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Synthesis, Characterization, Molecular Docking, Cell Viability and Biological Activity of New Cresol Analogues against Monilial Vulvovaginitis Triggering Pathogen

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High biological potential of existing cresols and azomethine scaffolds considers them as promising leads for antimicrobial therapy, however the development of resistance and side effects limits their application in treatment of monilial vulvovaginitis. In present study, new cresols derivatives (NCDs) were designed, synthesized and characterized using ATR-IR, $^{1}H/^{13}C$ NMR and direct-mass spectrometry. All the synthesized were initially screened through molecular docking against *C. albicans* CYP51 (PDB ID: 5TZ1) and *S. aureus* DNA Gyrase B protein (PDB ID: 4URM). Study involved molecular docking of NCDs against 5TZ1 and 4URM proteins of *C. albicans* and *S. aureus* respectively, followed by synthesis of NCDs *via* imination and Schiff reaction of hydrazide analogue of cresol, *in-vitro* antibacterial and antifungal activity using disk diffusion method and cytotoxicity evaluation towards HEK-293 cells with the MTT assay. Novel NCDs exhibited high docking score against 5TZ1 and 4URM, high *in vitro* antibacterial and antifungal activity against *C. albicans* and *S. aureus*, and minimal cytotoxicity at 7.81 µg/mL. Overall, the study presents chemically validated and biologically promising NBA candidates for future development as peri-implantitis inhibitors. Based on the experimental results, this study concludes successful synthesis of NCDs as antibacterial and antifungal activity with negligible toxicity. This research also proposed that, these NCDs in future needs further evaluation for preclinical and clinical significance in monilial vulvovaginitis treatment.

Keywords: Synthesis, Azomethines, Cresol, *S. aureus*, *C. albicans*, Docking studies, Monilial vulvovaginitis.

INTRODUCTION

Recent decades witnessed high rate of incidence infections [1], and today prevalence of vulvovaginitis is very common problem among women which is generally attributed to the poor psychosocial and reproductive environments [2]. In synthetic chemistry, cresols always withdraw the researchers' attention attributed to their high antibacterial and antifungal activities [3]. Various studies highlighted the synthesis of numerous analogues of cresol moiety, however, establishment of their safety/toxicity, mechanism and development of resistance was a concern [4,5]. Therefore, exploring newer, safer and non-resistant scaffolds is a priority for researchers. Facts suggest azomethines when incorporated to improve biological activity and physico-chemical properties [6].

Studies highlighted azomethines ability to form H-bonding and π-stacking within biological targets and thereby exhibiting high antimicrobial activities [7,8]. Reports suggest conversion of aromatic hydroxy group into ester using ethylchloroacetate and further conversion of ester derivative into azomethines *via* hydrazination and Schiff reaction [9,10]. The design and evaluation of new chemical entities through molecular docking using AutoDock Vina is a cornerstone of modern drug discovery [11]. Studies highlight the enhancement of virulence of *C. albicans* (vulvovaginal candidiasis major causative factor) *S. aureus* [12,13]. Evidence highlights effective

targeting of *C. albicans* CYP51 (PDB ID: 5TZ1) and *S. aureus* DNA Gyrase B protein (PDB ID: 4URM) [14,15]. Therefore, based on the facts over vulvovaginitis, the causative pathogens, the ongoing synthetic research and problems associated with the synthesized molecules and potential of cresols and azomethines altogether motivated to carry out the synthesis, characterization, molecular docking, cell viability and biological activity of some new cresol derivatives (NCDs) against monilial vulvovaginitis triggering pathogenability.

EXPERIMENTAL

The reagents, chemicals and biologicals for the present study were procured from Qrec Chemicals, Merck KGaA, HmbG®, Sigma-Aldrich and Friendemann Schmidt Chemicals. The synthesized NCDs were characterized by recording NMR spectra were at 700 MHz on an ASCEND™ spectrometer, IR spectra on Shimadzu ATR-FTIR spectrometer and mass spectra Direct Infusion Ion Trap MS. The NCDs purity was tested using open-capillary melting point method on SMP11 analogue instrument.

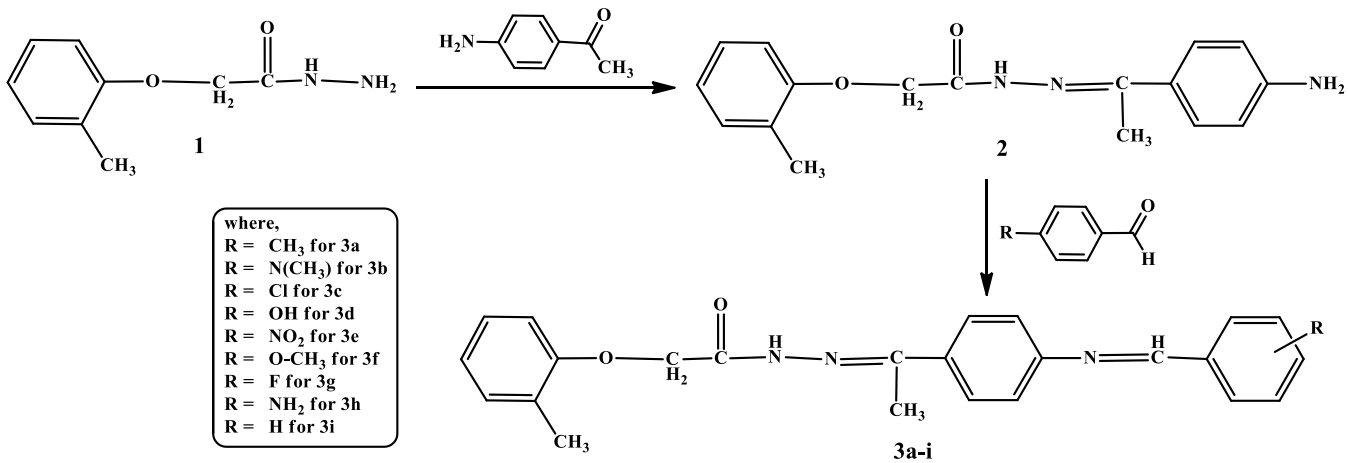
Synthesis of *N*-(1-(4-aminophenyl)ethylidene)-2-(*o*-tolyloxy)acetohydrazide (2): The NCD 2 was synthesized as per the established research protocol with minor modification [16], briefly, compound **1** was refluxed with 4-aminoacetophenone in equimolar concentration (0.0001 M) in absolute ethanol for 8 h at 78 ºC. The obtained crude product was subjected to recrystallization using methanol, to obtain pure NCD **2** (**Scheme-I**). The TLC was done by dissolving crystals into CH_3OH:$CHCl_3$ with a ratio of 1:1 to identify the purity of NCD **2.** White crystalline, yield: 82%, m.p.: 135 ºC, R_f: 0.52; IR (ν_{max}, KBr, cm^{-1}): 3250 (N-H), 3035 (aromatic C-H), 2926 (aliphatic C-H), 1672 (C=O), 1608 (C=N), 1460 (C=C); ^{1}H NMR (DMSO-d_6, δ ppm): 2.26 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 4.65 (s, 2H, OCH_2), 5.92 (s, 2H, NH_2), 6.41-7.82 (m, 8H, Ar-H) and 9.48 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, δ ppm): 16 (CH_3), 22 (CH_3), 72 (CH_2), 116, 121, 124, 126, 130, (Ar-C), 154 (N-N=C), 158 (Ar-C-O), 170 (N=C), 191 (O=C-NH); mass (*m/z*): 297 (M+ peak).

Synthesis of *N*-(1-(4-(substituted benzylideneamino)-phenyl)ethylidene)-2-(*o*-tolyloxy)acetohydrazide (3a-i): The synthesis of NCDs **3a-i** was done as per the standard protocol with minor modification [10]. Briefly, NCD **2** was refluxed with 4-methylbenzaldehyde in equimolar concentration (0.01 M) in absolute ethanol for 8 h at 78 ºC. The obtained crude was subjected to recrystallization using methanol, to yield the pure NCD **3a**. The TLC was done by dissolving crystals into methanol: chloroform with a ratio of 1:1 to identify the purity of NCD **3a**. Similarly, other NCDs **3b-i** were also synthesized (**Scheme-I**).

***N*-(1-(4-(4-Methyl-benzylideneamino)phenyl)ethylidene)-2-(*o*-tolyloxy)acetohydrazide (3a):** White crystalline, yield: 78%, m.p.: 142 ºC, R_f: 0.62; IR (ν_{max}, KBr, cm^{-1}): 3252 (N-H), 3038 (aromatic C-H), 2922 (aliphatic C-H), 1676 (C=O), 1611 (C=N), 1465 (C=C); ^{1}H NMR (DMSO-d_6, δ ppm): 1.94 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 4.64 (s, 2H, OCH_2), 6.42-7.81 (m, 12H, Ar-H), 9.48 (s, 1H, NH), 9.82 (s, 1H, =CH); ^{13}C NMR (DMSO-d_6, δ ppm): 14 (CH_3), 16 (CH_3), 22 (CH_3), 72 (CH_2), 116, 121, 124, 126, 128, 130, 132 (Ar-C), 154 (N-N=C), 158 (Ar-C-O), 165 (N=C), 170 (N=C), 192 (O=C-NH); mass (*m/z*): 399 (M+ peak).

***N*-(1-(4-(4-(Dimethylamino)benzylideneamino)phenyl)-ethylidene)-2-(*o*-tolyloxy)aceto hydrazide (3b):** Yellow crystalline, yield: 88%, m.p.: 154 ºC, R_f: 0.59; IR (ν_{max}, KBr, cm^{-1}): 3250 (N-H), 3033 (aromatic C-H), 2928 (aliphatic C-H), 1672 (C=O), 1606 (C=N), 1460 (C=C); ^{1}H NMR (DMSO-d_6, δ ppm): 2.22 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 3.92 (s, 6H, $N(CH_3)_2$, 4.68 (s, 2H, OCH_2), 6.40-7.83 (m, 12H, Ar-H), 9.44 (s, 1H, NH), 9.83 (s, 1H, =CH); ^{13}C NMR (DMSO-d_6, δ ppm): 16 (CH_3), 22 (CH_3), 46 ($N(CH_3)_2$), 71 (CH_2), 114, 122, 124, 126, 128, 130, 134 (Ar-C), 153 (N-N=C), 157 (Ar-C-O), 166 (N=C), 170 (N=C), 191 (O=C-NH); mass (*m/z*): 428 (M+ peak).

***N*-(1-(4-(4-Chloro-benzylideneamino)phenyl)ethylidene)-2-(*o*-tolyloxy)acetohydrazide (3c):** White crystalline, yield: 79%, m.p.: 149 ºC, R_f: 0.47; IR (ν_{max}, KBr, cm^{-1}): 3249 (N-H), 3031 (aromatic C-H), 2921 (aliphatic C-H), 1675 (C=O), 1602 (C=N), 1458 (C=C); ^{1}H NMR (DMSO-d_6, δ ppm): 2.21 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 4.61 (s, 2H, OCH_2), 6.38-7.78 (m, 12H, Ar-H), 9.40 (s, 1H, NH), 9.84 (s, 1H, =CH); ^{13}C NMR (DMSO-d_6, δ ppm): 16 (CH_3), 22 (CH_3), 71 (CH_2), 114, 122, 125, 128, 130, 132, 134 (Ar-C), 138 (Ar-C-Cl), 151



Scheme-I: Synthesis of NCDs 2 and **3a-i**

(N-N=C), 159 (Ar-C-O), 162 (N=C), 167 (N=C), 190 (O=C-NH); mass (*m/z*): 419 (M+ peak).

***N*-(1-(4-(4-Hydroxy-benzylideneamino)phenyl)ethylidene)-2-(*o*-tolyloxy)acetohydrazide (3d):** Pale yellow crystalline, yield: 72%, m.p.: 132 ºC, R_f: 0.58; IR (ν_{max}, KBr, cm^{-1}): 3244 (N-H), 3030 (aromatic C-H), 2928 (aliphatic C-H), 1676 (C=O), 1604 (C=N), 1455 (C=C); ^{1}H NMR (DMSO-d_6, δ ppm): 2.23 (s, 3H, CH_3), 2.47 (s, 3H, CH_3), 4.59 (s, 2H, OCH_2), 6.2 (brs, 1H, OH), 6.39-7.82 (m, 12H, Ar-H), 9.39 (s, 1H, NH), 9.80 (s, 1H, =CH); ^{13}C NMR (DMSO-d_6, δ ppm): 18 (CH_3), 21 (CH_3), 74 (CH_2), 115, 122, 125, 128, 130, 132, 134 (Ar-C), 151 (N-N=C), 159 (Ar-C-O), 162 (Ar-C-O), 164 (N=C), 167 (N=C), 191 (O=C-NH); mass (*m/z):* 401 (M+ peak).

***N*-(1-(4-(4-Nitro-benzylideneamino)phenyl)ethylidene)-2-(*o*-tolyloxy)acetohydrazide (3e):** Orange crystalline, yield: 84%, m.p.: 146 ºC, R_f: 0.49; IR (ν_{max}, KBr, cm^{-1}): 3256 (N-H), 3034 (aromatic C-H), 2926 (aliphatic C-H), 1672 (C=O), 1607 (C=N), 1454 (C=C); ^{1}H NMR (DMSO-d_6, δ ppm): 2.22 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 4.51 (s, 2H, OCH_2), 6.42-7.84 (m, 12H, Ar-H), 9.42 (s, 1H, NH), 9.81 (s, 1H, =CH); ^{13}C NMR (DMSO-d_6, δ ppm): 20 (CH_3), 22 (CH_3), 72 (CH_2), 116, 120, 123, 127, 131, 133, 136 (Ar-C), 150 (Ar-C-NO_2), 153 (N-N=C), 159 (Ar-C-O), 161 (Ar-C-O), 165 (N=C), 169 (N=C), 194 (O=C-NH); mass (*m/z*): 430 (M+ peak).

***N*-(1-(4-(4-Methoxy-benzylideneamino)phenyl)ethylidene)-2-(*o*-tolyloxy)acetohydrazide (3f):** White crystalline, yield: 74%, m.p.: 132 ºC, R_f: 0.58; IR (ν_{max}, KBr, cm^{-1}): 3241 (N-H), 3029 (aromatic C-H), 2924 (aliphatic C-H), 1675 (C=O), 1608 (C=N), 1458 (C=C); ^{1}H NMR (DMSO-d_6, δ ppm): 2.23 (s, 3H, CH_3), 2.47 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 4.59 (s, 2H, OCH_2), 6.2 (brs, 1H, OH), 6.39-7.82 (m, 12H, Ar-H), 9.39 (s, 1H, NH), 9.80 (s, 1H, =CH); ^{13}C NMR (DMSO-d_6, δ ppm): 18 (CH_3), 21 (CH_3), 74 (CH_2), 115, 122, 125, 128, 130, 132, 134 (Ar-C), 151 (N-N=C), 159 (Ar-C-O), 162 (Ar-C-O), 164 (N=C), 167 (N=C), 191 (O=C-NH); mass (*m/z*): 415 (M+ peak).

***N*-(1-(4-(4-Fluoro-benzylideneamino)phenyl)ethylidene)-2-(*o*-tolyloxy)acetohydrazide (3g):** White crystalline, yield: 80%, m.p.: 132 ºC, R_f: 0.58; IR (ν_{max}, KBr, cm^{-1}): 3244 (N-H), 3030 (aromatic C-H), 2928 (aliphatic C-H), 1676 (C=O), 1604 (C=N), 1455 (C=C); mass (*m/z*): 403 (M+ peak).

***N*-(1-(4-(4-Amino-enzylideneamino)phenyl)ethylidene)-2-(*o*-tolyloxy)acetohydrazide (3h):** Light brown crystalline, yield: 70%, m.p.: 132 ºC, R_f: 0.58; IR (ν_{max}, KBr, cm^{-1}): 3242 (N-H), 3028 (aromatic C-H), 2922 (aliphatic C-H), 1673 (C=O), 1610 (C=N), 1449 (C=C); mass (*m/z*): 400 (M+ peak).

***N*-(1-(4-(Benzylideneamino)phenyl)ethylidene)-2-(*o*-tolyloxy)acetohydrazide (3i):** White crystalline, yield: 65%, m.p.: 132 ºC, R_f: 0.58; IR (ν_{max}, KBr, cm^{-1}): 3240 (N-H), 3026 (aromatic C-H), 2919 (aliphatic C-H), 1672 (C=O), 1608 (C=N), 1460 (C=C); mass (*m/z*): 385 (M+ peak).

Antibacterial activity: The synthesized NCDs were subjected to evaluation of antibacterial activity against *S. aureus* using *in vitro* disc diffusion method [17]. Briefly, the freshly prepared culture of *S. aureus* was spread on the Mueller-Hinton Agar (MHA) plates, and sterile 6 mm diameter discs were impregnated with all test NCDs separately at a concentration of 100 μg/mL in 0.5% DMSO. Next discs were placed on the inoculated plates, followed by incubation at 37 ºC for 24 h and finally measurement of the zone of inhibition (mm) for each disc impregnated with test NCD was done. For this experiment, disc containing ciprofloxacin was taken a positive control whereas disc containing 0.5% DMSO taken as negative control.

Antifungal activity: The synthesized NCDs were also subjected to evaluation of antifungal activity against *C. albicans* by *in vitro* disc diffusion method using Sabouraud Dextrose Agar (SDA) [18]. Briefly, the freshly prepared culture of *C. albicans* was spread on agar surface, and sterile 6 mm diameter discs were impregnated with all test NCDs separately at a concentration of 100 μg/mL in 0.5% DMSO. Next, the discs were placed on the inoculated plates, followed by incubation at 28 ºC for 48 h and finally measurement of the zone of inhibition (mm) for each disc impregnated with test NCD was done. For this experiment disc containing fluconazole was taken a positive control whereas disc containing 5% DMSO taken as negative control.

Toxicity analysis (cell viability study): The synthesized NCDs were further subjected to cell viability/safety study by MTT assay with standard protocol [19]. Briefly, the HEK293 cells in DMEM were seeded in 96-well plates, followed by adherence (24 h), treatment of cells with test NCDs (in concentrations range of 7.8-500 μg/mL), and incubation (at 37 ºC, 5% CO_2 for 24 h). After cells treatment, the MTT solution (10 μL) was added to each well and incubated for 3-4 h to allow formazan crystal formation. The crystals were dissolved using DMSO (100 μL) and the absorbance was measured at 570 nm under microplate reader. Finally, the cell viability (%) was determined using eqns. 1 and 2:

$$\text{Cytotoxicity (\%)} = \frac{\text{Control} - \text{Sample}}{\text{Control}} \times 100 \quad (1)$$

$$\text{Cell viability (\%)} = 100 - \text{Cytotoxicity (\%)} \quad (2)$$

Molecular docking: The new analogues of cresol moiety were designed and evaluated for their biological potential *via* molecular docking (MD) with target proteins, namely: sterol 14-alpha demethylase CYP51 (PDB ID: 5TZ1) from *C. albicans* and DNA Gyrase B of *S. aureus* (PDB ID: 4URM) by AutoDock using standard protocol [20-22]. Briefly, the molecular docking of new cresol derivatives (NCDs) was done to study their interaction/binding mode the target proteins using Intel i7 with 16GB RAM. Study included protein prep-aration, NCDs designing followed by conversion into working format software using Discovery studio, Autodock v4.2.7, mgltools 1.5.7, ChemDraw and OpenBabel [23,24]. All NCDs 2D structures modeling was done using Chemsketch, further converted into respective 3D structures. The designed NCDs were optimized and processed for energy minimization [24]. The downloading of 3D structures 5TZ1 and 4URM proteins was done from RCSB Protein Data Bank (PDB). Preparation of 5TZ1 and 4URM proteins was done by Discovery Studio Visualizer where in prior heteroatoms and water molecules removal, and addition of hydrogen & charges using Molecular Graphics Laboratory (MGL) tools was done. Next, AutoDock v 4.2.7 was used to define grid parameters and MD using autodock_vina 11_2; and finally, MD results analysis was done using Discovery Studio Visualizer [25].

RESULTS AND DISCUSSION

Novel cresols derivatives (NCDs) were synthesized as per synthetic **Scheme-I**, using standard protocol with slight modification [10,16]. All the synthesized NCDs were characterized and similar results have been reported in other studies [25,26]. TR-FTIR spectra of NCDs **3a-i**, reflected the appearance of bands near 3256-3240 cm^{-1} attributed to presence of N-H, bands between 3031-3000 cm^{-1} attributed to = C–H, bands between 3000-2900 cm^{-1} attributed to aliphatic C-H and bands between 1690-1650 cm^{-1} attributed to C=O groups; which partially characterized the structure of compounds **3a-i**. FTIR results for NCDs **2**, and **3a-i** are in agreement with other studies too [10,16]. ^{1}H NMR spectra of NCDs **3a-i** exhibited characteristic signal between δ 9.80-9.84 ppm, that signifies formation of azomethine group and thereby confirmed the formation of NCDs **3a-i**. The structure of synthesized NCDs were also supported based on their ^{13}C NMR and mass data.

Docking studies: It was determined that among all *in silico* docking series of NCDs, the NCD **3a**, **3c-e** and **3h** offers good docking score with active site of DNA Gyrase B (4URM) of *S. aureus* (higher than ciprofloxacin), whereas all other NCDs also offered good score when compared with standard. On the other hand, it is determined that among all *in silico* docking series of NCDs (Table-1), the NCD **2**, **3a** and **3c-i** displayed high docking score with active site of CYP51 (5TZ1) of *C. albicans* (higher than fluconazole), however, other NCD **3b** also offered good score when compared with standard. Hence, based on the good docking score of all NCDs, further evaluation of cytotoxicity towards HEK 293 healthy cells has also been carried out.

The 2D interaction images (Fig. 1a) show that docked pose determines that hydrogen bond was formed between 'N' atom of 4-methyl-benzylideneamino group of NCD **3a** and the proline amino acid residue at position 462 in 'A' chain and oxygen atom with tyrosine amino acid at position 118 in chain A of the CYP51 (5TZ1) of *C. albicans*. Such interactions stabilize ligand binding inside the active site. For NCD **3g**, the hydrogen bond was formed between the 'O' atom of aceto-hydrazide group of and the threonine amino acid residue at position 173 in the chain A of DNA Gyrase B (4URM) of *S. aureus* (Fig. 2a). Such interactions stabilize ligand binding inside the active site.

The 3D presentation of MD complex (Fig. 1b) further supports the presence of such interaction and gives a view on the way the NCD **3a** fits onto the active site of CYP51 (5TZ1) of *C. albicans*. Similarly, the MD complex of NCD **3g** shows its fit within the active site of DNA Gyrase B (4URM) from *S. aureus* (Fig. 2b). Thus, the 2D and 3D images altogether reveal the high inhibitory potential of NCD **3a** and **3g** against *C. albicans* and *S. aureus*, respectively.

Cytotoxicity studies: The synthesized NCDs were further assessed for cell viability towards HEK 293 by applying MTT assay [19] and % viability of cells was determined and statistically analyzed using Graph Pad Prism 9.51 Software. The results establish that synthesized NCDs are non-toxic when compared with standards fluconazole and ciprofloxacin. The data presented in Table-2 on the cell viability of HEK 293 (normal) cells treated with NCDs **3a-i** (7.81 μg/mL) indicate that all NCDs maintain greater than 90% cell viability in normal cells.

Antimicrobial activities: The antimicrobial potential of the synthesized NCDs was evaluated at 100 μg/mL in 0.5% DMSO against *C. albicans* and *S. aureus* ATCC strains, the key pathogens responsible for monilial vulvovaginitis. The disc diffusion method was employed, using fluconazole as standard antifungal agent and ciprofloxacin as standard antibacterial agent. Among the tested compounds, NCD **3a** and **3g** showed the highest activity based on zones of inhibition against *C. albicans* and *S. aureus* (Table-3), respectively, in agreement with previous reports [27-29].

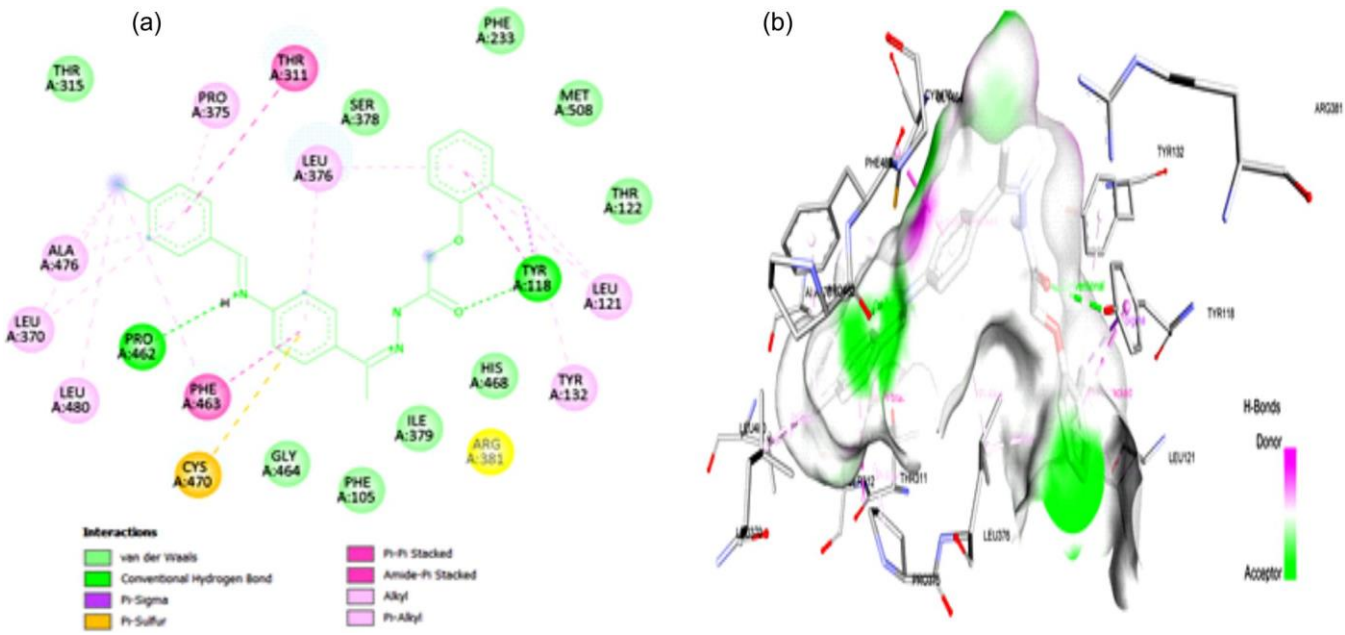
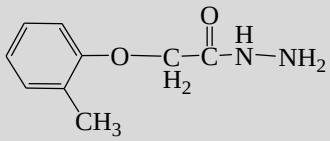
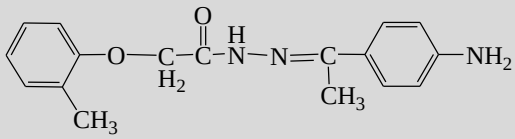
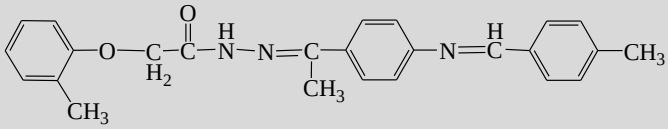
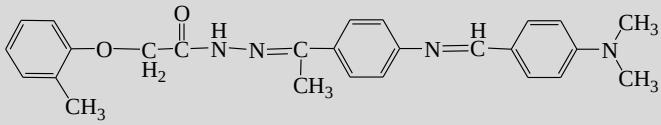
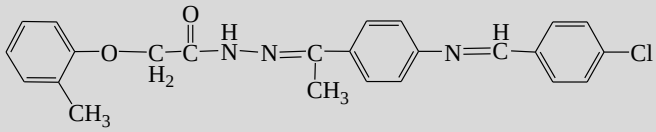
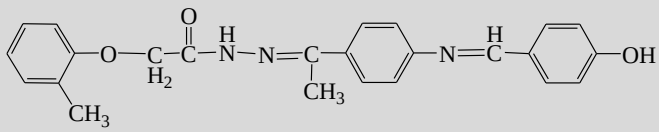
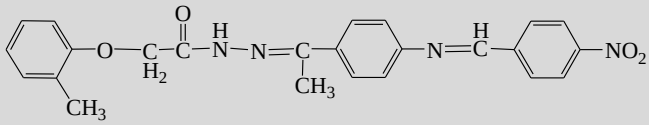
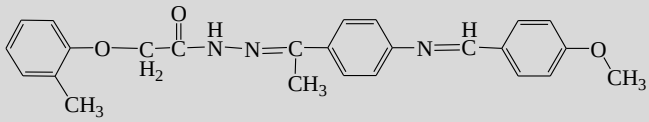
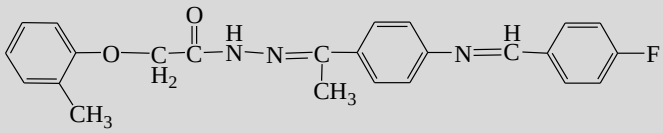
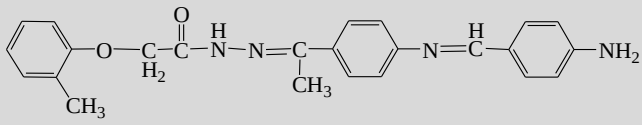
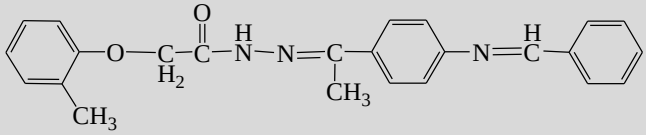


Fig. 1: 2D and 3D ligand interaction of NCD **3a** with 5TZ1

TABLE-1
DOCKING SCORE OF NCDS AGAINST 5TZ1 AND 4URM

Compound	Structure	Docking score (kcal/mol)	
		5TZ1	4URM
1 (Parent lead)		-6.9	-7.1
2		-8.2	-7.3
3a		-11.5	-7.7
3b		-10.3	-7
3c		-10.7	-7.3
3d		-10.7	-7.7
3e		-11.1	-8.5
3f		-9.6	-7.8
3g		-9.6	-8.7
3h		-11	-8.4
3i		-10.8	-8.3
Ciprofloxacin	–	-10.3	–
Fluconazole	–	–	-7.1

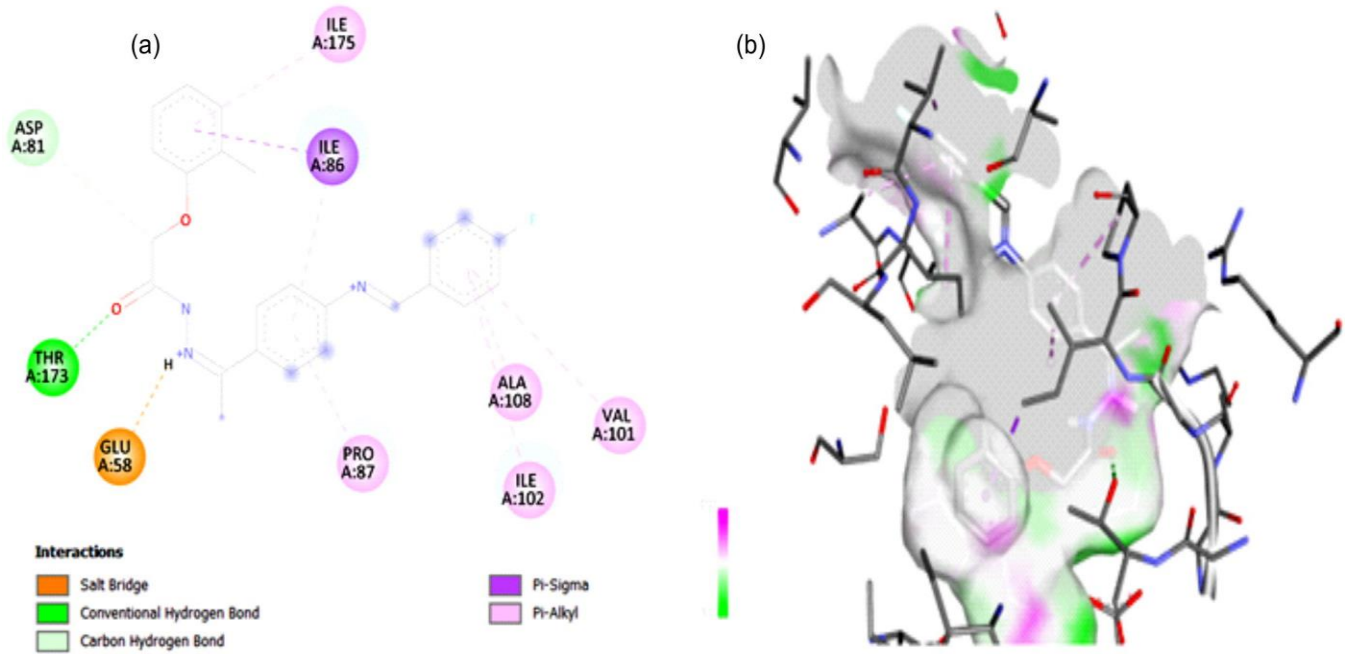


Fig. 2: 2D and 3D ligand interaction of NCD **3g** with 4URM

TABLE-2
In vitro CELL VIABILITY DATA OF NCDs*

Compd.	Cell Viability (%) at different concentrations in µg/mL						
	7.81	15.62	31.25	62.5	125	250	500
1	89.83 ± 0.84	85.49 ± 0.73	81.23 ± 0.18	76.02 ± 0.19	71.83 ± 1.82	64.77 ± 0.42	59.24 ± 0.96
2	91.46 ± 1.71	88.54 ± 0.39	85.38 ± 1.33	82.62 ± 0.21	78.23 ± 0.81	74.32 ± 1.03	69.27 ± 1.03
3a	94.82 ± 0.72	90.66 ± 1.14	86.59 ± 0.61	83.74 ± 0.39	80.42 ± 1.06	78.29 ± 1.53	74.33 ± 1.17
3b	90.27 ± 0.19	85.11 ± 0.73	81.77 ± 0.57	76.38 ± 0.26	71.08 ± 0.85	65.30 ± 0.18	61.95 ± 0.64
3c	91.05 ± 1.99	87.67 ± 1.25	82.19 ± 0.64	74.82 ± 0.45	69.88 ± 1.02	63.08 ± 1.36	59.24 ± 0.65
3d	90.83 ± 1.06	86.32 ± 1.11	81.57 ± 0.32	76.19 ± 1.26	71.59 ± 1.47	68.21 ± 1.79	62.04 ± 1.20
3e	91.46 ± 1.31	87.53 ± 1.28	82.36 ± 0.25	78.33 ± 0.17	72.42 ± 1.15	65.07 ± 1.13	61.49 ± 1.36
3f	91.57 ± 1.22	88.31 ± 1.67	85.59 ± 0.66	81.94 ± 0.48	78.91 ± 1.89	74.44 ± 1.69	69.24 ± 1.82
3g	93.70 ± 1.18	90.62 ± 1.77	86.18 ± 1.47	83.39 ± 0.63	81.09 ± 1.36	79.83 ± 2.05	76.19 ± 2.09
3h	91.46 ± 1.79	88.29 ± 1.92	81.57 ± 0.18	79.62 ± 0.50	74.39 ± 1.21	69.44 ± 1.71	63.71 ± 2.05
3i	91.27 ± 1.45	89.84 ± 1.06	86.29 ± 0.69	83.78 ± 1.63	80.86 ± 1.59	74.05 ± 1.23	69.26 ± 1.81
CIP	95.89 ± 0.74	93.26 ± 2.08	87.72 ± 1.34	82.39 ± 1.82	78.63 ± 1.28	76.88 ± 2.08	74.16 ± 0.92
FLC	97.33 ± 1.82	92.13 ± 1.19	88.55 ± 0.71	84.62 ± 0.53	81.91 ± 1.94	79.36 ± 0.92	77.24 ± 1.13

*Data is presented as mean ± standard deviation for each experiment in triplicate.

TABLE-3
ANTIMICROBIAL ACTIVITY

Compounds	Zone of inhibition (mm)	
	S. aureus	*C. albicans*
1	15	16
2	18	17
3a	23	22
3b	19	17
3c	20	17
3d	20	18
3e	21	20
3f	18	15
3g	24	22
3h	21	19
3i	20	18
CIP	25	–
FLC	–	25

Based on the cell viability results, antimicrobial data, and comparison with previous findings, the present study establishes that the synthesized NCDs not only possess strong antibacterial and antifungal activity against monilial vulvovaginitis associated pathogens (*C. albicans* and *S. aureus*) but also exhibit high safety toward normal HEK293 cells. Furthermore, the MD studies confirm that the NCDs display strong binding affinities, reflected by high docking scores, toward CYP51 (5TZ1) of *C. albicans* and DNA Gyrase B (4URM) of *S. aureus*.

Conclusion

This study highlights successful synthesis of new cresols derivatives (NCDs), and their characterization by IR, NMR and mass spectrometric data. Based on experimental results, it is found that all synthesized NCDs exhibit significant docking scores with compounds **3a** and **3g**, showing the highest

affinity against the 5TZ1 and 4URM proteins of *C. albicans* and *S. aureus*, respectively, pathogens responsible for vulvovaginitis. These findings were further supported by *in vitro* antibacterial and antifungal assays, confirming the activity of the synthesized NCDs against *C. albicans* and *S. aureus*. Moreover, the study demonstrates that the synthesized NCDs are highly safe, as evidenced by the high percent cell viability in HEK-293 cells. However, further preclinical and clinical investigations must be conducted to establish the efficacy of novel NCDs in the treatment of monilial vulvovaginitis.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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