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Research Article

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Design, Synthesis, and the Biological Evaluation of Some New Fused Thiazolotriazine Derivatives

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Abstract: Thiazolotriazine is an essential medicinal chemistry molecule due to its biological properties, particularly antifungal activity. Antifungal drug resistance is rising worldwide, necessitating the development of innovative, safer, and more effective antifungals. This study intended to uncover safer and more effective thiazolotriazine antifungals. ProTox II software was employed to forecast the toxicity of the designed thiazolotriazines. The pharmacokinetic parameters were calculated using the Swiss-ADME database. The Molecular Operating Environment software (2019.0102 version) was employed for the docking studies utilizing 14-α-demethylase protein (PDB ID: 3LD6). Compounds 4c, 4d, and 4e were prepared and evaluated for *in vitro* antifungal activity. The computational studies revealed compounds 4a, 4b, 5b, 5c, 6b, 6c and 6d as carcinogenic; 4a, 4b, 4c, 4d and 4e demonstrated better pharmacokinetic behaviour; and docking results of 4c, 4d, and 4e were superior than fluconazole (FLU). The molecular docking studies establish 4c, 4d, and 4e as SDM inhibitors, suggesting a mechanism similar to FLU and ketoconazole (KET). The antifungal activity evaluation revealed 4d (MIC = 6.25 µg/ml) as a more potent antifungal agent than KET (MIC = 12.5 µg/ml) and FLU (MIC = 12.5 µg/ml). Compounds 4c and 4e showed equal antifungal activity to KET (MIC = 12.5 µg/ml) and FLU (MIC = 12.5 µg/ml). Compounds 4c, 4d, and 4e displayed encouraging antifungal activity with a favorable safety profile. Assessing the broad spectrum of 4c, 4d, and 4e against various pathogenic fungi, including resistant forms, is recommended.

Keywords: Thiazolotriazine, *In silico* studies, 14-α-demethylase, Synthesis, Antifungal activity.

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1. INTRODUCTION

Thiazole and triazine heterocyclic rings are important templates in drug discovery [1,2]. Thiazolotriazine is a fused heterocycle that is particularly intriguing since it combines the structural characteristics of thiazole and triazine. The thiazolotriazine ring system is a significant structural system that has garnered considerable research attention due to its diverse applications in drug discovery. This is primarily due to its documented biological activities, such as antitumor activity[3], NS5B polymerase inhibitory activity [4], and antinociceptive activity[5]. Sterol 14α-demethylase (SDM) is a well-acknowledged focal point for developing antifungal agents [6]. SDM facilitates the transformation of sterols into ergosterol, vital for properly functioning the fungal cell membrane [6,7]. Various SDM inhibitors like fluconazole (FLU) and ketoconazole (KET) are utilized in clinical practice to treat diverse fungal infections[7,8]. However, these SDM inhibitors have limitations due to their adverse effects, safety concerns, and the surfacing of drug-resistant fungal strains [8,9]. The literature indicates that thiazolotriazine derivatives are untouched as SDM inhibitors, providing an opportunity to explore the potential of thiazolotriazine derivatives as SDM inhibitors [1-8]. Based on the above facts and to better understand the significance of thiazolotriazine as SDM inhibitors and their potential antifungal agents, we aimed to design, synthesize, and evaluate the biological activity of these new fused thiazolotriazine derivatives.

2. MATERIALS AND METHODS

2.1. Chemicals

The software and instruments employed in this report have been specified in the corresponding methods. The solvents, reagents, and chemicals utilized in this investigation were procured from Sigma (USA).

2.2. Designing of the compounds

The thiazolotriazine structures were designed based on the reactions provided in the literature utilizing the ChemSketch software (version 21) [10,11]. The important designed compounds (DCs) are provided in Figure 1.

2.3. Oral LD_{50} and toxicity calculation

The ProTox II software was utilized to forecast the toxicity parameters [12-14]. The Mole-Files of DCs, FLU, ciprofloxacin (CIP), and KET were uploaded into the software, the start button was hit, and the resulting data was documented (Table 1).

2.4. Pharmacokinetic parameters calculation

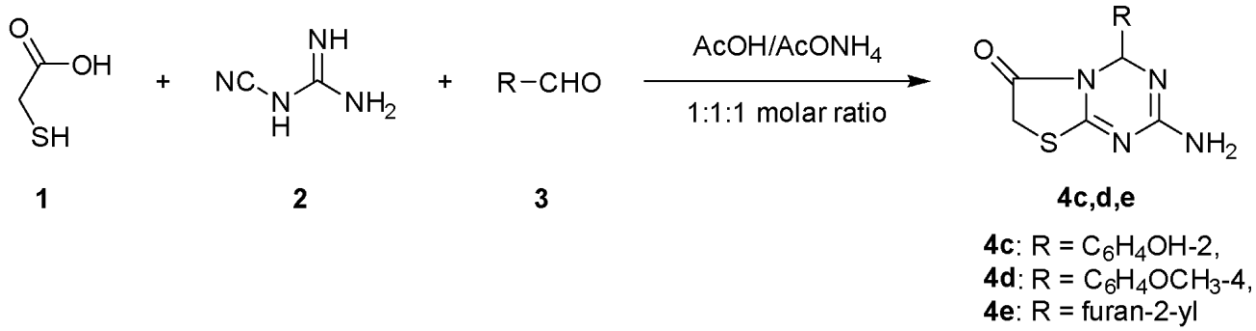
The Swiss-ADME software was utilized to foresee the pharmacokinetic properties and bioavailability radar [13-15]. The Mole-Files of DCs, FLU, CIP, and KET were uploaded into the software, the start button was hit, and the resulting data was documented (Table 2). The % absorption was computed using a formula (% absorption = 109 – (0.345 x TPSA))[13] (Table 2).

2.5. Docking studies

The Molecular Operating Environment software (MOE) (2019.0102 version, Chemical Computing Group Inc., Canada) was used for the docking studies of the DCs (Figure 1) with the 14-α-demethylase protein (PDB ID: 3LD6) and DNA gyrase protein (PDB ID: 6F86) [14,16]. The proteins were imported into the software, purified using the Quickpro function, and saved on the computer. Similarly, the software generated the MDB files for the DCs, CIP, KET, and FLU. The MDB files of the DCs, CIP, KET, and FLU were individually subjected to docking with the purified proteins. The root mean square deviation (RMSD) and the docking score (DS in kcal/mol) were predicted and documented in Table 3.

2.6. General preparation of 4c, 4d and 4e

The requisite aldehyde (namely, 2-hydroxybenzaldehyde, 4-methoxy benzaldehyde, furan-2-carbaldehyde 3a-c, 0.01 mol), thioglycolic acid (1, 0.01 mol), dicyandiamide (2, 0.01 mol) in AcOH (50 ml) in the presence of $AcNH_4$ (3 g) were heated under reflux for a certain time (monitored by TLC) during which the contents of the flask solidified. The solids were filtered off, washed with ethanol, dried, and recrystallized from the proper solvent to give 4c, 4d, and 4e [10].



Scheme 1. Synthesis of 4c, 4d, and 4e

The characterization data of the synthesized compounds is mentioned in Table 4.

2.7. Antifungal activity evaluation

The serial dilution method discussed in earlier publications was utilized to accomplish this task [14,17,18]. To summarize, diverse DCs, FLU, and KET dilutions were synthesized in varying dilutions. In addition to its role as a control, sterile DMSO was used as a solvent to prepare various DCs, FLU, and KET dilutions. The MICs (minimum inhibitory

concentrations) of DCs, FLU, and KET were determined utilizing an agar medium (Table 5).

3. STATISTICAL ANALYSIS

The experimental data was subjected to statistical analysis using SPSS software (version 20, Chicago, IL, USA). The results are deemed statistically significant if the p-value (N = 3; Mean SD) is below 0.05.

4. RESULTS AND DISCUSSION

4.1. *Designing of the compounds*

The DCs were prepared according to the literature [10,11]. These compounds were subjected to computational studies mentioned in the experimental sections. These studies revealed twelve compounds of interest (Figure 1).

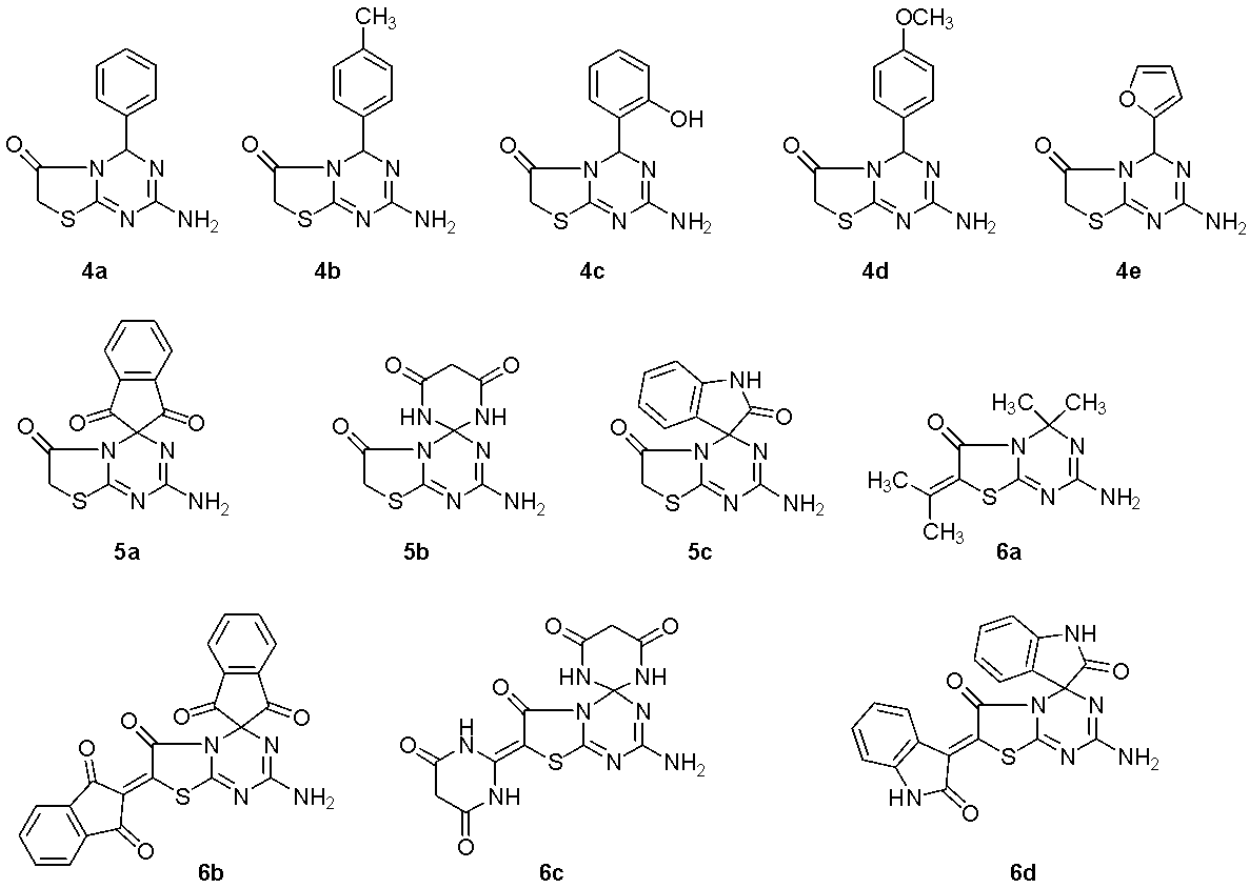


Fig 1: Chemical structures of the DCs

4.2. *Toxicity prediction*

The LD_{50} and toxicity of the twelve DCs (Figure 1) were predicted by ProTox II [12-14] (Table 1).

Table 1. Toxicity data of DCs, FLU, KET, and CIP

Compound	LD_{50} (mg/kg)	Toxicity class	Hepatotoxicity	Nephrotoxicity	Cardiotoxicity	Carcinogenicity	Immunotoxicity	Mutagenicity	Cytotoxicity
4a	534	4	Inactive	Inactive	Inactive	Active	Inactive	Inactive	Inactive
4b	300	3	Inactive	Inactive	Inactive	Active	Inactive	Inactive	Inactive
4c	534	4	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive
4d	2000	4	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive
4e	1000	4	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive
5a	300	3	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive
5b	534	4	Inactive	Inactive	Inactive	Active	Inactive	Inactive	Inactive
5c	10000	6	Inactive	Inactive	Inactive	Active	Inactive	Inactive	Inactive
6a	2000	4	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive
6b	2000	4	Active	Inactive	Inactive	Active	Inactive	Inactive	Inactive
6c	2000	4	Inactive	Inactive	Inactive	Active	Inactive	Inactive	Inactive
6d	2000	4	Active	Inactive	Inactive	Active	Inactive	Inactive	Inactive
CIP	2000	4	Inactive	Active	Inactive	Inactive	Inactive	Active	Inactive
FLU	1271	4	Active	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive
KET	166	3	Active	Active	Inactive	Inactive	Active	Inactive	Inactive

The predicted toxicity data of DCs revealed carcinogenic behavior of 4a, 4b, 5b, 5c, 6b, 6c, and 6d compared to FLU and KET. The 6b and 6d were also predicted as hepatotoxic.

4.3. Pharmacokinetic parameters

The pharmacokinetic parameters of the DCs (Figure 1) were predicted by Swiss-ADME software [13-15] (Table 2).

Table 2. Predicted lipophilicity, drug-likeliness, and pharmacokinetic data

Compound	TPSA	Lipophilicity (Log Po/w)	Drug-likeness (as per Lipinski's rule)	Calculated % of GI Absorption*	Pharmacokinetics							
					GI absorption	BBB permeant	P-gp substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor
4a	96.35	0.96	Yes	75.75	High	No	No	No	No	No	No	No
4b	96.35	1.37	Yes	75.75	High	No	No	No	No	No	No	No
4c	116.58	0.53	Yes	68.77	High	No	No	No	No	No	No	No
4d	105.58	1.04	Yes	72.57	High	No	No	No	No	No	No	No
4e	109.49	0.28	Yes	71.22	High	No	No	No	No	No	No	No
5a	130.49	0.38	Yes	63.98	High	No	No	Yes	No	No	No	No
5b	154.55	-1.80	Yes	55.68	Low	No	No	No	No	No	No	No
5c	125.45	0.10	Yes	65.71	Low	No	No	No	No	No	No	No
6a	100.98	1.33	Yes	74.16	High	No	No	Yes	No	No	No	No
6b	169.26	1.37	Yes	50.60	Low	No	No	No	No	No	No	No
6c	217.38	-2.89	Yes	34.0	Low	No	No	No	No	No	No	No
6d	159.18	0.88	Yes	54.08	Low	No	No	No	Yes	No	No	No
CIP	74.57	1.10	Yes	83.27	High	No	Yes	No	No	No	No	No
FLU	81.65	0.88	Yes	80.83	High	No	Yes	No	Yes	No	No	No
KET	69.06	3.57	Yes	85.17	High	Yes	No	No	Yes	Yes	Yes	Yes

Two compounds (5a and 6a) were identified as CYP1A2 inhibitors; 6d was a CYP2C19 inhibitor; five compounds (5b, 5c, 6b, 6c, and 6d) revealed low gastrointestinal absorption. Five compounds (4a, 4b, 4c, 4d, and 4e) demonstrated better pharmacokinetic behavior than CIP, FLU, and KET.

4.4. Docking studies

The DCs were docked with the 14-α-demethylase protein (PDB ID: 3LD6) and DNA gyrase protein (PDB ID: 6F86) [14,16] (Table 3).

Table 3. Predicted DS and RMSD values

Compound	DS (kcal/mol) against 14-α - demethylase (3LD6)		DS (kcal/mol) against DNA gyrase proteins (6F86)	
	DS	RMSD	DS	RMSD
4a	-5.11	1.34	-5.25	0.89
4b	-5.23	1.20	-5.36	1.47
4c	-6.41	1.29	-5.09	0.83
4d	-6.93	1.41	-5.71	1.10
4e	-6.22	0.80	-5.53	0.98
5a	-5.67	1.32	-5.33	1.33
5b	-5.58	1.08	-5.14	1.01
5c	-5.58	0.65	-5.02	0.88
6a	-5.94	1.44	-4.80	0.78
6b	-6.24	1.41	-5.35	1.15
6c	-6.36	1.41	-6.69	0.79
6d	-6.29	1.46	-5.66	1.44
CIP	-	-	-6.09	1.34
FLU	-6.04	1.27	-	-
KET	-8.74	1.17	-	-

The docking results revealed that 4c, 4d, 4e, 6b, 6c, and 6d were more potent than FLU concerning fungal protein (14-α-demethylase, 3LD6). The compound 6c displayed more potency than CIP concerning bacterial protein (DNA gyrase, 6F86), while other DCs displayed inferior potency concerning DNA gyrase proteins (6F86). 6b, 6c, and 6d exhibited carcinogenic characteristics (Table 1). Therefore, 6b, 6c, and 6d were not selected for synthesis and further biological evaluation. None of the DCs also

displayed potent activity against bacterial DNA gyrase protein (6F86). The interactions of 4c, 4d, 4e, FLU, and CIP with fungal 3LD6 protein are represented in Figure 2 and Figure 6, respectively.

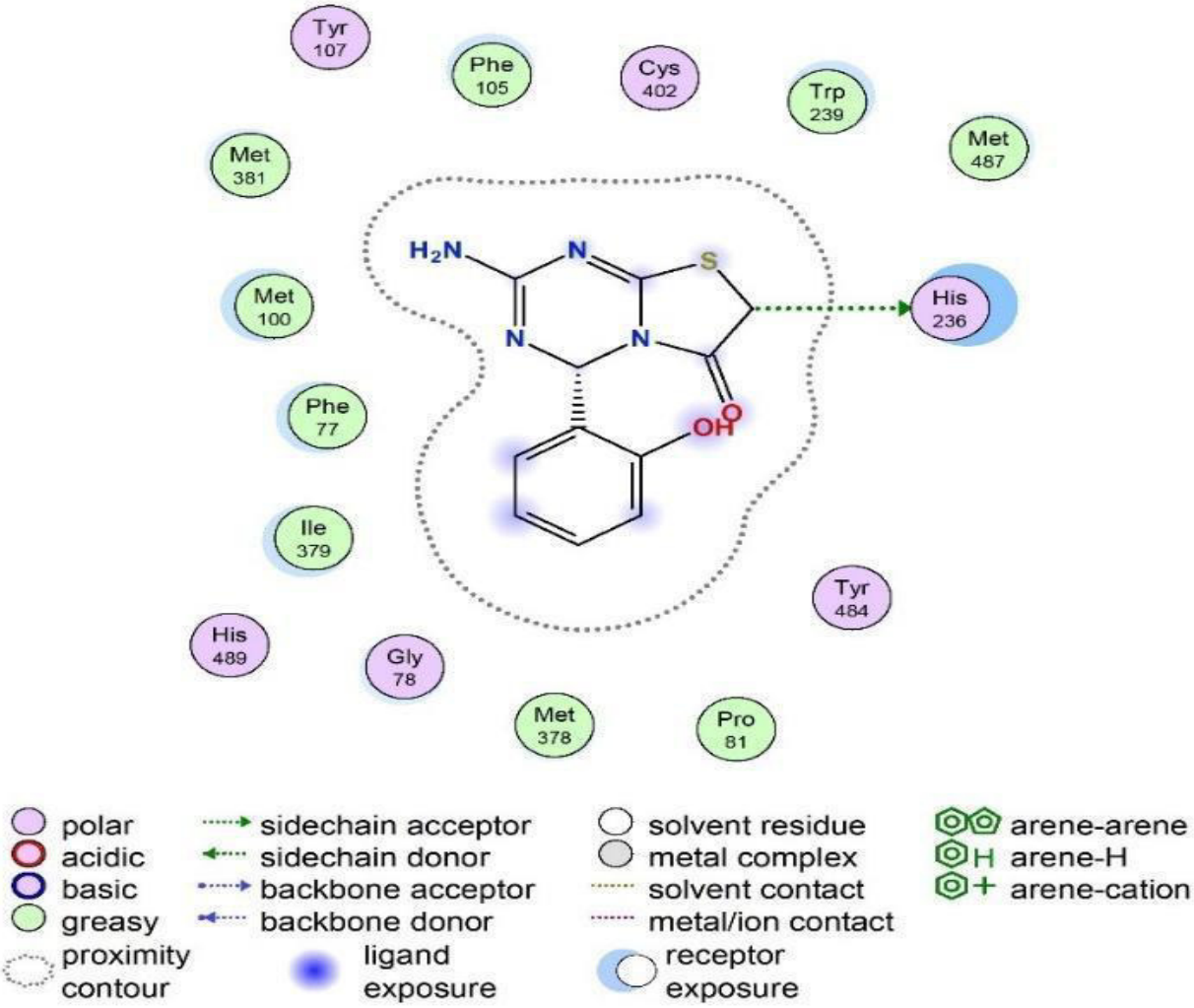


Fig 2: Interaction of 4c with 3LD6 protein

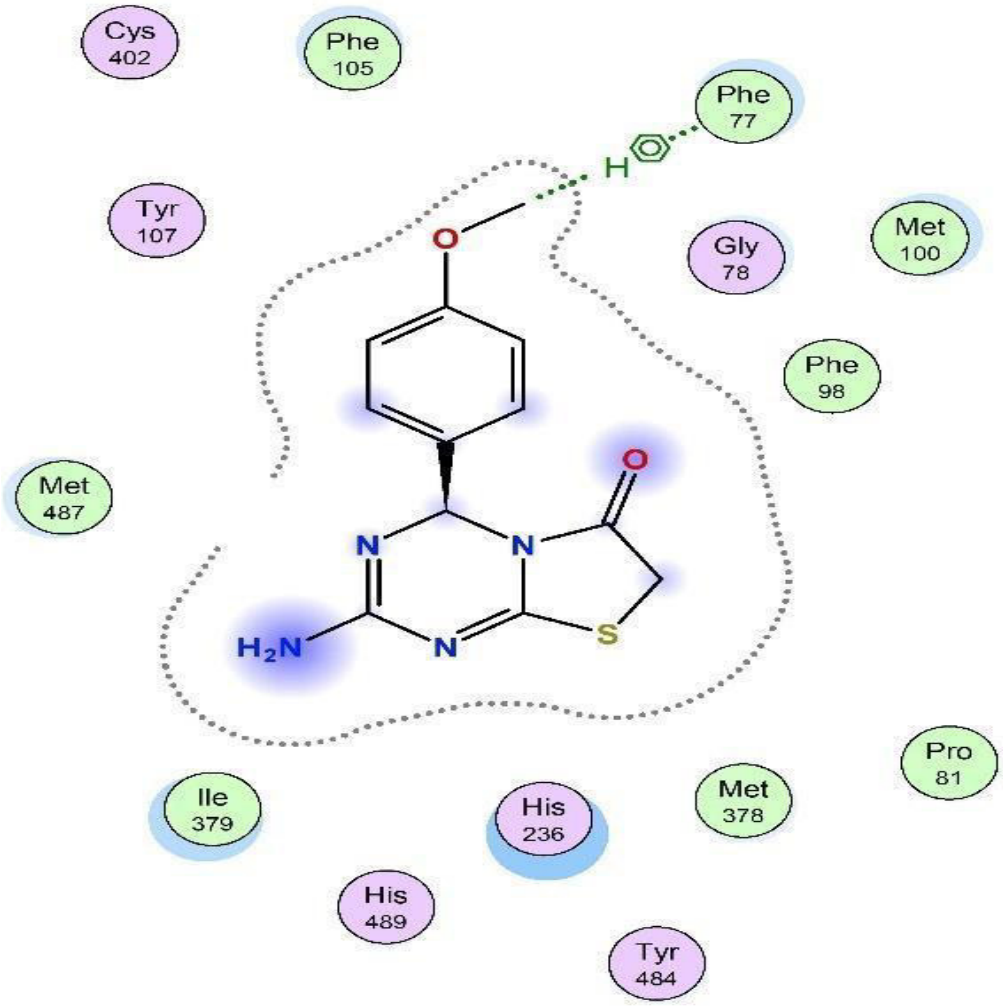


Fig 3: Interaction of 4d with 3LD6 protein

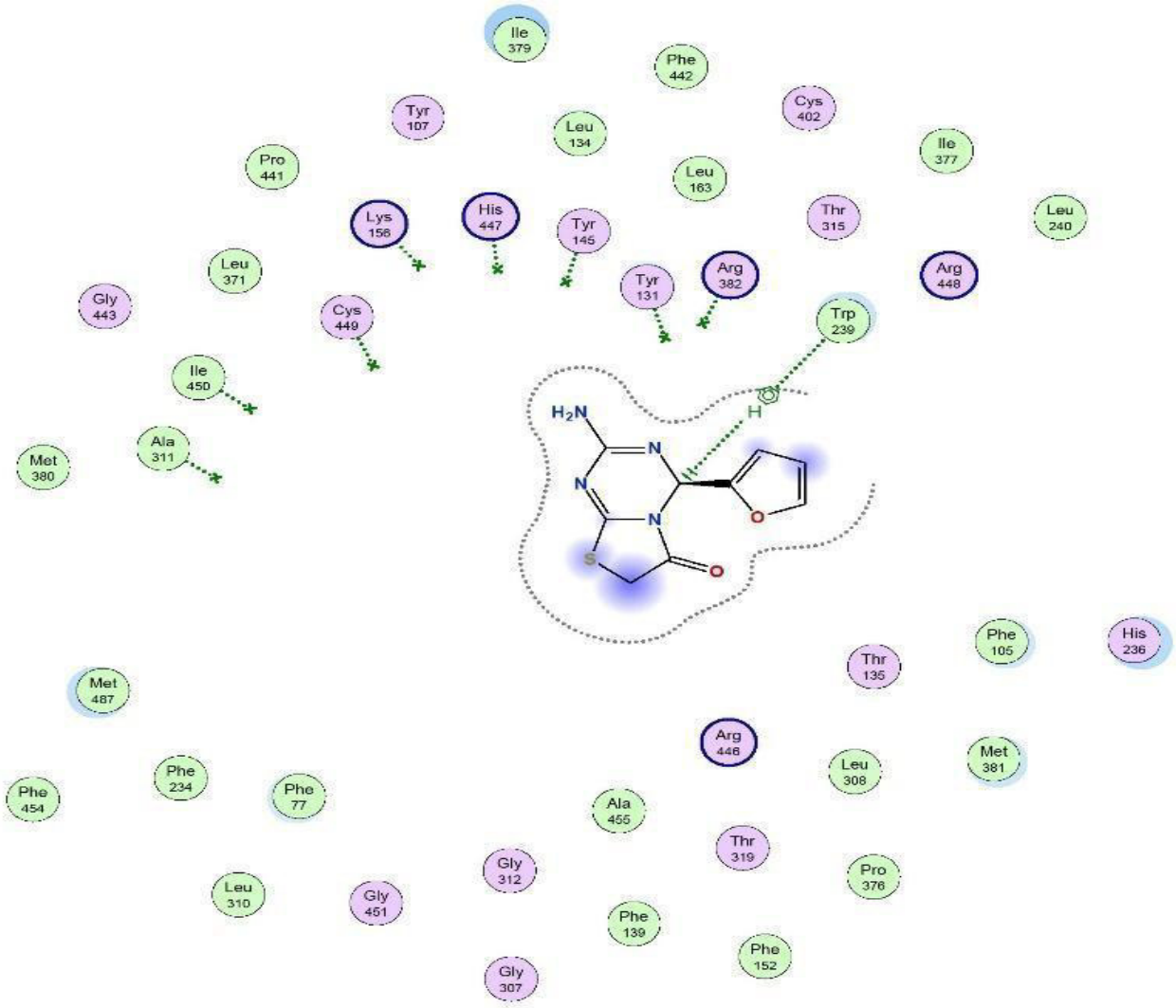


Fig 4: Interaction of 4e with 3LD6 protein

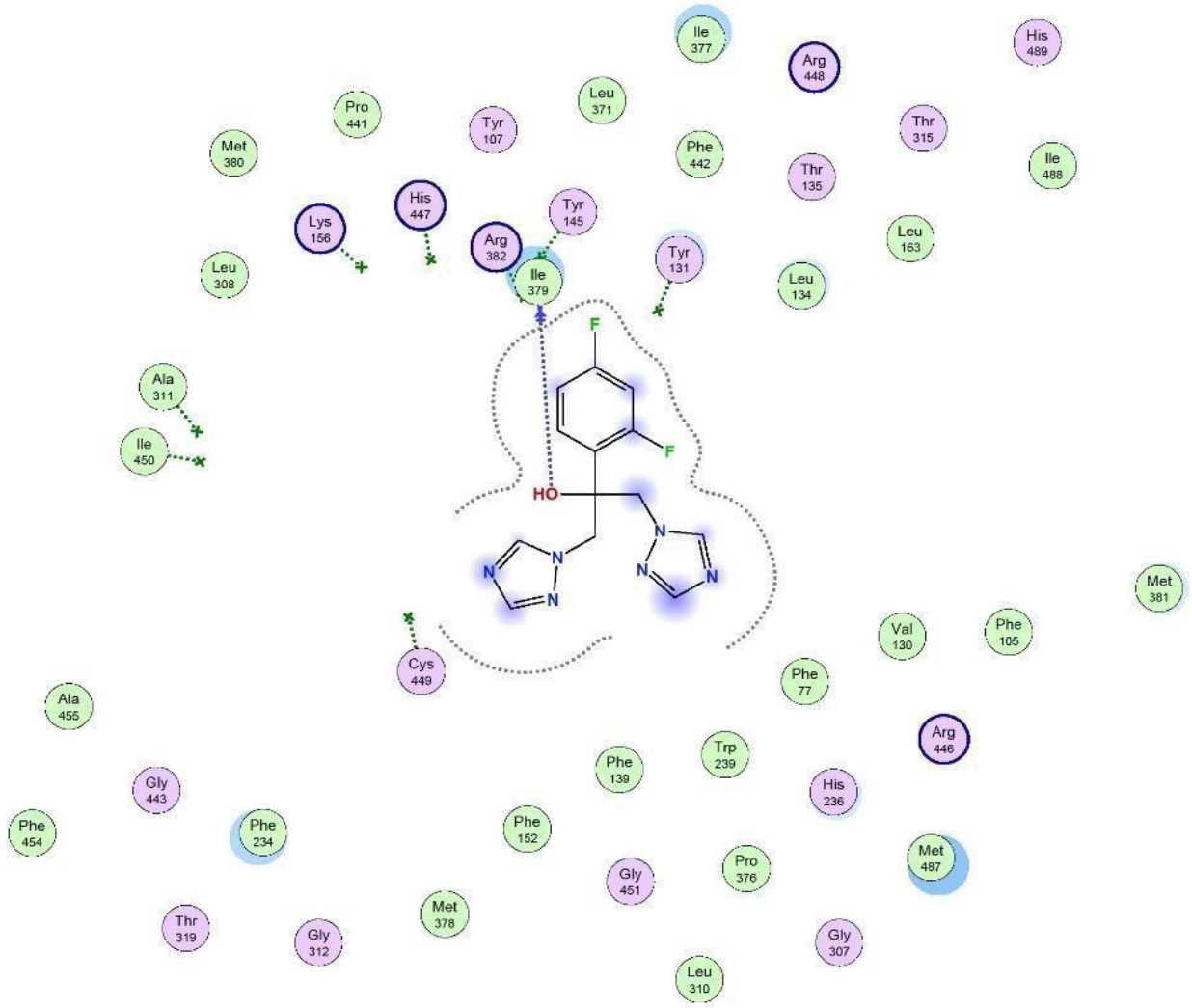


Fig 5: Interaction of FLU with 3LD6 protein

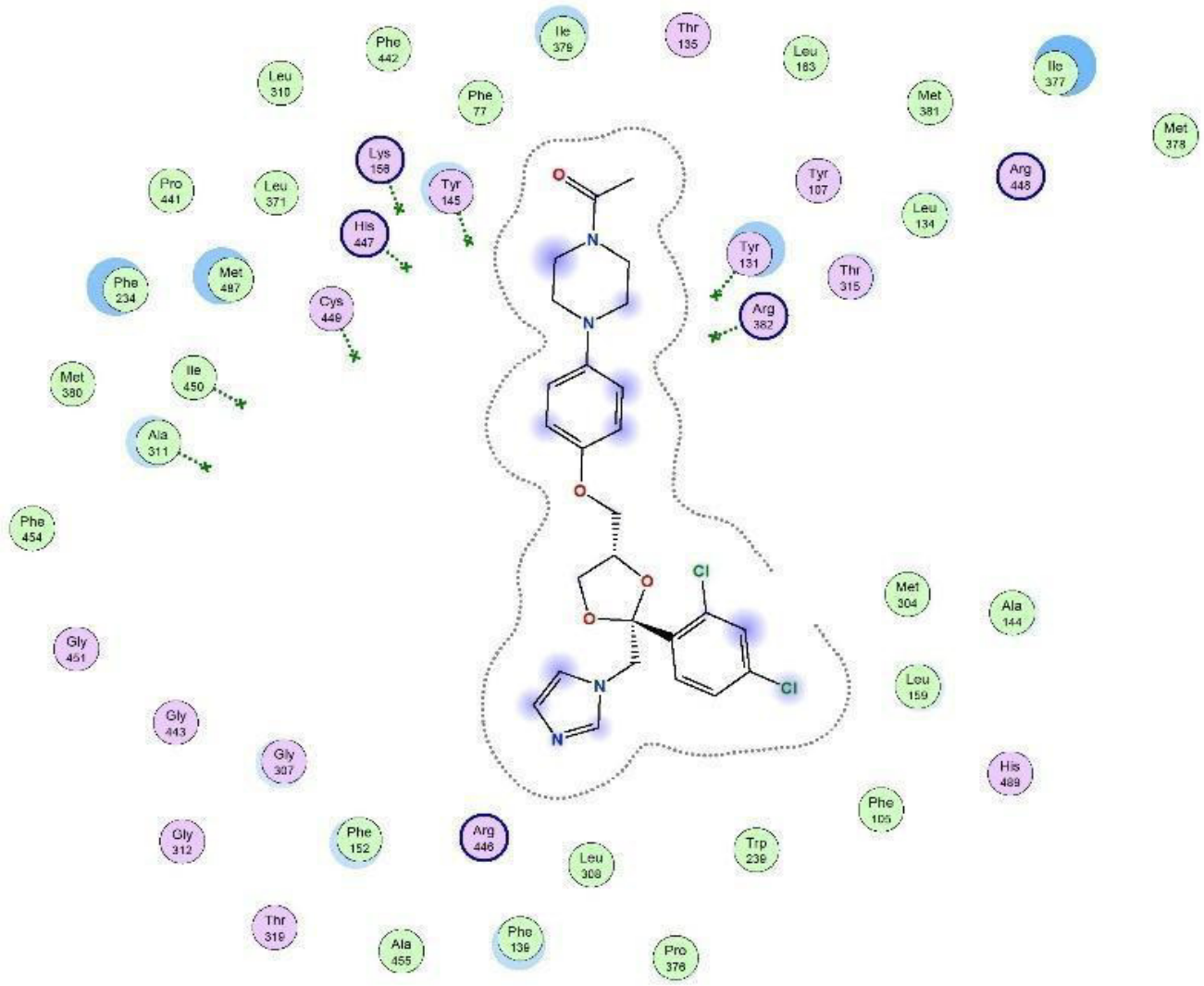


Fig 6: Interaction of KET with 3LD6 protein

The compounds 4c, 4d, and 4e were identified as promising antifungal agents with promising safety and pharmacokinetic profiles based on the *in silico* studies. This understanding was further strengthened by the bioavailability radar of 4c, 4d, 4e, FLU, and KET (Figure 7) [13-15].

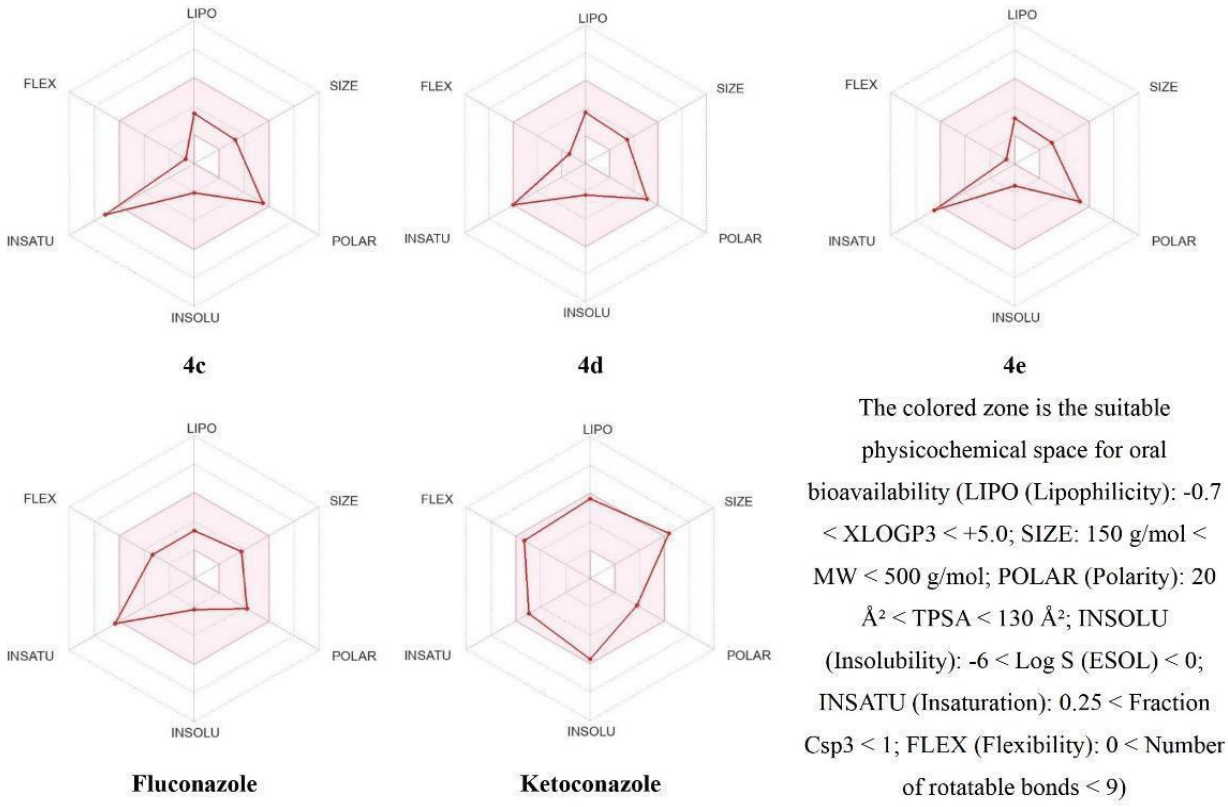


Fig 7: Bioavailability radar of 4c, 4d, 4e, fluconazole, and ketoconazole

The predicted bioavailability of 4c, 4d, 4e, FLU, and KET was comparable. Accordingly, three compounds (4c, 4d, and 4e) were selected for the synthesis and antifungal activity evaluation based on their toxicity profile (Table 1), pharmacokinetic properties (Table 2), and the DS against 6F86 protein (Table 3).

4.5. Synthesis of the compounds

Compounds 4c, 4d, and 4e were prepared per the literature (Scheme 1) (Table 4) [10].

Table 4. Physical data of 4c, 4d, and 4e

Compound	Melting point (°C)	Molecular formula	Molecular weight	Yield (%)
4c	280-282	$C_{11}H_{10}N_4O_2S$	262.29	93
4d	295-296	$C_{12}H_{12}N_4O_2S$	276.31	94
4e	284-86	$C_9H_8N_4O_2S$	236.25	87

4.6. Antifungal activity

The synthesized compounds (4c, 4d, and 4e) were evaluated against three fungi using established methods [14,17,18]. The data of the antifungal activity evaluation is provided in Table 5 and is also depicted in Figure 8.

Table 5. Antifungal activity of 4c, 4d, and 4e

Compound	Zone of inhibition in mm (MIC in µ g/ml)*		
	C. albicans	*C. tropicalis*	*A. fumigatus*
4c	22.55±0.32 (12.5)	24.99±0.62 (12.5)	21.11±0.14 (12.5)
4d	23.10±0.12 (6.25)	23.77±0.33 (6.25)	21.0±0.15 (6.25)
4e	24.20±0,29 (12.5)	21.45±0.22 (12.5)	22.33±0.61 (12.5)
FLU	24.22±0.48 (12.5)	23.47±0.34 (12.5)	21.15±0.48 (12.5)
KET	23.52±0.33 (12.5)	23.18±0.44 (12.5)	21.04±0.46 (12.5)

*$p < 0.05$.

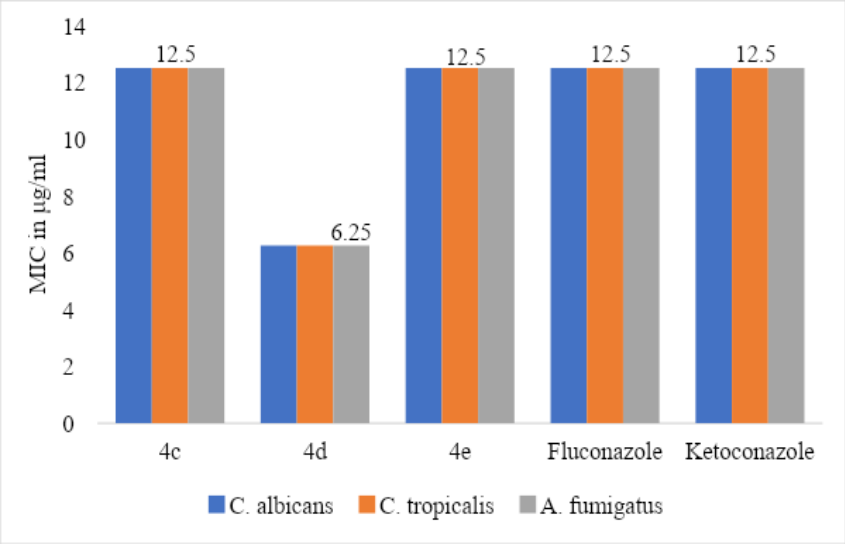


Fig 8: MIC of 4c, 4d, 4e, KET and FLU against the tested fungi

5. DISCUSSION

Various fused thiazolotriazine derivatives were designed. The important DCs are provided in Figure 1. The toxicity (Table 1), pharmacokinetic behavior and drug-likeliness properties (Table 2 and Figure 7), and the binding affinity of the compounds concerning the 3LD6 protein of SDM (Table 3, Figure 2 to Figure 6) were assessed by computerized methods [12-16]. The predicted non-toxic compounds (4c, 4d, and 4e) demonstrating good pharmacokinetic profile and DS concerning 3LD6 protein of SDM were selected for synthesis (Scheme 1 and Table 4) and *in vitro* antifungal activity evaluation (Table 5 and Figure 8) [14,17,18]. The molecular docking data against 3LD6 protein (Table 3) establish 4c, 4d, and 4e as SDM inhibitors. The binding patterns of 4c, 4d, and 4e (Figure 2 to Figure 4) indicate that these compounds inhibit SDM by binding in almost the same pocket where FLU and KET bind (Figure 5 to Figure 6). The 4c, 4d, and 4e exhibited better and more promising safety profiles (Table 1) than FLU (hepatotoxic) and KET (hepatotoxic, nephrotoxic, and immunotoxic). The predicted bioavailability of 4c, 4d, and 4e was also comparable to FLU and KET (Figure 7). 4c, 4d, and 4e may potentially treat diseases managed by FLU and KET [19,20]. The structure-activity relationship (SAR) relates to the effects of different substituents of a chemical compound on its biological activity [21-22]. The SAR of compounds concerning anti-fungal activity (Table 5 and Figure 8) revealed that the presence of a methoxy group at position 4 of the phenyl rings provides a more potent compound (4d; MIC = 6.25 µg/ml) than KET (MIC = 12.5 µg/ml) and FLU (MIC = 12.5 µg/ml). However, the predicted oral absorption 4d was less than KET and FLU (Table 2). Therefore, additional SAR studies are suggested to increase the oral absorption of the derivatives and isomers of 4d. One of the studies may be to assess the antifungal activity of 2-methoxy isomer and 3-methoxy isomer of 4d. Similarly, evaluating isomers of 4c (3-hydroxy and 4-hydroxy isomer) and 4e (furan-3-yl isomer) as antifungal agents are advocated. Replacing a 2-hydroxy group of 4c and furan ring of 4e with other hydrophilic groups and five-membered heterocycles are different options to get promising antifungal agents. The antifungal activity of 4c, 4d, and 4e has been carried out against three fungi. The quantitative structure-activity relationship (QSAR) studies correlate the measurable physicochemical properties of compounds with their biological effects [23-24]. Accordingly, the broad spectrum of 4c, 4d, and 4e against various pathogenic fungi, including resistant forms, and the QSAR studies must be reviewed.

6. CONCLUSION

Compounds 4c, 4d, and 4e show promising antifungal activity and favorable safety profiles. The molecular docking studies establish 4c, 4d, and 4e as SDM inhibitors, suggesting a mechanism similar to FLU and KET. Compound 4d had significant antifungal activity due to its methoxy group at position 4 of the phenyl ring. Exploring isomers and substituent changes of these compounds can lead to better antifungals. More structure-activity connection studies are needed to improve oral absorption and broaden efficacy against pathogenic fungi, particularly resistant strains.

7. ACKNOWLEDGEMENT

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8. AUTHORS CONTRIBUTION STATEMENT

Hamdy KH. Thabet., Mohd Imran, Saleh Alaqel, and Mohamed Hamdy Helal conceived the idea. Hamdy KH. Thabet, Mohd Imran, Abida, and Mohamed Hamdy Helal conducted the experiments. All authors contributed to the preparation of the final project/manuscript.

9. CONFLICT OF INTEREST

Conflict of interest declared none.

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