Docking, Synthesis, Spectral Characterization, and Evaluation of *In Vitro* Antifungal Activity of Bis/Monophenyl-1-aryl-1*H*-tetrazole-5-carboxylate

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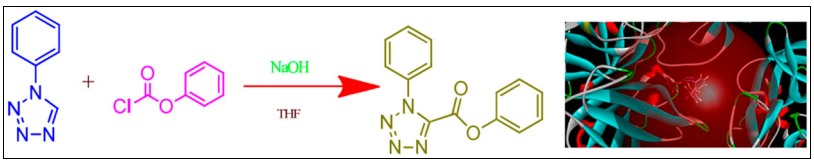

Some novel compounds of bis/monophenyl-1-aryl-1*H*-tetrazole-5-carboxylate were synthesized by the equimolar reaction between bis/mono-1-aryl-1*H*-tetrazole and phenyl chloroformate in the presence of NaOH in dry tetrahydrofuran. The content was stirred for 4 h at room temperature. Structures of these synthesized compounds were characterized by IR, ^{1}H-NMR, ^{13}C-NMR, and mass spectrometric methods. The *in vitro* antifungal activity study demonstrates that results of compounds **6g** and **6h** are excellent, **6e** a comparatively good one, and other compounds are moderate. The C docker energy of compounds **6g** and **6h** were −38.22 and −32.62 kcal/mol and that of compound **6e** was −21.26 kcal/mol.

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INTRODUCTION

Human fungal diseases show a significant, but often excluded, burden on public health, which is affecting over 1 million people worldwide [1]. Superficial fungal infections such as nail, skin, and urogenital infections affect most people during their lifetimes, but these can be cured by treating with antifungal drugs. If not treated with antifungal drugs means surely will affect the quality of life and burden health services [2,3]. Invasive fungal infections are more life-threatening opportunistic infections of the blood and organs affecting the immune systems. Invasive fungal infections cause a serious risk to immune-compromised people such as people living with human immunodeficiency virus/acquired immunodeficiency syndrome or receiving chemotherapy [4]. Fungi commonly causing infections on human beings (e.g. *Candida* species) or in the environment (e.g. *Aspergillus*, *Cryptococcus*, and *Pneumocystis* species) were normally without harm to healthy people [5]. The potential scientific challenge is to develop antifungal drugs to cure these diseases, which involve huge investment and long duration [6]. There are six major drugs used for the treatment of systematic infections, which are amphotericin B, flucytosine, fluconazole, itraconazole, voriconazole, and caspofungin [7]. Some antifungal drugs have face limitations, such as low drug activity, detrimental side effect, negative interaction with other drugs, and inappropriate for oral administration [8]. In fungi, lanosterol 14α-demethylase (CYP51) belongs to a superfamily of monooxygenase called cytochrome P450, which catalyzes the oxidative removal of the 14-methyl group (C-32) of lanosterol to give 14,15-desaturated intermediates in ergosterol biosynthesis in different biological kingdoms and serves the metabolic function such as membrane permeability and fluidity, enzyme activity, cell morphology, and cell cycle progression [9–11]. This enzyme is found in all eukaryotes (including human), because the azoles also interact with other cytochrome P450-dependent enzymes (CYP3A4), a selective inhibition of the enzyme emerging out with increased therapeutic index [12–14]. The active site of CYP51 is divided into four subsites: (i) coordination bond with iron of the heme group, (ii) the hydrophobic region, (iii) the hydrophilic region, and (iv) hydrogen bonding region and the narrow hydrophobic left formed. The binding interaction of azole with lanosterol 14α-demethylase is made by the affinity of coordination binding of N-4 in triazole, N-3 in imidazole of heme iron in the active site, N-1 substituent of the apoprotein in the enzyme and remaining part fits like how lanosterol in the hydrophobic groove of lanosterol 14α-demethylase [15–19]. Based on these special features of CYP51, a series of new azole derivatives with the broad antifungal spectrum have less potential to develop drug resistance. Tetrazoles are an aromatic heterocyclic compound (CHN_4) and seated as important place in tetrazole chemistry [20,21], explosives [22], rocket applicants, and chemical applications [23,24], 1-Substituted 1,2,3,4-tetrazoles are having antibacterial [25], antifungal [26], antiviral [27], analgesic [28], anti-inflammatory [29], antiulcer [30], and antihypertensive [31] activities. The function of tetrazole is resembled like the function of acid

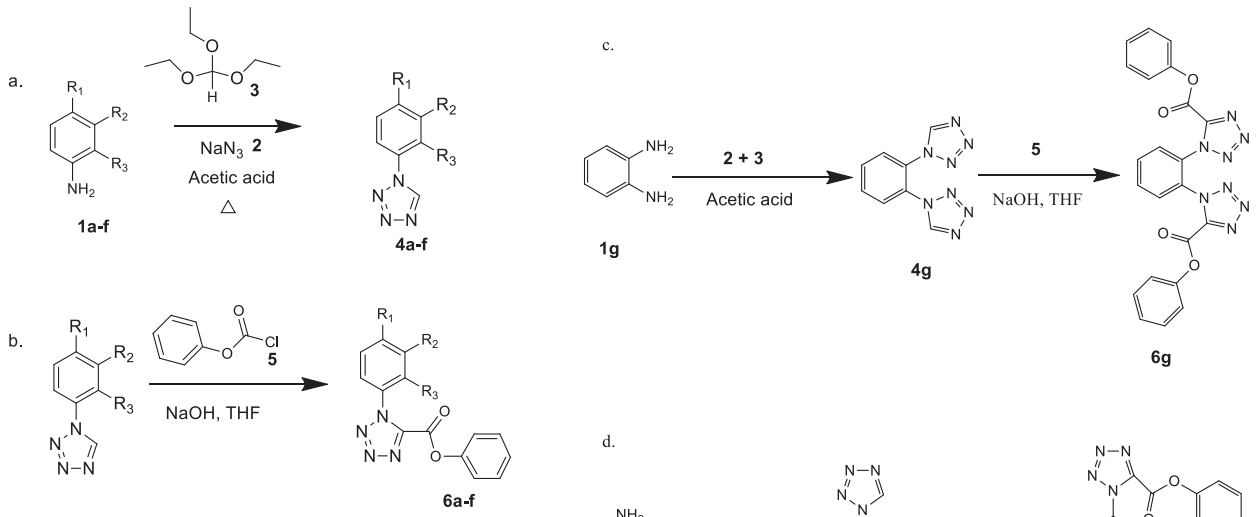
compound of carboxylic acid group, which has inspired many medicinal chemists to synthesize tetrazoles derivatives as potential medicinal agents.

RESULTS AND DISCUSSION

Chemistry. The novel synthetic tactics for the synthesis of bis/mono title compounds is portrayed in Scheme 1a–d. Bis/mono-1-aryl-1*H*-tetrazole (**4a–h**) was easily synthesized by the heterocyclic addition reaction of readily available bis/monosubstituted anilines (**1a–h**) reacting with sodium azide **2** and triethyl orthoformate **3** in acetic acid medium. The synthetic pathway for the synthesis of **4a–h** was given in Scheme 1a–d. Bis/mono-1-aryl-1*H*-tetrazole was treated with phenyl chloroformate **5** in dry tetrahydrofuran (THF). The content was stirred for 4 h at room temperature. To facilitate the reaction, a catalytic amount of 20% NaOH solution was added. The solid product was separated, filtered, and dried. The yield of mono/bisphenyl-(1-aryl-1*H*-tetrazole)-5-carboxylate (**6a–h**) (Scheme 1a–d) obtained was 80%. The chemical structure of compounds **6a–h** was supported by its spectral data. The presence of stretching frequency at 1761 cm^{-1} reveals the presence of the ester group. The absorption band appearing at 3061–3136 cm^{-1} attributed to aromatic rings. In ^{1}H-NMR spectrum recorded, resonated signals at 7.11–7.28 and 7.45–7.71 ppm attributed to two phenyl rings in the compound, which confirmed the presence of phenyl rings in the compound. ^{13}C-NMR spectrum exhibited resonated signals at 169.76, 152.15, and 150.94 ppm, which indicate the presence of carbonyl carbon, phenoxy carbon, and tetrazole carbon. The aromatic carbons signals appeared from 121.33 to 133.68 ppm.

Antifungal activity results. In present days, heterocyclic ring-containing systems exhibited excellent antifungal activities, which make our attention to evaluate the antifungal activity of the synthesized compounds. The *in vitro* antifungal activity was performed for all synthesized **6a–h** compounds, which were treated with various pathogenic fungi such as *Aspergillus fumigalis*, *Candida albicans*, and *Aspergillus niger*. The standard

Scheme 1. Synthetic pathway for the synthesis of phenyl-1-aryl-1*H*-tetrazole-5-carboxylate. (a) Reaction condition: refluxed at 80°C for 24 h. (b) Reaction condition: stirred for 4 h at room temperature. (c, d) Synthesis of **6g** and **6h** followed the same pathway of (a, b). Reactants **2**, **3**, and **5** are taken as double the mole ratio of the starting compound.



	R_1	R_2	R_3
6a	H	H	H
6b	OCH_3	H	H
6c	Cl	H	H
6d	CH_3CO	H	H
6e	H	Cl	Cl
6f	Br	H	H

drug fluconazole was used as a positive control. The results of minimum inhibitory concentration are tabulated in Table 1. The results revealed that compounds **6g** and **6h** show excellent activity, compound **6e** shows good activity, and other compounds have moderate activity. Hence, synthesized compounds **6a–h** have good antifungal activity.

Molecular docking results. To know the interaction between the title compounds and the protein lanosterol 14α-demethylase, all synthesized compounds **6a–h** were docked using Discovery Studio software. The crystal structure of CYP51 was downloaded from the protein bank (PDB ID: 1EA1). The values of C docker energy for monosubstituted title compounds **6a–f** (Table 2) are from −8.92 to −21.26 kcal/mol. The values of C docker energy for bis-substituted title compounds **6g–h** (Table 2) are from −32.62 to −38.22 kcal/mol. Compounds **6g** and **6h** are having more docking value of −38.22 and −32.22

Table 1

In vitro antifungal activity of compounds (minimum inhibitory concentration, μg/mL).

Compound	*Candida albicans*	*Aspergillus niger*	*Aspergillus fumigalis*
6a	0.625	1.25	0.625
6b	1.05	2.0	1.25
6c	0.625	2.5	0.625
6d	0.625	2.5	0.312
6e	**1.25**	**2.5**	**2.5**
6f	<0.16	<0.16	<0.16
6g	**2.5**	**5**	**5**
6h	**2.1**	**4.5**	**5**
Fluconazole	<0.16	0.625	2.5

Bold emphasis explain that the compounds possess good antifungal property.

Table 2

Molecular docking data of compounds **6a–j**.

Compound	–C docker energy (kcal/mol)	–C docker interaction (kcal/mol)
6a	10.47	22.51
6b	12.80	23.09
6c	8.92	24.39
6d	10.38	23.84
6e	**21.26**	**25.00**
6f	9.97	23.73
6g	**38.22**	**26.53**
6h	**32.62**	**39.40**

Bold emphasis explain that the compounds possess good antifungal property.

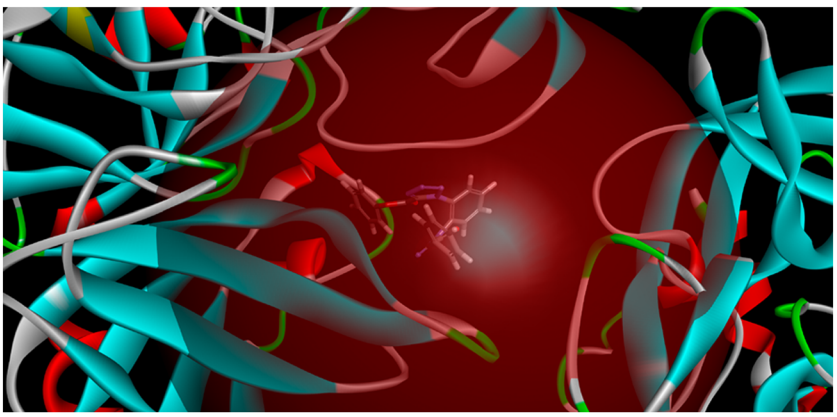


Figure 1. The three-dimensional interacting mode of compound **6g** with lanosterol 14α-demethylase. [Color figure can be viewed at wileyonlinelibrary.com]

kcal/mol, which revealed that the compounds are having excellent antifungal activity compared with the other compounds. The docking energy of compound **6e** is −21.26 kcal/mol having good antifungal activity, other compounds having moderate activity. The three-dimensional view of compound **6g** with protein 1EA1 is

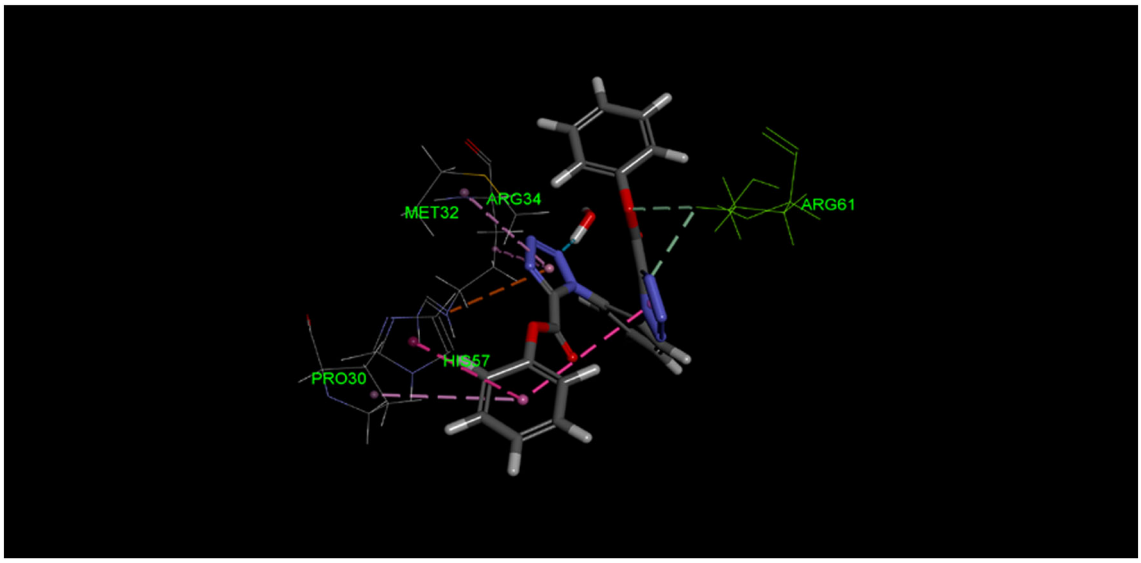


Figure 2. The two-dimensional interacting mode of compound **6g** with lanosterol 14α-demethylase. [Color figure can be viewed at wileyonlinelibrary.com]

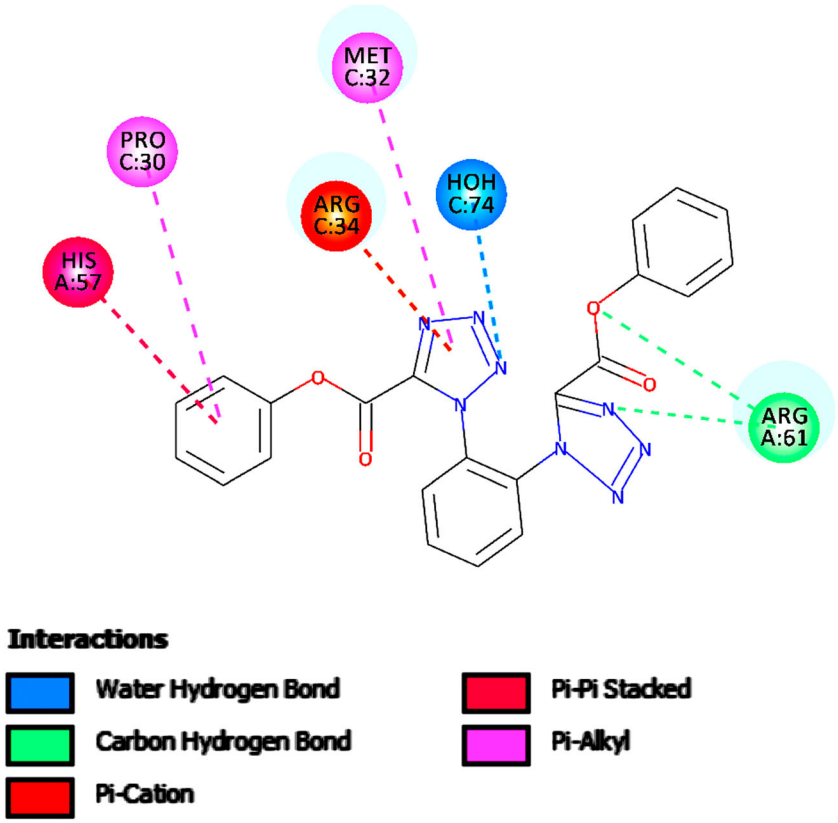


Figure 3. The description of bonding interactions in two-dimensional interacting modes of compound **6g** with lanosterol 14α-demethylase. [Color figure can be viewed at wileyonlinelibrary.com]

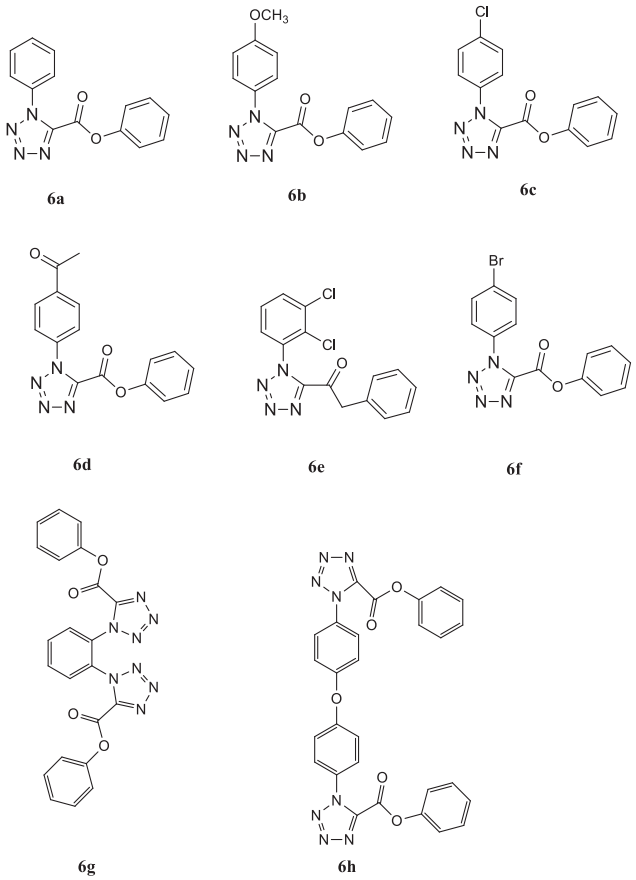


Figure 4. Structures of all synthesized compounds **6a–h**.

given in Fig. 1. The compounds interact with the CYP51 through HIS A: 57, PRO C: 30, ARG C: 34, ARG A: 61, MET C: 32, and HOH C: 74 (Fig. 2). The two-dimensional view of diagram (Fig. 3) of **6g** shows π–π stacked interaction of HIS A: 57 with O-phenyl ring, π-alkyl interaction of PRO C: 30 with O-phenyl ring, carbon–hydrogen bond interaction of ARG A: 61 with oxygen and tetrazole nitrogen, π-alkyl interaction of MET C: 32 with tetrazole ring, cation interaction of ARG C: 34 with tetrazole ring, and water hydrogen bond with one of the nitrogen tetrazole ring.

CONCLUSION

All the newly synthesized compounds are characterized by IR, ^{1}H-NMR, ^{13}C-NMR, and mass spectra. All the compounds are having good antifungal activities. Among these, compounds **6g** and **6h** exhibited excellent activity, compound **6e** exhibited good activity, and other compounds have moderate activity. Molecular docking of compounds **6g** and **6h** exhibited excellent –C docking energy, compound **6e** showed good –C docking energy, and the remaining compounds have moderate energy. Therefore, bis/monophenyl-1-aryl-1*H*-tetrazole-5-carboxylate has possessed good CYP51 inhibition; hence, it is concluded as active biologically novel compound.

EXPERIMENTAL

Materials and methods. Melting points (°C, uncorrected) were checked in open capillary tube by using (Labtronics 110; Labtronics, Panchkula, India) digital auto melting point apparatus and found uncorrected. The chemicals and solvents were purchased from Sigma-Aldrich (St. Louis, MO) and Merck, India (Mumbai, India). All the reactions were carried out at their appropriate conditions, and the products were checked by TLC silica gel 60 F254 using eluent solvents such as pet ether and benzene in the ratio 3:7. All the compounds were characterized by FT-IR spectrometer (Agilent Cary 650, Santa Clara, USA) using KBr pellets

and ^{1}H-NMR spectroscopy in DMSO (400 MHz, Bruker Corp., Billerica, MA) and ^{13}C-NMR spectroscopy in DMSO (100 MHz, Bruker Corp.) using tetramethylsilane as an internal standard. Mass–gas chromatography spectra were measured by Saturn 2200 (CP-3800; Varian, Palo Alto, California). Antifungal activity of all the synthesized compounds was determined by the minimum inhibitory concentration method. Docking studies of all the compounds were docked using Discovery Studio software.

General procedure for the synthesis of monophenyl-1-aryl-1 H-tetrazole-5-carboxylate (6a–f). The synthesis of tetrazole is followed by the literature method [32,33]. 1-Substituted aryl amine **1a–f** (10 mmol) was treated with sodium azide **2** (10 mmol) and triethyl orthoformate **3** (10 mmol) in acetic acid (100 mL) (Scheme 1a). The content was refluxed for 24 h at 80°C. The reaction progress was checked by TLC. Once the reaction was completed, the reaction mixture was transferred into a beaker containing ice. The solid product was separated on cooling, filtered, and dried. Then 1-aryl-substituted-1*H*-tetrazole **4a–h** (5 mmol) was treated with phenyl chloroformate **5** (5 mmol) in THF (100 mL) in the presence of NaOH (20%) (Scheme 1b). It was stirred for 4 h. Again, the reaction progress was checked by TLC. Once the reaction was completed, the reaction mixture was transferred into a beaker containing ice. The solid product was separated on cooling, filtered, and dried. The compound is purified by column chromatography using 7:3 of pet ether and benzene. The yield of products **6a–f** is from 82 to 90%. The structure of all the synthesized compound given in Fig. 4.

*Synthesis of phenyl-1-phenyl-1H-tetrazole-5-carboxylate **(6a)**.* Brown color solid, mp 54–64°C; IR ν (cm^{-1}): 1761 (ester group), 1659 (C═N), 3061–3136 (aromatic C─H); ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.11–7.28 ppm (m, 5H, O-phenyl ring), 7.45–7.71 ppm (m, 5H, N-phenyl ring); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 121.33, 121.84, 126.55, 126.79, 128.65, 128.93, 129.05, 129.14, 129.21, 129.49, 133.68, 150.94, 152.15, 169.76 ppm; MS (*m/z*): 267.02 $[M + H]^+$; *Anal*. Calcd for $C_{14}H_{10}N_4O_2$: C, 63.15; H, 3.79; N, 21.04; Found: C, 63.12; H, 3.81; N, 21.01.

*Synthesis of phenyl-1-(4-methoxyphenyl)-1H-tetrazole-5-carboxylate **(6b)**.* Brown color solid, mp 62–64°C; IR ν (cm^{-1}): 1768 (ester group), 1669 (C═N), 3061–3135 (aromatic C─H); ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.18–7.39 ppm (m, 5H, O-phenyl ring), 7.46–7.83 ppm (m, 4H, N-phenyl ring), 3.84 (s, 3H); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 56.14, 119.25, 121.00, 121.71, 123.40, 126.96, 127.38, 129.82, 130.18, 130.46, 133.01, 151.15, 152.12, 160.47, 168.18 ppm; MS (*m/z*): 297.08 $[M + H]^+$; *Anal*. Calcd for $C_{15}H_{12}N_4O_3$: C, 60.81; H, 4.08; N, 18.91; Found: C, 60.79; H, 4.11; N, 18.88.

*Synthesis of phenyl-1-(4-chlorophenyl)-1H-tetrazole-5-carboxylate **(6c)**.* Brown color solid, mp 68–74°C; IR ν (cm^{-1}): 1767 (ester group), 1658 (C═N), 3062–3125 (aromatic C─H); ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.13–7.34 ppm (m, 5H, O-phenyl ring), 7.62–7.96 ppm (m, 4H, N-phenyl ring); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 121.17, 121.69, 124.68, 126.62, 126.94, 127.03, 128.70, 128.99, 129.52, 130.16 133.03, 151.13, 152.15, 168.99 ppm; MS (*m/z*): 301.07 $[M + H]^+$; *Anal*. Calcd for $C_{16}H_9ClN_4O_2$: C, 55.92; H, 3.02; N, 18.63; Found: C, 55.90; H, 3.05; N, 18.61.

*Synthesis of phenyl-1-(4-acetylphenyl)-1H-tetrazole-5-carboxylate **(6d)**.* Brown color solid, mp 64–68°C; IR ν (cm^{-1}): 1768 (ester group), 1677 (C═N), 3058–3127 (aromatic C─H); ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.87–8.07 ppm (m, 5H, O-phenyl ring), 8.14–8.23 ppm (m, 4H, N-phenyl ring), 2.57 ppm (3H, s); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 26.82, 121.72, 123.43, 123.70, 125.47, 126.96, 129.80, 129.81, 130.13, 130.19, 137.29, 139.95, 151.15, 152.37, 168.71, 196.81 ppm; MS (*m/z*): 309.01 $[M + H]^+$; *Anal*. Calcd for $C_{16}H_{12}N_4O_3$: C, 62.33; H, 3.92; N, 18.17; Found: C, 62.30; H, 3.93; N, 18.21.

*Synthesis of phenyl-1-(2,3-dichlorophenyl)-1H-tetrazole-5-carboxylate **(6e)**.* Brown color solid, mp 94–98°C; IR ν (cm^{-1}): 1768 (ester group), 1664 (C═N), 3065–3101 (aromatic C─H); ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.00–7.35 ppm (m, 5H, O-phenyl ring), 7.36–7.47 ppm (m, 3H, N-phenyl ring); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 121.37, 121.68, 125.25, 125.60, 126.97, 128.32, 128.46, 129.84, 130.18, 130.45, 132.27, 151.11, 152.16, 169.41 ppm; MS (*m/z*): 335.02 $[M + H]^+$; *Anal*. Calcd for $C_{14}H_8Cl_2N_4O_2$: C, 50.17; H, 2.41; N, 16.72; Found: C, 50.15; H, 2.39; N, 16.68.

*Synthesis of phenyl-1-(4-bromophenyl)-1H-tetrazole-5-carboxylate **(6f)**.* Brown color solid, mp 70–75°C; IR ν (cm^{-1}): 1768 (ester group), 1665 (C═N), 3050–3117 (aromatic C─H); ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.32–7.46 ppm (m, 5H, O-phenyl ring), 7.47–7.87 ppm (m, 4H, N-phenyl ring); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 121.70, 121.95, 122.98, 123.57, 126.98, 129.91, 130.19, 130.46, 131.93, 133.45, 139.07, 151.12, 152.16, 169.06 ppm; MS (*m/z*): 346.01 $[M + H]^+$; *Anal*. Calcd for $C_{14}H_9BrN_4O_2$: C, 48.72; H, 2.63; N, 16.23; Found: C, 48.70; H, 2.59; N, 16.21.

General procedure for the synthesis of bisphenyl-1-aryl-1H-tetrazole-5-carboxylate (6g and 6h). The synthesis of tetrazole is followed by the literature method [24,25]. O-Phenylene diamines **1g**/4,4-oxydianiline **1h** (10 mmol) was treated with sodium azide **2** (20 mmol) and triethyl orthoformate **3** (20 mmol) in acetic acid (100 mL) (Scheme 1c,d). The reaction mixture was refluxed for 24 h at 80°C. The reaction progress was monitored by TLC. Once the reaction was completed, the reaction mixture was poured into ice. The solid product was separated on cooling, filtered, and dried. Then 1,2-di(1*H*-tetrazolyl)benzene **4g**/1,1-(oxybis(4,1-phenylene) bis(1H-tetrazole) **4h** (5 mmol) was treated with phenyl chloroformate **5** (10 mmol) in THF (100 mL) in the presence of NaOH (20%). The reaction mixture was stirred for 4 h. Again, the reaction progress was monitored by TLC. Once the reaction was completed, the reaction mixture was poured into ice. The solid product was separated on cooling, filtered, and dried. The compound is purified by column chromatography using 7:3 of pet ether and benzene. The yield of products **6g** and **6h** is from 82 to 85%.

*Synthesis of diphenyl-1,1'-(1,2-phenylene)bis(1H-tetrazole-5-carboxylate) (**6g**).* Brown color solid, mp 56–60°C; IR ν (cm^{-1}): 1779 (ester group), 1699 (C═N), 3065–3142 (aromatic C─H); ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.17–7.50 ppm (m, 10H, O-phenyl ring), 7.76–7.83 ppm (m, 4H, N-phenyl ring); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 120.88, 121.58, 125.06, 125.86, 126.82, 127.06, 127.22, 129.37, 129.77, 131.62, 150.90, 152.09, 169.76 ppm; MS (*m*/*z*): 455.01 $[M + H]^+$; *Anal*. Calcd for $C_{22}H_{14}N_8O_4$: C, 58.15; H, 3.11; N, 24.66; Found: C, 58.13; H, 3.09; N, 24.69.

*Synthesis of diphenyl-1,1'-(oxybis(4,1-phenylene)bis(1H-tetrazole-5-carboxylate) (**6h**).* Brown color solid, mp 66–70°C; IR ν (cm^{-1}): 1767 (ester group), 1665 (C═N), 3061–3161 (aromatic C─H); ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.07–7.39 (m, 10H, O-phenyl ring), 7.46–7.98 ppm (m, 8H, N-phenyl ring) ppm; ^{13}C-NMR (100 MHz, DMSO-d_6): δ 121.36, 121.72, 122.05, 122.40, 123.76, 129.01, 129.84, 129.92, 135.31, 151.13, 152.81, 157.32, 168.70 ppm; MS (*m*/*z*): 547.02 $[M + H]^+$; *Anal*. Calcd for $C_{28}H_{18}N_8O_5$: C, 61.54; H, 3.32; N, 20.50; Found: C, 61.52; H, 3.35; N, 20.49. The spectrum for compounds **6a–h** is given in the Supporting Information.

Antifungal activity. A serial dilution method is used to determine the *in vitro* antifungal activity for the title compounds, and it is measured by the minimum inhibitory concentration method. Different concentrations of compounds and standard positive control fluconazole were taken and dissolved in DMSO under specific condition. It was incubated for 24 h at 37 ± 1°C. After incubation, the assay tube concentrations were transferred into nutrient agar plate to study the inhibition of growth of the organism. All the experiments were carried in triplicates.

Molecular docking studies. All the title compounds were docked with protein 1EA1 using Discovery Studio software. Before the docking process, all the ligand energies were minimized. The crystal structure of protein 1EA1 was downloaded from the protein bank website (PDB IB: 1EA1). During the docking process, 10 poses of –C docker energy were obtained. Among them, one pose with less –C docker energy was confirmed for the energy for the respective compounds.

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