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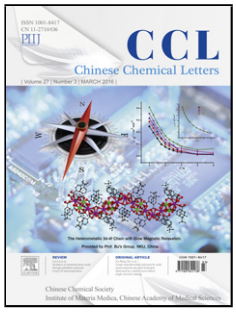

Title: 1,2,3-Triazole tethered acetophenones: Synthesis, bioevaluation and molecular docking study

Author: Mubarak H. Shaikh Dnyaneshwar D. Subhedar Vijay M. Khedkar Prakash C. Jha Firoz A. Kalam Khan Jaiprakash N. Sangshetti Bapurao B. Shingate

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Graphical Abstract

1,2,3-Triazole tethered acetophenones: Synthesis, bioevaluation and molecular docking study

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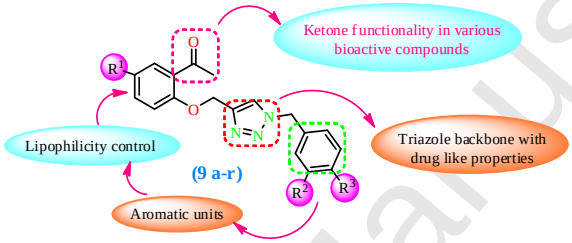

A small focused library of eighteen new 1,2,3-triazole tethered acetophenones has been efficiently prepared *via* click chemistry approach and evaluated for their antifungal and antioxidant activity.

Original article

1,2,3-Triazole tethered acetophenones: Synthesis, bioevaluation and molecular docking study

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ABSTRACT

A small focused library of eighteen new 1,2,3-triazole tethered acetophenones has been efficiently prepared *via* click chemistry approach and evaluated for their antifungal and antioxidant activity. The antifungal activity was evaluated against five human pathogenic fungal strains: *Candida albicans*, *Fusarium oxysporum*, *Aspergillus flavus*, *Aspergillus niger*, and *Cryptococcus neoformans*. Among the synthesized compounds, **9c**, **9i**, and **9p** found to be more potent antifungal agents that the reference standard. These 1,2,3-triazole based derivatives were also evaluated for antioxidant activity, and compound **9h** was found to be the most potent antioxidant as compared to the 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 14α-demethylase. Moreover, the synthesized compounds were also analyzed for ADME properties and showed potential as good oral drug candidates.

1. Introduction

In recent years, the incidence of systemic fungal infection has increased significantly due to an increase in the numbers of patients undergoing organ transplants, anticancer chemotherapy patients, and patients with AIDS. The commonly used azole antifungal agents fluconazole, itraconazole, miconazole, and voriconazole display 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 inhibit 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 the increase in resistance to these drugs [4].

Recently, click chemistry has emerged as a fast and powerful approach for the synthesis of novel compounds with biological importance. The copper-catalyzed 1,3-dipolar azide-alkyne cycloaddition (CuAAC) reaction [5] is the premier example of "click chemistry" as it is virtually quantitative and easy to perform. The formed triazole is essentially inert to reactive conditions such as oxidation, reduction, and hydrolysis. CuAAC is particularly useful for the synthesis of a variety of molecules ranging from enzyme inhibitors to molecular materials [6]. 1,2,3-Triazole based compounds are reported to possess a wide range of biological activities such as antifungal [7], antitubercular [8], antiallergic, antibacterial, anti-HIV activity [9], α-glycosidase inhibition [10], antimicrobial [11], anticoccidiostats [12], anticonvulsant [13], antimalarial [14], antiviral [15] and antimycobacterial activity [16]. Triazole has been used to improve the pharmacokinetic properties of desired drugs [17].

Acetophenones exhibit a wide range of biological activities like antagonist activity (Fig. 1, **A**) [18], anesthetics, pain control [19], and they are used as oral hypoglycemic agents [20] (Fig. 1, **B**) for the treatment of non insulin dependent diabetes mellitus. Some of the marketed drugs containing acetophenone moiety are used for the treatment of schizophrenia [20] (Fig. 1, **C**). Drugs containing acetophenone moiety also exhibit antidiabetic, sedative, antipsychotic [20] (Fig. 1, **D**), psychoactive (Fig. 1, **E**), anti-inflammatory [21], and antimicrobial [22] (Fig. 1, **F**) activity. Benzylidene acetophenone or chalcone (Fig. 1, **G**) shows antibacterial, antifungal, anti-inflammatory [21a], antitumor [20, 21b], and other activities.

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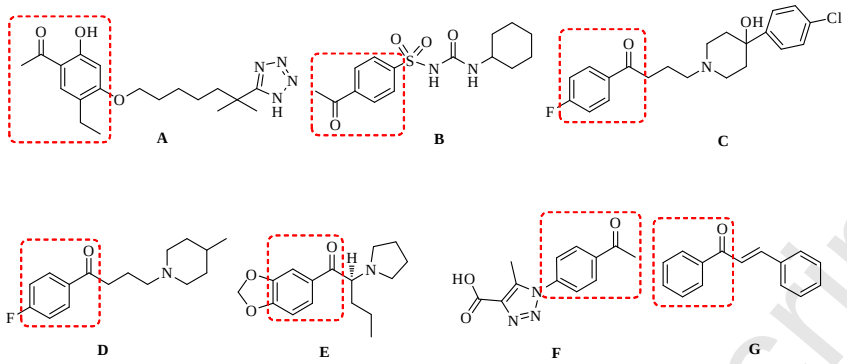


Fig. 1. Some bioactive compounds having acetophenone core.

Considering the importance of 1,2,3-triazole and acetophenone moieties as a single molecular scaffold, and in continuation of our recent reports on 1,2,3-triazole derivatives as antitubercular and antifungal agents and other bioactive heterocyclic compounds [23], we planned to synthesize some new synthetic 1,2,3-triazole tethered acetophenone derivatives to evaluate their antifungal and antioxidant activity. Computational characterizations included a docking study for antifungal activity and ADME prediction of synthesized 1,2,3-triazole-acetophenone conjugates **9a-r**.

2. Experimental

2.1. Chemistry

Synthesis of compounds **2a-c** and **3a-c** are given in the Supporting information.

General procedure for the synthesis of 2-(prop-2-yn-1-yloxy)phenylethanone (**4a-c**): K_2CO_3 (18 mmol) was added to a stirred solution of hydroxyacetophenone (15 mmol) in *N,N*-dimethylformamide (DMF) (8 mL). The reaction mixture was stirred at room temperature for 30 min, which results in the corresponding oxyanion. To this, propargyl bromide (15 mmol) was added and stirred for 2 h at room temperature. The progress of the reaction was monitored by TLC using ethyl acetate:hexane as a solvent system. The reaction mixture was quenched by crushed ice. If the product was solid (**4b** and **4c**), it was filtered and crystallized using aq. ethanol. When the product (**4a**) was liquid, it was extracted in ethyl acetate (20 mL × 3). The combined organic layers were dried over anhydrous $MgSO_4$. The solvent was removed under a reduced pressure and the product was used in further steps without purification.

General experimental procedure for the synthesis of substituted 2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)methoxyphenylethanone (**9a-r**)*:* A mixture of 2-(prop-2-yn-1-yloxy)phenylethanones **4a-c** (2 mmol), substituted benzyl azide **8a-f** (2 mmol) and copper diacetate ($Cu(OAc)_2$) (20 mole%) in *t*-BuOH-H_2O (3:1, 8 mL) was stirred at room temperature for 19-27 h. 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 (2×15 mL) and dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure to afford the corresponding crude compounds (**9a-r**). The obtained crude compounds were recrystallized using ethanol.

2.2. Biological activity

Antifungal activity: The antifungal activity was evaluated against five human pathogenic fungal strains, such as *Candida albicans* (NCIM 3471), *Fusarium oxysporum* (NCIM 1332), *Aspergillus flavus* (NCIM 539), *Aspergillus niger* (NCIM 1196), and *Cryptococcus neoformans* (NCIM 576), which are often encountered clinically. For each compound, antifungal activity was compared with standard drugs miconazole and fluconazole. Miconazole and fluconazole were purchased from TCI chemicals at 98% purity. Minimum inhibitory concentration (MIC) values were determined using the standard agar method [24].

Antioxidant activity: Antioxidant activity of the synthesized compounds has been assessed *in vitro* by the 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging assay [25] 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 DPPH. 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.

$$\% \text{ of scavenging} = [(A \text{ control} - A \text{ sample})/A \text{ blank}] \times 100$$

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 out in triplicate.

2.3. Computational study

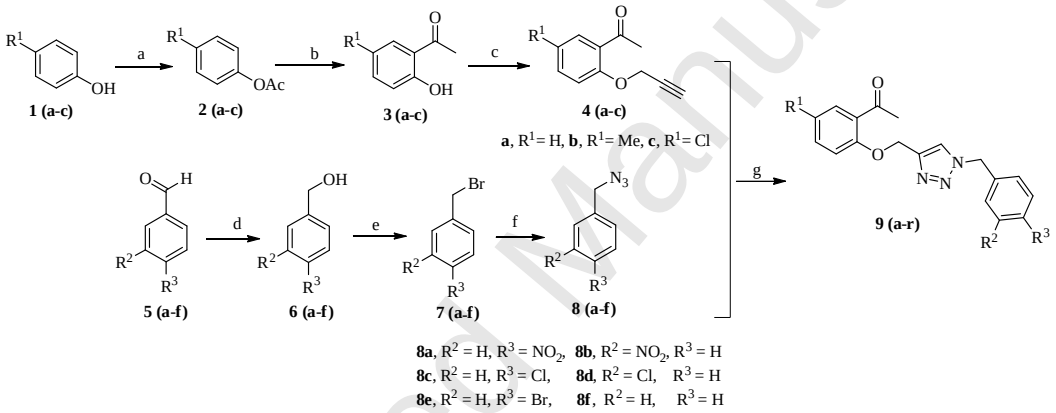
Molecular docking: Glide (Grid-Based Ligand Docking with Energetics) program integrated in the Schrodinger molecular modeling software [26] was used to study the binding mode of the title compounds into the active site of sterol 14*α*-demethylase (CYP51).

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, 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), and number of rotatable bonds (n-ROTB) were calculated using Lipinski's rule of five [27a] and the Molinspiration online property calculation toolkit [27b]. Absorption (% ABS) was calculated by: %ABS = 109-(0.345×TPSA) [27c].

3. Results and discussion

3.1. Chemistry

We have described the syntheses of a series of new 1,4-disubstituted 1,2,3-triazole based acetophenone derivatives **9a-r** as a potential antifungal and antioxidant agents from commercially available starting materials (Scheme 1).



Scheme 1. Reagents and conditions: (a) Ac_2O, pyridine, r.t., 4-5 h; (b) $AlCl_3$, 140-150 °C, 5-6 h; (c) Propargyl bromide, K_2CO_3, DMF, r.t., 2.5 h; (d) $NaBH_4$, methanol, 0 °C to r.t., 2 h; (e) PBr_3, CH_2Cl_2, 0 °C, 0.5 h; (f) NaN_3, acetone:H_2O (3:1), r.t., 24 h; (g) $Cu(OAc)_2$ (20 mol%), *t*-BuOH/H_2O (3:1), r.t., 19-27 h.

These compounds **9a-r** were formed by the fusion of benzyl azides and the terminal alkyne group of acetophenones *via* the click chemistry approach. The phenolic esters (**2a-c**) were synthesized by the acylation of corresponding phenol (**1a-c**) using acetic anhydride and pyridine at room temperature. The obtained phenolic esters on Fries rearrangement in the presence of Lewis acid $AlCl_3$ at 140-150 °C selectively produces *o*-hydroxy acetophenones (**3a-c**) in good yields. The treatment of *o*-hydroxy acetophenones (**3a-c**) with propargyl bromide in the presence of K_2CO_3 as a base in *N*,*N*-dimethylformamide (DMF) at room temperature afforded corresponding 2-(prop-2-yn-1-yloxy)phenylethanone (**4a-c**) in 90%-92% yield (Scheme 1). The benzyl azides **8a-f** were prepared from the corresponding benzaldehydes *via* $NaBH_4$ reduction, bromination, and nucleophilic substitution reaction of sodium azide according to the reported procedure [28] (Scheme 1). Finally, 1,3-dipolar cycloaddition reaction of benzyl azides **8a-f** and terminal alkyne group of acetophenones (**4a-c**), using a catalytic amount of copper diacetate $Cu(OAc)_2$ in *t*-BuOH-H_2O (3:1) mixture at room temperature for 19 to 27 h afforded the corresponding regioselective 1,4-disubstituted-1,2,3-triazole incorporated acetophenone derivatives **9a-r** in quantitative isolated yield (86%-90%) (Scheme 1).

The structures of compounds **9a-r** were confirmed by ^{1}H NMR, ^{13}C NMR, and HRMS analysis. Yields, reaction times and physical data of the individual compounds are given in the Supporting information.

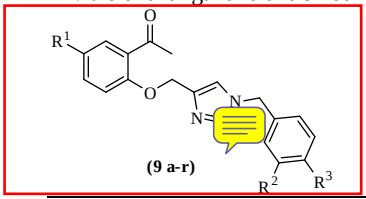
3.2. In vitro antifungal activity

The minimum inhibitory potentials of newly synthesized 2-((1-benzyl-1*H*-1,2,3-triazol-4-yl)methoxy)phenylethanone derivatives **9a-r**, were 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 standard drugs miconazole and fluconazole. The MIC values in µg/mL were estimated and the results are summarized in Table 1.

Some of the synthesized triazole incorporated acetophenone derivatives **9a-r** showed good antifungal activity as compared to the standard drug. Compounds **9c**, **9d**, **9j**, **9n**, **9o**, **9p**, and **9q** have been found to be good inhibitors of *C. albicans* with MIC values 25 µg/mL. These triazole derivatives were found to be equipotent to the standard drug miconazole. Compounds **9c**, **9d**, **9i**, **9o**, **9p,** and **9r**

with MIC value 25 µg/mL shows equivalent potency for fungal strain *F. oxysporum* as compared to the standard drug miconazole. Compounds **9c**, **9i**, and **9r** show equivalent potency for fungal strain *A. flavus* compared to the miconazole. In addition to this, compounds **9i** and **9p** show equivalent potency for fungal strain *A. niger* and *C. neoformans*, respectively, compared to the miconazole.

Table 1.
In vitro antifungal and antioxidant evaluation of 1,2,3-triazole based acetophenones (**9a-r**).



(9 a-r)

Entry	R^1	R^2	R^3	Antifungal Activity MIC (µg/mL)					Antioxidant activity IC_{50} (µg/mL)
				CA	*FO*	*AF*	*AN*	*CN*	
9a	H	H	NO_2	100	150	100	50	100	27.2
9b	H	NO_2	H	100	50	125	100	100	37.40
9c	H	H	Cl	25	25	25	50	100	44.12
9d	H	Cl	H	25	25	*	50	100	46.15
9e	H	H	Br	75	100	100	*	150	44.29
9f	H	H	H	100	100	100	150	*	55.63
9g	Me	H	NO_2	100	100	100	*	150	16.35
9h	Me	NO_2	H	100	50	100	100	100	14.14
9i	Me	H	Cl	50	25	25	25	50	26.26
9j	Me	Cl	H	25	50	50	100	150	24.29
9k	Me	H	Br	87.5	100	150	100	150	47.11
9l	Me	H	H	50	100	100	50	50	38.21
9m	Cl	H	NO_2	50	50	50	100	50	17.06
9n	Cl	NO_2	H	25	50	50	100	50	15.20
9o	Cl	H	Cl	25	25	50	100	50	16.39
9p	Cl	Cl	H	25	25	175	150	25	16.23
9q	Cl	H	Br	25	50	50	100	150	15.99
9r	Cl	H	H	50	25	25	50	100	15.29
MA	-	-	-	25	25	12.5	25	25	-
FA	-	-	-	6.25	6.25	6.25	12.5	6.25	-
BHT	-	-	-	-	-	-	-	-	16.47

* - No activity was observed up to 200 µg/mL, CA, *Candida albicans*; FO, *Fusarium oxysporum*; AF, *Aspergillus flavus*; AN, *Aspergillus niger*; CN, *Cryptococcus neoformans*; MA, *Miconazole*; FA, *Fluconazole*; BHT, *Butylated Hydroxy Toluene*; NT, *Not tested*.

3.3. Antioxidant activity

All the triazole derivatives **9a-r** shows good to moderate antioxidant activity as compared to the standard drug BHT (Table 1). According to the DPPH assay, compounds **9g**, **9h**, **9n**, **9o**, **9p**, **9q**, and **9r** exhibited promising radical scavenging activities when compared with synthetic antioxidant BHT (IC_{50} = 16.47 µg/mL), with IC_{50} values of 16.35, 14.14, 15.20, 16.39, 16.23, 15.99, and 15.29 µg/mL, respectively. Of the triazole derivatives **9a-f**, which all have a planar acetophenone moiety in their structure, none had antioxidant acitivities comparable to standard drug BHT. In contrast, the triazole derivatives **9g-l**, having methyl substituents on the acetophenone moiety, display moderate to excellent antioxidant activity. In particular, the compounds **9g** and **9h** with IC_{50} values 16.35 and 14.14 µg/mL, respectively, display good activity compared to standard. The compounds **9m-r**, with *chloro*- substitution on acetophenone, show excellent antioxidant activity compared to BHT.

3.4. Computational study

Molecular docking studies provide knowledge on structural and functional aspects of proteins and ligands along with information about the binding affinities, binding modes, and type of interactions guiding the protein-ligand complexation, which provides an immense opportunity for researchers for generating and analyzing the potential of existing lead molecules and their analogues. Therefore with the aim of rationalizing the promising *in vitro* results obtained for the most active title compounds (**9c-e**, **9i**, **9j-r**) and to investigate the molecular basis of their interactions, molecular docking study was carried out with fungal sterol 14α-demethylase (CYP51) as the target receptor. There are several reports [23c,d,e] on triazoles acting as antifungl agents *via* inhibition of CYP51, which motivated us to select this target to evaluate the binding affinity of the title compounds. Sterol 14α-demethylase (CYP51) is an ancestral activity of the cytochrome P450 superfamily required for ergosterol biosynthesis in fungi. It is a heme thiolate enzyme which converts lanosterol into 4,4'-dimethyl-cholesta-8,14,24-triene-3-β-ol. Inhibition of CYP51 leads to depletion of ergosterol coupled with an accumulation of 14-methyl sterols which results in impaired cell growth in fungi. The essential role of the CYP51 enzyme in fungi makes it an important target for antifungal drug design. Visual inspection of the lowest energy docked conformations of all 1,2,3-triazole derivatives revealed that they could snugly fit into the active site of CYP51, adopting a very similar orientation and co-

ordinates very close to that of the native ligand-fluconazole in the crystal structure. The resulting complexes were stabilized by formation of several steric and electrostatic interactions. The binding affinities of these compounds were evaluated according to many parameters, including: docking score (Glide score), the binding energies (kcal/mol), hydrogen bonding, π-π stacking, and the noncovalent molecular interaction (steric and electrostatic) by Glide (Grid-Based Ligand Docking with Energetics) program integrated in the Schrodinger molecular modeling software [26]. The binding energies for all the studied compounds were found to be negative, ranging from -44.836 kcal/mol to -30.489 kcal/mol, while their docking scores ranged from -7.32 to -6.60 with a significant correlation between the binding affinity and the obtained biological activity, wherein the active compounds have higher scores, while those with relatively low activity are also predicted to have a lower score.

The binding energy for the reference ligand-fluconazole was found to be -52.92 kal/mol with a docking score of -7.34. The more negative value of Glidescore and binding energy indicates a good binding affinity of the ligand towards the target enzyme. Furthermore, a detailed per-residue interaction analysis between the enzyme and the triazole derivatives has been carried out through which we can speculate regarding the detailed binding patterns in the cavity and the most significantly interacting residues, as well as the type of thermodynamic interactions governing the binding of these molecules. The intermolecular interaction energy values obtained from the docking calculation are presented in Table S1 in Supporting information.

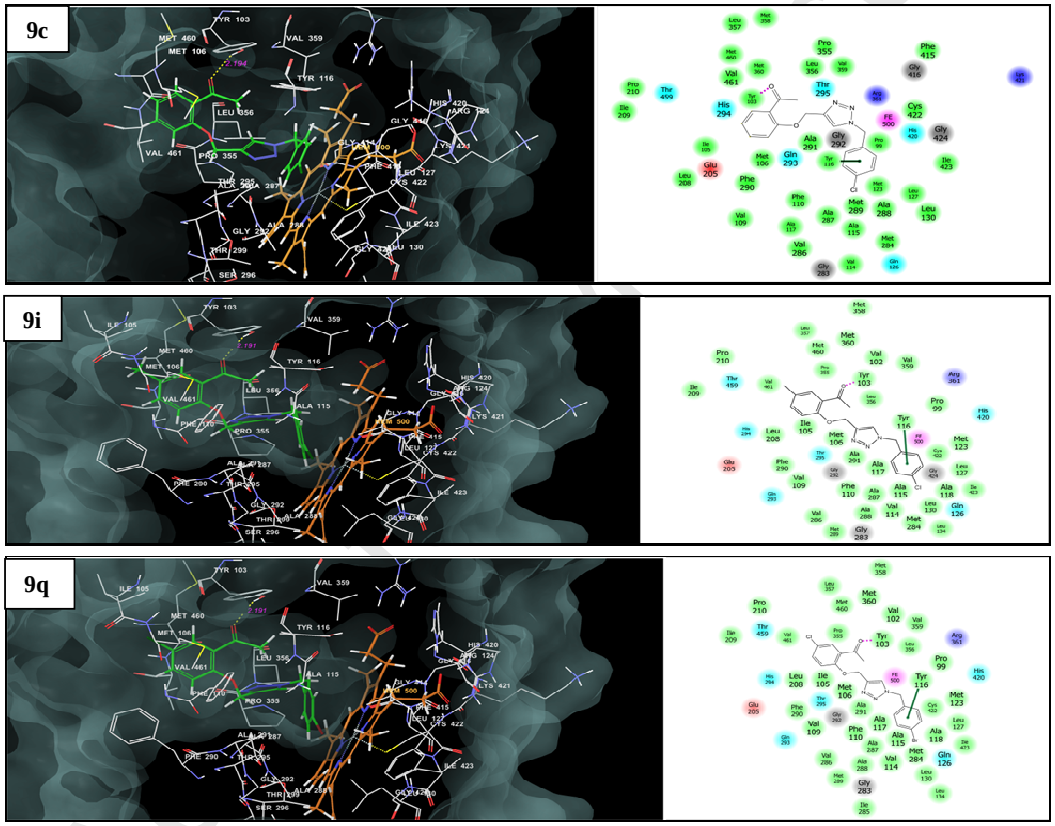


Fig. 2. Binding mode of compounds **9c**, **9i** and **9q** into the active site of sterol 14*α*-demethylase (CYP51).

A perusal of per-residual interactions of the lowest energy docked conformations revealed that the van der Waals contacts are more prevalent over the electrostatic contribution in the overall binding affinity towards CYP51 (Fig. 2, Fig. S1 in Supporting information). A very extensive network of van der Waals interactions was observed with Val461, Met460, Leu356, Phe290, Met106, and Tyr103 through the acetophenone constituent of each of these molecules, while the 1,2,3-trizole nucleus exhibited significant van der Waals interactions with Thr295, Ala291, and Phe110 residues. The substituted aromatic ring attached to the *N*-1 of triazole nucleus was also engaged in favorable van der Waals contacts with Ala288, Ala287, Met284, Leu127, and Tyr116 residues lining the active site of CYP51. Furthermore, a favorable electrostatic interaction observed with Tyr103 and Tyr116 residues also contributed to the binding affinity of these molecules. All the derivatives exhibited a notably significant van der Waals as well as electrostatic interaction with heme moiety present in the active site of CYP51, decreasing gradually with decreases in the observed antifungal activity, indicating the significance of this interaction in the activity. In addition to this, a very significant hydrogen bonding interaction between the carbonyl oxygen of the inhibitor and the Tyr103 added to the stability of these complexes. However, this interaction was missing for **9e**, **9j**, **9k**, **9m**, and **9o**. Furthermore a very prominent *π-π* stacking interaction was observed between the substituted aromatic ring of these compounds and Tyr116 residues except for **9l** where this interaction was observed with Phe110 residue in the active site. These

hydrogen-bonding and π-π stacking interactions serve as an "anchor", guiding the 3D orientation of the ligand in its active site and facilitate the steric and electrostatic interactions.

The success of a drug is determined by good efficacy and an acceptable ADME (absorption, distribution, metabolism and excretion) profile. In the present study, the drug-likeness model score (a collective property of physic-chemical properties, pharmacokinetics and pharmacodynamics of a compound represented by a numerical value) was computed by MolSoft software [29]. A computational study of all the synthesized compounds was performed for prediction of ADME properties and the value obtained is presented in supporting information, Table S2 in Supporting information. It is observed that the compounds exhibited a good % ABS (% absorption) ranging from 73 to 89%. Furthermore, none of the synthesized compounds **9a-r** violated Lipinski's rule of five (miLog $P \leq 5$). 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 [30]. The larger the value of the drug likeness model score, the higher the probability that the particular molecule will be active. All the tested compounds **9a-r** followed the criteria for orally active drugs, and therefore, these compounds may have good potential for eventual development as oral agents.

4. Conclusion

In conclusion, we have synthesized new triazole based acetophenone derivatives *via* the click chemistry approach and evaluated for biological activity. The synthesized compound displays promising antifungal and antioxidant activity compared to the standard drugs. Compounds **9c**, **9i**, and **9p** displayed significant antifungal activity as compared to the standard antifungal drug miconazole. Compound **9h** shows potential antioxidant activity (IC_{50} = 14.14 µg/mL) when compared with standard BHT. In addition to this, molecular docking study of these synthesized triazole derivatives demonstrates that they 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 the synthesized compounds predicted good drug like properties and potential for development as oral drug candidates. Thus, we suggest that compounds **9h** (antioxidant activity), **9c**, **9i**, and **9p** can be further optimized and developed as lead molecules for antifungal activity. Further work on utilization of triazole incorporated acetophenones leading to useful bioactive compounds is in progress.

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