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Der Pharma Chemica, 2014, 6(5):35-44
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X
CODEN (USA): PCHHAX

Design, *in silico* molecular docking studies, synthesis, spectral characterization and *in vitro* antifungal evaluation of 1-(4-(1*H*-tetrazole-1-yl) phenyl)-3-arylprop-2-en-1-ones

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ABSTRACT

A new series of 1-(4-(1H-tetrazole-1-yl)phenyl)-3-arylprop-2-en-1-ones ***(6a-j)*** *(Chalcones)****,*** *were synthesized by Claisen Schmidt condensation and characterised by their melting point, elemental analysis, FT-IR, MS,* ^{1}H*, and* ^{13}C *NMR spectral data. This set of synthesised compounds has been evaluated for in vitro antifungal activity. Results of preliminary biological tests showed that most of title compounds exhibited activity against the five common pathogenic fungi. Compound* ***6i*** *showed best antifungal activity with broad antifungal spectrum and proved to be more active against C. albicans, A. niger and A. fumigalis. Compounds* ***6e*** *and* ***6g*** *also had high activities. In an attempt to understand the ligand–protein interactions in terms of the binding affinity, docking studies were performed using Schrodinger GLIDE for the synthesized compounds. It was observed that the binding affinities calculated were in agreement with the MIC values.*

Key words: 1H-Tetrazole Chalcone; Claisen Schmidt condensation; Anti-fungal; Molecular Docking; Sterol 14α-demethylase.

INTRODUCTION

In recent years, the prevalent use of antifungal agents has resulted in the progress of resistance to these drugs by pathogenic microorganisms, leading to an increase in morbidity and mortality [1]. Thus, strong efforts in the drug discovery for antifungal agents are still considered to develop more promising and effectual antifungal. Oxidative amputation of the 14α-methyl group from sterol precursors by sterol 14α-demethylase is the significant pace in the biosynthesis of membrane sterols and steroid hormones. Sterol 14α-demethylase is a cytochrome P450 heme thiolate enclosing enzyme concerned in the biosynthesis of membrane sterols, including ergosterol in fungi, cholesterol in animals and a wide range of C24-modified sterols in plants and protozoa in the greater part of organisms in biological kingdoms from bacteria to animals [2]. For azole containing antifungal agents including fluconazole, voriconazole, itraconazole, ravuconazole, and posaconazole, 14α-demethylase has been a therapeutic target for several generations [3]. These drugs inhibit microbial development by distracting biosynthesis of ergosterol, which is the major component of the fungal membrane. Embarrassment of sterol biosynthesis has been demonstrated to be effectual in trypanosomatids [4] and Leishmania spp [5], which cause such tropical diseases as African leishmaniasis, sleeping sickness, Chagas disease. Even though mammalian 14α-demethylase enzymes execute the same catalytic reaction [6] as their fungal and protozoan orthologs, they share relatively modest overall sequence identity (within 30%) with them. Computational biology and Bioinformatics plays foremost responsibility in

designing drug molecules and encompass the probable of accelerating up the drug discovery process. Molecular docking of the receptor (target) with the drug molecules (ligands) reveal out the significant information about drug receptor interactions and is frequently used to find out the binding orientation of the protein target by the drug candidates in order to predict the affinity and activity.

The coordination chemistry of heterocyclic tetrazoles and roles played by nitrogen molecules, resulting in significant tetrazole chemistry [7, 8] as explosives [9], specialty applications, such as information systems, rocket propellants and chemical applications [10, 11]. In particular, tetrazoles can be used as an alternative to many biological advantages over other metabolic degradation pathways [12].

1-substituted 1, 2, 3, 4- tetrazoles are reported to posses antibacterial [13], antifungal [14], antiviral [15], analgesic [16], anti-inflammatory [17]**,** antiulcer [18]**,** and anti-hypertensive [19] activities. The tetrazole function is metabolically stable this feature has a close similarity between the acidic character of the tetrazole group and carboxylic acid group which have inspired medicinal chemists to synthesize substituted tetrazoles as potential medicinal agents.

Generally chalcones constitute an important class of natural products belonging to the flavonoids family. They have been known to exhibit anti-mitotic properties caused by the inhibition of tublin polymerization [20] chemically they are open chained molecules consisting of two aromatic rings linked by a three- carbon enone fragment.

Several research groups have been shown that the S-*Cis* conformation of chalcones is important for their biological activity**.** Their simple structure and ease of preparation make chalcones an attractive scaffold for structure -activity relationship (SAR) Studies, and a wide number of substituted chalcones have been synthesised to evaluate the effects of various functional group on biological activity. The biological activity includes anti-inflammatory [21]**,** anti- mitotic [22], anti-leishmanial [23], anti-invasive [24], anti-tuberculosis [25], anti-fungal [26], anti-malarial [27], anti-tumor, and anti-oxidant properties [28]**.**

Based on the above facts, we focused on designing a potent Ligand moiety by incorporating two different heterocyclic nucleuses (Tetrazole & Chalcones) as a potent anti-fungal agent. In the present study, synthesis, structural characterization and *in vitro* anti-fungal activity of the compound **6a-j** was established. The structure analysis studies were carried out using FT-IR, ^{1}H NMR, ^{13}C NMR and Mass Spectra. The molecular docking study was also performed on GLIDE (version 9.6, Schrodinger, LLC, New York, 2014) with the targeted protein sterol 14 alpha-demethylase.

MATERIALS AND METHODS

2.1 Materials :

Melting points (^{0}C, uncorrected) of the synthesized compounds were checked in open a capillary tube by using digital auto melting point apparatus (Labtronics 110, India) and found uncorrected. All the chemicals and solvents were purchased from Sigma–Aldrich and Merck, India. All reactions were carried out under atmospheric air and the products were checked by thin layer chromatography on TLC silica gel 60 F254 using eluting solvents such as ethyl acetate and hexane (1:1). All the compounds were characterized FT-IR spectrometer (IR 8400, Shimadzu, Japan) using KBr pellets, ^{1}H NMR spectroscopy in DMSO (400 MHz, Bruker), ^{13}C NMR spectroscopy in DMSO (125 MHz, Bruker) using tetramethylsilane (TMS) as internal standard. Coupling constants (J values) are reported in Hz. Mass spectra were measured by CI Mass spectra are recorded on a Varian Saturn GC-MS spectrometer. Molecular docking studies of all the synthesized compounds were studied by GLIDE program (version 9.6, Schrodinger, LLC, New York, 2014).

2.2 Synthesis

2.2.1 General Procedure for Synthesis of Compound 1-(4-(1H-tetrazole-1-yl) phenyl) ethanone (4)

A mixture of para amino acetophenone (1) 2g (0.01 mole), sodium azide (2) 1g (0.01 mole) and triethyl orthoformate (**3**) 10ml (0.01 mole) was dissolved in 25ml of acetic acid. The reaction mixture was refluxed at 60 °C for 24 hrs. Then this reaction was poured over crushed ice. The light yellow solid was obtained. Then the solid washed with water, dried and re-crystallized from ethanol afford pure 1-(4-(1H-tetrazole-1-yl) phenyl) ethanone **(4).**

2.2.2 General Procedure for Synthesis of Compounds 1-(4-(1H-tetrazole-1-yl) phenyl) -3-arylprop-2-en-1-ones (6a-k)

Substituted aldehydes (**5**) 1.1g (0.01mole) and compound 1-(4-(1*H*-tetrazole-1-yl) phenyl) ethanone (**4**) 2g **(**0.01 mole) was dissolved in 15ml ethanol, to this mixture sodium hydroxide (40% 2 ml), was added at 0-5 °C. The reaction mixture was stirred at room temperature for 2 hrs. Then the reaction mixture was poured over crushed ice. The yellow solid thus obtained was filtered, washed with water and dried. The residue was purified by column chromatography (silica gel 100-200 mesh with 20% ethyl acetate in hexane) to afford pure **1-(4-(1*H*-tetrazole-1-yl) phenyl) -3-arylprop-2-en-1-ones (6a-i).**

2.2.1. 1-(4-(1H-tetrazole-1-yl) phenyl)ethanone (4)
Pale yellow solid, m.p 152^{o}C. Yield 92%. Mol. Wt.: 188. FT-IR (KBr), υ cm^{-1}1678 (C=O), 2917(Ar C-H), 2849(C-H). ^{1}H NMR (400 MHz, DMSO) δ: 2.65(s, H-CH3), 8.20(d, *J*= 7.2Hz, 2H), 8.08(d, *J*=7.6Hz 2H), 10.23(s, 1H). ^{13}C NMR (400MHz, DMSO) δ: 26.86, 120.85, 130.07, 136.77, 137.13 (AR-C), 142.38(tetrazole-C) 196.92(C=O). MS-ESI *(m/z)*: 189.1[m+H]. Anal.Calcd for $C_9H_8N_4O$: C57.44; H, 4.28; N, 29.77. Found C, 57.23, H, 4.03, N, 29.54.

2.2.2. 1-(4-(1H-tetrazole-1-yl) phenyl) -3phenylprop-2-en-1-one (6a)
Yellow solid, mp.76^{o}C. Yield: 80%. Mol. Wt.: 276. FT-IR (KBr), υ cm^{-1}, 1661(C=O), 1607(C=C), 2923(C-H), 3112(Ar C-H). ^{1}H NMR (400 MHz, DMSO) δ: 7.92(d, J=15.6Hz 1H), 8.18(d, J=7.2 Hz, 2H), 7.88(d, J=8.2 Hz, 2H), 7.78(d, J=8.0Hz, 2H), 7.71(d=J15.6 Hz 1H) 7.46(d, J=8.4 Hz, 2H). Tetrazole proton shifted to solvent peak. ^{13}C NMR (400MHz, DMSO) δ: 121.84(C-CH), 114.75, 114.97, 128.76, 128.88, 129.04, 130.48, 130.88, 131.24, 131.71(Ar-C), 143.58(Tetrazole-C), 144.03(C-CH), 187.18(C-C=O). MS-ESI *(m/z)*:277 (m+H). Anal.Calcd for $C_{16}H_{12}N_4O$: C, 99.55; H, 4.38; N, 20.28. Found C, 99.37; Hs, 4.17; N, 20.06.

2.2.3. 1-(4-(1H-tetrazole-1-yl) phenyl) -3-(4-Fluorophenyl) prop-2-en-1-one (6b)
Dark yellow solid, m.p 88^{o}C.Yield 78%. Mol. Wt.: 294. FT-IR (KBr), υ cm^{-}, 1677(C=O), 1599(C=C), 2920(C-H), 3128(Ar C-H). ^{1}H NMR (400 MHz, DMSO): δ 7.89(d, *J*=15.6 Hz, (1H). 8.19(d, *J*= 8.0Hz 2H), 7.72(d, *J*=15.6 Hz, 1H), 7.05,(d, *J*=8.0Hz 2H), 7.10(d, *J*= 7.6 2H), 7.29(d, *J*=8.0 Hz, 2H), ^{13}C NMR (400MHz, DMSO) δ: 121.72(C-CH), 143.49(C-CH), , 130.47, 130.89, 131.09, 131.17, 131.37, 131.41, 131.91, (Ar-C), 142.25,(Tetrazole-C), 196.17(C-C=O). MS-ESI *(m/z)*: 295 [m+H]. Anal.Calcd for $C_{16}H_{11}N_4OF$: C, 65.30; H, 3.77; N, 19.04. Found: C, 65.11; H, 3.52; N, 18.89;

2.2.4. 1-(4-(1H-tetrazole-1-yl) phenyl) -3-(4-Cholophenyl) prop-2-en-1-one (6c)
Pale yellow solid, m.p 79^{o}C. Yield 82%. Mol. wt.: 310. FT-IR (KBr), υ cm^{-}, 1663(C=O), 1604(C=C), 2920(C-H), 3119(Ar- C-H). ^{1}H NMR (400 MHz, DMSO *d*6): 7.94(d, *J*=15.6Hz, 1H), δ 8.18 (d, *J*=7.2Hz, 2H), 7.08 (d, *J*=7.2Hz 2H), 7.70(d, *J*=15.6Hz, 1H), 7.52(d, *J*=6.5Hz, 2H), 7.92(d, *J*=7.2Hz, 2H). Tetrazole proton shifted to solvent peak. ^{13}C NMR (400MHz, DMSO *d*6) δ: 122.61 (C-CH), 144.38(C-CH), 114.78, 115.02, 128.91, 130.47, 130.93, 131.50, 133.71, 134.92(Ar-H), 144.38(Tetrazole-C), 187.02(C-C=O). MS-ESI *(m/z)*: 311 (m+H). Anal.Calcd for $C_{16}H_{11}N_4OCl$: C, 61.84; H, 3.57; N, 18.03. Found: C, 61.62; H, 3.34; N, 17.84.

2.2.5. 1-(4-(1H-tetrazole-1-yl) phenyl) -3-(4-Bromophenyl) prop-2-en-1-one (6d)
Yellow colour solid, m.p 83^{0}C. Yield 72%. Mol. Wt.: 355. FT-IR (KBr), υ cm$^{-1.}$ 1661(C=O), 1605(C=C), 2921(C-H), 3126(Ar C-H). ^{1}H NMR (400 MHz, DMSO *d*6): δ 7.68(d, *J*=6.0 Hz 2H), 7.77(d, *J*=15.9 Hz, 1H), 7.88(d, *J*=6.0 Hz, 2H), 8.42(d, *J*= 6.4Hz ,2H), 8.14(d, *J*=6.6Hz, 2H), 8.05(d, *J*=15.9 Hz, 1H), 10.26(Tetrazole-H). ^{13}C NMR (400MHz, DMSO *d*6) δ: 122.43,(C-CH) 124.24, 130.92, 131.88, 133.80, 136.83, 137.77,138.65 (Ar-C),143.37(C-CH), 142.42(Tetrazole-C), 187.86(C-C=O). MS-ESI *(m/z)*:356 (m+H). Anal.Calcd for $C_{16}H_{11}N_4OBr$: C, 54.15; H, 3.12; N, 15.77. Found: C, 53.87; H, 3.01; N, 15.52.

2.2.6. 1-(4-(1H-tetrazole-1-yl) phenyl) -3-(4-Nitrophenyl) prop-2-en-1-one (6e)
Dark yellow colour solid, mp 81^{0}C. Yield 78%. Mol. wt.: 321. FT-IR (KBr), υ cm^{-1}. 1669(C=O), 809(C-N), 2980(C-H), 3120(Ar C-H). ^{1}H NMR (400 MHz, DMSO *d*6): δ 8.29(d, *J*=8.0Hz, 2H), 8.228(d, *J*=8.0Hz,2H), 8.16(d, *J*=8.8 Hz, 2H), 7.80(d, J=15.6Hz,1H),7.6(d, J=15.6 Hz 1H), 7.05(d, *J*=9.2Hz.2H). Tetrazole proton shifted to solvent peak ^{13}C NMR (400MHz, DMSO *d*6) δ: 121.86, (C-CH), 123.21, 136.67, 123.44, 129.49, 131.86, 133.61, 135.73(Ar-C), 142.12(Tetrazole-C), 144.02(C-CH), 188, 76(C-C=O). MS-ESI *(m/z)*: 322 (m+H). Anal.Calcd for $C_{16}H_{11}N_5O_3$: C, 59.81; H, 3.45; N, 21.80. Found: C, 59.60; H, 3.24; N, 21.61.

2.2.7. 1-(4-(1H-tetrazole-1-yl) phenyl) -3-(p-tolylphenyl) prop-2-en-1-one (6f)
Pale yellow colour, m.p 79^{0}C. Yield 82%. Mol. wt.: 290. FT-IR (KBr), υ cm^{-1}. 1662(C=O), 1602(C=C), 2926(C-H), 3110(Ar C-H). ^{1}H NMR (400 MHz, DMSO *d*6): δ 8.18 (d, *J*=8.0Hz, 2H), 7.86(d, J=15.6Hz 1H), 7.10(d, *J*=8.0Hz,

2H), 7.96(d, *J*=7.6Hz, 2H), 7.76 (d, *J*=15.6Hz 1H), 7.27(d, *J*=7.2Hz, 2H), 1.25(S, 3H). Tetrazole proton shifted to solvent peak ^{13}C NMR (400MHz, DMSO *d*6) δ: 21.05(C-CH_3), 120.72(C-CH), 128.72, 129.51, 130.48, 130.83, 131.96 131.40, 132.09, 140.59(Ar-C), 143.59(C-CH) 143.20(Tetrazole-C), 196.20(C-C=O). MS-ESI *(m/z)*:291 (m+H). Anal.Calcd for $C_{17}H_{14}N_4O$: C, 70.33; H, 4.86; N, 19.30. Found: C, 70.21; H, 4.64; N, 19.11.

2.2.8. 1-(4-(1H-tetrazole-1-yl) phenyl) -3-(4-(dimethylamino) phenyl) prop-2-en-1-one (6g)
Dark yellow solid, m.p 89^{o}C. Yield 68%. Mol. Wt.: 319. FT-IR (KBr), υ cm^{-1}. 1670(C=O), 1601(C=C), 2924(C-H), 3105(ArC-H). ^{1}H NMR (400 MHz, DMSO *d*6):δ 8.13(d, J=6.8Hz, 2H),7.92 (d=15.6,Hz 1H), 7.68(d, J=6.0Hz,2H),7.66(d, J=15.6Hz 1H), 7.04(d, J=6.8Hz 2H),), 6.77(d, J=7.2Hz,2H), Tetrazole proton shifted to solvent peak ^{13}C NMR (400MHz, DMSO *d*6) δ: 21.05, 21.15(C-CH_3), 130.96, 121.72, 128.62, 128.51, 130.48, 130.73, 131.40, 132.19, 140.59(Ar-C), 143.28(C-CH), 142.59(Tetrazole-C), 195.20(C-C=O). MS-ESI *(m/z)*: 320 (m+H). Anal.Calcd for $C_{19}H_{17}N_5O$: C, 67.70; H, 5.37; N, 21.93. Found: C, 67.52; H, 5.23; N, 21.76.

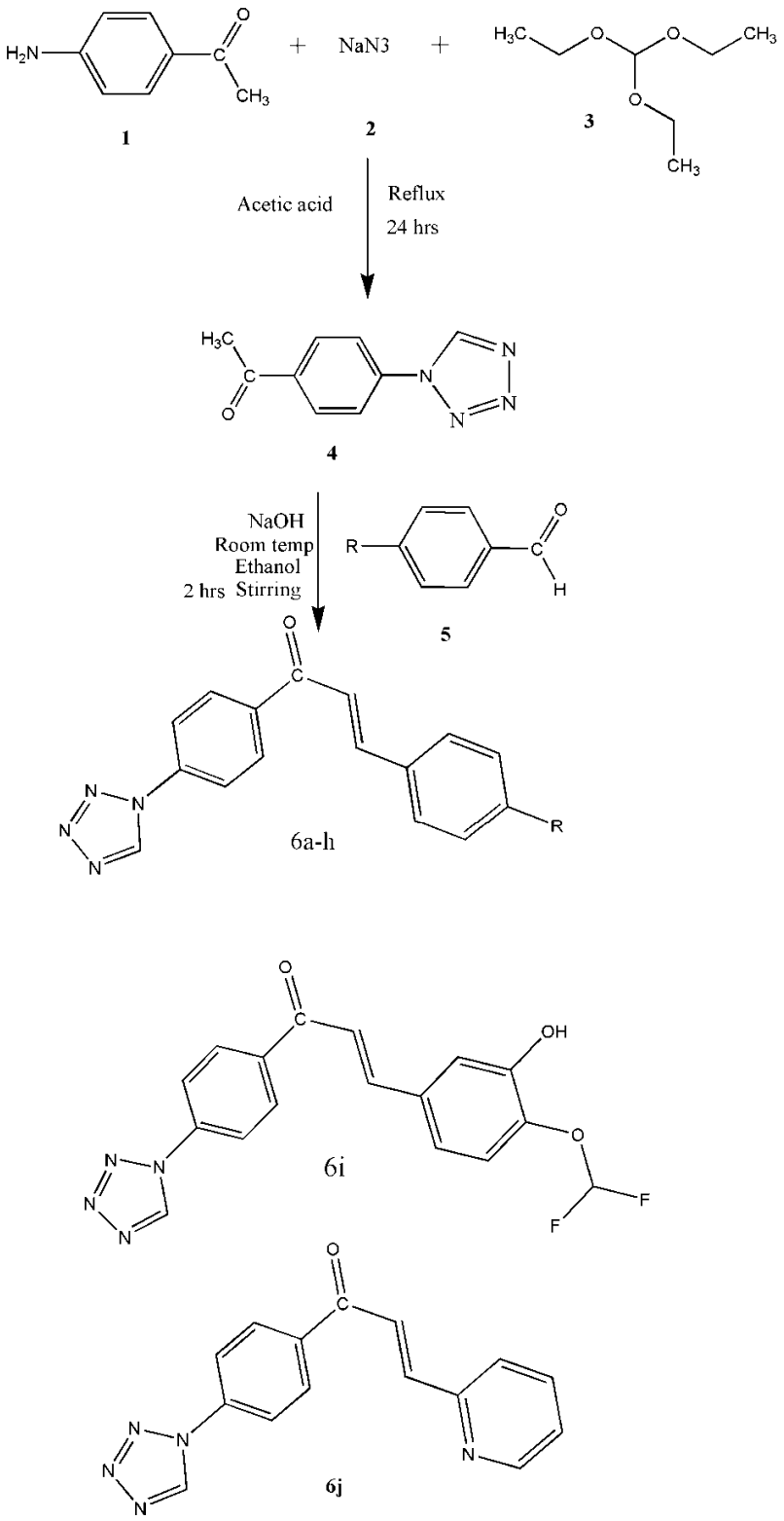
2.2.9. 1-(4-(1H-tetrazole-1-yl) phenyl) -3-(4-methoxy) phenyl) prop-2-en-1-one (6h)
Pale yellow colour solid, m.p 77^{0}C. Yield 81%. Mol. wt.: 306. FT-IR (KBr), υ cm^{-1}. 1667(C=O), 1602(C=C), 2868(C-H), 3112(ArC-H). ^{1}H NMR (400 MHz, DMSO *d*6): δ 8.16(d, J=7.6 Hz 2H), 7.92(d, J=15.6Hz 1H), 7.74(d, J-15.6Hz 1H), 7.42(d, J=6.8Hz 2H), 7.37(d, J=7.2Hz 2H), 7.05(d, J=7.6Hz 2H), CH_3O (S, 3.83, 3H). Tetrazole proton shifted to solvent peak ^{13}C NMR (400MHz, DMSO *d*6) δ: 55.27(C-OCH_3), 113.22, 115.25, 116.49, 121.53, 122.19, 129.90, 130.88, 136.18, 143.11, (Tetrazole-C), 159.60(C-CH), 186.97(C-C=O). MS-ESI *(m/z)*:307 (m+H). Anal.Calcd for $C_{17}H_{14}N_4O$: C, 66.66; H, 4.61; N, 18.29. Found: C, 66.41; H, 4.42; N, 18.02.

2.2.10. 1-(4-(1H-tetrazole-1-yl) phenyl)-3-(4-difluoromethoxy)-3-hydroxy phenyl) prop-2-en-1-one (6i)
Pale yellow colour, m.p 92^{0}C. Yield 71%. Mol. wt.: 345. FT-IR (KBr), υ cm^{-1}. 1668(C=O), 1612(C=C), 2923(C-H), 3108(Ar C-H). ^{1}H NMR (400 MHz, DMSO *d*6): 9.87(s, 1H). δ 7.84(d, J=8.4HZ, 1H), 7.70(d, J=15.6Hz 1H) 7.66(d, J=15.2HZ,2H), 7.51(d, J=8.0HZ, 1H), 7.42(d, J=5.6 HZ 2H), 7.32(d, J=7.6Hz 2H), 7.22(s,1H), Tetrazole proton shifted to solvent peak ^{13}C NMR (400MHz, DMSO *d*6) δ: 122.37(C-H), 116.20, 118.77, 120.77, 128.57, 129.54, 139.29, 129.61, 130.53(Ar-C). 134.06(C-OH) 143.59(tetrazole-C), 145.17(C-CH), 192.00(C-C=O), MS-ESI *(m/z)*: 346 (m+H). Anal.Calcd for $C_{16}H_{11}N_4O_3F_2$: C, 56.99; H, 3.38; N, 15.64. Found C, 56.73; H, 3.16; N, 15.44.

2.2.11. 1-(4-(1H-tetrazole-1-yl) phenyl) -3-(pyridine-2-yl) prop-2-en-1-one (6j)
Pale yellow colour solid, m.p 72^{o}C. Yield 90%. Mol. Wt.: 277. FT-IR (KBr), υ cm^{-1}. 1669(C=O), 1600(C=C), 2863(C-H), 3115(ArC-H). ^{1}H NMR (400 MHz, DMSO *d*6) δ: 8.29(d, J=7.2 Hz, 2H), 8.25(d, J=7.3 Hz 2H), 8.096(d, J=6.8 Hz, 2H), 7.967(d, J=15.6 Hz, 1H), 7.853(d, J=12.8Hz, 2H), 7.717(d, J=15.6 Hz, 1H). Tetrazole proton shifted to solvent peak. ^{13}C NMR (400MHz, DMSO *d*6) δ: 120.91, (C-CH), 123.08, 123.08, 123.32, 127.35, 129.15, 129.54, 136.82(Ar-C), 142.27(Tetrazole-C), 142.40(C-CH), 148.68, 150.34, 197.21(C-C=O). MS-ESI *(m/z)*:278 (m+H). Anal.Calcd for $C_{15}H_{11}N_5O$: C, 64.97; H, 4.00; N, 25.26; O, 5.77. Found: C, 64.74; H, 3.84; N, 25.02; O, 5.56

2.3 In vitro Anti-fungal Screening
The *in vitro* antifungal activity was measured by means of the minimal inhibitory concentrations (MIC) using the serial dilution method with 96-well Microtest plates. MICs were determined in RPM 1640 medium. The MIC was defined as the lowest concentration which resulted in a culture with turbidity less than or equal to the 80 % inhibition, when compared with the growth of the control. The compounds under study were dissolved in DMSO, serially diluted in growth medium, inoculated and incubated at 35 ℃. Growth MIC was determined at 48 h for the fungal species.

2.4 Molecular modeling
To understand the interaction of all the synthesized molecules (6a–6k) with Sterol 14α-demethylase, the molecular docking studies were performed using the GLIDE program (version 9.6, Schrodinger, LLC, New York, 2014). To analyze the docking results and execute the protocol, the maestro user interface (version 9.6, Schrodinger, LLC, New York, 2014) was employed and the validation of the protocol was evaluated by redocking. Sterol 14α-demethylase (**PDB ID: 1E9X**) was selected for docking studies as a reference sample and was prepared for docking through a protein preparation wizard. Structures of **6a–6k** were sketched using Marvin sketch (Freeware version). The GLIDE grid generation wizard has been used to define the docking space. Docking was performed using XP (Extra Precision mode) docking protocol [29].



Scheme 1: Synthesis of 1-(4-(1H-tetrazole-1-yl)phenyl)-3-arylprop-2-en-1-ones **(6a-j)**

Where, **R = H, F, Cl, Br, NO_2, CH_3, N $(CH_3)_2$, OCH_3** in **6a-6h**

RESULTS AND DISCUSSION

3.1. Chemistry

In the present investigation, we wish to report acetic acid mediated, catalyst free efficient procedure for the synthesis of 1-(4-(1H-tetrazole-1-yl) phenyl) ethanone **(4).** It has been prepared by Para amino acetophenone and sodium azide with triethyl orthofomate (**scheme-1**). Subsequent condensation of ketone **4** with various aldehydes led to compounds **6a-j.** The structure of synthesized compounds was assigned the basis of elemental analysis, FT-IR, ^{1}H, ^{13}C, MS). The IR spectrum of compound **6a** showed mainly absorption bands at 1661, 1607, 2923 cm^{-1} assigned to (C=O, C=C, C-H) stretching frequency. This value shows ketone stretching vibration. In the 1H NMR spectra of compound **6a,** α-H and β-H of propene-1-one appears each one as doublet at δ 7. 92 and 7.71. The coupling constant values of both α-H and β-H, *J*=15. 6 Hz. Which is agrees with ***trans*** configuration. Aromatic-protons are appeared at δ 8.18(d, J=7.2 Hz,2H), δ 7.88(d, J=8.2 Hz, 2H), δ 7.78(d, J=8.0Hz, 2H), δ 7.46(d, J=8.4 Hz, 2H). In ^{13}C NMR spectrum of compound 6, the signals of α-C and β-C are appearing at δ121. 84 and 144.03 respectively. In the HSQC spectrum shows α-H and β-H, of propane-1-one bonded with α-C and β-C of propene-2-one. Spectral data of remaining compounds are given in experimental parts. Further the compounds inveterate by microbial activity through *in silico* Molecular docking studies.

3.2 Biological evaluation

The *in vitro* antifungal activities of the synthesized compounds are presented in **Table 1**. The MIC values (inμg·mL^{-1}) against different pathogenic fungi, in comparison with fluconazole, are given. The results of the antifungal activities *in vitro* showed that all the target compounds were active against five pathogenic fungi to a certain extent. Compound **6e** and **6g** showed good inhibition against *A. fumigalis, C. albicans, A. niger* than fluconazole. Compound **6i** was the most effective antifungal agent with a broad antifungal spectrum and proved to be significantly more active against *C. albicans, A. niger* and *A. fumigalis* than the standard fluconazole.

Table1 Antifungal activities *in vitro* of compounds (MICμg·mL^{-1})

Compound	*C. albicans*	*S. griseus*	*A. niger*	*A. fumigalis*	*M. ruber*
6a	1.25	5	2.5	1.25	40
6b	1.25	1.25	0.625	2.5	40
6c	0.625	>80	2.5	5	>80
6d	0.16	2.5	2.5	0.625	40
6e	<0.16	2.5	0.16	<0.16	20
6f	0.625	2.5	1.25	0.625	>80
6g	<0.16	10	0.312	0.312	>80
6h	0.16	5	1.25	1.25	40
6i	<0.16	1.25	<0.16	<0.16	10
6j	2.5	10	5	2.5	40
Fluconazole	<0.16	1.25	0.625	2.5	2.5

3.3 Molecular docking studies

All the designed ligands and standards were evaluated for docking studies against sterol 14α-demethylase using GLIDE software. The docking results of the ligands with the top score when compared with standard were selected and given in the **Table 2**. The interaction energy comprises van der Waals energy, electrostatic energy, as well as intermolecular hydrogen bonding was calculated for every minimized complex. The docking score using GLIDE varied between -6.05 Kcal/mol and -8.13 Kcal/mol against sterol 14α-demethylase. The GLIDE Score for the standards Fluconazole docked with sterol 14α-demethylase was -6.94 Kcal/mol. This proves that 1-(4-(1*H*-tetrazole-1-yl) phenyl) -3-arylprop-2-en-1-ones (Chalcones) analogues could be potential drugs for Anti-fungal drug development. The GLIDE score is capable of being used as a semi-quantitative descriptor for the capability of ligands to bind to a specific conformation of the protein receptor. Generally, the ligand having low GLIDE score, will have superior kinship towards the receptor could be expected. Vnnnv showed the best inhibition with -8.13 Kcal/mol glide score . We ascertain a very good concurrence between the localization of the inhibitors upon docking and from the protein structure of sterol 14α-demethylase . Conformational analysis of docked complex shows that the residues PHE 83, PHE 78, TYR 76 plays a vital role in this receptor activity by having π- π stacking interactions and the residues PHE 255, ALA 256, VAL 434, LEU 321, ILE 323, VAL 435, MET 433, LEU 324, MET 79, ALA 73, PRO 320, PRO 93 by having Hydrophobic interactions with the ligand moiety (**Fig. 1-4**). Only the compound **6i** and standard flucnazole have hydrogen bonding interaction with the residue HIS 259, ALA 73 and TRY 76, GLN 72 respectively. Docking studies performed by GLIDE has established that above inhibitors fit into

the binding pocket of the sterol 14α-demethylase receptor as of the standard drug molecules. From the fallout, we could monitor that for docking liphophilic interactions between the ligand and the receptor are very important.

Table 2 Molecular docking data of compounds 6a-j

S.No	Compound Code	XP Score	Glide Energy	Glide E model	No. of Hydrogen Bonding Interaction
1.	**6a**	-6.21	-29.07	-46.53	Hydrophobic Interaction
2.	**6b**	-6.48	-29.50	-46.39	Hydrophobic Interaction
3.	**6c**	-6.41	-38.81	-51.27	Hydrophobic Interaction
4.	**6d**	-6.79	-28.57	-48.75	Hydrophobic Interaction
5.	**6e**	**-6.83**	**-41.41**	**-55.07**	Hydrophobic Interaction
6.	**6f**	-6.56	-35.40	-52.04	Hydrophobic Interaction
7.	**6g**	**-6.86**	**-38.47**	**-49.58**	Hydrophobic Interaction
8.	**6h**	-6.76	-37.01	-52.70	Hydrophobic Interaction
9.	**6i**	**-8.13**	**-44.25**	**-60.39**	1 (HIS 259)
10.	**6j**	-6.05	-35.90	-35.84	Hydrophobic Interaction
11.	**Fluconazole**	**-6.94**	**-33.34**	**-49.64**	2 (TRY 76, GLN 72)

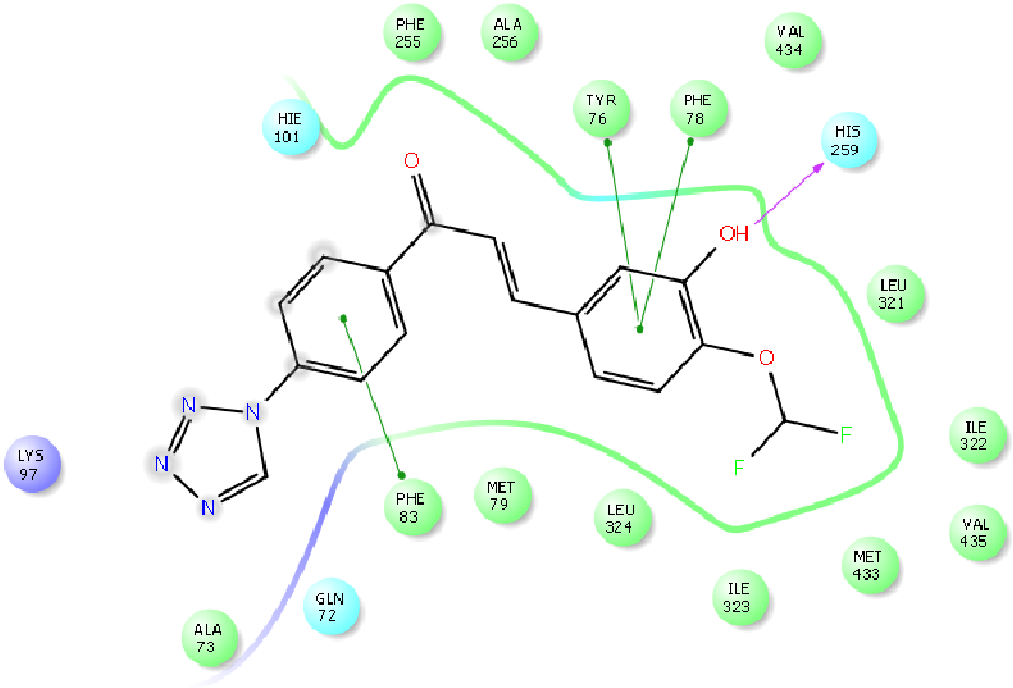


Figure 1. Docking model of compound 6j into the 14α-demethylase enzyme binding pocket

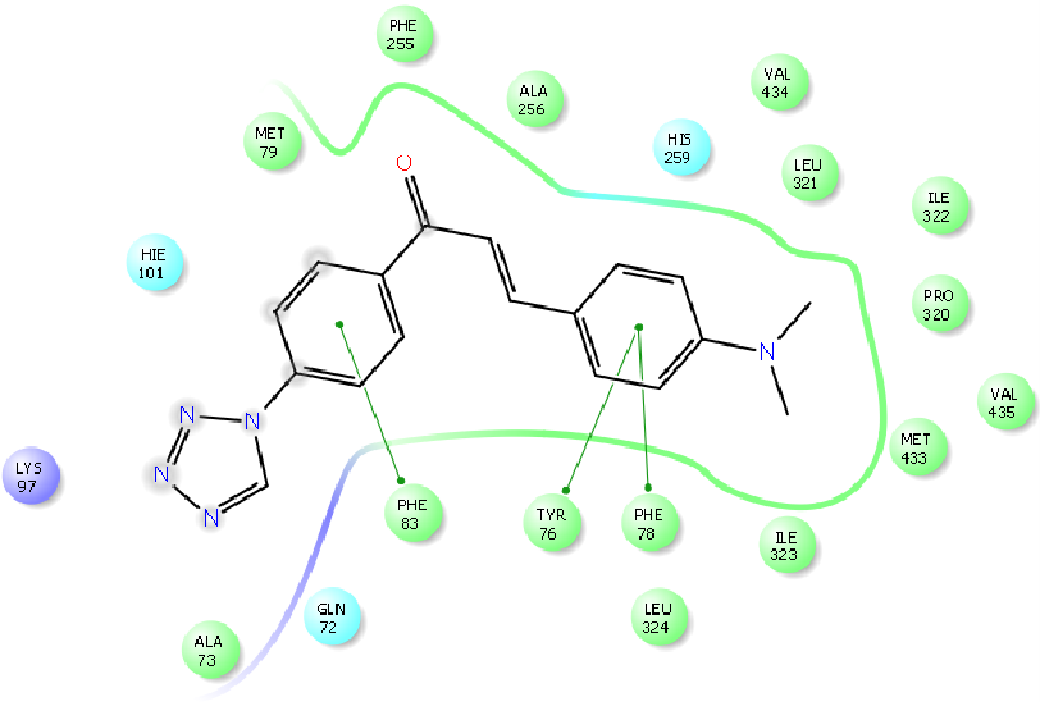


Figure 2. Docking model of compound 6g into the 14*α*-demethylase enzyme binding pocket

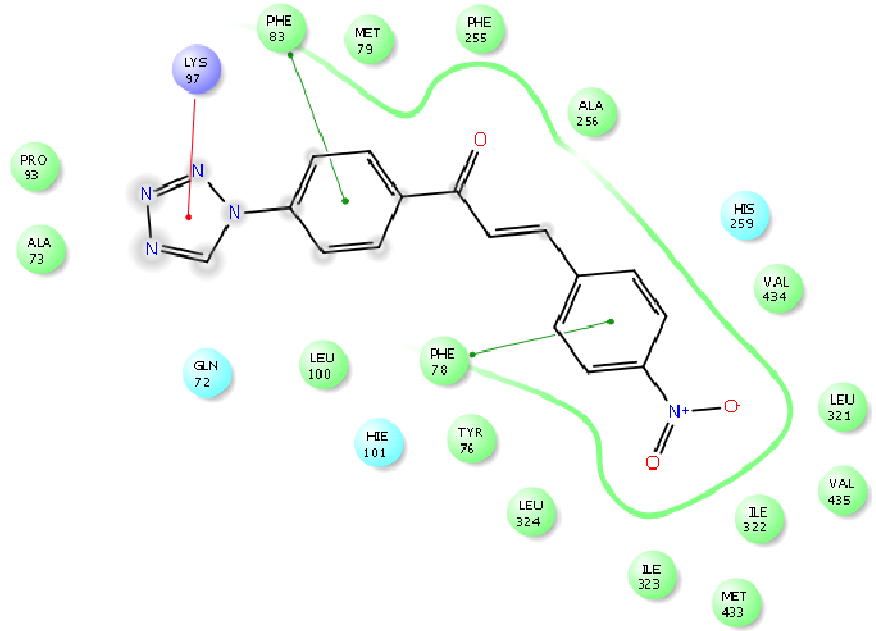


Figure 3. Docking model of compound 6e into the 14*α*-demethylase enzyme binding pocket

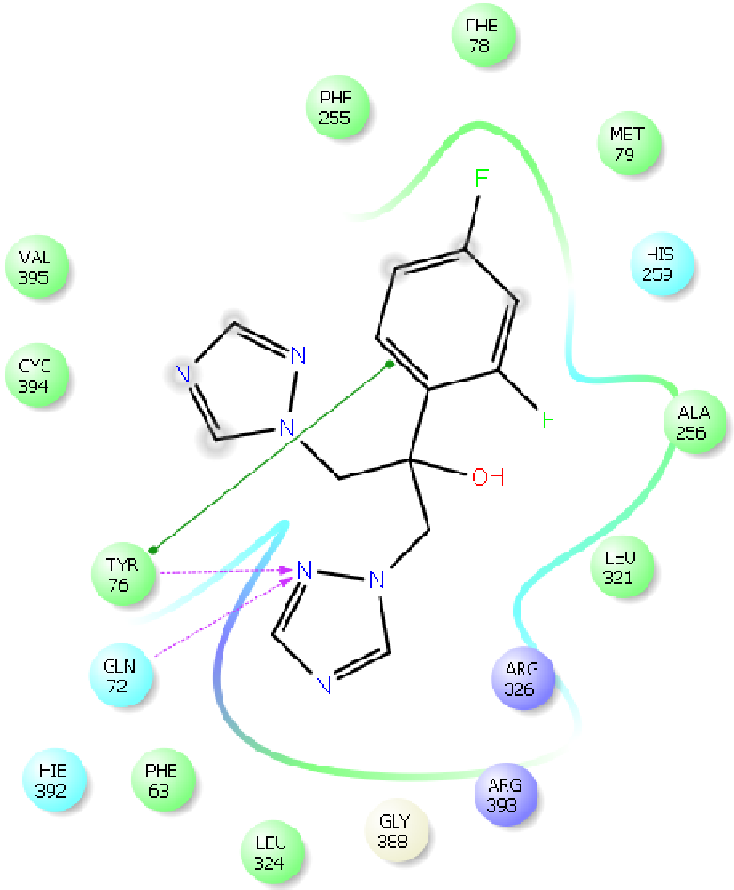


Figure 4. Docking model of compound Fluconazole into the 14α-demethylase enzyme binding pocket

CONCLUSION

A new series of 1-(4-(1*H*-tetrazole-1-yl) phenyl) -3-arylprop-2-en-1-ones (Chalcone) derivatives have been synthesized and characterized fully by FT-IR, ^{1}H, ^{13}C NMR and mass spectral analyses. *In vitro* Anti-fungal study of all the synthesized compounds were carried out and reported. It is found that compounds **6e**, **6g** and **6i** exhibited good inhibition activity against fungal stains. Molecular docking of compound **6i** was the one with the best glide and E model score of **-8.13** and **-60.39**, respectively, which is more than the glide score of Fluconazole (standard).

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