Synthesis And Characterization Of Novel Pyrimidine-4,5-Diamine As Anticancer Agent

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**ABSTRACT**
Unlike latent cells, cancer cells supply deoxyribonucleoside triphosphates to cells continuously and thereby, prop up the uncontrolled cancer growth. Pyrimidine has been concerned in the separation of leukemic cells, known as adenine bioisosteres, as well as its biological activities, especially its anticancer properties. In this context, a novel series of N_5-(3-substituted benzylidene)-N_4-phenyl pyrimidine-4,5-diamine [5A-5F] / N_5-(2-substituted benzylidene)-N_2,N_2-dimethyl-N_4-phenyl pyrimidine-2,4,5-triamine [5a-5f] were synthesized by using the starting ingredient formimidamide/4-(dimethylamino) benzimidamide and sodium ethoxide. The synthesized compounds were characterized by IR, ^1^H NMR, and Mass spectral analyses and screened for their biological studies. In the present study, pyrimidine derivatives and their insilico modeling were done by using c-Src kinase and p38 MAP kinase complex followed by the evaluation of their anticancer activity. The screening of synthesized scaffolds possessed significant activity against HeLa cell lines and showed similar activity compared to standard Cisplatin. Among all the synthesized compounds, N_5-(4-hydroxybenzylidene)-N_4-phenyl pyrimidine-4,5-diamine 5A, N_5-benzylidene-N_4-phenylpyrimidine-4,5-diamine 5C, N_2-benzylidene-N_2-benzylidene-N_4-benzylidene-N_2-dimethyl-N_2-phenyl pyrimidine-2,4,5-triamine 5c, and N_5-(4-methoxy benzylidene)-N_4-phenyl pyrimidine-4,5-diamine 5E showed the highest significant anticancer activity.

**INTRODUCTION**
The pyrimidine scaffold represents a widespread nucleus in a lot of pharmaceutically active compounds and suggestive of a broad range of pharmacological behavior; not only acting as kinase inhibitor but also stand for a well-designed option as initial material for the synthesis of pharmaceutical derivatives that possess diverse activities and show good protection profiles (Selvam et al., 12 a). One of the most important reports is that pyrimidine and fused pyrimidine derivatives acquire a variety of biological activities (Ismail et al., 2016). Various pyrimidine derivatives were tested for their anticancer activities in vitro and in vivo leading to hopeful lead motifs (Balbi et al., 2011). In the present study, we focus on the most significant aspect of pyrimidine, especially N_5-(3-substituted benzylidene)-N_4-phenyl pyrimidine-4,5-diamine [5A-5F] / N_5-(2-substituted benzylidene)-N_2,N_2-
dimethyl-N$_4$-phenyl pyrimidine-2,4,5-triamine [5a-5f]. A large number of pyrimidine and their derivatives are reported to possess a wide range of biological activities such as anticancer (Ahmed et al., 2009), anti-inflammatory (Popik et al., 2006), and antimicrobial (Selvam and Kumar, 10 b,a). Moreover, the pyrimidine derivatives are used as inhibitors of kinases, mainly to inhibit mediating signals of mitogen and other events of cellular activities (Saravanan et al., 2018; Selvam et al., 12 b) such as differentiation, cell proliferation, migration, metabolism, and immune response. Also, many of the observed data indicate that these derivatives might block the proliferation of various cancer cell lines (Kamal et al., 2013; Prabhu et al., 2015). The present review spotlight on pyrimidines as c-Src kinase and p38 MAP Kinase complex inhibitors. The c-Src kinase and p38 MAP Kinase complex signaling is a major resource of cellular processes like migration, survival, proliferation, and succession of a cell. The deregulation processes of mutation or over-expression of kinases is experiential in an integer of disease condition plus cancer and immunological disorders (Frey et al., 2008). Based on their catalytic action, the regulation of varied physiological mechanisms depends on movement, cell creation, differentiation, and metabolism (Arora and Scholar, 2005). The observed documents clearly showed that alterations in kinase activities such as mutations, hyperactivation, and hyper-production lead to the disorder of cascades of cell signaling and enhance several diseases such as diabetes, inflammation, neurological disorders, and cancer (Arora and Scholar, 2005). Thus kinases and their role were considered very important and targeting these kinases may lead to the anticancer drug development regime. Based on the aforementioned report, we had planned to synthesize novel N$_1$-(3-substituted benzylidene)-N$_2$-phenyl pyrimidine-4,5-diamine [5a-5f] / N$_1$-(2-substituted benzylidene)-N$_2$N$_2$-dimethyl-N$_4$-phenyl pyrimidine-2,4,5-triamine [5a-5f] scaffolds, which may display as a clinically significant anticancer agent and the derivatives might direct towards the improvement in bioactivity.

**Experimental Section**

**MATERIALS AND METHODS**

All laboratory-grade solvents used were purchased from SD Fine Chemicals and Merck, Mumbai, India. The Dr. Reddys laboratories Hyderabad, India had gifted the samples of standard Ciprofloxacin and Ketocanzole. Melting points were determined in open glass capillary tubes and were uncorrected. A thin layer chromatography plate was used for the analysis of purity and iodine chamber and UV lamp were used for visualization of TLC spots. The FT-IR spectrophotometers [KBr pellets] were used for the recording of IR spectra. Bruker DXP-300 NMR spectrometer in CDCl$_3$ was used for the recording of $^1$H-NMR spectra [ppm scale] with internal standard tetramethylsilane. JEOL-SX-102 mass spectra were used for the impact of ionization of electron. Perkin Elmer 240C analyzer was used for elemental analyses within the theoretical values of ± 0.4 %.

**General Procedure**

The Scheme 1 (Cui et al., 2018) to construct pyrimidine nucleus: In the first step, the equimolar quantity of formimidamide/ 4-(dimethylamino) benzimidamide [10 mmol], sodium ethoxide, (0.5 g in 5 mL water), and 25 ml of ethanol were stirred mechanically for 5 min. Then, ethyl 3-(dimethylamino)-2-nitroacrylate (10 mmol) was added and heated for 1 hr at 40 °C. It was recrystallized using ethyl alcohol to get pure 5-nitropyrimidine-4-ol/2-(4-(dimethylamino)phenyl)-5-nitropyrimidine-4-ol (1), and it was monitored by TLC. A mixture of 5-nitropyrimidine-4-ol/2-(4-(dimethylamino)phenyl)-5-nitropyrimidine-4-ol (1) underwent chlorination by using POCl$_3$ (10 mmol) and 10 mL of N, N-Diisopropylethylamine [DIEA]. Further, it was refluxed for 30 min on 80 °C, and it was recrystallized using ethyl alcohol to get pure product 4-chloro-5-nitropyrimidine/4-(4-chloro-5-nitropyrimidin-2-yl)-N,N-dimethylaniline. (2) A mixture of 4-chloro-5-nitropyrimidine/4-(4-chloro-5-nitro pyrimidine-2-yl)-N,N-dimethylaniline (2) (10 mmol) reacted with aniline (10 mmol) in 10 mL of DMF at 80 °C and quenched in ice water to get the precipitate. It was then filtered, washed with water, and recrystallized using ethyl alcohol to get 5-nitro-N-phenylpyrimidin-4-amine/2-(4-(dimethylamino)phenyl)-5-nitro-N-phenyl pyrimidin-4-amine (3). A mixture of 5-nitro-N-phenylpyrimidin-4-amine/2-(4-(dimethylamino)phenyl)-5-nitro-N-phenyl pyrimidin-4-amine (3) (10 mmol) reacted with Zn (3 mmol) and CuSO$_4$ (3 mmol) in the water on a magnetic stirrer for 3 h under room temperature to give N$_4$-phenylpyrimidine-4,5-diamine/ 2-(4-(dimethylamino)phenyl)-N$_4$-phenylpyrimidin-4,5-diamine (4). A mixture of 10mmol N$_4$-phenylpyrimidin-4,5-diamine/ 2-(4-(dimethylamino)phenyl)-N$_4$-phenylpyrimidin-4,5-diamine (4) It was added to a solution of an appropriate substituted aromatic aldehyde (10 mmol) in glacial acetic acid (20 mL) containing anhydrous sodium acetate (0.82 g, 10 mmol). It was heated under reflux for 2 h,
Figure 1: Interaction of active [5A-5F]/ [5a-5f] derivatives with the active site of the enzyme-PDBID: 2OIQ & 3LFF.
Table 1: Sureltex Docking score (kcal/mol) of the synthesized 5A-5F/ [5a-5f] derivatives

| Com code | Docking score | 2OIQ | 3LFF |
|----------|---------------|------|------|
| 5A       | -8.02         |      | -2.52|
| 5a       | -5.72         |      | -2.92|
| 5B       | -5.27         |      | -2.07|
| 5b       | -4.16         |      | -7.01|
| 5c       | -6.04         |      | -4.99|
| 5d       | -6.92         |      | -4.00|
| 5d       | -5.18         |      | -4.10|
| 5e       | -4.96         |      | -3.76|
| 5f       | -7.06         |      | -7.49|
| 5f       | -7.20         |      | -4.40|
| 5f       | -5.79         |      | -7.69|
| 5f       | -4.96         |      | -6.85|

Table 2: Anticancer activity of the synthesized compounds [5A-5F]/ [5a-5f]

| Compound          | Cell line | Compound concentration (μmol L⁻¹) | % Growth inhibition | IC₅₀ |
|-------------------|-----------|-----------------------------------|---------------------|------|
|                   |           | 5                                 | 12.5                | 15   | 40   |      |
| 5A 4-Hydroxy      | HeLa      | 61.11                             | 71.21               | 89.11| 97.12| 12.41|
| 5a Unsubstituted  |           | 64.11                             | 79.12               | 79.24| 94.14| 16.27|
| 5B 4-Fluoro       |           | 61.12                             | 74.11               | 86.25| 91.45| 15.12|
| 5b Unsubstituted  |           | 66.41                             | 78.21               | 89.41| 97.41| 12.15|
| 5C 4-Nitro        |           | 9.1                               | 11.12               | 18.21| 19.42| 100   |
| 5d Unsubstituted  |           | 8.12                              | 9.21                | 14.14| 16.41| 100   |
| 5E 4-Methoxy      |           | 6.44                              | 8.11                | 11.52| 15.14| 100   |
| 5f Unsubstituted  |           | 1.45                              | 4.14                | 6.14 | 10.11| 100   |
| 5f 4-Methyl       |           | 44.12                             | 64.11               | 74.11| 88.41| 19.47|
| Cisplatin         |           | 76.15                             | 81.42               | 86.21| 98.27| 10.11|

and then under reduced pressure, the solvent was evaporated. The produced solid was dried to get a crystallized form of N₅-(3-substituted benzylidene)-N₄-phenyl pyrimidine-4,5-diamine [5A-5F]/ N₅-(2-substituted benzylidene)-N₂,N₂-dimethyl-N₄-phenyl pyrimidine-2,4,5-triamine [5a-5f].

Detection Method

N₅-(4-hydroxybenzylidene)-N₂,N₂-dimethyl-N₁-phenylpyrimidine-4,5-diamine [5A]

IR: 3524 (OH), 3121 & 3059 (NH), 2980 (Ar-CH); ¹H NMR: 4.86 (s, 1H, =CH linkage), 4.21 (s, 1H, OH), 3.63 (s, 1H, Ar-CH); Mass: C₁₇H₁₄N₄O; calcd, 333 [M⁺], found, 333 [M⁺]; Elemental Analysis: calcd, C, 70.33; H, 4.86; N, 19.30; O, 5.51; found, C, 70.32; H, 4.83; N, 19.31; O, 5.54

N₅-(4-hydroxybenzylidene)-N₂,N₂-dimethyl-N₁-phenylpyrimidine-2,4,5-triamine [5a]

IR: 3361 (OH), 3032 (NH), 2980 (Ar-CH), 1660 (C=N), 1608 (C=C); ¹H NMR: 2.48 (s, 6H, CH₃), 3.63 (s, 1H, =CH linkage), 4.21 (s, 1H, OH), 5.31 (s, 1H, NH), 6.52-7.79 (m, 10H, Ar-H); calcd, 333 [M⁺], found, 333 [M⁺]; Elemental Analysis: calcd, C, 68.45; H, 5.74; N, 21.01; O, 4.80; found, C, 68.47; H, 5.73; N, 21.10; O, 4.82

N₅-(4-fluorobenzylidene)-N₂,N₂-dimethyl-N₁-phenylpyrimidine-4,5-diamine [5B]

IR: 3266 (OH), 3086 (Ar-CH), 1656 (C=N), 1606 (C=C);
Scheme 1: Synthesis of $N_5$-(3-substituted benzylidene)-$N_4$-phenylpyrimidine-4,5-diamine [5A-5F]/$N_5$-(2-substituted benzylidene)-$N_2,N_2$-dimethyl-$N_4$-phenylpyrimidine-2,4,5-triamine [5a-5f]

(C=C), 1166 (C-F); $^1$H NMR: 3.26 (s, 1H, =CH linkage), 5.26 (s, 1H, NH), 7.36-7.96 (m, 11H, Ar-H); Mass: $C_{17}H_{13}FN_4$; calcd, 292 [M+], found, 292 [M+]; Elemental Analysis: calcd, C, 69.85; H, 4.48; F, 6.50; N, 19.17; found, C, 69.83; H, 4.46; F, 6.53; N, 19.14

$N_5$-(4-fluorobenzylidene)-$N_2,N_2$-dimethyl-$N_4$-phenylpyrimidine-2,4,5-triamine [5b]

IR: 3122 (NH), 3080 (Ar-CH), 1678 (C=N), 1641 (C=C); $^1$H NMR: 2.23 (s, 6H, CH$_3$), 3.24 (s, 1H, =CH linkage), 5.18 (s, 1H, NH), 6.61-7.83 (m, 10H, Ar-H); Mass: $C_{19}H_{18}FN_5$; calcd, 335 [M+], found, 335 [M+]; Elemental Analysis: calcd, C, 68.04; H, 5.41; F, 5.66; N, 20.88; found, C, 68.08; H, 5.43; F, 5.68; N, 20.87

$N_5$-benzylidene-$N_4$-phenylpyrimidine-4,5-diamine [5c]

IR: 3122 (NH), 3080 (Ar-CH), 1678 (C=N), 1641 (C=C); $^1$H NMR: 2.23 (s, 6H, CH$_3$), 3.24 (s, 1H, =CH linkage), 5.18 (s, 1H, NH), 6.61-7.83 (m, 10H, Ar-H); Mass: $C_{19}H_{18}FN_5$; calcd, 335 [M+], found, 335 [M+]; Elemental Analysis: calcd, C, 68.04; H, 5.41; F, 5.66; N, 20.88; found, C, 68.08; H, 5.43; F, 5.68; N, 20.87

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IR: 3363 (NH), 3033 (Ar-CH), 1673 (C=C); 1H NMR: 2.23 (s, 6H, CH₃), 3.23 (s, 1H, =CH linkage), 5.13 (s, 1H, NH), 6.63-7.83 (m, 10H, Ar-H); Mass: C₂₁H₁₆N₅O₂; calcld, 317 [M+], found, 317 [M+]; Elemental Analysis: calcld, C, 71.90; H, 6.03; N, 21.90; found, C, 71.91; H, 6.05; N, 22.03

N₁-(4-nitrobenzylidene)-N₄-phenylpyrimidine-4,5-diamine [SD]
IR: 3118 (NH), 3080 (Ar-CH), 1641 (C=C), 1519 & 1336 (NO₂); 1H NMR: 2.31 (s, 6H, CH₃), 2.47 (s, 3H, OCH₃), 3.43 (s, 1H, =CH linkage), 5.15 (s, 1H, NH), 6.43-7.91 (m, 10H, Ar-H); Mass: C₁₅H₁₀N₄O₂; calcld, 304 [M+], found, 304 [M+]; Elemental Analysis: calcld, C, 70.34; H, 5.05; found, C, 70.36; H, 5.07; O, 5.23

N₁-(2-nitrobenzylidene)-N₂,N₂-dimethyl-N₄-phenylpyrimidine-2,4,5-triamine[SD]
IR: 3147 (NH), 3059 (Ar-CH), 1643 (C=C), 1519 & 1366 (NO₂); 1H NMR: 2.03 (s, 6H, CH₃), 2.47 (s, 3H, OCH₃), 3.43 (s, 1H, =CH linkage), 5.05 (s, 1H, NH), 6.51-7.54 (m, 10H, Ar-H); Mass: C₁₉H₁₆N₅O₂; calcld, 331 [M+], found, 331 [M+]; Elemental Analysis: calcld, C, 72.48; H, 6.39; N, 21.13; found, C, 72.47; H, 6.35; N, 21.12

In Silico Screening Methods
The in silico modelling (Kunjiappan et al., 2019) of N₁-(3-methoxy benzylidene)-N₄-phenyl pyrimidine-4,5-diamine [S1-25]/ N₁-(2-bromo benzylidene)-N₂,N₂-dimethyl-N₄-phenyl pyrimidine-2,4,5-triamine [R1-25] docked with the active site of c-Src kinase, Human p38 MAP Kinase complex. The crystal structures of c-Src kinase, p38 MAP Kinase complex (PDB ID: 2OIQ and 3LFF) were obtained from the Protein Data Bank. The preparation of protein file and SKETCH module and all other parameters were assigned by Surfex-Dock program software.

Anticancer Activity
MTT test
In the MTT assay, HeLa cell line was used, and it was obtained from the National Cancer Institute. Cisplatin was used as a standard and the proceeding was followed by the standard literature protocol (Kunjiappan et al., 2020). Various concentrations of cells were used to treat with the synthesized compounds. The microplate reader was used to measure the absorbance at 570 nm.

RESULTS AND DISCUSSION
Chemistry
The series of heterocycles, N₁-(3-substituted benzylidene)-N₄-phenyl pyrimidine-4,5-diamine [5A-5F]/ N₁-(2-substituted benzylidene)-N₂,N₂-dimethyl-N₄-phenyl pyrimidine-2,4,5-triamine [5A-5f], were synthesized by the reaction of formimidamide/4-(dimethylamino)benzimidamide with an appropriate solution of sodium ethoxide as presented in the Scheme 1. The novel compounds were characterized by FTIR, 1H-NMR, and mass spectroscopy. The IR spectrum of compounds [5A-5F]/ [5A-5f] showed bands of NH group at 3181-3385 cm⁻¹. In [5A-5F]/ [5A-5f], Ar-CH stretching bands appears at 2951-3089 cm⁻¹. The appearance of a strong intensity band in the IR spectra of compounds [5A-5F]/ [5A-5f] in the range of 3181-3385 cm⁻¹ attributable to -NH stretching and provides strong evidence for the confirmation of the conversion chlorine to -NH. The proton magnetic resonance spectra of [5A-5F]/ [5A-5f] and their corresponding derivatives have been recorded.
in CDCl$_3$. In this spectra [5A-5F]/[5a-5f], =CH linkage signals appear at 3.01-3.53 ppm. The presence of =CH linkage proton signals in the $^1$H-NMR spectra of the final compounds confirms the formation of benzylidene moiety. All these observed facts clearly envisage the formation of $N_4$-(3-substituted benzylidene)-$N_2$-phenyl pyrimidine-4,5-diamine [5A-5F]/ $N_4$-(2-substituted benzylidene)-$N_2$-$N_4$-dimethyl-$N_4$-phenyl pyrimidine-2,4,5-triamine [5a-5f] as indicated in the Scheme 1 and confirms the proposed structure [5A-5F]/[5a-5f].

**Molecular docking study**

The PDB-ID: 2OIQ and 3LFF were utilized for molecular docking study, and it exposed that compounds 5A and 5c were active as an inhibitor of c-Src kinase [2OIQ] and 5f and 5b were active as an inhibitor of p38 MAP Kinase complex [3LFF]. The results are given in Table 1 and Figure 1. The title molecules of $N_4$-(3-substituted benzylidene)-$N_2$-phenyl pyrimidine-4,5-diamine [S1-25]/ $N_5$-(2-substituted benzylidene)-$N_2$-$N_4$-dimethyl-$N_4$-phenyl pyrimidine-2,4,5-triamine [R1-25] were screened for their anticancer activity against cervical HeLa (ME 180) cells. To test the anticancer activity, different concentrations (5, 12.5, 25, and 40μmol L$^{-1}$) were used, and drug concentration was plotted after a specified time. IC$_{50}$ was calculated between Cisplatin and synthesized compounds. The results are shown in Table 2. The data from Table 2 reveal that the compounds 5A, 5a, 5B, and 5b exhibited significant activity compared to that of Cisplatin towards the HeLa cell lines and 5c, 5C, 5D and 5d were inactive in the concentration. In comparison with NO$_2$, unsubstituted pyrimidine compounds such as 5E, 5e, 5F, and 5f showed reasonable activity. In the observed results, among all the compounds, 5A and 5b with IC$_{50}$ values of 12.41 and 12.15 showed that both electron-donating -OH and withdrawing -F group with para position enhanced anticancer activity. Thus, nitro and unsubstitutions in pyrimidine showed inactive and other derivatives are considered as a most potent analogue against cancer.

**CONCLUSIONS**

In this review, we have compiled and discussed specifically the anticancer potential of $N_4$-(3-substituted benzylidene)-$N_2$-phenyl pyrimidine-4,5-diamine [5A-5F]/ $N_5$-(2-substituted benzylidene)-$N_2$-$N_4$-dimethyl-$N_4$-phenyl pyrimidine-2,4,5-triamine [5a-5f] derivatives through the inhibition of dissimilar kinase enzymes and their synthetic strategies. The conformation and orientation supplies for kinase binding site through molecular modeling studies indicate the importance of substituent’s [4-Hydroxy, 4-Fluoro, Unsubstituted, 4-Nitro, 4-Methoxy and 4-Methyl] effect. The finding of current studies could afford insight to a medicinal chemist and for clinical development of possible pyrimidine-based anticancer drugs.

**Conflict of interest statement**

The authors declare no competing financial interest.

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