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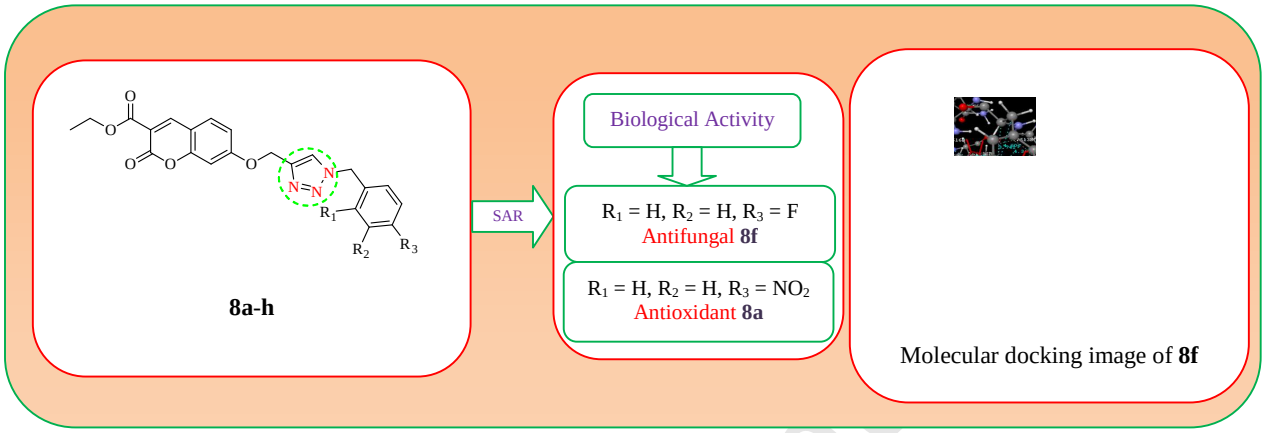
Graphical Abstract



A series of novel ethyl-7-((1-(benzyl)-1H-1,2,3-triazol-4-yl)methoxy)-2-oxo-2*H*-chromene-3-carboxylates **8a-h** as a potential antifungal agents were synthesized *via* click chemistry, and molecular docking study of the newly synthesized compounds was performed.

Original article

1,2,3-Triazole incorporated coumarin derivatives as a potential antifungal and antioxidant agents

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ABSTRACT

A series of novel ethyl-7-((1-(benzyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-2-oxo-2*H*-chromene-3-carboxylates **8a-h** as a potential antifungal agents were synthesized *via* click chemistry. The antifungal activity was evaluated against five human pathogenic fungal strains, such as *Candida albicans*, *Fusarium oxysporum*, *Aspergillus flavus*, *Aspergillus niger* and *Cryptococcus neoformans*. Compound **8c**, **8d**, **8e** and **8h** were found to be equipotent against *Candida albicans* when compared to miconazole and compound **8f** was found to be two-fold more active compared to miconazole and equipotent to fluconazole against *Candida albicans*. The coumarin based triazole derivatives were also evaluated for antioxidant activity and compound **8a** was found to be potent antioxidant as compared to standard drug. Furthermore, molecular docking study of the newly synthesized compounds was performed and results showed good binding mode in the active site of fungal *C. albicans* enzyme P450 cytochrome lanosterol 14*α*-demethylase. Moreover, the synthesized compounds were also analyzed for ADME properties and showed potential to build up as good oral drug candidates.

1. Introduction

In recent years, the incidence of systemic fungal infection is increasing significantly due to an increase in number of patients undergoing organ transplants, anticancer chemotherapy and patients with AIDS. Commonly used azole antifungal agents are fluconazole, itraconazole, miconazole and voriconazole displayed broad spectrum antifungal activity [1]. Azoles have broad spectrum activities against most yeasts and filamentous fungi and are the drug of choice for antifungal chemotherapy [2]. These antifungal drugs inhibiting CYP51 in the process of biosynthesis of ergosterol 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]. Hence there is an urgent need for the development of more potent, broad spectrum antifungal agents with fewer side effects and improved efficacy to cure fungal infections.

Coumarin and their derivatives have attracted much more considerable attention due to their extensive biological activities. In recent years, studies have shown that coumarin incorporated with some nitrogen-containing heterocyclic moieties; *viz.* azetidine, thiazolidine, thiazole and oxadiazole were not only significantly increases the antimicrobial efficiency but also broadens their antimicrobial spectrum [7,8]. Antioxidants play a vital role in the body defense

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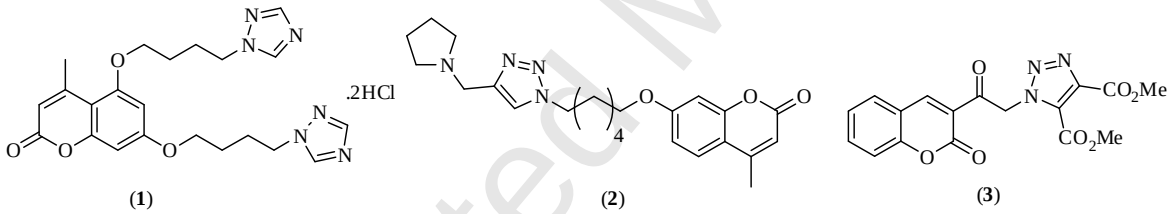
mechanism by regulating the generation and elimination of reactive oxygen species (ROS) such as hydroxyl radicals, superoxide radicals, singlet oxygen and hydrogen peroxide radicals those generated from excessive oxidative stress and normal metabolic activities. The regulating mechanism includes detoxification of excess ROS, if not, the high concentrations of free radical damages the normal cell structures, embedded proteins, lipids, carbohydrates and also damages the nitrogen bases of nucleic acids leading to mutations and also causes cancer, aging and neurodegenerative disorders such as Alzheimer's and Parkinson's diseases. In addition to the body's defense mechanism includes superoxide dismutase (SOD), catalase and glutathione peroxidase, antioxidants also regulate the concentration of ROS by interacting with them and prevent their influence on other molecules. Thus, the discovery and development of novel synthetic radical scavengers attained an immense importance in organic chemistry. Many coumarin derivatives have unique ability to scavenge reactive oxygen species (ROS) free radicals, such as hydroxyl, superoxide radicals or hypochlorous acid and to influence processes involving free radical injury [9,10]. Coumarin derivatives exhibit enormous biological activities such as, antimicrobial, anti-HIV, antibiotic, anticancer, muscle relaxant, anti-inflammatory and anticoagulant activity [11]. The 1,2,3-triazole based compounds are reported to possess a wide range of biological activities such as antifungal [12], antitubercular [13], antiallergic, antibacterial, anti-HIV activity [14], α-glycosidase inhibitor [15], antimicrobial [16], anticoccidiostats [17], anticonvulsant and antitumor [18], antimalarial [19], antiviral [20], and antimycobacterial [21]. Triazole has been used to improve the pharmacokinetic properties of the desired drug [22].

In recent years, a library of coumarin derivatives conjugated with 1,2,3-triazole moiety were synthesized and proved to possess antifungal activity. Therefore the incorporation of triazole moiety is essential for the enhancement of activity [23]. Coumarin based triazole **1** (Fig. 1) displays antifungal activity against three fungal strain *viz*. *Candida albicans*, *Saccharomyces cerevisiae* and *Aspergillus fumigatus* [23]. Similarly, 2*H*-chromen-2-one derivative **2**, decorated with 1,2,3-triazole moiety exhibits antifungal activity against four fungal strains, *viz. Aspergillus niger*, *Aspergillus fumigates*, *Aspergillus flavus* and *Candida albicans* [24] and 3-[1-(4,5-dicarbomethoxy-1,2,3-triazoloacetyl)]coumarin **3** displays good antifungal activity against the fungal strain *Aspergillus niger* [25] (Fig. 1).



(**1**) (**2**) (**3**)

Fig. **1**. Coumarin-triazole conjugates **1**-**3** displays antifungal activity

In continuation of our earlier work [26] on synthesis and biological properties of heterocyclic moieties and the importance of coumarin and 1,2,3-triazole moieties as a single molecular scaffold, herein we would like to report the design and syntheses of new coumarin linked triazole hybrids. The coumarin derivatives have been well reported for antioxidant activity and 1,2,3-triazole ring is good scaffold for antifungal activity. Thus, we have evaluated the synthesized compounds for their antifungal and antioxidant activities. The computational parameters like docking study for antifungal activity and ADME prediction of synthesized coumarin-triazole conjugates **8a-h** were also performed.

2. Experimental

2.1. Chemistry

All the solvents and reagents were purchased from commercial suppliers Spectrochem Pvt. Ltd., Sigma Aldrich and Rankem India Ltd. used without further purification. The progress of each reaction was monitored by ascending thin layer chromatography (TLC) using TLC aluminum sheets, silica gel F_{254} precoated, Merck, Germany and locating the spots using UV light as the visualizing agent or iodine vapors. Melting points were taken in open capillary method and are uncorrected. ^{1}H NMR spectra were recorded ($CDCl_3$/DMSO-d_6) on Bruker Avance 400 MHz NMR Spectrometer. ^{13}C NMR spectra were recorded (DMSO-d_6) on Bruker Avance100 MHz NMR Spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) using tetramethylsilane (TMS) as an internal standard. The splitting pattern abbreviations are designed as singlet (s); doublet (d); double doublet (dd); bs (broad singlet), bd (broad doublet), triplet (t); quartet (q) and multiplet (m). Bruker Daltonics MicroTOF-Q-II with electron spray ionization (ESI) was used for HRMS data. The

synthetic protocol employed for the synthesis of ethyl 7-((1-(benzyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-2-oxo-2*H*-chromene-3-carboxylates has been presented in Scheme 1.

General procedure for the synthesis of ethyl 7-((1-(benzyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-2-oxo-2*H*-chromene-3-carboxylates **8a-h**: To the solution of ethyl 2-oxo-7-(prop-2-yn-1-yloxy)-2*H*-chromene-3-carboxylate (**7**) (0.5 mmol), substituted benzyl azide **4a-h** (0.5 mmol) and copper diacetate ($Cu(OAc)_2$) (20 mole %) in *t*-BuOH-H_2O (3:1, 8 mL) and the resulting mixture was stirred at room temperature for 24-36 hrs. The progress of the reaction was monitored by TLC using ethyl acetate:hexane as a solvent system. The reaction mixture was quenched with crushed ice and extracted with ethyl acetate (2×25 mL). The organic extracts were washed with brine solution (2×25 mL) and dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure to afford the corresponding crude compounds. The obtained crude compounds were crystallized using ethanol.

2.2. Biological activity

2.2.1. 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), and *Cryptococcus neoformans* (NCIM576), which are often encountered clinically and were compared with standard drug miconazole. Minimum inhibitory concentration (MIC) values were determined using standard agar method [27].

2.2.2. Antioxidant activity

In the present study, antioxidant activity of the synthesized compounds has been assessed *in vitro* by the 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging assay [28] and the results were compared with standard synthetic antioxidant BHT (Butylated Hydroxy Toluene). The hydrogen atom or electron donation ability of the compounds was measured from the bleaching of the purple colored methanol solution of 1,1-diphenyl-1-picrylhydrazyl (DPPH). The spectrophotometric assay uses the stable radical DPPH as a reagent. 1 mL of various concentrations of the test compounds (5, 10, 25, 50 and 100 µg/mL) in methanol was added to 4 mL of 0.004% (w/v) methanol solution of DPPH. After a 30 min incubation period at room temperature, the absorbance was measured against blank at 517 nm. The percent inhibition (I %) of free radical production from DPPH was calculated by the following equation.

% of scavenging = [(A control - A sample)/A blank]×100

Where 'A control' is the absorbance of the control reaction (containing all reagents except the test compound) and 'A sample' is the absorbance of the test compound. Tests were carried at in triplicate.

2.3. Computational study

2.3.1. Molecular docking

The 3D model structure of cytochrome P450 lanosterol 14*α*-demethylase of *C. albicans* was built using homology modeling. 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 VLifeMDS 4.3 ProModel was used for modeling of the 3D structure of protein based on the amino acid sequences of a close homologue. Alignment of amino acid sequence of CA-CYP51 (P10613) and human CYP51 (3LD6_B) is shown in Fig. S1 (Supporting information). The Blosum-62 matrix was used with a gap penalty of 1. The model was then energy minimized using the MMFF94 force field [29]. Manual inspection was made to ensure the conserved motifs and loops were correctly aligned. The quality of generated *C. albicans* lanosterol 14α-demethylase model was assessed by using the well-validated program likes PROCHECK [30] and its structural validation is shown in Fig. S2 (Supporting information). The further structural superimposition was performed to know the structural coordinate of target protein and RMSD value was found within standard range of 0.997607 Å. The molecular docking study of the synthesized compounds **8a–h** and standard drugs fluconazole and miconazole were performed against homology built cytochrome P450 lanosterol 14*α*-demethylase of *C. albicans* to understand the binding interactions using VLife MDS 4.3 package following standard procedures [31].

2.3.2. ADME properties

The success of a drug is determined not only by good efficacy but also by an acceptable ADME (absorption, distribution, metabolism and excretion) profile. In this study, we calculated molecular volume (MV), molecular weight (MW), logarithm of partition coefficient (miLog*P*), number of hydrogen bond acceptors (n-ON), number of hydrogen

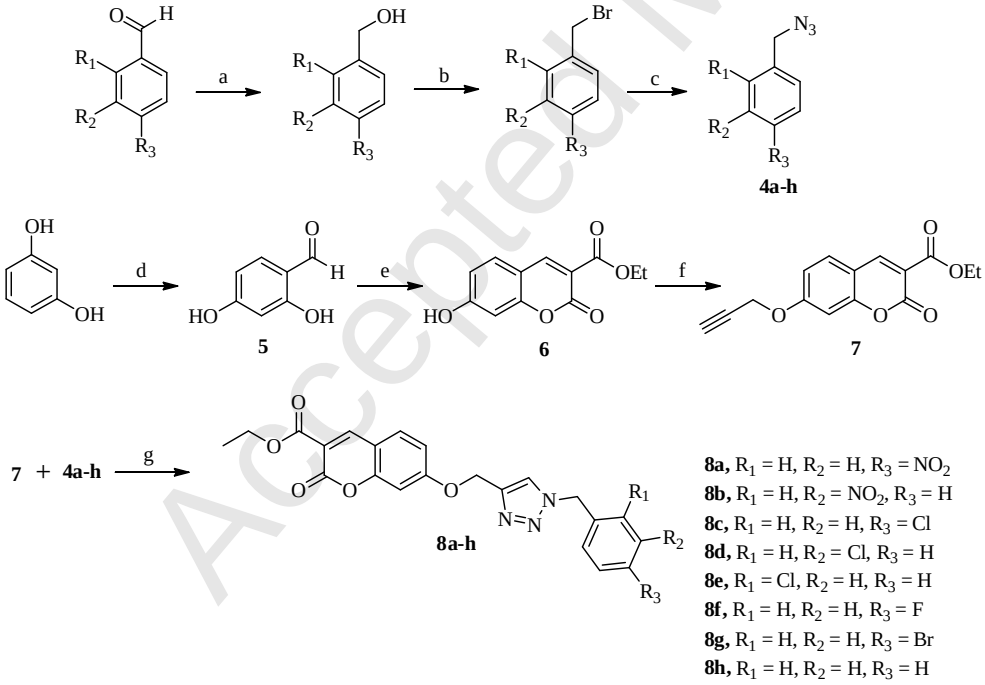
bonds donors (n-OHNH), topological polar surface area (TPSA), number of rotatable bonds (n-ROTB) and Lipinski's rule of five [32] using Molinspiration online property calculation toolkit [33]. Absorption (% ABS) was calculated by: % ABS = 109-(0.345×TPSA) [34]. Drug-likeness model score (a collective property of physic-chemical properties, pharmacokinetics and pharmacodynamics of a compound is represented by a numerical value) was computed by MolSoft software [35].

3. Results and discussion

3.1. Chemistry

We have described the syntheses of a series of new ethyl-7-((1-(benzyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-2-oxo-2*H*-chromene-3-carboxylates **8a-h** as a potential antifungal and antioxidant agents from commercially available starting materials. These compounds **8a-h** were formed by the fusion of benzyl azides and coumarin based alkyne *via* click chemistry approach. The benzyl azides **4a-h** has been prepared from the corresponding benzaldehydes *via* $NaBH_4$ reduction, bromination and nucleophilic substitution reaction of sodium azide according to the reported procedure [36] (Scheme 1). Synthesis of 2,4-dihydroxybenzaldehyde **5** was achieved from resorcinol by Vilsmeier-Haack reaction according to the literature procedure [37]. The synthesis of ethyl-7-hydroxy-2-oxo-2*H*-chromene-3-carboxylate **6** has been achieved *via* Pechmann condensation between 2,4-dihydroxybenzaldehyde **5** and diethylmalonate in the presence of acid [38] in 80% yield (Scheme 1). The treatment of compound **6** with propargyl bromide in presence of K_2CO_3 as a base in *N*,*N*-dimethylformamide (DMF) at room temperature afforded ethyl-2-oxo-7-(prop-2-yn-1-yloxy)-2*H*-chromene-3-carboxylate **7** in 95% yield (Scheme 1).

Finally, benzylazides **4a-h** and coumarin based alkyne **7**, on 1,3-dipolar cycloaddition reaction in *t*-BuOH-H_2O (3:1) mixture and catalytic amount of copper diacetate $Cu(OAc)_2$ at room temperature for 24 to 36 hours afforded the corresponding regioselective 1,4-disubstituted-1,2,3-triazole incorporated coumarin derivatives **8a-h** in quantitative isolated yield (88-93%) (Scheme 1).



Scheme1. Synthetic route for target compounds **8a-h**. Reagents and conditions: (**a**) $NaBH_4$, Methanol, 0 °C to rt, 2 hr; (**b**) PBr_3, DCM, 0 °C, 0.5 hr; (**c**) NaN_3, Acetone-H_2O (3:1), rt, 24 hr; (**d**) (i) $POCl_3$, DMF, CH_3CN, °C, 3 hr; (ii) H_2O, 50 °C, 2 hr; (**e**) Diethyl malonate, H_2SO_4, 0 °C, 6 hr; (**f**) Propargyl bromide, K_2CO_3, DMF, 3 hr; (**g**) $Cu(OAc)_2$ (20 mol%), *t*-BuOH-H_2O (3:1), rt, 24-36 hr.

The regioselective formation of 1,4-disubstituted 1,2,3-triazole based coumarin derivatives **8a-h** has been confirmed by physical data and spectroscopic methods such as ^{1}H NMR, ^{13}C NMR and HRMS. According to the ^{1}H NMR spectrum of representative compound **8b**, the triplet at 1.29-1.36 ppm for three protons (methyl group) attached to -OCH_2 group of

ester present on coumarin ring, the quartet at 4.24-4.35 ppm for two proton attached to methyl group and oxygen heteroatom. The characteristic two singlets at 5.35 and 5.84 ppm were also observed for -OCH_2 and -NCH_2 protons of triazole derivative **8b** respectively. In addition to this, a sharp singlet observed at 8.47 ppm assigned to triazole ring, thus confirming the regioselective formation of 1,4-disubstituted 1,2,3-triazole ring. Again, the peak was observed at 8.75 ppm, clearly indicates for the proton of coumarin ring. In addition, all the aromatic protons appeared at expected chemical shifts and integral values. The cyclisation of alkyne **7** with **4b** to triazole derivative **8b** was further confirmed by ^{13}C NMR spectral data, in which the carbon signals of -OCH_2 and -NCH_2 groups were resonated at 52.3 and 62.3 ppm respectively. The signals at 163.3 and 163.8 indicate the presence of two carbonyl carbon atom, while all other carbons gave peaks at expected values. Again, the formation of compound **8b** was confirmed by high resolution mass spectrometry (HRMS). The calculated $[M+Na]^+$ for compound **8b** is 473.1073 and observed $[M+Na]^+$ in HRMS at 473.1071. The physical data, yield and time required to complete the reactions and spectroscopic data of compounds are given in supporting information. The proposed structures were confirmed by ^1H NMR, ^{13}C NMR and HRMS (Supporting information). The products were obtained in good yield (88-93%).

3.2. In vitro antifungal activity

The minimum inhibitory potential of synthesized 1,4-disubstituted 1,2,3-triazole based coumarin derivatives **8a-h**, was evaluated *in vitro* against five different fungal strains: *C. albicans*, *F. oxysporum*, *A. flavus*, *A. niger* and *C. neoformans* strains and results were compared with their precursors **6** and **7** as well as standard drugs miconazole and fluconazole. The MIC values in µg/mL were estimated and the results are summarized in Table 1. The objective of this study was to see the effect of structural transformation on the 7-hydroxycoumarin derivative. The precursors **6** and **7** do not exhibit antifungal activity against all the tested strains. All the synthesized triazole derivatives **8a-h** showed many fold enhanced activity as compared to the precursor **6** and **7** against the fungal strain *C. albicans*. Compound **8f** having fluoro- group at *para* position of phenyl ring has been found to be good inhibitor of *C. albicans* with MIC values 12.5 µg/mL and two fold active as compared to the standard drug miconazole and equipotent to fluconazole. Compounds **8c** (chloro- group at *para*), **8d** (chloro- group at *meta*), **8e** (chloro- group at *ortho*) and **8h** with MIC values 25 µg/mL shows equivalent potency for fungal strain *C. albicans* compared to the standard drug miconazole. While the compounds **8a**, **8b** and **8g** with MIC values 50 µg/mL displays less potency against *C. albicans*. Compound **8e** with chloro- group at *ortho* position of phenyl ring shows two-fold more activity and compound **8d** with chloro- group at *meta* position of phenyl ring shows equivalent potency for fungal strain *F. oxysporum* compared to the miconazole. Most of the synthesized compounds **8a-h** is inactive against the fungal strain *A. flavus*, *A. niger* and *C. neoformans*. However, compound **8d** withchloro- groupat *meta* position of

Table1. *In vitro* antimicrobial and antioxidant evaluation of coumarin based triazoles and their precursor molecules.

Entry	MIC Values in µg/mL					Antioxidant activity (IC_{50}µg/mL)
	CA	*FO*	*AF*	*AN*	*CN*	DPPH scavenging activity
6	100	150	NA	NA	NA	58.21
7	NA	NA	175	NA	175	17.06
8a	50	100	125	50	150	15.20
8b	50	100	125	150	150	16.89
8c	25	50	25	100	150	16.00
8d	25	25	100	25	100	15.99
8e	25	12.5	150	175	150	15.29
8f	12.5	50	50	25	100	16.95
8g	50	50	125	125	150	29.12
8h	25	50	50	100	150	40.36
Miconazole	25	25	12.5	25	25	NT
Fluconazole	12.5	6.25	6.25	12.5	6.25	NT
BHT	NT	NT	NT	NT	NT	16.47

NA, No activity was observed up to 200 µg/mL, CA, *Candida albicans*; FO, *Fusarium oxysporum*; AF, *Aspergillus flavus*; AN, *Aspergillus niger*; CN, *Cryptococcus neoformans*; NT, Not tested; BHT, Butylated hydroxy toluene.

phenyl ring and **8f** with fluoro- group at *para* position of phenyl ring shows equivalent activity for fungal strain *A. niger* as compared to the standard drug miconazole. It is clear from the Table 1, that the incorporation of triazole ring on coumarin derivatives **6** and **7** increases the antifungal activity of the synthesized compounds **8a-h**.

3.3. Antioxidant activity

All the synthesized compounds **6**, **7** and **8a-h** show good to moderate antioxidant activity as compared to the standard drug BHT (Table 1). The antioxidant activity of these compounds may be related to their redox properties, which allow them to act as reducing agents or hydrogen atom donors and scavenge free radicals. The compounds **8a** having nitro-group at *para*, **8c**, **8d** and **8e** has chloro- substituent at *para*, *meta* and *ortho* position respectively of phenyl ring shows potent activity (IC_{50}= 15.20, 16, 15.99 and 15.29 µg/mL, respectively) as compared to the standard drug BHT. The compounds **8g** with bromo- group at *para* position, **8h** with no substitution on phenyl ring and **6** show less activity as compared to standard drugs.

3.4. Computational studies

3.4.1. Molecular docking study

The synthesized compounds **8a–h** and standard drugs (fluconazole and miconazole) 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 docking calculation and hydrogen bond and hydrophobic bond interactions are presented in Table 2. The interaction energy of the compounds **8a–h** and their antifungal activity (*C. albicans*) showed the corresponding results. The most active synthesized compound **8f** showed lowest interaction energy that is -72.29 kcal/mol. The standard drugs fluconazole and miconazole have also shown good interaction energy that is -69.76 and -71.90 kcal/mol, respectively. The docking results indicated that the coumarin-triazole core of these synthesized compounds was held in the active pocket by combination of various hydrogen and hydrophobic interactions with cytochrome P450 lanosterol 14α-demethylase. The various hydrophobic interactions occurred between the coumarin-triazole core active site chain of ALA343, GLY344, THR347, THR351, ILE402, LEU406, PRO410, LEU412, MET413, SER414, MET415, VAL440, SER441, PRO442, GLY443, PHE449, CYS506, GLY508, GLU509, ALA512, TYR513 and ILE516. The amino acid residues such as THR347, CYS506, ILE507 and ALA512 had formed hydrogen bonds with synthesized compounds. The amino acid THR347 had formed hydrogen bonding (2.22 Å) with nitrogen of triazole ring of synthesized compound **8a**. The amino acid residue CYS506 (2.07 Å) had formed hydrogen bonding with oxygen of $–NO_2$ and ILE507 (1.54 Å and 2.01 Å) had formed hydrogen bonding with oxygen of $–NO_2$ and nitrogen of $–NO_2$ of compound **8b**. The triazole ring of compound **8g** had shown hydrogen bonding with amino acid residues TYR513 (1.60 Å and 2.30 Å) and ALA512 (2.33 Å). The binding interactions for compound **8f** and fluconazole are shown in **Figure 2**. The fluoro- group at *para* position of benzyl ring is most active compound **8f** fitted well into the hydrophobic pocket. On the basis of activity data and docking result, it was found that compound **8f** had potential to inhibit cytochrome P450 lanosterol 14*α*-demethylase of *C. albicans*.

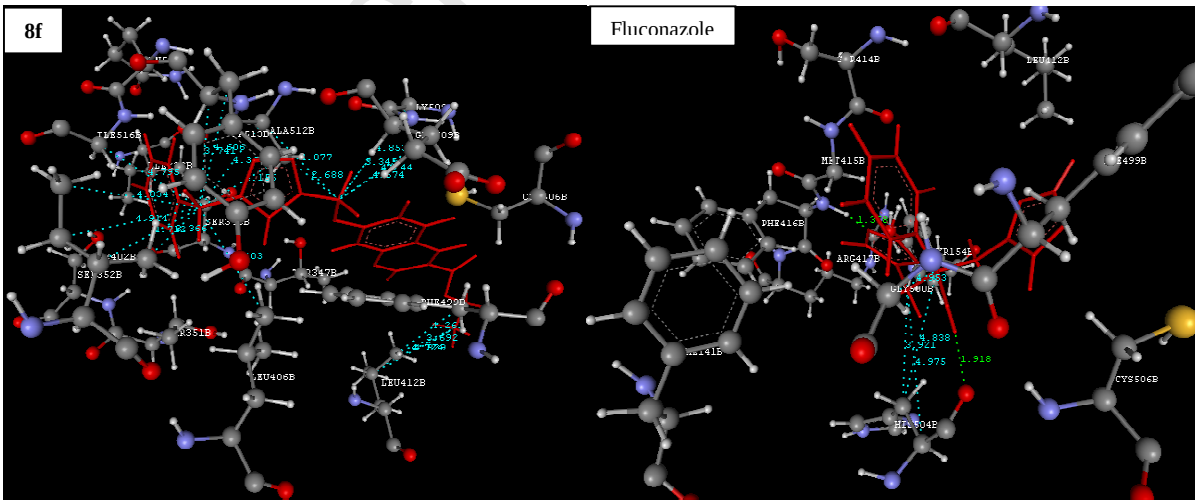


Fig. 2. Molecular docking of compound **8f** and fluconazole. Ligands are shown in red color. Hydrogen bonds are shown in green color. Hydrophobic bonds are shown in sky blue color.

Table 2. Molecular docking statistics of synthesized compounds **8a-h**.

Entry	Docking score (kcal/mol)	Hydrogen bonding interactions	Hydrophobic bonding interactions
8a	-55.43	1 (THR347)	27 (THR347, SER414, MET415, VAL440, SER441, PRO442, PHE449, GLY508, ALA512)
8b	-58.30	3 (CYS506, ILE507)	30 (ALA343, GLY344, THR347, PRO410, MET413, SER414, SER441, PRO442, GLY443)
8c	-61.67	0	21 (ILE402, LEU406, LEU412, GLY508, GLU509, ALA512, TYR513)
8d	-66.96	0	30 (ALA343, GLY344, THR347, PRO410, MET413, SER414, SER441, PRO442, GLY443, GLY508)
8e	-61.37	0	16 (THR351, ILE402, LEU406, PHE499, CYS506, GLU509, ALA512, TYR513)
8f	-72.29	0	20 (ILE402, LEU406, LEU412, GLY508, GLU509, ALA512, TYR513, ILE516)
8g	-56.07	3 (ALA512, TYR513)	16 (ILE402, LEU406, LEU412, GLY508, GLU509, ALA512, TYR513)
8h	-61.06	0	27 (ALA343, THR347, MET413, SER414, VAL440, SER441, PRO442, GLY443, PHE499)
Fluconazole	-69.76	2 (PHE416, HIS504)	4 (GLY500, HIS504)
Miconazole	-71.90	0	6 (LEU412, PHE499, GLY500

3.4.2. ADME properties

A computational study of all the synthesized compounds was performed for prediction of ADME properties and the value obtained is presented in **Table 3**. It is observed that compounds exhibited a good % ABS (% absorption) ranging from 59.90 to 86.31%. Furthermore, only compounds **8a** and **8b** violated Lipinski's rule of five (miLog$P \leq 5$). Remaining all other compounds did not violated Lipinski's rule of five.

Table 3. Pharmacokinetic parameters important for good oral bioavailability of the synthesized compounds **6**, **7** and **8a-h**.

Entry	% ABS	TPSA (A^2)	n-ROTB	MV	MW	miLog*P*	n-ON	n-OHNH	Lipinski violation	Drug likeness model score
Rule	-	-	-	-	< 500	≤ 5	< 10	< 5	≤ 1	-
6	86.31	65.75	5	237.96	272.25	2.34	5	0	0	-0.86
7	82.52	76.74	3	197.93	234.20	1.64	5	1	0	-0.57
8a	59.90	142.29	9	375.71	450.40	3.48	11	0	1	-0.52
8b	59.90	142.29	9	375.71	450.40	3.46	11	0	1	-0.34
8c	75.72	96.46	8	365.91	439.85	4.20	8	0	0	0.07
8d	75.72	96.46	8	365.91	439.85	4.18	8	0	0	0.03
8e	75.72	96.46	8	365.91	439.85	4.15	8	0	0	-0.14
8f	75.72	96.46	8	357.30	423.4	3.69	8	0	0	-0.03
8g	75.72	96.46	8	370.26	484.30	4.33	8	0	0	-0.21

8h	75.72	96.46	8	352.37	405.41	3.52	8	0	0	-0.30

A molecule likely to be developed as an orally active drug candidate should not show more than one violation of the following four criteria: miLog*P* (octanol-water partition coefficient) ≤ 5, molecular weight ≤ 500, number of hydrogen bond acceptors ≤ 10 and number of hydrogen bond donors ≤ 5 [39]. All the tested compounds except **8a** and **8b** followed the criteria for orally active drug and therefore, these compounds may have a good potential for eventual development as oral agents.

4. Conclusion

In summary, we have synthesized new triazole based coumarin derivatives *via* click chemistry and evaluated for biological activity. The synthesized compounds show promising antioxidant and antifungal activity as compared to the respective standard drugs. Compound **8a** shows potential antioxidant activity (IC_{50} = 15.20 μg/mL) when compared with standard BHT. Compound **8d**, **8e** and **8f** displayed significant antifungal activity as compared to the standard antifungal drug miconazole. In addition to this, molecular docking study of these synthesized triazole derivatives have a high affinity towards the active site of enzyme P450 cytochrome lanosterol 14α-demethylase which provides a strong platform for new structure based design efforts. Furthermore, analysis of the ADME parameters for synthesized compounds shown good drug like properties and can be developed as oral drug candidate. Thus, suggesting that compounds from present series **8a** (antioxidant activity), **8d**, **8e** and **8f** (antifungal activity) can be further optimized and developed as a lead molecule.

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