Green and Computational Chemistry Synergy in the Development of Chromene Compounds for Antifungal activity

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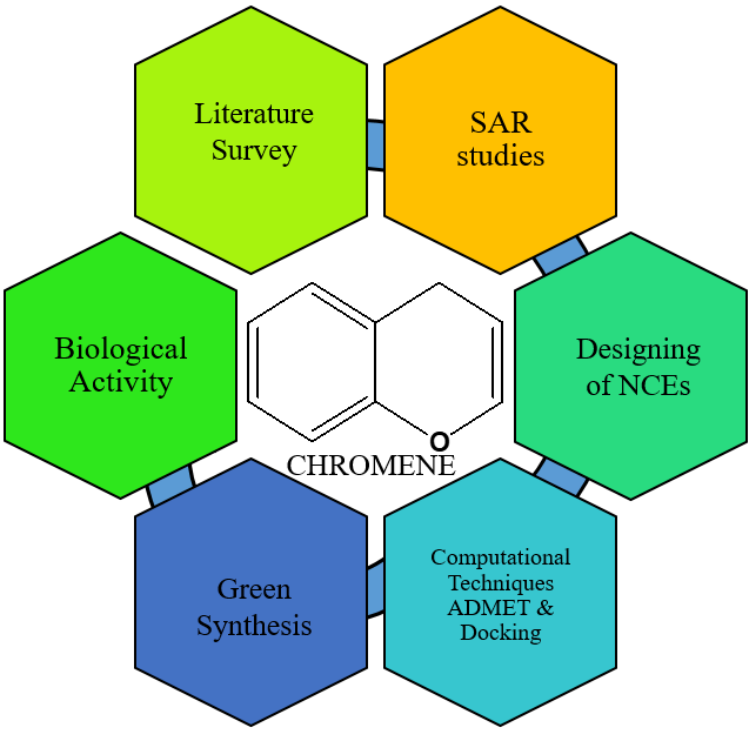
Graphical abstract



Graphical abstract

Abstract:

Background: Fungal infections, primarily caused by species such as *Candida albicans*, pose significant health challenges due to their resistance to existing treatments. These infections are increasingly prevalent, highlighting the urgent need for the development of novel antifungal agents to enhance therapeutic efficacy

Aim and objective: This study aims to combat fungal infections by developing potent antifungal agents through a green chemistry approach and computational techniques. The objective is to synthesize chromene derivatives using one-step multicomponent synthesis and to evaluate their efficacy via ADMET, docking studies and antifungal activity.

Material and method: Chromene derivatives were designed using SAR studies and subjected to insilico ADMET and docking screening using Schrodinger tool. Five novel chemical entities were synthesized and tested against *Candida albicans*.

Result and discussion: Five chromene-based NCEs with favourable ADMET properties and high docking scores were synthesized and tested for antifungal potential.

Conclusion: This study successfully synthesized five chromene-based novel chemical entities, with compound D21 showing good antifungal activity. The results underscore the potential of these derivatives as effective antifungal agents and demonstrate the efficacy of combining green chemistry with advanced computational techniques in drug development.

Keywords: Antifungal, chromene, Green chemistry, microwave, lanosterol 14 α-demethylase.

1. INTRODUCTION

Fungal infections represent a significant global health challenge; approximately 3.8 million people die from fungal infections annually, accounting for about 6.8% of all global deaths. This figure is nearly double the previous estimate, indicating a significant increase in global fatalities from fungal diseases over the past decade [1-4].Among these, *Candida albicans* infections are particularly prevalent, posing severe risks to immunocompromised individuals and leading to conditions ranging from oral thrush to life-threatening [5-7]. The increasing incidence of fungal infections is exacerbated by the rise in immunosuppressive therapies and chronic diseases highlighting the urgent need for effective antifungal agents [8-10]. Several antifungal drugs are available in the market, with Fluconazole being highly effective in inhibiting fungal growth [11,12].These antifungal drugs work selectively by inhibiting the lanosterol 14α-demethylase enzyme, thereby preventing the synthesis of ergosterol. Current antifungal therapies face significant challenges due to the emergence of drug-resistant strains. Resistance to commonly used antifungal agents such as Fluconazole has been steadily increasing, diminishing their efficacy and necessitating the development of new therapeutic options [13]. In this context, chromene derivatives have garnered considerable attention for their potential antifungal properties.

The chromene ring is known for its diverse biological activities, including antifungal, [14, 15] antibacterial, [16, 17] anti-inflammatory, [18,19] antiviral, [20, 21] antioxidant [22,23] and anticancer [24,25] effects. Recent structure-activity relationship (SAR) studies have indicated that modifications of the chromene scaffold can enhance its antifungal efficacy, making it a promising candidate for the development of novel antifungal agents. [26] This research aims to design and evaluate novel chromene-based antifungal agents using advanced computational tools and green synthesis methods. [27-29] By leveraging microwave-assisted one step synthesis and conducting comprehensive ADMET and docking studies, this study seeks to identify new chemical entities (NCE's) with potent antifungal activity against *Candida albicans* [30]. The ultimate goal is to contribute to the development of more effective treatments for fungal infections, addressing the critical need for new antifungal agents in the face of rising resistance. [31].This study aims to design and develop novel Chromene (benzopyran) derivatives as potent antifungal agents targeting lanosterol 14 α demethylase [32-34].The NCE's were subjected to In-silico ADMET studies to predict pharmacokinetic and toxicological profiles and molecular docking to evaluate binding affinity (PDB ID: 4WMZ) [35].The top five NCEs exhibiting interactions similar to the standard were selected for one-step green synthesis via microwave irradiation, followed by structural characterization using IR and NMR spectroscopy. Their biological activity was evaluated against *Candida albicans*.

2. MATERIAL AND METHOD

2.1 Literature Survey

Literature survey of Chromene pharmacophore as antifungal agents was carried out and based on the structure activity relationship seventy NCE's were designed. [36-48]

2.2 ADMET studies

ADMET refers to the evaluation of Absorption**,** Distribution**,** Metabolism**,** Excretion and Toxicity of a drug to predict its behavior and safety in the body. The designed NCE's were subjected to ADMET analysis and Lipinski rule of five using Quik Prop tool of Schrodinger software Lipinski rule of five helps to predict whether active molecule is likely to have the chemical and physical properties to be orally bioavailable. Lipinski rule of five states that a compound is more likely to be a good drug candidate if it meets the following criteria (i) 5 hydrogen-bond donors or less, (ii) 10 hydrogen-bond acceptors or less, (iii) a molecular weight less than 500, and (iv) a calculated Log P (cLogP) less than 5.[49-55]

2.3 Molecular Docking

Molecular docking is proved to be a valuable tool in drug synthesis and development by providing insights into the interaction between ligands and target proteins. In this study, Schrodinger software version 13.4 was used for docking studies on the protein with PDB ID 4WMZ having Fluconazole as a co-crystal ligand. The docking process involved preparing both the ligand and the protein by ensuring their structures were complete and by adding any missing atoms or residues. A grid was generated on the receptor and then the ligands were docked with the protein.

The best-scoring interactions were then analyzed to understand the binding mode and key interactions between the protein and the ligands. By simulating how ligands bind to the protein, molecular docking helped to predict the most promising candidates for further development. It also provided detailed information such as bonds between protein and ligands and their respective bond distance and type of bond as well as binding affinity, interaction sites and the stability of ligand-protein complexes, which are crucial for optimizing drug candidates. [56-72]

2.4 Synthesis

Based on ADMET and Molecular docking studies, the less toxic and most active NCE's were taken into consideration for synthesis. To save the time and cut down use of excessive solvents, synthesis was focused on one step and green chemistry methodologies (Figure 1). Purity of synthesized NCE's were determined by using thin layer chromatography technique on Silica gel coated thin layer chromatographic plate procured from Merck and suitable mobile phase finally visualized under UV light. The absence of TLC spots from base and appearance of new spots at different level ensures the reaction completion and purity respectively.IR and NMR spectra of synthesized NCE's were recorded

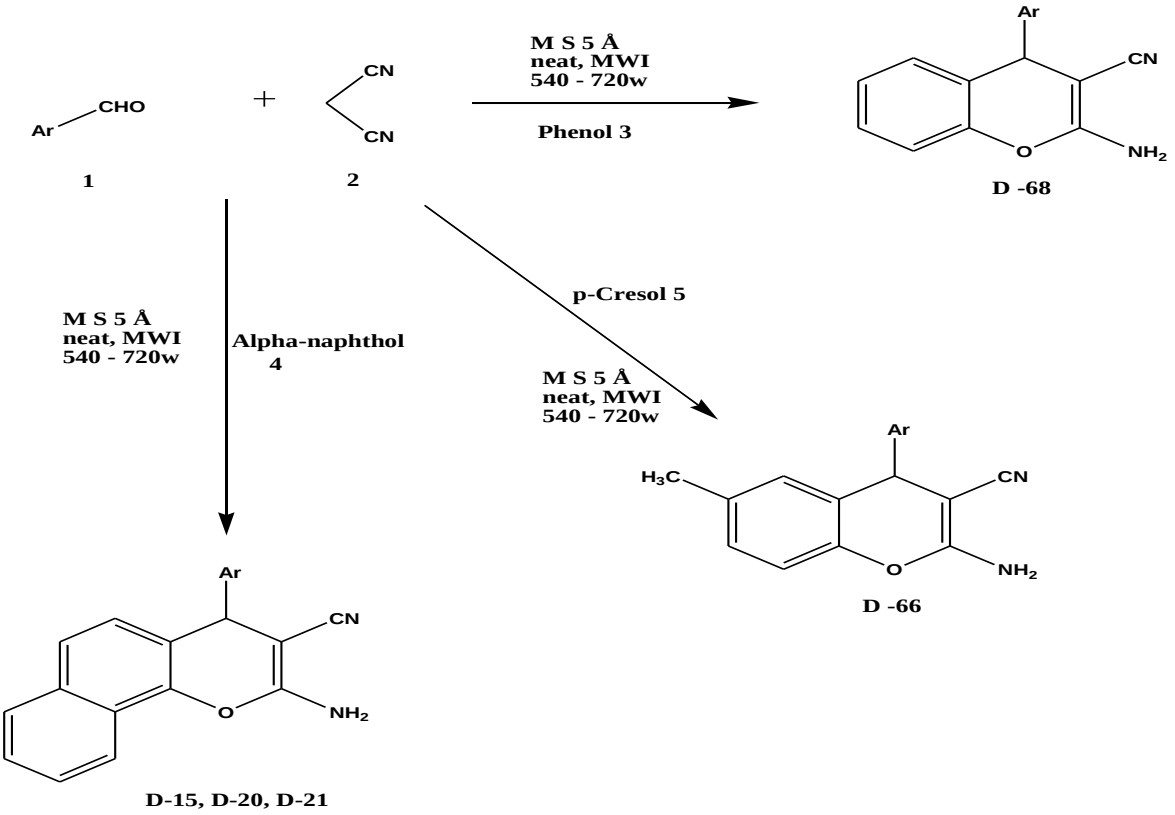


Figure 1: Synthesis Scheme

Mixture of substituted benzaldehyde (1) (1.0 mmol), an active methylene (2) (1.0 mmol) and Phenol (3)/ alpha Naphthol (4)/p- cresol (5) (1.0 mmol) finely powdered 5Å MS (0.5 – 1.0 g weight-equiv. rel. to phenol) was added. The mixture was subjected to microwave irradiation at moderate power (540 – 720 W) for 5 – 10 min (TLC monitoring). Then AcOEt was added, MS filtered, the AcOEt layer washed with water, dried using Na_2SO_4 , concentrated and the residue subjected to CC (AcOEt/hexane 1:1) to obtain the final product (D 15, 20, 21, 66, 68) [73].

2.5 Biological evaluation

Preparation of sample: Stock solutions of the synthesized compound were prepared at a concentration of 1 mg/ml in Ethanol. Next, 100 ug/ml concentrations of different samples were examined for antifungal activity using the modified agar well diffusion method. Each sample was loaded in well for the antifungal activity in the respective test organism plate**.** For further study, the respective test fungal pathogen suspension was prepared in sterile saline aseptically, then pathogen was spread on the surface of sterile MGYP medium [Malt Extract, Glucose, Yeast extract, Peptone agar] using a sterile spreader for the antimicrobial activity test. After spreading agar wells were prepared with the help of a sterilized cork borer of 0.7 cm diameter after that 100 µL of different test solutions[25 to 100 µg/ml] were loaded in the wells prepared on the agar plates. Then plates were placed at 4 °C for 10 to min for sample diffusion in culture medium and transferred to incubator at 27 °C for 48 h. [74, 75]

3. RESULT AND DISCUSSION

3.1 Literature survey and Designing of NCE's

Chromene and its derivatives are indeed significant in the development of antifungal agents. The structural versatility of Chromenes allows for various substitutions that can enhance their biological activity. Following SAR was derived based on the literature survey (Figure 2)-

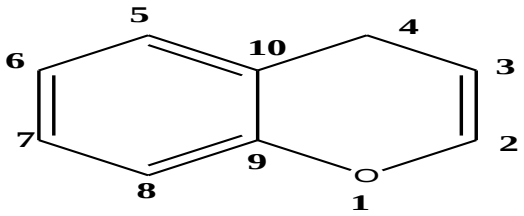
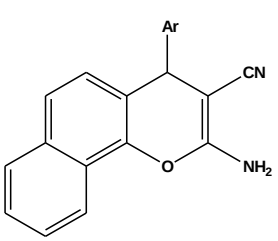


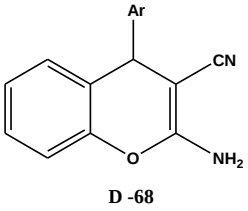
Figure 2: Chromene structure

- Substitution of Bromine, Cyanide at C-5 position showed increase in activity.
- Substitution of Methoxy group at C-6 position showed increase in activity and substitution of electron withdrawing group at C-6 position showed decrease in activity.
- Substitution of Hydrogen, Hydroxyl group, Methoxy and Chlorine group at C-7 position showed increase in activity.
- Substitutionof Amino and Phenyl group at C-2 position showed increase on activity.
- Substitution of Cyanide and tert butyl group at C-3 position showed increase in activity
- Substitution of 2-methoxy, 4-methoxy, 2-chloro, 4-chloro, 2-nitro, 3,4-Dimethoxy and Cinnamaldehyde have showed promising antifungal activity.
- Substitution of different types of phenolic groups also gives promising antifungal activity.

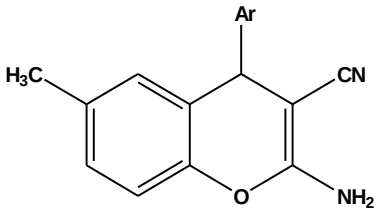
On the basis of literature survey various substituted Benzaldhydes and Phenolic group containing compounds such as Napthols, Phenol, Catechols, Eugenol, Hydroquinone, Cresols, Resorcinol were used to design seventy NCE's. NCE's that passed the ADMET studies and have shown best docking results (D15, D 20, D 21, D 66, D68) were synthesized (Table 1)



D-15, D-20, D-21



D -68



D -66

Table 1: Synthesized NCE's

Compound. no.	Ar-
D15	2,6-Dichlorophenyl
D20	N, N-Dimethylphenyl
D21	Cinnamyl
D66	4-Nitrophenyl
D68	4-Hydroxyphenyl

3.2 ADMET studies

NCE's listed below have shown compliance with Lipinski's parameter for rule of five with zero violations. Donor HB is hydrogen bond donor and its standard range is 0-5, Acceptor HB is hydrogen bond acceptor and its standard range is 0-10, QPlog Po/w is predicted octanol-water partition coefficient it helps to assess the drug-likeness of a compound and its oral bioavailability, QPlog HERG helps to assess the cardio toxicity potential of a compound, percent human oral absorption it helps predict how much of a drug will effect after oral administration. (Table 2)

Table 2: ADMET prediction of designed molecule.

Compound no.	**Donor HB**	**Acceptor HB**	**QPlog Po/w**	**QPlog HERG**	**% Human oral absorption**	**Rule Of Five**
D15	2	2.5	4.412	-5.512	100	0
D20	2	3.5	4.177	-5.988	100	0
D21	2	2.5	4.696	-6.516	100	0
D66	0	1.5	3.871	-5.097	100	0
D68	1	1.25	3.799	-4.991	100	0

3.3 Molecular docking Studies

Seventy NCE's were screened for ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) prediction using Lipinski's Rule of Five to evaluate their bioavailability. Out of the 70 compounds, 18 violated Lipinski's rule, indicating poor drug-like properties. As a result, 52 NCE's from the series were further screened for docking studies against the protein PDB ID 4WMZ. This screening aimed to identify promising drug candidates with good bioavailability and binding affinity to the target protein for potential antifungal activity. Compounds with dock score higher than the standard drug Fluconazole are shown in Table 3

Table 3: Docking result of designed NCE's and standard drug.

Compound no.	**Docking score Kcal/ mol**	**Glide energy Kcal/ mol**	**Type of interaction**	**Interactions atom of ligand**	**Amino acid**	**Distance (Å)**
D21	-7.947	-7.947	Pi-Pi stack	Pyran ring	**TYR140**	5.48
			Pi-Pi stack	Naphthol ring	HIE378	5.45
			H bond	-N of CN	LYS151	2.29
			H bond	$-NH_2$	HIS468	1.83
D68	-7.435	-7.437	H bond	$-NH_2$	GLY310	1.90
			H bond	-N of CN	**CSY470**	2.69
			H bond	-OH of Ald	HIS468	1.80
D15	-7.375	-7.375	H bond	-N of CN	LYS151	2.34
			H bond	$-NH_2$	HIS468	1.72
			Pi-Pi	Pyran ring	**TYR140**	5.48
			Pi-Pi	benzene	**TYR140**	5.90
D20	-7.290	-7.294	H bond	-O of Pyran	**TYR140**	2.49
			Pi-Pi	benzene	**TYR126**	4.99
			Pi-Pi	benzene	**TYR140**	5.48
D66	-6.960	-6.960	H bond	$-NH_2$	GLY310	2.02
			H bond	-O of NO_2 Ald	LYS151	2.23
			Salt bridge	2^{nd} O of NO_2 Ald	LYS151	4.79
			Pi-Pi stack	Benzene fused with Pyran	**TYR126**	5.16
Fluconazole	-6.041	-6.041	H bond	-OH	**TYR140**	1.99
			H bond	-N of Pyrazole	**CYS470**	2.80
			Pi-Pi stacking	Pyrazole ring	**TYR126**	4.87

NCE's that exhibit similar interactions with key amino acids as standard drug Fluconazole are higlighted in bold letters

Compound D 21 showed following four interactions-

a) The Pyran ring showed pi pi stacking with amino acid TYR 140 with a distance of 5.48 Å
b) Alpha naphthol showed pi pi stacking with amino acid HIE378 with a distance of 5.45 Å
c) N of Cyanide showed H bond with amino acid LYS151 with a distance of 2.29 Å
d) NH_2 showed H bond with amino acid HIS468 with a distance of 1.83 Å

Compound D 68 showed following interactions-

a) NH_2 showed H bond with amino acid GLY310 with a distance of 1.90 Å
b) N of Cyanide showed H bond with amino acid CYS470 with a distance of 2.69 Å
c) OH of hydroxyl aldehyde showed H bond with amino acid HIS468 with a distance of 1.80 Å

Compound D 15 showed following interactions-

a) N of Cyanide showed H bond with amino acid LYS151 with a distance of 2.34 Å
b) NH_2 showed H bond with amino acid HIS468 with a distance of 1.72 Å

c) Pyran ring showed pi pi stacking with amino acid TYR140 with distance 5.48 Å
d) Benzene ring showed pi pi stacking with amino acid TYR140 with distance 5.90 Å

Compound D 20 showed following interactions-

a) Oxygen of Pyran showed H bond with amino acid TYR140 with a distance of 2.49 Å
b) Benzene ring showed pi pi stacking with amino acid TYR126 with distance 4.99 Å
c) Benzene ring showed pi pi stacking with amino acid TYR140 with distance 5.48 Å

Compound D 66 showed following interactions-

a) NH_2 showed H bond with amino acid GLY310 with a distance of 2.02 Å
b) O of NO_2 Ald showed H bond with amino acid LYS151 with a distance of 2.23 Å
c) O of NO_2 Ald showed H bond with amino acid LYS151 with a distance of 4.79 Å
d) Benzene showed pi pi stacking with amino acid TYR126 with distance of 5.16 Å

Fluconazole showed following interactions-

a) OH showed H bond with amino acid TYR140 with distance 1.99 Å
b) N of Pyrazole showed H bond with amino acid CYS470 with distance 2.80 Å
c) Pyrazole ring showed pi pi stacking with amino acid TYR126 with distance 4.87 Å

3.4 Structural Characterization:

Compound D15: 2-amino-4-(2,6-dichlorophenyl)-4H-benzo[h]chromene-3-carbonitrile.
Brown Crystalline, Solid. m.p 450.00°c-452.50°c. IR (KBr) (ν_{max}/cm^{-1}): 3476 cm^{-1} and 3312 cm^{-1}: N-H stretching (amine groups), 3050 cm^{-1}: Aromatic C-H stretching, 2907 cm^{-1}: Aliphatic C-H stretching, 2228 cm^{-1}: C≡N stretching (nitrile group), 1659 cm^{-1} and 1631 cm^{-1}: C=O stretching (carbonyl groups) or C=C stretching in conjugation, 1402 cm^{-1}: Aromatic C=C bending or in-plane vibrations, 1257 cm^{-1}: C-N stretching (amine or aromatic amine).

Compound D20: 2-amino-4-(4-(dimethylamino)phenyl)-4H-benzo[h]chromene-3-carbonitrile.
Brown crystalline, Solid. m.p 432.66°C-435.66°C. IR(KBr) (ν_{max}/cm^{-1}):3346 cm^{-1}: N-H stretching (amine group), 2208 cm^{-1}: C≡N stretching (nitrile group), 1651 cm^{-1}: C=O stretching (chromene ring carbonyl), 1505 cm^{-1}: Aromatic C=C stretching, 1268 cm^{-1}: C-N stretching

Compound D 21: 2-amino-4-cinnamyl-4H-benzo[h]chromene-3-carbonitrile.
Brown Crystalline, Solid. m.p 390.50°c -395.80°c.IR (KBr) (ν_{max}/cm^{-1}): 3342 cm^{-1} and 3221 cm^{-1}: N-H stretching (Amine group), 3030 cm^{-1}: Aromatic C-H stretching, 2223 cm^{-1}: C≡N stretching (Cyanide group), 1726 cm^{-1}: C=O stretching (carbonyl group), 1648 cm^{-1} and 1628 cm^{-1}: C=C stretching in an aromatic or conjugated system, 1451 cm^{-1}: Aromatic ring C=C bending or in-plane deformation, 1275 cm^{-1}: C-N stretching (aromatic or aliphatic amine).^{1}H NMRδ2.17 (M5H), 2.43 (M 5H), 4.00 (T 2H), 6.14 (M 5H), 6.38 (D 1H), 7.17 (T2H), 7.23 (T 2H), 7.27 (D 1H), 7.41 (M 5H), 7.67 (S), 7.73 (T 2H), 7.97 (T 2H).

Compound D66: 2-amino-6-methyl-4-(3-nitrophenyl)-4H-chromene-3-carbonitrile.
Brown Crystalline, Solid. m.p 420.50°c -423.75°c IR (KBr) (ν_{max}/cm^{-1}): 3342 cm^{-1}: N-H stretching (Amine group), 3088 cm^{-1}: Aromatic C-H stretching (aromatic ring), 2237 cm^{-1}:

C≡N stretching (Cyanide group), 1615 cm^{-1}: C=C stretching (aromatic ring), 1565 cm^{-1}: C=C stretching (aromatic), 1436 cm^{-1}: C-H bending (aliphatic), 1073 cm^{-1}: C-O (stretching).

Compound D 68: 2,2-amino-4-(4-hydroxyphenyl)-6-methyl-4H-chromene-3-carbonitrile,Brown Crystalline, Solid, m.p 410.50°c -415.00°cIR (KBr) (ν_{max}/cm^{-1}): 3441 cm^{-1}: N-H stretching (amine group), 3646 cm^{-1}: O-H stretching (Phenol group), 3062 cm^{-1}: Aromatic C-H stretching (aromatic ring), 2223 cm^{-1}: C≡N stretching (Cyanide group), 1603 cm^{-1}: C=C stretching (aromatic), 1430 cm^{-1}: C-H bending (aliphatic group), 1205 cm^{-1}: C-O stretching.

3.5 Biological evaluation

All the NCE's showed comparable activity with Fluconazole. Compound D21 demonstrated most promising antifungal activity against *Candida albicans* with a zone of inhibition of 20 mm, 21 mm, 23 mm and 27 mm at concentrations of 25µg/ml, 50 µg/ml, 75 µg/ml and 100 µg/ml respectively. (Table 4)

Table 4: Antifungal activity of synthesised compounds.

Compound No.	**Zone of inhibition in mm against *Candida albicans***			
	25 µg/ml	50µg/ml	75 µg/ml	100 µg/ml
D15	15	20	20	26
D 20	18	18	21	25
D 21	20	21	23	27
D 66	15	19	19	24
D 68	16	20	20	25
Fluconazole	00	00	22	26

00 indicates no zone of inhibition

4. CONCLUSION

- Based on an antifungal literature survey and the structure-activity relationship (SAR) of the Chromene ring A total of 70 new chemical entities (NCEs) employing combination of various substituted aromatic aldehydes, phenols were designed.
- Out of the 70 NCEs, 52 compounds followed the Lipinski's Rule of Five, indicating favourable drug-like properties and oral bioavailability. These 52 NCEs were selected for further docking studies to assess their potential as antifungal agents.ADMET studies were done with Schrodinger software and resulted that substitutions like Bromine and Methoxy leads to the violations, while substitutions with 1-hydroxy , 2-Nitro , and 3-Nitro showed zero violations.
- NCE's were docked with PDB ID 4WMZ to evaluate their binding affinities and interactions. Five compounds D15, D20, D21, D66 and D68 showed higher dock scores, better glide energy, and similar interactions than the standard drug, making them promising candidates.
- These top five compounds (D15, D20, D21, D66, and D68) were synthesized and subjected to structural characterization.

- Synthesized compounds were tested for antifungal activity against *Candida albicans* using the agar well diffusion method. Among the tested NCEs, D21 showed the best antifungal activity compared to the standard drug, Fluconazole, highlighting its potential as a strong antifungal agent.

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CONFLICT OF INTEREST
Authors declared no conflict of interest.

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