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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 anticandidal agents makes them ineffective causing high incidence and accompanying mortality due to the 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 anticandidal 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 anticandidal potential in-vitro. Compounds **3a, 3b, 3i, 3k, and 3l** have shown better inhibition against C. albicans than Fluconazole (standard anticandidal agent). Compounds **3a, 3b, and 3i** also exhibited good antibiofilm activity suggesting their antibiofilm as well as anticandidal potential. The results show that the new compounds could serve as an important lead in the discovery of effective anticandidal agents to overcome the resistance problem associated with the existing anticandidal 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*.[1-3] Morphologically, is a versatile microbe that exists in three forms i.e. yeasts, pseudohyphae, 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 anticandidal with target cells.[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 anticandidal drugs. Biofilms formed by *Candida* turn them more resistant to anticandidal agents than planktonic cells.[13] The traditional treatment for *Candida* infections includes azoles (fluconazole, itraconazole, and voriconazole),

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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.[4,18] 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]

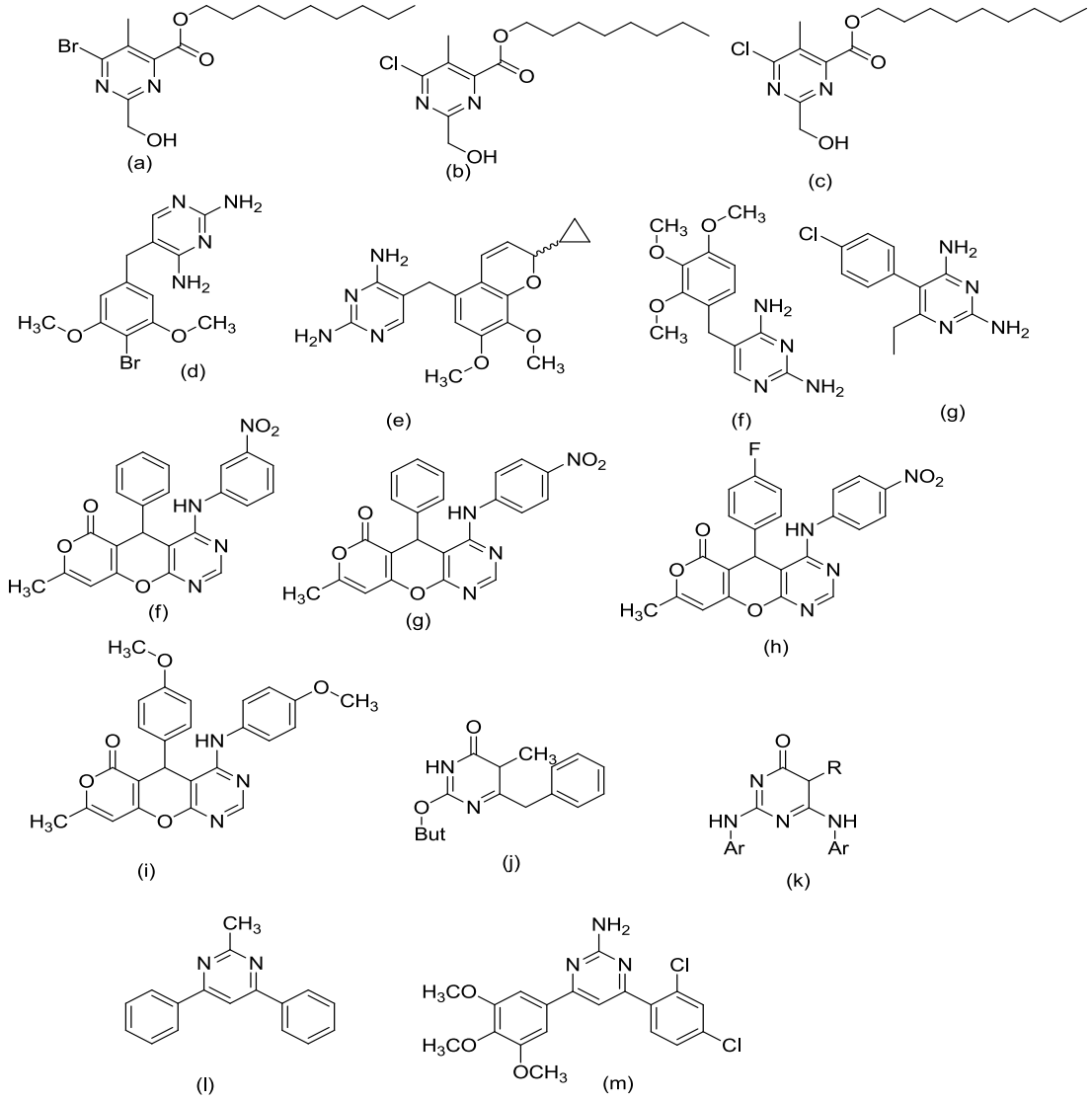


Fig. 1: Some bioactive pyrimidine derivatives.

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)-d6 using BRUKER AV 500MHz (Germany). Chemical shifts were reported in δ ppm with Tetramethylsilane as an internal standard (TMS, δ = 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-dimethoxypyrimidin-2-amine **1** (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): δ 9.90 (s, 1H, -CH=N), 7.87 (d, 2H, Phenyl C_2-H, C_6-H), 7.64 (s, 2H, Phenyl C_3-H, C_5-H), 6.68 (s, 1H, Pyrimidine -CH), 3.58 (s, 6H, -OCH_3) MS (LC-QTOF) $C_{13}H_{12}ClN_3O_2$ [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): δ8.44 (s, 1H, -CH=N), 7.87 (s, 1H, Phenyl C_6-H), 6.64 (s, 2H, Phenyl C_3-H, C_5-H), 6.48 (s, 1H, Pyrimidine -CH), 3.64 (s, 6H, Benzylidene -OCH_3), 3.58 (s, 6H, -OCH_3) MS (LC-QTOF) $C_{15}H_{17}N_3O_4$ [M+] Std: 303.31 Found: 303.14.

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

Yield: 88%; m.p. 216 °C; 1H-NMR (500 MHz, DMSO-d6): δ 8.44 (s, 1H, -CH=N), 7.84 (s, 1H, Phenyl C_6-H), 6.64 (s, 2H, Phenyl C_3-H, C_4-H), 6.48 (s, 1H, Pyrimidine -CH), 3.64 (s, 6H, Benzylidene -OCH_3), 3.58 (s, 6H, -OCH_3) MS (LC-QTOF) $C_{15}H_{17}N_3O_4$ [M+1] Std: 303.31 Found: 304.12.

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

Yield: 88%; m.p. 216 °C; 1H-NMR (500 MHz, DMSO-d6): δ 8.44 (s, 1H, -CH=N), 7.84 (s, 1H, Phenyl C_6-H), 6.64 (s, 2H, Phenyl C_2-H, C_5-H), 6.48 (s, 1H, Pyrimidine -CH), 3.64 (s, 6H, Benzylidene -OCH_3), 3.58 (s, 6H, -OCH_3) MS (LC-QTOF) $C_{15}H_{17}N_3O_4$ [M+1] Std: 303.31 Found: 304.12.

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

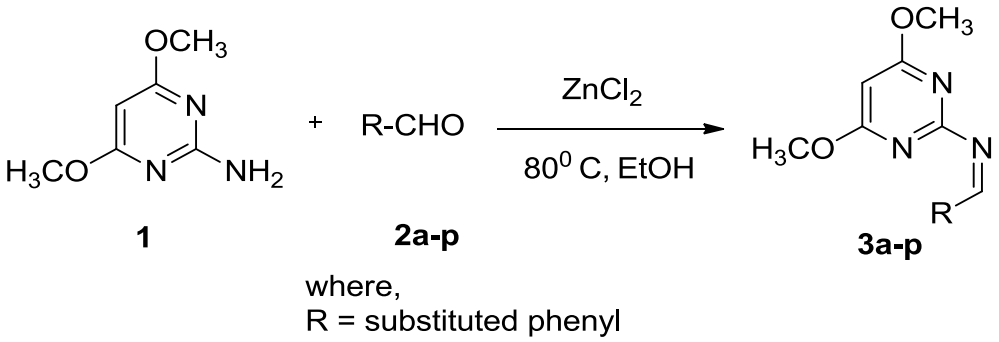
Yield: 82%; m.p. 224 °C; 1H-NMR (500 MHz, DMSO-d6): δ 8.44 (s, 1H, -CH=N), 7.34 (s, 2H, Phenyl C_2-H, C_6-H), 6.48 (s, 1H, Pyrimidine -CH), 3.64 (s, 9H, Benzylidene -OCH_3), 3.58 (s, 6H, -OCH_3) MS (LC-QTOF) $C_{15}H_{17}N_3O_4$ [M+1] Std: 333.34 Found: 334.13.

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

Yield: 88%; m.p. 228 °C; 1H-NMR (500 MHz, DMSO-d6): δ 8.44 (s, 1H, -CH=N), 7.38 (s, 1H, Phenyl C_6-H), 7.32 (s, 1H, Phenyl C_2-H), 6.94 (s, 1H, Phenyl C_5-H), 6.68 (s, 1H, Pyrimidine -CH), 3.58 (s, 6H, -OCH_3) MS (LC-QTOF) $C_{13}H_{12}ClN_3O_2$ [M+] 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): δ 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) $C_{13}H_{12}ClN_3O_2[M+1]^+$ 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 C_3-H,C_4-H, C_5-H), 6.68 (s, 1H, Pyrimidine -CH), 3.58 (s, 6H, -OCH_3) MS (LC-QTOF) $C_{13}H_{11}Cl_2N_3O_2$[M+] 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 C_2-H, C_6-H), 7.36 (d, 2H, Phenyl C_3-H, C_5-H), 6.49 (s, 1H, Pyrimidine -CH), 3.80 (s, 6H, -OCH_3) MS (LC-QTOF) $C_{13}H_{12}FN_3O_2$ $[M+1]^+$ Std: 261.25 Found: 262.75.

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 C_2-H, C_6-H), 8.09 (d, 2H, Phenyl C_3-H, C_5-H), 6.49 (s, 1H, Pyrimidine -CH), 3.80 (s, 6H, -OCH_3) MS (LC-QTOF) $C_{13}H_{12}ClN_4O_4$ $[M+1]^+$ 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 C_2-H, C_6-H), 6.81 (d, 2H, Phenyl C_3-H, C_5-H), 6.49 (s, 1H, Pyrimidine -CH), 3.80 (s, 6H, -OCH_3), 3.06 (s, 6H, N-CH_3) MS (LC-QTOF) $C_{13}H_{12}ClN_3O_2$ $[M+1]^+$ 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 C_2-H, C_6-H), 8.36 (s, 1H, -CH=N), 8.04 (d, 2H, Phenyl C_3-H, C_5-H), 6.49 (s, 1H, Pyrimidine -CH), 3.80 (s, 6H, -OCH_3) MS (LC-QTOF) $C_{14}H_{13}N_3O_4$ $[M+1]^+$ 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 C_2-H, C_6-H), 7.52 (m, 3H, Phenyl C_3-H, C_4-H, C_5-H), 6.49 (s, 1H, Pyrimidine -CH), 3.80 (s, 6H, -OCH_3) MS (LC-QTOF) $C_{13}H_{13}N_3O_2$ [M+] 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 C_5-H), 7.50 (s, 1H, -CH=N), 6.93 (d, 1H, furanyl C_3-H), 6.52 (t, 1H, furanyl C_4-H), 6.49 (s, 1H, Pyrimidine -CH), 3.80 (s, 6H, -OCH_3) MS (LC-QTOF) $C_{11}H_{11}N_3O_3$ [M+] 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 C_4-H), 7.55 (d, 1H, indolyl C_2-H), 7.54 (d, 1H, indolyl C_7-H), 7.19 (t, 1H, indolyl C_5-H), 7.01 (m, 1H, indolyl C_5-H), 6.49 (s, 1H, Pyrimidine -CH), 3.80 (s, 6H, -OCH_3) MS (LC-QTOF) $C_{15}H_{14}N_4O_2$ $[M+1]^+$ Std: 282.30 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, 2H, Phenyl C_2-H, C_6-H), 6.85 (d, 2H, Phenyl C_3-H, C_5-H), 6.49 (s, 1H, Pyrimidine -CH), 5.35 (s, 1H, OH) 3.80 (s, 6H, -OCH_3) MS (LC-QTOF) $C_{13}H_{13}N_3O_3$ [M+] Std: 259.26.

Biological evaluation

Antimicrobial activity

Newly synthesized derivatives were evaluated using the agar method for anticandidal and anti-biofilm activity by performing an assay against *C. albicans*.[30] Results were obtained in terms of respective IC_{50} 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 $-CH_3$ 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.[30] 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 (IC_{50} μM)
3a	$C_{13}H_{12}ClN_3O_2$	39.8	36.4
3b	$C_{15}H_{17}N_3O_4$	45.1	43.2
3c	$C_{15}H_{17}N_3O_4$	133.6	185.3
3d	$C_{15}H_{17}N_3O_4$	69.3	74.3
3e	$C_{16}H_{19}N_3O_5$	181.3	-
3f	$C_{13}H_{13}N_3O_4$	-	-
3g	$C_{13}H_{12}ClN_3O_2$	161.5	116
3h	$C_{13}H_{11}ClN_3O_2$	138.1	188.3
3i	$C_{13}H_{12}FN_3O_2$	42.6	41.5
3j	$C_{13}H_{12}N_4O_4$	108.3	103
3k	$C_{15}H_{18}N_4O_2$	43.2	58.3
3l	$C_{14}H_{131}N_3O_4$	49.1	62
3m	$C_{13}H_{13}N_3O_2$	61.5	49
3n	$C_{11}H_{11}N_3O_2$	-	-
3o	$C_{15}H_{14}N_4O_2$	91.2	95.6
3p	$C_{13}H_{13}N_3O_3$	88.4	91.3
Fluconazole	-	50	40

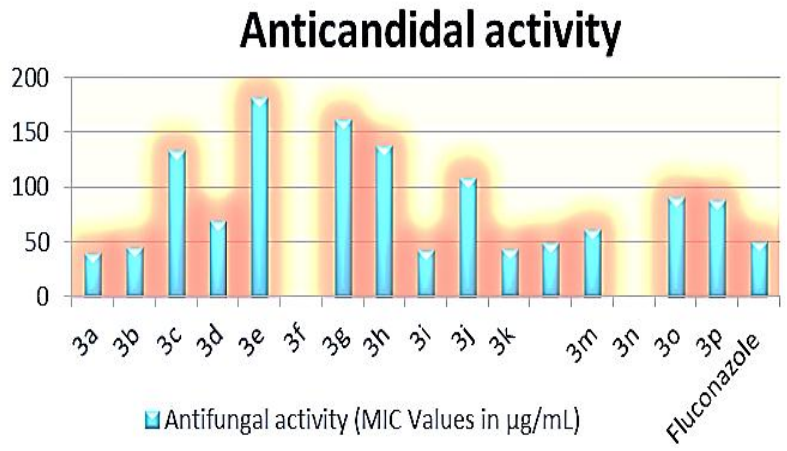


Fig. 1: Graphical representation of anticandidal activity of **3a-p.**

Antibiofilm activity

Compounds **3a, 3b, and 3i** also exhibited good antibiofilm activity with IC_{50} values of 36.4, 43.2, and 41.5µM, respectively, suggesting their antibiofilm as well as anticandidal potentials shown in Fig. 2. Also compounds **3l** and **3m** also showed moderate biofilm inhibitory potential during assay with IC_{50} values of 62 and 49 µM, respectively.

Similar to anticandidal activity, antibiofilm activity of the synthesized compounds was potentiated with the 4^{th} position substitutents present on the phenyl ring. Amongst the synthesized compounds, compound **3a** with 4-chloro substitution at the 4^{th} position of the side ring exhibited the most potent biofilm as well as candidal inhibition with MIC = 39.8 and IC_{50} = 36.4µM against C. *Albicans*. The compound **3i** with 4-fluoro substitutions also delivered potent anti-biofilm activity with IC_{50} = 41.5 µM. Interestingly, compounds 3a and 3i also delivered more potent anticandidal activity than fluconazole against *C. albicans* suggesting electron-withdrawing groups on the para position have better anticandidal 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.

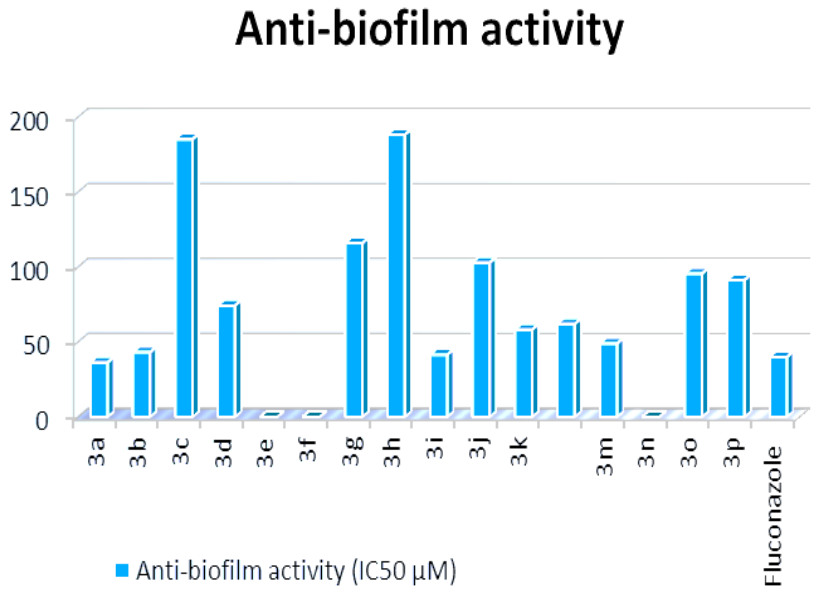


Fig. 2: Graphical representation of the anti-biofilm activity of **3a-p.**

Conclusion

In summary, a simple, facile anti-biofilm, anticandidal 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 anticandidal agent). Compounds **3a, 3b, and 3i** also exhibited good antibiofilm activity suggesting their antibiofilm as well as anticandidal 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 anticandidal agents to overcome the resistance problem associated with the existing anticandidal agents.

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Conflict of Interest

No conflict of interest was declared by theauthors.

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استكشاف إمكانات مضادات فطر المبيضات ومضادات الغشاء الحيوي لنظائر N- (بدائل بنزيليدين) -٤،٦-ثنائي ميثيل اوكسي بيريميدين-٢-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 الآلية الكامنة الأكثر شيوعًا في ظهور المقاومة. يتم تعريف الأغشية الحيوية على أنها مستعمرات ميكروبية معقدة مغلفة في مصفوفة مواد بوليمرية خارج الخلية (EPS). لا يزال تحدي للباحثين لتطوير مضادات المبيضات جديدة بمقاومة أقل. نحن هنا نقدم تقريرًا عن سلسلة من نظائر N- (بدائل بنزيليدين) -٤،٦-ثنائي ميثيل اوكسي بيريميدين-٢- امين جنبًا إلى جنب مع مضادات الغشاء الحيوي ومضادات المبيضات في المختبر. أظهرت المركبات ٣ أ و ٣ ب و ٣ ي و ٣ ك و ٣ ل تثبيطا أفضل ضد المطثية البيضاء مقارنة بالفلوكونازول (العامل القياسي المضاد للفطريات). أظهرت المركبات ٣ أ و ٣ ب و ٣ ي أيضًا نشاطا جيدًا كمضادات الغشاء الحيوي مما يشير إلى إمكانات وجود مضادات الغشاء حيوي 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.