Synthesis and Characterization of 2-methyl-4,6-disubstituted Pyrimidine derivatives

3.1. Introduction

Aryl and alkyl substituted amides exhibit different biological activity such as antibacterial [1-3], analgesic [4], anticancer [5], diuretic [6], anticonvulsant [7], insecticidal [8], antifungal, photosynthesis inhibitor [9] and antiviral activity [10, 11]. N-Formyl hydroxylamide derivatives act as a potent peptide deformylase inhibitor [12]. In addition to that, dihydroquinoline carboxylic amides have wide spectrum of biological effects including antitubercular and anti-inflammatory activity [13-15].

Amides of Pyrimidine derivatives possess important structural moiety for drug designing and acts as component in a number of useful drugs which are associated with many biological and therapeutical activities. Condensed pyrimidine derivatives have been reported as anticancer [16-19], anti-microbial [20-22] analgesic [23], anti-inflammatory, ulcerogenic [24, 25], anti-viral [26], anti-tumour [27], antioxidant [28, 29], antifungal [30], anti-HIV-1 [31], anthelmintic agents [32] and also used as drugs for COX-2[33] and dynamin inhibitors [34].

Valery V. Mezheritsky et al. [35] reported the synthesis of 4-acylhydrazinopyrazole[3,4-d]pyrimidine from 6-chloroprazolo[3,4-d]pyrimidine (2) from 6-chloropyralzolo[3,4-d]pyrimidine (1), dehydration of acylhydrazide (2) on heating gives rise to pyrazolo[4,3-e][1,2,4]triazolo[4,3-c]pyrimidine (3). Structure of the isomers has been established by XRD studies.

\[
\begin{align*}
   &\text{Cl} &\text{HN} &\text{HN} \\
   &\text{N} &\text{N} &\text{R} \\
   &\text{N} &\text{N} &\text{R} \\
   &\text{N} &\text{N} &\text{R} \\
   &\text{N} &\text{N} &\text{R} \\
   \end{align*}\]

\[R = \text{CH}_3, \text{C}_2\text{H}_5; \quad R^1 = 4-\text{ClC}_6\text{H}_5\]
Zhi - Hui Peng et al. [36] developed a highly regioselective amination using LiHMDS as base and Pd as catalyst, amination of 6-aryl-2,4-dichloropyrimidine (4) using LiHMDS and Pd catalyst which strongly favors the formation of the C4-isomers (5) and (6). The reaction is applicable to aliphatic secondary amines and anilines, both electron withdrawing and electron-donating C6-aryl groups gave high regioselectivity with catalyst.

\[
\begin{align*}
4 & \quad \text{Ar} = 4\text{-F-}C_6H_4, 4\text{-ClC}_6H_4 \\
5 & \quad \text{Ar} = 4\text{-F-}C_6H_4, 4\text{-ClC}_6H_4 \\
6 & \quad \text{Ar} = 4\text{-F-}C_6H_4, 4\text{-ClC}_6H_4 \\
\end{align*}
\]

A. V. Erkin and V. I Krutikov [37] synthesized a series of arylamino pyrimidines (7) and tested them for their anti-bacterial and anti-tubercular properties. Newly synthesized compounds showed in vitro activities against *Staphylococcus aureus*, but most of the compounds exhibited good anti-tubercular activity.

\[
\begin{align*}
7 & \quad \text{Ar} = \text{Ph, 3-MeC}_6H_4, 4\text{-MeC}_6H_4, 4\text{-MeOC}_6H_4, 4\text{-FC}_6H_4, 3\text{-ClC}_6H_4, 3\text{-BrC}_6H_4, 4\text{-BrC}_6H_4, 4\text{-IC}_6H_4. \\
\end{align*}
\]

Oliver R. Thiel et al. [38] worked for the development of small molecules which will antagonize TRPV1 gene in mice. In this direction, they synthesized the target molecule (8). Here they have explained the synthesis of the piperazine building block with pyrimidine nucleus in good yield adopting a highly efficient and selective coupling step using mild organic base. The compound (8) was found to be a good anti-inflammatory compound.
Benzylaminopyrimidine hydrochloride (9a) and (9b) benzylthiopyrimidine hydrochloride (9c) and (9d) and substituted amino pyrimidines (10) were prepared by A.V. Erkin et al. [39] The newly synthesized compounds showed significant antimicrobacterial activity against various bacterial and fungal strains.

9;  
\[ \text{a: Ar = 3-BrC_6H_4, X = NH,  b: Ar = 4-IC_6H_4, X = NH,} \]
\[ \text{c: Ar = 3-BrC_6H_4, X = S,  d: Ar = 4-IC_6H_4, X = S} \]

10;  
\[ \text{Ar = 3-BrC_6H_4,} \]

In view of identification of novel and efficient pyrimidine piperazine derivatives incorporated with morpholine and pyrazole ring systems as orally prescribable phosphatidylinositol-3-kinase (PI3K) inhibitors. Adrian J. Folkes et al. [40] synthesized number of derivatives via different scheme to obtain the title compounds. All the pyrimidine derivatives were screened for their anticancer activity against phophatidylinositol-3-kinase protein. Compound (11) exhibited excellent PI3K inhibitor, which was taken further for human clinical trial.
In search of novel medicine to treat Schizophrenia, E Pinard et al. [41] synthesized variety of compounds including pyrimidine piperazine derivative as non-dopaminergic agents. Among the synthesized compound (12) has shown significant activity.

In an effort to develop synthetic procedure for cross-coupling reaction of aromatic pyrimidine amines with halo compounds, J L. Henderson et al. [42] used a combination of RuPhos and RuPhospre catalyst for the cross coupling reaction of haloazindoles with aminopyrimidine. They have reported that, reaction using these catalysts afforded (13) in good yield during the cross coupling reactions compared to conventional method.

Timothy P. Heffron et al. [43] designed and synthesized small molecules by keeping morpholinothienopyrimidine as core moiety and synthesized piperazine with thienopyrimidine ring system to get (14). Optimization and testing of all the compounds for their PI3K and mTOR activity led to the discovery of number of PI3K and mTOR
inhibitors. Out of which one of the compounds (14) showed excellent potency as PI3K and mTOR inhibitor.

\[ R = \text{H, 1-methyl-4-(methylsulfonyl)piperazine, N-ethyl-N-methylmethanesulfonamide, (methylsulfonyl)benzene, (4-methylpiperazin-1-yl)(phenyl)methanone} \]

Mi–Yeon Jang et al. [44] in search of immunosuppressive agent synthesized 7-N-Piperazinylthiazolo[5,4-d]pyrimidine analogues. The newly synthesized compounds (15) and (16) were subjected for cell based MLR assay. Different series of compound of (15) (16) and (17) with (ring-B); thiazolo, oxazolo, purine and thieno system were prepared. Among these compounds thiazolo pyrimidine, thienopyrimidine and purine ring containing compounds were found to be effective one.

\[ R = \text{C}_{6}\text{H}_{11}, \ R^1 = \text{Br} \]

A Mollard et al. [45] synthesized pyrimidine derivatives and studied their *insilico* affinity for receptor tyrosine kinase AXL a potential oncology target. Computational data resulted in the synthesis of 2, 4, 5 trisubstitute pyrimidines (18) and (19) and checked for *in vitro* activity against several pancreatic cell lines and found to be potent.
D M. Goldstein et al. [46] synthesized two novel anti-inflammatory compounds adopting different routes for their synthesis. The synthesized compounds (20) and (21) were evaluated for their activity to inhibit the cytokine production, in a variety of *in vivo* and *in vitro* models. It has been found that compounds (20) and (21) showed very good P38 inhibition and reduce the pain associated with inflammation.

Y Yana et al. [47] in search of new injectable integrin α2β3/αIIIβ3 dual antagonists, focused on the synthesis of a series of mimetic of RGD tripeptide sequence. Small molecular antagonists 102 tricyclic piperazine/piperidine furnished molecules (22) and (23) by combinational use of comparative molecules field analysis (CoMFA), comparative similarity indices analysis (CoMSIA) and molecular docking reveal the requisite 3D structural features impacting for their antagonistic activity. Statistical results of their work satisfied internal and external predictability, along with good consistency between CoMFA and CoMSIA counter maps and the models were found to be reliable and robust from the docking studies.
With the objective to identify potent anticancer agents like pyrimidine piperazine derivatives, Jonathan B. Baell et al. [48] designed and synthesized quinazoline sulfonamides by adopting two synthetic pathways. First path involved reaction between 2,4-dinitrobenzene with N-Boc piperazine, followed by deprotection of Boc group. Deprotected product subjected to cyclization, followed by Suzuki coupling to get quinazoline sulfonamide derivatives (24). In second synthetic path tert-butyl-4-(4-cyano-3-nitrophenyl)piperazine-1-carboxylate was reduced and converted to amino quinazoline using formamide acetate followed by acid hydrolysis of the Boc protecting group was carried out to get intermediate compound. Intermediate obtained was coupled with appropriate sulfonamides in presence of copper (I) iodide and palladium tetrakis(triphenylphosphine)palladium(0) to get another set of quinazoline sulfonamide derivatives (25). All the compounds were tested for their binding affinity for Bcl-x2 and Bcl-2 proteins, only few compounds showed potent inhibition against the proteins.
Synthesis of amino pyrimidines and their anticancer activity was successfully carried out by Ahamed kamal et al. [49] Series of aniline substituted pyrimidine derivatives were synthesized using precursor’s2-methyl-5-nitroaniline, substituted acetophenone and 2-methyl-5-nitroaniline on treating with HNO₃ resulted in corresponding guanidine. Which on coupling with chalcones obtained from reaction of substituted acetophenone with DMF-DMA gave corresponding nitropyrimidines. Further upon reduction in presence of SnCl₂ gave amino compounds; these amino compounds were finally treated with appropriate sulfonyl chlorides to obtain title compounds. All the compounds were screened for inhibition of cell proliferation activity. Out of all the tested compounds, compounds (26) and (27) showed moderate inhibition while compound (28) proved to be more potent than the other two.
27

28
Present work

In recent year’s extensive research has been carried out on the design, synthesis and pharmacological evaluation of amide containing Pyrimidine ring for different activities, they have been proven to be important pharmacophores. Among them various substituted amide derivatives containing Pyrimidine ring are of important class of bioactive compounds with a wide spectrum of research importance, because of their pharmacological significance. Literature survey has given the positive information on amide with pyrimidine’s and their biological significance. This prompted us to plan for the synthesis of novel series of amide derivatives bearing 2-methyl-4, 6-disubstituted pyrimidine moiety with piperazine nucleus as shown in the Scheme 3.1 their biological activities such as antimicrobial, anthelmintic, anti-inflammatory and anticancer activity are discussed in detail in Chapter 6 of the thesis.

3.2. Materials and Methods

All the chemicals were purchased from Spectrochem, Merck India, SD Fine and Sigma–Aldrich. Chemicals and solvents used were of Laboratory Reagent grade. Completion of reaction was confirmed by thin layer chromatography using precoated TLC plates which involves separation of substances of a mixture over a thin layer of an adsorbent (silica gel or alumina) about 0.2 mm thickness is spread over a aluminum sheet of suitable size and solvent systems are dichloromethane / methanol (9:1) or petroleum ether / ethyl acetate (6:4). Further purification of compounds was done using column chromatography. Melting points were determined in one end open capillary tubes on a liquid paraffin bath and are uncorrected. Liquid chromatography mass spectra, $^1$H Nuclear Magnetic Resonance spectra and $^{13}$C nuclear magnetic resonance spectra were recorded for the compounds on Agilent Mass spectrometer, Bruker model avance II (399.65 MHz, $^1$H NMR) and Bruker model avance II (100 MHz, $^{13}$C NMR) instruments respectively. Chemical shifts were reported in parts per million (δ ppm) using tetramethylsilane (TMS) as an internal standard, LCMS was recorded using Water Allience 2795 separations module and Water micro mass detector and elemental analysis (CHN) was performed in an Elementary Micro cube analyzer.
3.3. Experimental

Reagents and conditions a) tetrakis, Cs$_2$CO$_3$, aq ethanol, 1,4-dioxane, Δ, 4 h. b) tetrakis, Cs$_2$CO$_3$, aq ethanol, 1,4-dioxane, Δ, 5 h. c) LiOH, aq THF, Δ, 1 h. d) EDC.HCl, HOBr, TEA, EDC, 12 h. e) 1,4-dioxane, HCl, EDC, Δ, 2 h. f) EDC.HCl, HOBr, TEA, EDC, 10 different acids (10a-j), 12 h.

Scheme 3.1
Procedure for the preparation of Methyl-2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine-4-carboxylate (3):
Bis(pinacolato)dibaron (2) (0.14 mol) was taken in 250 mL of 1,4-dioxane, ethanol and water solvent system (2:2:1) at room temperature under nitrogen atmosphere. The reaction mixture was degassed with argon for 15 min and Cs$_2$CO$_3$ (0.29 mol), tetrakis (0.05 mol) were added and content of the reaction again degassed with argon for 25 min. Compound (1) (0.18 mol) was added and the reaction mixture was heated 4 h at 65 °C. The mixture was cooled to RT and added ethyl acetate, filtered over celite which is washed with excess of ethyl acetate. Compound was extracted with ethyl acetate, dried over anhydrous MgSO$_4$ and concentrated to get the crude product which was further purified by column chromatography to get the title compound (3) as pale brown solid. IR (KBr, cm$^{-1}$): 2984.30 (CH stretching), 1589.06 (C=O stretching), 1559.17 (C=N stretching) (Fig 3.1); $^1$H-NMR (CDCl$_3$) δ ppm : 8.60 (s, 1H, Ar-H), 3.79 (s, 3H, O-CH$_3$), 2.81 (s, 3H, CH$_3$), 1.37 (s, 12H) (Fig 3.2); $^{13}$C NMR (CDCl$_3$) δ ppm: 159.45, 150.22 (2C), 141.15, 136.29, 84.87 (2C), 44.65 (O-CH$_3$), 24.73 (5C). 79.98, 46.88 (4C), 28.36 (3C) (Fig 3.3); MP: 177-178 °C; Yield: 65%.

Procedure for the preparation of methyl-6-(4-chloro-2-(trifluoromethyl)phenyl)-2-methylpyrimidine-4-carboxylate (5):
Compound (3) (0.071 mol) was taken in ethanol, 1,4-dioxane and water (200:200:100 ml) at RT under inert atmosphere. The reaction mixture was degassed with argon for 15 min and Cs$_2$CO$_3$ (0.179 mol), tetrakis (0.003 mol) were added and degassed for 25 min. 1-bromo-4-chloro-2-(trifluoromethyl)benzene (0.079 mol) (4) was added and the reaction mixture was heated at 65 °C for 5 h. Reaction mixture was cooled to RT and added ethyl acetate which was filtered over celite. The filtrate was washed with water and brine solution. The organic layer was dried over anhydrous MgSO$_4$ and concentrated to get the crude product which was purified by column chromatography to get the title compound (5). IR (KBr, cm$^{-1}$): 2974.66 (CH stretching), 1741.41 (C=O stretching), 1589.17 (C=N stretching) (Fig 3.4); $^1$H NMR (CDCl$_3$) δ ppm : 8.06 (s, 1H, Ar-H), 7.83 (d, J = 1.5 Hz, 1H, Ar-H), 7.69-7.66 (m, 1H, Ar-H), 7.50 (d, J = 8.3 Hz, 1H, Ar-H), 3.79 (s,3H, O-CH$_3$), 2.81 (s, 3H, Ar-CH$_3$) (Fig 3.5); $^{13}$C NMR (CDCl$_3$) δ ppm: 168.28, 167.44, 163.86, 155.63(CO), 136.48, 134.90, 132.48, 130.43 (CF$_3$), 127.34, 126.89, 124.17, 116.69, 50.59, 25.63, (Fig 3.6); MP:199-200 °C; Yield 60%.
Fig 3.1: IR spectrum of intermediate Compound 3
Fig 3.2: $^1$H NMR spectrum of intermediate Compound 3
Fig 3.3: $^{13}$C NMR spectrum of intermediate Compound 3
Fig 3.4: IR Spectrum of intermediate Compound 5
Fig 3.5: $^1$H NMR spectrum of intermediate Compound 5
Fig 3.6: $^{13}$C NMR spectrum of intermediate Compound 5
Procedure for the preparation of 6-(4-chloro-2-(trifluoromethyl)phenyl)-2-methylpyrimidine-4-carboxylic acid (6):

Compound (5) (0.010 mol) and lithium hydroxide (0.181 mol) taken in aqueous THF (200 ml) and heated the reaction mixture at 60 °C for 1 h. Cooled the reaction mixture to RT, adjusted to pH 6, precipitate was filtered and dried to get title compound (6). \(^1\)H-NMR (CDCl\(_3\)) \(\delta\) ppm: 8.06 (s, 1H, Ar-H), 7.83 (s, 1H, Ar-H) 7.69 (d, \(J = 8.3\) Hz, 1H, Ar-H), 7.50 (d, \(J = 8.3\) Hz, 1H, Ar-H) 2.89 (s, 3H, Ar-CH\(_3\)) (Fig 3.7). LCMS: 316.9 (M+1) complies with the calculated mass 315.9 (Fig 3.8). MP: 221-222 °C. Yield: 90 %.

General Procedure for the preparation for to tert-butyl 4-(6-(4-chloro-2-(trifluoromethyl)phenyl)-2-methylpyrimidine-4-carbonyl)piperazine-1-carboxylate (8):

Compound (6) (0.47 mol), N-Boc piperazine (7) (0.056 mol), EDC.HCl (0.117 mol), HOBt (0.23 mol) and TEA (0.14 mol) were stirred in dry ethylene dichloride (160 mL) under inert atmosphere at RT for 12 h. After completion of the reaction, the organic layer was washed with water, brine then dried over anhydrous Na\(_2\)SO\(_4\) and evaporated. Crude compound (8) was purified by neutral alumina column chromatography. \(^1\)H-NMR (CDCl\(_3\)) \(\delta\) ppm: 7.79 (s, 1H, Ar-H), 7.63 (d, \(J = 7.9\) Hz, 1H, Ar-H) 7.50 (d, \(J = 8.7\) Hz, 1H, Ar-H), 3.79 (t, \(J = 9.9\) Hz, 4H, CH\(_2\)NCH\(_2\)), 3.58 (t, \(J = 10.3\) Hz, 4H, CH\(_2\)NCH\(_2\)), 2.81 (s, 3H, Ar-CH\(_3\)), 1.48 (s, 9H, CH\(_3\)) (Fig 3.9); \(^1\)H-NMR (CDCl\(_3\)) \(\delta\) ppm: 173.71, 169.99, 167.76, 165.18, 159.65, 136.16, 132.51, 130.72, 125.91, 121.58, 115.10, 53.06, 45.80, 43.99, 42.99, 42.47, 25.99, 8.42, (3C) (Fig 3.10); MP:241-242 °C; Yield 83%.

Procedure for the preparation of (6-(4-chloro-2-(trifluoromethyl)phenyl)-2-methylpyrimidin-4-yl)(piperazin-1-yl)methanone (9):

Compound (8) (0.041 mol) was taken in 1,4-dioxane.HCl (200 ml) and refluxed for 2 h. solvent was distilled off, residue was triturated with pet ether to obtain the title compound (9). IR (KBr, cm\(^{-1}\)): 2695.03 (CH stretching), 1673.91 (C=O stretching), 1575.96 (C=N stretching), 1215.90 (CF\(_3\) bending) (Fig 3.11); \(^1\)H-NMR (CDCl\(_3\)) \(\delta\) ppm: 9.75 (s, 1H, NH), 7.80 (s, 1H, Ar-H), 7.67 (d, \(J = 7.9\) Hz, 1H, Ar-H), 7.61 (s, 1H, Ar-H), 7.50 (d, \(J = 8.3\) Hz, 1H, Ar-H), 4.11 (t, \(J = 5.4\) Hz, 4H, H\(_2\)CNCH\(_2\)), 3.34 (t, \(J = 5.2\) Hz, 4H, H\(_2\)CNCH\(_2\)), 2.81 (s, 3H, Ar-CH\(_3\)) (Fig 3.12); MP: 221-222 °C. Yield: 84 %.
Fig 3.7: $^1$HNMR spectrum of intermediate Compound 6.
Fig 3.8: LCMS of intermediate compound 6
Fig 3.9: $^1$H NMR spectrum of intermediate Compound 8
Fig 3.10: $^{13}$C NMR spectrum of intermediate Compound 8
Fig 3.11: IR Spectrum of intermediate Compound 9
Fig 3.12: $^1$H NMR of intermediate Compound 9
General Procedure for the preparation of (6-(4-chloro-2-(trifluoromethyl)phenyl)-2-methylpyrimidin-4-yl)(4-(substituted)piperazin-1-yl)methanone (11a-j):

Scaffold (9) (0.130 mol), different substituted acids (10a-j) (0.195 mol), EDC.HCl (0.325 mol), HOBt (0.0065 mol) and TEA (0.39 mol) were taken in dry ethylene dichloride (8 ml) stirred the reaction mixture under nitrogen at 80°C for 12 h. After completion of the reaction, the reaction mixture was washed with water and brine, then dried over anhydrous MgSO₄ and evaporated. Crude compound was purified by column chromatography to get amides of pyrimidine (11a-j) in good yield. Physical data of all the final compounds are entered in Table 3.1.

Spectral interpretation of final compounds (11a-j)

(6-(4-chloro-2-(trifluoromethyl)phenyl)-2-methylpyrimidin-4-yl)(4-(2,3-dichlorobenzoyl)piperazin-1-yl)methanone (11a):

IR: (KBr, cm⁻¹): 2924.52 (CH stretching), 1649.81 (C=O stretching), 1536.99 (C=N stretching), 1166.72 (CF₃ bending) (Fig 3.13); ¹HNMR (399.6 MHz, CDCl₃) δ ppm: 8.04 (d, J = 7.9 Hz, 1H, Ar-H), 7.79 (s,1H, Ar-H), 7.72 (d, J = 7.9 Hz, 1H, Ar-H), 7.66 (d, J = 8.3 Hz, 1H, Ar-H), 7.49 (d, J = 9.1 Hz, 2H, Ar-H), 7.40 (t, J = 15.9 Hz, 1H, Ar-H), 3.89 (t, J = 9.9 Hz, 2H, N-CH₂), 3.71 (t, J = 9.5 Hz, 2H, N-CH₂), 3.49 (t, J = 9.8, 4H, N-CH₂), 2.80 (s, 3H, -CH₃). (Fig 3.14); ¹³C NMR (100 MHz, CDCl₃) δ ppm: 167.70, 165.80 (C=O), 165.37 (C=O), 167.40, 138.10, 136.07, 135.54, 134.75, 132.48, 132.11, 130.58 (CF₃), 130.33, 129.80, 129.48, 127.30, 127.08, 124.25, 121.52, 116.75, 46.98, 45.89, 45.37, 42.20, 26.04. (Fig 3.15); LC-MS (m/z) Calculated (Found) 557.18 (559.00) (M+1) complies. (Fig 3.16); CHN analysis report complies with the calculated percentage (Fig 3.17).

(6-(4-chloro-2-(trifluoromethyl)phenyl)-2-methylpyrimidin-4-yl)(4-(4-fluorobenzoyl)piperazin-1-yl)methanone (11b):

IR: (KBr, cm⁻¹): 2915.84 (CH stretching), 1649.21 (C=O stretching), 1536.99 (C=N stretching), 1166.72 (CF₃ bending) (Fig 3.18); ¹HNMR (399.6 MHz, CDCl₃) δ ppm: 7.78 (s, 1H, Ar-H), 7.65 (d, J = 8.2 Hz, 1H, Ar-H), 7.58 (t, J = 5.1 Hz, 2H, Ar-H), 7.49 (t, J = 13.5 Hz, 3H, Ar-H), 7.38-7.33 (m, 1H, Ar-H), 3.92 (t, J = 10.3 Hz, 2H, NCH₂), 3.75 (t, J = 9.9 Hz, 2H, NCH₂), 3.21 (t, J= 9.9 Hz, 4H, CH₂NCH₂), 2.79 (s, 3H, CH₃). (Fig 3.19); ¹³CNMR (100 MHz, CDCl₃) δ ppm: 167.70, 165.83 (C=O), 165.29 (C=O), 163.77, 165.25, 160.29, 137.56, 136.13, 135.30, 132.50, 131.19 (CF₃), 127.12, 123.35, 121.53, 120.64, 120.43, 116.78, 115.08, 114.84, 46.37, 46.12, 45.60, 41.65, 26.06. (Fig 3.20); HPLC: 100% (Fig 3.21); CHN: CHN analysis report complies with the calculated percentage (Fig 3.22).
Fig 3.13: IR Spectrum of Compound 11a
Fig 3.14: $^1$H NMR spectrum of Compound 11a
Fig 3.15: $^{13}$C NMR spectrum of Compound 11a
Fig 3.16: LCMS of compound 11a
Fig 3.17: CHN Analysis of compound 11a

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Fig 3.18: IR Spectrum of Compound 11b
Fig 3.19: $^1$H NMR spectrum of Compound 11b
Fig 3.20: $^{13}$C NMR spectrum of Compound 11b
Fig 3.21: HPLC spectrum of compound 11b
Fig 3.22: CHN Analysis of compound 11b

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(6-(4-chloro-2-(trifluoromethyl)phenyl)-2-methylpyrimidin-4-yl)(4-(2,5-dimethoxybenzoyl)piperazin-1-yl)methanone (11c):
**IR:** (KBr, cm\(^{-1}\)): 2839.67 (CH stretching), 1632.45 (C=O stretching), 1494.52 (C=N stretching), 1154.19 (CF\(_3\) bending) (Fig 3.23); **\(^1\)H NMR** (399.6 MHz, CDCl\(_3\)) \(\delta\) ppm: 7.78 (s, 1H, Ar-H), 7.66 (d, \(J = 7.9\) Hz, 1H, Ar-H), 7.49-7.43 (m, 3H, Ar-H), 7.10 (d, \(J = 9.1\) Hz, 1H, Ar-H), 6.98 (d, \(J = 8.79\) Hz, 1H, Ar-H), 3.89 (t, \(J = 13.1\) Hz, 2H, NCH\(_2\)), 3.42 (t, \(J = 9.9\) Hz, 4H, CH\(_2\)NCH\(_2\)), 2.79 (s, 3H, -CH\(_3\)).

**13C NMR** (100 MHz, CDCl\(_3\)) \(\delta\) ppm: 167.79, 165.68 (C=O), 165.41 (C=O), 160.62, 153.07, 150.88, 136.07, 135.56, 132.51, 132.14, 129.26, (CF\(_3\)), 129.45, 127.07, 126.45, 121.54, 120.55, 116.59, 116.02, 114.01, 56.59, 55.96, 47.04, 46.08, 45.60, 42.29, 26.06. (Fig 3.25); **HPLC:** 100 % (Fig 3.26); CHN analysis report complies with the calculated percentage (Fig 3.27).

(6-(4-chloro-2-(trifluoromethyl)phenyl)-2-methylpyrimidin-4-yl)(4-(cyclopropanecarbonyl)piperazin-1-yl)methanone (11d):
**IR:** (KBr, cm\(^{-1}\)): 2928.36 (CH stretching), 1653.66 (C=O stretching), 1474.31 (C=N stretching), 1165.76 (CF\(_3\) bending) (Fig 3.28); **\(^1\)H NMR** (399.6 MHz, CDCl\(_3\)) \(\delta\) ppm: 7.80 (s, 1H, Ar-H), 7.67 (d, \(J = 8.3\) Hz, 1H, Ar-H), 7.52 (d, \(J = 3.9\) Hz, 1H, Ar-H), 3.93 (t, \(J = 9.9\) Hz, 2H, NCH\(_2\)), 3.73 (t, \(J = 9.9\) Hz, 2H, NCH\(_2\)), 3.46 (t, \(J = 10.3\) Hz, 4H, CH\(_2\)NCH\(_2\)) 2.86 (s, 3H, -CH\(_3\)).2.32 – 2.30 (m, 1H, junction proton), 1.21 – 1.19 (m, 2H, CH\(_2\)), 1.06-1.01 (m, 2H, -CH2-). (Fig 3.29); **\(^13\)C NMR** (100 MHz, CDCl\(_3\)) \(\delta\) ppm: 167.77, 165.81 (C=O), 165.41 (C=O), 160.49, 136.11, 135.36, 132.51, 132.15, 130.11 (CF\(_3\)), 129.48, 127.16, 124.28, 116.70, 46.80, 46.25, 45.75, 42.04, 26.08, 25.71 (junction C), 4.04 (2C). (Fig 3.30); **HPLC:** Purity 97.18 % (Fig 3.31); CHN analysis report complies with the calculated percentage (Fig 3.32).
Fig 3.23: IR Spectrum of Compound 11c
Fig 3.24: $^1$H NMR spectrum of Compound 11c
Fig 3.25: $^{13}$C NMR spectrum of Compound 11c
Fig 3.26: HPLC spectrum of compound 11c
Fig 3.27: CHN Analysis of compound 11c

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Fig 3.28: IR Spectrum of Compound 11d
Fig 3.29: $^1$HNMR spectrum of Compound 11d
Fig 3.30: $^{13}$C NMR spectrum of Compound 11d
Fig 3.31: HPLC spectrum of compound 11d
Fig 3.32: CHN Analysis of compound 11d

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1-(4-(6-(4-chloro-2-(trifluoromethyl)phenyl)-2-methylpyrimidine-4-carbonyl)piperazin-1-yl)-2-(2,4-dichlorophenyl)ethanone (11e):

IR: (KBr, cm\(^{-1}\)): 2859.92 (CH stretching), 1639.20 (C=O stretching), 1475.28 (C=N stretching), 1166.72 (CF\(_3\) bending) (Fig 3.33); \(^1\)H NMR (399.6 MHz, CDCl\(_3\)) \(\delta\) ppm: 7.79 (s, 1H, Ar-H), 7.66 (d, \(J = 8.3\) Hz, 1H, Ar-H), 7.52 (d, \(J = 6.3\) Hz, 2H, Ar-H), 7.42 (s, 1H, Ar-H), 7.25 (d, \(J = 1.5\) Hz, 2H, Ar-H), 3.83 (s, 2H, -CH\(_2\)-), 3.81 (t, \(J = 4.36\) Hz, 4H, CH\(_2\)NCH\(_3\)), 3.65 (t, \(J = 4.36\) Hz, 4H, CH\(_2\)NCH\(_2\)) 2.81 (s, 3H, -CH\(_3\)). (Fig 3.34); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) ppm: 169.84, 167.79, 165.59(C=O), 165.58 (C=O), 160.52, 149.27, 136.88, 136.96, 135.41, 135.83, 132.16, 130.39(CF\(_3\)), 129.88, 127.20, 125.39, 122.56, 121.62, 119.81, 116.83, 46.94 (4C), 42.41, 26.06. (Fig 3.35); HPLC: 100% (Fig 3.36); CHN analysis report complies with the calculated percentage (Fig3.37).

2-(benzo[d][1,3]dioxol-4-yl)-1-(4-(6-(4-chloro-2-(trifluoromethyl)phenyl)-2-methylpyrimidine-4-carbonyl)piperazin-1-yl)ethanone (11f):

IR: (KBr, cm\(^{-1}\)): 2862.81 (CH stretching), 1649.8 (C=O stretching), 1468.53 (C=N stretching), 1137.8 (CF\(_3\) bending) (Fig 3.38); \(^1\)H NMR (399.6 MHz, CDCl\(_3\)) \(\delta\) ppm: 7.79 (s, 1H, Ar-H), 7.66 (d, \(J = 7.99\) Hz, 1H, Ar-H), 7.48 (s, 2H, Ar-H), 6.78-6.66 (m, 3H, Ar-H), 5.91 (s, 2H, O-CH\(_2\)-O), 3.77-3.43 (m, 10H, CH\(_2\)(CH\(_2\)NCH\(_2\))), 2.81 (s, 3H, CH\(_3\)). (Fig 3.39); \(^13\)CNMR (100 MHz, CDCl\(_3\)) \(\delta\) ppm: 169.96, 169.80, 167.87, 165.78 (C=O), 1665.42, (C=O), 160.57, 148.09, 146.66, 136.12, 135.41, 132.53, 132.15, 129.57 (CF\(_3\)), 127.98, 124.30, 121.57, 121.44, 116.66, 108.52, 101.10 (O-CH\(_2\)-O), 46.80, 46.71, 45.58, 42.25, 40.36, 26.07. (Fig 3.40); LC-MS (m/z) Calculated (Found) 546.1(547.1) (M+1 and sodium adduct peak) complies; (Fig 3.41); CHN analysis report complies with the calculated percentage (Fig 3.42).

(6-(4-chloro-2-(trifluoromethyl)phenyl)-2-methylpyrimidin-4-yl)(4-(2,3-difluorobenzoyl)piperazin-1-yl)methanone (11g):

IR: (KBr, cm\(^{-1}\)): 2923.25 (CH stretching), 1648.10 (C=O stretching), 1563.99 (C=N stretching), 1166.27(CF\(_3\) bending); \(^1\)H NMR (399.6 MHz, CDCl\(_3\)) \(\delta\) ppm: 8.05 (d, \(J = 7.99\) Hz, 1H, Ar-H), 7.79 (s, 1H, Ar-H), 7.22 (d, \(J = 7.8\) Hz, 1H, Ar-H), 7.61(d, \(J = 8.2\) Hz, 1H, Ar-H), 7.49 (d, \(J = 9.1\) Hz, 2H, Ar-H) 7.40 (t, \(J = 15.98\) Hz, 1H, Ar-H), 3.88 (t, \(J = 9.8\) Hz, 2H, N-CH\(_2\)), 3.71 (t, \(J = 9.4\) Hz 2H, N-CH\(_2\)), 3.49 (t, \(J = 9.3\) Hz, 4H, CH\(_2\)NCH\(_2\)), 2.79 (s, 3H CH\(_3\)) ; \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) ppm: 167.60, 164.90 (C=O), 164.80 (C=O), 161.40, 138.10, 136.07, 135.32, 134.74, 132.46, 132.10, 130.56 (CF\(_3\)), 130.32, 129.78, 129.46, 127.28, 127.01, 124.25, 121.25, 116.57, 46.96, 45.89, 45.73, 42.02, 26.05; CHN analysis report complies with the calculated percentage (Fig 3.43).
Fig 3.33: IR Spectrum of Compound 11e
Fig 3.34: $^1$H NMR spectrum of Compound 11e
Fig 3.35: $^{13}$C NMR spectrum of Compound 11e
Fig 3.36: LCMS of compound 11e
**Fig 3.37: CHN Analysis of compound 11e**

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Fig 3.38: IR Spectrum of Compound 11f
Fig 3.39: $^1$H NMR spectrum of Compound 11f
Fig 3.40: $^{13}$C NMR spectrum of Compound 11f
Fig 3.41: LCMS of compound 11f
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Fig 3.42: CHN Analysis of compound 11f
Fig 3.43: LCMS of compound 11g
(6-(4-chloro-2-(trifluoromethyl)phenyl)-2-methylpyrimidin-4-yl)(4-(2,4-dimethoxybenzoyl)piperazin-1-yl)methanone (11h):

**IR: (KBr, cm\(^{-1}\))** 2840.67 (CH stretching), 1636.54 (C=O stretching), 1492.65 (C=N stretching), 1150.91(CF\(_3\) bending); \(^1H\) NMR: (399.6 MHz, CDCl\(_3\)) \(\delta\) ppm: 7.78 (s, 1H, Ar-H), 7.65 (d, J = 7.9 Hz 1H, Ar-H), 7.49-7.43 (m, 3H, Ar-H), 7.10 (d, J = 9.1 Hz, 1H, Ar-H) 6.98 (d, J = 8.7 Hz, 1H, Ar-H), 3.89 (t, J = 13.0 Hz, 2H, N-CH\(_2\)), 3.87 (s, 3H, O-CH\(_3\)), 3.79 (s, 3 H, O-CH\(_3\)), 3.79 (t, J = 9.9 Hz, 2H, NCH\(_2\)), 3.42 (t, J = 9.8 Hz, 4H, CH\(_2\)NCH\(_2\)), 2.79 (s, 3H, CH\(_3\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) ppm: 167.79, 165.68 (C=O), 165.40 (C=O), 160.61, 153.06, 150.87, 136.07, 135.36, 132.51, 132.14, 129.25 (CF\(_3\)), 129.14, 127.06, 126.45, 121.53, 120.54, 116.59, 116.02, 114.01, 56.54, 55.95, 47.03, 46.07, 45.59, 42.24, 26.05.

(6-(4-chloro-2-(trifluoromethyl)phenyl)-2-methylpyrimidin-4-yl)(4-(2,4-dimethoxybenzoyl)piperazin-1-yl)methanone (11i):

**IR: (KBr, cm\(^{-1}\))** 2920.48 (CH stretching), 1639.21 (C=O stretching), 1539.91 (C=N stretching), 1167.27 (CF\(_3\) bending);

\(^1H\) NMR (399.6 MHz, CDCl\(_3\)) \(\delta\) ppm: 7.78 (s, 1H, Ar-H), 7.66 (d, J = 8.2 Hz 1H, Ar-H), 7.58 (t, J = 5.1 Hz, 2H, Ar-H), 7.49 (m, 4H, Ar-H), 3.92 (t, J = 10.2 Hz, 2H, NCH\(_2\)), 3.75 (s, 3H, O-CH\(_3\)), 3.14 (t, J = 9.9 Hz, 4H, CH\(_2\)NCH\(_2\)), 2.79 (s, 3H, CH\(_3\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) ppm: 167.73, 165.81 (C=O), 165.17 (C=O), 163.74, 161.52, 160.29, 137.54, 136.31, 135.30, 132.51, 132.14, 129.25 (CF\(_3\)), 129.14, 127.06, 126.45, 121.53, 120.54, 116.59, 116.02, 114.01, 56.54, 55.95, 47.03, 46.07, 45.59, 42.24, 26.05; LC-MS (m/z) Calculated (Found) 523.33(524.31) (M+1) complies.

(6-(4-chloro-2-(trifluoromethyl)phenyl)-2-methylpyrimidin-4-yl)(4-(2,4-dimethoxy-6-methylbenzoyl)piperazin-1-yl)methanone (11j):

**IR: (KBr, cm\(^{-1}\))** 2839.67 (CH stretching), 1632.45 (C=O stretching), 1493.52 (C=N stretching), 1153.19 (CF\(_3\) bending); \(^1H\) NMR (399.6 MHz, CDCl\(_3\)) \(\delta\) ppm: 7.78 (s, 1H, Ar-H), 7.66 (d, J = 7.9 Hz 1H, Ar-H), 7.49 (s, 1H, Ar-H), 7.10(d, J = 9.1 Hz, 1H, Ar-H), 6.98 (s, 1H, Ar-H), 6.96 (s, 1H, Ar-H), 3.89 (t, J = 13.1 Hz, 4H, CH\(_2\)NCH\(_2\)), 3.87 (s, 3H, O-CH\(_3\)), 3.80 (s, 3H, O-CH\(_3\)), 3.61 (t, J = 9.9 Hz, 4H, CH\(_2\)NCH\(_2\)), 2.79 (s, 3H, CH\(_3\)), 2.77(s, 3H, CH\(_3\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) ppm: 167.79, 165.68 (C=O), 165.40 (C=O), 160.62, 153.07, 136.06, 135.36, 132.51, 132.14, 129.76 (CF\(_3\)), 129.45, 127.07, 126.46, 121.54, 120.55, 116.95, 116.02, 114.01, 56.59, 55.91, 47.04, 46.08, 45.60, 42.29, 26.06, 24.12.
Table 3.1: Physical data of final molecules (11a-j)

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3.4. Results and Discussion

In view of literature survey on the properties of pyrimidine, compound (3) was prepared via borylation reaction by reacting (1) with (2) in the presence of tetrakis and Cs$_2$CO$_3$ in 1,4-dioxane and aqueous ethanol. Then intermediate (3) was made to react with compound 4 in the presence of Cs$_2$CO$_3$ and catalytic amount of tetrakis undergo Suzuki reaction to give (5) which was then hydrolyzed in presence of lithium hydroxide to get intermediate (6), which was further reacted with reagent (7) to gave compound (8). Boc was cleaved from (8) to get key intermediate (9). The scaffold (9) was made to react with different carboxylic aids (10a-j) to get amides containing pyrimidine nucleus (11a-j).

In IR spectrum of compound (11a), CH stretching, C=O stretching, C=N Stretching and CF$_3$ bending frequencies appears in the range 2924.52, 1649.81, 1536.99 and 1166.72 cm$^{-1}$ respectively.

In proton-NMR spectrum of compound (11a), dichlorobenzene and 4-chloro-2-trifluoromethyl benzene protons appears in the range 8.04-7.40 ppm. Aromatic protons of dichlorobenzene appears as a multiplet in the range 7.61-7.40 ppm, other aromatic atoms of 4-chloro-2-trifluoromethylbenzene and pyrimidine 1H appears at 8.04 -7.79 ppm. Piperazine protons appears in the range 3.89-3.49 (t, 8H) and methyl protons appears at 2.80 (s, 3H).

In carbon-13 NMR spectrum of compound (11a), carbons of dichlorobenzene and 4-chloro-2-trifluoromethylbenzene appears in the range 135.34-116.75 ppm and ipso carbons C$_9$, C$_{11}$, C$_{15}$& C$_{24}$ appears at 167.70, 160.40, 138.10 and 136.07 ppm respectively. The carbonyl (C=O) carbons appears at 165.80 and 165.37 ppm and aliphatic carbon of piperazine ring C$_2$, C$_3$, C$_5$ and C$_6$ appears at 46.98-42.20 ppm. Methyl carbon attached to pyrimidine ring appears at 26.04 ppm. All these
evidences complies the assigned structure for the compound (11a). Similarly all the newly synthesized compounds were characterized.

### 3.5. Conclusion

The research work was focused on the efficient synthesis of amides containing 2-methyl-4,6-disubstituted pyrimidine nucleus. The reactions performed were ecofriendly as they are carried out at moderate temperature 50-60 °C by using solvents ethanol, 1,4-dioxane, HCl and ethylene dichloride to get final compounds with good yield, short time interval and high purity. Newly synthesized compounds were characterized by IR, $^1$H and $^{13}$C NMR, LCMS, HPLC and CHN analysis. The newly synthesized compounds were screened for their biological activities, such as antibacterial, antifungal, anthelmintic, anti-inflammatory and anticancer activities. The details of the biological results obtained have been presented in Chapter 6 of the thesis.
3.6. References


