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Jaiprakash N. Sangshetti [a,*], Firoz A. Kalam Khan [a], Rashmi S. Chouthe [a], Manoj G. Damale [b], Devanand B. Shinde [c]

[a] Department of Pharmaceutical Chemistry, Y.B. Chavan College of Pharmacy, Dr. Rafiq Zakaria Campus, Aurangabad 431001, India
[b] Department of Bioinformatics, MGM Institute of Biosciences and Technology, Aurangabad 431003, India
[c] Department of Chemical Technology, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad 431004, India

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ABSTRACT

A novel series of 5-((5-substituted-1*H*-1,2,4-triazol-3-yl)methyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridines **5(a–i)** has been synthesized from thienopyridine hydrazide, substituted aromatic nitriles using 4-dimethylaminopyridine (DMAP) as a catalyst under microwave irradiation and evaluated for their *in vitro* antifungal activity. Compound **5g** is found to be more potent against *Candida albicans* when compared with miconazole. Docking study of the newly synthesized compounds was performed, and results showed good binding mode in the active site of fungal enzyme P450 cytochrome lanosterol 14α-demethylase. ADMET properties of synthesized compounds were also analyzed and showed good drug like properties. The results of *in vitro* antifungal activity, docking study and ADMET prediction revealed that the synthesized compounds have potential antifungal activity and can be further optimized and developed as a lead compound.

1. Introduction

In recent years, the incidence of systemic fungal infection is increasing dramatically due to an increase in number of patients undergoing organ transplants, anticancer chemotherapy and patients with AIDS. Commonly used antifungal drugs are azoles (fluconazole, itraconazole, miconazole and voriconazole), polyenes (amphotericin B and nystatin), echinocandins (caspofungin and micafungin) and allylamines (naftifine and terbinafine) [1]. Azoles have broad-spectrum activities against most yeasts and filamentous fungi and are the drug of choice for antifungal chemotherapy [2]. Azoles, especially triazole, such as fluconazole, voriconazole and itraconazole, are leading drugs used for the treatment of invasive fungal infections. These antifungal drugs act by inhibiting CYP51 in the process of biosynthesis of ergosterols through a mechanism in which the heterocyclic nitrogen atom (*N*-4 of triazole) binds to the heme iron atom [3]. However, increasing use of these antifungal drugs has led to increase in resistance to these drugs [4–6].

The sulfur and nitrogen containing heterocycles, such as thiazole and its derivatives like thienopyridine and tetrahydrothienopyridine, have attracted continuing interest because of their varied biological activities [7–10]. The triazole ring, difluorophenyl group and hydroxyl group are the pharmacophores of antifungal agents, but the side chains located in the narrow hydrophobic cleft are also important [11–14]. The optimization of these side chains attached to the pharmacophores has attracted current researches for development of new antifungal agents. In this research work, we intended to alter the side chains to find potent and broad spectrum antifungal agents. The most commonly used method for the preparation of 1,2,4-triazole involves dehydrative condensation of hydrazide derivatives; other approaches involve the Pinner reaction and the Pellizzari reaction. However, these conventional methods involve high reaction temperature, long reaction times and also result in low yields of product [15].

Based on the above facts and our interest for search for new antifungal agents [16–21], we have reported a facile method for the synthesis of novel, 5-((5-substituted-1*H*-1,2,4-triazol-

* Corresponding author.
E-mail address: jnsangshetti@rediffmail.com (J.N. Sangshetti).

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3-yl)methyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridines **5a–i** as antifungal agents by using 4-dimethylaminopyridine (DMAP) as a catalyst under microwave irradiation. In present study, we have also reported molecular docking and ADMET properties of the synthesized compounds. The results suggest that the compounds could be exploited as an antifungal drug.

2. Experimental

2.1. Chemistry

2.1.1. Synthesis of 2-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl) acetohydrazide (4)

Ethyl-2(6,7-dihydrothieno[3,2-c]pyridine-5(4*H*)-yl)acetate (**3**) was obtained by the reaction of 4,5,6,7-tetrahydrothieno[3,2-c]pyridine hydrochloride (**1**) with ethyl-2-bromoacetate (**2**) using triethylamine as catalyst [22]. Equimolar quantities of ethyl-2(6,7-dihydrothieno[3,2-c]pyridine-5(4*H*)-yl)acetate (**3**) was refluxed with hydrazine hydrate in *n*-butanol using glacial acetic acid as catalyst to give product 2-(6,7-dihydrothieno[3,2-c]pyridin-5(4*H*)-yl)acetohydrazide (**4**) [23]. The structures were confirmed by spectral analysis (Mass, ^{1}H NMR and ^{13}C NMR) and in agreement with published data.

2.1.2. General procedure for the synthesis of 5-((5-substituted-1H-1,2,4-triazol-3-yl)methyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridines 5a–i

In an Erlenmeyer flask, 2-(6,7-dihydrothieno[3,2-c]pyridin-5(4*H*)-yl)acetohydrazide (**4**) (1.0 mmol), aromatic nitriles (1.0 mmol) and DMAP (30 mol%) were taken in ethanol (15 mL). The reaction mixture was irradiated inside a synthetic microwave oven (Make-Ethosi Milestone with temperature control) for about 20–25 min (700 W). After completion of reaction (monitored by TLC), the mixture was concentrated to obtain the solid product. The solid product formed was filtered, dried and recrystallized from ethanol.

2.2. In vitro antifungal activity

The synthesized compounds **5a–i** were screened for their *in vitro* antifungal activity. The antifungal activity was evaluated against five human pathogenic fungal strains, such as *Candida albicans* (NCIM3471), *Fusarium oxysporum* (NCIM1332), *Aspergillus flavus* (NCIM539), *Aspergillus niger* (NCIM1196), *Cryptococcus neoformans* (NCIM576), which are often encountered clinically, and were compared with standard drugs like fluconazole and miconazole. Minimum inhibitory concentration (MIC) values were determined using standard agar method [24].

2.3. Computational studies

2.3.1. Docking study

The 3D model structure of cytochrome P450 lanosterol 14α-demethylase of *C. albicans* was built using homology modeling with the help of VLifeMDS 4.3 ProModel. Amino acid sequence of enzyme was obtained from the Universal Protein Resource (http://www.uniprot.org/) (Accession Code: P10613) and sequence homologous was obtained from Protein Data Bank (PDB) using Blast search. Based on the result of blast search, we used the crystal structure of human lanosterol 14α-demethylase (CYP51) with azole as a template for homology modeling (PDB ID: 3LD6). The alignment of amino acid sequence of CA-CYP51 (P10613) and human CYP51 (3LD6_B) is given in Fig. S1 (Supporting information). The quality of the generated *C. albicans* lanosterol 14α-demethylase model was assessed by using the well-validated program like PROCHECK [25] and its structural validation is shown in Fig. S2 (Supporting information). The molecular docking study of the synthesized compounds **5a–i** was performed against homology built cytochrome P450 lanosterol 14α-demethylase of *C. albicans* to understand the binding interactions using VLife MDS 4.3 package following standard procedures [26].

2.3.2. ADMET properties

A computational study of synthesized compounds **5a–i** was performed for prediction of ADMET properties. In this study, we assessed ADMET properties using ADMET predictor FAFDrugs2 which runs on Linux OS. This tool is freely available and used for *in silico* ADMET filtering [27]. In particular, we calculated the compliance of synthesized compounds to the Lipinski's rule of five [28]. This approach has been widely used as a filter for substances that would likely be further developed for drug design programs. We have also assessed parameters like number of rotatable bonds ($>$10) and the number of rigid bonds which signify that the compound may have good oral bioavailability and good intestinal absorption [29].

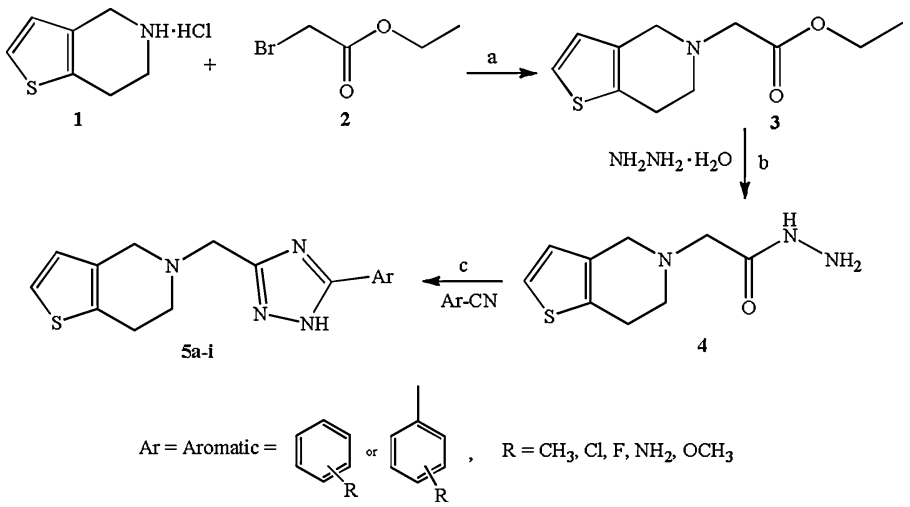
3. Results and discussion

3.1. Chemistry

The synthetic protocols employed for the synthesis of 5-((5-substituted-*1H*-1,2,4-triazol-3-yl)methyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine derivatives **5a–i** are presented in Scheme 1. For the synthesis of 5-((5-substituted-*1H*-1,2,4-triazol-3-yl) -methyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine derivatives **5a–i**, we first optimized the reaction conditions. The reaction of 2-(6,7-dihydrothieno[3,2-c]pyridin-5(4*H*)-yl)acetohydrazide (1.0 mmol) (**4**) and benzonitrile (1.0 mmol) in ethanol (15 mL) under microwave irradiation (700 W) was used as the model reaction. The catalysts (30 mol%) like K_2CO_3, triethylamine and 4-dimethylaminopyridine (DMAP) were used to test their efficacy for the synthesis of model reaction. Among the result, a good yield was obtained by the use of catalyst DMAP (91% yield) (Table S1, Supporting information). After deciding upon the catalyst DMAP, the effect of catalyst load was studied at various loads like 10, 20, 30 and 40 mol%. DMAP with 30 mol% gave good yield (91%) (Table S2, Supporting information). The effect of various solvents like acetonotrile, isopropylalcohol, *n*-butanol and ethanol were also studied and ethanol was found to be best among the studied solvents (Table S3, Supporting information). The synthetic protocol was extended for the synthesis of 5-((5-substituted-1*H*-1,2,4-triazol-3-yl)methyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridines **5a–i** using various substituted aromatic nitrites under microwave irradiation (700 W) in ethanol with DMAP (30 mol%) as catalyst for about 20–25 min. The purity of the synthesized compounds was checked by TLC and melting points were determined in open capillary tubes melting point apparatus and are uncorrected. The physical data of the synthesized compounds are presented in Table 1. The data obtained from ^{1}H NMR, ^{13}C NMR and Mass Spectrometry confirmed the proposed structures (Spectral data results are provided in Supporting information). The products were obtained in good yield (88%–91%) and required less reaction time (20–25 min).

3.2. In vitro antifungal activity

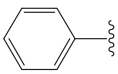
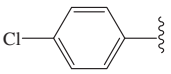
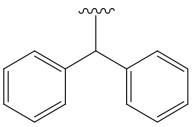
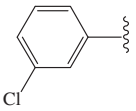
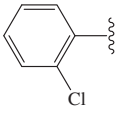
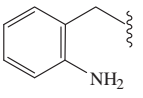
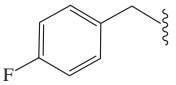
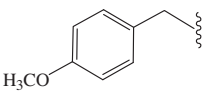
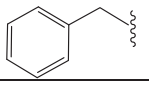
The results of *in vitro* antifungal activity (Table 2) showed that all the compounds had good to moderate antifungal activity. All the synthesized compounds **5a–i** were less active against *C. albicans*, *F. oxysporm*, *A. flavus*, *A. niger* and *C. neoformans* when compared with fluconazole. Among the synthesized compounds, compound **5g** showed significant activity against *C. albicans*, *A.*



Scheme 1. Synthetic route for target compounds **5a–i.** Reagents and conditions: (a) Acetonitrile, TEA, reflux, 5 h. (b) *n*-butanol, glacial acetic acid, reflux, 15 h. (c) DMAP, ethanol, microwave irradiation (700 W), 20–25 min.

flavus and *A. niger* when compared with fluconazole. The compound **5g** (MIC = 15 μg/mL) showed higher activity against *C. albicans* than miconazole (MIC = 25 μg/mL). The compounds **5b** (MIC = 25 μg/mL against *C. albicans*) and **5g** (MIC = 25 and 12.5 μg/mL against *F. oxysporm* and *A. niger*, respectively) were equipotent to miconazole (MIC = 25, 25 and 12.5 μg/mL against *C. albicans*, *F. oxysporm* and *A. niger*, respectively). The compounds **5g** (MIC = 15 μg/mL against *A. flavus*) and **5h** (MIC = 15 μg/mL against *A. niger*) showed moderate activity when compared with miconazole (MIC = 12.5 and 12.5 μg/mL against *A. flavus* and *A. niger*, respectively). The compounds **5a** and **5i**

Table 1
Physical data for 5-((5-substituted-1*H*-1,2,4-triazol-3-yl)methyl)-4,5,6,7 tetrahydrothieno[3,2-c]pyridine derivatives **5a–i**.[a]

Compd.	Ar	Mol. formula	Time (min)	Yield (%)[b]	Mp (°C)	R_f
5a		$C_{16}H_{16}N_4S$	20	91	216–218	0.62
5b		$C_{16}H_{15}ClN_4S$	24	90	192–194	0.59
5c		$C_{23}H_{22}N_4S$	22	91	189–190	0.65
5d		$C_{16}H_{15}ClN_4S$	25	90	184–186	0.60
5e		$C_{16}H_{15}ClN_4S$	22	88	178–180	0.59
5f		$C_{17}H_{19}N_5S$	23	90	202–204	0.55
5g		$C_{17}H_{17}FN_4S$	25	91	208–210	0.57
5h		$C_{18}H_{20}N_2OS$	22	90	200–202	0.53
5i		$C_{17}H_{18}N_4S$	25	91	192–194	0.55

[a] Eluants used in TLC were benzene: methanol (8:2) for all compounds.
[b] Isolated yields of two runs. Solvent of recrystallization was ethanol.

Table 2
Antifungal activity and results of docking study of compounds.

Compd.	MIC values[a] (μg/mL)					Docking score	No. of hydrogen bonding interactions	No. of hydrophilic bonding interactions
	C. albicans	*F. oxysporm*	*A. flavus*	*A. niger*	*C. neoformans*			
5a	75	100	[b]	[b]	150	−2.4727	0	12
5b	25	37.5	75	100	100	−3.9721	0	16
5c	100	150	150	[b]	[b]	−4.0792	0	10
5d	50	62.5	100	150	125	−3.0718	0	17
5e	50	50	100	150	125	−4.3320	0	16
5f	50	62.5	150	150	75	−3.9214	0	14
5g	15	25	15	12.5	37.5	−4.8201	1	17
5h	50	37.5	37.5	15	87.5	−0.5431	0	10
5i	100	150	[b]	[b]	[b]	−3.6561	1	12
Fluconazole	5	5	5	10	5	−3.3526	2	13
Miconazole	25	25	12.5	12.5	25	−3.1144	0	39

[a] Values are the average of three readings.
[b] No activity was observed upto 200 μg/mL.

against *A. flavus*, **5a**, **5c** and **5i** against *A. niger* and **5c** and **5i** against *C. neoformans* showed no activity up to the concentration of 200 μg/mL.

From the antifungal activity data in Table 2, it is observed that scaffolds 1,2,4-triazole and 4,5,6,7-tetrahydrothienopyridine are responsible for antifungal activity. The unsubstituted phenyl analog **5a** shows significant activity against *C. albicans* and *F. oxysporum* than against *C. neoforman*. Substituted phenyl analogs are more active than unsubstituted phenyl analogs against almost all of the tested organisms, except for compounds **5c** and **5i** where the activity is reduced due to substitution. Introduction of *p*-Cl to phenyl **5b** increases the antifungal activity against all of the tested organisms compared to unsubstituted analog **5a**. Replacement of *p*-Cl with *o*-Cl (**5e**) and *m*-Cl (**5d**) decreases the activity. Introduction of $-NH_2$ at 2-position of phenyl **5f** shows moderate activity against *C. albicans* and *F. oxysporum* and shows a decrease in activity against *A. flavus*, *A. niger*, *C. neoformans* compared to the unsubstituted analog **5a**. Introduction of 4-F to benzyl ring **5g** leads to a potent compound against all the tested fungal strains. Compound **5h** with 4-OH to benzyl ring shows enhanced activity against *A. niger*, *A. flavus* and *F. oxysporum* as compare to unsubstituted benzyl derivative **5i**.

3.3. Computational studies

3.3.1. Docking study

The synthesized compounds **5a–i** and standard drug (fluconazole) were docked into the active site of cytochrome P450 lanosterol 14α-demethylase of *C. albicans* using VLifeMDS 4.3 software package to understand the binding interactions. The data obtained from docking study is presented in Table 3. The docking results indicated that thienopyridine core of these compounds **5a–i** held in the active pocket by forming the hydrophobic interactions with amino acid residues ALA343, THR347, LEU406, LEU412, SER414, MET415, VAL440, SER441, PRO442, PHE499, GLY500, HIS504, ARG505, CYS506, GLY508, ALA512, GLU509, CYS506, LEU412, and ALA501. The compounds **5g** and **5i** had shown hydrogen bonding interaction with amino acid residues GLU509, CYS506 and LEU412, ALA501, respectively. The halogen substituted compounds **5b**, **5d**, **5e** and **5g** were more favorable for hydrophobic interactions as compare to other substituted (H, $-NH_2$, and OCH_3) compounds. The 4-F substituent at benzyl ring of most active compound **5g** fitted well into the hydrophobic pocket. The binding interactions for compound **5g** and fluconazole are shown in Fig. 1. On the basis of activity data and docking result, it was found that compound **5g** had potential to inhibit cytochrome P450 lanosterol 14α-demethylase of *C. albicans*.

3.3.2. ADMET properties

We had analyzed various physical descriptors and pharmaceutically relevant properties for ADMET prediction by using FAFDrugs2 and data is summarized in Table 3. All the compounds showed significant values for the various parameters analyzed and showed good drug-like characteristics based on Lipinski's rule of five. The data obtained for all the synthesized compounds **5a–i** was within the range of accepted values. None of the synthesized compounds had violated the Lipinski's rule of five. The value of polar surface area (PSA) for synthesized compounds **5a–i** indicated good oral bioavailability. The parameters, like number of rotatable bonds and number of rigid bonds are linked with intestinal absorption result, showed that all synthesized compounds **5a–i**

Table 3
Prediction of ADMET properties of compounds.

Compd.	MW	log *P*	HBA	HBD	PSA	Rigid bond	Rotatable bond	Lipinski violation	Toxicity
5a	296.39	3.02	3	1	73.05	21	3	0	N
5b	330.83	3.68	3	1	73.05	21	3	0	N
5c	386.51	4.54	3	1	73.05	27	5	0	N
5d	330.83	3.68	3	1	73.05	21	3	0	N
5e	330.83	3.68	3	1	73.05	21	3	0	N
5f	325.43	3.11	3	2	99.07	21	4	0	N
5g	328.40	3.09	3	1	73.05	21	4	0	N
5h	340.44	2.96	4	1	82.28	21	5	0	N
5i	310.41	2.95	3	1	73.05	21	4	0	N
Fluconazole	306.27	0.73	5	1	81.65	16	5	0	N
Miconazole	416.12	6.45	2	0	27.05	17	6	1	Y

N: non-toxic.
Y: toxic.

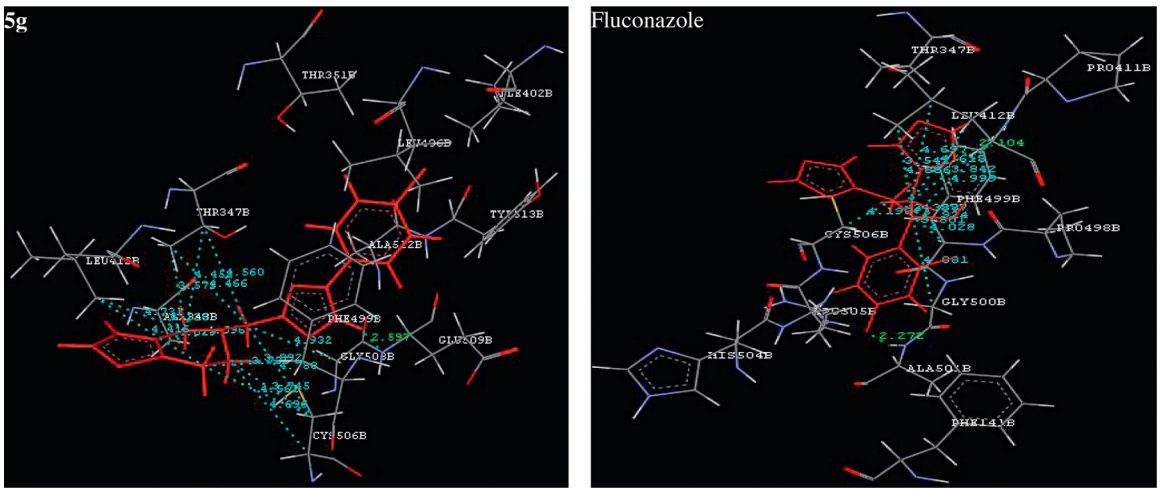


Fig. 1. Docking of compound **5g** (Upper left panel), Fluconazole (Upper right panel). Ligands are shown in red color. Hydrogen bonds are shown in green color. Hydrophobic bonds are shown in sky blue color.

had good absorption. All the synthesized compounds were found to be nontoxic.

4. Conclusion

In conclusion, synthesis and antifungal activity of a novel series of 5-((5-substituted-1*H*-1,2,4-triazol-3-yl)methyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine derivatives **5a–i** has been presented. Use of DMAP as catalyst with ethanol under microwave irradiation helped in fast conversion of 2-(6,7-dihydrothieno[3,2-c] pyridine-5(4*H*)-yl)acetohydrazide to 5-substituted-1,2,4-triazole derivatives in good yields, proving its advantage. Based on the activity data, structure-activity relationship (SAR) for the series has been developed and it is observed that compound **5b** was equipotent with miconazole against *C. albicans*, whereas compound **5g** was equipotent with miconazole against *F. oxysporum* and *A. niger* and more potent than miconazole against *C. albicans.* Also compounds **5d**, **5e**, **5f** and **5h** showed antifungal activity comparable to miconazole against *C. albicans*, *F. oxysporum*, *A. flavus* and *A. niger*. The structure activity relationship study has suggested that the compound from the present series with 4-Cl or 4-F substituent on phenyl group on 5-position and 4,5,6,7-tetrahydrothienopyridene on 3-position of 1,2,4-triazole can serve as an important gateway for the design and development of new antifungal agent with potent activity. The docking studies of synthesized compounds with lanosterol 14α-demethylase (CYP51) modeled protein showed good binding interactions and formed various hydrophobic interactions with active site residues. Furthermore, analysis of the ADMET parameters for newly prepared compounds showed good drug like properties and opens the possibility for further optimization of studied compounds.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.cclet.2014.04.003.

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