EXPLORING ANTICANDIDAL AND ANTIBIOFILM POTENTIALS OF SYNTHESIZED \(N\)-(SUBSTITUTEDBENZYLIDENE)-4,6-DIMETHOXYPYRIMIDIN-2-AMINE ANALOGUES

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The emergence of resistance in the immunocompromised patients against existing antifungal drugs makes them ineffective causing high incidence and accompanying mortality due to fungal infections. The generation of biofilms by various species of candida is the most frequent underlying mechanism in the emergence of resistance. Biofilms are defined as encapsulated complex microbial colonies in extracellular polymeric substances (EPS) matrix. The development of newer antifungal with lower resistance remains a challenging task for researchers. We herein report, a series of \(N\)-(substituted benzylidene)-4,6-dimethoxypyrimidin-2-amine analogs along with their antibiofilm and antifungal potential in-vitro. Compounds 3a, 3b, 3i, 3k, and 3l have shown better inhibition against C. albicans than Fluconazole (standard antifungal agent). Compounds 3a, 3b, and 3i also exhibited good antibiofilm activity suggesting their antibiofilm as well as antifungal potential. The results show that the new compounds could serve as an important lead in the discovery of effective antifungal agents to overcome the resistance problem associated with the existing antifungal agents.

Keywords: Pyrimidine Schiff bases; Anticandidal activity; Antifungal; Antibiofilm

INTRODUCTION

Candidiasis is a pathological condition that is mainly found in immunocompromised patients. Candidiasis is mainly caused by Candida albicans.¹³ Morphologically, is a versatile microbe that exists in three forms i.e. yeasts, pseudo-hyphae, and hyphae. The lifestyle of C. albicans has two forms, i.e. planktonic and biofilm form which is a dormant condition that helps in the survival of microbe in adverse environmental conditions.⁴⁻¹² The key virulent characteristic of C. albicans is morphogenetic [Yeast-to-Hypha (Y-H)] transitions that facilitate host tissue invasion by the microbe.⁶⁻¹⁰ Besides this Y-H transition, the other contributing factor in Candida infections is the formation of biofilms on host tissues or abiotic devices.⁸⁻¹⁰ Biofilms are defined as encapsulated complex microbial colonies in extracellular polymeric substances (EPS) matrix. An organism developing into a biofilm displays changes in morphology, cellular composition, polymeric substance secretion, and EPS synthesis.¹¹ The EPS contains extracellular nucleic acid and extracellular polymers that uphold the biofilm structure.¹¹ EPS possess nucleic acid which is mainly responsible for structural and protective properties in C. albicans biofilms. The other core of EPS is β 1,3-glucans, which play important role in the protection of biofilm by preventing contact of antifungal drugs.¹¹ The matrix of biofilm plays a dual role in biofilm; it contributes to biofilm structure by providing physical support as well as it is essential for increased tolerance to antifungal drugs. Biofilms formed by Candida turn them more resistant to antifungal agents than planktonic cells.¹³ The traditional treatment for Candida infections includes azoles (fluconazole, itraconazole, and voriconazole),
Echinocandins (anidulafungin, caspofungin, and micafungin), amphotericin B (deoxycholate and various lipid formulations), and flucytosine (5-FC). 14-17 Fluconazole is currently the choice of drug for mucosal and invasive candidiasis because the drug has fewer side effects than amphotericin B. 2,18 However, fluconazole has little effect against different strains of Candida due to the increased number of fluconazole-resistant strains. Furthermore, anticandidal resistance and side effects have made treatment options even more limited against C. albicans. 19 These limitations led scientists to develop newer anticandidal agents with enhanced antibiofilm potential.

Schiff bases are considered important antimicrobial scaffolds. Various synthetic routes were reported for the synthesis of diverse therapeutically active Schiff bases such as pyrimidine Schiff base, 20 piperazine Schiff bases for their antifungal and antibacterial activity, sulphonamide Schiff bases for antibacterial and antifungal activity, 21 piperazine, 22 piperazine, and sulphonamide coupled Schiff bases for antimicrobial activities. 23 On the other hand, pyrimidine nitrogen-containing heterocyclic compounds are of great significance as they are abundant in nature and a wide spectrum of biological activities exhibited by the synthetic/semisynthetic derivatives. 24,25 Pyrimidine derivatives have shown a wide spectrum of biological activities such as antifungal (f-h), 24-27 antibiofilm (f-h), 25,26 antibacterial (a-e), 27 antiviral (j-k), 28 and anticancer (l-m). 29

Fig. 1: Some bioactive pyrimidine derivatives.
Based on the above studies, in the present study, we synthesized novel series of some new N-substituted pyrimidine derivatives and studied their anti-microbial attributes such as anti-morphogenesis and anti-biofilm activities against C. albicans.

**EXPERIMENTAL**

**Chemical methods**

All the starting materials and reagents were of analytical grade purchased from commercial sources (Alfa Aesar) and were used without further purification. \(^1\)H NMR spectra were recorded (at NIPER Hyderabad) in solvent dimethyl sulfoxide (DMSO)-d\(_6\) using BRUKER AV 500MHz (Germany). Chemical shifts were reported in ppm with Tetramethylsilane as an internal standard (TMS, \(\delta = 0.0\)). Mass spectra were recorded on Hitachi LC-QTOF MS/MS (Tokyo, Japan). Melting points were recorded using the ‘ThermoScientific Melting point’ apparatus and are uncorrected.

**General procedure for the synthesis of (E)-N-(substituted benzylidene)-4,6-dimethoxypyrimidin-2-amine (3a-p)**

In a round bottom flask, a 4,6-dimethoxyprymidin-2-amine I (1 mmol) was allowed to react with the substituted aromatic aldehydes (1 mmol) 2a-p under the catalytic influence of ZnCl\(_2\) in ethanol (5 ml) under reflux for 2 h. After the completion of the reaction, as indicated by the TLC, it was cooled and poured into ice-cooled water. The solid product thus obtained was filtered and recrystallized from hot ethanol to obtain the pure product.

**N-(4-chlorobenzylidene)-4,6-dimethoxypyrimidin-2-amine (3a)**

Yield: 86%; m.p. 210 °C; 1H-NMR (500 MHz, DMSO-d6): \(\delta 9.90\) (s, 1H, -CH=N), 7.87 (d, 2H, Phenyl C\(_2\)-H, C\(_3\)-H), 7.64 (s, 2H, Phenyl C\(_2\)-H, C\(_3\)-H), 6.68 (s, 1H, Pyrimidine -CH), 3.58 (s, 6H, -OCH\(_3\)) MS (LC-QTOF) \(\text{C}_{13}\text{H}_{12}\text{ClN}_{3}\text{O}_{2}\) [M+2] Std: 277.71 Found: 279.06.

**N-(2,4-dimethoxybenzylidene)-4,6-dimethoxypyrimidin-2-amine (3b)**

Yield: 89%; m.p. 216 °C; 1H-NMR (500 MHz, DMSO-d6): \(\delta 8.44\) (s, 1H, -CH=N), 7.87 (s, 1H, Phenyl C\(_6\)-H), 6.64 (s, 2H, Phenyl C\(_3\)-H, C\(_7\)-H), 6.48 (s, 1H, Pyrimidine -CH), 3.64 (s, 6H, Benzoylidene -OCH\(_3\)), 3.58 (s, 6H, -OCH\(_3\)) MS (LC-QTOF) \(\text{C}_{13}\text{H}_{12}\text{ClN}_{3}\text{O}_{2}\) Std: 277.71 Found: 278.06.

**N-(2,5-dimethoxybenzylidene)-4,6-dimethoxypyrimidin-2-amine (3c)**

Yield: 88%; m.p. 216 °C; 1H-NMR (500 MHz, DMSO-d6): \(\delta 8.44\) (s, 1H, -CH=N), 7.84 (s, 1H, Phenyl C\(_7\)-H), 6.64 (s, 2H, Phenyl C\(_3\)-H, C\(_4\)-H), 6.48 (s, 1H, Pyrimidine -CH), 3.64 (s, 6H, Benzoylidene -OCH\(_3\)), 3.58 (s, 6H, -OCH\(_3\)) MS (LC-QTOF) \(\text{C}_{13}\text{H}_{17}\text{N}_{3}\text{O}_{4}\) [M+1] Std: 303.31 Found: 303.14.

**N-(3,4-dimethoxybenzylidene)-4,6-dimethoxypyrimidin-2-amine (3d)**

Yield: 88%; m.p. 216 °C; 1H-NMR (500 MHz, DMSO-d6): \(\delta 8.44\) (s, 1H, -CH=N), 7.84 (s, 1H, Phenyl C\(_7\)-H), 6.64 (s, 2H, Phenyl C\(_3\)-H, C\(_4\)-H), 6.48 (s, 1H, Pyrimidine -CH), 3.64 (s, 6H, Benzoylidene -OCH\(_3\)), 3.58 (s, 6H, -OCH\(_3\)) MS (LC-QTOF) \(\text{C}_{15}\text{H}_{17}\text{N}_{3}\text{O}_{4}\) [M+1] Std: 303.31 Found: 304.12.

**N-(3,4,5-trimethoxybenzylidene)-4,6-dimethoxypyrimidin-2-amine (3e)**

Yield: 82%; m.p. 224 °C; 1H-NMR (500 MHz, DMSO-d6): \(\delta 8.44\) (s, 1H, -CH=N), 7.34 (s, 2H, Phenyl C\(_2\)-H, C\(_6\)-H), 6.48 (s, 1H, Pyrimidine -CH), 3.64 (s, 9H, Benzoylidene -OCH\(_3\)), 3.58 (s, 6H, -OCH\(_3\)) MS (LC-QTOF) \(\text{C}_{15}\text{H}_{17}\text{N}_{3}\text{O}_{4}\) Std: 333.34 Found: 334.13.

**N-(3,4-dihydroxybenzylidene)-4,6-dimethoxypyrimidin-2-amine (3f)**

Yield: 88%; m.p. 228 °C; 1H-NMR (500 MHz, DMSO-d6): \(\delta 8.44\) (s, 1H, -CH=N), 7.38 (s, 1H, Phenyl C\(_6\)-H), 7.32 (s, 1H, Phenyl C\(_7\)-H), 6.94 (s, 1H, Phenyl C\(_7\)-H), 6.68 (s, 1H, Pyrimidine -CH), 3.58 (s, 6H, -OCH\(_3\)) MS (LC-QTOF) \(\text{C}_{13}\text{H}_{12}\text{ClN}_{3}\text{O}_{2}\) Std: 275.26 Found: 275.11.

**N-(2-chlorobenzylidene)-4,6-dimethoxypyrimidin-2-amine (3g)**

Yield: 86%; m.p. 212 °C; 1H-NMR (500 MHz, DMSO-d6): \(\delta 8.44\) (s, 1H, -CH=N), 7.87 (d, 1H, Phenyl C\(_6\)-H), 7.64 (d, 1H, Phenyl C\(_3\)-H), 7.56 (t, 1H, Phenyl C\(_4\)-H), 7.46 (d, 1H, Phenyl C\(_5\)-H) 6.68 (s, 1H, Pyrimidine -CH), 3.58 (s, 6H, -OCH\(_3\)) MS (LC-QTOF) \(\text{C}_{13}\text{H}_{12}\text{ClN}_{3}\text{O}_{2}\) [M+1] Std: 277.71 Found: 278.06.
Scheme 1: Synthesis of titled compounds 3a-p.

N-(2,6-chlorobenzylidene)-4,6-dimethoxypyrimidin-2-amine (3h)
Yield: 86%; m.p. 214 °C; 1H-NMR (500 MHz, DMSO-d6): δ 8.44 (s, 1H, -CH=N), 7.48 (m, 3H, Phenyl C6-H, C4-H, C3-H), 6.68 (s, 1H, Pyrimidine -CH), 3.58 (s, 6H, -OCH3) MS (LC-QTOF) C13H11ClN2O2 [M+H]+ Std: 312.15

N-(4-fluorobenzylidene)-4,6-dimethoxypyrimidin-2-amine (3i)
Yield: 89%; m.p. 218 °C; 1H-NMR (500 MHz, DMSO-d6): δ 8.36 (s, 1H, -CH=N), 7.81 (d, 2H, Phenyl C6-H, C4-H), 7.36 (d, 2H, Phenyl C5-H, C3-H), 6.39 (s, 1H, Pyrimidine -CH), 3.80 (s, 6H, -OCH3) MS (LC-QTOF) C13H13F3N2O2 [M+H]+ Std: 261.25 Found: 261.27.

N-(4-nitrobenzylidene)-4,6-dimethoxypyrimidin-2-amine (3j)
Yield: 86%; m.p. 210 °C; 1H-NMR (500 MHz, DMSO-d6): δ 8.36 (s, 1H, -CH=N), 8.33 (d, 2H, Phenyl C6-H, C4-H), 8.09 (d, 2H, Phenyl C5-H, C3-H), 6.49 (s, 1H, Pyrimidine -CH), 3.80 (s, 6H, -OCH3) MS (LC-QTOF) C13H12N3O2 [M+H]+ Std: 288.26

N-(4-dimethylaminobenzylidene)-4,6-dimethoxypyrimidin-2-amine (3k)
Yield: 90%; m.p. 222 °C; 1H-NMR (500 MHz, DMSO-d6): δ 9.95 (s, 1H, -CH=N), 7.50 (d, 2H, Phenyl C6-H, C4-H), 6.81 (d, 2H, Phenyl C5-H, C3-H), 6.49 (s, 1H, Pyrimidine -CH), 3.80 (s, 6H, -OCH3), 3.06 (s, 6H, N-CH3) MS (LC-QTOF) C13H15ClN2O2 [M+H]+ Std: 286.33 Found: 287.15.

N-(4-carboxybenzylidene)-4,6-dimethoxypyrimidin-2-amine (3l)
Yield: 86%; m.p. 208 °C; 1H-NMR (500 MHz, DMSO-d6): δ 11.0 (s, 1H, COOH), 8.37 (d, 2H, Phenyl C6-H, C4-H), 8.36 (s, 1H, -CH=N), 8.04 (d, 2H, Phenyl C5-H, C3-H), 6.49 (s, 1H, Pyrimidine -CH), 3.80 (s, 6H, -OCH3) MS (LC-QTOF) C14H14N2O4 [M+H]+ Std: 287.27 Found: 288.26.

N-(Benzylidene)-4,6-dimethoxypyrimidin-2-amine (3m)
Yield: 86%; m.p. 206 °C; 1H-NMR (500 MHz, DMSO-d6): δ 8.36 (s, 1H, -CH=N), 7.83 (d, 2H, Phenyl C6-H, C4-H), 7.52 (m, 3H, Phenyl C5-H, C3-H, C2-H), 6.49 (s, 1H, Pyrimidine -CH), 3.80 (s, 6H, -OCH3) MS (LC-QTOF) C13H13N2O3 [M+H]+ Std: 243.26 Found: 243.28.

N-(furan-2-ylmethylene)-4,6-dimethoxypyrimidin-2-amine (3n)
Yield: 90%; m.p. 214 °C; 1H-NMR (500 MHz, DMSO-d6): δ 7.75 (d, 1H, furanyl C5-H), 7.50 (s, 1H, -CH=N), 6.93 (d, 1H, furanyl C4-H), 6.52 (t, 1H, furanyl C3-H), 6.49 (s, 1H, Pyrimidine -CH), 3.80 (s, 6H, -OCH3) MS (LC-QTOF) C11H11O2N3 [M+H]+ Std: 233.22 Found: 233.07.

N-((1H-indol-3-yl)methylene)-4,6-dimethoxypyrimidin-2-amine (3o)
Yield: 80%; m.p. 230 °C; 1H-NMR (500 MHz, DMSO-d6): δ 10.1 (s, 1H, indolyl NH), 8.78 (s, 1H, -CH=N), 8.20 (d, 1H, indolyl C4-H), 7.55 (d, 1H, indolyl C2-H), 7.54 (d, 1H, indolyl C7-H), 7.19 (t, 1H, indolyl C5-H), 7.01 (m, 1H, indolyl C3-H), 6.49 (s, 1H, Pyrimidine -CH), 3.80 (s, 6H, -OCH3) MS (LC-QTOF) C15H14N2O3 [M+H]+ Std: 283.30 Found: 283.11.

N-(4-hydroxybenzylidene)-4,6-dimethoxypyrimidin-2-amine (3p)
Yield: 88%; m.p. 228 °C; 1H-NMR (500 MHz, DMSO-d6): δ 8.36 (s, 1H, -CH=N), 7.78 (d, 1H, Phenyl C6-H, C4-H), 6.85 (d, 2H, Phenyl C5-H, C3-H), 6.49 (s, 1H, Pyrimidine -CH), 5.35 (s, 1H, OH) 3.80 (s, 6H, -OCH3) MS (LC-QTOF) C15H15N2O4 [M+H]+ Std: 259.26.
Biological evaluation

Antimicrobial activity

Newly synthesized derivatives were evaluated using the agar method for antifungal and antibiofilm activity by performing an assay against C. albicans. Results were obtained in terms of respective IC₅₀ and MIC. To precise the results, all the experiments were performed in triplicates.

RESULT AND DISCUSSION

Chemistry

The target compounds N-(4-substituted benzylidene)-4,6-dimethoxypyrimidin-2-amine (3a-p) were synthesized through a one-step reaction approach. The formations of titled compounds were confirmed using 1H-NMR and Mass spectral data. The characteristic -CH=NH signal of the formed Schiff base appeared at δ 8.36-9.55 ppm. Besides this, the –CH₃ protons of the methoxy group give a characteristic singlet peak between δ 3-4 ppm. All the aromatic protons of substituted aldehyde 2a-p have appeared in the range of δ 6.52 – 8.37 ppm. On the other hand, -CH peak of pyrimidine appeared at δ 6.49 ppm. The characteristic peak also appeared in recorded mass spectra of almost all the compounds again confirming the successful synthesis of compounds 3a-p.

Anticandidal activity

The synthesized compounds 3a-p were evaluated for their in vitro anticandidal activity by the standard agar dilution method. Anticandidal assay results are shown in Table 1 depict good to excellent inhibition against C. albicans. Compounds 3a, 3b, 3i, 3k, and 3l as shown in Fig.1 displayed better inhibition against C. albicans than Fluconazole (MIC = 50μg/mL) with MIC values of 39.8, 45.1, 42.6, 43.2, and 49.1 μg/mL, respectively. Better anticandidal activity is controlled by the presence of substitution at the 4th position of the phenyl ring. However, more potent activity was shown by the compounds (3a, 3b, 3i) having electron-withdrawing group substitution at 4th position of the phenyl ring.

Table 1: Anticandidal activity, Anti-biofilm activity of compounds 3a-p.

| Entry | Chemical Formula | Anticandidal activity (MIC Values in μg/mL) | Anti-biofilm activity (IC₅₀ μM) |
|-------|------------------|-------------------------------------------|--------------------------------|
| 3a    | C₁₃H₁₂ClN₃O₂    | 39.8                                      | 36.4                          |
| 3b    | C₁₅H₁₇N₃O₄     | 45.1                                      | 43.2                          |
| 3c    | C₁₅H₁₇N₃O₄     | 133.6                                     | 185.3                         |
| 3d    | C₁₅H₁₇N₃O₄     | 69.3                                      | 74.3                          |
| 3e    | C₁₆H₁₉N₃O₅     | 181.3                                     | -                             |
| 3f    | C₁₃H₁₃N₁O₄     | -                                         | -                             |
| 3g    | C₁₃H₁₂ClN₅O₂   | 161.5                                     | 116                           |
| 3h    | C₁₃H₁₁ClN₃O₂   | 138.1                                     | 188.3                         |
| 3i    | C₁₃H₁₂FN₁O₂    | 42.6                                      | 41.5                          |
| 3j    | C₁₃H₁₂N₃O₂     | 108.3                                     | 103                           |
| 3k    | C₁₅H₁₈N₃O₂     | 43.2                                      | 58.3                          |
| 3l    | C₁₄H₁₃N₁O₄     | 49.1                                      | 62                            |
| 3m    | C₁₃H₁₃N₃O₂     | 61.5                                      | 49                            |
| 3n    | C₁₁H₁₁N₃O₂     | -                                         | -                             |
| 3o    | C₁₅H₁₄N₄O₂     | 91.2                                      | 95.6                          |
| 3p    | C₁₃H₁₃N₅O₃     | 88.4                                      | 91.3                          |
| Fluconazole | -            | 50                                         | 40                            |
Antibiofilm activity

Compounds 3a, 3b, and 3i also exhibited good antibiofilm activity with IC50 values of 36.4, 43.2, and 41.5 μM, respectively, suggesting their antibiofilm as well as anticanidal potentials shown in Fig. 2. Also, compounds 3l and 3m also showed moderate biofilm inhibitory potential during assay with IC50 values of 62 and 49 μM, respectively.

Similar to anticanidal activity, antibiofilm activity of the synthesized compounds was potentiated with the 4th position substitutents present on the phenyl ring. Amongst the synthesized compounds, compound 3a with 4-chloro substitution at the 4th position of the side ring exhibited the most potent biofilm as well as candidal inhibition with MIC = 39.8 and IC50 = 36.4 μM against C. Albicans. The compound 3i with 4-fluoro substituions also delivered potent anti-biofilm activity with IC50 = 41.5 μM. Interestingly, compounds 3a and 3i also delivered more potent anticanidal activity than fluconazole against C. albicans suggesting electron-withdrawing groups on the para position have better anticanidal and antibiofilm activity. On contrary, more than one substitution of the electron-withdrawing group, or the presence of substitution at other positions tends to have a negative impact on the activity of synthesized compounds.

Fig. 1: Graphical representation of anticanidal activity of 3a-p.

Fig. 2: Graphical representation of the anti-biofilm activity of 3a-p.
Conclusion

In summary, a simple, facile anti-biofilm, anticanidal potential of synthesized pyrimidine Schiff base was done. Compounds 3a, 3b, 3i, 3k, and 3l have shown better inhibition against C. albicans than Fluconazole (standard anticanidal agent). Compounds 3a, 3b, and 3i also exhibited good antibiofilm activity suggesting their antibiofilm as well as anticanidal potential. Compounds 3l and 3m also showed moderate biofilm inhibitory potential during the assay. The results show that the new compounds could serve as an important lead in the discovery of effective anticanidal agents to overcome the resistance problem associated with the existing anticanidal agents.

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Conflict of Interest

No conflict of interest was declared by the authors.

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استكشاف إمكانات مضادات فطر المبيضات ومضادات الغشاء الحيوي لنظام ن- (بدائل بنزيليدين) - 4-16-ثنائي ميثيل اوكسي بيريميدين-2-امين

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إن ظهور المقاومة لدى المرضى الذين يعانون من نقص المناعة ضد مضادات فطر المبيضات الموجودة يجعلها غير فعالة مما يؤدي إلى ارتفاع معدل الإصابة والوفيات المصاحبة بسبب العدوى الفطرية. إن إنتاج الأغشية الحيوية بواسطة أنواع مختلفة من المبيضات هو الأليلة الكامنة الأكثر شيوعًا في ظهور المقاومة. يتم تعريف الأغشية الحيوية على أنها مستعمرات ميكروبية معقدة مغلفة في مصفوفة مواد بوليميرية خارج الخلية (EPS). لا يزال تحدي للباحثين لتطوير مضادات المبيضات جديدة بمقاومة أقل. نحن هنا نقدم تقريبًا عن سلسلة من نظام ن- (بدائل بنزيليدين) - 4-16-ثنائي ميثيل اوكسي بيريميدين-2-امين جنبًا إلى جنب مع مضادات الغشاء الحيوي ومضادات المبيضات في المختبر. أظهرت المركبات 3 أ و 3 ب و 3 ك و 3 ل التحليلاً ضد المبطنة البيضاء مقارنة بالفلوكونازول (العامل القياسي المضاد للفطرية). أظهرت المركبات 3 أ و 3 ب و 3 ك أيضًا نشاطًا جيدًا كمضادات الغشاء الحيوي مما يشير إلى إمكانية وجود مضادات الغشاء الحيوي بالإضافة إلى مضادات المبيضات. أظهرت النتائج أن المركبات الجديدة يمكن أن تكون بمثابة دليل مهم في اكتشاف مضادات المبيضات و التغلب على مشكلة المقاومة المرتبطة مضادات المبيضات الموجودة.

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