamide (JPM-E):

Light yellow solid; mp 187-189°C; Rf:0.46(6:4 hexane-EtOAc); IR (KBr):3335, 2971, 2840, 1663, 1593, 1515, 1446, 1321, 1007, 849, 749, 688, 672 cm⁻¹; ¹H NMR(δ ppm): 1.25-1.27(d, 6H, -CH(CH₃)₂, J=4.8Hz), 1.37-1.39(d, 6H, -CH(CH₃)₂, J=5.2Hz), 3.22-3.31(m, 1H, -CH), 3.77(s, 8H, (-CH₂)₄), 4.28-4.39(m, 1H, -CH), 5.12(s, 1H, -NH), 6.85-6.87(d, 2H, Ar-H, J=8.7Hz), 7.04-7.06(d, 1H, Ar-H, J=7.6Hz), 7.18-7.20(d, 2H, Ar-H, J=8.1Hz), 7.34-7.37(t, 1H, Ar-H), 7.69-7.71(d, 1H, Ar-H, J=7.3Hz), 7.81-7.83(d, 1H, Ar-H, J=5.2), 7.96-7.98(d, 1H, Ar-H, J=8.1); ¹³C NMR(δ ppm): 21.05, 21.87, 31.95, 41.00, 52.08, 70.35, 113.17, 117.68, 117.91, 126.96, 128.07, 136.60, 137.34, 137.98, 158.26, 161.08, 165.23, 168.23 MS (m/z):640 (M⁺); Anal. Calcd for: C₃₃H₃₆Cl₂N₅O₂; C, 61.83; H, 5.66; N, 10.93; Found: C, 61.13; H, 5.45; N, 10.68.

4-((4-(bis(2-chloroethyl)amino)phenyl)amino)-N-(3-chloro-4-fluorophenyl)-2-(4-isopropoxyphenyl)-6-isopropylpyrimidine-5-carboxamide (JPM-F):

Light yellow solid; mp 173-175°C; Rf:0.45(6:4 hexane-EtOAc); IR (KBr): 3321, 2971, 2840, 1663, 1592, 1546, 1510, 1442, 1396, 1356, 1320, 1001, 919, 843, 742,
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692, 665, 631 cm\(^{-1}\); MS (m/z): 658 (M\(^+\)); Anal. Calcd for: C\(_{33}\)H\(_{35}\)Cl\(_3\)FN\(_5\)O\(_2\); C, 60.14; H, 5.35; N, 10.63; Found: C, 60.03; H, 5.22; N, 10.21.

\(\text{4-((4-(bis(2-chloroethyl)amino)phenyl)amino)-N-(3,4-dimethylphenyl)-2-(4-isopropoxyphenyl)-6-isopropylpyrimidine-5-carboxamide (JPM-G):}\)

Light yellow solid; mp 199-201°C; R\(_f\): 0.49 (6:4 hexane-EtOAc); IR (KBr): 3337, 2963, 2836, 1664, 1593, 1516, 1445, 1318, 1005, 850, 749, 688 cm\(^{-1}\); \(^{13}\)C NMR(δ ppm): 20.14, 21.11, 31.88, 41.01, 52.07, 72.41, 114.31, 119.86, 126.25, 129.31, 135.09, 137.93, 144.08, 144.63, 145.47, 157.02, 159.61, 160.02 MS (m/z): 633 (M\(^+\)); Anal. Calcd for: C\(_{35}\)H\(_{41}\)Cl\(_2\)N\(_5\)O\(_2\); C, 66.24; H, 6.51; N, 11.04; Found: C, 65.92; H, 6.31; N, 11.21.

\(\text{4-((4-(bis(2-chloroethyl)amino)phenyl)amino)-N-(2,4-dimethylphenyl)-2-(4-isopropoxyphenyl)-6-isopropylpyrimidine-5-carboxamide (JPM-H):}\)

Light yellow solid; mp 234-236°C; R\(_f\): 0.48 (6:4 hexane-EtOAc); IR (KBr): 3328, 2971, 2842, 1659, 1598, 1512, 1451, 1324, 1009, 857, 741, 682, 664 cm\(^{-1}\); MS (m/z): 633 (M\(^+\)); Anal. Calcd for: C\(_{35}\)H\(_{41}\)Cl\(_2\)N\(_5\)O\(_2\); C, 66.24; H, 6.51; N, 11.04; Found: C, 66.22; H, 6.31; N, 11.08.

\(\text{4-((4-(bis(2-chloroethyl)amino)phenyl)amino)-2-(4-isopropoxyphenyl)-6-isopropyl-N-(4-(trifluoromethyl)phenyl)pyrimidine-5-carboxamide (JPM-I):}\)

Light yellow solid; mp 186-188°C; R\(_f\): 0.41 (6:4 hexane-EtOAc); IR (KBr): 3346, 2965, 2839, 1664, 1592, 1549, 1520, 1442, 1401, 1078, 1001, 918, 743, 692 cm\(^{-1}\); MS (m/z): 673 (M\(^+\)); Anal. Calcd for: C\(_{34}\)H\(_{36}\)Cl\(_2\)F\(_3\)N\(_5\)O\(_2\); C, 60.54; H, 5.38; N, 10.38; Found: C, 60.21; H, 5.44; N, 10.22.

\(\text{4-((4-(bis(2-chloroethyl)amino)phenyl)amino)-N-(2-chlorophenyl)-2-(4-isopropoxyphenyl)-6-isopropylpyrimidine-5-carboxamide (JPM-J):}\)

Light yellow solid; mp 197-199°C; R\(_f\): 0.46 (6:4 hexane-EtOAc); IR (KBr): 3331, 3121, 2968, 2841, 1663, 1615, 1592, 1546, 1511, 1439, 1394, 1358, 1182, 1120, 1007, 823, 750, 692 cm\(^{-1}\); MS (m/z): 640 (M\(^+\)); Anal. Calcd for: C\(_{33}\)H\(_{36}\)Cl\(_3\)N\(_5\)O\(_2\); C, 61.83; H, 5.66; N, 10.93; Found: C, 61.04; H, 5.45; N, 10.85.
**4-((4-(bis(2-chloroethyl)amino)phenyl)amino)-N-(2-fluorophenyl)-2-(4-isopropoxyphenyl)-6-isopropylpyrimidine-5-carboxamide (JPM-K):**

Light yellow solid; mp 217-219°C; Rf:0.41(6:4 hexane-EtOAc); IR (KBr):3306, 3119, 2969, 2855, 1663, 1649, 1614, 1534, 1513, 1452, 1393, 1255, 1186, 1121, 915, 812, 750, 691 cm⁻¹; MS (m/z): 622(M⁺); Anal. Calcd for: C_{33}H_{36}Cl_{2}FN_{5}O_{2}; C, 63.46; H, 5.81; N, 11.21; Found: C, 63.21; H, 5.67; N, 11.02.

**4-((4-(bis(2-chloroethyl)amino)phenyl)amino)-N-(3,4-dimethylphenyl)-2-(4-isopropoxyphenyl)-6-isopropylpyrimidine-5-carboxamide (JPM-L):**

Light yellow solid; mp 191-193°C; Rf:0.41(6:4 hexane-EtOAc); IR (KBr): 3330, 3159, 2969, 2842, 1662, 1648, 1591, 1536, 1515, 1442, 1398, 1355, 1313, 1261, 1132, 1009, 942, 846, 812, 790, 742, 692 cm⁻¹; MS (m/z): 674(M⁺); Anal. Calcd for: C_{33}H_{35}Cl_{4}N_{5}O_{2}; C, 58.68; H, 5.22; N, 10.37; Found: C, 58.74; H, 5.15; N, 10.31.

**4-((4-(bis(2-chloroethyl)amino)phenyl)amino)-2-(4-isopropoxyphenyl)-6-isopropyl-N-(4-nitrophenyl)pyrimidine-5-carboxamide (JPM-M):**

Light yellow solid; mp 211-213°C; Rf:0.39(6:4 hexane-EtOAc); IR (KBr):3331, 2963, 1664, 1592, 1513, 1444, 1317, 1006, 859, 743, 687 cm⁻¹; ¹H NMR(δ ppm): 1.32(s, 6H, -CH(CH₃)₂), 1.40(s, 6H, -CH(CH₃)₂), 3.74(s, 8H, 4(-CH₂-)), 6.72-6.73(d, 2H, Ar-H, J=8.3Hz), 6.79-6.80(d, 1H, Ar-H, J=7.9Hz), 6.89-6.90(d, 2H, Ar-H, J=8.1Hz), 7.23-7.25(d, 1H, Ar-H, J=8.3Hz), 7.45-7.47(t, 1H, Ar-H), 7.80-7.82(t, 1H, Ar-H), 8.07(s, 1H, Ar-H), 8.24-8.25(d, 1H, Ar-H, J=8.1), 8.40(s, 1H, Ar-H); ¹³C NMR(δ ppm): 19.01, 19.72, 20.19, 21.34, 31.32, 41.01, 52.05, 72.58, 114.09, 124.42, 126.51, 129.39, 129.53, 134.82, 135.53, 136.81, 139.95, 141.43, 157.08, 158.04, 158.93, 161.84; MS (m/z):650 (M⁺); Anal. Calcd for: C_{33}H_{35}Cl_{2}N_{6}O_{4}; C, 60.83; H, 5.57; N, 12.90; Found: C, 60.71; H, 5.53; N, 12.87.
3.6 Spectra of synthesized compounds

Mass spectrum of JPM-A

IR spectrum of JPM-A
$^1$H NMR spectrum of JPM-A
$^{13}$C NMR spectrum of JPM-A
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Mass spectrum of JPM-C

![Mass spectrum of JPM-C](image)

IR spectrum of JPM-C

![IR spectrum of JPM-C](image)
$^1$H NMR spectrum of JPM-C
$^{13}$C NMR spectrum of JPM-C
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Mass spectrum of JPM-E

![Mass spectrum of JPM-E](image1)

IR spectrum of JPM-E

![IR spectrum of JPM-E](image2)
\( ^{1}H \) NMR spectrum of JPM-E
$^{13}$C NMR spectrum of JPM-E
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Mass spectrum of JPM-G

![Mass spectrum of JPM-G](image)

IR spectrum of JPM-G

![IR spectrum of JPM-G](image)
$^{13}$C NMR spectrum of JPM-G
Mass spectrum of JPM-M

![Mass spectrum of JPM-M](image)

IR spectrum of JPM-M

![IR spectrum of JPM-M](image)
$^1$H NMR spectrum of JPM-M
\( ^{13}C \) NMR spectrum of JPM-M
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References


